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Recent Developments in the Practical Application of Novel Carboxylic Acid Bioisosteres

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Abstract

Background: The carboxylic acid is an important functional group which features in the pharmacophore of some 450 drugs. Unfortunately, some carboxylic acid-containing drugs have been withdrawn from market due to unforeseen toxicity issues. Other issues associated with the carboxylate moiety include reduced metabolic stability or limited passive diffusion across biological membranes. Medicinal chemists often turn to bioisosteres to circumvent such obstacles.

Objective: The aim of this review is to provide a summary of the various applications of novel carboxylic acid bioisosteres which have appeared in the literature since 2013.

Results: We have summarised the most recent developments in carboxylic acid bioisosterism. In particular, we focus on the changes in bioactivity, selectivity or physiochemical properties brought about by these substitutions, as well as the advantages and disadvantages of each isostere.

Conclusion: The topics discussed herein highlight the continued interest in carboxylate bioisosteres. The development of novel carboxylic acid substitutes which display improved pharmacological profiles is testament to the innovation and creativity required to overcome the challenges faced in modern drug design.

Keywords: Isosteres; bioisosterism; carboxylic acids; drug design; acidity; lipophilicity.

Graphical Abstract

List of Abbreviations

ADME - Absorption, distribution, metabolism, and excretion

AKR1C3 - Aldo-keto reductase 1C3

ALR – Aldose/aldehyde reductase

AMAA - (R,S)-2-amino-2-(3-hydroxy-5-methyl-4-isoxazolyl)acetic acid

AMPA - (*S*)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid

Arg - Arginine

ARI - Aldose reductase inhibitor

AT_1 - Angiotensin II receptor type 1

ATP - Adenosine triphosphate

ATX - Autotaxin

AUC - Area under the curve

BEI - Binding efficiency index

BRS-3 - Bombesin receptor subtype 3

CF – Cystic fibrosis

CL - Clearance

cLog D - Calculated log of the octanol/water partition coefficient at pH 7.4

clog P - Calculated log of the octanol/water partition coefficient

cLog S - Calculated log of the solubility measured in mol/L

CNS - Central Nervous System

COPD - Chronic obstructive pulmonary disease

COX - Cyclooxygenase

DNA - Deoxyribonucleic acid

DPPH - 2,2-diphenyl-1-picrylhydrazyl

ER - Efflux ratio

ESKAPE - *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species

fu - Fraction unbound

GABA - γ-aminobutyric acid

Glu - Glutamate

Gly - Glycine

GyrB - Gyrase subunit B

hDHODH - Human dihydroorotate dehydrogenase

His – Histidine

HIV - Human immunodeficiency virus

HNE - Human neutrophil elastase

IR - Infrared

LE - Ligand efficiency

LipE - Lipophilic efficiency

Log D - Log of the octanol/water partition coefficient at pH 7.4

Log P - Log of the octanol/water partition coefficient

LT – Leukotriene

Lys – Lysine

MDCK - Madin-Darby Canine Kidney

MDM2 - Murine double minute 2

Met - Methionine

MIC - Minimal inhibitory concentration

$NADP^+$ - Nicotinamide adenine dinucleotide phosphate

NMDA - *N*-methyl-*D*-aspartic acid

NMR - Nuclear magnetic resonance

NSAID - Non-steroidal anti-inflammatory drug

PAMPA - Parallel Artificial Membrane Permeability Assay

P_{app} - Apparent permeability coefficient

PG - Prostaglandins

PI - Proteasome inhibitor

pK_a - Negative log of acid dissociation constant

PPB - Plasma protein binding

RBL - Rat basophilic leukaemia

RXRα - Retinoid X receptor α

SRB - Sulforhodamine B

Thr - Threonine

TP - Thromboxane A2 prostanoid

TPSA - Total polar surface area

Tyr - Tyrosine

t½ - Half-life

4-PHP - 4-(4-piperidyl)-1-hydroxypyrazole

4-PIOL - 5-(4-piperidyl)-3-hydroxyisoxazole

5-LOX - Arachidonate 5-lipoxygenase

1. Introduction

The term isosterism was coined by Irving Langmuir 100 years ago to describe the similarity between molecules and ions that share the same number of atoms and valence electrons.[1] Grimm's Hydride Displacement Law expanded this description to include groups with different numbers of atoms but equivalent valence electrons.[2] Hans Erlenmeyer was the first to extend the concept to biological systems in the 1930s.[3] He and his colleagues synthesised a range of *ortho*-substituted diazonium derivatives of tyrosine. These synthetic antigens contained either O, NH, or CH_2 as a linker element and phenyl or thiophene rings as an aromatic element. These azoproteins all retained similar antigenic properties, as the antibodies were unable to discriminate between the various linker and aromatic components. In 1951, Harris Friedman used the term bioisosterism to describe this phenomenon where broadly analogous structures produce similar biological effects.[4] The above examples can be categorised as classical bioisosteres i.e. mono-, di-, tri- and tetravalent atoms or groups as well as ring equivalents.[5] All other bioisosteres are considered non-classical.

There are numerous examples of bioisosterism in nature. Many amino acids are isosteric, for example serine (**1**) and cysteine (**2**) (Figure **1**).[6] The similarities between γ-aminobutyric acid (GABA) (**3**) and muscimol (**4**), or glutamate (**5**) and (*S*)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid (AMPA) (**6**), are examples of non-classical bioisosterism.

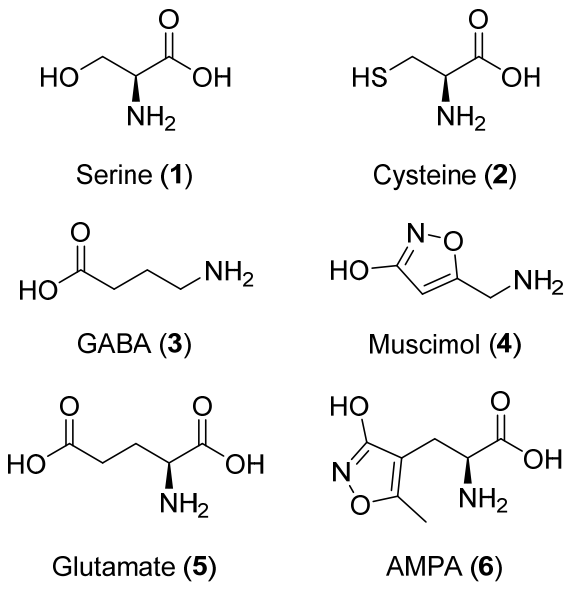


Figure 1 Examples of naturally occurring bioisosteres.

The application of bioisosterism to facilitate the rational modification of lead compounds is a well-established technique in modern drug design.[7, 8] These structural changes are often used to improve potency and selectivity. Although this strategy can be highly effective, the impact of the substitution cannot be accurately predicted due to myriad factors, and occasionally biological activity can even be reduced or reversed. Isosteric replacement is also employed to help alter physiochemical properties such as pK_a and lipophilicity, as well as absorption, distribution, metabolism, and excretion (ADME) properties.[9, 10]

The carboxylic acid functional group plays an integral role in all living systems. It is a key structural feature of the amino acids. It is unsurprising, therefore, that the carboxylic acid moiety appears in the pharmacophore of some 450 marketed drugs including non-steroidal anti-inflammatory drugs (NSAIDs), β-lactam antibiotics, statins and fibrates.[11]

As a reactive handle, the carboxylate residue presents many advantages. The ionised species can participate in strong ionic interactions (e.g. salt bridges) while the carbonyl and hydroxyl elements can establish intermolecular hydrogen bonds.[12] As well as improving affinity to the binding site, such interactions with surrounding water molecules can improve a drug's solubility.[11] In addition, their inherent acidity is often a contributory factor to their biological activity.

Unfortunately, some issues may arise due to the presence of a carboxylic acid moiety in a drug or drug candidate. The most notable of these are concerns relating to idiosyncratic drug toxicities.[13, 14] This usually manifests as hepatotoxicity linked to acyl glucuronidation (a major metabolic pathway in the elimination of many carboxylic acid-containing drugs).[15] However, evidence suggests that acyl glucuronide formation alone does not pose an increased risk compared to other drug metabolites.[16, 17] Nevertheless, Fung *et al.* reported that 17 (i.e. 14%) of the 121 prescription drugs withdrawn worldwide for safety reasons between 1960 and 1999 contained a carboxylic acid.[18]

Plasma protein binding (PPB) is related to lipophilicity and can play an important role in chemical-induced toxicity.[19] Studies have shown that lipophilic acids show a higher propensity for PPB.[20] Additionally, the high polarity and negative charge of carboxylates at physiological pH gives rise to unfavourable pharmacokinetic properties such as low bioavailability due to limited uptake.[21] This makes it very difficult for carboxylic acids to penetrate membranes such as the blood brain barrier, which is particularly problematic in the design of drugs targeting the central nervous system (CNS).[22, 23] To circumvent the obstacles related to passive diffusion, the active agent is often administered as a prodrug such as an ester or amide. The use of bioisosteres is another tactic which is employed to negate these issues.

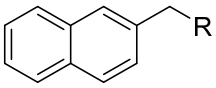
The benefits of these substitutions are varied and wide-ranging. Some of the best known and commonly used bioisosteres of the carboxylic moiety were thoroughly reviewed by Ballatore and co-workers in 2013.[24] This review focuses on carboxylic acid bioisosteres that have emerged in the subsequent period.

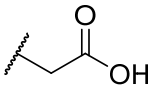
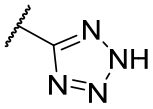
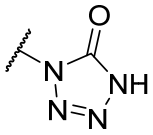
2. Tetrazolone

Tetrazoles are one of the most commonly employed carboxylic acid isosteres.[25-27] By contrast, the corresponding 1-substituted tetrazol-5-ones have been mostly absent from the literature until recently. A notable feature of the tetrazolones is their high degree of metabolic stability.[28] Replacing a carboxylic acid with a tetrazolone can result in lower lipophilicity, improved solubility or reduced toxicity.

The use of a 1-substituted tetrazol-5-one as a carboxylic acid isostere was first described by Kees and co-workers in their work on the generation new anti-diabetic lead structures.[29] Tetrazolone **9** exhibited similar levels of acidity (pK_a 6.36) (Table 1, entry 3) compared to the lead carboxylic acid (pK_a 6.52) (entry 1). The octanol/water partition coefficient (Log P) of the isostere was 0.79 which was 0.3 log units lower than the acid. The inferior lipophilicity of **9** was attributed to the keto form which the compound exclusively adopted.[29, 30] However, **9** readily ionises and is fully soluble in 1% aqueous sodium bicarbonate solution, a finding which may be of use to medicinal chemists in the candidate optimisation process. While the bioisosteric analogue failed to lower plasma glucose in diabetic db/db mice, its interesting physicochemical properties demonstrated the potential of the tetrazolone moiety as a suitable acid bioisostere.

Table 1 Comparison of physiochemical properties of carboxylic acid **7**, tetrazole **8** tetrazolone **9**.



