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Introduction to pharmacophore model and its use in drug discovery



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Pharmacophore

- A **pharmacophore** is an abstract description of molecular features that are necessary for molecular recognition of a ligand by a biological macromolecule.
- IUPAC defines a pharmacophore to be "an ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target and to trigger (or block) its biological response".
- A pharmacophore model explains how structurally diverse ligands can bind to a common receptor site. Furthermore, pharmacophore models can be used to identify through de novo design or virtual screening novel ligands that will bind to the same receptor.
- The most relevant **pharmacophore** features include hydrogen bond acceptors (e.g., hydroxyl or carbonyl groups), hydrogen bond donors (e.g., hydroxyl or amide groups), positively charged (e.g., guanidines) or negatively charged groups (e.g., carboxylates), and hydrophobic (e.g., cyclohexyl or isopropyl groups) or aromatic.



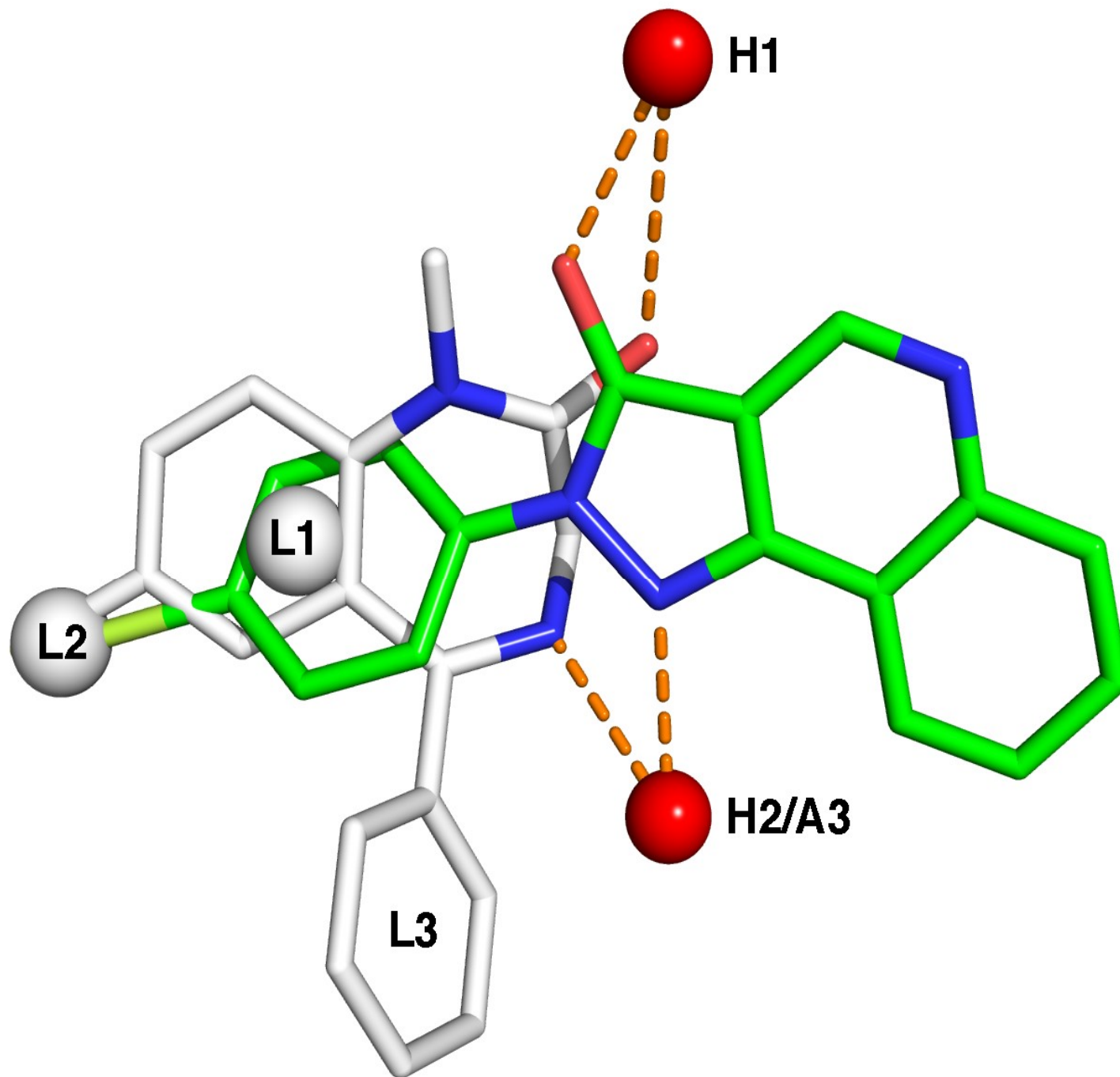
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Features

- Typical pharmacophore features include hydrophobic centroids, aromatic rings, hydrogen bond acceptors or donors, cations, and anions. These pharmacophoric points may be located on the ligand itself or may be projected points presumed to be located in the receptor.
- The features need to match different chemical groups with similar properties, in order to identify novel ligands. Ligand-receptor interactions are typically “polar positive”, “polar negative” or “hydrophobic”. A well-defined pharmacophore model includes both hydrophobic volumes and hydrogen bond vectors.



