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Biological Evaluation and Pharmacological Potential of Heterocyclic N-Bridged S-Triazole Scaffolds: A Comprehensive Review

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ABSTRACT

1,2,4-Triazole and its derivatives have emerged as crucial scaffolds in medicinal chemistry due to their diverse biological activities. This review comprehensively explores recent advancements in the synthesis and evaluation of 1,2,4-triazole derivatives for their antimicrobial, antifungal, antiproliferative, anticancer, anti-inflammatory, and insecticidal properties. Several studies have highlighted the potential of these compounds in treating tuberculosis, fungal infections, and various cancers, demonstrating their significance in drug discovery.

For instance, certain 1,2,4-triazole derivatives exhibit remarkable antimycobacterial activity by inhibiting the KatG enzyme, leading to oxidative damage in Mycobacterium tuberculosis. Other derivatives have demonstrated potent antifungal effects against Rhizoctonia solani by disrupting mycelial cell membranes. Additionally, specific compounds have shown promising cytotoxicity against cancer cell lines such as MCF-7, HeLa, and A549, with some derivatives outperforming standard chemotherapeutic agents. The structural modifications in triazole rings, including substitutions at different positions, have significantly influenced their biological activities, as evidenced by molecular docking and structure-activity relationship (SAR) studies.

Furthermore, triazole-based compounds have been investigated for their anti-inflammatory and insecticidal activities, revealing potential applications beyond traditional antimicrobial and anticancer therapies. The findings from various research articles emphasize the importance of continued exploration of 1,2,4-triazole derivatives to develop novel therapeutic agents with improved efficacy and selectivity. This review provides insights into the latest developments in triazole-based drug discovery, paving the way for future advancements in pharmaceutical research.

Keywords: 1,2,4-Triazole, N-Bridged, Biological, Heterocyclic.

INTRODUCTION

Heterocyclic compounds play a pivotal role in medicinal chemistry, with 1,2,4-triazole derivatives gaining

significant attention due to their broad spectrum of biological activities. The 1,2,4-triazole core is a five-membered nitrogen-containing ring that exhibits remarkable stability and versatility, making it an essential pharmacophore in drug design. Over the years, extensive research has been conducted on the synthesis and biological evaluation of these derivatives, leading to promising developments in antimicrobial, antifungal, anticancer, anti-inflammatory, and antiproliferative agents.

Among the various pharmacological applications, 1,2,4-triazole derivatives have shown notable efficacy against bacterial and fungal infections. Their antimycobacterial activity, particularly against Mycobacterium tuberculosis, has been linked to the inhibition of key enzymes such as KatG, which disrupts bacterial defense mechanisms. Similarly, antifungal studies have demonstrated their potential in inhibiting pathogenic fungi by targeting vital cellular components, thereby offering alternatives to existing antifungal drugs.

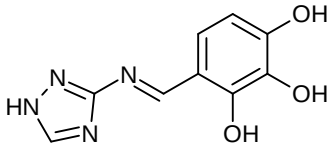
In oncology, 1,2,4-triazole derivatives have emerged as promising anticancer agents, displaying cytotoxicity against various cancer cell lines, including MCF-7, HeLa, and A549. Their mechanism of action often involves the inhibition of enzymes crucial for cancer cell proliferation, as confirmed through molecular docking and structure-activity relationship (SAR) studies. Additionally, their anti-inflammatory properties have been explored for potential therapeutic applications in chronic inflammatory diseases.

This review aims to provide a comprehensive overview of the latest advancements in 1,2,4-triazole derivatives, focusing on their synthesis, mechanisms of action, and biological significance. By summarizing key research findings, this study highlights the potential of these compounds in drug discovery and their role in addressing current medical challenges.

REVIEW OF LITERATURE

Antimycobacterial Activity:

1. **Meng-Yu Xia. *et. al.,*** 1,2,4-triazole derivatives were synthesised and evaluated for their antimycobacterial activity. Among the 15 compounds, compound 4 showed the strongest anti-Mtb activity with an MIC of 2 lg/mL. Molecule docking exhibited that compound 4 had a good affinity for Mtb KatG. The experiment indicated that compound 4 had inhibitory activity against KatG enzyme in a dose–response manner. In addition, Mtb showed intracellular accumulation of ROS after treatment with compound 4. Compound 4 caused shape changes and staining changes in Mtb at subinhibitory concentrations. These may be due to oxidative damage of cell wall components by ROS. Therefore, it can be concluded that the anti-Mtb effect of compound 4 may be related to its inhibition of KatG enzyme. This study provides a new idea for the development of novel anti-Mtb drugs[(1)].



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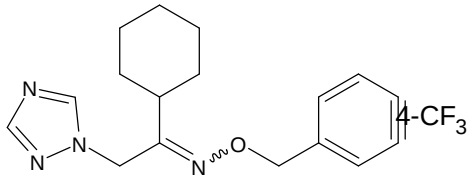
Antifungal Activity:

2. **Shengxin Sun. *et. al.*,** As a most promising target compound, (Z)-5o was found possessing excellent antifungal activity against R. solani with the EC50 value of 0.41 μg/mL in vitro and preventive efect of

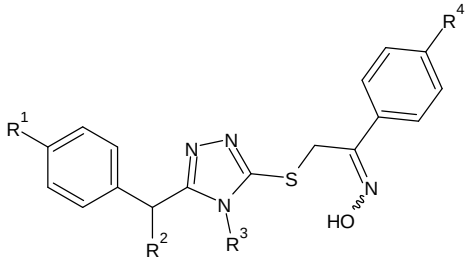
94.58% in vivo at 200 μg/mL, which was even comparable to the common commercialized fungicide tebuconazole. The compound (Z)-5o could signifcantly inhibit mycelial growth by destroying mycelial cell membrane. By comparing the molecular docking modes of (Z)-5o and (E)-5o with the potential target protein RsCYP51, it was preliminarily clarifed that (Z)-5o efectively reduced the binding energy through strong hydrogen bond interactions with the amino acid residues of the target protein and made its antifungal activity higher than compound (E)-5o[(2)].



5o

Antiproliferative and cytotoxic activities:

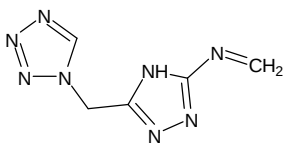
3. **Bahadır Bülbül. *et. al.,*** For the Ibuprofen-derived triazole compounds, an ethyl group at the triazole N4 position increased the cytotoxicity. The ten compounds showed moderate cytotoxic activity against MCF-7, HeLa, PC-3, and A549 cell lines. Among the triazole N4 methyl-bearing compounds, only 27 and 39 showed cytotoxic activity. The brome-bearing compound 27 showed only 49.46% inhibition against the A549 cell line, but its selectivity was very low. Compound 39 carried fuoride at the same location and showed 40.97% inhibition against the PC-3 cell line[(3)].



27: R^1:H,R^2:H,R^3:CH_3,R^4:H
39: R_1:isobutyl,R_2:CH_3,R_3:CH_3,R_4:4-F

Antimicrobial and Antifungal activities:

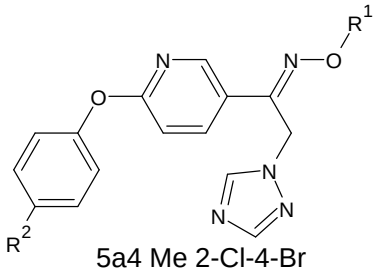
4. **Frolova Y. *et. al.,*** Considering the amino derivatives of 1,2,4-triazole, we can identify 5-(1H-tetrazole-1-yl)methyl-4H-1,2,4- -triazole-3-yl-1-(alkyl-, aryl) methanimines (11.4-11.7), which exceeded the antimicrobial and antifungal activity of the comparison drug against Staphyllococcus aureus and Candida albicans[(4)].



