Part I
General Aspects

Analogue-based Drug Discovery III, First Edition. Edited by János Fischer, C. Robin Ganellin, and David P. Rotella.

1
Pioneer and Analogue Drugs

János Fischer, C. Robin Ganellin, and David P. Rotella

A *pioneer drug* ("first in class") represents a breakthrough invention that affords a marketed drug where no structurally and/or pharmacologically similar drug was known before its introduction. The majority of drugs, however, are *analogue drugs*, which have structural and/or pharmacological similarities to a pioneer drug or, as in some cases, to other analogue drugs.

The aim of this chapter is to discuss these two drug types [1].

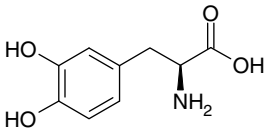
The term "pioneer drug" is not used very often, because only a small fraction of drugs belongs to this type and in many cases the pioneer drugs lose their importance when similar but better drugs are discovered. A pioneer drug and its analogues form a drug class in which subsequent optimization may be observed. Analogue drugs typically offer benefits such as improved efficacy and/or side effect profiles or dose frequency than a pioneer drug to be successful on the market.

The discovery of both *pioneer* and *analogue drugs* needs some serendipity. A pioneer drug must clinically validate the safety and efficacy of a new molecular target and mechanism of action based on a novel chemical structure. In the case of an analogue drug, it is helpful that a pioneer or an analogue exists; nevertheless, some serendipity is needed to discover a new and better drug analogue, because there are no general guidelines on how such molecules can be identified preclinically. The analogue approach is very fruitful in new drug research, because there is a higher probability of finding a better drug than to discover a pioneer one. A significant risk with this approach is based on the potential for one of the many competitors in the drug discovery area to succeed prior to others.

The similarity between two drugs cannot be simply defined. Even a minor modification of a drug structure can completely modify the properties of a molecule. Levodopa (**1**) and methyldopa (**2**) are applied in different therapeutic fields; however, their structures differ only in a methyl group. Both molecules have the same stereochemistry as derivatives of L-tyrosine. Levodopa [2] is used for the treatment of Parkinson's disease as a dopamine precursor, whereas methyldopa [3] was an important antihypertensive agent before safer and more efficacious molecules (e.g., ACE inhibitors) appeared on the market.

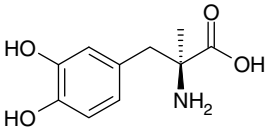
Analogue-based Drug Discovery III, First Edition. Edited by János Fischer, C. Robin Ganellin, and David P. Rotella.

Methyldopa (first synthesized at Merck Sharp & Dohme) has a dual mechanism of action: it is a competitive inhibitor of the enzyme DOPA decarboxylase and its metabolite acts as an α-adrenergic agonist.



levodopa

1

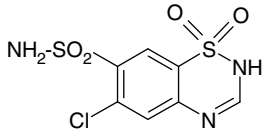


methyldopa

2

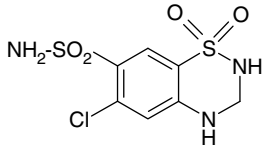
Levodopa and methyldopa are not analogues from the viewpoint of medicinal chemistry. Both are pioneer drugs in their respective therapeutic fields and can be considered as stand-alone drugs, because they have no successful analogues.

There are several examples, and it is a usual case that a minor modification of a drug molecule affords a much more active drug in the same therapeutic field. The pioneer drug chlorothiazide (**3**) and its analogue hydrochlorothiazide (**4**) from Merck Sharp & Dohme differ only by two hydrogen atoms; however, the diuretic effect of hydrochlorothiazide [4] is 10 times higher than that of the original drug. The pioneer drug chlorothiazide is rarely used, but its analogue, hydrochlorothiazide, is an important first-line component in current antihypertensive therapy as a single agent and in combination with other compounds.



chlorothiazide

3



hydrochlorothiazide

4

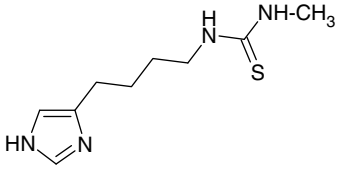
Chlorothiazide and hydrochlorothiazide are *direct analogues*, which term emphasizes their close relationship.

The terms "pioneer drugs" and "analogue drugs" will be discussed in the following sections.

