


Cite this: *RSC Adv.*, 2020, 10, 5610

Received 14th November 2019  
Accepted 8th January 2020

DOI: 10.1039/c9ra09510a

rsc.li/rsc-advances

# CuAAC-enssembled 1,2,3-triazole-linked isosteres as pharmacophores in drug discovery: review

Alisha Rani,<sup>a</sup> Gurjaspreet Singh,<sup>b</sup> Akshpreet Singh,<sup>b</sup> Ubair Maqbool,<sup>a</sup>  
Gurpreet Kaur<sup>\*c</sup> and Jandeep Singh<sup>id</sup> <sup>\*a</sup>

The review lays emphasis on the significance of 1,2,3-triazoles synthesized *via* CuAAC reaction having potential to act as anti-microbial, anti-cancer, anti-viral, anti-inflammatory, anti-tuberculosis, anti-diabetic, and anti-Alzheimer drugs. The importance of click chemistry is due to its 'quicker' methodology that has the capability to create complex and efficient drugs with high yield and purity from simple and cheap starting materials. The activity of different triazolyl compounds was compiled considering MIC, IC<sub>50</sub>, and EC<sub>50</sub> values against different species of microbes. In addition to this, the anti-oxidant property of triazolyl compounds have also been reviewed and discussed.

## Introduction

The consistently growing demand in the pursuit of medicinally potent compounds for drug discovery have given birth to simple and efficient synthetic routes for creating libraries of biologically active molecules.<sup>1</sup> The synthesis of current drug analogs is one among some of the most relevant approaches in medicinal chemistry and the drug discovery process. Since the past two decades, there has been enormous development in reaction methodologies with focus on three fundamentals principles of synthesis: versatility, efficiency, and selectivity. The extensively explored reactions performed under these principles are termed as 'Click Reactions'. They are further sub-classified into four brackets: (i) addition reaction to carbon-carbon multiple bonds, (ii) cycloaddition reactions (known under the title 'Huisgen 1,3-dipolar cycloaddition'), (iii) nucleophilic ring opening reactions of strained heterocyclic electrophiles, and (iv) none aldol carbonyl chemistry [MTC]. This Huisgen 1,3-dipolar cycloaddition between azides and alkynes yielding 1,2,3-triazoles (Fig. 1) is one of the most powerful among the click series of reactions.<sup>2-7</sup> The structural framework of 1,2,3-triazole enables it to mimic different functional groups, justifying its wide use as a bioisostere for the synthesis of new active molecules possessing a broad range of biological activities that include antimicrobial, anticancer, and antiviral, along with antidiabetic, anti-inflammatory, anti-Alzheimer, and antioxidant properties.<sup>8,9</sup> All these methodologies have permitted the

successful design of novel drug analogs *via* combinatorial synthesis.

The use of click chemistry to manufacture drugs with cohesively 1,2,3-triazole units *via* metal catalyzed alkyne-azide cycloaddition reaction have been developed to be an efficient tool. Click chemistry, as defined by Sharpless, involves high yielding reactions with wider scope, easily removable by-products, complete control of stereospecificity, and simplicity of procedure. The evolution of click chemistry is fine-tuned with pharmaceutical and materials research for generating libraries of molecules for drug discovery that makes it indispensable and evolutionary synthetic tool. The performance of this reaction on the cellular scale easily modifies biomolecules and cell surfaces for imaging purposes and functioning for physiological investigations.<sup>1</sup> The prerequisite of drug modification is to overcome drug resistance, explore highly selective and less toxic drugs, to improve the pharmacokinetic profile, resulting in the need for an optimized process.<sup>10</sup> The ability to obtain stable 1,2,3-triazolyl isosteres has resulted in their wide application in the drug discovery and drug design of bioactive molecules analogs. This necessity for novel chemotherapeutics has reinvigorated various research groups to synthesize triazole analogs.<sup>11,12</sup> A compiled report on the pharmacological applications of 1,2,3-triazole linked molecules created *via* copper catalysed alkyne-azide cycloaddition (CuAAC) reaction has not been published to the best of our knowledge. This review contains the compiled data of research articles published in the last 10 years (2010 onwards) with active pharmacological entities.

Triazoles including 1,2,3-triazole, 1,2,4-triazole, benzo-triazole, triazolopyrimidine (Fig. 2), and their derivatives have attracted continuous interest in medicinal chemistry, and many drugs marketed currently are based on triazoles, for example pramiconazole, fluconazole, and itraconazole as shown in Fig. 3.<sup>13</sup> Thus, the role of heterocyclic compounds has become

<sup>a</sup>Department of Chemistry, Lovely Professional University, Phagwara-144411, Punjab, India. E-mail: singhjandeep@gmail.com; Tel: +91 9815967272

<sup>b</sup>Department of Chemistry, Centre of Advanced Studies in Chemistry, Panjab University, Chandigarh-160014, India

<sup>c</sup>Department of Chemistry, Gujranwala Guru Nanak Khalsa College, Civil Lines, Ludhiana-141001, India

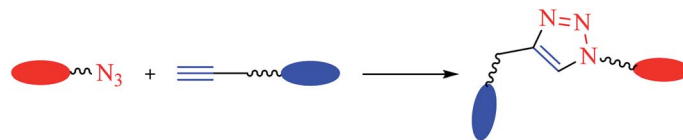



Fig. 1 Common reaction scheme leading to the formation of 1,2,3-triazole linked compounds.

increasingly important in designing a new class of structural entities of medicinal importance due to the favorable properties of 1,2,3-triazole ring such as moderate dipole character, hydrogen bonding capability, and rigidity and stability under *in vivo* conditions, which are responsible for their enhanced biological activities.<sup>14–17</sup>

## Anti-microbial activity

The 1,2,3-triazoles combine a framework consisting of *N,N*-backbone nuclei with various carbocyclic framework to act as potential anti-microbial agents, as compiled in Table 1. The activity of these dehydroacetic acid chalcone-1,2,3-triazoles (**1**) against bacterial strains (*B. subtilis* and *E. coli*) and fungal strains (*Aspergillus niger* and *Candida albicans*) prove their anti-microbial nature. The presence of a substituted methoxy group on the phenyl ring increases its potency with high activity towards these bacterial and fungal strains. It was observed that the compounds with terminal bromo and methoxy groups on the benzene ring exhibit better activity against most of the microorganisms, whereas in the case of presence of nitro group, better antifungal activity was observed in comparison to the methyl group. In addition, the molecular docking studies suggest that the activity of these compounds is a result of attachment of oxygen atom of the carbonyl group of compound **2** to form a hydrogen bond with Asn46 residue of the active site, whereas the phenoxy ring is hooked *via* in  $\pi$ -anion interaction with Glu50. Also, the triazole ring exhibits  $\pi$ -cation interaction with Arg136 with stacking of amide groups of Gly77 and Ile78 against the phenoxy ring.<sup>18–20</sup>

The merging of two pharmacophore units results into the formation of chalcone-1,2,3-triazole conjugates, which also serve as antimicrobial agents. Among the sequence of series of such triazoles screened, only compound **3** displayed high activity against *E. coli* and *S. epidermidis* due to presence of 4-nitro group. Molecular docking studies of compound **3** revealed that the carbonyl group participated in hydrogen bonding with His95, Ala96, and Ser121 residues. 1,4-Substituted triazole attached to the phenyl ring is engaged in  $\pi$ -alkyl interactions with  $\pi$ -electrons, while the same phenyl ring also demonstrated  $\pi$ -alkyl interactions with Val120.<sup>21</sup> Srivastava *et al.* created

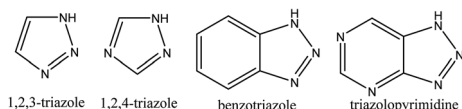


Fig. 2 The structure of pharmaceutically active triazole moieties.

a series of  $\beta$ -D-ribofuranosyl coumarinyl-1,2,3-triazoles using Cu(I) catalysed cycloaddition reaction having potent anti-mycobacterial activity against *mycobacterium tuberculosis* H37Rv. The pharmacophore entity **4** possesses excellent inhibitor capacity against *mycobacterium tuberculosis* in comparison to the standard drug. The target site of 1,2,3-triazole is mycobacterial InhA and DNA gyrase enzymes, and the binding of (**4**) molecule with these enzymes is essentially through hydrogen bonding.<sup>22,23</sup>

Another class of compounds, containing Schiff base linked to 1,2,3-triazole with terminal silatrane group, were synthesized by single step 'click silylation' reaction. Among the series of molecules screened by Singh *et al.*, it was discovered that only molecule **5** showed excellent inhibitor activity against *S. aureus*, MRSA, and *S. epidermidis* due to the presence of electron donating methoxy group.<sup>24</sup> In another series, novel dispiropyrrrolidine and dispiropyrrrolidine-fused triazole conjugates were prepared *via* a facile one-pot four-component cycloaddition reaction. Upon evaluation of the antibacterial and antifungal activities, it was noticed that the molecule containing bromo group (**6**) on the indolinone and triazole cycle leads to an increase in the activity. In the same fashion, another molecule containing methoxy group on the triazole ring and a bromo substituent on the indolinone ring results in increase in its antibacterial activity. The compounds having methyl substitution at the 1,2,3-triazole unit show excellent antifungal

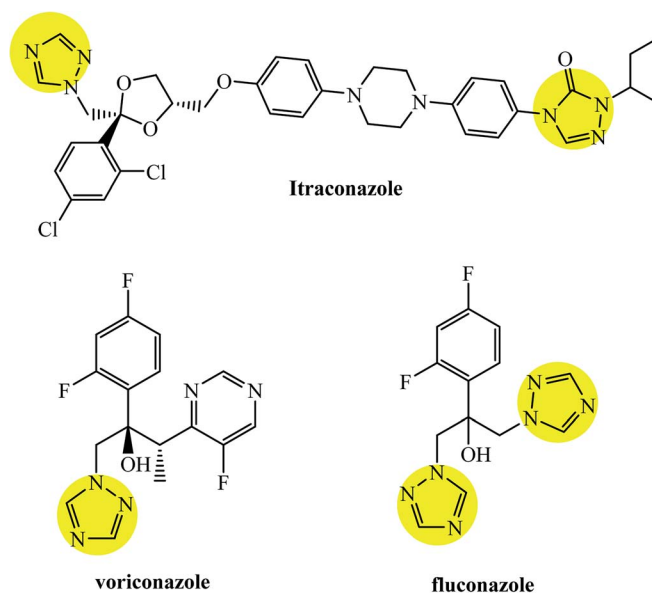


Fig. 3 The structures of itraconazole, voriconazole and fluconazole containing triazole moieties.

**Table 1** List of 1,2,3-triazolyl linked pharmacophores possessing anti-microbial activity observed using MIC and IC<sub>50</sub> values

Comp. no.	Parent compound	Biological target	Anti-microbial activity	Reference
1		H37Rv strain	MIC (μM) 4.11 μM	15
2		<i>E. coli</i> <i>B. subtilis</i> <i>A. niger</i> <i>C. albicans</i>	MIC (μM) 0.0030 0.0030 0.0060 0.0120	18
3		<i>E. coli</i> <i>S. epidermidis</i>	MIC (μmol mL <sup>-1</sup> ) 0.0032 0.0032	21
4		H37Rv	MIC (μM) 5.1	22
5		<i>S. aureus</i> , MRSA strain, 3.25 and <i>S. epidermidis</i>	MIC (μg mL <sup>-1</sup> ) 3.25	24
6		(Gram -ve bacteria) <i>E. coli</i> <i>P. aeruginosa</i> (Gram +ve bacteria) <i>S. aureus</i> <i>S. pyogenus</i> (Antifungal) <i>C. albicans</i>	MIC (μg mL <sup>-1</sup> ) 31.25 250 31.25 250 250	25



Table 1 (Contd.)

