Introduction

Bioactive Heterocyclic Compound Classes: Agrochemicals,
First Edition. Edited by Clemens Lamberth and Jürgen Dinges.

1
The Significance of Heterocycles for Pharmaceuticals and Agrochemicals*

Clemens Lamberth and Jürgen Dinges

1.1
Introduction

Heterocycles, their preparation, transformation, and properties, are undoubtedly a cornerstone of organic chemistry. Several books not only on heterocyclic chemistry [1–6] but also on some special aspects, such as heterocyclic name reactions [7], heterocyclic palladium-catalyzed reactions [8], heterocyclic carbene complexes [9], and fluorinated heterocycles [10], have been published recently.

Approximately more than 70% of all pharmaceuticals and agrochemicals bear at least one heterocyclic ring. In addition, some of the biggest commercial products to date, such as the blockbuster blood cholesterol reducer atorvastatin (Lipitor®, **1**) [11] for the treatment of dyslipidemia and the prevention of cardiovascular diseases and the broad-spectrum fungicide azoxystrobin (Amistar®, **2**) [12], currently applied against diseases of more than 100 different crops in more than 100 different countries, belong to this huge heterocyclic group of active ingredients (Figure 1.1).

There are two major reasons for the tremendous value of heterocycles for the lead optimization of pharmaceuticals and agrochemicals. The heterocyclic scaffold of a drug often has a positive impact on its synthetic accessibility and its physicochemical properties, driving these values of lipophilicity and solubility toward the optimal balanced range regarding uptake and bioavailability. Furthermore, heterocycles seem to be perfect bioisosteres of other iso- or heterocyclic rings as well as of several different functional groups, in most cases, delivering through their similarity in structural shape and electronic distribution equal or even better biological efficacy [13].

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* Identically published in both volumes of ''Bioactive Heterocyclic Compound Classes'', as different roles of heterocycles in pharmaceuticals and agrochemicals are explained in this introductory chapter.

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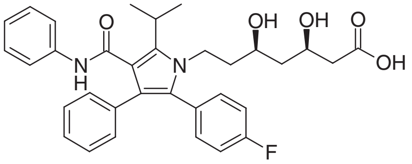
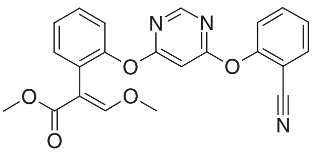


1

Atorvastatin
antilipemic



2

Azoxystrobin
fungicidal

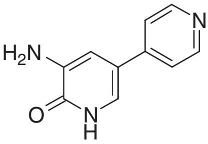
Figure 1.1 Atorvastatin (**1**) and azoxystrobin (**2**), two of the currently most successful pharmaceuticals and agrochemicals.

1.2
Heterocycles as Framework of Biologically Active Compounds

Several heterocycles possess excellent biological activity almost without bearing any substituents, which means that their heterocyclic core is definitely part of the pharmacophore. Examples of such scarcely substituted and highly active heterocycles are the two bipyridyl derivatives such as amrinone (**3**) [14], which is used in the treatment of congestive heart failure, and paraquat (**4**) [15], which is applied as a total herbicide (Figure 1.2).

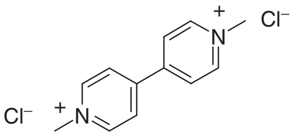
Another important role of the heterocyclic core of several pharmaceuticals and agrochemicals is that of an easily accessible scaffold, which carries the substituents that are responsible for the biological activity in the right orientation. There are several highly active per-substituted heterocycles, as demonstrated by the pyrazole derivatives propyphenazone (**5**) [16] and fipronil (**6**) [17], which are widely applied as efficient analgesic and insecticide, respectively, and synthetically available in only few steps (Figure 1.3).

Even simple aliphatic heterocycles display astonishing biological activities. The *gem*-diethyl-substituted barbituric acid derivative barbital (**7**) has been widely applied as a sleeping aid [18]. The pentamethylated piperidine pempidine (**8**) is used as a ganglionic blocker [19]. The trithiane thiocyclam (**9**), in comparison to the marine natural product nereistoxin enlarged by one additional ring sulfur atom, has been



3

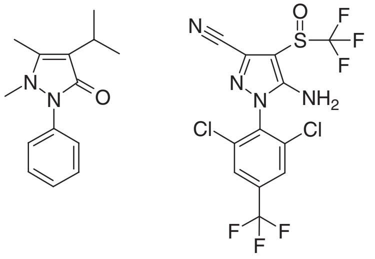
Amrinone
cardiotonic



4

Paraquat
herbicidal

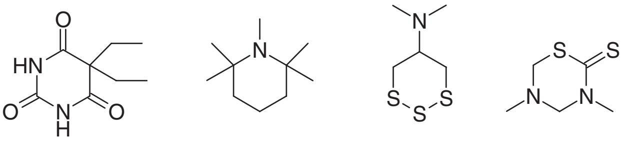
Figure 1.2 The highly active bipyridyl derivatives amrinone (**3**) and paraquat (**4**), each carrying only two small substituents.



