

Molecular Variations Based on Isosteric Replacements

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Things are not always what they seem; the first appearance deceives many; the intelligence of a few perceives what has been carefully hidden ...

Anonymous

I. INTRODUCTION

In a biologically active molecule the replacement of an atom or a group of atoms by another one presenting the same physiochemical properties is based on the concept of *isosterism*. The notion of isosterism was introduced in 1919 by Langmuir¹ who was mainly focused in the similarities of electronic and steric arrangement of atoms, groups, radicals, and molecules.

The concept of isosters was then broadened by Grimm in 1925 with the statement of Hydride Displacement Law, and, further on, Erlenmeyer extended Grimm's

classification defining isosters as atoms, ions, and molecules in which the peripheral layers of electrons can be considered identical. The extensive application of isosterism to modify a part of a biologically active molecule to get another one of similar activity, has given rise to the term of *bioisosterism* or non-classical isosterism. As initially defined by Friedman,² bioisosters include all atoms and molecules which fit the broadest definition for isosters and that elicit the similar biological activity. In medicinal chemistry, the concept of bioisosterism is a research tool of the utmost importance widely used in analogs design.

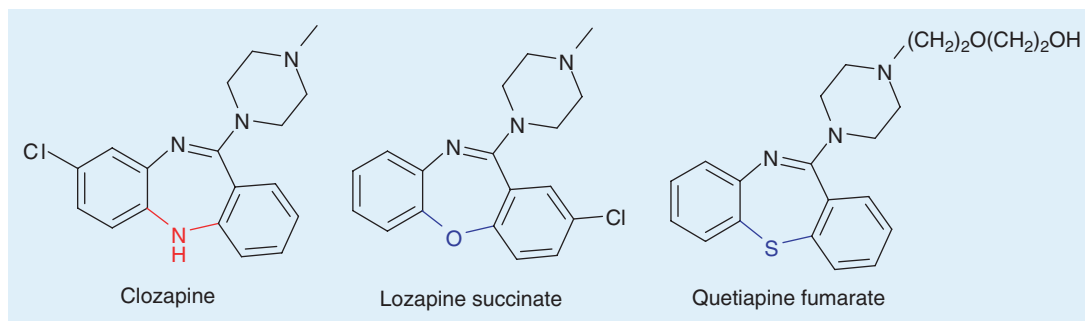


FIGURE 15.1 Isosteric replacements of —NH— with —O— and —S— in clozapine analogs.

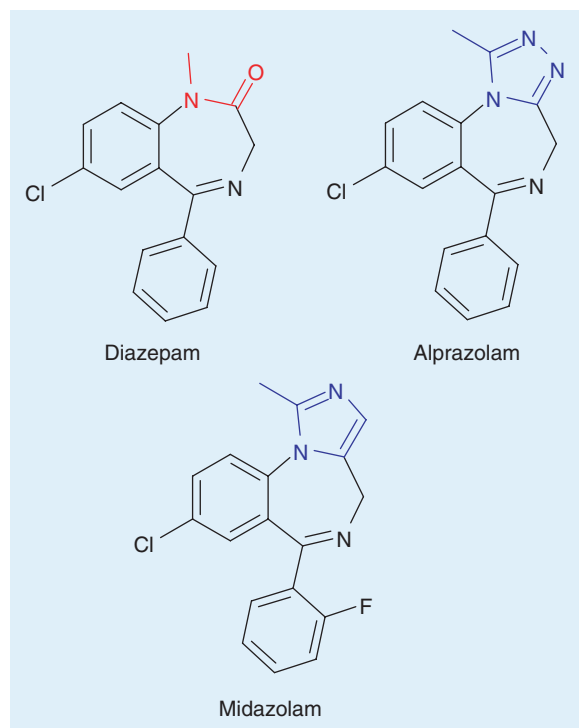


FIGURE 15.2 Example of bioisosteric replacement in the benzodiazepine series.

The term “analog” is derived from the Greek word *ἀναλογία* (analogia) and has been used to point out structural and functional similarity. Applied to drugs this means that an analog of an existing drug shares chemical and therapeutic similarity with the parent compound. This definition implies that three categories of drug analogs can be listed: (a) those presenting chemical and therapeutic similarity; (b) those presenting only similar chemical features; and (c) those eliciting the same pharmacological effect but displaying a completely different chemical scaffold. Isosters have been classified as either classical or non-classical according to the degree of electronic and steric likeness. Bioisosterism is used interchangeably with the term non-classical isosters. In Figure 15.1 it is reported clozapine and

two analogs as an example of classic isosteric replacement of NH with O and S.

An illustration of bioisosteric change is given in Figure 15.2 where the amide moiety of diazepam has been replaced by a triazole ring to give alprazolam.

Taken in its broadest meaning, bioisosterism include the replacement of the initial molecular scaffold by a different one, keeping the same biological activity. This approach, called scaffold hopping, is well illustrated by molecules like diazepam, zolpidem, zaleplon, and zopiclone which exert the same biological response acting as full agonists of GABA-A (γ -aminobutyric acid) receptor at the benzodiazepine site though being structurally different (see Figure 15.3).

Isosterism, bioisosterism, and scaffold hopping will be discussed in more details on the following paragraphs.

II. HISTORY: DEVELOPMENT OF THE ISOSTERISM CONCEPT

The development of the concept of isosterism takes its roots in the attempts to extend to the whole molecules the knowledge acquired for elements, namely that two elements possessing an identical peripheral electronic distribution do also possess similar chemical properties.

A. The molecular number

Allen, in 1918³ defined the *molecular number* of a compound in a similar way of the atomic number:

$$N = aN_1 + bN_2 + cN_3 + \cdots + zN_i$$

where N = molecular number

$N_1, N_2, N_3, \dots, N_i$ = respective atomic numbers of each element of the molecule.

$a, b, \dots, z$ = number of atoms of each element present in the molecule.

Example: Comparison of the ammonium and the sodium cations. The atomic number of nitrogen is 7 and that of hydrogen is 1. Thus the molecular number of the ammonium

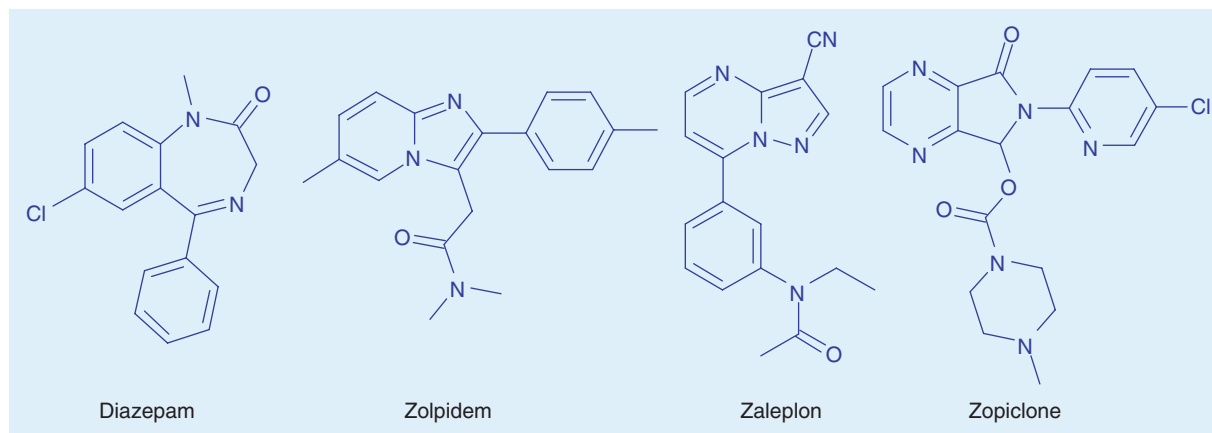


FIGURE 15.3 Scaffold hopping can be considered as the broadest example of bioisosterism: structurally different molecules elicit the same biological activity.

cation can be calculated and compared to that of the sodium ion:

	Atomic number		Molecular number
NH_4^+	$7 + (4 \times 1)$	=	11
Na^+	11	=	11

Possessing the same molecular number, the ammonium cation should resemble the sodium cation. This is roughly true. More generally, two compounds with identical molecular numbers present at least some similar physical properties (e.g. specific heat).

B. The isosterism concept

Independently from Allen, Langmuir in 1919⁴ defined the concept of isosterism:

“Comolecules are thus isosteric if they contain the same number and arrangement of electrons. The comolecules of isosteres must, therefore, contain the same number of atoms. The essential differences between isosteres are confined to the charges on the nuclei of the constituent atoms.”

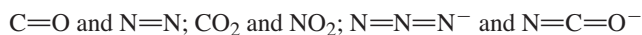
On the basis of these similarities, Langmuir identified a list of 21 groups of isosteres.⁵ Some of these are listed in Table 15.1. He further deduced from the octet theory that the number and arrangement of electrons in these molecules are the same. Thus, isosteres were initially defined as those compounds or groups of atoms that have the same number and arrangement of electrons. Then, he defined other relationships in a similar manner. Argon was viewed as an isostere of K^+ ion and methane as an isostere of NH_4^+ ion. He deduced that K^+ ions and NH_4^+ ions must be similar because argon and methane are very similar in physical properties. The biological similarity of molecules such as

TABLE 15.1 Groups of Isosteres as Identified by Langmuir

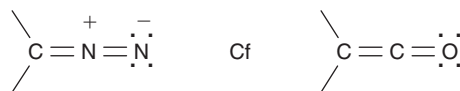
Groups	Isosteres
1	H^- , He, Li^+
2	O^{2-} , F^- , Ne, Na^+ , Mg^{2+} , Al^{3+}
3	S^{2-} , Cl^- , Ar, K^+ , Ca^{2+}
↓	↓
8	N_2 , CO, CN^-
9	CH_4 , NH_4^+
10	CO_2 , N_2O , N^{3+} , CNO^-
↓	↓
21	SeO_4^{2-} , AsO_4^{3-}

CO_2 and N_2O was later coincidentally acknowledged as both compounds were capable of acting as reversible anesthetics to the slime mold *Physarum polycephalum*.⁶

The first example clearly demonstrates that isosterism does not inevitably imply “isoelectric” structures (having the same total electric charge), but it becomes evident that isoelectronic isosteres show the closest analogies:



In the field of organic chemistry, Langmuir predicted the analogy between diazomethane and ketene, which was only discovered later.



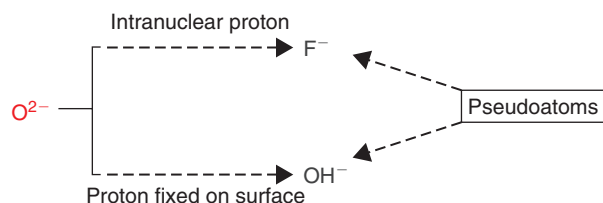


FIGURE 15.4 The notion of pseudoatoms.

TABLE 15.2 Hydride Displacement Law: In Each Vertical Column the Atom is Followed by its Pseudoatoms

Number of electrons					
6	7	8	9	10	11
C ⁴⁻	N ³⁻	—O—	—F	Ne	Na ⁺
	CH ³⁻	—NH—	—OH	FH	
		—CH ₂ —	—NH ₂	OH ₂	
			—CH ₃	NH ₃	OH ₃ ⁺
				CH ₄	NH ₄ ⁺

C. The notion of pseudoatoms and Grimm's hydride displacement law

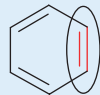
Later on, in 1925, Grimm⁷ formulated the “hydride displacement law” according to which the addition of hydrogen to an atom confers on an aggregate the properties of the atom of next highest atomic number. An isoelectronic relationship⁸ exists among such aggregates which were named *pseudoatoms*. Thus, when a proton is “added” to the O²⁻ ion in the nuclear sense, an isotope of fluorine is obtained (Figure 15.4).

When the same proton is introduced at the peripheral electronic level, a “pseudo-F,” in other words an OH⁻, is created. In this context, the H⁺ ion having penetrated into the electronic shell of the oxygen is assumed to be masked by the greater atom and to exert only negligible effect toward the outside. The fluoride anion F⁻ and the hydroxyl anion OH⁻ show therefore some analogies. The generalization of the pseudoatom concept represents the so-called “hydride displacement law” proposed in a tabular form by Grimm⁸ in each vertical column, the original atom is followed by its isosteric pseudoatoms (Table 15.2).

D. Erlenmeyer's expansion of the isosterism concept

Starting in 1932, Erlenmeyer⁹ published a series of detailed studies about the isosterism concept, and particularly,

TABLE 15.3 The Sulphur Atom is Approximately Equivalent to an Ethylenic Group (Size, Mass, Capacity to provide an Aromatic Lone Pair)

$M(-CH=CH-) = 26$ 		$M(S) = 32$ 	
Compound	E°C	Isostere	E°C
Benzene	80°	Thiophene	84°
Methylbenzene	110°	2-Methyl-thiophene	113°
Chlorobenzene	132°	2-Chloro-thiophene	130°
Acetylbenzene	200°	2-Acetyl-thiophene	214°

about its first applications to biological problems. Erlenmeyer proposed his own definition of isosteres as

elements, molecules or ions in which the peripheral layers of electrons may be considered identical.

Erlenmeyer also proposed three expansions of the isosterism concept:

1. To the whole group of elements present in a given column of the periodic table. Thus silicon becomes isosteric to carbon, sulfur to oxygen, etc.
2. To the pseudoatoms, with the aim of including groups which at a first glance seem totally different, but which, in practice, possess rather similar properties. This is the case for the pseudohalogens (e.g. $Cl \equiv CN \equiv SCN$, etc.)
3. To the ring equivalents: the equivalence between $-CH=CH-$ and $-S-$ explaining the well-known analogy between benzene and thiophene (Table 15.3).

E. Isosterism criteria: Present conceptions

The main criterion for isosterism is that two isosteric molecules must present similar, if not identical, volumes, and shapes. Ideally, isosteric compounds should be isomorphic and able to cocrystallize. Among the other physical properties that isosteric compounds usually share one can cite: boiling point, density, viscosity, and thermal conductivity. However, certain properties must be different: dipolar moments, polarity, polarization, size, and shape (e.g. in comparing F⁻ and OH⁻, the size and the shape of H cannot be totally neglected). After all, the external orbital may be hybridized differently.

In conclusion, it became evident to the physicists that the concept of isosterism, developed before quantum-mechanical theories, could not provide at the molecular level the same results as those that the periodic classification

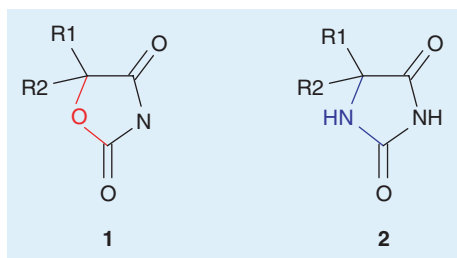


FIGURE 15.5 5,5'-Disubstituted oxazolidine-diones **1** and hydantoins **2** show similar antiepileptic profiles.

had provided for the elements, namely a correlation between electronic structure and physical and chemical properties. In the field of medicinal chemistry the isosterism concept, taken in its broadest sense, has proved to be a research tool of the utmost importance. The main reason for this is because isosteres are often much more alike in their biological than in their physical and chemical properties. An illustrative example is found in the comparison of oxazolidine-diones (**1**) and hydantoins (**2**) which possess different chemical reactivities but present a similar antiepileptic profile (Figure 15.5).

F. The bioisosterism concept: Friedman's and Thornber's definitions

Recognizing the usefulness of the isosterism concept in the design of biologically active molecules, Friedman² proposed to call *bioisosteres* compounds

"which fit the broadest definition of isosteres and have the same type of biological activity."

This definition received rapid acceptance and is now commonly used. Moreover, Friedman considers that isosteres that exhibit opposite properties (antagonists) have also to be considered as bioisosteres, since usually they interact with the same recognition site. This is the case for para-aminobenzoic acid and para-aminobenzene-sulfonamide^{10,11} and also for glutamic acid and its phosphonic analogs.^{12,13}

The use of the word isosterism has been largely taken beyond its original meaning when employed in medicinal chemistry and Thornber¹⁴ proposes a loose and flexible definition of the term bioisostere:

"Bioisosteres are groups or molecules which have chemical and physical similarities producing broadly similar biological effects."

III. CURRENTLY ENCOUNTERED ISOSTERIC AND BIOISOSTERIC MODIFICATIONS

In 1970, Burger¹⁵ classified and subdivided bioisosteres into two broad categories: classic and non-classic. Grimm's Hydride Displacement Law and Erlenmeyer's definition of

TABLE 15.4 Classic Bioisostere Atoms and Groups

Monovalent	Divalent	Trivalent	Tetravalent
—OH, —NH ₂ , —CH ₃ , —OR	—CH ₂ —	≡CH—	≡C—
—F, —Cl, —Br, —I, —SH, —PH ₂	—O—	≡N—	≡Si—
—Si ₃ , —SR	—S—	≡P—	≡N ⁺ ≡
	—Se—	≡As—	≡P ⁺ ≡
	—Te—	≡Sb—	≡As ⁺ ≡
			≡Sb ⁺ ≡

isosteres outline a series of replacement which have been referred to as classical bioisosteres. Classical bioisosteres^{5,16} have been traditionally divided into several distinct categories: (a) monovalent atoms or groups; (b) divalent atoms or groups; (c) trivalent atoms or groups; (d) tetravalent atoms, and (e) ring equivalents (Table 15.4).

Some non-classical isosteres are reported in Table 15.5 and from a brief glance it can be noticed that they do not obey the steric and electronic definition of classical isosteres. A second notable characteristic of non-classical bioisosteres is that they do not have the same number of atoms as the substituent or moiety for which they are used as a replacement.

As the distinction between isosteres and bioisosteres is rather of academic interest, it is preferred, in this chapter to treat both categories together. Consequently, for example, divalent series such as O=, HN=, and H₂C= can be discussed together with S=. However, the correct nomenclature will be used as much as possible, keeping in mind nevertheless that "isosteric replacement" embraces both true isosteres and bioisosteres.

A. Replacement of univalent atoms or groups

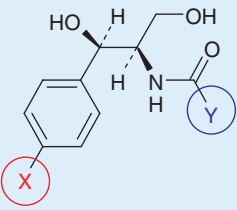
Halogens (particularly chlorine) can be replaced by other electron-attracting functions such as trifluoromethyl or cyano groups. In the antibiotic chloramphenicol, both the chlorine atoms of the dichloroacetic moiety and of the *para*-nitro-phenyl group yielded productive isosteric replacements (Table 15.6). Many other examples of univalent atoms or groups replacements are found in the chapter dealing with substituent effects (Chapter 20) and with quantitative structure–activity relationships (Chapter 23).

B. Interchange of divalent atoms and groups

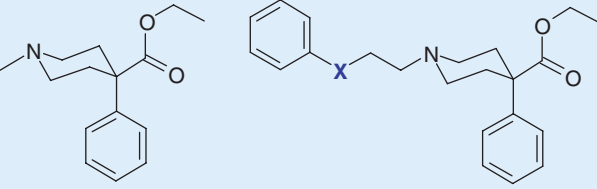
A first series of frequently interchanged divalent atoms or groups is represented by O, S, NH, and CH₂ and many

TABLE 15.5 Non-Classical Isosteres

—CO—	—COOH	—SO ₂ NH ₂	—H	—CONH—	—COOR	—CONH ₂
—CO ₂ —	—SO ₃ H	—PO(OH)NH ₂	—F	—NHCO—	—ROCO—	—CSNH ₂
—SO ₂ —	—tetrazole					
—SO ₂ NR—	—SO ₂ NHR —SO ₂ NH ₂		—OH —CH ₂ OH		—catechol	
—CON—	—3-hydroxyisoxazole				—benzimidazole	
—CH(CN)—	—2-hydroxychromones		—NHCONH ₂			C ₄ H ₄ S
R—S—R			—NH—CS—NH ₂			—C ₅ H ₄ N
(R—O—R)	≡N—					—C ₆ H ₅
R—N(CN)—	C(CN)=R'		—NH—C(=CHNO ₂)—NH ₂ —NH—C(=CHCN)—NH ₂			
—halide						—C ₄ H ₄ NH
	—CF ₃					
	—CN					
	—N(CN) ₂					
	—C(CN) ₃					

TABLE 15.6 Isosteric Replacements in the Amphenicol Family


Compound	X	Y
Chloramphenicol	—NO ₂	—CH—Cl ₂
Thiamphenicol	CH ₃ —SO ₂ —	—CH—Cl ₂
Cetophenicol	CH ₃ —CO—	—CH—Cl ₂
Azidamphenicol	—NO ₂	—CH ₂ —N ₃

TABLE 15.7 Meperidine Analogs[17]


X	Analgesic potency (Meperidine = 1)
O	12
NH	80
CH ₂	20
S	1,5

interesting examples are found in the literature. In a study on meperidine analogs (Table 15.7) potent analgesic compounds were found for X = O, NH, and CH₂.¹⁷ Surprisingly, the sulfur analog showed only moderate activity. As an *in vivo* test was used to assess the activity, the weaker effect may be attributable to a faster metabolism (sulfoxide or sulfone formation?).

Similar changes can be applied to cyclic series, for example, to a series such as piperidine–morpholine–

thiomorpholine–piperazine or in introducing oxygen or sulfur atoms into cyclic ketoprofen analogs.¹⁸

Nice isosteric variations were observed in a series of thermolysin inhibitors.¹⁹ For these isosteres the replacement of the phosphonamide (X = NH) function by a phosphonate (X = O) or a phosphinate (X = CH₂) function demonstrated clearly that the maximal activity was associated with the phosphonamide which is able to establish a hydrogen bond with alanine 113 (Figure 15.6).

In order to have a more stable analog of the acetylcholinesterase inhibitor alkaloid physostigmine, Chen *et al.*²⁰ prepared some 8-carbaisosteres of physostigmine (Table 15.8). The authors envisioned that replacing the *N*-methyl group at *N*₈ of the physostigmine nucleus by a methylene group would increase its chemical and metabolic stability, thanks to the change of the less stable amination group to a more stable amino group.

The carbaisosteres are as potent as or even more potent than the corresponding physostigmines. In addition, the (–)-enantiomers which possess the same absolute configuration at C_{3a} and C_{8a} as that of physostigmine are generally 6 to 12 times more potent in inhibiting acetylcholinesterase than the corresponding (+)-enantiomers.

Other interesting bioisosteric replacements of oxygen atoms were devised during the search of non-hydrolyzable phosphotyrosyl (pTyr) mimetics. The phosphoryl ester oxygen of pTyr has been replaced either by a methylene (Pmp)²¹ or by a difluoromethylene (F₂Pmp).²²

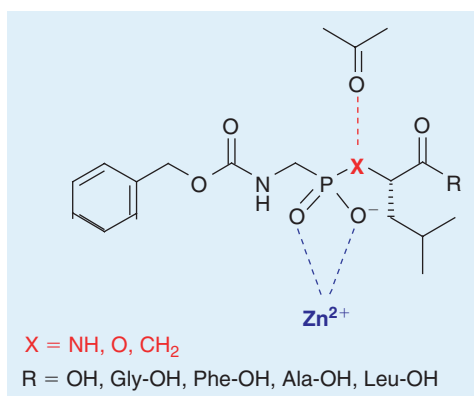


FIGURE 15.6 Isostery in thermolysin inhibitors.¹⁹

C. Interchange of trivalent atoms and groups

The substitution of —CH= by —N= in aromatic rings has been one of the most successful applications of classical isosterism (see Section III.D.). Interchange of trivalent atoms are found also in non aromatic rings. For example the 4-dimethylamino-antipyrene and its carba-isostere are about equally active as antipyretics²³(Figure 15.7).

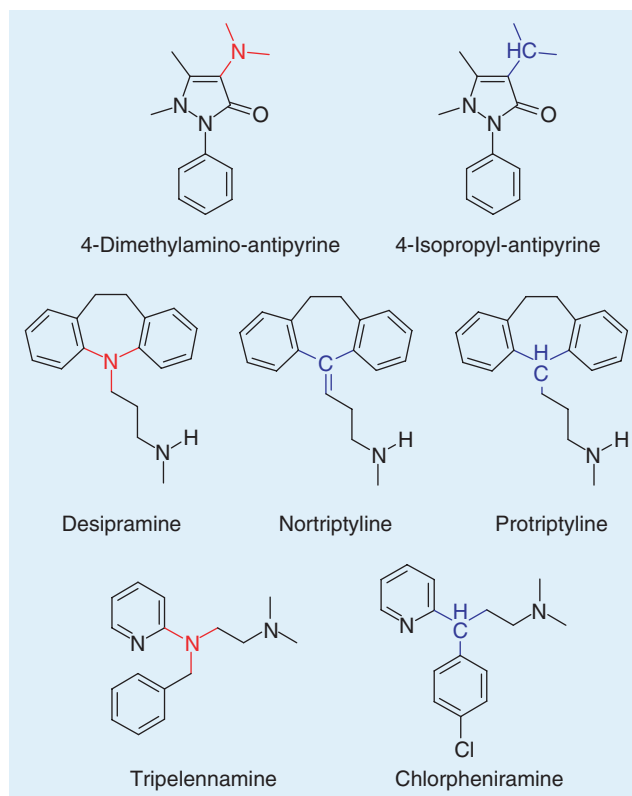


FIGURE 15.7 Interchange of trivalent atoms and groups.

