Original Article

Pharmacophore and Atom Based 3D QSAR Studies on the Novel 5-Alpha-Reductase Inhibitors

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ABSTRACT

Aim/Background: The anomalous production of dihydrotestosterone (DHT) observed in benign prostatic hyperplasia and prostate cancer particularly in tissues of the prostate gland. The primary male sex hormone, testosterone (T) is improved to a metabolite in cells by 5a-reductase (5aR) type II enzyme through NADPH. A metabolite is DHT which is more potent than T. Drug therapy is the best alternative for the treatment of benign prostatic hyperplasia (BPH). Drug therapy act by dropping the DHT formation through inhibiting the 5aR enzyme. Thus, this research work was undertaken to design a novel 5aR enzyme inhibitor by pharmacophore and Atom-based 3D QSAR technique. **Materials and Methods:** A dataset of twenty-nine ligands available with IC 50 chosen from the literature. Schrodinger molecular modelling software is having, phase 3.0 module implicated for generation of pharmacophore models. **Results:** Pharmacophore hypothesis with five features having two H-bond acceptors and three hydrophobic group was developed, i.e., AAHHH.715. This Pharmacophore hypothesis regarded as the finest one. This hypothesis resulted into statistically significant three-dimensional QSAR model. The statistical parameters were found to be 0.9804 as r2 value and 0.8321as q2 value. Out of 29 ligands, 23 ligands assigned as training set and 6 ligands as a test set. The squared correlation coefficient between training and test sets based on actual and predicted values were observed to be 0.96 and 0.87 respectively. **Conclusion:** The 5aR enzyme inhibitors predicting requirements can be done by this built model.

Key words: 5-alpha reductase, Pharmacophore, QSAR, DHT, BPH.

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INTRODUCTION

Male secondary sex organs development and maintenance of secretory function are dependent on androgens. The androgen found most abundantly in serum is testosterone (T), produced by Leydig cells in testes controlled by the hypothalamus and pituitary gland.[1, 2] The T is improved to a metabolite in cells by 5a-reductase type II enzyme through NADPH. A metabolite is a dihydrotestosterone (DHT) which is more potent than T.[3] The 5a-reductase (5aR) isozymes are type I (5aR1) and type II (5aR2) identified by molecular cloning.[4] The distribution of 5aR is skin, kidney, liver and lungs have 5aR1 whereas 5aR2 is found in prostate, seminal vesicle, epididymis and hair follicles.[5] The anomalous production of DHT observed in BPH and prostate cancer particularly in prostate tissue.[6,7] BPH has majorly two treatments available such as surgery and drug therapy. Clinically operation is effectual, but economical and post-operative complications are factors which limit it.[8,9] Pharmacological (Drug) therapy, hence is the best alternative for the treatment of BPH. Drug therapy act by dropping the DHT formation through inhibiting the 5aR enzyme. Thus, a strategy proposed for

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controlling levels of DHT in the prostate by restricting 5aR activity (i.e., hindering the formation of DHT from T).[10] In due course of time, various potential 5aR inhibitors have synthesized and the even large number investigated. Some steroidal 5aR inhibiting molecules with higher binding affinities have produced which produces greater inhibition.[11] Commercially, finasteride[12] and epristeride[13] used as treatment options for BPH. These steroidal molecules have hormonal adverse effects.[14] Thus, non-steroidal inhibitors are developed to overcome these adverse effects, but the activity of non-steroidal molecules as 5aR inhibition remain less.[15-18] Apart from this, there are only a few drugs available to treat prostate diseases and existing drugs are becoming resistant. So, there is an urgent need for a drug which is highly specific and less toxic. Hence, this research work was undertaken to design a novel 5aR enzyme inhibitor by pharmacophore and Atom-based 3D QSAR technique.

MATERIAL AND METHODS

Data set selection

A dataset of twenty-nine ligands available with IC 50 for 5aR chosen from literature. Out of 29 ligands, 23 ligands assigned as training set and 6 ligands as test set.[19,20] The model built by a training set and validation performed by the test set. The activity data, i.e. IC 50 values collected from the literature were transformed to PIC50 by choices present in the calculator.

Pharmacophore hypothesis generation:

Schrodinger molecular modeling software is having, Phase 3.0 module implicated for production of pharmacophore models. The minimum energy structural feature is required, to attain exact 3D descriptor values associated with QSAR studies. Maestro 2D sketch was used to draw the structures and these 2D structures converted to their respective 3D structures. OPLS force field was used to perform the geometry optimization. Two sets were formed, namely, training and test sets, of all ligands.

