CHAPTER 1

Privileged Scaffolds in Medicinal Chemistry: An Introduction

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1.1 Introduction

The 20th century has seen significant technological advances, as demonstrated by comparing technology's impact on everyday life at the beginning and end of the century. Many agree that this evolution can hardly have been predicted, nor the drastic changes to several scientific concepts. In many sectors, technological and scientific advancements made throughout the century were spectacular, in particular, in the ways in which we communicate, which is probably due to the evolution of computer science, among others.

The drug discovery process has also undergone huge changes and when we compare, even superficially, the stage that was achieved by the end of the century with that of earlier years, it is clear that there are significant differences. For example, at the end of the 19th century and beginning of the 20th century, when acetylsalicylic acid (ASA **1**; Figure 1.1), which may be considered the first drug to be industrially produced, was discovered, there was a completely different scientific environment to that of 1997, when

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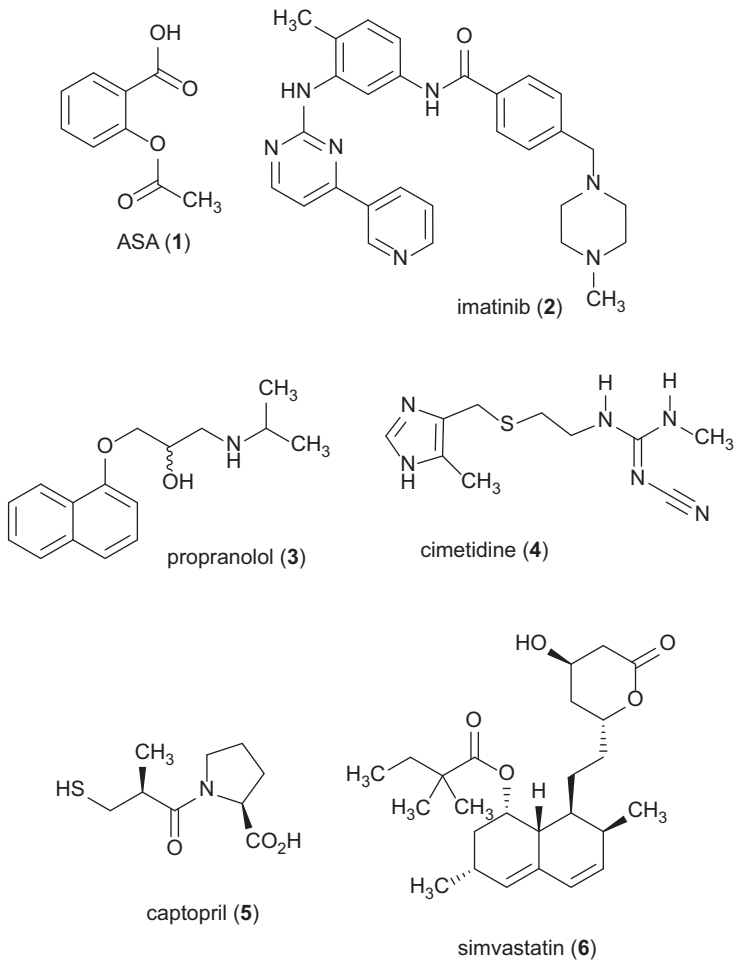


Figure 1.1 Structures of ASA, imatinib, propranolol, cimetidine, captopril, simvastatin.

imatinib (**2**, Figure 1.1), a powerful tyrosine-kinase (TK) inhibitor was created in Basel, Switzerland, in the Ciba-Geigy laboratories (currently Novartis)[1,2] and was launched in 2001 for the treatment of chronic myeloid leukemia. In the interval between both discoveries, we can see scientific and technological achievements that altered the paradigms of the drug discovery process. Obviously, most drugs that are now part of the contemporary therapeutic arsenal were created in the past century. Significant innovative examples include:

- propranolol (**3**, Figure 1.1), created by Black and co-workers[3] in the ICI laboratories in England in 1964;
- cimetidine (**4**, Figure 1.1),[4] created in 1975 at Smith, Kline & French (SK&F);

- captopril (**5**, Figure 1.1), created by Ondetti and Cushman[5,6] at Squibb laboratories; and,
- simvastatin (**6**, Figure 1.1), created by Patchett and collaborators[7] at Merck in 1998.[8]

All of these examples are the result of research efforts conducted in industrial laboratories and represent first-in-class drugs that are significant therapeutic innovations.

