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Sequential One-Pot CuAAC Synthesis and Structural Characterization of Novel Tryptanthrin-Based 1,2,3-Triazole Hybrids

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Abstract: Tryptanthrin is a naturally occurring indoloquinazoline alkaloid which has emerged as an attractive scaffold for the development of structurally diverse heterocyclic compounds because of its rigid fused-ring framework and ease of chemical functionalization. In the present study, an efficient sequential one-pot synthetic methodology was developed for the preparation of a series of novel tryptanthrin-based 1,2,3-triazole hybrids via copper-catalyzed azide alkyne cycloaddition (CuAAC). The synthetic strategy involved the preparation of propargylated tryptanthrin intermediates, followed by in situ generation of aryl azides from substituted anilines through diazotization using tert-butyl nitrite and sodium azide. Subsequent CuAAC under optimized reaction conditions afforded sixteen structurally diverse triazole derivatives in good to excellent isolated yields (75–91%) with excellent regioselectivity. The sequential one-pot protocol eliminated the need for isolation and handling of potentially hazardous organic azides, thereby improving operational safety, reducing purification steps, and enhancing overall synthetic efficiency. The developed methodology exhibited broad substrate tolerance toward both electron-donating and electron-withdrawing aromatic substituents, demonstrating its versatility for the rapid synthesis of molecularly diverse analogues. The structures of the synthesized compounds were comprehensively established by FTIR, ^{1}H and ^{13}C NMR spectroscopy, electrospray ionization mass spectrometry, elemental analysis, and melting point determination. The present work provides a practical, regioselective, and scalable synthetic approach for the construction of tryptanthrin-based 1,2,3-triazole hybrids and highlights the utility of sequential one-pot CuAAC chemistry for the efficient synthesis of natural product-inspired heterocyclic libraries.

Keywords: Tryptanthrin, Click chemistry, CuAAC, One-pot synthesis, 1,2,3-Triazoles, Molecular hybridization

Introduction

Natural products continue to serve as an indispensable source of structurally diverse and biologically relevant molecules for drug discovery. Their remarkable chemical diversity, evolutionary optimization, and inherent biological compatibility have inspired the development of numerous therapeutic agents across a wide range of disease areas. Among naturally occurring heterocyclic compounds, tryptanthrin (indolo[2,1-b]quinazoline-6,12-dione) has attracted considerable attention owing to its unique fused indoloquinazoline framework and broad spectrum of pharmacological activities. Originally isolated from several medicinal plants belonging to the Isatis, Polygonum, and Strobilanthes genera, tryptanthrin has been reported to exhibit antibacterial, antifungal, antiviral, anti-inflammatory, antioxidant, and anticancer properties. The rigid fused heteroaromatic structure of tryptanthrin provides a privileged molecular scaffold that can be readily functionalized, making it an attractive template for the development of structurally diverse bioactive molecules.

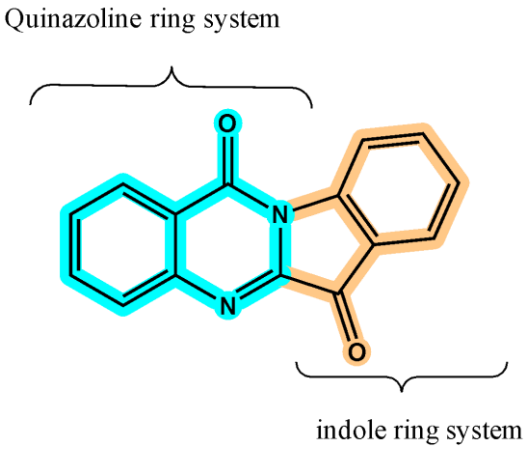

Figure 1: Fused ring structure of Tryptanthrin molecule

The quinazoline nucleus embedded within the tryptanthrin framework represents one of the most important heterocyclic pharmacophores in medicinal chemistry. Quinazoline derivatives constitute the core structures of numerous naturally occurring alkaloids and several clinically useful therapeutic agents. Their diverse biological activities have been attributed to their ability to interact with multiple biological targets through hydrogen bonding, π–π stacking, and hydrophobic interactions. Consequently, extensive efforts have been devoted to structural modification of the quinazoline scaffold to improve physicochemical properties and expand its chemical diversity. Incorporation of additional heterocyclic motifs into the tryptanthrin skeleton provides an effective strategy for generating novel molecular architectures with enhanced structural complexity and synthetic versatility.

