Review Article

A Pharmacological Expedition of Tetrazole Compounds Towards Medical Field - An Overview

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ABSTRACT

Tetrazole moiety exhibits a wide and increasing number of applications. The nitrogen-rich ring system is used extensively in pharmaceuticals. This paper is focused on biological activities of tetrazoles that have been reported earlier by various authors. They find a significant place in medical field as it has ring systems patented for the treatment of central nervous system disorders, sexual dysfunction, asthma, obesity, diabetes and various diseases.

Keywords: Tetrazole, central nervous system, diabetes, obesity.

INTRODUCTION

The tetrazoles, are characterized by a five membered, doubly unsaturated ring consisting of one carbon and four nitrogen atoms CN_4H_2. They are unknown in nature. Interest in tetrazole chemistry over the past few years has been increasing rapidly because of its wide range of applications, mainly as a result of the role played by this hetero cyclic functionality in medicinal chemistry as these offer a more favorable pharmacokinetic profile and a metabolically stable surrogate for carboxylic acid functionalities.[1] Tetrazoles are such a type of hetero cyclic which has excellent therapeutic application in the field of drugs and also has minimal side effect on the host.

Therefore, tetrazoles are the molecules having diverse activity and the potential role in biosciences. Moreover, lot many things to be explored about these versatile compounds. It has been known those tetrazole derivatives as ligands in coordination chemistry as surrogate molecule for carboxylic acid and their resistance to metabolically biological degradation mechanism; mostly it can be used as for synthesizing new drug especially anticancer molecules. This review highlights the important things about the potential possible role of terazole and summarizes biological activity of tetrazoles.

Medicinal Activity of Tetrazoles

Antimicrobial activity

Yildirir et al[2] have studied some new phenylselanyl-1-(toluene-4-sulfonyl)-1H-tetrazole derivatives which have been synthesized using dicyclohexylcarbodiimide/ dimethylaminopyridine. In addition, the antimicrobial activity of the synthesized compounds and two antibiotics [sulfamethoxazole (SMX) and sulfamerazine (SRZ)] were investigated against some microorganisms.

Dayanithi et al[3] have reported a series of novel 1-substituted tetrazole derivatives were synthesized and evaluated for their antibacterial and antifungal activity. All the derivatives were efficiently synthesized by four steps process. In this study, thiazole attached to tetrazole derivatives were most active than the piperazine attached tetrazole derivatives.

Umarani et al[4] have described the present work addresses a search for new lead antimicrobial agents by adopting a simple procedure for the synthesis of new series of tetrazolo quinoxalines. o-Phenyhlene diamine was condensed with oxalic acid using Philip's procedure to obtain quinoxaline -2,3-dione. The former chlorination followed by hydrazinolysis furnishing the formation of hydrazides, which undergoes cyclization with sodium azide afforded –hydrozino tetrazolo [1,5-*a*]quinoxaline. Inverstigation of *in vitro* antimicrobial activity of compound was done by cup-plate agar diffusion method. Some of the obtained compounds showed the interesting antimicrobial activity comparable to standard drugs Ofloxacin and Griseofulvin.

Varadaraji et al[5] have synthesized several 5-thio-substituted tetrazole derivatives were efficiently synthesized by a three-step process. The substituted tetrazol-5-thiol, namely, 1-benzyl-1*H*-tetrazole-5-thiol was prepared by refluxing commercially available benzyl isothiocyanate with sodium azide in water. The second step was the synthesis of 1-benzyl-5-[(3-bromopropyl)thio[-1*H*-tetrazole by thioalkylation of tetrazole-5-thiol with 1,3-dibromopropane in tetrahydrofuran. Finally, the 5-thio-substitued tetrazole derivatives were prepared by condensation with corresponding amine or thiol. All the synthesized compounds were screened for their antibacterial and antifungal activities.

Shu-Jun Chao et al[6] have reported several new 5-[4'-(5-phenyl-1,3,4-oxadiazol-2-ylsulfanylmethyl)-biphenyl-2-yl]-tetrazoles derivatives have been synthesized. The structures of these new compounds were confirmed by elementary analyses and spectral data. The antibacterial activities of the compounds were also evaluated.

