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REVIEW

1,2,3-Triazole Containing Hybrids as Potential Pharmacological Agents: A Review

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1,2,3-Triazoles constitute a versatile class of nitrogen containing five-membered heterocycles, exhibiting wide range of pharmacological properties which include antibacterial, antifungal, anticancer, antimalarial, antidiabetic, anti-inflammatory, antihypertensive and antioxidant, among various others. Medicinal chemists have been interested in this aromatic ring as a framework since the inception of click chemistry as considered as the building block of contemporary organic chemistry. Extensive research into this framework's linker characteristic has led to the synthesis and evaluation of numerous 1,2,3-triazole hybrids bearing a wide range of heterocyclic moieties as potential leads for various biological targets. This molecular hybridization has also added advantage of the improved pharmacological activity overcoming the problem of multiple drug resistance and reduced toxicity. This review summarizes the pharmacological activities of various 1,2,3-triazole containing hybrids and conjugates, covering articles published in past decade (2013 till date) and will be of great assistance to medicinal chemistry researchers in providing a useful direction for the future drug discovery.

Keywords: 1,2,3-Triazoles, Pharmacological activities, Molecular hybridization, Drug discovery.

INTRODUCTION

The incorporation of hetero atoms (*e.g.* N, O, S) other than carbon in the ring structure constitute heterocyclic compounds [1], however heterocyclic compounds with other heteroatoms like boron, iron phosphorus, magnesium, selenium, cobalt, arsenic, *etc.* are also common [2,3]. Heterocyclic compounds exhibit enhanced bioactivity because of the presence of heteroatoms, making them prevalent in several novel drugs. Moreover, heterocyclic compounds address the gap between chemistry and biology, where so much scientific discoveries and applications occur.

Among the heterocyclic compounds the most promising are five-membered nitrogen containing heterocycles-azoles [4-6]. For this reason, several azole-related publications were surveyed at the Scopus database (2013–2023) using the keywords *e.g.* triazole, tetrazole, pentazole, oxazole, imidazole and pyrazole. It was observed that triazole derivatives are most extensively studied owing to their synthetic and effective biological importance. In addition, it was also found that over the course of the last 10 years, the chemistry and biology of triazole derivatives, particularly 1,2,3-triazoles have become one of the most popular topics.

Triazoles, with molecular formula $C_2H_3N_3$ exists in two tautomeric forms *viz.* 1,2,3-triazole (**A**) and 1,2,4-triazole (**B**) (Fig. 1). In five-membered ring system, two nitrogen atoms are pyridine type and one nitrogen atom is a pyrrole-type. 1,2,3-Triazoles can be prepared easily by Cu(I) catalyzed Huisgen 1,3-dipolar azide-alkyne cycloaddition (CuAAC) reaction using click chemistry [7,8] and has received increasing attention over the past few years in synthetic chemistry, which led to the development of highly regioselective methodologies for 1,4-disubstituted 1,2,3-triazole synthesis (**Scheme-I**). Recently, various conventional and non-conventional methods for the synthesis of 1,2,3-triazole derivatives have also been adopted [9].

1,2,3-Triazole is a promising heterocyclic motif, its derivatives exhibit a wide variety of pharmacological properties, including antibacterial [10], antifungal [11,12], antimalarial [13], antileishmanial [14], antitubercular [15], antiviral [16], anticancer [17], antiepileptic [18], anti-inflammatory [19] and

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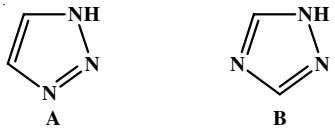
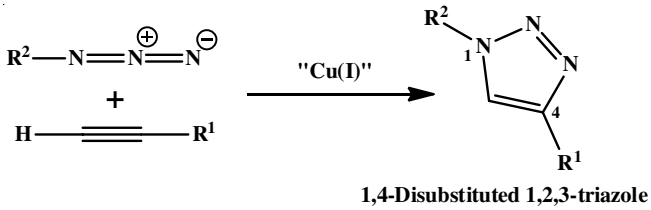


Fig. 1. Two tautomeric forms of triazole ring



Scheme-I: Synthetic route of 1,4-disubstituted 1,2,3-triazole using CuAAC reaction

α-glycosidase inhibitor activities, *etc.* [20]. Besides, several 1,2,3-triazole derivatives are already in the market and approved by FDA. Some examples are cefatrizine (broad spectrum cephalosporin antibiotic), tazobactam (β-lactum antibiotic), carboxyamidotriazole (anticancer drug) and rufinamide (anticonvulsant drug), *etc.* (Fig. 2). Based on the pharmacological importance of 1,2,3-triazole derivatives, conjugates and related compounds, an extensive assessment was conducted covering publications published between 2013 and 2023.

Pharmacological activities of 1,2,3-triazole derivatives: 1,2,3-Triazole acts as an effective amide surrogate in bioactive molecules possessing strong dipole moment (5 Debye) in comparison to amide (4 Debye) [21]. Some unique features like hydrogen bonding, π-stacking, dipole-dipole interactions, *etc.* make 1,2,3-triazole units an important scaffold in medicinal chemistry, binding efficiently with the biological targets due to their improved solubility. By means of weak bond interactions, they are capable of interacting with diverse protein/enzyme receptors in organisms, making them analogous to amides, carboxylic acids, and esters in terms of their biological properties. The pharmacological activities of 1,2,3-triazole derivatives can be classified into the following sections:

Antimicrobial activities: Bacterial infections are threat to public health and the situation is exacerbated by the emergence of multiple drug resistance creating obstacles in the disease treatment [22,23]. Due to rise in resistance of bacteria to current approved antibacterial agents, it is necessary to develop new inhibitors as chemotherapeutics against resistant bacterial pathogens [24]. Similarly, fungal infections are responsible for dangerous diseases both in humans as well as in plants [25,26] due to acquired multi-drug resistance. For encountering the menace of multi-drug resistance in microbial strains, the discovery of novel organic compounds as antimicrobials is a promising approach.

In this approach, Yadev *et al.* [27] using click chemistry synthesized a library of new pyrrole based chalcones linked 1,2,3-triazoles and evaluated their *in vitro* antimicrobial screening. All the prepared derivatives revealed their potential antimicrobial properties with minimum inhibition concentration (MIC) range of 0.0647 to 0.0127 μmol/mL. The potent derivative is the compound **1** (MIC = 0.0127 μmol/mL) and was found effective towards *P. aeruginosa*. They also evaluated the antimicrobial evaluation and synthesis of some pyrrole-1,2,3-triazole hybrids containing chalcone and amide moiety, wherein compounds **2a-b** with MIC value 1.56 μg/mL exhibited the highest efficiency toward *E. coli*, equivalent to the reference drug ciprofloxacin with MIC value 1.56 μg/mL [28].

A series of novel quinazoline-4(3*H*)-one linked triazole conjugates were synthesized by Manhas *et al.* [29] using CuAAC catalyst. The *in vitro* antibacterial activities of these compounds were evaluated using commercial drugs ciprofloxacin, ampicillin and levofloxacin as reference. Compounds **3a-d** exhibited potent activity inhibiting all bacterial strains at a concentration of 10 μg/mL with the zone of inhibition (ZI) values ranging between 8 and 33 mm. Amongst these, compound **3d** emerged as the most active possessing 12-fold superior activity than ampicillin against *Klebsiella pneumoniae*.

Similarly, Chen *et al.* [30] synthesized few novel triazole derivatives efficiently for their potential glucosamine-6-phos-

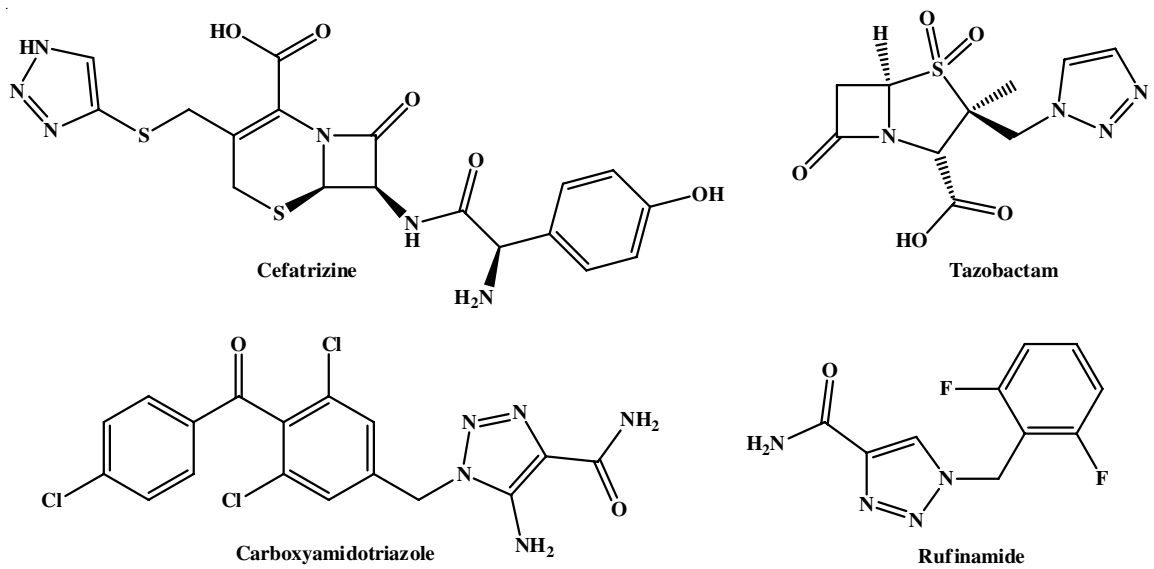


Fig. 2. Structure of some approved drugs containing 1,2,3-triazole rings

phate synthase (GlmS) inhibitor activity. The derivatives have been tested for their antifungal and enzyme inhibitory activity. The activity data on *Sclerotinia sclerotiorum* of compounds **4a-f** were particularly prominent (85.6%, 83.1%, 87.6%, 86.8%, 87.7% and 89.6%, respectively). Using click chemistry, a series of 1,2,3-triazole–thymol derivatives starting from thymol were reported by Addo *et al.* [31] and their antimicrobial acti-vities were evaluated against seven bacterial strains *viz. E. coli* (ATCC-25922), *S. aureus* (ATCC25923), methicillin resistant *S. aureus* (MRSA), *P. aeruginosa* (ATCC29853), *E. coli* (ESBL), *K. pneumoniae* (NCTC13438) and meropenem resistant *E. coli.* The derivatives revealed variable but significant antibacterial activity against the tested bacterial strains. Compound **5** was a lead with higher antibacterial activity (mean zone of inhibition of 38.7 mm) as compared to the positive control, ampicillin (zone size 30.0 mm) and shows three-fold potential than thymol at a concentration of 100 µg/mL (mean zone of inhibition of 11.0 mm) against MRSA.

Novel 1,2,3-triazole–ciprofloxacin conjugates were reported by Agarwal *et al.* [32] for their *in vitro* antimicrobial activity against various bacterial strains. Three compounds **6d-f** (MIC = 0.78 µM) showed strong activity and compound **6c** (MIC = 1.56 µM) was potential against clinical *S. typhi*. Compound **6a** with MIC value 3.12 µM was efficient against *S. aureus* (ATCC 25923) strain and clinical *S. typhi* strain. Similarly, compound **6b** (MIC = 3.12 µm) showed considerable bioactivity against *S. aureus* when compared with the reference drug, ciprofloxacin with MIC value 6.25 µM. Gandham *et al.* [33] reported a novel synthesis of dihydrobenzoxepin-1,2,3-triazole scaffolds and evaluated their pharmacological potential against different Gram-positive, Gram-negative bacterial strains and also against some fungal strains. Compounds **7a-e** were the most effective in respect of their antibacterial and antifungal activities with zone of inhibition ranging 33-30 mm and 32-28 mm, respectively and with MIC values of 1.2, 0.85, 2.1, 2.9, 38.4 µg/mL and 1.8, 1.3, 1.5, 6.7, 2.8 µg/mL, respectively.

Sharma *et al.* [34] synthesized a chalcone bearing, amide linked 1,4-disubstituted 1,2,3-triazole hybrids as antimicrobial agents. The *in vitro* activity results against tested microbial strains revealed that compound **8a** as an excellent lead against *S. aureus* and *B. subtilis* with MIC = 0.0138 µmol/mL. Similarly, compound **8b** and **8c** (MIC = 0.01292 µmol/mL) also displayed good efficacy against *E. coli*, *S. aureus* and *A. niger*, while compound **8d** (MIC = 0.1256 µmol/mL) showed excellent activity against the fungal strains *C. albicans* and *A. niger*. Nehra *et al.* [35] synthesized a novel 1,2,3-triazole hybrids bearing 2- or 4-hydroxyphenyl benzothiazole and naphthalen-1-ol or 8-hydroxyquinoline. The hybrids were screened for antimicrobial activity using agar-well diffusion method against two Gram-positive and two Gram-negative bacterial strains. Comparatively better result was displayed by compound **9** (zone of inhibition ranging 15.5-17.6 mm against *E. coli*). Compound **9** also displayed the best antifungal activity against two studied fungal strains (*C. tropicalis* and *A. terreus*).

Rayudu *et al.* [36] reported the synthesis of a series of novel 1,2,3-triazolyl-pyrazole-chalcone derivatives for *in vitro* antimicrobial activity against four bacterial strains using ampicillin as control and against two fungal strains using ketoconazole as control. Compound **10a** showed a best activity against *B. subtilis* and *A. niger* (MIC_{50} = 7.9 µg/mL and 9.2 µg/mL, respectively) while as three compounds **10b-d** (MIC_{50} = 9.9 µg/mL, 6.6 µg/mL and 9.5 µg/mL, respectively) showed best activity against *A. niger*. The synthesis and *in vitro* antimicrobial properties of novel series of *bis*-1,2,3- and 1,2,4-triazoles was reported by Bitla *et al.* [37]. The *in vitro* antimicrobial activity was investigated against Gram-positive and Gram-negative bacterial strains and antifungal activity against *A. niger* and *S. cerevisiae*. Most of the compounds showed favourable antimicrobial activity (MIC = 3.9 µg/mL) and antifungal activity (zone of inhibition = 1.5-8.2 mm). Compounds **11a** (MIC = 4.1 ± 0.05 µg/mL) and **11b** (MIC = 3.9 ± 0.05 µg/mL) exhibited the best antimicrobial activity against *S. aureus* strain. Using multi-component reaction approach, Gondru *et al.* [38] also synthesized new series of 1,2,3-triazole-thiazole conjugates and reported their *in vitro* antimicrobial activity. Most of the compounds exhibited potent antibacterial activity (2.8 to 15.7 µM) against the strains tested. Compounds **12a-e** revealed potential anticandidal activity with the spectrum values 5.9-14.2 µM against various *Candida* strains.

In the goal to develop novel antibacterial agents Aarjane *et al.* [39] designed and synthesized novel acridone derivatives bearing 1,2,3-triazole nucleus. Among the synthesized compounds, compound **13** with MIC = 19.6 µg/mL displayed significant antibacterial activities against *S. aureus* (MRSA). Kaur *et al.* [40] proposed the convenient synthesis of β-lactam-1,2,3-triazole conjugates efficiently and reported their antibacterial activity *in vitro* against Gram-positive and Gram-negative bacterial strains. Compound **14a** and **14b** (MIC = 1.25 µg/mL) revealed to be the most potent against both *B. subtilis* and *P. aeruginosa*.

Abedinifar *et al.* [11] synthesized a novel series of benzofuran-1,2,3-triazole conjugates and evaluated their antifungal potential against different fungal strains at different concentrations (500 ppm and 1000 ppm). Among the synthesized compounds, compound **15** was the most active at a concentration of 500 ppm against wet brown-rot (*Coniophora puteana*) fungi (23.86% inhibition) and *Gloeophyllum trabeum* fungi (47.16% inhibition). Using the click chemistry approach, Akolkar *et al.* [41] reported the efficient synthesis of new 1,2,3-triazole-tethered coumarin conjugates. The antifungal activity *in vitro* results of the conjugates against various fungal strains like *C. albicans*, *A. niger*, *A. flavus*, *C. neoformans* and *F. oxysporum* revealed that compounds **16a-c** and **17a-b** to be potent comparing with miconazole. Most of the reported compounds exhibited antifungal activity with MIC values in the range 12.5 to 25 µg/mL against the tested fungal strains.

