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Synthesis And Pharmacological Evaluation Of 1,2,4 Triazole

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Abstract: -
A variety of methods are constructive within a stable combination of 1, 2, 4-triazoles and such reactions have attracted a lot of interest in recent years. A literature study of 1, 2, 4-triazoles has shown that these extracts have a broad range of biological functions. In the last few decades, to include new heterocyclic compounds associated with their extracts that have been tested for its biological functions such as antimicrobial, antiviral, antitumor, anticonvulsant, antifungal, triazole moiety appears very small but within the biological profile. has attracted the attention of various researchers to examine this skeletal structure in its many strengths against several functions. This review focuses on synthetic strategies and pharmacological properties of 1, 2, 4-triazoles.

KEYWORDS:- Triazoles, 1,2,4-triazoles, Heterocycle compounds, Antifungal, Antimicrobial

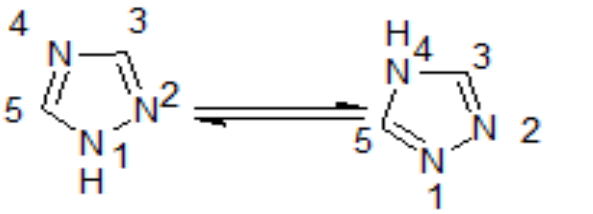
Introduction: -
The feat of imidazole as a prominent medicinal moiety (eg. Clotrimazole, Miconazole, and Losartan potassium) has led to the emergence of triazoles. Triazoles are the isosteres of imidazole in which the carbon atom of imidazole is isosterically replaced by nitrogen. Triazole derivatives are the promising heterocycles in the field of medicine

Heterocyclic chemistry is most challenging and amply rewarding field, and by far heterocycles are the largest class in organic chemistry. A majority of pharmaceuticals, biologically active agrochemicals, additives and modifiers used in industrial applications are heterocyclic by nature [1]. Synthetic organic chemists made significant progresses in discovering and developing wide range of heterocyclic compounds for the benefit of mankind. One remarkable structural feature and characteristic to heterocycles, which continue to be exploited, is their capability to accommodate the substituents around a central frame. Ever since their initial use in agriculture which began a century ago, the chemistry of nitrogen and sulfur containing heterocycles has made remarkable advances [2]. The pesticidal, fungicidal, antiviral and potential chemotherapeutic properties have been the inspiration for the overwhelming curiosity into the heterocyclic compounds in general, and the thiadiazoles, oxadiazoles, pyrazoles and triazoles in particular. Among the heterocyclic compounds, triazoles are one of the most key heterocycles exhibiting remarkable pharmacological activity as they are an essential constituent of all cells and living matter [3]. Triazole is a five-membered heterocyclic ring, which possesses three nitrogen atoms 1,2 and 4 positions. It is a much basic aromatic compound soluble in all organic solvents. The parent compound, triazole was synthesised for the first time by Fischer in 1878. Over 0.2 million 1,2,4-triazole derivatives have been reported in the literature and this class of organic compounds has become extraordinarily important due to their wide-ranging biological, agrochemical and chemical properties.The

advances in the synthesis and pharmacological activity of 1,2,4-triazoles from time to time have also been reviewed [4-8].

Tautomers of 1,2,4-triazoles

1, 2, 4-Triazoles have two tautomeric forms: 1H-1, 2, 4triazole (1) and 4H-1,2,4-triazole (2) [9]. Many studies have been indicated that is tautomer (1) more stable than tautomer (2) [10].



1*H* - tautomer (1) 4*H* - tautomer (2)

Spectroscopy of 1,2,4-triazole

NH2 Ultraviolet (UV), infrared (IR), nuclear magnetic resonance (NMR) and mass spectroscopic studies are very informative about the structure of 1, 2, 4-triazoles and their derivatives.

Ultraviolet spectroscopy (UV)

Holam and Straub, observed that in (UV) absorption spectrum,the un-substituted 1,2,4-triazole shows a very weak absorption at 205 nm. While in the case of N-acetyl1,2,4-triazole, Bathochromic shift occurs with the absorption band at 221.5 nm. A similar shift in the maximum absorption of 3,5-dimethyl-1,2,4-triazole appears in contrast with N-acetyl-3,5-dimethyl-1,2,4-triazole [11]

Infrared Spectroscopy (IR)

The infrared spectroscopy is very significant in characterization of triazole compounds. The absorption bands at 1570-1550 cm-1 due to N=N and in the region of 1600-1411 cm-1 due to C=N functions are the diagnostic features. In 5-substituted-4-amino-3-mercapto-1,2,4-triazoles, thion-thiol tautomeric forms can also be identified in IR spectra by the presence of C=S absorption band at about 1258-1166 cm-1 for thion and by characteristic SH absorption band at about 2700-2550 cm-1 for thiol forms. The primary N–H stretching vibrations have been observed as two weak absorption bands near 3350 cm-1 and 3250 cm-1 have also been found supportive of thion-thiol equilibrium. Also, the appearance of N–H bands in the regions of 3200-3100 cm-1

