A Summary of the Methods for Synthesizing, Analysing, and Applications of 1,2,4-Triazole Compounds

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***Abstract*—1,2,4-Triazole derivatives represent an essential category of nitrogen-containing heterocycles with extensive applications in medicinal, pharmaceutical, and agrochemical research. This review highlights the chemistry, synthesis, and applications of 1,2,4-triazole derivatives with an emphasis on their structural and biological importance. The literature outlines various synthetic approaches for the preparation of 1,2,4-triazole derivatives, such as traditional cyclization reactions, microwave-assisted synthesis, solid-phase synthesis, metal-catalyzed synthesis, and multicomponent synthesis, all of which have been designed to produce structurally diverse 1,2,4-triazole derivatives. The reviewed studies show that these methods result in compounds with varied structural characteristics and functional group patterns, which are noted for their high reaction efficiency. In addition, 1,2,4-triazole derivatives demonstrate a broad spectrum of biological activities, including antimicrobial, antifungal, anticonvulsant, antidepressant, anti-inflammatory, antioxidant, and anticancer effects, highlighting their importance in drug development. Overall, the literature suggests that the 1,2,4-triazole ring system is a vital structure with significant potential for therapeutic progress in the near future.**

***Index Terms*—1,2,4-Triazole derivatives; heterocyclic chemistry; synthetic methodologies; biological activities; medicinal chemistry; triazole scaffold**

I.INTRODUCTION

Nitrogen-containing heterocycles are a crucial structural class in medicinal chemistry because biologically active molecules and drugs that incorporate them occur frequently [[1],[2],[3]]. Triazoles are a significant category of five-membered aromatic compounds, distinguished by their ring structures comprising three nitrogen and two carbon atoms (Figure 1) [[4]].

1,2,4-Triazole are the two isomeric forms of triazoles, distinguished by the arrangement of nitrogen atoms in the heterocyclic ring [[5]]. 1,2,4-Triazole structure has garnered significant interest because of its exceptional chemical stability, aromatic characteristics, and capacity to engage in hydrogen bonding and coordination interactions with biological targets [[6],[7],[8]].

The exploration of triazole chemistry dates back to the late 19th century when Bladin introduced the term "triazole" during his research on nitrogen-rich heterocyclic compounds, thus laying the foundation for modern triazole chemistry [[9]]. Since then, numerous synthetic methodologies have been developed for the preparation of substituted triazole derivatives utilizing cyclization reactions, oxidative transformations, and multicomponent reactions [[10],[11],[12]].

The 1,2,4-triazole ring is considered a crucial pharmacophore in drug discovery, primarily because of its potential to interact with enzymes and receptors through mechanisms such as hydrogen bonding, dipole interactions, and coordination with metal ions within biological systems [[13],[14],[15]]. These structural attributes contribute to increased binding affinity and enhanced pharmacokinetic characteristics, including metabolic stability and bioavailability [[16]].

Numerous studies have demonstrated that 1,2,4-triazole derivatives exhibit a broad spectrum of biological activities, particularly antimicrobial activities against various bacterial and fungal

pathogens [[17],[18],[19]]. The antimicrobial potency of triazole derivatives is often linked to their ability to interfere with crucial enzymatic pathways necessary for microbial growth and survival [[20]]

In addition to their antimicrobial capabilities, several triazole derivatives have demonstrated anticonvulsant properties, suggesting their potential use in treating neurological conditions, such as epilepsy [[21],[22]]. Some substituted triazoles have antidepressant effects, likely by influencing neurotransmitter systems in the central nervous system [[23]].

Extensive research has focused on the anti-inflammatory effects of 1,2,4-triazole derivatives, with many compounds showing the ability to inhibit cyclooxygenase enzymes and other inflammatory mediators [[24],[25],[26]].

Moreover, numerous compounds containing triazoles have shown notable antitumor effects in a range of cancer cell lines, making them attractive candidates for anticancer drug development [[27],[28],[29]]. In addition, triazole derivatives are known to exhibit antioxidant properties, which could boost their therapeutic value in situations involving oxidative stress [[30]].

The importance of the 1,2,4-triazole structure is underscored by its inclusion in a variety of key pharmaceuticals and agrochemicals [[31]]. For instance, fluconazole and itraconazole are commonly used antifungal drugs that inhibit the fungal enzyme lanosterol 14-α-demethylase, thereby interfering with ergosterol synthesis in fungal cell membranes [[32]].

Letrozole, an aromatase inhibitor containing a triazole, is extensively used for the treatment of hormone-dependent breast cancer [[33]]. Other notable triazole-based compounds include ribavirin (an antiviral medication), diniconazole and bitertanol (used as fungicides), triazophos (a pesticide), diclobutrazol (a regulator of plant growth), and rilmazafone (a hypnotic drug) [[34],[35]].

The creation and biological assessment of new 1,2,4-triazole derivatives remains a vibrant and promising field of study in medicinal and heterocyclic chemistry, given their wide range of pharmacological properties and industrial uses [[6],[35]].

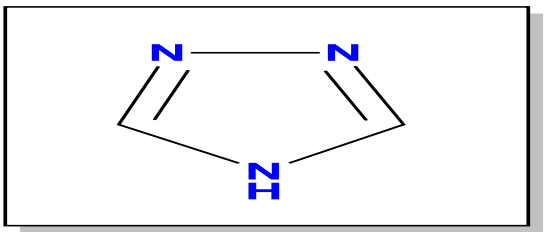
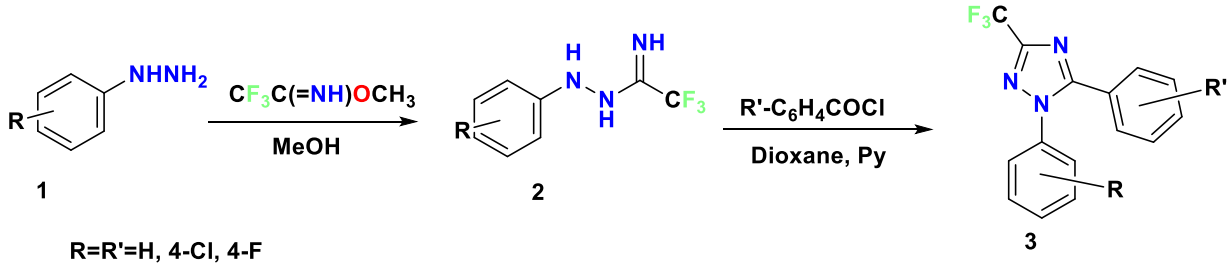


Figure 1. Triazole

II.DIFFERENT PREPARATION METHODS FOR SYNTHESIZING 1,2,4-TRIAZOLES

2.1. Preparation of 1,5-diphenyl-3-trifluoromethyl-1H-1,2,4-triazoles

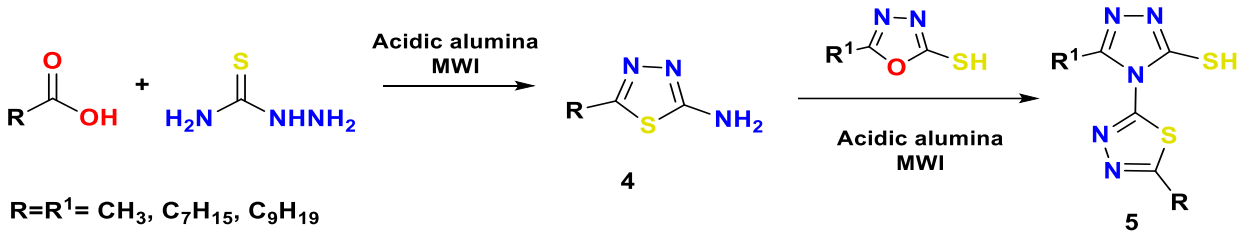
Czollner and his team reacted phenylhydrazines 1 with methyl trifluoroacetimidate to produce amidrazones 2. These amidrazones yield 1,2,4-tiazoles 3 upon further processing with benzoyl chlorides (Scheme 1), [[36]].



