Part I
General Aspects of Analogue-Based Drug Discovery

Analogue-based Drug Discovery. IUPAC, János Fischer, and C. Robin Ganellin (Eds.)

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1
Analogues as a Means of Discovering New Drugs

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1.1
Designing of Analogues

The term analogy, derived from the Latin and Greek *analogia*, is used in natural science since 1791 to describe structural and functional similarity [1]. Extended to drugs, this definition implies that the analogue of an existing drug molecule shares chemical and therapeutic similarities with the original compound. The chemical design of analogues makes use of simple and traditional procedures of medicinal chemistry such as the synthesis of homologues, vinylogues, isosteres, positional isomers, optical isomers, transformation of ring systems, and the synthesis of twin drugs. These approaches are well-documented in textbooks, and have been reviewed extensively [2–7]; thus, they will be considered only briefly hereafter.

1.1.1
Analogues Produced by Homologous Variations

1.1.1.1 Homology Through Monoalkylation

Simple homologous variations applied on a neuramidase-inhibiting lead [8] achieved a 6300-fold increase in potency (Fig. 1.1).

1.1.1.2 Polymethylenic Bis-Ammonium Compounds: Hexa- and Decamethonium

Compounds having the general formula $(CH_3)_3\ N^+\text{-}(CH_2)_n\text{-}N^+(CH_3)_3$ usually show high affinity for the cholinergic receptors. When the values of n are intermediate ($n = 5$ or 6: penta- or hexamethonium), these compounds behave like cholinergic *agonists* (towards the sympathetic ganglia). For higher values ($n = 10$: decamethonium), the compounds become *antagonists* of acetylcholine (at the muscular endplate). In both cases, increasing acetylcholine levels displace them from their binding sites. When considering neuromuscular blockade, one observes again a curve with an asymmetric profile: sudden changes between $n = 6$ and $n = 8$, and then progressive diminution between $n = 9$ and $n = 12$.

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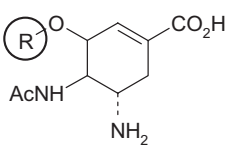
1.1.1.3 Homology in Cyclic Compounds

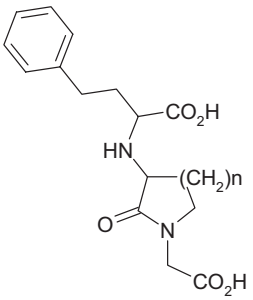
Homology in cyclic compounds can dramatically change the affinity of a ligand for its target. This is illustrated by a series of cyclic ACE inhibitors related to enalapril (Fig. 1.2).



Neuraminidase inhibition

R =	IC_{50} (nM)
H	6.300
CH_3 -	3.700
CH_3 - CH_2 -	2.000
CH3 - CH2 - CH2 -	180
CH_3 - CH_2 - CH_2 - CH_2 -	300
$(CH_3)_2$ -CH_2 - CH_2-	200
CH_3 - CH_2 - $CH(CH_3)$ -	10
$(CH_3$ - $CH_2)_2$ - CH -	1
(CH_3 - CH_2 - CH_2) CH -	16
Cyclopentyl	22
Cyclohexyl	60
Phenyl	530

Fig. 1.1 Monoalkylated, cyclohexene-derived, neuraminidase inhibitors.



ACE inhibition IC_{50}(nM)

n = 1 :	19,000
n = 2 :	1,700
n = 3 :	19
n = 4 :	4.8

Fig. 1.2 Homology in cyclic compounds.

For these compounds, an almost 4000-fold increase in activity was observed in passing from the five-membered to the eight-membered homologue [9].

1.1.2 Analogues Produced by Vinylogy

Tolcapone (Fig. 1.3) was designed as an inhibitor of the enzyme catechol O-methyltransferase, and is useful in the L-DOPA treatment of Parkinson's disease [10]. In avoiding the methylation of L-DOPA as well as that of dopamine, it prolongs the beneficial activities of these molecules.

Catechol O-methyltransferase inhibition represents therefore a valuable adjuvant to the L-DOPA decarboxylase inhibition. Unfortunately, tolcapone exhibited

severe liver damage and had to be removed from the market. The corresponding vinylogue *entacapone* is devoid of this side effect [8–10].

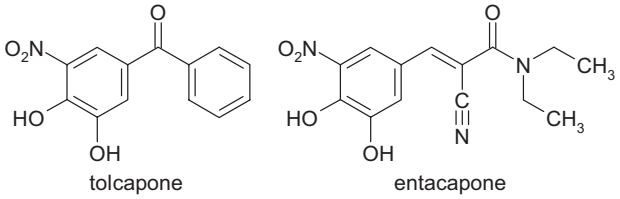


Fig. 1.3 The vinylogy principle applied to the catechol O-methyltransferase inhibitor, tolcapone.

1.1.2.1 **Zaprinast Benzologues**

A very convincing example of the usefulness of benzologues is provided by the synthesis of compound A, a linear benzologue of the prototypical phosphodiesterase type 5 (PDE_5) inhibitor zaprinast, and its optimization to potent and selective PDE_5 inhibitors such as compound B [11] (Fig. 1.4).

