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Computational design of a novel anti-inflammatory drug

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Abstract

Computer-aided drug design is among the most valuable tools we have in order to design new drug molecules. Herein, with the aid of the Drug Design Workshop platform, we describe our efforts to propose a new anti-inflammatory drug with a high selectivity upon the COX-2 target protein.

Keywords

Computer-aided drug design; ADME; NSAID; cyclooxygenase.

The COX isozymes

Cyclooxygenase, also known as COX, is a family of enzymes consisting of two isoforms, COX-1 and COX-2, which are responsible for the production of prostaglandins, chemical messengers that regulate certain body functions and are known to cause inflammation. The first isoform, COX-1, plays a vital role in the gastric mucosal defense against gastric acids as well as ensures normal kidney and platelet function. Thus, it can be located in parts of the body such as the stomach and the kidneys. On the other hand, COX-2 is responsible for catalyzing the production of prostaglandins and can be located in immune cells, endothelial cells of blood vessels as well as synovial fibroblasts, which are associated with the development of inflammation.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs)[1] are a category of drugs which target the COX isoforms and can be categorized as selective and non-selective NSAIDs. The selective NSAIDs target only the COX-2 isoform without affecting COX-1, thus minimizing chances of gastric hemorrhage, peptic ulcer and cardiovascular diseases. In contrast, non-selective drugs bind

to both isoforms, thus inhibiting inflammation but at the same time reducing the beneficial functions of COX-1.

A typical example of a non-selective NSAID is *ibuprofen*. It has anti-inflammatory, antipyretic and analgesic effects. While it can aid the prevention of inflammations, it is also connected with causing gastric side effects, although milder than other NSAIDs.

One of the most prominent selective NSAIDs is *celecoxib*, which has anti-inflammatory effects and is used in order to reduce fever as well as arthritic pain. It functions through an enhanced binding to COX-2 as compared to COX-1. Within the two target isozymes there are two potential binding pockets. The active site and the "neighboring" allosteric site. In this area COX-1 and COX-2 differ by one amino acid. More specifically, instead of isoleucine (Ile) in COX-1 there is valine (Val) in COX-2. However, due to the larger size of isoleucine as compared to valine, the entry of *celecoxib* into the allosteric pocket of COX-1 becomes difficult. Therefore, *celecoxib* is more strongly bound to the COX-2 isozyme. Thus, *celecoxib* meets the criteria of a good drug, as it binds strongly to the target protein, reducing prostaglandin production, while its weaker interaction to COX-1 does not cause significant side effects. The drug, commercially known as C*elebrex*, is currently the only available inhibitor of COX-2. On the other hand, the non-selective *ibuprofen*, which is a smaller molecule that *celecoxib*, binds only to the active site. In Figure 1 the relative LigPlot diagrams[2,3] are depicted, while in Figure 2 the interaction of *celecoxib* with both proteins is provided.

