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Review article

An insight on medicinal attributes of 1,2,4-triazoles

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ABSTRACT

The present review aims to summarize the pharmacological profile of 1,2,4-triazole, one of the emerging privileged scaffold, as antifungal, antibacterial, anticancer, anticonvulsant, antituberculosis, antiviral, antiparasitic, analgesic and anti-inflammatory agents, etc. along with structure-activity relationship. The comprehensive compilation of work carried out in the last decade on 1,2,4-triazole nucleus will provide inevitable scope for researchers for the advancement of novel potential drug candidates having better efficacy and selectivity.

Contents

1. Introduction

Among the various azaheterocyclic systems, azoles, in general, and 1,2,4-triazoles in particular are the focus of renewed interest among organic and medicinal chemists since several novel hybrids

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with broader spectrum have been synthesized based on molecular hybridization approach [1]. Among the azoles, triazoles are the most stable compounds and are difficult to cleave. 1,2,4-Triazole having molecular formula $C_2H_3N_3$ acts as isosteres of amide, ester and carboxylic acid. It may be formally derived from pyrazole by substitution of a carbon at position-4 by nitrogen atom. 1,2,4-Triazole exists in two tautomeric forms **A** and **B** in which 1*H*-1,2,4-triazole (**A)** is more stable than 4*H*-1,2,4-triazole (**B)** as depicted in Fig. 1 [2].

1,2,4-Triazoles act as important pharmacophores by interacting with the biological receptors with high affinity owing to their dipole character, hydrogen bonding capacity, rigidity and solubility. This motif is an integral part of a variety of drugs available in clinical therapy including antifungal (fluconazole, itraconazole, posaconazole, voriconazole, ravuconazole) anxiolytic, anticonvulsant and hypnotic (estazolam, alprazolam), anxiolytic and skeletal muscle relaxant (etizolam), antimigraine (rizatriptan), antiplatelet (trapidil), antidepressant (trazodone), anticancer (anastrozole), aromatase inhibitor (letrozole), antiviral (ribavirin) and anticonvulsant (loreclezole) (Fig. 2) [3,4]. Some commercial plant protection fungicides contain the triazole moiety, such as prothioconazole, triadimefon, metconazole, propiconazole, tebuconazole, epoxyconazole, triadimenol and cyproconazole [5].

1,2,4-Triazoles and their fused heterocyclic derivatives have been reported to possess a wide range of bioactivities such as neuroprotectant [6], antioxidant [7], antimalarial [8], antileishmanial [9], anti-urease [10], antiviral [11,12], anticonvulsant [13], cannabinoid CB1 receptor antagonists [14], PDE4A inhibitors [15] and γ-aminobutyric acid-A (GABA-A) α-2, α-3 and α-5 containing receptor antagonists [16]. Moreover, they have applications in ionic liquids, corrosion inhibitors, agrochemicals, polymers, supramolecular and material science [17–21].

Owing to the mounting importance of 1,2,4-triazoles in emerging domains, it is envisaged to bring out a comprehensive review of this privileged framework from 2010 onwards on the medicinal profile.

2. Biological activities of 1,2,4-triazole derivatives

2.1. Antifungal agents

The emergence of multidrug-resistant pathogens impelled the researchers to develop novel broad spectrum triazoles having high impact, ease of administration and low toxicity to conquer the resistance. The triazole antifungal drugs potently act by inhibiting the activity of cytochrome P450-dependent enzyme, the lanosterol 14α-demethylase (CYP51), which is the key enzyme in ergosterol biosynthesis of fungi [22].

Design, synthesis and antifungal activities of large number of 1-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)-4-substituted derivatives **1**–**15** as fluconazole or voriconazole or ravuconazole analogues have been carried out by Chinese group(s) (Fig. 3) [23–35]. Compound **1n** (MIC_{80}: 0.0156 μg/mL) exhibited 16 fold more antifungal activity than fluconazole against *Candida albicans* [23]. Docking study of compound **2** revealed the significance of 1,2,3-triazole group and the substituted benzyl as side chains for antifungal activity [24,25]. Compound **3** having $R_1 = CF_3$ group displayed broad antifungal spectrum with MIC_{80} values in the range of 0.00097–0.0156 μg/mL against human pathogenic fungi (*C. albicans, Candida parapsilosis, Candida tropicalis, Cryptococcus neoformans, Trichophyton rubrum, Fonsecaea compacta* and *Microsporum gypseum*) [26]. It exhibited 64 fold more potency than reference drugs fluconazole and voriconazole against *Aspergillus fumigatus* (MIC_{80}: 1 μg/mL). Molecular docking studies of **4** (R = 3-Cl) in active site of CACYP51 showed multiple molecular interactions of difluorophenyl group and terminal triazolone side chain with hydrophobic region as well as coordinate bond formation of triazole ring with iron of heme group [27]. Lengthening of the side chain by a double bond influences the spatial orientations of compounds **5** in target enzyme leading to low antifungal activities.

Compounds **6** demonstrated good antifungal activity (MIC: 0.0625–1 μg/mL) for *C. albicans* [28]. Among compounds **7** and **8**, analogue **7a** (R_1 = Br and R_2 = H) displayed excellent potency (MIC: 0.0313–1 μg/mL) against all tested fungal strains [29]. Triazole derivatives **9** and **10** having heterocycle-benzene bioisosteric replacement showed excellent antifungal activity with improved oral absorption. SAR study revealed that substituted piperazine derivatives **10** were comparable or superior to the corresponding *N*-methyl derivatives **9** and heterocyclic substitutions influenced the activity differently in compounds **9** and **10** [30]. The MIC_{80} values of compounds **11a**-**m** against *C. albicans* were ranged in nanomole levels (0.009–0.480 nmol/mL) [31].

Dithiocarbamate derivatives of fluconazole **12** exhibited high activity (MIC_{80}: <0.125–2 μg/mL) against *C. albicans*, *C. neoformans*, *C. parapsilosis* and *Candida glabrata* [32]. SAR indicated that among compounds **13**, two compounds **13e** and **13f** having R = 2-Cl and R = 3-Cl, respectively displayed the highest activity against *C. albicans* with MIC_{80} of 0.0039 μg/mL and were 16-, 64-, 128-, and 2051-fold more potent than voriconazole, itraconazole, fluconazole, and ketoconazole, respectively [33]. Isoxazole containing triazole analogues of ravuconazole **14a-c** displayed superior activity than ravuconazole against 8 fungal isolates [34]. Wu et al. synthesized and evaluated voriconazole analogues **15** having substituted amines or heterocycles as side chain for their *in vitro* and *in vivo* antifungal activity against several human pathogenic fungi [35]. From screening results and docking experiment, it was observed that compound having morpholine moiety exhibited the strongest activity to inhibit the growth of ten fungal pathogens (MIC_{80}: 0.0156–0.5 μg/mL).

In another concomitant study, a series of triazole alcohols having 4-(substituted-1*H*-indol-3-ylmethyl)-piperazinyl side chain **16** were synthesized and evaluated for antifungal activity against *C. albican*, *C. neoformans*, *C. krusei*, and *A. fumigatus* by Young Min Na [36]. SAR study revealed that multihalogenated indole derivatives of triazole were 4-fold more active against *C. Albicans*, *A. fumigatus* and *C. krusei* (Fig. 4). Several triazoles with fused-heterocycle nuclei were designed and synthesized by Cao et al. [37], among which the most potent compound **17** (Fig. 4) displayed excellent activity against *Candida*, *Cryptococcus*, *Aspergillus* species and selected fluconazole-resistant strains. Shrestha et al. [38] synthesized a series of alkylated-fluconazole derivatives **18** which exhibited low hemolytic activity, low cytotoxicity and good activity against *C. albicans*, non-*albicans Candida* and *Aspergillus* strains (Fig. 4).

Several carbazole-triazole conjugates **19** (Fig. 4) were synthesized and screened for their antifungal activities against *C. albicans*, *C. tropicalis*, *C. parapsilosis* and *A. fumigatus* by Zhang et al. [39]. Preliminary mechanistic study revealed that the most active

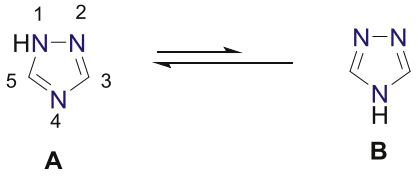


Fig. 1. Tautomeric forms of 1,2,4-triazole.

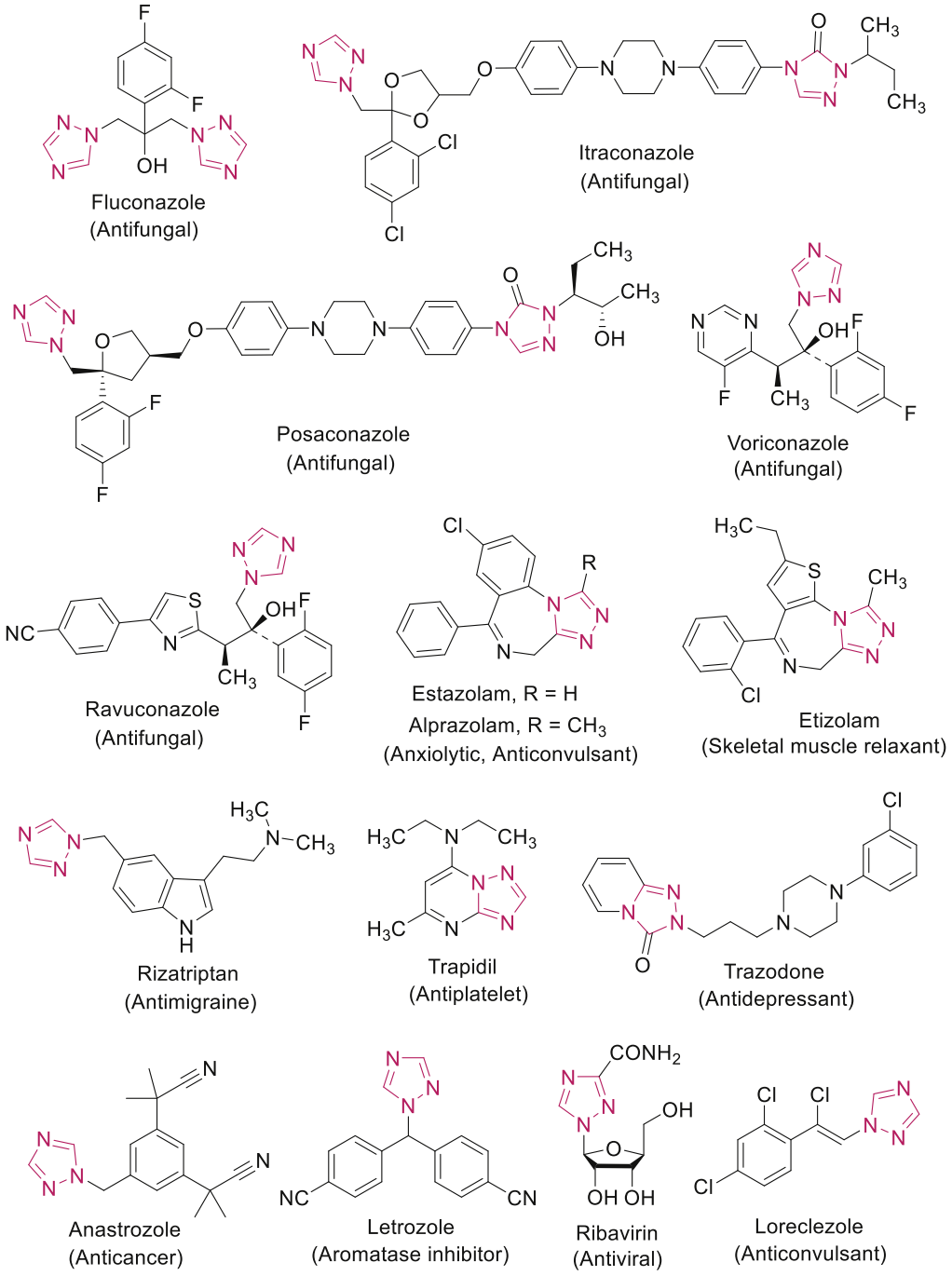


Fig. 2. Clinically used drugs having 1,2,4-triazole scaffold.

compound **19** having 3,6-dibromocarbazole could depolarize fungal membrane potential and intercalate into DNA to exhibit antifungal action. Coumarin-substituted triazole antifungals **20** were screened against a panel of *Candida* pathogens by Elias et al. [40] and live-cell imaging revealed that fluorescent 7-diethylaminocoumarin-based triazoles localized to the fungal cell endoplasmic reticulum (Fig. 4).

Luo et al. synthesized a series of 1,3,4-thiadiazole derivatives bearing 1,2,4-triazolo[1,5-*a*]pyrimidine moiety **21** (Fig. 5) and evaluated their antifungal activities against *Fusarium oxysporum f.sp. vasinfectum*, *Gibberella sanbinetti*, *Cercospora beticola Sacc*, *Physaclospora piricola* and *Rhizoctonia solani* [41]. SAR studies showed that compounds (**21d**, **21f**, **21h**, **21i**, **21k**, **21o**, **21t** and **21u**) having electron-withdrawing groups (Cl, Br, F, NO_2) at position 2 and 4 of the benzene ring exhibited better activity than others against *P. piricola*. Among them, compound **21t** bearing two electron-withdrawing F atoms at position 2 and 4 displayed best activity with 86% inhibition against *P. piricola* which was found to be more than carbendazim (74%).

A series of triazole-oxadiazole derivatives **22** (Fig. 5) was synthesized and evaluated for antifungal and apoptotic activities against *C. albicans, C. parapsilosis, C. krusei and C. glabrata* by Çavusoglu et al. [42]. The study unveiled that compound **22i** was equipotent to ketoconazole against *C. albicans* and *C. glabrata* and exhibited antifungal effect *via* apoptotic pathway. Among the synthesized quinoline based benzothiazolyl-1,2,4-triazoles **23**

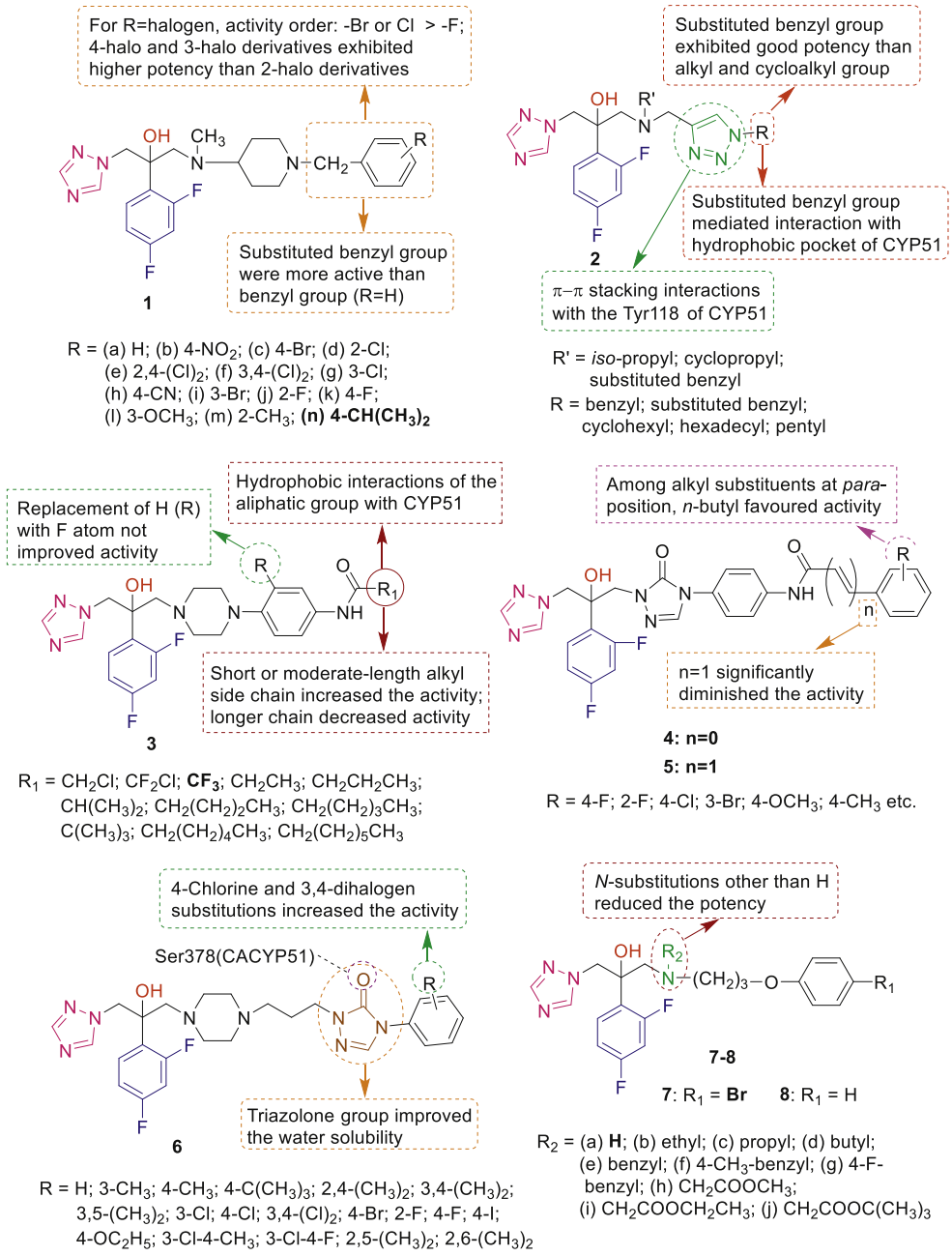


Fig. 3. SAR and antifungal activity profiles of 1-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)-4-substituted derivatives.

(Fig. 5), compounds **23f** and **23j** (MIC: 6.25 μg/mL) were 2-fold more potent than standard fluconazole (MIC: 12.5 μg/mL) against *C. albicans* while compounds **23g** and **23i** (MIC: 6.25 μg/mL) exerted high activities against *Aspergillus niger* and were equipotent to fluconazole (MIC: 6.25 μg/mL) [43].

Lin et al. have reported the synthesis and *in vitro* antifungal activity of a series of myrtenal derivatives bearing 1,2,4-triazole moiety **24** at 50 μg/mL [44]. The study revealed that most of the compounds showed enhanced activities than that of myrtenal, indicating that the incorporation of 1,2,4-triazole-thioether moiety into the myrtenal molecule was beneficial to the increase of antifungal activity (Fig. 5). Some of the compounds exhibited excellent activity against *P. piricola* with an inhibitory rate 90–98% comparable to commercial fungicide azoxystrobin 96%.

1,2,4-Triazole Schiff base **25** (EC_{50}: 0.0087–0.0309 g/L) exhibited higher antifungal activity than triadimefon (EC_{50}: 0.0195–0.0620 g/L) against *Gibberlla nicotiancola* and *Gibberlla saubinetii* (Fig. 5) [45]. Zoumpoulakis et al. have reported the synthesis and antifungal activity of sulfonamide-1,2,4-triazole derivatives **26** (MIC: 0.01–0.27 μmol/mL) against several fungal strains (Fig. 5) [46]. With certain fungi (e.g. *A. niger*, *Trichoderma viride*, and *Aspergillus flavus*) this activity was 10–70 times higher than the commercial antifungal agents bifonazole and ketoconazole. A series of amide derivatives of 1,2,4-triazole **27** (Fig. 5) was reported to exhibit moderate to high antifungal activity against *Gibberella azeae*, *Fusarium oxysporum*, *Cytospora mandshurica*, *Pellicularia sasakii*,

and *Phytophthora infestans* at 50 mg/L by Tang et al. [47]. SAR study revealed the significance of R group as shown in Fig. 5.

2.2. Antibacterial agents

Most of the synthesized clinafloxacin-triazole hybrids **28** (MIC: 0.25–2 μg/mL) endowed with good antibacterial and antifungal activities were comparable or more potent than the reference drugs chloramphenicol, clinafloxacin and fluconazole [48]. SAR studies revealed that compound **28g** with a 2,4-difluoro at phenyl ring exhibited most potent antimicrobial efficacy (MIC: 0.25–1 μg/mL) particularly against methicillin-resistant *Staphylococcus aureus* (MRSA) among the tested compounds as displayed in Fig. 6.

Most of the ciprofloxacin-1,2,4-triazole-5(4*H*)-thione hybrids **29** (MIC: 0.046–3.11 μM) were tested against a panel of pathogens and were found to have higher potency against MRSA than the references vancomycin (MIC: 0.68 μM) and ciprofloxacin (MIC: 2.96 μM) [49,50]. SAR analysis of hybrids **29** (Fig. 6) divulged that phenyl groups at C-3 position played crucial role in exerting high activity and electron-donating groups, particularly –OH on the phenyl ring favored the activity; while substituted phenyl group on *N*-4 position of the 1,2,4-triazole-5(4*H*)-thione moiety was not essential for activity; the length of the alkyl chain on position *N*-4 had influence on the activity and the longer alkyl chain decreased the activity significantly.

Mermer et al. synthesized quinolone-triazole hybrids **30** (Fig. 6) and evaluated for their antibacterial, DNA gyrase and topoisomerase IV inhibitory activities [51]. Among them, compounds **30a** and **30b** displayed the highest antibacterial activity (MIC: 0.125–8 μg/mL) against *S. aureus*, *Enterococcus faecalis*, *Escherichia coli*, *Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Acinetobacter haemolyticus*.

Two set of quinolone triazoles **31** and **32** (Fig. 6) were screened for their antimicrobial activities against a panel of bacterial and fungal strains in which **31d** having trifluoromethyl group at phenyl ring (MIC: 1–8 μg/mL) exhibited broader bioactive spectrum against all bacterial strains (*Micrococcus luteus*, *MRSA*, *S. aureus*, *P. aeruginosa*, *E. coli*, *Shigella dysenteriae* and *Eberthella typhosa*) than norfloxacin and chloromycin. Compound **31b** exhibited excellent antifungal activities against *A. flavus*, *C. albicans* and *B. yeast* (MIC: 0.5, 2 and 4 μg/mL, respectively) in comparison with fluconazole (MIC: 256, 1 and 16 μg/mL, respectively) [52].

Triazole-fused fluoroquinolones **33** with a functional Mannich-base moiety at the C-8 position (Fig. 6) exhibited considerable antibacterial activities [53]. Nalidixic acid based 1,2,4-triazolo[3,4-*b*] [1,3,4]thiadiazole derivatives **34** were evaluated for their antimicrobial activity against two Gram-positive bacteria (*S. aureus* and *Bacillus subtilis*), three Gram-negative bacteria (*P. aeruginosa*, *E. coli* and *K. pneumoniae*) and two fungi (*A. niger* and *F. oxysporum*) by Aggarwal et al. [54]. SAR study revealed that compound **34b** with

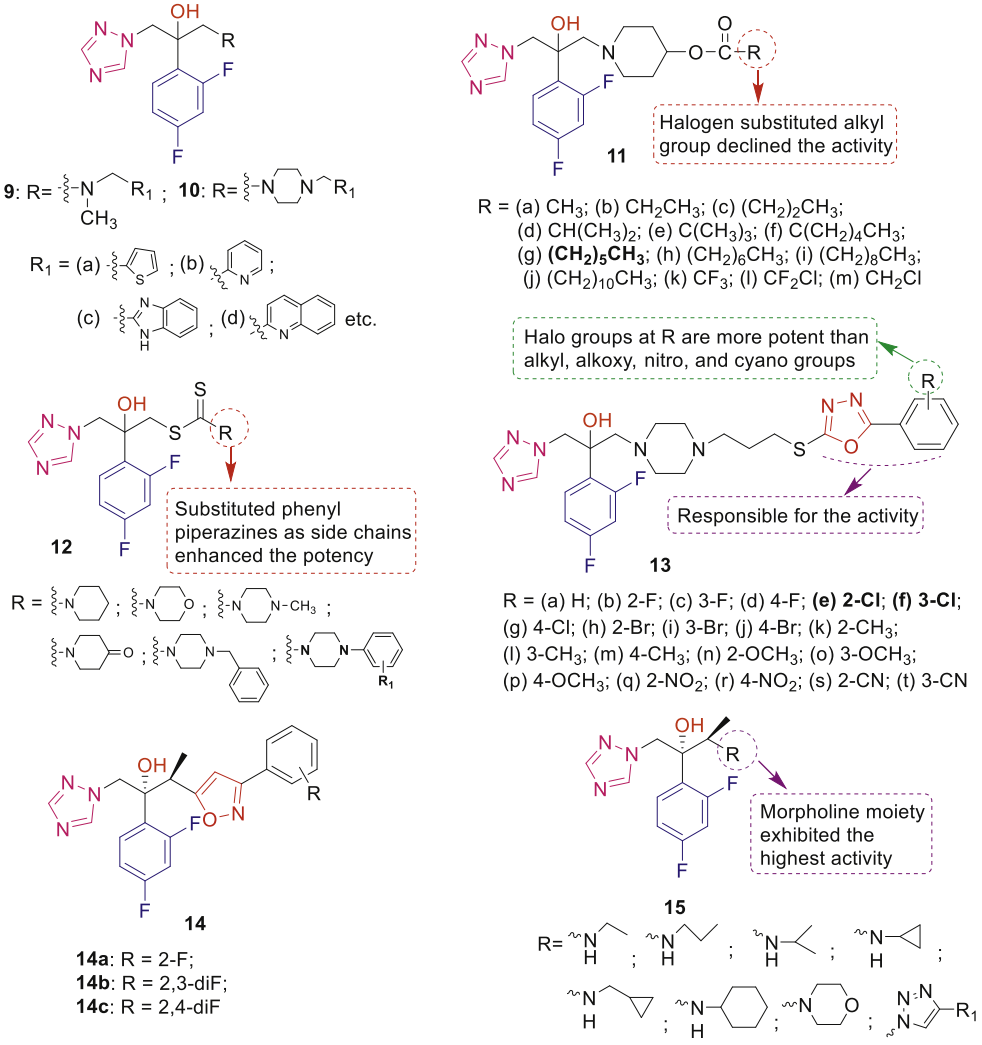


Fig. 3. (*continued*).

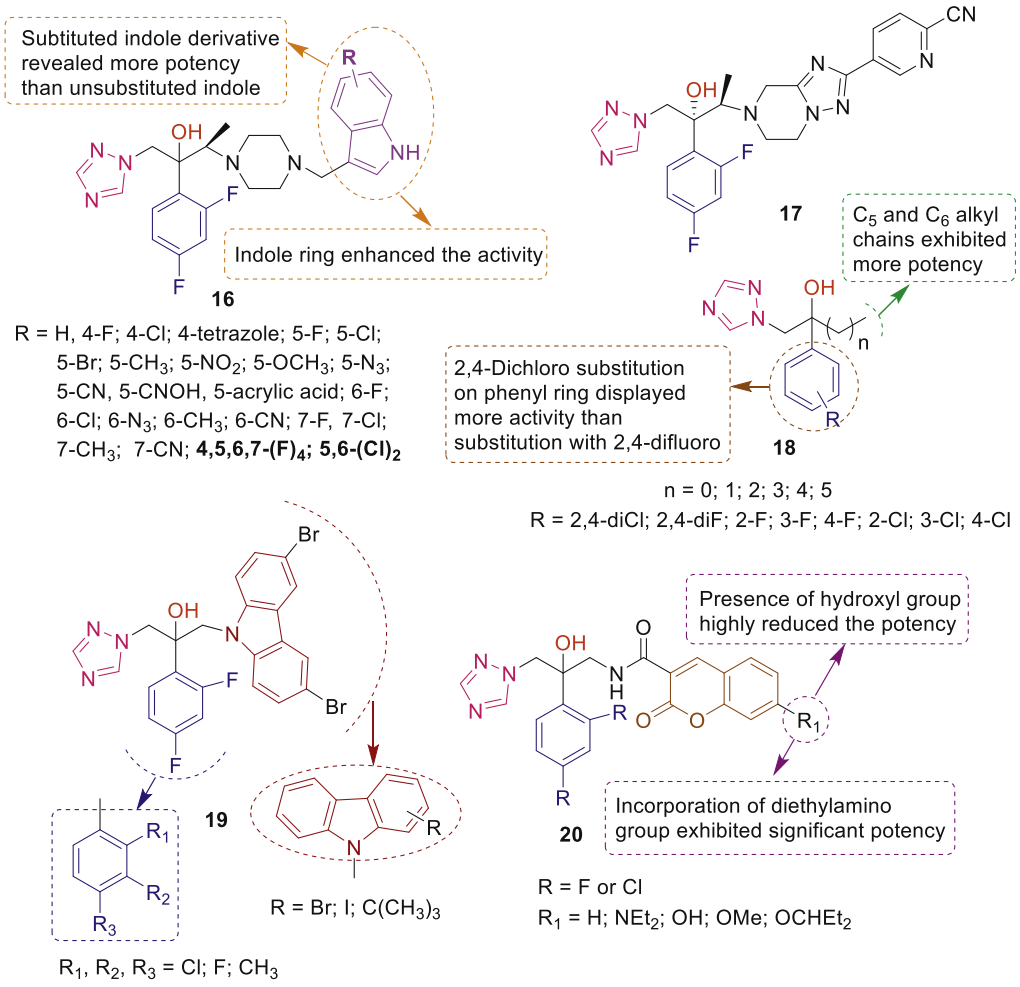


Fig. 4. SAR and antifungal activity profiles of 1-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)-4-substituted derivatives **16**–**20**.

MIC of 16 μg/mL was found to possess comparable antibacterial properties to streptomycin (MIC: 2–15 μg/mL) against all tested microorganisms, while **34e** with nitro on phenyl was detrimental to the activity (Fig. 6).

Antimicrobial activity of 1,2,4-triazole-naphthyridinone hybrids **35** and **36** as structural surrogates of nalidixic acid (Fig. 6) against resistant strains of Gram-positive, Gram-negative *and Mycobacterium phlei* indicated that hybrids **35a**, **35f**, **35g**, **36a** and **36d** (MIC: 3.68–5.30 μM/mL) showed remarkable selectivity against *B. subtilis,* which was resistant to nalidixic acid [55]. Further study revealed that the compounds **35c** and **36d** (IC_{50}: 3.67 and 3.21 μg/mL, respectively) elicited more potent inhibitory activity against *E. coli* DNA gyrase.

