Bruno Filipe Oliveira Nascimento

Synthetic Studies of Nitrogen-Containing Heterocycles under Microwave Irradiation

Tese orientada pelo Professor António Manuel d'Albuquerque Rocha Gonsalves
e pela Professora Marta Piñeiro Gómez e apresentada na Universidade de Coimbra
para obtenção do grau de Doutor em Química com especialidade de Síntese Orgânica

July 2013

· U C ·

Universidade de Coimbra

Bruno Filipe Oliveira Nascimento

Synthetic Studies of Nitrogen-Containing Heterocycles under Microwave Irradiation

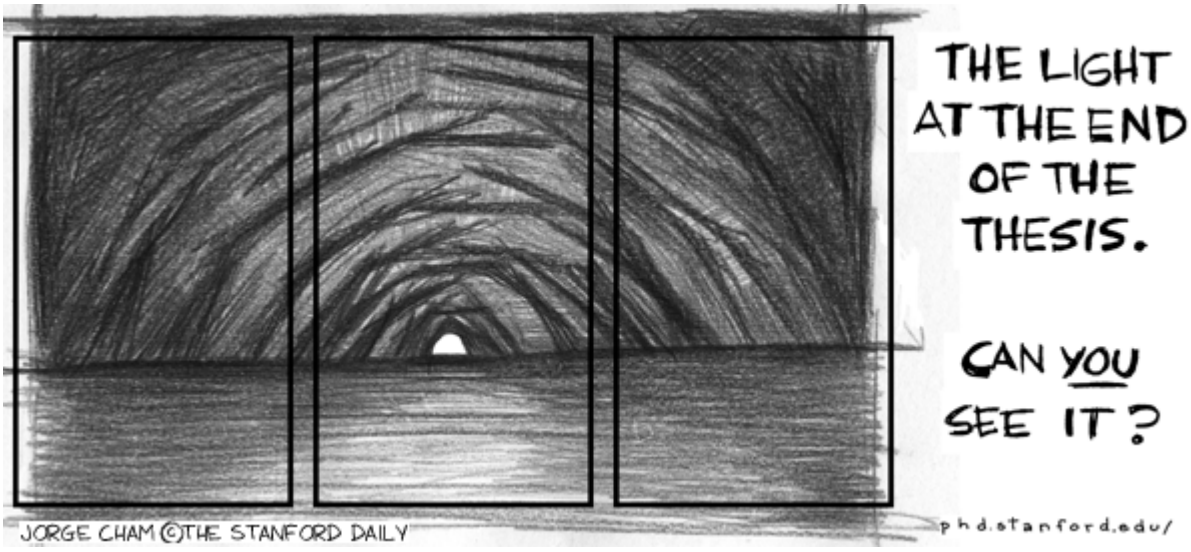
Tese orientada pelo Professor António Manuel d'Albuquerque Rocha Gonsalves
e pela Professora Marta Piñeiro Gómez e apresentada na Universidade de Coimbra
para obtenção do grau de Doutor em Química com especialidade de Síntese Orgânica

July 2013

· U C ·

UNIVERSIDADE DE COIMBRA

Aos elementos da FREQ, Frente Revolucionária do Enclave das Químicas.
Obrigado pela longa e intensa amizade... Aquele abraço!


THE LIGHT AT THE END OF THE THESIS.
CAN YOU SEE IT?
JORGE CHAM ©THE STANFORD DAILY
phd.stanford.edu/

Contents

Preface

"By three methods we may learn wisdom: first, by reflection, which is noblest; second, by imitation, which is easiest; and third, by experience, which is bitterest."

Confucius (551 - 479 BC)

The work presented in this dissertation was carried-out at the Research Laboratory on Organic Chemistry of the Department of Chemistry, Faculty of Sciences and Technology of the University of Coimbra, Portugal, between January 2008 and June 2012, and was by no means accomplished in an individual manner, but through several and fruitful interactions. Hence, it is of the essence to acknowledge the valuable contributions of all persons and entities involved.

To Prof. Marta Piñeiro Gómez, my supervisor, I acknowledge the enlightened and informal scientific guidance, always characterised by a generous amount of patience and good-humour, which was utterly determinant throughout this project. To Prof. António M. d'A. Rocha Gonsalves, my co-supervisor, I acknowledge the thoughts and opinions, always furnished in a singular and charismatic fashion, that were essential to the successful scrutiny of several queries. To Prof. Teresa M. V. D. Pinho e Melo, head of the Research Laboratory on Organic Chemistry, I acknowledge the useful clarifications that were fundamental to the investigation of various questions.

I am profoundly grateful to the following persons for their expertise and availability, regarding the technical features of the structural characterisation, spectral, photophysical and cytotoxicity studies of some of the compounds synthesised in this work: Prof. Maria Elisa S. Serra (Elemental Analysis), Pedro Cruz and Prof. Rui M. M. Brito (Nuclear Magnetic Resonance Spectroscopy), Júlio Sampaio (High-Resolution Mass Spectrometry), Alexandra Gonsalves (Mass Spectrometry), Sílvia Gramacho (Gas Chromatography-Mass Spectrometry), Prof. José A. Paixão (X-Ray Diffraction), Daniela Pinheiro, João Pina and Prof. J. Sérgio Seixas de Melo (Spectral and Photophysical Studies), Mafalda Laranjo, Ana Abrantes and Prof. Maria Filomena Botelho (Cytotoxicity Studies).

I wish to convey my deepest gratitude to all my laboratory co-workers, for their support, team-spirit and helpful sharing of ideas. In particular, I would like to thank Prof. Arménio C. Serra for the constant, proficient and good-humoured exchange of opinions, in spite of our differences at the musical level and, consequently, our customary disagreement concerning the frequency setting of the laboratory radio. I would also like to express recognition to my colleagues Cláudio Nunes, Nelson Pereira, Rui Nunes and Salomé Santos for their friendship, encouragement and the always riveting discussions, scientific, political or other, particularly when the best results of this work were not being achieved at the desired rate. Furthermore, thanks are due to Rita Navarro, for reading and correcting part of this manuscript and providing me with both precious and pertinent suggestions. Lastly, I wish to deeply acknowledge my parents, Fátima and Pedro, for their continual affection, endless support and, as long as I can remember, for instigating my free-will and freedom of thought.

Financial aid provided by Chymiotechnon, Coimbra Chemistry Centre, University of Coimbra and, particularly, *Fundação para a Ciência e Tecnologia*, which kindly presented me with a Ph.D. grant (SFRH/BD/QUI/41472/2007), is also gratefully appreciated.

Abstract

The central goal of the work presented in this doctoral dissertation was the application of microwave irradiation to the development of efficient, straightforward and reproducible synthetic methods of various interesting and broadly recognised nitrogen-containing heterocycles. Their reactivity under microwave heating conditions, particularly in oxidation processes, was also studied, inexpensive, undemanding and environment-friendly synthetic strategies being employed whenever possible.

The illustrious Paal-Knorr synthesis of pyrroles was revised, some 2,5-dimethyl-1*H*-pyrroles and bis-2,5-dimethyl-1*H*-pyrroles being readily prepared with high reaction yields through a solventless and microwave-activated procedure. A small compound library of 3,5-diaryl-2-methyl-1*H*-pyrroles, incorporating both electron-donating and electron-withdrawing scaffolds, was also synthesised under microwave irradiation using a solid-supported and multicomponent approach, albeit with low isolated yields. A few of these multisubstituted heterocycles were selected and further studied, some of their spectroscopic and photophysical properties being determined. The chalcone precursors required for their synthesis were prepared with high yields through the classic Claisen-Schmidt reaction.

A series of *meso*-substituted porphyrins was prepared through a microwave-activated one-pot methodology, the yields being usually higher than the ones achieved through the related conventional heating method or via our former microwave-assisted approach. The same protocol was also applied to the preparation of some novel unsymmetrical *meso*-tetraarylporphyrins. A two-step synthesis of porphyrins, in which microwave-activation was applied in the second reaction step and the low-budget and user-friendly activated manganese dioxide was used as oxidant, was also examined, low to moderate reaction yields being achieved. The di-imide-promoted reduction of porphyrins to their hydroporphyrin analogues was investigated under microwave irradiation. The bacteriochlorins were easily obtained with high yields, although contaminated with up to 35% of the corresponding chlorins. Selective dehydrogenation of the bacteriochlorin derivatives was accomplished under microwave heating using activated manganese dioxide, the respective chlorins being isolated with good yields, albeit contaminated with 10 to 35% of the corresponding porphyrins.

Several Hantzsch 1,4-dihydropyridines were effortlessly prepared via a multicomponent and solvent-free strategy under microwave activation, moderate to good reaction yields being obtained without the requirement of any chromatographic isolation procedure. Some Hantzsch pyridines were also rapidly synthesised through the microwave-assisted oxidative aromatisation of the corresponding 1,4-dihydropyridine analogues, either under heterogeneous reaction conditions using activated manganese dioxide or by means of a homogeneous methodology utilising potassium peroxydisulphate. An unforeseen oxidative dearylation process was observed in a few cases when activated manganese dioxide was employed, although further studies are necessary in order to elucidate the reaction mechanisms involved.

A compound library of Biginelli 3,4-dihydropyrimidines was synthesised under microwave heating conditions, good reaction yields and high purity being generally obtained, without the requirement of chromatographic purification techniques. The same approach was also applied to the multicomponent synthesis of some Biginelli bis-3,4-dihydropyrimidines. A two-pot two-step method, in which microwave irradiation was used at the second reaction stage, provided a series of interesting 4,6-diaryl-3,4-dihydropyrimidine-2(1*H*)-thiones. Again, no chromatographic separation procedure was needed for the isolation of the target products with high yields. Some of these Biginelli-type 3,4-dihydropyrimidines were selected and their *in vitro* cytotoxic activity was studied against a few human cancer cell lines. In general, all compounds tested were more active against MCF7 breast cancer cells, the brominated derivatives being the most active molecules. Various pyrimidin-2(1*H*)-ones, bearing

both electron-withdrawing and electron-donating functionalities, were synthesised through the microwave-assisted oxidation of the related 3,4-dihydropyrimidin-2(1*H*)-ones. Among the various oxidising agents employed, potassium peroxydisulphate was established as the only effective one under the reaction conditions studied. However, application of this oxidant to the dehydrogenation of 3,4-dihydropyrimidine-2(1*H*)-thiones was unsuccessful. Oxone and hydrogen peroxide were also tested as oxidants, but either failed completely or furnished unpredicted or unidentified by-products. The best outcome was obtained using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, although further work is required in order to effectively accomplish this extremely difficult synthetic enterprise.

Resumo

O principal objectivo do trabalho apresentado nesta dissertação doutoral foi a aplicação de irradiação de microondas ao desenvolvimento de métodos sintéticos simples, eficientes e reproduzíveis de vários heterociclos nitrogenados interessantes e largamente conhecidos. A sua reactividade sob aquecimento por microondas, particularmente em processos oxidativos, também foi estudada, tendo sido empregues sempre que possível estratégias sintéticas práticas, pouco dispendiosas e ambientalmente sustentáveis.

A célebre síntese de pirróis de Paal-Knorr foi revista, tendo sido preparados alguns 2,5-dimetil-1*H*-pirróis e bis-2,5-dimetil-1*H*-pirróis com rendimentos elevados através de um procedimento sem solvente e activado por microondas. Uma biblioteca de compostos de 3,5-diaril-2-metil-1*H*-pirróis, incorporando funcionalidades doadoras e atractoras de electrões, foi também sintetizada sob irradiação de microondas usando uma abordagem multicomponente em suporte sólido, embora com baixos rendimentos. Alguns destes heterociclos multisubstituídos foram selecionados, tendo sido determinadas algumas das suas propriedades espectroscópicas e fotofísicas. As chalconas precursoras requeridas para a sua síntese foram preparadas com bons rendimentos através da clássica reacção de Claisen-Schmidt.

Uma série de porfirinas *meso*-substituídas foi sintetizada através de uma metodologia *one-pot* activada por microondas, sendo os rendimentos geralmente mais altos do que os obtidos através do método de aquecimento convencional relacionado ou via a nossa anterior abordagem assistida por microondas. O mesmo protocolo foi também aplicado à preparação de algumas *meso*-tetraarilporfirinas assimétricas. Uma síntese bietápica de porfirinas, em que activação por microondas foi aplicada no segundo passo reaccional e dióxido de manganésio activado foi utilizado como agente oxidante, também foi examinada, tendo sido obtidos rendimentos baixos a moderados. A redução de porfirinas a hidroporfirinas promovida por di-imida foi investigada sob microondas. As bacteriolorinas foram facilmente obtidas com rendimentos elevados, embora contaminadas com até 35% das clorinas correspondentes. A desidrogenação selectiva das bacterioclorinas foi conseguida sob aquecimento de microondas usando dióxido de manganésio activado, tendo as respectivas clorinas sido isoladas com bons rendimentos, apesar de contaminadas com 10 a 25% das respectivas porfirinas.

Diversas 1,4-dihidropiridinas de Hantzsch foram preparadas via uma estratégia multicomponente e sem solvente sob microondas, tendo sido obtidos rendimentos moderados a bons sem a necessidade de qualquer procedimento cromatográfico de isolamento. Algumas piridinas de Hantzsch foram também rapidamente sintetizadas através da aromatização oxidativa assistida por microondas das respectivas 1,4-dihidropiridinas, sob condições heterogéneas usando dióxido de manganésio activado ou através de uma metodologia homogénea utilizando peroxidisulfato de potássio. Um inesperado processo de desarilação oxidativa foi observado em alguns casos quando dióxido de manganésio activado foi empregue, embora mais estudos sejam necessários para elucidar os mecanismos reaccionais envolvidos.

Uma biblioteca de compostos de 3,4-dihidropirimidinas de Biginelli foi sintetizada sob microondas, tendo sido obtidos genericamente bons rendimentos e elevada pureza, sem recorrer a técnicas de purificação cromatográfica. A mesma abordagem foi também aplicada à síntese muticomponente de algumas bis-3,4-dihidropirimidinas de Biginelli. Um método bietápico *two-pot*, em que irradiação de microondas foi usada na segunda etapa reaccional, providenciou uma série de 4,6-diaril-3,4-dihidropirimidina-2(1*H*)-tionas. Novamente, nenhum procedimento cromatográfico de separação foi necessário para o isolamento dos produtos alvo com rendimentos elevados. Algumas destas 3,4-dihidropirimidinas de tipo-Biginelli foram seleccionadas e a sua actividade citotóxica *in vitro* foi avaliada contra algumas linhas celulares de cancros humanos. Em geral, todos os compostos foram mais activos contra células do cancro da mama MCF7, tendo os derivados bromadas sido as moléculas mais activas.

Várias pirimidin-2(1*H*)-onas, contendo grupos funcionais atractores e doadores de electrões, foram sintetizadas através da oxidação assistida por microondas das respectivas 3,4-dihidropirimidin-2(1*H*)-onas. Entre os vários oxidantes empregues, o peroxidisulfato de potássio provou ser o único eficiente sob as condições reaccionais estudadas. Contudo, a aplicação deste oxidante à desidrogenação de 3,4-dihidropirimidina-2(1*H*)-tionas não foi bem sucedida. Oxone e peróxido de hidrogénio foram também testados como oxidantes, mas falharam completamente ou conduziram a produtos secundários imprevistos ou não identificados. O melhor resultado foi obtido usando 2,3-dicloro-5,6-diciano-1,4-benzoquinona, embora mais estudos sejam requeridos de forma a superar eficazmente esta tarefa sintética extremamente difícil.

Listing of Abbreviations

Ac	acetyl
AcOH	glacial acetic acid
AIDS	acquired immunodeficiency syndrome
ATP	adenosine triphosphate
AZT	azidothymidine
$BF_3.OEt_2$	boron trifluoride diethyl etherate
[bmin]BF_4	1-*n*-butyl-3-methylimidazolium tetrafluoroborate
Bn	benzyl
BODIPY	4,4-difluoro-4-boradipyrromethene
bp	boiling point (^oC)
BPH	benign prostatic hyperplasia
bs	broad singlet
[bsmim]OTs	butane-1-sulphonic acid-3-methylimidazolium tosylate
CAN	ceric ammonium nitrate
CCD	charge-coupled device
CF	continuous-flow
CI_{95}	95% confidence interval (μM)
^{13}C NMR	carbon nuclear magnetic resonance
CPCC	3-carboxypyridinium chlorochromate
d	doublet
DCB	1,2-dichlorobenzene
DCE	1,2-dichloroethylene
dd	double doublet
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl acetylenedicarboxylate
DFT	density functional theory
DHP	1,4-dihydropyridine
DHPM	3,4-dihydropyrimidine
DMA	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulphoxide
EI	electron impact ionisation
ESI	electro-spray ionisation
Et	ethyl
EtOH	ethanol
GABA	γ-aminobutyric acid
GC	gas chromatography
GCC	glycinium chlorochromate
GC-MS	gas chromatography-mass spectrometry
GS	ground state
HBV	hepatitis B virus
HIV	human immunodeficiency virus
^1H NMR	proton nuclear magnetic resonance
HPLC	high-performance liquid chromatography
HPLC-MS	high-performance liquid chromatography-mass spectrometry

HR-MS	high-resolution mass spectrometry
IC_{50}	half maximal inhibitory concentration (μM)
i-Pr	*i*-propyl
IR	infrared
IUB	International Union of Biochemistry
IUPAC	International Union of Pure and Applied Chemistry
LC-MS	liquid chromatography-mass spectrometry
m	multiplet
M^+	molecular ion
MALDI	matrix-assisted laser desorption/ionisation
MAOS	microwave-assisted organic synthesis
MCR	multicomponent reaction
Me	methyl
MeOH	methanol
mp	melting point (°C)
MS	mass spectrometry
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MW	microwave
NADH	reduced nicotinamide adenine dinucleotide
NADPH	reduced nicotinamide adenine dinucleotide phosphate
n-Bu	*n*-butyl
NEt_3	triethylamine
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NO_2Ph	nitrobenzene
n-Pr	*n*-propyl
OAc	acetate
OAc_2	acetic anhydride
OEt	ethoxy
OEt_2	diethyl ether
OMe	methoxy
o-TCQ	3,4,5,6-tetrachloro-1,2-benzoquinone
OTf	triflate
OTs	tosylate
PCC	pyridinium chlorochromate
PDT	photodynamic therapy
PDV	photodynamic inactivation of viruses
PEG	polyethylene glycol
Ph	phenyl
PPA	polyphosphoric acid
PPE	polyphosphate ester
ppm	parts per million
PSSA	polystyrenesulphonic acid
p-TCQ	2,3,5,6-tetrachloro-1,4-benzoquinone
p-TSA	*p*-toluenesulphonic acid
p-TSH	*p*-toluenesulphonyl hydrazide
q	quartet

quin	quintet
RADAR	radio detection and ranging
ROS	reactive oxygen species
RT	room temperature
s	singlet
SAR	structure-activity relationship
sex	sextet
t	triplet
T	temperature (^{o}C or K)
TBAB	tetra-*n*-butylammonium bromide
TBAPD	tetra-*n*-butylammonium peroxydisulphate
TBAPM	tetra-*n*-butylammonium peroxymonosulphate
TBHP	*t*-butyl hydroperoxide
t-Bu	*t*-butyl
TCA	trichloroacetic acid
TCB	1,2,4-trichlorobenzene
TCCA	trichloroisocyanuric acid
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TMSCl	chlorotrimethylsilane
TPB	5,10,15,20-tetraphenylbacteriochlorin
TPC	5,10,15,20-tetraphenylchlorin
TPP	5,10,15,20-tetraphenylporphyrin
t_R	retention time (min)
TS	transition state
USB	universal serial bus
UV	ultraviolet
UV-Vis	ultraviolet-visible
XRD	X-ray diffraction
$ZnEt_2$	diethyl zinc

Listing of Symbols

A	pre-exponential factor ($mol^{-1}\ s^{-1}$)
E_a	activation energy ($J\ mol^{-1}$)
E^o	standard oxidation/reduction potential (V)
h	Planck constant (J s)
J	coupling constant (Hz)
k	rate constant (s^{-1})
R	ideal gas constant ($J\ mol^{-1}\ K^{-1}$)
$\tan\delta$	loss factor
Φ	quantum yield
Φ_F	fluorescence quantum yield
Φ_{IC}	internal conversion quantum yield
Φ_P	phosphorescence quantum yield
Φ_T	triplet formation quantum yield
Φ_Δ	singlet oxygen formation quantum yield
δ	chemical shift (ppm)
ε	molar extinction coefficient ($M^{-1}\ cm^{-1}$)
ε_S	singlet molar extinction coefficient ($M^{-1}\ cm^{-1}$)
ε_T	triplet molar extinction coefficient ($M^{-1}\ cm^{-1}$)
ε'	dielectric constant
ε''	dielectric loss
λ	wavelength (nm)
λ_{exc}	excitation wavelength (nm)
λ_{max}	absorption wavelength maximum (nm)
λ_{max}^{F}	fluorescence emission wavelength maximum (nm)
λ_{max}^{P}	phosphorescence emission wavelength maximum (nm)
$\lambda_{max}^{T1\text{-}Tn}$	triplet absorption wavelength maximum (nm)
ν	frequency (Hz or s^{-1})

Listing of Schemes

Listing of Figures

Listing of Tables

Nomenclature

Tetrapyrrole is a broadly used term that refers to a class of compounds whose molecules have four rings of the pyrrole type, usually linked together by single-atom bridges between the α positions of the latter. The most common arrangements of these four pyrrolic moieties are macrocyclic, such as in porphyrins and related structures, and linear, e.g. the bile pigments. The first nomenclature system concerning tetrapyrrolic macrocyclic compounds was developed in the 1930s by the German chemist and physician Hans Fischer (Figure I).[1, 2] The pyrrolic units are designated by the Latin alphabet letters A, B, C and D, while the carbon atoms that establish the connections between these structural blocks, denominated *meso*, are identified by the Greek alphabet letters α, β, γ and δ. In every pyrrolic structure one can distinguish the respective α (1' to 8') and β (1 to 8) carbon atoms, in agreement with the usual designation relative to the pyrrole ring. The same author also adopted trivial names to a wide number of compounds of this family, regarding their natural occurrence or function.

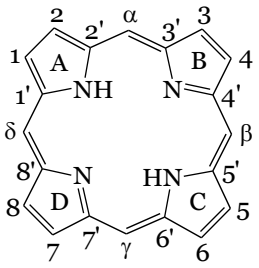


Figure I

A joint commission between IUPAC and IUB extended the systematic nomenclature to this type of compounds in the 1980s, aiming to facilitate the interdisciplinary communication and restrain the use of trivial names.[3] Hence, in the IUPAC system, the macrocyclic nucleus is denominated porphyrin, replacing the older name porphine, the carbon atoms are numbered from 1 to 20 and the nitrogen atoms from 21 to 24. Further, the *meso* positions correspond to numbers 5, 10, 15 and 20 and the substituents refer to the number of the carbon atom to which they are attached and ordered alphabetically (Figure II). It should be noticed that this structure is tautomeric with respect to the location of the two hydrogen atoms that do not participate in the peripheral conjugated system, these being associated with any two of the four nitrogen atoms. Withal, for nomenclature purposes, the word porphyrin implies that the saturated nitrogen atoms are located at positions 21 and 23.

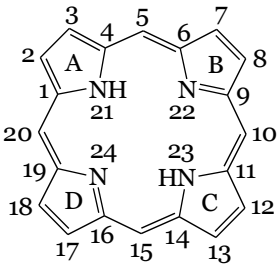
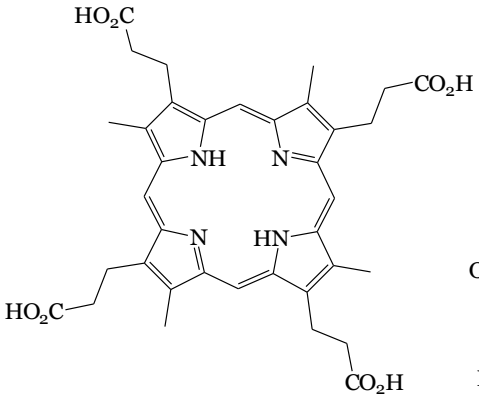
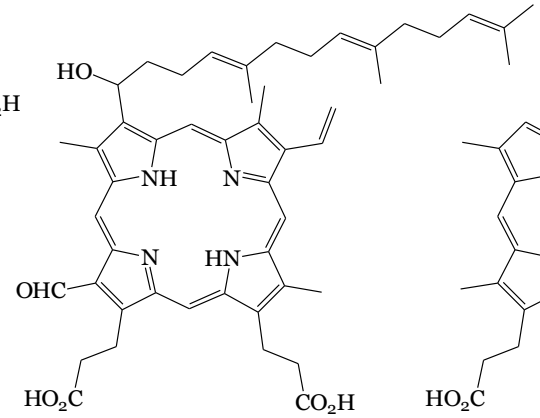


Figure II

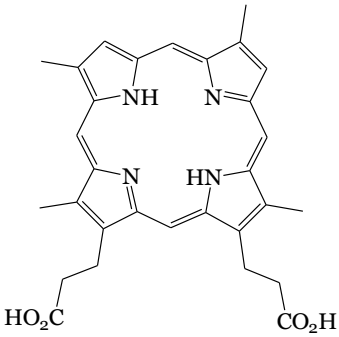
IUPAC and IUB allow the utilisation of both types of nomenclature, systematic and semi-systematic.[3] In the former all recommendations for the nomenclature of organic structures are adopted, while in the latter the use of 12 of the trivial names initially proposed by Fischer is permitted (Figure III).[1, 2] Despite the introduction of the systematic nomenclature, some of these older designations are still broadly used today, owing to their simplicity and convenience.



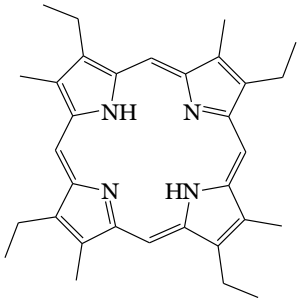
Coproporphyrin I



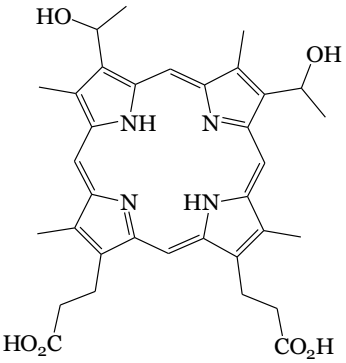
Cytoporphyrin



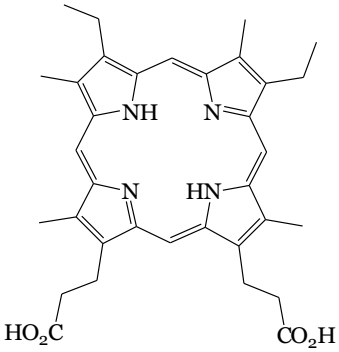
Deuteroporphyrin



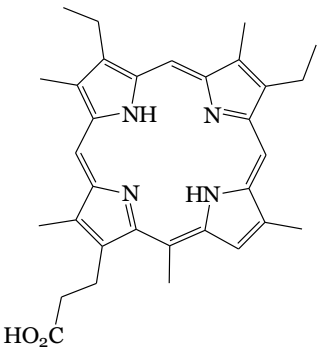
Etioporphyrin I



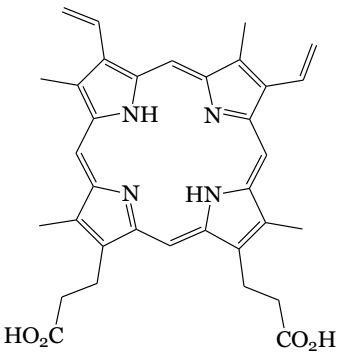
Hematoporphyrin



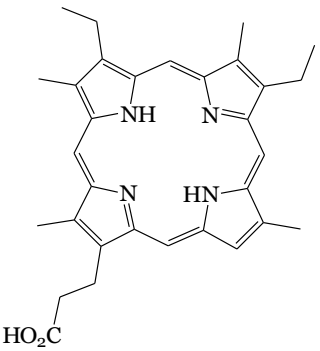
Mesoporphyrin



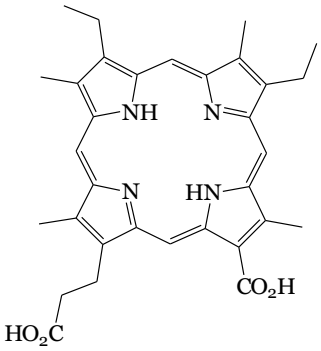
Phylloporphyrin



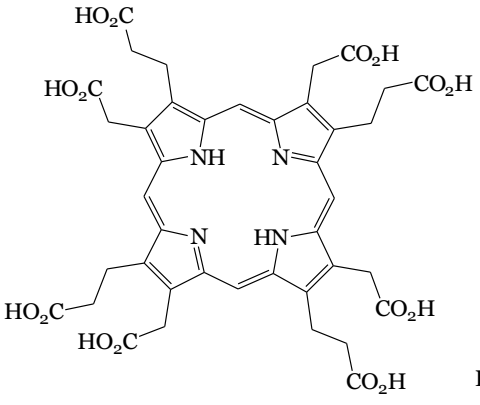
Protoporphyrin



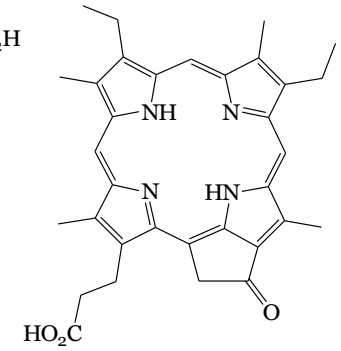
Pyrroporphyrin



Rhodoporphyrin



Uroporphyrin I



Phytoporphyrin

Figure III

The use of Roman numerals (I to IV) to identify the four possible positional isomers of coproporphyrin, etioporphyrin and uroporphyrin, in which the substituents located at the pyrrolic positions 2, 3, 7, 8, 12, 13, 17 and 18 are of two kinds only and one of each kind is present at each and every pyrrolic unit, is also accepted. These isomeric forms are generically numbered and oriented as depicted in Figure IV, substituent A being smaller than substituent B. Nevertheless, the employment of this sort of notation is not advisable nor recommended for porphyrins comprising more than four positional isomers.[3]

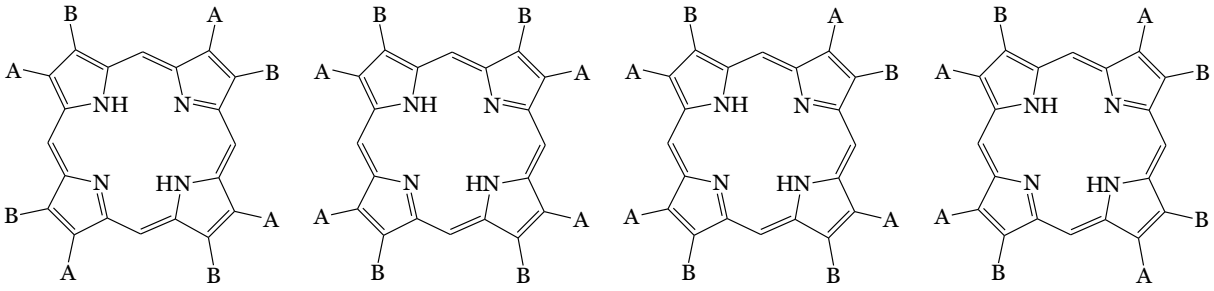


Figure IV

The IUPAC/IUB assignment of porphyrin derivatives displaying different oxidation states may also be replaced by the corresponding trivial names; thus, the designation of their substituted and functionalised analogues is based on this nomenclature (Figure V).

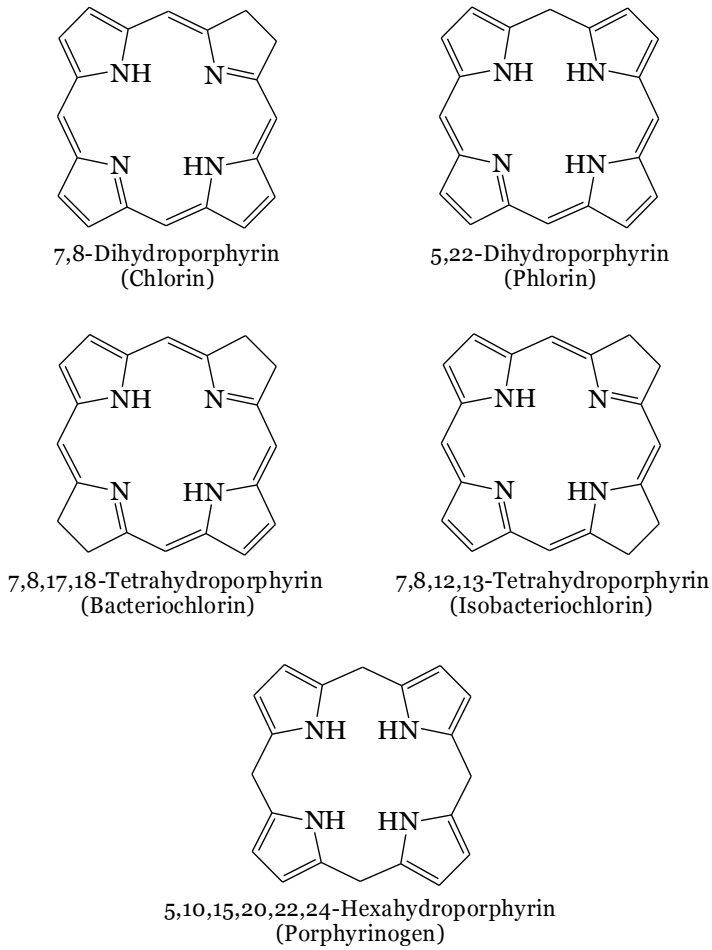
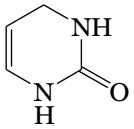
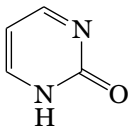


Figure V

The IUPAC/IUB semi-systematic nomenclature for tetrapyrrolic macrocyclic structures was applied in Chapter 3 of this dissertation. The denomination of other organic compounds obeyed the set of rules and regulations recommended by the same entities,[4-6] with the exception of the Biginelli and Biginelli-type derivatives discussed in Chapter 5. Although the IUPAC recommendations encourage the use of the systematic system for the designation of these compounds, the more ancient names presented under brackets in Figure VI are also accepted and, it must be stressed, still widely employed in the scientific literature.



2-Oxo-1,2,3,4-Tetrahydropyrimidine
(3,4-Dihydropyrimidin-2(1*H*)-One)



2-Oxo-1,2-Dihydropyrimidine
(Pyrimidin-2(1*H*)-One)

Figure VI

1. H Fischer, H Orth, *Die Chemie des Pyrrols*, Volume II.1, Akademische Verlagsgessellschaft, Leipzig, Germany, 1937.

2. H Fischer, A Stern, *Die Chemie des Pyrrols*, Volume II.2, Akademische Verlagsgessellschaft, Leipzig, Germany, 1940.

3. GP Moss, *Pure Appl. Chem.* 59 (**1987**) 779-782.

4. International Union of Pure Applied Chemistry, Division of Organic Chemistry, Commission on Nomenclature of Organic Chemistry, *A Guide to IUPAC Nomenclature of Organic Compounds, Recommendations 1993*, R Panico, WH Powell, JC Richer (Eds), Blackwell Science, Oxford, England, UK, 1993.

5. GJ Leigh, HA Favre, WV Metanomski, *Principles of Nomenclature, A Guide To IUPAC Recommendations*, Blackwell Science, Oxford, England, UK, 1998.

6. HA Favre, K-H Hellwich, GP Moss, WH Powell, JG Traynham, *Pure Appl. Chem.* 71 (**1999**) 1327-1330.

1

Microwave Chemistry

I. Introduction & Relevance

Since the seminal reports on the use of microwave irradiation to carry-out chemical transformations by the research groups of Gedye and Giguere in 1986,[1, 2] more than 5000 articles have been published on this field of study, commonly designated as microwave-assisted organic synthesis (MAOS).[3-15] In general, comparing to conventional heating methods, microwave heating has been shown to drastically reduce reaction times, increase reaction yields and enhance product selectivity by reducing unwanted side reactions. This technique has already proved to be invaluable in multi-step total synthesis,[16-18] medicinal chemistry and drug discovery,[19-25] and has also been exploited on related areas, such as polymer synthesis,[26-32] materials science,[33-36] nanotechnology[37-39] and biochemical processes.[40-44] In principle, any chemical reaction that requires heat can be advantageously performed under microwave conditions; hence, the use of this technology in chemistry has become rather popular within the scientific community, both in academia and in industry.

The short reaction times provided by microwave heating make it an ideal methodology for fast trial-and-error exploration and optimisation of reaction conditions. Arguably, it can be stated that one of the breakthroughs in MAOS, regarding its progress from laboratory curiosity to standard practice, started in the pharmaceutical industry around the year 2000. Medicinal chemists were among the first to recognize the capabilities of this enabling technology and, since then, microwave synthesis has proved to be an important tool for medicinal chemistry and drug discovery applications. Several reaction parameters, as well as novel reaction pathways, can be critically assessed in a short timespan, allowing the rapid synthesis of compound libraries, both in parallel or sequential/automated fashions.

In the early days, experiments were typically carried-out in sealed Teflon or glass vessels in a domestic microwave oven without any temperature or pressure monitoring. Understandably, this type of household appliance was not designed for laboratory use; solvents and acids rapidly corrode the interiors and there are no safety devices. Consequently, violent explosions due to fast and uncontrolled heating of organic solvents under closed-vessel conditions was a frequent outcome. In the 1990s various research teams started to explore dry-media reactions, which partially averted the danger of explosions. The reagents were adsorbed onto either a more or less microwave-transparent inorganic support (silica, alumina or clay) or a strongly absorbing one (graphite), that in addition may have been doped with a catalyst. This solventless approach was very popular, since it allowed the safer use of domestic microwave ovens and standard open-vessel methods. Although a great number of interesting microwave-assisted chemical transformations using solid supports have been reported,[45-49] serious difficulties, concerning heterogeneous heating and/or mixing and the correct determination of the reaction temperature, remained unresolved. Alternatively, microwave synthesis was often performed using organic solvents under open-vessel conditions, the boiling point of the solvent typically being the limit for the reaction temperature. In order to achieve high reaction rates, high-boiling and microwave-absorbing solvents were frequently used, although this presented serious challenges upon product isolation.[50, 51] Additionally, the risks related to the flammability of most organic solvents in a microwave field and the lack of commercially-available microwave reactors permitting adequate temperature and pressure control were major concerns.

The initial slow activity of microwave chemistry in the late 1980s and 1990s has often been imputed to its lack of reproducibility and controllability, coupled with a deficient perception of the basics of microwave dielectric heating. The use of domestic microwave ovens, combined with non-reliable temperature monitoring systems, also led to a widespread confusion in the scientific community, in addition to the large discussion around the topic of

microwave effects.[52, 53] Historically, the observed rate accelerations and sometimes different product distributions, compared to conventional heating experiments, led to strong speculation on the existence of specific or non-thermal microwave effects.[54-58] These were asserted whenever the outcome of a synthetic process accomplished under microwave irradiation was different from the conventionally-heated equivalent at the same apparent temperature. Currently, most researchers concur that, in the vast majority of cases, the explanation for the observed rate enhancements is of purely thermal/kinetic nature, that is, a consequence of the high reaction temperatures that are rapidly attained when irradiating microwave-absorbing materials in a microwave field. Nonetheless, effects that are caused by the uniqueness of the microwave dielectric heating mechanism should also be considered. Because of the recent availability of modern microwave reactors, displaying accurate monitoring of temperature, pressure and microwave power, some of the initial debate on microwave effects has settled.

Controlled MAOS in sealed vessels using standard solvents, a technique pioneered by Strauss and co-workers in the mid-1990s,[59-61] is presently the method of choice for performing microwave-heated reactions. This is clearly evident from surveying the recent literature in the area of microwave chemistry. Apart from several books[3-10] and review articles,[11-15, 62-76] special issues of journals,[77-80] feature articles,[81-89] online databases[90-92] and educational publications[93-96] provide extensive coverage on the subject.

Innovations in dedicated microwave instrumentation allow parallel and sequential/automated protocols under sealed-vessel conditions and the possibility of continuous- or stop-flow processing for scale-up purposes. Specially designed vessels and accessories for solid-phase synthesis, chemical transformations using pre-pressurised conditions or sub-ambient temperatures and a variety of other specific applications, have also been developed. Continuous temperature, pressure and microwave power measuring, built-in magnetic stirring, software operation and safety devices are provided by the microwave equipment manufacturers, Anton-Paar GmbH (Graz, Austria),[97] Biotage AB (Uppsala, Sweden),[98] CEM Corporation (Matthews, NC, USA)[99] and Milestone S.r.l. (Sorisole, Italy).[100] However, the low energy efficiency of the available microwave reactors in converting electrical to microwave energy, comparing to conventional heating instrumentation, particularly in small-scale open-vessel laboratory processing, is yet to be addressed.[101-102] Also, this fairly new technology remains somewhat expensive. While prices for MAOS reactors have considerably decreased since their first introduction in the late 1990s, the actual price range is still much higher than that of conventional heating equipment. As with any new technology, the present situation is bound to change over the next years and more energy- and cost-effective instruments should become accessible.

II. Microwave Fundamentals

The physical principles that determine the successful application of microwaves in organic synthesis are not broadly known by the majority of chemists. Nevertheless, it is essential for the synthetic chemist working on MAOS to have a basic knowledge of the underlying principles of microwave-matter interactions and the nature of microwave effects. Hence, a brief summary of the present-day understanding of microwaves and their interactions with matter is given in the following sections.

A. Microwave Radiation

Microwave radiation is electromagnetic radiation in the frequency range of 0.3 to 300 GHz, corresponding to wavelengths of 1 mm to 1 m. Thus, the microwave region of the electromagnetic spectrum lies between infrared and radio frequencies (Figure 1.1). The fundamental use of microwaves is either for transmission of information or for transmission of energy. Wavelengths between 1 and 25 cm are largely used for RADAR transmissions, while the remaining wavelength range is used for telecommunications. Both domestic microwave ovens and dedicated microwave reactors currently available operate at a frequency of 2.45 GHz, corresponding to a wavelength of 12.25 cm, in order to avoid interference with telecommunication, wireless networks and cellular phone frequencies.

There are other frequency allocations for microwave heating applications, but these are not generally employed in microwave reactors designed for synthetic chemistry.[103] As can be seen from the data presented in Table 1.1, the energy of a microwave photon at a frequency of 2.45 GHz, 1.6 x 10^{-3} eV, is too low to cleave molecular bonds.[103, 104] Therefore, microwaves can not induce chemical reactions by direct absorption of electromagnetic energy, as opposed to ultraviolet and visible radiation (photochemistry).

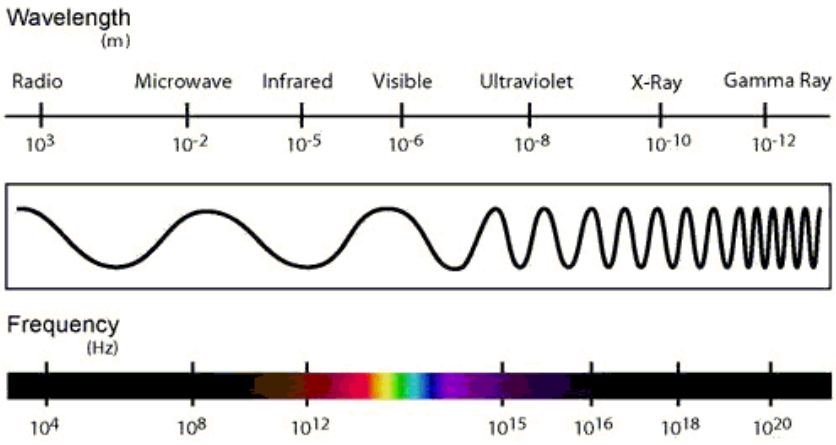


Figure 1.1. Wavelength and frequency ranges of the electromagnetic spectrum.

Table 1.1. Radiation types and energies *versus* bond types and energies.

Radiation Type	Frequency (Hz)	Quantum Energy (eV)	Bond Type	Bond Energy (eV)
γ-Rays	3×10^{17}	1.24×10^{6}	C-C	3.61
X-Rays	3×10^{16}	1.24×10^{5}	C=C	6.35
Ultraviolet	1×10^{12}	4.1	C-O	3.74
Visible	6×10^{11}	2.5	C=O	7.71
Infrared	3×10^{9}	1.2×10^{-2}	C-H	4.28
Microwave	2.45×10^{6}	1.6×10^{-3}	O-H	4.80
Radiofrequency	1×10^{3}	4×10^{-9}	Hydrogen Bond	0.04-0.44

B. Dielectric Heating

Microwave chemistry is based on the efficient heating of materials by microwave dielectric heating, which is dependent on the ability of a specific material, e.g. solvent, reagent or catalyst, to absorb microwave energy and convert it into heat.[105, 106] Microwaves are a type of electromagnetic radiation and, hence, possess both electric and magnetic field components (Figure 1.2). For most practical purposes related to microwave-assisted synthesis, only the electric component of the electromagnetic field is important for wave-material interactions, although in some instances, e.g. transition metal oxides, magnetic field interactions can also be relevant.[107-109] The electric component of an electromagnetic field causes heating by two primal mechanisms: dipolar polarisation and ionic conduction. The interaction of the electric field component with the matrix is called dipolar polarisation (Figure 1.3a).[105, 106] For a substance to be able to generate heat when subjected to microwave irradiation it must possess a dipole moment. When exposed to microwave frequencies, the dipoles of the sample align with the applied electric field. As the field oscillates, the dipoles attempt to realign themselves with the alternating electric field and, consequently, energy is lost in the form of heat through molecular friction and dielectric loss. The amount of heat rendered by this process is directly related to the capability of the matrix to align itself with the

frequency of the applied field. If the dipoles do not have enough time to realign (high frequency irradiation) or reorient too quickly (low frequency irradiation) with the applied field, no heating occurs. The assigned frequency of 2.45 GHz, used in all commercially available systems, lies between these two extremes and gives the molecular dipoles time to align, but not to follow the alternating field precisely. Therefore, as the dipoles reorient to align themselves with the electric field, this is already changing and generates a phase difference between the orientation of the field and that of the dipoles. This phase deviation causes energy to be lost from the dipoles by molecular friction, giving rise to dielectric heating. Summarising, field energy is transferred to the medium and electrical energy is converted into kinetic or thermal energy. It should be accented that the interaction between microwave radiation and polar molecules, which occurs when the frequency of the radiation approximately matches the frequency of the rotational relaxation process, is not a quantum mechanical resonance phenomenon. Transitions between quantised rotational bands are not involved and the energy transfer is not a property of a specific molecule, but the result of a collective phenomenon involving the whole bulk.[105, 106] The heat is generated by frictional forces occurring between the polar molecules, whose rotational velocity has been augmented by the coupling with the microwave irradiation.

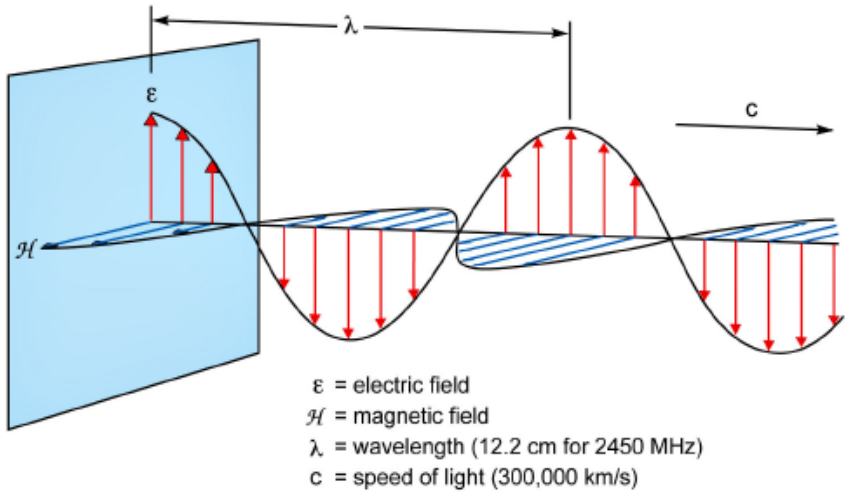


Figure 1.2. Electric and magnetic field components of microwaves.

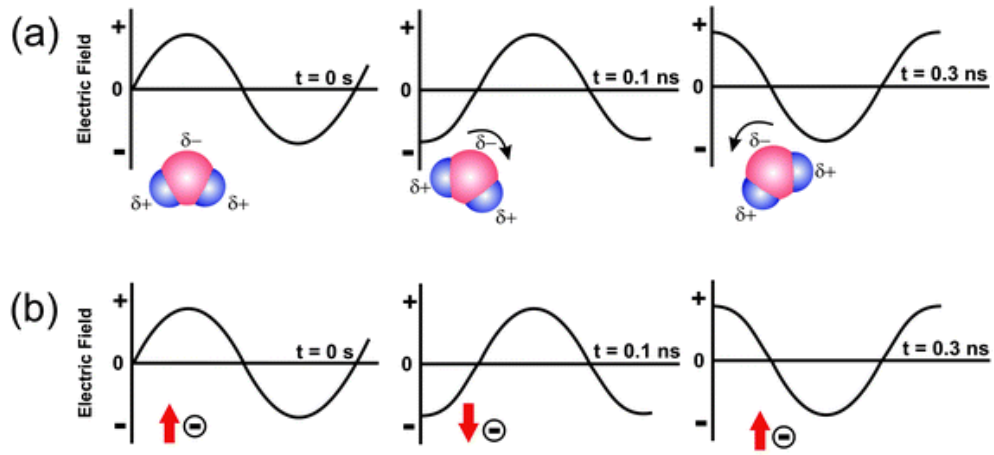


Figure 1.3. Dipolar polarisation (a) and ionic conduction (b) mechanisms typical of dielectric heating.

The second major mechanism behind dielectric heating is ionic conduction (Figure 1.3b).[105, 106] As the charged particles in a sample, commonly ions, oscillate back and forth under the influence of the microwave field, they clash with their neighbouring molecules or atoms. These collisions cause agitation and create heat. Hence, if

two samples containing equal amounts of distilled water and tap water, respectively, are heated at a fixed microwave power, the tap water sample will heat more rapidly due to its ionic content. Such ionic conduction effects are particularly important when considering the heating behaviour of ionic liquids in a microwave field. The conductivity principle is a much more powerful effect than the dipolar rotation mechanism, regarding the heat-generating capacity. Strongly conducting or semiconducting materials, such as metals, exhibit a related heating phenomenon, where microwave irradiation can induce a flow of electrons on the surface and, eventually, heat the material through resistance heating mechanisms.[28]

C. Dielectric Properties

The heating characteristics of a particular material under microwave irradiation depend on its dielectric properties. The ability of a specific substance to convert electromagnetic energy into heat, at a given frequency and temperature, is determined by a parameter called loss factor, tanδ. This is expressed as a ratio, $\tan\delta=\varepsilon''/\varepsilon'$, where ε'' is the dielectric loss, indicating the efficiency with which electromagnetic radiation is converted into heat, and ε' is the dielectric constant, describing the polarisability of the molecules in the electric field. A reaction medium with a high tanδ value is required for efficient microwave absorption and, consequently, for rapid heating. However, materials with a high dielectric constant, such as water (ε'=80.4 at 25 °C), may not also have a high tanδ value. In fact, ethanol has a significantly lower dielectric constant (ε'=24.3 at 25 °C), but heats much faster than water under a microwave field due to its higher loss factor (tanδ: ethanol=0.941, water=0.123). The boiling point, loss factor, dielectric loss and dielectric constant values of some commonly used organic solvents are indicated in Table 1.2.[10] Typically, solvents are classified as high ($\tan\delta>0.5$), medium ($0.1<\tan\delta<0.5$) and low ($\tan\delta<0.1$) microwave-absorbing. Other common solvents without a permanent dipole moment, such as carbon tetrachloride, benzene and dioxane, are more or less microwave-transparent. Nevertheless, a low tanδ value does not exclude a particular solvent from being used in a microwave-assisted reaction, since that some of the reagents and/or catalysts are likely to be polar and the overall dielectric characteristics of the reaction medium will allow sufficient heating by microwaves. Moreover, polar additives, e.g. alcohols or ionic liquids, or passive heating elements can be added to low microwave-absorbing reaction mixtures in order to increase the absorbance level of the whole medium.

It should also be pointed out that, while ε'' or tanδ values of a molecule can be used to assess the microwave-absorbing efficiency, the use of any single parameter oversimplifies the issue of effective microwave heating, given that a number of other factors may contribute to this. Properties such as specific heat capacity and heat of vaporisation of the substance, as well as the depth to which microwave radiation can penetrate into the sample, can sometimes have a bigger impact on the heating rate than its respective dielectric loss or loss factor. Additionally, dielectric loss and dielectric constant values are both frequency and temperature dependent, specific heat changes as a function of temperature and heat of vaporisation changes as a function of pressure. These can all affect microwave absorption individually and/or in combination. Room temperature distilled water, for instance, is most microwave-absorbent at approximately 18 GHz, but as temperature increases, so does the optimum frequency at which water converts microwave irradiation into heat. However, when synthetic chemists refer to good or bad microwave-absorbing substrates, a fixed 2.45 GHz irradiation source, a small depth of field (1-10 cm) and synthetically relevant temperatures (50-200 °C) are implied.

The penetration depth is defined as the point where 37% of the initially irradiated microwave power is still present.[103] It is inversely proportional to the loss factor and, hence, critically depends on temperature and irradiation frequency. Materials with relatively high tanδ values are thus characterised by low values of penetration depth and, therefore, microwave irradiation may be totally absorbed within the outer layers of these materials. For a solvent such as water (tanδ=0.123 at 25 °C and 2.45 GHz), the penetration depth at room temperature is only of the order of a few centimetres (Table 1.3).[10] Beyond this penetration depth, volumetric heating due to absorption of microwave energy becomes minimal. Hence, when performing microwave-assisted

experiments on a larger scale, only the outer layers of the reaction mixture are directly heated by microwave irradiation through dielectric heating mechanisms, while the inner part of the reaction mixture is mostly heated by classical convection and conduction phenomena. Issues relating to the penetration depth are therefore crucial when dealing with the scale-up of MAOS.

Table 1.2. Boiling point, loss factor, dielectric loss and dielectric constant values of common organic solvents at 25 °C and 2.45 GHz.

Solvent	bp (°C)	tanδ	ε''	ε'
Ethylene Glycol	197	1.350	49.950	37.0
Ethanol	78	0.941	22.866	24.3
Dimethylsulphoxide	189	0.825	37.125	45.0
2-Propanol	82	0.799	14.622	18.3
1-Propanol	97	0.757	15.216	20.1
Formic acid	100	0.722	42.237	58.5
Methanol	65	0.659	21.483	32.6
Nitrobenzene	211	0.589	20.497	34.8
1-Butanol	118	0.571	9.764	17.1
2-Butanol	100	0.447	7.063	15.8
1,2-Dichlorobenzene	180	0.280	2.772	9.9
N-Methyl-2-Pyrrolidone	204	0.275	8.855	32.2
Acetic Acid	113	0.174	1.079	6.2
N,*N*-Dimethylformamide	153	0.161	6.070	37.7
1,2-Dichloroethane	83	0.127	1.321	10.4
Water	100	0.123	9.889	80.4
Chlorobenzene	132	0.101	0.263	2.6
Chloroform	61	0.091	0.437	4.8
Acetonitrile	82	0.062	2.325	37.5
Ethyl Acetate	77	0.059	0.354	6.0
Acetone	56	0.054	1.118	20.7
Tetrahydofuran	66	0.047	0.348	7.4
Dichloromethane	40	0.042	0.382	9.1
Toluene	111	0.040	0.096	2.4
n-Hexane	69	0.020	0.038	1.9

Table 1.3. Penetration depth values of common materials at a given temperature.

Material	T (°C)	Penetration Depth (cm)
Water (Liquid)	25	1.4
Water (Liquid)	95	5.7
Water (Solid)	-12	1100
Polyvinyl Chloride	25	210
Glass	25	35
Teflon	25	9200
Quartz	25	16000

The loss factor and dielectric loss of pure water and many other organic solvents decrease with increasing temperature and, consequently, the absorption of microwave radiation in water diminishes at higher temperatures. Although it is relatively simple to heat water from room temperature to 100 ºC, in sealed-vessel conditions, it is significantly more troublesome to further heat water to 200 ºC and beyond. Most organic materials and solvents behave similarly, which might be somewhat inconvenient from a practical standpoint, since microwave heating at higher temperatures may often be compromised.[105, 106, 110, 111] However, the opposite situation, where a material becomes a stronger microwave-absorber with increasing temperature, is also possible; this is the case of some inorganic and polymeric materials,[105] thermal runaway and temperature overshooting during microwave irradiation being a frequently observed phenomenon.

Summing-up, the interaction of microwave irradiation with matter is characterised by three different processes: absorption, transmission and reflection. Highly dielectric materials, like polar organic solvents, usually lead to a strong absorption of microwaves and, accordingly, to a fast heating of the medium (Table 1.2).[28] Non-polar microwave-transparent materials display only small interactions with microwave irradiation (Table 1.4) and can thus be used as insulators for reactors because of their high penetration depth values (Table 1.3). If microwave radiation is reflected by the material surface, there is no or negligible coupling of energy into the system and the temperature increase is only marginal. This is particularly true for metals with high conductivity, although in some cases resistance heating for these materials can occur.

Table 1.4. Loss factor values of low-absorbing materials at 25 ºC and 2.45 GHz.

Material	tanδ (x 10^{-4})	Material	tanδ (x 10^{-4})
Quartz	0.6	Acrylic Glass	57
Ceramic	5.5	Polyester	28
Porcelain	11	Polyethylene	31
Phosphate Glass	46	Polystyrene	3.3
Borosilicate Glass	10	Teflon	1.5

D. Microwave *versus* Conventional Heating

Organic synthesis is traditionally carried-out by conductive heating with an external heat source, such as an oil-bath or a heating mantle. This is a rather slow and ineffective means for transferring energy into the reaction system, since it depends on the convection currents and thermal conductivity of the diverse materials that must be penetrated. Hence, the temperature of the reaction vessel is generally higher than that of the reaction mixture (Figure 1.4b). This is particularly true if reactions are performed under reflux conditions, where the temperature of the bath fluid is typically kept at 10 to 30 ºC above the boiling point of the reaction mixture, in order to ensure an efficient reflux. Moreover, a temperature gradient can develop within the sample and local overheating can lead to product, reagent or catalyst degradation. On the other hand, microwave irradiation produces efficient internal heating, in-core volumetric heating, by direct coupling of microwave energy with the molecules (solvents, reagents or catalysts) that compose the reaction mixture (Figure 1.4a). Therefore, microwave irradiation raises the temperature of the whole volume simultaneously, bulk heating, whereas in the conventionally-heated vessel the outer layer of the reaction mixture, which is in contact with the vessel wall, is heated first. Bearing in mind that the reaction vessels employed in current microwave reactors are typically made out of nearly microwave-transparent materials, such as borosilicate glass, quartz or Teflon (Table 1.4), the radiation passes through the walls of the vessel and an inverted temperature gradient is achieved with minimised wall effects, comparing to conventional heating. Nevertheless, it should be pointed out that microwave dielectric heating and classical thermal heating by conduction/convection processes are entirely different phenomena and that any comparison between the two is intrinsically challenging.

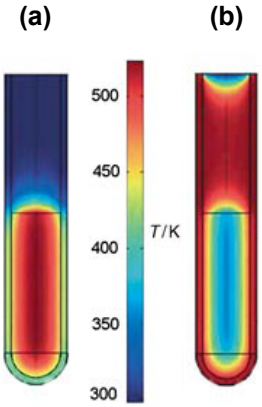


Figure 1.4. Microwave (a) and conventional (b) heating temperature gradients.

E. Microwave Effects

Currently, it is widely agreed by the scientific community that, in the vast majority of cases, the observed rate improvements and sometimes different product distributions in microwave-assisted reactions, comparing to conventionally-heated processes, are owed to the high reaction temperatures that can be rapidly achieved when irradiating polar materials and reaction mixtures in a microwave field and, thus, are a consequence of purely thermal/kinetic effects.[55, 57, 58, 96, 112, 113] Similarly, the existence of specific microwave effects, which can not be duplicated under classical heating conditions and result from the singularity of microwave dielectric heating, is largely accepted. Examples of this phenomenon are: the super-heating effect of solvents at atmospheric pressure, the selective heating of strongly microwave-absorbing heterogeneous catalysts or reagents in a less polar reaction medium and the elimination of wall effects caused by inverted temperature gradients. In opposition, the topic of non-thermal microwave effects is extremely debatable.[52, 53, 114] These have been proposed to result from the direct interaction of the electric field with specific molecules present in the reaction medium, which is not related to any macroscopic temperature effect. It has been argued that the presence of an electric field leads to specific orientation/collision effects of dipolar molecules or intermediates, changing the pre-exponential factor (A) or the activation energy (E_a) in the Arrhenius equation, $k=Ae^{-Ea/RT}$, where k is the rate constant of the reaction, R is the ideal gas constant and T is the reaction temperature, for certain kinds of chemical processes. An analogous effect has also been suggested for polar reaction mechanisms, the polarity being increased from the ground state to the transition state, resulting in an improvement of reactivity by decreasing the activation energy.[55, 57, 58, 96, 112, 113]

Considering that the application of microwaves in chemistry, particularly in organic synthesis, is a fast growing technology, and that the available literature is full of contradictory reports, regarding the involvement of specific or non-thermal microwave effects in a wide assortment of chemical reactions, it becomes evident that a scientific rationalisation for the observed phenomena and a critical study of the related influence of the electric field and, consequently, of the microwave power on chemical transformations is of the essence. Three possibilities for justifying microwave-assisted rate enhancements can be expressed: thermal/kinetic effects, specific microwave effects and non-thermal microwave effects.[14] Additionally, any given combination of these contributions may be accountable for the observed developments, which makes research on microwave effects an exceedingly challenging issue.

1. Thermal/Kinetic Effects

Nowadays, most of the published work on MAOS is performed in high-power density microwave reactors. Using this type of equipment, moderately strong microwave-absorbing solvents, such as *N*-methyl-2-pyrrolidone (bp=204 ºC, tanδ=0.275 at 25 ºC), can be promptly heated, even in an open vessel at atmospheric pressure.

Under sealed-vessel conditions, microwave-absorbing solvents with a relatively low boiling point, such as methanol (bp=65 ºC, tanδ=0.659 at 25 ºC), can be rapidly superheated to temperatures of more than 100 ºC above their boiling points. In other media characterised by extreme loss factor values, like ionic liquids, rapid increase in temperature can be even more noticeable, temperature leaps of about 200 ºC within a few seconds being ordinarily observed. Naturally, such temperature profiles are very difficult, if not impossible, to reproduce by classical thermal heating and, therefore, striking rate enhancements when comparing reactions that are performed under classical oil-bath conditions, i.e. heating under reflux, with high-temperature microwave-assisted processes are not exceptional. It has been pointed out that by simple application of the Arrhenius equation, a chemical transformation that requires 68 days to reach 90% conversion at 27 ºC, will exhibit the same degree of conversion after 1.61 s when carried-out at 227 ºC (Table 1.5).[105]

Table 1.5. Relation between temperature and time for a representative first order reaction ($A=4 \times 10^{10}$ mol^{-1} s^{-1}, $E_a=100$ kJ mol^{-1}).

T (ºC)	k (s^{-1})	Time (90% conversion)
27	1.55×10^{-7}	68 d
77	4.76×10^{-5}	13.4 h
127	3.49×10^{-3}	11.4 min
177	9.86×10^{-2}	23.4 s
227	1.43	1.61 s

Owing to the very fast heating and the intense temperatures achievable in microwave chemistry, it seams obvious that many of the reported rate improvements can be explained by effects of strictly thermal/kinetic nature. Nevertheless, in the absence of any specific or non-thermal microwave effects, it should be expected that reactions performed under open-vessel conditions proceed at the same reaction rate, regardless of whether they are heated by microwaves or in a standard thermal process. It should be stressed that, concerning purely thermal effects, the pre-exponential factor (A) and the entropic energy term or activation energy (E_a) in the Arrhenius equation are not affected, only the temperature term changes. Moreover, the typical rapid heating and cooling of small-scale microwave-assisted transformations may lead to altered product distributions, as compared to a conventional oil-bath reflux protocol, where both heating and cooling are not as fast and the reaction temperature is usually lower. It has been reasoned that the different heating profiles characteristic of microwave and conventional heating can lead to different reaction products if the product distribution is governed by complex temperature-dependent kinetic profiles.[3] This might explain why, in several reported cases, microwave-assisted reactions have been found to be cleaner, i.e. yielding less by-products, comparing to the classically-heated equivalents. Obviously, microwave heating will not always favour the desired reaction pathway and, consequently, there may be cases where, because of the higher reaction temperatures, unwanted reaction products, not determined during a conventionally-heated experiment performed at a lower temperature, can be formed.

2. Specific Microwave Effects

Specific microwave effects can be defined as accelerations of chemical transformations under a microwave field that can not be accomplished or replicated by conventional heating. A well known example is the super-heating of solvents at atmospheric pressure.[115-118] Several research groups have stated that the enthalpy of vaporisation under microwave and conventional heating is the same and that the rate of evaporation, as well as the temperature of both liquid and vapour at the interface, are heavily dependent on the experimental conditions.[119, 120] It was established in the 1990s that, at atmospheric pressure, microwave-heated liquids boil at temperatures above the equilibrium boiling point. The super-heating temperature of various solvents can be up to 40 ºC above the standard boiling point.[117, 118] Hence, the average temperature of a solvent can be

significantly higher than the corresponding atmospheric boiling point in a microwave reactor, because the microwave power is distributed over the entire volume of the solvent. Losing excess thermal energy by boiling under microwave conditions only occurs at the existing liquid-gas interface, in opposition to classically-heated solvents, where boiling usually occurs at nucleation points, such as cavities, pits and scratches on the glass surface of the reaction vessel.[115] The bulk temperature of a microwave-irradiated boiling solvent is due to numerous factors, like the physical properties of the solvent, the geometry of the reactor, the mass and heat transfer and the electric field distribution. However, it should be accented that most super-heating can be easily eliminated by an effective stirring or the addition of boiling chips. The kinetics of homogeneous organic reactions exhibit an extension of the typical Arrhenius behaviour into the superheated temperature area,[119, 120] up to 100-fold rate improvements being reached, which is generally only feasible under pressure. Nonetheless, given that dedicated microwave reactors offer magnetic or mechanical stirring options, and that the majority of the current microwave chemistry is carried-out under sealed-vessel conditions, super-heating effects at atmospheric pressure are practically irrelevant.

The elimination of wall effects due to the inverted temperature gradients characteristic of microwave heating, Figure 1.4a, can be viewed as another specific microwave effect. In general, the surface of the wall is not heated, since the microwave energy is liberated within the bulk liquid and, thus, the temperature of the inner surface of the reactor wall is lower than that of the bulk. In a conventional oil-bath process, Figure 1.4b, temperature-sensitive species, like catalysts, may decompose at the hot reactor surface. The removal of such a hot surface usually increases the lifetime of the catalyst and, consequently, leads to better conversions under microwave irradiation, comparing to classically-heated protocols. Mass or volumetric heating, i.e. the rapid and equal heating of the full reaction mixture, is also typical of microwave dielectric heating. Berlan and co-workers have exemplified this effect very plainly by heating urea at around 250 ^{o}C to form cyanuric acid.[121] The reaction is sluggish and the yields are quite low under classic heating conditions, owing to the generation of various by-products. The reason for this is that cyanuric acid, which decomposes without melting above 300 ^{o}C and is firstly formed as a solid at the walls of the reactor, is a poorly heat-conductive substance and it forms an insulating crust which prevents heat transfer to the rest of the reaction mixture. Increasing the temperature of the oil-bath and, subsequently, of the wall results in partial decomposition. On the other hand, high yields of cyanuric acid are obtained under microwave irradiation, without any secondary product being detected. However, this type of effects can only be seen on a relatively small scale, due to microwave penetration depth issues.

Another important specific microwave effect is an outcome of the selective heating of strongly microwave-absorbing heterogeneous catalysts or reagents in a less polar reaction medium.[122] This is based on the fact that in a sample containing more than one constituent, only the one which efficiently couples with microwaves is selectively heated; therefore, the non-absorbing components are heated by heat transfer. For heterogeneous reaction mixtures, particularly solid/gas systems involving heterogeneous gas-phase catalysis,[122, 123] selective heating of the catalysts is crucial, the rate improvements and altered product selectivity that sometimes are observed being imputed to the formation of localised macroscopic hot spots, up to 150 ^{o}C above the measured bulk temperature.[124] However, measuring the temperature distributions induced by microwave irradiation in solid materials is fairly complex and, accordingly, many local temperature variations are greater than those measured. Microwave-assisted transformations in organic solvents catalysed by a heterogeneous catalyst, e.g. solid/liquid systems using palladium-on-charcoal (Pd/C), are of greater relevance in organic chemistry. The reaction temperature at the catalyst surface is significantly higher than the bulk temperature of the solvent, since the catalyst is a strong microwave-absorber, particularly when a low tanδ solvent is selected (Table 1.2). The selective heating/activation provided by microwave irradiation of a Pd/C catalyst was exploited in the Pd-catalysed hydrogenation of various carbon-carbon double bond systems.[125] Analogous observations were made in similar microwave-assisted hydrogenation reactions.[126] The selective absorption of microwave energy by a heterogeneously-encapsulated palladium catalyst was also proposed for a series of very expeditious Suzuki couplings of aryl bromides, under both batch and flow microwave conditions.[127]

Selective heating processes can also be explored for high microwave-absorbing reagents. For instance, primary and secondary alcohols were oxidised in toluene with a chromium dioxide reagent under microwave conditions, surface temperatures of up to 360 °C being measured with an IR thermovision camera.[128, 129] Although the temperature of the solid oxidising agent was higher than the boiling point of the solvent, no boiling was observed inside the reaction vessel. The interaction of a microwave field with magnesium metal turnings was reported for the formation of Grignard reagents.[130] Irradiation of aryl halides in dry tetrahydrofuran with magnesium turnings led to arcing of the latter. The reaction was drastically faster under microwave conditions, comparing to conventional heating at the same measured temperature of 65 °C. This could be due to a cleansing effect (electrostatic etching), the removal of a layer of magnesium oxide from the magnesium, induced by microwave irradiation. It appears that heterogeneity plays a major function in the enhancement of microwave-assisted chemical transformations and that microwaves can change the energies and/or the real temperatures of individual species at the interfaces, as the result of Maxwell-Wagner interfacial microwave polarisation.[131] These reports furnish a clear indication for the existence of selective heating effects in MAOS involving heterogeneous reaction mixtures. However, it should be emphasised that the standard methods for measuring the temperature in microwave-heated reactions, i.e. external IR detectors or internal fibre-optic probes, only allow the determination of the average bulk temperature of the solvent, not the real reaction temperature on the surface of the solid reagent or at the interface.

Theoretically, similar arguments of selective heating can be made for liquid/liquid homogeneous mixtures, such as polar reagents in a microwave-transparent solvent. Sadly, the existence of such molecular radiators[44] is experimentally hard to establish.[105, 106, 110, 111] Moreover, it is infeasible to selectively activate polar functional groups, also known as antenna groups,[132] within a larger molecule. Localised rotations of such antenna groups are possible and microwave heating of molecules containing these structures may result in rate enhancements. However, dielectric heating mechanisms involve the rapid energy transfer from these groups to neighbouring molecules and it is impossible to store the energy in a specific part of the molecule.[106] The differential heating of multiphasic liquid/liquid systems is another specific microwave effect not easily duplicated by classic heating procedures. This was applied in a microwave-assisted Hofmann elimination reaction using a two-phase water/chloroform system.[133] The temperatures of the aqueous and organic phases were 110 and 50 °C, respectively, due to the different dielectric properties of the solvents (Table 1.2); this difference averted degradation of the final product, which is soluble in the cooler chloroform phase. Equal conditions would be very hard to obtain using standard heating methods. A similar effect has been documented in the preparation of β,β-diarylated aldehydes by hydrolysis of enol ethers in a two-phase toluene/aqueous hydrochloric acid system.[134]

Microwave heating of heterogeneous liquid/liquid systems will almost always result in differential heating phenomena, given that a difference in loss factor values between the two phases is highly probable. Because of the potentially different temperatures in the phases, mass and heat transfer across the phase boundaries may change, comparing to conventional heating where both phases present the same temperature. Evidently, temperature monitoring in these situations must be carefully realised, since it will be critically important in which phase the temperature is measured. Also, effective stirring should always be applied when dealing with heterogeneous mixtures.[135]

Again, it should be noted that the possible rate improvements pointed above under the concept of specific microwave effects, such as the super-heating of solvents at atmospheric pressure, the selective heating of strongly microwave-absorbing heterogeneous catalysts or reagents in a less polar reaction medium, differential heating of liquid/liquid multiphasic mixtures and the elimination of wall effects originated by inverted temperature gradients, are in essence still of thermal nature, i.e. a difference in temperature compared to standard heating by conduction/convection procedures, although it may be troublesome to accurately determine the reaction temperature experimentally.

3. Non-Thermal Microwave Effects

Non-thermal microwave effects can be outlined as accelerations of chemical transformations under a microwave field that can not be substantiated by either purely thermal/kinetic or specific microwave effects.[14] Fundamentally, non-thermal effects result from a suggested direct interaction of the electric field with specific molecules in the reaction medium. It has been contended by some researchers that the presence of an electric field leads to orientation effects of dipolar molecules and, thus, changes the pre-exponential factor (A)[136-138] or the activation energy (E_a)[139, 140] in the Arrhenius equation. Moreover, it has been reasoned that a related effect should be noticeable for polar reaction mechanisms, where the polarity increases going from the ground state to the transition state, resulting in the improvement of reactivity by lowering the activation energy. Various reports have been published using arguments like this to rationalise the outcome of a chemical reaction performed under microwave irradiation conditions.[55, 57, 58, 96, 112, 113] These results have been interpreted by the authors as proof for the participation of non-thermal microwave effects through electrostatic interactions of polar molecules with the electric field, i.e. the stabilisation of the transition state and the subsequent decrease in the activation energy.[141] It has also been argued that reactions that occur via a late product-like transition state presenting a large enthalpy of activation (Figure 1.5b), compared to reactions that involve early transition states (Figure 1.5a), would be prone to exhibit strong microwave effects.[55, 57, 58, 96, 112, 113]

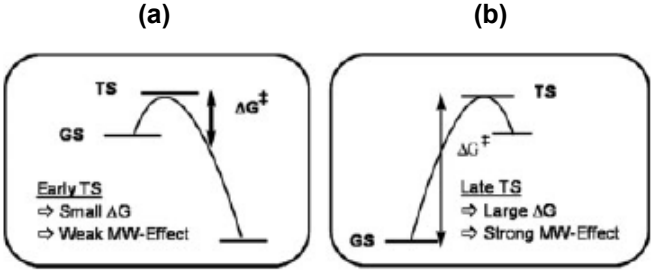


Figure 1.5. Proposed relation between early (a) and late (b) transition states and microwave effects.

As already referenced above, non-thermal microwave effects are extremely controversial. Several scientists criticise the existence of dipolar orientation effects in electric fields on the evidence of overriding disorientation phenomena (thermal agitation) that should prevent any statistically relevant alignment of dipoles.[110] Also, non-thermal microwave effects have generally been proposed for processes concerning solventless/dry-media reactions and/or transformations involving polar reaction intermediates or products, which will strongly absorb microwave energy.[55, 57, 58, 96, 112, 113] Considering the difficulties of meticulous online temperature monitoring under these conditions, it can be reasoned that, in many of the reported cases, the observed differences between microwave and conventional heating may be justified by inaccurate temperature measurements, often using external IR sensors, rather than being the consequence of an authentic non-thermal effect.[103]

The fairly recent conception that simultaneous external cooling of the reaction mixture or below-zero reaction temperatures under microwave irradiation leads to an improvement of the whole process is also related to the topic of non-thermal microwave effects.[10, 142, 143] The reaction vessel is cooled through a flow of compressed air during microwave irradiation, which allows a higher level of microwave power to be directly supplied to the reaction mixture, but prevents overheating by continuously removing latent heat. Some researchers have claimed that, since microwave energy is transferred into the sample much faster than molecular kinetic relaxation occurs, non-equilibrium conditions will be the outcome of a microwave-assisted reaction. Consequently, a higher instantaneous temperature, relative to the measured bulk temperature, will be determined as more power is applied into the system.[10, 143] Nevertheless, detailed utilisations of simultaneous air cooling methods are rather scarce.[125, 127, 135, 144-154] Moreover, the actual reaction temperatures have not been determined in

many reported situations.[146-153] The standard external IR detectors that are part of most microwave reactors can not be utilised to determine internal reaction temperatures under simultaneous cooling conditions. Given that the IR sensor will only supply the surface temperature of the reaction vessel, not the real reaction temperature inside the reactor, external cooling of the reaction vessel will not provide a dependable temperature measurement and, thus, care must be taken not to misread the results obtained with simultaneous cooling approaches.[103, 135, 144, 145] Several studies have described the application of simultaneous cooling conjugated with fibre-optic temperature monitoring.[125, 127, 135, 144, 145, 154-158] Although the effects compared to regular microwave heating were small in some instances,[135, 144, 145] in other cases important differences in conversion rates and product purity between the cooled and uncooled procedures were observed at the same measured bulk temperature.[125, 127, 154-158]

Besides simultaneous cooling, MAOS under sub-ambient temperature conditions is also possible. Once more, contradictory reports about the utility of this technology exist.[145, 155-158] Microwave-assisted chemistry carried-out by cooling the reaction mixture to as low as -176 ^{o}C was published by Hajek and co-workers.[159] Reaction rates were recorded under both microwave and conventional conditions. Higher reaction rates under microwave irradiation at sub-ambient temperatures were imputed to the super-heating of the heterogeneous catalyst used and, hence, to a specific microwave effect. Closely related to the simultaneous cooling methodology is the technique of using pre-cooled reaction vessels.[160, 161] Also, Ley and co-workers found that pulsed microwave irradiation with periodical cooling afforded higher conversions than continuous irradiation of the reaction mixture for an equal period of time and at the same temperature.[162-165] Speculation was made on whether recurrent temperature overshooting by the strongly microwave-absorbing reaction mixture in the pulsed experiments was accountable for the observed improvements.

There is no agreement in the scientific community about microwave effects and their consequences in microwave-assisted organic synthesis or even about a rigorous definition of terms. The classification of non-thermal microwave effects here presented is far from perfect and probably merits to be re-examined. Appreciable research efforts are still required before a unequivocal resolution about the existence or non-existence of these effects can be presented.[135]

III. Microwave Equipment

Although the pioneering experiments in MAOS were largely carried-out in domestic microwave ovens, dedicated instruments for chemical synthesis are currently the most used. In a domestic microwave oven, the irradiation power is generally controlled by on-off cycles of the magnetron and it is impossible to accurately measure the reaction temperature. The inhomogeneous microwave field produced by the low-cost designs, as well as the lack of safety controls, make the use of such equipment highly inadvisable for scientific ends. In opposition, all commercially accessible microwave reactors designed for chemical synthesis feature built-in magnetic stirrers or alternative agitation devices, temperature and pressure detectors and software that enables on-line temperature and pressure monitoring and control by regulation of the microwave power.[166] Two different approaches have emerged, regarding the microwave reactor design: multi-mode and single-mode. In multi-mode units, conceptually very similar to domestic microwave ovens, the microwaves that enter the generally large cavity move around and are reflected by the walls, rendering areas or modes of high and low energy as moving waves either reinforce or cancel each other (Figure 1.6a). In many of these systems a rotating device ensures that the field distribution is as homogeneous as possible. In the much smaller single-mode cavities, the electromagnetic irradiation is directed through a specifically designed wave-guide onto the reaction vessel, which is mounted at a fixed distance from the radiation source, creating a standing wave (Figure 1.6b).

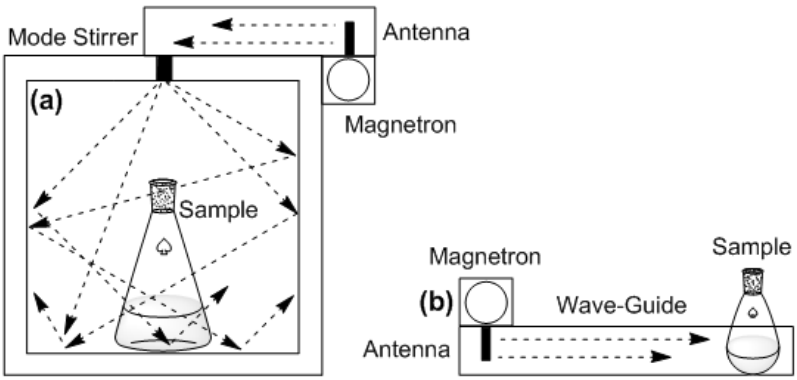


Figure 1.6. Schematics of multi-mode (a) and single-mode (b) microwave cavities.

A. Domestic Microwave Ovens

The generic lack of temperature and pressure control systems and the impossibility to stir the reaction mixture are some of the major practical disadvantages of using these inexpensive household appliances for performing chemical syntheses. Additionally, the pulsed irradiation and the resulting inhomogeneity of the microwave field usually leads to problems of reproducibility. Because of this heterogeneous energy distribution within the microwave cavity, some areas receive high amounts of energy (hot spots) whereas others receive less energy (cold spots).[167] If a load is placed inside the cavity the energy distribution is altered, comparing to the unloaded cavity; to compensate these heterogeneities, the samples are generally rotated in order to attain a more levelled energy distribution. Safety is another primary concern; violent bursts caused by electric arcs inside the cavity or sparking resulting from the on-off switching of the magnetron could be a dangerous outcome of heating organic solvents in open-vessel systems using a domestic microwave oven. Furthermore, working with pressurised sealed vessels without monitoring the temperature and pressure values may lead to vessel failures and severe accidents. Modifications of the accessible domestic ovens with self-made accessories, such as mechanical stirrers and reflux condensers, assembled through holes in the cavities have also been made, aiming to create low-budget instrumentation suitable for chemical synthesis, as depicted in Figure 1.7. Nevertheless, several safety risks remain, given that those instruments are not explosion-proof and leakage of microwave radiation, harmful to the synthetic chemist operating the system, could occur. Undoubtedly, the employment of any microwave equipment not specifically designed for organic synthesis can not be recommended and, presently, is prohibited in numerous academic and industrial research laboratories.

Figure 1.7. Modified domestic microwave oven.

B. Dedicated Microwave Reactors

Many of the current dedicated microwave equipment manufacturers offer a variety of different platforms with several degrees of technological sophistication, such as built-in magnetic or mechanical stirring, real-time temperature, pressure and microwave power monitoring and control, effective cooling during and/or after the irradiation phase, automation accessories, explosion-proof cavities and other safety features, computer-aided programming and database capabilities. A particularly problematic issue in microwave chemistry is the accurate measuring of the reaction temperature during the irradiation period. Classical temperature detectors, e.g. thermometers and thermocouples, are useless, given that they couple with the electromagnetic field. However, temperature measurements can be easily accomplished by means of an immersed temperature sensor, like a fibre-optic probe or a gas balloon thermometer, or via an external IR detector. Due to the volumetric nature of microwave dielectric heating, the surface temperature of the reaction vessel will not always indicate the precise temperature inside the reaction mixture.

Generally speaking, a microwave reactor consists of a microwave power source (magnetron), a transmission line (wave-guide), that delivers microwaves from the magnetron into an antenna, and a microwave applicator (cavity). Continuous microwaves are rendered in the magnetron, which can be viewed as a vacuum tube. The magnetron consists of a cylindrical cathode that is enclosed by an anode block, while a magnetic field is generated parallel to the axis of the cathode by external magnets. In addition, the anode block possesses small cavities. The electrons emitted from the cathode are deflected by the electric and magnetic fields and revolve around the cathode before they can reach the anode. Electron clusters are generated due to acceleration or deceleration of electrons in the cavities and, consequently, transform their energy into microwave oscillation. Lastly, microwave energy from one of the resonant cavities is coupled to the antenna that is attached to the wave-guide. Various modes can be excited when the energy is coupled into the wave-guide, the number being determined by the dimensions of the wave-guide cross-section. Therefore, an infinite series of modes can exist in microwave cavities. According to their dimensions and geometries, multi-mode or single-mode reactors are distinguishable. A state-of-the-art microwave reactor design should assure that all the incident power is absorbed by the load, since the magnetron can be severely damaged when too much energy is reflected back. Several methods to surmount this problem are incorporated in all dedicated microwave reactors.

In multi-mode instruments, microwave irradiation created by, normally, one or two magnetrons, is usually directed into the cavity through a wave-guide and distributed by a mode stirrer (Figure 1.6a). The microwaves are reflected from the walls of the cavity and interact with the sample in a disorganised way. Hence, multi-mode cavities may exhibit several energy pockets with multiple levels of energy intensity, which leads to the formation of hot and cold spots. In order to supply an equal energy distribution, the samples are continuously rotated within the cavity. Nonetheless, multi-mode instruments offer convenient platforms for the increase of reaction throughput by means of multi-vessel rotors for parallel synthesis or scale-up purposes. Even so, a main problem for multi-mode equipment is the fairly weak performance for small-scale processing, typically under 3 ml. Although the generated microwave power is high, commonly ranging from 1000 to 1600 W, the power density of the energy field is generally quite low, heating of small individual samples being rather troublesome. Therefore, the usage of multi-mode instruments for small-scale synthetic organic chemistry is not so extensive, when compared to the alternative single-mode units. The latter are capable of generating a single and nearly homogeneous energy field of high power intensity. Hence, these systems couple efficiently with small-volume samples and the maximum output power is typically much lower, reaching a maximum of 300 or 400 W. A single magnetron is sufficient to generate microwave energy, which is usually oriented through an appropriate circular or rectangular wave-guide to the sample, positioned at a maximised energy location (Figures 1.6b). Further technological advances have led to a wide variety of applications for single-mode microwave instruments, providing flow-through systems and many other special features, such as solid-phase peptide synthesis or

experiments at sub-ambient temperatures. Thus, the utilisation of single-mode microwave reactors has increased enormously since the beginning of the 21st century and this sort of equipment has become broadly popular in many research laboratories. However, it should be stressed that the type of instrumentation used should be supported on the desired scale and application rather than on the type of chemistry to be carried-out. Both multi- and single-mode microwave reactors enable various chemical transformations expeditiously and advantageously, comparing to conventionally-heated procedures.

C. CEM Discover S-Class

The CEM Discover unit, firstly presented in 2001, is a single-mode instrument based on a self-tuning circular wave-guide technology (Figure 1.8a). This automatically adjusts to ensure that the reaction receives the optimum amount of energy, irrespective of the reaction volume, providing access to automation, scale-up under open-vessel, closed-vessel and flow-through conditions, low-temperature synthesis and various applications in biosciences. All Discover instruments are equipped with a built-in keypad for programming the reaction parameters and allowing on-line modifications. The microwave power output can be set up to 300 W, which is more than enough to ensure an effective heating of most reaction mixtures. Regular temperature measuring is attained via an IR sensor positioned at the bottom of the cavity, directly below the reaction vessel (Figure 1.8b). This allows accurate temperature control of the reaction, even when using minimum amounts of materials. An optional fibre-optic probe for internal temperature monitoring is also available. A pressure measurement and management system named IntelliVent was also developed (Figure 1.8c). If the pressure inside a reaction vial exceeds 20 bar, the IntelliVent sensor assures a controlled venting of the pressure and automatically reseals the vial to maintain optimum safety.

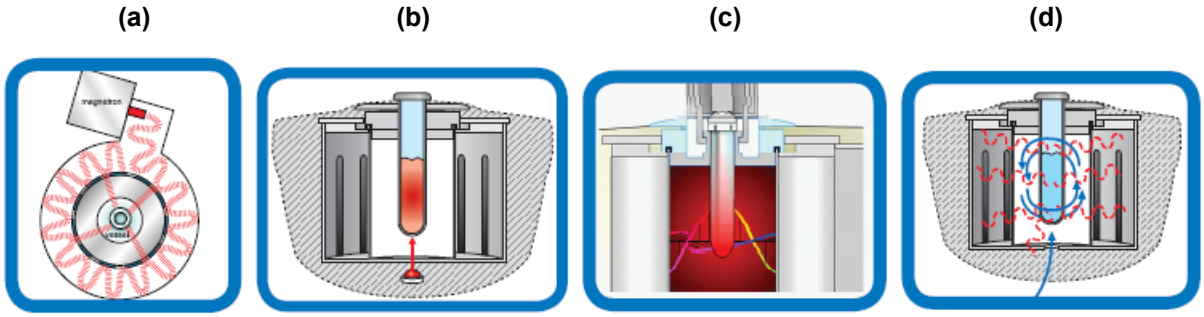


Figure 1.8. Self-tuning circular wave-guide (a), volume-independent infrared temperature sensor (b), IntelliVent pressure monitoring and control system (c) and PowerMAX simultaneous cooling system (d) featured in the CEM Discover S-Class single-mode microwave reactor.

In 2006, the Discover S-Class model was introduced (Figure 1.9). Supplemental to the above-mentioned attributes, common to the earlier Discover systems, the BenchMate and the LabMate, this instrument integrates a fully automated pressure control device and a USB interface. In addition to the 10 ml vials, 35 ml vessels with working volumes ranging from 2.5 to 25 ml are available, allowing low-level scale-up processing under sealed-vessel conditions. Larger volumes, up to 125 ml, can be processed in open-vessel procedures. Reactions can easily be run and programmed trough a computer with the Synergy software, included in the base package, which allows a more user-friendly interface, simple data treatment and straightforward real-time parameter regulation. A built-in cooling system titled PowerMAX, based on a continuous flow of compressed air, can be used simultaneously with and/or after microwave irradiation (Figure 1.8d). An interesting yet optional feature is the integrated CCD camera for *in situ* observation of the reaction vessels. A gas addition kit designed for reactions with gaseous reagents, e.g. hydrogenations or carbonylations, or simply to ensure an inert atmosphere during microwave heating is also available. This accessory allows purging of the reaction vessel and back-filling it with a gas at any

given time. During the reaction, the gas source is completely shut-off from the reactor, thereby ensuring adequate safety conditions. Another peculiar accessory of the Discover instruments is the CoolMate module, a below-zero cooling system designed to carry-out sub-ambient temperature chemistry, e.g. lithiations, carbohydrate synthesis or other temperature-sensitive chemical transformations. The reactor is equipped with a jacketed low-temperature vessel and a microwave transparent cooling media that keep the bulk temperature as low as -80 ºC.

Figure 1.9. CEM Discover S-Class single-mode microwave reactor.

The utilisation of a single-mode microwave equipment identical to the one portrayed in Figure 1.9 to the development of simple, efficient and reproducible microwave-assisted synthetic methodologies of several interesting and widely known nitrogen-containing heterocycles, namely pyrroles, porphyrins, hydroporphyrins, Hantzsch 1,4-dihydropyridines, Biginelli and Biginelli-type 3,4-dihydropyrimidines, was the primary objective of the research project that ultimately led to the present doctoral dissertation. The study of their reactivity under microwave irradiation, particularly in oxidation processes, was also a goal that was pursued, environment-friendly, low-cost and time-saving strategies being employed whenever possible.

IV. References

1. R Gedye, F Smith, K Westaway, H Ali, L Baldisera, L Laberge, J Rousell, *Tetrahedron Lett.* 27 (**1986**) 279-282.
2. RJ Giguere, TL Bray, SM Duncan, G Majetich, *Tetrahedron Lett.* 27 (**1986**) 4945-4948.
3. CO Kappe, A Stadler, D Dalinger, *Microwaves in Organic and Medicinal Chemistry*, Second Edition, Wiley-VCH, Weinheim, Germany, 2012.
4. *Microwave Heating as a Tool for Sustainable Chemistry*, NE Leadbeater (Ed), CRC Press, Boca Raton, 2011.
5. CO Kappe, D Dallinger, SS Murphree, *Practical Microwave Synthesis for Organic Chemists: Strategies, Instruments and Protocols*, Wiley-VCH, Weinheim, German y, 2009.
6. *Microwave Methods in Organic Synthesis*, M Larhed, K Olofsson (Eds), Springer, Berlin, Germany, 2006.
7. *Microwaves in Organic Synthesis*, Second Edition, A Loupy (Ed), Wiley-VCH, Weinheim, Germany, 2006.
8. *Microwave-Assisted Synthesis of Heterocycles*, E Van der Eycken, CO Kappe (Eds), Springer, Berlin, Germany, 2006.
9. *Microwave-Assisted Organic Synthesis*, JP Tierney, P Lidström (Eds), Blackwell Publishing, Oxford, England, UK, 2005.
10. BL Hayes, *Microwave Synthesis: Chemistry at the Speed of Light*, CEM Publishing, Matthews, NC, USA, 2002.
11. CO Kappe, D Dallinger, *Mol. Divers.* 13 (**2009**) 71-193.
12. CO Kappe, *Chem. Soc. Rev.* 37 (**2008**) 1127-1139.
13. V Molteni, DA Ellis, *Curr. Org. Synth.* 2 (**2005**) 333-375.
14. CO Kappe, *Angew. Chem. Int. Ed.* 43 (**2004**) 6250-6284.

15. P Lidström, JP Tierney, B Wathey, J Westman, *Tetrahedron* 57 (**2001**) 9225-9283.
16. DD Artman, AW Grubbs, RM Williams, *J. Am. Chem. Soc.* 129 (**2007**) 6336-6342.
17. P Appukkuttan, E Van der Eycken, *Top. Curr. Chem.* 266 (**2006**) 1-47.
18. IR Baxendale, SV Ley, M Nessi, C Piutti, *Tetrahedron* 58 (**2002**) 6285-6304.
19. A Chighine, G Sechi, M Bradley, *Drug Discov. Today* 12 (**2007**) 459-464.
20. J Alcazar, G Diels, B Schoentjes, *Mini-Rev. Med. Chem.* 7 (**2007**) 345-369.
21. M Larhed, J Wannberg, A Hallberg, *QSAR Comb. Sci.* 26 (**2007**) 51-68.
22. CO Kappe, D Dallinger, *Nat. Rev. Drug Discov.* 5 (**2006**) 51-64.
23. J Wannberg, K Ersmark, M Larhed, *Top. Curr. Chem.* 266 (**2006**) 167-198.
24. F Mavandadi, A Pilotti, *Drug Discov. Today* 11 (**2006**) 165-174.
25. K Ersmark, M Larhed, J Wannberg, *Curr. Opin. Drug Discov. Devel.* 7 (**2004**) 417-427.
26. MD Bowman, JL Holcomb, CM Kormos, NE Leadbeater, VA Williams, *Org. Proc. Res. Devel.* 12 (**2008**) 41-57.
27. JD Moseley, P Lenden, M Lockwood, K Ruda, J Sherlock, AD Thomson, JP Gilday, *Org. Proc. Res. Devel.* 12 (**2008**) 30-40.
28. D Bogdal, A Prociak, *Microwave-Enhanced Polymer Chemistry and Technology*, Blackwell Publishing, Oxford, England, UK, 2007.
29. R Hoogenboom, US Schubert, *Macromol. Rap. Commun.* 28 (**2007**) 368-386.
30. C Zhang, L Liao, S Gong, *Green Chem.* 9 (**2007**) 303-314.
31. S Sinwell, H Ritter, *Aust. J. Chem.* 60 (**2007**) 729-743.
32. D Bogdal, P Penczek, J Pielichowski, A Prociak, *Adv. Pol. Sci.* 163 (**2003**) 193-263.
33. SH Jhung, T Jin, Y Hwang, J-S Chang, *Chem. Eur. J.* 13 (**2007**) 4410-4417.
34. CJ Millos, AG Whittaker, EK Brechin, *Polyhedron* 26 (**2007**) 1927-1933.
35. J Perelaer, B-J de Gans, US Schubert, *Adv. Mat.* 18 (**2006**) 2101-2104.
36. Y-J Zhu, WW Wang, R-J Qi, X-L Hu, *Angew. Chem. Int. Ed.* 43 (**2004**) 1410-1414.
37. F Langa, P de la Cruz, *Comb. Chem. High Through. Screen.* 10 (**2007**) 766-782.
38. GA Tompsett, WC Conner, KS Yngvesson, *Chem. Phys. Chem.* 7 (**2006**) 296-319.
39. M Tsuji, M Hashimoto, Y Nishizawa, M Kubokawa, T Tsuji, *Chem. Eur. J.* 11 (**2005**) 440-452.
40. G Sabatino, AM Papini, *Curr. Opin. Drug Discov. Devel.* 11 (**2008**) 762-770.
41. B Rejasse, S Lamare, M-D Legoy, T Besson, *J. Enz. Inhib. Med. Chem.* 22 (**2007**) 518-526.
42. JM Collins, NE Leadbeater, *Org. Biomol. Chem.* 5 (**2007**) 1141-1150.
43. JR Lill, ES Ingle, PS Liu, V Pham, WN Sandoval, *Mass Spectrom. Rev.* 26 (**2007**) 657-671.
44. WN Sandoval, V Pham, ES Ingle, PS Liu, JR Lill, *Comb. Chem. High Through. Screen.* 10 (**2007**) 751-765.
45. K Bougrin, A Loupy, M Soufiaoui, *J. Photochem. Photobiol. C Photochem. Rev.* 6 (**2005**) 139-167.
46. RS Varma, *Tetrahedron* 58 (**2002**) 1235-1255.
47. M Kidwai, *Pure Appl. Chem.* 73 (**2001**) 147-151.
48. RS Varma, *Green Chem.* 1 (**1999**) 43-55.
49. A Loupy, A Petit, J Hamelin, F Texier-Boullet, P Jacquault, D Mathe, *Synthesis* (**1998**) 1213-1234.
50. AK Bose, MS Manhas, SN Ganguly, AH Sharma, BK Banik, *Synthesis* (**2002**) 1578-1591.
51. AK Bose, BK Banik, N Lavlinskaia, M Jayaraman, MS Manhas, *Chemtech* 27 (**1997**) 18-24.
52. N Kuhnert, *Angew. Chem. Int. Ed.* 41 (**2002**) 1863-1866.
53. CR Strauss, *Angew. Chem. Int. Ed.* 41 (**2002**) 3589-3591.
54. A Loupy, RS Varma, *Chim. Oggi Chem. Today* 24 (**2006**) 36-39.
55. A de La Hoz, A Díaz-Ortiz, A Moreno, *Chem. Soc. Rev.* 34 (**2005**) 164-178.
56. A de La Hoz, A Díaz-Ortiz, A Moreno, *Adv. Org. Synth.* 1 (**2005**) 119-171.
57. A de La Hoz, A Díaz-Ortiz, A Moreno, *Curr. Org. Chem.* 8 (**2004**) 903-918.
58. L Perreux, A Loupy, *Tetrahedron* 57 (**2001**) 9199-9223.

