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e-Drug3D: 3D structure collections dedicated to drug repurposing and fragment-based drug design

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ABSTRACT

Motivation: In the drug discovery field, new uses for old drugs, selective optimization of side activities and fragment-based drug design (FBDD) have proved to be successful alternatives to high-throughput screening. e-Drug3D is a database of 3D chemical structures of drugs that provides several collections of ready-to-screen SD files of drugs and commercial drug fragments. They are natural inputs in studies dedicated to drug repurposing and FBDD.

Availability: e-Drug3D collections are freely available at http://chemoinfo.ipmc.cnrs.fr/e-drug3d.html either for download or for direct *in silico* web-based screenings.

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Supplementary information: Supplementary data are available at *Bioinformatics* online.

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1 INTRODUCTION

Approved drugs represent very attractive and valuable starting point for drug discovery. Studies of drugs entering the market show that most of their drug progenitors (or lead structures) were known drugs or clinical candidates (Proudfoot, 2002; Teague, 2011). The rationale is that a drug usually acts on more than one target and may exhibit previously unknown functions due to promiscuous off-target interactions explaining efficacy and/or side-effects (Campillos *et al*., 2008). Examples of new therapeutic indications for old drugs include the anti-emetic and hypnotic Thalidomide originally withdrawn as a leprostatic agent (Teo *et al*., 2005) or the anti-neoplastic Finasteride for the treatment of hair loss (approved in 1997). Over the years, an increasing number of pharmaceutical companies have been interested in 'drug repurposing' in order to reduce the risk and cost of the development of new chemical entities (Tobinick, 2009). The fragment-based drug design (FBDD) approach represents another validated alternative to high-throughput screening (Murray and Blundell, 2010). It consists of identifying low molecular weight molecules that are able to interact with a defined binding site. Hits are then combined or grown into high-affinity ligands. Over the past decade, FBDD has become established as an effective approach and has led to the discovery of high-affinity bioactive molecules, some of which are in clinical development. The 'rule of three' provides a useful guideline when designing the fragment screening collection (Congreve *et al*., 2003), but the selection criteria may also include 'privileged structures' that are commonly found in known drug molecules (Hartshorn *et al*., 2005; Lepre, 2001). This strategy is based on the assumption that molecules resembling existing drugs are more likely to possess appropriate ADMET properties than random molecules. e-Drug3D has been purposely designed to provide free and ready-to-screen virtual collections of approved drugs and of their commercially available substructures (fragments). These collections of compounds are natural inputs for various cheminformatic and virtual screening applications.

2 e-DRUG3D COLLECTIONS

e-Drug3D is an annotated database based on the 'Drugs@FDA Data File' released by the US Food and Drug Administration (FDA). Over the years, several publicly available and drug-specific databases have emerged including DrugBank (Knox *et al*., 2011), ChEMBL/Drugs (Gaulton *et al*., 2012) and SuperDrug (Goede *et al*., 2005). SuperDrug was the first free resource that provided 3D conformers of drug structures. In developing e-Drug3D, our objective was to further expand such computed drug structures by adding recent approved drugs and providing a collection of commercially available drug fragments. e-Drug3D currently contains 1519 annotated 3D structures of 1305 different FDA-approved drugs of molecular weight <2000 (last update: June 2011). Chiral centers are checked and enantiomers are differentiated. We also provide two supplementary collections resulting from (i) the calculation of the most probable tautomeric and ionic states at pH 7.4 and (ii) the generation of multiple conformations for ring systems. Finally, we produced a collection of commercial substructures of drugs. The current collection contains 1383 commercial fragments that are represented by a single conformation. Preparation, analyses and comparisons of the two collections are given in the Supplementary Material. The e-Drug3D database is accessible through our web interface for browsing. It can be queried by keyword search, structural criteria or similarity search. Tools are also provided to select subsets of drugs for comparisons. Drug and fragment collections are directly linked to the *in silico* screening web server e-LEA3D (Douguet, 2010).