Prakash et al. synthesized dihydroindeno and indeno[1,2-*e*][1,2,4]triazolo[3,4-*b*] [1,3,4]thiadizines (**37** and **38**) (Fig. 7) and profiled them for their antibacterial activity against *S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa* and antifungal activity against two fungal strains namely, *A. niger* and *A. flavus* [56]. Compounds **37g**, **37i** and **37k** showed most potent inhibitory effect (MIC: 2–32 μg/mL) on tested bacteria. Moreover, compounds **37a-l** possessed more potent antibacterial activity than compounds **38a-l**.

1,2,4-Triazolo[3,4-*b*] [1,3,4]thiadiazines **39** (Fig. 7) were screened for their antibacterial activity against *S. aureus*, *E. coli*, *P. aeruginosa* and *Bacillus cereus* bacterial strains by Sumangala et al. [57]. Among the tested compounds, **39c** and **39h** (MIC: 3.125 μg/mL) showed excellent antibacterial activity against *E. coli* and *P. aeruginosa*, respectively. 1,2,4-Triazolo[3,4-*b*] [1,3,4]thiadiazine derivatives **40** (Fig. 7) at concentration 100 μg/mL exhibited moderate to good antibacterial activity against four human pathogenic bacteria (*E. coli*, *K. pneumonia*, *S. dysenteriae* and *Shigella flexnei*) [58]. Among them, compound **40d** with zone of inhibition more than standard neomycin and equal to streptomycin demonstrated potential inhibitory activities against all the bacteria.

Thiourea derivatives **41** having triazolopyrimidines core (Fig. 7) demonstrated moderate to high antimicrobial activities against various bacteria such as *S. aureus*, *B. subtilis, P. aeruginosa* and *E. coli* and fungi such as *A. fumigatus*, *Geotrichum candidum*, *C. albicans* and *Syncephalastrum racemosum* [59]. 1,2,4-Triazolo[1,5-*a*]pyrimidines containing quinazoline thioether moiety **42** (Fig. 7) possessed significant activities against the tested phytopathogenic bacteria, among which compound **42a** was found to be most active and it was 12-fold more potent against *Xanthomonas oryzae pv. oryzae* with EC_{50} value of 7.2 μg/mL than bismerthiazol (EC_{50}: 89.8 μg/mL) [60].

In vitro antibacterial activity of 1,2,4-triazolo[3,4-*b*] [1,3,4]thiadiazoles **43a-h** (Fig. 7) indicated high activity towards both drug-sensitive and drug-resistant Gram-positive bacteria, which was up to 16 times more than ampicillin [61]. Thiouracil derivatives containing a triazolo-thiadiazole moiety **44a-l** (Fig. 7) displayed good to potent activity against *Bacillus amyloliquefaciens*, *S. aureus* and *B. subtilis* [62]. Interestingly, compound **44d** exhibited

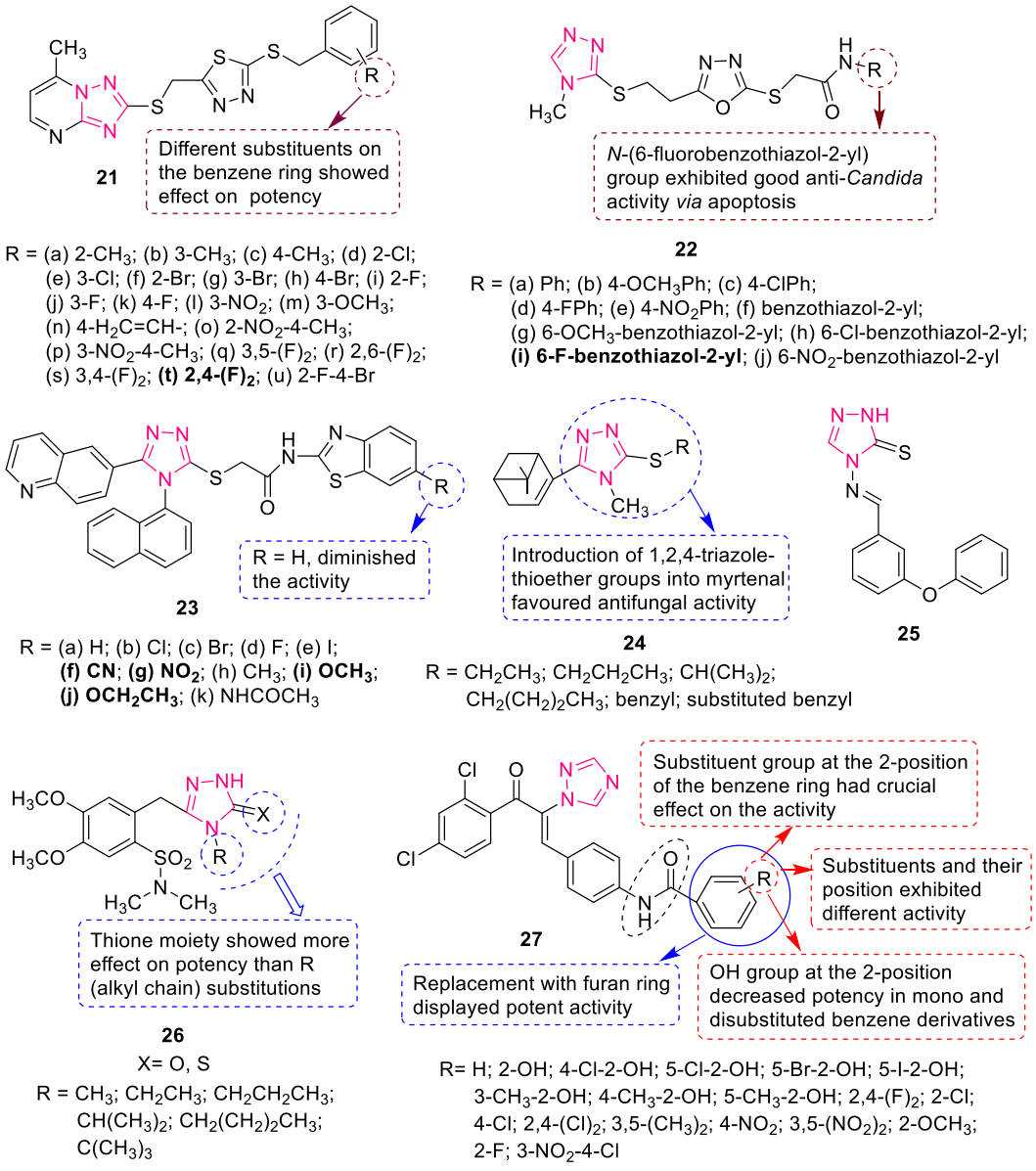


Fig. 5. 1,2,4-Triazole derivatives with antifungal activity.

inhibitory activity against SecA ATPase.

Barbuceanu et al. reported the synthesis and antibacterial activity of mercapto-1,2,4-triazoles bearing diphenylsulfone **45** against *S. aureus*, *B. cereus*, *E. coli*, *Enterobacter cloacae*, *Acinetobacter baumannii* and *P. aeruginosa* [63]. Among them, one of the compounds having bromo diphenylsulfone moiety at position-3 and 3,4,5-trimethoxyphenyl fragment at the nitrogen atom *N*-4 of triazole ring, exhibited the strongest action against *B. cereus* (MIC: 8 μg/mL) (Fig. 8).

A series of Schiff bases of 1,2,4-triazole **46**–**47** (Fig. 8) were synthesized and evaluated for *in vitro* antimicrobial potential against bacteria (*S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa*) and fungus (*C. albicans*) by Mange et al. [64]. All synthesized compounds **46**–**47** (MIC: 3.125 μg/mL) were equipotent with standard drug ceftriaxone against *S. aureus* whereas compounds **46a** and **47d** were more potent (MIC: 3.125 μg/mL) than ceftriaxone against *C. albicans*.

A series of 5-(2-aminothiazol-4-yl)-4-substituted phenyl-4*H*-1,2,4-triazole-3-thiols **48** and **49** (Fig. 8) were synthesized and assessed for their antibacterial activity against *S. aureus*, *B. subtilis*, *E. coli* and *P. aeuroginosa* by Hassan et al. [65]. SAR indicated that the compound **48g** having phenoxy moiety at *para*-postion of the phenyl ring exhibited broad spectrum antibacterial activity (MIC: 0.5–1 μM) which was comparable to gentamicin and ciprofloxacin.

Yang and Bao synthesized 1,2,4-triazole derivatives **50** bearing quinazolinylpiperidinyl moiety and *N*-(substituted phenyl)acetamide unit (Fig. 8) and evaluated them for their antimicrobial activities [66]. Compounds **50e**, **50g**, **50i**, **50l** and **50n** (EC_{50}: 34.5–47.5 μg/mL) had better bactericidal activity than control bismerthiazol (85.6 μg/mL) against phytopathogenic bacterium *X. oryzae pv. oryzae*. SAR study presented the significance of strongly electron-withdrawing substituents (such as 2,4-di-F, 3-F, 3-NO_2, 3-$COCH_3$, 2-NO_2, 2-CF_3 and 4-$COCH_3$) and their positions on the benzene ring for enhancing antibacterial activity. 1,2,4-Triazole-pyrimidine hybrids **51a** and **51b** (MIC: 1.8–4.7 μM, Fig. 8) displayed excellent activity against *S. aureus* and *E. coli* [67]. Moreover,

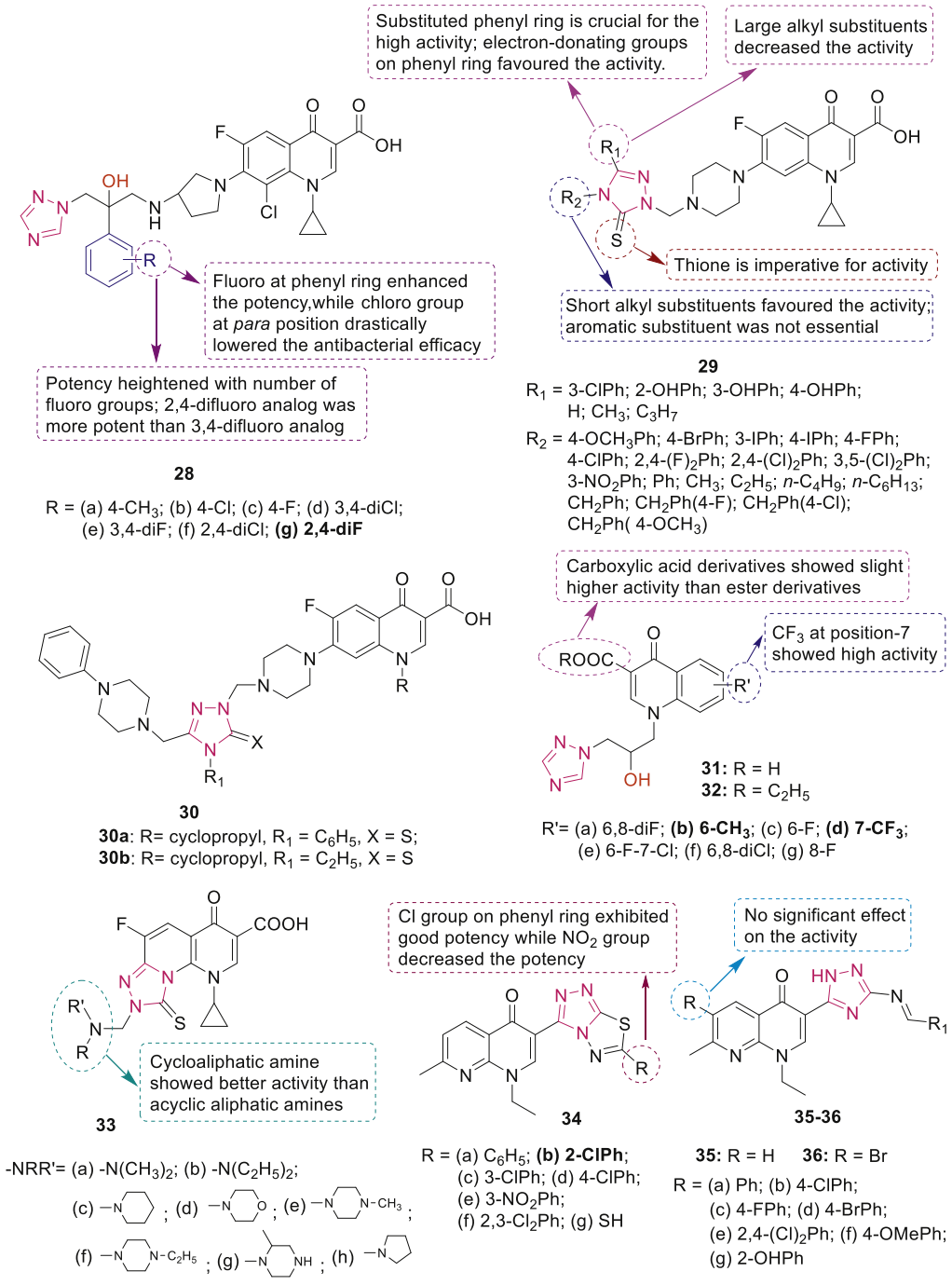


Fig. 6. 1,2,4-Triazole-quinolone hybrids with antibacterial activity.

compounds **51a** (MIC: 0.75 μg/mL) and **51b** (MIC: 0.43 μg/mL) were found to be 10->1600 fold more effective than most clinically used antibiotics against MRSA strain.

Coumarin-based 1,2,4-triazoles **52** and **53** (Fig. 9) were tested for their *in vitro* antibacterial activity against four Gram-positive (*S. aureus*, *MRSA*, *B. subtilis* and *M. luteus*) and four Gram-negative bacteria (*E. coli*, *Proteus vulgaris*, *Salmonella typhi* and *S. dysenteriae*) and antifungal activity against *C. albicans*, *Saccharomyces cerevisiae* and *A. fumigatus* by Shi and Zhau [68]. It was proposed that incorporation of triazole to coumarin enhanced the activity. The SAR of coumarin triazoles **52a-c** and **53a-c** (MIC: 1–32 μg/mL) indicated that the compounds with alkyl-substituent as spacer were more active than the analogues with aralkyl spacer **52d** and **53d** (MIC: 32–64 μg/mL). Further, bis-triazoles **53** displayed better antimicrobial activities than mono-triazoles **52**.

Antimicrobial evaluation of bis-1,2,4-triazole derivatives **54** revealed that triazole derivative with 3,4-dichlorobenzyl group showed more potent antibacterial activity against *B. proteus* (MIC: 0.5 μg/mL) than standard drugs norfloxacin and chloramphenicol [69]. SAR study showed that dihalobenzyl groups are more helpful for increasing antibacterial and antifungal efficacy in comparison with the monohalobenzyl ones (Fig. 9).

A series of isopropanol-bridged carbazole triazoles **55** (Fig. 9) were evaluated for their antibacterial activity against *E. faecalis, S.*

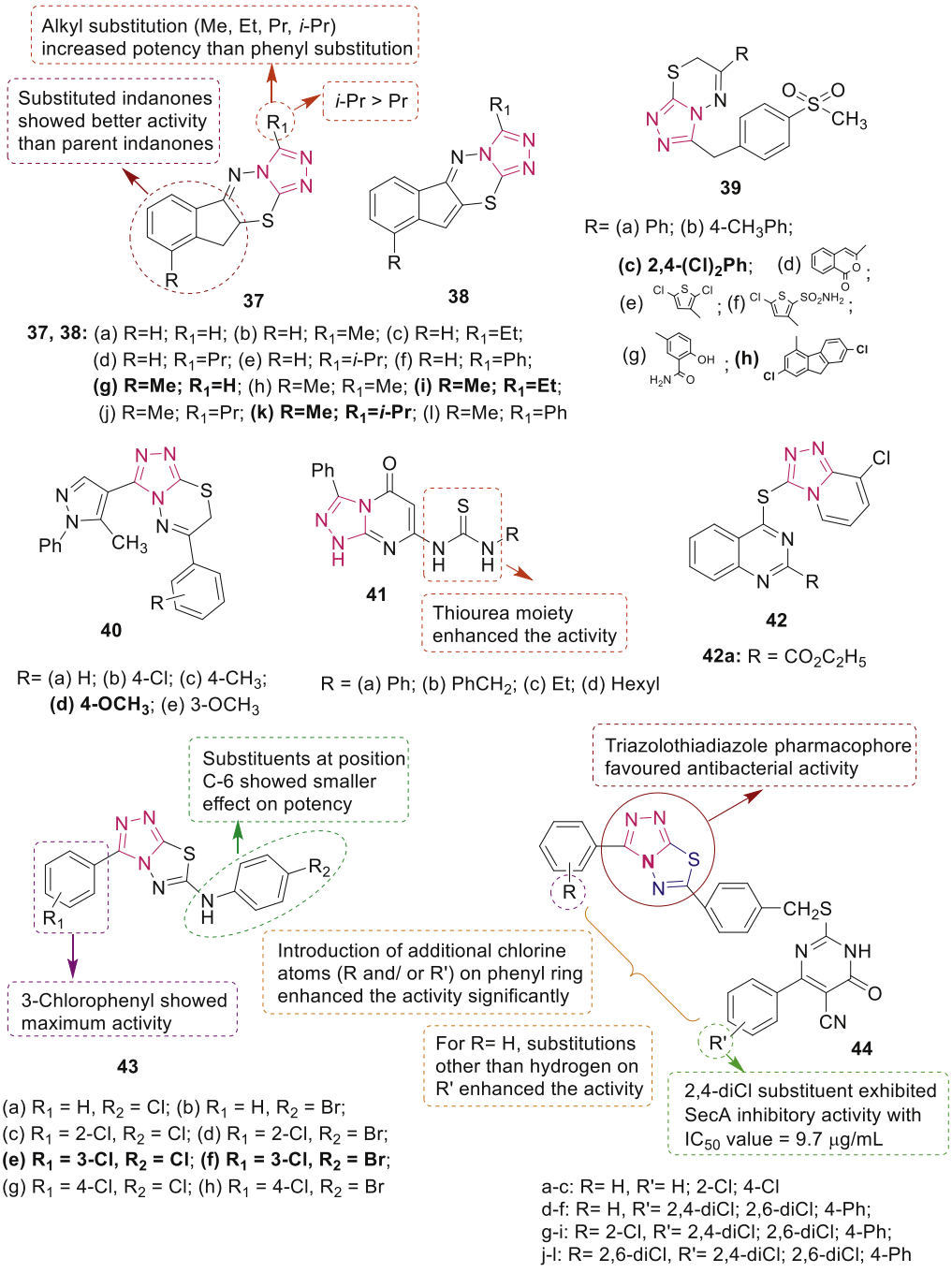


Fig. 7. SAR and antibacterial activity studies of fused 1,2,4-triazole derivatives.

aureus and *E. coli* by Zhang et al. [70]. Among them, compound **55a** (Fig. 9) exhibited highest potency against *E. faecalis* (MIC: 2 μg/mL) which might be due to intercalation into DNA. Among the α-triazolyl chalcones **56**, compound **56a** emerged as a promising candidate which exhibited excellent activity (MIC: 4 μg/mL) against MRSA and *M. luteus* than chloromycin (Fig. 9) [71].

2.3. Anticancer agents

Anticancer chemotherapeutic agents can exert diverse action mechanisms such as cell cycle arrest, enzyme inhibitors, tubulin modulators, angiogenesis inhibitors, DNA intercalators and groove binders, transcription regulators and gene regulators etc. [72]. A large number of chemical entities having 1,2,4-triazole motifs have emerged as promising anticancer agents such as vorozole, letrozole, and anastrozole.

2.3.1. Enzyme inhibitors

2.3.1.1. Kinase inhibitors. Kinases are a class of enzymes that catalyze activation of many proteins by phosphorylation of mostly serine, threonine, or tyrosine amino acids. Deregulation of kinases may lead to growth of cancer. Kinase inhibitors are being explored as antitumor agents due to their target specific action. PIM kinase family (PIM-1, PIM-2 and PIM-3), a class of serine/threonine kinase,

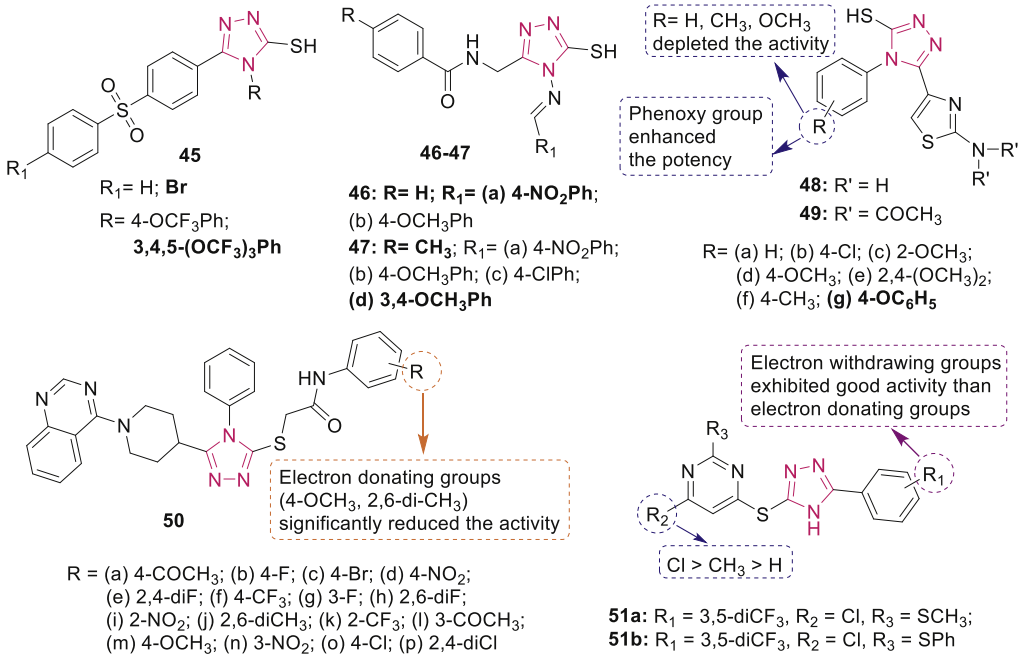


Fig. 8. Mercapto/thione/thio-substituted 1,2,4-triazole derivatives with antibacterial activity.

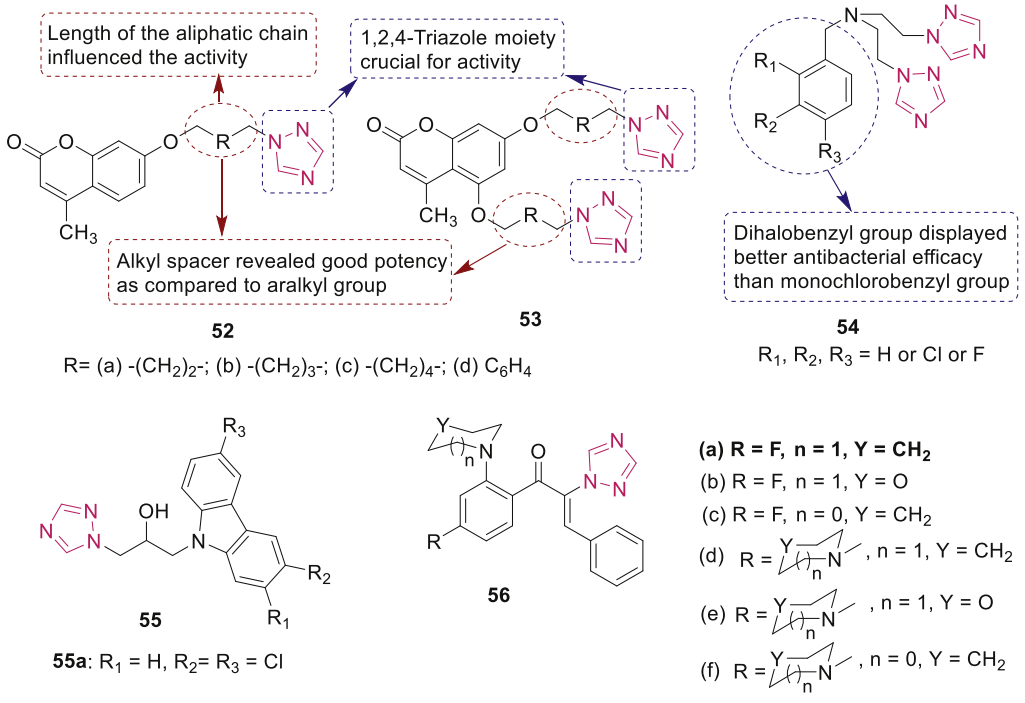


Fig. 9. 1,2,4-Triazoles derivatives **52**–**56** with antibacterial activity.

are key molecular targets for the development of selective inhibitors having therapeutics potential in cancer treatment.

Martínez-González et al. reported synthesis of a series of novel triazolo[4,3-*b*]pyridazin-3-yl-quinoline derivatives **57** (Fig. 10) as PIM inhibitors [73]. Lead optimization techniques identified compound **57q** as a selective PIM-1/3 inhibitor (IC_{50}: 7 nM/70 nM) and antiproliferative agent against several tumor cells lines with GI_{50} values of 1.48–25.4 μM.

Han et al. reported synthesis and antiproliferative evaluation of a series of 1,2,4-triazole containing hydrazide-hydrazones **58** (Fig. 11) derived from (*S*)-naproxen [74]. Compound **58a** showed best activity with IC_{50} values of 26.0, 34.5, and 48.8 μM against the prostate cancer cell lines PC-3, DU-145 and LNCaP, respectively. Molecular docking studies of **58a** on human methionine aminopeptidase-2 presented H-bonds and halogen interactions (Fig. 11). Molecular mechanism of anticancer potential of **58a** in PC-

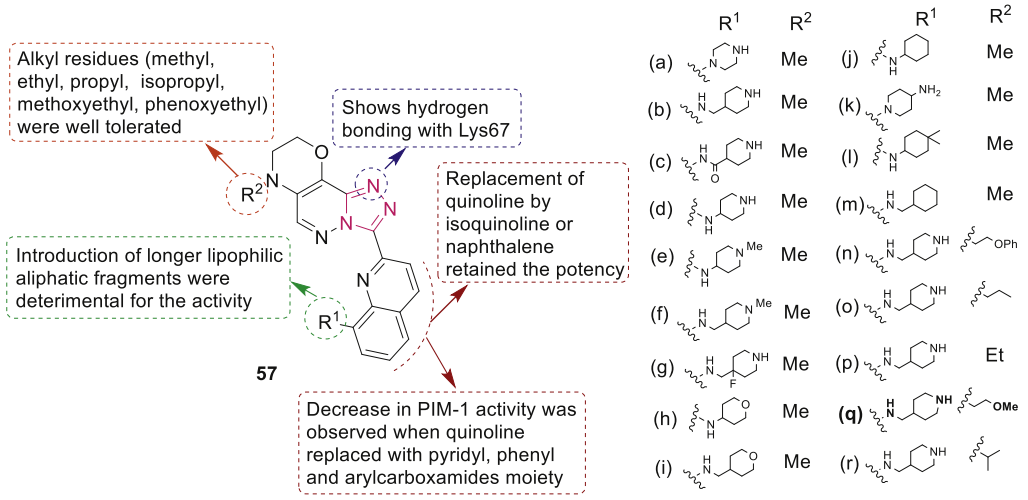


Fig. 10. 1,2,4-Triazole derivatives as PIM inhibitors.

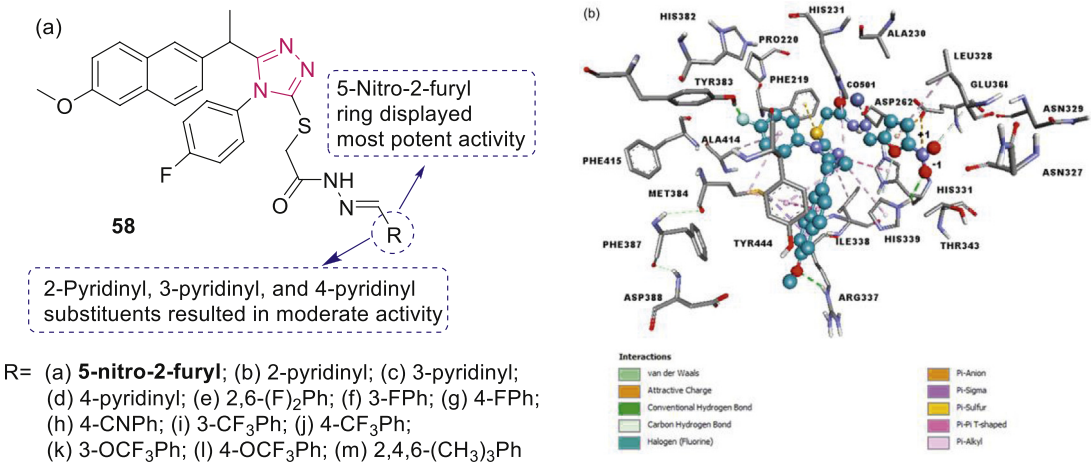


Fig. 11. (a) 1,2,4-Triazole derivatives as EGFR inhibitors. (b) 3D interactions of compound **58a** with amino acid residues in the catalytic channel of MetAP2 enzyme.

3 cells is revealed by reduction of EGFR, Akt phosphorylation and PI3K phosphorylation.

Batran et al. reported VEGFR-2 and p38α MAPK inhibitory activity of pentacyclic coumarinyltriazolopyrimidine derivatives **59a-c** (Fig. 12) along with antiproliferative activity [75]. Among these, compound **59a** was documented to exhibit most potent inhibitory activity against VEGFR-2 (94% inhibition at 117 ng/mL) and anticancer activity against MCF-7 cancer cells with IC_{50} value of 7.9 μg/mL than tamoxifen (IC_{50}: 8.38 μg/mL). Docking studies showed that compound **59a** binds to the active site of VEGFR-2 through H-bonds, arene-cation and hydrophobic interactions.

Qin et al. reported synthesis of 2-(4-(2-(dimethylamino)ethyl)-4*H*-1,2,4-triazol-3-yl)pyridine derivatives **60** and **61** (Fig. 13) along with antitumor activity [76]. Compound **60g**, displayed higher cytotoxicity against MKN-45, H460 and HT-29 cells with IC_{50} values of 51, 72 and 130 nM, respectively, which were 45.5, 30.4 and 27.8 folds more potent than sorafenib against these cell lines. SAR study revealed that the dimethylaminoethyl group was essential for high activity.

In another study, a series of diarylurea derivatives bearing a triazole moiety **62** (Fig. 13) were evaluated for antitumor activity [77]. The most potent compound **62i** exhibited significant inhibition (>80%) of tyrosine kinases including c-Kit, RET and FLT3 and antiproliferative activity against HT-29, H460 and MDA-MB-231 cancer cells, with IC_{50} values of 0.90, 0.85 and 1.54 μM, respectively. It was more potent than the reference sorafenib (IC_{50}: 2.25−3.37 μM) and also significantly induced apoptosis of HT-29 cells.