59. BA Roberts, CR Strauss, *Acc. Chem. Res.* 38 (**2005**) 653-661.
60. CR Strauss, *Aust. J. Chem.* 52 (**1999**) 83-96.
61. CR Strauss, RW Trainor, *Aust. J. Chem.* 48 (**1995**) 1665-1692.
62. V Polshettiwar, RS Varma, *Acc. Chem. Res.* 41 (**2008**) 629-639.
63. P Appukkuttan, E Van der Eycken, *Eur. J. Org. Chem.* (**2008**) 1133-1155.
64. Y Coquerel, J Rodriguez, *Eur. J. Org. Chem.* (**2008**) 1125-1132.
65. D Dallinger, CO Kappe, *Chem. Rev.* 107 (**2007**) 2563-2591.
66. CR Strauss, RS Varma, *Top. Curr. Chem.* 266 (**2006**) 199-231.
67. P Nilsson, K Olofsson, M Larhed, *Top. Curr. Chem.* 266 (**2006**) 103-144.
68. R Martinez-Palou, *Mol. Divers.* 10 (**2006**) 435-462.
69. S Bhattacharyya, *Mol. Divers.* 9 (**2005**) 253-257.
70. T Lange, S Lindell, *Comb. Chem. High Through. Screen.* 8 (**2005**) 595-606.
71. J Habermann, S Ponzi, SV Ley, *Mini-Rev. Org. Chem.* 2 (**2005**) 125-137.
72. NE Leadbeater, HM Torenius, H Tye, *Comb. Chem. High Through. Screen.* 7 (**2004**) 511-528.
73. B Desai, CO Kappe, *Top. Curr. Chem.* 242 (**2004**) 177-208.
74. V Santagada, F Frecentese, E Perissutti, L Favretto, G Caliendo, *QSAR Comb. Sci.* 23 (**2004**) 919-944.
75. S Stone-Elander, N Elander, *J. Label. Comp. Radiopharm.* 45 (**2002**) 715-746.
76. N Elander, JR Jones, S-Y Lu, S Stone-Elander, *Chem. Soc. Rev.* 29 (**2000**) 239-250.
77. A de la Hoz, A Díaz-Ortiz, *Comb. Chem. High Through. Screen.* 10 (**2007**) 773-934.
78. NE Leadbeater, *Tetrahedron* 62 (**2006**) 4623-4732.
79. E Van der Eycken, J Van der Eycken, *QSAR Comb. Sci.* 23 (**2004**) 823-986.
80. CO Kappe, *Mol. Divers.* 7 (**2003**) 95-307.
81. A Yarnell, *Chem. Eng. News* 85 (**2007**) 32-33.
82. NE Leadbeater, *Chem. World* 1 (**2004**) 38-41.
83. JR Minkel, *Drug Discov. Devel.* 7 (**2004**) 47-52.
84. V Marx, *Chem. Eng. News* 82 (**2004**) 14-19.
85. D Adam, *Nature* 421 (**2003**) 571-572.
86. G Dutton, *Gen. Eng. News* 22 (**2002**) 13-17.
87. KJ Watkins, *Chem. Eng. News* 80 (**2002**) 17-18.
88. P Edwards, *Drug Discov. Today* 6 (**2001**) 614.
89. SL Cresswell, SJ Haswell, *J. Chem. Educ.* 78 (**2001**) 900-904.
90. http://www.biotagepathfinder.com.
91. http://www.mwchemdb.com.
92. http://www.organicchemistry.org/Highlights/microwave.shtm.
93. SS Murphree, CO Kappe, *J. Chem. Educ.* 86 (**2009**) 227.
94. AR Katritzky, C Cai, MD Collins, EFV Scriven, SK Singh, EK Barnhardt, *J. Chem. Educ.* 83 (**2006**) 634-636.
95. C McGowan, NE Leadbeater, *Clean, Fast Organic Chemistry: Microwave-Assisted Laboratory Experiments*, CEM Publishing, Matthews, NC, USA, 2006.
96. D Bogdal, *Microwave-Assisted Organic Synthesis: One Hundred Reaction Procedures*, Elsevier, Oxford, England, UK, 2005.
97. http://www.anton-paar.com.
98. http://www.biotage.com.
99. http://www.cem.com.
100. http://www.milestonesci.com.
101. JD Moseley, CO Kappe, *Green Chem.* 13 (**2011**) 794-806.
102. T Razzaq, CO Kappe, *Chem. Sus. Chem.* 1 (**2008**) 123-132.
103. M Nüchter, B. Ondruschka, W Bonrath, A Gum, *Green Chem.* 6 (**2004**) 128-141.

104. E Neas, M Collins, in *Introduction to Microwave Sample Preparation: Theory and Practice*, HM Kingston, LB Jassie (Eds), American Chemical Society, Washington, DC, USA, 1988, Chapter 2, pp 7-32.
105. DR Baghurst, DMP Mingos, *Chem. Soc. Rev.* 20 (**1991**) 1-47.
106. C Gabriel, S Gabriel, EH Grant, BS Halstead, DMP Mingos, *Chem. Soc. Rev.* 27 (**1998**) 213-223.
107. DV Stass, JR Woodward, CR Timmel, PJ Hore, KA McLauchlan, *Chem. Phys. Lett.* 329 (**2000**) 15-22.
108. JR Woodward, RJ Jackson, CR Timmel, PJ Hore, KA McLauchlan, *Chem. Phys. Lett.* 272 (**1997**) 376-382.
109. CR Timmel, PJ Hore, *Chem. Phys. Lett.* 257 (**1996**) 401-408.
110. D Stuerga, in *Microwaves in Organic Synthesis*, Second Edition, A Loupy (Ed), Wiley-VCH, Weinheim, Germany, 2006, Chapter 1, pp 1-34.
111. DMP Mingos, in *Microwave-Assisted Organic Synthesis*, JP Tierney, P Lidström (Eds), Blackwell Publishing, Oxford, England, UK, 2005, Chapter 1, pp 1-22.
112. L Perreux, A Loupy, in *Microwaves in Organic Synthesis*, Second Edition, A Loupy (Ed), Wiley-VCH, Weinheim, Germany, 2006, Chapter 4, pp 134-218.
113. A de La Hoz, A Díaz-Ortiz, A Moreno, in *Microwaves in Organic Synthesis*, Second Edition, A Loupy (Ed), Wiley-VCH, Weinheim, Germany, 2006, Chapter 5, pp 219-277.
114. M Panunzio, E Campana, G Martelli, P Vicennati, E Tamanini, *Mater. Res. Innov.* 8 (**2004**) 27-31.
115. DR Baghurst, DMP Mingos, *J. Chem. Soc. Chem. Commun.* (**1992**) 674-677.
116. R Saillard, M Poux, J Berlan, M Audhuy-Peaudecerf, *Tetrahedron* 51 (**1995**) 4033-4042.
117. JP Gilday, P Lenden, JD Moseley, BG Cox, *J. Org. Chem.* 73 (**2008**) 3130-3134.
118. F Chemat, E Esveld, *Chem. Eng. Tech.* 24 (**2001**) 735-744.
119. G Roussy, JM Thibaut, P Collin, *Thermochim. Acta* 98 (**1986**) 57-62.
120. E Abtal, M Lallemant, G Bertrand, G Watelle, *J. Chem. Phys.* 82 (**1985**) 381-399.
121. J Berlan, *Rad. Phys. Chem.* 45 (**1995**) 581-589.
122. M Hajek, in *Microwaves in Organic Synthesis*, Second Edition, A Loupy (Ed), Wiley-VCH, Weinheim, Germany, 2006, Chapter 13, pp 615-652.
123. H Will, P Scholz, B Ondruschka, *Chemie-Ingenieur-Technik* 74 (**2002**) 1057-1067.
124. X Zhang, DO Hayward, DMP Mingos, *Catal. Lett.* 88 (**2003**) 33-38.
125. GS Vanier, *Synlett* (**2007**) 131-135.
126. E Heller, W Lautenschläger,U Holzgrabe, *Tetrahedron Lett.* 46 (**2005**) 1247-1249.
127. IR Baxendale, CM Griffith-Jones, SV Ley, GK Tranmer, *Chem. Eur. J.* 12 (**2006**) 4407-4416.
128. D Bogdal, M Lukasiewicz, J Pielichowski, A Miciak, SZ Bednarz, *Tetrahedron* 59 (**2003**) 649-653.
129. M Lukasiewicz, D Bogdal, J Pielichowski, *Adv. Synth. Catal.* 345 (**2003**) 1269-1272.
130. MHCL Dressen, BHP van de Kruijs, J Meuldijk, JAJM Vekemans, LA Hulshof, *Org. Proc. Res. Devel.* 11 (**2007**) 865-869.
131. WC Conner, GA Tompsett, *J. Phys. Chem. B* 112 (**2008**) 2110-2118.
132. R Laurent, A Laporterie, J Dubac, J Berlan, S Lefeuvre, M Audhuy, *J. Org. Chem.* 57 (**1992**) 7099-7102.
133. KD Raner, CR Strauss, RW Trainor, JS Thorn, *J. Org. Chem.* 60 (**1995**) 2456-2460.
134. P Nilsson, M Larhed, A Hallberg, *J. Am. Chem. Soc.* 123 (**2001**) 8217-8225.
135. MA Herrero, JM Kremsner, CO Kappe, *J. Org. Chem.* 73 (**2008**) 36-47.
136. C Shibata, T Kashima, K Ohuchi, *Jap. J. Appl. Phys.* 35 (**1996**) 316-319.
137. J Jacob, LHL Chia, FYC Boey, *J. Mat. Sci.* 30 (**1995**) 5321-5327.
138. JGP Binner, NA Hassine, TE Cross, *J. Mat. Sci.* 30 (**1995**) 5389-5393.
139. DA Lewis, JD Summers, TC Ward, JE McGrath, *J. Polym. Sci. A Polym. Chem.* 30 (**1992**), 1647-1653.
140. J Berlan, P Giboreau, S Lefeuvre, C Marchand, *Tetrahedron Lett.* 32 (**1991**) 2363-2366.
141. A Loupy, F Maurel, A Sabatie-Gogova, *Tetrahedon* 60 (**2004**) 1683-1691.
142. BL Hayes, MJ Collins Jr, World Patent WO 04002617, 2004.
143. BL Hayes, *Aldrichim. Acta* 37 (**2004**) 66-77.

144. NE Leadbeater, SJ Pillsbury, E Shanahan, VA Williams, *Tetrahedron* 61 (**2005**) 3565-3585.
145. M Hosseini, N Stiasni, V Barbieri, CO Kappe, *J. Org. Chem.* 72 (**2007**) 1417-1424.
146. A-L Villard, B Warrington, M Ladlow, *J. Comb. Chem.* 6 (**2004**) 611-622.
147. CJ Bennett, ST Caldwell, DB McPhail, PC Morrice, GG Duthie, RC Hartley, *Bioorg. Med. Chem.* 12 (**2004**) 2079-2098.
148. M Bejugam, SL Flitsch, *Org. Lett.* 6 (**2004**) 4001-4004.
149. JJ Chen, SV Deshpande, *Tetrahedron Lett.* 44 (**2003**) 8873-8876.
150. F Mathew, KN Jayaprakash, B Fraser-Reid, J Mathew, J Scicinski, *Tetrahedron Lett.* 44 (**2003**) 9051-9054.
151. K Crawford, SK Bur, CS Straub, A Padwa, *Org. Lett.* 5 (**2003**) 3337-3340.
152. CE Humphrey, MAM Easson, JP Tierney, NJ Turner, *Org. Lett.* 5 (**2003**) 849-852.
153. AR Katritzky, Y Zhang, SK Singh, PJ Steel, *Arkivoc* xv (**2003**) 47-65.
154. RK Arvela, NE Leadbeater, *Org. Lett.* 7 (**2005**) 2101-2104.
155. BK Singh, VP Mehta, VS Parmar, E Van der Eycken, *Org. Biomol. Chem.* 5 (**2007**) 2962-2965.
156. P Appukkuttan, M Husain, RK Gupta, VS Parmar, E Van der Eycken, *Synlett* (**2006**) 1491-1496.
157. BK Singh, P Appukkuttan, S Claerhout, VS Parmar, E Van der Eycken, *Org. Lett.* 8 (**2006**) 1863-1866.
158. NE Leadbeater, LM Stencel, EC Wood, *Org. Biomol. Chem.* 5 (**2007**) 1052-1055.
159. J Kurfürstová, M Hajek, *Res. Chem. Interm.* 30 (**2004**) 673-681.
160. AK Bose, SN Ganguly, MS Manhas, W He, J Speck, *Tetrahedron Lett.* 47 (**2006**) 3213-3215.
161. B Bacsa, B Desai, G Dibo, CO Kappe, *J. Pept. Sci.* 12 (**2006**) 633-638.
162. IR Baxendale, A-I Lee, SV Ley, *J. Chem. Soc. Perkin Trans.* (**2002**) 1850-1857.
163. W Yin, Y Ma, YJ Zhao, *J. Org. Chem.* 71 (**2006**) 4312-4315.
164. T Durand-Reville, LB Gobbi, BL Gray, SV Ley, JS Scott, *Org. Lett.* 4 (**2002**) 3847-3850.
165. IR Baxendale, SV Ley, M Nessi, C Piutti, *Tetrahedron* 58 (**2002**) 6285-6304.
166. For an extensive overview of commercially available microwave instruments see: CO Kappe, A Stadler, D Dalinger, *Microwaves in Organic and Medicinal Chemistry*, Second Edition, Wiley-VCH, Weinheim, Germany, 2012, Chapter 3, pp 41-81; CO Kappe, D Dallinger, SS Murphree, *Practical Microwave Synthesis for Organic Chemists: Strategies, Instruments and Protocols*, Wiley-VCH, Weinheim, Germany, 2009, Chapter 3, pp 45-85.
167. D Karstädt, K-P Möllmann, M Vollmer, *Physik in unserer Zeit* 35 (**2004**) 90-96.

2

Pyrroles

I. Introduction & Relevance

Pyrrole, a five-membered nitrogen-containing heterocycle, is broadly recognised as one of the simplest and most important aromatic heterocycles and can be found in a wide range of natural products and synthetic molecules. It was discovered by Runge in the mid-1830s, as a consequence of a series of distillation experiences of bone oil and coal tar, and isolated by Anderson in 1857 through similar procedures. Its first synthesis was accomplished by Schwanert in 1860, by heating the ammonium salt of mucic acid, and after its successful structural elucidation, achieved by von Bayer in the 1870s, and its identification as an essential fragment in several biologically relevant natural pigments, such as haem, chlorophyll or vitamin B_{12}, chemists became increasingly interested in pyrroles and their properties.[1-3] Representative examples of natural pyrrole-containing bioactive compounds are depicted in Figure 2.1, including some antibacterial halogenated pyrroles, e.g. pioluteorine and pentabromopseudiline, both isolated from bacterial sources. Pyrrole structures are particularly prominent in marine natural products. Some examples are nakamuric acid[4] and some marinopyrroles,[5] which exhibited good activity against methicillin-resistant *Staphylococcus aureus* strains.

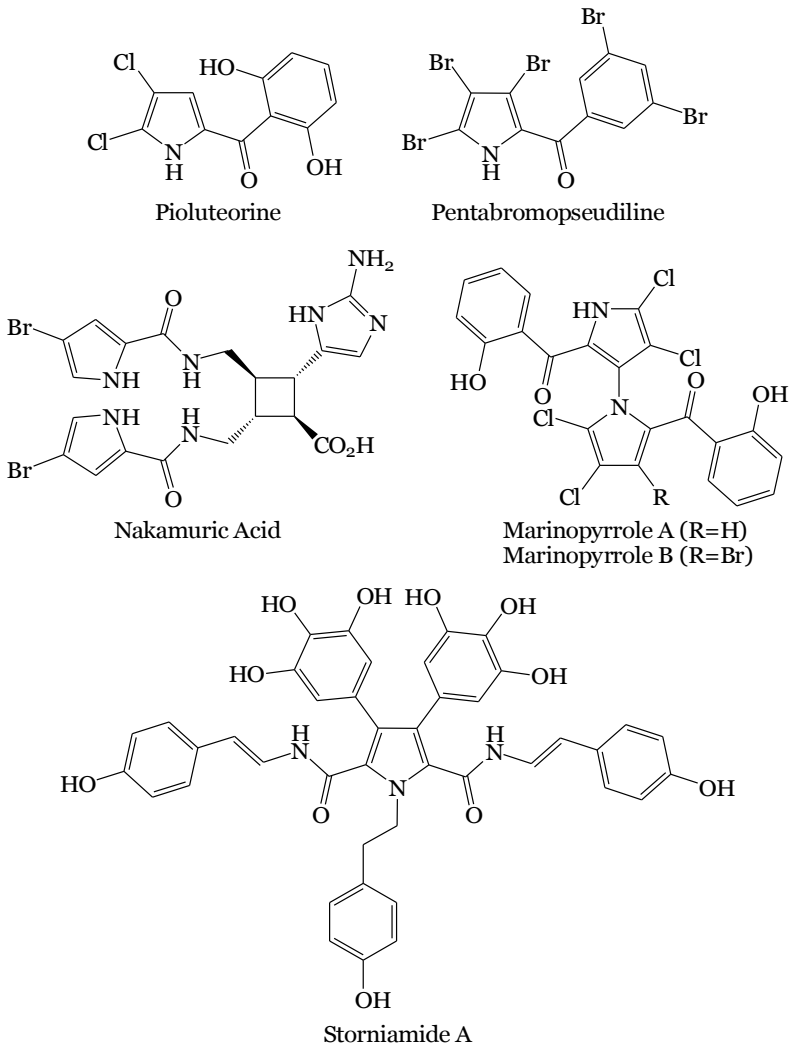


Figure 2.1. Representative examples of natural pyrrole-containing bioactive compounds.

The storniamide alkaloid family, isolated from a myriad of marine organisms, like molluscs, ascidians and sponges, and featuring 3,4-diarylpyrrole moieties, must also be emphasised. A series of methoxylated analogues of storniamide A have proved to be potent inhibitors of multidrug resistance phenomena,[6] regarded by several researchers as one of the primal obstacles to the development of a successful anticancer chemotherapy. Both natural and synthetic products containing polypyrrole motifs are often involved in coordination and molecular recognition phenomena. Besides the ubiquitous tetrapyrroles, such as porphyrins and related structures (see Chapter 3), a red dye synthesised by bacteria belonging to the *Serratia* genus, prodigiosin, has shown to have antibiotic properties[7] and behave as a transporter of protons and chloride anions across phospholipid membranes.[8] Moreover, the torsional flexibility associated with some polypyrrole systems linked by peptide bonds has proved to be crucial to molecular recognition phenomena involved in the interaction with DNA minor groove natural binders, such as netropsin, distamycin and related drugs.[9] Pyrrole substructures also exist in a large number of biologically active man-made molecules, including antitubercular compounds,[10, 11] and HIV fusion inhibitors.[12] The non-steroidal anti-inflammatory compound tolmetin,[13-16] the cholesterol-lowering agent atorvastatin (one of the best-selling drugs in pharmaceutical history)[17-20] and the anticancer drug candidate tallimustine[21-23] are a few relevant examples of pyrrole-based synthetic drugs (Figure 2.2).

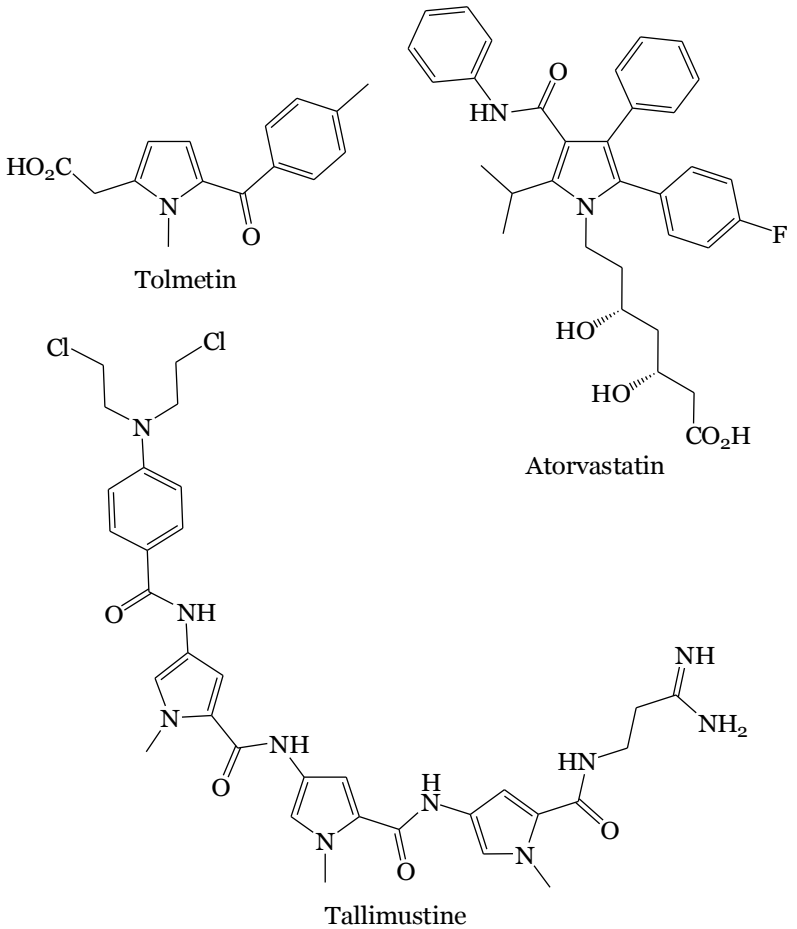
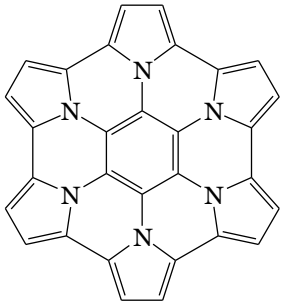
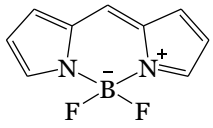


Figure 2.2. Representative examples of synthetic pyrrole-containing bioactive compounds.

Pyrrole derivatives are becoming exceedingly important in materials science. One can mention semiconducting materials derived from hexa(*N*-pyrrolyl)benzene,[24] glucose sensors based on polypyrrole-latex hybrid structures[25] and polypyrrole compounds capable of effective detection and discrimination of volatile organic compounds.[26] The 4,4-difluoro-4-boradipyrromethene (BODIPY) system and related dyes are characterised by a strong absorption in the UV region and a very intense fluorescence, displaying many promising applications, such as laser manufacture, chemosensing, optical imaging and chemotherapy, among many others (Figure 2.3).[27]



Hexa(*N*-Pyrrolyl)Benzene Derivative



BODIPY

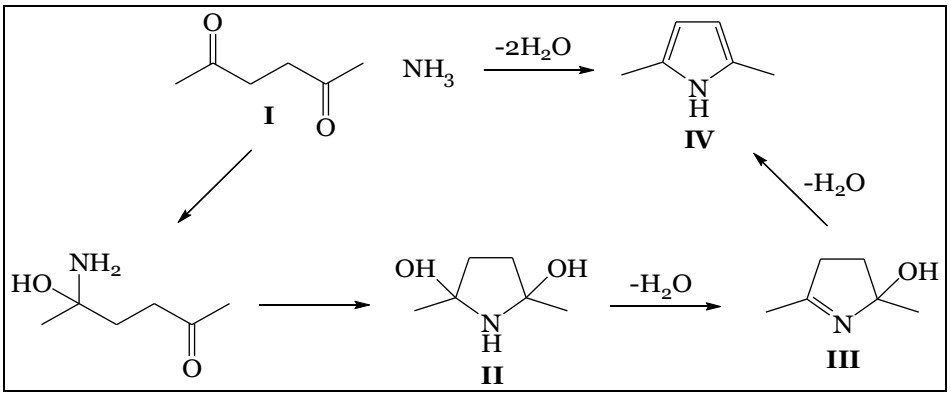
Figure 2.3. Representative examples of synthetic pyrrole-containing compounds relevant in materials science.

II. Classical Synthetic Methods

The synthesis of pyrroles became possible at the end of the 19th century with the pioneering work conducted by Knorr, Paal and Hantzsch, who presented plain and straightforward cyclisation strategies for the direct preparation of substituted pyrroles, starting from easily accessible reagents. Currently, a considerable amount of review literature on modified classical pyrrole synthesis is available.[28-31]

A. Paal-Knorr Synthesis

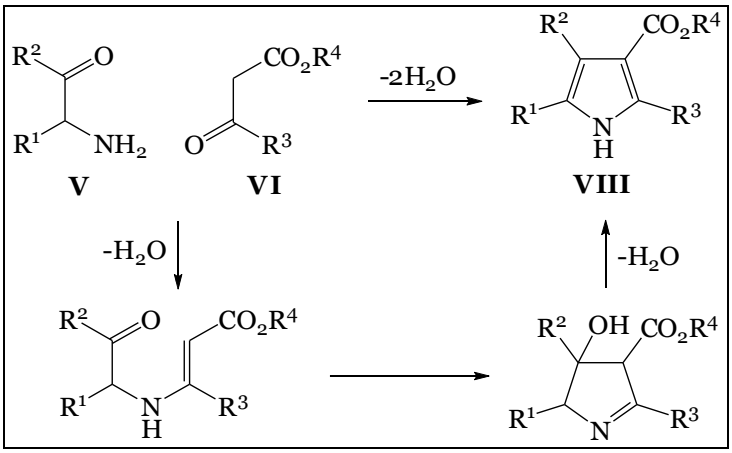
The Paal-Knorr procedure was reported independently by German chemists Carl Paal and Ludwig Knorr, in 1884, as a method for the preparation of substituted furans, pyrroles and thiophenes.[32, 33] The treatment of appropriately substituted 1,4-dicarbonyl compounds with ammonia, primary amines or ammonium or alkyl ammonium salts, usually in ethanol or acetic acid, leads to 2,5-disubstituted pyrroles. Although the widespread utilisation of the Paal-Knorr synthesis, its reaction mechanism was not fully comprehended until it was elucidated by Amarnath and co-workers in the 1990s.[34, 35] For instance, 2,5-hexanedione **I** reacts with ammonia furnishing a double hemiaminal **II** which, due to step-wise elimination of water, yields 2,5-dimethyl-1*H*-pyrrole **IV** through the corresponding imine **III** (Scheme 2.1).



Scheme 2.1. Paal-Knorr synthesis of pyrroles.

B. Knorr Synthesis

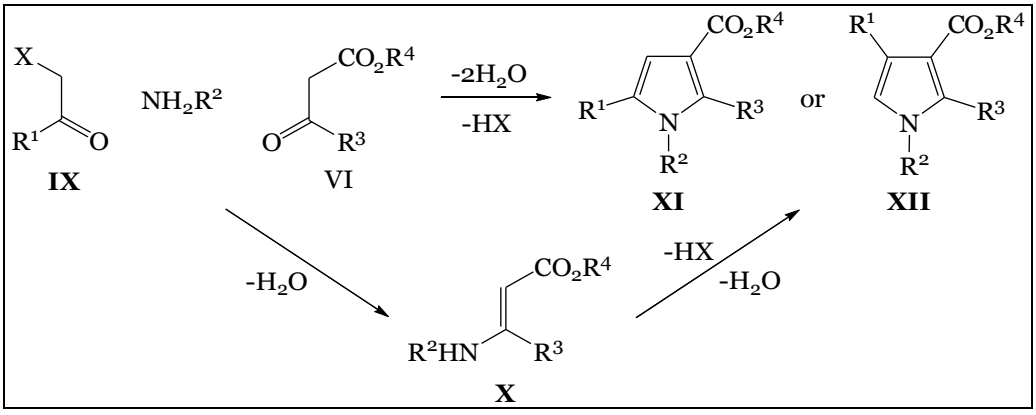
The cyclocondensation of α-aminoketones **V** with β-ketoesters or β-diketones **VI**, which proceeds through a β-enaminone intermediate **VII**[36] and affords 3-alkoxycarbonyl- or 3-acyl-substituted pyrrole derivatives **VIII**, respectively, was first published by Ludwig Knorr almost 130 years ago (Scheme 2.2).[37-39] Because most α-aminoketones self-condense very easily they are not employed as such, but generated *in situ* by reduction of the corresponding α-oximinoketones. The latter are commonly obtained by nitrosation of ketones with alkyl nitrites in the presence of sodium methoxide.



Scheme 2.2. Knorr synthesis of pyrroles.

C. Hantzsch Synthesis

3-Alkoxycarbonyl- or 3-acyl-substituted pyrroles can also be prepared by reaction of α-haloketones with ammonia or primary amines and β-ketoesters or β-diketones, respectively. This methodology was developed by the German chemist Arthur Rudolph Hantzsch over a century ago.[40, 41] The regioselectivity of the product depends on the substituents in the starting materials, but mainly renders the 1,2,3,5-tetrasubstituted pyrrole **XI**. Thorough investigations demonstrated that β-ketoesters **VI** react with ammonia or primary amines, yielding a β-aminoacrylic ester intermediate **X**. *C*-alkylation of the enamine group of **X** by the α-haloketone **IX** provides 1,2,3,5-tetrasubstituted pyrroles **XI**, while *N*-alkylation leads to 1,2,3,4-tetrasubstituted pyrroles **XII** (Scheme 2.3).



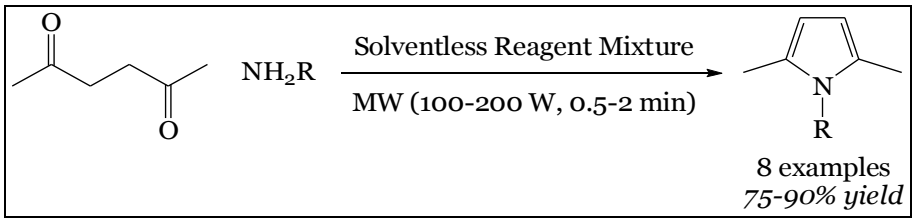
Scheme 2.3. Hantzsch synthesis of pyrroles.

III. Microwave-Assisted Synthetic Methods

A variety of synthetic strategies for the synthesis of substituted pyrrole derivatives is presently available.[1-3] However, hazardous and/or expensive reagents, solvents and catalysts, long reaction times and harsh reaction conditions are sometimes required, a number of unwanted by-products is frequently obtained and reaction yields are often low. Furthermore, pyrroles are commonly susceptible to chemical degradation, e.g. oxidation, which further restrains their isolation and purification processes. Therefore, more than 120 years after the first synthetic methods were developed, the preparation of highly substituted pyrrole compounds remains challenging. Microwave irradiation has already been successfully applied to the synthesis of several heterocyclic compounds;[42, 43] some selected examples regarding pyrroles, taken from the currently available scientific literature, are briefly described below.

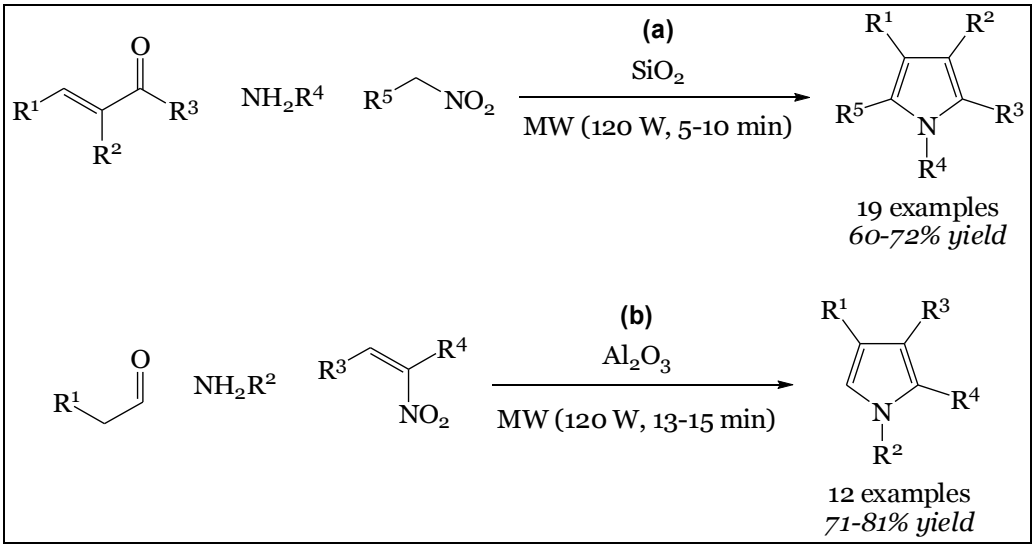
A. Literature Review & Selected Examples

Although the microwave-assisted preparation of pyrroles by dehydrogenation of previously synthesised pyrrolidines[44] and by reaction of 1,4-diketones with ammonia or other primary amines generated from urea-type compounds pre-adsorbed in montmorillonite clays[45] was published in 1994, the first microwave-activated Paal-Knorr reaction report appeared in 1999.[46] Danks achieved the successful synthesis of 2,5-dimethylpyrroles in less than 2 minutes, by irradiating neat mixtures of the starting materials, 2,5-hexanedione and primary amines, in a domestic microwave oven (Scheme 2.4).



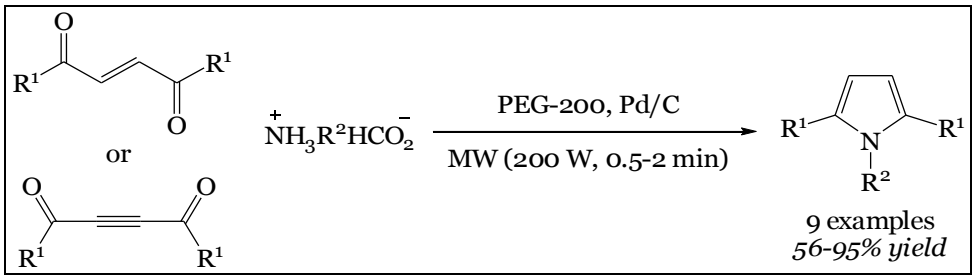
Scheme 2.4. Solventless Paal-Knorr synthesis of 2,5-dimethylpyrroles.

Several highly substituted pyrrole structures were synthesised with reasonably good yields under microwave irradiation by Ranu and co-workers in the early 2000s.[47, 48] The solid-supported three-component condensation of α,β-unsaturated aldehydes or ketones, primary amines and nitroalkanes in silicon dioxide (Scheme 2.5a) and of aldehydes or ketones, primary amines and α,β-unsaturated nitroalkenes in aluminium oxide (Scheme 2.5b) was conducted in a domestic equipment in short reaction times.



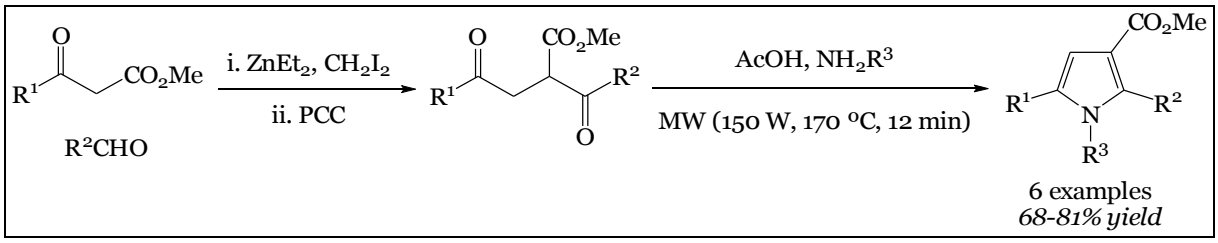
Scheme 2.5. Solid-supported three-component synthesis of highly substituted pyrroles.

Pyrroles bearing multiple aryl groups were conveniently prepared by a one-pot microwave-assisted Paal-Knorr strategy, starting from ammonium, alkyl ammonium or aryl ammonium formates and but-2-ene-1,4-diones or but-2-yne-1,4-diones, via palladium-mediated transfer hydrogenation of the carbon-carbon double or triple bond, followed by a reductive amination-cyclisation process.[49, 50] Using liquid polyethylene glycol as solvent and a domestic microwave oven, Rao and colleagues were able to rapidly obtain 2,5-diarylpyrroles with high yields (Scheme 2.6).



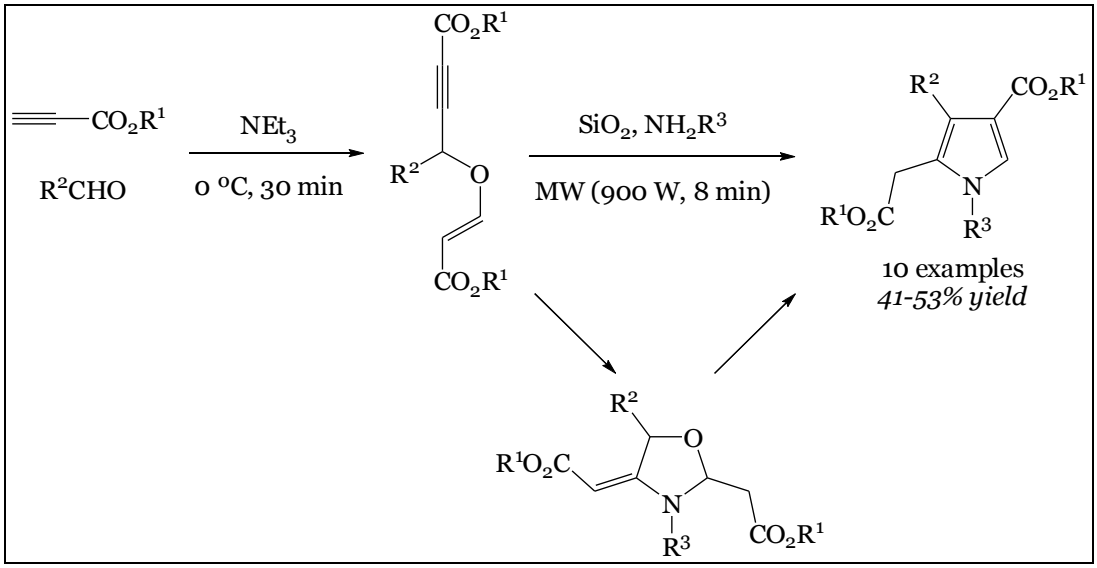
Scheme 2.6. Paal-Knorr synthesis of 2,5-diarylpyrroles in liquid polyethylene glycol.

A three-step synthesis of tetrasubstituted pyrroles was developed by the Taddei research team in 2004. Adequate functional homologation of a β-ketoester with an aldehyde, followed by oxidation with pyridinium chlorochromate provided substituted 1,4-dicarbonyl compounds, which were then rapidly cyclised with primary amines via a Paal-Knorr procedure using a dedicated single-mode microwave reactor (Scheme 2.7).[51] A very similar approach was explored by the same authors to prepare more than 60 pyrrole-based amino acids and some related constrained oligopeptides.[52, 53] The solution-phase microwave-assisted synthesis of a larger library containing 288 pyrrole-amide derivatives with medium to good yields was also accounted.[54]



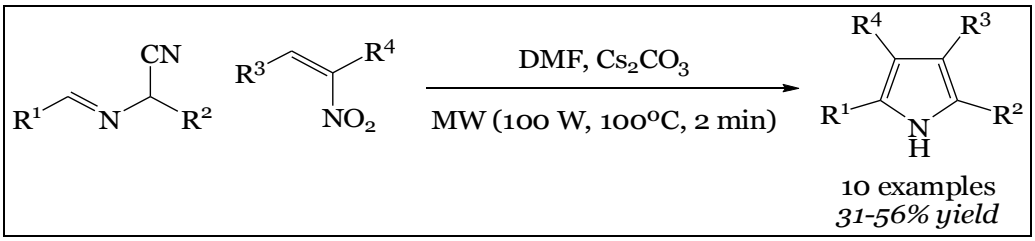
Scheme 2.7. Paal-Knorr synthesis of tetrasubstituted pyrroles.

Tetrasubstituted pyrrole compounds could also be obtained under solid-supported microwave conditions through skeletal rearrangement of 1,3-oxazolidines, which are accessible in solventless two-step domino processes. The first one occurs between commercially available alkyl propiolates and aldehydes affording enol ethers. Subsequent microwave-promoted reaction of the latter with primary amines on a silicon dioxide support yields the 1,3-oxazolidine intermediates, which easily rearrange *in situ* to the desired pyrroles in a second domino procedure (Scheme 2.8).[55] Hence, performing this domino sequence in a one-pot format utilising a household microwave apparatus resulted in a simple and diversity-oriented synthesis of tetrasubstituted pyrroles.



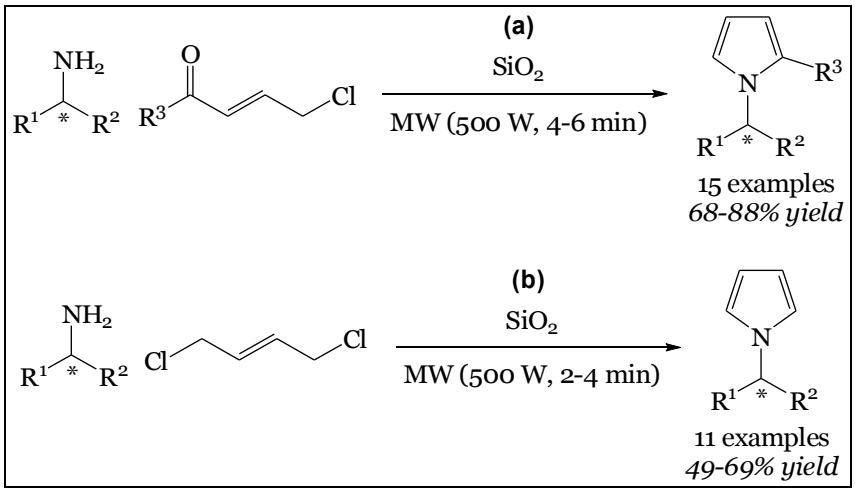
Scheme 2.8. Domino synthesis of tetrasubstituted pyrroles.

Another interesting example of the preparation of tetrasubstituted pyrrole derivatives was published by Bergner and Opatz in 2007.[56] The cycloaddition of α-(alkylideneamino)nitriles and nitro-olefins making use of a single-mode microwave reactor, followed by the elimination of hydrogen cyanide and nitrous acid, allowed the construction of the pyrrole ring in four steps, starting from a nitroalkane and three aldehydes, with high regioselectivity and low to moderate yields (Scheme 2.9).



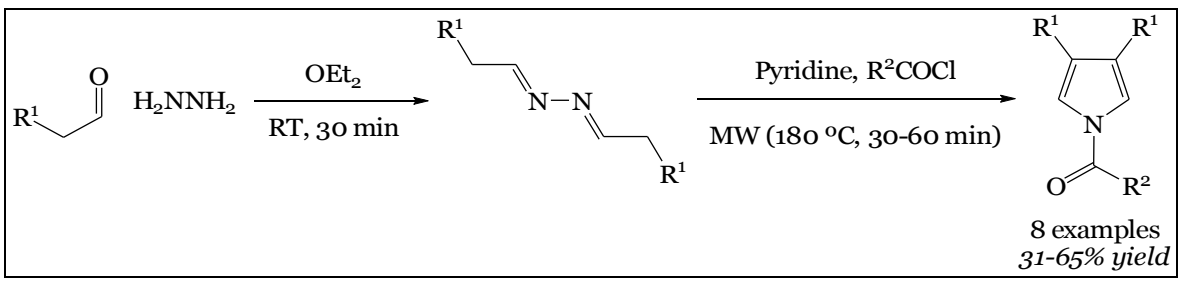
Scheme 2.9. Synthesis of tetrasubstituted pyrroles via cycloaddition.

A practical solid-supported and microwave-activated synthetic method of 1,2-disubstituted homochiral pyrroles, based on a two-component coupling of chloroenones and chiral primary amines, was devised by Aydogan and co-workers in 2005 (Scheme 2.10a).[57] A related approach, comprising a ring-closure reaction of 1,4-dichloro-but-2-ene with several amine compounds, was subsequently reported, also yielding *N*-substituted homochiral pyrrole structures (Scheme 2.10b).[58] Both methodologies were carried-out in a multi-mode microwave digestion equipment.



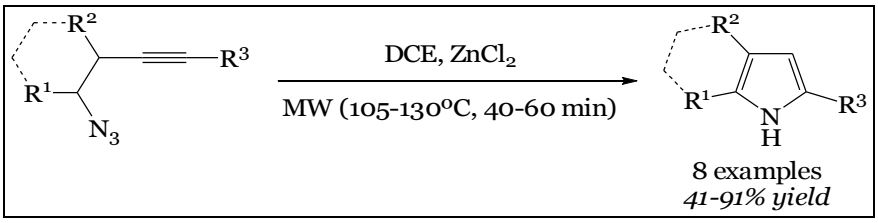
Scheme 2.10. Solid-supported synthesis of *N*-substituted homochiral pyrroles.

The two-step synthesis of 3,4-disubstituted *N*-acylpyrrole compounds was accomplished by Milgram and colleagues, starting from hydrazine and alkyl aldehydes, via a microwave-assisted Piloty-Robinson reaction (Scheme 2.11).[59] The utilisation of a dedicated microwave reactor greatly reduced the time necessary for this process comparing to classical heating conditions, notwithstanding the low to moderate reaction yields obtained.



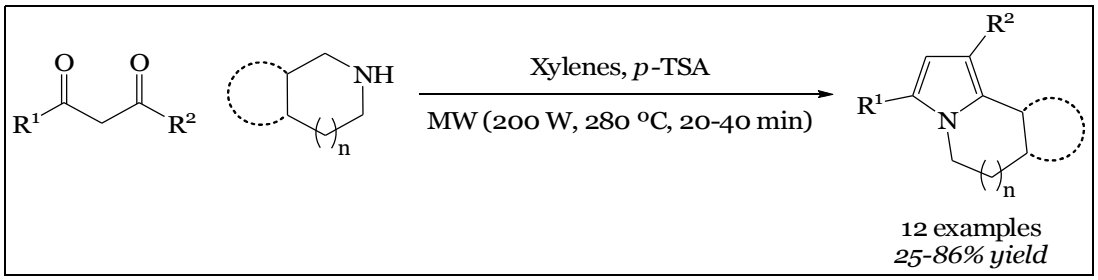
Scheme 2.11. Piloty-Robinson synthesis of *N*-acylpyrroles.

Highly substituted and *N*-unprotected pyrrole derivatives featuring aryl, alkyl and fused cycloalkyl groups were synthesised, in relatively brief reaction times and with moderate to high reaction yields, through a ligand-free microwave-promoted 5-*endo*-dig intramolecular cyclisation of previously prepared homopropargyl azides in the presence of zinc chloride (Scheme 2.12).[60] The catalyst proved to be more effective for aryl than for alkyl substituents.



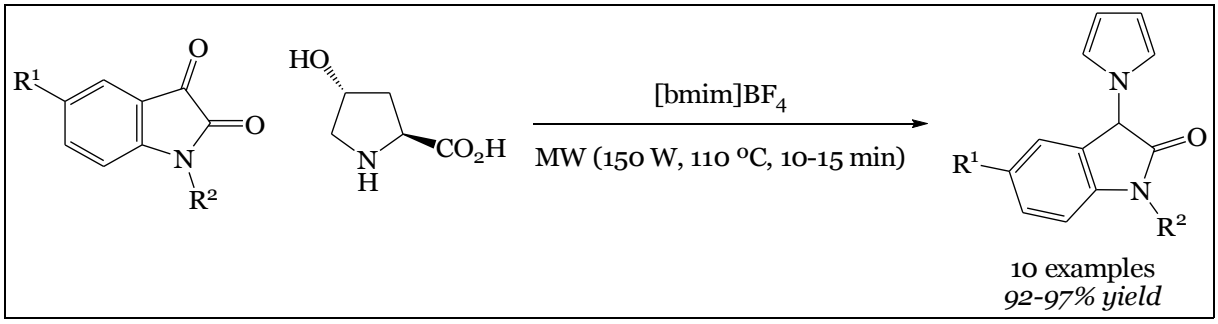
Scheme 2.12. Synthesis of highly substituted pyrroles via zinc chloride catalysis.

Deb and Seidel proposed the preparation of ring-fused pyrroles, through a high-temperature condensation of commercially available cyclic amines and 1,3-diketones, under microwave conditions (Scheme 2.13).[61] A competing retro-Claisen synthetic pathway was efficiently suppressed by employing *p*-toluenesulphonic acid as an additive.



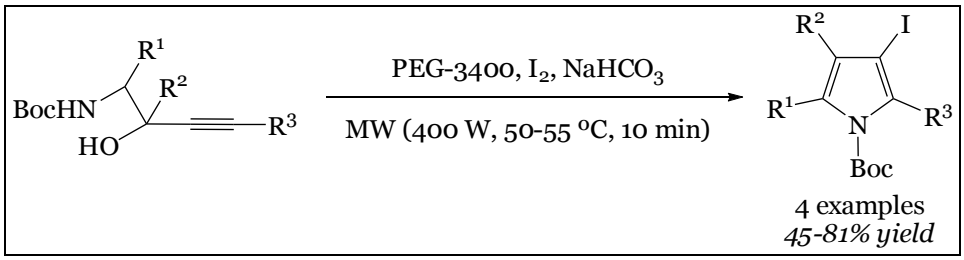
Scheme 2.13. Synthesis of *N*-substituted ring-fused pyrroles.

The rapid and high-yielding synthesis of *N*-substituted pyrrole compounds through condensation of 4-hydroxyproline with several substituted isatins, utilising an ionic liquid as the reaction medium and a single-mode microwave reactor, was described by Meshram and co-workers in 2010 (Scheme 2.14).[62] The recovered ionic liquid was reused for six cycles and the reaction proceeded without the addition of any acid promoter.



Scheme 2.14. Synthesis of *N*-substituted pyrroles in ionic liquids.

Recently, highly substituted β-iodopyrroles were easily prepared by reacting a mixture of *N*-protected 1,2-aminoalcohols, molecular iodine and a base in solid PEG-3400 as an alternative, eco-friendly and non-toxic reaction medium, in a short period of time and using a dedicated microwave apparatus (Scheme 2.15).[63] Albeit few examples were reported, the reaction yields were generally satisfactory and tedious purification procedures were avoided.



Scheme 2.15. Synthesis of β-iodopyrroles in solid polyethylene glycol.

B. Paal-Knorr Synthesis of 2,5-Dimethyl-1*H*-Pyrroles

In order to explore the capabilities of our, at that time, recently acquired CEM Discover S-Class single-mode microwave reactor, it was decided to use the simple microwave-assisted Paal-Knorr protocol for the preparation of 2,5-dimethyl-1*H*-pyrroles described by Danks.[46] Thence, a solventless reagent mixture comprising equimolar amounts of the selected amine and 2,6-hexanedione, in an appropriate and sealed glass vial, was irradiated using two approaches: a constant temperature of 100 °C and a constant microwave power of 100 W (Table 2.1, entries 1-8; Scheme 2.16a). Isolation of the reaction product was accomplished by drying the diethyl ether solution of the crude product mixture with anhydrous sodium sulphate, followed by filtration and silica gel flash column chromatography using the same solvent as eluent or recrystallisation in methanol. Although the reaction yields were high when benzylamine (entries 5 and 6) and *n*-butylamine (entries 7 and 8) were employed as reactants (86-95%), regardless of the temperature and microwave power settings used and after only one minute of microwave heating, the utilisation of aniline for the preparation of pyrrole **1** was clearly not successful (entries 1-4). The best result obtained was a 47% isolated yield after irradiating for 5 minutes at 100 W (entry 4).

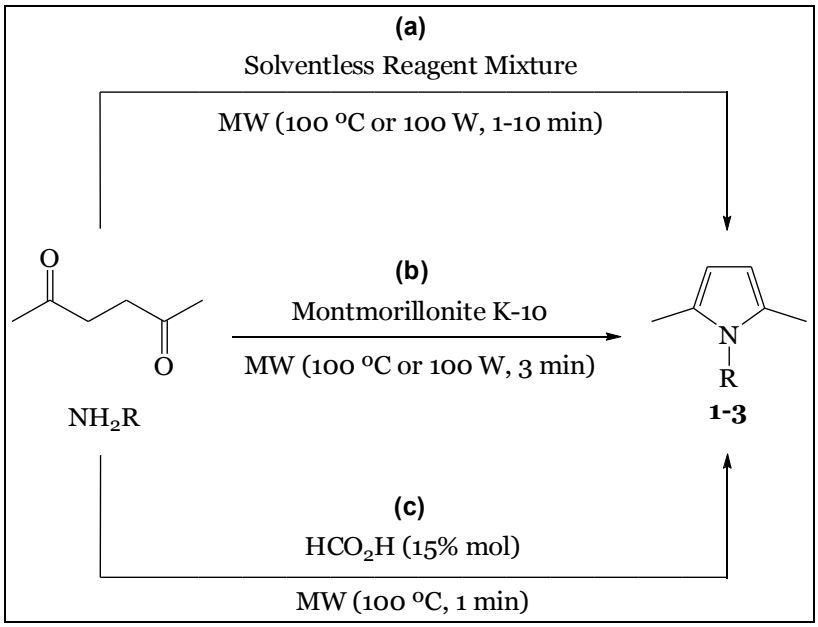
Table 2.1. Paal-Knorr synthesis of 2,5-dimethyl-1*H*-pyrroles **1-3** under microwave irradiation.

Entry	Compound	R	Time (min)	Yield[a] (%)
1	**1**	Ph	3	-[b, d]
2	**1**	Ph	10	35[b]
3	**1**	Ph	3	44[c]
4	**1**	Ph	5	47[c]
5	**2**	Bn	1	90[b]
6	**2**	Bn	1	95[c]
7	**3**	*n*-Bu	1	86[b]
8	**3**	*n*-Bu	1	93[c]
9	**1**	Ph	3	93[b, e]
10	**1**	Ph	3	-[c, e, g]
11	**1**	Ph	1	96[b, f]
12	**2**	Bn	1	97[b, f]
13	**3**	*n*-Bu	1	94[b, f]

All reactions were carried-out using the selected amine (10 mmol) and 2,6-hexanedione (10 mmol) in a closed vessel. [a]Yields refer to the isolated reaction products. [b]Constant temperature of 100 °C. [c]Constant microwave power of 100 W. [d]Only trace amounts of pyrrole **1** were detected by TLC analysis of the crude product mixture, along with the initial reagents. [e]Montmorillonite K-10 (5 g) was used as reaction medium. [f]Formic acid (1.5 mmol) was used as catalyst. [g]Only trace amounts of pyrrole **1** were detected by TLC analysis of the crude product mixture, along with several unidentified by-products.

A solid-supported strategy was then adapted, following part of the work reported by Abid and co-workers,[64] in an attempt to improve the reaction yield of 2,5-dimethyl-1-phenyl-1*H*-pyrrole **1**. Thus, a mixture of aniline and 2,6-hexanedione pre-adsorbed on the surface of montmorillonite K-10, a commercially available, inexpensive, non-corrosive, highly acidic and reusable solid catalyst,[65] was subjected to microwave irradiation for 3 minutes under closed-vessel conditions (Table 2.1, entries 9 and 10; Scheme 2.16b). While a 93% reaction yield was attained when a constant temperature of 100 ºC was applied (entry 9), after washing the crude product mixture with diethyl ether, removal of the inorganic solid support by filtration and chromatographic purification, irradiating the reaction system at a fixed power setting of 100 W proved to be deleterious, since TLC analysis of the crude product mixture revealed several unidentified by-products and only traces of the desired pyrrole (entry 10).

Another remarkably fast and effective alternative concerning the synthesis of this compound was found by adding a small amount of formic acid to the solvent-free reagent mixture referenced above, a 96% reaction yield being obtained after work-up (Table 2.1, entry 11; Scheme 2.16c). Zhu and colleagues used the same acid catalyst to prepare similar 2,5-dimethylpyrroles at room temperature;[66] however, reaction times of up to 6 hours were required to complete the synthetic process. Lastly, the same procedure was applied to the synthesis of 1-benzyl-2,5-dimethyl-1*H*-pyrrole **2** and 1-*n*-butyl-2,5-dimethyl-1*H*-pyrrole **3** with superior results (entries 12 and 13).[67]



Scheme 2.16. Paal-Knorr synthesis of 2,5-dimethyl-1*H*-pyrroles **1-3** under microwave irradiation.

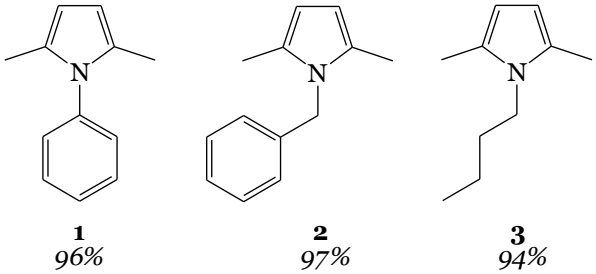


Figure 2.4. Structures and isolated yields of 2,5-dimethyl-1*H*-pyrroles **1-3** synthesised via a solventless, formic acid-catalysed, microwave-assisted, Paal-Knorr method.

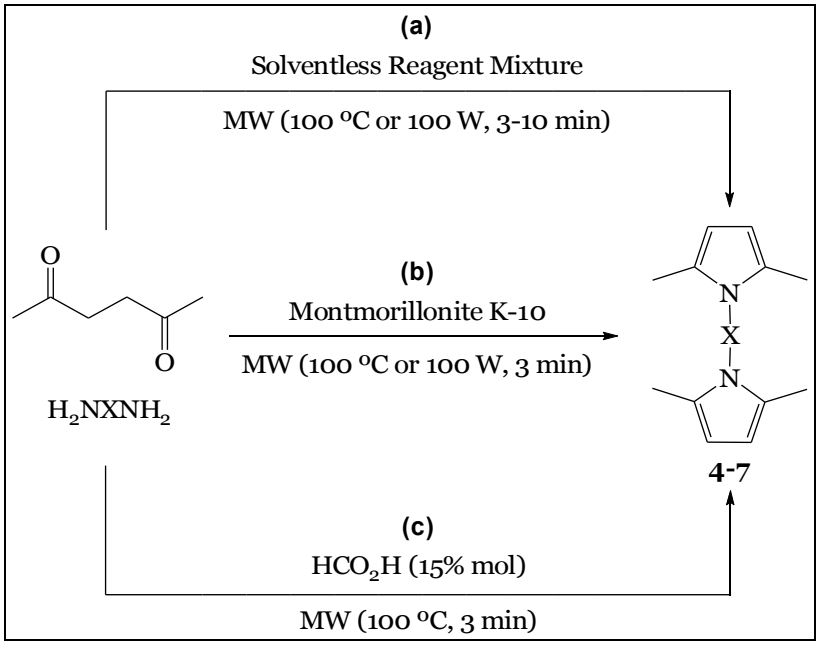
C. Paal-Knorr Synthesis of Bis-2,5-Dimethyl-1*H*-Pyrroles

The microwave-promoted methodologies described in the previous section were subsequently applied to the preparation of some bis-2,5-dimethyl-1*H*-pyrroles, which are far less investigated than their pyrrole analogues, starting from the selected diamine and a three-fold molar excess of 2,6-hexanedione, again, using either a constant reaction temperature of 100 ºC or a fixed microwave power setting of 100 W (Table 2.2; Scheme 2.17).

Table 2.2. Paal-Knorr synthesis of bis-2,5-dimethyl-1*H*-pyrroles **4-7** under microwave irradiation.

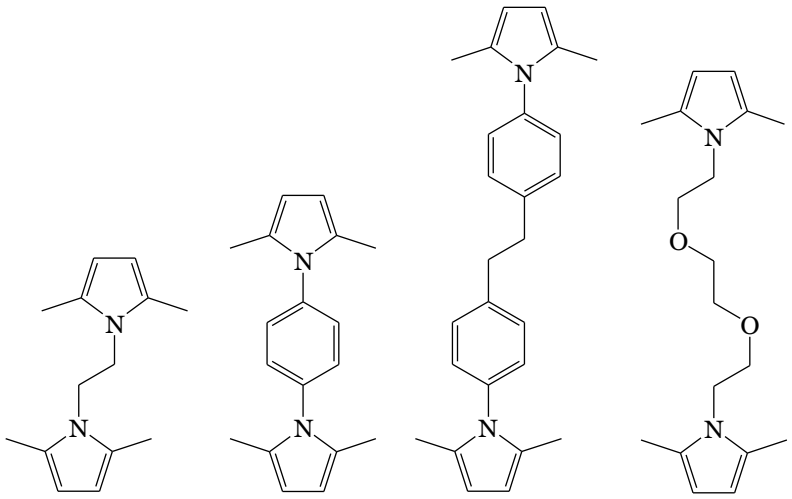
Entry	Compound	X	Time (min)	Yield[a] (%)
1	**4**	C_2H_4	3	82[b]
2	**4**	C_2H_4	3	92[c]
3	**5**	C_6H_4	3	80[b, d]
4	**5**	C_6H_4	10	93[c, d]
5	**5**	C_6H_4	3	85[b, e]
6	**5**	C_6H_4	3	92[c, e]
7	**6**	$C_6H_4C_2H_4C_6H_4$	3	90[b, e]
8	**6**	$C_6H_4C_2H_4C_6H_4$	3	94[c, e]
9	**4**	C_2H_4	3	95[b, f]
10	**5**	C_6H_4	3	92[b, f]
11	**6**	$C_6H_4C_2H_4C_6H_4$	3	96[b, f]
12	**7**	$C_2H_4OC_2H_4OC_2H_4$	3	90[b, f]

All reactions were carried-out using the selected diamine (10 mmol) and 2,6-hexanedione (30 mmol) in a closed vessel. [a]Yields refer to the isolated reaction products. [b]Constant temperature of 100 ºC. [c]Constant microwave power of 100 W. [d]GC-MS and NMR analyses confirmed that the reaction product obtained was in fact 1-aniline-2,5-dimethyl-1*H*-pyrrole. [e]Montmorillonite K-10 (5 g) was used as reaction medium. [f]Formic acid (1.5 mmol) was used as catalyst.



Scheme 2.17. Paal-Knorr synthesis of bis-2,5-dimethyl-1*H*-pyrroles **4-7** under microwave irradiation.

As can be seen from the data gathered in Table 2.2, all syntheses proceeded efficiently in very short reaction times, with the exception of entries 3 and 4, when 1,4-diaminobenzene was the nitrogen-containing reactant. In fact, structural characterisation of the final product demonstrated that the desired 1,4-bis(2,5-dimethyl-1*H*-pyrrol-1-yl)benzene **5** was not formed, 1-aniline-2,5-dimethyl-1*H*-pyrrole being obtained instead, even when irradiating at 100 W for 10 minutes, which resulted in temperature values as high as 192 ºC to be reached. Once more, when formic acid was employed as catalyst in the neat reagent mixture procedure, the desired bis-pyrrole was generated with a 92% isolated yield, after microwave heating at 100 ºC for 3 minutes (entry 10). Direct recrystallisation in methanol of the solid residue obtained from drying the diethyl ether solution of the crude product mixture with anhydrous sodium sulphate, filtration and evaporation of the solvent was the only work-up needed. Broadening this experimental procedure to other diamine starting materials rendered 1,2-bis(2,5-dimethyl-1*H*-pyrrol-1-yl)ethane **4**, 1,2-bis(4-(2,5-dimethyl-1*H*-pyrrol-1-yl)phenyl)ethane **6** and 1,2-bis(2-(2,5-dimethyl-1*H*-pyrrol-1-yl)ethoxy)ethane **7** with optimal reaction yields (entries 9, 11 and 12).[67]



4 *95%* **5** *92%* **6** *96%* **7** *90%*

Figure 2.5. Structures and isolated yields of bis-2,5-dimethyl-1*H*-pyrroles **4-7** synthesised via a solventless, formic acid-catalysed, microwave-assisted, Paal-Knorr method.

D. Multicomponent Synthesis of 3,5-Diaryl-2-Methyl-1*H*-Pyrroles

A multicomponent reaction (MCR) can be seen as a single chemical process in which three or more reagents, usually quite simple and readily available, are combined in such a way that the final product holds significant components of all of them. Thus, multicomponent reactions can lead to the connection of three or more starting materials with high bond-forming efficiency and atom economy, increasing structural complexity in an often experimentally straightforward way.[68] For this reason, MCRs have been perceived by the pharmaceutical and medicinal chemistry communities as a particularly suited approach for compound library synthesis, aimed at performing structure-activity relationship (SAR) studies of drug-like molecules.

As credited earlier, Ranu and co-workers have looked into this type of diversity-oriented methodologies to prepare highly substituted pyrrolic structures under microwave irradiation.[47, 48] Nevertheless, and in spite the reasonably fair reaction yields accomplished, the vast majority of the pyrrole substituents were linear or branched aliphatic groups, phenyl and 4-chlorophenyl being the only aromatic scaffolds reported. It was decided to extend this solid-supported strategy in order to prepare novel multisubstituted pyrroles bearing various aromatic groups at positions 3 and 5 of the pyrrolic unit. In our first studies, equimolar amounts of (*E*)-1,3-diphenylprop-2-en-1-one, commonly known as (*E*)-chalcone, benzylamine and a three-fold molar excess of nitroethane were pre-

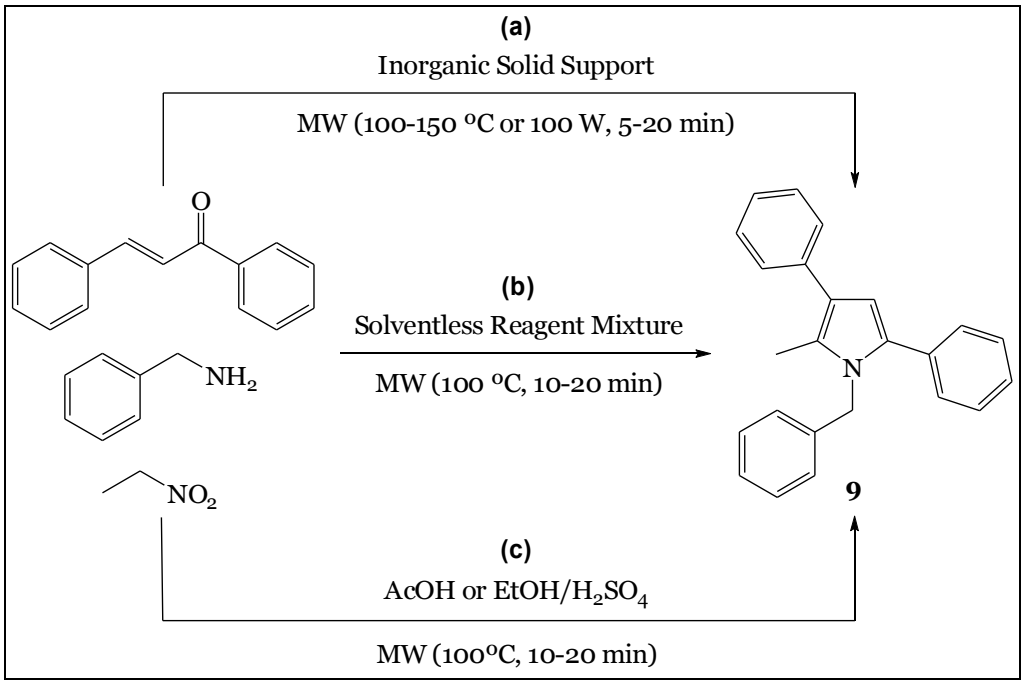
adsorbed on the surface of several inorganic solids and the resulting reaction mixtures were microwave-heated in sealed-vessel conditions; variation of some experimental parameters, such as reaction temperature and time or microwave power, was also assessed (Table 2.3, entries 1-9; Scheme 2.18a). The isolation protocol consisted in washing the crude product mixture with diethyl ether, followed by filtration of the inorganic solid support, SiO_2 flash column chromatography and recrystallisation in methanol, rendering 1-benzyl-2-methyl-3,5-diphenyl-1*H*-pyrrole **9** as a white solid. Sadly, the best result obtained was a 28% isolated yield, after heating at 100 ºC for 10 minutes and making use of SiO_2 60 (35-70 μm) as the solid support (entry 2). Increasing the reaction time to 20 minutes (entry 3) or performing the synthetic operation at 150 ºC (entry 4) did not improve the final outcome. When a constant microwave power of 100 W was applied (entry 5), temperature and pressure values of 180 ºC and 8 bar, respectively, were reached inside the reaction vessel and, besides numerous unidentified secondary products, only trace amounts of pyrrole **9** were observed by TLC analysis of the crude product mixture.

Table 2.3. Multicomponent synthesis of 1-benzyl-2-methyl-3,5-diphenyl-1*H*-pyrrole **9** under microwave irradiation.

Entry	Reaction Medium	Time (min)	Yield[a] (%)
1	SiO_2 60 (200-500 μm)[b]	10	19[d]
2	SiO_2 60 (35-70 μm)[b]	10	28[d]
3	SiO_2 60 (35-70 μm)[b]	20	27[d]
4	SiO_2 60 (35-70 μm)[b]	10	24[e]
5	SiO_2 60 (35-70 μm)[b]	5	-[f, g]
6	SiO_2 N (2-20 μm)[b]	10	23[d]
7	SiO_2 60/H_2SO_4 (35-70 μm)[b]	10	-[d, g]
8	Al_2O_3 (50-150 μm)[b]	10	25[d]
9	Montmorillonite K-10[b]	10	-[d, g]
10	Solventless	10	-[d, h]
11	Solventless	20	-[d, h]
12	AcOH[c]	10	-[d, h]
13	AcOH[c]	20	-[d, h]
14	EtOH/H_2SO_4[c]	10	-[d, h]
15	EtOH/H_2SO_4[c]	20	-[d, h]

All reactions were carried-out using (*E*)-1,3-diphenylprop-2-en-1-one (5 mmol), benzylamine (5 mmol) and nitroethane (15 mmol) in a closed vessel. [a]Yields refer to the isolated reaction products. [b]The selected solid support (8 g) was used as reaction medium. [c]The selected solvent (3 ml) was used as reaction medium. [d]Constant temperature of 100 ºC. [e]Constant temperature of 150 ºC. [f]Constant microwave power of 100 W. [g]Only trace amounts of pyrrole **9** were detected by TLC analysis of the crude product mixture, along with several unidentified by-products. [h]Only trace amounts of pyrrole **9** were detected by TLC analysis of the crude product mixture, along with the initial reagents.

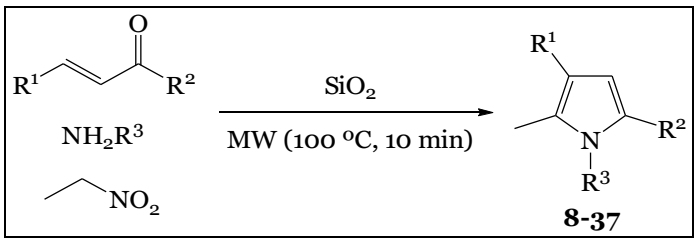
Although other silicon dioxide supports were tested (entries 1, 6 and 7), as well as aluminium oxide (entry 8) and montmorillonite K-10 (entry 9), the reaction yields were either lower or no product was isolated. Simplification of the procedure by eliminating the inorganic solid support, that is, carrying-out the reaction in solvent-free conditions (Scheme 2.18b), turned out to be even worse, since almost no pyrrole was formed (entries 10 and 11). The same phenomenon was observed upon application of a solvent-based approach (Scheme 2.18c), using glacial acetic acid (entries 12 and 13) or ethanol acidified with a few drops of concentrated sulphuric acid (entries 14 and 15).



Scheme 2.18. Multicomponent synthesis of 1-benzyl-2-methyl-3,5-diphenyl-1*H*-pyrrole **9** under microwave irradiation.

It should be stressed that our best result was less than half the one reported by Ranu for the same compound (65% yield), utilising an unmodified domestic microwave oven and silicon dioxide HF254 as the inorganic support, and quite similar to the one found by the same author when conventional heating conditions were employed, using THF/SiO_2 HF254 as the reaction medium (32% yield).[47, 48] We believe that the different microwave equipment used was not responsible for the discrepancies concerning the reaction yields achieved. On the other hand, the different characteristics of the SiO_2 employed as solid support could have hampered the reactivity of our microwave-mediated process, comparing to the one described by Ranu and co-workers.

Moreover, it was determined that there was no advantage in performing this three-component microwave-assisted methodology in closed reaction vials, given that an identical isolated yield of 28% was attained when open-vessel conditions were tested at the same reaction temperature and time. In fact, it became evident that the pressure build-up observed inside the sealed vessels during the synthetic process could sometimes be prejudicial, since small particles of the solid support were frequently released from the pressurised vial into the microwave apparatus, which can be seriously damaging to the equipment. Therefore, irradiation of the solid-supported reaction mixture utilising open glassware at atmospheric pressure averted this harmful situation, without altering the reaction yield. Other primary amines and chalcone materials were later employed as reagents, 3,5-diaryl-2-methyl-1*H*-pyrroles **8-37** being prepared (Scheme 2.19, Figure 2.6).



Scheme 2.19. Multicomponent synthesis of 3,5-diaryl-2-methyl-1*H*-pyrroles **8-37** under microwave irradiation.

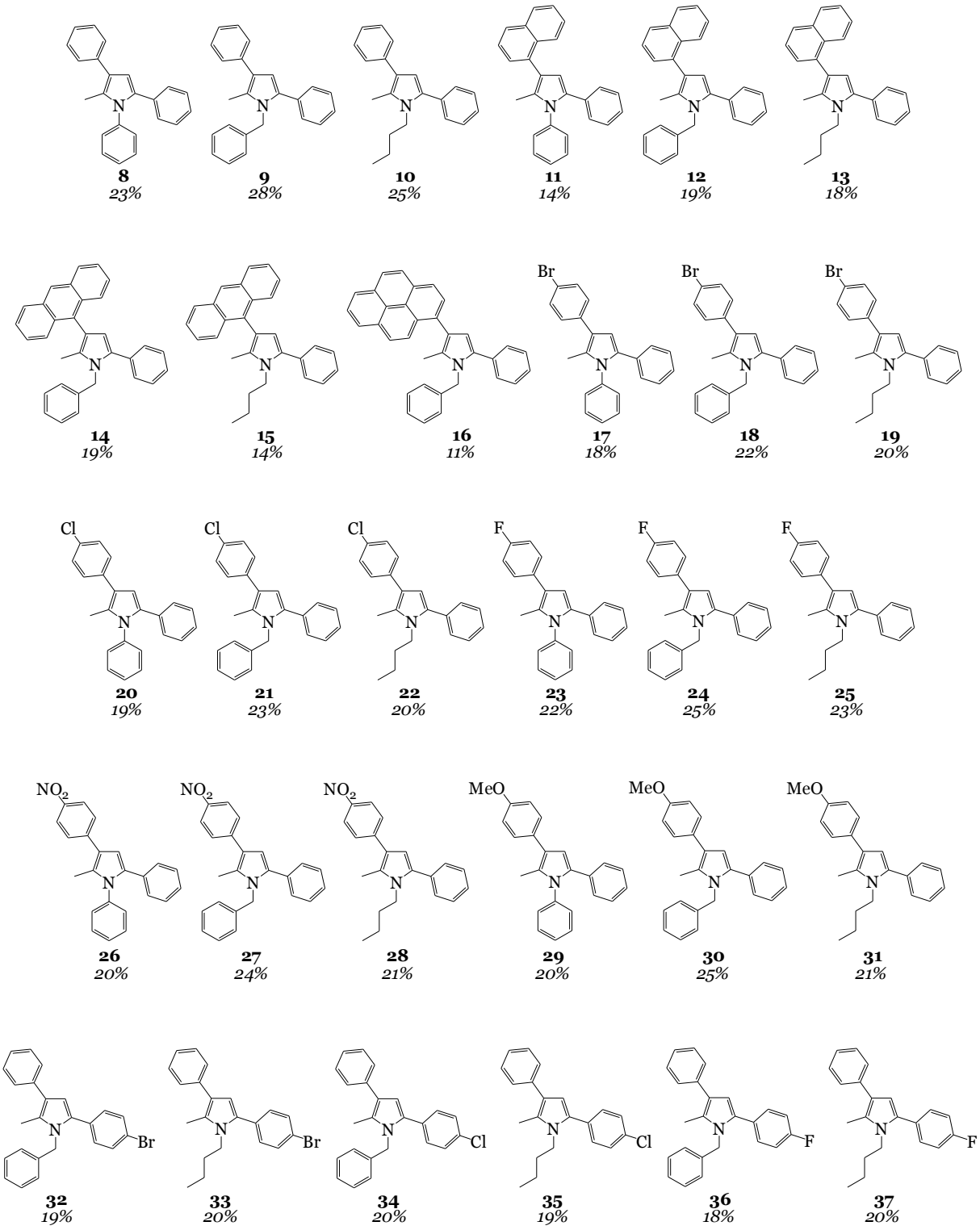
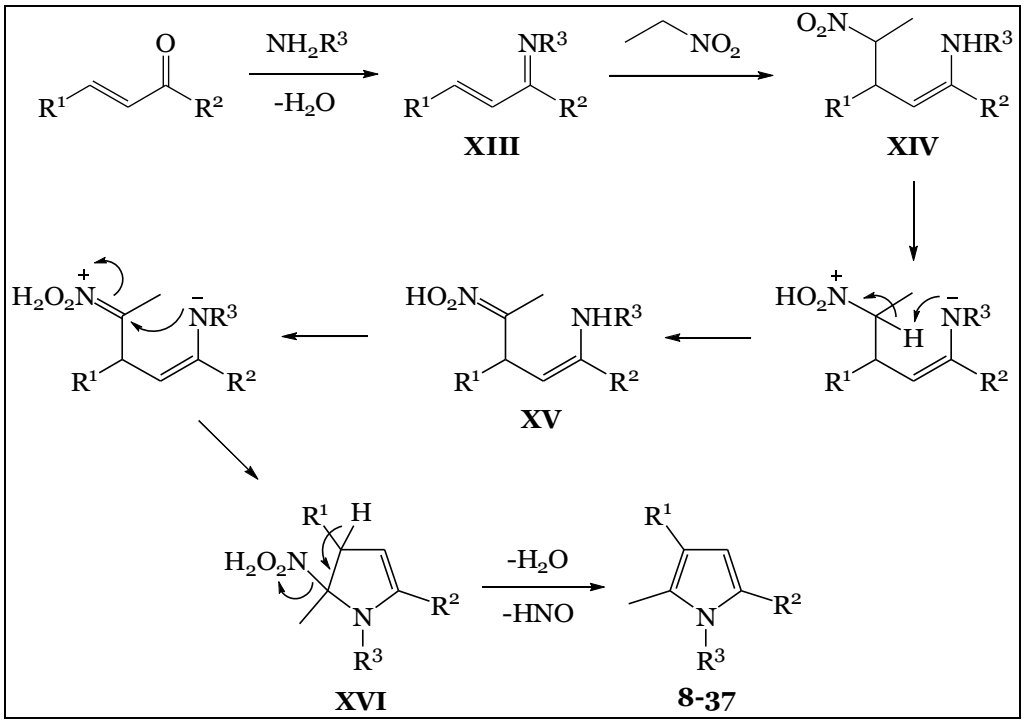


Figure 2.6. Structures and isolated yields of 3,5-diaryl-2-methyl-1*H*-pyrroles **8-37** synthesised via a solid-supported, multicomponent, microwave-assisted method.

A possible reaction pathway for the three-component preparation of the pyrrolic compounds depicted above is presented in Scheme 2.20, following the rationalisation proposed in the late 1990s by the Yshii research group regarding a related synthesis.[69, 70] Formation of an α,β-unsaturated imine **XIII** by condensation between the primary amine and the chalcone reagent is followed by coupling with nitroethane, generating an enamine intermediate **XIV**. Proton transfer leads to a related enamine structure **XV**, which in turn renders the pyrrole precursor **XVI** through intramolecular cyclisation. Finally, elimination of water and nitrosyl hydride by the latter affords the desired multisubstituted pyrrole.



Scheme 2.20. Mechanistic proposal for the multicomponent synthesis of 3,5-diaryl-2-methyl-1*H*-pyrroles **8-37**.

A few of these nitrogen-containing heterocycles, compounds **9**, **12**, **14** and **16**, were further investigated through a collaboration with the Photochemistry Group of the Coimbra Chemistry Centre of the University of Coimbra, some of their spectroscopic and photophysical properties being determined and compared to the ones of their simpler aromatic analogues, benzene, naphthalene, anthracene and pyrene.[71] The room temperature absorption and fluorescence emission spectra of the selected 3,5-diaryl-2-methyl-1*H*-pyrroles in methylcyclohexane solution, as well as of their aromatic counterparts, is portrayed in Figure 2.7.

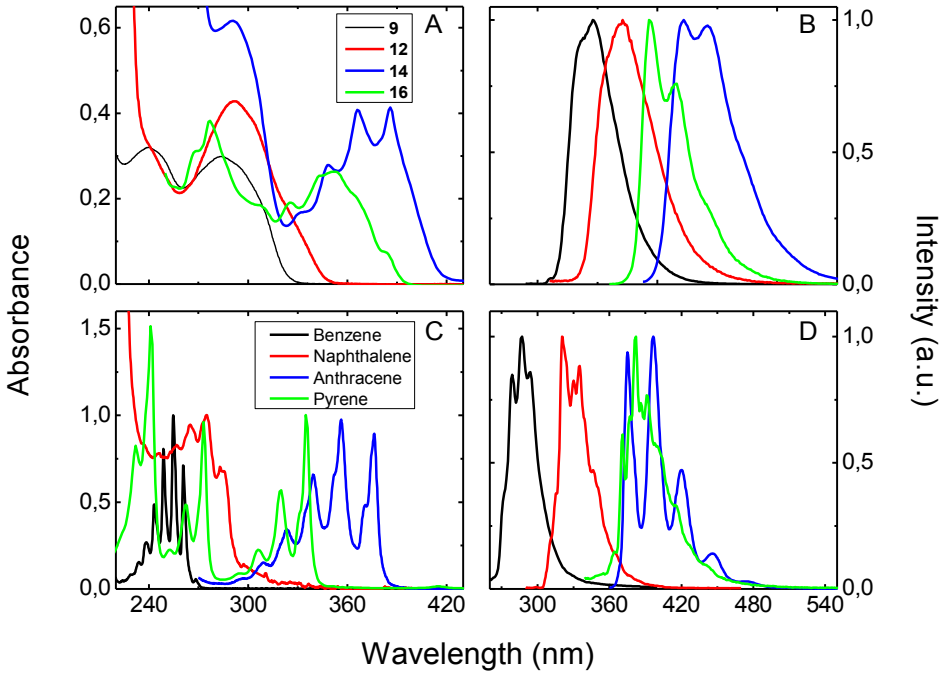


Figure 2.7. Normalised absorption (A and C) and fluorescence emission (B and D) spectra of 3,5-diaryl-2-methyl-1*H*-pyrroles **9**, **12**, **14** and **16**, as well as their aromatic counterparts, in methylcyclohexane at room temperature (293 K).

Methylcyclohexane was chosen as medium since it is a 'spectroscopically clean' solvent, i.e. absence of cut-off up to around 220 nm, and also exhibits superior glass-type media properties for low-temperature measurements. A significant decrease in vibrational structure, along with a very broad wavelength red-shift, particularly in the fluorescence emission spectra, was observed for all pyrrolic molecules under study, comparing to their aromatic analogues. The phosphorescence emission spectra of the 3,5-diaryl-2-methyl-1*H*-pyrroles were obtained in methylcyclohexane glasses at 77 K (Figure 2.8), with the exception of 3-(anthracen-9-yl)-1-benzyl-2-methyl-5-phenyl-1*H*-pyrrole **14**, given that the experimental set-up utilised in this work was unable to detect any signal. However, phosphorescence has been previously reported for anthracene in ether-pentane-alcohol glasses at the same temperature.[72, 73] As somewhat expected, it was ascertained that the phosphorescence emission spectra of compounds **9**, **12** and **16** closely resembled that of benzene, naphthalene and pyrene, respectively.[73] The relevant spectroscopic data of the investigated multisubstituted pyrroles, including absorption, fluorescence and phosphorescence emission and triplet absorption wavelength maxima, singlet and triplet molar extinction coefficients, is summed-up in Table 2.4.

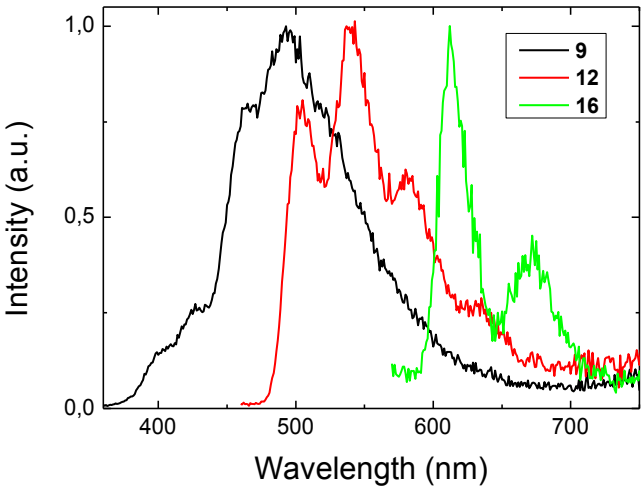


Figure 2.8. Normalised phosphorescence emission spectra of 3,5-diaryl-2-methyl-1*H*-pyrroles **9**, **12** and **16** in methylcyclohexane at 77 K.

Table 2.4. Relevant spectroscopic properties of 3,5-diaryl-2-methyl-1*H*-pyrroles **9**, **12**, **14** and **16** in methylcyclohexane at room temperature (293 K).

Entry	Compound	λ_{max} (nm)	ε_S (M^{-1} cm^{-1})	λ_{max}^F (nm)	λ_{max}^P (nm)	λ_{max}^{T1-Tn} (nm)	ε_T (M^{-1} cm^{-1})
1	**9**	239, 284	10990	347	493	370	14800
2	**12**	291	16480	371	503, 539, 581	360	18700
3	**14**	290, 348, 366, 385	7000	422, 441	-[a]	430	10400
4	**16**	277, 325, 352	23600	393, 415	612, 672	430	12300

[a]The experimental set-up used in this study was unable to detect any phosphorescence signal.

A series of photophysical properties of the selected 3,5-diaryl-2-methyl-1*H*-pyrroles, namely fluorescence, phosphorescence, internal conversion, triplet formation and singlet oxygen formation quantum yields, Φ_F, Φ_P, Φ_{IC}, Φ_T and Φ_Δ, respectively, are presented in Table 2.5. The radiationless phenomena, i.e. internal conversion and inter-system crossing (Φ_{IC} + Φ_T), constituted the main excited state deactivation pathway for the investigated molecules, with the exception of compound **12**, where a similar contribution was found between the radiative (Φ_F)

and radiationless ($\Phi_{IC} + \Phi_T$) excited state deactivation processes. Singlet oxygen formation quantum yields were acquired following photolysis of aerated methylcyclohexane solutions of the pyrrolic structures, the Φ_Δ values being in agreement with the ones obtained for Φ_T within the experimental error.

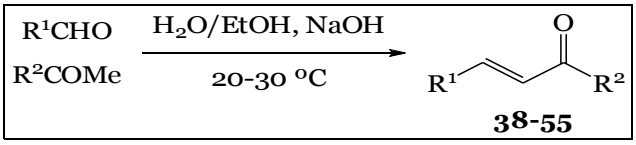
Table 2.5. Relevant photophysical properties of 3,5-diaryl-2-methyl-1*H*-pyrroles **9**, **12**, **14** and **16,** as well as their aromatic counterparts, in methylcyclohexane at room temperature (293 K) or 77 K.

Entry	Compound	Φ_F (293 K)	Φ_{IC} (293 K)	Φ_P (77 K)	Φ_T (293 K)	Φ_Δ (293 K)
1	**9**	0.29	0.50	0.021	0.21	0.22
2	Benzene[a]	0.06		0.150	0.25	
3	**12**	0.52	0.15	0.012	0.33	0.32
4	Naphthalene[a]	0.19		0.033	0.75	
5	**14**	0.34	0.32	-[b]	0.34	0.20
6	Anthracene[a]	0.30		0.0003[c]	0.71	
7	**16**	0.40	0.38	0.0010	0.22	0.24
8	Pyrene[a]	0.65		0.0021	0.37	

[a]Data obtained in non polar solvents.[73] [b]The experimental set-up used in this study was unable to detect any phosphorescence signal. [c]Data obtained in ether-pentane-alcohol glasses at 77 K.[72, 73]

It must be mentioned that, in addition to the spectroscopic and photophysical properties summarised in Tables 2.4 and 2.5, fluorescence decays and transient triplet-triplet absorption spectra of compounds **9**, **12**, **14** and **16**, as well as their fluorescence, phosphorescence and triplet lifetimes, were also determined in methylcyclohexane. Moreover, related spectral and photophysical studies in more polar solvents are currently being undertaken and the results are to be reported elsewhere in due time.[71]

The chalcone derivatives necessary for the synthesis of the pyrrole library were previously prepared through the Claisen-Schmidt procedure described by Kohler and Chadwell.[74] Briefly, a solution containing equimolar amounts of the selected aldehyde and the appropriate acetophenone and a slight excess of sodium hydroxide in distilled water/ethanol (1:1 v/v) was vigorously stirred, at a temperature between 20 and 30 ºC, until a solid precipitated. It should be emphasised that lower temperatures make the reaction sluggish and unwanted by-products usually start forming above 30 ºC. After filtration, washing with distilled water and recrystallisation in aqueous ethanol, 1,3-diarylprop-2-en-ones **38-55** were effortlessly obtained with very good yields (Scheme 2.21, Figure 2.7). In the case of pyrrolyl-chalcone **53**, the required pyrrole precursor **56** was synthesised beforehand, by reacting phosphorous oxychloride, *N*,*N*-dimethylacetamide and pyrrole at room temperature, following a previously published procedure.[75] After stirring overnight, the crude product mixture was subjected to neutralisation, liquid/liquid extraction, silica gel flash column chromatography and recrystallisation, the sought 2-acetyl-1*H*-pyrrole being obtained as a pale-yellow solid with a 70% isolated yield (Scheme 2.22).



Scheme 2.21. Base-catalysed Claisen-Schmidt synthesis of chalcones **38-55**.

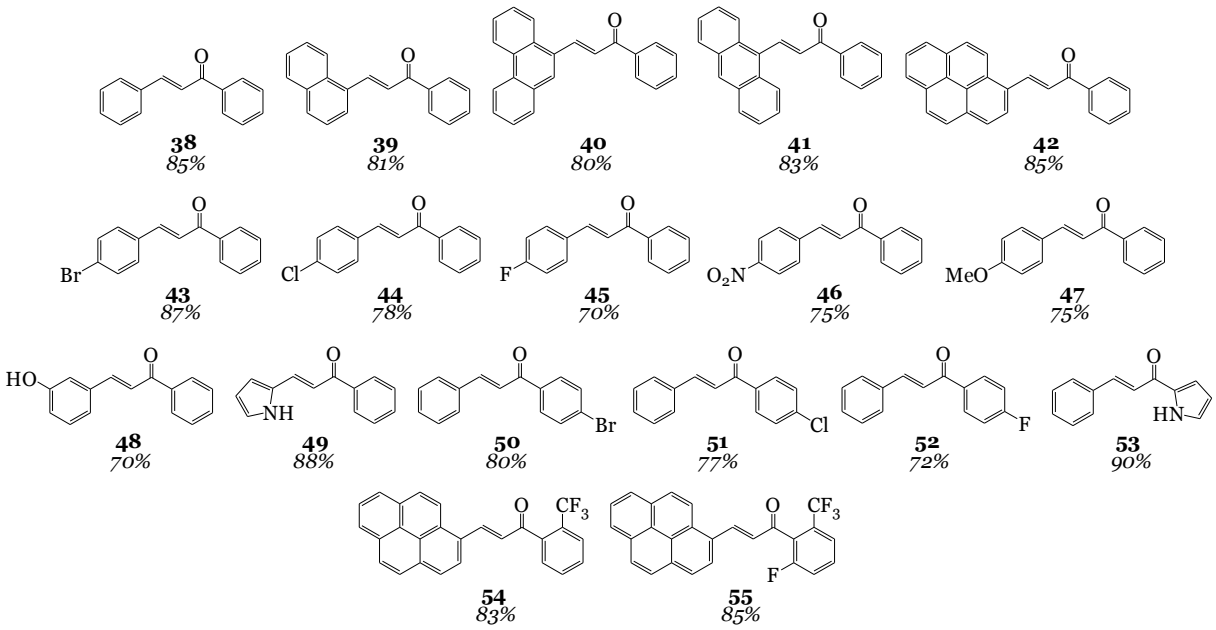
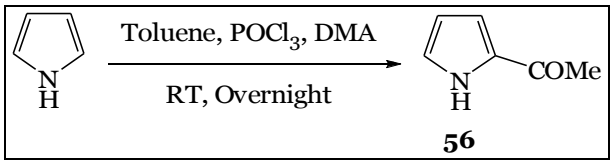


Figure 2.9. Structures and isolated yields of chalcones **38-55** synthesised via a base-catalysed Claisen-Schmidt condensation method.



Scheme 2.22. Regioselective Vilsmeier-Haack acetylation of pyrrole.

As expected, only the more stable (*E*)-isomeric form of the chalcones was formed. This was easily assessed by analysis of their ^{1}H NMR spectra, given that the coupling constants of the doublets corresponding to the hydrogen atoms of the carbon-carbon double bond were in the 15-16 Hz range, which is typical of the *trans* arrangement. Apart from being excellent starting materials for organic synthesis, as shown here for the preparation of highly substituted pyrrolic compounds, chalcone and chalcone-based molecules are widely recognised for their various biological activities, such as antibacterial,[76, 77] antifungal,[76, 78] anti-inflammatory,[76] antiviral[76] and antitumour,[79-81] and have also been reported to show interesting photophysical properties, being used as light-emitting diodes and fluorescent dyes and sensors.[82, 83]

IV. Summary

Both 2,5-dimethyl-1*H*-pyrroles **1-3** and bis-2,5-dimethyl-1*H*-pyrroles **4-7** were effortlessly synthesised via a solvent-free, microwave-mediated, Paal-Knorr protocol, utilising a small amount of formic acid as catalyst. The isolated yields ranged from 90 to 97% while the reaction times did not exceed 3 minutes. A small compound library of thirty structurally-diverse pyrroles **8-37**, incorporating both electron-donating and electron-withdrawing moieties, was also prepared under microwave irradiation using a solid-supported and multicomponent strategy, although with low reaction yields. Four of these interesting multisubstituted heterocycles, **9**, **12**, **14** and **16**, were selected and further studied, some of their spectroscopic and photophysical properties being determined. The different chalcone precursors required for the synthesis of the 3,5-diaryl-2-methyl-1*H*-pyrroles, as well as some others that were later employed in the preparation of other heterocyclic structures (see Chapter 5), were easily synthesised with very good yields (**38-55**, 70-90%) through a classical, base-catalysed, Claisen-Schmidt condensation reaction.

V. References

1. AF Pozharskii, A Soldatenkov, AR Katritzky, *Heterocycles in Life and Society: an Introduction to Heterocyclic Chemistry, Biochemistry and Applications*, Second Edition, Wiley, Chichester, England, UK, 2011.

2. JA Joule, K Mills, *Heterocyclic Chemistry*, Fifth Edition, Wiley, Chichester, England, UK, 2011.

3. T Eicher, S Hauptmann, *The Chemistry of Heterocycles: Structure, Reactions, Syntheses and Applications*, Second Edition, Wiley-VCH, Weinheim, Germany, 2003.

4. DP O'Malley, K Li, M Maue, AL Zografos, PS Baran, *J. Am. Chem. Soc.* 129 (**2007**) 4762-4775.

5. CC Hughes, A Prieto-Davo, PR Jensen, W Fenical, *Org. Lett.* 10 (**2008**) 629-631.

6. DL Boger, CW Boyce, MA Labroli, CA Sehon, Q Jin, *J. Am. Chem. Soc.* 121 (**1999**) 54-62.

7. NR Williamson, HT Simonsen, RA Ahmed, G Goldet, H Slater, L Woodley, FJ Leeper, GP Salmond, *Mol. Microbiol.* 56 (**2005**) 971-989.

8. JL Seganish, TJ Davis, *Chem. Commun.* (**2005**) 5781-5783.

9. C Avendaño, JC Menéndez, *Medicinal Chemistry of Anticancer Drugs*, Elsevier, Oxford, England, UK, 2008, Chapter 6, pp 177-198.

10. M Biava, GC Porretta, D Deidda, R Pompei, A Tafic, F Manettic, *Bioorg. Med. Chem.* 12 (**2004**) 1453-1458.

11. M Protopopova, E Bogatcheva, B Nikonenko, S Hundert, L Einck, CA Nacy, *Med. Chem.* 3 (**2007**) 301-316.

12. C Teixeira, F Barbault, J Rebehmed, K Liu, L Xie, H Lu, S Jiang, B Fan, F Maurel, *Bioorg. Med. Chem.* 16 (**2008**) 3039-3048.

13. N Cardoe, CE Steele, *Curr. Med. Res. Opin.* 4 (**1976-1977**) 688-694.

15. G Stacher, P Bauer, I Ehn, E Schreiber, *Int. J. Clin. Pharmacol. Biopharm.* 17 (**1979**) 250-255.

14. J Davies, AS Dixon, CE Steele, *Curr. Med. Res. Opin.* 7 (**1980**) 115-120.

16. A Calin, *J. Clin. Pharmacol.* 23 (**1983**) 301-308.

17. AD Marais, JC Firth, ME Bateman, P Byrnes, C Martens, J Mountney, *Arterioscler. Thromb. Vasc. Biol.* 17 (**1997**) 1527-1531.

18. BW McCrindle, L Ose, AD Marais, *J. Pediatr.* 143 (**2003**) 74-80.

19. HM Colhoun, DJ Betteridge, PN Durrington, GA Hitman, HA Neil, SJ Livingstone, MJ Thomason, MI Mackness, V Charlton-Menys, JH Fuller, Lancet, 364 (**2004**) 685-696.

20. SE Nissen, SJ Nicholls, I Sipahi, P Libby, JS Raichlen, CM Ballantyne, J Davignon, R Erbel, JC Fruchart, JC Tardif, P Schoenhagen, T Crowe, V Cain, K Wolski, M Goormastic, EM Tuzcu, *J. Am. Med. Assoc.* 295 (**2006**) 1556-1565.

21. C Sessa, O Pagani, MG Zurlo, J de Jong, C Hofmann, M Lassus, P Marrari, M Strolin Benedetti, F Cavalli, *Ann. Oncol.* 5 (**1994**) 901-907.

22. M Beran, S Jeha, S O'Brien, E Estey, L Vitek, MG Zurlo, MB Rios, M Keating, H Kantarjian, *Clin. Cancer Res.* 3 (**1997**) 2377-2384.

23. GR Weiss, I Poggesi, M Rocchetti, D DeMaria, T Mooneyham, D Reilly, LV Vitek, F Whaley, E Patricia, DD von Hoff, P O'Dwyer, *Clin. Cancer Res.* 4 (**1998***)* 53-59.

24. KI Lazerges, S Chane-Ching, S Aeiyach, S Chelli, B Peppin-Donnat, M Billon, L Lombard, F Maurel, M Jouini, *J. Solid State Electrochem.* 13 (**2009**) 231-238.

