Probing the Origins of 17β-Hydroxysteroid Dehydrogenase Type 1 Inhibitory Activity via QSAR and Molecular Docking

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Probing the origins of 17β-hydroxysteroid dehydrogenase type 1 inhibitory activity via QSAR and molecular docking

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ABSTRACT

It is generally known that proliferation of human breast cancer cells is stimulated by excess estrogen namely 17β-estradiol. Therefore, reduction of 17β-estradiol production by inhibiting 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1) is an interesting route for breast cancer treatment particularly during adjuvant therapy. This study investigated the structure–activity relationship of 17β-HSD1 inhibitors as to gain insights and understanding on the origins of 17β-HSD1 inhibitory activities. To meet this goal, multiple linear regression model was constructed and correspondingly the results revealed good predictivity ($N = 31$, $R^2 = 0.9438$, $Q^2 = 0.8530$). The model suggested that low molecular weight and energy were preferred as 17β-HSD1 inhibitors. Additionally, high molecular flexibility and high number of hydrogen bond donors were also shown to be important that is in correspondence to previously reported pharmacophore model of 17β-HSD1 inhibitors. Furthermore, molecular docking of inhibitors to 17β-HSD1 followed by anchor analysis suggested that three different pockets comprising of hydrogen bonding sites 1 and 2 as well as van der Waals contacts contributed to protein-ligand interactions. Post-docking analysis of potent compound **9** with 17β-HSD1 suggested that the binding modality was similar to the binding of substrate (i.e. estradiol) and its analog (i.e. equilin). Such information is useful in guiding the further design of novel and robust 17β-HSD1 inhibitors.

1. Introduction

Historically, 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1) is the first reported isoform of the 17β-hydroxysteroid dehydrogenase family [1]. This protein family constitutes a promising class of drug targets for diseases such as cancer and diabetes [2–4]. 17β-HSD1 is an enzyme involved in the sulfatase pathway in the last step of estrogen biosynthesis [5]. 17β-HSD1 has been characterized as a homodimer of 327 amino acid residues with a subunit mass of 35 kDa [6]. Particularly, the enzyme catalyzes reduction of the less potent estrone (E1) to the more potent 17β-estradiol (E2) [1,7] using either nicotinamide adenine dinucleotide (NADH) or nicotinamide adenine dinucleotide phosphate (NADPH) as the cofactor [6]. E2 can also be synthesized from the inactive adrenal precursor dehydroepiandrosterone (DHEA), particularly in postmenopausal women [5] as shown in Fig. 1.

In the treatment of hormone-sensitive breast cancer, it is necessary to block estrogen biosynthesis, in order to limit the proliferation of cancer cells [1,7]. This therapeutic approach has been successful in the case of aromatase inhibitors [8]. However, aromatase inhibitors may not be enough in reducing the estrogen concentration since E2 can also be synthesized from DHEA. Excessive expression of the mRNA levels of 17β-HSD1 and the higher E2/E1 ratio in postmenopausal women with breast cancer suggests the necessity for inhibiting 17β-HSD1 [5]. Inhibition of 17β-HSD1 is also a promising therapeutic approach for other estrogen-dependent diseases such as endometriosis. Therefore, inhibitors of 17β-HSD1 are promising candidates that are currently in the drug discovery pipeline [1,7,9].

Computer-aided drug design constitutes an arsenal array of computational tools that can be used in elucidating meaningful information pertinent for the design of highly potent inhibitors [10]. There are two major approaches for computational drug design: (i) structure-based and (ii) ligand-based methods. The

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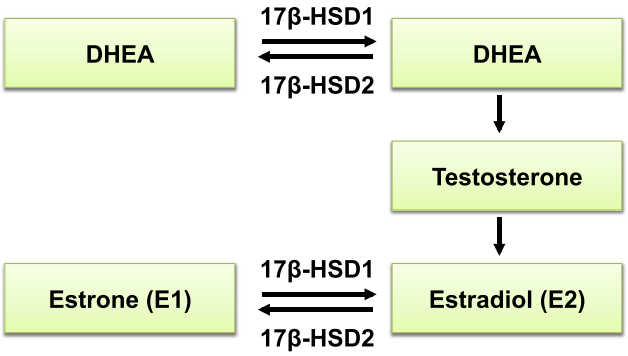

Fig. 1. Schematic representation of estrogen biosynthesis.