In addition to these discoveries, imatinib was a fantastic therapeutic innovation at the turn of the century (**2**).[1,2,9] It is used now in cancer chemotherapy, and was also created in an industrial research laboratory, involving modern medicinal chemistry strategies supported with HTS techniques. We understand that its discovery in the laboratories of Ciba-Geigy unraveled a new paradigm in which it was realized that multifactor diseases, generally chronic ones, need multitarget drugs. This new way of thinking among medicinal chemists, the discoverers of new drugs, has influenced the adoption of new approaches and the development of new terminology, in the latter half of the last century.

In 1988, Evans[10] published an article which mentioned the term 'privileged structures',[11] describing them as simple structural subunits present in the molecules of several drugs, with distinctive therapeutic uses, or affinities to several different receptors. This terminology has widened in its use, maybe in an excessively liberal way, and terms like 'molecular framework', 'chemotype', 'molecular fragment', and 'molecular scaffold', all of them synonymous, were created. In summary, some of these terms acquired different meanings, and due to current challenges in medicinal chemistry, they may be applied concurrently with other drug discovery techniques, such as molecular docking of fragments elected for the virtual screening in the search of new ligands of determinate targets, or in the construction of intelligent chemical libraries for use in HTS approaches, or to identify ligands, now called hits.[12] The identification of a new hit has widened the notion of molecular optimization through the use of classic medicinal chemistry techniques, to increase the affinity for the target in question, whether in potency or in selectivity. This establishes a certain hierarchy of the initial hit for the ligand, still without proof of concept for the prototype, now with pharmadynamic and pharmakinetic properties identified in functional pharmacological models.

Often the use of the terms 'privileged structure', 'fragment', or 'molecular scaffold' is mixed with the unique identity of each term being determined by molecular weight (in the case of fragments) or by the higher level of molecular simplification of a specific structural subunit for the use of molecular scaffold, here referring to cyclic structural subunits, aromatic or not. Both terms, however, refer to privileged structures. The bio IT experts use each term in a more precise way, which is mainly due to the function of the form or the elected molecular topology for each study.[13]

The evolution observed in the area of drug design and discovery throughout the last century may enable us to consider medicines as one of the biggest inventions of that century, because practically the entire contemporary therapeutic arsenal was invented or discovered then, with few examples of drugs being created and introduced in the 21st century.[14] The drug discovery process has seen changes throughout the last century, going beyond research laboratories of large pharmaceutical companies and reaching partnerships or multimember consortiums, involving university laboratories or high technology companies, or company–company joint ventures.[15]

Throughout the 20th century, or at least until its last decade, several drug discovery strategies were based on the paradigm inspired by the pioneering and masterful work of Hermann Emil Fischer and Paul Ehrlich, German Nobel Prize winners who established the basis for thought in this field throughout the 20th century. In 1902, Fischer was the first organic chemist to receive the Nobel Prize in Chemistry, mainly for the excellence of his work with carbohydrates, which inspired the key-lock model. The model explains, empirically, the differences observed in organoleptic properties among some sugars, with them being substances of similar chemical structures. This concept, together with Ehrlich's magic bullet,[16,17] for which he was awarded the Nobel Prize in Medicine in 1908, has inspired the thought of generations of scientists who were part of the discovery/invention process of new drugs throughout the 20th century.[18]

The Fischer–Ehrlich paradigm foresaw a few fundamental concepts for the design of new drugs, like that of complementary and molecular recognition between the bioreceptor and the drug, as well as the selectivity by a receptor as an attribute of efficacy and safety in the use of drugs. It was taken that, as corollary to safety in the use of drugs, its selectiveness for the therapeutic target and the possible future adverse side effects of a drug being related to lower selectivity or affinity for several receptors, or possible promiscuity. These ideas governed the thought of researchers in the area throughout most of the 20th century.[19]

1.2 The Privileged Scaffolds in Drug Discovery

Medicinal chemistry has as its main mission the understanding of molecular reasons for the activity of a drug or drug candidate. In this understanding, a few structural subunits of a certain bioactive molecule may be more relevant to a specific pharmacologic activity, governing the main interactions with a receptor. Those are the pharmacophoric contributions or pharmacophoric molecular groupings. Not unusually, the structures of drugs or their precursors have several functional groups, as well as the pharmacophoric ones, and all of them are called auxophoric subunits. Evidently, they all contribute to the total free energy of the drug-receptor complex, distinctively influencing the activity. Therefore, we may understand that some molecular scaffolds may have pharmacophoric characteristics for a certain type of receptor and not for others.[20] Some scaffolds may

have privileged characteristics, being recognized molecularly by distinctive receptors without being important pharmacophores.[21]

