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Digest

Conformational control in structure-based drug design

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ABSTRACT

In structure-based drug design, the basic goal is to design molecules that fit complementarily to a given binding pocket. Since such computationally modeled molecules may not adopt the intended bound conformation outside the binding pocket, one challenge is to ensure that the designed ligands adopt similar low energy conformations both inside and outside of the binding pocket. Computational chemistry methods and conformational preferences of small molecules from PDB and Cambridge Structural Database (CSD) can be used to predict the bound structures of the designed molecules. Herein, we review applications of conformational control in structure-based drug design using selected examples from the recent medicinal chemistry literature. The main purpose is to highlight some intriguing conformational features that can be applied to other drug discovery programs.

Complementarity between the target protein and bound ligand conformation is a prerequisite for good potency. The bound conformation of a ligand may not be the lowest energy conformation of free ligand, but is usually one of the low energy conformations.[1] For ligands with rotatable bonds, there are usually a number of low energy conformations. An earlier survey of X-ray crystal structures in the PDB demonstrated that polar molecules such as ATP, NAD, and FAD tend to bind to proteins in extended (unfolded) conformations with considerable variations among the bound conformations.[2] The variation is the greatest among unrelated proteins; lesser variation is observed within protein superfamilies.

Similarly, some drug-like molecules have been crystallized with more than one protein. The relationship between polypharmacology and conformational flexibility has been investigated by He et al.[3] One hundred ligands that had been crystallized with more than one protein but with similar binding potency in PDB were examined in detail. Fifty-nine of the 100 ligands show no significant conformational changes when binding to different proteins. On the other hand, some drugs, such as dasatinib and ritonavir, do display considerable conformational changes. It is also known that when a flexible drug molecule binds an unrelated off-target, the bound conformation may differ considerably. The shape of the bound fedratinib molecule in the Janus kinase 2 (JAK2) complex is completely different from that in the bromodomain-containing protein 4 (BRD4) complex.[4] In some cases, even when binding to a closely related protein, the bound conformation may undergo subtle changes. BMS948 is an antagonist of RARα, but a full agonist of RARβ. A recent structural investigation suggested that the two bound conformations differ by an 180° flip of the central amide linkage (Fig. 1).[5]

More interestingly, vitamin-D receptor (VDR) modulator **2a** binds to the VDR in both agonist and antagonist conformations in a single crystal in a 7 to 3 ratio, providing a good structural explanation for its partial agonism (PDB codes: 3WT5 and 3WT6).[6] Agonist **2b** only displays one conformation in the X-ray crystal structure (3WT7).

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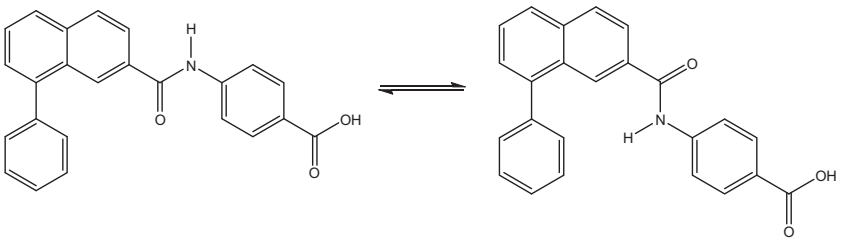
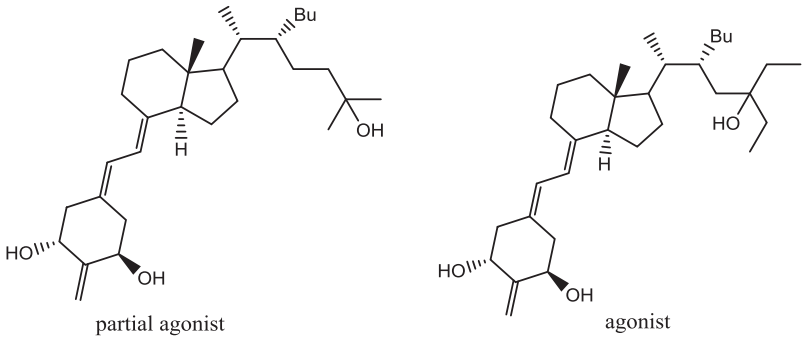


Fig. 1. Two binding modes of BMS948 (**1**).



2a **2b**

NMR derived structures have also been employed in SBDD. Recent work on inhibitors of HCV polymerase and NS3 protease are excellent illustrations of how NMR guided conformational restriction can be effectively used in drug discovery.[7,8] Interestingly, the hexapeptide Asp-Asp-Ile-Val-Pro-Cys (DDIVPC) derived HCV NS3 protease inhibitors also displayed a correlation between the binding affinity and the percentage of bioactive conformation in the free state.

The Cambridge Structural Database (CSD) is a rich source of conformations of small organic molecules. For the majority of neutral molecules, the crystal conformations stay essentially close to their gas-phase equilibrium structures. Some of the molecules in CSD have been crystallized under various conditions, providing useful information regarding the conformational variability of the same molecules under different conditions (*e.g.*, conformational polymorphism). Recently, Cruz-Cabeza and Bernstein provided a comprehensive review of conformational polymorphism of organic molecules in CSD.[9] One of the best-studied cases is ROY with at least nine different polymorphs. Seven of the nine polymorphs were investigated by X-ray diffraction methods and found to cluster into two distinct conformational regions on the gas phase potential energy surface (Fig. 2).

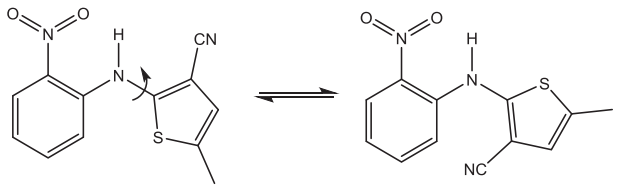


Fig. 2. Two conformations of ROY (**3**) (gas-phase minima at ~40° and ~140°).

Additionally, the energetic costs of conformational variations were estimated for 452 pairs of conformations. About half of the crystal conformers differ in energy from their gas phase conformers by <0.6 kcal/mol and ~90% by <2.5 kcal/mol. The remaining ~10%, with high energy differences between the gas phase and crystal state conformations, mostly correspond to molecules with multiple polar groups such as sugars.

In SBDD, given a binding pocket, one attempts to design molecules that fit complementarily to the binding pocket. Such computationally modeled molecules may not adopt the bound conformation outside the binding pocket. Conformational restriction can be used to control ligand conformation and bias molecules towards the desired conformation for binding.[10] Even though experimental methods such as X-ray diffraction and NMR can provide useful information about the small molecule conformations, for designed molecules which exist only *in silico*, different approaches have to be used. The CSD has been widely used to assess whether the conformation of a designed molecule is plausible or not either by directly searching for similar torsion profiles of the fragments of interest[11] or using rules derived from CSD torsion profiles.[12] It is desirable to design ligands that display similar or ideally the same conformation in both bound and free states to reduce strain energy. Another more general approach is to use molecular modeling tools to explore the conformational profile of the designed ligand computationally. Both approaches are routinely employed in our internal drug discovery programs.

In cases where the bound conformation of the designed ligand differs from the low energy conformation of the free ligand, appropriate constraints can be introduced to bias the conformational preference of the free ligand to be close to the conformation of the bound ligand. As an example, during our mineralocorticoid receptor (MR) project, the structure-based *de novo* design starting from the benzoxazinone fragment (**4**) led to a recurring structure