Pharmacological Importance of Triazole Derivatives: A Review

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Abstract:
In recent years, Triazole ligands and their metal complexes are very important in medicinal and pharmaceutical fields because of their wide spectrum of biological activities. There is an increasing demand for the preparation of new antimicrobial agents due to the developing resistance towards conventional antibiotics. The chemistry of triazole compounds has expected considerable interest due to their synthetic and effective biological properties like analgesic, anti-inflammatory, anti-oxidant, analeptic, sedatives, anti-anxiety, anti-microbials, anti-convulsant, anti-cancer, and other biological activities. There are various known drugs in market containing the triazole moiety like voriconazole, triazolam, fluconazole, intra conazole, furacilin, alprazolam, etizolam etc. This review can be helpful to develop various more new compounds possessing triazoles moiety that could be better in terms of efficacy and lesser toxicity.

Key words: Triazoles, Schiff bases, Metal complexes and Pharmacological properties.

1. Introduction
Medicinal chemistry is a part of pharmaceutical, medical and biological sciences and concerned with the discovery, design, development and recognition of biologically active drug molecules. It is also the study of metabolism, mode of action at the molecular level and the development of structure activity relationship (SAR) of the active pharmacophore for the discovery and development of new potent agents for treating different diseases or disorders [1]. Heterocyclic chemistry is a branch which is separable from mankind because human are totally dependent on the drugs derives from heterocyclic rings. Heterocyclic compounds also have so far been synthesized nearly due to wide range of biological activities [2,3]. One such class of compounds like five membered heterocyclic compounds two and three nitrogen as hetero atoms in its ring structure i.e. Pyrazoles, imidazole and triazole are an important class of hetero aromatic systems that find extension use in the pharmaceutical industry. Pyrazoles occupy unique positions and they have so far been synthesized mainly due to their higher pharmacological activities. They possess anti-microbial, anti-viral, anti-inflammatory, anti-amoebic properties [4-7]. The search for new agent is one of the most challenging tasks to the medicinal chemist. The synthesis of high nitrogen containing heterocyclic systems has been attracting increasing interest over the past decade because of their utility in various applications, such as propellants, explosives, pyrotechnics and especially chemotherapy. In recent years, the chemistry of triazoles and their fused heterocyclic derivatives has received considerable attention owing to their synthetic and effective biological importance. The derivatization of triazole is considered to be based on the phenomenon of bioisosterism in which replacement of oxygen of oxadiazole nucleus with nitrogen atom yields triazole analogue. There are two possible isomers of triazole 1,2,3-triazole and 1,2,4-triazole. Out of the two triazoles, 1,2,4-triazoles have drawn great attention to medicinal chemists from two decades due to its wide variety of activity [8], low toxicity and good Pharmacokinetic and Pharmacodynamic profiles.

II. Pharmacological activities of triazole derivatives
The synthesis of high nitrogen containing heterocyclic systems has been attracted to many pharmaceutical and agrochemical industries. The triazole nucleus is one of the most important heterocycles which is a feature of natural products and medicinal agents. Triazole nucleus is enjoying their importance as being the center of activity. The nitrogen containing heterocyclic’s are found in abundance in the most of the medicinal compounds. The triazoles are said to be the isosters of imidazoles in which the carbon atom of imidazole is isosterically replaced by nitrogen. Triazole & its derivatives have a wide range of application. The derivatization of Triazole ring is based on the phenomenon of bioisosterism in which replacement of oxygen of oxadiazole nucleus with nitrogen triazole analogue. The triazole derivatives are versatile and have been featured in a number of clinically used drugs. The most relevant and recent studies have revealed that triazole derivatives have a broad spectrum pharmacological activities. Triazoles and its derivatives possess a great importance in medicinal chemistry and can be used for the synthesis of numerous heterocyclic compounds with different biological activities. This review article covers the latest information over active triazoles derivatives having different pharma cological action. Triazole compounds are extensively used in clinic, and are currently one of the most important fields in the researches and developments of drugs the chemistry of triazoles and their fused heterocyclic derivatives has received considerable attention owing to their synthetic and effective biological importance. 1,2,4-triazole derivatives exhibit wide range of biological activities including Antibacterial [9-11], Anti fungal [12,13], Antitumour [14], Anti-inflammatory [15], Antitubercular [16], Hypoglycaemic [17,18], Antidepressant [19], Anti convulsant [20], Anticancer [21], Antimalarial [22], Antiviral [23], Anti proliferative [24], Analgesic [25] and antimigraine [26]. The first studies of 1,2,4-triazoles were concerned with structural isomers of. Modern instrumental and theoretical methods achieved much success in dealing with tautomerism problems, the complexity of which is one of the enduring charms of the chemistry of 1,2,4-triazoles. Example of tautomerisation is
shown by 3 Phenyl-1-H-1,2,4-triazol-5-amine with 5-