An example of a pharmacophoric scaffold[22] can be identified in the class of first generation β-lactamic antibiotics (Chapter 2), where we will find penicillins and cephalosporins, represented by the 7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane (**7**) ring present in penicillin-G (**8**) (Figure 1.2) (Chapters 3 & 7).

Another classical molecular pharmacophoric scaffold is the system cyclopenteneperhydrophenantrene (**9**), which is present in several natural hormones such as testosterone (**10**) and synthetic drugs like prednisolone (**11**), a synthetic glucocorticoid, as shown in Figure 1.3.

Additionally, other important natural privileged scaffolds are represented by the systems of chalcone (**12**),[23] 1,4-benzopyrone (**13**),[24] isoflavone (**14**), coumarin (**15**)[25] (Chapter 11) among those oxygenated and structural subunits that characterize several groups of alkaloids with distinctive pharmacological properties, like the quinoline ring (**16**),[26] isoquinoline (**17**) (Chapter 7), indole (**18**),[27] pyrrolidine (**19**) and other different possible combinations (Figure 1.4).[28–30]

The indole nucleus (**18**),[27] present in several natural and synthetic compounds (Chapters 13 & 14), is recognized as a central active scaffold, in several ergot alkaloids (*e.g.* ergotamine **20**) (Chapter 14) or in synthetic 3-carboxamide derivatives as ORG-28312 (**21**),[31] which presents agonistic affinity for CB1 receptors (Figure 1.4). The 3-carboxamide indole isosteres 4- and 6-azaindole ring appears in the structure of distinct active synthetic derivatives as **22** and **23**, described as potent renin inhibitors (Figure 1.5).[32]

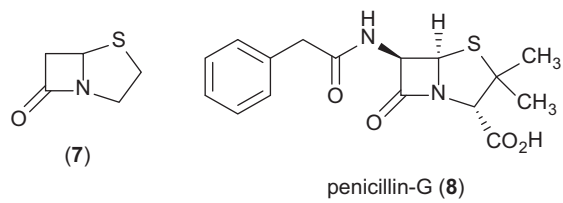


Figure 1.2 Structures of penicillin and its bicyclo system.

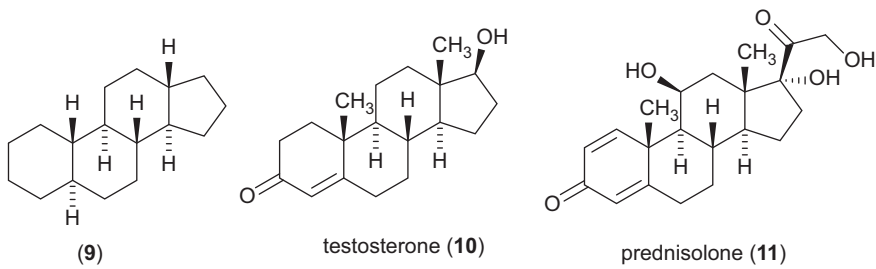


Figure 1.3 Structures of testosterone, prednisolone and its tetracyclo system.

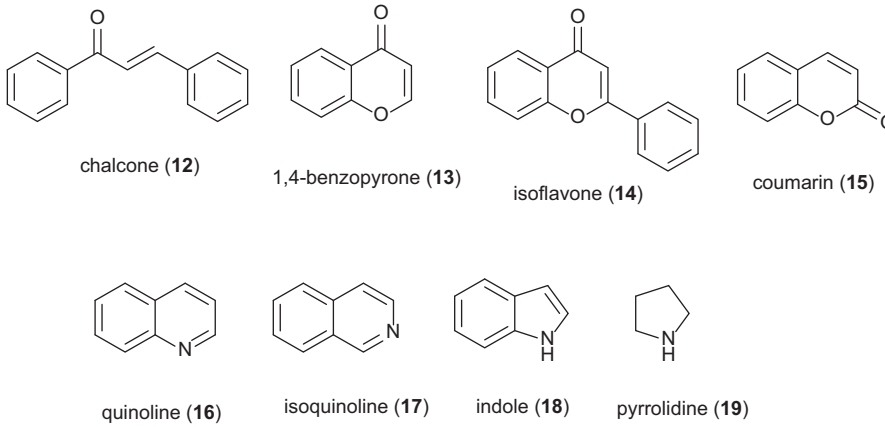


Figure 1.4 Representative natural privileged scaffolds.