Entry	Compound	R	pK_a	Log P	Dose (mg/kg)
1	**7**		6.52	1.09	100
2	**8**		5.77	0.72	20
3	**9**		6.36	0.79	100

Duncton and colleagues subsequently synthesised tetrazolone derivatives of several important drugs, including angiotensin receptor blocker telmisartan (**10**), anti-cancer agent bexarotene (**12**) and the non-steroidal anti-inflammatory drug indomethacin (**14**), and evaluated their biological activity (Figure 2).[31]

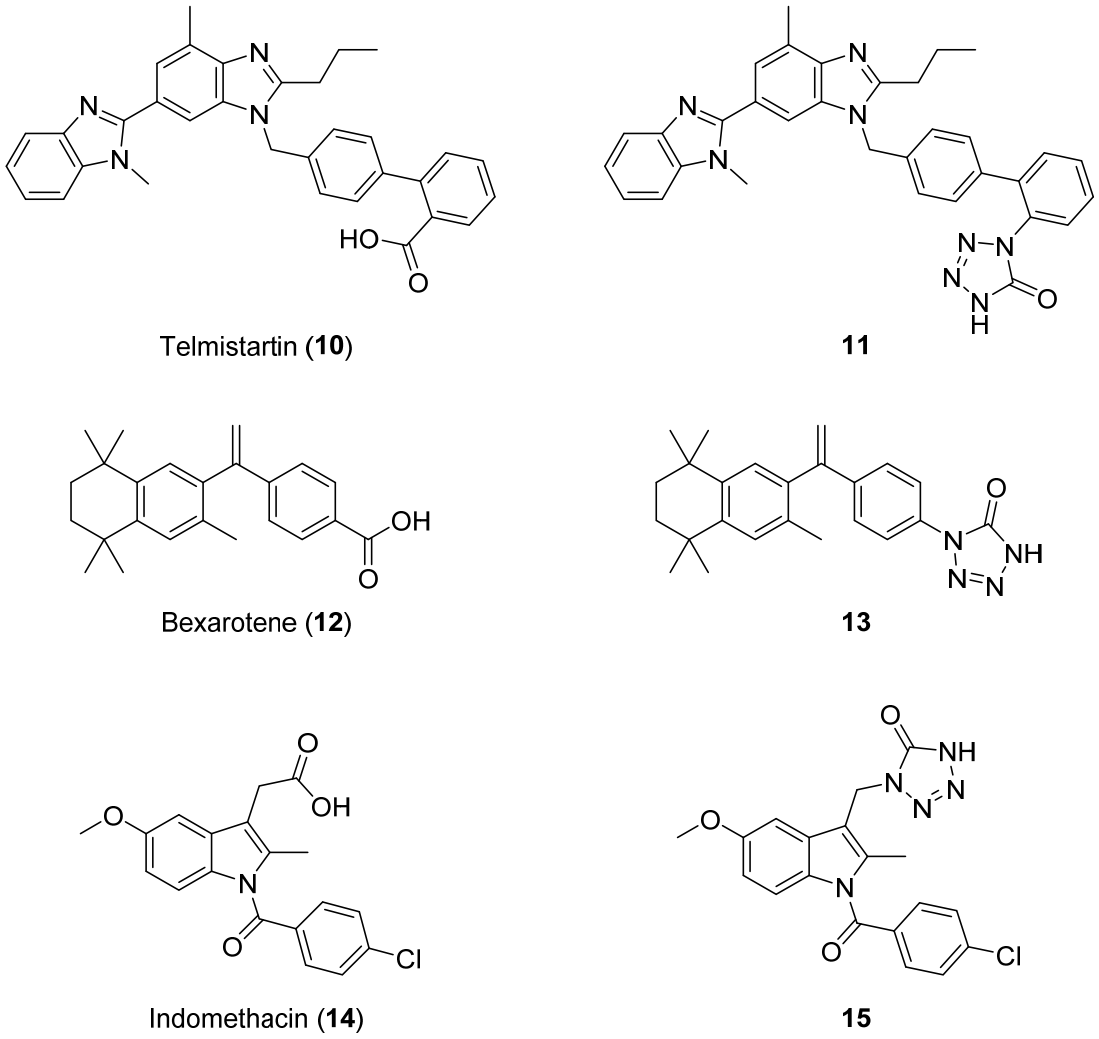


Figure 2 Marketed drugs containing a carboxylic acid and their tetrazolone counterparts.

The tetrazolone congener **11** performed better as an angiotensin II receptor type 1 (AT_1) inhibitor (K_b = 0.14 nM; IC_{50} = 1.7 nM, Table 2, entry 2) than telmisartan (K_b = 0.44 nM; IC_{50} = 5.7 nM, entry 1). Tetrazolone **11** also proved more potent than the tetrazole bioisostere and most other known AT_1 antagonists. In addition to these positive *in vitro* results, *in vivo* tests confirmed that tetrazolone **11** exhibited lower clearance, higher exposure and a slightly longer half-life (entry 2) than telmisartan (entry 1). Bexarotene and its corresponding tetrazolone **13**, were both evaluated as retinoid X receptor α (RXRα) agonists. While the tetrazolone was active (EC_{50} = 64 nM, entry 4), it was found to be less potent than the original lead (EC_{50} < 10 nM, entry 3). It did, however, elicit a similar maximal response (relative efficacy). This result is significant, as it illustrates how tetrazolone bioisosteres can function either as agonists (RXRα) or antagonists (AT_1). In the case of indomethacin (entry 5), tetrazolone analogue **15** (entry 6) displayed no significant activity as an inhibitor of cyclooxygenase (COX). This finding demonstrates that, as with most bioisosteres, the ultimate effect of incorporating a tetrazolone is not predictable.

The *in vitro* pharmacokinetic profiles presented by the tetrazolones were positive. All compounds exhibited robust microsomal stability when incubated with either human or rat microsomes (half-life ≥45 min) while also displaying significant binding to plasma proteins (99.9%). When examining the effect of tetrazolone substitution on

physicochemical properties, the results were consistent with the work of Kees and colleagues with a reduction of 0.4-1.0 in cLog P (Table 2).

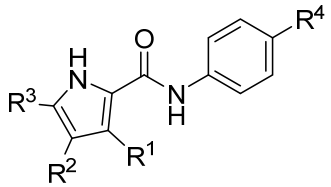
Table 2 Comparison of known drugs and their tetrazolone derivatives.

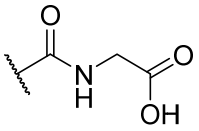
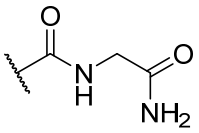
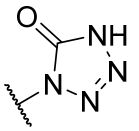
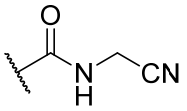
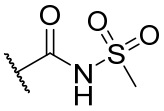
Entry	Cpd	hAT_1 IC_{50} [K_b] (nM)	hRXRα EC_{50} (nM)	hCOX-1 (% inhibition at 1 μM)	clog P	Clearance (mL min^{-1} kg^{-1})	$AUC_{0\text{-}24\ h}$ (ng mL^{-1} h^{-1})	Half-life *in vivo* (h)
1	**10**	5.7 [0.44]	-	-	6.48 ± 1.19	7.2 ± 1.1	1830 ± 245	3.6
2	**11**	1.70 [0.14]	-	-	6.00 ± 1.17	4.5 ± 0.6	2490 ± 249	5.4
3	**12**	-	<10	-	6.90 ± 0.53	-	-	-
4	**13**	-	64	-	5.90 ± 0.51	-	-	-
5	**14**	-	-	88%	4.25 ± 0.80	-	-	-
6	**15**	-	-	37%	3.85 ± 0.79	-	-	-

In vivo metabolism studies with rat bile indicated differences in metabolism between Telmisartan (**10**) and tetrazolone derivative **11**.[32] While an *O*-acyl glucuronide metabolite was the exclusive product of Telmisartan glucuronidation, two major glucuronide metabolites were observed for **11**. It is postulated that glucuronidation of the tetrazolone resulted in both the *N*-acyl (major) and *O*-acyl (minor) glucuronides. The *O*-tetrazolone glucuronide could potentially possess a similar reactivity to that of an acyl glucuronide. However, the author suggests that the poor electrophilicity of the tetrazolone carbonyl would make *N*-glucuronidated tetrazolone metabolites less prone to react with nucleophilic amino acid residues than their acyl glucuronide counterparts. Further studies involving the incubation of *O*- and *N*-glucuronide tetrazolones with nucleophiles mimicking *in vivo* conditions are required to confirm this theory.

In a recent study, Tiz *et al.* incorporated a tetrazolone isostere into a DNA gyrase and topoisomerase IV inhibitor which interacts with the ATP binding site.[33] The design was based on the co-crystal structure of **16**, a GyrB inhibitor in *E. coli* (Table 3).[34] Having proved to be a potent inhibitor of *E. coli* gyrase (IC_{50} = 77 nM, entry 3), tetrazolone **18** was tested for anti-bacterial activity using an ESKAPE panel. **18** inhibited the growth of *E. faecalis* and *S. aureus* by 99% (Minimal inhibitory concentration (MIC) 12.5 μM and 50 μM respectively, entry 3). Although it was inactive against *E. coli* (3% inhibition), **18** displayed significant activity against *E. coli* JW5503, a tolC deletion mutant with defective efflux pump (MIC 3.13 μM, entry 3). In addition to these favourable results, **18** possessed moderately low lipophilicity (cLog P 1.74), decent solubility (cLog S -4.32) and observed Lipinski's rule of five.

Table 3 Inhibitory activities of topoisomerase IV inhibitors **16**-**20** against various bacteria strains.



Entry	Cpd	R^1	R^2	R^3	R^4	IC_{50} *E. coli* gyrase (μM)	MIC *E. faecalis* (ATCC 29212) (μM)	MIC *E. coli* (JW5503) (μM)
1	**16**	H	Br	Br		0.45	-	-
2	**17**	H	Br	Br		2.2	-	-
3	**18**	Cl	Cl	Me		0.077	12.5	3.13
4	**19**	Cl	Cl	Me		0.41	25	12.5
5	**20**	Cl	Cl	Me		0.16	-	-

3. Hydroxypyrazoles

Extensive research into γ-aminobutyric acid (GABA) receptor ligands, glutamate derivatives and aldose reductase inhibitors (ARIs) has identified 1- and 3-hydroxypyrazoles as potential carboxylic acid isosteres.[35, 36] These acidic surrogates present some advantages over the closely related 3-hydroxyisoxazoles and isothiazoles which provided the inspiration for their design.[35] Firstly, hydroxypyrazoles possess an additional position for introducing reactive handles to access non-conserved regions of a receptor. Furthermore, the different configurations of 3-hydroxypyrazoles allow for regiodirection of substituents, thus affording the opportunity to extensively probe a binding site, something which is not possible with carboxylic acids (Figure 3).[36, 37] Hydroxypyrazoles also possess some of the benefits of 3-hydroxyisoxazoles. For example, the negative charge of the deprotonated hydroxyl is delocalized into the aromatic ring allowing the hydroxypyrazole to mimic the electrostatic profile of a carboxylate.[38] More generally, the reduced acidity and enhanced lipophilicity of hydroxypyrazoles may help to avoid problems often associated with carboxylic acids, such as poor membrane permeability.

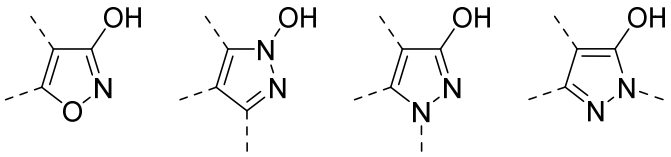
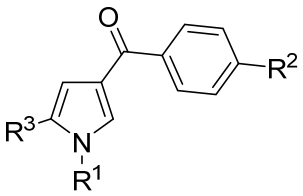
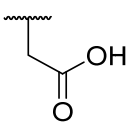
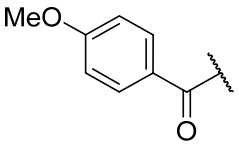
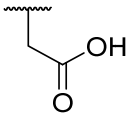
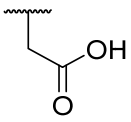
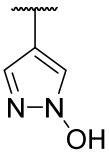
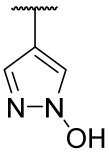


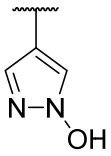
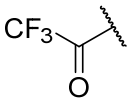
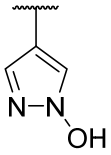
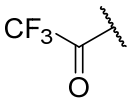
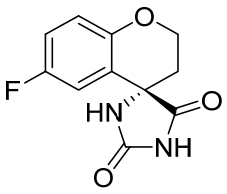
Figure 3 Substitution patterns of 3-hydroxyisoxazole, 1-hydroxypyrazole and 3-hydroxypyrazoles.

The main classes of ARIs include spirohydantoins, such as sorbinil (**28**) (Table 4), and carboxylic acid derivatives, such as epalrestat (**33**) (Table 6).[39] Despite the high activity of these compounds, they display poor membrane permeability. Papastavrou *et al.* have synthesised ARIs using the 1-hydroxypyrazole to overcome this obstacle.[40-42] Hydroxypyrazoles **24** (entry 4) and **25** (entry 5) both exhibited significant inhibitory activity (IC_{50} 0.708 and 0.698 μM respectively) and were comparable to the corresponding carboxylic acids **22** (entry 2) and **23** (entry 3). Both **24** (entry 4) and **25** (entry 5) displayed higher selectivity for ALR2 over ALR1. Further optimisation studies yielded hydroxypyrazoles **26** (entry 6) and **27** (entry 7). Both compounds were active at sub-micromolar concentrations (IC_{50} 0.078 and 0.043 μM respectively) and were superior to sorbinil (**28**) (entry 8) and carboxylic acid **23** (entry 3). The ALR2/ALR1 selectivity was also enhanced. The physicochemical profiles of these compounds were equally promising.

Table 4 Activity and selectivity of carboxylic acid and 1-hydroxypyrazole ALR2 inhibitors.



