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

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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 D_3 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 4-alkoxycarbonyl-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 TNFα-induced NF-κB-dependent transcription [86]. The ethynyl group replacement in Sazetidin-A, a selective α4β2 neuronal nicotinic acetylcholine receptor (nAChRs) desensitizer, led to a more selective α4β2 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.

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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

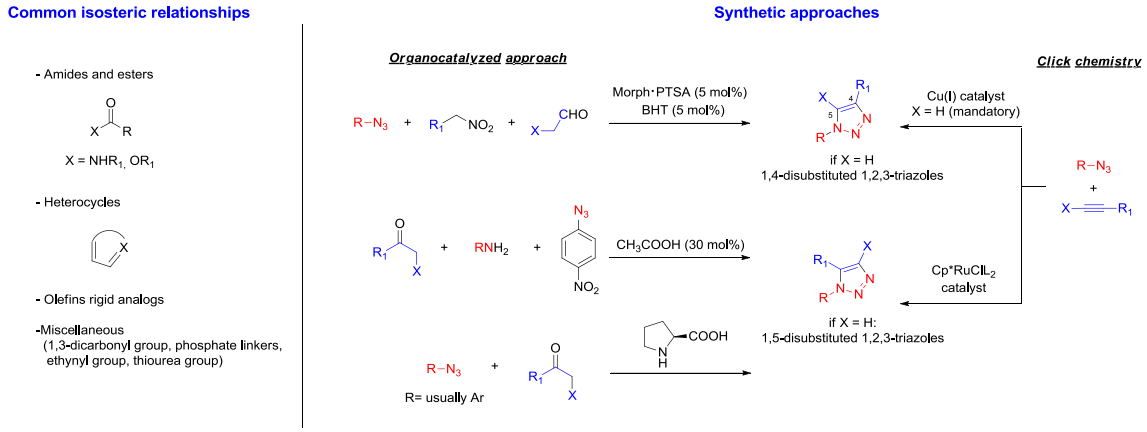

Figure 2

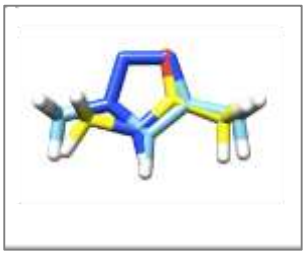

