

Preface

The idea is very straightforward: find and define all locations in space at a certain time of all substituents of a bioactive molecule that contribute to its biological activity. The readout would be a three-dimensional map – with respect to structure – that represents a minimal set of substituents which would adapt to a negative casting mold of the target binding site. By estimating or calculating the electronic and geometric properties of the substituents at their locations you would expand the 3D map to multiple dimensions. You call it a pharmacophore. After that, theoretically, you would walk through the Periodic Table and create a set of substituents, tied together by an appropriate backbone to fulfill all electronic and steric requirements of the pharmacophore. Finally, you obtain a new chemical entity with good prospects for activity at the target of choice.

But you get more. A “map” is a tool that relates objects to each other. These relations may be distances as they appear on a roadmap, it may be frequencies or densities on a web exploration map or it may be metabolism–emotion relationships in a brain map. Hence the pharmacophoric map can be used as a filter by matching the property vectors and a library of synthetic and/or virtual ligands, sorting out putative binders.

Well, “*Before the gates of excellence the high gods have placed sweat; long is the road thereto and rough and steep at first*” (Hesiod, *Work and Days*).

In the present book, Thierry Langer and Rémy Hoffmann give us a description of the long road with a firm sight on what can be done now and what is still to be achieved. Camille Wermuth, a doyen of the field, starts the arc of contributions shaping the history of the pharmacophore concept. The subsequent chapters are grouped into two major parts: “Pharmacophore Approaches” and “Pharmacophores for Hit Identification and Lead Profiling: Applications and Validation”. Much attention is devoted to the problem of alignment and cost of energy. The contributions face the problems not only from the small molecule, the ligand’s view, but also from the complementary side, the receptor’s binding site. Experience from both industrial research and development laboratories and academic research is covered, especially in the applications and validation part, which gives the reader a feeling for the feasibility and implementation of the approaches and bridges the gap between theory and practice.

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Hugo Kubinyi, Weisenheim am Sand
Gerd Folkers, Zürich
Raimund Mannhold, Düsseldorf