

QSAR Analysis of 3- and 4-substituted 7-hydroxycoumarins as Novel 17 β -HSD3 Inhibitors

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Abstract

A series of 3- and 4-substituted 7-hydroxycoumarins analogues were analyzed for structure–activity relationship using sphere exclusion algorithm method. The QSAR studies were analyzed and the structural features contributing to the enhancement of activity were identified. 2D-QSAR statistically significant model with coefficient of determination (r^2) of 0.8291 and cross validated correlation coefficient (q^2) of 0.7455. The 2D-QSAR results revealed that the presence of chloro or fluoro substituents would increase the 17 β -HSD3 inhibitory activity and presence of bulky electron withdrawing groups at R1 and R2 position of ring would increase the 17 β -HSD3 inhibitory activity. Based on the results obtained from these analysis some compounds were designed which show enhancement in activity compared to the parent compound.

Keywords Coumarin; Quantitative structure activity relationship; 2D Descriptors; 17 β -HSD3 inhibitors; Prostate cancer

Introduction

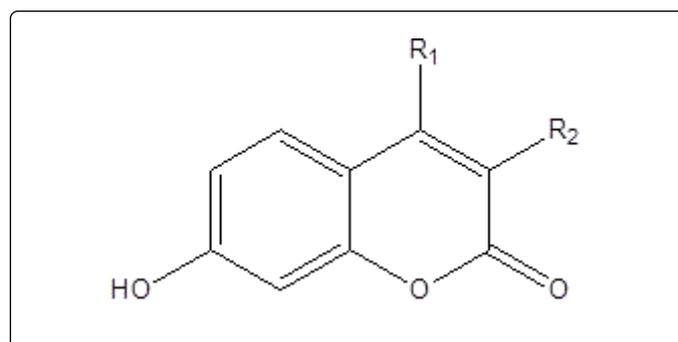
Prostate cancer (PCa) is the most enigmatic of the common solid malignancies. Second only to lung cancer as a killer of men beyond middle age, it warrants more attention than it currently receives from governments, researchers and the general public worldwide [1]. Prostate cancer is the most frequently diagnosed cancer in men. According to the American Cancer Society, an estimated 192,280 men were diagnosed with prostate cancer in the US during 2009. With an estimated 27,360 deaths in 2009, prostate cancer is the second-leading cause of cancer death in men [2]. The human prostate is a hormone-sensitive organ that depends on androgens for growth and development. The regulation of androgen biosynthesis or its action on the androgen receptor is central to the management of prostate cancer [3]. The early stages of prostate cancer tumor growth are androgen dependent and respond well to androgen ablation, [4-8] either via surgical castration or by chemical castration with a luteinizing hormone releasing hormone agonist in combination with an AR antagonist, such as bicalutamide. Recent evidence from both pre-clinical and clinical studies is consistent with the importance of re-activation of AR signaling in a majority of castrate-resistant prostate tumors [4-8]. 17 β -Hydroxysteroid dehydrogenases are oxidoreductases, which play a key role in estrogen and androgen steroid metabolism by catalyzing final steps of the steroid biosynthesis. The crucial role of estrogens and androgens in the genesis and development of hormone dependent diseases is well recognized [9]. Recent second-generation AR antagonists have been designed that retain antagonism in over-expressing cell lines, and among these agents enzalutamide [10] has recently successfully met efficacy criteria in a large Phase III clinical trial [11]. Quantitative structure-activity relationship (QSAR) is one of the most important applications of chemometrics, giving information useful for the design of new compounds acting on a specific target. QSAR attempts to find a consistent relationship

between biological activity or toxicity and molecular properties. Thus, QSAR models can be used to predict the activity of new compounds [12]. Considering the recent interest in 17 β -HSD3 inhibitors and for progression of design and development of such inhibitors, a QSAR investigation of the aforementioned series is carried out using two dimensional (2D) molecular descriptors. The present study aimed to establish relationship 17 β -HSD3 inhibitors for structurally related 3- and 4-substituted 7-hydroxycoumarins derivatives and the physicochemical descriptors in quantitative terms. The statistically validated two dimensional quantitative structure activity relationship (2D QSAR) model was obtained through multiple linear regression (MLR) analysis method using Vlife molecular design suits (MDS)

Experimental Section

Dataset and biological activity

The 17 β -HSD3 inhibitors activity was taken from the reported work [13]. We have converted the biological activity values [IC₅₀ (μ M)] reported in the literature to -log scale and subsequently used as the response variable for the QSAR analysis. The structures and in vitro activity of thirty five 3- and 4-substituted 7-hydroxycoumarins derivatives used in this study are listed in Table 1.



