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REVIEW

1,2,3-Triazoles: Lead Molecules For Promising Drugs: A Review

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A large number of heterocyclic compounds with five membered rings as the parent nucleus such as tetrazoles, imidazoles, triazoles, oxadiazoles, thiadiazoles, thiazoles, *etc*. have been studied extensively owing to their fascinating biological properties like anticancer, antifungal, antimicrobial, antitumor, anticonvulsant, antiviral, *etc*. 1,2,3-Triazoles are important class of five-membered biologically active heterocyclic compounds as they exhibit wide range of pharmacological activities. Triazoles are of two types *viz*. 1,2,3-triazole and 1,2,4-triazole. These compounds have drawn great attention from chemists and biologists since their discovery. In recent years, triazoles has emerged as an interesting field in drug design for many researchers due to their enormous pharmacological scope. The present review aims to sum up the medicinal significance of 1,2,3-triazoles as one of the most significant structures for the development of drug molecules like anticancer, antibacterial, HIV protease inhibitors, antifungal, anti-inflammatory (COX-1/COX-2 inhibitors), antiprotozoal, anticonvulsant, antioxidant and others, which are under clinical trials. Various benzyl and benzyl-halide functionalized 1,2,3-triazole derivatives like rufinamide, mubritinib (TAK-165) and suvorexant showing excellent biological activities have been used as medicine. In present review, more stress has been laid on the major developments in the therapeutic aspects of triazole pharmacophore for the last two decades.

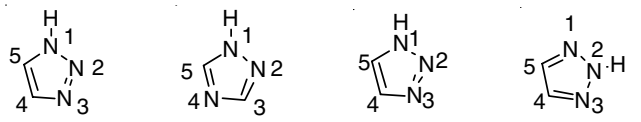
Keywords: 1,2,3-Triazole, Anticancer, Antibacterial, Antifungal, Anti-inflammatory, Anticonvulsant, Antiprotozoal, Antioxidant.

INTRODUCTION

Heterocyclic compounds with extensive distribution in nature are a vital component of various biological processes. For example, pyrimidine bases, namely cytosine, thymine, uracil and purine bases, namely adenine, guanine are important structural components of nucleic acids [1]. Some purines and pyrimidines base like puromycin can act as antibiotics, by interfering in DNA synthesis. Heme and chlorophyll which are vital for sustaining life are derivatives of porphyrin ring system. Similarly, vitamins riboflavin (vitamin B_2), thiamin (vitamin B_1), nicotinamide (vitamin B_3), pyridoxal (vitamin B_6) and ascorbic acid (vitamin C) also contain heterocyclic pharmacophore. Antibiotics like cephalosporin, penicillin; alkaloids like morphine, vinblastine, reserpine, *etc*. possess heterocyclic moiety. Because of their immense importance, chemists have always shown keen interest in them and exploited heterocyclic moieties for synthesis of various drugs. Researchers have already synthesized various drugs containing heterocyclic moiety like pioglitazone, sulphathiazole, zolpidem, fluconazole, atorvastatin, reserpine, ranitidine, omeprazole, barbiturates, antihistamines, *etc*. [2,3]. Some important heterocyclic compounds, which have been exploited by researchers for synthesizing bioactive molecules include tetrazoles, imidazoles, triazoles, oxadiazoles, thiadiazoles, thiazoles, *etc*.

One of the most significant and promising heterocyclic compounds are nitrogen heterocycle triazoles. These are five-membered heterocycles, which have three nitrogen atoms in their heterocyclic ring structure and exist in two isomeric forms. 1,2,3-triazoles and 1,2,4-triazoles.

Further 1,2,3-triazoles may exist in two different tautomeric forms, depending on the position of the N-H bond in the 1,2,3-triazole synthesis by azide-alkyne 1,3-dipolar cycloaddition had attracted the attention of the scientific community immensely. The pioneering work which is considered as a benchmark for regioselective synthesis of 1,4-disubstituted 1,2,3-



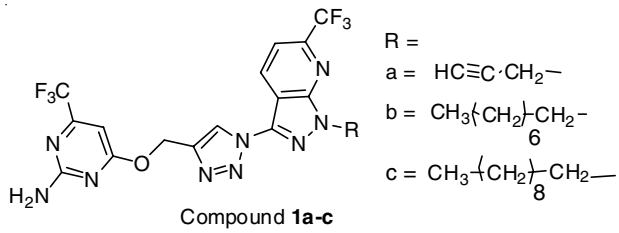
1,2,3-Triazoles 1,2,4-Triazoles 1*H*-1,2,3-triazoles 2*H*-1,2,3-Triazoles

triazole was reported by Sharpless [4] and Meldal [5] in 2002. Sharpless & Meldal, in their work, eliminated the shortcomings of Huisgen 1,3-dipolar cycloaddition. The regioselective synthesis at room temperature in presence of sodium ascorbate (reducing agent) and $CuSO_4$, which acted as a catalyst, proved as a breakthrough for regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles. Moreover, 1,2,3-triazoles and benzotriazoles are exceptionally stable towards oxidation, reduction, hydrolysis and even enzymatic breakdown. However, under drastic conditions, reductive cleavage occurs leading to their conversion into triazolium salts. Due to their high stability and non-harmful properties, these compounds have been widely used for drug discovery. They have proved to be effective substitutes for treating different diseases and disorders. Another important aspect of 1,2,3-triazoles, which has enhanced their significance in the field of pharmaceutical chemistry is their capability to undergo dipole-dipole and π-stacking interactions and form a hydrogen bond. This has resulted in enhanced solubility due to which they attach with the biological target with high affinity. Recognizing the individual biological and medicinal importance of 1,2,3-triazoles, a comprehensive review has been done to signify the importance of these compounds for medicinal use.

Literature survey on 1,2,3-triazole derivatives synthesized using various approaches show that these compound exhibit a broad spectrum of biological activities [6] including anticancer, antibacterial, antifungal, antitumor, anti-inflammatory, antitubercular, anticonvulsant, antimalarial, antiviral, antioxidant, *etc*.

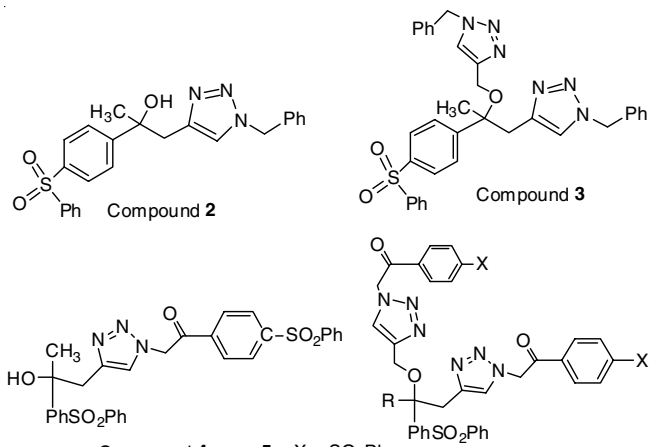
Biological significance: 1,2,3-Triazole moiety finds usage as bioisosteres in medicinal chemistry, building blocks for more complex biologically active compounds, pharmaceutical drugs such as mubritinib, tazobactam, *etc*. Though 1,2,3-triazole have been exploited by researchers for designing and synthesis of many medicinal scaffolds exhibiting vast range of biological actions like anti-HIV, anticancer, antibacterial activities, *etc*. Still a lot of research needs to be done to synthesize hybrids of 1,2,3-triazole with other heterocyclic compounds so as synthesize compounds of medicinal importance. The 1,2,3-triazole moiety has been incorporated into various therapeutically important agents. *N*-Substituted triazoles attached with different heterocyclic nuclei exhibit a number of biological activities [7] such as antibacterial, anti-inflammatory, antifungal, analgesic, anticancer, anticonvulsant, antitumor, antiviral, antileishmanial, antioxidant, *etc*. Triazole derivatives have been found to exhibit interesting biological activities as discussed below.

Multiple pharmacological activities (Antimicrobial, Anticancer, antioxidant, *etc*.): Nagender *et al*. [8] synthesized pyrazolo-pyridine and pyrazolo-pyrimidine derivatives bridged through triazole moiety, which exhibit the antimicrobial and anticancer activities. The screening against the various human cancer cell lines *viz*. MCF7-Breast (HTB-22), A549-Lung (CCL-185), HeLa-Cervical (CCL-2) and DU145-Prostate (HTB-81), revealed promising a anticancer activity for compounds **1a**, **1b** and **1c** against A549-Lung (CCL-185) and DU145-Prostate (HTB-81) cell lines ($IC_{50} \leq 6.3$ μM). The remaining compounds exhibited no cytotoxicity till 100 μg/mL concentration. The antimicrobial, anti-biofilm and minimum bactericidal concentration (MBC) activities of synthesized compounds was also evaluated. The results revealed that compound **1c** was the most effective amongst all the tested compounds.



Compound **1a-c**

Antibacterial, antifungal and antioxidant activities of a number of synthesized triazoles bearing diaryl sulfones was reported by Mady *et al*. [9] in 2014. The CuAAC reaction was used to synthesize compounds by using ultrasonic sound wave in eco-benign solvents. All the compounds were examined for fungicidal, antibacterial and antioxidant activities. Though all the screened compounds possessed good to moderate antimicrobial activity, compounds **2**, **3** and **5a-b** exhibited highest potency towards fungal infections with MIC = 25 mg/mL. Compound **4** was screened by DPPH radical scavenging assay, when it depicted remarkable antioxidant activity.



Compound **2** Compound **3**

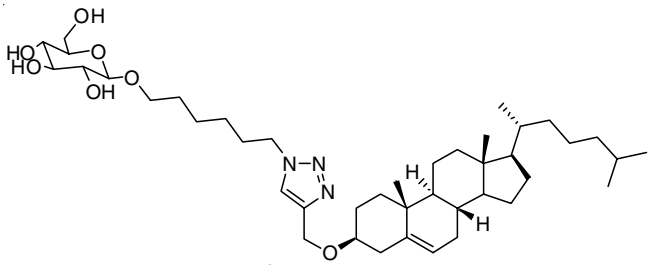
Compound **4**

5a: X = SO_2Ph
R = CH_3
5b: X = Br
R = CH_3

Compound **5a-b**

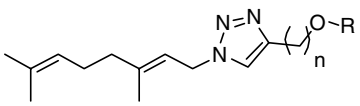
Antimicrobial and cytotoxic activity of triazole analogs, synthesized *via* Click Chemistry (CuAAC) by reacting two azido substrates with various terminal acetylenic derivatives was reported by Aly *et al*. [10]. *In vitro* screening for antimicrobial and cytotoxic activity, demonstrated that most of them exhibited significant antibacterial activity, however, cytotoxic and antifungal activities shown by them was not significant.

Compound **6** was most potent against *E.coli* and *S. aureus* with activity more than ampicillin. It also displayed considerable cytotoxic and antifungal activities.



Compound **6**

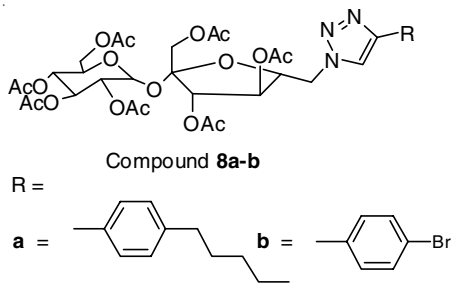
Antimicrobial and antioxidant activity of various triazole derivatives synthesized *via* CuAAC reaction was reported by Dubey *et al*. [11]. Micro-broth dilution procedure was employed to evaluate antibacterial activity of the reported compounds against a different strains of Gram positive bacteria (*S. aureus* MTCC 3160, *B. cereus* MTCC 430) and Gram negative bacteria (*P. aeruginosa* MTCC 2295 and *E. coli* MTCC 1610). Five synthesized compounds **7a-e** exhibited better to equivalent bacterial inhibition activity against Gram positive bacterial strains when compared with ciprofloxacin (reference drug). However, activity was less towards Gram-negative bacteria. DPPH assay was done on these compounds to evaluate their antioxidative behaviour. These compounds showed a remarkable free radical scavenging activity. The compound **7e** showed excellent scavenging activity, almost similar reference antioxidant compound.



Compound **7**: R =
a n=1 R = *p*-CHO-Ph
b n=1 R = *p*-Me-Ph
c n=1 R = *o*-Me-Ph
d n=1 R = *p*-Cl-Ph
e n=1 R = H, Cyclohexanyl

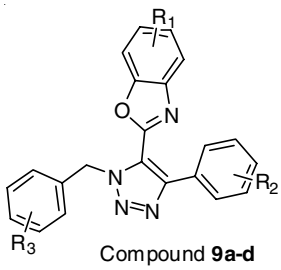
Antibacterial, antifungal and cytotoxic activities of triazole-sucrose hybrids was reported by Petrova *et al*. [12]. Though, most of the screened compounds displayed good inhibition activity towards important microbial pathogens, however 4-pentylphenyl triazole derivative (compound **8a**) exhibited highest potency against the tested strains of bacteria with MICs values in the range, 1.1 to 4.4 μM and MBCs (minimum bactericidal concentrations) values in the range 2.2 to 8.4 μM, whereas 4-bromophenyl triazole derivative (compound **8b**) exhibited antifungal property with MICs range from 0.6 to 4.8 μM and MFCs from 1.2 to 8.9 μM. In addition, moderate anticancer potency was also reported against lung, breast, cervical and liver cancer cell lines for few compounds, without showing hepatotoxicity.

Antibacterial and anticancer activity of benzoxazole-triazole scaffolds synthesized by alkynylation of benzoxazole followed by CuAAC was reported by Srivastava *et al*. [13]. The *in vitro* screening for antibacterial and anticancer activity, revealed compounds **9a-c** exhibited potent activity towards *Staphylococcus aureus* and *Escherichia coli*. Compound **9d**



Compound **8a-b**

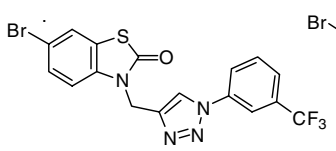
demonstrated a significant inhibitory activity against tested human cancer cell lines: HeLa (cervical), SKBr3 (breast) and HepG2 (immortalized cancer cell line of human liver). The preliminary bioassay evaluations conducted on these compounds strongly implies that synthesized hybrids has a better scope to act as therapeutic agents in medicinal chemistry.



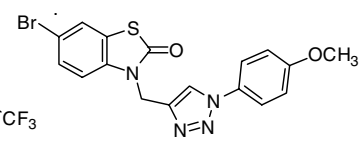
Compound **9**:
a R_1 = H, R_2 = H, R_3 = H
b R_1 = H, R_2 = H, R_3 = NO_2
c R_1 = H, R_2 = OCH_3, R_3 = H
d R_1 = CH_3, R_2 = OCH_3, R_3 = 2,4diF

Compound **9a-d**

Cytotoxic and antibacterial activity of series of new benzo-[*d*]thiazol-triazole hybrids was evaluated and reported by Nagavelli *et al*. [14] in 2016. These compounds were synthesized by one pot CuAAC reaction and evaluated for anticancer and antibacterial activitives. The anticancer activity against the tested cell lines was good when, compared with that of standard cisplatin. For example, compound **10a** exhibited inhibitory effect on MCF-7 cell line (of human breast) with IC_{50} value 13.04 ± 0.454 μM. Another analogue **10b** also demonstrated cytotoxic effect against MCF-7 with IC_{50} values 17.54 ± 1.189 and HeLa (cervical) with IC_{50} 12.15 ± 0.563 μM. *In vitro* examination for antibacterial activity against Gram-positive strains (*S. aureus* and *S. pyogenes*) and Gram negative strains of bacteria (*K. pneumoniae* and *P. aeruginosa*) by agar well diffusion technique revealed, good to normal activity as compared with standard streptomycin.



