Anusandhanvallari
Vol 2024, No.1
December 2024
ISSN 2229-3388

Tryptanthrin-Based Heterocyclic Scaffolds: Synthesis, Biological Evaluation and Medicinal Chemistry Perspectives

Keshav Kumar Jha[1], Vishwa Deepak Tripathi[2]

*Research Scholar, University Department of Chemistry, L.N.M.U.

**P. G. Department of Chemistry, C. M. Science College

(A Constituent Unit of Lalit Narayan Mithila University) Darbhanga, Bihar.

Abstract: Tryptanthrin, chemically identified as indolo[2,1-b]quinazoline-6,12-dione, is a naturally occurring indoloquinazoline alkaloid that has attracted considerable attention because of its structural simplicity, synthetic accessibility and diverse biological activities. The present review provides a concise overview of the chemistry and pharmacological significance of tryptanthrin and its derivatives. Its natural occurrence in medicinal plants and its structural features, including a rigid fused aromatic system and two reactive carbonyl functionalities, make it an attractive scaffold for medicinal chemistry. Various synthetic strategies reported for construction and functionalization of the tryptanthrin nucleus are discussed, ranging from conventional condensation reactions to catalytic, microwave-assisted, photochemical, electrochemical, green, biocatalytic and multicomponent approaches. Particular emphasis is given to structural modification at different positions of the scaffold and the resulting structure–activity relationships. Tryptanthrin and its derivatives exhibit antimicrobial, antifungal, antitubercular, anti-inflammatory, antiprotozoal and anticancer activities. Their anticancer effects have been associated with apoptosis induction, cell-cycle regulation, enzyme inhibition and modulation of important signalling pathways. Recent developments involving spiro derivatives, asymmetric synthesis and metal complexes further demonstrate the versatility of this scaffold. The review also highlights limitations related to solubility, selectivity, pharmacokinetics and in-vivo validation, and identifies future opportunities for developing improved tryptanthrin-based therapeutic agents.

Keywords: Tryptanthrin, Indoloquinazoline, Synthetic strategies, Biological activities, Medicinal chemistry

Introduction

Natural products continue to provide valuable structural frameworks for the discovery and development of biologically active molecules. Among the heterocyclic alkaloids investigated in medicinal chemistry, tryptanthrin has emerged as an especially attractive scaffold because of its structural simplicity, synthetic accessibility and broad pharmacological profile. Tryptanthrin, chemically designated as indolo[2,1-b]quinazoline-6,12-dione, is a naturally occurring weakly basic alkaloid consisting of a fused indole–quinazoline system containing carbonyl groups at the 6- and 12-positions.[1-2] Its rigid, planar and highly conjugated tetracyclic structure provides a favourable platform for interactions with biological macromolecules and enzymes. The historical chemistry of tryptanthrin can be traced to the oxidative degradation of indigo, from which a yellow crystalline compound was obtained and subsequently identified as tryptanthrin. Later phytochemical investigations established its occurrence in several medicinal plants, including Isatis tinctoria, Isatis indigotica, Strobilanthes cusia, Wrightia tinctoria, Calanthe discolor and Couroupita guianensis. These plants have traditionally been associated with the treatment of infections, inflammation, fever and various skin disorders. The repeated isolation of tryptanthrin from medicinal plants stimulated considerable interest in understanding its chemical and pharmacological significance.[3]

The importance of tryptanthrin is not restricted to its natural occurrence. The molecule possesses several structural features that are advantageous for medicinal chemistry. The fused aromatic system provides rigidity and chemical

stability, whereas the carbonyl oxygen atoms and ring nitrogen atoms provide potential hydrogen-bonding and coordination sites. Furthermore, the electronically deficient aromatic framework permits functionalization at several positions without necessarily disrupting the parent heterocyclic system. The relatively simple preparation of tryptanthrin from readily accessible precursors such as isatin and isatoic anhydride has made it particularly suitable for analogue development and structure–activity relationship studies. During the past several decades, research on tryptanthrin has expanded from isolation and structural characterization to synthetic modification, mechanistic pharmacology and drug-oriented investigations. The compound has demonstrated antimicrobial, antifungal, antitubercular, antiprotozoal, anti-inflammatory, antioxidant, antiallergic, antiangiogenic and anticancer properties. Among these activities, its anticancer potential has received particularly extensive attention. The present review summarizes the major developments in tryptanthrin chemistry, with particular emphasis on its natural occurrence, structural characteristics, synthetic methodologies, chemical modification, biological activities, structure–activity relationships and emerging medicinal chemistry applications.[4]

