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Structural analysis of selective agonists of thyroid hormone receptor β using 3D-QSAR and molecular docking

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ABSTRACT

Selective thyroid hormone receptor β (TRβ) binding over TRα is an important requirement for improved therapeutic profile of TRβ agonists. Since selective compounds might be tolerated at doses that lead to complete binding without side effects, thus a selectivity study is valuable. Initially, comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) models were developed on a series of agonists of TRβ and TRα, respectively. These models produced statistically significant results: TRβ-CoMFA (R^2_{cv}, R^2_{pred}: 0.634, 0.6825), TRβ-CoMSIA (R^2_{cv}, R^2_{pred}: 0.711, 0.5622), TRα-CoMFA (R^2_{cv}, R^2_{pred}: 0.602, 0.5384) and TRα-CoMSIA (R^2_{cv}, R^2_{pred}: 0.674, 0.5078). These cross-validated results suggest that the developed models have excellent internal and external predictability and consistency. To further explore the origin of the selectivity at the amino acid residue level, the comparison between molecular docking and contour maps was conducted, it is revealed that steric, electrostatic and hydrogen bonding interactions play critical roles on selectivity; and Arg316, Arg282, Asn331, His435 for TRβ, Arg228, Arg262, Ser277, His381 for TRα are the significant residues, an in-depth comparative investigation suggests that the single different amino acid Asn331/Ser277 in the ligand binding pocket mainly introduce the ligand selectivity. All these analyses provide valuable information for better understand the mechanism of ligand–receptor interaction and facilitate structural modifications of the agonists to increase activity and selectivity.

Abbreviations

CoMFA	comparative molecular field analysis
CoMSIA	comparative molecular similarity index analysis
NR	nuclear hormone receptor
TRβ	thyroid hormone receptor β
TRα	thyroid hormone receptor α
DBDs	DNA-binding domains
LBDs	ligand-binding domains
3D-QSAR	three-dimensional quantitative structure–activity relationship
PLS	partial least squares
LOO	leave-one-out
ONC	optimum number of components
GALS	genetic algorithm with local search
R^2_{cv}	cross-validated correlation coefficient
R^2_{ncv}	non-cross-validated correlation coefficient
SEE	standard error of estimate
R^2_{pred}	predicted correlation coefficient
SEP	standard error of prediction
N_C	optimal number of principal components

1. Introduction

The superfamily of nuclear receptors (NRs) includes the receptors for thyroid hormone (TRs), retinoic acid (RARs), retinoid X (RXRs), estrogen (ERs), vitamin D3 (VDRs), glucocorticoid (GRs), and androgen (ARs), which exhibit crucial roles in development, homeostasis and many disease processes, thus emerging as major targets for pharmaceutical agonists and antagonists [1–3]. Thyroid hormone receptor is a member of the NRs superfamily of ligand-dependent transcription factors, which regulates important genes in intestinal, skeletal, cardiac muscles, liver and central nervous system, and controls heart rate, triglyceride and cholesterol levels. Different from other nuclear receptors, TRs bind DNA in the absence of hormone, resulting in transcriptional repression [4,5]. Evidence demonstrates that the pharmacological actions of TRs are related to physiological conditions, such as obesity, hypercholesterolemia and diabetes [6–10].

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The main characteristic of the TRs is the presence of an N-terminal region (A/B), a DNA binding domain, an E region containing the ligand binding domain (LBD) and the residues responsible for receptor dimerization, and a hinge region D that links the DBD and the LBD. The DBD domain mainly anchors the TRs to specific DNA response elements (TREs) [2,3], the hinge region confers relative flexibility to the two structural elements (DBD and LBD), the carboxyl-terminal LBD is responsible for ligand and various corepressors and coactivators binding, this area mainly ensures specificity and selectivity in the cellular response [11]. When agonists bind to the receptor, conformational changes occur on the LBD (repositioning helix 12 over the lower part of helices 3 and 5) that facilitate dissociation of repressors and association of activators [12–14].

Two different TR subtypes, TRβ and TRα, have been identified which are the products of distinct genes. Most effects of thyroid hormones on the heart rate and rhythm are mediated through TRα [15], whereas the most actions of the hormones on the liver and other tissues are related to the β-forms of the receptor. Consistent with their distinct expression patterns, the different TR isoforms function distinctly, for instance, TRα mainly regulates cardiac output, whereas TRβ helps in the control of metabolism in the liver [16,17]. In addition, a TRβ subtype-selective thyromimetic has been found to be efficacious in both mouse and monkey hair growth models after topical applications [18]. These data have stimulated the search for selective TRβ agonists which can separate cardiac side effects from metabolic rate and cholesterol lowering and possess acceptable safety profile. Recently, a novel class of thyroid hormone receptor agonists selective for TRβ has been synthesized [19–25], these agonists are both highly selective for binding and activating.

