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1,2,4-Triazole as promising scaffold: Synthetic and Biological Aspects

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Abstract: 1,2,4-Triazoles are valuable scaffolds in medicinal chemistry due to their diverse biological activities. This review delves into synthesis strategies, such as iodine-mediated, microwave-assisted, solid-phase, and liquid-phase approaches, and their biological relevance. These methods yield efficient access to 1,2,4-triazoles, which demonstrate significant anticancer, anti-inflammatory, antimicrobial, antioxidant, and antiviral properties. Additionally, carbohydrate-based triazoles and coumarin-azole-sugar hybrid compounds also show remarkable activity. The potential of 1,2,4-triazoles in drug discovery and therapeutic applications underscores their role in medicinal chemistry.

Keywords: 1,2,4-triazole, synthesis strategies, biological activity, Carbohydrates, medicinal chemistry, bioactive compounds.

1. INTRODUCTION

The realm of medicinal chemistry offers a plethora of intriguing molecules for exploration, among which the class of 1,2,4-triazole compounds stands out. Renowned for their robust stability, effective bioavailability, and a broad spectrum of biological activities, these compounds have ignited significant interest in the scientific community.

This review will delve into the comprehensive exploration of 1,2,4-triazole, highlighting its significance as an integral member of heterocyclic compounds. To guide this investigation, we will commence with Section 1.1, detailing the landscape of heterocyclic compounds and their overarching importance in the pharmaceutical and biomedical field. Following this, Section 1.2 will zoom in on 1,2,4-triazole compounds, shedding light on their structure, synthesis, properties, and diverse applications.

Subsequently, in Section 1.3, the synthesis of 1,2,4-triazole compounds is discussed. Section 1.4 then expands on the biological significance of these compounds and the strategies employed in their synthesis. Section 1.5 explores the potential therapeutic uses of carbohydrate-based triazoles. The goal is to enhance understanding of these distinct compounds, particularly when they are linked to monosaccharide units.

1.1 Heterocycles compounds

Heterocyclic compounds, possessing atoms other than carbon and hydrogen in their cyclic structures, form a critical division in organic chemistry.[1] Their extensive variety, distinguished by diverse physical and chemical properties, is influenced by the count and hybridization of nitrogen atoms within the ring. These compounds, found in pharmaceuticals, pesticides, and food additives, also contribute to the development of novel materials like polymers and ceramics.[2] Everyday examples include pyridine-based caffeine and nicotine, pyrimidine components in DNA and RNA, imidazole compounds like histamine and histidine, and triazoles such as fluconazole and

itraconazole.[2] The therapeutic properties of nitrogen-based heterocycles have made them significant in medicinal chemistry, leading to the creation of pharmaceutically relevant molecules.[3]
Among the numerous heterocyclic systems, derivatives of pyrazole, pyridine, purine, pyrrole, pyrimidine, furan, and many others have exhibited a wide range of pharmacological activities. However, particular attention has been focused on structures with low toxicity, exemplified by the 1,2,4-triazoles.[4]

1.2 1,2,4-Triazole Compounds

Triazoles, also known as pyrrodiazoles, embody a unique class of organic heterocyclic compounds with a distinctive five-membered di-unsaturated ring structure. This ring comprises three nitrogen atoms and two carbon atoms in non-adjacent positions, adhering to the molecular formula $C_2H_3N_3$.[5] The triazole family encompasses two isomeric forms, namely 1,2,3-triazole and 1,2,4-triazole. However, the 1,2,4-triazole isomer, extant in two tautomeric forms, 1H and 4H, is of significant pharmacological interest [6] (Figure 1) and (Figure 2). Its atoms in sp_2 hybridization and planar arrangement, along with six pi (π) electrons delocalized around the ring, confer an aromatic character. The additional presence of three nitrogen atoms contributes to their status as energy-rich heterocycles.[7] Notably, 1,2,4-triazole distinguishes itself among various heterocycles, exhibiting capabilities for inducing pi-stacking, dipole–dipole interactions, hydrogen bonding, and hydrophobicity. As effective amide substitutes in bioactive molecules, triazole derivatives also demonstrate potential as linkers, showing bio-isosteric effects with different structures, which enhances the pharmaceutical, toxicokinetic, pharmacokinetic, and physiochemical aspects of compounds.[8]

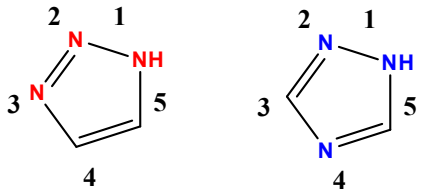


Figure 1. 1,2,3 and 1,2,4- triazole.

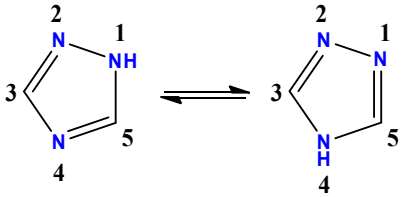


Figure 2. 1H- and 4H- Form of 1,2,4 triazole.

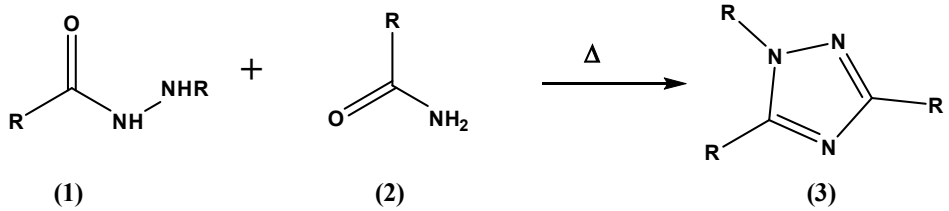
1.3 1,2,4-Triazole Synthesis Methods

This section delves into the synthesis methods of 1,2,4-triazoles. Beginning with a review of common methods (1.3.1), the discussion expands to highlight various specific approaches, from iodine-mediated synthesis (1.3.2) and direct synthesis of N1- and N4-Substituted Triazoles (1.3.3 and 1.3.4), to the synthesis of two 1,2,4-triazole rings (1.3.5). Further examination includes innovative methods like microwave synthesis (1.3.6), transformation of other heterocyclic systems (1.3.7), substitution of 1,2,4-Triazole (1.3.8), and solid and liquid phase synthesis (1.3.9 and 1.3.10). The goal is to provide a thorough understanding of the diversity of 1,2,4-triazole synthesis methods.

1.3.1 Common Methods for Triazole Synthesis

1.3.1.1 From Hydrazine and Formamide

The study of the triazole ring initiated in 1885 when experiments utilizing hydrazine (1) and formamide (2) led to the formation of the central ring structure This was an essential development in the field, with the formation reaction and mechanism illustrated in (Figure 3).[9,10]

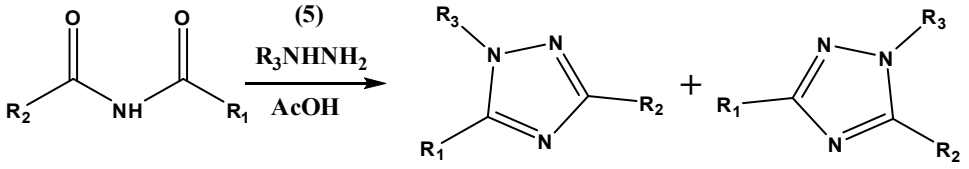


(1) (2) (3)

Figure 3. Depiction of 1,2,4-Triazole Ring Formation.

1.3.1.2 From Imides and Hydrazines

The synthesis of 1,2,4-triazole was revolutionized in 1914 by the introduction of a novel method involving the combination of various imides (6) with hydrazines (7). This breakthrough led to the discovery of the Einhorn-Brunner reaction, which produced high-quality derivatives of the compound. (Figure 4) depict the reaction.[9,11]

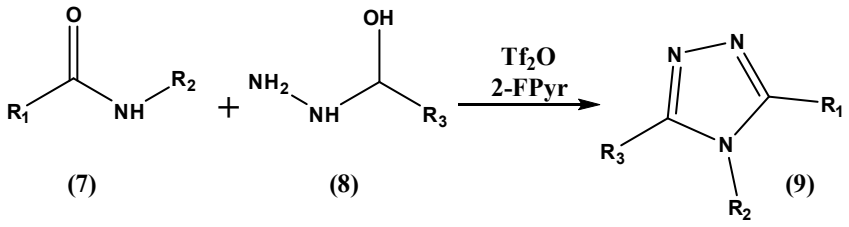


(4) (6a) (6b)

Figure 4. 1,2,4-triazole synthesis via the Einhorn-Brunner reaction.

1.3.1.3 From 2° Amides and Hydrazides

The synthesis of 3,4,5-Trisubstituted 1,2,4-triazole (**9**) has been accomplished through activating 2° amides (7) and hydrazides (8) by utilizing triflic anhydride as an activator, followed by the application of microwave-assisted cyclodehydration. The resultant 1,2,4-triazole moiety has shown notable utility as a crucial directing group in Ru-catalyzed C-H arylation reactions (Figure 5).[12]



(7) (8) (9)

Figure 5. Formation of 3,4,5-Trisubstituted 1,2,4-triazole using 2° amides and hydrazides.

1.3.1.4 From Amidines and Trialkyl Amines

A collection of compounds comprising 1,3-disubstituted-1,2,4-triazoles (**12**) were produced by leveraging the catalytic properties of copper (II) in the reaction process between amidines (10) and trialkyl amines (11), with potassium phosphate (K_3PO_4) employed as the base (Figure 6).[13,14]

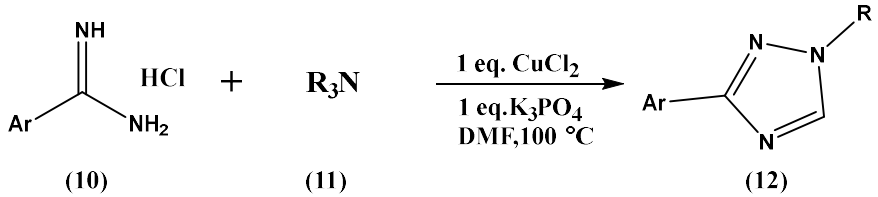


Figure 6. Formation of 1,2,4-triazole through amidine synthesis.

1.3.1.5 From Amidine and Benzonitrile

Successive oxidative coupling reactions leading to the formation of N-N and N-C bonds facilitate the formation of 1,2,4-triazole derivatives (**14**). This process employs a copper-catalyzed reaction, which occurs in the presence of cesium carbonate and dimethylsulfoxide under atmospheric air conditions. The procedure involves treating substituted amidine (10) and benzonitrile (13) (Figure 7). The reaction supports a wide array of functional groups, and the starting materials along with the copper catalyst showcase affordability and accessibility.[15,16]

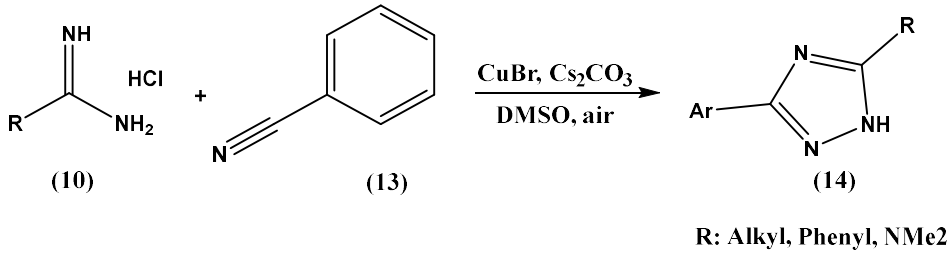


Figure 7. Formation of 1,2,4-triazole through amidine synthesis.