Comp. no.	Parent compound	Biological target	Anti-microbial activity	Reference
7		MRSA strain	MIC ( $\mu\text{g mL}^{-1}$ ) 4	26
8		<i>M. catarrhalis</i>	MIC ( $\mu\text{g mL}^{-1}$ ) 0.5	27
9		(Gram positive) MRSA strain <i>B. subtilis</i> <i>B. cereus</i> (Gram negative) <i>E. coli</i> <i>K. pneumonia</i> <i>P. vulgaris</i>	MIC ( $\mu\text{g mL}^{-1}$ )  12.5 12.9 12.0 15.5 25.3 28.4	29
10		(Gram positive) <i>B. cereus</i> <i>S. aureus</i> (Gram negative) <i>E. coli</i> <i>P. aeruginosa</i>	MIC ( $\mu\text{g mL}^{-1}$ )  32 27 27 22	30
11		H37Rv strain	MIC ( $\mu\text{g mL}^{-1}$ ) 0.78	31
12		<i>B. subtilis</i> <i>E. coli</i>	MIC ( $\mu\text{g mL}^{-1}$ ) 10 10	33
13		H37Rv	MIC ( $\mu\text{g mL}^{-1}$ ) 0.78	34

Table 1 (Contd.)

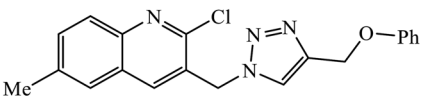
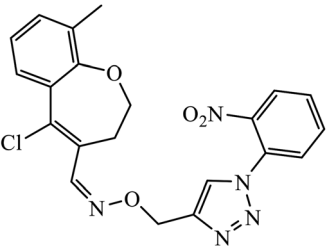
Comp. no.	Parent compound	Biological target	Anti-microbial activity	Reference
14		<i>S. aureus</i>	MIC ( $\mu\text{g mL}^{-1}$ ) 0.5	35
15		Antibacterial <i>S. aureus</i> <i>P. aeruginosa</i> <i>E. faecalis</i> Antifungal <i>C. albicans</i> <i>A. brasiliensis</i>	MIC ( $\text{mg mL}^{-1}$ ) 0.625 0.625 0.625 1.25 1.25	36
16		<i>S. aureus</i> <i>P. aeruginosa</i> <i>S. dysenteriae</i>	MIC ( $\mu\text{g mL}^{-1}$ ) 64 16 16	37
17		<i>P. falciparum</i>	IC <sub>50</sub> ( $\mu\text{M}$ ) 9.6	38
18		<i>E. coli</i> <i>B. subtilis</i> <i>P. aeruginosa</i>	$14 \pm 0.6$ $08 \pm 0.7$ $10 \pm 0.3$	39
19		<i>L. donovani</i> <i>P. falciparum</i> (D6 strain) <i>P. falciparum</i> (W2 strain)	IC <sub>50</sub> ( $\mu\text{M}$ ) 1.14 4.11 4.49	40

R<sub>1</sub> = Geranyl

Table 1 (Contd.)

Comp. no.	Parent compound	Biological target	Anti-microbial activity	Reference
20	 (a) $R_1 = H$ , $R_2 = 2\text{-Cl}, 4\text{-F}$ (b) $R_1 = H$ , $R_2 = H$	(a) (Antifungal) <i>F. oxysporum</i> <i>F. graminearum</i> (b) (Antibacterial) <i>E. coli</i> <i>P. putida</i> <i>S. aureus</i>	MIC ( $\mu\text{g mL}^{-1}$ ) >64 (128) >64 (128) >64 (>64) >64 (>64) >64 (>128) MIC ( $\mu\text{g mL}^{-1}$ )	41
21	 $R_1 = 6\text{-CH}_3$	H37Rv	0.2	42
22		<i>P. aeruginosa</i>	MIC ( $\mu\text{g mL}^{-1}$ ) 12.5	45
23		Antibacterial <i>B. subtilis</i> <i>E. coli</i> Antifungal <i>F. recini</i>	MIC ( $\mu\text{g mL}^{-1}$ ) 25 25 25	46
24		<i>E. faecalis</i>	MIC ( $\mu\text{g mL}^{-1}$ ) 12.5	47
25		Gram-positive <i>S. aureus</i> <i>B. subtilis</i> <i>S. epidermidis</i> Gram-negative <i>P. aeruginosa</i> <i>E. coli</i> <i>K. pneumonia</i>	Zone of inhibition (mm) 15 $\pm$ 0.1 15 $\pm$ 0.4 16 $\pm$ 0.3 14 $\pm$ 0.3 13 $\pm$ 0.3 14 $\pm$ 0.4	48

Table 1 (Contd.)

Comp. no.	Parent compound	Biological target	Anti-microbial activity	Reference
26		<i>E. coli</i>	Zone of inhibition (mm) 15	49
		<i>K. pneumonia</i>	22	
		<i>P. aeruginosa</i>	25	
		<i>P. vulgaris</i>	20	
		<i>S. typhi</i>	22	
		<i>P. putida</i>	10	
		Urinary tract infection organism	18	
27			Zone of inhibition (diameter in mm) at 0.5 mg per 100 µL	50
		<i>P. aeruginosa</i>	17 ± 0.2	
		<i>S. aureus</i>	12 ± 0.2	
		<i>K. pneumoniae</i>	12 ± 0.2	
		<i>E. coli</i>	15 ± 0.3	

activity.<sup>25</sup> Thus, a series of metronidazole-triazole hybrids were formulated having anti-methicillin resistant *S. aureus* activity. It was found out that the compounds with halogen substituent at the benzene nucleus show excellent activity as compared to other substituents, such as *t*-Bu, Me, CHO, and NO<sub>2</sub>, which display less inhibition activity towards MRSA strains. Compound 7 with 2,4-dichloro substituents at the phenyl ring displays excellent activity towards MRSA strains in comparison to the reference oxacillin drug.<sup>26</sup>

The benzo-fused nitrogen and sulfur heterocycles containing 1,2,3-triazole conjugates were synthesized as efficient antibacterial agents. The inhibition activity of N/S containing compounds was tested against selected Gram-negative and Gram-positive bacteria. Compound 8 bearing *p*-chlorophenyl or *p*-fluorophenyl group having linkage with 4<sup>th</sup> position of the triazole displayed outstanding inhibition activity against *M. catarrhalis*.<sup>27,28</sup> Click chemistry was used to create a novel series of 1,2,3-triazole compounds from ibuprofen. The activity of these compounds was tested against bacterial strains and the results indicated anti-bacterial activity for the compounds with benzyl or phenyl ring with 1,2,3-triazole moiety containing electron withdrawing group at *para* or *meta* position of the rings. Compound 9 with 4-nitrobenzyl group hooked to 1,2,3-triazole moiety resulted in excellent activity. The interactions of compound 9 in the COX-2 active site can possibly cause the higher activity.<sup>29</sup>

The use of geraniol as a precursor for synthesizing a new category of 1,2,3-triazole was made through cycloaddition reaction *via* click chemistry and their activity was evaluated against four bacterial strains. Compound 10 having electron withdrawing groups such as -OH and -Cl increased the activity against all the bacterial strains. Compound 10 is bound *via* van der Waals, hydrophobic,  $\pi$ -stacking, and hydrogen bond

interactions. It is deduced that the triazole derivative (10) is also surrounded by van der Waals linked residues. The hydroxyl substituent at C4-position of the triazole moiety is bound by a van der Waals pocket, which strengthened the binding affinity, thus leading to increased antimicrobial activity of the compound.<sup>30</sup>

Rajua *et al.* synthesized a novel series of pyrimidine based 1,2,3-triazoles *via* Cu(I) catalysed cycloaddition reaction, which act as anti-tubercular agents. All the synthesized compounds were tested against *Mycobacterium tuberculosis* H37Rv strain and the results indicate that the presence of electronegative atom on 1,2,3-triazolyl compound 11 led to the prominent activity of that compound. The molecular docking studies further verify this potent activity as a result of presence of moderately extensive hydrogen bonds of Ser228 and Cys387,  $\pi$ -alkyl with His132 and Tyr314, strong hydrophobic bonds of Pro316, Ala244, Lys134, Lys367, and Val365 along with Tyr314 van der Waals interaction with the triazole ring.<sup>31,32</sup>

In another set, a series of 2-chloro-3-((4-phenyl-1H-1,2,3-triazole-1-yl)methyl)quinolone derivatives were synthesized and were evaluated to have good antibacterial and antifungal activities. The activity of compound 12 was due to the attachment of methoxy group on the benzyl ring, which was proved to have excellent activity towards bacterial strains. Further, it was observed that upon replacement of the methoxy group with a methyl group, it is converted to a good antifungal agent.<sup>33</sup> The 1,2,3-triazole compounds linkage with spirochromone conjugates 13 have good activity against *Mycobacterium tuberculosis* (virulent strain H37Rv). Compound 13 displays high activity in comparison to the standard drug ethambutol, which further increases in presence of an aromatic group at 4<sup>th</sup> position of 1,2,3-triazole and cyclohexyl group at the 2<sup>nd</sup> position of the chromone ring.<sup>34</sup> 1,2,3-Triazole linked 4(3H)-quinazolinone





derivatives were synthesized and they were found to be good antibacterial agents. Compound **14** is highly active against a gram-particular positive bacterial strain, *i.e.*, *Staphylococcus aureus* but inactive towards gram-negative bacterial strains. Its high activity is due to the presence of an electronegative atom on the phenyl ring, which is directly attached to 1,2,3-triazole.<sup>35</sup> Another set of halogen linked 1,2,3-triazole containing quinazolin-4-one **15** was found to have excellent activity owing to the presence of a phosphonoalkyl group located at the C4 position in the 1,2,3-triazole ring. These pharmacophore drug molecules were potentially active against both gram-negative bacteria such as *S. aureus*, *P. aeruginosa*, and *E. faecalis* with the MIC value of 0.625 mg mL<sup>-1</sup>. Moreover, the linkage of bromo or nitro group at the C6 position of quinazolinone moiety led to a drastic fall in the activity towards the bacterial strain. In addition, the unsubstituted quinazolinone compounds exhibit potential antifungal activity against *C. albicans* and *A. brasiliensis* with MIC value of 1.25 mg mL<sup>-1</sup>.<sup>36</sup>

Sulfanilamide-derived 1,2,3-triazoles generated by click chemistry were examined as potent antibacterial and antifungal agents. The analysis indicated that compound **16** has good activity against three selected bacterial strains and contains two highly electronegative atoms on the phenyl ring. Fundamentally, the activity of such a compound depends upon the terminal alkyl chain and the substitution on the phenyl ring in the compound.<sup>37</sup> Similarly, the series of 7-chloroquinolino-triazoles having unique substituents in the 1,2,3-triazole moiety were synthesized and examined for the antimalarial activity. Compound **17** with a side chain hydroxyl group gives the best antimalarial activity.<sup>38</sup> Further, 8-trifluoromethylquinoline based 1,2,3-triazole **18** derivative showed antimicrobial activity due to the presence of electron withdrawing group such as -Cl, which enhances their activity.<sup>39</sup> 1,2,3-Triazolylsterols **19** synthesized using click chemistry were found to have excellent antiparasitic properties against *L. donovani*, *P. falciparum* (D6 strain), and *P. falciparum* (W2 strain). The activity of compound **19** depends upon the length of the substituent attached to 1,2,3-triazole, *i.e.*, the presence of a long chain on triazole increases the activity of the compound.<sup>40</sup>

Piperazine-triazole derivatives synthesized *via* click chemistry act as good antimicrobial agents with potential inhibition activity as antibacterial and antifungal agents. The studies prove that compound **20a** containing electron-withdrawing groups on phenyl ring has better antibacterial activity and in the case of no electron-withdrawing groups on the phenyl ring, it acts as an anti-fungal **20b**.<sup>41</sup> Mono and bis-aryloxy linked coumarinyl triazoles **21** act as anti-tubercular agent and the results indicated that bis-triazoles are more active than mono-triazoles. The activity of these compounds is regulated by the ability of 1,2,3-triazole and the phenoxy moiety to form hydrogen bonds with the protein at the site of the receptor. Moreover, the activity of these compounds increases in the presence of two triazoles and coumarin moieties in the compound. The high activity of these compounds is supported by the molecular docking studies carried out against InhA-D148G mutant in the complex with NADH, showing better hydrogen binding in the presence of two triazole rings. It was

discovered that by increasing the bulkiness of the compound, the ability to create good hydrogen bonding also increases, resulting in better activity against *Mycobacterium tuberculosis* H37Rv.<sup>42–44</sup>