TABLE 15.8 Physostigmines (a) and Carbaisosteres (b)²⁰

 (a) (b)				
Compound	R1	R2	IC ₅₀ (nM)	LD ₅₀ (mg/kg)
(–)-Physostigmine	CH ₃	CH ₃	128	0.88
(–)-Heptyl physostigmine	<i>n</i> -C ₇ H ₁₃	CH ₃	110	24
(±)-Carba-isostere 1	<i>n</i> -C ₇ H ₁₃	CH ₃	114	21
(–)-Carba-isostere 2a	<i>n</i> -C ₇ H ₁₃	C ₂ H ₅	36	6
(+)-Carba-isostere 2b	<i>n</i> -C ₇ H ₁₃	C ₂ H ₅	211	18

Similar interchanges are found in the proceeding from desipramine to nortriptyline and protriptyline (Figure 15.7) or among the antihistaminics, when comparing tripelenamine with chlorpheniramine (Figure 15.7).

D. Ring equivalents

The importance of chemical rings in drug discovery is never overstated. Looking at the best selling drugs in 2006 reported in Table 15.9, it can be noticed that 8 out of 10 molecules are small molecules and that all of them have a chemical ring in their structure. This trend is reflected

also by the other marketed drugs and by the ensemble of bioactive molecules. In bioactive molecules, rings have a multiple role. Rings are responsible of the basic shape of the molecule rendering it rigid or flexible and are also responsible for a suitable spatial orientation of the pharmacophoric groups. In other molecules, chemical rings are directly responsible of the biological activity as they interact directly with the receptors either *via* heteroatom forming hydrogen bonding either *via* hydrophobic interactions.

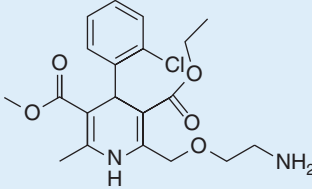
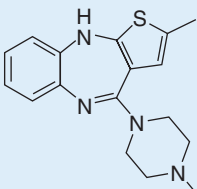
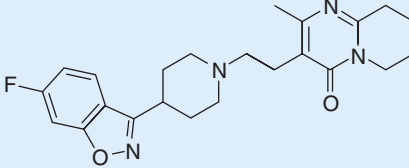
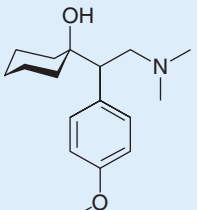
The ADME (absorption, distribution, metabolism, excretion) profile as well as the toxicity of biologically active molecules can rely on the nature of a given ring: such

TABLE 15.9 Best Selling Drugs in 2006

Structure	Leading brands	Indication	Company	2006 sales (US\$BN)
	Lipitor (atorvastatin)	High cholesterol	Pfizer	13.6
	Nexium (esomeprazole)	Gastroesophageal reflux	Astra-Zeneca	6.7
	Seretide/Advair (fluticasone + salmeterol)	Asthma	GlaxoSmithKlin	6.3
	Plavix (clopidogrel)	Coronary artery disease	Sanofi-Aventis Brustol-Myers Squibb	5.8

(Continued)

TABLE 15.9 (Continued)

Structure	Leading brands	Indication	Company	2006 sales (US\$BN)
	Norvasc (amlodipine)	Hypertension	Pfizer	5
165-Amino-acid-glycosylated protein hormone which contains 5 N-linked oligosaccharide chains	Aranesp (darbepoetin alfa)	Anemia	Amgen	5
	Zyprexa (olanzapine)	Schizophrenia	Eli Lilly	4,7
	Risperdal (risperidone)	Antipsychotic	Janssen Pharmaceutica	4,6
Recombinant human soluble tumor necrosis factor-alpha (TNF- α) receptor protein	Enbrel (etanercept)	Autoimmune diseases	Amgen-Wyeth	4,5
	Effexor (venlafaxine)	Depression	Wyeth	4

as the hydrophobicity, the polarity, the electronic properties, etc. Medicinal chemists use to change one ring with a bioisosteric one in order to improve the ADME-tox profile of a given molecule keeping the desired activity and selectivity.

In the conception of “me too” drugs as well as in getting a stronger patent position, bioisosteric replacement of ring systems has played a master role in drug design. The substitution of $-\text{CH}=\text{CH}-$ by $-\text{N}=\text{N}-$ or $-\text{CH}=\text{CH}-$ by $-\text{S}-$ in aromatic rings has been one of the most successful applications of classical isosterism. Early examples are found in the sulfonamide antibacterial with the development of sulphapyridine, sulphapyrimidine, sulphathiazole, etc. (Figure 15.8).

Other examples are found in the neuroleptic or antidepressant tricyclics, in the benzodiazepine tranquilizers and antiepileptics, and in the development of semi-synthetic penicillins and cephalosporins with broader spectra of activity and greater stability toward β -lactamases. In some instances, an aromatic ring can be replaced by an ethynyl group. In some instances an aromatic ring can be replaced by an ethynyl group. Such a replacement was reported by Wallace et al.²⁴ in a series of inhibitors of Endothelin-converting Enzyme (ECE-1) deriving from the biphenyl compound CGS 26 303 and its analogs (Figure 15.8).²⁵

In all these cases no essential activity difference is found between the original drug and its isostere. However,

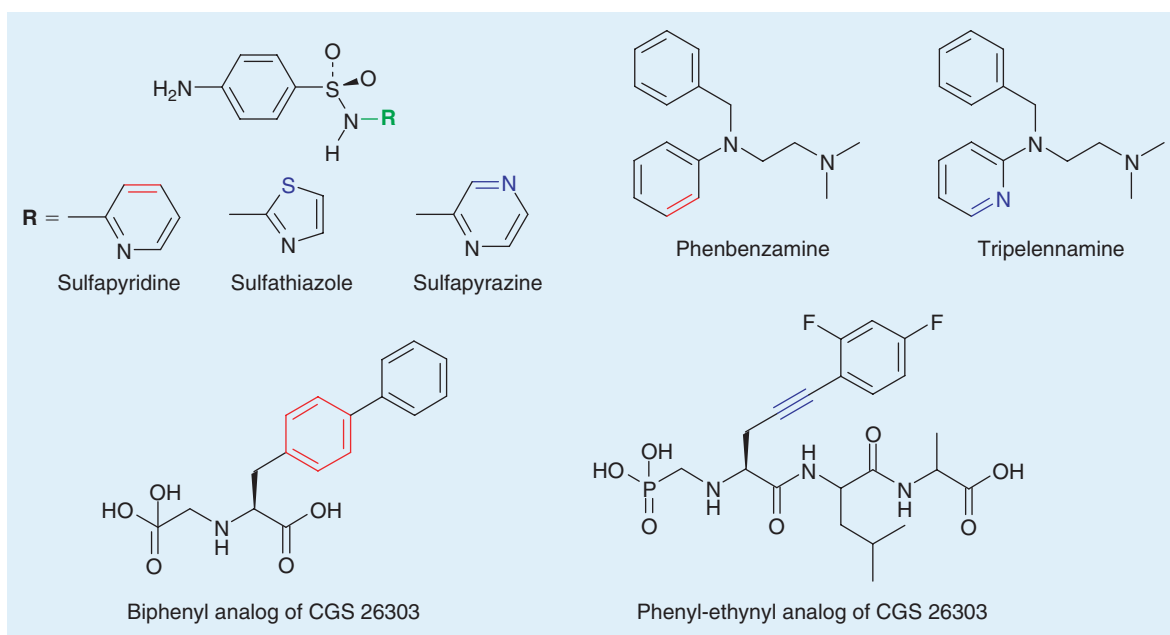


FIGURE 15.8 Classical ring equivalents.

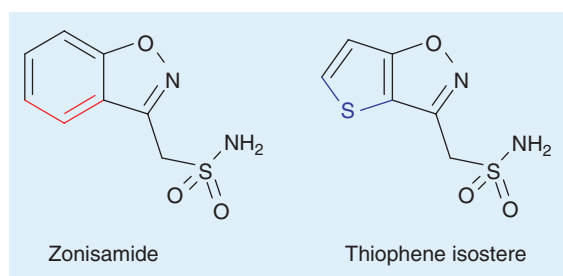


FIGURE 15.9 The thiophene isostere of zonisamide is practically inactive as an anticonvulsant.

it can happen that the procedure fails. Binder *et al.*,²⁶ for example, reported that thieno[2,3-*d*]isoxazole-3-methanesulfonamide, the thiophene analog of the anticonvulsant drug zonisamide (Figure 15.9),²⁷ was practically inactive against pentetrazole- or electroshock-induced convulsions in mice, even at high doses.

Because of the paramount role of ring systems in the drug discovery process a lot of attention has been given to the equivalence between rings. Indeed the efforts to replace rings or other functional groups in an active molecule form a large part of medicinal chemistry practice devoted also to extend the space of bioactive molecules in the chemistry universe. A typical lead optimization program often involves a trial and error process of replacing chemical functionality including rings and in most cases this intellectual exercise is based on a chemist's knowledge and recollection of his or her past experience. As a source of inspiration in the following paragraphs are listed some examples of bioisosters of the most encountered rings in biologically active molecules.

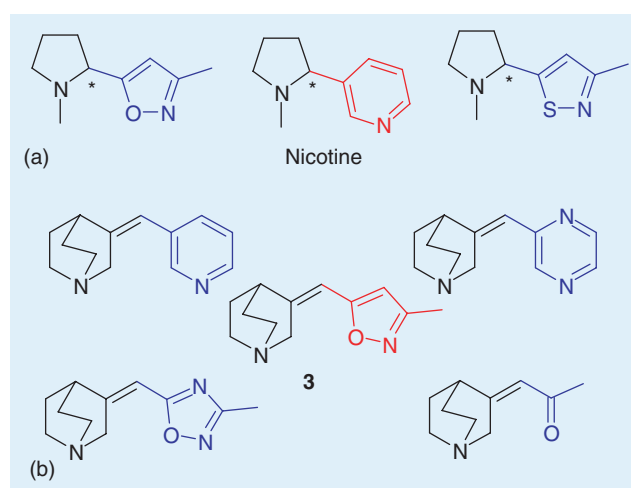


FIGURE 15.10 Ligands for central cholinergic receptors with different non-classical bioisosteres of the pyridine ring.

1. Bioisosteres of pyridine

One of the most used cycles in medicinal chemistry is the pyridine ring. The bioisosteres of this heterocycle are well known as ligands for the central nicotinic cholinergic receptors. The pyridine ring of nicotine can be replaced by different other rings like methyl-isoxazole or methyl-isothiazole^{28–30} (Figure 15.10a). A novel series of nicotinic agonists was described by Olesen *et al.*³⁰ In their paper, the bioisosteric replacement of the isoxazole ring in the (3-methyl-5-isoxazolyl)methylene-azacyclic compound (**3**, Figure 15.10b) with pyridine, pyrazine, oxadiazole, or an acyl group resulted in ligands with moderate to high affinity

for the central nicotinic cholinergic receptors ($IC_{50} = 2.0$ to $IC_{50} > 1,000$ nM) (Figure 15.10b).

Two other publications on the bioisosteric replacement of pyridine show similar results. The first paper reports the study of bioisosteric potential of diazines in the field of combined antithrombotic thromboxane A_2 synthetase inhibitors and receptor antagonists.^{31,32} On the basis of the structure–activity relationships (SAR) observed in this study, it turned out that only the 2-pyrazinyl, 4-pyridazinyl

and 5-pyrimidinyl systems are appropriate bioisosteric moieties for the 3-pyridyl system in the dual active platelet antiaggregatory compound Ridogrel (Figure 15.11). Gohlke *et al.*³¹ also observed the bioisosteric potential of diazines in the SAR of the compound DUB-165. The replacement of the 3-pyridyl group of DUB-165 by a 4-pyridazinyl, 5-pyrimidinyl, or 2-pyrazinyl moiety, resulted in ligands retaining affinity for nAChRs subtypes, thus demonstrating that the three isomeric diazines are appropriate bioisosteres of the 3-pyridyl moiety (Figure 15.11).

N-(6-Chloronaphthalen-2-yl)sulfonylpiperazine derivatives **4** and **5** (Figure 15.12) are potent factor Xa inhibitors. Haginoya *et al.*³³ proposed to replace the pyridine-phenyl or the pyridine-piperidine residue by a fused-bicyclic ring which contains an aliphatic amine and a pyridine to yield the compound **6** that has an interesting factor Xa inhibitor activity. The bioisosteric replacement of the pyridine moiety of the 6-methyl-5,6,7,8-tetrahydro-[1,6]naphthyridine by phenyl, thiophene, or thiazole analogs yielded analogs with similar or better antifactor Xa activity, but also to conserve a moderate bioavailability.

A nice example of pharmacophore equivalent of the 2,3-diaminopyridine with cyclopropylamino acid amide has been reported recently.³⁴ A series of 2,3-diaminopyridines represented by **7** acting as bradykinin (BK) B_1 antagonists, was thoroughly investigated with the aim to replace the metabolically labile diaminopyridine ring with a more bioavailable moiety. An accurate design strategy led researchers

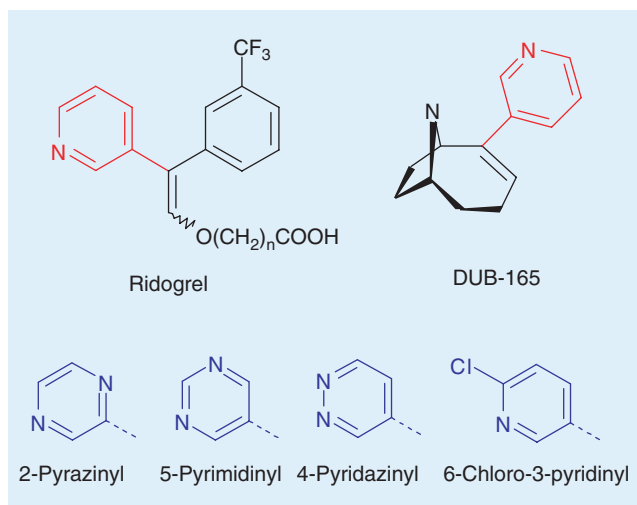


FIGURE 15.11 Bioisosteric moieties for the 3-pyridyl ring.

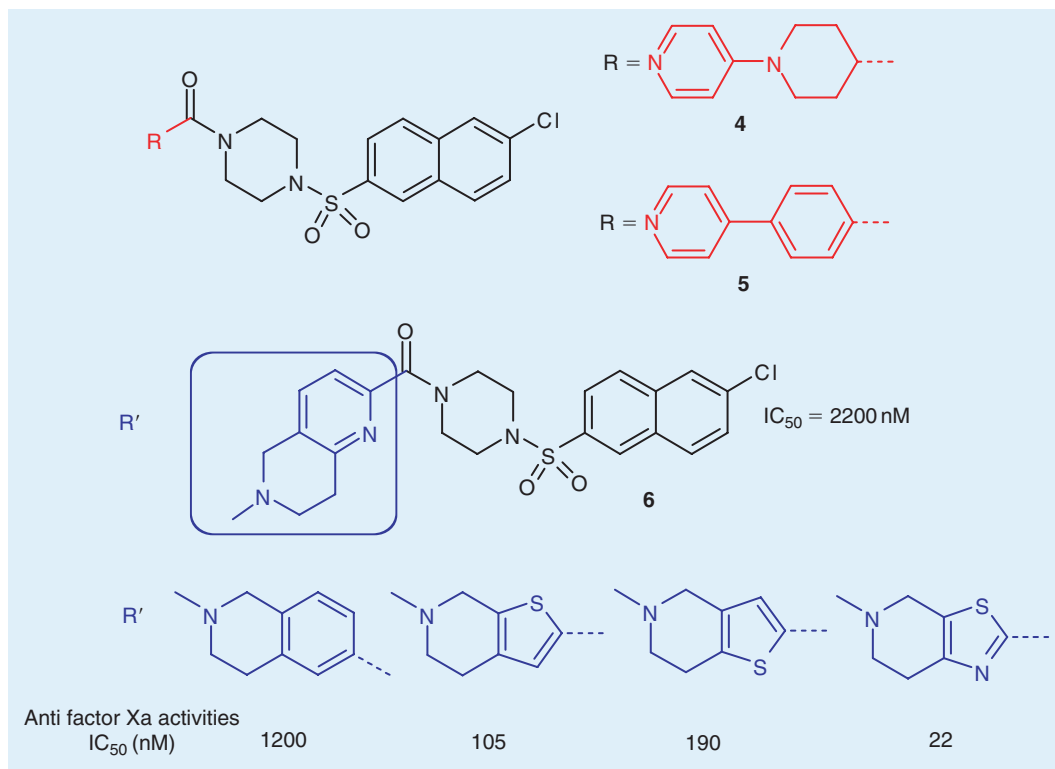


FIGURE 15.12 Bioisosteric replacements of the pyridine ring in a series of factor Xa inhibitors.

at Merck to replace the 2,3-diamino pyridine with a series of alkylamino acid amides. Among this series compound **8**, though less active than **7** as BK B₁ antagonist, showed a better pharmacokinetic profile with an improved bioavailability, an increased half-life, and a decreased clearance compared to **7** (Figure 15.13).

To demonstrate the generality of this bioisosteric equivalence, the same group applied the same substitution to **9**, a factor Xa inhibitor that yielded **10**. Compound **10** reflects the same loss in potency that was observed for **8** towards **7**, but reoptimization of the *N*-acyl group afforded quickly a significant gain of potency.

2. Imidazo[1,2-*a*]pyridine bioisosteres

Abe *et al.*³⁵ reported that the imidazo[1,2-*a*]pyridine moiety of the basic framework of a class of the non-peptide bradykinin B₂ receptor antagonists (**11**, Figure 15.14) could be successfully replaced by several heterocyclic bioisosteres. Among those, the 1-methyl-2-methoxy-1*H*-benzimidazole, 2-methylquinoxaline and 2-methylquinoline derivatives showed potent B₂ binding affinities against both human and guinea pig B₂ receptors (Figure 15.14).

3. Pyridazine bioisosteres

Since the antidepressant minaprine has been launched, several pyridazine analogs were proposed and synthesized.

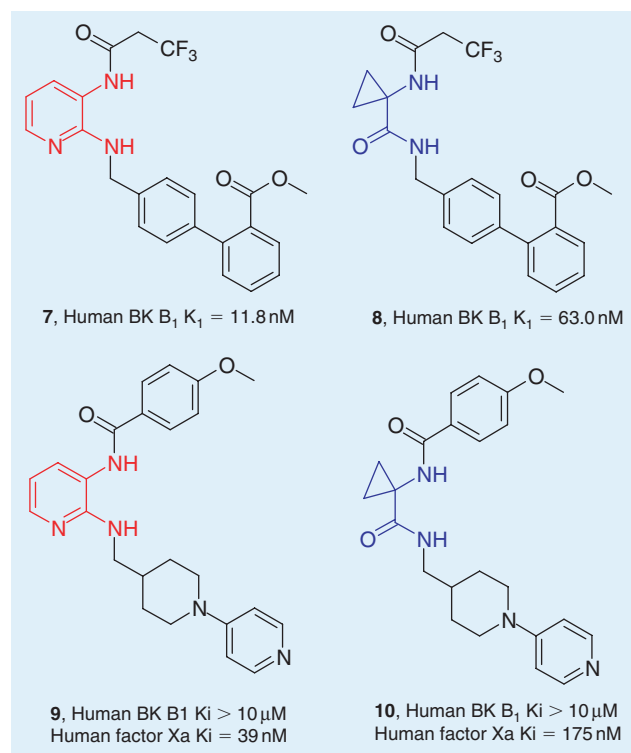


FIGURE 15.13 Cyclopropylamino acid amide as pharmacophoric replacement for 2,3-diaminopyridine. Application to the design of novel bradykinin B₁ receptor antagonist and factor Xa inhibitor.

Most of them showed different activities on the central nervous system. A series of these compounds (Figure 15.15) are acetylcholinesterase inhibitors with variable bioisosteres of the central pyridazine.^{36,37} The replacement by pyridine, 1,2,4-thiadiazole and triazines yields compounds with weaker but still acceptable activity.

Examples from literature show that there are several non-classical bioisosteres for the pyridine system or the pyridazine system. Which is the rationale behind this in order to choose the most appropriate analog to start with? An indication could be given by the comparison of the boiling points

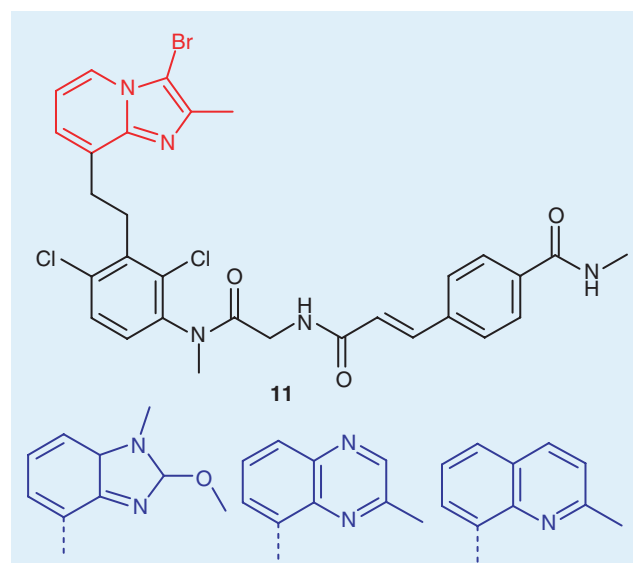


FIGURE 15.14 Novel class of orally active non-peptide bradykinin B₂ receptor antagonists showing valuable examples of imidazo[1,2-*a*]pyridine analogs.

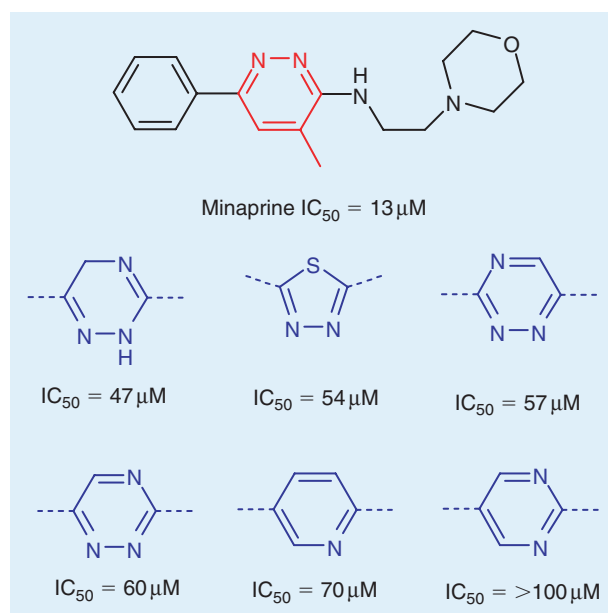


FIGURE 15.15 *In vitro* inhibition of acetylcholinesterase in rat striatum homogenates: pyridine, thiadiazole, and triazine replacement of the pyridazine ring.

of these heterocycles assuming that the most similar the boiling point is, the most appropriate the bioisostere is (Figure 15.16).³⁸ For example, while searching for a bioisostere of the pyridine ring, looking at the boiling points it appears that the best candidates are the pyrimidine, the pyrazine, and the 1,2,4-thiadiazole systems (Figure 15.16). The same could be extended to the pyridazine ring where this comparison permits the selection of the 1,2,4-triazine or the 1,3,4-thiadiazole rings (Figure 15.16). In fact, those findings confirm the

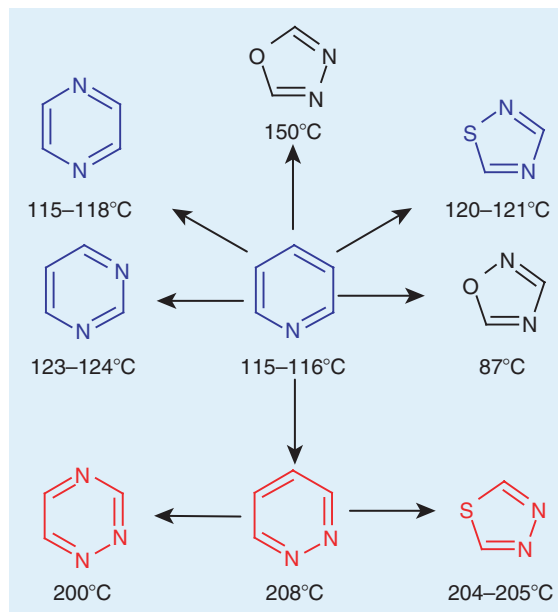


FIGURE 15.16 Structures and boiling points of pyridine and pyridazine isosteres.

examples found in the literature and reported in the previous part of this chapter about isosteres or bioisosteres of the pyridine and of the pyridazine ring.