Entry	Compound	Structure			IC_{50} (μM)	Selectivity ALR2/ALR1
		R^1	R^2	R^3		
1	**21**		OMe		2.36	-
2	**22**		OMe	H	1.602	62.42
3	**23**		Ph	H	0.344	152.66
4	**24**		OMe	H	0.708	11.23
5	**25**		Ph	H	0.698	88.92

6	**26**		F		0.078	858
7	**27**		SMe		0.043	650
8	Sorbinil (**28**)				0.25	-

The calculated pKa values of **24** (Table 5, entry 3) and **25** (entry 4) were higher than those of the corresponding carboxylic acids (entries 1 and 2). The introduction of the hydroxypyrazole isostere also improved lipophilicity with all hydroxypyrazoles exhibiting improved cLog D values. Hydroxypyrazoles **24**-**27** all fell within Lipinski's rule of five and possessed favourable binding efficiency index (BEI) and ligand efficiency (LE). The predicted total polar surface area (TPSA) of 77.13 $Å^2$ for both **26** and **27** suggests good oral bioavailability.

Table 5 Physicochemical properties of **22**-**27**.

Entry	Cpd	MW (g/mol)	Calculated pK_a	Log P	cLog D	BEI	LE	TPSA ($Å^2$)
1	**22**	259.26	3.97	2.45	-0.98	22.36	0.43	-
2	**23**	305.33	3.98	3.85	0.43	21.17	0.39	-
3	**24**	283.29	5.21	2.53	0.34	21.71	0.41	-
4	**25**	329.36	7.82	3.67	3.53	18.69	0.34	-
5	**26**	367.26	-	2.65	0.73	19.35	0.38	77.13
6	**27**	395.36	-	3.02	1.06	18.63	0.38	77.13

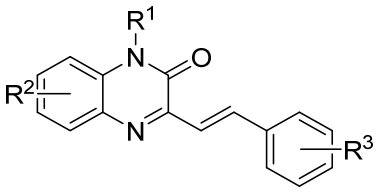
Hao *et al*. likewise exploited 1-hydroxypyrazoles in the design of their ARIs, some of which were equipotent with epalrestat (**33**) (Table 6).[43] Hydroxypyrazole derivatives **29** (entry 1), **30** (entry 2) and **31** (entry 3) all exhibited improved ALR2 inhibition compared to carboxylic acid **32** (entry 4). Additionally, these compounds displayed favourable selectivity for ALR2 over ALR1.

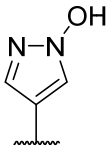
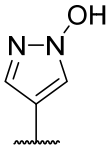
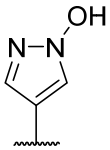
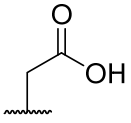
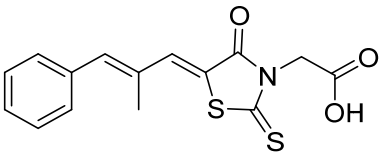
Molecular docking experiments were conducted on hydroxypyrazole **29** and carboxylic acid **32** docked in the anion-binding site of ALR2 using the crystal structure of ALR2 bound to lidorestat.[43] The carboxylate of **32** formed a hydrogen bond with the side chain of Tyr48 (2.93 Å) and participated in an electrostatic interaction with nicotinamide moiety of the cofactor $NADP^+$ (N-O = 4.07 Å). The 1-hydroxypyrazole ring of **29** presented a more favourable docking score, forming hydrogen bonds with the side chains of Tyr48 (2.83, 2.87 and 3.19 Å) and His110 (3.46 Å). These results agreed with the ALR2 inhibition assay. These findings were further consolidated by molecular docking experiments analysing **31** docked into the binding pocket of the human ALR2/$NADP^+$/minalrestat complex. It is proposed that the 1-

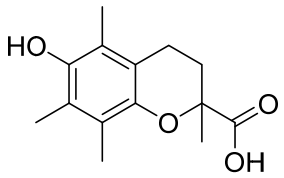
hydroxypyrazole ring of **31** could form three tight hydrogen bonds with the hydroxyl of Tyr48 (2.59, 2.64 and 3.06 Å), and one with the NE2 atom of His110 (2.39 Å) in the conserved anion-binding site of the ALR2 active site.

In addition to the ALR2 inhibition, assessment of radical scavenging and lipid peroxidation suppression revealed the antioxidant ability of these hydroxypyrazoles. Radical scavenging potential was measured using the model reaction with the stable free radical of 2,2-diphenyl-1-picrylhydrazyl (DPPH). **31** (entry 3) was the most potent hydroxypyrazole derivative and performed better than carboxylic acid **32** (entry 4). The powerful antioxidant potency of hydroxypyrazole **31** was further reinforced by a DPPH radical scavenging rate of 95.6% at a concentration of 100 µM, which was comparable to Trolox (**34**) (entry 6), a well-known vitamin E analogue. **31** also displayed considerable malondialdehyde inhibition compared to carboxylic acid **32** demonstrating its superior lipid peroxidation suppression.

Table 6 Rat lens ALR2 inhibition and DPPH radical scavenging activity of 1-hydroxypyrazole derivatives.



Entry	Cpd	Structure			ALR2 IC_{50} (µM)	Selectivity ALR2/ALR1	DPPH IC_{50} (µM)	DPPH radical scavenging rate at 100 µM (%)
		R^1	R^2	R^3				
1	**29**		H	4-OH	0.165	4.6	55.3	72.4
2	**30**		7-F	4-OH	0.107	4.8	78.9	65.3
3	**31**		H	3,4-$(OH)_2$	0.148	5.3	20.9	95.6
4	**32**		H	4-OH	0.798	-	51.5	71.8
5	Epalrestat (**33**)				0.083	-	-	-

6	Trolox (**34**)		-	-	6.8	97.8

Several studies on glutamate receptors have reported the use of 1-hydroxypyrazoles as an isosteric replacement of the distal carboxylic acid of glutamic acid (**5**), with Stensbøl and colleagues among the first to employ this strategy.[35] Their resulting (*S*)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid (AMPA) derivatives **35** and **36** exhibited moderate activities (EC_{50} 280 μM and EC_{50} 586 μM, respectively) and good affinity for [^{3}H]AMPA receptor binding sites (IC_{50} 2.7 μM and IC_{50} 2.6 μM respectively) (Figure 4). Similar affinities have been observed in 3-hydroxypyrazole derivatives **37** and **38** (IC_{50} 8.9 μM and IC_{50} 3.6 μM respectively).[37]

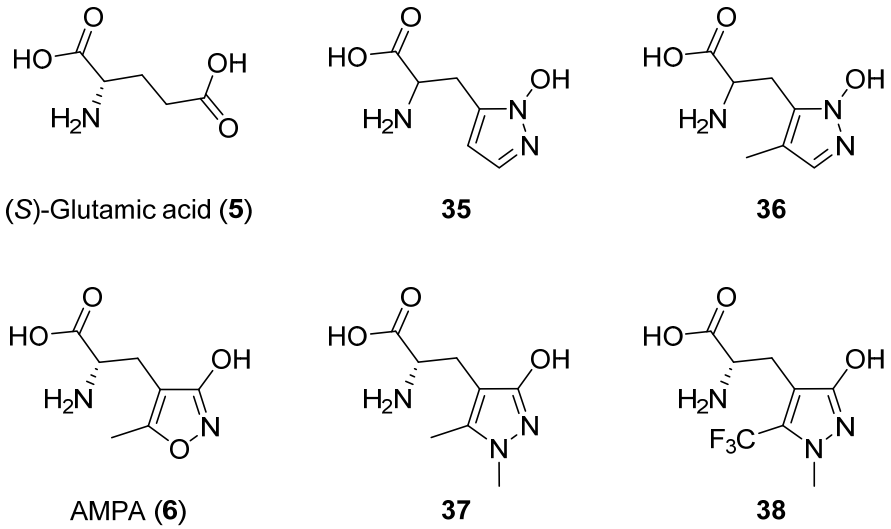


Figure 4 1-hydroxypyrazole derivatives of glutamic acid and AMPA.

Further work led to the development of 1-hydroxypyrazolyl glycine derivatives **40**, **41**, **43** and **44** of the classical glutamate receptor ligands ibotenic acid (**39**) and (*R*,*S*)-2-amino-2-(3-hydroxy-5-methyl-4-isoxazolyl)acetic acid (AMAA) (**42**) (Figure 5).[44-46] Interestingly, the unsubstituted analogues **40** and **43** were selective partial agonists (EC_{50} 140 μM and 82 μM respectively) of the *N*-methyl-*D*-aspartic acid (NMDA) receptor while substituted **41** and **44** exhibited NMDA receptor antagonism (IC_{50} 230 μM and 210 μM respectively).[45-47]

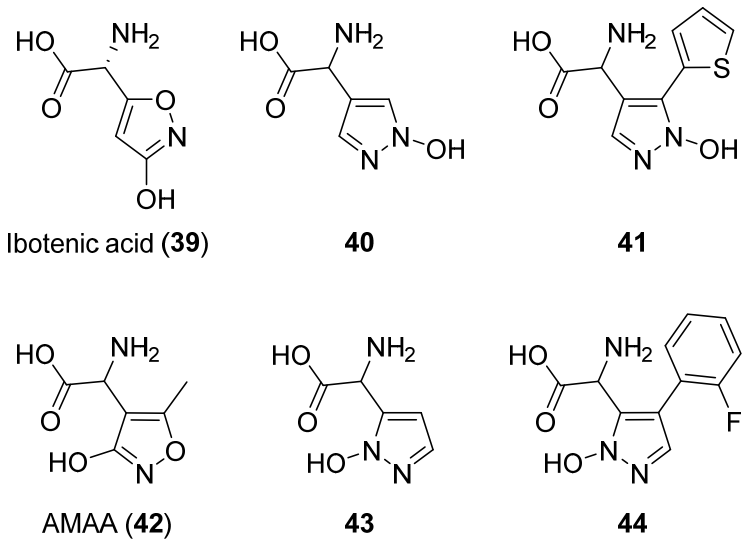


Figure 5 Substituted and unsubstituted 1-hydroxypyrazole analogues of ibotenic acid and AMAA.

Frølund and co-workers have conducted extensive studies on novel GABA receptor ligands.[48-50] Based on the proven success of 5-(4-piperidyl)-3-hydroxyisoxazole (4-PIOL) (**45**), they incorporated the 1-hydroxypyrazole isostere in their analogues of the classical ligand (Figure 6).[51] The resulting 4-(4-piperidyl)-1-hydroxypyrazoles (4-PHPs) (**46**) allowed for the exploration of potential cavities around the isoxazole oxygen of 4-PIOL.

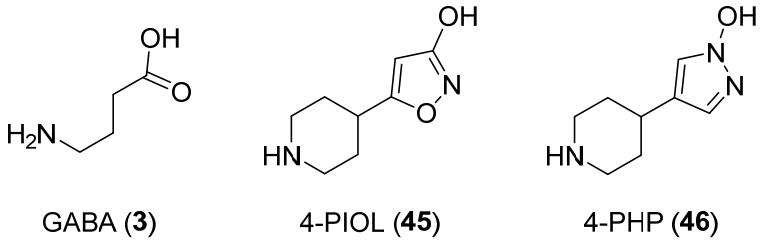
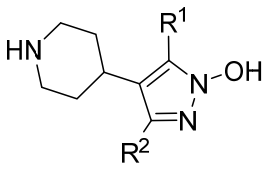


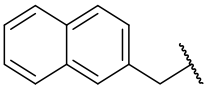
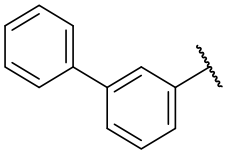
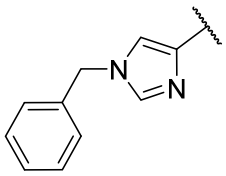
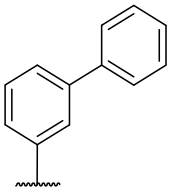
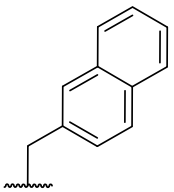
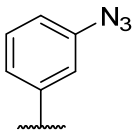
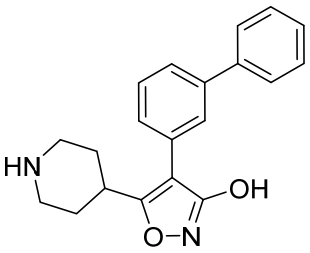
Figure 6 Structures of GABA, 4-PIOL and 4-PHP.

