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Review Article

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A REVIEW ON: DESIGN AND SYNTHESIS OF TRIAZOLE DERIVATIVES AS α - GLUCOSIDASE INHIBITORS

Pravin B. Akolkar*, S. G. Khange, Jyoti D. Kale and Amol P. Darwade

Department of Pharmaceutical Chemistry, Rashtriya College of Pharmacy Kannad.

***Corresponding Author: Pravin B. Akolkar**

Department of Pharmaceutical Chemistry, Rashtriya College of Pharmacy Kannad.

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ABSTRACT

Inhibition of α-glucosidase is an effective strategy for controlling **postprandial** hyperglycemia in diabetic patients. **To identify novel** inhibitors of this enzyme, a series of **novel (R)-1-(2-(4-bromo-2-methoxyphenoxy)propyl)-4-(4-(trifluoromethyl)phenyl)-1H-1,2, 3-triazole** derivatives (8a-d and **10a-e) were synthesized.** The **structure was** confirmed by NMR, mass spectrometry and, in **the** case of compound 8a, single crystal X-ray crystallography. The α-glucosidase inhibitory **activity was studied** in vitro. Most derivatives **showed** significant inhibitory activity against **α-glucosidase.** Their structure-activity relationship and molecular docking studies were performed to elucidate the active pharmacophore **of** this enzyme. **NMR-H, mass spectrometry** and **elemental** analysis. **Cytotoxic activity** of **synthetic** compounds. Finally, molecular docking studies were **also performed** to understand the mechanism **of action** and binding **methods** of these derivatives **as possible targets** in the **aromatase** binding **pocket.**

KEYWORDS: Triazoles, Anticancer, NMR, **Thin layer chromatography** (TLC), **Infrared** (IR).

INTRODUCTION

Triazoles, also known as pyrrolediazoles, are a class of organic heterocycles containing three nitrogen atoms and two carbon atoms in non-adjacent positions. In 1885, Bladin was the first scientist to name the carbon-nitrogen ring system triazole.[1-2]

1,2,4-triazole (the ligand in the coordinating compound, sometimes using the abbreviation of Htrz) is one of the few isomeric compounds, the molecular formula is C2H3N3, called triazoles, is a compound composed of two carbon atoms Composed of five-membered rings, three nitrogen atoms. 1,2,4-triazoles and their derivatives have a wide range of applications.

1,2,4-triazoles are planar molecules. The C-N and N-N distances were within a narrow range of 136-132 pm, consistent with aromaticity. Although two tautomers can be envisioned, only one actually exists.

1,2,4-Triazole is amphoteric and readily N-protonates and deprotonates in aqueous solution. 1,2,4-triazolium (C2N3H4+) has a pKa of 2.

45. The pKa of a neutral molecule is 10.26.[3]

Triazoles can form hydrogen bonds. This property is responsible for increasing the binding to the biomolecular target as well as the solubility of the compound. Triazoles can act as attractive linkers to connect two pharmacophores to form innovative bifunctional drugs. Therefore, these compounds are becoming increasingly useful and important in building bioactive and functional molecules. Notably, the bioisostere substitution between a triazole unit and its triazole bioisostere has received considerable attention in medicinal chemistry and represents an effective concept for the discovery and development of new triazole drugs. Triazole derivatives are known to exhibit various pharmacological properties such as antimicrobial, antituberculous, anticancer, anticonvulsant, anti-inflammatory, analgesic and antiviral. Triazoles are also included in a variety of drugs of therapeutic interest, including histamine H1/H2 receptor blockers, CNS stimulants, anxiolytics and sedatives.[4-5]

Disease Selection

Diabetes mellitus defines a group of metabolic disorders characterized by hyperglycemia due to abnormalities in

insulin secretion, insulin action, or both. It is one of the most common metabolic syndromes, as 200 million people worldwide suffer from diabetes; this requires understanding the etiology of the disease and the factors that influence its onset. Multiple pathogenic processes are implicated in the development of diabetes; these range from autoimmune destruction of pancreatic beta cells and consequent insulin deficiency to abnormalities leading to resistance to insulin action. A new classification system (American Diabetes Association 2004) identifies four types of diabetes: type 1, type 2, "other types specified" and gestational diabetes. Type 1 diabetes (T1D) is characterized by the destruction of beta cells by an autoimmune process, which results in absolute insulin deficiency.[6-7]

STRUCTURAL PROPERTIES OF TRIAZOLE

Aromaticity and Stability

Aromaticity is the main reason of stability of triazole nucleus. An aromatic sextet is formed by donation of one π electron from each atom connected by double bonds, in addition of the remaining two electrons from a nitrogen atom . Also, triazole nucleus is stabilized by resonance that it can be represented by tautomeric forms.[8]

Tautomerism in Triazoles

Tautomerism is possible in both the structural isomers of triazoles. Chapter 4 Selection of Ligand Skeleton.

