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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.

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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 C₂H₃N₃ 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 1H-1,2,4-triazole (A) is more stable than 4H-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), antimalarial (malarone), anti-inflammatory (ibuprofen), antiviral (ribavirin), antineoplastic (trapidil), antidepressant (trazodone), antiviral (amantadine), antiparkinsonian (levodopa), antihistaminic (cimetidine), antimalarial (chloroquine), antirheumatic (sulfasalazine), anticonvulsant (gabapentin), antipsychotic (haloperidol), antiplatelet (trapidil), antidepresant (trazodone), antiepileptic (carbamazepine), antifungal (miconazole), antipsychotic (haloperidol), antihistaminic (cimetidine), antihypertensive (clonidine), antineoplastic (5-fluorouracil), antiviral (zidovudine), anticonvulsant (valproic acid), antiplatelet (aspirin), antihypertensive (labetalol), antipsychotic (olanzapine), anticonvulsant (lamotrigine), antihyperglycemic (metformin), antihistaminic (chlorpheniramine), antiallergic (cetirizine), and anticonvulsant (topiramate) [3].

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 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-(1H-1,2,4-triazol-1-yl)proplyl)-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 (MIC₈₀ 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 side chains for antifungal activity [24,25]. Compound 3 having R₁ = CF₃ group displayed broad antifungal spectrum with MIC₈₀ 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 (MIC₈₀ 1 µg/mL). Molecular docking studies of 4 (R = 3–Cl) in active site of CACYPS1 showed multiple molecular interactions of difluorophenyl group and terminal triazole 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 (R₁ = Br and R₂ = H) displayed excellent potency (MIC 0.0131–1 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 MIC₈₀ 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 (MIC₈₀ <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 MIC₈₀ 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 against 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 (MIC₈₀ 0.0156–0.5 µg/mL).

In another concomitant study, a series of triazole alcohols having 4-(substituted-1H-indol-3-ylmethyl)-piperazinyl side chain 16 were synthesized and evaluated for antifungal activity against C. albicans, 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
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-α]pyrimidine moiety 21 (Fig. 5) and evaluated their antifungal activities against Fusarium oxysporum f.ssp. vasinfectum, Gibberella sanbinetti, Cercospora beticola Sacc, Physalospora piricola and Rhizoctonia solani [41]. SAR studies showed that compounds (21d, 21f, 21h, 21l, 21k, 21o, 21t and 21u) having electron-withdrawing groups (Cl, Br, F, NO2) 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 Cavusoglu 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...
For R=halogen, activity order: -Br or Cl > -F. 4-halo and 3-halo derivatives exhibited higher potency than 2-halo derivatives.

(Substituted benzylic group exhibited good potency than alkylation and cycloalkyl group)

n-π stacking interactions: with the Tyr118 of CYP51.

Replacement of H (R) with F atom not improved activity.

Hydrophobic interactions of the aliphatic group with CYP51.

Short or moderate-length alkyl side chain increased the activity; longer chain decreased activity.

4-Chlorine and 3,4-dihalogen substitutions increased the activity.

Triazole group improved the water solubility.

R = H, 3-CH₃, 4-CH₃, 4-C₆H₄(CH₃)₂, 2,4-(CH₃)₂, 3,4-(CH₃)₂, 3,5-(CH₃)₂; 4-Cl; 4-Br; 2-F; 4-F; 4-I; 4-OCH₃; 3-CN; 4-CN; 4-Br; 2-F; 4-F; 2,5-(CH₃)₂; 2,5-(CH₃)₂

(Substituted benzyl group mediated interaction with hydrophobic pocket of CYP51)

R’ = iso-propyl; cyclopropyl; substituted benzyl

R = benzy; substituted benzyl; cyclohexyl; hexadecyl; pentyl

n=1 significantly diminished the activity

N-substitutions other than H reduced the potency

R₂ = (a) H; (b) ethyl; (c) propyl; (d) butyl; (e) benzyl; (f) 4-CH₃-benzyl; (g) 4-F-benzyl; (h) CH₃COOCH₃; (i) CH₃COOCH₃CH₃; (j) CH₃COOC(CH₃)₃

