Journal of Computational Science 10 (2015) 217–224

Contents lists available at ScienceDirect

Journal of Computational Science

journal homepage: www.elsevier.com/locate/jocs

In search of novel anti-inflammatory agents: Computational repositioning of approved drugs

P.S. Kharkar*, S. Borhade, A. Dangi, S. Warrier

SPP School of Pharmacy and Technology Management, SVKM's NMIMS, V. L. Mehta Road, Vile Parle (West), Mumbai 400 056, India

ARTICLE INFO

Article history:
Received 11 October 2014
Received in revised form 16 January 2015
Accepted 22 January 2015
Available online 24 January 2015

Keywords:
Drug repositioning/repurposing
Computational drug repositioning
Drug rescue
Reverse virtual screening
Chemical space
mPGES-1

ABSTRACT

Computational drug repositioning is a powerful tool to guide the experimental drug repositioning campaigns. Both structure-based (e.g., reverse docking) and ligand-based (e.g., 3D pharmacophore) approaches can be used for the generation of repurposing hypotheses. In an attempt to discover novel anti-inflammatory agents, computational repurposing of approved small molecule drugs was undertaken using diclofenac (nonselective cyclooxygenase (COX) inhibitor), celecoxib (selective COX-2 inhibitor) and a potent microsomal prostaglandin E synthase – 1 (mPGES-1) inhibitor as query molecules for shape- and electrostatics-based virtual screening. Several approved drugs (other than anti-inflammatory) were amongst the top 5% of the hits. These hits (approved drugs) may serve as starting points for clinical repositioning (anti-inflammatory indication) or as lead structures in drug discovery programs.

1. Introduction

The present-day drug discovery is regarded as an extremely less-productive venture in terms of return-on-investment (ROI). Strict regulatory requirements, in addition to late-stage failures, are partly responsible for skyrocketing the drug development expenses in excess of US $ 2 billion [28]. To bridge the 'productivity gap', several small and big pharmaceutical companies worldwide have begun to focus on the plethora of knowledge gained from approved, shelved, withdrawn or experimental drugs. These processes, popularly known as drug repositioning/repurposing and drug rescue, have great potential in speeding up the drug development process with substantial time and cost savings [1,26]. Additionally, such approaches can be used for identifying innovative treatment options for unmet medical need. The discovery of sildenafil, repositioning of thalidomide for multiple myeloma, etc., are few of the many success stories of these useful strategies [19]. In brief, there is a renewed interest in this field. This is evident from the initiatives such as National Institutes of Health (NIH)'s program named 'discovering new therapeutic uses for existing molecules' started in 2012 with the aim of discovering innovative treatments using abandoned and existing molecules/drugs [8,24].

Computational repositioning, on similar lines, represents a systematic process involving design and validation of automated workflows capable of generating potential new indications hypotheses for a query drug [15]. It can accelerate the development time-lines further, depending on the amount and nature of clinical and/or safety data available for the abandoned, shelved or active drugs to be repurposed. In comparison to the traditional repositioning approaches, the computational investigations analyze the data for several drugs and diseases simultaneously. An excellent discussion on three computational repositioning methods namely, transcriptomic, side-effects and genetics-based methods, can be found in the literature [15]. Briefly, transcriptomic methods deal with the association of a drug with a specific aspect of the disease, followed by extrapolation of that knowledge to the disease itself, e.g., a new phenotype emerging from genome-wide gene expression. In side-effects method, a drug exhibiting particular side effect(s) is associated with a new disease indication by representing the disease on the basis of side effects associated with its treatment, e.g., sildenafil for erectile dysfunction. In the last method, genetics-based one, if the target of a drug is genetically associated with a disease that is different from its indications, the drug can be repositioned for that disease. The PubMed search with keywords 'computational drug repositioning' resulted in 80 hits (conducted on 09/07/2014); with majority of publications focusing on the network-based approaches in addition to the above mentioned methods. These studies were heavily dependent on the available data and differed with respect to the analytical tool/method used. Overall, repositioning hypotheses were generated using extensive experimental and clinical data analyses. Such working hypotheses can also be generated using computer-aided molecular design (CAMD) and molecular modeling tools and techniques.

* Corresponding author. Tel.: +91 22 4233 2016; fax: +91 22 2618 5422.
E-mail address: prashant.kharkar@nmims.edu (P.S. Kharkar).

http://dx.doi.org/10.1016/j.jocs.2015.01.002
1877-7503/

Utility of CAMD methods (ligand- and structure-based approaches) is well-known to the drug repositioning fraternity. Inverse virtual screening using molecular docking (also called reverse docking) represents a structure-based computational strategy wherein a small molecule ligand/drug is screened for its binding complementarity against a database of clinically-relevant macromolecular targets [17,32]. Similarly, ligand-based approaches such as pharmacophore [4], shape- and electrostatics screening, etc., have been used previously for reverse virtual screening or related applications [22,25].

