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1,2,3-TRIAZOLE DERIVATIVES AS A BIOLOGICALLY ACTIVE MOLECULE - A REVIEW

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ABSTRACT

Triazole is the most selected pharmacophore for research because of its various pharmacological activities. This page seeks to highlight the work that has been done and reported, as well as the chemistry and biological activity of 1,2,3-triazole and its derivatives, which have been synthesized in recent years. A heterocyclic molecule with three nitrogen and two carbon atoms is known as a triazole. Based on the difference in relative position, there are two types of isomers each triazole has two tautomer's which differs only by NH bond. Over the years, many studies have been done on the biological activity, synthesis and of different triazole derivatives. Antimicrobial, anti-inflammatory, antimalarial, antiviral antitubercular, anticancer, antidiabetic, antibacterial, antifungal, antiprotozoal, and receptor-selective biological action are all demonstrated by triazole compounds. The research of triazole derivatives biological evaluation has been a fascinating subject of pharmaceutical chemistry. This review article focuses on triazole's pharmacological profile, with various activities and examples presented in the form of figures.

Keywords: 1,2,3 Triazole, Anticancer, Antibacterial, Antifungal, Antiviral, Anti-diabetic

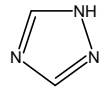
1. INTRODUCTION

Heterocyclic molecules are divided into three, five and six-component ring systems and there are many heterocyclic molecules such as thiazole, triazole, imidazole, oxazole, oxadiazole, etc. they produce many pharmacological activities such as anticancer, anti-diabetes, antimicrobial. A triazole is a heterocyclic

molecule with the chemical formula $C_2H_3N_3$, with three nitrogen and two carbon atoms in a five-membered ring structure.1,2,3-triazoles which is given below in **Figure 1**. Differ in the relative locations of the three nitrogen atoms.1,2,3-triazoles are sp^2 hybridized **[1]**. The formation of triazole ring is based on the bioisoterism phenomenon, which occurs when the oxygen in the oxadiazole nucleus is replaced with nitrogen analogues. 1,2,3-triazole have a wide variety of activities **[2]**.

These derivatives have a long history in heterocyclic compounds and have a wide range of biological actions, making them an interesting pharmacophore for further drug development. 1,2,3-triazole have been reported to have antifungal activity when compared to common antifungal medicines like fluconazole and Itraconazole, it also has good antifungal action. Death-causing infectious illnesses produced by a wide range of bacterial types like Gram-negative and Gram-positive bacteria. As a result, there is a strong desire to create new antibiotic classes to combat multidrug-resistant organisms. 1,2,3-triazole have been reported to have improved antibacterial activity against Gram-positive pathogens.

Cancer has become one of the deadliest diseases nowadays and 1,2,3-triazole also acts as an effective anticancer agent on comparing the standards like cisplatin and many other anti-cancer agents. Triazole and its derivatives have anticancer properties. Derivative of triazole present best anticancer activity in a number of various cell lines. Cancer prevention drugs are complex mixtures that reduce or eliminate free radicals, protecting cells from oxidative damage. Medications with anti-cancer and anti-free radical capabilities are being evaluated for the detection and care of illnesses that are authentically linked to the body's lack of cell reinforcement capacity **[3]**.



1,2,4 triazole

1,2,3 triazole

Diabetes is one of the most common diseases in the world and there are many different mechanism and types. Compared to acarbose reference 1,2,3-triazole shows significant antidiabetic action mainly as α-glucosidase and 11-HSD1 inhibitors When compared to traditional medications like chloroquine, triazole and its derivatives have good antimalarial action against *Plasmodium falciparum.* For the treatment of hepatitis C, a combination of interferon and ribavirin is now employed. Viral diseases although have many drugs to inhibit their multiplication by various mechanism of action but they cannot be killed. Free radical damage to cells is thought to have an important part in the

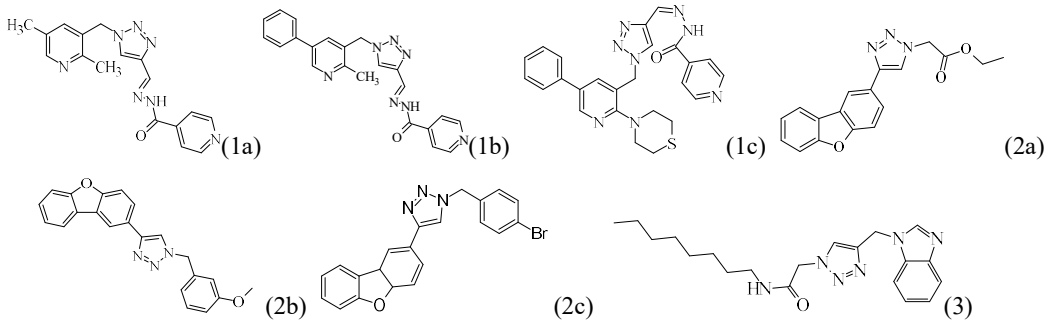
ageing process and disease development. Our first line of defense is antioxidants. Antioxidants become considerably more effective against free radical damage **[4]**. Triazole and its derivatives are active against the bacteria Mycobacterium tuberculosis (H37Rv).

When triazole derivatives are developed and tested against *Mycobacterium tuberculosis* it shows moderate to good activity on comparing with standard first-line drugs like rifampicin and Isoniazid. Triazole is also reported to have better antiprotozoal activity by comparing with the standards **[5]**. Triazole derivatives also possess Antileishmanial activity and analgesic activities. There are numerous 1,2,3-triazole derivatives, for example. Triazole can be made by combining various heterocyclic ring systems, such as the oxadiazole ring with triazole or the thiazole ring system with triazole. The two isoforms of the cyclooxygenase enzyme, COX-1 (constitutive form) and COX-2 (active form), are known to be inhibited by the majority of NSAIDs on the market (inducible form). While COX-2 selective NSAIDs have gastrointestinal benefits, they are outweighed by major cardiovascular side effects such as congestive heart failure and death. Triazole and its derivatives either as a sole nucleus or by fusion with other heterocyclic compounds shows good anti-inflammatory activity on comparison with standard NSAID's **[6]** .