Scheme 1: Preparation of 1,5-diphenyl-3-trifluoromethyl-1H-1,2,4-triazoles

2.2. Preparation of thiadiazolyl substituted triazoles

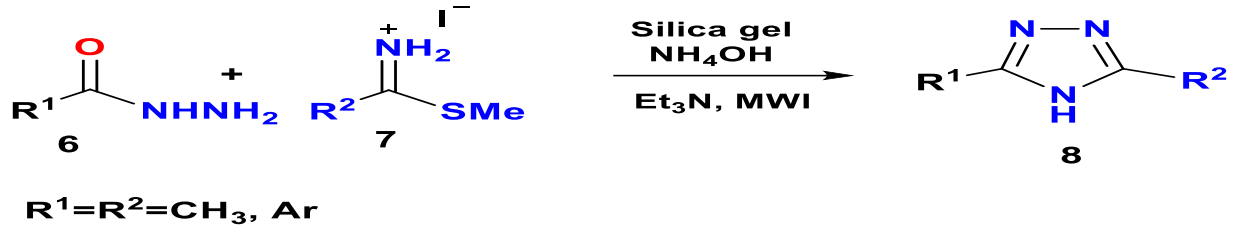
Kidwai et al. described a synthetic approach for the formation of 1,2,4-triazoles from 1,3,4-thiadiazoles via adsorption onto acidic alumina under microwave irradiation (MWI). 5-substituted-2-amino-1, 3, 4-thiadiazoles 4 were synthesized from thiosemicarbazide and the corresponding acids on a solid support under microwave conditions. The insertion reaction of 2-aminothiadiazoles 4 and 5-alkyl-2-mercapto-1,3,4-oxadiazoles using acidic alumina resulted in the formation of thiadiazolyl-substituted triazoles 5 within 40–80 s (Scheme 2), [[37]].



Scheme 2: Preparation of thiadiazolyl substituted triazoles

2.3. Preparation of triazole derivatives

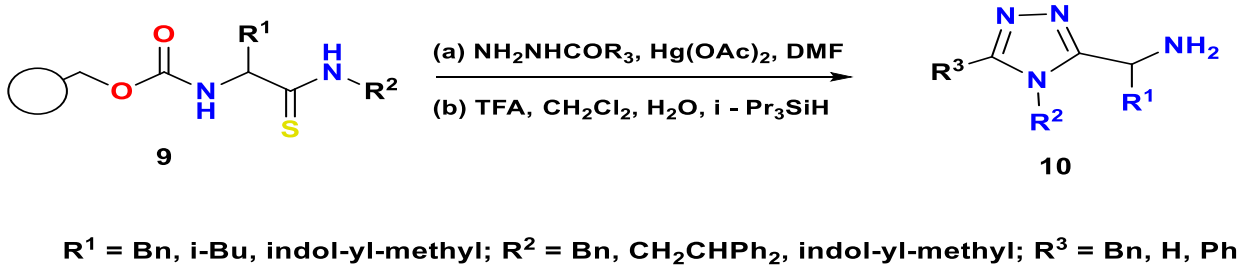
Rostamizadeh et al. conducted a solid-phase three-component condensation reaction involving acylhydrazines 6, S-methyl isothioamide hydroiodide 7, silica gel, and ammonium acetate under microwave irradiation to synthesize triazole derivative 8. Silica gel has been employed as a solid-acidic catalyst owing to its high selectivity, cost-effectiveness, and environmental safety (Scheme 3), [[38]].



Scheme 3: Preparation of thiadiazolyl triazoles derivatives

2.4. Preparation of 1,2,4-triazoles from hydrazides and various thioamides

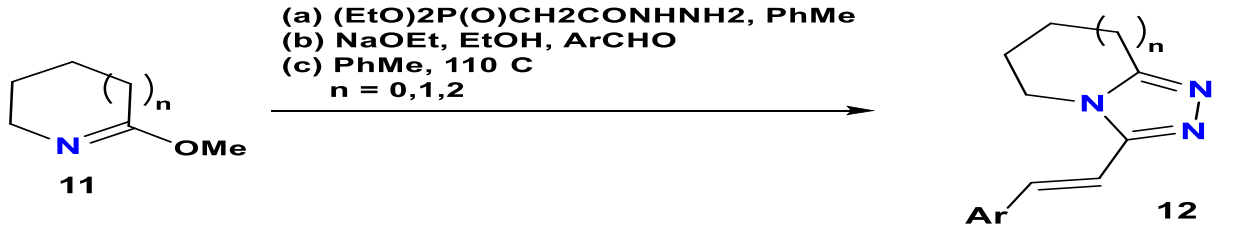
Boeghlin et al. synthesized compound 10 via solid-phase combinatorial methods, originating from hydrazides and a range of thioamides 9 (Scheme 4), [[39]].



Scheme 4: Preparation of 1,2,4-triazoles from hydrazides and various thioamides

2.5. Preparation of 1,2,4-triazoles from aldehydes and alkoxyimines

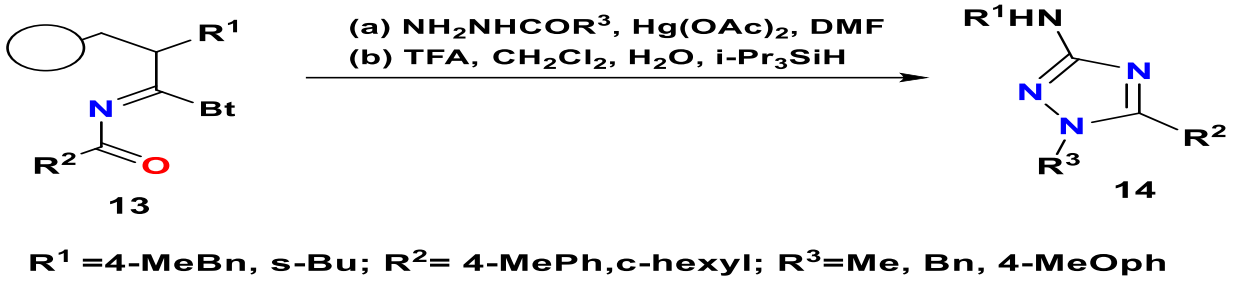
Liu et al. enhanced the utilization of diethoxyphosphinyl acetic acid hydrazide as a versatile reagent for synthesizing [5,5], [5,6], and [5,7]-3-[(E)-2-(aryl vinyl)]-1,2,4-triazoles 12, employing aldehydes and alkoxyimines 11 as substrates. This reagent is derived from acylhydrazines in combination with substituted imidates (Schemes 5), [[40]].