Natural Occurrence and Structural Features of Tryptanthrin

Tryptanthrin is a member of the indoloquinazoline class of alkaloids. Its natural occurrence has been documented in a number of plants belonging to different botanical families. Important sources include Isatis tinctoria, Isatis indigotica, Strobilanthes cusia, Wrightia tinctoria, Calanthe discolor and Couroupita guianensis. Several of these plants have a long history of use in traditional medicine, particularly in Asian medicinal systems. The presence of tryptanthrin in these plants provided an important link between traditional therapeutic applications and modern natural-product research. Structurally, tryptanthrin contains a planar tetracyclic indolo[2,1-b]quinazoline framework. The two carbonyl groups are positioned at C-6 and C-12, while the fused aromatic system generates an extended π-electron surface. This combination of planarity, rigidity, aromaticity and heteroatom functionality is important for its interaction with enzymes, DNA and other biological targets. The nitrogen and oxygen atoms also provide opportunities for metal coordination, which has subsequently been exploited in the development of tryptanthrin-based metal complexes.[5-6]

A B

Figure 2: Natura sources of Tryptanthrins A) Isatis indigotica seeds B) Isatis Tinctoria

Another important feature of tryptanthrin is its synthetic flexibility. Substitution can be introduced at several positions of the aromatic rings, while the carbonyl functionality at C-6 can be transformed into a variety of derivatives. This structural versatility has permitted the preparation of a large number of derivatives. Substituents including nitro, halogen, alkyl, methoxy, amino and cyano groups have been introduced at different positions. Similarly, oximes, hydrazones, imines, aminothiazoles, dicyanomethylene compounds and spiro derivatives have

been obtained through modification of the C-6 carbonyl group. N-Aryl and N-benzyl derivatives have also been explored to modify biological recognition and physicochemical behaviour.

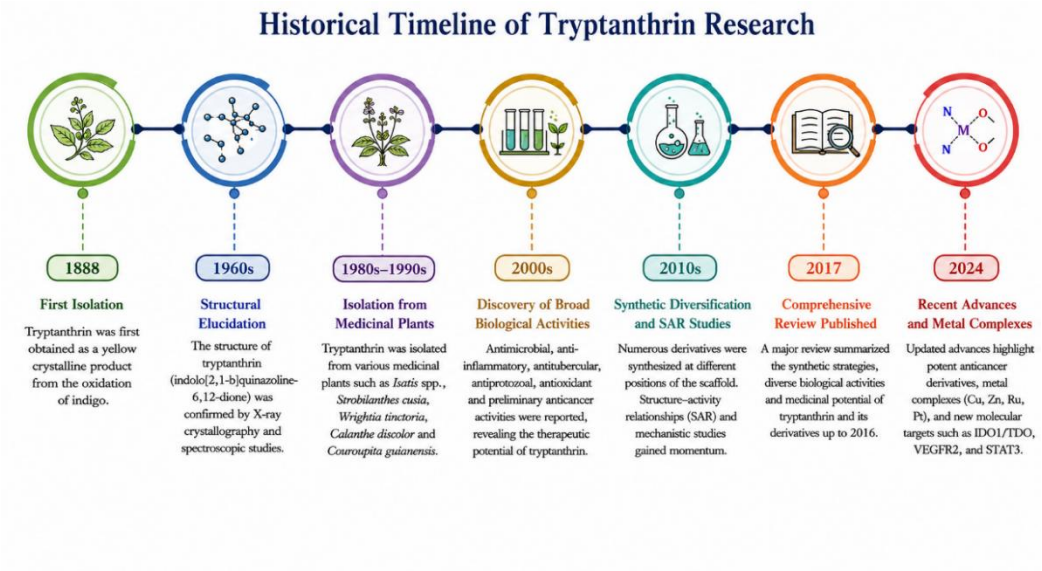

Figure 2: **The Schematic Representation of development in the study of Tryptanthrin and its derivatives**