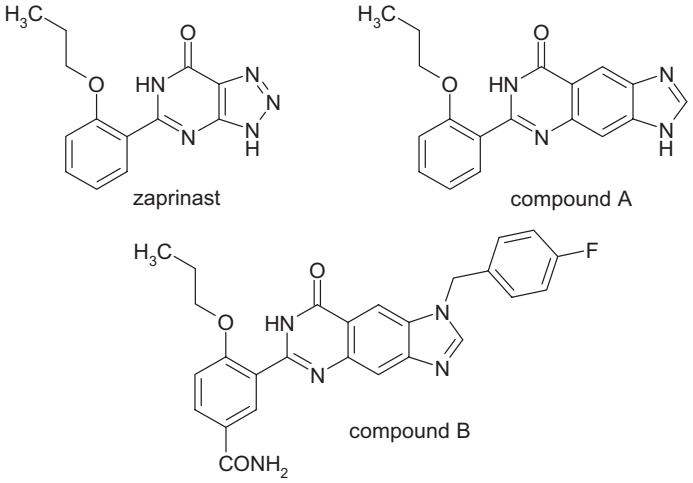


Fig. 1.4 Linear benzologues derived from zaprinast [11].

1.1.3
Analogues Produced by Isosteric Variations

1.1.3.1 **The Dominant Parameter is Structural**

Structural factors are 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 (Fig. 1.5).

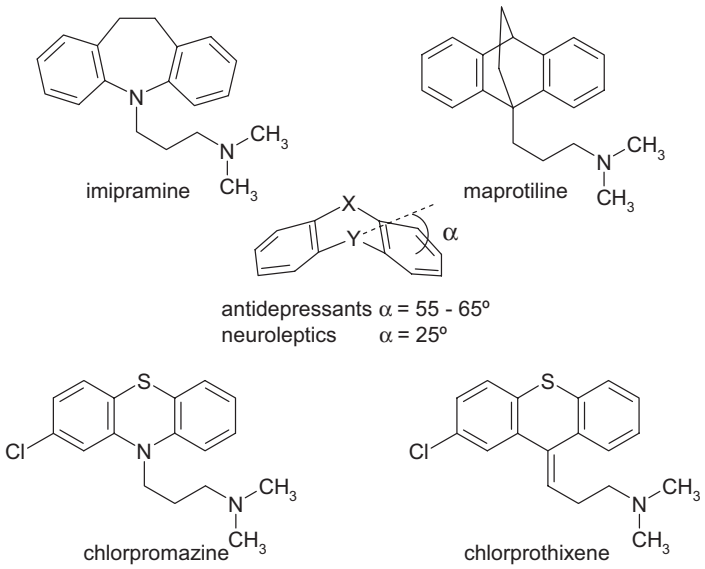


Fig. 1.5 The tricyclic antidepressants (imipramine and maprotiline) are characterized by a dihedral angle of 55° to 65° between the two benzo rings; this angle is only 25° for the tricyclic neuroleptics (chlorpromazine, chlorprothixene) [12].

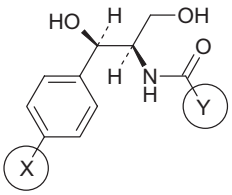
For the two antidepressants (imipramine and maprotiline), the bioisosterism is geometrical insofar that the dihedral angle a formed by the two benzo rings is comparable: $a = 65°$ for the dibenzazepine and $a = 55°$ for the dibenzocycloheptadiene [12]. This angle is only 25° for the neuroleptic phenothiazines and for 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.

1.1.3.2 **The Dominant Parameter is Electronic**

The electron-attracting nitro group in the antibiotic chloramphenicol (Tab. 1.1) has been replaced by other electron-attracting functions such as methyl-sulfonyl (thiamphenicol) or an acetyl (or cetophenicol). Apparently, the dominant feature is of electronic nature.

Similar electronic effects are found in the benzodiazepines series in which the chlorine atom of diazepam can be exchanged with a bromine (bromazepam) or with a nitro group (nitrazepam).

Tab. 1.1 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-	$-CH-Cl_2$

1.1.3.3 **The Dominant Parameter is Lipophilicity**

Typical examples of lipophilic analogues of prototypes are eptastigmine (*N*-heptyl-physostigmine), derived from physostigmine by replacement of the N-methyl group by a *n*-heptyl group [13,14], and tiagabine, in which a diaryl-butenyl chain is grafted to the nitrogen atom of nipecotic acid in order to yield a compound able to cross the blood–brain barrier [15] (Fig. 1.6).

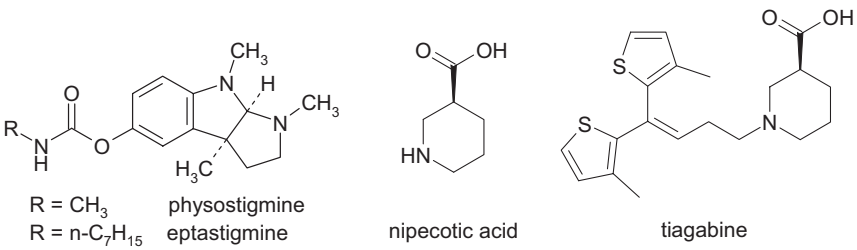


Fig. 1.6 Lipophilic analogues of physostigmine and of nipecotic acid.

1.1.4
Positional Isomers Produced as Analogues

In a series of nonpeptide corticotropin-releasing factor 1 (CRF1) antagonists, scientists from Neurocrine [16] observed a dramatic change in affinity simply by shifting one nitrogen atom of the pyrimidine ring (Fig. 1.7).

