ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 12, Issue, 08, pp.12950-12960, August, 2020

DOI: https://doi.org/10.24941/ijcr.39386.08.2020

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

REVIEW ARTICLE

1,2,4-TRIAZOLES: SYNTHETIC AND MEDICINAL PERSPECTIVES

Vagish, C.B., Sudeep, P., Jayadevappa, H.P. and Ajay Kumar, K.*

Department of Chemistry, Yuvaraja College, University of Mysore, Mysuru, India

ARTICLE INFO

Article History:
Received 30th May, 2020
Received in revised form
21st June, 2020
Accepted 10th July, 2020
Published online 30th August, 2020

Key Words:
Antifungal, anticancer, anti-inflammatory, complexes, hybrid, synthesis.

ABSTRACT

Triazoles can exists in two viz. 1,2,3- and 1,2,4- isomeric forms. The compounds with 1,2,4-triazole ring core have attracted the researchers all over the world due to their broad spectrum of synthetic and biological activities. There has been a significant interest in recent years in developing simple, clean, non-toxic, cost-effective and eco-friendly procedures for the synthesis with or without metal catalysts, and the exploration of these molecules to wide range of biological potencies. In this review, we have summarized the recent developments in the synthesis and their medicinal potencies of 1,2,4-triazole derivatives and the reports have been critically discussed.

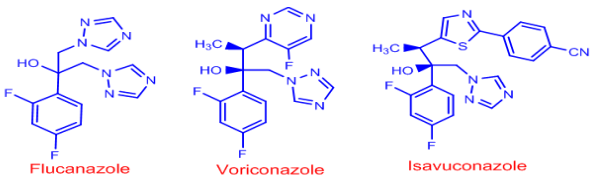
Citation: ***Vagish, C.B., Sudeep, P., Jayadevappa, H.P. and Ajay Kumar, K.*.. 2020.** "1,2,4-Triazoles: synthetic and medicinal perspectives", *International Journal of Current Research*, 12, (08), 12950-12960.

INTRODUCTION

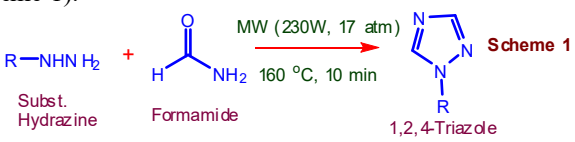
Heterocyclic compounds, in particular the compounds with 1,2,4-triazole core has attracted a continuously growing interest of synthetic organic chemists and those dealing with the medicinal compounds due to their versatile potential to interact with biological systems. The 1,2,4-triazole compounds possess a wide range of biological activities and are especially focused for antifungal behavior. Most of the currently available antifungal drugs contains 1,2,4-triazole core, few to mention are, Fluconazole used to treat various fungal infections that targets an enzymes Cytochrome P450 3A4, Cytochrome P450 2C9, Cytochrome P450 2C19, Cytochrome P450 51, and a transporter p-Glycoprotein 1; Voriconazole used to treat fungal infections, which targets Cytochrome P450 3A5, Cytochrome P450 2C19, Cytochrome P450 3A4; Isavuconazole is used to treat invasive aspergillosis and invasive mucormycosis in adults, which induces CYP2B6 and can decrease the amount of drugs that are metabolized by the enzyme, also inhibits P-Glycoprotein, BCRP, SLC22A2; Terconazole used to treat vaginal yeast infection, and it interact with the spermicide nonxynol-9. Although, currently many drugs available medicine, still there is a need for the development of new drugs as the currently available drugs are becoming ineffective due to the drug resistance developed by pathogens.

***Corresponding author:* Ajay Kumar, K.,**
Department of Chemistry, Yuvaraja College, University of Mysore, Mysuru, India

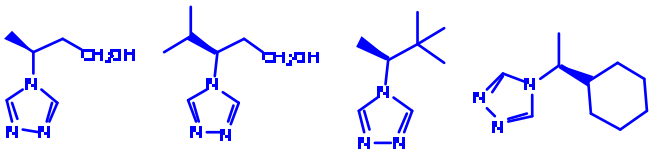
In this context, in this review article, we have summarized the developments in the synthetic protocols for 1,2,4-triazole ring system, their transformations to biologically important scaffolds, and medicinal applications. The prime focus was on the new methodologies that deal with the accessible and convenient synthesis, also wide range of medicinal properties of these classes of compounds.



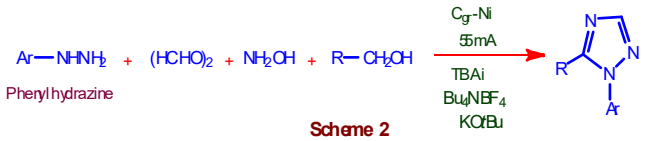
Synthesis of 1,2,4-triazoles: Most commonly employed, accessible route to synthesize 1,2,4-triazoles being; the reaction between an organic hydrazine and formamide under Microwave irradiation conditions. Organic hydrazide acts as a source on two nitrogen atoms, while formamide is a building block and is source of two carbons and a nitrogen atom of 1,2,4-triazole ring. For instance, Shelke and co-workers (1) reported a simple, efficient, and mild method for the synthesis of substituted 1,2,4-triazoles from hydrazines and formamide proceeds smoothly under microwave irradiation in the absence of a catalyst and shows excellent functional-group tolerance (Scheme 1).



1,2,4-triazoles attract attention as actively used medications and ligands for constructing coordination architectures. Guralskiy and co-workers(2) described four optically active 4-substituted 1,2,4-triazoles that have been prepared by Bayer's synthesis from the corresponding aliphatic chiral amines. Their approach tends to be universal towards different triazoles and permits to conserve a homochirality of substrates.

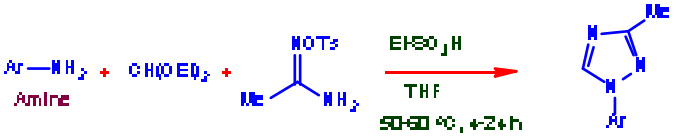


An electrochemical multicomponent reaction of aryl hydrazines, paraformaldehyde, NH_4OAc, and alcohols provides 1,5-disubstituted and 1-aryl 1,2,4-triazoles. Alcohols act as solvents as well as reactants and NH_4OAc is used as the nitrogen source (Scheme 2) (3). With the assistance of reactive iodide radical or I_2 and NH_3 electrogenerated *in situ*, this process effectively avoids the use of strong oxidants and transition-metal catalysts.



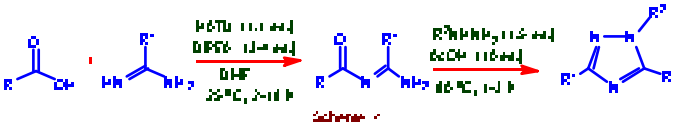
Scheme 2

A multicomponent process enables the synthesis of 1-aryl 1,2,4-triazoles directly from anilines, amino pyridines, and amino pyrimidines. It involves the one pot reaction between anilines or amino pyridines or aminopyrimidines, diethoxymethane, and *N*-(tosyloxy)acetimidamide in the presence of ethane sulphonic acid in THF as solvent (Scheme 3). Tam *et al* explored this reaction scope with different substrates, but the drawback observed is the longest reaction time, and there is need to improve the reaction time (4).

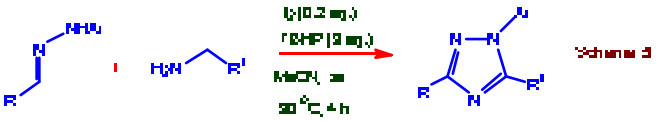


Scheme 3

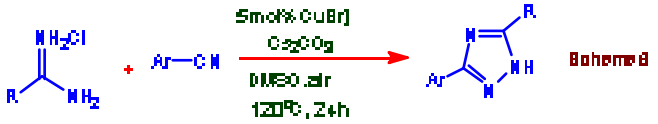
Mu *et al*(5) reported the synthesis of a series of triazole-pyrazole hybrids, and they were demonstrated that their synthetic analogues possess herbicidal against lettuce and bentgrass. A highly regioselective one-pot process provides rapid access to highly diverse 1,3,5-trisubstituted 1,2,4-triazoles from reaction of carboxylic acids, primary amidines, and monosubstituted hydrazines at acetic acid medium under reflux condition (Scheme 4) (6).



Chen *et al* reported a general and metal-free synthesis of 1,3,5-trisubstituted 1,2,4-triazoles from hydrazones and aliphatic amines has been achieved under oxidative conditions via a cascade C-H functionalization, double C-N bonds formation, and oxidative aromatization sequence in the presence of iodine as catalyst by air oxidation condition (Scheme 5) (7).

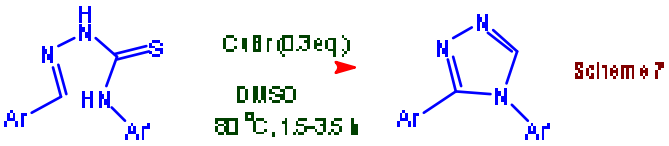


A copper-catalyzed reaction under an atmosphere of air provides 1,2,4-triazole derivatives by sequential N-C and N-N bond-forming oxidative coupling reactions (Scheme 6) (8) by Ueda *et al*. In the presence of readily available and inexpensive starting materials and the copper catalyst, Copper bromide in the presence of Cesium carbonate using DMSO as a solvent under reflux condition. A wide range of functional groups are tolerated.



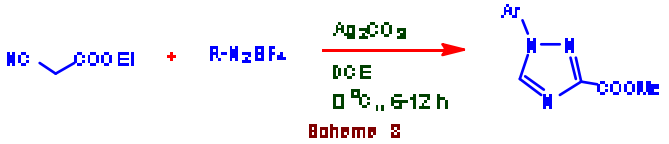
Scheme 6

Gogoi *et al* designed the triazole synthesis using Cu(I) catalyst which construct 4,5-disubstituted 1,2,4-triazole-3-thiones from arylidenearylthiosemicarbazides (Scheme 7) (9). Upon prolonging the reaction time under reflux condition, the in situ generated thiones are transformed to 4,5-disubstituted 1,2,4-triazoles via a desulfurization process, in the presence of Copper bromide and DMSO solvent.