III. Antibacterial and Antimicrobial Activities

Infectious diseases have been serious and growing threats to human health during the past few decades. The sensitivity decrease to antimicrobial agents have also been increasing for a great variety of pathogens and the resistance to multiple drugs is more and more prevalent for several microorganisms, especially for Gram-positive bacteria and some fungi. The literature survey of the recent studies done on triazole containing metal complexes indicates that they have antimicrobial activities like anti-bacterial and antifungal activities which have been summarized as given below:

Vikrant S. Palekar et al, had reported synthesis of 1,4-bis(6-(substituted phenyl)-[1,2,4]triazolo[3,4-b]-1,3,4-thiadiazoles an d 4-bis(substituted phenyl)-4-thiazolidin one derivatives and screened for their anti bacterial activity. Several of these compounds showed potential antibacterial activity[29]. Nuray Ulusoy et al, established a synthesis of new N-alkyl dene /aryliden-5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptoacetic acid hydrazides and tested for antimicrobial activity. Above mentioned compound showed antibacterial activity against some bacteria[18]. Gabriela Laura Almjan et al, synthesized 4-(Substituted-arylidene)amino-5-[4-(4-Xylenesulfonyl)phenyl]-2-(morpholin-4-ylmethy) -2,4-dihydro-3H-1,2,4-triazolo-3-thio ne evaluated for their anti bacterial activity[31]. Synthesis of new 1,2,4-tri and 1,3,4-thiadiazoles were prepared by Khosrow et al. This synthesis bearing isomer pyridyl and 1-naphthyl is reported using 1,4-disubstitutedthio semi carbazides in alkaline and acidic media, respectively. The methylthio and benzyl thio derivatives of the synthesized triazoles are also reported. All of the synthesized compounds were characterized by their FT-IR, 1H-NMR and mass spectral data. The antibacterial studies of some of the synthesized compounds against S. aureus and E. coli as MIC values are reported[32]. Synthesis of Indole-3-carboxylic acid hydrazide (2) was prepared by Abdel-Rahman et al. This synthesis was treated with aromatic aldehydes in ethanol to give the corresponding hydrazone derivatives in good yields. The indole carboxyhydrazide was incorporated into the 3-indolyloxadiazoles. This synthesized compound show good antibacterial and anti-fungal activity[33]. Kiran et al., had synthesized new organosilicon(IV) and or ganotin(IV) complexes by the reaction Me2MCl2 where (M= Si and Sn) with new ligands, 4-[4-(cyano-benzylidene)amine]-5-mercaptop-1H,2,4-triazole and 4-[4-(Cyanobenzyli dene)amino]-5mercapto-3-methyl-1,2,4-triazole in absolute methanol. The metal complexes had been proposed to have trigonal bipyramidal and octahedral geometries. This metal complex had confirmed the elemental analyses, molar conductance and spectral (UV, FT-IR, 1H, 13C, 29Si and 119Sn NMR) studies. In vitro antimicrobial activities of the compounds were evaluated. Me2Sn (L)2 was found to possess highest antimicrobial activity[34]. Singh et al., had synthesized Zn(II) complexes by the reactions of zinc(II) acetate with bidentate ligands of triazole Schiff bases derived from 3substituted phenyl-1-amino-5-hydrazone-1,2,4-triazole and benz aldehde,2-hydroxyacetophenone or indo line-2,3-dione. They were characterized by Elemental analyses, FT-IR, 1H NMR, 13C NMR and FAB mass. All these triazole Schiff bases and their complexes have also been screened for their antibacterial activities against Bacillus subtilis, Escherichia coli and antifungal activities against Colletotrichum falcatum, Aspergillus niger, Fusarium phenyl-1H-1,2,4-triazol-3-amine[28], oxysporium and Curvularia pallescens by petriplate methods. The compound [ZnL4(H2O)2] is more active against all bacteria and fungi because they have additional heterocyclic ring (indoline-2,3-dione)[35].

