



Bioactive Triazoles: A potential review

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ABSTRACT

In recent years, Triazole derivatives have acquired conspicuous significance due to 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. This review article covers the latest information over active triazole derivatives having different pharmacological action such as, antiviral, anticonvulsant, anti-inflammatory, antibacterial, antifungal and antituberculosis. It can act as an important tool for medicinal chemists to develop newer compounds possessing triazole moiety that could be better agents in terms of efficacy and safety.

Key Words: Triazoles, Antimicrobial, antifungal, anti-inflammatory and anticonvulsant

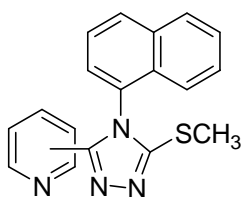
INTRODUCTION

In the previous years the synthesis of high nitrogen containing heterocyclic systems has been attracted to many pharmaceutical and agrochemical industries. In the pharmaceuticals, the triazole derivatives are used for the treatment of local and systemic fungal infections. They are also frequently observed in immune-compromised patients suffering from AIDS or subjected to invasive surgery, anti-cancer therapy. Triazole at positions 1 and 3 of the indole nucleus enhances the anti-inflammatory and CNS activity. The pharmacological activity of nitrogen containing heterocyclic system has been reported in the scientific literature in wide range. 1, 2, 4-triazol ring with diverse pharmacological effects have been reported as therapeutic agents in medicinal chemistry. Compounds having triazole moieties such as vorozole, anastrozole, and letrozole appear to be very effective aromatase inhibitors very useful for preventing breast cancer. It has also been reported that the conversion of the amino group in the 4 position in the 1, 2,4-triazole ring into an arylidene amino group causes antitumor activity. It is known that 1, 2, 4-triazole moieties interact strongly with the heme iron and aromatic substituents in the active site of aromatase. It also plays important roles in medicinal, agricultural and industrial fields. *N*-bridged heterocyclic derivatives derived from 1,2,4-triazoles show varied biological activities such as antimicrobial, anticonvulsant, anticancer, analgesic, anti HIV, and anti-inflammatory properties.

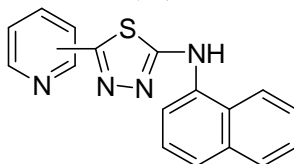
BIOLOGICAL ACTIVITIES ON TRIAZOLE AND THEIR DERIVATIVES

Antimicrobial activity

Synthesis of new 1,2,4-tri and 1,3,4-thiadiazoles (**1**) were prepared by Khosrow *et al.* [1] This synthesis bearing isomeric pyridyl and 1-naphthyl is reported using 1,4-disubstituted thiosemicarbazides in alkaline and acidic media, respectively. The methylthio and benzylthio 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.

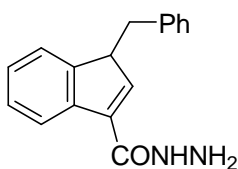


(1a)



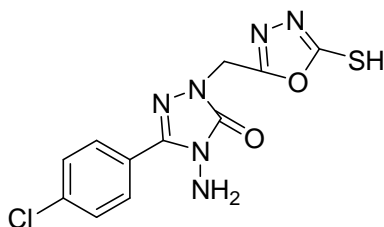
(1b)

Synthesis of Indole-3-carboxylic acid hydrazide (**2**) was prepared by Abdel-Rahman *et al.* [2] This synthesis was treated with aromatic aldehydes in ethanol to give the corresponding hydrazone derivatives in good yields. The indole carbohydrazide was incorporated into the 3-indolyloxadiazoles. This synthesized compound show good antibacterial and antifungal activity.



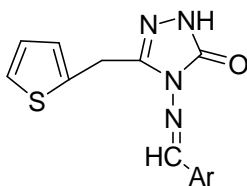
(2)

The synthesis of 4-amino-5-(4-chlorophenyl)-2-[(5-mercapto-1,3,4-oxadiazol-2-yl)methyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (**3**) was reported by Hakan *et al.* [3] This synthesis was performed starting from 4-Amino-5-(4-chlorophenyl)-2,4-dihydro 3H-1,2,4-triazol-3-one by four steps; then (3) was converted to the corresponding Schiff base (3a) by using 4-methoxybenzaldehyde. Finally, two Mannich base derivatives of (3a) were obtained by using morpholine or methyl piperazine as amine component. All newly synthesized compounds were screened for their antimicrobial activities and some of which were found to possess good or moderate activities against the test microorganisms.