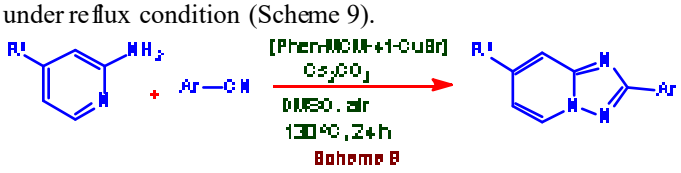
Scheme 7

Ethyl cyanoacetate is a useful reagent in the preparation of cyclopropyl system (10), pyrrolines (11, 12), isoxazoles (13, 14), piperidones (15, 16), and 1,2,4-triazoles. Liu and co-workers demonstrated the synthesis of 1,5-disubstituted 1,2,4-triazoles formed by Cu(II) catalysis in high yield, whereas Liu et.al report the 1,3-disubstituted 1,2,4-triazoles were selectively obtained under Ag(I) catalysis (Scheme 8) (17) using Silver(II) carbonate at water freezing temperature of 0°C. These regioselective catalytic methodologies provide a facile access to 1,2,4-triazole scaffolds with high efficiency, broad substrate scope, and excellent functional group compatibility.



Scheme 8

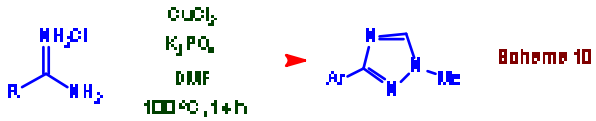
Xia *et al*(18) reported a cascade addition-oxidative cyclization of nitriles with 2-aminopyridines or amidines was achieved in the presence of 1,10-phenanthroline-functionalized MCM-41-supported copper(I) complex (Phen-MCM-41-CuBr) as the heterogeneous and recyclable catalyst and air as the oxidant under reflux condition (Scheme 9).



Scheme 9

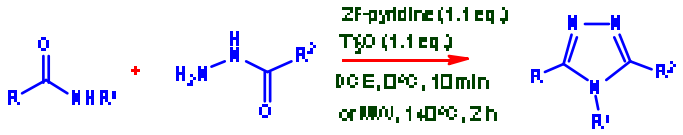
A facile and versatile catalytic system involving copper catalyst, K_3PO_4 as the base, and O_2 as the oxidant enables an efficient synthesis of 2,4,6-trisubstituted and 2,6-disubstituted 1,3,5-triazines and 1,3-disubstituted 1,2,4-triazoles from amidines with trialkylamines, DMSO, and DMF as the reaction

partners, respectively (Scheme 10). This protocol features an inexpensive catalyst, a green oxidant, good functional group tolerance, and high regioselectivity reported by Huang *et al*(19).



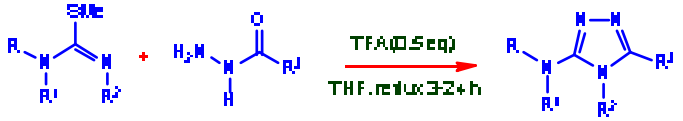
Scheme 10

Bechara *et al*(20) proposed the protocol involved, Triflic anhydride activation followed by microwave-induced cyclodehydration enables a one-pot synthesis of 3,4,5-trisubstituted 1,2,4-triazoles from secondary amides and hydrazides. In addition, the 1,2,4-triazole moiety is shown to be a useful directing group for Ru-catalyzed C-H arylation (Scheme 11). A Pd-catalyzed intramolecular C-H functionalization reaction allows access to 1,2,4-triazolophenanthridine.



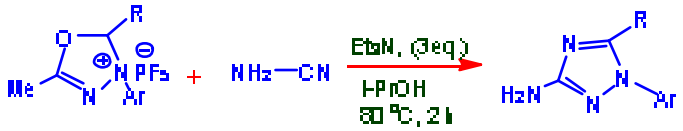
Scheme 11

Batchelor co-workers (21) reported the synthesis of a series of 3-*N,N*-Dialkylamino-1,2,4-triazoles, the method involve the reaction of *S*-methylisothioureas and acyl hydrazides in the presence of trifluoroacetic acid in THF medium under reflux conditions (Scheme 12). The reaction conditions are relatively mild and tolerate a broad range of functional groups.



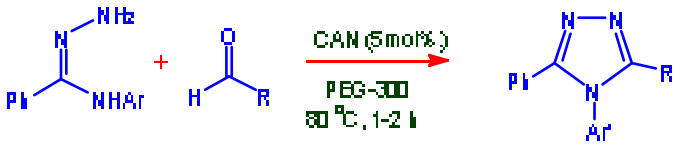
Scheme 12

Hexafluorophosphoric acid promotes the formation of 1,3,4-oxadiazolium hexafluorophosphate salts from *N'*-acyl-*N*-aroyl-*N*-arylhydrazides or *N'*-acyl-*N*-acyl-*N*-arylhydrazides under mild conditions. A subsequent reaction by Wong and co-workers with cyanamide in propan-2-ol in the presence of triethylamine generates 1,5-disubstituted 3-amino-1*H*-1,2,4-triazoles using the Et_3N base, isopropyl alcohol under reflux condition for about 2 hours to obtain good yields (Scheme 13) (22).



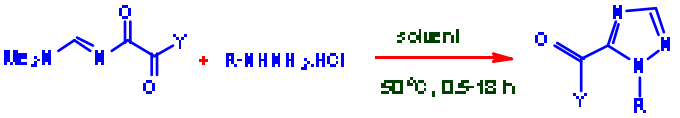
Scheme 13

Hydrazones were regarded as useful scaffolds for the generation of nitrile imines (23) useful reactive intermediates in 1,3-dipolar cycloaddition (24, 25), and in the construction of five membered heterocycles like pyrazoles (26), pyrazolines (27, 28), oxadiazoles (29, 30), (31, 32) and triazoles. For instances, An environmentally benign synthesis of various 3,4,5-trisubstituted 1,2,4-triazoles and *N*-fused 1,2,4-triazoles via ceric ammonium nitrate and PEG 300 catalyzed oxidative cyclization of amidrazones and aldehydes using polyethylene glycol as recyclable reaction medium is economic and potentially viable for commercial applications by Nakka *et al* under reflux condition (Scheme 14) (33).



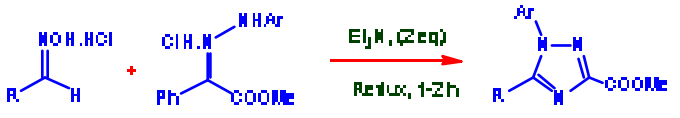
Scheme 14

Xu co-workers (34) reported a series of new oxamide-derived amidine reagents can be accessed in excellent yield with minimal purification necessary. A subsequent reaction of these reagents with various hydrazine hydrochloride salts efficiently generates 1,5-disubstituted-1,2,4-triazole compounds in good yields (Scheme 15). Both aromatic and aliphatic hydrazines react readily with the amidine reagents under very mild reaction conditions.



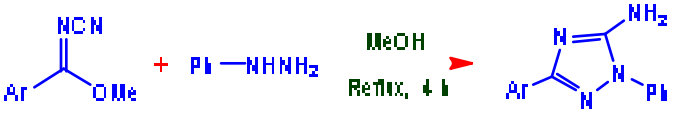
Scheme 15

Aromatic aldoximes are important reagents for the generation of nitrile oxides (35), and in the preparation of isoxazoles (36) and triazoles. For example, an effective 1,3-dipolar cycloaddition for the synthesis of 1,3,5-trisubstituted 1,2,4-triazole derivatives by reaction of oximes with hydrazonoyl hydrochlorides by Wang et.al using triethylamine as a base gave the desired 1,3,5-trisubstituted 1,2,4-triazoles in good yields (Scheme 16) (37). The reaction was applicable to aliphatic, cyclic aliphatic, aromatic and heterocyclic oxime substrates.



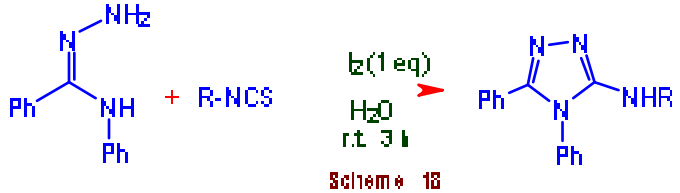
Scheme 16

A 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, Yin co-workers (38) reported the substituted *N*-cyanobenzimidate products may also undergo a cyclization reaction to give 1,2,4-triazole derivatives in high yields in the presence of methanol under reflux condition (Scheme 17).



Scheme 17

Jatangi and co-worker (39) reported the 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 at room temperature (Scheme 18). The scalable protocols exhibited excellent substrate tolerance.



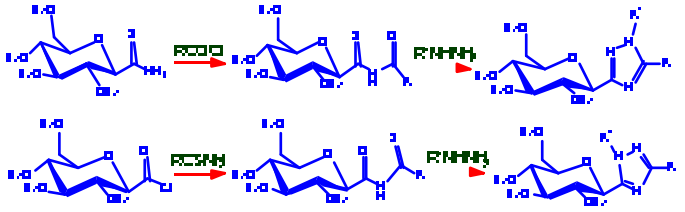
Scheme 18

Guirado *et al* (40) developed a convenient synthetic approach to 3-aryl-1,2,4-triazoles, which involves the reaction of

benzamides and chloral hydrate to form chloramides, which in turn reacted with a phosphorus pentachloride/phosphorus oxychloride mixture undergoing a near quantitative conversion to *N*-(1,2,2,2-tetrachloroethyl)benzimidoyl chlorides, which were treated with hydrazine hydrate to directly give 3-aryl-1,2,4-triazoles in high to quantitative yields (Scheme 19). The formation of these products involves a double condensation process followed by a spontaneous β-elimination of chloroform. Theoretical computational studies on aromatization of 3-aryl-5-trichloromethyl-1,2,4-triazolines via chloroform elimination and to determine relative stabilities of 3-phenyl-1,2,4-triazole tautomers were performed using *ab initio*, density functional (B3LYP) methods.

