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Monty Kier and the Origin of the Pharmacophore Concept

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Monty Kier and the Origin of the Pharmacophore Concept [#]

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Abstract

The historical evolution of the concept of a pharmacophore is presented, from its initial articulation by Kier in the late 1960's to its current implementations in commonly–used modeling software. Its impact on a variety of different areas of computer–aided drug design is described.

Keywords. Pharmacophore; virtual screening; receptor theory.

1 INTRODUCTION

One of the most enduring concepts of computer–aided drug design is that of a 'pharmacophore'. Simply stated, a pharmacophore is the spatial arrangement of functional groups essential for biological activity; it is a three–dimensional pattern that emerges from a set of biologically active molecules. It is widely believed that this is an ancient concept; some even credit Paul Ehrlich, the father of drug discovery, with the introduction of this term in the early 1900's, though this is erroneous. In fact, the concept of a pharmacophore was introduced by Monty Kier in a series of papers which were published 1967–1971, at a time when he was at the Battelle Institute in Ohio and lecturing as an adjunct professor at the University of Michigan.

2 THE EARLIEST DAYS

Kier [1], using Roald Hoffmann's extended–Hückel–theory quantum mechanics package in a study of muscarinic agonists, was the first to calculate a pharmacophore; in that 1967 paper he called it a 'proposed receptor pattern'. However, by 1971 [2] he labelled that identical figure a 'muscarinic pharmacophore'. That muscarinic pharmacophore which appears in both publications is reproduced here as Figure 1. In 1971, Kier was using the term 'pharmacophore' in the modern

sense, as defined above. The Oxford English Dictionary [3], also credits this 1971 Kier paper as the first appearance in the published English language of the word pharmacophore.
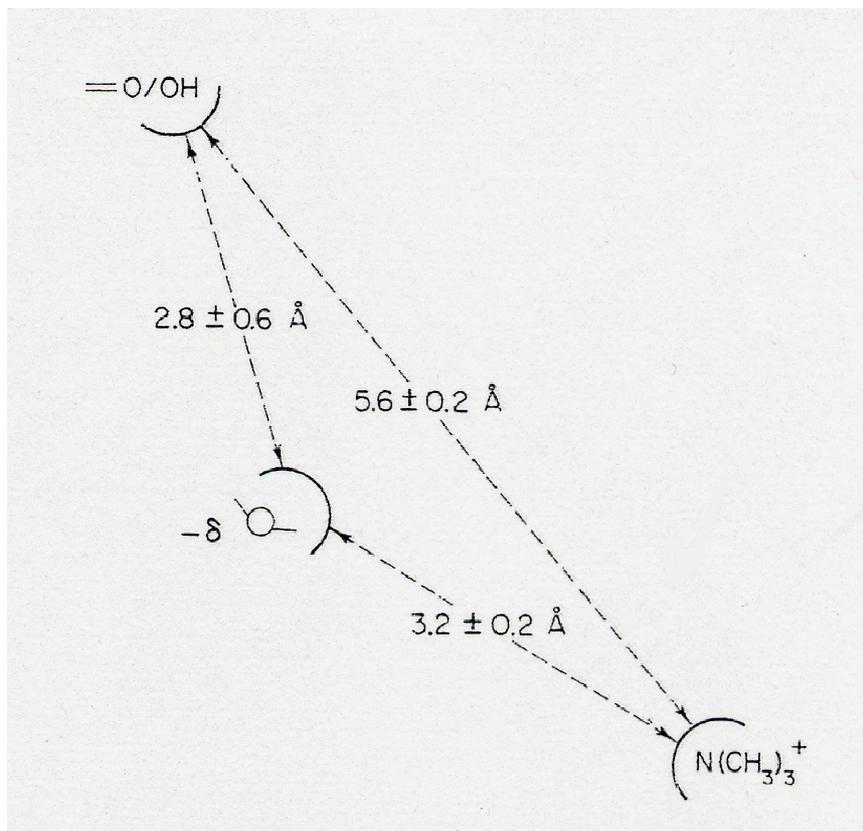

Figure 1. The first published pharmacophore, by Kier, for muscarinic agonists [1,3,4].