1.1
Monotarget Drugs

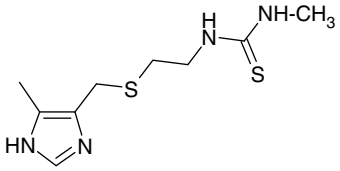
1.1.1
H_2 Receptor Histamine Antagonists

Before the launch of cimetidine (1976), only short-acting neutralization of gastric acid was possible by administration of various antacids (e.g., sodium bicarbonate, magnesium hydroxide, aluminum hydroxide, etc.) that did not affect gastric acid secretion. Cimetidine [5], the first successful H_2 receptor histamine antagonist, a pioneer drug for the treatment of gastric hyperacidity and peptic ulcer disease, was discovered by researchers at Smith, Kline & French. The inhibition of histamine-stimulated gastric acid secretion was first studied in rats. Burimamide (**5**) was the first lead compound, a prototype drug, that also served as a proof of concept for inhibition of acid secretion in human subjects when administered intravenously, but its oral activity was insufficient. Its analogue, metiamide (**6**), was orally active, but its clinical studies had to be discontinued because of a low incidence of granulocytopenia. Replacing the thiourea moiety in metiamide with a cyanoguanidino moiety afforded cimetidine (**7**). Its use provided clinical proof for inhibition of gastric acid secretion and ulcer healing and was a great commercial and clinical success in the treatment of peptic ulcer disease.



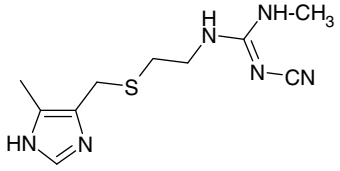
burimamide

5



metiamide

6

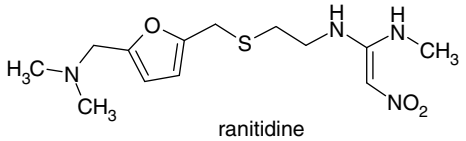


cimetidine

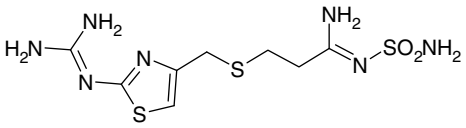
7

Although cimetidine was very effective for the treatment of peptic ulcer disease and related problems of acid hypersecretion, there were some side effects associated with its use, albeit at a very low level. A low incidence of gynecomastia in men can occur at high doses of cimetidine due to its antiandrogen effect. Cimetidine also inhibits cytochrome P450, an important drug metabolizing enzyme. It is therefore advisable to avoid coadministration of cimetidine with certain drugs such as propranolol, warfarin, diazepam, and theophylline.

Cimetidine led to the initiation of analogue-based drug research affording more potent analogue drugs such as ranitidine (**8**) and famotidine (**9**) that lack the above side effects of cimetidine.



ranitidine
8



famotidine
9

Ranitidine [6] also has a pioneer character, because ranitidine is the first H_2 receptor histamine antagonist that has no antiandrogen adverse effect and does not inhibit the cytochrome CYP450 enzymes. Famotidine is the most potent member of this drug class, which has been discussed in Volume I of this series [7].

Summary:

Pioneer H_2 receptor histamine antagonist: cimetidine.
First H_2 receptor histamine antagonist with no antiandrogen adverse effects and without inhibition of P450 enzymes: ranitidine.

1.1.2 ACE Inhibitors

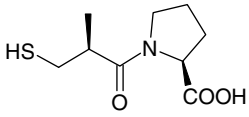
A natural product, the nonapeptide teprotide (**10**), was the pioneer drug for angiotensin-converting enzyme (ACE) inhibitors. Teprotide [8] was used as an active antihypertensive drug in patients with essential hypertension. It could only be administered parenterally, which is a great drawback for chronic use of a drug. A breakthrough occurred with the approval of the first orally active ACE inhibitor captopril (**11**) in 1980 by Squibb. Captopril [9] has a short onset time (0.5–1 h), and its duration of action is also relatively short (6–12 h); as a result, two to three daily doses are necessary. Captopril can be regarded as a pharmacological analogue of teprotide, but it is also the pioneer orally active ACE inhibitor. Captopril's discovery

initiated intensive research by several other drug companies to discover longer acting ACE inhibitors. Enalapril (**12**) was introduced by Merck in 1984. Enalapril [10] can be regarded as the first long-acting oral ACE inhibitor. The long-acting ACE inhibitors are once-daily antihypertensive drugs. There are several long-acting ACE inhibitors, whose differences have been discussed in the first volume of this book series [11].

pyro-Glu - Trp - Pro - Arg - Pro - Gln - Ile - Pro - Pro -OH

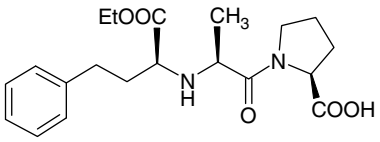
teprotide

10



captopril

11



enalapril

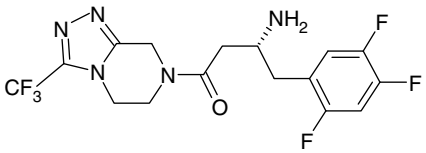
12

Summary:

Pioneer ACE inhibitor drug: teprotide.
First orally active ACE inhibitor drug: captopril.
First orally long-acting ACE inhibitor drug: enalapril.

