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Computational comparative QSAR analysis of 5α-reductase inhibitors of type-1

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ABSTRACT

The various QSAR models have been developed to predict the activities in terms of log 1/C for 29 compounds of 5α-Reductase Inhibitors of humans Type-1 derivatives of 4-Aza-3-oxo-5α-androst-1-ene-17 β-N(X-aryl)-carboxamide with the help of quantum chemical viz., HOMO energy, LUMO energy, absolute hardness, Softness, Chemical Potential and electronegativity and Physiochemical parameter Molar Refractivity (MR) , Molecular Volume (MV) , Parachor(Pc), Refraction Index(n), Surface Tension(ϒ), Density(D), Polarizability, (α), Average Mass. The comparison between these two type of descriptors models indicates that quantum chemical models are more informative than topological models. The parameter adopted in quantum chemical the calculation is the semi-empirical PM3 based. The QSAR model sixth provides a good arrangement between obs log 1/c & predicted activity.

Key words: Absolute hardness; Chemical potential; electronegativity; Global Softness; HOMO; LUMO, Molar Refractivity (MR). Molecular Volume (MV), Parachor, Refraction Index (n), Surface Tension, Density, Polarizability**,** Average Mass, PM3.

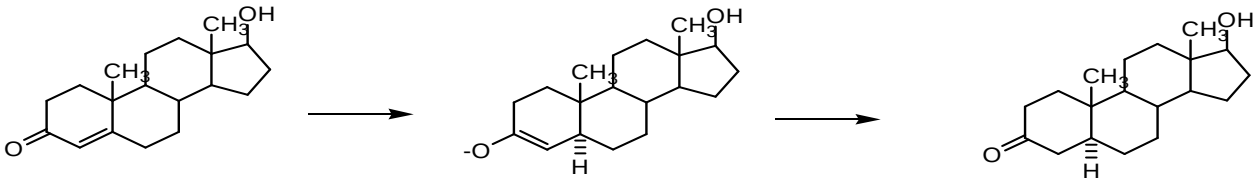
INTRODUCTION

Over the years it has been shown that the male sex hormone, testosterone (T), gets converted to dihydrotestosterone (DHT) by the enzyme 5 α- reductase (5AR). The nuclear chromatin of the prostate contains an androgen receptor that retains 5 α- DHT selectively, the most potent endogenous androgen for the growth of ventral prostrate of the rat, [1, 2] i.e., this androgen receptor is specific for DHT. The prostatic enzyme that catalyzes the reduction of T → DHT needs NADPH as a cofactor. It is a membrane-bound enzyme that delivers the pro-S-hydrogen of the cofactor to the less hindered α-face of the substrate, testosterone. The enolate (I) so formed is stabilized by the enzyme and subsequently protinated to generate 5 α- androstan-17 β-ol-3-ones, DHT (Figure 1). [3]

Testosterone and its more potent metabolite, DHT, are essential hormones for male phenotype sexual differentiation and maturation through their actions at the androgen receptor.[4-6] Normal growth and development of prostate depends on DHT, [7-10] which suggests the role of DHT, and hence 5AR in prostate diseases. Correlation between prostatic growth and elevated prostatic DHT has been observed in BPH patients.[11] Consistent with the elevated levels associated with BPH, several groups have shown an increase in steroid 5AR activity in tissue from BPH prostates relative to normal prostates. [12-14]

In addition to the role of 5AR in male sexual development, it has been found to play a significant role in other physiological processes also. High levels of activity are observed in the liver and skin. Even tissues of the central nervous system contain 5AR activity. In the liver it is believed to have a catabolic function, [15] the skin activity may mediate androgenic drive in that organ.[16-20] Its role in the brain is not well understood. The distribution of 5AR activity throughout the central nervous system and the lack of sexual dimorphism in its expression are

particularly intriguing. [21-23] recent evidence suggests that 5R-reduced metabolites of progesterone alter GABAA receptor function and play a part in sexual differentiation.[24].The quantity of the enzyme and its product, DHT, is elevated in the affected tissue of conditions such as benign prostatic hypertrophy, [11, 25] acne, certain forms of hirsutism (excessive hair growth of normal or abnormal distribution), and male pattern baldness. [16] Thus, conversion of T → DHT is related to the development of many endocrine diseases [26] such as BPH, [27] prostatic cancers, [28] male pattern baldness, [29] acne, [30] hirsutism in women, [32] etc.