A possible interpretation of these results can be the fact that in the heterocyclic series, the boiling point is correlated to the dipolar moment of the molecule and that, for two heterocyclic rings having the same aromatic geometry, the similarity of the dipolar moments may represent the dominant feature.

4. Bioisosteres of other heterocycles

Chemical rings are fundamental for drug molecules as a typical drug molecule consists of a combination of chemical rings, chains, and functional groups. The high proportion of chemical rings in drug molecules talks in favor of the large effort to synthesize and find new chemical ring equivalents, whether it is to design a new platform for a better patent position, replace a metabolically unstable moiety, look for a more favorable receptor interaction or have a better pharmacodynamic profile.

There are many examples of ring equivalents and so far it seems impossible to rationalize a method that could give a reliable indication which heterocycle could be the best substitute of another one. The best approach is to look at the examples reported in the literature and learn from those.

Selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) give a nice example of bioisosteres of heterocycles. The comparison of the most potent selective COX-2 inhibitors (Figure 15.17) suggests that isoxazoles, pyridines, and pyrazoles are good bioisosteres of each other as well as nitrophenol, and indanones.³⁹

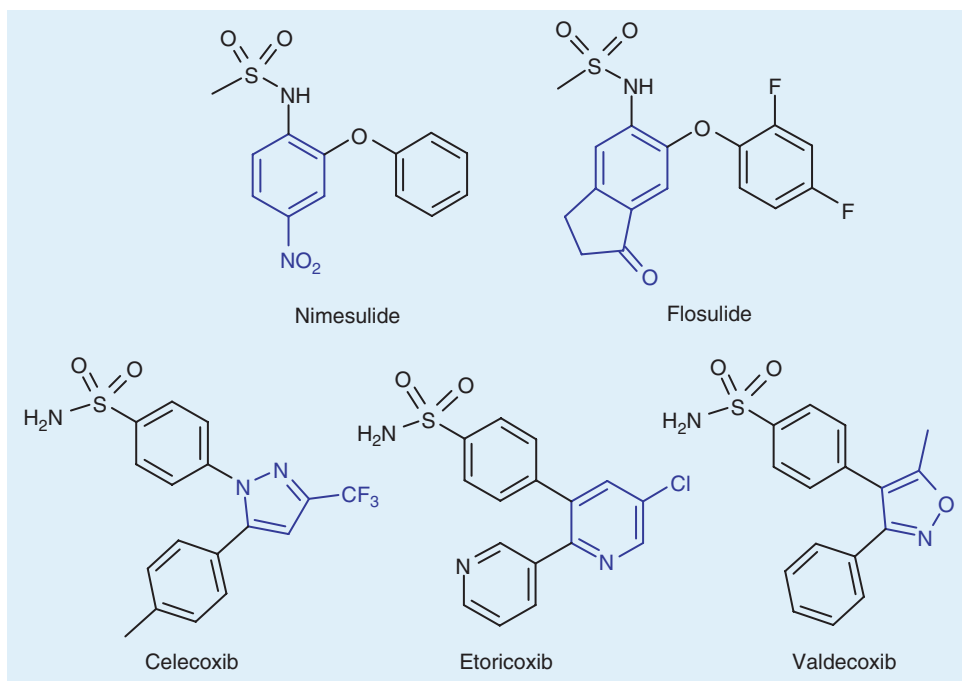


FIGURE 15.17 Examples of selective cyclooxygenase-2 inhibitors showing different ring equivalents.

Another nice example of heterocycle bioisosteres is given by the oxazolidinone antibacterials. Since the discovery of linezolid as potent antibacterial against Gram positive organisms,⁴⁰ many researchers have taken inspiration from the oxazolidinone scaffold in order to create new and potentially improved antibacterial agents. The structure of Linezolid (Figure 15.18) is divided in three parts: the A ring corresponding to the oxazolidinone moiety, the B ring corresponding to the Phenyl ring and the C ring corresponding to the morpholine. Some research groups have worked around the modification of the B and C rings.^{41,43}

The work of Snyder *et al.*, together with other examples found in the literature, shows that several level of activity can be identified amongst the different isosteres. It has to be kept in mind that the replacement of a ring by its isosteres does not always lead to an iso-active or more active compound (Figure 15.18). But in general, it is possible to obtain at least one or more equivalent systems.⁴²

Another particularly interesting example of ring bioisosterism is found in the development of the antiulcer H₂-receptor histamine antagonists in which the initial imidazole ring was changed to various other “equivalents” such as a furan, a thiazole, and finally a phenyl ring (Figure 15.19). A detailed and very interesting account of the discovery and the development of these compounds is found in Ganellin and Roberts’ book.⁴⁴

Better bioisosteric design possibilities are provided by quantum-chemical calculations. Mallamo *et al.*⁴⁵ made use of electrostatic potential surface maps complementarity in defining sulfonyl heterocycles bioisosteric to the steroidal

antiandrogenic drug zanoterone (Figure 15.20). Striking differences in the electrostatic potential surfaces accounted for the observed variability in the furan (active) and the thiophene (inactive) analogs of zanoterone. Good androgen receptor affinity was then anticipated and effectively found for the oxazole and the thiazole analogs of zanoterone.

The apparent failure of the isosterism concept for the inactive thiophene, inversed furan and pyrimidine is thus interpretable on a rational basis. In Table 15.10 are listed some more “exotic” examples of bioisosteric replacements of cyclic systems.

E. Groups with similar polar effects: functional equivalents

1. Carboxylic acid bioisosteres

Medicinal chemists have frequently to face the problem of developing surrogates for carboxylic acid groups. The availability of bioisosteric replacement for the carboxylic acid group has been critical to the development of novel medicinal agents especially in the area of neurochemistry. Less polar and more hydrophobic groups were needed to replace the carboxylic group of GABA in order to cross the blood–brain barrier, but keeping some of the physiochemical properties of the parent functional group like pK_a , partition coefficient, etc.

Thus, the two GABAergic agonists, isoguvacine and THIP (Figure 15.21), have similar pharmacological properties

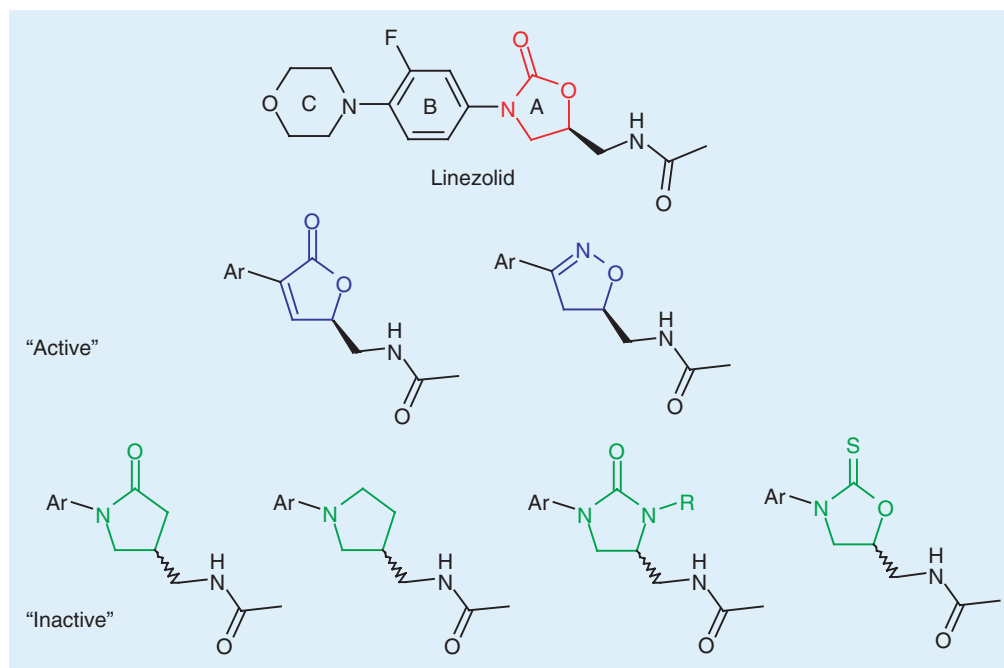


FIGURE 15.18 Oxazolidinone bioisosteres synthesized as antibacterial agents.

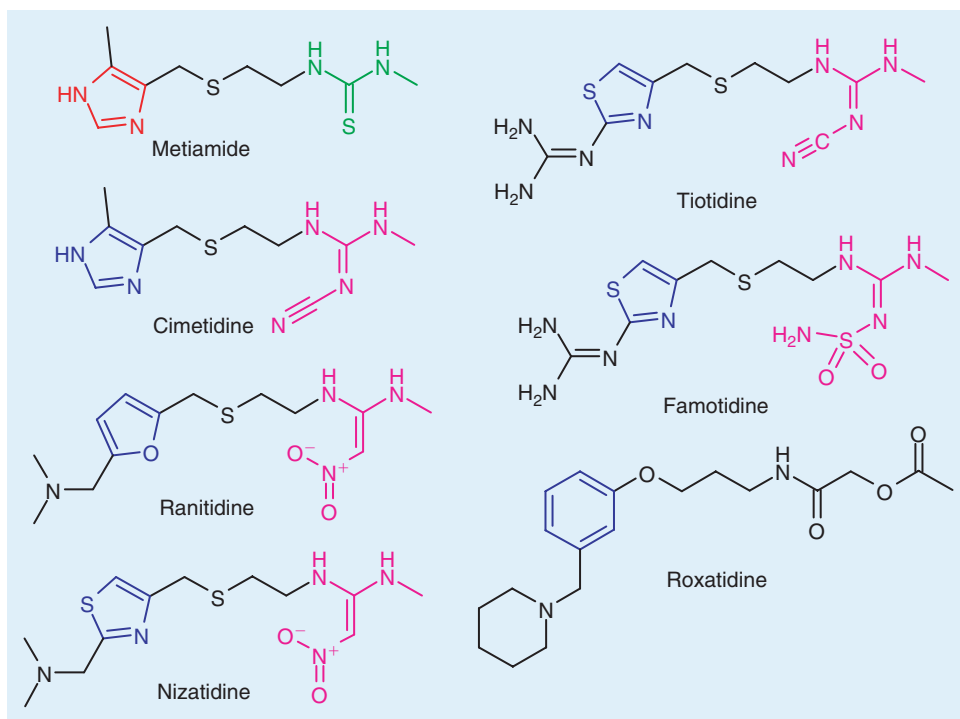


FIGURE 15.19 Antiulcer H_2 -receptor histamine antagonists: evolution of structures in the course of the time. Note the progressive use of a furan, a thiazole, and finally a phenyl ring in place of the original imidazole ring. On the same series it is noteworthy the bioisosterism of the urea moiety with different surrogates: thiourea, *N*-cyanoguanidine, *N*-nitro-ethene diamine, and *N*-aminosulfonyl guanidine.

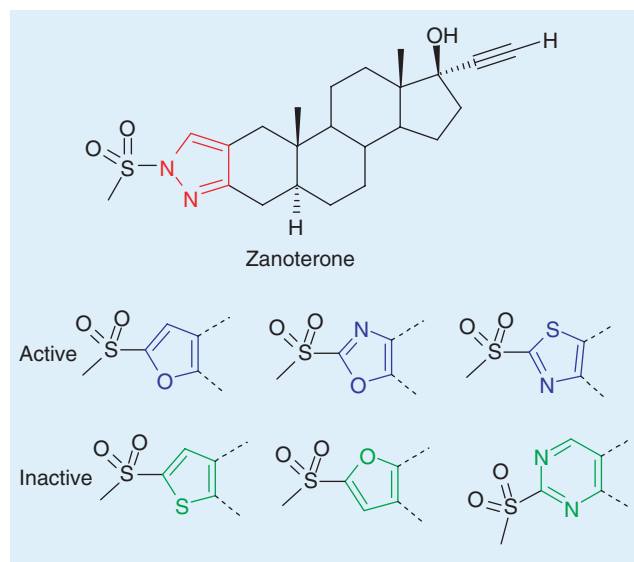


FIGURE 15.20 Zanolone isosteres.⁴⁵

to GABA itself. The key parameters in these compounds are the acidic ($pK_a < 4$) and the basic (protonated nitrogen) functions with a $< 5.1 \text{ \AA}$ interchange distance.

For the carboxylic function of active compounds, three different classes of bioisosters can be distinguished: (a) the direct derivatives (Table 15.11); (b) the planar acidic heterocycles (Table 15.12); and (c) the non-planar sulfur- or phosphorus-derived acidic functions (Table 15.5).

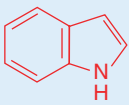
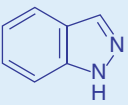
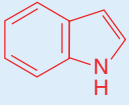
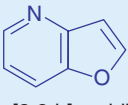
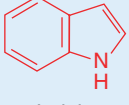
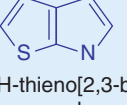
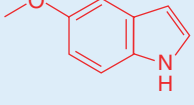
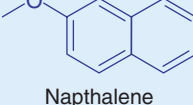
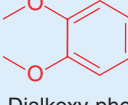
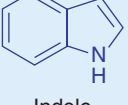
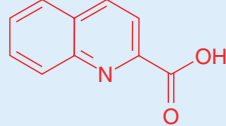
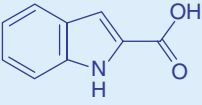
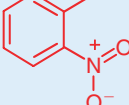
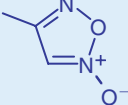
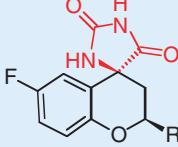
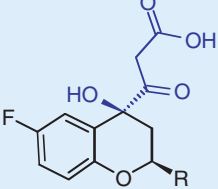
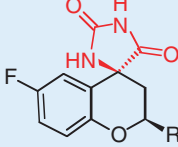
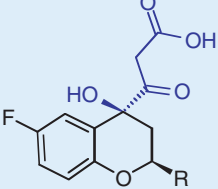
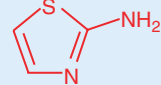
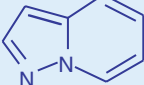
a. Direct derivatives

Direct derivatives of carboxylic acids are different functional groups which maintain an acidic proton and a hydrogen bond acceptor (the carbonyl) in order to have similar specific interactions with the receptor. Among the most common direct derivatives can be listed: the hydroxamic acids ($R-CO-NH-OH$), the acylcyanamides ($R-CO-NH-CN$) and the acylsulfonamides ($R-CO-NH-SO_2-R'$) (Table 15.11).

Hydroxamic acids: The hydroxamic acids have a high chelating power and they have found a wide application as inhibitors of enzymes having a metal ion like Zn^{2+} in the active site. Examples note of worth are found in the inhibitors of matrix metalloproteinases (MMP),^{65–67,76} tumor necrosis factor α converting enzyme (TNF α),⁶⁹ and histone deacetylase (HDAC)^{59,60} where the hydroxamic acid derivatives have given potent and bioavailable compounds despite this group is particularly prone to hydrolysis, reduction, and glucuronidation.⁶⁸ Another interesting example of exploitation of the hydroxamic acid is given by the antiinflammatory hydroxamates bufexamac,⁷⁷ ibuproxam,⁷⁸ and oxametacin⁷⁹ (Figure 15.22) where the hydroxamates can act either as a prodrug-like ibuproxam being metabolized to ibuprofen ($CONHOH \rightarrow COOH$) in man,⁸⁰ either as a true bioisostere like oxametacin being metabolically stable in man.^{81,82}

Acylsulfonamides: Acylsulfonamides are also quite used in drug discovery and have been employed in several therapeutic areas such as β_3 adrenergic receptor agonist,⁷⁴

TABLE 15.10 Other Ring Bioisosteres

Original ring	Bioisostere	Activity	Reference
 Indole	 Indazole	5-HT ₃ antagonists	Fludzinski <i>et al.</i> ⁴⁶
 Indole	 Furo[3,2-b] pyridine	5-HT _{1F} agonist	Mathes <i>et al.</i> ⁴⁷
 Indole	 6H-thieno[2,3-b] pyrrole	Hallucinogen serotonin agonist	Blair <i>et al.</i> ⁴⁸
 Indole	 Naphthalene	Agonist at melatonin receptors and antagonist at 5HT _{2c}	Yous <i>et al.</i> , ⁴⁹ Depreux <i>et al.</i> ⁵⁰
 3,4-Dialkoxy-phenyl	 Indole	Phospho diesterase inhibitors	Blaskó <i>et al.</i> ⁵¹
 Quinoline-2-carboxylate	 Indole-2-carboxylate	GABA uptake inhibitors	Kardos <i>et al.</i> ⁵²
 o-Nitro-phenyl	 Furoxane	Glycine antagonists	Salituro <i>et al.</i> ⁵³
 Spiro-hydantoin	 Spiro hydroxyacetic acid unit	Calcium antagonist	Calvino <i>et al.</i> ⁵⁴
 Spiro-hydantoin	 Spiro hydroxyacetic acid unit	Aldose reductase inhibitor	Lipinski <i>et al.</i> ⁵⁵
 Thiazol-2-ylamine	 Pyrazolo[1,5-a] pyridine	Dopamine D ₃ receptor agonist	Löber <i>et al.</i> ⁵⁶

chemokine receptor 1 (CXCR1) inhibitors,⁸³ hepatitis C virus (HCV) inhibitors,⁷⁵ angiotensin receptor agonists,⁸⁴ antitumoral compounds with antiproliferative properties,^{85,86} and prostaglandin EP4 receptor antagonists.⁸⁷ Acylcyanamides are mainly of academic interest.

b. Planar acidic heterocycles and aryl derivatives

In Table 15.12 are reported the planar acidic heterocycles and aryl derivatives that are commonly used as carboxylic acid bioisosters. The most used is the tetrazole ring which has found wide application in different therapeutic fields spanning from type 2 diabetes^{98,99} to hepatitis C virus (HCV),⁷⁵ malaria,¹⁰⁰ Alzheimer's disease (AD),¹⁰¹ anxiety treatment,¹⁰² and pain management.¹⁰³ The tetrazole has been employed to fix different issues, for example to improve bioavailability,¹⁰⁰ to enhance the blood–brain barrier penetration,^{102,103} to increase potency,^{99,104} to get a

better chemical stability,¹⁰¹ to bring some selectivity (the GABA tetrazole analog inhibits GABA-transaminase, but not succinic semialdehyde dehydrogenase)¹⁰⁵ or to be used as a prodrug.¹⁰⁶ However, in some instances, tetrazole analogs are poorly active.¹⁰⁷

Hydroxy-isoxazoles and other cognate heterocyclic phenols encompassing an acidity range from 3.0 to 7.1 were incorporated in GABA agonists, antagonists, and uptake inhibitors.^{108,109} The experience gained with 3-hydroxy-isoxazoles in the GABA field was also transferable to glutamate receptor ligands and led to selective antagonists for glutamic acid receptor subtypes.¹⁰⁸

Thiazolidinediones are another class of heterocyclic carboxylic acid surrogates commonly used for peroxisome proliferator-activated receptors (PPAR) agonists,^{93,94} as potent antihyperglycemic and lipid activity modulators. Other interesting, but less studied heterocyclic surrogates are: 3,5-dioxo-1,2,4-oxadiazolidine,¹¹⁰ 3-hydroxy-1,2,5-thiadiazoles,⁹¹ 1,2,4-oxadiazole-5(4*H*)-ones,⁹⁵ 1,2,4-thiadiazole-5(4*H*)-ones⁹⁵, 3,5-difluoro-4-hydroxyphenyl,^{96,97} and 3-hydroxy- γ -pyrones.^{92,111}

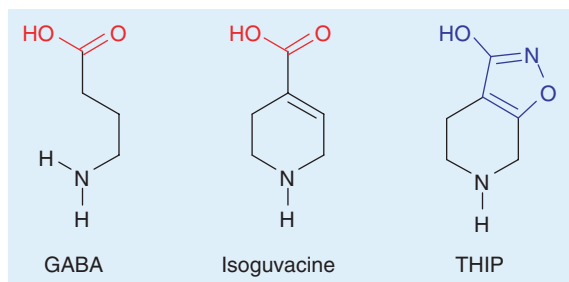


FIGURE 15.21 An example of bioisosterism, or non-classical isosterism: GABA, isoguvacine, and THIP are all agonists for the GABA-A receptor. The 3-hydroxy-isoxazole ring has a comparable acidity to that of a carboxylic acid function.⁵⁷

c. Non-planar sulfur- or phosphorous-derived acidic functions

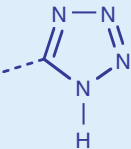
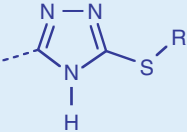
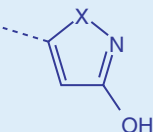
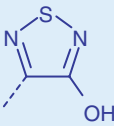
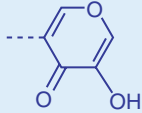
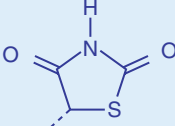
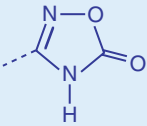
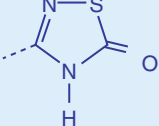
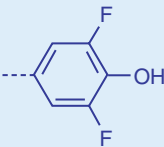
The most extensive use of phosphonates (Table 15.13) occurred in the design of amino acid neurotransmitter antagonists such as glutamate¹¹⁴ and GABA-B antagonists.¹¹²

Amongst a set of cholecystokinin (CCK) antagonists derived from the non-peptide CCK-B selective antagonist CI-988, Drysdale *et al.*¹¹⁵ prepared a series of carboxylate surrogates spanning a pK_a range from <1 (sulfonic acid) to >9.5 (thio-1,2,4-triazole). The affinity and the selectivity of the compounds were rationalized by considering pK_a values,

TABLE 15.11 Carboxylic Acid Isosteres: Direct Derivatives

	Hydroxamic acids	High chelating power Histone deacetylase inhibitors Matrix metalloproteinases inhibitors Tumor necrosis factor α converting enzyme	Almquist <i>et al.</i> ⁵⁸ Massa <i>et al.</i> , ⁵⁹ Lu <i>et al.</i> ⁶⁰ Remiszewski <i>et al.</i> , ⁶¹ Plumb <i>et al.</i> , ⁶² Kelly <i>et al.</i> , ⁶³ Buggy <i>et al.</i> ⁶⁴ Hanessian <i>et al.</i> ⁶⁵ Aranapakam <i>et al.</i> ^{66,67} Noe <i>et al.</i> ⁶⁸ Duan <i>et al.</i> ⁶⁹
	Acyl-cyanamides	Mainly academic interest	von Kohler <i>et al.</i> ⁷⁰ Kwon <i>et al.</i> ⁷¹
	Acyl-sulfonamides	Glycine, GABA, and β -alanine analogs Antiatherosclerotics pK_a # 4,5 β_3 Adrenergic receptor agonist hepatitis C virus	Drummond and Johnson ⁷² Albright <i>et al.</i> ⁷³ Uehling <i>et al.</i> ⁷⁴ Johansson <i>et al.</i> ⁷⁵

TABLE 15.12 Carboxylic Acid Isosteres: Planar Acidic Heterocycles and Aryl Derivatives

	Tetrazoles	Very popular, great number of publications. $pK_a = 6.6$ to 7.2	Bovy <i>et al.</i> ⁸⁸ Marshall <i>et al.</i> ⁸⁹
	Mercaptoazoles + Sulfinylazoles + Sulfonylazoles	Phosphonate isosteres pK_a mercapto: 8.2 – 11.5 pK_a sulfinyl: 5.2 – 9.8 pK_a sulfonyl: 4.8 – 8.7	Chen <i>et al.</i> ²⁰
 $X = O$ or S	Isoxazoles Isothiazoles	GABA and glutamic acid analogs	Krogsgaard-Larsen <i>et al.</i> ⁵⁷ Krogsgaard-Larsen ⁹⁰
	Hydroxy-thiadiazole	Isoxazole isostere $pK_a \# 5$	Lunn <i>et al.</i> ⁹¹
	Hydroxy-chromones	Kojic acid derivatives (as GABA agonists)	Atkinson <i>et al.</i> ⁹²
	Thiazolidinediones	Dual PPAR α/γ agonists	Hulin <i>et al.</i> , ⁹³ Henke ⁹⁴
	1,2,4-Oxadiazole-5(4H)-ones	Antimycobacterial	Gezginci <i>et al.</i> ⁹⁵
	1,2,4-Thiadiazole-5(4H)-ones	Antimycobacterial	Gezginci <i>et al.</i> ⁹⁵
	3,5-Difluoro-4-hydroxyphenyl	Aldose reductase inhibitor GABA analog	Nicolaou <i>et al.</i> ⁹⁶ Qiu <i>et al.</i> ⁹⁷

charge distribution, and geometry of the respective acid mimics (Table 15.14).