Tang *et al.* [42] reported the synthesis of hybrid compounds of 1,2,3-triazole moiety using the structure of pterostilbene as a scaffold to develop a novel anti-methicillin resistant *S. aureus* (MRSA) infection agent. Compound **18** proved to be the lead anti-MRSA agent (MIC = 1.2-2.4 µg/mL) and with a minimum bactericidal concentration (MBC) = 19.5-39 µg/mL. Yan *et al.* [43] synthesized carboxamide derivatives containing 1,2,3-triazole ring and evaluated their antifungal activities *in*

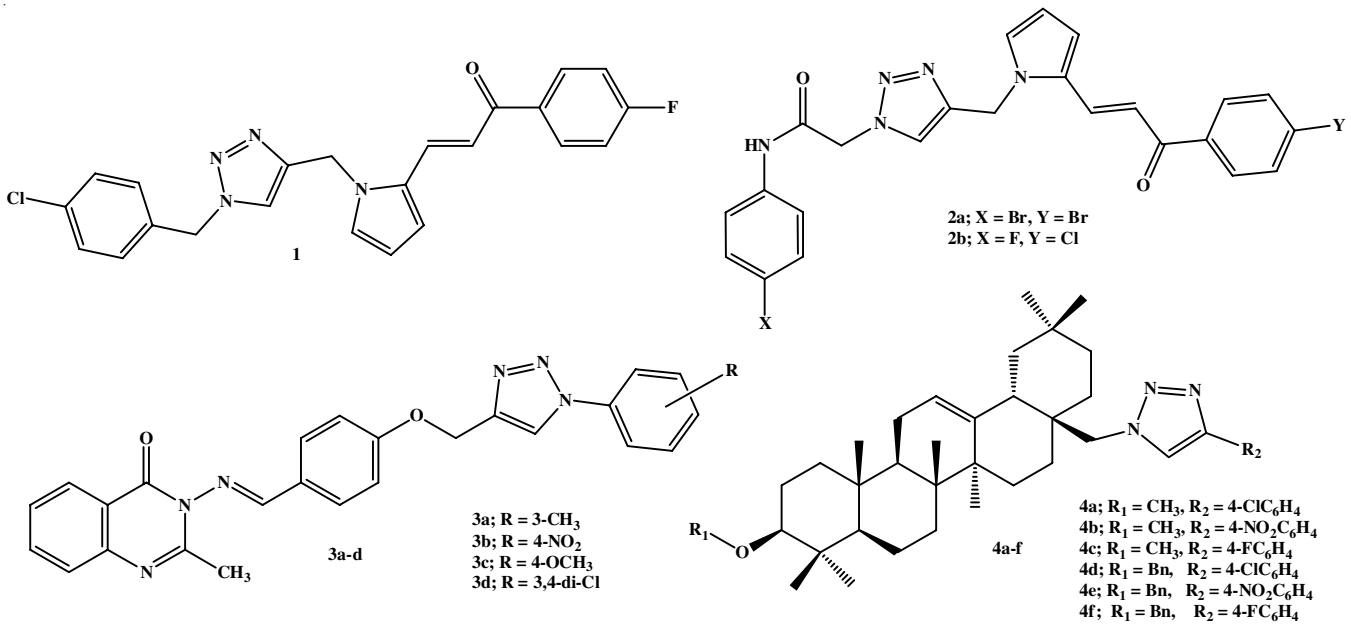
vitro against phytopathogenic fungi *Sclerotinia sclerotiorum*, *Botrytis cinerea*, *Rhizoctonia cerealis* and *Gaeumannomyces graminsis* using mycelia growth inhibition assay. Compound **19** against above strains demonstrated significant antifungal activity (IC_{50} = 1.08, 8.75, 1.67 and 5.30 µg/mL respectively), which is comparable to commercial succinate dehydrogenase (SDHI) boscalid. Compound **19** (at 200 µg/mL) was also found to suppressing cucumber grey mould, rape sclerotinia rot and wheat powdery mildew effectively caused by *Botrytis cinerea, Sclerotinia sclerotiorum* and *Blumeria graminis* fungi.

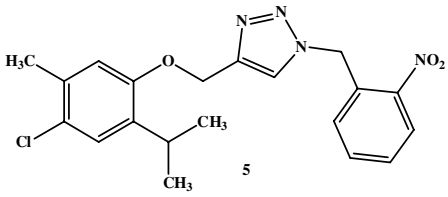
In like manner, synthesis of derivatives of 1,2,3-triazole were designed by Mishra *et al.* [44] as antimicrobial agents. The compounds possessed considerably better activity with some compounds in the series like **20a-e** exhibiting better activity against fungal strains *C. albicans* (MIC_{90} = 16 µg/mL) and *A. niger* (MIC_{90} = 32 µg/mL). Masood *et al.* [45] reported the synthesis of 1,2,3-triazole–quinazolinone conjugates employing the CuAAC reaction. All the synthesized compounds were evaluated for *in vitro* anticandidal activity against *Candida* strains *viz. C. albicans*, *C. glabrata* and *C. tropicalis*. The results demonstrated that compound **21** showed potent anticandidal activity against tested strains with IC_{50} in the range of 8.4 to 14.6 µg/mL. Similarly, a new series of 1,2,3-triazole derivatives were prepared by Wang *et al.* [46] and evaluated for their *in vitro* antifungal activity (utilizing the mycelium growth inhibition method) against phytopathogenic fungi. Compound **22** demonstrated potent anti-phytopathogenic activity against fungal strains (*R. solani*, *F. graminearum*, *S. sclerotiorum* and *M. oryzae*).

In order to afford 1,4-disubstituted-1,2,3-triazole chalcone and flavone derivatives, Kant *et al.* [47] utilized copper catalyzed click chemistry approach. The compounds were evaluated for their antibacterial activity using some Gram-positive bacteria (*S. aureus*, *E. faecalis*), Gram-negative bacteria (*P. aeruginosa*, *E. coli*, *S. boydii, K. pneumoniae*) and antifungal activity against some fungal strains and molds (*A. niger*, *A. fumigatus*, *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. neoformans*). Compounds **23a-c**, **25** and **27c** showed promising antibacterial activity while compounds **23d**, **24a**, **24b**, **25**, **26a-c**, **27a-b** showed promising antifungal activity in comparison to the standard drugs. In continuation of their interest, Kant *et al.* [48] also synthesized a series of novel *bis*-1,2,3-triazole linked ciprofloxacin conjugates and evaluated their *in vitro* antibacterial activities. The conjugates displayed enhanced activity against both Gram-positive and Gram-negative bacterial strains comparing to the parent drug ciprofloxacin. Compounds **28a-c** displayed two to ten-fold more potential activity against tested bacterial species than ciprofloxacin. In addition, compound **28d** possesses potent antibacterial activity (MIC = 1.09 µM) against bacterial strains *S. aureus*, *S. epidermidis*, *P. shigelloides* and *E. coli*) is 8 to 17-fold more potent than ciprofloxacin.

Starting from eight natural precursors, Irfan *et al.* [49] synthesized novel 1,2,3-triazole derivatives. The *in vitro* anticandidal activity of compounds performed against *C. albicans*, *C. glabrata* and *C. tropicalis* showed that compound **29** was found comparable to superior in activity (IC_{50} = 0.044 µg/mL, 12.022 µg/mL and 3.60 µg/mL, respectively) against three tested strains of *Candida* compared to fluconazole. Another series of eight novel 1,2,3-triazole derivatives were synthesized and screened for antifungal potential by Shaikh *et al.* [50]. Compound **30a-d** were found to be equally potent as that of miconazole and compound **30e** was found to be twice more active against *C. albicans* strain in comparison to miconazole and equally potent against *C. albicans* in comparison to fluconazole.

Petrova *et al.* [51] investigated a library of 1,2,3-triazole derivatives for antimicrobial and cytotoxic activities revealing that most of the compounds exhibited good inhibitory activity against a variety of microbial pathogens under consideration. Particularly the compound **31a** was found to be highly active (MICs ranging 1.1-4.4 µM) against all the tested bacterial strains with bactericidal concentrations (MBCs) ranging between 2.2-8.4 µM. Further, compound **31b** exhibited antifungal activity (MICs ranging 0.6-4.8 µM) and minimal fungicidal concentrations (MFCs) in the range 1.2-8.9 µM. Synthesis and anti-





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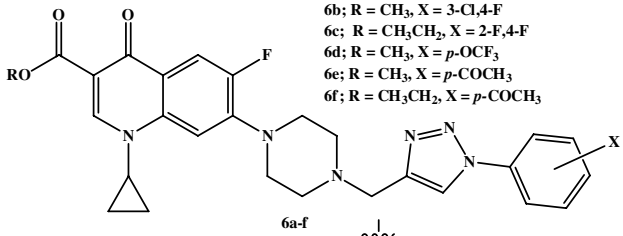
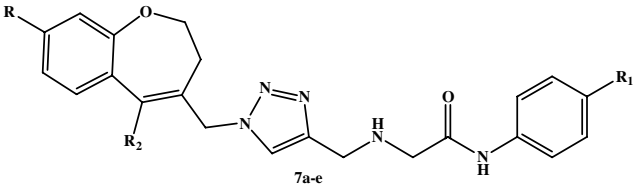


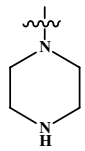
6a; R = $CH_3CH_2CH_2$, X = *p*-OCF_3
6b; R = CH_3, X = 3-Cl,4-F
6c; R = CH_3CH_2, X = 2-F,4-F
6d; R = CH_3, X = *p*-OCF_3
6e; R = CH_3, X = *p*-$COCH_3$
6f; R = CH_3CH_2, X = *p*-$COCH_3$

6a-f

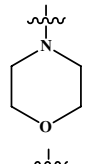


7a-e

7a; R = CH_3, R_1 = NO_2, R_2 =

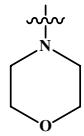


7b; R = CH_3, R_1 = Cl, R_2 =

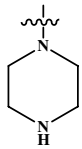


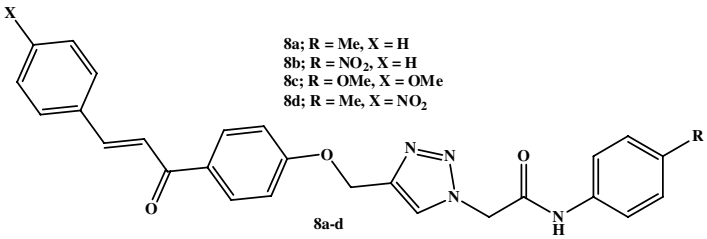
7c; R = OCH_3, R_1 = Cl, R_2 =

7d; R = Cl, R_1 = NO_2, R_2 =



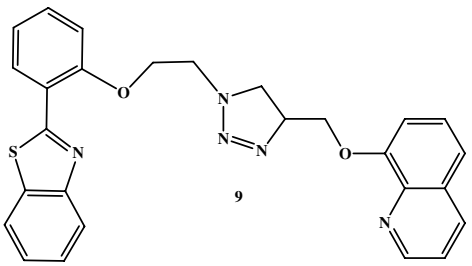
7e; R = OCH_3, R_1 = NO_2, R_2 =





8a; R = Me, X = H
8b; R = NO_2, X = H
8c; R = OMe, X = OMe
8d; R = Me, X = NO_2

8a-d



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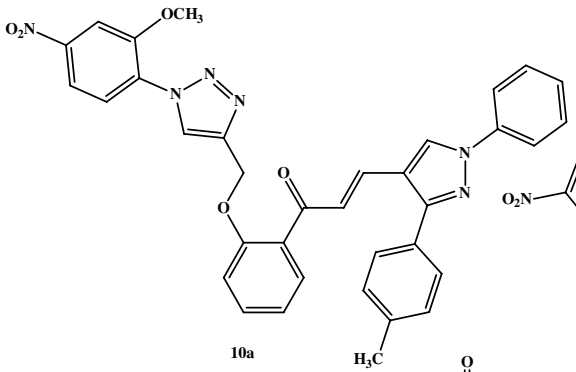
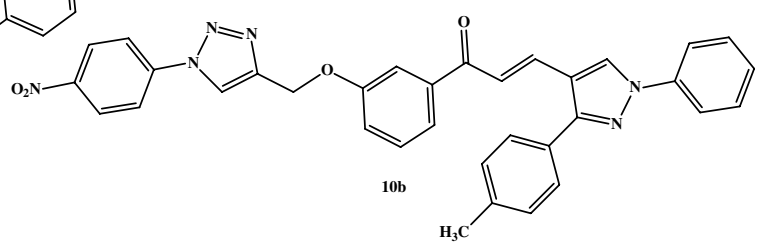
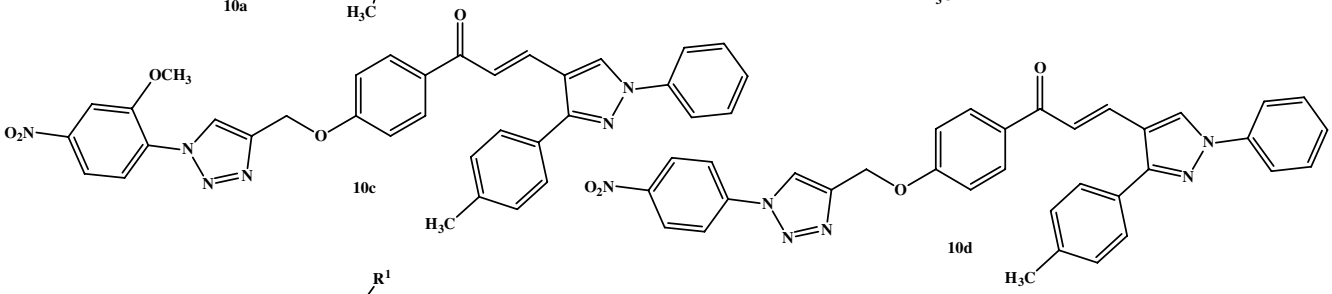


10a

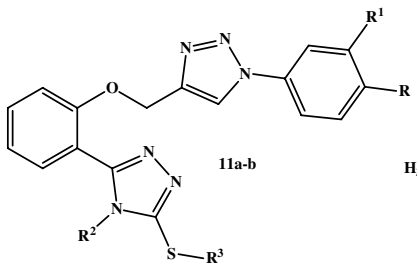


10b



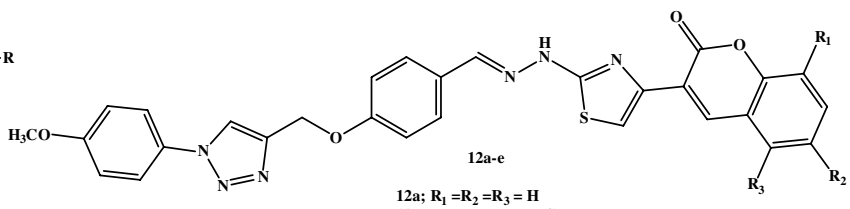
10c

10d



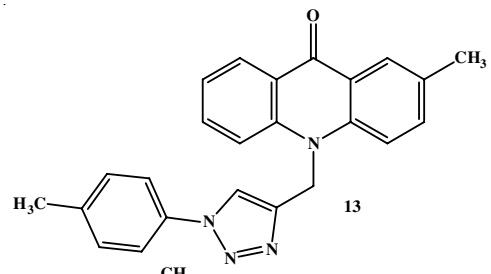
11a-b

11a; R = Cl, R^1 = H, R^2 = $PhCH_2$-, R^3 = *p*-ClPhCOCH_2-
11b; R = H, R^1 = H, R^2 = $PhCH_2$-, R^3 = PhCO-



12a-e

12a; R_1 =R_2 =R_3 = H
12b; R_1 = H, R_2-R_3 = C_2H_4
12c; R_1 = OCH_3, R_2 = R_3 = H
12d; R_1 = OCH_3, R_2 = Br, R_3 = H
12e; R_1 = R_2 = NO_2, R_3 = H



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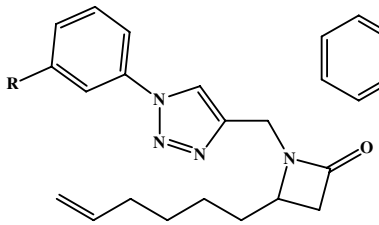
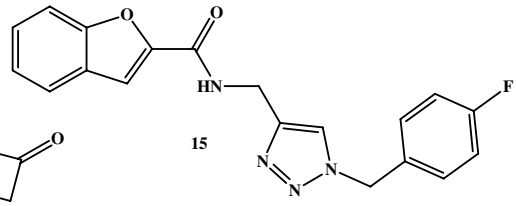


14a-b

14a; R = NO_2
14b; R =Cl



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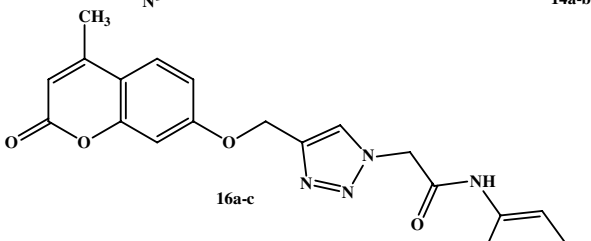
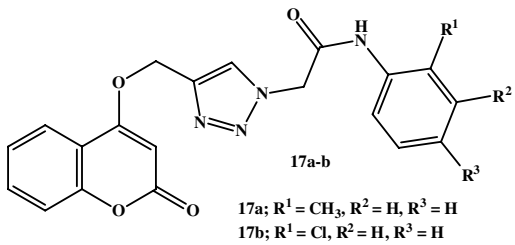


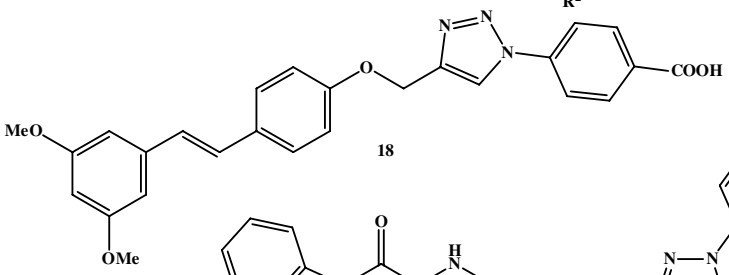
16a-c

16a; R^1 = CH_3, R^2 = H, R^3 = H
16b; R^1 = H, R^2 = H, R^3 = CH_3
16c; R^1 = Cl, R^2 = H, R^3 = H



17a-b

17a; R^1 = CH_3, R^2 = H, R^3 = H
17b; R^1 = Cl, R^2 = H, R^3 = H



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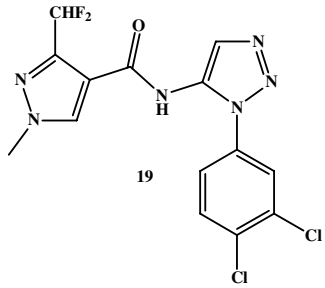

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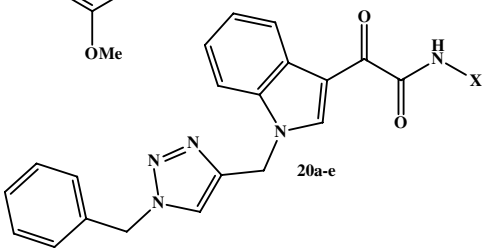
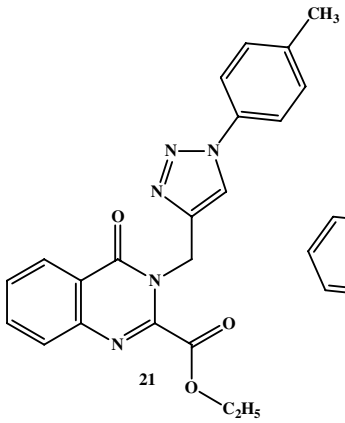