I **DTH**

Figure 1

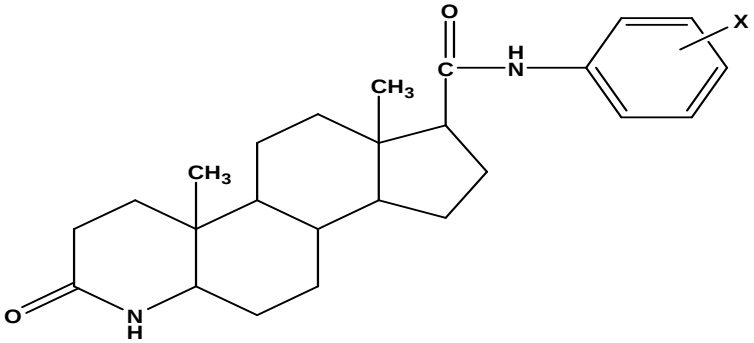
5α-Reductase is a system of two isozymes: [32] 5α- reductase Type 1 and 5R-reductase Type 2. The genetics, biochemistry, tissue distribution, and ontogeny of Type-1 and 2 5AR have been reviewed recently by Russel.[15] Selective inhibition of 5α- reductase has recently made possible a new therapeutic approach to the pharmacological treatment of these prevalent diseases.

A derivative of 5α-Reductase Inhibitors of humans Type-1 derivatives of 4-Aza-3-oxo-5α-androst-1-ene-17 β-N(X-aryl)-carboxamide has been taken from literature. [32].

In the present study we have taken structures of 5α-Reductase Inhibitors of humans Type-1 derivatives of 4-Aza-3-oxo-5α-androst-1-ene-17 β-N(X-aryl)-carboxamide from literature. [32] and then compared to the numerical values of a biological activity. The challenge here has been to find some numerical information for a molecule. This structure information and the measured property or activities are then converted into a mathematical model of relationship. From a quality model it is possible to predict and to design compounds for synthesis and testing that have a good possibility for activity. In this paper, the multi linear regression analysis has been applied for QSAR study. The relationship has been worked out between the Log1/C values of a series of compounds and certain quantum chemical descriptors and Physiochemical parameter models and find out the best corresponding model.

EXPERIMENTAL SECTION

The compounds taken for study are 5α-Reductase Inhibitors of humans Type-1



Derivatives of 4-Aza-3-oxo-5α-androst-1-ene-17 β-N(X-aryl)-carboxamide and shown in Fig.-2

The Quantum Chemical parameter based QSAR study was performed by the following important descriptors like Eigen value of Highest occupied molecular orbital (EHOMO), Eigen value of lowest unoccupied molecular orbital (ELUMO) [33], Absolute Hardness (η) [34], Chemical Potential (μ) [35], Global Softness (S) [36], Electronegativity (χ) [37], And topological descriptors Molar Refractivity (MR) , Molecular Volume (MV) **,** Parachor ((Pc) , Refraction Index**,** Surface Tension (γ) , Density(D), Polarizability (α)**,** Average Mass[38] **.**The comparison between these two type of descriptors models indicates that quantum chemical models are more informative than Physicochemical descriptors models. The molecules were drawn by spartan06v110, software and the geometries were optimized at PM3 level in conjunction with molecular mechanics. The global hardness and electronegativities were calculated using frontier orbital energies obtained from PM3 results and reported in table 2and 3. Multiple

linear regression analysis (MLR) is performed to establish the QSAR. A data set of 5α-Reductase Inhibitors of humans Type-1compounds were taken with their observed activity is shown in table 1.