(3)

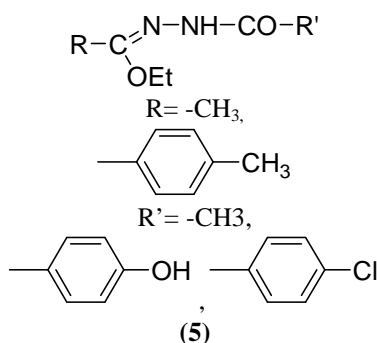
Synthesis of 4-[Arylidene-amino]-3-thiophen-2-ylmethyl-4,5-dihydro[1,2,4]triazole-5-one compounds (**4**) were reported by Yasemin *et al.* [4] This synthesis is obtained with Schiff base character from the reaction of 4-amino-3-thiophen-2-ylmethyl-4,5-dihydro-1H-[1,2,4]triazole-5-one) with various aldehydes. They were characterized by IR, NMR, ¹³C-NMR, and elemental analyses. The synthesized compounds showed good antifungal activity against yeast-like fungi.



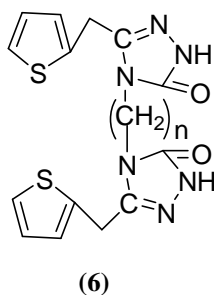
(4)

The syntheses of acylhydrazones (**5**) were reported by Nurhan *et al.* [5] A series of acylhydrazones were synthesized by the condensation of iminoester hydrochlorides with acyl hydrazine. 2, 5-Dialkyl 1, 3, 4-oxadiazoles were

obtained in the same reaction media. The treatment of acylhydrazones with hydrazine hydrate afforded 4-amino-3, 5-dialkyl-1, 2, 4- triazoles. This compound showed good antifungal activity only against yeast-like fungi.

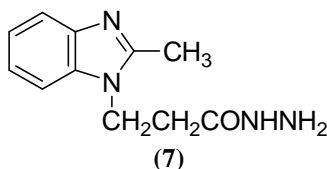


A series of novel di-[3(thiophen-2-yl-methyl)-4,5-dihydro-1H-[1,2,4]triazole-5-one-4yl]n-alkanes (**6**) were reported by Yasemin *et al.* [6] This series were obtained by the reaction of N¹-1-ethoxy-2-thiophen-2-yl-ethylene hydrazine carboxylic acid ethyl ester and diamines. The structures of the new compounds were inferred through IR, ¹H/¹³C NMR, elemental analyses, and mass spectral data. Many compounds were characterized by IR, ¹H/¹³C NMR, elemental analyses, mass, and X-ray spectral techniques. Mostly compounds showed good antifungal activity only against yeast fungi, while few compound showed antimicrobial activity against the bacteria *Pseudomonas aeruginosa* ATCC10145, *Enterococcus faecalis* ATCC29212 and the yeast fungi *Candida albicans* ATCC 60193 and *Candida tropicalis* ATCC 13803.



A series of acylhydrazones were reported by Mevlut *et al.* [7] This was synthesized from the reactions of iminoester hydrochlorides with acyl hydrazine. 2, 5-Dialkyl 1,3,4-oxadiazoles were obtained in the same reaction media. The treatment of acylhydrazones with hydrazine hydrate afforded 4-amino-3, 5-dialkyl-1, 2, 4-triazoles. All newly synthesized compounds were screened for their antimicrobial and antifungal activities using agar-well diffusion.

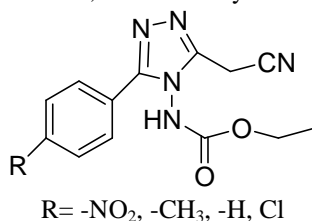
Reaction of 3-(2-methylbenzimidazol-1-yl) propanoic acid hydrazide (**7**) with CS₂/KOH was reported by Afaf *et al.* [8] This reaction gives oxadiazole which underwent Mannich reaction. Oxadiazole was treated with hydrazine hydrate to give triazole which was treated with both aldehydes and acetic anhydride to give and respectively. Some of these compounds showed potential antimicrobial activities.



1,2,4-triazole-3-thiol metronidazole derivatives were reported by Haythem *et al.* [9] This compound have been synthesized by treating 1,2,4-triazole-3-thiols with metronidazole tosylate (toluene-4-sulfonic acid 2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl ester) in DMF and in the presence of potassium carbonate as a base. S-alkylated and N-alkylated products were obtained, with the S-alkylated being the major products. All of the newly synthesized compounds were characterized by IR, ¹H NMR, ¹³C NMR, and high-resolution mass spectrometry. The antiparasitic activity of the compounds against *Entamoeba histolytica* and *Giardia intestinalis* was investigated. The antibacterial and antifungal activity of the compounds, assessed as minimal inhibitory concentration, was also investigated.

