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# 1,2,3-Triazole-containing hybrids as leads in medicinal chemistry: A recent overview

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ABSTRACT

The 1,2,3-triazole ring is a major pharmacophore system among nitrogen-containing heterocycles. These five-membered heterocyclic motifs with three nitrogen heteroatoms can be prepared easily using 'click' chemistry with copper- or ruthenium-catalysed azide-alkyne cycloaddition reactions. Recently, the 'linker' property of 1,2,3-triazoles was demonstrated, and a novel class of 1,2,3-triazole-containing hybrids and conjugates was synthesised and evaluated as lead compounds for diverse biological targets. These lead compounds have been demonstrated as anticancer, antimicrobial, anti-tubercular, antiviral, antidiabetic, antimalarial, anti-leishmanial, and neuroprotective agents. The present review summarises advances in lead compounds of 1,2,3-triazole-containing hybrids, conjugates, and their related heterocycles in medicinal chemistry published in 2018. This review will be useful to scientists in research fields of organic synthesis, medicinal chemistry, phytochemistry, and pharmacology.

## 1. Introduction

Heterocyclic organic chemistry is one of the most important and well-studied branches of medicinal chemistry. An important feature of heterocyclic bioactive compounds is their various constituent heteroatoms, including nitrogen,[1,2] sulphur,[3–6] oxygen,[7,8] and others.[9] These heteroatoms directly affect the reactivity of the target skeleton, activity (or toxicology) of the compounds, interactions between target drugs and different target inhibitors, as well as able to influence of metabolism and pharmacokinetics.

The most promising heterocyclic compounds are azoles,[10–14] which are five-membered nitrogen heterocycles. The nitrogen-containing azole skeleton offers the advantage of two nitrogen heteroatoms in the ring, which has an important effect on structural modifications and biological interactions. Over the past decade, the chemistry and biology of azole derivatives have emerged as very popular topics. We performed a search of the Scopus database (31 December 2018) using each of the azoles ('imidazole', 'pyrazole', 'triazole', 'tetrazole', and 'pentazole') as keywords to identify different published reports, and found that triazole motifs were the most frequently studied (Fig. 1),[15] particularly 1,2,3-triazoles.

It should be noted here that the advances in click chemistry (the copper-catalysed azide-alkyne cycloaddition [Cu-AAC] reaction), various synthetic methodologies for the 1,2,3-triazole scaffolds (e.g., derivatives, hybrids, and conjugates) have been used in medicinal chemistry (Fig. 2).[16] In 2018, various biological screenings were conducted[17–20] which led to the identification of anticancer,[21–23] antimicrobial,[24–28] anti-infective,[29,30] and antioxidant[31–33] properties of the studied 1,2,3-triazole-bearing hybrids. Moreover, triazole-linked derivatives were suggested to affect adenosine diphosphate ribosylation biology,[34] and were used widely in peptides to mimic a *trans*-amide bond, despite their hazardous effects on native peptide activity.[35]

In addition, a 1,2,3-triazole core provides diverse pharmacophore properties and hybrids are most commonly considered 'lead compounds' when they contain or are fused by a 1,2,3-triazole ring. Thus, in view of the above factors and the recent focus of researchers on 1,2,3-triazole compounds, we have discussed and highlighted the diverse biological activities of the 1,2,3-triazole hybrids, conjugates, and their related compounds as leads in medicinal chemistry, based on articles published in 2018.

## 2. Chemistry: synthesis and properties of the 1,2,3-triazoles

The general synthetic route of 1,2,3-triazoles using click chemistry is described in Scheme 1A. The most popular route to 1,2,3-triazoles is Cu(I)-catalysed Huisgen 1,3-dipolar cycloaddition, which is the

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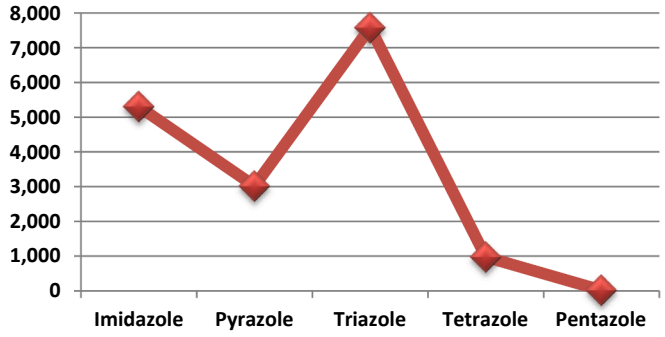



**Fig. 1.** Number of reports on each azole in the Scopus database for 2008–2018.

interaction between organic azides and alkynes that forms only the 1,4-regioisomeric 1,2,3-triazoles (Scheme 1, B).[36] If ruthenium catalysts are used instead of Cu(I) for this reaction, 1,5-regioisomeric 1,2,3-triazoles are the major products,[37] and there is a known non-catalytic thermal pathway that produces both regioisomeric 1,2,3-triazoles (Scheme 1B). Several other methods for the synthesis of 1*H*-1,2,3-triazoles including Cu-AAC; solid-phase synthesis; the three-component reaction of aldehydes, nitromethane, and sodium azide (Scheme 1C); the reaction of enamines with 4-methylbenzenesulfonyl azide (Scheme 1D); and the interaction of β-bromostyrenes with sodium azide in a palladium-catalysed reaction (Scheme 1E), were reviewed by Efimov in 2019.[38] In 2015, novel 'click' methods for 1,2,3-triazoles using classical reactions were reviewed by Totobenazara and Burke.[39]

Generally, triazoles are stable to hydrolysis under acidic or basic conditions, metabolic degradation, and redox conditions. These compounds can form H-bonds and π-π stacking interactions. Although the aromatic ring in 1,2,3-triazoles is fairly stable, it becomes more reactive when bonded to electronegative groups. For example, 1,2,3-triazole can form 1-$CF_3$-1,2,3-triazole, which decomposes at approximately 170 °C and generates highly reactive intermediates.[40] In addition, triazoles are weakly acidic and weakly basic. They are rarely oxidised but may tautomerise to 2*H*-1,2,3-triazoles. They are more sensitive to reducing agents. Furthermore, several other properties including strong dipole moments of the triazole system, bioisosteric effects,[41] and the nature of the heteroatoms all make triazole units an important scaffold in medicinal chemistry.

## 3. Biology

### 3.1. Anticancer activity

#### 3.1.1. 1,2,3-Triazole containing derivatives of natural compounds

Natural compounds and combination therapy are used widely in cancer therapies.[42,43] Although the 1,2,3-triazole moiety does not exist in nature, it has attracted interest as a candidate anticancer drug, particularly for the production of '1,2,3-triazole-natural compound' hybrids.[44] In this field, Ding et al.[45] reported the $Cu_2O$ nanoparticle-catalysed 'click' reaction that enabled the synthesis of melampomagnolide B-triazole conjugates, and evaluated their anticancer activities. The most potent derivative **1** (Fig. 3) (HCT116, $IC_{50}$ = 0.43 μM) that exhibited almost 11.5-fold potency than Melampomagnolide B (HCT116, $IC_{50}$ = 4.93 μM), did not affect normal cells (FHC, HPDE6-C7, 3T3), and significantly induced apoptosis as well as inhibition of proliferation and migration of cancer cell lines. The effect of **1** on HCT116 cell migration was measured using the Transwell assay and the number of migrated cells was distinctly lower after exposure to melampomagnolide B-triazole **1** for 48 h. In addition, the expression of epithelial proteins such us snail, zonula occludens-1 (ZO-1), and E-cadherin, as well as mesenchymal marker proteins such as vimentin, zinc finger E-box binding homeobox 1 (ZEB1), and *N*-cadherin was productively decreased after treatment with derivative **1**, which confirmed that triazole compound **1** may inhibit and affect the migration of HCT116 cells. Another melampomagnolide B-triazole conjugate, compound **2** (Fig. 3), was effective and potent against several cancer cell lines including leukaemia ($GI_{50}$ = 0.10–0.23 μM), colon ($GI_{50}$ = 0.14–1.17 μM), melanoma ($GI_{50}$ = 0.15–1.47 μM), renal ($GI_{50}$ = 0.02–0.70 μM), ovarian ($GI_{50}$ = 0.15–1.86 μM), prostate ($GI_{50}$ = 0.72–0.83 μM), and breast ($GI_{50}$ = 0.17–1.03 μM) cancer cell line subpanels.[46] Further investigation indicated that triazole compound **2** was a potent inhibitor of nuclear factor (NF)-kB and cell proliferation in TMD-231 (MDA-MB-231) cell line. Moreover, treatment of TMD-231 cells with derivative **2** decreased the DNA binding activity of NF-kB by inhibiting p65 phosphorylation mediated by inhibitor of NF-kB kinase (IKK)-b and increasing basal IkBα levels via inhibition of substantial NF-kB activation and IkBα turnover.

Yu et al.[47] synthesised a series of 1,2,3-triazolo-dihydroartemisinin-coumarin hybrids and screened their anticancer potentials in two types of cancer cells. These hybrids displayed modest cytotoxicity towards HT-29 and MDA-MB-231 cell lines, particularly under hypoxic condition. However, hybrid **3** (Fig. 3) was more active on HT-29 than MDA-MB-231 cell (normoxic $IC_{50}$ = 1.5 μM and under hypoxia $IC_{50}$ = 0.01 μM). Furthermore, this hybrid arrested HT-29 cells in the G0/G1 phase, inhibited the migration of tumour cells, and caused a large reduce in mitochondrial membrane capability, leading to apoptosis of HT-29 cells.

Diterpenoids with the 1,2,3-triazole moiety in Jiyuan Oridonin A were tested for their antiproliferative properties.[48] Derivative **4** (Fig. 3), containing a triazole ring, also displayed better antiproliferative activity with $IC_{50}$ values of 2.7 μM against the Eca109 cell line and 1.5 μM against the MCF-7 breast cancer cell line than against the other tested cells. Moreover, the $IC_{50}$ value of **4** was also evaluated in MGC-803 (0.6 μM) and PC-3 (0.6 μM) cancer cells. Cellular mechanistic studies demonstrated that compound **4** arrested the cell cycle at the G1 phase and induced potent apoptosis of the SMMC-7721 cell line; it also inhibited colony migration and formation through the Wnt signalling pathway in these cells. Another two series of *ent*-kaurene diterpenoid derivatives were screened for their antiproliferative properties in four cancer cell lines (Eca109, EC9706, SMMC7721, and MCF-7 cells).[49] Compound **5** (Fig. 3) displayed highly anticancer potential in all tested cell lines ($IC_{50}$ values of 2.70, 5.04, 4.44, and 4.76 μM, against the Eca109, EC9706, SMMC7721, and MCF-7 cell lines, respectively) than the positive control Oridonin did, confirming that 1,2,3-triazole is a beneficial heterocyclic moiety that affects the cytotoxicity of triazole-containing hybrids. Investigation of the anticancer mechanism showed that **5** increased reactive oxygen species (ROS) levels in cancer cell lines, leading to the decline of mitochondrial membrane potential and the release of cytochrome *c* into the cytoplasm. Furthermore, this effect was further enhanced and activated by caspase-9 to induce apoptosis.

Wei et al.[50] synthesised a series of 1,2,3-triazole-containing albiziabioside A derivatives and evaluated their anticancer potentials *in vitro* and *in vivo*. The target lead (**6**, Fig. 3) showed significant activity on HCT116 cells ($IC_{50}$ = 5.19 μM). Moreover, this triterpene saponin triazole derivative demonstrated favourable selectivity, and was effective on multidrug resistance (MDR) cancer cells where it induced ferroptosis and apoptosis as a p53 activator via the mitochondrial pathway. *In vivo* investigations revealed that the introduction of the triazole fragment into the triterpene skeleton considerably inhibited tumorigenesis without causing toxicity against normal cells (for **6**). Indeed, this study provided clinical evidence to support the consideration of the albiziabioside A derivative **6** as a potential cancer drug candidate with enhanced activity, and further information on its novel mechanism of action. Another series of 1,2,3-triazole-linked saponin hederacolchiside $A_1$ with aryl/amide portion were synthesised to improve the inhibitory activity, metabolic stability, and comprehensively determine the pharmacological mechanism.[51] The antiproliferative activities of the synthesised analogues were assayed on six types of human cancer cell lines, PC3, HT29, HepG2, A549, HL60, and U937 cell

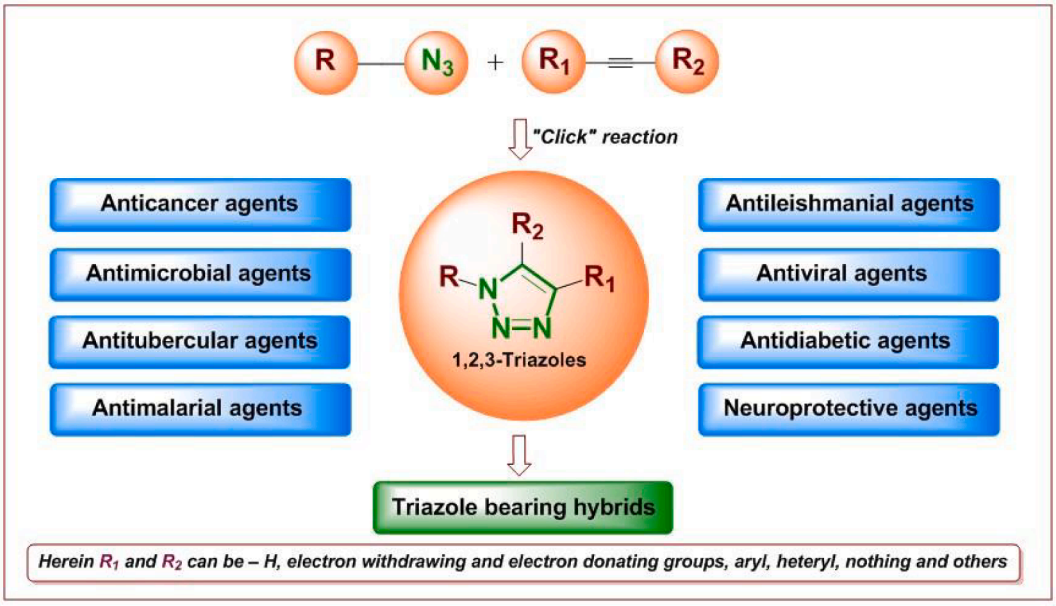
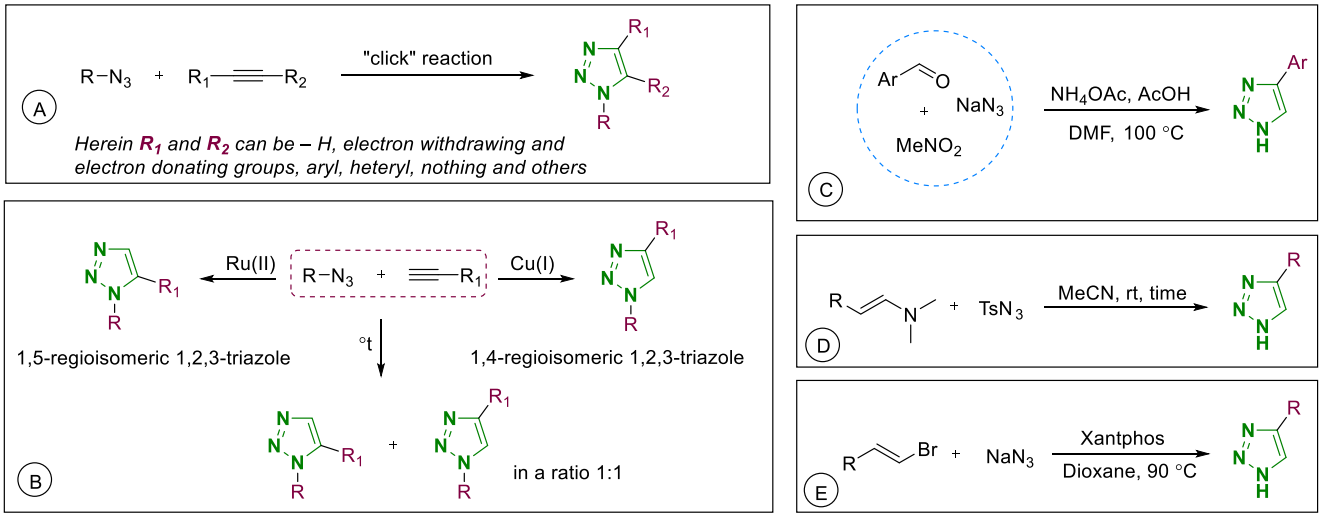



**Fig. 2.** Bioactive 1,2,3-triazoles using 'click' reaction.




**Scheme 1.** Synthetic routes to 1,2,3-triazoles.

lines. The results revealed that most of the synthesised hybrids with the *para*- and *meta*-substituents demonstrated strong cytotoxicity towards HL60 and U937 cells. In particular, derivative **7** (Fig. 3) showed strong anticancer potential against all selected cells compare with the positive controls 5-fluorouracil and hederacolchiside $A_1$. Moreover, the results of the cell cycle and apoptosis screening indicated that **7** clearly inhibited the proliferation of HepG2 cells via the induction of apoptosis and cell cycle arrest of the in the G1 and S phases.