Scheme 5: Preparation of 1,2,4-triazoles from aldehydes and alkoxyimines

2.6. Preparation of 1,2,4-triazole from N-acyl1H-benzotriazole-1-carboximidamides

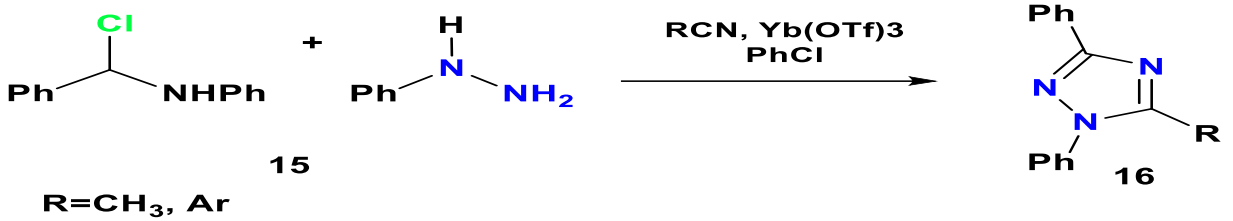
Makara et al. a reaction was carried out using hydrazines and polymer-supported N-acyl-1H-benzotriazole-1-carboximidamides 13, resulting in the creation of a series of 3-alkylamino-1,2,4-triazoles 14 (Scheme 6), [[41]].



Scheme 6: Preparation of 1,2,4-triazole from N-acyl1H-benzotriazole-1-carboximidamides

2.7. Preparation of 1,2,4-triazole from phenyl hydrazine and nitriles

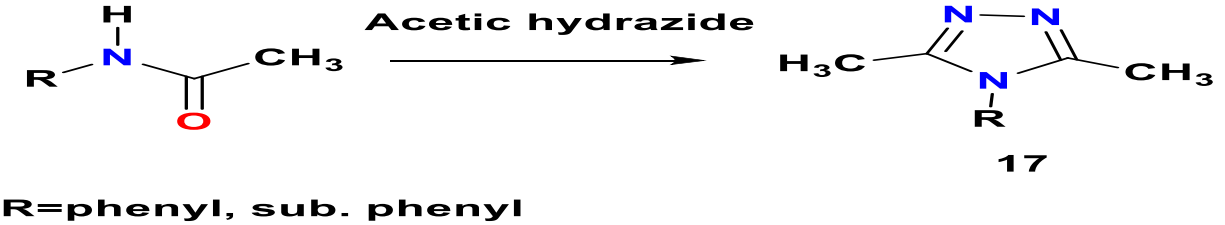
In the presence of a ytterbium (III) triflate catalyst, hydrazonyl chloride 15 undergoes intermolecular cyclization with phenyl hydrazine and nitriles, affording a series of 1,3,5-trisubstituted-1,2,4-triazoles 16 (Scheme 7), [[42]].



Scheme 7: Preparation of 1,2,4-triazole from phenyl hydrazine and nitriles

2.8. Preparation of 1,2,4-triazole from N-acetyl amines and acetic hydrazide

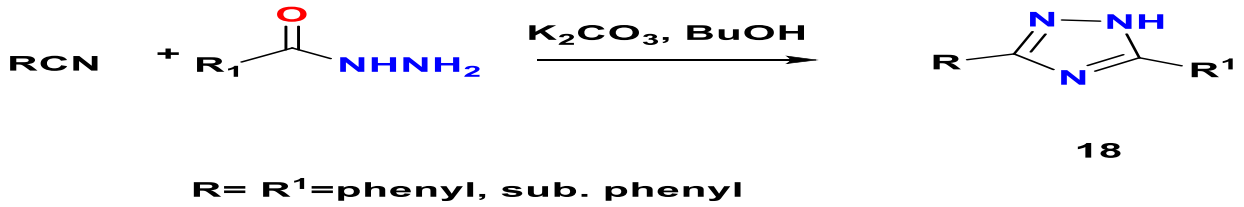
Price et al. documented the reaction between N-acetyl amines and acetic hydrazide, leading to the synthesis of 3, 5-dimethyl-1, 2, 4-triazoles 17 (Scheme 8), [[43]].



Scheme 8: Preparation of 1,2,4-triazole from N-acetyl amines and acetic hydrazide

2.9. Preparation of 3, 5-disubstituted-1,2,4-triazoles

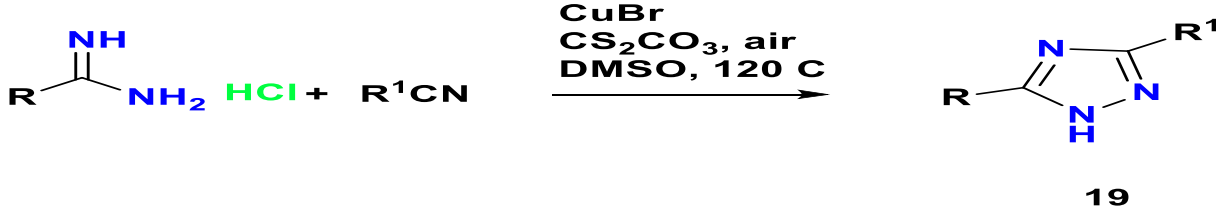
Yeung et al. outlined a simple method for synthesizing 3, 5-disubstituted-1, 2, 4-triazoles 18 using a one-step base-catalyzed reaction under microwave conditions. They assessed the compatibility of a wide range of functional groups in this process (Scheme 9), [[44]].



Scheme 9: Preparation of 3, 5-disubstituted-1,2,4-triazoles

2.10. Preparation of 1,2,4-triazole from amidines and nitriles

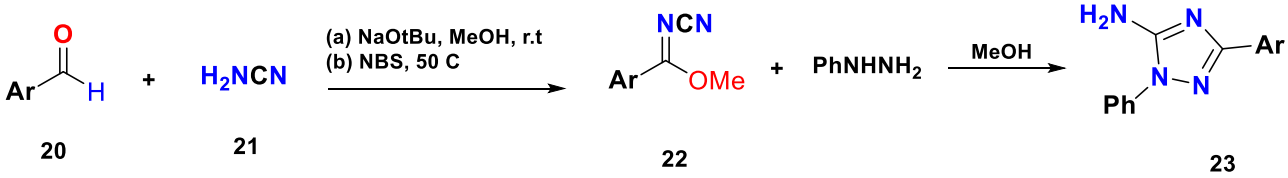
Ueda et al. reported a copper-catalyzed reaction occurring in atmospheric air, resulting in the synthesis of the 1,2,4-triazole derivative, 19, from amidines and nitriles. This process involves a sequential N-C and N-N bond-forming oxidative coupling reaction that is compatible with a wide array of functional groups. Notably, in the absence of the readily available and cost-effective copper catalyst, no product was formed. The reaction exploits the well-documented capacity of transition metals to activate nitriles (Scheme 10), [[45]].



Scheme 10: Preparation of 1,2,4-triazole from amidines and nitriles

2.11. Preparation of 5-amino-1,2,4-triazole derivatives

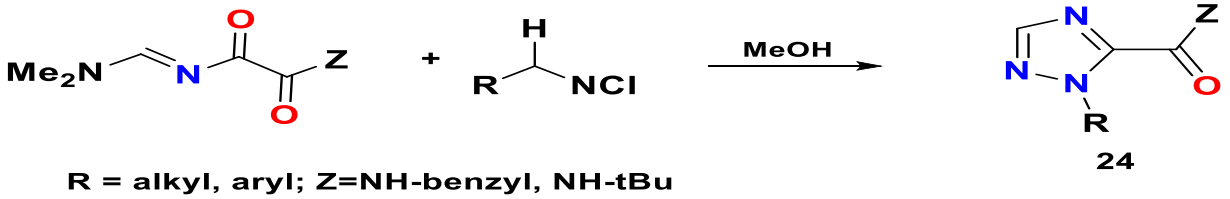
Yin et al. reported a mild one-pot cyanoimidation method for aldehydes 20, employing cyanamide 21 as the nitrogen source and N-bromosuccinimide as the oxidizing agent. The resulting substituted N-cyanobenzimidate derivatives 22 can subsequently undergo cyclization with hydrazine derivatives to produce 5-amino-1,2,4-triazole derivatives 23 in good yields (Scheme 11), [[46]].