Various quantitative structure–activity relationship (QSAR) models applying different molecular descriptors have been developed [26-32]. Vedani et al. developed the satisfactory 4D-6D QSAR models to study the selective thyroid ligands by using Quasar and Raptor software [28,29]; a predictive 2D-QSAR models for both TRβ and TRα have been constructed [30]; and a series of agonists of TRβ have been studied by a three dimensional quantitative relationships (3D-QSAR) model, which provides some useful information for designing novel agonists with desired activity [31]. All these researches may identify the structural requirements for better ligand binding affinity, and offer detailed clues for modifying new agonists. To date, no 3D-QSAR models have reported on this class of TRβ and TRα agonists simultaneously. 3D-QSAR as a systematic method has been widely used to assist the design of ligands with improved properties [33–35], this mathematical method produces contour maps of different fields, which are favorable or unfavorable for the ligand–receptor interactions. CoMFA and CoMSIA are popular 3D-QSAR approaches, having many promising cues, such as visualize the regions in space responsible for increase or decrease the values of binding affinity.

In the present paper, in view of the homology of TRβ and TRα in the ligand binding pocket, the sequences of them were compared; a multistep work combing 3D-QSAR and molecular docking was applied to investigate the detailed binding mode between agonists and the two TRs. The reliability and robustness of the developed QSAR models were estimated with cross-validation, and the external predictive abilities were further validated statistically with an external test set of agonists. Moreover, the probable binding modes of the same compound with different binding activity of TRβ and TRα were further analyzed by molecular docking. The good concordance between the 3D contour maps and the molecular docking results provides helpful information about the key features of ligand binding mechanism. These computational models can provide some insights into the structural characteristics that affect the ligand binding activity and provide some meaningful clues in the future synthesis of agonists selective for TRβ.

2. Methods and materials

2.1. Data sets and biological activity

A series of potent and selective agonists possessing TRβ and TRα binding activities [19-25] were chosen and used as the dataset for molecular modeling in the present study. In this work, the *in vitro* biological activities of these ligands (IC_{50}) were converted into the corresponding pIC_{50} ($-\log IC_{50}$) values. The pIC_{50} values were applied as dependent variables in the CoMFA and CoMSIA analyses. The total set of the ligands (75 compounds) was divided into training (60 compounds) and test (15 compounds) sets in the approximate ratio 4:1 (Tables S1 and S2), and some representative skeletons and molecules of the set are shown in Tables 1 and 2. The test set was selected manually such that their pIC_{50} values were randomly but uniformly distributed in the range of the values for the whole set. The 3D-QSAR models were generated using the training set; the predictive power of the constructed models was evaluated using the test set (compounds marked with [a] in Tables S1 and S2).

2.2. Molecular modeling

All molecular modeling and QSAR studies were performed using the Sybyl package (Tripos Associates, St. Louis, MO). Partial atomic charges were calculated by the Gasteiger–Huckel method [36], conformational search and energy minimization were performed by Tripos molecular mechanics force field [37]. In order to obtain the most stable conformation, the energy gradient convergence criterion was set to 0.05 kcal/mol Å and the maximum iterations were set to 1000.

2.3. Conformational sampling and alignment

The results of the CoMFA and CoMSIA models may be extremely sensitive to a number of factors such as alignment rules, overall orientation of the aligned compounds, lattice shifting step size and probe atom type [38]. The most crucial input for QSAR is the alignment method [39] and thus we applied different molecular alignments to align all ligands used in the present study in space. It is assumed that these ligands share a common structure, thus each ligand binds into the active site in a similar mode. In this work, three different alignment rules were employed to develop the most reliable QSAR models. The first alignment rule is template ligand-based alignment (superimposition I), in this method, we chose the most potent agonist (compound **44**) as a template to fit the remaining training and test set of compounds by using the "align database" function .The common substructure is depicted in blue (Fig. 1A), and the resulting alignment model is shown in Fig. 1B; the second alignment rule

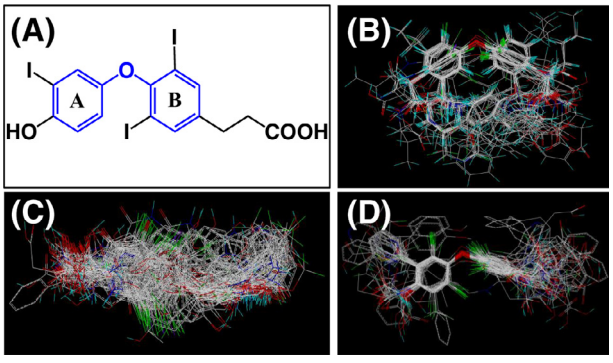

Fig. 1. (A) Compound **44** used as a template for template ligand-based alignment. The common substructure is shown in blue. (B–D) The alignments for TRβ from the superimpositions I, II and III, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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