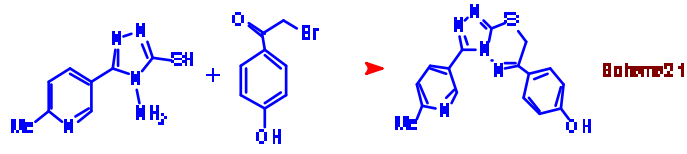
Scheme 19

Szabo *et al*(41) demonstrated a highly variable synthetic routes toward trisubstituted *C*-glycopyranosyl 1,2,4-triazoles, which involve acylation of *O*-perbenzoylated 2,6-anhydro-D-*glycero*-D-*gulo*-heptonothioamide *with acid chloride to get N*-Acyl-thioamides and amidation of *O*-perbenzoylated 2,6-anhydro-D-*glycero*-D-*gulo*-heptonoyl chloride to thioamides. These precursors reacted with substituted hydrazines in a regioselective manner to yield 3-β-D-glucopyranosyl-1,5-disubstituted- and 5-β-D-glucopyranosyl-1,3-disubstituted-1,2,4-triazoles, respectively (Scheme 20). It was observed that the analogous *N*-acyl-2,6-anhydro-heptonamides failed to give the triazoles with hydrazines.



Scheme 20

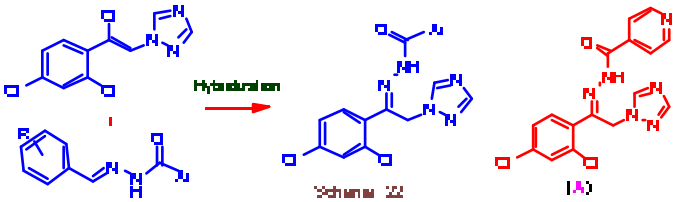
1,2,4-triazole-molecular hybrids: Heterocycles are in the center of research due to their versatile application. Fused heterocyclic triazoles also possess important clinical applications. In addition to these important biological applications, 1,2,4-triazoles are also of great utility in synthetic organic chemistry in their post-transformation to molecular hybrids of greater biological potencies. Literature reveals that 1,2,4-triazole hybrids possesses enhanced biological activities comparable to the corresponding precursors, and are of greater applications in agriculture and polymer industries, which attracted the researchers all over the globe to work in this field. For instance, Vora and co-workers (42) reported the efficient transformation of 1,2,4-triazole to fused 1,2,4-triazole-thiadiazines (Scheme 21), and evaluated for their antibacterial activity. The result indicated the enhanced antibacterial activity of the synthesized hybrids comparable to their precursors.



Scheme 21

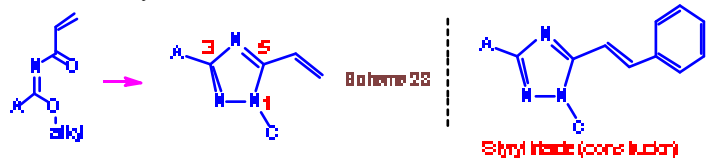
Aboeldahab and co-workers (43) synthesized two series of 3′,4′-dihydro-2′*H*-spiro(imidazolidine-4,1′-naphthalene)-2,5-dione and 1-(3-methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-1H-1,2,4-triazole-3-carboxamides as histone deacetylase inhibitors (HDACIs) involving two potential surface recognition moieties and evaluated for their anti-proliferative activities. Amongst them, the latter series of compounds have demonstrated as potential HDAC-tubulin dual inhibitors, promoted with structural similarities between (1-(3-methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,4-triazole-3-carboxamide) nucleus, and Combretastatin A4. They have also exhibited tubulin inhibitory activities with their docking into colchine binding site of β-tubulin, and therefore they behave as potent HDAC-tubulin dual inhibitor.

Dehestani *et al*(44) designed and synthesized a series of phenacyl triazole hydrazones from appropriate phenacyl triazoles and aryl acid hydrazidesscaffolds (Scheme 22) based on the hybridization as new anticonvulsant agents. The *in vivo* anticonvulsant evaluation of synthesized compounds by using MES and PTZ tests revealed that they are more effective in MES model respect to PTZ test. All compounds showed 33–100% protection against MES-induced seizures at the dose of 100 mg/kg. However, the isonicotinic acid hydrazide derivative (A) showed the best profile of activity in both models. Molecular docking studies of compound (A) with different targets (NMDA, AMPA, $GABA_A$ and sodium channel), postulated that the compound acts mainly via $GABA_A$ receptors.



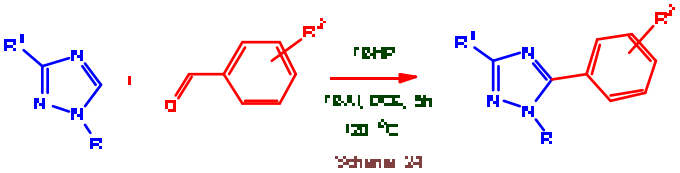
Scheme 22

The reaction of variously substituted acylimidates with hydrazine derivatives represents an efficient and easy to set synthetic entry towards 5-vinyl-1,2,4-triazole derivatives (Scheme 23) (45). The construction of the triazole ring allows the installation of variety of substituent combination at the N(1), C(3) and C(5) positions of the five-membered heterocycle in good to high yields. The method reveals selective towards 5-vinyl-1,2,4-triazoles avoiding the potential formation of seven- and five-membered side-products. First lines of Pd-catalyzed arylation of the vinyl fragment towards 5-styryl-1,2,4-triazoles and Cu-catalyzed arylation at the N(1) site are finally described.



Scheme 23

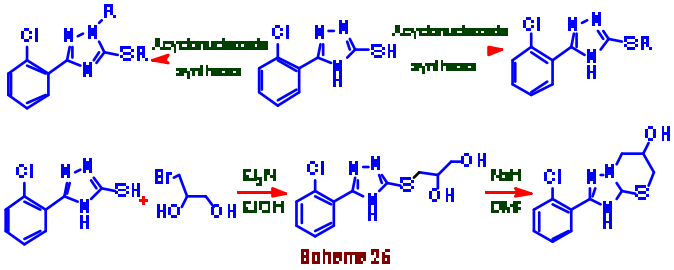
Agiso and co-workers (46) developed a simple, efficient and eco–friendly method for synthesis of 3,5–disubstituted–1,2,4–triazoles and 1,3,5–trisubstituted–1,2,4–triazoles from 3–monosubstituted–1,2,4–triazoles and 1,3–disubstituted–1,2,4–triazoles respectively using tetrabutylammonium iodide (TBAI) as catalyst and TBHP as oxidant under mid reaction conditions. Their method provides structurally diverse 3,5–disubstituted 1,2,4–triazoes and 1,3,5—trisubstituted–1,2,4–triazoles in good to excellent yields (Scheme 24). The synthesized compounds show antimicrobial activities.



Scheme 24

Aouad and co-workers (47) reported an efficient and convenient regioselective synthesis of a series of *S*- and *S,N*-

bis(acyclonucleoside) analogues carrying 5-(2-chlorophenyl)-2,4-dihydro-1,2,4-triazole-3-thione, and a facile and straightforward synthesis of triazolothiazines (Scheme 25). They were carried out synthetic compounds for cytotoxicity against three different types: human liver cancer cell line (Hep G2), Michigan cancer foundation-7 (MCF-7) and human colorectal carcinoma cell line (HCT116). Result indicated that these compounds have considerable anticancer activity. Biological data for most of the S-acyclonucleoside analogues and *S,N*-bis(acyclonucleoside) analogues showed excellent activity with micromolar (μM) half maximal inhibitory concentration (IC50) values against tumor cells. EGFR assay and tubulin inhibition assay analysis were performed for the most active compounds to get more details about their mechanism of action.



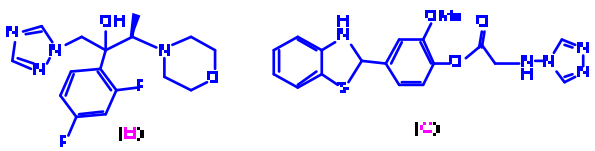
Bohome 26

1,2,4-triazole coordination complexes: Metal co-ordinate complexes of 1,2,4-triazoles have vital importance in pharmacological applications. In this context, researchers have done extensive studies on the preparation and their physic-chemical and biological applications. For instance, Li and co-workers (48) have reported two Cu(II) complexes, namely, $(Cu\mathbf{L}^1{}_2(OAc)_2)\cdot MeOH$ and $(Cu\mathbf{L}^2{}_2(OAc)_2)$ were synthesized based on two 1,2,4-triazole fungicides of paclobutrazol ($\mathbf{L}^1$) and diniconazole ($\mathbf{L}^2$). The result shows that both the complexes have similar structures and adopt octahedral coordination mode. The Cu(II) atoms in both the complexes lie on a crystallographic inversion center and are coordinated with two triazole groups and two acetate anions. Further, the prepared complexes have shown that the toxicity of latter complex was 6.96–23.39 times greater than that of former complex as it possesses both C=C linkage and 2,4-dichlorobenzene moiety, and shows higher synergy levels for the molecular-level mixture of copper cation. The results also show that both the synthesized complexes showed superior activities of 1.20–5.94 times to those of their ligands. The DFT calculation results of the title complexes and their ligands reveal that the complexes have a new active site of metal cation, smaller HOMO–LUMO energy gaps and lower polarity than their ligands, which should be responsible for the enhanced bioactivities after complexation.