Biologically relevant natural, synthetic, and hybrid compounds are a great resource for lead formation and the development of novel pharmaceuticals. Recently, 60 novel 1,2,3-triazole-containing pharmacophores related to the allogibberic acid fragments were synthesised by Wu et al.[52] The cytotoxic potential of all hybrid allogibberic triazole hybrids was tested to determine their anticancer activities on the A-549, HL-60, SMMC-7721, MCF-7, and SW480 cell lines. The most potent compound (**8**, Fig. 3) demonstrated satisfactorily higher cytotoxicity than the positive control drug cisplatin did towards all five tested tumour cell lines, with $IC_{50}$ values of 0.25–1.70 μM. Mechanistic exploration revealed that hybrid compound **8** induced cell cycle arrest at the S phase and apoptosis of SMMC-7721 cells.

A quinine derivative containing a triazolyl-phenol moiety (**9**, Fig. 3) was identified as a selective hybrid with activity against HT-29 cells ($IC_{50}$ = 0.65 μg/mL or 1.21 μM).[53] In addition, **9** and other analogues were evaluated in three different solid tumour (HT-29, MCF-7, A549, and DU-145) cell lines and one normal human epithelial (MCF-10A) cell line. The triazole-bearing alkaloid **9** also displayed good antiproliferative properties against the cells listed above; however, it may be a lead compound against HT-29 colon cancer, against which it was eight times more potent than cisplatin.

The acetoxymethyl 1,2,3-triazole compound **10** (Fig. 3) synthesised using Huisgen azide-alkyne cycloaddition, which is a synthetic analogue of natural meiogynin A, was investigated as a pan- B-cell lymphoma-2 (Bcl-2) inhibitor. This triazole hybrid induced apoptosis and was strongly cytotoxic to BL2, RS4;11, and H929 cells at rates of 93, 75.5, and 37.5, and 20.5%, respectively in Remb1 cells.[54] Here, it should be noted that the selected target proteins such as Bcl-2-associated X protein (Bcl-xL), myeloid cell leukaemia 1 (Mcl-1), and Bcl-2 and their interaction between new triazole hybrids were screened using fluorescence polarisation, and the results indicated that modulation of the lateral chain dramatically affected the compound by considerably

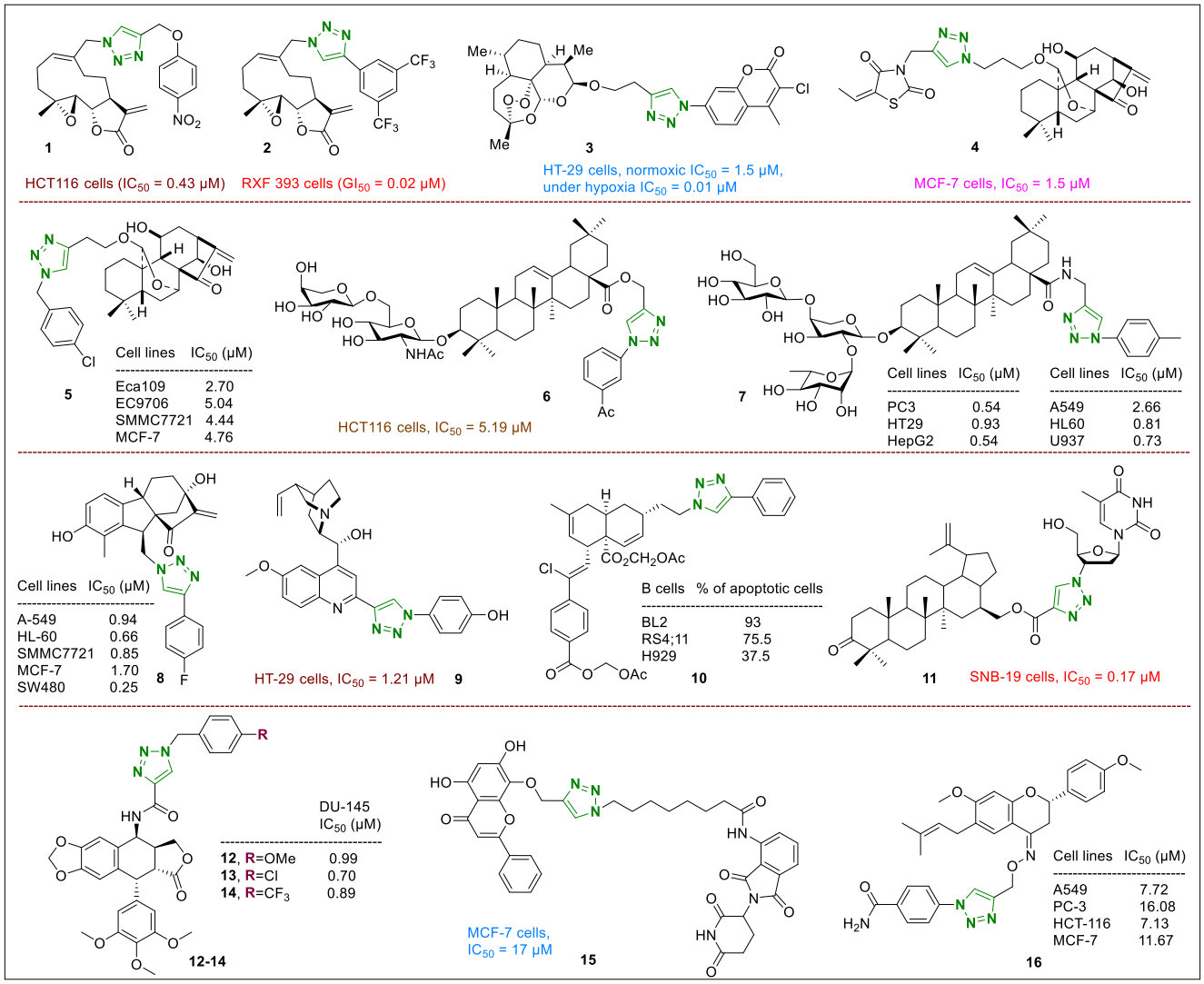



**Fig. 3.** 1,2,3-Triazole-bearing natural compounds (**1–16**) analogues as anticancer leads.

modifying its activity on target proteins. Other triazole-natural compound hybrids, triterpene derivative-linked 1,2,3-triazole moieties were prepared and their anticancer potentials were investigated on the selected cancer cells such as C-32, T47D, and SNB-19 using the WST-1 assay.[55] Hybrid derivative **11** (Fig. 3) displayed a significant $IC_{50}$ value (0.17 μM) toward the human glioblastoma SNB-19 cell line, which was nearly 5-fold higher that the value of the reference drug cisplatin.

Novel 4*β*-amidotriazole-containing podophyllotoxin hybrids were synthesised using click chemistry method and were screened for DNA topoisomerase-IIα inhibitory activity, as well as anticancer properties.[56] Aryl triazolic-amide derivatives containing chloro, fluoro, 3,4-methylenedioxy, 3,4-dimethoxy, and 3,4,5-trimethoxy substituents exhibited satisfactory cytotoxicity. For example, derivatives **12–14** (Fig. 3) showed promising inhibition of selected human cancer cell lines. Moreover, these three experimental compounds displayed $IC_{50}$ values of 0.99 (**12**), 0.70 (**13**), and 089 (**14**) μM on DU-145 cancer cells, and induced apoptosis of a prostate cancer cell line. The DNA topoisomerase-II inhibition assay showed that catenated DNA in the presence of topoisomerase II incubated with compounds **12–14** inhibited topoisomerase II activity represented by the presence of connected DNA in the wells. However, compounds **12** and **13** demonstrated clear linear DNA synthesis, and were analogous to etoposide in the well-characterised inhibition of topo-II.

Wogonin-based proteolysis-targeting chimeras related to the 1,2,3-triazole moiety have been developed and evaluated to study their mechanism of action on the degradation of CDK9 protein in breast cancer MCF-7 cells.[57] The most active triazole hybrid **15** (Fig. 3, $IC_{50}$ = 17 μM) demonstrated better antiproliferative potential on the MCF-7 cell line than wogonin ($IC_{50}$ = 30 μM) did at lower concentrations. The western blotting revealed that derivatives containing a triazole linker selectively downregulated the intracellular CDK9 level. Sample **15** was identified as a selective and leading chemical degrader of CDK9 with modest antiproliferative potential in various cancer cell lines and decreased the levels of Mcl-1, which is a prosurvival protein.

Novel derivatives of bavachinin-containing 1,2,3-triazoles were synthesised and evaluated for anticancer effects in four selected cancer cell lines.[58] The results of the 1,2,3-triazole analogue **16** (Fig. 3) showed $IC_{50}$ values of 7.72, 16.08, 7.13, and 11.67 μM against A549, PC-3, HCT-116, and MCF-7 cancer cell lines, respectively. Moreover, derivative **16** induced apoptotic cell death and morphological changes, and inhibited cell migration and colony formation.

### 3.1.2. *Quinazoline-based triazole hybrids*

Quinazoline and quinazolinone derivatives linked to 1,2,3-triazoles form part of a good arsenal of potential anticancer agents.[59,60] 4-Anilinoquinazoline-substituted 1,2,3-triazoles were screened for cytotoxic potential against HepG2, KB, and SK-Lu-1 cells by Le-Nhat-Thuy et al.[61] The most active compound, **17** (Fig. 4, $IC_{50}$, 0.04, 0.14, and 1.03 μM

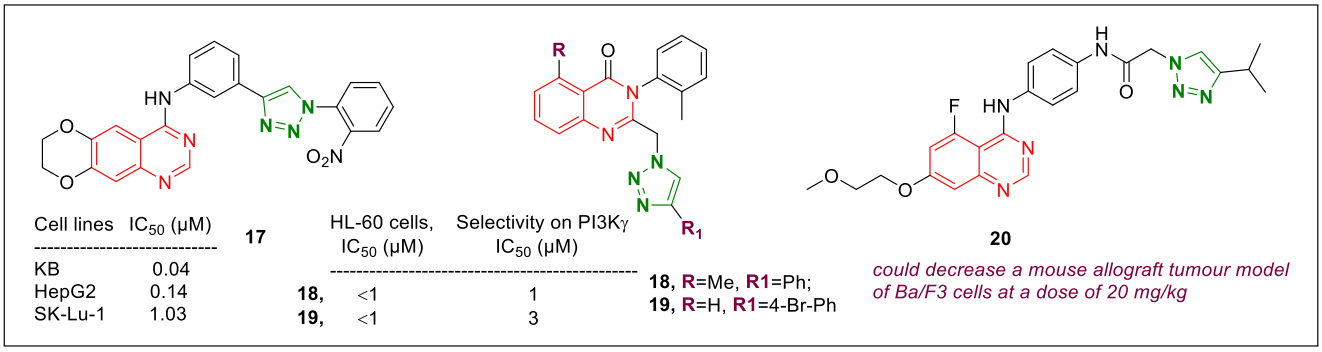



**Fig. 4.** 1,2,3-Triazole-quinazolines as anticancer leads (**17–20**).

against KB, HepG2, and SK-Lu-1, respectively), displayed up to 100-fold stronger activity than the positive control erlotinib did. Docking simulations of the lead compounds, including **17**, into the active ATP-binding site of various epidermal growth factor receptor (EGFR) kinases was conducted and the interaction of H-bonds of the 1,2,3-triazole fragment and the dense hydrophobisation of di-oxygenated portion of quinazolines with the remnants in the ATP pocket, was a major points in EGFR binding.

The phosphoinositide 3-kinase (PI3K)-γ-specific properties of 1,4-substituted 1,2,3-triazolo-quinazolinones has been investigated via in *in vitro* cytotoxicity test against several cancer cell lines (HL-60, Colo-205, HCT-116, MCF-7, and A549 cells).[62] Two compounds (**18** and **19**, Fig. 4) demonstrated less toxicity against HL-60 cells ($IC_{50}$ = 1 μM) than the other compounds did. The specificity of compounds **18** and **19** against various isoforms of PI3-Ks was examined using western blotting and they exhibited selectivity against PI3Kγ isoforms, with $IC_{50}$ values of 1 and 3 μM, respectively.

Kettle et al.[63] discovered that the quinazoline-triazole conjugate **20** (Fig. 4) is a potential Pan-KIT mutant inhibitor towards gastrointestinal stromal tumours. Triazole compound **20**, containing an $–OCH_3$ group at the C7 position, was expected to have an optimal balance between KDR selectivity and KIT mutant potency, and exhibited potential growth inhibition of KIT mutant cell lines, with a satisfactory KDR margin, and considerable improvements in the absorption, distribution, metabolism, and elimination (ADME) and physico-chemical properties. Evaluation of triazole hybrid **20** in a mouse allograft tumour model of Ba/F3 cells showed that **20** caused the tumour to decrease at a dose of 20 mg/kg. Importantly, the preclinical *in vivo* potency of **20**, which is marked as AZD3229 is encouraging, and may serve in near future treatment of patients with gastrointestinal stromal tumour.

### 3.1.3. 1,2,3-Triazole-linked peptide type compounds

Peptide-like derivatives are not orally bioavailable; however, protein therapy tends to exhibit specificity against its targets because it interacts with a greater number of substances, but this occurs at the expense of low bio-availability and metabolic instability.[64] The introduction of the 1,2,3-triazole ring in these macromolecules also demonstrated interesting effects. Using this connection, Chen et al.[65] synthesised a new series of nonpeptide inhibitors bearing two 1,2,3-triazole moieties toward the polo-box domain (PBD) of polo-like kinase 1. Among them, compound **21** (Fig. 5) that was related to the 1,4-regioisomer triazole portion showed considerable bioactivity with an $IC_{50}$ value of 3.37 μM, compared with that reported for phosphate peptide (PLHSpT, $IC_{50}$ = 0.62 μM), and it showed moderate activity against the PBD of Polo-like kinase 1. However, the authors suggested that the nonpeptide skeleton may confer advantages over other peptide-related inhibitors and further investigations of the novel nonpeptide PBD of Polo-like kinase 1 inhibitors could lead to the development of selective anticancer agents.

Matthiesen et al.[66] reported a new series of geranylgeranyl diphosphate synthase (GGDPS) inhibitors based on the α-methylated isoprenoid-triazoles. They focused on a grand design of masking the negatively charged bisphosphonates using pivaloyloxymethyl (POM) groups to use GGDPS inhibitors as anti-myeloma agents. The POM-version of **22** (compound **23**, Fig. 5) displayed more augmented cellular activity than the conforming salt did, with a nearly 10-fold improvement in potency.

Cao et al.[67] reported that leucine-ureido-triazole conjugates were synthesised as aminopeptidase N inhibitors using the 'click reaction'. In their study, compound **24** (Fig. 5) exhibited better aminopeptidase N inhibition than other compounds did, with an $IC_{50}$ of 0.089 μM (approximately 100-fold lower than that of the positive control bestatin). In addition, compared to bestatin, **24** showed favourable *in vitro* anti-angiogenesis potency in both the HUVEC tubular structure formation bio-assay and rat aortic ring model. Furthermore, *in vivo* screening of **24** exhibited more promising anti-metastasis in the mouse H22 pulmonary metastasis model with inhibitory rates of 71%, than bestatin, which showed 64% inhibition.