5
Propyphenazone
analgesic

6
Fipronil
insecticidal

Figure 1.3 The persubstituted pyrazole derivatives propyphenazone (**5**) and fipronil (**6**).



7
Barbital
sedative

8
Pempidine
antihypertensive

9
Thiocyclam
insecticidal

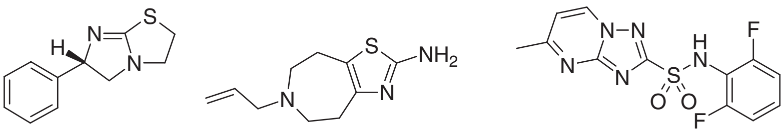
10
Dazomet
nematicidal

Figure 1.4 The saturated bioactive heterocycles barbital (**7**), pempidine (**8**), thiocyclam (**9**), and dazomet (**10**) [18–21].

developed as a broad-spectrum insecticide [20]. The cyclic dithiocarbamate dazomet (**10**) is a soil fumigant, which readily decomposes, yielding methyl isothiocyanate as principal toxicant against nematodes (Figure 1.4) [21].

Not only monocyclic heterocycles but also annelated bicyclic ring systems are applied as pharmaceuticals and crop protection agents, regardless of whether the biheterocyclic core consists of aliphatic, aliphatic and aromatic, or purely aromatic rings. The tetrahydroimidazothiazole levamisole (**11**) has been used as anthelmintic and immunomodulator [22]. The dopamine agonist talipexole (**12**) combines a five- and seven-membered ring and has been proposed as an antiparkinsonian agent [23]. The triazolopyrimidine sulfonanilide flumetsulam (**13**) is used for the control of broadleaf weeds in corn and soybean (Figure 1.5) [24].

Finally, there are also several examples of active ingredients, which bear two or more heterocycles in completely different positions of the molecule. For instance, the nonsteroidal anti-inflammatory drug meloxicam (**14**) consists of an amide with a benzothiazine-dione acid moiety and a thiazole amine component [25]. In addition, the agrochemical fungicide ethaboxam (**15**) contains an amide functionality, combining a thiazole carboxylic acid with a thiophene-containing amine (Figure 1.6) [26].

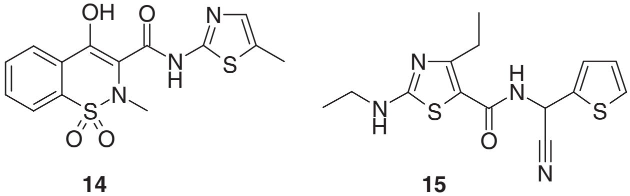


11
Levamisole
anthelmintic

12
Talipexole
antiparkinsonian

13
Flumetsulam
herbicidal

Figure 1.5 The highly active annelated bicyclic heterocycles levamisole (**11**), talipexole (**12**), and flumetsulam (**13**) [22–24].



14
Meloxicam
anti-inflammatory

15
Ethaboxam
fungicidal

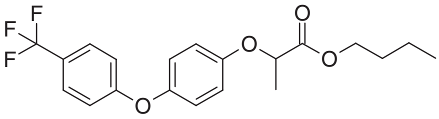
Figure 1.6 Meloxicam (**14**) and ethaboxam (**15**), two active ingredients carrying heterocycles in different parts of the molecule [25, 26].

1.3
Fine-Tuning the Physicochemical Properties with Heterocycles

The fact that in most cases aromatic heterocycles are more polar than their isocyclic analogs is often used for the lead optimization of pharmaceuticals and agrochemicals. For example, the replacement of the 4-trifluoromethylphenyl moiety of the herbicidal lead structure **16** by a 5-CF_3-pyrid-2-yl group resulting in the postemergence herbicide fluazifop-butyl (**17**) did not lead to any considerable enhancement of the herbicidal activity but significantly improved the ability of the target grass weeds to translocate into the plant tissue because of an optimum partition coefficient [27]. Furthermore, the replacement of the furane scaffold of the antiulcer histamine H_2-receptor antagonist ranitidine (**18**) by a thiazole resulted in nizatidine (**19**), which possesses not only a considerably lower log P value than ranitidine but also a much higher human oral bioavailability (Figure 1.7) [28].

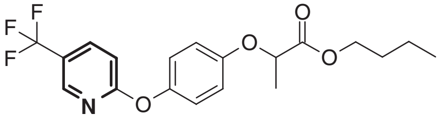
1.4
Heterocycles as Prodrugs

The efficacy of several heterocyclic active ingredients is based on the fact that the heterocycle is acting as a prodrug, itself being not efficacious against the target enzyme or organism but delivering the intrinsically active compound by



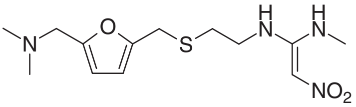
16

Herbicidal



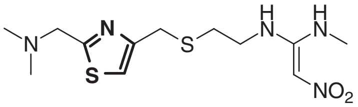
17

Fluazifop-butyl
herbicidal



18

Ranitidine
antiulcer



19

Nizatidine
antiulcer

Figure 1.7 Fluazifop-butyl (**17**) and nizatidine (**19**) possess optimum physicochemical properties to transport their high intrinsic activity to the target [27, 28].

