SUPPORTING INFORMATION

Molecular field similarity determination.

Molecular field analysis calculations were carried out with the software program Forge.[18] Forge describes molecules based on their molecular fields. The interaction between a ligand and a protein involves electrostatic fields and surface properties (e.g. hydrogen bonding, hydrophobic surfaces,…). The assumption is that two molecules that bind to a common active site, tend to make similar interactions with the protein and hence have highly similar field properties. Forge can also be used to align structurally diverse compounds based on the similarity between their fields. To generate these fields, the software uses the XED molecular mechanics force field,[19] which employs off-atom sites to more accurately describe the electron distribution in a molecule, as opposed to other force fields where charges are placed at the atomic nuclei only. The field calculation is carried out by placing a probe atom at each point of a grid around the molecule and calculating its interaction energy. The probe has the van der Waals parameters of oxygen and its charge is adjusted according to the field that is calculated. Forge calculates four field types:

- a van der Waals interaction potential, by using a neutral probe, describing possible surface/vdW interactions,
- a positive electrostatic potential, by using a probe with +1 charge, describing regions that are likely to interact with negatives/ H-bond acceptors on a protein,
- a negative electrostatic potential, by using a probe with -1 charge, describing regions that are likely to interact with positives/ H-bond donors on a protein,
- and a hydrophobicity potential, determined by calculating an attractive energy with a neutral probe.

For computational efficiency, Forge internally condenses these fields to a set of points around the molecule, the “field points”, which are the local extrema of each field.[20] These field points are used during the alignment of molecules to a reference molecule and to calculate a field

similarity score (FSim) that incorporates information on the actual fields of the two molecules compared. A shape similarity score (SSim) is also calculated and a global similarity score (Sim) is obtained by weighted sum of both (by default Sim = 0.5 FSim + 0.5 SSim, with possible values between 1, perfect alignment, and 0, not aligned).

Thus, the minimized structure of luteolin, a potent known inhibitor of cytochrome b5 reductase (**Figure S4**), was used as reference molecule to align SKi II and to determine the field-based similarity between both compounds. Conformations for SKi II and potential alignments to the reference molecule were generated within Forge using the default parameters (calculation quality: normal; 100 maximum conformations; 10 alignments per molecule). Similarly, conformations and alignments were also generated for two additional known inhibitors of CB5R, quercetin and (+)-taxifolin, for comparison purposes. **Figure S5** shows the overlaid structure of SKi II aligned to luteolin and **Figure S6** shows the comparison of the shapes and molecular fields of the two aligned molecules. The similarity scores from this alignment and from the best alignments obtained for quercetin and (+)-taxifolin (not shown) are summarized in **Table S1**.