The antiproliferative activity of 1,2,3-triazole-bearing β-glucuronidase-responsive albumin-binding prodrug **25** (Fig. 5) on the A549 cell line after a 3-day treatment showed that it did not affect the cell viability at the elevated dose of 200 nM when incubated alone. However, in combination with β-glucuronidase, the $IC_{50}$ value of **25** was 9.4 nM.[68]

### 3.1.4. Diverse 1,2,3-triazole-containing heterocyclic hybrids

Chen et al.[69] reported 1,2,3-triazole-bearing acridine hydroxamic acids as dual Topo and HDAC inhibitors. All the prepared derivatives exhibited potent antiproliferative potentials toward U937 cells. Here, the most active sample, **26** (Fig. 6), displayed nanomolar $IC_{50}$ values on U937 cells, and showed superior HDAC1/6 inhibition potency ($IC_{50}$ = 3.9 and 2.9 nM, respectively), that was several-fold more potent than the HDAC positive control, SAHA was ($IC_{50}$ = 14.3 and 6.9 nM, respectively). Moreover, **26** considerably activated cleaved caspases-9, -8, -3, and -7 at 0, 0.1, 0.5, 1, and 2.5 μM for 36 h, indicating that it induced both the death receptor and mitochondrial pathways leading to apoptosis.

Novel 1,2,3-triazole-containing–isoquinolines were suggested as P-gp inhibitors by Gao et al.[70] following cytotoxic and reversed MDR activity bioassays *in vitro* and *in vivo*. All synthesised samples demonstrated no or less cytotoxicity ($IC_{50}$ > 30 μM) in both K562 and K562/A02 cells. However, compound **27** (Fig. 6), with a 4-*tert*-butylphenyl substituent, reversed MDR in a concentration-dependent manner, with better activity than that of verapamil. Moreover, compound **27** significantly reduced the $IC_{50}$ of adriamycin (1.22 μM), demonstrating the strongest reversal activity (39-fold), which was close to that of tariquidar (reversal fold = 49.4).

Hybrid compounds containing a thiosemicarbazide moiety and 1,2,3-triazolopyrimide system were evaluated for their antiproliferative potentials against human cancer cell lines such as MGC-803,

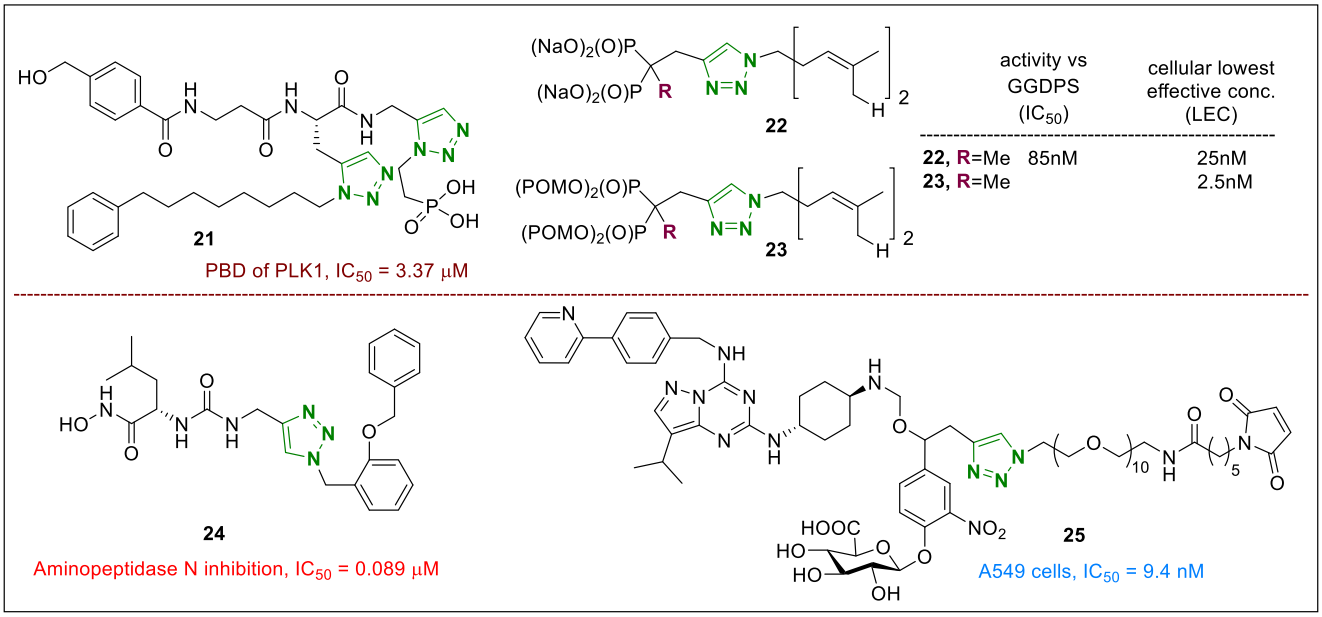



**Fig. 5.** Structures of the 1,2,3-triazole-linked peptide type compounds (**21–25**).

NCIH1650, and PC-3 cells.[71] The results indicated that compound **28** (Fig. 6) had the most potent antiproliferative activity ($IC_{50}$, 2.37, 5.26, and 7.67 μM in MGC-803, PC-3, and H1650 cells, respectively). Furthermore, mechanistic studies revealed that MGC-803 cells treated with compound **28**, showed slight inhibition of colonies (72% inhibition at 2 μM), indicating that the hybrid **28** inhibited the proliferation of cancer cells.

Yamada et al.[72] reported the synthesis and antitumor screening of target compounds based on the 4-substituted 1-benzyl-5-diphenylstibano-1,2,3-triazoles using CuAAC of ethynyldiphenylstibane with benzyl azide. The antitumor activities of the novel synthesised triazole samples were evaluated in eight cultured tumour cell lines, including human solid tumour cell lines such as colon, gastric, and breast tumours. Among them, 5-stibanotriazoles (**29–33**, Fig. 6) showed excellent antitumor activity in all tested tumour cell lines ($IC_{50}$, 0.25–1.38 μM. The cytotoxicity of **29–33** was tested in normal cells and all 5-stibanotriazoles exhibited higher cytotoxicity than their 5-unsubstituted 1,2,3-triazoles analogues did. In particular, compounds with 4-methylphenyl (**30**) and 1-cyclohexenyl (**33**) fragments exhibited satisfactory low cytotoxicity toward the normal cells.

The synthesis, characterisation, and cytotoxicity analysis of 1,2,3-triazoles against human breast cancer cells using the CuAAC reaction were performed by Gilandoust et al.[73] Compound 1-(2′-ethoxy-4′-fluoro-[1,1′-biphenyl]-4-yl)-4-phenyl-1*H*-1,2,3-triazole (**34**, Fig. 6) demonstrated the greatest cytotoxicity against selected breast cancer cell lines (MCF7, BT474, MDA-MB-231, and Ishikawa cells, with $IC_{50}$ values of 1.69, 4.08, 4.81, and 1.97 μM, respectively). Thus, **34** was suggested as a lead cytotoxic agent against MCF7 cells and was not toxic to BEAS-2B (normal lung epithelial) cells. In addition, **34** downregulated the expression of VEGFR1 in MCF-7 cells.

Hybrid compounds containing the pyrazolo[3,4-*d*]pyrimidinone and 1,2,3-triazole portions were evaluated against glioma cells such as human U87 and rat-C6.[74] 5-((1-(3-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl) methyl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**35**, Fig. 6) inhibited the proliferation of U87 cells by 47.69% and, owing to its good solubility in DMSO, was chosen for further evaluation. The flow cytometry assay showed that **35** arrested cells in the S phase of the cell cycle, indicating that the cells were unable to duplicate DNA, consequently, leading to a reduction in the M-phase cells. Moreover, the number of dead cells increased with increasing concentration of **35**. Furthermore, western blotting showed that p53 was upregulated with increasing concentrations of **35**, which confirmed its involvement in apoptosis.

The anticancer activity of the 1,2,3-triazole-tethered dasatinib derivatives were studied in HL60, K562 (leukaemia) and KG1a (leukaemia progenitor) cell lines.[75] Among the triazole-containing lead compounds, **36** (Fig. 6) showed superior inhibitory activity ($IC_{50}$ = 0.14 μM) in the KG1a cell line, following evaluation in MCF-7 and B16BL6 cells using the colony forming and cell wound scratch bioassays, respectively. The dasatinib-triazole hybrid **36** was significantly more potent than dasatinib was. The survival rate of mice dosed with **36** (200 mg/kg) once daily for 2 weeks was 100%, and after increasing the dose, mice treated with **36** also survived, indicating the low toxicity of **36**.

Compound **37** (Fig. 6) was discovered as a c-Met-targeting and apoptosis-inducing agent among the synthesised thiopyrimidine-triazole conjugates.[76] This lead compound demonstrated 3.7–5.4-fold greater activity than the positive control drug, foretinib, did toward the MCF-7, HepG2, and A549 cell lines with the $IC_{50}$ values of 1.1, 0.5, and 0.9 μM, respectively. Furthermore, enzyme-based experiments showed that **37** selectively inhibited c-Met, with an $IC_{50}$ of 16 nM, which was similar to that of foretinib (14 nM). Moreover, **37** induced late apoptosis of HepG2 cells in a concentration-dependent manner.

Newly synthesised imidazopyridine-triazole conjugates were assayed for their cytotoxicity against cancer cell lines such as A549, HCT-116, MDA-MB 231, and DU-145 cells.[77] The most active compound (**38**, Fig. 6) displayed significant antitumor potential in A549 lung cancer cells with $IC_{50}$ of 0.51 μM, while the value was 1.04 μM in the prostate cancer cell line (DU-145). The effect of **38** on the cell cycle of A549 cells was measured using flow cytometry, and 48 h treatment with 1 μM caused cell cycle arrest in the $G_2$/M phase, suggesting the inhibition of tubulin polymerisation.

The antiproliferative properties of benzimidazole-tethered 1,4-disubstituted 1,2,3-triazoles against selected human tumour cell lines (A549, CFPAC-1, HeLa, and SW620 cells) were evaluated. Compounds **39** and **40** (Fig. 6) exhibited strong and selective antiproliferative potentials in A549 cells with $IC_{50}$ values of 0.05 and 0.07 μM, respectively, and were further selected to elucidate their mechanism of action.[78] Compound **39** markedly decreased the viable cell population by 70.59%, and increased early and late apoptotic/primary necrotic cell populations by 27.81% and 40%, respectively. Furthermore, compound **40** also increased early and late apoptotic/primary necrotic cell

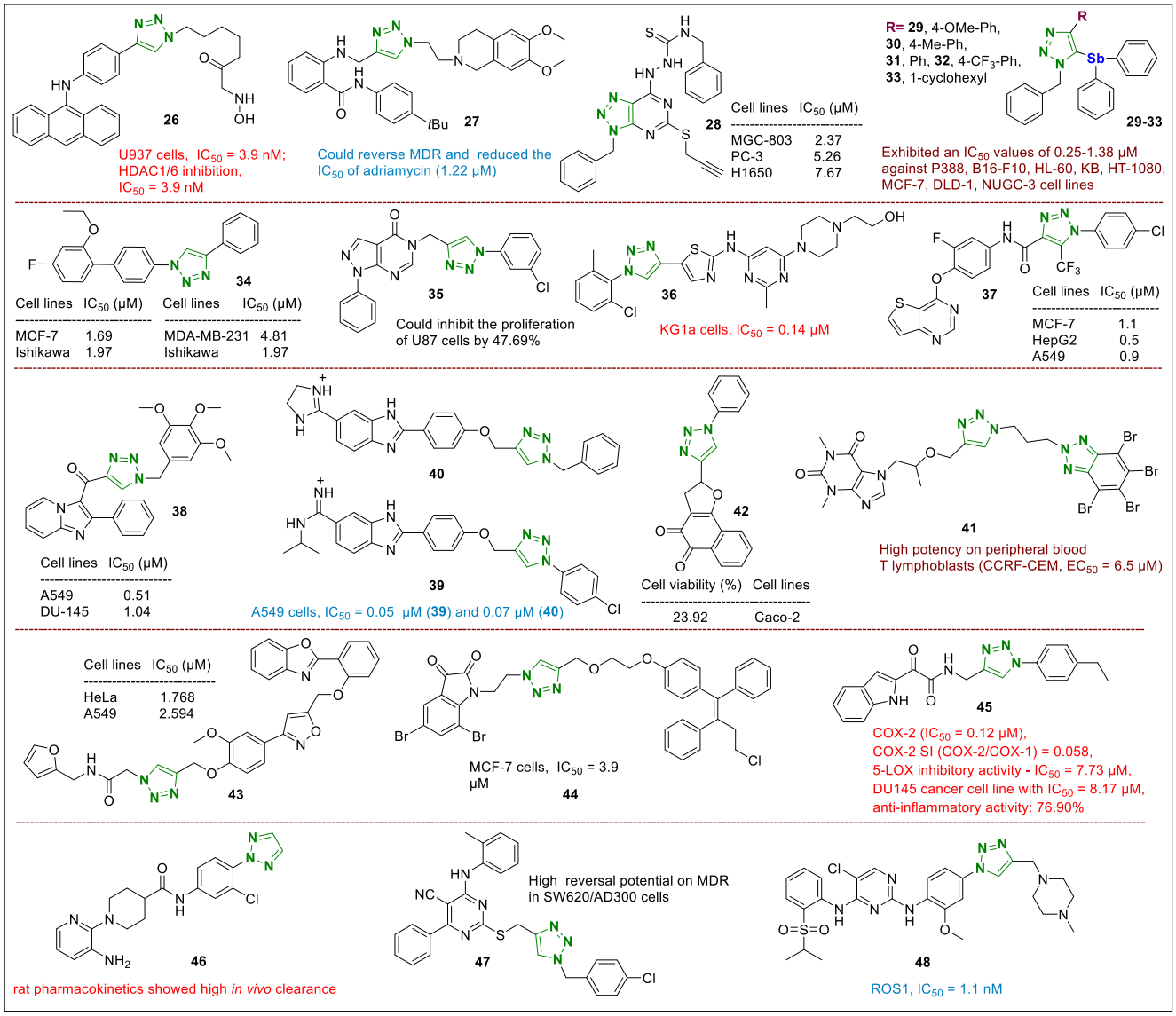



**Fig. 6.** 1,2,3-Triazole leads (**26–48**) containing various heterocyclic skeletons.

populations by 26.97% and 16.37%, respectively, however, the viable cell population decreased to 49.77%. The enzyme p38 mitogen-activated protein kinase (MAPK) was identified as the common target of the triazole leads **39** and **40** that inhibited the enzyme with slightly different activity.

It was suggested that hybrid derivative containing purine and two 1,2,3-triazole portions (**41**) (Fig. 6), inhibited the virulence of *Candida albicans* and exhibited *in vitro* antiproliferative potency and an *in vivo* nontoxicity. This derivative could be a lead compound for further development by averting cancer-associated biofilm *Candida* infections.[79] Moreover, lead compound **41** displayed high activity against peripheral blood T lymphoblasts (CCRF-CEM, $EC_{50}$ = 6.5 μM) and modest antineoplastic potential against the MCF-7 cell line ($EC_{50}$ = 80 μM). In addition, lead compound **41** was selective against *C. albicans* (lg R ≥ 3 at 20 μM), but not the mammalian normal cell line Vero *in vitro* ($IC_{50}$ ≥ 280 μM) and *Galleria mellonella in vivo*.

Another hybrid, 1,2,3-triazole-related naphthoquinone, inhibited cancer cells such as Caco-2, Calu-3, and MDA-MB231 cells, as well as normal Vero cells.[80] Among them, compound **42** (Fig. 6) with a cell viability of 23.92% on Caco-2 cells, showed 6-fold higher selectivity on Caco-2 than Vero cells (selectivity index [SI] = 6.25), confirming the potential of this derivative as a drug-like candidate. Furthermore, hemocompatibility studies revealed that **42** did not affect platelet aggregation caused by arachidonic acid or activated thromboplastin time, indicating that the activation of blood coagulation by the intrinsic and extrinsic pathway was preserved. In addition, **42** demonstrated no significant haemolytic profile after incubation for 3 h, confirming its good safety profile.

1,2,3-Triazole-linked isoxazole-benzothiazole-benzoxazole hybrids were prepared and their anticancer potency was evaluated on cancer A549 and HeLa cells, as well as normal HEK-293 cells.[81] The lead compound in the present study was compound **43** (Fig. 6, $IC_{50}$ = 1.768 [HeLa] and 2.594 [A549] μM). Moreover, the cell cycle of HeLa and A549 cell lines was analysed. Triazole derivative **43** displayed superior potency on A549 cells and in the cell cycle assay, the cell death percentage in the subG1 phase was 49.43%. In HeLa cells, compound **43** (42.58%) exhibited significant and enhanced apoptotic potency in the subG1 phase compared with the reference drugs TAK-165 and GW-610.