Biological Importance of Tryptanthrin

The biological profile of tryptanthrin is unusually broad for a relatively small heterocyclic natural product. Initial investigations demonstrated antimicrobial and antifungal properties, including activity against pathogenic bacteria and dermatophytic fungi. Tryptanthrin subsequently attracted attention because of its activity against Mycobacterium tuberculosis, including drug-resistant strains. Antiprotozoal activity against organisms such as Leishmania donovani, Trypanosoma brucei and Plasmodium falciparum has also been reported. The anti-inflammatory properties of tryptanthrin constitute another important aspect of its pharmacological profile. Studies described inhibition of cyclooxygenase-2, nitric oxide synthase and other inflammatory mediators. Additional investigations demonstrated effects on 5-lipoxygenase pathways and inflammatory signalling. Tryptanthrin has also been associated with antioxidant, antiallergic and antiangiogenic effects. The multiplicity of these activities indicates that the compound can influence several biochemical pathways rather than acting through a single biological mechanism.[7-9]

Antimicrobial and Antifungal Activity

The antimicrobial potential of tryptanthrin was among the earliest biological properties identified. The compound showed activity against several pathogenic microorganisms, including resistant bacterial strains. Its antifungal activity was also demonstrated against dermatophytes. These findings helped establish tryptanthrin as a biologically relevant natural product and encouraged further investigations into its structure and mechanism of action. The antimicrobial activity is particularly significant because the rigid, planar heteroaromatic structure can facilitate interaction with cellular components, while the carbonyl and nitrogen functionalities can participate in molecular recognition. Structural modification of the aromatic ring has subsequently been used to examine how electronic and steric factors influence antimicrobial potency.

Antitubercular and Antiprotozoal Activity

Tryptanthrin has attracted considerable interest as an anti-infective scaffold because of its reported activity against M. tuberculosis. Activity against multidrug-resistant strains is particularly noteworthy and suggests that the

scaffold may interact with targets that differ from conventional antitubercular agents. The compound also exhibits activity against protozoan pathogens. Reported activity against Leishmania, Trypanosoma and Plasmodium species indicates that the biological utility of tryptanthrin extends beyond antibacterial applications. Such observations have encouraged the synthesis of substituted derivatives aimed at improving potency and selectivity.[13-15]

Anti-inflammatory and Immunomodulatory Activity

Tryptanthrin has demonstrated significant anti-inflammatory potential. Its effects have been associated with inhibition of cyclooxygenase and lipoxygenase pathways as well as modulation of inflammatory signalling. In addition, inhibition of Th2 development, IgE-mediated degranulation and IL-4 production has been reported. These findings suggest that the compound can influence both enzymatic inflammatory mediators and cellular immune responses. The anti-inflammatory activity provides an additional rationale for investigating tryptanthrin derivatives as multifunctional therapeutic candidates. Modification of the scaffold may permit optimization of potency, selectivity and pharmacokinetic properties while retaining the pharmacophore responsible for interaction with inflammatory targets.[15]

Conventional Synthetic Approaches to Tryptanthrin

The classical synthesis of tryptanthrin generally involves condensation of isatin with isatoic anhydride. This route remains one of the most useful approaches because the starting materials are readily accessible and the reaction provides direct construction of the fused tetracyclic framework. The simplicity of the reaction has made it the foundation for the preparation of numerous substituted analogues. Alternative classical approaches have employed anthranilic acid derivatives, 2-chloro-3H-indol-3-ones and related intermediates. Phosphorus pentachloride and phosphorus oxychloride have also been used to activate appropriate precursors for cyclization. These approaches can provide good yields for selected substrates, although harsh reagents, limited substrate scope and solubility problems restrict their general applicability.

Another strategy involves oxidative or reductive cyclization of appropriately functionalized indole derivatives. For example, N-(2-nitrobenzoyl)oxindole can undergo reductive cyclization to produce the tryptanthrin framework. $SnCl_4$/HCl and hydrazine/Pd-C conditions have been reported to provide the corresponding products in high yields without requiring the high-pressure carbon monoxide conditions associated with some alternative procedures. Although classical approaches remain valuable, increasing emphasis on efficiency, sustainability and functional-group tolerance has stimulated the development of catalytic and modern synthetic methodologies.

