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Sulfur Derivatives of 1,2,4-Triazole: Recently Developed Compounds, Structure Activity Relationship, and Biological Activity: Review article

Azhar Mahdi Jasim[1] Tagreed N-A Omar[1] and Shayma L. Abdulhadi[*,1]

[1]Department of Pharmaceutical Chemistry, College of Pharmacy, University of Baghdad, Baghdad, Iraq

[*]**Corresponding author**

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Abstract

The term of heterocyclic chemistry focuses only on heterocyclic compounds, which consider as a percentage of organic chemistry, they are equal to greater than sixty-five. These compounds are widely found in nature and most of them are important to life. In the past few years, scientists fused on 1,2,4-triazoles and their condensed heterocyclic ring due to their medicinal significance, 1,2,4-triazole containing Sulphur atom is one of the important heterocyclic moieties due to its broad range of biological activities also their derivatives can accommodate one of the alternatives as electronic effect as exchanges of the electronic density (electron donating or withdrawing) groups ; for all what mentioned above they are consider as a core molecule in the development of a large number of medicinal compounds. 1,2,4-Triazole have wide range of pharmacological motivating drug possibilities such as analgesic, anti-microbial, anti-inflammatory, anti-convulsant, antioxidant, anti-septic, anti-cancer, diuretics, anti-diabetic, anti-urease, and anti-migraine agents. This review focuses on 1,2,4-triazole Sulfur based compounds about their different biological activities and the relationship with their chemistry.

Keywords: 1,2,4-triazole-3-thiones, 1,2,4-triazole-3-thiols, Heterocyclic Compound, Derivatives, Biological Activity

Introduction

The synthesis and development of new and secure compounds with therapeutic importance attract many researchers and scientists.[(1)]Among these compounds are the heterocyclic compounds, which their significant biological value has catalyzed a great deal of research on them[(2–6)] .

Heterocyclic are cyclic compounds with at least two different elements as ring member atoms [(7–10)]. Five-heterocyclic ring consist of nitrogen atom such as triazole which contain two carbon atoms with three nitrogen atoms at positions 1,2, 4 of the rings; are considered as a chromophore in pharmaceutical chemistry that possess different biological activities, [(11–13)]. Triazoles and their fused heterocyclics derivatives get lots of interest in its importance in pharmaceutical research.[(14–17)] 1,2,4-triazole and its derivatives are commonly used heterocycles pharmacophore representing a major class of heterocycles molecules with various biological activities like antibacterial[(18–21)], antiviral[(22)], antitubercular[(23)], anti-inflammatory[(24,25)], analgesic[(26, 27)], anticonvulsant[(28)], antidepressant[(29)], antifungal [(30, 31)], antioxidant[(32, 33)], Anticancer[(34–36)] and acetylcholinesterase Inhibitors[(37)]. Among 1,2,4-triazole derivatives, Sulfur-containing triazole heterocycles are also very important for their pharmacological applications. Among these heterocycles, thione and thiol substituted 1,2,4-triazoles have been well considered.[(38–40)]

As it is known, sulfur-triazole can occur in two tautomeric forms (Figure 1) in which the thione predominates in neutral solution and in solid state. [(41– 43)] However, there are several studies have described the presence of thiol forms.[(44, 45)] The thiol-thione tautomer has been shown that they obviously function a part in various processes concerning the biological activities like hydrogen bonds and protons transfer[(46, 47)] .

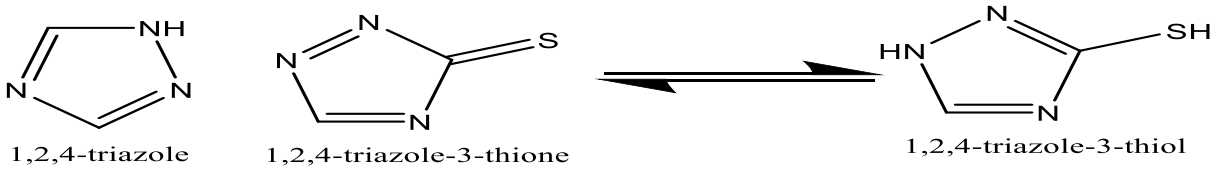


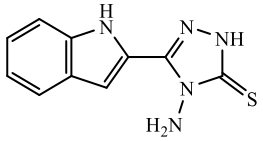
Figure 1. Tautomeric forms of sulfur containing triazole ring [(48)]

Often one of the tautomer's is biologically active and have diverse properties, so, the affinity of tautomer to receptors or enzymes is different. So, tautomerism could be a rational technique to regulate pharmacological to biological criterions[48]. The objective of this review is concerned on summarize the biological activity and its relationship with the chemistry of 1,2,4-triazole Sulfur based compounds.

Antibacterial Activity

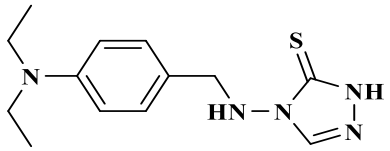
As a result of the prevalent use and misuse of antibacterial agents, bacterial resistance is increasing. Particularly, the development of multi-resistant bacteria seriously threatened the public health security of the people. Therefore, to curb the upgrowth of bacterial resistance, providing references for the expansion of novel antibacterial agents, establishing countermeasures versus bacterial resistance, and discovering novel agents are increasingly urgent.[49, 50]

The resistance of greatest concern involves *β*-lactam antibiotics, the common group of antimicrobials that involve penicillin's, cephalosporins, carbapenems, and monolactams.[51] The in operation of them to the effect of β-lactamases enzyme which results in opening the β-lactam rings.[52] They are classified as: Serine β-lactamases group (SBLS) A, C, and D and metallo-β-lactamases (MBL) as group B, which need metal ion(s) like one to two Zn^{2+} ions to produce its activity.[53–55] Sevaille L. *et al* produced several of 1,2,4-triazole-3-thione derivatives that have an activity to inhibit the dizinc Metallo- β -lactamases which are generated by serious Gram negative (G –ve) microorganisms. The compound [1] showed IC_{50} less than 50 mm against these enzymes which shows that the broad-spectrum inhibitors might be obtained by this combination. Moreover, a little other compound displays considerable inhibitory activity against the mono zinc MBLs submitting that the 1,2,4-triazoles - thione could also target [56].

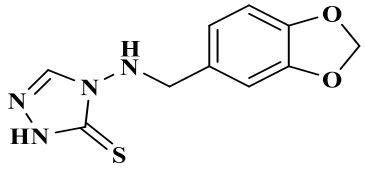


4-Amino-2,4-dihydro-5-(2-indolyl)-3H-1,2,4-triazole-3-thione

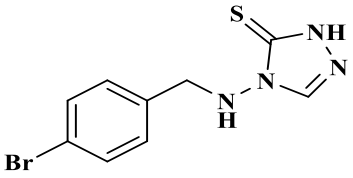
The most relevant mechanism that bacteria adept as inactivation β-lactamases anti-biotics, is by overexpression of the hydrolytic β- lactamases enzymes (BLs).[57–60] Linciano p. *et al* chose p-amino-1,2,4-triazole-3-thione as a starting chemical species to carry out and design a library of β-lactamase inhibitor with wide activity profiles. The synthesized derivatives were tested *in vitro* for their inhibitory activity against IMP-(imipenemase) and VIM-types (Verona integrin encoded MBL) and Klebsiella pneumoniae carbapenemase-2 (KPC-2) using a spectrophotometric assay; the compounds [2-5] exhibited cross-like micromolar inhibitory activity, therefore in silico analysis was performed to elucidate their binding modes in the serine and metallo- BLs catalytic pockets because of their different in structures. The results indicate that the candidates are following the expected direction in the development of broad-spectrum inhibitors.[61]



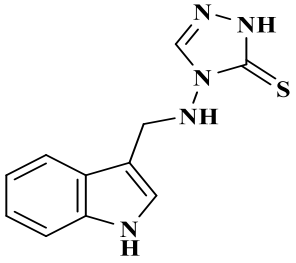
4-((4-(diethylamino)benzyl)amino)-2,4-dihydro-3H-1,2,4-triazole-3-thione [2]



4-((benzo[d][1,3]dioxol-5-ylmethyl)amino)-2,4-dihydro-3H-1,2,4-triazole-3-thione [3]



