This is the peer reviewd version of the followng article:

The 1,2,3-triazole ring as a bioisostere in medicinal chemistry / Bonandi, Elisa; Christodoulou, Michael S.; Fumagalli, Gaia; Perdicchia, Dario; Rastelli, Giulio; Passarella, Daniele. - In: DRUG DISCOVERY TODAY. - ISSN 1359-6446. - 22:10(2017), pp. 1572-1581. [10.1016/j.drudis.2017.05.014]

Terms of use:

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

21/07/2024 02:36

Accepted Manuscript

Title: The 1,2,3-triazole ring as a bioisostere in medicinal chemistry

Authors: Elisa Bonandi, Michael S. Christodoulou, Gaia Fumagalli, Dario Perdicchia, Giulio Rastelli, Daniele Passarella



 PII:
 \$1359-6446(17)30104-6

 DOI:
 http://dx.doi.org/doi:10.1016/j.drudis.2017.05.014

 Reference:
 DRUDIS 2032

To appear in:

Please cite this article as: Bonandi, Elisa, Christodoulou, Michael S., Fumagalli, Gaia, Perdicchia, Dario, Rastelli, Giulio, Passarella, Daniele, The 1,2,3-triazole ring as a bioisostere in medicinal chemistry.Drug Discovery Today http://dx.doi.org/10.1016/j.drudis.2017.05.014

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The 1,2,3-triazole ring as a bioisostere in medicinal chemistry

Elisa Bonandi¹, Michael S. Christodoulou^{1,2}, Gaia Fumagalli¹, Dario Perdicchia¹, Giulio Rastelli², and Daniele Passarella¹

¹Dipartimento di Chimica, Università degli Studi di Milano, Via Golgi 19, 20133 Milano, Italy ²Dipartimento di Scienze della Vita, Università degli Studi di Modena e Reggio Emilia, Via Campi 103, 41125 Modena, Italy

Corresponding author: Surname, initial (email address)

Teaser: 1,2,3-Triazole is an effective bioisostere and a convenient tool to creatively combine pharmacophores.

Highlights

Triazoles mimic different functional groups, justifying their wide employment as bioisosteres for the synthesis of new active molecules.

Triazoles present a marked stability under hydrolytic, oxidative and reductive conditions.

Triazoles exploitation in medicinal chemistry has recently received increasing attention, considering the development of new methodologies, which allows its regioselective synthesis

This review is focused on 1,2,3-triazoles. Among the plethora of the selected examples, the amide bond replacement is clearly a predominant approach.

1,2,3-Triazole is a well-known scaffold that has a widespread occurrence in different compounds characterized by several bioactivities, such as antimicrobial, antiviral, and antitumor effects. Moreover, the structural features of 1,2,3-triazole enable it to mimic different functional groups, justifying its wide use as a bioisostere for the synthesis of new active molecules. Here, we provide an overview of the 1,2,3-triazole ring as a bioisostere for the design of drug analogs, highlighting relevant recent examples.

Introduction

The synthesis of analogs of current drugs is currently one of the most relevant approaches in medicinal chemistry and the drug discovery process. Different issues, such as the need to overcome drug resistance, the search for more selective and less toxic drugs, or attempts to improve their pharmacokinetic profile, result in the need for a continuous optimization process. It is clear that analog design has a key role in this process [1], given that this strategy involves the structural modification of already active molecules rather than *ex novo* synthesis.

Application of a bioisosteric substitution is a widely used technique in the modification of active molecules, and triazoles, which are fundamental building blocks in different bioactive compounds, are among the most widespread bioisosteres. In fact, their structural characteristics, such as polarity, rigidity, and ability to act as both hydrogen bond donors (HBD) and acceptors (HBA), enable them to mimic the features of different functional groups (Figure

1), with the additional advantage of a marked stability under hydrolytic, oxidative, and reductive conditions. Over the past few years, the use of triazoles in medicinal chemistry has received increasing attention, thanks to research by Sharpless, Medal and colleagues, which led to the development of highly regioselective methodologies for triazole synthesis, based on the metal catalyzed Huisgen 1,3-dipolar cycloaddition between alkynes and azides [2– 4] (Figure 1).

However, new advanced synthetic routes has been recently developed to improve the regioselectivity and scope of copper and ruthenium catalysed cycloadditions, as well as to overcome some related drawbacks, such as the use of expensive and toxic metal catalysts. Among these new approaches, the use of metal-free organocatalyzed and multicomponent-cascade reactions are particularly noteworthy [5–8] (Figure 1). All these methodologies have enabled the successful design of novel drug analogs via combinatorial synthesis.

Here, we provide an overview of the potential of triazole rings as bioisosteres, highlighting various examples and focusing our attention on 1,2,3-triazoles to stimulate and to guide their use in drug design. Amide bond replacement is a predominant approach among the examples selected, demonstrating the versatility of this isosteric effect. In addition, heterocyclic substitutions are often used, whereas esters and carboxylic acid triazole isosteres are less common.

1,2,3-triazoles as amide bond isosteres

1,2,3-triazoles are among the most common amide bond isosteres. In fact, despite some differences concerning the overall dipolar moment and distance between the substituents, their structural features allow a good overlap with amide-binding moiety. For example, 1,4-disubstituted 1,2,3-triazoles are good Z-*trans*-amide isosteres, because the C-4 atom can act as electrophilic site, the C-H bond acts as a hydrogen bond donor (HBD), and the lone pair of N-3 electrons acts as a hydrogen bond acceptor (HBA). This isosteric replacement is illustrated in Figure 2, where the conformations of a *trans*-amide and a 1,4-disubstituted triazole moieties are superimposed for comparison.

Despite some polarization differences because of the replacement of the amide carbonyl group with a negatively polarized nitrogen atom, 1,5-disubstituted 1,2,3-triazoles are relatively good mimics of E-*cis*-amides as a result of the optimal spatial overlap between their substituent parts [9].

The ability to obtain stable amide isosteres has resulted in their wide application in the peptidomimetics field (reviewed in [10]) and in the design of analogs of bioactive molecules, including approved drugs. Figure 3 provides 22 examples in which the exploitation of the bioisosteric character of triazoles resulted in the development of active compounds. Table 1 lists the lead compounds and provides an indication of their biological activity, together with the corresponding reference.