Tikhonov and co-workers (49) studied spectroscopically the formation of coordination of silver ions in the polymer structure of poly-1-vinyl-1,2,4-triazole and its copolymers, which shows that the silver complexes are characteristic of the d^9 square planar complex of Ag(II) ion. However, they have detected the sites of polymer. Li *et al*(50) reported the preparation of two functionalized Schiff base ligands 4-(1*H*-imidazol-5-ylmethylene-amino)-4*H*-1,2,4-triazole (imztrz) and 4-(*p*-tolylidene-amino)-4*H*-1,2,4-triazole (toltrz), and a series of triazole based polynuclear Fe complexes. Compounds $\{(Fe^{II}(toltrz)_2(C_2O_4))\cdot 10H_2O\}_n$ and $\{(Fe^{II}(5\text{-imztrz})\ (C_2O_4))\cdot 2H_2O\}_n$ are oxalate bridged Fe^{II} complexes with triazole showing a linear 1D chain structure. Magnetic susceptibility measurements indicate that all three compounds show weak anti-ferromagnetic exchange interaction between the adjacent Fe centers.

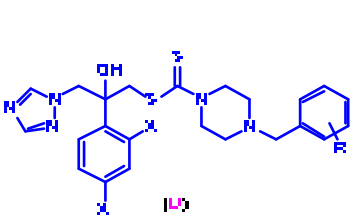
Medicinal applications: The compounds with 1,2,4-triazole core occupies the prime position in medicinal chemistry because of their versatile biological activity and clinical applications. A number of triazole derivatives are associated with good biological as well as pharmacological activities like antibacterial, anti-inflammatory, antihypertensive, antifungal, anticancer and antitumor activity. Research in the field of pharmaceutical has its most important task in the development of new better drugs and their successful introduction into clinical practice due to bacterial resistance over old drugs and other effects.

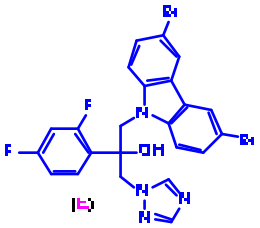
Antimicrobial and Antiviral activity: The incidence of life-threatening fungal infections has dramatically increased for decades. 1,2,4-Triazole is a very important scaffold in medicinal chemistry due to the wide spectrum of biological activities and mainly antifungal activity of 1,2,4-triazole derivatives. In an attempt to develop novel antifungal agents, a series of triazole conjugated novel 2,5-diaryl 1,3,4-oxadiazoles derivatives efficiently prepared starting from methyl salicylate have shown potent antibacterial and antifungal activities. The synthetic analogues have showed promising features in inhibiting the microorganisms by interacting with enzymes involved in peptidoglycan synthesis and bacterial cell wall biosynthesis (51). Exposure of tebuconazole, a triazole fungicide in soil selects in agriculture for resistance to triazoles in *A. fumigates, which is an* invasive aspergillosis causing high morbidity and mortality in immunocompromised patients.The probability of ARAF developing in soils depends upon the concentrations of tebuconazole after application (52).Wu and co-workers (53) synthesized two series of analogues of Voriconazole, (2*R*,3*R*)-1-(1*H*-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-(*N*-substitutied)-2-butanols, and studied their antifungal activities. It was observed from the results of their study, most of the target compounds possessed excellent antifungal activity; even some of them having better activities than flucanozole, in particular compound (**B**) of the series, had strong activity to inhibit the growth of ten fungal pathogens. But it didn't exhibit good activity in *in vivo* value, however, the docking experiments demonstrated that it possesses superior affinity with target enzyme by strong hydrogen bond from morpholine ring. Agri-vitality of benzimidazoles and 1,2,4-triazoles against ergosterol and β-tubulin prompted Ahuja and co-workers (54) to design a series of benzimidazolyl-1,2,4-triazoles as twin-enzyme targeted inhibitors. *In silico* molecular docking, Lipinski parameters, FMO approach and toxicity analysis of benzimidazoly-1,2,4-triazoles shows ten-fold enhanced antimycotic activity against *F. verticillioides*, *D. oryzae*, *C. lunata* and *F. fujikuroi* than the standard carbendazim. Remarkably, compound (**C**) inflicted the most promising activity against all the test fungi with ED_{50} value ranging from 16-21 μg/ml. Ultra microscopic details revealed compound 8 not only caused aberrant distortions resulting in collapsed hyphae but also efficiently shrunken the spores resulting in reproduction inhibition, as possible cause of fungal growth inhibition.



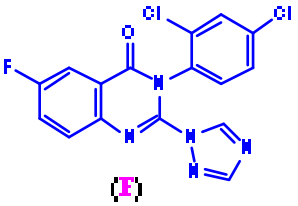
The mechanism of antifungal action of the 1,2,4-triazole core is inhibition of 14-alpha-demethylase enzyme (CYP51). Stingaci and co-workers (55) reported that their synthesized series of vinyl 1,2,4-triazoles have exhibited antibacterial and antifungal susceptibilities, in particular found most sensitive against the bacterium *Xanthomonas campestri*. In growing need for antifungal drugs to combat pathogenic bacteria and fungi, Beyzaei *et al*(56) synthesized 4,5-disubstituted 1,2,4-triazole-3-thiones by the reaction of hydrazides with isothiocyanates under optimized conditions in deep eutectic solvent of potassium carbonate-glycerol (1:5 M ratio). The report shows that the synthesized compounds possess promising antibacterial and antifungal activities, in particular, compound 5-(4-hydroxyphenyl)-4-(4-nitrophenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione has significant antioxidant activity. The possible interaction mechanism of synthetic triazoles with 1IYL enzyme on *A. fumigatus* investigated by molecular docking indicate that the hydrogen bond acceptor strength of N-1 in 1,2,4-triazole rings was the main cause of activities.

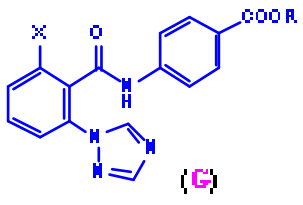
Mahamoudi *et al*(57) synthesized flucanazole analogues 1*H*-1,2,4-triazole alcohols containing *N*-(halobenzyl)piperazine carbodithioate moiety as potent antifungal agents. Their investigation result shows that compound (D) of the series possess excellent antifungal activity with MIC values of 0.063–0.5 µg/mL being 4–32 times more potent than fluconazole. Docking studies confirmed the better fitting of compound in the active site of lanosterol 14α-demethylase (CYP51) enzyme. The potency of this compound against fluconazole-resistant isolates along with its minimal toxicity against human erythrocytes and HepG2 cells make this prototype compound as a good lead for discovery of potent and safe antifungal agents. Zhang and co-workers (58) synthesized a series of carbazole-triazole conjugates and screened for their antifungal activities. The results shows that most of the compounds exhibited noticeable antifungal activities, particularly, compound 3,6-dibromocarbazolyl triazole (E) has displayed excellent inhibitory efficacy against tested fungal strains (MIC = 2–32 µg/mL), its combination use with flucanazole could enhance the antifungal efficacy, and it did not obviously trigger the development of resistance in *C. albicans*.


(D)

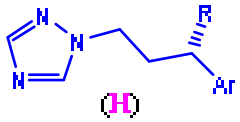

(E)

In recent times, the 1,2,4-triazole fungicides are widely used for crop diseases control, and their toxicity to wild lives and pollution to ecosystem have attracted greater attention. But, the challenge is the evaluation of these compounds toxicity quickly and efficiently to environmental organisms, which overcome by *in silico* QSAR studies, a potential tool for predicting the acute toxicity of 1,2,4-triazole fungicides to zebrafish embryos, and also the development of eco-friendly 1,2,4-triazole pesticides (59). Cheng and co-workers (60) prepared two series of 1,2,4-triazole-benzoyl arylamine derivatives, a Fluquincazole (F) analogues, and screened for their activities against *G. graminisvartritici*, *S. sclerotiorum* and *F. graminearum*. The results indicated that most of the synthesized derivatives displayed antifungal activities, particularly the compound (G) displayed the most potent antifungal activities with EC_{50} values of 0.01, 0.19 and 0.12 $\mu g\,mL^{-1}$ respectively, and it can be a lead compound for development of novel fungicide. The SAR shows that election-withdrawing group at *pata*-position of aniline was favourable for high activities, and the preferred groups were alkoxy carbonyls.

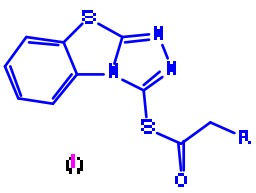

(F)

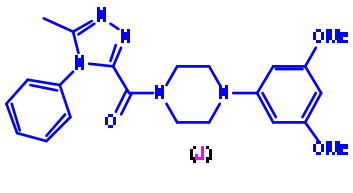

(G)

Cao and co-workers (61) prepared chiral triazole derivatives (**H**) via asymmetric synthesis, and which has been successfully characterized by optical rotations. Further, they investigated their *in vitro* antiviral activities against EV71 and CVB3 in cell-based assays. Result shows that 13 synthetic triazole derivatives inhibited the CPE of EV71 on RD cells, with EC_{50S} in the 5.3–15.9 µg/ml range and corresponding SI of 4.0–27.6 µg/ml. The most potential molecules are the compounds **are** with *S*-configuration, and which exhibit good SI values compared with the control Ribavirin.


(H)

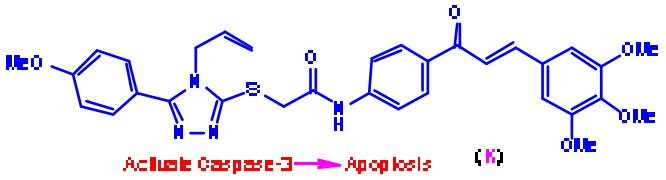
Anticancer, Antiproliferative and Antileishmanial activity: Abdelazeem and co-workers (62) reported the synthesis of *S*-benzo(4,5)thiazolo(2,3-*c*)(1,2,4)triazoles (**I**), and their cytotoxicity against three cancer cell lines, Hep3B, A549, and MCF-7. The compounds were screened by NCI for growth inhibitory activities against 60 cancer cell lines. The results revealed significant cytotoxic activities for these compounds, some exhibited the highest cytotoxicity against the selected cancer cell lines with IC_{50} values between 3.17 and 14.18 µM. The SAR of compounds indicated favorable cytotoxic results on the expansion of the cyclic amine and the substitution with aminothiazole moiety. Wang *et al*(63) synthesized a series of 5-methyl-4-aryl-3-(4-arylpiperazine-1-carbonyl)-4*H*-1,2,4-triazoles and evaluated for their antiproliferative and tubulin polymerization inhibitory activities. The study reveals that, some compounds of the series exhibited moderate activities *in vitro* against the three cancer cell lines SGC-7901, A549 and HeLa. Compound (**J**) of the series exhibited the highest potency against the three cancer cell lines, and inhibited the tubulin polymerization.