Some 3-substituted 4-PHPs such as **47**-**49** proved highly potent and exhibited affinities for $GABA_A$ receptor sites in the low nanomolar range (Table 7, entries 1-3).[52, 53] 5-Substituted 4-PHPs **50**-**52** were found to be effective antagonists (entries 4-6) and possessed binding affinities which were comparable to 4-PIOL **53** (entry 7) and gabazine (**54**), the $GABA_A$ receptor antagonist (entry 8). The efficient UV-inducible photoinhibition of $GABA_A$ receptors exhibited by 4-PHP azide analogue **52** was another notable feature of the study.[54]

Table 7 $GABA_A$ receptor binding affinities for **47**-**54**.



Entry	Compound	Structure		[^{3}H] muscimol binding K_i	$\alpha_1\beta_2\gamma_{2S}$ tsA201 cell line IC_{50} (μM)
		R^1	R^2		

				(μM)	
1	**47**	H		0.0030	0.17
2	**48**	H		0.030	0.21
3	**49**	H		0.28	0.21
4	**50**		H	0.0028	0.024
5	**51**		H	0.033	0.79
6	**52**		H	0.023	0.028
7	**53**			0.010	0.078
8	Gabazine (**54**)			0.074	0.24

4. Hydroxytriazoles

The 1,2,3-triazole is a popular scaffold which has been successfully employed as an amide or ester bond surrogate in several anti-microbial, anti-viral, and anti-cancer leads.[55, 56] Recently, the 4-hydroxy derivative was investigated as a potential carboxylic acid bioisostere. Varying the substitution pattern on the three nitrogen atoms affords the opportunity to regiodirect substituents in a chosen direction while also modulating the pK_a (Figure 7). Accordingly, 4-hydroxy-1,2,3-triazoles are more versatile than other heterocyclic systems such as oxadiazoles, thiadiazoles, pyrazoles, or isoxazoles.[57] Hydroxytriazoles are versatile bioisosteres and have proven to be effective surrogates for carboxylic acids in analogues of glutamic acid, $GABA_AR$ ligands and hDHODH inhibitors. Improved cell permeability is a key

characteristic of this particular isostere. The incorporation of a hydroxytriazole has been linked to reduced cytotoxicity in certain cases (*vide infra*).

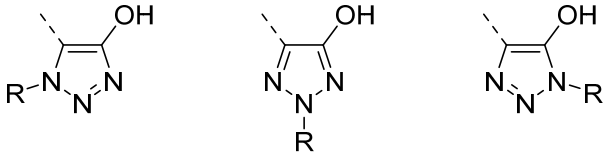
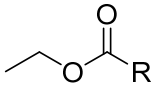
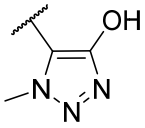
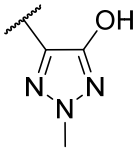
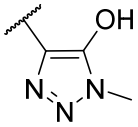
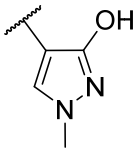
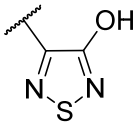


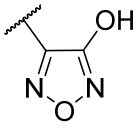
Figure 7 Substitution patterns of 4-hydroxy-1,2,3-triazoles.

Pippione *et al.* conducted some of the pioneering work to support the utility of these groups as carboxylic acid replacements (Table 8).[58] A library of *N*-substituted isomeric hydroxytriazoles **55-57** (entries 1-3), hydroxypyrazole **58** (entry 4), hydroxythiadiazole **59** (entry 5) and hydroxyfurazan **60** (entry 6) was created for comparative purposes. The pK_a of the triazole appears to be influenced by the substitution pattern of the ring nitrogens. The *N*1- and *N*2-substituted isomers **55** (entry 1) and **56** (entry 2) were slightly more acidic than *N*3-substituted isomer **57** (entry 3). The differing pKa values suggest the isomers exist predominantly in their deprotonated states at physiological pH, highlighting their potential as acid bioisosteres. The cLog P values of **55-57** (entries 1-3) were lower than hydroxypyrazole **58** (entry 4), hydroxythiadiazole **59** (entry 5) or hydroxyfurazan **60** (entry 6).

Table 8 Physiochemical properties of 4-hydroxytriazoles **55-57** and related carboxylic acid bioisosteres.



Entry	Compound	R	pK_a	cLog P
1	**55**		5.54	0.46
2	**56**		5.14	0.95
3	**57**		6.21	0.46
4	**58**		6.71	1.19
5	**59**		4.21	2.09

6	**60**		3.24	1.61

This work led to the design of 4-hydroxy-1,2,3-triazole analogues of (*S*)-glutamic acid (**5**), the major excitatory neurotransmitter in the CNS (Figure 8).[59] The structural refinement afforded by the regiosubstitution of the nitrogen atoms allowed for enhanced selectivity toward individual AMPA receptor subunits, which had previously been difficult to achieve. Hydroxytriazole **61** displayed high selectivity with an affinity of 0.71 μM at glutamate A2 (GluA2), an order of magnitude higher than the affinity for either GluA1 or GluA4. The X-ray crystal structure of **61** in complex with GluA2 agonist-binding domain revealed unprecedented weak electron density for methionine Met729. This results in increased flexibility of this residue in comparison to other ligands and provides a possible explanation for its pharmacological profile.

Hydroxytriazole **62** was found to activate the GluN1 and GluN2 subunits which recognise glycine and glutamic acid in the NMDA receptor. This finding suggested that **62** was recognised in two different states: negatively charged in the glutamic acid binding pocket and neutral in the glycine binding pocket. This behaviour was attributed to the relatively high pK_a of **62** (pK_a 6-7) which is characteristic of the hydroxy-1,2,3-triazole bioisostere.[58]

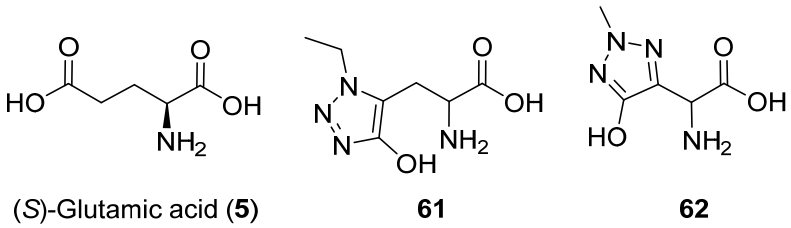
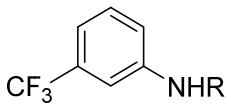


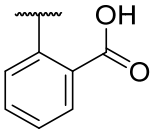
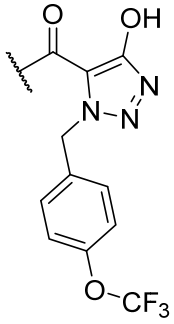
Figure 8 Structure of glutamic acid and its 4-hydroxy-1,2,3-triazole derivatives.

NSAIDs, such as flufenamic acid (**63**), are non-selective inhibitors of aldo-keto reductase 1C3 (AKR1C3), a key enzyme in the biosynthesis of androgens and an attractive target in prostate cancer.[60] Unfortunately, the carboxylic acid tends to form a salt bridge with Arg120 at the end of the long hydrophobic channel of the COX active site resulting in off-target effects.[61]

In an effort to develop novel AKR1C3 inhibitors, Pippione *et al.* sought to reduce COX1 activity by replacing the benzoic acid moiety of flufenamic acid (**63**) with hydroxylated azoles (Table 9).[62, 63] 4-Hydroxytriazole **64** (entry 2) displayed similar activity to flufenamic acid (**63**) (entry 1) and no significant COX1/2 off-target effects. In addition, **64** was 289-fold more selective for AKR1C3 over AKR1C2. In cell-based assays, **64** exerted a pronounced anti-proliferative effect (31.28 μM) and was shown to be almost four-fold more potent than flufenamic acid (115 μM). Compound **64** also reduced both prostate specific antigen secretion and testosterone production in AKR1C3-expressing 22RV1 prostate cancer cells in a dose-dependent manner. Moreover, co-administration of **64** with abiraterone or enzalutamide reduced cell viability by 10-25%, indicating a synergistic effect.

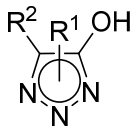
Table 9 Comparison of lipophilicity and biological activity of flufenamic acid (**63**) and hydroxytriazole **64**.



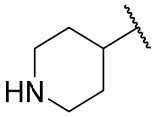
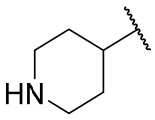
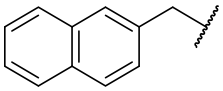
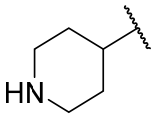
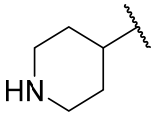
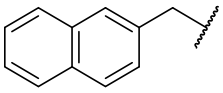
Entry	Cpd	R	cLog P	AKR1C3 IC_{50} (μM)	AKR1C2 IC_{50} (μM)	Ratio IC_{50} value (1C2:1C3)	SRB IC_{50} (μM)
1	Flufenamic Acid (**63**)		5.23	0.44	0.53	1.2	115
2	**64**		5.27	0.19	54.87	289	31.28

Giraudo and colleagues studied the effect of regiosubstitution on *N*1- and *N*2-functionalised 4-hydroxy-1,2,3-triazole derivatives of previously reported $GABA_A$ receptor ligands, including 4-PIOL and 4-PHP (Table 10).[57] Introduction of a 2-naphthylmethyl group at the 5-position of the *N*1-analogue (entry 5) resulted in a 20-fold increase in $GABA_AR$ affinity compared to the unsubstituted analogue **65** (entry 4). A similar trend was observed when a 2-naphtylmethyl was introduced at the 5-position of the *N*2-analogue (entries 6 vs 7). Mapping of the electrostatic potential revealed that 4-PHP and 4-PIOL interact in a bidentate manner with the conserved α1-Arg66 in the GABA binding site. The 4-hydroxy-1,2,3-triazole derivatives display a slightly different electrostatic profile which consequently compromises the bidentate interaction leading to reduced binding affinity. In addition, the higher pK_a likely results in a weaker interaction in the orthosteric $GABA_A$ receptor binding site**.**

Table 10 Comparison of 4-hydroxy-1,2,3-triazoles **65-68**.

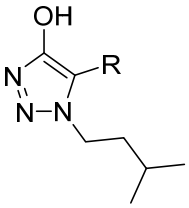


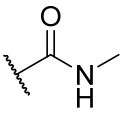
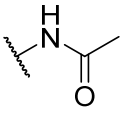
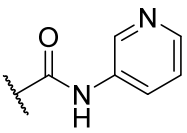
Entry	Compound	R^1		R^2	[^{3}H] muscimol binding K_i (μM)	pK_a
		*N*1	*N*2			
1	GABA (**3**)	-	-	-	0.049	4.04
2	4-PIOL (**45**)	-	-	-	9	5.3
3	4-PHP (**46**)	-	-	-	10	5.4

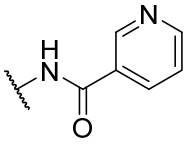
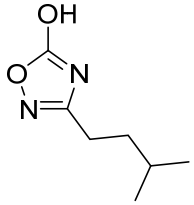
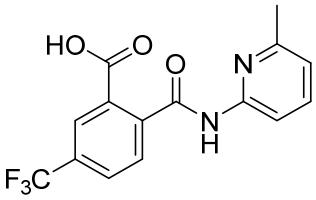
4	**65**		-	H	55	6.51
5	**66**		-		2.4	-
6	**67**	-		H	>100	6.36
7	**68**	-			3.3	-

Several novel sortillin inhibitors incorporating a 4-hydroxy-1,2,3-triazole bioisostere were synthesised by Andersen and co-workers (Table 11).[64] Triazoles **69** (entry 1) and **72** (entry 4) exhibited a ten-fold improvement in Madin-Darby Canine Kidney (MDCK) cell permeability compared to carboxylic acid AF38469 (**75**) (entry 7). X-ray crystallography indicated that **69** makes a bidentate interaction with the guanidine group in Arg292 at the ligand binding site of Sortilin, mimicking the behaviour of carboxylic acid **75**. A pK_a of 7.0 was experimentally determined for hydroxytriazole **69**. The authors suggest that the enol tautomer is favoured and the presence of a 1H singlet at 7.30 ppm in the ^{1}H-NMR spectrum supports this theory.

Table 11 Comparison of sortillin pIC_{50} values of 4-hydroxy-1,2,3-triazoles **69**-**73** with oxadiazolone **74** and carboxylic acid **75**.