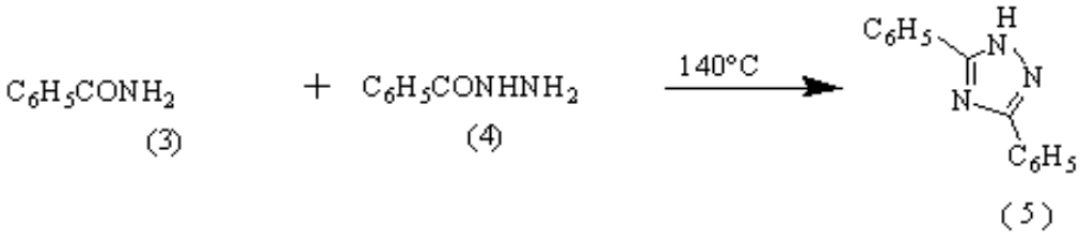
nuclear magnetic resonance (nmr)

Both 1H and 13C NMR are important to verify the structure of the derivatives, also they are useful in synthesis of isomers.

Method of synthesis: -

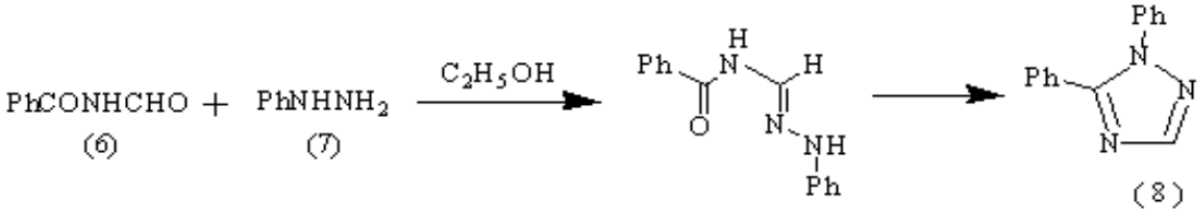
Pellizzari Reaction

The synthesis of 1,2,4-triazole derivatives by the mixture of amide and acyl hydrazide is generally referred to as the Pellizzari Reaction. It has been reported that heating the mixture of formamide and hydrazine hydrochloride with KOH yield of 1,2,4-triazole. For example benzamide and benzoyl hydrazide gave 3,5-diphenyl-1,2,4-triazole.[12-13]



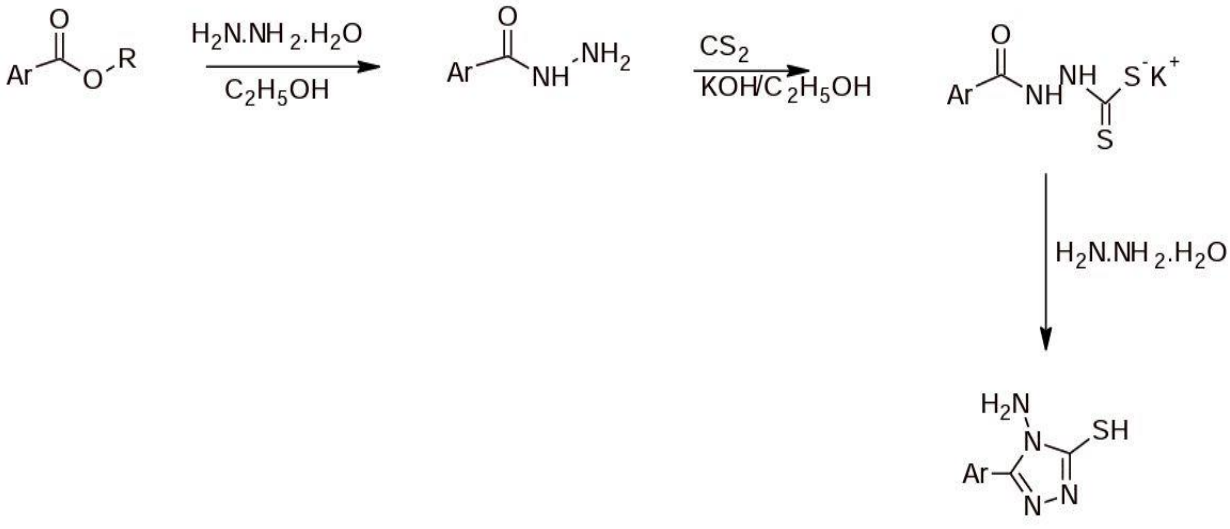
Einhorn- Brunner Reaction

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-diphenyl1,2,4-triazole [12-13]



