AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

A Review Novel on Synthesis of Triazole and Chemistry of Active Chemical Moiety

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ABSTRACT

The triazoles possess wide spectrum of biological activities like including antibacterial, antifungal, antiviral, anti-inflammatory, anticonvulsant, antidepressant, antihypertensive, analgesic, and hypoglycemic properties. The present reviews attempted to gather the basic developments in synthesis and biological activities of triazole derivatives. The novel chemical moiety used in medicinal active substance either (R) or (L) hence Dextro or Levo rotatory form. The broad spectrum of activity is due nitrogen hence nitrogen containing loan pair of electron transfer to another substance and formation of covalent bond.

Keywords Pharmacological activity, Triazole, Synthesis, Isomers, Bio conjugation

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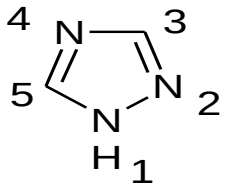
Received 20 June 2022, Accepted 19 July 2022

Please cite this article as: Roy S *et al*., A Review Novel on Synthesis of Triazole and Chemistry of Active Chemical Moiety. American Journal of PharmTech Research 2022.

INTRODUCTION

The Azoles are five-member heterocyclic compounds with two or more heteroatoms in which at least one is nitrogen. Azoles are found widely in natural sources[1, 2]. here we will focus on 1,2,4-Triazoles, which are by far the best-known class of triazoles five member heteroatoms with three nitrogen atoms in the ring and consist wide variety of medicinal activity. The action of azole on mycotic biochemistry and physiology has been studied extensively [2, 3]. At high concentrations (Micromolar) the azoles are fungicidal and at low concentrations (Nanomolar), they are fungi static [1,2,5]. See figure no. 1.



1*H*-1,2,4-triazole

Figure 1: Triazole activity of heterocyclic group 1 H-1, 2, 4-triazole

Advantages and Disadvantages of Triazole [13, 14]

Advantages:

- The reaction is very useful for peptide modification hoping to increase the metabolic stability of the peptides [13].
- The benefits regarding this selectivity, efficiency, and mild reaction condition in producing the desired compounds [13, 14].
- Applications in combinatorial chemistry, diversity-oriented synthesis, bioconjugation chemistry, and drug discovery [14].
- The application and anticipation of knowledge indicates that the pentapeptide GLTSK and hexapeptide GEGSGA and their triazole derivatives conveniently by solid phase peptide synthesis method in a short period of time with gives a high yield [14].

Disadvantages:

- The many and more methods proposed for the preparation of triazoles and thiadiazols derivative but, all of this reported method has several drawbacks like, use of organic solvents which causes, pollution, strong reaction conditions, time consuming reactions and use of expensive reagents.
- High dose causes the side effects to biological organs

Biological activity using Substitutes of 1,2,3-triazoles 1,2,4-triazoles [15, 16, 17]

The unique properties, 1,2,3-triazoles and 1,2,4-triazoles are attractive building blocks in drug discovery.

1. Anti-cancer activity
2. Anti-inflammatory activity
3. Antitubercular activity
4. Antimicrobial activity
5. Antiviral activity

The exceptional properties of this promising heterocycle facilitate its wide range of applications from material science to bio-conjugation [15, 16, 17].