Among nitrogen-containing heterocycles, 1,2,3-triazoles occupy a prominent position because of their exceptional chemical stability, aromatic character, and versatile applications in medicinal and synthetic chemistry. The triazole ring possesses high metabolic stability, resistance toward hydrolytic and oxidative degradation, and excellent hydrogen-bonding capability. Furthermore, it serves as an effective bioisostere for amide, ester, and peptide linkages while maintaining favourable electronic and conformational properties. These characteristics have made 1,2,3-triazoles valuable structural components in numerous pharmaceuticals, agrochemicals, functional materials, and biomolecular conjugates. Their rigid five-membered aromatic ring also functions as an efficient molecular linker capable of maintaining an optimal spatial orientation between two pharmacophoric units without significantly increasing conformational flexibility.

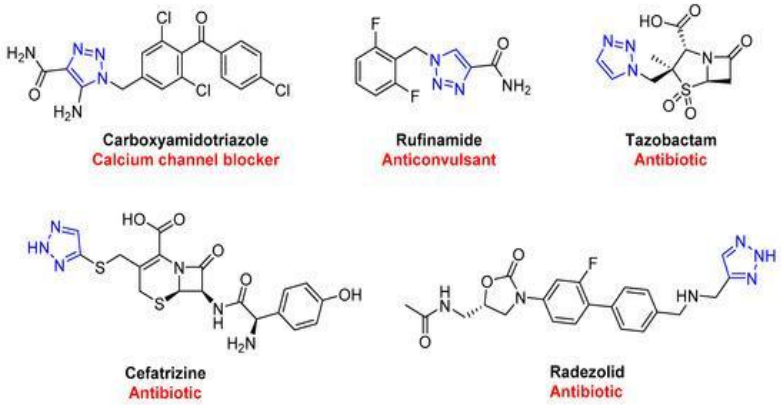

Figure 2: Structure of few triazole based drug molecules

The remarkable synthetic accessibility of 1,2,3-triazoles has largely been enabled by the development of click chemistry, particularly the copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC). Since its introduction CuAAC has become one of the most powerful and reliable synthetic transformations in modern organic chemistry because of its high regioselectivity, broad substrate tolerance, operational simplicity, and excellent functional group compatibility. The reaction proceeds under relatively mild conditions to afford exclusively 1,4-disubstituted 1,2,3-triazoles in high yields with minimal by product formation. These features have established CuAAC as an indispensable tool for medicinal chemistry, chemical biology, polymer chemistry, and materials science. Nevertheless, conventional CuAAC methodologies often require the prior synthesis and isolation of organic azides, many of which are unstable, moisture-sensitive, and potentially hazardous, thereby limiting their practical application in laboratory-scale synthesis.

To overcome these limitations, sequential one-pot CuAAC methodologies have emerged as an attractive alternative. In these approaches, organic azides are generated in situ from readily available precursors and immediately consumed in the cycloaddition reaction without isolation. Such protocols significantly improve operational safety by avoiding the handling of potentially explosive azide intermediates while simultaneously reducing purification steps, reaction time, solvent consumption, and chemical waste. The integration of diazotization, azidation, and cycloaddition into a single reaction vessel also enhances atom economy and contributes to greener and more sustainable synthetic processes. Consequently, one-pot CuAAC strategies have become increasingly valuable for the rapid construction of structurally diverse heterocyclic libraries suitable for medicinal chemistry and lead optimization studies.

Molecular hybridization has emerged as another effective strategy for the design of novel small molecules with improved structural diversity and physicochemical properties. The approach involves the rational fusion of two or more pharmacologically significant structural motifs into a single molecular framework while preserving the beneficial characteristics of each individual component. In the present study, this concept was employed by combining the naturally occurring tryptanthrin scaffold with a 1,2,3-triazole linker through a sequential one-pot CuAAC reaction. Structural diversification was achieved using a series of substituted aniline derivatives that generated aryl azides in situ, enabling rapid access to a library of functionalized tryptanthrin–triazole hybrids under mild reaction conditions.

