Tryptanthrin and its derivatives in drug discovery: synthetic insights

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ABSTRACT

Tryptanthrin is a golden-yellow naturally occurring alkaloid that can be obtained from multiple sources and through different synthetic methodologies and that displays several relevant biological activities. The potential of this tetracyclic alkaloid has been widely explored, and several researchers focused their attention in expanding the variety of tryptanthrin derivatives using different synthetic strategies. In this short-review, we aim to address recent developments in the synthesis of the tryptanthrin core, as well as the development of new strategies employed by synthetic organic chemists to obtain novel tryptanthrin derivatives with potential biological activity, using different tools from the chemists' toolbox, such as photocatalysis, solvent-free approaches, and multicomponent reactions.

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1. Introduction

Tryptanthrin (**1**) is a golden-yellow indoloquinazoline alkaloid. Its structure was proposed by Friedländer and Roschdestwensky in 1915, after preparing the tetracyclic compound from air oxidation of indigo (**2**) at high temperatures and also from the chemical reaction between isatin (**3**) and anthranilic acid (**4**).[1] The name tryptanthrin was coined later, in 1971, when the compound was isolated from *Candida lipolytica* grown in the presence of high concentration of tryptophan,[2] with its crystal structure being confirmed a few years later.[3]

Tryptanthrin has been isolated from several natural sources, including plants such as *Strobilanches cusia*, *Persicaria tinctoria*, *Isatis tinctoria*, *Couroupita guianensis*, *Wrightia* spp. and *Calanthe* spp., showing a wide natural and geographical distribution of the compound across different genus of the kingdom *Plantae*. Many of these plants are used in folk medicine and were traditional sources of dyes. The presence of tryptanthrin might, in some of the cases, not due to biosynthetic paths existent in the different plants but formed during the treatment of the natural sources (namely during drying and oxidation processes).[4] Recent studies indicate the potential of tryptanthrin to play an ecological role as a phytoalexin in *Isatis tinctoria*, being produced as a mechanism of defense against phytoparasites.[5]

This alkaloid has also been isolated from several microorganisms besides *Candida lipolytica*, including *Pseudomonas aeruginosa*, *Oceanibulbus indolifex*, *Cytophaga* sp. strain AM13.1, *Schizophyllum commune*, and *Leucopaxillus cerealis*.[6, 7] Among mammals, tryptanthrin was detected in the urine of the Asian elephant,[8] and in the wing sac liquid of *Saccopteryx bilineata* (greater sac-winged bat).[9]

Tryptanthrin has caught the attention of several researchers due to the wide biological activities that it displays. It already showed potential as antifungal,[10] antibacterial,[6, 11] antiviral,[12] anticancer,[13] antiangiogenic,[14] anti-inflammatory,[15] antioxidant,[16] and antiallergic[17] agent in several *in silico*, *in vitro* and *in vivo* studies. Besides its therapeutic potential, the pharmacokinetic profile of tryptanthrin is also very promising, since it presents good oral absorption and tissue distribution, including the ability to cross the blood-brain barrier.[18] In the quest for new bioactive compounds these features motivated multiple researchers to explore new synthetic routes to prepare tryptanthrin, as well as new tryptanthrin derivatives.[19, 20] In this work, we will highlight recent advances in the synthesis of tryptanthrin and its derivatives, relevant for the preparation of bioactive compounds like the ones depicted in **Figure 1.**

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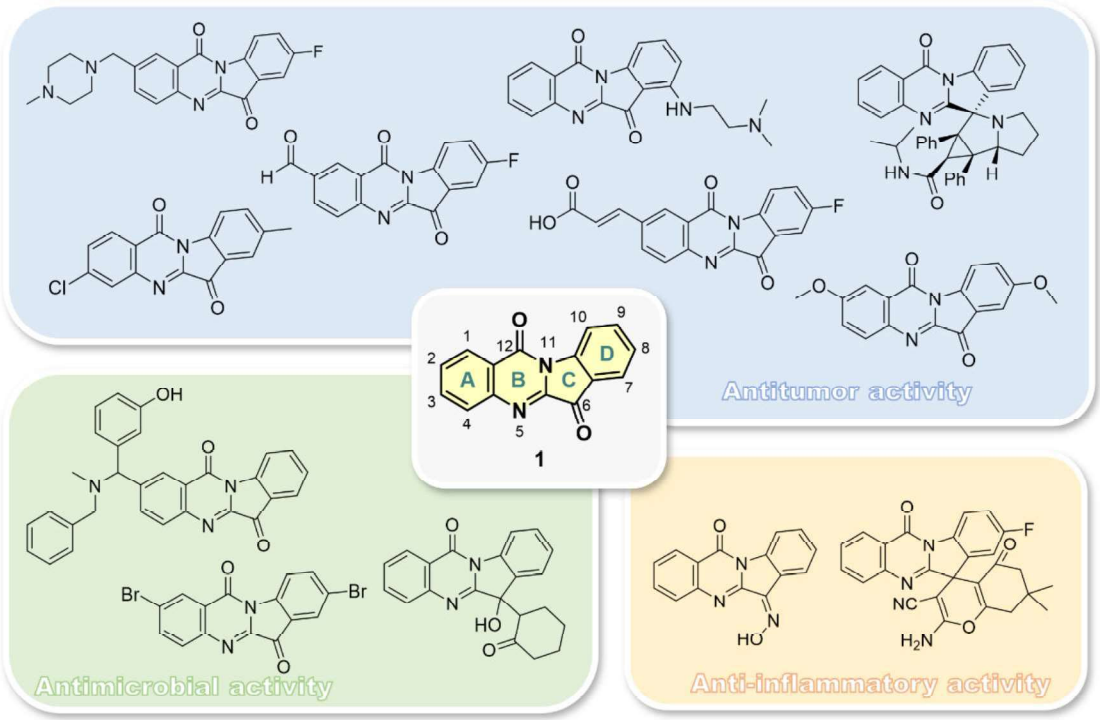


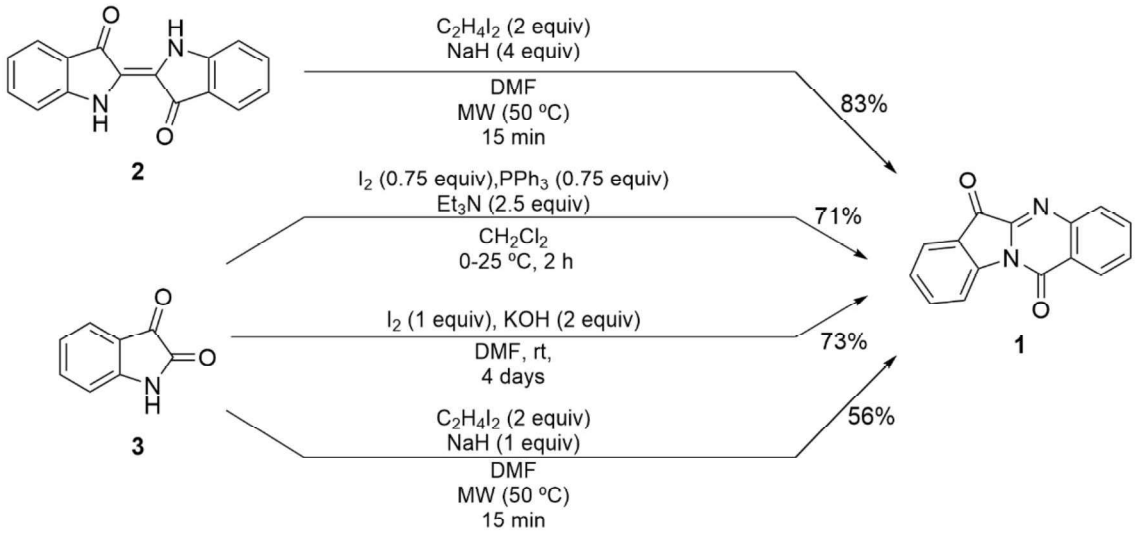
Figure 1. Tryptanthrin and examples of tryptanthrin derivatives with biological activity.