Liu et al. synthesized 41 compounds containing 1,2,4-triazolone moiety **63** (Fig. 14) and studied their cytotoxic activity [78]. Selected compounds **63a-k** exhibited excellent inhibitory activity against c-Met kinase (IC_{50}: 1.57−31.52 nM). Compound **63g** showed moderate selectivity (306.03 fold) to VEGFR-2 kinase and significant cytotoxicity against HT-29, H460, A549 and MKN-45 cell lines with IC_{50} values of 0.08 μM, 0.14 μM, 0.11 μM and 0.031 μM, respectively. Antitumor activity of **63g** was 1.1−2.3 folds higher than foretinib. SAR studies showed that the introduction of electron-withdrawing groups on the terminal phenyl rings enhanced the antitumor activity.

Xu et al. synthesized a novel [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazine derivative **64** (Fig. 14) which was found to be potent antiproliferative agent (IC_{50}: 1.30 μM for Bewo, 1.45 μM for HL-60 and 2.24 μM for MCF-7) and inhibited c-Met kinase (IC_{50}: 11.77 μM) [79]. The docking analysis rationalized the binding of compound **64**

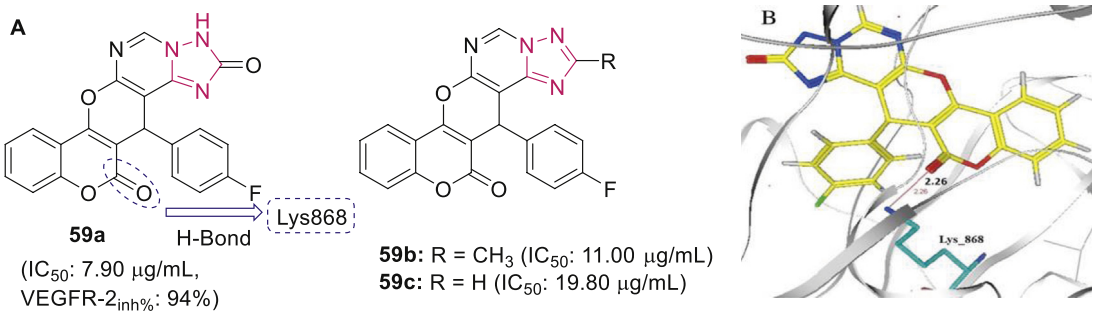


Fig. 12. (A) 1,2,4-Triazole derivatives as VEGFR inhibitors. (B) Predicted binding mode of compound **59a** in the active site of VEGFR-2 which shows H-bond between C=O group and Lys868.

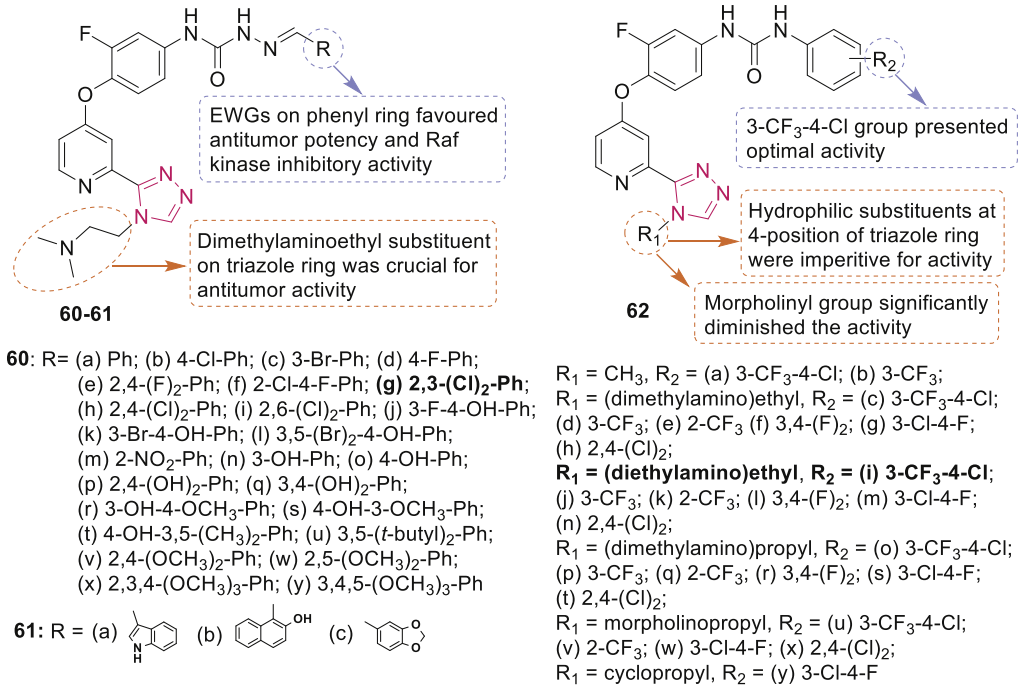


Fig. 13. 1,2,4-Triazole derivatives as tyrosine kinases inhibitors.

to c-Met kinase through three hydrogen bonding interactions.

Egile et al. reported the triazolopyridazine derivative **65** SAR125844 (Fig. 14) which strongly inhibited the kinase activity of wild-type MET enzyme with IC_{50} value of 4.2 nmol/L, as well the H1094Y, Y1235D, M1250T, L1195V, and D1228H kinase domain mutants with IC_{50} values of 0.22, 1.7, 6.5, 65, and 81 nmol/L, respectively [80]. It also inhibited the growth of tumor in MET-amplified xenograft model, autophosphorylation of AXL and cell proliferation of TPM-NTRK1-overexpressing KM12 cell line with IC_{50} values of 110 and 1400 nmol/L, respectively.

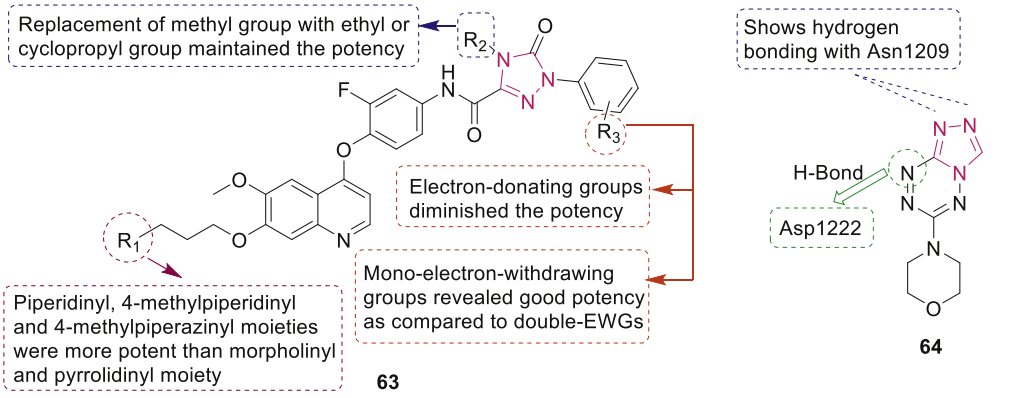
Zhan et al. synthesized a series of CH_2-/CF_2-linked triazolo-triazine derivatives among which compound **66** (Fig. 14) displayed the most potent inhibition with IC_{50} value of 0.24 nM against c-Met kinase and with IC_{50} value of 0.85 nM against EBC-1 cancer cell line [81]. Further, compound **66** exhibited excellent *in vivo* efficacy with 97.1% of tumor growth inhibition in EBC-1 xenograft mice model at dose of 25 mg/kg. X-ray crystallography revealed that compound **66** binds at the ATP-binding site of c-Met with a U shape.

Compound **67** (AMG 337) (Fig. 14) is identified as selective inhibitor of c-Met kinase (IC_{50}: 1 nM) which displayed exquisite selectivity profile over 402 kinases and sustained inhibition of MET phosphorylation in a mouse liver pharmacodynamic model [82]. Moreover, AMG 337 at dose of 3 and 10 mg/kg exhibited >90% tumor growth inhibition in the NIH-3T3/TPR-Met xenograft model.

Gu et al. synthesized a series of 2-substituted-4-(2-fluorophenoxy)pyridine derivatives **68** (Fig. 14) bearing pyrazolone and triazole moieties as dual c-Met/VEGFR-2 inhibitors [83]. Compound **68d** showed the most potent inhibition with IC_{50} values of 0.11 μM and 0.19 μM for c-Met and VEGFR-2, respectively. Various 8-fluorotriazolopyridines/triazolo[4,3-*b*]pyridazine derivatives were synthesized as inhibitors of c-Met activity [84,85].

2.3.1.2. Thymidine phosphorylase inhibitors. Shahzad et al. synthesized a series of 3-mercapto-1,2,4-triazole analogues **69** and 3-mercapto-1,2,4-triazole carboxylic acids **70** (Fig. 15) as thymidine phosphorylase (TP) inhibitors [86]. Compounds **70b-g** revealed a good inhibitory potential with IC_{50} in the range of 43.86–163.43 μM and angiogenic potential of compound **70c** was elicited using the chick chorionic allantoic membrane (CAM) assay.

Various synthesized 1,2,4-triazolo[1,5-*a*] [1,3,5]triazine derivatives were evaluated for their inhibitory effects on TP by Bera et al. [87]. Compounds **71** (IC_{50}: 10.84 μM) and **72** (IC_{50}: 2.95 μM)



R_1 = piperidinyl, R_2 = CH_3, (a) R_3 = 4-OCH_3;
R_1 = 4-methylpiperidinyl, R_2 = CH_3, (b) R_3 = 2-F; (c) R_3 = 4-F;
(d) R_3 = 4-$OCHF_2$; (e) R_3= 2,4-$(Cl)_2$;
R_1 = 4-methylpiperidinyl, R_2 = C_2H_5, (f) R_3 = 2-OCF_3;
R_1 = 4-methylpiperazinyl, R_2 = CH_3, (g) R_3 = 2-F; (h) R_3 = 3-F; (i) 2-OCF_3;
R_1 = 4-methylpiperazinyl, R_2 = cyclopropyl, (j) R_3 = 2-OCF_3; (k) R_3 = 2-Cl

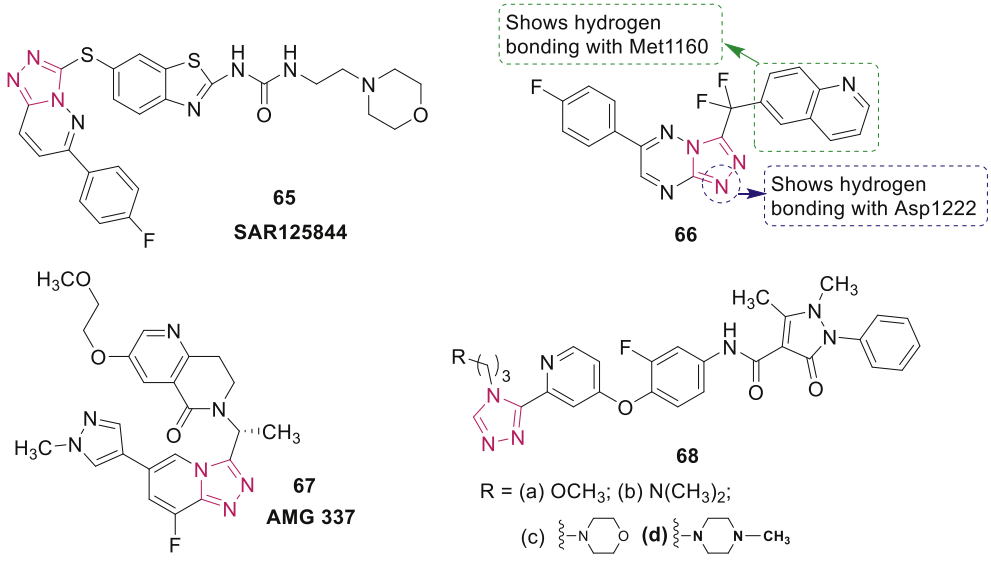
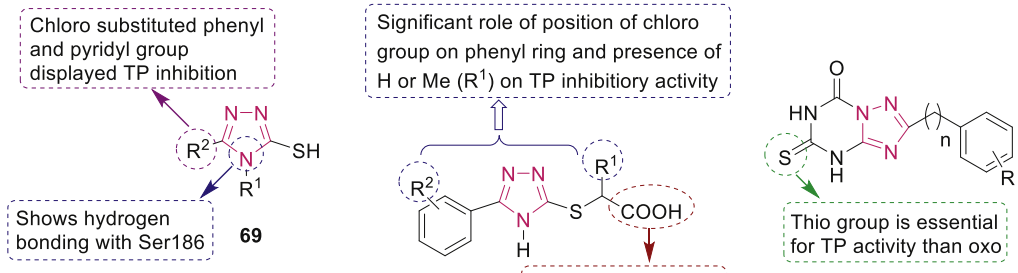


Fig. 14. 1,2,4-Triazole derivatives as c-MET kinase inhibitors.



R^1 = H, R^2 = (a) Ph; **(b) 3-ClPh**;
(c) 4-ClPh; (d) 4-CH_3Ph; (e) 4-NO_2Ph;
R^1 = Ph, R^2 = (f) Ph; (g) 4-CH_3Ph;
(h) 3,4,5-$(OCH_3)_3$Ph; (i) 3-ClPh,
(j) 4-ClPh; **(k) 3-pyridyl**; **(l) 4-pyridyl**

R^1 = H, R^2 = (a) H; (b) 3-Cl;
(c) 4-Cl; (d) 4-CH_3; (e) 4-NO_2;
R^1 = CH_3, R^2 = (f) 3-Cl; (g) 4-Cl

71: n= 0; R = 3,4-$(Cl)_2$
72: n= 1; R = 3,4-$(Cl)_2$

Fig. 15. 1,2,4-Triazole derivatives as thymidine phosphorylase inhibitors.

(Fig. 15) displayed the most promising activity as mixed-type inhibitors of TP.

2.3.1.3. Topoisomerase inhibitors. Eissa et al. synthesized two set of triazoloquinoxalines **73** and **74** (Fig. 16) and studied their cytotoxic activity against HepG2, Hep-2, and Caco-2 cancer cell lines [88]. Most promising compound **73d** significantly induced apoptosis in HepG2 cells *via* downregulating the Bcl-2 levels and arrested G2/M cell cycle. Results also indicated that compounds **73d** and **73e** exhibited potent topoisomerase II inhibitory activity (IC_{50}: 0.97 and 1.10 μM, respectively).

Ibrahim et al. synthesized new series of 1,2,4-triazolo[4,3-*a*] quinoxaline **75** and bis 1,2,4-triazolo[4,3-*a*:3′,4′-*c*]quinoxaline derivatives **76** (Fig. 16) and evaluated their inhibitory effects on topoisomerase II and cytotoxic effects against HepG2, Hep-2 and Caco-2 [89]. SAR indicated that bis 1,2,4-triazolo[4,3-*a*:3′,4′-*c*]quinoxaline derivatives **76a**, **76g**, and **76h** improved the activity than 1,2,4-triazolo[4,3-*a*]quinoxaline derivatives **75**. Compounds **75f-h**, **76a**, **76g**, and **76h** displayed good topoisomerase-II inhibitory activity (IC_{50}: 0.68–1.22 μM) and induced DNA intercalation significantly. Treatment of Caco-2 cells with **76g** induced apoptosis and resulted in G2/M cell cycle arrest.

2.3.1.4. Methionine aminopeptidase type II inhibitors. Hou et al. synthesized 1,2,4-triazole derivatives containing 1,4-benzodioxane fragment **77** (Fig. 17) and evaluated their methionine aminopeptidase type II (MetAP2) inhibitory activity in an enzyme assay [90]. From biological study of tested compounds it was observed that most of the compounds exhibited potent MetAP2 inhibitory effect and **77k** most effectively inhibited the growth of HepG2 cells and MetAP2.

2.3.1.5. COX inhibitors. Cui et al. explored diaryl-1,2,4-triazole-caffeic acid hybrids as COX-2/5-LOX dual inhibitors for cancer therapy [91]. The anticancer SAR of hybrids **78** (Fig. 18) indicated that amide derivatives **78e-g** with superior COX-2 inhibition activities were less potent (IC_{50}: 16.37–26.14 μM) than ester derivatives (**78d**, IC_{50}: 9.52–11.16 μM) against A549, Caco-2, PC-3 and B16–F10 cancer cell lines. Introduction of electron-withdrawing groups at *para*-position of *N*-1 phenyl ring (R^1) improved the antiproliferative activity. Most potent compound **78j** (IC_{50}: 6.78–9.05 μM) also demonstrated significant inhibition on tumor growth *in vivo*. The preliminary mechanism studies revealed that hybrid **78d** arrested the cell cycle in G2 phase and induced apoptosis in A549 cells in a dose-dependent manner.

A series of non-carboxylic naproxen analogues, bearing triazole

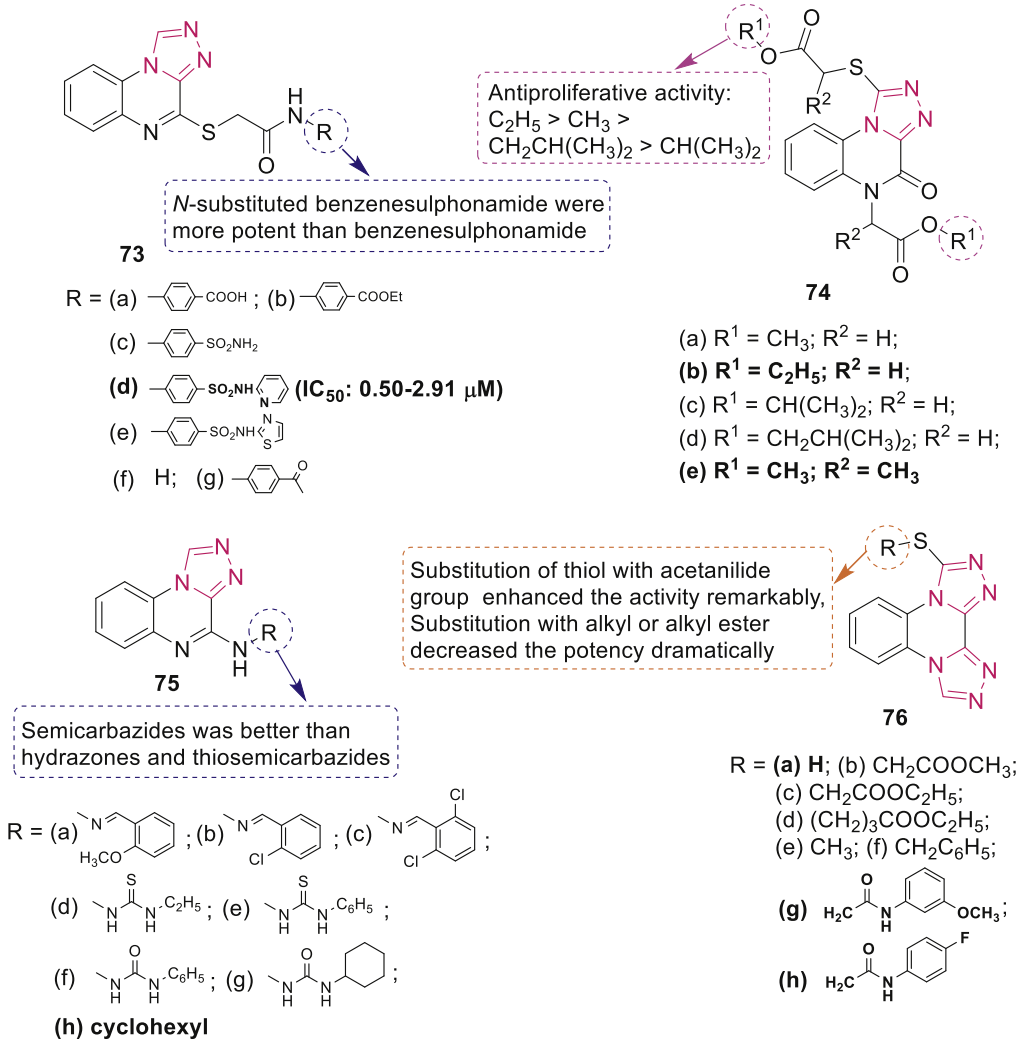
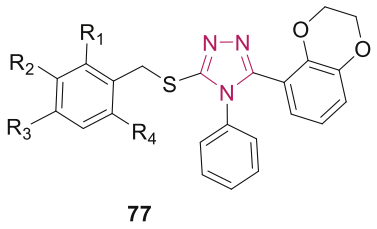


Fig. 16. 1,2,4-Triazole derivatives as topoisomerase inhibitors.



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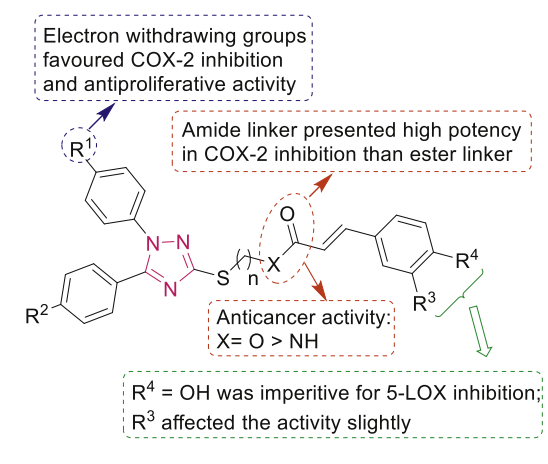
(a) R_1= R_2= R_3= R_4= H; (b) R_1=NO_2; R_2= R_3= R_4= H
(c) R_1= R_3= R_4= H; R_2= NO_2; (d) R_1= R_2= R_4= H R_3= NO_2
(e) R_1= Cl; R_2= R_3= R_4= H; (f) R_1= R_3= R_4= H; R_2= Cl
(g) R_1= R_2= R_4= H; R_3= Cl; (h) R_1= R_3= R_4= H; R_2= OCH_3
(i) R_1= CH_3; R_2= R_3= R_4= H; (j) R_1= R_2= R_4= H; R_3= CH_3
(k) R_1= F; R_2= R_3= R_4= H(IC_{50}: HepG2= 0.81μM, MetAP2= 0.93μM); (l) R_1= R_2= R_4= H; R_3= F

Fig. 17. 1,2,4-Triazole derivatives as methionine aminopeptidase type II inhibitors.



	R^1	R^2	n	X	R^3	R^4
(a)	F	NH_2SO_2	2	O	OAc	OAc
(b)	F	NH_2SO_2	3	O	OAc	OAc
(c)	Br	CH_3SO_2	3	O	OH	OH
(d)	**F**	**CH_3SO_2**	**3**	**O**	**OH**	**OH**
(e)	Br	CH_3SO_2	3	NH	OAc	OAc
(f)	F	CH_3SO_2	3	NH	OAc	OAc
(g)	F	CH_3SO_2	3	NH	OH	OH
(h)	Br	CH_3SO_2	2	O	OCH_3	OAc
(i)	F	CH_3SO_2	2	O	OCH_3	OAc
(j)	**CF_3**	**CH_3SO_2**	**2**	**O**	**OCH_3**	**OH**

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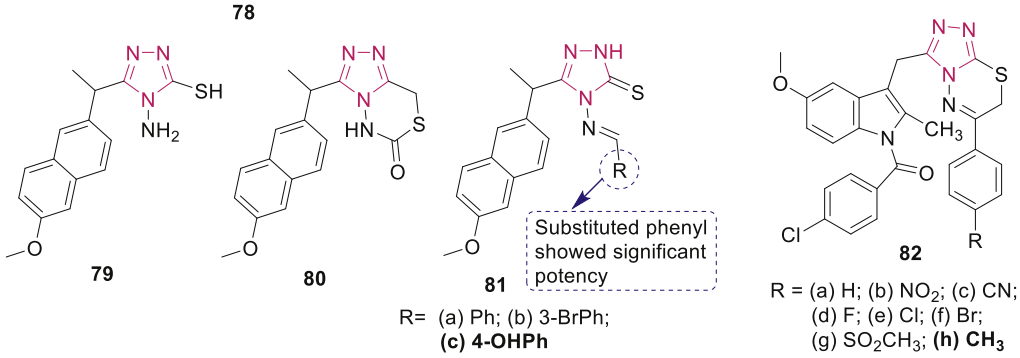


R= (a) Ph; (b) 3-BrPh; **(c) 4-OHPh**

R = (a) H; (b) NO_2; (c) CN; (d) F; (e) Cl; (f) Br; (g) SO_2CH_3; **(h) CH_3**

Fig. 18. 1,2,4-Triazole derivatives as COX-2 inhibitors.

ring **79**–**81** (Fig. 18) was synthesized by El-Husseiny et al., among which arylidene derivatives **81b-c** exhibited potent antitumor activities against cell lines MCF-7, MDA-231, HeLa, and HCT-116, with IC_{50} in the range of 4.83–12.07 μM [92]. Compound **81c** also exhibited the most potent COX-2 inhibitory activity with IC_{50} value of 0.40 μM and selectivity index (SI) value of >62.50 and showed strong interactions at the COX-2 binding site.

Sever et al. studied cytotoxic effects of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine derivatives **82** (Fig. 18) against T98 human glioma cell line [93]. Study revealed that the most potent compound **82h** exhibited dose-dependent anticancer effect *via* inhibition of COX-2 mRNA levels and similar binding pattern as indomethacin in active site of COX-2 enzyme.

2.3.1.6. Carbonic anhydrase inhibitors. SitaRam et al. synthesized a series of novel benzenesulfonamide bearing 1,2,4-triazole scaffolds **83**–**85** (Fig. 19) and studied their inhibitory activity against four isomers of the α-class of carbonic anhydrases (CAs, EC 4.2.1.1), comprising hCAs I and II (cytosolic, ubiquitous isozymes) and hCAs IX and XII (transmembrane, tumor associated isozymes) [94]. Compounds **83d**, **83f** and **84f** displayed excellent inhibitory potential against all of the four isozymes hCA I, II, IX and XII with *Ki* values in the range of 2.8–170 nM, 1.3–132 nM and 3–89 nM, respectively even better than the standard drug acetazolamide (*Ki*: 5.7–250 nM).

2.3.1.7. Aromatase inhibitors. Song et al. synthesized 4-*N*-nitrophenyl substituted amino-4*H*-1,2,4-triazole derivatives **86** (Fig. 20) as aromatase inhibitors [95]. SAR study revealed that the compounds containing substituted benzyl group on amine have improved aromatase inhibitory activities. Compound **86g** was the most active one with an IC_{50} of 9.02 nM.

2.3.1.8. Lysine-specific histone demethylase 1 (LSD1/KDM1A) inhibitors. Wang et al. designed and synthesized pyrazolo[1,5-*a*]pyrimidine derivatives as potent LSD1/KDM1A inhibitors [96]. Compounds **87a-c** and **88a-b** (Fig. 21) selectively inhibited growth of A549 cells with IC_{50} in the range of 3.23–10.58 μM. Compounds **87d** and **87e** were highly potent inhibitor of LSD1 (IC_{50}: 0.154 and 1.19 μM, respectively). Further, compound **87d** significantly

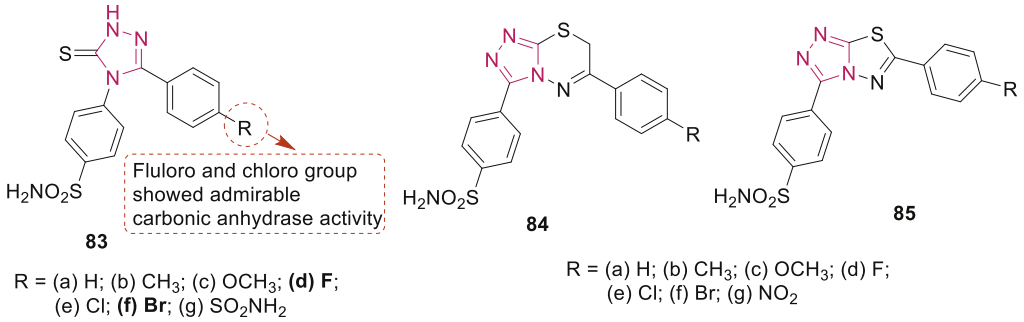


Fig. 19. 1,2,4-Triazole derivatives as carbonic anhydrase inhibitors.

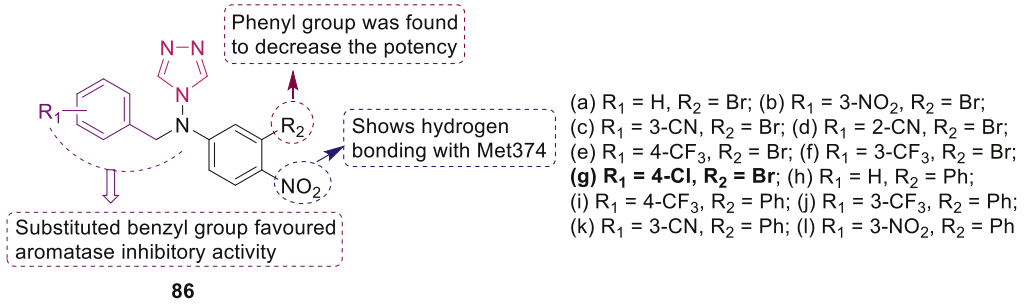


Fig. 20. 1,2,4-Triazole derivatives as aromatase inhibitors.

inhibited migration of A549 and PC-9 cells in a concentration-dependent manner. Following this work, Wang et al. designed new LSD1 inhibitors **89** (Fig. 21). From series, compound **89a** having selectivity over MAO-A/B, reversibly inhibited LSD1 (IC_{50}: 1.72 μM) and significantly inhibited migration of A549 cells. Docking studies presented that **89a** displayed FAD-competitive binding toward LSD1 (Fig. 21) [97].

2.3.1.9. Tankyrases (TNKSs) inhibitors. Liscio et al. designed and synthesized a series of 6,8-disubstituted triazolo[4,3-*b*]pyridazines **90** (Fig. 22) as tankyrases (TNKSs) inhibitors [98]. SAR study revealed that one of the compounds (R_1 = CH_3 and R_2= $(CH_2)_2$-Ph-4-OH) showed full inhibition of TNKS-1 and 82% of TNKS-2 at 1 μM. Replacement of hydroxyl group by benzoyl or amine resulted in the loss of activity. All the derivatives bearing 4-hydoxyphenyl in the side chain, were found to be the most potent TNKS inhibitor and assessed further at a concentration of 10 μM on several members of the PARP superfamily (PARP 1–3, 6–8, 10–12), exhibiting clean selectivity toward PARP-1 and 2 compared with AZD22816 (Olaparib).