Accordingly, the objective of this work was to develop an efficient, practical, and regioselective sequential one-pot synthetic methodology for the preparation of novel tryptanthrin-based 1,2,3-triazole derivatives. The strategy involved the synthesis of propargylated tryptanthrin intermediates followed by in situ generation of aryl azides from substituted anilines and subsequent copper(I)-catalyzed azide–alkyne cycloaddition to furnish a series of structurally diverse triazole hybrids. The synthesized compounds were isolated in good to excellent yields and comprehensively characterized using Fourier-transform infrared spectroscopy (FTIR), ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy, electrospray ionization mass spectrometry (ESI-MS), elemental analysis, and melting point determination. The developed methodology demonstrates an operationally simple, efficient, and broadly applicable approach for the synthesis of tryptanthrin-derived heterocyclic frameworks that may serve as versatile intermediates for future medicinal chemistry investigations.

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2. Experimental

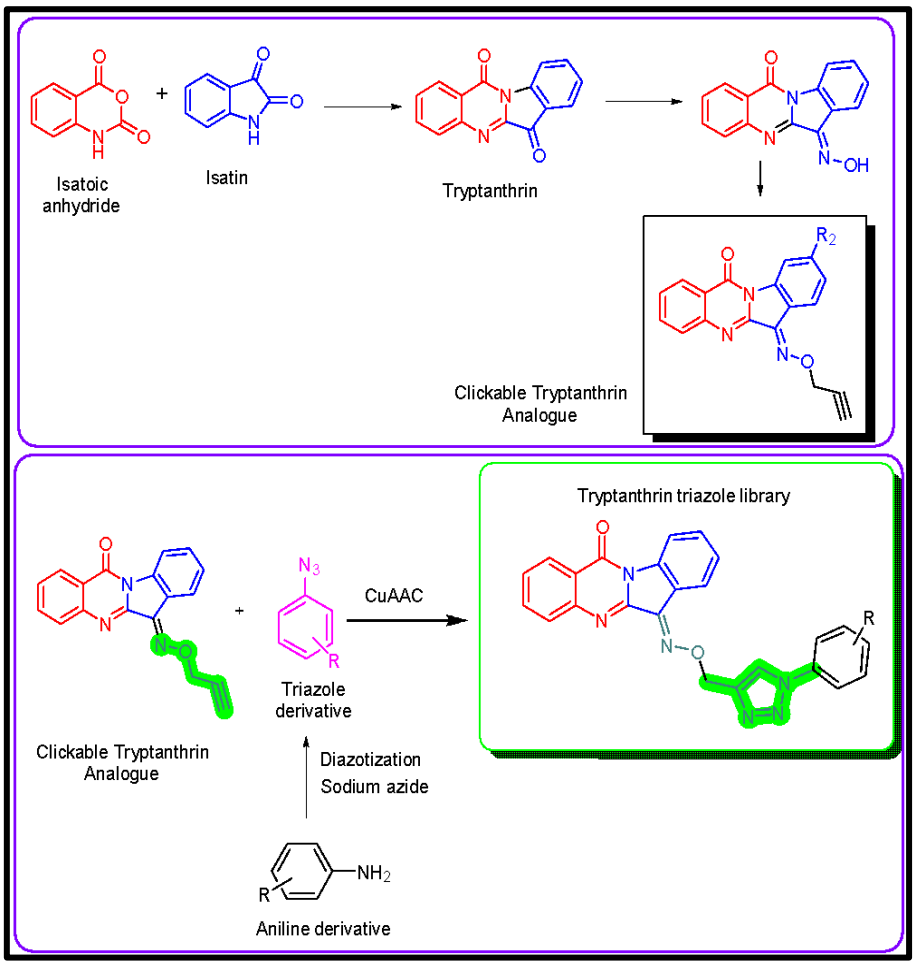

Figure 1: Designing of Tryptanthrin based triazole molecules

2.1. Materials and Methods

All reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise stated. Tryptanthrin derivatives were prepared according to the reported synthetic procedure and served as the starting materials for subsequent transformations. Thin-layer chromatography (TLC) was performed on silica gel 60 F254 aluminium-backed plates, and reaction progress was monitored under ultraviolet light (254 nm). Column chromatography was carried out using silica gel (100–200 mesh) with appropriate mixtures of petroleum ether and ethyl acetate as eluents.

