Ligand-based QSAR study for a series of steroids as progesterone receptor binders

Milen Todorov

Computational methods, such as quantitative structure activity relationships (QSARs) are already well recognized and used in drug development. The method could also aid the research on potential ligands toward variety receptor macromolecules. In the current study the capabilities for structure-activity modeling incorporated in the non commercial computational tool have been employed for investigation the binding effect of a set steroidal progesterone receptor ligands. A total of 52 molecules have been analyzed. The ultimate model provides knowledge about molecular descriptors that may influence the binding effect of PR ligands.

Key words: *Progesterone receptor (PR), QSAR, Toxicology, in silico tools*

INTRODUCTION

Progesterone receptor (PR) is a member of the nuclear receptor superfamily of ligand-inducible transcription factors [1] and has roles in multiple physiological processes. The endogenous PR ligand progesterone is involved in regulation of uterine cell proliferation/differentiation, implantation, ovulation, and mammary gland growth/differentiation [2]. Various synthetic PR agonists have been developed and used clinically to reduce estrogen-mediated endometrial cancer risk, and treatment of gynecological disorders [3].

Computational tools for early identification of potential ligands toward receptor macromolecules are becoming increasingly useful and accurate, and are now used extensively by medicinal and computational chemists. 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 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 a statistical or mathematical tool [54].

During the past decade a number of experimental structure-activity relationship studies have become available on a few classes of steroidal and non-steroidal PR modulators [4 and 5]. However, as all the other models these models are limited as well by the training sets used to generate them. In addition the accuracy of the predictions they give depends upon the similarity of the molecules being investigated to the molecules used in the training set. There is also a tendency for more-complex so called 'black box' models in that the reasoning behind a given prediction is difficult to interpret [6].

The current study presents development of QSAR model for prediction the binding effect for a set of 52 steroidal progesterone receptor binders. The primary objective was to identify the molecular properties that have a substantial effect on the binding affinity of the ligands. The PR binding potential was found to correlate with specific parameters such as effective diameter and polarizability of the investigated ligands. Secondly, the ultimate model in terms of structural and parametric boundaries was integrated and applied as external profiling scheme incorporated in the most popular free tool for chemical risk assessment – QSAR Toolbox.

EXPERIMENTAL

Progesterone receptor binding affinity data

The 52 compounds used as training data set were selected from literature source [4]. The values for relative binding affinities (RBA) of the ligands cover a wide range which allows analysis in terms of contrasting ligands in predefined affinity bins. RBAs were

determined using standard procedures [7] and expressed as percent compared to progesterone as referent compound.

OECD QSAR Toolbox

The QSAR Toolbox [8] is freely available software intended to be used for grouping approaches such as read across and category definition. Several grouping tools in terms of predefined specific (e.g. OECD HPV, US EPA HPV) or general (e.g. organic functional groups) chemical categories could be applied.

The Toolbox also includes a range of profilers to quickly evaluate chemicals for common mechanisms or modes of action. In order to support read-across and trend analysis, the Toolbox contains numerous databases with results from experimental studies. Another advantage of the system is the large number of built-in profilers for biological (e.g. receptor mediated) or toxicological (e.g. acute toxicity, genotoxicity) endpoints.

In addition it should be pointed out that the system could be used as a tool for development and application of new models which can be used as private schemes for prediction of specific biological/toxic endpoints.

RESULTS AND DISCUSSION

The training set of 52 chemicals was imported into the Toolbox as list of SMILES codes. As a result of analysis of all molecular structures it was found that most structural variation affects positions 11α, 11β, 17α, and 17β and to a lesser extent at positions 7α and 13β (Figure 1).