The oxazole conjoined 1,2,3-triazole derivative **22** presented good inhibition activity against *P. aeruginosa* with MIC value of 12.5 µg mL<sup>-1</sup> and mild activity against *S. epidermidis* with MIC value of 50 µg mL<sup>-1</sup>, which is attributed to the presence of an oxadiazole ring.<sup>45</sup> The 1,2,3-triazole ring fused with pyridine/pyrimidine was designed and its antimicrobial activity was evaluated. Compound **23** showed excellent antibacterial as well as antifungal activity.<sup>46</sup> Coumarin hooked *via* 1,2,3-triazole conjugate **24** to varied alkyl, phenyl, and heterocyclic moieties at the C-4 position of the triazole nucleus possessed phenomenal antibacterial activity against *E. faecalis*, which was a result of the compound having a 2-OMe-Ph group attached at the triazole nucleus and an -OCH<sub>2</sub>- linker.<sup>47</sup> A similar class of oxadiazole substituted 1,2,3-triazole derivative **25** containing the structural features of ibuprofen/naproxen appeared to be effective against both Gram-positive and Gram-negative bacteria. One of synthesized compound was identified as the most interesting as it exhibited activities against almost all the species because of the presence of Cl at the *o*-position on the benzene ring, which increases its activity.<sup>48</sup> A novel series of 1,2,3-triazolyl quinolones were designed *via* CuAAC and examined as antibacterial agents. The compound having unsubstituted phenyl moiety or phenoxyethylene **26** was more active as compared to the compound containing the electron donating methoxy functional group on the quinolone ring.<sup>49</sup> Moreover, the benzoxepine-oxime-1,2,3-triazole hybrid was capable of inhibiting the bacterial strains. Compound **27** was identified as the most interesting among all the designed compounds as it showed notable activities against almost all the bacterial strains and against the NCI-H226 cancer cell, it showed GI<sub>50</sub> value of 46.8 µM.<sup>50</sup>

## Anti-cancer activity

1,3,4-Substituted-1,2,3-triazoles were synthesized as potential antitumor drugs, as shown in Table 2. The analysis of their cytotoxicity against the tumor cell line HL-60 (myeloid leukemia), MCF-7 (breast cancer), HCT-116 (colon cancer), and non-tumor cells (vero cell) gave excellent results. Different IC<sub>50</sub> values were obtained for the tumor cells for compound **28**, clearly indicating a strong affect towards the HL-60 cancer cell line. The IC<sub>50</sub> value is below 10 µM for the cancer cell lines and for the non-tumor cell, IC<sub>50</sub> values were less than 100 µM.<sup>51</sup> Pyrazolo[3,4-*d*]pyrimidin-4(5H)-ones tied to 1,2,3-triazoles were synthesized with different substituents. Among the series of synthesized compounds, few were highly effective towards C6 glioma cell line and U87 cancer cell lines. Compound **29** has potential to capture the cell at the S-phase of the cell cycles and gave rise to apoptosis in the U87 GBM cell lines. These compounds are cytotoxic towards both C6 and U87 cell lines and IC<sub>50</sub> value for U87 is less as compared to that for C6, which means that U87 is highly affected by these compounds, as shown in Table 2. The ligand binds in the hydrophobic pocket



**Table 2** Compiled list of 1,2,3-triazole linked compounds possessing anti-cancer activity as observed using IC<sub>50</sub> values

Sr. no.	Parent compound	Biological target	Anti-cancer activity	Reference
28		HL-60 MCF-7	IC <sub>50</sub> (μM) 3.4 ± 1.9 <sup>a</sup> 18.2 ± 7.2 <sup>a</sup>	51
29		C6 U85	IC <sub>50</sub> (μM) 15.02 4.6	52
30		MDCK	IC <sub>50</sub> (μM) 0.6	56
31		GGDPS	IC <sub>50</sub> (μM) 1.3 ± 0.2	60
32	 <p>R<sub>1</sub>=2,6-dibromo-4-fluoro phenyl</p>	HeLa	IC <sub>50</sub> (μM) 7.93	61
33		HEP3B HT-29	IC <sub>50</sub> (μM) 0.5 5.7	62
34		A549	IC <sub>50</sub> (μM) 0.51 ± 0.32	67



Table 2 (Contd.)

Sr. no.	Parent compound	Biological target	Anti-cancer activity	Reference
35		A549 MDA-MB-231	IC <sub>50</sub> (μM) 2.9 ± 0.25 3.35 ± 0.37	68
36		HT29 DU145	IC <sub>50</sub> (μM) 4.4 ± 0.3 1.8 ± 0.5	71
37		DU145	IC <sub>50</sub> (μM) 8.17	74
38		Lung (A549)	IC <sub>50</sub> (μM) 5.54	75
39		EC-109 MCF-7 MGC-803	IC <sub>50</sub> (μM) 1.42 ± 1.25 6.52 ± 0.23 5.85 ± 0.15	76
40		GBM 95 GBM 02 U87	IC <sub>50</sub> (μM) 28.7 44.9 27.1	79



Table 2 (Contd.)

Sr. no.	Parent compound	Biological target	Anti-cancer activity	Reference
41		MGC-803 MCF-7 PC-3 EC-109	IC <sub>50</sub> (μM) 0.73 ± 0.11 5.67 ± 0.91 11.61 ± 1.59 2.44 ± 0.10	80
42		Hep-G2 HeLa	IC <sub>50</sub> (μM) 2.67 6.51	81
43		MCF-7 HeLa 7721	IC <sub>50</sub> (μM) 0.301 0.725 0.502	82
44		(a) HeLa (b) CaSki (c) SK-OV-3	IC <sub>50</sub> (μM) ± SD 17.754 ± 0.754 14.925 ± 0.078 33.259 ± 1.534	83
45		Aurora A Aurora B	IC <sub>50</sub> (μM) 0.37 3.58	84
46		HL-60 SMMC-7721 A-549 MCF-7 SW480	IC <sub>50</sub> (μM) ± SD 0.66 ± 0.04 0.85 ± 0.05 0.94 ± 0.05 1.70 ± 0.26 1.25 ± 0.03	85
47		Tyrosinase	IC <sub>50</sub> (μM) 26.20 ± 1.55	86



Table 2 (Contd.)

Sr. no.	Parent compound	Biological target	Anti-cancer activity	Reference
48		Abl kinase	IC <sub>50</sub> (μM) 1.9 ± 0.1	87
49		MCF-7 HT-29 MOLT-4	IC <sub>50</sub> (μM) 10.4 ± 1.7 6.8 ± 1.3 8.4 ± 0.6	88
50		HepG2	IC <sub>50</sub> (μM) 0.0267	89
51		MG-63 MDA-MB-231 HDF	IC <sub>50</sub> (μM) 18.05 ± 0.69 16.61 ± 1.20 22.83 ± 1.42	90
52		SKOV-3 PC-3 MDA-MB-231 MCF7	IC <sub>50</sub> (μM) 1.2 ± 0.1 0.9 ± 0.1 0.7 ± 0.1 0.8 ± 0.2	91
53		HCT-15 NCI-H226	GI <sub>50</sub> (μM) 52.5 41.3	92
54		HCT-15	IC <sub>50</sub> (μM) 22.4	93

Table 2 (Contd.)

Sr. no.	Parent compound	Biological target	Anti-cancer activity	Reference
55		A549 HepG2 HeLa DU145	IC <sub>50</sub> (μM) 6.7 ± 0.15 9.8 ± 0.12 7.9 ± 0.22 5.9 ± 0.15	94
56		PDE4B inhibition	IC <sub>50</sub> (μM) 5.014	95
57		A549	IC <sub>50</sub> (μM) 8.7 ± 0.24	96
58		A549 MCF 7	IC <sub>50</sub> (μM) 11.1 ± 0.16 10.8 ± 0.11	97
59		A549	IC <sub>50</sub> (μM) 9.8 ± 0.12	98

<sup>a</sup> Represents the maximum possible deviation from the results.

of the protein kinase domain and the binding mode is stabilized by the formation of hydrogen bonds between the ligand and active site residues of the protein.<sup>52–55</sup> Another compound **30** is a 1,2,3-triazole-based inhibitor, which is active against HGF-induced scattering of MDCK and GTL-16 cancer cells. The binding mode of the new compound is similar to that of the active compound triflorcas; also, the range of IC<sub>50</sub> of the new compound is similar to that of triflorcas. The molecular docking

studies show that the binding of benzothiazole ring occurs *via* weak hydrogen bonded interaction with the NH backbone of Met1160 through the S-atom, thus establishing hydrophobic contacts with Tyr1159.<sup>56–59</sup>

A series of bishomoisoprenoid triazole bisphosphonates were synthesized and were evaluated to have good inhibition of geranyl diphosphate synthase. The activity of these compounds was studied on the basis of chain length and the olefin



stereochemistry, and the results prove that compound **31** is the most potent inhibitor against GGDPS.<sup>60</sup> A class of novel isopropylidene uridine [1,2,3-triazole] hybrids were found to be highly active as anticancer and antibacterial agents. The results indicated that the compound containing the hydroxyl group on the benzene ring exhibited high activity towards MCF-7 (breast cancer) cancer cell, whereas compound **32** containing 2,6-dibromo group on the benzene ring is an excellent inhibitor of the HeLa cell lines. These results clearly exhibit the high activity in comparison to the standard drug cis-platin.<sup>61</sup>

The Cu(I) assisted cycloaddition reaction to create 1,4-disubstituted 1,2,3-triazole resulted in a series of triazoles with anticancer activity against hepatocellular carcinoma (HCC) Hep 3B cells and HT-29. Compound **33** exhibits excellent cytotoxic effect towards the cancer cell lines and on normal human umbilical vein endothelial cells but the effect is comparatively less as compared to standard anticancer agent Sorafenib. The activity of this molecule **33** is still better in a short time period and at low concentration. The activity of compound **33** was induced due to the apoptosis of Hep 3B cells and it did not cause the arrest of the cell cycle at the G0/G1, S, or G2/M phases. The decrease in the percentages of the cells at G0/G1, S, and G2/M may have been due to the increase in the cells at the Sub-G1 phase.<sup>62–66</sup>

Sayed *et al.* designed a new series of imidazopyridine linked triazole hybrid conjugates with robust anticancer inhibition activity with four cancer cell lines, *i.e.*, breast (MDAMB 231) cancer, human prostate (DU-145), human colon (HCT-116), and human lung (A549) cancer. Among all the synthesized molecules, compound **34** shows excellent cytotoxicity against the human lung cancer cell line because of the presence of electron donating trimethoxy group on the aromatic ring. Compound **34** exhibited various interactions with the residues with conventional hydrogen bonds between the carbonyl oxygen and Thr349, nitrogen atom of imidazopyridine ring and Ile332, and nitrogen atom of the triazole ring and Gly350. The oxygen atoms in the methoxy substituents were also involved in hydrogen bonding with the amino acid residues Asp179, Asn329, and Ile341.<sup>67</sup>

Ferrocenyl chalcogeno (sugar) triazole conjugates also exhibit strong anticancer activity. The evaluation of the activity of these triazoles with different cancer cell lines conclude that the sulphur containing triazole conjugates are cytotoxic towards the cancer cell but with lower activity. Moreover, the compounds containing selenium triazole **35** show very high activity towards the cancer cell lines.<sup>68–70</sup>