S. No	R1	R2	IC ₅₀	pIC ₅₀	Pred.	Res.
1	(CH ₂) ₂ -Phenyl	H	0.02	7.698	7.671	0.02
2	CH ₂ O-Phenyl	H	10	5	5.154	-0.15
3	CH ₂ S-Phenyl	H	0.093	7.031	7.251	-0.22
4*	CH ₂ NH-Phenyl	H	4	5.397	5.241	0.15
5	CH ₂ NMe-Pheny	H	6	5.221	5.286	-0.06
6	CH ₂ S-2-Pyridiyl	H	0.003	8.522	8.573	-0.05
7	CH ₂ S-4-Pyridyl	H	5	5.301	5.219	0.08
8	CH ₂ S-2-Pyrimidinyl	H	1	6	5.877	0.12
9*	CH ₂ S-2-Thienyl	H	0.42	6.376	6.297	0.07
10	CH ₂ S-1,3,4-Thiadiazol-2-yl	H	0.2	6.698	6.568	0.13
11	CH ₂ S-2-Thiazolyl	H	0.01	8	8.143	-0.14
12	CH ₂ S-2-Thiazolidinyl	H	0.096	7.017	7.166	-0.14
13	CH ₂ S-1-Methyl-2-imidazolyl	H	0.091	6.04	6.233	-0.19
14	CH ₂ S-5-Nitro-2-pyridyl	H	0.088	6.055	5.944	0.11
15*	CH ₂ S-5-Trifluoromethyl-2-pyridyl	H	0.23	6.638	6.559	0.07
16	CH ₂ S-6-Methyl-2-pyridyl	H	0.0015	8.823	8.736	0.08
17	(CH ₂) ₂ -6-Methyl-2-pyridyl	H	0.008	8.096	8.141	-0.04
18	(CH ₂) ₂ O-6-Methyl-2-pyridyl	H	1	6	6.115	-0.11
19	CH ₂ S-6-Methyl-2-pyridyl	F	0.027	7.568	7.403	0.16
20	CH ₂ S-6-Methyl-2-pyridyl	Cl	0.047	7.327	7.203	0.12
21*	CF ₃	CH ₂ S-2-pyridyl	0.32	6.494	6.388	0.1
22	Me	H	1	6	6.081	-0.08
23	Et	H	0.1	7	6.882	0.11
24	n-Pr	H	0.059	7.229	7.153	0.07
25	CF ₃	H	0.19	6.721	6.764	-0.04
26*	CH ₂ OMe	H	5	5.301	5.208	0.09
27	Ph	H	1	6	6.093	-0.09
28	CH ₂ Ph	H	10	5	5.192	-0.19
29	(CH ₂) ₂ Ph	H	0.02	7.698	7.71	-0.01
30*	H	Me	1	6	6.143	-0.14
31	Me	Me	0.21	6.677	6.641	0.03
32	Me	n-Pr	0.24	6.619	6.59	0.02
33*	Me	CH ₂ Ph	0.2	6.698	6.726	-0.02
34	CF ₃	CH ₂ Ph	0.03	7.522	7.452	0.07
35	Me	F	1	6	6.079	-0.07

36	Me	Cl	0.1	7	6.945	0.05
37	Me	CN	1	6	6.119	-0.11

Table 1: Structures and activities of 3- and 4-substituted 7-hydroxycoumarins as 17 β -HSD3 inhibitors

A statistical subset selection was made using sphere exclusion algorithm [14] method to select a balanced and chemically diverse test set. The training set of 28 molecules was used to adjust the parameters of the models, and the rest of molecules were used to evaluate models prediction ability. The QSAR models were generated using a training set of twenty eight molecules and remaining seven compounds as a test set (Table 1 marked with asterisk) for validating the quality of the models.

Generation of molecular descriptors

All the molecular modeling and statistical analysis was completed using Molecular Design Suite TM 3.5, 2008,) software [15]. The structures of the compounds were sketched using molecular sketching facilities provided in the modeling environment of Vlife MDS. Energy minimizations were performed using Merck molecular force field (MMFF) and MMFF charge [16] followed by considering distance-dependent dielectric constant of 1.0.

In our study, only 211 chemical descriptors were eventually used (after deleting these bookkeeping descriptors as well as those with zero value or zero variance). In this study to calculate AI descriptors, we have used following attributes, 2 (double bonded atom), 3 (triple bonded atom), C, N, O, S, H, F, Cl, Br and I and the distance range of 0–7. The program computes the best model based on squared correlation coefficient r^2 , crossed validated q^2 , F test, and pred_r^2 . A value of pred_r^2 greater than 0.5 indicates the good predictive capacity of the QSAR model. The squared correlation coefficient (or coefficient of multiple determination) r^2 , is a relative measure of quality of fitness by the regression equation.