Tautomerism in 1,2,3-triazoles

1,2,3-Triazoles have two tautomeric forms, 1H-1,2,3-triazole and 2H-1,2,3-triazole.

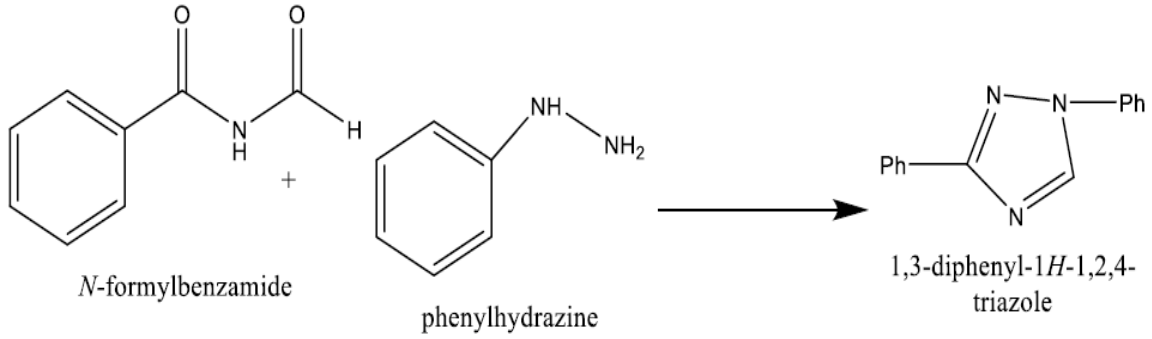
Tautomerism in 1,2,4-triazoles 1, 2, 4-Triazoles have two tautomeric forms: 1H-1, 2, 4- triazole and 4H-1,2,4-triazole. Many studies have been indicated that is tautomer more sTable than tautomer.[8-9]

METHODS OF SYNTHESIS

Synthesis of Triazole

1) Einhorn- Brunner Reaction

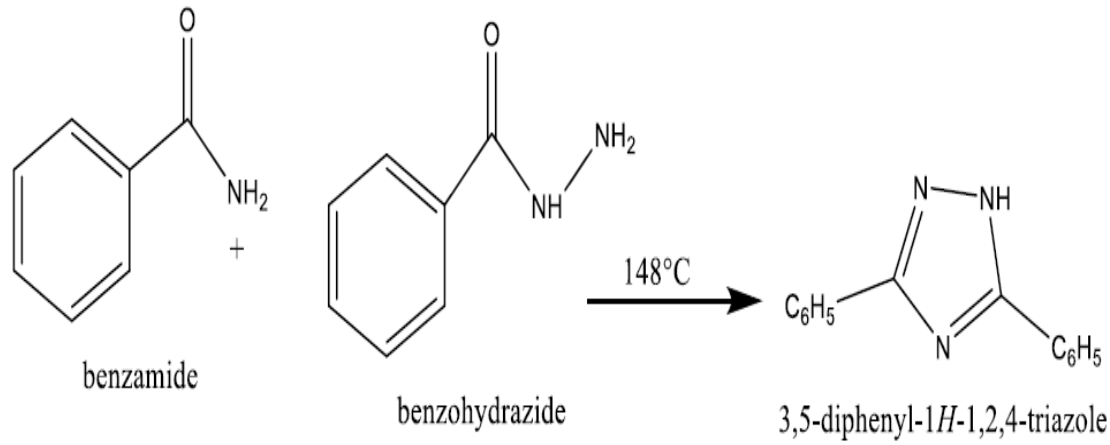
The synthesis of 1,2,4-triazoles by condensation between hydrazines or mono substituted hydrazine and diacylamines in the presence of weak acid is known as the Einhorn–Brunner reaction. For example: *N*-formyl benzamide and phenyl hydrazine gave 1,5-diphenyl-1,2,4-triazole.[8]