UV light, heat, moisture, or a metabolic transformation. Leflunomide (**20**), for example, is a prodrug against transplant rejection, which ring-opens quantitatively in the cellular system to the hydroxypropenamide (**21**), which is responsible for the immunosuppressive efficacy [29]. In addition, the isoxazole ring of the herbicide isoxaflutole (**22**) is metabolically converted in plants and soil to the 2-cyano-1,3-diketone (**23**), which is a potent inhibitor of *p*-hydroxyphenylpyruvate dioxygenase (HPPD), one of the most important molecular targets for herbicides [30]. The fungicidal activity of the benzothiadiazine derivative **24** originates from its ability to be converted by sulfur extrusion in aqueous solutions and in plants into the benzimidazole fungicide carbendazim (**25**) [31]. The *in vivo* isomerization of fluthiacet-methyl (**26**) by *glutathione-S-transferase* leads to the urazole derivative **27**, which is entirely responsible for the strong herbicidal activity (Figure 1.8) [32].

1.5
Heterocycles as Peptidomimetics

Several different heterocyclic rings have a proven record as perfect isosteric replacement of the amide function in peptides [33]. The highly active HIV-1 protease inhibitors saquinavir (**29**) [34] and (**30**) [35] are close analogs of telinavir (**28**) [36], in which part of its urea function have been replaced by either a decahydroisoquinoline or a tetrazole (Figure 1.9).

Also, other five-membered heterocycles have been applied as amide isosteres in HIV-1 protease inhibitors for the treatment of AIDS. Examples are the imidazole derivative **32** [37] and the pyrrolinone (**34**) [38], in which the heterocyclic ring replaces the amide function of the corresponding di- or tripeptides **31** and **33** (Figure 1.10). All four HIV-1 protease inhibitors, the peptidic drugs, as well as

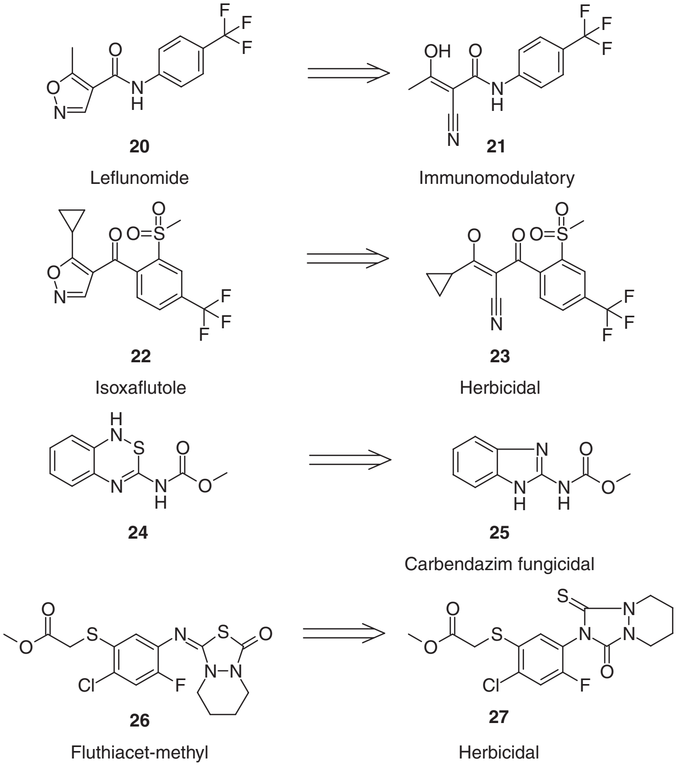


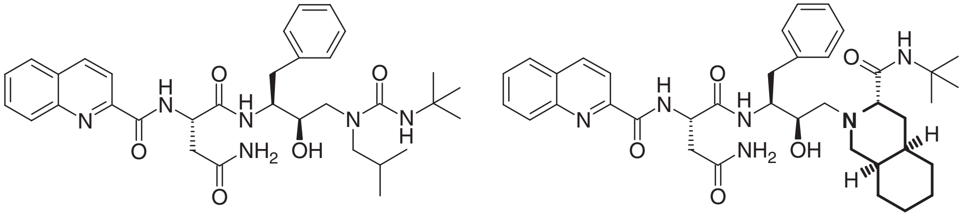
Figure 1.8 The heterocyclic prodrugs leflunomide (**20**), isoxaflutole (**22**), and fluthiacet-methyl (**26**) and (**24**).

their heterocyclic isosteres are active in the nanomolar range. The pyrrolidinone peptidomimetic **36** is 100 times more potent than the open-chain thrombin inhibitor NAPAP (**35**) [39]. The pyridine-based peptidomimetic **38** is a potent analog of PLG (**37**) (Pro-Leu-Gly-NH_2), an endogenous tripeptide found in the central nervous system, which is known to exert its pharmacological effects through the modulation of dopamine D2 receptors [40].