IV. Anti-Cancer Activity

Currently, the treatment for cancer primarily includes surgery and chemo therapy, but the curative effects of the existing chemotherapeutic drugs are not good enough and they have plentiful side effects. The development of more effective drugs for treating patients with cancer has been a main attempt over the past 50 years. Alias et, al, had synthesized two new complexes with formula [M(NMP.(5-(4-NitroPhenyl)-4-Amino-3-MercaptoPropen yl-1,2,4- Triazole)](H2O)2[(NO3)2] 3Et OH (where M is Ni and Co(II) ions res pectively, NMP. These complexes have been characterized by spectroscopic methods such as (ultraviolet-visible and infrared), as well as to thermal gravimetric, metal analyses, micro ana lyses, conductivity, magnetic moment and molar ratio method. To measure the biologic activity and potential anticancer efficacy of these compounds, they have been compared with cisplatin on human hepatocarcinoma HepG2 cell lines in different eight concentrations (2000, 1000, 500, 250, 125, 62.5, 31.25 and 15.625 µg/ml) respectively, in the time of exposure 72 hrs. The results exhibit that the three prepared complexes, i.e. ligand (NMP-TZ) and its metal complexes have shown higher ratios cytotoxicities compared to cisplatin against HepG2 cell lines in most selected concentrations. Based on the obtained results of biological test, these compounds with 144 may be potentially being considered as good anticancer candidates for further pharmacological studies[36]. Synthesis of a series of heterocycle-fused 1,2,3-triazoles by 1,3-dipolar cyclo addition of heterocyclic ketene aminals or N, O-acetals with sodiumamide and polyhaloisophthal nitrioles has been carried out and evaluated in vitro against a panel of human tumour cell lines.Com pound 4-Methoxy-phenyl substituted 1,3, ozazo heterocycle fused 1,2,3-triazole 29 was found to be most potent derivative against A431 and K62 human tumor cell lines[37]. A new series of 3,6-disubstituted triazolo[3,4b]thiadiazole derivatives has been synthesized by simple, high yielding routes. The newly synthesized compounds were evaluated for their cytotoxic activity against a panel of 60 human cancer cell lines by the National Cancer Institute (NCI) and some of them demonstrated inhibitory effects on the growth of a wide range of cancer cell lines generally at 10−5 M level and in some cases at 10−7 M concentrations. In this assay, the anti-tumor activity of the newly synthesized compounds could not be interpreted in terms of tyrosine kinase inactivation but more likely as a relatively broad specificity for the ATP-binding domain of other kinases. The pharmacological mechanism of action for these intriguing compounds has not, as yet, been successful[38]. A series of 4-aryliden amino-4H-1,2,4-triazole derivatives were reported by Olcay et al. This series were synthesized from the treatment of 4-amino-4H-1,2,4-triazole with certain aldehyde hydrides. Compounds were characterized by elemental analyses and 1H NMR, 13C NMR, IR and UV spectral data. In recent years, various 1,2,4-triazoles and 4,5-dihydro-1H-1,2,4-triazol-5-ones have been found to be associated with diverse pharmacological activities such as anti-convulsant, antifungal, anticancer, anti-inflammatory and anti bacterial[39].
V. Analgesic Activity
A series of 1,3,4-oxadiazole/thiadiazole and 1,2,4-triazole derivatives of biphenyl-1-yloxy acetic acid were synthesized in order to obtain new compounds with potential anti-inflammatory activity, analgesic activity and lower ulcerogenic potential. All compounds were evaluated for their anti-inflammatory activity by the carrageen an induced rat paw edema test method. The compounds possessing potent anti-inflammatory activity were further tested for their analgesic, ulcerogenic and antioxidant activities. These compounds showed significant analgesic effect and at an equimolar oral doses relative to flurbiprofen were also found to be non-gastrotoxic in rats. (81.81%) than the reference drug (79.54%), low ulcerogenic potential and protective effect on lipid peroxidation[40].

