CLAIMS

1. A method for designing a ligand *ab initio* that will bind to a binding site of a macromolecular target, or of identifying a modification to a ligand for improving the affinity of the ligand to a binding site of a macromolecular target, comprising:

a) identifying a target list of atoms forming the surface of the target binding site;

b) identifying each atom, hereinafter referred to as a theta atom, in the target list, as a particular theta atom type;

c) extracting from a structural database of biological macromolecules, information about non-bonding, intra-molecular or inter-molecular atom to atom contacts, where the first atom in a contacting pair of atoms is of a particular theta atom type and the opposing, second atom of the pair, hereinafter referred to as an iota atom, is of a particular iota atom type, said information comprising spatial and/or contextual data about the iota atom relative to the theta atom, and said data collected for a plurality of contacts of the given theta atom type from the said database is hereinafter referred to as a theta contact set;

d) for each theta atom identified in the target list in step b), superimposing in or around the target binding site data relating to a given iota atom type, or a predetermined group of related iota atom types, from the corresponding theta contact set extracted in step c);

e) combining and / or parsing the superimposed data in such a way as to predict one or more favoured regions of the binding site where the given iota atom type, or the predetermined group of related iota atom types, has high theoretical propensity; and

f) with a candidate ligand notionally docked into the binding site, comparing the type and position of one or more of the atoms of the candidate ligand with the predicted favoured regions for the respective iota atom types, to identify a modification to the candidate ligand, in terms of alternate and/or additional candidate ligand atoms, that will produce a greater intersection between the alternate and/or additional candidate ligand atoms and the respective iota atom type favoured regions, leading to an improvement in the affinity of the modified candidate ligand to the binding site compared to the unmodified candidate ligand;

wherein each non-bonding intra-molecular or inter-molecular contact in the database is defined as a contact between opposing residues of a protein fold or between opposing monomer units of a macromolecular fold or between two interacting macromolecular

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c) extracting from a structural database of biological macromolecules, information about non-bonding, intra-molecular or inter-molecular atom to atom contacts, where the first atom in a contacting pair of atoms is of a particular theta atom type and the opposing, second atom of the pair, hereinafter referred to as an iota atom, is of a particular iota atom type, said information comprising spatial and/or contextual data about the iota atom relative to the theta atom, and said data collected for a plurality of contacts of the given theta atom type from the said database is hereinafter referred to as a theta contact set;

d) for each theta atom identified in the target list in step b), superimposing in or around the target binding site data relating to a given iota atom type, or a predetermined group of related iota atom types, from the corresponding theta contact set extracted in step c);

e) processing the superimposed data to predict one or more favoured regions of the binding site where the given iota atom type, or the predetermined group of related iota atom types, has high theoretical propensity, the processing consisting of combining the superimposed data, parsing the superimposed data, or combining and parsing the superimposed data; and

f) with a candidate ligand notionally docked into the binding site, comparing the type and position of one or more of the atoms of the candidate ligand with the predicted favoured regions for the respective iota atom types, to identify a modification to the candidate ligand, in terms of alternate and/or additional candidate ligand atoms, that will produce a greater intersection between the alternate and/or additional candidate ligand atoms and the respective iota atom type favoured regions, leading to an improvement in the affinity of the modified candidate ligand to the binding site compared to the unmodified candidate ligand;

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