Nonsteroidal anti-inflammatory drugs (NSAIDs) form an important class of therapeutic agents used for the treatment of a variety of inflammatory conditions. These drugs primarily act on several targets such as cyclo-oxygenase-1 and -2 (COX-1 and COX-2) involved in the prostaglandin (PG) biosynthetic pathway. Despite the availability of several NSAIDs, hunt for safer anti-inflammatory drugs is still on due to some of the serious side effects exhibited by the current/withdrawn marketed drugs [13]. Clinically used COX inhibitors suffer from severe gastric and cardiovascular side effects. A target downstream of COX in the PG biosynthesis, microsomal prostaglandin E_2 synthase-1 (mPGES-1), has been regarded as safe compared to COXs since its deletion or inhibition was devoid of cardiovascular side effects seen with COX inhibitors [5]. Design and discovery of novel mPGES-1 inhibitors is an active area of anti-inflammatory research [14]. None of the mPGES-1 inhibitors has reached to the clinic yet. It would be potentially interesting to reposition the approved/experimental drugs for anti-inflammatory indication, with particular emphasis on mPGES-1.

The present investigation features the combined use of ligand- and structure-based methods for generating repurposing hypotheses for small molecule drugs in DrugBank database [18] using diclofenac (1), celecoxib (2), and an mPGES-1 inhibitor (3) [14] drugs/leads as query molecules. This study may also perturb novel 'chemical space' for the design and development of newer therapeutic agents for the treatment of inflammatory conditions.

2. Materials and methods

2.1. Hardware and software

All the molecular modeling studies described herein were performed on Lenovo UltraBook Laptop (Intel® Core™ i5–3317U CPU @ 1.70 GHz, RAM 4 GB) running Windows 7 Home Basic Operating System. OpenEye Scientific Software Products [27] were used for performing various molecular modeling studies described in this manuscript. Structure building and related operations were carried out using Vida version 4.2.1. The ionization constants (pK_a) were normalized (pH 7.4) and AM1BCC partial charges were calculated in QUACPAC version 1.5.0. All the molecules were subjected to tautomer generation using tautomers module implemented in QUACPAC 1.5.0. This was followed by multiconformer generation for every molecule using Omega version 2.4.6.

2.2. Data set

Drugs 1–3 (Fig. 1) were used for generation of query to be used for shape- and electrostatics screening in rapid overlay of chemical structures (ROCS) version 3.1.2 and EON version 2.1.0. A total of three runs using each query were performed. The screening collection consisted of 1135 approved small-molecule drugs downloaded from DrugBank [18]. The original set of 1541 drugs from DrugBank was pruned to remove metals (e.g., lithium), inorganic as well high molecular weight drugs (>700 daltons). The drugs database was processed – 2D to 3D conversion, pK_a normalization, calculation of AM1BCC partial charges, tautomer generation and generation of multiconformer databases – to yield the database ready for shape- and electrostatics screening. The multiconformer generation process is unique in Omega which involves two stages – model building and torsion driving. Initial models of the structures are built by assembling fragment templates along sigma bonds. Once built, Omega generates additional model by enumerating ring conformations and invertible N atoms. The acyclic sigma bonds that have at least one non-H atom attached to each end of the bond are selected for torsional search. The resulting best conformers are ranked according to their energy. The final ensemble, generated based on user-defined RMSD criteria, is populated to the maximum ensemble size (default = 200), or until the list of low energy conformers is exhausted.

2.3. Query generation and ROCS screening

A total of three queries were generated using 1–3 in vROCS with default settings. The structures of the queries were processed as described in Section 2.2, i.e., 2D–3D conversion, pK_a normalization, and calculation of AM1BCC partial charges, tautomer generation and generation of multiconformer databases. The minimum energy conformation of each query was then used for subsequent query generation process in vROCS. The generated queries for 1–3 are shown in Fig. 2. In this shape-based alignment method, a solid-body optimization process is used for maximizing the volume overlap between the molecules to be aligned. Only heavy atoms are used while hydrogens are ignored completely. Since shape and volume are closely related, maximization of volume overlap is analogous to shape similarity [30]. Even though ROCS is primarily a shape-based method, user-specified chemical features can be included in the alignment and similarity analyses, thereby considering both shape and chemistry during the alignment process. The chemistry alignment, called 'color', is helpful in selecting hits which match in both, shape and chemistry. Once the queries were generated, a simple ROCS run was performed with the multiconformer database of drugs generated previously. The default color force field, Implicit Mills Dean was used in the ROCS simple run. All the default settings were used as – best hits: 500; rank by: Tanimoto combo; color optimize: Yes; full optimization: Yes. These options alter how ROCS runs and affects the hits. The output of ROCS simple run served as input for the electrostatics-based screening in EON.

2.4. Electrostatics screening

EON, like ROCS, does not align the database molecules onto a query; rather it calculates electrostatic similarity (expressed as electrostatic Tanimoto (ET) score) between them [20]. ROCS-aligned molecules with high-quality partial charges, AM1BCC, were used for EON screening. Since electrostatics is largely affected by the ionization state(s) and the formal charges, a care was taken during the initial modeling operations such as pK_a normalization and the subsequent partial charge calculations using AM1BCC method. Calculation of electrostatic similarity is also dependent on the quality of alignment; ROCS-aligned molecules provide the best option. EON can take care of the subtle changes in the input conformations to maximize the ET score without changing the shape overlap with the query. All the default settings as implemented in EON were used for calculation of the electrostatic similarity between the query and the database molecules. The screening was performed with three separate queries listed in the ROCS output as the first molecule. The molecules were ranked according to ET_combo score (sum of shape Tanimoto and ET_pb). ET_pb uses outer dielectric of 80 in the Poisson–Boltzmann (PB) electrostatics calculation. Tables 1–3 list top 25 hits from each EON screening. The electrostatic potential maps generated in EON for query 1 and one of the hits, salsalate, are shown in Fig. 3a. The resulting molecular alignment of few hits,