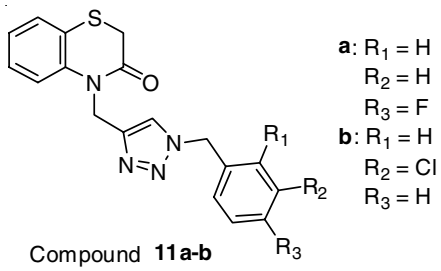
Compound **10a**



Compound **10b**

Antioxidant and antitubercular activity of benzothiazinone based triazoles synthesized *via* click chemistry was studied by Shaikh *et al*. [15]. Compounds **11a** and **11b** were the most potent of all compounds against *Mycobacterium tuberculosis* (MTB) and *Mycobacterium bovis (*BCG) as was substantiated by low experimental MIC values. Screening for anticancer potential using MTT assay against HeLa, A549 and A431 cell

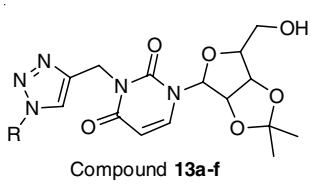
lines, showed that these compounds exhibit no significant cytotoxic activity. However, these compounds exhibited good antioxidant potential as per IC_{50} values ranging from 14.14 to 47.11 µg/mL. Molecular docking study was also done against a probable target MTB DprE1, when a signicant linkage was observed between the binding capability and biological action. *In vitro* and *in silico* study data of benzothiazinone functionalized 1,2,3-triazoles indicates that these compounds may prove to be the ideal structure for further development of novel therapeutic agents.



Compound **11a-b**

Anticancer and antimicrobial activities of theophylline functionalized triazoles with different nucleoside derivatives was reported by Ruddarraju *et al*. [16]. The screening results for anticancer and antimicrobial activities of these compounds demonstrated that compounds **12a** and **12b** displayed quite significant cytotoxic activity against all four tested human cancer cell lines *viz*. A549 (lung), IC_{50} = 2.56; HT-29 (colon), IC_{50} = 2.19; MCF-7 (breast) IC_{50} = 1.89 and A375 (melanoma) with IC_{50} = 4.89 mM. The MIC values showed that compound **12c** exhibited signicant antibacterial potency against *P. aeruginosa*, *Bacillus cereus*, *S. aureus* and *E. coli*. The docking studies performed has shown that compounds **12a** and **12b** and some other compounds possess good dock score as well as binding afnity with different therapeutic targets responsible for proliferation of cancer cells.

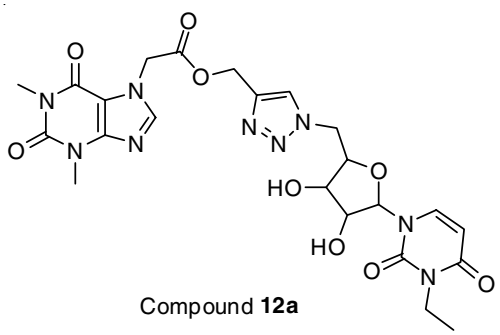
Anticancer and antibacterial activities of uridine-triazole hybrids was reported by Thatipamula *et al*. [17]. The synthesis of biologically active molecules was done by CuAAC. The evaluation for anticancer and antibacterial activities performed *in vitro* demonstrated that anticancer activity of compounds **13a** and **13b** against MCF-7 was equivalent to reference cisplatin whereas compound **13c** demonstrated very good activity against HeLa as compared to reference. The anticancer activity of rest of compounds against MCF-7 and HeLa cell lines was moderate to good. The screening results for antibacterial activity demonstrated that compounds **13c** and **13d** exhibited excellent inhibitory potential against *E. coli* and *B. subtilis* when compared with reference streptomycin, whereas compounds **13a** and **13e** exhibited encouraging activity against *P. vulgaris* and *S. aureus*, respectively and compound **13f** was found active against *S. aureus* and *B. subtilis*.



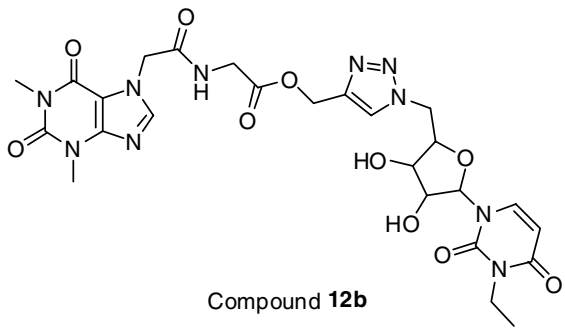
Compound **13a-f**

R =
a = 2-hydroxymethyl 5-fluoro phenyl
b = 4-chlorophenyl
c = 2,6-dibromo-4- fluoro phenyl
d = napthyl
e = 3-chlorophenyl
f = 3,5-dichloro phenyl

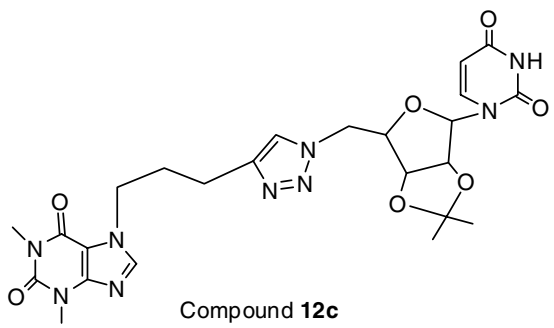
Antiproliferative and antimicrobial activities of imidazole functionalizedtriazolesulfonamides were reported by Al-blewi *et al*. [18]. *In vitro* screening of these compounds for antimicrobial property revealed that compound **14** was the most effective antimicrobial agent. The reported MIC values range was 32 to 64 µg/mL. The screening against human cancer cell lines *viz*. HepG2, PC-3 and HEK293 showed quite significant inhibitory activity (IC_{50} = 55-106 µM). Electronic, hydrophobic



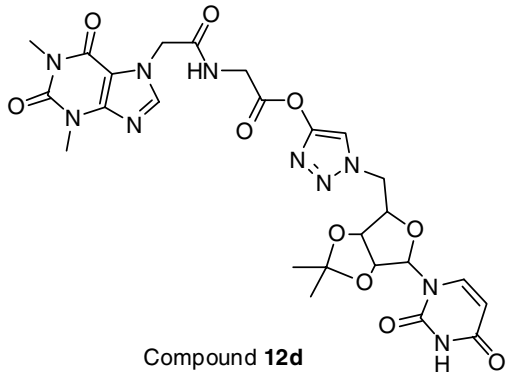
Compound **12a**



Compound **12b**

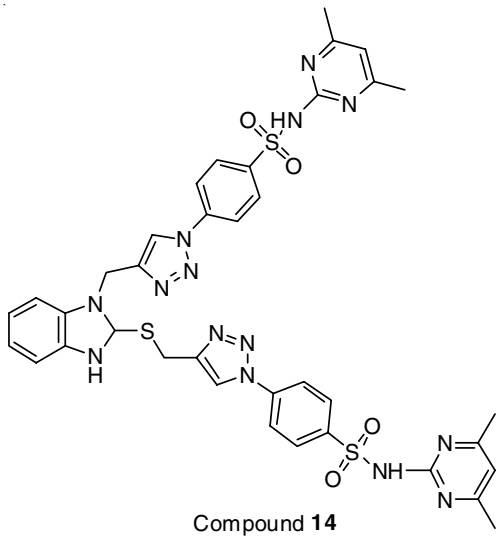


Compound **12c**



Compound **12d**

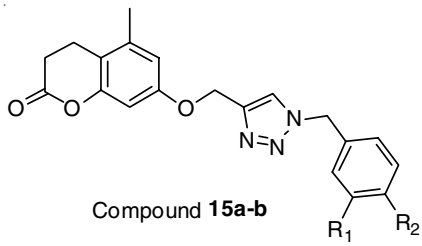
and steric properties were analyzed by receptor based electrostatic analysis and these were in accord with the experimental results. Experimental biological results were further endorsed by the *in silico* ADMET prediction findings and indicated that all compounds are neither mutagenic nor carcinogenic.



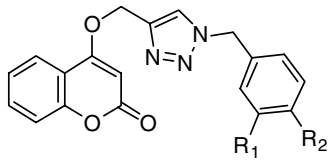
Compound **14**

Antitubercular, antimicrobial and antioxidant activity of coumarin-based triazole derivatives was reported by Shaikh *et al*. [19]. The *in vitro* screening for antitubercular activity towards *Mycobacterium tuberculosis*, H37Ra, revealed that compound **15a** exhibited most potent antitubercular activity against H37Ra (MIC = 1.80 µg/mL). Whereas *in vitro* screening for antibacterial activity towards different Gram positive (*S. aureus*, *M. luteus* and *B. cereus*) and Gram negative strains of bacteria (*E. coli*, *P. fluorescens* and *Flavobacterium devorans*) revealed that compound **15d** has significant antibacterial potential as compared to the traditional drugs like kanamycin, chloramphenicol, ampicillin used for curing bacterial ailments. The antifungal activity was explored *in vitro* against *Aspergillus niger*, *Penicillium chrysogenum* and *Curvularia lunata*, which revealed that compound **15b** exhibited significant antifungal activity as compared to reference drugs, amphotericin B, miconazole and fluconazole. The antioxidant activity test using DPPH radical scavenging assay revealed that compound **15c** demonstrated potent antioxidant activity as compared to BHT and ascorbic acid. Molecular docking study exhibited that there existed strong affinity between target compounds and active sites of DprE1 enzyme and hence, the study provides a pathway for synthesizing new structure based biologically active molecules.

Antimicrobial, anticancer and anti-plasmodial properties triazole-chalcones and triazole-flavones hybrids synthesized *via* by copper catalyzed click chemistry were reported by Kant *et al*. [20]. The screening for antibacterial potency against Gram positive (*Enterococcus faecalis*, *S. aureus*) and Gram negative (*E. coli*, *P. aeruginosa*, *K. pneumoniae*, *Shigella boydii*) strains of bacteria showed that compounds **16a-d** and **17a-b** exhibited quite significant antibacterial action. The antifungal activity was tested against three *Candida strains viz. tropicalis*, *albicans*

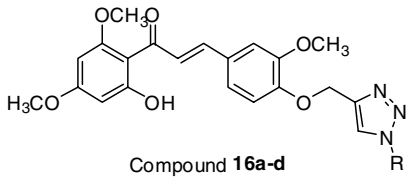


Compound **15a-b**

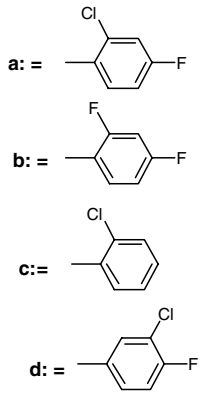


15a: R_1 = H; R_2 = H
15b: R_1 = Cl; R_2 = H
15c: R_1 = H; R_2 = Br
15d: R_1 = H; R_2 = NO_2

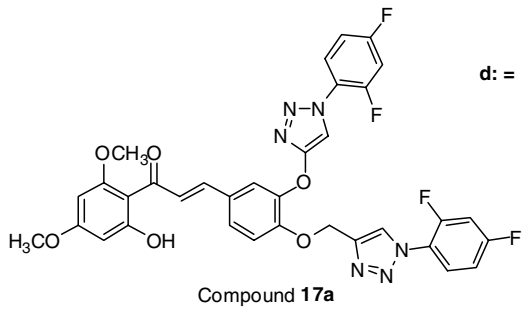
Compound **15c-d**



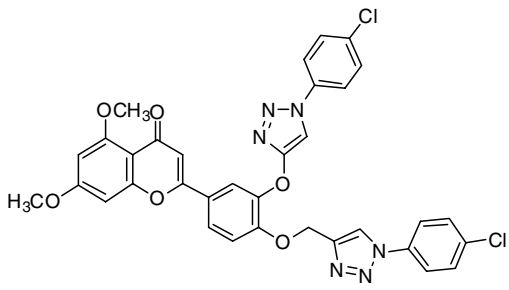
Compound **16a-d**



a: =
b: =
c:=
d: =



Compound **17a**

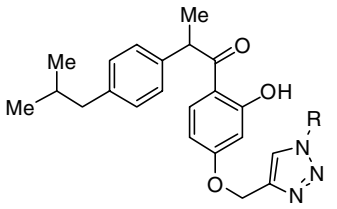


Compound **17b**

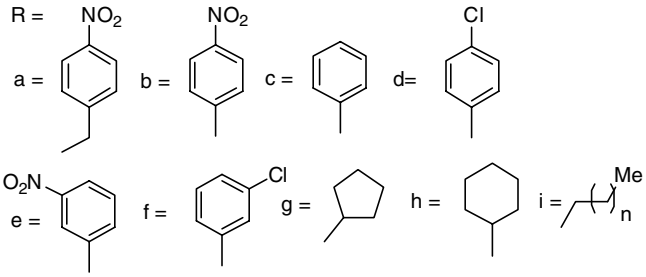
and *parapsilosis*, besides *Cryptococcus neoformans*, *Dermatophyte* and two *Aspergillus* molds (*niger* and *fumigatus*), when nine of them showed good antifungal activity. The antiplasmodial activity evaluation revealed that compound **16d** exhibited most potent activity against *Plasmodium falciparum*. Moderate to weak anti-plasmodial activity was reported for rest of compounds. However, these compounds exhibited no cytotoxic activities against Huh7 cells.

Anti-inflammatory and antibacterial activity of ibuprofen-based triazoles synthesized *via* click chemistry was reported by Angajala *et al*. [21]. *In vivo* screening for anti-inflammatory activity, compounds **18a-i** demonstrated more potency than

ibuprofen, the reference drug. Compounds **18b-i** also showed significant anti-inflammatory activity. The screening of compounds for antibacterial activity revealed that compounds **18a-b**, **18d** and **18f** displayed substantial antibacterial activity towards both Gram-positive and Gram-negative strains. The best in the series, compound **18a** showed the exceptional activity against MRSA (methicillin resistant *S. aureus*) with MIC = 12.5 and MBC = 15.1. Further, molecular docking studies performed into cyclooxygenase-2 active site showed a good correlation between the binding interactions of target compounds with COX-2 and their *vivo* anti-inflammatory activity.