PHASE uses a structure cleaning utility called ligprep, which adds hydrogen, generates stereoisomers and various conformers and predicts proper ionization states at a particular PH.PHASE provides two inbuilt approaches, employing the MacroModel conformational search engine. Due to the flexibility of ligands, all the possible conformers observed for each set of ligands and conformers close to the crystal structures could be sorted out. The conformational analysis was carried out using Monte Carlo Multiple Minimum methods. The ligands were separated on the basis of the activity threshold value into active and inactive sets.[21]

Creation of Pharmacophore sites

Five-point pharmacophoric features defined the local chemical environment of selected ligands such as two H-bond acceptors (A) and three hydrophobic group (H). The inter-site distance and angles were used to develop pharmacophore.

Scoring pharmacophores on the basis of their activity threshold

The scoring and ranking of pharmacophore done to identify the best pharmacophore hypothesis. The configuration of site points and magnitude of vectors, selectivity and activity with overall conformational energies was considered to be active contributions for the scoring algorithm.

Identifying common pharmacophores

Once, the best hypothesis, AAHHH (Figure 1A) selection is over, afterward, it was further analyzed (Table 1). The best hypothesis is the Pharmacophore, i.e. AAHHH. The pharmacophore, in this case, has unique characteristics as AA, i.e. two hydrogen bond acceptor and HHH, i.e. three hydrophobic groups. Pink sphere represents A with two arrows and H by green spheres (Figure 1B). Table 2 and Table 3 represents site scores of distances and angles respectively.

Building QSAR models

QSAR model was developed based on a selected common hypothesis by segregating the literature data into a training set as 70% and test set as 30% based on activity, structural similarity and functional group variation. PHASE provides binary options for the geometric alignment of 3dimensional structures. In the present study, an Atom-based QSAR model used and this technique is a useful tool for the study of structure-activity relationships. The

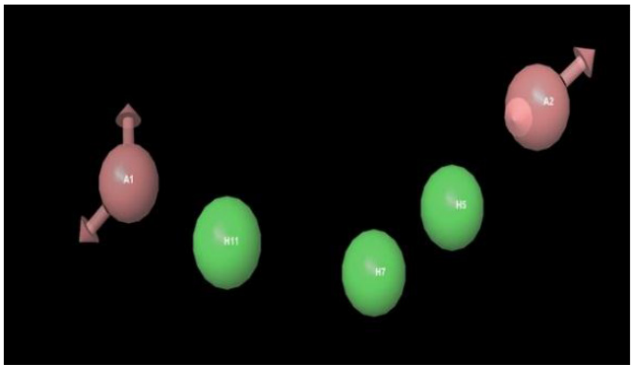

Figure 1: a. Common hypothesis.

Table 1: Common Pharmacophore Hypothesis AAHHH.										
In	ID	Survival	Survival -inactive	Site	Vector	Volume	# Matches	Energy	Activity	Inactive
0	AAHHH.715	4.917	3.307	0.5	0.932	0.629	12	0	7.62	1.61
0	AAHHH.669	4.917	3.307	0.5	0.932	0.629	12	0	7.62	1.61
0	AAHHH.371	4.917	3.307	0.5	0.932	0.629	12	0	7.62	1.61
0	AAHHH.325	4.917	3.307	0.5	0.932	0.629	12	0	7.62	1.61
0	AAHHH.721	4.913	3.311	0.51	0.928	0.624	12	0	8.284	1.602
0	AAHHH.675	4.913	3.311	0.51	0.928	0.624	12	0	8.284	1.602
0	AAHHH.377	4.913	3.311	0.51	0.928	0.624	12	0	8.284	1.602
0	AAHHH.331	4.913	3.311	0.51	0.928	0.624	12	0	8.284	1.602
0	AAHHH.272	4.834	3.199	0.49	0.896	0.593	12	0	7.62	1.634
0	AAHHH.606	4.834	3.199	0.49	0.896	0.593	12	0	7.62	1.634

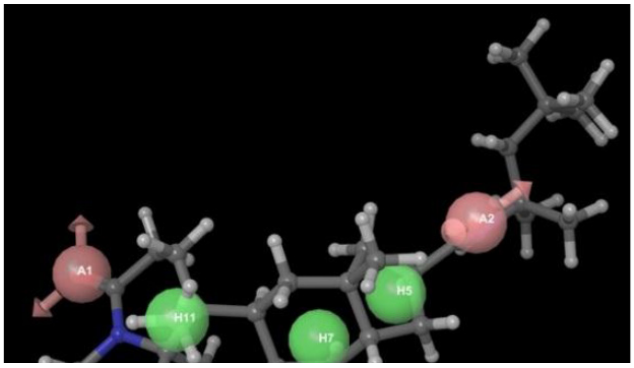

Figure 1: b. Common hypothesis on active molecule.