11.4

Fungicidal Activity:

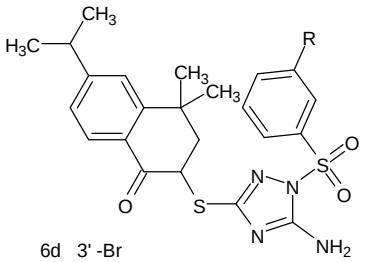
5. **Hui Bai. *et. al.,*** A series of novel 1, 2, 4-triazole fungicidal compounds with an oxime ether and phenoxypyridinyl moiety were designed and synthesized. The in vitro fungicidal activities against eight fungal pathogens were evaluated. Most of the compounds exhibited moderate to excellent fungicidal activities against tested phytopathogens. Especially, compound 5a4 displayed promising fungicidal activity with broad spectrum and 5b2 provided the highest inhibition rate towards S. sclerotiorum. In addition, other compounds towards certain fungus also exhibited high fungicidal activities[(5)].



5a4 Me 2-Cl-4-Br
5b2 Bn 2-Cl

Antitumor Activity:

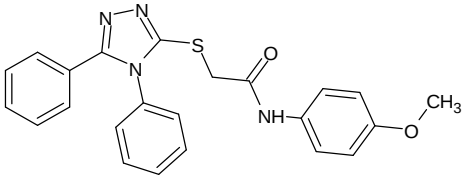
6. **Xia-Ping Zhu. *et. al.,*** Some compounds exhibited better anticancer activity against the tested cancer cell lines compared to positive control 5-FU. Some intriguing structure–activity relationships were found and discussed by theoretical calculation. Compounds 6g, 6h, and 6d, with excellent and broad-spectrum antitumor activity against almost all the tested cancer cell lines, were leading compounds for further investigation[(6)].



6d 3' -Br
6g 2',3',4'',5',6' -F
6h 3' -NO_2-4' -Cl

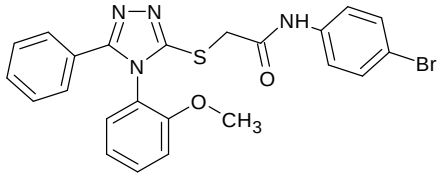
Anticancer activity:

7. **Abdallah Turky. *et. al.,*** Different substitution patterns were introduced at the phenyl groups at both C-5 of the triazole ring and the terminal hydrophilic tail to study the effect of such substituents on the cytotoxicity. Four of our designed derivatives showed good cytotoxicity effects against the human breast adenocarcinoma (MDA- MB-231) cell line as a proven model for A2B adenosine receptor subtype. Compounds 15 showed a more potent inhibitory effect than doxorubicin, with an IC50 value of 3.48 µM. Also, compound 20 revealed almost an equipotent activity with the reference cytotoxic drug against selected cancer cells, with an IC50 value of 5.95 µM[(7)].



Cytotoxicity:

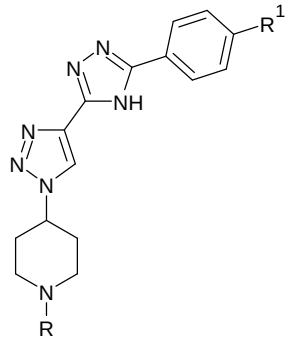
8. **Balasaheb D. *et. al.,*** It was observed that all the synthesized target compounds 9(a–l) exhibit decent activity against mushroom tyrosinase enzyme compared with reference kojic acid. Besides, among all the derivatives, compounds 9k (IC50= 0.0048 ± 0.0016 µM) are almost 3500-fold more active with the aggressive mechanism of action than standard drug kojic acid (IC50=16.8320±1.1600 µM)[8].



9k

Antifungal activity:

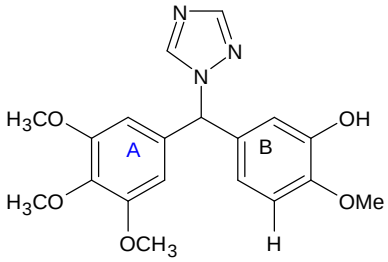
9. **Sangshetti JN. *et. al.,*** It can be said that compounds 3e and 3j are most active compounds from the series, thus suggesting that the present series containing 1,2,4- triazole with 1,2,3-triazole and piperidine ring with methyl sulfone group on piperidine nitrogen can serve as important pharmacophore for the design of new antifungal agent with potent activity[9].



3e R=SO_2CH_3 R_1=H
3j R=SO_2CH_3 R_1=4Cl

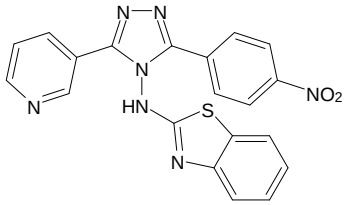
Anti-Mitotic Agent:

10. **Ana G. *et. al.,*** The aromatase inhibition of the most potent antiproliferative compounds 19e, 21l, and 24 was evaluated, and compound 19e was identified as the most potent with over 85% inhibition of CYP19 at 20 µM and an IC50 of 29 µM[10].



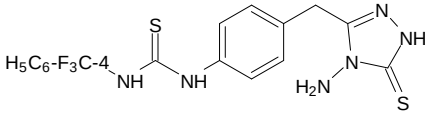
19e

11. **Patel NB. *et. al.,*** It was also observed that the promising antimicrobials have proved to be better antituberculars. Specially, compound 6j due to their better activity against H37Rv strain, is the best choice for the preparation of new derivatives in order to improve antitubercular activity in future[11].



6j 4Cl

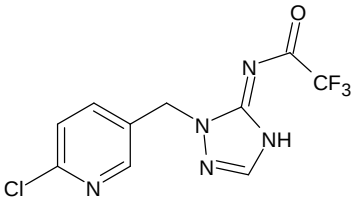
12. **Kocyigit-Kaymakcioglu B. *et. al.,*** Phomopsis cane and leaf spot (P. viticola) causes serious economic losses to the vine grape production in the United States of America and Europe, while P. obscurans causes Phomopsis leaf blight and fruit rot of strawberry. Compound 3d was the most active derivative among the tested compounds in a larvicidal assay against A. aegypti[12].



3d

Insecticidal activity

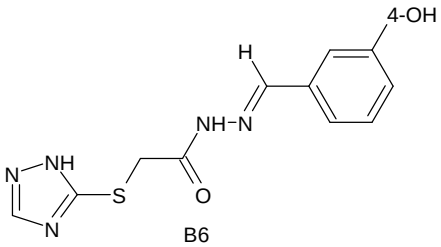
13. **Zhao F. *et. al.,*** From the analysis of the docking results and bioassay results, it can be seen that the replacement of the chloropyridine ring with a chlorothiazole ring will cause a larger conformational change in this type of structure. Although the compound 4-1 with the chloropyridine side chain has a relatively good binding conformation[13].