VI. Anticonvulsant activity
A series of novel 3-{{(substituted phenyl) methyl}[thio] -4-alkylaryl-5-(4-aminophenyl)-4H-1,2,4-triazoles and several related Schiff’s bases, 3-{{(substituted phenyl)methyl}[thio]-4-alkylaryl-5-[[[(s-bstituted phenyl)[5-nitro-2-furylmethylene] amino]-phenyl]-4H-1,2,4-triazoles were synthesized for evaluation of their biological properties. Structures of the synthesized compounds were confirmed by the use of their spectral data besides elemental analysis. All compounds were evaluated for their anticonvulsant activity by maximal electroshock (MES), subcutaneous pentylentetrazole (scPTZ) and neurotoxicity (NT) screens. A number of triazole derivatives, exhibited protection after intraperitoneal administration at the dose of 100 and 300 mg/kg in one or both models employed. Some of the tested compounds showed marginal activity against M. tuberculosis H37Rv[41]. A series of 4-(4-alkoxyphenyl)-3-ethyl-4H-1,2,4-triazole derivatives were synthesized as open chain analogues of 7-alkoxy-4,5-dihydro[1,2,4]triazolo[4,3-a]quinolines. Their anticonvulsant activity were evaluated by the maximal electroshock test (MES test) and their neurotoxicity was evaluated by the rotarod neurotoxicity test (Tox). MES test showed that 3-ethyl-4-(4-oxoalkylphenyl)-4H-1,2,4-triazole 3q was found to be the most potent with ED50 value of 8.3 mg/kg and protective index (PI = TD50/ED50) value of 5.5, but compound 3r, 3-ethyl-4-(4-octyloxyphenyl)-4H-1,2,4-triazole exhibited better PI value of 9.3, which was much greater than PI value of the prototype drug phenytoin. For explanation of the possible mechanism of action, the compound 3r was tested in pentylentetrazole test, isoniazid test, thio semicarbazide test, 3-mercapropionate nitric acid and strychnine test[42]. Several new N4-substituted triazolyl thiazoles were reported by Bineshmarvasti et al. These compound were prepared by the general method for 1,2,4-triazole ring closure. Anticonvulsant activity of compounds was measured against pentylenetetrazole-induced seizures in mice by intraperitoneal injections of different doses of the test compounds. Pretreatment of animals with flumazenil (10 mg/kg, i.p.) as a benzo diazepine receptor antagonist did not have any significant effect on anticonvulsant activity of the test compounds. These results demonstrate that the anticonvulsant activity of N4-substituted triazolylthiazole agents is not probably mediated by direct interaction with benzodiazepine receptor complex[43]. Various 3-[[substituted phe nyl]-1,3-thiazol-2-y]amine]-4-(substituted phenyl)-4,5-dihydro-1H,1,2,4-tri azole-5-thiones has been synthesised by clubbing thiazole and triazole moieties, keeping in view the structural requirement for the pharmacophore model for anticonvulsant activity. Two compounds 1a and 1b showed significant anticonvul sant activity in both MES and subcutaneous pentylenetetrazole (sc PTZ) screen along with wide safety margin with protective index (PI), median hypnotic dose (HD50) and median lethal dose (LD50) much higher than standard drugs[44]. A new series of 4,5-diphenyl-1H,1,2,4-triazol-3(4H)-one were synthesized to study the effect of cyclization of the semicarbazone moiety of aryl semi carbazones on the anticonvulsant activity. All compounds were evaluated for their anticonvulsant activity in four animal models of seizures, viz. maximal electroshock seizure (MES), subcutaneous pentylentetrazole (scPTZ), subcutaneous strychnine (scSTY), and subcutaneous picrotoxin (scPIC) induced seizure threshold tests. The compounds were also evaluated for neurotoxicity. Eight compounds exhibited anticonvulsant activity in all the four animal models of seizure[45].