(I)

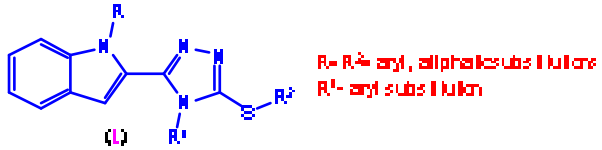

(J)

Ahmed and co-workers (64) prepared 1,2,4-triazole-chalcone hybrids, and screened for their cytotoxic activity against different cancer cell lines. Result of the investigations indicated that some compounds, in particular, compound (**K**) of the series, shown the highest cytotoxicity among the tested compounds against human lung adenocarcinoma A549 cells with IC_{50} ranging from 4.4 to 16.04 µM compared to cisplatin with IC_{50} of 15.3 µM. Flow cytometric analysis of the tested compounds showed an increase in the number of apoptotic cells in a dose-dependent manner. The

study demonstrated that 1, 2, 4-triazole-chalcone hybrids induced apoptosis *via* increased level of proapoptotic protein Bax, release of cytochrome c from mitochondria and activation of caspase-3/8/9 proteins.

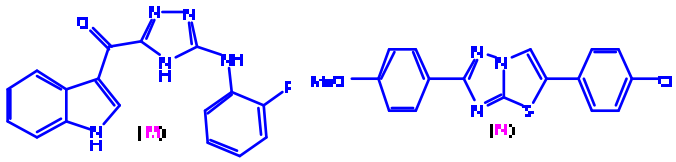


PARP-1, a nuclear protein, is one of the key member of the DNA repair assembly and thereby emerged as an attractive target in anti-cancer drug discovery. PARP-1 plays a key role in terms of base excision repair, which is an important pathway for cell survival in breast cancer with BRCA1/BRCA2-mutation. In this context, Boraei and co-workers (65) worked on structure based drug design, and explored that triazole-thione and alkylsulfanyl-triazole scaffolds (**L**) could act as novel prototypes of PARP-1 inhibitors for the development of antitumor therapeutics to treat breast cancer. The Results disclosed that the some lead molecules were efficiently impeding cell migration and cell proliferation, potentially by interfering with PARP-1 enzymatic activities, and some compounds have anti-proliferative activity in MCF-7 breast cancer cell lines.

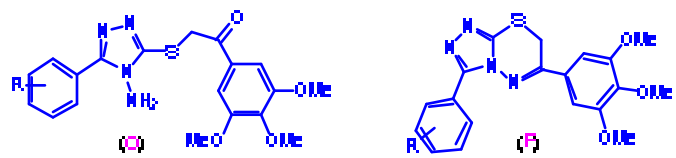


Zhao and co-workers (66) have synthesized a series of novel triazole nucleobase analogues containing steroidal/coumarin/quinoline moieties and evaluated *in vitro* for their anti-cancer activity in gastric cancer cell lines (MGC-803, SGC-7901) and normal gastric epithelial cells (GES-1). Results indicated that compounds significantly inhibited the proliferation of the tested cancer cells, and demonstrated good anti-proliferation activity against MGC-803 cells (IC_{50} = 1.48 µM) and SGC-7901 (IC_{50} = 2.28 µM) cells as well as the best selectivity between the cancer and normal cells, and therefore the compounds could be used as a promising skeleton for anti-gastric cancer agents with improved efficacy and less side effects.

Thymidine phosphorylase (TP) is over expressed in several solid tumors and its inhibition can offer unique target suitable for drug discovery in cancer. In this view, Shahzad and co-workers (67) demonstrated that a series of 1,2,4-triazoles can have inhibitory potential against thymidine phosphorylase enzyme. Their study reveals that, some compounds of the series have potent inhibition against thymidine phosphorylase with IC_{50} values of 61.98 ± 0.43 to 273.43 ± 0.96 µM, also, the compounds exhibited angiogenic response in the CAM assay. The SAR and docking studies of selected triazoles demonstrated that the compounds interacted with active site residues of thymidine phosphorylase enzyme through π-π stacking, thiolate and hydrogen bonding interactions. Naaz *et al*(68) prepared a set 1,2,4-Triazole (M) based topsentin analogues by replacing imizadole moiety of topsentin through a multistep synthesis, and screened the compounds for single dose (10 µM) against a NCI panel of 60-human cancer cell lines. Among all cancer cell lines, colon (HCC-2998) and Breast (MCF-7, T-47D) cancer cell lines were found to be more susceptible for this class of compounds. Some compounds of the series exhibited good anti-proliferative activity against various cancer cell lines with IC_{50} 2.42-3.30 µM against MCF-7 human cancer cell line than that of the standard drug doxorubicin IC_{50} 6.31 µM. *In silico* docking studies represented that compounds binding at colchicine binding site of β-tubulin. A series of novel compounds thiazolo(3,2-b)(1,2,4)-triazoles were designed and synthesized by El-Sherief *et al*(69). They were evaluated the synthesized compounds for their anti-proliferative activities against NCI 60 cell line. Compounds were selected for evaluation at single concentration of 10 µM towards panel of sixty cancer cell lines and results showed all the thiazolo (3,2-b)(1,2,4)-triazoles have remarkable antiproliferative activities against the cell lines. Among them, compound (N) showed high selectivity against renal subpanel with selectivity ratio of 6.99 at GI_{50} level, and showed promising EGFR inhibitory activity of cancer cell proliferation and also observed to be moderate BRAF and tubulin inhibitors.

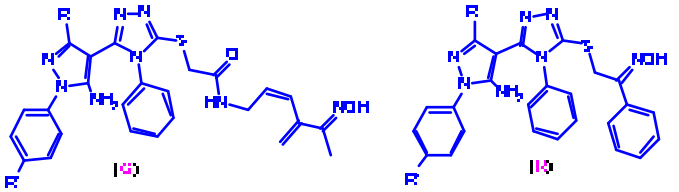


Several flexible and rigid analogs of 4*H*-1,2,4-triazoles compounds (58) and (59) bearing trimethoxyphenyl pharmacophoric unit, were designed and synthesized as potential anticancer agents. The in vitro cytotoxic assay indicated that both flexible and rigid analogs namely, (O) and (P) respectively, can potentially inhibit the growth of cancerous cells (A549, MCF7, and SKOV3), with IC_{50} values less than 5.0 µM. These compounds showed high selectivity towards cancer cells over normal cells, as they had no significant cytotoxicity against L929 cells (70). Suleymanoglu and co-workers (71) studied the synthesis, characterization by DFT and their antileishmanial activity of 4-amino-1-((5-mercapto-1,3,4-oxadiazole-2-yl) methyl)-3-(thiophene-2-ylmethyl)- 1*H*-1,2,4-triazole-5(4*H*)-one and 4-amino-1-((4-amino-5 mercapto-4*H*-1,2,4-triazole-3-yl)methyl)-3-(thiophene-2-ylmethyl)-1*H*-1,2,4-triazole-5(4*H*)-one, and demonstrated that these compounds have remarkavel potency against *Leishmania infantum* promastigots.



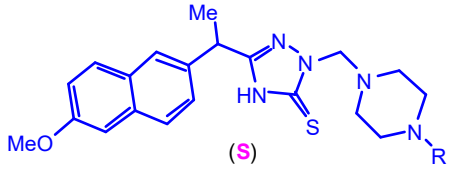
Anti-inflammatory and Anti-diabetic activity: Fadaly *et al*(72) synthesized series of hybrid structures (Q) and (R) containing 1,2,4-triazole-pyrazole hybrid with oxime as NO donor moiety and evaluated for anti-inflammatory, cytotoxic activities and NO release. Results indicated that all compounds were more selective for COX-2 isozyme having COX-2 selectivity indexes (S.I. = 9.78, 8.57, 10.78 and 10.47 respectively) in comparison to celecoxib (S.I. = 8.68). Similarly, some compounds of the series were most potent anti-inflammatory derivatives with ED_{50} = 46.98–54.45 µmol/kg better than celecoxib (ED_{50} = 76.09 µmol/kg), and were significantly less ulcerogenic (ulcer indexes = 2.79–3.95) upon comparison with ibuprofen (ulcer index = 20.25)

and comparable with celecoxib (ulcer index = 2.93). The target derivatives (Q) and (R) showed good activities against A-549, MCF-7, HCT-116 and PC-3 cancer cell lines. Docking mode of final designed compounds with celecoxib (ID: 3LN1) represented that their triazole ring adopted as the core aryl in Y shaped structure.



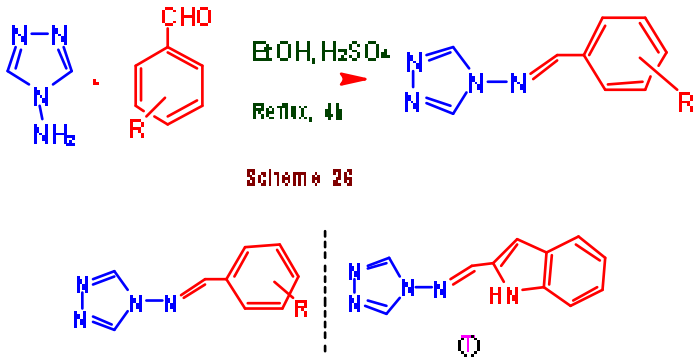
Naproxen analogs of 1,2,4-triazole-5-thione *N*-Mannich derivatives (**S**) were designed and synthesized using classical Mannich reaction by reacting triazole molecule, formaldehyde, and secondary amines in ethanol. The compounds were studied for their potential antinociceptive and anti-inflammatory activities using acetic acid induced-writhing and carrageenan-induced paw edema tests. The results revealed that all compounds induced peripherally-mediated antinociceptive activities, as well as notable anti-inflammatory effects with improved safety profile (73).