Further heterocycles, which have been successfully applied as amide isosteres, are pyrroles [41], thiazolidines [42], isoxazolines [43], imidazolines [44], oxazoles [45], triazoles [46], oxadiazoles [47], and benzimidazoles [48].

1.6
Heterocycles as Isosteric Replacement of Functional Groups

Heterocycles are also capable of mimicking other functional groups, besides the above-mentioned amide group. The most prominent examples are 5-substituted 1*H*-tetrazole as carboxylic acid replacements [49]. One of the success stories of

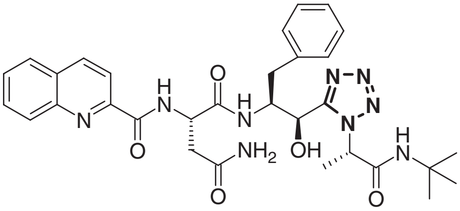


28

Telinavir
anti-HIV

29

Saquinavir
anti-HIV



30

Anti-HIV

Figure 1.9 Telinavir (**28**) and its peptidomimetics saquinavir (**29**) and (**30**).

the tetrazole-carboxylate isosterism is the angiotension II receptor antagonist losartan (**40**). This drug for the treatment of hypertension and its carboxylic acid lead structure **39** possess similar acidity (pK_a of **39**: 4.5, losartan: 5.0) but differ significantly in lipophilicity (log P of **39**: 1.2, losartan: 4.5). The higher lipophilicity of losartan results in considerably improved oral bioavailability [49]. Also, the two gamma-aminobutyric acid (GABA) agonists isoguvacine (**41**) and gaboxadol (THIP, **42**) possess similar pharmacological properties due to comparable acidity (p$K_a \approx 4$) (Figure 1.11) [50].

Moreover, triazoles [51], hydroxythiadiazoles [13a], hydroxychromones [52], oxadiazolones [53], and thiazolidinediones [54] have been reported as heterocyclic carboxylic acid bioisosteres.

If tetrazole is an excellent carboxylic acid replacement, then alkylated tetrazoles should be able to mimick esters. This is demonstrated by azimsulfuron (**44**), which shows longer persistence in rice paddy fields than its ethyl ester analog pyrazosulfuron-ethyl (**43**) [55]. Also, oxazoles [56] and oxadiazoles [57] have been successfully applied as bioisosteres of esters (Figure 1.12).

In search for more potent and selective dopamine D2 agonists for the treatment of psychiatric and neurological diseases such as schizophrenia and Parkinson’s disease, the indole moiety in **46** turned out to be an excellent bioisosteric replacement of the metabolically labile phenol function of the lead structure **45** [58].

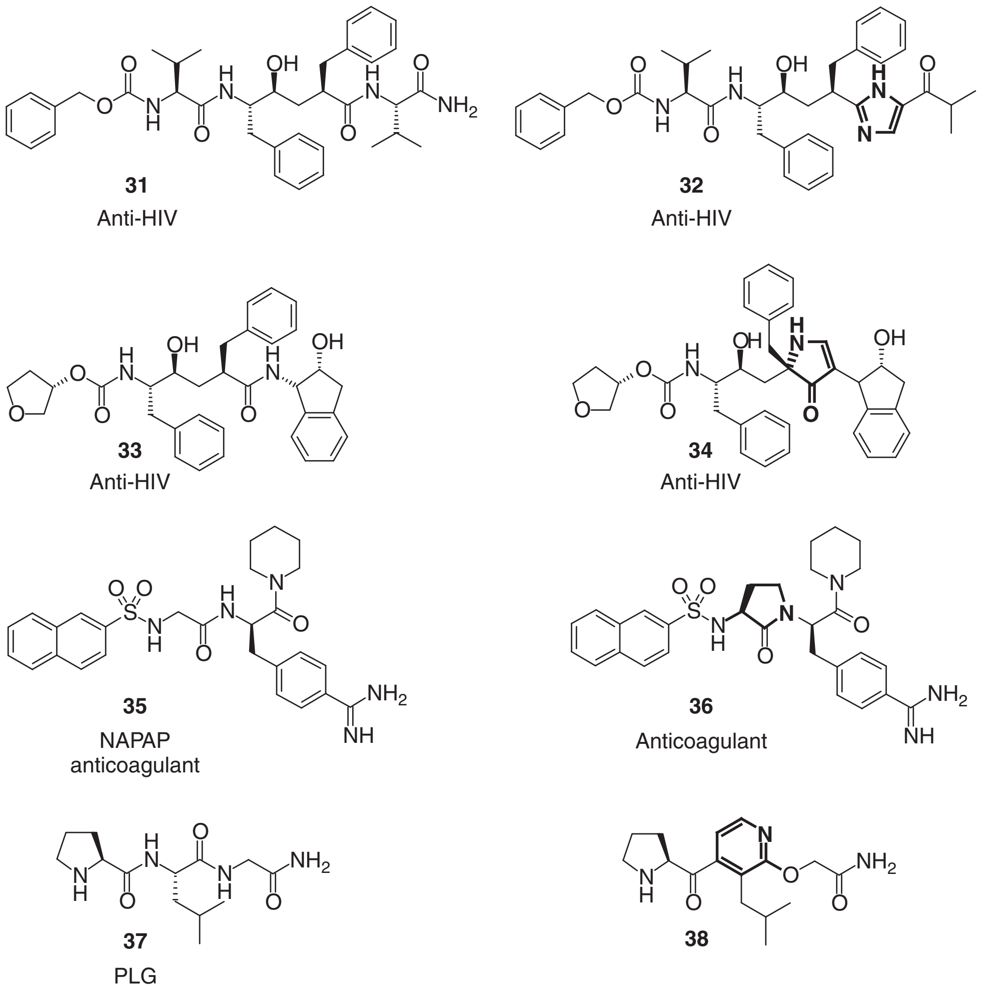
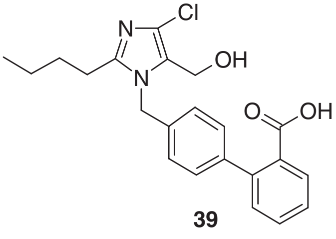


