MB-Isoster: A software for Bioisosterism Simulation

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Bioisosterism is a technique used in medicinal chemistry to optimize lead compounds in drug research. One can replace a substituent group in original molecule by another with similar physical chemistry properties and then test how this replacement affects biological activity. To help researchers in their bioisosteric replacement choose, computational efforts such as programs and databases was developed. In this article, it is presented MB-Isoster, a software that draws bioisosteric molecules. Starting from an input molecule, user selects a molecular subregion formed by connected atoms to be replaced and MB-Isoster queries an internal library to find bioisosteric substituents for selected subregion, and makes the bioisosteres. Another functionality is receptor–ligand pdb complex reading, in which nonbonded interactions are computed between receptor and ligand in a pdb file, helping in atom/subregion selection to bioisosteric replacement. Physical-chemical properties computing, and virtual screening evaluation is also available. MB-Isoster is freely available at http://molmod-cs.unifal-mg.edu.br/tools.html. © 2018 Wiley Periodicals, Inc.

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Introduction

Bioisosterism is a term used in medicinal chemistry to refer molecular structure changing by replacing a substituent in molecule by another with similar physical chemistry properties, this modified molecule must also remains biological activity in common with original molecule.[1] It is a strategy in drug design to modulate characteristics such as solubility, potency, decreasing toxic effects, increasing the half-life.[2,3] Bioisosterism is derived from the most general term isosterism, first proposed by Langmuir in 1919.[4] In his study, Langmuir showed that atoms or atom groups that have same number of electrons and same electron arrangement also have many physical chemistry properties in common. Such structure pairs are called isosteres from one another. Later, in 1925, Grimm creates hydride displacement law, according to which if an atom receives a covalent bond with a proton (hydride) it behaves such as the next atom that follows in periodic table.[5] Friedman, in 1951, defines the concept bioisosterism to describe compounds that are isosteres from one another and also have similar biological activity due acting in same biological receptor, while this activity can be agonistic or antagonistic.[6] Bioisosterism can be classified as classic and nonclassic[7]; classical bioisosterism is based on Langmuir isosteric principles and are subdivided into monovalent, divalent, trivalent, tetravalent, and ring equivalents; conversely, nonclassic bioisosteres do not obey principles found in classic bioisosterism. Cyclic versus acyclic, functional groups, and retroisosterism are examples for this classification. Bioisosterism relationship can be viewed, as an example, between drugs tenoxicam and piroxicam, that are equals, except by phenyl substituent in piroxicam and thiophenyl in tenoxicam, as shown in Figure 1; both are nonsteroidal anti-inflammatory drugs used in osteoarthritis treatment.[8] Another example is shown to drugs procaine[9] and procainamide,[10] used as local anesthetic and anti-arrhythmic in cardiac arrhythmias, respectively. Ester moiety in procaine is replaced by amide moiety in procainamide (Fig. 2). Computational efforts has been developed to help researchers in drug design applying bioisosterism strategy.[11] Among them one can cite Drug Guru and SwissBioisostere. Drug Guru is a program available as web-server to perform bioisosterism replacement in an input structure based on transformation rules encoded in SMIRKS format.[12] SwissBioisostere is a public database available in web, that reports bioisosteric replacements found in literature, to a molecular fragment provided by user.[13] In this article, we presents MB-Isoster, a graphical user interface program developed to draw molecules based on bioisosterism relationship. Fragments to replacement are selected by querying an internal library containing bioisosteric families obtained from literature. Users can download MB-Isoster at http://molmod-cs.unifal-mg.edu.br/tools.html.

Methods

Starting from an initial molecule, user selects region in molecule to be replaced (discussed in "Graphical User Interface" subsection). In this way, molecule is "broken" in two submolecules; a submolecule that will be replaced in bioisosteres is called here as "bioisostere fragment," and the biggest submolecule that is shared among all bioisosteres is defined as "root fragment".