1.3.1.6 By Utilizing Cu(II) and Ag(I) Catalysis Approaches for 1,2,4-Triazole Synthesis

Ethyl cyanoacetate (**16**) has been recognized as a valuable reagent for synthesizing 1,2,4-triazoles. Under Ag(I) catalysis utilizing Silver (II) carbonate at freezing water temperatures of 0°C, the selective formation of 1,3-disubstituted 1,2,4-triazoles (**17**) has been reported. Conversely, the utilization of Cu (II) catalysis has demonstrated remarkable efficiency in yielding high quantities of 1,5-disubstituted 1,2,4-triazoles (**18**). These region-specific catalytic methods provide direct access to 1,2,4-triazole frameworks, showcasing high efficiency, a broad substrate range, and exceptional functional group compatibility (Figure 8). The mechanism underlying the formation of compounds **17** and **18** is illustrated in (Schemes 1 and 2).[17,18]

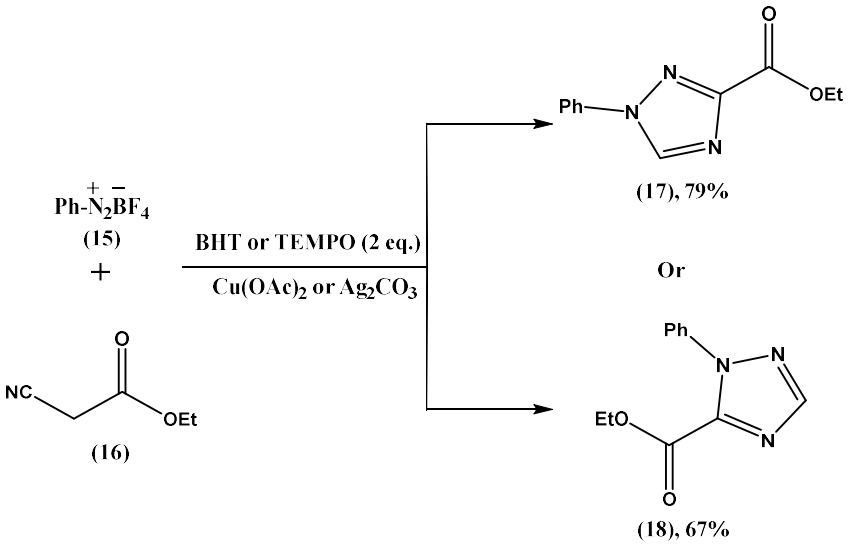
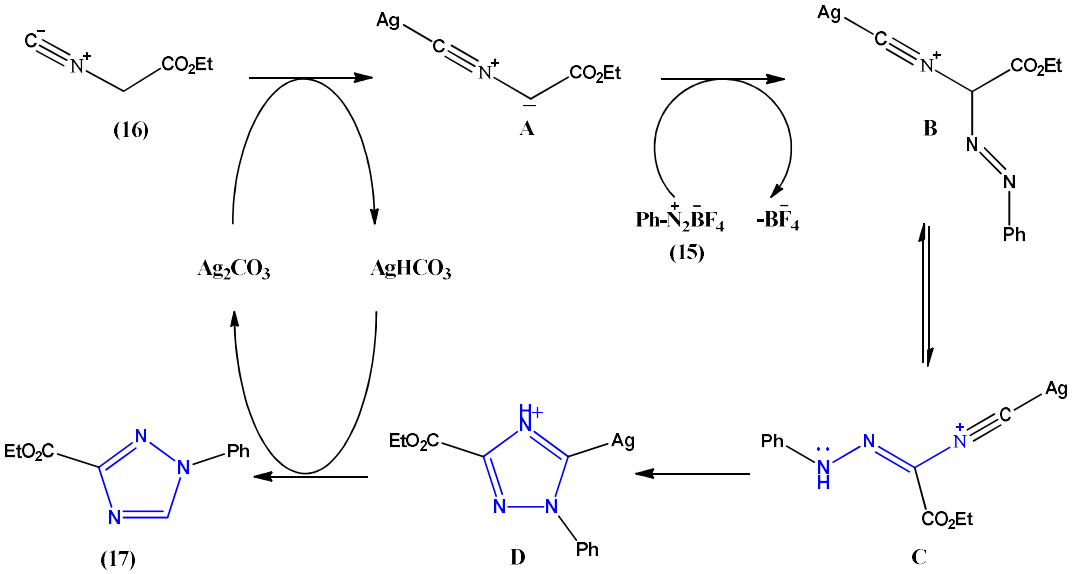
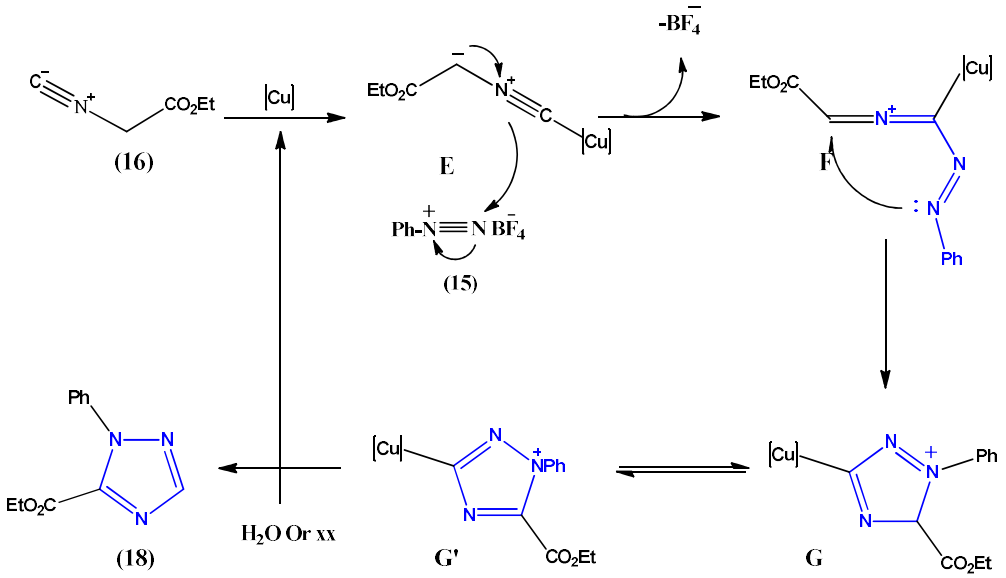


Figure 8. 1,3 and 1,5-disubistituted 1,2,4-triazole.



Scheme 1. Postulated mechanism for 1,3-disubstituted 1,2,4-triazoles (17).



Scheme 2. Postulated mechanism for 1,5-disubstituted 1,2,4-triazoles (18).

1.3.1.7 From One-Pot Cyanoimidation of Aldehydes

A highly efficient one-pot cyanoimidation of aldehydes (**19**), conducted without the need for a catalyst, enables the formation of *N*-cyanoimidates (**21**) using NBS as an oxidant in the presence of methanol under reflux conditions. This process facilitates cyclization and yields 1,2,4-triazole derivatives (**23**), providing notable advantages such as high yields.[19] (Figure 9)

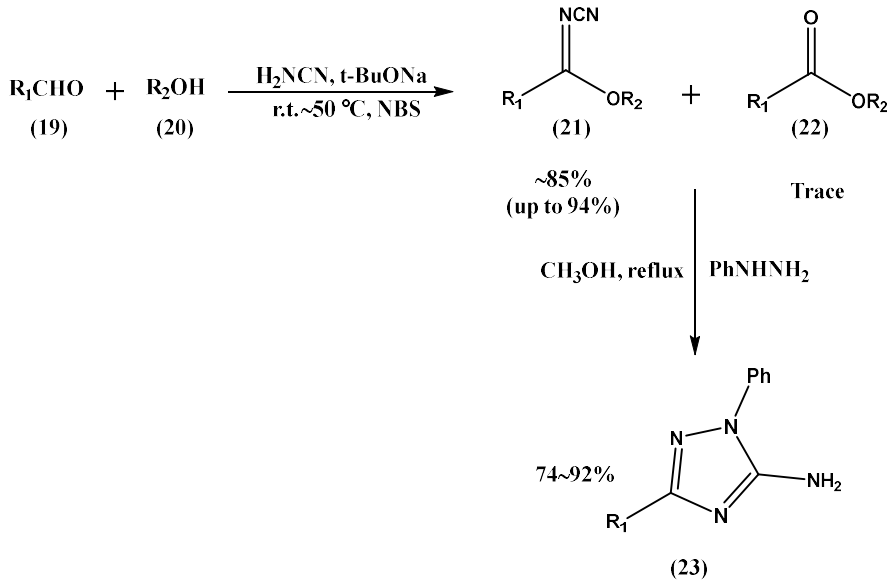


Figure 9. Examining the Cyanoimidation of Aldehydes Reaction.

1.3.1.8 From Hydrazinophthalazine and Carboxylic Acid Coupling

A facile and practical method has been developed for the preparation of new derivatives of 1,2,4-triazoles. The reaction between hydrazinophthalazine and carboxylic acid derivatives (24) using EDC and HOBT as coupling agents is employed. The yield of this procedure is largely dependent on the reaction conditions employed. Experiments have demonstrated that dichloromethane, when employed as a solvent, yielded considerably higher yields compared to other solvents investigated. The optimized conditions afford a simple, cost-effective, and scalable route to access novel derivatives of 1,2,4-triazoles with potential biological activities.[20] (Figure 10).

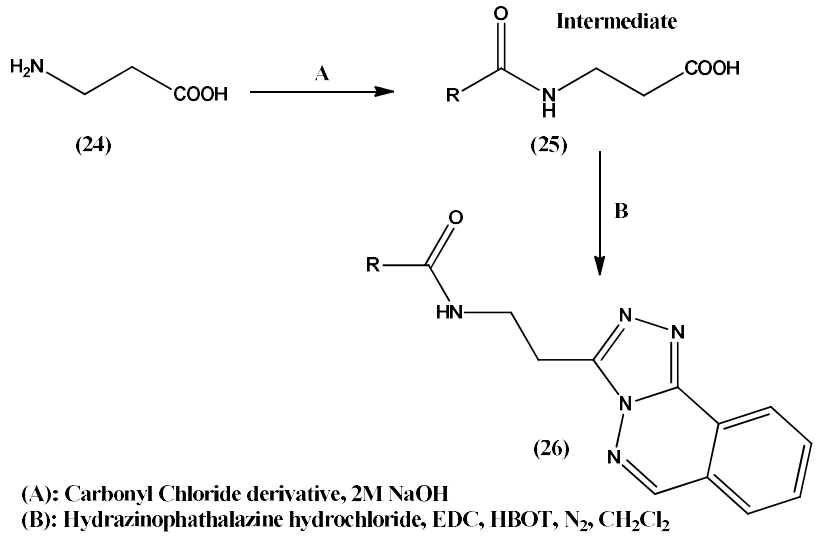
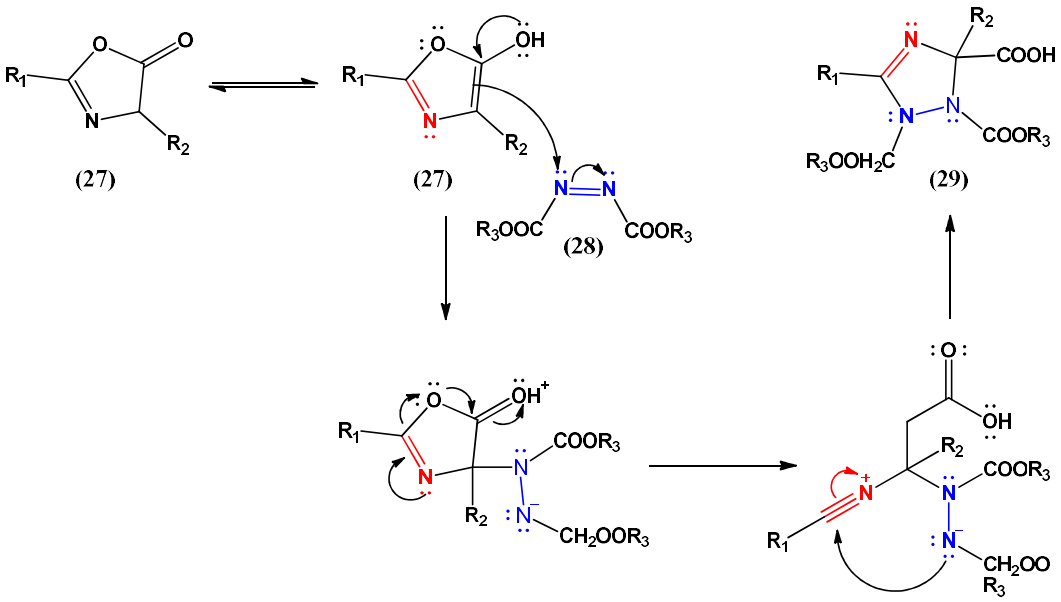


Figure 10. Synthesis of 1,2,4-Triazoles from Hydrazinophthalazine and Carboxylic Acid Coupling.

1.3.1.9 From Oxazolones and Azodicarboxylates

A convenient method for synthesizing 1,2,4-triazolines using oxazolones (**27**) and azodicarboxylates (**28**) at room temperature in acetonitrile is described. The mechanism of triazoline formation is explained in (Scheme 3). The reaction scope was assessed with various azodicarboxylate compounds and oxazolone substituents. The synthesized 1,2,4-triazolines (**29**), efficiently converted to biologically active 1,2,4-triazoles (**30**) using sodium hydroxide (NaOH), offer a mild reaction approach with readily available starting materials.[21] (Figure 11)



Scheme 3. Triazoline (29) Formation Mechanism.