Chemistry of Triazoles

Triazoles ring is basically of two types i.e., 1, 2, 3 and 1, 2, 4-Triazole.The derivatization of Triazole ring is based on the phenomenon of bio-isosterism in which replacement of oxygen of oxadiazole nucleus with nitrogen atom yields triazole analogue. Out of the two triazoles 1,2,4-triazole have wide variety of activity [4].1,2,4-Triazole is one of a pair of isomeric chemical with molecular formula $C_2H_3N_3$ called triazoles, which have a five membered ring of two carbon atoms and three nitrogen atoms. 1,2,4-Triazole is a basic aromatic heterocycle. 1,2,4-Triazoles can be prepared using the Einhorn-Brunner Reaction or The Pellizzari Reaction[5].1, 2, 4-Triazoles are cyclic hydrazidines with hydrogen atom (or substituent) on either hydrazide nitrogen or on amide nitrogen [3, 4]. The parent 1, 2, 4-triazole (1-H form) is in tautomeric equilibrium with 1, 3, 4-triazole (4H form). The interconversion of two tautomeric forms occurs rapidly and their separation is difficult [6]. 1, 2, 4-triazole tautomer is preferred over 1, 3, 4- triazole tautomer (less symmetrical 1H form is favored over symmetrical 4H- form)1, 2, 4-Triazole is considered to be derived from benzene by replacement of -CH=CH-by –NH- and the replacement of two –CH= by two –N= atoms. The replacement of -CH=CH- in benzene by –NH enhance the electron density and hence makes 1, 2, 4-triazole susceptible towards electrophilic attack as compared to benzene [6, 7]. But the replacement of two –CH=by two –N= atoms cause the resulting 1, 2, 4-triazole to be nearly unreactive towards electrophiles. Therefore 1, 2, 4-triazoles fails to undergo nitration, sulfonation, and N-oxidation. However, 1, 2, 4-triazole anion undergoes alkylation and acylation very readily [7].1, 2, 4-Triazoles undergo nucleophilic substitution, if substituted with electron withdrawing substituents, the reactivity of 1,2,4-triazole ring towards nucleophile is enhanced in 1,2,4-triazolium cations and meso-ionic 1,2,4-triazoles [5, 6, 7]. See figure no. 2

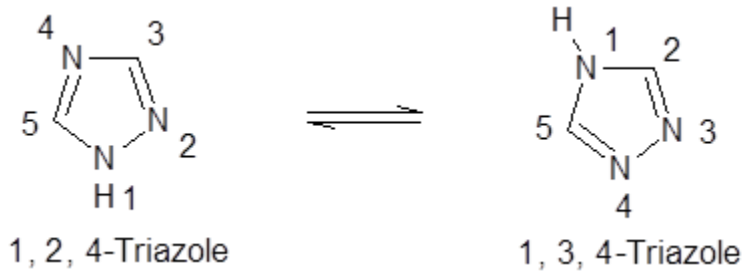


Figure 2: Symmetry of triazole SAR tautomer activity 1, 2, 4-triazole and 1, 3, 4 triazole

Tentative method of synthesis for reporting [8, 9]

- Khosrow Zamani reported the synthesis of several 5-(isomeric pyridyl)-4-aryl-1, 2, 4-triazole-3-thiol/yl-thiomethyl/yl-thioethyl/yl-thiobenzyl and yl-thioglycolic acids as possible biologically active agents.[8]
- Shuki Araki reported with Synthesis of 3-(phenylazo)-1,2,4-triazoles by a nucleophilic reaction of primary amines with 5-chloro-2,3-diphenyltetrazolium salt via meso-ionic 2,3-diphenyltetrazolium-5-aminides.[9] see figure 3.

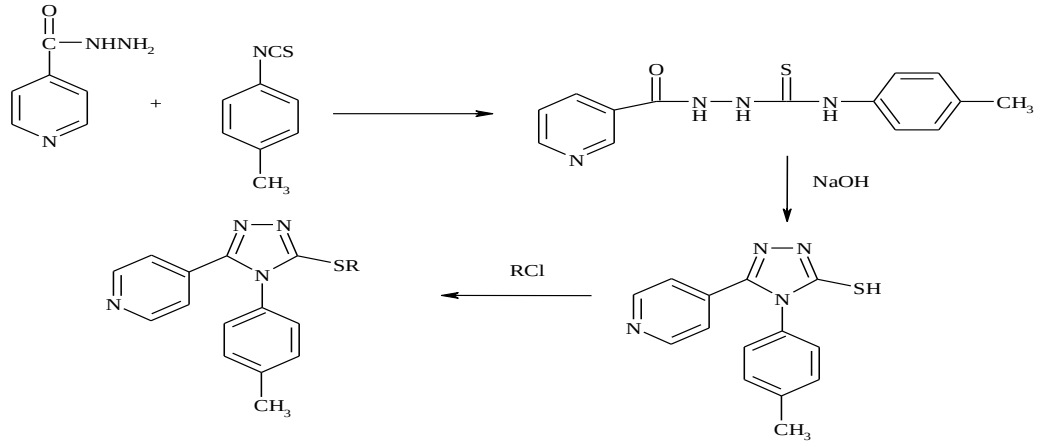


Figure 3: Method of synthesis active isomeric form

Pharmacological activities [11]

R.R. Somani reported with the synthesis of 5-(N-substituted carboxamidomethylthio)–3-(3'-pyridyl) - 1, 2, 4-triazoles for their antitubercular activity and antifungal activity.[10] The better understanding sees figure no. 4 and 5.