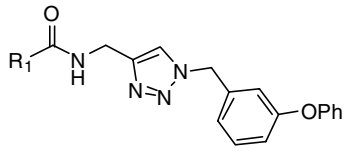
Compound **18a-i**



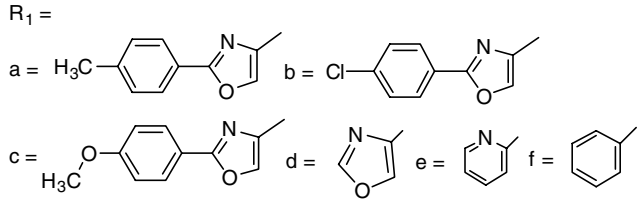
Anticancer activity: As per WHO statics, cancer is the second leading cause of death and has caused an estimated 9.6 million deaths worldwide in 2018. The most affected countries with low and middle-income. Late-stage detection, inaccessible diagnosis and treatment are common causes of morbidity and mortality. Hence due to its prevalence, high mortality rate and high cost involved in its treatment, there is undoubtedly a very strong need to discover novel anticancer drugs.

Anticancer activity of *N*-benzyl-triazole-methyl arylamides against MCF-7 (breast tumor cell line) was reported by Stefely *et al*. [22]. The compounds were synthesized *via* CuAAC. The screening of compounds for their anticancer activity revealed that compound **19** was most effective against MCF-7 (IC_{50} = 46 nM) The SAR study of the compounds further revealed that the antiproliferative activity is due to presence of phenoxy substituent at *m*-position of the benzyl substituent present on N-1 of triazole. A nice correlation to clinically beneficial anti-microtubular medications such as vincristine and paclitaxel was established by performing *in silico* comparison study of antiproliferative activity of the tested compound against panel of human tumor cell line (NCI-60). So, this study demonstrates tubulin polymerization and tumor cell inhibition potential of easily available *N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-arylamides.

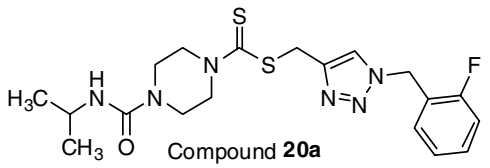
Antiproliferative activity of triazole-dithiocarbamate-urea hybrids was evaluated by Duan *et al*. [23] by MTT assay using the cancer cell lines of humans which included MGC-803



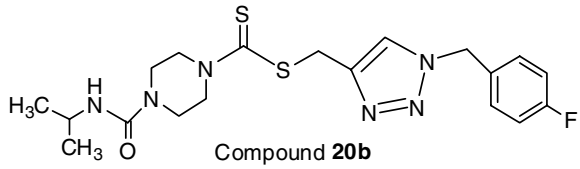
Compound **19a-f**



(gastric), MCF-7 (breast), SMMC-7721 (hepatocellular carcinoma cell line) and EC-9706 (esophagus). The cell metabolic activity was compared with 5-fluorouracil (an anticancer drug), when these compounds showed potent anticancer action towards the chosen cell lines. The most potent activity was shown by compound **20b**. Broad-spectrum anticancer activity was shown by compounds **20a** and **20b** with IC_{50} values in the range 1.62 to 20.84 µM and 0.76 to 13.55 µM, respectively. However, their maximum activity was against MGC-803 cells. Compounds **20a** and **20b** showed no cytotoxic effects towards normal cells (HEK-293) up to 55 µM and 70 µM, respectively. Flow cytometry along with other microscopic techniques were used to ascertain cell cycle arrest and apoptosis induction. This work encourages the further optimization of compounds **20a** and **20b** as more potent anticancer agents because of their synthetic accessibility, high selectivity and potent anticancer activity.



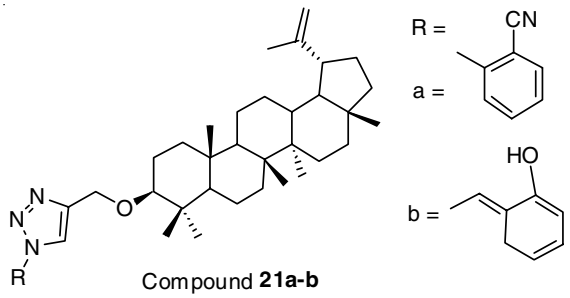
Compound **20a**



Compound **20b**

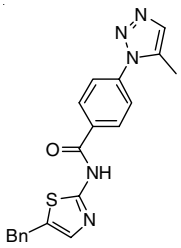
Cytotoxic activity of triazole bearing betulinic acid produced *via* click chemistry was reported by Majeed *et al*. [24]. The study of anticancer potential against nine human cancer cell lines showed that most of them possessed higher anticancer activity than the parent compound. However, two semi-synthetic derivatives *i.e*. compounds **21a** and **21b** showed higher potency. These compounds exhibited impressive IC_{50} values against HL-60, a leukemia cell line (2.5 and 3.5 mM, respectively) The potency of these compounds was 5 to 7 fold higher than parent compound. It was further evident from their biological evaluation that their first mode of action was inhibition migration and colony formation by cells, followed by interruption of mitochondrial membrane and DNA fragmentation and apoptosis.

Anticancer screening of triazoles functionalized with other heterocyclic moieties was done by Pokhodylo *et al*. [25]. The

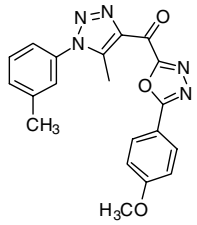


Compound **21a-b**

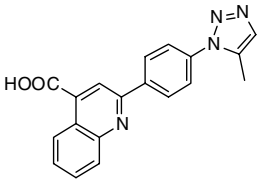
in vitro screening of synthesized compounds for antitumor activity against panel of NCI-60 cancer cell lines displayed slight or low activity on the tested cell lines. However, few of them selectively demonstrated potent antitumor activity towards most of tested cancer cell lines. For example, compound **22a** was significantly active towards K-562 cell line (leukemia) (GP = 21.47%). It also caused selective inhibition of colon cancer cell lines with moderate activity against OVCAR-4 (ovarian) and BT-549 (breast) and SK-MEL-5 (melanoma) cancer cell lines. The data further revealed that compound **22b** was reasonably effective against leukemia SR cell line whereas compound **22c** displayed very good activity against the renal cancer cell line (UO-31). Growth inhibition on UO- 31, breast cancer cell lines and leukemia were shown by most of the synthesized compounds.



Compound **22a**

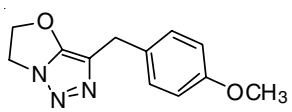


Compound **22b**



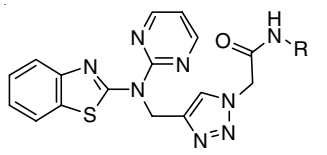
Compound **22c**

Anticancer activity of a number of synthesized heterocycle-fused triazoles was reported by Yan *et al*. [26]. The compounds were synthesized *via* one pot 1,3-dipolar cycloaddition without using catalyst. *In vitro* screening of compounds for anticancer activity against HL-60, K562, Skov-3, A549, A431, and HepG-2 (human tumour/cancer cell lines) revealed that compound 1,2,3-triazoles fused with 1,3-oxazoheterocycle show more potent activity than 1,2,3-triazoles fused with 1,3-diazoheterocycle. Compound **23** was most potent of all synthesized compounds. The IC_{50} value of the compound against A431 and K562 was lower than 1.9l g/mL.



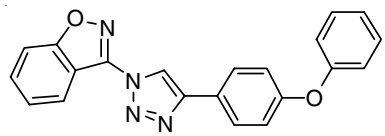
Compound **23**

Anticancer activity of triazole-pyrimidine-benzo[*d*]-thiazole conjugates was reported by Kumbhare *et al*. [27]. The authors screened them for anticancer profile towards various human cancer cell lines *i.e*. A549 (lung), MCF-7 (breast) and A375 (skin) and also studied their cytotoxicity towards normal epithelial cells of breast. The study revealed that the screened compounds induced G2/M arrest of MCF-7 cells. The screening of compounds **24a-d** for their apoptosis inducing capability and protein inhibition activity of various proteins (survivin, NF-kB, ERK1/2 and CYP1A1), which support survival and proliferation of cancerous cells. The study revealed that compounds **24c** and **24d** were the most potent. On the basis of results, these compounds can be exploited for further for research and drug development because of their ability to control cell proliferation and invasion process in highly malignant breast cancers.



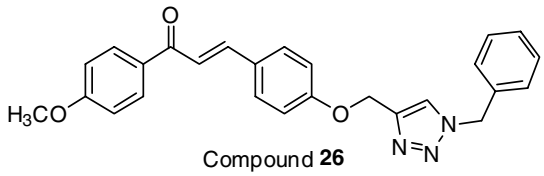
Compound **24a-d**

Anticancer activity of triazole-1,2-benzisoxazole conjugates, synthesized *via* CuAAC was reported by Ashwini *et al*. [28]. The MTT assay screening of these compounds has shown that compound **25** was the most effective antiproliferative agent against MV4-11 cells with $IC_{50} = 2$ μM. Cytotoxic study against human leukaemia cell lines (MOLM13, MOLM14, AML cells and MV4-11) revealed that compound **25** induced selective cytotoxicity by increasing cell death of AML cells as well as sub-G1 cells without affecting normal bone marrow cells (C57BL/6). *In silico* screening of compounds at protein level demonstrated that these compounds target histone deacetylases (HDACs), which was also experimentally verified. Molecular docking study conducted on title compound showed high level of shape complementarity at the binding interface *i.e*. second deacetylase domain (DD2) of HDAC6 enzyme.



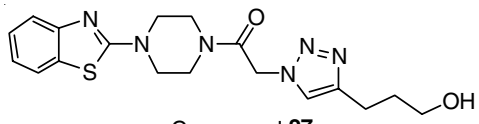
Compound **25**

Anticancer activity of a newly synthesized chalcones-1,2,3-triazole hybrids was studied by Yadav *et al*. [29]. The compounds were synthesized under benign conditions via click chemistry using copper nanoparticle (cellulose supported) catalyst in water. Screening for cytotoxicity was done using MTT assay against selected human cancer cell lines *i.e*. MIA-Pa-Ca-2 (pancreatic), MCF-7 (breast), A549 (adenocarcinoma alveolar basal epithelial cell line) and HepG2 (liver) to check their anticancer activity. The study demonstrated that compound **26** exhibit highest potency against all tested lines with IC_{50} values ranging from 4-11 μM. The activity shown was comparable to the reference drug. Compound **26** was found to induce cancerous cell death and G2/S arrest, mitochondrial potential loss in MIA-Pa-Ca-2 and trigger dose dependent activation of caspase-3 and PARP-1 enzyme cleavage, as confirmed by cell cycle analysis.



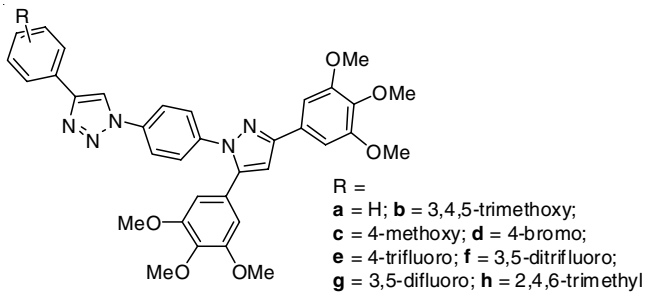
Compound **26**

Anticancer activity of a series of triazole-benzothiazole-piperazine conjugates was reported by Aouad *et al*. [30]. The regioselective synthesis of triazole derivatives was carried out both i.p.o. and in absence of Cu(I) catalyst using click chemistry. Authors screened the synthesized hybrids for antiproliferative activity against human cancer cell lines *viz*. MCF7, T47D (of breast) and HCT116, Caco-2 (of colon). Most of the 1,2,3-triazole hybrids exhibited reasonable activity against all the four tested cell lines. Further, SAR by *in silico* ADME analysis was established and it was in good accord with the '*in vitro*' activity of the tested compounds. Compound **27** with IC_{50} = 38 µM against T47D and 33 µM against MCF7 , and IC_{50} of 48 µM against HCT116 and 42 µM against Caco-2, was most potent antiproliferative of all.



Compound **27**

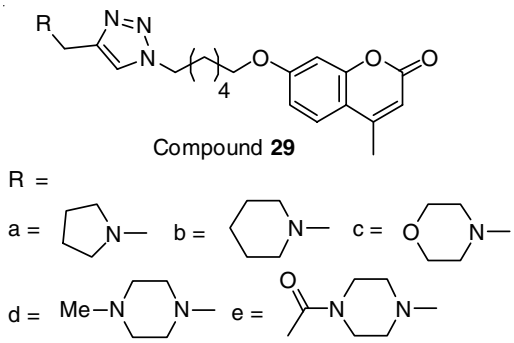
Anticancer activity of a number of synthesized triazole derivatives was reported by Lakkakula *et al*. [31]. Compounds **28a-j** were *in vitro* screened by MTT assay against MCF-7, A54 and A375 cancerous cell lines using doxorubicin as the positive control. All the compounds exhibited significant anti-cancer activity against tested cancer cell lines and IC_{50} values were in range from 0.13 to 9.34 µM. Compounds **28a**, **28d**, **28e**, **28g** and **28j** exhibited more potency than the positive control doxorubicin.



Compound **28a-j**

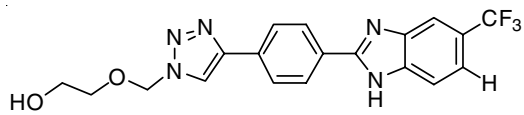
Antimicrobial activity: With indiscriminate use various antimicrobial drugs, some microbes have developed resistance towards them and started to resist them. It could result in a lack of effective treatments for some diseases and hence can cause a serious problem in near future. So due to surge in the number of drug resistant microbes, there is ever increasing demand for synthesizing new antimicrobial agents.

Antifungal and antibacterial activity of 2*H*-chromen-2-one-triazole hybrids was reported by Kushwaha *et al*. [32]. The compounds were synthesized using click chemistry and screened for their antifungal potential against four species of fungi (*A. fumigatus*, *A. niger*, *C. albicans* and *A. flavus*). Besides this, these compounds were also tested for antibacterial activity against three strains of Gram positive (*S. epidermis S. aureus* and *B. subtilis*) and four strains of Gram negative (*P. aeruginosa*, *E. coli*, *Salmonella typhi* and *Klebsiella pneumoniae*) bacteria. *In vitro*, bioassay study demonstrated that the target compounds exhibit brilliant antifungal activity against *A. fumigatus*, *A. flavus* and *C. albicans*, which was even superior than the reference drug miconazole in case of *Aspergillus fumigatus*. Compounds **29c** (R = morpholine) and **29e** (R = *N*-acetyl piperazine) demonstrated promising activity against the tested strains of bacteria. Compound **29e** selectively exhibited more activity against *Pseudomonas aeruginosa*. The *in silico* pharmacokinetic studies conducted on target compounds demonstrated that compounds **29a-e** possessed lower toxicity, higher drug score and good oral bioavailability and hence can be further explored for drug development.