The search for new drugs active against resistant strains of bacteria prompted Phillips *et al.* [11] to replace the acetamide group in linezolid with a triazole; one of the triazoles derivatives (1) displayed marked antimicrobial activity against both Gram-positive and linezolid-resistant bacteria. Monceaux and colleagues [12] exploited the amide-triazole isosteric relationship to design a library of analogs (2) inspired by potent Merck BACE1 inhibitors, as possible Alzheimer's disease therapy. Some of these derivatives proved to be relatively active, being also more potent than a similar triazole analog also developed by Merck [13].

This isosteric approach has also allowed the development of several HIV-1 protease inhibitors to treat AIDS. Mohammed and collaborators [14] synthesized a new class of antagonists (3) of the protein HIV-1 viral infectivity factor (Vif), based on a RN-18 structure, obtaining triazole analogs with enhanced activity, whereas Brik and colleagues [15–18] developed analogs of approved HIV-1 protease inhibitors, such as amprenavir, to address the issue of drug resistance resulting from viral mutations. Two compounds, AB2 and AB3 (4), showed nanomolar activity against wild-type and resistant HIV-1 proteases. Interestingly, crystallographic determination of the HIV-1 complexes showed that both inhibitors were bound in a position identical to that of amprenavir, confirming that the triazole was a suitable mimic of the peptide group (Figure 4) [16].

The need for novel chemotherapeutics has encouraged various groups to synthetize triazole analogs (5) of imatinib, an anticancer agent used for leukemia treatment. For example, **FA030** showed comparable or even enhanced potency against different cancer cell lines [19]. Furthermore, *in situ* click chemistry experiments performed on the Abl tyrosine kinases demonstrated that this enzyme was able to synthesize its best inhibitor. In fact, when the enzyme was simultaneously incubated with different azides and alkynes, the only detectable product was **FA030**, confirming the high affinity of this compound for Abl tyrosine kinases [20]. Other imatinib analogs showed good potency against leukemia cell lines and, in some cases, significant inhibitory activity against KG1a cells, suggesting possible applications in the treatment of leukemia stem-like cells [21].

The structure of vorinostat, an approved histone deacetylase inhibitor, was modified to prepare isosteres (6) characterized by similar cytotoxic activity and enzyme inhibitory properties [22]. To improve colchicine *in vivo* administration, which usually occurs via its encapsulation in nanosized liposomes, triazole analogs (7) were developed; in contrast to colchicine, no leaking outside the liposomes was observed [23].

The triazole ring has also been incorporated in macrocycle derivatives, such as the cryptophycin-52 analog (8) [24] and migrastatin analogs (9) [25]. Cryptophycin-52 is a synthetic derivative of a family of natural macrocycles known for their cytotoxic activity against multidrug-resistant cancer cells. Its triazole analog (8) was synthetized and maintained nanomolar activity, although this was lower than its parent compound. Migrastatin is an inhibitor of fascin, a protein involved in cell motility. The triazole analogs of an active lactam derivative of migrastatin (9), displayed comparable inhibitory activity of cancer cell migration. Research interest in resistant cancer cells, in

particular those with stem cell-like behaviors, resulted in researchers considering a structural modification of vismodegib, a synthetic Hedgehog signaling pathway inhibitor. Its triazole derivative (10) was found to be active in the lower micromolar range against different cancer and endothelial cells [26].

In an attempt to develop new potential anticancer agents, a triazole derivative of triflorcas (11), a Met signaling inhibitor, was developed. Its triazole analog displayed similar activity in the inhibition of HGF-induced scattering in epithelial cells and *in vitro* tumorigenesis in different cancer cell lines [27].

The triazole amide bioisosterism also has applications in the agrochemical field, as demonstrated by the synthesis of derivatives of mandipropamid, an antifungal compound used for the treatment of diseases of crop plants. Unfortunately, its triazole derivatives (12) exhibited a reduced activity, probably because of a weak HBD in the triazole [28].

In addition to the aforementioned studies, several authors have reported the synthesis of triazole derivatives of small bioactive molecules, such as *N*-acetyl β -D-glucopyranosylamine (13) [29–31], ceramides (14) [32–35], dopamine D₃ receptor ligands (15) [36–38], *N*-acyl-homoserine-lactone (16) [39,40], capsaicin (17) [41], hydroxyflutamide (18) [42], biocytin (19) [43], oroidin RA analogs (20) [44], 4-quinolone-3-carboxamides (21) [45], and α -lipoic acid amide derivatives (22) [46,47].

1,2,3-triazoles as ester bond isosteres

Here, we provide examples in which 1,2,3-triazoles are used as ester isostere to reduce their *in vivo* susceptibility to enzymatic degradation. The structures are detailed in Figure 5 and a summary of their biological activity is provided in Table 1. This isosteric relationship was used for the replacement of the lactone moiety in steganacin and podophyllotoxin, two naturally occurring antitubulin compounds; their triazole derivatives (**23** and **24**, respectively) displayed good activity against a neuroblastoma cell line (although with lower potency) and maintained the antitubulin properties of their parent compounds [48].

The need to improve the selectivity and the pharmacokinetic properties of arecoline, a natural muscarinic agonist that, during the 1990s, attracted considerable interest as a potential Alzheimer's disease therapy, resulted in the synthesis of a large library of triazole analogs (25) that contained compounds characterized by a range of efficacy, affinity, and selectivity [49]. The same approach was also used in an attempt to enhance the stability of the labile ester bond in β -glucogallin. Both amide and triazole derivatives were synthesized, but although the first were stable in extreme conditions and maintained the inhibitory activity of the parent compound, triazole isosteres (26) proved to be totally inactive. This was because the slight differences in the spatial arrangement of the substituents did not result in appropriate interactions with the receptor binding site [50].