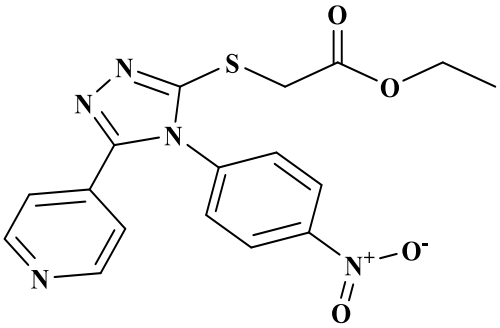
4-((4-bromobenzyl)amino)-2,4-dihydro-3H-1,2,4-triazole-3-thione [4]



4-(((1H-indol-3-yl)methyl)amino)-2,4-dihydro-3H-1,2,4-triazole-3-thione 9 [5]

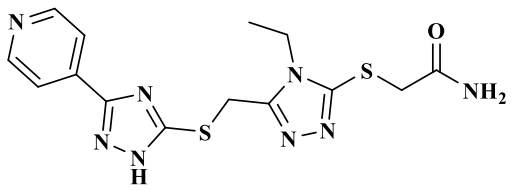
Triazoles and their derivatives have been extensively studied and confer remarkable antibacterial activity on this heterocyclic core.[62, 63] Due to the development of drug resistance, it is imperative to search for new antimicrobial molecules with new mechanisms of action and structural modifications or to optimize existing drugs by improving binding affinity and activity profile while maintaining bioavailability safety profiles.[64, 65]

Alyahyaoy H. A. *et al.* also synthesized a novel thiol derivative; they found that the synthesized compound [6] showed modest inhibitory effect against drug-resistant Pseudomonas aerogenes, whereas the cefepime, the standard reference drug; showed no action. As conclusion, they attribute the antibacterial effectiveness to the presence of the triazole ring that induce this effect through certain kinds of bacteria depend on the alkyl portion (adjacent to the thiol).(66)

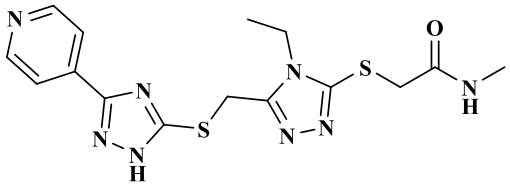


ethyl 2-((4-(4-nitrophenyl)-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetate[6]

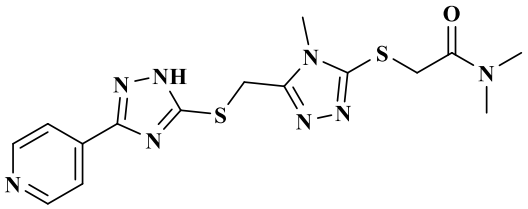
Karpun Y. *et al* designed, synthesized a new S-substituted1,2,4-triazole derivatives and evaluated their antimicrobial activity towards a number of G +ve and G -ve bacteria. They found that many derivatives possess antibacterial activity especially compound [7,8] has moderate inhibition of *Salmonella pullorum, Escherichia coli* and *Salmonella enteritidis* strains while compound [9] was sensitive toward ten tested bacteria at the same concentration. Molecular docking has been performed for compounds [7 and 8] is agreed with an experimental finding and the main structural of the inhibitor is complementary to the ligand structure is the trizole ring as 1,2,4 with one side as radical of ether and amide.(67)



2-((4-ethyl-5-(((3-(pyridin-4-yl)-1H-1,2,4triazole- 5-yl)thio)methyl)-4H-1,2,4-triazole-3-yl)thio)acetamide [7]



2-((4-ethyl-5-(((3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl) thio)methyl)-4H-1,2,4-triazol-3-yl)thio)-N-methylacetamide [8]

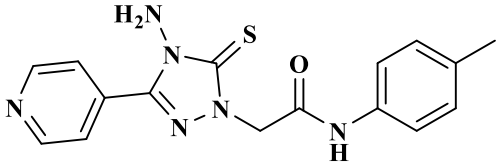


N,N-dimethyl-2-((4-methyl-5-(((3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)thio)methyl)-4H-1,2,4-triazol-3-yl)thio) acetamide [9]

Antitubercular Activity

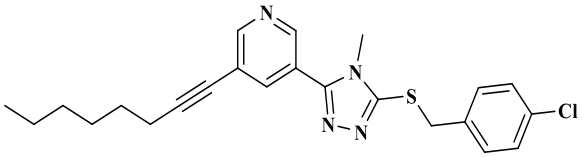
Mycobacterium tuberculosis (Mtb) was identified by World Health Organization's (WHO) as one of the main reasons of mortality and morbidity in the world.(68) The enoyl-thioester reductase (InhA) catalyzes an important step in fatty acid biosynthesis in Mycobacterium tuberculosis and is a potent target of antituberculosis drugs against multidrug-resistant M. tuberculosis strains.(69)

Vora D. et al designed and synthesized novel derivatives of 1,2,4-triazole-5-thione characterized as promising inhibitors of InhA. Anti-mycobacterial potential was confirmed by resazurin microtiter assay utilizing Mtb H37Rv strain. The mechanism of action of these compounds was proved by InhA enzyme inhibition studies who conclude that compound [10] is the most active one in the inhibition of InhA with IC_{50} of 90 nM. (70)

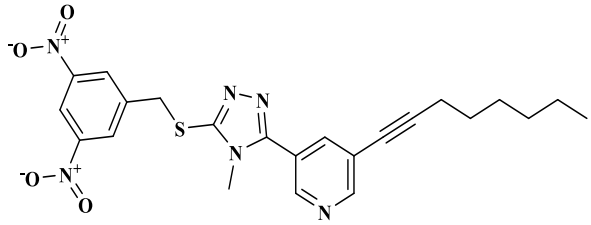


2-(4-amino-3-(pyridin-4-yl)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-N-(p-tolyl) acetamide [10]

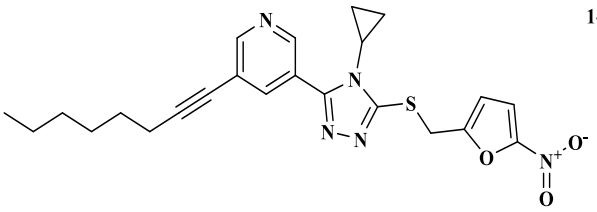
Berida T. *et al* discovered a novel 3-thiol derivatives of 1,2,4-triazole which cause inhibition of *Mycobacterium tuberculosis* (Mtb) both of growth and survival. Potent analogs compounds were identified by the aid of study structure-activity relationship; this study gives an indication about their inhibitor activity of potent analogs compounds [11-13] which displaying a nanomolar inhibitor activity also it gives a good indication about them from the side of a promising ADME/pharmacokinetic behaviors and no cytotoxicity in mammalian cells at over 100 times the efficient dose in Mtb. [71]



3-(5-((4-Chlorobenzyl)thio)-4-methyl-4H-1,2,4-triazol-3-yl)-5-(oct-1-yn-1-yl)pyridine [11]



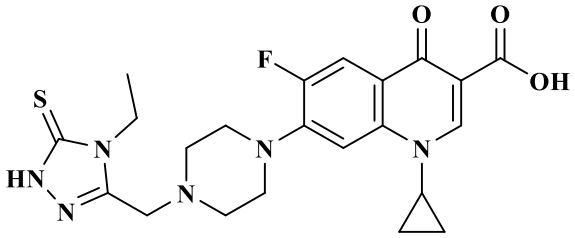
3-(5-((3,5-Dinitrobenzyl)thio)-4-methyl-4H-1,2,4-triazol-3-yl)-5-(oct-1-yn-1-yl)pyridine [12]



3-(4-Cyclopropyl-5-(((5-nitrofuran-2-yl)methyl)thio)-4H-1,2,4-triazol-3-yl)-5-(oct-1-yn-1-yl)pyridine [13]

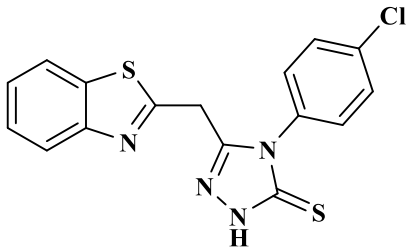
Antifungal Activity

Azoles are structural components of many antifungal drugs, such as itraconazole, fluconazole, and voriconazole, which are mostly used to treat invasive fungal infections and contribute significantly to mortality and morbidity in immunocompromised or critically ill patients.[72] Ezelarab H. A. A. *et al*, as a result of rapid development of fungal strains resistance, they synthesized a new compound by linking ciprofloxacin to heterocyclic rings including 1,2,4-triazole-3- thione. The resulting combination led to improve the antifungal activity toward *C. albicans*. The antifungal activity of hybrid triazole [14] was comparable to that of itraconazole when MIC /ml equal to 10.23 and 11.22, respectively. The molecular docking studies reveal that compound [14] can bind to the active site of lanosterol 14-α-demethylase CYP 51.[73]