The synthesis of ethyl [3-(cyanomethyl)-5-alkyl-4H -1,2,4-triazol-4-yl]carbamates (**8**) were reported by Hacer *et al.* [10] This synthesized compound was performed starting from ethyl 2-[ethoxy(4-(aryl)methylene) hydrazine

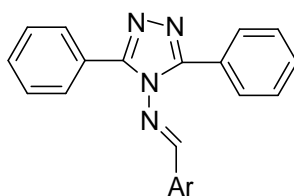
carboxylates. All the newly synthesized compounds were screened for their antimicrobial activities and were found to possess good or moderate antimicrobial activity. This paper presents the synthesis of a series of some new heterocyclic carbamates, conversion to Schiff bases, and the study of their antimicrobial activities.



(8)

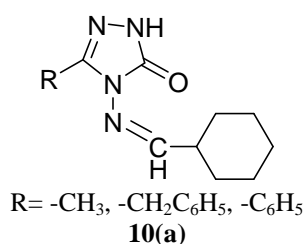
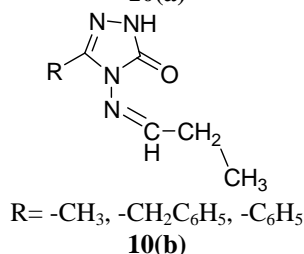
Anti-cancer Activity

A series of 4-arylidenamino-4H-1, 2, 4-triazole derivatives (**9**) were reported by Olcay *et al.* [11] This series were synthesized from the treatment of 4-amino-4H-1, 2, 4-triazole with certain aldehydes. 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 anticonvulsant, antifungal, anticancer, anti-inflammatory and antibacterial.



(9)

A series of novel 3-alkyl-4-cyclohexylmethylenamino-5-oxo-4,5-dihydro-[1,2,4]triazoles (**10a**) and 3-alkyl-4-hexylidenamino-5-oxo-4,5-dihydro-[1,2,4]triazoles (**10b**) were reported by Neslihan *et al.* [12] This were synthesized from the reaction of corresponding 3-alkyl-4-amino-5-oxo-4,5-dihydro-[1,2,4]triazole with cyclohexancarboxaldehyde and capronaldehyde. The *in vitro* antitumor activity of some selected compounds was screened by the National Cancer Institute (USA) against several human tumor cell lines. It is known that [1, 2, 4] triazole moieties interact strongly with the heme iron and aromatic substituents in the active site of aromatase.

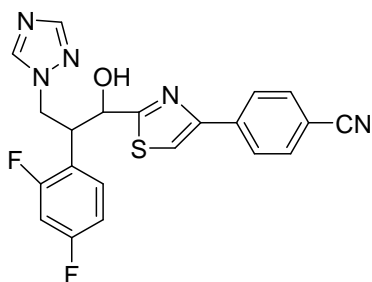
**10(a)****10(b)**

Anti- fungal Activity

The antifungal activity of UK 49,858, a difluorophenyl bis-triazole derivative reported by Kobayashi *et al.* [13] This was evaluated *in vitro* against seven strains of *Histoplasma capsulatum* and *in vivo* in AKR and C57BL/6 murine models of histoplasmosis. The therapeutic index of UK 49,858 was 4.3 for AKR mice and 7.1 for C57BL/6. The successful clinical trials of mono (N)-substituted imidazole compounds such as miconazole and ketoconazole against infections with yeasts and filamentous fungi (5) have led to the development of newer compounds in which the imidazole ring is replaced by the related 1,2,4-triazole ring. One such derivative, UK 49,858 [2-(2,4-

difluorophenyl) 1,3-bis(1H-1,2,4-triazol-1-yl)-2-propanol], was synthesized by Pfizer Central Research, Sandwich, England.