1,2,4-Triazole Schiff base 25 (EC₅₀: 0.0087–0.0309 g/L) exhibited higher antifungal activity than thiadimefon (EC₅₀: 0.0195–0.0620 g/L) against Gibberlla nicotiiancola and Gibberella 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 zeae, Fusarium oxysporum, Cytospora mandshurica, Pellicularia sasaki,
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 clinafloxicin-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, clinafloxicin 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(4H)-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(4H)-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).](image-url)
MIC of 16 μg/mL was found to possess comparable antibacterial properties to streptomycin (MIC: 2-15 μg/mL) against all tested microorganisms, while compound 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 μg/mL) showed remarkable selectivity against B. subtilis, which was resistant to nalidixic acid [55]. Further study revealed that the compounds 35c and 36d (IC50: 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][1,3,4]triazolo[3,4-b][1,3,4]thiadiazines (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 flexneri) [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 triazolopyrimidine 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 Syncphalastrum 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 EC50 value of 7.2 μg/mL than bismerthiazol (EC50: 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-I (Fig. 7) displayed good to potent activity against Bacillus amyloliquefaciens, S. aureus and B. subtilis [62]. Interestingly, compound 44d exhibited...
Barbuceanu et al. reported the synthesis and antibacterial activity of mercapto-1,2,4-triazoles bearing diphenylsulfone 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 mg/mL) (Fig. 8).

A series of Schiff bases of 1,2,4-triazole (Fig. 8) were synthesized and evaluated for in vitro antimicrobial potential against bacteria (S. aureus, B. subtilis, E. coli and P. aeruginosa) by Hassan et al. [65]. SAR indicated that the compound 48g having phenoxy moiety at para-position 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 bearing quinazolinylpiperidinyl moiety and N-(substituted phenyl)acetamide unit (Fig. 8) and evaluated them for their antimicrobial activities. Compounds 50e, 50g, 50i, 50l and 50n (EC50: 34.5–47.5 μg/mL) had better bactericidal activity than control bismuthiazol (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-NO2, 3-COCH3, 2-NO2, 2-CF3 and 4-COCH3) 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,
compounds 51a (MIC: 0.75 μg/mL) and 51b (MIC: 0.43 μg/mL) were found to be 10- to 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 Zhou [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. 6. 1,2,4-Triazole-quinolone hybrids with antibacterial activity.
*Staphylococcus aureus* and *Escherichia coli* by Zhang et al. [70]. Among them, compound 55a (Fig. 9) exhibited highest potency against *E. faecalis* (MIC: 2 mg/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 mg/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,
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 (IC50: 7 nM/70 nM) and antiproliferative agent against several tumor cells lines with GI50 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 IC50 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-
3 cells is revealed by reduction of EGFR, Akt phosphorylation and PI3K phosphorylation.

Batran et al. reported VEGFR-2 and p38MAPK 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 IC50 value of 7.9 μg/mL than tamoxifen (IC50: 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)-4H-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-7 cancer cells with IC50 value of 7.9 μg/mL than tamoxifen (IC50: 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.

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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 IC50 values of 0.90, 0.85 and 1.54 μM, respectively. It was more potent than the reference soraфи nb (IC50: 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 (IC50: 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 IC50 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 (IC50: 1.30 μM for Bewo, 1.45 μM for HL-60 and 2.24 μM for MCF-7) and inhibited c-Met kinase (IC50: 11.77 μM) [79]. The docking analysis rationalized the binding of compound 64...
to c-Met kinase through three hydrogen bonding interactions.

Egile et al. reported the triazolopyridazine derivative SAR125844 (Fig. 14) which strongly inhibited the kinase activity of wild-type MET enzyme with IC50 value of 4.2 nmol/L, as well the H1094Y, Y1235D, M1250T, L1195V, and D1228H kinase domain mutants with IC50 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 IC50 values of 110 and 1400 nmol/L, respectively.

Zhan et al. synthesized a series of CH2-/CF2-linked triazolo-triazine derivatives among which compound 66 (Fig. 14) displayed the most potent inhibition with IC50 value of 0.24 nM against c-Met kinase and with IC50 value of 0.85 nM against EBC-1 cancer cell line [81]. Further, compound 66 exhibited excellent in vivo pharmacological activity 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 (IC50: 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 pyrazoline and triazole moieties as dual c-Met/VEGFR-2 inhibitors [83]. Compound 68d showed the most potent inhibition with IC50 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-mercaptop-1,2,4-triazole analogues 69 and 3-mercaptop-1,2,4-triazole carboxylic acids 70 (Fig. 15) as thymidine phosphorylase (TP) inhibitors [86]. Compounds 68d-g revealed a good inhibitory potential with IC50 in the range of 43.86–163.43 μM and angiogenic potential of compound 70c was elicited using the chick chorioallantoic membrane (CAM) assay.