20a-e

X = 20a) Glysine, 20b) Tyrosine, 20c) Tryptophan, 20d) Aspartate, 20e) Glutamate



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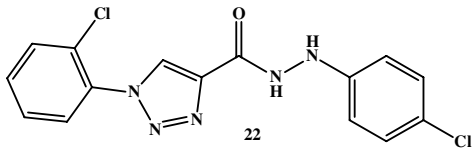

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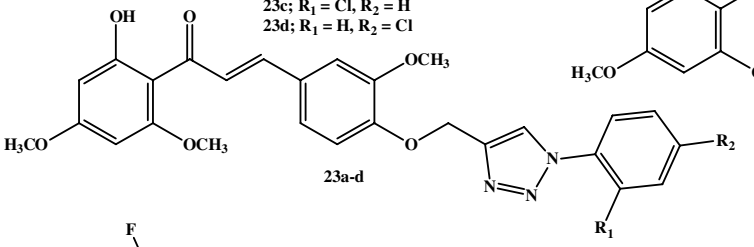
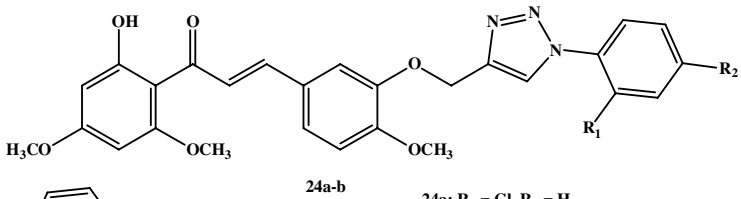


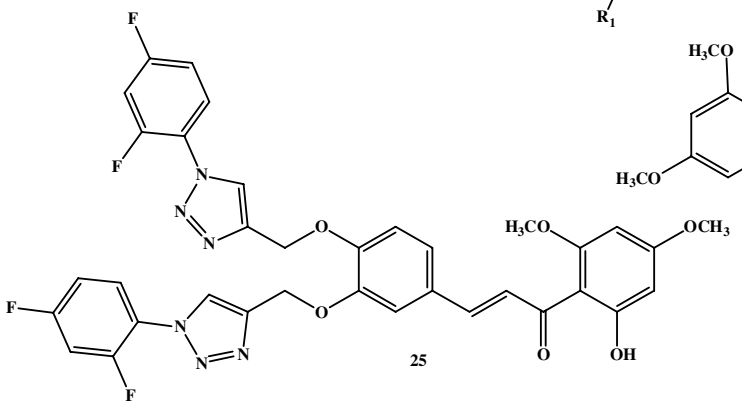
23a-d

23a; R_1 = Cl, R_2 = F
23b; R_1 = F, R_2 = F
23c; R_1 = Cl, R_2 = H
23d; R_1 = H, R_2 = Cl



24a-b

24a; R_1 = Cl, R_2 = H
24b; R_1 = H, R_2 = Cl



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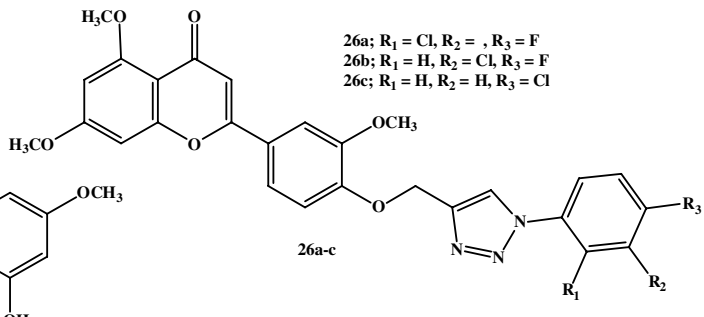
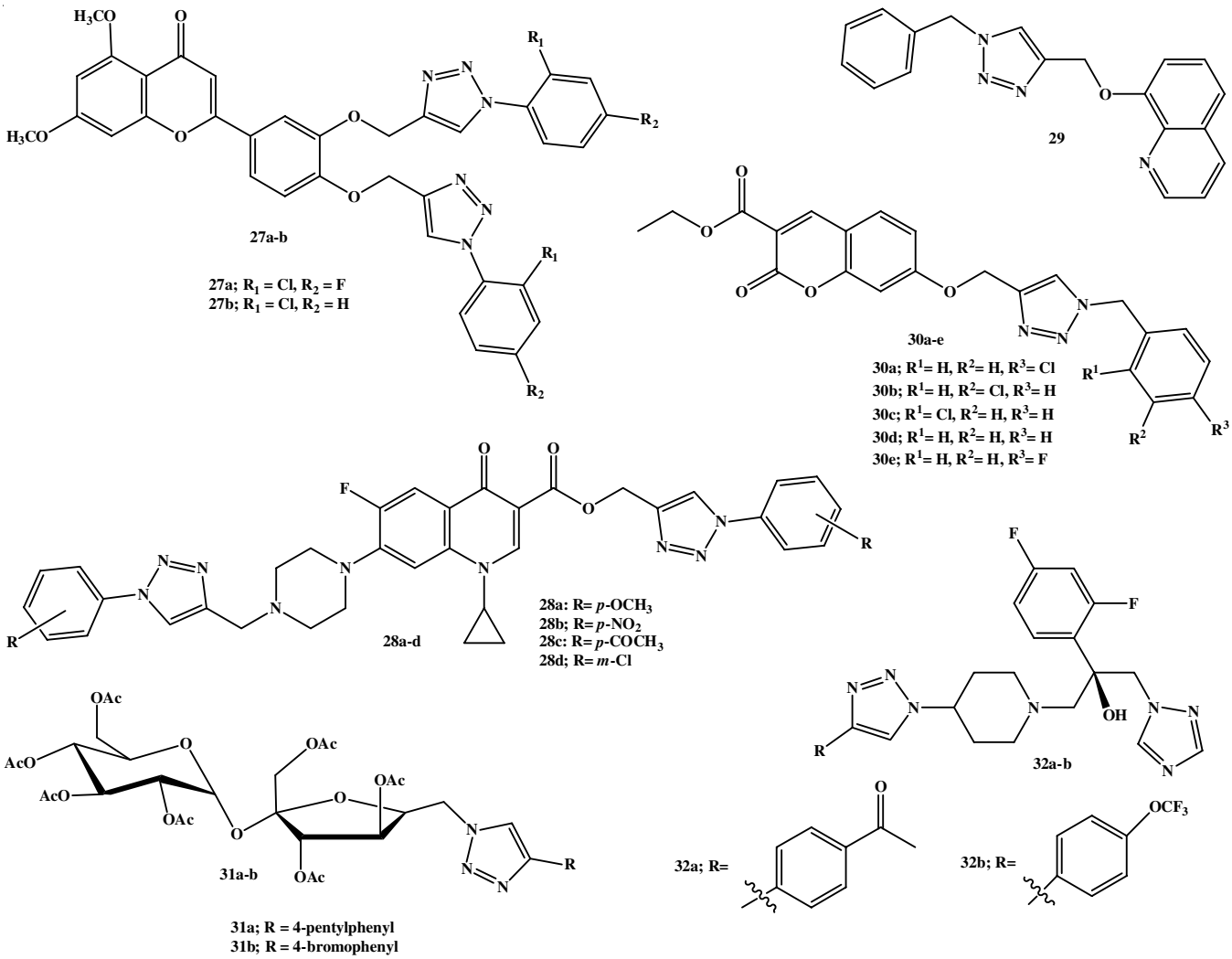


26a-c

26a; R_1 = Cl, R_2 = , R_3 = F
26b; R_1 = H, R_2 = Cl, R_3 = F
26c; R_1 = H, R_2 = H, R_3 = Cl



Structure of some 1,2,3-triazole derivatives (**1-32**) as antimicrobial agents

fungal properties of series of new triazoles with substituted 1,2,3-triazole-piperidine side chains were reported by Jiang *et al.* [52]. Good inhibitory activity was possessed by most compounds against some varied clinically important fungal pathogen strains. Compounds **32a-b** were efficient (MIC = 0.125-0.0125 µg/mL) against *C. albicans* and *Cryptococcus neoformans*.

Antitubercular activity: The attention of scientific community towards the infectious disease tuberculosis has been drawn due to the emergence of multiple drug resistant tuberculosis strains [53]. There is a growing need to design and synthesize novel drugs, which can adopt new mode of action differing from the drugs currently in use. In this direction, 1,2,3-triazoles conjugated to diverse heterocyclic moieties have been frequently evaluated and reported to demonstrate their anti-tubercular properties.

A series of novel isatin oxime ether grafted aryl 1*H*-1,2,3-triazole hybrids were synthesized by Kancharla *et al.* [6] as antitubercular agent against *M. tuberculosis* H37Rv (ATCC 27294) strain. Compounds **33a-d** with MIC value 0.78 µg/mL, 1.56 µg/mL, 1.56 µg/mL and 3.125 µg/mL, respectively, have shown good antitubercular activity compared to the standard drugs. The compounds were also less cytotoxic against RAW 264.7 cell lines. Sahoo *et al.* [54] synthesized few novel nitrobenzothiazinone congeners comprising of 2-mercapto and aminobenzothiazinone tethered 1,2,3-triazole hybrids and evaluated their antitubercular properties. Substantial *in vitro* potency was displayed by 10 compounds (MIC range of 0.5-8 µg/mL) in preliminary screening against *Mtb* H37Rv strain. The structural optimization of the initial lead, compound **34** (MIC value 0.5 µg/mL) led to identification of variant compounds **35a-d** which exhibiting potent anti-TB activity (MIC in range 0.03-0.12 µg/mL.

Based on hybridization approach, synthesis of new 1,2,3-triazole conjugates of imidazo[1,2-*a*]pyridine-3-carboxamide were reported by Nandikolla *et al.* [55]. The conjugates were assayed for anti-tubercular activity *in vitro* using LORA (low oxygen recovery assay) method against non-replicating and using MABA (microplate alamar blue assay) method against replicating *M. tuberculosis*. Results revealed that compound **36** has emerged as the lead (MIC values of 13.74 µg/mL and 24.63 µg/mL, respectively). Synthesis and antitubercular activity of 1,2,3-triazole based imidazole derivatives has been reported by Pradeep *et al.* [56]. The antitubercular screening was carried

against *M. tuberculosis* H37Rv (*Mtb*) strain and evaluation of cytotoxic activity was carried against mammalian Vero cell line. Compounds **37a** (MIC = 2.03 ± 0.31 μM) and **37b** (MIC = 1.47 ± 0.19 μM) displayed a potent *in vitro* antitubercular activity.

Melo de Oliveira *et al.* [57] synthesized alkynylated 1,2,4-oxadiazole/1,2,3-1*H*-triazole glycol conjugates and evaluated their *in vitro* antitubercular efficacy against *M. tuberculosis* (Mtb) H37Ra and H37Rv strains. Derivatives **38** (MIC = 10 mM) and **39** (MIC = 23.9 mM) were the most promising anti-tubercular agents. A novel quinoline-proline hybrids and hybrids of quinoline-proline-1,2,3-triazoles were reported by Ganesan *et al.* [58] using click chemistry. The *in vitro* antitubercular activity of compounds were carried by MABA and LORA assays. Compounds **40a** and **40b** exhibited promising activity against the *M. tuberculosis* H37Rv strain, MIC values MABA method 11.5 and 7.1 μg/mL respectively and LORA method 18.8 and 10.9 μg/mL respectively. Using click chemistry 1,2,3-triazoles tethered 2,4 thiazolidinedione hybrids were reported by Kulkarni *et al.* [59]. The compounds were assayed against *M. Bovis* BCG and *M. tuberculosis* (MTB) H37Ra strain. The results showed that compounds **41a-d** are highly potent with IC_{90} values range 1.20-2.70 μg/mL and 1.24-2.65 μg/mL, respectively against both the tested strains.

Phatak *et al.* [60] synthesized novel derivatives of indanol-1,2,3-triazoles in search for novel antitubercular agents. The compounds were assayed for their *in vitro* antitubercular (anti-TB) and antimicrobial potential. A good antitubercular activity was exhibited by most compounds against *M. tuberculosis* H37Rv strain. However, compound **42** has been identified as lead antitubercular agent (MIC = 1.56 μM) and is equivalent to ciprofloxacin and more potent than ethambutol. Three sets of pyrazine-1,2,3-triazoles were designed and synthesized by Reddyrajula & Dalimba [61]. The synthesized compounds were screened for their inhibitory potential against *M. tuberculosis* H37Rv strain *in vitro*. The conjugates synthesized through bio-isosteric modifications displayed improved activity comparing to rationally modified conjugates. The derivatives **43a-g** exhibited significant anti-TB activity (MIC = 1.56 μg/mL) and are twice potent than the parent pyrazinamide. Similarly, synthesis of new usnic acid enaminone-conjugated 1,2,3-triazoles as antimycobacterial agents was presented by Kantevari *et al.* [62]. Compound **44a** (saccharin derivative) exhibited the most activity (MIC = 2.5 μM), inhibiting *M. tuberculosis*, whereas compounds **44b** (with 3,4-difluorophenacyl group) with MIC = 5.4 μM and **44c** (with 2-acylnaphthalene group) with MIC = 5.3 μM inhibited *Mtb*.

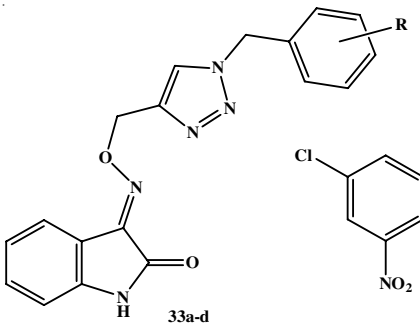
Garg *et al.* [63] reported a green synthesis of 1,4-disubstituted-1,2,3-triazole derivatives and the strategy was also applied for synthesizing novel amino acid bearing 1,2,3-triazole derivatives efficiently. Two synthesized compounds **45a** and **45b** (MIC value 3.12 μg/mL) exhibited good activity, however, phenylalanine containing triazoles, compound **45c** and **45d**, (MIC = 6.25 μg/mL) were also found to be potent. Badar *et al.* [15] synthesized a new series of isoniazid-1,2,3-triazole hybrids using click chemistry. The compounds were evaluated for their *in vitro* antimycobacterial and antimicrobial activities. The compound **46** with MIC value 1.56 μg/mL displayed a potent *in vitro* antitubercular profile against *M. tuberculosis* H37Rv.

New quinoline–triazole hybrid analogues as antitubercular agents were reported by Ramprasad *et al.* [64]. The *in vitro* antitubercular activity of hybrids against *M. bovis* show that two compounds **47a** (MIC = 31.5 μM) and **47b** (MIC = 34.8 μM) emerged as the most potent showing significant activity. Shiva Raju *et al.* [65] also reported the novel synthesis of 1*H*-pyrrolo[2,3-*d*]pyrimidine-1,2,3-triazole derivatives and *in vitro* anti-mycobacterial screening against *M. tuberculosis* H37Rv strain. Most of the compounds exhibited good antitubercular activity. The assay result demonstrated that the compounds **48a** and **48b** (MIC value 0.78 μg/mL) are lead compounds.

Shinde *et al.* [66] demonstrated the synthesis of a series of novel 1,2,3-triazole derivatives by click reaction approach. The compounds were screened *in vitro* for their antitubercular activity against *M. tuberculosis* H37Ra (MTB, ATCC 25177). With IC_{50} in range of 0.58-8.23 μg/mL most of the derivatives showed good activity. Compounds **49a** (MIC_{90} = 4.71 μg/mL) and **49b** (MIC_{90} = 2.22 μg/mL) exhibited good antitubercular activity. Ding *et al.* [67] synthesized a series of gatifloxacin-1,2,3-triazole-isatin hybrids and screened their antimycobacterial activity *in vitro*. The hybrids demonstrated considerable activity against *M. tuberculosis* H37Rv (MIC range 0.25-8 μg/mL) and two multidrug-resistant TB (MDR-MTB) strains. The hybrid **50** (MIC for MTB H37Rv = 0.25 μg/mL and MIC for MDR-MTB = 0.5 and 1 μg/mL) was the most active and not inferior to gatifloxacin (MIC value 0.5 μg/mL, 0.25 μg/mL and 0.5 μg/mL against all the three tested strains). The compound has been found more active (≥ 128-fold) than isoniazid (MIC value ≥ 64 μg/mL) and the drug rifampicin (MIC value > 128 μg/mL) against the two multi-drug resistant MTB strains.

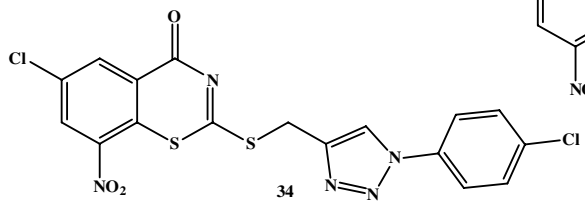
Maddali *et al.* [68] reported the synthesis of 1,4-disubstituted triazole derivatives by the Cu-catalyzed azide-alkyne cycloaddition reaction. The compounds were evaluated for their antitubercular activity against *M. tuberculosis* (H37Rv) by broth micro dilution. Most of the compounds **51a-e** (MIC range 7-11 μg/mL) displayed good antitubercular activity. Moreover, compound **51c** exhibited a promising activity (MIC value of 7 μg/mL), in comparison to reference drug, rifampicin. Sajja *et al.* [69] reported synthesis of benzosuberone bearing triazole derivatives *via* copper catalyzed click chemistry and their antimycobacterial activity. Compound **52a** (MIC value 3.125 μg/mL) and compounds **52b-d** (MIC value 6.25 μg/mL) demonstrated promising leads against *M. tuberculosis* H37Rv (ATCC27294) strain. Shanmugavelan *et al.* [70] presented the solvent-free, efficient synthesis of 1,2,3-triazole derivatives in excellent yield. The *in vitro* antitubercular activity revealed that compounds **53a-d** has potential activity against H37Rv strain with MIC values ranging 1.56-3.13 μg/mL.