2. New approaches for the synthesis of tryptanthrin

The synthetic approaches to attain this valuable tetracyclic alkaloid can be widely divided into two main groups, the condensation reactions and the oxidation reactions. While most conventional condensation approaches comprise the reaction between isatin and anthranilic acid derivatives, including isatoic anhydride (**5**), the oxidative processes usually involve the oxidation of indigo to isatin, which is further oxidized to isatoic anhydride, followed by the condensation of these two compounds, in the presence of strong oxidizing agents. Other indole derivatives can also be applied in this sort of chemical transformations.[19, 20] Since the last review on this topic was published in 2017,[20] in this follow-up short review we will focus our attention on reports published in the last five years and respective advances in this field.

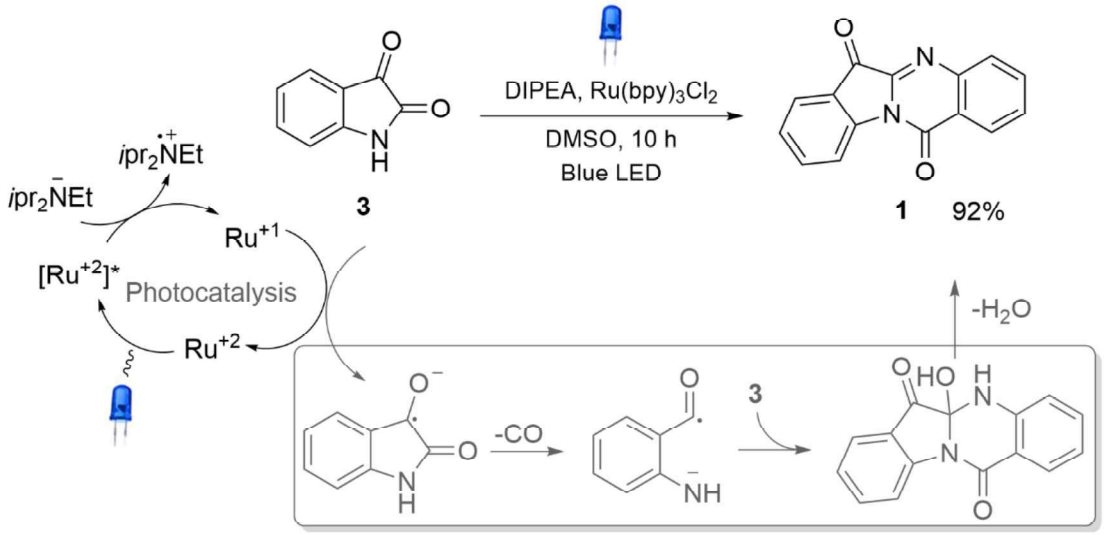
Molecular iodine is widely used in oxidative processes and metal-free catalysis, as well as the synthesis of valuable heterocycles.[21] Recent accounts report the application of iodine in the synthesis of tryptanthrin (**Scheme 1**) from isatin, aryl substituted isatins, and indigo. Pattarawarapan *et al.* used substoichiometric amounts of molecular iodine and triphenylphosphine in the presence of an excess of an organic base (triethylamine) in dichloromethane to achieve tryptanthrin (71%) and aryl substituted tryptanthrins (5 examples, 40-84% yield).[22] Amara *et al.* used stoichiometric quantities of molecular iodine in the presence of potassium hydroxide, using *N,N*-dimethylformamide (DMF) as

solvent. Tryptanthrin (73%) and aryl-substituted tryptanthrins (7 examples, 15-80% yield) were successfully obtained using this approach.[23] Using the same solvent, with sodium hydride as base, and other iodine sources besides I_2, like 1,2-diiodoethane, our group reported the successful synthesis of tryptanthrin from isatin (56% yield) and also from indigo (83% yield). The use of two other dyes, Tyrian Purple and Tina Blue, also led to the formation of the corresponding di- and tetra-bromotryptanthrin derivatives. This approach presents inherent advantages over the other two approaches not only with regard to the starting material and iodine source, but also that by using microwave irradiation (MW) there is considerable reduction in reaction time.[24]



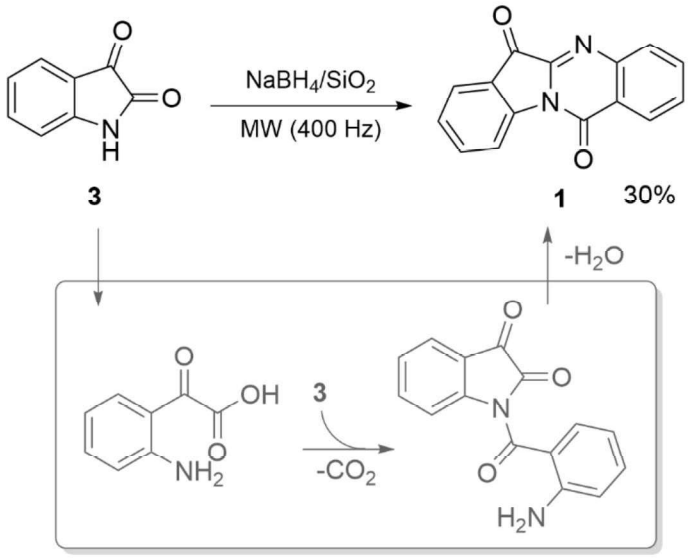
Scheme 1. Iodine-promoted approaches for tryptanthrin synthesis.

Tryptanthrin was also prepared from isatin via a photoredox process in aprotic solvents, using a ruthenium photocatalyst in the presence of a base. Briefly, $[Ru(bpy)_3Cl_2]$, in its photoexcited state, is able to accept an electron from the base to generate $[Ru]^{+1}$, which donates an electron to generate an isatin radical anion in order to revert to its original state and hence restart the catalytic cycle. In an aprotic solvent (DMSO), the decarbonylation of amides is promoted, leading to a new radical, which reacts with a second molecule of isatin, generating a tetracyclic framework which undergoes dehydration to form tryptanthrin (**Scheme 2**). This approach was suitable for the synthesis of tryptanthrin (92% yield) and di-substituted tryptanthrins (using aryl-substituted isatins) (6 examples, 72-93% yield).[25]



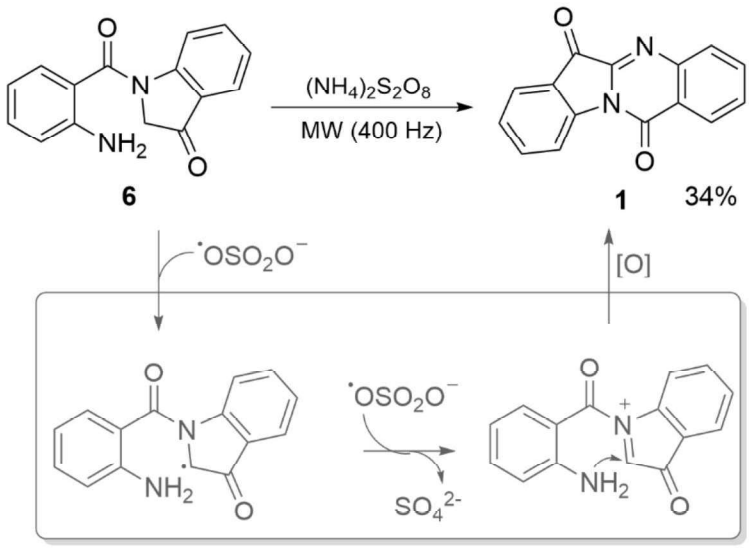
Scheme 2. Photoredox-catalyzed tryptanthrin synthesis from isatin.