Synthesis of 4-amino-3-mercapto- 5-substituted-1,2,4-triazole

A suspension of potassium dithiocarbazinate of the respective aromatic esters 2, (0.1 mol) in water (5 mL) and hydrazine hydrate (15 mL, 0.3 mol) was refluxed for 6–7 h with occasional shaking. The color of the reaction mixture changed to green with the evolution of hydrogen sulfide gas (lead acetate paper and odor). A homogenous reaction mixture was obtained during the reaction process. The reaction mixture was cooled to room temperature and diluted with water. On acidification with concentrated hydrochloric acid, the required triazole was precipitated. It was filtered, washed thoroughly with cold water, and recrystallized from ethanol. The completion of the reaction was monitored on TLC by using silica gel-G-coated plates by using ethyl acetate and petroleum ether as the eluent and observed in UV light.[14]



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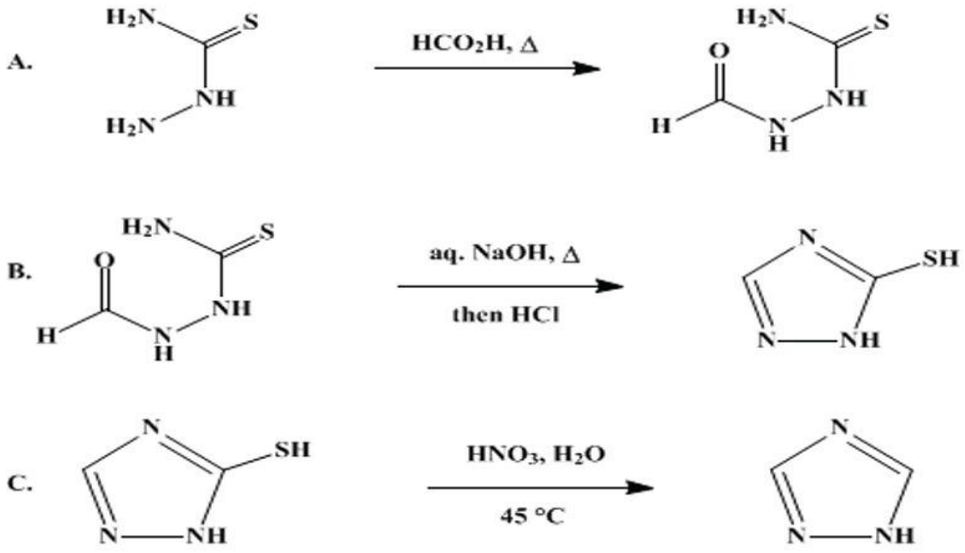
Cyclodehydration of thiosemicarbazides

A. 1-Formyl-3-thiosemicarbazide. Four hundred milliliters of 90% formic acid contained in a 2-l. round-bottomed flask is heated on a steam bath for 15 minutes, and then 182 g. (2 moles) of colorless thiosemicarbazide is added. The mixture is swirled until the thiosemicarbazide dissolves. The heating is continued for 30 minutes, during which time crystalline 1-formyl-3-thiosemicarbazide usually separates. Boiling water (600 ml.) is added, and the milky solution that results is filtered through a fluted filter paper. After standing for 1 hour, the filtrate is cooled in an ice bath for 2 hours, and the 1formyl-3-thiosemicarbazide that separates is collected by suction filtration and air-dried overnight. It weighs 170–192 g. (71–81%) and melts at 177–178° with decomposition.

B. 1,2,4-Triazole-3(5)-thiol. A solution of 178.5 g. (1.5 moles) of 1-formyl-3-thiosemicarbazide and 60 g. (1.5 moles) of sodium hydroxide in 300 ml. of water in a 2-l. round-bottomed flask is heated on a steam bath for 1 hour. The solution is cooled for 30 minutes in an ice bath and then is treated with 150 ml. of concentrated hydrochloric acid. The reaction mixture is cooled in an ice bath for 2 hours, and the 1,2,4-triazole-3(5)-thiol that precipitates is collected by suction filtration. The thiol is dissolved in 300 ml. of boiling water and the solution is filtered through a fluted filter paper. The filtrate is cooled in an ice bath for 1 hour, and the thiol is collected by suction filtration and air-dried overnight. The 1,2,4triazole-3(5)-thiol weighs 108–123 g. (72–81%) and melts at 220–222°. C. 1,2,4-Triazole. Caution! This preparation should be carried out in a ventilated hood to avoid exposure to noxious fumes.