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An example of a pharmacophore model of the benzodiazepine binding site on the GABA_A receptor. White sticks represent the carbon atoms of the benzodiazepine diazepam, while green represents carbon atoms of the nonbenzodiazepine CGS-9896. Red and blue sticks are oxygen and nitrogen atoms that are present in both structures. The red spheres labeled H1 and H2/A3 are, respectively, hydrogen bond donating and accepting sites in the receptor, while L1, L2, and L3 denote lipophilic binding sites.

Model development

The process for developing a pharmacophore model generally involves the following steps:

- **Select a training set of ligands** – Choose a structurally diverse set of molecules that will be used for developing the pharmacophore model. As a pharmacophore model should be able to discriminate between molecules with and without bioactivity, the set of molecules should include both active and inactive compounds.



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- **Conformational analysis** – Generate a set of low energy conformations that is likely to contain the bioactive conformation for each of the selected molecules.
- **Molecular superimposition** – Superimpose ("fit") all combinations of the low-energy conformations of the molecules. Similar (bioisosteric) functional groups common to all molecules in the set might be fitted (*e.g.*, phenyl rings or carboxylic acid groups). The set of conformations (one conformation from each active molecule) that results in the best fit is presumed to be the active conformation.
- **Abstraction** – Transform the superimposed molecules into an abstract representation. For example, superimposed phenyl rings might be referred to more conceptually as an 'aromatic ring' pharmacophore element. Likewise, hydroxy groups could be designated as a 'hydrogen-bond donor/acceptor' pharmacophore element.
- **Validation** – A pharmacophore model is a *hypothesis* accounting for the observed biological activities of a set of molecules that bind to a common biological target. The model is only valid insofar as it is able to account for differences in biological activity of a range of molecules.
- As the biological activities of new molecules become available, the pharmacophore model can be updated to further refine it.



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Use of Pharmacophore model in drug discovery

Ligand-based pharmacophore modeling

- Ligand-based pharmacophore modeling has become a key computational strategy for facilitating drug discovery in the absence of a macromolecular target structure.
- It is usually carried out by extracting common chemical features from 3D structures of a set of known ligands representative of essential interactions between the ligands and a specific macromolecular target.



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Structure-based pharmacophore modeling

- Structure-based pharmacophore modeling works directly with the 3D structure of a macromolecular target or a macromolecule– ligand complex. The protocol of structure-based pharmacophore modeling involves an analysis of the complementary chemical features of the active site and their spatial relationships, and a subsequent pharmacophore model assembly with selected features.
- The structure-based pharmacophore modeling methods can be further classified into two subcategories: macromolecule– ligand-complex based and macromolecule (without ligand)-based.



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Pharmacophore-model-based virtual screening

- Once a pharmacophore model is generated by either the ligand-based or the structure-based approach, it can be used for querying the 3D chemical database to search for potential ligands, which is so-called 'pharmacophore-based virtual screening' (VS). Pharmacophore-based VS and docking-based VS represent the mainstream of VS tools at the present time.
- In contrast to its counterpart, the docking-based VS method, pharmacophore-based VS reduces the problems arising from inadequate consideration of protein flexibility or the use of insufficiently designed or optimized scoring functions by introducing a tolerance radius for each pharmacophoric feature. In the pharmacophore-based VS approach, a pharmacophore hypothesis is taken as a template.
- The purpose of screening is actually to find such molecules (hits) that have chemical features similar to those of the template.



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Pharmacophore-based de novo design

- Besides the pharmacophore-based VS described above, another application of pharmacophore is de novo design of ligands. The compounds obtained from pharmacophore-based VS are usually existing chemicals, which might be patent protected.
- In contrast to pharmacophore-based VS, the de novo design approach can be used to create completely novel candidate structures that conform to the requirements of a given pharmacophore.
- The first pharmacophore-based de novo design program is NEWLEAD [53], which uses as input a set of disconnected molecular fragments that are consistent with a pharmacophore model, and the selected sets of disconnected pharmacophore fragments are subsequently connected by using linkers (such as atoms, chains or ring moieties).



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- Actually, NEWLEAD can only handle the cases in which the pharmacophore features are concrete functional groups (not abstract chemical features).
- Other shortcomings of the NEWLEAD program include that the sterically forbidden region of the binding site is not considered and that, as in traditional de novo design programs, the compounds created by the NEWLEAD program might be difficult to chemically synthesize. Other programs such as LUDI4 and BUILDER can also be used to combine identification of structure-based pharmacophore with de novo design.
- They, however, need the knowledge of 3D structures of the macromolecular targets.