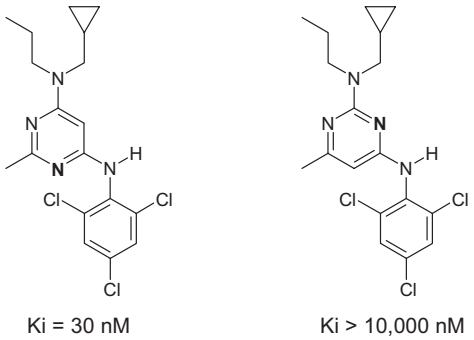


Fig. 1.7 A particularly striking effect of positional isomerism [K_i values for binding to the human corticotropin-releasing factor 1 (CRF1) receptor] [16].

1.1.5 Optical Isomers Produced as Analogues

Due to their almost identical chemical structure, enantiomers represent a subtle class of analogues. Often in a pair of enantiomers, the desired biological activity is concentrated in only one enantiomer. Then, the passage from a racemic mixture to the pure active eutomer – which is usually termed "racemic switch" – can produce an improved drug. However, in some cases and despite their similar constitution, both enantiomers can have totally different pharmacodynamic or pharmacokinetic profiles.

1.1.5.1 Racemic Switches

A general trend in the pharmaceutical industry is to switch from racemates to single enantiomers. Examples are given by (*R*)-(–)-verapamil, (*S*)-fluoxetin, (*S*)-ketoprofen, (*R*)-albuterol, levofloxacin, esomeprazole (see Chapter II-2), levocetirizine, and many others [17,18]. In addition to the quality improvement of the drug, this switch represents also a way to prolong its life insofar that the isolated eutomer is legally considered as a new drug entity.

1.1.5.2 Specific Profile for Each Enantiomer

The splitting of the anthelmintic drug tetramisole into its two components reveal nematocidal and immunostimulant properties for *S*(–)-levamisole and antidepressant properties for *R*(+)-dexamisole [19,20] (Fig. 1.8).

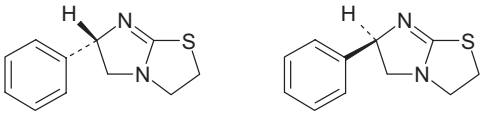


Fig. 1.8 The racemate tetramisole can be split into the nematocidal and immunostimulant *S*(–)-levamisole and into the antidepressant *R*(+)-dexamisole [19,20].

1.1.6
Analogues Produced by Ring Transformations

When active molecules contain cyclic systems, these can be opened, expanded, contracted, and modified in many other ways, or even abolished. Conversely, noncyclic molecules can be cyclized, attached to, or included in, ring systems.

Two interesting examples are found in cyclic analogues of β-blockers (Fig. 1.9). Cyclization to the morpholine yields the antidepressant viloxazine (mode 1), whereas cyclization to chromanols (mode 2) yields the potassium channel blocker cromakalim.

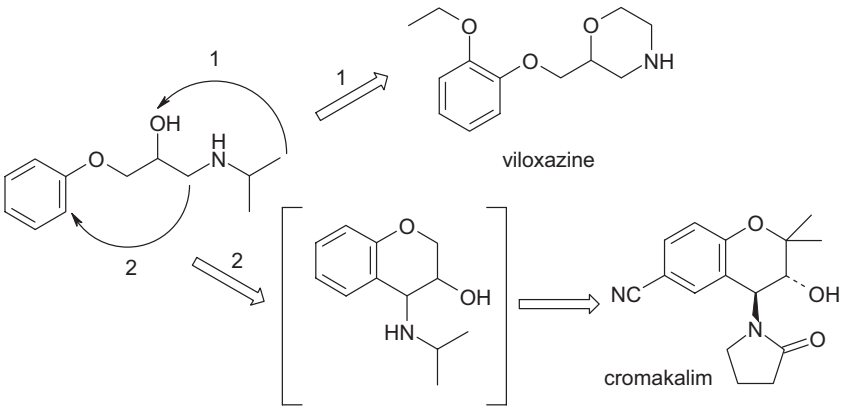


Fig. 1.9 Two modes of cyclization of the side chain in β-blockers yield the noradrenaline (NA) reuptake inhibitor viloxazine (mode 1) and the potassium channel blocker cromakalim (mode 2).

1.1.7
Twin Drugs

The search for cationic cholinergic agents has led to numerous twin drugs (Fig. 1.10). The bis-quaternary ammonium salts hexamethonium and decamethonium are potent blockers in ganglia and in neuromuscular junctions, respectively. Other

neuromuscular blocking agents such as succinyl and sebacyl dicholines can be regarded as pure acetylcholine twin drugs.

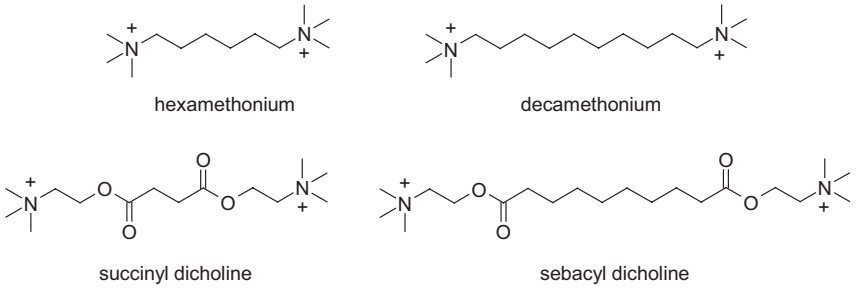


Fig. 1.10 Cholinergic twin drugs.

Other examples of twin drugs are the antioxidant probucol, which lowers the cholesterol level in blood, and cromolyn, a chromone heterocycle, which is useful in the inhalational treatment of bronchial asthma (Fig. 1.11).