2.Biological activities of 1,2,3-triazole derivatives

2.1. Antituberculosis

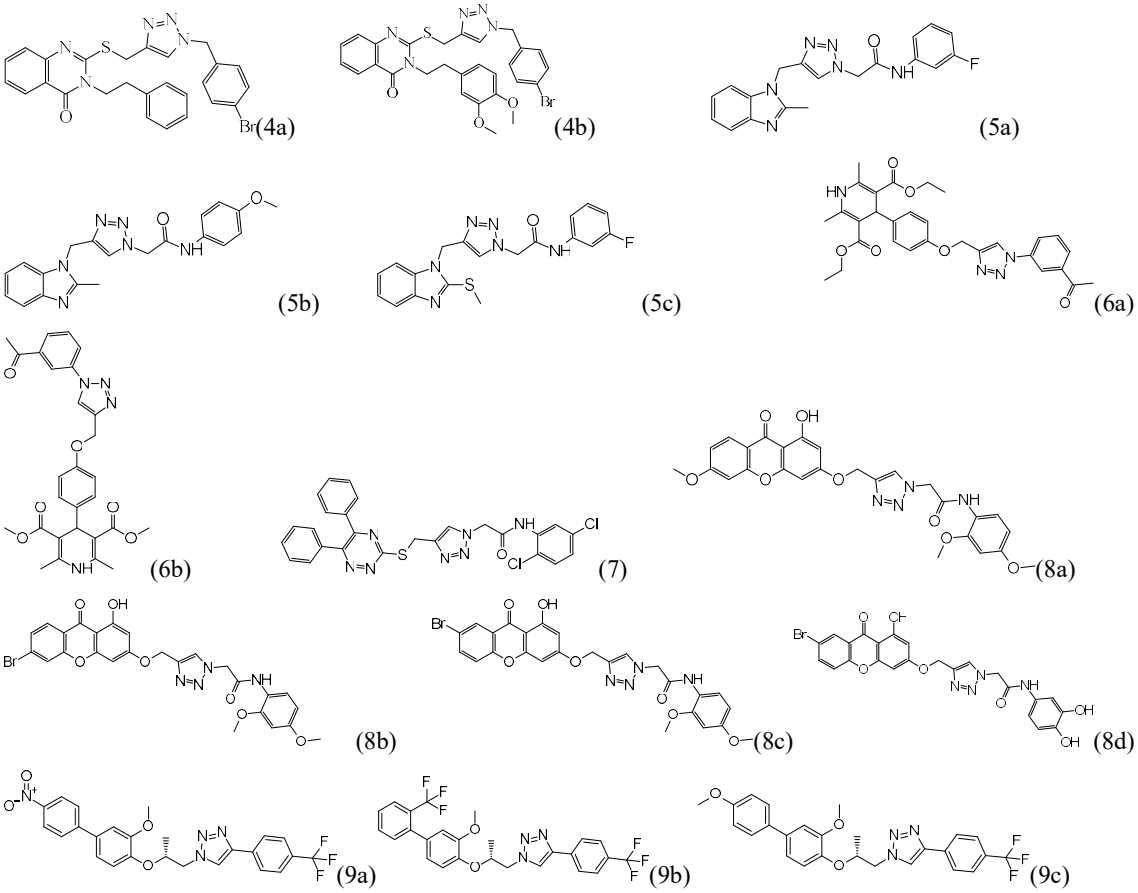
Ch Dayakar *et al* **[7]** synthesized 1*H*-1,2,3-triazolyl isonicotinyl hydrazides. These synthesized compounds were then investigated for anti-mycobacterial activity and concluded that the compound 1a, 1b and 1c shows good antimycobacterial activity and these derivatives have been chosen for cytotoxicity. Thirumal Yempala *et al* **[8]** synthesized new dibenzo [b, d] furan-1,2,3-triazole molecules, and are investigated against *Mycobacterium tuberculosis* activity against derivatives such as 2a,2b and 2c act as promising lead analogues, and it was concluded that (2c) was discovered to be the most effective antimycobacterial drug against the cell line (HEK_293T). Diego G. Ghiano *et al* **[9]** synthesized 1,2,3-triazolyl fatty acid derivatives which is investigated for antimycobacterial properties. Alkyl chain with different lengths and triazole were covered by the 1,4-disubstituted analogues. The triazole moiety is located on the C-2 position with an eight or ten carbon chain in the most potent member of the series 3.



2.2. Antidiabetic activity

Mina Saeedia *et al* **[10]** synthesized new quinazolinone-1,2,3-triazole hybrids. Antidiabetic efficacy and *in vitro* alpha glucosidase inhibitory action of quinazolinone 1,2,3 -triazole were examined in hybrids. The most active compounds in this group are 4a and 4b were had shown the greatest efficacy in suppressing alpha glucosidase enzyme. Laxmi Deswal *et al* **[11]** synthesized Some novel benzimidazole-tethered 1,2,3-triazole derivatives .These substances are then tested for anti-diabetic properties.. The most active compounds were discovered to be 5a, 5b and 5c.Praveenkumar E *et al* **[12]** synthesized a series of novel 4-(1-aryl-1H-1,2,3-triazol-4-yl)-1,4-dihydropyridine series and investigated against antidiabetic activity. *In vitro* as well as *in vivo* studies are done to test their ability to suppress 11-HSD1 diabetic mellitus. Among these compounds 6a and 6b displayed potent inhibitory activity. Compounds 6a and 6b was stable and efficient against 11-HSD1.Guangcheng Wang *et al* **[13]** synthesized and tested a novel derivatives of triazine-triazole series for inhibitory activities of *α-glucosidase.* When compared to the typical medication acarbose, compound 7 with a phenyl ring substituted with 2,5-dichloro shows effective inhibitory activity against α-glucosidase and was the most active molecule.