Scheme 11: Preparation of 5-amino-1,2,4-triazole derivatives

2.12. Preparation of 1,2,4-triazole from various hydrazine hydrochloride salts

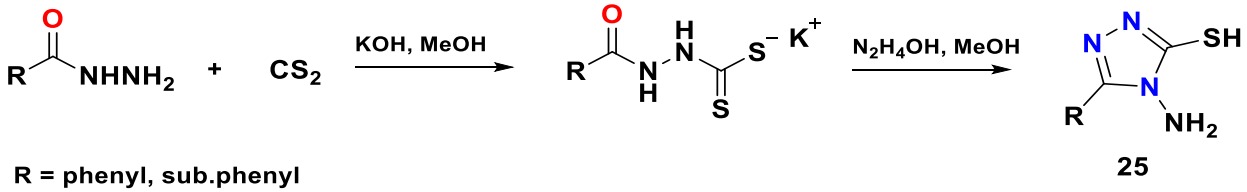
Xu et al. successfully created new amidine reagents derived from oxamide, which were then reacted with a variety of hydrazine hydrochloride salts to form 1,5-disubstituted-1,2,4-triazole derivatives 24. This entire procedure resulted in outstanding outcomes with minimal purification required. Both aromatic and aliphatic hydrazines easily reacted with the amidine reagents under mild reaction conditions (Scheme 12), [[47]].



Scheme 12: Preparation of 1,2,4-triazole from various hydrazine hydrochloride salts

2.13. Preparation of 3-mercapto-1,2,4-triazoles

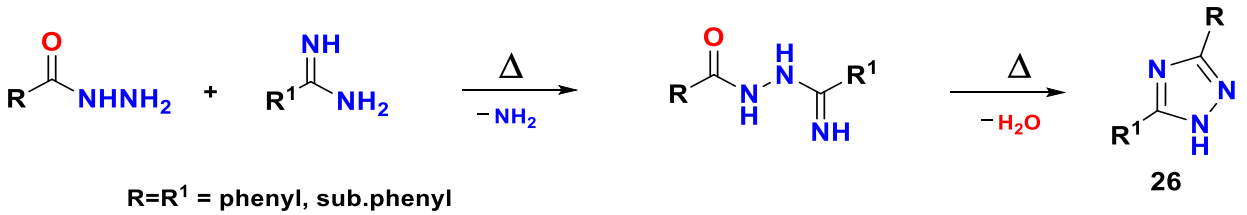
Cansiz et al. investigated the reaction of carbohydrazides with carbon disulfide in the presence of ethanolic potassium hydroxide, which led to the synthesis of dithiocarbazate. Subsequent reaction with hydrazine hydrate produced 4-amino-5-aryl-4H-1,2,4-triazole-3-thiol 25 (Schemes 13), [[48]].



Scheme 13: Preparation of 3-mercapto-1,2,4-triazoles

2.14. Preparation of 3, 5-disubstituted-1,2,4-triazoles

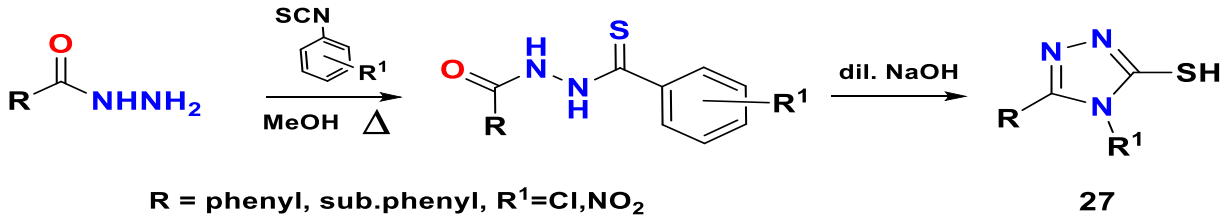
Poonian et al. carried out a reaction involving carbohydrazides and either acetamide or benzamide, which led to the synthesis of 1,2,4-triazole derivatives 26 (Scheme 14), [[49]].



Scheme 14: Preparation of 3, 5-disubstituted-1,2,4-triazoles

2.15. Preparation of 3-mercapto-1,2,4-triazoles

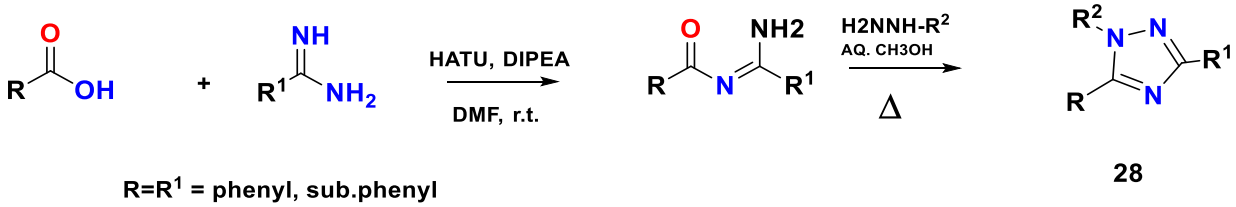
In a basic environment, the cyclodehydration of thiosemicarbazide leads to the formation of 1,2,4-triazole 27 (Scheme 15), [[50]].



Scheme 15: Preparation of 3-mercapto-1,2,4-triazoles

2.16. Preparation of 1,3,5-trisubstituted 1,2,4-triazoles

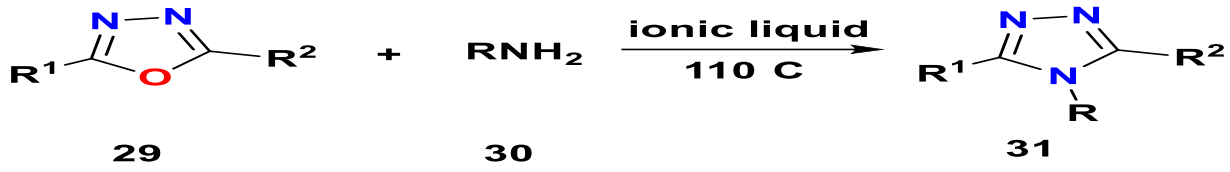
Castanedo et al. reported the synthesis of various 1,3,5-trisubstituted-1,2,4-triazoles 28 via the reaction of carboxylic acids, primary amidines, and monosubstituted hydrazines. In this highly regioselective acylanilide-forming process, HATU [2-(7-aza-1H-benzo triazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] serves as the peptide coupling reagent, DIPEA functions as the base, and DMF is used as the reaction solvent (Schemes 16), [[51]].