former approach entails the usage of X-ray crystallographic structures of proteins (if available) or predicted protein structures in molecular modeling studies that may involve molecular dynamics and molecular docking investigations on the dynamics or binding modalities of ligands with its respective target protein. The latter approach focuses on analyzing a series or library of compounds, irrespective of the availability of protein structures, by means of quantitative structure–activity relationship (QSAR) [11,12], comparative molecular field analysis (CoMFA) [13] and comparative molecular similarity indices analysis (CoMSIA) [14]. In the context of 17β-HSD1 drug design, several predictive models have been performed. Fischer et al. [15] developed a CoMFA model based on sets of ten training data and three validation data that afforded R^2 of 0.9. The chemotype investigated by Fischer et al. was based on the E1 or E2 scaffold with substituents at 6, 16, or 17 positions. Allan et al. [16] expanded the study of Fischer et al. by developing CoMSIA model using twelve training data and four validation data while achieving R^2 of 0.94 and Q^2 of 0.86. This work was based on modifications of position 16 on the E1 nucleus. Subsequently, Karkola et al. [17] reported a large-scale CoMFA study on a set of 37 molecules based on the thieno[2,3-*d*]pyrimidin-4(3*H*)-one chemotype. Their model could achieve Q^2 of 0.602 via leave-one-out cross-validation while affording R^2 of 0.91 on an external set consisting of six molecules. Heinzerling et al. [18] constructed classification models by combining local models from five separate models clustered according to *k*-means clustering and separately modeled using the .632 bootstrap estimator. The model was investigated on a large set of 125 molecules compiled from the literature as well as synthesized in-house.

In light of previous efforts on QSAR modeling of 17β-HSD1, it can be seen that most of these data sets were of limited size or even if the size is large its bioactivity were derived from different assay system. This study seeks to overcome these issues by assembling a large data set compiled from the literature based on the same bioactivity assay system. Furthermore, such compilation readily facilitates comparability of constituting compounds owing to uniformity of the assay used in measuring the bioactivity. QSAR and molecular docking, representing ligand and structure-based approaches, respectively, were employed as to shed light on the origins of 17β-HSD1 inhibitory activities. Insights gained from both approaches provide complementary knowledge that can serve as guidelines for future discovery and development of 17β-HSD1 inhibitors as breast cancer therapeutic agents.

2. Result and discussion

The aim of this study was to shed light on 17β-HSD1 inhibitory activity. This was achieved by performing QSAR modeling and molecular docking as to predict the inhibitory activity of 17β-HSD1 and identify important features governing its bioactivity, respectively. Inhibitors were compiled from reports using the same inhibition assay as tested on T47D breast cancer cell line. Their chemical structures are shown in Fig. 2.

Pearson's correlation coefficients (r) calculated for all pairs of descriptors was performed as to deduce their intercorrelation. As LUMO and HOMO-LUMO was found to be highly correlated ($r = 0.925$), one of the descriptor (i.e. HOMO-LUMO) was discarded from further analysis thereby leaving 12 descriptors for development of QSAR models. Such reduced set of twelve descriptors did not affect the overall coverage of molecular description since HOMO-LUMO is highly associated with either HOMO or LUMO. A heat map of the resulting set of descriptors along with the inhibitory activity is depicted in Fig. 3.

2.1. Prediction of 17βHSD1 inhibitory activity with MLR model

MLR was used to construct QSAR models of 17β-HSD1 inhibitors using a set of 12 selected molecular descriptors. The MLR model for the initial set of 42 inhibitors produced squared correlation coefficients of 0.57 and 0.22 for the training set (R^2) and the testing set (Q^2), respectively, with corresponding errors of $RMSE_{Tr} = 0.41$ and $RMSE_{CV} = 0.61$. Outlying compound **10** was identified in the first model using standardized residuals as described by Eq. (3). This was performed in an iterative process as summarized in Table 1.

A scatter plot showing the relative distribution of experimental versus predicted pIC_{50} values of 17β-HSD1 inhibitors from model 7 is shown in Fig. 4. It can be seen that the data points lie near the trend line with negligible variability implying robust predictive performance.