Sarvesh Kumar Pandey et al[7] have studied three series of novel and new fused heterocyclic systems, viz. triazolo[4,3-*a*]-quinazolin-7-ones, [1,2,4,5]-tetrazino[4,3-*a*]-quinazolin-8-ones and indolo[2,3-*c*][1,2,4]-triazino[4,3-*a*]-quinazolin-8-ones have been synthesized from the key intermediate 3-(substituted-phenyl)-2-hydrazino-quinazolin-4-ones. All the synthesized compounds have been screened for their antibacterial activity against Gram-negative bacteria, *Escherichia coli, Pseudomonas aeruginosa* and Gram-positive bacteria, *Streptococcus pneumonia, Bacilliun subtilis*, as well as demonstrated significant antifungal activity against fungi viz. *Candida albicans, Aspergillus fumigates, Aspergillus flavus,* and *Aspergillus niger.*

Yao-Wu He et al[8] have reported a series of new 5-(1-aryl-1H-tetrazol-5-ylsulfanylmethyl)-*N*-(2,3,4-tri-*O*-acetyl-β-D-xylopuranosyl)-1,3,4-thiadiazol-2-amines and 5-(1-aryl-1*H*-tetrazol-5-ylsulfanylmethyl)-*N*-(2,3,4-tri-*O*-acetyl–β-D-xylopyranosyl)-1,3,4-thiadiazole-2-amines respectively under mercuric acetate/ alcohol system of acetic anhydride/ phosphoric acid system, then deacetylated in the solution of CH_3ONa/ CH_3OH. Some of the synthesized compounds displayed PTP 1B inhibition and microorganism inhibitions.

Ram Shankar Upadhayaya et al[9] studied a series of (2*R*,3*S*)-2-(2,4-diflurophenyl)-3-(5-{2-[4-aryl-piperazin-1-yl]-ethyl}-tetrazol-yl)-1-[1,2,4]-triazol-1-yl-butan-ol has been synthesized. The antifungal activity of compounds was evaluated by *in vitro* agar diffusion and broth dilution assay.

Kategaonkar et al[10] have reported a series of new *a*-hydroxyphosphonate and *a*-acetoxyphosphate derivatives have been synthesized for the first time tetrazolo [1,5-*a*] quinoline derivatives. *In vitro* antimicrobial activities of the synthesized compounds were investigated against Gram-positive *Bacillus subtilis*, Gram-negative *Eschericha coli* and fungi *Candida albicans* and *Aspergillus niger*. Some of the tested compounds showed significant antimicrobial activity.

Antihypertensive activity

Sharma et al[11] synthesized some new 2-[(Substituted-phenyl amino)-phenyl-methyl]-1-[2'-(1H-tetrazol-5-yl)biphenyl-3-ylmethyl]-1H-benzoimidazol-5-ylamine derivatives were synthesized by 2-(α -hydroxy benzyl) benzimidazole was converted to 2-(α-bromo benzyl) benzimidazole by reacting with concentrated nitric acid, sulphuric acid, HBr and anhydrous $ZnCl_2$ Schiff bases react with ortho position attach biphenyl tetrazole with different substituents amino group cyclocondensation with appropriate reagents. All compounds studied in this work were screened for their antihypertensive activity by tail cuff method and direct method measurement.

A new series of 1-(4-{5-Amino-6-fluoro-1-[2'-(2H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1Hbenzoimidazol-2-yl}-phenyl)-3-chloro-4-(Substituted-phenyl)-azetidin-2-one derivatives MCS 06[1-15] has been synthesized and subjected to evaluate their antihypertensive activity. All the synthesized compounds of the series elicit remarkable activity in comparison to standard drug (Losartan).

Anticonvulsant activity

Bhaskar et al[13] have described here an easy and efficient method to obtain Schiff bases of 5-phenyl tetrazole using different aromatic aldehydes. Reaction of 5-phenyl tetrazole with ethyl chloroacetate to form ethyl (5-phenyl-1*H*-tetrazol-1-yl) acetate. The different biological activities were studied and the different derivatives were recommended for the screening of anticonvulsant activity.