Gao-Jie Ye *et al* **[14]** synthesized a number of new xanthone-triazole compounds were synthesised and tested them for anti-diabetic activity. Glucosidase inhibition and glucose absorption enhancement were examined in HepG2 cells. Compounds 8a,8b,8c, and 8d, among the synthesised compounds were active. Satya Kumar Avula *et al* **[15]** synthesized 1H-1,2,3-triazole derivatives and tested against antidiabetic activity by inhibiting alpha-glucosidase enzyme and docking studies are also performed to find the better binding efficacy of the synthesized molecules. Among these analogues 9a, 9b and 9c showed better α-glucosidase inhibitory activity than standard acarbose.

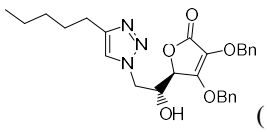


2.3. Anticancer activity

Andrijana Mescic Macan *et al* **[16]** synthesized (1,2,3-triazolyl)-2,3-dibenzyl-L-ascorbic acid. Antiviral activity and antitumor efficacy against a wide range of viruses and seven malignant tumor cell lines were examined. On breast cancer MCF-7 cells, Compound 8m had a selective and powerful antiproliferative action. The Para methoxy phenyl-substituted derivative 10c demonstrated the most anti-cytomegalovirus (CMV) activity, followed by the aliphatic-substituted derivatives 10a and 10b. Muralidhar Allam *et al* **[17]** synthesized a novel compounds of hybrid aza heterocycles with pyrazolo[3,4-d] pyrimidin-4(5H)-ones tethered to a 1,2,3-triazole scaffold, which were tested for anticancer efficacy. Compounds 11a,11b and 11c were the more potent drug than the other compounds in binding with TGFBR2. Compound 11b was discovered to be the most active. Pinki Yadav *et al* **[18]** synthesized and tested chalcone linked 1,2,3-triazole derivatives for anticancer activities. It was discovered that the compound 12 to be the effective against almost all of the cell lines of cancer cell which were tested. In terms of activity, compound 12 demonstrated superior or

equivalent results when compared to the reference medicine. Zhong-Hua Li *et al* **[19]** synthesized a series of [1,2,3]triazolo[4,5-d] pyrimidine derivatives having a hydrazone moiety and screened for efficacy of the synthesized compounds against various cancer cells for anticancer activity. Compound 13 showed the most effective antiproliferative activity and strong selectivity as well between cancer and normal cells among these compounds.

Yu Ke *et al* **[20]** synthesized and evaluated two new series of Jiyuan Oridonin A-1,2,3-triazole-azole hybrids for antiproliferative activities. Four cancer cell lines were used to investigate the anticancer activity of these compounds (MCF-7, MGC-803, Eca-109, PC-3). Compound 14 works by inhibiting the cell cycle in the (G1) phase which can cause a very strong apoptotic cell death in (SMMC-7721). The most active compound, 14 was found to be extremely effective against human cancer cells. Ilaria Frasson *et al* **[21]** synthesized a novel [1,2,3] Triazolo[4,5-h] [1,6] naphthyridines and [1,3] oxazolo[5,4-h] naphthyridines and tested them for photocytotoxicity against HT-29 (colorectal adenocarcinoma), A375 (malignant melanoma) cells, and MCF7 (mammary gland adenocarcinoma). On the MCF7 cell line, molecule 15 is quite active (breast cancer).Babita Aneja *et al* **[22]** synthesized Isatin-triazole hydrazones and investigated for anticancer activity. They developed and studied Isatin-triazole hydrazones in the search for potent MARK4 inhibitors. In the sub micromolar range, the compounds 16 demonstrated greater binding affinity and enzyme inhibitory ability.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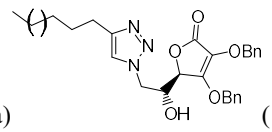
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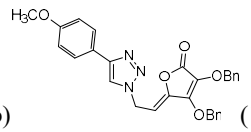
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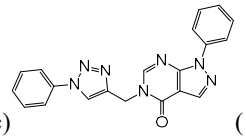
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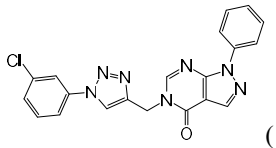
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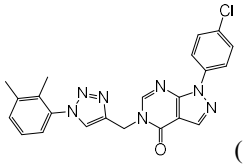
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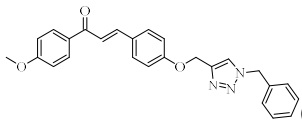
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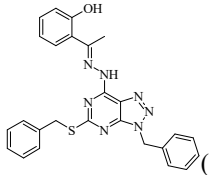
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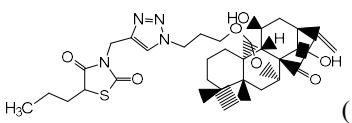
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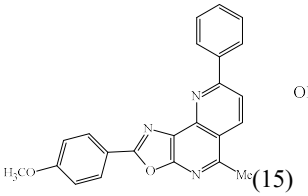
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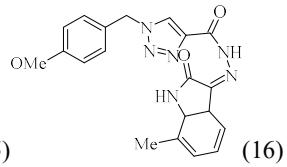
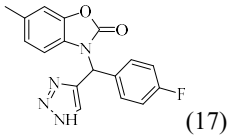

(16)

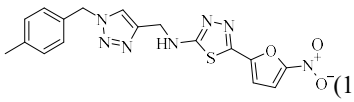
2.4. Anti-inflammatory activity

Saqlain Haider *et al* **[23]** synthesized novel bis-heterocycles based on benzoxazolinone 1,2,3- triazoles, which were tested for anti-inflammatory, antinociceptive and ulcerogenic risk. When compared to indomethacin, compound 17 had the most TNF-α inhibitory effect. In compared to the conventional medication celecoxib, the compound 17 showed the selective inhibitory effect on COX 2. The compound 17 was discovered to be the selective was also the most potent.