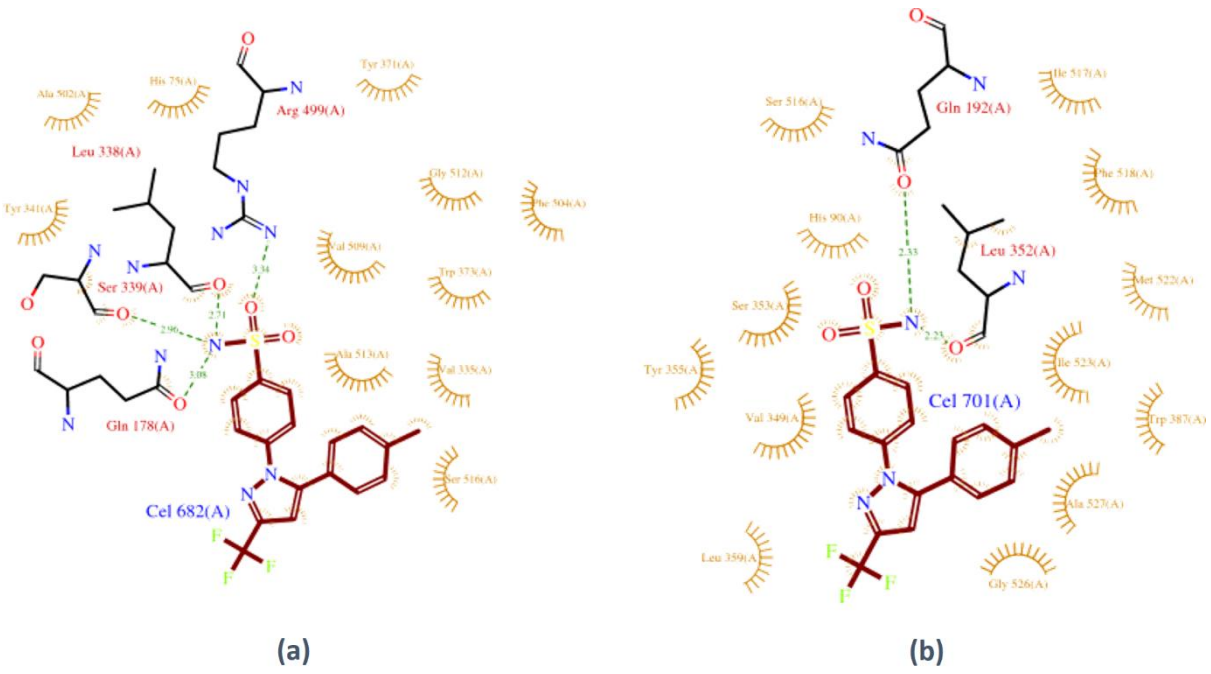


Figure 1: LigPlot diagrams of the *celecoxib* interacting with (a) COX-2[4] and (b) COX-1[5]. Binding to COX-2 is stronger.

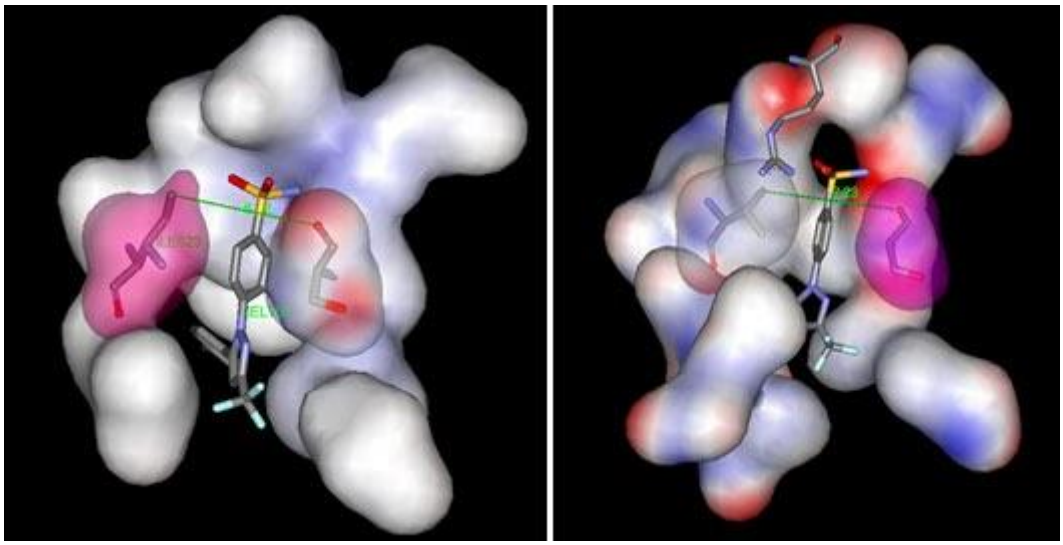


Figure 2: Interaction of *celecoxib* with COX1 (left) and COX2 (right).

Computer-aided drug design

In recent years, new methods have been developed for designing new drugs by using a computer. Thanks to them, the cost and time of discovering a new medicine that will be released on the market is reduced. More specifically, the branch of computational chemistry that deals with the above purpose is called Computer-Aided Drug Design (C.A.D.D.). Computational drug design can be approached in two ways, to date: computer-based macromolecular design (structure-based drug design) and computational design based on the substitute-binder (ligand-based drug design).