Results and Discussion

Correlations between different 17 β -HSD3 inhibitors activities and calculated variables were established through multiple linear regressions using the method of least squares. Statistically significant QSAR model generated for activity data are as follow: $\text{pIC}_{50}=0.5809$ (± 0.1377) $T_{2_Cl_1}+0.4599$ (± 0.0656) $SdsCHcount-0.4644$ (± 0.0937) $SdssS$ (sulfone) count $+0.6284$ (± 0.1433) $T_{C_F_1}$. $N_{\text{training}}=28$, $N_{\text{test}}=7$, $r^2=0.8291$, $q^2=0.7455$, $F_{\text{test}}=40.298$ $r^2_{\text{se}}=0.3177$, $q^2_{\text{se}}=0.4936$, $\text{pred}_r^2=0.7588$.

2D QSAR model shows good correlation between 17 β -HSD3 inhibitory activity of the molecules and number of $SdsCHcount$, $SdssS$ (sulfone) count, $T_{2_Cl_1}$ and number of $T_{C_F_1}$. $SdsCHcount$ (total number of –CH group connected with one double and one single bond) plays most important role in determining 17 β -HSD3 inhibitory activity, which mainly indicates the relationship with reference to variation at R2 position. The positive correlation of the descriptor with the 17 β -HSD3 inhibitory activity indicates that increase in the number of –CH group will increase activity of the title compounds. Other $T_{C_F_1}$ indicates number of carbon atom (single, double or triple bonded) separated from fluorine by single bond in a molecule. The descriptor is positively correlated with the biological activity in the model. So, it may be indicate that increase in the number of fluorine

like in the molecules is conducive for the 17 β -HSD3 inhibitory activity. Furthermore, the finding also suggests that increase in the fluorine group is detrimental to 17 β -HSD3 inhibitory potency. Model has been obtained with correlation coefficient (r^2)=0.8291 and the model explains about 82% variance in 17 β -HSD3 inhibitory activity exhibited by 3- and 4-substituted 7-hydroxycoumarins derivatives. In this procedure high cross validated r^2 ($q^2=0.7455$) value, reflect the good internal predictive power of the model. The descriptor $T_{2_Cl_1}$, count of number of double bond separated from chlorine atom by single bond distances in a molecule suggesting that the presence of substituents with chlorine on the substituted 7-hydroxycoumarins at the 3rd and 4th position with will lead to an increase in activity. Such positive effect indicates that the 17 β -HSD3 inhibitory activity was increase with the presence of chlorine and fluorine compounds such as compounds 13,17,30 and 35. Lastly descriptor $SdssS$ (sulfone) count signifies the total number of sulphone group connected with two single and one double bond emphasizing and negative contribution of this descriptor in the QSAR model demonstrates that increased sulphone group branching on the substituents on 7-hydroxycoumarins nucleus will reduce to 17 β -HSD3 inhibitory activity. As shown in Table 1, the predicted activity using developed QSAR equation was in close agreement with the reported activity. The contribution chart of selected descriptors are represented in Figure 1a and plots of predicted vs. observed values of pIC_{50} are shown in Figure 1b.

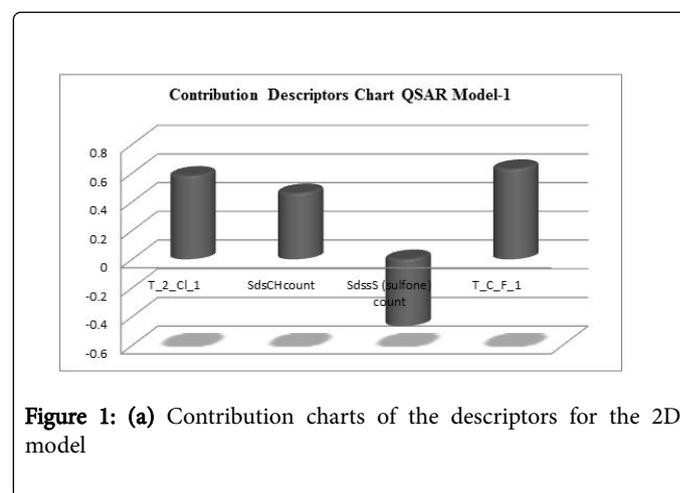
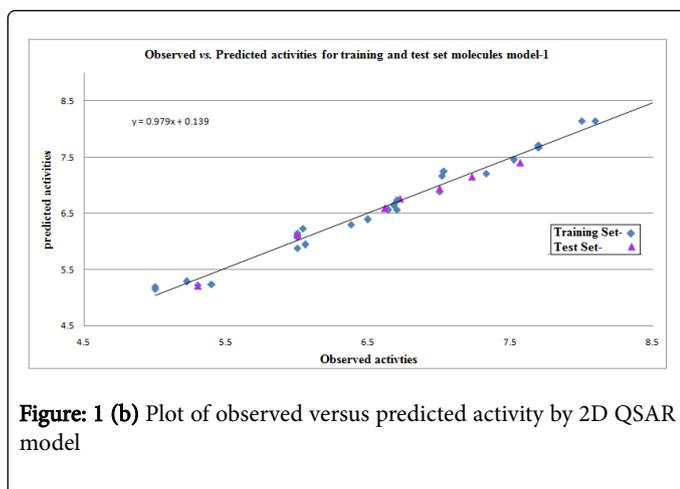