2.3.2. Transcription regulators and gene regulators

Bromodomain-containing protein 4 (BRD4), a transcriptional and epigenetic regulator, recognises acetylated lysine residues in histones and has been emerged as key target for cancer therapy. A series of 4,5-dihydro-[1,2,4]triazolo[4,3-*f*]pteridine derivatives **91** (Fig. 23) were designed and synthesized as BRD4 inhibitors by Bi et al. [99], among which the most potent compound **91r** exhibited antiproliferative activity against MV4; 11 (biphenotypic B myelomonocytic leukemia) with an IC_{50} of 1.53 μM through inducing apoptosis by downregulating c-Myc.

2.3.3. Tubulin modulators

Tubulin and microtubules are prime molecular targets for cancer chemotherapy which play fundamental role in mitosis and cell division. Saez-Calvo et al. reported anti-mitotic effect of 1,2,4-triazolo[1,5-*a*]pyrimidines **92** against A549 lung carcinoma cells [100]. It was unveiled that compounds act as vinca-site microtubule-stabilizing agents that mediate longitudinal tubulin contacts and are not affected by p-glycoprotein overexpression. Binding of compound **92a** to the vinblastine site is close to the bound GDP nucleotide of the β1-tubulin subunit as shown in Fig. 24.

Alswah et al. designed and synthesized novel chalcone derivatives bearing triazolo[4,3-*a*]quinoxaline moiety **93** (Fig. 24) as antiproliferative agents with dual inhibitory activity on EGFR kinase and tubulin polymerization effects [101]. Compound **93g** was the most active against MCF-7, HCT-116 and HepG2 cell lines with IC_{50} value of 1.65, 3.61 and 8.58 μM, respectively. Molecular docking analysis of **93g** demonstrated diverse interactions in the colchicine binding pocket of tubulin. Triazoloquinazolinone **94a** (Fig. 24) showed potential tubulin polymerization inhibitory activity (IC_{50}: 0.15 μM) and exhibited cytotoxic activity against human cancer cell lines panel including on HL-60(TB), NCI–H522, MDA-MD-435 and OVCAR-3 with GI_{50} values in the nanomolar range [102]. Molecular docking studies indicated that *N*-methylated amide group in compound **94a** could form hydrophobic contact with Leu248, which was responsible for its potent antitubulin activity.

El-Sherief et al. synthesized new 1,2,4-triazole scaffolds **95**–**99** (Fig. 24) and most of the tested compounds exhibited noteworthy antiproliferative effects against a panel of cancer cell lines with IC_{50} values < 2.0 μM [103]. SAR studies revealed that compounds **95**–**97** bearing free NH_2 group at triazole ring were more effective than compounds **98** and **99** in which 5-amino group was substituted with *N*-acyl and isothiocyanate, respectively. Mechanistic study against Tubulin, EGFR and $BRAF^{V600E}$ kinase enzymes showed that two compounds **95c** and **95d** have a capability to strongly inhibit tublin (957 and 872, respectively), EGFR (IC_{50}: 3.6 and 4.6 μM, respectively), and $BRAF^{V600E}$ (IC_{50}: 1.9 and 1.8 μM, respectively).

Yang et al. synthesized triazolylthioacetamides containing 3,4,5-trimethoxyphenyl moiety **100** (Fig. 25) and ten selected

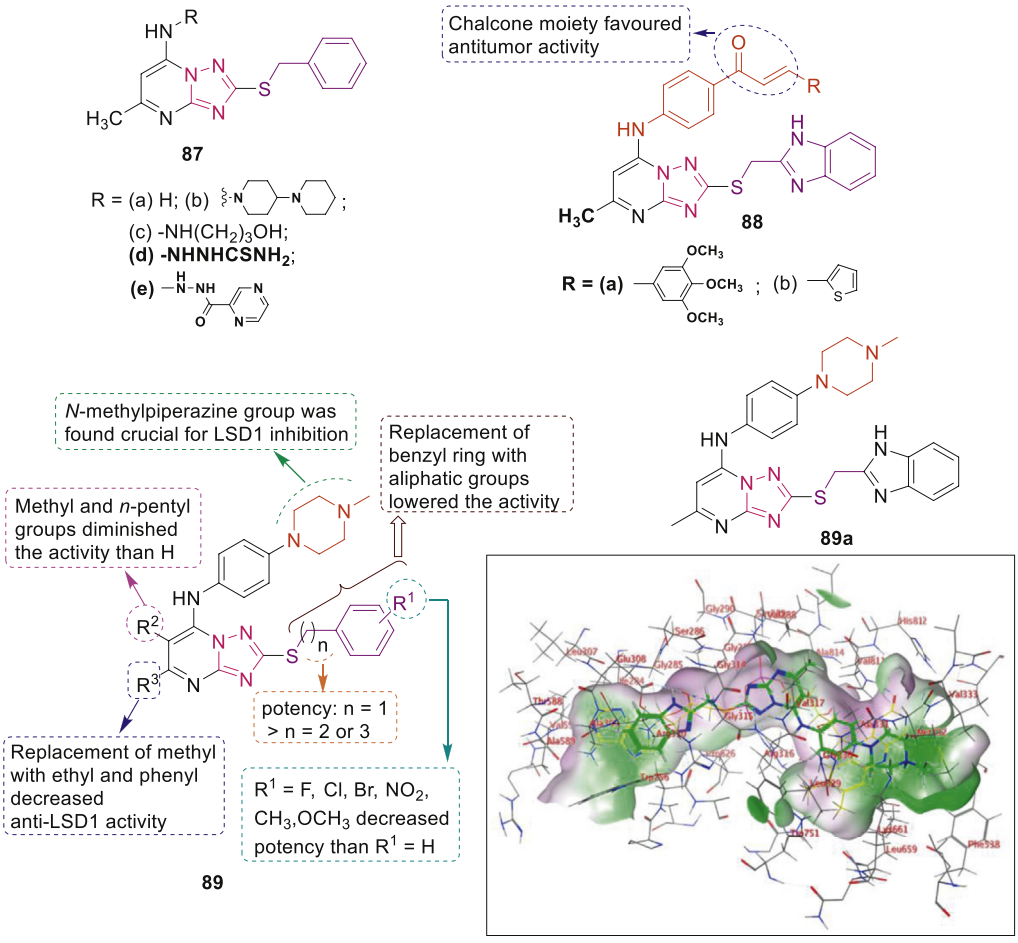
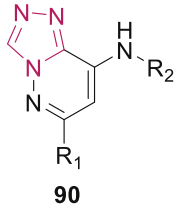
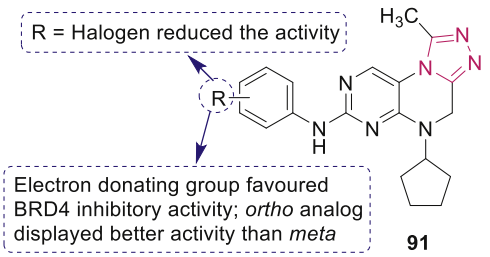


Fig. 21. 1,2,4-Triazole derivatives as LSD1/KDM1A inhibitors and binding of compound **89a** and FAD (colored in green and yellow, respectively) in the active site of LSD1. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)



R_1 = **CH_3**; C_2H_5; H;
R_2= $(CH_2)_2$-Ph-4-Cl; $(CH_2)_2$-Ph; $(CH_2)_2$-naph-2-yl;
$(CH_2)_2$-pyridin-2-yl; $(CH_2)_2$-thien-2-yl; $(CH_2)_2$-Ph-4-F;
$(CH_2)_2$-Ph-4-OCH_3; **$(CH_2)_2$-Ph-4-OH**; $(CH_2)_2$-Ph-4-OCOPh;
$(CH_2)_2$-Ph-4-NH_2; $(CH_2)_2$-*N*-morpholine; CH_2Ph; indan-2-yl; H

Fig. 22. 1,2,4-Triazole derivatives as TNKS inhibitors.



R = (a) H; (b) 2-OCH_3; (c) 3-OCH_3; (d) 4-OCH_3;
(e) 3,4-diOCH_3; (f) 2-CH_3; (g) 3-CH_3;
(h) 4-CH_3; (i) 4-*i*-propyl; (j) 4-butyl;
(k) 4-*t*-butyl; (l) 4-F; (m) 4-Cl; (n) 3-Cl;
(o) 4-NO_2; (p) 2-NO_2; (q) 4-methylsulfonyl;
(r) 4-NH_2 (IC_{50}: BRD4 inhibition = 79 nM)

Fig. 23. 1,2,4-Triazole derivatives as BRD4 inhibitors.

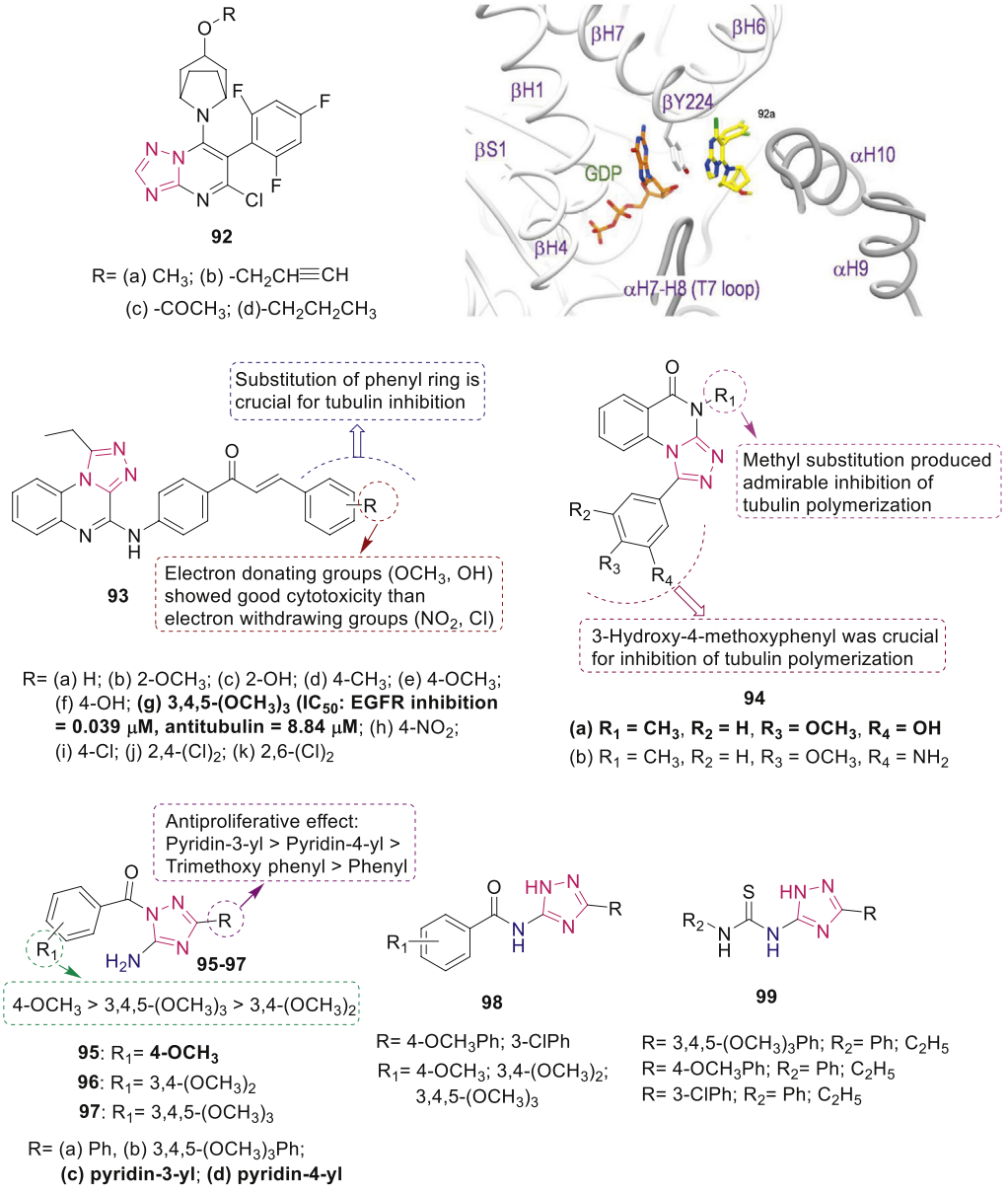


Fig. 24. 1,2,4-Triazole derivatives **92**–**99** as tubulin polymerization inhibitors.

compounds were evaluated as tubulin polymerization inhibitors [104]. Compounds **100c** and **100f** displayed most promising anticancer activity against MCF-7, HeLa and HT-29 cell lines with IC_{50} in the range 0.05–26.83 μM. SAR studies indicated that the substitution of *N*-4 and the *N*-substituted acetamide moiety at 3-position on the 1,2,4-triazole ring have considerable role in potency. Compound **100f** could induce significant cell cycle arrest at the G2/M phase in HeLa cell lines and have antitubulin activity with an IC_{50} value of 5.9 μM.

Mustafa et al. synthesized new combretastatin A4 analogues containing 1,2,4-triazole **101**–**102** (Fig. 25) and evaluated for their anticancer activity against different cancer lines including leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast cancers [105]. Compounds **101a**, **102a**, and **102c** showed the highest promising anticancer activities and compound **102c** arrested cell cycle at G2/M phase in HepG2 cells. Selected compounds **101a**, **101b**, **101e**, **102a** and **102c** also displayed *in vitro* tubulin polymerization inhibitory activity displaying almost similar binding feature towards tubulin as CA-4.

Romagnoli et al. synthesized a series of regioisomeric 1,5-diaryl-1,2,4-triazole derivatives **103** (Fig. 25) [106]. Among them, compounds **103e** (IC_{50}: 5–100 nM) and **103h** (IC_{50}: 3–20 nM) were found to have highest antiproliferative activity against six tumor cell lines namely HeLa, A549, HL-60, Jurkat, K562 and MCF-7. SAR study revealed the significance of the substituent pattern on the phenyl ring at the 5-position of the 1,2,4-triazole ring on inhibition of tubulin polymerization and antiproliferative activities. Compounds **103e** and **103h** induced arrest in G2/M phase in Jurkat cells and induced apoptosis by activating caspase-3 and downregulating Bcl-2.

1-(3′,4′,5′-Trimethoxybenzoyl)-5-amino-1,2,4-triazoles **104** were evaluated for their anticancer effect against five human cancer cell lines, Jurkat, RS4; 11, HeLa, HT29 and MCF-7 [107]. SAR study revealed the effects of different substituents and their position on the phenyl ring on antiproliferative activity. Only four compounds **104a-d** (Fig. 25) exhibited potent antiproliferative

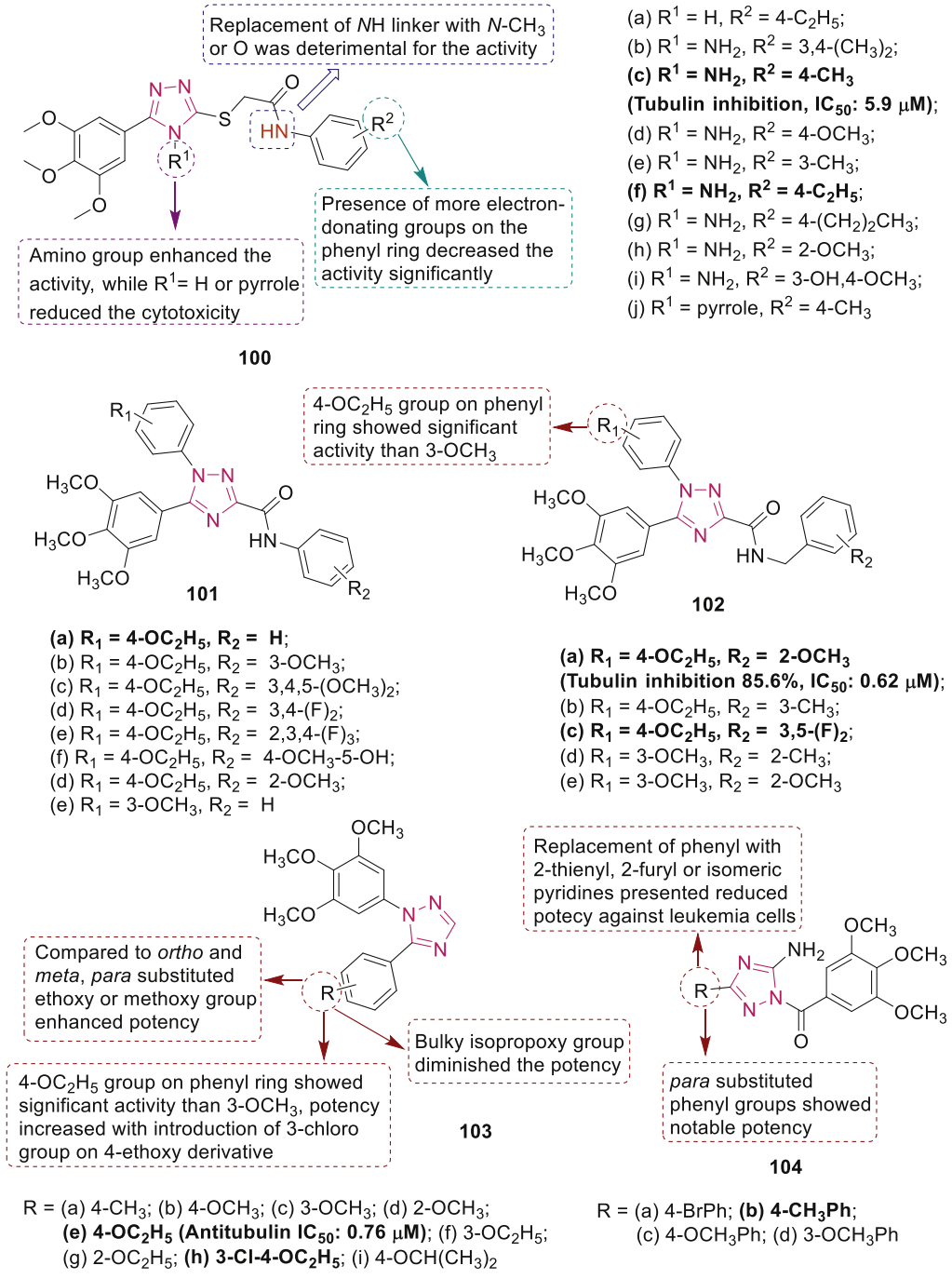


Fig. 25. 1,2,4-Triazole derivatives **100**–**104** as tubulin polymerization inhibitors.

activity (IC_{50} < 1 μM) against selected cancer cells. Compounds **104b** and **104c** act as more potent inhibitors of tubulin polymerization with IC_{50} value of 0.66 μM and 0.97 μM, respectively than CA-4 (IC_{50}: 1.2 μM).

2.3.4. Antiproliferatives

Wang et al. synthesized a series of [1,2,4]triazolo[1,5-*a*]pyridinylpyridines **105**–**106** (Fig. 26) and studied their anticancer activities against three human cancer cell lines- HCT-116, U-87 MG and MCF-7 [108]. Among the tested series, compound **105d** (IC_{50}: 0.84–1.82 μM) and **106d** (IC_{50}: 0.82–1.77 μM) exhibited potential activity and could inhibit the PI3K/AKT/mTOR pathway. Compound **105d** also exhibited *in vivo* inhibitory effect on tumor growth in mice bearing sarcoma S-180 model.

Xu et al. carried out three dimensional quantitative structure-activity relationship (3D-QSAR) on [1,2,4]triazolo[4,3-*b*][1,2,4,5] tetrazine derivatives with antitumor activities against MCF-7 cell [109]. The results of CoMFA (q^2: 0.716, r^2: 0.985) and CoMSIA (q^2: 0.723, r^2: 0.976) generated models with good predictive abilities. Compounds **107** and **108** (Fig. 26) showed significant potency against MCF-7, Bewo and HL-60 cells with IC_{50} values in 0.63–13.12 μM.

Fares et al. synthesized a series of pyrido[2,3-*d*] [1,2,4]triazolo [4,3-*a*]pyrimidines **109**–**111** (Fig. 26) and studied their *in-vitro* antiproliferative activities against PC-3 and A549 cell lines using the Sulfo-rhodamine B (SRB) colorimetric assay [110]. SAR studies

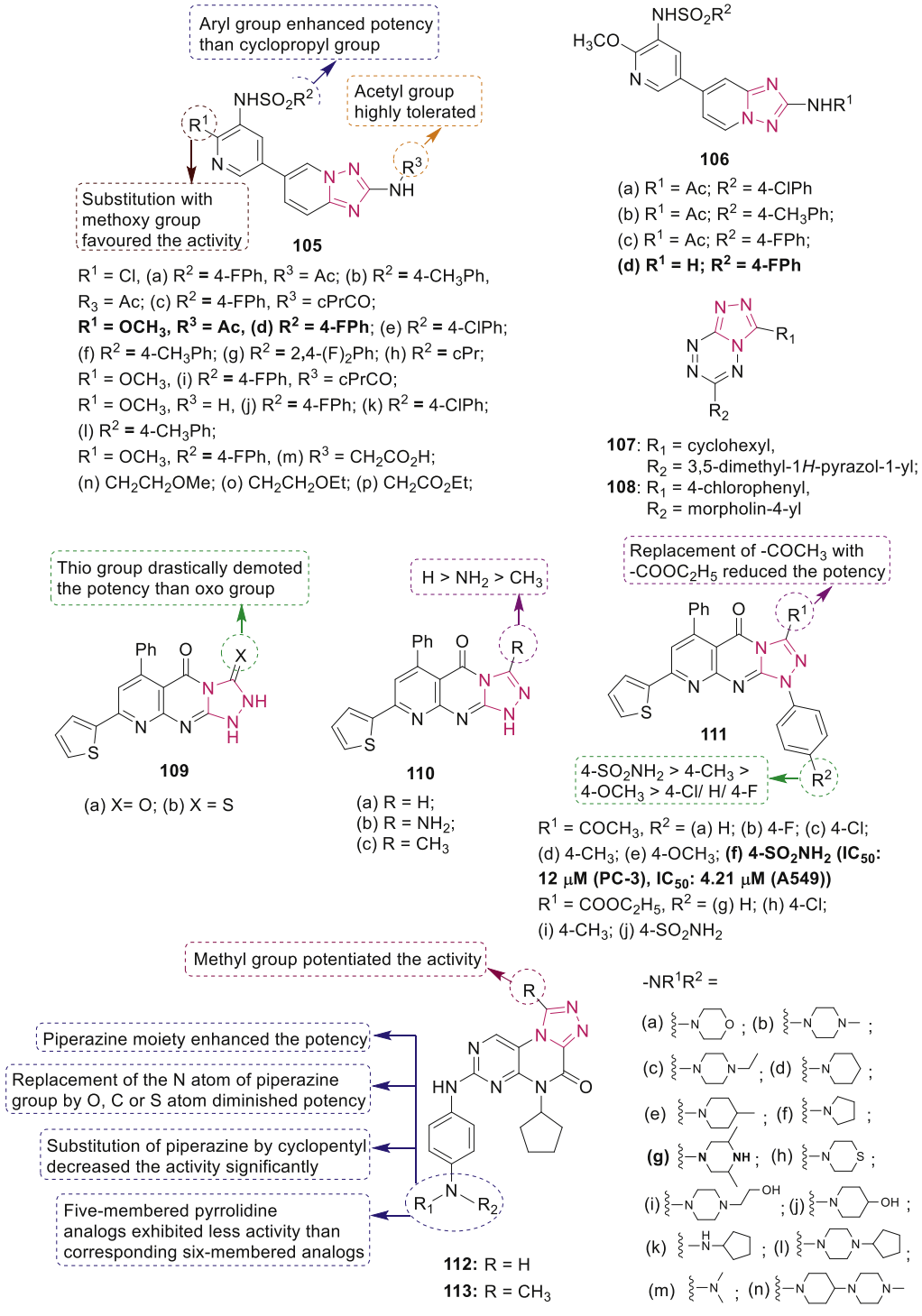


Fig. 26. Fused 1,2,4-triazole derivatives **105**–**113** as anticancer agents.

of 3-un/substituted derivatives **109**–**110** revealed that lipophilic group (thio and methyl) at C-3 position on the 1,2,4-triazole ring significantly diminished antitumor activity. Among 1,3-disubstituted triazolo derivatives **111**, compounds **111a**, **111c**, **111d** and **111f** with acetyl moiety at 3-position of 1,2,4-triazole ring were more potent than corresponding analogues **111g-j** having 3-ethyl carboxylate moiety and introduction of sulphonamide group on *N*-1 phenyl ring increased the activity. Mechanistic study revealed that compound **111f** exhibited good profile as apoptosis inducer *via* caspase-3 dependent pathway and arrested cell cycle at G1 phase in PC-3 cells line.

A series of novel 7-amino- [1,2,4]triazolo[4,3-*f*]pteridinone derivatives **112**–**113** (Fig. 26) was designed, synthesized and evaluated for their antitumor activity by Hou et al. [111]. SAR revealed that the presence of different hydrophilic amino groups on phenyl ring at C-7 position had a significant influence on potency. Of these 28 compounds, compound **113g** with 2,6-dimethylpiperazine displayed the most potent antiproliferative activity against A549, PC-3, HCT116, MCF-7 and MDA-MB-231 cell lines with IC_{50} values of 0.16 μM, 0.30 μM, 0.51 μM, 0.30 μM, and 0.70 μM, respectively.

Molecular docking and enzymatic studies demonstrated that compound **113g** inhibited PLK1 (86.4%) and cancer cell growth by inducing a great decrease in mitochondrial membrane potential leading to apoptosis and arresting G1 phase of A549 cells.

Kandeel et al. synthesized compounds **114** containing both chromenes and triazolopyrimidine moieties (Fig. 27) and evaluated their cytotoxic activity (IC_{50}: 0.007–0.039 μM) against MCF-7 cell line [112]. Most active compounds **114c** (IC_{50}: 0.007 μM), **114g** and **114h** (each having IC_{50}: 0.008 μM) displayed 1.5–2 folds superior activity than that of colchicine (IC_{50}: 0.013 μM). Further, anticancer activity of thieno[3,2-*e*]triazolo[4,3-*c*]pyrimidine derivatives **115** (Fig. 27) was evaluated against a panel of 59 human tumor cell lines, representing leukemia, melanoma and cancers of lung, colon, central nervous system (CNS), ovary, kidney, prostate as well as breast [113]. Among them, compound **115c** endowed with broad spectrum anticancer activity (GI_{50}: 0.495–5.57 μM) against 56 human cancer cell lines was highly selective against T-47D and MDA-MB-468 cell lines with GI_{50} 0.495 and 0.568 μM, respectively. Molecular mechanisms illustrated that compound **115c** could induce cell cycle arrest at G2/M phase and show accumulation of cells in pre-G1 phase in MDA-MB-468 cell line.

Botros et al. synthesized of a series of substituted benzothieno [3,2-*e*][1,2,4]triazolo[4,3-*a*]pyrimidines **116**–**119** (Fig. 27) and some selected compounds were screened for their *in vitro* cytotoxic activity against two human cancer cell lines, PC-3 and HCT-116 [114]. Two compounds **116l** and **119c** were found to be the most active against HCT-116 cell line with IC_{50} values of 6.56 and 6.12 μM as compared to doxorubicin (IC_{50}: 15.82 μM) and one of the compound **117c** (IC_{50}: 5.48 μM) showed highest activity against PC-3 cell line. SAR study illustrated the significance of phenylpiperazine moiety (R) and extending side chain (X) on bioactivity.

Recently our group synthesized a series of 6-chloro-3-substituted-[1,2,4]triazolo[4,3-*b*]pyridazines **120** (Fig. 27) and evaluated them for their antitumor activities [115]. Among the tested series, three compounds **120a-c** exhibited potential activity and 2–9 folds selectivity against SB-ALL and NALM-6 cell lines compared to MCF-7 cells. Further, these compounds efficiently induced apoptosis of NALM-6 cells *via* caspase 3/7 activation. SAR

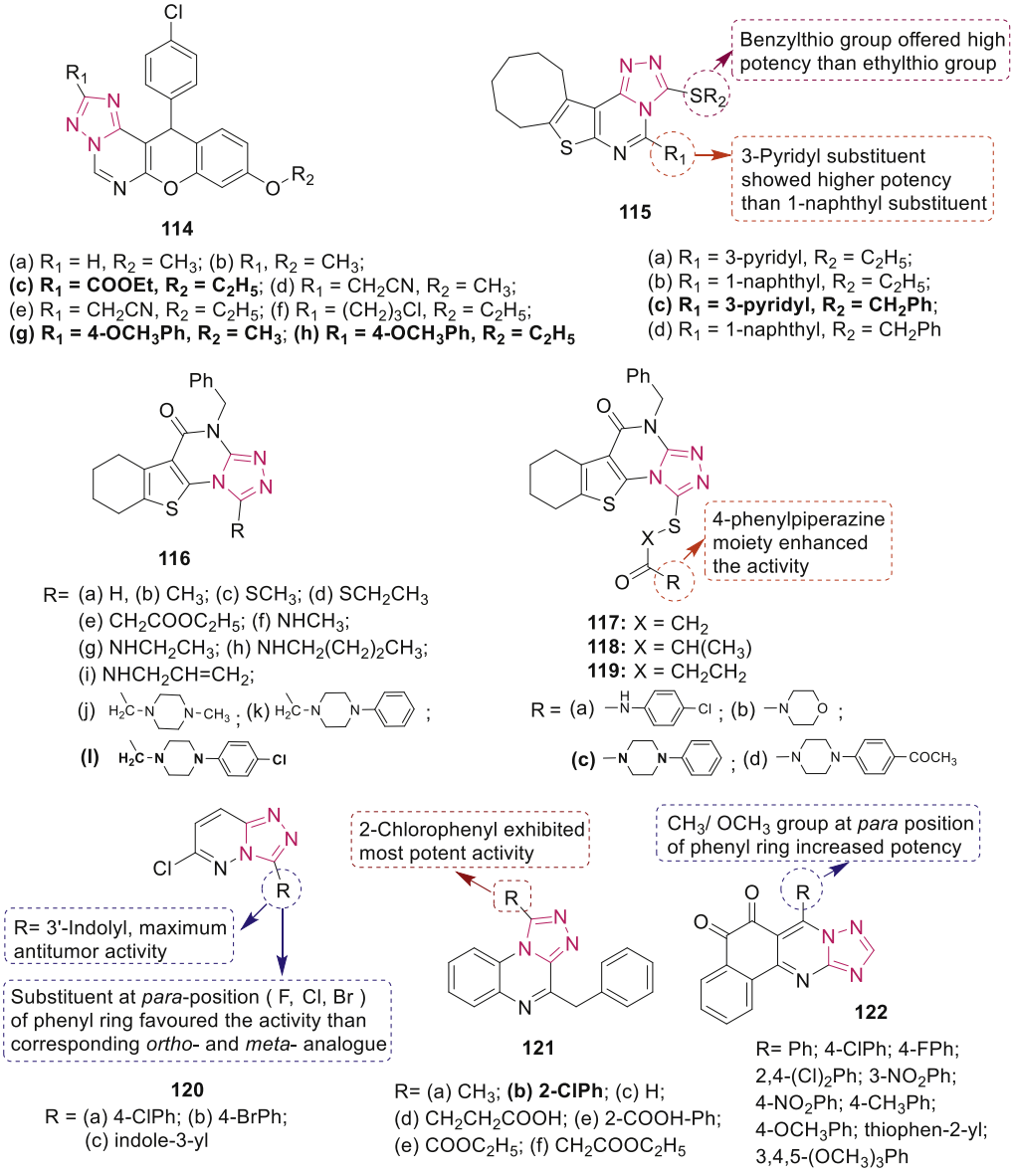


Fig. 27. Fused 1,2,4-triazole derivatives **114**–**122** as anticancer agents.

study revealed the significance of *para*-substituted phenyl group over *ortho*- and *meta*-derivative.