(17)

2.5. Antileishmanial activity

Azar Tahghighi *et al* **[24]**synthesized N-[(1-benzyl-1H-1,2,3-triazol-4-yl) methyl] 5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-amines bearing N- [(1 – benzyl - 1H -1, 2, 3-triazol- 4- yl) methyl] moiety. These compounds are being tested for antileishmanial activity against the Leishmania major form of promastigote. Among these compounds. 4-methylbenzyl was discovered to be the most effective chemical against promastigotes. The 4-methylbenzyl analogue 18 was discovered to be the most effective against promastigotes. Robson Ricardo Teixeira *et al* **[25]** developed a variety of eugenol-derived compounds with 1,2,3-triazolic components. Twenty-six eugenol derivatives are investigated for their leishmanicidal efficacy. In terms of antileishmanial activity, 19 outperformed glucantime and pentamidine among these substances.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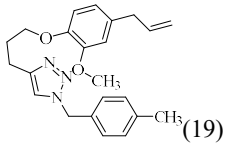
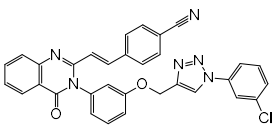

(19)

2.6. Antimicrobial activity

Srikanth Gatadi *et al* **[26]** synthesized and investigated 1,2,3-triazole coupled 4(3H)-quinazolinone compounds against *Staphylococcus aureus* for antibacterial activity. 3-chloro phenyl, 3-toluoyl and 3-fluoro phenyl containing compounds 20a 20b and 20c at N-3 displayed significant action in multi drug-resistant against the resistant strains of Vancomycin and *Staphylococcus aureus*. The compound 20a and 20d was found to

have selective and strong antibacterial action against *Staphylococcus aureus*. Yinhui Qin *et al* **[27]** created new 15-membered 11α-aza homo clarithromycin compounds with 1, 2, 3-triazole side chain. Antibacterial activity is being tested on these compounds. Compounds having no substituents on the phenyl group of the 1, 2, 3-triazole have better antibacterial activity than those with substituents. The bacteriostatic properties of compounds 21a, 21b, and 21c were excellent and were the most effective against resistant S. pneumoniae AB11 strains carrying the ermB and mefA genes.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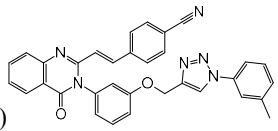
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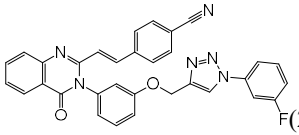
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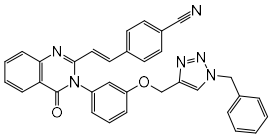
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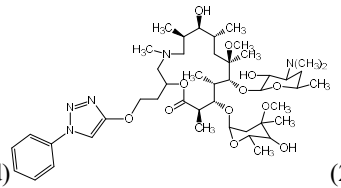
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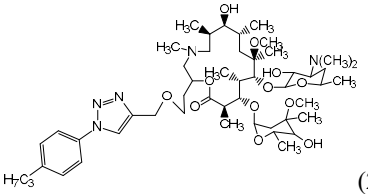
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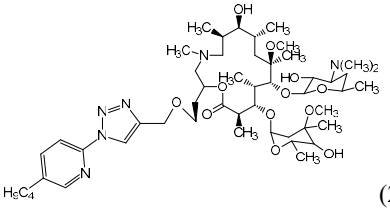
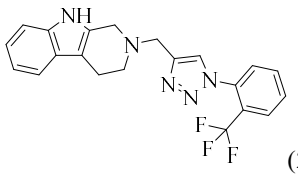

(21c)

2.7. TRPV1 antagonists

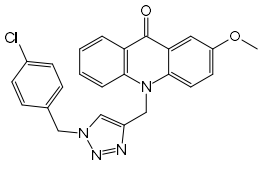
Jinyu Li *et al* **[28]** synthesis new 2,3,4,9-tetrahydro-1H-pyrido-[3,4-b]-indole triazole moiety and screened against for TRPV1antagonists activity. Compound 22 was a strong TRPV1 antagonist with good functional activity *in vitro* and Capsaicin as well as heat-induced pain models. The rTRPV1 model docking analysis revealed that 22 had a great binding efficacy to the binding site.


(22)

2.8. *Acetylcholinesterase* inhibitors

Maryam Mohammadi-Khanaposhtani *et al* **[29]** synthesised a new series of acridone compounds coupled to 1,2,3-triazole moiety and tested them for inhibitory activity against *butyrylcholinesterase* (BChE) and *acetylcholinesterase* (AChE) . Compound 23 resulted in significant interactions, as validated by docking studies, 23 was the most potent anticholinesterase inhibitors in comparison to rivastigmine. Zahra Najafi *et al* **[30]** synthesized a new family of tacrine-1,2,3-triazole hybrids. In this molecule, the activity of cholinesterase inhibitors is

studied. The anti-ACHE derivatives 24a was shown to be the most effective. The anti-*butyrylcholinesterase* activity of compound (24b) is the strongest.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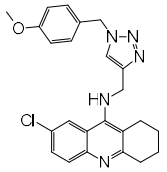
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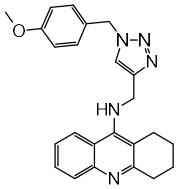
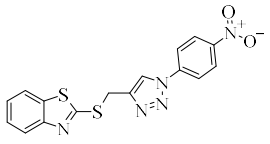
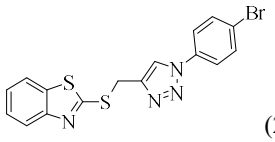
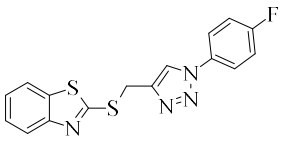