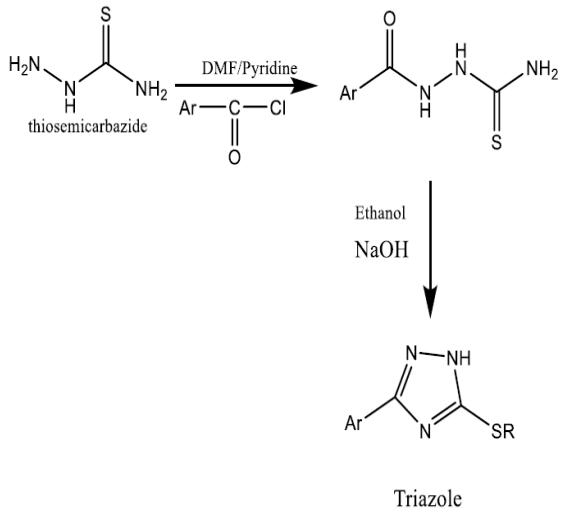
2) Pellizzari Reaction

The mixture of amide and hydrazide **to synthesize 1,2,4-triazole derivatives** is generally **called** the Pellizzari **reaction.**

Heating a mixture of formamide and hydrazine hydrochloride with KOH **has been reported to produce 1,2,4-triazoles.** For **example,** benzamide and **benzohydrazide give 3,5-diphenyl-1,2,4-triazoles.**[8-11]



General Scheme for Synthesis of Triazole



Triazole

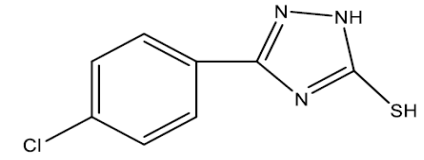
Step-I Synthesis of Aroyl Chloride

1. A mixture of 0.2 mol carboxylic acid and 0.4 mol Thionyl chloride (SOCl2) is heated slowly (~ 3 hrs) to reflux temperature which is maintain until gas release ceases.
2. The excess of Thionyl chloride is removed by evaporating it.
3. The acid chloride are used as such without any purification in the next step.

Step II) Synthesis of Aroyl thiosemicarbazide

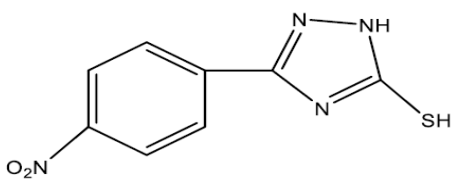
1. Dissolve 0.1 mole of thiosemicarbazide in 50 ml of NN-dimethylformamide, 0.11 mole of pyridine and 0.1 mole of acid chloride with stirring at room temperature.
2. Continue stirring the reaction mixture for 45 minutes at room temperature and 90 minutes at about 500°C.
3. Pour the reaction mixture into 250 ml of 30% HCl.
4. The resulting material was filtered, washed with water and characterized by TLC n-hexane:ethyl acetate (2:1).

III) Synthesis of Substituted Triazole



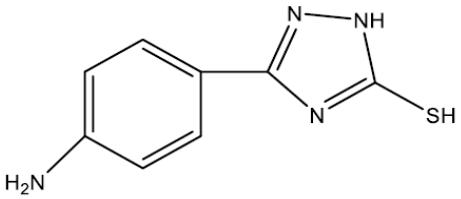
3-(4-chlorophenyl)-1*H*-1,2,4-triazole-5-thiol

S₁



3-(4-nitrophenyl)-1*H*-1,2,4-triazole-5-thiol

S₂



3-(4-aminophenyl)-1*H*-1,2,4-triazole-5-thiol

S₃

1. A mixture of 0.05 mol of Aroyl thio semicarbazide in ml of 1.4 M Sodium Hydroxide (NaOH) in ethyl alcohol is heated at reflux 6 – 7 hrs. until raw material is consumed (Chromatographic control).
2. After reflux evaporate the ethyl alcohol.
3. The semi-solid residue is dissolved in 200 ml of water.
4. After hot discoloration with activated carbon, the filtrate is cool and brought to PH = 1 with HCL separated by filtration and recrystallized by ethanol.
5. Characterization is carried out by TLC n-hexane : ethyl acetate (2:1).

III) Synthesis of compounds

i) Synthesis of 3-(4-chlorophenyl)-5-(methyl thio)-1 *H*-1,2,4-triazole (PA1)

3-(4-chlorophenyl)-1*H*-1,2,4-triazole-5-thiol (S1) 10mmol synthesized in step II were dissolved under stirring in 100 ml of ethanolic solution of sodium (10mmol). Colourless solution was obtained. After 1 minute 10 mmol of methyl iodide was added after which the immediate formation white ppt. was observed. The solution was maintained under stirring about 3 hrs. at room temperature. The solvent was evaporated to obtain a pure product which is characterized by TLC n-hexane : ethyl acetate (1:1).

ii) Synthesis of 3-(4-chlorophenyl)-5-(ethyl thio)-1 *H*-1,2,4-triazole (PA2)