3 A FBDD EXAMPLE

The FBDD approach was successfully used to identify novel inhibitors of human cyclophilins. These proteins are enzymes exhibiting a peptidyl-prolyl cis–trans isomerase activity and playing

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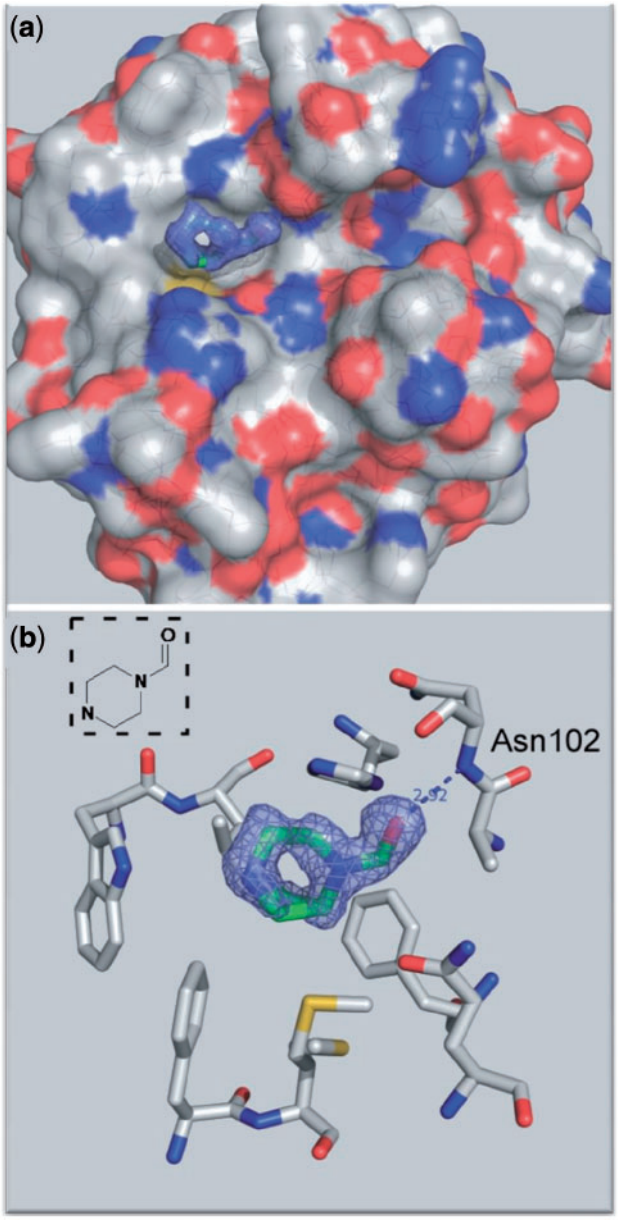

Fig. 1. (**a**) View of the 3D surface of the human cyclophilin D complexed with 1-formylpiperazine (PDB ID 3RCK). The fragment is represented by its electronic density in blue (map contour at 1.0 σ). (**b**) Residues implicated in the binding are shown along with the hydrogen bond between the carbonyl moiety of 1-formylpiperazine and the backbone nitrogen of residue Asn102. Inset— 2D sketch of 1-formylpiperazine. Pictures were generated by using the program Pymol.

a role in immunity and viral infection, including Hepatitis C virus (HCV; Guichou *et al*., 2011; Watashi, 2010). Several fragments were selected by virtual screening and soaked with cyclophilin D crystals (Schlatter *et al*., 2005). Among them, the compound 1-formylpiperazine corresponds to one fragment of our drug collection that is a substructure of the drugs Delavirdine, Doxazosin, Prazosin and Terazosin. Figure 1 shows the structure of the human cyclophilin D with this fragment (PDB ID 3RCK). Chemical optimization of several co-crystallized hit fragments led to the identification of submicromolar inhibitors of cyclophilin A, B and D (Guichou *et al*., 2011). These molecules show similar inhibition in infectious models and no cytotoxicity at the effective concentrations. The discovery of non-peptidic cyclophilin inhibitors is a breakthrough in the ongoing search for new anti-HCV agents as well as a successful example of the application of FBDD to difficult targets.

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