Catalytic and Transition-Metal-Mediated Synthesis

Catalytic methodologies have significantly expanded the synthetic toolbox for tryptanthrin. Copper-mediated tandem reactions provide an important example. One reported strategy uses 2-bromoacetophenones and 2-aminobenzamides, with molecular iodine and CuBr participating in a cascade sequence involving cyclocondensation followed by intramolecular Ullmann amidation. Tryptanthrin was obtained in 71% yield, while substituted derivatives were obtained in moderate to good yields. Copper-catalyzed reactions involving indoles and isatins provide another route. Optimization demonstrated that CuI was more effective than several other copper salts and that DMSO significantly improved product formation. A range of substituted indoles and isatins could participate, demonstrating the potential of this method for analogue generation. Zinc oxide nanoparticles have also been employed as heterogeneous catalysts. The ZnO nanoparticle method is attractive because the catalyst is relatively inexpensive, recyclable and operationally simple. Under mild conditions, tryptanthrin was obtained in high yield, and a series of substituted derivatives were also accessible. These catalytic methods demonstrate the transition from simple stoichiometric synthesis toward catalytic, recyclable and more selective methodologies.

Microwave-Assisted and Solvent-Free Synthesis

Microwave irradiation has emerged as an effective means of accelerating tryptanthrin synthesis. The principal advantage of microwave-assisted reactions is rapid heating, which can substantially reduce reaction times compared with conventional thermal methods. A solvent-free method involving isatin, sodium borohydride and silica was developed in which the reactants were mechanically mixed and subsequently subjected to microwave irradiation. Although the reported yield was moderate, the approach demonstrated the possibility of combining solvent-free processing with microwave activation.

Other microwave-assisted approaches have provided significantly higher yields under optimized conditions. The literature summarized in the source chapter includes microwave procedures producing tryptanthrin in very short reaction times, demonstrating the potential of microwave energy for rapid synthesis. Microwave chemistry is particularly valuable for medicinal chemistry because analogue libraries can be prepared rapidly. Nevertheless, scale-up, reproducibility and uniform energy distribution must be considered before such methodologies can be routinely translated to larger-scale synthesis.

Photochemical and Photoredox Approaches

Photochemical synthesis has provided several innovative routes to tryptanthrin. A ruthenium-based photoredox system has been employed for the transformation of isatin into tryptanthrin. The proposed pathway involves photoinduced electron transfer, generation of an isatin radical anion and subsequent coupling and cyclization steps. The method provided tryptanthrin in yields of up to 92%, with substituted derivatives also obtained in good yields.

Visible-light photocatalysis has also been investigated using organic dyes such as Rose Bengal. These methods demonstrate that light can be used to initiate radical pathways for construction of the fused heterocyclic framework. More recent visible-light protocols are particularly interesting from a green chemistry perspective because they avoid transition-metal catalysts, external photocatalysts and additional bases. The reaction can proceed under mild conditions using molecular oxygen as an oxidizing partner. Such approaches reduce the number of reagents and may provide a more sustainable alternative to conventional synthesis.

Green, Biocatalytic and Aqueous Synthetic Methods

Green chemistry has become an important direction in tryptanthrin synthesis. One notable strategy employs β-cyclodextrin as a catalyst in water. Cyclodextrins possess hydrophobic cavities capable of accommodating organic substrates, thereby facilitating host–guest interactions and promoting reactions in aqueous media. Among α-, β- and γ-cyclodextrins, β-cyclodextrin provided the best performance in the reported synthesis. The reaction proceeded in water at room temperature and afforded tryptanthrin in approximately 90% yield. In contrast, substantially lower yields were obtained with α- and γ-cyclodextrins, while no appreciable reaction occurred in the absence of cyclodextrin.

Multicomponent and One-Pot Strategies

Multicomponent reactions provide an efficient method for increasing molecular complexity while minimizing purification and isolation steps. Their application to tryptanthrin chemistry has resulted in diverse spiro and fused derivatives. Beyrati and co-workers reported a solvent-free three-component reaction involving tryptanthrin, malononitrile and C–H-activated carbonyl compounds in the presence of ammonium acetate. The catalyst simultaneously activates the C-6 carbonyl group of tryptanthrin and malononitrile, enabling efficient formation of spiroindoloquinazoline products. Twenty derivatives were prepared in yields ranging from 83–96%. A one-pot, two-step, four-component strategy was subsequently developed in which isatins and isatoic anhydrides first generated tryptanthrin intermediates in situ. These intermediates then participated in further multicomponent transformations to give spiro derivatives. Such approaches are particularly valuable for medicinal chemistry

because they provide structural diversity without requiring isolation of every intermediate. Other transformations have employed aryl halide-functionalized tryptanthrins in nucleophilic substitution, palladium-catalyzed coupling and Petasis-type multicomponent reactions. These methodologies provide additional opportunities for introducing amine, boron-containing, aryl and heterocyclic functionalities.