C. A mixture of 300 ml. of water, 150 ml. of concentrated nitric acid, and 0.2 g. of sodium nitrite is placed in a 2-l. three-necked flask equipped with a stirrer and a thermometer. The stirred mixture is warmed to 45°, and 2 g. of 1,2,4-triazole-3(5)-thiol is added. When oxidation starts, as indicated by the evolution of brown fumes of nitrogen dioxide and a rise in temperature, a bath of cold water is placed under the reaction flask to provide coolin g and an additional 99 g. (total, 101 g.; 1 mole) of 1,2,4triazole-3(5)-thiol is added in small portions over the course of 30–60 minutes. The rate of addition and the extent of cooling by the water bath are so regulated as to keep the temperature close to 45–47° all during the addition. The water bath is kept cold by the occasional addition of ice. When the addition is completed, the bath is removed and stirring is continued for 1 hour while the reaction mixture gradually cools to room temperature. Sodium carbonate (100 g.) is added in portions, followed by the cautious addition of 60 g. of sodium bicarbonate. The water is removed from the slightly basic solution by heating the solution in a 3-l. round-bottomed flask under reduced pressure on a steam bath. To aid in removing the last traces of water, 250 ml. of ethanol is added to the residue and the mixture is heated under reduced pressure on a steam bath until it appears dry. The residue is extracted twice with 600 ml. of boiling ethanol to separate the triazole from a large amount of inorganic salts. This extract is evaporated to dryness on a steam bath under reduced pressure, and the resulting residue is extracted with two 500-ml. portions of boiling ethyl acetate. The ethyl acetate extract is evaporated to dryness on a steam bath under reduced pressure. The crude 1,2,4-triazole remaining in the flask is dissolved by heating it with 50 ml. of absolute ethanol, and then 1 l. of benzene is added. The mixture is heated under reflux for 15 minutes, and the hot solution is filtered through a fluted filter paper. This extraction procedure is repeated. The two extracts are combined, cooled in an ice bath for 30 minutes, and filtered to remove colorless crystals of 1,2,4-triazole (m.p. 120–121°), weighing 28–30 g. after being dried in air. About 300 ml. of the filtrate is removed by slow distillation through a Claisen still-head to remove the bulk of the ethanol. The residual solution is cooled in an ice bath for 30 minutes and filtered to separate an additional 8–10 g. of colorless 1,2,4-triazole, m.p. 119120°. The total weight of 1,2,4-triazole is 36–40 g. (52–58% yield). [15-31]



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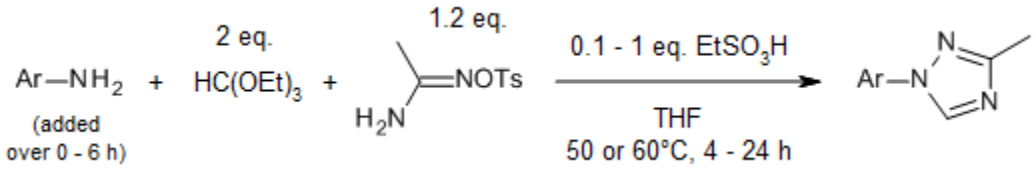
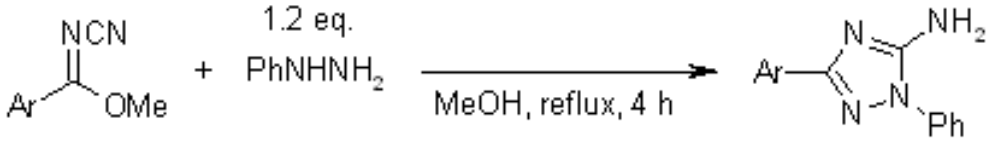
A multicomponent process enables the synthesis of 1-aryl 1,2,4-triazoles directly from anilines, amino pyridines, and pyrimidines. The reaction scope was explored with 21 different substrates. [32]



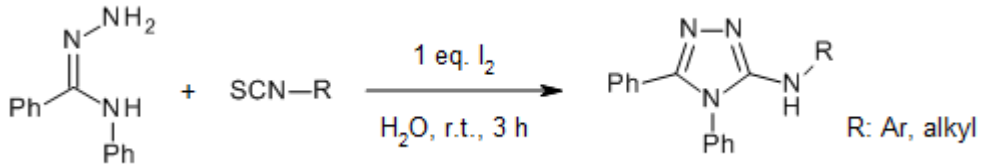
(11)

Mild, one-pot cyanoimidation of aldehydes using cyanamide as a nitrogen source and NBS as an oxidant was achieved in high yields without the addition of a catalyst. Subsequently, the substituted N-cyanobenzimidate products may also undergo a cyclization reaction to give 1,2,4-triazole derivatives in high yields.[33]