Melting points were determined in open capillary tubes using a digital melting-point apparatus and are uncorrected. Infrared (FTIR) spectra were recorded as KBr pellets and are reported in cm^{-1}. ^{1}H and ^{13}C NMR spectra were acquired on a 300 MHz Bruker spectrometer using $CDCl_3$ as the solvent, with tetramethylsilane (TMS) as the internal standard. Chemical shifts (δ) are reported in parts per million (ppm), and coupling constants (J) are expressed in hertz (Hz). Electrospray ionization mass spectra (ESI-MS) were recorded in positive ion mode. Elemental analyses were performed using a CHN elemental analyzer, and the experimental values were within ±0.4% of the calculated compositions.

2.2 Synthesis of Tryptanthrin Molecule: The tryptanthrin molecule was prepared by reaction of isatoic anhydride and isatin. Isatoic anhydride 1 mmol and isatin 1 mmol was mixed in 25 ml touluene and refluxed up to completion of reaction. The reaction progress was monitored by TLC. After completion toluene was evaporated under reduced pressure and crude was extracted with dichloromethane and water. The organic layer was dried over sodium sulphate and solvent evaporated by distillation. The residue was crystallized in ethanol to afford Tryptanthrin in 90% yiels.

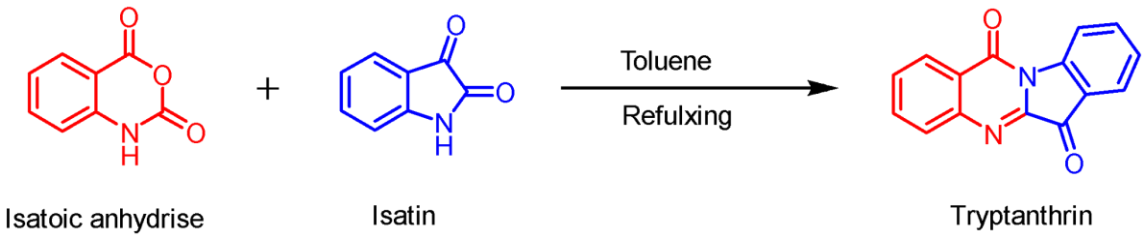

Figure 2: **Synthesis of Tryptanthrin molecule.**

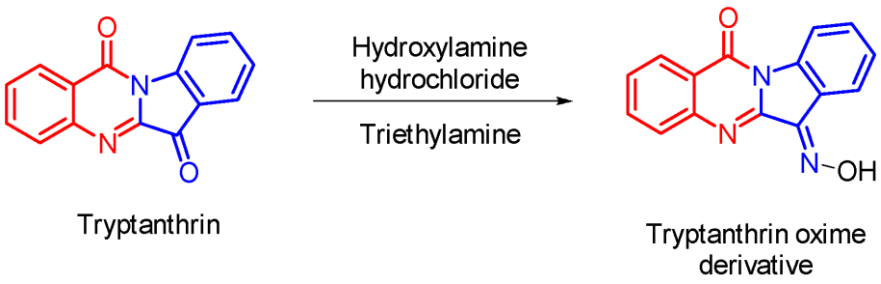

Figure 3: **Synthesis of tryptanthrin oxime derivatives**

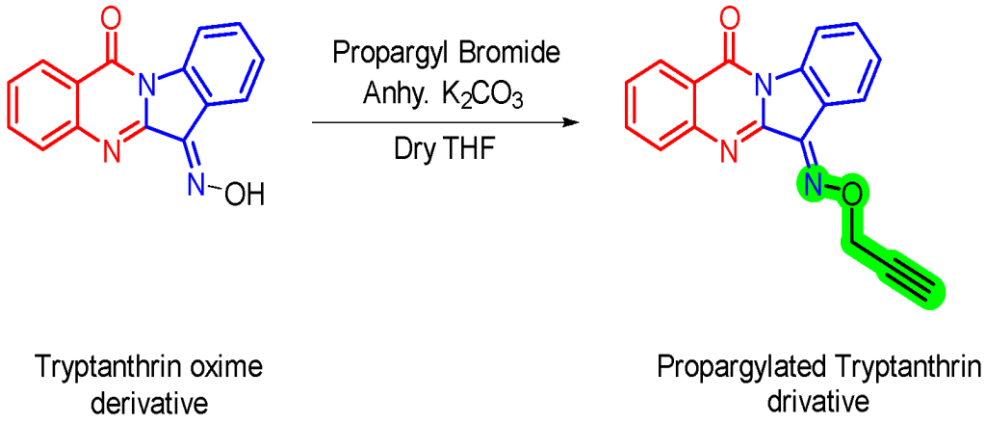

Figure 4: Synthesis of Propargylated Tryptanthrin derivatives

Synthesis of Propargylated Tryptanthrin Intermediates