Platinum(II) complexes incorporating bidentate pyridyl-1,2,3-triazole were synthesized and were highly active against different cancer cell lines. The results specify that compound **36** is an excellent inhibitor of different cancer cell lines as compared to the standard drug cis-platin.<sup>71</sup> Two novel series of 1,2,3-triazole tethered to indole-3-glyoxamide derivatives were evaluated for their anti-proliferative, anti-inflammatory, and inhibitory activities against 5LOX, COX-1, and COX-2. The activity of these compounds depends upon the nature and position of the substituent on the phenyl ring. The compounds

with ethyl and halogen groups at the *para* position show excellent activity against proliferative cancer cell lines.<sup>72,73</sup>

Compound **37** with *p*-ethyl substituent on the aromatic ring shows very high anti-proliferative activity. It displayed strong binding with Lys352 and Val238 amino acids and was also involved in hydrophobic bonding with Leu255 and Ile354 amino acids. It was found that this compound exhibited a similar kind of interaction as that of nocodazole in the catalytic domain of ATP at the Colchicine binding site of tubulin.<sup>74</sup> 1,2,3-Triazole derivatives of diosgenin were used as anti-tumor agents with inhibition activity examined on four cancer cell lines, *viz.*, HBL-100 (breast), A549 (lung), HT-29 (colon), and HCT-116 (colon). It was studied that the compounds with simple phenyl moiety attached through 1,2,3-triazole to the parent molecule **38** demonstrate very high activity against the A549 cancer cell line as compared to the positive control (BEZ-235).<sup>75</sup> The triazolyl pyrimidine hybrids that act as anticancer agents were tested on four cancer cell lines, *viz.*, EC-109 (human esophageal cancer cell line), MCF-7 (human breast cancer cell line), B16-F10 (mouse melanoma cell line), and MGC-803 (human gastric cancer cell line). The results signify the importance of having electron-donating groups on the aryl amine that exhibits high inhibition activity as compared to the compound having electron-withdrawing groups. The 4-substituted aryl-amine **39** shows excellent inhibition activity against MCF-7 and MGC-803.<sup>76–78</sup> This 1,4-disubstituted-1,2,3-triazole act as an anticancer agent and shows excellent activity against glioblastoma cell lines. The examination of anti-cancer activity of these compound at different concentrations and at two different time periods (48 h and 72 h) gives the information that compound **40** having methylenoxy or tosyl-hydrazone attached to 1,2,3-triazole led to an increase in the activity of the compound. Compound **40** indicated large H-bond acceptor peaks directed towards the tosyl and azide groups, suggesting a stronger acceptor region.<sup>79</sup>

A novel series of 1,2,3-triazole-dithiocarbamate **41** was obtained, which act as anticancer agents against four cancer cell lines as compared to the standard drug 5-fluorouracil because of the presence of electronegative atoms at the *ortho*-position of the benzyl ring.<sup>80</sup> Gregorić *et al.* synthesized a series of pyrimidine-2,4-dione-1,2,3-triazole and furo[2,3-*d*]pyrimidine-2-one-1,2,3-triazole as the anticancer agents. Their activity was examined against five cancer cell lines and compound **42** shows better activity against two cancer cell lines, *viz.*, hepatocellular and cervical carcinoma, as compared to the standard drug 5-fluorouracil. The structure of compound **43** indicated the absence of strong hydrogen-bonding donors and was linked only by weak interactions, two C–H...O hydrogen bonds, one C–H...N hydrogen bond, one C–H... $\pi$  interaction, and one  $\pi$ ... $\pi$  interaction.<sup>81</sup>

Two new series of 1,2,3-triazole-1,8-naphthalimides **43** were synthesized by click chemistry that act as anticancer agents. It was observed that the activity of these compounds depends on the type of the side chain that is attached to the 1,2,3-triazole moiety. It has also been reported that if the side chain contains terminal basic group, it results in the increase in the activity of the compound against the cancer cell lines. The UV-Vis spectra





**Table 3** List of 1,2,3-triazolyl compounds possessing anti-viral activity as observed using IC<sub>50</sub> and EC<sub>50</sub> values

Sr. no.	Parent compound	Biological target	Anti-virus	Reference
60		TK + VZV TK – VZV	EC <sub>50</sub> (μM) 3.62 7.85	10
61		HIV-1 proteases (wt)	IC <sub>50</sub> (nM) 6 ± 0.5	99
62		HIV-1 proteases (6X)	IC <sub>50</sub> (nM) 15.7	102
63		IIIB E138K	EC <sub>50</sub> (μM) 0.020 0.014	103
64		HIV-1 NL <sub>4-3</sub>	IC <sub>50</sub> (μM) 7.0 ± 0.8	104



Table 3 (Contd.)

Sr. no.	Parent compound	Biological target	Anti-virus	Reference
65		H9 cells	IC <sub>50</sub> (μM) 0.01	105

were used to investigate the interactions between compound **43** and DNA, which represented significant hypochromic and slight bathochromic shifts upon the addition of CT-DNA, suggesting that the transition of energy or electron occurred between the compounds and the base pairs of DNA. The results suggested that the **43**–DNA complexes were more stable with the aid of large *p*-conjugated systems formed by phenyl linked to 1,2,3-triazole moiety of **43**.<sup>82</sup>

The benzyl-1,2,3-triazolyl linked hesperetin derivatives were synthesized and examined to have anticancer as well as anti-oxidant activity. The anticancer activity was found against cancer cell lines such as HeLa, CaSki, and SK-OV-3. It was reported that compound **44a**, having an electron withdrawing substitution at the *ortho* and *para* positions on the phenyl ring, displays good activity against HeLa and compound **44b**, having a substitution at the *meta* position, increases its activity towards SK-OV-3, whereas in the case when molecule **44c** has an electron donating group, then its activity towards CaSki is very high.<sup>83</sup>

The linkage of 1,2,3-triazolyl moiety with salicylamides **45** leads to the design of the anticancer drug acting as an aurora kinase inhibitor. The binding of this inhibitor towards aurora kinase depends on the availability of –OH group on salicylamide, which is directly attached to 1,2,3-triazole. The inhibition activity towards aurora kinase may also be due to the presence of –CO<sub>2</sub>CH<sub>3</sub> group, wherein compound **45** interacts with Lys175, Glu194, and Gln190 through hydrogen bonding. The carbonyl group of the salicylamide scaffold acts as a hydrogen bonding acceptor and forms a hydrogen bond with the side chain N–H of Lys175, whereas the phenolic –OH of the salicylamide scaffold acts as a hydrogen bond donor and makes another hydrogen bond with the carboxylate of Glu194.<sup>84</sup>

The allogibberic acid derivatives of 1,2,3-triazole pharmacophore were found to have inhibition potential towards five cancer cell lines. From the results of the inhibition value, it was analysed that in the presence of an  $\alpha,\beta$ -unsaturated ketone moiety, compound **46** shows excellent inhibition potential against the cancer cell lines by arresting the S-phase of the cell cycle. Similarly, the phthalimide based 1,2,3-triazole derivatives attached to the substituted benzyl ring **47** were designed and examined for the inhibition activity against tyrosinase.<sup>85</sup>

The activity of this compound basically depends upon the atom substituted on the phenyl ring, *i.e.*, if an electron-donating atom is present, then it will decrease the activity of the

compound but if an electron-withdrawing atom is present on the phenyl ring, then it will give excellent inhibition activity against tyrosinase. Compound **47** was accommodated in the binding pocket of tyrosinase by hydrogen-bonding and  $\pi$ –H interactions. The oxygen atoms of the NO<sub>2</sub> group on the phenyl ring interacted *via* two strong hydrogen bonds with side chain N–Hs of Arg268 and phthalimide moiety involved in a  $\pi$ –H interaction with Val283.<sup>86</sup> Peruzzotti *et al.* developed N-[2-methyl-5(triazol-1-yl)phenyl]pyrimidin-2-amine derivatives through *in situ* click chemistry, which inhibit tyrosine kinase. This compound **48** displayed good inhibition activity against Abl kinase (IC<sub>50</sub> = 0.9 ± 0.1 μM).<sup>87</sup>

1,4-Naphthoquinone-1,2,3-triazole hybrids were synthesized and evaluated for their anticancer activity against three cancer cell lines including MCF-7 (human breast adenocarcinoma), HT-29 (human colorectal adenocarcinoma), and MOLT-4 (human acute lymphoblastic leukaemia) by MTT assay. Compound **49** with 4-trifluoromethyl-benzyl moiety possessed the highest cytotoxic activity (IC<sub>50</sub> = 6.8–10.4 μM) against all the three cancer cell lines, which were comparable to the activity of cisplatin (IC<sub>50</sub> = 2.4–19.1 μM) as the positive control. Flow cytometric analysis revealed that compound **49** arrested the cell cycle at the G0/G1 phase.<sup>88</sup>

Compound **50** consisting of three fluoro groups showed excellent anticancer activity against HepG2 cells with IC<sub>50</sub> value of 0.0267 μmol mL<sup>−1</sup>.<sup>89</sup> The formation of new organoplatinum complexes with triazole rings was examined for their cytotoxic effects on selected cancer (MG-63 and MDA-MB-231) and normal (HDF) cells, and the results were compared with that of cisplatin. The stats indicate that all the synthesised compounds were at least thrice times more toxic than cisplatin against MG-63, MDA-MB-231, and HDF cell lines, and the compound with highest toxicity was **51**.<sup>90</sup>

Notably, the additional potentially active compound **52** possessing 3-(tert-butoxycarbonylamino)phenyl-substituted triazole moiety not only exhibited obviously improved IC<sub>50</sub> values ranging from 0.7 to 1.2 μM against a panel of tested cancer cells but also showed very weak cytotoxicity on normal cells. Preliminary mechanistic studies indicated that compound **52** could induce apoptosis in MDA-MB-231 cells and was worth developing into a novel natural product-like anticancer agent by proper structural modification.<sup>91</sup> Another series of hybrid compounds was synthesized and



**Table 4** List of 1,2,3-triazolyl pharmacophore possessing anti-inflammatory activity as observed using IC<sub>50</sub> and K<sub>i</sub> ± SEM values

Sr. no.	Parent compound	Biological target	Anti-inflammatory activity	Reference
66		Dopamine D3 receptor	K <sub>i</sub> ± SEM (nM) 5.05 ± 0.141	106
67		<i>L. amazonensis</i>	IC <sub>50</sub> (μM) 7.4 ± 0.8	110
68		COX-2	IC <sub>50</sub> (μM) 0.12	74

tested against bacterial strains and cancer cell lines. Some of the benzoxepine-1,2,3-triazole hybrids **53** displayed excellent activity against *P. aeruginosa* strain in the 18 ± 0.3 zone of inhibition (diameter in mm) at 0.4 mg/50 μL. The activity of these drugs towards cancer cell lines HCT15 and NCI-H226 is notable owing to the presence of a –CH<sub>2</sub>–O– linkage between the triazole and heteroaryl moieties.<sup>92</sup>

In a unique reaction, for the creation of 1,2,3-triazole derivatives of nimesulide, compounds **54** were designed as potential inhibitors of PDE4B. One of the synthesized compounds was highly effective for PDE4B inhibitory properties with IC<sub>50</sub> value of 4.92 ± 0.53 μM. The docking studies revealed that the interaction of PDE4B with Gln443, His234, and His278 also had potent activity towards HCT-15 human colon cancer cells.<sup>93</sup> 1,2,3-Triazole linked nimesulide hybrids were studied against four cancer cell lines. The presence of –CH<sub>2</sub>O– moiety in the molecules proved to have better molecular interactions, as indicated by their activities against the cancer cell lines. Moreover, the docking studies of compound **55** indicated that the –NH group of the synthesized compounds formed H-bond with the ASP346 of PDE4B. The most probable reason for inhibitory properties against cancerous cell growth indicated by these compounds against various cancer cell lines could be due to their inhibition of PDE4B.<sup>94</sup> Furthermore, the 1,2,3-triazole derivatives of olanzapine **56** are capable of inhibiting PDE4B. The comparative results signify that the compounds having unsubstituted benzene ring attached with 1,2,3-triazole have better inhibition tendency as compared to mono-substituted benzene ring.<sup>95</sup> 2,2,4-Trimethyl-1,2-dihydroquinolinyl substituted 1,2,3-triazole derivatives **57** were developed and were

examined for their PDE4B inhibitor capacity as well as anti-cancer properties. The standard inhibition percentage of PDE4B at 30 μM is 58.2% and also has a notable value of IC<sub>50</sub> = 8.7 ± 0.24 towards the A549 cancer cell line.<sup>96</sup>