Scheme 16: Preparation of 1,3,5-trisubstituted 1,2,4-triazoles

2.17. Preparation of 1,2,4-triazole from oxadiazoles and organoamines

Xiaofeng and colleagues explored the application of protic ionic liquids in the reactions between oxadiazoles 29 and organoamines 30, resulting in the creation of sterically hindered 1,2,4-triazoles 31. In their evaluation of eco-friendly options, pyridinium trifluoroacetate and pyridinium acetate were found to be particularly effective in promoting reactions with arylamines and alkylamines, respectively (Scheme 17), [[52]].

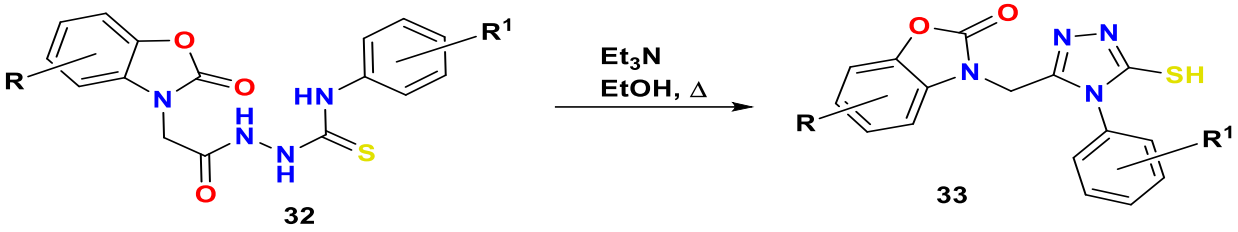


R=R¹= phenyl, sub. phenyl; R²= H, Me, phenyl

Scheme 17: Preparation of 1,2,4-triazole from oxadiazoles and organoamines

2.18. Preparation of 3-mercapto-1,2,4-triazoles

Haider et al. employed triethylamine in absolute ethanol to facilitate the cyclization of thiosemicarbazide 32 into their corresponding 3-mercapto-1,2,4-triazole derivatives 33 (Scheme 18), [[53]].

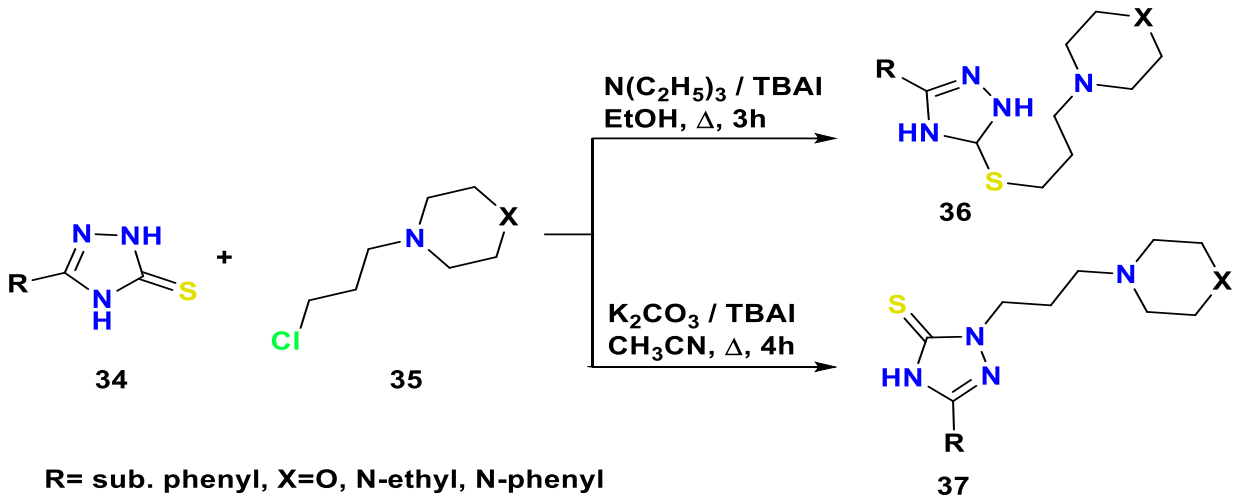


R= H,6-NO_2, 5-CH_3; R^1= H, 4-Cl, 4-F

Scheme 18: Preparation of 3-mercapto-1,2,4-triazoles

2.19. Preparation of 1,2,4-triazole derivatives from 5-substituted-1,2,4-triazole-3-thiones

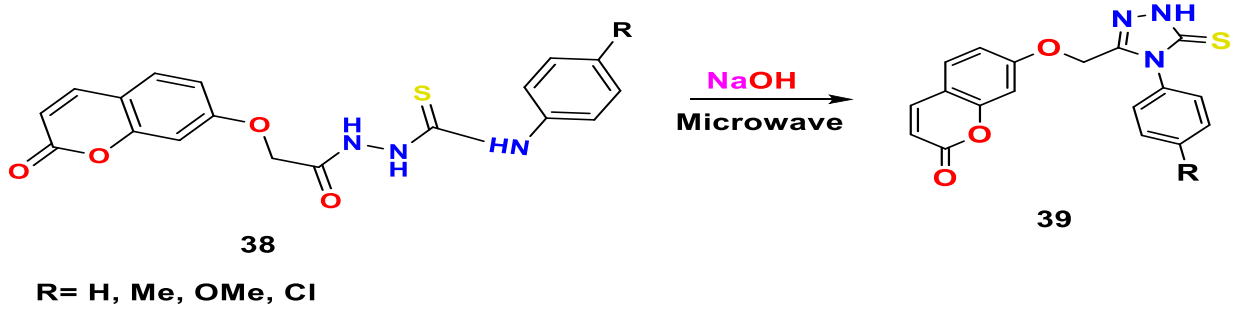
When 5-substituted-1,2,4-triazole-3-thiones 34 and 1-(3-chloropropyl)-4-substituted cyclicamines 35 were reacted with a catalytic amount of tetra-butyl ammonium iodide (TBAI) in the presence of triethylamine in ethanol, S-alkylated 3-{3-[4-(substituted)-1-cyclicamine propyl} thio-5-substituted-1,2,4-triazoles 36 were synthesized. In contrast, performing the same reaction in the presence of K_2CO_3 in acetonitrile with a catalytic amount of TBAI led to the formation of N-alkylated 2-{3-[4-(N-substituted)-1-cyclicamepropyl}-5-substituted-2,4-dihydro-3H-1,2,4-triazole-3-thiones 37 (Schemes 19), [[54]].



Scheme 19: Preparation of 1,2,4- triazole derivatives from 5-substituted-[1,2,4]-triazole-3-thiones

2.20. Preparation of 3-mercapto-1,2,4-triazoles

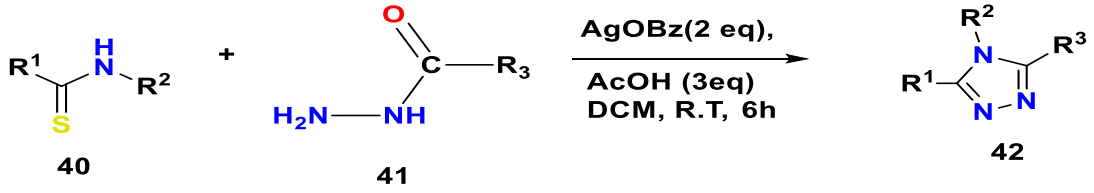
Reddy et al. employed microwave and grinding-accelerated synthesis techniques to produce 3-mercapto-1,2,4-triazole 39, which was derived from a substituted coumarin 38. Microwave irradiation yielded products more rapidly and with higher efficiency, whereas grinding served as an effective alternative heating source for organic transformations (Scheme 20), [[55]].