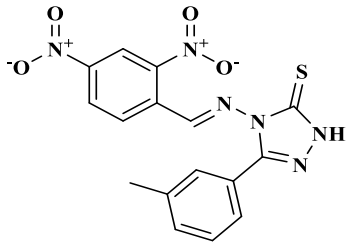
1-cyclopropyl-7-(4-((4-ethyl-5-thioxo-4,5-dihydro-1H1,2,4-triazol-3-yl)methyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid [14]

Hassan M.Z. *et al* synthesis of new derivatives contains 1,2,4-triazol-3-thione derivatives using an efficient and rapid protocol and evaluation of the antifungal activity of the resulting compounds. They found that compound [15] showed a good antifungal activity when MIC µg/ml equal to 12.5 and 0.39 versus both of *Aspergillus fumigatus* and *Candida albicans*, respectively.[74]

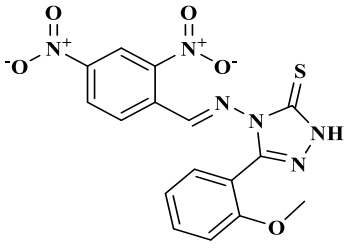


5-(benzothiazol-2-ylmethyl)-4-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione [15]

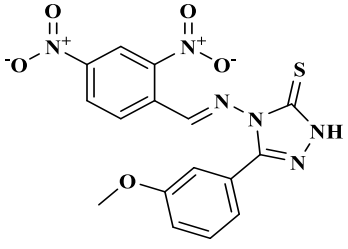
Wu S. *et al* were created a novel four different compounds [16 – 19] and evaluate their biological activity as antifungal agent *in vitro*. The outcome of the study pointed these compounds give good antifungal activities specially, compound [19] (its EC_{50} equal to 11.16 mg/L) which give a significant activity when tested with Wheat gibberellic, greater than Fluconazole (EC_{50} = 16.03 mg/L [75]).



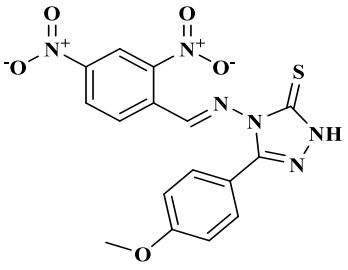
(*E*)-4-(2,4-dinitrobenzylideneamino) 5-m-tolyl-2H-1 ,2,4-triazole-3(4H) thione [16]



(*E*)-4-(2,4-dinitrobenzylideneamino)-5-(2-methoxyphenyl)-2H-1,2,4-triazole-3(4H)-thione [17]

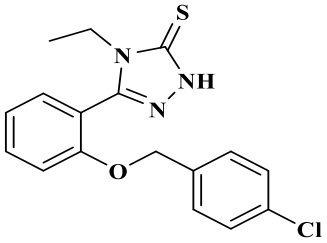


(*E*)-4-(2,4-dinitrobenzylideneamino)-5-(3-methoxyphenyl)-2H-1,2,4-triazole-3(4H)-thione [18]

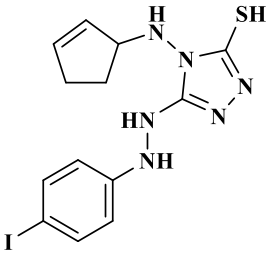


(*E*)-4-(2,4-dinitrobenzylideneamino)-5-(4-methoxyphenyl)-2H-1,2,4-triazole-3(4H)-thione [19]

Abdoh Radwan A. *et al* synthesized some heterocyclic derivatives and evaluated their antifungal activity. Among such derivatives is compound [20] which is sulfur containing triazole derivatives that is considered as the most active one which has MIC value equal to 0.08 μmol mL^{-1} against *Candida albicans* while fluconazole has 0.052 μmol mL^{-1}. In case of heterocyclic substituted ring with allyl group at position 4, it found that the allylic group leads to increase anti-*Candida albicans* activity in comparison with the benzene, methylbenzene, or sec-propyl group as a substituent and showed a binding mode and fluconazole x-ray structure. These differences, in activity, are related to the small bulk size of the allyl.(76)



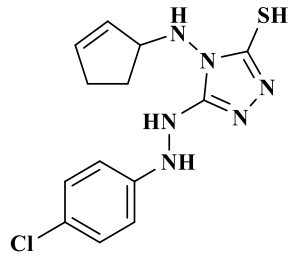
(5-(2-(4-chlorobenzyloxy)phenyl)-4-allyl-2H-1,2,4-triazole-3(4H)-thione) [20]



4-(cyclopent-1-en-3-ylamino)-5-(2-(4-iodophenyl) hydrazinyl)-4H-1,2,4-triazole-3-thiol [21]

Antiviral activity

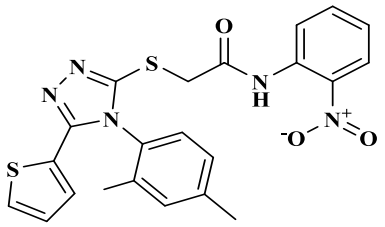
There are several triazoles that are used as antivirals, such as taribavirin which is an active against many types of viruses. Taribavirin is suitable against infections such as hepatitis C, severe respiratory syncytial virus, and other viral infections. Sulfanyltriazoles have also been used as treatment for human immunodeficiency virus (HIV-1). The presence of thione group either in 3- or 5-position in 1,2,4-tri-azoles are very remarkable derivatives that noticed by many biologists and chemists in the fields of medicinal and organic synthesis.(77) ZAHER N. H. *at el* used 1,2,4-triazol-3-thiol as the nucleus to synthesize new derivatives against the coronavirus that causes middle east respiratory syndrome (MERS-CoV) and all the synthesized compound has aromatic ring including halides (Br, Cl, F, I) l and their antiviral activity was detected by inhibition of helicase activity using a FRET assay. Biological results appeared that the maximum potency occurs with compounds [21] and [22] the experimental findings were supported by molecular docking.(78)



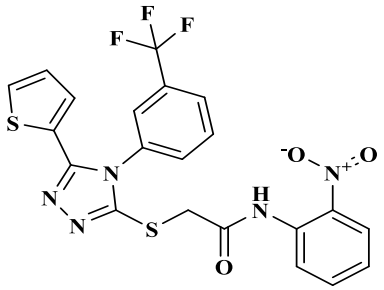
4-(cyclopent-1-en-3-ylamino)-5-[2-(4-chlorophenyl) hydrazinyl]-4H-1,2,4-triazole-3-thiol [22]

An azole regarding to be as a promising therapeutic approach for acquired immune-deficiency syndrome which led to the formation of non-nucleoside reverse transcriptase inhibitors (NNRTIs) of HIV-1; most of these compounds have the same azole ring core substituted with phenyl group bound to a 2-mercaptoacetamide group by other aromatic ring. Frączek T. *et al*, for the purpose of discovering a new extension for this fundamental structure, studying substitution at position 5.

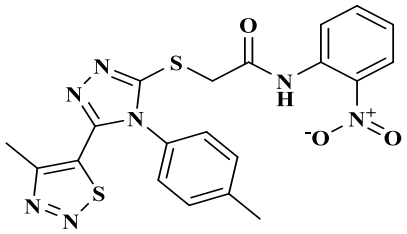
In case of incorporated triazole ring at C-5 with heterocyclic substituents are deleterious to the four-membered mercaptoacetamide linker as inhibitory activity, the above exchange possible in case of compounds less than two-membered linker. The maximum inhibitory activity was noticed by compounds [23- 26] have IC_{50} between 6–15mM. While compound [27] gives its activity when IC_{50} equals 43.5 mM or more. The structure activity relationship revealed the presence of methyl group in the p-methylphenyl substituent at the C4 of triazole enhanced the inhibitory activity. According to thioglycolamide linker, it gives good inhibitory activity when substituted with 2-chloro-4-sulfamoylphenyl group than 2-nitro-phenyl group. Furthermore, the presence of the 4-carboxy-2-chlorophenyl as seen in compound [28] allowed the formation of polar salts of the inhibitors and could lead to the discovery of new polar water-soluble salts of triazole NNRTIs.(79)