25. A Kros, SWFM van Hövel, RJM Nolte, NAJM Sommerdijk, *Sens. Actuators B* 80 (**2001**) 229-233.

26. S Hamilton, MJ Hepher, J Sommerville, *Sens. Actuators B* 107 (**2005**) 424-432.

27. A Loudet, K Burgess, *Chem. Rev.* 107 (**2007**) 4891-4932.

28. PW LeQuesne, Y Dong, TA Blythe, in *The Alkaloids: Chemical and Biological Perspectives*, SW Pelletier (Ed), Pergamon Press, New York, NY, USA, 1999, Volume 13, Chapter 3, pp 237-288.

29. VF Ferreira, MCBV de Souza, AC Cunha, LOR Pereira, MLG Ferreira, *Org. Prep. Proced. Int.* 33 (**2001**) 411-454.

30. C Schmuck, D Rupprecht, *Synthesis* (**2007**) 3095-3110.

31. V Estévez, M Villacampa, JC Menéndez, *Chem. Soc. Rev.* 39 (**2010**) 4402-4421.
32. C Paal, *Chem. Ber.* 17 (**1884**) 2756-2767.
33. L Knorr, *Chem. Ber.* 17 (**1884**) 2863-2870.
34. V Amarnath, DC Anthony, K Amarnath, WM Valentine, LA Wetterau, DG Graham, *J. Org. Chem.* 56 (**1991**) 6924-6931.
35. V Amarnath, K Amarnath, *J. Org. Chem.* 60 (**1995**) 301-307.
36. E Fabiano, BT Golding, *J. Chem. Soc. Perkin Trans. 1* (**1991**) 3371-3375.
37. L Knorr, *Chem. Ber.* 17 (**1884**) 1635-1642.
38. L Knorr, *Liebigs Ann. Chem.* 236 (**1886**) 290-332.
39. L Knorr, H Lange, *Chem. Ber.* 35 (**1902**) 2998-3008.
40. A Hantzsch, *Chem. Ber.* 23 (**1890**) 1474-1476.
41. F Feist, *Chem. Ber.* 35 (**1902**) 1537-1544.
42. M Rodriquez, M Taddei, *Top. Heteroc. Chem.* 1 (**2006**) 213-266.
43. E Suna, I Mutule, *Top. Curr. Chem.* 266 (**2006**) 49-101.
44. B Oussaid, B Garrigues, M Soufiaoui, *Can. J. Chem. 72 (***1994**) 2483-2485.
45. P Ruault, JF Pilard, B Touaux, F Texier-Boullet, J Hamelin, *Synlett* (**1994**) 935-936.
46. TN Danks, *Tetrahedron Lett.* 40 (**1999**) 3957-3960.
47. BC Ranu, A Jajra, U Jana, *Synlett* (**2000**) 75-76.
48. BC Ranu, A Hajra, *Tetrahedron* 57 (**2001**) 4767-4773.
49. HSP Rao, S Jothilingam, *Tetrahedron Lett.* 42 (**2001**) 6595-6597.
50. HSP Rao, S Jothilingam, HW Sheeren, *Tetrahedron* 42 (**2004**) 6595-6597.
51. G Minetto, LF Raveglia, M Taddei, *Org. Lett.* 6 (**2004**) 389-392.
52. M Alongi, G Minetto, M Taddei, *Tetrahedron Lett.* 46 (**2005**) 7069-7072.
53. G Minetto, LF Raveglia, A Sega, M Taddei, *Eur. J. Org. Chem.* (**2005**) 5277-5288.
54. I Bianchi, R Forlani, G Minetto, I Peretto, N Regalia, M Taddei, LF Raveglia, *J. Comb. Chem.* 8 (**2006**) 491-499.
55. D Tejedor, D González-Cruz, F García-Tellado, JJ Marrero-Tellado, ML Rodríguez, *J. Am. Chem. Soc.* 126 (**2004**) 8390-8391.
56. I Bergner, T Opatz, *J. Org. Chem.* 72 (**2007**) 7083-7090.
57. F Aydogan, AS Demir, *Tetrahedron* 61 (**2005**) 3019-3023.
58. F Aydogan, M Basarir, C Yolacana, AS Demir, *Tetrahedron* 63 (**2007**) 9746-9750.
59. BC Milgram, K Eskildsen, SM Richter, WR Scheidt, KA Scheidt, *J. Org. Chem.* 72 (**2007**) 3941-3944.
60. P Wyrebek, A Sniady, N Bewick, Y Li, A Mikus, KA. Wheeler, R Dembinski, *Tetrahedron* 65 (**2009**) 1268-1275.
61. I Deb, D Seidel, *Tetrahedron Lett.* 51 (**2010**) 2945-2947.
62. HM Meshram, BRV Prasad, DA Kumar, *Tetrahedron Lett.* 51 (**2010**) 3477-3480.
63. R Spina, E Colacino, B Gabriele, G Salerno, J Martinez, F Lamaty, *Synlett* 23 (**2012**) 1481-1484.
64. M Abid, A Spaeth, B Török, *Adv. Synth. Catal.* 348 (**2006**) 2191-2196.
65. M Balogh, P László, Organic Chemistry Using Clays, Springer-Verlag, Berlin, Germany, 1993.
66. X-H Zhu, G Chen, Z-L Xu, Y-Q Wan, *Chin. J. Org. Chem.* 28 (**2008**) 115-119.
67. BFO Nascimento, AMd'A Rocha Gonsalves, M Pineiro, *J. Heteroc. Chem.* (**2013**) [manuscript submitted for publication].
68. *Multicomponent Reactions*, J Zhu, H Bienaymé (Eds), Wiley-VCH, Weinheim, Germany, 2005.
69. H Shiraishi, T Nishitani, T Nishihara, S Sakaguchi, Y Ishii, *Tetrahedron* 55 (**1999**) 13957-13964.
70. H Shiraishi, T Nishitani, S Sakaguchi, Y Ishii, *J. Org. Chem.* 63 (**1998**) 6234-6238.
71. D Pinheiro, BFO Nascimento, J Pina, M Pineiro, JS Seixas de Melo, *J. Phys. Chem. A* (**2013**) [manuscript in preparation/to be submitted for publication].

72. G Heinrich, H Güsten, *Z. Phys. Chem.* 118 (**1979**) 31-41.

73. M Montalti, A Credi, L Prodi, MT Gandolfi, *Handbook of Photochemistry*, Third Edition, CRC Press, Boca Raton, FL, USA, 2006.

74. EP Kohler, HM Chadwell, *Org. Synth. Coll. Vol. 1* (**1941**) 78.

75. DO Alonso Garrido, G Buldain, B Frydman, *J. Org. Chem.* 49 (**1984**) 2619-2622.

76. Z Nowakowska, *Eur. J. Med. Chem.* 42 (**2007**) 125-137.

77. SF Nielsen,T Boesen, M Larsen, K Schønning, H Kromann, *Bioorg. Med. Chem.* 12 (**2004**) 3047-3054.

78. D Batovska, S Parushev, A Slavova, V Bankova, I Tsvetkova, M Ninova, H Najdenski, *Eur. J. Med. Chem.* 42 (**2007**) 87-92.

79. A-M Katsori, D Hadjipavlou-Litina, *Curr. Med. Chem.* 16 (**2009**) 1062-1081.

80. A Boumendjel, X Ronot, J Boutonnat, *Curr. Drug Targets* 10 (**2009**) 363-371.

81. ML Go, X Wu, XL Liu, *Curr. Med. Chem.* 12 (**2005**) 483-499.

82. Y Wei, G Qin, W Wang, W Bian, S Shuang, C Dong, *J. Lumin.* 131 (**2011**) 1672-1676.

83. TA Fayed, MK Awad, *Chem. Phys.* 303 (**2004**) 317-326.

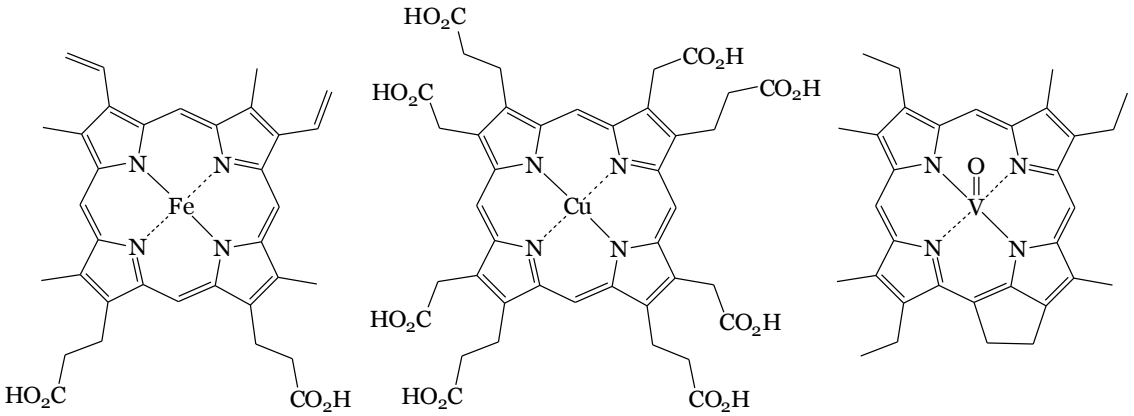
3

Porphyrins & Hydroporphyrins

I. Introduction & Relevance

Tetrapyrrolic macrocycles, as their name suggests, are cyclic conjugated molecules containing four pyrrole-type units, which can be linked together directly or through different sorts of atoms and bonds. The most important class of these compounds is that of porphyrins. Non-porphyrinic macrocycles can be divided into three main groups: contracted, isomeric and expanded.[1] Contracted macrocycles, although arranged in a conjugated fashion, display an inferior number of carbon atoms comparing to the skeletal core of porphyrins, corroles being one of the most studied examples. Structural variations of porphyrin possessing the same molecular formula are titled isomeric macrocycles, e.g. *N*-inverted porphyrins, porphycenes and corphycenes. Conjugated systems whose cycle is built by 24 atoms or more, such as texaphyrins, vinylogous porphyrins, porphocyanines and saphyrins, are designated by expanded macrocycles.

In spite of being a large family of compounds, tetrapyrrolic macrocyclic structures found in nature are exclusively of the porphyrin, hydroporphyrin and corrole types and are, nearly always, metal complexes. Among the naturally-occurring porphyrins one can emphasise: haem B, the iron(II) complex of protoporphyrin IX, which constitutes the prosthetic group of haemoglobin and mioglobine, biologically important proteins responsible for the transport and storage of oxygen in many living beings; the corresponding iron(III) complex present in cytochromes P450 and *c*, essential enzymes in oxidation/reduction processes involving the transfer of electrons and oxygen atoms;[2] the copper(II) complex of uroporphyrin III, produced through bio-oxidation of uroporphyrinogen and usually found in urine in small amounts; various geoporphyrins, specially metallic complexes of nickel and vanadium, most likely resultant from degradation of haem and chlorophyll and often present in crude oil and bituminous sands (Figure 3.1).[3, 4]



Haem B | Cu(II) Uroporphyrin III | V(IV) Phytoporphyrin Derivative

Figure 3.1. Representative examples of natural porphyrin compounds.

Hydroporphyrins that play fundamental roles concerning the development and maintenance of living organisms are also abundant. Some relevant examples of naturally-occurring chlorins are portrayed in Figure 3.2: chlorophylls *a* and *b*, crucial photosynthetic pigments found in plants, algae and cyanobacteria;[5] factor I, obtained from various vitamin B_{12}-producing bacteria; haem D, the prosthetic group present in cytochrome *d*, typical of the respiratory chain of several bacterial systems.[3] Amongst the natural bacteriochlorins, one can underline the relevant photosynthetic dyes found in diverse cyanobacteria, bacteriochlorophylls *a* and *b*.[5]

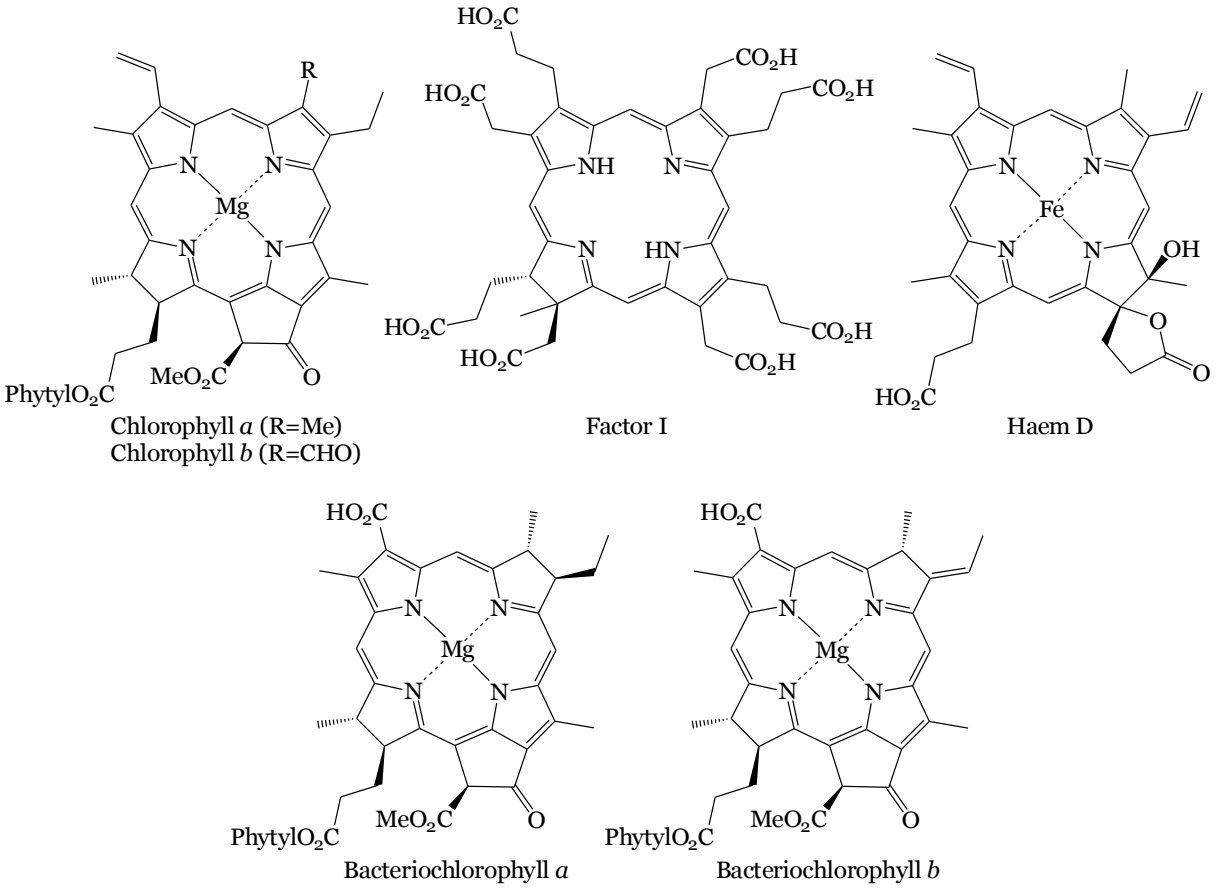


Figure 3.2. Representative examples of natural hydroporphyrin compounds.

The acknowledgement that porphyrin compounds were indispensable in a diversified ensemble of essential functionalities in nature triggered an increasing interest in multiple domains of the scientific community, from the better comprehension of those functions to the investigation of potential applications based on the very same natural phenomena. The role played by chlorophylls at the photosynthetic centres, where solar energy is converted to chemical energy, gave rise to the study of porphyrin systems in areas such as dye-sensitised solar cells,[6] molecular electronics and non-linear optics.[7-10] Mimicking the transport process of molecular oxygen and carbon dioxide within living cells inspired the use of this type of structures as sensors of small organic molecules, e.g. O_2, NO, CO_2 and NH_3,[11] as well as other targets, like amines, thiols and phosphines[7] and, generically, in molecular recognition mechanisms.[12-14] The reduction of molecular oxygen by cytochrome P450 led to the synthesis and application of a myriad of compounds as effective catalysts in a variety of oxidation reactions.[2, 15-17]

Other extremely relevant utilisations of porphyrins and hydroporphyrins are related to their enormous and inherent capabilities as photosensitisers in the activation of reactive oxygen species (ROS). These macrocyclic tetrapyrroles can be used to generate singlet oxygen and hydroxyl radicals, illustrious intermediaries in the oxidation of several substrates, from the simplest olefin to complex biological polymers, including cellular components.[18, 19] As molecular oxygen sensitising species, synthetic porphyrin derivatives have already been profoundly studied in photo-oxidation reactions,[18-21] as photoherbicides and photoinsecticides[22] and in various fields of medicine. The importance and utility of these compounds as therapeutic agents, for instance, in photodynamic therapy of cancer (PDT)[23-26] and photodynamic inactivation of viruses (PDV),[27-30] has also been undoubtedly demonstrated. Selected examples of porphyrin and hydroporphyrin sensitisers for photodynamic therapy purposes, either approved or in advanced clinical trials, are summarised in Figure 3.3.

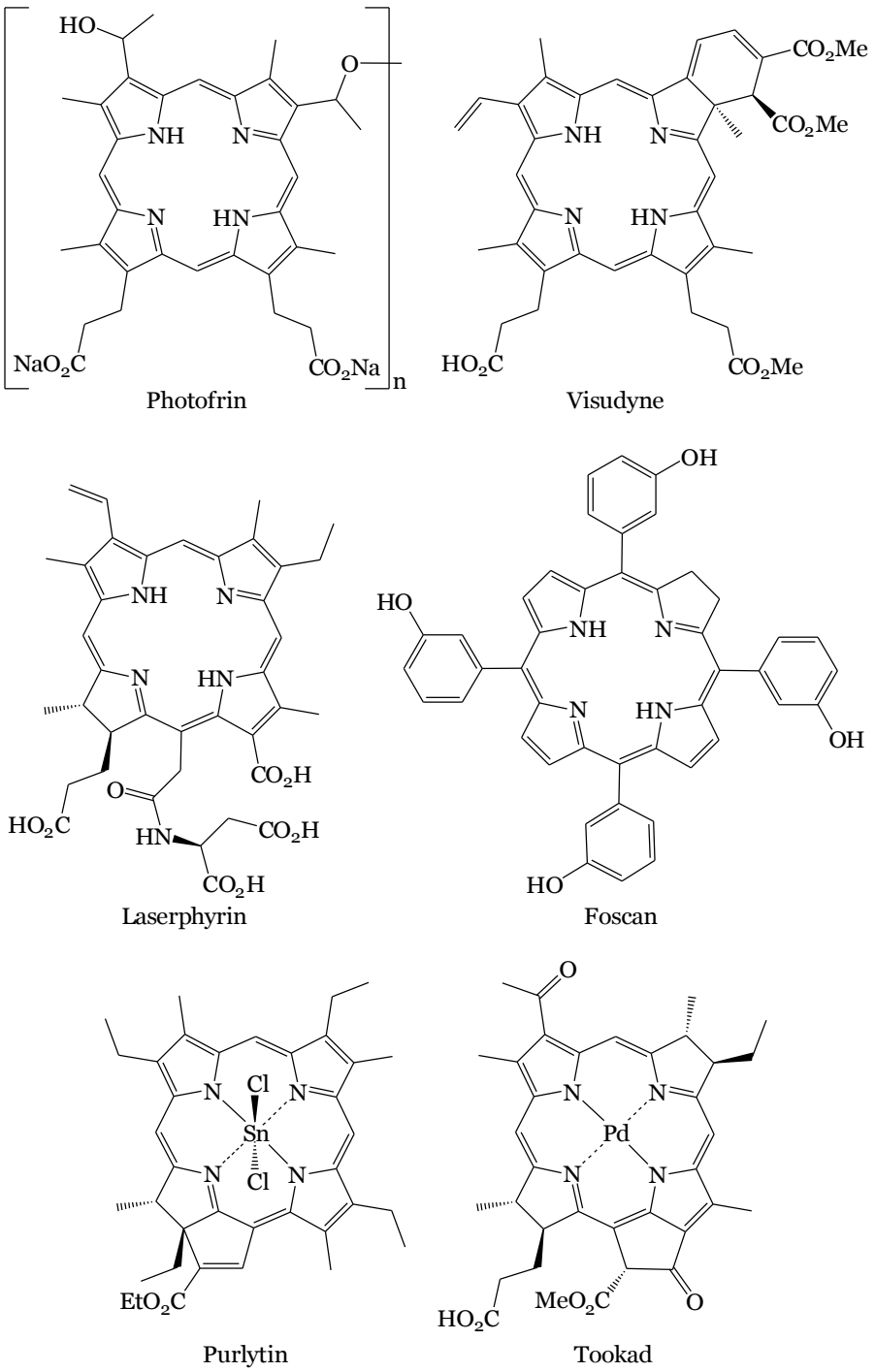


Figure 3.3. Representative examples of porphyrin and hydroporphyrin compounds relevant in PDT.

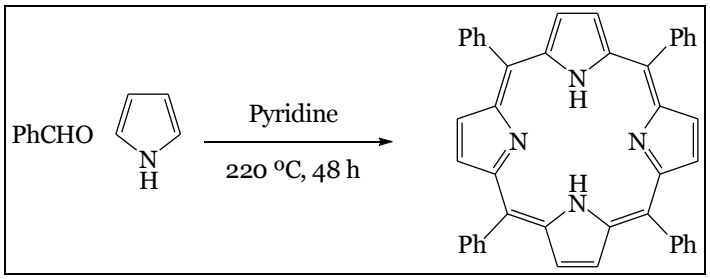
II. Classical Synthetic Methods

A. Porphyrins

The tremendous popularity and availability of porphyrin derivatives, particularly β- or *meso*-substituted ones, results from the elegant synthetic strategies that have been developed and improved over the years. Simple one- or two-step approaches (starting from suitable and widely accessible aldehydes and pyrrole) and more complex multi-step protocols (making use of previously synthesised pyrrolic precursors) can be applied to prepare these macrocycles.[31-33] Historically significant examples are presented in the following sections, methodologies devised to synthesise porphyrins substituted at the methylene positions being emphasised.

1. Rothemund Synthesis

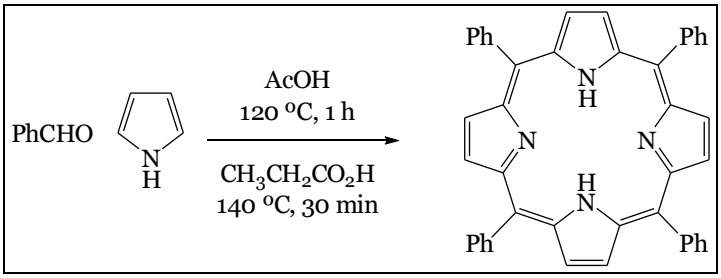
The synthesis of *meso*-substituted porphyrins was firstly investigated by Rothemund in the mid-1930s.[34-36] In this seminal work, pyrrole and one of a few different aldehydes were heated in a closed vial utilising methanol as solvent, spectroscopic evidence of the target porphyrins being found. However, only in a small number of cases was it possible to obtain extremely poor amounts of porphyrin crystals directly from the crude product mixture. In 1941, the same author described the reaction between benzaldehyde and pyrrole at 220 ºC, using pyridine as solvent and again in sealed-vessel conditions. 5,10,15,20-Tetraphenylporphyrin (TPP) crystallised upon slow cooling of the reaction medium, after 48 hours of heating, with isolated yields of up to 9% (Scheme 3.1).[37]



Scheme 3.1. Rothemund synthesis of 5,10,15,20-tetraphenylporphyrin.

2. Adler-Longo Synthesis

More than 20 years later, the research team of Adler and Longo continued this line of investigation, conducting several condensation reactions between pyrrole and benzaldehyde and making use of different acidic solvent media, various metal salts, high temperatures and aerobic conditions.[38] Although reasonable reaction yields were achieved employing acetic acid or acidified benzene, 30-40%, the utilisation of metallic salts as additives proved to be detrimental to the synthetic process. Further studies led to the use of equimolar quantities of the reagents (50 mM), propionic acid as solvent and a half-hour refluxing time, TPP crystals being collected with a 20% isolated yield (Scheme 3.2).[39, 40]

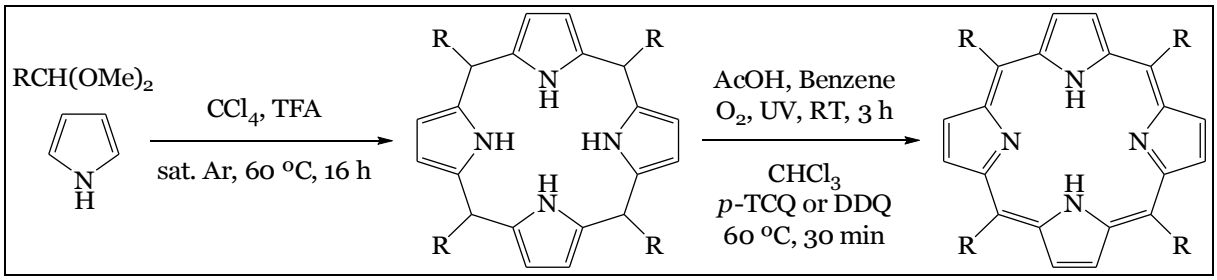


Scheme 3.2. Adler-Longo synthesis of 5,10,15,20-tetraphenylporphyrin.

It should be stressed that albeit the reaction proceeded faster in propionic acid, the yield was around half the one obtained when using acetic acid as reaction medium. However, it was established that TPP crystallised more promptly from the former solvent and, consequently, originated a final product of higher purity in an effortless fashion. Regrettably, contamination of the porphyrin product with up to 10% of the corresponding chlorin, as well as with large amounts of tarry side-products, was observed for various aldehyde starting materials, which made the purification procedure more troublesome. Moreover, synthesis involving alkyl aldehydes or aryl aldehydes bearing either acid-sensitive functionalities or bulky substituents at the *ortho* positions were not successful.[41, 42]

3. Rocha Gonsalves Two-Step Synthesis

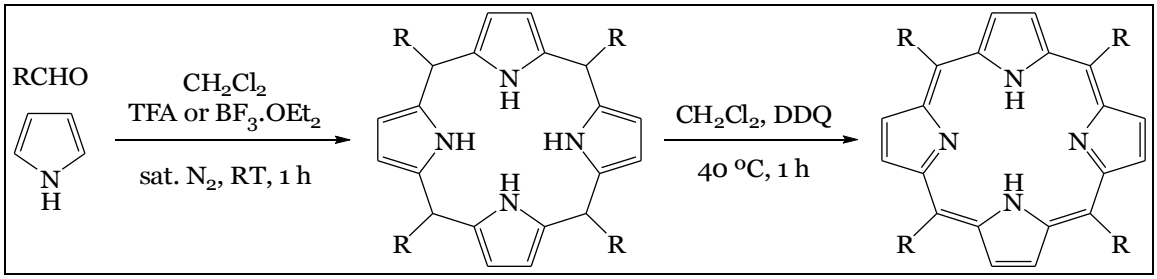
In 1985, Rocha Gonsalves and colleagues described a sequential two-step protocol for the preparation of *meso*-tetraalkylporphyrins (Scheme 3.3).[43] A solution of pyrrole and the methyl acetal of a chosen aliphatic aldehyde in trifluoroacetic acid-containing carbon tetrachloride was stirred at 60 ºC for 16 hours under a saturated argon atmosphere. The resulting porphyrinogen was then oxidised to the corresponding porphyrin, either photochemically or employing high oxidation potential quinones, such as 2,3,5,6-tetrachloro-1,4-benzoquinone or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, *p*-TCQ or DDQ, respectively. Isolated yields of up to 18% were accomplished after chromatographic work-up and recrystallisation.



Scheme 3.3. Rocha Gonsalves two-step synthesis of *meso*-tetraalkylporphyrins.

4. Lindsey Two-Step Synthesis

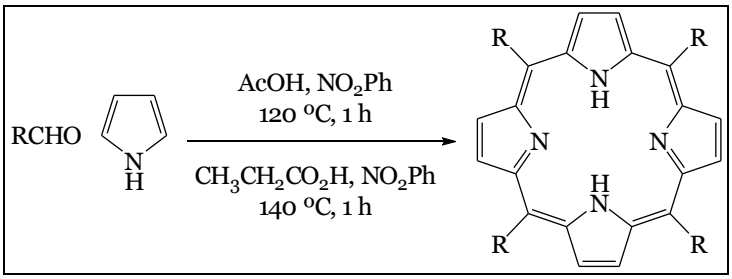
A rather similar stepwise strategy for the synthesis of *meso*-tetraarylporphyrins was presented shortly-after by Lindsey and co-workers (Scheme 3.4).[44-46] Condensation under a saturated nitrogen atmosphere of equimolar quantities of pyrrole and a selected aryl aldehyde (10 mM) in dichloromethane doped with catalytic amounts of trifluoroacetic acid or boron trifluoride diethyl etherate rendered the porphyrinogen after one hour. DDQ-promoted oxidation under reflux conditions for an additional hour, followed by chromatographic purification, afforded the corresponding porphyrin with isolated yields that reached 50% in the case of TPP.



Scheme 3.4. Lindsey two-step synthesis of *meso*-tetraarylporphyrins.

5. Rocha Gonsalves One-Step Synthesis

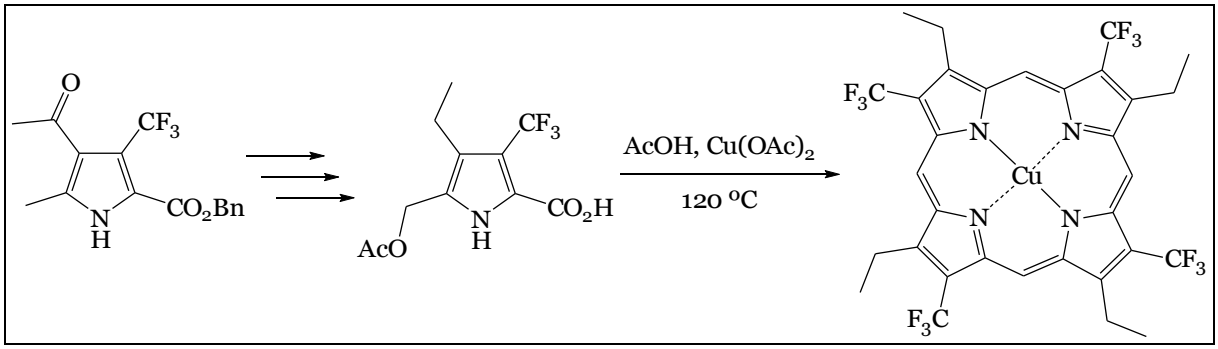
In the 1990s, the research group of Rocha Gonsalves looked into the possibility of preparing various porphyrins, containing both alkyl- and aryl-type functional groups in the methylene positions, via a simple one-step process.[47, 48] A mixture of an adequate aldehyde and pyrrole was refluxed in aerobic conditions for one hour, using either acetic acid or propionic acid, along with nitrobenzene, as the reaction medium (Scheme 3.5). Several porphyrins were obtained directly from the crude product mixture, after slow cooling to room temperature, filtration and washing with methanol, with isolated yields between 10 and 45%, depending on the nature of the *meso*-substituents. Given that no toxic and expensive quinone oxidants were required and, most importantly, that no chlorin contaminations were observed in the final products, complex and tedious chromatographic work-up was avoided.



Scheme 3.5. Rocha Gonsalves one-step synthesis of *meso*-tetraalkylporphyrins and *meso*-tetraarylporphyrins.

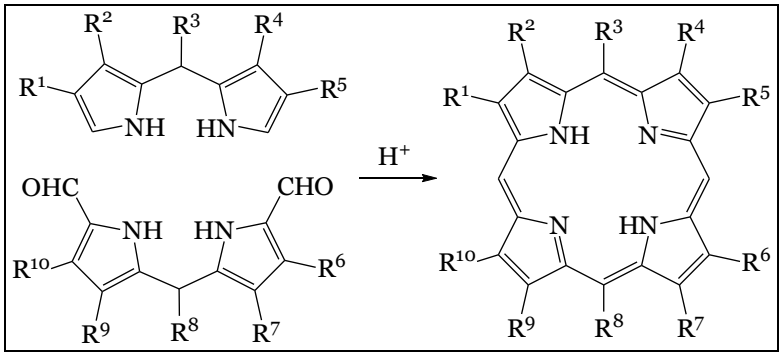
6. Other Syntheses

A method for the preparation of porphyrins containing non-equivalent β-substituents was described by Ogoshi and co-workers in the 1980s.[49, 50] It was based on the 'head-to-tail' condensation of four molecules of a pyrrole derivative under acidic reaction conditions (Scheme 3.6). One of the α-pyrrolic positions must possess a methyl group that promotes the generation of a highly electrophilic azafulvene in acid media, while the remaining α position should either be unsubstituted or have a group easily eliminated under the same conditions. A serious disadvantage was that several steps were necessary to synthesise the multisubstituted pyrrolic precursor.



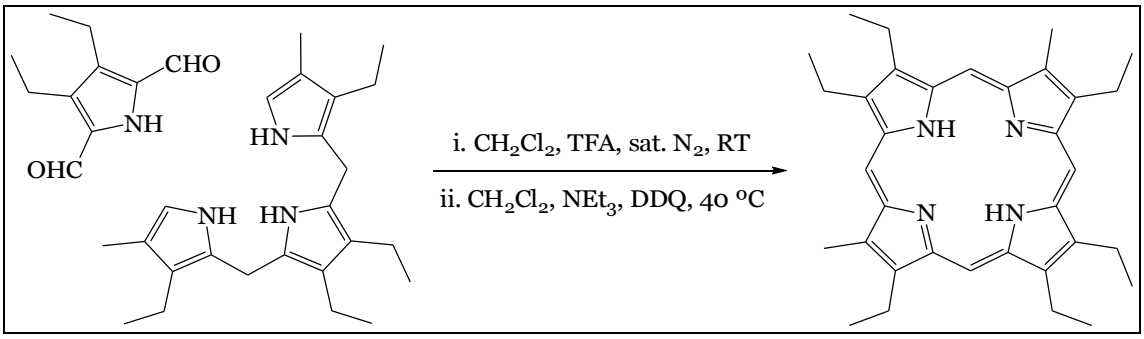
Scheme 3.6. Synthesis of a β-substituted porphyrin starting from a pyrrole derivative.

Porphyrins can also be prepared via an acid-catalysed '2+2' synthetic procedure using suitable dipyrromethanes as reagents. Early work was published by MacDonald in 1960,[51] the key synthetic route being depicted in Scheme 3.7. The original strategy involved one dipyrromethane with no α-substitution and another one bearing two formyl groups at the α positions of the pyrrolic structures. The β-positions on the pyrrole rings can be diversely substituted and the bridging carbon at the dipyrromethane units can also be functionalised. Originally, the exploration of this useful experimental approach was highly dependent on the synthetic accessibility of the dipyrromethane starting materials, a problem that was later overcame.



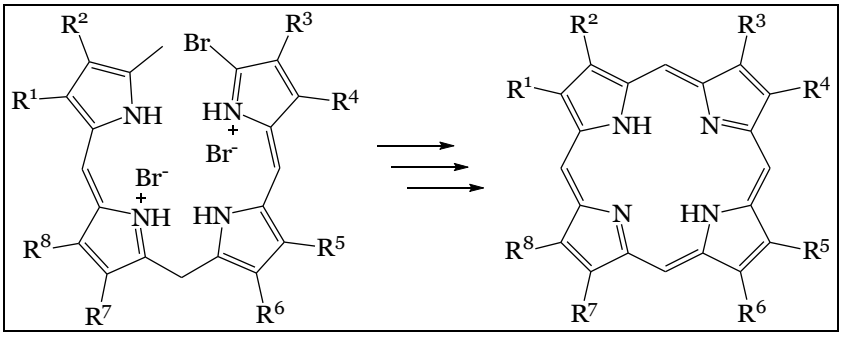
Scheme 3.7. '2+2' Synthesis of multisubstituted porphyrins.

The '3+1' condensation between a tripyrrane and a diformyl pyrrole affords interesting porphyrin derivatives, a methodology also applicable to the preparation of expanded porphyrins and other exotic structures.[52] Both simple and unusual porphyrin-type compounds have been prepared using this approach. Lash and colleagues employed a pyrrole dialdehyde and a substituted tripyrrane to synthesise a β-octaalkylporphyrin with a 60% isolated yield.[53] The corresponding porphyrinogen was formed under mild acid catalysis conditions and then oxidised using DDQ (Scheme 3.8).



Scheme 3.8. '3+1' Synthesis of a β-substituted porphyrin.

Porphyrins can also be obtained via cyclisation of linear tetrapyrroles. This strategy is generally used to prepare unsymmetrical porphyrins bearing various substituent groups at the β-positions. The oxidative cyclisation of appropriately functionalised *b*-bilenes has been described.[54] However, the most common tetrapyrrole precursors are *a*,*c*-biladiene structures. For instance, Dolphin and co-workers demonstrated that various porphyrins can be synthesised in several steps starting from previously prepared 1-bromo-19-methyl-*a*,*c*-biladiene intermediates (Scheme 3.9).[55, 56]



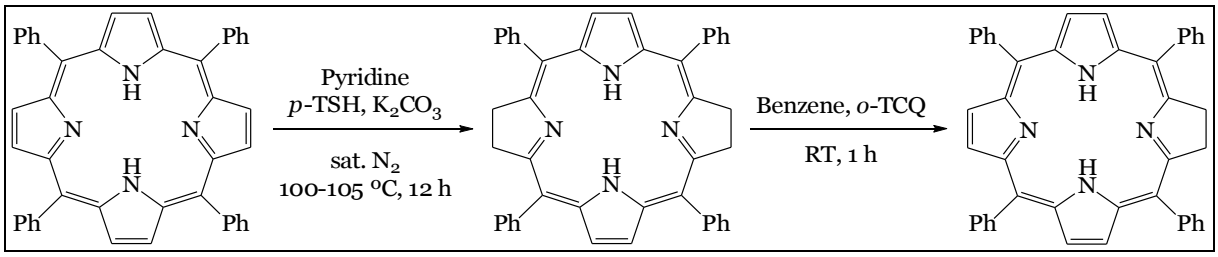
Scheme 3.9. Synthesis of β-substituted porphyrins starting from *a*,*c*-biladienes.

B. Hydroporphyrins

The preparation of hydroporphyrin derivatives is highly conditioned by their intrinsic thermodynamic stability and also by the kinetic barriers associated with the synthetic processes that lead to these macrocyclic structures.[57] These include various reactions at the periphery of porphyrins, such as reduction,[58-60] oxidation[61-63] and cycloaddition,[64-66] and the oxidation of porphyrinogens.[67] The modification of naturally occurring chlorins and bacteriochlorins[68] and the synthesis of hydroporphyrins starting from suitable pyrrole-containing fragments via '2+2'[69] or '3+1'[70] condensation strategies, as well as utilising linear tetrapyrroles,[71-74] have also been reported. Some classic and important exemplifications regarding the synthesis of hydroporphyrin macrocycles are given below.

1. Reduction of Porphyrins

Whitlock and colleagues studied the reduction of both β- and *meso*-substituted porphyrins in the late 1960s.[58] The hydrogenation of TPP by di-imide, which was generated *in situ* through the reaction between excess *p*-toluenesulphonyl hydrazide and base in pyridine for several hours, rendered a mixture of 5,10,15,20-tetraphenylchlorin (TPC) and 5,10,15,20-tetraphenylbacteriochlorin (TPB). Selective dehydrogenation of the bacteriochlorin component, using 3,4,5,6-tetrachloro-1,2-benzoquinone (*o*-TCQ) at room temperature, followed by digestion, liquid/liquid extraction and recrystallisation, provided TPC with a 72% yield (Scheme 3.10). Increasing the reaction time and the amount of di-imide precursors led to the formation of TPB as the major reaction product, which was isolated with a 50% yield after similar work-up.

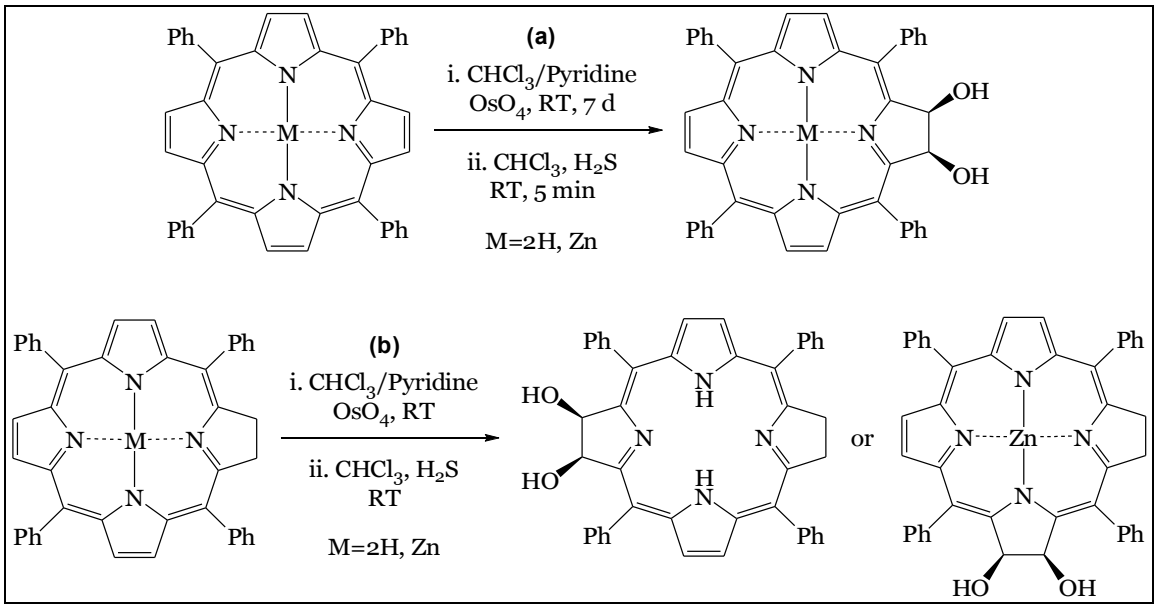


Scheme 3.10. Di-imide-promoted reduction of porphyrins. Synthesis of 5,10,15,20-tetraphenylchlorin and 5,10,15,20-tetraphenylbacteriochlorin.

About 20 years later, Bonnett and co-workers employed this procedure to the preparation of a series of *meso*-tetrahydroxyphenylchlorins and bacteriochlorins with moderate reaction yields.[59] One of them, 5,10,15,20-*tetrakis*(3-hydroxyphenyl)chlorin, also known by the commercial name Foscan (Figure 3.3), is presently used in several countries as a sensitiser drug in photodynamic therapy of certain tumours. Pereira and colleagues have recently applied a similar reduction methodology under solvent-free and sealed-vessel reaction conditions.[60]

2. Oxidation of Porphyrins

The osmium tetroxide-mediated oxidation of *meso*-tetraarylporphyrins and their metallated analogues was described by Brückner and Dolphin in 1995, affording β,β'-dihydroxylated *meso*-tetraarylchlorins and metallochlorins (Scheme 3.11a).[62]

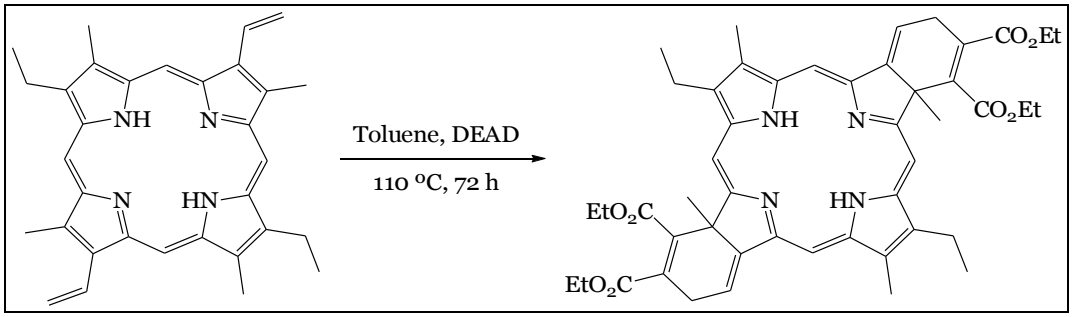


Scheme 3.11. Osmium tetroxide-promoted oxidation of porphyrins. Synthesis of β,β'-dihydroxylated 5,10,15,20-tetraphenylchlorin (a) and 5,10,15,20-tetraphenylbacteriochlorin (b).

The reaction was carried-out using a stoichiometric quantity of osmium tetroxide in chloroform doped with pyridine, the resulting osmate ester intermediate being quickly reduced with hydrogen sulphide. Although the oxidation was slow, up to one week in the case of TPP, isolated yields of up to 50% were achieved after chromatographic work-up. Furthermore, the same authors reacted previously prepared TPC and its zinc complex under similar reaction conditions, obtaining the corresponding β,β'-dihydroxylated bacteriochlorin and isobacteriochlorin counterparts, respectively (Scheme 3.11b).[63]

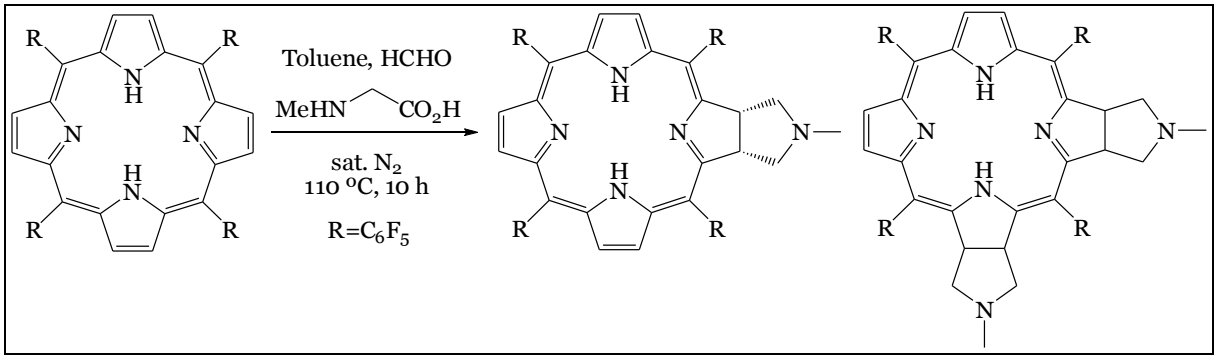
3. Cycloaddition of Porphyrins

The synthesis of β-substituted hydroporphyrins via Diels-Alder cycloaddition between *A*,*C*-divinylporphyrins and activated dienophiles was studied by the Dolphin research team more than two decades ago.[64] The reactions were conducted in degassed toluene under reflux conditions for 72 hours, using a 50-fold molar excess of the appropriate dienophile. When diethyl acetylenedicarboxylate (DEAD) was employed, a stable bacteriochlorin-type chromophore was obtained with a 52% isolated yield (Scheme 3.12).



Scheme 3.12. Diels-Alder cycloaddition of porphyrins. Synthesis of a β-substituted bacteriochlorin.

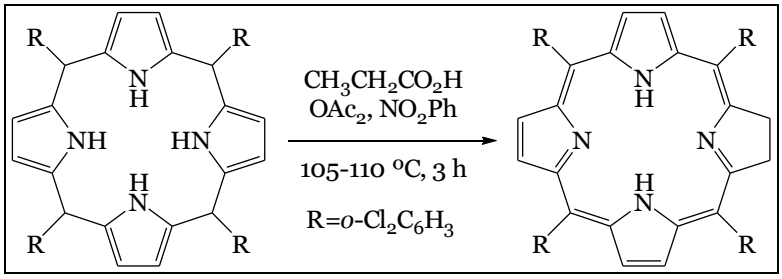
In 1997, Cavaleiro and colleagues revealed that *meso*-tetraarylporphyrins could also participate in Diels-Alder reactions as dienophiles, rendering the corresponding chlorin and bacteriochlorin structures.[65] A few years later, the same authors disclosed that the extremely electron-withdrawing 5,10,15,20-*tetrakis*(2,3,4,5,6-pentafluorophenyl)porphyrin could act as an effective dipolarophile in 1,3-dipolar cycloaddition processes with azomethine ylides, created *in situ* through the reaction between *p*-formaldehyde and *N*-methylglycine in refluxing toluene, affording the corresponding chlorin and isobacteriochlorin with moderate yields after chromatographic work-up (Scheme 3.13).[66]



Scheme 3.13. 1,3-Dipolar cycloaddition of porphyrins. Synthesis of a *meso*-tetraarylchlorin and isobacteriochlorin.

4. Oxidation of Porphyrinogens

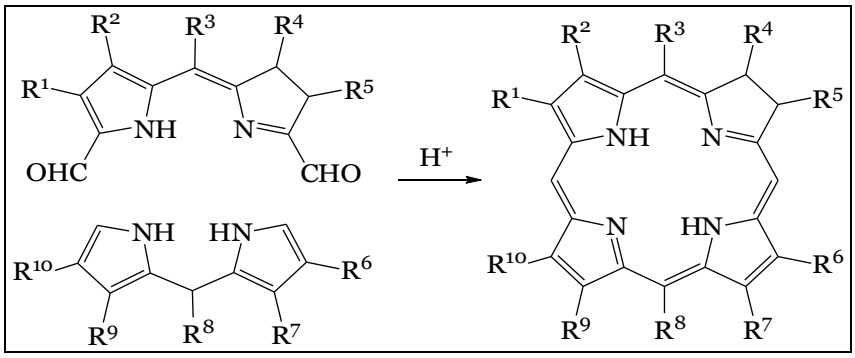
Recently, *meso*-tetraarylchlorins have been synthesised in acidic media through the selective oxidation of the respective porphyrinogens.[67] Serra and Rocha Gonsalves found that the structural characteristics of the latter, particularly the nature of the substituents on the *meso*-phenyl groups, is crucial to the successful outcome of the synthetic process. For instance, oxidation of 5,10,15,20-*tetrakis*(2,6-dichlorophenyl)porphyrinogen using a mixture of propionic acid, acetic anhydride and nitrobenzene as reaction medium, provided the desired chlorin, contaminated with merely 8% of the corresponding porphyrin, with an optimised yield of 28% (Scheme 3.14).



Scheme 3.14. Oxidation of porphyrinogens. Synthesis of 5,10,15,20-*tetrakis*(2,6-dichlorophenyl)chlorin.

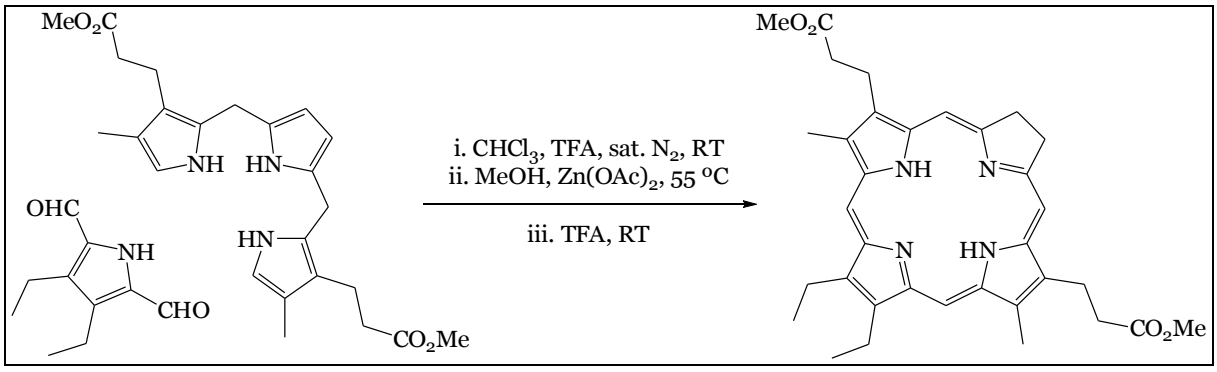
5. Other Syntheses

Jacobi and colleagues proposed the synthesis of some chlorin derivatives via a MacDonald-type approach, i.e. a '2+2' condensation in acidic media between two proper and previously prepared pyrrole-containing starting materials, as portrayed in Scheme 3.15.[69] Albeit the several steps required to attain the dipyrrolic-type precursors and the low-to-moderate overall yields, interesting multisubstituted chlorins may be obtained.

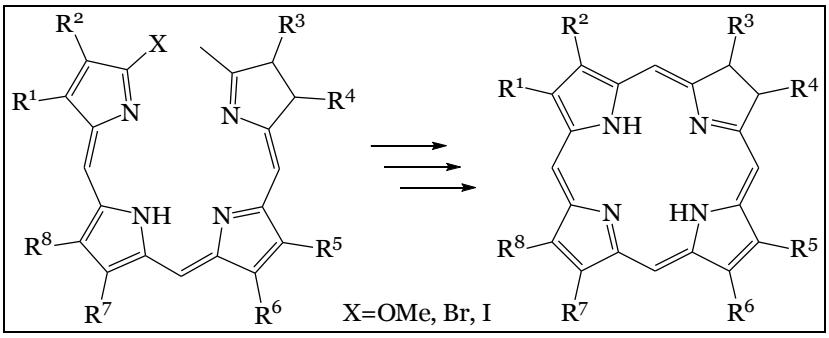


Scheme 3.15. '2+2' Synthesis of multisubstituted chlorins.

The regioselective '3+1' preparation of a chlorin macrocycle starting from a tripyrrane and a diformylated pyrrole was described in 2000 by the Lash research group (Scheme 3.16).[70] Yields as high as the ones achieved via '2+2' condensation strategies were reported. Chlorins can also be synthesised from linear tetrapyrrole derivatives, the preparation of bonellin, presented by Battersby and colleagues in the late 1980s, being a fascinating example.[71, 72] In general, this methodology is based upon either a photochemical or a thermally induced ring closure of appropriately functionalised bilatrienes (Scheme 3.17). The thermal cyclisation process requires copper chelation for activation and supplies chlorins with 5 to 10% yield after decomplexation (X=Br). The photochemical approach is higher yielding, up to 20%, but requires several days of irradiation of highly dilute solutions (X=OMe). A significant improvement to this procedure was developed by Montforts and co-workers, employing zinc as a template and performing the cyclisation reaction in alkaline conditions (X=Br, I).[73, 74]



Scheme 3.16. '3+1' Synthesis of a β-substituted chlorin.



Scheme 3.17. Synthesis of β-substituted chlorins starting from bilatrienes.

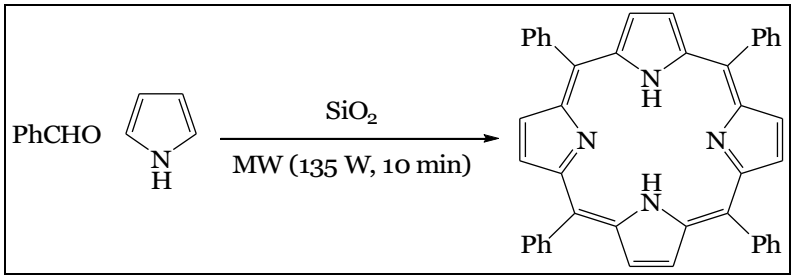
III. Microwave-Assisted Synthetic Methods

Although a vast amount of developments has been described over the years, the preparation of porphyrin and hydroporphyrin compounds continues to be a hot research topic to the organic synthesis community world-wide. Reaction yields are usually not as high as desired, particularly in the case of porphyrins, and effective scale-up methodologies are yet to be presented for both types of tetrapyrrolic structures. As with other heterocyclic molecules, microwave irradiation has been employed in the synthesis of these nitrogen-containing macrocycles, some of the methodologies already published being shortly reviewed in the next pages.

A. Literature Review & Selected Examples

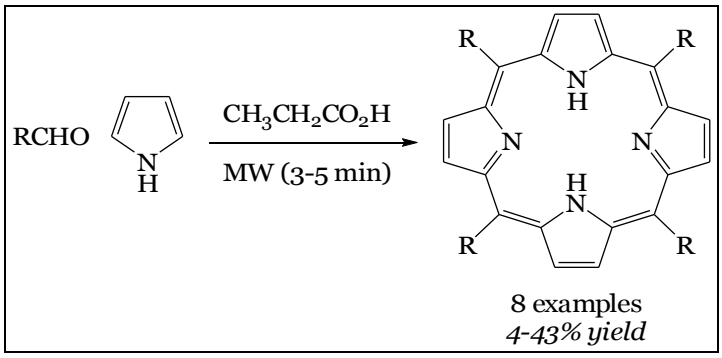
1. Porphyrins

The preparation of porphyrins under microwave activation was firstly described by Loupy and co-workers in 1992.[75] Irradiation of a mixture of pyrrole and benzaldehyde pre-adsorbed on the surface of silicon dioxide for 10 minutes, utilising a single-mode reactor and open-vessel conditions, afforded TPP with a 9.5% isolated yield (Scheme 3.18). A lower yield of 4% was reported by the same authors when a domestic microwave oven was used.



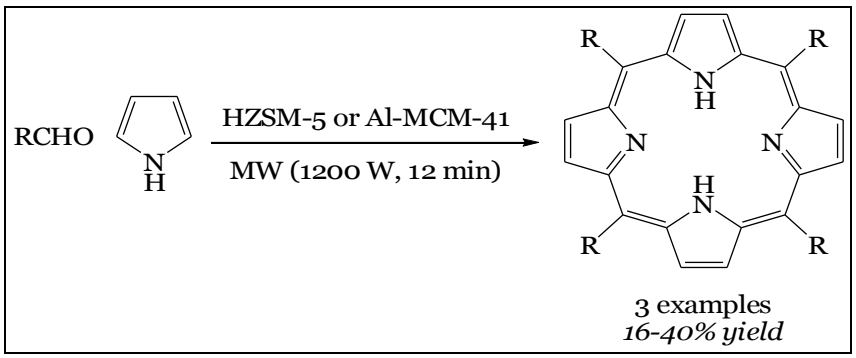
Scheme 3.18. Solid-supported synthesis of 5,10,15,20-tetraphenylporphyrin.

About 10 years later, Chauhan and colleagues presented the condensation of equimolar amounts of a series of aryl aldehydes and pyrrole in an open Pyrex reaction vial, employing propionic acid as solvent and making use of a household microwave equipment.[76] Although the microwave power applied was not disclosed, irradiation for 3 to 5 minutes, followed by cooling to room temperature, washing with water, extraction with dichloromethane, chromatographic purification and recrystallisation, rendered the target *meso*-substituted porphyrin compounds with poor to reasonable isolated yields (Scheme 3.19).



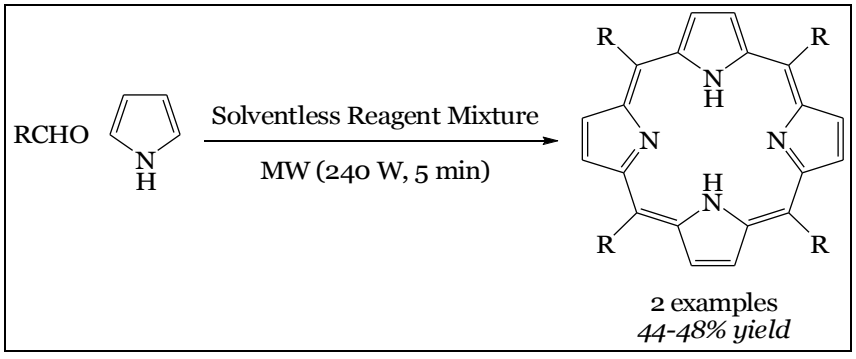
Scheme 3.19. Synthesis of *meso*-tetraarylporphyrins in propionic acid.

A solvent-free microwave-promoted synthesis of porphyrins under open-vessel conditions was published in 2004 by the research group of Raghavan.[77] The reactions were carried-out for 12 minutes in a domestic microwave apparatus operating at 1200 W, using HZSM-5 zeolites or Al-MCM-41 mesoporous molecular sieves as solid catalysts, the latter exhibiting a better performance (Scheme 3.20). Work-up involved removal of the catalyst by filtration and column chromatography of the crude product mixture, good reaction yields being obtained.



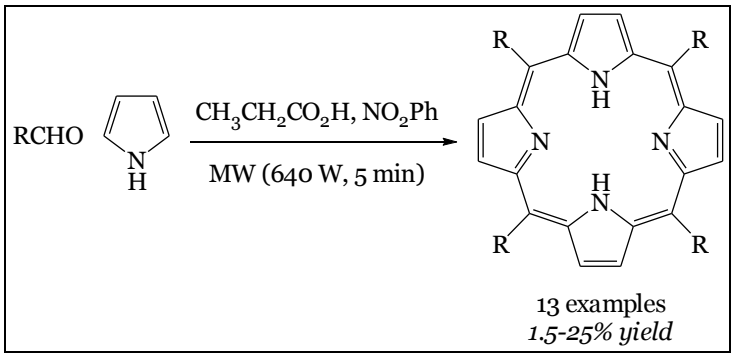
Scheme 3.20. Solventless synthesis of *meso*-tetraarylporphyrins using heterogeneous acid catalysts.

A simple, rapid, solvent-free and gram-scale procedure for the preparation of a couple of *meso*-tetraarylporphyrins was developed by Liu and co-workers in 2004.[78] An open Quartz reaction vial and an unmodified domestic microwave oven were utilised under the reaction conditions summarised in Scheme 3.21.



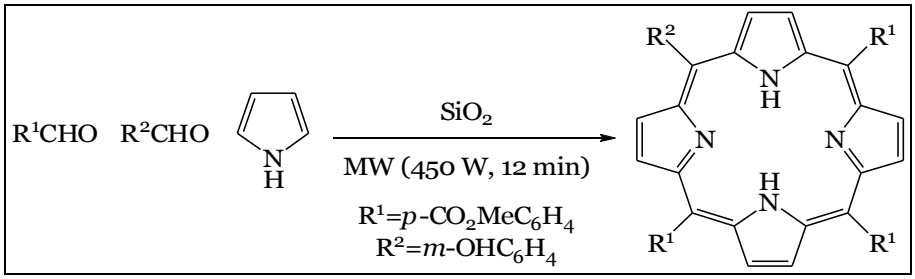
Scheme 3.21. Solventless synthesis of *meso*-tetraarylporphyrins.

The adaptation of the classical Rocha Gonsalves one-step synthesis of *meso*-tetrarylporphyrins to microwave technology was reported by our own research team in 2007.[79] Irradiation of stoichiometric quantities of one of 13 different aryl aldehydes and pyrrole in a mixture of propionic acid and nitrobenzene for 5 minutes, using a domestic microwave equipment set at 640 W, provided the corresponding porphyrins with low to moderate isolated yields (Scheme 3.22). As in the original method, chromatographic purification procedures were avoided in some cases.



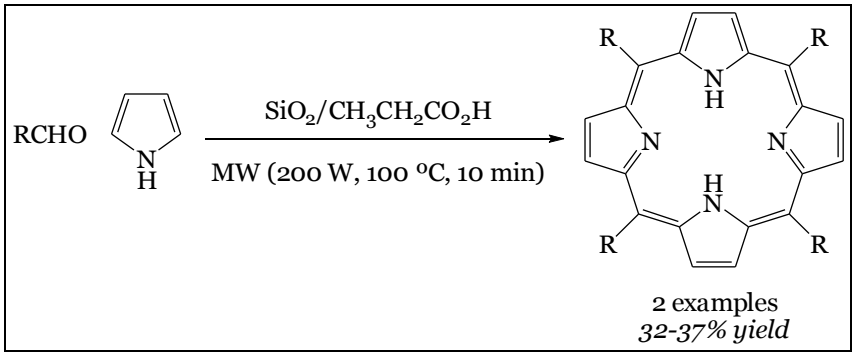
Scheme 3.22. Synthesis of *meso*-tetraarylporphyrins using nitrobenzene as oxidant.

An unsymmetrical *meso*-substituted porphyrin bearing two different aryl groups at the methylene positions in a 3:1 proportion (A_3B) was prepared under microwave heating by application of solid-supported and open-vessel reaction conditions.[80] A 3:1:4 molar ratio of methyl *p*-formylbenzoate, *m*-hydroxybenzaldehyde and pyrrole, pre-adsorbed on the surface of silica gel, was heated for 12 minutes at 450 W, the desired porphyrin being obtained with a 13% isolated yield after column chromatography and preparative TLC (Scheme 3.23).



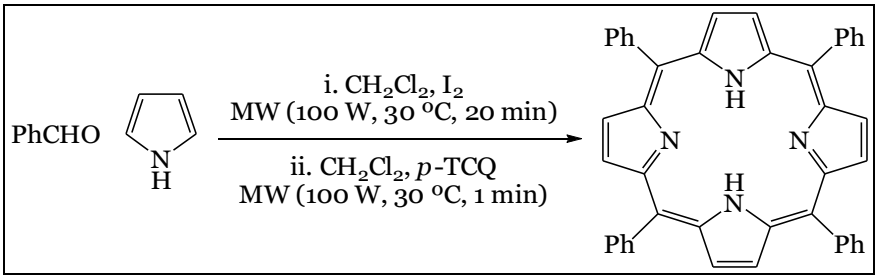
Scheme 3.23. Solid-supported synthesis of an unsymmetrical *meso*-tetraarylporphyrin.

Yaseen and colleagues have also presented a solid-supported synthesis of a few *meso*-tetraarylporphyrins under microwave heating with good yields.[81] Equimolar amounts of the selected aryl aldehyde and pyrrole, pre-adsorbed on the surface of previously prepared propionic acid-doped silica gel, were irradiated at 100 ºC for 10 minutes, affording the corresponding porphyrin compounds after chromatographic work-up (Scheme 3.24).



Scheme 3.24. Solid-supported synthesis of *meso*-tetraarylporphyrins.

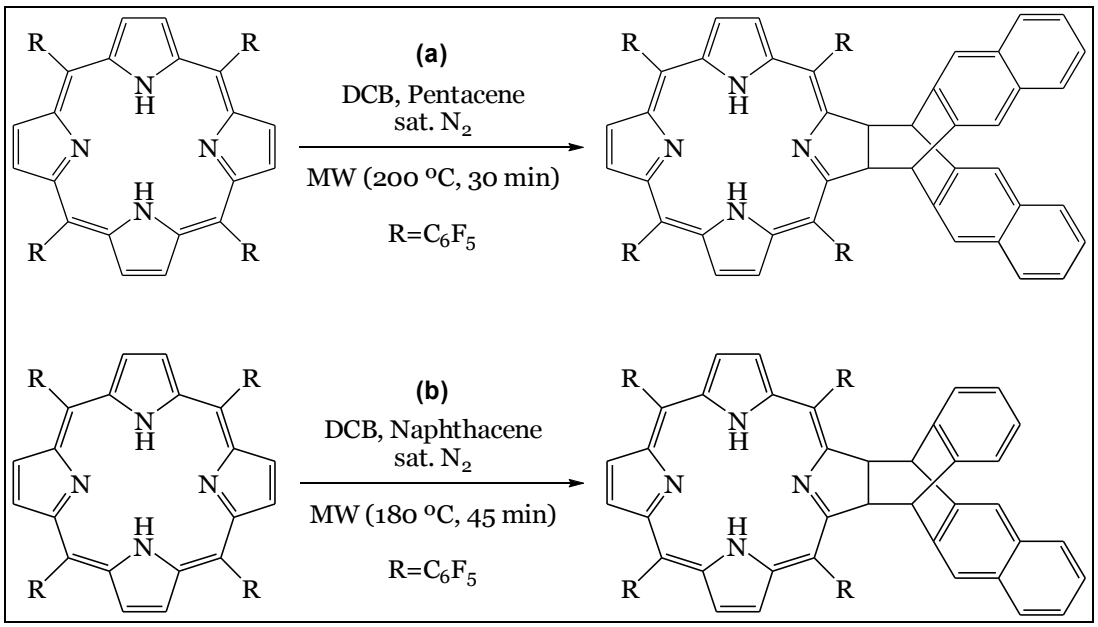
Lucas and co-workers described a microwave-assisted, small-scale, iodine-catalysed and two-step synthesis of TPP in 2008.[82] Pyrrole, benzaldehyde and dichloromethane were claimed to be employed as received, i.e. without prior purification protocols being used. A maximum isolated yield of 47% was achieved after chromatographic work-up, using a 10% molar equivalent of iodine as the catalyst in the first step and *p*-TCQ as the porphyrinogen oxidising agent in the second one (Scheme 3.25). The same authors subsequently employed this microwave-activated synthetic approach to the preparation of some A_3B unsymmetrical *meso*-tetraarylporphyrins, low to moderate yields being reported.[83]



Scheme 3.25. Synthesis of 5,10,15,20-tetraphenylporphyrin using iodine as catalyst.

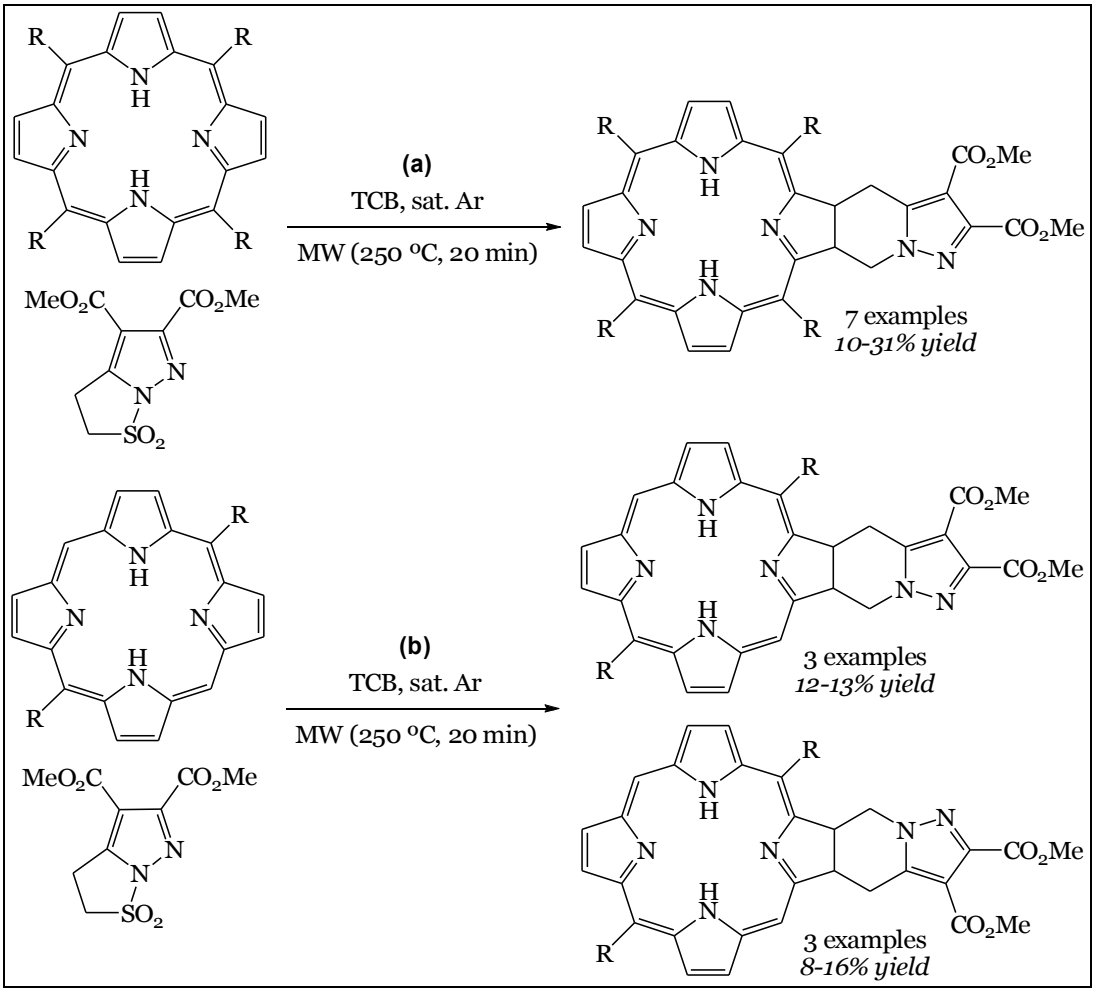
2. Hydroporphyrins

The Diels-Alder cycloaddition of 5,10,15,20-*tetrakis*(2,3,4,5,6-pentafluorophenyl)porphyrin with a three-fold molar excess of pentacene and naphthacene under microwave irradiation was reported by the Cavaleiro research group in 2005.[84] Both reactions were conducted in a single-mode microwave reactor at high temperature, utilising 1,2-dichlorobenzene (DCB) as solvent and under sealed-vessel conditions, the corresponding *meso*-substituted chlorins being obtained after chromatographic work-up, with 83 and 23% yield, respectively (Scheme 3.26). It should be noticed that the synthetic process proceeded far worse under conventional heating conditions, only 22% isolated yield after 8 hours at 200 °C and no reaction, respectively. Bacteriochlorin- and isobacteriochlorin-type compounds were also observed when pentacene was used as starting material, preparative HPLC being required to isolate them in low yields.



Scheme 3.26. Diels-Alder cycloaddition of porphyrins. Synthesis of *meso*-tetraarylchlorins.

The microwave-assisted synthesis of novel *meso*-tetraarylchlorins through '8π+2π' cycloaddition of a slight excess of the respective porphyrins and diazafulvenium methide, rendered *in situ* via thermal extrusion of sulphur dioxide from a suitable and previously prepared pyrazolo-thiazole, was recently described by Pereira and co-workers (Scheme 3.27a).[85, 86] When 5,15-diarylporphyrins were used as reagents the cycloaddition led to the synthesis of the corresponding chlorin compounds in a regioisomeric fashion (Scheme 3.27b). Both strategies were performed in 1,2,4-trichlorobenzene (TCB) under closed-vessel conditions and employing a dedicated microwave reactor. Although several reaction parameters were tested, the best results were accomplished by heating at 250 ºC for 20 minutes, followed by cooling to room temperature and purification of the crude product mixture by column chromatography. Bacteriochlorin-type structures were also prepared through related procedures but, in this case, microwave activation did not improve the synthetic process comparing to classical heating conditions.



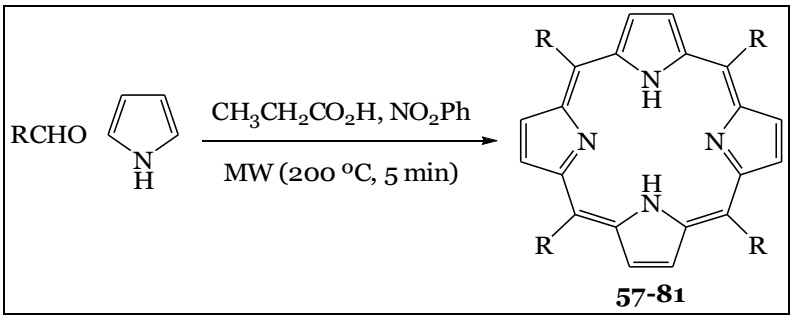
Scheme 3.27. '8π+2π' cycloaddition of porphyrins. Synthesis of *meso*-tetraarylchlorins.

Giving our long-standing interest in the chemistry of tetrapyrrolic macrocycles, particularly of the porphyrin and hydroporphyrin types,[33] it was decided to explore the preparation of these compounds using microwave technology. The efforts regarding the synthetic methodologies studied and the subsequent results are presented in detail within the pursuing sections.

B. Synthesis of *meso*-Tetraarylporphyrins

As mentioned above, we have looked into the Rocha Gonsalves one-step synthesis of porphyrins under microwave irradiation using a domestic multi-mode microwave oven.[79] However, albeit the several advantages

of this adaptation relatively to the classical heating method,[47, 48] such as reduced reaction times and minimisation of the amount of solvents employed and, consequently, of the overall cost of the synthetic process, the reaction yields were reasonably good but not as high as desired and, therefore, room for further improvements remained. Moreover, the possibility of broadening the scope of this procedure to a larger set of porphyrins utilising a dedicated single-mode microwave equipment and closed-vessel reaction conditions, which allows higher reaction temperatures to be reached, appeared promising. Hence, equimolar quantities of benzaldehyde and pyrrole (10 mmol) in 5 ml of propionic acid/nitrobenzene (7:3 v/v) were heated at 200 ºC for 5 minutes, with an initial power setting of 250 W, under sealed-vessel conditions (Scheme 3.28, R=Ph). Temperature values above 200 ºC were not easily attained unless a fixed microwave power was applied and a drastic increase of the pressure inside the reaction vial was observed, which could lead to its fissure and, consequently, to a dangerous outcome. After cooling to room temperature, the crude product mixture was washed with methanol and 5,10,15,20-tetraphenylporphyrin **57** was obtained as a dark-purple solid via filtration under reduced pressure with a 46% isolated yield and a typical molecular absorption spectrum in the UV-Vis region (Figure 3.4). This is more than twice the one achieved in our earlier studies using a household microwave apparatus (20%).[79]



Scheme 3.28. One-step synthesis of *meso*-tetraarylporphyrins **57-81** under microwave irradiation.

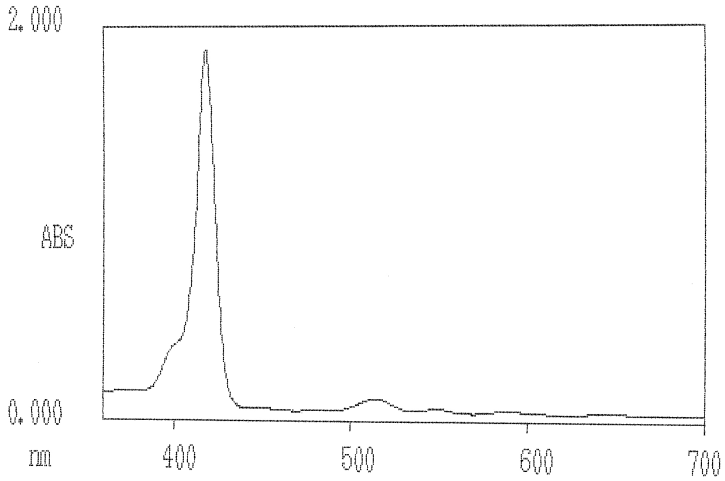


Figure 3.4. UV-Vis absorption spectrum of 5,10,15,20-tetraphenylporphyrin **57** in dichloromethane.

Various other aldehydes, bearing both electron-donating and electron-withdrawing substituents at different positions of the phenyl ring, as well as containing polycyclic aromatic hydrocarbons, were later employed as reagents, the corresponding *meso*-tetraarylporphyrins being obtained either directly by crystallisation or after flash column chromatography (Figure 3.5). Higher yields were usually achieved, comparing with the conventional heating methodology and also with our previously reported microwave-promoted approach, except in the cases where large aromatic groups (**58-60**) or phenyl rings carrying bulky substituents at the *ortho* positions (**62** and **63**) were present, which can be justified by steric hindrance effects.

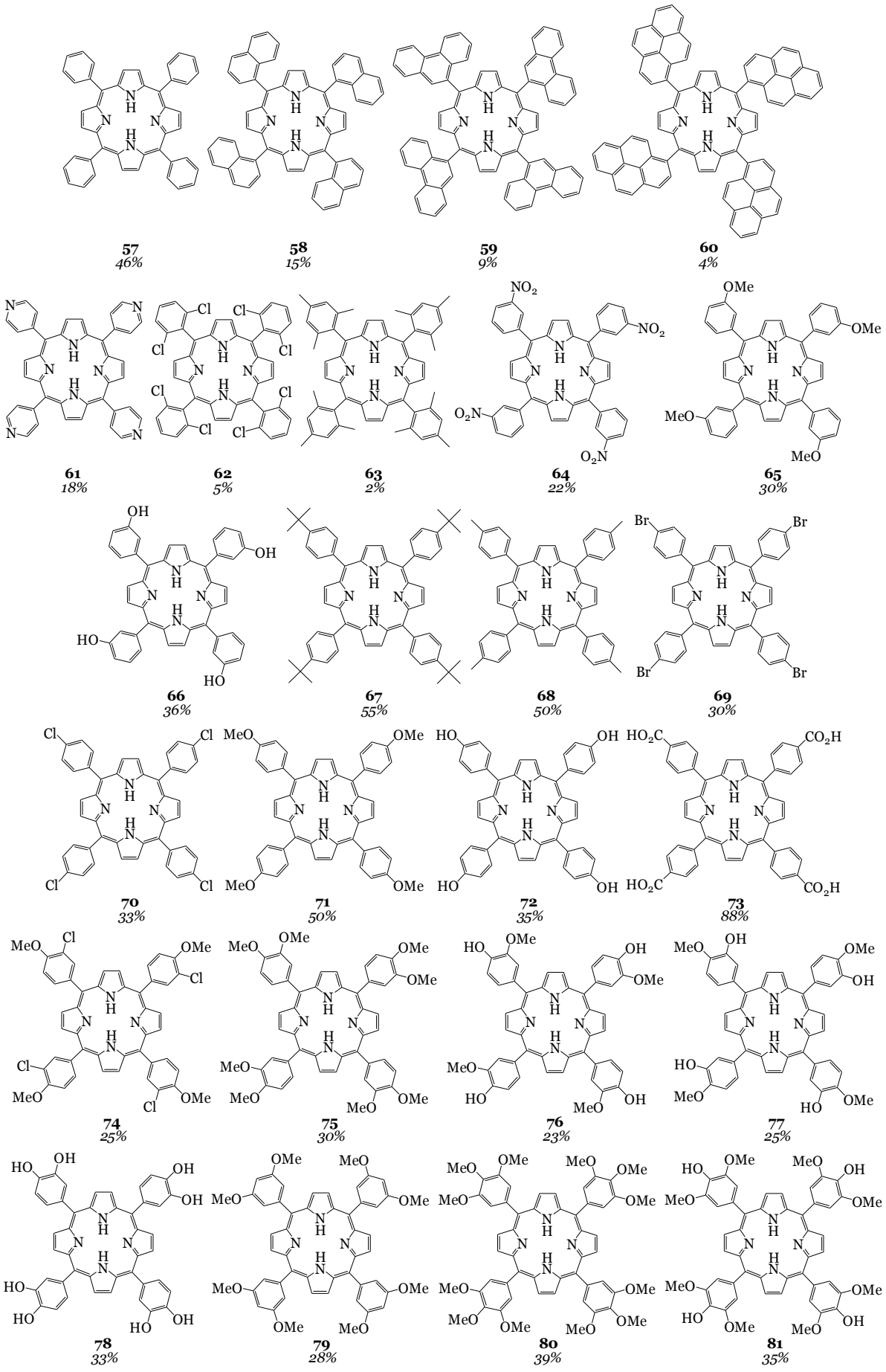
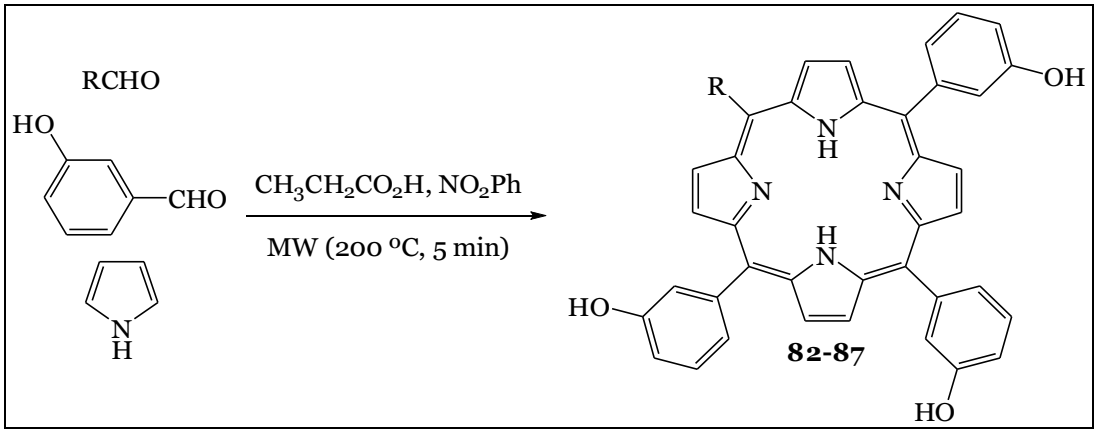


Figure 3.5. Structures and isolated yields of *meso*-tetraarylporphyrins **57-81** synthesised via a solvent-based, one-step, microwave-assisted method.

Regrettably, when 9-anthracenaldehyde, 4-fluorobenzaldehyde and 4-nitrobenzaldehyde were used as reactants, only trace amounts of the corresponding porphyrins were detected by TLC analysis of the crude product mixtures. Furthermore, utilising 4-dimethylaminobenzaldehyde as the starting aryl aldehyde led to an intense and dangerous pressure build-up inside the reaction vessel upon microwave irradiation, which may be explained by the rapid generation of dimethylamine as a reaction by-product. When 4-acetamidobenzaldehyde was used as reagent, several porphyrins were observed by TLC analysis of the crude product mixture. This could be owed to the partial deacetylation of the acetamido substituents, which are rather labile under the acidic and high-temperature reaction conditions employed. In fact, MS studies of the porphyrin product after flash column chromatography subsequently confirmed this assumption. On the other hand, isolation of porphyrins **67** (55%), **68** (50%), **71** (50%) and **73** (88%) provided our best results, without the demand of chromatographic work-up.

The same microwave-mediated formulation was also applied to the mixed-aldehyde synthesis of a small series of hydroxylated unsymmetrical *meso*-tetraarylporphyrins of the A_3B type, starting from a 3:1:4 molar ratio of 3-hydroxybenzaldehyde, another selected aryl aldehyde and pyrrole (Scheme 3.29). Although column chromatography procedures were mandatory to effectively provide the target porphyrin compounds, yields between 6 and 15% were attained, which are quite reasonable for this kind of synthesis (Figure 3.6). In all situations, 5,10,15,20-*tetrakis*(3-hydroxyphenyl)porphyrin **66** was also isolated with yields ranging from 9 to 13%.



Scheme 3.29. One-step synthesis of A_3B *meso*-tetraarylporphyrins **82-87** under microwave irradiation.

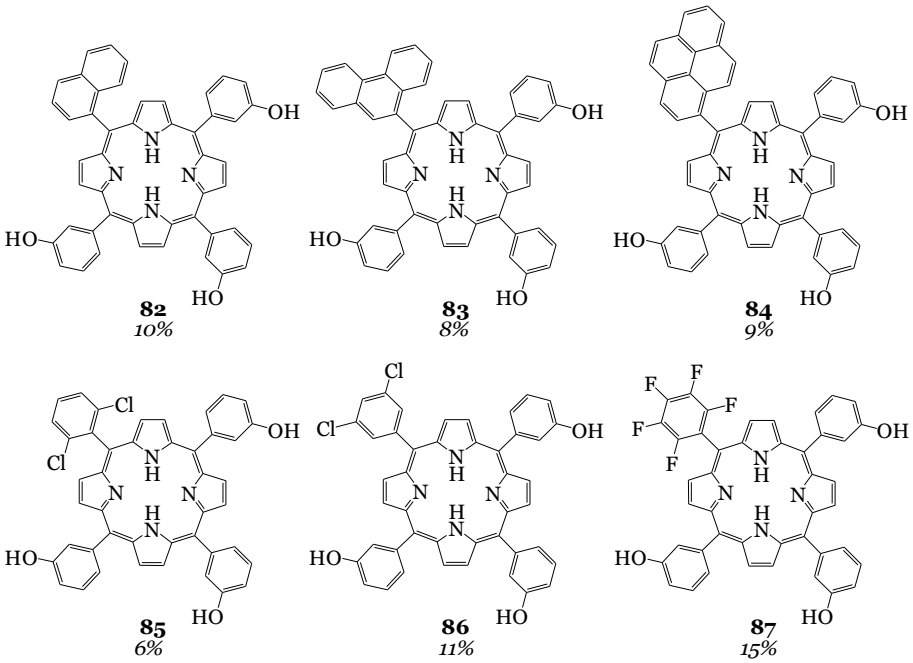
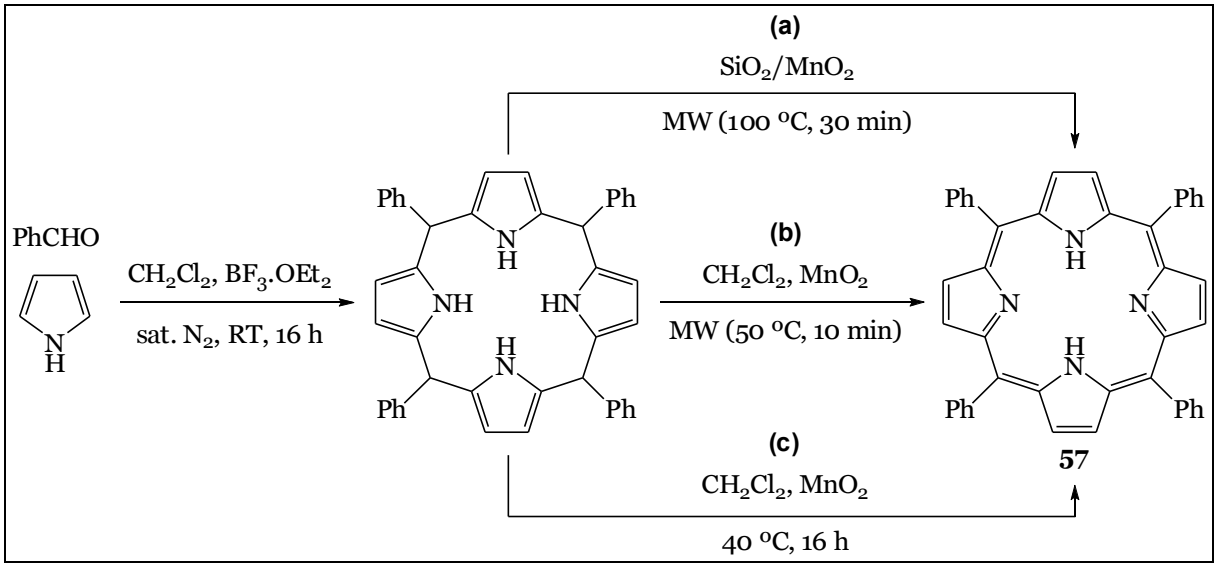


Figure 3.6. Structures and isolated yields of A_3B *meso*-tetraarylporphyrins **82-87** synthesised via a solvent-based, one-step, microwave-assisted method.

Introduction of microwave activation to the classical two-step synthesis of porphyrins was also investigated, porphyrin **57** being used as the model molecule. The equilibrium conditions reported by Lindsey and colleagues were applied to prepare 5,10,15,20-tetraphenylporphyrinogen,[45] which in turn was oxidised to the corresponding porphyrin under different reaction conditions. Trying to avert the utilisation of costly and toxic quinone oxidants, such as DDQ or *p*-TCQ, activated manganese dioxide was selected as an alternative oxidising agent, given its inexpensiveness, user-friendly character and wide and successful application in various processes, such as oxidation of alcohols and hydroxylated compounds, dehydrogenation and oxidative aromatisation.[87-89] Thus, heating the porphyrinogen adsorbed in the surface of MnO_2-doped silica gel at 100 ºC for 30 minutes, with an initial power setting of 200 W and under open-vessel conditions, followed by cooling to room temperature and washing the product mixture with an organic solvent, removal of the solid support via filtration through a small column of SiO_2, evaporation and recrystallisation, provided 5,10,15,20-tetraphenylporphyrin with a 22% isolated yield (Scheme 3.30a). Alternatively, a concentrated solution of the porphyrinogen and a 30-fold molar excess of activated manganese dioxide in dichloromethane was irradiated at 50 ºC for 10 minutes in a sealed reaction vial, applying an initial microwave power setting of 50 W, TPP being obtained with a related isolated yield of 20% after similar work-up (Scheme 3.30b). Finally, a conventional heating approach to the oxidation step was tested, refluxing the previously prepared porphyrinogen with excess MnO_2 in dichloromethane overnight (Scheme 3.30c). This last mentioned strategy afforded the best outcome, 32% yield of porphyrin **57**, although it was clearly not as good as the one achieved via the microwave-assisted one-step synthesis in propionic acid and nitrobenzene.

Nevertheless, we decided to extend this two-step methodology to some of the porphyrins that gave worse results in our one-step procedure, namely porphyrins **58** and **60**, isolated yields of 20 and 2%, respectively, being attained. While the reaction yield was slightly higher in the case of 5,10,15,20-*tetrakis*(naphthalen-1-yl)porphyrin, 5,10,15,20-*tetrakis*(pyren-1-yl)porphyrin was obtained with an even lower isolated yield. Hence, it was verified that activated MnO_2 can be applied in the oxidation of porphyrinogens to the corresponding porphyrins, under both classical and microwave heating, although the most efficient reaction conditions were not fully determined.[90] Even so, this cheap heterogeneous oxidant proved to be a valid option when compared to other oxidising compounds commonly used in this synthetic operation, i.e. DDQ and *p*-TCQ, particularly taking into account their inherent toxicity and the tedious chromatographic work-up required when these quinone compounds are employed. Albeit a large amount of MnO_2 is needed to achieve the dehydrogenation of the porphyrinogen in out two-step strategy, its straightforward removal by simple filtration constitutes an enormous advantage from both the synthetic and economical standpoints.



Scheme 3.30. Two-step synthesis of 5,10,15,20-tetraphenylporphyrin **57** using activated manganese dioxide as oxidant under microwave irradiation and conventional heating.

C. Synthesis of *meso*-Tetraarylhydroporphyrins

Aiming to synthesise hydroporphyrins of the chlorin and bacteriochlorin types starting from the corresponding porphyrins, we decided to explore the already referenced and broadly utilised di-imide-mediated reduction methodology, firstly described by Whitlock and co-workers in 1969 (Scheme 3.10),[58] under microwave irradiation. Again, TPP was chosen as the case-study compound. Using our single-mode microwave equipment, the best reaction conditions were found when a mixture of 5,10,15,20-tetraphenylporphyrin and a 100-fold molar excess of both anhydrous potassium carbonate and *p*-toluenesulphonyl hydrazide in 1,4-dioxane was irradiated at 120 ºC, for a 25-minute period of time, in sealed-vessel conditions. After cooling to room temperature, the crude product mixture was simply washed with distilled water and neutralised by the addition of hydrochloric acid. The solid that precipitated out of the aqueous solution was then filtrated and thoroughly washed with distilled water, in order to remove any water-soluble by-products and excess reagents, 5,10,15,20-tetraphenylbacteriochlorin **88** being obtained as a pinkish-brown solid with a 96% isolated yield, although contaminated with 25% of the respective chlorin (Table 3.1, entry 1; Scheme 3.31, R=Ph). The UV-Vis molecular absorption spectrum of the final product is presented in Figure 3.7. It should be stressed that smaller reaction times led to a larger amount of TPC as contaminant and longer ones did not improve the final outcome of the synthetic procedure. Also, 1,4-dioxane was selected as the reaction medium because of its versatility, since it can solvate different kinds of organic substrates and also many inorganic substances, like the anhydrous base used in this method.

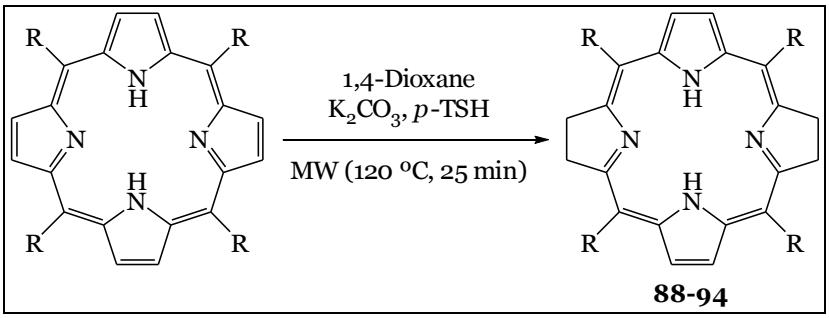
Other *meso*-substituted porphyrins were later employed as starting materials, the corresponding bacteriochlorin derivatives **89-94** being obtained with very high yields, albeit contaminated with 15 to 35% of the chlorin analogues (entries 2-6) and, in one case, also with 25% of the unreacted porphyrin (entry 7).[90] Analysing the data collected in Table 3.1, one can infer that the reduction of porphyrins comprising functionalities either at the *ortho* or the *meta* positions of the *meso*-phenyl rings (entries 2-4) afforded a more bacteriochlorin-rich product than that of porphyrins bearing *para*-substituted aromatic moieties (entries 5 and 6), regardless of the nature of the functional groups. Moreover, the reduction of 5,10,15,20-*tetrakis*(4-*t*-butylphenyl)porphyrin **67** proved to be challenging, given that 25% of the initial porphyrin reactant was present in the final product (entry 7). A reasonable explanation for these facts requires further investigation.

Purification of the bacteriochlorin components via SiO_2 and Al_2O_3 column chromatography was tested, but failed to provide the desired products in pure form. This was mainly due to the very similar affinities of the chlorin and bacteriochlorin compounds regarding the chromatographic stationary phases, which seriously hampered the isolation procedure. Furthermore, given that a relatively generous period of time is necessary in order to achieve an appropriate separation within the chromatographic column, it is quite possible that the bacteriochlorins start to oxidise to the respective chlorins during the purification process.

Table 3.1. Synthesis of *meso*-tetraarylbacteriochlorins **88-94** under microwave irradiation.

Entry	Compound	R	Yield[a] (%, Bacteriochlorin/Chlorin Ratio)[b]
1	**88**	Ph	96, 75/25
2	**89**	*o*-$Cl_2C_6H_3$	92, 85/15
3	**90**	*m*-$OMeC_6H_4$	95, 85/15
4	**91**	*m*-OHC_6H_4	93, 80/20
5	**92**	*p*-$OMeC_6H_4$	95, 65/35
6	**93**	*p*-BrC_6H_4	92, 65/35
7	**94**	*p*-*t*-BuC_6H_4	90, 45/30/25[c]

All reactions were carried-out using the selected porphyrin (25 mg), anhydrous potassium carbonate (100 molar equivalents), *p*-toluenesulphonyl hydrazide (100 molar equivalents) and 1,4-dioxane (2 ml) at 120 ºC for 25 minutes in a closed vessel. [a]Yields refer to the isolated reaction products. [b]Assessed by ^{1}H NMR analysis of the isolated reaction products. [c]Bacteriochlorin/Chlorin/Porphyrin ratio.



Scheme 3.31. Synthesis of *meso*-tetraarylbacteriochlorins **88-94** under microwave irradiation.