Figure 1.10 The heterocyclic peptidomimetics **32**, **34**, **36**, and **38**.

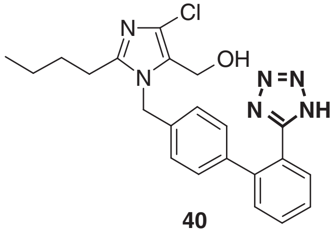
A widely used trick in lead optimization makes use of the fact that a carbon atom bearing a cyano function is often isosteric with an azomethine, often the ring nitrogen of an aromatic heterocycle. The potassium channel openers BMS182264 (**47**) and pinacidil (**48**), only differing by the replacement of a cyanophenyl ring by pyridine are both highly potent aortic smooth muscle relaxants [59].

The replacement of the highly basic benzamidine group in the thrombin inhibitor NAPAP (**35**) by a moderately basic 1-aminoisoquinoline moiety provides **49**, which displays potent enzyme inhibition and significant improvements in membrane transport and oral bioavailability [60].



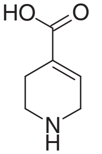
39

Antihypertensive



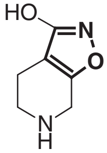
40

losartan
antihypertensive



41

Isoguvacine



42

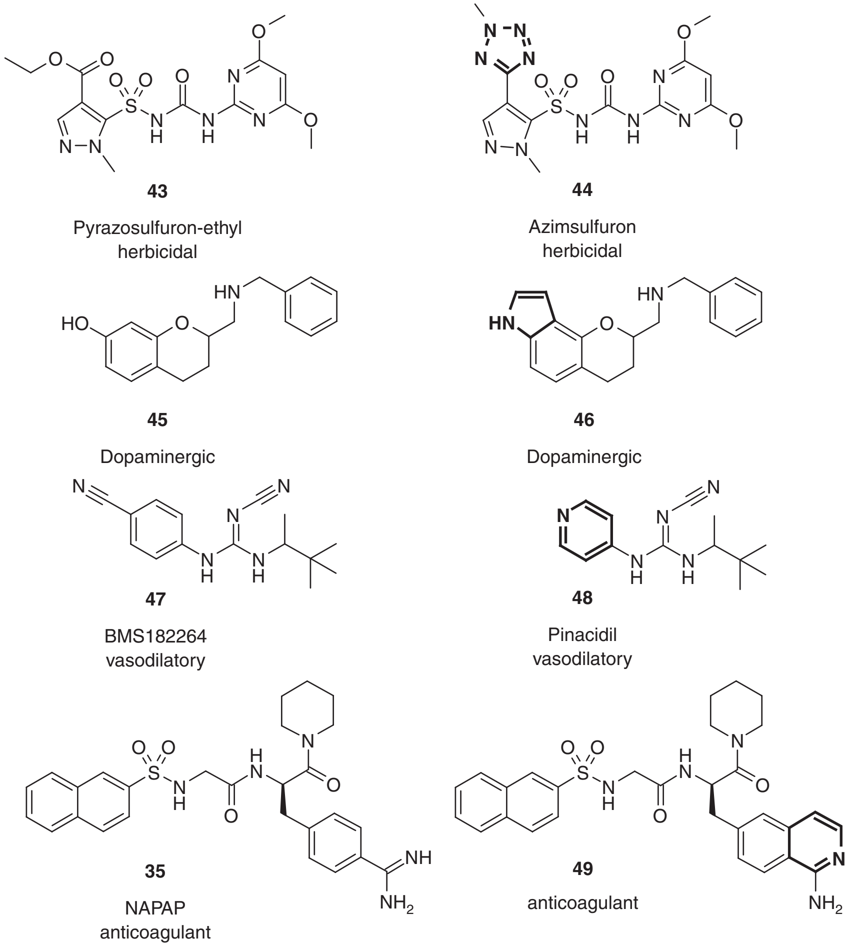
Gaboxadol (THIP)
sedative

Figure 1.11 The tetrazole derivative losartan (**40**) and the hydroxyisoxazole derivative gaboxadol (**42**) as carboxylic acid bioisosteres.