In computational design based on the macromolecule-target, the three-dimensional macromolecular structure (proteins or RNA) is studied, in order to identify the points where the biological function under investigation is performed. An effective drug can be designed based on these observations. One method is to find the compound from large databases with small molecules that is suitable for the macromolecule binding point using docking software. In addition, the structure of an existing drug can be improved / redesigned to bind to the macromolecule and meet the pharmacokinetic criteria of a drug (Lipinski's Rules)[6]. The improvement of the lead molecule becomes in terms of enhancing its affinity to target's binding sites in multiple trial-and-error cycles.

On the other hand, in computational design based on a well-known substitute-binder, the relationship between the structure and properties of the substitute and its biological function is examined (quantitative structure-activity relationships). Taking advantage of this relationship, existing drugs can be improved, or even more effective compounds can be redesigned. For example, if the substitute comes from nature, it is necessary to first locate the pharmacophore, that part of the compound that includes the groups responsible for the

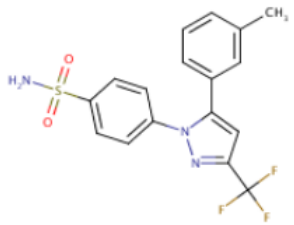
activity and to isolate it from the other substances in the natural product. Then, with a methodical chemical modification of the lead compound and screening of the new possible drugs, the process of finding the most suitable drug proceeds.
In our work we employ the Drug Design Workshop platform[7], developed by the Swiss Institute of Bioinformatics. The platform is set out to introduce computational chemistry and more accurately computational drug design to the public. It provides the opportunity to examine the interaction between an existing drug or an entire new molecule with a target-protein (COX-1, COX-2, BRAF V600E, BRAF wt, IDO1). In doing so, the docking of the ligand to the protein-target is taking place in real time in order to provide a variety of data concerning this inhibition, such as the score value which represents the stability of the inhibition, the probabilities of the ligand inhibiting different substrates and also several pharmacokinetic data concerning this ligand.

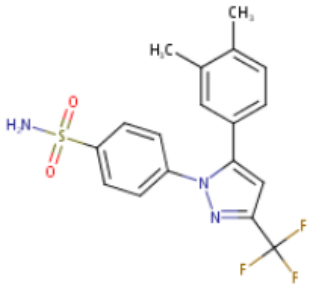
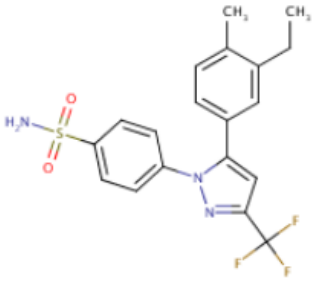
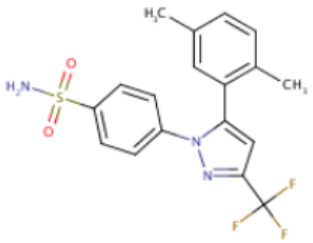
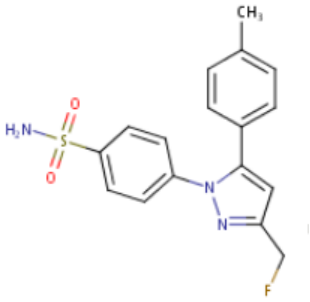
Designing non-steroidal anti-inflammatory drugs in the Drug Design Workshop platform

