Part I
Introduction

Pharmacophores and Pharmacophore Searches. Edited by T. Langer and R. D. Hoffmann

ISBN: 3-527-31250-1

1
Pharmacophores: Historical Perspective and Viewpoint from a Medicinal Chemist

Camille G. Wermuth

Since the appearance of computer-aided structure–activity studies, the term "pharmacophore" has become one of the most popular words in medicinal chemistry. However, depending on their scientific background and/or traditions, the different medicinal chemistry groups attribute various meanings to this term. Therefore, it appeared necessary to devote a brief paragraph to the definition of the word pharmacophore, and this is followed by a historical perspective and finally by some comments from a medicinal chemistry practitioner.

1.1
Definitions

Many authors use the term "pharmacophores" to define functional or structural elements possessing biological activity. This does not correspond to the official definition elaborated by an IUPAC working party and published in 1998 [1]: *A pharmacophore is the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure and to trigger (or to block) its biological response*. As a consequence:

1. The pharmacophore describes the essential, steric and electronic, function-determining points necessary for an optimal interaction with a relevant pharmacological target.
2. The pharmacophore does not represent a real molecule or a real association of functional groups, but a purely abstract concept that accounts for the common molecular interaction capacities of a group of compounds towards their target structure.
3. Pharmacophores are not specific functional groups (e.g. sulfonamides) or "pieces of molecules" (e.g. dihydropyridines, arylpiperazines).

A pharmacophore can be considered as the highest common denominator of a group of molecules exhibiting a similar pharmacological profile and which are recognized by the same site of the target protein. However, despite the official

Pharmacophores and Pharmacophore Searches. Edited by T. Langer and R. D. Hoffmann

ISBN: 3-527-31250-1

definition and the remarks made above, many medicinal chemists continue to call pharmacophores some specific functional groups, especially if they appear to be often associated with biological activity.

1.1.1 Functional Groups Considered as Pharmacophores: the Privileged Structure Concept

The retrospective analysis of the chemical structures of the various drugs used in medicine led medicinal chemists to identify some molecular motifs that are associated with high biological activity more frequently than other structures. Such molecular motifs were called privileged structures by Evans et al. [2], to represent substructures that confer activity to two or more different receptors. The implication was that the privileged structure provides the scaffold and that the substitutions on it provide the specificity for a particular receptor. Two monographs deal with the privileged structure concept [3, 4].

Among the most popular privileged structures, historical representatives are arylethylamines (including indolylethylamines), diphenylmethane derivatives, tricyclic psychotropics and sulfonamides. Dihydropyridines [5], benzodiazepines, [2, 5], *N*-arylpiperazines, biphenyls and pyridazines [6] are more recent contributions.

A statistical analysis of NMR-derived binding data on 11 protein targets indicates that the biphenyl motif is a preferred substructure for protein binding [7].

1.2 Historical Perspective

1.2.1 Early Considerations About Structure–Activity Relationships

In his interesting Edelstein award lecture, presented at the 224th American Chemical Society Meeting in Boston, MA, in August 2002 and entitled "To Bond or Not to Bond: Chemical Versus Physical Theories of Drug Action", John Parascandola [8] relates the early history of structure–activity relationships.

Regarding drug selectivity, he cites Earles, who states: "The fact that drugs may exert a selective action on specific organs of the body had long been recognized empirically and expressed vaguely in the traditional designation of certain remedies as cordials (acting on the heart), hepatics (acting on the liver), etc." [9].

One of the earliest to recognize structure–activity relationships was Robert Boyle in 1685, who tried to explain the specific effects of drugs in terms of mechanical philosophy by suggesting that since the different parts of the body have different textures, it is not implausible that when the corpuscles of a substance are carried by the body fluids throughout the organism, they may, according to their size, shape and motion, be more fit to be detained by one organ than another [10].

Later, at the turn of the 20th century, the German scientist Sigmund Fränkel argued that the selective action of drugs can only be understood by assuming that certain groups in the drug molecule enter into a chemical union with the cell substance of a particular tissue. Once fixed in the cell in this manner, the drug can exert its pharmacological action [11].