Also using isatin as starting material, Obafemi *et al*. reported a solid-state-supported sodium borohydride reduction reaction to attain tryptanthrin. The reaction proceeded by grinding isatin, sodium borohydride and silica in a mortar to a fine powder followed by MW irradiation under solvent-free conditions. The authors proposed a mechanism involving a first ring-opening step via a hydrolysis of the 2-carbonyl unit to form 2-aminophenylglyoxylic acid, followed by condensation with a second isatin molecule, with loss of CO_2, which further reacts via intramolecular cyclization to afford tryptanthrin in moderate yield (30%) (**Scheme 3**).[26]



Scheme 3. MW-assisted reduction of isatin to tryptanthrin using $NaBH_4/SiO_2$.

Using a different starting material, Zheng and co-workers explored the use of the oxidant $(NH_4)_2S_2O_8$ to promote C-H/N-H cross dehydrogenative coupling to attain several polycyclic quinazolinones, including tryptanthrin (34%). Mechanistically, the reaction seems to be reliant on the formation of a carbon-centered radical and amide iminium ion intermediate, using 1-(2-aminobenzoyl)indolin-3-one (**6**) as starting material. Homolysis of $S_2O_8^{2-}$ generates a radical anion under thermolysis which initiates the chemical transformation (**Scheme 4**).[27]



Scheme 4. Radical mediated synthesis of tryptanthrin from **6.**

Until this point, focus was given to approaches using one starting material to promote the synthesis of tryptanthrin. Below we will address recent advances in condensation reactions, in addition to those using isatin as the sole starting material to prepare this valuable alkaloid.

One of the most common synthetic methodologies applied is the condensation between isatin and isatoic anhydride (**Scheme 5**). Kaishap *et al.* reported a straightforward methodology employing MW for the synthesis of tryptanthrin (96%) and its derivatives (20 examples, 73-92% yields) through the use of different aryl-substituted isatins and aryl-substituted isatoic anhydrides. Besides the excellent yields obtained, the sustainability of this efficient protocol is supported by its short reaction times (15 minutes under MW) and its ability to be performed under solvent- and catalyst-free conditions.[28] In the quest for alternative reaction media for the synthesis of dihydroquinazolinones, Peña-Solórzano *et al.* explored the potential of deep eutectic solvents (DES) for this chemical transformation. Urea/zinc chloride proved to be suitable to synthesize tryptanthrin in excellent yield (91%).[29]

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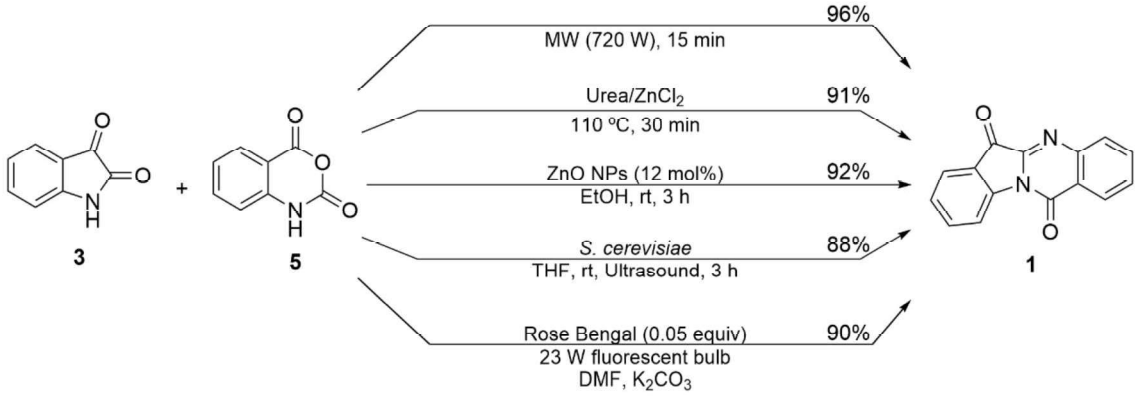
Some catalytic protocols have also been recently described as efficient synthetic pathways for the condensation of isatin and isatoic anhydride. The use of a low-cost, non-toxic and recyclable heterogeneous catalyst, such as zinc oxide nanoparticles (ZnO-NPs) enabled the preparation of tryptanthrin (92% yield) and tryptanthrin derivatives based on aryl-substituted isatins (5 examples, 82-94% yield) in an efficient manner under mild conditions (room temperature using ethanol as solvent).[30] Mane *et al*. reported the use of a biocatalytic process to synthesize tryptanthrin (88% yield) and tryptanthrin derivatives (21 examples, 88-94% yield) with excellent results. In this case, the reliable microorganism *Saccharomyces cerevisiae* (commonly known as baker's yeast), was used to promote the reaction under ultrasound irradiation at room temperature. The ultrasound promotes the disruption of the yeast membrane, releasing enzymes into the reaction medium and enabling the chemical reaction to occur.[31] In another approach, Rose Bengal, an organic dye, proved to be a suitable photocatalyst not only to promote the condensation of isatin and isatoic anhydride (as its aryl-substituted counterparts) to afford tryptanthrin and its derivatives, but also the condensation of two isatin molecules even at low catalyst load (0.05 equiv). The mechanism is promoted using visible light, which takes the catalyst to its photoexcited state, enabling the excitation of the starting materials to triplet state with concomitant radical formation, leading to tryptanthrin (90%)