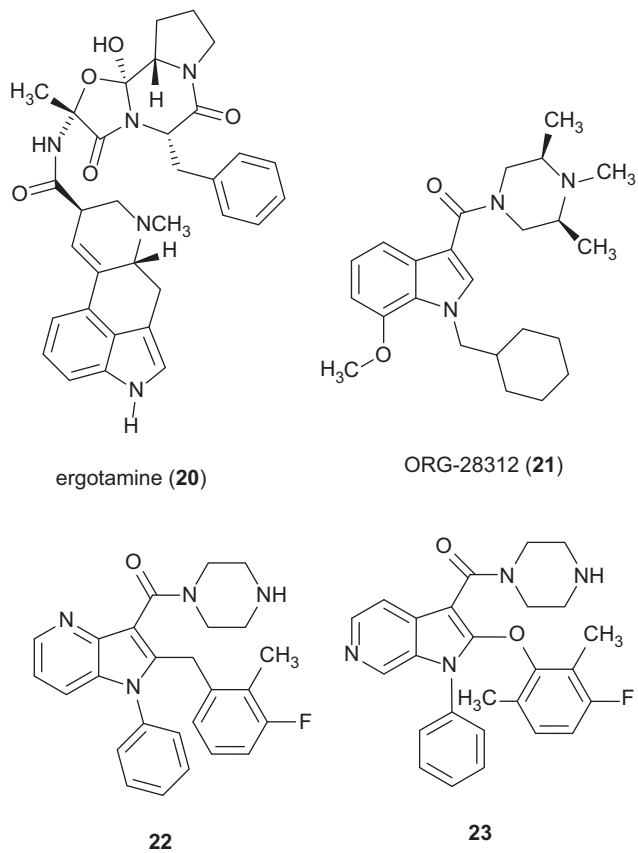


Figure 1.5 Structures of ergotamine, ORG-28312 and synthetic renin inhibitors.

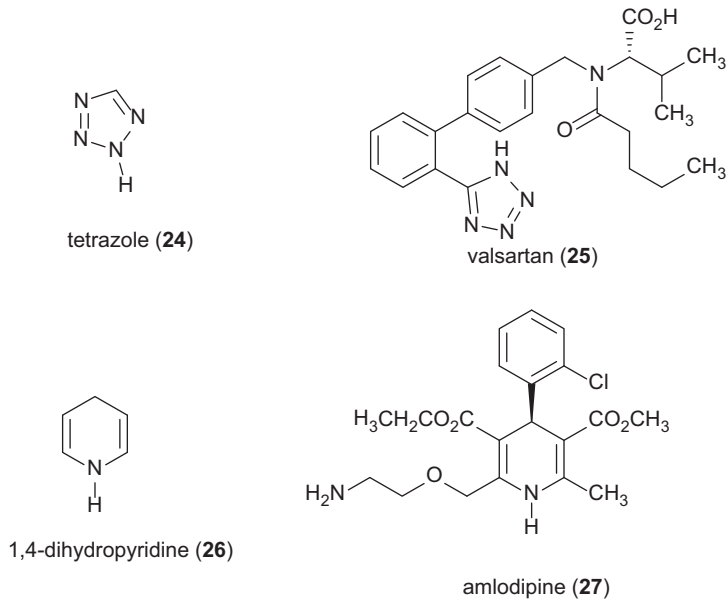


Figure 1.6 Structuers of valsartan and amlodipine with its heterocycles scaffolds.

