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Ministry Of Higher Education And Scientific Research
University Of Basra
College Of Pharmacy

Graduation Project Report On
Triazole applications

Under the guidance of
Dr. Seta Azad

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Department of Pharmaceutical chemistry
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Certification of the Supervisor

I certify that this project entitled " Triazole Applications" was prepared by the fifth- year students Zainab Mohammad, Zainab Hussein, Zahraa Hashim and Manar Raad under my supervision at the College of Pharmacy/University of Basra in Pharmaceutical chemistry.

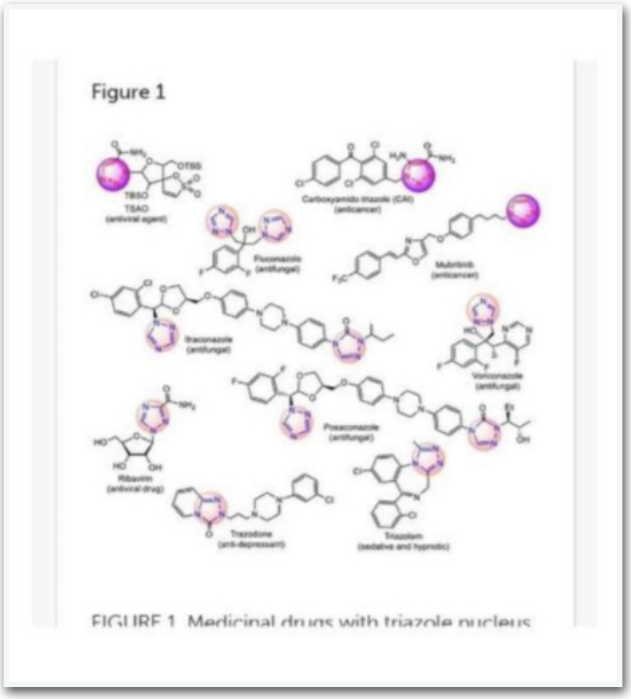
Supervisor name
Dr. Seta Azad

Abstract

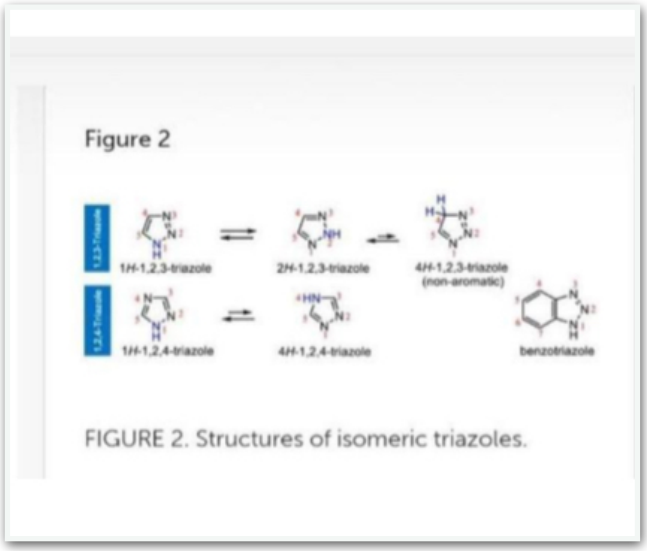
Among the nitrogen-containing heterocyclic compounds, triazoles emerge with superior pharmacological applications. Structurally, there are two types of five- membered triazoles:
1,2,3-triazole and 1,2,4-triazole. Due to the structural characteristics, both 1,2,3- and 1,2,4-triazoles are able to accommodate a broad range of substituents (electrophiles and nucleophiles) around the core structures and pave the way for the construction of diverse novel bioactive molecules. Both the triazoles and their derivatives have significant biological properties including antimicrobial, antiviral, antitubercular, anticancer, anticonvulsant, analgesic, antioxidant, anti-inflammatory, and antidepressant activities. These are also important in organocatalysis, agrochemicals, and materials science. Thus, they have a broad range of therapeutic applications with ever-widening future scope across scientific disciplines. However, adverse events such as hepatotoxicity and hormonal problems lead to a careful revision of the azole family to obtain higher efficacy with minimum side effects. This review focuses on the structural features, synthesis, and notable therapeutic applications of triazoles and related compounds.

INTRODUCTION

The name triazole was first coined by Bladin in 1885 to assign the five-membered three nitrogen-containing heterocyclic aromatic ring system having molecular formula C2H3N3 (Bladin, 1885). After the discovery of triazole, its chemistry was developed gradually and speeded up with the establishment of several facile and convenient synthetic techniques along with its versatile interaction with biological systems (Aneja et al., 2018; Shafiei et al., 2020; Farooq, 2021). For example, discovery of antifungal activities of azole derivatives in 1944 (Woolley, 1944) led to the invention of fluconazole, itraconazole, voriconazole, posaconazole, efinaconazole, etc. (Figure 1; Zonios and Bennett, 2008). Of these, voriconazole and posaconazole are active against fluconazole-resistant strains of Candida. The mechanism of such antifungal action is also well- established which involves the inhibition of ergosterol synthesis and blocking of the P450-dependent enzyme (CYP 51) (Odds et al., 2003). Triazole-type ring structure(s) can coordinate with the heme iron of the CYP enzyme (Zhang et al., 2014)