The equation for the final MLR model 7 was obtained as shown below:

$$\begin{aligned} pIC_{50} = {} & -0.5319(MW) - 0.0552(nCIC) + 0.3517(RBN) \\ & + 0.3877(nHDon) - 0.1562(nHAcc) - 0.2774(TPSA) \\ & - 0.1124(ALogP) - 0.1202(Q_m) - 0.6568(Energy) \\ & - 0.2572(\mu) - 0.2227(HOMO) - 0.2472(LUMO) \\ & + 0.3516 \end{aligned} \quad (1)$$

$N = 31$, $R^2 = 0.9438$, $RMSE_{Tr} = 0.1324$, $Q^2 = 0.8530$, $RMSE_{CV} = 0.2202$, F-ratio $= 51.1316$.

Regression coefficients from the MLR model can primarily identify the relative importance of investigated molecular descriptors. Prioritization of molecular descriptors deemed to be the most important from model 7 are as follows: Energy > MW > nHDon > RBN > TPSA. High coefficient values of energy suggested that decreased total energy of inhibitor molecules contribute favorably to the inhibitory activity. Likewise, inhibitors with small molecular weight were likely to exhibit stronger inhibitory activity towards 17β-HSD1. Higher number of hydrogen bond donors presented in the molecule (nHDon) also contributed to stronger inhibitory activity. Molecular flexibility of the molecules may be preferable as an inhibitor as suggested by the number of rotatable bonds (RBN) where higher number of RBN contributed to stronger inhibitory activity. In regards to the topological polar surface area (TPSA), which also indicates the water solubility of a molecule [19,20], it was observed that the inhibitory activity was likely stem from smaller polar surface area of the molecule. These findings were consistent with previously reported pharmacophore model of 17β-HSD1 inhibitors [7].

Robustness of models were further evaluated from the R^2–Q^2 metric proposed by Eriksson and Johansson [21], which describes