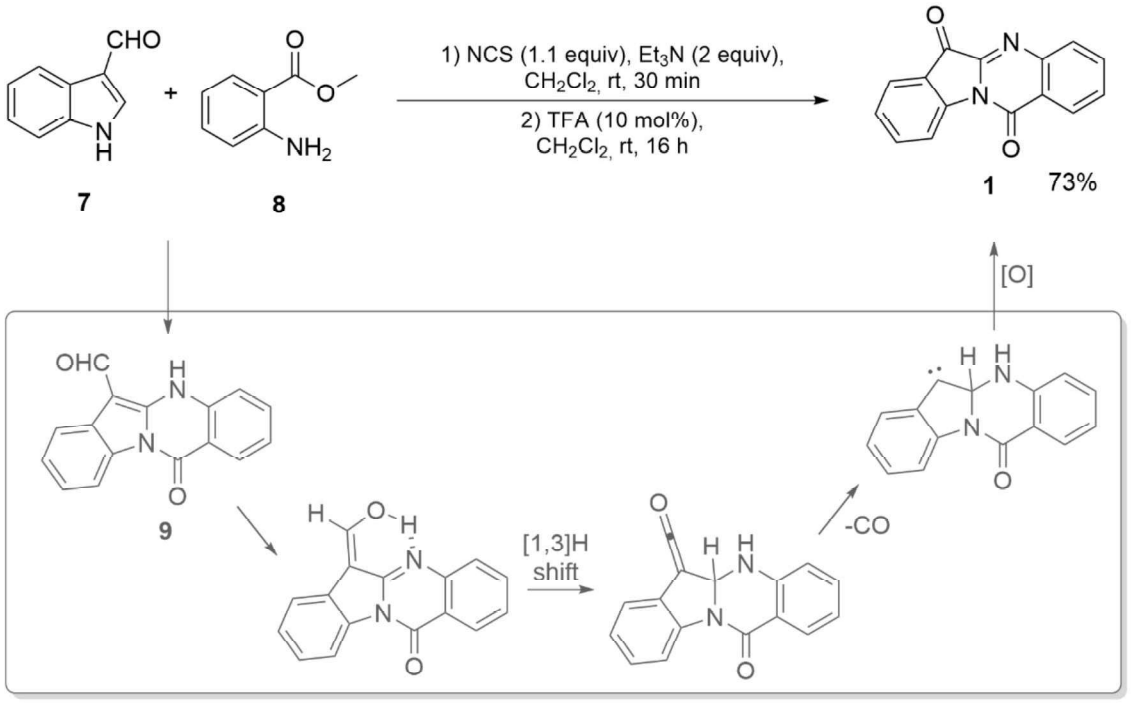


and its derivatives (14 examples, 44-98% yield) in moderate to very good yields under ecofriendly and inexpensive reaction conditions.[32]

Scheme 5. Synthesis of tryptanthrin via condensation of isatin (**3**) and isatoic anhydride (**5**).

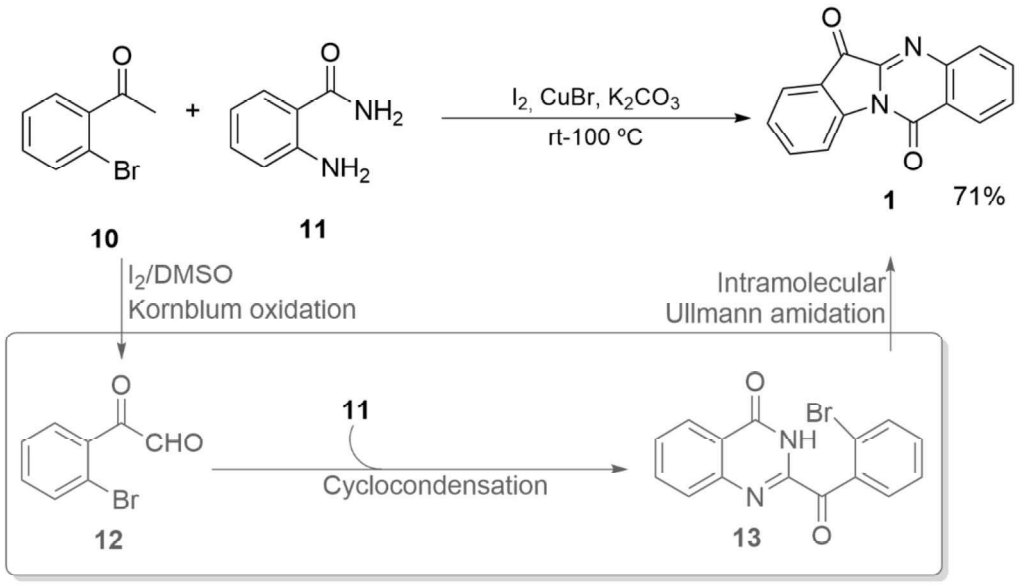
Condensation reactions involving different starting materials can also lead to the formation of tryptanthrin, sometimes even unexpectedly. That was the case reported by Abe and Terasaki, while exploring the reactivity of indole-3-carbaldehyde (**7**) and methyl anthranilate (**8**). They expected to obtain 12-oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carbaldehyde (**9**), since they were observing similar compounds when using indole-3-carboxylate. However, while the expected compound appears to be a synthetic

intermediate, the aldehyde group can work as an activating group and lead to the formation of tryptanthrin (73% yield). Mechanistically, it is hypothesized by the authors that **9** undergoes keto-enol tautomerization, followed by 1,3-hydrogen shift to afford a ketene intermediate. Decarbonylation and further oxidation leads to the formation of the final product, tryptanthrin (**Scheme 6**).[33]



Scheme 6. Synthesis of tryptanthrin from indole-3-carbaldehyde (**7**) and methyl anthranilate (**8**).

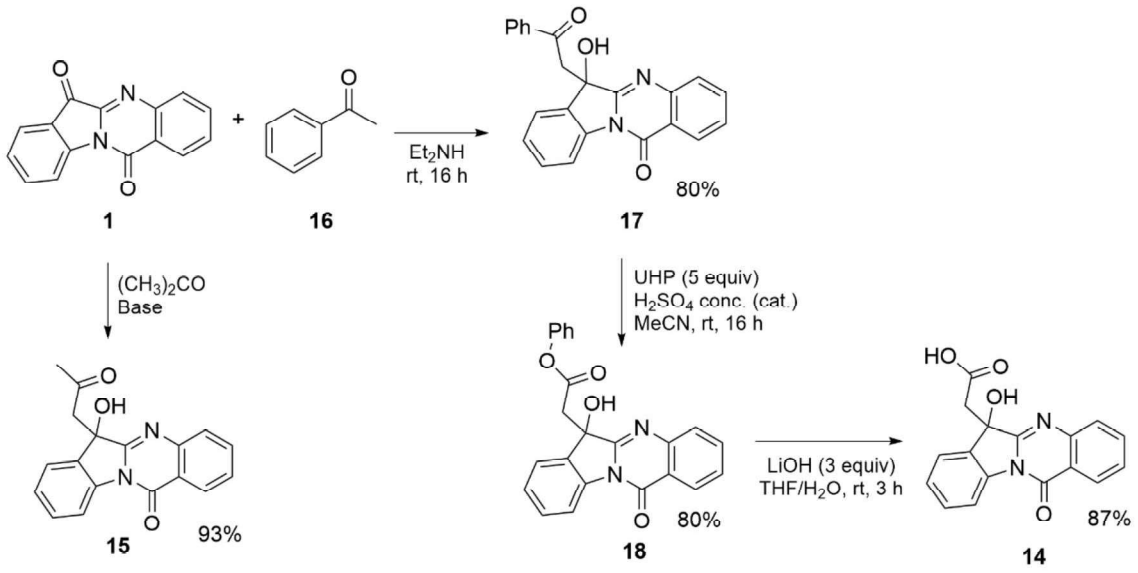
In another example of the use of molecular iodine for the synthesis of tryptanthrin, Guo *et al*. reported the cascade reaction involving 2'-bromoacetophenones (**10**) and 2-aminobenzamides (**11**) as substrates. Molecular iodine promotes the oxidation of the 2'-bromoacetophenone to intermediate **12**, which through cyclocondensation with **11** in the presence of CuBr and a base affords intermediate **13**, which undergoes an intramolecular Ullmann amidation to afford tryptanthrin (71% yield) and its derivatives (10 examples, 41-75% yield) (**Scheme 7**).[34]