1,2,3-triazoles as carboxylic acid isosteres

The 1,2,3-triazole ring does not appear among the typical carboxylic acid moiety isosteres. However, Pippione *et al.* [51] reported an interesting example in which the role of N-substituted 4-hydroxy-1,2,3-triazoles (27) (structure reported in Figure 5, biological activity summarized in Table 1) as possible carboxylic acids bioisosteres was investigated. This substitution should allow modulation of the acidic moieties present in lead molecules, as well as proper substituent regiodirection, depending on which of the triazole nitrogens is substituted. The replacement of the distal (S)-glutamic acid carboxyl group with a 4-hydroxy-1,2,3-triazole was considered as a possible tool to enhance the selectivity for AMPA glutamate receptors (GluRs). Two compounds (27) emerged as promising isosteres, displaying good activity and selectivity toward AMPA GluRs.

1,2,3-triazoles as olefins rigid analogs

1,2,3-triazoles, being flat bivalent elements, mimic the rigid conformational constrain exerted by double bonds in alkyl chains, avoiding typical olefin drawbacks, such as undesired isomerization or *in vivo* degradation. This principle was extensively used to fix the combretastatin [52–56] and cyanocombretatstin A-4 [56] *cis* configurations, preventing their isomerization in the more stable but less active *trans* isomers. Several of the different synthetized analogs (**28** and **29**) displayed nanomolar activity against different cell lines.

A similar approach was used for the design of constrained analogs of resveratrol (**30**) [57], resorcylic acid lactone (**31**) [58] (in which the triazole substituted a *cis*-enone system), and chalchones [59]. In the first two cases, the isosteres maintained some activity, whereas the chalcones analogs (**32**) proved to be inactive. The structures of these compounds are reported in Figure 5, while information regarding their bioactivities is detailed in Table 1.

1,2,3-triazoles as heterocycles isosteres

The triazole ring can efficiently mimic other heterocycles, in particular five-member nitrogen-containing cycles; this principle has been widely used for the synthesis of new active compounds. Figure 5 details 15 examples that highlight the versatility of triazoles as isosteres of different heterocycles, while their bioactivities are summarized in Table 1.

In terms of a imidazole isostere, Al-Azmi and collaborators [60] synthetized several losartan analogs (**33**), as potential nonpeptidic angiotensin (II) receptor antagonists. The same isosteric substitution was applied to improve EICAR antiviral and anticancer properties, leading to triazole analog (**34**) [61] and also to the synthesis of 2,4(1H)-diaryl imidazoles isosteres (**35**) as Nav1.6 sodium channel blockers [62].

In an interesting study, a 1,2,3-triazole ring was used as a miconazole imidazole bioisostere as well as a linker to join together two pharmacophores: the miconazole and a piperazine fragment of ketoconazole. Some of these hybrid compounds (**36**) showed moderate antifungal and antibacterial activity [63]. However, this isosteric substitution

failed in the synthesis of the triazole analogs (37) of a more active derivative of Imiquimod, showing that the efficiency of an isosteric replacement is rarely predictable and has to be evaluated on a case-by-case basis [64].

1,2,3-tirazoles can also be used as pyrazole ring isosteres, as in the case of rimonabant (**38**), a CB-1 receptor antagonist used in obesity treatment. Benzyl amide-containing analogs [65] and some members of a 4alkoxycarbonyl-1,5-diaryl-1,2,3-triazoles library [66] showed good activity and CB-1 selectivity, as well as potentially improved bioavailability, being less lipophilic than the parent compound. Other examples were the synthesis of analogs (**39**) of the insecticide fipronil, leading to promising inhibitors of the insect GABA receptor [67], the development of pyrazolo[3,4-d]pyrimidines analogs (**40**) as possible antifungal agents [68], and of new dopamine D_2 and D_4 receptors antagonists (**41**) [69,70].

1,2,3-triazoles act also as 1,2,4-triazole ring isosteres, as demonstrated by the synthesis of ribavirin and fluconazole derivatives. Ribavirin [71] is a well-known antiviral compound that is active against different viruses, such as HIV-1, herpes simplex virus (HSV), and hepatitis C virus. However, its cytotoxicity has limited its clinical application, encouraging the search for active analogs. One of these (42) was found to be more potent and less cytotoxic than ribavirin against certain viruses. To broaden the antifungal activity spectrum of fluconazole, the same approach was applied, resulting in potent antifungal compounds (43) that were also active against resistant fungi [72].

The isosteric replacement of the morpholine ring in linezolid led to active, but less potent antibacterial analogs (44) [73]. Interestingly, a double isosteric substitution, involving both morpholine and acetamide moieties, was also reported [74]. Other tested isosteric relationships involved the oxazole ring of the VEGFR2 inhibitor AAZ (analog 45) [75], the isoxazole ring of an Ebola virus inhibitor (analog 46) [76], and the oxazolidinone of a T box antiterminator RNA binder (analog 47) [77]. Finally, 1,2,3-triazoles are a possible nucleobase heterocycle bioisostere (for further details, please see [78–85]).

1,2,3-triazoles as miscellaneous isosteres

Here, we discuss examples of isosteric replacements that do not fit into the previous classifications. Their structures and their biological activities are detailed in Figure 6 and Table 1, respectively.

Some 1,2,3-triazoles-curcuminoids (48) were shown to mimic the curcumin 1,3-dicarbonyl group, maintaining some characteristics of the parental compound, such as enhanced cytotoxicity and similar inhibition of TNF α induced NF- κ B-dependent transcription [86]. The ethynyl group replacement in Sazetidin-A, a selective $\alpha 4\beta 2$ neuronal nicotinic acetylcholine receptor (nAChRs) desensitizer, led to a more selective $\alpha 4\beta 2$ nAChRs analog (49) [87], whereas the substitution of a labile thiourea resulted in the development of more cytotoxic derivatives (50) of PIT-1, a PIP3 antagonist responsible for the induction of apoptosis in cancer cells [88]. Docking studies also demonstrated that 1,2,3-triazoles can act as more stable isosteres of phosphate linkers [89]; examples include the synthesis of analogs of biotinyl-5'-AMP (51) [90,91] and cyclic di-GMP (52) [92], resulting in more selective compounds, or the development of novel NAD-mimetics (53), such as inosine monophosphate dehydrogenase inhibitors [93]. Again, the substitution of phosphate linkers led to oligothymidine triazole analogs (54) for antisense therapy [84] and to uncharged and rigidified nucleoside ATP mimetics (55), such as inhibitors of NTP-dependent enzymes [95].