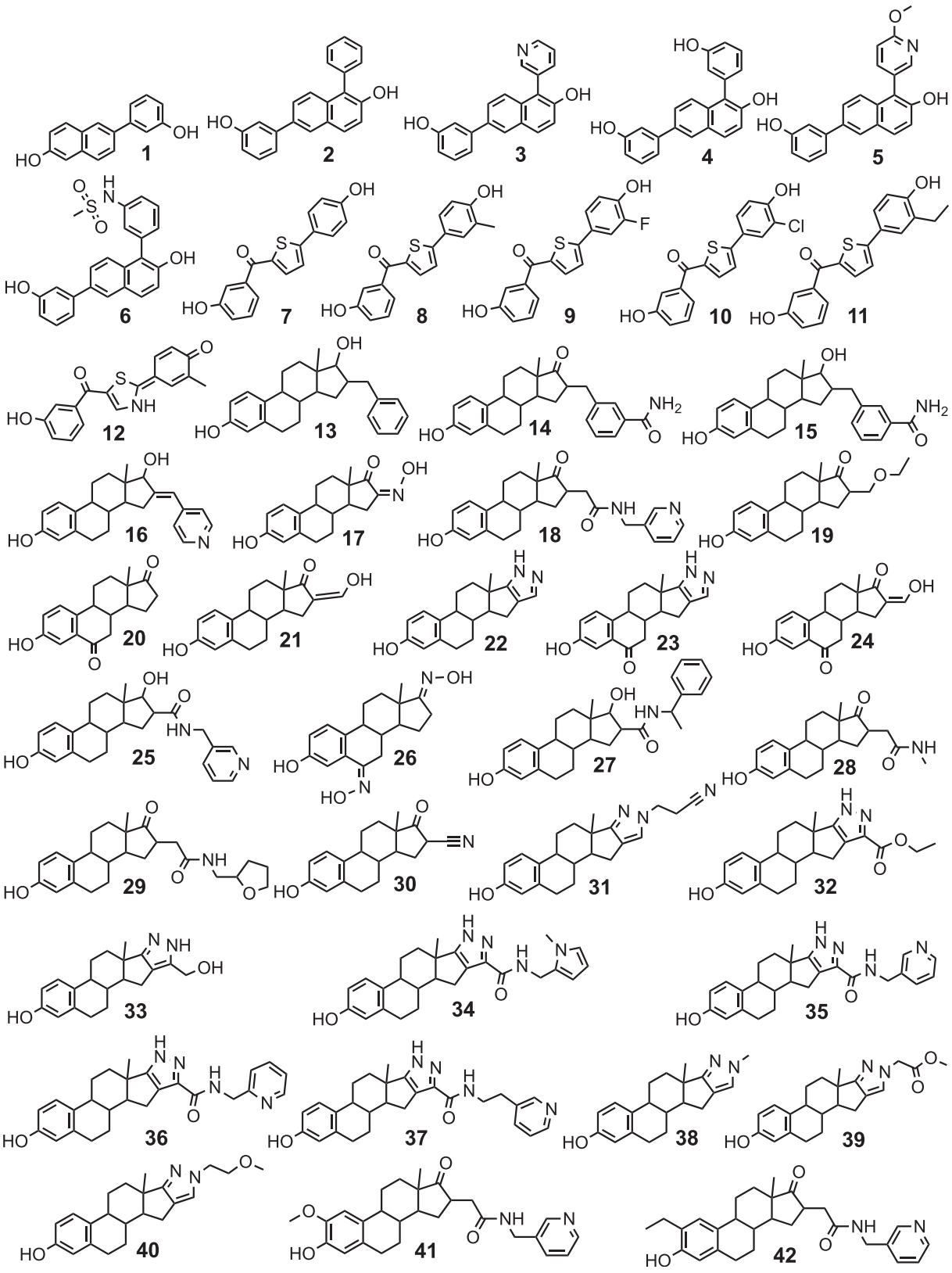

Fig. 2. Chemical structures of 17β-HSD1 inhibitors.

the fraction of **Y**-data accounted for by accumulated chance correlations where values higher than 0.2–0.3 is indicative of the risk of chance correlations or the presence of outliers in the data set. It was observed that R^2–Q^2 values gradually improved going from models 1 through 7. Model 7 afforded rather low R^2–Q^2 value of 0.091 thereby suggesting its robustness.

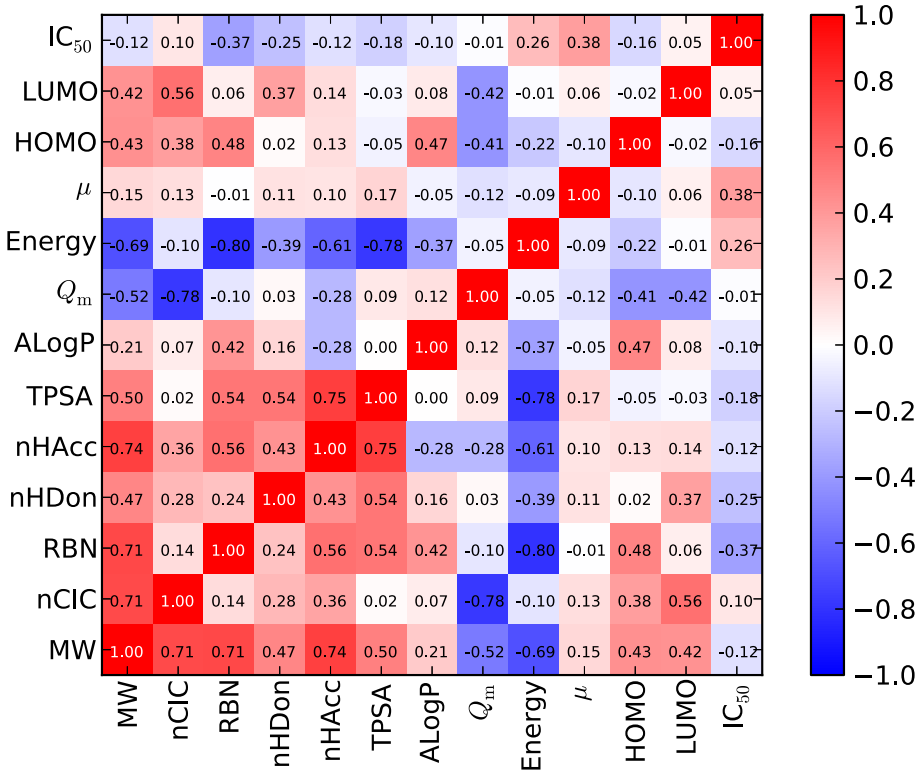

Fig. 3. Heat map of intercorrelation matrix of molecular descriptors and inhibitory activity.

Table 1
Summary of the predictive performance of MLR models.