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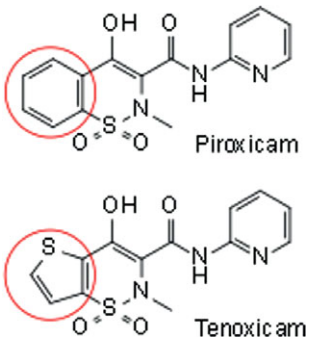

Figure 1. Bioisosterism relationship between drugs piroxicam and tenoxicam. [Color figure can be viewed at wileyonlinelibrary.com]

Both bioisostere fragment and root fragment are each one linked to a pseudo atom R in broken bond, as shown in Figure 3.

Steps to build bioisosteres are as follows:

1. Bioisostere fragment is converted to string representation;
2. This string representation is used to identify "bioisosteric family" for bioisostere fragment;
3. Another bioisosteric fragments belonging to the same bioisosteric family are recovered from an internal library;
4. Bioisosteres are built joining root fragment with bioisosteric fragments from library.

Library Building

To perform fragment selection to replace bioisostere fragment, a bioisosteric library was made in sdf file format. To build tridimensional coordinates for fragments in library, openbabel[14] program is used, with some editing. Each fragment has at least one pseudo atom referred as R1 (some fragments has two pseudo atoms, referred as R1 and R2, or three, referred as R1, R2, and R3), this pseudo atom marks relative position of atom in root fragment that must be linked with bioisosteric fragment. Fragments also contains two properties: bioisosteric family, that groups fragments that can be replaced one by another, and a string representation used to find desired fragments in library. As an example, it is shown library entry for bioisosteric fragments R1-O-R2, and R1-S-R2 (ether and thioether moiety, respectively), which are grouped in "ClassicalDivalent" family (box below).

```
oxygen


  3  2  0  0  0  0  0  0  0  0999
V2000
    0.9428   -0.0019   -0.0532 R1
0  0  0  0  0  0  0  0  0  0  0  0
    3.0956   -0.0562    0.0310 O
0  0  0  0  0  0  0  0  0  0  0  0
    3.7332    1.0597   -1.6990 R2
0  0  0  0  0  0  0  0  0  0  0  0
  1  2  1  0  0  0  0
  2  3  1  0  0  0  0
M  END
>  <BioisosterFamily>
ClassicalDivalent

>  <Representation>
R1-O-R2

$$$$
sulfur


  3  2  0  0  0  0  0  0  0  0999
V2000
    1.2185    0.2722    0.0117 R1
0  0  0  0  0  0  0  0  0  0  0  0
    3.7581   -0.1864   -0.1480 S
0  0  0  0  0  0  0  0  0  0  0  0
    4.3370    2.1935    0.6804 R2
0  0  0  0  0  0  0  0  0  0  0  0
  1  2  1  0  0  0  0
  2  3  1  0  0  0  0
M  END
>  <BioisosterFamily>
ClassicalDivalent

>  <Representation>
R1-S-R2

$$$$
```

Before searching in library, fragment selected to be changed in main molecule is converted in a string representation equivalent to those found in library, a catalog is consulted to find the family to which selected fragment belongs, then, a search in library returns all fragments belonging to this family, to each

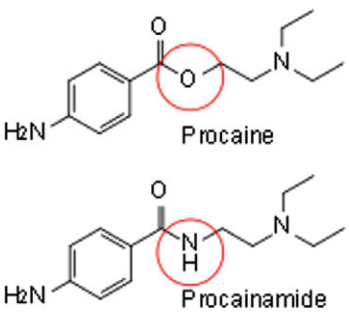

Figure 2. Bioisosterism relationship between drugs procaine and procainamide. [Color figure can be viewed at wileyonlinelibrary.com]

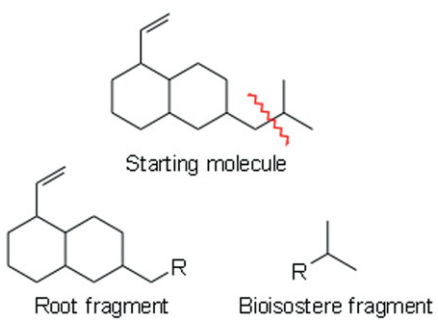

Figure 3. A generic input molecule broken into root fragment and bioisostere fragment. [Color figure can be viewed at wileyonlinelibrary.com]

fragment it is constructed a new molecule joining it with root fragment.