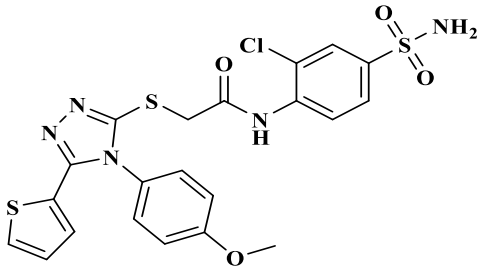
N-(nitrophenyl)-2-((2,4-Dimethylphenyl-5-Thiophen-2-yl-4H-1,2,4-triazol-3-yl)sulfanyl)acetamide [23]



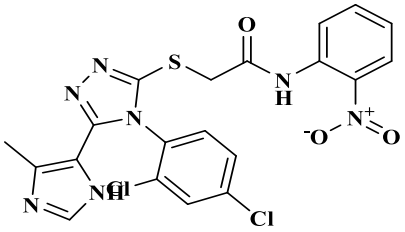
N-(nitrophenyl)-2-((3 (Trifluoromethyl)phenyl -5-Thiophen-2-yl-4H-1,2,4-triazol-3 yl)sulfanyl)acetamide [24]



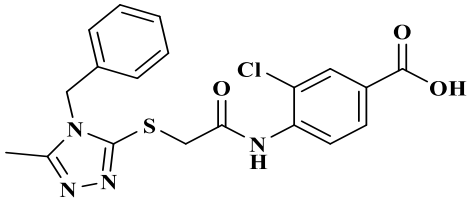
N-(nitrophenyl)-2-((4-Methylphenyl -5-4-Methyl-1,2,3-thiadiazol-5-yl -4H-1,2,4-triazol-3-yl)sulfanyl)acetamide [25]



N-(2-Chloro-4-sulfamoylphenyl)-2-((4-Methoxyphenyl -5-Thiophen-2-yl-4H-1,2,4-triazol-3-yl)sulfanyl)acetamide [26]



N-(nitrophenyl)-2-((2,4-Dichlorophenyl -5- 4-Methylimidazol-5-yl -4H-1,2,4-triazol-3-yl)sulfanyl)acetamide [27]



N-(4-carboxy-2-chlorophenyl)-2-((4-benzyl-5-methyl-4H-1,2,4-triazol-3-yl)sulfanyl)acetamide [28]

Antitumor Activity

Cancer is a major universal health issue and one of the causes of mortality, leading to enormous diseases all over the world. The anticancer drugs display diverse adverse side effects due to low selectivity and by uncontrolled and quick cell division. Cytotoxic drugs are the mainstay of cancer therapy: they have low penetration and efficacy; furthermore, various cytotoxic make tumors resistant to multiple chemotherapeutic drugs, 1,2,4 triazolo derivatives are among them [80]

Šermukšnyte A. *et al.* study the effect of its thiol compounds having a hydrazone group on cancer cell growth and migration breast, pancreatic cancer, and melanoma. They obtain hydrazones through the reaction of isatins with different types of aldehydes that contain either heterocyclic or aromatic groups. The cytotoxic activity was measured by the MTT assay using human triple-negative breast cancer, pancreatic carcinoma, and human melanoma cell lines. As a result, they obtain hydrazones [29],[30], and [31]have the highest hopeful one in thiol derivatives. These compounds are moderately cytotoxic for the cancer cell lines tested (EC_{50} values ranging from 2-17 µM). In addition, the selected compounds showed activity superior to or analogous to that of dacarbazine and erlotinib, which are approved for the treatment of malignant melanoma and pancreatic cancer. Furthermore, compound [32] was determined to be relatively precise for tumor tissues and displayed hopeful lead to migration assays in both of MDA-MB-231 and Panc-1 cells[81]

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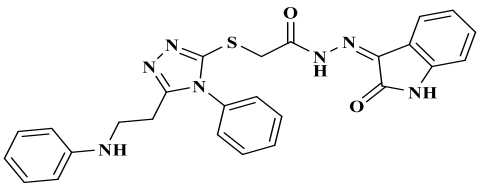
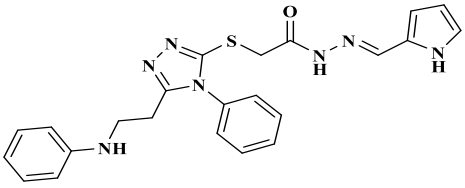
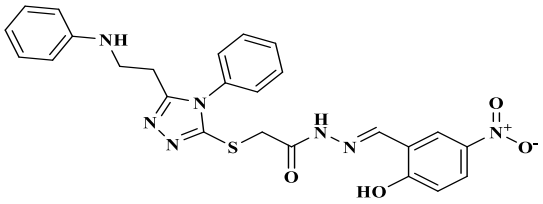


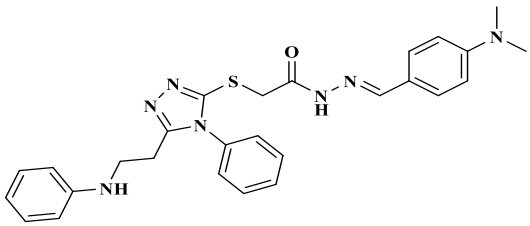
N'-(2-oxoindolin-3-ylidene)-2-((4-phenyl-5-(2-(phenylamino)ethyl)-4H-1,2,4-triazol-3-yl)thio)acetohydrazide [29]



N'-((1H-pyrrol-2-yl)methylene)-2-((4-phenyl-5-(2-(phenylamino)ethyl)-4H-1,2,4-triazol-3-yl)thio)acetohydrazide [30]

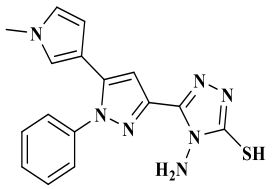


N'-(2-hydroxy-5-nitrobenzylidene)-2-((4-phenyl-5-(2-(phenylamino)ethyl)-4H-1,2,4-triazol-3-yl)thio)acetohydrazide[31]

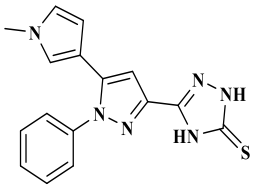


N'-(4-(dimethylamino)benzylidene)-2-((4-phenyl-5-(2-(phenylamino)ethyl)-4H-1,2,4-triazol-3-yl)thio)acetohydrazide [32]

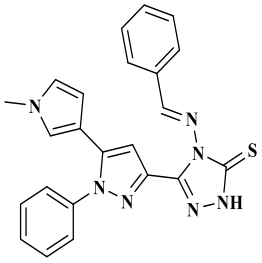
El-sayed M. A. produced a new derivative of triazole-3-thione and evaluated some of them towards human colon cancer cell lines, showing that the compound [33] has approximately cytotoxic activity comparable to standard compound, whereas compounds [34], [35 a-c] and [36] showed a modest cytotoxic activity.[82]



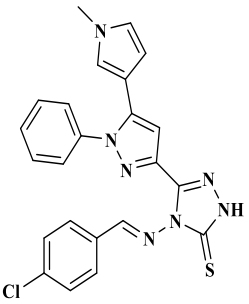
4-Amino-5-[5-(1-methyl-1H-pyrrol-3-yl)-1 phenyl-1H-pyrazol-3-yl]-4H-[1,2,4]triazole-3 thiol [33]



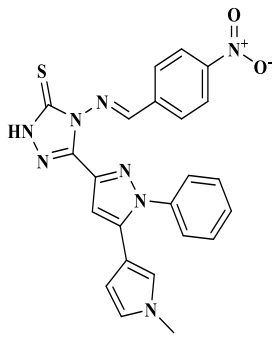
5-[5-(1-Methyl-1H-pyrrol-3-yl)-1-phenyl-1H-pyrazol-3-yl]-2,4-dihydro-[1,2,4]triazole-3-thione [35]



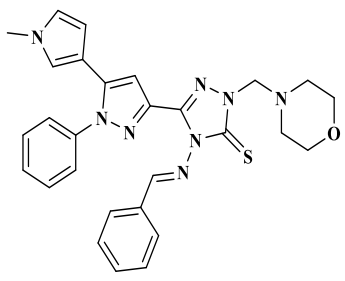
4-(Benzylidene-amino)-5-[5-(1-methyl-1H-pyrrol-3-yl)-1-phenyl-1H-pyrazol-3-yl]-2,4-dihydro-[1,2,4]triazole-3-thione [35a]