Concluding remarks

In conclusion, here we have highlighted the importance of bioisosterism in the drug discovery process, focusing on the successful synthesis of various triazole compounds*. Interestingly, more than half of the studies cited were published over the past 10 years (2007–2017), demonstrating that this approach is only a relatively recently developed tool for the design of pharmaceutically active compounds. Acknowledament

The authors express their gratitude to Ioana Stupariu for revision of the manuscript.

References

- 1 El-Dakdouki, M.H. and Erhardt, P.W. (2012) Analogue-based drug discovery: contributions to medicinal chemistry principles and drug design strategies. Microtubule stabilizers as a case in point (Special Topic Article). *Pure Appl. Chem.* 84, 1479–1542
- 2 Sharpless, B.K. et al. (2003) The growing impact of click chemistry on drug discovery. Drug Discov. Today 8, 1128–1137
- 3 Boren, B. et al. (2008) Ruthenium-catalysed azide-alkyne cycloaddition: scope and mechanism. J. Am. Chem. Soc. 130, 8923-8930
- 4 Totobenazara, J. and Burke, A.J. (2015) New click-chemistry methods for 1,2,3-triazoles synthesis: recent advances and applications. Tetrahedron Lett. 56, 2853-2859
- 5 Wei, F. et al. (2016) Regioselective synthesis of multisubstituted 1,2,3-triazoles: moving beyond the copper-catalysed azide-alkyne cycloaddition. Chem. Commun. 52, 14188-14199
- 6 John, J. et al. (2015) Organocatalytic routes toward substituted 1,2,3-triazoles. Chem. Commun., 51, 10797-10806
- 7 Dehaen, W. et al. (2016) A general metal-free route towards the synthesis of 1,2,3-triazoles from readily available primary amines and ketones. Chem. Commun. 52, 2885-2888
- 8 Dehaen, W. et al. (2015) Tandem organocatalysed knoevenagel condensation/1,3-dipolar cycloaddition towards highly functionalized fused 1,2,3-triazoles. Eur. J. Org. Chem. 2015, 4922–4930
- 9 Tron, G.C. et al. (2008) Click chemistry reactions in medicinal chemistry: applications of the 1,3-dipolar cycloaddition between azides and alkynes. Med. Res. Rev. 28, 278–308
- 10 Valverde, I.E. and Mindt, T.L. (2013) 1,2,3-triazoles as amide-bond surrogates in peptidomimetics. CHIMIA 67, 262–266
- 11 Phillips, O. et al. (2003) Synthesis and antibacterial activity of 5-substituted oxazolidinones. Bioorg. Med. Chem. 11, 35-41
- 12 Monceaux, C.J. et al. (2011) Triazole-linked reduced amide isosteres: an approach for the fragment-based drug discovery of anti-Alzheimer's BACE1 inhibitors. Bioorg. Med. Chem. Lett. 21, 3992–3996
- 13 Rajapakse, H.A. et al. (2010) SAR of tertiary carbinamine derived BACE1 inhibitors: role of aspartate ligand amine pK a in enzyme inhibition. *Bioorg. Med. Chem. Lett.* 20, 1885–1889
- 14 Mohammed, I. et al. (2016) 1,2,3-triazoles as amide bioisosteres: discovery of a new class of potent HIV-1 Vif antagonists. J. Med. Chem. 59, 7677-7682
- 15 Brik, A. et al. (2003) Rapid diversity-oriented synthesis in microtiter plates for in situ screening of HIV protease inhibitors. ChemBioChem 4, 1246–1248
- 16 Brik, A. et al. (2005) 1,2,3-triazole as a peptide surrogate in the rapid synthesis of HIV-1 protease inhibitors. ChemBiochem 6, 1167-1169
- 17 Brik, A. et al. (2008) A copper(I)-catalysed 1,2,3-triazole azide-alkyne click compound is a potent inhibitor of a multidrug-resistant HIV-1 protease variant. J. Med. Chem. 51, 6263–6270
- 18 Ghosh, A. and Anderson, D. (2011) Tetrahydrofuran, tetrahydropyran, triazoles and related heterocyclic derivatives as HIV protease inhibitors. Future Med. Chem. 3, 1181–1197
- 19 Arioli, F. et al. (2011) N-2-methyl-5-(triazol-1-yl)phenyl]pyrimidin-2-amine as a scaffold for the synthesis of inhibitors of Bcr-Abl. ChemMedChem 6, 2009-2018
- 20 Passarella, D. et al. (2013) Probing the binding site of Abl tyrosine kinase using in situ click chemistry. ACS Med. Chem. Lett. 4, 274-277
- 21 Li, Y. et al. (2016) Syntheses and biological evaluation of 1,2,3-triazole and 1,3,4-oxadiazole derivatives of imatinib. Bioorg. Med. Chem. Lett. 26, 1419–1427
- 22 Pirali, T. et al. (2008) Triazole-modified histone deacetylase inhibitors as a rapid route to drug discovery. J. Comb. Chem. 10, 624-627
- 23 Kuznetsova, N. et al. (2013) Lipophilic prodrugs of a triazole-containing colchicine analogue in liposomes: biological effects on human tumor cells. Russ. J. Bioorg. Chem. 39, 543–552
- 24 Nahrwold, M. et al. (2010)'Clicktophycin-52': a bioactive cryptophycin-52 triazole analogue. Org. Lett. 12, 1064–1067
- 25 Passarella, D. et al. (2017) Synthesis and biological evaluation of migrastatin macrotriazoles. Eur. J. Org. Chem. 2017, 60-69
- 26 Passarella, D. et al. (2015) Click reaction as a tool to combine pharmacophores: the case of vismodegib. ChemPlusChem 80, 938-943
- 27 Passarella, D. et al. (2012) 'Click' synthesis of a triazole-based inhibitor of Met functions in cancer cells. Bioorg. Med. Chem. Lett. 22, 4693–4696
- 28 Su, N. et al. (2011) Synthesis and biological evaluation of isosteric analogs of mandipropamid for the control of oomycete pathogens. Chem. Biol. Drug Des. 78, 101–111
- 29 Bokor, E. et al. (2010) Synthesis of 1-(D-glucopyranosyl)-1,2,3-triazoles and their evaluation as glycogen phosphorylase inhibitors. Bioorg. Med. Chem. 18, 1171–1180
- 30 Chrysina, E. et al. (2009) Amide-1,2,3-triazole bioisosterism: the glycogen phosphorylase case. Tetrahedron Asymm, 20, 733-740
- 31 Goyard, D. et al. (2012) Synthesis of 1,2,3-triazoles from xylosyl and 5-thioxylosyl azides: evaluation of the xylose scaffold for the design of potential glycogen phosphorylase inhibitors. Carbohydr. Res. 364, 28–40
- 32 Kim, S. et al. (2007) Design, synthesis, and preliminary biological evaluation of a novel triazole analogue of ceramide. Bioorg. Med. Chem. Lett. 17, 4584-4587
- 33 Verma, Y.K. et al.(2016) Design, synthesis, and immunological evaluation of benzyloxyalkyl-substituted 1,2,3-triazolyl α-GalCer analogues. ACS Med. Chem. Lett. 7, 172–176
- 34 Lee, T. et al. (2007) Synthesis and evaluation of 1,2,3-triazole containing analogues of the immunostimulant alpha-GalCer. J. Med. Chem. 50, 585–589
- 35 Pilgrim, W. et al. (2013) Synthesis of alpha-O- and alpha-S-glycosphingolipids related to sphingomonous cell wall antigens using anomerisation. Molecules 18, 11198-11218
- 36 Insua, I. et al. (2013) Synthesis and binding affinity of new 1,4-disubstituted triazoles as potential dopamine D3 receptor ligands. Bioorg. Med. Chem. Lett. 23, 5586-5591
- 37 Peng, X. et al. (2015) Synthesis, pharmacological evaluation and molecular modeling studies of triazole containing dopamine D3 receptor ligands. Bioorg. Med. Chem. Lett. 25, 519-523
- 38 Keck, T. et al. (2015) Using click chemistry toward novel 1,2,3-triazole-linked dopamine D₃ receptor ligands. Bioorg. Med. Chem. 23, 4000–4012
- 39 Sabbah, M. et al. (2012) Synthesis and biological evaluation of new N-acyl-homoserine-lactone analogues, based on triazole and tetrazole scaffolds, acting as LuxR-dependent quorum sensing modulators. Bioorg. Med. Chem. 20, 4727–4736
- 40 Brackman, G. et al. (2012) Synthesis and evaluation of the quorum sensing inhibitory effect of substituted triazolyldihydrofuranones. Bioorg. Med. Chem. 20, 4737–4743
- 41 Appendino, G. et al. (2007) The 1,2,3-triazole ring as a peptido- and olefinomimetic element: discovery of click vanilloids and cannabinoids. Angew. Chem. Int. Ed. 46, 9312–9315
- 42 Altimari, J. et al. (2014) Preliminary investigations into triazole derived androgen receptor antagonists. Bioorg. Med. Chem. 22, 2692–2706
- 43 Germeroth, A. et al. (2013) Triazole biotin: a tight-binding biotinidase-resistant conjugate. Org. Biomol. Chem. 11, 7700-7704
- 44 Ballard, T.E. et al. (2008) Synthesis and antibiofilm activity of a second-generation reverse-amide oroidin library: a structure-activity relationship study. Chem. Eur. J. 14, 10745-10761