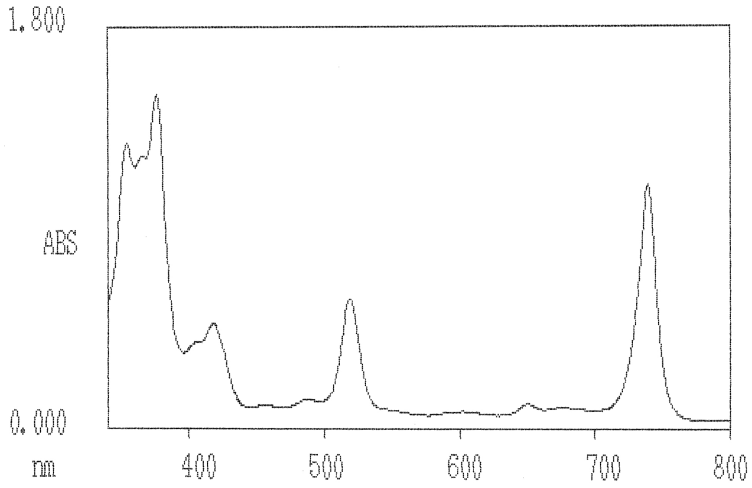
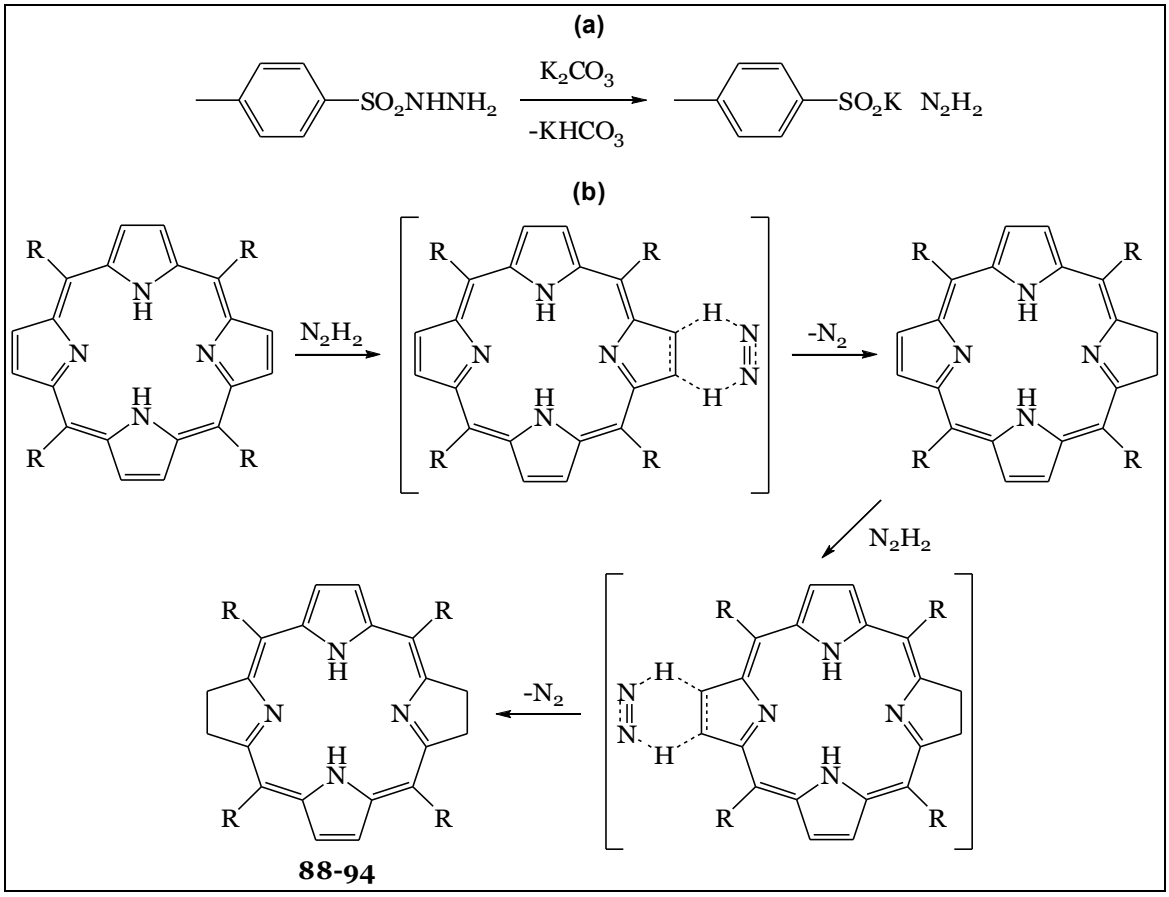


Figure 3.7. UV-Vis absorption spectrum of 5,10,15,20-tetraphenylbacteriochlorin **88** in dichloromethane.



Scheme 3.32. Mechanistic proposal for the *in situ* generation of di-imide (a) and the synthesis of *meso*-tetraarylbacteriochlorins **88-94** (b).

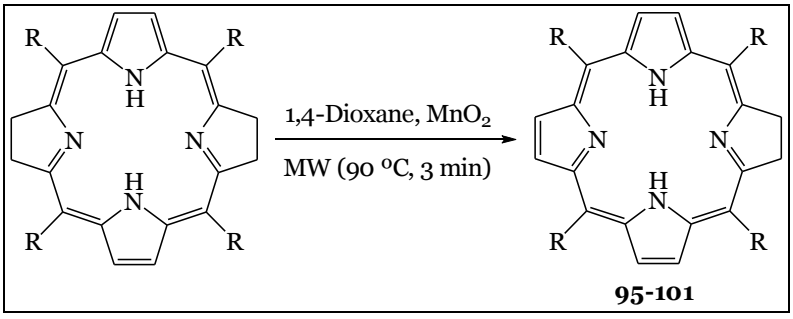
A large excess of *p*-toluenesulphonyl hydrazide and anhydrous potassium carbonate were required to ensure that enough di-imide was being formed *in situ* and, consequently, becoming available to hydrogenate the exocyclic double bonds of the porphyrin. A mixture of both (*E*) and (*Z*) isomers of di-imide is produced, both of which are quite unstable. The (*E*)-(*Z*) equilibrium favours the latter structure owing to its consumption upon reaction with the unsaturated substrate.[91] A possible mechanistic pathway for the preparation of bacteriochlorins **88-94** through di-imide-promoted reduction of the corresponding porphyrins is given in Scheme 3.32. Briefly, formation of di-imide via base-assisted cleavage of *p*-TSH is followed by a concerted hydrogen transfer to one of the exocyclic unsaturated centres of the porphyrin, rendering the respective chlorin. A second hydrogen transfer of di-imide to the remaining exocyclic double bond affords the target bacteriochlorin. It was observed that the internal pressure inside the closed reaction vial raised substantially in the first minutes of the synthetic process and then became increasingly steadier. This can be rationalised by the formation of gaseous nitrogen as a by-product of the reduction reaction, as well as the result of di-imide disproportionation, which renders both nitrogen gas and hydrazine. In fact, it is well known that this rapid decomposition phenomenon is an important competitive process regarding the hydrogenation of double and triple bonds.[91, 92]

We then turned our attention to the microwave-assisted synthesis of some *meso*-substituted chlorins via selective dehydrogenation of the bacteriochlorin analogues that were previously prepared as described above. Activated manganese dioxide was again chosen as the oxidising agent. After a few trials using TPB **88** as the initial reagent, in order to study the influence of both the reaction time and temperature and also the stoichiometry of the heterogeneous oxidant, it was determined that the most effective reaction conditions were microwave heating a mixture of the selected bacteriochlorin and an excess of activated MnO_2 in 1,4-dioxane at 90 ^oC for 3 minutes. Washing the crude product mixture with a suitable organic solvent, followed by filtration through a small column of SiO_2 and evaporation under reduced pressure, provided the desired chlorin compounds **95-101** with high yields, although contaminated with the corresponding porphyrins (Table 3.2; Scheme 3.33).[90] As an example, the absorption spectra of 5,10,15,20-tetraphenylchlorin in the UV-Vis region is depicted in Figure 3.8.

Table 3.2. Synthesis of *meso*-tetraarylchlorins **95-101** under microwave irradiation.

Entry	Compound	R	Yield[a] (%, Chlorin/Porphyrin Ratio)[b]
1	**95**	Ph	92, 80/20
2	**96**	*o*-$Cl_2C_6H_3$	85, 75/25
3	**97**	*m*-$OMeC_6H_4$	93, 90/10
4	**98**	*m*-OHC_6H_4	88, 65/35
5	**99**	*p*-$OMeC_6H_4$	90, 90/10
6	**100**	*p*-BrC_6H_4	88, 85/15
7	**101**	*p*-*t*-BuC_6H_4	86, 70/30

All reactions were carried-out using the selected bacteriochlorin (23-24 mg), activated manganese dioxide (50 molar equivalents) and 1,4-dioxane (2 ml) at 90 ^oC for 3 minutes in a closed vessel. [a]Yields refer to the isolated reaction products. [b]Assessed by ^1H NMR analysis of the isolated reaction products.



Scheme 3.33. Synthesis of *meso*-tetraarylchlorins **95-101** under microwave irradiation.

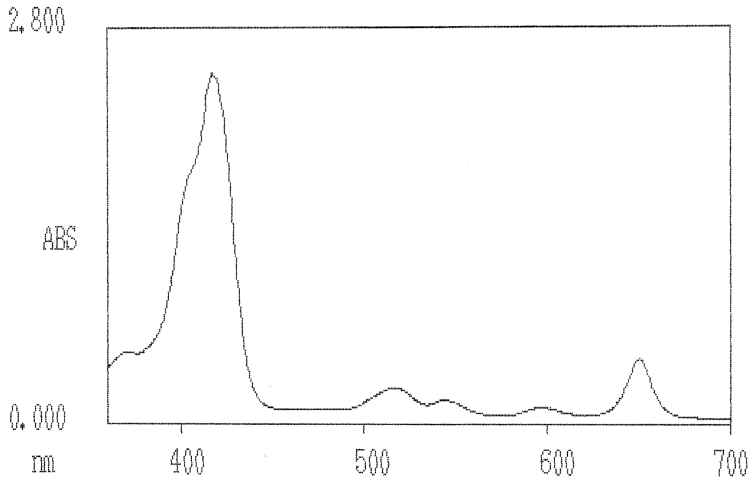


Figure 3.8. UV-Vis absorption spectrum of 5,10,15,20-tetraphenylchlorin **95** in dichloromethane.

It may be stated from the data summarised in Table 3.2 that, in general, *meso*-tetraarylchlorins were efficiently prepared through this microwave-activated and MnO_2-promoted process, reaction yields ranging from 85 to 93% being attained. For instance, methoxylated chlorins **97** and **99** were obtained with superior reaction yields, only 10% of the final product being the respective porphyrin contaminants (entries 3 and 5). The selectivity in the oxidation of the bacteriochlorin chromophore can be seen in the synthesis of chlorin **101** (entry 7). Dehydrogenation of a mixture containing a bacteriochlorin/chlorin/porphyrin proportion of 45/30/25, afforded the target chlorin contaminated with 30% of the corresponding porphyrin. Hence, the amount of porphyrin remained nearly unaltered after the reaction took place, demonstrating that all the bacteriochlorin component of the starting material was oxidised to the respective chlorin and only a tiny fraction of the pre-existing chlorin was oxidised to the porphyrin. Furthermore, the replacement of *o*-TCQ, the traditionally utilised yet highly toxic and expensive oxidising agent, by the much cheaper activated manganese dioxide proved to be a beneficial modification to the classic Whitlock methodology, both from the economical and environmental perspectives, even considering the demand of using a larger excess of the oxidant in our heterogeneous approach. Additionally, simple filtration through a small amount of SiO_2 was sufficient to isolate the chlorin compounds, numerous and tedious extraction processes and rather complex and lengthy chromatographic separations being averted.

IV. Summary

A series of *meso*-tetraarylporphyrins **57-81** was rapidly synthesised through a one-pot methodology under microwave irradiation. The isolated yields achieved were usually higher than the ones attained via the related conventional heating method or through our previously reported microwave-assisted approach using a domestic microwave oven. The same procedure was also successfully applied to the preparation of some unsymmetrical *meso*-tetraarylporphyrins of the A_3B type **82-87**. An alternative two-step synthesis of *meso*-substituted porphyrins, in which microwave-heating was applied in the second reaction step and the expensive, toxic and conventionally utilised quinone oxidants, i.e. *o*-TCQ, *p*-TCQ and DDQ, were replaced by the much cheaper and user-friendly activated manganese dioxide, was investigated under different reaction conditions, compounds **57**, **58** and **60** being obtained with low to moderately good reaction yields. The broadly known di-imide-mediated reduction of porphyrins to their hydroporphyrin analogues was revised and studied under microwave-assisted conditions. Bacteriochlorins **89-94** were readily obtained with very high yields (90-96%), albeit contaminated with up to 35% of the corresponding chlorins and, in one case, also with 25% of the porphyrin starting material. Lastly, the selective MnO_2-promoted dehydrogenation of the previously prepared bacteriochlorins was carried-out under microwave irradiation. The target chlorin compounds **95-101** were quickly synthesised and easily isolated with high yields (85-93%), although contaminated with 10 to 35% of the corresponding porphyrins.

V. References

1. JL Sessler, SJ Weghorn, *Expanded, Contracted & Isomeric Porphyrins*, Pergamon Press, Oxford, England, UK, 1997.
2. D Wöhrle, *J. Porph. Phthal.* 4 (**2000**) 418-424.
3. LR Milgrom, *The Colours of Life: an Introduction to the Chemistry of Porphyrins and Related Compounds*, Oxford University Press, Oxford, England, UK, 1997.
4. RS Czernuszewicz, *J. Porph. Phthal.* 4 (**2000**) 426-431.
5. AR Battersby, *Nat. Prod. Rep.* 17 (**2000**) 507-526.
6. WM Campbell, AK Burrell, DL Officer, KW Jolley, *Coord. Chem. Rev.* 248 (**2004**) 1363-1379.
7. KS Suslick, NA Rakow, ME Kosal, J-H Chou, *J. Porph. Phthal.* 4 (**2000**) 407-413.
8. J-H Chou, HS Nalwa, ME Kosal, NA Rakow, KS Suslick, in *The Porphyrin Handbook*, KM Kadish, KM Smith, R Guilard (Eds), Academic Press, San Diego, CA, USA, 2000, Volume 6, Chapter 41, pp 43-132.
9. AK Burrell, MR Wasielewski, *J. Porph. Phthal.* 4 (**2000**) 401-406.
10. NR Armstrong, *J. Porph. Phthal.* 4 (**2000**) 414-417.
11. T Malinski, in *The Porphyrin Handbook,* KM Kadish, KM Smith, R Guilard (Eds), Academic Press, San Diego, CA, USA, 2000, Volume 6, Chapter 44, pp 231-256.
12. H Ogoshi, T Mizutani, T Hayashi, Y Kuroda, in *The Porphyrin Handbook*, KM Kadish, KM Smith, R Guilard (Eds), Academic Press, San Diego, CA, USA, 2000, Volume 6, Chapter 46, pp 279-340.
13. MK Chan, *J. Porph. Phthal.* 4 (**2000**) 358-361.
14. BG Maya, *J. Porph. Phthal.* 4 (**2000**) 393-397.
15. T Aida, S Inoue, in *The Porphyrin Handbook*, KM Kadish, KM Smith, R Guilard (Eds), Academic Press, San Diego, CA, USA, 2000, Volume 6, Chapter 42, pp 133-156.
16. AMd'A Rocha Gonsalves, MM Pereira, *J. Mol. Catal. A Chem.* 113 (**1996**) 209-221.
17. JT Groves, *J. Porph. Phthal.* 4 (**2000**) 350-352.
18. G Ohloff, *Pure Appl. Chem.* 43 (**1975**) 481-502.
19. HH Wasserman, JL Ives, *Tetrahedron* 37 (**1981**) 1825-1852.
20. EA Lissi, MV Encinas, E Lemp, MA Rubio, *Chem. Rev.* 93 (**1993**) 699-723.
21. D Murtinho, M Pineiro, MM Pereira, AMd'A Rocha Gonsalves, LG Arnaut, MG Miguel, HD Burrows, *J. Chem. Soc. Perkin Trans. 2* (**2000**) 2441-2447.
22. TB Amor, L Bortolotto, G Jori, *Photochem. Photobiol.* 68 (**1998**) 314-318.
23. RK Pandey, G Zheng, in *The Porphyrin Handbook*, KM Kadish, KM Smith, R Guilard (Eds), Academic Press, San Diego, CA, USA, 2000, Volume 6, Chapter 43, pp 157-230.
24. R Bonnett, *Chemical Aspects of Photodynamic Therapy*, Gordon & Breach Science Publishers, Amsterdam, The Netherlands, 2000.
25. AC Serra, M Pineiro, NAM Pereira, AMd'A Rocha Gonsalves, M Laranjo, M Abrantes, MF Botelho, *Oncol. Rev.* 2 (**2008**) 235-249.
26. S Bonneau, C Vever-Bizet, *Expert Opin. Ther. Patents* 18 (**2008**) 1011-1025.
27. S Rywkin, E Ben-Hur, Z Malik, AM Prince, Y-S Li, ME Kenney, NL Oleinik, B Horowitz, *Photochem. Photobiol.* 60 (**1994**) 165-170.
28. F Buchard, N Ansgar, *Angew. Chem. Int. Ed.* 34 (**1995**) 1795-1811.
29. E Ben-Hur, B Horowitz, *Photochem. Photobiol.* 62 (**1995**) 383-388.
30. L Costa, MAF Faustino, MGPMS Neves, A Cunha, A Almeida, *Viruses* 4 (**2012**) 1034-1074.
31. S Shanmugathasan, C Edwards, RW Boyle, *Tetrahedron* 56 (**2000**) 1025-1046.
32. V Král, J Králová, R Kaplánek, T Bríza, P Martasék, *Physiol. Res.* 55 (**2006**) S3-S26.
33. AMd'A Rocha Gonsalves, AC Serra, M Pineiro, *J. Porph. Phthal.* 13 (**2009**) 429-445.
34. P Rothemund, *J. Am. Chem. Soc.* 57 (**1935**) 2010-2011.

35. P Rothemund, *J. Am. Chem. Soc.* 58 (**1936**) 625-627.
36. P Rothemund, *J. Am. Chem. Soc.* 61 (**1939**) 2912-2915.
37. P Rothemund, AR Menotti, *J. Am. Chem. Soc.* 63 (**1941**) 267-270.
38. AD Adler, FR Longo, JD Finarelli, J Goldmacher, J Assour, L Korsakoff, *J. Org. Chem.* 86 (**1964**) 3145-3149.
39. AD Adler, FR Longo, JD Finarelli, J Goldmacher, J Assour, L Karsakoff, *J. Org. Chem.* 32 (**1967**) 476-477.
40. AD Adler, L Sklar, FR Longo, JD Finarelli, *J. Heteroc. Chem.* 5 (**1968**) 669-678.
41. FR Longo, JD Finarelli, JB Kim, *J. Heteroc. Chem.* 6 (**1969**) 927-931.
42. JB Kim, JJ Leonard, FR Longo, *J. Am. Chem. Soc.* 94 (**1972**) 3986-3992.
43. AMd'A Rocha Gonsalves, MM Pereira, *J. Heteroc. Chem.* 22 (**1985**) 931-933.
44. JS Lindsey, HC Hsu, IC Schreiman, *Tetrahedron Lett.* 27 (**1986**) 4969-4970.
45. JS Lindsey, IC Schreiman, HC Hsu, PC Kearney, AM Marguerettaz, *J. Org. Chem.* 52 (**1987**) 827-836.
46. JS Lindsey, RW Wagner, *J. Org. Chem.* 54 (**1989**) 828-836.
47. AMd'A Rocha Gonsalves, JMTB Varejão, MM Pereira, *J. Heteroc. Chem.* 28 (**1991**) 635-640.
48. RAW Johnstone, MLPG Nunes, MM Pereira, AMd'A Rocha Gonsalves, AC Serra, *Heterocycles* 43 (**1996**) 1423-1437.
49. M Homma, K Aoyagi, Y Aoyama, H Ogoshi, *Tetrahedron Lett.* 24 (**1983**) 4343-4346.
50. K Aoyagi, H Toi, Y Aoyama, H Ogoshi, *Chem. Lett.* (**1988**) 1891-1894.
51. GP Arsenault, E Bullock, SF MacDonald, *J. Am. Chem. Soc.* 82 (**1960**) 4384-4389.
52. MJ Broadhurst, R Grigg, AW Johnson, *J. Chem. Soc. C* (**1971**) 3681-3690.
53. TD Lash, *J. Porph. Phthal.* 1 (**1997**) 29-44.
54. PS Clezy, L van Thuc, *Aust. J. Chem.* 37 (**1984**) 2085-2092.
55. TP Wijesekera, D Dolphin, *Synlett* (**1990**) 235-244.
56. P-Y Hin, TP Wijesekera, D Dolphin, *Can. J. Chem.* 68 (**1990**) 1867-1875.
57. N Otero, S Fias, S Radenkovic, P Bultinck, AM Graña, M Mandado, *Chem. Eur. J.* 17 (**2011**) 3274-3286.
58. HW Whitlock, R Hanauer, MY Oester, BK Bower, *J. Am. Chem. Soc.* 91 (**1969**) 7485-7489.
59. R Bonnett, RD White, U-J Winfield, MC Berenbaum, *Biochem. J.* 261 (**1989**) 277-280.
60. MM Pereira, AR Abreu, NPF Gonçalves, MJF Calvete, AVC Simões, CJP Monteiro, LG Arnaut, ME Eusébio, J Canotilho, *Green Chem.* 14 (**2012**) 1666-1672.
61. HH Inhoffen, W Nolte, *Liebigs Ann. Chem.* 725 (**1969**) 167-176.
62. C Brückner, D Dolphin, *Tetrahedron Lett.* 36 (**1995**) 3295-3298.
63. C Brückner, D Dolphin, *Tetrahedron Lett.* 52 (**1995**) 9425-9428.
64. Y-H Paul, TP Wijesekera, D Dolphin, *Tetrahedron Lett.* 32 (**1991**) 2875-2878.
65. AC Tomé, PSS Lacerda, MGPMS Neves, JAS Cavaleiro, *Chem. Commun.* (**1997**) 1199-1200.
66. AMG Silva, AC Tomé, MGPMS Neves, AMS Silva, JAS Cavaleiro, *Chem. Commun.* (**1999**) 1767-1768.
67. AC Serra, AMd'A Rocha Gonsalves, *Tetrahedron Lett.* 51 (**2010**) 4192-4194.
68. AN Kozyrev, V Suresh, S Das, MO Senge, M Shibata, TJ Dougherty, RK Pandey, *Tetrahedron* 56 (**2000**) 3353-3364.
69. PA Jacobi, S Lanz, I Ghosh, SH Leung, F Löwer, D Pippin, *Org. Lett.* 3 (**2001**) 831-834.
70. DH Burns, DC Shi, TD Lash, *Chem. Commun.* (**2000**) 299-300.
71. AR Battersby, CJ Dutton, CJR Fookes, SPD Turner, *J. Chem. Soc. Chem. Commun.* (**1983**) 1235-1237.
72. AR Battersby, CJ Dutton, CJR Fookes, *J. Chem. Soc. Perkin Trans. 1* (**1988**) 1569-1576.
73. F-P Montforts, UM Schwartz, *Liebigs Ann. Chem.* (**1991**) 709-725.
74. Y Abels, F-P Montforts, *Tetrahedron Lett.* 38 (**1997**) 1745-1748.
75. A Petit, A Loupy, P Maillard, M Momenteau, *Synth. Commun.* 22 (**1992**) 1137-1142.
76. SMS Chauhan, BB Sahoo, KA Srinivas, *Synth. Commun.* 31 (**2001**) 33-37.
77. M Radha Kishan, V Radha Rani, MRVS Murty, P Sita Devi, SJ Kulkarni, KV Raghavan, *J. Mol. Catal. A Chem.* 223 (**2004**) 263-267.

78. MO Liu, C-H Tai, C-W Chen, W-C Chang, AT Hu, *J. Photochem. Photobiol. A Chem.* 163 (**2004**) 259-266.
79. BFO Nascimento, M Pineiro, AMd'A Rocha Gonsalves, MR Silva, AM Beja, JA Paixão, *J. Porph. Phthal.* 11 (**2007**) 77-84.
80. R Socoteanu, R Boscencu, V Nacea, AS Oliveira, LF Vieira Ferreira, *Rev. Chim.* 59 (**2008**) 969-972.
81. M Yaseen, M Ali, MN Ullah, MA Munawar, I Khokhar, *J. Heteroc. Chem.* 46 (**2009**) 251-255.
82. R Lucas, J Vergnaud, K Teste, R Zerrouki, V Sol, P Krausz, *Tetrahedron Lett.* 49 (**2008**) 5537-5539.
83. B Boëns, P-A Faugeras, J Vergnaud, R Lucas, K Teste, R Zerrouki, *Tetrahedron* 66 (**2010**) 1994-1996.
84. AMG Silva, AC Tomé, MGPMS Neves, JAS Cavaleiro, CO Kape, *Tetrahedron Lett.* 46 (**2005**) 4723-4726.
85. NAM Pereira, AC Serra, TMVD Pinho e Melo, *Eur. J. Org. Chem.* (**2010**) 6539-6543.
86. NAM Pereira, SM Fonseca, AC Serra, TMVD Pinho e Melo, HD Burrows, *Eur. J. Org. Chem.* (**2011**) 3970-3979.
87. A Fatiadi, *Synthesis* (**1976**) 65-104.
88. A Fatiadi, *Synthesis* (**1976**) 133-167.
89. AT Soldatenkov, KB Polyanskii, NM Kolyadina, SA Soldatova, *Chem. Heteroc. Comp.* 45 (**2009**) 633-657.
90. BFO Nascimento, AMd'A Rocha Gonsalves, M Pineiro, *Inorg. Chem. Commun.* 13 (**2010**) 395-398.
91. S Hünig, HR Müller, W Thier, *Angew. Chem. Int. Ed.* 4 (**1965**) 271-280.
92. F Aylward, M Sawistowska, *Chem. Ind.* (**1962**) 484-491.

4

Hantzsch 1,4-Dihydropyridines

I. Introduction & Relevance

Described over 130 years ago by the German chemist Arthur Rudolph Hantzsch,[1, 2] the synthesis of 1,4-dihydropyridines (DHPs) has attracted considerable interest as a multicomponent reaction that provides six-membered nitrogen-containing heterocycles of pharmacological significance.[3] It was uncovered in the 1930s that the DHP motif was an active part of the reduced nicotinamide adenine dinucleotide co-enzymes NADH, NADPH and their analogues, which are responsible for mediating crucial hydride transfer reactions in biological systems (Figure 4.1).[4] Analgesic properties were not reported until the mid-1970s and an enormous amount of papers and patents dealing with the chemistry, biochemistry and pharmacology of Hantzsch DHPs as antihypertensive and hypoglycaemic substances was presented after the seminal publication of Loev and colleagues.[5] Several commercial DHP derivatives are currently recognised as important therapeutic agents in the treatment of cardiovascular diseases, such as angina, hypertension and arrhythmia (Figure 4.2). It has been established that their successful application in this field is related to their efficacy to bind to calcium channels and, consequently, to decrease the passage of the transmembrane calcium current, associated in smooth muscle with a long lasting relaxation and in cardiac muscle with a reduction of contractility throughout the heart.[5-7]

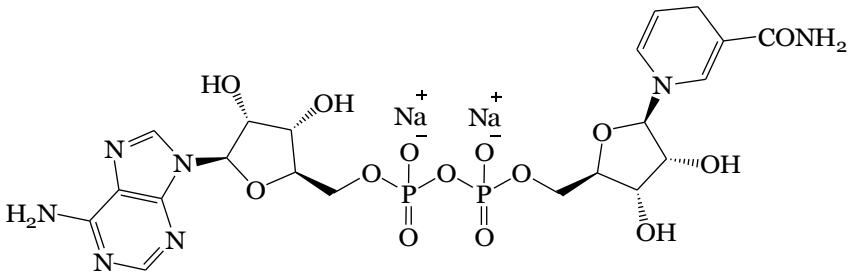


Figure 4.1. Structure of the reduced nicotinamide adenine dinucleotide NADH.

It is known that some dihydropyridine scaffolds play a decisive role in brain-targeted chemical delivery systems. For instance, the attachment of a dihydropyridyl unit to a given pharmacophore enhances the lipophilicity of the conjugate and, therefore, improves the access to the central nervous system. Once inside, the enzyme-promoted oxidation to the corresponding pyridinium salt locks this compound in the inner side of the blood-brain barrier and subsequent hydrolysis liberates the active compound.[8] This concept has been applied to the transport of neuropeptides,[9] hormone analogues,[10] antioxidants,[11] AZT derivatives[12] and even to some Hantzsch 1,4-dihydropyridines.[13] The remarkable affinity of dihydropyridine structures to bioreceptors, e.g. α_{1a}-adrenergic,[14] A_3-adenosine[15] and neuropeptide YY_1 receptors,[16] has also been assessed, resulting in novel, selective and potent antagonists. Moreover, it has been suggested that multidrug resistance may be surmounted by dihydropyridine-containing molecules without severe side effects.[17] A non-competitive inhibition of topoisomerase I was observed for dexniguldipine, an antitumour and multidrug resistance reverting dihydropyridine.[18] Radioprotection[19] and modulation of cocaine dependence in animals[20] were also described for Hantzsch DHPs. Finasteride, a 4-azasteroid drug employed in the treatment of benign prostatic hyperplasia, was shown to exert its inhibition on a NADPH-dependent enzyme by forming a covalent dihydropyridine adduct with the NADP moiety.[21] Furthermore, new and efficient gene delivery systems based on cationic liposomes bearing charged amphiphilic 1,4-dihydropyridines have been described.[22] Several DHP derivatives exhibiting anticonvulsant[23] and antitubercular activities[24] have also been reported.

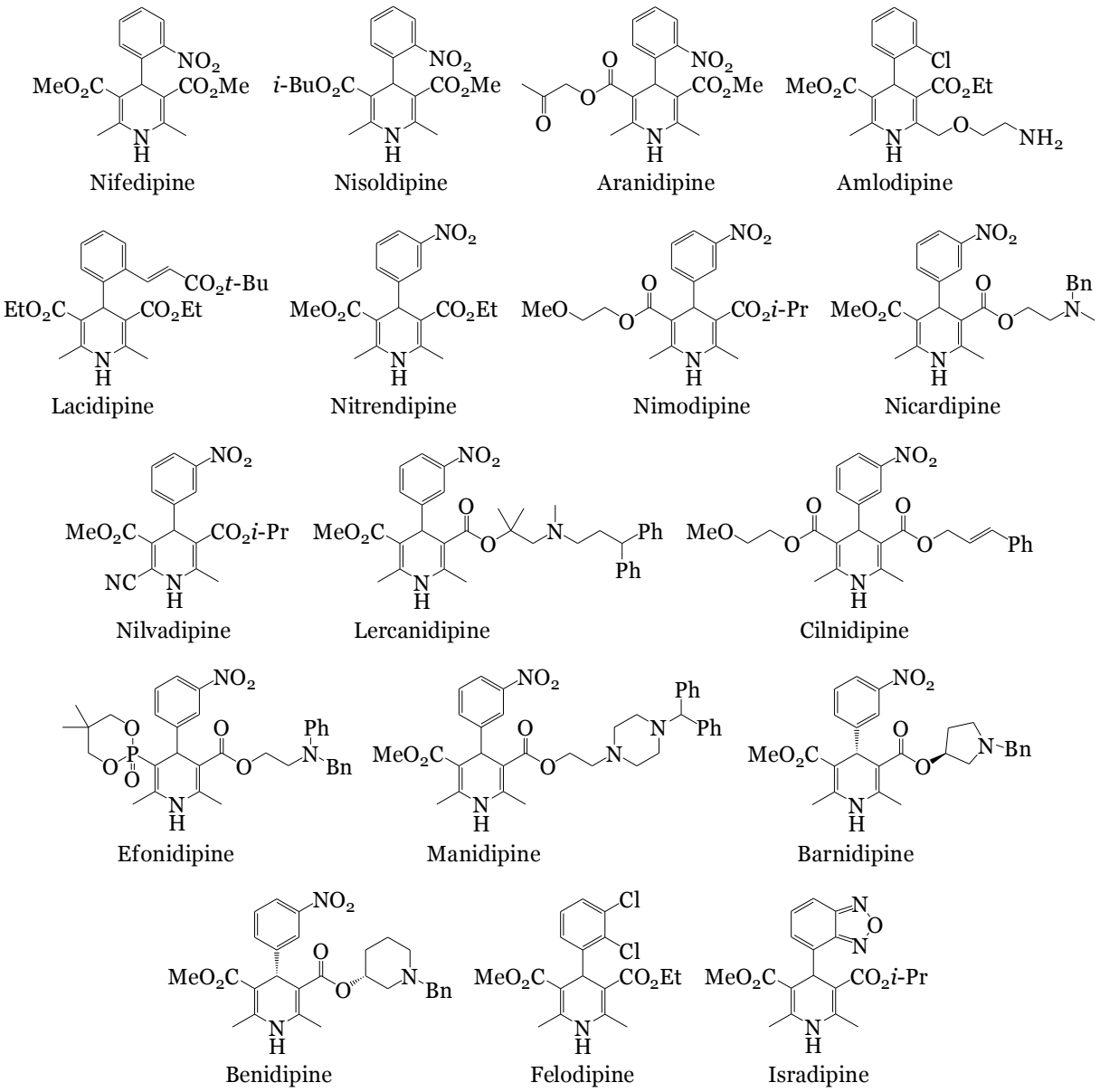


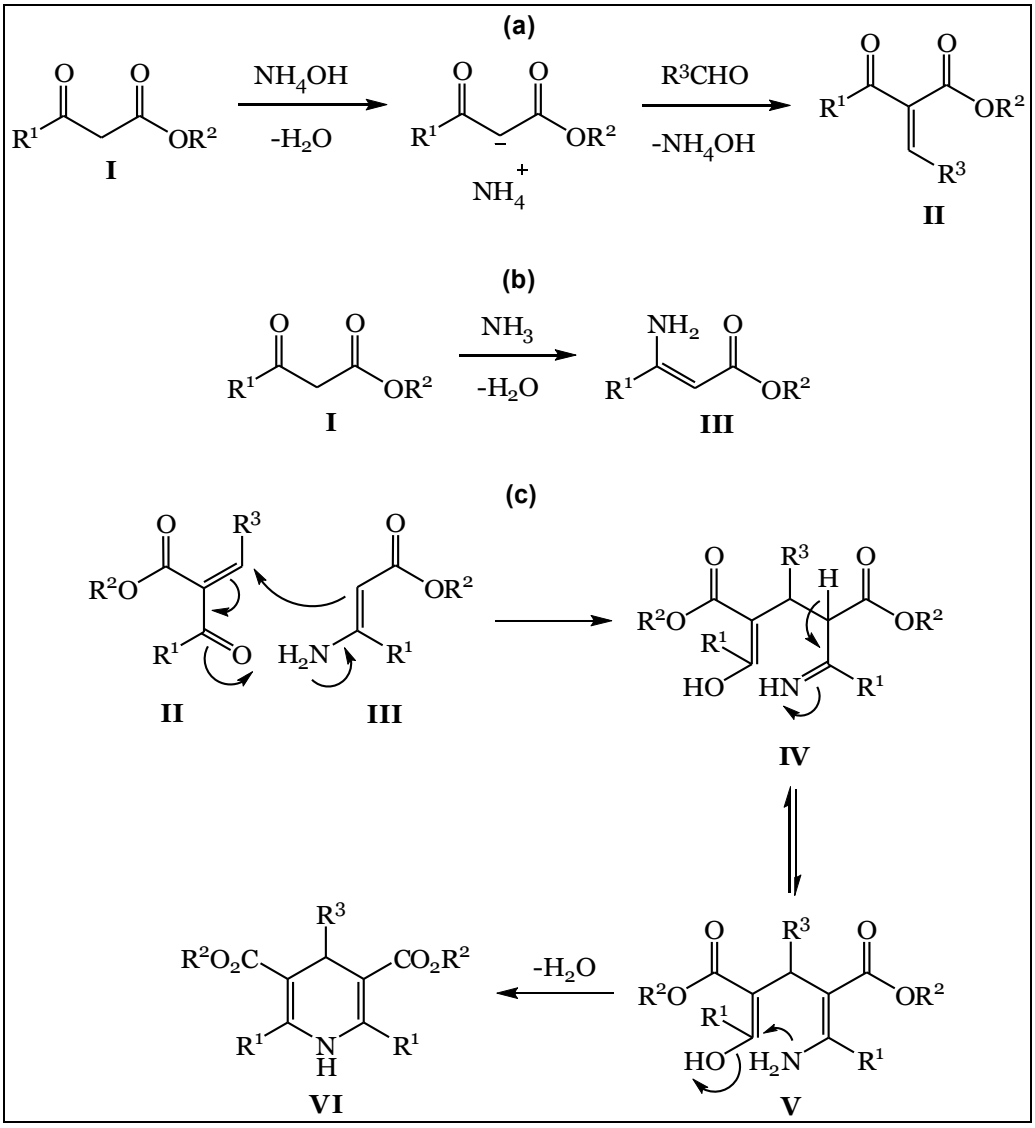
Figure 4.2. Representative examples of Hantzsch 1,4-dihydropyridine compounds relevant in cardiovascular diseases as calcium channel antagonists.

On a related matter, the oxidative aromatisation of Hantzsch 1,4-dihydropyridines has been the subject of a vast number of studies in the last 25 years or so, since Böcker and Guengerich demonstrated that the *in vivo* metabolism of these molecules involved an important oxidative process catalysed by cytochrome P450.[25] The resulting pyridines, although devoid of the pharmacological properties of their preceding heterocycles, may be further and properly modified, rendering other biologically interesting molecules. In fact, several commercial drugs possessing antiseptic, antihistaminical and antirheumatismal activities display a multisubstituted pyridine as the key structural element.[26, 27]

II. Classical Synthetic Methods

As pointed-out above, the first report on the preparation of 1,4-dihydropyridines was produced by Hantzsch in the 19th century and it described the one-pot condensation reaction of an aldehyde, a β-ketoester and ammonium hydroxide in refluxing ethanol.[1, 2] Apart from Hantzsch, Beyer[28] and Knoevenagel[29] were amongst the first researchers to study this synthetic process (Scheme 4.1). It can be visualised as proceeding through a Knoevenagel

condensation product, i.e. an arylidene- or alkylidene-type 1,3-dicarbonyl compound **II**, as a key intermediate (a). A second intermediate is an enaminone-like structure **III**, which is formed by condensation of a second equivalent of the β-ketoester **I** with ammonia (b). Further condensation between these key fragments affords the DHP derivative **VI** via cyclisation of an imine **IV**/enamine **V** system (c).

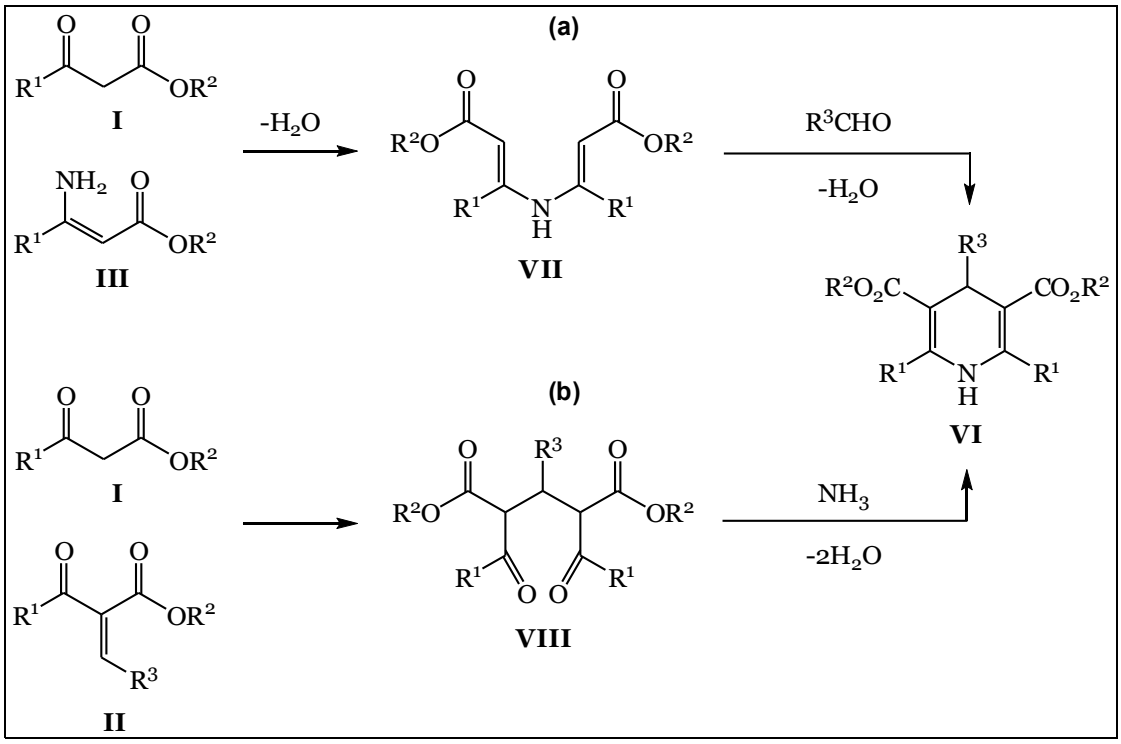


Scheme 4.1. Mechanistic proposal for the Hantzsch synthesis of 1,4-dihydropyridines.

Another possible mechanistic pathway involves the reaction between enaminone **III** and β-ketoester **I**, followed by condensation of the resulting intermediate **VII** with the aldehyde starting material (Scheme 4.2a). Also, a 1,5-diketone structure **VIII** may be generated through the reaction of the Knoevenagel intermediate **II** and β-ketoester **I**. Further condensation with ammonia provides the target 1,4-dihydropyridine **VI** (Scheme 4.2b). It should be stressed that the reaction mechanism of the Hantzsch 1,4-dihydropyridine synthesis was exhaustively studied by NMR spectroscopy in the 1980s and it was established that the synthetic operation occurs through the intermediates depicted in Scheme 4.1.[30, 31]

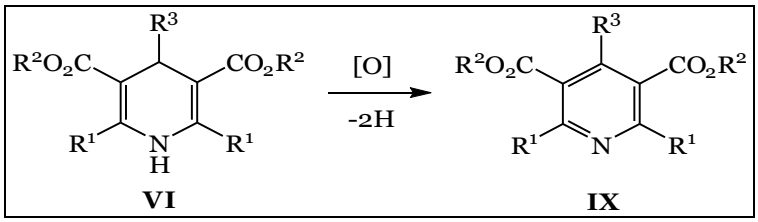
Generally speaking, DHPs can be prepared via the Hantzsch methodology, reduction of or addition to appropriate pyridines and several cycloaddition reactions.[32-34] Being a simple and widely tolerable protocol, the Hantzsch reaction is still one of the most broadly utilised procedures to access variously substituted DHPs in a large number of areas, such as stereoselective synthesis and green chemistry strategies.[35-41] Nevertheless, given the rapid progress of the chemical and pharmaceutical industries, some limitations of this classical multicomponent approach have been observed. One of them is that the 1,4-dihydropyridines synthesised are all

symmetrical in the heterocyclic moiety, since this unit is built by using two molecules of the same 1,3-dicarbonyl reagent. Although two different 1,3-dicarbonyl compounds can be employed, the symmetrical DHPs formed by the homocondensation of the starting materials are still produced in large quantities, which lowers the reaction yields and makes the purification process more troublesome. Considering biological screening, one can state that obtaining several diversified structures of a given pharmacophore is an efficient strategy for discovering new biologically active lead compounds.[42] Notwithstanding many reported 1,4-dihydropyridines possessing promising biological activities are symmetrical, this was not a specific requirement of the biological receptors studied, but the result of employing the Hantzsch method for the preparation of the majority of the known DHP derivatives. Therefore, the synthesis of novel, structurally-diverse and bioactive 1,4-dihydropyridines, including some unsymmetrical DHP systems, remains a riveting and continuously growing subject to the organic synthesis, chemical biology and medicinal chemistry communities.



Scheme 4.2. Alternative mechanistic proposals for the Hantzsch synthesis of 1,4-dihydropyridines.

A wide assortment of oxidants has been applied to the oxidative aromatisation of Hantzsch 1,4-dihydropyridines and subsequent preparation of the respective pyridine heterocycles **IX** (Scheme 4.3): solid-supported ferric and cupric nitrates,[43] ceric ammonium nitrate (CAN),[44] clay-supported cupric nitrate under ultrasounds,[45] MnO_2,[46] DDQ,[46] nitric oxide,[47] bismuth(III) nitrate,[48] pyridinium chlorochromate (PCC),[49] cobalt(II) *tetrakis*(pyridine) dichromate,[50] nicotinum dichromate,[51] *S*-nitrosoglutathione,[52] N_2O_4/18-crown-6,[53] 3-carboxypyridinium chlorochromate (CPCC),[54] $KMnO_4$,[55] HNO_3,[56] HNO_2,[57] *t*-butyl hydroperoxide (TBHP),[58] phenyliodine(III) bis(trifluoroacetate),[59] elemental sulphur,[59] combination of inorganic and acidic salts with sodium nitrite or sodium nitrate,[60] polystyrene-bound metalloporphyrin/$NaIO_4$,[61] metalloporphyrin/*n*-Bu_4NIO_4,[62] triazolinediones,[63] H_2O_2/$Co(OAc)_2$,[64] $Zr(NO_3)_4$,[65] urea nitrate,[66] cobalt(II) peroxydisulphate,[66] hypervalent iodine reagents,[67] I_2/MeOH,[68] SeO_2,[69] heteropolyacid/$NaNO_2$/SiO_2,[70] $Mn(OAc)_3$,[71] *N*-hydroxyphthalimide/O_2/$Co(OAc)_2$,[72] $Fe(ClO_4)_3$/AcOH,[73] manganese(III)-salophen/$NaIO_4$,[74] Pd/C in acetic acid,[75] HgO/I_2,[76] urea/H_2O_2,[77] vanadium(V) salts,[78] electrochemical[79] and photochemical[80] methods, among others. Even so, many of the published oxidation methods require extended periods of time for completion, make use of a large excess of strong oxidising agents, afford moderate reaction yields, generate by-products which are difficult to remove and utilise highly toxic and expensive oxidants and/or catalysts.



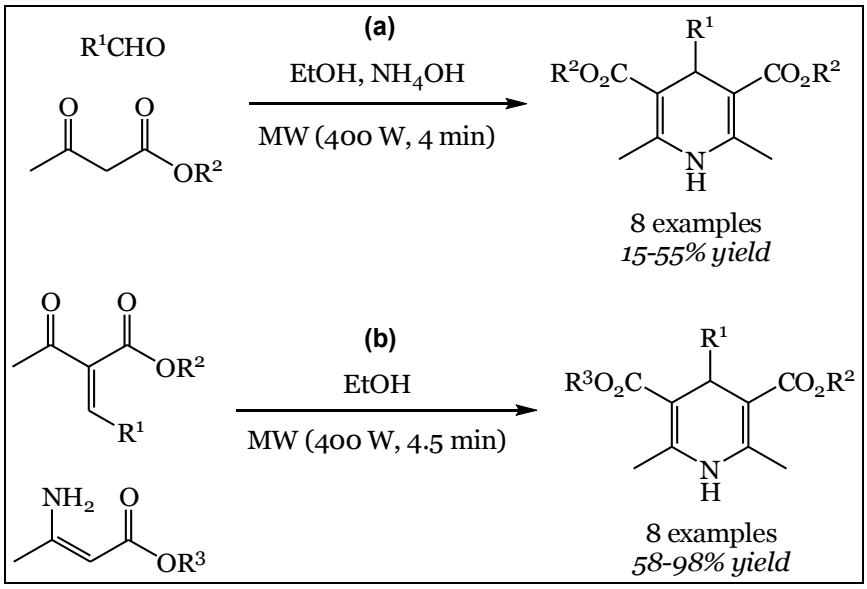
Scheme 4.3. Oxidative aromatisation of Hantzsch 1,4-dihydropyridines.

III. Microwave-Assisted Synthetic Methods

Several modifications to the classical Hantzsch protocol and recent advances that extend far beyond it have been the topic of interesting review papers,[81-83] the successful application of microwave irradiation also being addressed in detail.[84-87] Some examples of the microwave-assisted preparation of Hantzsch DHPs, as well as of their corresponding pyridine derivatives, are summarised in the following section.

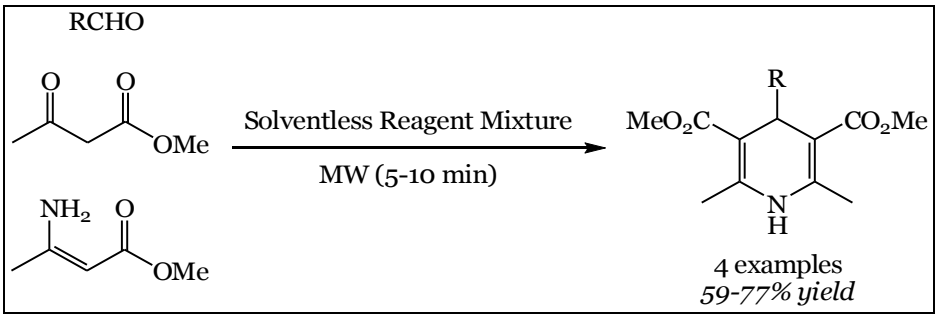
A. Literature Review & Selected Examples

The ground-breaking report on the employment of microwaves to the preparation of Hantzsch DHPs was published in 1992 by Alajarin and co-workers.[88] A small series of 4-aryl derivatives was obtained in only 4 minutes making use of ethanol as solvent, closed Teflon reaction vessels and a household microwave equipment (Scheme 4.4a). Although the yields were poor to moderate and chromatographic purification was mandatory, the group claimed that conventional heating procedures required a reflux period of 12 hours in order to afford equal structures in similar yields. A few years later the same authors extended their work to the synthesis of some unsymmetrical 1,4-dihydropyridines, starting from suitable arylidene-type 1,3-dicarbonyl compounds and alkyl 3-aminocrotonates (Scheme 4.4b). Again, chromatographic work-up was necessary to obtain the pure products.[89]



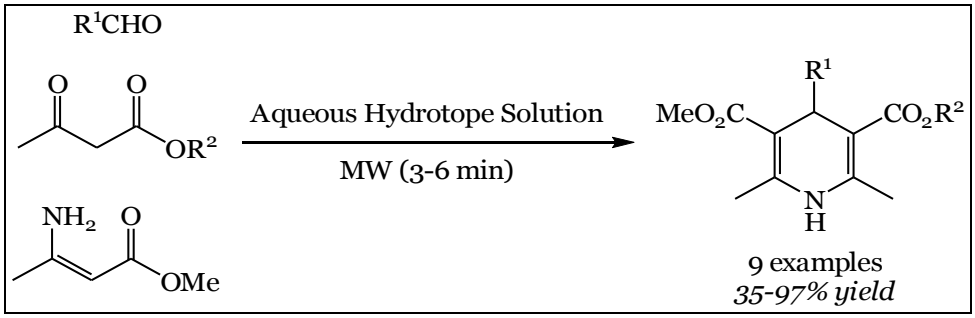
Scheme 4.4. Synthesis of Hantzsch 1,4-dihydropyridines in ethanol.

Zhang and colleagues presented a solvent-free synthesis of 1,4-dihydropyridines under microwave irradiation in 1995.[90] Yields ranging from 59 to 77% were achieved under 10 minutes using a domestic oven, the reaction vials being fitted with a condenser containing chilled xylenes (Scheme 4.5). In the same year and utilising identical starting materials, but in the presence of an unreported amount of ethanol as solvent, the research team of Khadilkar described the preparation of some Hantzsch DHPs with isolated yields between 32 and 80%.[91]



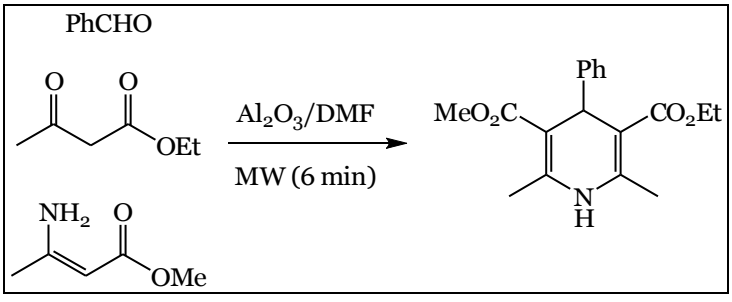
Scheme 4.5. Solventless synthesis of Hantzsch 1,4-dihydropyridines.

Khadilkar and co-workers also explored the microwave-promoted synthesis of 1,4-dihydropyridines in an aqueous hydrotrope solution, sodium *n*-butylmonoglycosulphate, to be exact.[92] The experiments were carried-out in a domestic apparatus, using methyl 3-aminocrotonate, alkyl acetoacetates and aliphatic or aromatic aldehydes as reagents (Scheme 4.6). It should be noticed that these methods were performed by microwave heating the reaction mixtures in vessels equipped with a condenser charged with pre-cooled carbon tetrachloride, in order to prevent any loss of volatile materials.[91, 92] Furthermore, the same research group later published the scale-up preparation of some clinically important Hantzsch DHPs utilising a modified household microwave oven and evaluated different aqueous hydrotrope solutions as reaction media, both in batch and in continuous-flow processes.[93]



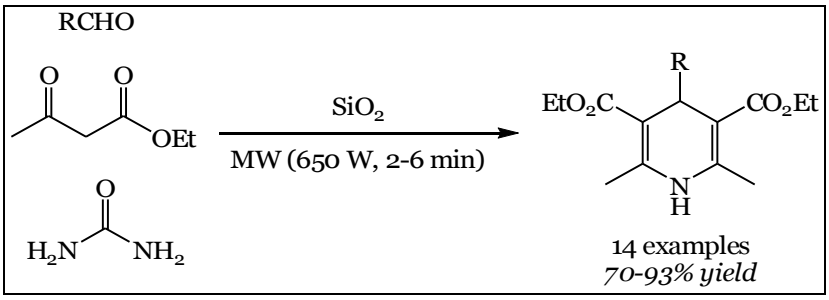
Scheme 4.6. Synthesis of Hantzsch 1,4-dihydropyridines in an aqueous hydrotope solution.

A solid-supported and microwave-mediated strategy was presented by Suarez and colleagues in 1996.[94] An unsymmetrical 1,4-dihydropyridine was obtained after 6 minutes of irradiation in a domestic oven, followed by standard chromatographic purification, with an 85% isolated yield (Scheme 4.7). Aiming to reach higher temperatures, a small amount of DMF was added to the reaction mixture and used as an energy transfer medium.



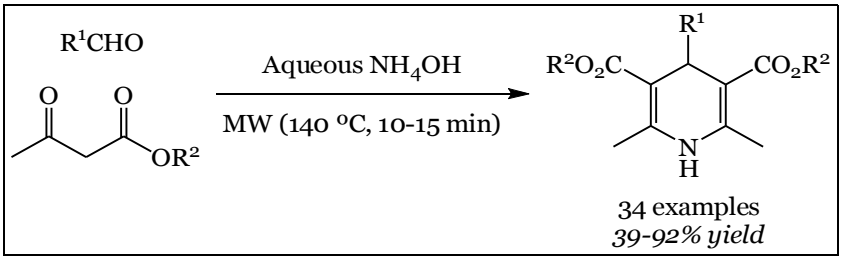
Scheme 4.7. Solid-supported synthesis of an unsymmetrical Hantzsch 1,4-dihydropyridine.

Five years later Yadav and co-workers described the rapid microwave-activated condensation of ethyl acetoacetate, urea and a series of aryl and alkyl aldehydes on the surface of silica gel.[95] Open-vessel reaction conditions were employed in a domestic microwave equipment operating at 650 W, 14 Hantzsch 1,4-dihydropyridines being obtained with high yields after column chromatography (Scheme 4.8).



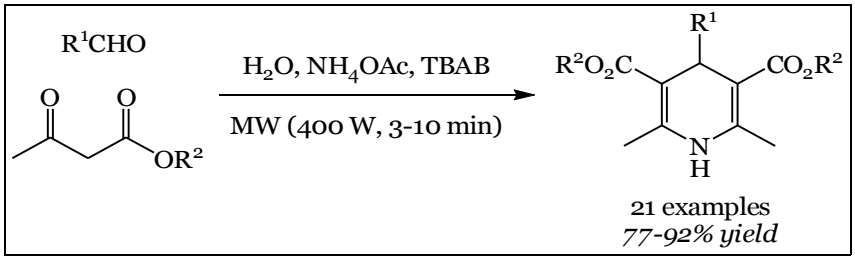
Scheme 4.8. Solid-supported synthesis of Hantzsch 1,4-dihydropyridines.

A single-mode microwave reactor was utilised by Öhberg and Westman to prepare several 4-aryl and 4-alkyl Hantzsch DHP derivatives with low to very good yields in 10 to 15 minutes (Scheme 4.9).[96] The syntheses were performed in sealed vessels and no solvent was added as reaction medium. Comparing with the same procedure under conventional heating and the microwave-mediated process carried-out in a domestic oven, higher yields and shorter reaction times were attained after chromatographic purification and/or recrystallisation. However, the purity of the compounds varied greatly, ranging from 53 to 99%, as determined by LC-MS.



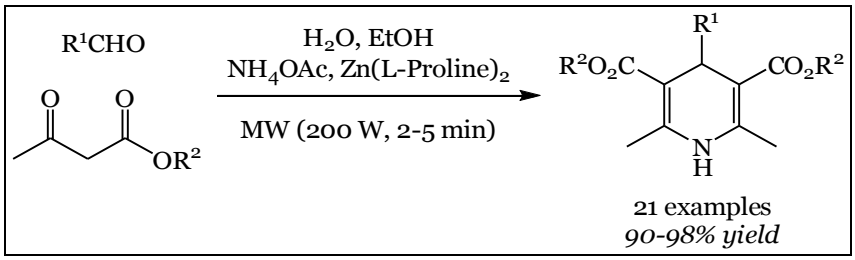
Scheme 4.9. Synthesis of Hantzsch 1,4-dihydropyridines in aqueous ammonium hydroxide.

The synthesis of various 1,4-dihydropyridines has also been accomplished through the reaction of aldehydes, alkyl acetoacetates and ammonium acetate in water, utilising tetra-*n*-butylammonium bromide (TBAB) as a phase transfer agent and catalyst under microwave irradiation (Scheme 4.10).[97] High yields and brief reaction times were generally observed using a modified household microwave apparatus.



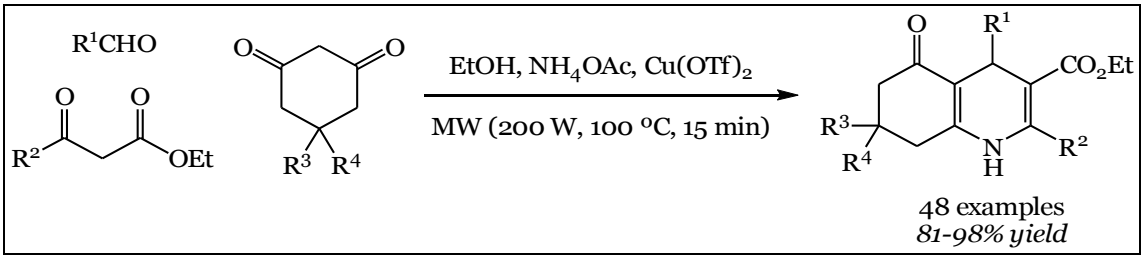
Scheme 4.10. Synthesis of Hantzsch 1,4-dihydropyridines in water using TBAB as catalyst.

A water soluble Lewis acid complex, Zn(L-proline)$_2$, was employed in 2006 as catalyst for the microwave-assisted, multicomponent, Hantzsch 1,4-dihydropyridine synthesis, using aqueous ethanol as reaction medium and a domestic microwave oven operating at 200 W (Scheme 4.11).[98] Isolated yields of up to 98% were reported without the need of chromatographic work-up. Moreover, the authors claimed that the catalyst could be recycled up to five times without loss of activity.



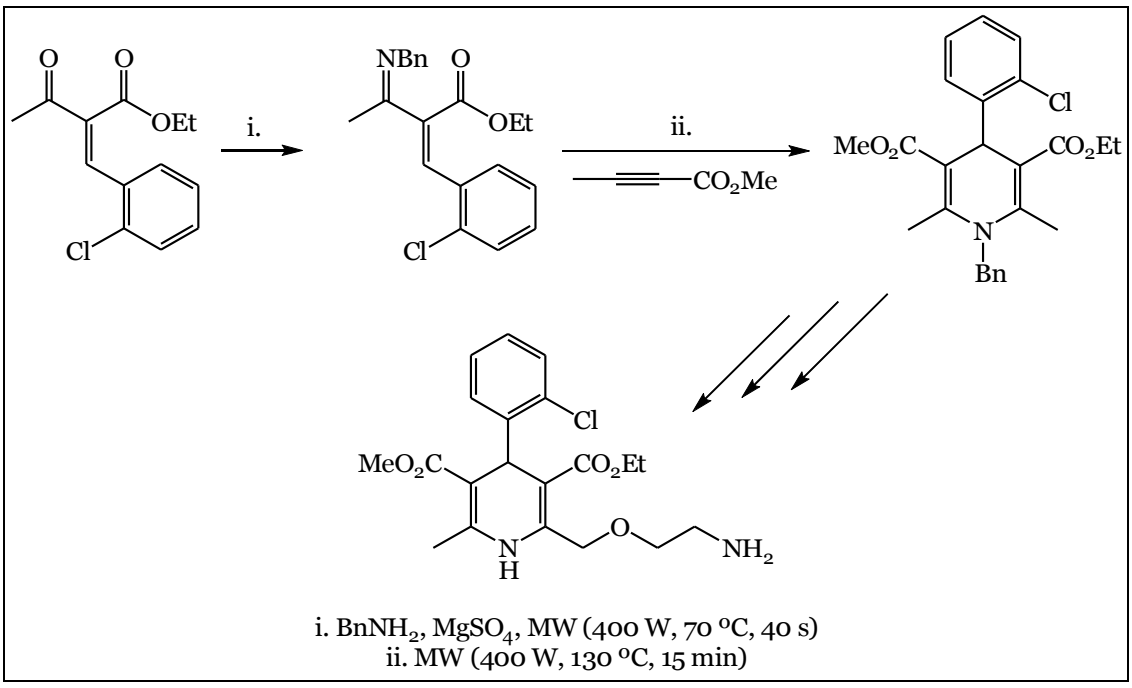
Scheme 4.11. Synthesis of Hantzsch 1,4-dihydropyridines in aqueous ethanol using $Zn(L\text{-proline})_2$ as catalyst.

A copper-catalysed one-pot preparation of diverse 1,4-dihydropyridine structures using a single-mode microwave reactor was described by Pasunooti and co-workers in 2010.[99] Fairly mild reaction conditions and low catalytic loading furnished a compound library of 48 DHP analogues for medicinal chemistry applications, with exceedingly high yields, after cooling of the crude product mixtures to room temperature, filtration and washing with *n*-hexane (Scheme 4.12).



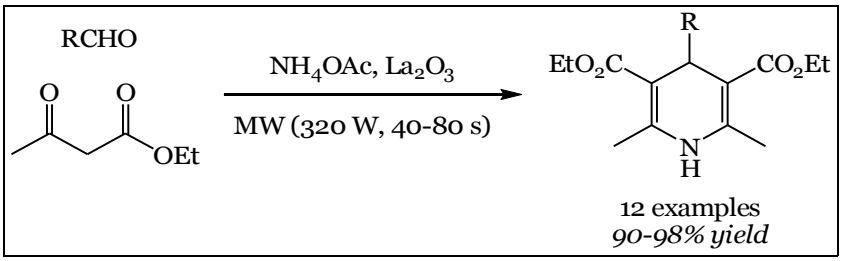
Scheme 4.12. Synthesis of Hantzsch 1,4-dihydropyridines in ethanol using $Cu(OTf)_2$ as catalyst.

An aza-Diels-Alder strategy under microwave heating was utilised by Lee and Kim for the synthesis of an unsymmetrical Hantzsch DHP motif with a 31% isolated yield, after column chromatography followed by recrystallisation (Scheme 4.13).[100] This was further converted to amlodipine after several steps, providing a new approach for the preparation of this well known anti-hypertensive drug.



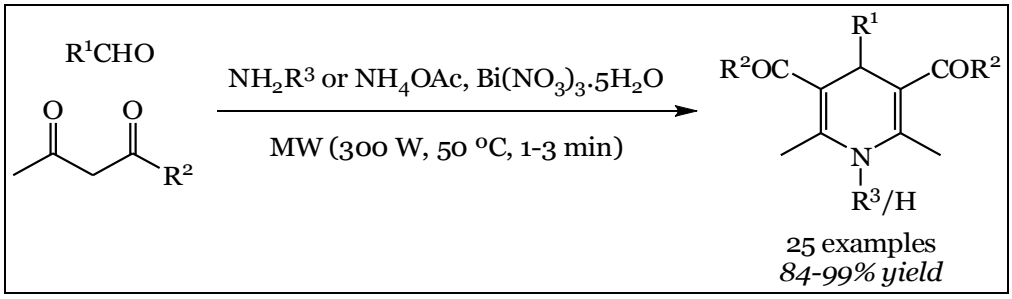
Scheme 4.13. Aza-Diels-Alder synthesis of an unsymmetrical Hantzsch 1,4-dihydropyridine leading to the anti-hypertensive drug amlodipine.

Some 1,4-dihydropyridine derivatives have been prepared with excellent yields and within remarkably short reaction times by employing a small amount of lanthanum oxide as catalyst in a solvent-free and microwave-assisted Hantzsch protocol (Scheme 4.14).[101] Other catalysts were tested but the isolated yields dropped to less than half the ones achieved using La_2O_3. Open-vessel reaction conditions and a domestic microwave equipment were applied in all syntheses.



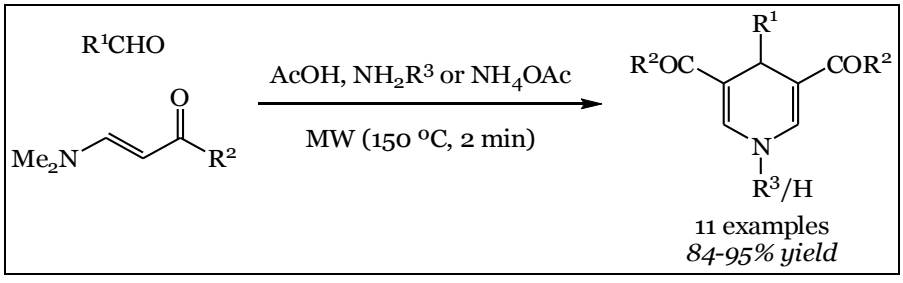
Scheme 4.14. Solventless synthesis of Hantzsch 1,4-dihydropyridines using La_2O_3 as catalyst.

Quite recently, Bandyopadhyay and colleagues asserted that bismuth(III) nitrate pentahydrate can act as an efficient catalyst for the one-pot solvent-free synthesis of Hantzsch DHPs, under microwave activation and sealed-vessel conditions, starting from diverse primary amines or ammonium acetate, 1,3-dicarbonyl compounds and aryl, heteroaryl or alkyl aldehydes (Scheme 4.15).[102] Albeit the small scale of this synthetic methodology, superior results were reported within 1 to 3 minutes of irradiation in a dedicated microwave apparatus, followed by washing the crude products with brine, liquid/liquid extraction and chromatographic purification.



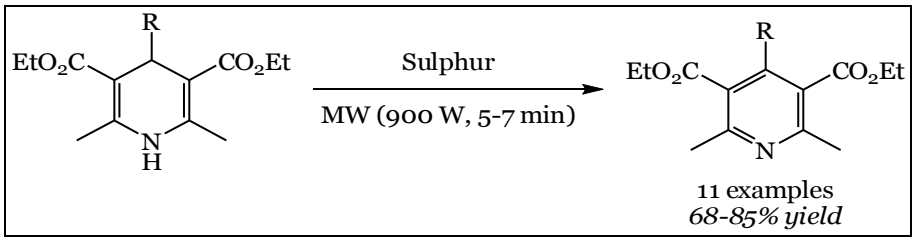
Scheme 4.15. Solventless synthesis of Hantzsch 1,4-dihydropyridines using $Bi(NO_3)_3.5H_2O$ as catalyst.

A small-scale, multicomponent and microwave-assisted procedure that provided a rapid access to functionalised 1,4-dihydropyridines bearing no substituents at positions 2 and 6 of the heterocyclic moiety was published by Al-Awadi and co-workers in 2012.[103] Making use of ammonium acetate or primary amines, previously prepared enaminones and aryl aldehydes as reactants, glacial acetic acid as solvent, a single-mode microwave reactor and closed reaction vials, 11 compounds were prepared with high yields in only 2 minutes of irradiation (Scheme 4.16). When chiral primary amines were employed, chiral DHP derivatives were obtained. Isolation was simple and usually included washing the crude product mixtures with ice-cold water, followed by filtration of the resulting solid and recrystallisation in an appropriate solvent.



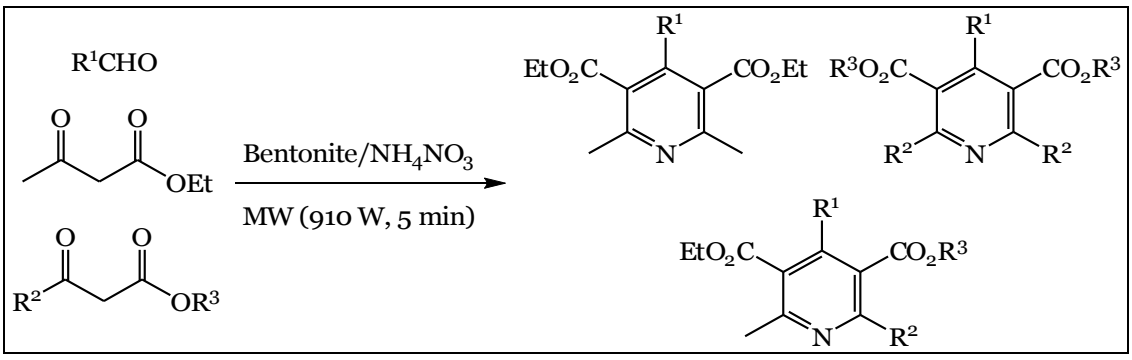
Scheme 4.16. Synthesis of Hantzsch 1,4-dihydropyridines in glacial acetic acid.

The microwave-assisted oxidation of Hantzsch 1,4-dihydropyridines was firstly described in 1991 by Delgado and colleagues.[104, 105] A series of DHP compounds was heated in a domestic microwave oven using a mixture of manganese dioxide and bentonite clay as reaction medium in open-vessel conditions. Short reaction times, up to 10 minutes, and fair to quantitative isolated yields, 47 to 100%, were reported. Interestingly, when DHPs bearing a methyl, ethyl or *n*-propyl substituent at position 4 of the nitrogen-containing heterocycle were utilised as starting materials, mixtures of the corresponding 4-alkylpyridines and 4-unsubstituted pyridines were obtained. A couple of years later, the same research group claimed that these 4-alkyl-1,4-dihydropyridine derivatives did not afford the dealkylated products when subjected to microwave irradiation in the presence of a nitric acid-doped bentonite clay.[56] The oxidative aromatisation of 1,4-dihydropyridines was also studied by Varma and Kumar in the late 1990s.[59] The solvent-free oxidation of several DHPs, using a slight excess of elemental sulphur as the oxidising agent in an unmodified household microwave apparatus, provided the dehydrogenated derivatives after column chromatography, irrespective of the nature of the substituent present at position 4 of the dihydropyridine unit (Scheme 4.17).



Scheme 4.17. Solventless oxidative aromatisation of Hantzsch 1,4-dihydropyridines using sulphur as oxidant.

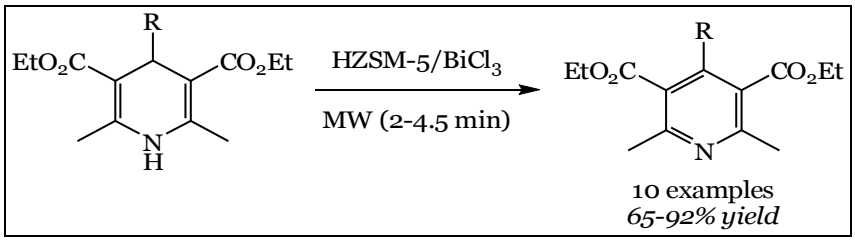
Cotterill and co-workers presented the application of microwave activation in the context of combinatorial synthesis in 1998: a multicomponent domino Hantzsch synthesis of diversely substituted symmetrical and unsymmetrical pyridines in a 96-well microplate.[106] The reactions were carried-out on a NH_4NO_3/bentonite clay support. Ammonium nitrate acted both as the nitrogen source and the oxidising agent, the initially formed DHPs being rapidly dehydrogenated to their pyridine analogues (Scheme 4.18). Given that a domestic microwave equipment was used, the reaction temperature could not be accurately measured and the microwave energy distribution over the microplate was rather uneven. Nonetheless, the products were obtained with purity levels above 70%, determined by HPLC-MS techniques, although no isolated yields were indicated.



Scheme 4.18. Solid-supported domino synthesis of symmetrical and unsymmetrical Hantzsch pyridines.

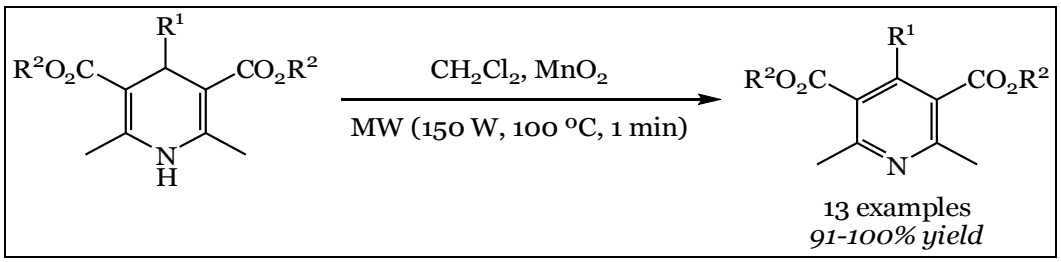
In another solid-supported methodology, Hantzsch 1,4-dihydropyridines were employed in the reduction of olefins, both in a domestic multi-mode oven and in a dedicated single-mode reactor, the pyridine counterparts being obtained as side-products.[107] The authors found that the efficiency of the reduction/oxidation reaction was highly dependent on steric effects in the DHP derivatives and on electronic effects exhibited by the different

olefins. In 2005, Heravi and Ghassemzadeh published the use of a bismuth(III) chloride/HZSM-5 zeolite system as a mild and clean oxidant of 1,4-dihydropyridines under microwaves.[108] No chromatographic purification procedures were necessary in order to furnish the pyridine products with generally good yields (Scheme 4.19). The same research team also employed a HZSM-5/MnO_2 support under similar reaction conditions with very good results.[109]



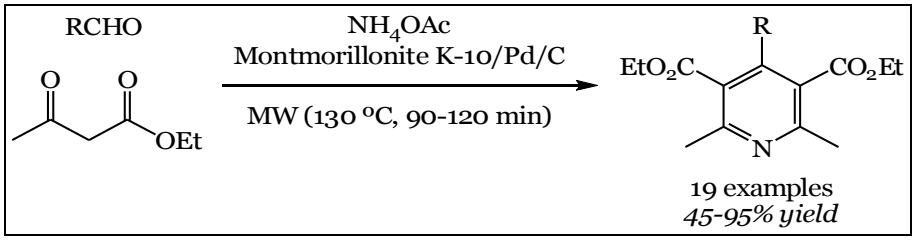
Scheme 4.19. Solid-supported oxidative aromatisation of Hantzsch 1,4-dihydropyridines using $BiCl_3$ as oxidant.

Shortly after, Bagley and Lubinu reported that 4-aryl- and 4-alkyl-1,4-dihydropyridines were readily and effectively oxidised by activated manganese dioxide, in only one minute of microwave irradiation, using sealed-vessel conditions and a commercial microwave reactor (Scheme 4.20).[110] The authors also tested other oxidising agents, such as Pd/C, molecular iodine or *o*-iodoxybenzoic acid, under a series of microwave-assisted reaction conditions, but with poor results. The reaction proceeded either through oxidative aromatisation, for 4-aryl or linear 4-alkyl substrates, or via oxidative dealkylation, for branched 4-alkyl or 4-benzyl derivatives. MnO_2 was easily removed by simple filtration through a small column of Celite.



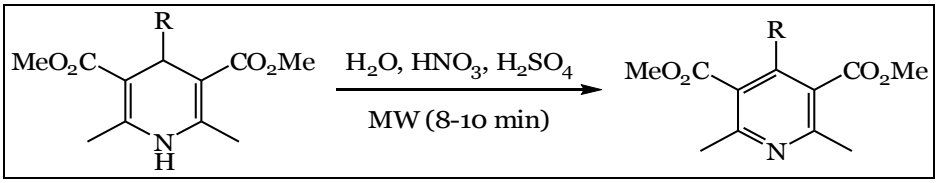
Scheme 4.20. Oxidative aromatisation of Hantzsch 1,4-dihydropyridines using MnO_2 as oxidant.

Another one-pot domino approach for the preparation of Hantzsch pyridines was presented by the research group of Török in 2008.[111] The process was based on the employment of microwaves (single-mode reactor) and a noble metal-solid acid catalyst (montmorillonite K-10/Pd/C). The cyclisation occurred on the surface of the acidic solid-support, followed by the palladium-promoted dehydrogenation of the 1,4-dihydropyridine intermediate to the corresponding pyridine product (Scheme 4.21). Albeit the catalyst is easily removable by filtration of the cooled crude product mixture and, in theory, can be recycled, it must be emphasised that the reaction times reported were quite high for a microwave-assisted methodology, up to 2 hours, and the reaction yields varied significantly.



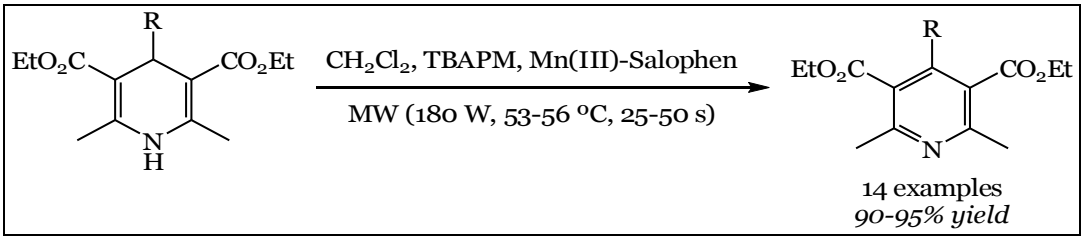
Scheme 4.21. Solid-supported domino synthesis of Hantzsch pyridines.

The oxidative aromatisation of a few Hantzsch DHPs in water and under 10 minutes was also described in 2008, using a typical nitrating mixture composed of nitric and sulphuric acids as the oxidising agent and a domestic multi-mode microwave apparatus (Scheme 4.22).[112] No reference of reaction temperature, microwave power setting or even isolated yields was made.



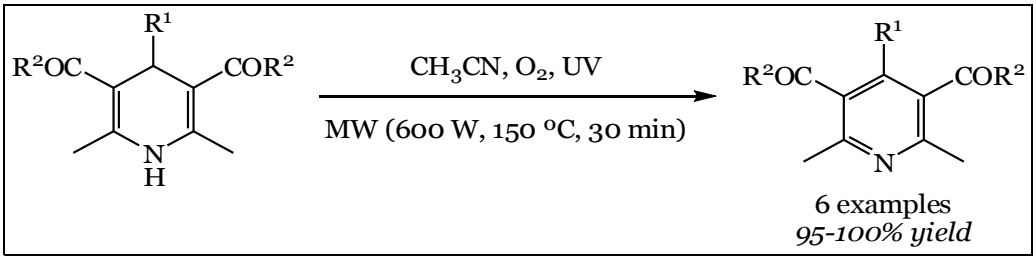
Scheme 4.22. Oxidative aromatisation of Hantzsch 1,4-dihydropyridines in water using HNO_3/H_2SO_4 as oxidant.

The fast and effective dehydrogenation of some 1,4-dihydropyridines with tetra-*n*-butylammonium peroxymonosulphate (TBAPM) catalysed by manganese(III) Schiff base complexes, under both low-temperature activation utilising a closed vessel and dedicated microwave equipment or mechanical stirring at room temperature, was published in 2009 by Nasr-Esfahani and co-workers (Scheme 4.23).[113] High yields were reported in all microwave-assisted syntheses after standard chromatographic work-up.



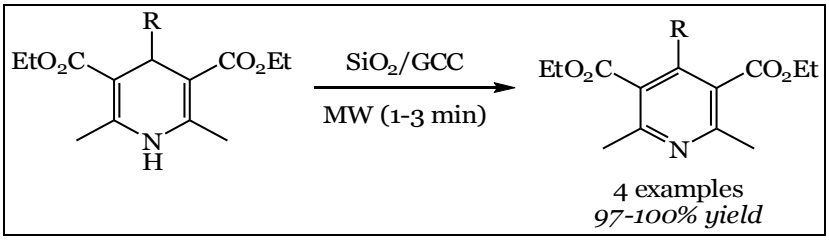
Scheme 4.23. Oxidative aromatisation of Hantzsch 1,4-dihydropyridines using TBAPM as oxidant and Mn(III)-salophen as catalyst.

The Leadbeater research team utilised tandem UV irradiation and microwave heating for the oxidation of some Hantzsch DHPs to the corresponding pyridines.[114] The reactions were performed in closed vessels using acetonitrile as solvent, 1000 kPa of molecular oxygen as oxidant and an electrodeless discharge lamp as the UV irradiation source (Scheme 4.24). It was shown that both oxygen and ultraviolet irradiation were key to the success of this protocol, although the need for heating in conjunction with irradiation was not unequivocally demonstrated. Still, this strategy was significantly faster than others previously described using photoactivation in the presence of molecular oxygen.



Scheme 4.24. Oxidative aromatisation of Hantzsch 1,4-dihydropyridines using oxygen as oxidant and UV irradiation.

The solid-supported oxidative aromatisation of a few 1,4-dihydropyridines with glycinium chlorochromate (GCC) was studied in 2009, using silica gel as reaction medium and open-vessel conditions in a domestic microwave oven.[115] The authors claimed that quantitative yields were obtained in very short reaction times, without the requirement of any chromatographic purification procedure (Scheme 4.25).

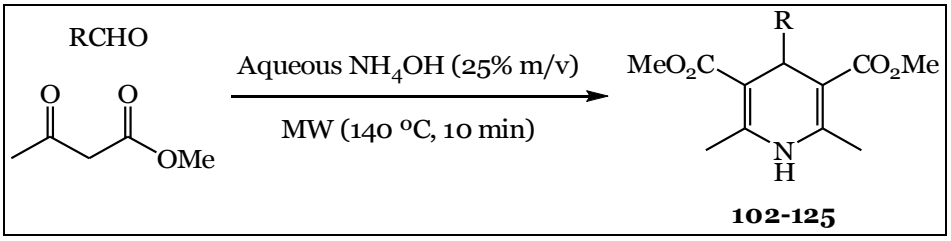


Scheme 4.25. Solid-supported oxidative aromatisation of Hantzsch 1,4-dihydropyridines using GCC as oxidant.

Various Hantzsch DHPs were oxidised to the corresponding pyridine derivatives by Memarian and co-workers, both at room temperature and under microwave irradiation conditions, using DDQ as the oxidising compound.[116] It was established that this reaction was greatly influenced by the nature of the substituents located at positions 3, 4 and 5 of the dihydropyridine ring, the type of solvent and the presence of an oxygen or argon atmosphere. One year later, the same authors reported that tetra-*n*-butylammonium peroxydisulphate (TBAPD), either in combination with basic aluminium oxide in refluxing acetonitrile or under microwave heating in the absence or presence of basic alumina, could also produce pyridines via dehydrogenation of the preceding 1,4-dihydropyridines.[117]

B. Multicomponent Synthesis of Hantzsch 1,4-Dihydropyridines

Following part of the work carried-out by Bagley and Lubinu,[110] and firstly by Öhberg and Westman,[96] we decided to synthesise a small compound library of Hantzsch 1,4-dihydropyridines under microwave irradiation through a low-budget and solvent-free method. The purpose was not to modify the microwave-assisted procedure reported by the above mentioned authors, but to make use of its straightforwardness to prepare some novel 4-aryl-DHPs comprising several different substituents of both electron-donating and electron-withdrawing character and also to further explore these heterocycles as substrates in oxidation reactions under microwave activation. Hence, a mixture of the selected aryl aldehyde, a five-fold molar excess of methyl acetoacetate and a four-fold molar excess of aqueous ammonium hydroxide was heated at 140 ºC for 10 minutes, with an initial power setting of 150 W, under closed-vessel conditions (Scheme 4.26). Contrary to that described in the reports of Westman[96] and Bagley,[110] in which chromatographic purification processes were often needed in order to get the final product with a high level of purity, the isolation protocol in our approach was significantly easier and much more effective. The yellow solid that precipitated out of the cooled crude product mixture was simply filtrated under reduced pressure, washed with distilled water and recrystallised in aqueous ethanol, Hantzsch 1,4-dihydropyridines **102-125** being obtained as yellowish solids with moderate to good isolated yields, ranging from 30 to 72% (Figure 4.3).



Scheme 4.26. Multicomponent synthesis of Hantzsch 1,4-dihydropyridines **102-125** under microwave irradiation.

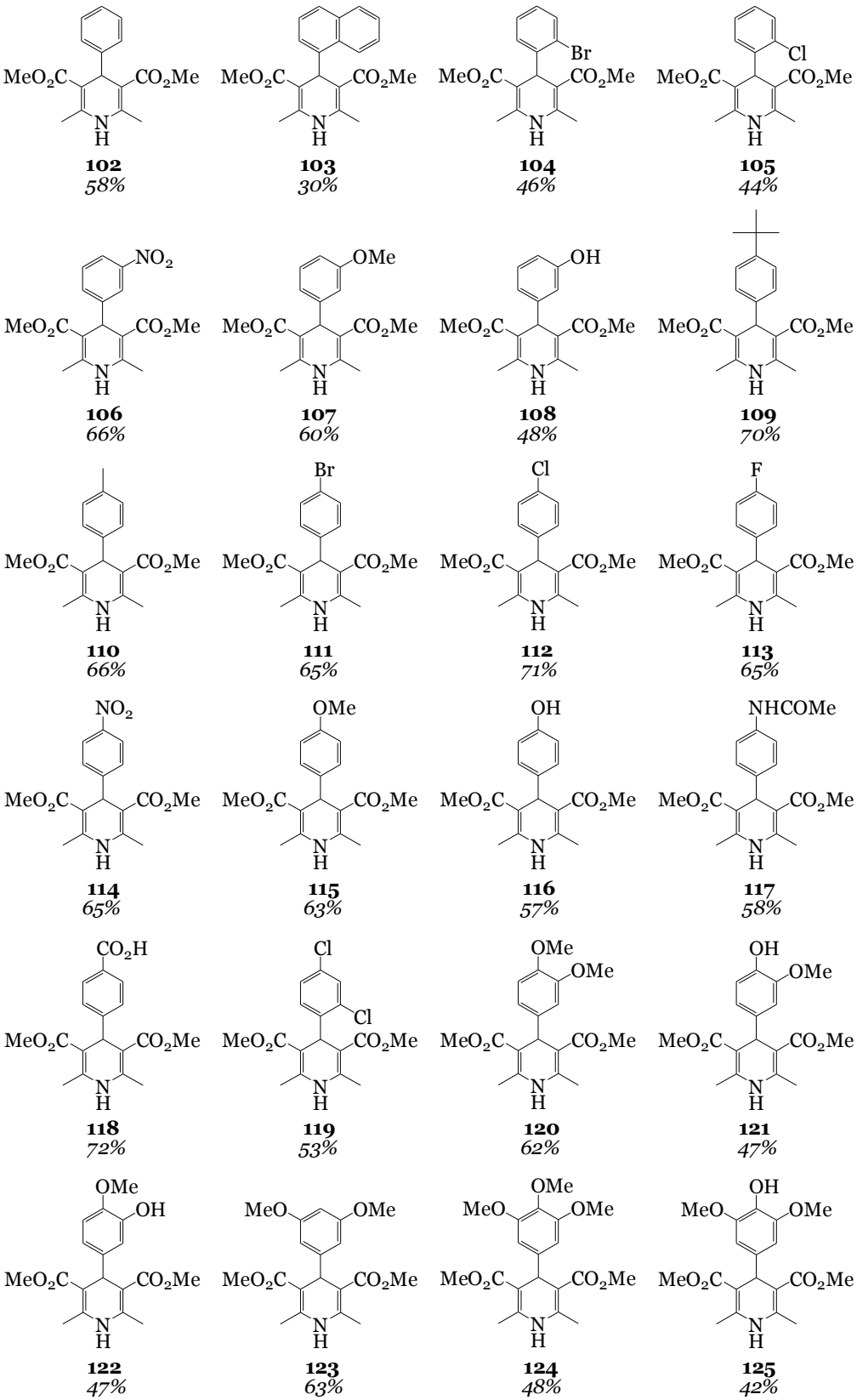


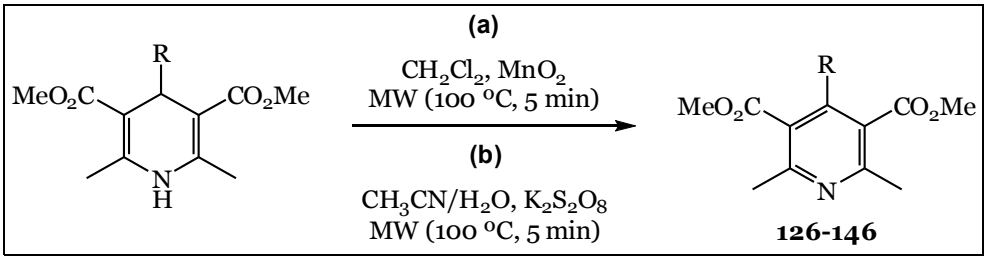
Figure 4.3. Structures and isolated yields of Hantzsch 1,4-dihydropyridines **102-125** synthesised via a solventless, multicomponent, microwave-assisted method.

It should be emphasised that, as far as we know, compounds **109**, **117**, **118**, **121**, **122** and **125** have never been reported in the scientific literature. Also, when 9-phenanthrenaldehyde, 9-anthracenaldehyde, 2,6-dichlorobenzaldehyde and mesitylaldehyde were used as reagents, only trace amounts of the corresponding dihydropyridine derivatives were detected by TLC analysis of the crude product mixtures, which can be explained

by steric impediment phenomena. Moreover, using 4-dimethylaminobenzaldehyde as the starting aryl aldehyde, a strong, fast and unsafe pressure accumulation was detected inside the reaction vessel upon microwave activation, which was most likely due to the release of dimethylamine as a secondary product.

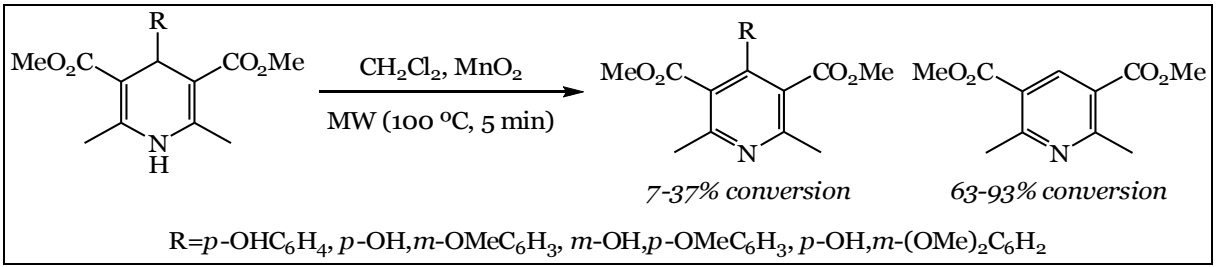
C. Oxidation of Hantzsch 1,4-Dihydropyridines

Based in the methodology presented by Bagley and Lubinu,[110] nearly all the previously prepared 4-aryl-DHP structures depicted in Figure 4.3 were promptly oxidised to the corresponding 4-arylpyridines with isolated yields above 90%. Briefly, a mixture of the selected Hantzsch 1,4-dihydropyridine and a 10-fold stoichiometry of activated manganese dioxide in dichloromethane was irradiated at 100 ºC for 5 minutes in an appropriate sealed vessel. After cooling to room temperature, the excess MnO_2 and any oxidation by-products were easily removed by simple filtration through a small silica gel column. Evaporation of the filtrate under reduced pressure, followed by recrystallisation, afforded the desired Hantzsch pyridine as a white or yellowish solid or oil (Scheme 4.27a).



Scheme 4.27. Synthesis of Hantzsch pyridines **126-146** under microwave irradiation.

Interestingly, the heterogeneous oxidative aromatisation of DHP **118** using activated manganese dioxide was entirely unsuccessful, the starting heterocyclic material being recovered unaltered upon work-up. Broadening the reaction time to 10 and 20 minutes or changing the reaction medium to a more polar solvent, e.g. ethyl acetate, was also ineffective. However, full conversion to the respective dimethyl 4-(4-carboxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate **142** was achieved through a homogeneous oxidative aromatisation strategy, utilising potassium peroxydisulphate as oxidant, an acetonitrile/distilled water mixture as solvent and equal reaction conditions (Scheme 4.27b). Work-up was extremely simple and involved washing the crude product mixture with brine and filtering the solid that precipitated out of the resulting aqueous solution. It must be pointed-out that the MnO_2-promoted oxidation of DHPs **116**, **121**, **122** and **125** provided the desired pyridine derivatives as minor reaction products, 37, 8, 22 and 7% conversion, respectively, as verified by GC-MS examinations after isolation. It was established that, in these cases, dimethyl 2,6-dimethylpyridine-3,5-dicarboxylate, rendered via an unforeseen and, to the best of our knowledge, unreported oxidative dearylation process, was the major component in the final products, 63 to 93% conversion (Scheme 4.28).



Scheme 4.28. MnO_2-promoted oxidative aromatisation/dearylation of Hantzsch 1,4-dihydropyridines **116**, **121**, **122** and **125** under microwave irradiation.

Unlike the oxidative dealkylation reaction in some 4-alkyl-DHPs, which has already been determined both under classical conditions and microwave irradiation, further investigation is clearly necessary in order to

elucidate what drives this surprising oxidative aromatisation/dearylation phenomenon. In this regard, and although no studies were performed and no proof was substantiated, we consider that the presence of hydroxyl and methoxyl functionalities at the aromatic ring of the 1,4-dihydropyridine motif should be of great influence, given that these are the only common substituents present at the compounds in which this process was observed. Application of the $K_2S_2O_8$-mediated homogeneous oxidative aromatisation approach to the supra-cited Hantzsch 1,4-dihydropyridines, i.e. **116**, **121**, **122** and **125**, was only successful in the first situation, dimethyl 4-(4-hydroxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate **140** being easily isolated. Unfortunately, the other DHP reactants were recovered unchanged upon work-up, even after extended microwave irradiation at 100 ºC for 10 and 20 minutes. Apparently, the existence of both hydroxyl and methoxyl functional groups at the phenyl ring of the 1,4-dihydropyridine skeleton somehow hampered the formation of the hydropyridinoyl radical intermediate, which is essential for the oxidation reaction to succeed (Scheme 4.30). This could be related to the balance of inductive and resonance effects caused by these particular substituents. Nonetheless, a series of twenty one Hantzsch pyridines was easily prepared through the microwave-assisted oxidation of the corresponding and previously synthesised 1,4-dihydropyridine analogues, with isolated yields between 83 and 95% (Figure 4.4).