3-(4-chlorophenyl)-1*H*-1,2,4-triazole-5-thiol (S1) 10mmol synthesized in step II were dissolved under stirring in 100 ml of ethanolic solution of sodium (10mmol). Colourless solution was obtained. After 1 minute 10 mmol of ethyl iodide was added after which the immediate formation white ppt. was observed. The solution was maintained under stirring about 3 hrs. at room temperature. The solvent was evaporated to obtain a pure product which is characterized by TLC n-hexane : ethyl acetate (2:1).

iii) Synthesis of 5-(methyl thio)-3-(4-nitrophenyl) -1 *H*-1,2,4-triazole (PA3)

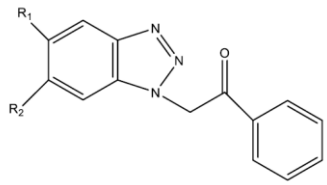
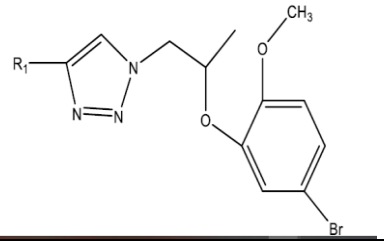
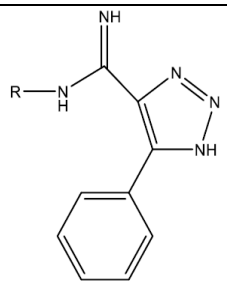
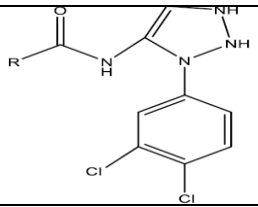
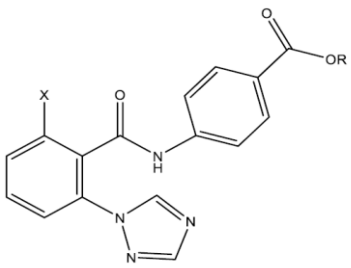
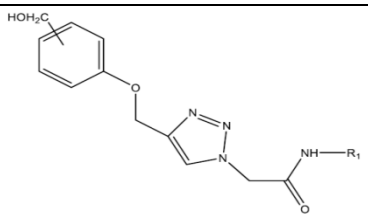
3-(4-nitrophenyl)-1*H*-1,2,4-triazole-5-thiol (S2) 10mmol synthesized in step II were dissolved under stirring in 100 ml of ethanolic solution of sodium (10mmol). Colourless solution was obtained. After 1 minute 10mmol of methyl iodide was added after which the immediate formation white ppt. was observed. The solution was maintained under stirring about 3 hrs. at

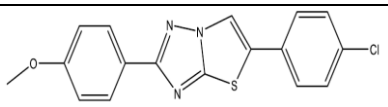
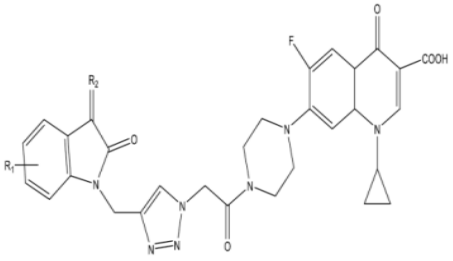
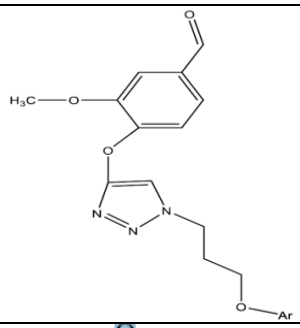
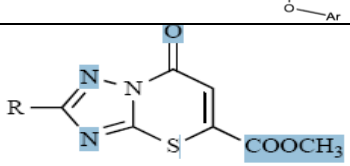
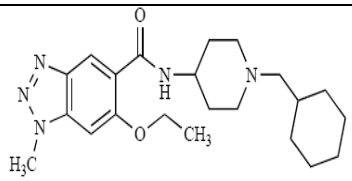
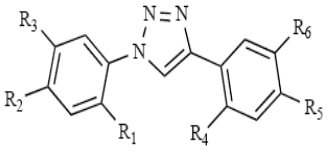
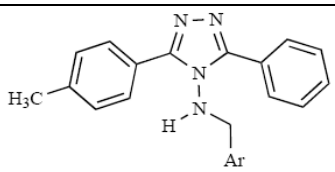
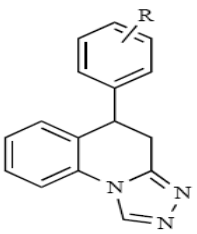
room temperature. The solvent was evaporated to obtain a pure product which is characterized by TLC n-hexane : ethyl acetate (2:1).