1.13 Asymmetric Synthesis and Advanced Functionalization

The development of asymmetric synthesis has expanded the chemical space accessible from tryptanthrin. Direct aldol reactions between tryptanthrin and ketones have been used for the synthesis of chiral phaitanthrin derivatives. Natural amino-acid salts have served as inexpensive chiral catalysts and enabled formation of products in high yields with excellent enantioselectivities. Reported yields ranged from 78–98%, while enantioselectivities reached approximately 90–99% ee for suitable substrates. Copper-catalyzed asymmetric decarboxylative aldol reactions have also generated chiral tryptanthrin analogues. Interestingly, the counter-ion associated with the copper salt can influence the stereochemical outcome, demonstrating the sensitivity of these reactions to catalyst composition. Yields of up to 95% and enantioselectivities exceeding 99% ee were reported for several derivatives. Nickel(II)/oxazoline catalytic systems have further provided highly stereoselective decarboxylative aldol reactions. These approaches illustrate the increasing sophistication of tryptanthrin chemistry and provide access to three-dimensional derivatives that may possess different biological properties from the planar parent scaffold.

Current Limitations and Research Gaps

Despite substantial progress, several challenges remain before tryptanthrin derivatives can be considered mature drug candidates. The first major limitation is the physicochemical profile of the parent compound. Poor aqueous solubility can restrict absorption, distribution and intracellular delivery. Structural modifications that improve solubility may, however, alter membrane permeability or target affinity. Therefore, optimization must balance potency with physicochemical properties. A second challenge concerns selectivity. Although many derivatives show impressive activity against cancer cells, the difference between malignant and normal-cell toxicity is not always sufficient. Greater emphasis should therefore be placed on selectivity indices and mechanistic validation rather than simply reporting cytotoxic potency.

The third challenge is incomplete understanding of structure–activity relationships. Although several substitution patterns have been associated with enhanced activity, the available data do not establish a universal relationship between electronic properties and biological potency. The effects of substitution can differ according to the target and biological model. Systematic analogue libraries combined with computational modelling and quantitative SAR approaches may help resolve these uncertainties. Another major limitation is the relatively small number of compounds that have progressed beyond in vitro studies. Extensive investigations of pharmacokinetics, metabolic stability, toxicity, bioavailability and in vivo efficacy are required. The source chapter specifically identifies pharmacokinetic, toxicity and in vivo efficacy studies as important areas requiring further attention.

For synthetic chemistry, future work should focus on scalable green methods, recyclable catalysts, solvent minimization, continuous-flow processing and one-pot strategies. Although several methods provide excellent yields on laboratory scale, their environmental and economic performance needs to be assessed using appropriate green chemistry metrics.

Future Perspectives

Tryptanthrin represents a particularly promising scaffold for future medicinal chemistry because its chemistry and biology can be developed simultaneously. The rigid indoloquinazoline framework offers a well-defined pharmacophore, while multiple functionalization sites permit systematic optimization. Future analogue design should integrate conventional SAR with computational approaches, molecular docking, molecular dynamics,

quantitative structure–activity relationships and physicochemical-property prediction. Such approaches may help identify substitutions capable of improving potency while maintaining solubility and selectivity. The development of multifunctional derivatives is another promising direction. Hybrid molecules combining tryptanthrin with pharmacologically relevant heterocycles may provide enhanced biological activity or improved pharmacokinetic behaviour. Similarly, metal complexes deserve further investigation because coordination can alter DNA interaction, redox behaviour and cellular uptake.

Green synthesis is likely to become increasingly important. Visible-light reactions, electrochemical transformations, aqueous cyclodextrin catalysis, biocatalysis, microwave irradiation and solvent-free multicomponent reactions provide a foundation for more sustainable tryptanthrin chemistry. The combination of these approaches may ultimately permit efficient preparation of large analogue libraries with reduced environmental impact. Particular attention should also be directed toward biological validation. Potent derivatives identified through cell-based assays should be evaluated using target-specific biochemical assays, resistance models, normal-cell controls and appropriate in vivo systems. This will help distinguish genuine target-mediated activity from nonspecific cytotoxicity.