Scheme 7. I_2/CuBr promoted synthesis of tryptanthrin from **10** and **11.**

3. Synthesis of new tryptanthrin derivatives

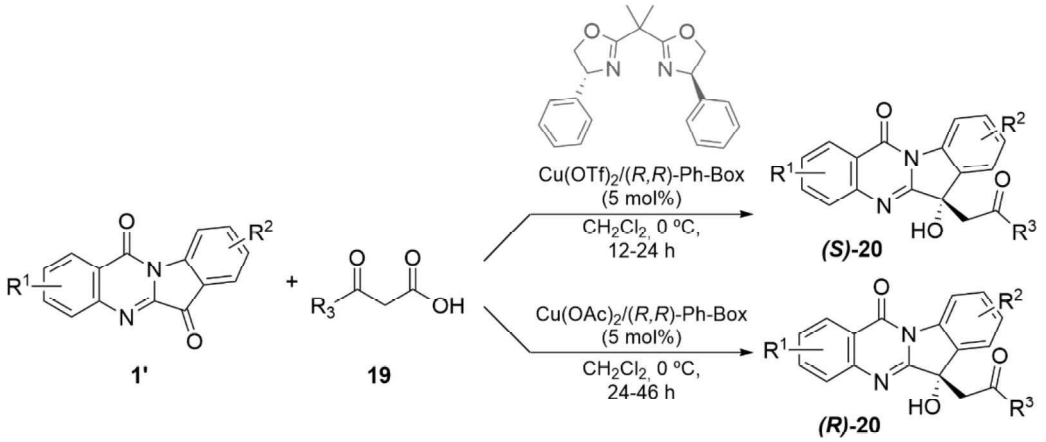
As a natural product, tryptanthrin and some of its derivatives have been isolated from several natural sources. But many other related compounds have been successfully isolated and characterized, such as cephalanthrin A (**14**) and phaitanthrin A (**15**).[35] These alkaloids are characterized for the presence of a hydroxyl group at position 6 of the tryptanthrin core. Due to the biological activities displayed by these compounds, some researchers focused their efforts on the total synthesis of these natural products and their analogs. Using tryptanthrin as starting material, (±)-cephalanthrin A can be obtained through the reaction of **1** with acetophenone (**16**) to achieve **17**, followed by Baeyer-Villiger oxidation to obtain the ester derivative (**18**), which can be hydrolyzed to achieve **14** (87% yield) (**Scheme 8**).[36] Phaitanthrin A can also be easily obtained from the



reaction between tryptanthrin and acetone in the presence of a base. Its analogs can be accessed by using different ketones.[37]

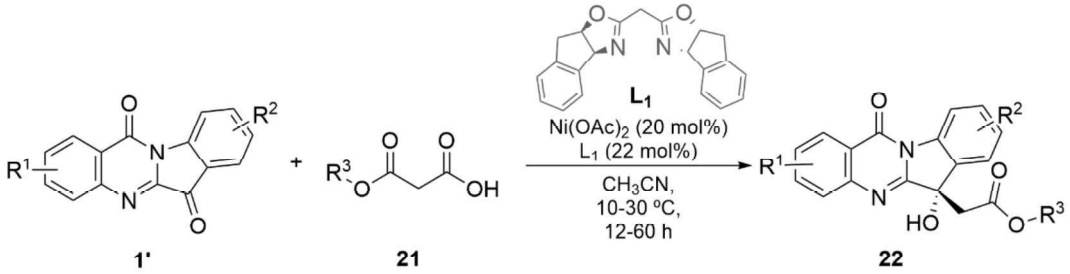
Scheme 8. Synthesis of cephalanthrin A (**14**) and phaitanthrin A (**15**) from tryptanthrin (**1**) (UHP = urea hydrogen peroxide).

Enantioselective synthesis of phaitanthrin A (**15**), or related compounds such as compound **17**, has been recently explored by Feng *et al.*, via copper-catalyzed asymmetric decarboxylative aldol reaction. The authors reported a surprising counter-anion effect while promoting the reaction between tryptanthrins (**1'**) and different β-keto acids (**19**), with two different copper salts leading to the formation of different enantiomers, even in the presence of the same chiral ligand (**Scheme 9**). Several analogs (**20**) could be attained using this approach, in overall excellent yields (up to 95%) and enantioselectivities (62->99% *ee*), although no enantioselectivity could be observed for phaitanthrin A.[38]



Scheme 9. Copper-catalyzed asymmetric decarboxylative aldol reaction.

In another example, a nickel(II)/oxazoline complex promoted the decarboxylative aldol reaction between tryptanthrins and malonic acid hald-oxyesters (**21**). This method proved to achieve great enantioselectivity (90->99% *ee*) for the synthesis of several analogs **22** (16 examples) in good to excellent yields (73-99%) (**Scheme 10**).[39]



Scheme 10. Nickel-catalyzed asymmetric decarboxylative aldol reaction.