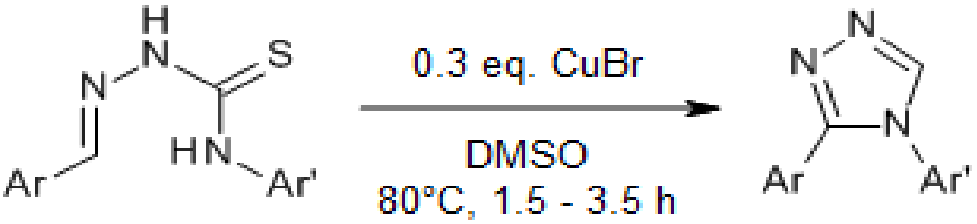
(12)

I_2 mediated oxidative C-N and N-S bond formations in water enable a metal-free, environmentally benign and convenient strategy for the synthesis of 4,5-disubstituted/N-fused 3-amino-1,2,4-triazoles and 3-substituted 5-amino-1,2,4-thiadiazoles from isothiocyanates.[34]



(13)

cu(II) catalyzes the construction of 4,5-disubstituted 1,2,4-triazole-3-thiones from arylidenearylthiosemicarbazides. Upon prolonging the reaction time, the in situ generated thiones are transformed to 4,5-disubstituted 1,2,4-triazoles via a desulfurization process.[35]



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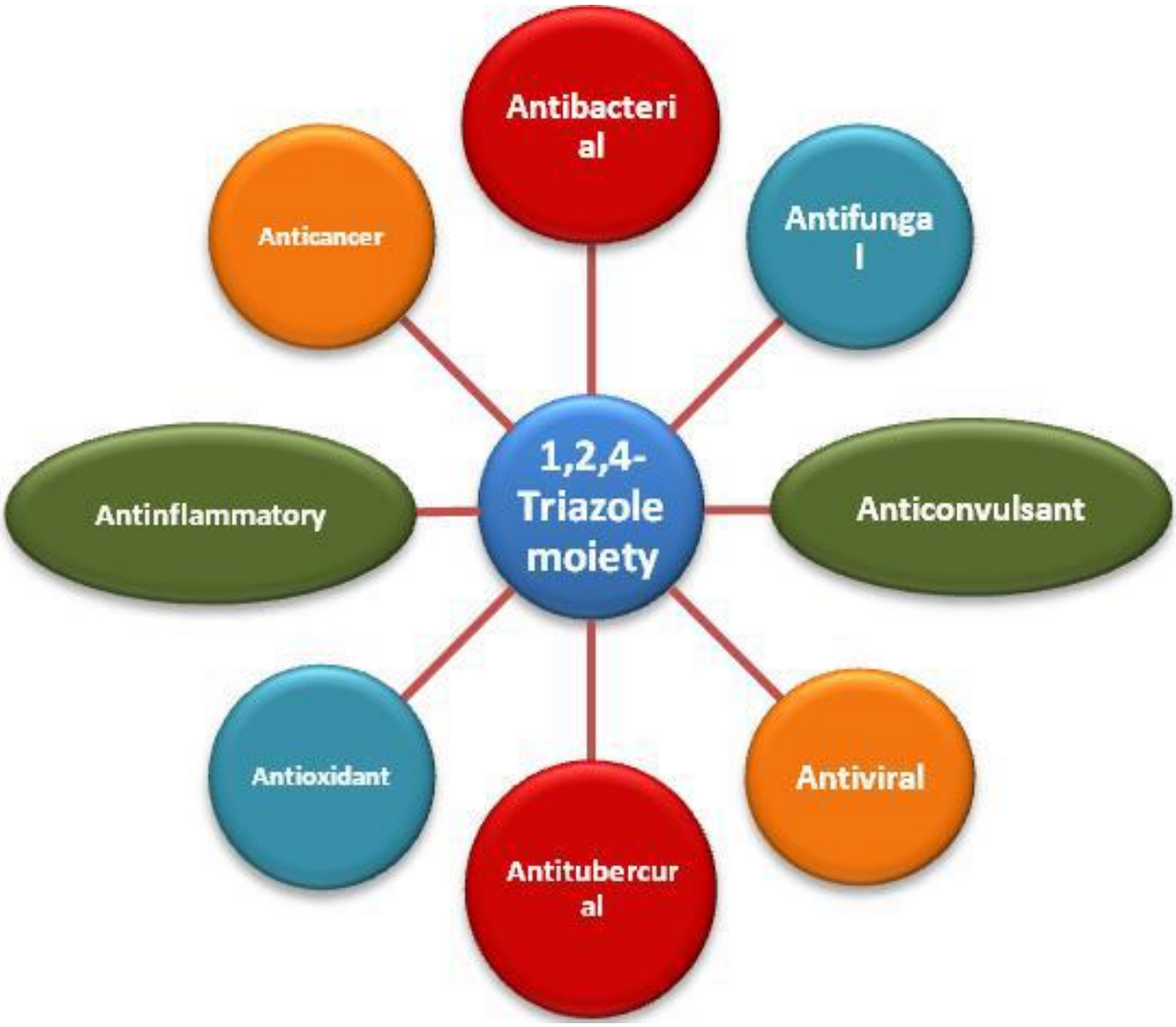
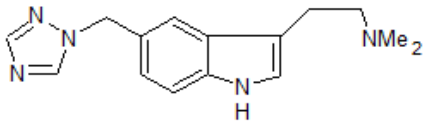
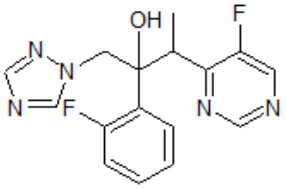