The required propargylated tryptanthrin derivatives were synthesized in two consecutive steps. Initially, the corresponding tryptanthrin derivatives were converted into their oxime analogues by treatment with hydroxylamine hydrochloride under appropriate reaction conditions. The isolated oximes were subsequently subjected to O-propargylation using propargyl bromide in the presence of a suitable base to afford the corresponding terminal alkyne intermediates. These propargylated derivatives served as key precursors for the copper-catalyzed azide–alkyne cycloaddition reaction.

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General Procedure for the Sequential One-Pot Synthesis of Tryptanthrin-Based 1,2,3-Triazoles

A substituted aniline (1.0 mmol) was dissolved in anhydrous dimethylformamide (DMF, 10 mL) in a 100 mL round-bottom flask equipped with magnetic stirring. To this solution, tert-butyl nitrite (t-BuONO, 2.5 mmol) was added dropwise at room temperature, and the reaction mixture was stirred for 15 min to facilitate the formation of the corresponding diazonium intermediate. Sodium azide (2.5 mmol) was then added portion-wise, and stirring was continued for an additional 30 min to generate the corresponding aryl azide **in situ**. Subsequently, the appropriate propargylated tryptanthrin derivative (1.0 mmol) and copper(I) iodide catalyst (10 mol%) were introduced into the reaction mixture. The resulting suspension was heated at 80 °C with continuous stirring until completion of the reaction, as monitored by TLC.

After completion, the reaction mixture was cooled to room temperature and poured into water (50 mL). The product was extracted with ethyl acetate (3 × 25 mL), and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate as the eluent to afford the corresponding tryptanthrin-based 1,2,3-triazole derivatives as pure solids. The developed sequential one-pot protocol enabled the synthesis of a diverse series of triazole derivatives in good to excellent isolated yields without requiring isolation of the intermediate aryl azides.