In addition, triazole heterocyclic structures are found to form many weak nonbond interactions with the receptors and enzymes in biological systems (Hitchcock et al., 1990). These inherent properties of triazole compounds have established them as key chromophores with immense medicinal value and attract scientists of all disciplines, including chemical, agricultural, supramolecular, pharmaceutical, polymer, and materials sciences (Chang



et al., 2011). Among the medicinal drugs, triazole- based antibacterial, antifungal, antiviral, anti-inflammatory, anticoagulant, antitubercular, antidiabetic, antioxidant, and anticancer drugs are available (Kumar et al., 2021). The appearance of multidrug-resistant (MDR) pathogens, especially, resistance to triazole drugs makes microbial treatment less effective, a worse prognosis of infection, and problematic (Sagatova et al., 2016). For example, Candida albicans and Candida krusei strains (responsible for 75-88% of fungal infections) are resistant to the most common azole drug fluconazole (Berkow and Lockhart, 2017). Azole-derived several drugs have also become resistant against A. fumigatus and C. glabrata strains (Faria-Ramos et al., 2014 n addition, many adverse effects such as rash, diarrhea, headache, hepatotoxicity, and gastrointestinal problems including several severe problems (heart failure, renal failure, liver problems, Stevens-Johnson syndrome, etc.) are reported for many triazole drugs (Yang et al., 2021). Thus, the prudential development of new triazole drugs with bioisosteric replacement and molecular hybridization is necessary to overcome MDR pathogens and reduce the side effects of the available drugs. In this review, structural features, synthetic approaches, and biological properties of 1,2,3- and 1,2,4-triazoles are discussed, highlighting the related research works since 2015. Chemistry of Triazoles Due to a wide range of applications across scientific disciplines, triazoles gained an exceptional structural motif and are notably related to the chemistry of triazoles. The basic skeleton of triazoles comprises a five-membered heterocyclic ring consisting of two carbon and three nitrogen atoms with the molecular formula C2H3N3. In the five- membered ring, a maximum of two types of positional arrangement of nitrogen atoms led to the formation of two substantial isomers, namely, 1,2,3-triazole (v- triazole) and 1,2,4-triazole (s-triazole). Each of them shows mainly two tautomers depending on the hydrogen bonded to ring nitrogen (Figure 2). The 4H-1,2,3-triazole structure is

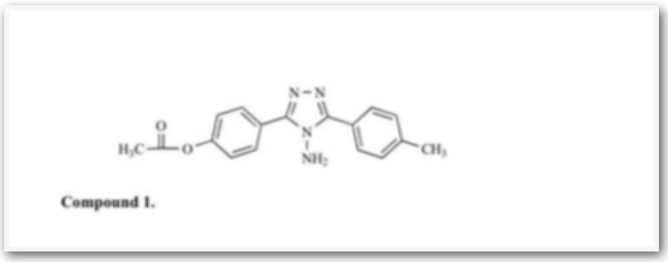
nonaromatic and hence is discarded. All the atoms in both the triazoles are in sp2 hybridized and are planar. Six pi (r) electrons are available in both forms, which are delocalized around the ring to generate their aromatic character. Moreover, the presence of 3 N atoms makes triazoles energy-rich heterocycles (Tao et al., 2009; Gao and Shreeve, 2011)

When a benzene ring is fused at the 4,5-positions of 1,2,3-triazoles, it is termed benzotriazoles (Figure 2). In the monocyclic 1,2,3-triazoles, both 1H- and 2H-1,2,3- triazoles are generally in equilibrium in both solution and gas phases and exist as an equimolar mixture in the solid state. However, in an aqueous solution, 2H-1,2,3- triazole exists as major compared to the other tautomer (2H:1H = 2:1) (Albert and Taylor, 1989). The parent 1H-1,2,3-triazole is a clear liquid with a bp of 203˚C (Ram et al., 2019), computed topological polar surface area of 41.6 Å2, and is soluble in H2O. Most of the 1,2,3-triazoles are prepared from azides. The presence of one pyrrole- type and two pyridine-type nitrogen atoms makes 1,2,3-triazole rings very stable and difficult for quaternization. It easily undergoes electrophilic substitution at carbon or at nitrogen. In 1,2,4-triazoles, the parent 1H-1,2,4-triazole is a white powder solid (mp 120-121°C, bp 260°C). Like 1H-1,2,3-triazole, it is very soluble in water. It is also soluble in organic solvents. The two tautomers (1H- and 4H-) of 1,2,4-triazoles are in rapid equilibrium. However, 1H-1,2,4- triazole is more stable than the 4H-1,2,4-triazole (Potts, 1961). Chemically, 1H-1,2,4-triazole shows both electrophilic and nucleophilic substitution reactions. Due to high electron density, electrophilic substitution occurs at nitrogen atoms only. Under mild reaction conditions, nucleophilic substitution occurs at both the ring carbon atoms. This is because both the ring carbon atoms are attached to two electronegative nitrogen atoms and become л-deficient, which makes them susceptible to nucleophiles. Synthetic Approaches Huge applications, promising research directions, and lower molecular toxicity of various triazoles and their derivatives have promoted the researchers to design many synthetic strategies. Availability of reagents and simplicity of synthetic procedures justified the fact. 1,2,3- Triazole Analogs In neoteric chemistry, the 1,2,3-triazole group is one of the most significant functional aromatic heterocyclic systems.