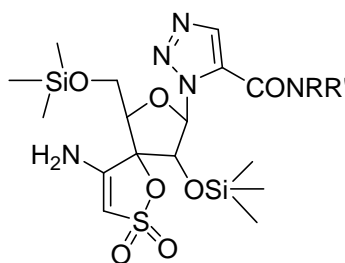
ER-30346 (**11**) was reported by Katsura *et al.* [14] This is a novel oral triazole with a broad spectrum of potent activity against a wide range of fungi. ER-30346, with MICs at which 90% of the strains tested are inhibited (MIC90s) ranging from 0.025 to 0.78 mg/ml, was 4 to 32 times more active than itraconazole, fluconazole, and amphotericin B against *Candida albicans*, *Candida parapsilosis*, and *Candida glabrata*. ER-30346 was 2 to 8 times more active than itraconazole and amphotericin B and 32 to >256 times more active than fluconazole. ER-30346 also showed good activity against dermatophytes, with MICs ranging from 0.05 to 0.39 mg/ml. Of the drugs tested, ER-30346 was the most effective drug against systemic aspergillosis. We studied the levels of ER-30346 in mouse plasma. The maximum concentration of drug in plasma and the area under the concentration-time curve for ER-30346 showed good linearity over a range of doses from 2 to 40 mg/kg of body weight.



(11)

Anti- Viral Activity

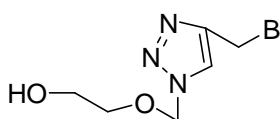
Synthesis of 5-*N*-alkyl and 5-*N,N*-dialkylcarbamoyl (**12a**) were reported by Velazquez *et al.* [15] This synthesis have been prepared and evaluated as inhibitors of HIV-1 replication. A new regiospecific synthetic procedure is described. The compounds were prepared by cycloaddition of the appropriate glycosylazide to 2-oxoalkylidetriphenyl- phosphoranes, followed by treatment with primary or secondary amines, to yield, exclusively, 5-substituted 1, 2, 3-triazole- TSAO analogues (**12b**). Several 5-substituted 1,2,3-triazole- TSAO derivatives proved to be potent inhibitors of HIV-1 replication with higher antiviral selectivity than that of the parent TSAO prototype.



R=H, CH₃; R'=H, CH₃

(12)

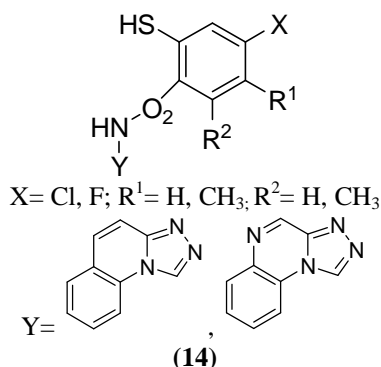
Synthesis of 1,2,3- triazole acyclonucleosides (**13**) were reported by Lazrek *et al.* [16] This is synthesized via 1,3-dipolar cycloaddition of *N*-9/*N*-1-propargylpurine/ pyrimidine with azidopseudo-sugar is described and none of them had Anti HIV activity. The synthesis and biological evaluation of modified nucleoside analogues have been very active research area for a no. of years. Substances containing a five membered heterocyclic base are important target in chemical synthesis because of their pronounced biological activities. Among them, ribavirin (virozole) which contains a substituted 1, 2, 4-triazole ring, represent the most successful one. The most common method described in literature for the preparation of 1, 2, 3-triazole ring is the 1,3-dipolar cycloaddition between substituted acetylenes as dipolarophiles and alkyl azide derivatives.



B= Uracil-1-yl, Chlorouracil-1-yl, Brmouracil-1-yl, fluorouracil-1-yl

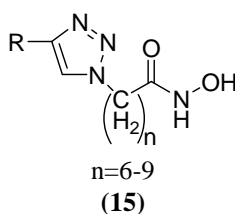
(13)

A series of 2-mercapto -N-(1,2,4-triazole-3-yl) benzene sulfonamide derivatives (**14**) reported by zazislaw *et al.* [17] This series containing the triazole moiety fused with a variety of heteromatic ring was obtained by reaction of 3-methylthio-1,4,2-benzodithiazine 1,1-dioxide derivatives with hydrazine. Preliminary screening data indicated that compounds were anti-HIV inactive whereas other compounds showed a high, fairly high or moderate activity against ten selected HIV mutants.



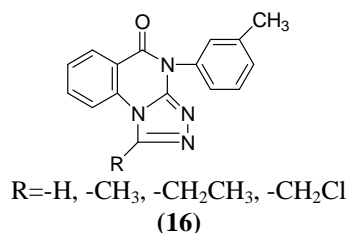
Anti-Malarial Activity

Histone deacetylase inhibitors (HDACi) (**15**) were reported by Patil *et al.* [18] These inhibitors are endowed with plethora of biological functions including anti-proliferative, anti-inflammatory, anti-parasitic, and cognition-enhancing activities. Parsing the structure-activity relationship (SAR) for each disease condition is vital for long-term therapeutic applications of HDACi. We report in the present study specific cap group substitution patterns and spacer-group chain lengths that enhance the antimalarial and antileishmanial activity. The anti-parasite properties of several of these compounds tracked well with their anti-HDAC activities.