Issa et al. reported 1,2,4-triazolo[4,3-*a*]quinoxalines derivatives **121** (Fig. 27) as antiproliferative agents [116]. Among these, the most active compound **121b** was further evaluated against 60 human cell lines and exhibited significant antitumor activity against leukemia SR, non-small cell lung cancer HOP-92, NCI—H460, colon cancer HCT-116, HCT-15, CNS cancer U251, melanoma LOX IMVI, renal cancer A498, prostate cancer PC-3, and breast cancer MDA-MB-468 cell lines (GI_{50}: 3.91, 3.45, 3.49, 3.21, 1.96, 5.18, 3.69, 1.80, 5.19, and 5.55 μM, respectively). Several 6-aryl-benzo[*H*] [1,2,4]-triazolo[5,1-*b*]quinazoline-7,8-diones **122** (Fig. 27) were screened for their cytotoxicity against human gastric carcinoma cell line SCG7901 and hepatoma cell line HepG2 by Wu et al. [117]. SAR study revealed that *ortho*-quinone moiety and presence of electron-rich aromatic ring at the C-6 position improved the cytotoxicity.

Xue et al. synthesized a series of 1,2,4-triazolo[3,4-*a*]phthalazine derivatives **123** (Fig. 28) and studied their cytotoxic activities (IC_{50}: 1.7—124.5 μM) against four human cancer cell lines (MGC-803, EC9706, HeLa and MCF-7) [118]. Among the series, the most active compound **123h** was more potent than 5-fluorouracil and exhibited cytotoxicity *via* induction of apoptosis in EC-9706 cells.

Husain et al. have screened a series of triazolothiadiazoles **124** and triazolothiadiazines **125** (Fig. 28) for their *in vitro* anticancer activity for 60 cell line panel representing full nine human systems as leukemia, melanoma and cancers of lung, colon, brain, breast, ovary, kidney and prostate [119]. One compound, **124i** exhibited remarkable anticancer activity against all tested cell lines (IC_{50}: 0.20—2.58 μM) and emerged as promising lead with broad spectrum of anticancer activities against tumor cell lines.

Hu et al. synthesized novel 2,4-diaminopyrimidine derivatives possessing triazolopiperazine scaffolds **126** (Fig. 28) and screened them against a panel of kinases (CDK4, JAK2, VEGFR2, PI3Kα and FLT3) and four tumor cell lines [120]. Among them, compound **126k** exhibited most potent antitumor activities against A549, HCT-116, PC-3 and MCF-7 cell lines with IC_{50} values of 2.14 μM, 3.59 μM, 5.52 μM and 3.69 μM, respectively. Significance of R group on phenyl ring and amino groups (R_1) of terminal aniline on the pyrimidine core is shown in Fig. 28. Furthermore, mechanistic studies revealed that compound **126k** could suppress the migration of tumor cells, induce apoptosis, and prolonged the A549 cell cycle distribution, representing blockage at the G2-M phase and accumulation at the S phase.

Zhang et al. designed a series of 1,2,4-triazolo[3,4-*b*] [1,3,4] thiadiazines **127** containing furan and thiophene nuclei (Fig. 29) and evaluated them for antitumor activity [121]. Among the series, compound **127a** presented eleven-, three-, and two-fold improvement compared to positive control fluorouracil in inhibiting HepG2, PC-3, and A549 cell proliferation with IC_{50} values of 5.09, 3.70 and 12.74 μM, respectively and arrested G_2/M cell cycle in PC-3 cells.

Zhao et al. have reported the synthesis and anticancer activity of 3,4-disubstituted-5-(3,4,5-trimethoxyphenyl)-4*H*-1,2,4-triazoles **128** and some novel 5,6-dihydro-[1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazoles **129** (Fig. 29) [122]. Among them, compound **129b** showed promising activity against HepG2 cell line with an IC_{50} value of 0.58 μM, whereas compound **129c** (IC_{50}: 3.17—13.79 μM) exhibited broad spectrum of antitumor activity against HepG2, MCF-7 and MKN45. SAR studies revealed that 1,2,4-triazoles fused with thiadiazole ring **129** were highly potent as compared to 1,2,4-triazole derivatives **128** containing iminoacyl moiety on the 4-position.

Kamel and Abdo have reported the synthesis and anticancer activity of a series of *N*-substituted-3-mercapto-1,2,4-triazoles **130**, triazolo[3,4-*b*][1,3,4]thiadiazoles **131**, and triazolo[3,4-*b*][1,3,4]

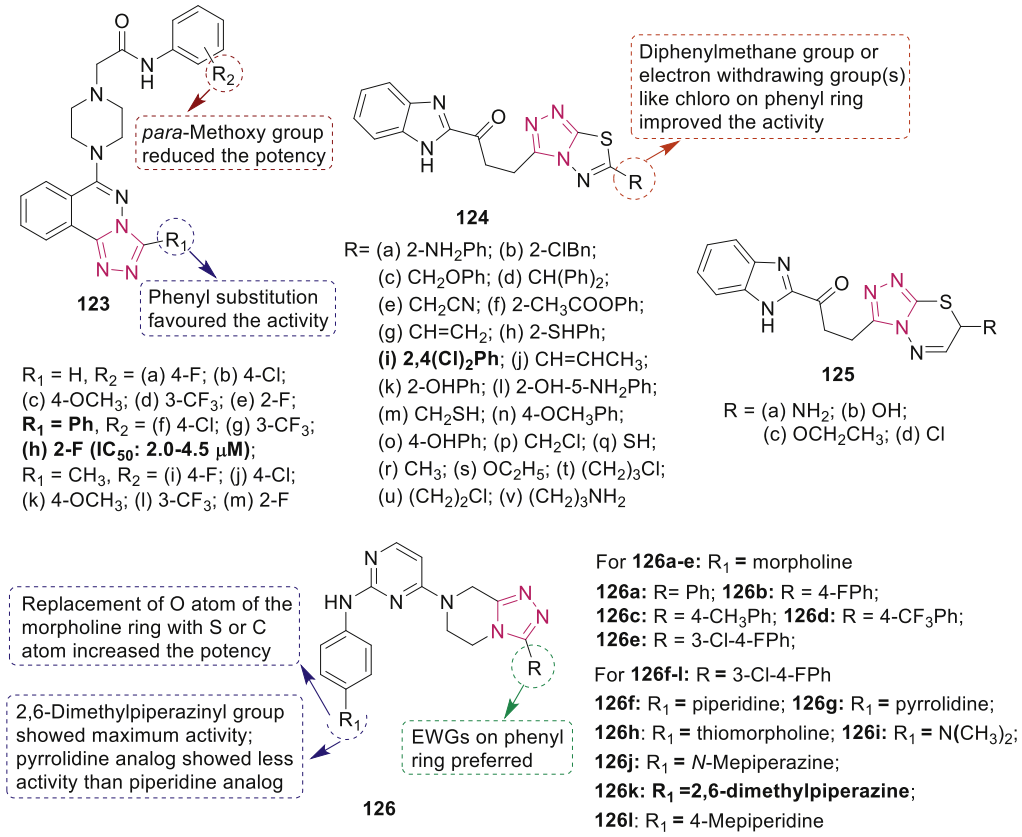


Fig. 28. Fused 1,2,4-triazole derivatives **123**—**126** as anticancer agents.

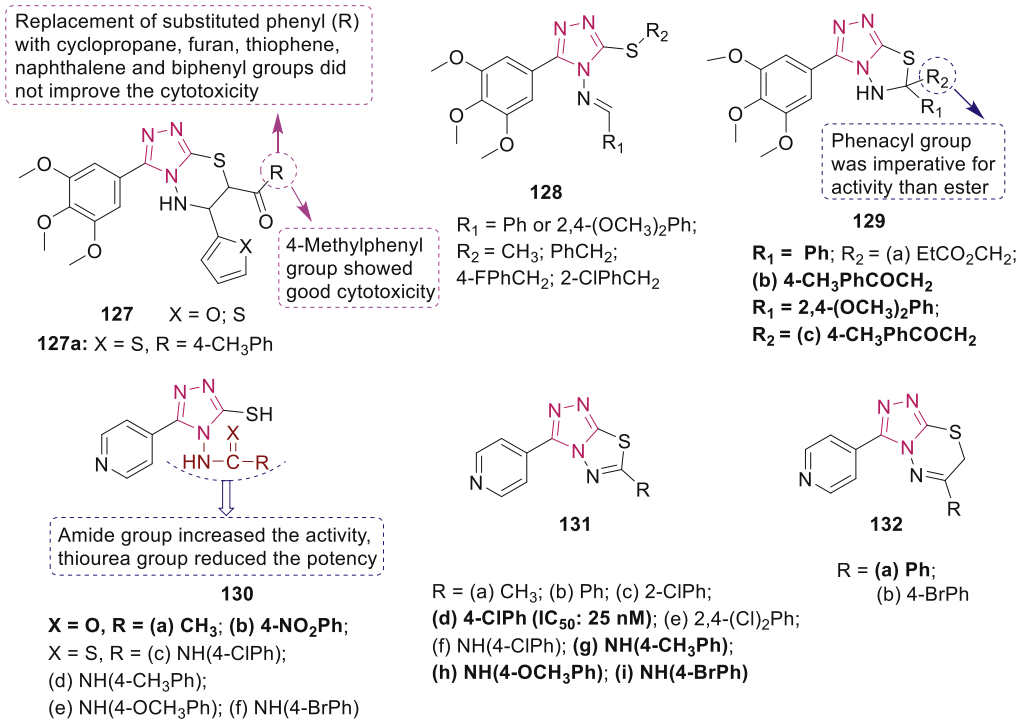


Fig. 29. Fused 1,2,4-triazole derivatives **127**–**132** as anticancer agents.

thiadiazines **132** (Fig. 29) against six human cancer cell lines gastric cancer (NUGC), human colon cancer (DLD1), human liver cancer (HA22T and HepG2), nasopharyngeal carcinoma (HONE1), human breast cancer (MCF) and normal fibroblast cells (WI38) [123]. Seven of the tested compounds (**130a**, **130b**, **131d**, **131g-i** and **132a**) showed remarkable activity with IC_{50} values < 800 nM. Compound **131d** displayed equivalent cytotoxic effect to the standard CHS 828 against gastric cancer cell line.

Pharmacological evaluation of synthesized 2-(4*H*-1,2,4-triazole-3-ylthio)acetamide derivatives **133** (Fig. 30) was carried out against the full panel of 60 human cancer cell lines. Results demonstrated that compounds **133a**, **133b** and **133c** exhibited antiproliferative activity against PC-3 cells (IC_{50}: 5.96 μM), A549/ATCC cells (IC_{50}: 7.90 μM) and K-562 cells (IC_{50}: 7.71 μM), respectively [124]. Compounds **133a-c** revealed significant increase in caspase-3 activity in a dose-dependent manner and decreased the mitochondrial membrane potential and the expression of Bcl-2.

Zhao et al. synthesized a series of isoindoline-1,3-diones containing 1,2,4-triazole moiety and three representative compounds **134a-c** (Fig. 30) exhibited more potent antitumor activities against four human cancer cell lines (HepG2, A549, PC-3M and MKN45) than the reference 5-fluorouracil [125]. Notably, the flow-activated cell sorting analysis revealed that compound **134b** dose-dependently inhibit the proliferation of HepG2 cells *via* inducing apoptosis. Further, a series of novel 3-alkylsulfanyl-4-amino-1,2,4-triazoles **135** (Fig. 30) was designed and evaluated for antitumor activity [126]. Compound **135d** was found to have the highest potency with IC_{50} values of 0.37, 2.94 and 31.31 μM against HCT116, HeLa and PC-3, respectively. Mechanistic studies demonstrated that it not only induces cell cycle arrest in a dose-dependent manner in HeLa cells at G2/M phase but also induced apoptosis.

Wang et al. synthesized nonsymmetrical disulfides bearing 1,2,4-triazole moiety **136**–**137** (Fig. 30) and evaluated their antiproliferative activity against human cancer cell lines SMMC-7721, HeLa, A549, and normal cell lines L929 by CCK-8 assay [127]. Most of the tested compounds exhibited better activity than positive control 5-fluorouracil. Compound **136d** exhibited the best inhibition against A549 cells (IC_{50}: 2.79 μM) and **137c** was found to be the most potent against SMMC-7721 cells (IC_{50}: 2.97 μM).

Tokala et al. reported that out of twenty five 1,2,4-triazole-linked urea and thiourea conjugates screened for anticancer activity against five cancer cell lines, compounds **138a-h** (Fig. 30) displayed good cytotoxicity (IC_{50}: <50 μM) against breast (MCF-7, MDA-MB-231), lung (A549) prostate (DU-145) and one mouse melanoma (B16–F10) cell line [128]. SAR revealed that the thiourea congeners **138d-h** were comparatively more potent than the urea derivatives **138a-c**. Compound **138g** (IC_{50}: 4.51–11.75 μM) was found to have significant activity against all cell lines and was more potent than 5-fluorouracil. Moreover, compound **138g** induced apoptosis of MCF-7 cells, inhibited colony formation in MCF-7 cells and arrested tumor cell cycle at the G0/G1 phase.

Mavrova et al. synthesized thieno[2,3-*d*]pyrimidin-4(3*H*)-ones containing 1,2,4-triazoles **139** (Fig. 30) and evaluated for their cytotoxicity against four human cancer cell lines (HT-29, MDA-MB-231, HeLa, HepG2) and normal diploid cell (Lep3) [129]. Amongst them, compound **139c** with IC_{50} 9.5 X 10^{-4} μM was found to be most toxic to HeLa cells.

Boraei et al. designed, synthesized and evaluated indolyl-triazole hybrids **140**–**142** (Fig. 31) for antitumor activity [130]. *N*-unsubstituted triazole **140** showed higher activity with IC_{50} of 3.58 μg/mL and 4.53 μg/mL against HepG2 and MCF-7, respectively than corresponding *N*-2 substituted analogues **141** (10.8->100 μg/mL) and *N*-1 substituted analogues **142** (11.5–16.6 μg/mL). Hybrid **141b** (IC_{50}: >100 μg/mL) demonstrated lower activity than its analogues and positional isomer **142c**, implying sugar fragment at *N*-1 position was deterimental for the activity. Molecular docking analysis rationalized that hybrid **140** inhibit EGFR through the hydrogen bonding with Asp 855 and several interactions with the key amino acids in the EGFR active site (Fig. 31).

A series of triazole-pyrazolylcoumarin derivatives **143** (IC_{50}:

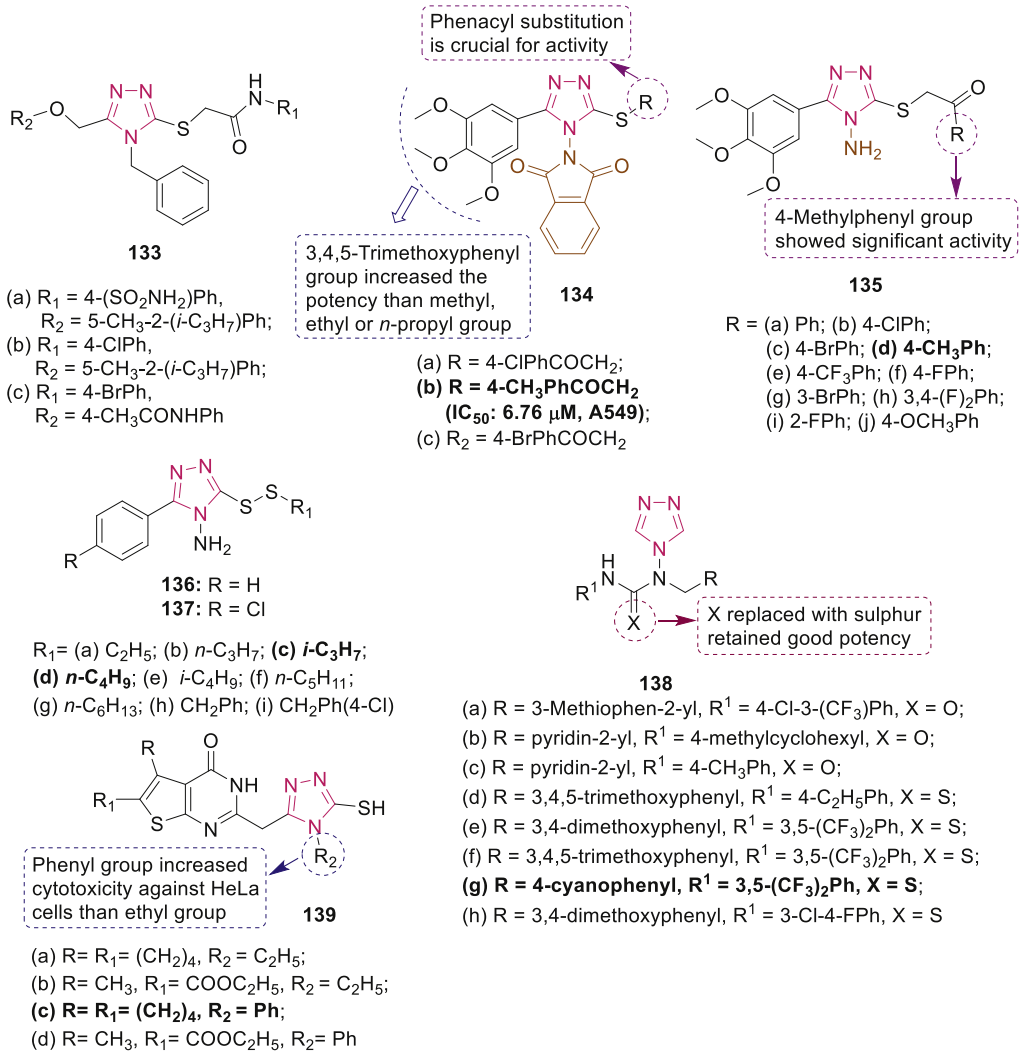


Fig. 30. Thio-substituted 1,2,4-triazole derivatives as anticancer agents.

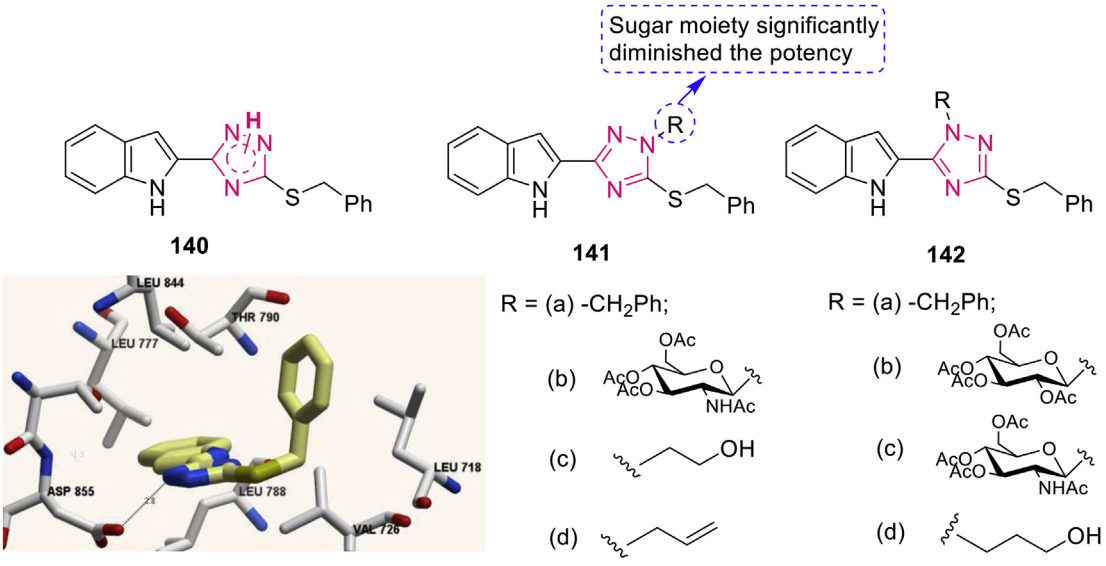


Fig. 31. Thio-substituted 1,2,4-triazole derivatives as anticancer agents. Compound **140** interaction with key residues in the active site of EGFR enzyme.

0.42–4.54 μm) (Fig. 32) displayed growth inhibitory effect against human prostate cancer cell lines LNCaP and PC-3 [131]. Compound **143g** exhibited more potent activity as inhibitor of 5α-reductase with ED_{50} of 0.15 μm than anastrozole (ED_{50} of 1.09 μm). Antitumor activity of coumarin-triazole hybrids **144** (IC_{50}: 3.1–37.9 μg/mL) was evaluated against four cancer cell lines (BT-20, SK-Mel-128, DU-145 and A549, MTT assay) by Kahveci et al. [132]. Hybrids **144d** and **f** (Fig. 32) showed better selectivity index value (SI: 5.2 and 2.7) against BT-20 cell line than cisplatin (SI: 2).

Coumarin-3-yl-thiazol-3-yl-1,2,4-triazolin-3-ones **145** (IC_{50}: 0.16–1.12 μM) (Fig. 32) showed promising activity against MDA-MBA-231, A549, K562 and HeLa cancer cell lines [133]. SAR studies reveal that electron-donating group at R_1 position and electron-withdrawing group at R_2 position highly enhanced the potency as evident in case of compound **145f** (IC_{50}: 0.16–0.31 μg/mL). Docking studies of compounds **145i** into the active site of EGFR-TKD revealed polar and hydrophobic interactions (Fig. 32).

Among the synthesized 4-(1*H*-1,2,4-triazol-1-yl)benzoic acid hybrids **146**–**148** (Fig. 33), compounds **148b** (IC_{50}: 15.6 μM) and **148c** (IC_{50}: 23.9 μM) displayed potent activity against MCF-7 and HCT-116 cancer cell lines, respectively when compared with doxorubicin (IC_{50}: 19.7 and 22.6 μM, respectively) [134]. A mechanistic study illustrated that compounds **146b** and **148b** induced apoptosis in MCF-7 cells.

2.4. Anticonvulsant agents

Deng et al. have repoted synthesis of several triazolo[1,5-*a*]pyrimidin-5(4*H*)-ones **149** (Fig. 34) as anticonvulsant agents [135]. SAR study indicated the significance of position of halogen on phenyl ring on the anticonvulsant activity. Compound **149i** displayed most promising activity in maximal electroshock test (MES) with ED_{50} value of 19.7 mg/kg and protective index (PI) value of 34.8 *via* inhibiting voltage-gated ion channels and modulating GABAergic activity against several chemically induced seizures.

Biological assessment of 1,2,4-triazolo[1,5-*a*]pyrimidinones **150** as new agonists of benzodiazepine receptors indicated that most of the compounds have higher affinity for benzodiazepine binding site in radioligand receptor binding assay than diazepam [136]. Particularly, compound **150c** (Fig. 34) with highest binding affinity (*Ki*: 0.42 nM and IC_{50}: 0.68 nM) exhibited substantial hypnotic and weak anticonvulsant activities with no impairment on learning and memory *in vivo*.

Anticonvulsant activity of 2,5-disubstituted [1,2,4]-triazolo[1,5-*a*]pyrimidine-7(4*H*)-one derivatives **151** (Fig. 34) as positive modulators of $GABA_{A1}$ was evaluated by MES and pentylenetetrazole (PTZ) and rotarod neurotoxicity test by Huang et al. [137]. Results revealed that compounds **151a** and **151b** showed significant anticonvulsant activities in PTZ-induced epilepsy model with ED_{50} values at 31.81 mg/kg and 40.95 mg/kg, respectively. Both

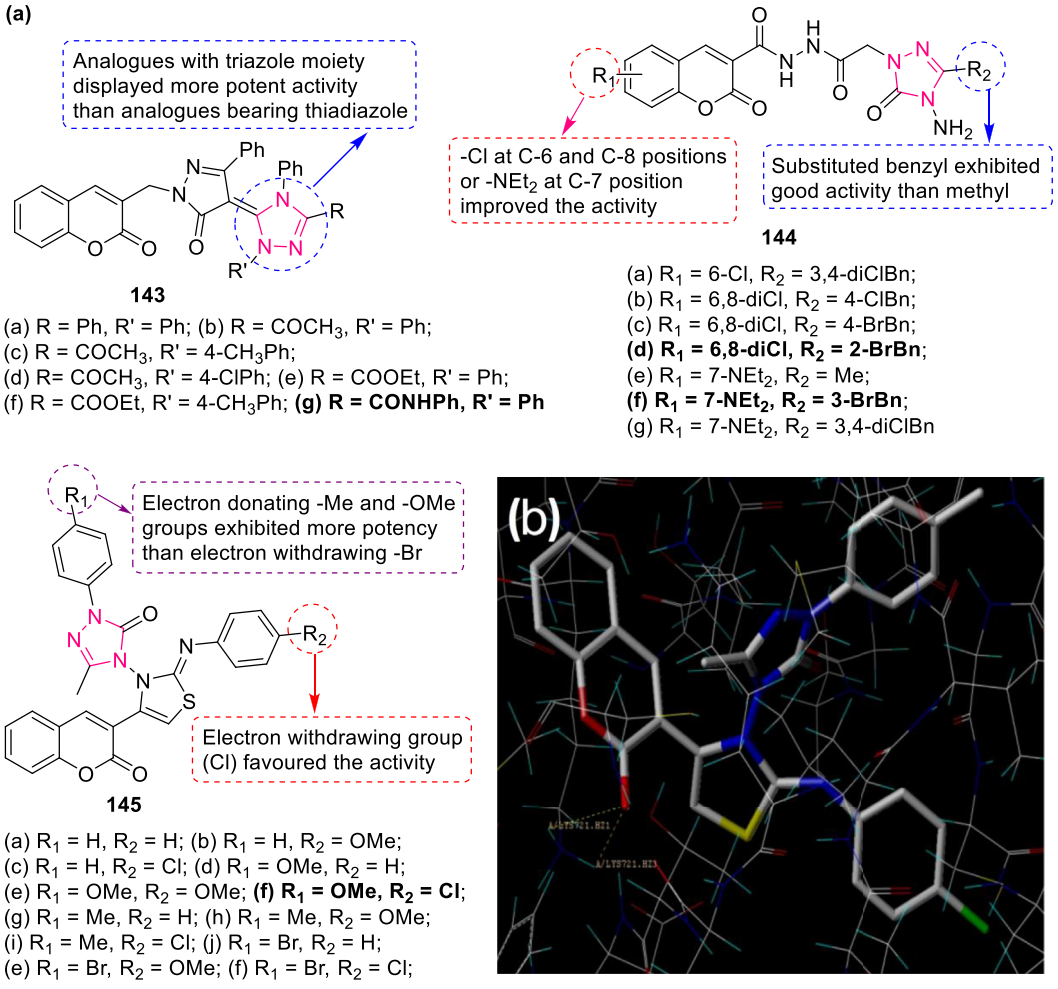


Fig. 32. (a) Coumarin-1,2,4-triazole derivatives as anticancer agents. (b) Stereoview of compound **145i** docked into the active site of EGFR-TKD which shows two hydrogen binding interaction of oxygen atom of carbonyl group at coumarin ring with hydrogen atom of the amino acid residue Lys721.

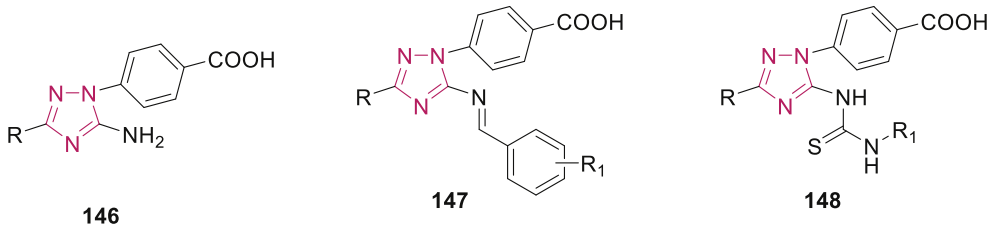


Fig. 33. 4-(1*H*-1,2,4-Triazol-1-yl)benzoic acid hybrids as anticancer agents.

compounds displayed higher PI value of 17.22 and 9.09 than four standard drugs.

Several 10-alkoxy-5,6-dihydro-triazolo[4,3-d]benzo[*f*][1,4]oxazepines **152** and 8-alkoxy-4,5-dihydrobenzo[*b*][1,2,4]triazolo[4,3-*d*][1,4]thiazepine derivatives (**153** and **154**) (Fig. 34) were synthesized and their *in vivo* anticonvulsant activity were evaluated using MES screens by Deng et al. [138,139]. SAR study of compounds **152** revealed the role of alkyl groups and their size on anticonvulsant activity. Among them, compound **152g** (R = *n*-heptane) was the most potent (ED_{50}: 6.9 mg/kg and PI: 9.5) and exhibited anticonvulsant activity *via* GABA-modulating mechanisms in sc-PTZ, isoniazid, 3-MP, thiosemicarbazide and Bicuculline induced seizures tests. Compound **154a** exhibited promising anti-MES activity with an ED_{50} of 26.3 mg/kg and a superior PI value of 12.6.