Model no.	N	Outliers	R^2	Q^2	R^2-Q^2	$RMSE_{Tr}$	$RMSE_{CV}$	*F* ratio[a]
1	42	**10**	0.573	0.224	0.349	0.410	0.609	7.537
2	41	**8**, **11**, **15**	0.605	0.279	0.326	0.397	0.566	8.177
3	38	**21**, **42**	0.661	0.363	0.298	0.355	0.516	9.069
4	36	**18**	0.776	0.526	0.250	0.277	0.424	14.190
5	35	**31**	0.826	0.575	0.251	0.236	0.386	18.225
6	34	**16**, **22**, **26**	0.862	0.671	0.191	0.213	0.339	22.623
7	31	–	0.944	0.853	0.091	0.132	0.220	51.132

[a] Critical *F* values for model numbers 1–7 are 2.104, 2.118, 2.165, 2.204, 2.226, 2.250 and 2.340, respectively.

2.2. Docking of 17β-HSD1 inhibitors

In order to predict the binding modality of 17β-HSD1 inhibitors, all forty-two active compounds were docked into the ligand-binding site of the 17β-HSD1 structure (PDB code 1EQU). Two docked compounds (i.e. **20** and **40**) found to be bound outside the binding pocket of the enzyme were removed prior to further analyses. The SiMMap server was subsequently used to deduce the common binding mode for the remaining compounds. On the basis of the forty docked inhibitors, the server identified three different binding anchors (*HB-1*, *HB-2* and *VDW*) and moiety preferences for these anchors (Fig. 5 and Supplementary Table S1). Such anchors, denoted as *HB-1* and *HB-2*, contained only Glu282 and the nicotinamide ring of $NADP^+$ in the binding pocket, respectively. Both anchors were found to prefer to engage in hydrogen bonding interaction with either hydroxyl or keto moieties of the inhibitors. On the other hand, the *VDW* anchor is consisted of several hydrophobic residues including Gly94, Leu95, Leu96, Phe192, Met193 and Tyr218 as well as the polar residue Asn152. This pocket prefers to form van der Waals interactions with three different six-membered rings (i.e. phenyl, hydroxyphenyl and heterocyclic moieties) of the inhibitors.

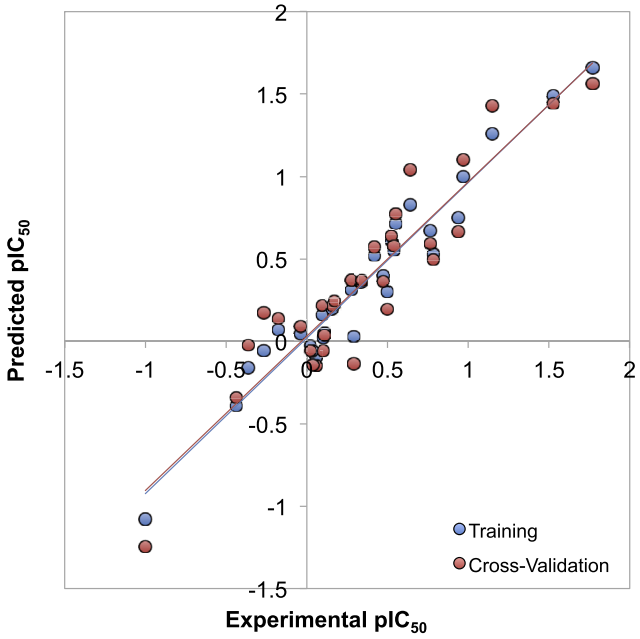

Fig. 4. Plot of experimental versus predicted 17β-HSD1 inhibitory activity (pIC_{50}). Data samples from the training and cross-validation sets are shown in blue and red, respectively. Trend lines are shown as solid line using the same color scheme. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Amongst the forty investigated compounds, only six of these (i.e. **3**, **5**, **7**, **9**, **12**, and **13**) were shown to interact with all three