Anti-Histaminic Activity

A series of novel 1-substituted-4-(3-methylphenyl)-1,2,4-triazolo[4,3-a]quinazolin-5(4H)-ones (**16**) were reported by Veerachamy *et al.* [19] This series were synthesized by the cyclization of 2-hydrazino-3-(3-methylphenyl)quinazolin-4(3H)-one with various one carbon donors. The starting material 2-hydrazino-3-(3-methylphenyl)quinazolin-4(3H)-one, was synthesized from 3-methyl aniline by a novel innovative route. When tested for their *in vivo* H1-antihistaminic activity on conscious guinea pigs, all the test compounds protected the animals from histamine induced bronchospasm significantly; hence it could serve as prototype molecule for further development as a new class of H1-antihistamines.



Anticonvulsant Activity

A series of 5-[2-(phenylthio)phenyl]-1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole derivatives were reported by Ali *et al.* [20] Compounds were evaluated *in vivo* for their anticonvulsant and muscle relaxant activities using PTZ and rotarod tests, respectively. Only compound 3-amino-5-[2-(phenylthio)phenyl]-4H-1,2,4-triazole showed weak anticonvulsant activity. However, most of the compounds were active in Rota rod test and the most effective compound was 5-[2-(phenylthio)phenyl]-1,3,4-oxadiazole-2(3H)-one which had comparable activity with diazepam.

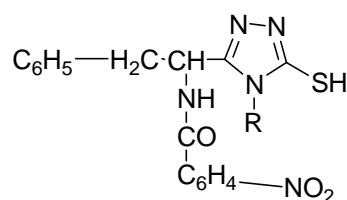
Several new N4-substituted triazolylthiazoles were reported by Bineshmarvasti *et al.* [21] These compound were prepared by the general method for 1,2,4-triazole ring closure. Anticonvulsant activity of compounds was measured

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 benzodiazepine receptors 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.

A new series of substituted quinoline-2(1*H*)-one and 1,2,4- triazolo[4,3-*a*]-quinoline derivatives were reported by Guan *et al.* [22] This series were designed and synthesized to meet the structural requirements essential for anticonvulsant properties. they do not provide satisfactory seizure control in all patients and typically cause notable adverse side effects (2, 3). Research to find more effective and safer antiepileptic drugs, is, therefore, imperative and challenging in medicinal chemistry.

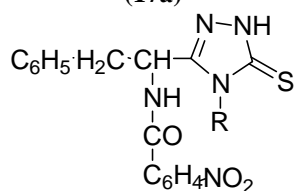
Anti-Inflammatory Activity

New 1,2,4-triazole derivatives (**17a,b**) containing a phenylalanine moiety were reported by Mihaela *et al.* [23] These derivatives have been synthesized by intramolecular cyclization of 1,4-disubstituted thiosemicarbazides in acid and alkaline media, respectively. The toxicity of the synthesized compounds was evaluated and the anti inflammatory study of the triazole compound established an appreciable antiinflammatory activity that is comparable with that of other nonsteroidal anti-inflammatory agents. It is known that many 1,3,4- thiadiazole and 1,2,4-triazole derivatives have biological activity, with their antibacterial, antimycobacterial, antimycotic, antifungal, antidepressive, and cardiotoxic action being notable. Recent research has also established for these heterocycles an analgesic and anti-inflammatory activity.



R= -C₆H₄Br

(17a)



(17b)

Current aspects of triazole derivative

Current FDA-approved triazole agents (fluconazole, itraconazole, posaconazole, and voriconazole) are widely prescribed for invasive fungal infections, and several other triazoles are in development (albaconazole, isavuconazole, ravuconazole). Although the relative risk of liver toxicity with triazoles appears low, dose-limiting toxicities and pharmacokinetic drug-drug interactions may complicate the use of these agents. New corrosion inhibitors, namely 3-vanilidene amino 1,2,4-triazole phosphonate (VATP) and 3-anisalidene amino 1,2,4-triazole phosphonate (AATP) were synthesised and their action along with biocide on corrosion control of copper in neutral aqueous environment has been studied.

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