BIOLOGICAL ACTIVITIES OF TRIAZOLE DERIVATIVES

Antimicrobial Activity

Gumrukcuoglu et al. [70] have reported a series of 4- amino-3,5-dialkyl-1,2,4-triazoles of the type (Compound 1) and evaluated them for antimicrobial activity.



Compound 1.

The antibacterial activity of novel 1-triazolylethyl- benz[g]indole derivatives of the type (Compound 2) was reported [71] by Bhovi et al. Kagoshima et al. [72] have studied antifungal activity of the following novel water- soluble prodrug of antifungal triazole (Compound 3).

Compound 2.

Compound 3.

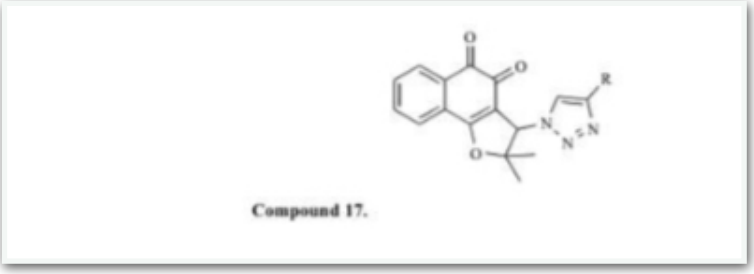
Kumar et al. [73] have reported the antifungal activity of the triazole, viz., 2-(3'- bromophenyl)-5-(p-bromophenyl) thiazolo[3,2-b]-s-triazoles (Compound 4). A new class of quinoline derivatives containing 1,2,4-triazole (Compound 5) moiety of 4- hydroxy-8-(trifluoromethyl)quinoline-3- carbohydrazide possessing antibacterial activity was reported [74] by Eswaran et al.

Compound 4.

Compound 5.

Cytotoxic Activity

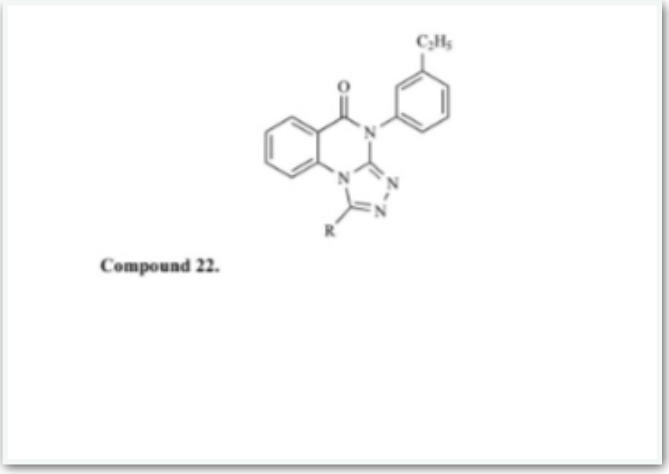
Junior et al. [86] have studied the cytotoxic activity of five nor--lapachone based 1,2,3-triazoles of the type (Compound 17) against six neoplastic cancer cell lines such as, SF-295 (central nervous system), HCT-8 (colon), MDAB-435 (melonama), HL- 60 (leukaemia), PC-3 (protease) and B-16 (murine melanoma). IC50 values ranging from 0.43 to 9.48 M were obtained. The great majority of the compounds are strongly or moderately cytotoxic against
all cancer cell lines within the range of 0.43 to 9.48 M



Compound 17.

Antihistaminic Activity

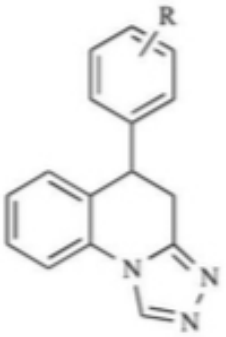
Alagarsamy et al. [91] have reported a series of novel 4- (3-ethylphenyl)-1-substituted- 4H-[1,2,4]triazolo[4,3-a]quin- azolin-5-ones of the type (Compound 22) and tested them for their in vivo H1-antihistaminic activity on conscious guinea pigs. All the test compounds protected the animals from histamine induced bronchospasm



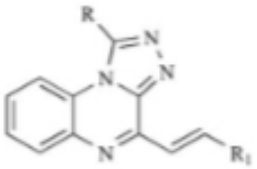
Compound 22.

Anticonvulsant Activity

Guan et al. [92] synthesized a new series of 1,2,4- triazolo[4,3-]-quinoline derivatives of the type (Compound 23) to meet the structural requirements essential for anticonvulsant properties. The compounds were screened for preliminary anticonvulsant activity. The compounds possessing electronegative group showed good activity when compared to the other compounds. These authors have concluded that the introduction of electron donor groups such as methyl or methoxy to the phenyl ring reduced anticonvulsant activity, whereas the electron acceptor groups such as –Cl or –F have increased the anticonvulsant activity. Wagle et al. [93] have reported the synthesis of some new 1-substituted-4-styryl[1,2,4]triazolo[4,3-a]- quinoxaline deri- vatives of the type (Compound 24) as potent anticonvulsants.