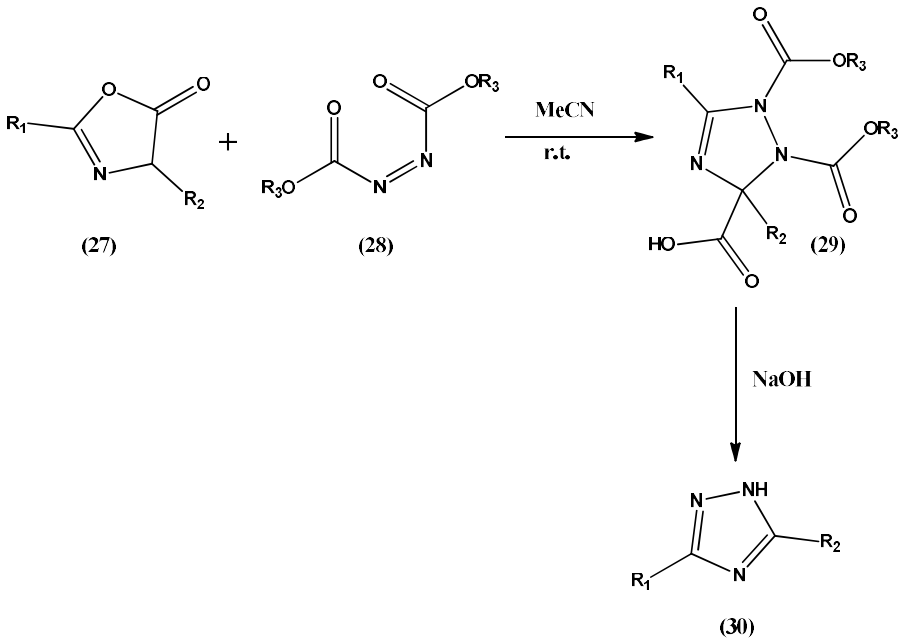
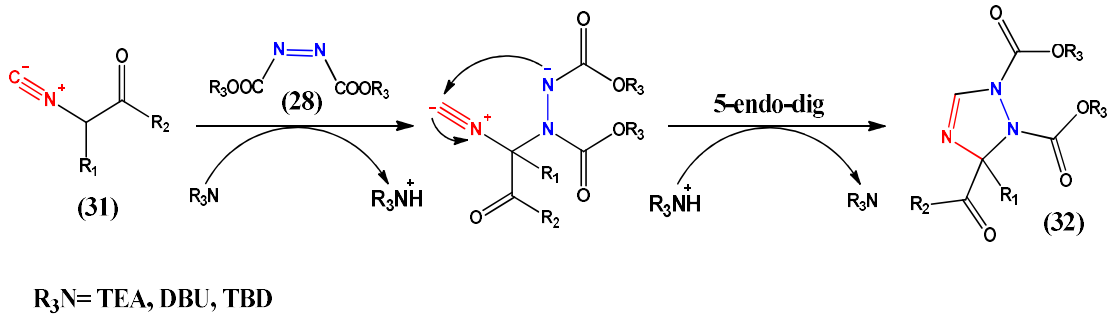


Figure 11. Synthesis of 1,2,4-Triazoles from Oxazolones and Azodicarboxylates.

1.3.1.10 From Alpha-Isocyano Esters/Amides and Azodicarboxylates: An Efficient Cascade Reaction

An expedient and highly effective approach for the production of 1,2,4-triazolines through the utilization of alpha-isocyano esters/amides (**31**) and azodicarboxylates (**28**) is showcased. The mechanism of triazoline formation is explained in (Scheme 4). The reaction cascade involves a base-catalyzed hydrazination-type reaction followed by cyclization, resulting in the formation of triazolines with yields ranging from 75% to 99%. Additionally, the exploration of phosphine-catalyzed and preliminary asymmetric phase-transfer catalysis approaches is discussed, offering potential enhancements to the synthesis. This methodology provides a valuable route for accessing diverse 1,2,4-triazolines (**32**) with promising applications in various scientific fields.[22] (Figure 12).



Formation Mechanism. Scheme 4. Triazoline (32)

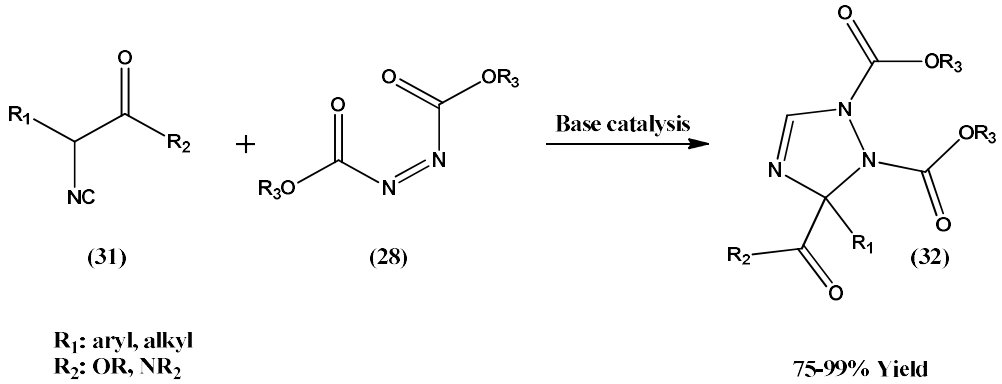


Figure 12. Base-Catalyzed Hydrazination and Cyclization for the Formation of 1,2,4-Triazolines.

1.3.1.11 From thiosemicarbazides: Cyclization to 1,2,4-triazole-5-thiol Derivatives.

The base-catalyzed cyclization of thiosemicarbazides (**34**) or their thio derivatives is a well-established approach for the synthesis of 1,2,4-triazole-5-thiol derivatives (**35**), as illustrated in (Figure 13). This method has gained widespread use due to its ability to afford the desired compounds in moderate to high yields. Consequently, it is recognized as a highly effective and extensively applied strategy for the preparation of 1,2,4-triazole-5-thiol derivatives.[23]

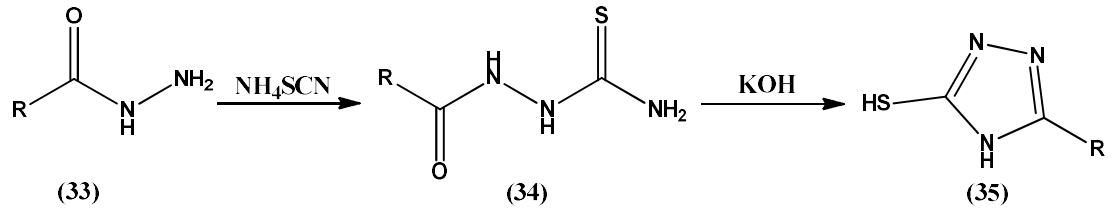


Figure 13. Synthesis of 1,2,4-Triazole-5-thiol Derivatives through Cyclization of Thiosemicarbazides.

1.3.1.12 From aminoacylhydrazines and acyl halides: Cyclization to synthesize diverse 1,2,4-triazole derivatives.

Several distinct synthetic strategies have been devised for the fabrication of 1,2,4-triazole and its derivatives. Among these methods, the cyclization of aminoacylhydrazines (**36**) and acyl halides (**37**), as depicted in (Figure 14), has

emerged as an effective approach. This synthetic pathway has been extensively employed to generate diverse 1,2,4-triazole derivatives (**38**) with a range of substituents. It offers an efficient and versatile approach for synthesizing these noteworthy heterocyclic compounds. Occasionally, this method can also be applied to the formation of certain 1,3,4-oxadiazole derivatives.[23]

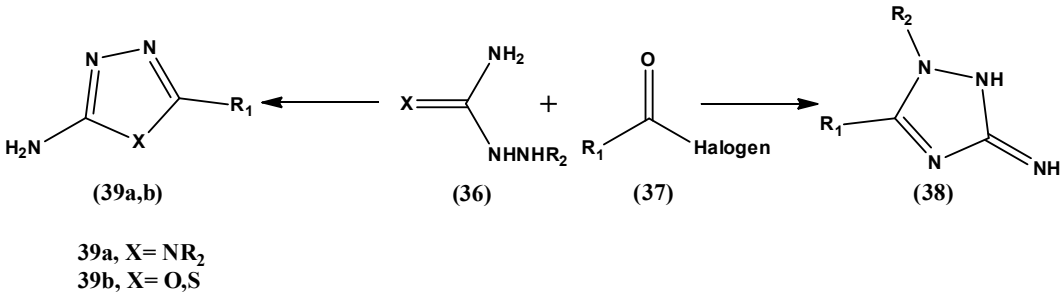


Figure 14. Cyclization of Aminoacylhydrazines and Acyl Halides for 1,2,4-Triazole Derivative Synthesis.

1.3.2 Iodine-Mediated Synthesis of 1,2,4-Triazoles.

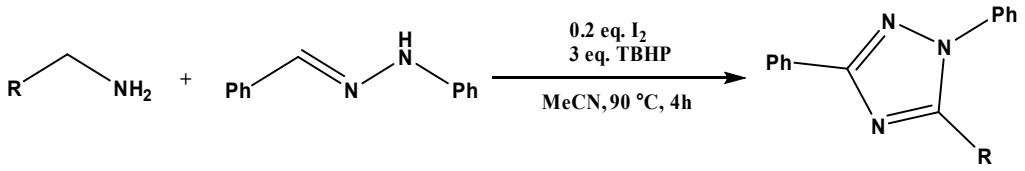
1.3.2.1 From Isothiocyanates

Through an environmentally friendly method, the efficient synthesis of novel 1,2,4-triazoles has been accomplished, derived from isothiocyanates (**40**) and *N*-phenylbenzamidrazone (**41**). This procedure, which encompasses iodine-mediated oxidative formation of C-N and N-S bonds, culminates in the production of 4,5-disubstituted 3-amino-1,2,4-triazoles (**42**).[13,24] (Figure 15)

Figure 15. I_2-mediated oxidative formation of C-N and N-S bonds.

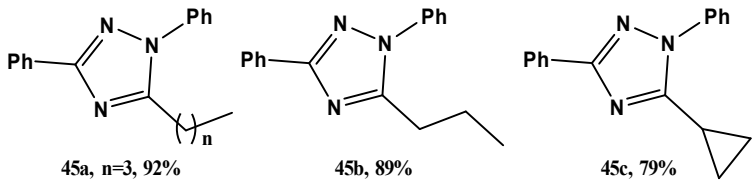
1.3.2.2 From Aliphatic Amines and Hydrazones.

Through the implementation of a cascade mechanism that combines C-H functionalization, an oxidative aromatization sequence, and the formation of double C-N bonds, the synthesis of 1,2,4-triazoles from aliphatic amines (**43**) and hydrazones (**44**) has been successfully accomplished, with iodine serving as the catalyst (Figure 16). Numerous derivatives are produced, and our attention was drawn to the derivatives with a high yield.[25]



(43) **(44)** **(45) a,b,c-w 40-92%**

Presented here are select examples of compounds, each displaying a distinct yield:



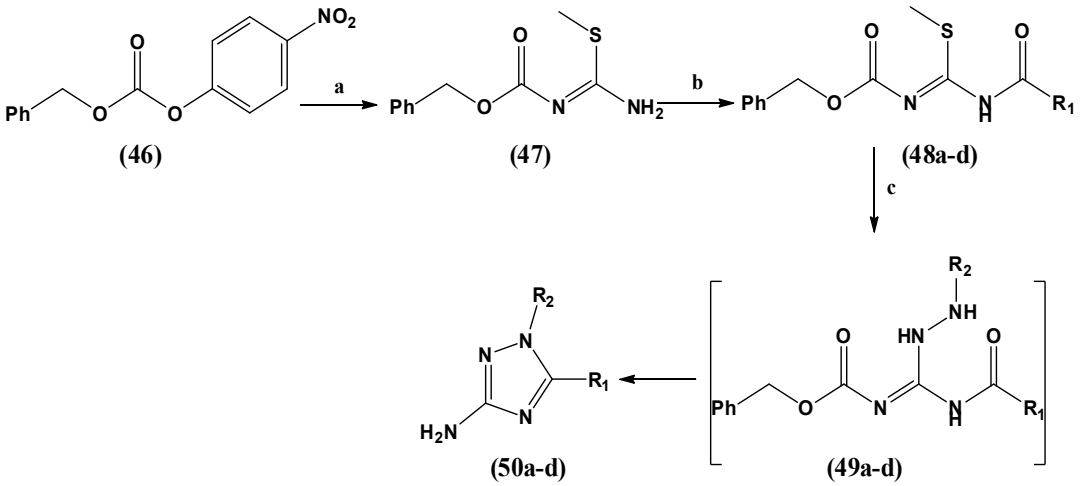
45a, n=3, 92% **45b, 89%** **45c, 79%**

Figure 16. Synthesis of 1,2,4-triazoles from hydrazones and aliphatic amines.

1.3.3 Direct Synthesis of N1-Substituted Triazoles.

1.3.3.1 From carboxylic acids and hydrazines

A microwave-assisted synthesis of *N*[1]-substituted 1,2,4-triazoles was reported, yielding reasonable results. Utilizing a three-step method, researchers employed commercially available carboxylic acids and hydrazines to efficiently produce regioselective N1-substituted 1,2,4-triazoles. The crucial intermediate compound (47) was achieved by reacting carbonic acid benzyl ester 4-nitrophenyl ester (46) with S-methylisothiouronium sulfate and subsequently coupling it with different carboxylic acids. These intermediates were then reacted with various hydrazines under microwave conditions, yielding triazole products. The process generated amino-triazole products with isolated yields of 50-70%. Additionally, the synthesized triazoles can function as starting materials for further acylation or alkylation, resulting in the formation of tri-substituted triazoles featuring regioselective substitution patterns.[26] (Scheme 5).