Anticancer activity: As confirmed, 1,2,3-triazole is a favoured motif and several of its derivatives are currently being analyzed in clinical trials or used in clinics to combat cancer. For the treatment of cancer, a valuable therapeutic intervention may be provided by hybridization/conjugation of 1,2,3-triazoles with other anticancer pharmacophores [71].

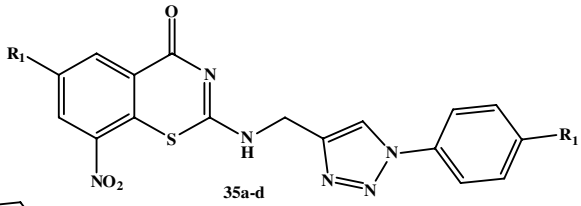


33a-d

33a; R = 4-F
33b; R = 4-Cl
33c; R = 4-CF_3
33d; R = 3-CF_3

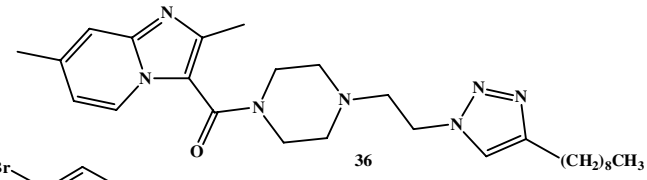


34

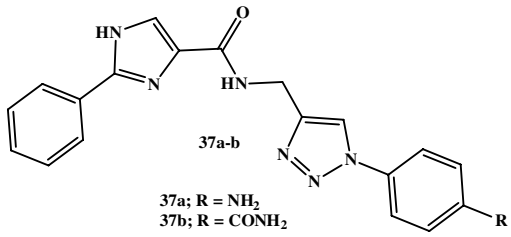


35a-d

35a; R_1 = Cl, R_2 = Cl
35b; R_1 = F, R_2 = Cl
35c; R_1 = Br, R_2 = Cl
35d; R_1 = CF_3, R_2 = Cl

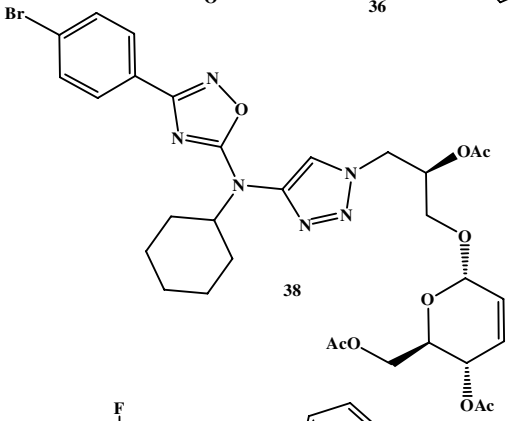


36



37a-b

37a; R = NH_2
37b; R = $CONH_2$



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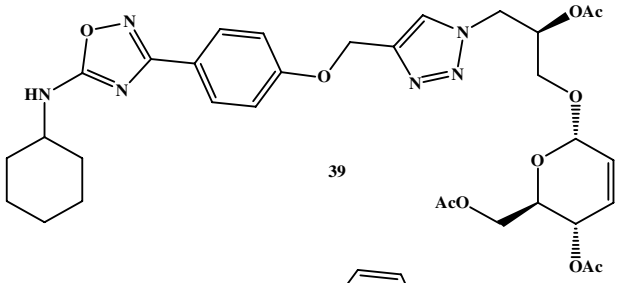

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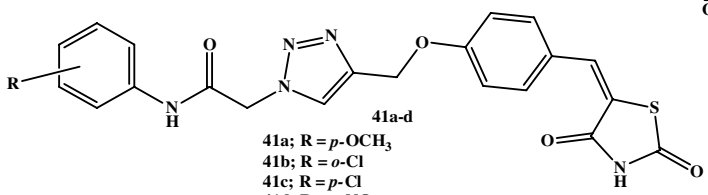
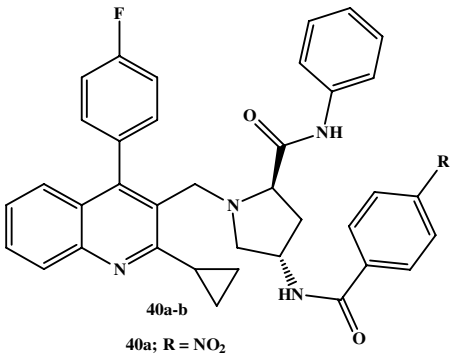


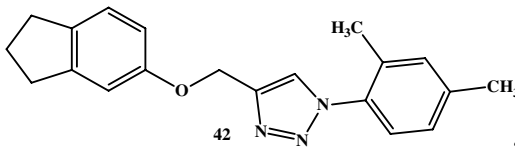
41a-d

41a; R = *p*-OCH_3
41b; R = *o*-Cl
41c; R = *p*-Cl
41d; R = *p*-NO_2



40a-b

40a; R = NO_2
40b; R = F



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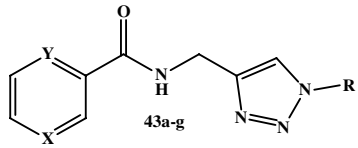
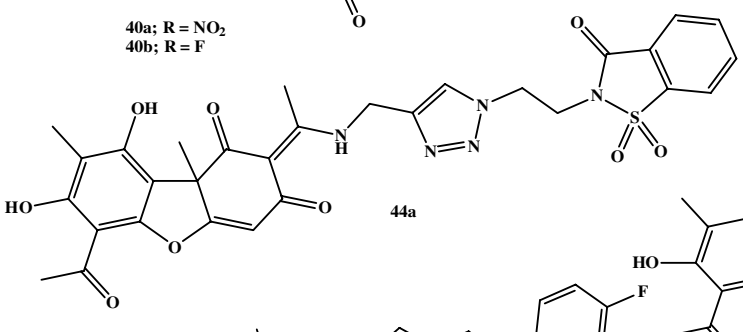
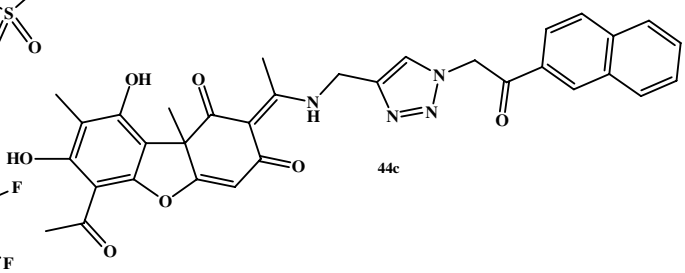


43a-g

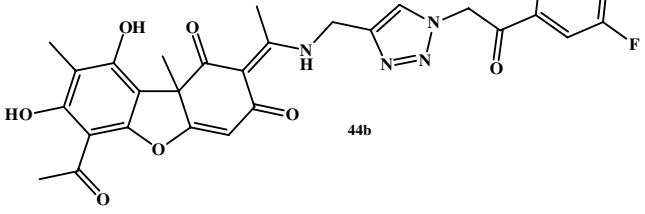
43a; X = N, Y = N, R = 4-cyano benzyl
43b; X = N, Y = N, R = 4-nitro benzyl
43c; X = N, Y = N, R = 4-fluoro benzyl
43d; X = N, Y = N, R = 4-trifluoro methyl benzyl
43e; X = N, Y = CH, R = 4-cyano benzyl
43f; X = N, Y = CH, R = 4-nitro benzyl
43g; X = N, Y = CH, R = 4-trifluoro methyl benzyl



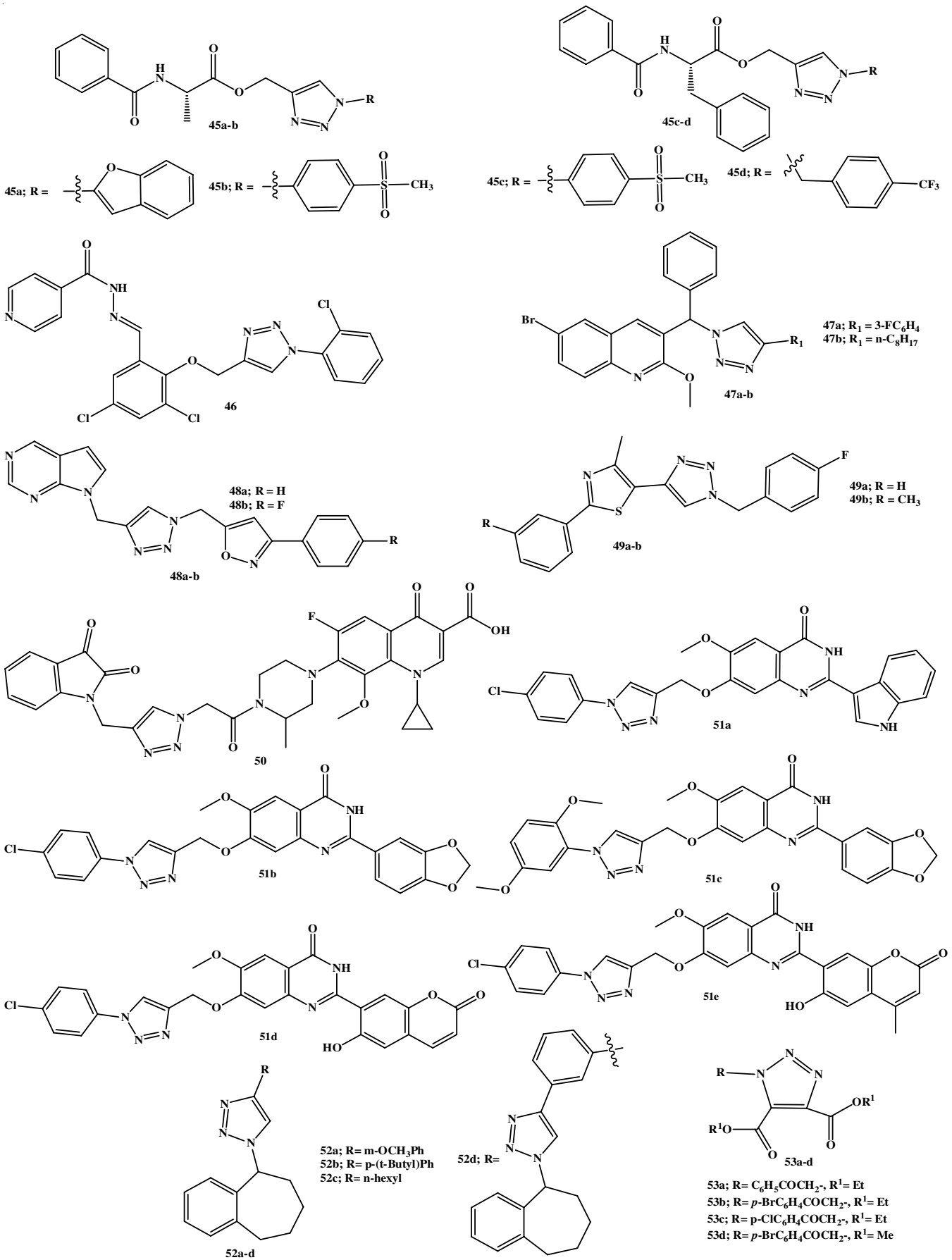
44a



44c



44b



Structure of some 1,2,3-triazole derivatives (**33-53**) as antitubercular agents

Wu *et al.* [72] designed and synthesized novel 1,2,3-triazole benzothiazole derivatives utilizing the molecular hybridization strategy and explored their antiproliferative activities against MGC-803, Kyse30 and HCT-116 cells. Among them, compound **54**, exhibited the strongest proliferation inhibitory activity with IC_{50} values 0.042 μM and 0.038 μM against esophageal cancer cells Kyse30 and EC-109, respectively. Further, this compound induces the degradation of oncogenic protein YAP *via* the UPS pathway and possesses significant potential for treatment of esophageal cancers. Based on the hybrid pharmacophore approach, Al-blewi *et al.* [73] synthesized novel imidazole-1,2,3-triazole hybrids using copper catalyzed click reaction. The resulted hybrids were evaluated by the MTT assay for anticancer activity against four cancer cell lines *viz*. Caco-2, HCT116, HeLa and MCF-7. Compound **55** was found to be one of the most potent (IC_{50} value 0.38 μM) against MCF-7 cell lines demonstrating similar potency to standard reference drug, doxorubicin.

Al-Sheikh *et al.* [74] reported synthesis of conjugates of substituted 1,2,3-triazoles linked to 1,2,4-triazoles through Cu(I)-catalyzed cycloaddition starting from S-propargylated 1,2,4-triazoles. Both classical and microwave methods were used to synthesize the desired triazoles. The anticancer screening of compounds against MCF-7, Caco-2, HCT116 and HeLa cancer cell lines revealed that compounds **56a-c** had a significant anticancer activity with IC_{50} = 0.31 μM and 4.98 μM against MCF-7 and Caco-2 cancer cell lines, respectively, comparing to the standard reference drug, doxorubicin. Almalki *et al.* [75] synthesized a library of 1,2,3-triazole-incorporated with thymol-1,3,4-oxadiazoles as anticancer and antimicrobial agents. Compounds **57a-e** demonstrated a significant antiproliferative activity and compound **57c** demonstrated to be potent compound against the tested MCF-7, HCT-116, HepG2 cell lines with IC_{50} value of 1.1 μM, 2.6 μM and 1.4 μM, respectively comparing with doxorubicin and 5-fluorouracil (standard drugs). The compound also displays significant thymidylate synthase (TS) inhibitory activity with IC_{50} value in the range of 1.95-4.24 μM, than the standard drug, pemetrexed with IC_{50} = 7.26 μM.

Synthesis of a series of six 1,2,3-triazole derivatives and their cytotoxicity profiles evaluation against Hela cancer cell line was reported by Sahin *et al.* [76]. Results showed that compounds **58a** (IC_{50} value 10.8 μg/mL, **58b** with (IC_{50} value 8.8 μg/mL) and **58c** (IC_{50} value 11.7 μg/mL) exhibited significant anticancer activity. For anticancer activity the synthesis of a series of novel amide-linked 1,4-disubstituted 1,2,3-triazoles was also reported by Kaushik *et al.* [77] using click chemistry. The compounds were screened against PC3, A549, MIAPACA and Fr2 cancer cell lines. Compounds **58a** and **58b** demonstrated moderate activity against the test cancer cell lines while compound **58c** demonstrated good activity against PC3 only.

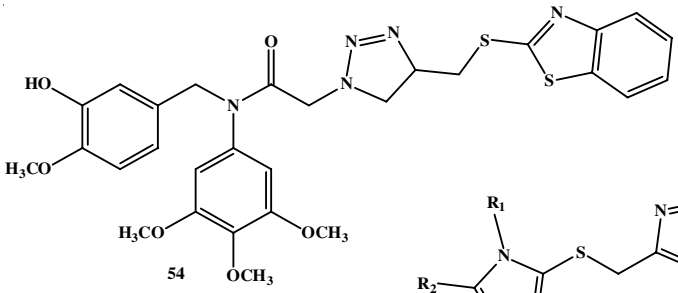
Compound **60** exhibited potent anticancer activity against HepG2, A549 and MCF-7 cell lines with IC_{50} value of 3.42 μM, 1.26 μM and 5.96 μM, respectively, among synthesized 1,2,3-triazole derivatives reported by Nipate *et al.* [78] using click reaction. Azab *et al.* [79] reported *in vitro* antitumor screening of novel series of 1,2,3-triazole-containing hybrids synthesized *via* CuAAC reaction. The compounds were screened against the HepG-2, MCF-7 and HCT-116 cancer cell lines. Compound **61** was found most potent cytotoxic candidate with IC_{50} value of 12.22, 14.64 and 14.16 μM towards HepG-2, MCF-7 and HCT-116, respectively, in comparison to the standard drug doxorubicin with IC_{50} of 11.21, 12.46 and 13.45 μM against the tested cell lines.

Aouad *et al.* [80] designed and synthesized benzothiazole-piperazine based 1,4-di and 1,4,5-trisubstituted-1,2,3-triazole conjugates. The conjugates were screened for their antiproliferative inhibition activity against MCF7, T47D, HCT116 and Caco2 human cancer cell lines. Compound **62** exhibited the most potent antiproliferative activity against the breast carcinoma cell lines T47D and MCF7 with IC_{50} value of 38 μM and 33 μM, respectively. This compound also showed good activity against the colon carcinoma cell lines of HCT116 and Caco2 with IC_{50} value of 48 μM and 42 μM, respectively. Bêbenek *et al.* [81] synthesized 1,2,3-triazoles of 3-acetylbetulin and betulone using the CuAAC reaction. The *in vitro* anticancer activity of derivatives were carried on the human cancer cell lines C-32, T47D and SNB-19. Compound **63** exhibited to possess a significant activity against SNB-19 cell line (IC_{50} = 0.17 μM), five-fold higher potent in comparison with reference drug, cisplatin.

Safavi *et al.* [82] reported the synthesis of novel quinazolin-4(3*H*)-one linked to 1,2,3-triazoles and *in vitro* anticancer activity of compounds against three MCF-7, MDA-MB-231, T-47D (human breast), A549 (lung) and PC3 (prostate) cancer cell lines. The presence of methoxy (-OCH_3) group on the linker between triazole and quinazolinone moieties selectively affects the anticancer activity of the compounds. The IC_{50} values of compounds **64a-d** depict their cytotoxicity against tested breast cancer cell lines and is even more effective than etoposide, the reference drug. Compounds **64a** and **64d** were also found to be effective against A549 cell lines, as compared with erlotinib. Similarly, Kapkoti *et al.* [83] designed and reported the copper(I) catalyzed azide alkyne cycloaddition (CuAAC) synthesis of two series of novel 1,2,3-triazole based artemisinin derivatives and investigated their antiproliferative activity by MTT assay against various human cancer cell lines. Compound **65a** demonstrated potent antiproliferative activity (IC_{50} = 4.06 μM) against the human epidermoid carcinoma (A431) cell line and compound **65b** displayed potent activity (IC_{50} = 7.16 μM) against the human lung adenocarcinoma (A549) cell line.