Antiproliferative evaluation

Gundugola et al[14] have reported a series of 1,4-diaryl tetrazol-5-ones were synthesized by copper mediated N-arylation of 1-phenyl-1H-tetrazol-5(4H)-one with aryl boronic acids. The 1,4-diaryl tetrazol-5-ones sybstituted with OMe, Cl, CF_3, Br_2 underwent with Lawesson's reagent to yield the corresponding 5-thio derivatives. The 1-(2-bromophenyl)-4-phenyl-1*H*-tetrazole-5(*4H*)-thione so obtained was subjected to lithiation/ protonation and Sonogashira coupling to produce 1,4-diphenyl-1*H*-tetrazole-5(4H)-thione and 1-(-ethynylphenyl)-4-phenyl tetrazole-5-thione, respectively. Three of these novel compounds were found to inhibit L1210 leukemia cell proliferation and SK – BR-3 breast cancer cell growth over several days in culture *in vitro*. Shorter tetrazole derivative treatments also reduced the expression of the Ki-67 marker of cell proliferation in SK-BR-3 cells and the rate of DNA synthesis in L1210 cells.

Cytotoxic activity

Popsavin et al[15] reported 3(5)-Carbozamido-4-(β-D-ribofuranosyl)pyrazoles bearing 2'-benzamido and 3'-mesyloxy isosteric groups, as well as the terazole *C*-nucleosides with 2-benzamido-2-deoxy-β-D-ribofuranose and 3-azido-3-deoxy-β-D-xylofuranose as sugar segments, have been synthesized starting from D-glucose, by utilizing the, 2,5-anhydro-D-glucose ethylene acetal derivatives and as divergent intermediates. The *C*-nucleotides were shown to be moderate inhibitors of the *in vitro* growth of both N2a and BHK 21 tumor cell lines, whereas showed a selective, although not potent cytotoxic activity against N2a cells.

Voitekhovich et al[16] have studied the complexes CuL_3Cl_2, PdL_2Cl_2 and PtL_2Cl_2, where L is a novel ligand from the series of 2-substituted 5-aminotetrazoles, namely 5-amino-2-*tert*-butyltetrazole have been synthesized by the reaction of metal(II)chlorides. The crystallographic structural analysis of these complexes revealed that act as

a mono dentate ligand coordinated to the metal *via* endocyclic N4 atom. Platinum complex demonstrates promising cytotoxicity against human cervical carcinoma cells with IC_{50} value average between those of cisplatin and carboplatin.

Antihyperglycemic activity

Sharon et al [17]have reported a series of 5-[(5-aryl-1*H*-pyrazol-3-yl)methyl]-1*H*-tetrazoles have been synthesized and evaluated for their in vivo anti-hyperglycemic activity. Some of the synthesized compounds have shown significant glucose lowering activity in male Sprague-Dawley rats in sucrose loaded model. These compounds were also evaluated for their peroxisome proliferator activated receptor anti agonistic property, but none of them displayed any significant activity.

Hypoglycemic activity

Gao et al[18] have studied novel tetrazole-bearing N-glycosides have been designed and synthesized as SGLT2 inhibitors *via* a conventional protocol starting from substituted phenylacetic acids and two monosaccharides, D-glucose and D-galactose, and their hypoglycemic activity has been tested *in vivo* by mice glucose tolerance test (OGTT). Two compounds are compounds are found to be more potent than the positive control Dapagliflozin. The structure activity relationship has also been investigated.

Ashoke Sharon et al[17] synthesized a series of 5-[(5-aryl-1H-pyrazol-3-yl)methyl]-1H-tetrazoles 3a–h have been synthesized and evaluated for their in vivo anti hyperglycemic activity. Some of the synthesized compounds have shown significant glucose lowering activity in male Sprague– Dawley rats in sucrose loaded model. These compounds were also evaluated for their peroxisome proliferator activated receptor agonistic property, but none of them displayed any significant activity.