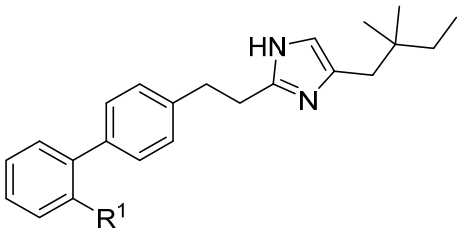


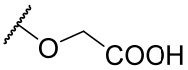
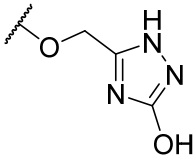
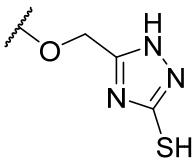
Entry	Compound	R	pIC_{50}	cLog P	MDCK permeability ($cm/s \times 10^{-6}$)
1	**69**	H	4.2	1.3	2.9
2	**70**		4.4	0.85	<0.1
3	**71**		4.5	0.54	<0.1
4	**72**		5.4	2.2	2.9

5	**73**		4.9	1.3	<0.1
6	**74**		3.9	-	-
7	AF38469 (**75**)		6.5	2.23	0.3

The hydroxytriazole moiety has also been exploited in the development of agonists for the treatment of obesity (Table 12).[65] 3-Hydroxy-1,2,4-triazole **78** possessed moderate binding affinity and potency (entry 3). The corresponding values for 1,2,4-triazole-3-thiol **79** (entry 4) were on a par with carboxylic acids **76** and **77** (entries 1 and 2, respectively).

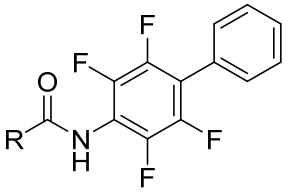
Table 12 Activity of BRS-3 agonists in human and mice BRS-3 receptors.

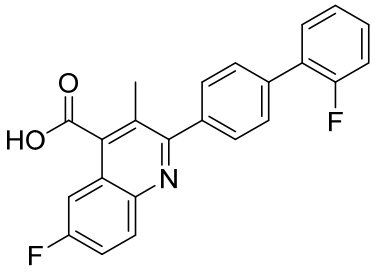


Entry	Cpd	R^1	hBRS-3 binding IC_{50} (nM)	hBRS-3 function EC_{50} (nM) (Activation%)	mBRS-3 function EC_{50} (nM) (Activation%)
1	**76**	COOH	11	25	9.6
2	**77**		103	54	-
3	**78**		31	336	-
4	**79**		6.1	41	5.8

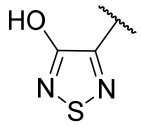
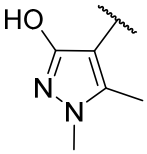
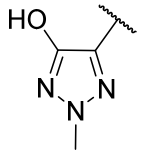
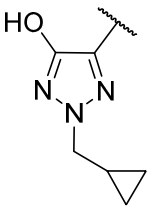
Sainas and colleagues introduced a hydroxytriazole as a replacement for the quinolinecarboxylate moiety in a new generation of immunosuppressive agents (Table 13).[66] Hydroxytriazole **85** displayed good activity *in vitro* (entry 6) and compared favourably with brequinar (**80**), a powerful human dihydroorotate dehydrogenase (hDHODH) inhibitor (entry 1). Comparison of regiosubstitution patterns revealed that *N*1-substituted hydroxytriazoles (entries 6 and 7) exhibited lower IC_{50} values than their *N*2-substituted counterparts (entries 4 and 5) while methyl groups (entries 4 and 6) were better tolerated than cyclopropylmethyl substituents (entries 5 and 7). The hydroxytriazoles displayed a moderate inhibitory effect when tested for cell proliferation (IC_{50} 1.88-7.13 μM) compared to brequinar (0.93 μM). *N*2-Methyl substituted analogue **83** (entry 4) did not affect cell viability while hydroxypyrazole **82** (entry 3) was somewhat cytotoxic but at a higher concentration than brequinar (entry 1).

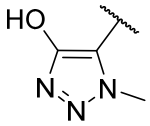
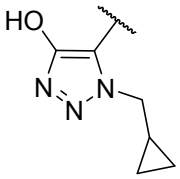
Table 13 Comparison of hDHODH IC_{50} values of hydroxytriazoles **83**-**86** with hydroxythiadiazole **81**, hydroxypyrazole **82** and Brequinar (**80**).





Brequinar (**80**)

Entry	Compound	R	hDHODH IC_{50} (nM)	Proliferation IC_{50} (μM)	Cytotoxicity (effect≥30%) (μM)	Immuno-suppression IC_{50} (μM)
1	Brequinar (**80**)	-	1.8	0.93	45	4.3
2	**81**		16	1.04	78	6.2
3	**82**		41	2.22	82	10.7
4	**83**		45	1.88	>100	8.9
5	**84**		108	7.13	11	-

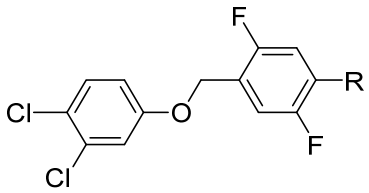
6	**85**		18	5.82	8.3	-
7	**86**		36	3.22	6.0	-

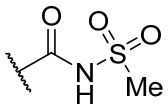
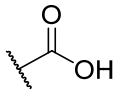
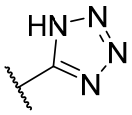
5. 1,2,4-Triazolsulfone

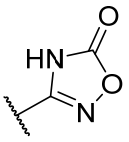
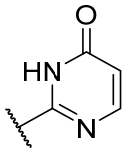
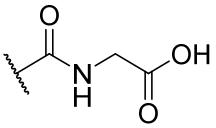
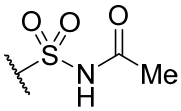
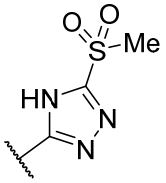
While still relatively untested, the 1,2,4-triazolsulfone has significant potential as a carboxylic acid substitute. 1,2,4-Triazolsulfones warrant further investigation given their reduced acidity, favourable *in vivo* pharmacokinetics and superior bioavailability.

The $Na_v1.1$-$Na_v1.9$ voltage-gated sodium channels generate and conduct electrical impulses in excitable cells and the $Na_v1.7$ channel is of particular significance.[67] Gain-of-function and loss-of-function mutations in *SCN9A*, which encodes $Na_v1.7$, result in severe neuropathic pain and insensitivity to pain respectively.[68] In recent years, $Na_V1.7$ inhibitors have gained significant interest as an alternative to opioid pain therapeutics.[69] In the design of voltage-gated sodium channel $Na_V1.7$ inhibitors, the presence of an acidic group which is fully ionized at physiological pH is considered critical.[70] Both aryl sulfonamides and acyl sulfonamides have proven successful in previous inhibitors. Recently, Boezio and colleagues at Amgen identified the 1,2,4-triazolsulfone as effective bioisostere for this role. In an initial screen based on existing inhibitor **87**, several carboxylic acid and sulfonamide isosteres were evaluated for $Na_V1.7$ inhibition (Table 14). Of these, 1,2,4-triazolsulfone **94** established itself as the most promising candidate (entry 8).

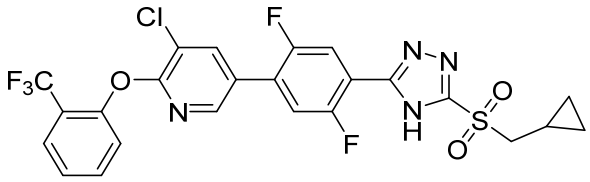
Table 14 Evaluation of potential acidic replacements for the acyl sulfonamide in **87**.



Entry	Compound	R	$Na_V1.7$ inhibition at 5 μM	pK_a
1	**87**		-	3.1
2	**88**		4%	3.1
3	**89**		4%	NA

4	**90**		4%	4.3
5	**91**		6%	NA
6	**92**		5%	3.4
7	**93**		13%	3.7
8	**94**		55%	4.8

Further optimisation ultimately led to triazolsulfone **95** which displayed good potency (IC_{50} 0.10 μM) and selectivity (IC_{50} $Na_V1.7$/ $Na_V1.5$ = 124) (Figure 9). In addition, the observed *in vivo* pharmacokinetics, such as the low clearance (CL 0.068 L/h/kg) and half-life ($t_{1/2}$ 3.7 h), were also favourable. Inhibitor **95** displayed oral bioavailability of 140% when dosed at 10 mg/kg. According to the authors, observed oral bioavailability of greater than 100% can be indicative of nonlinear pharmacokinetics or saturation of a drug metabolizing enzyme or transporter.



95

Figure 9 Optimised triazolsulfone **95**.

6. Cyclopentanediones

Cyclic polyones represent a significant scaffold in the context of carboxylic acid bioisosterism. Thiazolidinediones, [71, 72] and squaric acids[73, 74] have been utilised to replace the carboxylate moiety in the development of potent agonists. More recently, both 1,2- and 1,3-cyclopentanediones have emerged as promising additions to this isosteric class. Cyclopentanediones are structurally versatile groups and alteration of the attachment point can have a significant impact on biological activity.[75] Furthermore, nuclear magnetic resonance (NMR), infrared (IR) spectroscopy and X-Ray crystal studies have confirmed that 1,3-cyclopentanediones undergo rapid keto-enol tautomerisation as outlined in Figure 10-A.[76] The geometry of hydrogen bonding in cyclopentanediones is noteworthy. The 1,2-isomer forms dimers

characterised by two-point interactions, similar to a carboxylic acid, while 1,3-cyclopentanediones form "head-to-tail" intermolecular hydrogen bonds (Figure 10-B). Accordingly, the vinylogous 1,3-cyclopentanedione (pK_a ~4) is much more acidic than its 1,2-isomer (pK_a ~9), thus facilitating the design of analogues with a variety of pK_a values.

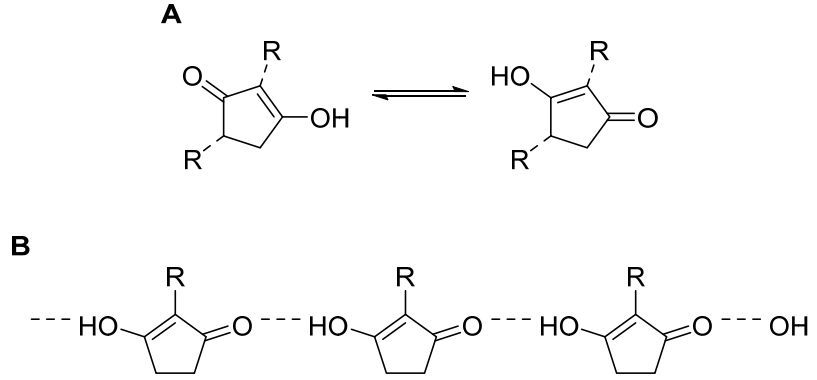
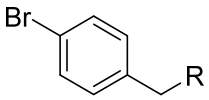
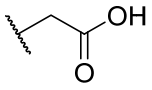
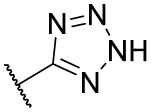
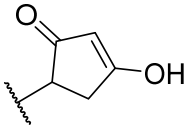
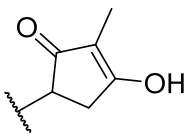


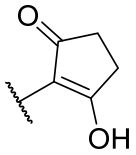
Figure (10) A The tautomeric structures of 1,3-cyclopentanediones including the two possible points of attachment. **B** Head-to-tail intermolecular interaction established by 1,3-cyclopentanediones.

Ballatore and co-workers have explored the utility of cyclopentanediones as carboxylic acid replacements in drug design.[75] They compared the physicochemical properties of carboxylic acid **96** (Table 15, entry 1) with tetrazole **97** (entry 2) and cyclopentanediones **98-100** (entries 3-5). The acidity of the cyclopentanediones was in the same range as the carboxylic acid, a finding in line with previous studies.[76] Ballatore further demonstrated that the lipophilicity of the cyclopentanediones was comparable to the corresponding carboxylic acid and tetrazole.

Table 15 Physiochemical properties of carboxylic acid **96**, tetrazole derivative **97** and 1,3-cyclopentanedione derivatives **98-100**.

