

RECENT ADVANCES IN COMPUTATIONAL CHEMISTRY FOR IDENTIFICATION OF LIGANDS FOR BIOLOGICAL RECEPTORS: INTERDISCIPLINARY ASPECTS

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A – study design, B – data collection, C – statistical analysis, D – interpretation of data, E – manuscript preparation, F – literature review, G – sourcing of funding

ABSTRACT

Background: Computational (*in silico*) methods, such as quantitative structure-activity relationships (QSARs) are already well recognized and used in many screening programs related to environmental, industrial and medical chemistry. The main idea of the QSAR is that there is a relationship between molecular structure and ultimate biological effect caused by a chemical compound. In this respect the approach could be used successfully for prediction of various biological endpoints caused by chemical compounds including receptor binding affinity.

Aim of the study: In the current study the capabilities for structure-activity modelling incorporated in non-commercial software tool have been employed for investigating the binding effect of xenobiotics toward estrogen and human pregnane X receptor.

Material and methods: The analysis was performed by making use of the non-commercial software platform QSAR Toolbox. This system allows application of a set of built-in models for different biological effects, and also allows incorporation of new models for other endpoints.

Results: Two models have been applied for predicting the binding effect toward estrogen and human pregnane X receptors of a large number of chemicals collected in a single database of high practical concern. The results show that there are many chemicals which are able to bind the investigated receptors. Since those chemicals are encountered in the environment, they could be considered as potential threat for society.

Conclusions: The obtained results could be used as initial step for further experimental testing of those chemicals in order to confirm their potential to harm biological systems in the body.

KEYWORDS: QSAR, computational chemistry, nuclear receptors, human health

BACKGROUND

Nuclear receptors (NRs) are a superfamily of ligand-dependent transcription factors that mediate the effects of hormones and other endogenous ligands to regulate the expression of specific genes. Members of the NR superfamily include receptors for various steroid hormones (estrogen, androgen, progesterone, and several corticosteroids), retinoic acid, thyroid hormones, vitamin D, and dietary lipids (the peroxisome proliferator activated receptor (PPAR)). A large number of 'orphan' NRs (e.g. pregnane X receptor, farnesoid X receptor and liver X receptor) have also been identified whose cognate ligands are still unknown [1].

Many environmental chemicals can interfere with NRs, resulting in adverse biological effects. For example, in recent years, various agricultural, industrial, and household chemicals have been shown to directly

or indirectly interfere with the endocrine system of wildlife species and humans [2]. These chemicals called endocrine disrupting chemicals (EDCs) have the ability to mimic or inhibit the endogenous hormones such as estrogens and androgens. In this respect they have a potential to affect development and/or reproductive function in wildlife and humans [3].

Computational tools for early identification of potential ligands toward receptor macromolecules are becoming increasingly useful and accurate and are now used extensively by computational chemists in the field of environmental, industrial, and medicinal chemistry (Figure 1).

The Quantitative Structure-Activity Relationship (QSAR) method is now becoming an essential part of modern drug design, resulting in cost savings by reducing the laboratory resources needed and the time


Ligands	Target	Effect(s)	Environment/Drug design
estradiol	estrogen receptor	natural	
testosterone	androgen receptor	natural	
ligand	progesterone receptor	natural	
...	
Synthetic molecules	Various	UNKNOWN	

Figure 1. The role of QSAR for the identification of chemicals which are potential ligands for endogenous receptors.

required to create and investigate new compounds. QSAR is based on the concept that the differences observed in the biological activity of a set of compounds can be quantitatively correlated with differences in their structural or physicochemical properties by means of statistical or mathematical tools [4].

Recent findings have proven QSAR's value in predicting the binding effect of organic molecules toward many receptors including estrogen [5] and human pregnane X (PXR) receptors [6]. However, it should be pointed out that each model has its own limitations of applicability as a result of limited experimental data used for model development. To overcome this limitation researchers are encouraged to improve their models constantly by adding new experimental data. Another important question concerning the usage of models is that they are only available commercially, or require high level programming skills in order to be applied. Recently, authorities such as European Chemical Agency (ECHA) [7] and the Organisation for Economic Co-operation and Development (OECD) [8] have joined efforts to promote and support development of non-commercial tools for chemical risk assessment called the *OECD QSAR Toolbox* [9]. Currently, this tool is accepted and used in many companies, organizations, and national authorities for in silico predictions of different biological endpoints, including receptor mediated effects. An added advantage for users of *OECD QSAR TOOLBOX* is the ability to manually incorporate new models. Therefore, this software can be used for prediction of any biological endpoint if experimental data is available and the model is in agreement with OECD principles for reliability [10].

In this study, new model for identification of potential ligands toward human pregnane X (PXR) receptor was applied for screening of a large chemical database. From the same database chemicals with possible estrogenic effect were identified by making use of built-in model for this effect in the *OECD QSAR Toolbox*.

MATERIAL AND METHODS

OECD QSAR Toolbox

This software tool, created and maintained by the Laboratory of mathematical chemistry, is specially designed for chemical risk assessment, [11]. A key part

of this system is the ability to categorize chemicals, which allows for the grouping of chemical substances into categories. These categories of substances possess similar physicochemical, toxicological, and ecotoxicological properties, they behave similarly in environmental and occupational surroundings, and they can have similar chemical structures. An important advantage of the system is the large number of built-in models (profilers) for different biological/toxic endpoints. Each profile consists of a set of rules related to specific or general criteria associated to the respective endpoint.