The collaborative effect of quinoline, triazole, and dihydroquinoline in a single pharmacophoric group has the capability of inhibiting PDE4B and some cancer cell lines. Compound **58** is the most active against these two different cancer cell lines A549 and MCF 7. The interactions of nitrogen of the quinoline ring participated in the H-bonding interaction with the Gln443 residue of PDE4B. Additionally, arene-cation and arene-arene interactions were observed with the His234 and Phe446 residue.<sup>97</sup> Quinoline, triazole, and oxime ether are coupled and converged into a single molecular entity **59**, and these molecules were screened for their inhibitory effects on the growth of four cancer cell lines and on the inhibition of PDE4B. Among all the molecules screened, the compound **59** is highly active against the A549 cancer cell line as compared to the standard drug doxorubicin. The study, supported by molecular docking, depicts that the nitrogen atom of both the quinoline rings formed hydrogen bonds with the conserved residues such as Gln443 of the Q pocket and His 234 of the metal binding pocket in the active site of PDE4B. The conserved π interaction with Phe446 was also observed commonly in all these compounds.<sup>98</sup>

## Anti-viral activity

1,2,3-Triazole linked dihydropyrimidinone hybrid molecules **60** were developed and evaluated for their antiviral activity against VZV, which is the causative agent for chickenpox.



**Table 5** List of 1,2,3-triazolyl pharmacophore molecules possessing anti-diabetic activity as observed using IC<sub>50</sub> values

Sr. no.	Parent compound	Biological target	Anti-diabetic	Reference
69		$\alpha$ -Glucosidase	IC <sub>50</sub> ( $\mu$ M) $0.8 \pm 0.01$	111
70		$\alpha$ -Glucosidase	IC <sub>50</sub> ( $\mu$ M) $181.0 \pm 1.4$	113
71		$\alpha$ -Glucosidase	IC <sub>50</sub> ( $\mu$ M) 2.06	114
72		HepG2	IC <sub>50</sub> ( $\mu$ g mL <sup>-1</sup> ) 72.19	115
73		$\alpha$ -Glucosidase	IC <sub>50</sub> ( $\mu$ M $\pm$ SEM) $72.71 \pm 1.09$	116

Many such compounds with such activities have been compiled in Table 3. It was observed that in the presence of *p*-nitro group on the benzyl ring, the activity of the molecule

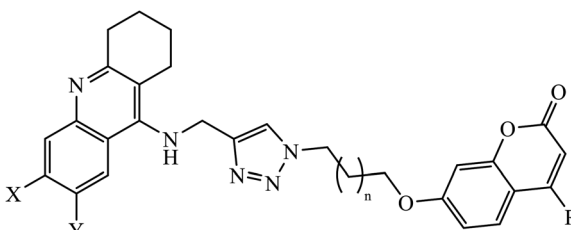
increases against the TK + VZV strain. Molecule **60** with *N,O*-triazole moiety is such that its activity is unaffected by the midline kinase resistance.<sup>10</sup>

**Table 6** List of some of the 1,2,3-triazole linked pharmacophore molecules possessing anti-Alzheimer's activity as observed using IC<sub>50</sub> values

Sr. no.	Parent compound	Biological target	IC <sub>50</sub> (μM)	Reference
74		BACE1	2.0	117
75		AChE BChE	2.000 ± 0.030 1.55 ± 0.012	119
76		Aβ <sub>42</sub> aggregation	8.065 ± 0.129	120
77		BACE1	2.2	121
78		Acetylcholinesterase	1.80	122



Table 6 (Contd.)

Sr. no.	Parent compound	Biological target	IC <sub>50</sub> (μM)	Reference
79		(a) AChEI	0.027 ± 0.009	123
		BChEI	0.104 ± 0.018	
		(b) AChEI	0.095 ± 0.014	
		BChEI	0.006 ± 0.002	
		(a) n = 1, R = Me, X = Cl, Y = H		
		(b) n = 3, R = H, X = H, Y = H		

The activity of 1,2,3-triazolyl compounds to act as peptide surrogates, which is used as anti-HIV agent, is largely prominent. Compound **61** has very high activity against wild type and mutant HIV-1 proteases. Interestingly, the crystallographic studies indicate that the position of this inhibitor is similar to that of amprenavir and 1,2,3-triazole is a suitable mock of the peptide group. The comparative study proved that the 1,2,3-triazole is an effective replacement for a peptide group in the HIV-1 protease inhibitors, thus leading to high activity.<sup>99–101</sup> Further, these triazolyl compounds **62** too have the potential to act as anti-HIV-1 protease inhibitor, with high activity of this compound against wild type protease [(IC<sub>50</sub>) 6.0 nm]. Its high activity is due to interaction with selected residues and maintenance of hydrogen bonding to main chain atoms.<sup>102</sup>

Tian *et al.* created a library of diarylnicotinamide 1,4-disubstituted 1,2,3-triazoles, which work as good anti-HIV1 agents with activity against wild type HIV-1 and mutant HIV-1 strains in MT-4 cells. The activity of these compounds was tested against many strains including IIB, K103N + Y181C, L100I, K103N, E138K, Y181C, Y188L, and F227L + V106A. The results indicate that the presence of nitro and cyano group at the 3<sup>rd</sup> position on benzyl ring **63** increases the activity of the compound against HIV-1, as shown in the molecule.<sup>103</sup>

Phenylalanine derivatives that were also synthesized *via* click chemistry exhibit excellent anti-HIV activity. Compound **64** has very high activity against HIV-1 NL4-3 strain with much lesser toxicity because of the presence of β-substituted naphthalene, which is directly bound to triazole. The results conclude that compound **64** potentially has two different binding modes with the HIV-1 CA monomer, which has implications for the precise manner of CA protein inhibition in each of the discrete stages of replication.<sup>104</sup> Furthermore, 1,2,3-triazoles along with amide bioisosteres were also found to be anti-HIV against H9 cells. The activity of these compounds depends upon the different substituent attached to the benzyl ring. Compound **65** has particularly high activity against the H9 cell line because of the presence of methoxy and nitro groups on two different benzyl rings.<sup>105</sup>

## Anti-inflammatory activity

The 1,2,3-triazole conjoined compound of 4-phenylpiperazine produces the target molecule **66** bearing 2,3-dichlorophenyl-containing indolyltriazole group having strong dopamine D3 receptor activity.<sup>106–109</sup> Eugenol derivatives bearing 1,2,3-triazole functionalities were used to cure *L. amazonensis* disease. Compound **67** demonstrates the best activity among the series of derivatives of triazoles synthesized with lower toxicity as compared to the standard drugs pentamidine and glucantime, which is currently used in the treatment of leishmaniasis.<sup>110</sup>

Two novel series of 1,2,3-triazole tethered to indole-3-glyoxamide derivative were evaluated for their inhibition as anti-inflammatory agents. The activity of compound **68** depends on the nature and position of the substituent on the benzene ring, *i.e.*, the substitution at the *para* position of the phenyl ring gives good anti-inflammatory activity whereas the *p*-ethyl substituent on the aromatic ring exhibits very high anti-inflammatory activity,<sup>74</sup> and are compiled in Table 4.

## Anti-diabetic activity

Iqbal *et al.* synthesized new carbazole linked 1,2,3-triazole that acts as an inhibitor against α-glucosidase. The results indicate that most of these compounds show better inhibition activity against α-glucosidase as compared to the standard drug acarbose, whereas some of them do not show activity due to the presence of methyl group. In fact, compound **69** is highly active due to the presence of the N-hetero atom in the pyridine ring.<sup>111,112</sup>

The quinazolinone based 1,2,3-triazole acts as an anti-diabetic agent with inhibition activity against α-glucosidase. The synthesized compounds show excellent activity as compared to the standard drug that is acarbose, as shown in Table 5. One of the compounds having 4-bromobenzyl **70** represents the highest activity due to hooking of bromine at *ortho* position on benzyl group. It was observed that upon replacement of bromine with fluorine or chlorine group, the activity of the compound decreases drastically. The activity of





compound **70** was due to the interaction with His279, Pro309, Arg312, Val305, and Val316 residues. The quinazolinone moiety interacted *via* hydrogen bonding and  $\pi$ - $\pi$  interaction with His279. The phenyl-ethyl group and the sulphur of compound **70** interacted with Arg312 and a hydrophobic interaction between Pro309 and the 1,2,3-triazole ring was observed. Moreover, the 4-bromobenzyl group also interacted with Val305 and Val316 through the 4-bromo substituent and hydrophobic interaction with Pro309 through the phenyl ring.<sup>113</sup>

Xanthone-triazole derivatives were investigated for their  $\alpha$ -glucosidase inhibitory activities and compound **71** was observed to have the highest inhibition activity, with  $IC_{50}$  value of 2.06  $\mu$ M. The interactions between compound **71** and the allosteric sites of the enzyme were studied by molecular docking, which reveal that the increase in the activities is an outcome of hydrogen bonding and  $\pi$ - $\pi$  or  $\pi$ -cation interaction of the aromatic ring substituted triazole moiety with the enzyme. In addition, molecule **71** promotes glucose uptake.<sup>114</sup>

Berberine derivatives were designed and evaluated for their activity against HepG2 cell lines. It was observed that compound **72** mannose (berberine derivative) produces the best activity with an  $IC_{50}$  ( $\mu$ g  $mL^{-1}$ ) value of 72.19, which is approximately 1.5-fold of that of berberine and mannose.<sup>115</sup>

1,4-Dihydropyridine derivatives, upon synthesis, were evaluated for their anti-diabetic activity. The study with 11-beta hydroxysteroid dehydrogenase-1 proves that molecule **73** adopts L-shaped conformation while binding to 11 $\beta$ -HSD1. This was a result of the development of CH- $\pi$  interaction with the Phe-

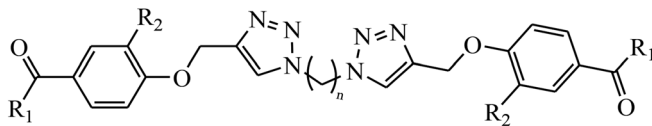
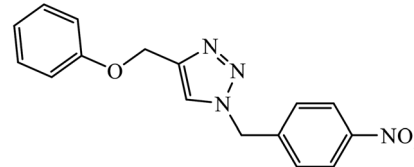
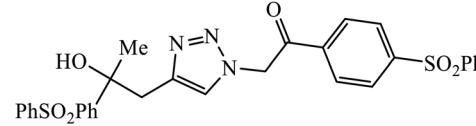
300 residue. Also, compound **73** developed anion- $\pi$  interactions with Glu-276 and Asp-349 residues.<sup>116</sup>

## Anti-Alzheimer activity

1,2,3-Triazole-linked reduced amide isosteres were analysed for their anti-Alzheimer BACE1 inhibitor activity, as given in Table 6. Some of these amide isosteres were found to have very high activity, as measured by their  $IC_{50}$  values. Compounds **74** have large activities as BACE1 inhibitors.<sup>117,118</sup> Another class of novel tacrine-1,2,3-triazole hybrids acted as cholinesterase inhibitors as most of these compounds exhibit good inhibition activities towards acetyl cholinesterase (AChE) and butyrylcholinesterase (BChE). Compound **75** with methoxy group has very high activity against AChE and if this methoxy group is replaced by methyl, fluorine, chlorine, and hydrogen, then the activity decreases against AChE; unsubstituted acridine displayed the maximum activity against BChE.<sup>119</sup>