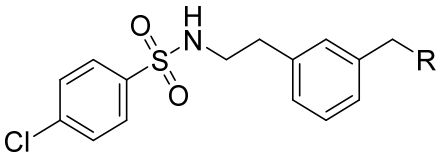


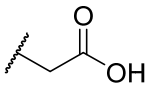
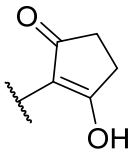
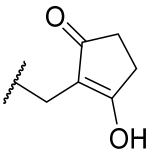
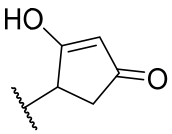
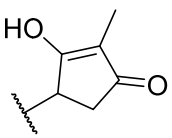
Entry	Compound	R	pK_a	Log P	Log D
1	**96**		4.33	3.00	0.01
2	**97**		4.62	2.21	-0.42
3	**98**		3.96	3.02	-0.42
4	**99**		4.24	3.28	0.11

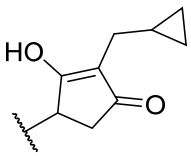
5	**100**		4.20	3.01	-0.19

The same group subsequently evaluated the biological activity of 1,3-cyclopentanedione derivatives of a known thromboxane A2 prostanoid (TP) receptor antagonist **101** (Table 16, entry 1). This study highlighted the significance of the point of attachment to the isostere. The C4-substituted derivatives **104** (entry 4) and **105** (entry 5) displayed relatively good human TP receptor inhibition and receptor affinity. By contrast, the compounds substituted at the C2 position were inactive (entries 2 and 3) and exhibited poor binding affinity (K_d 11400 nM, entry 2). It has been suggested that the π orbitals take part in effective electrostatic interactions with the binding pocket and that the orientation of C2-substituted 1,3-cyclopentanediones is, therefore, unfavourable.[9, 75]

Table 16 TP-receptor antagonist activity and binding affinity of **101**-**106**.

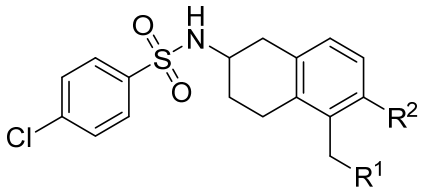


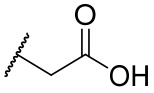
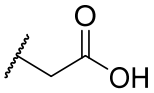
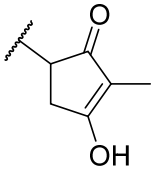
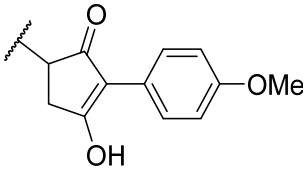
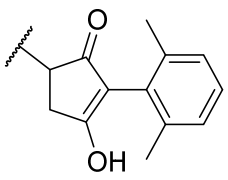
Entry	Compound	R	Human TP Activity	
			IP1 Assay IC_{50} (nM)	Scintillation Proximity Assay K_d (nM)
1	**101**		61	141
2	**102**		>10000	11400
3	**103**		>10000	-
4	**104**		250	203
5	**105**		131	328

6	**106**		41	-

Further work by Ballatore illustrated the significant effects which result on altering the cyclopentanedione substitutents.[77] Several compounds bearing alkyl and aryl substituents at the C2 position were synthesised and assayed for TP receptor inhibition (Table 17). Aryl-substituted cyclopentanediones **110** (IC_{50} 0.052 nM, entry 4) and **111** (IC_{50} 0.015 nM, entry 5) exhibited IC_{50} values that were considerably lower than those of the highly potent human TP receptor antagonists Terutroban (**107**) (IC_{50} 16.4 nM, entry 1) and its desmethyl analogue **108** (IC_{50} 10.7 nM, entry 2).[78] Furthermore, incorporation of a cyclopentanedione group was accompanied by a clear leftward shift on the dose response curve. Interestingly, the choice of substituent also appeared to have an impact on the degree of reversibility of inhibition. Aliphatic analogue **109** (entry 3) displayed reversible antagonism similar to lead compounds **107** (entry 1) and **108** (entry 2) while apparent irreversible inhibition was exhibited by aryl-substituted isosteres **110** (entry 4) and **111** (entry 5).

Table 17 Effect of cyclopentanedione substitution pattern on TP receptor inhibition.



Entry	Compound	R^1	R^2	IC_{50} (nM)
1	Terutroban (**107**)		Me	16.4
2	**108**		H	10.7
3	**109**		H	11.2
4	**110**		H	0.052
5	**111**		H	0.015

The 1,2-cyclopentanedione and its 1,3-isomer share some similarities. Both offer two distinct points of attachment and mainly exist in an enol-ketone form (Figure 11 A).[79] However, the substitution pattern of the 1,2-cyclopentanedione can affect stability and may result in one tautomer being favoured over the other.[80] In addition, the 1,2-enol-ketone tautomers are not vinylogous and are, therefore, less acidic ($pK_a \approx 9$) than their 1,3-counterparts.[81] The geometries of hydrogen bonding established by the two cyclopentanediones is the most significant difference in the context of bioisosterism. While the 1,3-isomer is characterised by head-to-tail interactions, X-ray crystal studies confirm that the 1,2-isomer behaves like a carboxylic acid, forming dimers characterised by two-point interactions (Figure 11 B).[79]

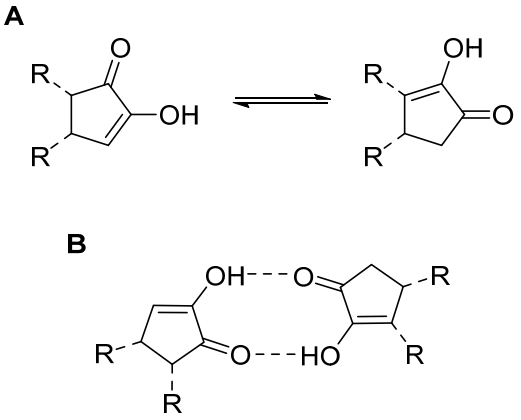
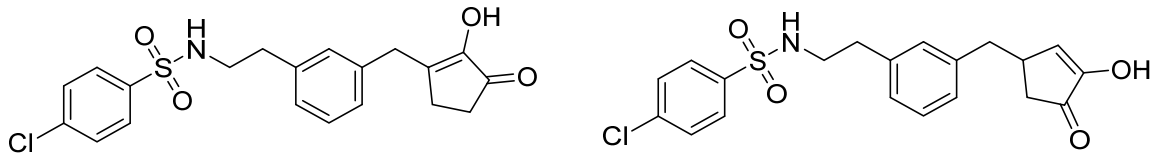


Figure (11) A The tautomeric structures of 1,2-cyclopentanediones including the two possible points of attachment. **B** Dimeric structure resulting from two-point intermolecular interaction.

A recent study by Ballatore *et al.* demonstrated that 1,2-cyclopentanediones were active in a human TP (hTP) receptor functional assay.[79] C3-substituted analogue **112** (IC_{50} 0.054 nM), which exhibited activity comparable to parent carboxylic acid **101** (IC_{50} 0.190 nM), was far more potent than C4-substituted **113** (IC_{50} 1.140 nM) (Figure 12). This finding suggests that, as per 1,3-pentanediones, the point of attachment can have a considerable impact. Increased metabolic stability was another notable feature of the 1,2-cyclopentanedione analogues.



112 **113**

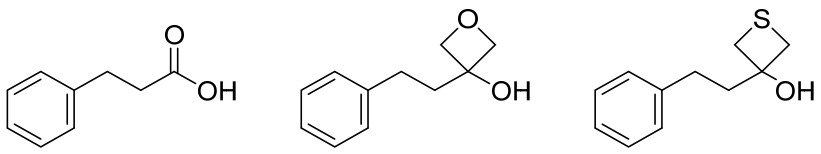
Figure 12 Structures of C3-substituted and C4-substituted 1,2-cyclopentanediones **112** and **113**.

7. Oxetan-3-ol and Thietan-3-ol

Bioisosteres based on the oxetane ring are well established. The four-membered heterocycle has been used to replace several functional groups, including *gem*-dimethyls, esters and amides.[82, 83] In recent times, oxetan-3-ols/thietan-3-ols have been investigated as a potential carboxylic acid isosteres. The physicochemical properties of these functional groups are promising. Oxetan-3-ols/thietan-3-ols are significantly less acidic ($pK_a \geq 12$) than their carboxylic acid equivalents and also exhibit improved lipophilicity with an increase in Log D of approximately 2 log units.[84, 85] This combination

of enhanced membrane permeability and reduced acidity is particularly attractive in the context of drugs targeted at the central nervous system.

Ballatore and co-workers demonstrated that these replacements cause a far less dramatic reduction in the hydrogen bond donating strength.[85] For example, the hydrogen bonding equilibrium constant (K_{eq}) of oxetan-3-ol **115** and thietan-3-ol **116** derivatives of phenylpropionic acid (**114**) were within two orders of magnitude of the K_{eq} of the carboxylic acid (Figure 13). A Parallel Artificial Membrane Permeability Assay (PAMPA) confirmed that **115** and **116** were more lipophilic and permeable than carboxylic acid **114**. In fact, the oxetan-3-ol and thietan-3-ol derivatives displayed greater permeability than most other derivatives tested, including the 5-oxo-1,2,4-thiadiazole and cyclopentane-1,2-dione.

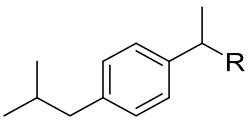


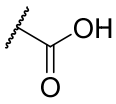
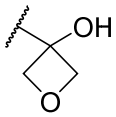
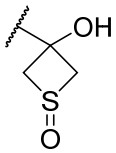
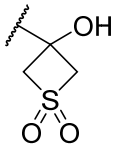
114 **115** **116**

Figure 13 Structures of phenylpropionic acid (**114**), oxetan-3-ol **115** and thietan-3-ol **116**.

The same group synthesised oxetan-3-ol **118**, related sulfoxide **119** and sulfone **120** as derivatives of the COX inhibitor, ibuprofen (**117**) (Table 18). These analogues were evaluated using a rat basophilic leukaemia (RBL-1) cell assay. Ibuprofen (entry 1) inhibited the formation of COX-derived prostaglandins (PG) more effectively than **118**-**120** (entries 2-4). By contrast, these isosteres proved to be more potent inhibitors of 5-LOX-derived leukotriene (LT) formation than ibuprofen.

Table 18 IC_{50} Values of Test Compounds in the PGE_2/D_2 and LTB_4 Assays.



Entry	Compound	R	PGE_2/D_2 Assay IC_{50} (μM)	LTB_4 Assay IC_{50} (μM)
1	**117**		0.6	>100
2	**118**		34.1	8.4
3	**119**		17.4	11.7
4	**120**		14.6	20.2

8. Sulfonimidamides

In recent years, the use of sulfonimidamides in medicinal chemistry has come to the fore. Sulfonimidamides are often employed as bioisosteric replacements of either dipeptides[86] or sulfonyl ureas[87, 88] and have also found use as sulfonamide mimics.[89, 90] Sulfonamides tend to be more potent than the corresponding sulfonimidamides. For example, the sulfonamide-containing γ-secretase inhibitor Begacestat is eight times more potent than its sulfonimidamide analogue.[89] However, sulfonimidamide derivatives often possess superior phyiscochemical properties e.g. solubility, lipophilicity, plasma protein binding, permeability, and metabolic stability.[90, 91]

The sulfonimidamide motif contains some noteworthy structural features which could prove useful to medicinal chemists. The most distinctive of these is the stereogenic tetrahedral sulfur. Although the presence of a chiral centre may pose challenges during synthesis, exploiting enantiomeric differences can unlock valuable pharmacodynamic and pharmacokinetic properties.[91] Additionally, the preparation of enantiomeric bioisosteres opens up the possibility of differentiating between structurally similar biological receptors. The sp^2-hybridised nitrogen offers another handle for functionalisation and affords further control over the overall physicochemical and biological properties.[92] If left unsubstituted, this imine can act as both a hydrogen bond acceptor and donor.[93]

An acyl sulfonimidamide bearing an acidic proton can adopt four possible tautomeric forms **I**-**IV** (Figure 14). The level of tautomerisation is dependent on the substitution patterns on the nitrogen atoms. Computational studies suggest tautomers **I** and **II** (nitrogen protonated) are more stable than **III** and **IV** (oxygen protonated). **I** is calculated to be the most stable tautomer which is in agreement with X-ray crystal data.[93, 94]

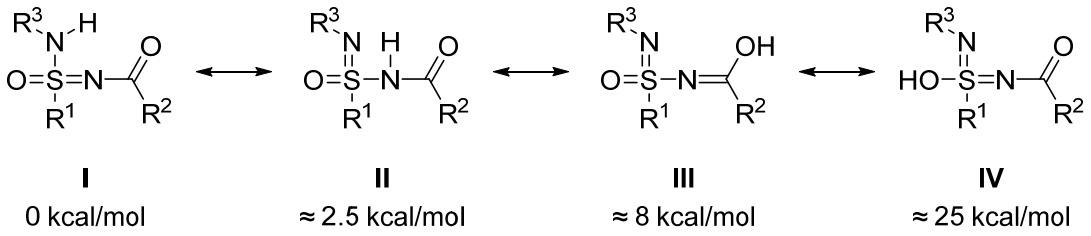
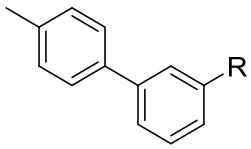
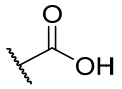
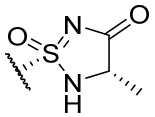
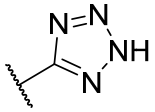


Figure 14 The possible tautomers of an acyl sulfonimidamide and their respective calculated energies.