(E)-4-((4-chlorobenzylidene)amino)-5-(5-(1-methyl-1H-pyrrol-3-yl) -1-phenyl-1H-pyrazol-3-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione[35b]

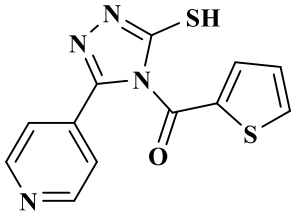


5-[5-(1-Methyl-1H-pyrrol-3-yl)-1-phenyl-1H-pyrazol-3-yl]-4-[(4-nitro-benzylidene)-amino]-2,4-dihydro-[1,2,4]triazole-3-thione [35c]

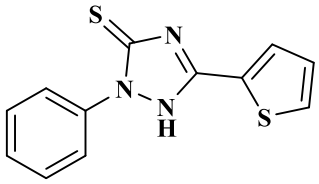


4-(Benzylidene-amino)-5-[5-(1-methyl-1H-pyrrol-3-yl)-1-phenyl-1H-pyrazol-3-yl]-2-morpholin-4-ylmethyl-2,4-dihydro-[1,2,4]triazole-3-thione [36]

Haggam RA *et al*. synthesized some heterocyclic compounds and evaluated their anticancer activity. Among these heterocyclic compounds are sulfur derivatives of 1,2,4-triazole; the compounds were evaluated for their inhibitory effect on the growth of the MCF-7 human breast cancer cell line in vitro. Almost all the selected compounds were able to inhibit the growth of the tested human tumor cell lines. The results showed that compound [37] showed the most potent inhibitory effect on the MCF-7 cell line compared to the control doxorubicin. At the same time, compound [38] showed the highest inhibitory effect.[83]

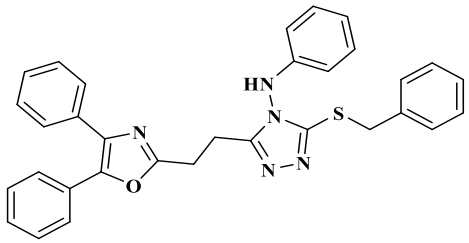


(3-mercapto-5-(pyridin-4-yl)-4H-1,2,4-triazol-4-yl)(thiophen-2-yl)methanone [37]

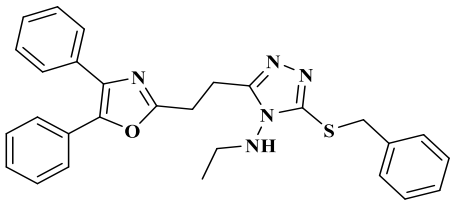


1,2-dihydro-2-phenyl-5-(thiophen-2-yl)-1,2,4-triazole-3-thione [38]

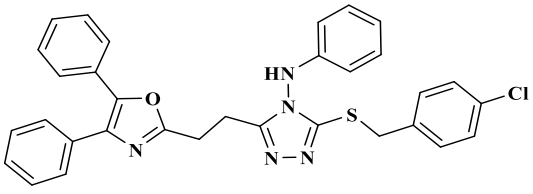
Maddali N.K. *et al.* design and synthesized a novel series of 4,5 diphenyl oxazole derivatives of 1,2,4 trazole-3-thiols and evaluate its anti-cancer activity against the prostate lung cancer cell lines. The result they obtained is reinforced by docking study to know the possible interaction between compound produced and fibroblast growth factor1 (FGFR1) and the Ser-/Thr-specific kinase Akt protein (Akt) as target proteins. The result of this study shows that compounds [39,40,42] give potential anti-cancer activity against PC-93 cell line with the IC_{50} values of 13.12, 15.34, and 16.34 µM, respectively. Compounds [39,41,42] displayed potential anti-cancer activity versus HBT-55 cell line with IC_{50} value 17.28, 16.48, and 15.12 µM respectively, when compared with doxorubicin. Molecular docking studies indicated that different amino acid residues in proteins consist of in the H-bond formation and hydrophobic interactions with synthesized compounds.[84]



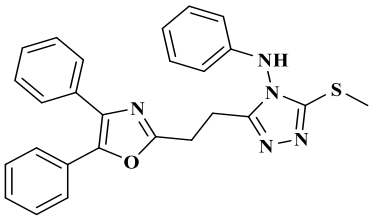
3-(Benzylthio)-5-(2-(4,5-diphenyloxazole-2-yl)ethyl)-N-phenyl-4H1,2,4-triazole-4-amine [39]



3-(Benzylthio)-5-(2-(4,5-diphenyloxazole-2-yl)ethyl)-N-ethyl-4H1,2,4-triazole-4-amine [40]



3-((4-Chlorobenzyl)thio)-5-(2-(4,5-diphenyloxazole-2-yl)ethyl)-N-phenyl-4H1,2,4-triazole-4-amine [41]

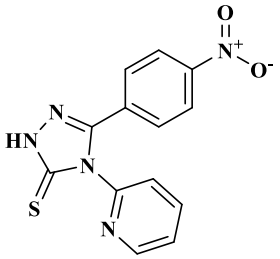


3-(2-(4,5-diphenyloxazole-2-yl)ethyl)-5-(methylthio)-N-phenyl-4H1,2,4-triazole-4-amine [42]

Both cancer and neurodegenerative disorders were due to overexpression and abnormal functioning of casein kinase enzymes led to synthesis of new casein kinase inhibitors as a basis for the development of new anticancer agents.[85]

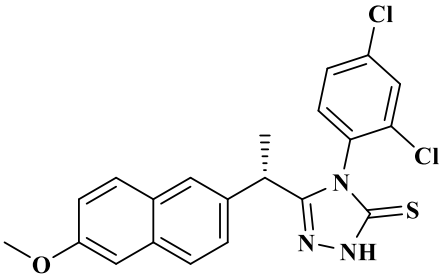
Pitucha M. *et al* produced numbers of derivatives of 1,2,4-triazolin-5-thione to act as CK1γ kinase inhibitors. The anti-proliferative activity of these derivatives was tested against cancer cells lines: lung adenocarcinoma (A549), hepatoma (HepG2), and breast adenocarcinoma (MCF-7). Compound [43] produced anti-proliferative potency versus A549 cancer cells and was identified by a selective anti-proliferative effect. As well as this compound has significant apoptotic activity versus A549, HepG2, MCF-7 cells and led to a small number of

necrotic cells only in these cell lines. The result obtained is clarified with molecular docking which shows the interaction of most active compound, compound [43], with enzyme is look like interactions of a standard inhibitor. The compound forms an H-bonding with fundamental atoms of enzyme and kept in the pocket through the effect of H- bonds that are formed by water molecules. In addition, compound [43] interacts with enzyme by a salt bridge between its NO_2- group and through a H-bond of triazole nitrogen hydrogen atom and the side chain of amino acid. (86)



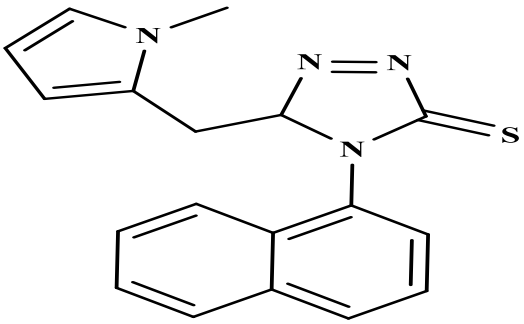
3-(4-Nitrophenyl)-4-(pyridin-2-yl)-4,5-dihydro-1H-1,2,4-triazol-5-thione [43]

Han M.İ. *et al* synthesized a series of novel derivatives of (S)-Naproxen having a thiosemicarbazide /1,2,4-triazole-3- thione moiety. In this series the compound [44] showed high potent anti-cancer activity with good selectivity. The study indicates that the compound [44] inhibits the number of cells in the G2/M phase and elevates the cells in the S phase in a dose-dependent manner. In addition, this compound gives anti-cancer activity and minimizes the tumor size at both low and high doses (60 mg/ kg and 120 mg /kg) respectively in mice.(87)



(S)-4-(2,4-dichlorophenyl)-5-[1-(6-methoxynaphthalen-2-yl)ethyl]-4H-1,2,4 triazole-3-thione [44]