Triazole-based compounds were evaluated as multi-target-directed ligands against Alzheimer's disease that included A $\beta$  aggregation, metal-induced A $\beta$  aggregation, metal dys-homeostasis, and oxidative stress. The synthetic compounds **76** have *o*-CF<sub>3</sub> group on the phenyl ring with the most potent inhibitory activity (96.89% inhibition,  $IC_{50} = 8.065 \pm 0.129 \mu$ M) against A $\beta_{42}$  aggregation, compared to the reference compound curcumin (95.14% inhibition,  $IC_{50} = 6.385 \pm 0.009 \mu$ M). The formation of amyloid fibrils was significantly reduced in the presence of drug **76**, which highlights the inhibition of A $\beta_{42}$

**Table 7** List of 1,2,3-triazole linked pharmacophore molecules possessing potent anti-oxidant activity

Sr. no.	Parent compound	Biological target	$IC_{50}$ ( $\mu$ M)	Reference
		(a) AChE (b) DPPH (c) SOD	50.80 ( $\pm 1.01$ ) 113.63 ( $\pm 0.05$ ) 45.12 ( $\pm 0.04$ )	
80	<p>(a) <math>R_1=CH_3</math>, <math>R_2=H</math>, <math>n=10</math></p> <p>(b) <math>R_1=CH_3</math>, <math>R_2=OCH_3</math>, <math>n=4</math></p> <p>(c) <math>R_1=CH_3</math>, <math>R_2=H</math>, <math>n=3</math></p>			124
81		DPPH	10.1	125
82		DPPH	20	126



aggregation. In addition, molecular docking studies highlighted that molecule **76** binds preferably to the C-terminus region of A $\beta$ 42 by hydrogen bonds and hydrophobic contacts.<sup>120</sup>

Multifunctional iminochromene-2*H*-carboxamide derivatives containing different aminomethylene triazole having potential of BACE1 inhibition, and neuroprotective and metal chelating properties that target Alzheimer's disease. Derivative **77** was found to have IC<sub>50</sub> value of 2.2  $\mu$ M against BACE1 and was supported by the molecular docking studies, with two residues of the binding site Asp32 and Asp228 being involved in the hydrogen bonding interactions with the amino methylene triazole linker and amide linker, respectively. The additional hydrogen bonding interaction with Gly230 as the second important amino acid was observed through the amide linker.  $\pi$ - $\pi$  stacking interaction was also observed in between Tyr71 and the bromophenyl ring. The phthalimide moiety establishes favourable  $\pi$ - $\pi$  stacking interaction with the side chain of Thr76.<sup>121</sup>

1,2,3-Triazole supported chromenone carboxamides were evaluated for their cholinesterase inhibitory activity, with compound **78** being the best for acetylcholinesterase inhibitory activity (IC<sub>50</sub> = 1.80  $\mu$ M) in comparison to donepezil as the reference drug (IC<sub>50</sub> = 0.027  $\mu$ M).<sup>122</sup> The tacrine-coumarin structured hybrids linked to 1,2,3-triazole proved to be potential dual binding sites of cholinesterase inhibitors (ChEIs) for the treatment of Alzheimer's disease. Among all these, compound **79a** was the most potent anti-AChE derivative (IC<sub>50</sub> = 27 nM) and compound **79b** displayed the best anti-BChE activity (IC<sub>50</sub> = 6 nM), which is much more active than tacrine and donepezil as the reference drugs.<sup>123</sup>

## Anti-oxidant property

The symmetrically 1,4-disubstituted 1,2,3-bis-triazole derivatives were examined to possess anti-oxidant (AChE inhibition, DPPH, and SOD) activity. This property is based upon the number of carbon atoms present in the chain, which combines with the two 1,2,3-triazole moieties. Compounds **80a**, **80b**, and **80c** show excellent activity against AChE, DPPH, and SOD.<sup>124</sup> Another class of compounds with similar disubstituted derivatives displayed good antioxidant activity against DPPH as compared to the standard drug ascorbic acid. Compound **81** is the most active due to the presence of NO<sub>2</sub> group in the compound.<sup>125</sup> The diaryl sulfone moiety coupled triazoles were designed and evaluated for their potential as anti-oxidants. Molecule **82** was the strongest radical scavenger owing to the presence of diaryl sulfone moiety, which increased its anti-oxidant activity,<sup>126</sup> as provided in Table 7.

## Conclusion and challenges

Click chemistry has been developed as an effective technique for the synthesis of 1,2,3-triazoles that have the potential to act as anti-microbial, anti-cancer, anti-viral, anti-inflammatory, anti-diabetic, anti-Alzheimer, and anti-oxidant drugs. In most of the synthesized compounds, the presence of electron withdrawing groups increases the activity whereas the presence of

electron donating group shows the reverse affect. The generation of low-cost compounds with high purity can significantly boost the pharmaceutical and medicinal chemistry efforts towards new drug discovery and development. The detailed pharmacological and pharmacokinetic studies of 1,2,3-triazolyl compounds still appeared to be an under-explored area. The efforts towards these directions may enhance the value and significance of 1,2,3-triazolyl compounds in various drug discovery programs.

## Conflicts of interest

There are no conflicts to declare.

## List of abbreviations

5LOX	5-Lipoxygenase
<i>A. brasiliensis</i>	<i>Aspergillus brasiliensis</i>
<i>A. niger</i>	<i>Aspergillus niger</i>
A549	Adenocarcinomic human alveolar basal epithelial cells
AChE	Acetylcholinesterase
<i>B. subtilis</i>	<i>Bacillus subtilis</i>
<i>B. cereus</i>	<i>Bacillus cereus</i>
B16-F10	Mouse melanoma cell line
BACE1	$\beta$ -site APP-cleaving enzyme 1
BChE	Butyrylcholinesterase
BEZ-235	Dactolisib
<i>C. albicans</i>	<i>Candida albicans</i>
C6	Rat glioma cell lines
CaSki	Cervical cancer cell line
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
DPPH	2,2-Diphenyl-1-picrylhydrazyl
DU-145	Human prostate cancer cell line
<i>E. coli</i>	<i>Escherichia coli</i>
<i>E. faecalis</i>	<i>Enterococcus faecalis</i>
EC-109	Human esophageal cancer cell line
<i>F. graminearum</i>	<i>Fusarium graminearum</i>
<i>F. oxysporum</i>	<i>Fusarium oxysporum</i>
<i>F. recini</i>	<i>Fusarium recini</i>
GBM	Glioblastoma multiforme
GGDPS	Geranylgeranyl diphosphate synthase
GTL-16	Human gastric carcinoma cell line
H9	Non-permissive
HBL-100	Breast cancer cell line
HCT-116	Human colon tumor cell line 116
HCT-15	Colon cancer cell line
HeLa	Henrietta Lacks (cervical cancer cell line)
Hep 3B cells	Hepatocellular carcinoma cells
Hep-G2	Hepatocellular carcinoma
HGF	Hepatocyte growth factor
HIV	Human immunodeficiency virus
HL-60	Human leukemia cell line 60 (myeloid leukemia)
HT-29	Human colorectal cancer cells



K.	<i>Klebsiella pneumoniae</i>
<i>pneumoniae</i>	
L.	<i>Leishmania amazonensis</i>
<i>amazonensis</i>	
L. donovani	<i>Leishmania donovani</i>
M.	<i>Moraxella catarrhalis</i>
<i>catarrhalis</i>	
MCF-7	Michigan cancer foundation-7 cell line (breast cancer)
MDA-MB 231	M. D. Anderson-metastasis breast cancer
MDCK	Madin-Darby canine kidney
MDR	Multi-drug resistant
MGC-803	Human gastric cancer cell line
MIC	Minimum inhibitory concentrations
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
NCI-H226	Lung cancer cell line
<i>P. aeruginosa</i>	<i>Pseudomonas aeruginosa</i>
<i>P. falciparum</i>	<i>Plasmodium falciparum</i>
<i>P. putida</i>	<i>Pseudomonas putida</i>
<i>P. vulgaris</i>	<i>Proteus vulgaris</i>
PC-3	Human prostate cancer cell line
PDE4B	Phosphodiesterase 4B
<i>S. aureus</i>	<i>Staphylococcus aureus</i>
<i>S. dysenteriae</i>	<i>Shigella dysenteriae</i>
<i>S. epidermidis</i>	<i>Staphylococcus epidermidis</i>
<i>S. epidermidis</i>	<i>Staphylococcus epidermidis</i>
<i>S. typhi</i>	<i>Salmonella typhi</i>
<i>S. pyogenus</i>	<i>Staphylococcus pyogenus</i>
SK-OV-3	Ovarian cancer cell line
SMMC-7721	Human liver carcinoma
SOD	Superoxide dismutase
SW480	Human colon carcinoma
TB	Tuberculosis
TK	Thymidine kinase
U87	Human glioma cell lines
VZV	Varicella-zoster virus

## References

- 1 M. R. El Syed Aly, H. A. Saad and M. A. M. Mohamed, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 2824–2830.
- 2 D. Dheer, V. Singh and R. Shankar, *Bioorg. Chem.*, 2017, **71**, 30–54.
- 3 P. Thirumurugan, D. Matosiuk and K. Jozwiak, *Chem. Rev.*, 2013, 4905–4979.
- 4 H. C. Kolb and K. B. Sharpless, *Drug Discovery Today*, 2003, **8**, 1128–1137.
- 5 H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004–2021.
- 6 P. Appukkuttan, W. Dehaen, V. V. Fokin and E. Van Der Eycken, *Org. Lett.*, 2004, **6**, 4223–4225.
- 7 G. Schneider, *Nat. Rev. Drug Discovery*, 2018, **17**, 97–113.
- 8 S. K. Avula, A. Khan, N. U. Rehman, M. U. Anwar, Z. Al-abri, A. Wadood, M. Riaz, R. Csuk and A. Al-harrasi, *Bioorg. Chem.*, 2018, **81**, 98–106.
- 9 G. Wang, Z. Peng, J. Wang, J. Li and X. Li, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 5719–5723.
- 10 H. Kaoukabi, Y. Kabri, C. Curti, M. Taourirte, J. C. Rodriguez-Ubis, R. Snoeck, G. Andrei, P. Vanelle and H. B. Lazrek, *Eur. J. Med. Chem.*, 2018, **155**, 772–781.
- 11 E. Bonandi, M. S. Christodoulou, G. Fumagalli, D. Perdicchia, G. Rastelli and D. Passarella, *Drug Discovery Today*, 2017, **22**, 1572–1581.
- 12 P. V. Babu, S. Mukherjee, D. R. Gorja, S. Yellanki, R. Mediseti, P. Kulkarni, K. Mukkanti and M. Pal, *RSC Adv.*, 2014, **4**, 4878–4882.
- 13 S. Zhang, Z. Xu, C. Gao, Q. C. Ren, L. Chang, Z. S. Lv and L. S. Feng, *Eur. J. Med. Chem.*, 2017, **138**, 501–513.
- 14 K. D. Thomas, A. V. Adhikari and N. S. Shetty, *Eur. J. Med. Chem.*, 2010, **45**, 3803–3810.
- 15 D. Ashok, P. Chiranjeevi, A. V. Kumar, M. Sarasija, V. S. Krishna, D. Sriram and S. Balasubramanian, *RSC Adv.*, 2018, **8**, 16997–17007.
- 16 D. Li, T. Mao, J. Huang and Q. Zhu, *Chem. Commun.*, 2017, **53**, 1305–1308.
- 17 A. Dongamanti, V. K. Aamate, M. G. Devulapally, S. Gundu, M. K. Kotni, V. Manga, S. Balasubramanian and P. Ernala, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 898–903.
- 18 K. Lal, P. Yadav, A. Kumar, A. Kumar and A. K. Paul, *Bioorg. Chem.*, 2018, **77**, 236–244.
- 19 J. H. Cheng, C. F. Hung, S. C. Yang, J. P. Wang, S. J. Won and C. N. Lin, *Bioorg. Med. Chem.*, 2008, **16**, 7270–7276.
- 20 N. R. Emmadi, C. Bingi, S. S. Kotapalli, R. Ummanni, J. B. Nanubolu and K. Atmakur, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 2918–2922.
- 21 P. Yadav, K. Lal, L. Kumar, A. Kumar, A. Kumar, A. K. Paul and R. Kumar, *Eur. J. Med. Chem.*, 2018, **155**, 263–274.
- 22 S. Srivastava, D. Bimal, K. Bohra, B. Singh, P. Ponnann, R. Jain, M. Varma-Basil, J. Maity, M. Thirumal and A. K. Prasad, *Eur. J. Med. Chem.*, 2018, **150**, 268–281.
- 23 W. Zhang, Z. Li, M. Zhou, F. Wu, X. Hou, H. Luo, H. Liu, X. Han, G. Yan, Z. Ding and R. Li, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 799–807.
- 24 G. Singh, J. Singh, A. Singh, J. Singh, M. Kumar, K. Gupta and S. Chhibber, *J. Organomet. Chem.*, 2018, **871**, 21–27.
- 25 R. Sakly, H. Edziri, M. Askri, M. Knorr, C. Strohmman and M. Mastouri, *C. R. Chim.*, 2018, **21**, 41–53.
- 26 B. Negi, D. Kumar, W. Kumbukgolla, S. Jayaweera, P. Ponnann, R. Singh, S. Agarwal and D. S. Rawat, *Eur. J. Med. Chem.*, 2016, **115**, 426e–437.
- 27 S. Maračić, T. G. Kraljević, H. Č. Paljetak, M. Perić, M. Matijašić, D. Verbanac, M. Cetina and S. Raić-Malić, *Bioorg. Med. Chem.*, 2015, **23**, 7448–7463.
- 28 C. Gill, G. Jadhav, M. Shaikh, R. Kale, A. Ghawalkar, D. Nagargoje and M. Shiradkar, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 6244–6247.
- 29 K. K. Angajala, S. Vianala, R. Macha, M. Raghavender, M. K. Thupurani and P. J. Pathi, *Springerplus*, 2016, **5**, 423.
- 30 N. Dubey, M. C. Sharma, A. Kumar and P. Sharma, *Med. Chem. Res.*, 2015, **24**, 2717–2731.