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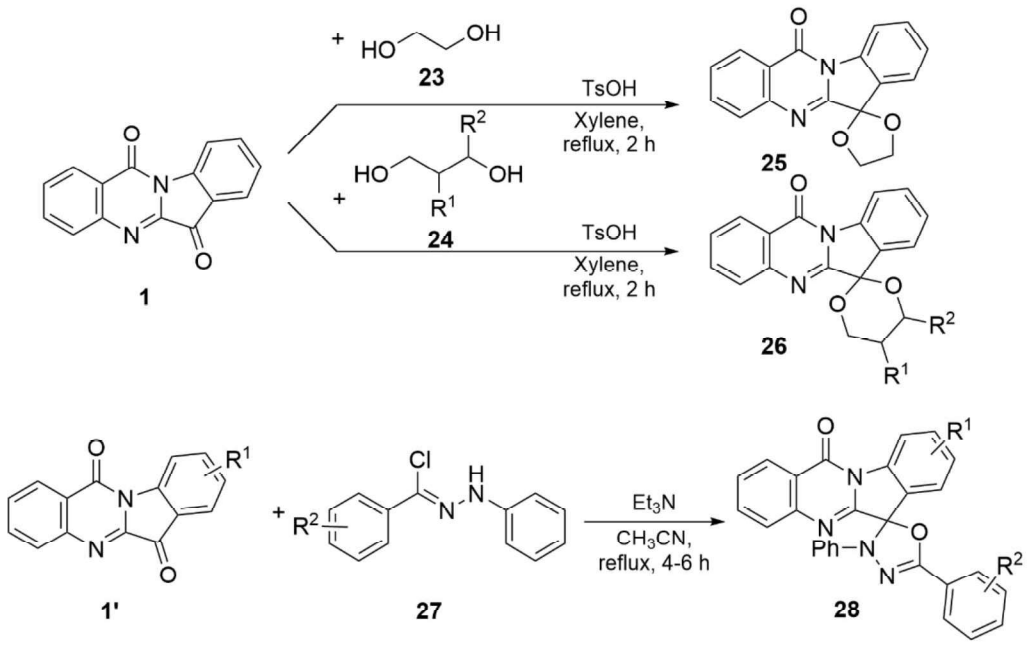
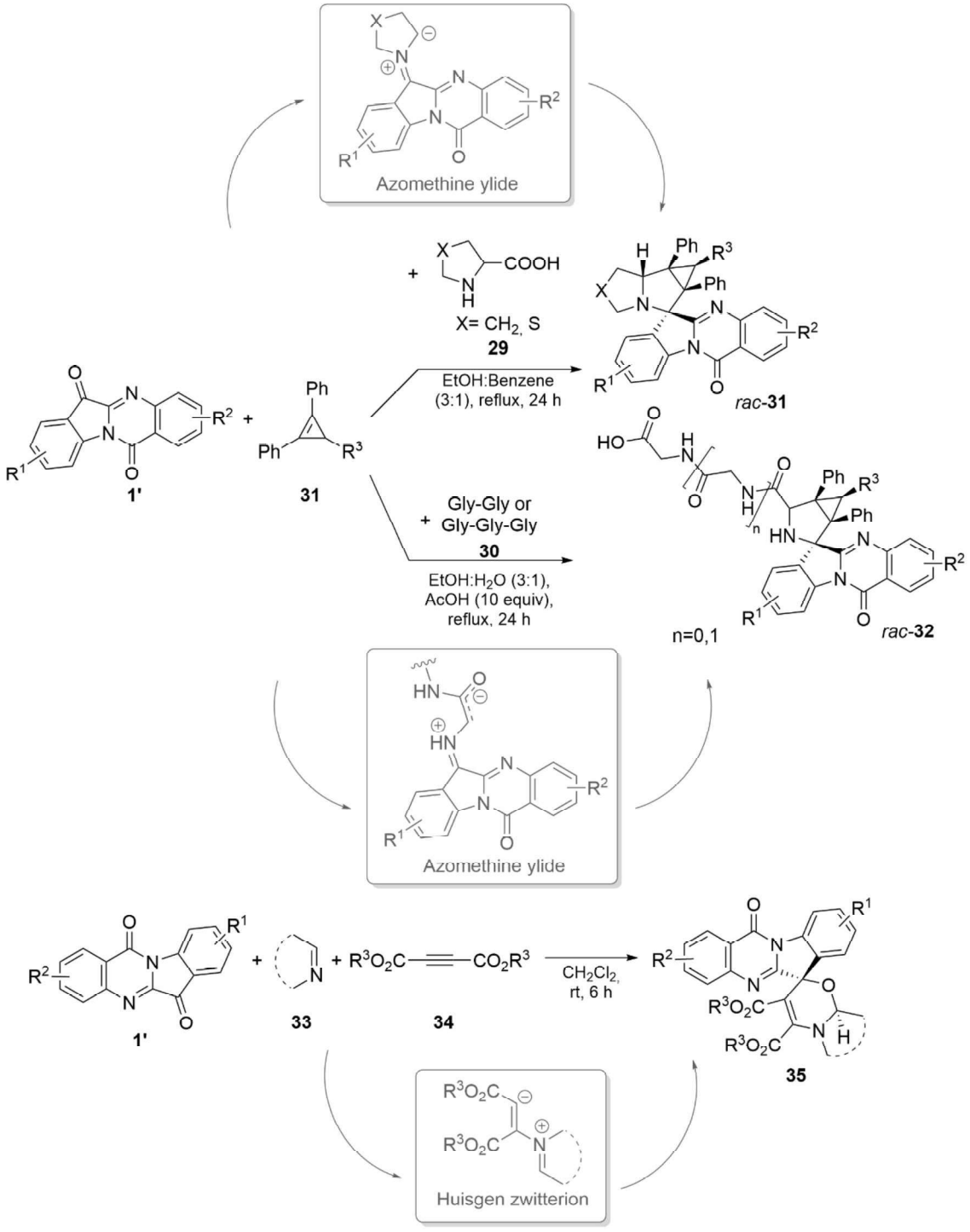
The reactivity at position 6 of the tryptanthrin core can be further explored for the synthesis of spiro derivatives. Spiro dioxolane derivatives **25** and **26** (4 examples) were synthesized via the reaction of tryptanthrin with different diols (**23** and **24**) promoted by *p*-toluenesulfonic acid (TsOH), in excellent yields (92-96% yields) (**Scheme 11**).[40] Another examples of spiro thriptanthrin derivatives, this time bearing the oxadiazole heterocycle, was reported by Yavari *et al.*, achieved through the reaction between tryptanthrins (**1'**) and hydrazonoyl chlorides (**27**) promoted by triethylamine. This approach enabled the preparation of several analogs **28**, (13 examples) in very good yields (80-90%) (**Scheme 11**).



Scheme 11. Examples of spiro compounds prepared from tryptanthrin.

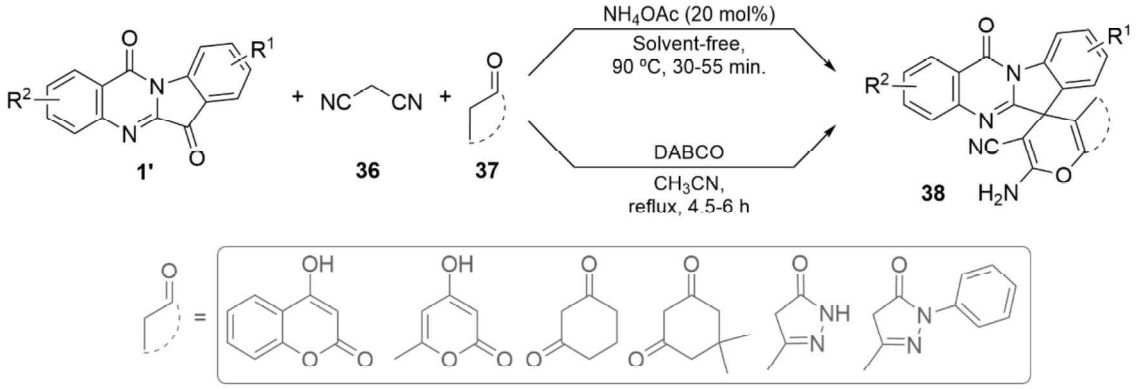
The use of multicomponent reactions (MCRs) is also a suitable strategy for the preparation of new tryptanthrin-based derivatives. Filatov *et al.* explored the 1,3-dipolar cycloaddition of *in situ* formed azomethine ylides (obtained from the reaction between tryptanthrins (**1'**) and α-amino acids (**29**) or simple peptides (**30**)) and cyclopropenes (**31**). This approach allowed the preparation of 25 spiro derivatives (**31**, 43-80% yield, and **32**, 31-77% yield) in moderate to very good yields (**Scheme 12**).[41] In another MCR-based approach, a 1,4-dipolar cycloaddition was performed involving tryptanthrins (**1'**) and *in situ* formed Huisgen zwitterionic intermediates, obtained from the reaction between *N*-heterocycles (**33**) and acetylenic esters (**34**). The resulting spiro compounds **35** (10 examples) bearing the 1,3-oxazine heterocycle, were obtained in overall very good yields (70-85% yield) (**Scheme 12**), under catalyst-free conditions.[42]



Scheme 12. Spiro tryptanthrin derivatives prepared via MCRs.

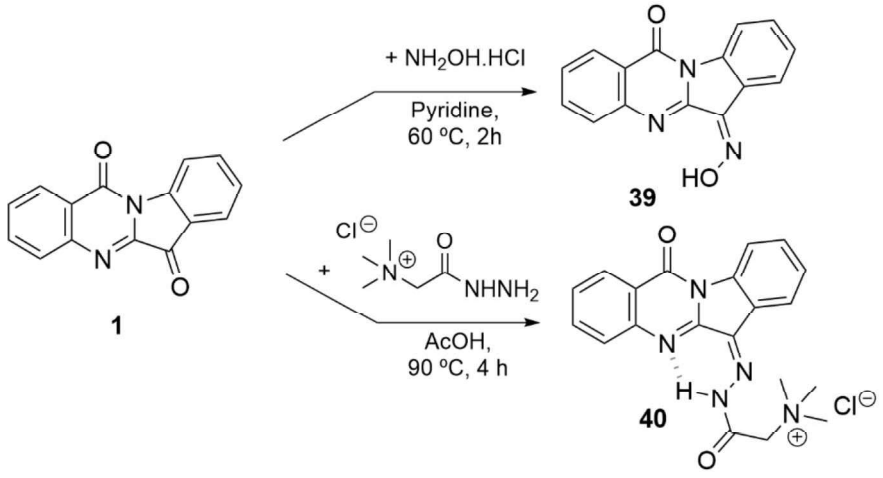
Beyrati and co-workers also developed two MCR-based approaches for the synthesis of spiro tryptanthrin derivatives. Both methodologies consist of the reaction between tryptanthrin, malononitrile (**36**), and C-H activated carbonyl compounds (**37**). In the first example, a solvent-free protocol was developed, using ammonium acetate as a dual activating catalyst, as it activates the carbonyl group at C6 position of the