Table 2: Site Score Distances.			
Entry	Site1	Site2	Distance
AAHHH.715	A1	A2	10.851
AAHHH.715	A1	H5	8.677
AAHHH.715	A1	H7	7.042
AAHHH.715	A1	H11	5.118
AAHHH.715	A2	H5	2.796
AAHHH.715	A2	H7	5.077
AAHHH.715	A2	H11	8.16
AAHHH.715	H5	H7	2.352
AAHHH.715	H5	H11	5.935
AAHHH.715	H7	H11	3.98

group of overlying van der Waal's spheres considered for every molecule in the study of atom based QSAR. Each atom placed into one of the three categories like positive ionic interactions, negative ionic interactions and hydrophobic non-polar interactions. The training set ligands arranged in regular Grid of cubes to develop

Table 3: Site Score Angles.				
Entry	Site1	Site2	Site3	Angle
AAHHH.715	A2	A1	H5	10.4
AAHHH.715	A2	A1	H7	22.1
AAHHH.715	A2	A1	H11	45.9
AAHHH.715	H5	A1	H7	12.4
AAHHH.715	H5	A1	H11	41.8
AAHHH.715	H7	A1	H11	33.7
AAHHH.715	A1	A2	H5	34
AAHHH.715	A1	A2	H7	31.5
AAHHH.715	A1	A2	H11	26.7
AAHHH.715	H5	A2	H7	8.7
AAHHH.715	H5	A2	H11	30.8
AAHHH.715	H7	A2	H11	22.6
AAHHH.715	A1	H5	A2	135.6
AAHHH.715	A1	H5	H7	40.1
AAHHH.715	A1	H5	H11	35.1
AAHHH.715	A2	H5	H7	160.9
AAHHH.715	A2	H5	H11	135.2
AAHHH.715	H7	H5	H11	26.8
AAHHH.715	A1	H7	A2	126.4
AAHHH.715	A1	H7	H5	127.5
AAHHH.715	A1	H7	H11	45.6
AAHHH.715	A2	H7	H5	10.4
AAHHH.715	A2	H7	H11	128.2
AAHHH.715	H5	H7	H11	137.7
AAHHH.715	A1	H11	A2	107.4
AAHHH.715	A1	H11	H5	103.2
AAHHH.715	A1	H11	H7	100.7
AAHHH.715	A2	H11	H5	14
AAHHH.715	A2	H11	H7	29.3
AAHHH.715	H5	H11	H7	15.5

best fit QSAR model. The cubes are labeled in a binary bit format to show different atom types and their features. The resulted data can be used to generate a partial least square regression model (PLS). The training set (23) was used to create atom-based QSAR models for the selected hypothesis using three PLS factors. The remaining molecules took under test set.[21]

RESULTS AND DISCUSSION

Undertaken research work intended to throw light on the three-dimensional structural properties of inhibitors of 5aR. The Phase module was used to carry out the pharmacophore modeling and QSAR studies of Schrodinger suite. This Phase module helps in envisaging the relative binding of test ligands to the active site of the receptor of the generated hypothesis. The pharmacophore dependent alignment was used to create the 3D-QSAR model for identification of structural features needed to inhibit 5aR.

The pharmacophore model generated by considering 29 compounds, having activity against 5-alpha reductase. These compounds have significant structural properties mandatory for binding to the receptor site. The most active compounds identified on the basis of having common properties as four minimum site and five maximum sites. The hypothesis AAHHH (Refer Table 1) was selected based on survival active and inactive scores. This pharmacophore hypothesis implicated in generating 3D QSAR model. Predictive ability of both training and test set implicated in assessing the 3D QSAR model (Table 4). For a given set of PLS factors, the equation was analyzed on the basis of regression coefficient value and crossed validation coefficient value. The QSAR model based on the unique features of the atoms attached to the core ring system. The features studied are positive ionic interactions, negative ionic interactions and hydrophobic non-polar interactions (Figure 2 a,b and c).

Table 4: Table Showing QSAR Studies' Activity Prediction Graphs.