- 31 K. Shiva Raju, S. AnkiReddy, G. Sabitha, V. Siva Krishna, D. Sriram, K. Bharathi Reddy and S. Rao Sagurthi, *Bioorg. Med. Chem. Lett.*, 2019, **29**, 284–290.
- 32 P. V. B. Reddy, V. Kamala Prasad, G. Manjunath and P. Venkata Ramana, *Ann. Pharm. Fr.*, 2016, **74**, 350–357.
- 33 A. H. Kategaonkar, P. V. Shinde, A. H. Kategaonkar, S. K. Pasale, B. B. Shingate and M. S. Shingare, *Eur. J. Med. Chem.*, 2010, **45**, 3142–3146.
- 34 M. Muthukrishnan, M. Mujahid, P. Yogeewari and D. Sriram, *Tetrahedron Lett.*, 2011, **52**, 2387–2389.
- 35 S. Gatadi, J. Gour, M. Shukla, G. Kaul, S. Das, A. Dasgupta, S. Malasala, R. S. Borra, Y. V. Madhavi, S. Chopra and S. Nanduri, *Eur. J. Med. Chem.*, 2018, **157**, 1056–1067.
- 36 I. E. Głowacka, P. Grzonkowski, P. Lisiecki, Ł. Kalinowski and D. G. Piotrowska, *Arch. Pharm.*, 2019, **352**, 1–14.
- 37 X. L. Wang, K. Wan and C. H. Zhou, *Eur. J. Med. Chem.*, 2010, **45**, 4631–4639.
- 38 G. R. Pereira, G. C. Brandão, L. M. Arantes, H. A. De Oliveira, R. C. De Paula, M. F. A. Do Nascimento, F. M. Dos Santos, R. K. Da Rocha, J. C. D. Lopes and A. B. De Oliveira, *Eur. J. Med. Chem.*, 2014, **73**, 295–309.
- 39 B. Garudachari, A. M. Isloor, M. N. Satyanarayana, H. K. Fun and G. Hegde, *Eur. J. Med. Chem.*, 2014, **74**, 324–332.
- 40 E. O. J. Porta, P. B. Carvalho, M. A. Avery, B. L. Tekwani and G. R. Labadie, *Steroids*, 2014, **79**, 28–36.
- 41 P. Khedar, K. Pericherla, R. P. Singh, P. N. Jha and A. Kumar, *Med. Chem. Res.*, 2015, **24**, 3117–3126.
- 42 A. Anand, R. J. Naik, H. M. Revankar, M. V. Kulkarni, S. R. Dixit and S. D. Joshi, *Eur. J. Med. Chem.*, 2015, **105**, 194–207.
- 43 D. Kumar, Beena, G. Khare, S. Kidwai, A. K. Tyagi, R. Singh and D. S. Rawat, *Eur. J. Med. Chem.*, 2014, **81**, 301–313.
- 44 Y. Shi and C. H. Zhou, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 956–960.
- 45 A. A. M. Alkhalidi, M. A. Abdelgawad, B. G. M. Youssif, A. O. El-Gendy and H. P. De Koning, *Trop. J. Pharm. Res.*, 2019, **18**, 1101–1108.
- 46 N. Marepu, S. Yeturu and M. Pal, *Bioorg. Med. Chem. Lett.*, 2018, **28**, 3302–3306.
- 47 P. López-Rojas, M. Janeczko, K. Kubiński, Á. Amesty, M. Maslyk and A. Estévez-Braun, *Molecules*, 2018, **23**, 1–18.
- 48 P. Neeraja, S. Srinivas, K. Mukkanti, P. K. Dubey and S. Pal, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 5212–5217.
- 49 J. Mareddy, K. S. S. Praveena, N. Suresh, A. Jayashree, S. Roy, D. Rambabu, N. Y. S. Murthy and S. Pal, *Lett. Drug Des. Discovery*, 2013, **10**, 343–352.
- 50 N. Kuntala, J. R. Telu, V. Banothu, S. Balasubramanian, J. S. Anireddy and S. Pal, *Mini-Rev. Med. Chem.*, 2018, **18**, 803–809.
- 51 E. M. De Souza-fagundes, J. Delp, P. D. M. Prazeres, B. Marques, A. Maria, L. Carmo, P. Henrique, F. Stroppa, N. Glanzmann, J. Kisitu, D. Szamosvári, T. Böttcher, M. Leist and A. David, *Chem.-Biol. Interact.*, 2018, **291**, 253–263.
- 52 M. Allam, A. K. D. Bhavani, A. Mudiraj, N. Ranjan, M. Thippaana and P. P. Babu, *Eur. J. Med. Chem.*, 2018, **156**, 43–52.
- 53 M. M. Kandeel, L. W. Mohamed, M. K. Abd El Hamid and A. T. Negmeldin, *Sci. Pharm.*, 2012, **80**, 531–545.
- 54 B. D. Manning, *Sci. Signal.*, 2009, **2**, 1–3.
- 55 B. S. Holla, M. Mahalinga, M. S. Karthikeyan, P. M. Akberali and N. S. Shetty, *Bioorg. Med. Chem.*, 2006, **14**, 2040–2047.
- 56 F. Colombo, C. Tintori, A. Furlan, S. Borrelli, M. S. Christodoulou, R. Dono, F. Maina, M. Botta, M. Amat, J. Bosch and D. Passarella, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 4693–4696.
- 57 F. Arioli, S. Borrelli, F. Colombo, F. Falchi, I. Filippi, E. Crespan, A. Naldini, G. Scalia, A. Silvani, G. Maga, F. Carraro, M. Botta and D. Passarella, *ChemMedChem*, 2011, **6**, 2009–2018.
- 58 S. G. Agalave, S. R. Maujan and V. S. Pore, *Chem.-Asian J.*, 2011, **6**, 2696–2718.
- 59 E. D. Chrysina, É. Bokor, K. M. Alexacou, M. D. Charavgi, G. N. Oikonomakos, S. E. Zographos, D. D. Leonidas, N. G. Oikonomakos and L. Somsák, *Tetrahedron: Asymmetry*, 2009, **20**, 733–740.
- 60 V. S. Wills, J. I. Metzger, C. Allen, M. L. Varney, D. F. Wiemer and S. A. Holstein, *Bioorg. Med. Chem.*, 2017, **25**, 2437–2444.
- 61 R. K. Thatipamula, S. Narsimha, K. Battula, V. Rajendra Chary, E. Mamidala and N. Vasudeva Reddy, *J. Saudi Chem. Soc.*, 2017, **21**, 795–802.
- 62 C. L. Su, C. L. Tseng, C. Ramesh, H. S. Liu, C. Y. F. Huang and C. F. Yao, *Eur. J. Med. Chem.*, 2017, **132**, 90–107.
- 63 K. Oh and Z. Guan, *Chem. Commun.*, 2006, 3069–3071.
- 64 J. H. Van Maarseveen, W. S. Horne and M. R. Ghadiri, *Org. Lett.*, 2005, **7**, 4503–4506.
- 65 M. Whiting, J. Muldoon, Y. C. Lin, S. M. Silverman, W. Lindstrom, A. J. Olson, H. C. Kolb, M. G. Finn, K. B. Sharpless, J. H. Elder and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2006, **45**, 1435–1439.
- 66 Ahsanullah, P. Schmieder, R. Kühne and J. Rademann, *Angew. Chem., Int. Ed.*, 2009, **48**, 5042–5045.
- 67 I. B. Sayeed, M. V. P. S. Vishnuvardhan, A. Nagarajan, S. Kantevari and A. Kamal, *Bioorg. Chem.*, 2018, **80**, 714–720.
- 68 S. Panaka, R. Trivedi, K. Jaipal, L. Giribabu, P. Sujitha, C. G. Kumar and B. Sridhar, *J. Organomet. Chem.*, 2016, **813**, 125–130.
- 69 S. Ferreira, A. C. R. Soderro, M. F. C. Cardoso, E. S. Lima, C. R. Kaiser, F. P. Silva and V. F. Ferreira, *J. Med. Chem.*, 2010, **53**, 2364–2375.
- 70 D. J. Lee, K. Mandal, P. W. R. Harris, M. A. Brimble and S. B. H. Kent, *Org. Lett.*, 2009, **11**, 5270–5273.
- 71 B. J. Pages, J. Sakoff, J. Gilbert, Y. Zhang, F. Li, D. Preston, J. D. Crowley and J. R. Aldrich-Wright, *J. Inorg. Biochem.*, 2016, **165**, 92–99.
- 72 R. Huang, G. Langille, R. K. Gill, C. M. J. Li, Y. Mikata, M. Q. Wong, D. T. Yapp and T. Storr, *J. Biol. Inorg. Chem.*, 2013, **18**, 831–844.
- 73 H. C. Bertrand, S. Clède, R. Guillot, F. Lambert and C. Policar, *Inorg. Chem.*, 2014, **53**, 6204–6223.
- 74 F. Naaz, M. C. Preeti Pallavi, S. Shafi, N. Mulakayala, M. S. Yar and H. M. S. Kumar, *Bioorg. Chem.*, 2018, **81**, 1–20.
- 75 Masood-ur-Rahman, Y. Mohammad, K. M. Fazili, K. A. Bhat and T. Ara, *Steroids*, 2017, **118**, 1–8.