1.7
Heterocycles as Isosteric Replacement of Alicyclic Rings

A phenyl ring in biologically active compounds can often be replaced by a thiophene without any loss of activity because the sulfur atom is equivalent to an ethylenic group with respect to size, mass, and capacity to provide an aromatic lone pair [61]. For instance, a phenyl ring of the biologically active compound piroxicam (**50**) can be exchanged by thiophene, leading to tenoxicam (**51**) with similar anti-inflammatory activity (Figure 1.13) [62]. The thiophene derivative sufentanil (**53**) is at least five times more potent than its phenyl-analog fentanyl (**52**) [63]. The replacement of the *o*,*o*′-dialkylated phenyl ring of the chloroacetamide herbicide metolachlor (**54**) by a 2,4-dimethylthiophene results in dimethenamid (**55**) with comparable biological activity [64]. Also, in the area of *acetolactate-synthase*-inhibiting sulfonylurea herbicides, the ester-substituted phenyl ring could be successfully replaced by thiophene, leading from metsulfuron-methyl (**56**) to thifensulfuron-methyl (**57**) [65].

In addition, other heterocycles are able to mimic the phenyl ring of biologically active compounds. The substitution of one of the benzene rings of promazine's phenothiazine scaffold by pyridine led to prothipendyl (**59**) with improved neuroleptic activity and reduced undesired sedative and extrapyramidal effects (Figure 1.14)



43

Pyrazosulfuron-ethyl
herbicidal

44

Azimsulfuron
herbicidal

45

Dopaminergic

46

Dopaminergic

47

BMS182264
vasodilatory

48

Pinacidil
vasodilatory

35

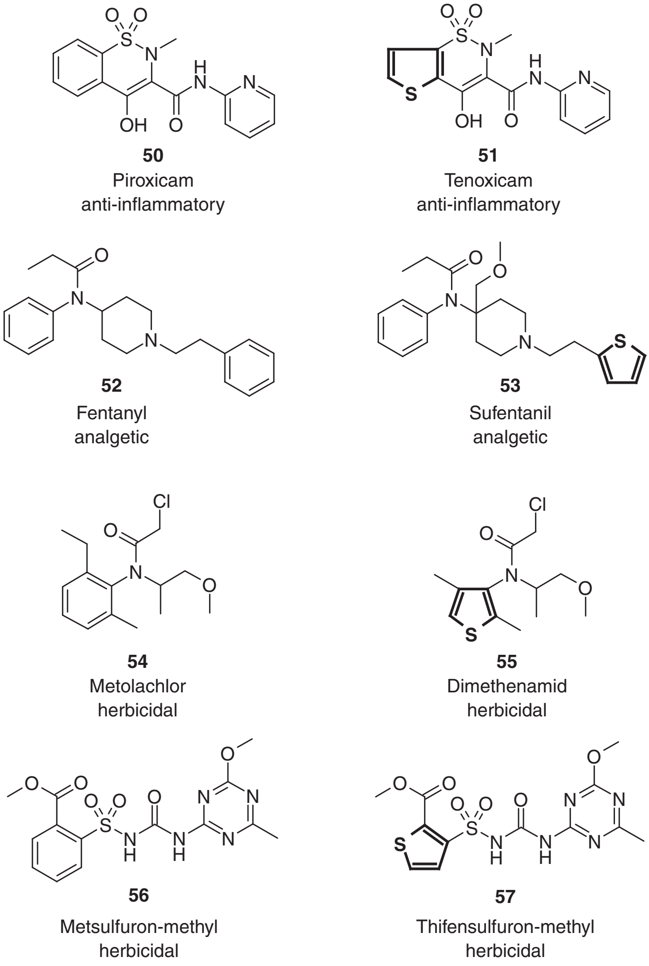
NAPAP
anticoagulant

49

anticoagulant

Figure 1.12 Ring nitrogen atoms of heterocycles **44**, **46**, **48**, and **49** are able to mimic functional groups such as ester, phenol, nitrile, and amidine, respectively.

[66]. Both compounds are structurally related to the antidepressants maprotiline (**60**) and imipramine (**61**), the latter also a heterocyclic isostere of the tetracarbocyclic maprotiline (**60**) [67]. Interestingly, molecular geometry is determining the direction of pharmacological activity of these four psychotropic drugs [13b]. A dihedral angle between both planes of the two annelated phenyl rings higher than 50°, as is the case for the dibenzobicyclo[2.2.2]octane **60** and the dibenzazepine **61**, results in the preponderance of antidepressive activity [68]. If the same angle is only around 25°, as in the phenothiazines **58** and **59**, then neuroleptic efficacy prevails.