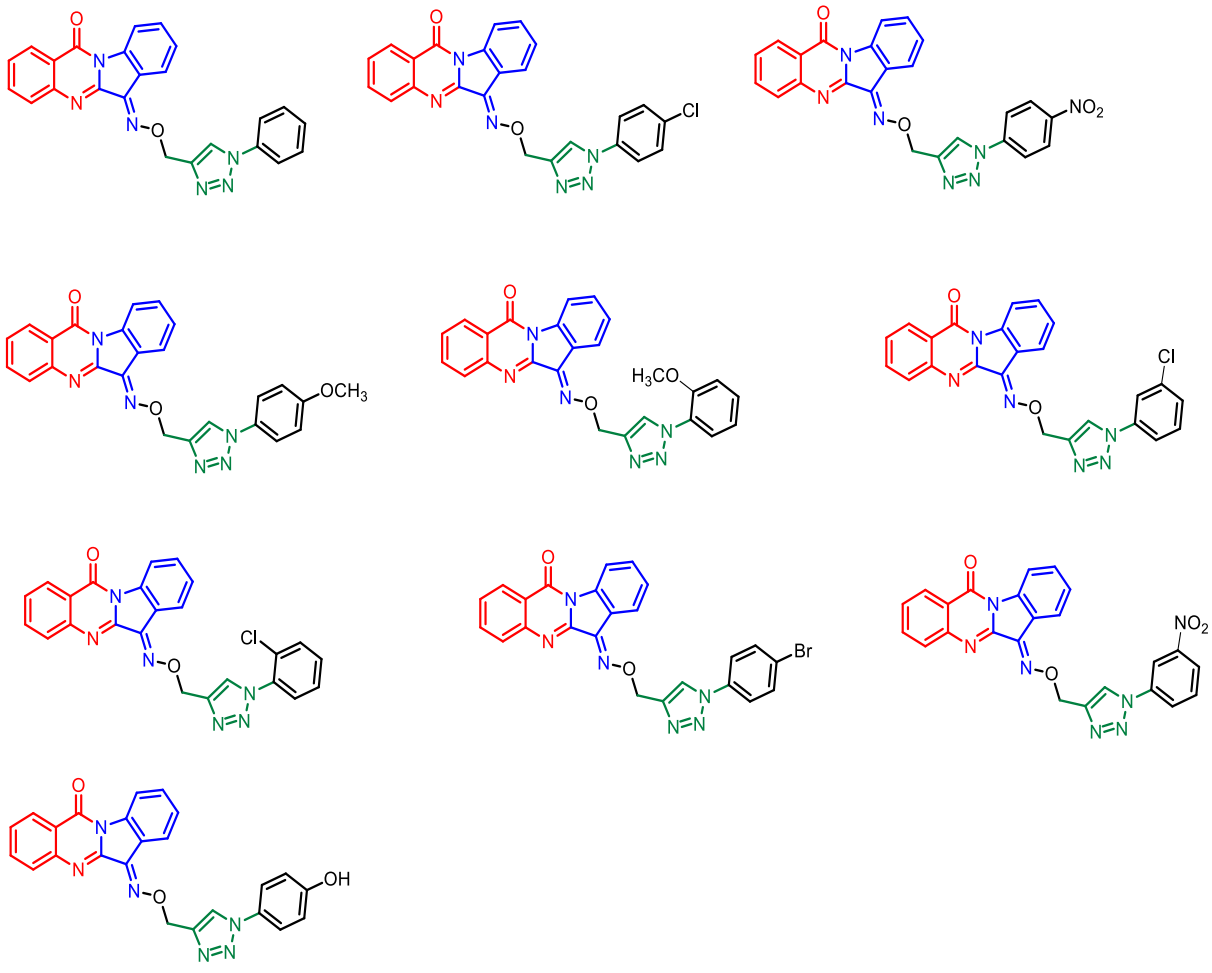

Figure 5: **The synthesized tryptanthrin triazole library**

Product Characterization

All synthesized compounds were isolated as crystalline solids in isolated yields ranging from **75–91%**. Their structures were established by a combination of FTIR, ^{1}H NMR, ^{13}C NMR, ESI-MS, and elemental analysis. Formation of the triazole ring was confirmed by the disappearance of the terminal alkyne proton signal of the precursor molecules and the appearance of a characteristic methylene singlet at δ 5.80–5.91 ppm in the ^{1}H NMR spectra. The ^{13}C NMR spectra exhibited resonances corresponding to the carbonyl carbons of the tryptanthrin framework (δ 181–184 ppm) together with signals attributable to the triazole-linked methylene carbon (δ 63–64 ppm). Molecular ion peaks observed in the ESI mass spectra agreed well with the calculated molecular weights, while elemental analyses further confirmed the identity and purity of all synthesized compounds.

Results and Discussion

Molecular Design and Synthetic Strategy

The present work was designed based on the molecular hybridization approach, wherein the naturally occurring alkaloid tryptanthrin was selected as the central molecular scaffold owing to its rigid indoloquinazoline framework and the availability of a chemically accessible carbonyl functionality suitable for further derivatization. To enhance the structural diversity of the scaffold and provide a versatile synthetic platform, a 1,2,3-triazole ring was incorporated through copper-catalyzed azide–alkyne cycloaddition (CuAAC). The triazole nucleus serves as a chemically robust linker while preserving the aromatic character of the parent molecule and allowing the introduction of structurally diverse aryl substituents.