Compound **29**

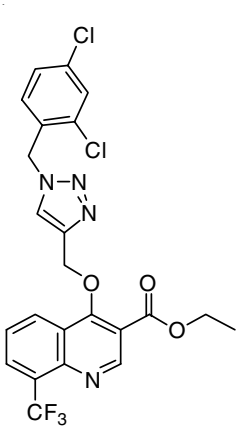
Antibacterial activity of triazole hybrid molecules was evaluated by Ouahrouch *et al*. [33]. The compounds were synthesized *via* CuAAC by microwave irradiation under benign conditions. *In vitro* screening for antibacterial activity against both Gram positive (*E. faecalis*, *S. aureus*, *S. pneumoniae*) and Gram negative (*Haemophilus*, *E. coli* and *P. aeruginosa*) bacteria using standard techniques and MIC values revealed that all the synthesized compounds lack antibacterial activity with MICs greater than 64 µg/mL when compared with linezolid and ciprofloxacin (standard drugs). The compounds were screened *in vitro* for their antifungal potential towards two phytopathogenic strains of fungi: *Fusarium oxysporum* (f. sp.) albedinis (Foa) and *verticillium dahliae* Kleb (VD). The antifungal activity was studied using mycelia linear growth rate method and sporulation test, when compound **30** exhibited moderate inhibition (30%) in the FOA sporulation.



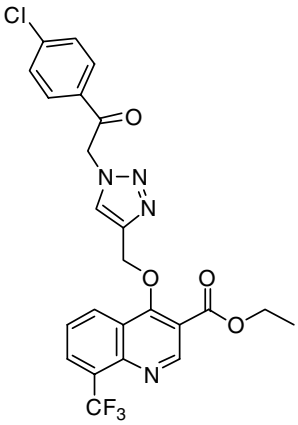
Compound **30**

Antibacterial activity of 8-trifluoromethylquinoline based triazoles which were synthesized using multi-step reaction *via* click chemistry approach has been reported by Garudachari

et al. [34]. *In-vitro* screening for antimicrobial activity by well plate method, demonstrated good inhibitory potential of these compounds against different bacteria compared to the standard drug. Compounds **31a** and **31b** exhibited higher antibacterial potential against tested bacterial strains than the standard. The enhanced antibacterial potential of compounds **31a-b** was because of presence of -Cl substituent at the fourth position in 4-benzyl[1,2,3]triazole of 8-trifluoromethylquinoline-3-carboxylic ester.

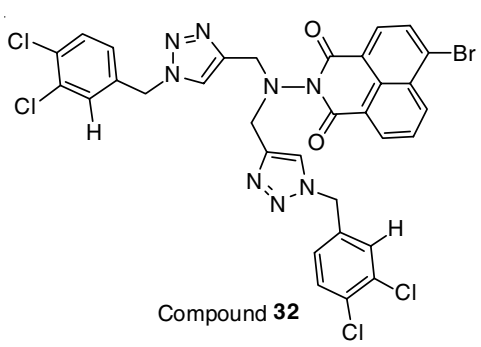


Compound **31a**



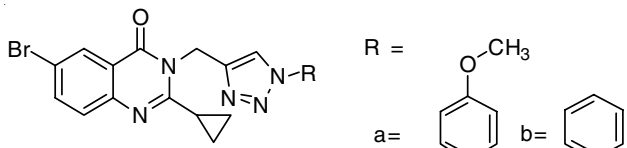
Compound **31b**

Antimicrobial activity of a number of triazole derivatives of naphthalimides was reported by Lv *et al*. [35]. The compounds were synthesized through multistep reaction by copper catalyzed cycloaddition reaction i.p.o. THF/H_2O at room temperature and screened *in vitro* for antimicrobial activity by a two-fold dilution technique against each of four strains of Gram positive and Gram-negative bacteria, and three strains of fungi. The antimicrobial screening results showed that some of them exhibit good to superior antibacterial and antifungal activities against the tested strains as compared to reference drugs. Bioactive assay demonstrated compound **32** and its corresponding hydrochloride exhibited better antibacterial activity towards *E. coli* than standard drugs (norfloxacin and chloromycine). A preliminary study about the interaction of compound **32** with calf thymus DNA showed that it effectively intercalates into DNA and develops interaction with it, which may block replication of DNA and hence cause of its antimicrobial activity. Further study showed that the human serum albumin (HAS) efficiently stored and carried compound **32** through electrostatic interaction. This study demonstrated importance of triazoles.

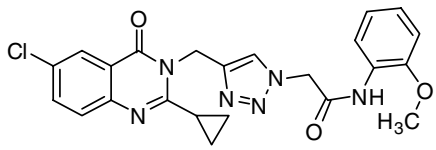


Compound **32**

Antibacterial and antifungal activities of triazole-quinazolinone conjugates was reported by Vani *et al*. [36]. The screening of compounds using agar well diffusion method against both Gram positive (*S. aureus*, *B. subtilis*) and Gram negative (*E. coli*, *P. aeruginosa*) bacteria showed that compounds **33a** and **33c** showed good activity *versus* all the tested bacterial strains, whereas activity shown by rest of the molecules was moderate when compared with standard drug ciprooxacin. The screening for antifungal activity against *C. albicans* and *A. niger* using potato dextrose agar (PDA) revealed that compound **33b** demonstrated good antifungal activity and rest exhibited moderate activity when compared with standard drug fluconazole.

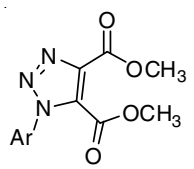


Compound **33a-b**

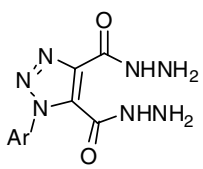


Compound **33c**

Antimicrobial activity of fluorinated triazoles diesters and dihydrazides synthesized by convenient green click process was reported by Aouad [37]. *In vitro* screening for antimicrobial activity was done by using the broth-dilution method against three Gram positive (*S. pneumonia*, *B. subtilis* and *S. aureus)*, three Gram negative bacteria (*P. aeruginosa*, *E. coli* and *K. pneumoniae*) and two fungal strains (*A. fumigatus* and *C. albicans)*. The antibacterial activity of compounds **34a-d** was good to moderate against all the tested bacteria's (MIC range = 16 to 31.25 μg mL^{-1}), whereas no activity was observed against fungal strains. Dihydrazides **35a-d** screening showed that the compounds **35a-b** exhibit excellent antibacterial activity against all tested Gram positive bacteria (MIC range = 4 to 8 μg mL^{-1}), though activity against Gram negative (MIC = 16 μg mL^{-1}) excellent antifungal activity was observed with compound **35d** (MIC = 8 μg mL^{-1}).



Compound **34a-d**

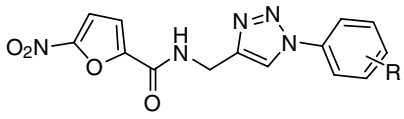


Compound **35a-d**

Ar =
a = 2-fluorophenyl; b = 4-fluorophenyl
c = 3-fluoro -4-ethylphenyl; d = 2-fluoro -4-iodophenyl

Antimicrobial potentiality of triazole and 5-nitrofuran conjugates was reported by Kamal *et al*. [38]. The synthesized triazoles were screened *in vitro* for their antmicrobial activity,

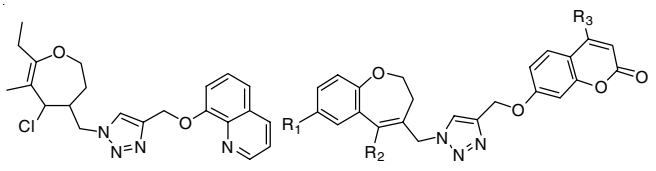
when the synthesized compounds exhibited promising bacterial inhibition of Gram positive strains, whereas inhibition of Gram-negative strains was mild. Some compounds **36a-d** possessed excellent inhibitory activity (MIC = 1.9 µg/mL). All the compounds exhibited excellent antifungal activity, almost equally potent to standard drug miconazole against some of the tested fungal strains whereas it was good against rest. For example, compound **36a** was found two times more potent (MIC = 3.9 µg/mL) than the reference drug miconazole (MIC = 7.8 µg/mL) against *C. albicans* and *C. parapsilosis*. Compound **36a** also exhibited excellent anti-biofilm activity with biofilm inhibitory concentration (BIC = 0.8 µg/mL). Rest of the compounds also effectively inhibited biofilm formation. Further study revealed the antifungal effects shown by compound **36a** is because of its property to inhibit the ergosterol biosynthesis. Molecular modeling studies carried out further correlated the binding modes of compound **36a** in line with the antifungal activity and was further validated by ergosterol biosynthesis inhibition assay data. Their cytotoxicity to the normal cells was ten times lower as compared to their antimicrobial activity.



Compound **36**

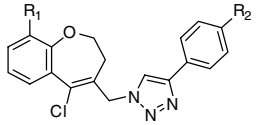
R =
a = 2,3-dichloro; b = 3,4-dimethoxy
c = H; d = 4-fluoro-2-nitrophenyl

Antibacterial activity of twenty oxepin-triazole derivatives synthesized using CuAAC was examined by Kuntala *et al*. [39]. Screening for antibacterial activity demonstrated that some of them exhibited good activity against Gram-negative bacteria (*E. coli*) over the Gram-positive strains. Though activity of all good compounds was reasonable, but compounds **37** and **38a-b** showed better activity against *Pseudomonas aeruginosa* (-ve) whereas compounds **38c-d** showed excellent activity against *Escherichia coli* (-ve). Compounds **38c** and **38e** showed medium activity against *Klebsiella* (+ve) while others exhibited lower inhibition. Anticancer activity against lung and colon cancer cell lines was also observed for these compounds.



Compound **37**

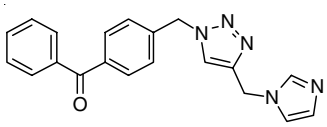
Compound **38a-b**



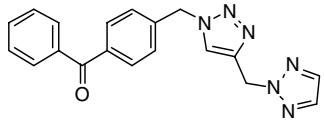
Compound **38c-e**

a: $R_1 = CH_3$; $R_2 = Cl$; $R_3 = H$
b: $R_1 = Cl$; $R_2 = Cl$; $R_3 = CH_3$
c: $R_1 = CH_3$; $R_2 = CH_3$
d: $R_1 = CH_3$; $R_2 = H$
e: $R_1 = H$; $R_2 = H$

Antibacterial activity of triazoles linked benzophenone was reported by Fichtali *et al*. [40]. These compounds were synthesized *via* click chemistry using CuAAC reaction and screened them for their antibacterial potential against both Gram-positive (*B. subtilis* and *S. aureus*) and Gram-negative bacteria (*E. coli*) as well as against fungi (*Candida albicans*). The antimicrobial activity profile of compounds **39a-b** was good against all the tested strains except *E. coli*, which was slightly resistant. The most susceptible was *Candida albicans* among all microorganisms against all compounds studied, having the lowest MIC value (15.63 µg/mL).



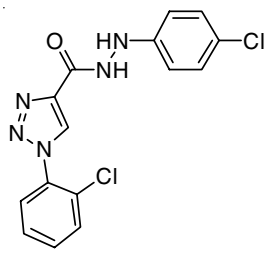
Compound **39a**



Compound **39b**

Antifungal activity of triazole hydrazide derivatives was reported by Wang *et al*. [41]. The *in vitro* the antifungal activity of synthesized compounds against phytopathogenic fungi were also studied. They used mycelium growth inhibition method for their study and found that compound **40** was most potent anti-phytopathogenic, against four fungi strains: *Fusarium graminearum* (EC_{50} value of 0.18 µg/mL), *Rhizoctonia solani* (EC_{50} value of 0.35 µg/mL), *Sclerotinia sclerotiorum* (EC_{50} values of 0.37 µg/mL) and *Magnaporthe oryzae* (EC_{50} values of 2.25 µg/mL).

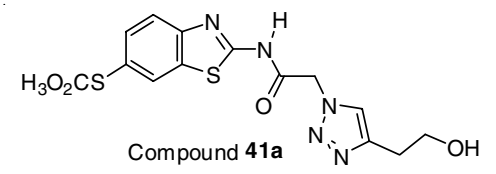
Further, *in vivo* screening of compound **40** demonstrated that this compound is effective in controlling various diseases caused by above mentioned phytopathogens like rice sheath blight and Sclerotinia stem rot of rape, rice blast and fusarium head blight. Thus, the work of researchers shows that combination bioactive 1,2,3-triazole moiety with hydrazide moiety may result in an encouraging fungicidal scaffold in the future.



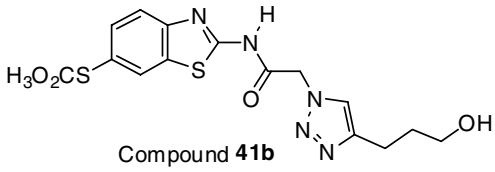
Compound **40**

Antimicrobial activity of thiazol-triazol-acetamides was reported by Rezki [42]. 1,3-Dipolar cycloaddition reaction was used to synthesize these hybrids both i.p.o. and in absence of ultrasound irradiation. The screening of compounds for their activity against three Gram positive (*S. pneumonia*, *B. subtilis*, and *S. aureus*), three Gram negative strains of bacteria (*E. coli*, *P. aeuroginosa* and *K. pneumonia*) and two fungal strains (*A. fumigates* and *C. albicans*) demonstrated encouraging antimicrobial activity against most of them at MIC of 4-16 µg/mL. The most potent was however shown by compounds **41a-b** against all the studied microbes at MIC 4-16 µg/mL.

Antimicrobial properties of triazole-thiazole-imidazothiazoles hybrids were reported by Abdel-Wahab *et al*. [43]. The screening results of antimicrobial activity revealed that compound **42a** exhibited excellent antibacterial activity as compared

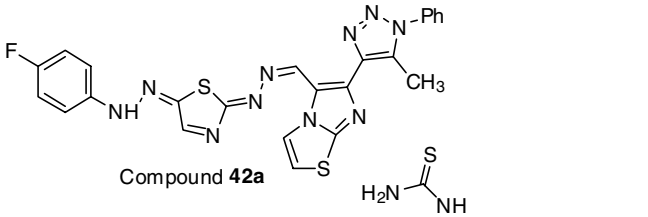


Compound **41a**

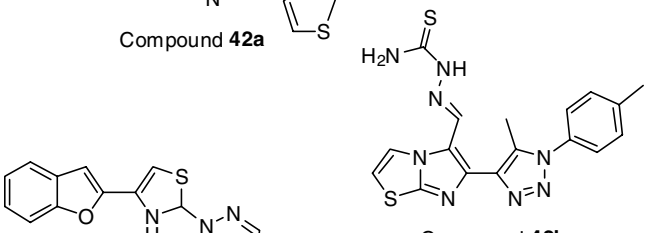


Compound **41b**

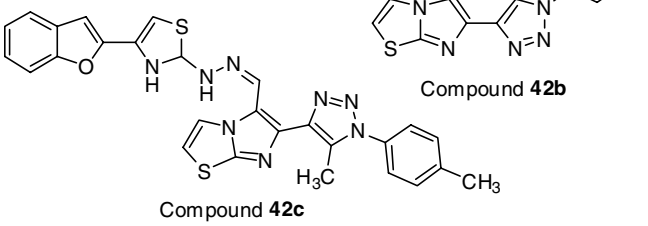
with reference drug vancomycine, whereas compounds **42b-c** exhibited good results against yeast. The MIC values of compounds revealed that compound **42a** demonstrated good antibacterial activity for both the Gram-positive and Gram-negative strains of bacteria with lowest MIC against Gram-positive bacteria while compound **42b** showed the lowest MIC against yeast. Also, compounds **42b-c** showed good antibacterial activities against *S. aureus* (ATCC 29213) and showed antifungal activities against *Saccharomyces cervesia* and *Candida albicans*.