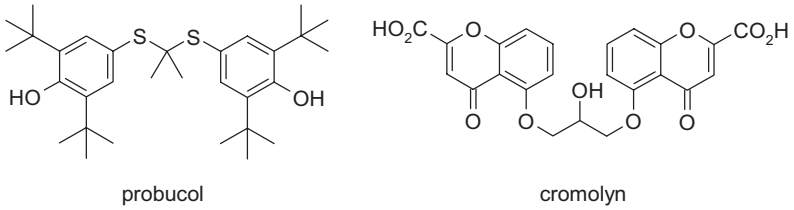


Fig. 1.11 Probucol and cromolyn are also twin drugs.

1.2 The Pros and Cons of Analogue Design

The usual objectives of analogue design are the identification and development of a possibly improved version of a prototype drug. Such compounds are often "direct analogues", and therefore are chemically and pharmacologically similar to the prototype drug. It should also present some advantages over the prototype. However, to achieve these goals is not always an easy task.

1.2.1 The Success is Almost Warranted

A reassuring aspect of making therapeutic copies resides in the quasi-certainty to end with active drugs in the desired therapeutic area. It is indeed extremely rare – and practically improbable – that a given biological activity is unique to a single molecule. Molecular modifications allow the preparation of additional products for which one can expect, if the investigation has been sufficiently prolonged, a

comparable activity to that of the copied model, and perhaps even a better one. This factor is comforting for the medicinal chemist, as well as for the financiers that subsidize him or her. It is necessary, however, to bear in mind that the original inventor of a pioneer drug possesses a technological and scientific advantage over analogue producers and, moreover, they are able to design a certain number of analogues of their own drug much earlier than the competitors.

1.2.2 The Information is Available

A second element which favors R&D based on analogues, comes from the information already gained with the original prototype. As soon as the pharmacological models that served to identify the activity profile of a new prototype are known, it suffices to apply them to the analogues. In other words, the pharmacologist will know in advance to what kind of activity he/she will meet and which tests he/she will have to apply to select the desired activity profile. In addition, during clinical investigations, the original studies undertaken with the lead compound, will serve as a reference and can be adopted unchanged to the evaluation of the analogues.

One criticism of this approach is that, in selecting a new active molecule by means of the same pharmacological models as were used for the original compound, one will inevitably end up with a compound presenting an identical activity profile; thus, the innovative character of such a research is very modest.

1.2.3 Financial Considerations

Finally, financial arguments can play in favor of analogue research. Thus, it may be important – and even vital – for a pharmaceutical company or for a national industry, to have its own drugs rather than to subcontract a license. Indeed, in paying license fees, an industry impoverishes its own research. Moreover, the financial profitability of a research based on *direct analogues* can appear to be higher, because no investment in fundamental research is required. The counterpart is that placing the copy on the market will naturally occur later than that of the original drug, and thus it will make it more difficult to achieve a high sales ranking – all the more so because the *direct analogues* will be in competition with other analogues targeting a similar market.

In reality, the situation is more subtle because very often the synthesis of *direct analogues* is justified by a desire to improve the existing drug. Thus, for penicillins the chemical structure that surrounds the beta-lactam ring is still being modified. Current antibiotics that have been derived from this research (e.g., the cephalosporins) are more selective, more active on resistant strains, and can be administered by the oral route. They are as different from the parent molecule as a recent car compared to a 40-year-old model! In other words, innovation can result from the sum of a great number of stepwise improvements, as well as from a major breakthrough.

1.2.4
Emergence of New Properties

It can happen that, during the R&D period of an analogue, a totally new property which was not present in the original molecule appears unexpectedly. Thanks to the emergence of such a new activity, the therapeutic copy becomes in turn a new lead structure. This was the case for imipramine, which was initially synthesized as an analogue of chlorpromazine and presented to the investigators for study of its antipsychotic profile [21]. During its clinical evaluation, this substance demonstrated much more activity against depressive states than against psychoses. Imipramine has truly opened, since 1954, a therapeutic avenue for the pharmacological treatment of depression.

Preparing totally new drugs emerging from already well-known lead structures is certainly one of the most exciting parts of medicinal chemistry, and will form the basis of the following sections.

1.3
Analogue Design as a Means of Discovering New Drugs

1.3.1
New Uses for Old Drugs

In some cases, a new clinical activity observed for an old drug is sufficiently potent and interesting to justify the immediate use of the drug in the new indication, and this is illustrated below.

Amiodarone, for example (Fig. 1.12), was introduced as a coronary dilator for angina, but concern about corneal deposits, discoloration of skin exposed to sunlight and thyroid disorders led to the withdrawal of the drug in 1967. However, in 1974 amiodarone was found to be highly effective in the treatment of a rare type of arrhythmia known as the Wolff–Parkinson–White syndrome. Accordingly, amiodarone was reintroduced specifically for that purpose [22].

Benziodarone was initially used in Europe as a coronary dilator, and proved later to be a useful uricosuric agent. However, it is now withdrawn from the market due to several cases of jaundice associated with its use [22]. The corresponding brominated analogue, benzbromarone was specifically marketed for its uricosuric properties.

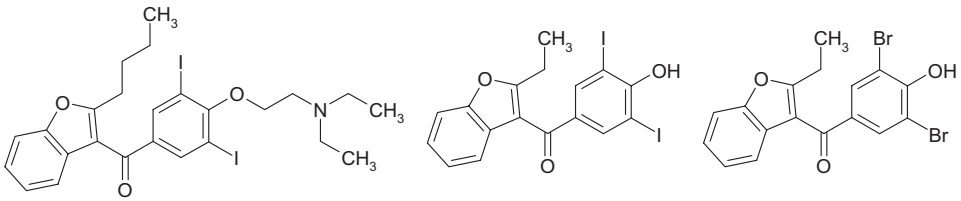


Fig. 1.12 Structures of the arones.