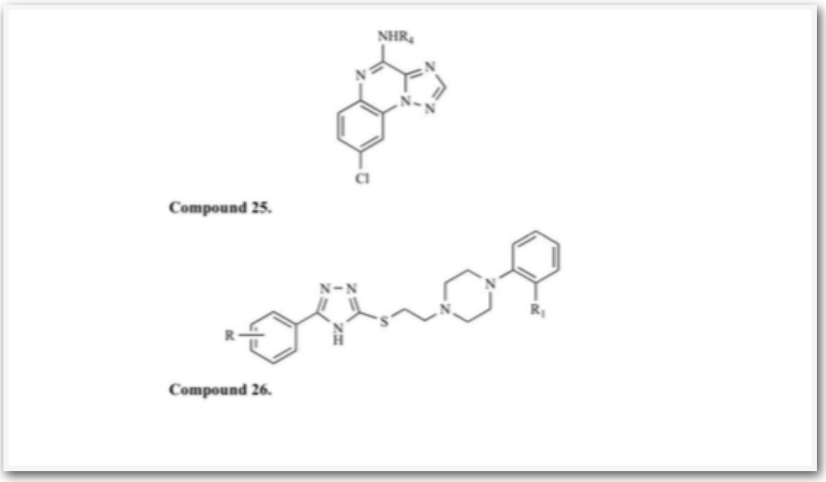
Compound 23.



Compound 24.

Receptor Binding Activity

Catarzi et al. [94] have reported the synthesis of a new set of 4-amino-8-chloro-1,2,4- triazolo[1,5-a]quinoxalines (Compound 25) containing at position-2 an ethyl carboxylate group or a hydrogen atom as a adenosine receptor antagonists. Salerno et al. [95] have reported the synthesis of new 5-phenyl[1,2,4]triazole derivatives (Compound 26) with the aim of obtaining new selective 5- HT1A ligands with reduced affinity for the 1-adrenoceptor subtypes. New compounds were tested in radioligand binding experiments where many of them showed preferential affinity for the 5- HT1A receptor.

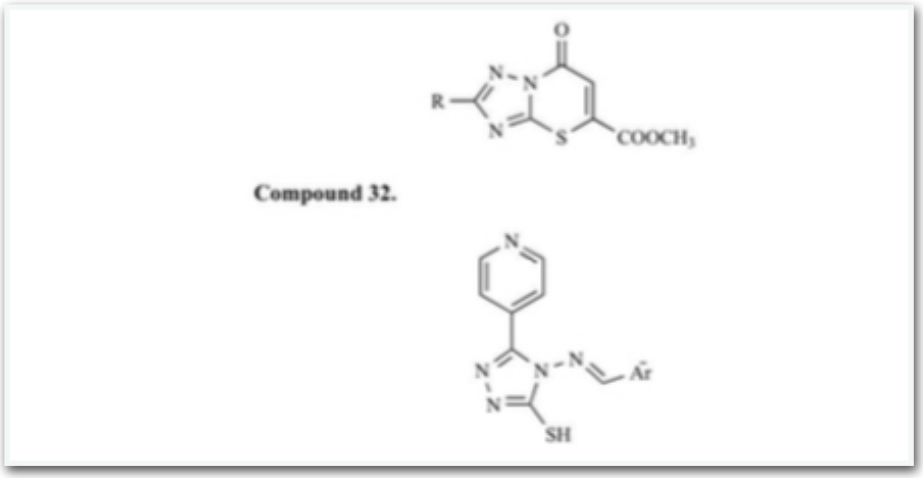


Compound 25.

Compound 26.

Analgesic Activity

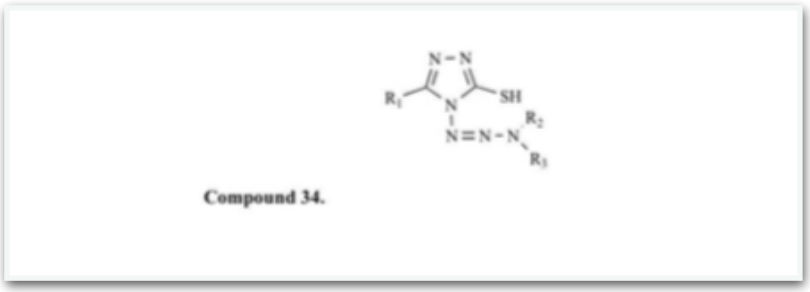
Tozkoparan et al. [101] have synthesized a series of 5-carbomethoxy-2-substituted- 7H-1,2,4-triazolo[3,2-b]-1,3- thiazine-7-ones (Compound 32). The compounds were screened for preliminary pharmacological assay to evaluate their analgesic activities. Siddiqui et al. [102] have synthesized various 4-[{1-(aryl)methylidene}-amino]-3-(4- pyridyl)-5-mercapto-4H-1,2,4-triazole derivatives of the type (Compound 33) starting from isonicotinic acid hydrazide. The synthesized compounds were screened for in- vivo analgesic activity by the tail-flick method.



Compound 32.