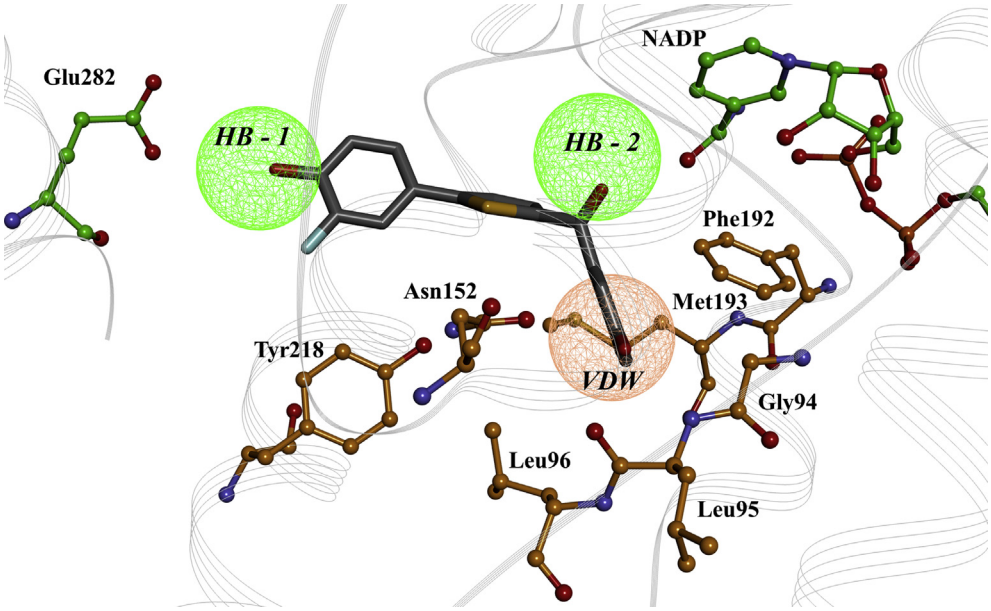

Fig. 5. The anchor-binding mode of all active compounds at the binding pocket of 17β-HSD1. The ligand moiety anchors, which are *HB-1*, *HB-2* and *VDW*, represents hydrogen-bonding sites 1 and 2 (green ball meshes) as well as van der Waals anchors (brown ball mesh), respectively. Conserved interacting residues are shown as balls and sticks. The active compound **9** is shown as a representative ligand docked in the binding pocket. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

identified anchors (Supplementary Table S2). Post-docking analyses of compound **9**, which exhibited the highest SiMMap score, inside the binding pocket revealed that the inhibitor form several types of interaction with the enzyme (Supplementary Fig. S1). In addition to amino acid residues involved in the binding pocket as identified by SiMMap, residues in the vicinity of the anchors also contributed to such interactions. Notably, His221 was found to engage in several hydrogen bonds with the fluorohydroxyphenyl moiety while Leu149, Pro187 and Val225 as well as the catalytic residue Tyr155 form several π-type hydrophobic interactions to all three π-rings of the inhibitor. Those residues were shown to interact with both estradiol [22] and equilin, an equine estrogen used in estrogen replacement therapy [23]. These aforementioned results on the binding modality of active compounds within the binding pocket of 17β-HSD1 serve as general guidelines on the future design of novel inhibitors towards 17β-HSD1.

3. Conclusion

QSAR modeling by means of MLR was applied for predicting the inhibitory activity of 17β-HSD1 inhibitors. Results suggested that small and flexible molecules having low total energy, high number of electron donors and good water solubility were predicted to have stronger inhibitory activity towards 17β-HSD1. In addition, molecular docking analysis also suggested the significance of several hydrogen bonds, van der Waals contacts as well as π-type hydrophobic interactions between inhibitors and key residues in the binding pocket of the enzyme. Findings presented herein could potentially be used to guide the design of novel inhibitors of 17β-HSD1 as well as paving the way towards its utilization in the treatment of breast cancer and other estrogen-related diseases.

4. Materials and methods

4.1. Data set

Forty-two inhibitors with reported inhibitory activity (IC_{50}) against 17β-HSD1 as tested on T47D estrogen-positive breast cancer cell line were compiled from the literature. This is comprised of the following sets of compounds: hydroxyphenylnaphthol (**1**–**6**) were reported by Marchais-Oberwinkler et al. [24], hydroxyphenylmethanones (**7**–**12**) by Oster et al. [25], C16 derivatives of E1 and E2 (**13**–**15**) by Laplante et al. [26], modifications at positions 6, 16 and 17 of E1 (**16**–**29**) by Allan et al. [16], modifications at positions 6, 16 and 17 of E1 and E2 (**30**–**40**) by Fischer et al. [15] and further E1 modifications (**41**–**42**) by Lawrence et al. [6]. Chemical structures of these 17β-HSD1 inhibitors are shown in Fig. 2. Prior to analysis, the half maximal inhibitory concentration (IC_{50}) were subjected to negative logarithmic transformation to the base of 10 (pIC_{50}) in order to obtain a more uniformly distributed data.