Reagents and conditions:
(a) 2-methyl-2-thiopseudourea sulfate, DMF, 23 °C, 12 h, 95%
(b) carboxylic acid, 4-methylmorpholine, N-(3-dimethylaminopropyl)-N0- ethylcarbodiimide hydrochloride, 1-hydroxy benzotriazole, DMF, 23 °C, 12 h, 40%
(c) substituted hydrazine, triethylamine, microwave, 160 °C, 30 min, 34–70%

Scheme 5. N1-Substituted Triazoles: Direct Synthesis Approach.

Comp. 50 (a-d)	R_1	R_2	Yield %
a			70
b			56
c			56
d			48

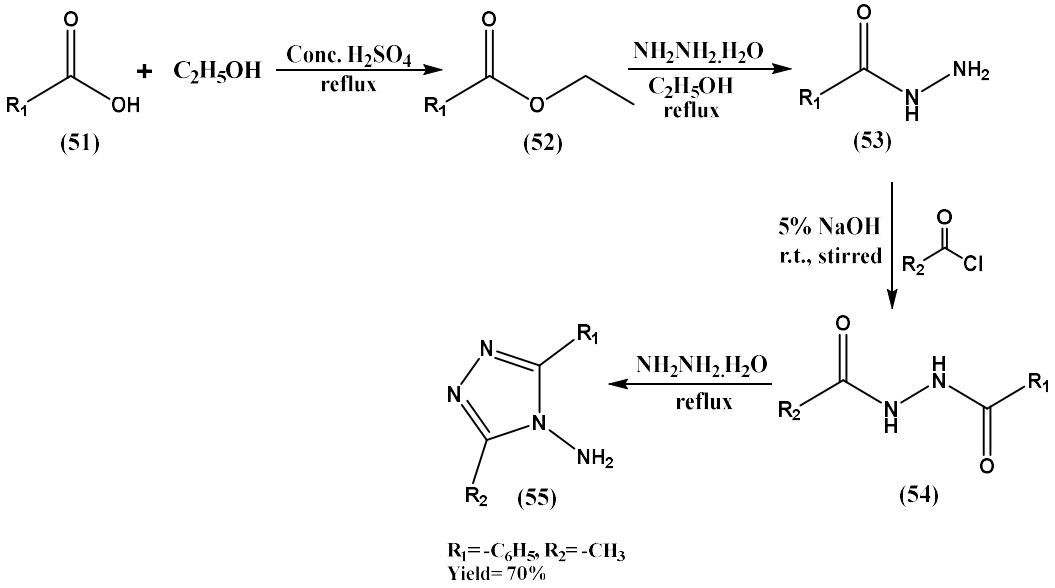
Table 1- Yields of N^1-Substituted Triazoles (Comp. 50a-d) in Direct synthesis Approach.

1.3.4 Direct Synthesis of N4-Substituted Triazoles.

1.3.4.1 From carboxylic acids and hydrazine hydrate

In the presence of a few drops of H_2SO_4, an ethanolic solution of carboxylic acid (51) was refluxed for 8 hours, resulting in the formation of an ethyl ester (**52**). Treatment of the ester with hydrazine hydrate yielded an acid

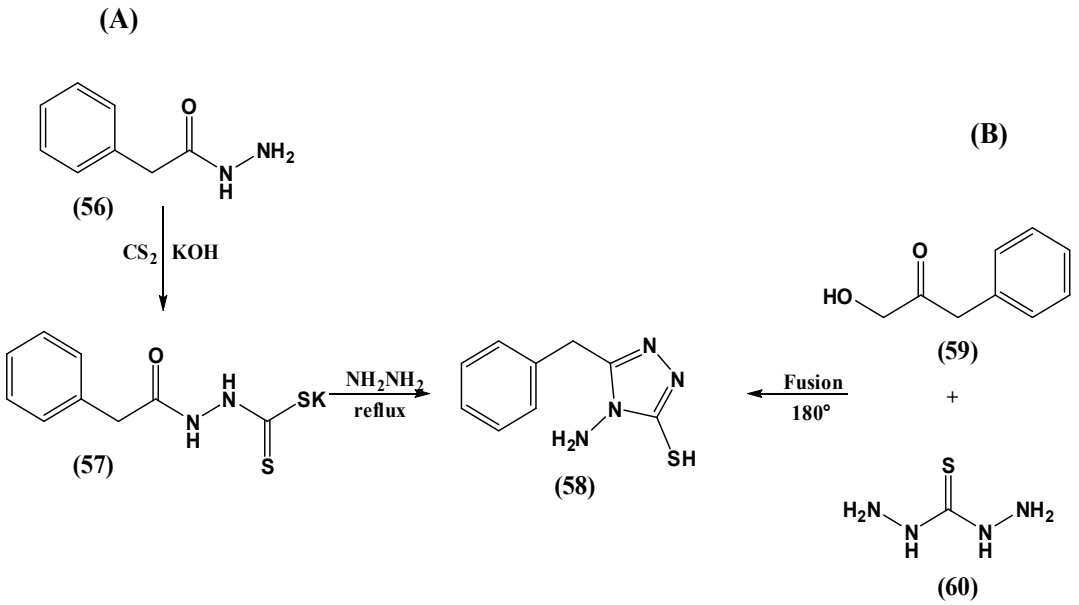
hydrazide (**53**). Unsymmetrical N, N′-diacylhydrazine (**54**) was produced when the hydrazide was subjected to treatment with acid chloride at room temperature and with constant stirring. A combination of equimolar N, N′-diacylhydrazine and hydrazine hydrate was refluxed for 5 to 6 hours. The resulting compound was isolated from the product using column chromatography (silica gel) and a mixture of ethyl acetate and petroleum ether as the eluent. A yield of 70% was obtained for Compound (**55**).[27] (Scheme 6)



Scheme 6. *N*⁴-Substituted Triazoles: Direct Synthesis Approach.

1.3.4.2 From Phenylacetic Acid Hydrazide and Thiocarbohydrazide: A Comparison of Methods in Synthesizing 4-Amino-5-Benzyl-4H-[1,2,4]Triazole-3-Thiol

Two distinct methods were reported in prior literature for synthesizing 4-amino-5-benzyl-4H-[1,2,4]triazole-3-thiol (**58**). The initial method entailed treating phenylacetic acid hydrazide (**56**) with carbon disulfide in ethanolic potassium hydroxide, followed by refluxing the resulting potassium salt (**57**) with hydrazine hydrate. The alternative method involved fusing phenylacetic acid (**59**) with thiocarbohydrazide (**60**) at 180°C. The first method (A) yielded the compound with a 53% yield, while the second method (B) achieved a 68% yield. In this investigation, method (B) was selected for preparing compound (**58**) owing to its superior yield, as depicted in (Scheme 7). This study presented a comparative evaluation of the two approaches for synthesizing 4-amino-5-benzyl-4H-[1,2,4]triazole-3-thiol (**58**) and offered insights into the factors impacting the reaction yield.[28]

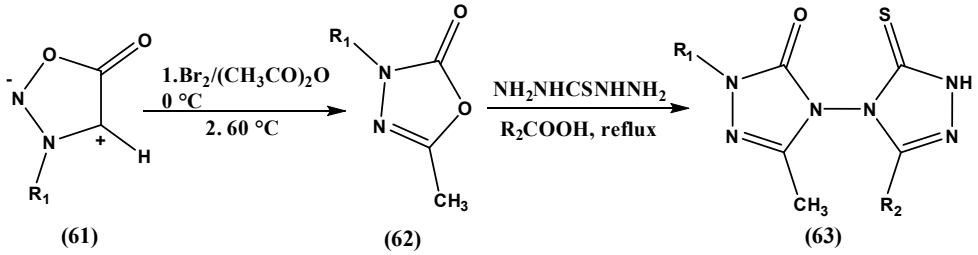


Scheme 7. Dual techniques for creating compound (**58**).

1.3.5 Synthesis of two 1,2,4-triazole rings.

1.3.5.1 From 3-Arylsydnones: A High-Yielding Method for the Synthesis of Two 1,2,4-Triazole Rings

Using 3-arylsydnones as a starting point, a simple and efficient method was engineered for the high-yielding synthesis of two 1,2,4-triazole rings.[29] This innovative technique has not only revolutionized synthetic chemistry by simplifying the creation of complex molecular structures but also holds promise for future chemical advancements and potential therapeutic applications. (Scheme 8)



Scheme 8. Synthesis of 3-Substituted Phenyl, 4H-1,2,4-Triazoles: The Semicarbazide Precursor Approach.

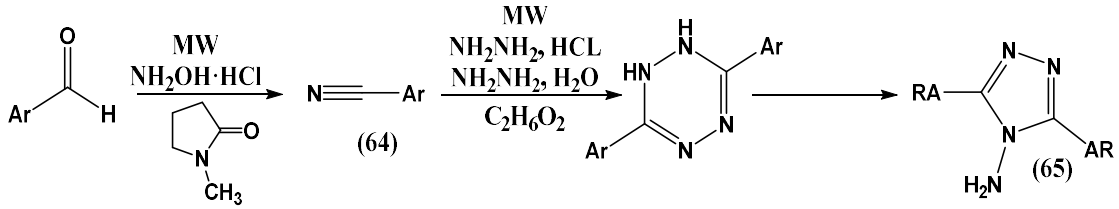
1.3.6 Synthesis of Triazole using Microwave:

The application of microwave-assisted synthesis can lead to significant time savings, reducing reaction times from several hours or even days to just a few minutes once eventual success is achieved. Although initial failures may occur, consuming a few minutes being prepared for such setbacks is crucial to fully harness the benefits of microwave-assisted synthesis. The shortened reaction duration makes microwave synthesis highly suitable for rapid reactions.[30]

1.3.6.1 Synthesis of 3,5-disubstituted 4-amino-1,2,4-triazoles under microwave irradiation

Researchers focused on rapidly synthesizing 4-amino-1,2,4-triazoles, which have potential as effective corrosion inhibitors for metals. Microwave heating was utilized to significantly decrease reaction times and streamline separation processes. Symmetrically 3,5-disubstituted 4-amino-1,2,4-triazoles (**65**) were prepared through a single-

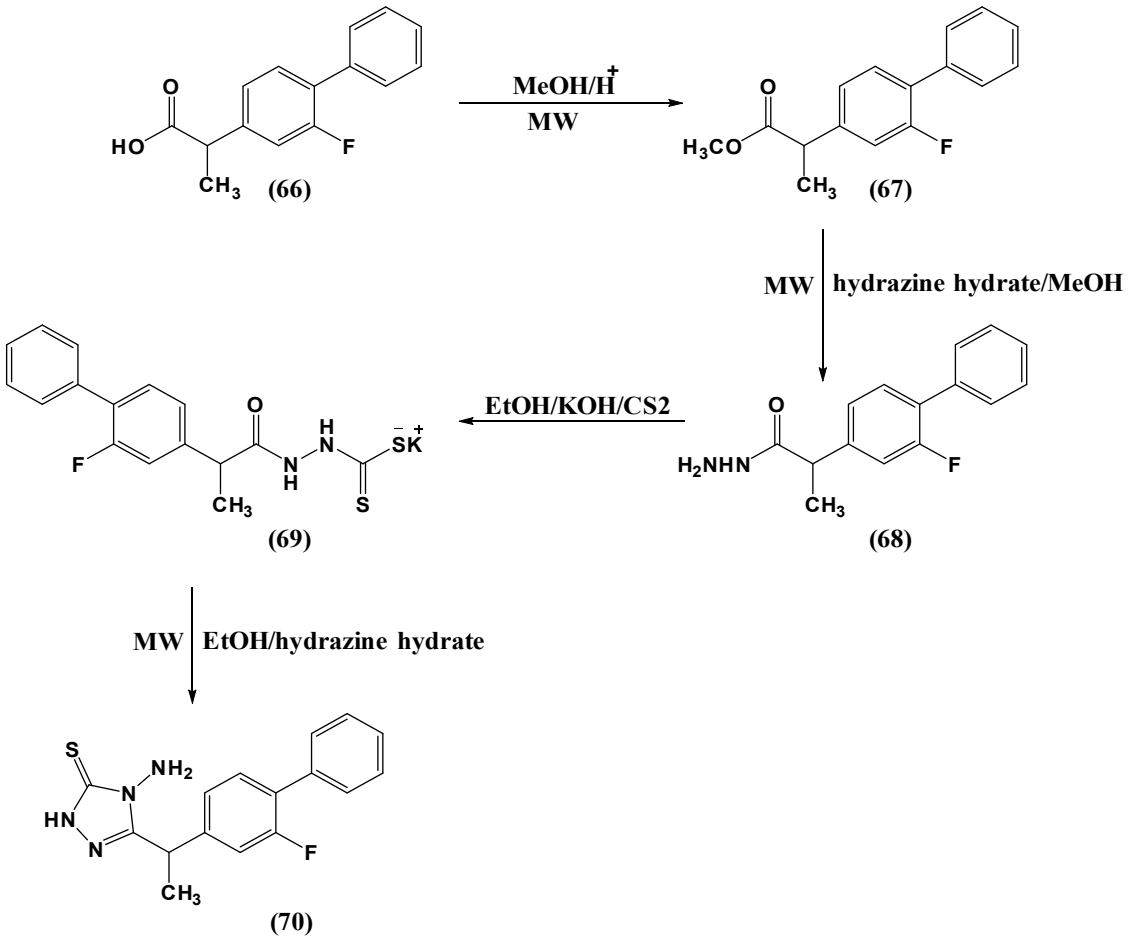
step reaction involving aromatic nitriles (64), dihydrotetrazines, and hydrazine dihydrochloride. Microwave heating was employed to significantly decrease the reaction time from hours to minutes. Furthermore, aromatic nitriles were swiftly produced using aldehydes and hydroxylamine hydrochloride in N-methyl-2-pyrrolidinone (NMP) with microwave heating. By synergistically integrating microwave-assisted reactions without the requirement for separation, a more practical and efficient approach was achieved for the synthesis of 4-amino-1,2,4-triazoles, employing readily available and cost-effective aldehydes.[31] (Scheme 9)



Scheme 9. Microwave-Assisted Synthesis of 3,5-Disubstituted 4-Amino-1,2,4-Triazoles.