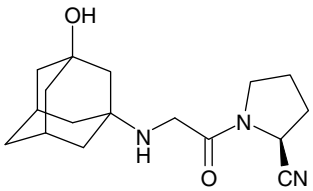
1.1.3 DPP IV Inhibitors

Sitagliptin (**13**) [12], a pioneer dipeptidyl peptidase IV (DPP IV) inhibitor, was launched in 2006 by Merck for the treatment of type 2 diabetes. The medicinal chemistry team began its research in 1999 when some DPP IV inhibitor molecules were known as substrate-based analogues. The lead molecule derived from this research was vildagliptin (**14**) [13]; discovered at Novartis in 1998, it was the second compound to be introduced to the market.



sitagliptin

13



vildagliptin

14

The pioneer drug sitagliptin is a commercial success with 2010 sales greater than USD 3 billion. Vildagliptin was the first successful discovery in this drug class, but its development time was longer and it was introduced in 2007, after sitagliptin. Vildagliptin is only moderately selective over DPP-8 and DPP-9 compared to sitagliptin that is a highly selective DPP IV inhibitor. Based on long-term safety studies, these selectivity differences do not influence the toxicity of vildagliptin. Sitagliptin and vildagliptin show similar clinical efficacies. Vildagliptin has a short half-life (3 h) and its dosing regimen is twice a day, whereas sitagliptin has a long half-life (12 h) and once-daily dosing is used. DPP IV inhibitors are typical early-phase analogues that result from a highly competitive industry, and not the first candidate (vildagliptin) but a follow-on drug (sitagliptin) became the pioneer drug on the market ("first-in-class drug"). Further DPP IV inhibitors are available (alogliptin, saxagliptin, and linagliptin) and the individual compounds differ significantly in their mode of metabolism and excretion and these differences help the treatment of patients with type 2 diabetes in an individual way [14] (see Chapter 5 of Volume II of this book series).

Summary:

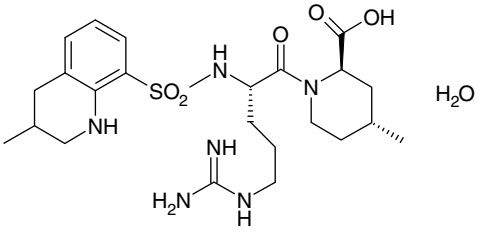
Pioneer DPP IV inhibitor drug: sitagliptin (long-acting inhibitor).
First DPP IV inhibitor analogue drug: vildagliptin (short-acting inhibitor).

1.1.4 Univalent Direct Thrombin Inhibitors

Thrombin is a serine protease enzyme whose inhibition plays an important role in the mechanism of several anticoagulants. Univalent direct thrombin inhibitors bind only to the active site of the enzyme, whereas bivalent direct thrombin inhibitors (e.g., hirudin and bivalirudin) block thrombin at both the active site and exosite 1.

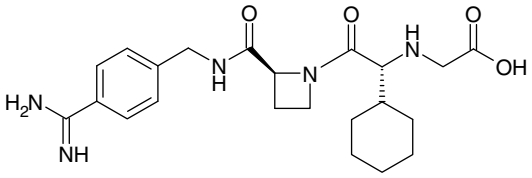
The pioneer univalent direct thrombin inhibitor is argatroban monohydrate (**15**) [15] that was launched by Daiichi Pharmaceutical and Mitsubishi Pharma in 1990. Argatroban was approved by the FDA for prophylactic anticoagulation in the treatment of thrombosis in patients with heparin-induced thrombocytopenia. Argatroban is a rather selective reversible inhibitor for human thrombin. Despite its low molecular weight, argatroban is administered parenterally due to the presence of the highly basic guanidine moiety that prevents absorption from the

gastrointestinal tract. This characteristic limits the clinical use of the compound. The first oral direct thrombin inhibitor was ximelagatran (**17**) [16], which was introduced in 2004 by AstraZeneca. Ximelagatran is a double prodrug derivative of melagatran (**16**) with a bioavailability of about 20%, a measurable improvement compared to melagatran with oral bioavailability of 5.8%. Ximelagatran was withdrawn from the market in 2006 because of unacceptable hepatic side effects (alanine aminotransferase increased threefold and bilirubin level increased twofold above the normal upper limit) [17]. In this drug class, dabigatran etexilate (**18**) [18] was discovered by Boehringer Ingelheim as a new direct thrombin inhibitor without adverse liver effects [19] (see Chapter 10)