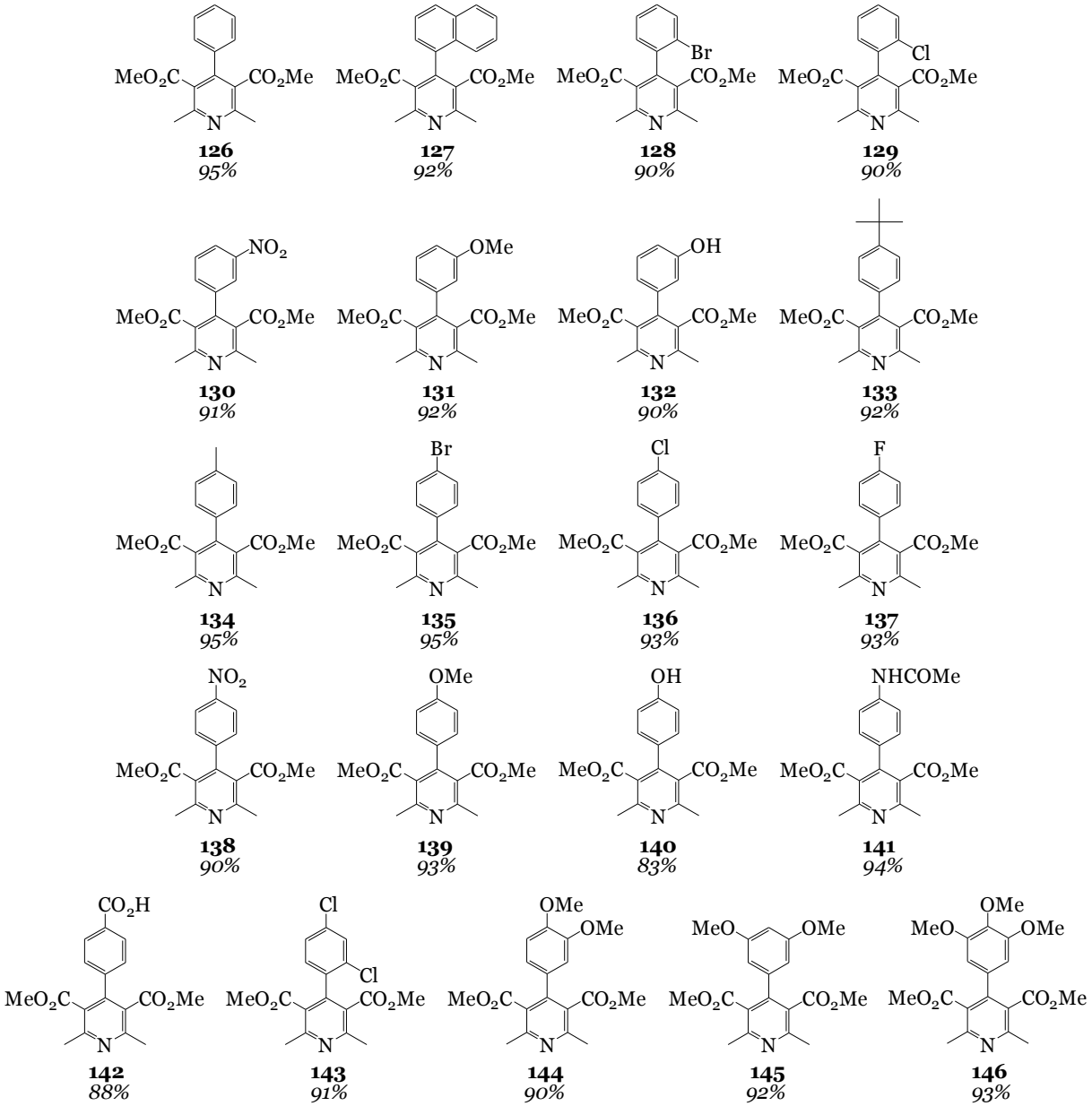
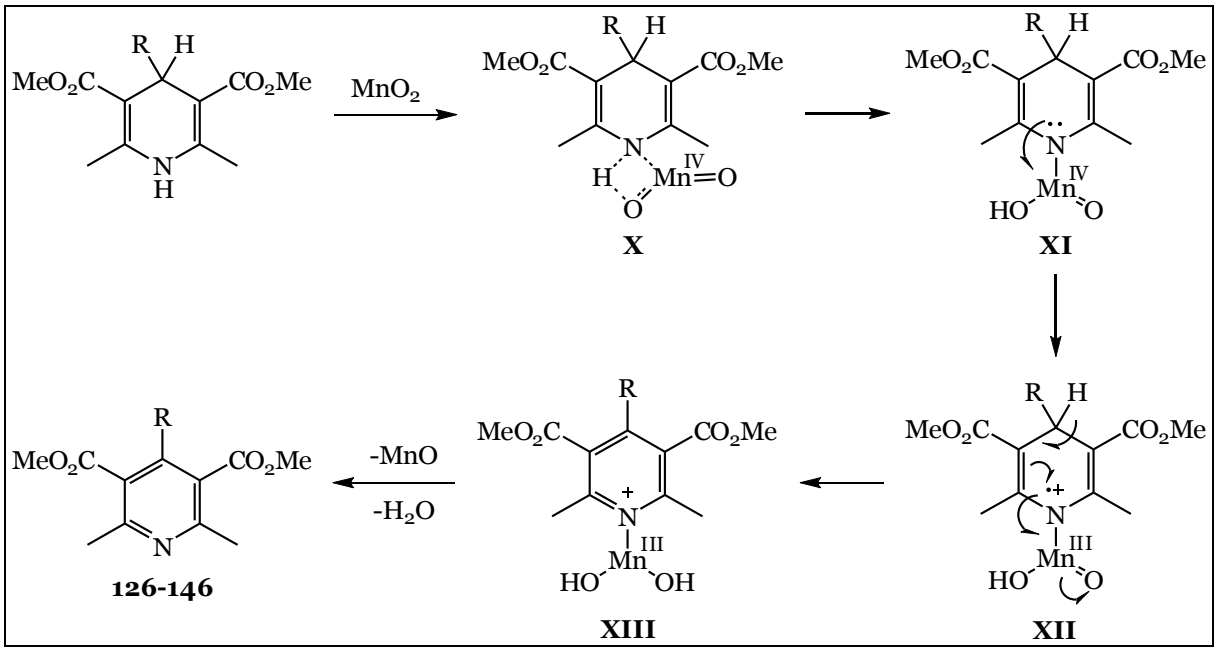


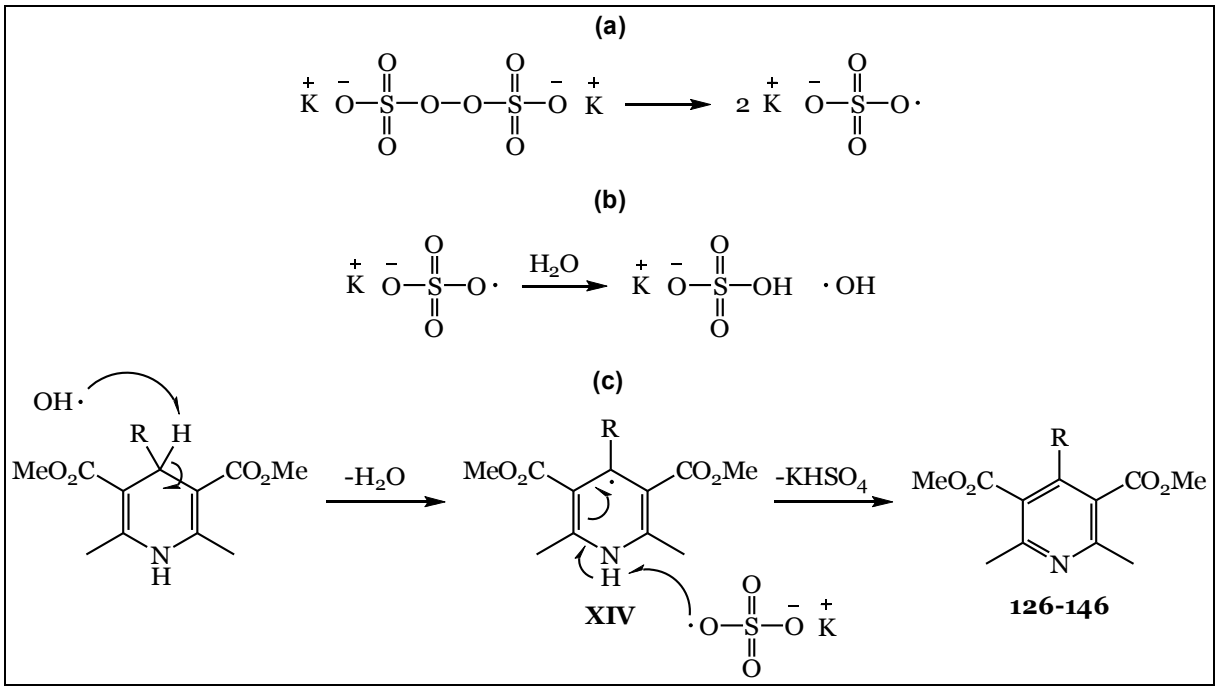
Figure 4.4. Structures and isolated yields of Hantzsch pyridines **126-146** synthesised via solvent-based, microwave-assisted, oxidative aromatisation methods.

Activated manganese dioxide is characterised by a high standard oxidation/reduction potential (E^o[Mn(IV)/Mn(II)]=1.23 V), acting as a strong oxidising agent in acidic conditions (E^o=1.57 V), but only as a mild oxidant in neutral media. On the other hand, its oxidation potential in alkaline conditions is negligible (E^o=0.05 V).[118, 119] MnO_2 can perform both as a powerful two-equivalent and also a one-electron oxidant, selective oxidation being usually achieved at room temperature. However, its oxidising ability increases greatly above 70 ºC, although commonly with loss of selectivity.[120] Nevertheless, many dehydrogenation reactions, as well as the complete aromatisation of several types of saturated ring systems, can be accomplished by the utilisation of this inexpensive and user-friendly inorganic oxidant.[119] A mechanistic rationalisation for the MnO_2-promoted heterogeneous oxidative aromatisation of the Hantzsch 1,4-dihydropyridines studied in this work is portrayed in Scheme 4.29. DHP adsorption to the surface of MnO_2 **X** and hydrogen abstraction renders a coordination complex **XI**. The oxidation proceeds through an intramolecular one-electron transfer, generating a radical cation intermediate **XII**, followed by a hydrogen atom transfer **XIII**, which results in the formation of the target pyridine structure, as well as water and MnO as by-products.[118, 119]



Scheme 4.29. Mechanistic proposal for the synthesis of Hantzsch pyridines **126-146** using activated manganese dioxide as the oxidising agent under heterogeneous oxidative aromatisation conditions.

The peroxydisulphate ion is generally recognised as one of the strongest oxidising agents available (E^o[$S_2O_8^{2-}/SO_4^{2-}$]=2.01 V)[121] and has been widely and successfully employed in various oxidative processes, including the dehydrogenation of Hantzsch 1,4-dihydropyridines.[122] Regarding our preparation of Hantzsch pyridines via the $K_2S_2O_8$-mediated homogeneous oxidative aromatisation of the corresponding DHPs, a possible reaction pathway is represented in Scheme 4.30. Thermal decomposition of the weakest O-O bond in potassium peroxydisulphate yields a sulphate radical anion (a), which preferentially abstracts a hydrogen atom from the water molecules present within the reaction medium to furnish a hydroxyl radical (b). The oxidation is presumed to be initiated through a hydrogen abstraction at position 4 of the heterocyclic structure by the previously formed hydroxyl radical, affording a hydropyridinoyl radical intermediate **XIV** and water. Lastly, abstraction of the nitrogen-linked hydrogen atom by another sulphate radical anion generates the desired pyridine compound along with potassium bisulphate as a secondary product (c).



Scheme 4.30. Mechanistic proposal for the synthesis of Hantzsch pyridines **126-146** using potassium peroxydisulphate as the oxidising agent under homogeneous oxidative aromatisation conditions.

IV. Summary

A small compound library of Hantzsch 1,4-dihydropyridines **102-125**, including some novel and unreported structures, was rapidly and effortlessly synthesised via a multicomponent and solvent-free strategy under microwave activation, moderate to good reaction yields being obtained (30-72%) without the requirement of any chromatographic isolation procedure. Hantzsch pyridines **126-146** were also efficiently prepared through the fast and microwave-assisted oxidative aromatisation of the corresponding DHP analogues, isolated yields ranging from 83 to 95% being attained, either under heterogeneous reaction conditions using the cheap and useful activated manganese dioxide as the oxidising agent or by means of a homogeneous methodology utilising potassium peroxydisulphate as the alternative oxidant. An unexpected oxidative dearylation process was observed in a few cases when MnO_2 was employed as the oxidising species, although further studies are manifestly needed in order to clarify the reaction mechanisms involved.

V. References

1. A Hantzsch, *Chem. Ber.* 14 (**1881**) 1637-1638.

2. A Hantzsch, *Liebigs Ann. Chem.* 215 (**1882**) 1-82.

3. GM Reddy, M Shiradkar, AK Chakravarthy, *Curr. Org. Chem.* 11 (**2007**) 847-852.

4. D Mauzeral, FH Westheimer, *J. Am. Chem. Soc.* 77 (**1955**) 2261-2264.

5. B Loev, MM Goodman, KM Snader, R Tedeschi, E Macko, *J. Med. Chem.* 17 (**1974**)956-965.

6. F Bossert, H Meyer, E Wehinger, *Angew. Chem. Int. Ed.* 20 (**1981**) 762-769.

7. NL Benowitz, in *Basic & Clinical Pharmacology*, Twelfth Edition, BG Katzung, SB Masters, AJ Trevor (Eds), Lange/McGraw-Hill, New York, NY, USA, 2012, Chapter 11.

8. L Prokai, K Prokai-Tatrai, N Bodor, *Med. Res. Rev.* 20 (**2000**) 367-416.

9. P Chen, N Bodor, W-M Wu, L Prokai, *J. Med. Chem.* 41 (**1998**) 3773-3781.

10. L Prokai, X Ouyang, K Prokai-Tatrai, JW Simpkins, N Bodor, *Eur. J. Med. Chem.* 33 (**1998**) 879-886.
11. E Pop, F Soti, WR Anderson, JA Panetta, KS Estes, NS Bodor, ME Brewster, *Int. J. Pharm.* 140 (**1996**) 33-44.
12. W Kawczynski, B Czochralska, L Lindqvist, PF Torrence, *Bioelectrochem. Bioenerg.* 39 (**1996**) 263-266.
13. S Yiu, EE Knaus, *J. Med. Chem.* 39 (**1996**) 4576-4582.
14. MA Patane, RM DiPardo, RC Newton, RP Price, TP Broten, RSL Chang, RW Ransom, J Di Salvo, D Nagarathnam, C Forray, C Gluchowski, MG Bock, *Bioorg. Med. Chem. Lett.* 10 (**2000**) 1621-1624.
15. J Jiang, A-H Li, S-Y Jang, L Chang, N Melman, S Moro, X Ji, EB Lobkovsky, JC Clardy, KA Jacobson, *J. Med. Chem.* 42 (**1999**) 3055-3065.
16. RE Malmström, KC Balmér, J Weilitz, M Nordlander, M Sjölander, *Eur. J. Pharmacol.* 418 (**2001**) 95-104.
17. S Tasaka, H Ohmori, N Gomi, M Iino, T Machida, A Kiue, S Naito, M Kuwano, *Bioorg. Med. Chem. Lett.* 11 (**2001**) 275-277.
18. T Straub, C Boesenberg, V Gekeler, F Boege, *Biochem.* 36 (**1997**) 10777-10783.
19. IO Donkor, X Zhou, J Schmidt, KC Agrawal, V Kishore, *Bioorg. Med. Chem.* 6 (**1998**) 563-568.
20. A Kuzmin, S Semenova, NF Ramsey, EE Zvartau, JM Van Ree, *Eur. J. Pharmacol.* 295 (**1996**) 19-25.
21. HG Bull, M Garcia-Calvo, S Andersson, WF Baginsky, HK Chan, DE Ellsworth, RR Miller, RA Stearns, RK Bakshi, GH Rasmusson, RL Tolman, RW Myers, JW Kozarich, GS Harris, *J. Am. Chem. Soc.* 118 (**1996**) 2359-2365.
22. Z Hyvönen, A Plotniece, I Reine, B Chekavichus, G Duburs, A Urtti, *Biochim. Biophys. Acta* 1509 (**2000**) 451-466.
23. J Tusell, S Barron, J Serratosa, *Brain Res.* 622 (**1993**) 99-104.
24. B Desai, D Sureja, Y Naliapara, A Shah, AK Saxena, *Bioorg. Med. Chem.* 9 (**2001**) 1993-1998.
25. RH Böcker, FP Guengerich, *J. Med. Chem.* 29 (**1986**) 1596-1603.
26. S Goldman, J Stoltefuss, *Angew. Chem. Int. Ed.* 30 (**1991**) 1559-1578.
27. *Pharmaceutical Chemistry - Volume 1: Drug Synthesis*, HJ Roth, A Kleemann (Eds), John Wiley & Sons, New York, NY, USA, 1988.
28. C Beyer, *Chem. Ber.* 24 (**1891**) 1662-1670.
29. E Knoevenagel, W Ruschhaupt, *Chem. Ber.* 31 (**1898**) 1025-1033.
30. AR Katritzky, DL Ostercamp, TI Yousaf, *Tetrahedron* 42 (**1986**) 5729-5738.
31. AR Katritzky, DL Ostercamp, TI Yousaf, *Tetrahedron* 43 (**1987**) 5171-5186.
32. U Eisner, J Kuthan, *Chem. Rev.* 72 (**1972**) 1-42.
33. DM Stout AI Meyers, *Chem. Rev.* 82 (**1982**) 223-243.
34. A Sausins, G Duburs, *Heterocycles* 27 (**1988**) 269-289.
35. C de Graaff, E Ruijter, RVA Orru, *Chem. Soc. Rev.* 41 (**2012**) 3969-4009.
36. A Dömling, W Wang, K Wang, *Chem. Rev.* 112 (**2012**) 3083-3135.
37. H Pellissier, *Adv. Synth. Catal.* 354 (**2012**) 237-294.
38. A Moyano, R Rios, *Chem. Rev.* 111 (**2011**) 4703-4832.
39. N Isambert, MM Sanchez Duque, J-C Plaquevent, Y Génisson, J Rodriguez, T Constantieux, *Chem. Soc. Rev.* 40 (**2011**) 1347-1357.
40. F Shi, L-Z Gong, *Acc. Chem. Res.* 44 (**2011**) 1156-1171.
41. A Dondoni, A Massi, *Acc. Chem. Res.* 39 (**2006**) 451-463.
42. J-P Wan, Y Liu, *Synthesis* (**2010**) 3943-3953.
43. M Balogh, I Hermecz, Z Meszaros, P Laszlo, *Helv. Chim. Acta* 67 (**1984**) 2270-2272.
44. JR Pfister, *Synthesis* (**1990**) 689-690.
45. A Maquestiau, A Mayence, JJ Vanden Eynde, *Tetrahedron Lett.* 32 (**1991**) 3839-3840.
46. JJ Vanden Eynde, F Delfosse, A Mayence, Y Van Haverbeke, *Tetrahedron* 51 (**1995**) 6511-6516.
47. T Itoh, K Nagata, M Okada, A Ohsawa, *Tetrahedron Lett.* 36 (**1995**) 2269-2272.
48. SH Mashraqui, MA Karnik, *Synthesis* (**1998**) 713-714.

49. JJ Vanden Eynde, A Mayence, A Maquestiau, *Tetrahedron* 48 (**1992**) 463-468.
50. B Wang, Y Hu, H Hu, *Synth. Commun.* 29 (**1999**) 4193-4199.
51. MM Sadeghi, I Mohammadpoor-Baltork, HR Memarian, S Sobhani, *Synth. Commun.* 30 (**2000**) 1661-1665.
52. YZ Mao, MZ Jin, ZL Liu, LM Wu, *Org. Lett.* 2 (**2000**) 741-742.
53. MA Zolfigol, MH Zebarjadian, MM Sadeghi, I Mohammadpoor-Baltork, HR Memarian, M Shamsipur, *Synth. Commun.* 31 (**2001**) 929-934.
54. I Mohammadpoor-Baltork, MM Sadeghi, HR Memarian, RJ Pairow, *J. Chem. Res.* (**2000**) 40-41.
55. JJ Vanden Eynde, RD Orazio, Y Van Haverbeke, *Tetrahedron* 50 (**1994**) 2479-2484.
56. O Garcia, F Delgado, AC Cano, C Alvarez, *Tetrahedron Lett.* 34 (**1993**) 623-625.
57. B Loev, KM Snader, *J. Org. Chem.* 30 (**1965**) 1914-1916.
58. SP Chavan, SW Dantale, UR Kalkote, VS Jyothirmai, RK Kharul, *Synth. Commun.* 28 (**1998**) 2789-2792.
59. RS Varma, DJ Kumar, *J. Chem. Soc. Perkin Trans. 1* (**1999**) 1755-1757.
60. MA Zolfigol, M Kiany-Borazjani, MM Sadeghi, I Mohammadpoor-Baltork, HR Memarian, *Synth. Commun.* 30 (**2000**) 3919-3923.
61. M Moghadam, M Nasr-Esfahani, S Tangestaninejad, V Mirkhani, *Bioorg. Med. Chem. Lett.* 16 (**2006**) 2026-2030.
62. M Moghadam, M Nasr-Esfahani, S Tangestaninejad, V Mirkhani, *Bioorg. Med. Chem. Lett.* 15 (**2005**) 3276-3278.
63. MA Zolfigol, A Ghorbani Choghamarani, M Shahamirian, M Safaiee, I Mohammadpoor-Baltork, S Mallakpour, M Abdollahi-Alibeik, *Tetrahedron Lett.* 46 (**2005**) 5581-5584.
64. MM Hashemi, Y Ahmadibeni, H Ghafuri, *Monatsh. Chem.* 134 (**2003**) 107-110.
65. G Sabitha, GSKK Reddy, CS Reddy, N Fatima, JS Yadav, *Synthesis* (**2003**) 1267-1271.
66. M Anniyappan, D Muralidharan, PT Perumal, *Tetrahedron* 58 (**2002**) 5069-5073.
67. JW Lee, KY Ko, *Bull. Korean Chem. Soc.* 25 (**2004**) 19-20.
68. JS Yadav, BVS Reddy, G Sabitha, GSKK Reddy, *Synthesis* (**2000**) 1532-1534.
69. X Cai, H Yang, G Zhang, *Can. J. Chem.* 83 (**2005**) 273-275.
70. K Niknam, MA Zolfigol, SM Razavian, I Mohammadpoor- Baltork, *Heterocycles* 65 (**2005**) 657-660.
71. RS Varma, D Kumar, *Tetrahedron Lett.* 40 (**1999**) 21-24.
72. B Han, Z Liu, Q Liu, L Yang, ZL Liu, W Yu, *Tetrahedron* 62 (**2006**) 2492-2496.
73. MM Heravi, FK Behbahani, HA Oskooie, RS Hekmat, *Tetrahedron Lett.* 46 (**2005**) 2775-2777.
74. M Nasr-Esfahani, M Moghadam, S Tangestaninejad, V Mirkhani, AR Momeni, *Bioorg. Med. Chem.* 14 (**2006**) 2720-2724.
75. N Nakamichi, Y Kawashita, M Hayashi, *Org. Lett.* 4 (**2002**) 3955-3957.
76. M Montazerozohori, B Karami, MH Habibi, *S. Afr. J. Chem.* 59 (**2006**) 62-64.
77. M Filipan-Litvic, M Litvic, V Vinkovic, *Tetrahedron* 64 (**2008**) 5649-5656.
78. M Filipan-Litvic, M Litvic, V Vinkovic, *Tetrahedron* 64 (**2008**) 10912-10918.
79. B Turovska, I Goba, I Turovskis, S Grinberga, S Belyakov, S Stupnikova, E Liepinsh, J Stradins, *Chem. Heteroc. Comp.* 44 (**2008**) 1483-1490.
80. J Mielcarek, T Osmatek, M Kruszynska, *Chromatographia* 69 (**2009**) 503-506.
81. R Lavilla, *J. Chem. Soc. Perkin Trans. 1* (**2002**) 1141-1156.
82. A Saini, S Kumar, JS Sandhu, *J. Sci. Ind. Res.* 67 (**2008**) 95-111.
83. J-P Wan, Y Liu, *RSC Adv.* 2 (**2012**) 9763-9777.
84. JJ Vanden Eynde, A Mayence, *Molecules* 8 (**2003**) 381-391.
85. J Westman, in *Microwave Assisted Organic Synthesis*, JP Tierney, P Lidström (Eds), Blackwell Publishing, Oxford, England, UK, 2005, Chapter 5, pp 105-106.
86. MC Bagley, MC Lubinu, in *Microwave-Assisted Synthesis of Heterocycles*, E Van der Eycken, CO Kappe (Eds), Springer, Berlin, Germany, 2006, Chapter 2, pp 36-39.

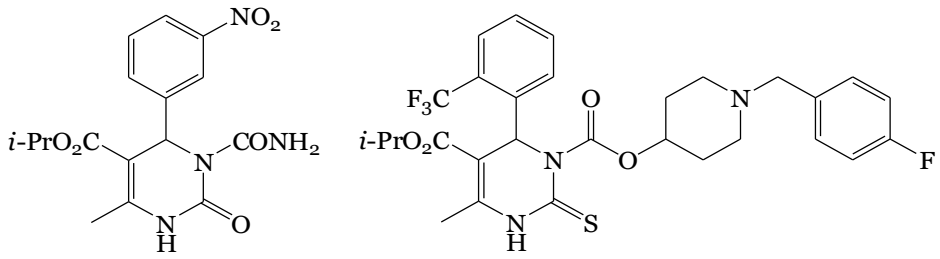
87. E Suna, I Mutule, in *Microwave Methods in Organic Synthesis*, M Larhed, K Olofsson (Eds), Springer, Berlin, Germany, 2006, Chapter 3, pp 79-82.
88. R Alajarin, JJ Vaquero, JL García Navio, J Alvarez-Builla, *Synlett* (**1992**) 297-298.
89. R Alajarin, P Jordán, JJ Vaquero, J Alvarez-Builla, *Synthesis* (**1995**) 389-391.
90. Y-W Zhang, Z-X Shan, B Pan, X-H Lu, M-H Chen, *Synth. Commun.* 25 (**1995**) 857-862.
91. BM Khadilkar, AA Chitnavis, *Ind. J. Chem.* 34B (**1995**) 652-653.
92. BM Khadilkar, VG Gaikar, AA Chitnavis, *Tetrahedron Lett.* 36 (**1995**) 8083-8086.
93. BM Khadilkar, VR Madyar, *Org. Proc. Res. Devel.* 5 (**2001**) 452-455.
94. M Suarez, A Loupy, E Perez, L Moran, G Gerona, A Morales, M Autié, *Heteroc. Commun.* 2 (**1996**) 275-280.
95. JS Yadav, BVS Reddy, PT Reddy, *Synth. Commun.* 31 (**2001**) 425-430.
96. L Öhberg, J Westman, *Synlett* (**2001**) 1296-1298.
97. H Salehi,Q-X Guo, *Synth. Commun.* 34 (**2004**) 4349-4357.
98. V Sivamurugan, A Vinu, M Palanichamy, V Murugesan, *Heteroatom Chem.* 17 (**2006**) 267-271.
99. KK Pasunooti, CN Jensen, H Chai, ML Leow, D-W Zhang, X-W Liu, *J. Comb. Chem.* 12 (**2010**) 577-581.
100. YA Lee, C Kim, *J. Ind. Eng. Chem.* 17 (**2011**) 401-403.
101. A Kuraitheerthakumaran, S Pazhamalai, M Gopalakrishnan, *Chin. Chem. Lett.* 22 (**2011**) 1199-1202.
102. D Bandyopadhyay, S Maldonado, BK Banik, *Molecules* 17 (**2012**) 2643-2662.
103. NA Al-Awadi, MR Ibrahim, MH Elnagdi, E Johh, YA Ibrahim, *Beilstein J. Org. Chem.* 8 (**2012**) 441-447.
104. C Alvarez, D Delgado, O Garcia, S Medina, C Marquez, *Synth. Commun.* 21 (**1991**) 619-624.
105. F Delgado, C Alvarez, O Garcia, G Penieres, C Marquez, *Synth. Commun.* 21 (**1991**) 2137-2141.
106. IC Cotterill, AY Usyatinsky, JM Arnold, DS Clark, JS Dordick, PC Michels, YL Khmelnitsky, *Tetrahedron Lett.* 39 (**1998**) 1117-1120.
107. S Torchy, G Cordonnier, D Barbry, JJ Vanden Eynde, *Molecules* 7 (**2002**) 528-533.
108. MM Heravi, M Ghassemzadeh, *Phos. Sul. Sil. Rel. El.* 180 (**2005**) 347-351.
109. MM Heravi, FSS Moosavi, YS Beheshtiha, M Ghassemzadeh, *Heteroc. Commun.* 10 (**2004**) 415-418.
110. MC Bagley, MC Lunibu, *Synthesis* (**2006**) 1283-1288.
111. O De Paolis, J Baffoe, SM Landge, B Török, *Synthesis* (**2008**) 3423-3428.
112. S Mehta, N Swarnkar, R Vyas, J Vardia, PB Punjabi, SC Ameta, *Phos. Sul. Sil. Rel. El.* 183 (**2008**) 105-114.
113. M Nasr-Esfahani, M Moghadam, G Valipour, *Synth. Commun.* 39 (**2009**) 3867-3879.
114. CM Kormos, RM Hull, NE Leadbeater, *Aust. J. Chem.* 62 (**2009**) 51-57.
115. R Hekmatshoar, A Rezaei, M Haghighi, AJ Ojghaz, SS Hekmatshoar, *J. Chin. Chem. Soc.* 56 (**2009**) 40-42.
116. HR Memarian, M Ghazaie, SK Mehneh, *Z. Naturforsch.* 64B (**2009**) 1187-1192.
117. HR Memarian, B Barati, *Z. Naturforsch.* 65B (**2010**) 1143-1147.
118. A Fatiadi, *Synthesis* (**1976**) 65-104.
119. A Fatiadi, *Synthesis* (**1976**) 133-167.
120. AT Soldatenkov, KB Polyanskii, NM Kolyadina, SA Soldatova, *Chem. Heteroc. Comp.* 45 (**2009**) 633-657.
121. DA House, *Chem. Rev.* 62 (**1962**) 185-203.
122. HR Memarian, I Mohammadpoor-Baltork, MM Sadeghi, ZS Samani, *Indian J. Chem.* 40B (**2001**) 727-728.

5

Biginelli 3,4-Dihydropyrimidines

I. Introduction & Relevance

The preparation of 3,4-dihydropyrimidines (DHPMs) was firstly described 120 years ago by the Italian chemist Pietro Biginelli.[1] This simple, one-pot and multicomponent approach to partly reduced pyrimidine derivatives, nowadays broadly recognised as the Biginelli synthesis, was mostly neglected in the following decades and, consequently, the biological activity of this class of nitrogen-containing heterocycles remained unexplored. However, interest in these compounds increased sharply since the early 1980s, in particular among synthetic and medicinal chemists.[2] This was largely due to the structural resemblance of DHPMs to the profoundly studied calcium channel blockers and α_{1a}-adrenergic receptor antagonists of the Hantzsch 1,4-dihydropyridine type. In fact, it was soon corroborated that several Biginelli 3,4-dihydropyrimidines exhibited improved pharmacological profiles, comparing to some widely known DHP pharmacophores employed against common cardiovascular diseases, an incredible progress in this area being observed in the 1990s.[2-6] As an example, two orally active and long-lasting antihypertensive DHPM agents are depicted in Figure 5.1.



SQ 32926 SQ 32547

Figure 5.1. Representative examples of Biginelli 3,4-dihydropyrimidine compounds relevant in cardiovascular diseases as calcium channel antagonists.

3,4-Dihydropyrimidines represent much more than just aza-analogues of Hantzsch DHPs. The evolution of combinatorial chemistry technology allowed the rapid generation of several DHPM compound libraries, which were then subjected to high-throughput screening techniques; hence, other interesting biological properties have been observed over the last 20 years and have been reviewed extensively.[7-12] Batzelladine A and B, which are obtained from marine natural sources and contain dihydropyrimidine moieties, have demonstrated promising anti-human immunodeficiency virus (HIV) activity (Figure 5.2). These low molecular weight alkaloids block the binding of HIV gp120 glycoproteins to CD_4 receptors and, therefore, are reasoned as potential leads for acquired immunodeficiency syndrome (AIDS) therapy.[13] It should also be mentioned that batzelladines C, D and E were found to be cytotoxic[13] and batzelladines F and G might be helpful for the treatment of several autoimmune disorders.[14] The discovery of monastrol is currently seen as a ground-breaking development regarding the pharmacology of Biginelli DHPM derivatives. In their pioneering work, Mayer and associates reported that this compound specifically suppressed the motor activity of human mitotic kinesin Eg5 as the first cell-permeable small molecule.[15] Given that Eg5 plays a pivotal role in the assembly of bipolar mitotic spindle, inhibition of this protein causes cell cycle arrest during the mitosis stage and, thus, it is considered a valid and effective strategy for cancer chemotherapy.[16, 17] Moreover, enzymatic experiments and *in vivo* assays indicated that (*S*)-monastrol presented a much higher activity than the corresponding (*R*)-enantiomer.[18] Also, both steady-state ATPase and cell-based assessments revealed that the inhibition potency of several monastrol-like compounds was even greater (Figure 5.3).

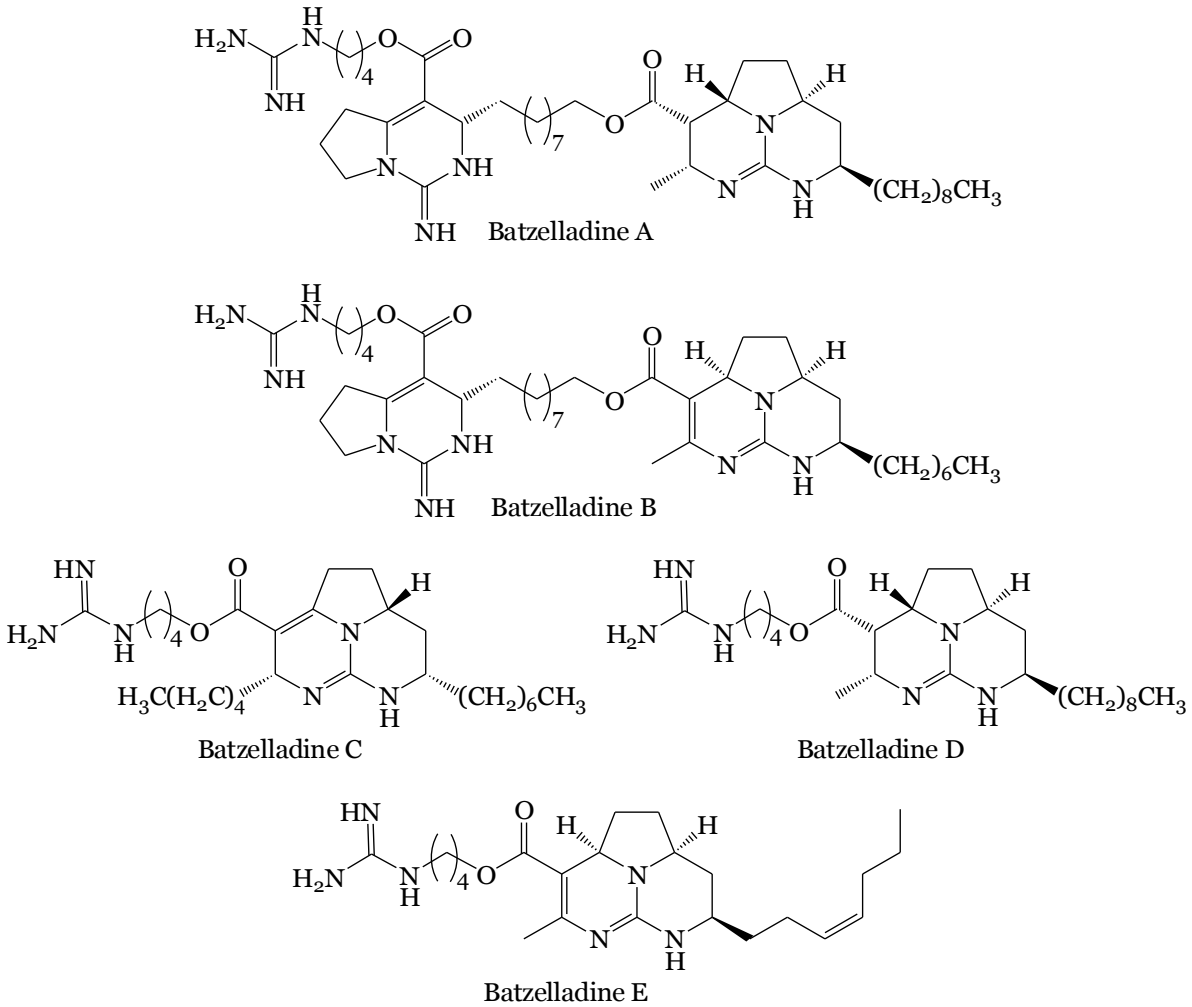


Figure 5.2. Representative examples of natural dihydropyrimidine-containing bioactive compounds.

Phenobarbital is the oldest and most widely used anticonvulsant drug world-wide,[19] targeting γ-aminobutyric acid (GABA) receptors in the central nervous system and is also known for possessing sedative and hypnotic properties. Due to structural similarities to this barbiturate molecule, some Biginelli 3,4-dihydropyrimidines have been analysed and were found to be auspicious anti-epileptic agents.[20] Various DHPM-amide derivatives, such as JAB 75, DMT 3024 and MAL 3-39, have been investigated as a new kind of heat shock protein Hsp70 modulators, quenching the replication of the malaria-causing parasite *Plasmodium falciparum* in human red blood cells.[21] It was also uncovered that SNAP 6201 and SNAP 7941, two multifunctionalised DHPMs, were powerful and selective antagonists of α_{1a}-adrenergic receptors and, thence, good lead compounds for the treatment of benign prostatic hyperplasia (BPH), presenting a good pharmacokynetic profile and no adverse cardiovascular effects (Figure 5.3).[6, 22]

A few heteroaryl-dihydropyrimidine structures, namely HAP1, Bay41-4109 and Bay39-5493, which were designed and synthesised at Bayer pharmaceutical company, have proven to efficiently bind to the protein shell that protects the nucleus of the hepatitis B virus (HBV) and, consequently, disrupt the replication mechanism of the latter.[23-25] A series of pyrazolyl-dihydropyrimidines were evaluated *in vitro* for their antitubercular properties against a *Mycobacterium tuberculosis* H37Rv strain,[26] a couple of compounds demonstrating to be more potent than isoniazid, the first-line medication in prevention and handling of tuberculosis (Figure 5.3). Furthermore, some Biginelli DHPM scaffolds bearing isoxazole substituents have shown an assortment of biological activities, such as antimicrobial, antibacterial, antifungal and antimalarial.[27] Also, significant anti-inflammatory properties have been reported in several 3,4-dihydropyrimidine-propionic acid derivatives.[28-30]

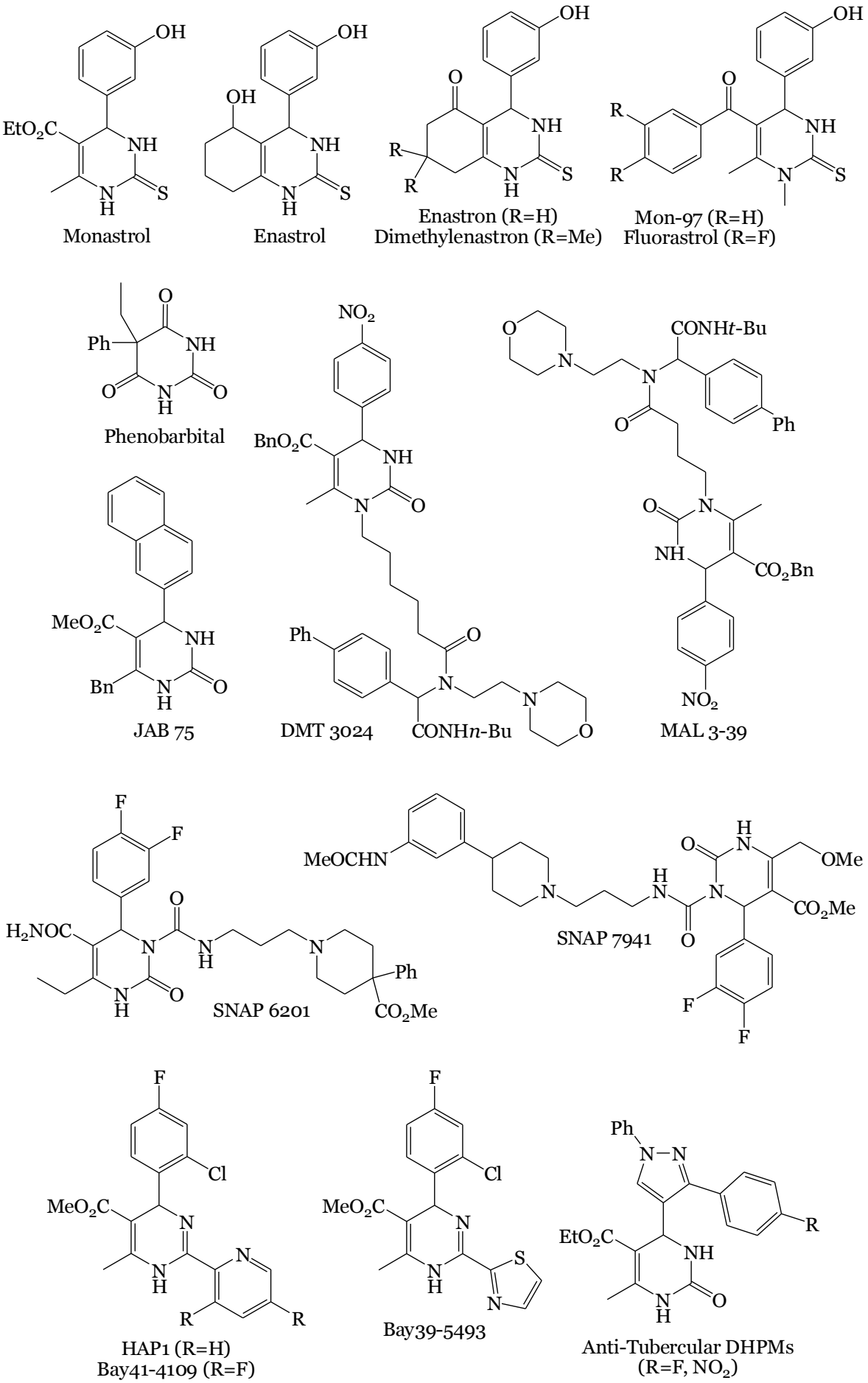
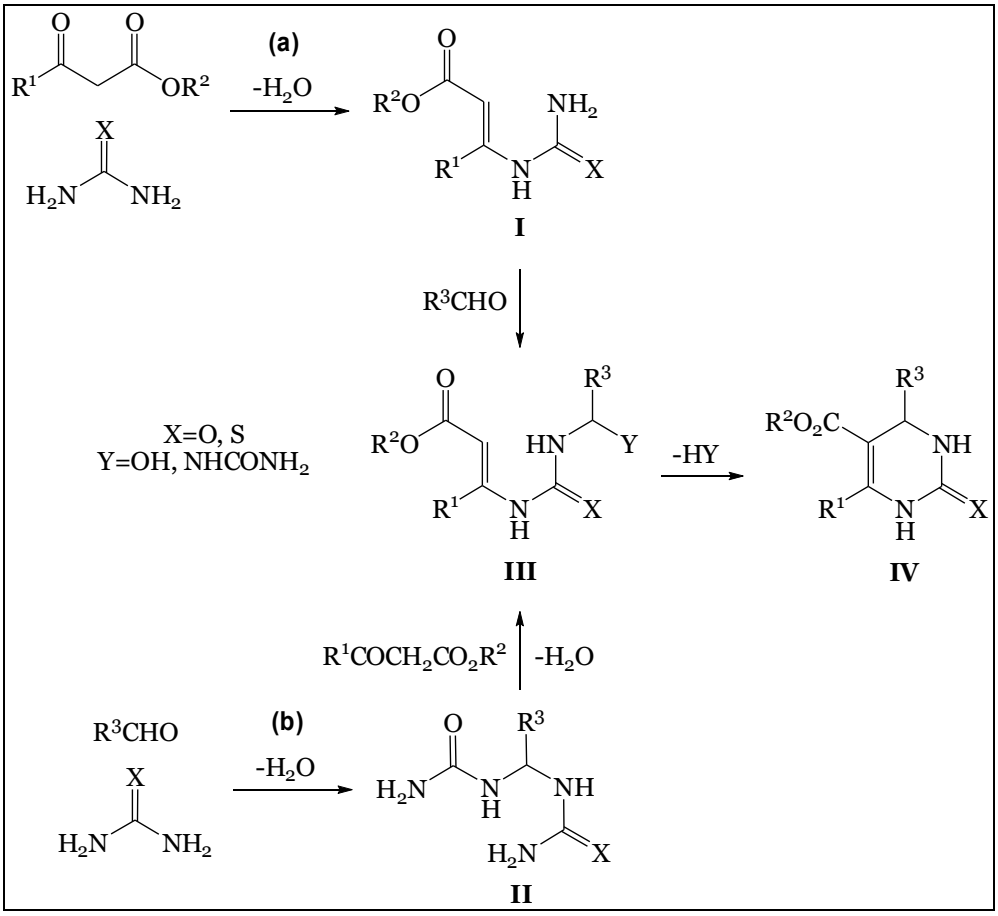


Figure 5.3. Representative examples of synthetic dihydropyrimidine-containing bioactive compounds.

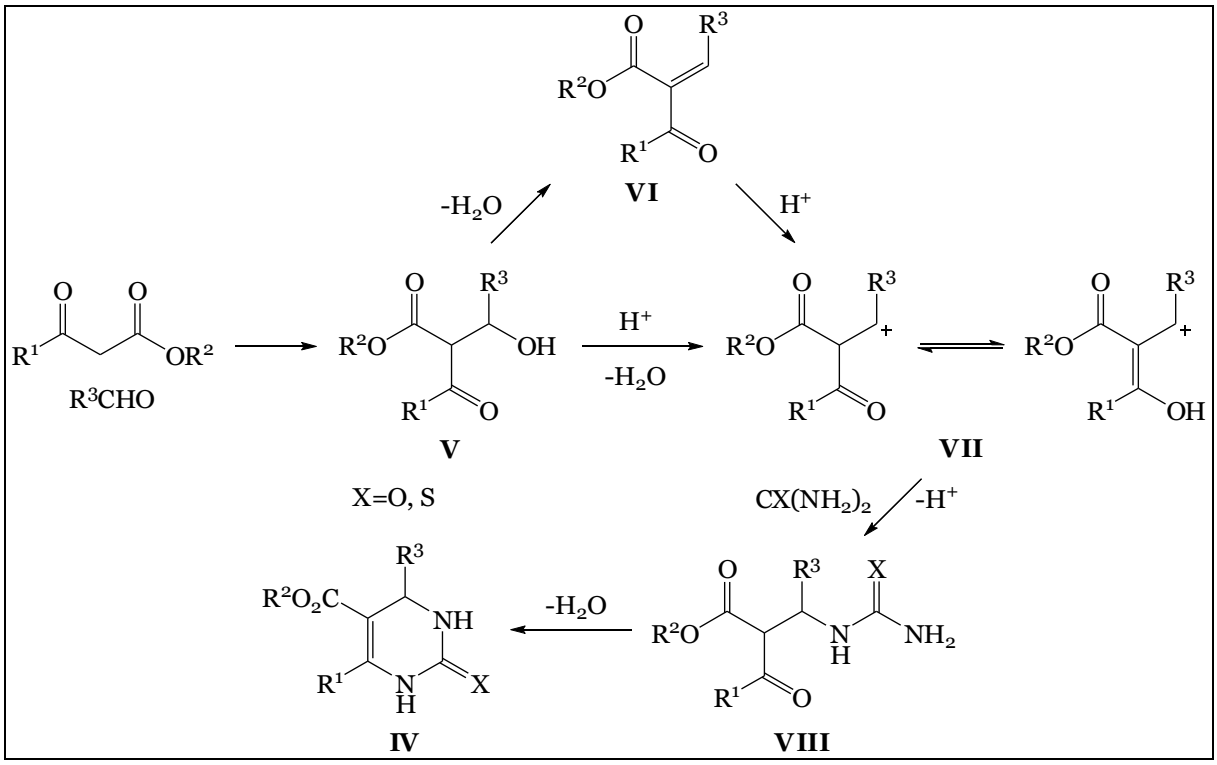
II. Classical Synthetic Methods

As credited above, the first paper on the synthesis of 3,4-dihydropyrimidines was authored by Biginelli in the late 19th century.[1] It discussed the three-component condensation of benzaldehyde, ethyl acetoacetate and urea in refluxing ethanol doped with a small amount of hydrochloric acid as catalyst, followed by filtration of the solid that precipitated upon slow cooling to room temperature and recrystallisation in ethanol. Seminal research concerning the mechanism of this reaction was produced by Folkers and Johnson in the early 1930s[31, 32] and is summarised in Scheme 5.1. The open-chain ureide-type scaffold **III**, either derived from intermediate **I** or **II**, which are the result of a preceding bimolecular condensation process, Scheme 5.1a and 5.1b, respectively, was suggested as the key chemical structure.



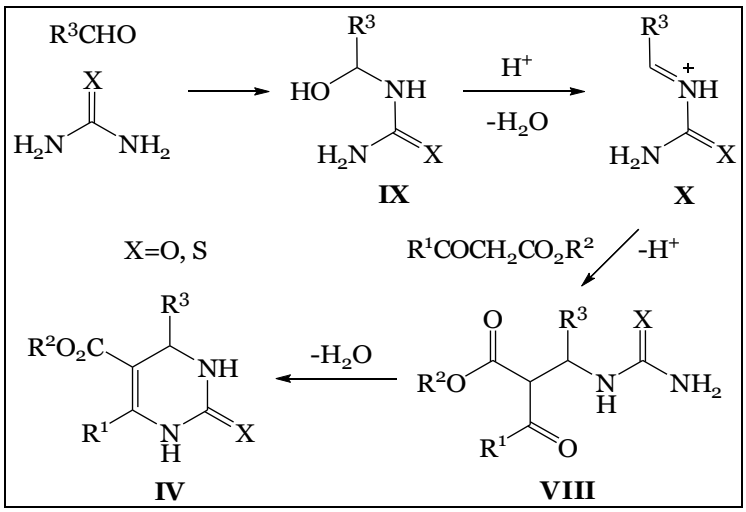
Scheme 5.1. Folkers and Johnson mechanistic proposal for the Biginelli synthesis of 3,4-dihydropyrimidines.

Four decades later, Sweet and Fissekis reinvestigated the Biginelli condensation and proposed a different mechanistic pathway involving a preliminary acid-catalysed aldol condensation between the aldehyde and β-ketoester reagents, followed by reaction of urea/thiourea with the carbenium ion intermediate **VII**, rendered either from the aldol structure **V** or from the α,β-unsaturated ketone **VI**, this being generated through dehydration of the same aldol condensation product (Scheme 5.2).[33] Sixteen years ago Kappe employed trapping experiments and both ^{1}H and ^{13}C NMR spectroscopic techniques in order to study this synthetic process, establishing that the crucial step in the preparation of Biginelli DHPMs concerned the acid-catalysed creation of an *N*-acyliminium ion intermediate **X** via protonation of the previously formed condensation product **IX** (Scheme 5.3).[34] Interception of this species by the β-ketoester starting material, presumably through its enol tautomer, affords the open-chain ureide **VIII,** which later undergoes cyclisation and water elimination leading to the target 3,4-dihydropyrimidine compound **IV**.



Scheme 5.2. Sweet and Fissekis mechanistic proposal for the Biginelli synthesis of 3,4-dihydropyrimidines.

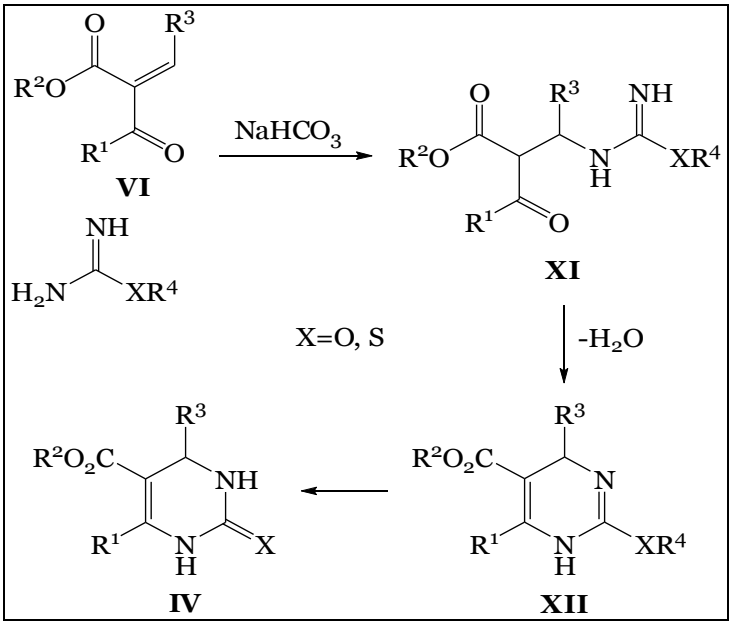
In short, the Kappe mechanism can be seen as an α-ureidoalkylation;[35] the carbenium ion intermediate approach disclosed by Sweet and Fissekis and depicted in Scheme 5.2 is not a prevailing synthetic route. Withal, minute quantities of α,β-unsaturated ketone **VI** were occasionally detected as a by-product. Albeit the extremely reactive *N*-acyliminium structure **X** was not isolated or experimentally observed, further indication for this mechanistic rationalisation was later found using β-ketoester reactants bearing bulky[36] or electron-deficient[37] substituents. More recently, ESI-MS assessments and DFT calculations carried-out by de Souza and colleagues have demonstrated that the *N*-acyliminium ion mechanism is the thermodynamically and kinetically favoured pathway in the one-pot three-component Biginelli synthesis.[38] However, new information reported by Kolosov and co-workers reintroduced the discussion, arguing that the mechanism suggested by Kappe is only credible for reactions occurring in highly acidic media, when Brønsted acids are used, and no longer reasonable in the case of Lewis acid- or non-catalysed reactions and of non-acidic reaction conditions.[39]



Scheme 5.3. Kappe mechanistic proposal for the Biginelli synthesis of 3,4-dihydropyrimidines.

An alternative strategy for the preparation of Biginelli DHPMs was presented by the research group of Atwal in the late 1980s.[40-42] This two-step methodology involves the base-catalysed condensation of a previously synthesised alkylidene- or arylidene-type 1,3-dicarbonyl compound **VI** with urea or thiourea derivatives, ureide adduct **XI** being the proposed reaction intermediate. Cyclisation and water elimination of the latter to structure **XII**, followed by simple deprotection of the nitrogen atom ultimately furnishes the 3,4-dihydropyrimidinone (X=O) or its thione equivalent (X=S) **IV** (Scheme 5.4). Moreover, it was disclosed that piperidine can act as both solvent and base in the multicomponent Biginelli condensation process, the corresponding Hantzsch 1,4-dihydropyridine analogues also being isolated as secondary products, which are assumed to be formed due to decomposition of urea and subsequent generation of ammonia within the reaction medium.[43]

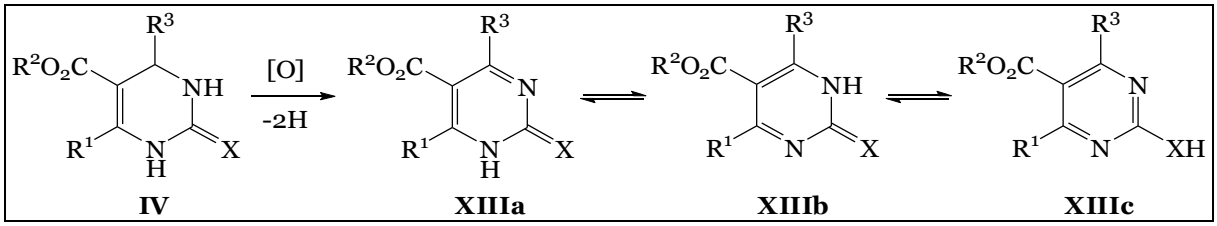
Regardless of whether the Biginelli synthesis is performed under acid or alkaline catalysis conditions, the generally accepted mechanistic routes that have been presented over the years clearly display common features and evidence strongly supports that open-chain ureides, such as **VIII** or **XI**, although of different synthetic origins, are important intermediates preceding the ring-closing step. On the other hand, experimental studies on the reaction mechanisms of non-catalysed approaches to Biginelli DHPMs are scarce and, consequently, some controversy continues in the academic community.



Scheme 5.4. Atwal mechanistic proposal for the alternative Biginelli synthesis of 3,4-dihydropyrimidines.

Unlike Hantzsch 1,4-dihydropyridines, in which oxidative aromatisation is typically an easy procedure, the oxidation of Biginelli 3,4-dihydropyrimidines, portrayed in a generic fashion in Scheme 5.5, is rather difficult and no efficient, practical and broad method has been disclosed so far. In fact, it was pointed-out 20 years ago that the resistance of DHPMs to oxidative processes may explain the extended duration of cardioprotective activity as compared to DHP-type calcium channel modulator drugs.[4, 5] Biginelli DHPMs have proven to be quite stable towards powerful oxidising agents, such as sodium nitrite in acetic acid, PCC, clay-supported $KMnO_4$, activated manganese dioxide, *p*-TCQ and DDQ,[44] as well as some common oxidants successfully utilised in the dehydrogenation of Hantzsch DHPs, e.g. Br_2,[45] elemental sulphur,[46] $FeCl_3$,[47, 48] bismuth(III) nitrate,[48] *o*-iodoxybenzoic acid[48] and ceric ammonium nitrate in acetic acid.[49] It was discovered that Pd/C-promoted oxidation at high temperature only worked for 3,4-dihydropyrimidines that did not incorporate sensitive functional groups[50] and oxidants such as selenium dioxide[51] and $Co(NO_3)_2.6H_2O/K_2S_2O_8$[52] often led to unwanted oxidation by-products. However, formation of a few pyrimidine products could be accomplished through an electrochemical methodology on a carbon electrode.[53] Nitric acid was also described as a selective reagent for the dehydrogenation of some DHPMs.[54] Furthermore, a mixture of a slight excess of *t*-butyl

hydroperoxide and catalytic amounts of potassium carbonate and a copper salt demonstrated to be satisfactory for the oxidation of 3,4-dihydropyrimidine derivatives.[55] More recently, CAN was reinvestigated under alkaline reaction conditions and it was reported that conversion of several DHPMs into the corresponding oxidised structures was attained.[56] Additionally, potassium peroxydisulphate[57] and UV irradiation[58] also proved to be effective in the dehydrogenation of various 3,4-dihydropyrimidinones. Notwithstanding, it must be emphasised that, to the best of our knowledge, a study dealing with the successful oxidation of Biginelli DHPMs of the thione kind (Scheme 5.5, X=S) has never been published.



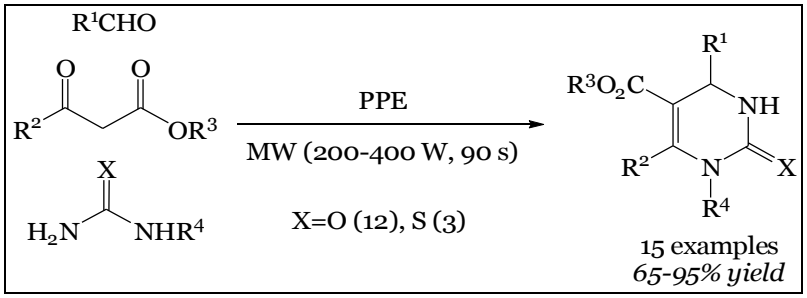
Scheme 5.5. Oxidation of Biginelli 3,4-dihydropyrimidines.

III. Microwave-Assisted Synthetic Methods

Various review papers focussing on the tremendous amount of different alterations to the centennial multicomponent Biginelli reaction, including the thriving usage of microwave activation, have appeared in the scientific literature.[2, 10, 59-61] Novel developments regarding the reactivity and functionalisation of 3,4-dihydropyrimidine compounds have also been addressed in detail[2, 10, 61, 62] and even an interesting biographical survey on Pietro Biginelli has been issued.[63] Selected illustrations on the microwave-assisted organic synthesis of Biginelli DHPM derivatives, as well as some of their related oxidised analogues, are shortly presented in the following pages.

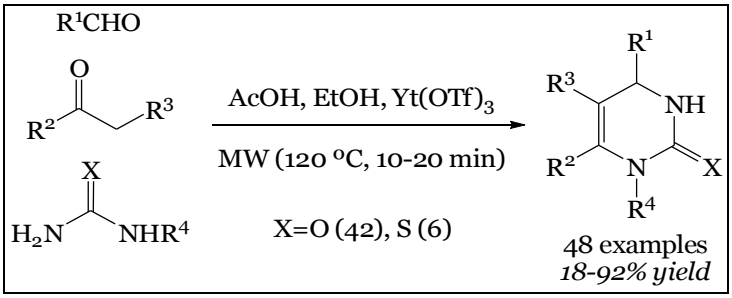
A. Literature Review & Selected Examples

Early work on the application of microwaves to the synthesis of Biginelli DHPMs was published in the late 1990s[64-70] and was mainly centred on the employment of household microwave ovens under solventless reaction conditions,[64-66] briefer reaction times comparing to conventional heating approaches and moderate to high yields being reported. A series of 3,4-dihydropyrimidines was prepared by Kappe and co-workers in 1999 utilising a solvent-free methodology and polyphosphate ester (PPE) as the reaction promoter (Scheme 5.6).[64] Heating the multicomponent reaction mixture for only 90 seconds in a domestic microwave apparatus, followed by simple precipitation in water and filtration, afforded the desired DHPMs with isolated yields up to 95%, 1 to 50 mmol scale protocols being successfully performed. However, PPE had to be prepared beforehand, since it was not commercially available.



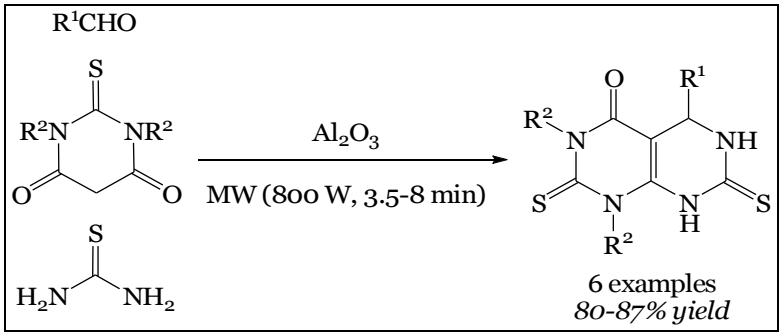
Scheme 5.6. Solventless synthesis of Biginelli 3,4-dihydropyrimidines using PPE as catalyst.

The application of other acidic catalysts under solvent-free and microwave heating conditions, such as aluminium(III) chloride hexahydrate,[71] aluminium hydrogen phosphate,[72] alumina-sulfuric acid[73] and oxalic acid[74] to the Biginelli condensation was reported more recently. The automated synthesis of a DHPM compound library, starting from several combinations of carbonyl compounds, aldehydes and urea or thiourea derivatives, was accomplished in a single-mode microwave reactor by Stadler and Kappe in 2001.[75] The use of ytterbium(III) triflate as Lewis acid catalyst in an acetic acid/ethanol solvent mixture at 120 °C for 10 to 20 minutes, following precipitation of the product upon cooling or crystallisation in water, rendered the Biginelli structures (Scheme 5.7). Forty eight DHPMs were prepared within 12 hours with a 52% average isolated yield and a 90% minimum purity using this sequential process. Dallinger and Kappe later revisited this strategy and found that the thione derivatives were generally obtained with improved yields when acetonitrile was utilised as solvent.[76]



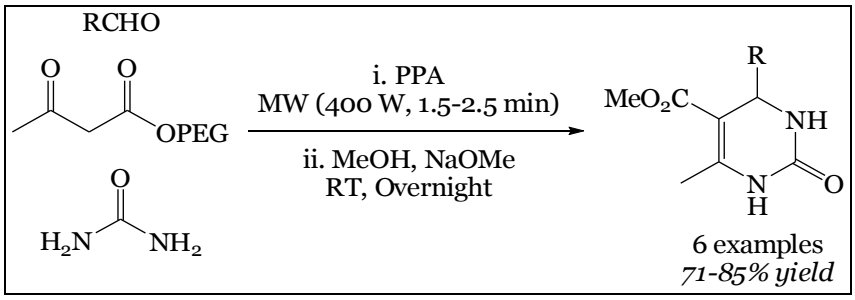
Scheme 5.7. Synthesis of Biginelli 3,4-dihydropyrimidines using $Yt(OTf)_3$ as catalyst.

A microwave-mediated and solid-supported Biginelli-like method was published by Kidwai and colleagues in 2003,[77] six thiobarbituric acid derivatives being synthesised with good yields in a short time-span, after washing-off the products from the acidic alumina support with ethanol, evaporation of the solvent under reduced pressure and recrystallisation in methanol (Scheme 5.8).



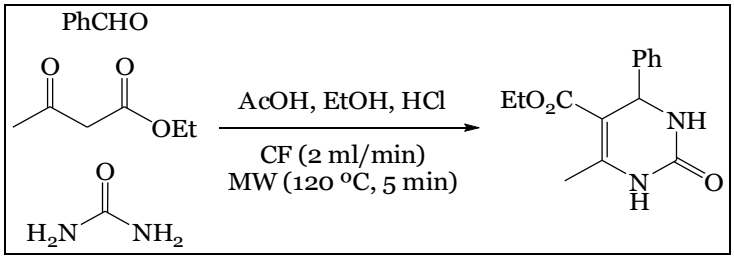
Scheme 5.8. Solid-supported synthesis of Biginelli-type 3,4-dihydropyrimidines using Al_2O_3.

The solvent-free synthesis of some DHPMs was carried-out by Xia and Wang using a polyethylene glycol-linked reagent.[78] A mixture comprising previously prepared PEG-4000-bound acetoacetate, urea, aryl aldehydes and polyphosphoric acid (PPA) as catalyst was heated in an unmodified household microwave oven operating at 400 W, furnishing the expected polymer-bound 3,4-dihydropyrimidinones in very brief reaction times. Subsequent cleavage from the polymeric material with sodium methoxide in methanol at room temperature and appropriate work-up rendered the target Biginelli structures with good isolated yields (Scheme 5.9).



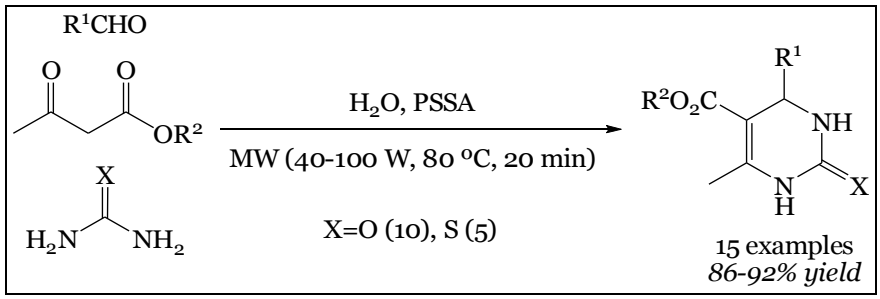
Scheme 5.9. Solventless synthesis of Biginelli 3,4-dihydropyrimidines using PPA as catalyst.

Glasnov and associates developed a microwave-assisted continuous-flow (CF) Biginelli protocol in 2006.[79] A freshly prepared solution of benzaldehyde, ethyl acetoacetate and urea in acetic acid/ethanol doped with a 10% molar equivalent of hydrochloric acid (1.3 M) was introduced through a HPLC pump in an appropriate flow cell at a 2 ml min^{-1} flow rate and heated at 120 °C, the desired DHPM being obtained with a 52% yield after 13 minutes of total processing time (5 minutes of residence time inside the flow cell), allowing the synthesis of the product on a 25 g h^{-1} scale (Scheme 5.10).



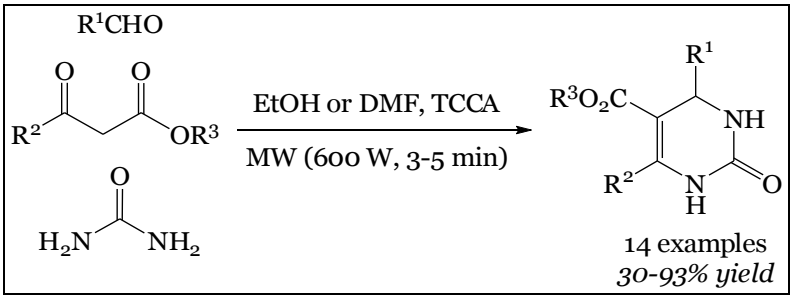
Scheme 5.10. Continuous-flow synthesis of a Biginelli 3,4-dihydropyrimidine using HCl as catalyst.

The microwave-activated preparation of some Biginelli 3,4-dihydropyrimidines using polystyrenesulphonic acid (PSSA) as catalyst was presented by Polshettiwar and Varma in 2007.[80] The reaction proceeded efficiently in a single-mode reactor, under closed-vessel conditions, using water as reaction medium. Simple filtration of the precipitated products after cooling to room temperature, followed by recrystallisation in an appropriate organic solvent, was the only work-up needed in order to achieve isolated yields of up to 92% (Scheme 5.11).



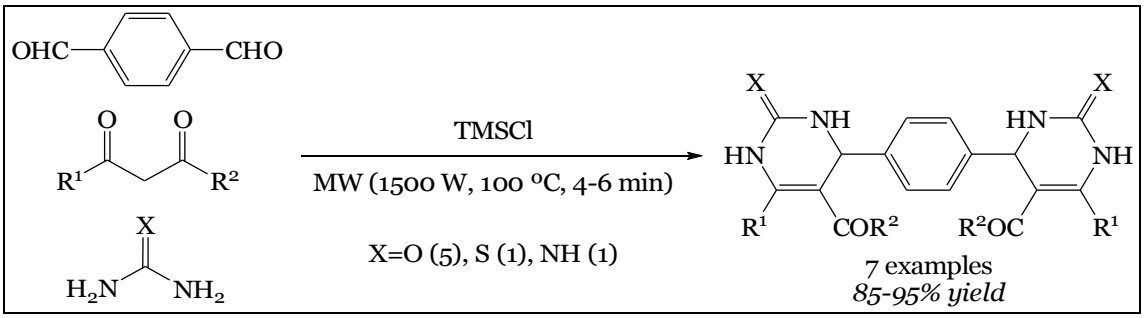
Scheme 5.11. Synthesis of Biginelli 3,4-dihydropyrimidines in water using PSSA as catalyst.

Trichloroisocyanuric acid (TCCA), a known industrial disinfectant for swimming pools and dyestuffs and also a bleaching agent used in the textile industry, was employed as catalyst in the microwave-assisted Biginelli reaction by Bigdeli and colleagues.[81] Both ethanol and DMF were found to be suitable solvents, fourteen DHPMs being obtained with generally high yields in short reaction times after irradiation in a domestic microwave equipment operating at 600 W, no chromatographic isolation procedures being required (Scheme 5.12).



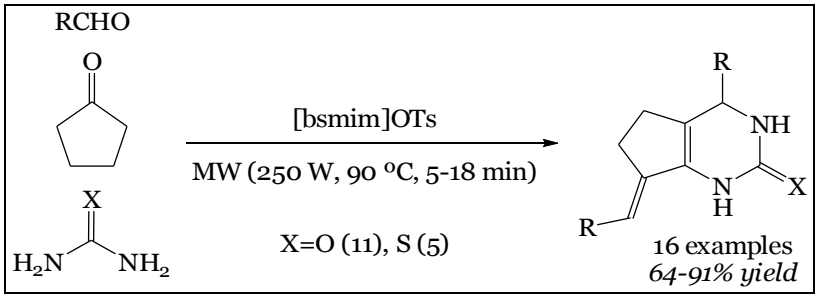
Scheme 5.12. Synthesis of Biginelli 3,4-dihydropyrimidines using TCCA as catalyst.

The solventless synthesis of some Biginelli bis-DHPM compounds using chlorotrimethylsilane (TMSCl) as catalyst was reported in 2010 by the research team of Miri.[82] Condensation between terephthalaldehyde, 1,3-dicarbonyl compounds and urea, thiourea or guanidine was carried-out in a multi-mode microwave reactor at 100 °C for 4 to 6 minutes, the target 3,4-dihydropyrimidine derivatives being prepared with very high yields (Scheme 5.13). Mirza and associates have recently explored a rather similar strategy for the preparation of this type of heterocycles, replacing chlorotrimethylsilane by a heterogeneous nanosilica catalyst (50 nm average particle size and 200 $m^2 g^{-1}$ specific surface area), fourteen bis-3,4-dihydropyrimidines being synthesised in 3 to 4 minutes with isolated yields ranging from 81 to 93%.[83] Nonetheless, no data regarding the commercial availability or synthetic process of the catalyst was provided, albeit the authors asserted that it was inexpensive and could be recycled several times.



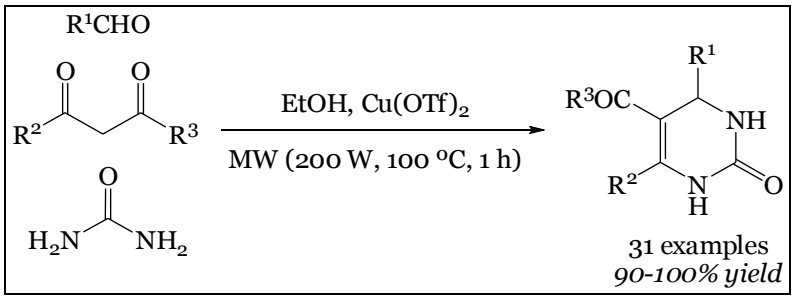
Scheme 5.13. Solventless synthesis of Biginelli bis-3,4-dihydropyrimidines using TMSCl as catalyst.

A simple and effective methodology for the synthesis of heterobicyclic 3,4-dihydropyrimidine scaffolds using a dedicated microwave equipment was presented by Rahman and colleagues in 2010.[84] The one-pot condensation of aryl aldehydes, cyclopentanone and urea or thiourea in the presence of a previously prepared Brønsted acidic ionic liquid, namely butane-1-sulfonic acid-3-methylimidazolium tosylate ([bsmim]OTs), furnished sixteen DHPM compounds with moderately good to high yields (Scheme 5.14). The authors claimed that the ionic liquid could be reutilised six times without any noticeable decrease in its activity.



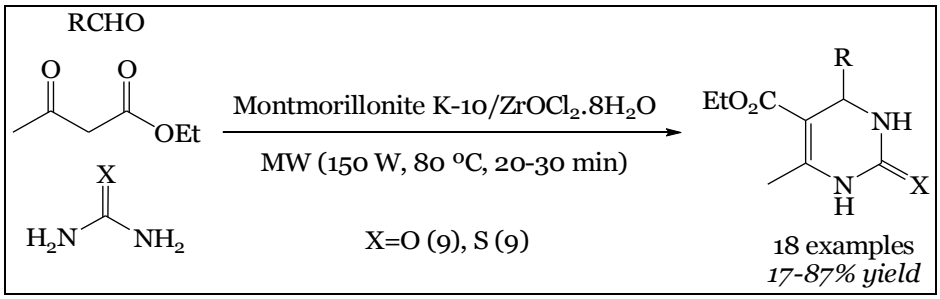
Scheme 5.14. Synthesis of Biginelli-type 3,4-dihydropyrimidines in ionic liquids.

An efficient and eco-friendly method to generate 3,4-dihydropyrimidines via a microwave-activated Biginelli condensation was described by Pasunooti and associates.[85] Utilising a single-mode microwave reactor and catalytic quantities of copper(II) triflate in ethanol, thirty one DHPMs were synthesised under relatively mild conditions (Scheme 5.15). Although the reaction times were reduced comparing to classical heating procedures, the authors needed to heat the reaction mixtures at 100 °C for one hour, which is much longer than other microwave-assisted Biginelli or Biginelli-like protocols that have been reported.



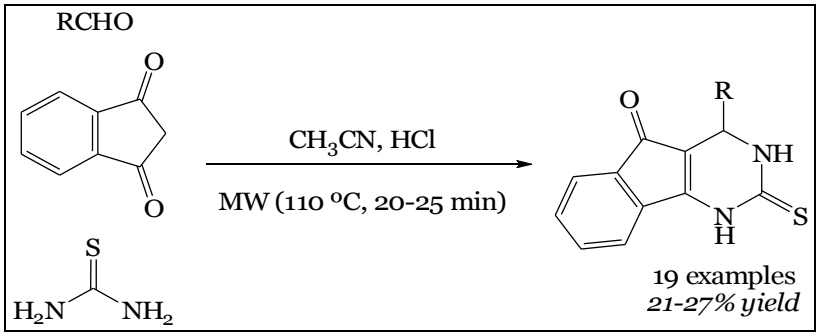
Scheme 5.15. Synthesis of Biginelli 3,4-dihydropyrimidines using $Cu(OTf)_2$ as catalyst.

Montmorillonite K-10-supported zirconium(IV) oxychloride octahydrate was able to promote the Biginelli reaction under microwave irradiation and in the absence of any organic solvent.[86] A microwave power setting of 150 W, a reaction temperature of 80 °C and a 40% molar equivalent of $ZrOCl_2.8H_2O$ were found to be the best reaction conditions, some 3,4-dihydropyrimidines being prepared with low to good isolated yields after work-up (Scheme 5.16). It was claimed that the montmorillonite K-10/$ZrOCl_2.8H_2O$ system, which had to be prepared beforehand and properly activated, could be regenerated and reused without significant loss in its activity.



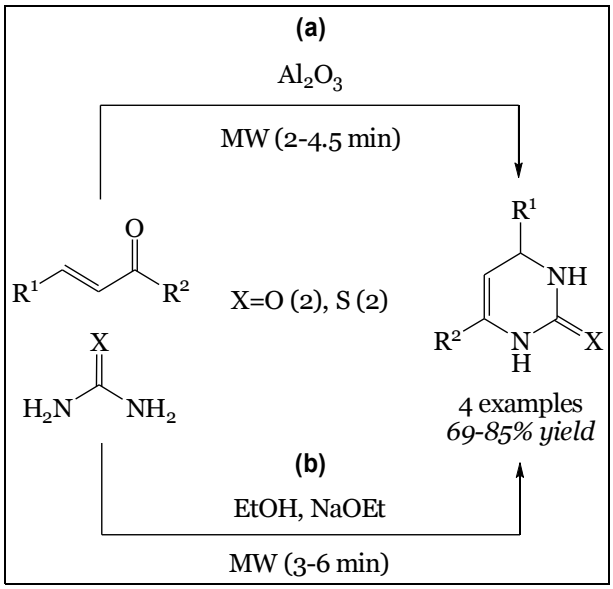
Scheme 5.16. Solid-supported synthesis of Biginelli 3,4-dihydropyrimidines using montmorillonite K-10/ $ZrOCl_2.8H_2O$.

A series of tricyclic 3,4-dihydropyrimidine derivatives was synthesised under microwave-activation by Gijsen and colleagues in 2012,[87] starting from various aryl aldehydes, thiourea and 1,3-indandione as reagents and using hydrochloric acid as catalyst. No information about the type of microwave apparatus employed or even the microwave power applied was given. All products were obtained with low isolated yields (Scheme 5.17).



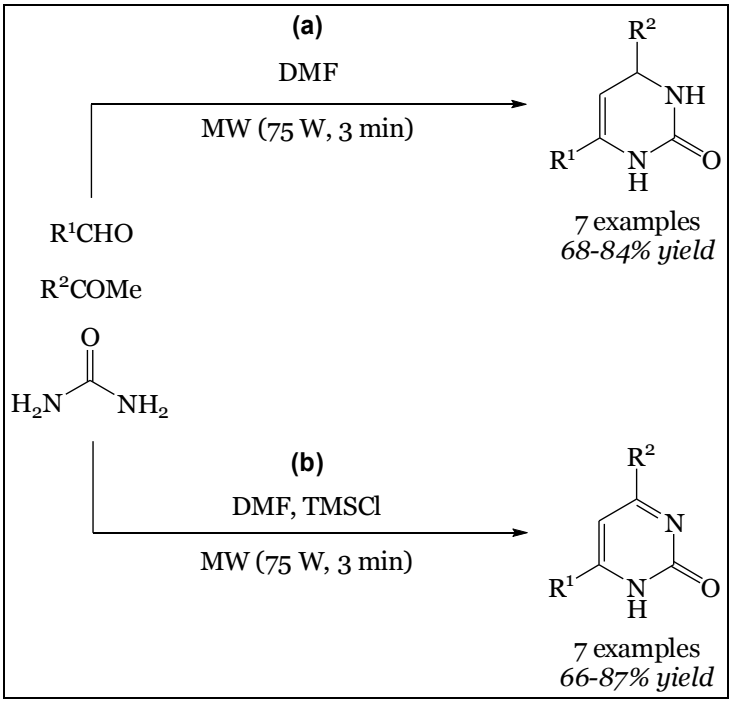
Scheme 5.17. Synthesis of Biginelli-type 3,4-dihydropyrimidines using HCl as catalyst.

Starting from suitable and previously synthesised chalcones and urea or thiourea as reagents and employing neutral aluminium oxide as solid support, the Kidwai research group prepared four Biginelli-type 3,4-dihydropyrimidines with good reaction yields utilising a domestic microwave equipment (Scheme 5.18a).[88] The authors also tested a microwave-assisted procedure in ethanol, making use of sodium ethoxide as catalyst, the same compounds being obtained with similar isolated yields under 6 minutes (Scheme 5.18b). However, no information concerning the reaction temperature or even the microwave power applied was given.



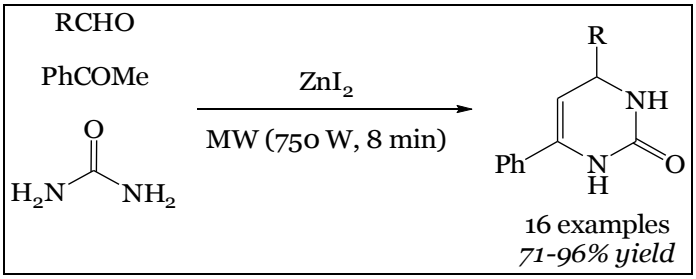
Scheme 5.18. Solid-supported (a) and solvent-based (b) synthesis of Biginelli-type 3,4-dihydropyrimidines.

Lin and co-workers studied the microwave-assisted three-component reaction of aryl aldehydes, substituted acetophenones and urea in *N*,*N*-dimethylformamide, a few Biginelli-like 3,4-dihydropyrimidines being prepared with good to high yields, after only 3 minutes of irradiation using a domestic microwave oven, cooling to room temperature, washing with distilled water, filtration and recrystallisation in ethanol (Scheme 5.19a).[89] Furthermore, it was claimed that performing the same protocol in the presence of chlorotrimethylsilane afforded the corresponding dehydrogenated pyrimidinone derivatives with satisfactory isolated yields (Scheme 5.19b).



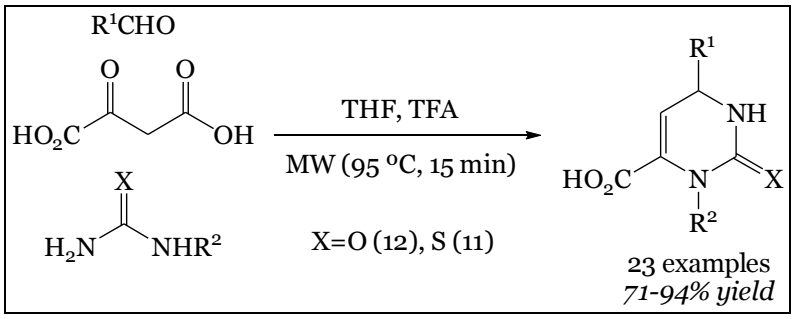
Scheme 5.19. Synthesis of Biginelli-type 3,4-dihydropyrimidines (a) and pyrimidinones (b).

Liang and co-workers described the three-component and one-pot Biginelli-type condensation of aryl aldehydes, acetophenone and urea, under solvent-free and microwave heating conditions, utilising zinc iodide as catalyst.[90] The corresponding Bigineli-like 3,4-dihydropyrimidines were produced with good isolated yields after 8 minutes of irradiation in an unmodified household apparatus and an easy work-up protocol (Scheme 5.20).



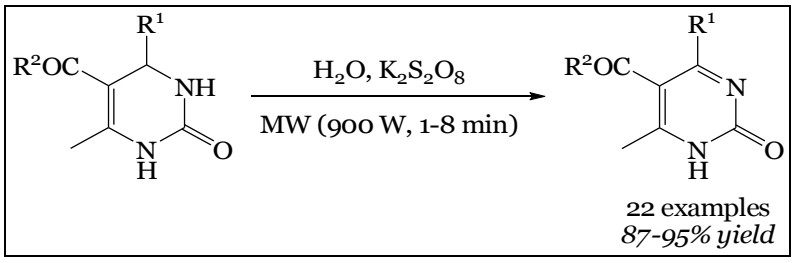
Scheme 5.20. Solventless synthesis of Biginelli-type 3,4-dihydropyrimidines using ZnI_2 as catalyst.

Fang and Lam developed a fast and convenient strategy for the preparation of a series of 5-unsubstituted Biginelli-type structures in 2011,[91] involving the one-pot reaction between selected aryl aldehydes, oxalacetic acid and urea or thiourea derivatives, under single-mode microwave heating and sealed-vessel conditions, the desired DHPM structures being obtained with good yields after a simple isolation procedure (Scheme 5.21).



Scheme 5.21. Synthesis of Biginelli-type 3,4-dihydropyrimidines using TFA as catalyst.

A simple and cost-effective methodology for the dehydrogenation of Biginelli DHPMs under microwave heating conditions was presented by Memarian and colleagues in 2009,[92] potassium peroxydisulphate being employed as oxidising agent and water as solvent (Scheme 5.22). Although high isolated yields were reported under 8 minutes of irradiation using an unmodified domestic equipment, the reactions were carried-out in a rather small scale (0.23 mmol of the reactants) and the oxidation process of the thione analogues was not investigated. It should also be stressed that the reaction mixtures were irradiated in 30-second time intervals in order to avert uncontrollable super-heating phenomena and, due to evaporation upon microwave irradiation, water had to be constantly added in order to maintain an invariable concentration of the reaction mixtures.



Scheme 5.22. Oxidation of Biginelli 3,4-dihydropyrimidines in water using $K_2S_2O_8$ as oxidant.

B. Multicomponent Synthesis of Biginelli 3,4-Dihydropyrimidines

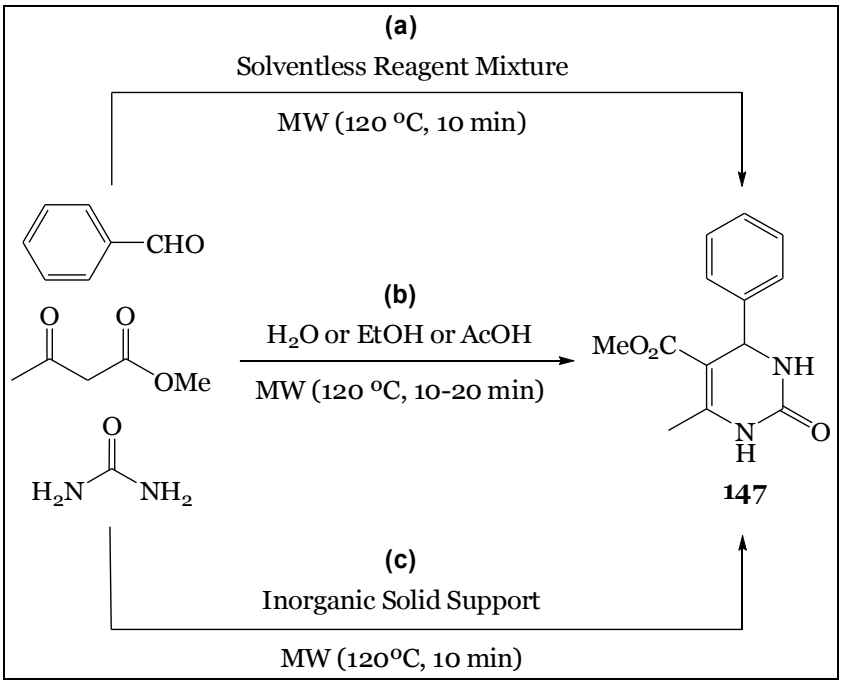
Aiming to prepare a medium-sized compound library of structurally-diverse Biginelli DHPMs through a simple, inexpensive and both environment- and user-friendly strategy under microwave activation, we decided to synthesise methyl 6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate **147** in order to optimise the reaction conditions and, particularly, select a suitable reaction medium (Scheme 5.23). In our first studies, a three-component mixture of benzaldehyde, a 1.5 molar equivalent of methyl acetoacetate and a two-fold molar excess of urea was microwave-heated at 120 ºC for 10 minutes, under sealed-vessel conditions, with an initial power setting of 100 W (Scheme 5.23a). After cooling to room temperature, a small amount of a yellowish solid precipitated out of the crude product mixture. This was filtered, washed with distilled water and recrystallised in aqueous ethanol, the desired 3,4-dihydropyrimidine being obtained as a pale-yellow solid with a slim 24% yield (Table 5.1, entry 1). Given that this solvent- and catalyst-free approach proved to be ineffective, a water-based protocol was tested under equal reaction conditions; however, an even worse result was achieved (entry 2). Furthermore, the addition of catalytic amounts of acids, namely concentrated sulphuric acid, *p*-toluenesulphonic acid (TSA) and trifluoroacetic acid (TFA), did not significantly alter the final outcome (entries 3-5).

Ethanol was then chosen as the reaction solvent, a 27% isolated yield being attained after similar work-up (entry 6). Unlike before, the acidification of the reaction medium demonstrated to be slenderly advantageous, yields between 50 and 53% being accomplished (entries 7-9). When glacial acetic acid was employed as both solvent and acidic catalyst, the yield after isolation increased sharply to 83%, after 10 minutes of microwave heating at 120 ºC (entry 10). Nevertheless, changing the reaction time to 20 minutes was not beneficial to the synthetic process (entry 11). In terms of the reaction yield, this result is very similar to the one found by Yu and co-workers,[93] which described the preparation of the related ethyl 6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate derivative with an 80% isolated yield, after carrying-out the reaction under conventional heating conditions for 3 hours at 90 ºC using a 10% molar equivalent of acetic acid as catalyst.

Table 5.1. Multicomponent synthesis of methyl 6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate **147** under microwave irradiation.

Entry	Reaction Medium	Time (min)	Yield[a] (%)
1	Solventless	10	24
2	H_2O[b]	10	20
3	H_2O/H_2SO_4[b]	10	25
4	H_2O/TSA[b]	10	22
5	H_2O/TFA[b]	10	25
6	EtOH[b]	10	27
7	$EtOH/H_2SO_4$[b]	10	53
8	EtOH/TSA[b]	10	50
9	EtOH/TFA[b]	10	53
10	AcOH[b]	10	83
11	AcOH[b]	20	80
12	SiO_2 60 (35-70 μm)[c]	10	20
13	SiO_2 60/H_2SO_4 (35-70 μm)[c]	10	75
14	Montmorillonite K-10[c]	10	57

All reactions were carried-out using benzaldehyde (10 mmol), methyl acetoacetate (15 mmol) and urea (20 mmol) at 120 ºC. [a]Yields refer to the isolated reaction products. [b]The selected solvent (2.5 ml) was used as reaction medium in closed-vessel conditions, an initial microwave power of 100 W being applied. [c]The selected solid support (10 g) was used as reaction medium in open-vessel conditions, an initial microwave power of 200 W being applied.



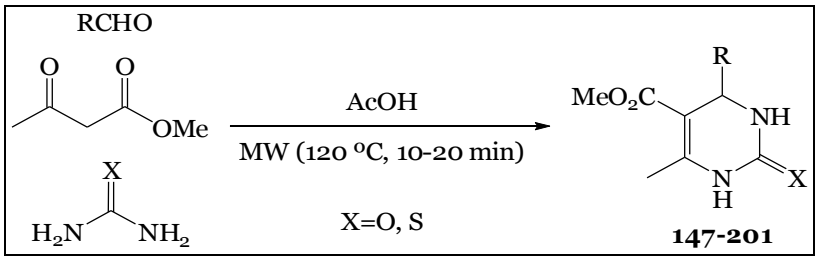
Scheme 5.23. Multicomponent synthesis of methyl 6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate **147** under microwave irradiation.

Apart from the solvent-based methodologies (Scheme 5.23b), a few inorganic solid supports were also tested as reaction medium (Table 5.1, entries 12-14; Scheme 5.23c), sulphuric acid-doped silica gel being the one that produced better results, since methyl 6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate **147** was obtained with a 75% isolated yield, after heating at 120 °C for 10 minutes under open-vessel conditions and using an initial microwave power setting of 200 W. The isolation protocol was facile and consisted in washing the crude product mixture with ethyl acetate, followed by removal of the solid support through filtration, evaporation of the solvent under reduced pressure and recrystallisation of the resulting yellow residue in aqueous ethanol. The application of unmodified silicon dioxide (entry 12) or montmorillonite K-10 (entry 14) as the solid support rendered much lower isolated yields of the target Biginelli product, 20 and 57%, respectively.

We then turned our attention to the preparation of the thione analogue, methyl 6-methyl-4-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate **175**, by replacing urea for thiourea and making use of the best reaction conditions found in our previous studies: microwave heating at 120 °C for 10 minutes in an appropriate sealed vessel utilising 2.5 ml of glacial acetic acid as both solvent and acid catalyst; withal, the yield dropped drastically to 29%. Increasing the reaction time to 20 minutes doubled the amount of DHPM **175**, a 57% isolated yield being attained. Sadly, irradiation for longer periods of time (up to 30 minutes) did not further improve the reaction yield. The application of the second best set of reaction parameters, i.e. heating for 10 minutes at 120 °C under microwave-assisted and open-vessel conditions using 10 g of SiO_2 60/H_2SO_4 as solid support, was entirely impossible, given that the synthetic process had to be aborted due to fast and severe decomposition of thiourea upon microwave irradiation.

It should be noted that significant formation of by-products occurred when performing the synthesis of both compounds **147** and **175** at higher reaction temperatures, as shown by TLC analysis of the crude product mixtures, owing to decomposition phenomena of urea and thiourea. This has also been reported by various other research groups. Moreover, it became evident that our AcOH-based Biginelli reaction was slower and furnished a lower yield when utilising thiourea. This might be explained by the possible delocalisation of the lone electron

pairs of the nitrogen atoms in the thiourea molecule to the sulphur atom *d*-orbitals, which can cause a decrease of the nucleophilic character of the nitrogen atoms towards the aldehyde carbonyl group. Several other aryl aldehydes, bearing both electron-withdrawing and electron-donating substituents, as well as some polycyclic aromatic moieties, were later employed as reactants, fifty five Biginelli DHPMs being prepared in short reaction times, using a small amount of glacial acetic acid as solvent and acid catalyst under microwave activation (Scheme 5.24). The isolated yields were generally very good, ranging from 35 to 90% for 3,4-dihydropyrimidin-2(1*H*)-ones **147-174** (Figure 5.4) and between 28 and 78% in the case of 3,4-dihydropyrimidine-2(1*H*)-thiones **175-201** (Figure 5.5). The single-crystal X-ray diffraction structure obtained for methyl 6-methyl-4-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate **175** is presented in Figure 5.6.



Scheme 5.24. Multicomponent synthesis of Biginelli 3,4-dihydropyrimidines **147-201** under microwave irradiation.

In general, 3,4-dihydropyrimidin-2(1*H*)-ones were obtained with better yields comparing to the related 3,4-dihydropyrimidine-2(1*H*)-thiones. Nevertheless, the use of 3,4- or 3,5-dimethoxybenzaldehyde and 3,4,5-trimethoxybenzaldehyde as the starting aryl aldehyde provided good and similar isolated yields for both types of Biginelli DHPMs; apparently, in these cases and under the reaction conditions tested, the lower reactivity of the thiourea reagent did not affect the final outcome of the procedure. Also, the worse results found when utilising bulky aryl aldehydes as reagents, such as 9-anthracenaldehyde, 2,6-dichlorobenzaldehyde or mesitylaldehyde, can easily be explained by steric impediment factors. Lastly, it must be mentioned that when 4-nitrobenzaldehyde and thiourea were employed, only trace amounts of the corresponding 3,4-dihydropyrimidine-2(1*H*)-thione were noticed by TLC analysis of the crude product mixture, along with some other reaction by-products. It is known that 4-nitrobenzaldehyde, as well as other nitrobenzene derivatives, possesses a relatively high oxidation potential. Therefore, it seems possible that competition between the multicomponent Biginelli condensation and some-sort of oxidative process, most likely involving the thiourea component, is responsible for the failure of our microwave-assisted approach in this particular instance.

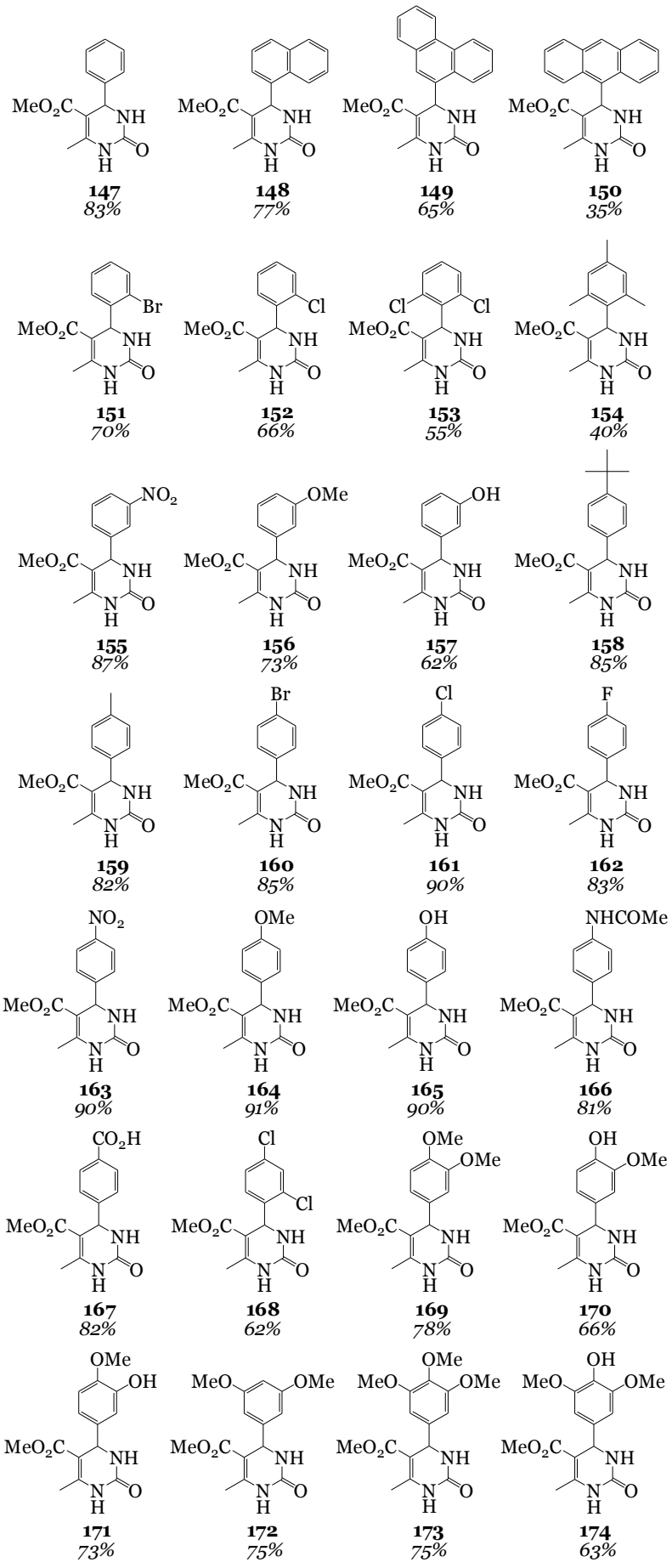


Figure 5.4. Structures and isolated yields of Biginelli 3,4-dihydropyrimidin-2(1*H*)-ones **147-174** synthesised via a solvent-based, multicomponent, microwave-assisted method.

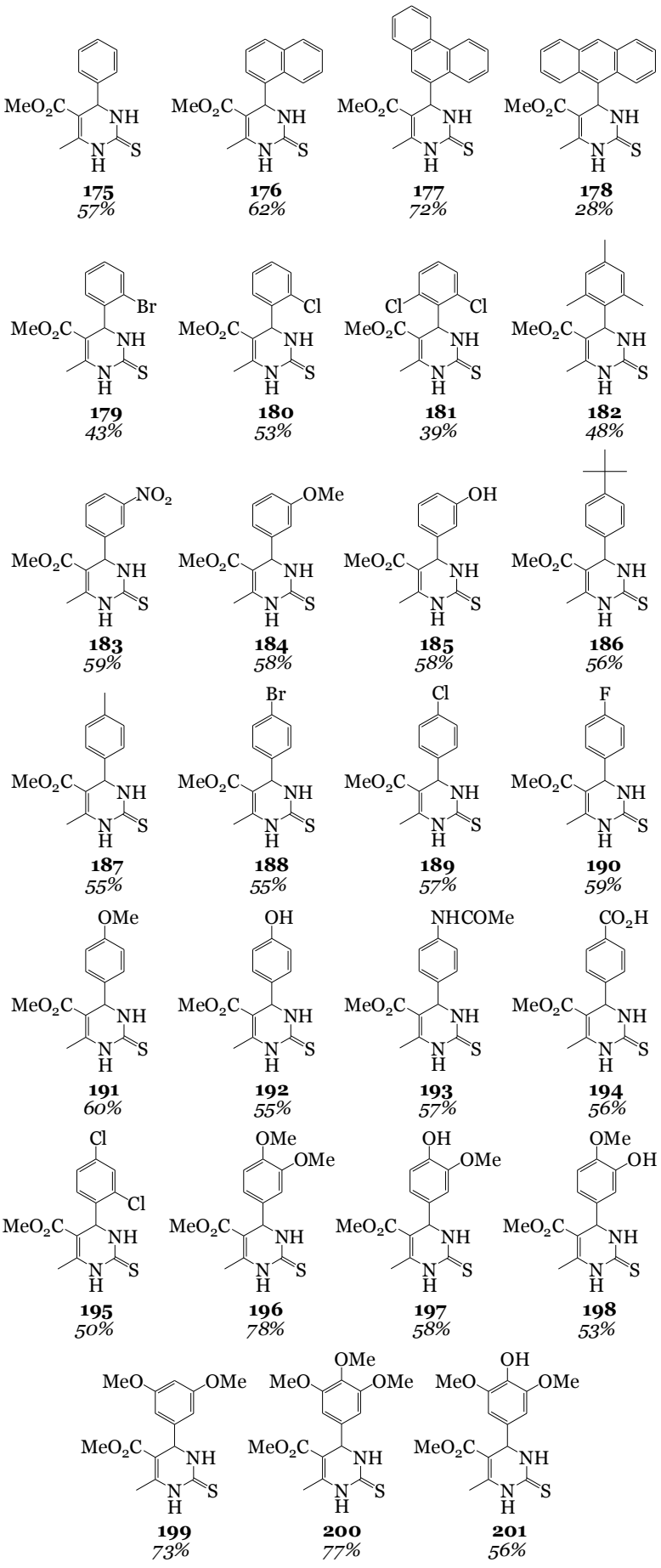


Figure 5.5. Structures and isolated yields of Biginelli 3,4-dihydropyrimidine-2(1*H*)-thiones **175-201** synthesised via a solvent-based, multicomponent, microwave-assisted method.