Mareddy *et al.* [84] used mild and greener CuAAC reaction to synthesize new hybrids of nimesulide-1,2,3-triazole moiety, removing the problematic nitro group of nimesulide. Three of the synthesized compounds **66a-c** demonstrated promising growth inhibition (IC_{50}~6-10 μM) against four cancer cell lines A549, HepG2, HeLa and DU145 while less significant effects on cancer cell line HEK293. In the same manner, Yadav *et al.* [85] applied greener click reaction to synthesize a chalcone linked-1,2,3-triazoles for their anticancer potential by cytotoxicity assay against four A549, MCF-7, MIA-Pa-Ca-2, HepG2 human cancer cell lines. Compound **67** demonstrated efficient activity against the cancer cell lines under observation.

Synthesis of a series of 1,2,3-triazole–coumarin hybrids was reported by Kraljevic *et al.* [86] using click chemistry



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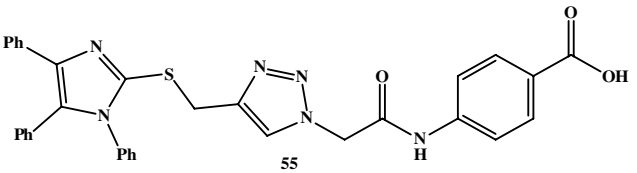

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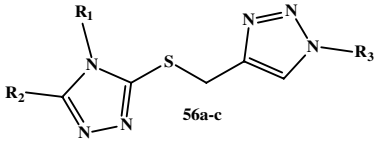
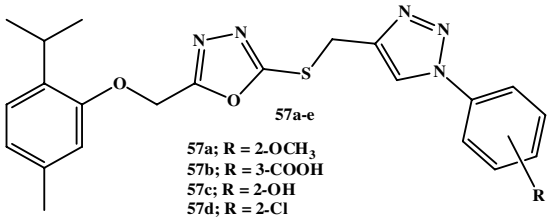


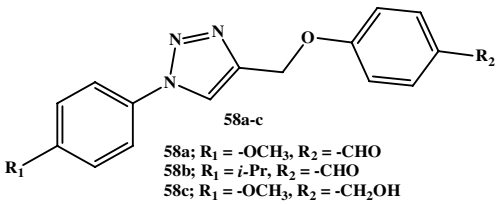
56a-c

56a; R_1 = Ph, R_2 = Ph, R_3 = $CH_3(CH_2)_{14}CH_2$-
56b; R_1 = Ph, R_2 = Ph, R_3 = 4-BrPh
56C; R_1 = Ph, R_2 = Me, R_3 = 4-BrPh



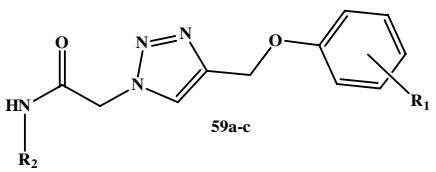
57a-e

57a; R = 2-OCH_3
57b; R = 3-COOH
57c; R = 2-OH
57d; R = 2-Cl
57e; R = 3-Cl



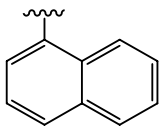
58a-c

58a; R_1 = -OCH_3, R_2 = -CHO
58b; R_1 = *i*-Pr, R_2 = -CHO
58c; R_1 = -OCH_3, R_2 = -CH_2OH

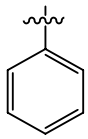


59a-c

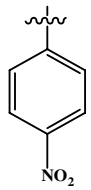
59a; R_1 = *o*-CH_2OH, R_2 =

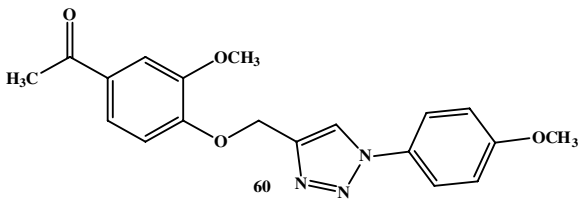


59b; R_1 = *m*-CH_2OH, R_2 =

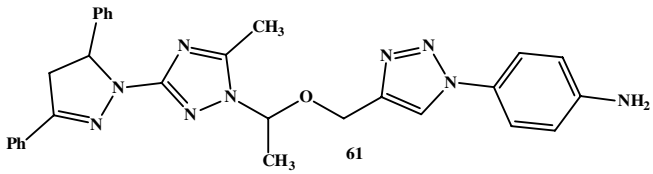


59c; R_1 = *p*-CH_2OH, R_2 =

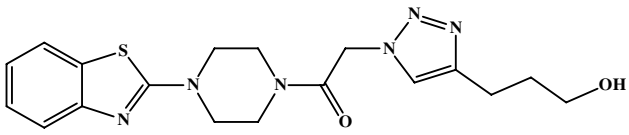




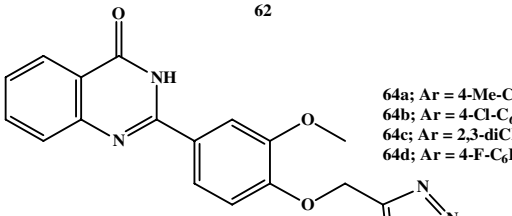
60



61

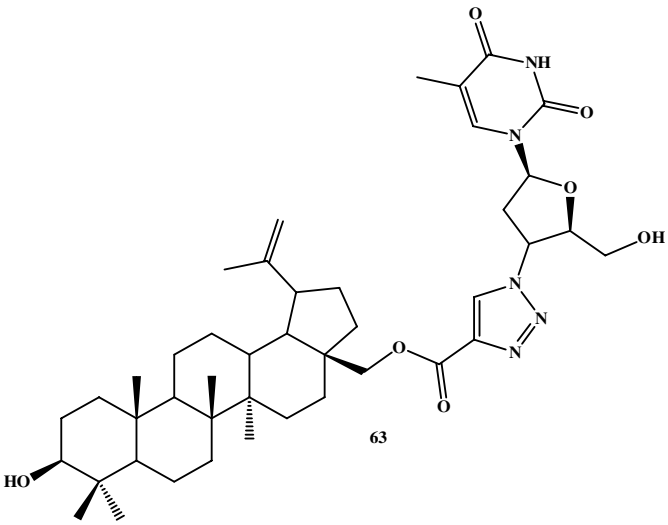


62

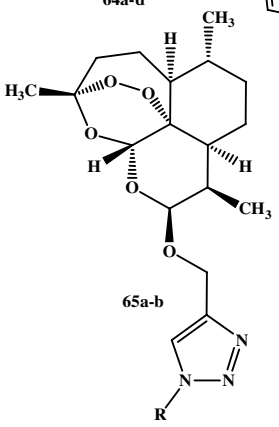


64a-d

64a; Ar = 4-Me-C_6H_4
64b; Ar = 4-Cl-C_6H_4
64c; Ar = 2,3-diCl-C_6H_3
64d; Ar = 4-F-C_6H_4

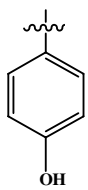


63

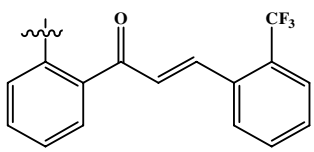


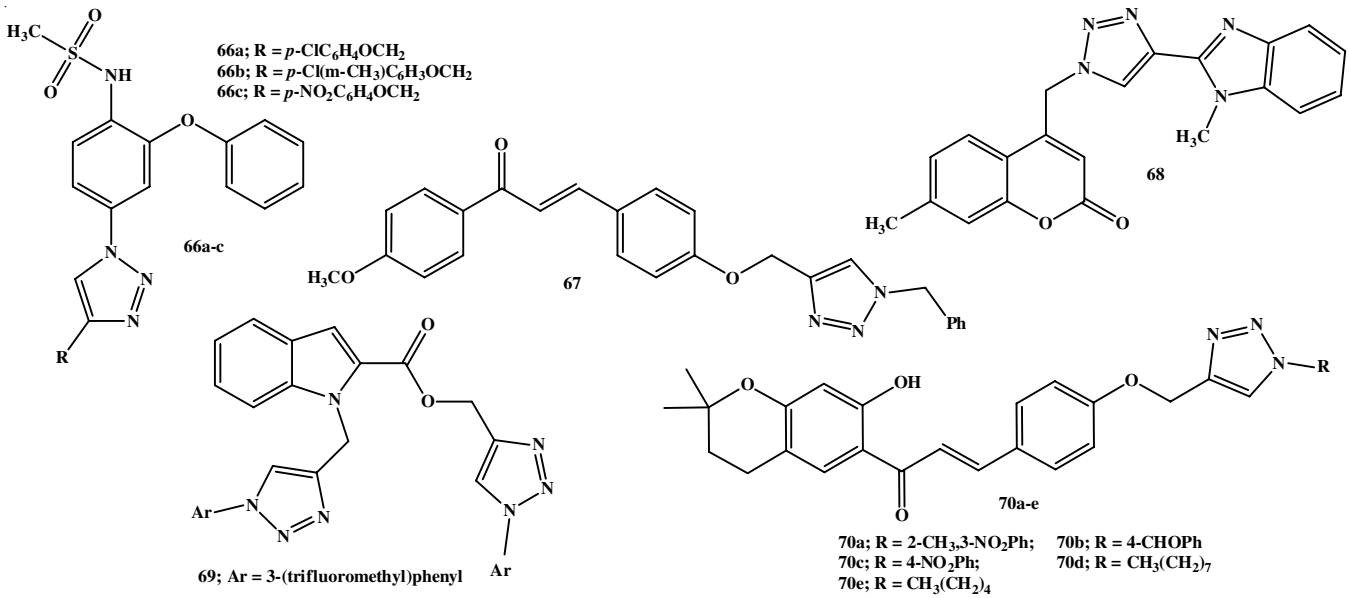
65a-b

65a; R =



65b; R =





Structure of some 1,2,3-triazole derivatives **(54-70)** as anticancer agents

method. The results revealed that compound **68** was a lead with the highest cytotoxicity (IC_{50} = 0.9 µM) against HepG2 cell lines and with high selectivity index (SI = 50). Narsimha *et al.* [87] presented the synthesis of a series of new indole-2-carboxylic acid derived mono and *bis*-1,4-disubstituted 1,2,3-triazoles for their *in vitro* and *in vivo* anticancer activities. The *in vitro* anticancer screening revealed that compound **69** shows potential activity against MCF-7 with IC_{50} value 13.26 ± 2.344 µM, HeLa with IC_{50} value 9.89 ± 1.758 µM and HEK-293 with IC_{50} value 9.08 ± 0.684 µM as compared to the standard reference drug cisplatin. Chinthala *et al.* [88] also reported the anticancer activity and click synthesis of a series of novel chalcone-triazole derivatives. The anticancer activity was carried on human cancer cell lines-neuroblastoma (IMR32), hepatoma (HepG2) and breast adenocarcinoma (MCF-7), prostate carcinoma (DU-145) and lung adenocarcinoma (A549) *in vitro*. Among the synthesized compounds, compounds **70a** with IC_{50} value 65.86 µM, **70b** with IC_{50} value 66.28 µM, **70c** with IC_{50} value 35.81 µM, **70d** with IC_{50} value 50.82 µM and **70e** with IC_{50} value 48.63 µM possess better activity in A549 cell line alone, comparing the standard drug doxorubicin (IC_{50} = 69.33 µM).

Antiviral activity: In a viral infection\\, all organs and systems of a host organism are infected by the disease, resulting in latent, acute and chronic forms of infection. Severe viral infections like COVID-19 are emerging and are the common causes of human illness and death now a days. Presently, limited antiviral chemotherapeutic agents to prevent and treat these infections are available, so it is the need to develop potential antiviral drugs against various harmful and fatal viral infections. The necessity of antiviral agents is still inevitable [89].

Recently, a series of fourteen 1,2,3-triazole-vanillin derivatives were synthesized by Silva-Rodrigues *et al.* [90] *via* alkylation of vanillin followed by CuAAC reaction and evaluated for their cytotoxicity of Vero cells and their effect on the Zika virus. It was found that the most effective was compound **71** with EC_{50} = 27.14 µM and IC_{50} = 334.9 µM. The compound blocks the Zika virus infection by acting on the viral particle *in vitro*. Kutkat *et al.* [91] reported *in vitro* and *in vivo* antiviral activity and synthesis of novel 1,2,3-triazole glycosides with benzimidazole, benzooxazole or benzotriazole cores. The *in vitro* antiviral activity of all compounds against H5N1 and H1N1 viruses was high in mice. Compound **72a** (IC_{50} value 2.280 µM) and compound **72b** (IC_{50} value 2.75 µM) were lead. Further, compound **72a** was safe and full protection was achieved from H1N1 infection and 80% protection from H5N1 virus.

Viegas *et al.* [16] also synthesized and evaluated antiviral activity of 1,4-disubstituted-1,2,3-triazole hybrids. Antiviral activity was carried against Herpes simplex virus 1 (HSV-1) acute infection. Compounds **73** and **74** were the lead, with an EC_{50} value of 16 and 21 µM and CC_{50} value of 285 and 2,593 µM, respectively. Compound **71** interferes with virus egress and able to inhibit acyclovir-resistant strain replication [16]. Similarly, a series of novel 4-substituted-1,2,3-triazole derivatives were reported by Abuduaini *et al.* [92] and their antiviral activities against HIV, HBV and SARS-CoV-2 were screened. Compound **75** exhibited 62% inhibition at 10 µM against the HBV in Huh7 cell cultures without significant cytotoxic activity at 10 µM with IC_{50} value 66.4 uM in HepG2 cells.

Dantas *et al.* [93] evaluated the antiviral and cytotoxicity activities of hybrid compounds of 1,2,3-triazole, phthalimide and naphthoquinone groups. Compound **76** was the lead with IC_{50} value 146.0 µM against Zika virus (ZIKV) in the post-infection test and SI of 2.3. Similarly, synthesis and antiviral activity of a series of 1,2,3-triazolyl nucleoside analogues was presented by Andreeva *et al*. [94]. The antiviral activity was carried against influenza virus H1N1 and coxsackie virus B3. Compound **77a** demonstrated best values of IC_{50} = 30 µM and SI = 24 and compound **77b** demonstrated IC_{50} = 15 µM and SI = 5.

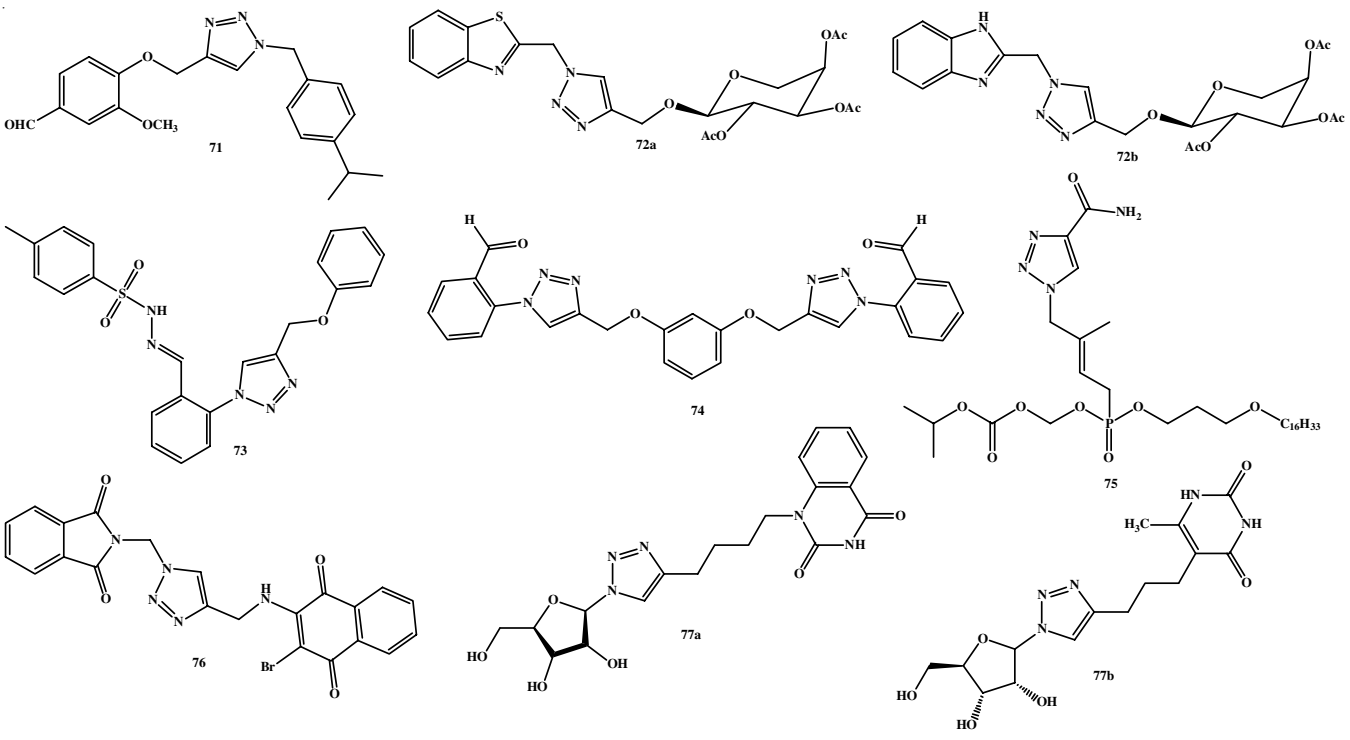
Sun *et al.* [95] also reported the antiviral (HIV-1) activity and synthesis of a series of 4-phenyl-1*H*-1,2,3-triazole phenyl-