(24b)

2.9. Analgesic activity

Syed Shafi *et al* **[31]** synthesized novel bis-heterocycles based on 2-mercapto benzothiazole and 1,2,3-triazole were tested for anti-inflammatory efficacy. Among the compounds studied, compounds 25a and 25b have more analgesic activity than the standard drug Ibuprofen, whereas compounds 25c and 25d have similar activity to the reference drug. Yasar Dürüst *et al* **[32]** synthesized the dihydropyrrolo [3,4-d] [1,2,3] triazoles and investigated for activity of anti-protozoal as well as cytotoxicity. Among these novel derivatives the compounds 26a, 26b and 26c. At low mg/mL, the produced compounds demonstrated the maximum susceptibility to *L. donovani*. The fluoro derivative (26d) has minimal cytotoxic potential. The compounds 30a, 30b and 30c shows the good antiprotozoal activity.


(25a)


(25b)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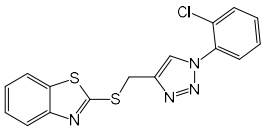
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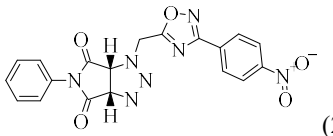
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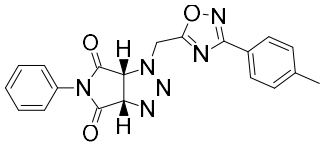
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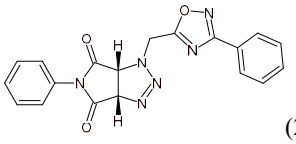
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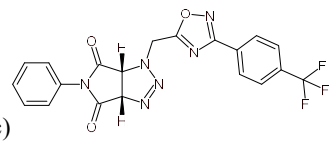
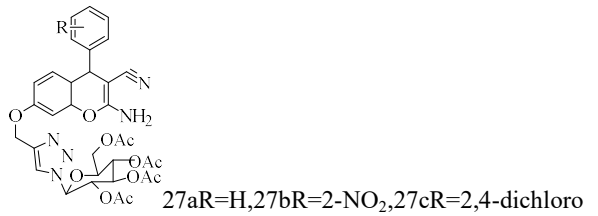

(26d)

2.10. Antifungal activity

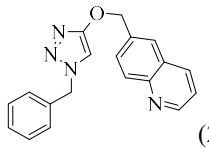
Nguyen Dinh *et al* **[33]** synthesized 1H-1,2,3-triazole-tethered 4H chromene D-glucose moiety and activity of these derivatives were screened for antibacterial in vitro and MRSA against *K. pneumoniae*, B. s*ubtills*, *P. aeruginosa*, *S, epidermidis*, *E.coli, S. aureus*, *S. typhimurium* and antifungal activities against *Aspergillus Niger*. Three clinical MRSA isolates were resistant to the triazoles 27a,27b,27c. Mohammad Irfan *et al* **[34]** synthesized

1,2,3-triazoles derived from naturally bioactive scaffolds. These compounds are screened for anticandidal efficacy in vitro against three distinct Candida strains. Compound 28 was found to be more active than fluconazole among these compounds.

The derivative 28 was shown to be the most effective inhibitor against *Candida tropicalis, Candida albicans* and C*andida glabrata*. Zhigan Jiang *et al* **[35]** synthesized 1,2,3-triazole-piperidine side chains. *Cryptococcus neoformans* and *Candida albicans* are tested with the synthesized compounds. Compounds 29a and 29b were reported to highly effective against *C. albicans* and *Cryptococcus neoformans*, respectively. Nina Fu *et al* **[36]** synthesized fatty acids containing 1,2,3-triazole derivatives. The synthesized compounds are tested for antifungal activity against *C. albicans.* Among these (30c) performed marginally better than BDSF in terms of antifungal activity. The most effective inhibitor is 30c, which has the longest alkyl chain, followed by 30a and 30b. The inhibitory effect-concentration trends of 30c were comparable to those of BDSF.



27aR=H,27bR=2-NO_2,27cR=2,4-dichloro



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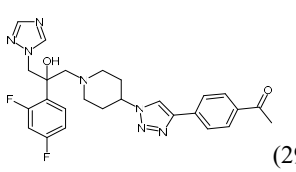

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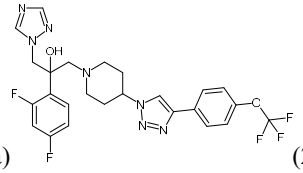
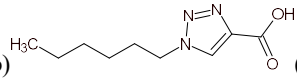
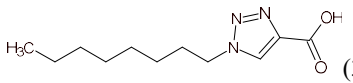


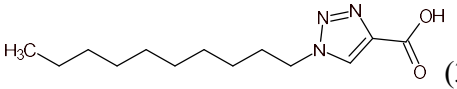
(29b)



(30a)



(30b)

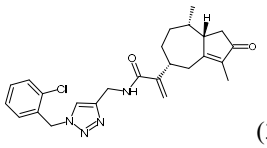


(30c)