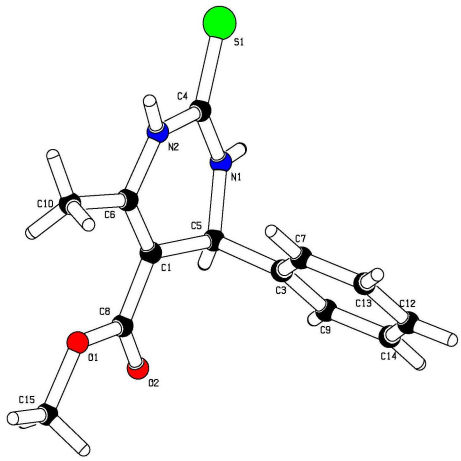
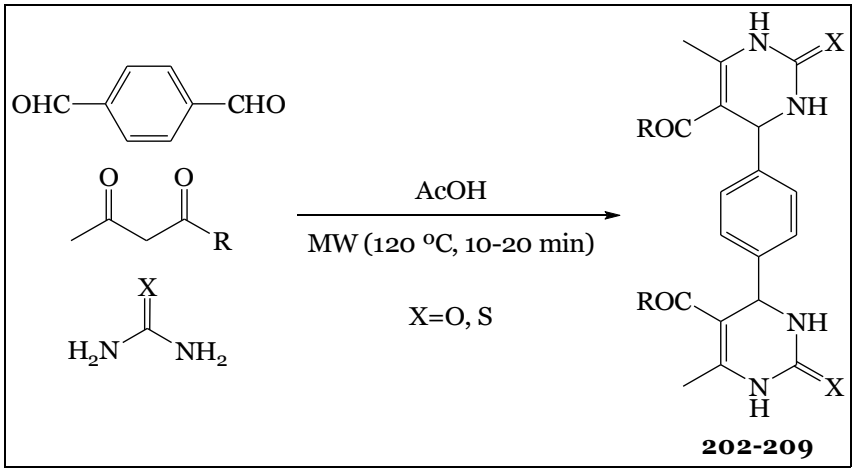


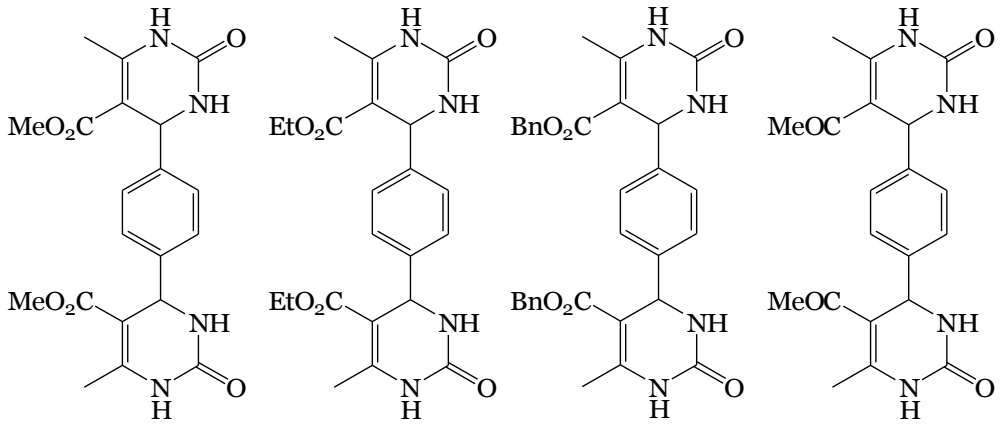
Figure 5.6. Single-crystal X-ray diffraction structure of methyl 6-methyl-4-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate **175**.

C. Multicomponent Synthesis of Biginelli Bis-3,4-Dihydropyrimidines

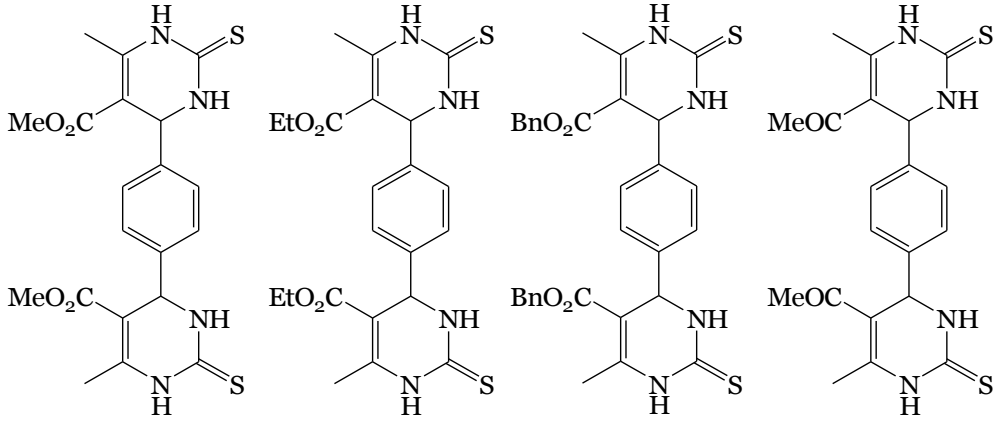
The synthesis of a small series of Biginelli bis-3,4-dihydropyrimidines was later achieved by application of the microwave-promoted methodology discussed in the preceding section. Briefly, a mixture comprised of terephthalaldehyde (5 mmol), the selected 1,3-dicarbonyl compound (15 mmol) and urea or thiourea (20 mmol) in 2.5 ml of glacial acetic acid was heated at 120 ºC for 10 or 20 minutes, with an initial microwave power setting of 100 W (Scheme 5.25). After cooling to room temperature a yellow solid precipitated from the crude product mixture. This was filtered, washed with distilled water and recrystallised in aqueous ethanol, rendering the target DHPM derivatives **202-209** with low to good isolated yields (Figure 5.7). As somewhat expected, bis-3,4-dihydropyrimidin-2(1*H*)-ones **202-205** were prepared with higher yields comparing to the equivalent bis-3,4-dihydropyrimidine-2(1*H*)-thiones **206-209**, except in the case of structures **205** and **209**, when acetylacetone was utilised as starting material, quite resembling and good reaction yields being obtained. On the other hand, the worse results were found when benzyl acetoacetate was used as reactant, which clearly demonstrates that this β-ketoester is far less reactive when compared to methyl or ethyl acetoacetate in the reaction conditions tested. As referenced in section 5.III.A, some of these interesting and less studied Biginelli structures have recently and efficiently been prepared under solvent-free and microwave heating conditions, although in a smaller 1 mmol scale.[82, 83] Cytotoxicity evaluations on a few human cancer cell lines revealed that these bis-DHPM derivatives, specially compound **209**, may be viewed as helpful candidates for future design and drug discovery.[82]



Scheme 5.25. Multicomponent synthesis of Biginelli bis-3,4-dihydropyrimidines **202-209** under microwave irradiation.



202 *80%* **203** *75%* **204** *55%* **205** *78%*



206 *53%* **207** *50%* **208** *25%* **209** *75%*

Figure 5.7. Structures and isolated yields of Biginelli bis-3,4-dihydropyrimidines **202-209** synthesised via a solvent-based, multicomponent, microwave-assisted method.

D. Synthesis of Biginelli-Type 3,4-Dihydropyrimidine-2(1*H*)-Thiones

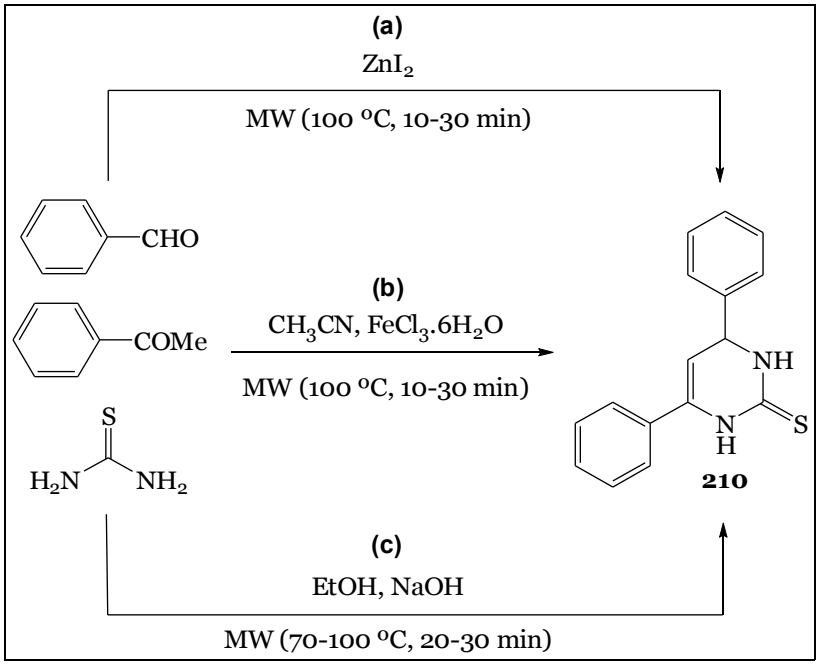
Although an extensive work on the synthesis of Biginelli-like 3,4-dihydropyrimidin-2(1*H*)-ones can be found in the scientific literature, particularly dealing with Lewis acid-catalysed condensation reactions,[90, 94-99] the number of reports on the development of a Biginelli-type process under basic conditions is quite small and studies focusing on the thione analogues are even scarcer.[100-102] Hence, our recent efforts regarding the preparation of some novel Biginelli-type 3,4-dihydropyrimidine-2(1*H*)-thiones are presented and discussed in the following pages. The first approach for the synthesis of these DHPM derivatives was based on the application of common Lewis acids, such as zinc iodide and iron(III) chloride hexahydrate, which were previously described as successful catalysts for the preparation of 4,6-diaryl-3,4-dihydropyrimidin-2(1*H*)-ones,[90, 94] and a one-pot, three-component, microwave-assisted strategy, starting from equimolar amounts of benzaldehyde and acetophenone and a 1.5 molar equivalent of thiourea (Table 5.2, entries 1-6; Schemes 5.26a and 5.26b). However, none of these endeavours led to the formation of the desired 4,6-diphenyl-3,4-dihydropyrimidine-2(1*H*)-thione **210**. Pursuing the studies of Shen and colleagues,[101] which synthesised various 4,5,6-triaryl-3,4-dihydropyrimidin-2(1*H*)-ones and their corresponding thiones under alkaline and classical heating conditions, we decided to utilise a small amount of ethanol as solvent and an equimolar quantity of sodium hydroxide as reaction promoter (Scheme 5.26c). Heating the multicomponent reaction mixture at 70 °C for 20 minutes under microwave irradiation, followed by cooling to room temperature, pouring the crude product mixture over crushed-ice, filtration of the yellow solid that precipitated and recrystallisation in aqueous ethanol, provided compound **210**

with a 45% isolated yield (entry 7). Interestingly, increasing the reaction temperature to 100 ºC did not alter the final outcome of the synthetic process (entry 8), while a longer reaction time negatively affected the yield obtained (entry 9). Also, it must be stressed that performing the reaction at 70 ºC for 18 hours, under conventional heating conditions, using a 1:1:2:1 stoichiometric ratio of benzaldehyde, acetophenone, urea and sodium hydroxide in 25 ml of ethanol, furnished the target DHPM with a lower isolated yield of 38% after similar work-up. Moreover, replacing the starting aryl aldehyde by 4-bromobenzaldehyde, 4-chlorobenzaldehyde or 4-methoxybenzaldehyde and carrying-out the reaction using the parameters of entry 8 in Table 5.2, proved that the electron-donating or electron-withdrawing nature of the substituents present at the *para* position of the phenyl ring in the aldehyde reagent did not change the overall yield of the respective 4-aryl-6-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione (32-33%).

Table 5.2. Multicomponent synthesis of 4,6-diphenyl-3,4-dihydropyrimidine-2(1*H*)-thione **210** under microwave irradiation.

Entry	Reaction Medium	Catalyst	Time (min)	Yield[a] (%)
1	Solventless	ZnI_2[c]	10	-[f, h]
2	Solventless	ZnI_2[c]	20	-[f, h]
3	Solventless	ZnI_2[c]	30	-[f, h]
4	CH_3CN[b]	$FeCl_3.6H_2O$[d]	10	-[f, h]
5	CH_3CN[b]	$FeCl_3.6H_2O$[d]	20	-[f, h]
6	CH_3CN[b]	$FeCl_3.6H_2O$[d]	30	-[f, h]
7	EtOH[b]	NaOH[e]	20	45[g]
8	EtOH[b]	NaOH[e]	20	45[f]
9	EtOH[b]	NaOH[e]	30	36[f]

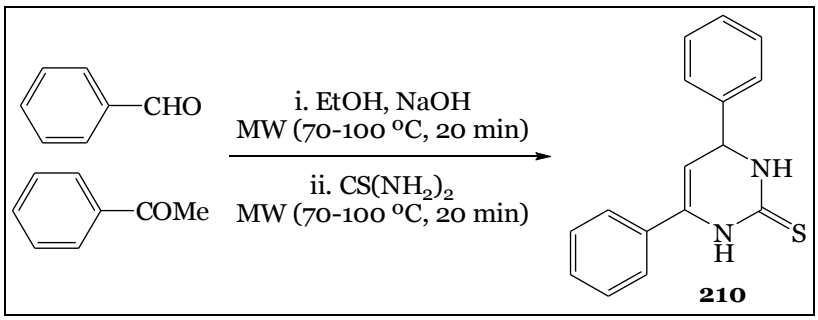
All reactions were carried-out using benzaldehyde (5 mmol), acetophenone (5 mmol) and thiourea (7.5 mmol) in a closed vessel. [a]Yields refer to the isolated reaction products. [b]The selected solvent (3 ml) was used as reaction medium, an initial microwave power of 100 W being applied. [c]ZnI_2 (1 mmol), [d]$FeCl_3.6H_2O$ (1 mmol) and [e]NaOH (5 mmol) were used as catalysts. [f]Constant temperature of 100 ºC. [g]Constant temperature of 70 ºC. [h]Only trace amounts of DHPM **210** were detected by TLC analysis of the crude product mixture, along with the initial reagents.



Scheme 5.26. Multicomponent synthesis of 4,6-diphenyl-3,4-dihydropyrimidine-2(1*H*)-thione **210** under microwave irradiation.

In the already cited work authored by Shen and associates concerning the base-catalysed three-component synthesis of 4,5,6-triaryl-3,4-dihydropyrimidine-2(1*H*)-thiones,[101] the formation of a 1,2,3-triarylprop-2-en-1-one reaction intermediate was suggested. In addition, we have found a few reports dealing with the base-mediated preparation of 4,6-diaryl-3,4-dihydropyrimidine-2(1*H*)-thiones, starting from the corresponding 1,3-diarylprop-2-en-1-ones, ordinarily known as chalcones, and thiourea. In 1999, Kidway and Misra synthesised two 4,6-diaryl-3,4-dihydropyrimidine-2(1*H*)-thiones, using a domestic microwave equipment and either neutral alumina or an ethanolic solution of sodium ethoxide as reaction medium, with yields of up to 85%.[88] Mahmoud and El-Shahawi prepared 6-*p*-tolyl-4-(3,4,5-trimethoxyphenyl)-3,4-dihydropyrimidine-2(1*H*)-thione with a quite moderate isolated yield of 44% by heating a mixture of the corresponding chalcone, thiourea and sodium hydroxide in ethanol under classic heating conditions,[100] mentioning an experimental protocol published earlier by the same research team. Al-Abdullah described the related preparation of two 4,6-diarylpyrimidine-2(1*H*)-thiones in 2011, refluxing the chalcone and thiourea reagents in an aqueous ethanol solution of potassium hydroxide for 24 hours, both compounds being obtained with yields that did not exceed 28%.[102]

In order to examine the low efficiency of our multicomponent approach, we attempted the synthesis of 4,6-diphenyl-3,4-dihydropyrimidine-2(1*H*)-thione **210** via a two-step one-pot method (Scheme 5.27). Thus, equimolar amounts of benzaldehyde, acetophenone and sodium hydroxide in ethanol were microwave-heated in a sealed vessel at 100 ºC for 20 minutes, followed by the addition of a 1.5 molar equivalent of thiourea and microwave irradiation for another 20 minutes at the same temperature, the desired product being prepared with a 15% isolated yield. It should be highlighted that diminishing the temperature to 70 ºC in both microwave-activated steps provided only trace quantities of the Biginelli-type DHPM and that GC-MS analysis of the crude product mixtures prior to the addition of thiourea demonstrated that less than 40% of the expected chalcone was present, the remaining unidentified components exhibiting higher molecular weights. Furthermore, neither modifying the reaction time nor the reactants concentration afforded larger amounts of the chalcone intermediate. Interestingly, subtracting the thiourea starting material from the process, i.e. microwave heating an alkaline ethanolic solution of previously prepared (*E*)-1,3-diphenylprop-2-en-1-one **38** at 70 or 100 ºC for 20 minutes, supplied a closely resembling result. Hence, our overall low reaction yields, attained either via a three-component strategy or following a two-step methodology, are apparently related to the ineffective *in situ* generation of the chalcone intermediate and also to some-sort of degradation mechanism that occurs with it under microwave irradiation.



Scheme 5.27. One-pot two-step synthesis of 4,6-diphenyl-3,4-dihydropyrimidine-2(1*H*)-thione **210** under microwave irradiation.

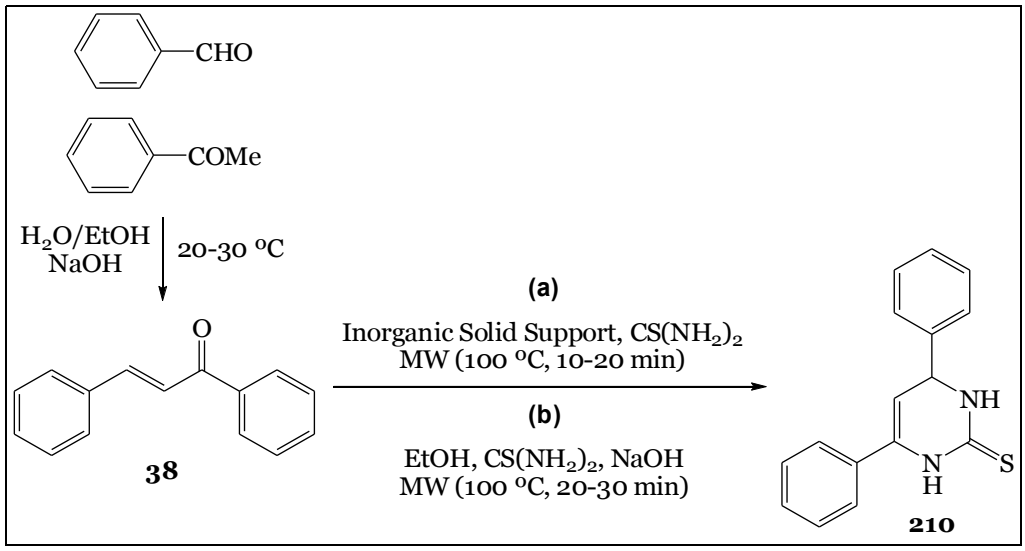
Since both our multicomponent (Scheme 5.26) and one-pot two-step (Scheme 5.27) methods either failed or furnished only moderate results, a two-pot two-step formulation was employed in order to improve the reaction yield of 4,6-diphenyl-3,4-dihydropyrimidine-2(1*H*)-thione **210** (Scheme 5.28). (*E*)-1,3-diphenylprop-2-en-1-one **38**, which was synthesised with an 85% isolated yield through a base-promoted Claisen-Schmidt procedure,[103] served as starting material, along with a slight molar excess of thiourea, in a microwave-activated second step. The reaction conditions tested in this final synthetic stage are summarised in Table 5.3. Contrary to what Kidwai and Misra described,[88] microwave heating using alumina as solid support yielded only residual amounts of the

target Biginelli-type DHPM (entries 1 and 2). Replacing aluminium oxide by silica gel provided very low yields that did not surpass 11% (entries 3 and 4). Delightfully, compound **210** was prepared with an 86% isolated yield by performing the reaction at 100 ºC for 20 minutes in a small volume of ethanol and making use of sodium hydroxide as base (entry 5). Work-up was very straightforward and involved forcing the precipitation of the product in crushed-ice, followed by filtration, washing with distilled water and recrystallisation in aqueous ethanol. TLC analysis of the crude product mixture resulting of shorter time periods under microwave irradiation revealed that the reaction was far from completion, while longer reaction times did not further improve the final outcome of the synthetic process (entry 6).

Table 5.3. Two-pot two-step synthesis of 4,6-diphenyl-3,4-dihydropyrimidine-2(1*H*)-thione **210** under microwave irradiation.

Entry	Reaction Medium	Catalyst	Time (min)	Yield[a] (%)
1	Al_2O_3 (50-150 μm)[b]	-	10	-[e]
2	Al_2O_3 (50-150 μm)[b]	-	20	-[e]
3	SiO_2 60 (35-70 μm)[b]	-	10	5
4	SiO_2 60 (35-70 μm)[b]	-	20	11
5	EtOH[c]	NaOH[d]	20	86
6	EtOH[c]	NaOH[d]	30	83

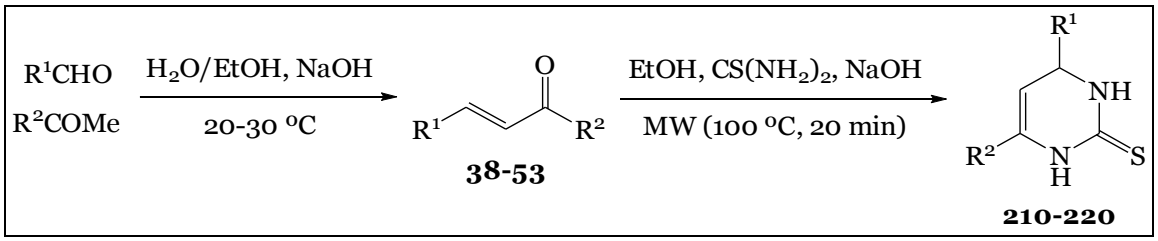
All reactions were carried-out using chalcone **38** (5 mmol) and thiourea (7.5 mmol) at 100 ºC. [a]Yields refer to the isolated reaction products. [b]The selected solid support (5 g) was used as reaction medium in open-vessel conditions, an initial microwave power of 200 W being applied. [c]EtOH (3 ml) was used as reaction medium in closed-vessel conditions, an initial microwave power of 100 W being applied. [d]NaOH (5 mmol) was used as reaction catalyst. [e]Only trace amounts of DHPM **210** were detected by TLC analysis of the crude product mixture, along with the initial reagents.



Scheme 5.28. Two-pot two-step synthesis of 4,6-diphenyl-3,4-dihydropyrimidine-2(1*H*)-thione **210** under microwave irradiation.

Several other previously prepared chalcones were later employed as reagents (see Chapter 2 for details concerning their syntheses and structures), some of the corresponding and novel 4,6-diaryl-3,4-dihydropyrimidine-2(1*H*)-thiones **210-220** being synthesised with high reaction yields and great purity (Scheme 5.29; Figure 5.8).[104] As an example, the X-ray diffraction structure of 4-(naphthalen-1-yl)-6-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione **211**, obtained from a single crystal, is depicted in Figure 5.9. It should be referenced that no reaction occurred when (*E*)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one **46** was utilised as starting material, this being recovered unchanged after work-up. Also, when pyrrolyl-chalcones **49** and **53** were

used, solely trace quantities of the respective Biginelli-like DHPMs were detected in the crude product mixtures, which consisted of several unknown side-products. Lastly, carrying-out the reaction with the fluorinated chalcones **45** and **52** provided the expected 3,4-dihydropyrimidine-2(1*H*)-thione compounds, although heavily contaminated with what seems to be their isomeric adducts, a similar phenomenon being already reported by Wang and colleagues.[94] All the same, further work is required to undoubtedly identify these by-products.



Scheme 5.29. Two-pot two-step synthesis of Biginelli-type 3,4-dihydropyrimidine-2(1*H*)-thiones **210-220** under microwave irradiation.

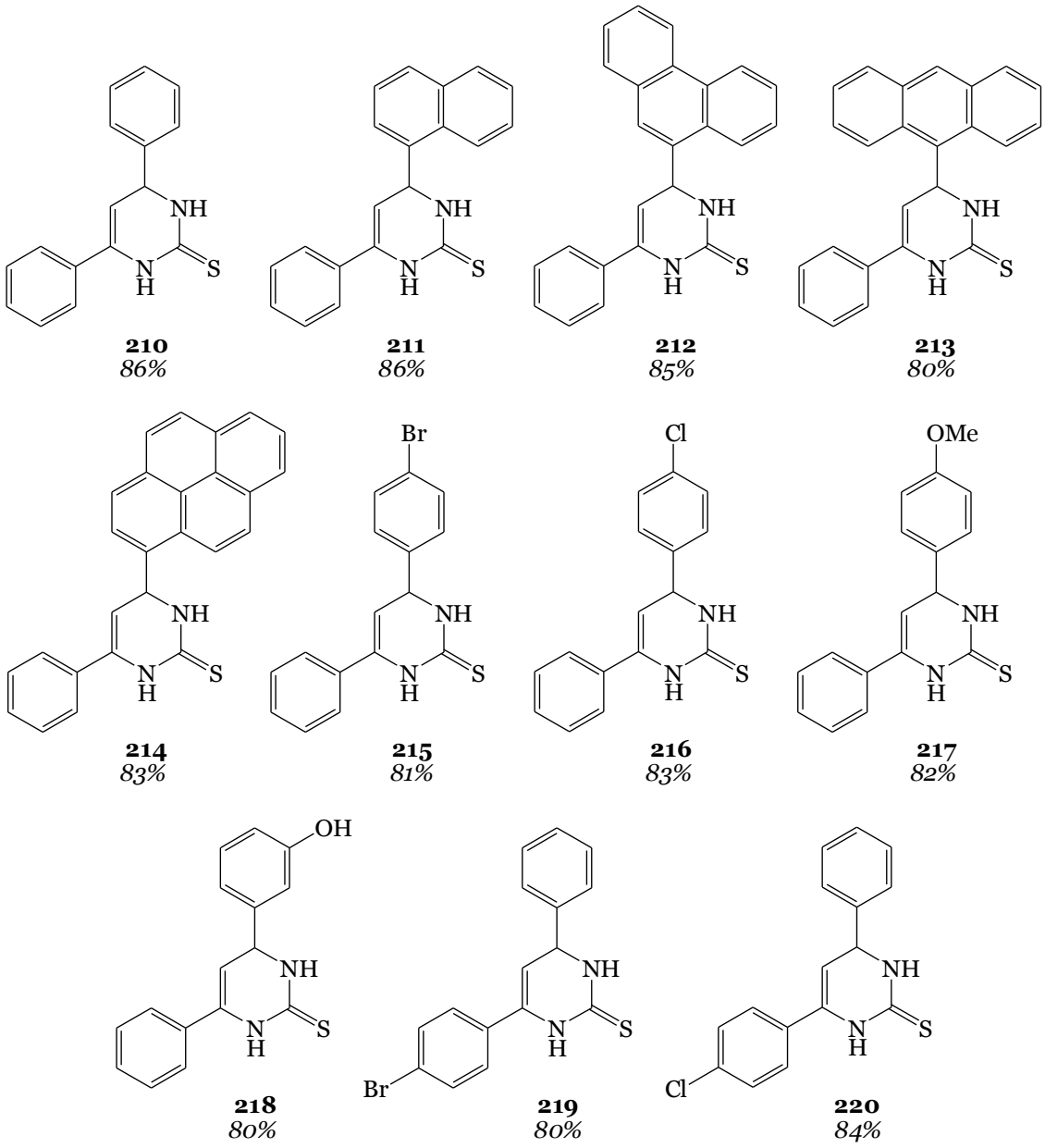


Figure 5.8. Structures and isolated yields of Biginelli-type 3,4-dihydropyrimidine-2(1*H*)-thiones **210-220** synthesised via a solvent-based microwave-assisted method.

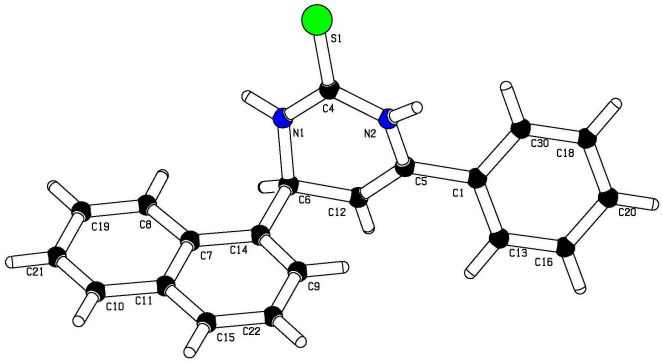
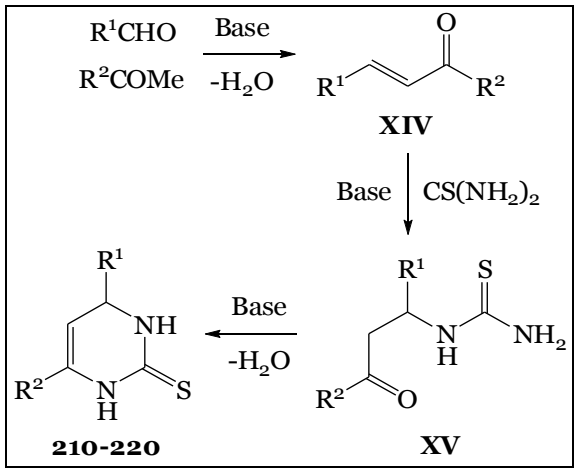


Figure 5.9. Single-crystal X-ray diffraction structure of 4-(naphthalen-1-yl)-6-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione **211**.

A possible reaction pathway for the two-pot two-step preparation of the Biginelli-like structures portrayed in Figure 5.8 is presented in Scheme 5.30 and supported by the one suggested by Shen and co-workers.[101] A base-mediated aldol condensation between an aryl aldehyde and a suitable acetophenone renders chalcone **XIV**. Subsequent aza-Michael addition of thiourea to the latter in alkaline conditions leads to the open-chain ureide **XV**, which undergoes a 1,2 addition of the amino functionality to the carbonyl group, followed by water elimination, the target 4,6-diaryl-3,4-dihydropyrimidine-2(1*H*)-thione being obtained.



Scheme 5.30. Mechanistic proposal for the two-pot two-step synthesis of Biginelli-type 3,4-dihydropyrimidine-2(1*H*)-thiones **210-220**.

The cytotoxicity of 4,6-diaryl-3,4-dihydroprimidine-2(1*H*)-thiones **215-220** was assessed *in vitro* against four cancer cell lines, A375 human malignant melanoma, WiDr human colon adenocarcinoma, HCC1806 and MCF7 human breast carcinomas, through a collaboration with the Centre of Investigation in Environment, Genetics and Oncobiology (CIMAGO) and the Institute for Biomedical Imaging and Life Sciences (IBILI) of the University of Coimbra.[104] It was found that the selected compounds exhibited a concentration-dependent inhibition of cell proliferation and, considering the half maximal inhibitory concentration (IC_{50}) values presented in Table 5.4, it can be inferred that they were generally more active against MCF7 human breast cancer cells; the brominated Biginelli-type DHPMs **215** and **219** were the most active compounds, IC_{50} values of 24.2 and 22.2 μM being determined, respectively. The related Biginelli compound monastrol is known for suppressing human mitotic kinesin Eg5.[15] Compared with the traditional chemotherapeutic agents, kinesin inhibitors do not lead to neuropathic side effects and, thus, kinesin spindle protein has become an attractive anticancer target.[105] Inhibition of human mitotic kinesin Eg5 using monastrol has prevented the growth of oestrogen-treated MCF7 cells, an IC_{50} value of 29.7 μM being reported, while simultaneous suppression of the oestrogen receptor function

with the selective down-regulator fulvestrant increased the IC_{50} value to 112.7 μM.[106] Biginelli-type structures **215** and **219** were found to be effective against MCF7 cell lines, without the addition of any oestrogen receptor inhibitor. Also, these compounds were 3.7 and 3.2 times more active against MCF7 human breast carcinoma cells than against HCC1806 triple-negative human breast cancer cells, respectively.

Table 5.4. IC_{50} and CI_{95} values for Biginelli-type 3,4-dihydropyrimidine-2(1*H*)-thiones **215-220** against MCF7, HCC1806, WiDr and A375 human cancer cell lines.

		Human Cancer Cell Line							
Entry	Compound	MCF7		HCC1806		WiDr		A375	
		IC_{50} (μM)	CI_{95} (μM)	IC_{50} (μM)	CI_{95} (μM)	IC_{50} (μM)	CI_{95} (μM)	IC_{50} (μM)	CI_{95} (μM)
1	**215**	24.2	21.9; 26.7	89.2	73.1; 108.8	45.7	42.9; 48.6	42.8	40.4; 45.2
2	**216**	67.4	62.2; 73.1	72.6	68.7; 76.8	68.2	62.8; 74	>100	-
3	**217**	60.2	57.6; 62.9	>100	-	85.2	83.4; 87.1	>100	-
4	**218**	78.4	75.2; 81.7	64.4	59.1; 70.2	>100	-	>100	-
5	**219**	22.2	19.5; 25.3	70.8	63; 79.6	69.9	67.6; 71.6	56.3	53.1; 59.6
6	**220**	63.2	59.7; 66.9	75.4	64.7; 87.8	>100	-	73.6	69.7; 77.6

It must be mentioned that, apart from the cytotoxicity results shown in Table 5.4, flow cytometry, cell viability, cell cycle and Bax/Bcl-2 ratio analyses were also performed using some of these compounds.[104] Furthermore, the employment of selected Biginelli-type 4,6-diaryl-3,4-dihydropyrimidine-2(1*H*)-thiones to the synthesis of some of their corresponding transition metal complexes is presently being addressed through a collaboration with the Inorganic Chemistry Department of the University of Vigo. Their full structural characterisation and evaluation of anticancer properties is currently being tackled and will be reported elsewhere in a near future.

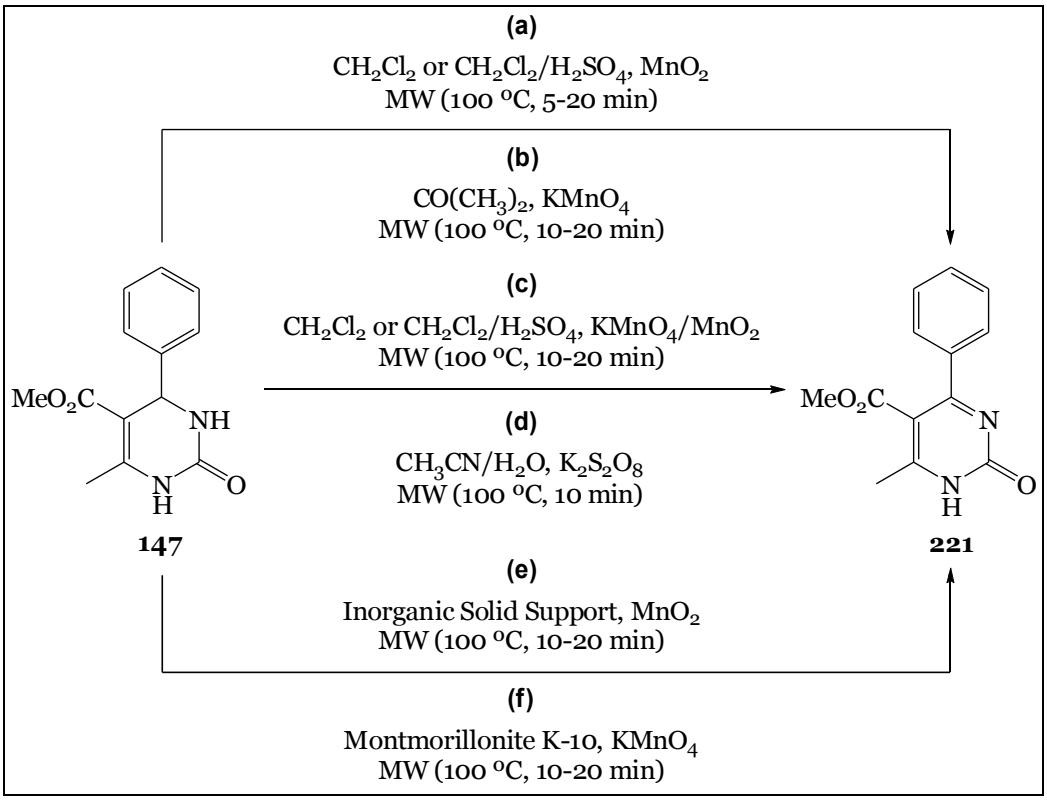
E. Oxidation of Biginelli 3,4-Dihydropyrimidines

It is broadly recognised that Biginelli 3,4-dihydropyrimidines, particularly the thione-containing structures, are not easily dehydrogenated. In fact, after carefully reviewing the available scientific literature, we can confirm that no general and efficient method for the oxidation of 3,4-dihydropyrimidine-2(1*H*)-thiones has been reported so far. Hence, we decided to employ some common, inexpensive and widely utilised oxidising agents and microwave irradiation in order to establish weather or not a synergistic effect could be achieved in this oxidative process. The previously synthesised methyl 6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate **147** was selected as the model DHPM compound for the oxidation studies, both under solvent-based and solid-supported reaction conditions. Activated manganese dioxide, potassium permanganate, a mixture of the two prepared beforehand following the available literature[107] and potassium peroxydisulphate were used as oxidants, the results being summarised in Table 5.5 and Scheme 5.31. Remarkably, apart from entries 5 and 6, i.e. application of 10 molar equivalents of MnO_2 in sulphuric acid-doped dichloromethane, which furnished methyl 6-methyl-4-phenylpyrimidin-2(1*H*)-one-5-carboxylate **221** with only 6 and 15% conversion, after heating at 100 ºC in an appropriate sealed vessel for 10 and 20 minutes, respectively, all attempts to dehydrogenate the starting DHPM using heterogeneous oxidising agents failed completely. However, full conversion to the expected partially oxidised derivative **221** was accomplished using a slight molar excess of potassium peroxydisulphate in an acetonitrile/distilled water mixture at 100 ºC for 10 minutes (entry 13), shorter reaction times providing incomplete outcomes. Work-up was quite simple and involved washing the crude product mixture with brine, followed by liquid/liquid extraction with ethyl acetate, collection of the organic layer and drying with anhydrous sodium sulphate, filtration, evaporation under reduced pressure and, lastly, recrystallisation in diethyl ether or ethyl acetate/*n*-hexane.

Table 5.5. Synthesis of methyl 6-methyl-4-phenylpyrimidin-2(1*H*)-one-5-carboxylate **221** under microwave irradiation.

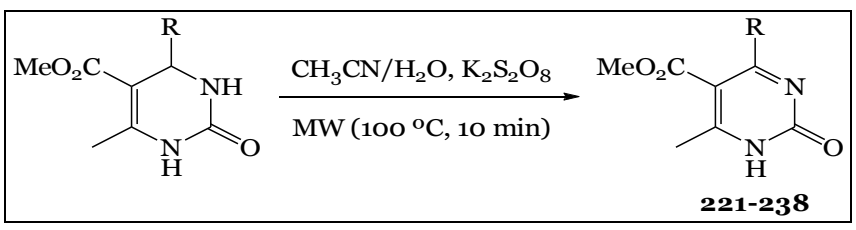
Entry	Reaction Medium	Oxidant	Time (min)	Conversion[a] (%)
1	CH_2Cl_2[b]	MnO_2[e]	5	0[i]
2	CH_2Cl_2[b]	MnO_2[e]	10	0[i]
3	CH_2Cl_2[b]	MnO_2[e]	20	0[i]
4	CH_2Cl_2/H_2SO_4[b]	MnO_2[e]	5	0[i]
5	CH_2Cl_2/H_2SO_4[b]	MnO_2[e]	10	6
6	CH_2Cl_2/H_2SO_4[b]	MnO_2[e]	20	15
7	$CO(CH_3)_2$[b]	$KMnO_4$[f]	10	0[i]
8	$CO(CH_3)_2$[b]	$KMnO_4$[f]	20	0[i]
9	CH_2Cl_2[b]	$KMnO_4/MnO_2$[g]	10	0[i]
10	CH_2Cl_2[b]	$KMnO_4/MnO_2$[g]	20	0[i]
11	CH_2Cl_2/H_2SO_4[b]	$KMnO_4/MnO_2$[g]	10	0[i]
12	CH_2Cl_2/H_2SO_4[b]	$KMnO_4/MnO_2$[g]	20	0[i]
13	CH_3CN/H_2O[c]	$K_2S_2O_8$[h]	10	100[j]
14	SiO_2 60 (35-70 μm)[d]	MnO_2[e]	10	0[i]
15	SiO_2 60 (35-70 μm)[d]	MnO_2[e]	20	0[i]
16	SiO_2 60/H_2SO_4 (35-70 μm)[d]	MnO_2[e]	10	0[i]
17	SiO_2 60/H_2SO_4 (35-70 μm)[d]	MnO_2[e]	20	0[i]
18	Montmorillonite K-10[d]	MnO_2[e]	10	0[i]
19	Montmorillonite K-10[d]	MnO_2[e]	20	0[i]
20	Montmorillonite K-10[d]	$KMnO_4$[f]	10	0[i]
21	Montmorillonite K-10[d]	$KMnO_4$[f]	20	0[i]

All reactions were carried-out using DHPM **147** (1 mmol) and the selected oxidant at 100 °C. [a]Conversion was assessed by GC-MS analysis of the isolated reaction products. [b]The selected solvent (3 ml) was used as reaction medium in closed-vessel conditions, an initial microwave power of 100 W being applied. [c]CH_3CN/H_2O (3:2 v/v, 5 ml) was used as reaction medium in closed-vessel conditions, an initial microwave power of 80 W being applied. [d]The selected solid support (5 g) was used as reaction medium in open-vessel conditions, an initial microwave power of 200 W being applied. [e]MnO_2 (10 mmol), [f]$KMnO_4$ (2.5 mmol), [g]$KMnO_4/MnO_2$ (2 g) and [h]$K_2S_2O_8$ (1.2 mmol) were used as oxidants. [i]No reaction occurred, the starting DHPM **147** being recovered upon work-up. [j]An 85% isolated yield was obtained.



Scheme 5.31. Synthesis of methyl 6-methyl-4-phenylpyrimidin-2(1*H*)-one-5-carboxylate **221** under microwave irradiation.

Various other 3,4-dihydropyrimidin-2(1*H*)-ones were later employed as the initial reactant under equal microwave-assisted, closed-vessel and oxidative reaction conditions (Scheme 5.32), the corresponding pyrimidin-2(1*H*)-ones **221-238** being isolated with very good yields (Figure 5.10). Nevertheless, the oxidations of anthracenyl-DHPM **150** and hydroxylated 3,4-dihydropyrimidines **157** and **165** were totally unsuccessful, the starting heterocyclic scaffolds being recovered unchanged upon work-up, even after prolonged microwave irradiation at 100 °C for 20 and 30 minutes. Moreover, when DHPMs **169** and **173** were employed as reagents, several unidentified by-products were detected, along with the unreacted methyl 4-(3,4-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate and methyl 6-methyl-4-(3,4,5-trimethoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, respectively. This data was assessed via NMR and GC-MS studies of the reaction products after isolation. Contrary to the work published by Memarian and co-workers,[92] in which related 3,4-dihydropyrimidin-2(1*H*)-ones were successfully oxidised utilising a similar microwave-activated procedure, albeit with a 4-times smaller stoichiometry, we could not use simply water as solvent, given that our DHPMs were completely insoluble in this medium, even after microwave heating. Moreover, since the authors employed an open-vessel strategy using an unmodified domestic oven, the reaction temperature could not be monitored or controlled and, consequently, water had to be constantly added to the reaction mixtures in order to compensate the one that evaporated upon microwave irradiation. This was avoided in our methodology due to the use of focused microwave irradiation, built-in IR temperature monitoring and sealed-vessel reaction conditions.



Scheme 5.32. Synthesis of Biginelli pyrimidin-2(1*H*)-ones **221-238** under microwave irradiation.

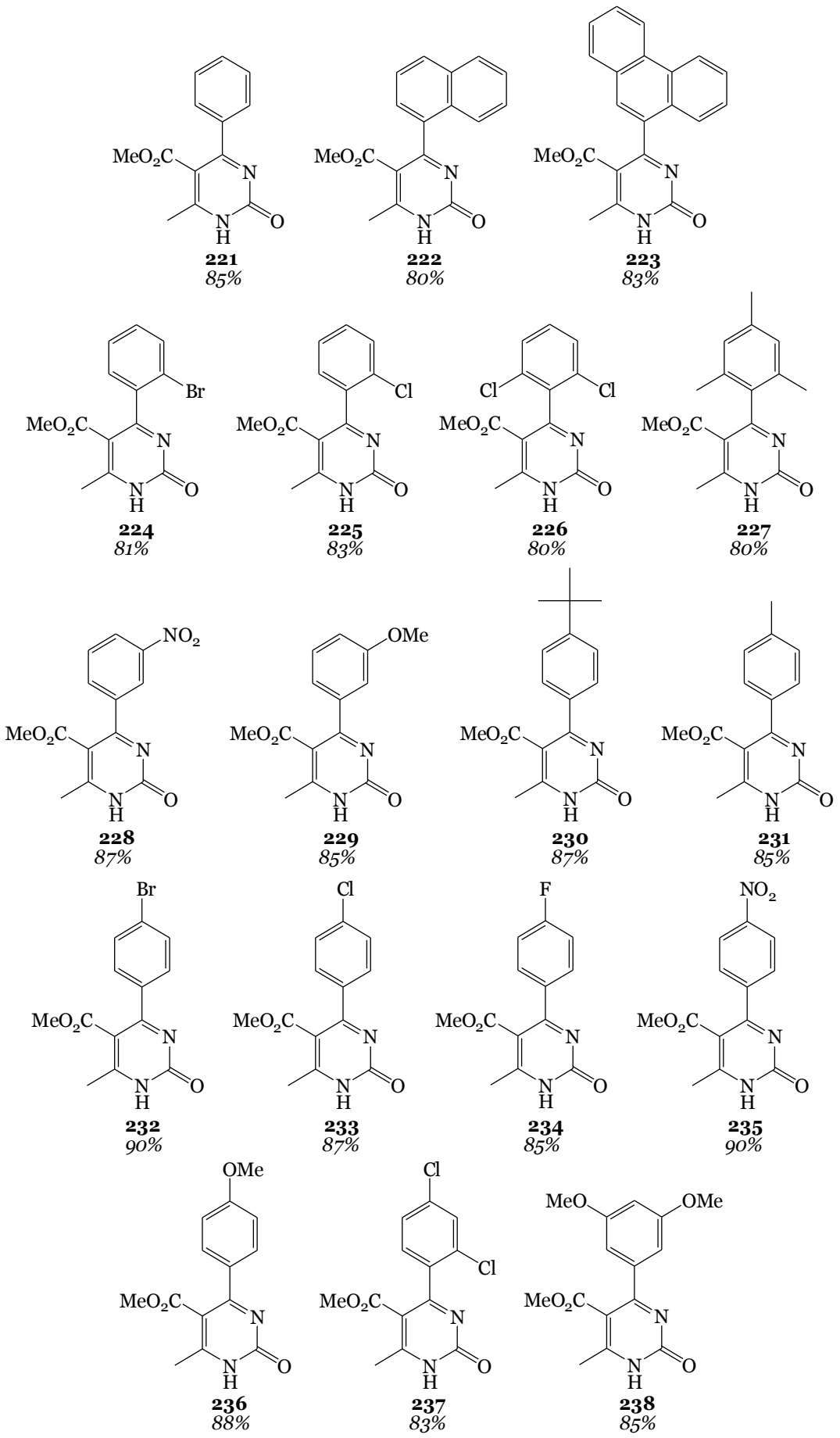
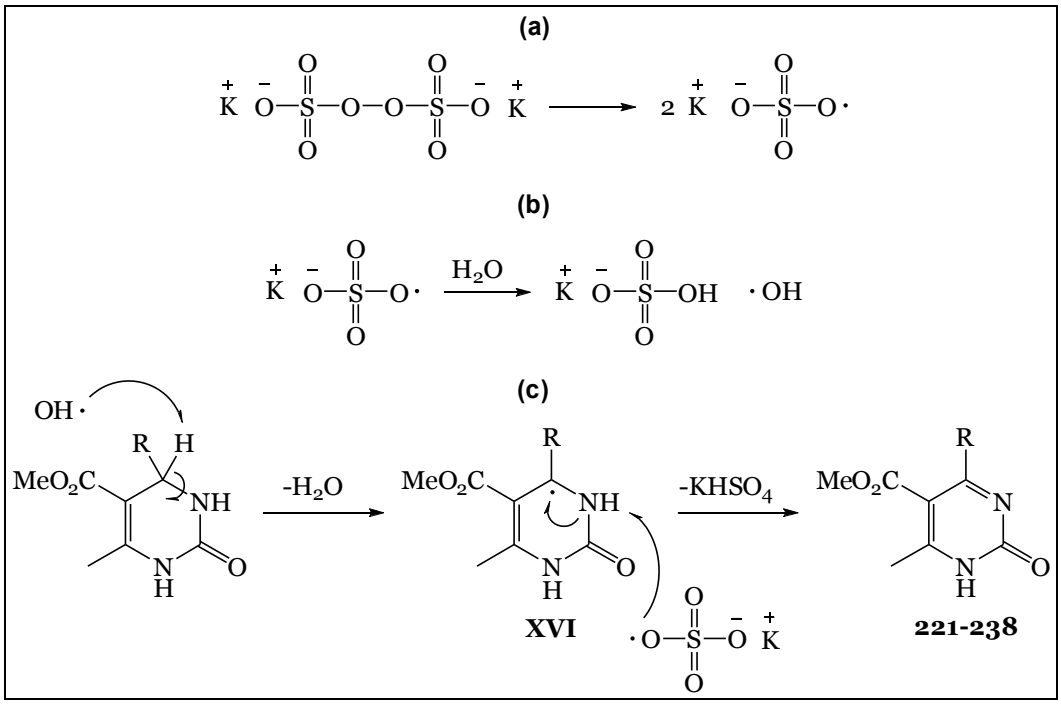


Figure 5.10. Structures and isolated yields of Biginelli pyrimidin-2(1*H*)-ones **221-238** synthesised via a solvent-based microwave-assisted method.

In recent years, the Memarian research group has thoroughly investigated this oxidative process under thermal,[57] sonochemical,[108, 109] photochemical[58] and voltammetric[110] conditions, analogous results regarding product selectivity and isolated yields being found comparing to the ones obtained under microwave heating. Therefore, it is our opinion that the observed rate enhancements in this oxidation reaction, including the ones verified in our own work, are not due to any specific microwave effect, as postulated by Memarian and colleagues,[92] but are instead the consequence of the reaction temperature being quickly reached under microwave irradiation, i.e. a strictly thermal/kinetic phenomenon. The reaction mechanism is thought to be closely related to the $K_2S_2O_8$-promoted dehydrogenation of Hantzsch 1,4-dihydropyridines described before (see Chapter 4) and is depicted below in Scheme 5.33. Thermal decomposition of the weakest O-O bond in potassium peroxydisulphate renders a sulphate radical anion (a), which in turn abstracts a hydrogen atom from the water present in the reaction medium affording a hydroxyl radical (b). Hydrogen abstraction at position 4 of the heterocyclic moiety by the previously generated hydroxyl species furnishes a hydropyrimidinoyl radical intermediate **XVI** and water. Finally, abstraction of the neighbouring hydrogen atom by another sulphate radical anion yields the desired Biginelli pyrimidin-2(1*H*)-one, along with potassium bisulphate as by-product (c).

It must be mentioned that the removal of the CH-4 hydrogen atom and subsequent generation of intermediate **XVI** is believed to be the rate-determining step, since this is a quite stable radical species with both allylic and benzylic characteristics which, accordingly, should lower the activation energy of its formation. However, the fact that the oxidation of DHPMs **157**, **165**, **169** and **173** either totally failed or afforded poor results may be justified by the possible destabilisation of the corresponding hydropyrimidinoyl structures, which can be reasoned by the balance of electronic effects (resonance and induction) caused by the hydroxyl or methoxyl substituents present at the phenyl ring in those cases, a similar phenomenon being already observed in the $K_2S_2O_8$-mediated oxidative aromatisation of some closely related Hantzsch DHPs (see Chapter 4). In the case of 3,4-dihydropyrimidin-2(1*H*)-one **150**, the large anthracene moiety should be nearly perpendicular to the radical centre at C-4 and, consequently, a strong stabilisation phenomenon through conjugation with the polycyclic aromatic ring would be expected, thus facilitating the dehydrogenation process. However, it was noted during our studies that this particular DHPM was poorly soluble in the acetonitrile/distilled water mixture used as solvent, which can explain why the oxidation reaction was unsuccessful.



Scheme 5.33. Mechanistic proposal for the synthesis of Biginelli pyrimidin-2(1*H*)-ones **221-238** using potassium peroxydisulphate as the oxidising agent.

Regarding the structural identification of the dehydrogenation products, it should be noticed that due to tautomerisation phenomena in solution, specifically of NH-1 to N-3 and NH-1 or NH-3 to the carbonyl group at position 2 of the heterocyclic skeleton, three different arrangements are possible and must be reasoned (Scheme 5.5, **XIIIa-c**). Although X-ray diffraction studies have undoubtedly confirmed that the oxidation of Biginelli 3,4-dihydropyrimidin-2(1*H*)-ones renders products of type **XIIIa** in the solid state, i.e. with a CONH-1 amide group,[49, 52] Yamamoto and colleagues reported the preparation of several pyrimidine structures of type **XIIIc** via oxidation of the corresponding DHPMs[55] and the NH-1 to N-3 interconversion (and subsequent formation of **XIIIb**-type scaffolds) in solution has also been described in the scientific literature.[49, 54] The absence of the NH-3 and CH-4 resonances in the ^{1}H NMR spectra of compounds **221-238** clearly demonstrates that our microwave-assisted oxidation method was successful and pointed towards the formation of pyrimidin-2(1*H*)-one compounds. Nonetheless, the expected and typically broad and low-field NH-1 signal was also absent in many instances, namely in compounds **221-223**, **226-228**, **230**, **231**, **235** and **238**, indicating that the above mentioned tautomerisations were occurring in many of our synthesised compounds in solution. Further evidence of these rapid interconversion processes was uncovered through ^{13}C NMR analysis; the C-4 and C-6 carbon resonances in the entire series of oxidation products **221-238**, along with the signals of the directly bonded carbon atoms of their substituent moieties, aryl and methyl, respectively, were quite difficult to locate, if not impossible, due to their extremely low intensity. Extending the acquisition time of the spectra and/or increasing the temperature at which they were recorded did not improve the signal-to-noise ratio. Similar observations have also been described earlier.[49, 52, 54]

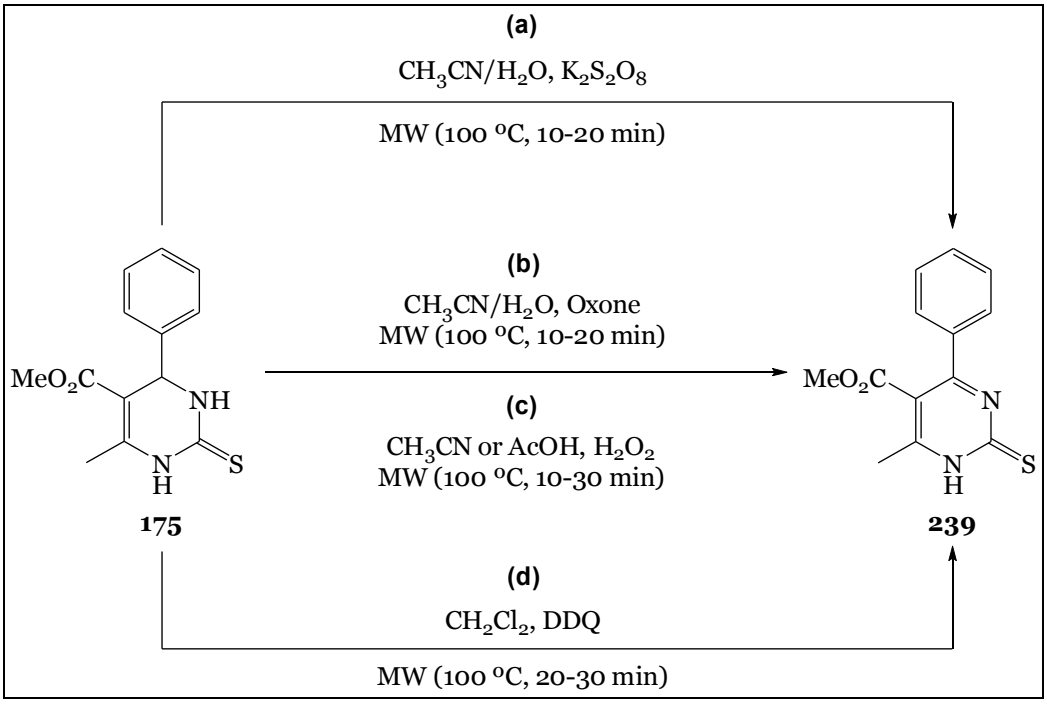
Attempting to oxidise Biginelli 3,4-dihydropyrimidine-2(1*H*)-thiones to the corresponding pyrimidine-2(1*H*)-thiones, a synthetic endeavour that, as far as we know, as never been effectively accomplished, it was decided to employ the previously prepared methyl 6-methyl-4-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate **175** as the model compound and make use of the oxidising reaction conditions that proved to be highly successful in the dehydrogenation of most of its related 3,4-dihydropyrimidin-2(1*H*)-ones, i.e. microwave heating the selected 3,4-dihydropyrimidine **175** and a slight molar excess of potassium peroxydisulphate in an acetonitrile/distilled water mixture for 10 minutes at 100 ºC under closed-vessel conditions (Table 5.6, entry 1; Scheme 5.34a). Since absolutely no reaction occurred, the starting heterocyclic reagent being retrieved after work-up, the irradiation time was increased to 20 minutes, methyl 6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate **147** being formed with a 10% conversion (entry 2). This interesting but unexpected oxidative desulphurisation reaction, that is, the loss of the sulphur atom of the thione reactant and replacement by an oxygen, was also observed, and in a much greater extent, when $K_2S_2O_8$ was replaced by Oxone (Scheme 5.34b), a versatile potassium triple salt of molecular formula $2KHSO_5.KHSO_4.K_2SO_4$ and strong oxidising agent ($E^o[HSO_5^-/HSO_4^-]$=1.85 V), often utilised in chemical reactions and abundantly used as a swimming pool shock oxidant, odour control agent in waste-water treatment and bleach component in denture cleansers and laundry formulations, among other applications.[111] In fact, a 57 and 67% conversion of DHPM **175** to its analogue **147** was attained after 10 and 20 minutes of microwave irradiation, respectively (entries 3 and 4), a plausible mechanistic rationalisation being depicted in Scheme 5.35 following the work of Kim and colleagues, which reported a similar phenomenon a few years ago.[112] Presumably, the thione group of DHPM **175** is transformed in the cyclic sulphate intermediate **XVII**, which is subsequently oxidised to sulphite structure **XVIII**, DHPM **147** being finally rendered via elimination of sulphur dioxide. We then turned our attention to another powerful, inexpensive and environmentally-benign oxidant, aqueous hydrogen peroxide ($E^o[H_2O_2/H_2O]$=1.78 V), which is widely employed in dilute form as a domestic disinfectant for small skin wounds, as well as in research and development in organic synthesis and several industrial applications, particularly pulp and paper bleaching. However, no reaction was observed when a 20-fold molar excess of aqueous H_2O_2 (35% m/v) was used in acetonitrile at 100 ºC (entries 5-7; Scheme 5.34c). Altering the reaction medium to glacial acetic acid and heating the reaction mixture at the same temperature for 10 or 20 minutes under microwave activation afforded a

complex mixture of several unidentified products (entries 8 and 9). It is noteworthy to emphasise that neither the starting DHPM **175** nor the desired and corresponding dehydrogenated compound **239** were obtained. Also, the oxidative desulphurisation process that characterised the application of Oxone and led to the formation of Biginelli 3,4-dihydropyrimidin-2(1*H*)-one **147**, was absent when using H_2O_2 under the reaction conditions tested.

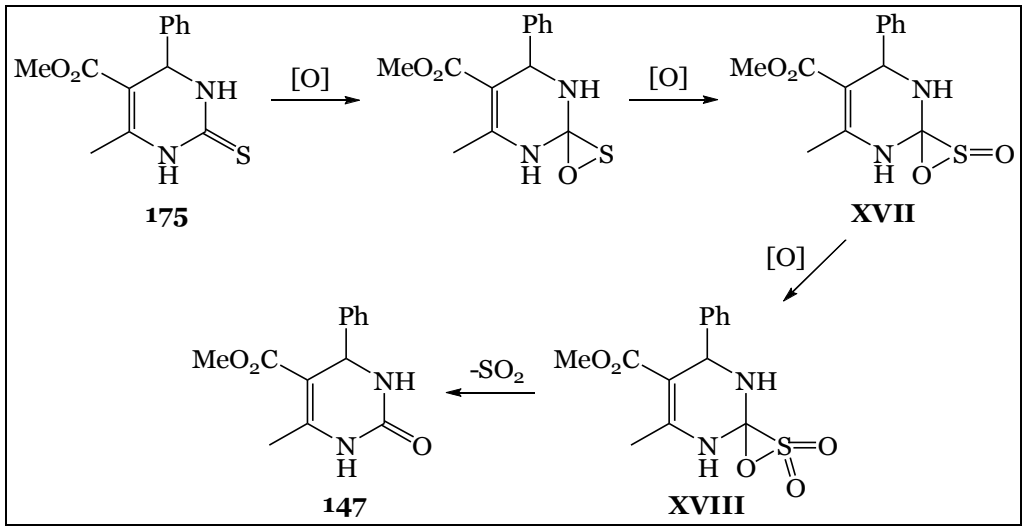
Table 5.6. Synthesis of methyl 6-methyl-4-phenylpyrimidine-2(1*H*)-thione-5-carboxylate **239** under microwave irradiation.

Entry	Reaction Medium	Oxidant	Time (min)	Conversion[a] (%)
1	CH_3CN/H_2O[b]	$K_2S_2O_8$[d]	10	0[h]
2	CH_3CN/H_2O[b]	$K_2S_2O_8$[d]	20	10[i]
3	CH_3CN/H_2O[b]	Oxone[e]	10	57[i]
4	CH_3CN/H_2O[b]	Oxone[e]	20	67[i]
5	CH_3CN[c]	H_2O_2[f]	10	0[h]
6	CH_3CN[c]	H_2O_2[f]	20	0[h]
7	CH_3CN[c]	H_2O_2[f]	30	0[h]
8	AcOH[c]	H_2O_2[f]	10	-[j]
9	AcOH[c]	H_2O_2[f]	20	-[j]
10	CH_2Cl_2[c]	DDQ[g]	20	78[k]
11	CH_2Cl_2[c]	DDQ[g]	30	22[l]

All reactions were carried-out using DHPM **175** (1 mmol) and the selected oxidant at 100 °C in a closed vessel. [a]Conversion was assessed by GC-MS analysis of the isolated reaction products. [b]CH_3CN/H_2O (3:2 v/v, 5 ml) was used as reaction medium, an initial microwave power of 80 W being applied. [c]The selected solvent (3 ml) was used as reaction medium, an initial microwave power of 100 W being applied. [d]$K_2S_2O_8$ (1.2 mmol), [e]Oxone (1.2 mmol), [f]H_2O_2 (35% m/v, 20 mmol) and [g]DDQ (1.2 mmol) were used as oxidants. [h]No reaction occurred, the starting DHPM **175** being recovered upon work-up. [i]DHPM **147** was obtained via oxidative desulphurisation, along with the initial DHPM **175**. [j]Several unidentified products were observed. [k]Pyrimidine-2(1*H*)-thione **239** was obtained, along with secondary oxidation product **240**. [l]Pyrimidine-2(1*H*)-thione **239** was obtained, along with secondary oxidation products **240** and **241**.



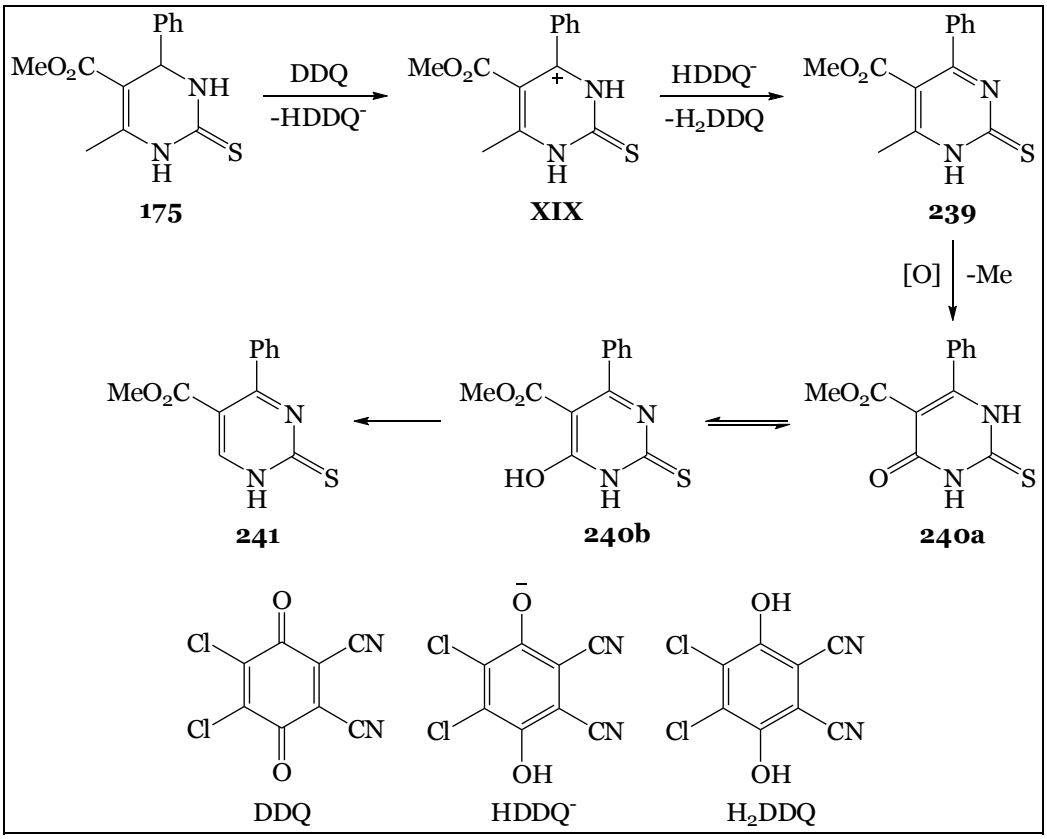
Scheme 5.34. Synthesis of methyl 6-methyl-4-phenylpyrimidine-2(1*H*)-thione-5-carboxylate **239** under microwave irradiation.



Scheme 5.35. Mechanistic proposal for the oxidative desulphurisation of methyl 6-methyl-4-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate **175** using Oxone as the oxidising agent.

Lastly, DDQ was employed as oxidant and dichloromethane as solvent (Scheme 5.34d), pyrimidine-2(1*H*)-thione **239** being prepared with a 78% conversion, along with compound **240** as by-product, after heating at 100 ºC for 20 minutes under microwave irradiation, followed by chromatographic purification through a small silica gel column (using dichloromethane and dichloromethane/ethyl acetate, 9:1 and 7:3 v/v, as eluents) and recrystallisation in diethyl ether or ethyl acetate/*n*-hexane (Table 5.6, entry 10). Extending the reaction time to 30 minutes did not improve the synthetic process, given that oxidation product **239** was obtained with a much lower conversion (22%), heterocycles **240** and **241** being the major reaction products, with 32 and 46% conversion, respectively (entry 11). A non-microwave-assisted, room temperature and slow (up to 48 hours) approach using DDQ was also tested, but a closely related outcome was determined, given that the same oxidation products were formed. While compound **239** was synthesised through microwave-activated and DDQ-promoted dehydrogenation of DHPM **175** (a possible reaction mechanism being initiated by a hydride transfer from the starting Biginelli 3,4-dihydropyrimidine-2(1*H*)-thione to DDQ, leading to the formation of hydropyrimidinium structure **XIX** and derivative $HDDQ^-$, followed by a $HDDQ^-$-mediated proton abstraction from the aforementioned carbocation intermediate and subsequent generation of the target pyrimidine-2(1*H*)-thione and secondary product H_2DDQ), the unwanted compounds **240** and **241** were most likely formed via oxidative demethylation and dehydroxylation reactions occurring at a second stage on product **239** (Scheme 5.36).

It must be mentioned that after GC-MS analysis of the yellowish solid obtained through application of the reaction conditions summarised in entry 10 of Table 5.6, our first impression was that the contaminant species was simply unreacted DHPM **175** (m/z=262). However, a closer look showed that both the fragmentation pattern in the mass spectrum and, particularly, the retention time in the chromatogram were somewhat different, t_R (**175**) and t_R (**240**) being 13.20 and 12.87 minutes, respectively, which pointed towards the synthesis of oxidation by-product **240** instead of contamination with the starting material. Moreover, it did not make any sense that by increasing the reaction time (entry 11), the amount of unreacted DHPM present in the final product was higher. Finally, the preparation of compound **240** with a higher conversion and the formation of secondary oxidation product **241** (m/z=246; t_R=11.84 min) after 30 minutes of microwave heating supports our rationalisation. Thus, although our synthetic efforts either failed, furnished unforeseen results like the oxidative desulphurisation process or did not efficaciously provide the desired dehydrogenation product **239** with high purity, a re-evaluation of DDQ as oxidant (e.g. changing the reaction medium, temperature and/or time) and the use of other quinone-type oxidising agents, *o*-TCQ or *p*-TCQ, might be interesting and, hopefully, advantageous in future oxidation studies of Biginelli 3,4-dihydropyrimidine-2(1*H*)-thiones under microwave irradiation.



Scheme 5.36. Mechanistic proposal for the synthesis of Biginelli pyrimidine-2(1*H*)-thione **239** and by-products **240** and **241** using DDQ as the oxidising agent.

IV. Summary

Making use of glacial acetic acid as both solvent and acid catalyst and microwave heating under sealed-vessel conditions, a medium-sized compound library of fifty five Biginelli DHPMs was effortlessly synthesised with high purity and without the requirement of any chromatographic purification protocol. Broadly speaking, the isolated yields were quite good, 35-90% for 3,4-dihydropyrimidin-2(1*H*)-ones **147-174** and 28-78% in the case of 3,4-dihydropyrimidine-2(1*H*)-thiones **175-201**. The same synthetic approach was also effectively applied to the multicomponent preparation of some Biginelli bis-DHPMs, bis-3,4-dihydropyrimidin-2(1*H*)-ones **202-205** being generally obtained with higher yields comparing to the equivalent bis-3,4-dihydropyrimidine-2(1*H*)-thiones **206-209**. A two-pot two-step strategy, in which microwave irradiation was used at the second stage of the reaction, proved to be the best course of action for the efficient synthesis of a series of 4,6-diaryl-3,4-dihydropyrimidine-2(1*H*)-thiones **210-220**. Again, no chromatographic separation technique was necessary for the isolation of the target products with high yields (80-86%). Six of these Biginelli-type DHPMs, **215-220**, were later selected and their *in vitro* cytotoxic activity examined against four human cancer cell lines. In general, all compounds studied were more active against MCF7 breast cancer cells, the brominated derivatives **215** and **219** being the most active Biginelli-type molecules. Eighteen pyrimidin-2(1*H*)-ones **221-238**, bearing both electron-withdrawing and electron-donating functionalities, were rapidly prepared through the microwave-assisted dehydrogenation of the related 3,4-dihydropyrimidin-2(1*H*)-ones. Among the several oxidants employed, potassium peroxydisulphate was established as the only effective one under the reaction conditions tested. Withal, application of this oxidising agent to the dehydrogenation of 3,4-dihydropyrimidine-2(1*H*)-thione **175** was disappointing. Oxone and hydrogen peroxide were also studied as oxidants, but either failed or rendered unexpected or unidentified by-products. The best result was attained using DDQ, a 78% conversion to the desired pyrimidine-2(1*H*)-thione being determined. Further efforts are undoubtedly needed in order to accomplish this exceedingly difficult synthetic endeavour.

V. References

1. P Biginelli, *Gazz. Chim. Ital.* 23 (**1893**) 360-413.

2. CO Kappe, *Tetrahedron* 49 (**1993**) 6937-6963.

3. KS Atwal, GC Rovnyak, J Schwartz, S Moreland, A Hedberg, JZ Gougoutas, MF Malley, DM Floyd, *J. Med. Chem.* 33 (**1990**) 1510-1515.

4. KS Atwal, BN Swanson, SE Unger, DM Floyd, S Moreland, A Hedberg, BC O'Reilly, *J. Med. Chem.* 34 (**1991**) 806-811.

5. GC Rovnyak, KS Atwal, A Hedberg, SD Kimball, S Moreland, JZ Gougoutas, BC O'Reilly, J Schwartz, MF Malley, *J. Med. Chem.* 35 (**1992**) 3254-3263.

6. JC Barrow, PG Nantermet, HG Selnick, KL Glass, KE Rittle, KF Gilbert, TG Steele, CF Homnick, RM Freidinger, RW Ransom, P Kling, D Reiss, TP Broten, TW Schorn, RSL Chang, SS O'Malley, TV Olah, JD Ellis, A Barrish, K Kassahun, P Leppert , D Nagarathnam, C Forray, *J. Med. Chem.* 43 (**2000**) 2703-2718.

7. CO Kappe, *Eur. J. Med. Chem.* 35 (**2000**) 1043-1052.

8. K Singh, D Arora, K Singh, S Singh, *Mini-Rev. Med. Chem.* 9 (**2009**) 95-106.

9. J-P Wan, Y Pan, *Mini-Rev. Med. Chem.* 12 (**2012**) 337-349.

10. S Sandhu, KS Sandhu, *Arkivoc* i (**2012**) 66-133.

11. M Pineiro, BFO Nascimento, AMd'A Rocha Gonsalves, *Mini-Rev. Med. Chem.* (**2013**) [manuscript in preparation/to be submitted for publication].

12. M Pineiro, BFO Nascimento, AMd'A Rocha Gonsalves, in *Quinones: Occurrence, Medicinal Uses and Physiological Importance*, ER Price, SC Johnson (Eds), Nova Science Publishers, Hauppauge, NY, USA, 2013, Chapter 1: *Dihydropyrimidinone Derivatives: Redox Reactivity, Pharmacological Relevance and Medicinal Applications*, pp 1-56 [manuscript accepted for publication/at press].

13. AD Patil, NV Kumar, WC Kokke, MF Bean, AJ Freger, C Debrossi, S Mai, A Truneh, DJ Faulkner, B Carte, AL Breen, RP Hertzbery, RK Johnson, JW Westley, BCM Potts, *J. Org. Chem.* 60 (**1995**) 1182-1188.

14. AD Patil, AJ Freyer, PB Taylor, B Carte, G Zuber, RK Johnson, DJ Faulkner, *J. Org. Chem.* 62 (**1997**) 1814-1819.

15. TU Mayer, TM Kapoor, SJ Haggarty, RW King, SL Schreiber, TJ Mitchison, *Science* 286 (**1999**) 971-974.

16. KW Wood, WD Cornwell, JR Jackson, *Curr. Opin. Pharmacol.* 1 (**2001**) 370-377.

17. W Rao, VJ South, Y Zhang, JP Davide, L Farrell, NE Kohl, L Sepp-Lorenzino, RB Lobell, *Cancer Cell* 8 (**2005**) 49-59.

18. S DeBonis, J-P Simorre, I Crevel, L Lebeau, DA Skoufias, A Blangy, C Ebel, P Gans, R Cross, DD Hackney, RH Wade, F Kozielski, *Biochem.* 42 (**2003**) 338-349.

19. P Kwan, MJ Brodie, *Epilepsia* 45 (**2004**) 1141-1149.

20. RW Lewis, J Mabry, JG Polisar, KP Eagen, B Ganem, GP Hess, *Biochem.* 49 (**2010**) 4841-4851.

21. AN Chiang, J-C Valderramos, R Balachandran, RJ Chovatiya, BP Mead, C Schneider, SL Bell, MG Klein, M Huryn, XS Chen, BW Day, DA Fidock, P Wipf, JL Brodsky, *Bioorg. Med. Chem.* 17 (**2009**) 1527-1533.

22. D Nagarathnam, SW Miao, G Chiu, J Fang, B Lagu, DTG Murali, J Zhang, S Tyagarajan, MR Marzabadi, F Zhang, WC Wong, W Sun, D Tian, JM Wetzel, C Forray, RSL Chang, T Broten, T Schorn, TB Chen, S O'Malley, R Ransom, K Schneck, R Bendesky, CM Harrel, C Gluchowski, *J. Med. Chem.* 42 (**1999**) 4764-4777.

23. K Deres, CH Schröder, A Paessens, S Goldmann, HJ Hacker, O Weber, T Krämer, U Niewöhner, U Pleiss, J Stoltefuss, E Graef, D Koletzki, RNA Masantschek, A Reimann, R Jaeger, R Groß, B Beckermann, K-H Schlemmer, D Haebich, H Rübsamen-Waigmann, *Science* 299 (**2003**) 893-896.

24. HJ Hacker, K Deres, M Mildenberger, CH Schröder, *Biochem. Pharmacol.* 66 (**2003**) 2273-2279.

25. SJ Stray, A Zlotnick, *J. Mol. Recognit.* 19 (**2006**) 542-548.

26. AR Trivedi, VR Bhuva, BH Dholariya, DK Dodiya, VB Kataria, VH Shah, *Bioorg. Med. Chem. Lett.* 20 (**2010**) 6100-6102.

27. E Rajanarendar, MN Reddy, KR Murthy, KG Reddy, S Raju, M Srinivas, B Praveen, MS Rao, *Bioorg. Med. Chem. Lett.* 20 (**2010**) 6052-6055.
28. SS Bahekar, DB Shinde, *Acta Pharm.* 53 (**2003**) 223-229.
29. SS Bahekar, DB Shinde, *Bioorg. Med. Chem. Lett.* 14 (**2004**) 1733-1736.
30. SN Mokale, SS Shinde, RD Elgire, JN Sangshetti, DB Shinde, *Bioorg. Med. Chem. Lett.* 20 (**2010**) 4424-4426.
31. K Folkers, HJ Harwood, TB Johnson, *J. Am. Chem. Soc.* 54 (**1932**) 3751-3758.
32. K Folkers, TB Johnson, *J. Am. Chem. Soc.* 55 (**1933**) 3784-3791.
33. F Sweet, JD Fissekis, *J. Am. Chem. Soc.* 95 (**1973**) 8741-8749.
34. CO Kappe, *J. Org. Chem.* 62 (**1997**) 7201-7204.
35. H Petersen, *Synthesis* (**1973**) 243-292.
36. EH Hu, DR Sidler, U-H Dolling, *J. Org. Chem.* 63 (**1998**) 3454-3457.
37. CO Kappe, F Falsone, WMF Fabian, F Belaj, *Heterocycles* 51 (**1999**) 77-84.
38. ROMA de Souza, ET da Penha, HMS Milagre, SJ Garden, PM Esteves, MN Eberlin, OAC Antunes, *Chem. Eur. J.* 15 (**2009**) 9799-9804.
39. MA Kolosov, VD Orlov, DA Beloborodov, VVA Dotsenko, *Mol. Divers.* 13 (**2009**) 5-25.
40. BC O'Reilly, KS Atwal, *Heterocycles* 26 (**1987**) 1185-1188.
41. KS Atwal, BC O'Reilly, JZ Gougoutas, MF Malley, *Heterocycles* 26 (**1987**) 1189-1192.
42. KS Atwal, GC Rovnyak, BC O'Reilly, J Schwartz, *J. Org. Chem.* 54 (**1989**) 5898-5907.
43. AA Bakibaev, VD Filimonov, *Russ. J. Org. Chem.* 27 (**1991**) 854-859.
44. JJ Vanden Eynde, N Audiart, V Canonne, S Michel, Y Van Haverbeke, CO Kappe, *Heterocycles* 45 (**1997**) 1967-1978.
45. CA Snyder, MA Thorn, JE Klijanowicz, PL Southwick, *J. Heteroc. Chem.* 19 (**1982**) 603-607.
46. RS Varma, D Kumar, *J. Chem. Soc. Perkin Trans. 1* (**1999**) 1755-1758.
47. J Lu, Y Bai, Z Wang, B Yabg, W Li, *Synth. Commun.* 31 (**2001**) 2625-2630.
48. M Shibuya, S Ito, M Takahashi, Y Iwabuchi, *Org. Lett.* 6 (**2004**) 4303-4306.
49. P Shanmugam, PT Perumal, *Tetrahedron* 62 (**2006**) 9726-9734.
50. CO Kappe, P Roschger, *J. Heteroc. Chem.* 26 (**1989**) 55-64.
51. EL Khanina, G Duburs, *Khim. Geterotskl. Soedin.* (**1982**) 535-538.
52. P Shanmugam, PT Perumal, *Tetrahedron* 63 (**2007**) 666-672.
53. V Kadis, J Stradins, EL Khanina, G Duburs, *Electrochim. Acta* 34 (**1989**) 899-904.
54. A Puchala, F Belaj, J Bergman, CO Kappe, *J. Heteroc. Chem.* 38 (**2001**) 1345-1352.
55. K Yamamoto, YG Chen, FG Buono, *Org. Lett.* 7 (**2005**) 4673-4676.
56. AR Gholap, KS Toti, F Shirazi, MV Deshpande, KV Srinivasan, *Tetrahedron* 64 (**2008**) 10214-10223.
57. HR Memarian, A Farhadi, *J. Iran. Chem. Soc.* 16 (**2009**) 638-646.
58. HR Memarian, A Farhadi, *Monatsh. Chem.* 140 (**2009**) 1217-1220.
59. CO Kappe, *Acc. Chem. Res.* 33 (**2000**) 879-888.
60. J-P Wan, Y Liu, *Synthesis* (**2010**) 3943-3953.
61. K Singh, K Singh, *Adv. Heteroc. Chem.* 105 (**2012**) 223-308.
62. M Matache, C Dobrota, N Bogdan, DP Funeriu, *Curr. Org. Synth.* 8 (**2011**) 356-373.
63. GC Tron, A Minassi, G Appendino, *Eur. J. Org. Chem.* (**2011**) 5541-5550.
64. CO Kappe, D Kumar, RS Varma, *Synthesis* (**1999**) 1799-1803.
65. JL Krstenansky, Y Khmelnitsky, *Bioorg. Med. Chem.* 7 (**1999**) 2157-2162.
66. HA Stefani, PM Gatti, *Synth. Commun.* 30 (**2000**) 2165-2173.
67. R Gupta, AK Gupta, S Paul, PL Kachroo, *Ind. J. Chem.* 34B (**1995**) 151-152.
68. A Dandia, M Saha, H Taneja, *J. Fluor. Chem.* 90 (**1998**) 17-21.
69. A Stadler, CO Kappe, *J. Chem. Soc. Perkin Trans. 1* (**2000**) 1363-1368.

70. JS Yadav, BV Subba Reddy, E Jagan Reddy, T Ramalingarm, *J. Chem. Res.* (**2000**) 354-355.
71. D Kumar, S Sandhu, JS Sandhu, *Ind. J. Chem.* 49B (**2010**) 360-363.
72. HR Shaterian, A Hosseinian, M Ghashang, *Phos. Sul. Sil. Rel. El.* 184 (**2009**) 126-134.
73. HR Shaterian, A Hosseinian, M Ghashang, *Phos. Sul. Sil. Rel. El.* 184 (**2009**) 197-205.
74. N Gangwar, VK Kasanajg, *Med. Chem. Res.* 21 (**2012**) 4506-4511.
75. A Stadler, CO Kappe, *J. Comb. Chem.* 3 (**2001**) 624-630.
76. D Dallinger, CO Kappe, *Nature Protocols* 2 (**2007**) 1713-1721.
77. M Kidwai, R Mohan, S Saxena, *Russ. Chem. Bull. Int. Ed.* 52 (**2003**) 2457-2460.
78. M Xia, Y-G Wang, *Synthesis* (**2003**) 262-266.
79. TN Glasnov, DJ Vugts, MM Koningstein, B Desai, WMF Fabian, RVA Orru, CO Kappe, *QSAR Comb. Sci.* 25 (**2006**) 509-518.
80. V Polshettiwar, RS Varma, *Tetrahedron Lett.* 48 (**2007**) 7343-7346.
81. MA Bigdeli, S Jafari, GH Mahdavinia, H Hazarkhani, *Catal. Commun.* 8 (**2007**) 1641-1644.
82. J Azizian, MK Mohammadi, O Firuzi, B Mirza, R Miri, *Chem. Biol. Drug Des.* 75 (**2010**) 375-380.
83. B Mirza, M Sagordan, R Fazaeli, *Asian J. Chem.* 24 (**2012**) 1421-1424.
84. M Rahman, A Majee, A Hajra, *J. Heteroc. Chem.* 47 (**2010**) 1230-1233.
85. KK Pasunooti, H Chai, CN Jensen, BK Gorityala, S Wang, X-W Liu, *Tetrahedron Lett.* 52 (**2011**) 80-84.
86. B Vijayakumar, GR Rao, *J. Porous Mater.* 19 (**2012**) 491-497.
87. HJM Gijsen, D Berthelot, MAJ De Cleyn, I Geuens, B Brône, M Mercken, *Bioorg. Med. Chem. Lett.* 22 (**2012**) 797-800.
88. M Kidwai, P Misra, *Synth. Commun.* 29 (**1999**) 3237-3250.
89. A Lin, Z Ling, Z Youguang, X Yunsheng, M Jie, L Ling, L Yi, *Chin. J. Org. Chem.* 32 (**2012**) 1108-1111.
90. B Liang, X Wang, J-X Wang, Z Du, *Tetrahedron* 63 (**2007**) 1981-1986.
91. Z Fang, Y Lam, *Tetrahedron* 67 (**2011**) 1294-1297.
92. HR Memarian, H Sabzyan, A Farhadi, *Z. Naturforsch.* 64B (**2009**) 532-540.
93. Y Yu, D Liu, C Liu, G Luo, *Bioorg. Med. Chem. Lett.* 17 (**2007**) 3508-3510.
94. Z-T Wang, L-W Xu, C-G Xia, H-Q Wang, *Tetrahedron Lett.* 45 (**2004**) 7951-7953.
95. G Sabitha, KB Reddy, R Srinivas, JS Yadav, *Helv. Chim. Acta* 88 (**2005**) 2996-2999.
96. A Saini, S Kumar, JS Sandhu, *Ind. J. Chem.* 46B (**2007**) 1690-1694.
97. Y-M Ren, C Cai, *Monatsh. Chem.* 140 (**2009**) 49-52.
98. Z Poughobadi, F Deerkvand, *Chin. Chem. Lett.* 21 (**2010**) 269-272.
99. M Phukan, MK Kalita, R Borah, *Green Chem. Lett. Rev.* 3 (**2010**) 329-334.
100. MR Mahmoud, MM El-Shahawi, *Phos. Sul. Sil. Rel. El.* 183 (**2008**) 3097-3108.
101. Z-L Shen, X-P Xu, S-J Ji, *J. Org. Chem.* 75 (**2010**) 1162-1167.
102. ES Al-Abdullah, *Molecules* 16 (**2011**) 3410-3419.
103. EP Kohler, HM Chadwell, *Org. Synth. Coll. Vol. 1* (**1941**) 78.
104. BFO Nascimento, M Laranjo, AM Abrantes, MF Botelho, AMd'A Rocha Gonsalves, M Pineiro, *Eur. J. Med. Chem.* (**2013**) [manuscript submitted for publication].
105. Y Zhang, W Xu, *Anti-Cancer Agents Med. Chem.* 8 (**2008**) 698-704.
106. MD Planas-Silva, S Filatova, *Anti-Cancer Drugs* 18 (**2007**) 773-779.
107. A Shaabani, P Mirzaei, S Naderia, DG Lee, *Tetrahedron* 60 (**2004**) 11415-11420.
108. HR Memarian, A Farhadi, *Ultrasonics Sonochem.* 15 (**2008**) 1015-1018.
109. HR Memarian, A Farhadi, A Sabzyan, *Ultrasonics Sonochem.* 17 (**2010**) 579-586.
110. HR Memarian, M Soleymani, H Sabzyan, M Bagherzadeh, H Ahmadi, *J. Phys. Chem. A* 115 (**2011**) 8264-8270.
111. http://www2.dupont.com/Oxone/en_US/assets/downloads/K20102_Oxone_Technical_Bulletin.pdf
112. SS Kim, BS Choi, JH Lee, KK Lee, TH Lee, YH Kim, H Shin, *Synlett* (**2009**) 599-602.

6

Experimental

I. Instrumentation

A. Microwaves

Microwave-assisted reactions were performed in a CEM Discover S-Class single-mode microwave reactor, featuring continuous temperature, pressure and microwave power monitoring.

B. Melting Points

Uncorrected melting points were determined in an Ernst Leitz 799 heated-plate microscope, using an AmaDigit ad1700th digital thermometer.

C. Elemental Analysis

Quantitative determination of carbon, hydrogen and nitrogen elements was accomplished in a Fisons Instruments EA-1108 CHNS-O analyser.

D. Ultraviolet-Visible Absorption Spectroscopy

UV-Vis absorption spectra were obtained in a Hitachi U-2001, Shimadzu UV-2100 or Ocean Optics USB 4000 spectrometer.

E. Nuclear Magnetic Resonance Spectroscopy

^{1}H NMR spectra were registered at room temperature in a Bruker AMX or Bruker Avance III spectrometer, operating at 300 and 400 MHz, respectively. ^{13}C NMR spectra were recorded at ambient temperature in a Bruker Avance III spectrometer, operating at 100 MHz. TMS was the internal standard used. Chemical shifts (δ) and coupling constants (J) are indicated in ppm and Hz, respectively.

F. Gas Chromatography-Mass Spectrometry

GC-MS spectra were obtained in a Hewlett-Packard 5973 MSD spectrometer, using EI (70 eV), coupled to a Hewlett-Packard Agilent 6890 chromatograph, equipped with a HP-5 MS column (30 m x 0.25 mm x 0.25 μm).

G. Mass Spectrometry

MS spectra were recorded in a Thermo Finnigan LCQ Advantage or Bruker Daltonics Autoflex III Smartbeam spectrometer, using ESI and MALDI, respectively. HR-MS were registered in a Waters Micromass VG Autospec M or Thermo Scientific Q Exactive spectrometer, using ESI.

H. X-Ray Diffraction

XRD studies were performed at 293 K in a Bruker-Nonius Kappa Apex II diffractometer, equipped with a 4KCCD detector, using graphite-monochromated MoKα radiation (λ=0.71073 Å). The structures were solved by direct methods (SHELXS-97) and refined by full-matrix least-squares methods (SHELXL-97). All non-hydrogen atoms were refined anisotropically.

II. Materials

A. Reagents

All commercially acquired reagents were high-grade chemicals and were utilised without any additional purification, with the following exceptions: aniline (Riedel-de Haën, 99.5%), distillation under reduced pressure, 1,4-diaminobenzene (Aldrich, 99%), recrystallisation in ethanol and pyrrole (Aldrich, 98%), distillation under reduced pressure or filtration through a small column of Al_2O_3, type 507C neutral, Brockmann Grade I, 50-150 μm (Fluka).

B. Solvents

All commercially acquired solvents were purified according to literature procedures prior to their usage,[1] with the following exceptions: acetonitrile (Fisher Scientific, 99.9%), carbon tetrachloride (Panreac, 99.9%), deuterated chloroform (Aldrich, 99.9% D, 0.03% v/v TMS; Euriso-Top, 99.8% D, 0.03% v/v TMS), deuterated dimethylsulphoxide (Aldrich, 99.9% D; Euriso-Top, 99.8% D, 0.03% v/v TMS), *N*,*N*-dimethylformamide (Merck, 99.8%), dimethylsulphoxide (Fisher Scientific, 99.9%), 1,4-dioxane (Panreac, 99.5%), glacial acetic acid (Panreac, 99.7%), methylcyclohexane (Aldrich, 99%), nitrobenzene (Merck, 99%) and propionic acid (Panreac, 99%).

C. Others

Solid-supported reactions using SiO_2 60, 200-500 μm (Fluka) and 35-70 μm (Acros Organics), SiO_2 60/H_2SO_4, 35-70 μm (Acros Organics), SiO_2 N, 2-20 μm (Macherey-Nagel), montmorillonite K-10, 220-270 $m^2\ g^{-1}$ surface area (Aldrich) and Al_2O_3, type 507C neutral, Brockmann Grade I, 50-150 μm (Fluka), were preceded by drying the solid support in an oven at 120 ºC for 24 hours. In the reactions employing heterogeneous oxidising agents, activated manganese dioxide (Aldrich, 85%) and potassium permanganate (Riedel-de Haën, 99%), these were also previously dried in an oven at 120 ºC for 24 hours. TLC-monitoring of the reactions was performed utilising SiO_2 60 F254-coated aluminium plates (Merck). Flash column chromatography purification of the reaction products was carried-out using SiO_2 60, 35-70 μm (Acros Organics) or 35-63 μm (Panreac).

III. Methods

A. Pyrroles

1. Paal-Knorr Synthesis of 2,5-Dimethyl-1*H*-Pyrroles

A mixture of the selected amine (10 mmol), 2,5-hexanedione (10 mmol, 1.21 ml) and formic acid (1.5 mmol, 60 μl) was thoroughly mixed in an appropriate 10 ml thick-walled glass vial. This was tightly sealed with a Teflon cap and the reaction mixture was stirred and heated at 100 ºC for 1 minute, under microwave irradiation, with an initial power setting of 100 W. After cooling to room temperature, the reaction product was washed with diethyl ether (50 ml) and the resulting solution was dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The yellow solid obtained was recrystallised in methanol, yielding the desired 2,5-dimethyl-1*H*-pyrrole as a pale-yellow solid (**1** and **2**). Regarding pyrrole **3**, the isolation process afforded a yellow oil that was purified through SiO_2 flash column chromatography (8x2 cm), using diethyl ether as eluent. The pyrrole-containing fraction was collected and evaporated under reduced pressure, yielding the desired 2,5-dimethyl-1*H*-pyrrole as a pale-yellow oil.

2,5-Dimethyl-1-phenyl-1*H*-pyrrole, 1. Yield: 96%, 1.650 g (pale-yellow solid); mp (°C): 50-51 (Lit. 51-52);[2] $C_{12}H_{13}N$: calculated (%) = C 84.17, H 7.65, N 8.18; found (%) = C 84.38, H 7.72, N 8.18; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.450 (2H, t, J = 7.2, Ph), 7.382 (1H, t, J = 7.2, Ph), 7.207 (2H, d, J = 7.2, Ph), 5.903 (2H, s, CH), 2.029 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm =138.954, 129.029, 128.783, 128.225, 127.612, 105.590, 13.007; GC-MS (EI): m/z (t_R, min) = 171 (9.45) (M^+).

1-Benzyl-2,5-dimethyl-1*H*-pyrrole, 2. Yield: 97%, 1.800 g (pale-yellow solid); mp (°C): 44-45 (Lit. 46-48);[2] $C_{13}H_{15}N$: calculated (%) = C 84.28, H 8.16, N 7.56; found (%) = C 83.92, H 8.57, N 7.75; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.268 (2H, t, J = 7.2, Ph), 7.198 (1H, t, J = 7.2, Ph), 6.867 (2H, d, J = 7.2, Ph), 5.853 (2 H, s, CH), 4.984 (2H, s, CH_2), 2.123 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 138.504, 128.669, 127.992, 126.957, 125.588, 105.372, 46.648, 12.412; GC-MS (EI): m/z (t_R, min) = 185 (10.21) (M^+).

1-*n*-Butyl-2,5-dimethyl-1*H*-pyrrole, 3. Yield: 94%, 1.420 g (pale-yellow oil); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 5.756 (2H, s, CH), 3.710 (2H, t, J = 7.6, N*CH*$_2$$CH_2CH_2CH_3$), 2.214 (6H, s, CH_3), 1.593 (2H, quin, J = 7.6, NCH_2*CH*$_2$$CH_2CH_3$), 1.364 (2H, sex, J = 7.6, NCH_2CH_2*CH*$_2$$CH_3$), 0.950 (3H, t, J = 7.6, $NCH_2CH_2CH_2$*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 127.333, 104.870, 43.414, 33.137, 20.183, 13.853, 12.484; GC-MS (EI): m/z (t_R, min) = 151 (8.46) (M^+).

2. Paal-Knorr Synthesis of Bis-2,5-Dimethyl-1*H*-Pyrroles

A mixture of the selected diamine (10 mmol), 2,5-hexanedione (30 mmol, 3.63 ml) and formic acid (1.5 mmol, 60 μl) was thoroughly mixed in an appropriate 10 ml thick-walled glass vial. This was tightly sealed with a Teflon cap and the reaction mixture was stirred and heated at 100 °C for 3 minutes, under microwave irradiation, with an initial power setting of 100 W. After cooling to room temperature, the reaction product was washed with diethyl ether (50 ml) and the resulting solution was dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The yellow solid obtained was recrystallised in methanol, yielding the desired bis-2,5-dimethyl-1*H*-pyrrole as a pale-yellow solid (**4-6**). Regarding bis-pyrrole **7**, the isolation process afforded a yellow oil that was purified through SiO_2 flash column chromatography (8x2 cm), using diethyl ether as eluent. The bis-pyrrole-containing fraction was collected and evaporated under reduced pressure, yielding the desired bis-2,5-dimethyl-1*H*-pyrrole as a pale-yellow oil.