4-1

Anti-inflammatory activity

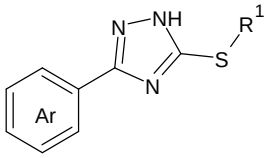
14. **Khan B. *et. al.,*** The presence of phenyl ring with two hydroxyl groups as substituents in B6 Figure 14. Illustrated pathway showing B6 and its role in blocking inflammation is suggested to explain a better B6 efficacy, implicating B6 as an important scaffold for the synthesis of new compounds targeted against PTGS in inflammation and infections[14].



B6

Antitubercular activity

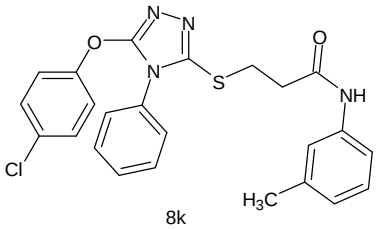
15. **Rode ND. *et. al.,*** A series of 3-aryl-5-(alkyl-thio)-1H-1,2,4-triazoles (1,2,4- Triazole) derivatives were synthesized and evaluated against Mtb (H37Ra) and their cytotoxicity was assessed using four FIGURE 4 Binding mode of 7b into the active site of CYP121 [Colour figure can be viewed at wileyonlinelibrary.com] 1214 | RODE et al. human cancer cell lines. Of particular note, eight triazoles were found to have the most promising antituberculosis activity (MICs of 2b, 3a–3d, 10b, 12a and 12b against DMTB ranged from 4.18 to 9.86 μg/ml and IC50 from 0.03 to 0.60 μg/ml) along with low cytotoxicity (CC50: >100 μg/ ml) and high aqueous solubility (>1,280 μm)[15].



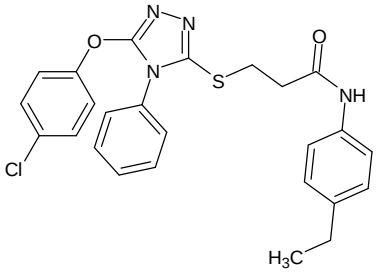
2b 2-Me, 3-NO_2
3a-3d 3-Me,4-NO_2
10b 3-CF3

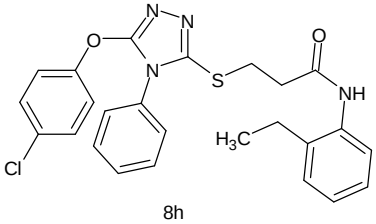
Anti-proliferative activity

16. **Ali S. *et. al*.,** The biological evaluation of the library suggested compound 8k as the hit compound along with 8h, 8i showing prominent activities. Compound 8k was docked with the enzyme to understand the interaction of the molecule with the protein for further structure optimizations[16].



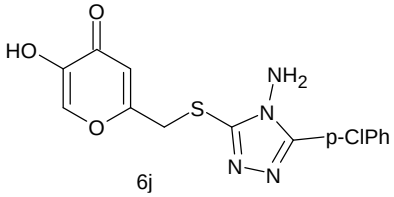
8k





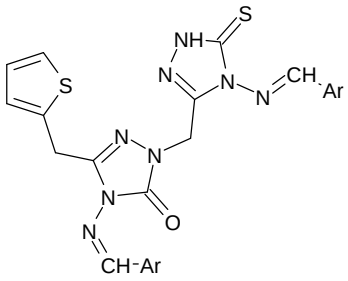
8h

17. **Xie W. *et. al*.,** A series of novel 5-substituted-3- [5-hydroxy-4-pyrone-2-yl-methylmercapto]-4-amino-1,2,4- diazole derivatives (6a-6l) have been synthesized, and their inhibitory activity on mushroom tyrosinase has been evaluated. The results showed most of them displayed higher inhibitory activity on tyrosinase than kojic acid. Among the compounds synthesized, compound 6j showed the strongest inhibitory activity with IC50 value of 4.50 0.34 lM[17].

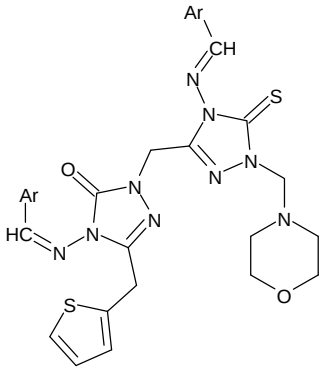


6j

18. **Ünver Y. *et. al.***, Among all the synthesized triazole derivatives the nitro substituted thiophene containing compounds 4d and 5d showed high promising antimicrobial activity[18].

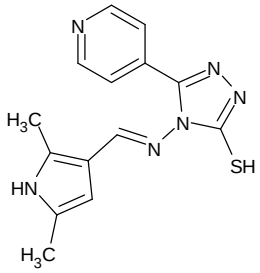


4d



5d

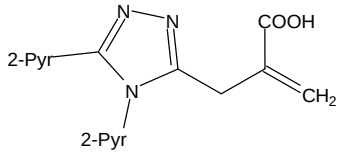
19. **Ogunyemi OO. *et. al.***, The synthesis of a small series of hydrazone linked arylpyrrole-1,2,4-triazole hybrids, which showed modest antimycobacterial activity. The unsubstituted pyrrole-1,2,4-triazole derivative 13, MIC90=3.99 μM, represents the most active member of the series with no apparent effect on HeLa cell-line[19].



13

Anti-Inflammatory Activity

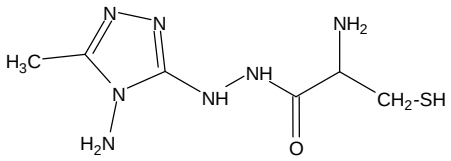
20. **Paprocka R. *et. al.,*** Owing to their high anthelmintic potential, which was proved to be higher than that of the recommended drug albendazole, we have selected compounds 12 and 14 as potential candidates for further research. Derivative 12 also showed anti-inflammatory activity (by inhibiting TNF-α production), which constitutes an additional advantage[20].



12-14

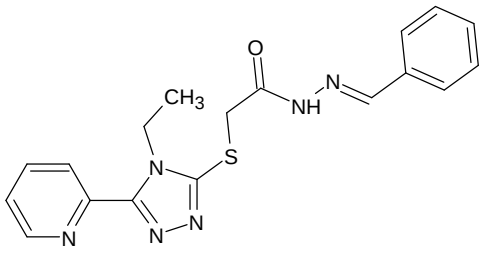
Antifungal Activity

21. **El-Hazek RM. *et al.,*** New hybrid triazole–amino acid derivatives were synthesized in this study for the evaluation of antifungal activity. Cysteine derivative 6 showed the most potent activity against C. parapsilosis isolates. It induced inhibition of hyphal formation and cell distortion. In addition, compound 6 was effective in completely inhibiting the virulence enzyme gelatinase. Moreover, it showed good antibacterial activity[21].

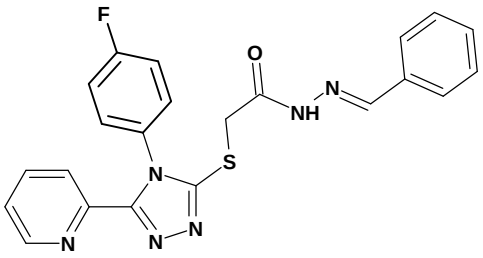


6

22. **Khalid W. *et al.*, :** In the present study, six new 1,2,4-triazole derivatives ZE-4(a–c) and ZE-5(a–c) were synthesized. ZE-4b, ZE-4c, ZE-5a and ZE-5b were obtained in good yield and further evaluated for their antiplatelet and anticoagulant potential. The test compounds showed antiplatelet activity less than the standard drug, however, hydrazone derivatives ZE-4b and ZE-4c were found to be more potent as compared to sulphonamide derivatives. ZE-4c also exhibited potent anticoagulant activity by increasing PRT and BT time. Further, the molecular interactions of test compounds were investigated by molecular docking studies against selected targets of blood aggregation and coagulation pathways. Test compounds possessed high affinity for COX-1, GP-IIb/IIIa and F-X receptors. The in vitro and in vivo studies also confirmed antiplatelet and anticoagulant potential of test compounds[22].