The use of the sulfonimidamide as a carboxylic acid bioisostere was first reported by scientists at AstraZeneca in 2012.[93] Their five-membered cyclic sulfonimidamide ring systems were proposed as novel chiral heterocyclic mimics of the acid moiety and their physiochemical properties were subsequently investigated (Table 19). The pK_a of sulfonimidamide **122** (entry 2) was approximately two log units higher than that of acid **121** (entry 1) or tetrazole **123** (entry 3). While the Log D values of sulfonimidamide **122** (Log D 1.6) and tetrazole **123** (Log D 4.1) at physiological pH were similar, the cyclic sulfonimidamide possessed the lowest cLog P of the three compounds under evaluation (entry 2). Novel heterocyclic isostere **122** displayed improved permeability (P_{app} = 66) and lower efflux ratio (ER = 0.50) than corresponding tetrazole **123**. Although these compounds were not subjected to biological evaluation, their physiochemical properties were promising, and warranted further investigation.

Table 19 Physiochemical properties of carboxylic acid **121**, cyclic sulfonimidamide **122** and tetrazole **123**.



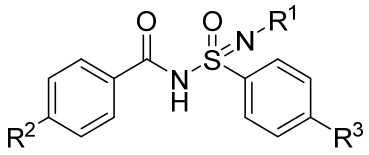
Entry	Compound	R	pK_a	Log D	cLog P	P_{app}	ER
1	**121**		4.0	N.D.	4.3	N.D.	N.D.
2	**122**		6.0	1.6	3.1	66.0	0.50
3	**123**		4.1	1.3	4.0	7.3	10.4

Similar trends have been observed by Borhade and co-workers when comparing novel acyclic acyl sulfonimidamides such as **124**-**127** to the corresponding acyl sulfonamide **128**, tetrazole **129**, and carboxylic acid **130** (Table 20).[94] While these acyclic sulfonimidamides were less acidic (pK_a 5.9-7.6) than other common bioisosteres, their pK_a values could be modulated by varying the substitution pattern of the sp^2-nitrogen (entry 2) or the aryl rings (entries 3-4).

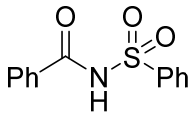
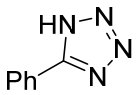
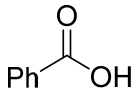
The *N*-substituted derivative **125** displayed similar lipophilicity (entry 2) to carboxylic acid **130** (entry 7), acyl sulfonamide **128** (entry 5) and tetrazole **129** (entry 6) as measured by Log $D_{7.4}$ at physiological pH. The less acidic unsubstituted analogues **124**, **126** and **127** were slightly more lipophilic (entries 1, 3 and 4) giving rise to very high cell permeation (entry 1 vs entry 5) which is promising for achieving greater oral bioavailability. The evaluated compounds did not affect the Caco-2 monolayer integrity which is sometimes used as an indicator of apparent cytotoxicity.

A combination of low pK_a and high Log D as a consequence of modifications to the aryl ring and/or the imine nitrogen atom, resulted in a high degree of plasma protein binding (PPB) e.g., **127** (fraction unbound (fu): 0.1%, entry 4) compared to **124** (entry 1) or **128** (entry 5). The authors also noted the minor intestinal efflux, good apparent buffer solubility and low metabolism of the sulfonimidamide analogues.

Table 20 *In vitro* physiochemical and pharmacokinetic properties sulfonimidamide analogues **124**-**127**, sulfonamide **128**, tetrazole **129** and carboxylic acid **130**.



Entry	Cpd	R^1	R^2	R^3	pK_a	Log D	cLog P	PPB fu (%)	P_{app}	ER	t½ (min)
1	**124**	H	H	H	7.55	1.2	1.9	4.7	261	0.5	>40
2	**125**	CO_2Et	H	H	5.92	-1.0	2.9	1.0	0.3	2.1	>40
3	**126**	H	OMe	H	7.30	1.6	2.2	0.8	ND	ND	>40

4	**127**	H	CF_3	CF_3	6.62	4.2	4.0	0.1	38	1.89	>40
5	**128**				3.96	-1.3	2.1	3.6	2	0.90	>40
6	**129**				4.20	-1.0	1.1	2.1	ND	ND	>40
7	**130**				3.96	-1.5	1.8	ND	ND	ND	ND

9. Boronic Acids

The boronic acid is an increasingly important moiety in drug design and development, and its application has been reviewed by Trippier[95] and Plescia.[96] Boronic acids possess some attractive properties and their introduction, in place of a carboxylic acid, can result in increased potency and improved pharmacokinetics. Additionally, hydrogen bonding in boronic acids is similar to that of carboxylic acids. Boronic acids possess pK_a values of 8-10 and are typically protonated at physiological pH. They display good toxicology profiles, an important consideration in drug development.

There are many examples in the literature of biologically active α-amino boronic acids (e.g. peptide mimics) where the carboxylic acid has been replaced by a bioisosteric boronic acid.[97, 98] These can act as reversible covalent inhibitors and some have been employed to great effect in the development of proteasome inhibitors (PIs) for first-line treatment of multiple myeloma. Bortezomib (**132**), marketed as Velcade™, is a first-in-class PI developed by Millennium Pharmaceuticals (Figure 15).[99, 100] It was the first boron-containing drug to gain approval for medical use from the FDA and European authorities and is now listed on the World Health Organization's List of Essential Medicines (Table 21).[101, 102] More recently, a second-generation PI, namely Ixazomib (**134**), has also gained approval.[103] Ixazomib citrate (brand name Ninlaro™) is administered as the boronate ester prodrug and was the first oral PI to be developed. Some notable features include its high efficacy and good safety profile in patients with multiple myeloma. Another α-amino boronic acid, Delanzomib (**136**), is currently in clinical trials for multiple myeloma and other diseases.[104]

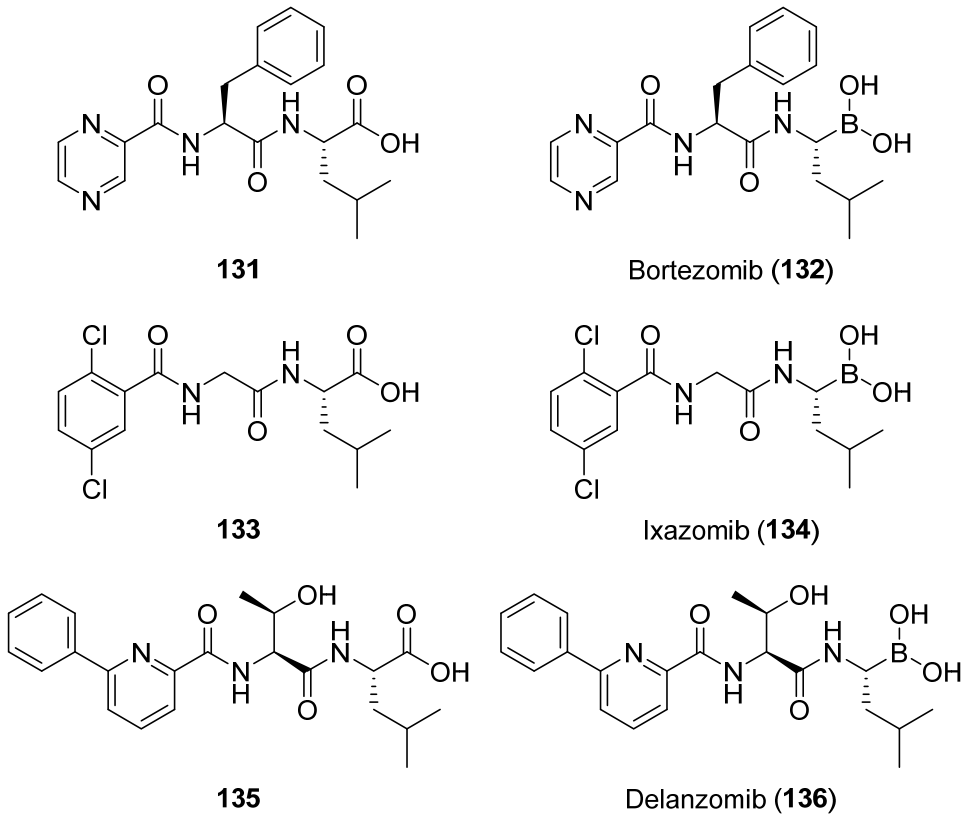


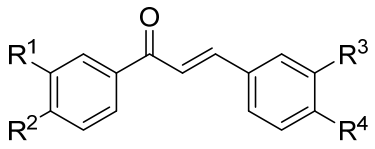
Figure 15 Boronic acid containing drugs and their corresponding carboxylic acids.

Table 21 Chemical and pharmacological features of boronic acid proteasome inhibitors.

Entry	Compound	Binding Kinetics	IC_{50} β5 (nM)	Half-Life (h)	Route of Administration
1	Bortezomib (**132**)	Reversible	5.7	1.83	SC/IV
2	Ixazomib (**134**)	Reversible	5.9	0.3	Oral
3	Delanzomib (**136**)	Reversible	5.6	62	Oral

Disruption of the interaction between tumour suppressor protein p53 and the oncogene murine double minute 2 (MDM2) has been postulated as an anticancer treatment. Carboxylic acid-containing chalcones such as **139** (Table 22, entry 3) and **141** (entry 5) are capable of such interference by forming a salt bridge with Lys51 and simultaneously breaking the salt bridge with Glu25 of MDM2.[105] However, these derivatives are equally toxic to both cancer and normal breast tissue. Kumar and colleagues designed a series of boronic acid chalcones to address the issues regarding this lack of specificity.[106] The authors proposed that the electron-deficient boronic acid moiety would be capable of forming a stronger salt bridge with Lys51 (p53 binding domain) of MDM2 at neutral pH compared to carboxylates. Analogues **138**, **140** and **142** (entries 2, 4 and 6 respectively) preferentially inhibited the growth of human breast cancer cell lines (2-10-fold more toxic to cancer cells than normal cells), a reasonable improvement compared to the corresponding carboxylic acids **137**, **139** and **141** (entries 1, 3 and 5 respectively). Additionally, some of these compounds also induced accumulation of p53 and p21 proteins and showed significantly greater cytotoxicity in p53 cells compared with p53 null cells.

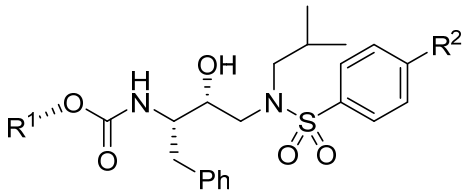
Table 22 Comparison of carboxylic and boronic acid chalcones and growth inhibition of human breast cell lines.

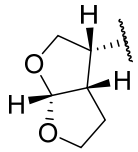
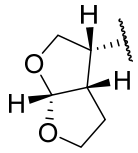
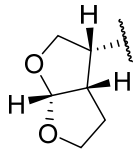
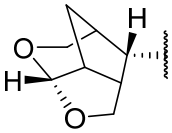


Entry	Cpd	R^1	R^2	R^3	R^4	Human Breast Cancer Cells IC_{50} (μM)			Normal Breast Epithelial Cells IC_{50} (μM)	
						MDA-MB-435	MDA-MB-231	Wt-MCF 7	MCF-10A	MCF-12A
1	**137**	H	I	H	OCH_2CO_2H	18	44	9	44	38
2	**138**	H	I	H	$B(OH)_2$	10	8.8	7.0	75	63
3	**139**	Cl	Cl	H	OCH_2CO_2H	9	9	13	13	15
4	**140**	Cl	Cl	H	$B(OH)_2$	3.5	9.5	5.0	18	11
5	**141**	H	OCH_2CO_2H	Cl	Cl	13	18	15	12	28
6	**142**	H	$B(OH)_2$	Cl	Cl	4	8	5.5	18	15

Darunavir is a HIV protease inhibitor that is often used as a first-line therapy for rescue treatment.[107] The emergence of multidrug-resistant HIV-1 variants necessitates the development of novel antiviral drugs with a high genetic barrier. Ghosh *et al.* prepared several carboxylic acid and boronic acid analogues of Darunavir (**143**) (Table 23).[107] Derivatives **144**, **145** and **146** all inhibited the HIV-protease enzyme in the picomolar range (entries 2-4). However, only the boronic acids exhibited antiviral activity in MT-2 and MT-4 cells (entries 3 and 4). Boronic acids **145** and **146** exhibited relatively high antiviral activity against Darunavir-resistant HIV-1 variants ($HIV_{DRV}{}^{R}{}_{P20}$, $HIV_{DRV}{}^{R}{}_{P30}$ and $HIV_{DRV}{}^{R}{}_{P51}$). The fold-loss of activity between the resistant variants and the wild type was much lower for **145** (entry 3) and **146** (entry 4) than Darunavir (entry 1). X-ray crystallography determined that the boronic acid analogues displayed similar binding modes to their carboxylic acid counterparts. An additional water-mediated hydrogen bond with the Gly48′ amide stabilised the flexible flap of HIV-1 protease. The superior antiviral activity of boronic acids **145** and **146** was, therefore, attributed to improved efflux profiles and the poor membrane permeability of carboxylic acid **144**.