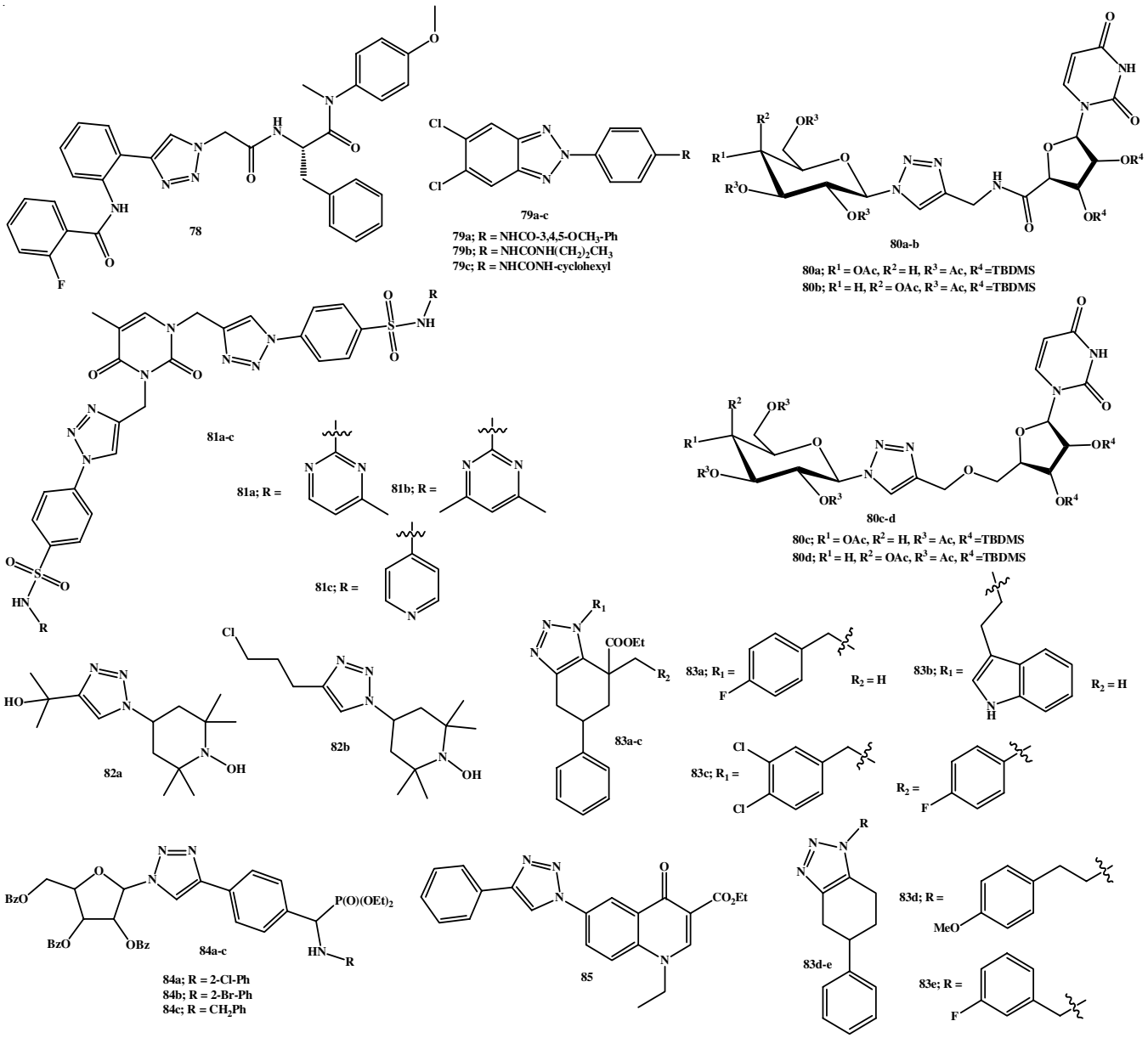
alanine derivatives. Most compounds exhibited potent antiviral activities. The antiviral (HIV-1) activity of compound **78** with EC_{50} value 3.13 μM and CC_{50} > 16.48 μM is particularly prominent. Further, compound **78** also displayed the effects both in early as well as late stages of HIV-1 replication. In similar manner, Sanna *et al.* [96] synthesized 1,2,3-triazole derivatives and screened them against human respiratory syncytial virus (HRSV). They identified three promising lead compounds, **79a-c** which are characterized by significant inhibitory activity (20 μM) against Hantaan virus, *in vitro* and more potent (10-fold) than the nucleoside analogue ribavirin (RBV), only antiviral with acknowledged *in vitro* and *in vivo* activity. Another novel type of uridine glycoconjugates containing amide and/or 1,2,3-triazole moiety in the linker structure were synthesized by Brzuska *et al.* [97] and evaluated for antiviral activity *in vitro*. The antiviral assay was carried against two viral strains [tick-borne *encephalitis virus* (TBEV), a highly virulent Hypr strain and less virulent Neudoerfl strain]. The data shows that four compounds **80a-d** possess strong activity (IC_{50} between 15.1 and 3.7 μM) against both TBEV strains.

Synthesis of 1,4-disubstituted-1,2,3-triazolethymine derivatives was presented by Almashal *et al.* [98] for their *in vitro* antiviral activity against the HIV-1 and HIV-2 replication in MT-4 cell lines. The synthesized derivatives **81a-c** possesses a potent activity with IC_{50} values = 11.42, ≥ 15.25 and = 14.36 μM, respectively against HIV-1 replication. Cunha *et al.* [99] also presented the synthesis of 4-substituted-1,2,3-1*H*-1,2,3-triazole linked nitroxyl radical and their ability to inhibit the HSV-1 replication *in vitro* using the drug acyclovir as positive control. Among them, compounds **82a** (IC_{50} value 0.80 μM and with selectivity index CC_{50}/IC_{50} value 3886) was 4.5 times and compound **82b** (IC_{50} value 1.10 μM and with selectivity index CC_{50}/IC_{50} value 6698) was 7.7 times more selective than acyclovir (IC_{50} value 0.99 μM and with selectivity index CC_{50}/IC_{50} value 869).

Synthesis of fused 1,2,3-triazole derivatives was described by Karypidou *et al.* [100] and screening of synthesized compounds against various viruses was carried. The results show promising antiviral activity for compounds **83a** (EC_{50} value of 8.95 μM), **83b** (EC_{50} value of 9.45 μM), **83c** (EC_{50} value of 9.45 μM), **83d** (EC_{50} value of 8.9 μM) and **83e** (EC_{50} value of 11.95 μM) against HCoV-229E. Ouahrouch *et al.* [101] presented the synthesis of ribonucleosides of 1,2,3-triazolylbenzyl-aminophosphonates and their screening against various of DNA and RNA viral strains. The compounds **84a** and **84b** demonstrated as potent antivral activity against RSV and compound **84c** displayed potent antivral activity against Coxsackie virus B4 strain. Boechat *et al.* [102] reported another novel synthesis of 1,2,3-triazolyl-4-oxoquinolines congeners. The compounds were screened for their ability to inhibit oseltamivir resistant influenza viral strains. Congener **85** demonstrated the most potent activity, inhibiting 94% of wild type (WT) influenza neuraminidase. It has also been found to inhibit influenza virus replication (EC_{50} = 0.2 μM) with less cytotoxic than oseltamivir and inhibit different oseltamivir resistant neuraminidases. The results also showed that 1,2,3-triazolyl-4-oxoquinoline congeners establish to be promising lead molecules for further anti-influenza drug discovery.

Antileishmanial, antitrypanosomal and antiplasmodial activity: The treatment failures for many infectious parasitic diseases, such as leishmaniasis, trypanosomiasis and malaria has increased with an alarming rate in recent years, owing to the development of drug resistance [103,104]. Therefore, there is a need to replace commonly used medications associated with parasite resistance with alternatives. In view of this fact, many researchers are working in this area to develop new





Structure of some 1,2,3-triazole derivatives **(71-85)** as antiviral agents

bioactive molecules containing 1,2,3-triazole framework, in combating protozoal disease in a more efficient way.

In search for new antileishmanial agents, Zuma *et al.* [105] appended a clinical antibiotic nitrofurantoin to 1,2,3-triazole scaffold through alkylene linkers of various chain length and the resulting hybrids were evaluated for their antileishmanial activity against two strains of *Leishmania* (*L.*) parasite *in vitro*. Hybrid **86** having a *n*-pentylene linker was observed as a leishmanicidal hit with IC_{50} value of 1.7 μM against antimonial-resistant *L. donovani* (9515) strain. However, Teixeira *et al.* [106] reported that 1,2,3-triazole derivative **87** presents significant antileishmanial activity and for promastigote form (IC_{50} = 7.4 μmol L^{-1}) and amastigote form (IC_{50} = 1.6 μmol L^{-1}). The cytotoxic analysis of derivative **87** against the macrophage cells was found to have an IC_{50} value 211.9 μmol L^{-1} with the selective index 132.5 and outperformed two commonly used drugs in the clinics *viz.* glucantime and pentamidine.

Glanzmann *et al.* [107] synthesized novel compounds derived from 4-aminoquinoline and 1,2,3-triazoles and evaluated their biological evaluation against *L. amazonensis* species. The results showed that compound **88** exhibited the best antileishmanial action against pro-mastigotes and amastigotes of *L. amazonensis* with IC_{50} values of 5.7 μM and 1.1 μM, respectively and is better than reference drug miltefosine (IC_{50} of 22.0 μM and 4.2 μM, respectively). Nandikolla *et al.* [108] also synthesized novel imidazo[1,2-*a*]pyridine-3-carboxamide analogues of 1,2,3-triazoles screened them against parasites (*Leishmania major* and *Trypanosoma brucei*). Among the compounds, compounds **89a-e** reported a significant inhibition (IC_{50} values in the range 15-47 μM) on the growth of *L. major* promastigote forms. The most active compound was compound **89b** (IC_{50} = 15.1 μM), which showed comparable activity as that of standard drug, miltefosine (IC_{50}= 12.6 μM). Three compounds **89d**, **89f** and **89g** exhibited substantial activity with IC_{50}

= 5.5 μM, 7.4 μM and 0.7 μM, respectively against *T. brucei* parasite.

Using click chemistry strategy, Assunção *et al.* [109] carried over the synthesis of 1,4-disubstituted-1,2,3-triazole analogues of benznidazole and screened their antitrypnosomal activity against *T. cruzi* amastigote form. Compound **90a** (without substituents on phenyl ring) showed similar biological activity (IC_{50} value 3.1 μM and SI > 64.5) as that of benznidazole (IC_{50} value 3.0 μM, SI > 65.3). Compound **90b** (IC_{50} value 0.65 μM) was 5-fold more active than benznidazole and showing selectivity index (SI > 307.7). Compound **90c** (IC_{50} value 1.2 μM and relevant SI > 166.7), also demonstrated higher activity than benznidazole. Moreover, Almeida-Souza *et al.* [110] synthesized and evaluated *in vitro* antileishmanial activity of new 1,4-disubstituted-1,2,3 triazole derivatives. Compound **91** exhibited a good activity against promastigotes (IC_{50} value 14.64 ± 4.392 μM), against intracellular amastigotes (IC_{50} value 17.78 ± 3.257 μM) and against the BALB/c peritoneal macrophages (CC_{50} value 547.88 ± 3.256 μM).

Another types of series of 1,2,3-triazole-naphthoquinone conjugates were synthesized by Oramas-Royo *et al.* [13] using CuAAC and screened for their *in vitro* antimalarial activity against chloroquine sensitive *P. falciparum.* The most active antimalarial compounds with best activity were compounds **92a** (IC_{50} value 0.8 μM) and **92b** (IC_{50} value 1.2 μM). Thakur *et al.* [111] synthesized new glycohybrids of phenylhydrazono-indolinones *via* acid catalyzed reaction and screened their anti-plasmodial activity *in vitro* against two *P. falciparum* strains 3D7 and K1 strains. Compounds **93a-d** exhibited significant activity (IC_{50} = 1.27 μM, 1.96 μM and 1.64 μM, respectively) against chloroquine sensitive *Pf*3D7 strain. Compounds **93b** (IC_{50} = 1. 93 μM) and **93c** (IC_{50} = 1. 61 μM) demonstrated good activity against the chloroquine resistant *Pf*K1 strain.

Starting from isoprenyl azides and different alkynes, Porta *et al.* [112] synthesized novel prenyl 1,2,3-triazoles and screened their antiparasitic activity against *Trypanosoma cruzi* and *Leishmania donovani*. Compound **94** is the best candidate (IC_{50} = 27 μM) in the family of monoterpenyl triazoles against *T. cruzi*. Masood *et al.* [113] synthesized novel 1,2,3-triazoles derivatives appended with *L*-amino acid (Phe/Pro/Trp) tail *via* click chemistry. The synthesized compounds were screened for anti-leishmanial activity against of *L. donovani* (Dd8 strain) promastigote form. The derivatives **95a-c** (IC_{50} value 88.83 ± 2.93, 96.88 ± 12.88 and 94.45 ± 6.51 μM, respectively) were identified to possess promising anti-leishmanial activity with no cytotoxicity towards macrophage cells. Compound **95b** also showed the highest selectivity index (SI value 8.05).

Doherty *et al.* [114] presented the development of 1,2,3-triazole-based vinyl sulfone compound **96a**, which show potent anti-trypanosomal activity. The other most active compounds was allyl sulfone **96b** (EC_{50} value 1.94 μM), which originates from the isomerization of vinyl sulfone **96a**.

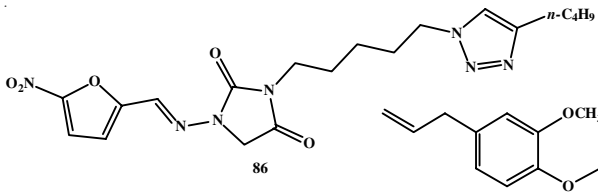
Balabadra *et al.* [115] synthesized a novel naphthyl bearing 1,2,3-triazoles and evaluated their antiplasmodial activity *in vitro* against pyrimethamine-resistant and sensitive strains of *P. falciparum*. The derivatives **97a** (IC_{50} = 24.0 μM), **97b** (IC_{50} = 31.03 μM) and **97c** (IC_{50} = 13.6 μM) against pyrimethamine resistant Dd2 strain exhibited enhanced antiplasmodial activity than control drug pyrimethamine with IC_{50} = 33.95 μM. Kumar *et al.* [116] synthesized 1*H*-1,2,3-triazole linked 4-amino-quinoline-chalcone/*N*-acetylpyrazoline conjugates and screened their antiplasmodial activity against cultured chloroquine resistant strain. The activities result revealed that conjugate **98** (IC_{50} = 53.7 nM) is the most potent as well as non-cytotoxic and showing comparable antiplasmodial activity to that of chloroquine.

Cassamale *et al.* [117] also another synthesized type of compounds having 1,2,3-triazole scaffold (*e.g.* 1,4-diaryl-1,2,3-triazoles) derived from the natural products and evaluated their anti-leishmanial activity. It was found that compound **99a** (IC_{50} = 1.1 μM and 19.5 μM), positional isomers **99b** (IC_{50} = 3.71 μM and 15.4 μM) and **99c** (IC_{50} = 7.23 μM and 5.2 μM) show the high activity against *L. amazonensis* and *L. infantum*, respectively. They exhibited moderate activity against *T. cruzi* trypomastigotes (IC_{50} = 109.6 μM, 108.1 μM and 56.1 μM, respectively). Compounds **99a-c** were also more active than pentamidine (IC_{50} 8.9 μM) against *L. amazonenis*. In 2016, Daligaux *et al.* [118] synthesized a series of 52-aryl substituted deoxyguanosine triazole analogues and evaluated their antileishmanial activity *in vitro* against *L. donovani* axenic amastigotes stage and intra-macrophage amastigotes stage. The compound **100** (IC_{50} = 8.6 μM) was found to be the most potent on axenic amastigotes.

In a quest to discover novel antiparasitic drugs, Devender *et al.* [119] reported novel β-amino alcohol attached 1,2,3-triazole hybrids and screened their *in vitro* antiplasmodial activity and *in vivo* antimalarial activity. Compound **101a** (IC_{50} value 0.87 μM) and **101b** (IC_{50} value 0.3 μM) exhibited potent activity against CQ-sensitive (*Pf3*D7) strain, while compounds **101c** and **101d** (IC_{50} = 0.5 μM each) showed better activity *in vitro* against CQ-resistance strain (*Pf*K1), than the reference drug. Gontijo *et al.* [120] evaluated anti-leishmanial activity *in vitro* of a series of 16 simple long-chain alkyltriazoles and two novel alkylphosphocholine derivatives tethered with an azide moiety. Among the alkyltriazole derivatives, compounds **102a** (IC_{50} = 28.52 ± 0.73 μM and 14.25 ± 0.92 μM) and **102b** (IC_{50} = 37.17 ± 4.5 μM and 76.68 ± 4.76 μM) were found most promising against promastigote and amastigote forms respectively, as compared to established leishmanicidal drugs pentamidine and amphotericin B.

Adam *et al.* [121] prepared triazole compounds **103a-c** and screened their antiprotozoal activity against *L. braziliensis*, *L. infantum*, *L. guyanensis* and *L. amazonensis*. Compounds **103a** (IC_{50} = 19.54 μM) and **103c** (IC_{50} = 13.88 μM) showed more activity *in vitro* against *L. infantum* amastigotes than miltefosine, a reference drug (IC_{50} = 23.7 μM). Further, compound **103a** (IC_{50} = 84.93 ± 21.73 μM) exhibited high leishmanicidal activity *in vivo* against *L. infantum* spleen forms. Hamann *et al.* [122] also reported the synthesis of another type of novel triazole linked compounds and screened their biological activity *in vitro* against *Plasmodium falciparum* (a chloroquine-sensitive strain NF54). The compound **104** (IC_{50} = 1.00 μM) exhibiting the best activity.