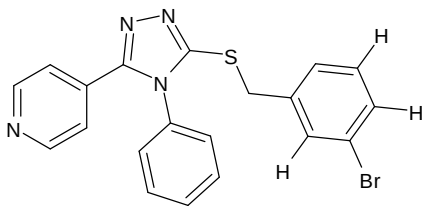


ZE-4b

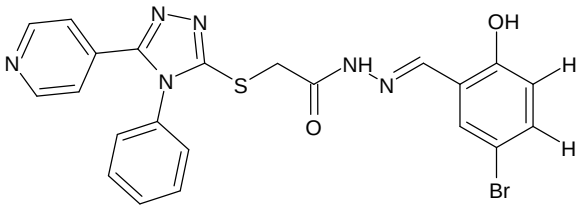


ZE-4c

23. **Zhang YB. *et al.*, :** Two series of 1,2,4-triazole derivatives containing pyridine have been synthesis and evaluated for their anti-tumor activities. Compound **3e** and **6j** demonstrated the most potent inhibitory activity. **3e** inhibited the growth of the three cell lines with IC_{50} values range from 7.04 to 10.04 μM, while **6j** inhibited the growth of the three cell lines with IC_{50} values range from 1.99 to 6.46 μM. Besides **6j** also inhibited the activity of FAK with IC_{50} of 2.41 μM, which was comparable to the positive control staurosporine. In order to gain deeper understanding of the SARs observed at the FAK, molecular docking of the most potent inhibitor **3e** and **6j** into the binding site of FAK was performed on the binding model based on the FAK complex structure. Analysis of the compound **6j**'s binding conformation demonstrated that compound **6j** was stabilized by hydrogen bonding interaction with CYS502. Apoptosis assay and western-blot results showed the compound **6j** was a potential anti-tumor agent[23].

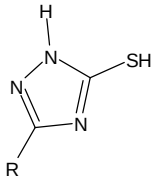


3e



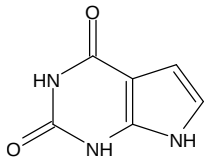
6j

24. **Lazrak F. *et al.*,:** The main focus of this research was to synthesize and characterize new 1,2,4-triazole-5-thione derivatives. The structures of these compounds were confirmed by spectral data (IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry). The results observed showed that the macrocyclization of 1,2,4-triazole thione involved the tautomeric form **1b**, highlighting that the sulfanyl group as well as the N-1 triazolic atom are the most reactive sites. The ADMET, drug-likeness, and molecular docking study revealed that **3** may act as a potent inhibitor of DNA-dependent protein kinase (DNA-PK). **3** showed moderate anticancer activity, compared to that of doxorubicin[(24)].



1b

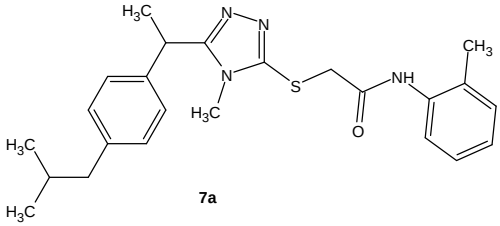
25. **Korol N. *et al.*, :** Novel series of *bis*-1,2,4-triazoles, exploring their potential as antibacterial and fungicidal agents, efficient inhibitors of thymidine phosphorylase (TP), and promising anti-tumor compounds. Our results demonstrate that most of the synthesized compounds possess significant biological activity against various bacteria. Notably, the alkylated derivatives displayed excellent TP inhibition, with two compounds exhibiting higher inhibitory activity than the standard reference, 7-deazaxanthine (IC_{50} = 41.0 ± 1.63 µM). Besides, molecular docking analysis revealed a specific interaction between the lead compound **2** and Lys190 through a hydrogen bond. These results provide valuable insights for the design of advanced compounds with enhanced inhibitory activity against the TP enzyme, thus offering potential prospects for their utilization as effective anti-tumor agents[(25)].



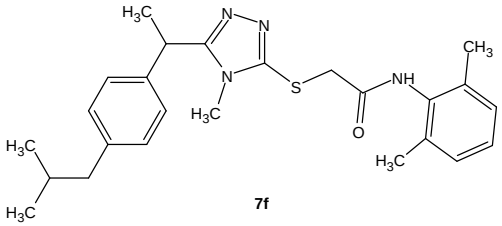
7-Deazaxanthine

26. **Akhter N. *et al.*, :** These triazole-based acetamide derivatives also exhibited low cytotoxicity, with values ranging from 7.33% to 1.19% in comparison to the 100% cytotoxicity exhibited by the reference standard Triton X100. Compounds **7f** and **7a** showed the highest anti-cancer potential, with IC_{50} values of 16.782 µg/mL and 20.667 µg/mL, respectively. On the other hand, the triazole derivative containing an electron-withdrawing chloro moiety demonstrated the least anti-proliferative activity with an IC_{50} value of 39.667 µg/mL. The sequence of anti-cancer potential was found to

be **7f** > **7a** > **7b** > **7c** > **7e** > **7d**. The anti-cancer potential of all of the compounds was further investigated by molecular docking studies and the results were in accordance with in-vitro studies. In silico studies have shown that the molecules have strong affinity for kinase targets. Molecules **7f** and **7a** have shown their anti-cancer effects, especially by affecting Akt and c-lit molecular targets[26].

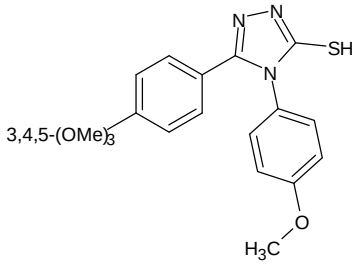


7a



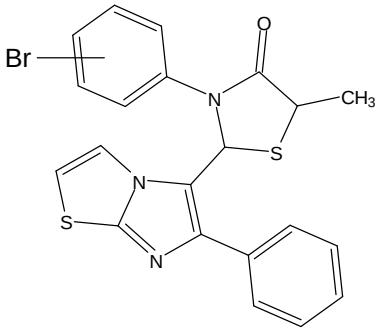
7f

27. **Ghanaat J. *et al.*, :** Designed and synthesized new analogs of 3-mercapto-1,2,4-triazole potential derivatives for antiproliferative activity. Cytotoxic activity of the synthesized compounds was evaluated against three human cancer cell lines: lung (A549), breast (MCF7) and ovarian (SKOV3). Anti-proliferative results showed that all tested compounds potentially could inhibit the growth of cancerous cells, in particular, in case of compounds 4d and 4e[27].