Despite this pioneering view, the understanding of the nature of chemical bonding and of cellular structure and function was still in its infancy at the beginning of the 20th century. Thus there was significant controversy over whether the physical or the chemical properties of a substance could best explain its pharmacological action and over the value of attempts to relate the physiological activity of a drug to its chemical structure. As an example, in 1903 Arthur Cushny, Professor of Materia Medica and Therapeutics at the University of Michigan, published a paper in the *Journal of the American Medical Association* entitled "The pharmacologic action of drugs: is it determined by chemical structure or by physical characters?" [12]. To a chemist today, such a question might seem odd. Finding convincing answers to it became possible only after the discovery of the existence and role of pharmacological receptors.

1.2.2
Early Considerations About the Concept of Receptors

The idea that drugs act upon receptors began with Langley in 1878 [13], who introduced the term "receptive substance" [14]. However, the word "receptor" was introduced later, by Paul Ehrlich [15, 16]. During the first half of the 20th century, several observations highlighted the critical features associated with the concept of receptors [17].

"Three striking characteristics of the actions of drugs indicate very strongly that they are concentrated by cells on small, specific areas known as receptors. These three characteristics are (i) the high dilution (often 10^{-9} M) at which solutions of many drugs retain their potency, (ii) the high chemical specificity of drugs, so discriminating that even D- and L-isomers of a substance can have different pharmacological actions, and (iii) the high biological specificity of drugs, e.g. adrenaline has a powerful effect on cardiac muscle, but very little on striatal muscle." [17].

1.2.3
Ehrlich's "Magic Bullet"

Selective interaction of a drug molecule with the corresponding receptor was not always accepted. One of the most brilliant demonstrations came from Paul Ehrlich's discovery of salvarsan, which gave rise to the concept of a chemotherapeutic "magic bullet" against specific infectious organisms. Beginning with dyes and later extending his studies to include arsenical compounds, Ehrlich modified the chemical structure of numerous molecules to produce effective drugs against trypanosome and later spirochete infections. They tested hundreds of

compounds before they came upon one, number 606, that Ehrlich thought was the chemotherapeutic agent he was searching for. Clinical tests confirmed the potential of the drug in treating syphilis and trypanosomiasis. The discovery was announced in 1910. Ehrlich named the drug salvarsan. The German physician, bacteriologist and chemist Paul Ehrlich shared the Nobel Prize in 1908 with Ilya Metchnikoff for their contributions to immunity.

1.2.4
Fischer's "Lock and Key"

Ehrlich's seminal discoveries reinforced the assertion made in 1894 by another brilliant German chemist, Emil Fischer. In a publication dealing with the effect of glucoside conformation on the interaction with enzymes, he wrote: "Um ein Bild zu gebrauchen, will ich sagen, dass Enzym und Glucosid wie Schloss und Schlüssel zu einander passen müssen, um eine chemische Wirkung auf einander ausüben zu können" (To illustrate, I would like to say that enzyme and glucoside must fit together like lock and key, in order to have a chemical effect on each other) [18]. The image of "lock and key" is still used today, even if it suggests a rigid structure of the receptor or enzyme protein. Probably another image, such as "hand in a glove", would be more accurate. Effectively, in addition to the steric complementarity, it would account for chirality and receptor flexibility.

1.3
Pharmacophores: the Viewpoint of a Medicinal Chemist

Even before the advent of computer-aided drug design, simple pharmacophores were described in the literature and considered as tools for the design of new drug molecules. Initial structure–activity relationship considerations were accessible in the 1940s thanks to the knowledge of the bond lengths and the van der Waals sizes which allowed the construction of simple two-dimensional model structures. With the availability of X-ray analysis and conformational chemistry, access to three-dimensional models became possible in the 1960s.

1.3.1
Two-dimensional Pharmacophores

1.3.1.1 Sulfonamides and PABA

The recognition of the quantitatively almost unmatched ability of *p*-aminobenzoic acid (PABA) to oppose the bacteriostatic efficiency of the sulfonamides led Woods and Fildes [19, 20] to formulate the fundamentals of the theory of metabolite antagonism (Fig. 1.1).