1.3.6.2 Synthesis of F-aryl-linked 4-amino-3-ethyl-1,2,4-triazole-5-thione under microwave irradiation

Target triazole derivatives synthesis involved a multi-step strategy. Initially, 2-(2-fluoro-[1,1′-biphenyl]-4-yl)propanoic acid (**66**) experienced esterification with the aid of microwave irradiation. followed by hydrazinolysis to obtain 2-(2-fluoro-[1,1′-biphenyl]-4-yl)-propanehydrazide (**68**). Microwave use in both steps significantly reduced reaction time and increased yield, with esterification yield rising from 82% to 98.81% and hydrazinolysis yield increasing from 74.94% to 95.12%. Subsequently, the conversion of 2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanehydrazide (**68**) to potassium 2-(2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanoyl)hydrazinecarbodithioate (**69**) was achieved via a reaction involving carbon disulfide and potassium hydroxide. Finally, a reaction with hydrazine hydrate led to the formation of 4-amino-3-(1-(2-fluoro-[1,1'-biphenyl]-4-yl)ethyl)-1H-1,2,4-triazole-5(4H)-thione (**70**).[32] (Scheme 10)



Scheme 10. Microwave-Assisted Synthesis of F-Aryl-Linked 4-Amino-3-Ethyl-1,2,4-Triazole-5-Thione.

1.3.7 Synthesis of triazoles by transformation of other heterocyclic systems

The transformation of a non-triazole ring system into a triazole typically involves the replacement of a heteroatom with nitrogen within a five-membered ring. This process often entails nucleophilic ring-opening of the heterocycle, followed by ring closure and subsequent elimination of the other atom (Figure 17).[33]

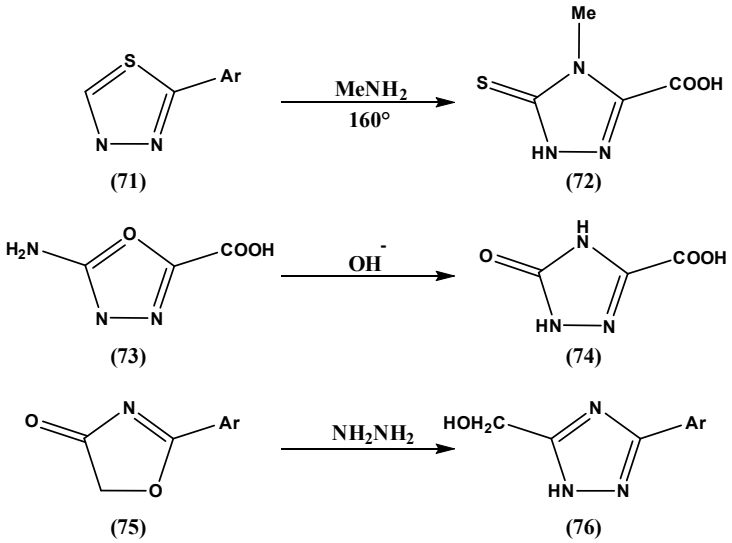


Figure 17. Preparation of substituted 1,2,4-Triazole.

1.3.8 Synthesis by Substitution of 1,2,4-Triazole

1.3.8.1 Arylation

The use of copper (II) oxide as a catalyst in the arylation process of 1,2,4-triazole under Ullmann reaction conditions predominantly leads to the formation of 1-aryl-1,2,4-1H-triazoles (**78**), particularly when conducted in a refluxing pyridine environment (Figure 18). Incorporating halopyridines (**79**) into the reaction yields a combination of 1- and 4-substituted 1,2,4-triazoles, with the primary products being 1-(α,β, and γ-pyridyl)-1,2,4-triazoles (**80**). This versatile method enables the synthesis of a diverse range of triazole derivatives, expanding their potential applications in fields such as medicinal chemistry and materials science.[34]

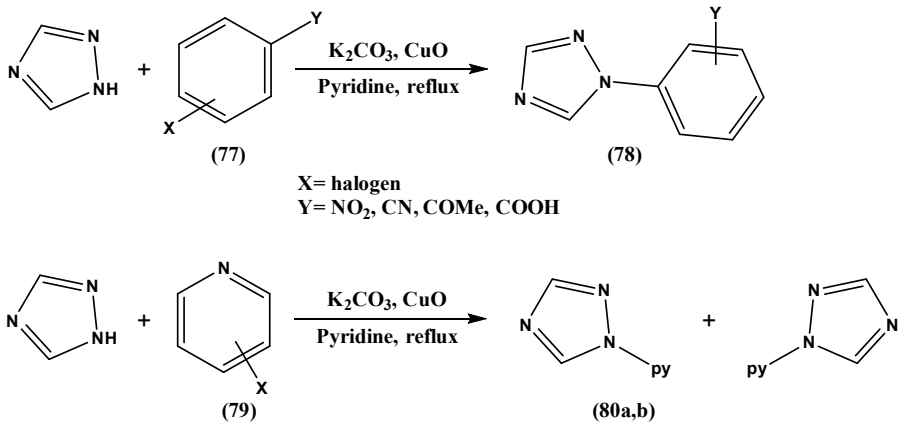


Figure 18. Copper-Catalyzed Arylation of 1,2,4-Triazoles.

1.3.8.2 Alkylation

Selective alkylation of a single nitrogen atom in polynitrogen heteroaromatic compounds such as 1,2,4-triazole poses a challenge in heterocyclic chemistry. Due to the presence of two possible tautomeric forms, alkylation can occur on either nitrogen atom, resulting in a mixture of isomers and, in some cases, a dialkylated cation (Figure 19). The resulting ratios are influenced by the choice of alkylating agent and reaction conditions, thereby adding complexity to each experimental setup.[34]

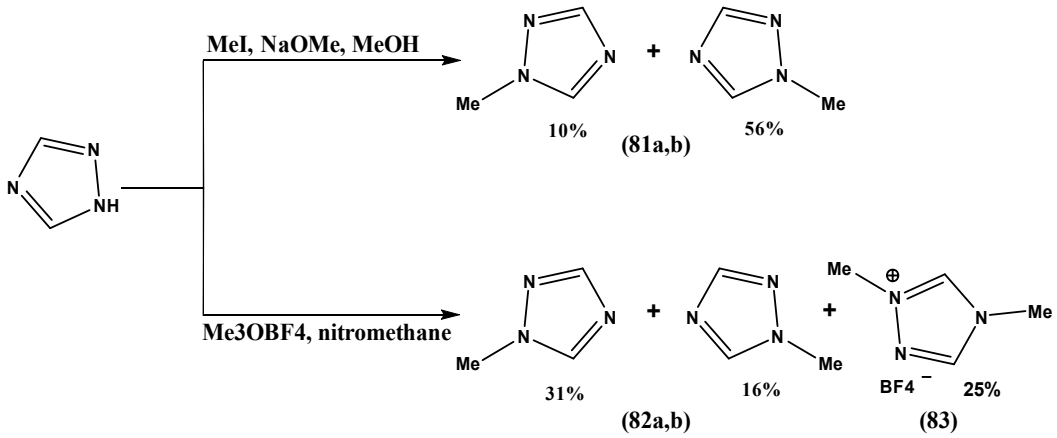
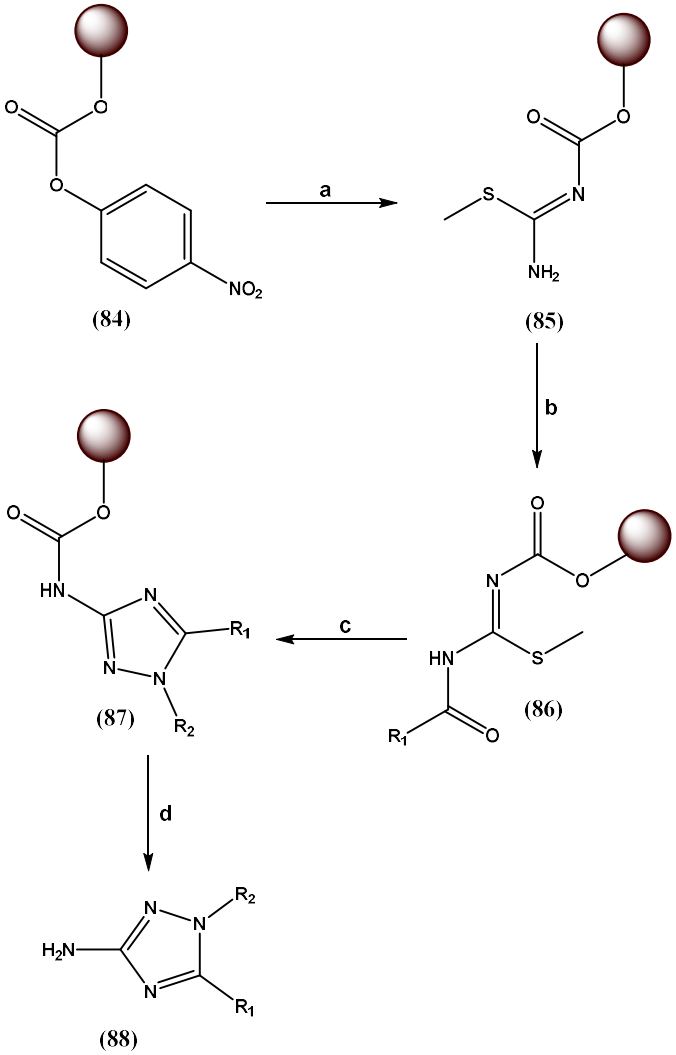


Figure 19. Exploring Selective Alkylation in 1,2,4-Triazoles.

1.3.9 Synthesis of 1,2,4-triazole by Solid phase:

1.3.9.1 From p-nitrophenylcarbonate resin to Triazoles

Pharmaceutically beneficial heterocyclic compounds, such as 3-aminotriazoles, were synthesized using a solid-phase methodology. Starting with p-nitrophenylcarbonate resin (**84**), S-methylisothiouronium sulfate is attached in the presence of cesium carbonate in DMF. The resin-bound S-methylisothiourea (**85**) reacts with carboxylic acid to form S-methyl-N-acylisothioureas (**86**). This substance then reacts with hydrazines, leading to cyclization and the formation of resin-bound products (**87**). The final step involves cleavage of the 3-amino-1,2,4-triazoles from the resin, resulting in high-purity products.[35] (Scheme 11)

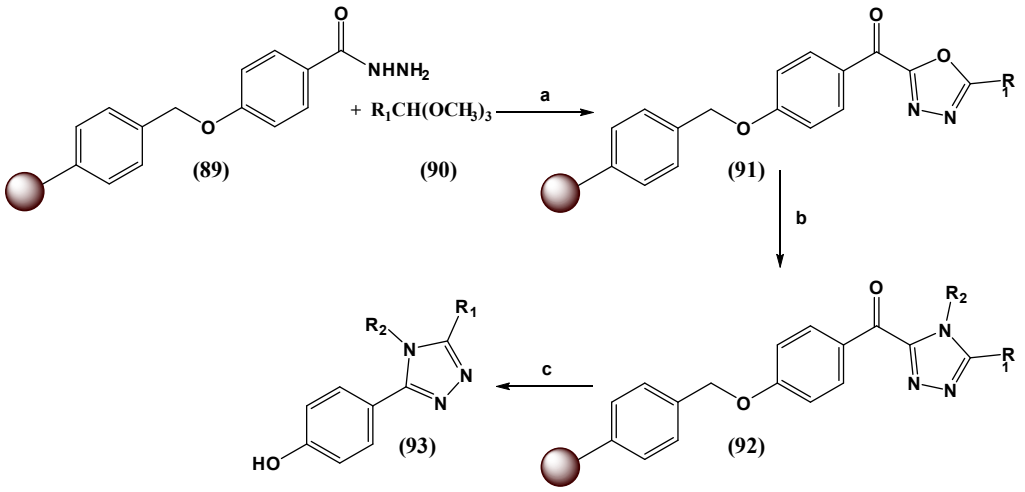


Reagents and conditions:
(a) S-methylisothiouronium sulfate (6 equiv., 0.1 M), Cs2CO3 (12 equiv., 0.2 M) in DMF, rt, 48 h.
(b) R1COOH (10 equiv., 0.1 M), DIC (10 equiv., 0.1 M), HOBt (10 equiv., 0.1 M) in DMF, rt, overnight.
(c) R2NHNH2 (6 equiv., 0.1 M) in DMF, 40°C, overnight.
(d) TFA/DCM (1:1), 1 h.