The *in vivo* hypoglycemic activity of series of 5-[(5-aryl1H-pyrazol-3-yl) methyl]-1H-tetrazoles[17] bearing N-glycosides as SGLT2 inhibitors of have been evaluated. Some of the compounds have shown significant glucose lowering activity. These compounds were also evaluated for their peroxisome proliferator activated receptor agonistic property, but none of them displayed any significant activity.

Anti-inflammatory activity

Umanrani et al[19] have synthesized a novel synthetic methodology of Schiff's bases incorporating tetrazolo quioxalines. *O*-phenylene diamine on condensation with oxalic acid using Philip's procedure yielded the corresponding quinoxalin-2,3-dione. The later on chlorination affored 2,3- dichloroquinoxaline. This on hydrazinolysis gave the known 3-chloro-2-hydrazino quinoxaline, which further undergoes cyclization with sodium azide to obtain 2-hydrazion tetrazolo[1,5-*a*]quinoxaline. All the newly synthesized heterocycles have been screened for their *in vitro* antimicrobial and anti-inflammatory activities. Few of them exhibited promising activity. The ambient conditions, excellent product yields and easy work up procedures make this synthetic strategy a better protocol for the synthesis of newer Schiff's derivatives.

Shukla et al[20] have described the reaction of phenoxy methyl imidazole and phenoxy methyl benzimidazole in presence of sodium ethoxide yielded N-(*β*-cycanoethyl)-2-(substituted phenoxy methyl) benzimidazole derivatives. They were subjected to cyclization with sodium azide to give 5-{β-[N-(2-substituted phenoxy methyl benzimidazolyl/ imidazolyl) ethyl} tetrazoles. All the compounds were tested for their anti-inflammatory activity on albino mice at the oral dose of 1/5 ALD_{50} (approximate lethal dose in 50% of animals) according to the technique of Srimal and Dhawan.

Bhaskar et al[21]have studied an attempt to find new pharmacologically active molecules, we report here the synthesis and *in vitro* anti-inflammatory activity of various 1-[5-(substituted phenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl]-5-phenyl-1H-tetrazole. The anti-inflammatory activity of title compounds were examined by denaturation of proteins method. All the compounds exhibited weak to potent anti-inflammatory activity. Some derivatives bearing a methoxy group exhibited very good anti-inflammatory activity.

Bepary S et al[22] have synthesized a number of a number of indanyl tetrazolederivatives namely 5-(6'-chloroindan-1'-yl)tetrazole (CIT), 5-(6'-bromoindan-1'-yl)tetrazole (BIT), 5-(6'-chloroindan-1'-yl)methyltetrazole (CIMT), 5-(6'-bromoindan-1'-yl)methyltetrazole(BIMT) were evaluated for the anti-inflammatory activity in carragennan induced rat paw edema in Swiss *albino* Wister rats for 24-hour period at the dose of 100 mg/kg of body weight by intra peritoneal route, where phenylbutazone (PBZ) was used as the standard. All of these compounds exhibited inhibition on rat paw edema with peak actions observed following 3 hours after administration. Moreover, compounds CIMT and BIMT were further evaluated at dose of 50 mg/kg of body weight. Among the compounds, CIMT showed higher activity than others and was very close to standard phenylbutazone.

A novel synthetic methodology of schiff's bases incorporating tetrazolo quinoxalines were synthesized and were screened for their *in vitro* antimicrobial and anti-inflammatory activities. Few of them exhibited promising activity. The ambient conditions, excellent product yields and easy work up procedures make this synthetic strategy a better protocol for the synthesis of newer schiff's derivatives.[19]

Maria Dorathi Anu et al[23] has synthesized 5 [1,1 dimethyl-3-(phenyl (1H-tetrazole-1-yl) methyl amino urea] which exhibited potential anti-inflammatory activity when

compared to standard phenylbutazone (PB2)at 5mg/kg/p.o.

Shiny George et al[24] has synthesised 3-(1-substituted phenyl -1H – tetrazole -5-yl) pyridine derivatives. Synthesized compounds were screened for anti-inflammatory activity by carrageen induced paw edema method using Diclofenac sodium as standard drug. All the compounds of the series exhibited 22–70% protection against carrageen induced edema in the tested animals.