Anti-inflammatory Activity

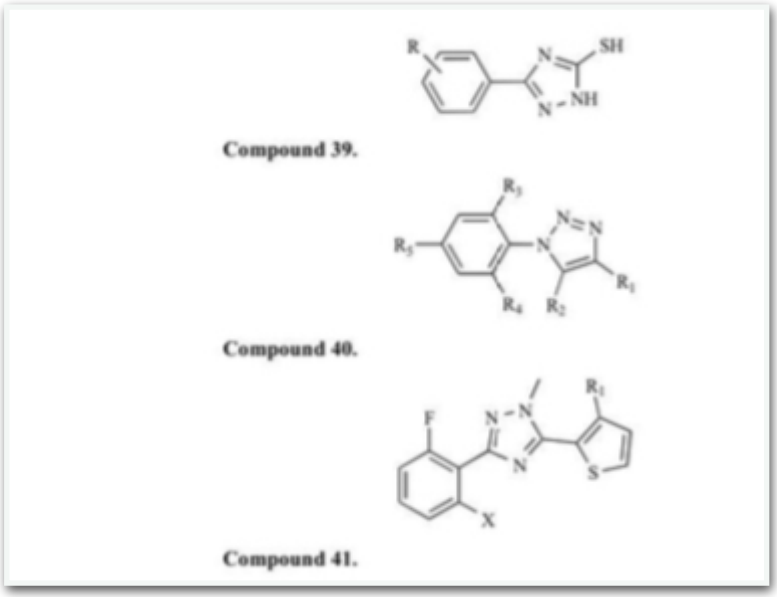
Goyal et al. [103] have reported some new derivatives of 3-substituted-4H-1,2,4- triazoles of the type (Compound 34) and evaluated for antiinflammatory activities. Most of the compounds showed potent and significant results compared to standard Ibuprofen.



Compound 34.

Insecticidal Activity

Chai et al. have synthesized some novel 1,2,4- triazole derivatives of the type (Compound 39) and studied their insecticidal activity. The compounds showed potent insecticidal activity against Aphis rumicis Linnaeus. Alam et al. have synthesized a series of 4- or 5-alkyl-(or phenyl)-1-phenyl-1H-1,2,3-triazoles of the type (Compound 40) and examined them for their ability to inhibit the specific binding of [3H]-4'-ethynyl-4-n-propylbicycloorthobenzoate (EBOB), a noncompetitive antagonist, to the housefly and rat GABA receptors, as well as to the 3-subunit homo- oligomer of the human GABA receptor. 4-substituted 1-phenyl-1H-1,2,3-triazoles were found to be more potent competitive inhibitors than the 5-substituted regioisomers in the case of all receptors. The 4-tert-butyl or 4-n-propyl analogue of 1-(2,6-dichloro-4-trifluoromethylphenyl)-1H- 1,2,3-triazole exhibited the highest level of inhibition of [3H]EBOB binding to all receptors. Thus the authors claim that 1-phenyl-1H-1,2,3- triazoles with the appropriate substituent exert insecticidal activity by selectively acting at the site for noncompetitive antagonism of insect GABA receptors. Cudworth et al.have reported the dihaloaryl triazole compounds of the type (Compound 41) as insecticides and acaricides agents.



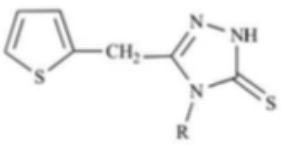
Compound 39.

Compound 40.

Compound 41.

Antimycotic Activity

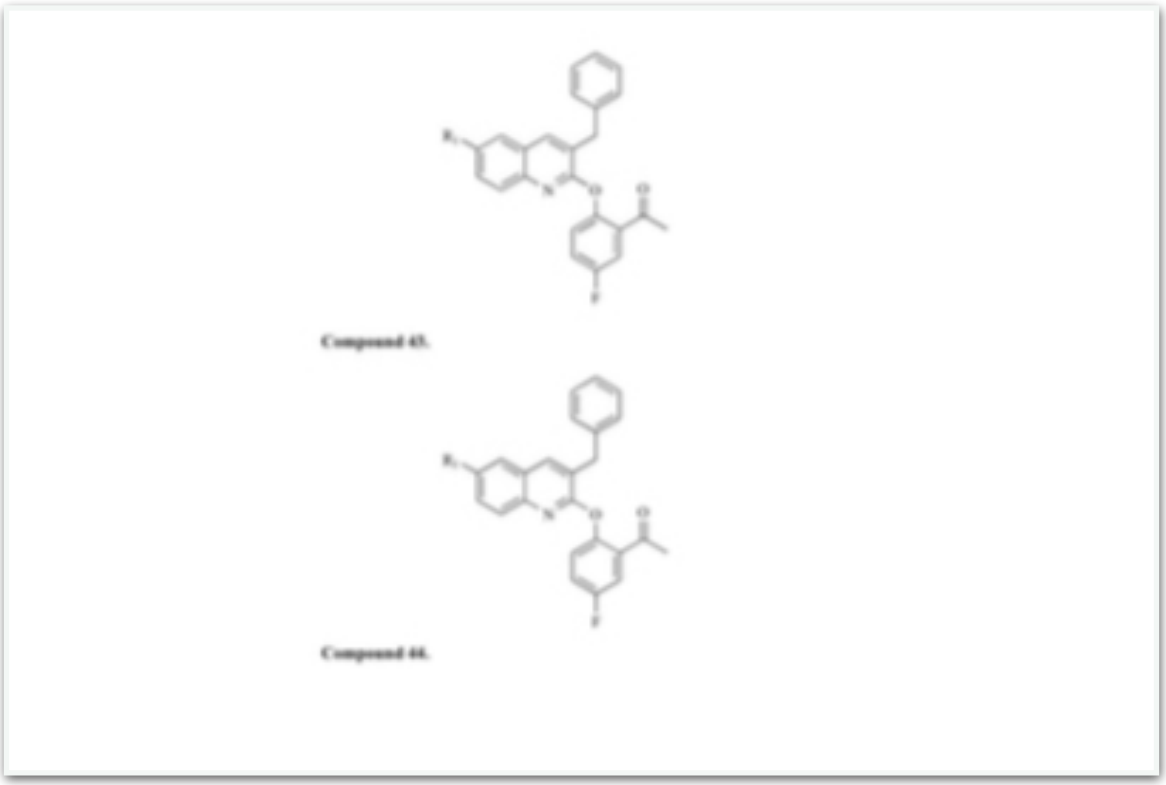
Wujec et al. [109] have carried out the reaction of hydrazide of thiophene-2-acetic acid with isothiocyanates and obtained thiosemicarbazides. Further cyclization with 2% NaOH led to formation of 4-substituted-3-(thiophene-2- yl-methyl)-1,2,4-triazoline- 5-thiones. The compounds of the type (Compound 42) showed promising antimycotic activity.