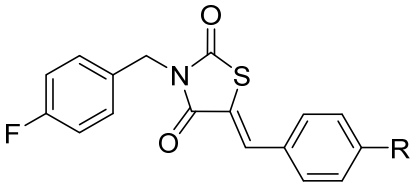
Table 23 Structures and antiviral activity of carboxylic and boronic acid derivatives of Darunavir (**143**).

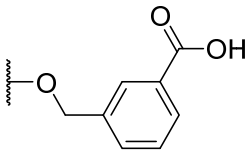


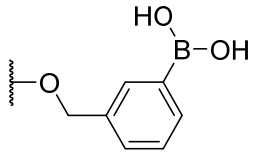
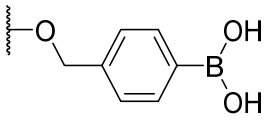
Entry	Cpd	R^1	R^2	K_i (HIV-protease) (pM)	IC_{50} (nM)			
					$cHIV_{LAI}^{WT}$	$HIV_{DRV}^{R}{}_{P20}$	$HIV_{DRV}^{R}{}_{P30}$	$HIV_{DRV}^{R}{}_{P51}$
1	Darunavir (**143**)		NH_2	-	3.2	525.8	601	5429.7
2	**144**		CO_2H	12.9	>1000	-	-	-
3	**145**		$B(OH)_2$	0.5	48.9	219.3	946.4	>1000
4	**146**		$B(OH)_2$	15.5	37.7	71.2	532.3	>1000

Ovaa and co-workers have synthesised and evaluated a range of boronic acid-based Autotaxin (ATX) inhibitors (Table 24).[108-110] The boronic acid derivative **148** (entry 2) was almost 40-fold more potent than corresponding carboxylic acid **147** (entry 1). There was also a significant leftward shift on the dose response curve and a reduction in residual ATX activity from 7% to 0%. Modification of the substitution pattern from *meta*- to *para*- resulted in a further 5-fold increase in potency (entry 3). A crystal structure of ATX in complex with **149** revealed that the boron atom forms a reversible covalent bond with the Thr210 oxygen nucleophile in the ATX active site, while one of the two boron hydroxyl groups is further stabilized between the two zinc ions.[111]

Table 24 Analysis of ATX inhibition by carboxylic acid **147** and boronic acids **148-149**, as measured by choline release from lysophosphatidylcholine (40 μM).

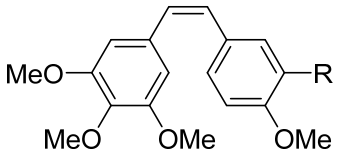


Entry	Compound	R	IC_{50} (nM)
1	**147**		1070

2	**148**		28
3	**149**		5.7

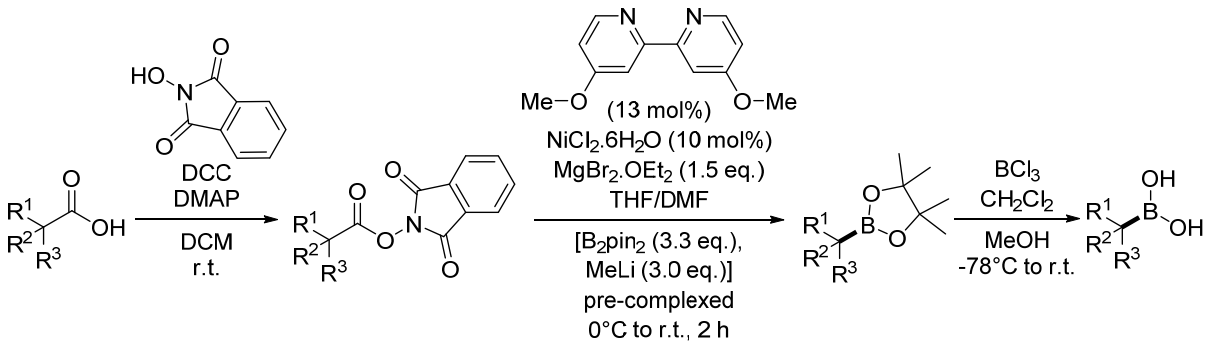
Combrestatins have long been investigated for their potential anti-cancer activity. Nakamura *et al.* synthesised several combretastatins analogues and tested their activity towards mouse B-16 melanoma, human lung carcinoma 1-87 cell lines and tubulin polymerisation inhibition (Table 25).[112] Boronic acid derivative **152** displayed IC_{50} values in the nanomolar range (0.0063 μM and 0.013 μM respectively, entry 3) towards the B-16 and 1-87 cell lines. This represented a 10,000-fold increase in cell growth inhibition compared to the corresponding carboxylic acid **151** (160 μM and 110 μM respectively, entry 2) and was comparable to combretastatin A-4 (**150**) (0.0046 μM and 0.0085 μM respectively, entry 1). While **152** also exhibited significant inhibitory activity towards *in vitro* tubulin polymerization (22 μM, entry 3), combretastatin A-4 was ten times more potent (1.8 μM, entry 1). This suggests that boronic acids may selectively affect cellular processes over inhibition of tubulin polymerization.

Table 25 Inhibition of B-16 and 1-87 cell lines and tubulin polymerisation by combretastatin A-4 (**150**), carboxylic acid **151** and boronic acid **152**.



Entry	Compound	R	IC_{50} (μM)		
			B-16	**1-87**	**Tubulin**
1	Combretastatin A-4 (**150**)	OH	0.0046	0.0085	1.8
2	**151**	CO_2H	160	110	>100
3	**152**	$B(OH)_2$	0.0063	0.013	22

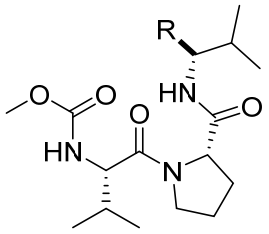
The decarboxylative borylation method reported by Baran and co-workers provides a simple means for the late stage introduction of a boronic acid functional group (Scheme 1).[113] This has opened up the potential development of many more drug candidates bearing this isosteric moiety.



Scheme 1 Standard reaction conditions of the Ni-catalysed decarboxylative borylation reaction of redox-active esters.

Baran has demonstrated the successful application of this methodology to several bioactive molecules, including potent human neutrophil elastase (HNE) inhibitors (Table 26). For example, boronic acid **155** was more potent and more lipophilic (entry 3) than carboxylic acid **153** (entry 1) or trifluoromethyl ketone **154** (entry 2).

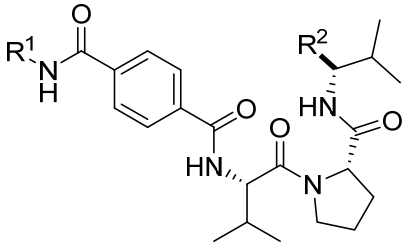
Table 26 Comparison of inhibitory activities of carboxylic acid **153**, trifluoromethyl ketone **154** and boronic acid **155**.

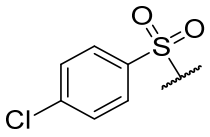
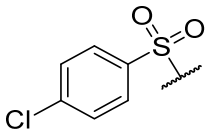
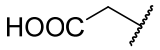


Entry	Cpd	R	Purified HNE		CF Sputum		COPD Sputum	
			IC_{50} (nM)	LipE	IC_{50} (nM)	LipE	IC_{50} (nM)	LipE
1	**153**	CO_2H	Not Active	N.A.	N.A.	N.A.	N.A.	N.A.
2	**154**	$C(O)CF_3$	135	4.57	358	4.15	179	4.45
3	**155**	$B(OH)_2$	0.27	8.37	0.51	8.09	0.274	8.36

Other boronic acid derivatives such as **156** (Table 27, entry 1) and **158** (entry 3) displayed inhibitory activities which compared well with lead clinical candidates alvelestat (entry 4) and BAY 85-8501 (entry 5). Excellent IC_{50} values were also observed in more clinically relevant sputum samples of cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD) patients.

Table 27 Inhibitory activities of boronic acids **156** and **158**, trifluoromethyl ketone **157** and lead clinical candidates alvelestat and BAY 85-8501.



Entry	Cpd	Structure		Purified HNE		CF Sputum		COPD Sputum	
		R^1	R^2	IC_{50} (nM)	LipE	IC_{50} (nM)	LipE	IC_{50} (nM)	LipE
1	**156**		$B(OH)_2$	0.030	7.33	0.096	6.83	0.022	7.46
2	**157**		$C(O)CF_3$	290	1.95	833	1.49	282	1.96
3	**158**		$B(OH)_2$	0.015	10.1	0.043	9.62	0.013	10.2
4	Alvelestat			2.62	7.32	4.08	7.11	2.98	7.22
5	BAY 85-8501			0.031	6.76	0.40	5.87	0.024	6.85

The *in vitro* ADME properties of **156** (entry 1) and **158** (entry 3) were similarly promising (Table 28). The kinetic solubility, metabolic stability and the levels of **156** and **158** remaining in CD-1 mouse plasma after 2 hours were comparable to the corresponding trifluoromethyl ketone analogue **157** (entry 2). Additionally, reasonable permeability (P_{app}) in human Caco-2 cells was observed. These findings clearly suggest that boronic acids constitute a viable option in drug design.

Table 28 Pharmacokinetic profile of HNE inhibitors **152-154**.

Entry	Cpd	Kinetic Solubility (pH 6.8) (µM)	CD-1 Mouse Plasma % remaining after 2 hours (%)	Microsomal stability (mouse extraction ratio)	P_{app} A-B (10^{-6} cm/s)	ER
1	**156**	>200	90.3%	<0.3	<0.16	>3.91
2	**157**	174.28	106.6%	0.5	<0.08	NA
3	**158**	>200	79.2%	<0.3	-	-

10. Conclusion

The carboxylic acid moiety is present in the pharmacophore of over 450 drugs and is undoubtedly a significant functional group in the drug discovery space. Since the development of Prontosil in the 1930s, an array of carboxylic acid bioisosteres have been key to the clinical development of several important therapeutic agents. This review has highlighted several promising carboxylic acid bioisosteres reported in the literature over the past decade or so. We have placed particular emphasis on their practical application to overcome common challenges in drug design.

An important aspect of these recent bioisosteres includes the desirable properties which they share with carboxylic acids. Cyclopentanediones, sulfonimidamides and boronic acids, for instance, engage in hydrogen bonding interactions similar to their carboxylic acid counterparts. However, in the case of the cyclopentanediones, the extent of bonding may be modified by altering the ring substituents and this, in turn, affects biological activity. In a similar vein, the different configurations of hydroxypyrazoles and hydroxytriazoles provide access to compounds with subtly different binding

interactions. The increased flexibility of these novel bioisosteres allows for previously unexplored areas of an active site to be probed. Many of the isosteric groups discussed in this review result in reduced acidity and increased lipophilicity relative to their carboxylic acid leads. This is highly desirable from a drug design perspective, as poor membrane permeability is a stumbling block often associated with highly ionised, carboxylic acid-containing compounds. As a case in point, we have noted in this review how replacement of a carboxylic acid with a hydroxytriazole was accompanied by a ten-fold increase in cell permeability for a series of sortillin inhibitors. Several of these novel bioisosteres display improved pharmacokinetics with triazolsulfones and boronic acids, for example, exhibiting increased oral bioavailability. Additionally, compounds incorporating sulfonimidamide or cyclopentanedione isosteres are typically more metabolically stable than the original carboxylic acids. Each of isosteric groups profiled in this review offers a unique combination of these different features.

As noted previously, the results of bioisosteric replacements are not always predictable. It is axiomatic, therefore, that the broader the selection of bioisosteres available to the medicinal chemist, the better the chances of a identifying a suitable replacement. It is hoped that this review will help inform the decision-making process in future drug development studies which necessitate the replacement of a problematic carboxylic acid group.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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