In order to choose the best carboxylic acid bioisoster pK_a and $\log P$ are important parameters to look at before proceeding with one surrogate or another. An interesting study comparing pK_a and $\log P$ values of some aryl phosphonic acids, aryl tetrazoles, and aryl sulfonamides has been published by Franz.¹¹⁶ The values of pK_a and $\log P$ are very important parameters in drug design. Several published examples show that the interchange of carboxylic acid for tetrazole and

sulfonamide often results in useful drugs. This study indicates that the $\log P$ will be lowered by about 1 log unit substituting a phosphonic acid by a carboxylic acid group. There is an increase in acidity which may be a limiting factor in the absence of active transport. Replacing a carboxylic acid group by a phosphonic acid group gives a much more acidic compound; replacing it with a sulfonamide group results in a much less acidic compound; and with a tetrazole replacement, acidity is essentially unchanged (Figure 15.23). If one wants to lower the $\log P$, and if increased acidity of the compound was not a limiting factor, substitution of a phosphonic acid group for a carboxylic acid would be a viable approach (Figure 15.24).

Diamino-cyclobutene-diones as α -amino carboxylic acid surrogates: Diamino-cyclobutene-dione was proposed by Kinney *et al.*¹¹⁷ as an original surrogate of the α -amino carboxylic acid function (Figure 15.25).

Carboxylic functions as phosphonates surrogates: pTyr mimetics serve as important components of many competitive protein-tyrosine kinases inhibitors. To date, the most potent of these inhibitors have relied on phosphonate-based structures to replace the 4-phosphoryl group of the parent pTyr residue (Figure 15.26). Interestingly, it was found that carboxy-based pTyr analogs can be utilized to introduce the anionic oxygen functionality of the parent phosphate. Particularly, when *p*-(2-malonyl)phenylalanine (Pmf) was incorporated as pTyr replacement in the high-affinity Grb2 SH2 domain binding sequence, potencies approaching one of phosphonate mimetics were obtained.¹¹⁸

The above example is an elegant illustration of the possibility to mimic the pyramidal structure of phosphates or phosphonates by means of two planar carboxylic groups, the three-dimensionality originating from the malonic methylenic carbon atom.

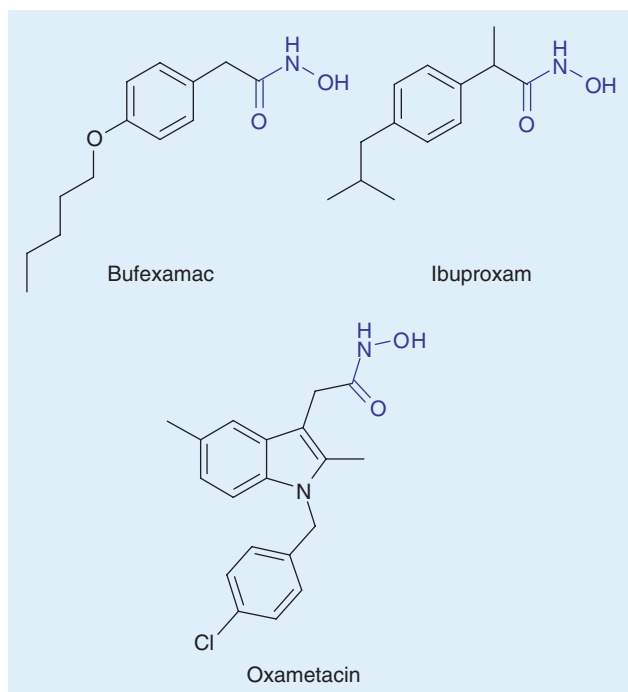
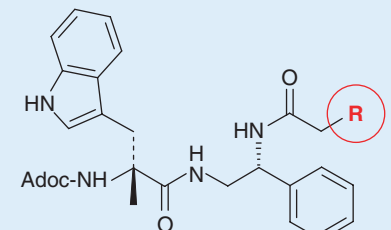
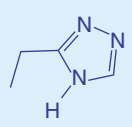
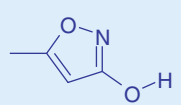
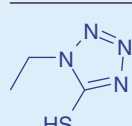
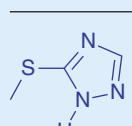
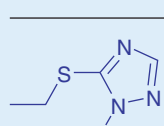
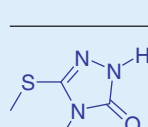
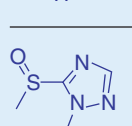
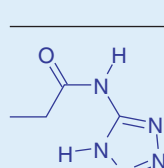


FIGURE 15.22 Hydroxamate isosteres of antiinflammatory drugs.

TABLE 15.13 Carboxylic Acid Isosteres: Non Planar Sulfur- or Phosphorus-Derived Acidic Functions

	X = H X = OH X = NH₂ X = CH(OR)₂	Phosphinates Phosphonates Phosphonamides	Many examples in glutamate and in GABA _B antagonist series	Froestl <i>et al.</i> ¹¹²
		Sulfonates	Sulphonic analogs of GABA and glutamic acid	Rosowski <i>et al.</i> ¹¹³
		Sulfonamides	Weak acids, used rather as equivalents of phenolic hydroxyls in the design of catecholamine analogs	von Kohler <i>et al.</i> ⁷⁰

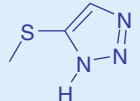
TABLE 15.14 Exploration of the Carboxyl Isosterism Possibilities in a Series of CCK Antagonists.

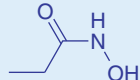
				
R	IC ₅₀ (nM) CCK-B	IC ₅₀ (nM) CCK-A	A/B ratio	pK _a
R—CH ₂ —COOH	1.7	4500	2500	5.6
Charge distributed monoanionic acid mimics				
	6.0	970	160	5.4
	2.6	1700	650	6.5
	2.4	620	260	4.3
	2.5	680	270	>9.5
	16	850	53	>9.5
	4.3	660	150	7.7
	1.7	940	550	7.0
	6.3	1300	200	5.2

(Continued)

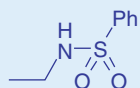
TABLE 15.14 (Continued).

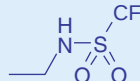
Charge distributed monoanionic acid mimics

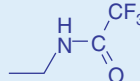
	18	600	33	>8.2
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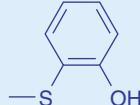
	14	1300	93	>9.5
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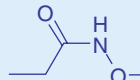
Point charge monoanionic acid mimics

	70	300	4.3	>9.5
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	77	680	9	7.9
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	110	790	7	>9.5
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	80	510	6.4	>9.5
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	21	1500	71	>9.5
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Tetrahedral acid mimics

P(O)(OH) ₂	27	5200	190	3.4; 7.7
CH ₂ —P(O)(OH) ₂	23	2700	120	3.4; 7.8
P(O)(OH)(OEt)	12	480	40	6.5
P(O)(OH)Me	12	1700	140	3.8
CH ₂ —P(O)(OH)Me	23	4400	190	3.7
CH ₂ —SO ₃ Na	1.3	1010	780	—

2. Carboxylic esters bioisosteres

Carboxylic esters are nice tools for SAR studies investigation but they are not valuable group to be left in drug molecules because they lack the proper of *in vivo* stability. As matter of fact they are hydrolyzed quite quickly by the esterases which are quite ubiquitous and are present in the blood, the liver, the kidneys, and other organs. To overcome

this problem the carboxylic ester in the most promising compounds has been replaced by bioisosteric groups leading to molecules with improved pharmacokinetic profile.

One of the first examples of ester bioisoster is the amide bond as it is illustrated by the local anesthetic procaine where the readily hydrolyzable ester group was replaced with an amide to give procainamide as more stable analog (Figure 15.27).

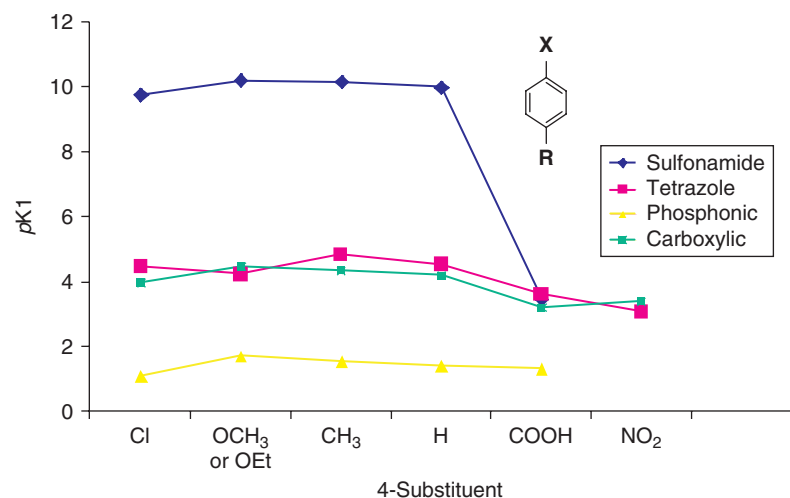


FIGURE 15.23 pK_1 values for aromatic compounds (redrawn after Franz¹¹⁶).

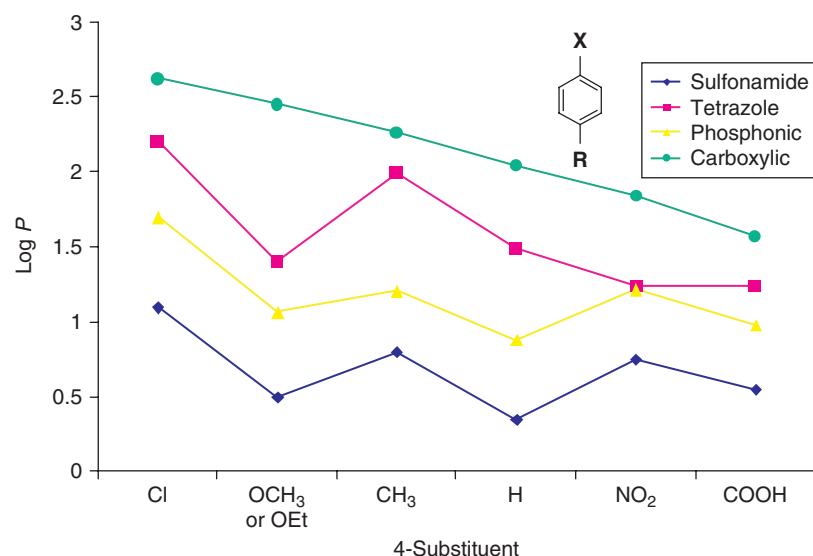


FIGURE 15.24 $\log P$ values for aromatic compounds (redrawn after Franz¹¹⁶).

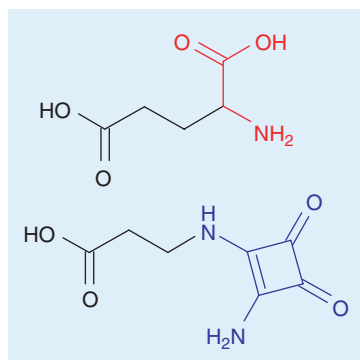


FIGURE 15.25 3,4-Diamino-3-cyclobutene-1,2-dione as surrogate of the α -amino carboxylic acid function.

Similarly, the lactone ring of the muscarinic agonist pilocarpine was changed into various, still active isosteres such as the corresponding thiolactone, lactam, lactol, and thiolactol.¹¹⁹ A series of aspirin isosteres has been prepared

by replacing the carboxylic ether oxygen successively by a nitrogen, sulfur, or carbon isosteric equivalent.¹²⁰ None of the isosteric compounds showed any activity. This result is readily understood since the particular role of aspirin as an acylating agent of the enzyme cyclooxygenase has been demonstrated.¹²¹

Pilocarpine is widely used as a topical miotic for controlling the elevated intraocular pressure associated with glaucoma. Beside its low lipophilicity, which stimulated the search for prodrugs,¹²² pilocarpine has a short duration of action, its lactonic ring being rapidly opened to yield pilocarpic acid. In pilocarpine, by substituting the lactonic ester function by its carbamate equivalent, a much more stable analog, which is as effective as pilocarpine, was obtained.¹²³

In addition to these classical changes more exotic groups and radicals have been proposed and tested as valuable carboxylic ester surrogates like five-membered heterocycles and alkyl oximes. Studies about the design and the synthesis

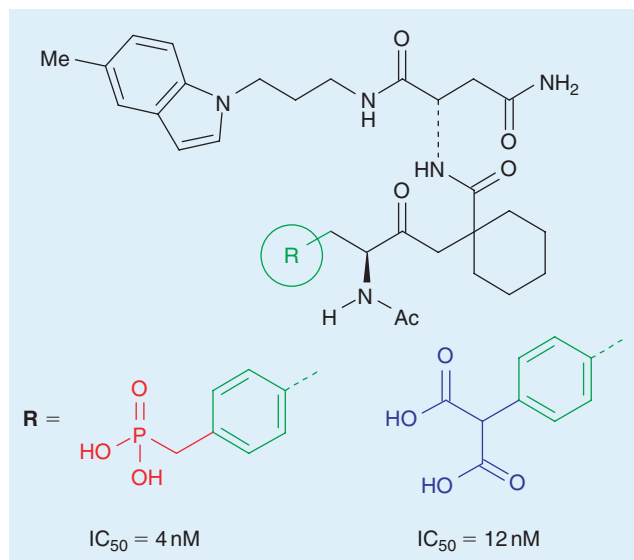


FIGURE 15.26 Malonates as surrogates of phosphonates.

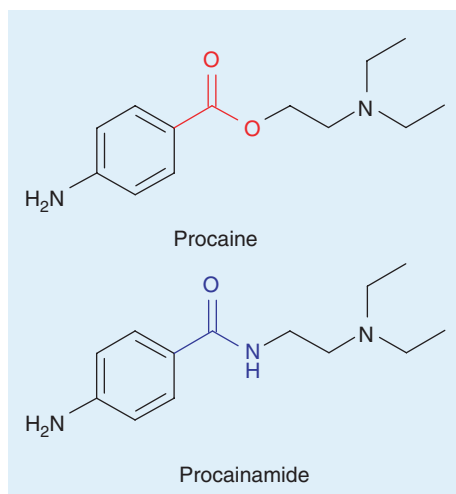


FIGURE 15.27 Amide as an ester surrogate of the local anesthetic procaine.

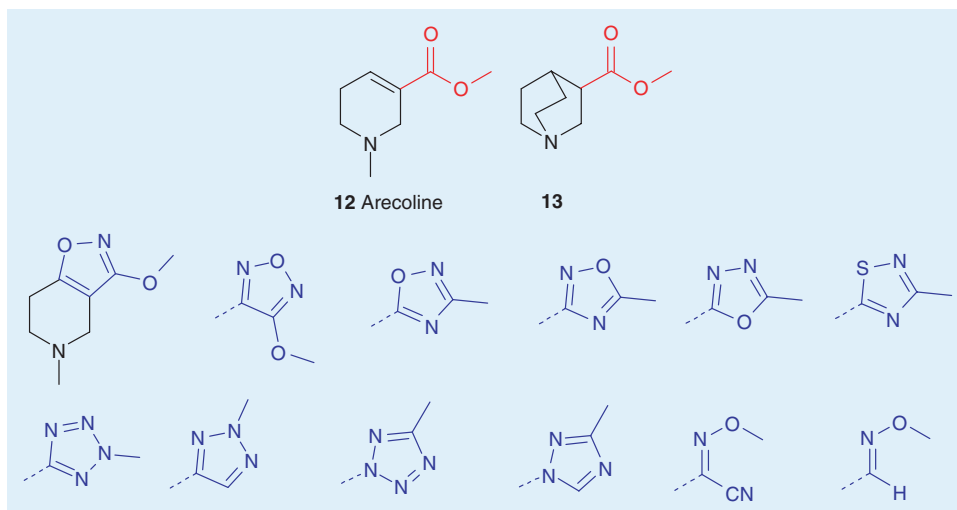


FIGURE 15.28 Muscarinic ligands derived from the ester bioisoster replacement of arecoline **12** and quinuclidine methyl ester **13**.

of more metabolically stable muscarinic ligands have shown that it is possible to replace the methyl ester of arecoline **12** and of the quinuclidine **13** with a series of five-membered rings like oxadiazoles, thiadiazoles, triazoles, and tetrazoles to give potent muscarinic agonist (Figure 15.28).^{124–130}

Note of worth is also the successful replacement of the methyl ester with oxime ethers and *N*-methoxy imido nitrile in the design of muscarinic agonists (Figure 15.28).^{131,132}

Several 1,2,4-oxadiazoles and the other five-membered heterocycles are employed also for other therapeutic indications like monoamine transporter and opioid receptors,^{133,134} 5-HT agonists,¹³⁵ bradykinin B₁ receptor antagonists,¹³⁶ and vascular endothelial growth factor receptor (VEGFR-2) inhibitors.¹³⁷

Recently it has been published a nice example of the use of the methyl ester bioisosters in the design of a series of metabolically stable HIV inhibitors (Figure 15.29).^{138,139} Starting from an alkenyldiarylmethane containing three methyl esters, the systematic substitution of one ester at the time with the appropriate biomimetic group led to a molecule with an enhanced metabolic stability in rat plasma ($t_{1/2}$ = 61 hour) along with the ability to inhibit HIV-1 reverse transcriptase (Figure 15.29).

A confirmation of the alkyl oxime ether as metabolically stable isoster of an ester has been reported by Watson *et al.* in the synthesis of a capsid binder active against Human Rhinovirus¹⁴⁰ (Figure 15.30).

The change in (–)-cocaine of the carbomethoxy substituent into carbethoxyisoxazole doubles the potency in [³H] mazindol binding and [³H] dopamine (DA) uptake (Figure 15.31). Astonishingly the replacement of the carbomethoxy group by a chlorovinyl moiety produces a comparable gain in potency thus arguing against the involvement of the carbomethoxy group in H-bonding.¹⁴¹

Another rather unusual example of ester isosterism is the replacement of the ether oxygen by a fluoro-nitro group (Figure 15.32a) as mentioned by Lipinski.¹⁴² Other

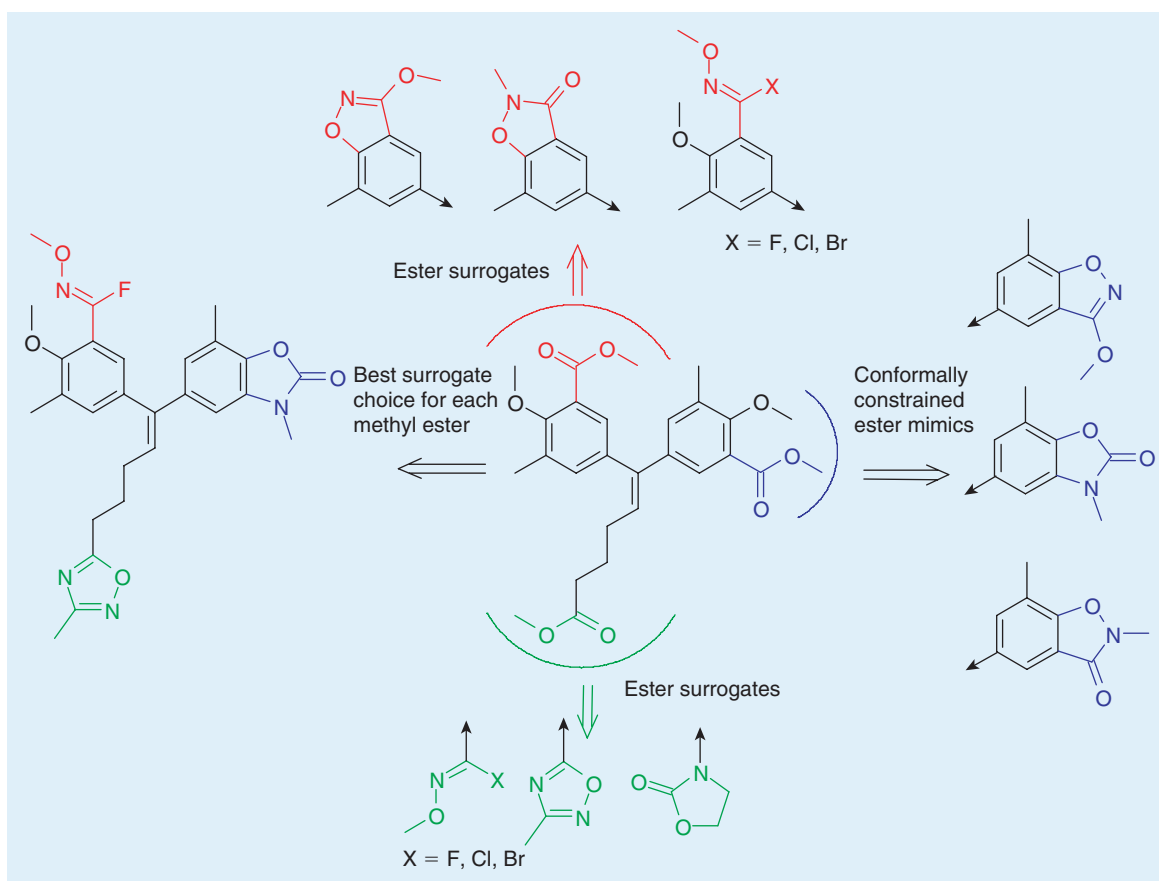


FIGURE 15.29 Design of new metabolically stable HIV inhibitor.

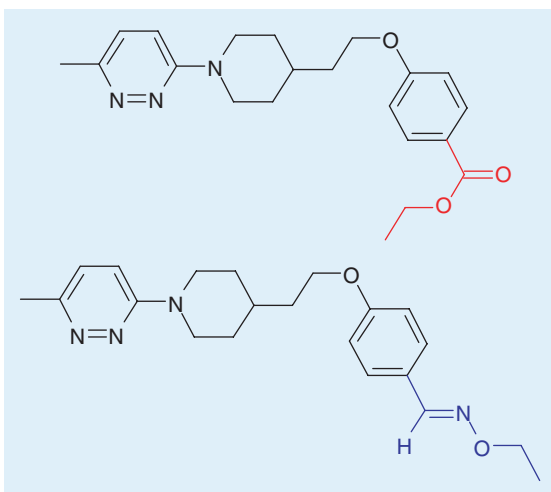


FIGURE 15.30 Ethyl oxime ether as ester replacement gave an improved bioavailability.

uncommon examples are found in the replacement of the ester function of acetylcholine by exo–endo amidinic functions of 3-aminopyridazines in muscarinic agonists (Figure 15.32b)¹⁴³ and of the carbomethoxy group of α -yohimbine

(rauwolscine) by a *N*-methylsulfonamide function (Figure 15.32c).¹⁴⁴

3. Carboxamide bioisosteres

Biologically active molecules containing amide bonds suffer usually of pharmacokinetic liability. In order to increase their stability, bioisosteric transformation of the carboxamide have been performed and yielded a lot of successful examples especially in the area of peptidomimetic. The isosteric replacements for peptidic bonds have been summarized by Spatola¹⁴⁵ and by Fauchère.¹⁴⁶ The most used and well-established modifications are: *N*-methylation, configuration change (*D*-configuration at C_{α}), formation of a retroamide or an α -azapeptide, use of aminoisobutyric or dehydroamino acids, replacement of the amidic bond by an ester [depsipeptide], ketomethylene, hydroxyethylene or thioamide functional group, carba replacement of the amidic carbonyl, and use of an olefinic double bond (Figure 15.33).

In other cases carboxamides are converted to sulfonamides as illustrated by the synthesis of the hypoglycemic sulfonyl isostere of glybenclamide.¹⁴⁷

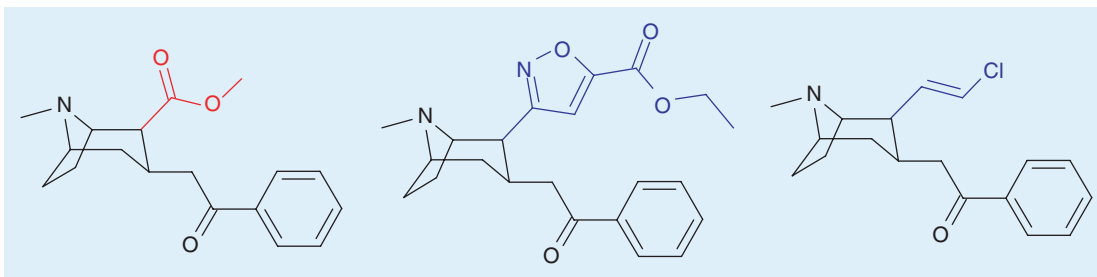


FIGURE 15.31 Replacement in (–)-cocaine of the carbomethoxy group by a carbethoxyisoxazole and a chlorovinyl moiety.