RESULTS AND DISCUSSION

Multiple Linear Regression (MLR) analysis MLR analyses were performed using Minitab 16 software. The quantum mechanical descriptor and physicochemical parameters were used as independent variables and the Obsd log1/C50 values as the dependent variables separately. In the statistical analyses, the systematic search was performed to determine the significant descriptors. The correlation matrix was developed to minimize the effect of co-linearity and to avoid dependencies between subsets of the variables and multi-co-linearity (high multiple correlations between subsets of the variables). The MLR equations of different QSAR models are as follows-

QSAR model MLR equation of Quantum QSAR model P log 1/C is given by-

First QSAR model
Obsd log 1/C = 7.99 + 0.552 E LUMO (e.v)
S = 0.209919
PRESS = 1.36119
r^2= 60.8%

Second QSAR model
Obsd log 1/C = 7.91 + 0.633 E LUMO (e.v) - 0.298 E HOMO (e.v)
S = 0.188345
PRESS = 1.06978
r^2= 69.6%

Third QSAR model
Obsd log 1/C = 8.15 + 0.791 E LUMO (e.v) - 0.195 E HOMO (e.v) + 0.0273 S
S = 0.181874
PRESS = 1.05731
r^2= 72.8%

QSAR model MLR equation of physicochemical descriptors QSAR model P log 1/C is given by-

First QSAR model
Obsd log 1/C = 7.44 + 0.00211 MR (cm3/mol)
S = 0.334928
PRESS = 3.38730
r^2= 0.3%

Second QSAR model
Obsd log 1/C = 6.58 - 0.0466 MR (cm3/mol) + 0.0187 MV (cm3/mol)
S = 0.273867
PRESS = 2.42768
r^2= 35.8%

Third QSAR model
Obsd log 1/C = 7.16 + 0.0007 MR (cm3/mol) + 0.0315 MV (cm3/mol)- 0.0116 Parachor (cm3/mol)
S = 0.276050
PRESS = 2.60402
r^2 = 37.3%

Fourth QSAR model
Obsd log 1/C = 112 + 0.311 MR (cm3/mol) - 0.107 MV (cm3/mol)+ 0.0019 Parachor (cm3/mol) - 66.4 Refraction Index
S = 0.26664
PRESS = 3.90799
r^2 = 43.8%

Fifth QSAR model
Obsd log 1/C = - 58 - 0.452 MR (cm3/mol) - 0.221 MV (cm3/mol) + 0.144 Parachor (cm3/mol) + 61 Refraction Index - 0.702 Surface T (dyne/cm)
S = 0.264058
PRESS = 3.92292
r^2 = 47.2%

Sixth QSAR model
Obsd log 1/C = 2 - 0.185 MR (cm3/mol) - 0.230 MV (cm3/mol) + 0.113 Parachor (cm3/mol) + 18 Refraction Index - 0.556 Surface T (dyne/cm) + 1.66 Density (g/cm3)
S = 0.262752
PRESS = 4.52255
r^2 = 50.0%

Seventh QSAR model
Obsd log 1/C = 8 - 0.9 MR (cm3/mol) - 0.235 MV (cm3/mol) + 0.113 Parachor (cm3/mol) + 14 Refraction Index - 0.553 Surface T (dyne/cm) + 1.63 Density (g/cm3)+ 1.9 Polarizability (cm3)
S = 0.268902
PRESS = 5.28193
r^2 = 50.0%

Eighth QSAR model
Obsd log 1/C = - 103 + 6.9 MR (cm3/mol) - 0.222 MV (cm3/mol) + 0.147 Parachor (cm3/mol) + 97 Refraction Index - 0.838 Surface T (dyne/cm) - 5.25 Density (g/cm3) - 18.7 Polarizability (cm3) + 0.0200 Average Mass (Da)
S = 0.266592
PRESS = 6.83059
r^2 = 53.2%