Fig.1 Significant pharmacological activities of 1,2,4-triazole derivatives

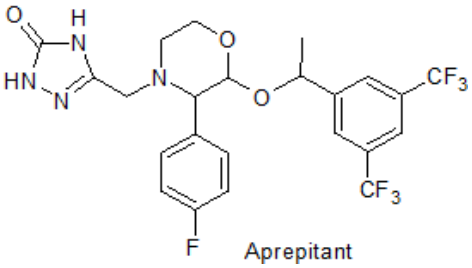
Active pharmaceutical products containing 1,2,4-triazole ring



Rizatriptan benzoate



Voriconazole



Aprepitant

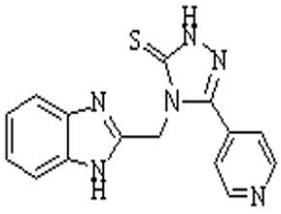
Applications and pharmacological Activities: -

1,2,4-Triazole and its derivatives are an imperative type of compounds whichnpossess environmental industrial, agricultural and pharmacological activities, including, antifungal, antibacterial, antitubercular, anticancer, anti-oxidant,anti-inflammatory,antiviral,anticonvulsant activities.

Antibacterial Activity

After years of mistreatment and overuse of antibiotics,bacteria are becoming antibiotic resistant, resulting in a potential global health disaster. It is recommended to use new antibacterial agents with enhanced broad-spectrum potency. Therefore, recent efforts have been directed toward exploring novel antibacterial agents.Many antibiotics are now chemically modified from original compounds present naturally. They are classified in two types based on their mode of action as bactericidal agents (kill bacteria directly) and bacteriostatic agent (stop bacteria from growing) [36]

Barot et al synthesized a series of novel 1,2,4-triazole-5-thione derivatives of benzimidazole (13) and were evaluated for antibacterial and antifungal activities. Some of the synthesized compounds showed good antibacterial and antifungal activities with 2.0 and 2.5 g/ml MIC, respectively. Stains used were Bacillus cereus, Enterococcus faecalis, S. aureus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia for the antibacterial activity and Candida albicans, Aspergillus niger and Fusarium oxyspora for the antifungal activity. Ofloxacin and Metronidazole were used as standard for antibacterial activity and Fluconazole was used as standard for antifungal activity[37]



R- $-C_6H_5$; $-CH_2C_6H_4$; $-CH_2CH_2OCH_3$

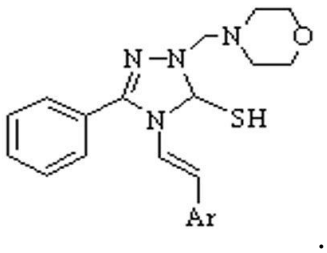
(15)

Antifungal activity

Antifungals are the class of drugs that are used to eradicate fungal infections from the human body. Fungi are heterotropic microorganisms that are distinguished from algae by lack of photosynthetic ability. Fungi include

both yeast and moulds. The former are spherical, oval and mucosid colonies in agar medium and the latter consists of elongated cells that usually reproduce by budding and forming branches of cells.

Gupta et al afforded a series of 4-(4- substituted benzylideneamino)-2-(morpholinomethyl). 5(substituted phenyl)-2H-1,2,4-triazole-4(4H)thione (12) by the reaction of corresponding Schiff base with formaldehyde and morpholine with the formation of iminium ion. The investigation of antifungal screening data revealed that five compounds are more potent than fluconazole (standard antifungal drug) for A. niger with MIC value 64 µg/ml. Some synthesized compounds are equipotent as fluconazole against C. albican with MIC value of 32 µg/ml. The good activity is attributed to the presence of electronegative group, 4-chloro and 2,4-dichloro groups at aryl moiety attached to 5th position of triazole nucleus.[38]



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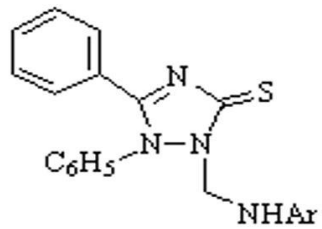
Antitubercular activity