Bioisostere Building

Molecule building is done as shown in Figure 4. Root molecule has a pseudo atom defined as **R1'** and an "anchor" atom (the atom bonded to pseudo atom) defined as **A'**, bioisosteric fragment has also a pseudo atom and anchor atom defined as **R1** and **A**, respectively. Initially, bioisosteric fragment is translated so that **R1** coordinates becomes the same as **A'** coordinates; bioisosteric fragment is rotated around **R1** atom until **R1-A** bond aligns with **R1'-A'** bond; a bond is made between atoms **A** and **A'**, atoms **R1** and **R1'** are deleted. The new formed bond **A-A'** has its length changed to ideal bond length between atoms **A** and **A'**; finally, if bond **A-A'** defines at least one dihedral angle, a dihedral rotation is made on bond **A-A'** to find best dihedral angle for it.

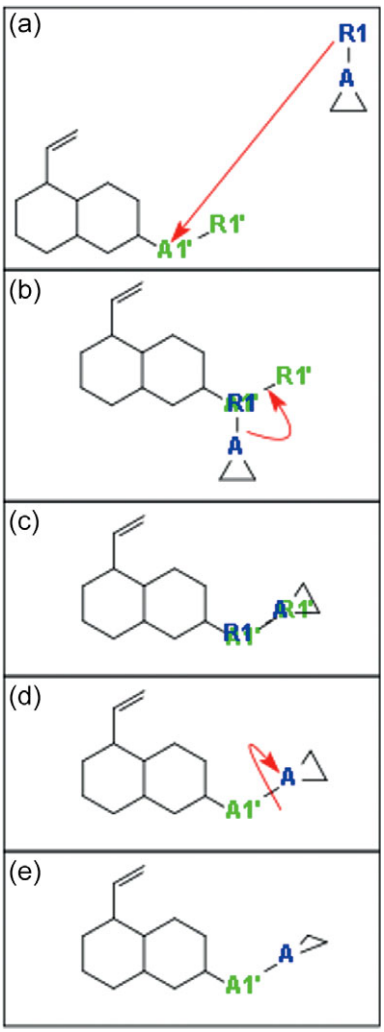

Figure 4. Bioisostere building scheme. a) bioisostere fragment translation; b) bioisostere fragment rotation around R1; c) A-A′ bond formation and R1 and R1′ atoms removal; d) bond length and dihedral changing; e) final bioisostere. [Color figure can be viewed at wileyonlinelibrary.com]

Geometry Minimization

General geometry minimization, which may be done to input molecule before bioisostere building, is performed by molecular mechanics; MMFF94s is implemented as force field,[15] and minimization algorithm is divided in five steps: (1) ring geometries in molecule are minimized by copying coordinates from rings in a ring template library, with some translation and rotation to best accommodate ring in molecule; (2) each noncyclic bond has its length changed to its ideal bond length, according with force field adopted; (3) angles are changed using coordinate templates from an angle template library; (4) if a noncyclic bond participates in at least one dihedral angle, its dihedral are rotated to find best angle; (5) nonlinear conjugate gradients with Newton–Raphson and Fletcher–Reeves[16] is used to refine final molecular geometry.

Molecule Building by H-Substitution

It is implemented a command to construct new molecules in which for each hydrogen in input molecule, this hydrogen is replaced by one among 35 fragments in a special library, each new molecule generated has only one hydrogen replaced. The special library is formed by fragments representing common chemical moieties, such as methyl, ethyl, hydroxyl, amine, and phenyl; molecule construction is performed as described in "Bioisostere building" subsection. A filter is used to prevent molecule building by hydrogen replacement if any hydrogen is equivalent to another already considered.

Reading Molecule from Receptor–Ligand Complex in Pdb File

An input molecule can be read from a receptor–ligand complex in pdb file. In this way, nonbonded interactions (van der Waals and electrostatic) can be computed between receptor and ligand, helping in atom/fragment selection to bioisosteric replacement. First, ligand geometric center is computed, molecule radius (i.e., the bigger distance between an atom from ligand and ligand geometric center) is calculated; to this value is added a cutoff of 4 Å, generating an "active site cutoff." The cutoff of 4 Å is chosen since it is maximal distance to weak hydrogen bond.[17] Each atom from receptor whose distance from ligand geometric center is less than or equal to "active site cutoff" is defined as belonging to active site. Nonbonded interactions are computed to each atom in ligand against all atoms from defined receptor active site. Thus, atoms from ligand with greater calculated energies are suggested as possible chooses to bioisosteric replacement.