Thalidomide was initially launched as a sedative/hypnotic drug (Fig. 1.13), but withdrawn because of its extreme teratogenicity. However, under restricted conditions (no administration during pregnancy, or to any woman of childbearing age), it found a new use as an immunomodulator. Thalidomide seems particularly effective in the treatment of erythema nodosum leprosum, a possible complication of the chemotherapy of leprosy [23].

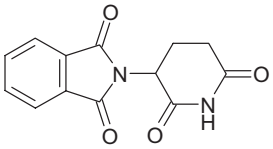


Fig. 1.13 Structure of thalidomide. The marketed compound is the racemate.

In 2001, the antimalarial drug *quinacrine* and the antipsychotic drug *chlorpromazine* (Fig. 1.14) were shown to inhibit prion infection in cells. Prusiner and coworkers [24] identified the drugs independently, and found that they inhibited the conversion of normal prion protein into infectious prions, and also cleared prions from infected cells. Both drugs can cross over from the bloodstream to the brain, where the prion diseases are localized.

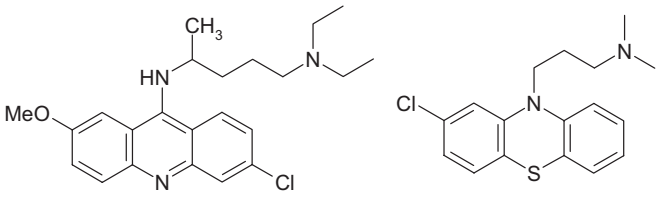


Fig. 1.14 Old drugs, new use. The antimalarial drug quinacrine and the antipsychotic drug chlorpromazine are able to inhibit prion infection [24].

Another recent example is provided by the discovery of the use of sildenafil (Viagra®; Fig. 1.15), a phosphodiesterase type 5 (PDE_5) inhibitor, as an efficacious, orally active agent for the treatment of erectile dysfunction [25,26]. Initially, this compound was brought to the clinic as an hypotensive and cardiotonic substance, but its usefulness in erectile dysfunction resulted unexpectedly from clinical observations made during a 10-day toleration study in Wales [27].

In many therapeutic families, each generation of compounds induces the birth of the following one. This happened in the past for the sulfamides, penicillins, steroids, conazoles, prostaglandins, and tricyclic psychotropics families, and one can draw real genealogical trees representing the progeny of the discoveries. More recent examples are found in the domain of ACE inhibitors, histaminergic H_2 antagonists, angiotensin II receptor antagonists, and HMG-CoA reductase inhibitors.

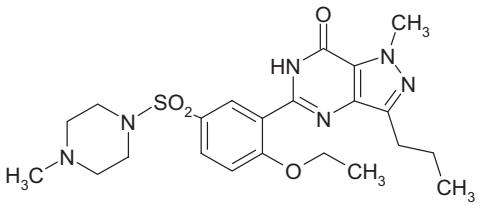


Fig. 1.15 Structure of the phosphodiesterase type 5 (PDE_5) inhibitor sildenafil [25,26].

Research programs based on the exploitation of side effects are of great interest in the discovery of new paths, in so far as they depend on information about activities *observed directly in man* and not in animals. On the other hand, they allow the detection of new therapeutic activities *even when no pharmacological models in animals exist*.

1.3.2 The PASS Program

Another very valuable tool, which allows simultaneous evaluation of the "drug-likeness" and prediction of the probable activity profile, is found in the program PASS (Prediction of Activity Spectra for Substances) developed by Poroikov and his team [28]. This approach consists of comparing a newly prepared molecule to a training set of about 35 000 active compounds for which the main and the side pharmacological effects, the mechanism of action, the mutagenicity, the carcinogenicity, the teratogenicity, and the embryotoxicity are (at least partly) known. The program then predicts the potential biological activity of the new molecule. In a published example [28], PASS was applied to a set of 130 pharmaceuticals from the list of the top 200 medicines. The known pharmacological effects were found in the predicted activity spectrum in 93.2% of cases. Additionally, the probability of some additional effects was also predicted to be significant, including angiogenesis inhibition, bone formation stimulation, possible use in cognition disorders treatment, and multiple sclerosis treatment. These predictions, if confirmed experimentally, may provide new leads from drugs that are already on the market. Most of the known side and toxic effects were also predicted by PASS.

1.3.3 New Leads from Old Drugs: The SOSA Approach

1.3.3.1 Definition

The SOSA approach (SOSA = Selective Optimization of Side Activities) represents an original alternative to high-throughput screening (HTS) [29–31]. SOSA consists of two steps:

- Perform screening assays on newly identified pharmacological targets only with a limited set (approximately 1000 compounds)

of well-known drug molecules. For these drugs, bioavailability and toxicity studies have already been performed, and they have proven usefulness in human therapy.
- Once a hit is observed with a given drug molecule, the task is then to prepare analogues of this molecule in order to transform the observed "side activity" into the main effect and to strongly reduce or abolish the initial pharmacological activity.

1.3.3.2 **Rationale**

The rationale behind the SOSA approach lies in the fact that, in addition to their main activity, almost all drugs used in human therapy show one or several side effects. In other words, if they are able to exert a strong interaction with the main target, they exert also less strong interactions with some other biological targets. Most of these targets are unrelated to the primary therapeutic activity of the compound. The objective is then to proceed to a reversal of the affinities, with the identified side effect becoming the main effect, and vice-versa.