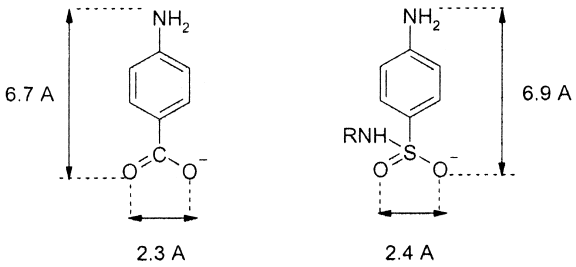

Fig. 1.1 PABA and *p*-aminobenzenesulfonamide show similar critical distances. The incorporation of the sulfonamide instead of PABA inhibits the biosynthesis of tetrahydrofolic acid.

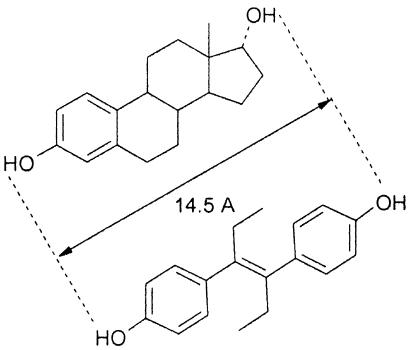

Fig. 1.2 Analogy between estradiol and *trans*-diethylstilbestrol.

1.3.1.2 **Estrogens**

Another early achievement (Fig. 1.2) was the synthesis and the pharmacological evaluation of *trans*-diethylstilbestrol as an estrogenic agent showing similarities with estradiol [21]. Here again the proposed model was two-dimensional [22], despite the fact that the non-planar conformation of estradiol was already known.

1.3.2 **An Early Three-dimensional Approach: the Three-point Contact Model**

When an asymmetric center is present in a compound, it is thought that the substituents on the chiral carbon atom make a three-point contact with the receptor. Such a fit insures a very specific molecular orientation which can only be obtained for one of the two isomers (Fig. 1.3). A three-point fit of this type was first suggested by Easson and Stedman [23], and the corresponding model proposed by Beckett [24] in the case of (*R*)-(–)-adrenaline [= (*R*)-(–)-epinephrine]. The more active natural (*R*)-(–)-adrenaline establishes contacts with its receptor through the three interactions shown in Fig. 1.3.

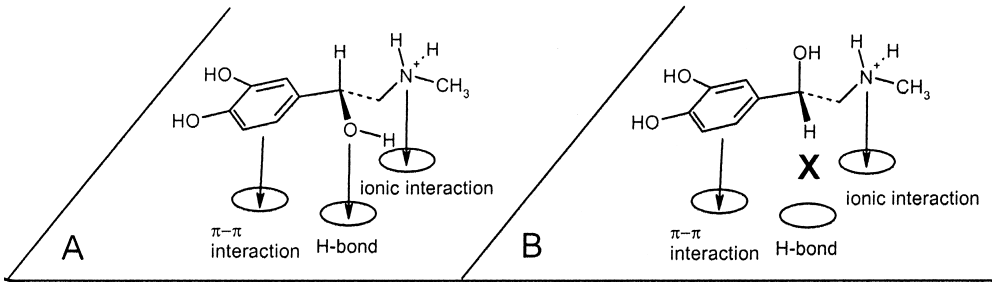

Fig. 1.3 Interaction capacities of the natural (*R*)-(–)-epinephrine and its (*S*)-(+)-antipode.

In simply assuming that the natural (*R*)-(–)-epinephrine establishes a three-point interaction with its receptor (A), the combination of the donor–acceptor interaction, the hydrogen bond and the ionic interaction will be able to generate energies of the order of 12–17 kcal mol^{-1}, which corresponds [25] to binding constants of 10^{-9}–10^{-12}. The less active isomer, (*S*)-(+)-epinephrine, may establish only a two-point contact (B). The loss of the hydrogen bond interaction equals $\sim$3 kcal mol^{-1}, hence this isomer should possess an $\sim$100-fold lesser affinity. Experience confirms this estimate. If we consider less abstract models, it becomes apparent that the less potent enantiomer also is able to develop three intermolecular bonds to the receptor, provided that it approaches the receptor in a different manner. However, the probability of this alternate binding mode to trigger the same biological response is close to zero.