Compound 42.

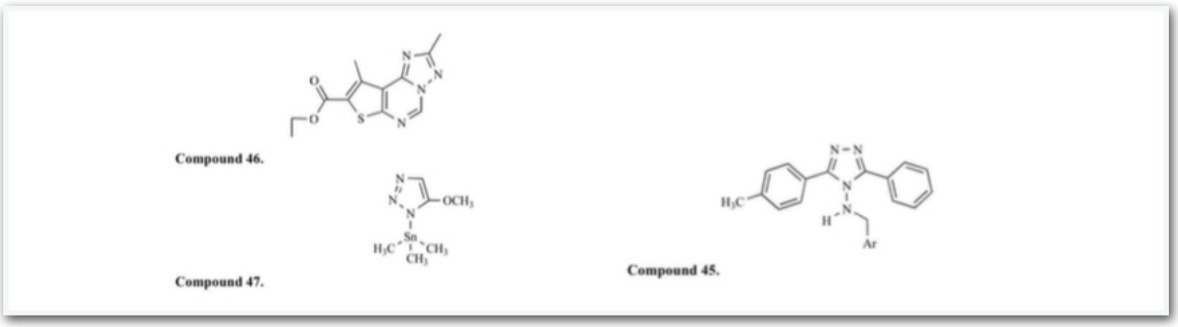
Antimycobacterial Activity

Upadhayaya et al. [110] have synthesized triazole compounds of the type (Compound 43) and studied their antimycobacterial properties. Compounds inhibited Mycobacterium tuberculosis H37Rv, at affixed concentration of 6.25 g/ mL. Molecular docking calculations suggest that critical hydrogen bonding and electrostatic interactions between the polar functional groups of the anti- mycobacterial compounds and amino acids of ATP – synthase of M. tuberculosis, could be the probable reason for observed anti-mycobacterial action.
Banfi et al. [111] have described the synthesis of new antimycobacterial and antifungal drugs that act by binding to sterol 14-demethylase the drug-target protein interactions using computer-based molecular simulations. Different series of triazole derivatives of the type (Compound 44) having an azomethine linkage to pyridine 2-carbomamidrazone were designed and synthesized. Molecular modeling investigations showed that the active new compounds may interact at the active site of both the fungal and the mycobacterial cytochrome P450-dependent sterol-14- demethylase. It is also observed that the calculated binding free energy values are in agreement with the corresponding MIC value.



Anticancer Activity

Bekircan et al. [112] have synthesized a series of 4-arylidenamino-4H-1,2,4-triazole derivatives of the type (Compound 45). The compounds were tested for anticancer activity against MCF7, NCI-H460 and SF-268 cancer cell lines. Shaaban et al. [113] have synthesized new derivatives of triazolothieno[2,3-d]pyrimidines of the type (Compound 46) and evaluated for their antitumor activity against iv-vitro cell lines, (HEPG-2 and MCF-7). Compounds showed significant in-vitro cytotoxic activity against hepatocellular carcinoma compared to the reference drug Doxorubicin. The antitumor activity of triazole derivatives of the type (Compound 47) was evaluated, in vitro against human solid tumor cell lines such as breast cancer (MCF 7) and liver cancer (HEPG 2). The compounds showed values close to that recorded by the reference drug Doxorubicin.



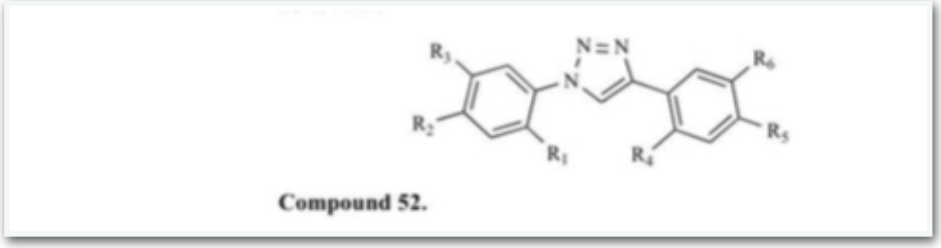
Compound 46.

Compound 47.

Compound 45.