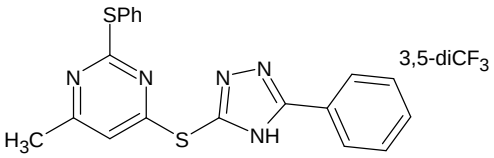
4d

28. **Kamboj P. *et al.*, :** A new series of imidazothiazoles coupled with thiazolidinone moiety were designed and synthesised in multiple steps by reagent-based approach and evaluated for their EGFR kinase inhibitory, anticancer and anti-inflammatory activities. All the synthesized derivatives were evaluated for cytotoxicity against three cancer cell lines A549, MCF7, HCT116 and one normal human embryonic kidney cell line HEK293 which displayed moderate to potent inhibitory activities. Among all the tested compounds, **4c** demonstrated broad-spectrum anticancer activity with excellent inhibitory potency and showed an IC_{50} value 10.74 ± 0.60 and 18.73 ± 0.88 µM against the cancer line A549 and MCF7 respectively[28].

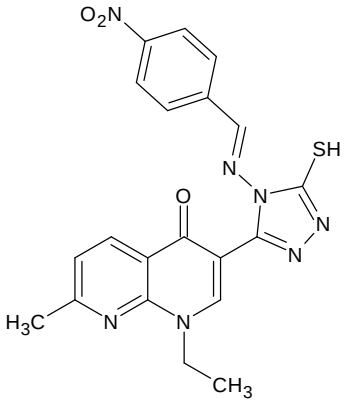


4c

29. **Gao F. *et al.*, :**The antibacterial activity of 1,2,4-triazole hybrids including 1,2,4-triazole-azole, 1,2,4-triazole-coumarin, 1,2,4-triazole-β-lactam, 1,2,4-triazole-pyrimidine, 1,2,4-triazole-quinoline, 1,2,4-triazole-quinolone, and triazole-quinazoline hybrids. Hybrids 21a and 29 were highly active against both drug-sensitive and drug-resistant pathogens and were no inferior to the first-line antibacterial agents, could act as leads for further investigations. The SAR is also discussed, and the enriched SAR may afford useful information for further rational design of the candidates with higher activity[29].

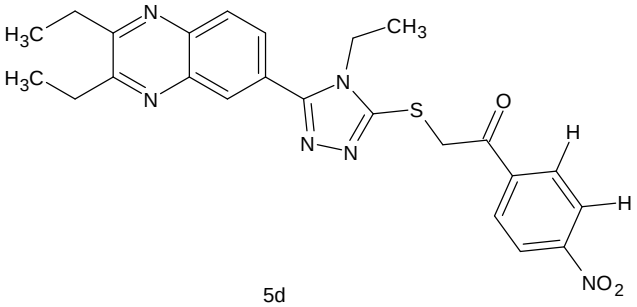


21a



29

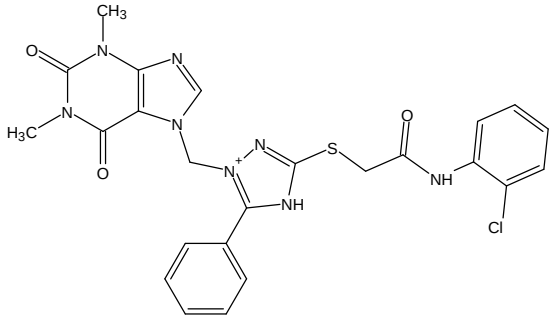
30. **Osmaniye D. *et al.*, :** This is exactly the purpose of the synthesis of new triazole derivatives within the scope of this study. In this study, 17 new triazole derivatives were synthesized. Structure determinations of the compounds were made using ^{1}H-NMR, ^{13}C-NMR and HRMS techniques. In addition, structure determination was validated for compound **5d** using the 2D-NMR technique. In addition to the antifungal activities of the compounds, the percent biofilm inhibition values were tested on *Candida* strains by *in vitro* methods. As a result of activity studies, compound **5d** exhibited a similar antifungal potential with fluconazole. It was even 8 times more active on *C. krusei* than fluconazole[30].



5d

31. **Saeed S. *et al.*,** The ultrasonic-assisted method demonstrated advantages such as shorter reaction times and higher yields of 1,2,4-triazole products (69%–95%). Notably, among the synthesized structural hybrids, the 1,2,4-triazole compound 4c (IC50 = 0.015 ± 0.25 mg), featuring a 4-chlorophenyl ring, exhibited superior serine protease inhibitory activity compared to the standard drug ribavirin (IC50 = 0.165 ± 0.053 mg). Molecular docking studies revealed that triazole compound 4b exhibited a stronger binding affinity score than 4c and the control drug 5 with the active site of serine protease enzyme. DFT study results were consistent with in vitro and molecular docking findings. In terms of inhibition,

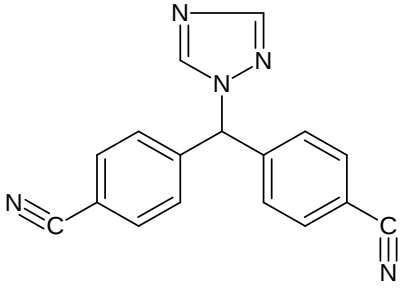
compound 4b demonstrated higher inhibition (86%) of serine protease compared to 3,4-dichlorophenyl compound 4c (76%) and the standard drug ribavirin (81%). Thus, compounds 4b and 4c emerged as more promising serine protease inhibitors than the standard drug, ribavirin[31].



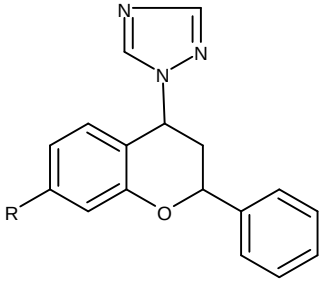
4b

32. **Leila Emami *et al*.,(2022)**: The target 1,2,4 triazole derivatives were designed based on the chemical structures of Letrozole (a), Anastrozole (b) and 4-tria-zolylflavans (c) which act as aromatase inhibitor. Aromatase is a member of the cytochrome P450 superfamily that catalyzes the estrogen biosynthesis and can be considered as a therapeutic target due to its overexpression in breast cancer. Anastrozole and Letrozole are potent aromatase inhibitors that use in the treatment of ER-positive breast cancer.[32]

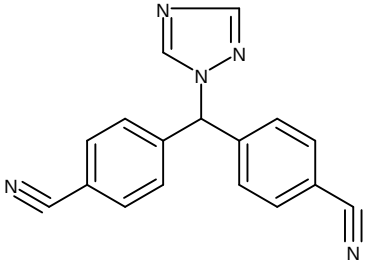
Letrozole (a)



4-triazolylflavans derivatives (c)

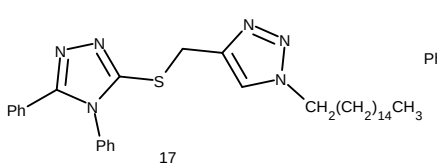


33. **Harshita Sachdeva *et al*.,(2022)**: This review examines the anticancer potential of 1,2,3-triazole coupledoleanolic acid/ dithiocarbamate and 1,2,4-triazole substituted methanone derivatives, acridine-based 1,2,4-triazole derivatives. Highlights he key finding in the area of cancer therapy. Triazole derivatives possess anticancer activity against various human cancer cell lines, and hence the triazole core may act a lead molecule for the synthesis of novel anticancer drugs.[33]