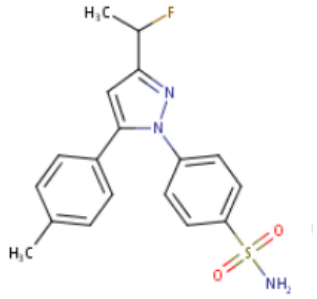
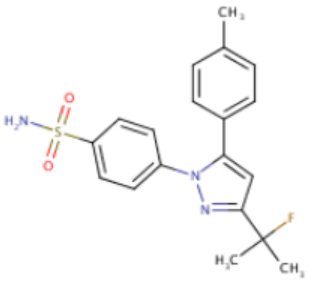
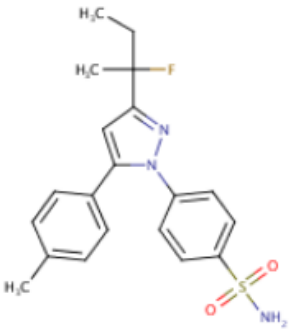
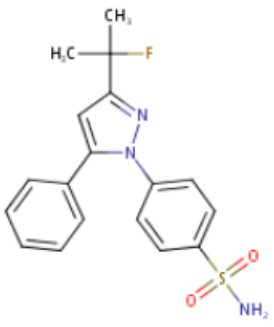
The objective of this research is to employ basic docking techniques, as they are provided by the publicly available Drug Design Workshop platform, in order to design a molecule with a high affinity to the COX-2 pocket and a low affinity to the relative isoenzyme. Within this framework the drug molecule should inhibit the target-protein, while the side effects due to the COX-1 isoform should be reduced. Moreover, pharmacokinetic data, as provided by the SwissADME[8] prediction tool, are used to support our docking experiments.

Several candidate molecules have been tested starting from the celecoxib as the lead compound. We followed a systematic change pathway in celecoxib's initial structure adding and subtracting electrophilic and nucleophilic groups to the main chain. From this extended trial-and-error approach ten compounds have been selected. These compounds show high affinity to the COX-2 pocket along with high selectivity towards the target isozyme. The resulting candidate drug molecules along with their predicted properties are depicted in Tables 1 and 2.

Table 1: Candidate drug molecules and predicted properties.

Molecule	Lead compound	Structure	Score
1	*celecoxib*		12.2

2	**1**		12.6
3	**1**		12.3
4	**1**		11
5	*celecoxib*		11.2

6	**5**		9.6
7	**5**		11.2
8	**5**		8.9
9	**7**		11.9

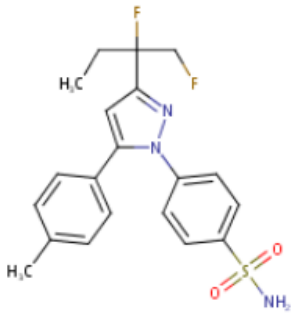
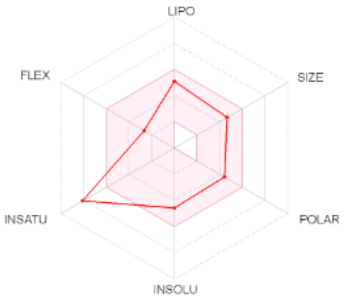
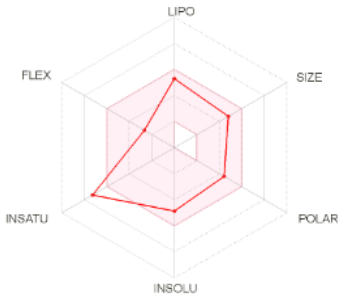
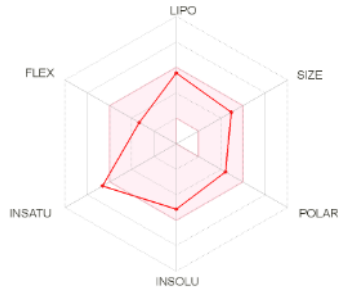
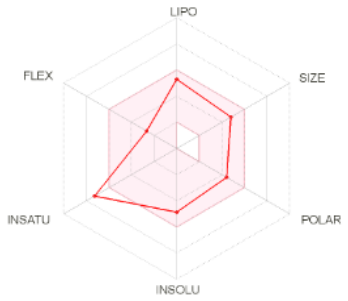
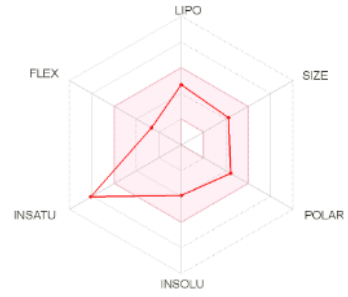
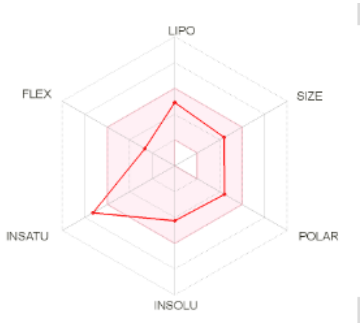
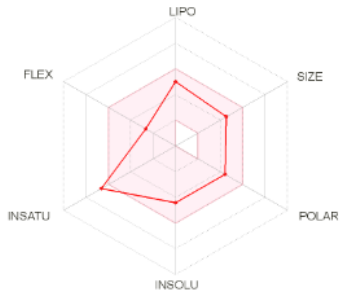
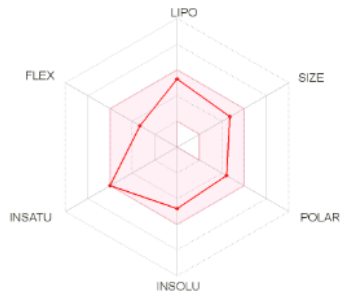
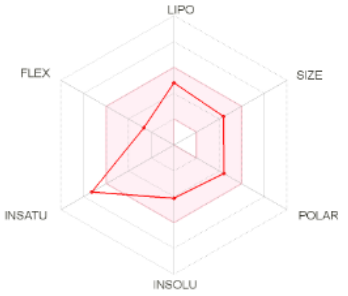
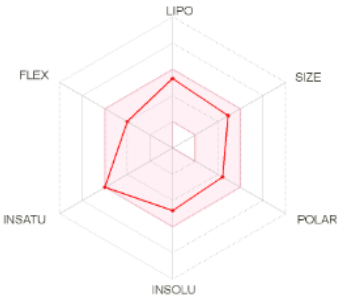
10	**8**		11.0