Kumar et al.[82] studied several 1,2,3-triazoles containing isatin-ospemifene system for their antiproliferative activity against triple-negative MDA-MB-231 (ER-) and MCF-7 (ER+) cell lines. The evaluation studies revealed that compound **44** (Fig. 6) demonstrated high potency with an $IC_{50}$ of 1.56 μM in the MCF-7 cell line. The structure–activity relationship (SARs) analysis showed that selected triazoles with Br-

substituents at the C-5 and C-7 positions of the isatin portion with an ethyl/propyl group as a spacer were more active. For example, the best lead compound exhibited a 30-fold higher potency than tamoxifen in MCF-7 cells.

Using a 'hybrid conjugation of bioactive ligands' approach, 1,2,3-triazole-linked indole-3-glyoxamide fragment derivatives have been investigated as potential dual inhibitors of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) as a cancer chemotherapy.[83] Here, lead compound **45** (Fig. 6) not only exhibited dual inhibition of COX-2 and 5-LOX, but also displayed high antiproliferative potential on the prostate cancer cell line DU145, an excellent COX-2SI, as well as satisfactory *in vivo* anti-inflammatory activity with no ulcerogenic effects. In addition, the effect on tubulin polymerisation revealed that compound **45** interfered with the microtubule dynamics to act as a microtubule-destabilising agent.

Schlapbach et al.[84] reported a novel and highly selective MALT1 protease inhibitor based on the *N*-aryl-piperidine-4-carboxamide derivative related to triazole ring. In the Jurkat T and lymphoma OCI-Ly3 cell lines, hybrids demonstrated activity in a mechanistic T cell activation assay (IL-2 RGA), which suggests the possibility of using MALT1 inhibitors in the treatment of diseases such as autoimmune disorders and B-cell lymphomas with a dysregulated NF-κB pathway. It should be noted that *para*-substituent tethered to a 1,2,3-triazole moiety was detected as the most beneficial group among other studied substituents (compound **46**, Fig. 6). In addition, rat pharmacokinetics showed high *in vivo* clearance for **46**.

The pyrimidine-triazole hybrids have been identified as strong and effective ATP-binding cassette subfamily B member 1 (ABCB1)-dependent MDR modulators.[85] The evaluation of their effect on MDR reversal potency in SW620/AD300 cells (paclitaxel resistance) showed that compound **47** (Fig. 6) exhibited a high reversal potential, that was approximately 7-fold higher than that of verapamil (positive control). Compound **47** was more effective on ABCB1-mediated Rh123 accumulation and efflux than the positive control, and 2 μM increased the stockpiling and decreased the efflux of Rh123 in SW620/AD300 cells more than the verapamil did ($p < 0.05$).

Among 1,2,3-triazole-bearing 2,4-diarylaminopyrimidines, derivative **48** (Fig. 6) was identified as a promising anaplastic lymphoma kinase dual inhibitor ($IC_{50}$ = 1.4 nM; ROS proto-oncogene 1 [ROS1] $IC_{50}$ = 1.1 nM).[86] Moreover, **48** demonstrated significant inhibitory activities on the ROS1-positive HCC78 ($IC_{50}$ = 40 nM), anaplastic lymphoma kinase-dependent H2228 ($IC_{50}$ = 95 nM), and KARPAS299 ($IC_{50}$ = 21 nM) cell lines. In addition, the acridine orange/ethidium bromide and western blot assays suggested that **48** induced cell apoptosis and highly inhibited cellular anaplastic lymphoma kinase and ROS1 activities.

### 3.2. Antimicrobial activity

Azoles, particularly triazoles, have been the source of several drugs, such as antibacterial and antifungal agents. In contrast, the recently discovered fused (with different heterocycles) triazoles exhibit novel antimicrobial properties. For example, 1,2,3-triazoles fused with a pyridine ring were investigated as novel lead compounds for the development of potential antimicrobial agents.[87] Two selected potential antibacterial agents (**49** and **50**, Fig. 7), which were regioselectively synthesised using the Buchwald's strategy with the *N*-heteroarene system. Compound **49** displayed a zone of inhibition of 13 and 10 against *Bacillus subtilis* and *Escherichia coli*, compared with 16 and 13 mm, respectively for streptomycin. The hybrid compound **50** displayed a zone of inhibition of 12 and 11 mm towards *B. subtilis* and *E. coli*, respectively and these triazolopyridines exhibited minimum inhibitory concentrations (MICs) similar to those of streptomycin on the *B. subtilis* strain.

Szałaj et al.[88] investigated the antibacterial properties (targeted towards the inhibition of *Ec*LepB [*E. coli* SPase I]) of the macrocyclic lipopeptides that contain *P*2–*P*1′ boronic ester fragment and 1,2,3-triazole ring. Peptide **51** (Fig. 7) demonstrated activity against all selected gram-negative bacterial strains. However, macrocycle **51** exhibited a 2-fold lower inhibition of *Ec*LepB ($IC_{50}$ = 175 nM) than other synthesised triazole-peptides whereas, in contrast, macrocycle **51** exhibited a 2-fold stronger antibacterial potency. In addition, peptides were also screened against HepG2 cells to evaluate the cytotoxicity and haemolytic potential in human blood. The results indicated that for compound **51**, the cytotoxicity was decreased (8 μM) while the haemolysis was halved (10.6%). The 1,2,3-triazole ring has become one of the major antimicrobial pharmacophore and the effect of the 1,2,3-triazole unit against wild bacterial photogenes is clear. In this regard, a set of 1,2,3-triazole-linked dehydroacetic acid-chalcone derivatives were synthesised for antimicrobial evaluation.[89] The hybrid compounds containing a substituted benzene portion exhibited more promising activity than dehydroacetic acid and dehydroacetic acid-chalcone alkyne. Among them, derivative **52** (Fig. 7) was identified as a lead compound, which displayed strong activity against *E. coli*, with an MIC of 0.0030 μM/mL.

1,2,3-Triazole-bearing benzo[*d*]-imidazo[2,1-*b*]thiazoles were also investigated for potential antimicrobial properties.[90] Compound **53** (Fig. 7) demonstrated positive anti-*E. coli*, anti-*B. subtilis*, anti-*Salmonella typhi*, and anti-*Pseudomonas aeruginosa* potency, showing low MIC values (2–8 mg/mL) that were noticeably higher than those of the positive control drugs norfloxacin, chloromycin, and fluconazole. In addition, the interaction of derivative **53** with calf thymus DNA indicated that hybrid **53** might append to DNA, forming a **53**-DNA complex that could block DNA replication to impart considerable antimicrobial activities.

Another triazole compound **54** (Fig. 7) showed stronger antifungal activities towards fungal strains, such as *Aspergillus niger* and *C. albicans* than the other synthesised hybrids did.[91] The zone of inhibition and MIC of **54** were 16 mm for *C. albicans* and 15 and $^{>}$32 μg/mL for *A. niger*, respectively. Moreover, the bio-safety analysis of compound **54** against sheep blood cells also indicated it was not cytotoxic at 1 mg/mL.

A set of hybrid compounds tethered to different fragments, which were 1,2,3-triazole, biphenyl, 2-alkoxy-3-phosphorylpropanoate, and an amine linker were synthesised and tested for bacterial transglycosylase inhibitory potency against *Acinetobacter baumannii*.[92] The transglycosylase inhibitory activities of the synthesised samples were lower at 500 μM than those of compounds **55–57** (Fig. 7), which showed much higher transglycosylase inhibitory activity (99% for each sample) at 200 μM. It should be noted that among the prepared 2-alkoxy-3-phosphorylpropanoate triazoles, the biphenyl fragment and methylene bridge affected the activity. In addition, compounds **55** and **57** also exhibited a good antibacterial potency on *Staphylococcus aureus* (MIC = 6.3 μM)

Another 1,2,3-triazole derivative was studied for antibacterial effects against several selected microorganisms including gram-positive strains, *S. aureus*, *B. subtilis*, *S. aureus* PR and gram-negative pathogens, *Klebsiella pneumoniae* and *E. coli*.[93] 4-(3-((2-Ethylhexyl)oxy)phenyl)-1*H*-1,2,3-triazole (**58**) (Fig. 7) was identified as a lead compound (2, 2, 4, and 4 μg/mL) against *S. aureus*, *B. subtilis*, *S. aureus* PR, and *K. pneumoniae*, respectively. Collectively, this report indicated the potential progress the 1,2,3-triazole moiety as a terminal amide-mimetic element, which maintained and modulated amide-tethered bioactivity.

*N*-coumaroyltyramines linked to a triazole ring were investigated as potential lead compounds, which positively controlled bacterial biofilms control.[94] Three gram-negative strains *Pseudoalteromonas ulvae* (TC14), *Pseudoalteromonas lipolytica* (TC8), and *Paracoccus* sp. (4 M6) species were selected for their ability to form biofilms. The $–OCH_3$ substituent on the tyramine fragment affected the potency and the $4–OCH_3$ derivative **59** (Fig. 7) displayed the best anti-biofilm activity, which was more effective than ampicillin was against TC14 species (11.3 and 9.3 μM for ampicillin).

Quinazolinones linked by the 1,2,3-triazole moiety showed superior

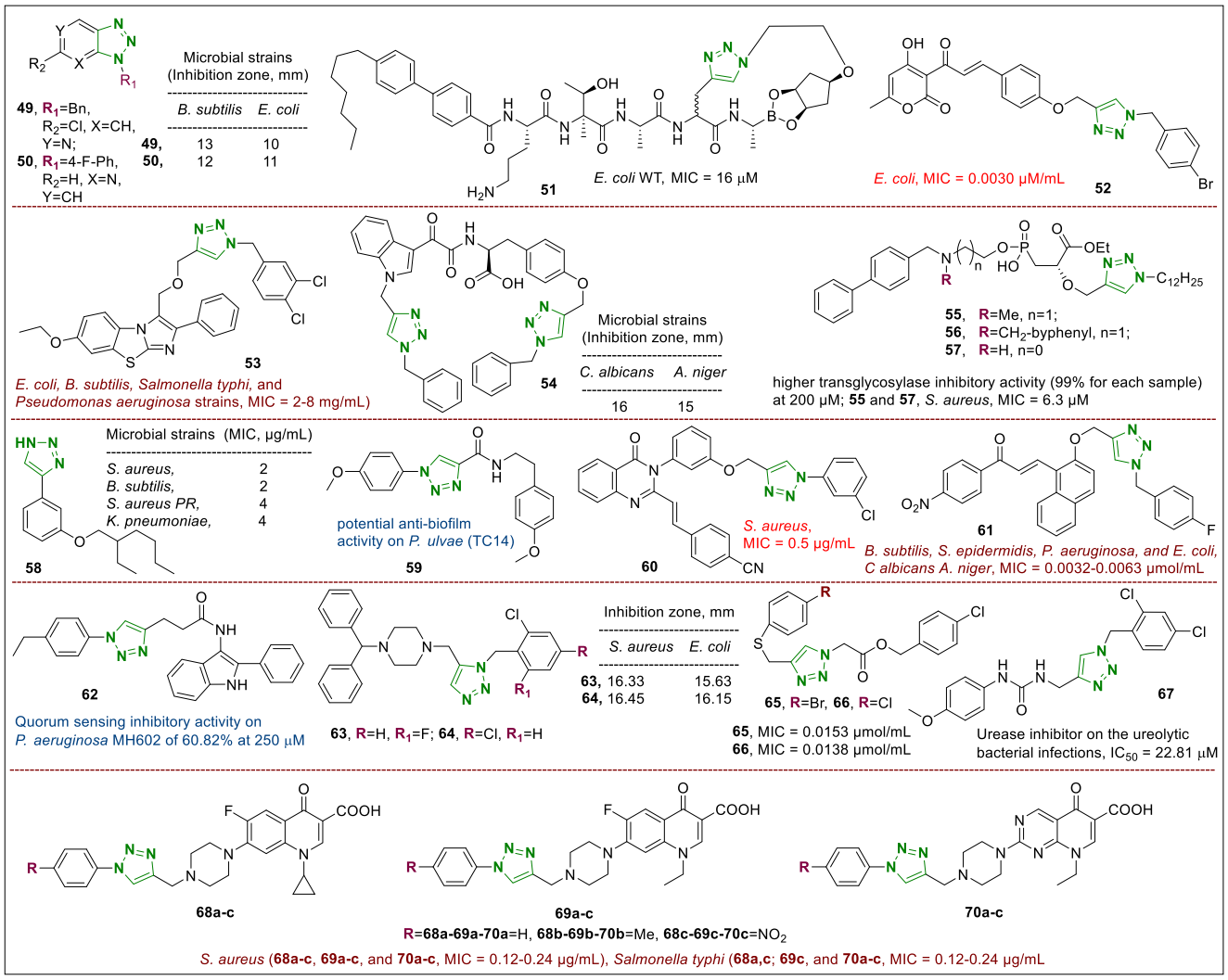



**Fig. 7.** Antimicrobial 1,2,3-triazole-linked hybrids (**49–70**).

antibacterial potential against MDR *S. aureus*.[95] Compound **60** (Fig. 7) possessed specific and strong potency against *S. aureus* (MIC = 0.5 μg/mL) and was inactive against gram-negative pathogens *A. baumannii* and *E. coli* (MIC ≥ 64 μg/mL). In addition, the hybrid compound **60** was surmounted the MDR mechanism, exhibiting highly potent inhibitory effects on MDR *S. aureus* including strains resistant to vancomycin (MIC values 0.5–32 μg/mL).

The target compound (**61**) (Fig. 7), which contained the 4-F-benzyl-, 1,2,3-triazole, –$OCH_3$-naphthalen, and 4-$NO_2$-propen-2 fragments demonstrated a unique activity against bacterial strains such as *B. subtilis*, *Staphylococcus epidermidis*, *P. aeruginosa*, and *E. coli*, as well as the fungal species, *C albicans* and *Aspergillus niger*, with MIC values of 0.0032–0.0063 μmol/mL.[96] The 1,2,3-triazole moiety and chalcone fragment clearly synergised the biological activity and the conjugation of these pharmacophoric units, indicating their synergistic properties. In addition, the docking simulation of **61** into *E. coli* topoisomerase II DNA Gyrase B showed that these triazole-chalcone conjugates may feasibly inhibit DNA topoisomerase.

The indole-triazole hybrid **62** (Fig. 7), named 4-(1-heptyl-1*H*-1,2,3-triazol-4-yl)-*N*-(2-phenyl-1*H*-indol-3-yl)butanamide, was found to have promising quorum sensing inhibitory activity against *P. aeruginosa* MH602 of 60.82% at 250 μM among the synthesised 2-phenylindole-amide-triazoles.[97] SAR analysis showed that an ethyl group at position four of the aryl portion positively affected the activity, whereas other groups, such as the bromo (-Br) derivative, exhibited moderate activity.

A set of 1,4-disubstituted 1,2,3-triazoles tethered to a benzhydrylpiperazine fragment were assayed for their antibacterial potentials against *S. aureus* and *E. coli* using the agar well diffusion method.[98] The triazole derivatives **63** and **64** (Fig. 7) were found to be more active than ciprofloxacin was (zones of inhibition: 16.33 and 16.45 mm against *S. aureus*; 15.63 and 16.15 mm against *E.coli* respectively). The combination of a 1,2,3-triazole ring with the benzhydrylpiperazine moiety increased the biological activity, demonstrating that further modifications of benzhydrylpiperazine scaffolds containing a 1,2,3-triazole portion could be a feasible strategy for developing antibacterial agents.

Several microbes (bacterial and fungal strains) including *S. epidermidis*, *B. subtilis*, *P. aeruginosa*, *E. coli*, *C. albicans*, and *A. niger* were selected to analyse the inhibitory activity of 1,4-disubstituted 1,2,3-triazole scaffolds.[99] The synthesised compound **65** (Fig. 7) displayed equal antimicrobial activity on all selected strains (MIC = 0.0153 μmol/mL) except for *A. niger*, while another lead derivative **66** (Fig. 7) showed comparable antimicrobial potential against all the microbial species (MIC = 0.0138 μmol/mL), except for *A. niger* and *B. subtilis*. The introduction of halogen substituents in the thiophenyl/benzyl fragment was found to increase the inhibitory potency.