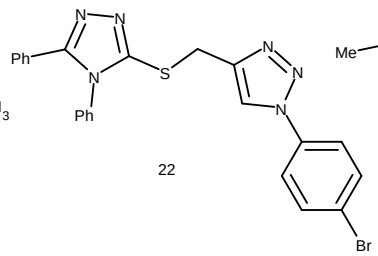


4-triazolylflavans derivatives

34. **Adeeb Al Sheikh Ali *et al.,(2021)*:** A focused library of 1,2,3-triazoles encompassing 1,2,4-triazole cores was designed and successfully synthesized through a click reaction of a proper S-propargylated 1,2,4-triazoles **7** and **8** using the Cu(I)-catalyst. The reaction proceeded effectively either by classical or MWI and yielded the desired click adduct **16–27** in good to excellent yields. The anticancer screening was also investigated against some cancer cell lines including Caco-2 and HCT116, HeLa, and MCF-7. The results revealed that the compound **17** emerged as the most potent tested compounds against the MCF-7 cancer cell line with an IC_{50} value of 0.31 μM while compounds **22** and **25** exhibited good anticancer activity against the MCF-7 cancer cell line with IC_{50} values of 4.98 and 7.22 μM, respectively.(34)



17



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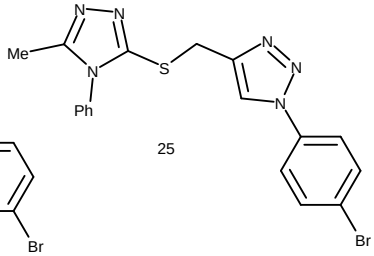
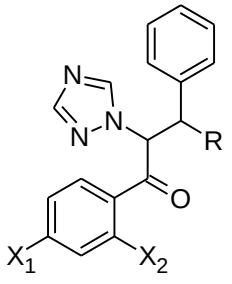
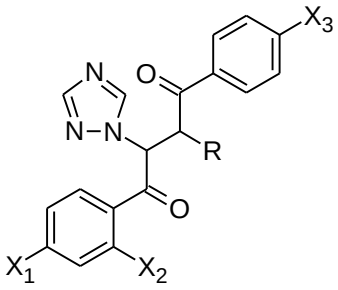


25

35. **Hossein Sadeghpour *et al.*,(2022):** designed and synthesized nineteen new 1,2,4- triazole-based derivatives starting from different phenyl halide analogues through three or four different steps. Their chemical structures were fully confirmed by IR, ^{1}H-NMR, Mass spectra and elemental analysis. In vitro cytotoxic activity of the synthesized compounds were evaluated against three human cancer cell lines including MCF-7, Hela and A549, using MTT assay. The obtained results indicated that the synthesized compounds possessed relatively high to moderate antiproliferative activities against MCF-7 and Hela cancer cell lines. Compounds ***7d***, ***7e***, ***10a*** and ***10d*** were the most potent ones against three tested cell lines. Based on structure activity relationship (SAR) studies, it was found that the presence of electronegative substituents on the phenyl ring, as well as the presence of one-carbonyl group, resulted in a relative increase in the cytotoxic activity of the synthesized compounds.(35)



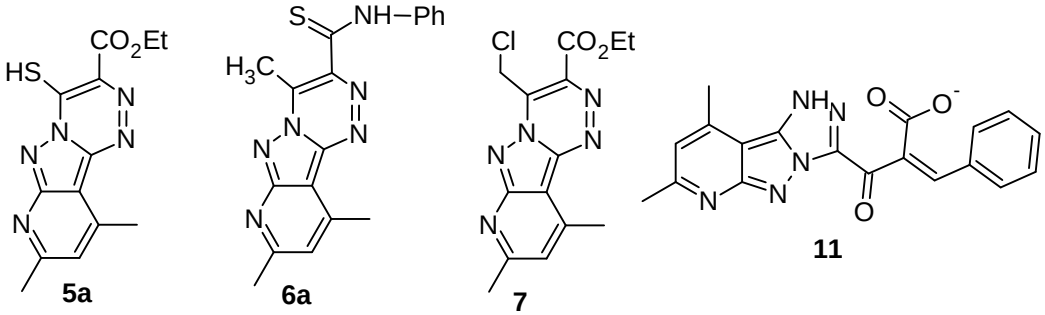
7d-e
7d:X_1:Br, X_2:H, R:Ph
7e: X_1:Cl, X_2:Cl, R:Ph



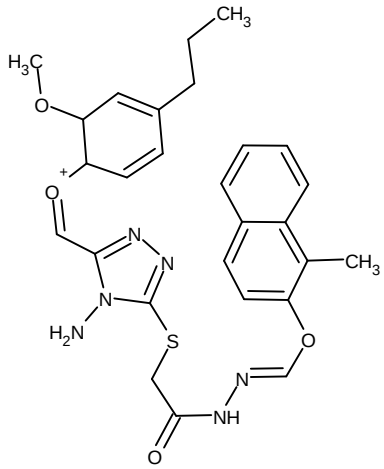
10 a & d
10 a: X_1:H, X_2:H, X_3: H, R:H
10 d: X1:Br, X2:H, X3: Cl, R:H

36. **Mohamed R. Elmorsy *et al.*,(2023):** There is agreement between the theoretically predicted and experimentally obtained results, where compounds **5a**, **6a**, **7**, and **11** showed highly biological activities and also exhibited an eminent free energy score. The binding energy score of pyridopyrazolo derivatives, which came through H-bonds, *pi–pi*, and *pi*–H interactions with the suitable receptors,

follows the order 6a > 5a > 7 > 11 with S = − 7.8182, − 7.7362, − 7.2146, and − 7.2031 kcal/mol, respectively.[36]

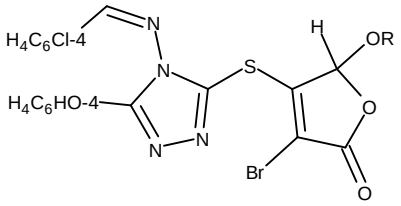


37. Mohammad Mahboob Alam *et al.*,(2024) :natural product eugenol was utilized to develop new eugenol based 1,2,4-triazole derivatives as antiCOX-2 and antiproliferative agents. From the antiproliferative study, compound (E)-2-((4-amino-5-((2-methoxy-4-propylphenoxy)methyl)-4H-1,2,4-triazol-3-yl)thio)-N'-((2-hydroxynaphthalen-1-yl)methylene)acetohydrazide (**10)** emerged to be equipotent to doxorubicin with IC_{50}5.69 µMand1.42, towards PC3 and MDA-MB 231 carcinomas, respectively and inhibted COX-2 with IC_{50}0.28 µM. Compound **10** was also non carcinogenic, non mutagenic with good drug likeness property as depicted by in silico physicochemical and pharmacokinetic studies. The docking results against COX-2 protein showed highest binding energy for compound **10** which was in favor of its highest cytoxicity and COX-2 result. In conclusion, compound **10** could harness COX-2 and cell proliferation and could be a promising molecule in cancer therapy.[37]

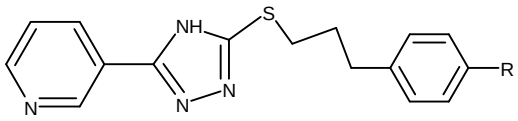


10

38. Namratha B. *et al.*,(2014) : Xiang Li et. al., have reported potent anticancer activities exhibited by new chiral 1,2,4-triazole compound. This review illustrates several attractive alternatives over classical solution phase synthesis of potentially bioactive 1,2,4-triazole. 1,2,4-triazole are also observed to have bright prospect as anticancer agents.[38]