Table 2: Predicted properties of **1**-**10**.

Molecule	Substrate with higher probability of inhibition*	Diagram of pharmacokinetic parameters**	Annotations concerning the candidate's drug likeness
1	100% towards COX2 82% towards COX1		high molecular weight, too lipophilic
2	100% towards COX2 90% towards COX1		high molecular weight, too lipophilic
3	80% towards COX2 65% towards COX1		high molecular weight, too lipophilic

4	98% towards COX2 50% towards COX1		high molecular weight, too lipophilic
5	75% towards COX2 75% towards COX1		
6	45% towards COX2 25% towards COX1		high molecular weight
7	45% towards COX2 20% towards COX1		high molecular weight

8	20% towards COX2 10% towards COX1		high molecular weight, too lipophilic
9	40% towards COX2 15% towards COX1		high molecular weight
10	10% towards COX2 10% towards COX1		high molecular weight, too lipophilic

* Through a combination of 2D and 3D similarity with a library of 370000 known actives on more than 3000 proteins from three different species there were found the most probable macromolecular targets for the molecule.

** LIPO: Lipophilicity, POLAR: Polarity, INSOLU: Insolubility, INSATU: Insaturation and FLEX: Flexibility

Among compounds **1**-**10**, the most promising one was found to be **2** (Figure 3). It shows a high score (12.6) and high drug likeness. Furthermore, it's highly probable it can be administered *per se* as it has almost all the suitable physicochemical properties for oral bioavailability. However, there are certain downsides. The compound in question has high molecular weight and is too lipophilic, thus it is not expected to show very favorable ADMET properties, especially towards absorption and distribution.