Filtering Based on Drug-like Properties

Bioisosteric replacement can significantly alter molecular properties that affect druglikeness.[18] Drastic changes in some properties like logP and logS may invalidate a compound as drug candidate. User can computes some drug-like properties of bioisosteres to delete molecules with low druglikeness. User is

free to define property value ranges and what properties are used as filter criterion. Following properties can be computed:

- Molecular weight: sum over all atomic weight of atoms in molecule;
- Number of hydrogen bond acceptors: counting over all oxygen, nitrogen, fluorine, and sulfur atoms that can participate in hydrogen bonding;
- Number of hydrogen bond donors: counting over all hydrogen atoms that can participate in hydrogen bonding;
- logP: octanol–water partition coefficient, computed by XLOGP3-AA algorithm described in Zhao et al., 2007[19];
- logS: aqueous solubility, computed by algorithm described in Hou et al., 2004[20];
- TPSA: topological polar surface area, computed by algorithm described in Ertl et al., 2000.[21]

Virtual Screening

Another question in bioisosterism is how bioisosteric replacement can improve interaction between a molecule and a biologic receptor. Methodologies such as molecular docking and virtual screening can predict these interactions. It is implemented a function to perform virtual screening with bioisosteres against a receptor. AutoDock Vina program[22] is used as molecular docking engine; user must have vina installed to execute virtual screening. First step is to select a receptor in pdb file format. This receptor must have at least one cocrystallized ligand to define active site and constructs grid box; grid box center is set to cocrystallized ligand geometric center. Grid box size is defined as follow: molecule radius of each bioisostere is computed; the biggest value is multiplied by three and set as grid box edge. Cocrystallized ligand is removed from receptor, receptor and bioisosteres are converted to pdbqt file format using charges from MMFF force field. Then, vina is invoked to perform molecular docking for each bioisostere against receptor.

Graphical User Interface

MB-Isoster is a stand-alone graphical user interface application written in java. When this program is opened, three panels can be viewed; upper left panel is Molecule Panel, input molecule is displayed in this panel, upper right panel is Bioisostere Panel, bioisosteric molecules are displayed in this panel after bioisosteric building, bottom left panel is Log Panel to display log messages (Fig. 5).

To open an input molecule, user chooses **File** → **Open**, and then select desired molecule in dialog window. Four file formats are supported: mol (versions V2000 and V3000), sdf (versions V2000 and V3000), mol2, and pdb. To rotate molecule, user uses arrow keys in keyboard to rotate in *X* and *Y* axis, or "Z" and "X" keys in keyboard to rotate in Z axis; zooming in is done by "V" key in keyboard and zooming out by "C" key, maximum zooming is twice molecule standard size (size in which