Scheme 11. Solid-Phase Synthesis of 1,2,4-Triazole Derivatives From p-nitrophenylcarbonate resin.

1.3.9.2 From Resin-bound Acylhydrazine to Triazoles

The synthesis of 1,2,4-triazole derivatives (**93**) was achieved through a series of steps, starting with the preparation of resin-bound acylhydrazine (**89**) from the Merrifield resin. This was followed by a reaction with orthoesters (**90**), catalyzed by alum, yielding resin-bound 1,3,4-oxadiazoles (**91**). The condensation of aniline hydrochloride with resin (**91**) in pyridine produced resin-bound triazoles (**92**). Finally, the cleavage of resin 4 using TFA/DCM released the desired 1,2,4-triazole derivatives (93) in high yields and purity.[36] (Scheme 12)



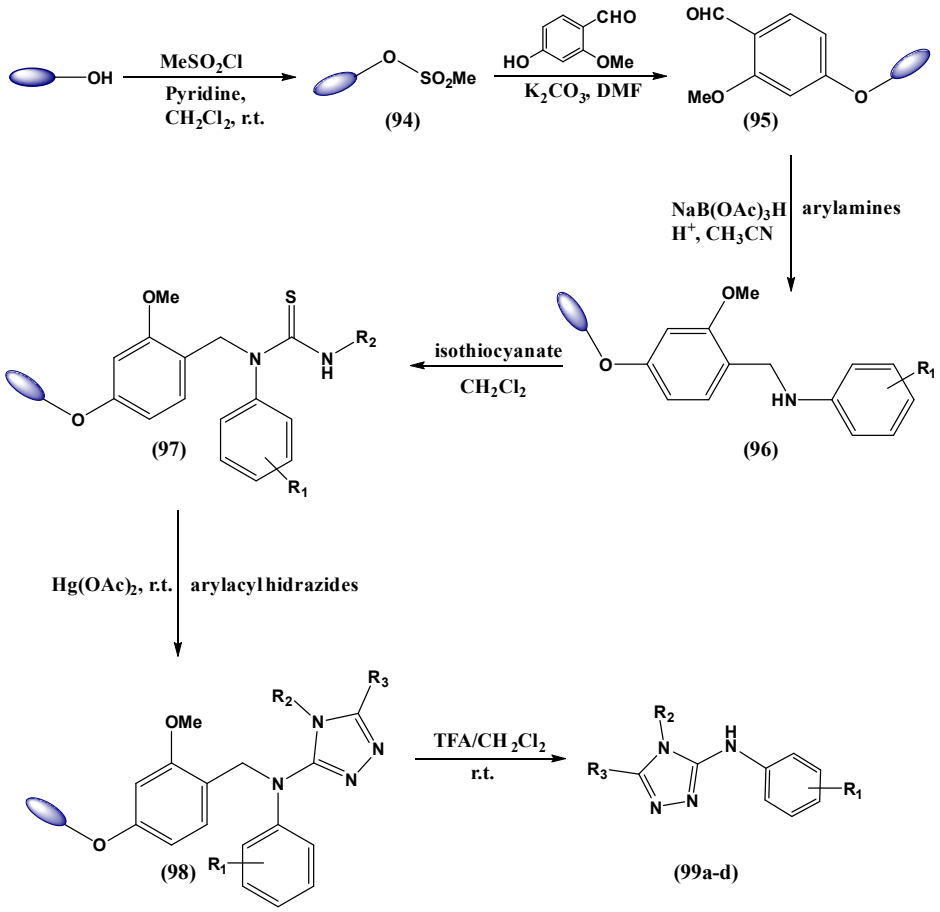
Reagents and conditions:
(a) $KAl(SO_4)_2 \cdot 12H_2O$ (40 mmol%), reflux, 10 h.
(b) $R_2NH_2 \cdot HCl$, pyridine, reflux 12 h.
(c) TFA/CH_2Cl_2 (1/4). r. t. 1 h.

Scheme 12. Solid-Phase Synthesis of 1,2,4-Triazole Derivatives from Resin-bound Acylhydrazine.

1.3.10 Synthesis of 1,2,4-triazole by Liquid phase.

1.3.10.1 From PEG-Supported Aldehyde to 1,2,4-Triazole Derivatives.

Liquid-phase synthesis using soluble supports like Poly (ethylene glycol) (PEG) has gained popularity due to its ability to combine the benefits of both homogeneous solution and solid-phase chemistries, such as high reactivity, easy analysis, and simple product isolation. PEG's versatile solubility makes it ideal for this method.
In this approach, PEG-supported aldehyde (**95**) was converted to compound (**96**), which reacted with isothiocyanates to form thioureas (**97**). Upon subjecting thioureas to specific reaction conditions, 1,2,4-triazoles (**98**) were obtained. The desired compounds (**99a-j**) were acquired by cleaving PEG-supported 98. Ten compounds appear with varying yield degrees, and our attention was drawn to the compounds with a high yield. This procedure enabled the synthesis of various 3-alkylamino-4,5-disubstituted-1,2,4-triazoles, making the process particularly advantageous.[37] (Scheme 13)



Scheme 13. Liquid-Phase Synthesis of 1,2,4-Triazole Derivatives.

Comp.99 (a-d)	R_1	R_2	R_3	Yield %
a	4-CH_3	Ph-CH_2	4-$CH_3OC_6H_4$	96
b	4-CH_3O	Ph-CH_2	CH_3	92
c	4-CH_3	Ph-CH_2	Ph	89
d	4-CH_3	Ph-CH_2	4-Br-C_6H_4	89

Table 1-2. Yields of 1,2,4-Triazole Derivatives (**99a-d**) in a Liquid-Phase Synthesis Approach.

1.4 Biological Significance and Synthetic Strategies of 1,2,4-Triazole

The 1,2,4-triazole scaffold has gained significant attention in the pharmaceutical industry due to its biological significance, leading to the development of various synthetic methods to access compounds with this structure and its derivatives. Although several multistep synthetic routes have been reported to date, the demand for convenient and rapid synthetic methods to access 1,2,4-triazole-containing compounds has increased, as highlighted in recent literature.

The 1,2,4-triazole ring is a key component of various drugs used in clinical therapy, including triazolam (sedative and hypnotic), cyproconazole (fungicide), bittertanol (fungicide), terconazole (antifungal) and trazodone (antidepressant) as shown in (Figure 20). These drugs exemplify the versatility of the 1,2,4-triazole scaffold in the development of novel therapeutics.[38]

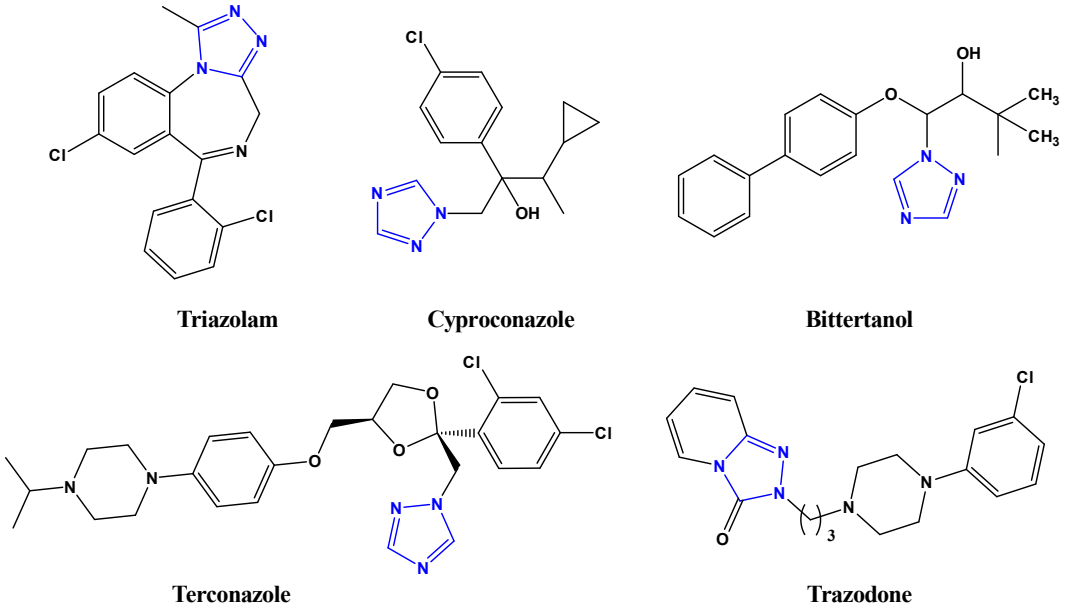


Figure 20. Therapeutic Diversity of 1,2,4-Triazole-Containing Drugs.

In recent decades, researches have focused on the synthesis of 1,2,4-triazole derivatives with comprehensive biological activities, given their immense potential as effective bioactive molecules. The 1,2,4-triazole-embedded heterocycles have garnered considerable attention as a result of their diverse range of pharmacological properties, which include anticancer[39–41], anti-inflammatory[42], antimicrobial[43,44], antiviral[5,45], antioxidant[46–48], antifungal[49,50], antiparasitic , antitubercular[50], antihypertensive[51], CNS stimulants[52], antimalarial[53] and diuretic activities[54]. This has made them a fascinating area of research that holds immense promise for the discovery of novel therapeutic agents.

1.4.1 Anticancer Activity:

The development of effective and potent antineoplastic drugs is a major goal of contemporary medicinal chemistry, considering that cancer is a life-threatening disease and a significant global health issue, ranking as the second most prevalent disease after cardiovascular diseases. The chemistry of 1,2,4-triazoles and their fused heterocyclic derivatives has garnered considerable attention due to their synthetic and effective biological importance.[55] Currently, Letrozole (**100**), Anastrozole (**101**), and Vorozole (**102**) , which are 1,2,4-triazole-based drugs, are widely used in the treatment of estrogen-dependent breast cancer. Furthermore, the potential of 1,2,4-triazoles as antineoplastic agents has been established in a study, in which a series of 1,2,4-triazole derivatives, including compound (103), were reported to exhibit potent inhibitory activity against the HepG2 cancer cell line.[41] In another investigation, a series of 3-(2,4-dichloro-5-fluorophenyl)-6-(substituted phenyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines were synthesized and assessed for their antitumor potential. In vitro antitumor activity was observed for some of the compounds, with moderate to excellent growth inhibition displayed against a panel of sixty cancer cell lines, compound (104) (Figure 21).[56]

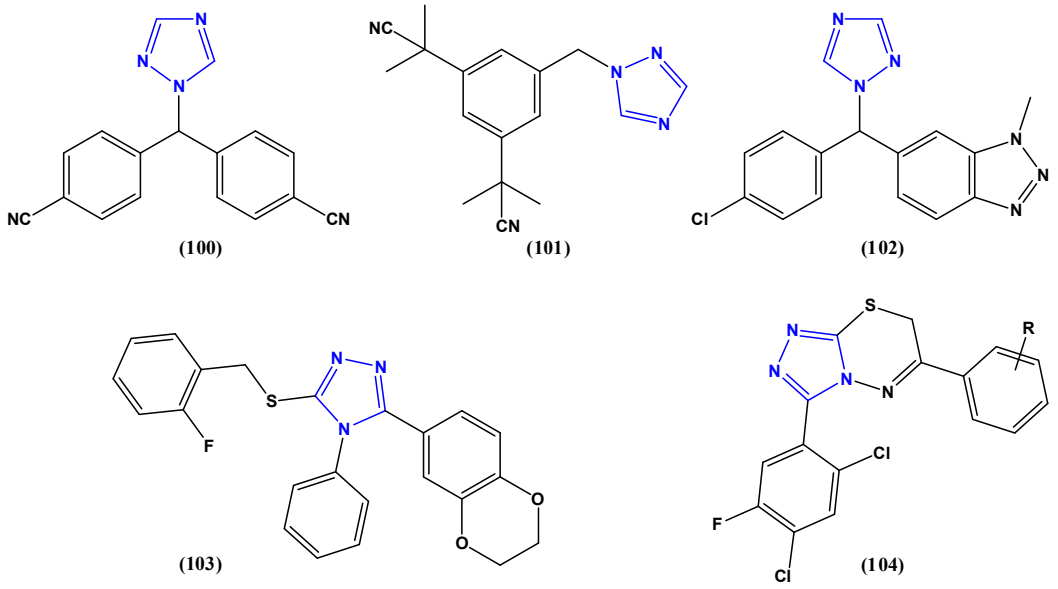
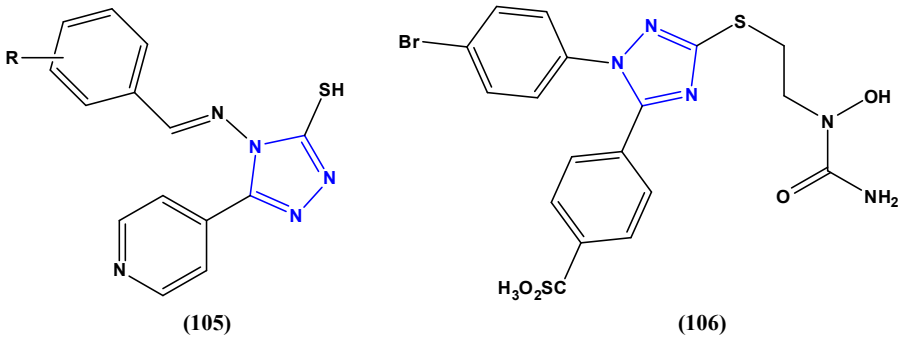


Figure 21. Triazole-Based Anticancer Agents: Biologically Potent Compounds.