Compound **42a**

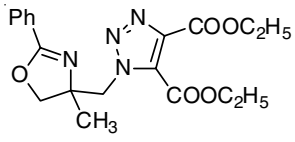


Compound **42b**



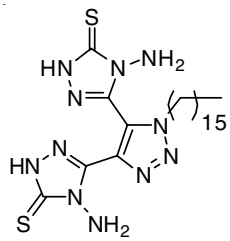
Compound **42c**

Antibacterial activity of compound **43** synthesized by 1,3-dipolar cycloaddition reaction was reported by Boukhssas *et al.* [44]. *In vitro* evaluation for antibacterial activity of compound **43** against *S. aureus* (Gram-positive) and *E. coli* (Gram-negative) by liquid serial dilution method exhibited inhibitory action against both (MIC = 1.25 mg/mL). The MBC against *S. aureus*, *E. coli* and *B. subtilis* was 2.5 mg/mL. The MBC/MIC ratio calculations revealed that compound **43** possessed good bactericidal activity against both the tested strains.



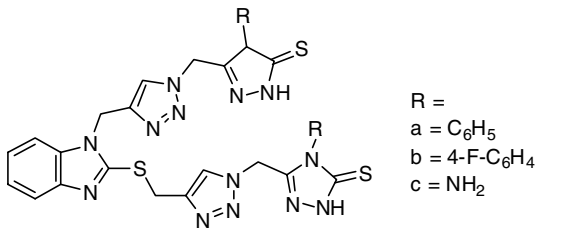
Compound **43**

Antimicrobial activity of new 4,5-diesters derivatives of 1,2,3-triazole and triazoles bearing two moieties of 1,2,4-triazole-3-thiones substituted with lipophilic groups was reported by Aouad *et al.* [45]. The target compounds were synthesized *via* free click chemistry in a green, efficient way and screened for antimicrobial potential when compound **44** showed most potent antimicrobial activity which was almost same as that of standard drug against all tested microorganisms. Further, *in silico* and molecular docking study demonstrated that these compounds exhibit good binding energy (–10.49 to –5.72 kJ/mol) towards the target protein. Moreover, these compounds possess a good affinity for active sites of the enzyme and hence seem to have good inhibitory effect on glucosamine-6-phosphate synthase.

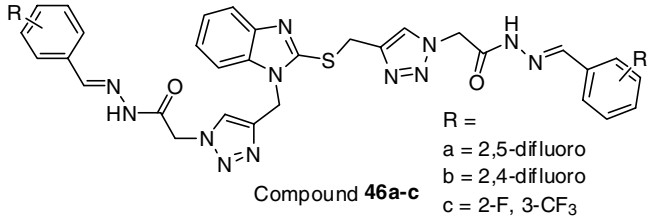


Compound **44**

Antimicrobial activity of 1,2,3-triazole-benzimidazole ring system incorporated with 1,2,4-triazole moiety and/or hydrazone linkage synthesized *via* green microwave was reported by Rezki [46]. The results revealed that some of them exhibited even more antimicrobial inhibitory effect than reference drug whereas most of them exhibited good *in vitro* inhibitory potential. This study revealed importance of incorporation 1,2,4-triazole moiety and/or hydrazone link in the structure of the 1,2,3-triazole-benzimidazole ring system as it resulted in enhancement of antimicrobial activity. Compound **45c** exhibited the inhibitory activity higher than the standard drug ciprofloxacin against *B. cereus* (MIC = 1 mg/mL), *P. aeruginosa* (MIC = 4 mg/mL) and *E. coli* (MIC = 0.5 mg/mL). Of all Schiff bases synthesized, three of them (**46a-c**) carrying flouro group at position 2 showed the greatest antibacterial activity (MIC = 1-8 mg/mL). Triazoles **45a-c** also exhibited the very good antifungal activity (MIC = 0.5-4 mg/mL) and hence showed more potency than the reference drug fluconazole.

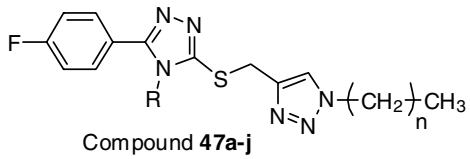


Compound **45a-c**



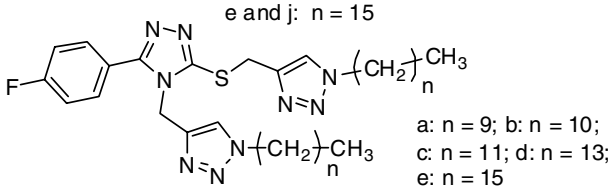
Compound **46a-c**

Antimicrobial activity of 1,2,3-triazoles-1,2,4-triazole hybrids was reported by Rezki *et al*. [47]. The *in vitro* bioassay results of screening of synthesized compounds demonstrated that some of the compounds possess promising activity against six bacteria (*S. pneumonia*, *B. subtilis*, *P. aeruginosa*, *S.aureus* and *K. pneumonia*) and two fungal strains (*C. albicans* and *A. fumigatus*). Compounds **47a-j** demonstrated promising antibacterial potentiality towards Gram positive bacteria (MIC = 8-16 µg/mL) whereas inhibitory activity towards Gram-negative bacteria was moderate to good (MIC = 16-31.25 µg/mL). Bioassay results further revealed that *bis*-1,2,3-triazoles **48a-e** were more effective against all examined bacterial strains (MIC = 4-16 µg/mL. Further, alkylated *bis*-1,2,3-triazoles **49c-e** with C_{12}-C_{16} lipophilic side chains exhibited potent antibacterial activity against all tested bacteria (MIC = 4-8 µg/mL).



Compound **47a-j**

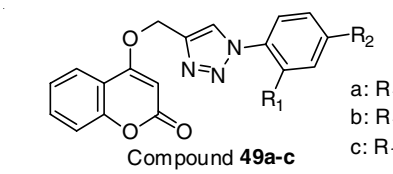
a-e: R= H; f-j: R = Et
a and f: n = 9 ; b and g: n = 10
c and h: n = 11; d and i: n = 13
e and j: n = 15



a: n = 9; b: n = 10;
c: n = 11; d: n = 13;
e: n = 15

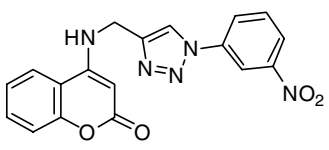
Compound **48a-e**

Antimicrobial activity of triazole-coumarin conjugates was reported by López-Rojas *et al*. [48], where the compounds were synthesized *via* CuAAC reaction. The *in vitro* screening against Gram-positive (*S. aureus* and *E. faecalis*), Gram-negative bacteria (*E. coli*, *K. pneumonia* and *P. aeruginosa*) and the yeast (*C. albicans*) revealed that most of the compounds don't show any considerable activity. However, some of the triazole-coumarin hybrids, compounds **49a-c**, **50** and **51** showed quite a substantial antibacterial action against *E. faecalis* (MIC = 12.5-50 µg/mL) and exhibited fairly lower toxicity against human erythrocyte. The best activity in the series was shown by compound **49b** in which triazole nucleus carries 2-OMe-Ph group and there is -OCH_2- linker between triazole and coumarin (MIC = 12.5 µg/mL).

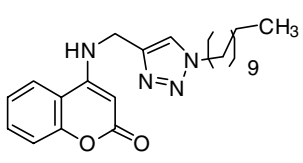


a: R_1 = H; R_2 = H
b: R_1 = OCH_3; R_2 = H
c: R_1 = H; R_2 = F

Compound **49a-c**

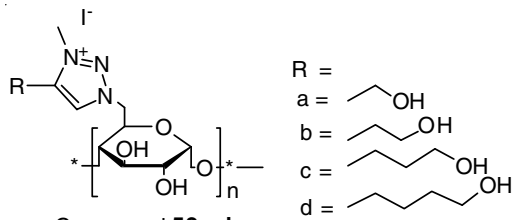


Compound **50**



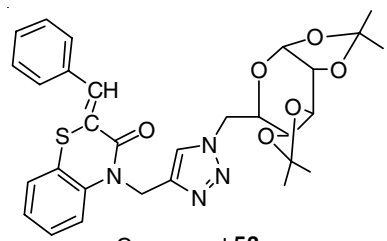
Compound **51**

Four triazolium-functionalized starch derivatives was synthesized by using CuAAC of 1,2,3-triazole with iodomethane [49]. After structural characterization by spectroscopic techniques, *in vitro* antifungal screening of all four compounds against *Watermelon fusarium*, *Colletotrichum lagenarium* and *Fusarium oxysporum* revealed that inhibitory indices of compound **52a** {6-(4-hydroxymethyl-3-methyl-l,2,3-triazolium- l-y l)-6-deoxy starch iodine} was more than 70% at l.0 mg/mL against the plant threatening fungi under reference. Triazolium-starch derivatives exhibited enormously improved the antifungal activity as compared to starch and starch derivatives of 1,2,3-triazole. It was also found that variation of alkyl chain length affected their antifungal activity and it decreases with increase in length of alkyl groups *e.g*. antifungal activity of triazolium-starch derivatives decreased in the order **52a** > **52b** > **52c** > **52d**. As triazolium-starch derivatives can be synthesized efficiently and displayed excellent antifungal activity, hence this synthetic approach may offer an effective way to make new novel antifungal compounds.



Compound **52a-d**

Antibacterial activity of series triazole -1,4-benzothiazin-3-one conjugates was reported by Ellouz *et al*. [50]. Authors synthesized the target compounds by CuAAC reaction and then *in vitro* screened for antibacterial activity against different Gram positive (*S. aureus* ATCC 25923 and *S. aureus* MLSB) and Gram negative bacterial strains (*E. coli* ATCC-25922, *P. aeruginosa* ATCC-27853, *K. pneumonia* ESBL, *E. coli* ESBL, *Acinetobacter* ATCC 17978 and Acinetobacter ESBL) at a conc. of 500 µg/mL. Among all , only compound **53** showed great antibacterial activity against *Pseudomonas aeruginosa* ATCC 27853 and *Acinetobacter* ESBL (MIC = 31.2 µg mL^{-1}) as compared with chloramphenicol as reference standard.

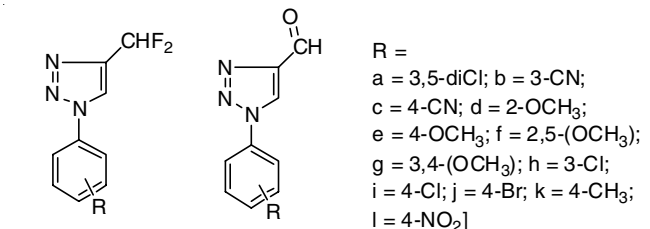


Compound **53**

Antitubercular activity: Emergence of multi-drug-resistant and extensively drug-resistant tuberculosis strains, which are resistant even to the most effective drugs (isoniazid; rifampicin) and high susceptibility of HIV infected persons to the disease, have again drawn the attention of scientific community towards this infectious disease. Hence, there is a growing need and urgency to design and synthesize compounds which

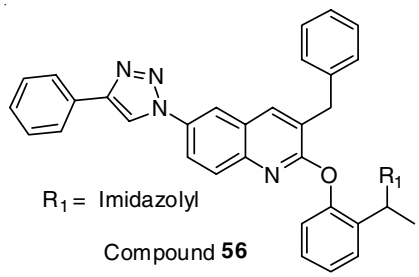
can adopt different mode of action from those drugs which are currently being used. Designing of new TB drugs has remained a significant challenge for chemists and biochemists in recent years.

Antitubercular activity of *N*-substituted triazole-carbaldehydes (**54a-i**) and *N*-substituted difloromethyltriazoles (**55a-i**) against *Mycobacterium tuberculosis* H37Rv (ATCC 27294) strain was reported by Costa *et al*. [51]. *In vitro* screening performed on synthesized compounds by microplate alamar blue assay (MABA), revealed inhibitory potential of all the reported compounds. Interestingly, best inhibition activity was shown by compound **54k** (MIC = 2.5 μg mL^{-1}), which was similar to antitubercular medicines currently available in market.



Compound **54a-i** Compound **55a-i**

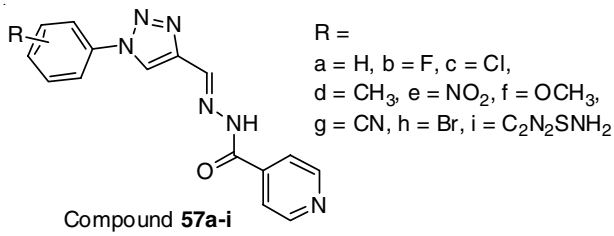
Antimycobacterial activity of newly synthesized quinoline derivatives (twenty) substituted with triazolo, ureido and thioureido groups was evaluated by Upadhayaya *et al*. [52]. Along with other derivatives, the triazolo derivative **56** inhibited *M. tuberculosis* H37Rv up to 96%, at a fixed dosage of 6.25 μg/mL. MIC for compound **56** was obtained as 3.125 lg/mL. Molecular docking calculations done on the tested compounds suggested that the antimycobacterial activity may be due to different type of interaction (H-bonding and electrostatic interactions) of polar functional groups of target compound with amino acids (Arg186 and Glu61) of *M. tuberculosis*.



Compound **56**

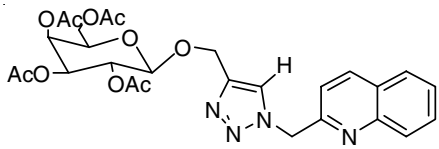
Antitubercular activity of 4-substituted *N*-phenyl-triazole derivatives was reported by Boechat *et al*. [53]. The synthesized compounds were done *via* click chemistry and screened the synthesized compounds *in vitro* using the MABA susceptibility test for their antitubercular potential against *Mycobacterium* H37Rv (ATCC 27294). Compounds **57a-i** were found to exhibit signicant antitubercular activity (MIC = 2.5 to 0.62 μg/mL), with low cytotoxicity against liver and kidney cells, which shows their high therapeutic index. Hence, these compounds possess the potential of developing new isoniazid hybrids for mycobacterial infections.

Anti-tubercular activity of quinoline coupled triazole sugar hybrids against *Mycobacterium tuberculosis* H37Rv was reported



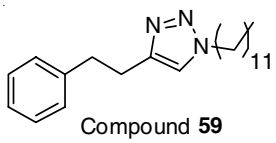
Compound **57a-i**

by Kumar *et al*. [54]. Among a series of quinoline coupled triazoles so synthesized by 'click chemistry', quinoline coupled triazole sugar hybrid, *i.e*. compound **58** was found to exhibit highest potency with 76.41% reduction of mycobacterial activity even at 5 μg/mL . SAR study performed to investigate the effect of substitution at the C-4 of triazole moiety revealed that insertion of -C_6H_5 group at the C-4 position induced good enough inhibition against *M. tuberculosis* H37Rv. This study demonstrated that that the insertion of large sized and lipophilic substituents greatly enhances inhibition activity. Further SAR study revealed that quinoline coupled triazole sugar hybrids with 3,4-*trans*-diacetyl orientation (3*S*,4*R*), show higher inhibition activity as compared to 3,4-*cis*-diacetyl orientation.