- 45 Mugnaini, C. *et al.* (2012) Investigations on the 4-quinolone-3-carboxylic acid motif part 5: modulation of the physicochemical profile of a set of potent and selective cannabinoid-2 receptor ligands through a bioisosteric approach. *ChemMedChem* 7, 920–934
- 46 Koufaki, M. et al. (2007) Design and synthesis of 1,2-dithiolane derivatives and evaluation of their neuroprotective activity. Bioorg. Med. Chem. Lett. 17, 4223–4227
- 47 Koufaki, M. et al. (2009) Design and synthesis of novel neuroprotective 1,2-dithiolane/chroman hybrids. Bioorg. Med. Chem. 17, 6432–6441
- 48 Imperio, D. *et al.* (2007) Replacement of the lactone moiety on podophyllotoxin and steganacin analogues with a 1,5-disubstituted 1,2,3triazole via ruthenium-catalysed click chemistry. *Bioorg. Med. Chem.* 15, 6748–6757
- 49 Moltzen, E.K. et al. (1994) Bioisosteres of arecoline: 1,2,3,6-tetrahydro-5-pyridyl-substituted and 3-piperidyl-substituted derivatives of tetrazoles and 1,2,3-triazoles. Synthesis and muscarinic activity. J. Med. Chem. 37, 4085–4099
- 50 Li, L. *et al.* (2014) Design of an amide N-glycoside derivative of β -glucogallin: a stable, potent, and specific inhibitor of aldose reductase. *J. Med. Chem.* 57, 71–77
- 51 Pippione, A.C. et al. (2015) Substituted 4-hydroxy-1,2,3-triazoles: synthesis, characterization and first drug design applications through bioisosteric modulation and scaffold hopping approaches. Med. Chem. Commun. 6, 1285–1292
- 52 Madadi, N.R. et al. (2015) Synthesis and biological evaluation of novel 4,5-disubstituted 2H-1,2,3-triazoles as cis-constrained analogues of combretastatin A-4. Eur. J. Med. Chem. 103, 123–132
- 53 Beale, T.M. et al.(2012) Increased endothelial cell selectivity of triazole-bridged dihalogenated A-ring analogues of combretastatin A-1. Bioorg. Med. Chem. 20, 1749–1759
- 54 Demchuket, D.V. al. (2014) Synthesis and antiproliferative activity of conformationally restricted 1,2,3-triazole analogues of combretastatins in the sea urchin embryo model and against human cancer cell lines. *Bioorg. Med. Chem.* 22, 738-755
- 55 Odlo, K. *et al.* (2008) 1,5-Disubstituted 1,2,3-triazoles as *cis*-restricted analogues of combretastatin A–4: synthesis, molecular modeling and evaluation as cytotoxic agents and inhibitors of tubulin. *Bioorg. Med. Chem.* 16, 4829–4838
- 56 Penthala, N.R. et al. (2015) Synthesis and anti-cancer screening of novel heterocyclic-(2H)-1,2,3-triazoles as potential anti-cancer agents. Med. Chem. Commun. 6, 1535–1543
- 57 Pagliai, F. et al. (2006) Rapid synthesis of triazole-modified resveratrol analogues via click chemistry. J. Med. Chem. 4, 467-470
- 58 Chen, A. et al. (2014) Synthesis and Biological Studies of a Triazole Analogue of Resorcylic Acid Lactone LL-Z1640-2. Eur. J. Org. Chem., 7239–7244
- 59 Mesenzani, O. et al. (2011) Replacement of the double bond of antitubulin chalcones with triazoles and tetrazoles: synthesis and biological evaluation. Bioorg. Med. Chem. Lett. 21, 764–768
- 60 Al-Azmi, A. et al. (2007) Alkylation of azoles: synthesis of new heterocyclic-based AT₁-non-peptide angiotensin (II) receptor antagonists. J. Heterocyclic Chem. 44, 515–520
- 61 Ostrowski, T. and Zeidler, J. (2008) Synthesis of 5-ethynyl-1-β-D-ribofuranosyl-1H-1,2,3]triazole-4-carboxylic acid amide (isosteric to EICAR) and its derivatives. Nucleic Acids Symp Ser 52, 585–586
- 62 Rivara, M. et al. (2012) Inhibition of Nav1.6 sodium channel currents by a novel series of 1,4-disubstituted-triazole derivatives obtained via copper-catalysed click chemistry. Bioorg. Med. Chem. Lett. 22, 6401–6404
- 63 Khedar, P. et al. (2015) Click chemistry inspired synthesis of piperazine-triazole derivatives and evaluation of their antimicrobial activities. Med. Chem. Res. 24, 3117–3126
- 64 Shukla, N. et al. (2010) Structure-activity relationships in human toll-like receptor 7-active imidazoquinoline analogues. J. Med. Chem. 53, 4450–4465
- 65 Hou, D. et al. (2009) 1,2,3-Triazole derivatives as new cannabinoid CB1 receptor antagonists. Bioorg. Med. Chem. Lett. 19, 1022-1025
- 66 Shu, H. et al. (2009) Synthesis and CB1 cannabinoid receptor affinity of 4-alkoxycarbonyl-1,5-diaryl-1,2,3-triazoles. Bioorg. Med. Chem.
- Lett. 19, 891-893
 67 Alam, M.S. et al. (2006) Synthesis and structure-activity relationships of 1-phenyl-1H-1,2,3-triazoles as selective insect GABA receptor antagonists. J. Agric. Food Chem. 54, 1361-1372
- 68 Baraldi, P. et al. (2002) Antimicrobial and antitumor activity of N-heteroimmine-1,2,3-dithiazoles and their transformation in triazolo-, imidazo-, and pyrazolopirimidines. Bioorg. Med. Chem. 10, 449-456
- 69 Löberet, S. al. (2006) Synthesis and biological investigations of dopaminergic partial agonists preferentially recognizing the D4 receptor subtype. Bioorg. Med. Chem. Lett. 16 2955-2959
- 70 Neves, G. et al. (2010) Searching for multi-target antipsychotics: discovery of orally active heterocyclic N-phenylpiperazine ligands of D₂-like and 5-HT_{1A} receptors. Bioorg. Med. Chem. 18, 1925–1935
- 71 Ferreira, M. et al. (2014) Design, synthesis, and antiviral activity of new 1H-1,2,3-triazole nucleoside ribavirin analogs. Med. Chem. Res. 23, 1501–1511
- 72 Pore, V.S. et al. (2012) Synthesis and antifungal activity of 1,5-disubstituted-1,2,3-triazole containing fluconazole analogues. Med. Chem. Commun. 3, 484-488
- 73 Genin, M.J. et al.(2000) Substituent effects on the antibacterial activity of nitrogen-carbon-linked (azolylphenyl)oxazolidinones with expanded activity against the fastidious Gram-negative organisms Haemophilus influenza and Moraxella catarrhalis. J. Med. Chem. 43, 953–970
- 74 Hauck, S. et al. (2007) New carbon-linked azole oxazolidinones with improved potency and pharmacokinetics. Bioorg. Med. Chem. Lett. 17, 337-340
- 75 Vojtickova, M. et al. (2015) Ynamide click chemistry in development of triazole VEGFR2 TK modulators. Eur. J. Med. Chem. 103, 105–122
- 76 Yermolina, M. et al. (2011) Discovery, synthesis, and biological evaluation of a novel group of selective inhibitors of filoviral entry. J. Med. Chem. 54, 765–781
- 77 Acquaah-Harrison, G. et al. (2010) Library of 1,4-disubstituted 1,2,3-triazole analogs of oxazolidinone RNA-binding agents. J. Comb. Chem. 12, 491–496
- 78 Amblard, F. et al. (2009) Cu(I)-catalysed huisgen azide-alkyne 1,3-dipolar cycloaddition reaction in nucleoside, nucleotide, and oligonucleotide chemistry. Chem. Rev. 109, 4207–4220
- 79 Li, L. et al. (2008) A concise route for the preparation of nucleobase-simplified cADPR mimics by click chemistry. Tetrahedron Lett. 49, 4491-4493
- 80 Li, L. et al. (2010) Novel nucleobase-simplified cyclic ADP-ribose analogue: a concise synthesis and Ca²⁺-mobilizing activity in Tlymphocytes. Org. Biomol. Chem. 8, 1843–1848
- 81 Lim, F. and Dolzhenko, A. (2014) 1,3,5-Triazine-based analogues of purine: from isosteres to privileged scaffolds in medicinal chemistry. Eur. J. Med. Chem. 85, 371–390
- 82 Paul, N. et al. (2003) DNA polymerase template interactions probed by degenerate isosteric nucleobase analogs. Chem. Biol. 10, 815-825
- 83 Vibhute, A.M. et al. (2015) Triazolophostins: a library of novel and potent agonists of IP3receptors. Org. Biomol. Chem. 13, 6698–6710
- 84 Vibhute, A.M. et al. (2016) Synthesis of dimeric analogs of adenophostin A that potently evoke Ca²⁺release through IP₃ receptors. RSC Adv. 6, 86346–86351