In	Ligand Name	QSAR Set	Activity	# Factors	Predicted Activity	Prediction Error
0	alp1	training	6.569	4	6.62627	0.057266
0	alp4	training	6.377	2	6.3719	-0.0051
0	alp5	training	6.77	4	6.5583	-0.2117
0	alp6	training	5.824	3	5.95404	0.13004
0	alp10	training	7.77	4	7.78301	0.013014
0	alp11	test	7.959	4	7.88328	-0.07572
0	alp12	training	7.62	4	7.62856	0.008561
0	alp13	training	7.62	4	7.59629	-0.02371
0	alp14	training	7.398	3	7.43792	0.039915
0	alp15	training	8.252	4	8.30671	0.054707
0	alp16	training	8.284	1	8.29908	0.015083
0	alp17	test	7.699	1	7.76122	0.062225
0	alp18	training	8	4	8.02758	0.02758
0	alp19	training	7.824	4	7.82526	0.001256
0	alp20	training	8.086	1	8.07192	-0.01408
0	alp21	test	6.538	4	6.27768	-0.26032
0	alp22	training	7.699	2	7.70942	0.010416
0	alp23	training	7.824	4	7.10512	0.051028
0	alp25	training	5.409	3	5.39927	-0.00973
0	alp26	training	6.081	4	6.31708	0.236083
0	alp29	training	2.4	4	7.61106	0.018493
0	alp2	test	6.77	4	6.73722	-0.03278
0	alp3	training	6.824	4	6.58318	-0.24082
0	alp7	training	6.553	4	6.69828	0.145282
0	alp8	test	7.027	2	7.45904	0.432042
0	alp9	training	7.398	3	7.36283	-0.03517
0	alp24	test	5.845	2	6.18911	0.344114
0	alp27	training	6.959	4	7.04492	0.085915
0	alp28	training	2.2	4	7.80152	0.106814

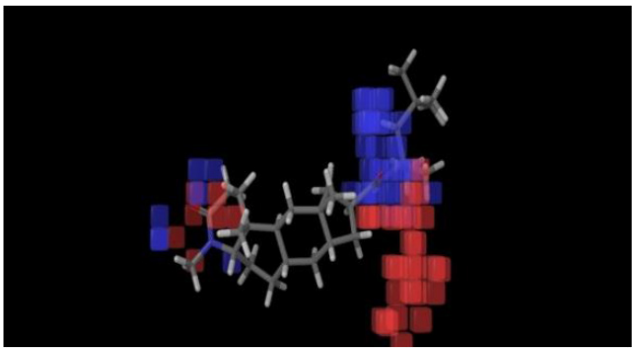

Figure 2: QSAR models for different types of interactions. a. Positive ionic interactions.

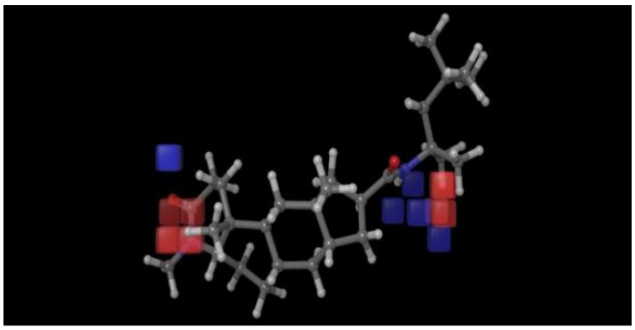

Figure 2: QSAR models for different types of interactions. b. Negative ionic interactions.

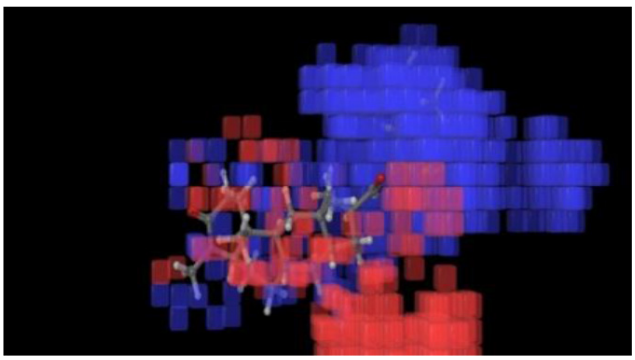

Figure 2: QSAR models for different types of interactions c. Hydrophobic non-polar interactions.

A dataset of twenty-nine ligands available with IC 50 chosen from literature. Pharmacophore hypothesis with five features having two H-bond acceptors and three hydrophobic group developed, i.e. AAHHH.715. This Pharmacophore hypothesis regarded as the finest hypothesis. The hypothesis resulted into statistically significant three-dimensional QSAR model. The statistical parameters were found to be 0.9804 as r^2 value and 0.8321as q^2 value (refer Table 5). The created model was applied effectively on both sets respectively.

Table 5: QSAR Statistics.