Compound **58**

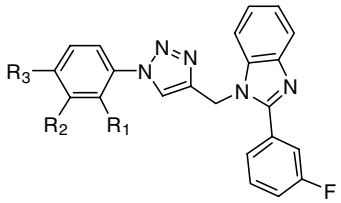
Antitubercular activity of 1,4-disubstituted triazoles or α-ketotriazole derivatives against InhA was reported by Menendez *et al*. [55]. The synthesized compounds by CuAAC reaction of alkynes and various azide. Screening of compounds for their inhibitory potentiality demonstrated that α-ketotriazoles are poor inhibitors of InhA as compared to dialkyl substituted triazoles. Moreover, introduction of an alkyl chain in position 4 on triazole resulted in low MIC values. Among all disubstituted triazoles, compound **59** demonstrated excellent inhibition activity with MIC values less than 2 μg/mL for InhA. Further enhancement of activity was observed with increase in lipophilic alkyl chain. Further studies revealed that compound with no carbonyl group in their molecule were more active than compounds having carbonyl group like α-ketotriazoles. When the carbonyl group was replaced with/reduced to methylene group, there was decrease in MIC values.



Compound **59**

Antitubercular activity of triazole-benzo[*d*]imidazole derivatives (**60a-k**) was reported by Gill *et al*. [56]. Antimycobacterial screening of these compounds demonstrated that these compounds inhibited proliferation of H37Rv strain of *M. tuberculosis* and hence can be potentially beneficial for the treatment of tuberculosis. Some of the derivatives showed

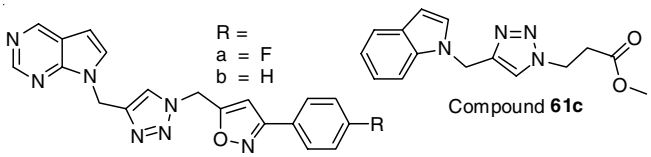
considerably better activity as compared to rifampin. The most potent were compounds **60b, 60c** and **60g**. So the synthesized compounds may act as good precursors for the preparations of new derivatives.



Compound **60a-k**

Compd.	R_1	R_2	R_3
a	F	F	F
b	H	F	F
c	H	F	H
d	OMe	H	H
e	H	H	OMe
f	F	H	Me
g	F	H	F
h	H	H	H
i	H	H	CF_3
j	Me	H	H
k	H	H	Me

Antimycobacterial activity of a series of pyrrolopyrimidine-triazole derivatives was reported by Raju *et al*. [57]. The *in vitro* evaluation of the synthesized compounds for activity against *Mycobacterium tuberculosis* H37Rv strain by using MABA revealed that out of 24 compounds screened for their antimycobacterial activity, three compounds *viz*. **61a**, **61b** and **61c** were active with MIC = 0.78-1.56 µg/mL as compared with standard antitubercular drugs (ciprofloxacin and ethambutol).The antimycobacterial assay results showed that the minimum inhibitory concentration of compounds **61a** and **61b** were 0.78 µg/mL. These two compounds also found to show highest MolDock score in molecular docking study. Other compounds showed moderate activity, when compared with standard antituberculosis drugs like rifampicin and isoniazid.

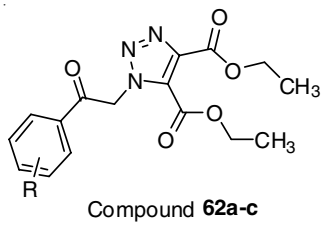


Compound **61a-b**

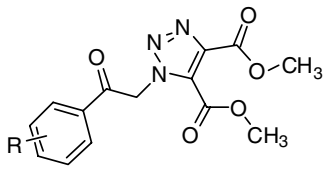
Compound **61c**

Antimycobacterial activity of triazole derivatives was studied by Shanmugavelan *et al*. [58]. The target compounds were synthesized in good yield under solvent free conditions *via* Huisgen's 1,3-dipolar cycloaddition reaction and screened *in vitro* against *Mycobacterium tuberculosis* H37Rv strain using reference drugs ethambutol and isoniazid. The screening results revealed that the more potent antitubercular compounds were those which contain aromatic ring substitution. The most potent compounds **62a-c** and **63b** have MIC values 3.13, 1.56, 3.13 and 3.13 µg/mL, respectively. The most potent compound **62b**, (MIC= 1.56 µg/mL) was 2.08 times more potent than ethambutol (MIC = 3.25 lg/mL). However, none of the tested compound was more active than isoniazid (MIC 0.75 lg/mL).

Antiviral activity: The worldwide spread of HIV-1 continues to remain a severe public health issue. The therapeutic drugs presently available like reverse transcriptase, protease, and integrase inhibitors are very costly. Moreover, no vaccine, is yet available. Hence, because of these limitations, there is an increasing necessity and urgency to design new cost-effective



Compound **62a-c**



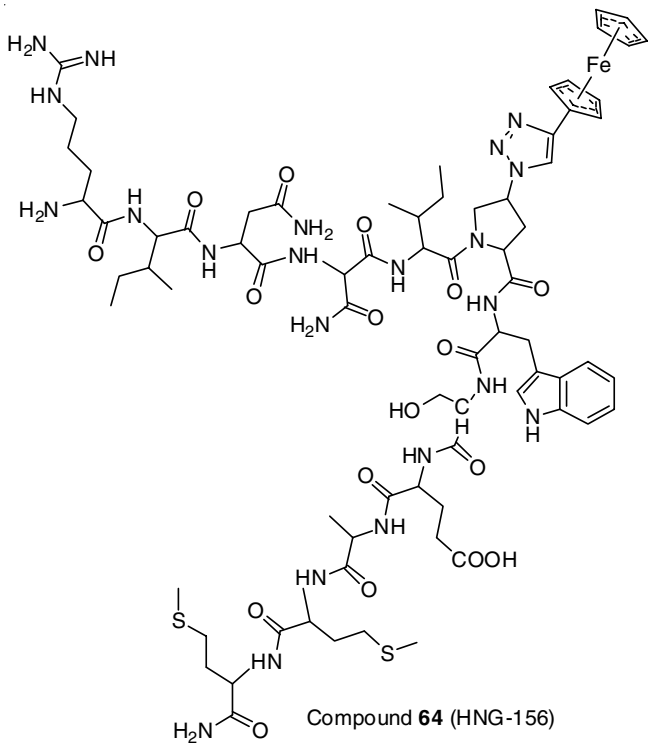
Compound **63a-c**

R: a = H, b = Br, c = Cl

alternatives, with minimal side effects such as a topical microbicides or an oral preexposure prophylactic (PrEP).

Antiviral activity of HNG-156 (most effective antiviral peptide triazole), alone and in combination with other entry inhibitors, was studied by McFadden *et al*. [59]. Screening of the compounds for inhibitory extent, cytotoxicity, and efficacy against HIV-1 demonstrated that HNG-156 inhibited activity of group of subtype B and C isolates of HIV-1. Moreover HNG-156 inhibited cell infection caused by replication-capable isolates of HIV-1. HNG-156 was found to possess excellent inhibitory effect, when it was combined with various entry inhibitors or tenofovir, which is reverse transcriptase inhibitor.

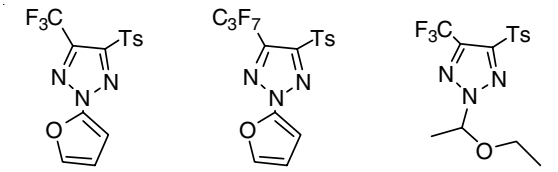
Overall HNG-156 is a non-cytotoxic, possesses broad inhibition profile and can be paired with several other inhibitors of the HIV-1. It can be constructively combined with many entry inhibitors at the higher concentrations likely to be used as treatment. This study will encourage the researchers to design and synthesize peptide triazole family inhibitors of HIV-1.



Compound **64** (HNG-156)

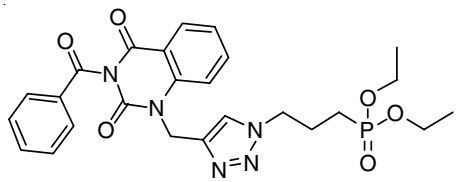
Anti-Epstein-Barr virus (EBV) activity and cytotoxicity of the synthesized pyranosyl derivatives of triazoles was reported by Kanishchev *et al*. [60]. Some of the compounds exhibited high selectivity index when they were evaluated for anti-EBV activity (PCR-method) cytotoxic nature (trypan blue and MTT

methods). Out of 15 compounds screened, 2-furan-2-yl-4-(toluene-4-sulfonyl)-5-trifluoromethyl-2*H*-[1,2,3]triazole (compound **65a**) and 2-furan-2-yl-4-heptafluoropropyl-5-(toluene-4-sulfonyl)-2*H*-[1,2,3]triazole (compound **65b**) at 2.5 μM concentrations showed 100% and 81% inhibition of EBV replication, respectively. 2-(1-Ethoxyethyl)-4-(toluene-4-sulfonyl)-5-trifluoromethyl-2*H*-[1,2,3]triazole (compound **65c**) showed clear dose-dependent action with 2.8 μM concentrations resulting in 20% EBV replication inhibition, while in 28 μM concentration, 100% inhibition was observed.



Compound **65a** Compound **65b** Compound **65c**

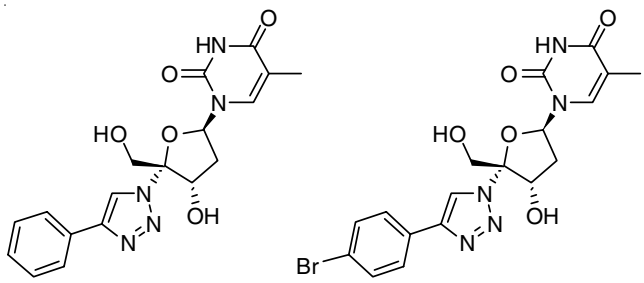
Antiviral activity of 1,2,3-triazoloacyclonucleotides against a wide range of RNA of DNA viruses and proliferation inhibition activity against HeLa cells , murine leukemia (L1210), human T-lymphocyte (CEM) was reported by Glowacka *et al.* [61]. Compound **66** was found active against feline herpes virus (EC_{50} = 24 μM) and HSV-1, HSV-2 (herpes simplex viruses) (EC_{50} = 17 μM). Proliferation inhibition activity of CEM cells was also observed for most of compounds.



Compound **66**

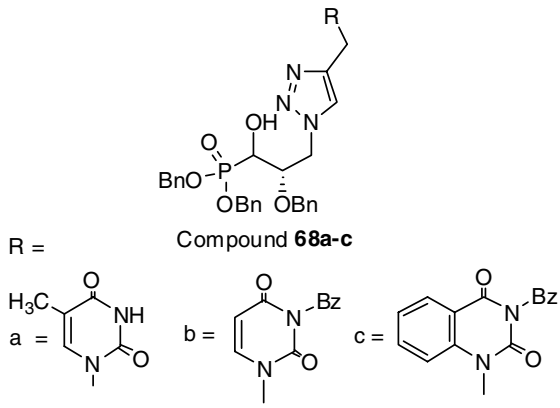
Antiviral activity of antiviral 4′-(1,2,3-triazol-1-yl)thymidines was reported by Vernekar *et al.* [62]. Screening against HIV-1 with a cytoprotection assay based on viral cytopathic effects demonstrated that two compounds *viz.* **67a** and **67b** exhibit significant antiviral activities whereas four other in the series exhibit modest (18-31%) cell protection. However, rest of analogues of the series were either marginally active or completely inactive. A parallel cell control of these compounds with mock infection revealed that these 4′-triazole analogues do not exhibit cytotoxicity, which encouraged researchers for additional screenings against three RNA viruses: influenza A, WNV and HCV. The screening results exhibited that with the exception of the moderate inhibitory activities observed with a few analogues against HIV-1 and/or influenza A virus, ADRT-derived triazoles generally lack the potency to be considered viable antiviral scaolds.

Antiviral and proliferation inhibition activity of ω-(1*H*-1,2,3-triazol-1-yl)(polyhydroxy)alkylphosphonates was reported by Glowacka *et al.* [63]. The *in vitro* antiviral potential was studied using wide variety of RNA and DNA viruses whereas cytostatic potential was studied using murine leukemia (L1210), CEM and HeLa cells. Compound **68a** demonstrated



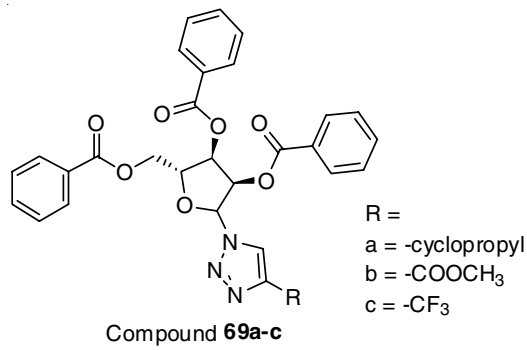
Compound **67a** Compound **67b**

antiviral activity against Influenza A with EC_{50} =20 μM and MCC > 100 μM, CC_{50} >100 μM in MDCK cell culture. Whereas compound **68b** exhibited activity against vesicular stomatitis virus (EC_{50} = 9) and respiratory syncytial virus (EC_{50} = 12 μM) in HeLa cells. Compound **68c** exhibited antiviral activity against both kinds of herpes simplex viruses *i.e.* HSV-1 (EC_{50} = 2.9) and HSV-2 (EC_{50} = 2 4 μM) in HEL cells and feline herpes virus in CRFK cells (EC_{50} = 4 μM). However, compound **68c** was cytotoxic towards normal cells. Other synthesized compounds also caused some inhibition of proliferation of L1210, CEM and HeLa cells (IC_{50} = 4-50 μM).



Compound **68a-c**

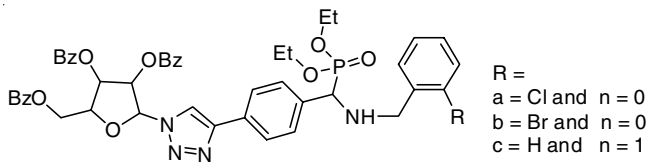
Antiviral activity of nucleoside ribavirin analogs was reported by Ferreira *et al.* [64]. The ribavirin analogs **69a-c** were screened against Inuenza A , HSV- 1 replication and HIV-1 reverse transcriptase (HIV-1 RT), when compound **69b** exhibited most potent inhibitory action against Inuenza A (IC_{50} = 14 μM) and HIV-1 RT, (IC_{50} = 3.8 μM).