Moghimi et al.[100] were synthesised a triazole-linked aryl urea hybrids as urease inhibitors toward on the ureolytic bacterial infections. The di-chloro-containing triazole compound **67** (Fig. 7) demonstrated superior activity with an $IC_{50}$ of 22.81 μM in the Berthelot colorimetric

assay, indicating it was a urease inhibitor. This compound bearing the 4-$OCH_3$ substituent had acceptable ADME properties and was suggested to be an attractive candidate for further design and modification in the search for novel urease inhibitors.

1,2,3-Triazole-related quinolone conjugates were also assayed in antibacterial screenings against the following selected bacterial strains: *Streptococcus pyogenes*, *S. aureus*, *E. coli*, *P. aeruginosa*, and *Salmonella typhi*.[101] Compounds **68a-c**, **69a-c**, and **70a-c** (Fig. 7), which bear aryl fragments, demonstrated high antibacterial potency against the selected *S. aureus* (for **68a-c**, **69a-c**, and **70a-c**, 0.12–0.24 μg/mL), as well as on *Salmonella typhi* (**68a**,**c**; **69c**, and **70a-c**, 0.12–0.24 μg/mL). Moreover, the statistical two-dimensional quantitative SAR (2D-QSAR) models validated the remarkable ADMET activity compound **70a** among all the prepared samples.

### 3.3. Anti-tubercular activity

Triazoles have been infrequently evaluated for their anti-tubercular properties. In contrast, 1,2,3-triazoles conjugated to diverse heterocyclic fragments were reported to demonstrate potential anti-tubercular properties in 2018. For example, 1,2,3-triazoles containing 1,3,5-triazaspiro[5.5]undeca-2,4-diene and the coumarin moiety were assayed for anti-mycobacterial activity and mycobacterial dihydrofolate reductase (*Mtb* DHFR) inhibition.[102] Among them, compounds **71** and **72** (Fig. 8) displayed strong anti-mycobacterial potency ($MIC_{50}$: 0.01–0.2 μM) on *Mycobacterium bovis* BCG than other synthesised analogues did. Both compounds also demonstrated anti-tubercular activity with $MIC_{50}$ values of 0.01 and 0.025 μM against *Mycobacterium tuberculosis* H37Rv. The cytotoxicity of these two samples was examined in the HepG2 cell line, whereas low haemolytic activity was confirmed using red blood cells (up to 100 μM). Further studies showed that **72** exhibited higher binding affinity to *Mtb* DHFR than to human DHFR. This investigation was in agreement with the selectivity observation in the enzyme inhibition assay.

Spain et al.[103] investigated Cu and Zn complexes of the triazole-cyclam bearing ligands with activity against virulent and drug-resistant *M. tuberculosis* strains. SAR analyses of the cyclam compounds with a cyclic cyclam fragment tethered to two equal naphthalimide pendants through triazole linkers were studied. The 1,2,3-triazole-linked compound **73** (Fig. 8) exhibited good water solubility (10.7 μM) and reduced bacterial load *in vivo*. It should be noted that zebrafish embryos were used to investigate the *in vivo* toxicity of a range of doses of **73** complex using the embryo survival assay.

Recently, the alkoxy-triazolequinolones **74** and **75** (Fig. 8, MIC = 6.9 and 6.6 μM, respectively) were found to be the most active compounds against *M. tuberculosis* H37Rv.[104] Moreover, they exhibited $IC_{50}$ values of 27–28 μM compared to that of ciprofloxacin (10.6 μM) when screened against *M. tuberculosis* DNA gyrase using a DNA supercoiling activity bio-assay. Compared with clinical strains including MDRs, compound **74** showed similar potency to that exhibited against ciprofloxacin-resistant strains. However, in this case ciprofloxacin may have higher *in vitro* inhibitory activity against *M. tuberculosis* DNA gyrase than derivative **74**.

A series of propylene-1,2,3-triazoles containing isatin-moxifloxacin hybrids were synthesised an evaluation for their anti-tuberculosis properties.[105] *In vitro* anti-mycobacterial potentials on *M. tuberculosis* $H_{37}Rv$ and multidrug-resistant tuberculosis (MDR-TB) strains were determined by the rapid direct susceptibility test method. All derivatives (MIC: 0.05–2.0 μg/mL) demonstrated promising MIC values against *M. tuberculosis* $H_{37}Rv$ and MDR-TB strains, however several of them were notably less active than the positive control moxifloxacin (MIC = 0.10 and 0.12 μg/mL). The most active hybrid **76** (Fig. 8) displayed equal MIC values (0.05 μg/mL) with the reference drug isoniazid, and at the same time was exhibited 2–8-fold more potency than moxifloxacin and rifampicin (MIC = 0.39 μg/mL) against *M. tuberculosis* $H_{37}Rv$. Regarding on the MDR-TB, **76** had from 2- to > 2048-fold stronger activity compared with reference drugs moxifloxacin, rifampicin, and isoniazid (MIC = 0.12, 32 and > 128 μg/mL, respectively).

Another triazole derivative **77** (Fig. 8) ($N^1$-(β-D-ribofuranosyl)-$C^4$-(4-methylcoumarin-7-oxymethyl)-1,2,3-triazole) synthesised using CuAAC was also found to be a promising anti-*M. tuberculosis* agent against the $H_{37}Rv$ strain (MIC = 5.1 μM) and MDR clinical isolate (MIC = 10.3 μM).[106] It should be noted that the authors envisioned that coumarin and triazole fragments conjugated to a –$OCH_2$- bridge would possess greater pliable as a molecule to bind to the needed or expected target. Furthermore, the minimum bactericidal concentration (MBC) of the triazole conjugates was also determined, and the results revealed that conjugate **77** containing the –OH group demonstrated low potency (MBC = 6.4 μM against the positive control isoniazid [11.5 μM]) and MDR clinical isolate. Moreover, assays on the activity of the test

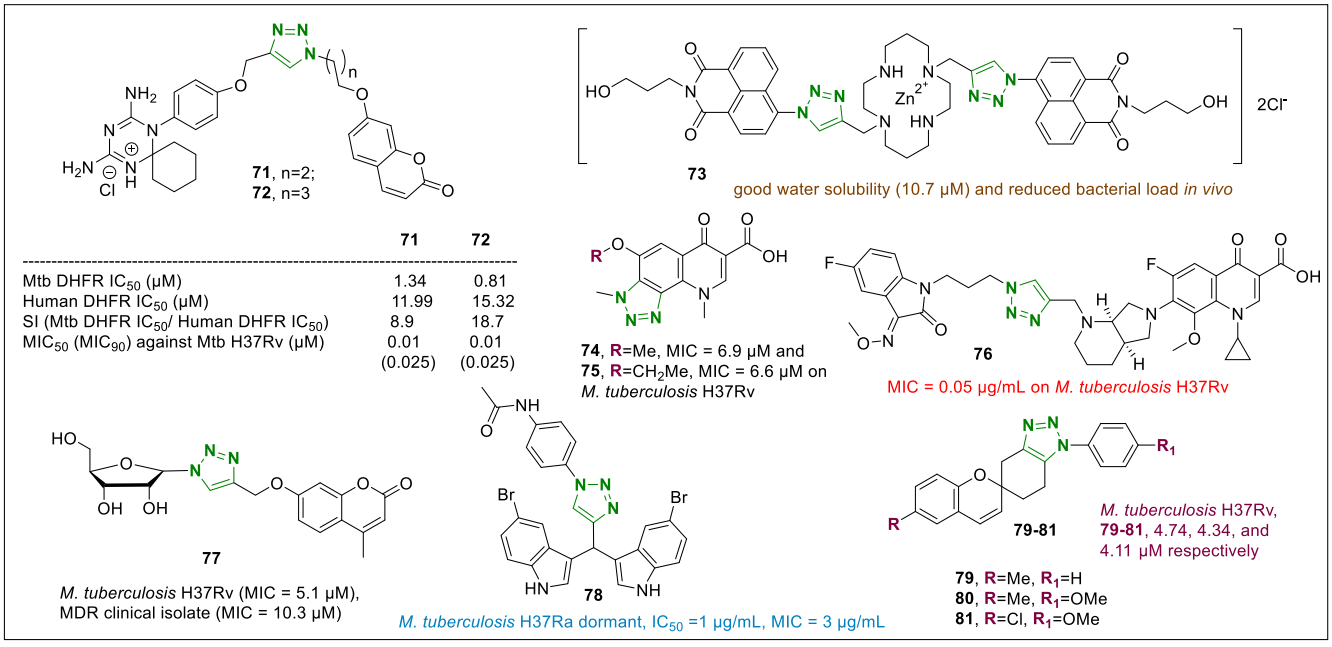



**Fig. 8.** Structures of the 1,2,3-triazole hybrids (**71–81**) with anti-tubercular activity.

samples on DNA gyrase and bacterial InhA showed that **77** significantly inhibited the enzyme activity.

The *in vitro* anti-tubercular properties of the triazole-indole hybrid derivatives were evaluated against *M.* tuberculosis H37Ra in the active and dormant state.[107] The most active compound (**78**, Fig. 8) showed superior anti-tubercular potency against *M.* tuberculosis H37Ra dormant, with $IC_{50}$ and MIC values of 1 and 3 μg/mL, respectively. Based on SARs, it was observed that the presence of a Br substituent on indole portion in derivative **78** and other Br-related indole-triazole conjugates conferred significantly higher potency than that of the unsubstituted bis-indole-triazoles.

The anti-mycobacterial evaluation of the 1,2,3-triazole-fused spirochromene scaffolds was conducted using the microplate Alamar Blue assay and the results revealed that most 1,2,3-triazoles condensed with spirochromenes showed modest to good potency.[108] Compounds **79–81** (Fig. 8) demonstrated excellent activity: 4.74, 4.34, and 4.11 μM respectively, against *M. tuberculosis* H37Rv strain.

### 3.4. Antiparasitic activity

The dipeptidyl nitriles bearing 1,2,3-triazole moiety were evaluated from the structure-diversity design point of view to search for selective trypanocidal rhodesain inhibitors.[109] Among them, compound **82** (Fig. 9) demonstrated interesting activity by inhibiting the cell growth of *Trypanosoma brucei rhodesiense* following incubation for 48 h ($IC_{50}$ = 0.064 μM). In addition, the authors also studied the pharmacokinetic properties of the synthesised compounds to further evaluate their mechanisms of action, and compare their brain penetration (by MDR1 on LLCPK1 cells) with that of other macrocyclic series. Interestingly, the MDR1 efflux ratio of **82** was improved to 6 and 20 in human and mouse MDR1, compared to 26 and 53, respectively exhibited by its lead macrocycle series.

The imidazole-triazole hybrids bearing $NO_2$-substituent along with a styryl fragment exhibited anti-amoebic potency. The target compound **83** (Fig. 9), which contains the fragments described above, was found to be the most active (0.0084 μM) against *Entamoeba histolytica* among the metronidazole-triazole-styryl hybrids.[110]

An analogue of natural lignans named 3-(3,4-dimethoxyphenyl)-5-((4-(4-pentylphenyl)-1*H*-1,2,3-triazol-1-yl)methyl)isoxazole (**84**, Fig. 9) was also identified as a lead compound with antiparasitic activity.[111] This lead hybrid and other prepared samples inhibited leukaemia THP-1 cells infected with *Trypanosoma cruzi* amastigotes *in vitro*. The assays revealed that the potency of derivative **84** was equal to that of the positive control benznidazole ($GI_{50}$ = 10.2 μM, SI > 49.1). It was observed that the introduction of the hydrophobic 4-pentyl- fragment to the compound **84** increase the potency, and because of the pliable property of the pentyl-moiety, it may interact with the hydrophobic side of the molecular target. In addition, all synthesised compounds, including triazole **84**, were assayed against amastigotes of *Leishmania amazonensis* but no significant results were obtained even at 100 μM.

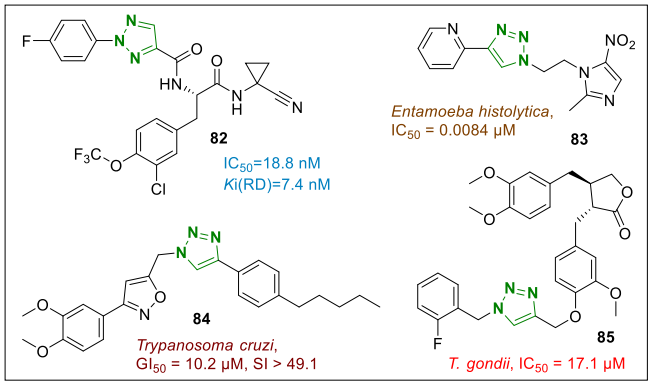



**Fig. 9.** 1,2,3-Triazole-bearing antiparasitic leads (**82–85**).

The anti-*Toxoplasma* activity of the synthesised arctigenin scaffold bearing a 1,2,3-triazole ring was evaluated *in vitro* and *in vivo*.[112] The lead compound (**85**, Fig. 9) displayed strong *in vitro* anti-*Toxoplasma gondii* activity and less cytotoxicity ($IC_{50}$ in *T. gondii* and HeLa cell line = 17.1 and 600.0 μM, respectively; SI = 35.09), indicating more promising results than those of arctigenin and spiramycin. In addition, pharmacological bioassays suggested that **85** also lead to partial tachyzoite malformation ($P < 0.05$), which suggested that arctigenin-derived compounds are potential antiparasitic drug-like units that warrant further in-depth mechanistic development.

#### 3.4.1. Antimalarial activity

Malaria still remains one of the most deadly diseases in the world, and natural and synthetic 1,2,3-triazoles have been successfully used against malaria in medicinal chemistry.[113,114] Brandão et al.[115] synthesised naphthoquinonolyl-tethered 1,2,3-triazole hybrids using CuAAC, based on a lapachol modification and their antiplasmodial potentials against malaria were reported. Hybrid products were assayed against chloroquine-resistant *Plasmodium falciparum* (W2) and a HepG2 cell line. Among them, several derivatives, in particular, compound **86** (Fig. 10, $IC_{50}$ = 5.2 μM, SI = 197.7) exhibited stronger antimalarial potency and selectivity than lapachol did ($IC_{50}$ = 123.5 μM, SI ≥ 33.4). Other 1,2,3-triazole hybrids bearing pyrimidine-chloroquinolines were screened for their antiplasmodial potential against chloroquine-sensitive NF54 strains of *P. falciparum*.[116] The lead compound (**87**, Fig. 10) with $IC_{50}$ of 0.048 μM demonstrated excellent activity, and a superior SI (317.50; $IC_{50}$ in Vero cells = 15.24 μM). It should be noted that the SAR analysis revealed that the nature of the substituent on the triazole-linked pyrimidine core (in the case of **87**, the *p*-nitro group) obviously enhanced the antiplasmodial properties.

The antiplasmodial activity of the novel coumarin-triazole hybrid **88** (Fig. 10) was evaluated on a chloroquine-sensitive 3D7 strain of *P. falciparum*, and exhibited higher activity ($IC_{50}$ = 0.763 mg/mL.[117] This lead compound contained two electron-donating $–OCH_3$ substituents in the benzene portion, which apparently affected the antimalarial activity. In addition, the effect of **88** on the supercoiling potency of DNA gyrase relaxed the plasmid DNA and inhibited the supercoiling activity, which could be attributable to the prevention of ATP hydrolysis needed for the inhibition of the gyrase DNA binding and on enzymatic cycle.

Triazole-linked glycohybrids of the isatin hydrazones were synthesised to develop compounds with the antimalarial potential and antiplasmodial properties.[118] Derivative **89** (Fig. 10) and its diacetonide galactose analogue (at the sugar portion), which exhibited equal activity to that of the lead compound **88** with a $–OCH_3$ substituent in the benzene ring of hydrazone part, displayed good potency against the sensitive strain 3D7, with $IC_{50}$ values of 1.27 and 1.64 μM, respectively. In addition, hybrid **89** and its diacetonide galactose analogue with $IC_{50}$ values < 2 μM against *Pf*3D7 strain, showed strong $CC_{50}$ values of 62.52 and 105.25 μM, respectively. These results clearly show that these active derivatives had promising $CC_{50}$ values and their safety was also reflected by their high SI values of 49.22 and 64.17 μM, respectively, for the *Pf*3D7 strain.