1.4.2 Anti-inflammatory Activity:

Derivatives of 4-(substituted benzylideneamino)-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-thiol (**105**) have been investigated for their anti-inflammatory properties. Due to the potential side effects of non-steroidal anti-inflammatory drugs (NSAIDs) used in the treatment of various arthritic conditions, such as gastrointestinal haemorrhage and ulceration, newer drugs with potent anti-inflammatory effects and minimal adverse reactions have been developed. A promising group of these drugs are the hybrids of diaryl-1,2,4-triazole and Nhydroxyurea (106), which have been synthesized and evaluated as novel anti-inflammatory agents. These compounds have demonstrated significant analgesic activity in acetic acid-induced writhing response and hotplate assay.[57] (Figure 22)



R= 4-Cl, 3-OH, 4-OCH_3, 2-NO_2, 4-$N(CH_3)_2$

Figure 22. Promising Anti-Inflammatory Drugs Derived from 1,2,4-Triazole Compounds

1.4.3 Antimicrobial Activity

Bacteria, which are unicellular organisms that can originate independently or in clusters, have provided a challenging field for medicinal chemists in the synthesis of new antimicrobial agents, given the large number of highly effective and relatively non-toxic drugs available for the treatment of bacterial infections. Compounds (**107**) and (**108**) have demonstrated excellent efficacy against a broad range of pathogenic fungal stains, including

Aspergillus fumigates. Some analogues of ciprofloxacin (**109**) have exhibited antimicrobial activity as well. In these compounds, ciprofloxacin was incorporated into a series of Schiff bases of 1,2,4-triazole through the Mannich reaction. At a concentration of 10 µg/mL, the compounds demonstrated in vitro antimicrobial activity against both gram-positive and gram-negative bacteria, such as B. subtilis, K. pneumoniae, and P. aeruginosa[5] (Figure 23).

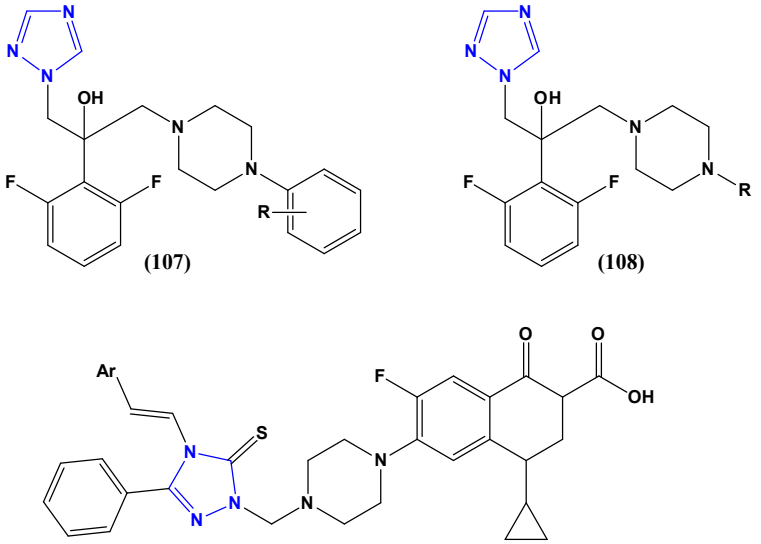


Figure 23. 1,2,4-Triazole Derivatives: Potent Antimicrobial Agents.

1.4.4 Antioxidant Activity:

Antioxidants, which prevent harmful reactions and protect cells from free radical damage, are important in preventing serious diseases like cancer, Alzheimer's, and Parkinson's. Inadequate antioxidant intake can lead to health issues. In order to develop new molecules that can fight diseases more effectively and have fewer side effects, scientists are exploring the potential of the 1,2,4-triazole system[47].

The role of antioxidants in defending against free radical damage, which is implicated in the aging process and the development of diseases, is crucial. With increasing exposure to free radicals from factors such as pollution, illness, exercise, and stress, there is a need for better understanding of antioxidants. Tri-substituted triazoles (110) and (111) were found to have potent antioxidant properties during the synthesis and evaluation of 4-amino-5-phenyl-4H-1,2,4-triazole-3-thiol derivatives (Figure 24)[58].

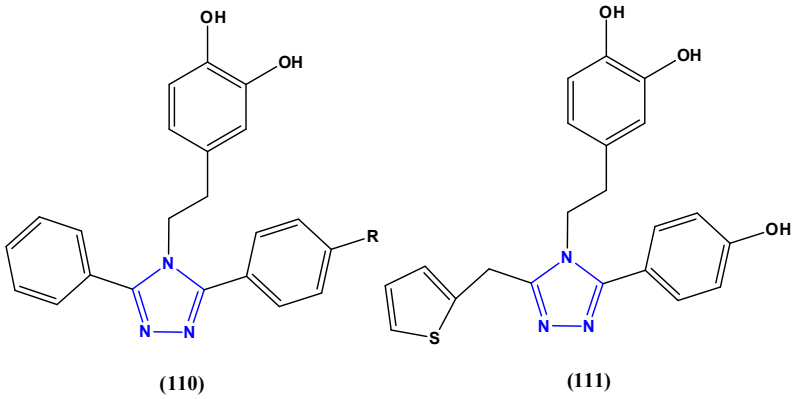


Figure 24. Antioxidant Components in Tri-substituted Triazoles.

1.4.5 Antifungal Activity

The surge in immunocompromised individuals has resulted in an upsurge in severe fungal infections, presenting substantial risks to patients that can outweigh the impact of the underlying disease. Azole compounds, such as fluconazole, voriconazole, and itraconazole[49], are essential antifungal agents acting by competitively inhibiting lanosterol 14a-demethylase (CYP51). However, challenges such as toxicity and drug resistance persist. There is an urgent need for broad-spectrum, low-toxicity antifungal agents[59].
Triazole antifungal drugs face difficulties due to drug resistance. Efforts concentrate on modifying existing drugs, enhancing biological activities, and investigating novel triazole agents. These approaches aim to address drug resistance and develop innovative antifungal agents[50]. (Figure 25).

Figure 25. Some examples of antifungal drugs.

1.5 Carbohydrates

Carbohydrates, the most abundant biological molecules, have essential roles in energy storage, transportation, and structural components in organisms, as well as in signaling and recognition events. Due to their diverse structures and easy accessibility, carbohydrates are suitable for various synthetic applications, including the creation of biologically active compounds and serving as chiral auxiliaries in asymmetric synthesis. Additionally, carbohydrates possess appealing properties, such as the capacity for hydrogen bonding and increased water solubility from multiple hydroxyl groups, making them useful as catalysts and ligands.[60]

Monosaccharides, also known as carbohydrates, are molecules that follow the general formula $\mathbf{C_x(H_2O)_n}$ and contain a carbonyl group, which can be either an aldehyde or a ketone. Typically, they exist as cyclic structures, such as pyranose or furanose, with an additional asymmetric center known as the "anomeric carbon". The anomeric carbon possesses an anomeric hydroxyl group that plays a crucial role in the formation of glycosidic bonds in polysaccharides or glycan chains. It determines the α-/β-configuration with the hydroxyl group positioned differently from the adjacent saccharide. Notably, cellulose illustrates this configuration with a linear chain composed of β-1,4-linked D-Glc units.[61] (Figure 26)

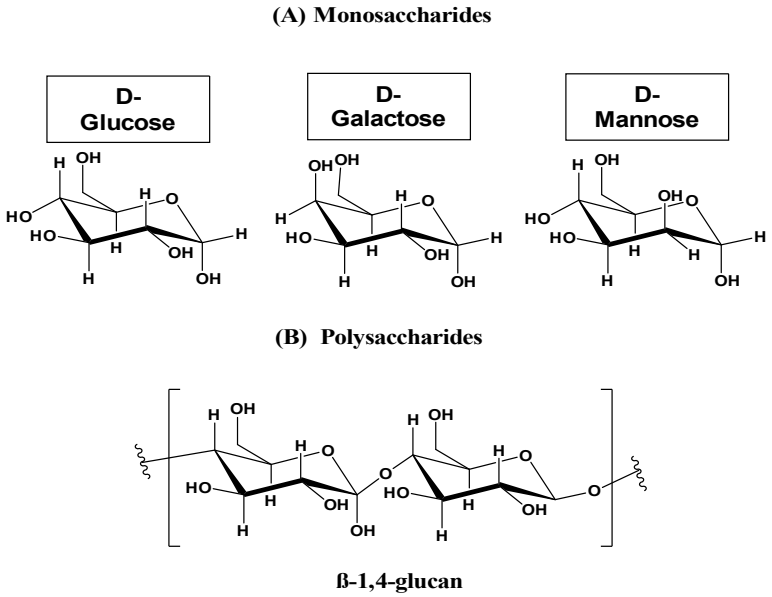


Figure 26. Examples of (A) Monosaccharides and (B) Polysaccharides.

1.5.1 Carbohydrate-based Triazoles: Therapeutic Potential

Two compound classes—carbohydrates and triazoles—have been identified for their diverse biological activities, which include antifungal, antibacterial, and anticancer properties. A surge of interest in recent years has been observed in the formulation of carbohydrate-based triazoles (CBTs) as potential candidates for novel pharmaceuticals[62-66].

Typically, CBTs are produced through the reaction of a carbohydrate with a triazole, with the carbohydrate component being derived from various sugars, such as fructose, glucose, or galactose. The triazole segment, on the other hand, may either be a simple triazole or a more intricate derivative thereof. In the scientific literature, the CBT known as compound (**112**) has been recognized as demonstrating notable biological activity, displaying impressive efficacy against the Monilia albican fungus, as evidenced by its MIC value of 16 µg/mL.[67] (Figure 27)

An enhancement in antimicrobial activity has been reported upon the introduction of sugar groups to the 1,2,4-triazole structure via a thioglycosidic bond. For instance, Compound (**113**) of 1,2,4-triazole thioglycosides, has exhibited promising antimicrobial effects.[44] (Figure 27).

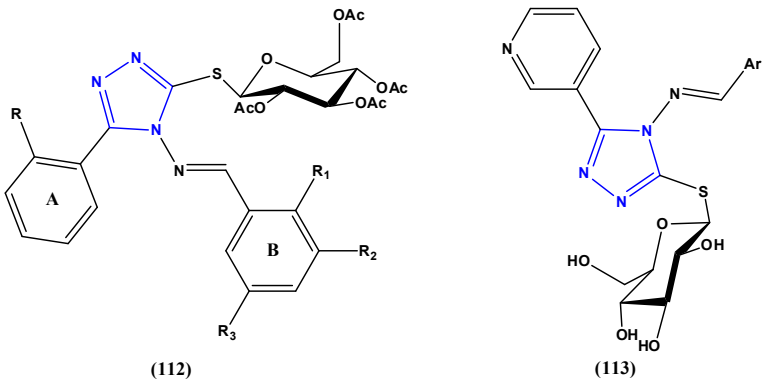


Figure 27. Some Therapeutic Applications of Carbohydrate-based Triazoles.

Ribavirin is an antiviral drug with activity against various RNA and DNA viruses, such as hepatitis C, influenza A and B, and herpes types 1 and 2. Ongoing studies are evaluating its potential to treat coronavirus infections, hantavirus, and various hemorrhagic fevers. It is believed to work by mimicking the purine guanosine cycle, thus influencing viral replication.

Zhurilo et al. synthesized ribavirin analogs, known as (**115**), where the carboxamide component was replaced with an isosteric 1,2,4-oxadiazole ring.[68] These analogs have demonstrated potent antiviral activity against hepatitis C, herpes simplex type 1, and influenza A. Their structure is depicted in (Figure 28).