Bakri and co-workers (74) demonstrated the ring transformation of 6-methyl-7*H*(1,2,4)triazolo (4,3-b)(1,2,4) triazepine-8(9*H*)-ones in the presence of acetic anhydride to get a series of condensed 1,2,4-triazole derivatives. They were tested for their (i) inhibitory potential on digestive enzymes (*α*-amylase and *α*-glucosidase), and (ii) antioxidant activity using radical scavenging (DPPH and ABTS radicals) and ferric reducing power assays. Result of their investigation shows that the compounds possess interesting and promising antidiabetic activities compared to the reference drug Acarbose. Molecular docking study showed the strength of intermolecular hydrogen bonding in ligand-receptor complexes as an important descriptor in rationalizing the observed inhibition results.



Yeye *et al*(75) synthesized thirty-three Schiff's bases 4-amino-1,2,4-triazole derivatives by the reaction of 4-amino-1,2,4-triazole with a variety of benzaldehydes (Scheme 26). Subsequent to the synthesis, they were evaluated the compounds for their anti-hyperglycemic potential. The report shows that all compounds exhibited good to moderate *in vitro* *α*-amylase and *α*-glucosidase inhibitory activities in the range of IC_{50} values 2.01 ± 0.03–6.44 ± 0.16 and 2.09 ± 0.08–6.54 ± 0.10 µM as compared to the standard acarbose (IC_{50} = 1.92 ± 0.17 µM) and (IC_{50} = 1.99 ± 0.07 µM), respectively.

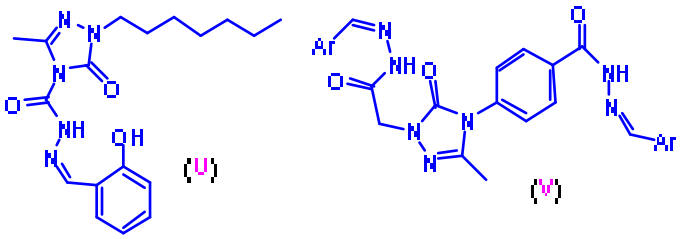
The in silico structure-activity relationship studies suggested that both triazole ring and different substitutions on aryl part of the compounds playing an important role in the binding interactions of inhibitors within the enzyme pocket, and hence the activity. It was observed that, triazole-indole Schiff's base (**T**) exhibited remarkable anti-hyperglycemic potential.



Scheme 26

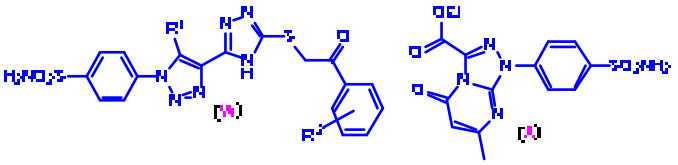
Carbonic anhydrase, Tyrosinase and Cathepsin X inhibition activity: Carbonic anhydrase (CA) II plays major roles in pH regulation of body, protection of electrolyte balance, transportation of water and some metabolic pathways. Therefore, CA II inhibitors are very important molecules for drug design. CA II as a target molecule is also important for eliminating some pathological conditions such as glaucoma, cancer, epilepsy, ulcer and obesity. Carbonic anhydrase enzymes are metalloenzyme families that catalyze the rapid conversion of H_2O and CO_2 to HCO_3^- and H^+. CAs are found in different tissues where they participate in various significant biochemical processes such as ion transport, carbon dioxide respiration, ureagenesis, lipogenesis, bone resorption, electrolyte secretion, acid-base balance, and gluconeogenesis. In such processes, many CAs are significant therapeutic targets because of their inhibitory potentials especially in the treatment of some diseases such as edema, glaucoma, obesity, cancer, epilepsy, and osteoporosis.

Akin and co-workers (76) reported the synthesis of 1,2,4-triazole derivatives and screening for their CA II inhibition potentials. Result of their investigation shows that, compound (**U**) of the synthesized series has been found most potent inhibitor with the lowest IC_{50} value at micromolar level. The inhibition in the range of 18.41–64.97% was observed in the presence of newly synthesized molecules at their reachable maximum concentration in the reaction mixtures. Kinetic studies showed that the inhibition mechanism of compound on carbonic anhydrase activity was reversible and uncompetitive, and was supported by the molecular docking, which indicated that it could bind to the active site of the enzyme by weakly interacting with especially Gln102, Leu240, Ala241 and Trp243. Ozil and co-workers (77) reported the effective synthesis of 5-methyl-2,4-dihydro-3*H*-1,2,4-triazole-3-one's aryl Schiff base derivatives (**V**) and also their CA and cholinesterases inhibitory properties. Their findings showed that these Schiff base derivatives, with triazole ring, found as strong CA and cholinesterases inhibitors.



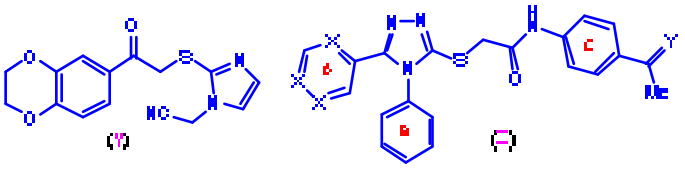
Vats and co-workers (78) developed a tail approach synthesis of a library of benzenesulfonamides incorporating triazole and dual triazole moieties (**W**), and studied their efficacy as inhibitors of carbonic anhydrase human (h) isoforms.

The results of their investigation shows that most of the synthesized compounds strongly inhibited glaucoma associated isoforms hCA II and IV in low nanomolar range (K_I = 8.0 nM–0.903 µM). Said and co-workers (79) designed triazolopyrimidine and triazole-based benzenesulfonamides, and assessed for their inhibitory activities toward four human metalloenzyme carbonic anhydrase isoforms. The examined isoforms were inhibited by the prepared sulfonamides in variable degrees with KIs ranges: 94.4-4953.5 nM for hCA I, 6.9-837.6 nM for hCA II, 3.3-85.0 nM for hCA XI, and 4.4-105.0 nM for hCA XII. Interestingly, triazolopyrimidine-based sulfonamide (**X**) was found to be the most selective hCA IX inhibitors over hCA I (SI ¼ 100.85) and hCA II (SI ¼ 18.54).



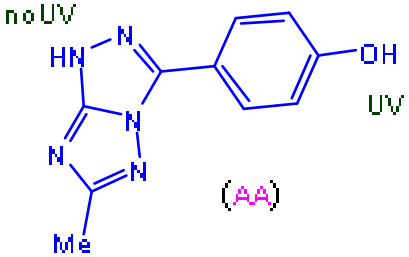
Tyrosinase plays a central role in the biosynthesis pathway of melanin pigment and its activity has also been linked to Parkinson's and other neurodegenerative diseases. Melanin functions in the formation of skin color and its unusual levels cause some skin disorders such as pregnancy scar, oldness spots and especially skin cancer (melanoma). In addition, melanin plays a critical role as a defense molecule for insects during molting process and wound healing and is important for their life. Therefore, determination of inhibitor molecules for tyrosinase activity has a promising potential for therapies of some diseases and is an alternative method for keeping insects under control. With this in view, Akin *et al*(80) synthesized 2-Heptyl-5-methyl-2,4-dihydro-3*H*-1,2,4-triazole-3-one and 4-(substituebenzyl)-2-heptyl-5-methyl-2,4,-dihydro-3*H*-1,2,4-triazole-3-one starting from4-amino-2-heptyl-5-methyl-2,4-dihydro-3H-1,2,4-triazole-3-one, and evaluated for their tyrosinase inhibiton efficiencies. One of the compounds among the synthesized series found the most effective inhibitor with the smallest IC_{50} value (5 mM). Cathepsin X is a cysteine carboxypeptidase is involved in various physiological and pathological processes, particularly in highly elevated expression and activity of cathepsin X was observed in cancers and neurodegenerative diseases. The chemical variations to either benzodioxine or triazole moieties to (**Y**) explored the importance of the central ketomethylenethio linker, and improved inhibitory potencies against cathepsin X with IC_{50} values of 7.1 µM–13.6 µM.

The ketomethylenethio linker was crucial for cathepsin X inhibition, whereas changes of the triazole heterocycle did not alter the inhibitory potencies to a greater extent (81). Geranylgeranyl diphosphate synthase (GGDPS) inhibitors are of potential therapeutic interest as a consequence of their activity against the bone marrow cancer multiple myeloma. A series of bisphosphonates linked to an isoprenoid tail through an amide linkage has been prepared and tested for the ability to inhibit GGDPS in enzyme and cell-based assays. The designed triazole-amides shows GGDPS inhibitory activity in both enzyme and cell assays, with potency dependent on chain length and olefin stereochemistry (82). Shaykoon and co-workers (83) synthesized series of 1,2,4-triazol-3-yl-thioacetamide derivatives (**Z**) were evaluated in vitro anti-trypanosomal activity against *Trypanosoma brucei*, employing α-difluoromethylornithine (DFMO) as a control drug. Results of the study indicated that one compound of the series found more potent to an extent of eight fold greater than the reference DFMO (IC_{50} = 6.10 µM) with IC_{50} of 0.79 µM. The tested compounds showed moderate cytotoxicity with selectivity indices ranging from 12 to 102 against L6 cells.