CONCLUSION

The quantum mechanical descriptor and physicochemical parameters Values of the descriptors of the Derivatives of 4-Aza-3-oxo-5α-androst-1-ene-17 β-N(X-aryl)-carboxamide derivatives have been calculated using PM3 method and are given in table-2. With the help of these values of quantum QSAR descriptors of models fourth have been developed using MLR analysis in different combinations of quantum descriptors. The Chemical Potential (μ) and Absolute Hardness (η) and Electronegativity (χ) descriptors have no predicting power and hence not included in the models. Best quantum and physicochemical QSAR models are the model third and eighth respectively listed below-

Third QSAR model
Obsd log 1/C = 8.15 + 0.791 E LUMO (e.v) - 0.195 E HOMO (e.v) + 0.0273 S
S = 0.181874
PRESS = 1.05731
r^2= 72.8%

Eighth QSAR model
Obsd log 1/C = - 103 + 6.9 MR (cm3/mol) - 0.222 MV (cm3/mol) + 0.147 Parachor (cm3/mol) + 97 Refraction Index - 0.838 Surface T (dyne/cm) - 5.25 Density (g/cm3) - 18.7 Polarizability (cm3) + 0.0200 Average Mass (Da)
S = 0.266592
PRESS = 6.83059
r^2 = 53.2%

Thus from above conclusion we conclude that quantum chemical descriptor is the best descriptor comparatively physiochemical descriptor. QSAR model third can efficiently be used for the prediction of activity of any derivative of compound. The normal probability plot of responses is obsd log 1/C is shown in fig-2, which is clearly illustrates the high predictive power of the QSAR model third.