#### 3.4.2. Anti-leishmanial activity

Leishmaniasis is one of the public health problem and its treatment is quite challenging and there are concern for the emergence of resistant strains.[119] To address this issue, novel hybrid compounds bearing 1,2,3-triazole and thiosemicarbazone moieties were identified by Temraz et al. [1 2 0] and evaluated for anti-leishmanial potential.[120] Notably, hybrid **90** (Fig. 11) demonstrated nanomolar activity against *Leishmania major* promastigotes ($IC_{50}$ = 140.3 nM), while against axenic amastigotes, the $IC_{50}$ value was 1 μM, indicating an 8-fold higher activity than that of miltefosine. *In vivo* acute toxicity testing revealed no toxicity after treatment with the lead compound **90**, and the liver, lung, spleen, and kidney isolated from mice administered 75 mg/kg

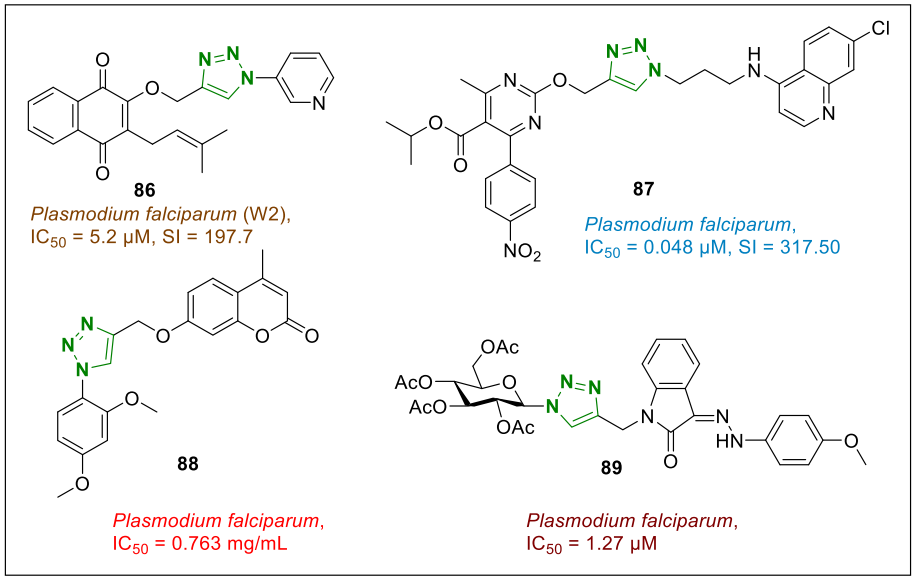



**Fig. 10.** 1,2,3-Triazole-bearing antimalarial leads (**86–89**).

parenterally or 125 mg/kg orally demonstrated normal texture.

Teixeira et al.[121] investigated the synthetic pathway and anti-parasitic activity of eugenol (a natural compound)-based compounds tethered to 1,2,3-triazole rings, considering the leishmanicidal effect of eugenol compounds and studies that have shown the anti-leishmanial activity of 1,2,3-triazole-containing compounds. A 4-(3-(4-allyl-2-methoxyphenoxy)propyl)-1-(4-methylbenzyl)-1*H*-1,2,3-triazole (**91**, Fig. 11) was found to be more active ($IC_{50}$ = 7.4 μmol $L^{-1}$) than the other triazole-linked eugenol derivatives were, which was also assayed in *Leishmania* parasites peritoneal macrophages ($IC_{50}$ = 1.6 μmol $L^{-1}$) and showed effects on cell viability. The cytotoxic potential of **91** on macrophage cells was evidenced by an $IC_{50}$ of 211.9 μmol $L^{-1}$, while the SI was 132.5. In addition, the triazole derivative **91** demonstrated higher effects than those of pentamidine and glucantime (drugs used clinically).

In anti-leishmanial research, other 1,2,3-triazole-linked heterocycles containing quinolone skeleton were synthesized.[122] All triazole hybrids synthesised were evaluated against intracellular amastigotes and extracellular promastigotes of luciferase expressing *Leishmania donovani*. (1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl 6-chloro-2-methyl-4-phenylquinoline-3-carboxylate (**92**, Fig. 11) exhibited promising anti-amastigote potency with an $IC_{50}$ of 7 μM. Derivative **92** and some of the other synthesised derivatives were prepared for further *in vivo* assay. The effects of the compounds in a golden hamster model were evaluated at 50 mg $kg^{-1}$ administered intraperitoneally for 5 consecutive days, and triazole **92** exhibited continuous activity (~46% parasite inhibition) after treatment day 28.

It was suggested that the triazole-based dipeptide containing leucine moiety (**93**, Fig. 11) has promising anti-leishmanial activity.[123] The $IC_{50}$ value calculated based on normal growth inhibition and $IC_{50}$ value of **93** on *Leishmania major* promastigotes was 11 μg/mL. The most relevant factors were the cytotoxicity, lipophilicity and antiparasitic activity of the lead compounds a substantial points for the design of a new anti-leishmanial agents. Furthermore, the dipeptide **93** was more lipophilic than other prepared dipeptides were in this investigation.

### 3.5. Antiviral activity

Notwithstanding the existence of various types of antiviral drugs in clinical treatment, human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) still remain an increasing challenge to public health.[124] Therefore, the 1,2,3-triazole hybrids were

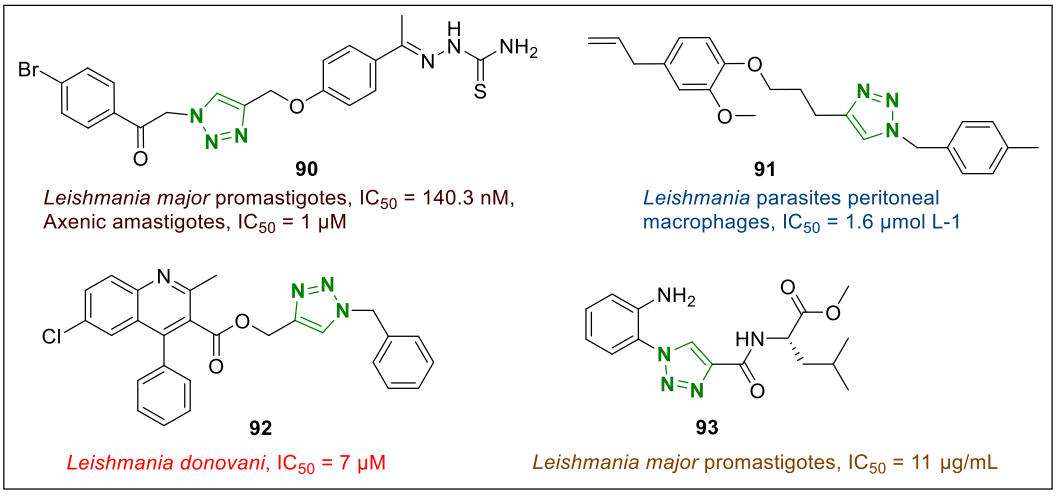



**Fig. 11.** 1,2,3-Triazole-related anti-leishmanial leads (**90–93**).

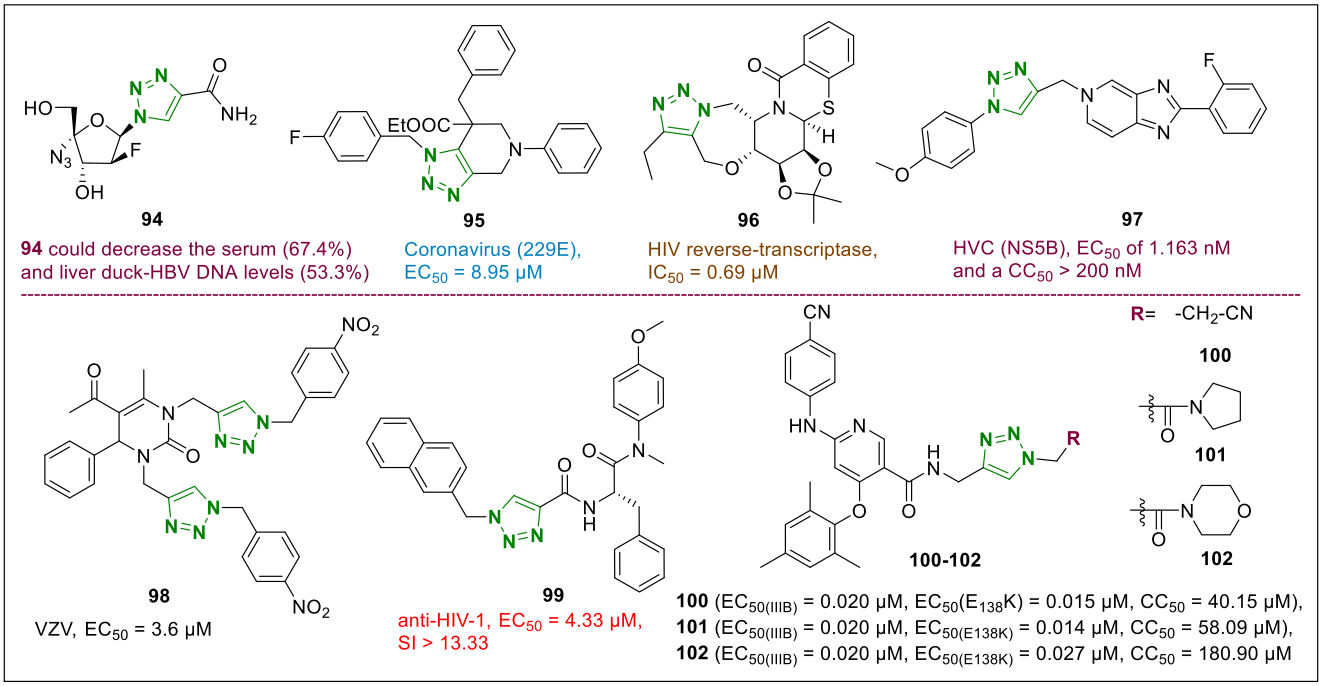



**Fig. 12.** Structures of the 1,2,3-triazole hybrids (**94–102**) with antiviral activity.

identified as lead candidates, indicating superior effects on diverse viral types. Anti-hepatitis B virus (HBV) properties of a novel hybrid with 4-monosubstituted 2′-deoxy-2′-β-fluoro-4′-azido-β-D-arabinofuranosyl-1,2,3-triazole scaffolds were studied by Liu et al.[125] It was observed that triazole compound **94** (Fig. 12) had promising antiviral potentials and impressive activity against the lamivudine-resistant HBV mutants, which were also screened against HBV-infected duck models. The results showed that both the serum (67.4%) and liver duck-HBV DNA levels (53.3%) clearly decreased after treatment with **94**.

A series of fused 1,2,3-triazole heterocycles and their antiviral properties have been explored by Karypidou et al.[126] All synthesised hybrids were tested against several types of viruses such as HIV (types 1 and 2), herpes simplex viruses (types 1, 1 TK$^-$, and 2), adeno virus-2, coronavirus, and vaccinia virus and values were compared with the appropriate positive control drugs (zidovudine, brivudine, cidofovir, ganciclovir, acyclovir, alovudine, and Urtica dioica agglutinin, and zalcitabine). However, antiviral assays indicated that the majority of compounds had slight or no activity against selected viruses. Among them only derivative **95** (Fig. 12) with an $EC_{50}$ value of 8.95 μM was an averagely active compound against the human coronavirus (229E), but displayed nearly 50-fold lower inhibitory potency than Urtica dioica agglutinin ($EC_{50}$ = 0.2 μM).

The pentacyclic iminosugar compounds were constructed by fusing triazolo[5,1-*c*][1,4]oxazepine scaffolds and were investigated for their HIV reverse-transcriptase inhibitory potentials.[127] All synthesised samples demonstrated inhibitory activity against reverse-transcriptase. In particular, derivative **96** (Fig. 12), which displayed an $IC_{50}$ value of 0.69 μM against reverse-transcriptase was identified as a lead compound. Another triazole compound **97** (Fig. 12), which was synthesised by replacing the pyridazine moiety with a 1,2,3-triazole ring, was suggested to have potential non-nucleoside inhibitory activity against hepatitis C virus (HVC) NS5B.[128] Compound **97** showed an $EC_{50}$ of 1.163 nM and a $CC_{50}$ > 200 nM in a cell-based HCV replicon system experiments, with respect to potency and pharmacokinetics.

Hybrid molecules containing triazole and dihydropyrimidinone rings synthesised via Huisgen azide-alkyne cycloaddition were evaluated against human varicella-zoster virus activity.[129] Here, hybrid **98** (Fig. 12) demonstrated a strong antiviral potential, with an $EC_{50}$ of 3.6 μM on TK$^+$ varicella zoster virus (VZV) strain, which decreased to 7.8 μM against the TK$^-$ strain. Additionally, it should be noted that the replacement of the benzyl fragment by 4-$NO_2$-benzyl (in the case of **98**) enhanced the antiviral potencies against TK$^+$ VZV strains and considerably reduced the cell growth inhibition.

Antiviral activity investigation of the novel 1,2,3-triazole-phenylalanine derivatives obtained by CuAAC against HIV-1 CA protein inhibitors showed that derivative **99** (Fig. 12) showed superior anti-HIV-1 potency ($EC_{50}$ = 4.33 μM, SI > 13.33), which was equal to that of the HIV-1 capsid inhibitor 2-methyl-*N*-[(1*S*)-2-(methylphenylamino)-2-oxo-1-(phenylmethyl)ethyl]-1*H*-indole-3-acetamide ($EC_{50}$ = 5.95 μM, SI > 11.85).[130] Moreover, **99** interacted strongly with recombinant HIV-1 CA and exhibited antiviral potential in the early and late stages of HIV-1 replication.

New 1,4-disubstituted 1,2,3-triazole-bearing diarylnicotinamides were examined for anti-HIV potentials against wild-type (WT, IIIB and ROD) and multiple mutant strains by Tian et al.[131] Three of the most potent lead derivatives identified were **100** ($EC_{50(IIIB)}$ = 0.020 μM, $EC_{50(E138K)}$ = 0.015 μM, $CC_{50}$ = 40.15 μM), **101** ($EC_{50(IIIB)}$ = 0.020 μM, $EC_{50(E138K)}$ = 0.014 μM, $CC_{50}$ = 58.09 μM), and **102** ($EC_{50(IIIB)}$ = 0.020 μM, $EC_{50(E138K)}$ = 0.027 μM, $CC_{50}$ = 180.90 μM; Fig. 12), which showed equal promising potency against the E138K mutant strain. However, it also demonstrated lower cytotoxicity than the other derivatives. Compounds **101** and **102** were also evaluated for possible inhibitory activity against the reverse transcriptase of HIV-1, and they displayed average inhibitory potency of with $IC_{50}$ of 2.70 and 1.57 μM, respectively, which are approximately 1–3-fold less potent than that of the reference drug etravirine (0.75 μM). Nevertheless, **101** and **102** were suggested as leading compounds against HIV-1 non-nucleoside reverse transcriptase inhibitors.

### 3.6. Antidiabetic activity

Quinazolinone-1,2,3-triazole possessing a 4-Br-benzyl fragment in the triazole portion (**103**, Fig. 13) was identified as a superior lead compound with antidiabetic properties and it inhibited α-glucosidase in a competitive manner, with a Ki value of 117 μM. Docking studies of this lead compound confirmed it was well-docked in the active site of α-

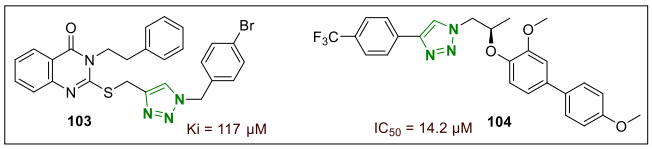



**Fig. 13.** Structures of 1,2,3-triazole leads (**103** and **104**) with antidiabetic activity.

glucosidase where critical interactions occur.[132] *α*-Glucosidase inhibition is an efficacious method for controlling post-prandial hyperglycaemia in diabetes patients. The recently synthesised lead hybrid, (*R*)-1-(2-((3,4′-dimethoxy-[1,1′-biphenyl]-4-yl)oxy)propyl)-4-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (**104**, Fig. 13), exhibited activity against the target enzyme, which was the best among all the synthesised triazole derivatives, with $IC_{50}$ value of 14.2 μM in inhibition of the *α*-glucosidase enzyme.[133] Moreover, molecular modelling analysis revealed that **104** displayed a preferential binding mode by interacting with three active site residues Arg312, Glu304, and Phe158, which suggested that further developments of **104** may provide new lead compounds as antidiabetic drugs.