Mohite P.B et al[25] has utilized benzonitrile and sodium azide in presence of ammonium chloride to synthesize 5-phenyl 1 -acetyl tetrazole, which reacted with different aromatic aldehydes in presence of alkaline medium, to yield corresponding chalcones. Chalcones on further reaction with isonicotinic acid hydrazide affords pyrazolines. The compounds were identified by spectral data and screened for *in-vitro* anti-inflammatory activity.

Anticancer activity

Bhaskar et al[26] have studied different tetrazole derivatives containing isoxazole has been synthesized. 5-phenyl tetrazoles was cyclized using sodium azide and ammonium chloride and benzonitrile. The 5-phenyl tetrazoles on treatment with acetic anhydride forms 5-phenyl 1-acetyl tetrazole which on reaction with different aromatic aldehydes forms chalcones. The chalcones further undergo cyclization with hydroxylamine hydrochloride in presence of KOH to form 5-phenyl-1-(5-substituted phenyl isoxazo-3-yl)-1*H*-tetrazole. Among the synthesized tetrazole derivatives, eight compounds have been selected and evaluated for their anticancer activity at the National Cancer Institute for testing against a panel of approximately 60 different human tumor cell lines derived from nine neoplastic cancer types. Relations between structure and activity are discussed.

Antagonist activity

Singh et al[27] have reported several regioisomeric tetrazolyl indole derivatives with structurally modified alkyl substituents at the tetracyclic indole nitrogen containing *N*-ethyl amino tetrazole moiety have been synthesized and screened for their ER binding affinity, agonist (estrogenic) and antagonist (antiestrogenic) activities. *N*-2 regio isomers were found to be moderately antagonists and one compound showed 100% contraceptive efficacy at 10 mg/ kg dose.

Nelson et al[28] have synthesized 1-benzyl-5-aryltetrazoles were discovered to be novel antagonists for the $P2X_7$ receptor. Structure- activity relationship (SAR) studies were conducted around both the benzyl and phenyl moieties. In addition, the importance of the region chemical substitution on the tetrazole was examined. Compounds were evaluated for activity to inhibit calcium flux in both human and rat recombinant $P2X_7$ cell lines using fluoro metric imaging plate reader technology. Analogues were also assayed for their ability to inhibit IL-1β release and to inhibit $P2X_7$-mediated pore formation in human THP -1cells.

Yasuhisa Kohara et al[29] have studied the design, synthesis and biological activity of benzimidazole -7-carboxylic acids bearing 5-oxo-1,2,4-oxadoazole, 5-oxo-1,2,4-thiadiazole, 5-thioxo-1,2,4-oxadiazole and 2-oxo-1,2,3,5-oxathiadiazole rings are described. These compounds were efficiently prepared from the key intermediates, the amidoximes. The synthesized compounds were evaluated for *in vitro* and *in vivo* angiotensin II receptor antagonistic activities.

Ornstein et al[31] have explored the excitatory amino acid antagonist activity in a series of decahydrosioquinoline-3-carboxylic acids and within this series found the potent and selective AMPA antagonist (3SR, 4a*RS*, 6*RS*, 8a*RS*)-6-(2-(1*H*-tetrazol-5-yl)ethyl)decahydroisoquinoline-3-carboxylic acid. In this and the preceding paper, the authors looked at the structure –activity relationships for AMPA antagonist activity in this series of compounds.

Antidepressant activity

Harfenist et al[31] have reported the inhibition of monoamine oxidase A (MAO-A) is believed to cause antidepressant and possibly antianxiety effects. It is shown in this paper that the same *in vitro* SAR can be carried over to tricycles whose potentially toxic amide function is replaced by an approximately substituted imidazoline, a 1,2,4- or 1,3,4-oxadiazole or an alkylated tetrazole moiety.

CONCLUSIONS

The introduction of drugs to the society is ancient as ailment and disease, and it has been considered to exist from the birth of humankind. The search for remedies from the areas of medicinal chemistry, pharmacology has led to the phenomenal growth in the drug industry. This paper reviews about the nitrogen - rich ring system of tetrazoles having diverse biological activity and which are still to be explored.

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