1.3.2.1 Clonidine and Its Interaction with the α-Adrenergic Receptor

In the early 1970s, it was accepted that the hypotensive activity of clonidine was due to its direct interaction with the central norepinephrine receptor [26]. To trigger the α-adrenergic receptor, it was accepted that norepinephrine binds to its receptor by means of three bonds [27, 28]:

1. an ionic bond between the protonated amino function and an anion (carboxylate, phosphate) of the receptor active site;
2. a hydrogen bond between the secondary alcoholic hydroxyl and a, NH–CO function of the receptor;
3. a stacking (or charge transfer?) between the aromatic ring and an electron-deficient ring such as a protonated imidazole of a histidine residue.

In addition, it was known that the phenolic hydroxyls are not essential for α activity and that the cationic head should not be too bulky.

Pullmann et al. [29], in their model of the α-adrenergic receptor, found the following critical intramolecular distances: D=5.1–5.2 Å from N^+ to the center of the aromatic ring and H=1.2–1.4 Å for the elevation of the positive charge to the plane of the aromatic ring (Fig. 1.4).

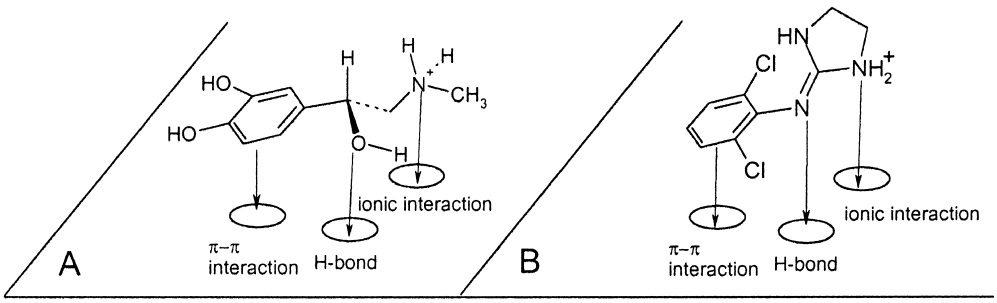

Fig. 1.4 In clonidine (B) the restricted rotation resulting from *o*- and *o'*-substitution imposes a quasi-perpendicular orientation of the imidazolic ring towards the phenyl ring. As a result, clonidine can yield the same kind of interactions than norepinephrine (A).

At first glance, the similarity between clonidine and norepinephrine was not evident; However an NMR structural study of clonidine demonstrated the restricted rotation resulting from *o*- and *o'*-substitution and imposing a quasi-perpendicular orientation of the imidazolic ring towards the phenyl ring [30]. As a result, clonidine can yield the same kind of interactions as norepinephrine.

Taken together, the examples shown above illustrate typically some pre-computer attempts to elucidate pharmacophoric patterns usable as guides for the design of new drugs. They prepared the minds for Garland Marshall's seminal publications (see references in [31, 32]) on computer-aided pharmacophore identification and all the derived applications that will be presented in the following chapters.

1.3.3
Criteria for a Satisfactory Pharmacophore Model [32]

To be recognized as a useful tool, a pharmacophore model has to provide valid information for the medicinal chemist exploring structure–activity relationships.

1. First, it has to highlight the functional groups involved in the interaction with the target, the nature of the non-covalent bonding and the different intercharge distances. This means that worthless images of ribbon and spaghetti models [33], without indication of the molecular features of the interacting partners, have to be avoided. This is true also for many unnecessary and opaque theoretical digressions. The model also has to show some *predictive power* and lead to the design of new, more potent compounds or, even better, of totally novel chemical structures, not evidently deriving from the translation of structural elements from one active series into the other. An interesting aspect of pharmacophore-based analogue design is referred to as scaffold hopping. It consists in the design of functional analogues by searching within large virtual compound libraries of isofunctional structures, but based on a

different scaffold. The objective is to escape from a patented chemical class in identifying molecules in which the central scaffold is changed but the essential function-determining points are preserved and form the basis of a relevant pharmacophore [34].