# Factors	SD	R^2	R^2 CV	R^2 Scramble	Stability	F	P	RMSE	Q^2	Pearson-r
1	0.3264	0.8559	0.6153	0.4999	0.861	106.9	5.33E-09	0.3	0.8207	0.9096
2	0.2253	0.9352	0.6678	0.7116	0.774	122.6	7.93E-11	0.28	0.8438	0.9244
3	0.1828	0.9598	0.6461	0.8566	0.741	127.5	2.22E-11	0.29	0.8375	0.922
4	0.1317	0.9804	0.6204	0.923	0.662	188	1.28E-12	0.29	0.8321	0.9266

Table 6: Ligand Structures with IC_{50} values.[19,20]		
Sr. No.	**IUPAC Name**	**IC_{50}**
1	1,4a,6a-Trimethyl-2-oxo-N-(2,4,4-trimethyl-2-pentanyl)hexadecahydro-1H-indeno[5,4-f] quinoline-7-carboxamide	2.7 nM
2	4a,6a-Dimethyl-2-oxo-N-(2,4,4-trimethyl-2-pentanyl)hexadecahydro-1H-indeno[5,4-f]quinoline-7-carboxamide	1.08 nM
3	4a,6a-Dimethyl-2-oxo-N-(2,4,4-trimethyl-2-pentanyl)hexadecahydro-1H-indeno[5,4-f]quinoline-7-carboxamide	0.495 nM
4	N-tert-butyl-1,4a,6a-trimethyl-2-oxohexadecahydro-1H-indeno[5,4-f]quinoline-7-carboxamide	5.4 nM
5	4-Azaandrostane-17-carboxamide, N,N-diethyl-4-methyl-3-oxo-, (5α,17β)-	19.8 nM
6	(4aR,4bS,6aS,7S,9aS,9bS,11aR)-N,N-Diethyl-4a,6a-dimethyl-2-oxohexadecahydro-1H-indeno[5,4-f]quinoline-7-carboxamide	5.49 nM
7	4a,6a-Dimethyl-7-(3-methylbutanoyl)hexadecahydro-2H-indeno[5,4-f]quinolin-2-one	1.62 nM
8	1,4a,6a-Trimethyl-7-(3-methylbutanoyl)hexadecahydro-2H-indeno[5,4-f]quinolin-2-one	27 nM
9	1,4a,6a-Trimethyl-7-(2-methylbutanoyl)hexadecahydro-2H-indeno[5,4-f]quinolin-2-one	45 nM
10	4a,6a-Dimethyl-7-(2-methylbutanoyl)hexadecahydro-2H-indeno[5,4-f]quinolin-2-one	6.84 nM

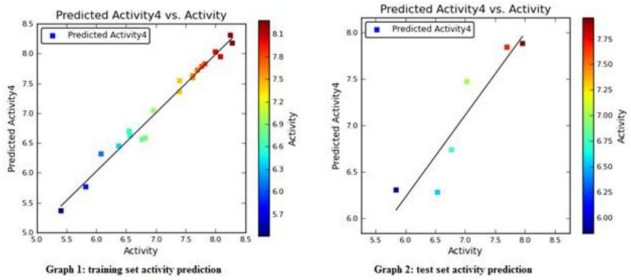

Figure 3: Graph of test and training set.

CONCLUSION

The squared correlation coefficient for the test set and training set was observed to be 0.87 and 0.96 respectively (actual v/s predicted values) (Figure 3). The model could be used to design potent inhibitors against 5aR.

ACKNOWLEDGMENT

The authors would like to acknowledge the facilities provided by the Manipal College of Pharmaceutical Sciences and Manipal Academy for Higher Education in executing this research work.

CONFLICT OF INTEREST

None.

ABBREVIATIONS

T: Testosterone; DHT: Dihydrotestosterone; 5aR: 5a-reductase; QSAR: Quantitative structure-activity relationship; IC_{50}: Half-maximal inhibitory concentration; OPLS: Optimized Potential for Liquid Simulations; A: H-bond acceptor; H: Hydrophobic group; PLS: Partial least square.

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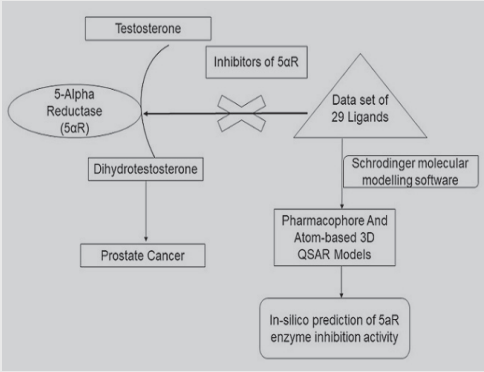
PICTORIAL ABSTRACT



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- The 5aR enzyme inhibitors can be analyzed In-silico to predict requirements of the ligands by this built model.

About Authors

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