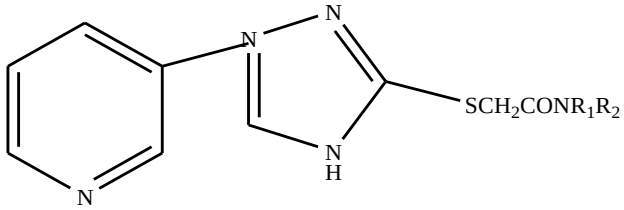


Figure 4: Pharmacological active moiety of 5-(N-substituted carboxamidomethylthio)-3-(3'-pyridyl)-1, 2, 4-triazoles

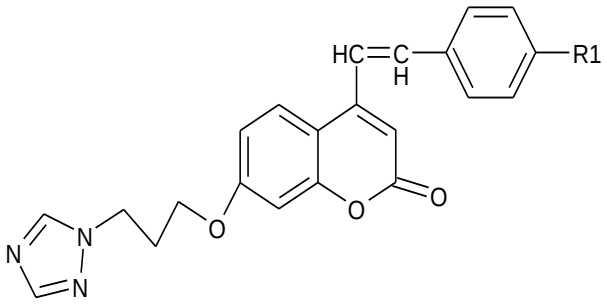


Figure 5: 7-hydroxy-4-methylcoumarin active moiety of fungicidal activity

Ganesh R. Kokil reported with the synthesis of novel triazole derivatives of 7-hydroxy-4-methylcoumarin using various substituted aromatic aldehydes and evaluated for their in vitro fungicidal activity against Candida albicans at various concentrations to obtain minimum inhibitory concentration (MIC).[11]

Therapeutic Application [12, 18]

The presence of the three nitrogen atoms in triazole structures afforded opportunities for a structural modification with the generation of novel therapeutically potential agents, which is different from heterocyclic compounds [12]. Thus, triazoles are a significant platform in medicinal chemistry and chemical biology, which play key functional roles in various biological mechanisms related to infections, cancer, convulsions, inflammation and oxidative stress. Relatedly, many drugs are available in the commercial to markets [12]. However, the synthesis of novel triazoles is in a continuous process for unexplored and advanced pharmacological implications [12].

Derivatives The triazole antifungal drugs:

The triazole antifungal drugs include fluconazole, isavuconazole, itraconazole, voriconazole, pramiconazole, ravuconazole, and posaconazole [18].

The triazole plant protection fungicides:

The triazole plant protection fungicides include epoxiconazole, triadimenol, propiconazole, prothioconazole, metconazole, cyproconazole, tebuconazole, flusilazole and paclobutrazol [18].

The triazole plant growth retardants:

paclobutrazol and uniconazole are used as plant growth retardants. The benzotriazole is used in chemical photography as a restrainer and fog-suppressant [18].

CONCLUSION

The concept of this review indicates a general study and wide spectrum of pharmacological activities exhibited by 1, 2, 4 triazole derivatives. The biological profiles of these new generations of 1, 2, 4 Triazoles would represent a fruitful matrix for further development of better medicinal agents. An attempt is made to focus on some synthetic methods of triazoles including Base

catalyzed synthesis and Traceless synthesis. It can act as an important tool for medicinal chemistry to develop newer compounds possessing triazole active moiety that could be better agents in terms of efficacy and safety. The nitrogen contains loan pairs of electrons and passes to another substance and formation of covalent bonds hence shows antibacterial and antifungal activity. There are many plants shows the antifungal and antibacterial activity because of nitrogen containing triazole chemical entity.

ACKNOWLEDGEMENTS

Authors are thankful to the Intelliscend NDDR, Thane for providing the necessary service in collecting the several data needed for the preparation of this article. Special thanks devoted to Dr. Sunil B Roy, Managing Director of Intelliscend NDDR, Thane.