tryptanthrin and the malononitrile. A total of 20 derivatives **38** were obtained in excellent yields (83-96%) and short reaction times (**Scheme 13**).[43] In the second methodology, an one-pot, two-step, four-component reaction was reported. In the first step, the condensation of isatins with isatoic anhydrides led to the formation of tryptanthrins (**1'**) *in situ*. The second step consists of the reaction of tryptanthrins with malononitrile and C-H activated carbonyl compounds. This MCR is performed in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO). A total of 16 derivatives **38** were obtained in good to excellent yields (64-90%), in refluxing acetonitrile (**Scheme 13**).[44]



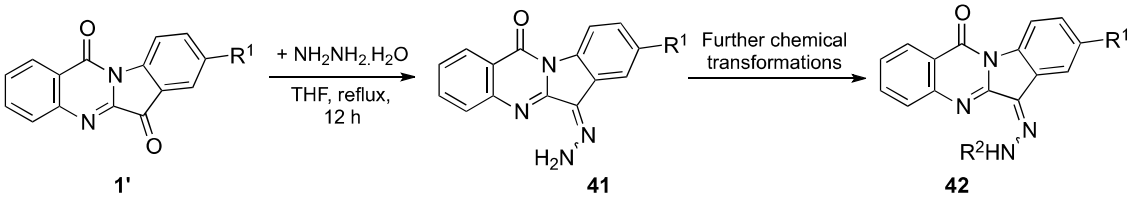
Scheme 13. Spiro tryptanthrin derivatives prepared via MCRs involving tryptanthrin, malononitrile and C-H activated carbonyl compounds.

The replacement of the oxygen atom at position 6 by a nitrogen atom has also been explored by several researchers over recent years. Tryptanthrin-6-oxime (**39**) was obtained from the treatment of tryptanthrin with hydroxylamine hydrochloride in very good yield (95%) (**Scheme 14**).[45] Popov *et al*. reported the synthesis of the water soluble tryptanthrin derivative mostotrin (**40**), resulting from the condensation of tryptanthrin with Girard reagent T (acethydrazide trimethylammonium chloride), in 67% yield (**Scheme 14**).[46]



Scheme 14. Synthesis of tryptanthrin-6-oxime (**39**) and mostotrin (**40**) from tryptanthrin.

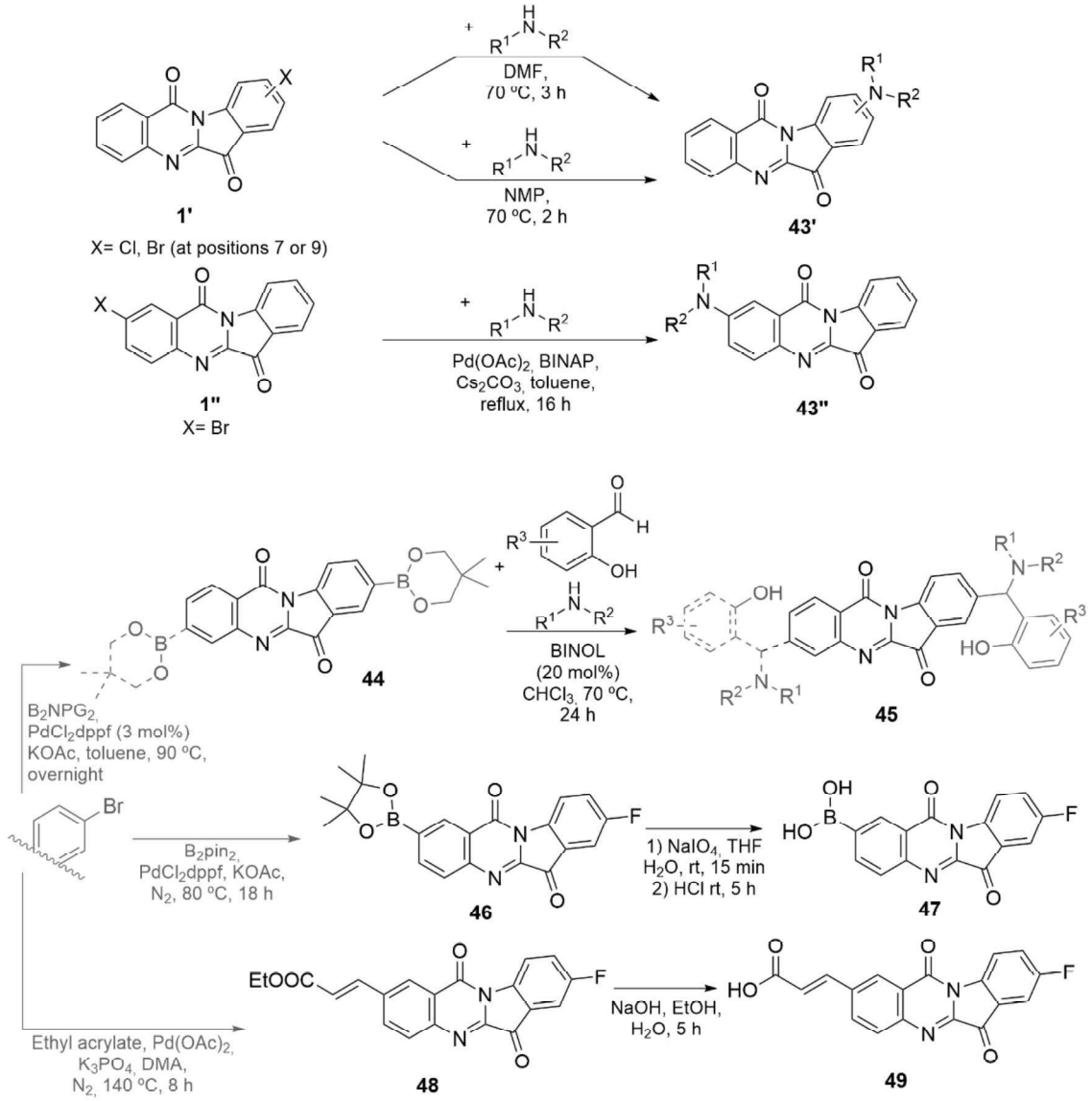
Guda *et al*. reported the synthesis of several tryptanthrin-hydrazone derivatives (**41**, 64-78% yield, and **42**, 54-72% yield) (**Scheme 15**). A total of 18 new derivatives, based on 8-substituted tryptanthrins (**1'**), were successfully prepared using a multistep methodology showing broad structural diversity.[47]



Scheme 15. Synthesis of tryptanthrin-hydrazone derivatives.