Czylkowska A. forms a new derivative of 1,2,4-triazoline-3-thione and its metal complexes such as with (Mn^{+2}, Fe^{+2}, Ni^{+2}, Cu^{+2}, Zn^{+2}), their anti-cancer activities were studied against both human colon adenocarcinoma and human lung cancer cell lines. The complex [1] of compound [45] exhibited a potential activity in both of them while the complex [3] gave remarkable activity versus only the human colon adenocarcinoma cell line. This study demonstrates the importance of some metals in the development and uses of coordination complexes in the treatment of tumors. Compound [45] has a high absorption in the gastrointestinal tract (GIT), therefore this compound is considered as an effective drug only, but it is not considered as a substrate of P-glycoprotein, which means it is a perfect candidate versus multidrug resistant cancer cells and has good bioavailability which meets the requirement of Lipinski's five rule.(88)



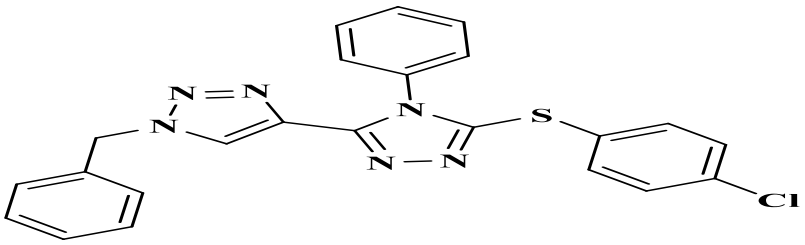
5-((1-methyl-pyrrol-2-yl)methyl)-4-(naphthalen-1-yl)-1,2,4-triazoline-3-thione [45]

$Mn(C45)Cl_2$ MeOH 1
$Fe(C45)Cl_2$ MeOH 2
$Ni(C45)Cl_2$MeOH 3
$Cu(C45)_2Cl_2$ 4
$Zn(C45)_4Cl_2$ 5

Anti-Inflammatory, Analgesic, and Antipyretic Activity

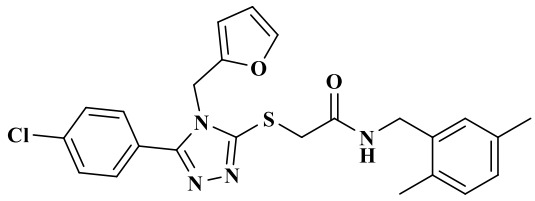
Inflammation is a biological response resulting in the host in response to Infection and/ or injury.(89) It was mentioned that triazole compounds both of 1,2,3 and 1,2,4-triazole have both of anti-inflammatory, and analgesic activities over other actions. (90) For finding novel compounds with rising analgesic, antipyretic and anti-inflammatory activities and minimum toxicity, Liu C. *et al* synthesized a new compound by linking 1,2,3-triazole and 1,2,4-triazole groups and planned based on association principle. All the synthesized

triazole-3-thiol derivatives were estimated (*in vitro*) to prove the anti-inflammatory activities. The results of their research showed that compound [46] has the best suppression on the expression of IL-6 in LPS induced macrophage cells.[91]

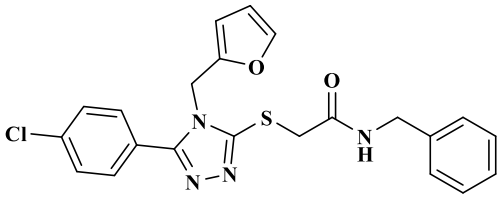


1-Benzyl-4-[5-(4-chloro-phenylsulfanyl)-4-phenyl-4H-[1,2,4]triazol-3-yl]-1H-[1,2,3]triazole [46]

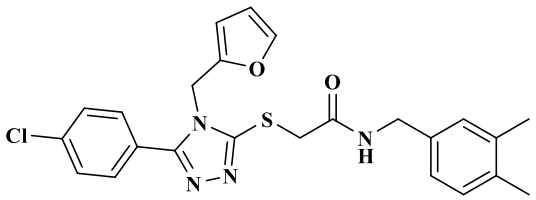
Yasin M. *et al* produced a novel derivative of N-furfuryl 5-(4-chlorobenzyl)-4H-1,2,4-triazole and evaluated its anti-inflammatory activity. *In vitro*, the inhibitory capacity of the final products [47-51] against soybean 15-LOX was determined by chemiluminescence and confirmed potent activities. In addition, they showed 79.5 to 98.8% cell viability as tested by the MTT assay at 0.25 mM. The structure-activity relationship has shown the position and type of the substituents attached to the phenyl group are significant in determining of inhibitory activity of 15-LOX.



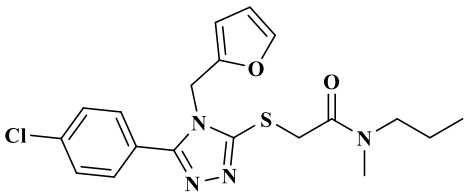
2-((5-(4-Chlorophenyl)-4-(furan-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)-N-(2,5-dimethylphenyl)-methylacetamide [47]



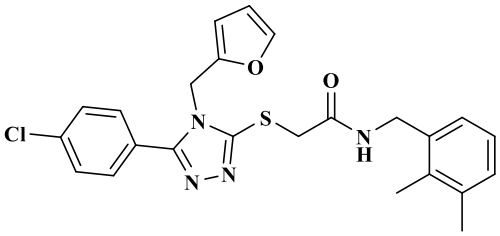
2-((5-(4-Chlorophenyl)-4-(furan-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)-N-phenylmethylacetamide [48]



2-((5-(4-Chlorophenyl)-4-(furan-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)-N-(3,4-dimethylphenyl)-methylacetamide [49]

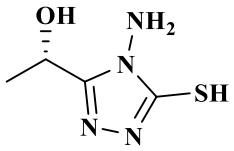


2-((5-(4-Chlorophenyl)-4-(furan-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)-N-n-propylmethylacetamide [50]



2-((5-(4-Chlorophenyl)-4-(furan-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)-N-(2,3-dimethylphenyl)-methylacetamide [51]

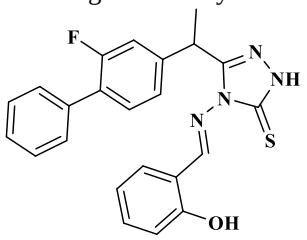
Azim T. *at el* were tested *in vivo* the analgesic, antipyretic, and anti-inflammatory activities of



(*S*)-1-(4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)ethan-1-ol [52]

Both of these compounds have been shown to be effective therapeutic agents as: analgesic, antipyretic, and anti-inflammatory. The last effect was produced activity higher than the ibuprofen, the standard drug, in carrageenan treatment groups and by using egg-induced paw oedema in mice and the % age inhibition of acetic acid induced wriths, formalin-induced nociception and tail-flick in mice display analgesic activity related to standard ibuprofen. Also, the anti-pyretic activity of produced derivatives was estimated through stimulating fever in rats after taking of brewer's yeast in all collections also show a significant effect to the tested triazole derivatives related to standard compound. [93]

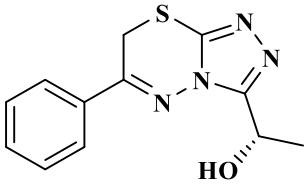
Zaheer M. *et al* convert Flurbiprofen by an efficient microwave-assisted synthesis to triazole−thione derivatives. Tail flick, hot plate, and writing methods were used to assess its potential as an analgesic. The outcomes of this *in vivo* study appeared that the number of compounds were powerful analgesics, especially compound [54] has considerable analgesic activity in all assays used.[94]



(*E*)-5-(1-(2-fluoro-[1,1'-biphenyl]-4-yl)ethyl)-4-((2-hydroxybenzylidene)amino)-2,4-dihydro-3H-1,2,4-triazole-3-thione [54]

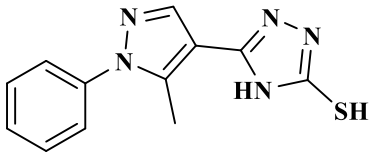
Due to their negative effect on the heart which associated with selective COX-2 inhibitors, these drugs have been withdrawn from the market. Abdellatif K.R.*et al*. designed and synthesized a new series of triazole- pyrazoles as selective COX-2 inhibitors with minimal cardio protective side effects. They found that compound [55] showed both of the highest selectivity for the COX-2 enzyme and the major activity as anti-inflammatory agent. Interestingly, their cardiovascular structure revealed cardiac biomarkers and inflammatory

novel synthesized compounds [52] and [53] that have 1,2,4-triazole ring.