An intervening publication by Kier in 1970 reveals more deeply his thought processes [4]. These thought processes were astonishingly prescient, defining the process of 'receptor mapping', which became much of what was molecular modeling in drug design prior to the era of structure–based drug design:

"A useful concept to the scientist interested in drug phenomena in the body is that there is some substance present in tissue which possesses features enabling the tissue to interact with a drug molecule. Langley (J. Physiol., 1878, 1:339) first proposed that there was some substance in tissue which made it capable of this interaction with a drug molecule, and the term 'receptor' has since been generally used to describe this tissue feature. Considering all that has been written, receptors and drug–receptor interactions remain remarkably elusive to physical and chemical description. Indeed, not a great deal more is known about the nature of the receptor or its drug interaction than was known in the days of Langley. The characterization of receptors by isolation and structural analysis of tissue components has not met with success. The view is widely held that the receptor is not an unalterable physical entity but a pattern of forces arrayed over the secondary and even tertiary structures of biopolymers. A conventional isolation and analysis could thus disrupt this

pattern of forces, leaving only a biopolymer devoid of features complementary and susceptible to the drug molecule. It has become necessary to attempt to characterize the nature of receptors indirectly, by characterizing the interacting drug molecule. This approach has centered around the elucidation of key atoms, groups, charged regions, and their spatial interrelation, all of which impart biological activity of a defined sort to a drug molecule. The approach is predicated on the hypothesis that the key features of a drug molecule are complementary (either upon initial interaction or sequentially upon subsequent engagement) to receptor features. It must be recognized that complementarity must be defined more broadly than within the rigid context of the 'lock and key' connotation. This is necessary since it is conceivable that a primary engagement of a drug–molecule feature with a receptor feature may induce a change in the receptor which brings into juxtaposition additional drug and receptor features. Nevertheless, the key features of an active drug molecule must still be optimally positioned in the molecule to participate in the ultimate drug–receptor interaction in an efficacious manner, regardless of the sequence of events. *The medicinal chemist and the molecular pharmacologist have thus addressed themselves to the problem of defining the properties and positions of these essential drug–molecule features, and the term 'pharmacophoric moiety' has been used to designate this receptor–specific pattern*. An early approach was the dissection of large active drug molecules (from natural sources) into smaller synthetic version in which a variety of original features were retained. Classical examples are the dissection of atropine into smaller molecules possessing the bulky group and the aminoethanol 'spasmophoric' moiety, and the dissection of cocaine into smaller molecules possessing the local–anesthetic moiety. With subsequent synthetic modification of these molecules and testing, the essential nature of certain atoms in specific relationships was deduced and some insight into the possible nature of the complementary receptor pattern was gained. As an extension of this early work, a large amount of information has been accumulated on the effect of different chemical groups in different positions on the molecule. This has given rise to a host of empirical 'structure–activity relationships' (SAR) for many drug classes. Using valence–bond reasoning (resonance theory) and SAR, medicinal chemists have reached conclusions on the nature of electronic charges at certain positions in the molecule. The problem of relating SAR information to complementary receptor features and to the design of active synthetic analogs has been complicated by the fact that the conformation of many potent drug molecules is not readily apparent from inspection or chemical intuition. Single bonds (sigma bonds) have in the past been generally regarded as being 'free to rotate', hence their conformations were not readily predictable. One attempt to circumvent this dilemma was to synthesize rigid molecules containing the presumed active sites in configurations in which interatomic distances could be nearly exactly calculated; comparative activity data were then used to select the configuration which had the optimum key interatomic distances. Out of all of these efforts have emerged some receptor hypotheses and some successful rationale for the design of new and useful drug molecules".

3 WORK FOLLOWING KIER'S PIONEERING EFFORTS

Kier's work, though now largely forgotten, inspired much of what was to follow. The first paper to follow in his footsteps was one from 1973 by Y. C. Martin and colleagues in the calculation of a dopamine agonist pharmacophore [5]; this work followed his approach closely, and cited Kier's work as reference 1.