The overall synthetic strategy involved three sequential transformations. Initially, tryptanthrin derivatives were converted into the corresponding oximes using hydroxylamine hydrochloride, providing a suitable functional handle for subsequent O-propargylation. Alkylation of the oxime hydroxyl group with propargyl bromide afforded terminal alkyne intermediates that served as click partners for the CuAAC reaction. In the final step, substituted anilines were transformed into the corresponding aryl azides in situ through diazotization with tert-butyl nitrite followed by nucleophilic substitution with sodium azide. The generated azides immediately underwent cycloaddition with the propargylated tryptanthrin derivatives under copper(I)-catalyzed conditions to furnish the desired tryptanthrin–triazole hybrids. This modular synthetic route enabled rapid preparation of structurally diverse analogues while avoiding the isolation and handling of potentially hazardous organic azides.

Optimization of the Sequential One-Pot CuAAC Reaction

The efficiency of the click cycloaddition was strongly influenced by the reaction protocol employed. Initial experiments were performed by mixing substituted aniline, the propargylated tryptanthrin derivative, copper sulfate, sodium ascorbate, and a tert-butanol/water (1:1) solvent system under conventional CuAAC conditions. Although triazole formation was observed, thin-layer chromatographic analysis indicated that only trace amounts of the desired product were formed after several hours, while a significant proportion of the alkyne precursor remained unreacted. To improve the efficiency of the process, various reaction media were investigated. Among the solvents examined, dimethylformamide (DMF) provided improved solubility of the reactants and enhanced conversion; however, simultaneous addition of all reaction components still afforded only modest product yields. A substantial improvement was achieved by adopting a sequential one-pot protocol. In this approach, substituted aniline was first treated with tert-butyl nitrite to generate the corresponding diazonium intermediate, followed by addition of sodium azide to produce the aryl azide in situ. After complete formation of the azide intermediate, the propargylated tryptanthrin derivative and CuI catalyst were introduced into the reaction mixture, resulting in rapid and nearly complete conversion to the corresponding 1,4-disubstituted triazole derivatives.

The sequential addition strategy not only increased the overall conversion but also improved isolated yields and minimized the formation of side products. Furthermore, the methodology eliminated the need for isolation of

unstable aryl azides, thereby enhancing operational safety and simplifying the experimental procedure. These observations demonstrate that controlled generation and immediate consumption of the azide intermediate represent critical factors governing the efficiency of the one-pot CuAAC process.

Synthesis of Tryptanthrin–Triazole Hybrids

Using the optimized reaction conditions, a focused library of tryptanthrin-based 1,2,3-triazole derivatives was synthesized employing a range of substituted anilines bearing electron-donating and electron-withdrawing substituents. The methodology tolerated a wide variety of functional groups, including methoxy, hydroxy, methyl, nitro, bromo, and chloro substituents, without requiring any modification of the reaction conditions. The sequential one-pot protocol proved highly versatile, furnishing sixteen triazole derivatives in consistently good to excellent isolated yields ranging from **75 to 91%** with reaction times between **4 and 7 h**. Methoxy-substituted derivatives generally afforded the highest isolated yields (approximately 90–91%), whereas hydroxy- and nitro-substituted substrates required slightly longer reaction times and gave comparatively lower yields. Nevertheless, all reactions proceeded cleanly, and the desired products were isolated after simple chromatographic purification.

The broad substrate compatibility observed in the present study demonstrates the robustness of the sequential one-pot methodology. The tolerance towards both electron-rich and electron-deficient aromatic amines indicates that the diazotization–azidation sequence proceeds efficiently irrespective of the electronic nature of the aromatic substituent. Likewise, the subsequent CuAAC reaction exhibited excellent regioselectivity, producing exclusively the corresponding 1,4-disubstituted triazole derivatives. These results confirm that the developed methodology represents a convenient and efficient route for the rapid synthesis of structurally diverse tryptanthrin-based molecular hybrids.

Proposed Reaction Pathway

The reaction is believed to proceed through a sequential diazotization–azidation–cycloaddition process. Initially, substituted aniline reacts with tert-butyl nitrite to generate the corresponding aryldiazonium intermediate. Subsequent nucleophilic substitution by sodium azide affords the corresponding aryl azide in situ. Simultaneously, copper(I) activates the terminal alkyne of the propargylated tryptanthrin derivative to form a copper acetylide complex. Cycloaddition of the activated alkyne with the aryl azide proceeds through a six-membered copper-containing metallacyclic intermediate, which undergoes ring contraction and protonation to furnish the 1,4-disubstituted 1,2,3-triazole product while regenerating the copper catalyst. The exclusive formation of the 1,4-regioisomer is consistent with the well-established mechanism of copper-catalyzed azide–alkyne cycloaddition.