Physico-chemical properties: Demirbas *et al* (84) reported the synthesis of tetra 4-(4-fluorophenyl)-5-(4-methoxyphenyl)-4H-1,2,4-triazole-3-thio substituted non-peripherally metal free, zinc(II), lead (II) and copper(II) phthalocyanine complexes, and studied their redox properties. The compounds displayed ring-based, reversible and/or quasi-reversible reduction and oxidation processes and aggregation of the complexes influenced the redox character of the processes. Warad and co-workers (85) reported the synthesis of the (*E*)-4-((3,4-difluorobenzylidene)amino)-2,4-dihydro-5-methyl-3*H*-1,2,4-triazole-3-thione through an eco-friendly microwave assisted route and studied its prototropic thione/thiol tautomerism *via* single and double H's transfer mechanism. They observed the gaseous-phase prototropic thione thiol tautomerism occurrence probability *via* single-proton intramigration and push/pull protons self-assemble double proton transfer exchange was DFT method. Abdurahman and co-workers (86) reported the synthesis and aggregation-induced emission (AIE) blue-emission materials, namely 4-*N*-(naphthalen-l-yl)-3,5-bis(4-diphenylamine) phenyl-4*H*-1,2,4-triazole behaves as donor (D) type molecule and 4-*N*-(naphthalen-l-yl)-3-(4-diphenlamin)phenyl-4*H*-1,2,4-triazole acts as D-A type molecule, both possessed excellent AIE properties. Additionally, they exhibited significant fluorescence quenching and color responses toward Fe^{3+} in aqueous solution, which suggested them fluorometric/colorimetric dual-channel probe to Fe^{3+}. They can be used as a fluorimetric/ colorimetric dual-channel probe to Fe^{3+} probes in aqueous solution, with high selectivity, remarkable anti-interference.

The triazolo-triazole scaffold (AA) exhibits long range photo tautomerism in water, whereas in alcoholic solution, only photoacidity of the phenol group is observed. The protonated nitrogen of the triazolo-triazole ring is a weak photoacid. It is shown that 4-methyl-7-(4-hydroxyphenyl)-(1,2,4)-triazolo(3,2-c)(1,2,4)triazole exhibits a rich photoinduced protolytic behavior: Forster cycle shows that the protonated nitrogen of the triazolo-triazole ring is a weak photoacid; furthermore, at moderately basic pH its deprotonated monoanion exhibits a long distance water mediated phototautomerism, in which the hydroxyl group releases a proton to solvent and a basic nitrogen of the triazolo-triazole fused ring (87). Fizer *et al*(88) synthesized 3-methylthio-4-phenyl-5-phenylamino-1,2,4-triazole and confirmed its structure by X-ray diffraction and DFT studies, the result insights the changes in the structure of a polyfunctional substituted triazole upon its protonation and explains these changes with the analysis of weak interactions.



Conclusion

1,2,4-Triazole analogues possess greater importance in synthetic organic and medicinal chemistry, and are promising molecules of medicine for the scientists working in this area of research. In this, review article, we have attempted to summarize the developments in the synthetic protocols of 1,2,4-triazole derivatives, and their explorations as medicinally useful agents in the recent years together. The synthetic methods were discussed in depth, also discussion was made on Antimicrobial, Antiviral, Anticancer, Antiproliferative, Antileishmanial, Anti-Inflammatory and Anti-Diabetic Activities; Carbonic Anhydrase, Tyrosinase and Cathepsin X Inhibition properties; Physico-Chemical properties of 1,2,4-triazole derivatives, and would be useful for researchers working in this area.

REFERENCES

(1) G.M. Shelke, V.K. Rao, M. Jha, T.S. Cameron, A. Kumar, Synlett. 26 (2017) 404-407.
(2) I.A. Guralskiy, V.A. Reshetnikov, I.V. Omelchenko, A. Szebesczyk, E. Gumienna-Kontecka, I.O. Fritxky, J. Mol. Struct. 1127 (2017) 164-168.
(3) N. Yang, G. Yuan, J. *Org. Chem.*,83 (2018) 11963-11969.
(4) A. Tam, I.S. Armstrong, T.E. La Cruz, *Org. Lett.*, 15 (2013) 3585-3589.
(5) J.-X. Mu, Z.-W. Zhai, C.-X. Tan, J.-Q. Weng, H.-K. Wu, S.O. Duke, Y.-G. Zhang, X.-H. Liu, *J. Heterocycl. Chem.* 56 (2019) 968-971.
(6) G.M. Castanedo, P.S. Seng, N. Blaquiere, S. Trapp, S.T. Staben, *J. Org. Chem.*, 76 (2011) 177-1179.
(7) Z. Chen, H. Li, W. Dong, M. Miao, H. Ren, *Org. Lett.*, 18(2016) 1334-1337.
(8) S. Ueda, H. Nagasawa, *J. Am. Chem. Soc.*, 131 (2009) 15080-15081.
(9) A. Gogoi, S. Guin, S. Rajamanickam, S.K. Rout, B.K. Patel, *J. Org. Chem.*, 80 (2015) 9016-9027.
(10) K. Ajay Kumar, Brief review on cyclopropane analogs: Synthesis and their pharmacological applications, *Int.J. Pharm. and Pharm. Sci.* 5(1) (2013) 467-472.
(11) K. Ajay Kumar, K.M. Lokanatha Rai, K.B. Umesha, *Tetrahedron*, 57 (2001) 6993-6996.
(12) (12) K. Ajay Kumar, M. Chandramouly, D.M. Lokeshwari, G. Vasanth Kumar, Synthetic strategies and significances of pyrroline analogs, *Res. J. Pharm. Tech.* 6(2) (2013) 137-142.
(13) K. Ajay Kumar, K.M. Lokanatha Rai, K.B. Umesha, *J. Chem. Res. (S)*, (2001) 436-438.
(14) P. Jayaroopa, G. Vasanth Kumar, N. Renuka,K. Ajay Kumar, *IOSR J. App. Chem.,* 1(4) (2012) 20-23.
(15) K. Ajay Kumar, K.M. Lokanatha Rai, K.B. Umesha, *Ind. J. Heterocycl. Chem.* 11 (2002) 341-342.
(16) K. Ajay Kumar, K.M. Lokanatha Rai, G. Vasanth Kumar, B.N. Mylarappa, *Int.J. Pharm. Pharm. Sci.*, 4(Suppl 4) (2012) 564-568.
(17) J.-Q. Liu, X. Shen, Y. Wang, X.-S. Wang, X. Bi, *Org. Lett.*, 20 (2018) 6930-6933.
(18) J. Xia, X. Huang, M. Cai, *Synthesis*, 51 (2019) 2014-2022.
(19) H. Huang, W. Guo, W. Wu, C.-J. Li, H. Jiang, Org. Lett., 17 (2015) 2894-2897.
(20) W.S. Bechara, I.S. Khazhieva, E. Rodriguez, A.B. Charette, *Org. Lett.*, 17 (2015) 1184-1187.
(21) D.V. Batchelor, D.M. Beal, T.B. Brown, D. Ellis, D.W. Gordon, P.S. Johnson, H.J. Mason, M.J. Ralph, T.J. Underwood, S. Wheeler, *Synlett*, 16 (2008) 2421-2424.
(22) B. Wong, A. Stumpf. D. Carrera, C. Gu, H. Zhang, *Synthesis*, 45 (2013) 1083-1093.
(23) K. Ajay Kumar, M. Govindaraju, G. Vasanth Kumar, *Int.J. Res. Pharm. Chem.*, 3(1) (2013) 140-152.
(24) K. Ajay Kumar, *Int.J. ChemTech Res.*, 5(6) (2013) 3032-3050.
(25) K. Ajay Kumar, D.M. Lokeshwari, G. Pavithra, G. Vasanth Kumar, *Res. J. Pharm. Tech.*, 5(12) (2012) 1490-1496.
(26) P. Gurunanjappa, R. Nagamallu, A.K. Kariyappa, *Int.J. Pharm. Pharm. Sci.*, 7(2) (2015) 379-381.
(27) P. Jayaroopa, K. Ajay Kumar, *Int.J. Pharm. Pharm. Sci.*, 5(4) (2013) 431-433.
(28) D.M. Lokeshwari, V.H. Kameshwar, A.K. Kariyappa, *Biointerface Res. App. Chem.*, 7(5) (2017) 2158-2165.
(29) K. Ajay Kumar, K.M. Lokanatha Rai, *Bulg. Chem. Comm.*, 36 (2004) 249-252.
(30) P. Jayaroopa, K. Ajay Kumar, G. Vasanth Kumar, *Int.J. ChemTech Res.*, 5(5) (2013) 2516-2520.
(31) K. Ajay Kumar, N. Renuka, G. Vasanth Kumar, *Int.J. PharmTech Res.*, 5(1) (2013) 239-248.
(32) P. Gurunanjappa, A.K. Kariyappa, *Curr. Chem. Lett.,* 5(3) (2016) 109-122.
(33) M. Nakka, R. Tadikonda, S. Rayavarapu, P. Sarakula, S. Vidavalur, *Synthesis*, 47 (2015) 517-525.
(34) Y. Xu, M. McLaughlin, E.N. Bolton, R.A. Reamer, *J. Org. Chem.*, 75 (2010) 8666-8669.
(35) K. Ajay Kumar, M. Govindaraju, P. Jayaroopa, G. Vasanth Kumar, *Int.J Pharm., Chem. Biolog. Sci.,* 3(1) (2013) 91-101.
(36) K. Ajay Kumar, M. Govindaraju, G. Vasantha Kumar, *Ind. J. Heterocycl. Chem.*, 20 (2010) 183-184.
(37) L.-Y. Wang, W.-C. Tseng, H.-Y. Lin, F. F. Wong, *Synlett*, 10 (2011) 1467-1471.
(38) P. Yin, W.-B. Ma, Y. Chen, W.-C. Huang, Y. Deng, L. He, *Org. Lett.*, 11 (2009) 5482-5485.
(39) N. Jatangi, N. Tumula, R. K. Palakodety, M. Nakka, *J. Org. Chem.*, 83(2018) 5715-5723.
(40) A. Guirado, L. Lopez-Caracena, J.I. Lopez-Sanchez, J. Sandoval, M. Vera, D. Bautista, J. Galvez, Tetrahedron, 72 (2016) 8055-8060.
(41) K.E. Szabo, A. Pahi, L. Somsak, Tetrahedron, 73 (2017) 3810-3822.
(42) J.J. Vora, D.R. Patel, N.V. Bhimani, P.V.Ajudia, *J. Chil. Chem. Soc.*, 56, Nº 3 (2011) 771-773.
(43) A.M.B. Aboeldahab, E.M.A. Beshi, M.E.Shoman, S.M. Rabea, O.M. Aly, Eur. J. Med. Chem. 146 (2018) 79-92.
(44) L. Dehestani, N. Ahangar, S.M. Hasemi, H. Irannejad, P.H. Masihi, A. Shakiba, S. Emami, *Bioorg. Chem.* 78 (2018) 119-129.
(45) S. Azzouni, A. Abdelli, A. Gaucher, Y. Arfaouni, M.L. Efrit, D. Prim, *Tetrahedorn*, 74 (2018) 6972-6978.
(46) H.A. Agiso, H. Esatu, S. Hairat, M. Zaki, *Tetrahedron* Lett. 61 (2020) 151989.
(47) M.R. Aouad, H.M. Al-Mohammad, F.F. Al-blewi, S. Ihmaid, H.M. Elbadawy, S.S. Althagfan, N. Rezki, *Bioorg. Chem.* 94 (2020) 103446.
(48) J. Li, G.-Y. Ren, Y. Zhang, M.-Y. Yang, H.-X. Ma, Polyhedron, 157 (2019) 163-169.
(49) N.I. Tikhonov, S.S. Khutsishvili, L.I. Larina, A.S. Pozdnyakov, A.I. Emelyanov, G.F. Prozorova, A.V.