The oldest publication indexed in Medline which includes the word pharmacophore dates from 1974, a paper by Höltje [6]. Höltje was a post–doc of Kier's at that time, learning about receptor mapping and pharmacophores while with Kier at the Massachusetts College of Pharmacy; Höltje used this work for his Habilitation upon his return in Germany. Höltje has continued on that path ever since; Kier moved on to other research topics.

Kier's work on 'quantum pharmacology' inspired a young Graham Richards to switch his interest in chemical quantum mechanics from di– and triatomic molecules to biomolecules. Richards, at Oxford for many years, continues along this path, while branching out in many fertile directions.

An independent but slightly later appearance of the use of pharmacophores came from Peter Gund, while a student in the lab of Todd Wipke at Princeton. Peter has recently said that his inspiration for writing the MOLPAT program, the first software for performing 3D database searching using a pharmacophore as a query, came from reading Korolkovas' *Essentials of Molecular Pharmacology* [7]. Korolkovas does *not* abstract this into the general pharmacophore concept – he usually depicts specific ligands bound to imaginary receptors, sometimes with distances. It was evidently the insight of Gund that took the leap from Korolkovas' pictures to the atom–based pharmacophores of MOLPAT [8]. Gund's MOLPAT paper cites Kier's muscarinic pharmacophore, though it's unclear whether Kier's work directly impacted Gund's thinking. Gund moved to Merck in 1980, and discontinued work on MOLPAT. Peter Willett's work beginning in the mid–1980's on 3D database searching was directly inspired by MOLPAT.

The person that many associate closely with the pharmacophore concept is Garland Marshall, who both founded Tripos Associates in the late 1970's, a pioneer in commercializing molecular modeling software, and the Journal of Computer–Aided Molecular Design in the mid–1980's. Marshall's seminal paper on the Active Analog Approach [9], cites only Peter Gund's MOLPAT paper as the reference for pharmacophores. Marshall's Tripos software implicitly embedded many of his active analog concepts, and was used by many in the pharmaceutical industry for the development of their first pharmacophores, many of which were published in the early volumes of the Journal of Computer–Aided Molecular Design.

This author's work with Yvonne Martin at Abbott 1986–1989 on ALADDIN pharmacophoric 3D database searching [10] was directly inspired by Marshall's work, though, as cited above,

Yvonne's earlier interest was stimulated by Kier's 'receptor mapping'. With ALADDIN, we aimed to make the concept of a pharmacophore precise and unambiguous, and to use pharmacophores to look for known molecules with unanticipated biological activities, a process which became known as 'virtual screening'. ALADDIN was used to perform the first successful virtual screen, the discovery of a novel D1 agonist lead [11].
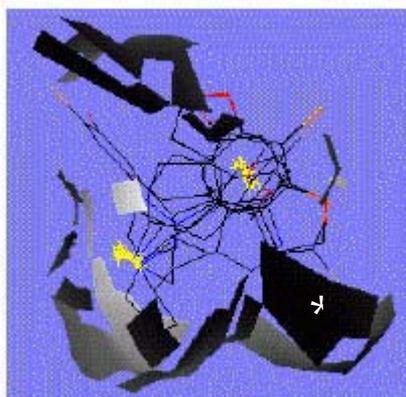