### 3.7. 1,2,3-Triazoles as neuroprotective agents

Neuroprotection is one of the most challenging aspects of current medical research for the development of treatment of neurological disorders, including Alzheimer's, Parkinson's, and Huntington's diseases. Furthermore, the design, synthesis, and modification of neuroprotective agents based on the 1,2,3-triazole-linked hybrids has remained an important research direction in recent years.[134] 1,2,3-Triazoles bearing longanlactone analogues were synthesised for potential enhanced neurotrophic activity.[135] The *in vitro* cell cytotoxic potentials of the synthesised natural product derivatives were examined against mouse neuroblastoma cells (Neuro-2a). Among the 1,2,3-triazole-containing derivatives, **105** (Fig. 14) demonstrated strong neurotrophic activity in Neuro-2a cells, which was confirmed by a battery of cell-based and neurite outgrowth assays. Derivative **105** distinctly increased neurite length compared to dimethyl sulfoxide (DMSO).

Lou Gehrig's disease (also known as amyotrophic lateral sclerosis [ALS]) is a neurological malady of the central nervous system (CNS). The pathology includes a progressive loss of motor neurons in the CNS, which control motor functions that normally leads to death within 3–5 years after diagnosis. Using a set of triazole-riluzole-hybrids and a novel motor neuron screening approach, Sweeney et al.[136] identified several novel triazoles as neuroprotective agents. The derivatives with substituents that tethered a pyridyl fragment, such as compounds **106** and **107** (Fig. 14), demonstrated higher neuroprotective potency than riluzole against two independent *in vitro* bioassays in primary neurons.

Gamma-aminobutyric acid (GABA) is an important inhibitor of neurotransmitters in the CNS. In this regard, Giraudo et al.[137] investigated derivatives bearing hydroxy (OH) substituents in the 1,2,3-triazole moiety as promising biomimetics of GABA inhibitors. The authors studied all synthesised triazoles for receptor binding research to determine the binding affinities of the derivatives to native GABA receptor, using rat brain membrane preparations. Pharmacological assays revealed that the diphenylpropyl-substituted lead compound **108** (Fig. 14) showed a higher *K*i value (1.6 μM) and molecular modelling analysis showed that **108** adopted a binding pose where the triazole portion was orientated at a 180° flip. In addition, the authors suggested that alkylation of the triazole molecule is a potential strategy for the further development of this heterocyclic system for activity on $GABA_A$ receptors.

Novel fused triazole 6-methyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine derivatives were synthesised as P2X7 receptor antagonists by Chrovian et al.[138] The 1,2,3-triazole-fused lead **109** (Fig. 14) increased the plasma free fraction that exhibited potential P2X7 receptor occupancy in the hippocampus of rats, with a low $ED_{50}$ value of 0.07 mg/kg, and unbound plasma $EC_{50}$ value of 12 ng/mL. Moreover, **109** suppressed brain interleukin (IL)-1*β* release *in vivo* in freely moving rats challenged with the P2X7 agonist Bz-ATP. In addition, the hybrid derivative **109** had notable solubility and showed good tolerability in preclinical studies, resulting in an acceptable cardiovascular safety profile *in vivo*. In addition, the lead compound **109** was selected as a candidate for investigation in clinical trials (phase I) to evaluate the safety and tolerability in healthy humans towards development for the treatment of mood disorders.

Luo et al.[139] synthesised several F-18-linked oxadiazole-triazole hybrids with activity on sphingosine-1-phosphate receptor 1 for effects on neuroinflammatory diseases of CNS. The radiosynthesised sample **110** (Fig. 14) was subjected to primary screening to test its permeability across the blood–brain barrier in rodents *in vivo*, because of its high sphingosine-1-phosphate receptor 1 binding potency ($IC_{50}$ = 9.7 nM). It was observed that **110** had satisfactory radiochemical yield (~14.1%), high (> 98%) radiochemical purity, nearly 54.1 GBq/μmol specific activity, and showed no defluorination *in vivo*.

Volinanserin (also known as M100907) is a strong 5-HT2AR receptor antagonist for the treatment of diseases such as sleep disorders and schizophrenia. Gilbertson et al.[140] synthesised active, selective (+)-volinanserin enantiomer along with a series of derivatives containing a 1,2,3-triazole ring, which were evaluated to elucidate and develop their activity on 5-HT2AR in the CNS. However, in this investigation, the prepared samples did not exert the antagonistic ability of the bivalent ligand. However, although compound **111** (Fig. 14, $pIC_{50}$ = 7.44; $IC_{50}$ = 36.5 nM) exhibited less activity than that of the parent compound (+)-volinanserin ($pIC_{50}$ = 8.32; $IC_{50}$ = 4.8 nM), this compound exhibited comparable activity to that of a recently synthesised series of 5-HT2AR bivalent ligands, which bear several ethylene glycol linkers.

#### 3.7.1. 1,2,3-Triazoles as Alzheimer's disease agents

A novel series of 1,2,3-triazol-coumarin-lipoic acid conjugates were investigated for neuroprotective and anti-acetylcholinesterase (anti-AChE) activities as multi-target-directed ligands for the treatment of Alzheimer's disease.[141] Specifically, compound **112** (Fig. 14) identified as a potential AChE inhibitor (16.4 μM), displayed satisfactory inhibition of Aβ peptide aggregation (51.2%). In addition, derivative **112** showed selective bio-metal chelation, protecting against intracellular ROS formation, as well as neuroprotection against $H_2O_2$- and $Aβ_{1-42}$-induced cytotoxicity.

To evaluate the neuroprotective effects using hybridisation approach, another benzo[*f*]coumarin, **113** (Fig. 14), was synthesised and identified as the most active derivative with $IC_{50}$ values of 7.3 μM for AChE and 68.6 μM for butyrylcholinesterase (BuChE).[142] The steady-state inhibition assay showed that high concentrations of derivative **113** showed increase inhibitory potency.

Novel sarsasapogenin-triazolyl hybrids were prepared and reported as promising anti-Alzheimer's agents.[143] These hybrids were screened for their $Aβ_{1-42}$ aggregation inhibitory potentials and several derivatives, including **114** (Fig. 14, 84.74%; positive control curcumin = 5.87%) showed high activity in inhibiting the formation of $Aβ_{1-42}$ fibrils, and moderate (25 μM) neuroprotective activity against hydrogen peroxide ($H_2O_2$)-induced neurotoxicity in SH-SY5Y cells.

To target Alzheimer's disease, the inhibitory effects of a series of novel tacrine-1,2,3-triazole compounds were investigated on *Electrophorus electricus* AChE and horse serum BChE.[144] Among the synthesised derivatives, hybrid **115** (Fig. 14) strongly inhibited AChE (75%) and BChE (90%) with $IC_{50}$ values of 4.89 and 3.61 μM at a concentration of 100 μM, respectively. It should be noted that, although the inhibition of cholinesterase by compound **115** was slightly lower than that by the positive control drug tacrine, their unique binding mode suggested by the appropriate analysis made them lead compounds for the development of novel dual inhibitors of AChE and BChE.

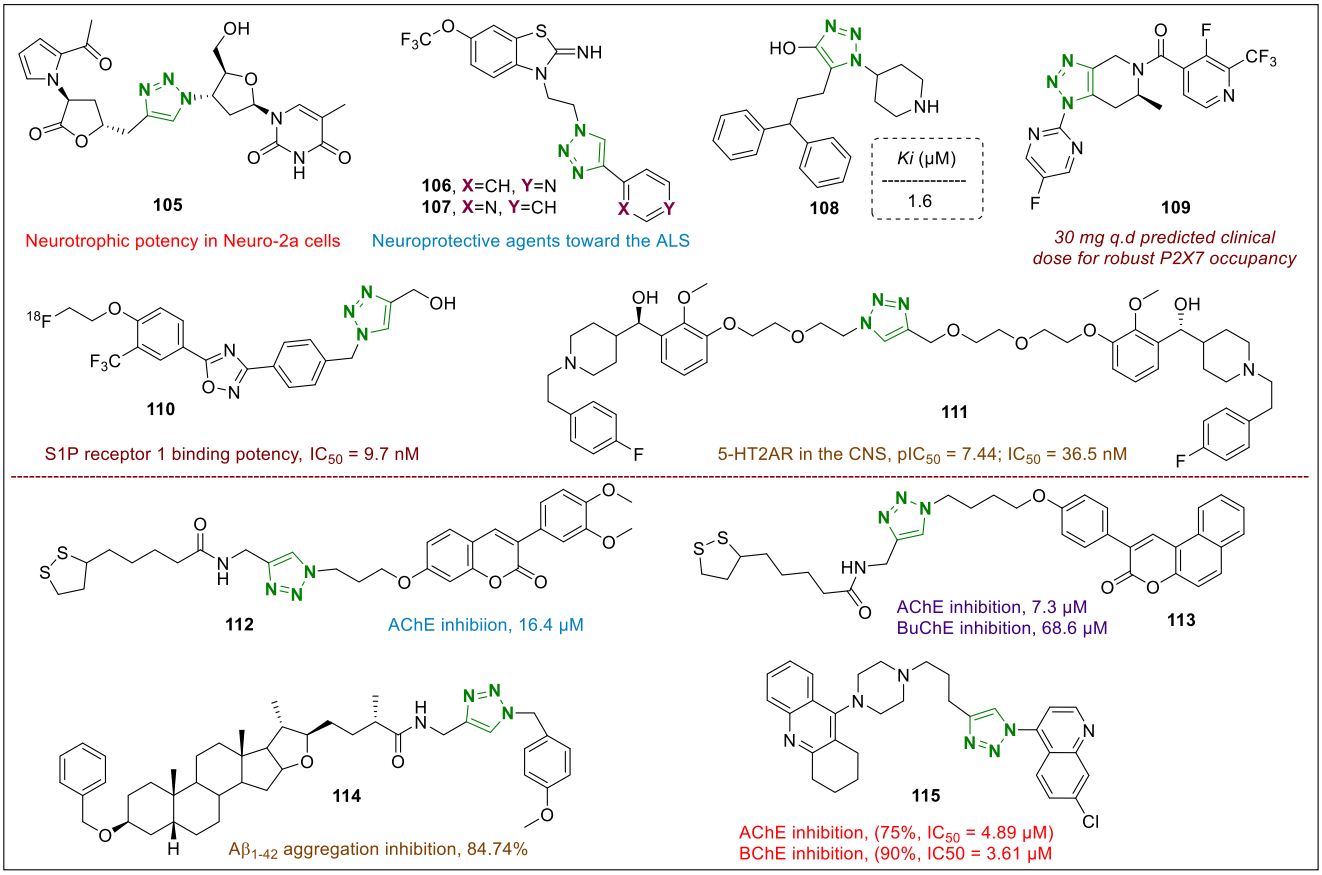



**Fig. 14.** Neuroprotective and Alzheimer's disease agents based on 1,2,3-triazole units (**105–115**).

### 3.8. 1,2,3-Triazoles as anti-inflammatory agents

Novel thioquinazolinone-1,2,3-triazole compounds were synthesised using Huisgen azide-alkyne cycloaddition to identify new anti-inflammatory agents targeting COX-2 and LOX inhibition.[145] Among them, **116–118** (Fig. 15) inhibited COX-2 with $IC_{50}$ values 0.19, 0.11, and 0.16 μM, respectively while the 15-LOX inhibition analysis showed $IC_{50}$ values of 4.33, 7.62, and 5.21 μM, respectively. The COX-2 inhibition values of these three compounds were compared to those of celecoxib, diclofenac, and indomethacin, while 15-LOX inhibition rates were compared with zileuton and meclofenamate sodium as reference drugs. In addition, the thioquinazolinone-1,2,3-triazole **118** inhibited monocyte to macrophage differentiation efficiently ($IC_{50}$ = 5.63 μM, $IC_{50}$ = 4.86 μM for diclofenac sodium) after challenged by PMA-induced THP-1 differentiation assays.

The 1,2,3-triazole-coumarin hybrids tethered to HO-substituents and phenyl-sulfonate fragment at the position 7, were synthesised and their anti-inflammatory properties, were studied focusing on the assay of proinflammatory cytokines such as tumour necrosis factor (TNF)-α, in the lipopolysaccharide (LPS)-stimulated U937 cell line.[146] The most potent compound, **119** (Fig. 15), potently suppressed TNF-α at 10 μM (62%), and the $IC_{50}$ value in LPS-stimulated U937 cells was 8.01 μM. Moreover, **119** was evaluated for inhibitory activity on TNFSF11-induced osteoclastogenesis in RAW 264.7 cells. The mechanism of action studies showed that the hybrid derivative **119** displayed dose-dependent inhibition of TNFSF11-induced osteoclastogenesis by suppressing the NF-kB pathway. TNFSF11 stimulation considerably enhanced the phosphorylation of NF-kB (ser 536), IkBα (ser 32), and IKKα/β (ser 176/180), while the lead compound, **119**, dose-dependently (2.5, 5, and 10 μM) decreased their phosphorylation.

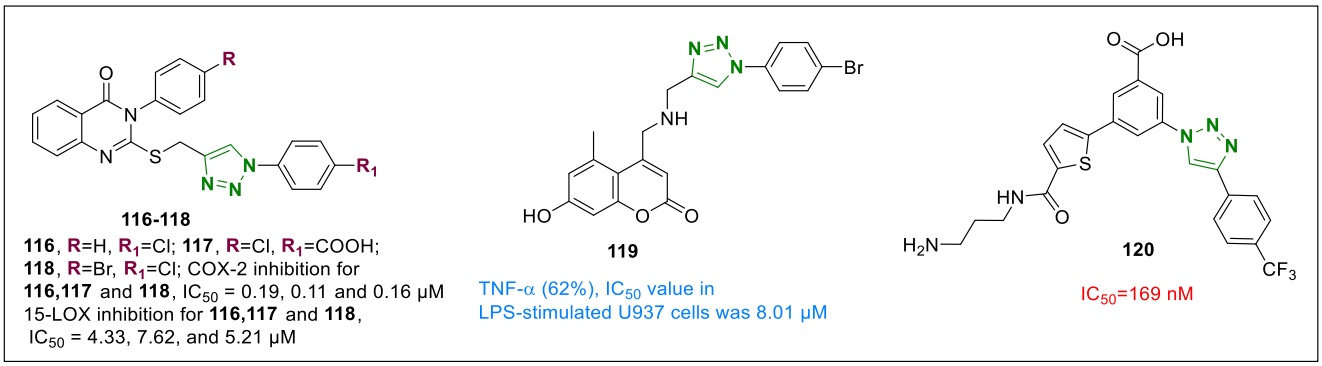



**Fig. 15.** 1,2,3-Triazole-bearing lead compounds (**116–120**) with anti-inflammatory activity.

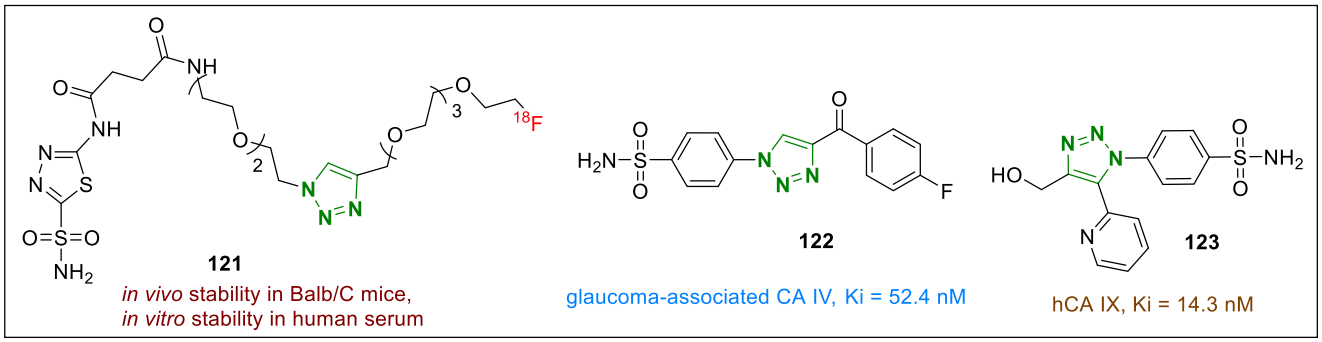



**Fig. 16.** Structures of 1,2,3-triazole hybrids (**121–123**) with carbonic anhydrase activity.

Yu et al.[147] reported the activity of a modified 1,2,3-triazole-linked $P2Y_{14}R$ antagonist for the reduction of inflammation. It was observed that compound **112** exhibited the most potent antagonists properties (Fig. 15) in the fluorescent assay, and **112** has three $CH_2$ chains between two amines tethered to the thiophene ring via an amide linker.