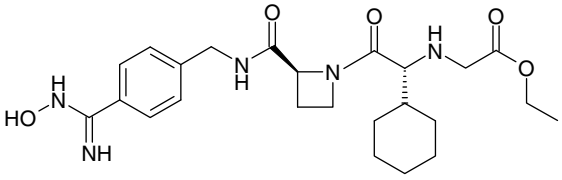
argatroban monohydrate

15



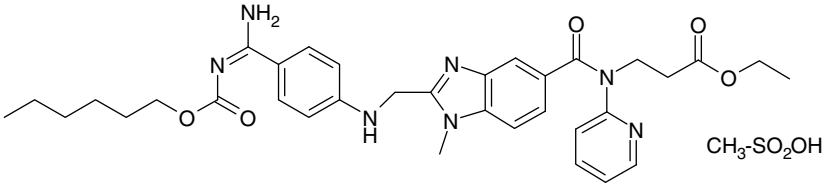
melagatran

16



ximelagatran

17



dabigatran etexilate mesylate

18

Summary:

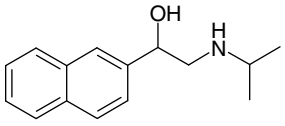
Pioneer univalent direct thrombin inhibitor drug: argatroban.
First orally active univalent thrombin inhibitor: ximelagatran.
First orally active univalent thrombin inhibitor without adverse liver affects: dabigatran etexilate.

1.2 Dual-Acting Drugs

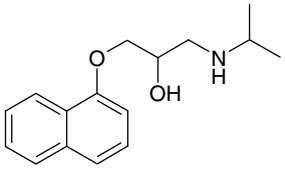
1.2.1 Monotarget Drugs from Dual-Acting Drugs

1.2.1.1 Optimization of Beta-Adrenergic Receptor Blockers

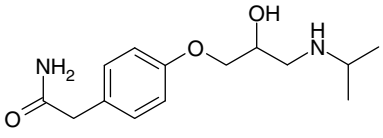
James W. Black and coworkers at ICI invented propranolol as a product of analogue-based drug discovery (ABDD) using their prototype drug, pronethalol (**19**), as a lead compound. Pronethalol [20] was an active drug for the treatment of angina pectoris in humans, but its development was discontinued because it proved to be carcinogenic in mice in long-term toxicology studies. Continuation of the analogue-based drug discovery afforded propranolol (**20**), where an oxymethylene link was inserted between the 1-napthyl group and the secondary alcohol moiety of pronethalol. Propranolol [21] was more potent than pronethalol. Propranolol became the pioneer nonselective β-adrenergic receptor antagonist, a true antagonist without partial agonist properties (intrinsic sympathomimetic activity). It was a breakthrough discovery for the treatment of arrhythmias, angina pectoris, and hypertension.



pronethalol
19



propranolol
20



atenolol
21

The pioneer drug propranolol has equal antagonist affinity for β_1 and β_2 adrenergic receptors; however, β_1 receptors are located only in the heart and the nonselective propranolol also blocks β_2 receptors in bronchial smooth muscle. Therefore, propranolol is not used in patients with bronchial asthma. Several analogues have been tested in a battery of *in vivo* pharmacological tests resulting in the discovery of atenolol (**21**) [22]. A guinea pig bronchospasm test served for investigation and demonstration of β_1 selectivity. Atenolol had no intrinsic sympathomimetic effect (partial agonism), similar to propranolol (see Chapter 8 of Volume I (Part II) of this book series).

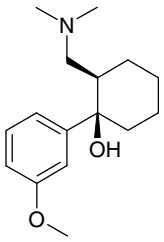
Summary:

Pioneer dual-acting (β_1 and β_2) beta-adrenergic receptor antagonist: propranolol. First β_1 selective antagonist drug without intrinsic sympathomimetic activity: atenolol.

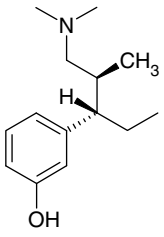
1.2.2 Dual-Acting Drugs from Monotarget Drugs

1.2.2.1 Dual-Acting Opioid Drugs

Most ligands designed from the morphine template are mu (μ) opioid receptor (MOP) agonists. A simplified version of the morphine skeleton afforded tramadol that is marketed in its racemic form. The (+)-isomer is a weak MOP agonist, whereas the (−)-isomer inhibits neurotransmitter reuptake. Tramadol (**22**) [23] was discovered by Grünenthal and was introduced in 1977 for the treatment of moderate to severe pain.



tramadol
22



tapentadol
23

Grünenthal continued analogue-based drug research using tramadol as a starting compound, and out of several analogues, tapentadol (**23**) [24] was selected and developed. It was introduced in 2009 to the market as a new opioid analgesic drug with dual activity: a MOP agonist and an inhibitor of norepinephrine reuptake. Tramadol is thousands of times less potent than morphine on the mu opioid receptor, whereas tapentadol's analgesic activity is comparable to that of oxycodone with reduced constipation and respiratory depression (see Chapter 12).