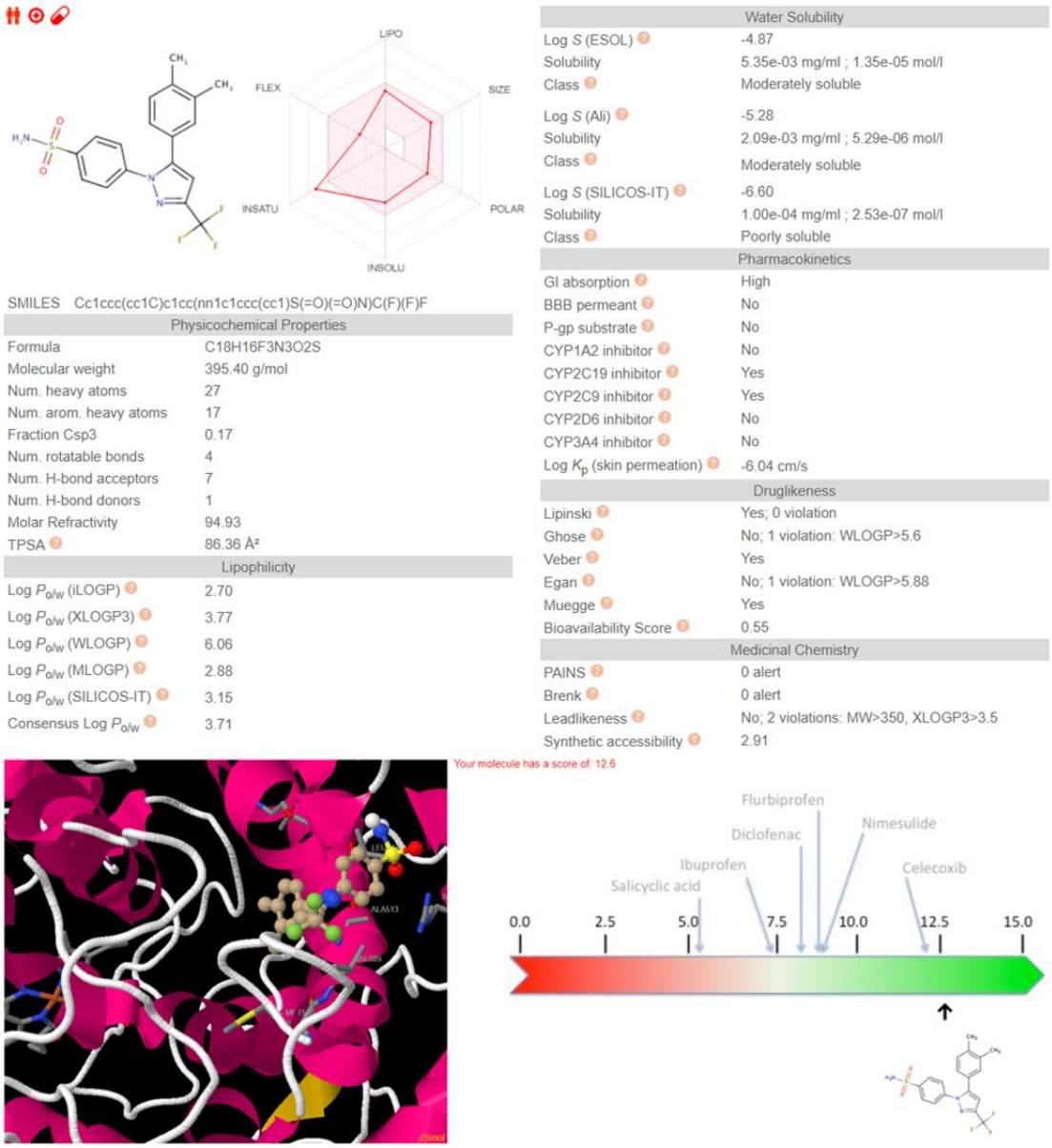


Figure 3: Pharmacokinetic data of the compound **2** from the SwissADME platform (up), interaction of the compound **2** with COX2 (down left) from the Drug Design Workshop platform and score value of the compound **2** (down right) from the Drug Design Workshop platform.

Conclusions

Herein we report the design of a new non-steroidal anti-inflammatory drug which is anticipated to own high selectivity upon the target isozyme COX-2. In order to achieve our goal, we employed *celecoxib* as the lead compound and in several steps, we modified its structure testing new compounds' potential activity with the docking platform Drug Design Workshop. We found that with a slight modification in the parent structure, i.e., the addition of a m-methyl group, an enhancement of the target-drug affinity can be achieved, without a significant change to druglikeness to be occurred.

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