1.3.3.3 **Availability**

A chemical library available for the SOSA approach is the Prestwick Chemical Library [32]. This contains 1120 biologically active compounds with high chemical and pharmacological diversity, as well as known bioavailability and safety in humans. About 90% of the compounds are well-established drugs, and about 10% are bioactive alkaloids. For scientists interested in drug-likeness, such a library certainly fulfills in the most convincing way the quest for "drug-like" leads!

1.3.3.4 **Examples**

Antihypertensives

A typical illustration of the SOSA approach is given by the development of *selective ligands for the endothelin ET_A receptors* by scientists from Bristol-Myers-Squibb [28,33]. Starting from an in-house library, the antibacterial compound sulfathiazole (Fig. 11.6) was an initial, but weak, hit (IC_{50} = 69 μM). Testing of related sulfonamides identified the more potent sulfisoxazole (IC_{50} = 0.78 μM). Systematic variations led finally to the potent and selective ligand BMS-182874. *In vivo*, this compound was orally active and produced a long-lasting hypotensive effect.

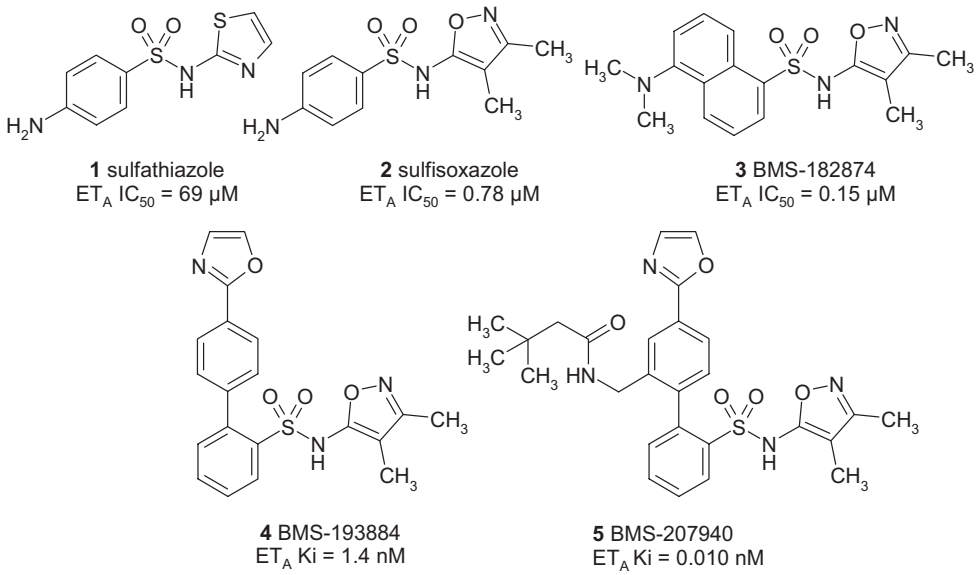


Fig. 1.16 A successful SOSA approach allowed the identification of the antibacterial sulfonamide sulfathiazole as a ligand of the endothelin ET_A receptor and its optimization to the selective and potent compounds BMS-182874, BMS-193884, and BMS-207940 [34,35].

Further optimization guided by pharmacokinetic considerations led the Bristol-Myers-Squibb team to replace the naphthalene ring by a diphenyl system [35]. Among the prepared compounds, **4** (BMS-193884, ET_A $K_i = 1.4$ nM; ET_B $K_i = 18\,700$ nM) showed promising hemodynamic effects in a Phase II clinical trial for congestive heart failure. More recent studies led to the extremely potent antagonist **5** (BMS-207940 ET_A $K_i = 10$ pM) presenting an 80 000-fold selectivity for ET_A versus ET_B. The bioavailability of **5** is 100% in rats, and it exhibits oral activity already at a 3 μM kg^{-1} dosing [35].

Cholinergic Agonists

In a second example, the starting lead was the antidepressant minaprine (Fig. 1.17). In addition to reinforcing serotonergic and dopaminergic transmission, this amino-pyridazine possesses weak affinity for muscarinic M_1, receptors ($K_i = 17$ μM). Simple chemical variations allowed the dopaminergic and serotonergic activities to be abolished, and the cholinergic activity to be boosted to nanomolar concentrations [36–38].

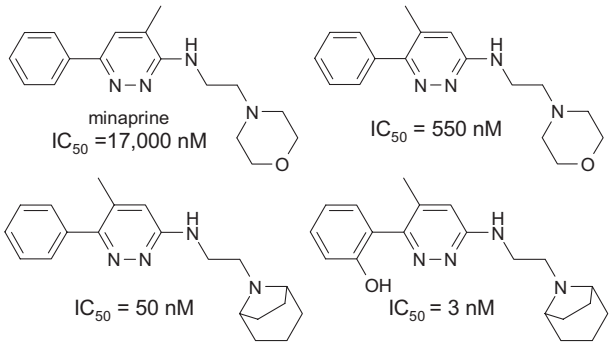


Fig. 1.17 Progressive passage from minaprine to a potent and selective partial muscarinic M_1 receptor agonist [36–38].

Acetylcholinesterase Inhibitors

Starting from the same minaprine lead, it was imagined that this molecule, in being recognized by the acetylcholine receptors, should also be recognized by the acetylcholine enzyme. It transpired that minaprine had only a very weak affinity for acetylcholinesterase (600 μM on electric eel enzyme), but relatively simple modifications (creation of a lipophilic cationic head, increase of the side chain length, and bridging the phenyl and the pyridazinyl rings) led to nanomolar affinities (Fig. 1.18) [39,40].