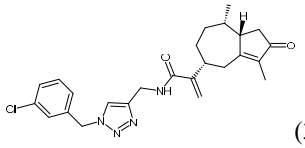
2.11. Antiviral activity

Yao-Wu He *et al* **[37]** synthesized 2 series of rupestonic acid derivatives, (1-substituted-1H-1,2,3-triazol-4-yl)methyl2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octa hydro azulen-5-yl) acrylate and N-(1-substituted-1H-1,2,3-triazol-4-yl) methyl. Antiviral activity of these compounds was evaluated against a variety of influenza A and B virus strains. On comparing the conventional standard drugs Oseltamivir and Ribavirin, For Influenza B virus, the compounds 31a, 31b, exhibited superior. Anindya Das *et al* **[38]** synthesized 1,2,3-triazole-containing N-acyl zanamivir analog. These compounds were screened for neuraminidase inhibitors (H1N1) and (H3N2). Compound 32 was found to be the most effective inhibitor of H1N1 and H3N2 among these substances.

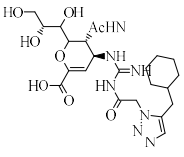
The high efficacy of inhibitor 32 could be due to the favorable hydrophobic contacts seen in this area. Iwona E. Głowackaa *et al* **[39]** synthesized a new acyclonucleotide with a 1,2,3-triazole linker. These compounds are being examined for antiviral and cytostatic activity against human T-lymphocyte, murine leukemia and cervix cancer HeLa cells. The compounds (33a, 33b,33c and 33d) were found to be the most effective towards T-LGL.



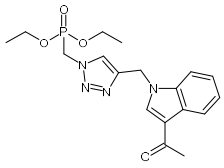
(31a)



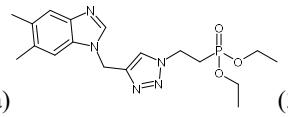
(31b)



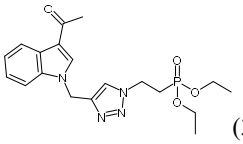
(32)



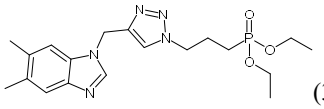
(33a)



(33b)



(33c)



(33d)

3. CONCLUSION

This review highlights the chemistry and pharmacological activity of triazole and their derivatives.1,2,3-triazole shows good activity as the anticancer agents, anti-oxidant, antiviral agents, antibacterial agents, anti-fungal, anti-tubercular, anti-diabetic, antiviral, anti-protozoal and anti-inflammatory activities. This article high lightened the research work reported in literature by various researchers. This review article presented the potent 1,2,3-derivatives of triazole and its pharmacological activity. More research is needed to assess the 1,2,3-triazole's potential for treating a variety of ailments that are tough to treat in the medical sciences.

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CONFLICT OF INTERESRT

The authors declare no conflict of interest

REFERENCES

[1] Sahu JK, Ganguly S, Kaushik A. Chinese Journal of Natural Medicines Triazoles: A Valuable Insight into Recent Developments and Biological Activities,*Chin. J. Nat. Med*, 11(5) 2013, 456-465.

[2] Vishnu Ji Ram, Arun Sethi, Mahendra Nath, Ramendra Pratap,

Five- Membered Heterocycles, *Chem. Heterocycles,* 1, 2019, 1-489.

[3] Deepali. D, Prabhakar K.V, Rakesh K.M.A review on 'triazoles': their chemistry, synthesis and pharmacological. Potentials,*J. Iran. Chem. Soc,*18(10), *2021,* 2535–2565.

[4] El-Sebaey S. A. A. Recent Advances in 1,2,4-Triazole Scaffolds as Antiviral Agents, *Chemistry. Select,*5(37), *2020*, 11654–11680.

[5] Seong-Min Lee, Min-Sun Kim, Faisal Hayat, Dongyun Shin. Recent Advances in the discovery of Novel Antiprotozoal Agent,*Molecules*, 24(21), 2019, 3886.

[6] Carol A. Rouzer, Lawrence J. Marnett. Cyclooxygenases: structural and functional insights, J. Lipid Res, 50, 2009, S29–S34.

[7] Dayakar Ch, Suman P, Rajkumar K, Yogeeswari P, Sriram D, China Raju B. Synthesis and Anti-Mycobacterial Activity of 1H-1,2,3-Triazolylisonicotinohydrazides, *Indian J. Chem,* 55, *2016,* 882–887.

[8] Yempala T, Sridevi JP, Yogeeswari P, Sriram D, Kantevari S. Rational Design and synthesis of Novel Dibenzo[b,d]Furan-1,2,3-Triazole Conjugates as Potent Inhibitors of *Mycobacterium tuberculosis*, *Eur. J. Med. Chem,*71(7), 2014, 160–167.

[9] Diego G. Ghiano, Agustina de la Iglesia, Nina Liu, Peter J. Tonge, Héctor R. Morbidoni, Anti-tubercular Activity of 1,2,3-Triazolyl Fatty Acid Derivatives, Eur. J. Med. Chem, 125, 2017, 842–852.

[10] Saeedi M, Mohammadi-Khanaposhtani M, Pourrabia P, Razzaghi N, Ghadimi R, Imanparast S, Bandarian F, Esfahani EN, Safavi M, Rastegar H, Larijani B, Mahdavi M, Akbarzadeh T. Design and Synthesis of Novel Quinazolinone-1,2,3-Triazole Hybrids as New Anti-Diabetic Agents:In Vitro α-Glucosidase Inhibition, Kinetic and Docking Study,*Bioorg . Chem,*83,2019, 161–169.

[11] Laxmi D, Vikas V, Devinder K, Chander P K, Ashwani K, Yogesh D, Suman P. Synthesis and Antidiabetic Evaluation of Benzimidazole-Tethered 1,2,3-triazoles, *Arch. Pharm. (Weinheim),* 353(9), 2020, 2000090.