Figure 2. The author's 5–HT2c pharmacophore [13], created using his DANTE software. The asterisk marks one of the many sterically–forbidden regions.
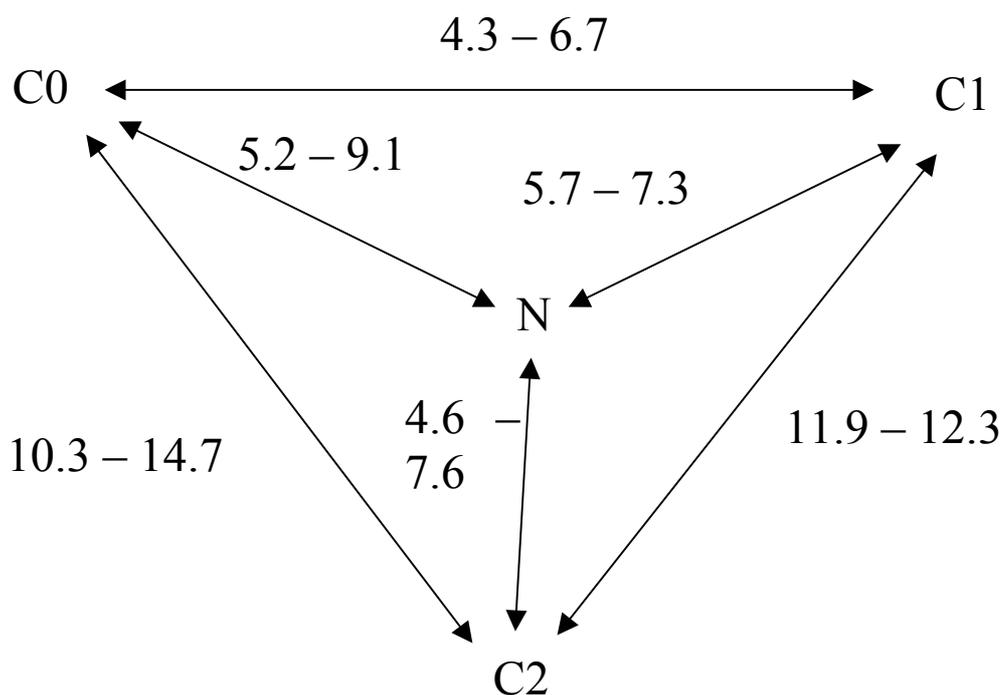

Figure 3. Simplified rendition of the hERG pharmacophore of Cavalli *et al*. [14]. N represents a basic amine, and C0, C1, C2 are the centroids of aromatic rings.

This author helped found the company BioCAD in 1990, where we developed the Catalyst software, following the approach used with ALADDIN. Catalyst is now marketed by Accelrys, acquired in the wake of the BioCAD's demise in 1994. Catalyst has done much to popularize the

use of pharmacophores in drug design; it was the first piece of modeling software to be constructed around the concept of a pharmacophore. 3D database searching is now routinely used in the pharmaceutical industry, to perform virtual screening [12]. Modern examples of pharmacophores are shown in Figures 2 and 3, a 5–HT2c pharmacophore developed by this author [13] and a hERG pharmacophore developed by Cavalli *et al*. [14].

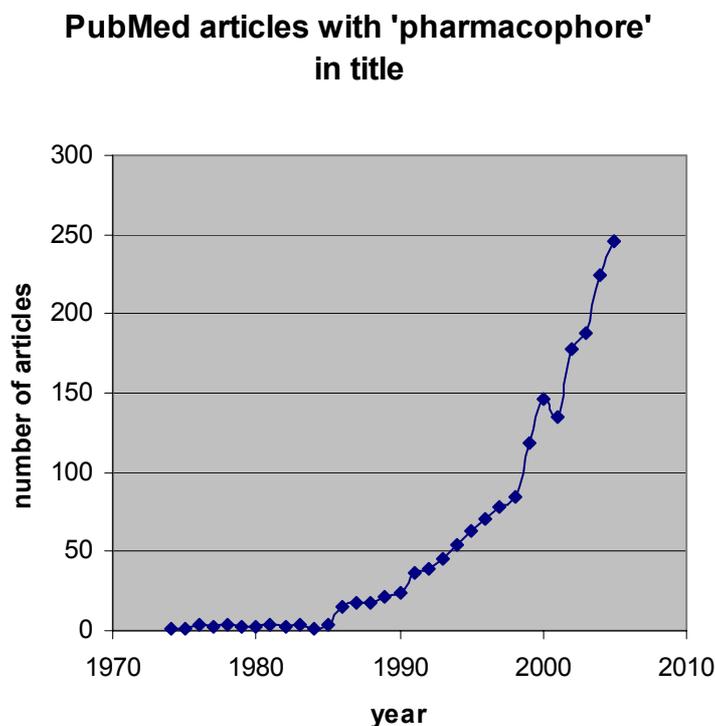**PubMed articles with 'pharmacophore'
in title**

Figure 4. Growth of use of the pharmacophore concept, as measured
by appearances of that word in publications indexed by PubMed.

Figure 4 shows the growth of the use of the pharmacophore concept. Tallied here is the number of PubMed citations, where pharmacophore appears in the title or abstract, since the first in 1974. Clearly, the concept of a pharmacophore is one which does not go out of fashion, a testament to its fundamental utility and practicality.