Deng et al. synthesized a set of 6-(substituted-phenyl)thiazolo[3,2-*b*][1,2,4]triazole derivatives **155** (Fig. 34) to screen their anticonvulsant activity [140]. Results indicated that compound **155c** was found to be more selective in MES screen with an ED_{50} and PI value of 49.1 and 1.9 respectively, while **155n** was found to be active in both MES test and PTZ test. In the PTZ screening, compound **155n** exhibited an ED_{50} value 63.4 mg/kg and a TD_{50} of 105.6 mg/kg, resulting in a high PI value of 1.7 when compared with standard carbamazepine (PI < 0.44). Further, neurotoxicity of the compounds was measured using rotarod test, which indicated that most of the compounds exhibited high level of neurotoxicity.

Cao et al. synthesized a series of 7-alkoxy-2,4-dihydro-1*H*-benzo[*b*][1,2,4]triazolo[4,3-*d*][1,4]-thiazin-1-ones **156** (Fig. 34) and evaluated for their anticonvulsant activity [141]. Compound **156a** exhibited significant anticonvulsant activity in MES test with ED_{50} value of 9.2 mg/kg and PI value of 15.4 which was superior to standard carbamazepine (ED_{50} and PI values of 11.8 and 6.4, respectively).

Several triazolo[4,3-*a*]quinazolin-5(4*H*)-ones **157** and pyrido[3,2-*e*][1,2,4]triazolo[4,3-*a*]pyrimidin-5(6*H*)-ones **158** (Fig. 34) were synthesized as anticonvulsant agents by Zhang et al. [142,143]. Based on the anticonvulsant and neurotoxicity screening data, compounds **157a** and **157b** showed wide margins of safety with PI value of >25.5 and > 26.0, and significant oral activity against MES-induced seizures in mice with an ED_{50} of 88.0 and 94.6 mg/kg, respectively. SAR study of compounds **158** revealed that presence of halogen atom (F and Cl) and the position of the halogen atom on the benzyl group influenced the activity and in *N*-alkyl derivatives the anticonvulsant activity gradually decreased with increase in the alkyl chain length.

Guan et al. have reported synthesis and anticonvulsant activity of 6-alkoxy- [1,2,4]triazolo[4,3-*b*]pyridazine derivatives **159** (Fig. 34) in which compound **159i** showed anticonvulsant activity with median effective dose (ED_{50}) of 17.3 mg/kg and median toxicity dose (TD_{50}) of 380.3 mg/kg, and PI of 22.0 in the anti-MES test [144].

Phenytoin-1,2,4-triazole hydrids **160** (Fig. 35) were synthesized and evaluated for their anticonvulsant activity using MES and scPTZ screens in mice by Botros et al. [145]. Hybrids **160b-e**, containing aromatic ring at *N*-4 position of the triazole, displayed higher protection in MES screen against electrically induced seizures than the ethyl substituted analogue **160a** at a dose of 100 mg/kg.

Several 1,2,4-triazole-3-thione derivatives having 4-aryl group **161** and 4-alkyl group **162** (Fig. 35) were evaluated for their anticonvulsant activity by Plech et al. [146,147]. The MES and neurotoxicity tests demonstrated that compound **161a** with the ED_{50} of 35.2 mg/kg, TD_{50} of 136.7 mg/kg and PI of 3.9 possess the most potent activity. Compounds **162a-g** showed better activity as compared to standard drug valproate. Results revealed that elongation of alkyl fragment from $-C_2H_5$ to $-C_4H_9$ at 4-position of 1,2,4-triazole increased the activity approximately 4-fold (from 152 mg/kg to 38.5 mg/kg), due to increase in the lipophilicity of the molecule. Chromatographic tests showed that analogues **162h** and **162i** with C_{10} and C_{12} alkyl chain, respectively lack anticonvulsant effect due to the inability to cross the blood brain barrier (BBB).

To gain more insights into SARs, Plech's et al. synthesized several 4-alkyl-1,2,4-triazole-3-thiones by replacing the 5-(3-chlorophenyl) group by 5-(3-chlorobenzyl/2,3-dichlorophenyl). In the analogues containing 5-(3-chlorobenzyl) group **163** (Fig. 35), the presence of $-CH_2-$ linker improves the potency, time-course profile and safety due to increase in molecule flexibility [148]. Based on the activity and toxicity profile, compound **163d** showed the most promising potential as anticonvulsant agent (ED_{50}: 72.1 mg/kg, TD_{50}: >1000 mg/kg and PI: >13.9 after 15 min). Radioligand binding assay indicated that these compounds excluded the possibility of direct or allosteric modulation of $GABA_A$ receptors.

Deng et al. have reported the synthesis of some new triazole-containing quinolinones **164** (Fig. 36) and screened for their anticonvulsant and antidepressant activity by using MES and forced swimming test (FST) [149]. Compound **164a** exhibited most potent antidepressant activity and higher efficacy than the reference drug fluoxetine. SAR study revealed that compounds **164b** and **164c** having an *n*-pentyl and a hexyl chain attached to the core quinolinone fragment, respectively showed the highest anticonvulsant activities and provided 100% protection at the dose of 100 mg/kg.

A series of purine containing triazoles **165** (Fig. 36) were synthesized and evaluated for anticonvulsant activity using MES and scPTZ models in mice by Wang et al. [150]. Among the tested compounds, **165a** was the most active compound with ED_{50} of 23.4 mg/kg and PI value of >25.6, which is higher than the

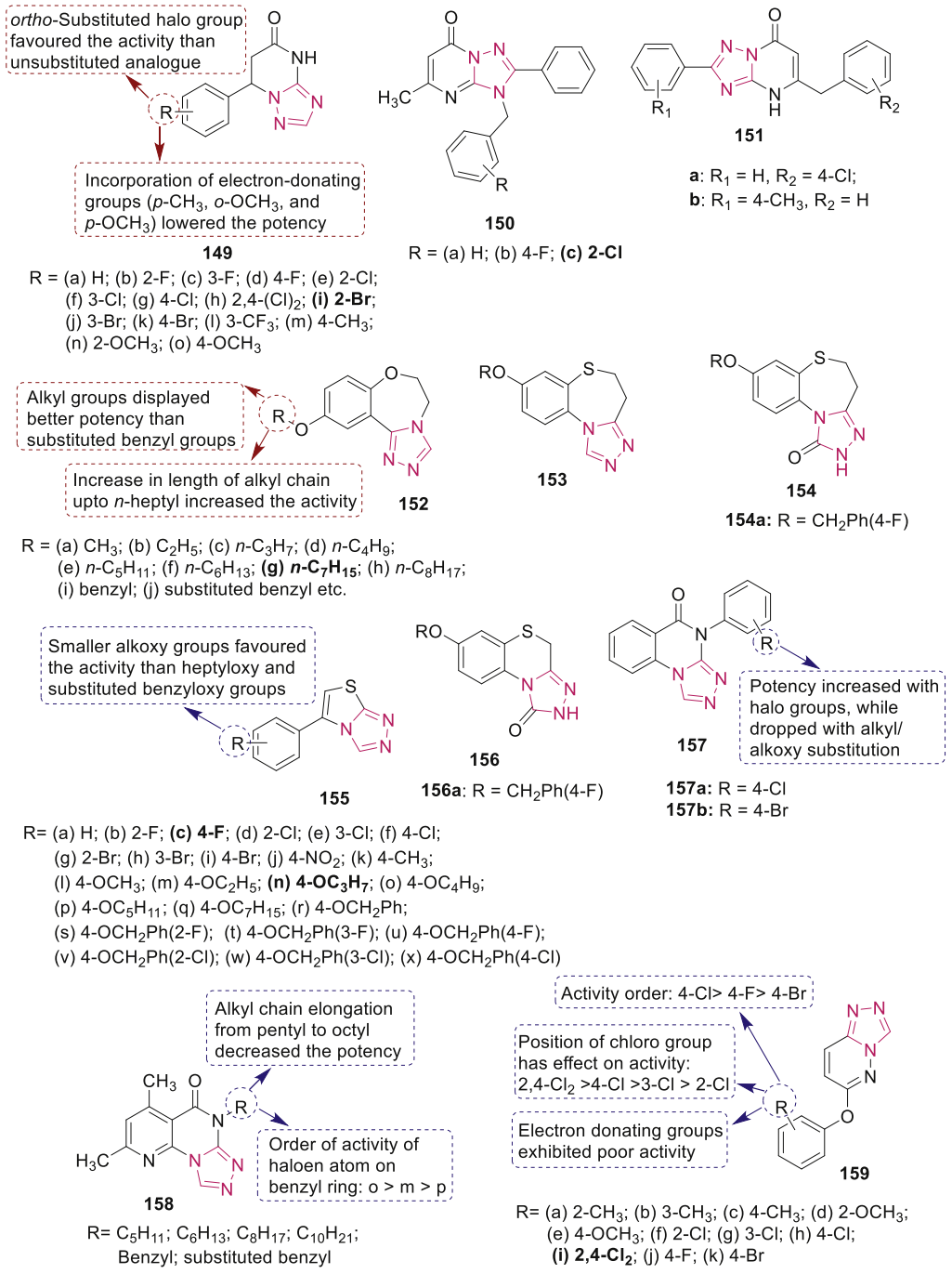


Fig. 34. Fused 1,2,4-triazole derivatives as anticonvulsant agents.

reference drug, carbamazepine whose PI value was 6.4. Moreover, compound **165a** exhibited significant oral activity against MES-induced seizures (ED_{50}: 39.4 mg/kg). SAR study revealed the significance of triazole ring as shown in Fig. 36.

Sari et al. synthesized a series of ester derivatives of 1-(2-naphthyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone oxime **166** (Fig. 36) and evaluated them *in vivo* for anticonvulsant and neurotoxic effects by MES, scMET-induced seizures and rotarod tests [151]. Docking study using homology models of Na^+ channel inner pore and $GABA_AR$ revealed that the compounds exerted anticonvulsant activity by inhibiting voltage-gated sodium channels (VGSC) and allosterically modulating $GABA_AR$.

Abuelhassan et al. reported the anticonvulsant activity of 1,5-diaryl-1*H*-1,2,4-triazole-3-carboxamide derivatives **167** (Fig. 36) against MES, scPTZ and Strychnine animal screen methods [152]. Most of the compounds showed parallel activity pattern with standard phenytoin and valparate. Compound **167a** and **167b** showed 100% of sodium valproate activity and phenytoin activity, respectively after 0.5 and 4 h in scPTZ model. The pharmacophoric results for the selected compounds revealed that the compounds showed good fitting on the pharmacophoric query with good RMSDX results.

Liu et al. have synthesized and evaluated 1,2,4-triazole-3-thiol derivatives **168** (Fig. 36) for their anticonvulsant activity and neurotoxicity by using MES, scPTZ, and rotarod tests. Among them, compounds **168a** and **168b** exhibited significant anticonvulsant

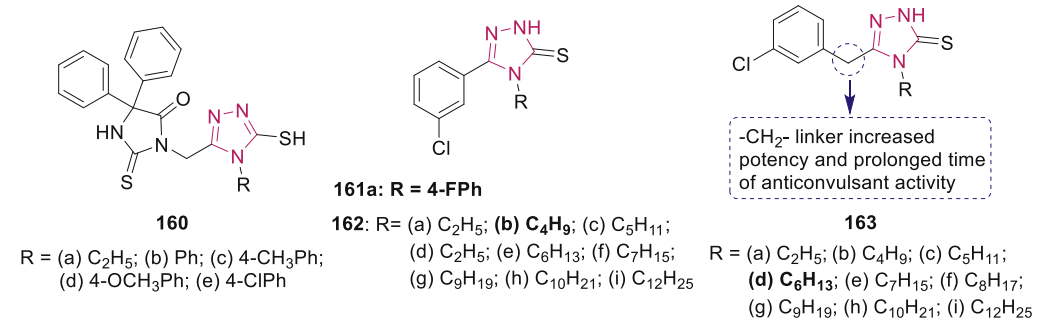


Fig. 35. Substituted triazolthiones with anticonvulsant activity.

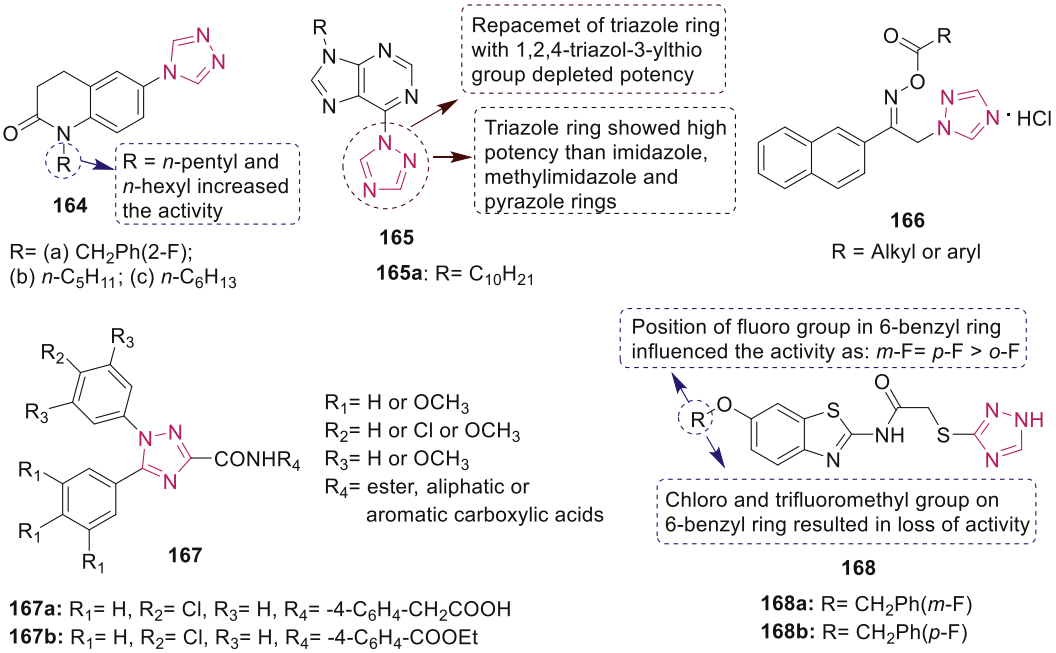


Fig. 36. 1,2,4-Triazoles derivatives **164**–**168** with anticonvulsant activity.

activity with the ED_{50} value of 50.8 and 54.8 mg/kg in the MES test and 76.0 and 52.8 mg/kg in the scPTZ seizures test, respectively [153].

2.5. Antituberculosis agents

Isoniazid (isonicotinic acid hydrazide) is the most effective antimycotic drug used for treatment of tuberculosis (TB) for more than 5 decades. Unfortunately, side effect of isoniazid and the emergence of drug-resistant tuberculosis provoked medicinal chemists to design novel anti-TB agents. Several 1,2,4-triazole derivatives have been synthesized with the aim to explore new anti-TB agents.

Krishana et al. reported the synthesis of a series of diphenylamine containing 1,2,4-triazoles **169**–**172** (Fig. 37) and screened against *Mycobacterium tuberculosis* $H_{37}RV$ (*Mtb* $H_{37}Rv$) species using standard Microplate Alamar Blue Assay (MABA) and agar dilution method [154]. Among the tested compounds, compounds **169a**, **169d** and **169e** displayed potent antimycobacterial activity with MIC value in the range of 0.2–3.125 μM. Compound **169a** showed more significant activity comparable to the standard drug isoniazid. SAR study revealed that mannich base **169** and **170** displayed better activity as compared to triazoloquinazolinones **171** and triazolothiazolidinones **172**. The cytotoxicity of the most active compounds were evaluated against Vero (African Green monkey kidney epithelial cells) and HepG2 cell line. It was observed that compounds were not cytotoxic.

Castelino et al. have reported the design and synthesis of Schiff bases of 1,2,4-triazole-bearing haloarene moiety **173** (Fig. 37) and screened for *in vitro* anti-TB properties using disc diffusion method (ZOI test) and microplate Alamar Blue assay (MABA) method (MIC test) towards *Mtb* $H_{37}Rv$ strain [155]. Compounds **173a** and **173h** having two fluorine atoms at positions 2 and 4 were found to exhibit the highest activity for antituberculosis screening as well as for neutrophil function test. Acute oral toxicity studies revealed that some of the compounds were safe even at the dose of 2000 mg/kg body weight.

S-Substituted 4-alkyl-5-(3,5-dinitrophenyl)-4*H*-1,2,4-triazole-3-thiols and their 3-nitro-5-(trifluoromethyl)phenyl analogues **174** (MIC: 0.03–2 μM) (Fig. 37) were endowed with excellent and selective antimycobacterial activities against *Mtb* strains, including clinically isolated MDR strains [156]. SAR studies revealed the crucial role of position of 3,5-dinitrophenyl fragment on anti-TB activity.

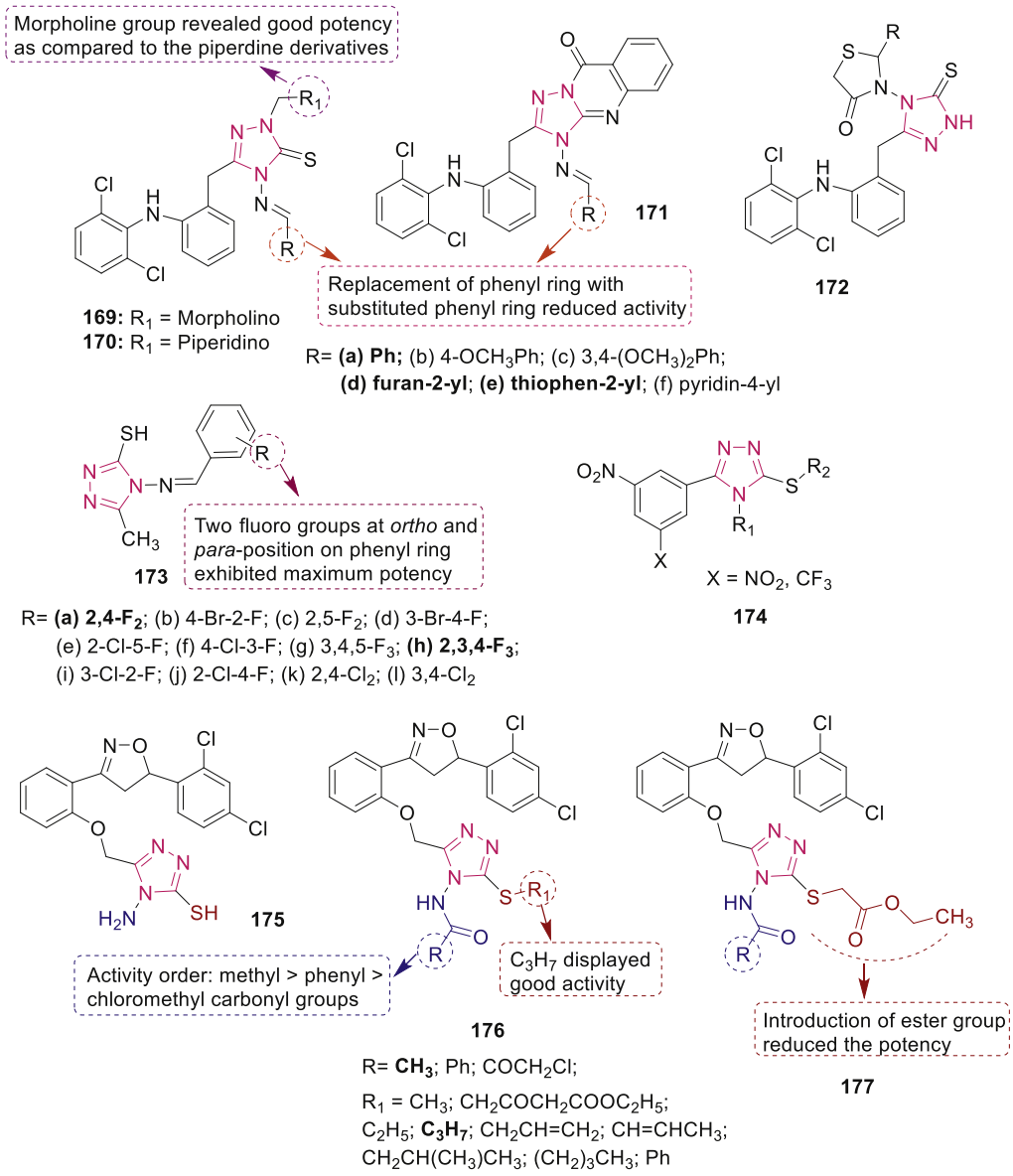


Fig. 37. Substituted triazolthiones **169**–**177** with anti-TB potential.

Several hybrid triazoles **175**–**177** (Fig. 37) were designed, synthesized and evaluated by Dixit et al. [157] as growth and efflux inhibitor of TB against *Mtb* $H_{37}Rv$ and *M. smegmatis* mc^2155. Pharmacologically active compounds were further tested for their cytotoxicity against human monocyte to assess their *ex-vivo* cytotoxicity toward eukaryotic cells. Further, the compounds which exhibited higher inhibition and less toxicity were subjected to secondary evaluation of growth and efflux inhibition on *Mtb* $H_{37}Rv$ and synergistic action with first line and second line anti-TB drugs. One of the compounds **176** having R = CH_3 and $R_1 = C_3H_7$ exhibited potent inhibitory growth in both *M. tuberculosis* and *M. smegmatis* mc^2155 as well as efflux (5 fold better than thioridazine (TZ)) have found to show very less toxicity compared to TZ towards human macrophages (16 folds) and proved as a better dual inhibitor which is better than TZ devoid of any CNS related side effects.

Evaluation of a series of novel 3-substituted triazolophthalazines **178** (Fig. 38) for anti-TB activity revealed that compounds **178a-d** exhibited moderate to excellent *in vitro* activities (MIC: 0.5–4 μg/mL) against *Mtb* $H_{37}Rv$ [158]. Furthermore, the most active compounds **178b-d** showed activity to a similar extent against various MDR-*Mtb* strains, thus revealing a distinct mode of action.

Various triazolopyrimidines **180** (Fig. 38) were designed and synthesized as anti-TB agents by Zuniga et al. [159] *via* the by modification of compound **179**, identified from a whole-cell screen against *M. tuberculosis*, at the C-5, C-7 and C-2 positions. A number of compounds exhibited sub-micromolar activity against *M. tuberculosis* with MIC_{90} value in the range of 0.52–10 μM with no cytotoxicity against HepG2 cells. Three compounds **179**, **180a** and **180b** displayed selectivity with MIC_{99} values of 3.1, 13 and 1.6 μM, respectively for *M. tuberculosis* over *M. smegmatis*, *E. coli*, *P. aeruginosa*, *B. subtilis* and yeast *S. cerevisiae*.

A series of isopropylthiazole clubbed triazole derivatives **181** and dihydro triazolothiadiazoles **182** were synthesized and screened for their anti-TB activity by Kumar et al. [160,161]. Compounds **181a**, **181b**, **182a** and **182b** exhibited potent *in vitro* activity

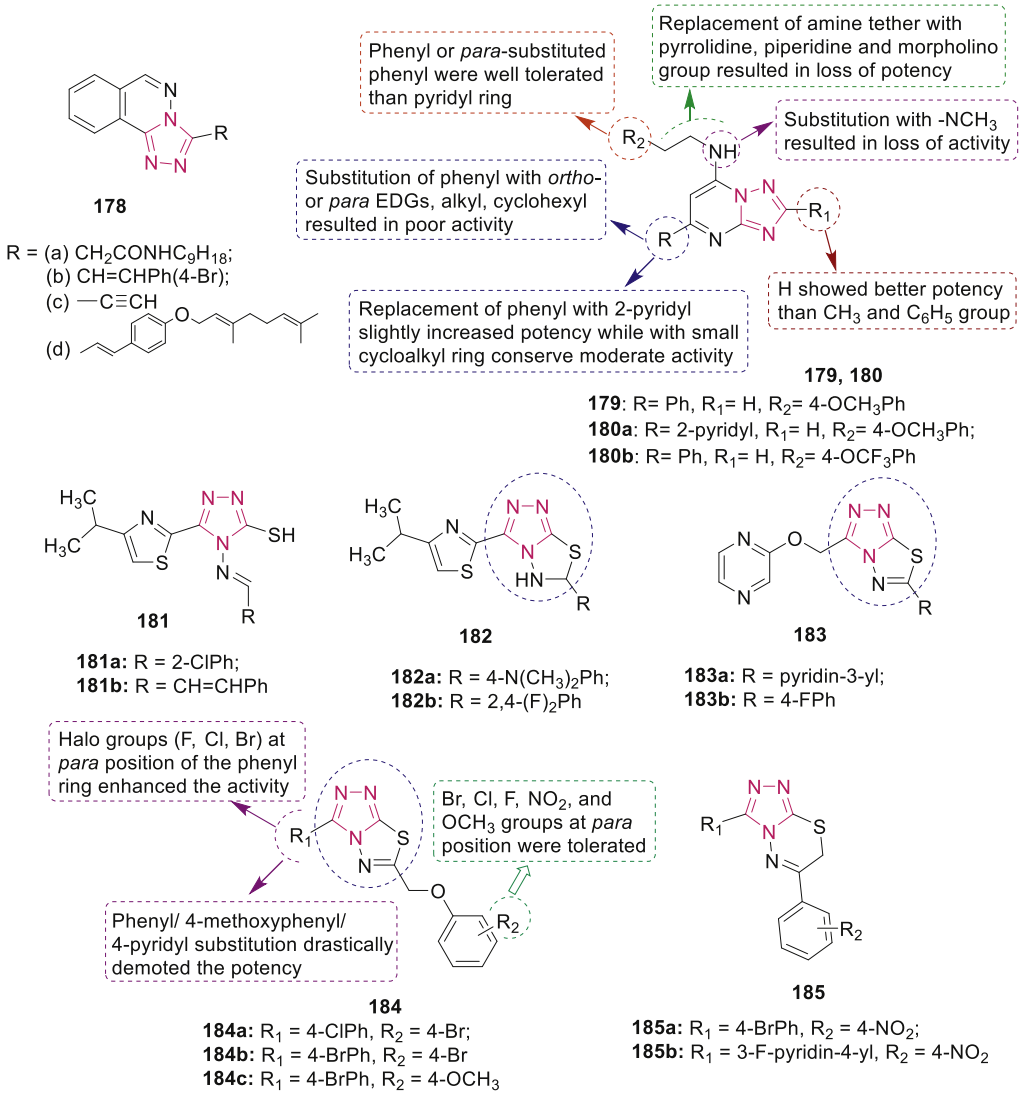


Fig. 38. Fused 1,2,4-triazoles anti-TB potential.

against *Mtb* $H_{37}Rv$ strain at MIC 4 μg/mL (Fig. 38). Bonde et al. reported that among the ten screened 1,2,4-triazolo[3,4-*b*] [1,3,4] thiadiazoles containing pyrazin-2-yloxymethyl moiety **183**, two compounds **183a** (MIC: 0.4 μg/mL) and **183b** (MIC: 1.0 μg/mL) exhibited a promising antimycobacterial activity against $H_{37}Rv$ strain (Fig. 38) [162].

Several triazolothiadiazoles and triazolothiadiazines **184** and **185** (Fig. 38) with structural modifications at C-3 and C-6 positions of fused system were reported to inhibit the growth of *Mtb* $H_{37}Rv$, MDR-TB (isoniazid and rifampin resistant strains) and DR-TB (rifampin resistant strains) by Li et al. [163,164]. SAR revealed that the electron-withdrawing groups at *para* position of the phenyl ring at the 3-position and *p*-bromophenoxymethyl group at the 6-position on the triazolothiadiazole **184** displayed significant enhancement in potency. Two highly active lead compounds **184a** and **184b** (MIC for $H_{37}Rv$: 0.5 μg/mL; MDR-TB: 4.0 μg/mL; DR-TB: 0.5–1.0 μg/mL) also showed potential inhibitory activity on *M. tuberculosis* shikimate dehydrogenase (*Mtb* SD) with IC_{50} value of 6.82 μg/mL and 14.42 μg/mL, respectively. SAR of triazolothiadiazines **185** regarding anti-TB activity led to the identification of two highly potent compounds **185a** (MIC for *Mtb* $H_{37}Rv$, DR-TB and MDR-TB strains: 0.25, 0.25 and 2.0 μg/mL) and **185b** (MIC for *Mtb* $H_{37}Rv$, DR-TB and MDR-TB strains: 1.0, 2.0 and 4.0 μg/mL) which were endowed with potent *Mtb* SD inhibitory properties with IC_{50} values 86.39 and 73.57 μg/mL, respectively. Triazolothiadiazole IMB-SD62 **184c**, inhibitor of *Mtb* SD, showed *in vivo* anti-TB activity against acute *Mtb* $H_{37}Rv$ infection in mice with a 1.7 log reduction in the lung CFU counts and 14% oral bioavailability in a preliminary pharmacokinetic study [165].

Papadopoulou et al. screened the anti-TB potential of 3-nitro-1,2,4-triazole-linked sulfonamides **186** and amides **187**–**188** (Fig. 39) against *Mtb* $H_{37}Rv$ under aerobic or hypoxic conditions [166,167]. Among them, compounds **186a** and **186b** exhibited excellent activity MIC of 1.56 and 3.13 μg/mL, respectively, superior to ethambutol (MIC: 6.25 μg/mL). The study revealed the reduction in aerobic anti-TB activity with decrease in length of the linker from a 4-methylene to a 3-methylene and 2-methylene linker between the nitrotriazole ring and the sulfamido group. Among amides, compounds **187a** and **187b** active against aerobic and hypoxic *Mtb* displayed bactericidal and intracellular antitubercular activities. Moreover, compound **188** was selectively active against aerobic *Mtb* and exhibited good *in vitro* ADMET characteristics, representing excellent caco-2 permeability, an efflux ratio of 0.39, good microsomal stability and lack of hepatotoxicity (Fig. 39).

A set of coumarin-3-yl-methyl-1,2,3-triazolyl-1,2,4-triazol-3(4*H*)-ones **189** (Fig. 39) were synthesized and screened for their anti-TB activity by using the Microplate Alamar Blue assay by Somagond et al. [168]. The preliminary *in vitro* results indicated that compounds **189a-g** displayed excellent anti-TB activities against *Mtb* $H_{37}Rv$ with MIC of 1.60 μg/mL and were ~2 folds more active than standard drug pyrazinamide (MIC: 3.12 μg/mL). Docking studies illustrated that **189d** and **189g** fitted well into the binding pocket of InhA-D148G (4DQU).