Summary:

Pioneer dual-acting (MOP agonist and norepinephrine reuptake inhibitor) opioid drug racemate: tramadol.
First dual-acting (MOP agonist and norepinephrine reuptake inhibitor) opioid drug in a single molecule: tapentadol.

1.3 Multitarget Drugs

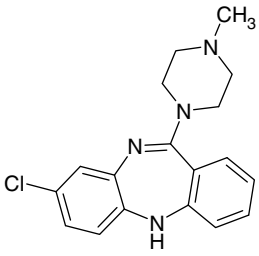
1.3.1 Multitarget Drug Analogue to Eliminate a Side Effect

1.3.1.1 Clozapine and Olanzapine

Clozapine (**24**) [25] is the pioneer drug in the class of atypical antipsychotic agents. It was a serendipitous discovery by researchers at Wander in Switzerland in 1960 from the structural analogue antidepressant amoxapine (**25**). Its discovery was unexpected from the structurally very close analogue and therapeutically it had a great advantage over the typical antipsychotic drugs such as chlorpromazine and haloperidol because clozapine produced no extrapyramidal side effects (EPS). Clozapine causes agranulocytosis in about 1% of the patients, and this side effect limited its application. Analogue-based drug design afforded quetiapine (**26**) [26], a clozapine analogue without this side effect. It was discovered at ICI in 1986 and it became one of the main products of AstraZeneca. Instead of the dibenzodiazepine nucleus of clozapine, the analogue quetiapine has a dibenzothiazepine scaffold. Both clozapine and quetiapine have affinity for a number of receptors. The antipsychotic activity is believed to be associated primarily by virtue of affinity for D_2 and 5-HT_{2A} receptors. Chapter 3 discusses metabolic aspects that may contribute to the distinct adverse event profiles of these two drugs (see the chapter of Volume I on clozapine analogues).

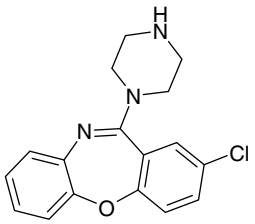
Summary:

Pioneer atypical antipsychotic drug: clozapine.
First atypical clozapine-like antipsychotic drug without the side effect of agranulocytosis: quetiapine.



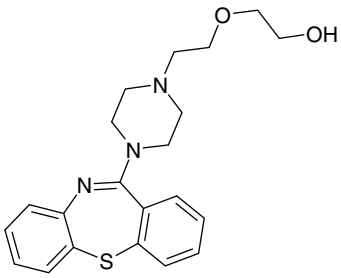
clozapine

24



amoxapine

25



quetiapine

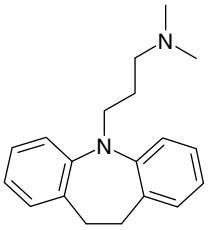
26

1.3.2

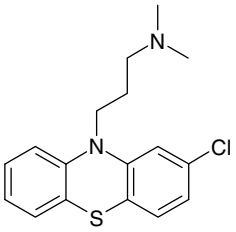
Selective Drug Analogue from a Pioneer Multitarget Drug

1.3.2.1 Selective Serotonin Reuptake Inhibitors

From a retrospective viewpoint, imipramine (**27**) was the pioneer antidepressant drug with a multitarget receptor profile, where serotonin and norepinephrine reuptake inhibition played an important role, but no *in vitro* activities were known at the time of its serendipitous discovery. Researchers at Geigy first synthesized the molecule in 1948. It was an analogue of the antipsychotic chlorpromazine (**28**), but the Swiss psychiatrist Roland Kuhn [27] found imipramine to be an effective antidepressant drug. It was launched by Geigy in 1959.

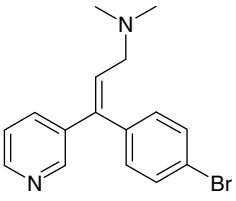


imipramine
antidepressant
27



chlorpromazine
antipsychotic
28

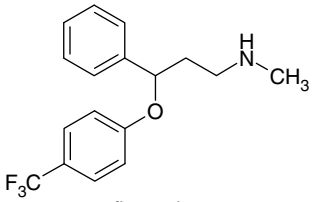
Imipramine and the analogue tricyclic antidepressants inhibit the reuptake of serotonin and norepinephrine but they also exhibit a variety of side effects. The anticholinergic side effects include dry mouth, blurred vision, and sinus tachycardia. The histamine H_1 receptor antagonist activity likely contributes to the sedative effects associated with the compound.