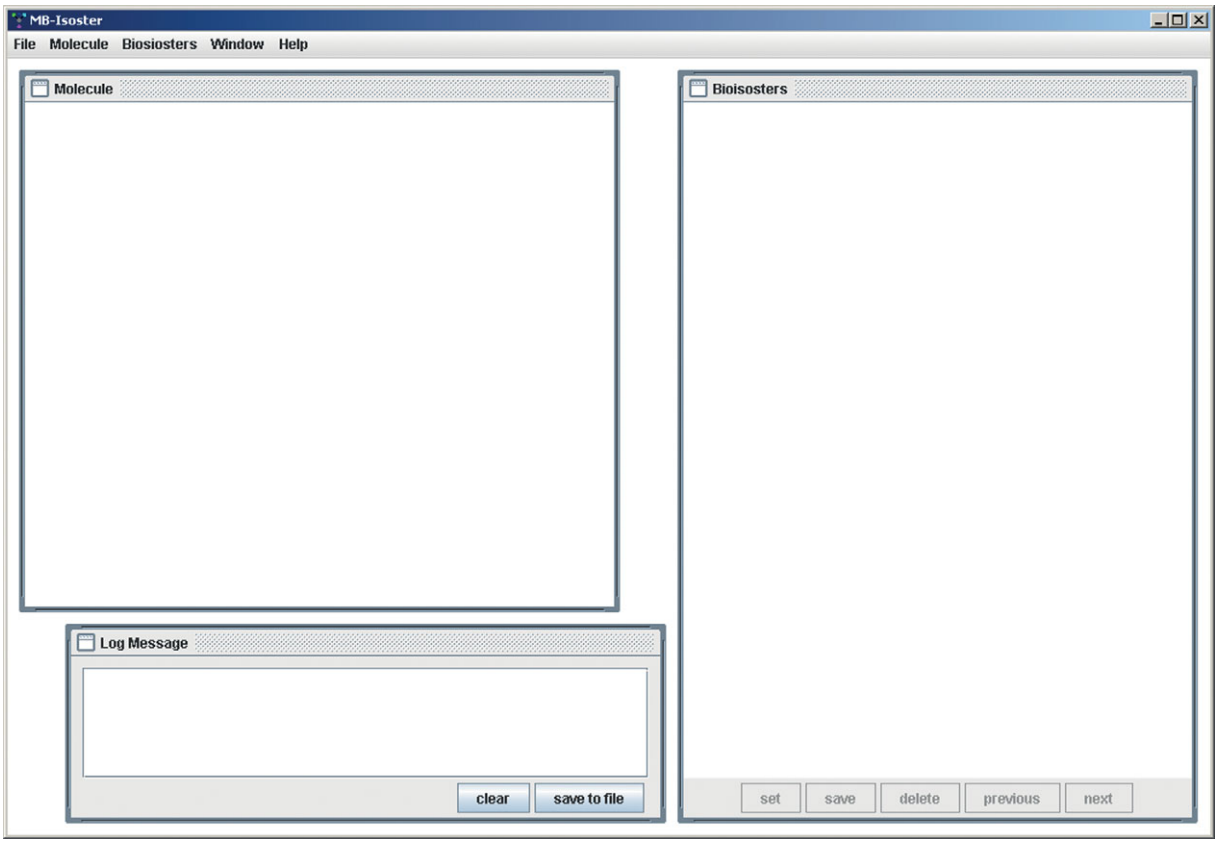

Figure 5. Starting MB-Isoster software. [Color figure can be viewed at wileyonlinelibrary.com]