Conclusion

Tryptanthrin, an indolo[2,1-b]quinazoline-6,12-dione alkaloid, has developed from a naturally occurring plant metabolite into an important scaffold in modern medicinal chemistry. Its rigid planar structure, multiple heteroatom functionalities, synthetic accessibility and broad biological activity make it an attractive platform for drug discovery. The compound has demonstrated antimicrobial, antifungal, antitubercular, antiprotozoal, anti-inflammatory, antiallergic, antiangiogenic and anticancer properties. Its anticancer activity is particularly significant because it involves multiple biological mechanisms, including apoptosis, cell-cycle regulation, topoisomerase inhibition and modulation of several signalling pathways. Synthetic chemistry has progressed considerably beyond the classical isatin–isatoic anhydride condensation. Copper- and zinc-based catalysis, microwave irradiation, photoredox chemistry, visible-light activation, electrochemistry, ionic liquids, β-cyclodextrin catalysis, biocatalysis and multicomponent reactions have expanded the available synthetic toolbox. At the same time, asymmetric catalysis and spirocyclization have provided access to increasingly complex three-dimensional derivatives.

Acknowledgement: Authors are thankful to Lalit Narayan Mithila University for necessary support.

References:

[1] Kaur, R., Manjal, S. K., Rawal, R. K., & Kumar, K. (2017). Recent synthetic and medicinal perspectives of tryptanthrin. Bioorganic & Medicinal Chemistry, 25(17), 4533–4552. https://doi.org/10.1016/j.bmc.2017.07.003

[2] Honda, G., Tabata, M., & Tsuda, M. (1985). The constituents of Strobilanthes cusia O. Kuntze. Journal of the Pharmaceutical Society of Japan, 105, 854–856.

[3] Danz, H., Stoyanova, S., Thomet, O. A. R., Simon, H.-U., Dannhardt, G., Ulbrich, H., & Hamburger, M. (2002). Inhibitory activity of tryptanthrin on prostaglandin and leukotriene synthesis. Planta Medica, 68(10), 875–880. https://doi.org/10.1055/s-2002-34922

[4] Pergola, C., Jazzar, B., Rossi, A., Northoff, H., Hamburger, M., Sautebin, L., & Werz, O. (2012). On the inhibition of 5-lipoxygenase product formation by tryptanthrin: Mechanistic studies and efficacy in vivo. British Journal of Pharmacology, 165(3), 765–776. https://doi.org/10.1111/j.1476-5381.2011.01605.x

[5] Ishihara, T., Kohno, K., Ushio, S., Iwaki, K., Ikeda, M., & Kurimoto, M. (2000). Tryptanthrin inhibits nitric oxide and prostaglandin E_2 synthesis by murine macrophages. European Journal of Pharmacology, 407(3), 197–204.

[6] Kumar, D., Kumar, N. M., Ghosh, S., & Shah, K. (2011). Tryptanthrin inhibits proliferation and induces apoptosis in human chronic myeloid leukemia K562 cells. International Journal of Molecular Sciences, 12(6), 3831–3845.

[7] Zhang, Y., et al. (2014). Cytotoxicity and reversal of multidrug resistance by tryptanthrin-derived indoloquinazolines. BioMed Research International, 2014, Article 513095.

[8] Wang, X., et al. (2021). Tryptanthrin exerts anti-breast cancer effects both in vitro and in vivo through modulating the inflammatory tumor microenvironment. Acta Pharmacologica Sinica / Acta Pharmacologica Sinica-associated publication. https://doi.org/10.2478/acph-2021-0020

[9] Kumar, A., et al. (2015). Synthesis and biological evaluation of phaitanthrin congeners as anti-mycobacterial agents. Bioorganic & Medicinal Chemistry Letters. https://doi.org/10.1016/j.bmcl.2015.07.057

[10] Eguchi, S., Takeuchi, H., & Matsushita, Y. (1992). Short-step synthesis of rutaecarpine and tryptanthrin via intramolecular aza-Wittig reaction. Heterocycles, 33, 153–156. https://doi.org/10.3987/COM-91-S62

[11] Nelson, A. C., et al. (2013). Formation of tryptanthrin compounds upon oxone-induced dimerization of indole-3-carbaldehydes. Tetrahedron Letters.

[12] Wang, Y., et al. (2017). Design, synthesis and biological evaluation of 8-substituted-6-hydrazonoindolo[2,1-b]quinazolin-12(6H)-one scaffolds as potential cytotoxic agents: IDO-1 targeting molecular docking studies. Bioorganic Chemistry.

[13] Zhou, X., et al. (2024). Synthesis and evaluation of tryptanthrin derivatives as promising anticancer agents: In vitro, in silico, and SAR insights. Journal of Molecular Structure, 1311, 138365. https://doi.org/10.1016/j.molstruc.2024.138365