Vashchenko, T.I. Vakulskaya, J. Mol. Struct. 1180 (2019) 272-279.
(50) A.-M. Li, E. Rentschler, Polyhedron, 154 (2028) 364-372.
(51) S. Bitla, S.R. Sagurthi, R. Dhanavath, M.R. Puchakayala, S. Birudaraju, A.A. Gayathri, V.K Bhukya, K.R. Atcha, *J. Mol. Struct.* 1220 (2020) 128705.
(52) (51) Duantao Cao, Ruilin Wu, Suxia Dong, Feiyan Wang, Chao Ju, Sumei Yu, Shiji Xu, Hua Fang, Yunlong Yu, https://www.sciencedirect.com/science/article/abs/pii/S0269749120304218#!Triazole resistance in *Aspergillus fumigatus* in crop plant soil after tebuconazole applications, *Environmental Pollution*, (2020) 115124,
(53) J. Wu, T. Ni, X. Chai, T. Wang, H. Wang, J. Chen, Y. Jin, D. Zhang, S. Yu, Y. Jiang, Eur. J. Med. Chem. 143 (2018) 1840-1846.
(54) R. Ahuja, A. Sidhu, A. Bala, D. Arora, P. Sharma, *Arab. J. Chem.* 13 (2020) 5832–5848.
(55) E. Stingaci, M. Zveaghinteva, S. Pogrebnoi, L. Lupascu, V. Valica, L. Uncu, A. Smetanscaia, M. Drumea, A. Petrou, A. Ciric, J. Glamoclija, M. Sokovic, V. Kravtsov, A. Geronikaki, F. Macaev, *Bioorg. Med. Chem. Lett.* 30 (2020) 127368.
(56) H. Beyzaei, M.G. Kudeyani, H.S. Delarami, R. Aryan, *J. Mol. Struct.* 1215 (2020) 128273.
(57) Y. Mahamoudi, H. Badali, S.M. Hashemi, M. Ansari, H. Fakhim, M. Fallah, M. Shokrzadeh, S. Emami, Bioorg. Chem. 90 (2019) 103060.
(58) Y. Zhang, V.K.R. Tangadanchu, R.R.Y. Bheemanaboina, Y. Cheng, C.-H. Zhou, *Eur. J. Med. Chem.* 155 (2018) 579-589.
(59) K. Qiao, W. Fu, Y. Jiang, L. Chen, S. Li, Q. Ye,W. Gui, *Environ. Pollution*, 265B (2020) 114837.
(60) Y.-N. Cheng, Z.-H. Jiang, L.-S. Sun, Z.Y. Su, M.-M. Zhang, H.-L. Li, Eur. J. Med. Chem. 200 (2020) 112463.
(61) X.F. Cao, W. Wang, S. Wang, L. Bao, Eur. J. Med. Chem. 139 (2017) 718-725.
(62) A.H. Abdelazeem, A.M. Alqahtani, H.A. Omar, N.S.A. Bukhari, A.M. Gouda, *J. Mol. Struct*. 1219 (2020) 128567.
(63) C. Wang, Y. Li, T. Liu, Z. Wang, Y. Zhang, K. Bao, Y. Wu, Q. Guan, D. Zuo, W. Zhang, *Bioorg. Chem.* (2020) 103909.
(64) F.F. Ahmed, A.A. Abd El-Hafeez, S.H. Abbas, D. Abdelhamid, M. Abdel-Aziz, Eur. J. Med. Chem. 151 (2018) 705-722.
(65) A.T.A. Boraei, P.K. Singh, M. Sechi, S. Satta, *Eur. J. Med. Chem.* 182 (2019) 111621.
(66) J.-W. Zhao, Z.-H. Wu, J.-W. Guo, M.-J. Huang, Y.-Z. You, H.-M. Liu, L.-H. Huang, *Eur. J. Med. Chem.* 181 (2019) 111520.
(67) S.A. Shahzad, M. Yar, Z.A. Khan, L. Shahzadi, S.A.R. Naqvi, A. Mahmood, S. Ullah, A.J. Shaikh, T.A. Sherazi, A.T. Bale, J. Kukulowicz, M. Bajda, *Bioorg. Chem.* 85 (2019) 209-220.
(68) F. Naaz, F. Ahmad, B.A. Lone, Y.B. Pokharel, N.K. Fuloria, S. Fuloria, M. Ravichandran, L. Parrabhiraman, S. Shafi, M.S. Yar, *Bioorg. Chem.* 95 (2020) 103519.
(69) H.A.M. El-Sherief, B.G.M. Youssif, S.N.A. Bukhari, A.H. Abdelazeem, M. Abdel-Aziz, H.M. Abdel-Rahman, *Eur. J. Med. Chem.* 156 (2018) 774-789.
(70) M. Ansari, M. Shokrzadeh, S. Karima, S. Rajaei, S.M. Hashemi, H. Mirzaei, M. Fallah, S. Emani, *Bioorg. Chem.* 93 (2019) 103300.
(71) N. Suleymanoglu, Y. Unver, R. Ustabs, S. Direkel, G. Alpaslan, J. Mol. Struct. 1144 (2017) 80-86.
(72) W.A.A. Fadaly, Y.A.M.M. Elshaier, E.H.M. Hassanein, K.R.A. Abdellatif, *Bioorg. Chem.* 98 (2020) 103752.
(73) A. Avco, H. Tasci, U. Kandemir, O.D. Can, N. Gokhan-Kelekci, B. Tozkoparan, *Bioorg. Chem.* 100 (2020) 103892.
(74) Y.E. Bakri, I. Marmouzi, M.E. Jemli, E.H. Anouar, S. Karthikeyan, A. Harmaoui, M.E.A. Faouzi, J.T. Mague, E.M. Essassi, *Bioorg. Chem.* 92 (2019) 103193.
(75) E.O. Yeye, Kanwal, K.M. Khan, S. Chigurupati, A. Wadood, A.U. Rehman, S. Perveen, M.K. Maharajan, S. Shamim, S. Hameed, S.A. Aboaba, M. Taha, *Bioorg. Med. Chem.* 28 (2020) 115467.
(76) S. Akin, H. Ayaloglu, E. Gultekin, A. Colak, O. Bekeican, M.Y. Akatin, Bioorg. Chem. 83 (2019) 170-179.
(77) M. Ozil, H.T. Bakaydm, M. Senturk, *Bioorg. Chem.* 86 (2019) 705-713.
(78) L. Vats, R. Kumar, S. Bua, A. Nocentini, P. Gratteri, C.T. Supuran, P.K. Sharma, *Eur. J. Med. Chem.* 183, (2019) 111698.
(79) M.A. Said, W.M. Eldehna, A. Nocentini, A. Bonardi, S.H. Fahim, S. Bua, D.H. Soliman, H.A. Abdel-Aziz, P. Gratteri, S.M. Abou-Seri, C.T. Supuran, *Eur. J. Med. Chem.* 185 (2020) 111843.
(80) S. Akin, E.A. Demir, A. Colak, Y. Kolcuoglu, N. Yildirim, O. Bekircan, *J. Mol. Struct*. 1175 (2019) 280-286.
(81) U.P. Fonovic, D. Knez, M. Hrast, N. Zidar, M. Proj, S. Gobec, J. Kos, *Eur. J. Med. Chem.* 193 (2020) 112218.
(82) D.B. Goetz, M.L. Varney, D.F. Wiemer, S.A. Holstein, *Bioorg. Med. Chem.* (2020) 115604.
(83) M. Sh. Shaykoon, A.A. Marzouk, O.M. Soltan, A.S. Wanas, M.M. Radwan, A.M. Gouda, B.G.M. Youssif, M. Abdel-Aziz, *Bioorg. Chem.* 100 (2020) 103933.
(84) U. Demirbas, D. Akyuz, H.T. Akcay, A. Koca, O. Bekircan, H. Kantekin, J. Mol. Struct. 1155 (2018) 380-388.
(85) M.R. Aouad, M. Messali, N. Rezki, M.A. Said, D. Lentz, L. Zubaydi, I. Warad, *J. Mol. Struct*. 1180 (2019) 455-461.
(86) A. Abdurahman, L. Wang, Z. Zhang, Y. Feng, Y. Zhao, M. Zhang, Dyes and Pigments, 174 (2020) 108050.
(87) A. Capobianco, M.D. Donato, T. Causo, R. Centore, A. Lapini, C. Manfredi, A. Velardo, S. Volino, A. Peluso, J. Mol. Struct. 1203 (2020) 127368.
(88) Fizer, M. M. Slivka, R. Mariychuk, V. Baumer, V. Lendel, J. Mol. Struct. 1161 (2018) 226-236.

****