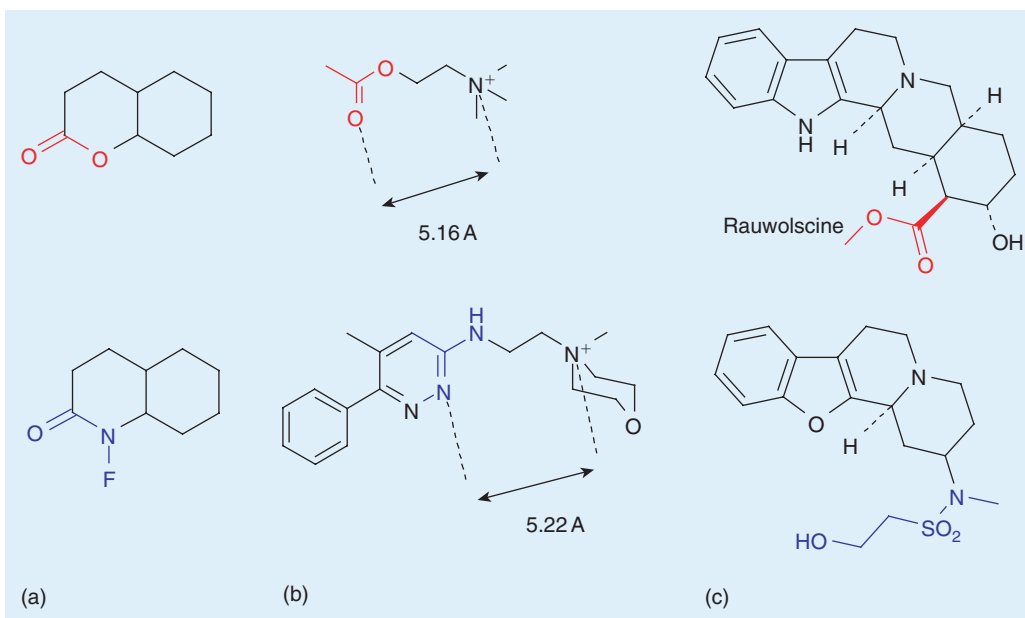


FIGURE 15.32 (a) Replacement of ester ether oxygen by a fluoro-nitrogen; (b) Exo-endo amidine in place of a carboxylic ester functionality; (c) *N*-methylsulfonamide analog of α -yohimbine (rauwolscine).

More unusual isosteric replacements for the peptidic bond were proposed and are reported in Figure 15.34. Among them, hydroxyethylureas were used in the design of a novel class of potent HIV-1 protease inhibitors, diacylcyclopropanes in the design of novel renin inhibitors, and pyrroline-3-ones for various proteolytic enzyme inhibitors.^{148,149} Vinyl fluorides can probably be considered as representing the closest possible bioisosteres of the peptide bond. The synthetic methods available allow, by an appropriate selection of the precursors, the preparation of analogs of dipeptidic combinations of amino acids bearing no other functionalities in their side chains, for example Gly, Ala, Val, Phe, and Pro.¹⁵⁰ Vinyl fluorides have been used in the design of bioisosteres of peptide bonds as in the case of the analgesic dipeptide 2,6,-dimethyl-L-tyrosyl-D-alanine-phenylpropionamide.¹⁵¹

Other structural modifications of the amide bond proposed to create more chemically stable and orally available molecules include heterocyclic rings such as 1,2,4-oxadiazoles and 1,3,4-oxadiazoles (Table 15.15). 1,2,4-Oxadiazoles

have been used as bioisosteres of the carboxamide moiety in SH2 inhibitors of tyrosine kinase ZAP-70,¹⁵² 5-HT_{1D} receptor agonists,¹³⁵ histamine H₃ receptor antagonists,¹⁵³ and 5-HT₃ receptor antagonists.¹⁵⁴ An example worthy of note is given by the β_3 adrenergic receptor agonists where the replacement of the amide bond with 1,2,4-oxadiazoles lead to compounds with improved oral bioavailability retaining the β_3 AR agonist activity.^{155–159} 1,3,4-Oxadiazoles have also been used as amide bond surrogates in several therapeutic areas like benzodiazepine receptor agonists,¹⁶⁰ muscarinic receptor agonists,¹⁶¹ NK1 receptor antagonists¹⁶² and they have also been used as Phe-Gly peptidomimetics.¹⁶³

Other heterocyclic replacements of the amide bond include oxazole rings,^{164,165} cyclic amidines,^{166,167} pyrrole rings,¹⁶⁸ and phenylimidazole¹⁶⁹ (Table 15.15).

In the case of aryl amides, heterocyclisation was explored in order to overcome the pharmacokinetic liability. The search for transient receptor potential vanilloid 1 (TRPV1) antagonists as potential analgesic has led to the discovery of

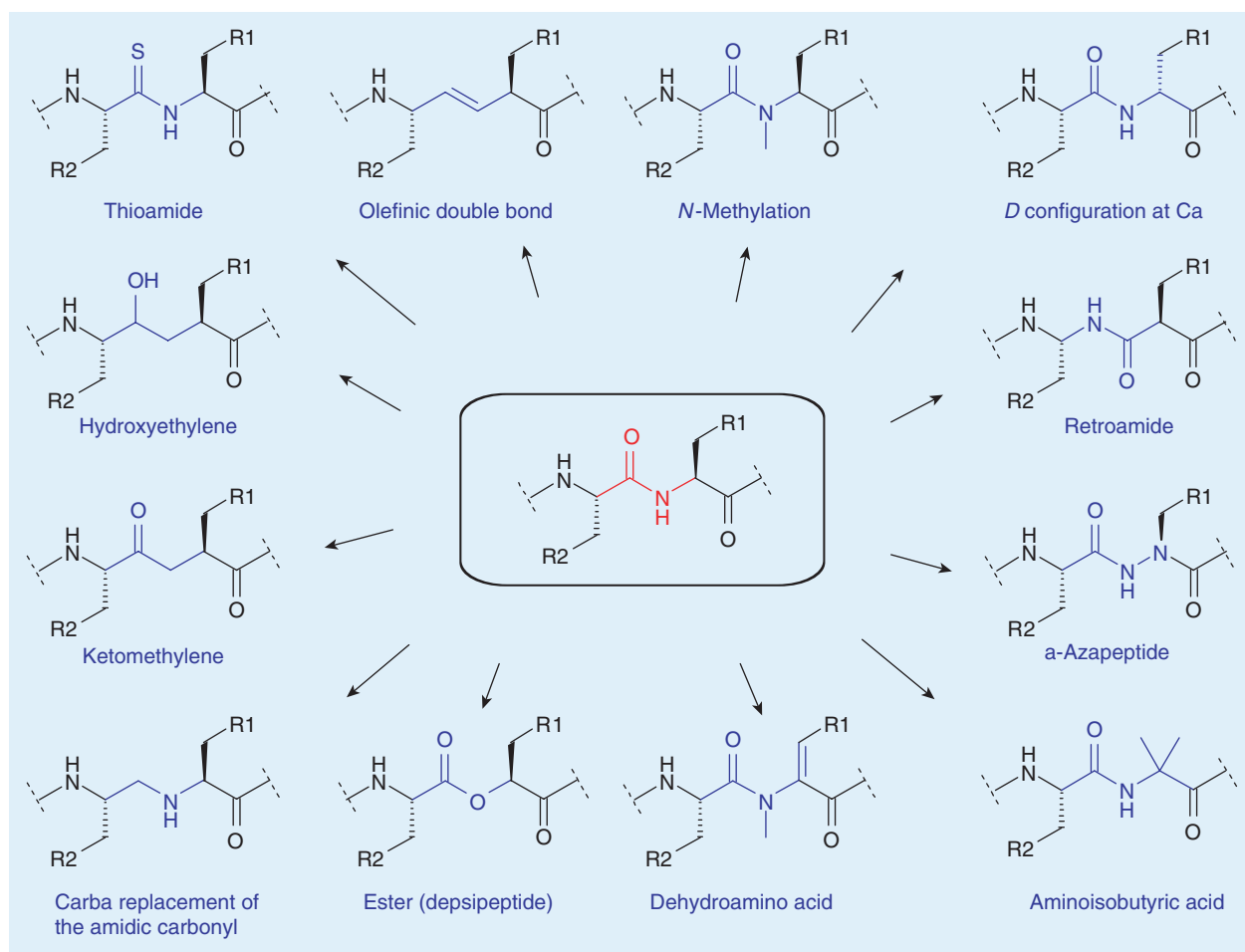


FIGURE 15.33 Well-established isosteric replacements for peptidic bonds.

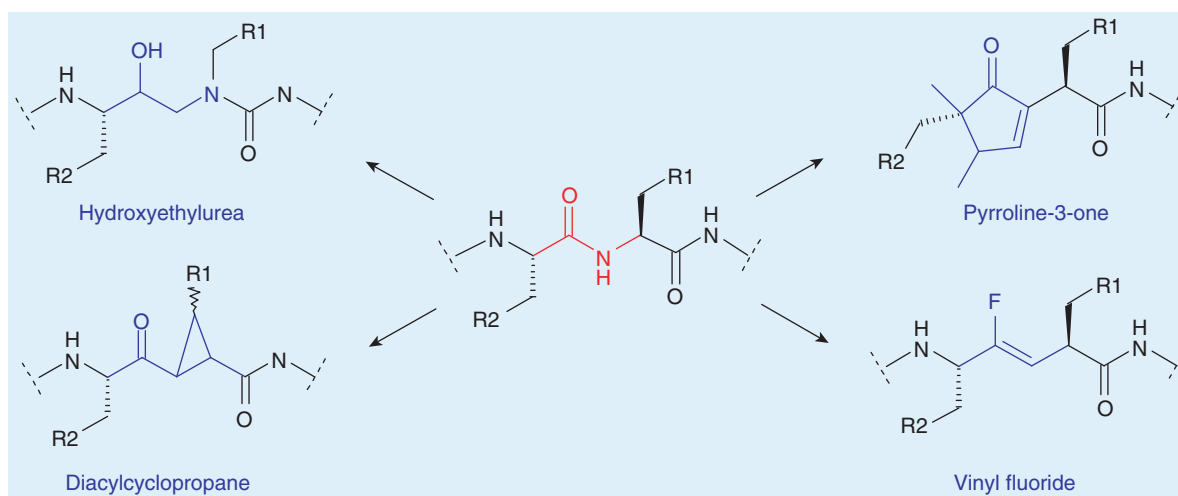
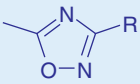
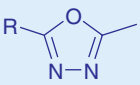
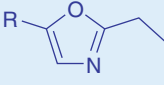
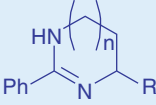
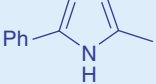
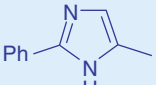


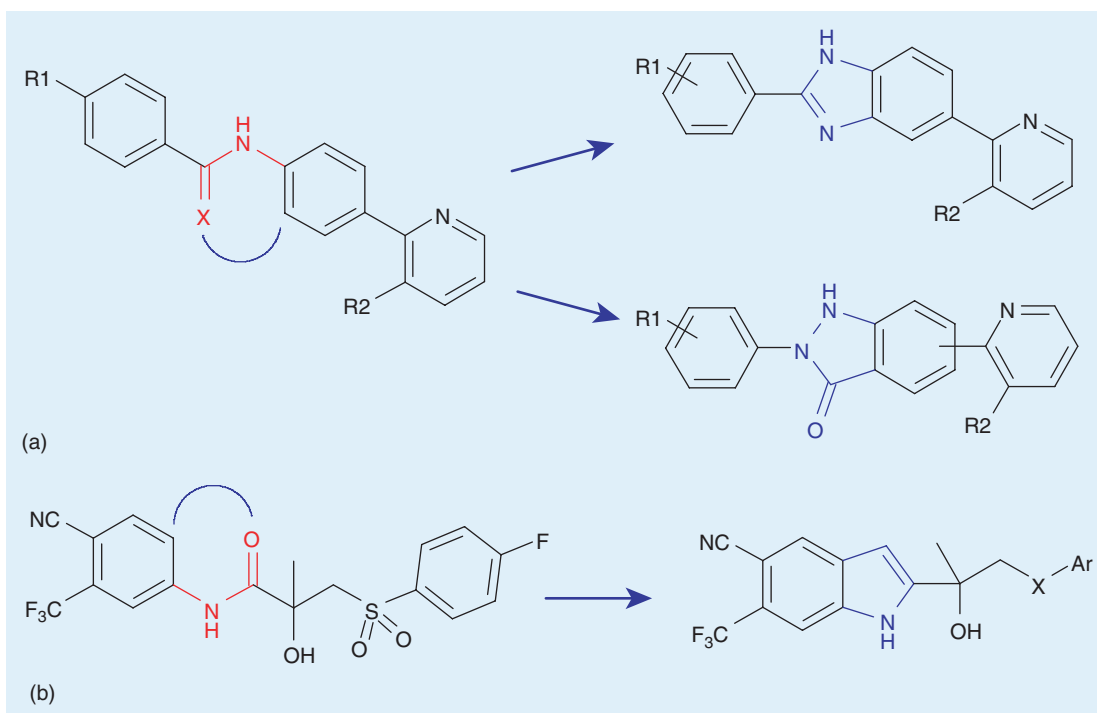
FIGURE 15.34 Unusual isosteric replacements for the peptidic bond.

a series of biaryl amides such as those reported in (Figure 15.35a) which suffer of pharmacokinetic liability.¹⁷⁰ In order to overcome this problem heterocyclization was explored and has yielded benzimidazoles and indazolones as promising

[carboxamides bioisosters¹⁷⁰ (Figure 15.35a). Other examples of benzimidazoles as aryl amides isosters has also been reported as melanin-concentrating hormone receptor 1 (MCH R1) antagonists.^{171,172}

TABLE 15.15 Heterocyclic Surrogates of the Amide Bond

	1,2,4-Oxadiazoles	β_3 adrenergic receptor agonist	Naylor <i>et al.</i> , ^{157,158} Feng <i>et al.</i> , ¹⁵⁶ Biftu <i>et al.</i> , ¹⁵⁵ Parmee <i>et al.</i> ¹⁵⁹
		Fatty acid oxidation inhibitors	Elzein <i>et al.</i> , ¹⁶⁴ Koltun <i>et al.</i> ¹⁶⁵
	1,3,4-Oxadiazoles	Phe-Gly peptidomimetics NK1 receptor antagonists	Borg <i>et al.</i> ¹⁶³ Ladduwahetty <i>et al.</i> ¹⁶²
	Oxazoles	Fatty acid oxidation inhibitors	Elzein <i>et al.</i> , ¹⁶⁴ Koltun <i>et al.</i> ¹⁶⁵
	Cyclic amidines	Dopamine D4 receptor agonists	Einsiedel <i>et al.</i> ^{166,167}
	Pyrroles	D3 antagonists	Einsiedel <i>et al.</i> ¹⁶⁸
	Phenylimidazoles	D4 receptor ligand	Thurkauf <i>et al.</i> ¹⁶⁹

**FIGURE 15.35** Benzimidazoles, indazolones, and indoles as carboxamides bioisosters.

The indole ring has also been reported as valuable carboxamide bioisoster (Figure 15.35b) of the non-steroidal antiandrogen bicalutamide.¹⁷³

4. Urea and thiourea bioisosteres

Chemical modifications of the thiourea group of the metiamide led to the discovery of *N*-cyanoguanidine, *N*-nitro-ethene diamine, and *N*-aminosulfonyl guanidine as successful bioisosteres of the urea group⁴⁴ (Figure 15.19). This successful example of bioisosterism has been applied to the sulfonyl-urea function of torsemide,¹⁷⁴ a diuretic loop (Figure 15.36). This investigation led to the design and synthesis of the corresponding thiourea, cyanoguanidine, and diaminonitroethylene group. The structure, the electronic

features (charges, molecular electrostatic potential, molecular orbitals) and the lipophilic properties of these three analogs were determined. In conclusion, cyanoguanidine and diaminonitroethylene turned out to be valuable isosteres of the (thio)urea function as they share common geometric and electronic properties. In addition, they cover a range of lipophilicity that makes them suitable for compound pharmacomodulation as illustrated by the diuretic and antiepileptic properties of analogs of torsemide.

In a study undertaken on antagonists of the dihydropyridine neuropeptide Y₁ receptor, common bioisosteres such as thiourea and cyanoguanidine were examined as urea replacement (Figure 15.37) and also more uncommon derivatives like squaric acid and thiadiazole oxide.^{175,176} Both cyanoguanidine and thiourea derivatives demonstrated

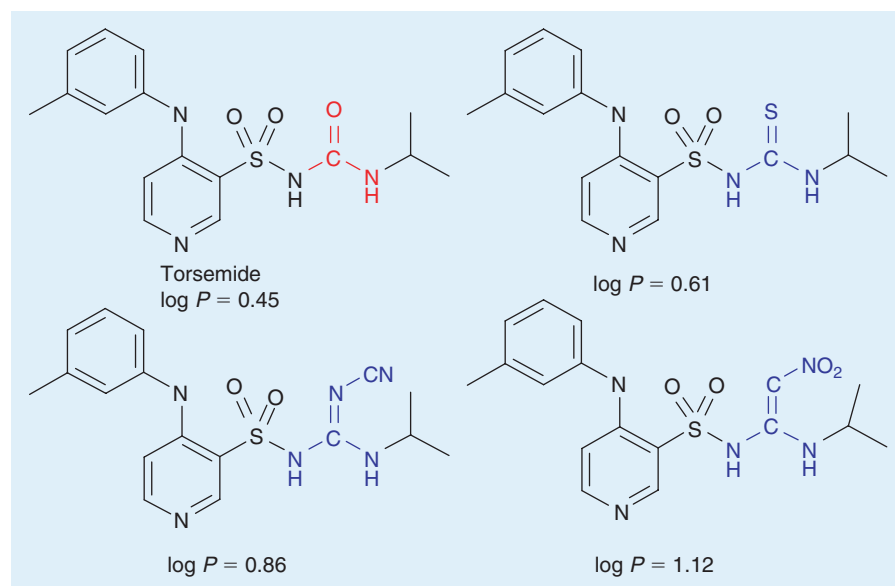


FIGURE 15.36 Structure of torsemide and its urea bioisosteres.

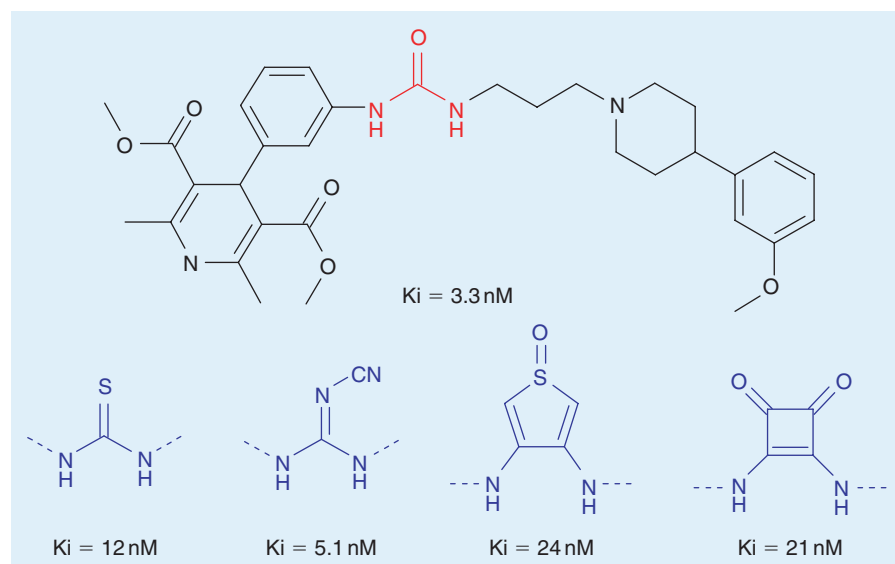


FIGURE 15.37 Binding affinities for various urea bioisosteres acting as antagonists at the NPY Y₁ receptor.

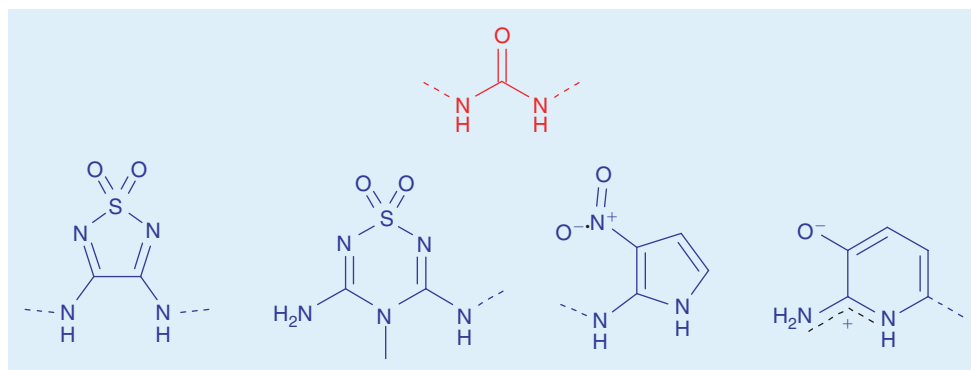


FIGURE 15.38 Less common urea equivalents.

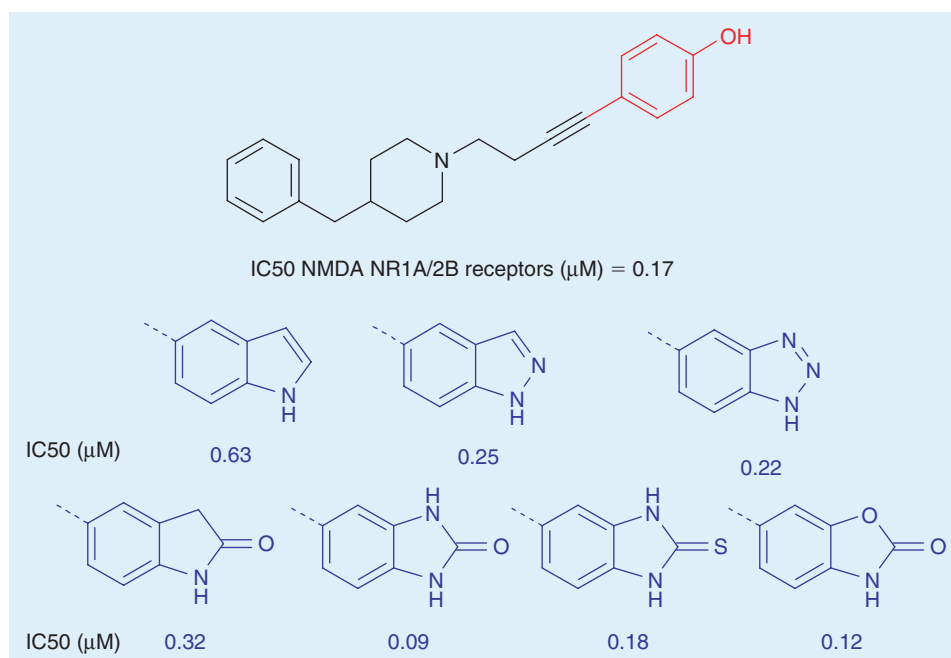


FIGURE 15.39 Bioisosteric replacements of the phenol function in the design of *N*-methyl-D-aspartate (NMDA) receptor antagonists.

potent binding affinity at the Y₁ receptor. The two heterocycle replacements, squaric acid, and thiadiazole oxide, demonstrated good binding affinity although both were 10 times less active compared to parent urea.

Among more exotic surrogates, the 3,4-diamino thiadiazole dioxide moiety was proposed as a weakly acidic urea equivalent (Figure 15.38).¹⁷⁷ The similar thiatriazole dioxide is found in the H₂ antagonist tuvatinine (HUK 978). Other bioisosteres are exo–endo amidinic heterocycles bearing an electron-attracting function in the α position^{178,179} (Figure 15.38).

5. Bioisosteres of the phenol function

The optimal bioisosteres of the phenolic function should have approximately the same size of the hydroxyl itself and

should have approximately the same acidity range (weak acid) and be able to form hydrogen bonds.

The most popular surrogates for phenolic functions are NH groups rendered acidic through the presence of an electron-attracting group. In Figure 15.39 it is reported an application of this bioisostery in the design of *N*-methyl-D-aspartate (NMDA) receptor antagonists.¹⁸⁰ In this case, the replacement of the phenol by heterocyclic NH-containing rings was performed in order to slow metabolism and hence to improve oral bioavailability. Indeed the potent and NR1A/2B-receptor selective benzimidazolone analog was obtained demonstrating oral activity in a rodent model of Parkinson's disease at 10 and 30 mg/kg.

Using this analogy, Wu *et al.*¹⁸¹ prepared a series of phenolic bioisosteres of benzazepine D₁/D₅ antagonists (Figure 15.40).