Various synthesized 1,2,4-triazole[1,5-a] [1,3,5]triazine derivatives were evaluated for their inhibitory effects on TP by Bera et al. [87]. Compounds 71 (IC50: 10.84 μM) and 72 (IC50: 2.95 μM)
**Fig. 14.** 1,2,4-Triazole derivatives as c-MET kinase inhibitors.

**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 triazoloquinazolines 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 (IC50: 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 (IC50: 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-cafeic 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 (IC50: 16.37–26.14 μM) than ester derivatives (78d, IC50: 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 (R1) improved the antiproliferative activity. Most potent compound 78j (IC50: 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
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 IC50 in the range of 4.83–12.07 μM [92]. Compound 81c also exhibited the most potent COX-2 inhibitory activity with IC50 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-4H-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 IC50 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 IC50 in the range of 3.23–10.58 μM. Compounds 87d and 87e were highly potent inhibitor of LSD1 (IC50: 0.154 and 1.19 μM, respectively). Further, compound 87d significantly
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 \(\mu\)M) and significantly inhibited migration of A549 cells. Docking studies presented that \(89a\) displayed FAD-competitive binding toward LSD1 [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 (R1 = CH\(_3\) and R2 = (CH\(_2\))\(_2\)-Ph-4-OH) showed full inhibition of TNKS-1 and 82% of TNKS-2 at 1 \(\mu\)M. Replacement of hydroxyl group by benzoyl or amine resulted in the loss of activity. All the derivatives bearing 4-hydroxyphenyl in the side chain, were found to be the most potent TNKS inhibitor and assessed further at a concentration of 10 \(\mu\)M 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 \(\mu\)M 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 \(\beta\)-tubulin subunit as shown in Fig. 24.

Alsawah et al. designed and synthesized novel chalcone derivatives bearing triazolo[4,3-\(a\)]quinazoline 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 \(\mu\)M, 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 \(\mu\)M) 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 \(\mu\)M [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-acetyl 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 tubulin (957 and 872, respectively), EGFR (IC\(_{50}\): 3.6 and 4.6 \(\mu\)M, respectively), and BRAF\(^{V600E}\) (IC\(_{50}\): 1.9 and 1.8 \(\mu\)M, respectively).

Yang et al. synthesized triazolothioacetamides 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.)

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

Fig. 23. 1,2,4-Triazole derivatives as BRD4 inhibitors.
compounds were evaluated as tubulin polymerization inhibitors [104]. Compounds 100c and 100f displayed most promising anti-cancer activity against MCF-7, HeLa and HT-29 cell lines with IC50 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 IC50 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 (IC50: 5–100 nM) and 103h (IC50: 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;1, 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
activity (IC50 < 1 μM) against selected cancer cells. Compounds 104b and 104c act as more potent inhibitors of tubulin polymerization with IC50 value of 0.66 μM and 0.97 μM, respectively than CA-4 (IC50: 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 (IC50: 0.84–1.82 μM) and 106d (IC50: 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 (q2: 0.716, r2: 0.985) and CoMSIA (q2: 0.723, r2: 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 IC50 values in 0.63–13.12 μM.

Fares et al. synthesized a series of pyrido[2,3-d] 1,2,4-triazolo [4,3-b]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...
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-ethylcarboxylate 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 111g with 2,6-dimethylpiperazine displayed the most potent antiproliferative activity against A549, PC-3, HCT116, MCF-7 and MDA-MB-231 cell lines with IC50 values of 0.16 μM, 0.30 μM, 0.51 μM, 0.30 μM, and 0.70 μM, respectively.