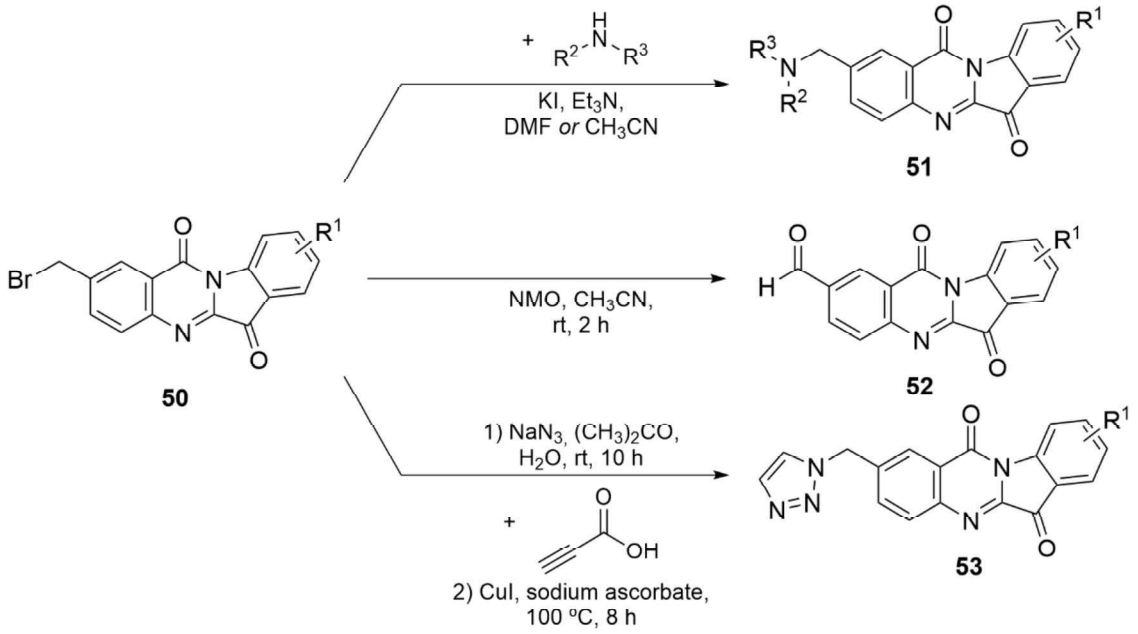
But chemical transformations can also be performed in other positions of the tryptanthrin core, namely in the aromatic rings. Aryl halide derivatives of tryptanthrin (**1'**) can easily undergo nucleophilic substitution with various amines. Three accounts were recently reported on this strategy, one using aryl bromides and primary and secondary amines which afforded 10 derivatives (**43'**) in moderate to good yields (49-71%);[48] the second example using aryl chloride tryptanthrin derivatives and secondary amines, achieving a library of 32 examples (**43'**) in variable yields (31-92%);[49] and in a third example, 6 derivatives (**43''**) were obtained by reacting aryl bromide derivative of tryptanthrin **1''** with secondary amines, in a reaction catalyzed by $Pd(OAc)_2$, achieving the products in 40-76% yield (**Scheme 16**).[50]

In our group, we used brominated tryptanthrins (bearing the Br atom in ring A or D), which were further converted into the corresponding borylated tryptanthrin (**44**) and then engaged in the Petasis MCR, with secondary amines and salicylaldehydes, in a reaction organocatalyzed by (±)-BINOL ((±)-1,10-bi-2-naphthalene-2,20-diol). A library of 20 derivatives (**45**) was obtained (10-80% yields) (**Scheme 16**), and an asymmetric version of the reaction was also successfully developed, using *(R)*-BINOL, with excellent enantioselectivity (99% *ee*).[51] Li and co-workers also promoted the preparation of another borylated tryptanthrin (**46**, 83% yield), and hydrolyzed it to attain the corresponding boronic acid derivative, via oxidative cleavage promoted by $NaIO_4$ (**47**, 72% yield). The same authors also explored a palladium-catalyzed Heck reaction of brominated tryptanthrin with ethyl acrylate to afford a tryptanthrin-cinnamic acid ester derivative (**48**, 51% yield), which was then hydrolyzed to afford the corresponding acid (**49**, 82% yield) (**Scheme 16**).[52]



Scheme 16. Using aryl-halides for the synthesis of novel tryptanthrin derivatives.

Another alternative to unveil new tryptanthrin derivatives is to use 2-bromomethyltryptanthrin (**50**) as a synthetic precursor. This compound, which can be obtained from the bromination of 2-methyltryptanthrin, can undergo several chemical transformations, including the nucleophilic substitution with various secondary amines, affording *N*-benzyl substituted tryptanthrins (**51**, 60-82% yield); oxidation to the corresponding aldehyde (**52**, 67% yield) in the presence of *N*-methylmorpholine-*N*-oxide (NMO); and conversion to an azide functional group followed by reaction with propiolic acid, followed by temperature induced decarboxylation, to afford the corresponding triazole derivative (**53**, 56% yield) (**Scheme 17**).[50, 52]



Scheme 17. 2-Bromomethyltryptanthrin as starting point for several chemical transformations.

4. Conclusions

Tryptanthrin is a valuable privileged structure in drug discovery. As discussed in this short-review, several strategies have been recently reported concerning the synthesis of this alkaloid with high efficiency and sustainability, compared to classic strong oxidation methodologies. The use of tryptanthrin as a starting point for the generation of structurally diverse libraries also permits the expansion of chemical space, and the discovery of new bioactive compounds with great potential in the field of medicinal chemistry. ~~Future endeavors in this field will likely focus their attention in the further improvement of the eco-friendliness of chemical processes to obtain tryptanthrin and its derivatives, as well as in the further expansion of the complexity of tryptanthrin derivatives structures, in the quest for new bioactive compounds.~~

"Future endeavors in this field will likely be focused on improvement of the eco-friendliness of the chemical processes leading to tryptanthrin and derivatives, including further expansion of the complexity of bioactive tryptanthrin structures."

Conflict of Interest

There are no conflicts to declare.

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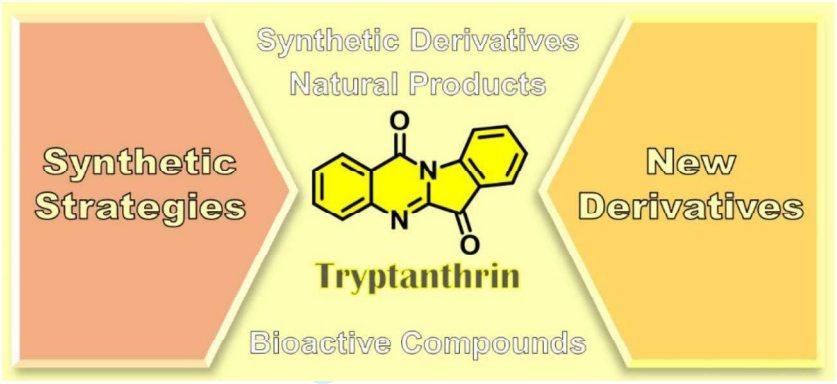
Graphical Abstract



Biosketches

Marta Pineiro studied Chemistry at the University of Santiago de Compostela where she graduated in 1996 and got her PhD in Organic Chemistry in 2002 at the University of Coimbra. Marta Pineiro is currently Assistant Professor at the University of Coimbra and member of the Organic Chemistry Group, Coimbra Chemistry Centre (CQC). She was assistant secretary of Portuguese Chemical Society (2013-2016) and deputy Director of the Department of Chemistry, University of Coimbra (2009-2011). Her research interests are mainly in the area of Green Chemistry and sustainable methods for the synthesis of heterocycles with applications in Medicinal Chemistry and unique photophysical properties. She has published more than 80 peer-reviewed papers in international journals and 8 book chapters.