50
Piroxicam
anti-inflammatory

51
Tenoxicam
anti-inflammatory

52
Fentanyl
analgetic

53
Sufentanil
analgetic

54
Metolachlor
herbicidal

55
Dimethenamid
herbicidal

56
Metsulfuron-methyl
herbicidal

57
Thifensulfuron-methyl
herbicidal

Figure 1.13 The thiophene derivatives **51**, **53**, **55**, and **57** as highly active heterocyclic isosteres of the corresponding phenyl analogs **50**, **52**, **54**, and **56**.

1.8
Heterocycles as Isosteric Replacement of other Heterocyclic Rings

It seems that all kinds of heterocyclic rings, aromatic and nonaromatic ones, can be replaced by other heterocycles, resulting in similar biological activity. The fact that aromatic heterocycles with a similar boiling point are often suitable bioisosteres is an interesting observation [13b]. For instance, a pyridazine (b.p. 208 °C) can be replaced successfully by an aromatic heterocycle with one additional ring nitrogen (1,2,4-triazine, b.p. 200 °C) but not by a ring with one nitrogen atom less (pyridine, b.p. 115–116 °C) or another diazine, in which one of

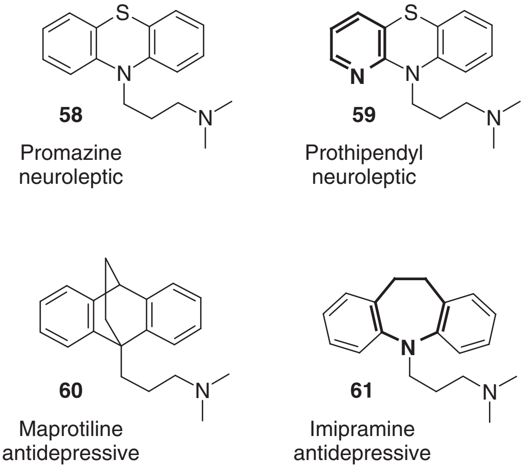


Figure 1.14 Prothipendyl (**59**) and imipramine (**61**), two psychotropic heterocyclic isosteres of promazine (**58**) and maprotiline (**60**).

the ring nitrogen is moved to another place (pyrimidine, b.p. 123–124 °C, or pyrazine, b.p. 115–118 °C) [13b].

One ring nitrogen and one carbon atom changing places turns a dihydropyrazolo[4,3-d]pyrimidine scaffold into a dihydroimidazo[5,1-f][1,2,4]triazine framework, thereby producing vardenafil (**63**) from sildenafil (**62**) [69]. The C-nucleosides oxazofurin (**64**) and selenazofurin (**65**) both inhibit the NAD-dependent inosine monophosphate dehydrogenase and show antiviral activities because of the impact of this inhibition of DNA synthesis (Figure 1.15). In contrast to oxazofurin, selenazofurin is also highly active against certain types of leukemia because it is readily metabolized to analogs of NAD, which may be attributed to the higher basicity of selenazole moiety [70]. The muscarinic agonist pilocarpine (**66**) is widely employed as topical miotic for lowering the elevated intraocular pressure associated with glaucoma, but the duration of this effect lasts only about 3 h, which is mainly due to the hydrolytic instability of the lactone ring. Replacement of one of the chiral carbon atoms in pilocarpine's dihydrofuranone ring by nitrogen results in the cyclic carbamate **67**, which is equipotent with pilocarpine and less susceptible to hydrolysis [71]. A ring contraction, which has been successfully applied in pharmaceutical lead optimization, is the replacement of the heptacyclic dihydrobenzodiazepine scaffold of the anticonvulsant α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor antagonist GYKI-53655 (**68**) by a dihydrophthalazine ring system, as in SYM-2207 (**69**) [72].

The bleaching herbicide fluridone (**70**) as well as its tetrahydropyrimidinone analog **71**, a cyclic urea, are very active against monocotyledonous and dicotyledonous weeds [73]. In animal health, the triaminated triazine cyromazine (**72**)