(*S*)-1-(6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)ethan-1-ol [53]

cytokines that were almost like the control group. In addition, histopathological studies of cardiac and gastric muscle were included, and the results indicated that compound [55] had a main favorable cardiovascular profile than celecoxib. ADME studies were also tested and showed the significant activity of the new synthesized compounds as novel oral anti-inflammatory agents. As a conclusion, the newly synthesized compound [55] shows a potential COX-2 selective NSAID drug candidate with minimal cardiovascular risk**.**[95]

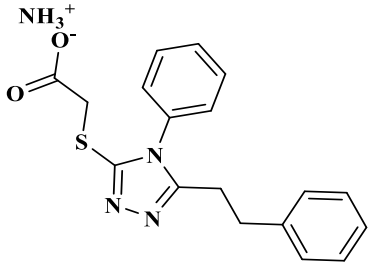


5-(5-Methyl-1-phenyl-1H-pyrazol-4-yl)-4H-1,2,4-triazole-3-thiol [55]

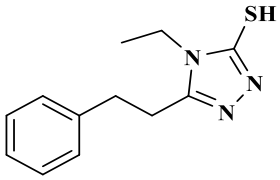
Antioxidant activity

Antioxidants activity may be explained as the ability of preventing the oxidation of substrates even if found in minute concentrations. It's stabilized molecules that give an electron to undesirable free radical species to prevent its further damage to corpus.[96] its well known that 1,2,4 triazolo derivatives to have antioxidant activity.[97,98]

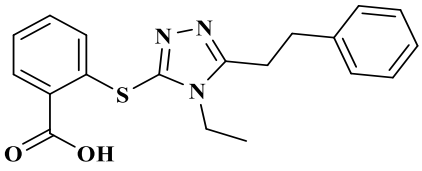
Ihnatova T. *et al* form a new derivative of 1,2,4-triazole-3-thiols and estimated their antioxidant activity *in vitro* by using the non-enzymatic initiation of bio-chemical oxygen demand (BOD) with salts of Fe (II). As a result, they got some synthesized compounds that were more potent than the standard compound vitamin C. The results of the determination of antioxidant activity show many derivatives have antioxidant activity but the most is compound [56] which decreases the content of TBC-AP by 38.79% ($p < 10^{-3}$), which showed more than the reference drug, vitamin C, by 5.38%. Also, compounds [57-59] had high antioxidant activity, which decreases the TBC-AP content by (32.40 - 33.06) % ($p < 10^{-3}$).[99]



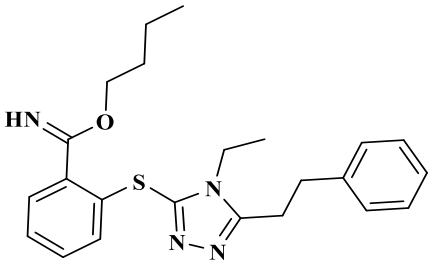
Methylammonium 2-((4-phenyl-5-phenethyl-4H-1,2,4-triazol-3-yl)thio)acetate [56]



4-ethyl-5-phenethyl-4H-1,2,4-triazole-3-thiol [57]

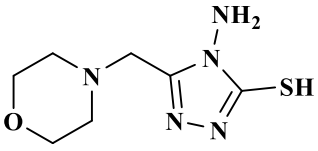


2-((4-ethyl-5-phenethyl-4H-1,2,4-triazole-3-yl)thio)benzoic acid [58]



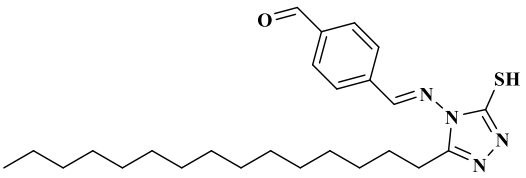
Butyl 2-((4-ethyl-5-phenethyl-4H-1,2,4-triazole-3-yl) thio)benzimidate [59]

In vitro antioxidant activity of morpholine derivatives of 1,2,4-triazol-3-thiols and its alkyl derivatives were investigated by Shcherbyna R. *et al* using a non-enzymatic lipid peroxidation initiation method. Among the tested compounds, compound [60] had the most significant antioxidant activity. It has been found that, in most cases, the presence of free amino groups in alkyl derivatives of 4-R-3-(morpholinomethyl)-4H-1,2,4-triazol-3-thiol or in substitution of 1 ,2, The 4-triazole nucleus with a phenyl group on the N_4 atom was accompanied by an increase in the antioxidant activity of the test substance. In almost all cases, the presence of a methyl or ethyl group on the N_4 atom had the opposite effect, even when compared to the control.[100, 101]

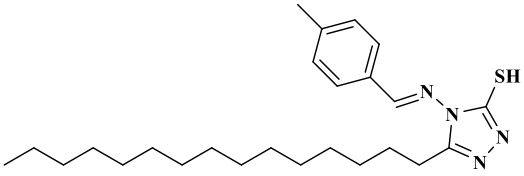


4-amino-3-(morpholinomethyl)-4H-1,2,4-triazole-5-thiol [60]

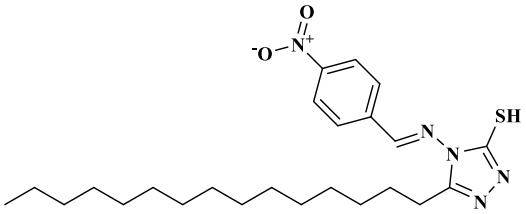
Kumari M. synthesized several heterocyclic 1,2,4-triazole derivatives and evaluated their biological activity. The compound [61] and [62] displayed considerable antioxidant activity in comparison with ascorbic acid while compound [61] and [64] have the most potent anticancer activity against HCT116 cell lines as tested with the standard 5-Fluorouracil 5-FU. They found that compound [62] was the most potent urease inhibitor amongst the synthesized derivatives when compared to thiourea as a standard. Also, both compounds [63] and [65] produced potent antimicrobial activity in comparison with ciprofloxacin, amoxicillin, and fluconazole. Structural activity relationship studies indicate that if aromatic ring substituted on m- and p- position with methoxy group that will lead to improve their anti-microbial activity, like in compounds [63], against G +ve, G-ve bacterial and *C. albicans* fungal strains while the p-substitution of nitro group developed the antifungal activity against *A. niger*. In case of (compound [61]); the substitution of methyl group at p-position lead to increase the anti-urease activity whereas the substitution of aldehyde may enhance the anti-cancer activity against HCT116 cell line; compound [64] which contain o-substituted group as hydroxyl was shown the same activity Also the antioxidant activity was improved by incorporate p-substituents such as aldehyde and methyl groups (compound [62]). [102]



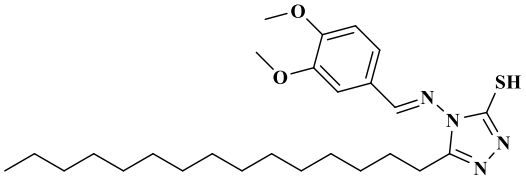
(E)-4-(((3-Mercapto-5-pentadecyl-4H-1,2,4-triazole-4 yl)imino)methyl)benzaldehyde [61]



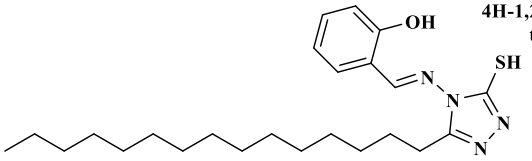
(E)-4-((4-Methylbenzylidene)amino)-5-pentadecyl-4H-1,2,4-triazole-3-thiol [62]



(E)-4-((4-Nitrobenzylidene)amino)-5-pentadecyl-4H-1,2,4- triazole-3-thiol [63]



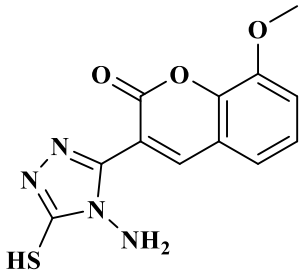
(E)-4-((3,4-Dimethoxybenzylidene)amino)-5-pentadecyl-4H-1,2,4- triazole-3-thiol [64]



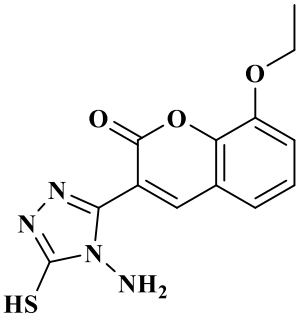
(E)-2-(((3-Mercapto-5-pentadecyl-4H-1,2,4-triazole-4 yl)imino)methyl)phenol [65]