- 85 Alvarez, R. et al. (1994) 1,2,3-Triazole-2',5'-bis-O-(tert-butyldimethylsilyl)-β-D-ribofuranosyl]-3'-spiro-5'-(4"-amino-1',2'-oxathiole 2',2"dioxide) (TSAO) analogues: synthesis and anti-HIV-1 activity. J. Med. Chem. 37, 4185–4194
- 86 Caprioglio, D. et al. (2016) Triazole-curcuminoids: a new class of derivatives for 'tuning' curcumin bioactivities? Bioorg. Med. Chem. 24, 140-152
- 87 Liu, Y. et al. (2014) Synthesis and pharmacological characterization of new neuronal nicotinic acetylcholine receptor ligands derived from Sazetidine-A. Bioorg. Med. Chem. Lett. 24, 2954–2956
- 88 Kommagalla, Y. et al. (2014) Optimization of the anti-cancer activity of the phosphatidylinositol-3 kinase pathway inhibitor PITENIN-1: switching thiourea with 1,2,3-triazole. Med. Chem. Comm. 5, 1359–1363
- 89 Montgomery, A. et al. (2016) Computational characterisation of the interactions between human ST6Gal I and transition-state analogue inhibitors: insights for inhibitor design. J. Mol. Recognit. 29, 210–222
- 90 da Costa, T. et al. (2012) Selective inhibition of biotin protein ligase from Staphylococcus aureus. J. Biol. Chem. 287, 17823–17832
- 91 Tieu, W. et al. (2014) Heterocyclic acyl-phosphate bioisostere-based inhibitors of Staphylococcus aureus biotin protein ligase. Bioorg. Med. Chem. Lett. 24, 4689–4693
- 92 Fernicola, S. et al. (2015) Synthesis of triazole-linked analogues of c-di-GMP and their interactions with diguanylate cyclase. J. Med. Chem. 58, 8269–8284
- 93 Chen, L. et al. (2010) Triazole-linked inhibitors of inosine monophosphate dehydrogenase from human and Mycobacterium tuberculosis. J. Med. Chem. 53, 4768–4778
- 94 Nuzzi, A. *et al.* (2007) Model studies toward the synthesis of thymidine oligonucleotides with triazole internucleosidic linkages via iterative Cu(I)-promoted azide–alkyne ligation chemistry. *QSAR Comb. Sci.* 26, 1191–1199
- 95 Rowan, A. et al. (2009) Nucleoside triphosphate mimicry: a sugar triazolyl nucleoside as an ATP-competitive inhibitor of B. anthracis pantothenate kinase. Org. Biomol. Chem. 7, 4029–4036
- 96 Peng, L. et al. (2012) Targeting heat shock factor 1 with a triazole nucleoside analog to elicit potent anticancer activity on drug-resistant pancreatic cancer. Cancer Lett. 318, 145–153