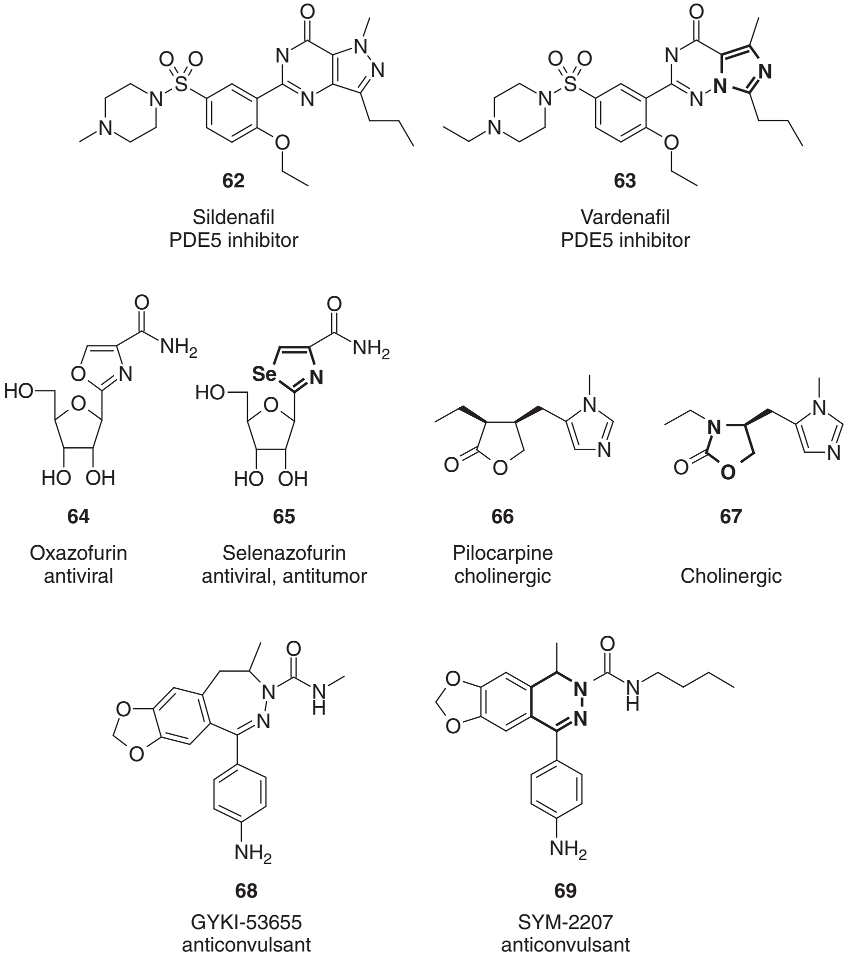
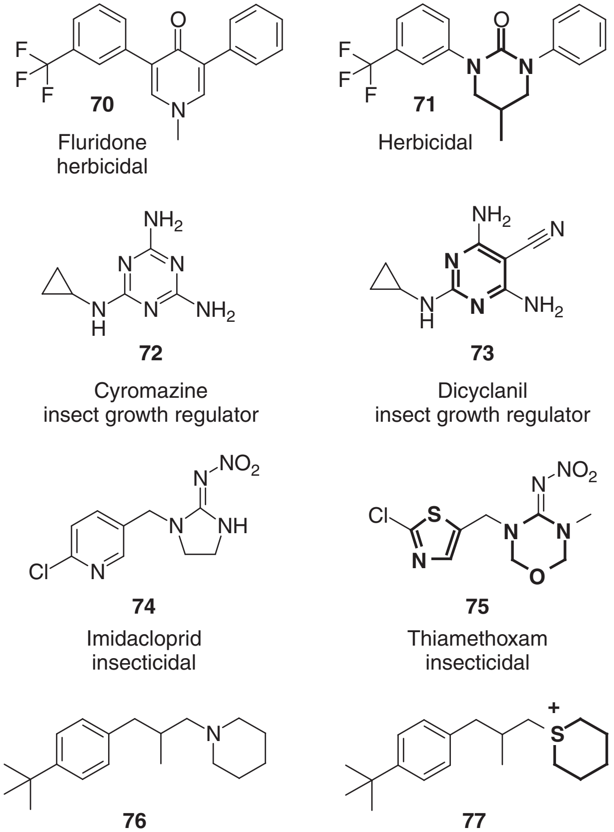


Figure 1.15 The biologically active compounds **63**, **65**, **67**, and **69**, bearing a slightly modified heterocycle compared to their analogs **62**, **64**, **66**, and **68**.

and its pyrimidine analog dicyclanil (**73**) are both very efficient against blowfly strike on sheep and screwworm infestation of cattle [74]. Both compounds are insect growth regulators, inhibiting the biosynthesis of chitin. Both aromatic and aliphatic heterocycles of imidacloprid (**74**) are replaced in the second-generation neonicotinoid thiamethoxam (**75**) by an isosteric ring with a different ring size [75]. The sulfonium salt **77**, an ionized thiane mimicking successfully the N-protonated fenpropidin (**76**), which is the active form of this fungicidal sterol biosynthesis inhibitor, shows activity against different wheat phytopathogens (Figure 1.16) [76].



70
Fluridone
herbicidal

71
Herbicidal

72
Cyromazine
insect growth regulator

73
Dicyclanil
insect growth regulator

74
Imidacloprid
insecticidal

75
Thiamethoxam
insecticidal

76
Fenpropidin
fungicidal

77
Fungicidal

Figure 1.16 The biologically active compounds **71**, **73**, **75**, and **77**, bearing a slightly modified heterocycle compared to their analogs **70**, **72**, **74**, and **76**.

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