Among synthetic drugs, the presence of tetrazole scaffold **24** in several synthetic drugs with selective antagonist properties of AT1 receptors, characterizes the sartan group of antihypertensive drugs as valsartan (**25**)[33] (Figure 1.6), while the 1,4-dihydropyridine scaffold **26** present in several Ca^{++} channel blockers such as amlodipine (**27**), an important blockbuster drug belonging to a secondary class of antihypertensive drugs.[34]

The *N*-phenylpyrazole scaffold **28** (Chapter 5) is present in a great number of drugs or drug candidates[35] as the recent disclosed direct factor Xa inhibitor apixaban (**29**; BMS-562247-01, Eliquis™),[36] an anticoagulant agent indicated for the treatment of venous thromboembolic disease, where this structural subunit is included in the dihydropyrazolo[5,4-*c*]pyridine-3-carboxamide moiety **30**. The celecoxib (**31**),[37] a selective COX-2 inhibitor also has this privileged scaffold **28** in its structure, included in the terphenyl like motif **32**. This system *per se* also represents an important privileged scaffold, present in the bestselling statin compound atorvastatin **33**. In addition, the terphenyl-like scaffold represented by the pyridinylimidazole system (Chapter 4), is present also in MAPKp38 inhibitor SB-203580 (**34**) (Scheme 6). This compound, presents in the central ring of the terphenyl-like system an imidazole ring representing a bioisosteric[38] system (**35**) of the 1,5-diarylpyrazole motif **32** (Figure 1.7) (Chapter 5).

The 1*H*-pyrazolo[3,4-*d*]pyridine scaffold **36** (Chapter 5) is present in numerous bioactive derivatives, as demonstrated by the derivative BAY418543 (**37**),[39,40] which is described as soluble guanylate cyclase stimulators (sGC), and is useful to control pulmonary hypertension disease (Figure 1.8) and in

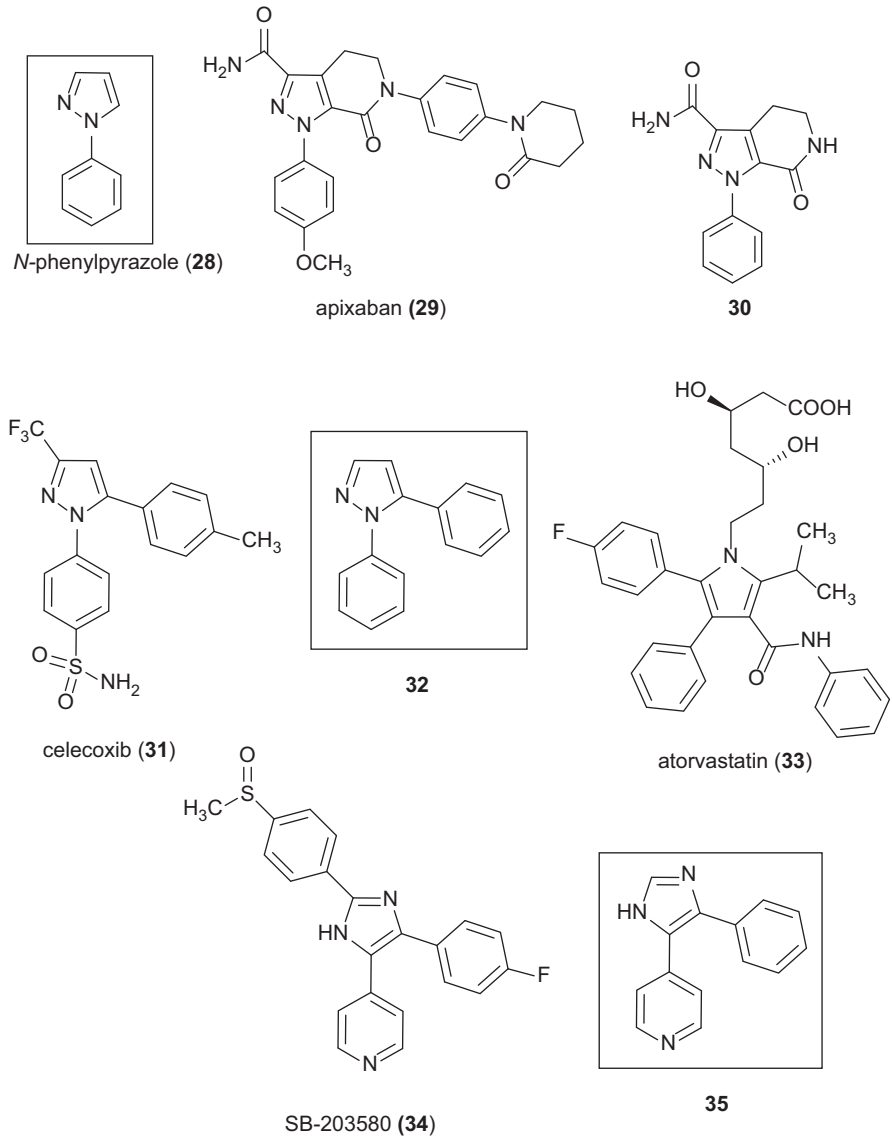
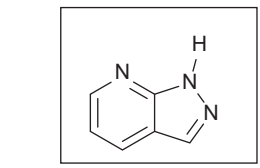