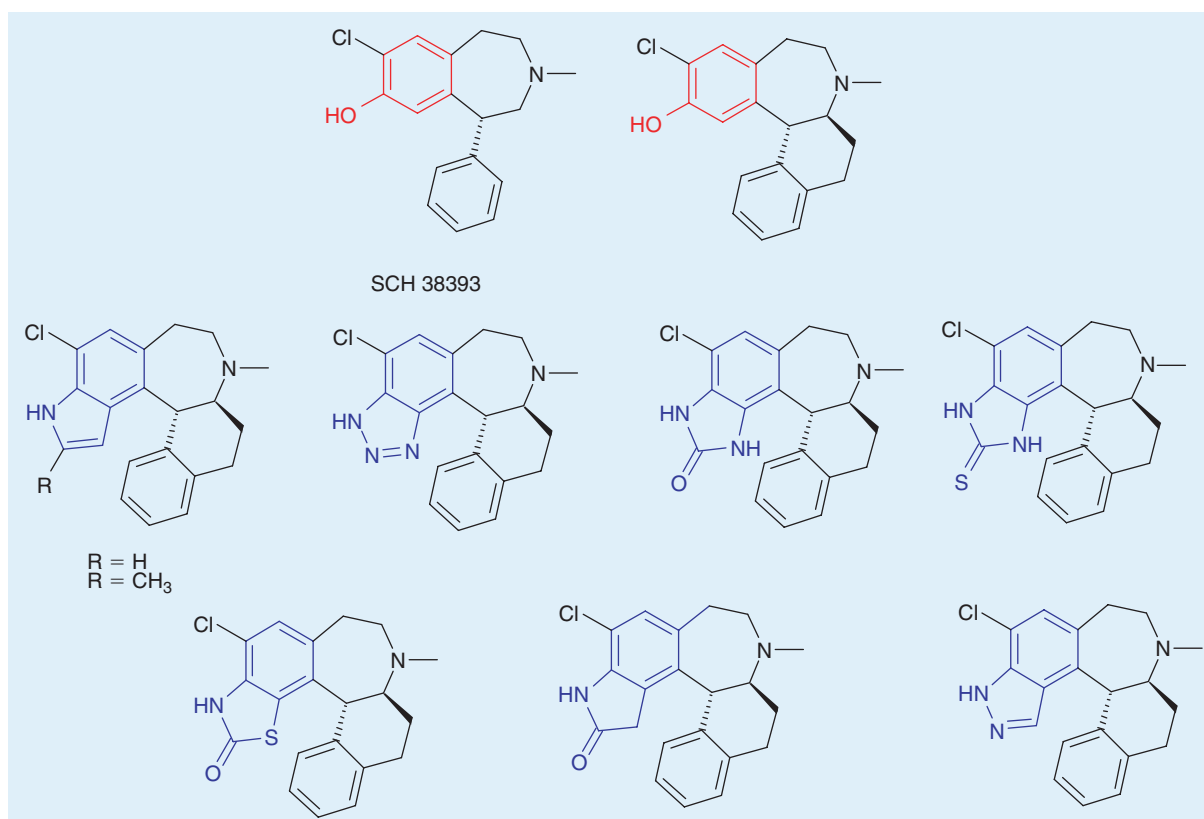


FIGURE 15.40 Phenol bioisosteres of benzazepine D₁/D₅ antagonists.

Compared to the reference compound SCH 38393 they exhibit similar or more potent activities, high selectivity over D₂–D₄ receptors and improved *in vivo* pharmacokinetics. The optimization of the hydrogen bond donating capacity of various heterocycles allowed the identification of several potent D₁/D₅ antagonists with high selectivity D₂–D₄, α_{2a} adrenergic receptors, and the 5-HT transporter keeping at the same time excellent pharmacokinetic profiles.

Other popular phenol bioisosteric substituents^{182,183} include methanesulfamide (CH₃SO₂NH—), hydroxymethyl (HOCH₂—) or hydroxyisopropyl (HOC(CH₃)₂—), various amide groups (—NHCHO, —NHCOCH₃, —NHCOC₆H₅, methanesulfamidomethyl (CH₃SO₂NHCH₂—), dimethylaminosulfonamide ((CH₃)₂NSO₂NH—), and others groups with an ionizable proton next to or near an aromatic ring.

Hacksell *et al.*¹⁸⁴ described the compound (±)-3-(1-propyl-3-piperidinyl)phenol [(±)-3-PPP] as highly selective for presynaptic brain DA receptors. However, the clinical potential of these molecules (Figure 15.41) as antischizophrenic or antiparkinsonian agents, may be limited by their relatively low oral bioavailability and their short duration of action.¹⁸⁵ Thus, a heterocyclic analog of 3-PPP might retain some of its pharmacological activity while having improved oral bioavailability and duration of action.¹⁸⁶ In the case of talipexole (B-HT 920) (Figure 15.41), a DA agonist which

has been reported to be selective for DA autoreceptor, 2-aminothiazolyl moiety was used as a replacement for the phenol ring.

This successful example led successively to the discovery of the PD 118440, a dopamine-autoreceptor agonist,¹⁸⁶ and pramipexole, a DA agonist with preference for the DA D₃ (over DA D₂) receptor.^{187–189}

6. Catechol bioisosteres

All the previous examples can be applied to the catechol family. Many of these bioisosteres share with the catechols the ability to chelate metal atoms and to form hydrogen-bonded second rings. In benzimidazole this H-bond ring is mimicked by way of a covalent ring structure (Figure 15.42).

A recent case described the synthesis of more stable bioisosteres of inhibitors of the insulin-like growth factor-1 receptor kinase (Figure 15.43). Based on the structure of AG 538¹⁹⁰ which contains two catechol rings and is sensitive to oxidation in cell, a new series of kinase inhibitors were developed. The catechol moiety was replaced by a benzoxazolone ring resistant to oxidation yielding two compounds GB19 and AGL2263 which maintain same potency as AG 538.

Until now, 2-aminothiazole derivatives or other aromatic heterocyclic systems have been used as a bioisosteric

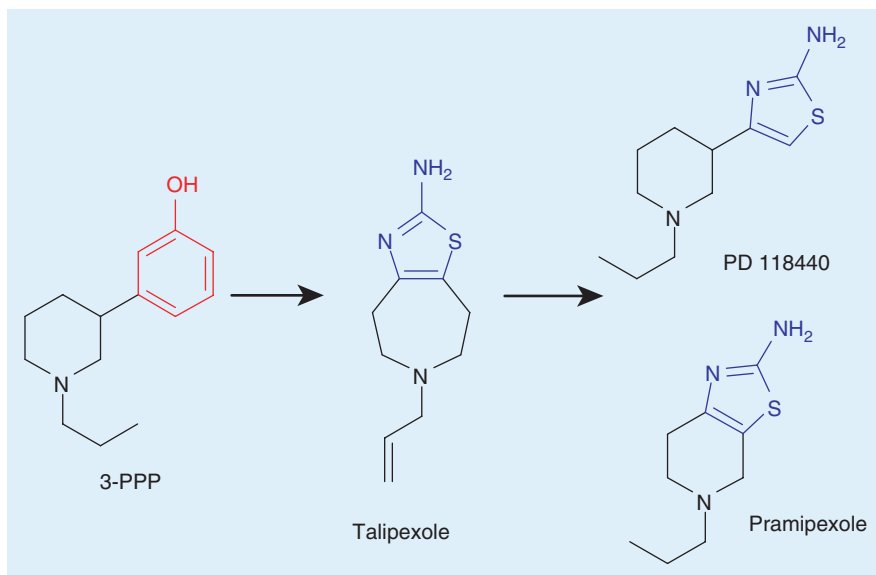


FIGURE 15.41 2-Aminothiazole bioisostery applied to the dopamine agonist 3-PPP.

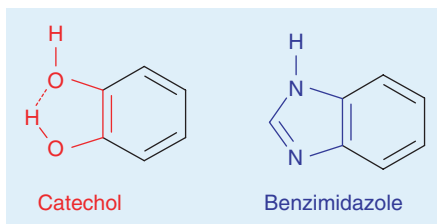


FIGURE 15.42 The bioisostery catechol/benzimidazole.

surrogate for the catechol nucleus (*cf.* studies around the pramipexole).¹⁸⁷ Hübner *et al.*^{191–193} evaluated non-aromatic catechol bioisosteres (Figure 15.44). They were able to demonstrate that the π -electronic system of the non-aromatic endiynes FAUC 88 and 73 can be used as an efficient bioisostere for the catechol fragment of dopamine. Combined with conformational rigidization, this approach led to dopamine-receptor agonists with high affinity for the subtypes of D_2 -family and especially for D_3 .

7. Sulfonamides bioisosters

The introduction of the 5-HT_{1D} receptor agonist sumatriptan for the acute treatment of migraine has marked an intense research effort to discover more potent and selective 5-HT_{1D} receptor agonists with improved pharmacokinetic profiles.¹⁹⁴ The H-bond acceptor ability of the 5-position is crucial for 5-HT_{1D} receptor affinity and selectivity as it was revealed by reference compounds (5-HT and sumatriptan). The search for other analogs with better bioavailability led to the replacement of the methyl sulfonamide with different heterocycles which are able to be H-bond acceptors. The amino-oxadiazole analog, L-695,894 (Figure 15.45), has a better oral bioavailability but lack of the good selectivity in fact it has a significant

affinity for 5-HT_{2A} and 5-HT_{2C} receptors.¹³⁵ Alternative five-membered heteroaromatic rings were explored to find analogs with $\log D_s < -0.5$ in order to minimize the central nervous system penetration.¹⁹⁴ Simple unsubstituted imidazoles, triazoles and tetrazoles (Table 15.16) have high affinity and good selectivity for the 5-HT_{1D} receptor. The 1,2,4-triazole 1, MK-462, was shown to have the optimal pharmacokinetic profile with rapid oral absorption and high bioavailability.

Using a different approach, Glen *et al.*¹⁹⁵ built a pharmacophore based on the pharmacological activities of a series of novel C- and N-linked hydantoin analogs. Their model was used as a framework for the design of a diverse series of analogs with good affinity and selectivity for 5-HT_{1D}. Suitable with the constraints required for good oral absorption, a potent selective 5-HT_{1D} agonist, S-5-methyl-2-oxazolidinone analog, has been described.

The dipolar azido group is a bioisostere¹⁹⁶ of the SO₂NH₂ and SO₂Me hydrogen bonding pharmacophores present in many selective COX-2 inhibitors and the azido analogs **14** and **15** are useful biochemical agents for photoaffinity labeling of the COX-2 enzyme (Figure 15.46).

F. Reversal of functional groups

The reversal of the peptidic functional groups is often used in peptide chemistry. The obtained *retropeptides* are generally more resistant to enzymatic attacks (Figure 15.33).^{146,197} For thiorphan and *retro*-thiorphan an identical binding mode to the zinc protease thermolysin was demonstrated.¹⁹⁸ Similar inhibition values for thermolysin and neutral endopeptidase were observed, whereas, for another zinc protease, angiotensin-converting enzyme (ACE), noticeable differences for inhibition were found (Figure 15.47).

Compounds	Name	IC ₅₀ Values [μ M]			
		IGF-1R	IR	SRC	PKB
	AG 538	0.06	0.12	2	76
	GB 19	0.37	0.6	1.5	21
	AGL 2263	0.43	0.4	2.2	55

FIGURE 15.43 Inhibition of IGF-1R and other kinases by AG 538 bioisosteres and analogs.

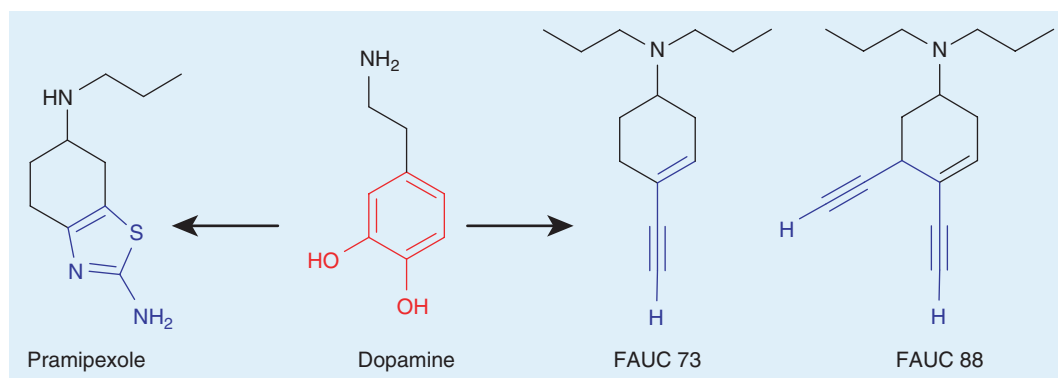


FIGURE 15.44 Aromatic and non-aromatic dopamine isosteres.

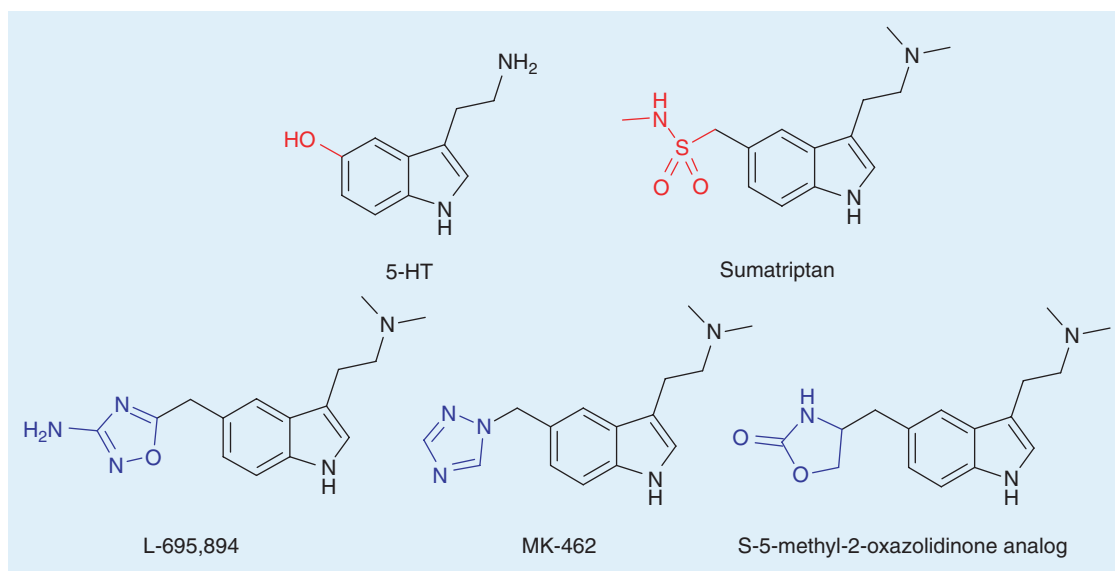
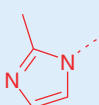


FIGURE 15.45 Replacement of the phenolic function of serotonin by various functions able to serve as H-bond acceptors.

TABLE 15.16 Displacement of [³H]-5-HT to 5-HT_{1D} Recognition Sites in Pig Caudate Membranes by N-Linked Imidazoles, Triazoles and Tetrazoles and Standard 5-HT_{1D} Agonists

Compound	Het	pIC ₅₀	log D ^a
5-HT		8.0	
Sumatriptan		7.7	-1.17
L-695,894		7.6	-0.67
1, MK-462		7.3	-0.74
2		7.5	-0.53
3		7.2	-0.74
4		7.3	-0.70
5		6.6	-0.20
6		7.4	-0.64
7		7.4	-0.34

^alog P measured at pH 7.4.

But the strategy of functional inversion can also be applied to non-peptidic compounds. A historical example is the change from orthoform to neo-orthoform (orthocaine; Figure 15.48). The unwanted side effects, often encountered with aromatic para-amino substituted compounds (“para effects,” essentially of allergic origin) are abolished in the meta amino isomer whereas the local anesthetic activity is

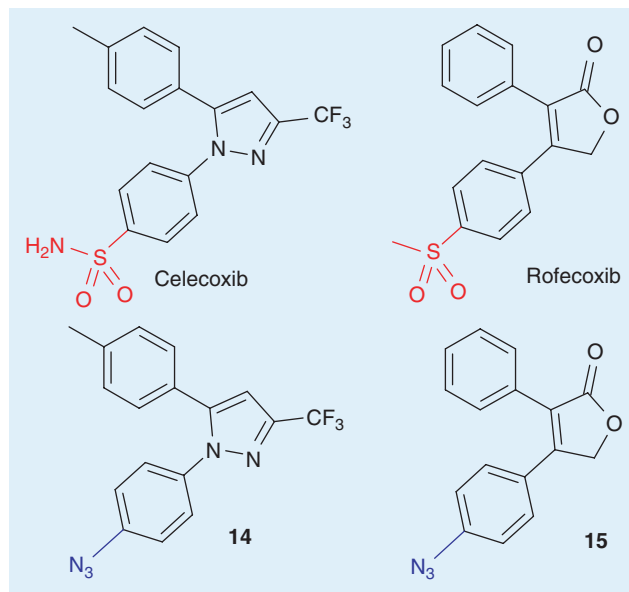


FIGURE 15.46 Selective COX-2 inhibitors and their azido bioisosteres.

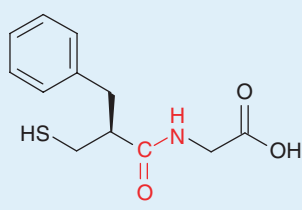
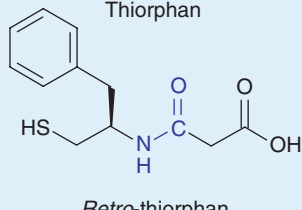
	Enzyme	K _i value in μM
 Thiorphan	NEP 24.11	0.0019
	Thermolysin	1.8
	ACE	0.14
	Enzyme	K _i value in μM
 Retro-thiorphan	NEP 24.11	0.0023
	Thermolysin	2.3
	ACE	>10

FIGURE 15.47 Inhibition values of thiorphan and *retro*-thiorphan for three zinc proteases.

maintained. Similarly the “meta” isomer of benoxinate has a local anesthetic activity identical to that benoxinate itself.¹⁹⁹

The β-blocking agent practolol which was one of the first cardioselective β-blocker, was rapidly replaced by its isomeric analog atenolol which presents less side effects (Figure 15.49).

The inversion of the ester function of *meperidine* leads to 1-methyl-4-phenyl-4-propionyloxy piperidine (Figure 15.50) which is five times more potent as an analgesic drug than meperidine and represents the model compound of the series of inverted esters.¹⁷

The change from indomethacin to clometacin, although representing a clean example of functional group reversal, causes more profound alterations than that shown in the

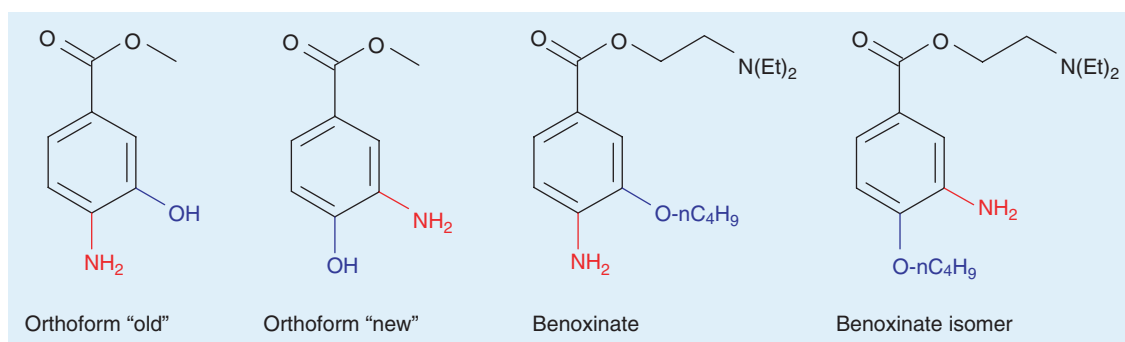


FIGURE 15.48 Positional isomers in local anesthetics.¹⁹⁹

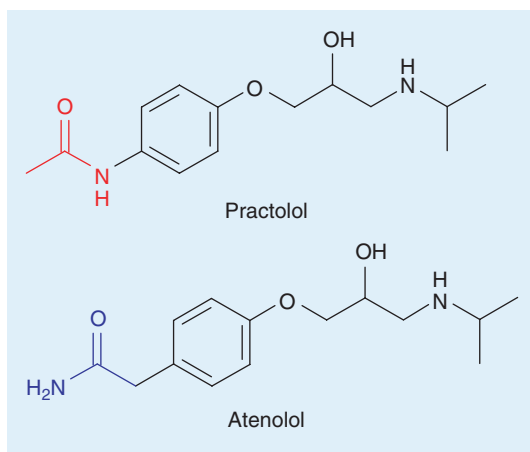


FIGURE 15.49 Reversal of functional groups in practolol yields atenolol.

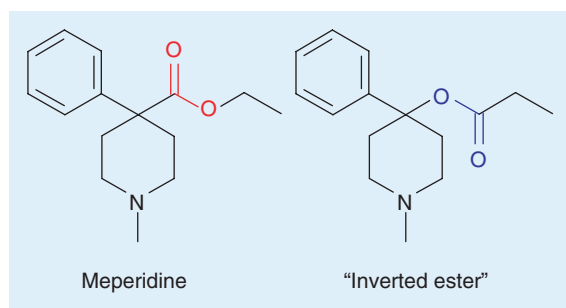


FIGURE 15.50 Meperidine and the corresponding inverted ester.¹⁷

previous examples (Figure 15.51). At a first glance, this change can even seem too drastic; however, in returning the molecule of clometacin by 180°, the resemblance with the parent molecule becomes evident.

Indomethacin is mainly used as a non-steroidal anti-inflammatory agent and occasionally as an analgesic; clometacin on the other hand is usually recommended as an analgesic and shows weak antiinflammatory properties. Applied to serotonin, a similar reversal of a functional moiety yielded 5HT_{2C} receptor selective agonists²⁰⁰ (Figure 15.52).

IV. SCAFFOLD HOPPING

Scaffold hopping is a useful technique used by medicinal chemists to discover structurally novel compounds starting from known active molecules by changing the molecular backbone of the template. Medicinal chemists have quite often the need of “jumping” in a different chemical space: new chemical entities offer the choice of easier chemical accessibility and so possibility of speeding up the lead optimization process. Switching to a different molecular backbone can help to avoid some undesirable ADME-tox properties. Scaffold hopping come to a rescue also to move from complex natural molecules to easier synthesizable small molecules. Moreover “jumping” in a new chemical series isofunctional with a given one is fundamental when new IP position is looked for.

A. Successful examples of serendipitous scaffold hopping

The concept of scaffold hopping relies upon the assumption that structurally and chemically distinct templates interact with the same receptor inducing equivalent biological activity. This seems to contradict the leading principle of the lead optimization process and drug design that is based on the concept that chemical similarity is reflected by similar biological activity. On the other hand this concept is not always true. In fact not always structural and chemical analogy predicts similar biological affinity as it is shown in Figure 15.53. In fact promethazine, imipramine, and chlorpromazine that are strictly similar from a structure point of view, interact with different receptors and present complete different therapeutic profiles acting respectively as H1 antagonist, uptake inhibitor and dopamine antagonist.

Indeed scaffold hopping can be interpreted as the broadest expansion of the bioisosterism concept. The idea of scaffold hopping is indeed not new, it is rather a new term to designate known experimental evidences. A retrospective analysis of the marketed drugs and/or of the ligands acting

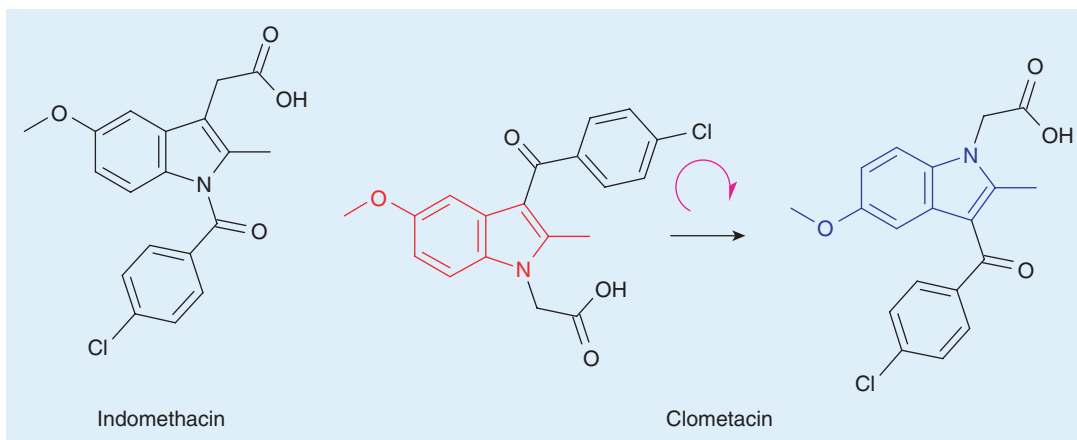


FIGURE 15.51 Functional inversion applied to indomethacin.