Fig. 26. Fused 1,2,4-triazole derivatives 105–113 as anticancer agents.
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 (IC50: 0.007–0.039 μM) against MCF-7 cell line [112]. Most active compounds 114e (IC50: 0.007 μM), 114g and 114h (each having IC50: 0.008 μM) displayed 2.5 folds superior activity than that of colchicine (IC50: 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 (G50: 0.495–5.57 μM) against 56 human cancer cell lines was highly selective against T-47D and MDA-MB-468 cell lines with G50 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 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 116i and 119c were found to be the most active against HCT-116 cell line with IC50 values of 6.56 and 6.12 μM as compared to doxorubicin (IC50: 15.82 μM) and one of the compound 117c (IC50: 5.48 μM) showed highest activity against PC-3 cell line. SAR study illustrated the significance of phenylpiperazone 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...
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]quinazolines 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, 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 (GI50: 3.91, 3.45, 3.49, 3.21, 1.96, 3.69, 1.80, 5.19, and 5.55 μM, respectively). Several 6-aryl-benzothiazol[1,2,4]triazolo[5,1-b][1,2,4]triazinolines 121 (Fig. 27) were screened for their cytotoxicity against human gastric carcinoma cell line SGC7901 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 (IC50: 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, breast, ovary, kidney and prostate [119]. One compound, 124i exhibited remarkable anticancer activity against all tested cell lines (IC50: 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 activity against A549, HCT-116, PC-3 and MCF-7 cell lines with IC50 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 (R1) 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 IC50 values of 5.09, 3.70 and 12.74 μM, respectively and arrested G2/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)-4H-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 IC50 value of 0.58 μM, whereas compound 129c (IC50: 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 iminoacetyl 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]...
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-i and 132a) showed remarkable activity with IC50 values < 800 nM. Compound 131d displayed equivalent cytotoxic effect to the standard CHS 828 against gastric cancer cell line.

Pharmacological evaluation of synthesized 2-(4H-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 (IC50: 5.96 nM) against breast (MCF-7, MDA-MB-231, 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 (IC50: 2.79 μM) and 137c was found to be the most potent against SMMC-7721 cells (IC50: 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 (IC50: < 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 (IC50: 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(3H)-ones containing 1,2,4-triazole moieties 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 IC50 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]. A series of triazole-pyrazolylcoumarin derivatives 143 (IC50:...
**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}: 0.16–11.2 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 R1 position and electron-withdrawing group at R2 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-(1H-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 reported synthesis of several triazolo[1,5-a]pyrimidin-5(4H)-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 149h 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 (K_{i}: 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(4H)-one derivatives 151 (Fig. 34) as positive modulators of GABA_{A} was evaluated by MES and pentylentetrazole (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...
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]benzofuran[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 was 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 (ED50: 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 ED90 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]triazoles 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 ED50 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 ED50 value 63.4 mg/kg and a TD50 of 105.6 mg/kg, resulting in a high PI value of 17 when compared with standard carbamazepine (PI < 0.44). Further, neurotoxicity of the compounds was measured using rotorod 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-1Hbenzo[b][1,2,4]triazolo[4,3-d][1,4]-thiazin-1-ones 156 (Fig. 34) and evaluated for their anticonvulsant activity [141]. Based on the activity and toxicity profile, compound 156a exhibited significant anticonvulsant activity in MES test with ED50 value of 9.2 mg/kg and PI value of 15.4 which was superior to standard carbamazepine (ED50 and PI values of 11.8 and 6.4, respectively).

Several triazolo[4,3-q]quinazolin-5(4H)-ones 157 and pyrido[3,2-e][1,2,4]triazolo[4,3-]pyrimidin-5(6H)-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 ED50 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 (ED50) of 17.3 mg/kg and median toxicity dose (TD50) 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-c, 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 ED50 of 35.2 mg/kg, TD50 of 136.7 mg/kg and PI of 3.9 possesses the most potent activity. Compounds 162a-g showed better activity as compared to standard drug valproate. Results revealed that elongation of alkyl fragment from –C2H5 to –C6H5 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 C9 and C12 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 –CH2– 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 (ED50: 72.1 mg/kg, TD50: >1000 mg/kg and PI: >3.9 after 15 min). Radioligand binding assay indicated that these compounds excluded the possibility of direct or allosteric modulation of GABAA 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 ED50 of 23.4 mg/kg and PI value of >25.6, which is higher than the
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-(1H-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 GABAAR revealed that the compounds exerted anticonvulsant activity by inhibiting voltage-gated sodium channels (VGSC) and allosterically modulating GABAAR.