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Figure 3

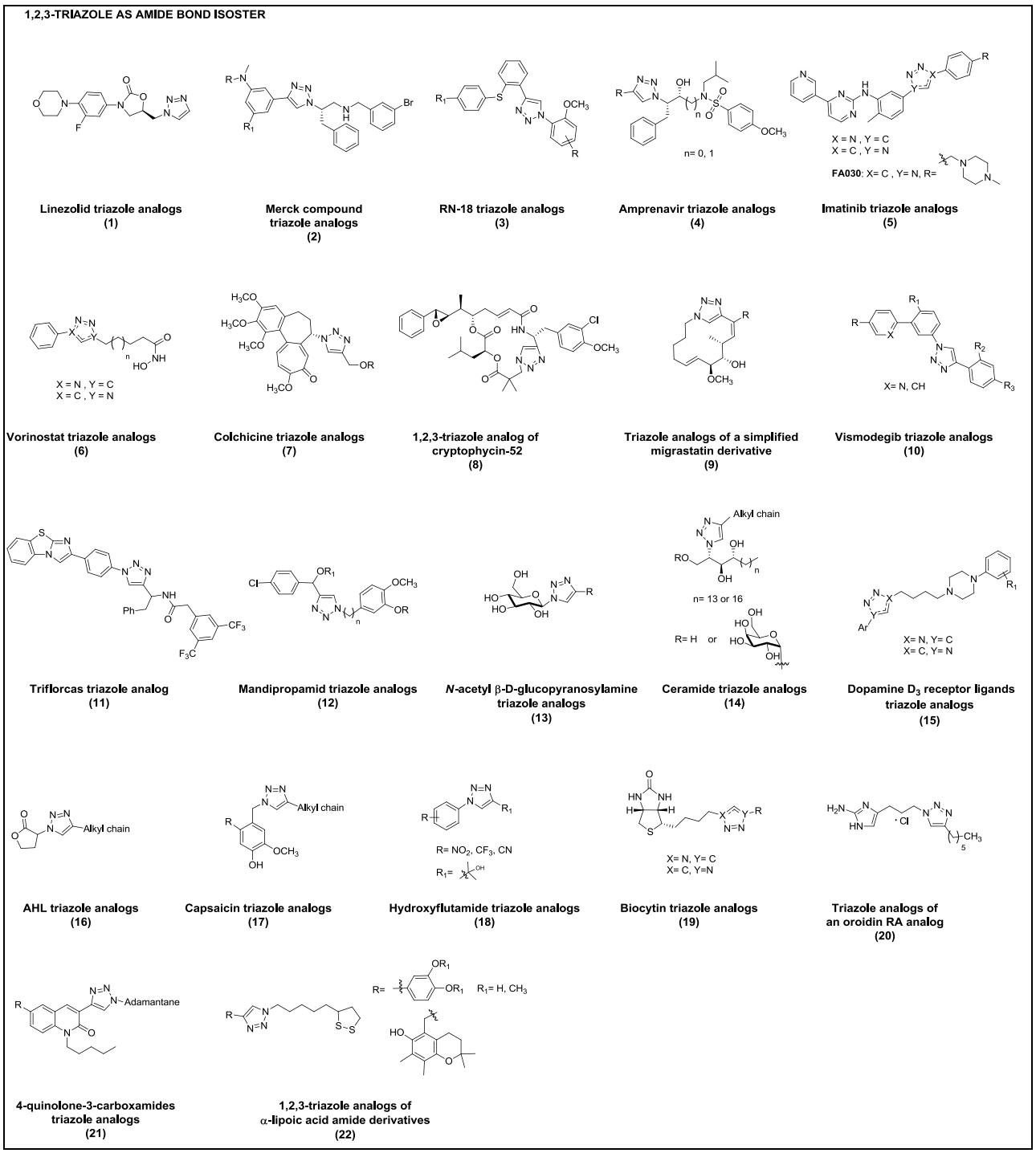

Figure 4

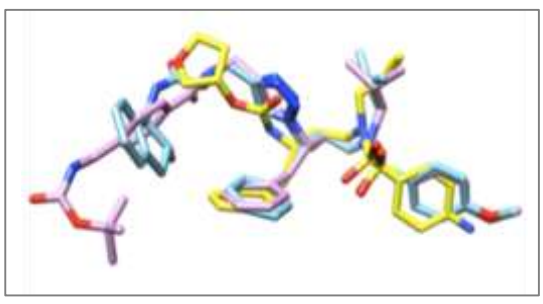

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Figure 5

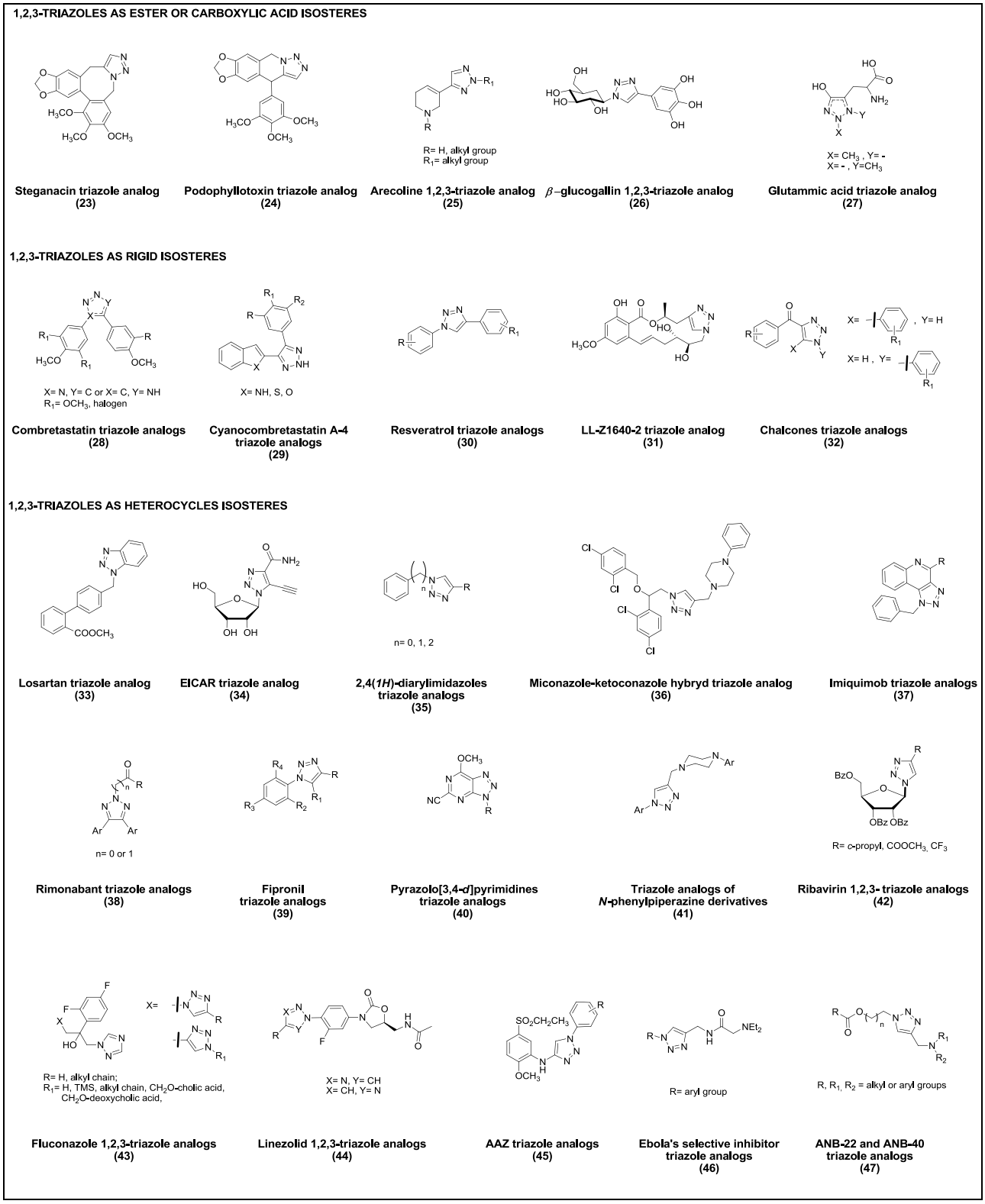

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Figure 6

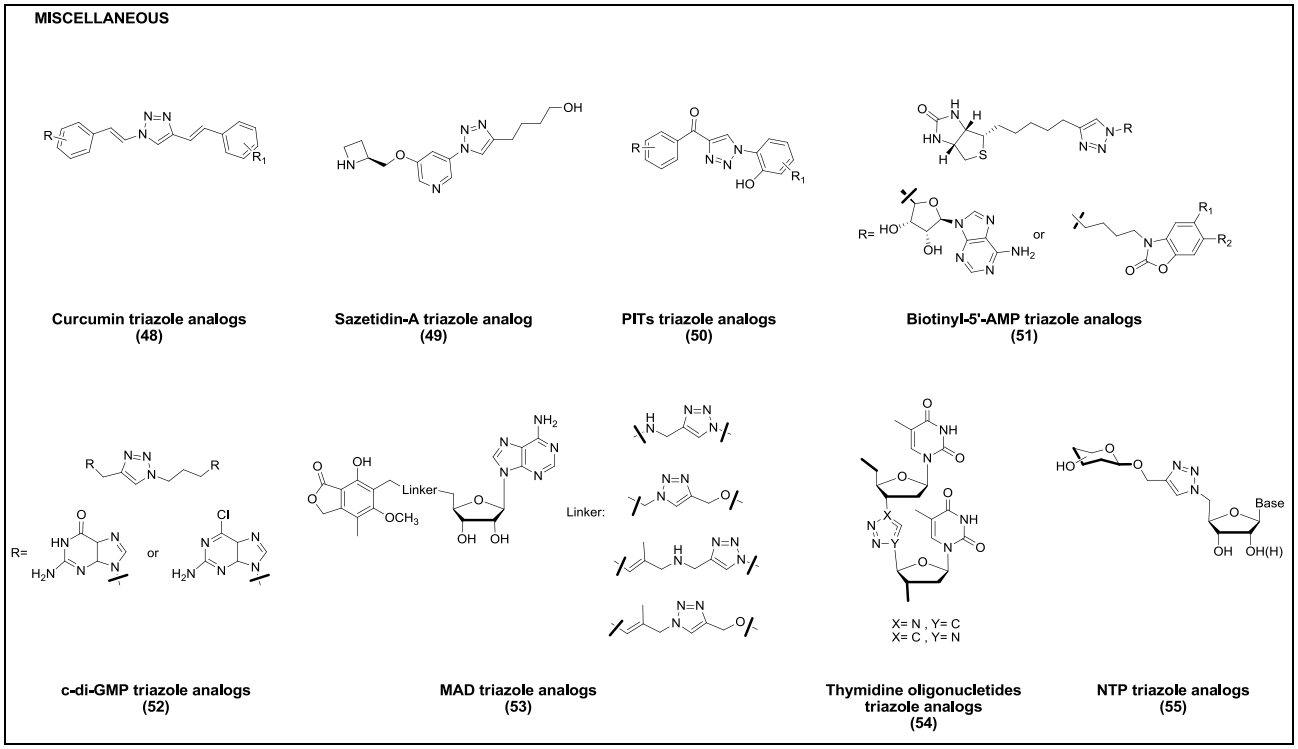

Table 1. The activity of 1,2,3-triazole analogs[a,b,c]