Figure 1. Synthetic strategies aimed at 1,2,3-triazoles regioselective synthesis (b) and the principal isosteric relationships (a).

Figure 2. Superimposition of the conformations of *trans*-amide (yellow) and 1,4-disubstituted 1,2,3-triazole (cyan) moieties.

Figure 3. Structures of the principal amide triazole isosteres discussed in the main text.

Figure 4. Superimposition of the crystal structures of HIV-1 protease in complex with amprenavir [yellow; Protein Data Bank (PDB) code: 1HPV] and the two triazole analogs AB2 and AB3 (cyan, PDB codes: 1ZP8 and 1ZPA, respectively). For the sake of clarity, only the co-crystallized ligands are shown.

Figure 5. Structures of the principal triazole analogs as bioisosteres of esters, carboxylic acids, heterocycles, and rigidifying elements, as discussed in the main text.

Figure 6. Structures of the miscellaneous triazole isosteres discussed in the main text.

Figures

Figure 1





[continue in the next page]









[continue in the next page]



Table 1. The activity of 1,2,3-triazole analogs^{a,b,c}

Compound	Parent compound	Biological target	Isostere activity evaluation	Parent compound activity evaluation	Refs
Amide isoste	eres				
1	Linezolid	Staphylococcus aureus	0.5–1 Mg/ml ⁱⁱ	0.5–2 Mg/ml ⁱⁱ	[11]
2	Merck compound	BACE1	2.0 MM ^{iv}	16.3 MM ^{iv}	[12]
3	RN-18	H9 cells (HIV-1 Vif)	0.001 MM ^{iv}	6 MM ^{iv}	[14]
4	Amprenavir	HIV-1Pr wt	6±0.5 nM ⁱ	_	[15–18]
		HIV-1Pr _{6X}	15.7 nM ^{iv}	_	
5	Imatinib	K562 (Bcr-Abl)	0.89±0.003 MM ^{iv}	0.37±0.09 MM ^{iv}	[19,20]
			0.03 MM ^{iv}	0.38 MM ^{iv}	[21]
6	Vorinostat	K562 (HDACs)	1.21±0.2 MM [™]	1-10 MM [™]	[22]
7	Colchicine	BJAB	4 nM [™]	20 nM ^{iv}	[23]
8	Cryptophycin-52	KB-VI	32 nM [™]	0.7 nM [™]	[24]
9	Migrastatin analog	MDA-MB-361	-		[25]
10	Vismodegib	BAEC	0.42±0.04 MM [™]	50±4 MM [™]	[26]
11	Iritlorcas	MDCK (HGF scatter factor)	0.6 MM™	0.2 MM [®]	[27]
12	Mandipropamid	Pseudoperonospora cubensis	90% inhibition	-	[28]
<u>13</u> 14	N-Acetyl-β-D-glucopyranosylamines	RMGPb			[29-31]
	Ceramides		8.2 IVIIVI'''	35.1 1/11/1"	[32]
		INK I (I-cells receptor)	-	-	[33,34]
45	1150 4 401	D. recentor	- 2.7.pMi		[30]
15	WC10		_2.7 111VI		[30]
	WCIU			0.8 ±0.1 MM	[37]
16	MAaul homoopring lastons	Vibria fizabari (LuvP)	5.05 ± 0.141 miv	0.233±0.0089 1101	[30]
10	N-Acyi-nomosenne-lacione	Vibrio lischen (LuxR)		_	[39]
		(Las P)	49.9±20.1 %Q3	_	[40]
17	Capsaicin			>5.6 MMi	[41]
17	Capsaicin			>5.0 MM	[41]
18	Hydroxyflutamide	INCAP (androgen recentor)			[/2]
10	Biocytin	Avidin (biotinidase)	Picomolar Ka		[42]
20		P aeruginosa 14		- 40 MM ^{iv}	[43]
21		hCB2	11 1+3 6 nM ⁱ	0.7+0.2 pM ⁱ	[45]
22	q-l ippic acid amide derivatives	HT22	0 90+0 04 MM ⁱⁱⁱ	2 10+0 4 MM ⁱⁱⁱ	[46 47]
<u></u>		11122	0.3010.04 10101	2.1010.4 Milli	[10,17]
Ester isoster	() Staganosia				[40]
23	(-)-Sieganacin		1.1 ± 0.4 IVIIVI ^{III}		[48]
24		Guipos Big iloum (mussarinia	1.5 ± 0.7 IVIIVI"	100 pMii	[40]
23	Areconne	receptors)	130 1101**	190 110	[49]
26	β-Glucogallin	AKR1B1	Inactive	8±1 MM ^{iv}	[50]
COOH isoste	res			021 1111	[00]
27	Glutamic acid	AMPA receptors (GluRs)	1.4 MM ⁱ	0.34 MM ^{iv}	[51]
Triazoles as	rigid analogs				