Scheme 20: Preparation of 3-mercapto-1,2,4- triazoles

Preparation of 3,4,5-trisubstituted 1,2,4-triazoles from silver benzoate

Optically pure 3,4,5-trisubstituted 1,2,4-triazoles were synthesized using silver benzoate. Specifically, thioamide 40 was reacted with hydrazide 41 in acetic acid (AcOH) and stirred for 6 h at room temperature (RT) in the presence of silver benzoate, resulting in the formation of compound 42 (Scheme 21), [[56]].

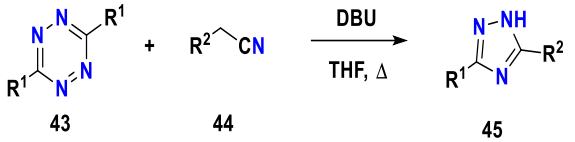


Scheme 21: Preparation of 3,4,5-trisubstituted 1,2,4-triazoles from silver benzoate

2.21. Preparation of 3,6-diphenyl-(NH)-1,2,4-triazole

3,6-Diphenyl-1,2,4,5-tetrazine 43 was introduced into an anhydrous tetrahydrofuran (THF) solution containing benzyl cyanide 44. After adding DBU, the mixture was heated to reflux for three hours. The organic layer was then washed with water and dilute

HCl, dried using anhydrous Na_2SO_4, and evaporated under reduced pressure to produce compound 45 (Schemes 22), [[57]].

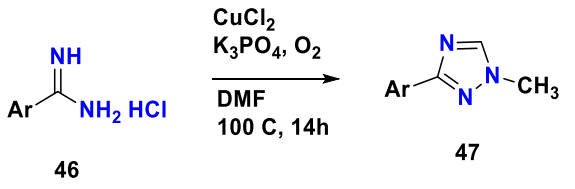


R^1=C_6H_5, $C_6H_4Br(4-)$; R^2 =C_6H_5, $C_6H_4NO_2(2-)$

Scheme 22: Preparation of 3,6-diphenyl-(NH)-1,2,4-triazole

2.22. Preparation of 1,2,4-triazoles from amidines

A mixture comprising aryl amidine 46, copper chloride, and K_3PO_4 in DMF was subjected to reflux at 100°C for 14 h, resulting in the formation of compound 47 (Scheme 23), [[58]].

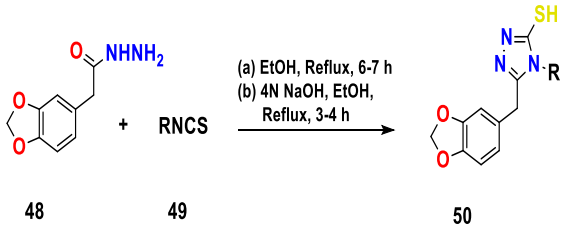


Ar= C_6H_5, $C_6H_4CF_3(4-)$, $C_6H_4Cl(4-)$, $C_6H_4CH_3(4-)$

Scheme 23: Preparation of 1,2,4-triazoles from amidines

2.22. Preparation of benzo[d] [1,3] dioxole-tethered 1,2,4-triazole hybrids

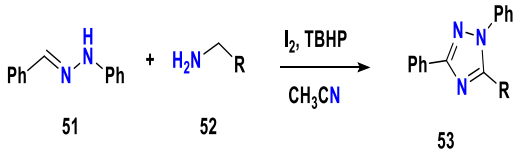
The ester derivatives of 3,4-(methylenedioxy) phenylacetic acid and 5-bromofuranoic acid were obtained through esterification. These hydrazides were then reacted with various substituted phenyl isothiocyanates (RNCS), resulting in the formation of intermediates. The final 1,2,4-triazole hybrids 50 were produced by cyclizing these intermediates under basic conditions using 4 N sodium hydroxide (Scheme 24), [[59]].



Scheme 24: Preparation of benzo[d] [1,3] dioxole-tethered 1,2,4-triazole hybrids

2.23. Preparation of 1,3-diphenyl-5-(substituted phenyl/alkyl)-1H-1,2,4-triazole

Bisarylhydrazone 51 and 4-methylbenzylamine 52 were heated to reflux in CH3CN at 90°C for 4 h in the presence of I2 and TBHP to afford the intended cyclized compound 53 (Scheme 25), [[60]].

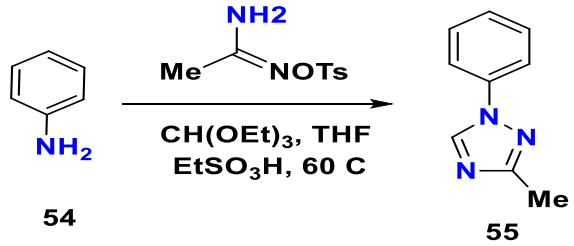


R= C6H5, $C_6H_4CH_3(4-)$, $C_6H_4CH_3(3-)$, $C_6H_5CH_2$, cyclopropyl

Scheme 25: Preparation of 1,3-diphenyl-5-(substituted phenyl/alkyl)-1H-1,2,4-triazole

2.24. Preparation of 1-aryl 1,2,4-triazole from anilines

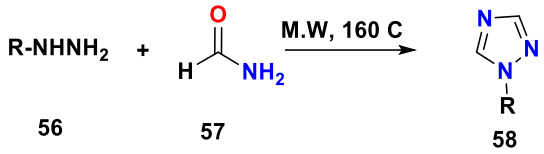
Aniline was slowly introduced to a mixture of tosylate and EtSO3H prepared in THF. This mixture was then heated to reflux at 60 °C for 4 h and cooled to room temperature, resulting in the formation of the compound (Scheme 26), [[61]].



Scheme 26: Preparation of 1-aryl 1,2,4-triazole from anilines

2.25. Preparation of 1-substituted phenyl-1H-1,2,4-triazole

Phenyl hydrazine 56 and formamide 57 were combined in a dried microwave tube. The tube was then sealed using a plastic microwave septum and placed in a microwave cavity. It was exposed to irradiation at 160°C, 250 psi, and 230 W for 10 min. The organic extracts obtained were dried with Na_2SO_4, filtered, and concentrated under reduced pressure, resulting in compound 58 (Scheme 27), [[62]].

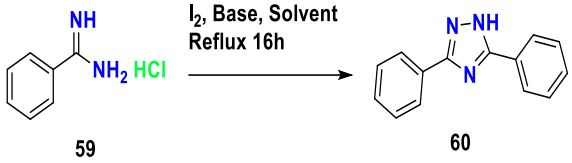


R= t-butyl, C_6H_{10}, C_6H_5, $C_6H_4Br(4-)$, C6H4OCH3(3-)

Scheme 27: Preparation of 1-substituted phenyl-1H-1,2,4-triazole

2.26. Preparation of 3,5- diphenyl-1H-1,2,4-triazole

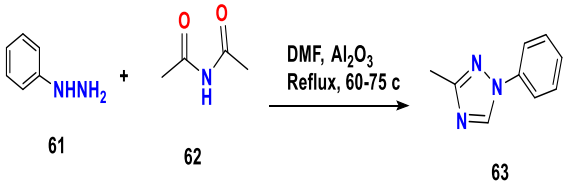
To synthesize compound 60, compound 59 was stirred with a base and iodine in a solvent for 16 h, maintaining the temperature between room temperature and 130°C (Scheme 28), [[63]].