Abuelhassan et al. reported the anticonvulsant activity of 1,5-diaryl-1H-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 valproate. 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 activity.
activity with the ED50 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 H37RV (Mtbb H37Rv) 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 triazolequinazolinones 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 Mtbb H37Rv 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)-4H-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 Mtbb strains, including clinically isolated MDR strains [156]. SAR studies revealed the crucial role of position of 3,5-dinitrophenyl fragment on anti-TB activity.
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* H37Rv and *M. smegmatis* mc2155. 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* H37Rv and synergistic action with first line and second line anti-TB drugs. One of the compounds 176 having R = CH₃ and R₁ = CH₂H exhibited potent inhibitory growth in both *M. tuberculosis* and *M. smegmatis* mc²155 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 triazolothiophene 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* H37Rv [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 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 MIC₉₀ values in the range of 0.52–10 μM with no cytotoxicity against HepG2 cells. Three compounds 179, 180a and 180b displayed selectivity with MIC₉₀ 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, 181a and 182b exhibited potent in vitro activity
against Mtb H37Rv 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, two compounds 183a (MIC: 0.4 μg/mL) and 183b (MIC: 1.0 μg/mL) exhibited a promising antimycobacterial activity against H37Rv 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 H37Rv, 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 group at para position of the phenyl ring at the 3-position and p-bromophenoxyethyl group at the 6-position on the triazolothiadiazole 184 displayed significant enhancement in potency. Two highly active lead compounds 184a and 184b (MIC for H37Rv: 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 IC50 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 H37Rv, 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 IC50 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 H37Rv 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 amidines 187–188 (Fig. 39) against Mtb H37Rv 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 amidines, 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(4H)-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 H37Rv 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 NO2, Cl and F atoms on phenyl ring is found to increase antimycobacterial activity remarkably.

A series of novel substituted 4H-1,2,4-triazol-3-yl cycloalkanols 191 (Fig. 39) has been designed and screened for anti-TB activity against Mtb H37Rv 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 H37Rv 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-1H-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
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 (ED₅₀ 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(4H)-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 pyrindinyl triazole derivative 198 (Fig. 40) exhibited highly potent activity against HCMV with IC₅₀ of <0.05 µM than that of reference drug ganciclovir (IC₅₀: 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 IC₅₀ values of 0.47 and 0.51 µmol/L, respectively.

Zhan et al. designed and synthesized a series of 2-(2-(2,4-dichlorophenyl)-2H-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
HIV-1 (IIIb) replication with EC\textsubscript{50} value ranged from 2.78 to 6.21 \mu M than reference drug didoxynosine. Compound 202c showed most promising potency with EC\textsubscript{50} value of 2.78 \mu M and SI of 67 against HIV-1(IIIb) and EC\textsubscript{50} value of 7.42 \mu M against K103N mutant strain.

In another work, two series of [1,2,4]triazolo[1,5-\alpha]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\textsubscript{50} value of 0.02 \mu M and 7.61 \mu M, respectively. Among the series 204, compound 204a with an EC\textsubscript{50} value of 8.1 \mu M 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\textsubscript{50} of 54.8 nM against wt HIV-1 was more potent than reference lamivudine (EC\textsubscript{50}: 12.8 \mu M) and comparable to doravirine (EC\textsubscript{50}: 13 nM).

### 2.7. Antiparasitic agents

Bhatt et al. reported in vitro antimalarial efficacy of pyrazole-linked triazole-pyrimidine hybrids 206 (Fig. 42) and active hybrids (IC\textsubscript{50}: 0.034–0.09 \mu g/mL) for inhibition of Plasmodium falciparum dihydrofolate reductase (PfDHFR) via docking and in vitro studies [182]. The SAR of hybrids 206 indicated the significance of electron-withdrawing group at R1 position; -Br group at R2 position and substitution with methyl group at R3 position for antimalarial potency. Compound 206a with IC\textsubscript{50} value of 0.023 \mu g/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\textsubscript{50}: 0.041–1.50 \mu g/mL) (Fig. 42) displayed significant antimalarial activities. Among them, compounds 207d, 207e and 207g (IC\textsubscript{50}: 0.041, 0.054 and 0.092 \mu g/mL) displayed more potent activity against the P. falciparum strain in comparison to reference quinine (IC\textsubscript{50}: 0.286 \mu M) [183].

The antiplasmodial activities of triazolium salts 208 (Fig. 42) against chloroquine resistant 3G strain of P. falciparum were assessed by Vlahakis et al. [184]. Among them, compound 208a was found to be highly potent with IC\textsubscript{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\textsubscript{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\textsubscript{50} and ED\textsubscript{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 carbamoxides 210 (Fig. 42) with improved profile. Further optimization of substitution pattern (R) on phenyl ring adjacent to cyclopropyl ring identified compound 210a (IC\textsubscript{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\textsubscript{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\textsubscript{50} of 0.023 and 0.025 \mu g/mL, respectively against chloroquine resistant strain of P. falciparum, were comparable to chloroquine (IC\textsubscript{50}: 0.020 \mu g/mL) and 10-fold more potent than quinine (IC\textsubscript{50}: 0.268 \mu g/mL) [187].