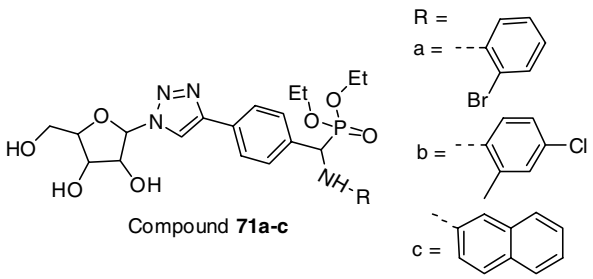
Compound **69a-c**

Antiviral activity of a series of newly synthesized ribonucleosides of 1,2,3-triazolylbenzylamino phosphonates was

reported by Ouahrouch *et al*. [65]. The compounds were synthesized *via* iodine catalyzed Kabachnik-Fields reaction and copper catalyzed cycloaddition reaction. All the synthesized compounds were screened against wide variety of DNA and RNA viruses like herpes simplex viruses (HSV-1 & 2, HIV-1 & 2, vesicular stomatitis virus (VSV), acyclovir-resistant virus (TK - Kos, ACV-1), varicella-zoster virus (VZV),vaccinia virus, adenovirus-2, human cytomegalovirus (HCMV), Coxsackie virus B4, RSV, parainuenza-3 virus, Sindbis virus, reovirus-1, Coxsackie virus B4, Punta Toro virus and feline corona virus (FIPV), *etc*. Compounds **70a-b** caused modest inhibition of RSV, compound **70c** caused modest inhibition of Coxsackie virus B4. Whereas compounds **71a-c** exhibited the modest inhibitory activity against varicellazoster virus.

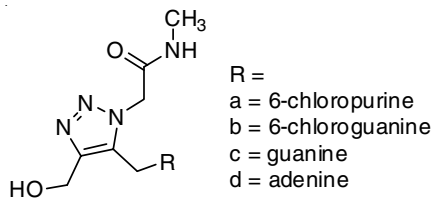


Compound **70a-c**



Compound **71a-c**

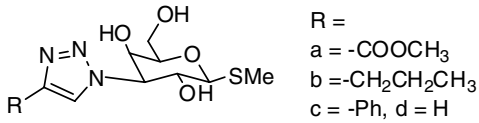
Antiviral activity of triazole-purine nucleoside analogs synthesized *via* Huisgen 1,3-dipolarcycloaddition was studied against various types of herpes viruses using HEL cell-based assays as reported by Wen *et al*. [66]. However, none of the compound **72a-d** exhibited significant antiviral activity.



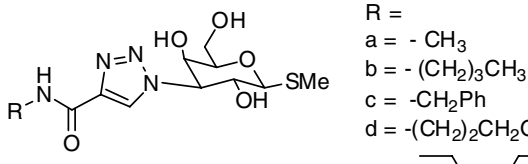
Compound **72a-d**

Anti-inflammatory activity: Inflammation is our body's immune response to injury caused to our cells due to internal or external reasons. However, most of time inflammation is accompanied by irritating pain any damage to our body parts may not be able to heal without inflammation. Moreover, at the same time chronic inflammation may lead to rheumatoid arthritis and even cancer. Hence, there is always a need for synthesizing safe and effective therapeutic non-steroidal anti-inflammatory drugs so as to minimize safety and tolerability concerns associated with currently available drugs. Triazole moiety is one such choice, which can be exploited to make NSAIDs.

Anti-inflammatory and antitumor activities of triazole-galactoside conjugates bearing substituents at the C-4 of triazole was reported by Salameh *et al*. [67]. These compounds **73a-e** and **74a-e** were found to exhibit inhibitor action on galectin-3, a protein rinsible for tumor and inflammation. The K_d value was as low as 107 μM, equivalent to the natural disaccharide inhibitors lactose and *N*-acetyllactosamine.

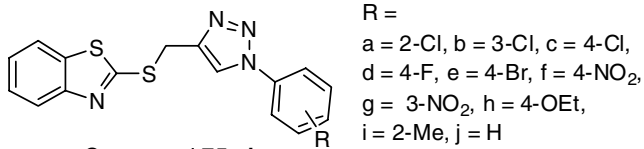


Compound **73a-e**



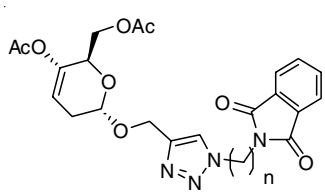
Compound **74a-e**

Anti-inammatory activity of 2-mercapto benzothiazole-triazoles conjugates synthesized using click chemistry was reported by Shafi *et al*. [68]. Screening of compounds revealed that compound **75d**, is a potent as well as selective COX-2 inhibitor (COX-2/COX-1 = 0.44). Compounds **75a**, **d**, **e** and **f** were found to possess good anti-inammatory potential in carrageenan-induced hind paw edema as compared to reference ibuprofen. These four compounds when, further explored for their antinociception activity by writhing test, showed a comparable activity with the reference ibuprofen. Further none of the tested compound cause gastric ulceration as revealed by ulcerogenic studies.

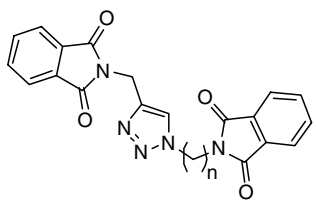


Compound **75a-j**

Anti-inammatory activity of triazole-phthalimide derivatives was reported by Oliveira Assis *et al*. [69], where the synthesized triazole derivatives were obtained in decent yields *via* 1,3-dipolar cycloaddition. The synthesized compounds **76a-c** and **77a-c** exhibited decent anti-inammatory activity against inammation induced in right hind paw of Swiss white mice by carrageenan . The best in the series were compounds **76b** and **77c**, which reduced carrageenan-induced edema by 69% and 56.2%, respectively.

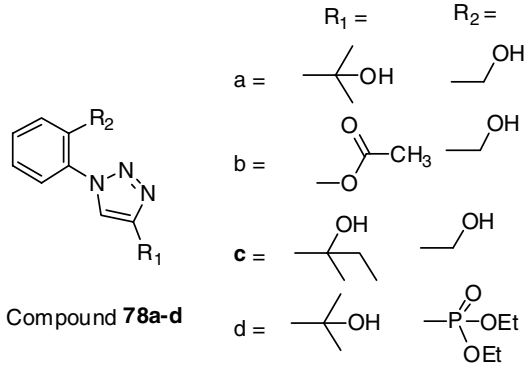


Compound **76a-c** {n = 2, 3, 4}



Compound **77a-c** {n = 2, 3, 4}

Anti-inflammatory activity of phenyl-1*H*-1,2,3-triazole derivatives was reported by Kim *et al.* [70]. The synthesized compounds were screened using xylene-induced ear edema model in rats. Compounds **78a-d** showed more potent activity as compared to diclofenac at the same dose (25 mg kg^{-1}). Further SAR was investigated using three-dimensional quantitative structure-activity relationships (CoMFA) in xylene-induced ear edema. The study showed that compound **78c** exhibited the best anti-inflammatory activity in ear edema induced by xylene. *In silico* docking was used to study molecular binding mode between compound **78c** and COX-2.

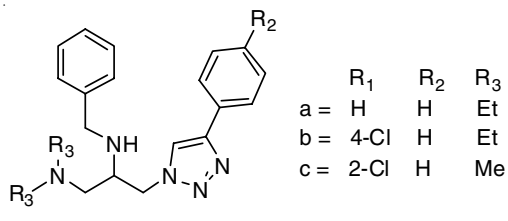


Compound **78a-d**

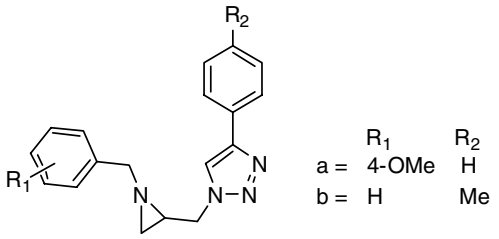
Antiplasmodial activity: Malaria which is still a a major health issue, particularly in developing countries like India is caused by four different species of *Plasmodium viz. P. ovale*, *P. falciparum*, *P. malariae* and *P. vivax*. According to WHO, it affects 40% of the global population, with annual death rate of one million people on an average. Chemotherapy is still the method for treating of this disease in spite of recent developments in the advancement of a vaccine. As the number of drug resistance strains has increased, there is ever increasing need to synthesize new anti-plasmodial drugs so as to overcome this resistance.

The anti-plasmodial activity of compounds **79a-c** and **80a-b** triazole derivatives was reported by D'hooghe *et al.* [71]. These compounds were synthesized by CuAAC reaction by treating *N*-(arylmethyl)aziridine azides with arylacetylene in CH_3CN and refluxing reaction mixture for 16 h. Finally, microwave assisted ring opening of aziridine moiety of newly synthesized 2-[(1,2,3-triazol-1-yl)methyl]aziridines by diethlyamines was carried out to synthesize functionalized aminopropanes as potential antimalarial agents. *In vitro* screening for anti-plasmodial activity against a chloroquine sensitive strain of *P. falciparum* (D10) revealed that compounds **79a-c** showed anti-plasmodial activity (IC_{50} values = 11.3 to 25.9 µM), whereas screening against, another chloroquine resistant strain of *P. falciparum* (Dd2) showed that compound **79c** exhibited anti-plasmodial activity with IC_{50} values 13.03 µM . Moreover, compounds **80a-b** also exhibited weak anti-plasmodial activity.

Antimalarial activity of 4-aminoquinoline-triazole hybrids and 4-aminoquinoline-triazine-triazole hybrids against two strains of *Plasmodium falciparum* (D6 and W2) was studied by Manohar *et al.* [72]. Screening of thirty-two compounds revealed that some of them possessed encouraging antimalarial

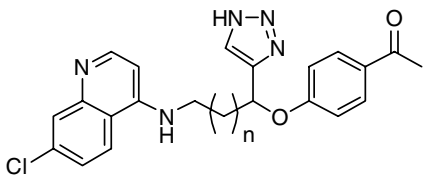


Compound **79a-b**

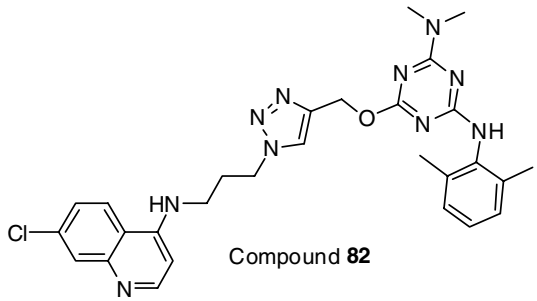


Compound **80a-b**

activity with no toxicity against vero cells. Among this series of analogues, compound **82** was the most potent analogue against D6 (IC_{50} = 0.58 µM) and W2 (IC_{50} = 0.73 µM). Simple aliphatic analogues of compound **81a-b** containing $COCH_3$ functional group at *para*-position of benzene ring displayed enhanced antimalarial activity against chloroquine-sensitive as well as chloroquine-resistant strains. Further study revealed that compounds with three carbon atom spacer showed better antimalarial activity than two carbon atoms. This may be due to the increase in lipophilicity as the same trend was observed in analogs of both compounds **81** and **82**.



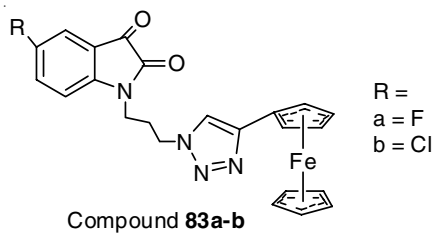
Compound **81a-b** {n = 1 & 2}



Compound **82**

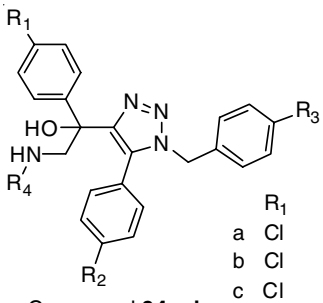
The anti-plasmodial activity of triazole-isatin-ferrocene conjugates against chloroquine-sensitive (3D7) and chloroquine resistant (W2) strains of *P. falciparum* was reported by Kumar *et al.* [73]. Among the various compounds synthesized, the conjugates **83a** and **83b** exhibited most potent activity with no cytotoxicity. Compound **83a** was most effective against 3D7 (IC_{50} = 3.76 µM) and compound **83b** was found most potent against W2 strains (IC_{50} = 4.58 µM).

Anti-plasmodial (*in vitro*) and antimalarial efficacy (*in vivo*) of a α-amino alcohol imbedded 1,2,3-triazoles was done by Devender *et al.* [74]. The anti-plasmodial activity against



Compound **83a-b**

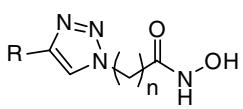
chloroquine-sensitive (Pf3D7) strain and chloroquine-resistance strain (PfK1) was evaluated which showed that compounds **84a-b** were most active against Pf3D7 with IC_{50} = 0.87 and 0.3 μM, respectively. Compounds **84c-d** on the other hand exhibited greater *in vitro* activity the reference drug against PfK1 with IC_{50} = 0.5 μM. Further studies revealed that p53 protein levels substantially increased when the most active compounds were administered.



	R_1	R_2	R_3	R_4
a	Cl	Br	H	4-bromophenyl
b	Cl	isopropyl	H	4-bromophenyl
c	Cl	Cl	H	3,4-difluorophenyl
d	Br	H	H	4-bromophenyl

Compound **84a-d**

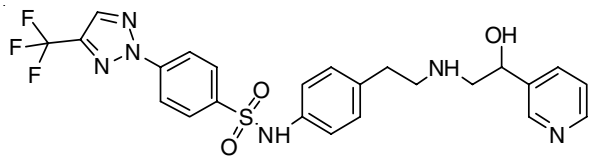
Antimalarial and antileishmanial activities of aryltriazolyl-hydroxamates based histone deacetylase inhibitors (HDACi) was studied by Patil *et al.* [75]. SAR study revealed that changing the chain length of spacer group (n value) with specific cap group substitution greatly affects the antimalarial and antileishmanial activities of these histone deacetylase inhibitors (HDACi). For a given cap group, the optimum activity was with n = 5 or 6. Most of the synthesized compounds **85a-k** exhibited selective cytotoxicity to the plasmodium parasites, which was much higher as compared to standard HDACi. Moreover, some of them also exhibited antileishmanial activity almost equivalent to that of miltefosine, the only available oral drug for visceral leishmaniasis. The antiparasitic attributes of these compounds were in good agreement with their anti-HDAC activities.



Compound **85a-k**

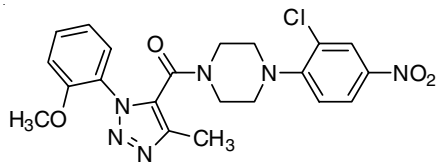
a: n = 7, R = Ph; b: n = 6, R = 2-Tol; c: n = 8, R = Ph
d: n = 7, R = 3-Bp; e: n = 7, R = DMA; f: n = 8, R = 3-Bp
g: n = 8, R = DMA; h: n = 7, R = PyP; I: n = 6, R = 3-Py
j: n = 7, R = Nap; k: n = 7, R = 3-Py

Adrenergic receptor agonists: β_3-Adrenergic receptor agonists activity of benzenesulfonamide substituted 1,2,3-triazoles **86** was reported by Brockunier *et al.* [76]. Triflouoromethyl-benzyl analogue of compound was found to be most potent with β_3 EC_{50}'s of 14 nM and with 1500 times more selectivity over binding to both β_1 and β_2 receptors. Moreover, lipolysis stimulation in the rhesus monkey (ED_{50} = 0.36 mg/kg) was also reported. Its bioavailability in the dogs was 25%.