Antiprotozoal Activity

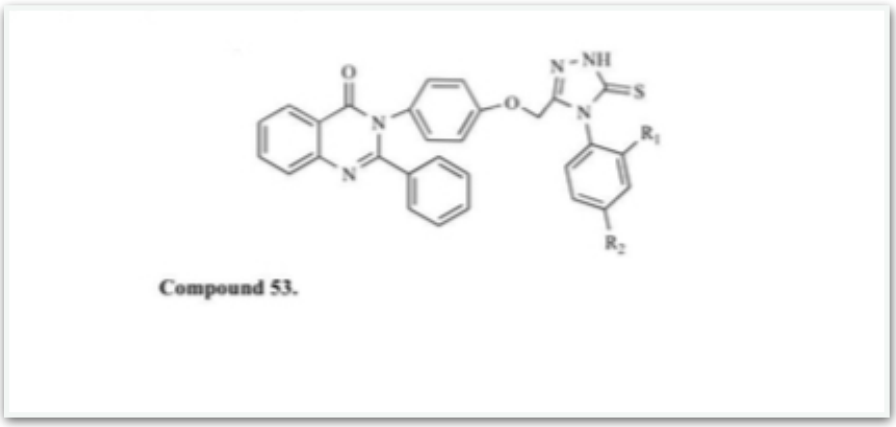
Bakunov et al. [117] synthesized some novel dicationic triazoles of the type (Compound 52) by the Pinner method from the corresponding dinitriles, prepared via the copper(I)- catalyzed azide-alkyne cycloaddition (CuAAC). The type and the placement of cationic moieties as well as the nature of aromatic substituents influenced in vitro antiprotozoal activities of compounds against Trypanosoma brucei rhodesiense, Plansmodium falciparum and Leishmania donovani.



Compound 52.

Antimalarial Activity

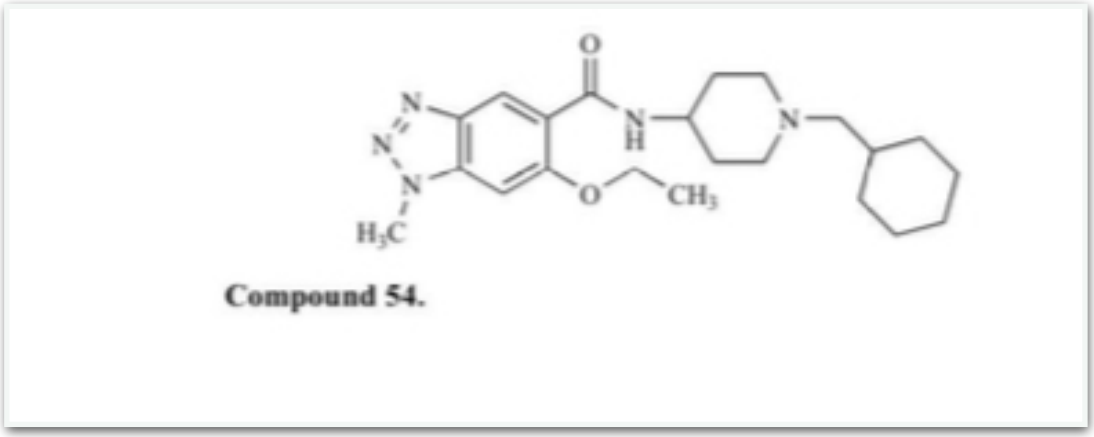
Havaldar et al. [118] have synthesized a series of 3-[4-(4- substituted phenyl-5-thioxo- 4,5-dihydro-1H-1,2,4-triazol-3- yl-methoxy)-phenyl]-2-phenyl-3H-quinazolin-4-one of the type (Compound 53) and screened for their antimalarial activity.



Compound 53.

Anti-ulcer Activity

Srinivasalu et al. [119] have derived a new triazole analogue of cinitrapride (Compound 54). Anti-ulcer activity of all the derivatives studied in mice, and most of the compounds possess potent anti-ulcer activity.



Compound 54.

Result

Compounds having fivemembered nitrogen-and oxygen- containing heterocycles, such as triazole [1][2][3][4], indazole [5][6][7][8][9], and benzisoxazole [10][11][12], have a wide range of biological activity. A number of compounds containing a triazole [13], indazole [14], or benzisoxazole [15] structural fragment are used in many modern drugs, including antitumor, antiviral, antiinflammatory, antibacterial, and other pharmaceuticals. Some drugs are at the stage of clinical trials, such as the antitumor drug SNX-5422, the pharmaceutical substance of which contains a derivative of tetrahydroindazolone [16].

The results of bioassays showed the promise of further ... search for compounds with cytostatic activity in this heterocycles series. 13 C, 15 N NMR spectra were recorded on a Bruker-Biospin AVANCE 500 spectrometer with operating frequencies of 500.13, 470.59, 125.77, 50.70 MHz for 1 H, 19 F, 13 C, 15 N nuclei, respectively, using a 5 mm sensor (BBO) with Z-gradient.