- 76 L. Y. Ma, B. Wang, L. P. Pang, M. Zhang, S. Q. Wang, Y. C. Zheng, K. P. Shao, D. Q. Xue and H. M. Liu, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 1124–1128.
- 77 S. R. Patpi, L. Pulipati, P. Yogeewari, D. Sriram, N. Jain, B. Sridhar, R. Murthy, T. Anjana Devi, S. V. Kalivendi and S. Kantevari, *J. Med. Chem.*, 2012, **55**, 3911–3922.
- 78 Y. C. Duan, Y. C. Zheng, X. C. Li, M. M. Wang, X. W. Ye, Y. Y. Guan, G. Z. Liu, J. X. Zheng and H. M. Liu, *Eur. J. Med. Chem.*, 2013, **64**, 99–110.
- 79 V. D. da Silva, B. M. de Faria, E. Colombo, L. Ascari, G. P. A. Freitas, L. S. Flores, Y. Cordeiro, L. Romão and C. D. Buarque, *Bioorg. Chem.*, 2019, **83**, 87–97.
- 80 Y. C. Duan, Y. C. Ma, E. Zhang, X. J. Shi, M. M. Wang, X. W. Ye and H. M. Liu, *Eur. J. Med. Chem.*, 2013, **62**, 11–19.
- 81 T. Gregorić, M. Sedić, P. Grbčić, A. Tomljenović Paravić, S. Kraljević Pavelić, M. Cetina, R. Vianello and S. Raić-Malić, *Eur. J. Med. Chem.*, 2017, **125**, 1247–1267.
- 82 X. Li, Y. Lin, Y. Yuan, K. Liu and X. Qian, *Tetrahedron*, 2011, **67**, 2299–2304.
- 83 B. Mistry, R. V. Patel and Y. S. Keum, *Arabian J. Chem.*, 2017, **10**, 157–166.
- 84 D. Song, Y. Park, J. Yoon, W. Aman, J. M. Hah and J. S. Ryu, *Bioorg. Med. Chem.*, 2014, **22**, 4855–4866.
- 85 M. J. Wu, D. M. Wu, J. B. Chen, J. F. Zhao, L. Gong, Y. X. Gong, Y. Li, X. D. Yang and H. Zhang, *Bioorg. Med. Chem. Lett.*, 2018, **28**, 2543–2549.
- 86 M. B. Tehrani, P. Emani, Z. Rezaei, M. Khoshneviszadeh, M. Ebrahimi, N. Edraki, M. Mahdavi, B. Larijani, S. Ranjbar, A. Foroumadi and M. Khoshneviszadeh, *J. Mol. Struct.*, 2019, **1176**, 86–93.
- 87 C. Peruzzotti, S. Borrelli, M. Ventura, R. Pantano, G. Fumagalli, M. S. Christodoulou, D. Monticelli, M. Luzzani, A. L. Fallacara, C. Tintori, M. Botta and D. Passarella, *ACS Med. Chem. Lett.*, 2013, **4**, 274–277.
- 88 M. Gholampour, S. Ranjbar, N. Edraki, M. Mohabbati, O. Firuzi and M. Khoshneviszadeh, *Bioorg. Chem.*, 2019, **88**, 102967.
- 89 J. Han, J. X. Ran, X. P. Chen, Z. H. Wang and F. H. Wu, *Tetrahedron*, 2018, **74**, 6985–6992.
- 90 K. Singh, A. Gangrade, A. Jana, B. B. Mandal and N. Das, *ACS Omega*, 2019, **4**, 835–841.
- 91 W. Hou, Z. Luo, G. Zhang, D. Cao, D. Li, H. Ruan, B. H. Ruan, L. Su and H. Xu, *Eur. J. Med. Chem.*, 2017, **138**, 1042–1052.
- 92 N. Kuntala, J. R. Telu, V. Banothu, N. S. Babu, J. S. Anireddy and S. Pal, *Med. Chem. Commun.*, 2015, **6**, 1612–1619.
- 93 J. Mareddy, S. B. Nallapati, J. Anireddy, Y. P. Devi, L. N. Mangamoori, R. Kapavarapu and S. Pal, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 6721–6727.
- 94 J. Mareddy, N. Suresh, C. G. Kumar, R. Kapavarapu, A. Jayasree and S. Pal, *Bioorg. Med. Chem. Lett.*, 2017, **27**, 518–523.
- 95 S. B. Nallapati, B. Y. Sreenivas, R. Bankala, K. V. L. Parsa, S. Srielly, K. Mukkanti and M. Pal, *RSC Adv.*, 2015, **5**, 94623–94628.
- 96 K. S. S. Praveena, S. Durgadas, N. Suresh Babu, S. Akkenapally, C. Ganesh Kumar, G. S. Deora, N. Y. S. Murthy, K. Mukkanti and S. Pal, *Bioorg. Chem.*, 2014, **53**, 8–14.
- 97 K. S. S. Praveena, E. V. V. Shivaji Ramarao, N. Y. S. Murthy, S. Akkenapally, C. Ganesh Kumar, R. Kapavarapu and S. Pal, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 1057–1063.
- 98 K. S. S. Praveena, E. V. V. S. Ramarao, Y. Poornachandra, C. G. Kumar, N. S. Babu, N. Y. S. Murthy and S. Pal, *Lett. Drug Des. Discovery*, 2016, **13**, 210–219.
- 99 A. Brik, J. Alexandratos, Y. C. Lin, J. H. Elder, A. J. Olson, A. Wlodawer, D. S. Goodsell and C. H. Wong, *ChemBioChem*, 2005, **6**, 1167–1169.
- 100 A. Brik, J. Muldoon, Y. C. Lin, J. H. Elder, D. S. Goodsell, A. J. Olson, V. V. Fokin, K. B. Sharpless and C. H. Wong, *ChemBioChem*, 2003, **4**, 1246–1248.
- 101 W. S. Horne, M. K. Yadav, C. D. Stout and M. R. Ghadiri, *J. Am. Chem. Soc.*, 2004, **126**, 15366–15367.
- 102 M. J. Giffin, H. Heaslet, A. Brik, Y. Lin, G. Cauvi, D. E. Mcree, J. H. Elder, C. D. Stout and B. E. Torbett, *J. Med. Chem.*, 2008, 6263–6270.
- 103 Y. Tian, Z. Liu, J. Liu, B. Huang, D. Kang, H. Zhang, E. De Clercq, D. Daelemans, C. Pannecouque, K. H. Lee, C. H. Chen, P. Zhan and X. Liu, *Eur. J. Med. Chem.*, 2018, **151**, 339–350.
- 104 G. Wu, W. A. Zalloum, M. E. Meuser, L. Jing, D. Kang, C. H. Chen, Y. Tian, F. Zhang, S. Cocklin, K. H. Lee, X. Liu and P. Zhan, *Eur. J. Med. Chem.*, 2018, **158**, 478–492.
- 105 I. Mohammed, I. R. Kummetha, G. Singh, N. Sharova, G. Lichinchi, J. Dang, M. Stevenson and T. M. Rana, *J. Med. Chem.*, 2016, **59**, 7677–7682.
- 106 T. M. Keck, A. K. Banala, R. D. Slack, C. Burzynski, A. Bonifazi, O. M. Okunola-Bakare, M. Moore, J. R. Deschamps, R. Rais, B. S. Slusher and A. H. Newman, *Bioorg. Med. Chem.*, 2015, **23**, 4000–4012.
- 107 J. M. Kwak, J. S. Moon, J. I. Choi, R. N. Murugan, W. K. Park, J. Y. Gong, H. Y. Lee and H. Y. Koh, *Bull. Korean Chem. Soc.*, 2013, **34**, 3467–3470.
- 108 A. Adibekian, B. R. Martin, C. Wang, K. L. Hsu, D. A. Bachovchin, S. Niessen, H. Hoover and B. F. Cravatt, *Nat. Chem. Biol.*, 2011, **7**, 469–478.
- 109 F. Micheli, L. Arista, B. Bertani, S. Braggio, A. M. Capelli, S. Cremonesi, R. Di-Fabio, G. Gelardi, G. Gentile, C. Marchioro, A. Pasquarello, S. Provera, G. Tedesco, L. Tarsi, S. Terreni, A. Worby and C. Heidbreder, *J. Med. Chem.*, 2010, **53**, 7129–7139.
- 110 R. R. Teixeira, P. A. R. Gazolla, A. M. da Silva, M. P. G. Borsodi, B. R. Bergmann, R. S. Ferreira, B. G. Vaz, G. A. Vasconcelos and W. P. Lima, *Eur. J. Med. Chem.*, 2018, **146**, 274–286.
- 111 S. Iqbal, M. A. Khan, K. Javaid, R. Sadiq, S. Fazal-ur-Rehman, M. I. Choudhary and F. Z. Basha, *Bioorg. Chem.*, 2017, **74**, 72–81.
- 112 M. Aqeel Khan, A. Saleem, N. Ghouri, A. Hameed, M. Choudhary and F. Basha, *Lett. Drug Des. Discovery*, 2015, **12**, 597–606.
- 113 M. Saedi, M. Mohammadi-Khanaposhtani, P. Pourrabia, N. Razzaghi, R. Ghadimi, S. Imanparast, M. A. Faramarzi, F. Bandarian, E. N. Esfahani, M. Safavi, H. Rastegar,



- B. Larijani, M. Mahdavi and T. Akbarzadeh, *Bioorg. Chem.*, 2019, **83**, 161–169.
- 114 G. J. Ye, T. Lan, Z. X. Huang, X. N. Cheng, C. Y. Cai, S. M. Ding, M. L. Xie and B. Wang, *Eur. J. Med. Chem.*, 2019, **177**, 362–373.
- 115 L. Han, W. Sheng, X. Li, A. Sik, H. Lin, K. Liu and L. Wang, *Medchemcomm*, 2019, **10**, 598–605.
- 116 E. P. Kumar, N. Gurrapu, P. Kumar Kolluri, V. Yerragunta, B. Reddy Kunduru and N. J. P. Subhashini, *Bioorg. Chem.*, 2019, **90**, 1–9.
- 117 C. J. Monceaux, C. H. Fukae, P. C. H. Lam, M. M. Totrov, Y. Matsuoka and P. R. Carlier, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 3992–3996.
- 118 A. K. Ghosh, N. Kumaragurubaran, L. Hong, S. Kulkarni, X. Xu, H. B. Miller, D. Srinivasa Reddy, V. Weerasena, R. Turner, W. Chang, G. Koelsch and J. Tang, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 1031–1036.
- 119 Z. Najafi, M. Mahdavi, M. Saeedi, E. Karimpour-Razkenari, R. Asatouri, F. Vafadarnejad, F. H. Moghadam, M. Khanavi, M. Sharifzadeh and T. Akbarzadeh, *Eur. J. Med. Chem.*, 2017, **125**, 1200–1212.
- 120 A. Kaur, S. Mann, A. Kaur, N. Priyadarshi, B. Goyal, N. K. Singhal and D. Goyal, *Bioorg. Chem.*, 2019, **87**, 572–584.
- 121 A. Iraj, O. Firuzi, M. Khoshneviszadeh, M. Tavakkoli, M. Mahdavi, H. Nadri, N. Edraki and R. Miri, *Eur. J. Med. Chem.*, 2017, **141**, 690–702.
- 122 A. Rastegari, H. Nadri, M. Mahdavi, A. Moradi, S. S. Mirfazli, N. Edraki, F. H. Moghadam, B. Larijani, T. Akbarzadeh and M. Saeedi, *Bioorg. Chem.*, 2019, **83**, 391–401.
- 123 Z. Najafi, M. Mahdavi, M. Saeedi, E. Karimpour-Razkenari, N. Edraki, M. Sharifzadeh, M. Khanavi and T. Akbarzadeh, *Bioorg. Chem.*, 2019, **83**, 303–316.
- 124 E. Düğdü, D. Ünlüer, F. Çelik, K. Sancak, Ş. A. Karaoğlu and A. Özel, *Molecules*, 2016, **21**, 1–13.
- 125 M. H. Shaikh, D. D. Subhedar, L. Nawale, D. Sarkar, F. A. Kalam Khan, J. N. Sangshetti and B. B. Shingate, *Medchemcomm*, 2015, **6**, 1104–1116.
- 126 M. F. Mady, G. E. A. Awad and K. B. Jørgensen, *Eur. J. Med. Chem.*, 2014, **84**, 433–443.