The model for identification of estrogen receptor binders requires only chemical structure information describing the two-dimensional structure of molecules as an input. According to the classification scheme, cyclic chemical structures weighting less than 500 Daltons (Da) and bearing a hydroxyl (OH) and/or amino (NH₂) group are considered as binders. On the other hand, a chemical is considered as a non-binder if it does not satisfy these rules or if its OH or NH₂ groups are impaired by ortho di-substitutions [12]. In addition, each rule is associated with predefined binding potency which corresponds to very strong, strong, moderate or weak binding effects.

QSAR model for Pregnane X receptor

The activation of human pregnane X receptor (hPXR) regulate the expression of metabolizing enzymes such as cytochrome P450 (CYP3A4, CYP2B6 and CYP2C8/9) and glutathione-S-transferases, as well as important drug transporters (P-glycoprotein, multidrug resistance protein as well as others) [13]. Because the CYP enzymes metabolize the majority of clinically important drugs, inadvertent upregulation by hPXR agonists may increase the metabolism and excretion of co-administered therapeutic agents and cause undesirable drug-drug interactions or the generation of toxic levels of a drug metabolite. Hence, the activation of hPXR has the potential to initiate a broad spectrum of adverse effects, and in this respect identification of hPXR ligands is important information for evaluating health risk of drugs and environmental chemicals. As a result of analysis of training data, a set of eleven rules associated with specific chemical categories related to hPXR activators has been proposed [14].

OECD HPV database

The database consists of 4843 chemicals compiled based upon submissions from member countries including the European Union's high production volume (HPV) chemical list according to EC Regulation 793/93 [15]. This database includes all chemicals reported to be produced or imported at levels greater than 1000 tons per year in at least one Member country or in the EU region. One of the strategic goals related to this collection is constant addition of toxicological data for each chemical which will allow ultimate evaluation of the whole toxicological profile of the chemicals in the list.

RESULTS

The model for predicting the binding effect to estrogen receptor (ER) was firstly applied on the OECD high production volume (HPV) database. It should be pointed out that the model could be applied for predicting organic chemicals only. In this respect it was found that 2874 chemicals out of the total number 4843 are inorganic or structures with unknown or variable composition. Thus, the predictions have been generated for a total of 1969 discrete organic compounds. The results show positive predictions for 167 chemicals, and in addition there is information for binding potency for each chemical (Table 1).

Table 1. Predictions for ER binding for OECD HPV chemicals segmented by ER binding categories.

Effect	Very strong	Strong	Moderate	Weak
# of chemicals	7	42	18	35

In a similar manner, the model for identification of possible chemicals as activators of the hPXR receptor was applied over the HPV database. It was found that 67 chemicals contain structural and parametric characteristics that fit these defined rules.

DISCUSSION

The potency toward estrogen receptor could be associated with *very strong*, *strong*, *moderate* and *weak* binding effects. The benefit of this categorization is the prioritization of potential ER binders that may need further experimental testing or additional data. For example, seven chemicals are predicted to be *very strong* ER binders. From a practical point of view this is very convenient because financial resources will only be needed for seven experimental tests. In the same manner the focus can be set on *weak binders*. For example -alkylphenols which possess weak estrogenic effects are considered to be available in the environment due to their use in large scale industrial productions. Identification of chemicals with weak binding effect will result in their prevention to be used and further released in the environment.

The activation of the human pregnane X receptor (hPXR) is a contributing factor in drug–drug interactions due to its capability of binding a variety of

structurally diverse molecules. The induction of metabolizing enzymes and transporters by hPXR has also been regarded as one of the major mechanisms of drug resistance in humans [16]. Activation of hPXR may accelerate the metabolism and elimination of chemotherapeutic agents, which can contribute to resistance to chemotherapy.

The identification of binders to human pregnane X receptors was performed by using a set of structural rules applied as a new profiling scheme (model) in the OECD QSAR Toolbox. A total number of 67 chemicals from the OECD HPV database were found to have structural characteristics that can activate the receptor. Compared to the ultimate number of discrete organic chemicals (1969) in the database this number corresponds to value below 4%. Considering the biological role of the PXR (to sense the presence of xenobiotics) it was expected that a larger number of chemicals would be identified by the model. As a result, it can be concluded that additional work for improvement of the model is needed.

CONCLUSIONS

In the last few years there has been a growing interest in QSAR studies which consist of important methodology used in medicinal, industrial, and environmental chemistry. Frequently, the experimental determination of biological properties of substances is very complex, time consuming, and costly. However, the use of QSAR can reduce these problems through calculations and structural analysis that predict which substances will be active or toxic, saving time and money.

In the present study, we identified a set of high production volume OECD chemicals that may have the ability to bind estrogen or human pregnane X receptors. The evaluation was performed by making use of the non-commercial platform for chemical risk assessment OECD QSAR Toolbox. For estrogen binding, an existing profiling scheme was used, and an external set of structural rules associated with PXR binding was constructed as a new model. The obtained results show that both models could be used for identification of potential binders toward both receptors. This data can be used to prioritize possible estrogen or human pregnane X binders, and significantly reduce the cost required for experimental testing.

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