Figure 1: (a) Contribution charts of the descriptors for the 2D model



Conclusion

We have developed quantitative structure–activity relationship (QSAR) models for 17 β -hydroxysteroid dehydrogenase inhibitors for potential treatment of prostate cancer of substituted 7-hydroxycoumarins derivative. This method utilizes multiple descriptors such as molecular connectivity indices, which are derived from two-dimensional molecular topology. After splitting the datasets, the respective descriptors were selected from pool of descriptors using the multiple linear regression method. By this method the most relevant descriptors were selected to build the model. These investigations will further help in rationalizing the design of 17 β -HSD3 inhibitory activity molecules.

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References

1. Kirby RS, Partin AW, Parsons JK, Feneley MR (2008) Treatment Methods for Early and Advanced Prostate Cancer; Informa Healthcare: London.
2. Jeanne C, Carmen R (2009) Cancer Facts & Figures.
3. van Bokhoven A, Varella-Garcia M, Korch C, Johannes WU, Smith EE, et al. (2003) Molecular characterization of human prostate carcinoma cell lines. *Prostate* 57: 205-225.
4. Feldman BJ, Feldman D (2001) The development of androgen-independent prostate cancer. *Nat Rev Cancer* 1: 34-45.
5. Chen Y, Sawyers CL, Scher HI (2008) Targeting the androgen receptor pathway in prostate cancer. *Curr Opin Pharmacol* 8: 440-448.
6. Taplin ME (2008) Androgen receptor: role and novel therapeutic prospects in prostate cancer. *Expert Rev Anticancer Ther* 8: 1495-1508.
7. Yap TA, Zivi A, Omlin A, de Bono JS (2011) The changing therapeutic landscape of castration-resistant prostate cancer. *Nat Rev Clin Oncol* 8: 597-610.
8. Courtney KD, Taplin ME (2012) The evolving paradigm of second-line hormonal therapy options for castration-resistant prostate cancer. *Curr Opin Oncol* 24: 272-277.
9. Marchais-Oberwinkler S, Henna C, Möller G, Klein T, Negri M, et al. (2011) 17 β -Hydroxysteroid dehydrogenases (17 β -HSDs) as therapeutic targets: Protein structures, functions, and recent progress in inhibitor development. *Journal of Steroid Biochemistry & Molecular Biology* 125: 66-82.
10. Jung ME, Ouk S, Yoo D, Sawyers CL, Chen C, et al. (2010) Structure-activity relationship for thiohydantoin androgen receptor antagonists for castration-resistant prostate cancer (CRPC). *Journal of Medicinal Chemistry* 53: 2779-96.
11. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, et al. (2012) Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 367: 1187-1197.
12. Roy K, Paul S (2010) Docking and 3D QSAR studies of protoporphyrinogen oxidase inhibitor 3H-pyrazolo[3,4-d][1,2,3]triazin-4-one derivatives. *J Mol Model* 16: 137-153.
13. Harada K, Kubo H, Tomigahara Y, Nishioka K, Takahashi J, et al. (2010) Coumarins as novel 17 β -hydroxysteroid dehydrogenase type 3 inhibitors for potential treatment of prostate cancer. *Bioorganic & Medicinal Chemistry Letters* 20: 272-275.
14. Golbraikh A, Tropsha A (2002) Predictive QSAR modeling based on diversity sampling of experimental datasets for the training and test set selection. *Journal of Computer-Aided Molecular Design* 16: 357-369.
15. VLife MDS 3.5(2008) Molecular design suite. Vlife Sciences Technologies Pvt. Ltd., Pune.
16. Halgren TA (1996) Merck molecular force field. II. MMFF94 vander Waals and electrostatic parameters for intermolecular interactions. *Journal of Computational Chemistry* 17:520-552.