1,2-Bis(2,5-dimethyl-1*H*-pyrrol-1-yl)ethane, 4. Yield: 95%, 2.050 g (pale-yellow solid); mp (°C): 130-132 (Lit. 134);[3] $C_{14}H_{20}N_2$: calculated (%) = C 77.73, H 9.32, N 12.95; found (%) = C 77.54, H 9.53, N 12.77; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 5.746 (4H, s, CH), 3.921 (4H, s, CH_2), 2.006 (12H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 127.462, 105.540, 43.712, 11.742; GC-MS (EI): m/z (t_R, min) = 216 (11.33) (M^+).

1,4-Bis(2,5-dimethyl-1*H*-pyrrol-1-yl)benzene, 5. Yield: 92%, 2.420 g (pale-yellow solid); mp (°C): 238-240; $C_{18}H_{20}N_2$: calculated (%) = C 81.78, H 7.63, N 10.60; found (%) = C 81.58, H 7.57, N 10.52; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.293 (4H, s, Ph), 5.934 (4H, s, CH), 2.085 (12H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 138.478, 128.972, 128.924, 106.211, 13.190; GC-MS (EI): m/z (t_R, min) = 264 (12.67) (M^+).

1,2-Bis(4-(2,5-dimethyl-1*H*-pyrrol-1-yl)phenyl)ethane, 6. Yield: 96%, 3.520 g (pale-yellow solid); mp (°C): 151-153; $C_{26}H_{28}N_2$: calculated (%) = C 84.74, H 7.66, N 7.60; found (%) = C 84.45, H 7.59, N 7.45; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.224 (4H, d, J = 8.4, Ph), 7.103 (4H, d, J = 8.4, Ph), 5.891 (4H, s, CH), 3.026 (4H, s, CH_2), 2.016 (12H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 140.838, 136.947, 129.102, 128.761, 128.081, 105.535, 37.336, 12.958; GC-MS (EI): m/z (t_R, min) = 368 (21.92) (M^+).

1,2-Bis(2-(2,5-dimethyl-1*H*-pyrrol-1-yl)ethoxy)ethane, 7. Yield: 90%, 2.740 g (pale-yellow oil); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 5.738 (4H, s, CH), 3.917 (4H, t, J = 6.4, N*CH*$_2$CH$_2$OCH$_2$), 3.570 (4H, t, J = 6.4, NCH$_2$*CH*$_2$OCH$_2$), 3.484 (4H, s, NCH$_2$CH$_2$O*CH*$_2$), 2.213 (12H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 127.683, 105.261, 70.764, 70.579, 43.313, 12.515; GC-MS (EI): m/z (t_R, min) = 304 (13.96) (M^+).

3. Multicomponent Synthesis of 3,5-Diaryl-2-Methyl-1*H*-Pyrroles

A mixture of the selected amine (5 mmol), the adequate chalcone* (5 mmol), nitroethane (15 mmol, 1.12 ml) and SiO_2 (8 g) in diethyl ether (50 ml) was stirred at room temperature for 5 minutes in a 100 ml round-bottomed flask, followed by evaporation under reduced pressure. The reaction mixture was heated at 100 ºC for 10 minutes, under microwave irradiation, with an initial power setting of 200 W. After cooling to room temperature, the reaction product was washed with diethyl ether (50 ml) and the resulting suspension was filtered and evaporated under reduced pressure, in order to remove the solid support. The yellow oil obtained was purified through SiO_2 flash column chromatography (8x2 cm), using *n*-hexane/diethyl ether (9:1 v/v) as eluent. The pyrrole-containing fraction was collected and evaporated under reduced pressure and the yellow solid obtained was recrystallised in methanol, yielding the desired 3,5-diaryl-2-methyl-1*H*-pyrrole as a white or yellowish solid (**8-37**).

*The chalcones needed for the synthesis of 3,5-diaryl-2-methyl-1*H*-pyrroles **8-37** were previously prepared through a procedure described by Kohler and Chadwell (see section 6.III.A.4., pages 139-141).[4]

2-Methyl-1,3,5-triphenyl-1*H*-pyrrole, 8. Yield: 23%, 350 mg (white solid); mp (ºC): 161-163; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.513 (2H, d, J = 7.6, Ph), 7.425-7.337 (5H, m, Ph), 7.255-7.214 (3H, m, Ph), 7.147-7.095 (5H, m, Ph), 6.564 (1H, s, CH), 2.248 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 139.264, 136.927, 133.891, 133.216, 129.018, 128.681, 128.395, 128.060, 127.977, 127.948, 127.894, 127.561, 125.883, 125.452, 122.766, 109.313, 12.420; GC-MS (EI): m/z (t_R, min) = 309 (16.34) (M^+).

1-Benzyl-2-methyl-3,5-diphenyl-1*H*-pyrrole, 9. Yield: 28%, 460 mg (white solid); mp (ºC): 115-116; $C_{24}H_{21}N$: calculated (%) = C 89.12, H 6.54, N 4.33; found (%) = C 89.47, H 6.78, N 4.11; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.466 (2H, d, J = 7.6, Ph), 7.386 (2H, d, J = 7.2, Ph), 7.377-7.279 (6H, m, Ph), 7.256-7.192 (3H, m, Ph), 6.993 (2H, d, J = 7.2, Ph), 6.449 (1H, s, CH), 5.183 (2H, s, CH_2), 2.262 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 138.810, 137.146, 134.346, 133.396, 128.783, 128.734, 128.422, 128.342, 128.054, 127.049, 126.896, 126.668, 125.658, 125.266, 122.478, 108.611, 47.971, 11.374; GC-MS (EI): m/z (t_R, min) = 323 (16.61) (M^+).

1-*n*-Butyl-2-methyl-3,5-diphenyl-1*H*-pyrrole, 10. Yield: 25%, 360 mg (white solid); mp (ºC): 88-90; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.447-7.353 (8H, m, Ph), 7.326-7.294 (1H, m, Ph), 7.204 (1H, t, J = 7.2, Ph), 6.295 (1H, s, CH), 3.909 (2H, t, J = 7.6, N*CH*$_2$CH$_2$CH$_2$CH$_3$), 2.437 (3H, s, CH_3), 1.611 (2H, quin, J = 7.6, NCH$_2$*CH*$_2$CH$_2$CH$_3$), 1.225 (2H, sex, J = 7.6, NCH$_2$CH$_2$*CH*$_2$CH$_3$), 0.883 (3H, t, J = 7.6, NCH$_2$CH$_2$CH$_2$*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 137.327, 134.069, 133.634, 129.132, 128.353, 128.288, 128.103, 126.809, 125.934, 125.118, 122.039, 108.438, 44.214, 33.277, 19.913, 13.632, 11.444; GC-MS (EI): m/z (t_R, min) = 289 (14.34) (M^+).

2-Methyl-3-(naphthalen-1-yl)-1,5-diphenyl-1*H*-pyrrole, 11. Yield: 14%, 250 mg (yellow solid); mp (ºC): 106-108; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.208 (1H, d, J = 7.2, Ph), 7.898 (1H, d, J = 7.2, Ph), 7.826-7.804 (1H, m, Ph), 7.551-7.478 (4H, m, Ph), 7.433-7.340 (3H, m, Ph), 7.301 (2H, d, J = 7.2, Ph), 7.168-7.085 (5H, m, Ph), 6.591 (1H, s, CH), 2.042 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 139.529, 134.905, 133.921, 133.330, 133.237, 132.644, 129.365, 129.029, 128.629, 128.202, 128.011, 127.745, 127.714, 127.481, 126.853, 126.687, 125.747, 125.586, 125.537, 125.454, 120.878, 111.585, 12.202; MS (MALDI): m/z = 359 (M^+).

1-Benzyl-2-methyl-3-(naphthalen-1-yl)-5-phenyl-1*H*-pyrrole, 12. Yield: 19%, 350 mg (yellow solid); mp (°C): 101-103; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.126 (1H, d, J = 7.6, Ph), 7.863 (1H, d, J = 7.6, Ph), 7.776 (1H, d, J = 7.2, Ph), 7.507-7.435 (4H, m, Ph), 7.392 (2H, d, J = 7.2, Ph), 7.350-7.282 (4H, m, Ph), 7.261-7.211 (2H, m, Ph), 7.038 (2H, d, J = 7.6, Ph), 6.470 (1H, s, CH), 5.240 (2H, s, CH_2), 2.028 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 139.036, 135.151, 133.953, 133.943, 133.503, 132.755, 128.808, 128.666, 128.450, 128.165, 127.740, 127.056, 126.811, 126.780, 126.581, 125.642, 125.528, 125.462, 125.402, 120.724, 110.915, 48.052, 11.194; HR-MS (ESI): m/z = 374.18940 ($[M+H]^+$, $C_{28}H_{24}N$: required = 374.19033).

1-*n*-Butyl-2-methyl-3-(naphthalen-1-yl)-5-phenyl-1*H*-pyrrole, 13. Yield: 18%, 310 mg (yellow solid); mp (°C): 61-63; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.101 (1H, d, J = 7.6, Ph), 7.870 (1H, d, J = 7.6, Ph), 7.777 (1H, d, J = 8, Ph), 7.513-7393 (8H, m, Ph), 7.305 (1H, t, J = 7.6, Ph), 6.321 (1H, s, CH), 3.978 (2H, t, J = 7.2, N*CH*$_2$CH$_2$CH$_2$CH$_3$), 2.214 (3H, s, CH_3), 1.665 (2H, quin, J = 7.2, NCH$_2$*CH*$_2$CH$_2$CH$_3$), 1.262 (2H, sex, J = 7.2, NCH$_2$CH$_2$*CH*$_2$CH$_3$), 0.863 (3H, t, J = 7.2, NCH$_2$CH$_2$CH$_2$*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 135.349, 134.136, 133.890, 133.145, 132.732, 128.951, 128.380, 128.113, 127.677, 127.428, 126.933, 126.628, 126.392, 125.423, 120.096, 110.683, 44.364, 33.316, 19.935, 13.706, 11.359; MS (MALDI): m/z = 339 (M^+).

3-(Anthracen-9-yl)-1-benzyl-2-methyl-5-phenyl-1*H*-pyrrole, 14. Yield: 19%, 400 mg (yellow solid); mp (°C): 161-163; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.426 (1H, s, Ph), 8.074 (2H, d, J = 8.4, Ph), 8.016 (2H, d, J = 8.4, Ph), 7.456 (2H, d, J = 7.6, Ph), 7.423-7.211 (10H, m, Ph), 7.107 (2H, d, J = 7.6, Ph), 6.483 (1H, s, CH), 5.326 (2H, s, CH_2), 1.795 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 139.189, 134.274, 133.582, 132.549, 131.615, 131.255, 129.529, 128.844, 128.626, 128.504, 128.374, 127.547, 127.109, 126.735, 125.844, 125.655, 124.960, 117.939, 112.109, 48.115, 11.119; HR-MS (ESI): m/z = 424.20548 ($[M+H]^+$, $C_{32}H_{26}N$: required = 424.20598).

3-(Anthracen-9-yl)-1-*n*-butyl-2-methyl-5-phenyl-1*H*-pyrrole, 15. Yield: 14%, 280 mg (yellow solid); mp (°C): 134-136; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.421 (1H, s, Ph), 8.022 (4H, d, J = 8.4, Ph), 7.530 (2H, d, J = 7.2, Ph), 7.458-7.361 (6H, m, Ph), 7.309 (1H, t, J = 7.2, Ph), 6.324 (1H, s, CH), 4.068 (2H, t, J = 7.6, N*CH*$_2$CH$_2$CH$_2$CH$_3$), 1.973 (3H, s, CH_3), 1.696 (2H, quin, J = 7.6, NCH$_2$*CH*$_2$CH$_2$CH$_3$), 1.293 (2H, sex, J = 7.6, NCH$_2$CH$_2$*CH*$_2$CH$_3$), 0.889 (3H, t, J = 7.6, NCH$_2$CH$_2$CH$_2$*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 134.347, 133.422, 132.997, 131.633, 131.303, 128.861, 128.811, 128.548, 128.319, 127.711, 126.524, 125.651, 124.941, 124.846, 117.333, 111.988, 44.420, 33.394, 19.911, 13.765, 11.269; MS (MALDI): m/z = 389 (M^+).

1-Benzyl-2-methyl-5-phenyl-3-(pyren-1-yl)-1*H*-pyrrole, 16. Yield: 11%, 235 mg (yellow solid); mp (°C): 167-169; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.331 (1H, d, J = 8.8, Ph), 8.196 (1H, d, J = 7.6, Ph), 8.149 (2H, t, J = 6.4, Ph), 8.092-7.998 (4H, m, Ph), 7.979 (1H, t, J = 7.6, Ph), 7.450 (2H, d, J = 7.6, Ph), 7.405-7.239 (6H, m, Ph), 7.105 (2H, t, J = 7.6, Ph), 6.597 (1H, s, CH), 5.308 (2H, s, CH_2), 2.090 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 138.997, 134.275, 133.452, 132.995, 131.517, 131.162, 129.845, 129.295, 128.870, 128.718, 128.505, 127.497, 127.124, 126.876, 126.828, 126.786, 126.334, 125.782, 125.692, 125.109, 125.036, 124.672, 124.527, 124.488, 121.324, 111.151, 48.143, 11.379; HR-MS (ESI): m/z = 448.20583 ($[M+H]^+$, $C_{34}H_{26}N$: required = 448.20598).

3-(4-Bromophenyl)-2-methyl-1,5-diphenyl-1*H*-pyrrole, 17. Yield: 18%, 350 mg (pale-yellow solid); mp (°C): 163-165; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.518 (2H, d, J = 8.4, Ph), 7.404-7.346 (5H, m, Ph), 7.206 (2H, d, J = 6.8, Ph), 7.168-7.081 (5H, m, Ph), 6.520 (1H, s, CH), 2.219 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 139.006, 135.847, 134.114, 132.958, 131.458, 129.542, 129.072, 128.592, 128.011, 127.894, 127.691, 126.043, 121.602, 119.178, 108.940, 12.414; GC-MS (EI): m/z (t_R, min) = 387 (22.19) (M^+).

1-Benzyl-3-(4-bromophenyl)-2-methyl-5-phenyl-1*H*-pyrrole, 18. Yield: 22%, 435 mg (pale-yellow solid); mp (°C): 130-131; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.477 (2H, d, J = 8, Ph), 7.322-7.210 (10H, m, Ph), 6.977 (2H, d, J = 8, Ph), 6.394 (1H, s, CH), 5.161 (2H, s, CH_2), 2.223 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 138.592, 136.110, 134.598, 133.185, 131.381, 129.578, 128.810, 128.754, 128.452, 127.119, 127.053, 126.751, 125.635, 121.345, 118.981, 108.332, 47.991, 11.358; GC-MS (EI): m/z (t_R, min) = 401 (24.03) (M^+).

3-(4-Bromophenyl)-1-*n*-butyl-2-methyl-5-phenyl-1*H*-pyrrole, 19. Yield: 20%, 370 mg (pale-yellow solid); mp (°C): 90-91; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.478 (2H, d, J = 8.4, Ph), 7.406-7.396 (4H, m, Ph), 7.348-7.316 (1H, m, Ph), 7.292 (2H, d, J = 8.4, Ph), 6.250 (1H, s, CH), 3.896 (2H, t, J = 7.6, N*CH*$_2$CH$_2$CH$_2$CH$_3$), 2.405 (3H, s, CH_3), 1.594 (2H, quin, J = 7.6, NCH$_2$*CH*$_2$CH$_2$CH$_3$), 1.216 (2H, sex, J = 7.6, NCH$_2$CH$_2$*CH*$_2$CH$_3$), 0.826 (3H, t, J = 7.6, NCH$_2$CH$_2$CH$_2$*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 136.238, 133.858, 133.791, 131.334, 129.587, 129.128, 128.388, 126.970, 126.019, 120.850, 118.815, 108.113, 44.211, 33.222, 19.881, 13.620, 11.428; GC-MS (EI): m/z (t_R, min) = 367 (18.11) (M^+).

3-(4-Chlorophenyl)-2-methyl-1,5-diphenyl-1*H*-pyrrole, 20. Yield: 19%, 330 mg (pale-yellow solid); mp (°C): 167-169; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.432 (2H, d, J = 8.4, Ph), 7.391-7.357 (5H, m, Ph), 7.210 (2H, d, J = 6.8, Ph), 7.152-7.083 (5H, m, Ph), 6.522 (1H, s, CH), 2.224 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 139.026, 135.374, 134.078, 132.977, 131.125, 129.170, 129.071, 128.600, 128.521, 128.011, 127.894, 127.683, 126.033, 121.601, 108.997, 12.408; GC-MS (EI): m/z (t_R, min) = 343 (19.92) (M^+).

1-Benzyl-3-(4-chlorophenyl)-2-methyl-5-phenyl-1*H*-pyrrole, 21. Yield: 23%, 410 mg (pale-yellow solid); mp (°C): 103-104; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.376 (2H, d, J = 8, Ph), 7.339-7.224 (10H, m, Ph), 6.982 (2H, d, J = 8, Ph), 6.397 (1H, s, CH), 5.169 (2H, s, CH_2), 2.230 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 138.631, 135.656, 134.577, 133.219, 130.956, 129.214, 128.820, 128.768, 128.456, 127.126, 127.053, 126.748, 125.651, 121.365, 108.395, 48.002, 11.360; GC-MS (EI): m/z (t_R, min) = 357 (21.05) (M^+).

1-*n*-Butyl-3-(4-chlorophenyl)-2-methyl-5-phenyl-1*H*-pyrrole, 22. Yield: 20%, 320 mg (pale-yellow solid); mp (°C): 97-98; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.409-7.398 (4H, m, Ph), 7.365-7.319 (5H, m, Ph), 6.251 (1H, s, CH), 3.899 (2H, t, J = 7.6, N*CH*$_2$CH$_2$CH$_2$CH$_3$), 2.409 (3H, s, CH_3), 1.597 (2H, quin, J = 7.6, NCH$_2$*CH*$_2$CH$_2$CH$_3$), 1.219 (2H, sex, J = 7.6, NCH$_2$CH$_2$*CH*$_2$CH$_3$), 0.829 (3H, t, J = 7.6, NCH$_2$CH$_2$CH$_2$*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 135.767, 133.817, 130.767, 129.206, 129.129, 128.392, 126.959, 126.006, 120.855, 108.164, 44.214, 33.233, 19.887, 13.625, 11.426; GC-MS (EI): m/z (t_R, min) = 323 (16.76) (M^+).

3-(4-Fluorophenyl)-2-methyl-1,5-diphenyl-1*H*-pyrrole, 23. Yield: 22%, 360 mg (white solid); mp (°C): 149-151; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.450 (2H, dd, J = 8.4, 5.6, Ph), 7.407-7.328 (3H, m, Ph), 7.215 (2H, d, J = 7.2, Ph), 7.170-7.076 (7H, m, Ph), 6.511 (1H, s, CH), 2.216 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 161.163 (C, d, J = 242.7), 139.150, 133.903, 133.071, 132.916 (C, d, J = 3.3), 129.420 (2xCH, d, J = 7.5), 129.050, 128.626, 127.999, 127.881, 127.739, 127.623, 125.964, 121.811, 115.200 (2xCH, d, J = 21), 109.164, 12.307; GC-MS (EI): m/z (t_R, min) = 327 (16.95) (M^+).

1-Benzyl-3-(4-fluorophenyl)-2-methyl-5-phenyl-1*H*-pyrrole, 24. Yield: 25%, 430 mg (white solid); mp (°C): 130-132; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.391 (2H, dd, J = 8.4, 5.6, Ph), 7.337-7.271 (6H, m, Ph), 7.250-7.195 (2H, m, Ph), 7.054 (2H, t, J = 8.4, Ph), 6.981 (2H, d, J = 7.2, Ph), 6.389 (1H, s, CH), 5.164 (2H, s, CH_2), 2.217 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 161.054 (C, d, J = 242.4), 138.723, 134.383, 133.284, 133.174 (C, d, J = 2.9), 129.429 (2xCH, d, J = 7.5), 128.801, 128.728, 128.449, 127.090, 126.977, 126.457, 125.644, 121.555, 115.118 (2xCH, d, J = 21), 108.507, 47.977, 11.252; GC-MS (EI): m/z (t_R, min) = 341 (17.68) (M^+).

1-*n*-Butyl-3-(4-fluorophenyl)-2-methyl-5-phenyl-1*H*-pyrrole, 25. Yield: 23%, 350 mg (white solid); mp (°C): 110-112; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.409-7.350 (6H, m, Ph), 7.334-7.292 (1H, m, Ph), 7.057 (2H, t, J = 8.4, Ph), 6.240 (1H, s, CH), 3.900 (2H, t, J = 7.6, N*CH*$_2$CH$_2$CH$_2$CH$_3$), 2.399 (3H, s, CH_3), 1.600 (2H, quin, J = 7.6, NCH$_2$*CH*$_2$CH$_2$CH$_3$), 1.219 (2H, sex, J = 7.6, NCH$_2$CH$_2$*CH*$_2$CH$_3$), 0.829 (3H, t, J = 7.6, NCH$_2$CH$_2$CH$_2$*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 160.972 (C, d, J = 242.2), 133.904, 133.646, 133.298 (C, d, J = 3.1), 129.423 (2xCH, d, J = 7.6), 129.110, 128.374, 126.885, 125.728, 121.067, 115.061 (2xCH, d, J = 21), 108.288, 44.215, 33.256, 19.893, 13.631, 11.335; GC-MS (EI): m/z (t_R, min) = 307 (14.58) (M^+).

2-Methyl-3-(4-nitrophenyl)-1,5-diphenyl-1*H*-pyrrole, 26. Yield: 20%, 350 mg (yellow solid); mp (°C): 190-193; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.268 (2H, d, J = 8.8, Ph), 7.638 (2H, d, J = 8.8, Ph), 7.449-7.380 (3H, m, Ph), 7.214 (2H, d, J = 6.8, Ph), 7.175-7.093 (5H, m, Ph), 6.605 (1H, s, CH), 2.291 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 145.233, 144.002, 138.586, 134.952, 132.572, 129.580, 129.222, 128.545, 128.112, 128.053, 128.005, 127.740, 126.443, 123.987, 120.914, 108.834, 12.825; MS (MALDI): m/z = 353 ([M-H]$^+$).

1-Benzyl-2-methyl-3-(4-nitrophenyl)-5-phenyl-1*H*-pyrrole, 27. Yield: 24%, 440 mg (yellow solid); mp (°C): 93-94; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.235 (2H, d, J = 8.8, Ph), 7.582 (2H, d, J = 8.8, Ph), 7.329-7.266 (8H, m, Ph), 6.990 (2H, d, J = 7.6, Ph), 6.484 (1H, s, CH), 5.197 (2H, s, CH_2), 2.311 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 145.139, 144.257, 138.155, 135.443, 132.789, 128.934, 128.911, 128.574, 128.373, 127.783, 127.477, 127.330, 125.628, 123.932, 120.668, 108.387, 48.103, 11.800; MS (MALDI): m/z = 367 ([M-H]$^+$).

1-*n*-Butyl-2-methyl-3-(4-nitrophenyl)-5-phenyl-1*H*-pyrrole, 28. Yield: 21%, 350 mg (yellow solid); mp (°C): 94-96; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.228 (2H, d, J = 8.4, Ph), 7.552 (2H, d, J = 8.4, Ph), 7.448-7.337 (5H, m, Ph), 6.338 (1H, s, CH), 3.920 (2H, t, J = 7.6, N*CH*$_2$CH$_2$CH$_2$CH$_3$), 2.481 (3H, s, CH_3), 1.596 (2H, quin, J = 7.6, NCH$_2$*CH*$_2$CH$_2$CH$_3$), 1.222 (2H, sex, J = 7.6, NCH$_2$CH$_2$*CH*$_2$CH$_3$), 0.830 (3H, t, J = 7.6, NCH$_2$CH$_2$CH$_2$*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm 144.970, 144.422, 134.690, 133.384, 129.244, 128.494, 127.680, 127.627, 127.377, 123.911, 120.187, 108.215, 44.274, 33.137, 19.856, 13.595, 11.846; MS (MALDI): m/z = 333 ([M-H]$^+$).

3-(4-Methoxyphenyl)-2-methyl-1,5-diphenyl-1*H*-pyrrole, 29. Yield: 20%, 340 mg (pale-yellow solid); mp (°C): 117-119; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.431 (2H, d, J = 8.4, Ph), 7.400-7.336 (3H, m, Ph), 7.219 (2H, d, J = 7.2, Ph), 7.164-7.088 (5H, m, Ph), 6.967 (2H, d, J = 8.4, Ph), 6.517 (1H, s, CH), 3.848 (3H, s, OCH_3), 2.223 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 157.668, 139.310, 133.672, 133.246, 129.481, 129.114, 128.992, 128.655, 127.959, 127.853, 127.480, 125.806, 122.359, 113.880, 109.275, 55.306, 12.345; GC-MS (EI): m/z (t_R, min) = 339 (21.01) (M^+).

1-Benzyl-3-(4-methoxyphenyl)-2-methyl-5-phenyl-1*H*-pyrrole, 30. Yield: 25%, 440 mg (pale-yellow solid); mp (°C): 82-84; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.382 (2H, d, J = 8.4, Ph), 7.342-7.222 (8H, m, Ph), 6.993 (2H, d, J = 7.2, Ph), 6.936 (2H, d, J = 8.4, Ph), 6.396 (1H, s, CH), 5.172 (2H, s, CH_2), 3.820 (3H, s, OCH_3), 2.230 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 157.549, 138.901, 134.160, 133.461, 129.770, 129.112, 128.768, 128.696, 128.409, 127.021, 126.820, 126.185, 125.674, 122.094, 113.839, 108.555, 55.289, 47.970, 11.295; GC-MS (EI): m/z (t_R, min) = 353 (22.35) (M^+).

1-*n*-Butyl-3-(4-methoxyphenyl)-2-methyl-5-phenyl-1*H*-pyrrole, 31. Yield: 21%, 330 mg (pale-yellow solid); mp (°C): 53-55; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.409-7.394 (4H, m, Ph), 7.353 (2H, d, J = 8.4, Ph), 7.317-7.286 (1H, m, Ph), 6.931 (2H, d, J = 8.4, Ph), 6.246 (1H, s, CH), 3.898 (2H, t, J = 7.6, N*CH*$_2$CH$_2$CH$_2$CH$_3$), 3.828 (3H, s, OCH_3), 2.405 (3H, s, CH_3), 1.608 (2H, quin, J = 7.6, NCH$_2$*CH*$_2$CH$_2$CH$_3$), 1.223 (2H, sex, J = 7.6, NCH$_2$CH$_2$*CH*$_2$CH$_3$), 0.832 (3H, t, J = 7.6, NCH$_2$CH$_2$CH$_2$*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 157.415, 134.076, 133.423, 129.901, 129.139, 129.072, 128.332, 126.724, 125.471, 121.610, 113.759, 108.333, 55.271, 44.207, 33.291, 19.912, 13.643, 11.363; GC-MS (EI): m/z (t_R, min) = 319 (17.05) (M^+).

1-Benzyl-5-(4-bromophenyl)-2-methyl-3-phenyl-1*H*-pyrrole, 32. Yield: 19%, 380 mg (pale-yellow solid); mp (°C): 135-136; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.461-7.364 (6H, m, Ph), 7.341-7.304 (2H, m, Ph), 7.271-7.224 (2H, m, Ph), 7.184 (2H, d, J = 8.4, Ph), 6.976 (2H, d, J = 7.2, Ph), 6.433 (1H, s, CH), 5.156 (2H, s, CH_2), 2.266 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 138.526, 136.938, 133.052, 132.311, 131.904, 131.585, 130.173, 128.898, 128.389, 128.080, 127.214, 125.557, 125.431, 122.736, 120.959, 109.012, 47.970, 11.343; GC-MS (EI): m/z (t_R, min) = 401 (23.62) (M^+).

5-(4-Bromophenyl)-1-*n*-butyl-2-methyl-3-phenyl-1*H*-pyrrole, 33. Yield: 20%, 360 mg (pale-yellow solid); mp (°C): 87-88; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.523 (2H, d, J = 8.4, Ph), 7.423-7.349 (4H, m, Ph), 7.278 (2H, d, J = 8.4, Ph), 7.207 (1H, t, J = 7.2, Ph), 6.278 (1H, s, CH), 3.884 (2H, t, J = 7.6, N$CH_2$$CH_2CH_2CH_3$), 2.419 (3H, s, CH_3), 1.587 (2H, quin, J = 7.6, $NCH_2CH_2$$CH_2CH_3$), 1.225 (2H, sex, J = 7.6, $NCH_2CH_2CH_2$$CH_3$), 0.847 (3H, t, J = 7.6, $NCH_2CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 137.091, 132.989, 132.302, 131.543, 130.509, 128.325, 128.102, 126.507, 125.272, 122.322, 120.818, 108.884, 44.263, 33.275, 19.914, 13.656, 11.420; GC-MS (EI): m/z (t_R, min) = 367 (20.69) (M^+).

1-Benzyl-5-(4-chlorophenyl)-2-methyl-3-phenyl-1*H*-pyrrole, 34. Yield: 20%, 360 mg (pale-yellow solid); mp (°C): 99-101; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.456 (2H, d, J = 7.6, Ph), 7.387 (2H, t, J = 7.6, Ph), 7.326 (2H, t, J = 7.6, Ph), 7.274-7.208 (6H, m, Ph), 6.980 (2H, d, J = 7.6, Ph), 6.433 (1H, s, CH), 5.156 (2H, s, CH_2), 2.268 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 138.501, 136.902, 133.018, 132.803, 131.791, 129.842, 128.881, 128.620, 128.382, 128.048, 127.191, 127.109, 125.528, 125.404, 122.619, 108.922, 47.929, 11.335; GC-MS (EI): m/z (t_R, min) = 357 (21.66) (M^+).

1-*n*-Butyl-5-(4-chlorophenyl)-2-methyl-3-phenyl-1*H*-pyrrole, 35. Yield: 19%, 300 mg; mp (°C): 79-80; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.416 (2H, d, J = 7.2, Ph), 7.386-7.325 (6H, m, Ph), 7.207 (1H, t, J = 7.2, Ph), 6.274 (1H, s, CH), 3.883 (2H, t, J = 7.6, N$CH_2$$CH_2CH_2CH_3$), 2.422 (3H, s, CH_3), 1.587 (2H, quin, J = 7.6, $NCH_2CH_2$$CH_2CH_3$), 1.224 (2H, sex, J = 7.6, $NCH_2CH_2CH_2$$CH_3$), 0.844 (3H, t, J = 7.6, $NCH_2CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 137.118, 132.728, 132.540, 132.300, 130.229, 128.591, 128.325, 128.102, 126.414, 125.260, 122.268, 108.856, 44.250, 33.273, 19.914, 13.651, 11.420; GC-MS (EI): m/z (t_R, min) = 323 (18.97) (M^+).

1-Benzyl-5-(4-fluorophenyl)-2-methyl-3-phenyl-1*H*-pyrrole, 36. Yield: 18%, 310 mg (white solid); mp (°C): 95-97; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.462 (2H, d, J = 7.6, Ph), 7.388 (2H, t, J = 7.6, Ph), 7.341-7.206 (6H, m, Ph), 7.015-6.971 (4H, m, Ph), 6.404 (1H, s, CH), 5.143 (2H, s, CH_2), 2.271 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 162.015 (C, d, J = 245.2), 138.619, 137.003, 133.167, 130.461 (2xCH, d, J = 7.9), 129.469 (C, d, J = 3.2), 128.844, 128.370, 128.036, 127.145, 126.561, 125.559, 125.334, 122.373, 115.342 (2xCH, d, J = 21.3), 108.606, 47.857, 11.348; GC-MS (EI): m/z (t_R, min) = 341 (17.93) (M^+).

1-*n*-Butyl-5-(4-fluorophenyl)-2-methyl-3-phenyl-1*H*-pyrrole, 37. Yield: 20%, 300 mg (white solid); mp (°C): 59-60; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.422 (2H, d, J = 7.2, Ph), 7.387-7.351 (4H, m, Ph), 7.204 (1H, t, J = 7.2, Ph), 7.094 (2H, t, J = 8.2, Ph), 6.249 (1H, s, CH), 3.863 (2H, t, J = 7.6, N$CH_2$$CH_2CH_2CH_3$), 2.424 (3H, s, CH_3), 1.577 (2H, quin, J = 7.6, $NCH_2CH_2$$CH_2CH_3$), 1.216 (2H, sex, J = 7.6, $NCH_2CH_2CH_2$$CH_3$), 0.831 (3H, t, J = 7.6, $NCH_2CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 162.011 (C, d, J = 244.6), 137.219, 132.449, 130.849 (2xCH, d, J = 7.9), 130.179 (C, d, J = 3.2), 128.310, 128.088, 125.843, 125.185, 121.993, 115.287 (2xCH, d, J = 21.2), 108.504, 44.140, 33.262, 19.904, 13.626, 11.414; GC-MS (EI): m/z (t_R, min) = 307 (16.51) (M^+).

4. Base-Catalysed Claisen-Schmidt Synthesis of Chalcones

A solution of sodium hydroxide (63 mmol, 2.486 g) in distilled water/ethanol (1:1 v/v, 50 ml) was stirred at room temperature in a 100 ml round-bottomed flask. This was placed in a water bath and the selected acetophenone or 2-acetyl-1*H*-pyrrole* (50 mmol) was added, followed by the adequate aldehyde or 2-formyl-1*H*-pyrrole (50 mmol). The reaction mixture was left stirring at 20-30 ºC until a thick yellow solid precipitated. This was filtered under reduced pressure, thoroughly washed with distilled water and recrystallised in aqueous ethanol, yielding the desired chalcone as a yellowish solid (**38-47** and **49-55**). Chalcone **48** did not easily precipitate from the alkaline reaction medium. Hence, the synthetic process was followed over time by TLC and, once completed, the reaction product was washed with distilled water (50 ml) and neutralised by the addition of aqueous hydrochloric acid (37% m/v) until a yellow solid precipitated. This was filtered under reduced pressure, thoroughly washed with distilled water and recrystallised in aqueous ethanol, yielding the desired chalcone as a pale-yellow solid. Chalcones **41** and **42** were prepared via a 10 mmol stoichiometry of acetophenone and the adequate aldehyde. Chalcones **54** an **55** were synthesised through a 5 mmol stoichiometry of the selected acetophenone and pyren-1-carbaldehyde.

*The 2-acetyl-1*H*-pyrrole needed for the synthesis of chalcone **49** was previously prepared through a procedure described by Alonso-Garrido and co-workers (see section 6.III.A.5., page 142).[5]

(*E*)-1,3-Diphenylprop-2-en-1-one, 38. Yield: 85%, 8.850 g (pale-yellow solid); mp (ºC): 53-55 (Lit. 55-57);[6] $C_{15}H_{12}O$: calculated (%) = C 86.51, H 5.81; found (%) = C 86.25, H 5.55; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.020 (2H, d, J = 7.6, Ph), 7.811 (1H, d, J = 16, CH-3), 7.643-7.626 (2H, m, Ph), 7.582 (1H, d, J = 7.2, Ph), 7.531 (1H, d, J = 16, CH-2), 7.482 (2H, d, J = 7.2, Ph), 7.410-7.396 (3H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 190.490, 144.814, 138.152, 134.826, 132.787, 130.543, 128.943, 128.612, 128.486, 128.441, 122.001; GC-MS (EI): m/z (t_R, min) = 208 (11.69) (M^+).

(*E*)-3-(Naphthalen-1-yl)-1-phenylprop-2-en-1-one, 39. Yield: 81%, 10.400 g (yellow solid); mp (ºC): 79-81; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.654 (1H, d, J = 15.6, CH-3), 8.219 (1H, d, J = 8.4, Ph), 8.060 (2H, d, J = 7.6, Ph), 7.889-7.837 (3H, m, Ph), 7.596 (1H, d, J = 15.6, CH-2), 7.558 (2H, d, J = 7.6, Ph), 7.548-7.458 (4H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 190.292, 141.731, 138.196, 133.771, 132.962, 132.358, 131.805, 130.898, 128.828, 128.745, 128.652, 127.035, 126.361, 125.507, 125.149, 124.616, 123.521; GC-MS (EI): m/z (t_R, min) = 258 (15.57) (M^+).

(*E*)-3-(Phenanthren-9-yl)-1-phenylprop-2-en-1-one, 40. Yield: 80%, 2.475 g (yellow solid); mp (ºC): 121-123; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.722 (1H, d, J = 8, Ph), 8.645 (1H, d, J = 15.6, CH-3), 8.638 (1H, d, J = 8, Ph), 8.252 (1H, d, J = 7.6, Ph), 8.116-8.094 (3H, m, Ph), 7.927 (1H, d, J = 8, Ph), 7.685 (1H, d, J = 15.6, CH-2), 7.718-7.647 (3H, m, Ph), 7.611 (2H, t, J = 7.6, Ph), 7.533 (2H, t, J = 7.6, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 190.245, 142.464, 138.133, 132.930, 131.558, 131.245, 131.154, 130.471, 130.276, 129.247, 128.707, 128.641, 127.754, 127.141, 127.062, 127.011, 126.587, 125.201, 124.456, 123.208, 122.670; GC-MS (EI): m/z (t_R, min) = 308 (24.49) (M^+).

(*E*)-3-(Anthracen-9-yl)-1-phenylprop-2-en-1-one, 41. Yield: 83%, 12.850 g (bright-yellow solid); mp (ºC): 118-120; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.785 (1H, d, J = 16, CH-3), 8.442 (1H, s, Ph), 8.289 (2H, d, J = 8.4, Ph), 8.078 (2H, d, J = 7.2, Ph), 8.010 (2H, d, J = 7.2, Ph), 7.613-7.576 (2H, m, Ph), 7.543 (1H, d, J = 16, CH-2), 7.506-7.467 (5H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 189.648, 141.892, 137.834, 133.091, 131.256, 130.963, 130.107, 129.585, 128.896, 128.744, 128.704, 128.424, 126.416, 125.405, 125.262; GC-MS (EI): m/z (t_R, min) = 308 (24.11) (M^+).

(*E*)-1-Phenyl-3-(pyren-1-yl)prop-2-en-1-one, 42. Yield: 85%, 2.825 g (bright-yellow solid); mp (ºC): 157-158; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.973 (1H, d, J = 15.6, CH-3), 8.524 (1H, d, J = 8, Ph), 8.396 (1H, d, J = 8, Ph), 8.210 (2H, d, J = 7.2, Ph), 8.180-8.101 (5H, m, Ph), 8.061-8.001 (2H, m, Ph), 7.800 (1H, d, J = 15.6, CH-2), 7.622 (1H, t, J = 7.2, Ph), 7.551 (2H, t, J = 7.2, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 190.234, 141.465, 138.427, 132.943, 132.834, 131.300, 130.715, 130.350, 128.708, 128.599, 127.320, 126.315, 126.065, 125.921, 125.032, 124.975, 124.597, 124.186, 123.960, 122.578; MS (MALDI): m/z = 332 (M^+).

(*E*)-3-(4-Bromophenyl)-1-phenylprop-2-en-1-one, 43. Yield: 87%, 12.500 g (pale-yellow solid); mp (ºC): 117-119; $C_{15}H_{11}OBr$: calculated (%) = C 62.74, H 3.86; found (%) = C 62.62, H 3.90; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.014 (2H, d, J = 7.2, Ph), 7.737 (1H, d, J = 15.6, CH-3), 7.613-7.574 (3H, m, Ph), 7.546 (2H, d, J = 8, Ph), 7.506 (1H, d, J = 15.6, CH-2), 7.496 (2H, d, J = 8, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 190.179, 143.350, 137.957, 133.756, 132.950, 132.187, 129.787, 128.669, 128.488, 124.792, 122.476; GC-MS (EI): m/z (t_R, min) = 286 (13.86) (M^+).

(*E*)-3-(4-Chlorophenyl)-1-phenylprop-2-en-1-one, 44. Yield: 78%, 9.500 g (pale-yellow solid); mp (ºC): 110-111 (Lit. 113-117);[7] $C_{15}H_{11}OCl$: calculated (%) = C 74.23, H 4.57; found (%) = C 74.18, H 4.34; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.019 (2H, d, J = 7.2, Ph), 7.742 (1H, d, J = 16, CH-3), 7.618-7.590 (1H, m, Ph), 7.580 (2H, d, J = 8.4, Ph), 7.530-7.494 (2H, m, Ph), 7.511 (1H, d, J = 16, CH-2), 7.396 (2H, d, J = 8.4, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 190.236, 143.321, 138.001, 136.431, 133.351, 132.949, 129.595, 129.248, 128.680, 128.499, 122.417; GC-MS (EI): m/z (t_R, min) = 242 (13.24) (M^+).

(*E*)-3-(4-Fluorophenyl)-1-phenylprop-2-en-1-one, 45. Yield: 70%, 7.880 g (pale-yellow solid); mp (ºC): 85-86 (Lit. 84-88);[8] $C_{15}H_{11}OF$: calculated (%) = C 79.63, H 4.90; found (%) = C 79.33, H 5.31; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.016 (2H, d, J = 7.8, Ph), 7.773 (1H, d, J = 15.8, CH-3), 7.628 (2H, dd, J = 8.4, 5.6, Ph), 7.576 (1H, d, J = 7.8, CH-2), 7.509 (2H, d, J = 7.8, Ph), 7.462 (1H, d, J = 15.8, CH-2), 7.101 (2H, t, J = 8.4, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 190.284, 164.041 (C, d, J = 250.2), 143.501, 138.086, 132.868, 131.112 (C, d, J = 3.2), 130.359 (2xCH, d, J = 9.2), 128.654, 128.478, 121.694, 116.126 (2xCH, d, J = 21.8); GC-MS (EI): m/z (t_R, min) = 226 (12.22) (M^+).

(*E*)-3-(4-Nitrophenyl)-1-phenylprop-2-en-1-one, 46. Yield: 75%, 9.500 g (bright-yellow solid); mp (ºC): 155-158 (Lit. 158-160);[9] ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.289 (2H, d, J = 8.8, Ph), 8.046 (2H, d, J = 7.2, Ph), 7.831 (1H, d, J = 16, CH-3), 7.799 (2H, d, J = 8.8, Ph), 7.656 (1H, d, J = 16, CH-2), 7.638 (1H, t, J = 7.2, Ph), 7.542 (2H, t, J = 7.2, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 189.659, 148.549, 141.535, 141.038, 137.517, 133.400, 128.954, 128.841, 128.607, 125.684, 124.241; GC-MS (EI): m/z (t_R, min) = 253 (14.71) (M^+).

(*E*)-3-(4-Methoxyphenyl)-1-phenylprop-2-en-1-one, 47. Yield: 75%, 8.950 g (pale-yellow solid); mp (ºC): 71-72 (Lit. 73-76);[10] $C_{16}H_{14}O_2$: calculated (%) = C 80.65, H 5.92; found (%) = C 80.76, H 5.69; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.006 (2H, dd, J = 7.2, 1.2, Ph), 7.801 (1H, d, J = 15.6, CH-3), 7.584 (2H, dd, J = 8.8, 2, Ph), 7.562-7.534 (1H, m, Ph), 7.503-7.458 (2H, m, Ph), 7.410 (1H, d, J = 15.6, CH-2), 6.602 (2H, dd, J = 8.8, 2, Ph), 3.820 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 190.584, 161.742, 144.761, 138.540, 132.651, 130.324, 128.641, 128.487, 127.633, 119.753, 114.480, 55.458; GC-MS (EI): m/z (t_R, min) = 238 (13.79) (M^+).

(*E*)-3-(3-Hydroxyphenyl)-1-phenylprop-2-en-1-one, 48. Yield: 70%, 7.850 g (pale-yellow solid); mp (ºC): 156-158; ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 9.661 (1H, bs, OH), 8.145 (2H, d, J = 7.6, Ph), 7.839 (1H, d, J = 15.6, CH-3), 7.698-7.644 (1H, m, Ph), 7.679 (1H, d, J = 15.6, CH-2), 7.566 (2H, t, J = 7.6, Ph), 7.321 (1H, d, J = 7.6, Ph), 7.287-7.257 (2H, m, Ph), 6.905 (1H, d, J = 7.6, Ph); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ, ppm = 189.214, 157.737, 144.266, 137.584, 135.910, 133.047, 129.863, 128.742, 128.464, 121.889, 119.840, 117.834, 115.265; GC-MS (EI): m/z (t_R, min) = 224 (13.84) (M^+).

(*E*)-1-Phenyl-3-(1*H*-pyrrol-2-yl)prop-2-en-1-one, 49. Yield: 88%, 8.500 g (yellow solid); mp (°C): 127-129; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 9.297 (1H, bs, NH), 7.975 (2H, d, J = 7.6, Ph), 7.769 (1H, d, J = 15.6, CH-3), 7.546 (1H, t, J = 7.6, Ph), 7.461 (2H, t, J = 7.6, Ph), 7.191 (1H, d, J = 15.6, CH-2), 6.991 (1H, s, CH-5-pyrrole), 6.714 (1H, s, CH-3-pyrrole), 6.327 (1H, d, J = 2.4, CH-4-pyrrole); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 190.770, 138.703, 134.942, 132.399, 129.342, 128.559, 128.293, 123.353, 115.792, 115.348, 111.516; GC-MS (EI): m/z (t_R, min) = 197 (10.94) (M^+).

(*E*)-1-(4-Bromophenyl)-3-phenylprop-2-en-1-one, 50. Yield: 80%, 11.420 g (pale-yellow solid); mp (°C): 99-100 (Lit. 103-105);[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.877 (2H, d, J = 8.4, Ph), 7.807 (1H, d, J = 15.6, CH-3), 7.629 (4H, d, J = 8.8, Ph), 7.485 (1H, d, J = 15.6, CH-2), 7.421-7.406 (3H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 189.304, 145.368, 136.921, 134.688, 131.914, 130.737, 130.012, 128.994, 128.506, 127.875, 121.475; GC-MS (EI): m/z (t_R, min) = 286 (13.60) (M^+).

(*E*)-1-(4-Chlorophenyl)-3-phenylprop-2-en-1-one, 51. Yield: 77%, 9.350 g (pale-yellow solid); mp (°C): 94-95 (Lit. 97-101);[12] ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.960 (2H, d, J = 8.4, Ph), 7.810 (1H, d, J = 16, CH-3), 7.637-7.624 (2H, m, Ph), 7.478 (1H, d, J = 16, CH-2), 7.469 (2H, d, J = 8.4, Ph), 7.425-7.411 (3H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 189.085, 145.294, 139.188, 136.499, 134.699, 130.717, 129.899, 128.988, 128.923, 128.501, 121.489; GC-MS (EI): m/z (t_R, min) = 242 (13.03) (M^+).

(*E*)-1-(4-Fluorophenyl)-3-phenylprop-2-en-1-one, 52. Yield: 72%, 7.870 g (pale-yellow solid); mp (°C): 134-136; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.050 (2H, dd, J = 8.6, 5.6, Ph), 7.807 (1H, d, J = 15.6, CH-3), 7.640-7.619 (2H, m, Ph), 7.496 (1H, d, J = 15.6, CH-2), 7.416-7.401 (3H, m, Ph), 7.160 (2H, t, J = 8.4, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 188.776, 165.603 (C, d, J = 253), 145.024, 134.775, 134.542 (C, d, J = 2.8), 131.093 (2xCH, d, J = 9.2), 130.651, 128.990, 128.475, 121.583, 115.736 (2xCH, d, J = 21.7); GC-MS (EI): m/z (t_R, min) = 226 (12.02) (M^+).

(*E*)-3-Phenyl-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one, 53. Yield: 90%, 8.900 g (yellow solid); mp (°C): 134-136; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 10.186 (1H, bs, NH), 7.834 (1H, d, J = 15.6, CH-3), 7.639 (2H, d, J = 7.6, Ph), 7.414-7.397 (3H, m, Ph), 7.352 (1H, s, CH-5-pyrrole), 7.116 (1H, d, J = 15.6, 1H, CH-2), 7.096 (1H, s, CH-3-pyrrole), 6.353 (1H, d, J = 3.2, CH-4-pyrrole); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 178.967, 142.299, 135.074, 133.198, 130.224, 128.921, 128.343, 125.669, 122.076, 116.561, 110.984; GC-MS (EI): m/z (t_R, min) = 197 (12.03) (M^+).

(*E*)-3-(Pyren-1-yl)-1-(2-(trifluoromethyl)phenyl)prop-2-en-1-one, 54. Yield: 83%, 1.660 g (bright-yellow solid); mp (°C): 135-136; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.506 (1H, d, J = 16, CH-3), 8.301 (1H, d, J = 8.4, Ph), 8.215-8.182 (3H, m, Ph), 8.132-8.082 (3H, m, Ph), 8.035-7.993 (2H, m, Ph), 7.847 (1H, d, J = 7.6, Ph), 7.733-7.611 (3H, m, Ph), 7.318 (1H, d, J = 16, CH-2); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 194.720, 144.046, 139.357, 133.266, 131.811, 131.253, 130.565, 130.228, 130.022, 129.002, 128.920, 128.272, 127.745, 127.324, 126.876, 126.830, 126.378, 126.294, 126.069, 125.128, 124.867, 124.487, 124.342, 121.989; MS (MALDI): m/z = 400 (M^+).

(*E*)-1-(2-Fluoro-6-(trifluoromethyl)phenyl)-3-(pyren-1-yl)prop-2-en-1-one, 55. Yield: 85%, 1.780 g (bright-yellow solid); mp (°C): 193-194; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.485 (1H, d, J = 15.8, CH-3), 8.308 (1H, d, J = 8.4, Ph), 8.229-8.095 (6H, m, Ph), 8.047-8.004 (2H, m, Ph), 7.652-7.609 (2H, m, Ph), 7.475-7.435 (1H, m, Ph), 7.295 (1H, d, J = 15.8, CH-2); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 190.442, 160.515, 158.043, 144.167, 133.389, 131.332, 131.257, 130.564, 130.238, 129.086, 129.009, 127.597, 127.339, 126.398, 126.357, 126.116, 125.139, 124.870, 124.548, 124.489, 122.491, 121.917, 119.902, 119.682; MS (MALDI): m/z = 418 (M^+).

5. Vilsmeier-Haack Acetylation of Pyrrole

A solution of *N*,*N*-dimethylacetamide (100 mmol, 9.36 ml) in toluene (50 ml) was stirred at room temperature in a 250 ml round-bottomed flask. This was placed in a water/ice bath and a solution of phosphorous oxychloride (100 mmol, 9.25 ml) in toluene (50 ml) was added drop-wise during 30 minutes. The reaction mixture was stirred at room temperature for 30 minutes, placed again in a water/ice bath and a solution of pyrrole (100 mmol, 7.14 ml) in toluene (20 ml) was added drop-wise during 30 minutes. The reaction mixture was left stirring at room temperature overnight (16-18 hours) under moisture exclusion conditions (calcium chloride tower). After cooling in an ice bath, the reaction product was washed with distilled water (100 ml), neutralised by addition of solid sodium bicarbonate, alkalised to pH=12 by addition of aqueous sodium hydroxide (40% m/v) and stirred at room temperature for 1 hour. The aqueous phase was separated and extracted with dichloromethane (3x100 ml), the organic extracts being collected and pooled with the initial toluene phase. The resulting solution was dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure and the yellow oil obtained was purified through SiO_2 flash column chromatography (12x3 cm), using dichloromethane as eluent. The pyrrole-containing fraction was collected and evaporated under reduced pressure and the yellow solid obtained was recrystallised in ethyl acetate/*n*-hexane, yielding the desired 2-acetyl-1*H*-pyrrole as a pale-yellow solid (**56**).

2-Acetyl-1*H*-pyrrole, 56. Yield: 70%, 6.450 g (pale-yellow solid); mp (ºC): 86-87 (Lit. 88-89);[5] ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 10.326 (1H, bs, NH), 7.061 (1H, s, CH-5), 6.928 (1H, s, CH-3), 6.262 (1H, s, CH-4), 2.444 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 188.320, 132.197, 125.240, 117.240, 110.545, 25.450; GC-MS (EI): m/z (t_R, min) = 109 (6.92) (M^+).

B. Porphyrins

1. Synthesis of *meso*-Tetraarylporphyrins

i. One-Step Methodology

A mixture of the selected aldehyde (10 mmol) and pyrrole (10 mmol, 0.72 ml) in propionic acid/nitrobenzene (7:3 v/v, 5 ml) was thoroughly mixed in an appropriate 10 ml thick-walled glass vial. This was tightly sealed with a Teflon cap and the reaction mixture was stirred and heated at 200 ºC for 5 minutes, under microwave irradiation, with an initial power setting of 250 W. After cooling to room temperature, the reaction product was purified through SiO_2 flash column chromatography (12x3 cm), using dichloromethane/*n*-hexane (5:1 v/v, **58-60**, **62-64**, **69** and **70**), dichloromethane/ethyl acetate (9:1 v/v, **65**, **74**, **75**, **79** and **80**; 1:1 v/v, **66**, **72**, **76-78** and **81**) or dichloromethane/methanol (95:5 v/v, **61**) as eluents. The porphyrin-containing fraction was collected and evaporated under reduced pressure and the reddish-brown solid obtained was recrystallised in dichloromethane/methanol (**58-60**, **62-65**, **69**, **70**, **74**, **75**, **79** and **80**) or ethyl acetate/*n*-hexane (**61**, **66**, **72**, **76-78** and **81**), yielding the desired porphyrin as a dark-purple solid. Porphyrins **57**, **67**, **68** and **71** were easily crystallised from the reaction product by addition of methanol (100 ml). The dark-purple solid obtained was filtered under reduced pressure and thoroughly washed with methanol. Porphyrin **73** was easily crystallised from the reaction product by addition of acetone (100 ml). The dark-purple solid obtained was filtered under reduced pressure and thoroughly washed with acetone.

5,10,15,20-Tetraphenylporphyrin, 57. Yield: 46%, 710 mg (dark-purple solid); mp (ºC) > 300; $C_{44}H_{30}N_4$: calculated (%) = C 85.97, H 4.92, N 9.11; found (%) = C 86.13, H 5.02, N 8.85; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 416 (100), 513.5 (6.7), 548 (3.6), 588.5 (2.9), 645.5 (2.8); ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm = 8.847 (8H, s, CH), 8.236-8.305 (8H, m, Ph), 7.792-7.731 (12H, m, Ph), -2.787 (2H, bs, NH); MS (ESI): m/z = 615 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(naphthalen-1-yl)porphyrin, 58. Yield: 15%, 315 mg (dark-purple solid); mp (ºC) > 300; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 277 (8.2), 423 (100), 515 (6.3), 547 (2.7), 589 (3), 648 (2.1); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.474 (8H, s, CH), 8.295-8.208 (8H, m, Ph), 8.102 (4H, d, J = 7.6, Ph), 7.820 (4H, t, J = 7.6, Ph), 7.463 (4H, t, J = 7.6, Ph), 7.232-7.107 (8H, m, Ph), -2.241 (2H, bs, NH); MS (ESI): m/z = 815 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(phenanthren-9-yl)porphyrin, 59. Yield: 9%, 225 mg (dark-purple solid); mp (ºC) > 300; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 253 (56.5), 292 (14.2), 426 (100), 516 (7.8), 548 (3), 589 (3.3), 650 (2.2); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.953 (8H, t, J = 7.6, Ph), 8.609 (8H, s, CH), 8.574-8.506 (4H, m, Ph), 8.030 (4H, d, J = 7.6, Ph), 7.843 (4H, t, J = 7.6, Ph), 7.766-7.731 (4H, m Ph), 7.620 (4H, t, J = 7.6, Ph), 7.347-7.194 (8H, m, Ph), -2.092 (2H, bs, NH); MS (ESI): m/z = 1015 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(pyren-1-yl)porphyrin, 60. Yield: 4%, 100 mg (dark-purple solid); mp (ºC) > 300; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 241 (86), 274 (50), 324 (31.1), 337 (35.2), 371 (19.3), 431 (100), 519 (10.1), 555 (5.2), 591 (4.3), 648 (2.9); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.857-8.750 (4H, m, Ph), 8.459-8.411 (4H, m, Ph), 8.425 (8H, s, CH), 8.337-8.242 (12H, m, Ph), 8.092-8.001 (8H, m, Ph), 7.752-7.697 (4H, m, Ph), 7.643-7.603 (1H, m, Ph), 7.554 (1H, d, J = 9.2, Ph), 7.489 (2H, d, J = 9.2, Ph), -1.945 (2H, bs, NH); MS (ESI): m/z = 1111 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(pyridin-4-yl)porphyrin, 61. Yield: 18%, 275 mg (dark-purple solid); mp (ºC) > 300; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 415 (100), 510.5 (7.7), 544 (3.7), 585.5 (3.9), 641.5 (2.7); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 9.067 (8H, d, J = 4.2, Ph), 8.872 (8H, s, CH), 8.163 (8H, d, J = 4.2, Ph), -2.917 (2H, bs, NH); MS (ESI): m/z = 619 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(2,6-dichlorophenyl)porphyrin, 62. Yield: 5%, 110 mg (dark-purple solid); mp (ºC) > 300; $C_{44}H_{22}N_4Cl_8$: calculated (%) = C 59.36, H 2.49, N 6.29; found (%) = C 59.56, H 2.73, N 6.35; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 416.5 (100), 511.5 (8.1), 541 (3.2), 587 (4.1), 655.5 (2.4); ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm = 8.677 (8H, s, CH), 7.851-7.653 (12H, m, Ph), -2.530 (2H, bs, NH-pyrrole); MS (ESI): m/z = 890 ($[M+H]^+$).

5,10,15,20-Tetramesitylporphyrin, 63. Yield: 2%, 30 mg (dark-purple solid); mp (ºC) > 300; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 417 (100), 513.5 (6.7), 546 (3.2), 589.5 (3.1), 646 (2.3); ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm = 8.614 (8H, s, CH), 7.255 (8H, s, Ph), 2.619 (12H, s, CH_3), 1.848 (24H, s, CH_3), -2.512 (2H, bs, NH); MS (ESI): m/z = 783 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(3-nitrophenyl)porphyrin, 64. Yield: 22%, 435 mg (dark-purple solid); mp (ºC) > 300; $C_{44}H_{26}N_8O_8$: calculated (%) = C 66.50, H 3.30, N 14.10; found (%) = C 66.69, H 3.54, N 13.98; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 420 (100), 512.5 (10.1), 547 (5.9), 586.5 (6.1), 644.5 (5.1); ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm = 9.092 (4H, s, Ph), 8.820 (8H, s, CH), 8.721 (4H, d, J = 7.8, Ph), 8.565 (4H, d, J = 7.8, Ph), 7.999 (4H, t, J = 7.8, Ph), -2.828 (2H, bs, NH); MS (ESI): m/z = 795 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(3-methoxyphenyl)porphyrin, 65. Yield: 30%, 550 mg (dark-purple solid); mp (ºC) > 300; $C_{48}H_{38}N_4O_4$: calculated (%) = C 78.45, H 5.21, N 7.62; found (%) = C 78.12, H 5.02, N 7.43; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) 417.5 (100), 513.5 (5.7), 548.5 (2.9), 588 (2.7), 644.5 (2.3); ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm = 8.886 (8H, s, CH), 7.812-7.794 (8H, m, Ph), 7.637 (4H, t, J = 8.4, Ph), 7.328 (4H, dd, J = 8.4, 2.5, Ph), 3.978 (12H, s, OCH_3), -2.807 (2H, bs, NH); MS (ESI): m/z = 735 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(3-hydroxyphenyl)porphyrin, 66. Yield: 36%, 615 mg (dark-purple solid); mp (°C) > 300; $C_{44}H_{30}N_4O_4$: calculated (%) = C 77.86, H 4.46, N 8.25; found (%) = C 77.62, H 4.32, N 8.12; UV-Vis (CH_3OH): λ_{max}, nm (relative absorbance, %) = 413 (100), 510.5 (7.1), 545.5 (4.1), 586 (3.5), 643 (3.1); ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 9.889 (4H, bs, OH), 8.894 (8H, s, CH), 7.600-7.578 (12H, m, Ph), 7.266 (4H, d, J = 8.4, Ph), -2.968 (2H, bs, NH); MS (ESI): m/z = 679 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(4-*t*-butylphenyl)porphyrin, 67. Yield: 55%, 1.150 g (dark-purple solid); mp (°C) > 300; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 416 (100), 513.5 (6.7), 548 (3.6), 588.5 (2.9), 645.5 (2.8); ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm = 8.871 (8H, s, CH), 8.143 (8H, d, J = 8.2, Ph), 8.03 (8H, d, J = 8.2, Ph), 1.607 (36H, s, CH_3), -2.751 (2H, bs, NH); MS (ESI): m/z = 839 ($[M+H]^+$).

5,10,15,20-Tetra-*p*-tolylporphyrin, 68. Yield: 50%, 830 mg (dark-purple solid); mp (°C) > 300; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 419 (100), 515 (6), 551 (3.9), 589.5 (2.9), 647 (2.8); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.848 (8H, s, CH), 8.092 (8H, d, J = 7.6, Ph), 7.547 (8H, d, J = 7.6, Ph), 2.699 (12H, s, CH_3), -2.769 (2H, bs, NH); MS (ESI): m/z = 671 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(4-bromophenyl)porphyrin, 69. Yield: 30%, 715 mg (dark-purple solid); mp (°C) > 300; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 418 (100), 513.5 (6.6), 548 (4.1), 588.5 (3.5), 645 (2.9); ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm = 8.841 (8H, s, CH), 8.069 (8H, d, J = 8.3, Ph), 7.903 (8H, d, J = 8.3, Ph), -2.880 (2H, bs, NH); MS (ESI): m/z = 931 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(4-chlorophenyl)porphyrin, 70. Yield: 33%, 615 mg (dark-purple solid); mp (°C) > 300; $C_{44}H_{26}N_4Cl_4$: calculated (%) = C 70.23, H 3.48, N 7.45; found (%) = C 70.45, H 3.70, N 7.22; (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 417.5 (100), 513.5 (6.3), 548.5 (3.8), 587.5 (3.2), 645 (2.6); ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm = 8.841 (8H, s, CH), 8.133 (8H, d, J = 8.4, Ph), 7.750 (8H, d, J = 8.4, Ph), -2.868 (2H, bs, NH); MS (ESI): m/z = 753 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(4-methoxyphenyl)porphyrin, 71. Yield: 50%, 920 mg (dark-purple solid); mp (°C) > 300; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 420 (100), 517 (7.3), 554 (5.8), 592.5 (4.3), 649.5 (4.4); ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm = 8.864 (8H, s, CH), 8.244 (8H, d, J = 8.4, Ph), 7.290 (8H, d, J = 8.4, Ph), 4.102 (12H, s, OCH_3), -2.758 (2H, bs, NH); MS (ESI): m/z = 735 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(4-hydroxyphenyl)porphyrin, 72. Yield: 35%, 590 mg (dark-purple solid); mp (°C) > 300; UV-Vis (CH_3OH): λ_{max}, nm (relative absorbance, %) = 417.5 (100), 516 (5.5), 553.5 (4.5), 589.5 (2.8), 649.5 (3); ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 10.009 (4H, bs, OH), 8.862 (8H, s, CH), 7.993 (8H, d, J = 8, Ph), 7.209 (8H, d, J = 8, Ph), -2.884 (2H, bs, NH); MS (ESI): m/z = 679 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(4-carboxyphenyl)porphyrin, 73. Yield: 88%, 1.750 g (dark-purple solid); mp (°C) > 300; UV-Vis (CH_3OH): λ_{max}, nm (relative absorbance, %) = 414.5 (100), 511.5 (7.3), 545.5 (4.9), 587 (4.1), 644 (3.6); ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 8.863 (8H, s, CH), 8.393 (8H, d, J = 8, Ph), 8.349 (8H, d, J = 8, Ph), -2.938 (2H, bs, NH); MS (ESI): m/z = 791 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(3-chloro-4-methoxyphenyl)porphyrin, 74. Yield: 25%, 540 mg (dark-purple solid); mp (°C) > 300; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 421.5 (100), 516 (7.2), 552.5 (4.9), 589 (3.7), 647.5 (3.3); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.873 (8H, s, CH), 8.243 (4H, s, Ph), 8.052 (4H, d, J = 8, Ph), 7.313 (4H, d, J = 8, Ph), 4.201 (12H, s, OCH_3), -2.848 (2H, bs, NH); MS (ESI): m/z = 873 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(3,4-dimethoxyphenyl)porphyrin, 75. Yield: 30%, 650 mg (dark-purple solid); mp (ºC) > 300; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 424.5 (100), 518 (6.3), 556 (4.4), 591 (3), 649 (3.2); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.930 (8H, s, CH), 7.406-7.390 (8H, m, Ph), 6.898 (4H, s, Ph), 3.958 (24H, s, OCH_3), -2.826 (2H, bs, NH); MS (MALDI): m/z = 855 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(4-hydroxy-3-methoxyphenyl)porphyrin, 76. Yield: 23%, 450 mg (dark-purple solid); mp (ºC) > 300; UV-Vis (CH_3OH): λ_{max}, nm (relative absorbance, %) = 421 (100), 516 (6.7), 553.5 (5.2), 592.5 (3.3), 650 (3.5); ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 9.507 (4H, bs, OH), 8.914 (8H, s, CH), 7.778 (4H, s, Ph), 7.587 (4H, d, J = 8, Ph), 7.217 (4H, d, J = 8, Ph), 3.904 (12H, s, OCH_3), -2.859 (2H, bs, NH); MS (ESI): m/z = 799 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(3-hydroxy-4-methoxyphenyl)porphyrin, 77. Yield: 25%, 500 mg (dark-purple solid); mp (ºC) > 300; UV-Vis (CH_3OH): λ_{max}, nm (relative absorbance, %) = 420 (100), 515.5 (6.7), 552.5 (5), 590.5 (3.6), 648 (3.4); ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 9.453 (4H, bs, OH), 8.886 (8H, s, CH), 7.630 (4H, s, Ph), 7.573 (4H, d, J = 8, Ph), 7.340 (4H, d, J = 8, Ph), 4.059 (12H, s, OCH_3), -2.932 (4H, bs, NH); MS (ESI): m/z = 799 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(3,4-dihydroxyphenyl)porphyrin, 78. Yield: 33%, 620 mg (dark-purple solid); mp (ºC) > 300; UV-Vis (CH_3OH): λ_{max}, nm (relative absorbance, %) = 421 (100), 517 (6.2), 556 (4.9), 590.5 (3.3), 649.5 (3.3); ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 9.406 (4H, bs, OH), 9.361 (4H, bs, OH), 8.902 (8H, s, CH), 7.591 (4H, s, Ph), 7.452 (4H, d, J = 7.6, Ph), 7.167 (4H, d, J = 7.6, Ph), -2.905 (2H, bs, NH); MS (ESI): m/z = 743 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(3,5-dimethoxyphenyl)porphyrin, 79. Yield: 28%, 590 mg (dark-purple solid); mp (ºC) > 300; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 420 (100), 513.5 (6.8), 548 (3.1), 587 (3.1), 643.5 (2.2); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.930 (8H, s, CH), 7.398 (8H, s, Ph), 6.898 (4H, s, Ph), 3.958 (24H, s, OCH_3), -2.826 (2H, bs, NH); MS (ESI): m/z = 855 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(3,4,5-trimethoxyphenyl)porphyrin, 80. Yield: 39%, 950 mg (dark-purple solid); mp (ºC) > 300; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 422.5 (100), 515.5 (7.4), 552 (3.9), 589 (3.2), 646.5 (2.7); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.961 (8H, s, CH), 7.472 (8H, s, Ph), 4.185 (12H, s, OCH_3), 3.971 (24H, s, OCH_3), -2.775 (2H, bs, NH); MS (ESI): m/z = 975 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(4-hydroxy-3,5-dimethoxyphenyl)porphyrin, 81. Yield: 35%, 800 mg (dark-purple solid); mp (ºC) > 300; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 424 (100), 518 (7.8), 555 (5), 590.5 (3.9), 648.5 (3.5); ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 8.937 (8H, s, CH), 7.471 (8H, s, Ph), 5.888 (4H, bs, OH), 4.007 (24H, s, OCH_3), -2.753 (2H, bs, NH); MS (ESI): m/z = 919 ($[M+H]^+$).

A mixture of the selected aldehyde (2.5 mmol), 3-hydroxybenzaldehyde (7.5 mmol, 945 mg) and pyrrole (10 mmol, 0.72 ml) in propionic acid/nitrobenzene (7:3 v/v, 5 ml) was thoroughly mixed in an appropriate 10 ml thick-walled glass vial. This was tightly sealed with a Teflon cap and the reaction mixture was stirred and heated at 200 ºC for 5 minutes, under microwave irradiation, with an initial power setting of 250 W. After cooling to room temperature, the reaction product was purified through SiO_2 flash column chromatography (12x3 cm), using dichloromethane/ethyl acetate (1:1 v/v) as eluent. A broad fraction containing a mixture of porphyrins and other by-products was collected and evaporated under reduced pressure and the reddish-brown oil obtained was further purified through SiO_2 flash column chromatography (12x4 cm), using dichloromethane and dichloromethane/

ethyl acetate (firstly 9:1 v/v, followed by 7:3 v/v and, finally, 1:1 v/v) as eluents. The porphyrin-containing fraction was collected and evaporated under reduced pressure and the reddish-brown solid obtained was recrystallised in ethyl acetate/*n*-hexane, yielding the desired porphyrin as a dark-purple solid (**82-87**).

5,10,15-Tris(3-hydroxyphenyl)-20-(naphthalen-1-yl)porphyrin, 82. Yield: 10%, 170 mg (dark-purple solid)**;** mp (ºC) > 300; UV-Vis (CH_3OH): λ_{max}, nm (relative absorbance, %) = 276 (8.9), 415 (100), 512 (7.8), 545 (3.7), 587 (3.4), 643 (2.6); ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 9.866 (3H, bs, OH), 8.904 (4H, s, CH), 8.797 (2H, d, J = 4.4, CH), 8.512 (2H, d, J = 4.4, CH), 8.425 (1H, d, J = 8.4, Ph), 8.322 (1H, d, J = 7.6, Ph), 8.261 (1H, d, J = 8.4, Ph), 7.969 (1H, t, J = 7.6, Ph), 7.613-7.528 (11H, m, Ph), 7.301-7.248 (2H, m, Ph), 7.221 (2H, d, J = 8.4, Ph), -2.976 (2H, bs, NH); MS (ESI): m/z = 713 ($[M+H]^+$).

5,10,15-Tris(3-hydroxyphenyl)-20-(phenanthren-9-yl)porphyrin, 83. Yield: 8%, 160 mg (dark-purple solid); mp (ºC) > 300; UV-Vis (CH_3OH): λ_{max}, nm (relative absorbance, %) = 251 (20.4), 416 (100), 512 (6.9), 546 (3.5), 587 (3.3), 645 (2.7); ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 9.884 (3H, bs, OH), 9.170 (2H, d, J = 8.4, Ph), 8.915 (4H, s, CH), 8.794 (2H, d, J = 4.4, CH), 8.687 (1H, s, Ph), 8.665 (2H, d, J = 4.4, CH), 8.229 (1H, d, J = 7.6, Ph), 7.946 (1H, t, J = 7.6, Ph), 7.855 (1H, t, J = 7.6, Ph), 7.729-7.553 (11H, m, Ph), 7.303-7.257 (2H, m, Ph), 7.219 (2H, d, J = 8.4, Ph), -2.757 (2H, bs, NH); MS (ESI): m/z = 763 ($[M+H]^+$).

5,10,15-Tris(3-hydroxyphenyl)-20-(pyren-1-yl)porphyrin, 84. Yield: 9%, 180 mg (dark-purple solid); mp (ºC) > 300; UV-Vis (CH_3OH): λ_{max}, nm (relative absorbance, %) = 240 (23.6), 260 (26.2), 272 (14), 321 (10.5), 335 (11.9), 416 (100), 512 (7.6), 547 (4.1), 587 (3.7), 644 (3.1); ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 9.875 (3H, bs, OH), 8.930 (4H, s, CH), 8.850 (1H, d, J = 7.6, Ph), 8.781 (2H, d, J = 4.6, CH), 8.674 (1H, d, J = 7.6, Ph), 8.521 (1H, d, J = 8.4, Ph), 8.457 (1H, d, J = 8.4, Ph), 8.445 (2H, d, J = 4.6, CH), 8.210-8.188 (1H, m, Ph), 8.126 (1H, t, J = 7.6, Ph), 7.807-7.795 (1H, m, Ph), 7.641-7.534 (10H, m, Ph), 7.302-7.264 (2H, m, Ph), 7.210 (2H, d, J = 7.6, Ph), -2.718 (2H, bs, NH); MS (ESI): m/z = 787 ($[M+H]^+$).

5,10,15-Tris(3-hydroxyphenyl)-20-(2,6-dichlorophenyl)porphyrin, 85. Yield: 6%, 105 mg (dark-purple solid); mp (ºC) > 300; UV-Vis (CH_3OH): λ_{max}, nm (relative absorbance, %) = 415.5 (100), 511.5 (7.4), 545 (3.6), 586.5 (3.6), 643.5 (2.7); ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 9.892 (3H, bs, OH), 8.911-8.879 (6H, m, CH), 8.695 (2H, d, J = 4.4, CH), 8.016 (2H, d, J = 8, Ph), 7.926 (1H, t, J = 8, Ph), 7.638-7.577 (9H, m, Ph), 7.244 (3H, d, J = 7.6, Ph), -2.891 (2H, bs, NH); MS (ESI): m/z = 731 ($[M+H]^+$).

5,10,15-Tris(3-hydroxyphenyl)-20-(3,5-dichlorophenyl)porphyrin, 86. Yield: 11%, 195 mg (dark-purple solid); mp (ºC) > 300; UV-Vis (CH_3OH): λ_{max}, nm (relative absorbance, %) = 415.5 (100), 511 (6.7), 545 (3.3), 586.5 (3), 643 (2.3); ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 9.906 (3H, bs, OH), 8.910-8.884 (8H, m, CH), 8.330 (2H, s, Ph), 8.116 (1H, s, Ph), 7.616-7.579 (9H, m, Ph), 7.252 (3H, d, J = 7.6, Ph), -2.987 (2H, bs, NH); MS (ESI): m/z = 731 ($[M+H]^+$).

5,10,15-Tris(3-hydroxyphenyl)-20-(2,3,4,5,6-pentafluorophenyl)porphyrin, 87. Yield: 15%, 290 mg (dark-purple solid); mp (ºC) > 300; UV-Vis (CH_3OH): λ_{max}, nm (relative absorbance, %) = 412.5 (100), 509 (6.5), 542 (3.3), 584.5 (3.4), 643 (2.7); ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 9.914 (3H, bs, OH), 9.168 (2H, d, J = 4.4, CH), 8.965 (2H, d, J = 4.4, CH), 8.916 (4H, s, CH), 7.642-7.590 (8H, m, Ph), 7.258 (4H, d, J = 7.6, Ph), -2.976 (2H, bs, NH); MS (MALDI): m/z = 753 ($[M+H]^+$).

ii. Two-Step Methodology

A solution of the selected aldehyde (5 mmol) and boron trifluoride etherate (50 μl) in dichloromethane (500 ml) was stirred at room temperature for 10 minutes in a 1 l round-bottomed flask and de-oxygenated with a continuous flow of gaseous nitrogen, followed by the addition of pyrrole (5 mmol, 0.36 ml). The reaction mixture was left stirring at room temperature overnight (16 hours), under a gaseous nitrogen atmosphere and ambient-light exclusion conditions. Triethylamine (125 μl) was added, in order to neutralise the acid catalyst, complete the first reaction step and obtain the porphyrinogen, followed by activated manganese dioxide (30 molar equivalents/porphyrinogen, 37.5 mmol, 3.836 g) and the reaction mixture was left stirring at 40 ºC overnight (16 hours). After cooling to room temperature, the reaction product was filtered through a small column of SiO_2, in order to remove the excess oxidising agent and oxidation by-products. The resulting solution was evaporated under reduced pressure and the reddish-brown solid obtained was recrystallised in dichloromethane/methanol, yielding the desired porphyrin as a dark-purple solid (**57, 58** and **60**).

5,10,15,20-Tetraphenylporphyrin, 57. Yield: 32%, 245 mg (dark-purple solid); elemental analysis and UV-Vis, ^{1}H NMR and MS spectroscopic information identical to the one described in page 142.

5,10,15,20-*Tetrakis*(naphthalen-1-yl)porphyrin, 58. Yield: 20%, 210 mg (dark-purple solid); UV-Vis, ^{1}H NMR and MS spectroscopic information identical to the one described in page 143.

5,10,15,20-*Tetrakis*(pyren-1-yl)porphyrin, 60. Yield: 2%, 25 mg (dark-purple solid); UV-Vis, ^{1}H NMR and MS spectroscopic information identical to the one described in page 143.

C. Hydroporphyrins

1. Synthesis of *meso*-Tetraarylbacteriochlorins

A mixture of the selected porphyrin (25 mg), anhydrous potassium carbonate (100 molar equivalents) and *p*-toluenesulphonyl hydrazide (100 molar equivalents) in 1,4-dioxane (2 ml) was thoroughly mixed in an appropriate 10 ml thick-walled glass vial. This was tightly sealed with a Teflon cap and the reaction mixture was stirred and heated at 120 ºC for 25 minutes, under microwave irradiation, with an initial power setting of 100 W. After cooling to room temperature, the reaction product was washed with distilled water (50 ml) and neutralised by the addition of aqueous hydrochloric acid (37% m/v). The reddish-brown solid obtained was filtered under reduced pressure and thoroughly washed with distilled water, yielding the desired bacteriochlorin (major product) and the corresponding chlorin (minor product) as a pinkish-brown solid (**88-94**).

5,10,15,20-Tetraphenylbacteriochlorin, 88. Yield: 96%, 24 mg (pinkish-brown solid, bacteriochlorin/chlorin ratio = 75/25); mp (ºC) > 250; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 354 (83.8), 376 (100), 490 (8.5), 520 (40.6), 677 (6.3), 740 (75.2); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.919 (4H, s, CH), 7.803 (8H, d, J = 6, Ph), 7.684-7.604 (12H, m, Ph), 3.965 (8H, s, CH), -1.318 (2H, bs, NH); MS (ESI): m/z = 619 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(2,6-dichlorophenyl)bacteriochlorin, 89. Yield: 92%, 23 mg (pinkish-brown solid, bacteriochlorin/chlorin ratio = 85/15); mp (ºC) > 250; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 351 (100), 363 (79.4), 377 (96.6), 484 (10.6), 515 (39.6), 681 (5.3), 746 (66.9); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.884 (4H, s, CH), 7.549-7.433 (12H, m, Ph), 3.931 (8H, s, CH), -1.254 (2H, bs, NH); MS (ESI): m/z = 894 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(3-methoxyphenyl)bacteriochlorin, 90. Yield: 95%, 24 mg (pinkish-brown solid, bacteriochlorin/chlorin ratio = 85/15); mp (ºC) > 250; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 355 (83.1), 377 (100), 489.5 (7), 520 (40.9), 677 (5.9), 740 (79.6); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.988 (4H, s, CH), 7.532 (4H, t, J = 8, Ph), 7.398-7.362 (8H, m, Ph), 7.151 (4H, dd, J = 8, 1.6, Ph), 4.007 (8H, s, CH), 3.900 (12H, s, OCH_3), -1.372 (2H, bs, NH); MS (ESI): m/z = 739 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(3-hydroxyphenyl)bacteriochlorin, 91. Yield: 93%, 23 mg (pinkish-brown solid, bacteriochlorin/chlorin ratio = 80/20); mp (ºC) > 250; UV-Vis (CH_3OH): λ_{max}, nm (relative absorbance, %) = 351 (89.8), 371 (100), 485 (11.5), 516 (45.5), 671 (6.2), 734 (77.9); ^{1}H NMR (400 MHz, CD_3OD): δ, ppm = 7.965 (4H, s, CH), 7.484-7.379 (8H, m, Ph), 7.211-7.179 (8H, m, Ph), 3.951 (8H, s, CH); MS (ESI): m/z = 683 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(4-methoxyphenyl)bacteriochlorin, 92. Yield: 95%, 24 mg (pinkish-brown solid, bacteriochlorin/chlorin ratio = 65/35); mp (ºC) > 250; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 357 (80.6), 378 (100), 495 (7.7), 525 (36.8), 678 (6.1), 741 (78.7); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.940 (4H, s, CH), 7.702 (8H, d, J = 8.4, Ph), 7.152 (8H, d, J = 8.4, Ph), 3.994 (12H, s, OCH_3), 3.969 (8H, s, CH), -1.340 (2H, bs, NH); MS (ESI): m/z = 739 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(4-bromophenyl)bacteriochlorin, 93. Yield: 92%, 23 mg (pinkish-brown solid, bacteriochlorin/chlorin ratio = 65/35); mp (ºC) > 250; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 356 (88.6), 378 (100), 490 (8.8), 521 (41.6), 679 (5.6), 743 (75.8); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.925 (4H, s, CH), 7.761 (8H, d, J = 8, Ph), 7.655 (8H, d, J = 8, Ph), 3.949 (8H, s, CH), -1.420 (2H, bs, NH); MS (ESI): m/z = 934 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(4-*t*-butylphenyl)bacteriochlorin, 94. Yield: 90%, 23 mg (pinkish-brown solid, bacteriochlorin/chlorin/porphyrin ratio = 45/30/25); mp (ºC) > 250; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 356 (85.4), 376 (100), 493 (9.4), 522 (39.7), 676 (6.1), 739 (70.2); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.918 (4H, s, CH), 7.711 (8H, d, J = 8, Ph), 7.607 (8H, d, J = 8, Ph), 3.967 (8H, s, CH), 1.505 (36H, s, CH_3), -1.304 (2H, bs, NH); MS (ESI): m/z = 843 ($[M+H]^+$).

2. Synthesis of *meso*-Tetraarylchlorins

A mixture of the selected bacteriochlorin (23-24 mg) and activated manganese dioxide (50 molar equivalents) in 1,4-dioxane (2 ml) was thoroughly mixed in an appropriate 10 ml thick-walled glass vial. This was tightly sealed with a Teflon cap and the reaction mixture was stirred and heated at 90 ºC for 3 minutes, under microwave irradiation, with an initial power setting of 100 W. After cooling to room temperature, the reaction product was washed with dichloromethane or ethyl acetate (50 ml) and filtered through a small column of SiO_2, in order to remove the excess oxidising agent and oxidation by-products. The resulting solution was evaporated under reduced pressure, yielding the desired chlorin (major product) and the corresponding porphyrin (minor product) as a dark-purple solid (**95-101**).

5,10,15,20-Tetraphenylchlorin, 95. Yield: 92%, 23 mg (dark-purple solid, chlorin/porphyrin ratio = 80/20); mp (ºC) > 250; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 417.5 (100), 517.5 (8.6), 545.5 (6), 596 (4.2), 651 (13.6); ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm = 8.564 (2H, d, J = 4.9, CH), 8.416 (2H, s, CH), 8.172 (2H, d, J = 4.9, CH), 8.104 (4H, dd, J = 7.2, 2.4, Ph), 7.887-7.856 (4H, m, Ph), 7.714-7.643 (12H, m, Ph), 4.156 (4H, s, CH), -1.446 (2H, bs, NH); MS (ESI): m/z = 617 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(2,6-dichlorophenyl)chlorin, 96. Yield: 85%, 21 mg (dark-purple solid, chlorin/porphyrin ratio = 75/25); mp (ºC) > 250; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 418 (100), 513.5 (10.2), 540 (3.8), 601 (3.9), 657.5 (16.4); ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm = 8.459 (2H, d, J = 4.8, CH), 8.268 (2H, s, CH), 8.085 (2H, d, J = 4.8, CH), 7.799-7.544 (12, m, Ph), 4.094 (4H, s, CH), -1.314 (2H, bs, NH); MS (ESI): m/z = 892 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(3-methoxyphenyl)chlorin, 97. Yield: 93%, 23 mg (dark-purple solid, chlorin/porphyrin ratio = 90/10); mp (ºC) > 250; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) 417.5 (100), 516.5 (10.1), 543.5 (6.8), 596 (4.7), 650 (18.2); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.615 (2H, d, J = 4.6, CH), 8.460 (2H, s, CH), 8.227 (2H, d, J = 4.6, CH), 7.715-7.674 (4H, m, Ph), 7.594-7.555 (4H, m, Ph), 7.460-7.420 (4H, m, Ph), 7.275-7.200 (4H, m, Ph), 4.193 (4H, s, CH), 3.939 (12H, s, OCH_3), -1.494 (2H, bs, NH); MS (ESI): m/z = 737 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(3-hydroxyphenyl)chlorin, 98. Yield: 88%, 22 mg (dark-purple solid, chlorin/porphyrin ratio = 65/35); mp (ºC) > 250; UV-Vis (CH_3OH): λ_{max}, nm (relative absorbance, %) = 414.5 (100), 514 (10.9), 542.5 (7), 592.5 (5.1), 649 (11.1); ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 8.632 (2H, d, J = 4.8, CH), 8.368 (2H, s, CH), 8.239 (2H, d, J = 4.8, CH), 7.540-7.468 (6H, m, Ph), 7.295-7.235 (10H, m, Ph), 4.159 (4H, s, CH), -1.650 (2H, bs, NH); MS (ESI): m/z = 681 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(4-methoxyphenyl)chlorin, 99. Yield: 90%, 22 mg (dark-purple solid, chlorin/porphyrin ratio = 90/10); mp (ºC) > 250; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 420.5 (100), 521 (9.1), 550 (7.1), 597.5 (4.2), 650.5 (14.3); ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm = 8.582 (2H, d, J = 4.8, CH), 8.438 (2H, s, CH), 8.185 (2H, d, J = 4.8, CH), 8.009 (4H, d, J = 8.5, Ph), 7.755 (4H, d, J = 8.5, Ph), 7.211 (4H, d, J = 8.3, Ph), 7.191 (4H, d, J = 8.3, Ph), 4.143 (4H, s, CH), 4.050 (12H, s, OCH_3), -1.429 (2H, bs, NH); MS (ESI): m/z = 737 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(4-bromophenyl)chlorin, 100. Yield: 88%, 22 mg (dark-purple solid, chlorin/porphyrin ratio = 85/15); mp (ºC) > 250; (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 418 (100), 518 (11.6), 544.5 (6.6), 597 (4.5), 651 (15.5); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.553 (2H, d, J = 4.8, CH), 8.389 (2H, s, CH), 8.179 (2H, d, J = 4.8, CH), 7.938 (4H, d, J = 8, Ph), 7.814 (8H, d, J = 8, Ph), 7.721 (4H, d, J = 8, Ph), 4.138 (4H, s, CH), -1.525 (2H, bs, NH); MS (ESI): m/z = 933 ($[M+H]^+$).

5,10,15,20-*Tetrakis*(4-*t*-butylphenyl)chlorin, 101. Yield: 86%, 21 mg (dark-purple solid, chlorin/porphyrin ratio = 70/30); mp (ºC) > 250; UV-Vis (CH_2Cl_2): λ_{max}, nm (relative absorbance, %) = 419.5 (100), 520.5 (10.4), 548 (7.5), 596 (4.9), 650 (12.3); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.587 (2H, d, J = 4.8, CH), 8.434 (2H, s, CH), 8.167 (2H, d, J = 4.8, CH), 7.764 (8H, d, J = 8.4, Ph), 7.672 (8H, d, J = 8.4, Ph), 4.148 (4H, s, CH), 1.562 (18H, s, CH_3), 1.536 (18H, s, CH_3), -1.406 (2H, bs, NH); MS (ESI): m/z = 841 ($[M+H]^+$).

D. Hantzsch 1,4-Dihydropyridines

1. Multicomponent Synthesis of Hantzsch 1,4-Dihydropyridines

A mixture of the selected aldehyde (10 mmol), methyl acetoacetate (50 mmol, 5.45 ml) and aqueous ammonium hydroxide (25% m/v, 40 mmol, 6.23 ml) was thoroughly mixed in an appropriate 35 ml thick-walled glass vial. This was tightly sealed with a Teflon cap and the reaction mixture was stirred and heated at 140 ºC for 10 minutes, under microwave irradiation, with an initial power setting of 150 W. After cooling to room temperature a yellow solid precipitated. This was filtered under reduced pressure, thoroughly washed with distilled water and recrystallised in aqueous ethanol, yielding the desired Hantzsch 1,4-dihydropyridine as a yellowish solid (**102-125**).

Dimethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate, 102. Yield: 58%, 1.750 g (pale-yellow solid); mp (°C): 199-200 (Lit. 198-199);[13] ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.257 (2H, d, J = 7.2, Ph), 7.207 (2H, t, J = 7.2, Ph), 7.124 (1H, t, J = 7.2, Ph), 5.832 (1H, bs, NH), 5.006 (1H, s, CH), 3.639 (6H, s, OCH_3), 2.319 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.091, 147.423, 144.292, 128.039, 127.622, 126.210, 103.862, 50.987, 39.302, 19.529; GC-MS (EI): m/z (t_R, min) = 301 (13.55) (M^+).

Dimethyl 2,6-dimethyl-4-(naphthalen-1-yl)-1,4-dihydropyridine-3,5-dicarboxylate, 103. Yield: 30%, 1.050 g (pale-yellow solid); mp (°C): 219-221; $C_{21}H_{21}NO_4$: calculated (%) = C 71.78, H 6.02, N 3.99; found (%) = C 72.05, H 6.26, N 4.08; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.568 (1H, d, J = 8, Ph), 7.755 (1H, d, J = 8, Ph), 7.637 (1H, d, J = 8, Ph), 7.525-7.484 (2H, m, Ph), 7.425-7.332 (2H, m, Ph), 5.811 (1H, s, CH), 5.761 (1H, bs, NH), 3.400 (6H, s, OCH_3), 2.321 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.273, 146.763, 143.496, 133.360, 130.929, 128.088, 127.180, 127.031, 125.850, 125.274, 125.197, 125.115, 105.630, 50.744, 34.559, 19.542; GC-MS (EI): m/z (t_R, min) = 351 (17.65) (M^+).

Dimethyl 4-(2-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, 104. Yield: 46%, 1.750 g (pale-yellow solid); mp (°C): 167-168 (Lit. 163-165);[13] ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.429 (1H, d, J = 7.6, Ph), 7.377 (1H, dd, J = 7.6, 1.2, Ph), 7.173 (1H, t, J = 7.6, Ph), 6.949 (1H, t, J = 7.6, Ph), 5.693 (1H, bs, NH), 5.354 (1H, s, CH), 3.626 (6H, s, OCH_3), 2.312 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.009, 147.880, 143.929, 132.649, 131.229, 127.708, 127.574, 122.659, 104.328, 50.810, 39.385, 19.444; GC-MS (EI): m/z (t_R, min) = 379 (13.76) (M^+).

Dimethyl 4-(2-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, 105. Yield: 44%, 1.480 g (pale-yellow solid); mp (°C): 190-191 (Lit. 192-193);[13] 1H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.366 (1H, dd, J = 7.6, 1.2, Ph), 7.235 (1H, d, J = 7.6, Ph), 7.127 (1H, t, J = 7.6, Ph), 7.036 (1H, t, J = 7.6, Ph), 5.622 (1H, bs, NH), 5.402 (1H, s, CH), 3.609 (6H, s, OCH_3), 2.317 (6H, s, CH_3); 13C NMR (100 MHz, $CDCl_3$): δ, ppm = 167.958, 145.878, 143.980, 132.420, 131.206, 129.277, 127.309, 126.910, 103.993, 50.812, 37.219, 19.437; GC-MS (EI): m/z (t_R, min) = 335 (13.21) (M^+).

Dimethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, 106. Yield: 66%, 2.270 g (yellow solid); mp (°C): 206-208 (Lit. 210-211);[13] ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.096 (1H, s, Ph), 8.002 (1H, d, J = 8, Ph), 7.629 (1H, d, J = 8, Ph), 7.376 (1H, t, J = 8, Ph), 5.810 (1H, bs, NH), 5.107 (1H, s, CH), 3.650 (6H, s, OCH_3), 2.369 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 167.506, 149.550, 148.416, 144.910, 134.200, 128.733, 122.755, 121.433, 103.203, 51.158, 39.662, 19.671; GC-MS (EI): m/z (t_R, min) = 346 (15.22) (M^+).

Dimethyl 4-(3-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, 107. Yield: 60%, 2.000 g (pale-yellow solid); mp (°C): 172-173 (Lit. 175-176);[13] ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.137 (1H, t, J = 8, Ph), 6.866 (1H, d, J = 8, Ph), 6.826 (1H, s, Ph), 6.687 (1H, dd, J = 8, 2, Ph), 5.644 (1H, bs, NH), 5.001 (1H, s, CH), 3.765 (3H, s, OCH_3), 3.654 (6H, s, OCH_3), 2.332 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 167.989, 159.375, 148.950, 144.260, 128.897, 120.146, 113.931, 110.930, 103.750, 55.076, 51.004, 39.208, 19.604; GC-MS (EI): m/z (t_R, min) = 331 (13.78) (M^+).

Dimethyl 4-(3-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, 108. Yield: 48%, 1.530 g (yellow solid); mp (°C): 223-225 (Lit. 227-229);[13] ^{1}H NMR (400 MHz, $CDCl_3$/$(CD_3)_2SO$): δ, ppm = 8.701 (1H, bs, OH), 8.504 (1H, bs, NH), 6.904 (1H, t, J = 8, Ph), 6.550 (2H, d, J =8, Ph), 6.448 (1H, d, J = 8, Ph), 4.801 (1H, s, CH), 3.596 (6H, s, OCH_3), 2.268 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$/$(CD_3)_2SO$): δ, ppm = 166.852, 156.714, 148.700, 144.851, 127.956, 117.314, 113.821, 112.455, 101.511, 49.861, 37.901, 17.918; GC-MS (EI): m/z (t_R, min) = 317 (14.17) (M^+).

Dimethyl 4-(4-*t*-butylphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, 109. Yield: 70%, 2.500 g (pale-yellow solid); mp (°C): 215-217; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.213 (2H, d, J = 8.4, Ph), 7.157 (2H, d, J = 8.4, Ph), 5.612 (1H, bs, NH), 4.987 (1H, s, CH), 3.655 (6H, s, OCH_3), 2.335 (6H, s, CH_3), 1.271 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.132, 148.675, 144.199, 144.050, 127.077, 124.923, 104.042, 50.989, 38.567, 34.305, 31.380, 19.621; GC-MS (EI): m/z (t_R, min) = 357 (13.68) (M^+).

Dimethyl 2,6-dimethyl-4-*p*-tolyl-1,4-dihydropyridine-3,5-dicarboxylate, 110. Yield: 66%, 2.080 g (pale-yellow solid); mp (°C): 175-177 (Lit. 174-175);[13] ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.149 (2H, d, J = 8, Ph), 7.018 (2H, d, J = 8, Ph), 5.744 (1H, bs, NH), 4.965 (1H, s, CH), 3.640 (6H, s, OCH_3), 2.320 (6H, s, CH_3), 2.272 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.090, 144.545, 144.143, 135.651, 128.775, 127.485, 104.005, 50.975, 38.801, 21.052, 19.575; GC-MS (EI): m/z (t_R, min) = 315 (14.09) (M^+).

Dimethyl 4-(4-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, 111. Yield: 65%, 2.450 g (pale-yellow solid); mp (°C): 195-197 (Lit. 192);[13] ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.325 (2H, d, J = 8.4, Ph), 7.136 (2H, d, J = 8.4, Ph), 5.732 (1H, bs, NH), 4.958 (1H, s, CH), 3.639 (6H, s, OCH_3), 2.322 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 167.833, 146.508, 144.364, 131.093, 129.505, 120.001, 103.573, 51.044, 39.052, 19.574; GC-MS (EI): m/z (t_R, min) = 379 (15.88) (M^+).

Dimethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, 112. Yield: 71%, 2.380 g (pale-yellow solid); mp (°C): 191-193 (Lit. 194-196);[13] $C_{17}H_{18}NO_4Cl$: calculated (%) = C 60.81, H 5.40, N 4.17; found (%) = C 60.52, H 4.99, N 3.93; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.195 (2H, d, J = 8.8, Ph), 7.167 (2H, d, J = 8.8, Ph), 5.772 (1H, bs, NH), 4.970 (1H, s, CH), 3.639 (6H, s, OCH_3), 2.325 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 167.851, 146.006, 144.332, 131.830, 129.091, 128.144, 103.660, 51.038, 38.972, 19.578; GC-MS (EI): m/z (t_R, min) = 335 (14.91) (M^+).

Dimethyl 4-(4-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, 113. Yield: 65%, 2.080 g (pale-yellow solid); mp (°C): 174-175 (Lit. 171);[13] $C_{17}H_{18}NO_4F$: calculated (%) = C 63.94, H 5.68, N 4.39; found (%) = C 63.78, H 5.37, N 4.17; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.213 (2H, dd, J = 8.4, 5.2, Ph), 6.881 (2H, t, J = 8.4, Ph), 5.903 (1H, bs, NH), 4.979 (1H, s, CH), 3.641 (6H, s, OCH_3), 2.318 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.004, 161.417 (C, d, J = 242.3), 144.293, 143.370 (C, d, J = 3), 129.114 (2xCH, d, J = 7.8) 114.712 (2xCH, d, J = 20.9), 103.857, 51.018, 38.756, 19.510; GC-MS (EI): m/z (t_R, min) = 319 (13.53) (M^+).

Dimethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, 114. Yield: 65%, 2.270 g (yellow solid); mp (°C): 200-202 (Lit. 198-199);[13] ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.083 (2H, d, J = 8.8, Ph), 7.429 (2H, d, J = 8.8, Ph), 5.712 (1H, bs, NH), 5.105 (1H, s, CH), 3.644 (6H, s, OCH_3), 2.361 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 167.450, 154.713, 146.472, 144.828, 128.617, 123.477, 103.104, 51.166, 39.881, 19.700; GC-MS (EI): m/z (t_R, min) = 346 (17.75) (M^+).

Dimethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, 115. Yield: 63%, 2.100 g (pale-yellow solid); mp (°C): 183-185 (Lit. 186-188);[14] ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.175 (2H, d, J = 8.6, Ph), 6.752 (2H, d, J = 8.6, Ph), 5.657 (1H, bs, NH), 4.942 (1H, s, CH), 3.750 (3H, s, OCH_3), 3.644 (6H, s, OCH_3), 2.326 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.185, 158.065, 143.978, 140.028, 128.702, 113.501, 104.264, 55.231, 51.066, 38.526, 19.686; GC-MS (EI): m/z (t_R, min) = 331 (15.01) (M^+).

Dimethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, 116. Yield: 57%, 1.800 g (yellow solid); mp (ºC): 232-235 (Lit. 230-232);[15] ^{1}H NMR (400 MHz, $CDCl_3$/$(CD_3)_2SO$): δ, ppm = 8.612 (1H, bs, OH), 8.397 (1H, bs, NH), 6.897 (1H, d, J = 8.4, Ph), 6.529 (2H, d, J = 8.4, Ph), 4.723 (1H, s, CH), 3.573 (6H, s, OCH_3), 2.249 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$/$(CD_3)_2SO$): δ, ppm = 166.971, 155.141, 144.499, 138.288, 127.541, 114.249, 102.067, 49.860, 37.261, 17.914; GC-MS (EI): m/z (t_R, min) = 317 (14.02) (M^+).