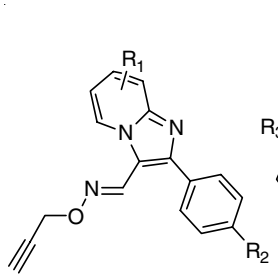
Compound **86**

Anti-influenza activity: Anti-influenza activity of newly synthesized anti-influenza A agents was reported by Cheng *et al.* [77]. Nucleozin, an NP inhibitor a known anti-influenza moiety was used as lead molecule for synthesizing new series of triazole-carboxamide conjugates. Screening of compounds for anti-influenza revealed that compound **87** was most potent replication inhibitor of H3N2 and H1N1 strains of influenza A (IC_{50} range = 0.5 to 4.6 μM). The same compound was found as highly potent replication inhibitor of other strains of influenzas with IC_{50} values in sub-μM range. It was found effective against amantadine-resistant A/WSN/33 (H1N1), H5N1 (RG14) and oseltamivir-resistant A/WSN/1933 (H1N1, 274Y). *In silico* studies performed on compound **87** suggested that its inhibition activity might be due to its direct attack on influenza virus A nucleoprotein.



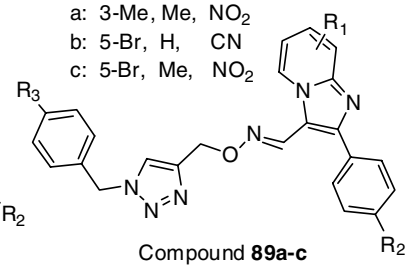
Compound **87**

Anticonvulsant activity: Anticonvulsant activity of 2-arylimidazo[1,2-*a*]pyridines bonded to 1,2,3-triazoles was reported by Ulloora *et al.* [78]. Triazole derivatives **89a-c** were prepared from biologically active compound **88** by treating it with sodium azide and appropriate benzyl halide i.p.o CuI as catalyst *via* click chemistry. The anticonvulsant study was screened by using MES (maximal electroshock seizure method and scPTZ (subcutaneous pentylenetetrazol) while rotarod method was used to see their toxicity. Compounds **89a-c** were most effective with potency same as standard drug diazepam. The tested compounds demonstrated full protection against seizure, comparable with standard drug. Most of them were non-toxic.



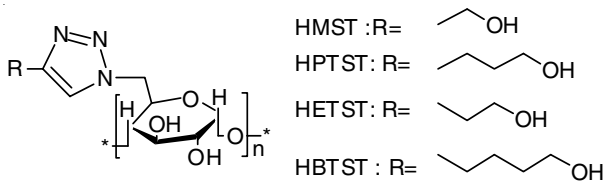
Compound **88**

	R_1	R_2	R_3
a:	3-Me,	Me,	NO_2
b:	5-Br,	H,	CN
c:	5-Br,	Me,	NO_2



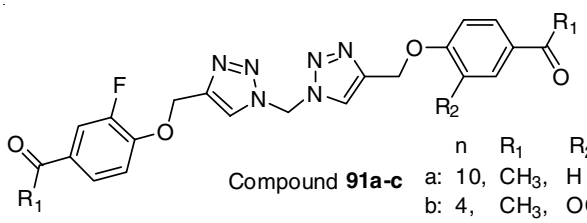
Compound **89a-c**

Antioxidant activity: Antioxidant activity of triazole-starch conjugates was reported by Tan *et al*. [79]. The compounds were synthesized by copper(I) catalyzed Huisgen azide-alkyne reaction. The antioxidant activity of compounds **HMTST, HETST**, **HPTST**, and **HBTST** were evaluated *in vitro* against three types of radicals *i.e*. hydroxyl, DPPH and superoxide-radical. The study revealed that the tested compounds exhibit remarkable improvement in antioxidant property over starch. The scavenging effect were higher than 60% at 1.6 mg/mL against hydroxyl and DPPH radical, whereas it was more than 90% against superoxide radical at 0.1 mg/mL. The antioxidant activity increased in the order: starch < **HMTST** < **HETST** < **HPTST** < **HBTST**. Antioxidant activity was in line with the electron releasing potential of different substituents (R) present at C-4 of triazole.



Compound **90**

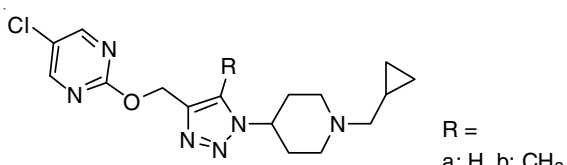
Antioxidant properties of a series of newly synthesized symmetric *bis*-1,2,3-triazole compounds *via* click chemistry were reported by Dugdu *et al*. [80]. These compounds when screened for antioxidant activity showed that compound **91a** was most effective AChE inhibitor, whereas, compound **91b** was strongest inhibitor DPPH radical and compound **91c** was most effective for SOD activity.



Compound **91a-c**

	n	R_1	R_2
a:	10,	CH_3,	H
b:	4,	CH_3,	OCH_3
c:	3,	CH_3,	OCH_3

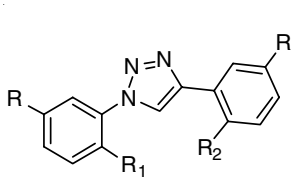
Neuroprotective activity: Neuroprotective activity of triazole-based fibroblast growth factor receptor modulators was reported by Sakai *et al*. [81]. Of all synthesized analogs, compound **109**, showed improved the neuroprotective activity and negligible mechanical brain injury (MBI) activity. An introduction of -CH_3 group at the position-5 of compound **92**, a markedly enhanced the neuroprotective activity *i.e*. in compound **92b**. Compounds **92a-b** may be potentially useful agents for the therapy of neurodegenerative diseases. Because of the reduced phosphor lipidosis risk, sufficient systemic exposure, and their high CNS penetration.



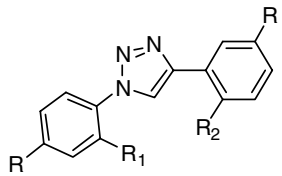
Compound **92a-b**

R =
a: H, b: CH_3

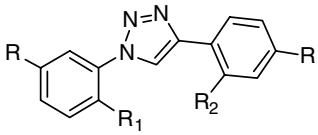
Antiprotozoal activity: Antiprotozoal activity of a series of 60 dicationic triazoles was reported by Bakunov *et al*. [82]. The antiprotozoal activity of all sixty compounds was evaluated, when the activity was found to be markedly influenced by nature and the position of cationic moiety. Eight analogues displayed anti-trypanosomal activity with IC_{50} less than 10 nM. The thirty-nine other analogues were more effective against *P. falciparum* than pentamidine, while eight others were more effective than artemisinin. Compound **96o** exhibited anti-plasmodial activity with IC_{50} value of 0.6 nM. Seven compounds were tested against acute mouse model of African trypanosomiasis (with dosages of 4 × 5 mg/kg) and they cured 75%. Similarly, another compound **96a** , at dosage of 4 × 1 mg/kg, cured all infected mice with better anti-trypanosomal effectiveness than standard drug melarsoprol.



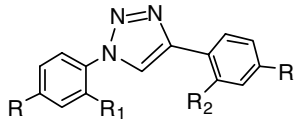
Compound **93a-o**



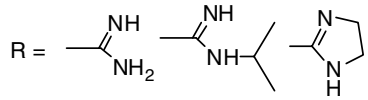
Compound **94a-o**



Compound **95a-o**

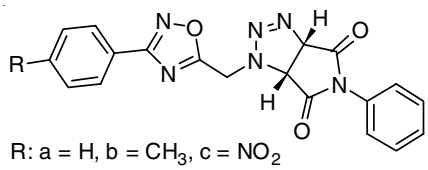


Compound **96a-o**



R_1 = H; R_2 = H, OMe, OH

Antiprotozoal activity of oxadiazolyl-pyrrolo-triazole-diones were reported by Durust *et al*. [83]. The compounds were synthesized *via* 1,3-dipolar cycloaddition reaction and screened *in vitro* for anti-protozoal potency against *Trypanosoma brucei rhodesiense*, *Trypanosoma cruzi*, *Leishmania donovani* and *Plasmodium falciparum*. Compounds **97a-c** showed activity against all four parasitic species with variable potencies. The most potent activity was shown by compound **97a** against *Trypanosoma brucei rhodesiense* with (IC_{50} value 7.0 µg/mL) followed by compounds **97b** and **97c** with IC_{50} values (8.4 and 8.0 µg/mL).

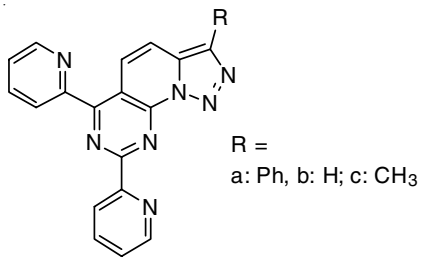


R: a = H, b = CH_3, c = NO_2

Compound **97a-c**

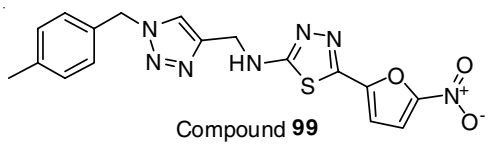
Antiprotozoal and DNA photocleaver activity of newly synthesized triazolopyridopyrimidines analogs was reported by Adam *et al*. [84]. Compounds **98a-c** were screened for anti-protozoal potency against four different species of Leishmania

(*L. amazonensis*, *L. infantum*, *L. braziliensis*, *L. guyanensis*). Compounds **98a** and **98c** exhibited more *in vitro* activity and selectivity against *L. infantum* amastigotes than standard miltefosine, whereas *in vivo* study of compound **98a** showed high antileishmanial activity against *L. infantum*.



Compound **98a-c**

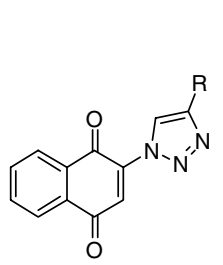
Antiprotozoal activity of triazole bearing 5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-amines against promostigote was reported by Tahghighi *et al*. [85]. The compounds were synthesized *via* click chemistry and screened *in vitro* for antileishmanial activity when they found to possess good activity against the promastigote (Leishmania major). Compound **99** was most active as it signicantly reduced the number of intracellular amastigotes.



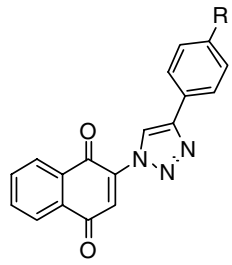
Compound **99**

Antiparasitic compounds which included seven naphthoquinones coupled to triazoles (compounds **100a-b**), ten α-lapachone based triazoles (compound **101**) and five Nor-β-lapachone based triazoles (compound **102**) were reported by Guimaraes *et al*. [86]. The compounds were screened against antimony resistant strains of promastigote for antileishmanial activity, when target compounds were found more effective than an antimonial drug, (IC_{50} values = 1.0 to 50.7 mM). Highest antileishmanial activity was detected with Nor-β-lapachone derivatives, with selectivity index (CC_{50} /IC_{50}) ranging from 10-15. One of the tested compounds showed cross-resistance in Sb-resistant Leishmania, which may be of help to investigate the multidrug resistance in Leishmania parasites.

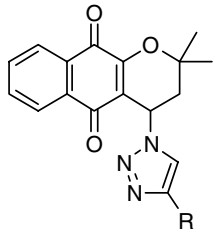
Miscellaneous activity: Cannabinoid CB1 receptor antagonists activity of a series of newly synthesized 1,2,3- triazole derivatives was reported by Hou *et al*. [87]. Initially synthesized compounds were modified by introducing additional methylene group between the triazole and the carbonyl group to increase the rotational freedom of the carbonyl group. Triazoles **103** and **104** found to possess enhanced efficacy to the CB1 receptor with IC_{50} and EC_{50} values of these triazoles in almost nanomolar range Among the triazoles screened, symmetrical triazoles **103** with 4,5- *bis*-(2,4-dichlorophenyl) substituents are more effective than the unsymmetrical triazoles **104** with 4-(2,4-dichlorophenyl)-5-(4-chlorophenyl) substituents. The most potent were benzyl amides derivatives (**103a-h**). The best potent activity was shown by fluorinated benzyl amides (**103a**



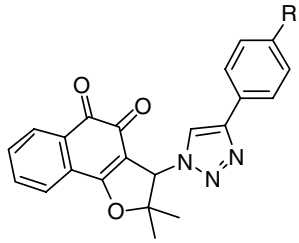
Compound **100a**



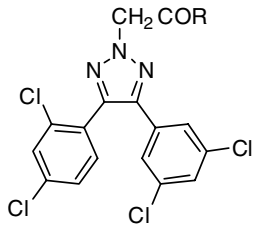
Compound **100b**



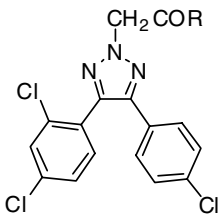
Compound **101**



Compound **102**



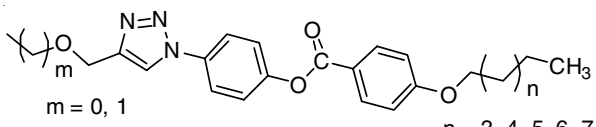
Compound **103a-h**



Compound **104a-c**

and **103b**) (IC_{50} < 20 nM). However, their screening for CB2 receptor exhibited that that they have very low affinity to CB2 receptor.

The mesomorphic properties of the heterocyclic liquid crystalline compounds with [1,2,3]-triazole ring at the terminal position was analyzed by Srividhya *et al*. [88]. The triazole moiety was introduced into the target compound *via* click chemistry reaction between aromatic phenolic azide and alkyl propargyl ethers. All the synthesized compounds exhibited thermotropic liquid crystalline mesophase.



Compound **105**

Conclusion

This review article has summarized various pharmacological activities exhibited by 1,2,3-triazoles. The pharmacolo-

gical activities discussed here to prove the biological importance of 1,2,3-triazole moiety. So, the literature review clearly demonstrates that 1,2,3-triazole ring containing a heterocyclic system has a wide range of medicinal applications. We hope that in the future many new biological profiles will be added to it and more probes shall be carried out to design new triazole based hybrids, which can bind to multiple targets so that effective treatment for diseases like cancer, Alzheimer's disease, *etc*. whose treatments are challenging in the field of medical sciences can be found. Thus by studying all the derivatives of 1,2,3-triazoles showing variety of activities, it can be concluded that that 1,2,3-triazole ring has been explored in past years and but still a lot of scope for future development of new drugs that could be better in terms of potency and lesser toxicity against various diseased conditions.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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