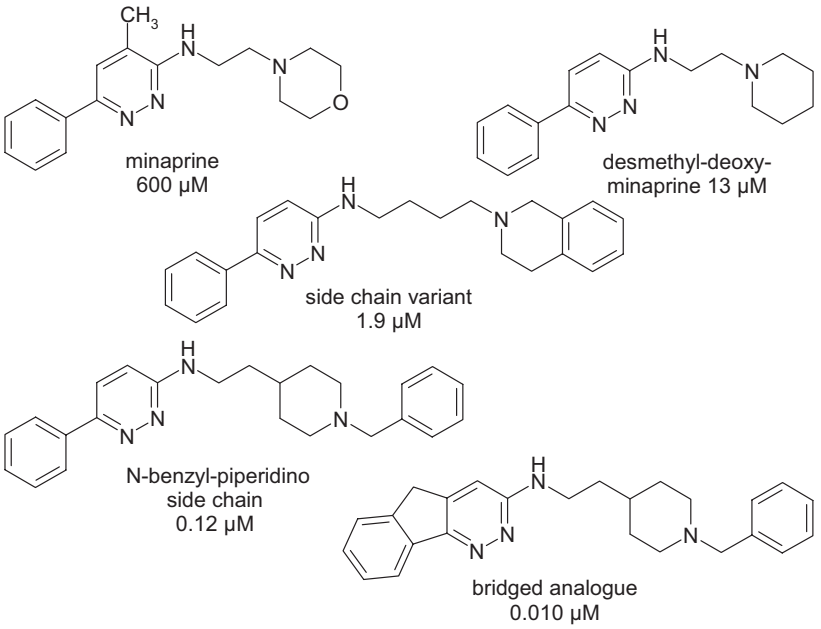


Fig. 1.18 IC_{50} values for acetylcholinesterase inhibition (electric eel enzyme) [39,40].

Corticotropin-Releasing Factor (CRF) Antagonists

Another interesting switch consisted in the progressive passage from desmethylminaprine **6** to the bioisosteric thiadiazole **7** (Fig. 1.19), and then to the bioisosteric thiazoles. Tri-substitution on the phenyl ring and replacement of the aliphatic morpholine by a pyridine led to compound **8** which exhibited some affinity for the receptor of the 41 amino-acid neuropeptide CRF. Further optimization led to nanomolar CRF antagonists such as **9** [41,42].

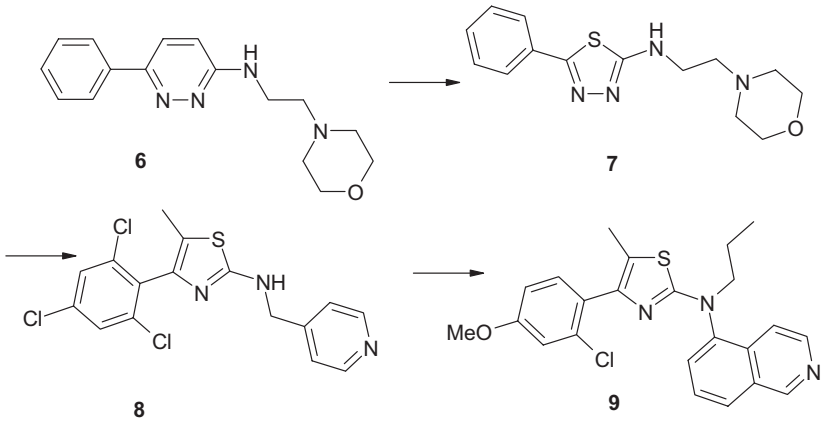


Fig. 1.19 Switch from the antidepressant molecule minaprine to the potent CRF receptor antagonist 9 [41,42].

Subtype-Selective Dopamine D_3 Receptor Ligands

In another study, chemical variations of the D_2/D_3 nonselective antagonist sulpiride (Fig. 1.20) led to the compound Do 897, a selective and potent D_3 receptor partial agonist [43].

1.3.3.4 Discussion

The SOSA approach appears to be an efficient strategy for drug discovery, particularly as it is based on the screening of drug molecules and thus automatically yields drug-like hits. Before starting a costly HTS campaign, SOSA can represent a seductive alternative. Once the initial screening has provided a hit, it will be used as the starting point for a drug discovery program. Using traditional medicinal chemistry as well as parallel synthesis, the initial "side activity" is transformed into the main activity and, conversely, the initial main activity is strongly reduced or abolished. This strategy leads with a high probability to *safe*, *bioavailable*, *original*, and *patentable* analogues.

Safety and Bioavailability

During years of practicing SOSA approaches, it has been observed at Prestwick that, starting with a drug molecule as a lead substance in performing analogue