iv) Synthesis of 4-(5-(ethyl thio)-3-(4-nitrophenyl) -1 *H*-1, 2,4-triazol-3yl) aniline (PA4)

3-(4-aminophenyl)- 1 *H*-1,2,4-triazole-5-thiol(S3) 10mmol synthesized in step II were dissolved under stirring in 100 ml of ethanol solution of sodium (10mmol). Colorless solution was obtained. After 1 minute 10 mmol of ethyl iodide was added after which the immediate formation white ppt. was observed. The solution was maintained under stirring about 3 hrs. at room temperature. The solvent was evaporated to obtain a pure product which is characterized by TLC n-hexane: ethyl acetate (1:1).[29-33]

Pharmacological activities of 1,2,4- triazole derivatives

Sr. No.	Drug	Chemical Structure	Pharmacological activity	References
1	Benztriazole		Antidiabetic activity	12
2	1H-1, 2, 3-triazole		Antidiabetic activity	13
3	xanthone-triazole	------	Antidiabetic activity	14
4	1, 2, 3-triazole-5-carboxaimidamide		Antidiabetic activity	15
5	1, 2, 3-triazole amide		Antifungal Activity	16
6	1, 2, 3-triazole benzoyl arylamine		Antifungal Activity	17
7	1, 4-disubstituted 1, 2, 3-triazoles		Anticancer Activity	18

8	Triazole-benzimidazole-chalcone hybride sharing a chloro substituent and 1-n-benzyl-1, 2, 3-triazole	--------	Anticancer Activity	19
9	Triazole derivative.		Anticancer Activity	20
10	Hybride of ciprofloxacine-1,2,3-triazole		Antibacterial activity	21
11	Triazoles		Antibacterial activity	22
12	5-carbomethoxy-2-substituted-7*H*-1,2,4-triazolo[3,2-*b*]-1,3-thiazine-7-ones		**Analgesic Activity**	23
13	Triazole analogue of cinitrapride		**Anti-ulcer Activity**	24
14	Dicationic triazoles		**Antiprotozoal Activity**	25
15	4-arylidenamino-4*H*-1,2,4-triazole		Anticancer Activity	26
16	1,2,4-triazolo[4,3-□]-quinoline derivatives		**Anticonvulsant Activity**	27

Pharmacological Applications

Over the last few decades, the biological and pharmaceutical properties of 1,2,4-triazoles have been formed considerable attention in their synthesis and characterization. 1,2,4- Triazole and its derivatives possess widely different biological activities.[28]

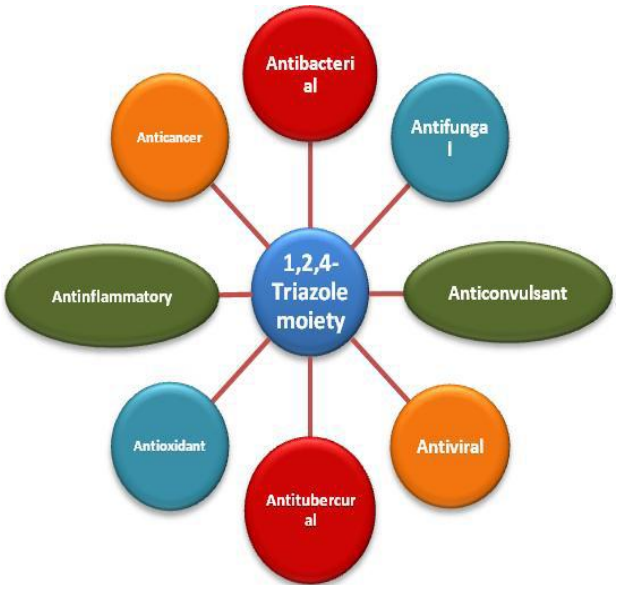


Fig. Pharmacological activities of triazole moiety.

DISCUSSION

The presented overview focuses on the design and synthesis of triazole derivatives with various synthetic and pharmacological activities as α-glucosidase inhibitors, mainly antibiotic, antiviral. Anticancer, analgesic, anticonvulsant, antiulcer, antibacterial, antifungal.

CONCLUSION

kinds of triazole compounds are used as antibacterial agents, cytotoxic agents, antihistamine agents, anticonvulsant agents, analgesics, anti-inflammatory agents, insecticides, antifungal agents, antimycobacterial agents, anticancer agents, antiprotozoal agents, antimalarials and antiulcers have made the subject of considerable attention. in medicinal chemistry. This review focuses on investigating the different synthetic strategies used to synthesize these compounds and their various biological applications over the past decade.

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