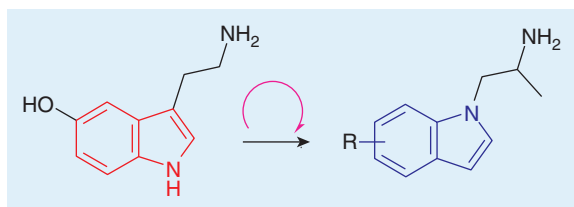


FIGURE 15.52 Serotonin analogs resulting from a functional reversal.²⁰⁰

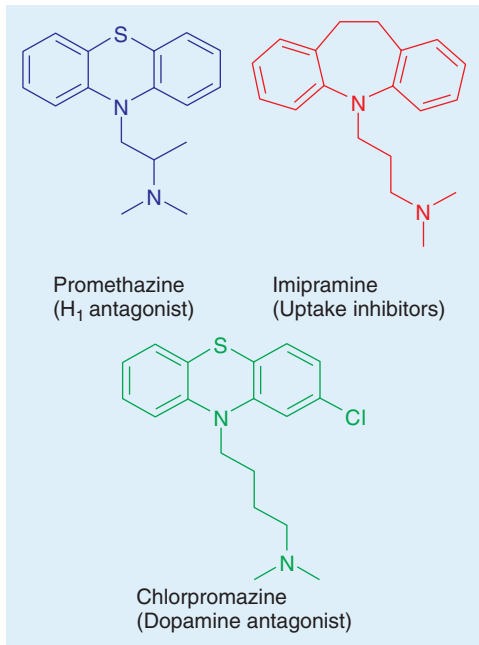


FIGURE 15.53 Structure and chemical similarity are not always synonymous of similar biologically active compounds.

on the same receptors brings up some interesting examples of structurally different molecules eliciting the same biological activity. A nice example is given by the non-steroidal anti-inflammatory drugs (NSAIDs) COX-2 inhibitors as illustrated

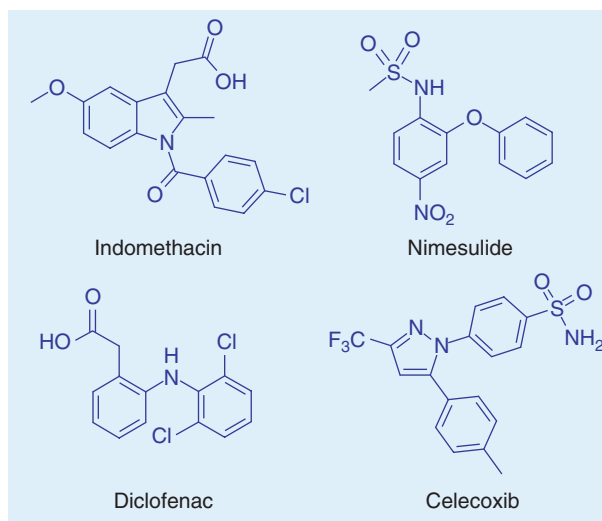


FIGURE 15.54 An example of scaffold hopping: four structurally different molecules have similar therapeutic properties by interacting with the same receptor.

in Figure 15.54 where there are reported four know traditional NSAIDs: indomethacin, nimesulide, diclofenac, and celecoxib.

Actually the GABA-A ligands at the benzodiazepine site give a nice picture of matching and mismatching of scaffold hopping and bioisosterism (Figure 15.55). Looking at diazepam, zolpidem, zopiclone, and zaleplon, a structural analogy is barely found. Despite this they are all GABA-A ligands acting as full agonists. The same can be said about the inverse agonists DMCM, **16**, **17**, FG 8094, and **18**: chemically different compounds have comparable biological activity. On the other hand similar compounds like FG 8094, Bretazenil, and Ro 15-1788, do not give the same biological response.

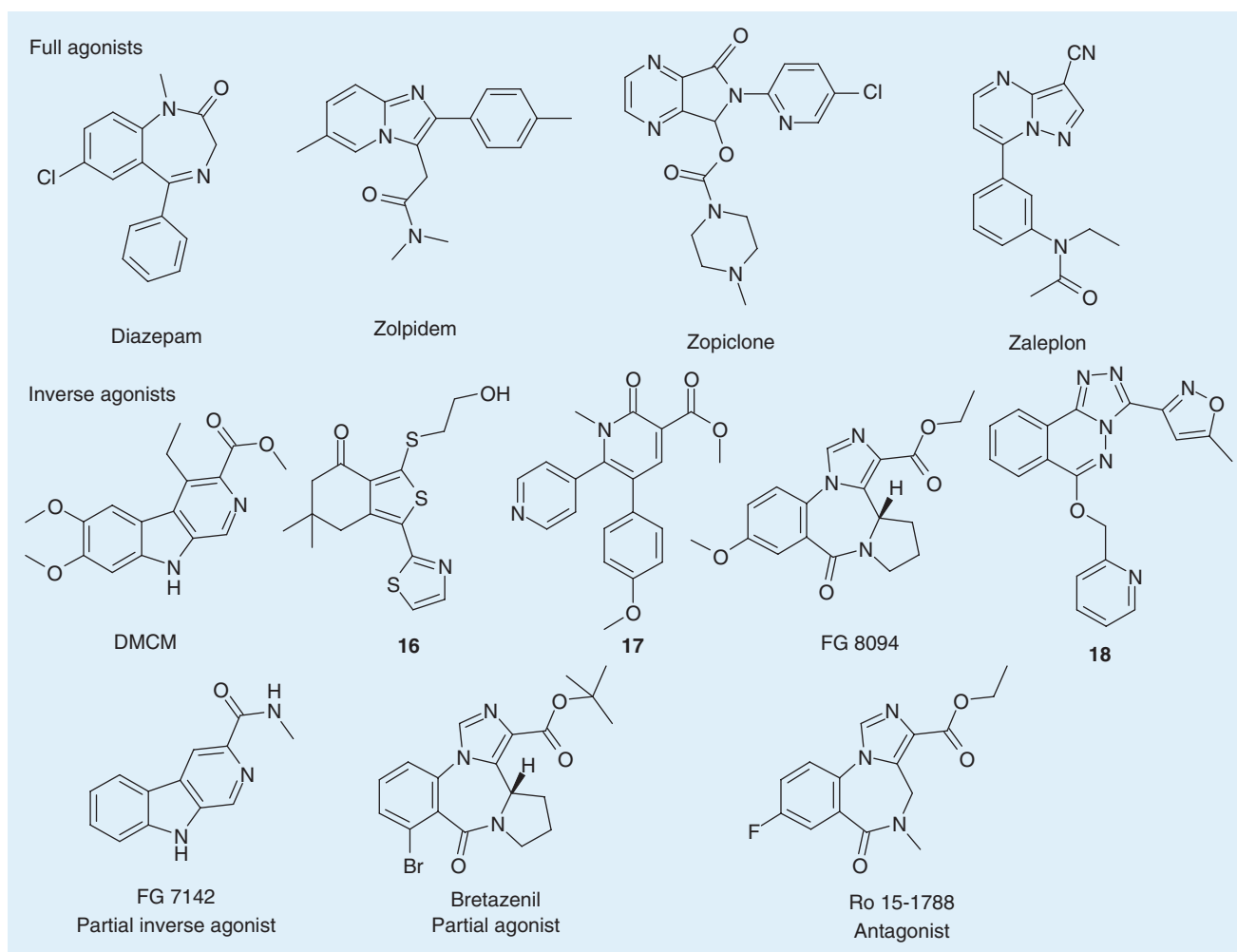


FIGURE 15.55 GABA-A ligands binding at benzodiazepine site.

B. Scaffold hopping and virtual screening

The examples cited in the above paragraph illustrated that similar biological activity can be obtained with structurally different molecules which seems to contradict the bioisosterism principle discussed in this chapter. The serendipitous examples of scaffold hopping described above have been generated either by high-throughput screening (HTS) either by selective optimization of side activity, the SOSA approach.²⁰¹ In other studies the “hopping” in a different molecular scaffold has relied upon the intuition and/or the experience of the medicinal chemist working on the project. Most of the virtual screening studies aiming to hop in iso-functional molecules are based on the bioisosterism concept that structural likeness predicts analogous biological activity. At a first glance it can be concluded that a rational approach to scaffold hopping is not possible. Indeed molecular modeling and chemoinformatics experts have set up a lot of softwares and methods to address the paradox of scaffold hopping and bioisosterism and find a logical process.^{202,203}

Among the virtual screening techniques reported so far four types of computational approaches for the scaffold hopping can be distinguished: (a) shape matching, (b) pharmacophore searching, (c) fragment replacement, and (d) similarity searching. Most of the programs offer combinations of several approaches and they are used, according to the case scenario of a given project, either as on a ligand-based virtual screening base either on a structure (receptor)-based screening. Other studies have reported a combination of the two methods to increase the performance of the virtual screening. In a case where more active ligands are known and no information are known about the receptor structure, it will be more useful to proceed through shape matching combined with a pharmacophore searching. Instead when the receptor structure is known, a virtual screening based on molecular docking is a powerful and successful technique. A detailed description of the computational approaches of scaffold hopping goes beyond the scope of this chapter and only few illustrative examples will be reported. In Figure 15.56 it is reported an example of scaffold hopping

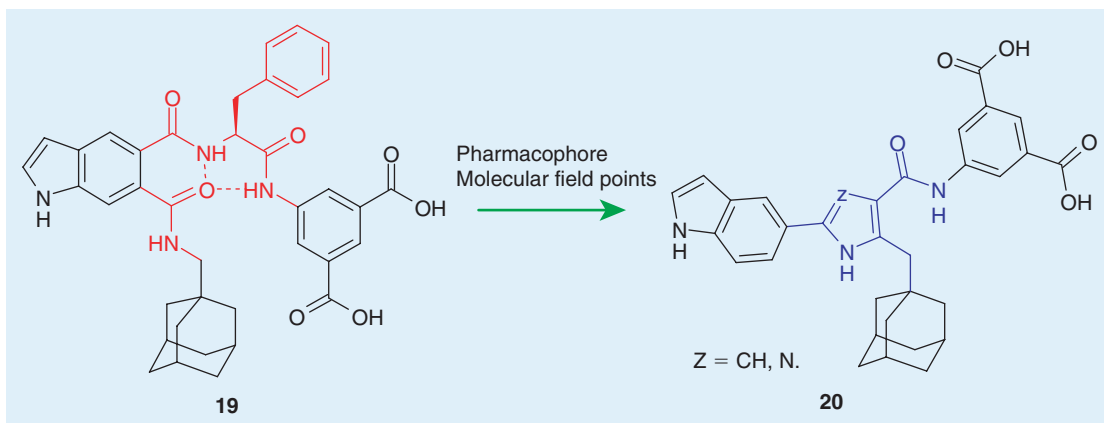


FIGURE 15.56 Design of a novel CCK₂ antagonist via a scaffold hopping approach from a known series of indoles.

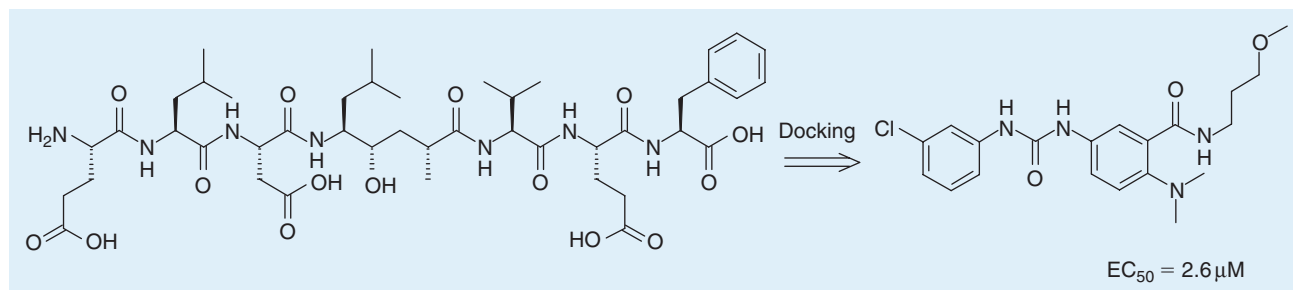


FIGURE 15.57 Discovery of non-peptide inhibitor of β -secretase by high-throughput docking.

related to the design of a novel cholecystokinin-2 (CCK₂) antagonist.²⁰⁴ Starting from a known series of indoles (**19**) with high *in vitro* affinity and selectivity but poor bioavailability, a CCK₂ pharmacophore receptor has been identified and used to design new scaffolds to overcome the problems associated with the high level of biliary elimination of the compound **19**. Two new series of pyrroles and imidazoles (**20**) were identified and, although they are not as potent as the original indole derivative *in vitro*, they have greater potential as drug candidates because of their reduced tendency to biliary excretion.

Scaffold hopping is an extremely useful technique to switch from peptide ligands to small molecule ligands. A fragment-based docking procedure followed by substructure search were used to identify a set of small molecules as β -secretase inhibitors.²⁰⁵ In Figure 15.57 is reported one of a ligand identified with the virtual screening that may serve as starting point for further optimization for Alzheimer disease.

Most of the studies based on virtual screening use a hierarchical approach combining several conceptually different techniques.²⁰⁶ The most common combination used is a 3D pharmacophore modeling followed by a docking study. In Figure 15.58 is reported an illustrative example of this combined use: a set of 10 known inhibitors of Human Rhinovirus Coat protein was used to design a 3D pharmacophore

that was subsequently used for a docking study of the Maybridge DB.²⁰⁶

A set of 10 compounds was retrieved according to the score fit of the molecules. The 10 molecules were tested *in vitro* and all of them displayed antirhinoviral activity in the micromolar range. Particularly promising results were achieved with the compound reported in Figure 15.58 which shows an EC₅₀ of 4.3 μ M.

V. ANALYSIS OF THE MODIFICATIONS RESULTING FROM ISOSTERISM

It is rare that the replacement of a part of a molecule by an isosteric or bioisosteric group leads to a *strictly identical* active principle. In practice that is even not sought, and one prefers that the new compound produces a change as compared to the parent molecule. In general the isosteric replacement, even though it represents a subtle structural change, results in a modified profile: some properties of the parent molecule will remain unaltered, others will be changed. Bioisosterism will be productive if it increases the potency, the selectivity and the bioavailability or decreases the toxicity and undesirable effects of the compound. In proceeding to isosteric modifications one will focus *predominantly* on a given parameter: structural, electronic,

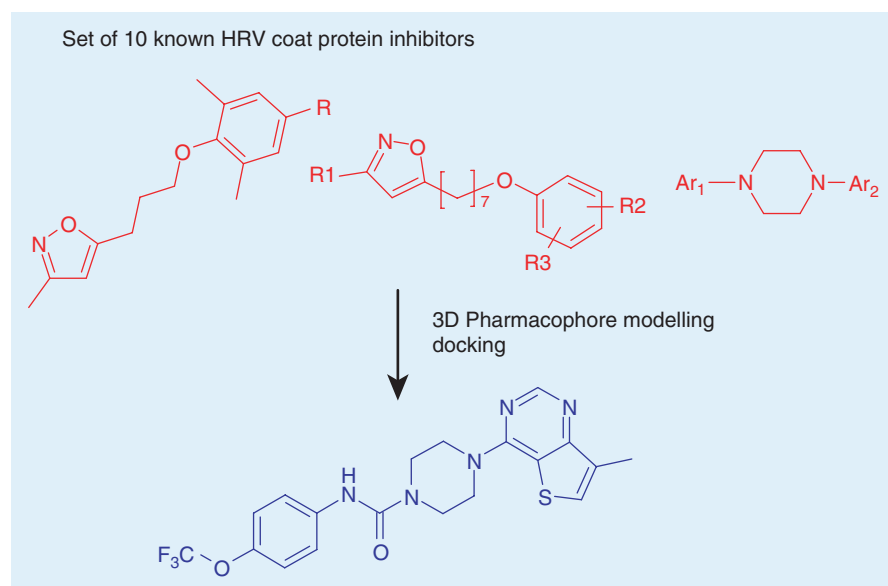


FIGURE 15.58 A set of 10 known HRV coat protein inhibitors was used for 3D pharmacophore modeling followed by docking study afforded new candidate structure suitable for an optimization process.

hydrophilic, but it is all but impossible not to alter simultaneously several parameters simultaneously.

A. Structural parameters

These will be important when the portion of the molecule involved in the isosteric change serves to maintain other functions in a particular geometry. That is the case for tricyclic psychotropic drugs (Figure 15.59).

In the two antidepressants (imipramine and maprotiline), the bioisosterism is geometrical insofar that the dihedral angle α formed by the two benzo rings is comparable: $\alpha = 65^\circ$ for the dibenzazepine and $\alpha = 55^\circ$ for the dibenzocycloheptadiene.²⁰⁷ This same angle is only 25° for the neuroleptic phenothiazines and the thioxanthenes. In these examples the part of the molecule modified by isosterism is not involved in the interaction with the receptor. It serves only to position correctly the other elements of the molecule.

The structure of various bioisosteric retinoic acid receptor agonists highlights the dominantly geometric parameter of this bioisostery (Figure 15.60).²⁰⁸

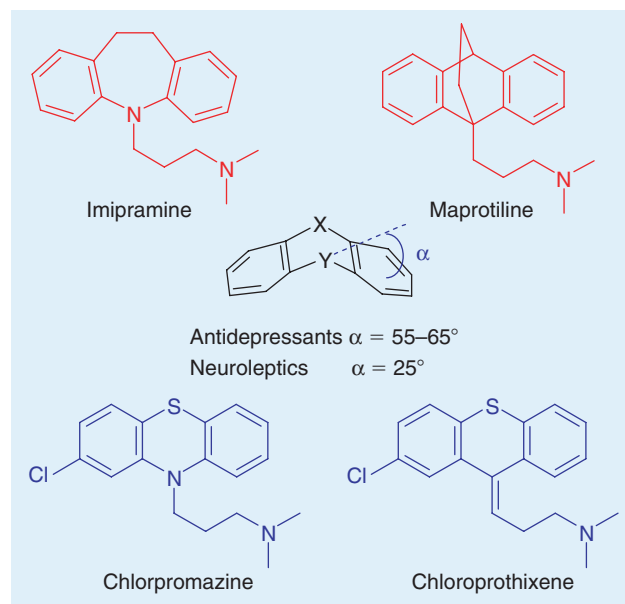


FIGURE 15.59 The tricyclic antidepressants (imipramine and maprotiline) are characterized by an dihedral angle of 55° to 65° between the two benzo rings, this angle is only 25° for the tricyclic neuroleptics (chlorpromazine, chlorprothixene).²⁰⁷

B. Electronic parameters

Electronic parameters govern the nature and the quality of ligand–receptor or ligand–enzyme interactions. The relevant parameters will be inductive or mesomeric effects, polarizability, pK_a , capacity to form hydrogen bonds, etc. Despite their very different substituents in the *meta* position, the two epinephrine analogs (Figure 15.61) exert comparable biological effects: they are both β -adrenergic agonists. In fact the key parameter resides in the very close pK_a values.¹⁹⁷

C. Solubility parameters

When the functional group involved in the isosteric change plays a role in the absorption, the distribution or the excretion of the active molecule, the hydrophilic–lipophilic parameters become important.

Imagine in an active molecule the replacement of $-\text{CF}_3$ ($\pi = +0.88$) by $-\text{CN}$ ($\pi = -0.57$) (Figure 15.62). The electron-attracting effect of the two groups will be comparable, but the molecule with the cyano function will be

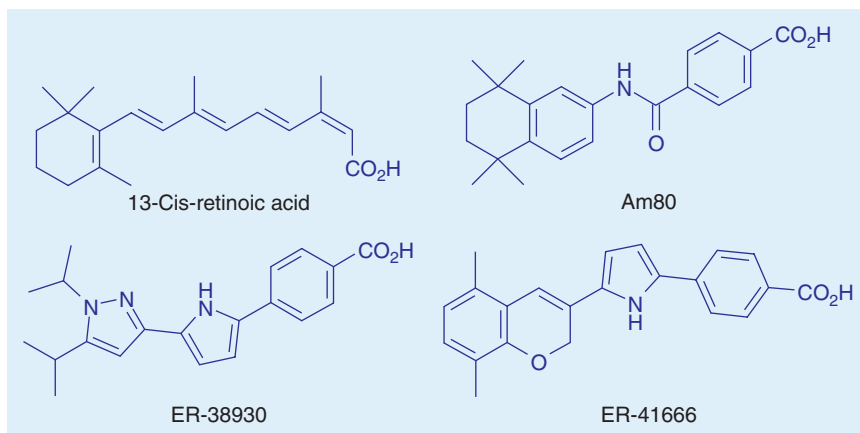


FIGURE 15.60 Bioisostery in its broadest sense.

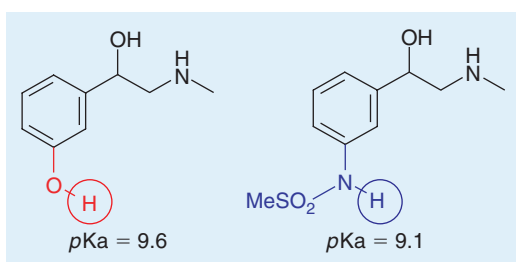


FIGURE 15.61 An example of bioisosterism, or non-classical isosterism, the methylsulfonamide substituent has comparable acidity to the phenolic hydroxyl group.¹⁹⁷

clearly more hydrophilic. This loss in lipophilicity can then be corrected in attaching elsewhere on the molecule a propyl, isopropyl, or cyclopropyl group.

D. Anomalies in isosterism

In this paragraph two applications of the bioisosterism concept that imply unusual behaviors of commonly encountered atoms or groups are discussed.

1. Fluorine–hydrogen isosterism

There is an anomaly residing in the fact that fluorine does not resemble other halogens, notably chlorine, and that, on the other hand, it often mimics an atom of hydrogen.²⁰⁹

1. *Steric aspects:* The fluorine atom is considerably smaller than the rest of the halogen atoms. Seen from the steric point of view it resembles more hydrogen than chlorine (Table 15.17). Effectively fluoro-derivatives differ from the other halogenated derivatives because fluorine forms with carbon particularly stable bonds and, in contrast to other halogens, is only rarely ionized or displaced. Because it is both chemically inert and of small size organic fluorine is often compared to hydrogen.

One understands especially the incorporation by living organisms of fluoroacetic acid in place of acetic²¹⁰ acid or of 5-fluoro-nicotinic acid and 5-fluoro-uracil as antimetabolites. This “fraudulent” incorporation leads to lethal syntheses.²¹¹ This is generally not the case with the corresponding chlorinated, brominated, or iodinated analogs.

2. *Electronic aspects:* Fluorine is the most electronegative of the halogens (Table 15.17) and forms particularly stable bonds with carbon atoms. This chemical inertia explains why fluoro-derivatives are more resistant to metabolic degradation (Figure 15.63). Thus for the β -haloalkylamines (nitrogen mustards), the alkylating activity is lost when chlorine or bromine are replaced by fluorine or by hydrogen.²¹²

The isosterism between H and F will therefore often serve to give analogs that are more resistant to metabolic degradation (obstructive halogenation: flunarizine and in flufenisal; Figure 15.63). Similarly the CF_3 group is biostable whereas CH_3 is easily oxidized.²⁰⁹

3. *Absence of d orbitals:* Another difference between fluorine and the other halogens comes from the absence of a d orbital for fluorine, and thus its incapacity to participate in resonance effects with a donor of π electrons (Figure 15.64).

This explains among why *para*-fluorophenol is slightly less acidic than phenol while for other *para*-halogenated phenols the acidity changes in parallel with the atomic number (Table 15.18²⁰⁹).

4. *Case study:* A good example of continuous variation of activity in halogenated compounds is provided by a series of antihistaminic drugs related to tripeleminamine (Figure 15.65, X = H).

Apparently we are dealing here with a classical isosteric series: F, Cl, Br, I, but sensitive to steric hindrance in the *para* position. Probably what happens *in vivo*, is *para*-hydroxylation of the benzene ring. The best candidate becomes then the *para*-fluoro compound, since it is not bulkier than the unsubstituted compound while being biostable.

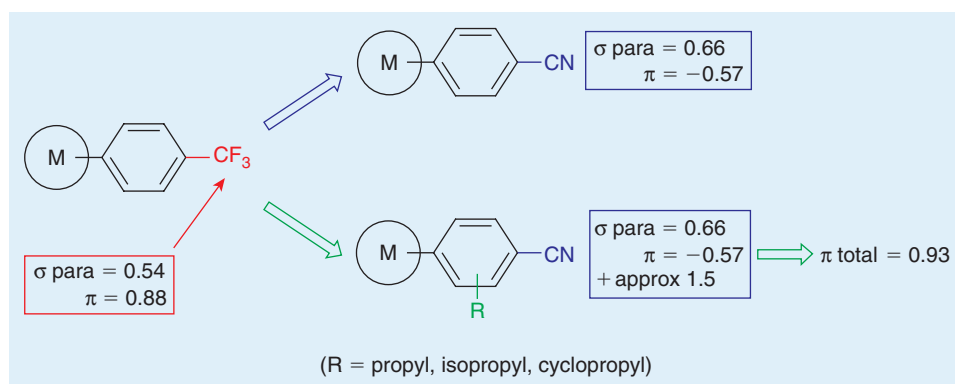


FIGURE 15.62 The loss in lipophilicity resulting from the bioisosteric exchange of a CF_3 for a CN has to be compensated by the equivalent of a three carbon residue.