2. The second criterion for a valid pharmacophore model is that it should discriminate stereoisomers. Stereospecificity is one of the principal attributes of pharmacological receptors and a perfect stereochemical complementarity between the ligand and the binding-site protein is an essential criterion for high affinity and selectivity. A convincing example of enantiomeric discrimination was observed for GABA-A receptor antagonists [35].
3. In a similar manner, the ideal model should distinguish between agonists and antagonists. This is relatively easy for the specific category of antagonists which, according to Ariëns et al. theory [36], derive from the agonists simply through the addition of some supplementary aromatic rings which play the role of additional binding sites (e.g. the passage from muscarinic agonists to muscarinic antagonists [37] or from GABA agonists to GABA antagonists [35]). The discrimination between the two categories becomes less evident when the passage from agonist to antagonist relies on relatively subtle changes such as one observes for glutamate, oxotremorine and benzodiazepine antagonists.
4. Sometimes a good pharmacophore model can *explain* apparently *paradoxical observations*, e.g. the unexpected affinity reversal found in *R*- and *S*-enantiomers of the sulpiride series on changing *N*-ethyl to *N*-benzyl derivatives [38].
5. Finally, it has to account for the *lack of activity* of certain analogues of the active structures. The knowledge of structural or electronic parameters leading to poorly active or inactive compounds is a cost-lowering factor that allows the number of compounds to be synthesized to be reduced.

1.3.4 Combination of Pharmacophores

Some highly specific mono-target drugs have clearly proven the usefulness of mono-target medicine. Examples are phosphodiesterase 5 inhibitors such as sildenafil, the α-1a antagonist drugs such as tamsulosine, selective COX-2 inhibitors such as celecoxib and kinase-specific anticancer drugs such as imatinib. However, in addition to one-target drugs, clinicians are more and more convinced that modulating a multiplicity of targets can be an asset in treating a range of disorders. An extreme example of a multi-target drug is clozapine, which exhibits nanomolar affinities for more than a dozen different receptors.

As a consequence of this trend, an increasing number of publications reflect an awakening of interest in the rational design of multiple ligands and may suggest an ongoing re-evaluation of the "one disease, one drug" paradigm which has dominated thinking in the pharmaceutical industry for the last few decades. Although there is little chance of switching back to the animal-centric approach of the past, it is now widely recognized that high specificity for a single target

may not deliver the required efficacy versus side-effect profile and, in many cases, a balanced activity at several targets may produce a superior effect.

In a recent paper, entitled "From magic bullets to designed multiple ligands", Morphy et al. [39] discuss the opportunity and the advantages attached to the design of ligands acting on two (or more) specific targets, such *intentionally* designed multiple ligands (DM ligands) being opposed to *serendipitous* multiple ligands. It is highly probable that computer-driven combinations of two pharmacophores can lead to the design of new active entities combining in one molecule the critical structural elements of two partners.

1.4 Conclusion

For medicinal chemistry practitioners, the term "pharmacophore" covers two different meanings: "pieces of molecules conferring activity, often referred too as privileged structures" and "the highest common denominators of a group of molecules exhibiting a similar pharmacological profile and which are recognized by the same site of the target protein". The knowledge of the first meaning and its daily use belong to the medicinal chemists' "culture générale".

The second meaning aims to approach drug design by rational, computer-aided reasoning. It usefulness covers three major domains. The first is the establishment of a relevant pharmacophore model, consistent with structure–activity relationships in a series of molecules and allowing the design of optimal ligands. The second is scaffold hopping, which consists in the design of functional analogues by searching within large virtual compound libraries of isofunctional structures, but based on a different scaffold. The third deals with computer-driven combinations of two pharmacophores in the hope of designing new active entities combining in one molecule the critical pharmacophoric elements of two partners. All these applications will be presented and discussed in the following chapters of this book.