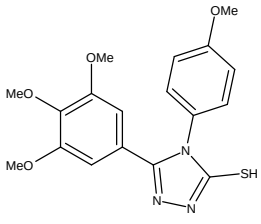


39. Namratha Patel *et al.*,(2022): By treating pyridine linked 1,2,4-triazole-3-thiol with different substituted benzyl halides, a new series of diverse 1,2,4-triazoles connected with substituted benzyl groups through thio linkage derivatives was created, using a simple, appropriate, and well-organized synthetic approach. TLC, IR, NMR, and MS were used to confirm the physical and analytical properties of the newly synthesized 1, 2, 4- triazole derivatives. Following that, pharmacological testing revealed that the derivative 3-(5-(4-bromobenzylthio)-4H-1, 2, 4- triazol-3-yl) pyridine had more anticancer activity than other compounds. As a result, we believe that the findings of this study could open the way for the creation of innovative anticancer drugs with high efficacy and fewer side effects.[39]



3-(5-substituted-benzylthio)-4H-1,2,4-triazole-pyridine

40. Sadiq Al-Mansury *et al.*,(2019) : Series of 3-mercapto-1,2,4-triazole derivatives have been designed as combretastatin A-4 analogues with different aliphatic substituents attached to the S atom (4, 5a-j). The target compounds were synthesized and characterized by different spectroscopic techniques. The cytotoxicity of 4, 5a-j was evaluated against colon cancer line (SW480), compound 5a was found to be the most potent one and showed a kind of selectivity to cancer cells when subjected to evaluating its cytotoxicity against MDCK normal cell lines at 10µM concentration (IC50). The results revealed 5a is a promising anticancer agent to be subjected for further studies.[40]



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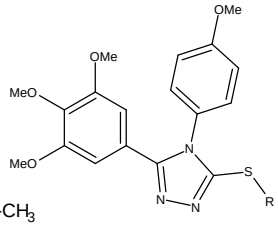

5a R= $-CH_3$
5b R= $-CH_2CH_3$
5c R= $-CH_2(CH_2)_2CH_3$
5d R= $-CH_2(CH_2)_4CH_3$
5e R= $-CH_2-CH-(CH_3)_2$
5f R= $-CH_2-CH=CH_2$
5g R= $-CH(CH_3)_2$
5h R= -cyclohexyl

REFERENCES

1. Xia MY, Cai YX, Chen JX, Zhao X, Dong HM, Yang ZC. Synthesis, antimycobacterial evaluation, and molecular docking study of 1,2,4-triazole derivatives. *J Enzyme Inhib Med* Chem. 2023;38:1-5.

2. Sun S, Yan J, Tai L, Chai J, Hu H, Han L, Lu A, Yang C, Chen M. Novel (Z)/(E)-1,2,4-triazole derivatives containing oxime ether moiety as potential ergosterol biosynthesis inhibitors: design, preparation, antifungal evaluation, and molecular docking. *Molecular Diversity* (2023) 27:145–157.
3. Bülbül B, Ding K, Zhan C-G, Çiftçi G, Yelekçi K, Gürboğa M, Özakpınar ÖB, Aydemir E, Baybağ D, Şahin F, Kulabaş N, Helvacıoğlu S, Charehsaz M, Tatar E, Özbey S, Küçükgüzel İ. Novel 1,2,4-triazoles derived from Ibuprofen: synthesis and in vitro evaluation of their mPGES-1 inhibitory and antiproliferative activity. *Mol Divers*. 2023;27:2185–2215.
4. Frolova Y, Kaplaushenko A, Yurii S, Romanina D, Morozova L. Investigation of the antimicrobial and antifungal activities of some 1,2,4-triazole derivatives. *Čes Slov Farm*. 2022;71:149-158.
5. Bai H, Liu X, Chenzhang P, Xiao Y, Fu B, Qin Z. Design, synthesis and fungicidal activity of new 1,2,4-triazole derivatives containing oxime ether and phenoxyl pyridinyl moiety. *Molecules.* 2023;28(5):1253.
6. Zhu XP, Lin GS, Duan WG, Li QM, Li FY, Lu SZ. Synthesis and antiproliferative evaluation of novel longifolene-derived tetralone derivatives bearing 1,2,4-triazole moiety. *Molecules.* 2023;28(5):1253.
7. Turky A, Sherbiny FF, Bayoumi AH, Ahmed HEA, Abulkhair HS. Novel 1,2,4-triazole derivatives: Design, synthesis, anticancer evaluation, molecular docking, and pharmacokinetic profiling studies. **Arch Pharm (Weinheim)**. 2020;1-13.
8. Vanjare BD, Mahajan PG, Dige NC, Raza H, Hassan M, Han Y, Kim SJ, Seo SY, Lee KH. Novel 1,2,4-triazole analogues as mushroom tyrosinase inhibitors: synthesis, kinetic mechanism, cytotoxicity and computational studies. *Mol Divers*. 2021;25(4):2089-2106.
9. Sangshetti JN, Lokwani DK, Sarkate AP, Shinde DB. Synthesis, antifungal activity, and docking study of some new 1,2,4-triazole analogs. *Chem Biol Drug Des.* 2011;78(5):800-809.
10. Ana G, Kelly PM, Malebari AM, Noorani S, Nathwani SM, Twamley B, Fayne D, O'Boyle NM, Zisterer DM, Pimentel EF, Endringer DC, Meegan MJ. Synthesis and biological evaluation of 1-(diarylmethyl)-1H-1,2,4-triazoles and 1-(diarylmethyl)-1H-imidazoles as a novel class of anti-mitotic agents for activity in breast cancer. *Pharmaceuticals*. 2021; 14: 169.
11. Patel NB, Khan IH. Synthesis of 1,2,4-triazole derivatives containing benzothiazoles as pharmacologically active molecules. *J Enzyme Inhib Med Chem.* 2011;26(4):527-34.
12. Kocyigit-Kaymakcioglu B, Celen AO, Tabanca N, Ali A, Khan SI, Khan IA, Wedge DE. Synthesis and biological activity of substituted urea and thiourea derivatives containing 1,2,4-triazole moieties. *Molecules*. 2013;18(4):3562-3576.
13. Zhao F, Tang X, Liu M, Qin Z, Li JQ, Xiao Y. Synthesis and insecticidal activity of novel 1,2,4-triazole derivatives containing trifluoroacetyl moieties. *Mol Divers.* 2022;26:2149-58.
14. Khan B, Naiyer A, Athar F, Ali S, Thakur SC. Synthesis, characterization and anti-inflammatory activity evaluation of 1,2,4-triazole and its derivatives as a potential scaffold for the synthesis of drugs against prostaglandin-endoperoxide synthase. *J Biomol Struct Dyn*. 2021;39(2):457-75.
15. Rode ND, Sonawane AD, Nawale L, Khedkar VM, Joshi RA, Likhite AP, Sarkar D, Joshi RR. Synthesis, biological evaluation, and molecular docking studies of novel 3-aryl-5-(alkyl-thio)-1H-1,2,4-triazoles derivatives targeting Mycobacterium tuberculosis. *Chem Biol Drug Des*. 2017;90:1206–1214.