Compound	Parent compound	Biological target	Isostere activity evaluation	Parent compound activity evaluation	Refs
Amide isosteres					
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[iv]	–	[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[iv]	1-10 MM[iv]	[22]
7	Colchicine	BJAB	4 nM[iv]	20 nM[iv]	[23]
8	Cryptophycin-52	KB-VI	32 nM[iv]	0.7 nM[iv]	[24]
9	Migrastatin analog	MDA-MB-361	–	–	[25]
10	Vismodegib	BAEC	0.42±0.04 MM[iv]	50±4 MM[iv]	[26]
11	Triflorcas	MDCK (HGF scatter factor)	0.6 MM[iv]	0.2 MM[iv]	[27]
12	Mandipropamid	*Pseudoperonospora cubensis*	90% inhibition	–	[28]
13	*N*-Acetyl-β-D-glucopyranosylamines	RMGPb	14 MM[i]	18 MM[i]	[29–31]
14	Ceramides	K-562	8.2 MM[iii]	35.1 MM[iii]	[32]
		iNKT (T-cells receptor)	–	–	[33,34]
			–	–	[35]
15	USCA401	D_3 receptor	2.7 nM[i]	2.6 nM[i]	[36]
	WC10	D_3 receptor	<4 nM[i]	0.8 ±0.1 nM[i]	[37]
		D_3 receptor	5.05 ± 0.141 nM[i]	0.233±0.0089 nM[i]	[38]
16	*N*-Acyl-homoserine-lactone	*Vibrio fischeri* (LuxR)	51±2 MM[iv]	–	[39]
		Pseudomonas aeruginosa (LasR)	49.9±20.1 %QS inhibition	–	[40]
17	Capsaicin	hCB1	0.44 MM[i]	>5.6 MM[i]	[41]
		hTRPV1	0.69±0.16 MM[iv]	–	
18	Hydroxyflutamide	LNCaP (androgen receptor)	40 MM[iv]	-	[42]
19	Biocytin	Avidin (biotinidase)	Picomolar K_D	-	[43]
20	Oroidin RA analog	*P. aeruginosa 14*	27±4 MM[iv]	40 MM[iv]	[44]
21	4-Quinolone-3-carboxamides	hCB2	11.1±3.6 nM[i]	0.7±0.2 nM[i]	[45]
22	α-Lipoic acid amide derivatives	HT22	0.90±0.04 MM[iii]	2.10±0.4 MM[iii]	[46,47]
Ester isosteres					
23	(-)-Steganacin	SH-SY5Y	1.1 ± 0.4 MM[iv]	-	[48]
24	(-)-Podophyllotoxin	SH-SY5Y	1.5 ± 0.7 MM[iv]	7.0 ± 0.9 nM[iv]	[48]
25	Arecoline	Guinea Pig ileum (muscarinic receptors)	130 nM[iii]	190 nM[iii]	[49]
26	*β*-Glucogallin	AKR1B1	Inactive	8±1 MM[iv]	[50]
COOH isosteres					
27	Glutamic acid	AMPA receptors (GluRs)	1.4 MM[iv]	0.34 MM[iv]	[51]
Triazoles as rigid analogs					
28	Combretastatin	Cancer cell line panel	<10 nM[v]	-	[52]
		SK-OV-3	0.9–32.4 nM[iv]	1.7 nM[iv]	[53]
		Cancer cell line panel	<10 nM[v]	0.0032 nM[v]	[54]
		Cancer cell line panel	3.9–5.1 nM[iv]	2.8–6.0 nM[iv]	[55]