Taribavirin, like ribavirin, is an antiviral drug based on a triazole core structure, effectively combating various DNA and RNA viruses. Its representation is provided in (Figure 29).[68]

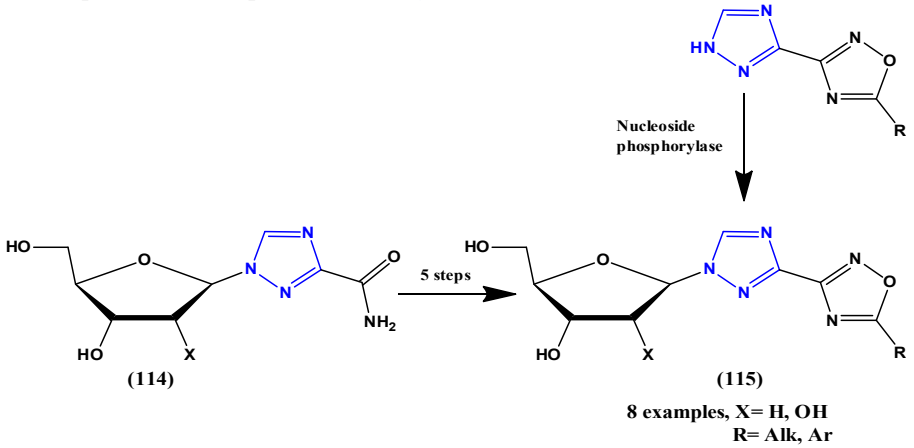


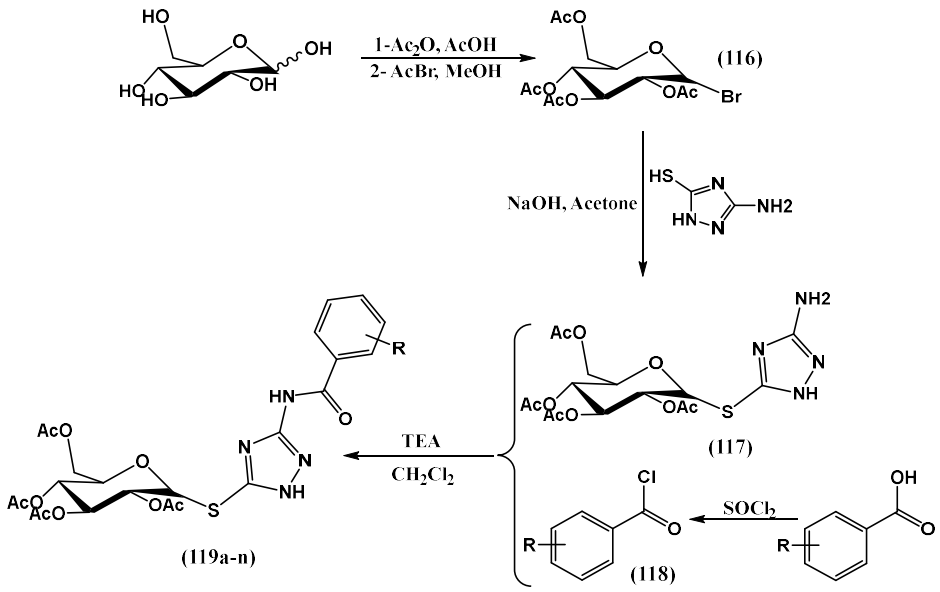
Figure 28. Effectiveness of Ribavirin Analogs in the Fight Against Viral Infections.

Figure 29. Antiviral Action of Ribavirin and Taribavirin.

1.5.2 An Overview of the Synthesis and Bioactivity of 1,2,4-Triazole Glycosides

1.5.2.1 Antifungal and Antibacterial Potential of Glycoside-based 1,2,4-Triazoles Synthesized from Aromatic Acids

Compounds labeled **4a-4n** were synthesized from an aromatic acid in a two-step process. Firstly, the acid was converted into intermediates (**118a-118n**) using $SOCl_2$. Then, these intermediates reacted with another compound under the presence of triethyl amine to form (**119a-119n**) compounds, yielding a success rate of 58-72%. After purification, these compounds displayed moderate to high antifungal and antibacterial activity against various organisms. Compounds **119g**, **119k**, **119m**, and **119n** were notably effective against P. Infestans, and **119j** and **119m** showed potential against T. Cucumeris. In antibacterial trials, compounds **11**9g, **119m,** and **119n** were especially potent against Xcc and Xoo, with **119g**, **119i**, and **119n** demonstrating significant activity against Xoo.70 (Scheme 14)



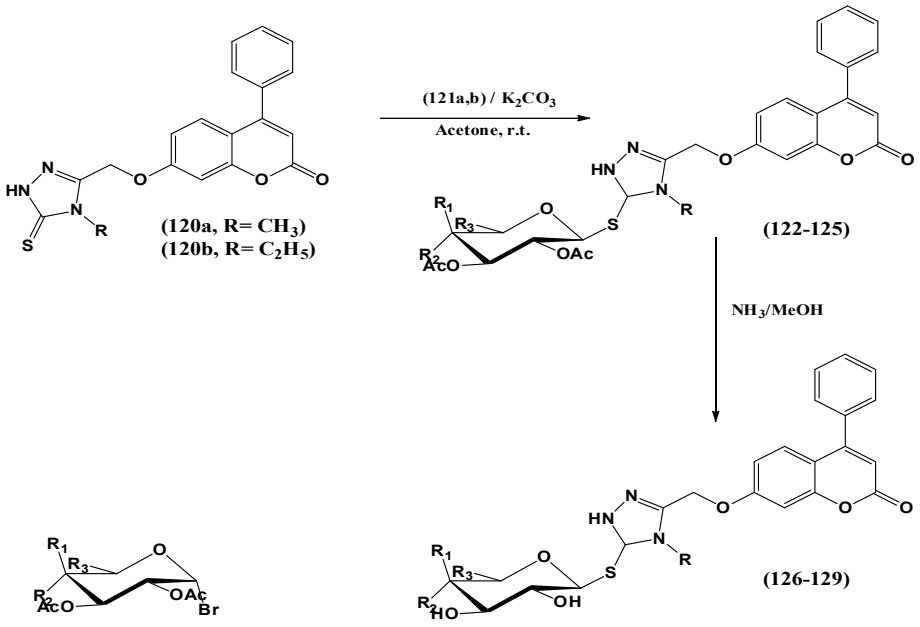
Scheme 14. Glycoside-based 1,2,4-triazoles synthesized from Aromatic Acids.

Comp. 119 (a-g)	R	Comp. 119 (h-n)	
a	2-CH_3	h	2-Br
b	3-CH_3	i	3-Br
c	4-CH3	j	4-Br
d	3-OCH_3	k	2-F
e	4-OCH_3	l	3-F
f	3-Cl	m	4-F
g	4-Cl	n	2-NO_2

Table 1-3. Glycoside-Based 1,2,4-Triazole Derivatives (Compounds 119a-g) Synthesized from Aromatic Acids.

1.5.2.2 Anticancer Properties and Synthesis of Coumarin-Azole-Sugar Hybrid Compounds

Coumarin-azole-sugar hybrid compounds were synthesized using different methods. Glycosylation and heterocyclization techniques produced glycoside products and derivatives. Coumarin-1,2,4-triazole-thioglycoside hybrids were formed, showing a yield of 70-73%. Among the compounds tested, coumarin-triazole (129) demonstrated the highest potency and safety with promising anticancer activity.[71] (Scheme 15)



121a, R_1= OAc, R_2= H, R_3= CH_2OAc
121b, R_1= H, R_2= OAc, R_3= H

Scheme 15. Glycosylation in Coumarin-Triazole Anticancer Synthesis.

Comp. (122-129)	R	R1	R2	R3
122	CH_3	OAc	H	CH_2OAc
123	CH_3	H	OAc	H
124	C_2H_5	OAc	H	CH_2OAc
125	C_2H_5	H	OAc	H
126	CH_3	OH	H	CH_2OAc
127	CH_3	H	OH	H
128	C_2H_5	OH	H	CH_2OAc
129	C_2H_5	H	OH	H

Table 1-4. Glycosylated Coumarin-Triazole Derivatives (Compounds 122-129) in Anticancer Synthesis.

1.6 Enzymes:

Triazole derivatives have been studied as enzyme inhibitors for a wide range of applications in fields such as medicine, biology, and drug discovery. These compounds show promise in inhibiting the activity of various enzymes associated with diseases and biological processes.

1.6.1 Inhibitory Effects of 1,2,4-Triazoles on Diverse Enzymes: Exploring Therapeutic Applications and Drug Resistance Inhibition:

1,2,4-Triazole derivatives serve as potent enzyme inhibitors, playing significant roles in targeting enzymes associated with severe diseases such as Parkinson's and Alzheimer's. These compounds exhibit their potential by inhibiting tyrosinase, a contributor to Parkinson's, alpha amylase and alpha glucosidase, which are associated with promising hypoglycemic drug behavior, and cholinesterases, pivotal to Alzheimer's. Moreover, they demonstrate notable capabilities in tackling drug resistance and addressing other neurodegenerative conditions.72

In the studies, triazole derivatives were synthesized and evaluated as enzyme inhibitors, with specific attention given to compounds 130a, 130b, and 130c. These compounds demonstrated notable inhibitory effects against enzymes such as urease, lipoxygenase, acetylcholinesterase, and α-glucosidase. In addition, their enzymatic inhibition potential was quantified in terms of inhibition percentages and IC_{50} values.[73]

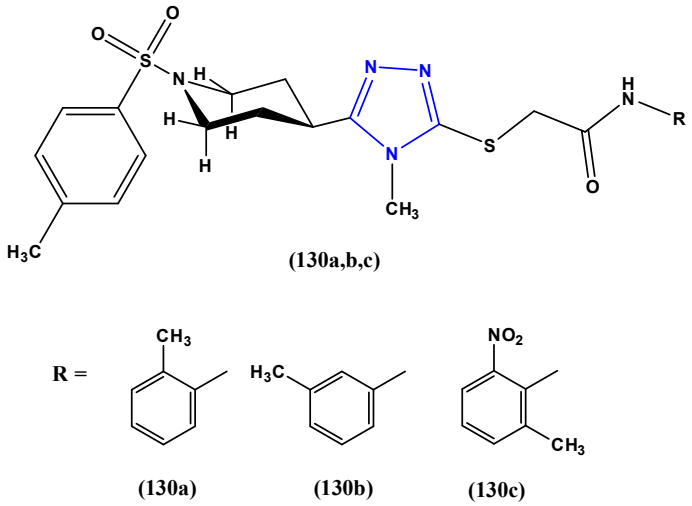


Figure 30. Display of Triazole Derivatives 130a, 130b, and 130c as Enzyme Inhibitors.

Table 1-5. AChE and -Glucosidase Inhibition Activity of (**130a,b,c**).

Comp. 130 (a-c)	AChE inhibition		Comp. 130 (a-c)	-glucosidase inhibition	
	Inhibition ( ) at 0.5 mM	IC_{50} (μM)		*1) Inhibition ( ) at 0.5 mM*	*2) IC_{50} (μM)*
a	82.36 ± 0.67	134.61 ± 0.53	a	72.45 ± 1.75	327.82 ± 1.57
b	98.78 ± 0.78	0.73 ± 0.54	b	91.52 ± 1.43	36.74 ± 1.24
c	81.53 ± 0.96	129.63 ± 0.73	c	72.23 ± 1.51	285.64 ± 1.23
Standard	91.27 1.17[a]	0.04 0.001[a]	Standard	65.73 1.93[b]	375.82 1.76[b]

Table 1-6. Urease and LOX Inhibition Activity of **(130a,b,c)**.

Comp. 130	**urease inhibition**		**Comp. 130**	**LOX inhibition**	
(a-c)	**Inhibition ( ) at 0.5 mM**	**IC_{50} (μM)**	**(a-c)**	*3) Inhibition ( ) at 0.5 mM*	*4) IC_{50} (μM)*
a	**75.45 ± 1.72**	**163.82 ± 1.45**	**a**	**36.47 ± 0.76**	**____**
b	**98.22 ± 1.65**	**19.35 ± 1.28**	**b**	**68.34 ± 0.82**	**32.57 ± 0.42**
c	**56.35 ± 1.67**	**241.76 ± 0.42**	**c**	**64.28 ± 0.73**	**93.81 ± 0.34**
Standard	**98.28 1.73[a]**	**21.37 1.36[c]**	**Standard**	**89.25 0.62[b]**	**2.34 0.35[d]**

Note: a: Eserine, **b:** Acarbose, **c:** Thiourea, **d:** Quercetin.

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الملخص العربي

4,2,1-ترايازول كهيكل واعد: الجوانب الاصطناعية والبيولوجية

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ملخص: تعتبر 4,2,1-تريازولات أساسات ذات قيمة في الكيمياء الطبية نظرًا لتنوع أنشطتها البيولوجية. تستعرض هذه المقالة استراتيجيات التخليق مثل الطرق المدعومة باليود، المساعدة بالميكروويف، الطور الصلب، والطور السائل، وأهميتها البيولوجية. توفر هذه الطرق إمكانية الوصول بكفاءة إلى 4,2,1-تريازولات، والتي تظهر خصائص مهمة مضادة للسرطان، مضادة للالتهاب، مضادة للميكروبات، مضادة للأكسدة، ومضادة للفيروسات. بالإضافة إلى ذلك، تظهر تريازولات الكربوهيدرات والمركبات الهجينة كومارين-أزول-سكر نشاطًا ملحوظًا. تؤكد إمكانيات 4,2,1-تريازولات في اكتشاف الأدوية وتطبيقاتها العلاجية على دورها في الكيمياء الطبية.

الكلمات المفتاحية"4,2,1-تريازول، استراتيجيات التخليق، النشاط البيولوجي، الكربوهيدرات، الكيمياء الطبية، المركبات البيوكيميائية.