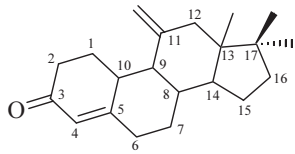
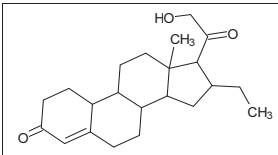
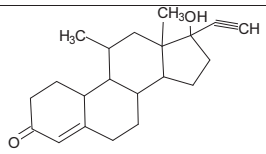
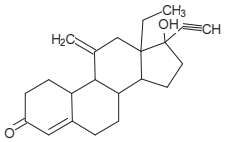
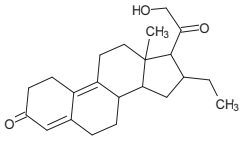
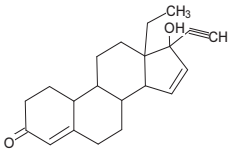
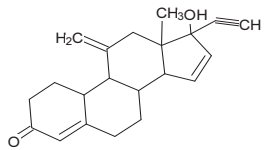
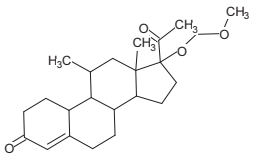
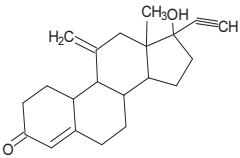
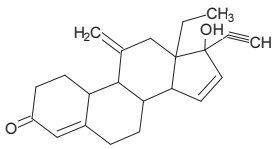


Figure 1. General representation of the molecular structures of the investigated PR ligands.

Due to the large number of possible combinations between substituents, the main structural element of PR ligands was defined as steroidal skeleton with at least one substitutient at 11α, 11β, 17α, 17β, 7α and 13β positions. As at is shown in Table 1 the most potent binders (RBA>100%) may contain different substituents at 11α, 11β, 17α, and 17β.

Because all of the PR ligands exert positive binding effect they were divided into three categories based on potency: a set of strong PR binders with RBA≥100 (9 chemicals); a set of weak binders RBA<40 (34 chemicals) and a set of moderate binders 0.2≤RBA<40 (9 chemicals).

Table 1. The most potent PR ligands used in this study (RBA,%).

		
1 (RBA=100)	2 (RBA=120)	3 (RBA=191)
		
4 (RBA=129)	5 (RBA=182)	6 (RBA=220)
		
7 (RBA=182)	8 (RBA=107)	9 (RBA=200)

1) (16a)-16-Ethyl-21-hydroxy-19-norpregn-4-ene-3,20-dione; 2) (11[3,17a)-17-Hydroxy-11-methyl-19-norpregn-4-en-20-yn-3-one; 3) (17a)-13-Ethyl-17-hydroxy-11-methylene-18,19-dinorpregn-4-en-20-yn-3-one; 4) (16a)-16-Ethyl-21-hydroxy-19-norpregna-4,9-diene-3,20-dione; 5) (17a)-13-Ethyl-17-hydroxy-18,19-dinorpregna-4,15-dien-20-yn-3-one; 6) (17a)-17-Hydroxy-11-methylene-19-norpregna-4,15-dien-20-yn-3-one; 7) (11[3)-17-(Acetyloxy)-11-methyl-19-norpregn-4-ene-3,20-dione; 8) 170-17-Hydroxy-11-methylene-19-norpregn-4-en-20-yn-3-one; 9) 17a)-13-Ethyl-17-hydroxy-11-methylene-18,19-dinorpregna-4,15-dien-20-yn-3-one

In order to identify inherent molecular characteristics for strong, moderate and weak binders each group were contrasted to the other. The obtained results are presented in Table 2.

Table 2. Prediction results for PR binders based on molecular descriptors associated to ligand-receptor interactions.

Analyzed group	Chemicals in group	Discriminating parameter	Sensitivity, %	Specificity, %
Strong vs moderate+weak	52	Effective diameter	100	84
Moderate vs weak	44	Volume polarizability	70	85

Initial analysis was performed by contrasting strong versus combined group of moderate and weak PR binders. To explain the difference between both groups a large number of molecular descriptors (preliminary calculated in the Toolbox) have been used. The best discriminating parameter was found to be the effective diameter (Diameff.) of the ligands. The meaning of this descriptor is associated to the molecular volume. Theoretically, it is defined as cylinder with minimum diameter within which the molecule could be inscribed.