TABLE 15.17 Fluorine–Hydrogen Isosterism. Observe the Comparable Sizes of the Two Atoms, whereas Chlorine is Close to the Methyl and Trifluoromethyl

Parameter	H	F	Cl	CH_3	CF_3
Atomic radius	0.29	0.64	0.99	–	–
Van der Waals radius	1.2	1.35	1.80	<2	<2
Molecular refractivity	1.03	0.92	6.03	5.65	5.02
Electronic effect (<i>para</i> σ) ^a	0.00	0.06	0.23	–0.17	0.54
Resonance effect (R) ^a	0.00	–0.34	–0.15	–0.13	0.19
Electronic effect (σ^*) ^b	–	3.08	2.68	0.00	2.85

^aFor aromatic systems.

^bfor aliphatic systems.

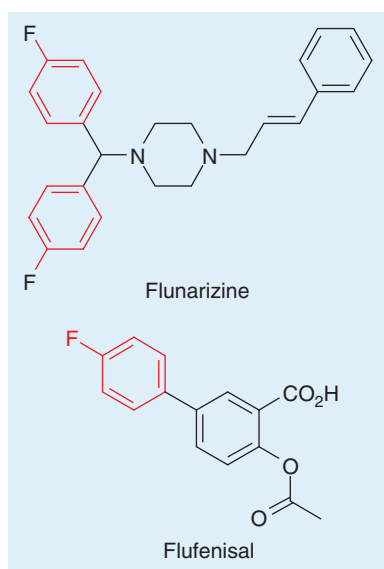


FIGURE 15.63 In flunarizine and in flufenisal fluorine atoms in para position prevent metabolic hydroxylation.

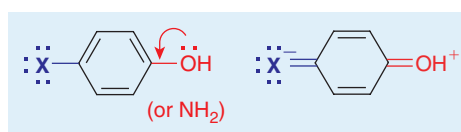


FIGURE 15.64 The resonance between the OH lone pair and the X group is not possible if $\text{X} = \text{F}$.

2. Exchange of ether oxygen and methylene group

Ether oxygen atoms and methylene groups possess a similar tetrahedral structure and should normally be isosteric. In fact the isosterism between O and CH_2 yields very often anomalous results and brought Friedman²¹⁴ to the interesting observation “that the omission of the ether oxygen changes biological activity much less in some cases than the replacement by the isosteric methylene group” (Figure 15.66). In the meperidine series, for example, the change from the *N*-phenoxypropyl derivative to the isosteric phenoxybutyl decreases the analgesic potency by

a factor of ten, whereas the omission of the ether oxygen yields a slightly more potent compound.¹⁷ A list of seven other examples is given by Schatz in the second edition of Burger's Medicinal Chemistry.²¹⁵

The explanation for this anomalous behavior may be that the omission of the ether oxygen yields a closer

compound in terms of lipophilicity than its replacement by a methylene. An example which can be compared to Friedman's paradox is found in the resemblance of the phenylethyl type β -blockers (e.g. dichloroisoprenaline, sotalol) with the phenoxypropanol type (e.g. practolol, acebutolol).

TABLE 15.18 Dissociation Constants of *p*-Halogenated Phenols²⁰⁹

Compound	Dissociation constant $K_a \times 10^{-10}$
Phenol	0.32
<i>p</i> -Fluorophenol	0.26
<i>p</i> -Chlorophenol	1.32
<i>p</i> -Bromophenol	1.55
<i>p</i> -Iodophenol	2.19

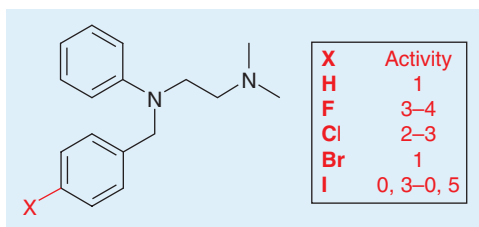


FIGURE 15.65 Variation of activity in a series of antihistaminic compounds as a function of the halogenated para-substituent.²¹³

VI. MINOR METALLOIDS-TOXIC ISOSTERS

In this section we describe some "exotic" applications of the bioisostery concept implying the utilization of unusual elements such as silicon, boron, selenium, arsenic, and antimony. The use of those elements as bioisosteres of carbon in existing drugs is a different approach enabling the introduction of a new drug-like chemical space into the drug discovery and development process.

A. Carbon-silicon bioisosterism

Silicon is directly below carbon in the periodic table so, according to the Erlenmeyer's expansion of the isosterism concept, carbon and silicon can be considered as true isosters. Sila-substitution (C/Si exchange) of biologically active substances is an approach to search for new drug-like candidates with improved pharmacological properties and stronger IP position. The application of this isosterism remains however limited. For reviews on the subject, see Fessenden and Fessenden,²¹⁶ Tacke and Zilch,^{217,218} Ricci *et al.*,²¹⁹ and Showell and Mills.²²⁰

Silicon is more electropositive than carbon (and even more if compared to oxygen and nitrogen) and the covalent silicon-carbon bonds in the sp^3 hybridization state, are

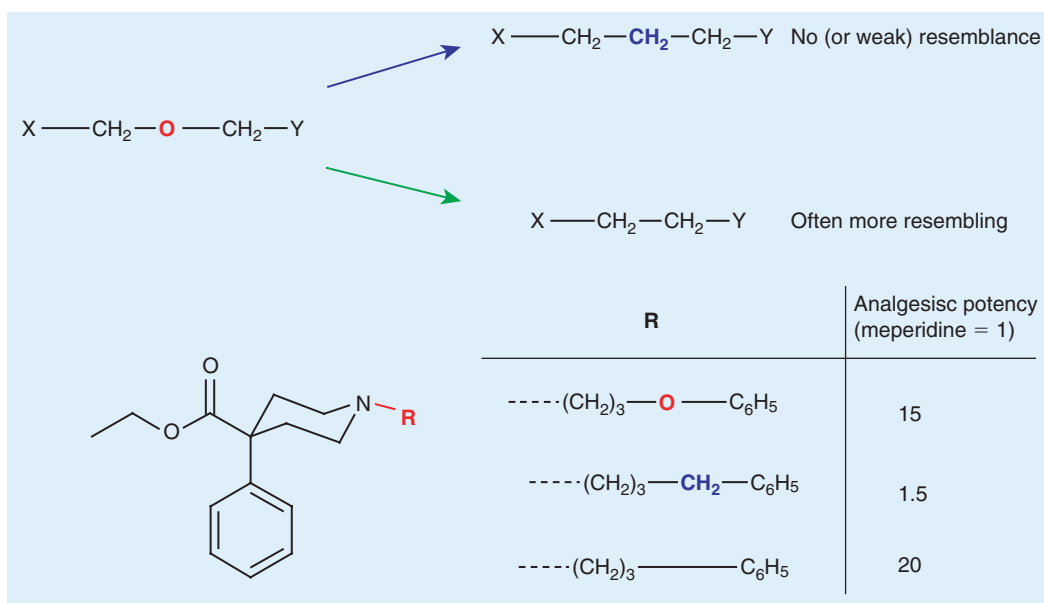


FIGURE 15.66 Friedman's ether oxygen-methylene group paradox.²

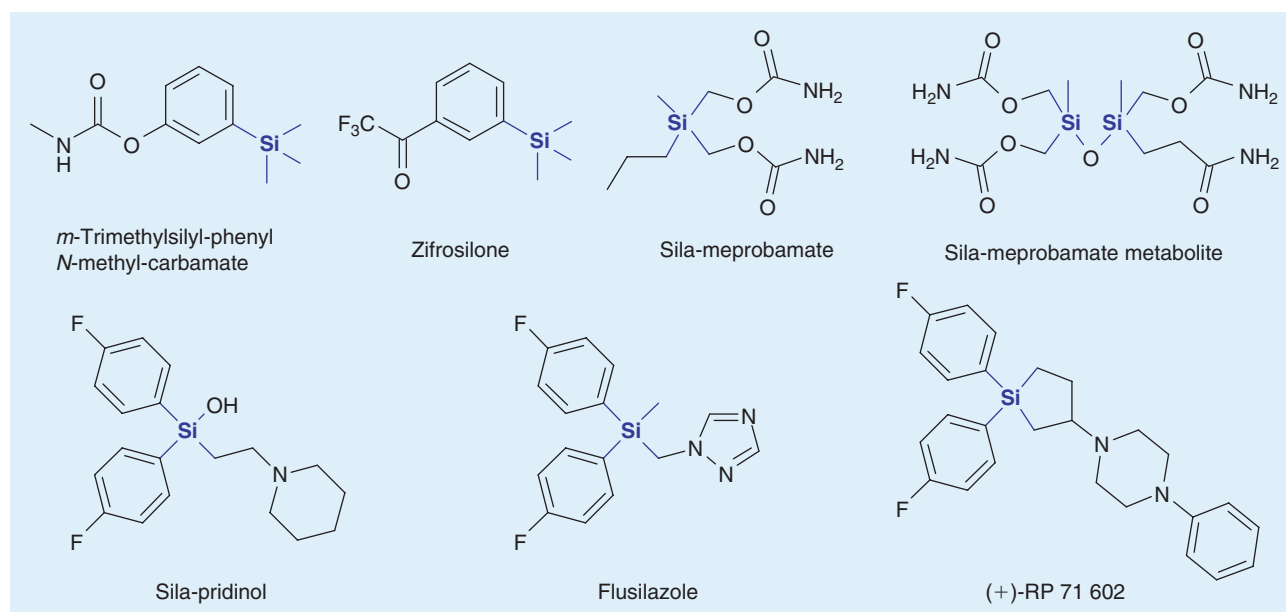


FIGURE 15.67 Organosilicon active substances.

20% longer than the corresponding carbon–carbon bond. This difference is reflected on the properties of the sila-isosters compared to the corresponding carbon analogs. For example acidity, the hydrogen bond strength of the silanol is more favorable as a donor than that of carbinol. In this respect the silanol isosters may be beneficial in those pharmacophores where the H-bonding has a predominant role. From a lipophilicity point of view the silicon-containing analogs are more lipophilic than their carbon analogs and when an increase in lipophilicity is sought this stragem could be used. The C = O double bond of a ketone is quite stable, whereas the formation of a Si = O double bond is disfavored over its hydrate form, the silicon diol. The chemistry of silicon relies mainly on the chemistry of single bonds which have led to its appropriate use as a tetrahedral bioisostere of carbon. In Figure 15.67 are reported some of examples of the sila-substitution of existing drugs. Among these, *m*-trimethylsilyl-phenyl *N*-methylcarbamate and *m*-trimethylsilyl- α -trifluoroacetophenone (zifrosilone) are acetylcholinesterase inhibitors^{221–223}, sila-meprobamate is a CNS depressant²²⁴ sila-pridinol is an anticholinergic²²⁵, flusilazole is a fungicide for agricultural use²²⁶, and (+)-RP 71,602 is a potent and selective 5-HT_{2A} antagonist.²²⁷

A silicon-containing hypocholesterolemic squalene epoxidase inhibitor,^{228,229} the silicon analog of the α_2 -adren-ergic antagonist atipamezole,²³⁰ a highly potent, stable and CNS-penetrating silatecan²³¹ some ACE inhibitors²³², a HIV protease inhibitors²³³, the (*R*)-sila-analog of the antidepressant venlafaxine²³⁴, and a trimethylsilylpyrazole as novel inhibitor of p38 MAP kinase²³⁵ (mitogen-activating protein) were published (Figure 15.68). As for the preceding molecules, the silicon atom of these compounds is quaternary and

thus expected to be less sensitive to metabolic degradation (Figure 15.68).

Compared to their carbon bioisosteres, silicon-containing molecules are more sensitive to hydrolysis and to nucleophilic attack in general, even when located in the center of a quaternary structure, the risk exists that the silicon atom will be attacked. Thus, 1-chloro-1-sila-bicyclo-(2,2,1)-heptane can still be hydrolyzed by an attack on the vacant d orbital;²³⁶ this attack is *lateral* and therefore possible even in the cases where the corresponding carbon derivative would have been inert toward a S_N2 reaction (Figure 15.69).

This sensitivity toward lateral attacks explains the four times shorter duration of action of sila-meprobamate compared to its carbon isostere on a model of tranquillizing activity in mice (rotarod test, potentiation of hexobarbital-induced sleep, and intraperitoneal injection).²²⁴ On the other hand, when given orally, sila-meprobamate is practically inactive. One of the first metabolites formed has been characterized as being a di-siloxane²¹⁶ (Figure 15.67). For the two phenyl-trimethylsilyl-derived AChE inhibitors, the rather positively charged trimethyl-silyl group mimics the trimethyl-ammonium function present in acetylcholine. For these compound metabolic oxidation does not take place on the silicon, but on one of methyl groups (Si-CH₃ → Si-CH₂-OH).²²¹

B. Carbon–boron isosterism

Boron is essential for plant growth and development. In medicinal chemistry its main use is related to that of coupling reagent. The most important employment of boron as drug relies upon the treatment of certain tumors by Boron Neutron

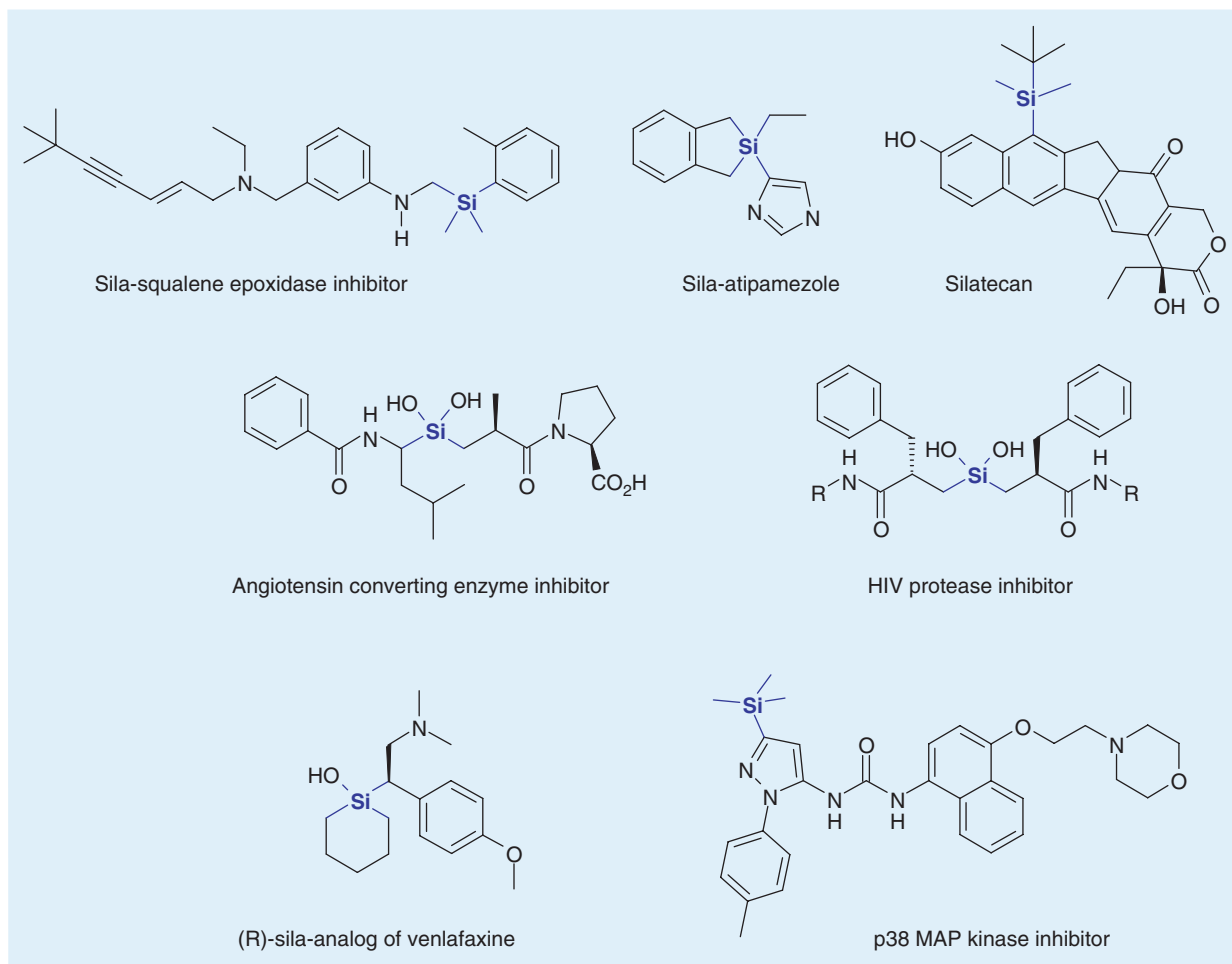


FIGURE 15.68 Structures of silicon-containing compounds which are biologically active.

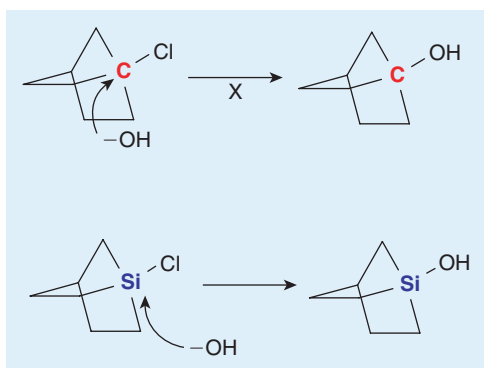


FIGURE 15.69 Due to the presence of a vacant d orbital, a lateral attack can substitute for dorsal attacks in organo-silicon derivatives.²³⁶

Capture Therapy (BNCT).^{237–239} BNCT is a binary treatment modality that can selectively irradiate tumor tissue. The delivery to the tumor cells of a drug containing the ^{10}B isotope followed by a low energy irradiation (neutrons) causes the ^{10}B to split, releasing an alpha particle a lithium nucleus.

These products of the $^{10}\text{B}(\text{n},\alpha)^7\text{Li}$ reaction are very damaging to cells but have a combined path length in tissue of approximately $14\mu\text{m}$, or roughly the diameter of two cells. Thus, most of the ionizing energy imparted to tissue is localized to ^{10}B -loaded cells. The problem here is to insure a sufficient concentration of the product in the tumor being treated.

Few medicines based on boron are known, in general boric acid or a boronic acid serve to esterify an α -diol or an ortho-diphenol. This is the case for the emetic antimony borotartrates of the ancient pharmacopoeias, for the injectable catecholamine solutions, for tolboxane²⁴⁰, that is close to meprobamate and that was commercially available as a tranquillizer some decades ago, or also for the phenylboronic esters of chloramphenicol.²⁴¹ Boromycine was the first natural product containing boron isolated.²⁴² It is a complex between boric acid and a polyhydroxylated tetradentate macrocycle.²⁴³ Another natural product is aplasmomycin with antibiotic properties.²⁴⁴

Some of the boron-containing molecules biologically active are reported in Figure 15.70. Some boronic analogs of amino acids were prepared as chymotrypsin and elastase

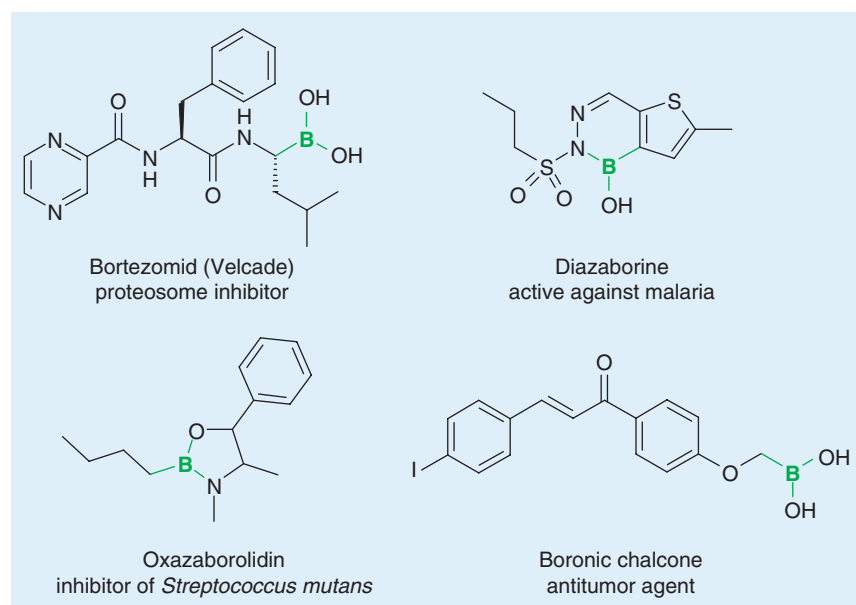


FIGURE 15.70 Boron-containing molecules with a biological activity.

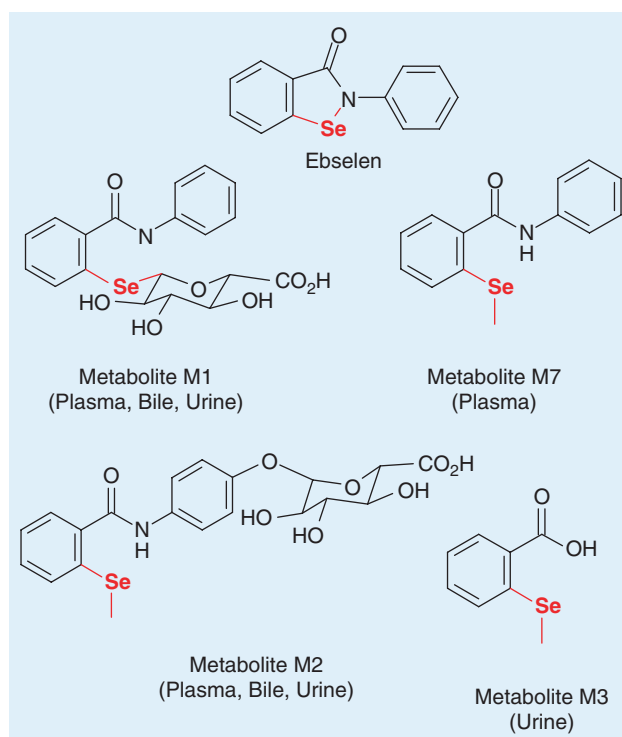


FIGURE 15.71 Ebselen and its main metabolites.²⁵⁶

inhibitors,²⁴⁵ and more recently as antineoplastic agent (Velcade, a proteasome inhibitor reported in Figure 15.70).²⁴⁶ Carboxyboranes complexed with a tertiary amine ($R_3N.H_2B-COOH$) are considered as boron amino acid isosteres due to the isoelectronic features. Compounds-containing carboxy boranes have shown anticancer, hypolipidemic, and antifungal activity.²⁴⁷ Diazaborines are active against malaria,²⁴⁸ and oxazaborolidines possess antibacterial activity

(Figure 15.70).²⁴⁹ Boronic chalcones are reported to be anti-tumor agents (Figure 15.70).²⁵⁰

Organoboron derivatives, even more than organosilicon compounds, are sensitive to hydrolytic degradation that always leads to the final formation of boric acid. But boric acid has teratogenic properties in chickens. It produces the same malformations as those produced by a riboflavin (vitamin B₂) deficiency and the administration of riboflavin prevents these toxic effects.^{251,252} The mechanism by which boric acid produces a deficiency in riboflavin is not known. In man the chronic utilization of boron derivatives results in cases of borism (dry skin, cutaneous eruptions, and gastric troubles).²⁵³

C. Bioisosteres involving selenium

Selenium can be considered the best isoster of sulfur as it is just below it in the periodic table. These two atoms have very similar physical properties: the radius of selenium is only 12.5% bigger than that of sulfur, and their electronegativity is rather similar.

Selenium and its derivatives are highly toxic and with the exception of ⁷⁵Se derivatives which serve diagnostic purposes (e.g. ⁷⁵Se-selenomethionine, used as a radioactive imaging agent in pancreatic scanning), there is no chemically defined seleno-organic drug on the market. Klayman reviewed a large number of selenium derivatives as chemotherapeutic agents in 1973.²⁵⁴ Selenium bioisosteres of sulfur compounds are mainly used as research tools (e.g. bis [2-chloroethyl] selenide as selenium bioisostere of the classical sulfur mustards²⁵⁵). Selenocysteine is present in the catalytic site of mammalian glutathione-peroxidase and this explains the importance of selenium as an essential trace element.

The only selenium-containing drug candidate is *ebesen* (Figure 15.71) which owes its antioxidant and antiinflammatory properties to its interference with the selenoenzyme glutathione-peroxidase.²⁵⁷ Because of its strongly bound selenium moiety only metabolites of low toxicity are formed.²⁵⁶

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