29	Cyanocombretatstin A-4	Cancer cells line panel	Nanomolar range[v]	–	[56]
30	Resveratrol	MDA-MB-231	1 MM–100 nM[iv]	–	[57]
31	LL-Z1640-2	MNK2	7.2 MM[iv]	–	[58]
32	Chalcones	H-SY5Y	Inactive	0.21 nM[iv]	[59]
Heterocycles					
33	Losartan	Ang (II) receptor	–	–	[60]
34	EICAR	–	–	–	[61]
35	2,4(*1H*)-diarylimidazoles isosteres	rNa_V1.6	28.5 MM[iv]	19.6 MM[iv]	[62]
36	Miconazole-Ketoconazole hybrid	*Escherichia coli*	>64 Mg/ml[ii]	–	[63]
37	Imiquimod derivative	TLR7	Inactive	2.0 MM[iii]	[64]
38	Rimonabant	hCB1	11.6 ± 3.4 nM[iv]	15.0 ± 1.8 nM[iv]	[65]
			4.6± 0.012 nM[i]	–	[66]
39	Fipronil	Housefly GABA receptor	9.04 nM[iv]	2.3–6.3 nM[iv]	[67]
40	Pyrazolo[3,4-*d*]pyrimidines	Gram-negative bacteria	–	–	[68]
41	*N*-phenylpiperazine derivatives	D_4receptor	2.7 nM[i]	12 nM[i]	[69]
		D_2 receptor	0.74 MM[i]	–	[70]
42	Ribavirin	HIV-1 RT	3.8 MM[iv]	–	[61]
43	Fluconazole	*Candida albicans*	0.0011 Mg/ml[ii]	0.5 Mg/ml[ii]	[62]

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 entry)	5 MM[iv]	30 MM[iv]	[76]
47	ANB-22 and ANB-40	–	–	–	[77]
Miscellaneous					
48	Curcumin	HeLa	1.5 ± 0.3 MM[iv]	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* (*Sa*BPL)	0.09 ± 0.01 MM[i]	–	[90,91]
52	c-di-GMP	PleD (DGCs)	17.5 ± 1.1mM[vii]	–	[92]
53	MAD	*mt*IMPDH	1.5 MM[viii]	>100 MM	[93]
		*h*IMPDH2	0.044 MM[i]	0.038 MM[i]	
54	Thymidine oligonucleotides	–	–	–	[94]
55	Nucleoside triphosphates	*Ba*PanK	164 MM[i]	510±19 MM (K_M for ATP)	[95]

[a]The 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.

[b]The biological activity is expressed as: [i] inhibition constant (K_i); [ii] minimum inhibitory concentration (MIC); [iii] half maximal effective concentration (EC_{50}); [iv] half maximal inhibitory concentration (IC_{50}); [v] half maximal growth inhibitory concentration (GI_{50}); [vi] half maximal cytotoxic concentration (CC_{50}); [vii] residual enzymatic activity; [viii] uncompetitive K_{iu}, compared with NAD; – = exact value not reported or not yet determined.

[c]For 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.