4 PREDECESSORS TO THE PHARMACOPHORE CONCEPT

As mentioned in the introduction, it is widely but erroneously thought that the term pharmacophore is due to Ehrlich. Frequently, the coinage of the term is attributed to Ehrlich in his 1909 Chemische Berichte article "Über den jetzigen Stand der Chemotherapie", but studying the original article one does not see the term pharmakophor appear anywhere in that article. This author has not yet found among Ehrlich's papers his published use of this term. Judging from Ehrlich's use

of related terms, haptophore and toxophore, *e.g.* as in his 1908 Nobel Prize address [15], one might expect that he invented the term pharmacophore to refer to those molecular features responsible for triggering a signal at a receptor, distinct from the haptophore, those features responsible for binding to the receptor. However, Ehrlich scholar J. Parascandola, in his article on the origins of receptor theory [16] describes Ehrlich's *reluctance* to extend the concepts of haptophore/toxophore to the actions of drugs, suggesting this was due to the poor understanding of weak intermolecular interactions at the time; furthermore, Parascandola does not recall ever encountering the term 'pharmacophore' in Ehrlich's work [17], nor do other Ehrlich scholars whom this author has contacted. Gund's paper [8] is the source of this erroneous citation to Ehrlich, and in a recent communication he admits he never chased down the actual source, but instead he propagated Ariens' erroneous citation to that Ehrlich paper [18].

Korolkovas' qualitative depictions of receptors, previously cited as Gund's inspiration for MOLPAT, are similar to those in Ariëns 1964 book [19], which cites as a source a review by Beckett [20]. One of the earliest of such depictions is in that Beckett review, citing [21], where they depict qualitatively the opioid receptor to explain enantioselectivity for stereoisomers of morphine. All of these were *qualitative*, pictorial representations, unlike Kier's *quantitative* concept of a pharmacophore.

Note also that the term pharmacophore is frequently subject to misuse by medicinal chemists. As stated in the IUPAC definition of the term [22],

> "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.
>
> A **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. The **pharmacophore** can be considered as the largest common denominator shared by a set of active molecules. This definition discards a misuse often found in the medicinal chemistry literature which consists of naming as **pharmacophores** simple chemical functionalities such as guanidines, sulfonamides or dihydroimidazoles (formerly imidazolines), or typical structural skeletons such as flavones, phenothiazines, prostaglandins or steroids."

This misuse of the term may skew slightly the statistics shown in Figure 4.

5 CONCLUSIONS

The concept of a pharmacophore is now deeply embedded into the thought processes of all scientists studying structure–activity relationships, providing a simple way to understand how a molecule's three–dimensional properties give rise to that SAR. When used in virtual screening, pharmacophores routinely identify known molecules with unanticipated biological activities. As the pharmacophore concept becomes more widely adopted in software commonly used by medicinal chemists and molecular modelers, we will likely witness its growing impact on drug design.

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Biographies

John H Van Drie joined the Novartis Institutes for Biomedical Research in 2004 as the Director of Computer–Aided Drug Discovery for the Cambridge, MA site. His work in the molecular modeling arena prior to joining Novartis includes both contributions to drug discovery teams, as well as development of novel computational methodology. In drug discovery, he worked on Hepatitis C virus protease (HCVP) inhibitors while at Vertex; oxazolidinone antibiotics and various cancer targets at Pharmacia; HIV protease inhibitors and dopamine agonists at Abbott. On the methodology side, he was a founding member of a Silicon Valley startup, BioCAD, whose Catalyst software remains a popular tool for pharmacophore–based modeling and virtual screening. Catalyst was based ALADDIN, the pioneering effort in pharmacophore–based virtual screening which he developed in collaboration with Yvonne Martin at Abbott. His most recent effort in methodology development was DANTE, which he developed while at Pharmacia, software for performing pharmacophore discovery. He was trained as a theoretical chemist at Caltech and the Université Libre de Bruxelles. He was the Chair of the 2003 Gordon Research Conference on Computer–Aided Drug Design, and has served on multiple NIH Study Sections and editorial boards.