Figure 1.7 Structure apixaban, celecoxib, atrovastatin, SB-203580 and important scaffolds *N*-phenylpyrazole and terphenyl.

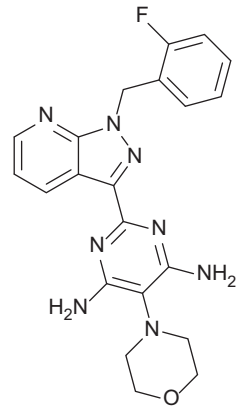
the B-Raf^{V600E} inhibitor **38**, recently described by Wenglowsky and co-workers[41] as a potent agent in preclinical evaluation to treat primary and metastatic melanomas (Figure 1.8).[42] This 7-azaindazole compound has an isostere system as present in PLX4032 (**39**),[43] a difluorophenylsulfonamide substructure with the pyrrolo-pyridine scaffold **40**, a 7-azaindole ring,[44] described as being useful to control metastatic melanoma.

Several isosteres of azabicyclic aromatic[45] represent important privileged scaffolds **41–47**, present in numerous drugs such as the one in the bioactive compounds in Figure 1.9.

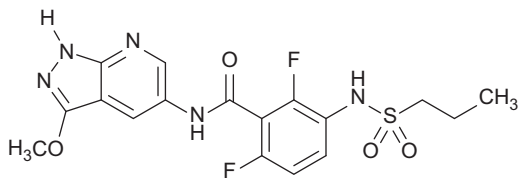
The scaffold **41** is present in the compound **48** a pyrimido[4,5-*b*]indole derivative possessing a thiophenyl moiety,[46] described as a dual agent acting as a kinase inhibitor on EGFR and PDGFR-β, with $IC_{50} = 10{,}41$ and $40{,}3$ μM, respectively, promoting antiangiogenic effect. This scaffold in a tautomeric form **42** (Figure 1.9) is present in ruxolitinib (**49**),[47] described as being an antimyelofibrosis (MF) agent acting also as a dual inhibitor of Janus kinase JAK-1 and JAK-2.



1*H*-pyrazolo[3,4-*d*]pyridine (**36**)



BAY 418543 (**37**)



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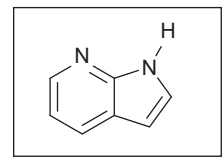
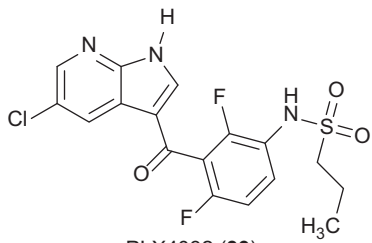


pyrrolo-pyridine (**40**)



PLX4032 (**39**)

Figure 1.8 Structure of important heterocyclic scaffold (**36** and **40**) and compounds BAY 418543, PLX4032 and **38**.