Dimethyl 4-(4-acetamidophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, 117. Yield: 58%, 2.060 g (pale-yellow solid); mp (ºC): 259-261; ^{1}H NMR (400 MHz, $CDCl_3$/$(CD_3)_2SO$): δ, ppm = 9.673 (1H, bs, NH), 8.640 (1H, bs, $NHCOCH_3$), 7.363 (2H, d, J = 8.4, Ph), 7.054 (2H, d, J = 8.4, Ph), 4.831 (1H, s, CH), 3.563 (6H, s, OCH_3), 2.267 (6H, s, CH_3), 2.015 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$/$(CD_3)_2SO$): δ, ppm = 167.964, 167.496, 145.366, 142.947, 137.086, 127.250, 119.026, 101.876, 50.420, 38.084, 23.844, 18.269; GC-MS (EI): m/z (t_R, min) = 358 (21.32) (M^+).

Dimethyl 4-(4-carboxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, 118. Yield: 72%, 2.475 g (pale-yellow solid); mp (ºC): 238-240; ^{1}H NMR (400 MHz, $CDCl_3$/$(CD_3)_2SO$): δ, ppm = 8.702 (1H, bs, NH), 7.805 (2H, d, J = 8, Ph), 7.267 (2H, d, J = 8, Ph), 4.961 (1H, s, CH), 3.575 (6H, s, OCH_3), 2.294 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$/$(CD_3)_2SO$): δ, ppm = 167.496, 167.335, 152.819, 146.026, 137.086, 129.168, 128.509, 127.234, 101.390, 50.500, 39.052, 18.348; MS (MALDI): m/z = 344 ([M-H]$^+$).

Dimethyl 4-(2,4-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, 119. Yield: 53%, 1.950 g (pale-yellow solid); mp (ºC): 191-193 (Lit. 188-189);[13] ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.295 (1H, d, J = 8.4, Ph), 7.254 (1H, s, Ph), 7.108 (1H, dd, J = 8.4, 1.6, Ph), 5.627 (1H, bs, NH), 5.352 (1H, s, CH), 3.608 (6H, s, OCH_3), 2.315 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 167.727, 144.561, 144.189, 133.165, 132.129, 132.109, 128.914, 127.235, 103.638, 50.867, 37.051, 19.473; GC-MS (EI): m/z (t_R, min) = 369 (14.31) (M^+).

Dimethyl 4-(3,4-dimethoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, 120. Yield: 62%, 2.250 g (pale-yellow solid); mp (ºC): 157-159; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 6.870 (1H, s, Ph), 6.772 (1H, d, J = 8.4, Ph), 6.723 (1H, d, J = 8.4, Ph), 5.741 (1H, bs, NH), 4.961 (1H, s, CH), 3.834 (3H, s, OCH_3), 3.816 (3H, s, OCH_3), 3.660 (6H, s, OCH_3), 2.333 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.103, 148.365, 147.444, 143.978, 140.301, 119.452, 111.485, 110.955, 103.966, 55.786, 50.987, 38.764, 19.570; GC-MS (EI): m/z (t_R, min) = 361 (14.46) (M^+).

Dimethyl 4-(4-hydroxy-3-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, 121. Yield: 47%, 1.640 g (yellow solid); mp (ºC): 219-220; ^{1}H NMR (400 MHz, $CDCl_3$/$(CD_3)_2SO$): δ, ppm = 8.554 (1H, bs, OH), 8.405 (1H, bs, NH), 6.725 (1H, s, Ph), 6.612 (1H, d, J = 8, Ph), 6.539 (1H, dd, J = 8, 1.2, Ph), 4.801 (1H, s, CH), 3.746 (3H, s, OCH_3), 3.587 (6H, s, OCH_3), 2.268 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$/$(CD_3)_2SO$): δ, ppm = 167.677, 146.762, 145.129, 144.621, 139.405, 119.405, 115.007, 111.405, 102.143, 55.466, 50.384, 38.029, 18.289; GC-MS (EI): m/z (t_R, min) = 347 (16.22) (M^+).

Dimethyl 4-(3-hydroxy-4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, 122. Yield: 47%, 1.630 g (yellow solid); mp (ºC): 178-180; ^{1}H NMR (400 MHz, $CDCl_3$/$(CD_3)_2SO$): δ, ppm = 8.670 (1H, bs, OH), 8.575 (1H, bs, NH), 6.683 (1H, d, J = 8, Ph), 6.619 (1H, s, Ph), 6.531 (1H, dd, J = 8, 1.4, Ph), 4.780 (1H, s, CH), 3.716 (3H, s, OCH_3), 3.570 (6H, s, OCH_3), 2.255 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$/$(CD_3)_2SO$): δ, ppm = 167.550, 145.918, 145.787, 145.105, 140.783, 117.545, 114.697, 111.647, 101.858, 55.564, 50.424, 37.628, 18.219; GC-MS (EI): m/z (t_R, min) = 347 (16.68) (M^+).

Dimethyl 4-(3,5-dimethoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, 123. Yield: 63%, 2.280 g (pale-yellow solid); mp (ºC): 147-149; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 6.453 (2H, s, Ph), 6.268 (1H, s, Ph), 5.823 (1H, bs, NH), 4.986 (1H, s, CH), 3.746 (6H, s, OCH_3), 3.664 (6H, s, OCH_3), 2.315 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.014, 160.434, 149.714, 144.430, 106.032, 103.510, 97.689, 55.168, 51.011, 39.338, 19.551; GC-MS (EI): m/z (t_R, min) = 361 (16.10) (M^+).

Dimethyl 4-(3,4,5-trimethoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, 124. Yield: 48%, 1.860 g (pale-yellow solid); mp (ºC): 178-180; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 6.498 (2H, s, Ph), 5.811 (1H, bs, NH), 4.989 (1H, s, CH), 3.796 (9H, s, OCH_3), 3.680 (6H, s, OCH_3), 2.342 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.074, 152.792, 144.200, 142.979, 136.571, 104.794, 103.696, 60.736, 56.016, 51.029, 39.394, 19.539; GC-MS (EI): m/z (t_R, min) = 391 (16.85) (M^+).

Dimethyl 4-(4-hydroxy-3,5-dimethoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, 125. Yield: 42%, 1.600 g (yellow solid); mp (ºC): 222-223; ^{1}H NMR (400 MHz, $CDCl_3$/$(CD_3)_2SO$): δ, ppm = 8.708 (1H, bs, OH), 7.972 (1H, bs, NH), 6.370 (2H, s, Ph), 4.805 (1H, s, CH), 3.694 (6H, s, OCH_3), 3.583 (6H, s, OCH_3), 2.266 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$/$(CD_3)_2SO$): δ, ppm = 167.504, 147.482, 145.190, 138.203, 134.058, 104.583, 101.767, 55.821, 50.422, 38.230, 18.142; GC-MS (EI): m/z (t_R, min) = 377 (18.03) (M^+).

2. Oxidation of Hantzsch 1,4-Dihydropyridines

i. Heterogeneous Oxidative Aromatisation

A mixture of the selected Hantzsch 1,4-dihydropyridine (1 mmol) and activated manganese dioxide (10 mmol, 1.023 g) in dichloromethane (3 ml) was thoroughly mixed in an appropriate 10 ml thick-walled glass vial. This was tightly sealed with a Teflon cap and the reaction mixture was stirred and heated at 100 ºC for 5 minutes, under microwave irradiation, with an initial power setting of 100 W. After cooling to room temperature, the reaction product was washed with ethyl acetate and filtered through a small column of SiO_2, in order to remove the excess oxidising agent and oxidation by-products. The resulting solution was evaporated under reduced pressure and the yellow solid obtained was recrystallised in diethyl ether or ethyl acetate/*n*-hexane, yielding the desired Hantzsch pyridine as a white or yellowish solid (**126**, **127**, **130-139**, **141** and **144-146**). Regarding pyridines **128**, **129** and **143**, the isolation process afforded a pale-yellow oil.

ii. Homogeneous Oxidative Aromatisation

A mixture of the selected Hantzsch 1,4-dihydropyridine (1 mmol) and potassium peroxydisulphate (1.2 mmol, 324 mg) in acetonitrile/distilled water (3:2 v/v, 5 ml) was thoroughly mixed in an appropriate 10 ml thick-walled glass vial. This was tightly sealed with a Teflon cap and the reaction mixture was stirred and heated at 100 ºC for 5 minutes, under microwave irradiation, with an initial power setting of 80 W. After cooling to room temperature, the reaction product was washed with brine (50 ml) and a yellow solid precipitated. This was filtered under reduced pressure and thoroughly washed with distilled water, yielding the desired Hantzsch pyridine as a pale-yellow solid (**140** and **142**).

Dimethyl 2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate, 126. Yield: 95%, 285 mg (white solid); mp (ºC): 137-138 (Lit. 135-136);[16] ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.375-7.363 (3H, m, Ph), 7.247-7.229 (2H, m, Ph), 3.521 (6H, s, OCH_3), 2.595 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.406, 155.575, 146.221, 136.466, 128.531, 128.220, 127.782, 126.769, 52.164, 22.969; GC-MS (EI): m/z (t_R, min) = 299 (12.18) (M^+).

Dimethyl 2,6-dimethyl-4-(naphthalen-1-yl)pyridine-3,5-dicarboxylate, 127. Yield: 92%, 320 mg (pale-yellow solid); mp (°C): 106-107; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.848 (2H, d, J = 8, Ph), 7.491-7.402 (4H, m, Ph), 7.273 (1H, d, J = 6.8, Ph), 3.215 (6H, s, OCH_3), 2.656 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 167.989, 156.004, 145.572, 133.776, 133.025, 130.887, 128.837, 127.983, 127.591, 126.298, 126.249, 126.089, 125.754, 124.711, 51.923, 23.242; GC-MS (EI): m/z (t_R, min) = 349 (14.09) (M^+).

Dimethyl 4-(2-bromophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate, 128. Yield: 90%, 340 mg (pale-yellow oil); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.593 (1H, d, J = 7.6, Ph), 7.322 (1H, t, J = 7.6, Ph), 7.213 (1H, t, J = 7.6, Ph), 7.166 (1H, d, J = 7.6, Ph), 3.520 (6H, s, OCH_3), 2.640 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 167.347, 156.497, 146.043, 137.435, 132.234, 130.036, 129.733, 126.629, 126.183, 122.193, 52.013, 23.366; GC-MS (EI): m/z (t_R, min) = 377 (11.98) (M^+).

Dimethyl 4-(2-chlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate, 129. Yield: 90%, 300 mg (pale-yellow oil); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.413 (1H, d, J = 7.6, Ph), 7.322-7.255 (2H, m, Ph), 7.166 (1H, d, J = 7.6, Ph), 3.524 (6H, s, OCH_3), 2.642 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 167.520, 156.560, 144.675, 135.467, 132.617, 130.032, 129.744, 129.130, 126.746, 126.196, 52.099, 23.398; GC-MS (EI): m/z (t_R, min) = 333 (11.67) (M^+).

Dimethyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate, 130. Yield: 91%, 315 mg (yellow solid); mp (°C): 112-113; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.273-8.245 (1H, m, Ph), 8.162 (1H, s, Ph), 7.589 (2H, d, J = 4.8, Ph), 3.589 (6H, s, OCH_3), 2.625 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 167.726, 156.330, 147.951, 143.708, 138.048, 134.096, 129.310, 126.396, 123.518, 123.088, 52.417, 23.194; GC-MS (EI): m/z (t_R, min) = 344 (12.75) (M^+).

Dimethyl 4-(3-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate, 131. Yield: 92%, 300 mg (white solid); mp (°C): 64-65; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.282 (1H, t, J = 7.6, Ph), 6.907 (1H, dd, J = 7.6, 1.8, Ph), 6.818 (1H, d, J = 7.6, Ph), 6.790 (1H, s, Ph), 3.792 (3H, s, OCH_3), 3.567 (6H, s, OCH_3), 2.589 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.460, 159.357, 155.568, 145.973, 137.712, 129.398, 126.699, 120.258, 114.703, 113.032, 55.288, 52.257, 22.962; GC-MS (EI): m/z (t_R, min) = 329 (11.97) (M^+).

Dimethyl 4-(3-hydroxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate, 132. Yield: 90%, 285 mg (pale-yellow solid); mp (°C): 179-181; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.526 (1H, bs, OH), 7.364 (1H, t, J = 7.6, Ph), 6.974 (1H, d, J = 7.6, Ph), 6.814 (1H, s, Ph), 6.772 (1H, d, J = 7.6, Ph), 3.759 (6H, s, OCH_3), 2.730 (6H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 167.199, 156.972, 154.253, 145.129, 136.899, 128.457, 125.891, 117.674, 115.160, 114.187, 51.344, 22.093; GC-MS (EI): m/z (t_R, min) = 315 (15.35) (M^+).

Dimethyl 4-(4-*t*-butylphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate, 133. Yield: 92%, 325 mg (white solid); mp (°C): 127-128; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.382 (2H, d, J = 8.4, Ph), 7.160 (2H, d, J = 8.4, Ph), 3.518 (6H, s, OCH_3), 2.584 (6H, s, CH_3), 1.322 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.605, 155.449, 151.532, 146.317, 133.421, 127.535, 126.901, 125.101, 52.102, 34.669, 31.235, 22.934; GC-MS (EI): m/z (t_R, min) = 355 (12.38) (M^+).

Dimethyl 2,6-dimethyl-4-*p*-tolylpyridine-3,5-dicarboxylate, 134. Yield: 95%, 295 mg (white solid); mp (°C): 89-90 (Lit. 90-91);[16] ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.178 (2H, d, J = 8, Ph), 7.125 (2H, d, J = 8, Ph), 3.563 (6H, s, OCH_3), 2.582 (6H, s, CH_3), 2.367 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.588, 155.393, 146.228, 138.398, 133.375, 129.002, 127.631, 126.879, 52.219, 22.961, 21.312; GC-MS (EI): m/z (t_R, min) = 313 (12.54) (M^+).

Dimethyl 4-(4-bromophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate, 135. Yield: 95%, 355 mg (white solid); mp (°C): 160-161; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.517 (2H, d, J = 8, Ph), 7.115 (2H, d, J = 8, Ph), 3.573 (6H, s, OCH_3), 2.590 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.162, 155.804, 144.940, 135.306, 131.467, 129.544, 126.539, 123.027, 52.346, 23.022; GC-MS (EI): m/z (t_R, min) = 377 (13.25) (M^+).

Dimethyl 4-(4-chlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate, 136. Yield: 93%, 310 mg (white solid); mp (°C): 136-137 (Lit. 137-139);[17] ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.364 (2H, d, J = 8.4, Ph), 7.180 (2H, d, J = 8.4, Ph), 3.574 (6H, s, OCH_3), 2.592 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.193, 155.770, 144.929, 134.793, 129.243, 129.097, 128.536, 126.603, 52.365, 23.020; GC-MS (EI): m/z (t_R, min) = 333 (12.79) (M^+).

Dimethyl 4-(4-fluorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate, 137. Yield: 93%, 295 mg (white solid); mp (°C): 114-115; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.227 (2H, dd, J = 8.4, 5.2, Ph), 7.018 (2H, t, J = 8.4, Ph), 3.566 (6H, s, OCH_3), 2.591 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.298, 162.759 (C, d, J = 247), 155.662, 145.093, 132.297 (C, d, J = 3.4), 129.770 (2xCH, d, J = 8.3), 126.806, 115.388 (2xCH, d, J = 21.6), 52.310, 23.001; GC-MS (EI): m/z (t_R, min) = 317 (12.10) (M^+).

Dimethyl 2,6-dimethyl-4-(4-nitrophenyl)pyridine-3,5-dicarboxylate, 138. Yield: 90%, 310 mg (yellow solid); mp (°C): 150-151 (Lit. 148);[17] ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 8.265 (2H, d, J = 8.4, Ph), 7.427 (2H, d, J = 8.4, Ph), 3.562 (6H, s, OCH_3), 2.626 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 167.676, 156.376, 147.831, 144.120, 143.205, 129.097, 126.037, 123.380, 52.463, 23.198; GC-MS (EI): m/z (t_R, min) = 344 (13.98) (M^+).

Dimethyl 4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate, 139. Yield: 93%, 305 mg (white solid); mp (°C): 117-118 (Lit. 115);[17] ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.177 (2H, d, J = 8.8, Ph), 6.903 (2H, d, J = 8.8, Ph), 3.830 (3H, s, OCH_3), 3.581 (6H, s, OCH_3), 2.577 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.669, 159.709, 155.358, 145.804, 129.133, 128.529, 126.984, 113.731, 55.212, 52.282, 22.949; GC-MS (EI): m/z (t_R, min) = 329 (13.21) (M^+).

Dimethyl 4-(4-hydroxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate, 140. Yield: 83%, 260 mg (pale-yellow solid); mp (°C): 175-176; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.715 (1H, bs, OH), 7.050 (2H, d, J = 8.4, Ph), 6.847 (2H, d, J = 8.4, Ph), 3.625 (6H, s, OCH_3), 2.572 (6H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 167.491, 157.566, 154.100, 145.168, 128.359, 126.261, 126.123, 114.748, 51.320, 22.086; GC-MS (EI): m/z (t_R, min) = 315 (12.47) (M^+).

Dimethyl 4-(4-acetamidophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate, 141. Yield: 94%, 335 mg (white solid); mp (°C): 183-185; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.534 (2H, d, J = 8.4, Ph), 7.397 (1H, bs, NH), 7.193 (2H, d, J = 8.4, Ph), 3.581 (6H, s, OCH_3), 2.582 (6H, s, CH_3), 2.173 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.544, 168.346, 155.519, 145.527, 138.424, 131.486, 128.580, 126.830, 118.994, 52.366, 24.714, 22.965; GC-MS (EI): m/z (t_R, min) = 356 (16.30) (M^+).

Dimethyl 4-(4-carboxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate, 142. Yield: 88%, 300 mg (pale-yellow solid); mp (°C): 270-272; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 7.995 (2H, d, J = 8, Ph), 7.249 (2H, d, J = 8, Ph), 3.505 (6H, s, OCH_3), 2.521 (6H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 167.020, 166.465, 154.940, 144.453, 139.983, 130.956, 129.030, 127.400, 125.836, 51.885, 22.390; HR-MS (ESI): m/z = 344.1130 ($[M+H]^+$, $C_{18}H_{18}NO_6$: required = 344.1134).

Dimethyl 4-(2,4-dichlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate, 143. Yield: 91%, 335 mg (pale-yellow oil); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.447 (1H, d, J = 1.6, Ph), 7.279 (1H, dd, J = 8, 1.6, Ph), 7.114 (1H, d, J = 8, Ph), 3.584 (6H, s, OCH_3), 2.641 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 167.336, 156.794, 143.640, 135.035, 134.062, 133.590, 130.858, 129.071, 126.635, 126.300, 52.255, 23.483; GC-MS (EI): m/z (t_R, min) = 367 (12.18) (M^+).

Dimethyl 4-(3,4-dimethoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate, 144. Yield: 90%, 320 mg (pale-yellow solid); mp (°C): 123-124; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 6.872 (1H, d, J = 8.2, Ph), 6.826 (1H, s, Ph), 6.815 (1H, d, J = 8.2, Ph), 3.906 (3H, s, OCH_3), 3.852 (3H, s, OCH_3), 3.600 (6H, s, OCH_3), 2.577 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.742, 155.405, 149.212, 148.670, 145.684, 128.815, 126.942, 120.565, 111.192, 110.843, 55.908, 55.823, 52.364, 22.913; GC-MS (EI): m/z (t_R, min) = 359 (12.74) (M^+).

Dimethyl 4-(3,5-dimethoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate, 145. Yield: 92%, 330 mg (pale-yellow solid); mp (°C): 125-127; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 6.453 (1H, d, J = 2, Ph), 6.403 (2H, d, J = 2, Ph), 3.769 (6H, s, OCH_3), 3.613 (6H, s, OCH_3), 2.584 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.502, 160.599, 155.547, 145.919, 138.264, 126.598, 105.904, 101.093, 55.419, 52.360, 22.951; GC-MS (EI): m/z (t_R, min) = 359 (13.67) (M^+).

Dimethyl 4-(3,4,5-trimethoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate, 146. Yield: 93%, 360 mg (pale-yellow solid); mp (°C): 125-126; ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 6.497 (2H, s, Ph), 3.879 (3H, s, OCH_3), 3.827 (6H, s, OCH_3), 3.622 (6H, s, OCH_3), 2.583 (6H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 168.670, 155.525, 153.070, 145.698, 138.068, 131.755, 126.688, 105.264, 60.941, 56.145, 52.439, 22.911; GC-MS (EI): m/z (t_R, min) = 389 (14.30) (M^+).

E. Biginelli 3,4-Dihydropyrimidines

1. Multicomponent Synthesis of Biginelli 3,4-Dihydropyrimidines

A mixture of the selected aldehyde (10 mmol), methyl acetoacetate (15 mmol, 1.64 ml) and urea or thiourea (20 mmol, 1.213 or 1.538 g) in glacial acetic acid (2.5 ml) was thoroughly mixed in an appropriate 10 ml thick-walled glass vial. This was tightly sealed with a Teflon cap and the reaction mixture was stirred and heated at 120 °C for 10 or 20 minutes, under microwave irradiation, with an initial power setting of 100 W. After cooling to room temperature a yellow solid precipitated. This was filtered under reduced pressure, thoroughly washed with distilled water and recrystallised in aqueous ethanol, yielding the desired Biginelli 3,4-dihydropyrimidine as a yellowish solid (**147-202**).

Methyl 6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 147. Yield: 83%, 2.050 g (pale-yellow solid); mp (°C): 210-211 (Lit. 209-212);[18] ^{1}H NMR (400 MHz, $CCl_4/(CD_3)_2SO$): δ, ppm = 9.091 (1H, bs, NH-1), 7.610 (1H, bs, NH-3), 7.303-7.187 (5H, m, Ph), 5.156 (1H, d, J = 2.8, CH), 3.549 (3H, s, OCH_3), 2.263 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CCl_4/(CD_3)_2SO$): δ, ppm = 165.317, 151.861, 148.246, 144.580, 127.842, 126.667, 125.954, 98.741, 53.647, 50.177, 17.577; GC-MS (EI): m/z (t_R, min) = 246 (12.22) (M^+).

Methyl 6-methyl-4-(naphthalen-1-yl)-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 148. Yield: 77%, 2.275 g (yellow solid); mp (°C): 233-235 (Lit. 234-236);[19] ^{1}H NMR (400 MHz, $CCl_4/(CD_3)_2SO$): δ, ppm = 9.202 (1H, bs, NH-1), 8.298 (1H, d, J = 8, Ph), 7.903 (1H, d, J = 8, Ph), 7.802 (1H, d, J = 8, Ph), 7.653 (1H, bs, NH-3), 7.585-7.498 (2H, m, Ph), 7.448 (1H, t, J = 8, Ph), 7.390 (1H, d, J = 8, Ph), 6.045 (1H, d, J = 2.8, CH), 3.388 (3H, s, OCH_3), 2.383 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CCl_4/(CD_3)_2SO$): δ, ppm = 165.371, 151.526, 148.900, 139.710, 133.363, 129.921, 128.157, 127.620, 125.690, 125.298, 125.202, 123.642, 123.433, 98.482, 50.281, 49.475, 17.636; GC-MS (EI): m/z (t_R, min) = 296 (15.42) (M^+).

Methyl 6-methyl-4-(phenanthren-9-yl)-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 149. Yield: 65%, 2.240 g (yellow solid); mp (°C): 263-265; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.259 (1H, bs, NH-1), 8.837-8.815 (1H, m, Ph), 8.732 (1H, d, J = 8, Ph), 8.385-8.363 (1H, m, Ph), 7.912 (1H, d, J = 8, Ph), 7.718-7.699 (2H, m, Ph), 7.699 (1H, bs, NH-3), 7.645 (1H, t, J = 8, Ph), 7.599 (1H, s, Ph), 7.575 (1H, d, J = 8, Ph), 6.086 (1H, d, J = 2.8, CH), 3.418 (3H, s, OCH_3), 2.478 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.363, 151.645, 149.448, 137.134, 130.826, 130.328, 129.508, 129.131, 128.502, 126.467, 126.419, 126.323, 126.073, 124.157, 124.080, 122.939, 122.218, 97.898, 50.327, 49.834, 17.718; GC-MS (EI): m/z (t_R, min) = 346 (25.27) (M^+).

Methyl 4-(anthracen-9-yl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 150. Yield: 35%, 1.200 g (yellow solid); mp (°C): 252-254 (Lit. 250-253);[19] ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.346 (1H, bs, NH-1), 8.451-8.483 (3H, m, Ph), 8.027 (2H, d, J = 8, Ph), 7.494-7.436 (4H, m, Ph), 7.453 (1H, bs, NH-3), 6.990 (1H, s, CH), 2.993 (3H, s, OCH_3), 2.272 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.431, 150.497, 146.022, 134.962, 127.831, 125.341, 124.337, 124.152, 99.324, 50.153, 49.670, 17.563; GC-MS (EI): m/z (t_R, min) = 346 (24.25) (M^+).

Methyl 4-(2-bromophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 151. Yield: 70%, 2.270 g (pale-yellow solid); mp (°C): 222-223 (Lit. 220-222);[20] ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.224 (1H, bs, NH-1), 7.525 (1H, d, J = 7.6, Ph), 7.468 (1H, bs, NH-3), 7.349-7.299 (2H, m, Ph), 7.156 (1H, t, J = 7.6, Ph), 5.606 (1H, d, J = 2.4, CH), 3.473 (3H, s, OCH_3), 2.312 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.002, 151.048, 149.090, 143.134, 132.304, 128.822, 128.383, 127.921, 122.026, 97.855, 53.681, 50.222, 17.456; GC-MS (EI): m/z (t_R, min) = 324 (13.26) (M^+).

Methyl 4-(2-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 152. Yield: 66%, 1.860 g (pale-yellow solid); mp (°C): 223-225 (Lit. 226-229);[21] ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.205 (1H, bs, NH-1), 7.435 (1H, bs, NH-3), 7.341 (1H, d, J = 7.6, Ph), 7.310-7.204 (3H, m, Ph), 5.637 (1H, d, J = 2.4, CH), 3.477 (3H, s, OCH_3), 2.315 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 164.949, 151.158, 149.138, 141.394, 131.659, 129.017, 128.398, 128.268, 127.095, 97.456, 51.157, 50.163, 17.464; GC-MS (EI): m/z (t_R, min) = 280 (12.83) (M^+).

Methyl 4-(2,6-dichlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 153. Yield: 55%, 1.730 g (pale-yellow solid); mp (°C): > 300; ^{1}H NMR (400 MHz, $CDCl_3$/TFA): δ, ppm = 8.658 (1H, bs, NH-1), 7.362 (2H, d, J = 8, Ph), 7.220 (1H, t, J = 8, Ph), 6.801 (1H, bs, NH-3), 6.529 (1H, s, CH), 3.614 (3H, s, OCH_3), 2.350 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$/TFA): δ, ppm = 167.011, 154.945, 147.864, 135.829, 134.449, 130.181, 129.715, 98.379, 52.656, 52.123, 18.541; GC-MS (EI): m/z (t_R, min) = 314 (13.81) (M^+).

Methyl 4-mesityl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 154. Yield: 40%, 1.150 g (pale-yellow solid); mp (°C): 269-271; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 8.988 (1H, bs, NH-1), 7.171 (1H, bs, NH-3), 6.722 (2H, s, Ph), 5.784 (1H, s, CH), 3.373 (3H, s, OCH_3), 2.317 (6H, s, CH_3), 2.200 (3H, s, CH_3), 2.136 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.571, 150.575, 146.177, 136.750, 136.345, 135.083, 129.587, 96.511, 50.695, 49.802, 20.222, 19.061, 17.323; GC-MS (EI): m/z (t_R, min) = 288 (13.21) (M^+).

Methyl 6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 155. Yield: 87%, 2.520 g (yellow solid); mp (°C): 274-276 (Lit. 273-275);[22] ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.298 (1H, bs, NH-1), 8.104-8.087 (2H, m, Ph), 7.831 (1H, bs, NH-3), 7.670 (1H, d, J = 7.6, Ph), 7.597 (1H, t, J = 7.6, Ph), 5.295 (1H, d, J = 3.2, CH), 3.571 (3H, s, OCH_3), 2.290 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.138, 151.572, 149.386, 147.617, 146.640, 132.459, 129.518, 121.816, 120.845, 97.830, 53.145, 50.424, 17.703; GC-MS (EI): m/z (t_R, min) = 291 (14.60) (M^+).

Methyl 4-(3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 156. Yield: 73%, 2.005 g (pale-yellow solid); mp (°C): 193-195 (Lit. 192-195);[23] ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.099 (1H, bs, NH-1), 7.613 (1H, bs, NH-3), 7.188 (1H, t, J = 7.8, Ph), 6.810 (1H, d, J = 7.8, Ph), 6.782 (1H, s, Ph), 6.754 (1H, d, J = 7.8, Ph), 5.135 (1H, d, J = 2.8, CH), 3.754 (3H, s, OCH_3), 3.563 (3H, s, OCH_3), 2.264 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.377, 158.986, 151.998, 148.255, 145.976, 128.946, 117.926, 112.067, 111.790, 98.643, 54.506, 53.495, 50.249, 17.593; GC-MS (EI): m/z (t_R, min) = 276 (13.20) (M^+).

Methyl 4-(3-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 157. Yield: 62%, 1.620 g (pale-yellow solid); mp (°C): 190-192; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.128 (1H, bs, NH-1), 9.062 (1H, bs, OH), 7.558 (1H, bs, NH-3), 7.041 (1H, t, J = 8, Ph), 6.670-6.657 (2H, m, Ph), 6.588 (1H, d, J = 8, Ph), 5.079 (1H, d, J = 2.8, CH), 3.565 (3H, s, OCH_3), 2.255 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.447, 157.191, 152.101, 147.997, 145.849, 128.757, 116.529, 113.922, 112.962, 99.040, 53.599, 50.267, 17.631; GC-MS (EI): m/z (t_R, min) = 262 (13.80) (M^+).

Methyl 4-(4-*t*-butylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 158. Yield: 85%, 2.570 g (pale-yellow solid); mp (°C): 161-162; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.095 (1H, bs, NH-1), 7.575 (1H, bs, NH-3), 7.289 (2H, d, J = 8, Ph), 7.163 (2H, d, J = 8, Ph), 5.130 (1H, d, J = 2.8, CH), 3.564 (3H, s, OCH_3), 2.259 (3H, s, CH_3), 1.290 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.399, 152.084, 149.025, 148.138, 141.617, 125.625, 124.664, 98.946, 53.161, 50.243, 33.894, 30.950, 17.594; GC-MS (EI): m/z (t_R, min) = 302 (13.68) (M^+).

Methyl 6-methyl-4-*p*-tolyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 159. Yield: 82%, 2.130 g (pale-yellow solid); mp (°C): 203-205 (Lit. 204-206);[24] ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.045 (1H, bs, NH-1), 7.532 (1H, bs, NH-3), 7.120 (2H, d, J = 8, Ph), 7.065 (2H, d, J = 8, Ph), 5.116 (1H, d, J = 2.8, CH), 3.540 (3H, s, OCH_3), 2.302 (3H, s, CH_3), 2.256 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.293, 151.872, 148.020, 141.649, 135.701, 128.399, 125.875, 98.853, 53.356, 50.090, 20.506, 17.540; GC-MS (EI): m/z (t_R, min) = 260 (12.72) (M^+).

Methyl 4-(4-bromophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 160. Yield: 85%, 2.760 g (pale-yellow solid); mp (°C): 213-215 (Lit. 210-212);[20] ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.155 (1H, bs, NH-1), 7.663 (1H, bs, NH-3), 7.428 (2H, d, J = 8, Ph), 7.186 (2H, d, J = 8, Ph), 5.135 (1H, d, J = 2.8, CH), 3.549 (3H, s, OCH_3), 2.260 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.182, 151.678, 148.639, 143.765, 130.802, 128.106, 120.060, 98.248, 53.138, 50.243, 17.604; GC-MS (EI): m/z (t_R, min) = 324 (13.88) (M^+).

Methyl 4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 161. Yield: 90%, 2.520 g (pale-yellow solid); mp (°C): 205-207 (Lit. 204-207);[18] ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.149 (1H, bs, NH-1), 7.658 (1H, bs, NH-3), 7.288 (2H, d, J = 8.4, Ph), 7.238 (2H, d, J = 8.4, Ph), 5.147 (1H, d, J = 3.2, CH), 3.548 (3H, s, OCH_3), 2.259 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.207, 151.683, 148.622, 143.312, 131.702, 127.885, 127.725, 98.325, 53.074, 50.253, 17.605; GC-MS (EI): m/z (t_R, min) = 280 (13.32) (M^+).

Methyl 4-(4-fluorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 162. Yield: 83%, 2.200 g (pale-yellow solid); mp (°C): 190-191 (Lit. 188-190);[25] ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.129 (1H, bs, NH-1), 7.637 (1H, bs, NH-3), 7.258 (2H, dd, J = 8, 5.6, Ph), 7.033 (2H, t, J = 8, Ph), 5.150 (1H, d, J = 2.8, CH), 3.547 (3H, s, OCH_3), 2.260 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.465, 160.183 (C, d, J = 217.2), 151.913, 148.619, 140.860, 128.027 (2xCH, d, J = 8), 114.783 (2xCH, d, J = 21.1), 98.832, 53.202, 50.447, 17.798; GC-MS (EI): m/z (t_R, min) = 264 (12.17) (M^+).

Methyl 6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 163. Yield: 90%, 2.615 g (yellow solid); mp (°C): 234-236 (Lit. 235-237);[18] ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.280 (1H, bs, NH-1), 8.163 (2H, d, J = 8.8, Ph), 7.811 (1H, bs, NH-3), 7.503 (2H, d, J = 8.8, Ph), 5.279 (1H, d, J = 2.8, CH), 3.559 (3H, s, OCH_3), 2.276 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.075, 151.642, 151.515, 149.322, 146.411, 127.213, 123.267, 97.681, 53.289, 50.364, 17.672; GC-MS (EI): m/z (t_R, min) = 291 (15.12) (M^+).

Methyl 4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 164. Yield: 91%, 2.510 g (pale-yellow solid); mp (°C): 193-195 (Lit. 192-194);[18] ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.060 (1H, bs, NH-1), 7.544 (1H, bs, NH-3), 7.147 (2H, d, J = 8.4, Ph), 6.805 (2H, d, J = 8.4, Ph), 5.101 (1H, d, J = 2.8, CH), 3.741 (3H, s, OCH_3), 3.541 (3H, s, OCH_3), 2.253 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.380, 158.132, 151.901, 147.916, 136.734, 127.065, 113.219, 99.057, 54.595, 53.049, 50.184, 17.560; GC-MS (EI): m/z (t_R, min) = 276 (13.52) (M^+).

Methyl 4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 165. Yield: 90%, 2.350 g (pale-yellow solid); mp (°C): 235-236 (Lit. 232-234);[20] ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.121 (1H, bs, NH-1), 9.032 (1H, bs, OH), 7.512 (1H, bs, NH-3), 7.014 (2H, d, J = 8.4, Ph), 6.651 (2H, d, J = 8.4, Ph), 5.045 (1H, d, J = 2.8, CH), 3.537 (3H, s, OCH_3), 2.241 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.533, 158.358, 151.996, 147.698, 135.037, 127.031, 114.710, 99.329, 53.154, 50.275, 17.595; GC-MS (EI): m/z (t_R, min) = 262 (13.96) (M^+).

Methyl 4-(4-acetamidophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 166. Yield: 81%, 2.460 g (pale-yellow solid); mp (°C): 295-297; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.742 (1H, bs, NH-1), 9.075 (1H, bs, NH-3), 7.573 (1H, bs, $NHCOCH_3$), 7.476 (2H, d, J = 8.4, Ph), 7.131 (2H, d, J = 8.4, Ph), 5.108 (1H, d, J = 2.8, CH), 3.543 (3H, s, OCH_3), 2.257 (3H, s, CH_3), 2.012 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 167.552, 165.445, 152.026, 148.016, 139.101, 138.217, 126.192, 118.776, 99.034, 53.337, 50.269, 23.648, 17.635; HR-MS (ESI): m/z = 304.1291 ($[M+H]^+$, $C_{15}H_{18}N_3O_4$: required = 304.1297).

Methyl 4-(4-carboxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 167. Yield: 82%, 2.370 g (pale-yellow solid); mp (°C): 285-287; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.159 (1H, bs, NH-1), 7.882 (2H, d, J = 8.4, Ph), 7.690 (1H, bs, NH-3), 7.338 (2H, d, J = 8.4, Ph), 5.217 (1H, d, J = 2.8, CH), 3.550 (3H, s, OCH_3), 2.269 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 166.704, 165.200, 151.756, 149.040, 148.709, 129.607, 129.257, 125.955, 98.268, 53.560, 50.232, 17.636; HR-MS (ESI): m/z = 291.0975 ($[M+H]^+$, $C_{14}H_{15}N_2O_5$: required = 291.0981).

Methyl 4-(2,4-dichlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 168. Yield: 62%, 1.950 g (pale-yellow solid); mp (°C): 252-253 (Lit. 254-255);[26] ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.332 (1H, bs, NH-1), 7.746 (1H, bs, NH-3), 7.554 (1H, d, J = 2, Ph), 7.404 (1H, dd, J = 8.4, 2, Ph), 7.311 (1H, d, J = 8.4, Ph), 5.581 (1H, d, J = 3.2, CH), 3.454 (3H, s, OCH_3), 2.290 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.284, 151.153, 149.615, 140.716, 132.575, 132.539, 130.116, 128.728, 127.902, 97.293, 51.060, 50.680, 17.694; GC-MS (EI): m/z (t_R, min) = 314 (13.85) (M^+).

Methyl 4-(3,4-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 169. Yield: 78%, 2.380 g (pale-yellow solid); mp (°C): 104-105; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.082 (1H, bs, NH-1), 7.580 (1H, bs, NH-3), 6.843 (1H, d, J = 2, Ph), 6.808 (1H, d, J = 8, Ph), 6.712 (1H, dd, J = 8, 2, Ph), 5.107 (1H, d, J = 3.6, CH), 3.755 (3H, s, OCH_3), 3.739 (3H, s, OCH_3), 3.557 (3H, s, OCH_3), 2.261 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.510, 152.051, 148.449, 148.121, 147.899, 137.040, 117.613, 111.409, 110.419, 98.867, 55.259, 55.149, 53.202, 50.301, 17.587; GC-MS (EI): m/z (t_R, min) = 306 (14.32) (M^+).

Methyl 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 170. Yield: 66%, 1.930 g (pale-yellow solid); mp (°C): 250-252 (Lit. 253-254);[22] ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.032 (1H, bs, NH-1), 8.640 (1H, bs, OH), 7.519 (1H, bs, NH-3), 6.790 (1H, d, J = 2, Ph), 6.660 (1H, d, J = 8, Ph), 6.596 (1H, dd, J = 8, 2, Ph), 5.063 (1H, d, J = 3.2, CH), 3.765 (3H, s, OCH_3), 3.553 (3H, s, OCH_3), 2.249 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.543, 152.034, 147.850, 147.002, 145.647, 135.456, 117.988, 114.919, 110.671, 99.063, 55.296, 53.273, 50.266, 17.577; GC-MS (EI): m/z (t_R, min) = 292 (14.12) (M^+).

Methyl 4-(3-hydroxy-4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 171. Yield: 73%, 2.150 g (pale-yellow solid); mp (°C): 217-219; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.040 (1H, bs, NH-1), 8.674 (1H, bs, OH), 7.510 (1H, bs, NH-3), 6.757 (1H, d, J = 8, Ph), 6.685 (1H, d, J = 1.6, Ph), 6.607 (1H, dd, J = 8, 1.6, Ph), 5.029 (1H, d, J = 3.2, CH), 3.753 (3H, s, OCH_3), 3.556 (3H, s, OCH_3), 2.248 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.482, 151.999, 147.728, 146.544, 146.238, 137.382, 116.501, 113.475, 111.679, 99.187, 55.390, 53.136, 50.237, 17.574; GC-MS (EI): m/z (t_R, min) = 292 (14.60) (M^+).

Methyl 4-(3,5-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 172. Yield: 75%, 2.300 g (pale-yellow solid); mp (°C): 185-187; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.100 (1H, bs, NH-1), 7.608 (1H, bs, NH-3), 6.366 (2H, d, J = 2, Ph), 6.320 (1H, t, J = 2, Ph), 5.091 (1H, d, J = 3.6, CH), 3.729 (6H, s, OCH_3), 3.574 (3H, s, OCH_3), 2.258 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.412, 160.177, 151.998, 148.447, 146.541, 104.064, 98.446, 98.067, 54.647, 53.394, 50.308, 17.559; GC-MS (EI): m/z (t_R, min) = 306 (14.39) (M^+).

Methyl 4-(3,4,5-trimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 173. Yield: 75%, 2.500 g (pale-yellow solid); mp (°C): 201-203; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.110 (1H, bs, NH-1), 7.602 (1H, bs, NH-3), 6.500 (2H, s, Ph), 5.118 (1H, d, J = 3.2, CH), 3.762 (6H, s, OCH_3), 3.661 (3H, s, OCH_3), 3.587 (3H, s, OCH_3), 2.269 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.475, 152.528, 152.030, 148.385, 139.924, 136.639, 103.178, 98.543, 59.581, 55.543, 53.528, 50.341, 17.590; GC-MS (EI): m/z (t_R, min) = 336 (15.09) (M^+).

Methyl 4-(4-hydroxy-3,5-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, 174. Yield: 63%, 2.020 g (pale-yellow solid); mp (°C): 215-217; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.035 (1H, bs, NH-1), 7.963 (1H, bs, OH), 7.510 (1H, bs, NH-3), 6.465 (2H, s, Ph), 5.087 (1H, d, J = 3.2, CH), 3.759 (6H, s, OCH_3), 3.574 (3H, s, OCH_3), 2.266 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.475, 152.029, 147.880, 147.428, 134.967, 134.479, 103.737, 98.877, 55.679, 53.503, 50.181, 17.535; GC-MS (EI): m/z (t_R, min) = 322 (16.19) (M^+).

Methyl 6-methyl-4-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 175. Yield: 57%, 1.500 g (pale-yellow solid); mp (°C): 220-221 (Lit. 222);[27] ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.173 (1H, bs, NH-1), 9.515 (1H, bs, NH-3), 7.322-7.212 (5H, m, Ph), 5.195 (1H, d, J = 3.6, CH), 3.583 (3H, s, OCH_3), 2.314 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 174.044, 165.062, 144.886, 143.274, 127.914, 126.974, 126.111, 100.243, 53.792, 50.370, 16.941; GC-MS (EI): m/z (t_R, min) = 262 (13.17) (M^+).

Methyl 6-methyl-4-(naphthalen-1-yl)-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 176. Yield: 62%, 1.940 g (yellow solid); mp (°C): 254-255; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.211 (1H, bs, NH-1), 9.448 (1H, bs, NH-3), 8.391 (1H, d, J = 8, Ph), 7.860 (1H, d, J = 8, Ph), 7.784 (1H, d, J = 8, Ph), 7.569 (1H, t, J = 8, Ph), 7.516-7.441 (2H, m, Ph), 7.401 (1H, d, J = 8, Ph), 6.095 (1H, d, J = 2.8, CH), 3.421 (3H, s, OCH_3), 2.445 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 173.697, 164.949, 145.422, 138.896, 133.269, 129.928, 127.959, 127.889, 125.600, 125.250, 125.115, 124.467, 123.637, 100.226, 50.296, 49.600, 16.986; GC-MS (EI): m/z (t_R, min) = 312 (17.84) (M^+).

Methyl 6-methyl-4-(phenanthren-9-yl)-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 177. Yield: 72%, 2.600 g (yellow solid); mp (°C): 250-252; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.306 (1H, bs, NH-1), 9.531 (1H, bs, NH-3), 8.798-7.775 (1H, m, Ph), 8.691 (1H, d, J = 8, Ph), 8.502-8.479 (1H, m, Ph), 7.910 (1H, d, J = 8, Ph), 7.718-7.695 (2H, m, Ph), 7.633 (1H, t, J = 8, Ph), 7.585 (1H, s, Ph), 7.554 (1H, d, J = 8, Ph), 6.128 (1H, d, J = 3.6, CH), 3.451 (3H, s, OCH_3), 2.529 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 173.844, 164.981, 146.006, 136.165, 130.745, 130.253, 129.650, 128.969, 128.620, 126.467, 126.265, 126.135, 126.003, 125.042, 124.307, 122.681, 122.030, 99.566, 50.406, 49.866, 17.035; GC-MS (EI): m/z (t_R, min) = 362 (16.54) (M^+).

Methyl 4-(anthracen-9-yl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 178. Yield: 28%, 1.010 g (yellow solid); mp (°C): 225-227; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.315 (1H, bs, NH-1), 9.324 (1H, bs, NH-3), 8.477-8.411 (3H, m, Ph), 8.024 (2H, d, J = 8, Ph), 7.539-7.441 (4H, m, Ph), 6.984 (1H, s, CH), 3.026 (3H, s, OCH_3), 2.310 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 172.863, 164.886, 142.530, 133.729, 128.055, 125.290, 124.106, 123.865, 100.803, 50.163, 49.552, 16.614; GC-MS (EI): m/z (t_R, min) = 362 (13.47) (M^+).

Methyl 4-(2-bromophenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 179. Yield: 43%, 1.470 g (pale-yellow solid); mp (°C): 167-168; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.277 (1H, bs, NH-1), 9.370 (1H, bs, NH-3), 7.531 (1H, d, J = 7.6, Ph), 7.372-7.295 (2H, m, Ph), 7.174 (1H, t, J = 7.6, Ph), 5.602 (1H, d, J = 2.8, CH), 3.504 (3H, s, OCH_3), 2.344 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 173.649.164.700, 145.328, 142.270, 132.318, 129.024, 128.935, 127.917, 121.994, 99.666, 53.751, 50.327, 16.740; GC-MS (EI): m/z (t_R, min) = 340 (14.54) (M^+).

Methyl 4-(2-chlorophenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 180. Yield: 53%, 1.575 g (pale-yellow solid); mp (°C): 174-175; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.256 (1H, bs, NH-1), 9.356 (1H, bs, NH-3), 7.350 (1H, d, J = 7.6, Ph), 7.297-7.228 (3H, m, Ph), 5.651 (1H, d, J = 2.8, CH), 3.500 (3H, s, OCH_3), 2.339 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 173.804, 164.798, 145.486, 140.493, 131.764, 129.139, 128.913, 128.818, 127.227, 99.360, 51.361, 50.425, 16.837; GC-MS (EI): m/z (t_R, min) = 296 (13.94) (M^+).

Methyl 4-(2,6-dichlorophenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 181. Yield: 39%, 1.280 g (pale-yellow solid); mp (°C): 247-248; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.173 (1H, bs, NH-1), 9.306 (1H, bs, NH-3), 7.357 (2H, d, J = 7.6, Ph), 7.254 (1H, t, J = 7.6, Ph), 6.164 (1H, s, CH), 3.416 (3H, s, OCH_3), 2.212 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 173.607, 164.783, 145.836, 136.288, 135.499, 129.008, 128.734, 95.776, 51.955, 49.992, 16.807; GC-MS (EI): m/z (t_R, min) = 330 (15.46) (M^+).

Methyl 4-mesityl-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 182. Yield: 48%, 1.455 g (pale-yellow solid); mp (°C): 230-232; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.961 (1H, bs, NH-1), 9.047 (1H, bs, NH-3), 6.735 (2H, s, Ph), 5.755 (1H, s, CH), 3.404 (3H, s, OCH_3), 2.312 (6H, s, CH_3), 2.202 (3H, s, CH_3), 2.164 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 172.761, 165.424, 143.011, 137.000, 135.827, 135.735, 129.659, 98.315, 50.916, 50.091, 20.309, 19.132, 16.692; GC-MS (EI): m/z (t_R, min) = 304 (14.62) (M^+).

Methyl 6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 183. Yield: 59%, 1.800 g (yellow solid); mp (°C): 237-239 (Lit. 239);[27] ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.362 (1H, bs, NH-1), 9.659 (1H, bs, NH-3), 8.101-8.006 (2H, m, Ph), 7.646-7.571 (2H, m, Ph), 5.330 (1H, d, J = 3.6, CH), 3.588 (3H, s, OCH_3), 2.324 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 174.537, 165.099, 147.839, 146.161, 145.325, 132.623, 129.747, 122.275, 121.237, 99.531, 53.334, 50.829, 17.251; GC-MS (EI): m/z (t_R, min) = 307 (16.45) (M^+).

Methyl 4-(3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 184. Yield: 58%, 1.710 g (pale-yellow solid); mp (°C): 205-207; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.161 (1H, bs, NH-1), 9.494 (1H, bs, NH-3), 7.199 (1H, t, J = 8, Ph), 6.806-6.753 (3H, m, Ph), 5.174 (1H, d, J = 3.6, CH), 3.764 (3H, s, OCH_3), 3.597 (3H, s, OCH_3), 2.309 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 174.146, 165.095, 159.006, 144.995, 144.616, 128.987, 118.016, 112.169, 112.093, 100.119, 54.433, 53.614, 50.413, 16.955; GC-MS (EI): m/z (t_R, min) = 292 (14.42) (M^+).

Methyl 4-(3-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 185. Yield: 58%, 1.630 g (pale-yellow solid); mp (°C): 217-219; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.178 (1H, bs, NH-1), 9.507 (1H, bs, OH), 9.231 (1H, bs, NH-3), 7.074 (1H, t, J = 8, Ph), 6.654-6.615 (3H, m, Ph), 5.099 (1H, d, J = 3.6, CH), 3.588 (3H, s, OCH_3), 2.298 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 173.999, 165.308, 157.275, 144.793, 144.439, 128.972, 116.643, 114.336, 113.085, 100.356, 53.693, 50.620, 17.012; GC-MS (EI): m/z (t_R, min) = 278 (15.23) (M^+).

Methyl 4-(4-*t*-butylphenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 186. Yield: 56%, 1.780 g (pale-yellow solid); mp (°C): 203-204; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.161 (1H, bs, NH-1), 9.480 (1H, bs, NH-3), 7.306 (2H, d, J = 8, Ph), 7.152 (2H, d, J = 8, Ph), 5.160 (1H, d, J = 2.8, CH), 3.596 (3H, s, OCH_3), 2.304 (3H, s, CH_3), 1.292 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 174.056, 165.121, 149.360, 144.793, 140.359, 125.771, 124.745, 100.379, 53.324, 50.430, 33.907, 30.892, 16.951; GC-MS (EI): m/z (t_R, min) = 318 (15.24) (M^+).

Methyl 6-methyl-4-*p*-tolyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 187. Yield: 55%, 1.525 g (pale-yellow solid); mp (°C): 162-164; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.109 (1H, bs, NH-1), 9.443 (1H, bs, NH-3), 7.119 (2H, d, J = 8, Ph), 7.080 (2H, d, J = 8, Ph), 5.152 (1H, d, J = 3.6, CH), 3.571 (3H, s, OCH_3), 2.310 (3H, s, CH_3), 2.256 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 173.905, 165.054, 144.741, 140.385, 136.127, 128.523, 126.089, 100.347, 53.562, 50.303, 20.561, 16.936; GC-MS (EI): m/z (t_R, min) = 276 (13.79) (M^+).

Methyl 4-(4-bromophenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 188. Yield: 55%, 1.870 g (pale-yellow solid); mp (°C): 123-125; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.243 (1H, bs, NH-1), 9.543 (1H, bs, NH-3), 7.443 (2H, d, J = 8.4, Ph), 7.171 (2H, d, J = 8.4, Ph), 5.165 (1H, d, J = 3.6, CH), 3.578 (3H, s, OCH_3), 2.306 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 174.075, 164.980, 145.311, 142.391, 130.962, 128.226, 120.566, 99.767, 53.238, 50.508, 16.994; GC-MS (EI): m/z (t_R, min) = 340 (15.55) (M^+).

Methyl 4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 189. Yield: 57%, 1.690g (pale-yellow solid); mp (°C): 135-137 (Lit. 136-138);[20] ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.206 (1H, bs, NH-1), 9.511 (1H, bs, NH-3), 7.280 (2H, d, J = 8.4, Ph), 7.221 (2H, d, J = 8.4, Ph), 5.180 (1H, d, J = 3.2, CH), 3.567 (3H, s, OCH_3), 2.301 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 174.175, 165.099, 145.371, 142.017, 132.348, 128.125, 127.963, 99.992, 53.320, 50.589, 17.114; GC-MS (EI): m/z (t_R, min) = 296 (14.57) (M^+).

Methyl 4-(4-fluorophenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 190. Yield: 59%, 1.650 g (pale-yellow solid); mp (°C): 180-181; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.260 (1H, bs, NH-1), 9.563 (1H, bs, NH-3), 7.249 (2H, dd, J = 8.4, 5.8, Ph), 7.072 (2H, t, J = 8.4, Ph), 5.181 (1H, d, J = 3.2, CH), 3.570 (3H, s, OCH_3), 2.305 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 174.040, 165.184, 161.379 (C, d, J = 243), 145.169, 139.363, 128.121 (2xCH, d, J = 8.2), 114.911 (2xCH, d, J = 21.1), 100.195, 53.137, 50.664, 17.043; GC-MS (EI): m/z (t_R, min) = 280 (13.09) (M^+).

Methyl 4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 191. Yield: 60%, 1.740 g (pale-yellow solid); mp (°C): 171-172 (Lit. 172-174);[20] ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.164 (1H, bs, NH-1), 9.487 (1H, bs, NH-3), 7.138 (2H, d, J = 8.4, Ph), 6.830 (2H, d, J = 8.4, Ph), 5.124 (1H, d, J = 3.2, CH), 3.746 (3H, s, OCH_3), 3.570 (3H, s, OCH_3), 2.301 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 173.795, 165.191, 158.415, 144.653, 135.402, 127.287, 113.378, 100.487, 54.625, 53.181, 50.483, 16.941; GC-MS (EI): m/z (t_R, min) = 292 (14.87) (M^+).

Methyl 4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 192. Yield: 55%, 1.520 g (pale-yellow solid); mp (°C): 223-225 (Lit. 225-227);[20] ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.102 (1H, bs, NH-1), 9.430 (1H, bs, OH), 9.136 (1H, bs, NH-3), 7.005 (2H, d, J = 8.4, Ph), 6.670 (2H, d, J = 8.4, Ph), 5.071 (1H, d, J = 3.2, CH), 3.567 (3H, s, OCH_3), 2.292 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 173.665, 165.255, 156.682, 144.385, 133.704, 127.226, 114.803, 100.708, 53.322, 50.444, 16.939; GC-MS (EI): m/z (t_R, min) = 278 (15.49) (M^+).

Methyl 4-(4-acetamidophenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 193. Yield: 57%, 1.820 g (pale-yellow solid); mp (°C): 252-254; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.161 (1H, bs, NH-1), 9.780 (1H, bs, NH-3), 9.492 (1H, bs, $NHCOCH_3$), 7.504 (2H, d, J = 8.4, Ph), 7.115 (2H, d, J = 8.4, Ph), 5.125 (1H, d, J = 2.8, CH), 3.569 (3H, s, OCH_3), 3.175 (3H, s, CH_3), 2.014 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 173.866, 167.580, 165.247, 144.745, 138.568, 137.704, 126.382, 118.784, 100.420, 53.438, 50.552, 23.653, 17.003; HR-MS (ESI): m/z = 320.1065 ($[M+H]^+$, $C_{15}H_{18}N_3O_3S$: required = 320.1069).

Methyl 4-(4-carboxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-one-5-carboxylate, 194. Yield: 56%, 1.700 g (pale-yellow solid); mp (°C): 239-241; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.256 (1H, bs, NH-1), 9.579 (1H, bs, NH-3), 7.904 (2H, d, J = 8, Ph), 7.324 (2H, d, J = 8, Ph), 5.249 (1H, d, J = 3.2, CH), 3.579 (3H, s, OCH_3), 2.312 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 174.250, 166.677, 165.064, 147.593, 145.389, 130.016, 129.418, 126.139, 99.845, 53.666, 50.577, 17.057; HR-MS (ESI): m/z = 307.0748 ($[M+H]^+$, $C_{14}H_{15}N_2O_4S$: required = 307.0753).

Methyl 4-(2,4-dichlorophenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 195. Yield: 50%, 1.650 g (pale-yellow solid); mp (°C): 201-203; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.292 (1H, bs, NH-1), 9.396 (1H, bs, NH-3), 7.387 (1H, s, Ph), 7.320-7.266 (2H, m, Ph), 5.611 (1H, d, J = 2.8, CH), 3.510 (3H, s, OCH_3), 2.336 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 173.741, 164.545, 145.687, 139.457, 132.853, 132.628, 130.199, 128.503, 127.368, 98.910, 50.957, 50.343, 16.785; GC-MS (EI): m/z (t_R, min) = 330 (15.15) (M^+).

Methyl 4-(3,4-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 196. Yield: 78%, 2.515 g (pale-yellow solid); mp (°C): 192-193; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.127 (1H, bs, NH-1), 9.451 (1H, bs, NH-3), 6.835 (1H, s, Ph), 6.803 (1H, d, J = 8, Ph), 6.708 (1H, d, J = 8, Ph), 5.139 (1H, d, J = 3.2, CH), 3.7776 (3H, s, OCH_3), 3.752 (3H, s, OCH_3), 3.591 (3H, s, OCH_3), 2.308 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 173.937, 165.180, 148.484, 148.114, 144.736, 135.740, 117.840, 111.375, 110.447, 100.305, 55.133, 55.041, 53.342, 50.397, 16.928; GC-MS (EI): m/z (t_R, min) = 322 (16.05) (M^+).

Methyl 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 197. Yield: 58%, 1.800 g (pale-yellow solid); mp (ºC): 252-253; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.069 (1H, bs, NH-1), 9.401 (1H, bs, NH-3), 8.602 (1H, bs, OH), 6.782 (1H, s, Ph), 6.679 (1H, d, J = 7.8, Ph), 6.590 (1H, d, J = 7.8, Ph), 5.097 (1H, d, J = 2.4, CH), 3.787 (3H, s, OCH_3), 3.584 (3H, s, OCH_3), 2.298 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 173.834, 165.326, 147.059, 146.013, 144.537, 134.172, 118.314, 115.049, 110.749, 100.587, 55.285, 53.509, 50.484, 16.988; GC-MS (EI): m/z (t_R, min) = 308 (15.05) (M^+).

Methyl 4-(3-hydroxy-4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 198.Yield: 53%, 1.640 g (pale-yellow solid); mp (ºC): 221-222; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.085 (1H, bs, NH-1), 9.412 (1H, bs, NH-3), 8.706 (1H, bs, OH), 6.763 (1H, d, J = 8, Ph), 6.664 (1H, s, Ph), 6.602 (1H, d, J = 8, Ph), 5.060 (1H, d, J = 3.2, CH), 3.748 (3H, s, OCH_3), 3.570 (3H, s, OCH_3), 2.295 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 173.872, 165.432, 147.008, 146.432, 144.647, 136.080, 116.941, 113.756, 111.765, 100.724, 55.475, 53.486, 50.642, 17.109; GC-MS (EI): m/z (t_R, min) = 308 (16.70) (M^+).

Methyl 4-(3,5-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 199. Yield: 73%, 2.350 g (pale-yellow solid); mp (ºC): 208-209; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.204 (1H, bs, NH-1), 9.509 (1H, bs, NH-3), 6.354 (2H, d, J = 1.6, Ph), 6.339 (1H, t, J = 1.6, Ph), 5.135 (1H, d, J = 3.2, CH), 3.735 (6H, s, OCH_3), 3.609 (3H, s, OCH_3), 2.301 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 174.256, 165.211, 160.259, 145.150, 145.090, 104.145, 100.000, 98.406, 54.643, 53.495, 50.567, 16.956; GC-MS (EI): m/z (t_R, min) = 322 (16.05) (M^+).

Methyl 4-(3,4,5-trimethoxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 200. Yield: 77%, 2.730 g (pale-yellow solid); mp (ºC): 214-216; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.177 (1H, bs, NH-1), 9.464 (1H, bs, NH-3), 6.485 (2H, s, Ph), 5.157 (1H, d, J = 3.2, CH), 3.775 (6H, s, OCH_3), 3.670 (3H, s, OCH_3), 3.625 (3H, s, OCH_3), 2.307 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 174.311, 165.248, 152.616, 144.972, 138.592, 136.897, 103.236, 100.207, 59.522, 55.376, 53.637, 50.526, 17.000; GC-MS (EI): m/z (t_R, min) = 352 (17.03) (M^+).

Methyl 4-(4-hydroxy-3,5-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate, 201. Yield: 56%, 1.900 g (pale-yellow solid); mp (ºC): 211-213; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 10.068 (1H, bs, NH-1), 9.390 (1H, bs, NH-3), 7.960 (1H, bs, OH), 6.441 (2H, s, Ph), 5.113 (1H, d, J = 3.2, CH), 3.748 (6H, s, OCH_3), 3.586 (3H, s, OCH_3), 2.292 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 174.088, 165.457, 147.604, 144.679, 135.322, 133.365, 103.888, 100.674, 55.806, 53.841, 50.626, 17.115; GC-MS (EI): m/z (t_R, min) = 338 (18.03) (M^+).

2. Multicomponent Synthesis of Biginelli Bis-3,4-Dihydropyrimidines

A mixture of terephthalaldehyde (5 mmol, 677 mg), the selected alkyl acetoacetate or acetylacetone (15 mmol) and urea or thiourea (20 mmol, 1.213 or 1.538 g) in glacial acetic acid (2.5 ml) was thoroughly mixed in an appropriate 10 ml thick-walled glass vial. This was tightly sealed with a Teflon cap and the reaction mixture was stirred and heated at 120 ºC for 10 or 20 minutes, under microwave irradiation, with an initial power setting of 100 W. After cooling to room temperature a yellow solid precipitated. This was filtered under reduced pressure, thoroughly washed with distilled water and recrystallised in aqueous ethanol, yielding the desired Biginelli bis-3,4-dihydropyrimidine as a yellowish solid (**202-209**).

Dimethyl 4,4'-(1,4-phenylene)bis(6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate), 202. Yield: 80%, 1.660 g (pale-yellow solid); mp (ºC) > 300; ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 9.196 (2H, bs, NH-1/1'), 7.706 (2H, bs, NH-3/3'), 7.183 (4H, s, Ph), 5.112 (2H, d, J = 2.4, CH), 3.537 (6H, s, OCH_3), 2.244 (6H, s, CH_3); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ, ppm = 165.789, 152.137, 148.678, 148.627, 143.735, 126.276, 98.901, 53.477, 50.814, 17.794; HR-MS (ESI): m/z = 415.1612 ($[M+H]^+$, $C_{20}H_{23}N_4O_6$: required = 415.1618).

Diethyl 4,4'-(1,4-phenylene)bis(6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate), 203. Yield: 75%, 1.650 g (pale-yellow solid); mp (ºC) > 300; ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 9.127 (2H, bs, NH-1/1'), 7.676 (2H, bs, NH-3/3'), 7.174 (4H, s, Ph), 5.118 (2H, s, CH), 3.969 (4H, q, J = 6, O$CH_2$$CH_3$), 2.228 (6H, s, CH_3), 1.079 (6H, t, J = 6, OCH_2CH_3); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ, ppm = 165.373, 152.174, 148.284, 143.781, 126.264, 99.279, 59.296, 53.556, 17.707, 13.982; HR-MS (ESI): m/z = 443.1926 ($[M+H]^+$, $C_{22}H_{27}N_4O_6$: required = 443.1931).

Dibenzyl 4,4'-(1,4-phenylene)bis(6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate), 204. Yield: 55%, 1.550 g (yellow solid) mp (ºC): > 300; ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 9.266 (2H, bs, NH-1/1'), 7.722 (2H, bs, NH-3/3'), 7.298-7.260 (7H, m, Ph), 7.152-7.113 (m, 3H, Ph), 7.128 (4H, s, Ph), 5.159 (2H, d, J = 2.8, CH), 5.066 (2H, d, J = 12.8, CH_2), 5.009 (2H, d, J = 12.8, CH_2), 2.277 (6H, s, CH_3); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ, ppm = 165.014, 151.984, 149.245, 143.760, 136.455, 128.248, 127.689, 127.543, 126.328, 98.699, 64.798, 53.560, 17.839; HR-MS (ESI): m/z = 567.2233 ($[M+H]^+$, $C_{32}H_{31}N_4O_6$: required = 567.2244).

4,4'-(1,4-phenylene)bis(5-acetyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one), 205. Yield: 78%, 1.490 g (pale-yellow solid); mp (ºC) > 300; ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 9.158 (2H, bs, NH-1/1'), 7.768 (2H, bs, NH-3/3'), 7.192 (4H, s, Ph), 5.222 (2H, s, CH), 2.277 (6H, s, CH_3), 2.110 (6H, s, $COCH_3$); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ, ppm = 194.131, 152.087, 148.050, 143.390, 126.534, 109.683, 53.498, 53.445, 30.366, 18.874; HR-MS (ESI): m/z = 383.1715 ($[M+H]^+$, $C_{20}H_{23}N_4O_4$: required = 383.1719).

Dimethyl 4,4'-(1,4-phenylene)bis(6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate), 206. Yield: 53%, 1.175 g (pale-yellow solid); mp (ºC) > 300; ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 10.344 (2H, bs, NH-1/1'), 9.630 (2H, bs, NH-3/3'), 7.192 (4H, s, Ph), 5.148 (2H, s, CH), 3.568 (6H, s, OCH_3), 2.288 (6H, s, CH_3); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ, ppm = 174.258, 165.576, 145.343, 142.809, 126.617, 126.584, 100.304, 53.610, 53.566, 51.144, 17.193; HR-MS (ESI): m/z = 447.1156 ($[M+H]^+$, $C_{20}H_{23}N_4O_4S_2$: required = 447.1161).

Diethyl 4,4'-(1,4-phenylene)bis(6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate), 207. Yield: 50%, 1.175 g (pale-yellow solid); mp (ºC) > 300; ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 10.311 (2H, bs, NH-1/1'), 9.606 (2H, bs, NH-3/3'), 7.188 (4H, s, Ph), 5.147 (2H, s, CH), 4.010 (4H, q, J = 6.8, O$CH_2$$CH_3$), 2.282 (6H, s, CH_3), 1.103 (6H, t, J = 6.8, OCH_2CH_3); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ, ppm = 174.198, 165.067, 145.031, 144.995, 142.976, 126.579, 100.618, 100.568, 59.594, 53.737, 17.134, 13.969; HR-MS (ESI): m/z = 475.1470 ($[M+H]^+$, $C_{22}H_{27}N_4O_4S_2$: required = 475.1474).

Dibenzyl 4,4'-(1,4-phenylene)bis(6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate), 208. Yield: 25%, 760 mg (yellow solid); mp (ºC) > 300; ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 10.217 (2H, bs, NH-1/1'), 9.514 (2H, bs, NH-3/3'), 7.254-7.159 (10H, m, Ph), 7.117 (4H, s, Ph), 5.214 (2H, s, CH), 5.093 (2H, d, J = 12, CH_2), 4.980 (2H, d, J = 12, CH_2), 2.341 (6H, s, CH_3); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ, ppm = 174.115, 164.656, 145.571, 142.867, 135.974, 128.047, 127.617, 127.514, 126.657, 100.188, 65.018, 53.935, 17.311; HR-MS (ESI): m/z = 599.1780 ($[M+H]^+$, $C_{32}H_{31}N_4O_4S_2$: required = 599.1787).

4,4'-(1,4-phenylene)bis(5-acetyl-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione), 209. Yield: 75%, 1.550 g (pale-yellow solid); mp (ºC) > 300; ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ, ppm = 10.264 (2H, bs, NH-1/1'), 9.704 (2H, bs, NH-3/3'), 7.191 (4H, s, Ph), 5.259 (2H, s, CH), 2.324 (6H, s, CH_3), 2.174 (6H, s, $COCH_3$); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ, ppm = 194.629, 174.137, 174.086, 144.544, 142.521, 142.453, 126.798, 126.741, 110.609, 53.472, 53.366, 30.524, 18.249; HR-MS (ESI): m/z = 415.1256 ($[M+H]^+$, $C_{20}H_{23}N_4O_2S_2$: required = 415.1262).

3. Synthesis of Biginelli-Type 3,4-Dihydropyrimidine-2(1*H*)-Thiones

A mixture of the selected chalcone* (5 mmol), thiourea (7.5 mmol, 578 mg) and sodium hydroxide (5 mmol, 202 mg) in ethanol (3 ml) was thoroughly mixed in an appropriate 10 ml thick-walled glass vial. This was tightly sealed with a Teflon cap and the reaction mixture was stirred and heated at 100 ºC for 20 minutes, under microwave irradiation, with an initial power setting of 100 W. After cooling to room temperature, the reaction product was poured over crushed-ice and a yellow solid precipitated. This was filtered under reduced pressure, thoroughly washed with distilled water and recrystallised in aqueous ethanol, yielding the desired Biginelli-type 3,4-dihydropyrimidine-2(1*H*)-thione as a white or yellowish solid (**210-217**, **219** and **220**). 3,4-Dihydropyrimidine-2(1*H*)-thione **218** did not easily precipitate from the alkaline reaction medium poured over crushed-ice. Hence, the reaction product was washed with distilled water (50 ml) and neutralised by the addition of aqueous hydrochloric acid (37% m/v) until a yellow solid precipitated. This was filtered under reduced pressure, thoroughly washed with distilled water and recrystallised in aqueous ethanol, yielding the desired Biginelli-type 3,4-dihydropyrimidine-2(1*H*)-thione as a white solid.

*The chalcones needed for the synthesis of Biginelli-type 3,4-dihydropyrimidine-2(1*H*)-thiones **211-221** were previously prepared through a procedure described by Kohler and Chadwell (see section 6.III.A.4., pages 139-141).[4]

4,6-Diphenyl-3,4-dihydropyrimidine-2(1*H*)-thione, 210. Yield: 86%, 1.140 g (white solid); mp (ºC): 171-173; ^{1}H NMR (400 MHz, $CCl_4/(CD_3)_2SO$): δ, ppm = 9.271 (1H, bs, NH-1), 8.906 (1H, bs, NH-3), 7.512 (2H, m, Ph), 7.372-7.321 (7H, m, Ph), 7.279-7.264 (1H, m, Ph), 5.201 (1H, s, CH-4), 5.156 (1H, d, J = 2, CH-5); ^{13}C NMR (100 MHz, $CCl_4/(CD_3)_2SO$): δ, ppm = 174.671, 143.802, 134.213, 133.388, 128.253, 128.176, 127.871, 127.113, 126.388, 125.531, 100.279, 55.197; HR-MS (ESI): m/z = 267.0951 ($[M+H]^+$, $C_{16}H_{15}N_2S$: required = 267.0956).

4-(Naphthalen-1-yl)-6-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione, 211. Yield: 86%, 1.355 g (pale-yellow solid); mp (ºC): 221-223; ^{1}H NMR (400 MHz, $CCl_4/(CD_3)_2SO$): δ, ppm = 9.705 (1H, bs, NH-1), 9.000 (1H, bs, NH-3), 8.198 (1H, d, J = 8.2, Ph), 7.927 (1H, d, J = 8.2, Ph), 7.834 (1H, d, J = 7.2, Ph), 7.598-7.510 (4H, m, Ph), 7.451-7.437 (2H, m, Ph), 7.308-7.294 (3H, m, Ph), 5.955 (1H, s, CH-5), 5.401 (1H, d, J = 4, CH-4); ^{13}C NMR (100 MHz, $CCl_4/(CD_3)_2SO$): δ, ppm = 175.703, 139.227, 134.210, 133.417, 133.269, 129.146, 128.476, 127.996, 127.642, 126.210, 125.624, 125.475, 123.850, 122.209, 100.640, 52.014; HR-MS (ESI): m/z = 317.1109 ($[M+H]^+$, $C_{20}H_{17}N_2S$: required = 317.1112).

4-(Phenanthren-9-yl)-6-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione, 212. Yield: 85%, 1.560 g (white solid); mp (ºC): 223-224; ^{1}H NMR (400 MHz, $CCl_4/(CD_3)_2SO$): δ, ppm = 9.642 (1H, bs, NH-1), 9.048 (1H, bs, NH-3), 8.817-8.794 (1H, m, Ph), 8.707 (1H, d, J = 8, Ph), 8.248-8.225 (1H, m, Ph), 7.951 (1H, d, J = 7.2, Ph), 7.751 (1H, s, Ph), 7.705-7.685 (2H, m, Ph), 7.664-7.577 (2H, m, Ph), 7.471-7.453 (2H, m, Ph), 7.290-7.276 (3H, m, Ph), 5.979 (1H, s, CH-5), 5.462 (1H, d, J = 3.2, CH-4); ^{13}C NMR (100 MHz, $CCl_4/(CD_3)_2SO$): δ, ppm = 175.899, 137.026, 134.479, 133.269, 130.922, 130.339, 129.342, 128.345, 128.192, 127.745, 126.548, 126.343, 126.330, 126.065, 125.536, 124.406, 123.468, 123.039, 122.114, 100.100, 52.296; HR-MS (ESI): m/z = 367.1266 ($[M+H]^+$, $C_{24}H_{19}N_2S$: required = 367.1269).

4-(Anthracen-9-yl)-6-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione, 213. Yield: 80%, 1.460 g (yellow solid); mp (°C): 175-177; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.630 (1H, bs, NH-1), 8.945 (1H, bs, NH-3), 8.536 (3H, bs, Ph), 8.064 (2H, d, J = 7.6, Ph), 7.536-7.479 (4H, m, Ph), 7.489 (2H, d, J = 7.6, 2H, Ph), 7.316 (3H, bs, Ph), 6.928 (1H, s, CH-5), 5.197 (1H, s, CH-4); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 175.083, 133.950, 133.229, 132.419, 131.046, 129.607, 128.816, 128.229, 128.144, 127.860, 125.607, 125.415, 124.399, 101.157, 50.710; HR-MS (ESI): m/z = 367.1266 ($[M+H]^+$, $C_{24}H_{19}N_2S$: required = 367.1269).

6-Phenyl-4-(pyren-1-yl)-3,4-dihydropyrimidine-2(1*H*)-thione, 214. Yield: 83%, 1.620 g (yellow solid); mp (°C): 225-227; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.757 (1H, bs, NH-1), 9.188 (1H, bs, NH-3), 8.460 (1H, d, J = 9.2, Ph), 8.295 (1H, d, J = 8, Ph), 8.250-8.206 (3H, m, Ph), 8.103 (3H, bs, Ph), 8.030 (1H, t, J = 7.6, Ph), 7.469-7.462 (2H, m, Ph), 7.291 (3H, bs, Ph), 6.295 (1H, s, CH-5), 5.444 (1H, s, CH-4); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 175.612, 137.239, 134.091, 133.296, 130.786, 130.154, 130.109, 128.469, 128.002, 127.756, 127.143, 127.013, 126.256, 125.873, 125.647, 125.165, 125.095, 124.803, 124.421, 124.203, 124.125, 122.241, 100.867, 52.190; HR-MS (ESI): m/z = 391.1263 ($[M+H]^+$, $C_{26}H_{19}N_2S$: required = 391.1269).

4-(4-Bromophenyl)-6-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione, 215. Yield: 81%, 1.400 g (white solid); mp (°C): 199-200; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.477 (1H, bs, NH-1), 8.987 (1H, bs, NH-3), 7.501-7.487 (4H, m, Ph), 7.322-7.287 (5H, m, Ph), 5.204 (1H, s, CH-4), 5.127 (1H, s, CH-5); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 174.739, 142.918, 134.568, 133.170, 131.057, 128.261, 127.770, 125.558, 120.583, 99.683, 54.263; HR-MS (ESI): m/z = 345.00484 ($[M+H]^+$, $C_{16}H_{14}N_2SBr$: required = 345.00556).

4-(4-Chlorophenyl)-6-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione, 216. Yield: 83%, 1.250 g (white solid); mp (°C): 167-168; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.524 (1H, bs, NH-1), 8.995 (1H, bs, NH-3), 7.503-7.493 (2H, m, Ph), 7.352-7.328 (7H, m, Ph), 5.218 (1H, s, CH-4), 5.141 (1H, s, CH-5); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 174.762, 142.488, 134.557, 133.180, 132.279, 128.329, 128.170, 1297.935, 127.829, 125.595, 99.858, 54.177; HR-MS (ESI): m/z = 301.05562 ($[M+H]^+$, $C_{16}H_{14}N_2SCl$: required = 301.05607).

4-(4-Methoxyphenyl)-6-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione, 217. Yield: 82%, 1.220 g (white solid); mp (°C): 178-180; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.392 (1H, bs, NH-1), 8.879 (1H, bs, NH-3), 7.515-7.501 (2H, m, Ph), 7.344-7.329 (3H, m, Ph), 7.265 (2H, d, J = 8.4, Ph), 6.878 (2H, d, J = 8.4, Ph), 5.203 (1H, d, J = 3.6, CH-5), 5.073 (1H, s, CH-4), 3.769 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 174.363, 158.594, 135.894, 134.088, 133.370, 128.246, 127.869, 127.570, 125.529, 113.542, 100.576, 54.677, 54.372; HR-MS (ESI): m/z = 297.10663 ($[M+H]^+$, $C_{17}H_{17}N_2OS$: required = 297.10561).

4-(3-Hydroxyphenyl)-6-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione, 218. Yield: 80%, 1.125 g (white solid); mp (°C): 204-205; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.470 (1H, bs, NH-1), 9.255 (1H, bs, OH), 8.910 (1H, bs, NH-3), 7.515-7.501 (2H, m, Ph), 7.345-7.331 (3H, m, Ph), 7.129 (1H, t, J = 7.6, Ph), 6.762 (2H, bs, Ph), 6.663 (1H, d, J = 7.6, Ph), 5.224 (1H, s, CH-4), 5.028 (1H, s, CH-5); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 174.663, 157.582, 145.158, 134.012, 133.346, 129.154, 128.370, 127.973, 125.614, 116.737, 114.394, 113.221, 100.716, 54.902; HR-MS (ESI): m/z = 283.08993 ($[M+H]^+$, $C_{16}H_{15}N_2OS$: required = 283.08996).

6-(4-Bromophenyl)-4-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione, 219. Yield: 80%, 1.370 g (white solid); mp (°C): 221-223; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.581 (1H, bs, NH-1), 8.899 (1H, bs, NH-3), 7.452 (4H, bs, Ph), 7.352-7.342 (4H, m, Ph), 7.275-7.255 (1H, m, Ph), 5.219 (1H, s, CH-5), 5.124 (1H, s, CH-4); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 174.683, 143.649, 133.388, 132.390, 130.759, 128.142, 127.498, 127.095, 126.324, 121.913, 100.782, 55.080; HR-MS (ESI): m/z = 345.00513 ($[M+H]^+$, $C_{16}H_{14}N_2SBr$: required = 345.00556).

6-(4-Chlorophenyl)-4-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione, 220. Yield: 84%, 1.320 g (white solid); mp (°C): 215-217; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 9.670 (1H, bs, NH-1), 8.960 (1H, bs, NH-3), 7.516 (2H, d, J = 8.8, Ph), 7.362-7.338 (4H, m, Ph), 7.327 (2H, d, J = 8.8, Ph), 7.288-7.268 (1H, m, Ph), 5.256 (1H, d, J = 4, CH-5), 5.130 (1H, s, CH-4); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 174.722, 143.698, 133.456, 133.271, 131.938, 128.180, 127.83, 127.306, 127.126, 126.262, 100.922, 54.918; HR-MS (ESI): m/z = 301.05636 ($[M+H]^+$, $C_{16}H_{14}N_2SCl$: required = 301.05607).

4. Oxidation of Biginelli 3,4-Dihydropyrimidin-2(1*H*)-Ones

A mixture of the selected Biginelli 3,4-dihydropyrimidin-2(1*H*)-one (1 mmol) and potassium peroxydisulphate (1.2 mmol, 324 mg) in acetonitrile/distilled water (3:2 v/v, 5 ml) was thoroughly mixed in an appropriate 10 ml thick-walled glass vial. This was tightly sealed with a Teflon cap and the reaction mixture was stirred and heated at 100 °C for 10 minutes, under microwave irradiation, with an initial power setting of 80 W. After cooling to room temperature, the reaction product was washed with brine (50 ml) and extracted with ethyl acetate (2x25 ml). The organic phase was collected, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure and the yellow solid obtained was recrystallised in diethyl ether or ethyl acetate/*n*-hexane, yielding the desired Biginelli pyrimidin-2(1*H*)-one as a yellow solid (**221-238**).

Methyl 6-methyl-4-phenylpyrimidin-2(1*H*)-one-5-carboxylate, 221. Yield: 85%, 205 mg (yellow solid); mp (°C): 205-207; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 7.448-7.429 (5H, m, Ph), 3.468 (3H, s, OCH_3), 2.408 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 166.049, 160.703, 155.157, 137.761, 129.614, 127.599, 127.227, 108.460, 51.216, 18.035; GC-MS (EI): m/z (t_R, min) = 244 (12.05) (M^+).

Methyl 6-methyl-4-(naphthalen-1-yl)pyrimidin-2(1*H*)-one-5-carboxylate, 222. Yield: 80%, 235 mg (yellow solid); mp (°C): 217-219; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 7.975-7.958 (2H, m, Ph), 7.835 (1H, d, J = 7.8, Ph), 7.583-7.511 (3H, m, Ph), 7.406 (1H, d, J = 7.8, Ph), 3.096 (3H, s, OCH_3), 2.555 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.161, 155.105, 132.680, 130.313, 129.801, 128.925, 127.936, 126.172, 125.704, 124.939, 124.680, 124.508, 108.938, 50.921, 19.182; MS (ESI): m/z = 295 ($[M+H]^+$).

Methyl 6-methyl-4-(phenanthren-9-yl)pyrimidin-2(1*H*)-one-5-carboxylate, 223. Yield: 83%, 285 mg (yellow solid); mp (°C): 248-250; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 8.793 (1H, d, J = 7.8, Ph), 8.755 (1H, d, J = 8, Ph), 7.960 (1H, d, J = 8, Ph), 7.819 (1H, d, J = 8, Ph), 7.738-7.572 (5H, m, Ph), 3.022 (3H, s, OCH_3), 2.558 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.059, 155.203, 130.307, 129.922, 129.515, 128.876, 128.786, 127.188, 126.683, 126.454, 126.022, 125.439, 122.701, 122.379, 110.079, 50.894, 17.519; MS (ESI): m/z = 354 ($[M+H]^+$).

Methyl 4-(2-bromophenyl)-6-methylpyrimidin-2(1*H*)-one-5-carboxylate, 224. Yield: 81%, 260 mg (yellow solid); mp (°C): 188-190; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 12.585 (1H, bs, NH), 7.580 (1H, d, J = 7.6, Ph), 7.412 (1H, t, J = 7.6, Ph), 7.318-7.252 (2H, m, Ph), 3.419 (3H, s, OCH_3), 2.536 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 164.218, 161.786, 161.665, 154.824, 154.752, 131.630, 129.560, 128.889, 126.765, 119.525, 108.385, 51.108, 18.775; MS (ESI): m/z = 323 ($[M+H]^+$).

Methyl 4-(2-chlorophenyl)-6-methylpyrimidin-2(1*H*)-one-5-carboxylate, 225. Yield: 83%, 230 mg (yellow solid); mp (°C): 197-199; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 12.580 (1H, bs, NH), 7.378-7.353 (3H, m, Ph), 7.315-7.294 (1H, m, Ph), 3.427 (3H, s, OCH_3), 2.534 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 164.324, 154.886, 130.327, 129.587, 129.104, 128.460, 126.307, 108.638, 51.094, 18.850; MS (ESI): m/z = 279 ($[M+H]^+$).

Methyl 4-(2,6-dichlorophenyl)-6-methylpyrimidin-2(1*H*)-one-5-carboxylate, 226. Yield: 80%, 250 mg (yellow solid); mp (°C): 156-158; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 7.441-7.344 (3H, m, Ph), 3.475 (3H, s, OCH_3), 2.588 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 163.451, 154.857, 137.195, 131.630, 129.594, 127.265, 107.848, 51.198, 19.717; MS (ESI): m/z = 313 ($[M+H]^+$).

Methyl 4-mesityl-6-methylpyrimidin-2(1*H*)-one-5-carboxylate, 227. Yield: 80%, 230 mg (yellow solid); mp (°C): 162-164; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 6.828 (2H, s, Ph), 3.391 (3H, s, OCH_3), 2.446 (3H, s, CH_3), 2.303 (3H, s, CH_3), 2.062 (s, 6H, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.044, 155.273, 135.895, 133.836, 127.379, 126.833, 109.981, 51.171, 20.750, 19.161, 19.087; MS (ESI): m/z = 287 ($[M+H]^+$).

Methyl-6-methyl-4-(3-nitrophenyl)pyrimidin-2(1*H*)-one-5-carboxylate, 228. Yield: 87%, 250 mg (yellow solid); mp (°C): 191-193; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 8.327 (1H, d, J = 7.8, Ph), 8.308 (1H, s, Ph), 7.849 (1H, d, J = 7.8, Ph), 7.725 (1H, t, J = 7.8, Ph), 3.538 (3H, s, OCH_3), 2.475 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 169.431, 165.530, 161.865, 154.969, 147.472, 139.796, 133.597, 129.461, 124.345, 122.243, 108.215, 51.654, 18.227; MS (ESI): m/z = 290 ($[M+H]^+$).

Methyl 4-(3-methoxyphenyl)-6-methylpyrimidin-2(1*H*)-one-5-carboxylate, 229. Yield: 85%, 235 mg (yellow solid); mp (°C): 127-129; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 12.356 (1H, bs, NH), 7.310 (1H, t, J = 8, Ph), 7.041 (1H, s, Ph), 6.981 (2H, d, J = 8, Ph), 3.843 (3H, s, OCH_3), 3.505 (3H, s, OCH_3), 2.410 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 166.266, 158.957, 155.298, 128.775, 128.739, 119.510, 115.940, 112.942, 108.761, 54.850, 51.462, 18.284; MS (ESI): m/z = 275 ($[M+H]^+$).

Methyl 4-(4-*t*-butylphenyl)-6-methylpyrimidin-2(1*H*)-one-5-carboxylate, 230. Yield: 87%, 260 mg (yellow solid); mp (°C): 158-160; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 7.418 (4H, s, Ph), 3.511 (3H, s, OCH_3), 2.398 (3H, s, CH_3), 1.355 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 168.164, 166.393, 155.332, 152.801, 127.346, 124.556, 108.654, 51.356, 34.429, 30.918, 18.386; MS (ESI): m/z = 301 ($[M+H]^+$).

Methyl 6-methyl-4-*p*-tolylpyrimidin-2(1*H*)-one-5-carboxylate, 231. Yield: 85%, 220 mg (yellow solid); mp (°C): 177-179; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 7.381 (2H, d, J = 7.6, Ph), 7.212 (2H, d, J = 7.6, Ph), 3.507 (3H, s, OCH_3), 2.417 (3H, s, CH_3), 2.400 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 169.436, 166.347, 161.452, 155.307, 139.672, 134.823, 128.368, 127.515, 108.474, 51.308, 21.024, 18.258; MS (ESI): m/z = 259 ($[M+H]^+$).

Methyl 4-(4-bromophenyl)-6-methylpyrimidin-2(1*H*)-one-5-carboxylate, 232. Yield: 90%, 290 mg (yellow solid); mp (°C): 186-187; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 12.430 (1H, bs, NH), 7.562 (2H, d, J = 8.4, Ph), 7.398 (2H, d, J = 8.4, Ph), 3.523 (3H, s, OCH_3), 2.419 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.764, 164.554, 160.865, 155.010, 137.028, 130.691, 129.158, 123.806, 108.053, 51.277, 17.887; GC-MS (EI): m/z (t_R, min) = 322 (12.87) (M^+).

Methyl 4-(4-chlorophenyl)-6-methylpyrimidin-2(1*H*)-one-5-carboxylate, 233. Yield: 87%, 245 mg (yellow solid); mp (°C): 165-167; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 12.428 (1H, bs, NH), 7.470 (2H, d, J = 8.4, Ph), 7.403 (2H, d, J = 8.4, Ph), 3.519 (3H, s, OCH_3), 2.420 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 165.799, 155.023, 136.503, 135.370, 128.937, 127.757, 108.090, 51.248, 17.932; GC-MS (EI): m/z (t_R, min) = 278 (12.40) (M^+).

Methyl 4-(4-fluorophenyl)-6-methylpyrimidin-2(1*H*)-one-5-carboxylate, 234. Yield: 85%, 225 mg (yellow solid); mp (°C): 151-153; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 12.382 (1H, bs, NH), 7.524 (2H, dd, J = 8.4, 5.6, Ph), 7.163 (2H, t, J = 8.4, Ph), 3.528 (3H, s, OCH_3), 2.417 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 169.273, 166.106, 163.302 (C, d, J = 248), 161.238, 155.157, 134.073, 129.777 (2xCH, d, J = 8.6), 114.861 (2xCH, d, J = 21.7), 108.369, 51.483, 18.166; MS (ESI): m/z = 263 ($[M+H]^+$).

Methyl-6-methyl-4-(4-nitrophenyl)pyrimidin-2(1*H*)-one-5-carboxylate, 235. Yield: 90%, 260 mg (yellow solid); mp (°C): 220-222; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 8.283 (2H, d, J = 8.6, Ph), 7.690 (2H, d, J = 8.6, Ph), 3.512 (3H, s, OCH_3), 2.480 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 169.776, 165.303, 162.027, 154.926, 148.076, 144.485, 128.611, 122.899, 108.103, 51.453, 18.248; MS (ESI): m/z = 290 ($[M+H]^+$).

Methyl 4-(4-methoxyphenyl)-6-methylpyrimidin-2(1*H*)-one-5-carboxylate, 236. Yield: 88%, 240 mg (yellow solid); mp (°C): 189-191; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 12.227 (1H, bs, NH), 7.451 (2H, d, J = 8.4, Ph), 6.918 (2H, d, J = 8.4, Ph), 3.842 (3H, s, OCH_3), 3.535 (3H, s, OCH_3), 2.377 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 166.475, 160.920, 155.202, 129.494, 129.179, 113.096, 108.153, 54.734, 51.298, 18.120; GC-MS (EI): m/z (t_R, min) = 274 (13.09) (M^+).

Methyl 4-(2,4-dichlorophenyl)-6-methylpyrimidin-2(1*H*)-one-5-carboxylate, 237. Yield: 83%, 260 mg (yellow solid); mp (°C): 197-199; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 12.645 (1H, bs, NH), 7.428 (1H, s, Ph), 7.389 (1H, d, J = 8.6, Ph), 7.326 (1H, d, J = 8.6, Ph), 3.494 (3H, s, OCH_3), 2.540 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 164.111, 154.573, 137.589, 134.129, 131.332, 130.676, 128.075, 126.659, 108.311, 51.161, 18.783; MS (ESI): m/z = 313 ($[M+H]^+$).

Methyl 4-(3,5-dimethoxyphenyl)-6-methylpyrimidin-2(1*H*)-one-5-carboxylate, 238. Yield: 85%, 260 mg (yellow solid); mp (°C): 200-201; ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 6.576 (2H, s, Ph), 6.507 (1H, s, Ph), 3.800 (6H, s, OCH_3), 3.532 (3H, s, OCH_3), 2.394 (3H, s, CH_3); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm = 166.313, 160.021, 155.335, 139.357, 108.894, 105.168, 102.208, 54.920, 51.497, 18.190; MS (ESI): m/z = 305 ($[M+H]^+$).

F. Spectral & Photophysical Studies

Absorption and fluorescence emission spectra of the selected 3,5-diaryl-2-methyl-1*H*-pyrroles were recorded at room temperature (293 K) on a Shimadzu UV-2100 and a Horiba-Jobin-Ivon Fluorolog 3-22 spectrometer, respectively, using methylcyclohexane as solvent. Ground state or singlet molar extinction coefficients (ε_S) were obtained according to the Beer-Lambert law from absorption measurements using solutions of six different concentrations. Fluorescence quantum yields (Φ_F) were measured utilising quinine sulphate in a 0.5 M H_2SO_4 solution as reference (Φ_F=0.545). The experimental set-up used in order to obtain room temperature triplet absorption spectra and triplet formation quantum yields (Φ_T) has been described elsewhere.[28, 29] Special care was taken in determining the latter, namely to have optically matched dilute solutions (absorbance ≈ 0.2 in a 1 cm square cell) and low laser energy (< 2 mJ) to avoid multiphoton and triplet-triplet annihilation effects. The triplet molar extinction coefficients (ε_T) were found either by the singlet depletion[30] or the partial saturation methodology.[30, 31] Phosphorescence emission spectra of the selected 3,5-diaryl-2-methyl-1*H*-pyrroles were registered in methylcyclohexane glasses at 77 K using a Horiba-Jobin-Ivon Fluorolog 3-22 spectrometer equipped with a 1934 D phosphorimeter. Phosphorescence quantum yields (Φ_P) were determined utilising benzophenone (Φ_P=0.84) as standard.[32] All fluorescence and phosphorescence emission spectra were corrected for the wavelength response of the system. Room temperature singlet oxygen phosphorescence was detected at 1270 nm

using a Hamamatsu R5509-42 photomultiplier, cooled to 193 K in a liquid nitrogen chamber (Products for Research model PC176TSCE-005), following laser excitation of the aerated solutions at 266 nm or 355 nm, with an adapted Applied Photophysics flash kinetic spectrometer, as reported elsewhere.[33] Biphenyl in cyclohexane (λ_{exc}=266 nm, Φ_{Δ}=0.73) or phenalen-1-one in toluene (λ_{exc}=355 nm, Φ_{Δ}=0.93) were employed as standard.[34, 35]

G. Cytotoxicity Studies

MCF7, HCC1806, WiDr and A375 cell cultures were incubated with different solutions of the selected Biginelli-type 3,4-dihydropyrimidine-2(1*H*)-thiones, concentration values ranging from 1 to 100 μM. After 48 hours of incubation, cell proliferation was assessed by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay.[36] Two control experiments were performed in all tests: untreated cultures and cultures treated solely with dimethylsulfoxide (DMSO), the administration vehicle of the compounds. Cytotoxicity was expressed as the inhibition percentage of cultures subjected to the compounds correlated with cultures treated only with DMSO. Dose-response curves were obtained using the OriginPro 8.0 software by fitting to a sigmoidal curve, the concentration inhibiting the proliferation of the cells in 50% (IC_{50}) being calculated. Differences between concentration-response curves were determined through one-way ANOVA followed by Bonferroni's *post hoc* analysis for pairwise comparisons. The statistical significance level was set at 0.05.

IV. References

1. WLF Armarego, DD Perrin, *Purification of Laboratory Chemicals*, Fourth Edition, Butterworth-Heinemann, Oxford, MA, USA, 1997.
2. CAC Haley, P Maitland, *J. Chem. Soc.* (**1951**) 3155-3174.
3. F Texier-Boullet, B Klein, J Hamelin, *Synthesis* (**1986**) 409-411.
4. EP Kohler, HM Chadwell, *Org. Synth. Coll. Vol. 1* (**1941**) 78.
5. DO Alonso Garrido, G Buldain, B Frydman, *J. Org. Chem.* 49 (**1984**) 2619-2622.
6. *Beilstein* **7**, 478.
7. http://www.sigmaaldrich.com/catalog/product/aldrich/558311?lang=en&region=GB.
8. *Beilstein* **7**, 1659.
9. *Beilstein* **7**, 482.
10. *Beilstein* **8**, 192.
11. http://www.sigmaaldrich.com/catalog/product/aldrich/s455393?lang=en&region=GB.
12. http://www.sigmaaldrich.com/catalog/product/aldrich/558303?lang=en&region=GB.
13. RA Coburn, M Wierzba, MJ Suto, AJ Solo, AM Triggle, DJ Triggle, *J. Med. Chem.* 31 (**1988**) 2103-2107.
14. C López-Alarcón, H Speisky, JA Squella, C Olea-Azar, C Camargo, LJ Núñez-Vergara, *Pharm. Res.* 21 (**2004**) 1750-1757.
15. H Salehi, Q-X Guo, *Synth.Commun.* 34 (**2004**) 4349-4357.
16. RH Böcker, FP Guengerich, *J. Med. Chem.* 29 (**1986**) 1596-1603.
17. SP Chavan, RK Kharul, UT Kalkote, I Shivakumar, *Synth. Commun.* 33 (**2003**) 1333-1340.
18. EH Hu, DR Sidler, U-H Dolling, *J. Org. Chem.* 63 (**1998**) 3454-3457.
19. I Cepanec, M Litvic, A Bartolincic, M Lovric, *Tetrahedron* 61 (**2005**) 4275-4280.
20. A Arfan, L Paquin, JP Bazureau, *Russ. J. Org. Chem.* 43 (**2007**) 1058-1064.
21. SA Kotharkar, MR Jadhav, RR Nagawade, SS Bahekar, DB Shinde, *Lett. Org. Chem.* 2 (**2005**) 662-664.
22. W Su, J Li, Z Zheng, Y Shen, *Tetrahedron Lett.* 46 (**2005**) 6037-6040.
23. SP Maradur, GS Gokavi, *Catal. Commun.* 8 (**2007**) 279-284.

24. NY Fu, Y F Yuan, Z Cao, SW Wang, JC Wang, C Peppe, *Tetrahedron* 58 (**2002**) 4801-4807.

25. D Dalinger, CO Kappe, *Nature Protocols* 2 (**2007**) 1713-1721.

26. Y Ma, C Qian, L Wang, M Yang, *J. Org. Chem.* 65 (**2000**) 3864-3868.

27. AK Misra, G Agnihotri, SK Mahusudan, *Ind. J. Chem. B* 43B (2004) 2018-2020.

28. J Pina, HD Burrows, RS Becker, FB Dias, AL Maçanita, JS Seixas de Melo, *J. Phys. Chem. B* 110 (**2006**) 6499-6505.

29. J Pina, JS Seixas de Melo, HD Burrows, A Bilge, T Farrell, M Forster, U Scherf, *J. Phys. Chem. B* 110 (**2006**) 15100-15106.

30 C Ian, LH Gordon, *J. Phys. Chem. Ref. Data* 15 (**1986**) 1-250.

31. E Oliveros, P Suardimurasecco, T Aminiansaghafi, AM Braun, HJ Hansen, *Helv. Chim. Acta* 74 (1991) 79-90.

32. M Montalti, A Credi, L Prodi, MT Gandolfi, *Handbook of Photochemistry*, Third Edition, CRC Press, Boca Raton, FL, USA, 2006.

33. J Pina, JS Seixas de Melo, *Phys. Chem. Chem. Phys.* 11 (**2009**) 8706-8713.

34. C Flors, S Nonell, *Helv. Chim. Acta* 84 (**2001**) 2533-2539.

35. M Kristiansen, RD Scurlock, KK Iu, PR Ogilby, *J. Phys. Chem.* 95 (**1991**) 5190-5197.

36. T Mosmann, *J. Immunol. Meth.* 65 (**1983**) 55-63.