Tuberculosis is still a major treat to mankind. The increasing problem of Multi-Drug Resistant-tuberculosis has focused attention on developing new drugs that are not only active against drug resistant tuberculosis, but also shorten the lengthy therapy. There is urgent need and significant interest in developing new tubercular drugs. In developing new tubercular drugs, it is essential to think about which targets in the tubercule bacillus are good drug targets.[39]

Godhani-et-al synthesized a series of 2-((arylamino)methyl)-5-(3-methoxyphenyl)-1-phenyl-1H-1,2,4-triazole-3-thione (17) and screened for antitubercular activity against Mycobacterium tuberculosis H37Rv strain by using LJ slope method. Fourcompounds shown good anti-tubercular activity at 250 g/ml concentration compared to standard drug Isoniazid. The activity depends upon electronegative nature of substituent groups[40]



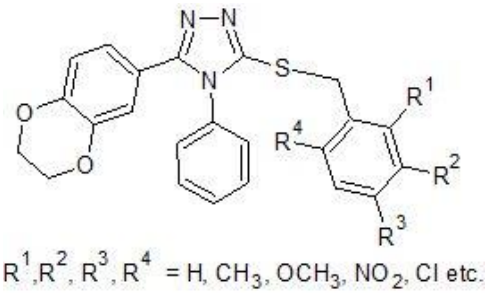
Ar- 4-NO_2-C_6H_4; 4-CH_3-C_6H_4; 4-F-C_6H_4; 3-Cl-C_6H_4

(17)

Anticancer activity

Cancer is uncontrolled proliferation of cells which may be benign or malignant type. The uncontrolled division of cells is due to the defect in the DNA of cells which may be inherited or due to environmental factors. Over 1.5 million new cancer cases are estimated in the united states. There is multiple form of cancers many of which can be treated. A wide variety of drugs are available clinically to treat cancer but still there is a need of cytotoxic drug selective to the cancer with minimal effect to the normal cells. Therefore, there is a need to develop effective medicine to treat the uncontrolled growth of abnormal cells without affecting the activity of normal cells [41]

Ya-Ping Hou et al., have screened a series of 1,2,4-triazole derivatives containing 1,4 benzodioxan (18)for their ability to anti proliferative activity against HEPG2, HELA, SW1116 and BGC823 [42]. The tested compounds show potent activities against HEPG2 than other three cancer cell lines. Analysis of structure-activity relationship (SAR) indicates that compounds with electron-withdrawing group show stronger activity than that with electron-donating group, with all the IC50 values below 50 lM against HEPG2. Compounds with different electron-withdrawing groups, are able to portray different antitumor activities, and the potency order follows F (fluorine) >Cl (chlorine) > Br (bromine)> NO2 (nitro-group). With regard to the F-substituted compounds, monosubstitution is preferred over di-substitution. The placement of substituents based on their effects is ortho- > meta- >para-. The work is continued with MetAP2 inhibitory assay, apoptosis assay, and Western-blot assay..

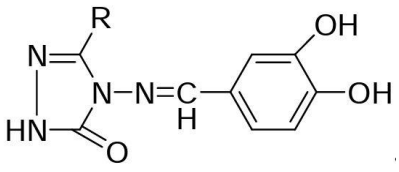


(18)

Antioxidant activity

Damage to cells caused by free radical is supposed to play an essential role in the aging process and in disease development. antioxidants are our first line of protection against free radical damage, The antioxidants became even more critical with amplified exposure to free radicals. pollution, cigarette smoke, drugs, illness, stress and even exercise can increase free radical exposure[43].

Yuksek, H. et al[44] some 4-benzyl-idenamino-4,5-dihydro-1H-1,2,4-triazole-5-one derivatives (19) and investigated for antioxidant property. Their study indicatesthat the compounds with phenyl substitute group possess good antioxidant property**.**

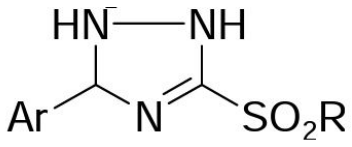


(19)

Anti-inflammatory activity

Therapeutic use of non-steroidal anti-inflammatory drugs (NSAIDs) which are used in treatment of a number of arthritic diseases is limited because of their side effects, such as, gastrointestinal haemorrhage and ulceration. So, new drugs having effective anti-inflammatory activity with minimum side effects have been developed [45]

Birsen Tozkoparan et al[46] prepared a series of 5-aryl-3-alkylthio-1,2,4-triazoles (20) and corresponding sulfones, these compounds showing better significant analgesic–antiinflammatory activity with minimum ulcerogenic risk.

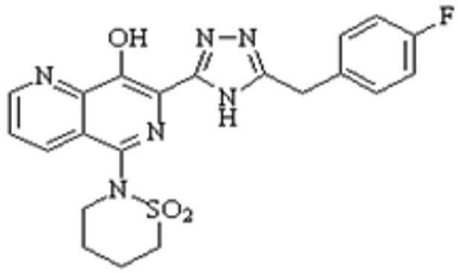


(20)

Anti-viral activity

Antiviral drugs are a class of medication used specifically for treating viral infections. specific antivirals are used for specific viruses [47].