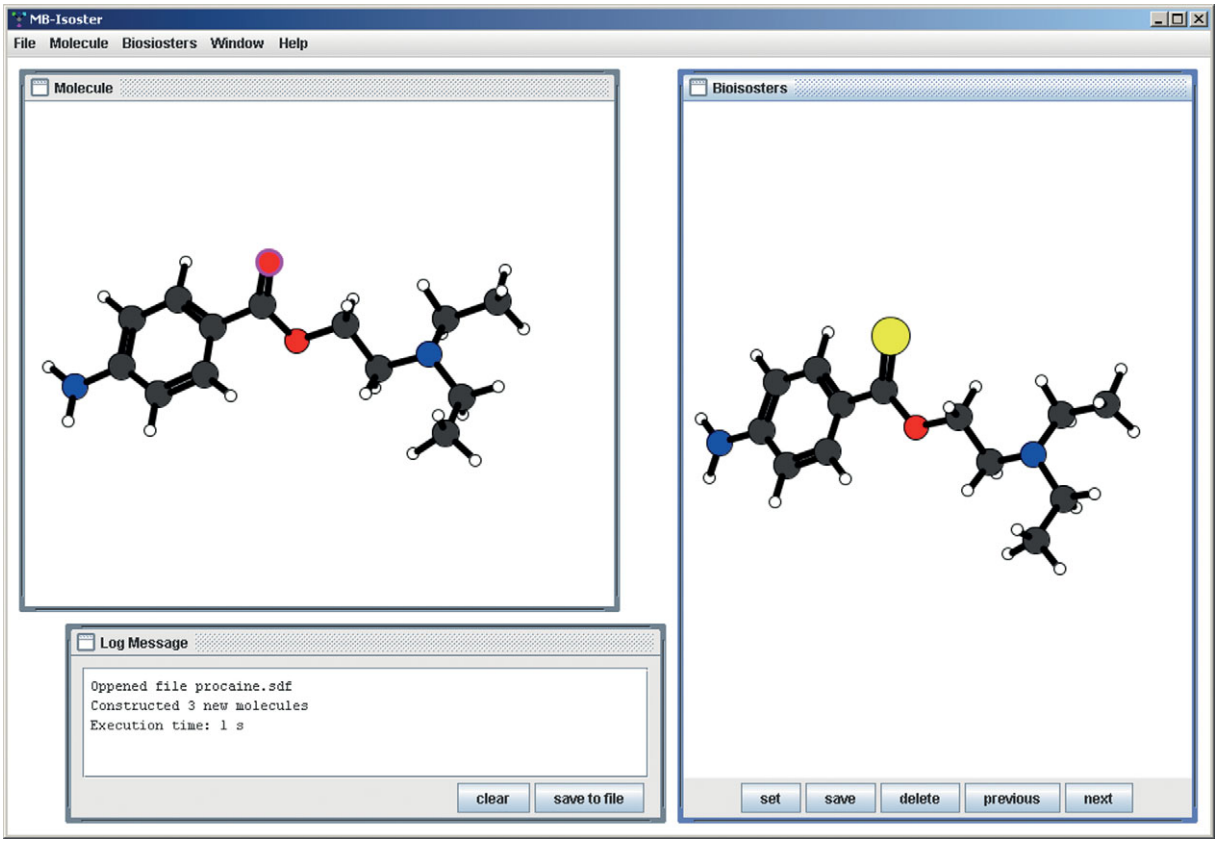

Figure 6. MB-Isoster application example. In Molecule Panel is displayed procaine, oxygen double bonded to carbon is selected. In Bioisostere Panel resulting bioisosteres are displayed. [Color figure can be viewed at wileyonlinelibrary.com]

molecule is first displayed) and minimum zooming is half molecule standard size; no translation is available. User must click one or more atoms in input molecule to select them and choose **Molecule** → **Make bioisosteres** to start bioisostere building. Bioisostere molecules are displayed in Bioisostere Panel, user clicks "next" and "previous" buttons to navigate among bioisosteres, "delete" button deletes showed molecule, "save" button saves showed molecule in a supported file format, "set" button makes a copy of showed molecule and sends it to Molecule Panel (Fig. 6).