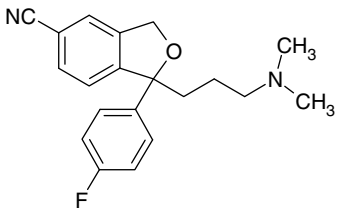
zimelidine
29

Arvid Carlsson initiated research on selective serotonin reuptake inhibitors (SSRIs) in order to get new antidepressants with less side effects. The first SSRI was zimelidine (**29**) [28]. It was launched by Astra in 1982, but it had to be withdrawn shortly afterward because of serious peripheral nerve side effects. Further research was continued at several pharmaceutical companies. The first successful SSRIs were fluoxetine (**30**) [29] (Lilly, 1988) and citalopram (**31**) [30] (Lundbeck, 1989). The antihistamine diphenhydramine (**32**) served as a lead compound for fluoxetine, whereas talopram (**33**) was the lead structure for citalopram. The

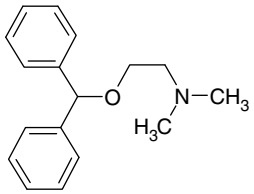
discovery of citalopram and its refinement to escitalopram is discussed in Chapter 11.



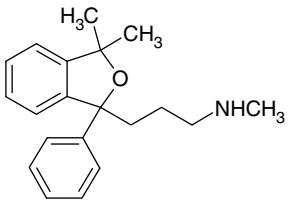
fluoxetine
30



citalopram
31



diphenhydramine
(lead for fluoxetine)
32



talopram
(lead for citalopram)
33

Summary:

Pioneer multitarget nonselective serotonin/norepinephrine reuptake inhibitor antidepressant drug: imipramine.
First (but unsuccessful) selective serotonin reuptake inhibitor: zimelidine.
First selective serotonin reuptake inhibitors: fluoxetine and citalopram.

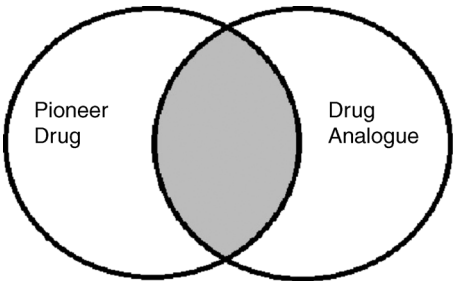


Figure 1.1 Pioneer drugs and drug analogues have overlapping properties.

1.4 Summary

Pioneer drugs open up new therapeutic treatments. They are also called "first-in-class" drugs.

Analogue-based drug discovery is a very important part of medicinal chemistry, because the analogues frequently are intended to optimize drug therapy. There is a continuous development in a drug class and in several cases the pioneer drugs disappear from the market and analogue drugs achieve a dominant role. It is the main reason why so many successful drugs are among the analogue drugs. The above examples focused on some cases where these drugs have a unique character in a drug class.

For early-phase analogues, it is possible that a pioneer drug derives from the analogue-based drug discovery for different reasons; for example, a more convenient lead compound or a more successful optimization can strongly influence which drug will be introduced to the market as a pioneer drug.

There are several examples where a new prototype drug candidate was discontinued at the late phase of drug research and then an analogue was introduced to the market as a successful pioneer drug.

The properties of pioneer and analogue drugs overlap (Figure 1.1). The drug analogues preserve some properties of the pioneer drug and they have to achieve some new and better properties in order to be successful on the market.

Acknowledgments

We thank Klaus Peter Bøgesø, Helmut Buschmann, Jens-Uwe Peters, and Henning Priepke for carefully reading and reviewing the manuscript.

References

1 Fischer, J. (2011) Pioneer and analogue drugs. 43rd IUPAC World Chemistry Congress, August 3, 2011, San Juan, Puerto Rico, Abstract No. 848.

2 Carlson, A. (1971) *Recent Advances in Parkinson's Disease* (eds F.H. McDowett and C.H. Markham), Davis, Philadelphia, PA, pp. 1–10.

3 Oates, J.A., Gillespie, S., Udenfriend, S., and Sjoerdsma, A. (1960) Decarboxylase inhibition and blood pressure reduction of alpha methyl-3,4-dihydroxy-DL-phenylalanine. *Science*, **131**, 1890–1891.

4 DeStevens, G., Werner, L.H., Holamandris, A., and Ricca, S., Jr. (1958) Dihydrobenzothiazine dioxides with potent diuretic effect. *Experientia*, **14**, 463.

5 Ganellin, C.R. (1982) Cimetidine, in *Chronicles of Drug Discovery*, vol. 1 (eds J.S. Nindra and D. Lednicer), John Wiley and Sons, Inc., New York, pp. 1–38.