Structural Characterization

The structures of the synthesized tryptanthrin–triazole hybrids were established using a combination of FTIR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy, electrospray ionization mass spectrometry (ESI-MS), elemental analysis, and melting point determination. In the FTIR spectra, all compounds exhibited characteristic absorption bands corresponding to the carbonyl groups of the tryptanthrin framework together with bands attributable to the oxime ether functionality. Formation of the triazole derivatives was further supported by the disappearance of absorptions associated with the terminal alkyne stretching vibration of the propargylated intermediates.

The ^{1}H NMR spectra provided clear evidence for successful cycloaddition. A characteristic singlet corresponding to the methylene bridge connecting the triazole ring and the oxime oxygen appeared consistently at **δ 5.80–5.91 ppm** in all synthesized derivatives. Aromatic protons of both the tryptanthrin nucleus and substituted phenyl rings resonated within the expected region of **δ 6.8–8.7 ppm**, while methoxy-substituted derivatives exhibited an additional singlet at approximately **δ 3.86–3.88 ppm**. Importantly, the disappearance of the terminal alkyne proton signal observed in the precursor molecules confirmed complete conversion of the propargyl intermediates into the corresponding triazole products.

The ^{13}C NMR spectra further corroborated the assigned structures by displaying characteristic resonances for the carbonyl carbons of the tryptanthrin framework in the region of **δ 181–184 ppm** together with signals attributable to aromatic carbons, triazole-linked methylene carbon (δ 63–64 ppm), and methoxy carbon atoms near **δ 54 ppm** where applicable. The observed carbon chemical shifts were fully consistent with the proposed molecular structures. ESI-MS analysis of all synthesized compounds showed molecular ion peaks corresponding to the expected [M+H]^+ species, thereby confirming the molecular masses of the products. In addition, elemental analyses showed excellent agreement between calculated and experimentally determined carbon, hydrogen, and nitrogen contents, providing further confirmation of the high purity and correct molecular composition of the synthesized compounds.

Advantages of the Developed Methodology

Compared with conventional multistep click synthetic procedures, the present sequential one-pot methodology offers several practical advantages. The protocol avoids isolation of unstable aryl azides, thereby improving laboratory safety and reducing the risk associated with handling energetic intermediates. Integration of diazotization, azidation, and cycloaddition into a single reaction vessel minimizes solvent consumption, simplifies purification, and shortens the overall reaction sequence. Furthermore, the methodology displays broad substrate scope, excellent regioselectivity, and consistently high isolated yields under relatively mild reaction conditions. These features make the protocol an attractive and operationally simple synthetic platform for the preparation of structurally diverse tryptanthrin-derived 1,2,3-triazole hybrids and may facilitate the rapid generation of related heterocyclic libraries for future synthetic and medicinal chemistry applications.

Conclusion

A practical and efficient sequential one-pot synthetic methodology has been developed for the preparation of a series of novel tryptanthrin-based 1,2,3-triazole hybrids through copper-catalyzed azide–alkyne cycloaddition (CuAAC). The strategy combines in situ generation of aryl azides from readily available substituted anilines with regioselective cycloaddition to propargylated tryptanthrin derivatives in a single reaction vessel, thereby eliminating the need for the isolation and handling of potentially hazardous organic azide intermediates. This operationally simple protocol significantly improves the safety, convenience, and overall efficiency of the synthetic process while adhering to the principles of step economy and green chemistry. The developed methodology demonstrated broad substrate compatibility, successfully accommodating a diverse range of electron-donating and electron-withdrawing substituents on the aromatic ring to furnish the desired triazole derivatives in good to excellent isolated yields (75–91%) with high regioselectivity. The modular nature of the synthetic route provides a convenient platform for the rapid generation of structurally diverse tryptanthrin-based molecular hybrids from readily accessible starting materials under relatively mild reaction conditions.

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