28	Combretastatin	Cancer cell line papel	<10 nM ^v		[52]
20	Combretastatin	SK-OV-3	0 9_32.4 nM ^{iv}	1 7 nM ^{iv}	[52]
		Cancer cell line papel		0.0032 nM ^v	[54]
		Cancer cell line panel	3951 nM ⁱ ∕	$2.8-6.0 \text{ nM}^{iv}$	[55]
29	Cvanocombretatstin A-4	Cancer cells line panel	Nanomolar range ^v	_	[56]
30	Resveratrol	MDA-MB-231	1 MM-100 nM ^{iv}	_	[57]
31	11-71640-2	MNK2	7.2 MM ^{iv}	_	[58]
32	Chalcones	H-SY5Y	Inactive	0.21 nM ^{iv}	[59]
Hotoroovala			indeare	0.2.1.1.1	[00]
22		Ang (III) recentor			[60]
24	ElCAR	Ang (ii) receptor	-	-	[00]
34 25	2 1(1H)-dian/limidazoles isosteros	 rNav1 6			[01] [62]
36	Miconazola-Katoconazola hybrid	Escherichia coli	>64 Ma/m ^{lii}	13.0 10101	[02]
30			204 IVIQ/ITII"		[64]
38	Pimonabant				[04]
	RIHUHADAHL		1.0 ± 3.4 [1]VI'' 1.6 ± 0.012 pMi	13.0 ± 1.8 NW	[66]
20	Fipropil	Housefly CAPA recenter			[00]
<u></u> 40	Purozolo[2.4 dipurimidipos	Gram pogative bactoria	9.04 HIVI	2.3-0.3 111/1	[60]
<u>40</u> 41	Appenditional and the second s				[00]
			-2.7 MM^{i}	1 Z 1 IIVI	[70]
42	Ribavirin	HIV-1 RT	3.8 MM ^{iv}		[61]
43	Fluconazole	Candida albicans	0.0011 Ma/mlii	0.5 Ma/ml ⁱⁱ	[62]
			5.0011 Mg/III	0.0 Mg/III	[02]

44	Linezolid	S. aureus	0.5 Mg/ml ⁱⁱ	2 Mg/ml ⁱⁱ	[63]
		Streptococcus pneumoniae	2 Mg/ml ⁱⁱ	1 Mg/ml ⁱⁱ	[74]
45	AAZ	VEGFR2 TK	6.96 MM ^{iv}	22 nM ^{iv}	[75]
46	Ebola virus inhibitor	293T (Ebola GP-mediated viral	5 MM ^{iv}	30 MM ^{iv}	[76]
		entry)			
47	ANB-22 and ANB-40	-	-	—	[77]
Miscella	neous				
48	Curcumin	HeLa	1.5 ± 0.3 MM ⁱ	21.8±1.2 MM ^{iv}	[86]
49	Sazetidin-A	α4β2 nAChRs	1.3 nM ⁱ	0.062±0.06 nM ⁱ	[87]
50	PIT-1	A2780 (PI3K)	11.9 MM ⁱⁱⁱ	_	[88]
51	Biotinyl-5'-AMP	S. aureus (SaBPL)	0.09 ± 0.01 MM ⁱ	_	[90,91]
52	c-di-GMP	PleD (DGCs)	17.5 ± 1.1mM ^{vii}	_	[92]
53	MAD	<i>mt</i> IMPDH	1.5 MM ^{viii}	>100 MM	[93]
		hIMPDH2	0.044 MM ⁱ	0.038 MM ⁱ	
54	Thymidine oligonucleotides	-	-	_	[94]
55	Nucleoside triphosphates	BaPanK	164 MM ⁱ	510±19 MM (K _M for ATP)	[95]

^aThe table summarizes the activity of the triazole analogs detailed in the main text, reporting the name of the parent compound, the biological target on which the analogs were tested, and the activity evaluation of both the isosteres and the corresponding parent compounds.

^bThe biological activity is expressed as: ⁱ inhibition constant (K_i); ⁱⁱ minimum inhibitory concentration (MIC); ⁱⁱⁱ half maximal effective concentration (EC₅₀); ^{iv} half maximal inhibitory concentration (IC₅₀); ^v half maximal growth inhibitory concentration (GI₅₀); ^{vi} half maximal cytotoxic concentration (CC₅₀); ^{vii} residual enzymatic activity; ^{viii} uncompetitive K_{iu}, compared with NAD; – exact value not reported or not yet determined.

^cFor the activity evaluation, the best results for each analog class are reported. Tests on other targets are therefore omitted.

*It is noteworthy that 1,2,4-triazoles also find applications as bioisosteres, although their use is less common compared with their 1,2,3-triazole regioisomers. The description of 1,2,4-triazoles applications in analog syntheses is beyond the scope of this review, but examples are reviewed in [96] and references therein.