6 Pearce, P. and Funder, J.W. (1980) Histamine H_2-receptor antagonist: radioreceptor assay for antiandrogenic side effects. *Clin. Exp. Pharmacol. Physiol.*, **7**, 442.

7 Ganellin, C.R. (2006) Development of antiulcer H_2-receptor histamine antagonists, in *Analogue-Based Drug Discovery* (eds J. Fischer and C.R. Ganellin), Wiley-VCH Verlag GmbH, Weinheim, pp. 71–80.

8 Bakhle, Y.S. (1972) Inhibition of converting enzyme by venom peptides, in *Hypertension* (eds J. Genest and E. Koiw), Springer, Berlin, pp. 541–547.

9 Ondetti, M.A., Rubin, B., and Cushman, D.W. (1977) Design of specific inhibitors of angiotensin-converting enzyme: new class of orally active antihypertensive agents. *Science*, **196**, 441–444.

10 Patchett, A.A., Harris, E., Tristram, E.W., Wyvratt, M.J., Wu, M.T., Taub, D., Peterson, E.R., Ikeler, T.J., Ten Broeke, J., Payne, G., Ondeyka, D.L., Thorsett, E.D., Greenlee, W.J., Lohr, N.S., Hoffsommer, R.D., Joshua, H., Ruyle, J., Rothrock, W., Aster, S.D., Maycock, A.L., Robinson, F.M., Hirschmann, R., Sweet, C.S., Ulm, E.H., Gross, D.M., Vassil, C., and Stone, C.A. (1980) A new class of angiotensin-converting enzyme inhibitors. *Nature*, **288**, 280–283.

11 Alföldi, S. and Fischer, J. (2006) Optimizing antihypertensive therapy by angiotensin converting enzyme inhibitors, in *Analogue-Based Drug Discovery* (eds J. Fischer and C.R. Ganellin), Wiley-VCH Verlag GmbH, Weinheim, pp. 169–179.

12 Biftu, T., Scapin, G., Singh, S., Feng, D., Becker, J.W., Eiermann, G., He, H., Lyons, K., Patel, S., Petrvov, A., Sinha-Roy, R., Zhang, B., Wu, J., Zhang, X., Doss, G.A., Thornberry, N.A., and Weber, A.E. (2007) Rational design of a novel, potent and orally bioavailable cyclohexylamine DPP-4 inhibitor by application of molecular modeling and X-ray crystallography of sitagliptin. *Bioorg. Med. Chem. Lett.*, **17**, 3384–3387.

13 Villhauer, E.B., Brinkmann, J.A., Naderi, G.B., Burkey, B.F., Dunning, B.E., Prasad, K., Mangold, B.L., Russell, M.E., and Hughes, T.E. (2003) 1-[[(3-Hydroxy-1-adamantyl)amino]acetyl]-2-cyano-(*S*)-pyrrolidine: a potent, selective, and orally bioavailable dipeptidyl peptidase IV inhibitor with antihyperglycemic properties. *J. Med. Chem.*, **46**, 2774–2789.

14 Peters, J.-U. and Mattei, P. (2010) Dipeptidyl peptidase IV inhibitors for the treatment of type 2 diabetes, in *Analogue-Based Drug Discovery II* (eds J. Fischer and C.R. Ganellin), Wiley-VCH Verlag GmbH, Weinheim, pp. 109–134.

15 Jeske, W., Walenga, J.M., Lewis, B.E., and Fareed, J. (1999) Pharmacology of argatroban. *Expert Opin. Invest. Drugs*, **8** (5), 625–654.

16 Gustafsson, D. and Elg, M. (2003) The pharmacodynamics and pharmacokinetics of the oral direct thrombin inhibitor ximelagatran and its active metabolite melagatran: a mini-review. *Thromb. Res.*, **109** (Suppl. 1), S9–S15.

17 Lee, W.M., Larrey, D., Olsson, R., Lewis, J. H., Keisu, M., Auclert, L., and Shet, S. (2005) Hepatic findings in long-term clinical trials of ximelagatran. *Drug Saf.*, **28** (4), 351–370.

18 Hauel, N.H., Nar, H., Priepke, H., Ries, U., Stassen, J.M., and Wienen, W. (2002) Structure-based design of novel potent nonpeptide thrombin inhibitors. *J. Med. Chem.*, **45**, 1757–1766.

19 Eikelboom, J.W. and Weitz, J.I. (2010) Update on antithrombotic therapy. New anticoagulants. *Circulation*, **121**, 1523–1532.

20 Black, J.W. and Stephenson, J.S. (1962) Pharmacology of a new adrenergic beta-receptor-blocking compound. *Lancet*, **2** (7251), 311–314.