References

1 Wermuth, C.G., Ganellin, C.R., Lindberg, P., Mitscher, L.A., Glossary of terms used in medicinal chemistry (IUPAC Recommendations 1997). *Annu. Rep. Med. Chem.* **1998**, *33*, 385–395.

2 Evans, B.E., Rittle, K.E., Bock, M.G., DiPardo, R.M., Freidinger, R.M., Whitter, W.L., Lundell, G.F., Veber, D.F., Anderson, P.S., Chang, R.S., Lotti, V.J., Cerno, D.J., Chen, T.B., Kling, P.J., Kunkel, K.A., Springer, J.P., Hirshfield, J., Methods for drug discovery: development of potent, selective, orally effective cholecystokinin antagonists. *J. Med. Chem.* **1988**, *31*, 2235–2246.

3 Trainor, G., Privileged structures – an update. *Annu.Rep. Med. Chem.* **2000**, *35*, 289–298.

4 Sheridan, R.P., Miller, M.D., A method for visualizing recurrent topological substructures in sets of active molecules. *J. Chem. Inf. Comput. Sci.* **1998**, *38*, 915–924.

5 Thompson, L.A., Ellman, J.A., Synthesis and applications of small molecule libraries. *Chem. Rev.* **1966**, *96*, 555–600.

6 Wermuth, C.G., Search for new lead compounds: the example of the chemical and pharmacological dissection of aminopyridazines. *J. Heterocycl. Chem.*, **1998**, *35*, 1091–1100.

7 Hajduk, P.J., Bures, M., Praestgaard, J., Fesik, S.W., Privileged molecules for protein binding identified from NMR-based screening. *J. Med. Chem.* **2000**, *43*, 3443–3447.

8 Parascandola, J., To bond or not to bond. *Bull. Hist. Chem.* **2003**, 28.

9 Earles, M.P., Early theories of the mode of action of drugs and poisons. *Ann. Sci.* **1961 (publ. 1963)**, *17*, 97–110.

10 Boyle, R., *Of the Reconcileableness of Specific Medicines to the Corpuscular Philosophy.* Samuel Smith, London, **1685**, pp. 72–75.

11 Fränkel, S., *Die Arzneimittel-Synthese auf Grundlage der Beziehungen zwischen chemischem Aufbau und Wirkung.* Julius Springer, Berlin, **1901**, pp. 13–41.

12 Cushny, A.R., The pharmacologic action of drugs: is it determined by chemical structure or by physical characters? *J. Am. Med. Assoc.* **1903**, *41*, 1252–1253.

13 Langley, J.N., On the physiology of the salivary secretion. Part II. On the mutual antagonism of atropin and pilocarpin, having especial reference to their relations in the sub-maxillary gland of the cat. *J. Physiol.* **1878**, *1*, 339–369.

14 Langley, J.N., On the reaction of cells and nerve-endings to certain poisons, chiefly as regards the reaction of striated muscle to nicotine and to curari. *J. Physiol.* **1905**, *33*, 374–413.

15 Ehrlich, P., Morgenroth, J., Über Haemolysine. Dritte Mitteilung. *Berl. Klin. Wochnschr.* **1900**, *37*, 453–457.

16 Maehle, A.H., Prull, C.R., Halliwell, R.F., The emergence of the drug receptor theory. *Nat. Rev. Drug Discov.* **2002**, *1*, 637–641.

17 Albert, A., *Selective Toxicity. The Physicochemical Basis of Therapy.* Chapman and Hall, London, **1979**, p. 23

18 Fischer, E., Einfluss der Konfiguration auf die Wirkung der Enzyme. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 2985–2993.

19 Woods, D.D., The relation of *p*-aminobenzoic acid to the mechanism of the action of sulphonamide. *Br. J. Exp. Pathol.* **1940**, *21*, 74–90.

20 Woods, D.D., Fildes, P., The anti-sulphanilamide activity (*in vitro*) of *p*-aminobenzoic acid and related compounds. *Chem. Ind.* **1940**, *59*, 133–134.

21 Dodds, E.C., Lawson, W., Molecular structure in relation to oestrogenic activity. Compounds without phenanthrene nucleus. *Proc. R. Soc. London, Ser. B* **1938**, *125*, 122–132.