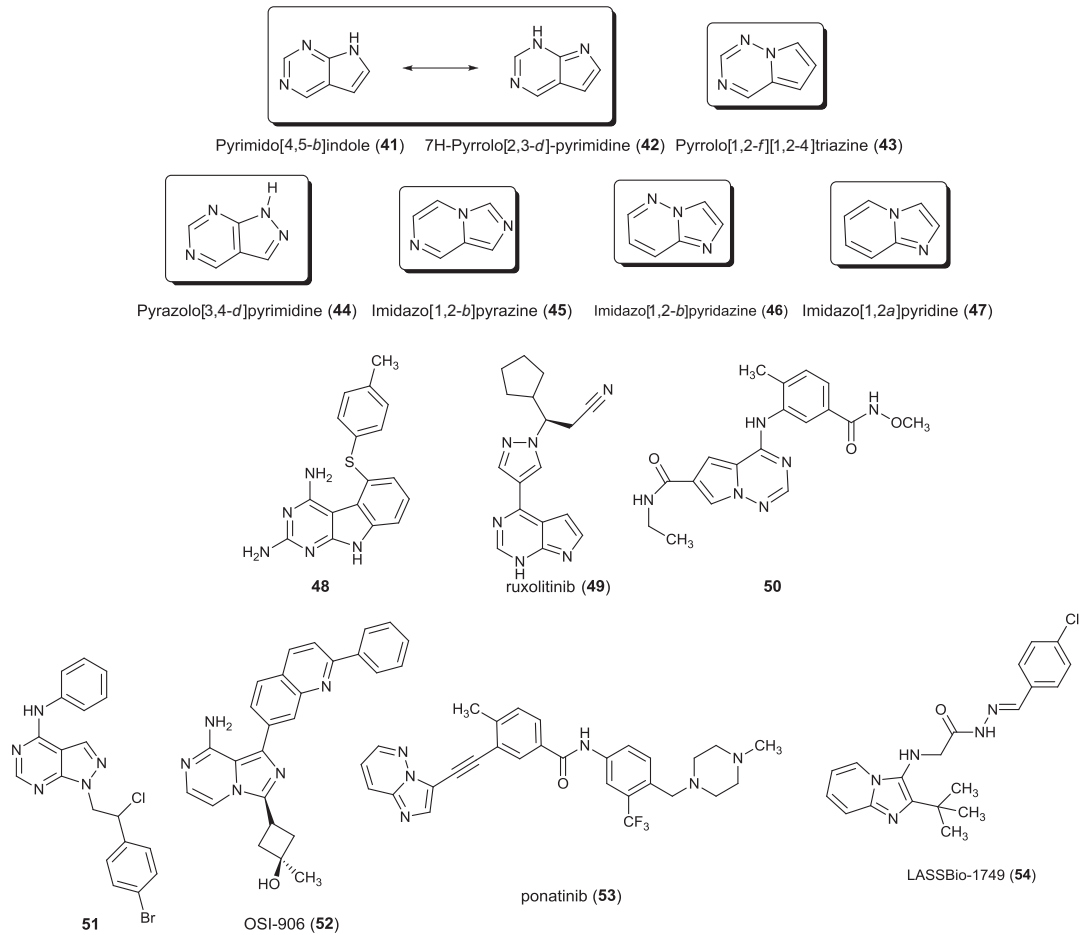


Figure 1.9 Structure of important azaheterocyclic scaffolds with examples.

The scaffold **43** (Figure 1.9), belonging to pyrrolo[1,2-*f*][1,2,4]triazine system,[48] appears in derivative **50** (BMS-582949),[49] with an *N*-methoxybenzamide moiety and was described as a potent multiple p38 MAP kinase inhibitor. Compound **51** (Figure 1.8) was discovered applying a cross-docking approach on a library of the pyrazolo[3,4-*d*]pyrimidine privileged scaffold **44** (Chapter 5).[50] This derivative having a bromine atom in the *para* position of the side chain phenyl ring was active at submicromolar potency against T315l Bcr-Abl expressing cells.[51]

The derivative OSI-906 (**52**),[52] shown in Figure 1.9, is a six-membered compound, possessing the imidazo[1,2*b*]pyrazine scaffold **45** (Chapter 4). This derivative is in Phase III clinical trials as a selective dual antagonist of insulin and IGF-I receptor with IC_{50} 0.024 μM in LISN cells.[53] The imidazo[1,2*b*]pyridazine scaffold **46** (Figure 1.9) appears in ponatinib (**53**),[54] an oral drug approved by the US Food Drug Administration in 2012, for patients with resistant or intolerant chronic myeloid leukemia (CML). It is a multitargeted tyrosine-kinase inhibitor derivative with an acetylenic benzamide chemotype. The only bisazo isosteric aromatic scaffold shown in Figure 1.8, the imidazo[1,2*a*]pyridine **47**, is present in the *N*-acylhydrazone compound LASSBio-1749 (**54**), described by Lacerda and co-workers as being a potent anti-TNFα agent.[55]

1.3 Conclusion

This introductory chapter provides a brief perspective about the privileged scaffold concept use in medicinal chemistry. This approach can be used alone or as a combined strategy, mixing other molecular design techniques such as bioisosterism.

The reader can find several more important details with a major number of examples of this useful strategy of drug design and discovery, in the following chapters of this book.

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