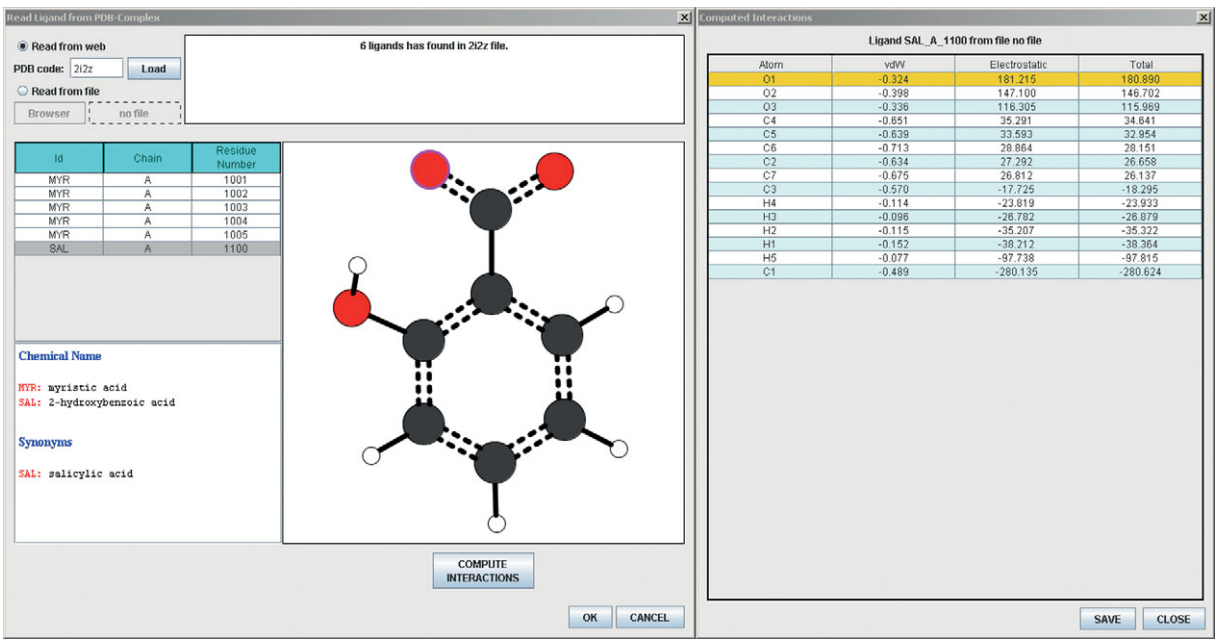

Figure 7. Molecules read from receptor–ligand complex. It is shown nonbonded interactions to ligand labeled as "SAL" (salicylic acid) from pdb file "2i2z". [Color figure can be viewed at wileyonlinelibrary.com]

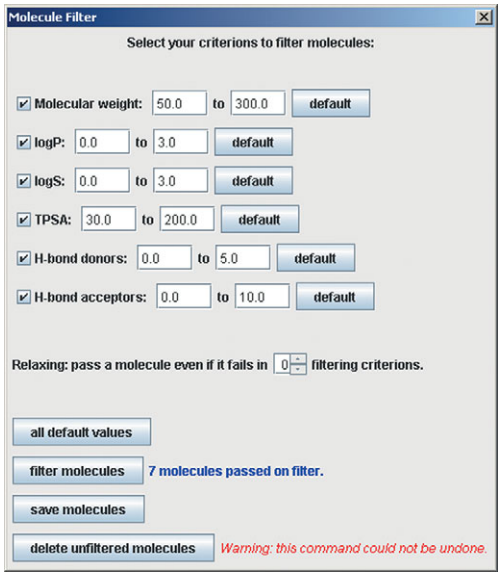

Figure 8. Filter used to select bioisosteres based on drug-like properties. [Color figure can be viewed at wileyonlinelibrary.com]

To save all bioisosteres, user chooses **Bioisosters** → **Save bioisosters** → and selects a file format; it is options to save molecules in separated files or all molecules in same file. To perform building by H-substitution, user chooses **Molecule** → **Build over all H**; no atom selection is need, output molecules also are shown in Bioisostere Panel. By choosing **File - > Extract from PDB-complex**, user opens "Read Ligand from PDB-complex" dialog window. User can either read a pdb file from web selecting "Read from web" or read a pdb file from hard disc selecting "Read from file". A table shows all small molecules found in this pdb file; by selecting an entry in this table, corresponding molecule is shown beside. To compute nonbonded interactions between receptor and selected ligand, user clicks "COMPUTE INTERACTIONS" button; after computing, another table is opened, showing nonbonded interactions for each atom in ligand against receptor active site, clicking a entry in this table selects corresponding atom, user then clicks "OK" button to close dialog window and send selected ligand to Molecule Panel (Fig. 7).

After bioisostere building, drug-like properties are automatically computed for each bioisostere, user can filter them by