[12] Ragip A, Fikret T, Umit Y, Abdulmelik A, Enes E, Tijen O.

Synthesis, Anti-Diabetic Evaluation and Molecular Docking Studies of 4-(1-Aryl-1H-1, 2, 3-Triazol-4-Yl)-1,4-DihydropyridineDerivatives as Novel 11β-Hydroxysteroid dehydrogenase-1 (11β-HSD1) Inhibitors,*Bioorg. Chem, (*90), 2019, 103056.

[13] Guangcheng W, Zhiyun P, Jing W, Xin L, Juan L. Synthesis,"In Vitro Evaluation and Molecular Docking Studies of Novel Triazine-Triazole Derivatives as Potential α-Glucosidase Inhibitors, *Eur. J. Med. Chem,*125,2017, 423–429.

[14] Gao-Jie.Y, Tian L, Zhi-Xin H, Xiao-Ning C, Chao-Yun C, Sen-Miao D, Min-Li X, Bo W. Design and Synthesis of Novel Xanthone-Triazole Derivatives as Potential Antidiabetic Agents: α-Glucosidase Inhibition and Glucose Uptake Promotion,*Eur. J. Med. Chem,* 177, 2019, 362–373.

[15] Satya Kumar A, Ajmal K, Najeeb Ur R, Muhammad U A, Zahra A, Abdul W, Muhammad R, Rene C, Ahmed H. Synthesis of 1H-1,2,3-Triazole Derivatives as New α-Glucosidase Inhibitors and their Molecular Docking Studies, *Bioorg. Chem,* 81, 2018, 98–106.

[16] Andrijana Mescic M, Anja H, Ines C, Marko K, Visnja S, Kresimir P, Sandra K, Dominique S, Graciela A, SilvanaRaic M. Antitumor and Antiviral Activities of 4-Substituted 1,2,3-Triazolyl-2,3-Dibenzyl-L-Ascorbic Acid Derivatives, *Eur. J. Med. Chem,*184, 2019, 111739.

[17] Allam M, Bhavani AKD, Mudiraj A, Ranjan N, Thippana M, Babu PP. Synthesis of Pyrazolo[3,4-d]Pyrimidin-4(5H)-Ones Tethered to 1,2,3-triazoles and Their Evaluation as Potential Anticancer Agents, *Eur. J. Med. Chem,*156, 2018, 43-52.

[18] Pinki Y, Kashmiri L, Ashwani K,Santosh Kumar G, Sundeep J, Sashi B. Green Synthesis and Anticancer Potential of Chalcone Linked-1,2,3-triazoles, *Eur. J. Med. Chem,* 126, 2017, 944–953.

[19] Li Z, Yang D, Geng P, Zhang J, Wei H, Hu B, Guo Q, Zhang X, Guo W, Zhao B,Yu B, Ma Y, Liu H.Design, Synthesis and Biological Evaluation of [1,2,3]Triazolo[4,5-d]Pyrimidine Derivatives Possessing a Hydrazone Moiety as Antiproliferative Agents,*Eur. J. Med. Chem,* 124,2016, 967–980.

[20] Ke Y, Liang J, Hou R, Li M, Zhao

L, Wang W, Liu Y, Xie H, Yang R, Hu T, Wang J, Liu H.Synthesis and Biological Evaluation of Novel Jiyuan Oridonin A-1,2,3-T riazole Azole Derivatives as Antiproliferative Agents,*Eur. J. Med. Chem.* 157, 2018, 1249–1263.

[21] Frasson I, Spano V, Di Martino S, Nadai M, Doria F, Parrino B,Carbone A, Cascioferro S, Diana P, Cirrincione G, Freccero M, Barraja P, Richter S.N, Montalbano A.Synthesis and Photocytotoxic Activity of [1,2,3] Triazolo [4,5-h] [1,6] Naphthyridines and [1,3] Oxazolo[5,4-h][1,6] Napht-hyridines, *Eur. J. Med. Chem,*162, 2019, 176–193.

[22] Babita A, Nashrah S, Parvez K, Aarfa Q, Afza, H, Tabish R, Alajmi F, EI-Seedi R, Imtaiyaz H, Mohammad A. Design and Development of Isatin-Triazole Hydrazones as Potential Inhibitors of Microtubule Affinity-Regulating Kinase 4 for the Therapeutic Management of Cell Proliferation and Metastasis, *Eur. J. Med. Chem,* 163, 2019, 840–852.

[23] Haider S, Alam M, Hamid H, Shafi S, Nargotra A, Mahajan P, Nazreen S,Kalle A, Kharbanda C,Alam Y.Ali, Amulya K.Synthesis of Novel 1,2,3-Triazole Based Benzoxazolinones: Their TNF-α Based Molecular Docking with in-Vivo Anti-Inflammatory, Antinociceptive Activities and Ulcerogenic Risk Evaluation*, Eur. J. Med. Chem,*70, 2013, 579–588.

[24] Tahghighi A, Razmi S, Mahdavi M, Foroumadi P, Ardestani S.K, Emami S, Kobarfard F, Dastmalchi S, Shafiee A, Foroumadi A.Synthesis and Anti-Leishmanial Activity of 5-(5-Nitrofuran-2-Yl)-1,3,4-Thiadiazol-2-Amines Containing N-[(1-Benzyl-1H-1,2,3-Triazol-4-Yl)Methyl] Moieties, *Eur. J. Med. Chem,* 50, 2012, 124–128.

[25] Robson Ricardo T, Poliana Aparecida Rodrigues G, Adalberto Manoel da S, Maria Paula Gonçalves B, Bartira Rossi B, Rafaela Salgado F, Boniek Gontijo V, Gessica Adriana V, Wallace Pacienza L. Synthesis and Leishmanicidal Activity of Eugenol Derivatives Bearing 1,2,3-Triazole Functionalities, *Eur. J. Med. Chem,* 146, 2018, 274–286.