From mechanistic point of view the effective diameter represent spatial characteristics of the interaction between ligands and progesterone receptor macromolecule. In terms of

values of Diameff. it was found that all strong binders fall in the range of 8.25÷8.95 Å. On the other hand it was found that 84% (37/44) of the ligands with lower binding potential are out of the specified range for effective diameter. In addition, it can be assumed that structural variations which lead to higher values than 8.95 Å in steroidal ligands may decrease the binding effect. This is observed for 27 out of all 44 lower PR binders.

The investigation related to discrimination of moderate from weak PR binders was performed following the same sequence of steps. Both groups were combined and technically processed in the Toolbox. It was found that the best discriminating molecular descriptor is Volume polarizability [eV/(a.u.)^2]. It is defined as a sum of atomic self-polarizabilities and describes the averaged ability of a compound to change electron density as its atoms during chemical interactions.

The volume polarizability could be associated with the interaction forces – considered to be electrostatic between ligands and the PR macromolecule. In terms of "activity" interval it was found that 6 out of 9 moderate binders (70%) have values in the range of 1.45÷1.51 eV/(a.u.)^2. In respect to the weak binders 85% (29/34) from ligands are correctly predicted in agreement with their experimental RBA data.

CONCLUSIONS

In this study a QSAR method to explore the receptor-ligand interactions influencing receptor binding affinity of progesterone receptor ligands is described. The analysis was performed on a series of 52 publicly available PR binding compounds comprising a set of steroidal structures. By contrasting predefined groups of strong, moderate and weak PR binders specific molecular descriptors were found to explain the binding effect. The strong binding potential could be evaluated by spatial molecular characteristics (effective diameter of the molecule), whereas the moderate effect is associated to the volume polarizability of the ligands.

The presented model could be applied as profiling scheme in the QSAR Toolbox for virtual screening of chemical databases. It will be especially valuable in the early stages of drug discovery projects. Any target that has structural data available can be assessed in terms of potential binding effect toward the progesterone receptor.

REFERENCES

[1] Mangelsdorf D.J., C. Thummel, M. Beato, P. Herrlich, G. Schuetz, K. Umesono, B. Blumberg, P. Kastner, M. Mark, The nuclear receptor superfamily: the second decade, Cell 83 (1995) 835-839.

[2] Zhang Z., C. Funk, S.R. Glasser, J. Mulholland, Progesterone regulation of heparin-binding epidermal growth factor-like growth factor gene expression during sensitization and decidualization in the rat uterus: effects of the antiprogestin, ZK-98299, Endocrinology 135 (1994) 1256-1263.

[3] Torgerson D.J., S.E. Bell-Syer, Hormone replacement therapy and prevention nonvertebral fractures: a meta-analysis of randomized trials, J. Am. Med. Assoc. 285 (2001) 2891e2897.

[4] Van Helden S.P., H. Hamersma, V.J. Van Geerestein, Prediction of the Progesterone Receptor Binding of Steroids using a Combination of Genetic Algorithms and Neural Networks. Genetic Algorithms in Molecular Modeling, 1996, Pages 159-192.

[5] Winneker, R. C.; Fensome, A.; Wrobel, J. E.; Zhang, Z.; Zhang, P. Nonsteroidal progesterone receptor modulators: structure activity relationships. Semin. Reprod. Med. 2005, 23, 46-57.

[6] Cherkasov, A. (2014) QSAR modeling: where have you been? Where are you going to?. J. Med. Chem. 57, 4977–5010.

[7] Bergink, E .W., van Meel, E, Turpijn, E .W., and van der Vies, J. (1983) . Binding of progestagens to receptor proteins in MCF-7 cells. J. Steroid Biochem. 19, 1563-1570.

[8] OECD QSAR Tollbox assessment/theoecdqsartoolbox.htm (last accessed 15.09.2015)

About the author

Milen Todorov, PhD, Department of Inorganic Chemistry, Faculty of Natural Sciences, University "Prof. Assen Zlatarov", 1 Prof. Yakimov str., Burgas, Bulgaria, tel. 056/716 491, e-mail: mtodorov@btu.bg

This paper has been reviewed