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

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**Fig. 41. 1,2,4-Triazole derivatives as anti-HIV 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 triazolopyrimidine ring have poor species selectivity toward DHODH [191]. Further exploration of antimalarial drug candidate 213a by replacing SF$_5$-phenyl moiety with a series of CF$_3$-pyridyls 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 for $Pf$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].

Franklin 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 5-alkylated-triazoles 216a-c (Fig. 43) exhibited significant trypansomidal 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-1H-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 up to 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$_{50}$ ranging from 0.117 to 0.435 μM levels and SI of 220–973. In addition, 3-nitrotiazole 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-1H-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 nitrotiazole have shown moderate activity profile against the axenic form of *L. donovani*. The SAR of 3-nitrotiazole-based heteroarylamides/sulfonamides revealed that chlorinated thiophene sulfonamides and benzothiophene amides 230 (Fig. 43) were the most active antichagasic agents.
compounds, displaying up to 14 fold higher potency than the standard benznidazole [204].

Papadopoulou et al. designed 3-nitrotiazole based aryloxypentlamides 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-nitrotiazole-based aryloxypentaclamides 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 anti-trypansomal 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-nitrotiazole-based amides and carbinols (analogues of fluconazole) were synthesized as potent anti-trypansomal agents via their dual functioning as excellent substrates for trypanosomaltype 1 nitroreductase (NTR) and as inhibitors of sterol 14α-demethylase (T. cruzi CYP51) enzyme [207]. Carbinols 233 (Fig. 43) displayed excellent in vitro activity with IC50 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 (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 (IC50: 0.0312–0.8866 µg/mL) were 36–100 folds more potent than the reference miltefosine (IC50: 3.1924 µg/mL) and comparable to amphotericin B deoxycholate (IC50: 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)-4H-1,2,4-triazole-3-thiol derivatives 237 and 238 (IC50: 79.0–382.4 µM, Fig. 45) for in vitro antileishmanial activity against L. donovani promastigotes, makes compounds 237a (IC50: 79.0 µM) and 238a (IC50: 79.0 µM) the most promising antileishmanial agent as compared to standard sodium stibogluconate (IC50: 490.0 µM) [210].

Among coumarin-triazolothiadiazine hybrids, 239 (Fig. 45) demonstrated the highest inhibition (IC50: 0.89 µM) in vitro against the promastigote form of L. major [211]. Suleymanoglu 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 IC50/COX-2 IC50) 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 (IC50: 0.98 µM and SI: 8.05).

Biological screening of Schiff and Mannich bases derivatives of

![Image of chemical structures](image-url)

Fig. 44. Kinetoplastid proteasome inhibitors.
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.

Parkocka 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(6H)-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-inflammatory and analgesic activity by Ashour et al. [227]. Compounds 256a-c (ED50: 23.45–28.15 mg/kg) showed equivalent to moderate anti-inflammatory 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(4H)-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 a series of 3-(2,4-dichlorophenoxy)methyl)-1,2,4-triazolo (thiadiazoles and thiazolones) 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-alphalazine-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. 45. 1,2,4-Triazole derivates as antileishmanial agents.](image-url)
Several thiazolo[3,2-b]-1,2,4-triazoles derived from naproxen exhibited significant analgesic and anti-inflammatory activities with low gastric risk. 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.

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(5H)-ones 269 (Fig. 48) as effective DNA photocleavers. Among all the synthesized molecules, compounds 268c and 269k showed significant photocleavage of supercoiled plasmid $\Phi$X174 and pMaxGFP, respectively under UV irradiation at $\lambda_{\text{max}}$ 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 ($O_2^{-}$) (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. 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$_{50}$...
values 0.065 and 0.092 μM, respectively and high selectivity for AChE over BuChE by ~28 fold. Notably, these compounds exhibited better Cu²⁺-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 (Fig. 48) as phosphodiesterase 4B inhibitors [244]. The study revealed that compounds 272a and 272b with EC₅₀ values of 18.6 and 57.1 μM, respectively, showed better bronchodilator activity than the reference theophylline (EC₅₀: 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 antifungal 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.
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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