### 3.9. 1,2,3-Triazoles as carbonic anhydrase agents

The 1,2,3-triazole-linked [$^{18}$F]-PET tracer (**121**, Fig. 16) was identified as a potential carbonic anhydrase IX (CA-IX) inhibitor in both *in vitro/in vivo* bioassays and mechanism of action was reported by More et al.[148] The authors began their *in vivo* experiments by injecting the lead compound **121** into CA-IX expressing 4T1 and HT-29 skin cells to evaluate the effect of PET tracer on the absorption in cell lines. In particular, evaluation of the activity of compound **121** as a CA-IX inhibitor showed that it was distributed in the bodies of the mice, and after harvesting various body organs, a biodistribution assay also was carried out. The results revealed that sample **121** localised in the tumour in trace amounts but was mostly accumulated in the intestine in both tumour types. The pharmacokinetic of **121** was evaluated by assessing its distribution coefficient, *in vivo* stability in Balb/C mice, and *in vitro* stability in human serum.

Benzenesulfonamide derivatives containing the 1,2,3-triazole moiety were evaluated for potential carbonic anhydrase properties on the isoforms CA-I–IX, and the inhibition rates of the target compounds were compared with that of acetazolamide, which is a clinically used positive control drug.[149] All the newly synthesised derivatives exhibited superior Ki values (86.8 nM) on the CA I, while their effects against other tumour-associated isoforms were weaker than the reference drug or moderate. Derivative **122** (Fig. 16) demonstrated excellent inhibitory potency against glaucoma-associated CA IV ($K_i$ = 52.4 nM) compared with acetazolamide. It is generally understood that sulphonamide bearing scaffolds are the most important CA inhibitors. Therefore, this strategy was used to develop other novel benzenesulfonamides bearing 1,5-diaryl-1,2,3-triazoles moieties, which were screened for their CA-I–IX inhibition.[150] In the stopped flow carbon dioxide hydration assay, all synthesised samples highly inhibited the cytosolic isoform CA-I, displaying Ki values of 53.2 nM to 7.616 μM. Regarding the investigation of the tumour-associated *trans*-membrane isoform CA-IX, derivative **123** (Fig. 16) demonstrated better inhibition than acetazolamide did (Ki = 14.3 nM).

### 3.10. 1,2,3-Triazoles towards on treatment of renal anaemia

Wu et al.[151] suggested that the triazole compound **124** (Fig. 17) is a highly potent candidate for the treatment of renal anaemia. They confirmed the activity of the HIF-PHD inhibitor **124** ($IC_{50}$ = 62.23 nM), which was 10-fold higher than that of roxadustat ($IC_{50}$ = 591.4 nM). Furthermore, the *in vivo* biological assays revealed its upregulation of haemoglobin in cisplatin-induced anaemic mice (120 g/L) to normal levels (160 g/L) with no obvious toxicity.

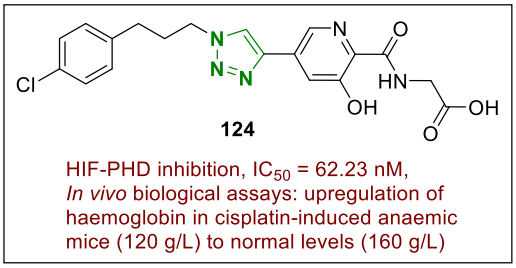



**Fig. 17.** Structure of lead 1,2,3-triazole **124**.

### 3.11. 1,2,3-Triazoles as anti-adipogenic agents

The indole-triazole hybrids were synthesised using the click method and studied for anti-adipogenic properties.[152] In this study, a *N*-((1-(2,3-difluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4-methyl-*N*-((1-tosyl-1*H*-indol-3-yl)methyl)benzenesulfonamide (**125**, Fig. 18) was identified as a promising anti-adipogenic agent with an $IC_{50}$ of 1.67 μM, which was more potent than that of its parent compound. Further evaluation revealed that the anti-adipogenic activity of this lead compound was evident in the early stage of adipogenesis, which in the mitotic clonal expansion it was controlled the G1 to S phase cell cycle arrest. The mechanistic investigations revealed that the hybrid derivative **125** exhibited anti-adipogenic properties by activating the Wnt/β-catenin pathway, and adipogenic genes such as *PPARγ* and *C/EBPα*. Moreover, **125** showed correlating decreased of PPARγ and increased expression of β-catenin in epididymal white adipose tissue *in vivo*.

### 3.12. Antioxidant activity

A series of newly functionalised 1,2,3-triazole-pyrimido[4,5-*c*]isoquinolines were synthesised for antioxidant screening.[153] *In vitro* antioxidant activity analysis (by 2,2-diphenyl-1-picrylhydrazyl (DPPH) method) revealed that compound **126** (Fig. 19) exhibited stronger antioxidant potency with an $IC_{50}$ value 6.02 μM than the positive control drug Trolox did (1.94-fold higher activity than the positive control drug Trolox). It should be noted that the most common derivatives with tethered electron-withdrawing substituents (such as F, Cl and $NO_2$) in

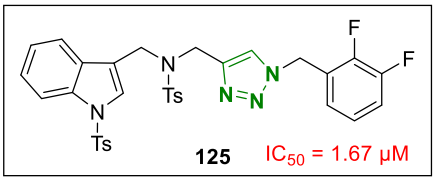



**Fig. 18.** Structure of lead 1,2,3-triazole **125**.

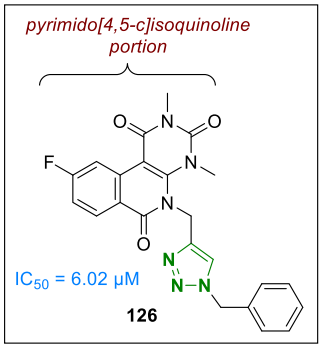



**Fig. 19.** Structure of lead 1,2,3-triazole **126**.

the triazole moiety and pyrimidoisoquinoline system showed average to high antioxidant properties.

### 3.13. Multi-target investigation of the various activities of 1,2,3-triazoles

Several 1,2,3-triazole-containing coumarino-pyrazole compounds were synthesised and evaluated for AChE, anti-tyrosinase, anti-5–5-LOX, and anticancer potentials.[154] The 1,4-substituted triazole regioisomers **127** and **128** (Fig. 20) demonstrated satisfactory activities in all target bioassays. For example, the anti-BChE activity results showed that tri-chlorine-related compounds **127** (29.0 μM) and **128** (18.0 μM) were more active than the other synthesised cycloadducts were, while the anti-5-LOX activity assay showed the same observation, i.e., **127** and **128** were displayed strong activity with $IC_{50}$ values of 24.0 and 21.0 μM, respectively. Anti-tyrosinase activity assays of these two cycloadducts showed they were 58 and 72%, less active than the other samples were. However, compound **128** ($IC_{50}$ = 6.0 μM) showed the highest cytotoxicity against the HCT-116 cells, among all evaluated 1,2,3-triazole tethered coumarinopyrazole conjugates.

### 3.14. Miscellaneous activities

1,2,3-Triazole-bearing disaccharides were investigated as RNase A inhibitors for the first time by Kayet et al.[155] It was suggested that except a linker type action of the triazole moiety to carbohydrates, these azoles could direct the sugar fragments to the binding sites of enzymes. The bio-physical assays revealed that compound **129** (Fig. 21) decreased the ribonucleolytic potency most efficiently, whereas derivative **130** (Fig 21) also exhibited higher inhibitory activity in the agarose gel electrophoresis than other prepared compounds with a missing –COOH substituent did. Kinetics studies showed that the triazole hybrid **130** had weaker RNase A activity (*Ki* = 65 μM) than its homolog, **129** (*Ki* = 50 μM), did, which confirm that introducing a carboxylic functional group at C-3 positions of furanose rings decreased the *Ki* values.

Kozarski et al.[156] reported a set of 7-methylguanosine phosphate substances bearing a 1,2,3-triazole ring at the position 5 as promising inhibitors of human cNIIIB. Among the four prepared analogues, compound **131** (Fig. 21) inhibited cNIIIB potency with an $IC_{50}$ value of 87.8 μM), while the other three substances were inactive. Moreover, the effect of **131** was studied on the human decapping scavenger enzyme (hDcpS). The results revealed that despite the slight inhibitory potency against hDcpS (5.8-fold less than that of 7-methylguanosine phosphate), **131** was identified as selective inhibitor in the $^{Hs}$cNIIIB simple biochemical assay.

Peterson et al.[157] prepared symmetrical thiodigalactoside derivatives carrying aryltriazolyl portions to optimise the binding near R144 of galectin-3. Introduction of additional fluorine on the phenyltriazole ring produced the lead 3,4,5-F-phenyltriazole hybrid (**132**, Fig. 21). This thiodigalactoside slightly increased the galectin-3 affinity and improved the galectin-3 selectivity 50-fold more than that of galectin-1.

The benzamide scaffolds linked by a 1,2,3-triazole ring were discovered to be promising human dihydroorotate dehydrogenase (hDHODH) inhibitors by Lu et al.[158] The hDHODH inhibitors play an important role in the rate-limiting step of pyrimidine biosynthesis, while pyrimidine plays a critical role in the DNA and RNA biosynthesis. In this study, the most potent compound was **133** (Fig. 21), which displayed superior suppression of hDHODH with an $IC_{50}$ of 2.1 μM. The immunosuppression assay revealed that **133** also potently inhibited proliferation of activated peripheral blood mononuclear cells.

Syeda et al.[159] described a new ouabagenin triazole analogue in the development of safe male contraceptives, that is a selective and promising inhibitor of Na,K-ATPase α4, and sperm function. Results showed that compound **134** (Fig. 21) specifically targets Na,K-ATPase α4. The activity of the lead derivative **134** was determined in rat sperm *V*m, pH, and $[Ca^{2+}]_i$. The prepared cell samples were treated in the presence and absence of $10^{-8}$ M **134** for 1 h, and sperm *V*m, pH, and $[Ca^{2+}]_i$ were measured using various fluorophores and derivative **134** caused sperm plasma membrane depolarisation, escalating *V*m by almost 40%, causing intracellular sperm acidification. Overall, except for the decreased ability of sperm to swim and reach the egg, **134** demonstrated decreased hyperactivity of sperm movability. All the above potential activities of **134** could serve in the future development of drug candidates for male contraception.

Several inhibitors of autotaxin that were used to determine the binding mode of the known inhibitor PF-8380 as an example, were developed by Thomson et al.[160] The modification results showed that replacing the benzoxazolone fragment with a triazole zinc-binding motif decreased the crystallinity and increased solubility. Among these agents, compound **135** (Fig. 21) was selected for its high affinity as an

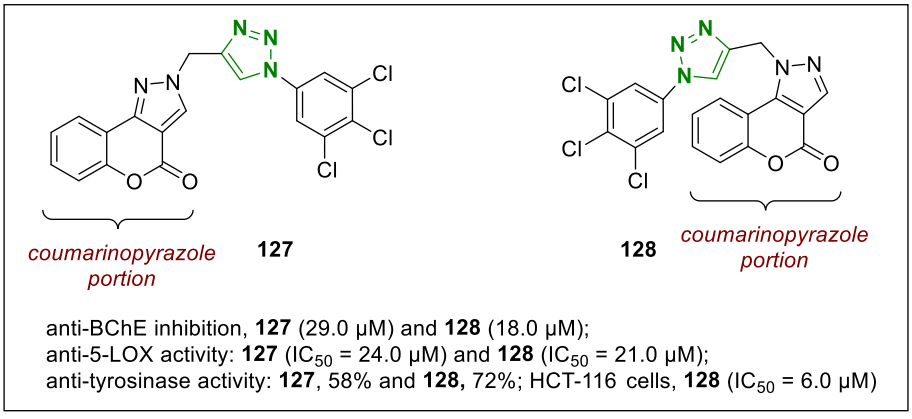



**Fig. 20.** Structures of lead 1,2,3-triazoles **127** and **128**.

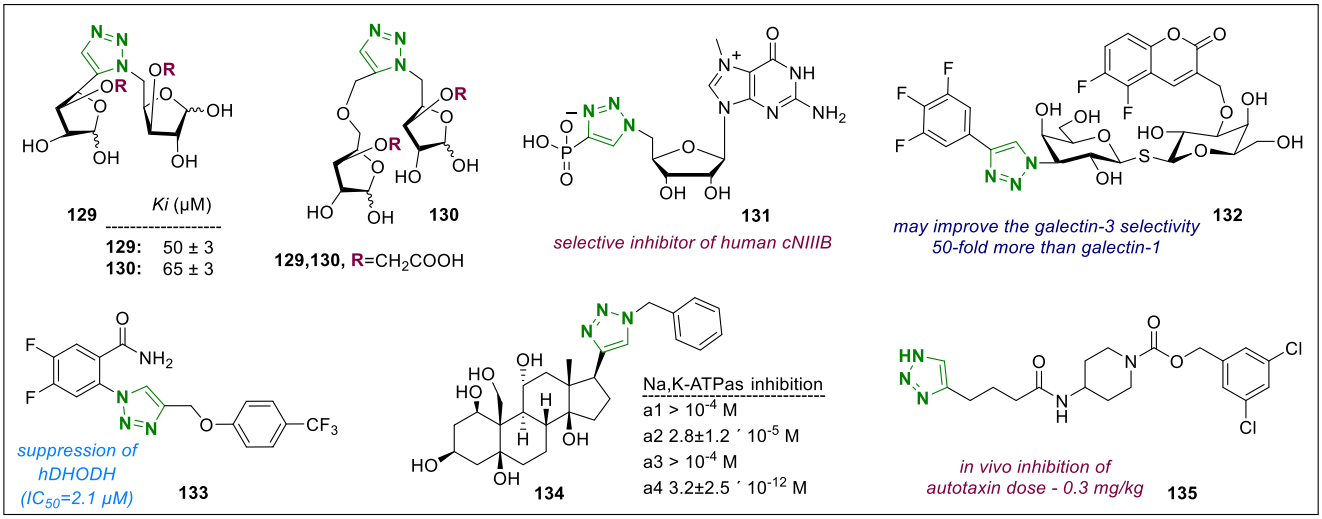



**Fig. 21.** Structures of lead 1,2,3-triazoles **129–135**.

orally bioavailable inhibitor of autotaxin. The lead **135** concentration-dependently inhibited autotaxin and the formation of LPA *in vivo* when used at 0.3 mg/kg in Sprague Dawley rats. A robust decrease in all four LPA levels was observed, with the peak reduction of approximately 70–80%, which was in agreement with the $C_{max}$ of **135**.

## 4. Conclusion

In conclusion, lead compounds containing the 1,2,3-triazole moiety will serve as effective drug candidates in their current forms or following appropriate chemical and biological modifications in future. Indeed, the developments in Cu-AAC have generated 1,2,3-triazole-hybrids with a broad profile of activities. The present review shows that most synthesised triazoles have favoured activities in which these motifs not only acted as a linker, showing CH-π interaction between the 1,2,3-triazole and enzymes, but also directed the appropriate side-rings (the fused ring in the triazole hybrid system) to the binding sites of enzymes or amino acids. These properties of triazoles in the hybrid molecules make them a unique motif that is an important factor in drug design and delivery. Although the selectivity and solubility of the most common triazole-hybrids have been well improved, the *in vivo* assay results indicate that further developments are needed. There should also be a focus on fused 1,2,3-triazole heterocyclic compounds, because triazole linkers have been well studied and their mechanism of action is clear. For example, we propose that if a 1,2,3-triazole ring was inserted instead of the imidazole portion in the purine skeleton, this type of fused pyrimidines may exhibit interesting properties for medicinal chemistry. In addition, the present review indicated that a proportion of studies have been dedicated to coumarin modification using Cu-AAC method. In the future, we believe there will be further elucidation of 1,2,3-triazole chemistry and biology, which would facilitate the development of 1,2,3-triazole-based lead compounds with lower toxicity and higher selectivity.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmc.2019.07.005.

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