Ozadali et al. synthesized some thiazolylhydrazones **190** (Fig. 39) and reported their anti-TB activity [169]. Compounds **190a-d** with MIC value of 3.76–4.33 μM were found to be equally active as ethambutol (MIC: 7.65 μM) and ciprofloxacin (MIC: 4.71 μM). In general, the presence of NO_2, Cl and F atoms on phenyl ring is found to increase antimycobacterial activity remarkably.

A series of novel substituted 4*H*-1,2,4-triazol-3-yl cycloalkanols **191** (Fig. 39) has been designed and screened for anti-TB activity against *Mtb* $H_{37}Rv$ using resazurin microtiter assay by Desai et al. [170]. SAR revealed that compounds **191a-e** with 4-pyridyl substituent on triazole ring exhibited excellent anti-TB activity with MIC value in the range 0.59–0.95 μg/mL and low cytotoxicity against the Vero Cell line C1008 with SI > 28.

Twenty 1,2,4-triazol-1-yl-pyrazole based spirooxindolopyrrolizidines **192** (Fig. 39) were synthesized and evaluated for their anti-TB potential against *Mtb* $H_{37}Rv$ by Pogaku et al. [171]. Among all, most active compound **192a** was 2 folds more potent (MIC: 0.78 μg/mL) than the standard drug ethambutol and compounds **192b-g** were equally potent to ethambutol (MIC: 1.56 μg/mL). SAR study revealed the significance of substituents at 5-position of isatin ring and substituents at *para*- and *meta*-positions of the aryl ring attached to the pyrrolizidine ring (Fig. 39). Compounds **192a-g** exhibited low cytotoxicity against RAW 264.7 cells.

2.6. Antiviral agents

Goma'a et al. designed and synthesized several 1,2,4-triazole derivatives with ethyl 2-((5-amino-1*H*-1,2,4-triazol-3-yl)thio)acetate as the starting material. Among the compounds studied, compound **193** (Fig. 40) was found to be the most potent compound, which could reduce the viral plaques by 50% at a dose of 80 μM against *herpes simplex virus-1* (HSV-1), grown on *Vero* African green monkey kidney cells. Moreover, compound **193** possessed higher selectivity than acyclovir (>200 μM *vs* 80 μM) [172]. Docking studies revealed that compound **193** interacted into the active site of HSV-1 thymidine kinase mainly by making many hydrogen bonds.

Henen et al. reported synthesis of number of 1,2,4-triazolo[4,3-*a*]quinoxaline derivatives as antiviral and antimicrobial agents. Among them, compound **194** (Fig. 40) showed most promising

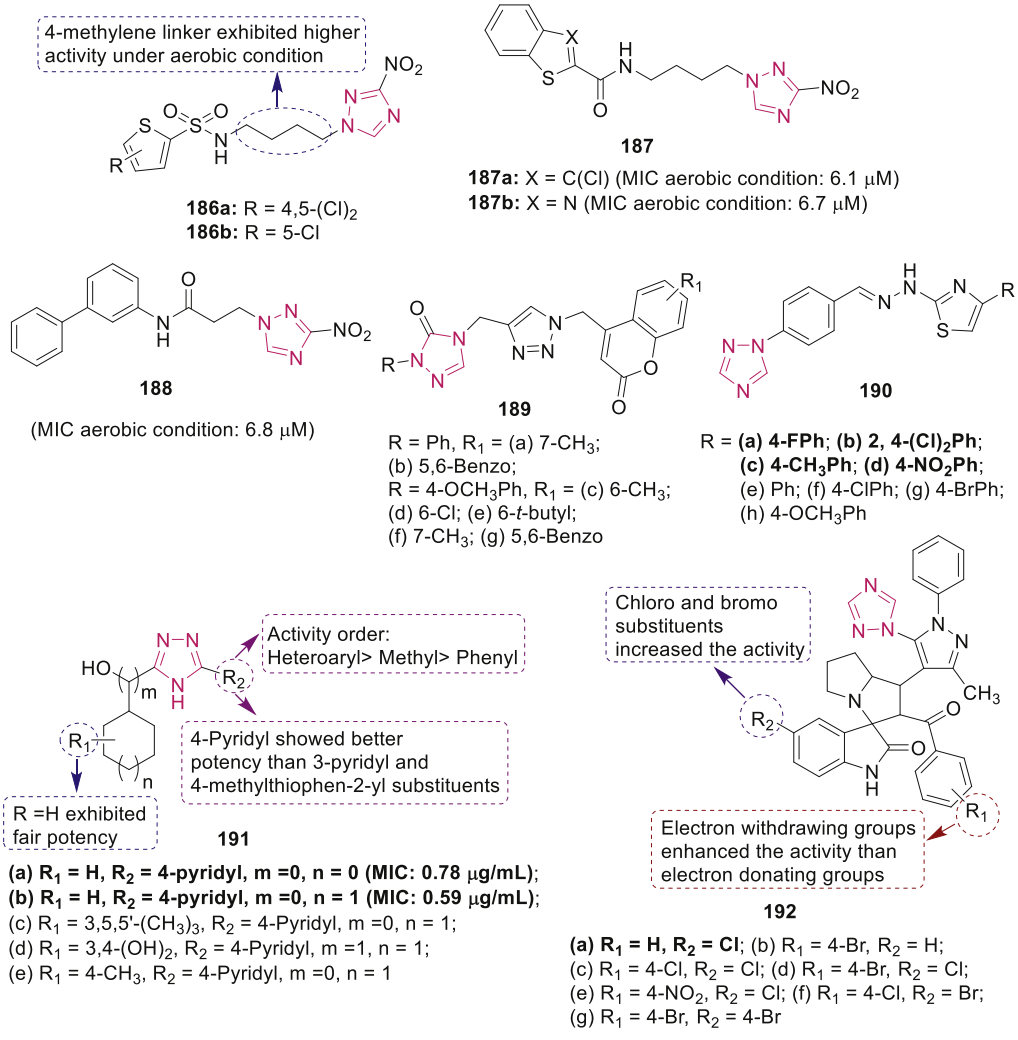


Fig. 39. Various 1,2,4-triazoles with anti-TB potential.

anti-HSV-1 activity with 25% plaque reduction at 20 mg/mL [173]. Pandey et al. synthesized 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines **195** (Fig. 40) and screened them for their antiviral activity against *Japanese encephalitis virus* (JEV) and HSV-1 [11]. Among them, compound **195c** (ED_{50} 7.8 μg/mL) showed moderate anti-JEV activity with 50% inhibition and therapeutic index (TI) value 32.

Cao et al. synthesized forty-four chiral triazole derivatives **196** and screened them for their *in vitro* antiviral activities against enterovirus 71 (EV71) and coxsackievirus B3 (CVB3) [12]. In this study, compounds **196a** and **196b** (Fig. 40) showed significant potency against the tested viruses with a SI of 21.7 and 24.7, respectively more active than ribavirin (SI: 15) for EV71. Compound **196a** (16 μg/mL) exhibited 88.1% inhibition against EV71. SARs indicated that short alkyl chain (R) and 4-methoxyphenyl or benzyl units (Ar) are favourable for antiviral activities.

Evaluation of a series of synthesized [1,2,4]triazolo[4,3-*a*]pyrimidin-5(4*H*)-ones **197** (Fig. 40) for antiviral potential against representative human enteroviruses including Coxsackievirus B1 (Cox B1), Coxsackievirus B3 (Cox B3), Poliovirus 3 (PV3), Human Rhinovirus 14 (HRV14), Human Rhinovirus 21 (HRV 21) and Human Rhinovirus 71 (HRV 71), makes compound **197a** (1.6–8.85 μM) promising lead compound for developing broad spectrum anti-enterovirus drugs [174].

Nine quinoxaline derivatives were prepared and evaluated for their antiviral activity against hepatitis C virus (HCV), hepatitis B virus (HBV), HSV-1, and human cytomegalovirus HCMV by El-Zahabi [175]. The *in vitro* screening data indicated that the pyridinyl triazole derivative **198** (Fig. 40) exhibited highly potent activity against HCMV with IC_{50} of <0.05 μM than that of reference drug ganciclovir (IC_{50}: 0.59 μM). In addition, it also exhibited eleven times higher SI (>3000 μM) against HCMV than ganciclovir (SI > 256 μM).

Massari et al. *via* hit-to-lead optimization studies identified two hybrid molecules **199** and **200** (Fig. 40), having triazolopyrimidine and cycloheptathiophene scaffolds, as potent Flu polymerase PA-PB1 subunits inhibitors [176]. Along with PA-PB1 interaction inhibitor, **199** also exhibited broad anti-Flu activity with no cytotoxicity.

Sixteen triazole derivatives **201** (Fig. 40) were evaluated for their anti-MERS-CoV activity through the inhibition of helicase and ATPase activity using the FRET assay by Zaher et al. [177]. Among them, compounds **201a** and **201b** were the most potent MERS-CoV helicase inhibitors with ATPase IC_{50} values of 0.47 and 0.51 μmol/L, respectively.

Zhan et al. designed and synthesized a series of 2-(2-(2,4-dichlorophenyl)-2*H*-1,2,4-triazol-3-ylthio)-*N*-arylacetamide derivatives **202** as potent HIV-1 inhibitors [178]. Among them, six compounds **202a-f** (Fig. 41) exhibited better inhibition of wild-type

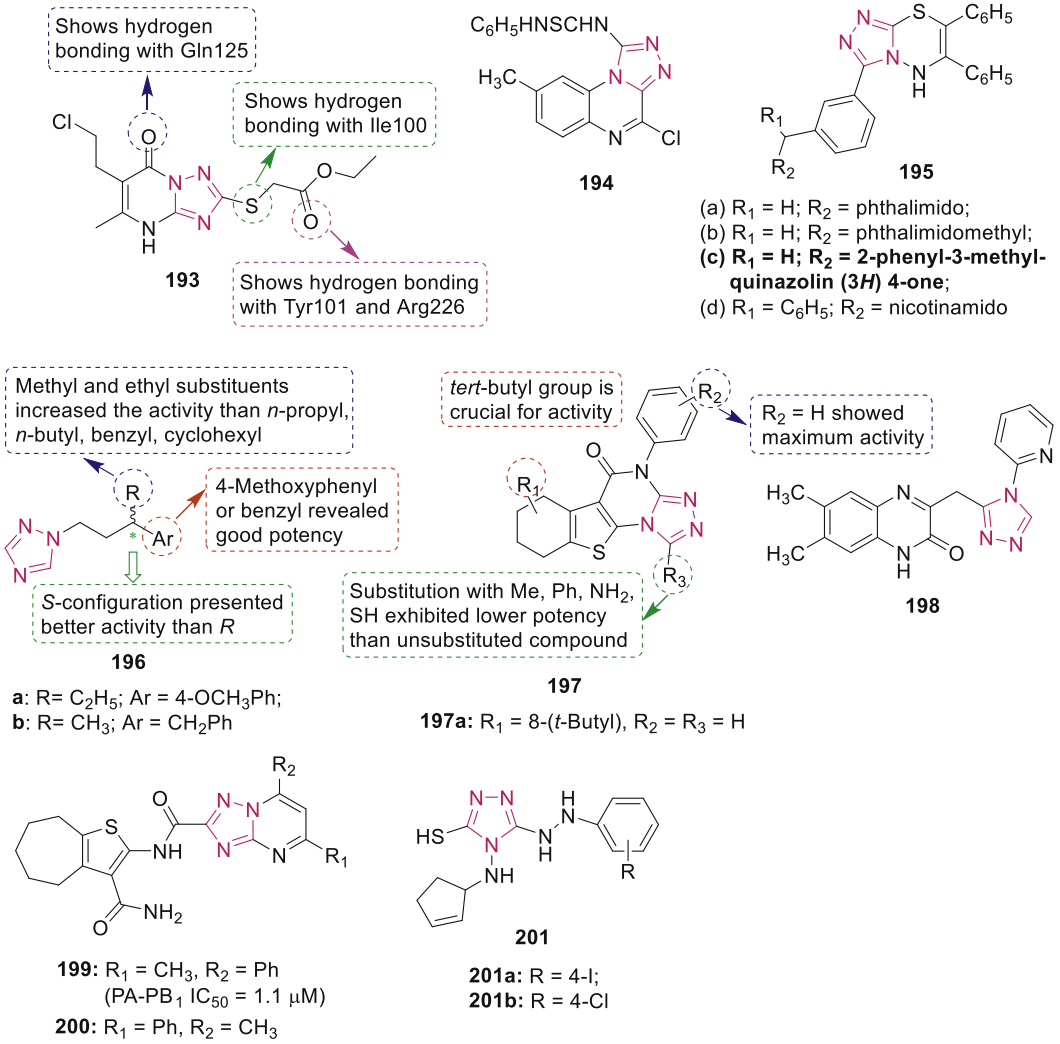


Fig. 40. 1,2,4-Triazole derivatives as antiviral agents.

HIV-1 (IIIB) replication with ED_{50} value ranged from 2.78 to 6.21 μM than reference drug dideoxyinosine. Compound **202c** showed most promising potency with EC_{50} value of 2.78 μM and SI of 67 against HIV-1(IIIB) and EC_{50} value of 7.42 μM against K103N mutant strain.

In another work, two series of [1,2,4]triazolo[1,5-*a*]pyrimidine derivatives **203** and **204** (Fig. 41) were rationally designed *via* structure-based core refining approach, synthesized and evaluated for their anti-HIV activities by same group [179,180]. Among the series of **203**, compound **203a** was the most active against wild-type and double resistant mutant strain (K103N + Y181C) of HIV-1 with EC_{50} value of 0.02 μM and 7.61 μM, respectively. Among the series **204**, compound **204a** with an EC_{50} value of 8.1 nM against wt HIV-1 exhibited 38−2800 folds more potent activity than references didanosine, lamivudine, nevirapine and delavirdine mesylate.

A set of acetamide derivatives of doravirine were synthesized as potent HIV-1 NNRTIs using the structure-based drug design strategy by Wang et al. [181]. The study indicated that most active compound **205** (Fig. 41) with EC_{50} of 54.8 nM against wt HIV-1 was more potent than reference lamivudine (EC_{50}: 12.8 μM) and comparable to doravirine (EC_{50}: 13 nM).

2.7. Antiparasitic agents

Bhatt et al. reported *in vitro* antimalarial efficacy of pyrazole-linked triazolo-pyrimidine hybrids **206** (Fig. 42) and active hybrids (IC_{50}: 0.034−0.09 μg/mL) for inhibition of *Plasmodium falciparum* dihydrofolate reductase (*Pf*DHFR) *via* docking and *in vitro* studies [182]. The SAR of hybrids **206** indicated the significance of electron-withdrawing group at R_1 position; -Br group at R_2 position and substitution with methyl group at R_3 position for antimalarial potency. Compound **206a** with IC_{50} value of 0.023 μg/mL and SI of 652 exhibited good inhibitory activity in DHFR inhibition assay than reference pyrimethamine.

Prasad et al. reported that triazole-pyrazole hybrids **207** (IC_{50}: 0.041−1.50 μg/mL) (Fig. 42) displayed significant antiplasmodial activities. Among them, compounds **207d**, **207e** and **207g** (IC_{50}: 0.041, 0.054 and 0.092 μg/mL) displayed more potent activity against the *P. falciparum* strain in comparison to reference quinine (IC_{50}: 0.286 μM) [183].

The antiplasmodial activities of triazolium salts **208** (Fig. 42) against chloroquine resistant ItG strain of *P. falciparum* were assessed by Vlahakis et al. [184]. Among them, compound **208a** was found to be highly potent with IC_{50} value of 100 nM and SI of 1430. They hypothesized that potency of compounds in parasite cultures is due to presence of an electron deficient core attached to hydrophobic side groups which interact with a negatively charged moiety on the parasite merozoite.

McConville et al. used a rational approach to investigate carbamoyl triazoles **209**, known serine protease inhibitors, as promising antimalarial agents [185]. Among them, compound **209a** exhibited potent *in vitro* antiplasmodial activity (IC_{50}: 10 nM) against 3D7 strain of *P. falciparum* with *in vivo* oral efficacy in a SCID mouse model of *P. falciparum* infection with an ED_{50} and ED_{90} of about 100 and 150 mg/kg, respectively. SAR study revealed the significance of *N*-methyl and R group on benzyl ring as shown in Fig. 42.

The selection from the Tres Cantos Anti-Malarial Set (TCAMS) and an extensive SAR exploration of three carboxamide series by Rueda et al. [186] resulted in cyclopropyl carboxamides **210** (Fig. 42) with improved profile. Further optimization of substitution pattern (R) on phenyl ring adjacent to cyclopropyl ring identified compound **210a** (IC_{50}: 3 nM) as a highly potent *in vitro* inhibitor of *P. falciparum* 3D7 strain. Notably, compound **210a** exhibited 55% oral bioavailability in CD-1 mice and *in vivo* activity with the ED_{50} of 12 mg/kg in nonmyelo-depleted *P. falciparum* murine model.

Among several triazole sulphonamide derivatives **211** (Fig. 42), compounds **211a** and **211b** with IC_{50} of 0.023 and 0.025 μg/mL, respectively against chloroquine resistant strain of *P. falciparum*, were comparable to chloroquine (IC_{50}: 0.020 μg/mL) and 10-fold more potent than quinine (IC_{50}: 0.268 μg/mL) [187].

Among the synthesized triazole Schiff bases **212** (Fig. 42), compounds **212a-c** (IC_{50}: 0.230−0.282 μM) displayed higher antimalarial potency against *P. falciparum* than pyrimethamine (IC_{50}: 1.005 μM) [188]. Further *in vitro* enzyme inhibition study indicated that **212b** with IC_{50} of 0.0259 μM was found to be most potent DHFR

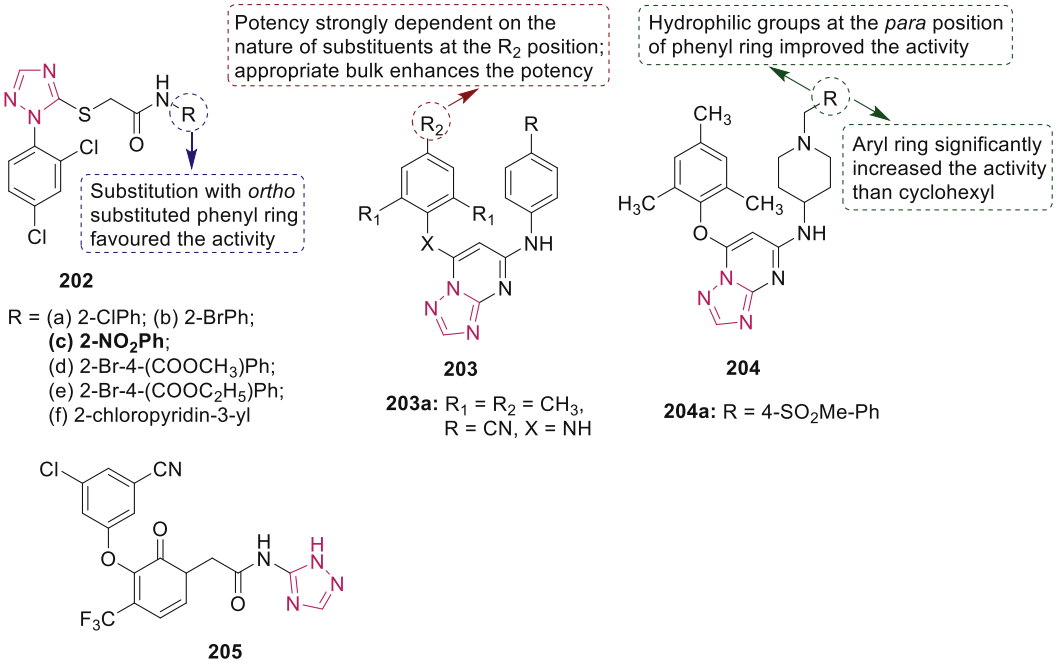


Fig. 41. 1,2,4-Triazole derivatives as anti-HIV agents.

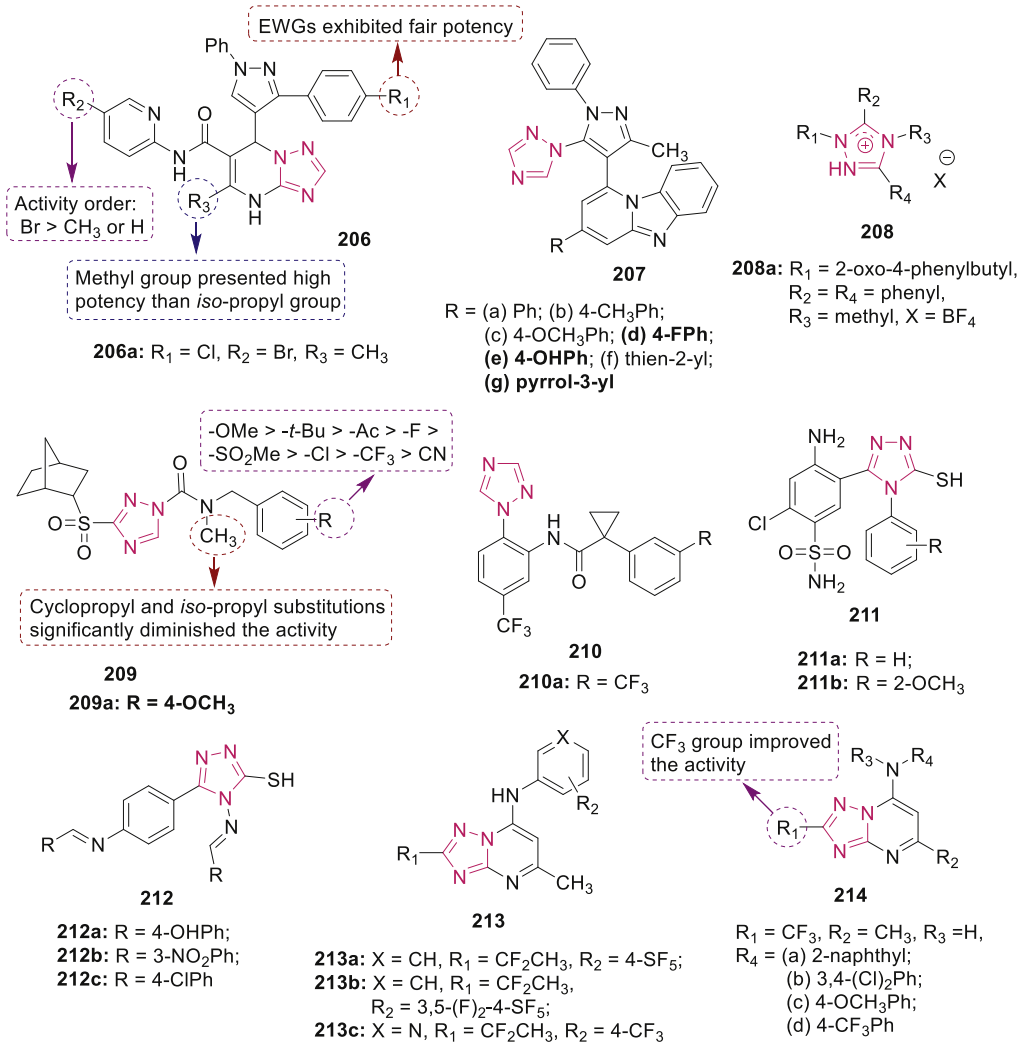


Fig. 42. 1,2,4-Triazole derivates as antimalarial agents.

inhibitor as compared to chloroquine (IC_{50}: 0.0301 μM) and pyrimethamine (IC_{50}: 0.1007 μM).

Dihydroorotate dehydrogenase (DHODH), enzyme in the de novo biosynthetic pathway, has emerged as promising target for development of novel antimalarial agents. Phillips and his co-workers [189–193] synthesized a library of triazolopyrimidine derivatives **213** (Fig. 42) as potent *P. falciparum* DHODH (*Pf*DHODH) inhibitors. Structure-guided lead optimization of the substitution pattern on [1,2,4]triazolo-[1,5-*a*]pyrimidine scaffold identified the most promising and selective inhibitor **213a** (DSM265, IC_{50}: 33 nM), which exhibited antimalarial activity with EC_{50} values in a range of 15–57 nM against drug sensitive and resistant strains *via* DHODH inhibition, a long half-life after oral administration in rodents and *in vivo* efficacy against *P. falciparum* in SCID mouse model with ED_{90} value of 8.1 mg/kg [190]. Subsequent optimization highlighted that compound **213b** with both *meta*-fluorines on the aniline ring and fluoroethyl at C-2 of the triazoloprymidine ring have poor species selectivity toward DHODH [191]. Further exploration of antimalatial drug candidate **213a** by replacing SF_5-phenyl moiety with a series of CF_3-pyridinyls identified a promising compound **213c** (DSM421, Fig. 42) with more enhanced drug-like properties which displayed 2-fold higher activity with IC_{50} of 0.053 μM on *Pf*DHODH than for *P. vivax* DHODH (IC_{50}: 0.094 μM) [193]. Notably, it also showed equivalent activity against field isolates of *P. falciparum* and *P. vivax*.

Antimalarial evaluation of twenty six [1,2,4]triazolo[1,5-*a*]pyrimidine derivatives **214** (Fig. 42) against chloroquine-resistant W2 strain of *P. falciparum* revealed that compounds **214a-d** displayed most effective antimalarial activity with IC_{50} in the range of 0.023–0.55 μM [194].

Neglected diseases (NDs) are a diverse group of diseases that affect millions of people. These include Chagas disease, human African trypanosomiasis (HAT), leishmaniasis, soil-transmitted helminthiasis which is caused by *Trypanosoma cruzi*, *Trypanosoma brucei*, *Leishmania* spp., and helminths respectively. Literature analysis also reveals the relevance of 1,2,4-triazole derivatives in neglected diseases [195,196].

Franklim et al. designed and synthesized 1,2,4-triazole derivatives by optimization of previously reported N_4-cyclohexyl-1,2,4-triazole **215** having anti-*T. cruzi* activity [197]. The study revealed that *S*-alkylated-triazoles **216a-c** (Fig. 43) exhibited significant trypanocidal profile with IC_{50} values 3.18–3.52 and 3.61–4.15 μmol/L against epimastigote and amastigote forms of *T. cruzi*, respectively, in comparison to lead compound **215** (IC_{50}: 18.30 and 8.87 μmol/L against the epimastigote and amastigote forms, respectively) [198].

Silva et al. synthesized 1,2,4-triazole derivatives **217** (Fig. 43) employing the bioisosterism and molecular hybridization approaches as nitrofurazone analogues, which have shown selectivity against intracellular amastigotes of *T. cruzi* Y strain [199]. Compound **217a** with IC_{50} of 5.53 μM and SI > 36 was equipotent to drug benznidazole, but exhibited lower efficacy. Furthermore, **217a** was found to be 26 fold more potent than analogue **217b**, highlighting the impact of nitro group on antitrypanosomal activity.

Papadopoulou et al. reported antichagasic activity of 3-nitro-1*H*-1,2,4-triazole-based aliphatic and aromatic amines [200–202]. Compounds **218**–**227** (Fig. 43) have shown high efficacy against the amastigotes forms of *T. cruzi* (IC_{50}: 0.04–0.57 μM, SI: 208–1725) and were upto 33.8 fold more potent than the standard drug benznidazole. The SAR revealed that presence of nitro group on the triazole ring is positively correlated with antiparasitic activity. Compounds **218**–**220** also exhibited significant activity against bloodstream-form (BSF) *Trypanosoma brucei rhodesiense* trypomastigotes with IC_{50} ranged from 0.117 to 0.435 μM levels and SI of 220–973. In addition, 3-nitrotriazole based piperazine **225a**, benzothiazoles (**226a** and **226b**) and quinoline derivative **227** exhibited significant anti-HAT activity against *T. b. rhodesiense* trypomastigotes with IC_{50} of 0.231, 0.204, 0.355 and 0.038 μM, respectively [201,202].

Most of the synthesized 3-nitro-1*H*-1,2,4-triazole-based amides and sulphonamides (IC_{50}: 28 nM-3.72 μM, SI: 66–2782) were also reported to exhibit significant *in vitro* activity against *T. cruzi* intracellular amastigotes by Papadopoulou et al. [203]. Among them, compounds **228** and **229** (Fig. 43) were found to be most active against *T. cruzi* and 36–58 fold more potent than benznidazole (IC_{50}: 1.562 μM). Further, some nitrotriazole have shown moderate activity profile against the axenic form of *L. donovani*. The SAR of 3-nitrotriazole-based heteroarylamides/sulfonamides revealed that chlorinated thiophene sulfonamides and benzothiophene amides **230** (Fig. 43) were the most active antichagasic

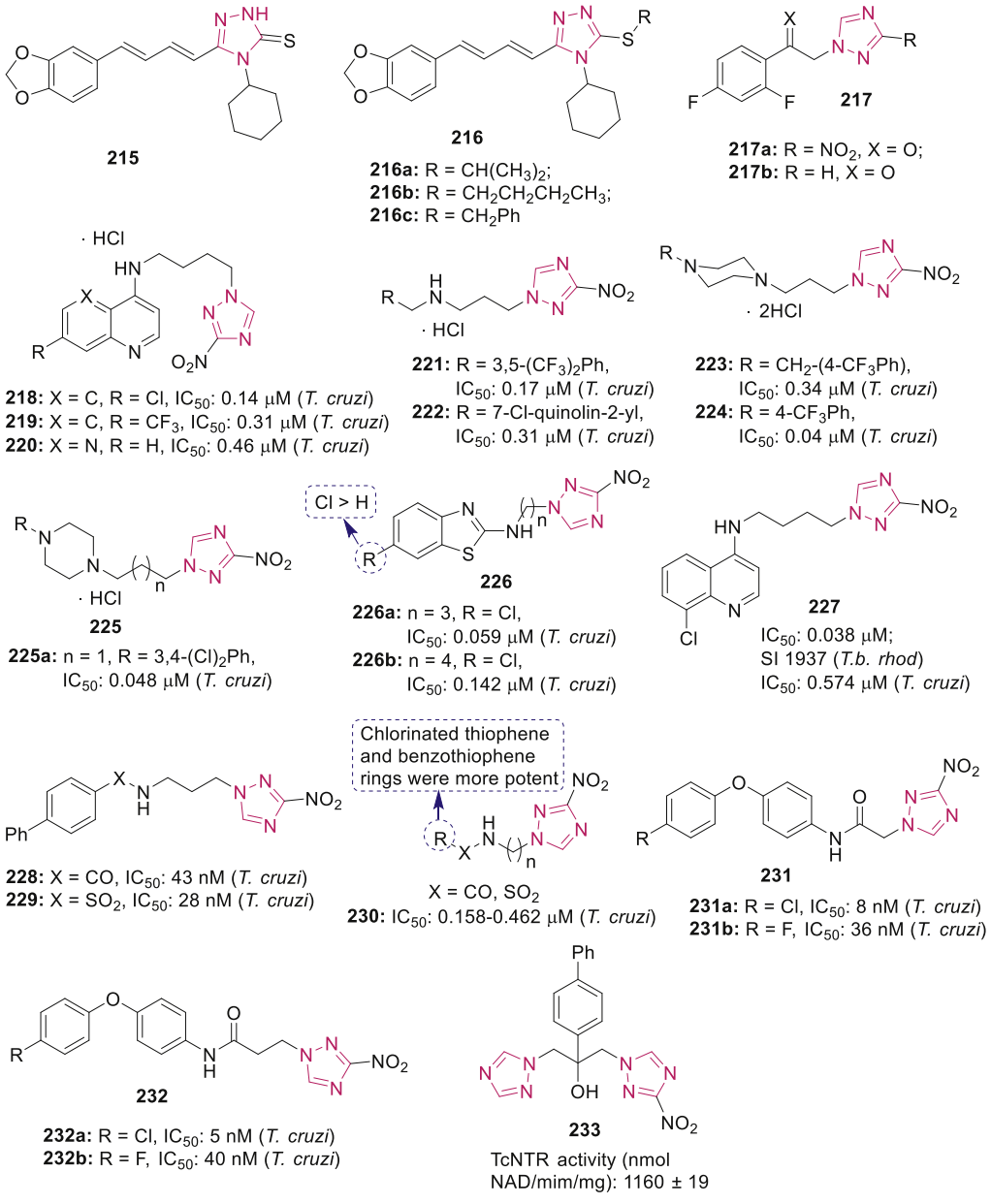


Fig. 43. 1,2,4-Triazole derivates as antitrypanosomal agents.

compounds, displaying up to 14 fold higher potency than the standard benznidazole [204].