REFERENCES

1. John HK, John MB. Wilson and Gisvold's Text book of Organic medicinal and Pharmaceutical Chemistry. 11th Edition, Philadelphia: Lippincott Williams and Wilkins; 2004: 1-4.
2. Wang JY, Hsueh PR, Jan IS. "Empirical treatment with a fluoroquinolone delays the treatment for tuberculosis and is associated with a poor prognosis in endemic areas". Thorax. 2006; 61 (10): 903–8.
3. David HL, "Probability distribution of drug-resistant mutants in unselected populations of Mycobacterium tuberculosis". Applied Microbiology 1970; 20 (5): 810–4.
4. Khosrow zamani, Khalil faghihi, M. Reza sangi and Javad zolgharnein, Synthesis of Some New Substituted 1,2,4-Triazole and 1,3,4-Thiadiazole and Their Derivatives, Turk J Chem 2003; 119-125.
5. Shuki Araki, Satoshi Hirose, Yoshikazu Konishi, Masatoshi Nogura and Tsunehisa Hirashita, Synthesis of 3-(phenylazo)-1,2,4-triazoles by a nucleophilic reaction of primary amines with 5-chloro-2,3-diphenyltetrazolium salt via meso ionic 2,3-diphenyltetrazolium-5-aminides**,** Beilstein Journal of Organic Chemistry 2009; *5(*8).
6. Chandrakanta Dash, Mobin M shaikh and Prasenjit ghosh, silver complexes of 1,2,4-triazole derived N-heterocyclic carbenes: Synthesis, structure and reactivity studies**,** J. Chem. Sci 2011; 123 (2): 97–106.
7. Akbar Mobini khaledi, Naser Foroughifara, Mansooreh Khanpoura and Sattar Ebrahimi, Synthesis of some novel Schiff bases containing 1,2,4-triazole ring, European Journal of Chemistry 2010; 1 (1): 33-36.

8. Olcay Bekircan and Hakan Bektas, Synthesis of New Bis-1,2,4-Triazole Derivatives, Molecules 2006; 11: 469-477.
9. Alan R. Katritzky, Alfredo Pastor, and Michael Voronkov. Novel One-Step Synthesis of Thiazolo [3,2-*b*]1,2,4-triazoles, http://pubs.acs.org.
10. Yinwei Ruan, Linhong Jin, Jiang He, Song Yang, Pinaki S. Bhadury, Ming He, Zhenchao Wang and Baoan Song, Synthesis and antifungal activity of new 1-(2,4-dichloro phenyl)-3-aryl-2-(1*H*-1,2,4-triazol-1-yl) prop-2-en-1-one derivatives, African Journal of Pharmacy and Pharmacology 2011; 5(5): 602-607.
11. Li-Ping Guan AB Qing-Hao JB, Guan-Rong Tian, Kyu-Yun CC and Zhe-Shan Quan, Synthesis of some quinoline-2 (1H)- one and 1, 2, 4 - triazolo [4, 3 -a] quinoline derivatives as potent anticonvulsants**,** J Pharm Pharmaceut Sci 2007; 10 (3): 254-262**.**
12. Mohammed M. Matin. Triazoles and Their Derivatives: Chemistry, Synthesis, and Therapeutic Applications, Mol. Bio Sci 2022: 864286.
13. Maryam Baharloui, Sayed Ahmmad Mirshokraee, Azam Monfared, and Mohammad Hassan Houshdar Tehrani. Design and Synthesis of Novel Triazole-based Peptide Analogues as Anticancer Agents, Iran J Pharm Res. 2019; 18 (3): 1299–1308.
14. kaddouri Y, Abrigach F, Ouahhoud, S, Benabbes R, Kodadi, M, Alsalme A, Al-Zaqri N, Warad I, Touzani R. Synthesis, characterization, reaction mechanism prediction and biological study of mono, bis and tetrakis pyrazole derivatives against Fusarium oxysporum, Albedinis with conceptual DFT and ligand-protein docking studies. Bioorg. Chem 2021; 110.
15. Dheer D, Singh V, Shankar R. Medicinal attributes of 1,2,3-triazoles: Current developments. Bioorganic Chemistry 2017; 71: 30-54.
16. Schulze B, Schubert US. Beyond click chemistry–Supramolecular interactions of 1,2,3-triazoles. Chemical Society Reviews 2014; 43: 2522-2571.
17. Liang L, Astruc D. The copper (I)-catalysed alkyne-azide cycloaddition (CuAAC) reaction and its applications. An overview. Coordination Chemistry Reviews 2011; 255: 2933-2945.
18. Gisi U, Sierotzki H, Cook A, Mc Caffery A. Pest Management Science 2002; 58: 859- 867.

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