22 Schueler, F.W., Sex hormonal action and chemical constitution. *Science* **1946**, *103*, 221–223.

23 Easson, L.H., Stedman, E., Studies on the relationship between chemical constitution and physiological action. V. Molecular dissymmetry and physiological activity. *Biochem. J.* **1933**, *27*, 1257–1266.

24 Beckett, A.H., Stereochemical factors in biological activity. In *Fortschritte der Arzneimittel Forschung*, Birkhäuser Verlag, Basel, **1959**, pp. 455–530.

25 Farmer, P.S., Ariëns, E.J., Speculations on the design of nonpeptide peptidomimetics. *Trends Pharmacol. Sci.* **1982**, *3*, 362–365.

26 Anden, N.E., Corrodi, H., Fuxe, K., Hoekfelt, B., Hoekfelt, T., Rydin, C., Svensson, T., Evidence for a central noradrenaline receptor stimulation by clonidine. *Life Sci.* **1970**, *9*, 513–523.

27 Barlow, R.B., *Introduction to Chemical Pharmacology*, 2nd edn. Methuen, London, **1964**.

28 Belleau, B., An analysis of drug-receptor interactions. In *Modern Concepts in the Relationship Between Structure and Pharmacological Activity*, Brunings, K.J. (ed.). Pergamon Press, Oxford, **1963**, pp. 75–99.

29 Pullmann, B., Coubeils, J.L., Courrière, P., Gervois, J.P., Quantum mechanical study of the conformational properties of phenethylamines of biochemical and medicinal interest. *J. Med. Chem.* **1972**, *15*, 17–23.

30 Wermuth, C.G., Schwartz, J., Leclerc, G., Garnier, J.P., Rouot, B., Conformation de la clonidine et hypothèses sur son interaction avec un récepteur alpha-adrénergique. *Chim. Thér.* **1973**, *1*, 115–116.

31 Marshall, G. R., Binding-site modeling of unknown receptors. In *3D QSAR in Drug Design, Theory Methods and Applications*, Kubinyi, H. (ed.). ESCOM, Leiden, **1993**, pp. 80–116.

32 Wermuth, C. G., Langer, T., Pharmacophore identification. In *3D QSAR in Drug Design. Theory Methods and Applications*, Kubinyi, H. (ed.). ESCOM, Leiden, **1993**, pp. 117–136.

33 Wermuth, C. G., The impact of QSAR and CADD methods in drug design. In *Rational Approaches to Drug Design*, Hoeltje, H. D., Sippl, W. (eds.). Prous Science, Barcelona, **2001**, pp. 3–20.

34 Schneider, G., Giller, T., Neidhart, W., Schmid, G., "Scaffold-hopping" by topological pharmacophore search: a contribution to virtual screening. *Angew. Chem. Int. Ed.* **1999**, *38*, 2894–2896.

35 Rognan, D., Boulanger, T., Hoffmann, R., Vercauteren, D. P., André, J. M., Durant, F., Wermuth, C. G., Structure and molecular modeling of GABAA antagonists. *J. Med. Chem.* **1992**, *35*, 1969–1977.

36 Ariëns, E. J., Rodrigues de Miranda, J. F., Simonis, A. M., The pharmacon-receptor–effector concept: a basis for understanding the transmission of information in biological systems. In *The Receptors*, O'Brien, R. D. (ed.). Plenum Press, New York, **1979**, pp. 33–91.

37 Wermuth, C. G., Aminopyridazines–an alternative route to potent muscarinic agonists with no cholinergic syndrome. *Farmaco* **1993**, *48*, 253–274.

38 Rognan, D., Sokoloff, P., Mann, A., Martres, M. P., Schwartz, J. C., Costentin, J., Wermuth, C. G., Optically active benzamides as predictive tools for mapping the dopamine D2 receptor. *Eur. J. Pharmacol. Mol. Pharmacol. Sect.* **1990**, *3*, 59–70.

39 Morphy, R., Kay, C., Rankovic, Z., From magic bullets to designed multiple ligands. *Drug Discov. Today* **2004**, *9*, 641–651.