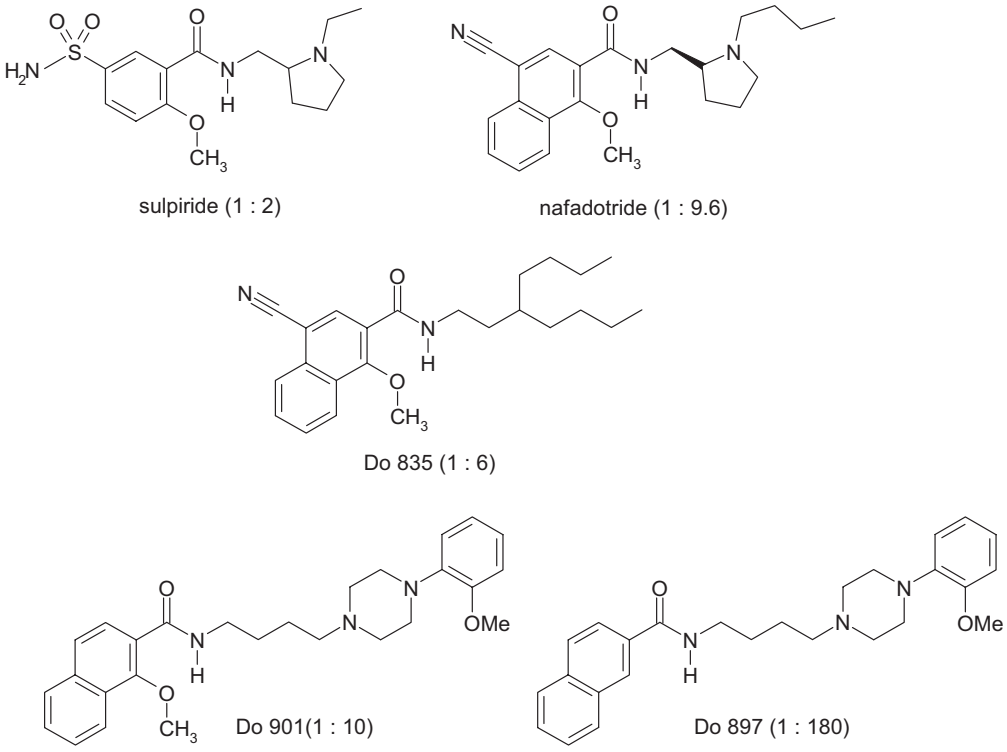


Fig. 1.20 The progressive change from the D_2/D_3 receptor nonselective antagonists to the highly D_3-selective compound Do 897 [43]. The numbers in parentheses indicate the D_2/D_3 affinity ratio.

synthesis, has increased notably the probability of obtaining safe new chemical entities. In addition, most of these satisfy Lipinski's [44], Veber's [45], Bergström's [46], and Wenlock's [47] observations in terms of solubility, oral bioavailability, and drug-likeness.

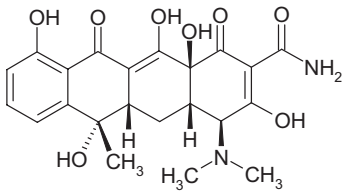
Patentability

When a well-known drug hits with a new target, there is a risk that several hundreds or thousands of analogues of the original drug molecule are already synthesized by the original inventors and their competitors. These molecules are usually protected by patents, or already belong to the public domain. Thus, at a first glance, a high risk of interference appears probable. In fact, in optimizing another therapeutic profile than that of the original inventors, the medicinal chemist will rapidly prepare analogues with chemical structures very different from that of the original hit. As an example, a medicinal chemist interested in a phosphodiesterase (PDE) and using diazepam as lead, will rapidly prepare compounds which are beyond the scope of the original patents, precisely because in becoming PDE inhi-

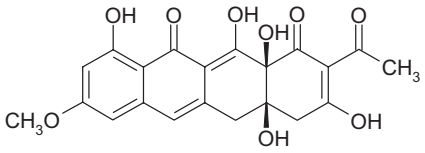
bitors they present modified (and thus patentable) structures and have lost their affinity for the benzodiazepine receptor.

Originality

On occasion, the screening of a library of several hundred therapeutically diverse drug molecules ultimately produces very surprising results. A nice example of unexpected findings resulting from a systematic screening is found in the tetracyclic compound **11** (BMS-192548) extracted from *Aspergillus niger* WB2346 (Fig. 1.21).



10: tetracycline



11: BMS-192548

Fig. 1.21 Unexpected CNS activity of the tetracycline analogue 11 (BMS-192548) [48].

For any medicinal chemist or pharmacologist, the similarity of this compound with the antibiotic tetracycline is striking. However, none of them would *a priori* forecast that BMS-192548 exhibits CNS activities. Actually, the compound turns out to be a ligand for the neuropeptide Y receptor preparations [48].

Orphan Diseases

As mentioned above, a differentiating peculiarity of this type of library is that it is constituted by compounds that have already been safely given to humans. Thus, if a compound were to "hit" with sufficient potency on an orphan target, there is a high chance that it could rapidly be tested in patients for Proof of Principle. This possibility represents another advantage of the SOSA approach.

1.4 Conclusion

Formally, three classes of drug analogues can be considered: (a) analogues presenting chemical and pharmacological similarities (e.g., lovastatin and simvastatin); (b) analogues presenting only structural similarities (e.g., chlorpromazine and imipramine); and (c) chemically different compounds displaying similar pharmacological properties (e.g., chlorpromazine and haloperidol).

The design of analogues of the first category – *direct analogues* – is one of the most rewarding activities of medicinal chemists, and forms part of their daily activity. Indeed, it justifies to a great extent the theme of the present book.

The design of analogues of the second category is sometimes fortuitous, as the result of a pharmacological or a clinical feed-back. For these "structural analogues", the observation of a new activity can also result from a planned and systematic investigation such as provided by the use of the PASS program or the SOSA approach.

Finally, the design of the third category of analogues – "pharmacological analogues" – is not within the scope of this chapter, but is typically relevant from computer-aided drug design (docking, virtual design).

Together, it can be taken for granted that analogue design has been – and continues to be – one of the most fruitful of the methodologies leading to important and useful drug molecules.

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