Scheme 28: Preparation of 3,5- diphenyl-1H-1,2,4-triazole

2.27. Preparation of N-aryl-1,2,4-triazole

Compound 63 was synthesized by heating a combination of hydrazine 61 and imide 62 at 60°C for 12 h, followed by passing the mixture through Al_2O_3 for filtration (Schemes 29), [[64]].



Scheme 29: Preparation of N-aryl-1,2,4-triazole

III. CONCLUSIONS

This review underscores the importance of 1,2,4-triazole derivatives, which are key nitrogen-containing heterocyclic compounds with extensive applications in medicinal chemistry, pharmaceutical science, and agrochemical development. The structural adaptability, aromatic stability, and capacity of the triazole ring to engage in hydrogen bonding and coordination interactions make it a desirable pharmacophore for crafting biologically active molecules. Numerous studies have shown that triazole-based compounds possess a wide range of pharmacological activities, including antimicrobial, antifungal, anticonvulsant, antidepressant, anti-inflammatory, antioxidant, and anticancer activities, leading to their inclusion in several clinically significant drugs and agrochemicals.

This review summarizes a broad spectrum of synthetic strategies for the preparation of 1,2,4-triazole derivatives, ranging from classical cyclization reactions to modern methodologies, including microwave-assisted synthesis, solid-phase reactions, metal-catalyzed transformations, and multicomponent reactions. These approaches provide efficient routes to structurally diverse triazole frameworks and enable the introduction of various functional substituents that can modulate biological activity. The availability of such versatile synthetic methodologies has significantly contributed to the rapid expansion of triazole chemistry and its applications in drug discovery and materials science.

Despite substantial progress in the synthesis and biological evaluation of triazole derivatives, several challenges and opportunities remain. Future research should focus on developing greener and more sustainable synthetic approaches under catalytic, solvent-free, and environmentally benign reaction conditions. Additionally, advanced computational tools, structure–activity relationship (SAR) studies, and molecular docking techniques may further accelerate the identification of potent triazole-based drug candidates. The exploration of hybrid molecules incorporating a triazole scaffold with other biologically active heterocycles may also provide new therapeutic leads with enhanced selectivity and reduced toxicity.

In summary, the 1,2,4-triazole framework serves as an important foundation in both heterocyclic and medicinal chemistry, and presents significant opportunities for the discovery of new biologically active substances. Ongoing interdisciplinary efforts that combine synthetic chemistry, biological assessments, and computational modeling are essential for broadening the future therapeutic and industrial applications of triazole derivatives.

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V. DATA AVAILABILITY STATEMENT

All data belonging to this work are presented here.

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VII. CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

[1] E Vitaku, E., Smith, D. T., & Njardarson, J. T. (2014). Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among US FDA approved pharmaceuticals: miniperspective. Journal of medicinal chemistry, 57(24), 10257-10274.

[2] J.A. Joule, K. Mills (2010). Heterocyclic Chemistry, 5th ed., Wiley-Blackwell, Oxford.

[3] Brown, D. G., & Bostrom, J. (2016). Analysis of past and present synthetic methodologies on medicinal chemistry: where have all the new reactions gone? Miniperspective. Journal of medicinal chemistry, 59(10), 4443-4458.

[4] Potts, K. T. (1961). The Chemistry of 1, 2, 4-Triazoles. *Chemical reviews*, *61*(2), 87-127.

[5] Katritzky, A. R., Karelson, M., Sild, S., Krygowski, T. M., & Jug, K. (1998). Aromaticity as a quantitative concept. 7. Aromaticity reaffirmed as a multidimensional characteristic. *The Journal of Organic Chemistry*, *63*(15), 5228-5231.

[6] Aly, A. A., A. Hassan, A., Makhlouf, M. M., & Bräse, S. (2020). Chemistry and biological activities of 1, 2, 4-triazolethiones—antiviral and anti-infective drugs. *Molecules*, *25*(13), 3036.

[7] M. Kumari, S. Singh, P. Tiwari (2020). Triazole derivatives as potential pharmacological agents. Chem. Cent. J. 14, 102.

[8] H. Singh, A. Chawla, P. Kapoor (2013). Synthesis and biological evaluation of triazole derivatives. Bioorg. Med. Chem. 21, 5536–5545.

[9] Bladin, J. A. (1885). Ueber von dicyanphenylhydrazin abgeleitete verbindungen. *Berichte der deutschen chemischen Gesellschaft*, *18*(1), 1544-1551.

[10] M. Shaikh, S. Patel (2014). Synthesis and biological evaluation of novel triazole derivatives. Eur. J. Med. Chem. 72, 1–13.

[11] R. Kharb, P.C. Sharma, M.S. Yar (2011). Pharmacological significance of triazole derivatives. Eur. J. Med. Chem. 46, 497–505.

[12] R. Chawla, S. Arora (2017). Synthesis and biological activities of substituted triazoles. Bioorg. Chem. 74, 178–187.

[13] H. Zhang, S. Liu (2018). Triazole scaffold in medicinal chemistry. Drug Discov. Today 23, 150–165.

[14] N. Rani, S. Sharma (2017). Pharmacological applications of triazole derivatives. Bioorg. Med. Chem. 25, 413–424.

[15] A.R. Bhat (2015). Synthesis and pharmacological evaluation of triazole derivatives. Eur. J. Med. Chem. 101, 264–273.

[16] R.S. Keri, K.M. Patil, S.A. Budagumpi, B.M. Nagaraja (2015). Triazole pharmacophore: A review of synthetic strategies and biological applications. Eur. J. Med. Chem. 100, 257–269.

[17] P. Singh, R. Anand, V. Kumar (2014). Antimicrobial activities of triazole derivatives. Bioorg. Med. Chem. 22, 232–241.

[18] V. Patil, A. Patil (2015). Antibacterial activity of triazole derivatives. Eur. J. Med. Chem. 89, 531–539.

[19] S. Sharma, S. Goyal (2015). Antifungal activity of substituted triazoles. Med. Chem. Res. 24, 2987–2996.

[20] L.E. Cowen (2008). The evolution of fungal drug resistance: Modulating the trajectory from genotype to phenotype. Nat. Rev. Microbiol. 6, 187–198.

[21] Siddiqui, N., & Pandeya, S. N. (2009). Anticonvulsant activity of triazole derivatives.

Bioorganic & Medicinal Chemistry Letters, 19, 3074–3078.

[22] Gupta, R., & Kumar, A. (2012). CNS active triazole derivatives. *European Journal of Medicinal Chemistry, 49*, 231–236.

[23] Kumar, P., & Sharma, P. (2017). Antidepressant activity of triazole derivatives. *Bioorganic Chemistry, 72*, 1–8.

[24] Abdel-Wahab, B. F. (2015). Synthesis of anti-inflammatory triazoles. *European Journal of Medicinal Chemistry, 90*, 339–347.

[25] Noolvi, M. N., & Patel, H. M. (2011). COX inhibitory triazole derivatives. *Bioorganic & Medicinal Chemistry, 19*, 682–690.

[26] Rao, Y., & Yang, X. (2015). Anti-inflammatory heterocyclic compounds. *European Journal of Medicinal Chemistry, 95*, 286–294.

[27] Holla, B. S., & Malini, K. V. (2003). Antitumor activity of triazole derivatives. *Bioorganic & Medicinal Chemistry, 11*, 487–495.

[28] Sahu, S., & Sahu, R. (2016). Anticancer triazole derivatives. *European Journal of Medicinal Chemistry, 124*, 447–460.