triazole containing heterocycles and those which - 4 ,2 ,1 possess 1, 2, 4-triazoles as condensation products with another nucleus system form a very diverse class of compounds, which possess antibacterial, antifungal, antiinflammatory, and antitumor activities. Moreover, they have been reported as CNS depressants, antiproliferative, anti-HIV, antitubercular, analgesic, antioxidant, and anti-inflammatory (Matin et al., 2022). Several other drugs have been reported consisting of 1, 2, 4 Triazole nucleus; these include anti-psychotic, anti- migraine, sedative and hypnotic, anti-depressant, antiviral,

analgesic, and aromatase inhibitors (Aggarwal and Sumran, 2020).Schiff bases are documented with an inclusive range of chemotherapeutic doings; azomethine on Schiff bases attributes to their extended chemical and biological properties Moreover, the ability to form intermolecular hydrogen bonds and transferable protons play their part in extended bioactivity (Said et al., 2021).Schiff bases are derived from aliphatic and aromatic aldehydes, but later are more stable due to conjugation, and the former are liable to polymerization (Hasan et al., 2015).Heterocyclic Schiff bases have been reported as: antibacterial, anti-proliferative (Al-Hiyari et al., 2021), antioxidant (Kizilkaya et al., 2020) antifungal (Shafiei et al., 2021) antiviral (Alotaibi et al., 2022), anti-inflammatory (Hamid and Salih, 2022) and anti-tumoral (Iacopetta et al., 2021).

The core triazole ring structures with higher aromatic stabilization energy are modified for improving solubility and selectivity with the interacting binding site of the enzyme and acted as linkers among various pharmacophores . Thus , they have been shown to play a vital role in al wide range of biological activities , including fragment - based drug design , biomolecular mimetics , and bioorthogonal methodologies . In addition to the available triazole drugs , researchers are engaged to explore and develop new scaffolds based on triazole cores with huge applications in biomedical and biotechnology fields . In the present review , structural features . recent synthetic developments , and new biological applications of triazoles are highlighted , which might facilitate in - depth understanding and further development / discovery of these compounds .

Discussion

Recently, there has been considerable interest in the development of novel triazole-based antibiotics agents. The search for potent triazole with more selectivity and lower toxicity continues intensively in medicinal chemistry. In our review, we have tried to depict the recent researches which made in the design and development of novel compounds with triazole nucleus. Anticonvulsant activity to quinoline derivatives of the type (Compound 23) and quinoxaline derivatives of the type (Compound 24) . Structurally, the introduction of electron donor groups such as methyl or methoxy to the phenyl ring reduced anticonvulsant activity, whereas the electron acceptor groups such as –Cl or –F have increased the anticonvulsant activity.The triazole, modified series showed stronger anticonvulsant effects than the parent compounds, showed the strongest anticonvulsant effect with ED50 of 27.4mg/kg and 22.0mg/kg in the anti-MES and anti-PTZ test, respectively.

Antiprotozoal activity of Novel dicationic triazoles 1-60 were synthesized by the Pinner method from the corresponding dinitriles, prepared via the (CuAAC). Structurlly, the type and the placement of cationic moieties as well as the nature of aromatic substituents influenced in vitro against Trypanosoma brucei rhodesiense, Plasmodium falciparum, and Leishmania donovani and their cytotoxicity for mammalian cells.Eight congeners displayed antitrypanosomal IC50 values below 10 nM. Thirty-nine dications were more potent against P. falciparum than pentamidine (IC50 = 58 nM) and eight analogues were more active than artemisinin (IC50 = 6 nM). Diimidazoline 60 exhibited antiplasmodial IC50 value of 0.6 nM. Seven congeners administered at 4 × 5 mg/kg by the intraperitoneal route cured at least three out of four animals in the acute mouse model of African trypanosomiasis. At 4 × 1 mg/kg, diamidine 46 displayed better antitrypanosomal efficacy than melarsoprol, curing all infected mice.
Antimycotic activity of thiosemicarbazide derivatives.Clinically ,showed promising antifungal activity against some species belonging to Trichophyton spp. known as the causative agents of superficial mycoses. The most effective derivatives have the carbon ring substituted with a methyl or methoxy group. Although MICS values for the newly synthesized compounds were higher than those for currently available triazoles (e.g., fluconazole, itraconazole), we found them as a

good basis for further research.Besides, some of it affected the growth of dermatophytes by 80-90% at a concentration of 125 mg L-1. It is noting that even MICS of some triazoles currently worth used in the treatment of mycoses, including dermatophytoses, showed high variability in activity against different species of Trichophyton (e.g., for itraconazole MIC range from 0.015 to 8 mg L- 1, for fluconazole from 0.5 to 64 mg L-1).

Antimycobacterial properties of series quinoline derivatives possessing triazolo, ureido and thioureido substituents have been evaluated to inhibited Mycobacterium tuberculosis H37Rv up to 96%, 98% and 94% respectively, at a fixed concentration of 6.25 microg/mL. Minimum inhibitory concentration of 3.125 microg/mL was obtained for compound 10 and 24, while for compound 22 it was 6.25 microg/ mL. Molecular docking calculations suggest critical hydrogen bonding and electrostatic interactions between polar functional groups (such as quinoline-nitrogen, urea-carbonyl and hydroxyl) of (anti-TB) compounds and amino acids (Arg186 and Glu61) of ATP-synthase of M. tuberculosis.
Among them, triazoles and derivatives were considered more greatly by medicinal chemist for lead generation in the field of many disorders.
The activity effects of triazole containing compounds have been studied in different phases. Many of triazole-based compounds showed potent activities with high selectivity and low toxicity which turn them in to promising lead compounds. The representative lead compounds in each category can prove to be useful for further designing new agents.

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