Johns et al synthesized a series of HIV-1 integrase inhibitors containing a novel metal binding motif consisting of the 8-hydroxy-1,6-naphthyridine core and triazole (21). The synthesized compounds were subjected to antiviral activity. A preliminary examination of C5 substitution showed significant improvements in antiviral activity[48].



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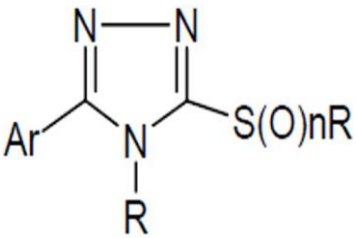
Anticonvulsant activity

John M Kane et al. Reported the preparation of a series of isomeric alkylthio-1, 2, 4-triazole derivatives and evaluation of anti-convulsant activity [49].



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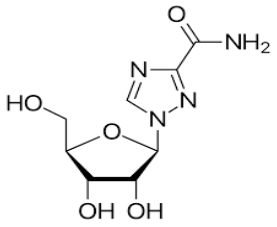
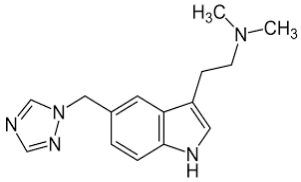
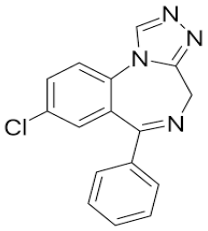
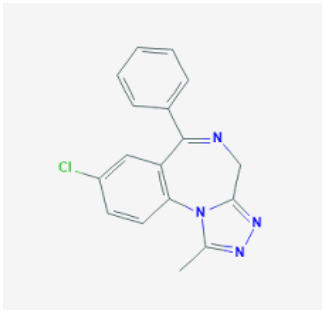
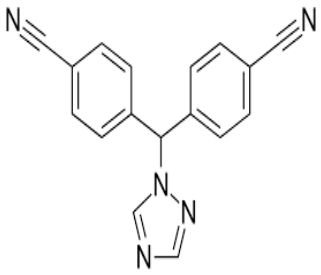
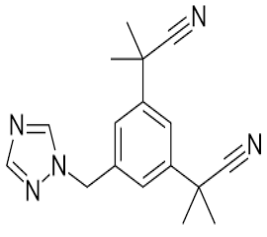
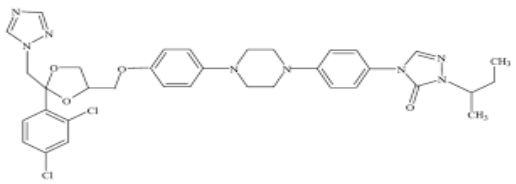
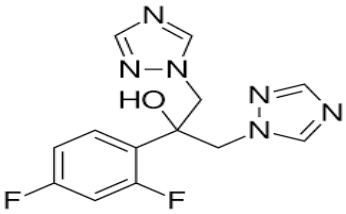
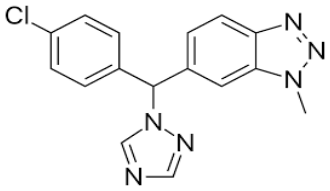
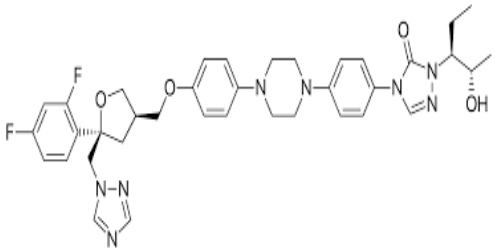
Clinically used 1,2,4-triazole containing drugs;-

Sr. no.	Drug	Chemical structure	Pharmacological activity
1	Ribavirin		Antiviral
2	Rizatriptan		Anti-migraine
3	Estazolam		Anxiolytic
4	Alprazolam		Anxiolytic
5	Letrozole		Breast cancer
6	Anastrozole		Breast cancer

7	Itraconazole		Anti-fungal
8	Fluconazole		Anti-fungal
9	Vorozole		Aromatase inhibitor
10	Posaconazole		Anti-fungal

Conclusion

Triazoles have pronounced biological and medicinal significance, and occupy unique place in the organic chemistry and our lives. With the enormous literature continuously accumulating over the years, the chemistry of triazoles sus-tains to be a promising field in the years to come. The multi-purpose synthetic applicability and pharmaceutical activity of these heterocycles will facilitate the medicinal chemists to plan, design and implement new approaches towards the discovery of novel drug.

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