Papadopoulou et al. designed 3-nitrotriazole based aryloxyphenylamides **231** (Fig. 43) as potent and selective anti-*T. cruzi* agents [205]. Notably, two most potent compounds **231a** and **231b** reduced the parasite load after 5 days of treatment at 13 mg/kg/day (ip) in infected mice. Moreover, compounds **231** exhibited selective activity against *L. donovani axenic* amastigotes. Further optimization of 3-nitrotriazole-based aryloxyphenylacetamides **231** *via* inserting one additional methylene group between the nitrotriazole ring and the amidic carbonyl resulted in corresponding propanamides **232** (Fig. 43) with a broad spectrum antitrypanosomal activity [206]. *In vitro* evaluation of compounds **232** revealed excellent and comparable antichagasic activity, 4–214 fold greater anti-HAT activity and smaller antileishmanial activity to that of the corresponding acetamides **231**.

Several linear, rigid 3-nitrotriazole-based amides and carbinols (analogues of fluconazole) were synthesized as potent antitrypanosomal agents *via* their dual functioning as excellent substrates for trypanosomaltype I nitroreductase (NTR) and as inhibitiors of sterol 14α-demethylase (*T. cruzi* CYP51) enzyme [207]. Carbinols **233** (Fig. 43) displayed excellent *in vitro* activity with IC_{50} of 33 nM and SI of 3308 against *T. cruzi* amastigotes as well as *in vivo* activity in *T. cruzi* infected murine model.

Khare et al. using hit-to-lead optimization approach reported a selective kinetoplastid proteasome inhibitor **234** (GNF6702, Fig. 44) that does not inhibit the human proteasome [208]. It also exhibited *in vivo* efficacy which cleared parasites in mouse models of leishmaniasis, Chagas disease and HAT. Inhibition of the proteasome chymotrypsin-like activity is demonstrated as primary mechanism of parasite growth inhibition by GNF6702.

Compounds **234** (GNF6702) and its analogue **235** (NITD689, Fig. 44) showed *in vitro* concentration-time dependent trypanocidal activity with favourable *in vivo* pharmacokinetics and significant brain penetration [209]. Importantly, both compounds, act by inhibiting chymotrypsin activity of the 20S proteasome in *T. brucei*, are efficacious for achieving complete cure in HAT hemolymphatic (1 and 10 mg/kg, respectively, once daily, for four days) and meningoencephalic mouse models (at 30 and 60 mg/kg dose, respectively).

A series of amino acid-coupled 1,2,4-triazoles **236** (Fig. 45) were evaluated for their *in vitro* antileishmanial activity on *L. major* promastigotes by El-Saghier et al. [9]. Among them, compounds **236a-d** (IC_{50}: 0.0312–0.0866 μg/mL) were 36–100 folds more potent than the reference miltefosine (IC_{50}: 3.1924 μg/mL) and comparable to amphotericin B deoxycholate (IC_{50}: 0.0472 μg/mL). Reverse docking approach illustrated mitogen-activated protein kinase (MAPK) as a possible putative antileishmanial target. SAR analysis suggested the hydrophobic moiety with certain topology like isopropyl and indolyl groups is favourable for antileishmanial activity.

Evaluation of a series of 5-(pyrazin-2-yl)-4*H*-1,2,4-triazole-3-thiol derivatives **237** and **238** (IC_{50}: 79.0–382.4 μM, Fig. 45) for *in vitro* antileishmanial activity against *L. donovani* promastigotes, makes compounds **237a** (IC_{50}: 79.0 μM) and **238a** (IC_{50}: 79.0 μM) the most promising antileishmanial agent as compared to standard sodium stibogluconate (IC_{50}: 490.0 μM) [210].

Among coumarin-triazolothiadiazine hybrids, **239** (Fig. 45) demonstrated the highest inhibition (IC_{50}: 0.89 μM) *in vitro* against the promastigote form of *L. major* [211]. Süleymanoğlu et al. reported that 4-amino-1,2,4-triazole derivative **240** (Fig. 45) presented antileishmanial activity with MIC of 625 μg/mL *in vitro* study against *L. infantum* (MON-183) by microdilution broth assay [212].

2.8. Analgesic and anti-inflammatory agents

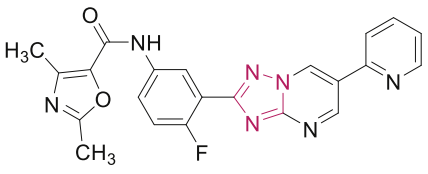
A set of hydrazone derivatives of 1,2,4-triazole **241** (Fig. 46) was evaluated for radical scavenging and anti-inflammatory activities *in vitro* and *in vivo* by Khan et al. [213]. The most potent compound **241a** with 64.44% inhibition of edema and a potency of 0.92 at 20 mg/kg body weight after 5 h of inducing inflammation was comparable to reference indomethacin (potency 1.00). Docking study revealed that compound **241a** occupied celecoxib binding site in COX with high affinity (Fig. 46) and binding free energy of −10.5 and −11.2 kcal/mol for COX-1 and COX-2, respectively.

Abdel-Aziz et al. reported the synthesis and anti-inflammatory activity of 1,2,4-triazole-3-carboxamides derivatives **242** and **243** (Fig. 46) [214,215]. Compounds **242** and **243** exhibited good anti-inflammatory activity (52–78%) after 3 h with lower ulcerogenic risk compared to indomethacin (78% activity). *In vitro* COX-1/COX-2 inhibition and docking studies revealed compounds **242f** and **242g** having less bulky group on amide nitrogen as the most potent COX inhibitors. Compounds **243** demonstrated excellent selectivity towards human COX-2 with selectivity indices (COX-1 IC_{50}/COX-2 IC_{50}) ranged from 62.5 to 2127 [215].

Interestingly, NO-triazole hybrids **244** (Fig. 46) were found to be more potent anti-inflammatory agents than the corresponding ketone intermediates [216]. Among the synthesized oximes, compound **244a** exhibited high anti-inflammatory activity (79%) after 4 h and lower ulcerogenicity (ulcer index 0.25). In another study, quinoline incorporating 1,2,4-triazole/oxime hybrids **245a-c** (Fig. 46) displayed significant anti-inflammatory activity compared to indomethacin with % edema inhibition of 100%, 101% and 111%, respectively [217].

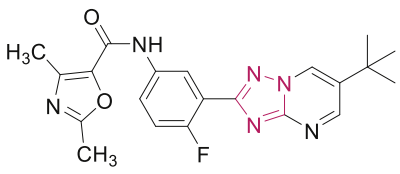
Lamie et al. screened a series of triazole Schiff bases containing *N*-substituted indole **246** (Fig. 46) for their *in vitro* anti-inflammatory activity [218]. Compound **246a** was found to be the most potent inhibitors of cytokine Eselectin and COX-2 enzyme (IC_{50}: 0.98 μM and SI: 8.05).

Biological screening of Schiff and Mannich bases derivatives of



234 (GNF6702)

L. donovani EC_{50}: 18 nM
T. brucei EC_{50}: 70 nM
T. cruzi EC_{50}: 120 nM



235 (NITD698)

T. brucei EC_{50}: 30 nM

Fig. 44. Kinetoplastid proteasome inhibitors.

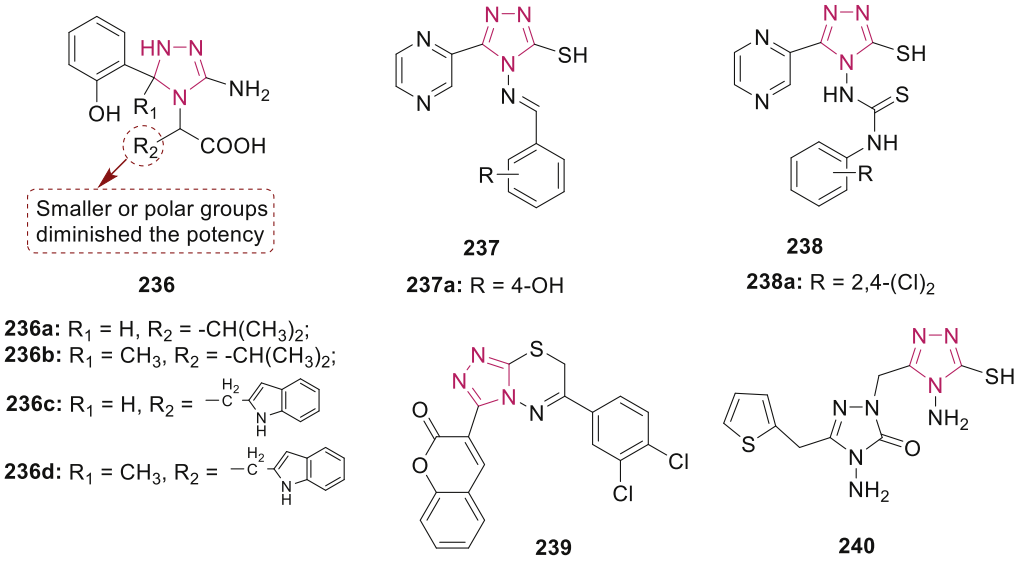


Fig. 45. 1,2,4-Triazole derivates as antileishmanial agents.

1,2,4-triazoles **247** (Fig. 46) at a dose of 20 mg/kg in rats by Gowda et al. revealed that compounds **247c** and **247d** showed good anti-inflammatory activity compared to indomethacin whereas compounds **247a**, **247b** and **247d** showed significant analgesic effects [219].

Receptor interacting protein 1 (RIP1) kinase is critical regulator of necroptosis and inflammation. DNA-encoded library (DELs) screening and lead optimization has resulted in identification of clinical candidate GSK2982772 (**248**, Fig. 46) as first-in-class RIP1 inhibitor which is currently in pre-clinical trials for inflammatory diseases, including psoriasis, rheumatoid arthritis, and ulcerative colitis [220].

Two series of 1,2,4-triazole based benzothiazole derivatives **249** and **250** (Fig. 46) were synthesized and evaluated for their *in vitro* anti-inflammatory activity and p38α MAP kinase inhibition by Tariq et al. [221,222]. Among the selected compounds for *in vivo* evaluation, compounds **249a** and **250a** emerged as the most potent compound with edema inhibition of 84.43% and 85.31%, respectively.

Paprocka et al. reported that 1,2,4-triazole derivatives **251** (Fig. 46) containing methacrylic acid moiety exerted anti-inflammatory activity *via* modulation of monocytes activation [223]. A novel series of celecoxib derivatives with triazole moiety have been screened for their anti-inflammatory potential by CPE test by Mustafa et al. and most of the them showed higher activity compared to Celecoxib [224].

The pharmacology screening a series of 6-substituted thiazolo [3,2-*b*]-1,2,4-triazole-5(6*H*)-one derivatives of ibuprofen revealed that compounds **252a-c** (Fig. 47) displayed potential *in vivo* analgesic/anti-inflammatory activity without a gastrointestinal side effect [225].

Various thieno[3,2-*e*]triazolo[4,3-*a*]pyrimidine derivatives were evaluated for anti-inflammatory activity by Rizk et al. [226]. Compounds **253**–**255** (Fig. 47) showed prominent anti-inflammatory activity comparable with diclofenac Na in the acute and sub-acute inflammatory models. A set of thieno[2,3-*d*] [1,2,4]triazolo [1,5-*a*] pyrimidines **256** (Fig. 47) was synthesized and evaluated for their anti-infammatory and analgesic activity by Ashour et al. [227]. Compounds **256a-c** (ED_{50}: 23.45–28.15 mg/kg) showed equivalent to moderate anti-infammatory activity at 20 mg/kg oral dose in both acute and sub-acute models compared to reference diclofenac as well as good analgesic profile with a delayed onset of action.

Pan et al. synthesized a series of 4-phenylthieno[2,3-*e*] [1,2,4] triazolo[4,3-*a*]pyrimidine-5(4*H*)-ones **257** (Fig. 47) and screened for their anti-inflammatory activity by xylene-induced ear-edema test [228]. The study indicated that the most potent compound **257a** with 50.48% activity at 30 min after intraperitoneal administration was more active than the reference drug indomethacin.

El Shehry et al. synthesized of a series of 3-(2,4-dichlorophenoxy)methyl)-1,2,4-triazolo (thiadiazoles and thiadiazines) and screened for their anti-inflammatory activity [229]. Among them, compounds **258**–**261** (Fig. 47) showed 36–56% anti-inflammatory activity comparable to the standard indomethacin.

Maddila et al. reported that among the triazolo[3,4-*b*]thiadiazole derivatives **262** (Fig. 47) screened for their anti-inflammatory potential in the CPE test at 10 mg/kg oral dose, compounds **262a** (82.24%) and **262b** (83.06%) exhibited potent anti-inflammatory activity than indomethacin (81.55%) [230].

SAR studies on [1,2,4]triazolo[4,3-*a*] [1,8]naphthyridine scaffold were conducted by Bracci et al. with the objective of improving potency for anti-inflammatory and/or analgesic activities [231]. Results revealed that compound **263b-f** (Fig. 47) exhibited good anti-inflammatory activity ranging from 34% to 80% and compound **263c** was found to be more potent and effective than the parent compound **263a** [232]. Whereas compounds **264a-c** (Fig. 47) were endowed with prevalent analgesic activity (74%–96% inhibition in the writhing test in mice, $P < 0.01$, 50 mg/kg dose) frequently associated with sedative effects.

Guirado et al. synthesized a series of triazolo[4,3-*a*]quinoxalines **265** (Fig. 47) and evaluated for their anti-inflammatory activity as inhibitors of the pro-inflammatory cytokines TNF-α and IL-6 [233]. Results revealed that compound **265c** was found to be the most potent while compounds **265a-d** exhibited good levels of inhibition against both cytokines.

Liu et al. synthesized a series of triazolo[3,4-*a*]phthalazine-3-carboxamide derivatives **266** (Fig. 47) as potent anti-inflammatory agents, which acted on tumor necrosis factor (TNF-α) as inhibitors of NF-κB activation [234]. Moreover, compound **266a** exhibited excellent anti-inflammatory activity with 58.19% inhibition at 50 mg/kg (i.p.) against xylene-induced ear edema, with equal efficacy as the standard drug indomethacin (100 mg/kg i.p; 59.21% inhibition).

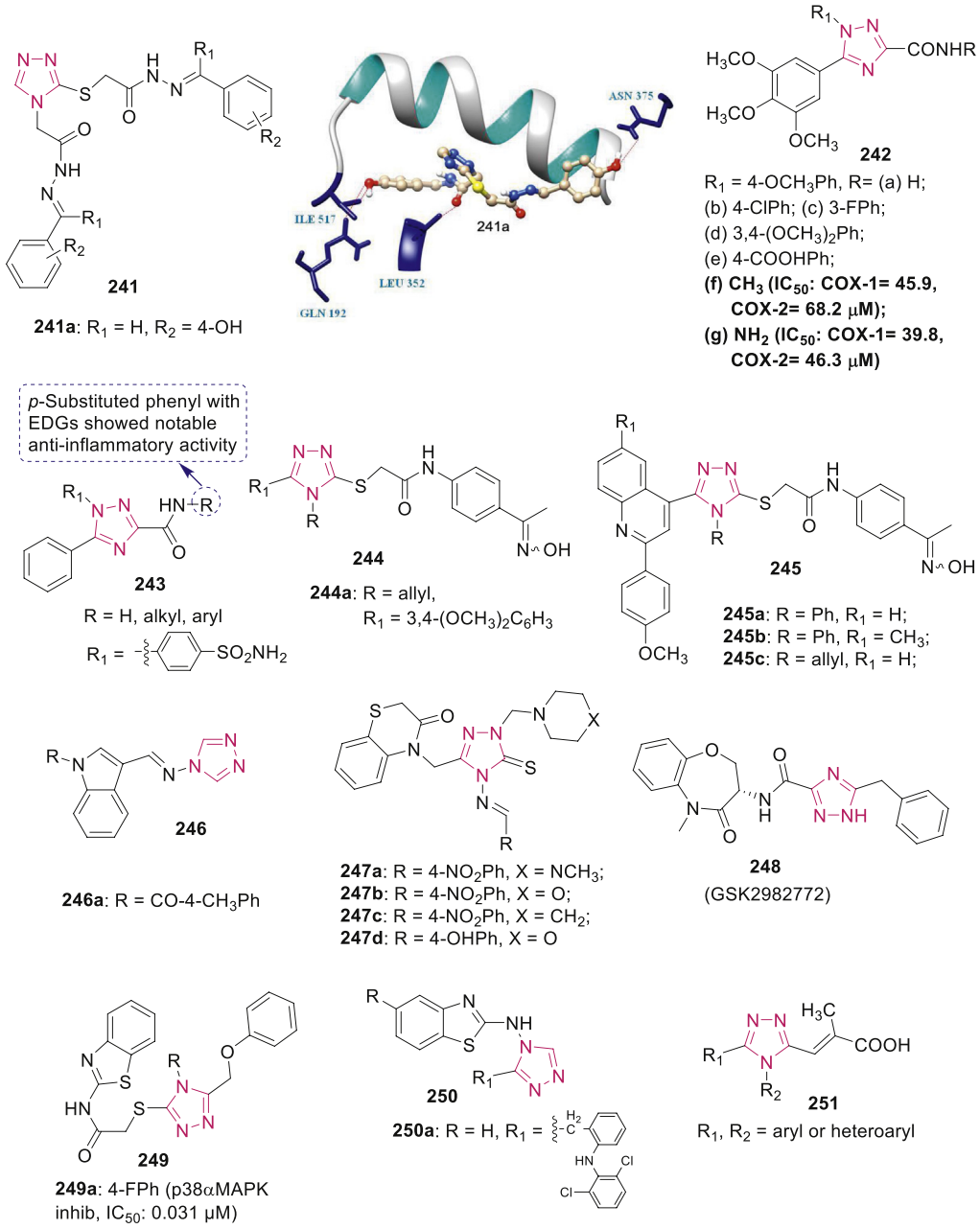


Fig. 46. 1,2,4-Triazole derivates as anti-inflammatory agents and illustration of the binding of compound **241a** in the COX-2 active site.

Several thiazolo[3,2-*b*]-1,2,4-triazoles derived from naproxen **267** (Fig. 47) exhibited significant analgesic and anti-inflammatory activities with low gastric risk [235]. Moreover, compound **267a** was found to be the most selective COX-2 inhibitor with IC_{50} of 20.5 μM and SI > 4.87.

Some other 1,2,4-triazole derivatives have been synthesized and screened for anti-inflammatory and analgesic activities [236–238].

3. Miscellaneous

Aggarwal et al. reported 1,2,4-triazolo[4,3-*a*]quinoxaline derivatives **268** and 1,2,4-triazolo[4,3-*a*]quinoxalin-4(5*H*)-ones **269** (Fig. 48) as effective DNA photocleavers [239,240]. Among all the synthesized molecules, compounds **268c** and **269k** showed significant photocleavage of supercoiled plasmid ΦX174 and pMaxGFP, respectively under UV irradiation at λ_{max} 312 nm. DNA cleaving efficiency of **269** was found to be dependent on its structure, concentration, and strictly on photoirradiation time. Mechanistic investigations on compound **269k** revealed that the DNA photocleavage reaction involves superoxide anion radicals ($O_2^{-\bullet}$) (Type-I pathway).

1,2,4-Triazolo[1,5-*a*]pyrimidin-7-one **270** (WS-10, Fig. 48) was identified as nontoxic and selective modulator of ABCB1 transporter which plays key roles in the development of multidrug resistance of chemotherapeutic drugs [241]. WS-10 enhanced the intracellular accumulation of paclitaxel in ABCB1 overexpressed SW620/Ad300 cells without affecting the expression or localization of the ABCB1 protein.

A series of triazolopyrimidine hybrids was designed and synthesized as multifunctional anti-Alzheimer agents by Jameel et al. [242,243]. Compounds **271a** and **271b** (Fig. 48) exhibited more potent acetylcholinesterase (AChE) inhibitory potential with IC_{50}

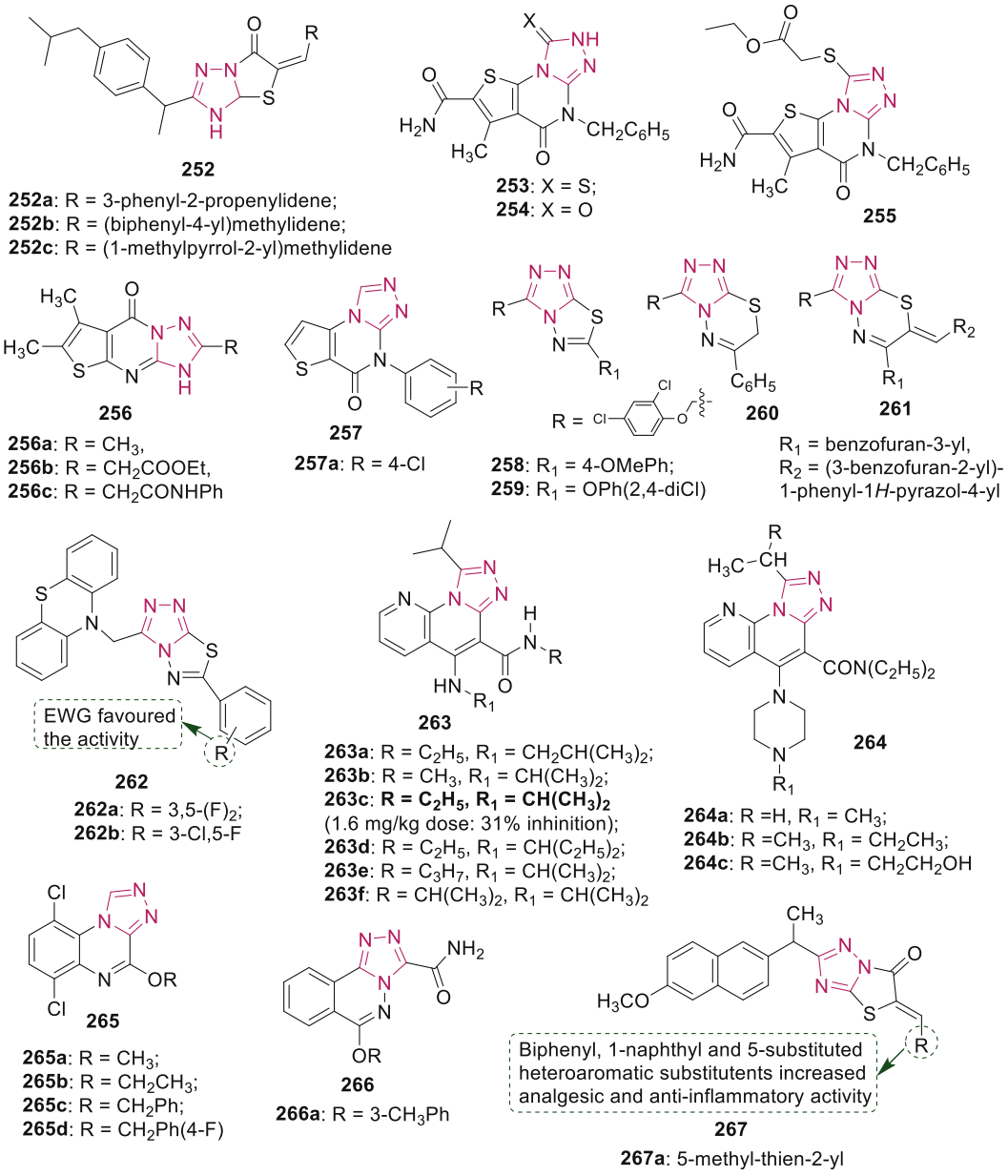


Fig. 47. Fused 1,2,4-triazole derivates as anti-inflammatory agents.

values 0.065 and 0.092 μM, respectively and high selectivity for AChE over BuChE by ~28 fold. Notably, these compounds exhibited better Cu^{2+}-induced Aβ1-42 aggregation inhibitory potency.

El-Aleam et al. reported the bronchodilator activity of a set of 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives **272** (Fig. 48) as phosphodiesterase 4B inhibitors [244]. The study revealed that compounds **272a** and **272b** with EC_{50} values of 18.6 and 57.1 μM, respectively, showed better bronchodilator activity than the reference theophylline (EC_{50}: 425 μM).

4. Future perspective

Contemporary medicinal chemistry faces many challenges from several directions, including the need for both potency and specificity of any therapeutic agent. Therefore, in the present perspective, 1,2,4-triazole with broad spectrum biological profile have matured into indispensable heterocyclic scaffold. The work compiled in this review article highlights the findings on 1,2,4-triazoles as a privileged scaffolds endowed with extensive potential therapeutic utility besides applicability in corrosion inhibition, polymers, supramolecular chemistry and material science. Clinical drugs containing triazole nucleus are being used in treating several ailments. Development of resistance in *Candida* spp against fluconazole, the most efficient anticandiada commercial drug, prompted the pharmacologist to synthesize triazole alcohols as fluconazole analogues to treat fluconazole-resistant fungal strains. 1,2,4-Triazole moiety *via* hydrogen bonding and dipole interaction can improve the solubility and affinity of the compounds with bimolecular targets. Among the broad spectrum of bioactivities, we comprehensively reviewed the advances in antifungal, antibacterial, anticancer, anticonvulsant, antituberculosis, antiviral, antiparasitic, analgesic and anti-inflammatory activities of 1,2,4-triazole derivatives particularly reported over the past decade.

1,2,4-Triazole derivatives mediate curative effects by acting as promising selective protein/enzyme inhibitors, modulators and receptor antagonists. In this review, we aimed to provide medicinal

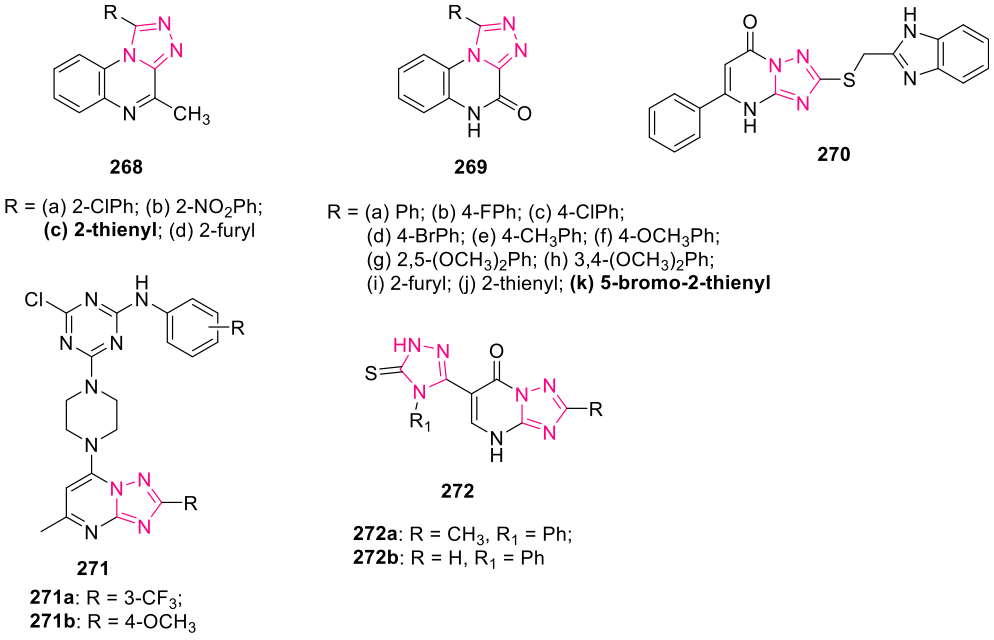


Fig. 48. 1,2,4-Triazolo derivatives with miscellaneous activity.

and pharmaceutical chemists working in area of drug designing and development with a wide data resource about 1,2,4-triazoles derivatives, thus helping them to perform a more organized and fertile drug discovery operation during their experimental studies.

SARs, HTS, hit to lead optimization, molecular hybridization as well as 3D computer modeling would be valuable in structural modifications of 1,2,4-triazole scaffolds for target oriented synthesis, enhancing bioactivities and pharmacokinetic properties and resolving the challenges of multidrug resistance.

5. Conclusion

1,2,4-Triazole is a privileged scaffold in medicinal chemistry having ample potential therapeutic applications continue to expand. This review article is an effort to summarize medicinal chemistry investigations of 1,2,4-triazole derivatives over the last decade, in search for new azaheterocycles which may be a rich source of promising biological activities. It will help the scientific community for rational design and development of novel, target oriented, optimized and varied 1,2,4-triazole based drugs for the treatment of multifactorial diseases. The enriched SAR may pave the way to further explore and develop new 1,2,4-triazole derivatives with improved potency to overcome the resistance.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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