$$pIC_{50} = -log(IC_{50}) \quad (2)$$

4.2. Geometry optimization and descriptors calculation

Compound structures were drawn with ChemAxon Marvin [27] and geometrically optimized at B3LYP/6-31g(d) level. Quantum chemical descriptors were calculated using Gaussian 09 W [28] while molecular descriptors were computed using DRAGON 5.5 Professional [29]. Selected molecular descriptors used to generate the QSAR model consisted of (1) mean absolute charge (Q_m), (2) total energy (Energy), (3) dipole moment (μ), (4) highest occupied molecular orbital (HOMO), (5) lowest unoccupied molecular orbital (LUMO), (6) gap between energies of the HOMO and LUMO state (HOMO-LUMO), (7) molecular weight (MW), (8) rotatable bound number (RBN), (9) number of rings (nCIC), (10) number of hydrogen bond donors (nHDon), (11) number of hydrogen bond acceptors (nHAcc), (12) Ghose-Crippen octanol–water partition coefficient (ALogP) and (13) topological polar surface area (TPSA). This set of thirteen descriptors was selected as they can optimally provide an overall account of the general features of a molecule [30]. Furthermore, one of the descriptor in pairs having Pearson's coefficient greater than 0.9 were subjected to removal as to eliminate

inherent redundancy in the descriptor set.

4.3. Multivariate analysis

QSAR models of 17β-HSD1 inhibitors were created using multiple linear regression (MLR) model. Quantum chemical and molecular descriptors were treated as the independent variables and the log-transformed inhibitory activity (pIC_{50}) was treated as the dependent variable. In order that all the independent variables were comparable, normalization with mean and standard deviation was applied to all the independent variables. MLR was computed using the Waikato Environment for Knowledge Analysis (Weka), version 3.4.5 [31].

4.4. Data sampling

Data sampling using cross validation is necessary for small data set to validate the model by separating the data set into a training set and a testing set. Leave-one-out cross-validation (LOO-CV) was used to validate the MLR model. LOO-CV will randomly select one data sample (out of N samples) as the testing set and use the remaining N-1 samples as the training set. This internal validation method allows each of the data samples to be used as the testing set [32].

4.5. Outlier identification

MLR models were iteratively revised via the identification and removal of outliers on the basis of calculated standardized residuals. Calculated dependent variables (pIC_{50}) were used to compute the standardized residuals as described by the following equation:

$$x_{res} = \frac{x_i - \overline{x}}{\frac{1}{N}\sum_{i=1}^{N}(x_i - \overline{x})^2} \quad (3)$$

where x_{res} is the standardized residual, x_i is the pIC_{50} residual of the ith compound and $\overline{X}$ is the arithmetic mean of all residuals. Outlying compounds having standardized residual error exceeding 2-folds of standard deviation were subjected to removal from the data set. This process is repeated iteratively until no outlier could be detected in the model.

4.6. Model evaluation

The performance of developed QSAR models was assessed using squared correlation coefficient to describe the degree of fit in the training set (R^2) and the testing set (Q^2). Root mean square error was used to evaluate the prediction error in both training ($RMSE_{Tr}$) and testing ($RMSE_{CV}$) sets according to the following equation:

$$RMSE = \sqrt{\frac{\sum_{i=1}^{N}\left(x_{predicted} - x_{actual}\right)^2}{N}} \quad (4)$$

where $x_{predicted}$ and x_{actual} are the pIC_{50} from the model and the experiment respectively.

4.7. Molecular docking and anchor analysis

Structures of all forty-two compounds were docked into the crystal structure of 17β-HSD1 (PDB code 1EQU) using AutoDock Vina [33] and PyRx (http://pyrx.scripps.edu). The grid was centered at the ligand (equilin) binding site of the protein structure (x, y, z coordinates of 14.13, 21.98, and 30.98, respectively). The grid point spacing was 0.375 Å with a box dimension of 28 × 27 × 39 Å. Other parameters in AutoDock Vina were left as default. All resultant docked poses were subsequently submitted to SiMMap server (http://simmap.life.nctu.edu.tw) [34] in order to analyze their anchor-binding mode with the protein structure. The server provided a site-moiety map of the binding pocket showing conserved residues, moiety preferences and interaction types. Structural models and non-bonded interactions of the protein-ligand complexes were analyzed and prepared with Discovery Studio 4.0 Visualizer [35].

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2015.04.024.

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