VII. Antifungal activities
Yasemin et al, prepared a new series of 1-(2-hydroxy-2-phenyl-ethyl)-3-thiophen-2-ylmethyl-14-[arylidene-amino]-4,5-dihydro-1H-[1,2,4]triazole-5-ones and 1-(2-hydroxy-2-phenyl-ethyl)3-thiophen-2-yl methy1-4-[aryl-amino]-4,5-dihydro-1H-[1,2,4]triazole-5-ones from 2-(1-ethoxy-2-thio phen-2-yl)ethylidenehydrazinocarbox ylate and hydrazine hydrate. The newly synthesized compounds were screened for their antifungal activity. The derivatives of compound exhibited significant antifungal activity[46]. Bijul Lakshman synthesized twenty eight derivative of 4-amino-5-substituted aryl-3-mercapto-1,2,4-triazoles and these compounds has been tested in vitro against Rhizoctonia solani. Sclerotium rolfsii, Fusarium oxysporum, Pythium aphanidermatum, Puccinia recondite and Bipolaris sorokiniana . The compound exhibits highest activity against Bipolaris sorokiniana (ED 50= 27 mg/ml)[47]. Monikaet and co-workers synthesized derivative of the 9-substituted-3-aryl-5H,13a-H-quinolinol[3, 2f] [1,2,4] triazole[4,3-b] [1,2,4]triazole pines from the 5-aryl-1,3,4-di amino-1, 2,4-triazols and 2-chloro-3-formylquinolines using catalytic amount of p-TsOH and N,N-dimethyl formamide as an energy transfer medium using microwave heating as well as solvent using oil-bath and the synthesized compounds were screened for anti-fungal activity against Aspergillus flavus, Aspergillus niger, Rhizopus species and Penicillium notatum species by paper disc technique against two concentration 500μg/ml and 1000μg/ml. the compounds showed excellent anti-fungal activity against Aspergillus niger and Penicillium notatum at 500μg as well as and 1000μg[48]. Yan Zou et al, prepared a series of 1-(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3 substituted-2-propanols. The in vitro antifungal activity of all the target compounds were evaluated against eight human pathogenic fungi. Compound showed the best antifungal activity[49]. Xiaoyun Chai et al, synthesized a series of 1-(1H-1,2,4-triazol-1-yl)-2-(2,4-di fluoro phenyl)-3-[(4-substituted trifluoromethyl phenyl) piperazin-1-yl)-propan-2-ols and evaluated for their antifungal activity. Some of the compounds showed excellent anti-fungal activity[50].
VIII. Conclusion
Triazole is a unique moiety that is responsible for various biological active ties. This article highlighted research work of many researchers reported in literature for different pharmacological activities on synthesized triazole compounds. Triazole compounds have finalized much signify cance as they have also been explored for their diverse biological activities. Different new and potent compounds will prepared to explore more effective and potent molecule by substitution of different atoms or groups on triazole ring with different pharmacological activities.

IX. References
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