21 Black, J.W., Crowther, A.F., Shanks, R.G., Smith, L.H., and Dornhorst, A.C. (1964) A new adrenergic beta-receptor antagonist. *Lancet*, **1** (7342), 1080–1081.

22 Barrett, A.M., Carter, J., Fitzgerald, J.D., Hull, R., and Le Count, D. (1973) A new type of cardioselective adrenoceptive blocking drug. *Br. J. Pharmacol.*, **48**, 3408.

23 Flick, K., Frankus, E., and Friderichs, E. (1978) Studies of chemical structure and analgetic activity of phenyl substituted aminomethylcyclohexanoles. *Arzneim.-Forsch./Drug Res.*, **28** (I), 107–113.

24 Buschmann, H., Strassburger, W., and Friderichs, F. (2001) 1-Phenyl-3-dimethylaminopropane compounds with a pharmacological effect. EP 693 475.

25 Schmutz, J. and Eichenberger, E. (1982) Clozapine, in *Chronicles of Drug Discoveries*, vol. 1 (eds J.S. Bindra and D. Lednicer), John Wiley & Sons, Inc., New York, pp. 39–60.

26 Szegedi, A., Wiesner, J., Hillert, A., Hammes, E., Wetzel, H., and Benkert, O. (1993) ICI 204,636, a putative "atypical" antipsychotic, in the treatment of schizophrenia with positive symptomology: an open clinical trial. *Pharmacopsychiatry*, **26**, 197.

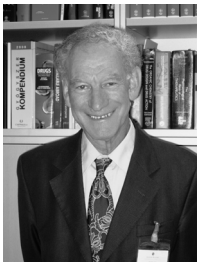
27 Kuhn, R. (1957) Über die Behandlung depressiver Zustände mit einem Iminodibenzyl Derivat (G 22355). *Schweiz. Med. Wochensch.*, **87**, 1135.

28 Montgomery, S.A., McAuley, R., Rani, S.J., Roy, D., and Montgomery, D.B. (1981) A double blind comparison of zimelidine and amitriptyline in endogenous depression. *Acta Psychiatr. Scand. Suppl.*, **290**, 314–327.

29 Wong, D.T., Horng, J.S., Bymaster, F.P., Hauser, K.L., and Malloy, B.B. (1974) A selective inhibitor of serotonin uptake: Lilly 110140, 3-(*p*-trifluoromethylphenoxy)-*N*-methyl-3-phenylpropylamine. *Life Sci.*, **15**, 471–479.

30 Bigler, A.J., Bùgesù, K.P., Toft, A., and Hansen, V. (1977) Quantitative structure–activity relationships in a series of selective 5-HT uptake inhibitors. *Eur. J. Med. Chem.*, **12**, 289–295.

János Fischer is Senior Research Scientist at Richter Plc. (Budapest, Hungary). He received his education in Hungary with M.Sc. and Ph.D. degrees in Organic Chemistry from Eotvos University of Budapest with Professor A. Kucsman. Between 1976 and 1978, he was a Humboldt Fellow at the University of Bonn with Professor W. Steglich. He has worked at Richter Plc. since 1981, where he participated in the research and development of leading cardiovascular drugs in Hungary. His main current interest is analogue-based drug discovery. He is author of some 100 patents and scientific publications. In 2012, he was reelected Titular Member of the Chemistry and Human Health Division of IUPAC. He received an honorary professorship at the Technical University of Budapest.



C. Robin Ganellin studied chemistry at London University, receiving a Ph.D. in 1958 under Professor Michael Dewar, and was a Research Associate at MIT with Arthur Cope in 1960. He then joined Smith, Kline & French Laboratories in the United Kingdom and was one of the co-inventors of the revolutionary drug cimetidine (also known as Tagamet®), eventually becoming Vice President for Research. In 1986, he was made a Fellow of the Royal Society and appointed to the SK&F Chair of Medicinal Chemistry at University College London, where he is now Professor Emeritus of Medicinal Chemistry. Professor Ganellin is co-inventor on over 160 patents and has authored over 250 scientific publications. He was President of the Medicinal Chemistry Section of IUPAC and is currently Chairman of the IUPAC Subcommittee on Medicinal Chemistry and Drug Development.

David P. Rotella is the Margaret and Herman Sokol Professor of Medicinal Chemistry at Montclair State University. He earned a B.S. Pharm. degree at the University of Pittsburgh (1981) and a Ph.D. (1985) at The Ohio State University with Donald. T. Witiak. After postdoctoral studies in organic chemistry at Penn State University with Ken S. Feldman, he worked as an Assistant Professor at the University of Mississippi. David worked at Cephalon, Bristol-Myers, Lexicon, and Wyeth, where he was involved in neurodegeneration, schizophrenia, cardiovascular, and metabolic disease drug discovery projects.