[29] Zhang, Y., & Wang, L. (2014). Cytotoxic activity of triazole compounds. *Bioorganic & Medicinal Chemistry Letters, 24*, 1096–1100.

[30] Patel, R., & Desai, A. (2019). Antioxidant activity of triazole derivatives. *Bioorganic Chemistry, 82*, 341–350.

[31] Katritzky, A. R., Ramsden, C. A., Joule, J. A., & Zhdankin, V. V. (2010). *Handbook of heterocyclic chemistry* (3rd ed.). Elsevier.

[32] Sheehan, D. J., Hitchcock, C. A., & Sibley, C. M. (1999). Current and emerging azole antifungal agents. *Clinical Microbiology Reviews, 12*, 40–79.

[33] Bhatnagar. (2007). The discovery and mechanism of action of letrozole. *Journal of Steroid Biochemistry and Molecular Biology, 106*, 23–32.

[34] De Clercq, E. (2002). Antiviral activity of ribavirin. *Antiviral Research, 55*, 1–13.

[35] Food and Agriculture Organization. (2018). *Triazole fungicides in agriculture*. FAO.

[36] Czollner, L., Szilagyi, G., Lango, J., & Janaky, J. (1988). Synthesis of 1,5-diphenyl-3-trifluoromethyl-1H-1,2,4-triazoles. *Monatshefte für Chemie, 119*, 349–353.

[37] Kidwai, M., Misra, P., Bhushan, K. R., & Dave, B. (2000). A novel route to 1,2,4-triazoles. *Synthetic Communications, 30*, 3031–3040.

[38] Rostamizadeh, S., Tajik, H., & Yazdanfarahi, S. (2003). Solid phase synthesis of 1,2,4-triazoles under microwave irradiation. *Synthetic Communications, 33*, 113–117.

[39] Boeglin, D., Cantel, S., Heitz, A., Martinez, J., & Fehrentz, J. A. (2003). Solution and solid-supported synthesis of trisubstituted triazole-based peptidomimetics. *Organic Letters, 5*, 4465–4468.

[40] Liu, F., Palmer, D. C., & Sorgi, K. L. (2004). Preparation of fused triazoles using hydrazide reagents. *Tetrahedron Letters, 45*, 1877–1880.

[41] Makara, G. M., Ma, Y., & Margarida, L. (2004). Solid-phase synthesis of alkylamino triazoles. *Organic Letters, 4*, 1751–1754.

[42] Su, W., Yang, D., & Li, J. (2005). Ytterbium-catalyzed synthesis of triazoles. *Synthetic Communications, 35*, 1435–1440.

[43] Price, D. A., Gayton, S., Selby, M. D., Ahman, J., & Hycock-Lewandowski, S. (2005). Practical synthesis of substituted triazoles. *Synlett*, 1133–1134.

[44] Yeung, K. S., Farkas, M. E., Kadow, J. F., & Meanwell, N. A. (2005). Base-catalyzed synthesis of disubstituted triazoles. *Tetrahedron Letters, 46*, 3429–3432.

[45] Ueda, S., & Nagasawa, H. (2009). Copper-catalyzed synthesis of triazoles. *Journal of the American Chemical Society, 131*, 15080–15081.

[46] Yin, P., Ma, W. B., Chen, Y., Huang, W. C., Deng, Y., & He, L. (2009). Cyanoimidation of aldehydes. *Organic Letters, 11*, 5482–5485.

[47] Xu, Y., McLaughlin, M., Bolton, E. N., & Reamer, R. A. (2010). Synthesis of functionalized triazoles. *Journal of Organic Chemistry, 75*, 8666–8669.

[48] Cansiz, A., Koparir, M., & Demirdag, A. (2004). Oxadiazole and triazole thiol tautomerism. *Molecules, 9*, 204.

[49] Alan, A. H., & Ahmed, M. S. (2010). *Chemistry and heterocyclization of carbohydrates*. Wiley.

[50] Tashfeen, A., Shahid, H., Khalid, M. K., Ajmal, K., & Choudhary, M. I. (2010). Urease inhibition studies of triazoles. *Journal of Enzyme Inhibition and Medicinal Chemistry, 25*, 572–576.

[51] Castanedo, G. M., Seng, P. S., Blaquiere, N., Trapp, S., & Staben, S. T. (2011). Rapid synthesis of substituted triazoles. *Journal of Organic Chemistry, 76*, 1177–1179.

[52] Xiaofeng, C., Rui, L., Yuan, X., & Gang, Z. (2012). Ionic liquid-assisted synthesis of triazoles. *Tetrahedron, 68*, 4813–4819.

[53] Haider, S., Alam, M. S., Hamid, H., Dhulap, A., Umar, S., Yar, M. S., Bano, S., Nazreen, S., Ali, Y., & Kharbanda, C. (2014). Triazoles as cytokine inhibitors. *Medicinal Chemistry Research, 23*, 4250–4268.

[54] Murty, M. S. R., Ram, K. R., Rao, B. R., Rao, R. V., Katiki, M. R., Rao, J. V., Pamanji, R., & Velatooru, L. R. (2014). Anticancer triazole derivatives. *Medicinal Chemistry Research, 23*, 1661–1671.

[55] Reddy, K. R., Mamatha, R., Babu, M. S. S., Kumar, K. S., Jayaveera, K. N., & Narayanaswamy, G. (2014). Antimicrobial triazole derivatives. *Journal of Heterocyclic Chemistry, 51*, 132–137.

[56] Bibian, M., Blayo, A. L., Moulin, A., Martinez, J., & Fehrentz, J. A. (2010). Mercury-free synthesis of trisubstituted triazoles. *Tetrahedron Letters, 51*, 2660–2663.

[57] Haddadin, M. J., & Zadeh, E. H. G. (2010). Synthesis of disubstituted triazoles. *Tetrahedron Letters, 51*, 1654–1656.

[58] Huang, H., Guo, W., Wu, W., Li, C. J., & Jiang, H. (2015). Copper-catalyzed synthesis of triazoles. *Organic Letters, 17*, 2894–2897.

[59] Hakkimane, S. S., Gaonkar, S. L., et al. (2025). Triazole hybrids as anticancer agents. *Scientific Reports, 15*, 1–17.

[60] Chen, Z., Li, H., Dong, W., Miao, M., & Ren, H. (2016). I2-catalyzed oxidative coupling reactions of hydrazones and amines and the application in the synthesis of 1, 3, 5-trisubstituted 1, 2, 4-triazoles. Organic letters, 18(6), 1334-1337.

[61] Tam, A., Armstrong, I. S., & La Cruz, T. E. (2013). Multicomponent synthesis of 1-aryl 1, 2, 4-triazoles. Organic letters, 15(14), 3586-3589.

[62] Shelke, G. M., Rao, V. K., Jha, M., Cameron, T. S., & Kumar, A. (2015). Microwave-assisted catalyst-free synthesis of substituted 1, 2, 4-triazoles. Synlett, 26(03), 404-407.

[63] Inturi, S. B., Kalita, B., & Ahamed, A. J. (2016). I2 mediated one-pot synthesis of 1, 2, 4-triazoles from amidines and imidates. *Tetrahedron Letters*, *57*(21), 2227-2230.

[64] Neuhaus, W. C., & Moura-Letts, G. (2016). Alumina-promoted synthesis of N-aryl-1, 2, 4-triazoles from substituted hydrazines and imides. *Tetrahedron Letters*, *57*(45), 4974-4977.