Kumar *et al.* [123] synthesized 1*H*-1,2,3-triazole grafted isatin-ferrocene conjugates and screened their antiplasmodial



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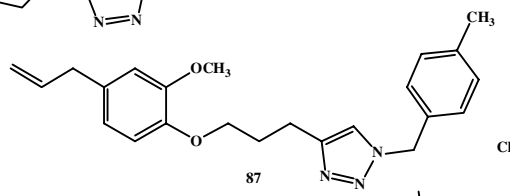

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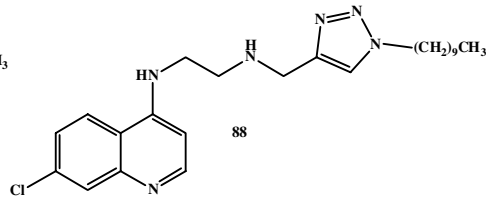

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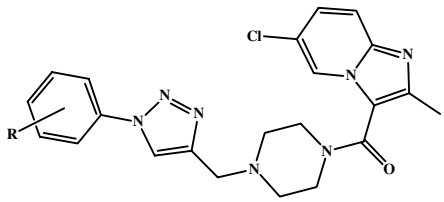
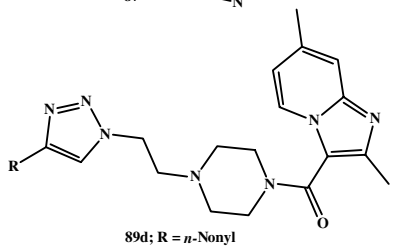
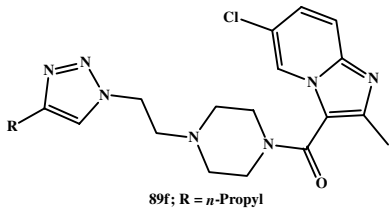


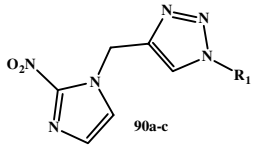
89a; R = 4-C_2H_5
89b; R = 4-Br
89c; R = 3-Cl



89d; R = *n*-Nonyl
89e; R = 4-*t*-Butyl phenyl

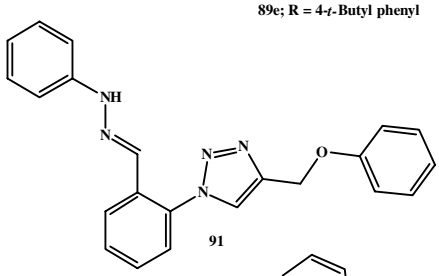


89f; R = *n*-Propyl
89g; R = *n*-Nonyl

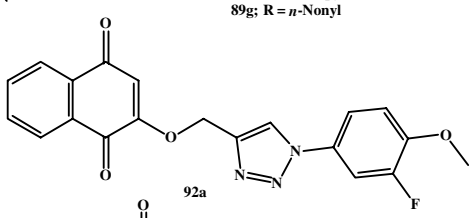


90a-c

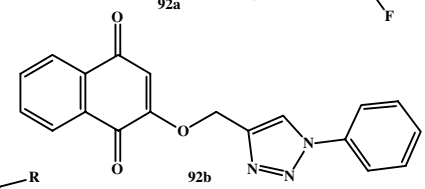
90a; R_1 = Ph
90b; R = 3,4-di-OCH_3-Ph
90c; R = 3-NO_2, 4-CH_3-Ph



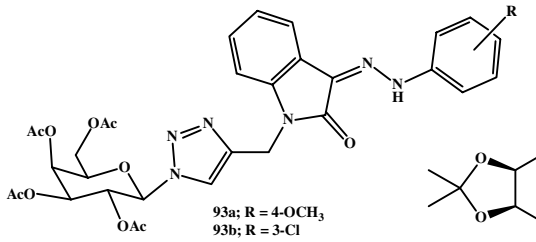
91



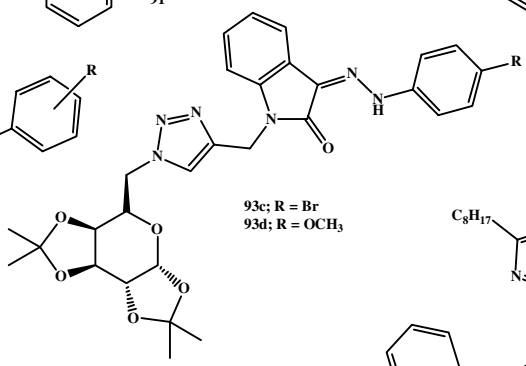
92a



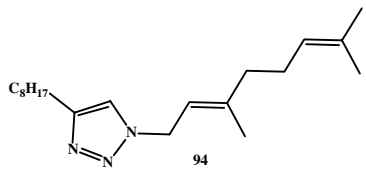
92b



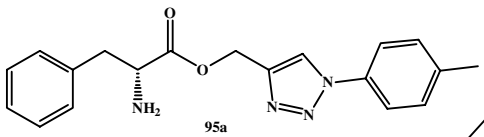
93a; R = 4-OCH_3
93b; R = 3-Cl



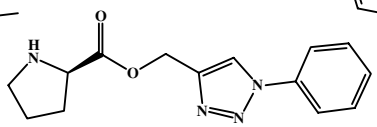
93c; R = Br
93d; R = OCH_3



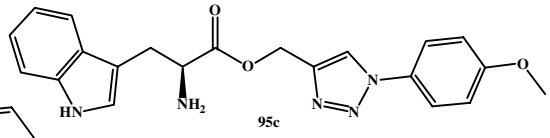
94



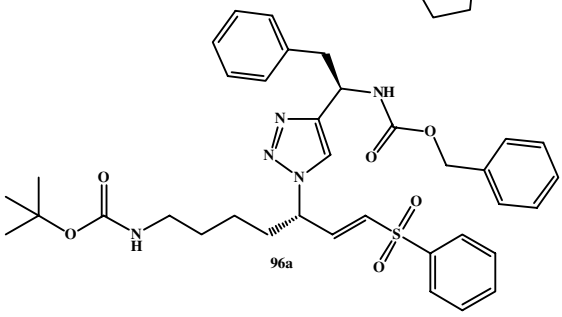
95a



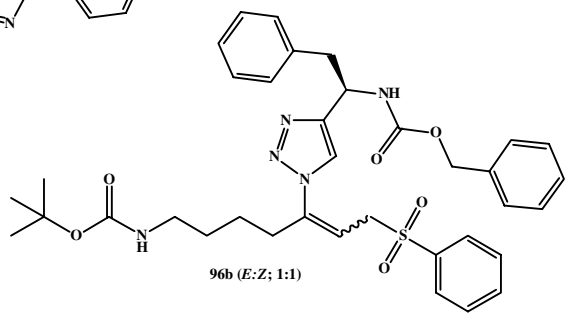
95b



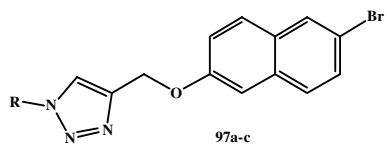
95c



96a

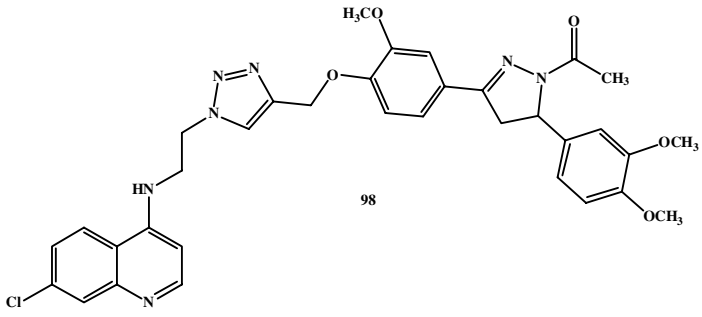


96b (*E*:*Z*; 1:1)

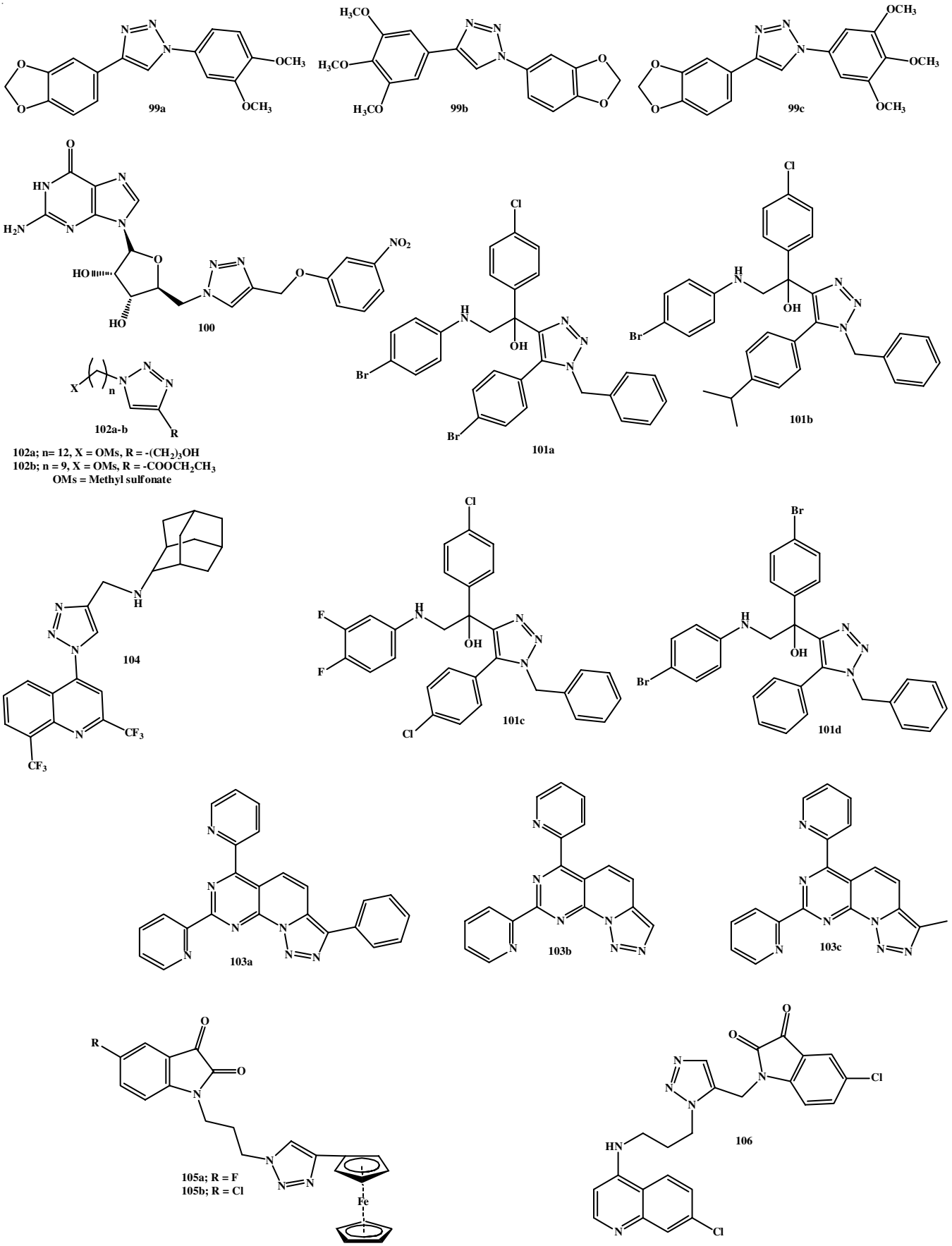


97a-c

97a; R = isopropyl
97b; R = isobutyl
97c; R = 4-nitrobenzyl



98



Structure of some 1,2,3-triazole derivatives (**86-106**) as antileishmanial, antitrypanosomal and antiplasmodial agents

activities *in vitro* against 3D7 and W2 strains of *P. falciparum*. The derivatives **105a** (IC_{50} = 3.76 and 5.97 μM) and **105b** (IC_{50} = 8.49 and 4.58 μM) demonstrated to be most potent and non-cytotoxic against 3D7 and W2 strains, respectively. Raj *et al.* [124] also reported the synthesis of 1*H*-1,2,3-triazole tethered 7-chloroquinoline-isatin hybrids using Cu-mediated click chemistry and screened their antimalarial activities. Compound **106** displayed the best activity among the screened compounds against W2-strain of *P. falciparum*.

Anti-inflammatory activity: Inflammation a hallmark of many metabolic diseases in which the body tissue are affected by inflammation, swelling, redness as well as pain.

In order to discover new anti-inflammatory agents, Zhang *et al.* [125] reported a series of compounds by joining 1,2,3-triazole moieties on ursolic acid. The anti-inflammatory activity of compounds was tested using an ear edema model. The *in vitro* cyclooxygenase COX-1/COX-2 inhibition assays was carried on potent anti-inflammatory compound. Compound **107** with 82.81% inhibition exhibited the highest activity of all of the compounds synthesized, better than positive control, celecoxib. The studies further revealed that effective COX-2 inhibitory activity was exhibited by compound **107** (IC_{50} = 1.16 μM) and selectivity index (SI = 64.66), close to that of celecoxib with IC_{50} = 0.93 μM and SI = 65.47. The results further suggest a promising lead as a new COX-2-targeting anti-inflammatory agent. Using click chemistry approach, Begam *et al.* [126] synthesized a naphthalimide tethered 1,2,3-triazole novel derivatives and evaluated their *in vitro* anti-inflammatory potential. The synthesized compounds at 200 μM show their significant selective inhibitions. Compound **105** showed inhibition against the protein denaturation assays of bovin serum albumin (92.3%) and that of egg albumin (92.3%). The molecular docking studies of compound **108** shows a strong inhibitory effect against COX1 and COX2 with the reasonable free energy of binding -13.58 and -10.42 kcal mol^{-1}, respectively.

Ankali *et al.* [127] also synthesized novel 1,3-thiazole linked-1,2,3-triazoles. The *in vivo* activity result of the synthesized compounds demonstrated that the compounds **109a-d** possess maximum anti-inflammatory activity against carrageenan induced acute inflammation in rats as compared to a reference drug, diclofenac.Using biochemical assays, Cheng *et al.* [19] demonstrated the anti-inflammatory, viability and antioxidant potential of novel synthesized ferrocene-1*H*-1,2,3-triazole hybrids. Compound **110** showed the potent anti-inflammatory effect on rat mesangial cells (RMCs). The molecular docking with cPLA2 and COX-2 enzymes as well as ADMET profiling supplement the results. Tan [128] synthesized novel 1,2,3-triazole bearing carbasugar s by using CuAAC. The *in vitro* inhibition effects of compounds were investigated on the xanthine oxidase enzyme. The results revealed that compounds **111a** and **111b** with IC_{50} = 0.586 ± 0.017 μM and 0.751 ± 0.021 μM, respectively, showed potent inhibition than allopurinol (IC_{50} value 1.143 ± 0.019 μM), a gout drug, used for inhibition of the enzyme. Search for novel drugs with higher anti-inflammatory activities and lower cytotoxicity Liu *et al.* [129] synthesized 1,2,3-triazole derivatives and evaluated their bioactivities *in vitro*. The results indicated that compound **112** exhibited potent inhibition on the expression of IL-6 in LPS-induced RAW 264.7 macrophage cell.

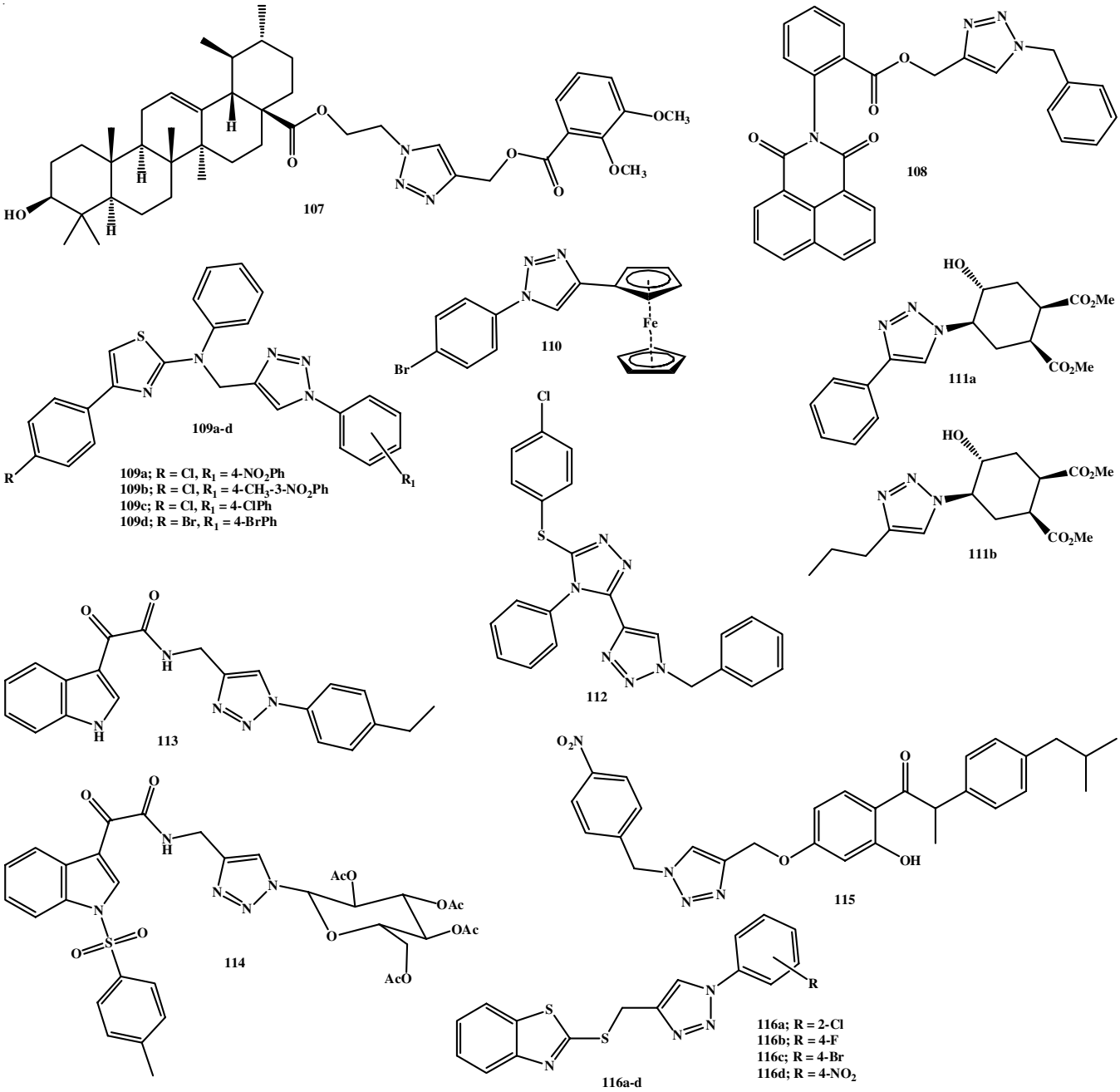
Naaz *et al.* [130] synthesized novel 1,2,3-triazole grafted indole-3-glyoxamide derivatives employing click chemistry approach and evaluated their *in vitro* COX-1, COX-2 and 5-LOX inhibitory potencies as well as *in vivo* antiinflammatory and *in vitro* antiproliferative activities. The derivatives **113** and **114** with IC_{50} = 0.12 μM exhibited potent inhibition of COX-2. With IC_{50} value 7.73 μM and 7.43 μM, respectively, the compounds also showed comparable 5-LOX inhibitory activity compared to standard norhihydroguaiaretic acid (NDGA) with IC_{50} value 7.31 μM.