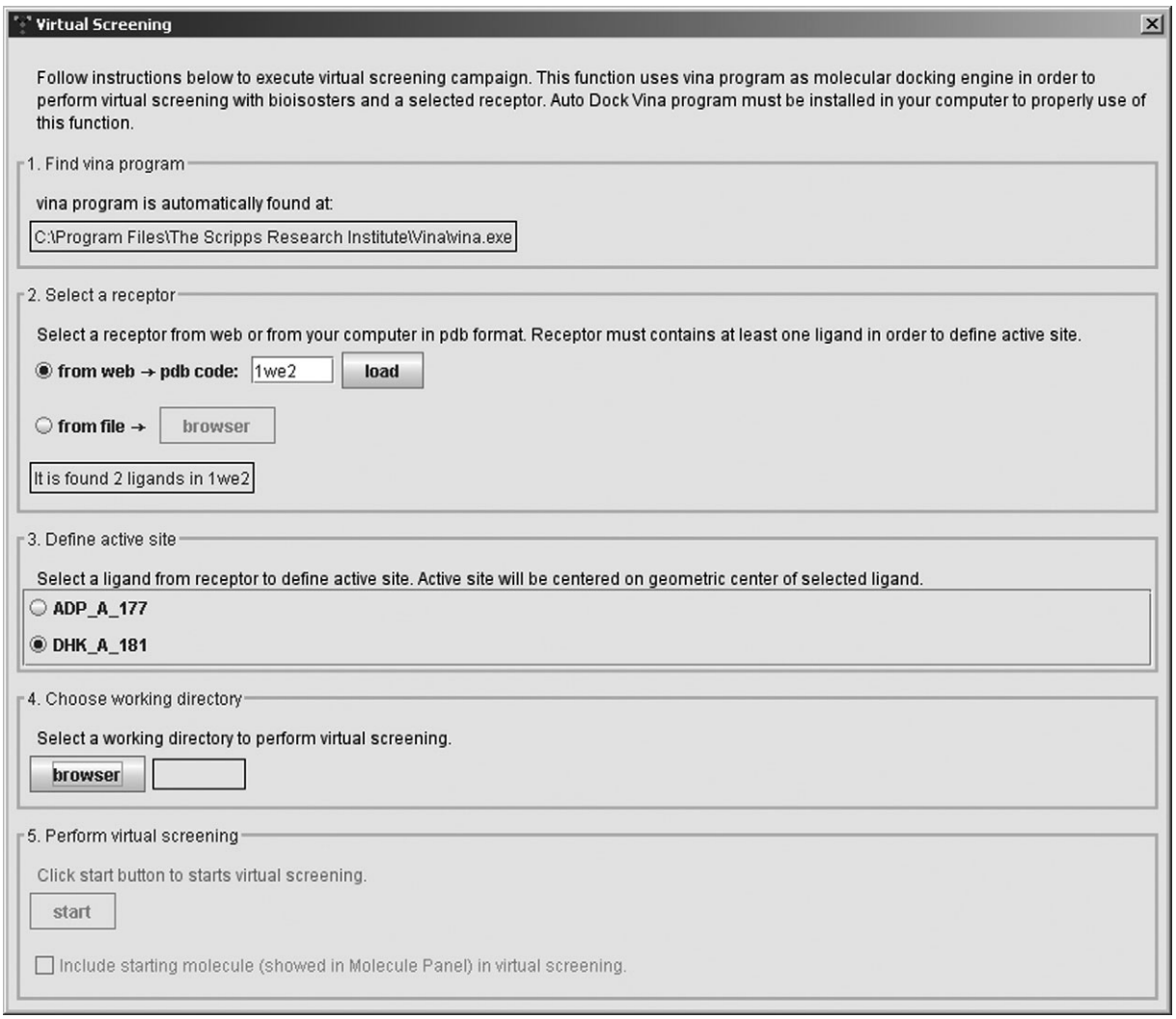

Figure 9. Dialog Window to perform virtual screening with bioisosteres and a selected receptor.

choosing **Bioisosters** → **Filter bioisosters**; a window dialog is displayed as shown in Figure 8.

User checks properties that he/she wants to use as filter criterion, optionally changing value range, and clicks "filter molecules" button. Number of accepted molecules is shown beside "filter molecules" button. User clicks "save molecules" to save accepted molecules in some supported file format and "delete unfiltered molecules" to delete rejected molecules. Virtual screening is performed by choosing **Bioisosters** → **Virtual Screening**; (Fig. 9). MB-Isoster automatically searches for vina executable in PATH system variable and in home user directory, if not found, user is asked about vina location. Receptor is read from a file or from web in a manner similar to "Read Ligand from PDB-complex" dialog window. User selects a cocrystallized ligand to define grid box center and chooses working directory to store input and output files. Finally, "start" button is clicked to start virtual screening.

Conclusions

In this article, we describe MB-Isoster, whose purpose is to make new molecules from an input molecule based on bioisosteric replacement. Bioisosteres are automatically built and can be saved in some common molecule file format. Also it is possible to choose atoms to replacement based on nonbonded interactions computed between a receptor and its ligand. Drug-like properties computation and virtual screening is also performed in order to select best bioisosteres. MB-Isoster can help researchers in drug design. Next step is to improve bioisostere library so that many output molecules may be made.

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