16. Ali S, Siddiqui SZ, Abbasi MA, Rehman A, Shah SA, Khan KM, Saleem RZ, Manzoor S, Ashraf M, Zia-ur-Rehman. Synthesis and evaluation of novel 1, 2, 4-substituted triazoles for urease and anti-proliferative activity. *Pak J Pharm Sci*. 2022 Jan;35(1 Suppl):209-217.
17. Xie W, Zhang J, Ma X, Yang W, Zhou Y, Tang X, et al. Synthesis and biological evaluation of kojic acid derivatives containing 1,2,4-triazole as potent tyrosinase inhibitors. *Chem Biol Drug Des.* 2015;86:1087–92.
18. Ünver Y, Deniz S, Çelik F, Akar Z, Küçük M, Sancak K. Synthesis of new 1,2,4-triazole compounds containing Schiff and Mannich bases (morpholine) with antioxidant and antimicrobial activities. *J Enzyme Inhib Med Chem.* 2016;31(S3):89–95.
19. Ogunyemi OO, Jordaan A, Seldon R, Isaacs M, Hoppe HC, Warner DF, Tukulula M, Khanye SD. Hydrazone-Tethered 5-(Pyridin-4-yl)-4H-1,2,4-triazole-3-thiol hybrids: synthesis, characterisation, in silico ADME studies, and in vitro antimycobacterial evaluation and cytotoxicity. *ChemMedChem*. 2023;18:1-8.
20. Paprocka R, Kołodziej P, Wiese-Szadkowska M, Helmin-Basa A, Bogucka-Kocka A. Evaluation of anthelmintic and anti-inflammatory activity of 1,2,4-triazole derivatives. *Molecules*. 2022;27(13):4488.
21. El-Hazek RM, Elkenawy NM, Zaher NH, El-Gazzar MG. Green synthesis of novel antifungal 1,2,4-triazoles effective against γ-irradiated Candida parapsilosis. *Arch Pharm*. 2022;355.
22. Khalid W, Badshah A, Khan AU, Nadeem H, Ahmed S. Synthesis, characterization, molecular docking evaluation, antiplatelet and anticoagulant actions of 1,2,4 triazole hydrazone and sulphonamide novel derivatives. *Chem Cent J.* 2018;12:11.
23. Zhang YB, Liu W, Yang YS, Wang XL, Zhu HL, Bai LF, Qiu XY. Synthesis, molecular modeling, and biological evaluation of 1,2,4-triazole derivatives containing pyridine as potential anti-tumor agents. *Med Chem Res.* 2013;22(8):3193-3203.
24. Lazrak F, Lahmidi S, Anouar EH, Alanazi MM, Alanazi AS, Essassi EM, Mague JT. Synthesis, X-ray Crystal Structure, Anticancer, Hirshfeld Surface Analysis, DFT, TD-DFT, ADMET, and Molecular Docking of 3-Phenyl-1,2,4-triazolo[3,4-h]-1,3,4-thiaza-11-crown-4. *Molecules*. 2023;28(7).
25. Korol N, Holovko-Kamoshenkova OM, Slivka M, Pallah O, Onysko MY, Kryvovyaz A, Boyko NV, Yaremko OV, Mariychuk R. Synthesis, biological evaluation, and molecular docking studies of novel series of bis-1,2,4-triazoles as thymidine phosphorylase inhibitor. *Adv Appl Bioinform Chem*. 2023;16:93-102.
26. Akhter N, Batool S, Khan SG, Rasool N, Anjum F, Rasul A, Adem Ş, Mahmood S, ur Rehman A, Nisa M, Razzaq Z, Christensen JB, Abourehab MAS, Shah SAA, Imran S. Bio-oriented synthesis and molecular docking studies of 1,2,4-triazole based derivatives as potential anti-cancer agents against HepG2 cell line. *Pharmaceuticals*. 2023;16(2):211.
27. Ghanaat J, Khalilzadeh MA, Zareyee D. Molecular docking studies, biological evaluation and synthesis of novel 3-mercapto-1,2,4-triazole derivatives. *Mol Divers.* 2020;24(4):1445-56.
28. Kamboj P, Anjali, Imtiyaz K, Rizvi MA, Nath V, Kumar V, Husain A, Amir M. Design, synthesis, biological assessment and molecular modeling studies of novel imidazothiazole-thiazolidinone hybrids as potential anticancer and anti-inflammatory agents. *Sci Rep*. 2024;14:8457.

29. Gao F, Wang T, Xiao J, Huang G. Antibacterial activity study of 1,2,4-triazole derivatives. *Eur J Med Chem*. 2019 Apr 15;167:78-88.
30. Osmaniye D, Bozkurt NB, Levent S, Yardımcı GB, Sağlık BN, Ozkay Y, Kaplancıklı ZA. Synthesis, Antifungal Activities, Molecular Docking and Molecular Dynamic Studies of Novel Quinoxaline-Triazole Compounds. *ACS Omega.* 2023 Jun 26;8(27):23254–66.
31. Saeed S, Shahzadi I, Zahoor AF, Al-Mutairi AA, Kamal S, Faisal S, Irfan A, Al-Hussain SA, Muhammed MT, Zaki MEA. Exploring theophylline-1,2,4-triazole tethered N-phenylacetamide derivatives as antimicrobial agents: unraveling mechanisms via structure-activity relationship, in vitro validation, and in silico insights. *Front Chem*. 2024 Apr 5;12.
32. Emami L, Sadeghian S, Mojaddami A, Khabnadideh S, Sakhteman A, Sadeghpour H, Faghih Z, Fereidoonnezhad M, Rezaei Z, et al. Design, synthesis and evaluation of novel 1,2,4-triazole derivatives as promising anticancer agents. *BMC Chem.* 2022;16:91.
33. Sachdeva, H., Saquib, M., & Tanwar, K. Design and development of triazole derivatives as prospective anticancer agents. *Anti-cancer Agents in Medicinal Chemistry*, 2022; 22(19), 3269-3279..
34. Al Sheikh Ali A, Khan D, Naqvi A, Al-blewi FF, Rezki N, Aouad MR, Hagar M. Design, synthesis, molecular modeling, anticancer studies, and density functional theory calculations of 4-(1,2,4-triazol-3-ylsulfanylmethyl)-1,2,3-triazole derivatives. *ACS Omega*. 2021;6(1):301-316.
35. Sadeghpour H, Faghih Z, Fereidoonnezhad M, Rezaei Z, et al. Design, synthesis and evaluation of novel 1,2,4-triazole derivatives as promising anticancer agents. *BMC Chem.* 2022;16:91.
36. Elmorsy MR, Abdel-Latif E, Gaffer HE, Mahmoud SE, Fadda AA. Anticancer evaluation and molecular docking of new pyridopyrazolo-triazine and pyridopyrazolo-triazole derivatives. *Sci Rep*. 2023;13:2782.
37. Alam MM. New 1,2,4-triazole based eugenol derivatives as antiCOX-2 and anticancer agents. J Umm Al-Qura Univ Appl Sci. 2024; 1:12.
38. Namratha B, Santosh L, Li X, Gaonkar. 1,2,4-triazole: synthetic strategies and pharmacological profiles. *Int J Pharm Pharm Sci*. 2014;6(8):ISSN- 0975-1491.
39. Patel N, Chakraborty AK, Karole S, Loksh KR. Design, synthesis and anticancer activity studies of some novel 1,2,4 triazole pyridine derivatives. *Int J Pharm Chem Anal*. 2022;9(1):56-61.
40. Al-Mansury S, Balakit AA, Alkazazz FF, Madlum KN, Ghaleb RA. Synthesis and anti-colon cancer activity of 1,2,4-triazole derivatives with aliphatic S-substituents. *Oriental J Chem*. 2019;35(1):77-84.