Similarly, considering the individual medicinal and biological properties of ibuprofen and 1,2,3-triazoles, Angajala *et al.* [131] synthesized novel ibuprofen-based 1,4-disubstituted 1,2,3-triazole hybrids using click chemistry. Among the synthesized hybrids, compound **115** has shown potent effect than the reference anti-inflammatory drug, ibuprofen at 10 mg/kg of body weight. Shafi *et al.* [132] synthesized novel 1,2,3-triazole hybrids utilizing click chemistry and screened the anti-inflammatory activity of hybrids using biochemical assays. Compound **116b** exhibited a significant selective COX-2 inhibition potential with COX-2/COX-1 ratio of 0.44. Further, the results from carrageenan-induced hind paw edema revealed that compounds **116a-d** exhibit significant anti-inflammatory activity in comparison to ibuprofen.

Antidiabetic activity: 1,2,3-Triazoles have been also frequently screened for their antidiabetic properties. Particularly, 1,2,3-triazoles conjugated to diverse heterocyclic scaffolds have been reported to reveal potential antidiabetic activities.

A series of novel aryl benzylidenethiazolidine-2,4-dione tethered 1,2,3-triazole derivatives were synthesized by Patnam *et al.* [133]. The new derivatives were tested for antidiabetic activity *in vitro* by inhibition of aldose reductase enzyme. The activity results were compared with standard reference sorbinil with half inhibition concentration (IC_{50}) = 3.45 ± 0.25 μM. Among all the synthesized compounds **117a** (IC_{50} = 1.42 ± 0.21 μM), **117b** (IC_{50} = 1.85 ± 0.39 μM), **118** (IC_{50} = 1.94 ± 0.27 μM) and **117c** (IC_{50} = 1.98 ± 0.58 μM) showed the highest potent activity. Similarly, Iraji *et al.* [134] presented the synthesis of a novel cyanoacetohydrazide linked to 1,2,3-triazoles and evaluated their anti-α-glucosidase activity. Almost all compounds revealed potent inhibitory activity (IC_{50} values ranging 1.00 ± 0.01 μM to 271.17 ± 0.30 μM), in comparison to reference acarbose with IC_{50} =value 754.1 ± 0.5 μM. The kinetic binding energy studies indicated that the most active derivatives are **119a** with IC_{50} value 1.50 ± 0.01 μM and **119b** with IC_{50} value 1.00 ± 0.01 μM and potent α-glucosidase inhibitor.

Gorantla *et al.* [135] synthesized the 1,2,3-triazole-α-D-glucoside derivatives. Among the synthesized derivatives, several compounds exhibited strong inhibition of human lysosomal α-glucosidase activity. Compounds **120** (IC_{50} = 18 μm) and **121** (IC_{50} = 17 μm) were possessing more than 60-fold lower IC_{50} values compared to acarbose, the reference inhibitor. Some novel benzimidazole grafted 1,2,3-triazole hybrids were reported by Deswal *et al.* [136] using click reaction and their



Structure of some 1,2,3-Triazole derivatives (**107-116**) as anti-inflammatory agents

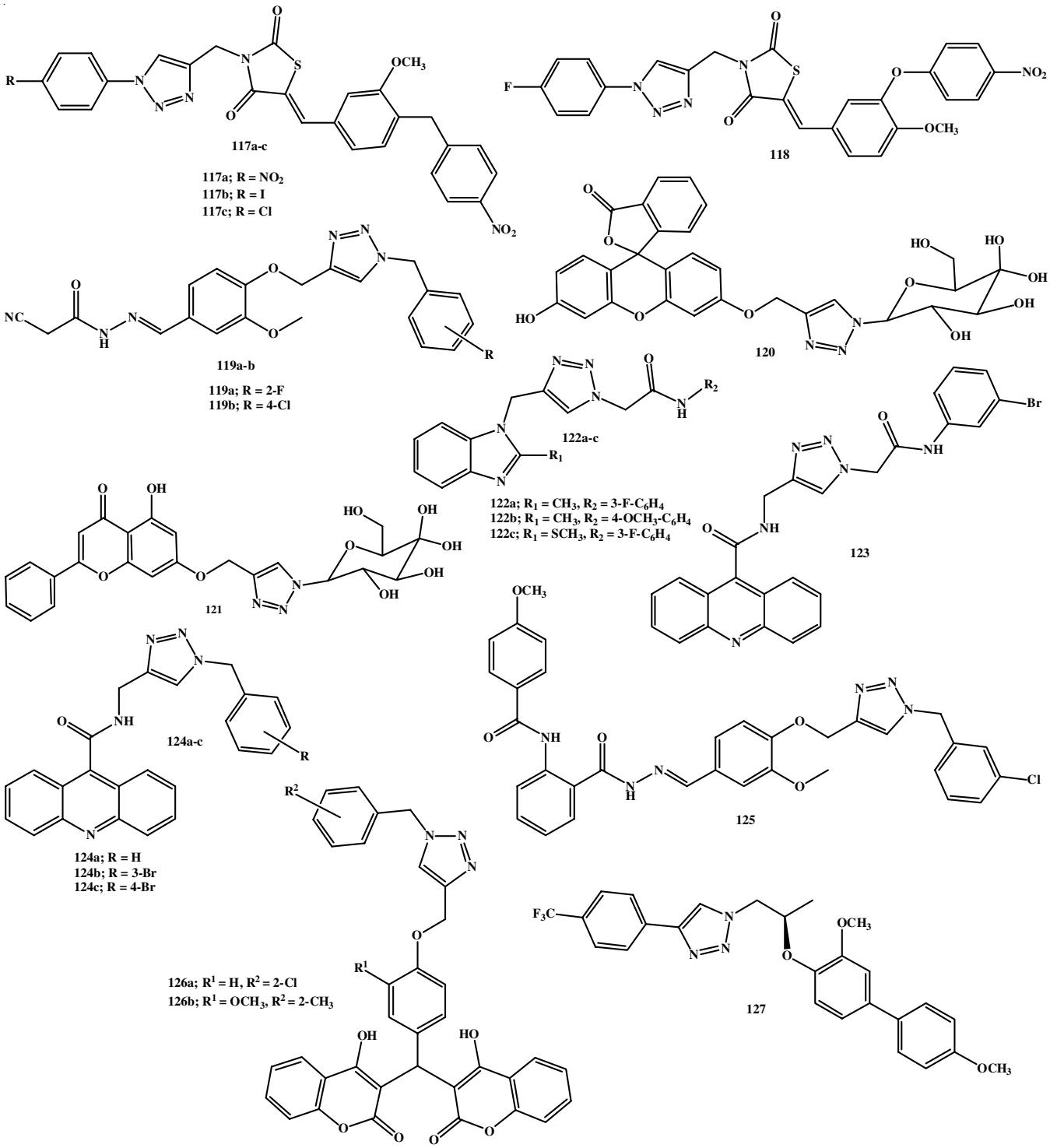
antidiabetic activity screened. All the compounds exhibited a good-to-moderate α-amylase inhibitory activity as well as α-glucosidase inhibitory activity. Hybrids **122a** (IC_{50} = 5.304 μg/mL), **122b** (IC_{50} = 5.8 μg/mL) and **122c** (IC_{50} = 6.44 μg/mL) were observed to be the most active comparing with the standard inhibitor acarbose (IC_{50} = 4.12 μg/mL).

Sepehri *et al.* [137] also synthesized a novel acridine-9-carboxamide tethered to 1,2,3-triazole-*N*-phenylacetamide derivatives and evaluated their potential for α-glucosidase inhibitor activity. All the derivatives demonstrated excellent to good inhibitory activity (IC_{50} = 80.3 ± 0.9 to 564.3 ± 7.2 μM) in comparison to acarbose, a standard drug (IC_{50} value = 750.0 ± 10.5 μM), against α-glucosidase enzyme. The lead compound was found to be **123** with inhibitory activity around 9.3 times more than standard acarbose. Asgari *et al.* [138] also designed and synthesized novel acridine-9-carboxamide-1,2,3-triazole derivatives and evaluated their novel α-glucosidase inhibitor properties. Results showed that most of the derivatives possess more potency as compared to standard inhibitor, acarbose. The lead derivatives were compounds **124a** (IC_{50} = 157.6 ± 1.6 μM), **124b** (IC_{50} = 151.1 ± 1.4 μM) and **124c** (IC_{50} = 120.2 ± 1.0 μM) comparing to standard acarbose (IC_{50} = 750.0 ± 10.0 μM).

Nasli-Esfahani *et al.* [139] synthesized new 1,2,3-triazole bearing Schiff bases and evaluated their α-glucosidase inhibitor properties. Compounds were more promising than the standard drug acarbose in inhibiting α-glucosidase. *In vitro* α-glucosidase inhibitory activity of the lead compound **125** (IC_{50} = 107.1 ±

1.4 μM) demonstrated that the compound is the competitive inhibitor of α-glucosidase. Asgari *et al.* [140] synthesized a novel biscoumarin-1,2,3-triazole derivatives and evaluated their α-glucosidase inhibitory properties. Compounds **126a** (IC_{50} = 13.0 ± 1.5 μM) and **126b** (IC_{50} = 16.4 ± 1.7 μM) were found to exhibited the highest inhibitory activity against α-glucosidase in comparison with the acarbose (IC_{50} = 750.0 ± 12.0 μM). The compounds were also found non-cytotoxic towards normal fibroblast cells. In the quest for identification of novel inhibitors of α-glucosidase enzyme, Avula *et al.* [141] synthesized 1,2,3-triazole derivatives, where most of the derivatives exhibited significant inhibitory activity against the enzyme and compound **127** was the lead analogue (IC_{50} = 14.2 μM).

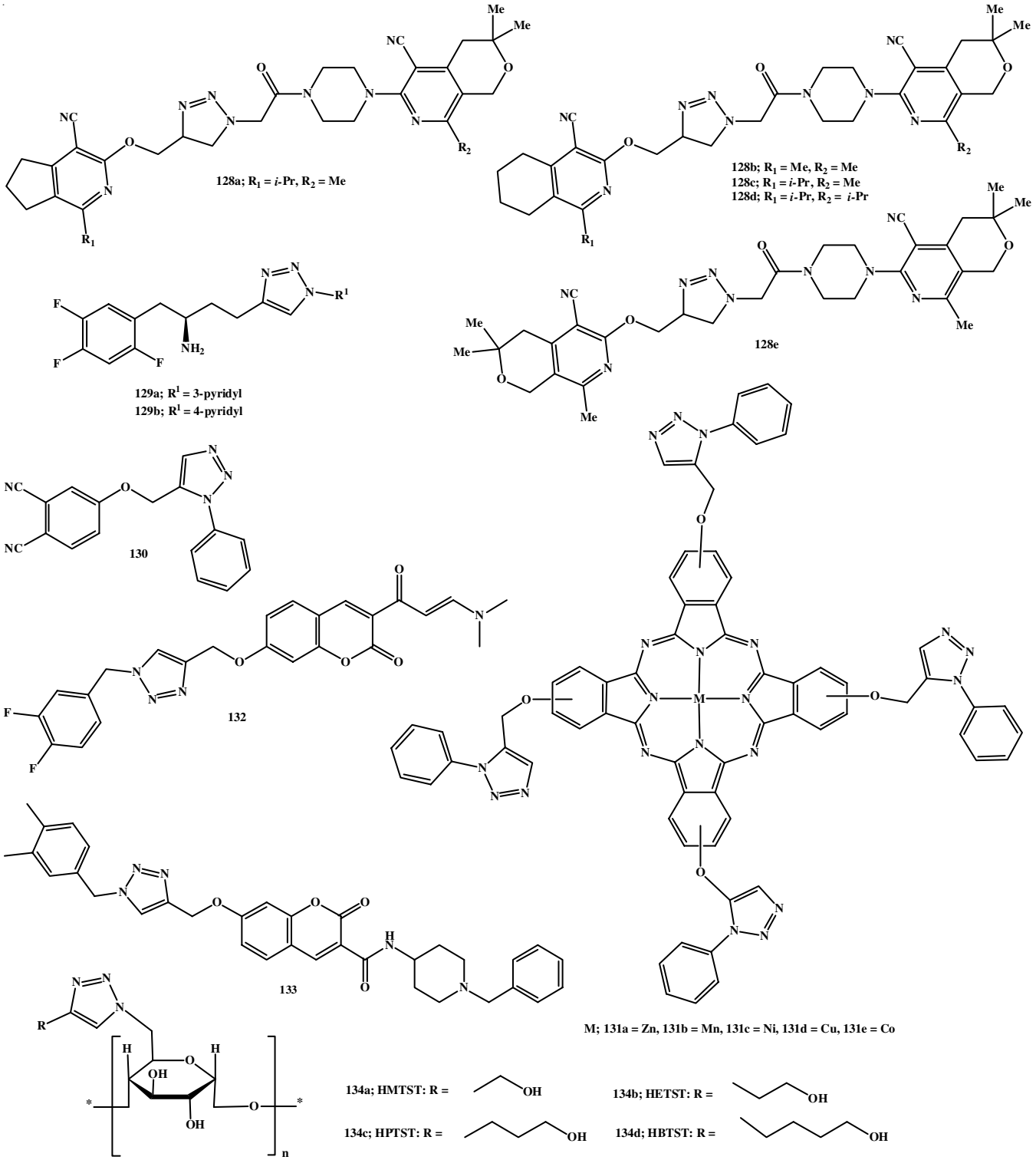
Miscellaneous activities: The anticonvulsant activity and some psychotropic properties of new bicyclic pyridine-based hybrids tethered to 1,2,3-triazoles were studied by Sirakanyan *et al.* [142] using a click reaction. The biological assays proved



Structure of some 1,2,3-triazole derivatives (**117-127**) with antidiabetic agents

that some compounds showed high anticonvulsant activities and psychotropic properties. The five lead compounds **128a-e** possess anticonvulsant activity with ED_{50} of 20, 16, 18, 22 and 15 mg/kg, respectively using pentylenetetrazole antagonism test. Whereas Vo *et al.* [143] synthesized novel 1,2,3-triazole analogues and their inhibitory activity was evaluated against dipeptidyl peptidase 4 (hDPP-4). All the analogues demonstrated moderate (265~780 nM) hDPP-4 inhibitory activities *in vitro*. The results showed that compounds **129a** and **129b** exhibit excellent potency with IC_{50} of 28 and 14 nM, respectively, against hDPP-4 enzyme.

For enzyme inhibition activities, Koçyigit *et al.* [144] reported the synthesis of 1,2,3-triazole group substituted metallophthalocyanine derivatives. The derivatives **131a-e** inhibited acetylcholinesterase (AChE) effectively with K_i values ranging 40.11 ± 5.61 to 78.27 ± 15.42 μM. Compounds **130** and **131a**



Structure of some 1,2,3-triazole derivatives (**128-134**) exhibiting pharmacological activities

were most effective for α-glycosidase activity with K_i values 16.11 ± 3.13 and 18.31 ± 2.42 μM, respectively. Likewise, Karimi *et al.* [145] designed and synthesized a novel series of 1,2,3-triazole-chromenone derivatives and evaluated for biological activities *in vitro* like AChE and BuChE inhibition including neuroprotective efects, anti-Aβ aggregation and metal-chelating properties. Compound **132** was the lead compound and possesses highly selective BuChE inhibitory activity.

1,2,3-Triazole-chromenone carboxamide derivatives were synthesized by Rastegari *et al.* [146] for cholinesterase inhibitory activity. Compound **133** (IC_{50} = 1.80 μM) demonstrated the best acetylcholinesterase inhibitory activity. Moreover, compound **133** was also evaluated for its β-secretase (BACE1) inhibitory activity, the result confirmed desired inhibitory activity with IC_{50} = 21.13 μM. Further, the compound exhibited satisfactory neuroprotective activity against H_2O_2-induced cell death in PC12 neurons at the concentration of 50 μM and also revealed satisfactory metal chelating ability toward metal ions Fe^{2+}, Cu^{2+} and Zn^{2+}. Based on the click chemistry, Tan *et al.* [147] developed the novel synthesis of 1,2,3-triazole-linked starch derivatives. The *in vitro* antioxidant properties of compounds against DPPH-radical, hydroxyl-radical and superoxide-radical was evaluated. Compounds **134a-d** showed significant improvement over starch and scavenging effect indices higher than 60% at 1.6 mg/mL against DPPH-radical and hydroxyl-radical. Moreover, against superoxide-radical the scavenging effect of the synthesized compounds was found to be < 90% at 0.1 mg/mL.

Conclusion

This review article summarized various pharmacological activities exhibited by 1,2,3-triazole hybrids clearly demonstrating their wide range of medicinal applications. It is anticipated that many new pharmacological profiles will be added to this versatile framework by designing new 1,2,3-triazole containing hybrids and conjugates binding to multiple targets so as to achieve effective breakthrough in the treatment of challenging diseases like cancer, Alzheimer's disease, *etc*. Finally, it can be concluded that there is still a lot of scope to explore 1,2,3-triazole rings for future development of novel drugs that could be better in terms of their potency against various diseased conditions and with lesser toxicity thereby making life better to live.

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CONFLICT OF INTEREST

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

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