[26] Gatadi S, Gour J, Shukla M, Kaul

G, Das S, Dasgupta A, Malasala S, Borra R,Madhavi Y.V, Chopra S,Nanduri S. Synthesis of 1,2,3-Triazole Linked 4(3H)-Quinazolinones as Potent Antibacterial Agents against Multidrug-Resistant *Staphylococcus aureus*, *Eur. J. Med. Chem,* 157, 2018, 1056–1067.

[27] Yinhui Q, Yuetai T, Ruixin M, Fangchao B, Zhiyang L, Panpan Z, Shutao M.Design, Synthesis and Antibacterial Evaluation of Novel 15-Membered 11α-Azahomo-clarithromycin Derivatives with the 1, 2, 3-Triazole Side Chain, *Eur. J. Med. Chem,*180, 2019, 321–339.

[28] Jinyu L, Cubin N, Yue Q, Jing H, Qifei L, Qiang W, Xiaohui P, Lin Y, Hai Q. Design, Synthesis and Biological Evaluation of Novel 2,3,4,9-Tetrahydro-1H-Pyrido[3,4-b]Indole Triazole Derivatives as Potent TRPV1 Antagonists, *Eur. J. Med. Chem,* 178, 2019, 433–445.

[29] Maryam Mohammadi K, Mohammad M, Mina S, Reyhaneh S, Maliheh, Mahnaz K, Alireza F,Abbas S, Tahmineh A.Design, Synthesis, Biological Evaluation, and Docking Study of *Acetylcholinesterase* Inhibitors: New Acridone-1,2,4-Oxadiazole-1,2,3-Triazole Hybrids, *Chem. Biol. Drug Des,* 86, 2015, 1425–1432.

[30] Najafi Z, Mahdavi M,Saeedi M, Karimpour R, Asatouri R, Vafadarnejad F, Moghadam F, Khanavi M, Sharifzadeh M, Akbarzadeh T. Novel Tacrine-1,2,3-Triazole Hybrids: *In vitro* and *in vivo* Biological Evaluation and Docking Study of *Cholinesterase* Inhibitors, *Eur. J. Med. Chem,* 125, 2017, 1200–1212.

[31] Syed S, Mahboob M, Naveen M, Chaitanya M, Vanaja G, Arunasree M, Reddanna P. Synthesis of Novel 2-Mercapto Benzothiazole and 1,2,3-Triazole Based Bis-Hetero cycles: Their Anti-inflammatory and Antino-ciceptive Activities, *Eur. J. Med. Chem,* 49, 2012, 324-333.

[32] Yasar D, Kamza K, Marcel K, Deniz T. Synthesis and Anti-Protozoal Activity of Novel Dihydropyrrolo [3,4-d] [1,2,3] Triazoles, *Eur. J. Med. Chem,* 48, 2012, 296–304.

[33] Nguyen D, Do Son H, Vu Thi Ngoc B, Pham Thi Thu H, Nguyen Thi Ky D, Nguyen Thi M, Tran Thi D, Vu Ngoc T, Hoang Thi

Kim V, Le Hai D, Duong Ngou T, Tran Thi Thanh V. Efficient Click Chemistry towards Novel 1H-1,2,3-Triazole-Tethered 4H-Chromene-d-Glucose Conjugates: Design, Synthesis and Evaluation of *in vitro* Antibacterial, MRSA and Antifungal Activities, *Eur. J. Med. Chem,* 167, 2019, 454–471.

[34] Mohammad Irfan, Babita A, Umesh Y, Shabana K, Nikhat M, Constantin G.D, Mohammad A.Synthesis, QSAR and Anticandidal Evaluation of 1,2,3-triazoles Derived from Naturally Bioactive Scaffolds*, Eur. J. Med. Chem,* 93, 2015, 246–254.

[35] Zhigan J, Julin G, Chen W, Shengzheng W, Na L,Yan J, Guoqiang D, Yan W, Yang L, Jianzhong Y, Zhenyuan M, Wannian Z, Chunquan S. Design, Synthesis and Antifungal Activity of Novel Triazole Derivatives Containing Substituted 1,2,3-Triazole Piperdine Side Chains, *Eur. J. Med.Chem,* 82, 2014, 490–497.

[36] Nina F, Suiliang W, Yuqian Z, Caixia Z, Dongliang Y, Lixing W, Baomin Z, Lian hui W. Efficient Click Chemistry towards Fatty Acids Containing 1,2,3-Triazole: Design and Synthesis as Potential Antifungal Drugs for Candida Albicans*, Eur. J. Med. Chem,* 136, 2017, 596–602.

[37] Yao Wu H, Chang Zhi D, Jiang-Yu Z, Lin-Lin M, Yu-Huan L, Haji Akber A.1,2,3-Triazole-Containing Derivatives of Rupestonic Acid: Click-Chemical Synthesis and Antiviral Activities against Influenza Viruses, *Eur. J. Med. Chem,* 76, 2014, 245–255.

[38] Das A, Adak A, Ponnapalli K, Lin C, Hsu K, Hsu T, Lin C. Design and Synthesis of 1,2,3-Triazole-Containing N-Acyl Zanamivir Analogs as Potent *Neuraminidase* Inhibitors, *Eur. J. Med. Chem,* 123, 2016, 397–406.

[39] Glowacka I.E, Balzarini J, Wroblewski A. E. The Synthesis, Antiviral, Cytostatic and Cytotoxic Evaluation of a New Series of Acyclonucleotide Analogues with a 1,2,3-Triazole Linker, *Eur. J. Med. Chem,* 70, 2013, 703–722.