24. Pharmacophore vs. pharmacophoric group and pharmacophoric element

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There is general agreement in attributing to Paul Ehrlich, the father of chemotherapy, the creation of the pharmacophore concept, defined as "*a molecular framework that carries (phoros) the essential features responsible for a drug's (pharmakon) biological activity*" (Ehrlich, 1909). The first modern definition, proposed seventy years later by Peter Gund, remained very faithful to the origin of the term by defining a pharmacophore as "*a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity*" (as cited in Güner, 2002).

Currently, the definition adopted by IUPAC may be considered the reference: "*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*" (Wermuth et al., 1998). It is important to note in this context that a pharmacophore does not represent a real molecule or a real association of functional groups, but rather a purely abstract concept that accounts for the common molecular interaction capabilities of a group of substances with respect to their target structure. Thus, a pharmacophore can be regarded as the greatest common denominator shared by a set of active molecules, rather than simple chemical functions such as sulfonamides or typical structural scaffolds such as steroids or phenothiazines, for example (Wermuth et al., 1998).

What, then, is the difference between a pharmacophore and a pharmacophoric group (or pharmacophoric element)?

In the language of chemistry, a given set of atoms is often referred to as a group; therefore, the term "**pharmacophoric group**" is frequently used in the literature in association with specific groups that, taken together, would constitute the complete "pharmacophore" (a hydroxyl group, for instance, could be considered a "pharmacophoric group" that, together with others, would form the pharmacophore). On the other hand, in the more specific language of medicinal chemistry, the terms "pharmacophoric feature" or "**pharmacophoric element**" are preferred over "group." In this case, a carbonyl moiety, for example, would be described not as a group but as a hydrogen bond acceptor. The element describes an interaction property rather than specific atoms; it is more general and implicitly acknowledges that multiple functional groups may provide the same pharmacophoric element. Thus, it is the **pharmacophoric elements that collectively constitute the pharmacophore.**

In practice, a pharmacophore is defined through **pharmacophoric descriptors** (also referred to as pharmacophoric elements or pharmacophoric features), such as hydrogen bond acceptors and donors, hydrophobic and electrostatic interaction sites

defined by atoms, ring centers, and virtual points, which may be supplemented, when necessary, by indicators of directionality (Wermuth et al., 1998).

The first computer program capable of recognizing pharmacophoric patterns (MOLPAT) was developed by Gund, Wipke, and Langridge at Princeton University in 1974 (Güner, 2002). Many others have since emerged, including freely accessible online tools such as ZINCPharmer (Koes and Camacho, 2012). These tools are highly valuable, as pharmacophore models or maps (sets of pharmacophoric elements aligned in three-dimensional space with information on the distances between them) are widely used to develop predictive models (e.g., 3D-QSAR), to design molecules with specific desired attributes, and to assess molecular similarity and diversity based on their "fingerprints" (arrangements of molecular descriptors).

It is worth noting that the pharmacophore concept applies not only to receptors and enzymes in describing the pharmacodynamic action of drugs on their molecular targets, but also to metabolizing enzymes and transport proteins that affect drug pharmacokinetics. Examples include cytochrome P450 (CYP) enzymes present in the intestinal epithelium and hepatocytes, as well as P-glycoprotein (P-gp), an efflux pump expressed in epithelial cells of the intestine and in endothelial cells of the blood-brain barrier.

References

Ehrlich P. Über den Jetzigen Stand der Chemotherapie. *Chem. Ber.* 42:17, 1909. Quoted by Ariens E.J. "Molecular Pharmacology, a Basis for Drug Design," *Progr. Drug. Res.* 10:429, 1966.

Güner O.F. History and Evolution of the Pharmacophore Concept in Computer-Aided Drug Design. *Curr. Topics Med. Chem.* 2:1321-1332, 2002.

Koes D.R., Camacho C.J. ZINCPharmer: pharmacophore search of the ZINC database. *Nucleic Acids Res.* 40:W409-W414, 2012.

Wermuth C.G., Ganellin C.R., Lindberg P., Mitscher L.A. Glossary of terms used in medicinal chemistry (IUPAC Recommendations 1998). *Pure Appl. Chem.* 70:1129-1143, 1998.