Anti-diabetic activity

The prevalence of diabetes has been extremely increasing in the latest years all over the world, therefore the seeking of small molecules, like Five-membered heterocycles 1,2,4-triazoles, with strong antidiabetic activities are very important fields of research. Basappa V. Ch. *et al* were created a novel derivatives by link coumarin and 1.2,4 triazole-3-thiol then they were evaluated to evaluate their antidiabetic activity by measuring α-amylase inhibitory potential; the investigated results indicated that both of [66 and 67] compounds showed promising inhibitory effects on the enzyme at the same time they could serve as lead molecules for antidiabetic activity.[103]



3-(4-Amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)-8-methoxy-2*H*-chromen-2-one [65]



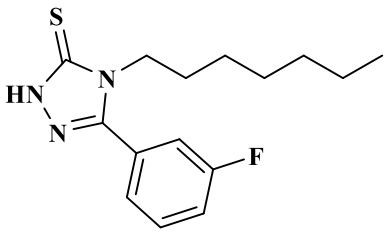
3-(4-Amino-5-mercapto-4H-1,2,4-triazol-3-yl)-8-ethoxy-2Hchromen-2-one [66]

Anticonvulsant Activity

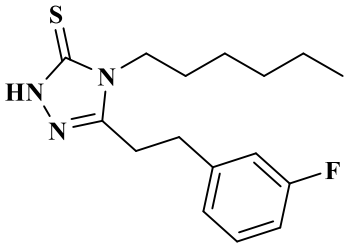
Epilepsy is a chronic neurological disease that affects millions of people worldwide. This is despite the observed advances in the development of novel antiepileptic drugs (AEDs). The discovery of a new anticonvulsant has the highest potency, and the lower toxicity led to the synthesis of many triazole derivatives as anticonvulsants, demonstrating the importance of the heterocyclic as a core in drug design and discovery.[104]

Kapron B., *et al*., they carried out their work based on the combined results of using radioligand binding assays and animal studies to develop a series of derivatives which have broad-spectrum anti-convulsant activity. Synthetic of derivatives of 4-alkyl-5-substituted-1,2,4-triazole-3-thione are mainly used in maximal electroshock (MES)-induced epilepsy assays in mice. Then, the expected

two major promising compounds [68], [69] were tested in models of psychomotor seizures. The protective activity of compound [69] was almost like that of the well-known anticonvulsant drug levetiracetam. As well as no one among these compounds cause genotoxic and hemolytic changes in human cells and are characterized by low cytotoxicity. Considering the structural necessity for significant anti-convulsant activity of 4-alkyl-5-aryl-1,2,4-triazole-3-thiones, small electron-withdrawing substituents are key to the affinity and protective activity of VGSC.[105]

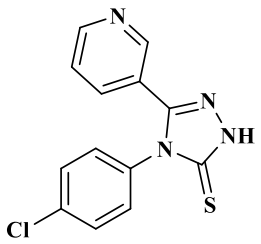


5-(3-Fluorophenyl)-4-heptyl-2,4 dihydro-3H-1,2,4-triazole-3-thion[67]

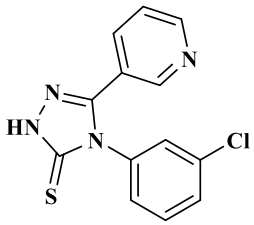


5-[2-(3-Fluorophenyl)ethyl]-4-hexyl-2,4-dihydro-3H-1,2,4-triazole-3-thione [68]

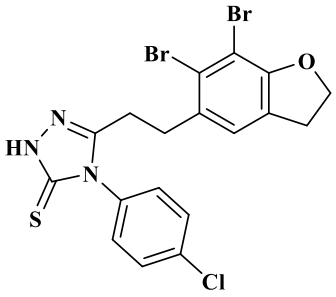
Verma K.K. *et al*. was design and synthesis some 4,5-disubstituted-2,4-dihydro-3H-1,2,4-triazole-3-thione derivatives and their activities as anticonvulsant and neurotoxic were estimated. Both compounds [70] and [71] gave significant pharmacological activity and were found to interact with the LYS329 residue of GABA aminotransferase through hydrogen bonding. Molecular docking studies have also been performed using GABA aminotransferase receptor to establish the correlation between bioactive responses and docking outcomes. By comparing the results, it was concluded that most of the anticonvulsant activity had a 3-pyridyl or 4-pyridyl group at the 5-position of the triazole ring, but the compound with the dihydrobenzofuran ring (compound [72]) was more potent in interacting with the receptor according to docking study.[106]



4-(4-chlorophenyl)-5-(pyridin-3-yl)-2,4-dihydro-3H -1,2,4-triazole-3-thione [70]



4-(3-chlorophenyl)-5-(pyridin-3-yl)-2,4-dihydro-3H -1,2,4-triazole-3-thione [71]



4-(4-chlorophenyl)-5-[2-(6,7-dibromo-2,3-dihydro-1-benzofuran-5-yl)ethyl]-2,4dihydro-3H-1,2,4-triazole-3-thione [72]

Conclusion

The core of triazole ring (which acts as linkers between different pharmacophores), with higher benzene ring stabilization energy are changed to increase solubility and selectivity with the interaction binding site of the enzyme. They have been demonstrated to be essential in a variety of biological processes, for example: fragment-based drug design, bio-molecular mimicry, and bio-orthogonal. One of the important heterocyclic moieties is 1,2,4-triazole due to its broad range of biological activities also their derivatives are able to accommodate a (electrophilic and nucleophilic substituents) for all the above it considered as a core molecule in design and synthesis of different pharmaceutical product as well as due to its heterocyclic behavior,1,2,4-Triazole have broad spectrum of therapeutically interesting drug candidates such as analgesic, antiseptic, antimicrobial, diuretics, antioxidant, anti-migraine,

anti-inflammatory, anti-cancer, anti-convulsant, antidiabetic, and anti-urease agents ,therefore till now researchers are working to discover and create novel scaffolds based on triazole cores that have enormous potential in the biomedical and biotechnology industries. The review summarizes biological activity and its relationship with the chemistry of 1,2,4-triazole sulfur-based compounds.

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Conflicts of Interest

The authors declare that there is no conflict of interest for this article.

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None.

Ethics Statements

None.

Author Contribution

Authors were responsible for writing the whole manuscript and approved the final manuscript draft.

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مشتقات الكبريت من ١،٢،٤-ترايازول: المركبات المطورة حديثًا، علاقة التركيب بالفعالية، والنشاط الحيوي

ازهار مهدي جاسم [١]، تغريد نظام الدين عمر [١] وشيماء لؤي عبد الهادي [١،*]

[*]فرع الكيمياء الصيدلانية، كلية الصيدلة، جامعة بغداد، بغداد، العراق

الخلاصة

يركز مصطلح الكيمياء الحلقية غير المتجانسة فقط على المركبات الحلقية غير المتجانسة، والتي تعتبر كنسبة مئوية من الكيمياء العضوية، وهي تساوي أكثر من خمسة وستين. توجد هذه المركبات على نطاق واسع في الطبيعة ومعظمها مهمة للحياة. في السنوات القليلة الماضية، انشغل العلماء في حلقة ١،٢،٤-تريازول ومركباتها الاخرى غير المتجانسة بشكل كبير نظرًا لأهميتها الطبية، ١،٢،٤-تريازول التي تحتوي على ذرة الكبريت هي واحدة من المركبات الحلقية غير المتجانسة المهمة نظرًا لفعاليتها البيولوجية الواسعة، أيضًا يمكن لمشتقاتها أن تستوعب أحد البدائل كتأثير إلكتروني مثل تبادل مجموعات الكثافة الإلكترونية (التبرع بالإلكترون أو سحبها)؛ لكل ما ذكر أعلاه، فهي تعتبر جزيئا أساسيًا في تطوير عدد كبير من المركبات الطبية. تتواجد ١،٢،٤-تريازول في مجموعة واسعة من الأدوية مثل المسكنات، مضادات للميكروبات، المضادة للالتهابات، مضادات الاختلاج، مضادات الأكسدة، مضاد الإنتان، مضاد للسرطان، مدرات البول، مضاد للسكري، مضاد لليورياز، والادوية المضادة للصداع النصفي. تركز هذه المراجعة على المركبات القائمة على الكبريت ١،٢،٤-تريازول وحول أنشطتها البيولوجية المختلفة والعلاقة مع الكيمياء الخاصة بهم.

الكلمات المفتاحية: ١،٢،٤-تريازول-٣-ثيونات، ١،٢،٤-تريازول-٣-ثيولز، مركب حلقية غير متجانسة، مشتقات، نشاط حيوي