Fig-2

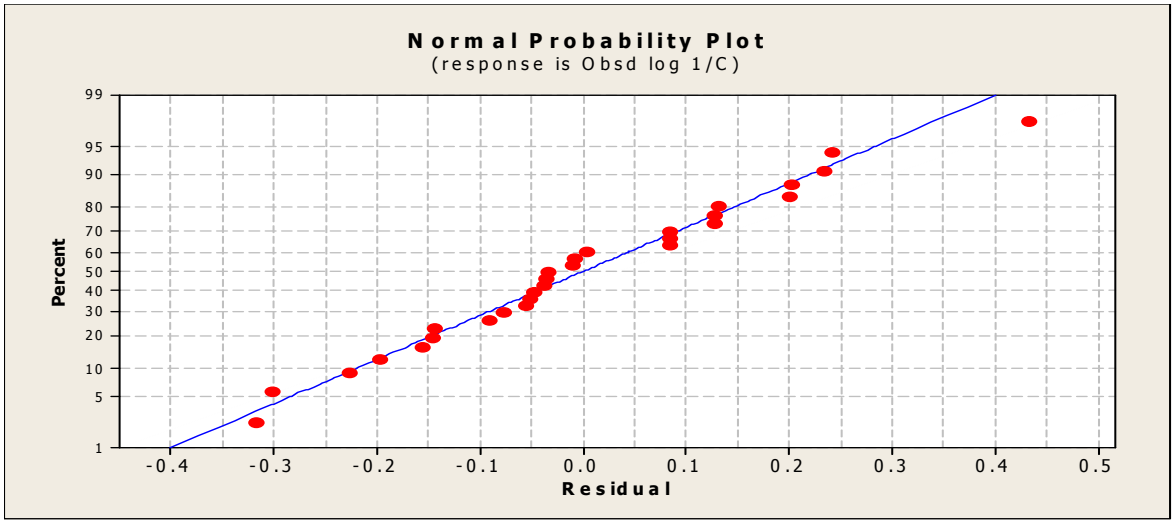


Table-1

Comp. No.	M.F	X	Obsd log 1/C
1	$C_{25}H_{32}N_2O_2$	H	7.70
2	$C_{25}H_{31}FN_2O_2$	2-F	8.10
3	$C_{25}H_{31}FN_2O_2$	3-F	7.64
4	$C_{25}H_{31}FN_2O_2$	4-F	7.65
5	$C_{26}H_{31}F_3N_2O_2$	$2CF_3$	8.25
6	$C_{26}H_{31}F_3N_2O_2$	$3CF_3$	7.90
7	$C_{26}H_{31}F_3N_2O_2$	$4CF_3$	7.68
8	$C_{27}H_{30}F_6N_2O_2$	2,5-di-CF_3	8.24
9	$C_{25}H_{31}ClN_2O_2$	2-Cl	7.84
10	$C_{25}H_{31}ClN_2O_2$	3-Cl	7.74
11	$C_{25}H_{31}ClN_2O_2$	4-Cl	8.17
12	$C_{25}H_{31}BrN_2O_2$	3-Br	7.69
13	$C_{26}H_{34}N_2O_2$	2-Me	7.52
14	$C_{26}H_{34}N_2O_2$	3-Me	7.61
15	$C_{26}H_{34}N_2O_2$	4-Me	7.76
16	$C_{27}H_{36}N_2O_2$	2,6-di-Me	7.85
17	$C_{26}H_{34}N_2O_3$	2-OMe	7.96
18	$C_{26}H_{34}N_2O_3$	3-OMe	7.72
19	$C_{26}H_{34}N_2O_3$	4-OMe	7.59
20	$C_{31}H_{36}N_2O_2$	2-C_6H_5	7.42
21	$C_{31}H_{36}N_2O_2$	3-C_6H_5	7.85
22	$C_{31}H_{36}N_2O_2$	4-C_6H_5	7.46
23	$C_{25}H_{32}N_2O_3$	2-OH	7.89
24	$C_{25}H_{32}N_2O_3$	3-OH	7.28
25	$C_{25}H_{32}N_2O_3$	4-OH	7.13
26	$C_{25}H_{33}N_3O_2$	2-NH_2	6.89
27	$C_{25}H_{33}N_3O_2$	3-NH_2	7.03
28	$C_{32}H_{36}N_2O_3$	3-COC_6H_5	7.92
29	$C_{32}H_{36}N_2O_3$	4-COC_6H_5	7.72

Table 2- Values of Quantum descriptors predicted with biological activities of series 'A

E LUMO (e.v)	E HOMO (e.v)	μ	η	S	χ	Obsd log 1/C
-0.09	-0.090	-0.090	0.000	-11.021	0.090	7.7
-0.134	-0.134	-0.134	0.000	-7.329	0.134	8.1
-0.111	-0.111	-0.111	0.000	-8.898	0.111	7.64
-0.326	-0.326	-0.326	0.000	-2.741	0.326	7.65
-0.354	-0.125	-0.240	-0.115	-2.700	0.240	8.25
-0.723	-0.723	-0.723	0.000	-0.660	0.723	7.9
-0.693	-0.693	-0.693	0.000	-0.750	0.693	7.68
-0.145	-1.192	-0.669	0.524	-5.705	0.669	8.24
-0.18	-0.180	-0.180	0.000	-5.376	0.180	7.84
-0.236	-0.236	-0.236	0.000	-4.001	0.236	7.74
-0.191	-0.340	-0.266	0.075	-4.896	0.266	8.17
-0.976	-0.976	-0.976	0.000	-0.049	0.976	7.69
-0.913	-0.913	-0.913	0.000	-0.182	0.913	7.52
-0.873	-0.873	-0.873	0.000	-0.272	0.873	7.61
-0.079	-0.079	-0.079	0.000	-12.579	0.079	7.76
-0.082	-0.082	-0.082	0.000	-12.113	0.082	7.85
-0.145	-0.145	-0.145	0.000	-6.752	0.145	7.96
-0.133	-0.133	-0.133	0.000	-7.386	0.133	7.72
-0.176	-0.176	-0.176	0.000	-5.506	0.176	7.59
-0.976	-0.976	-0.976	0.000	-0.049	0.976	7.42
-0.21	-0.210	-0.210	0.000	-4.552	0.210	7.85
-0.566	-0.566	-0.566	0.000	-1.201	0.566	7.46
-0.095	-0.095	-0.095	0.000	-10.431	0.095	7.89
-1.258	-0.104	-0.681	-0.577	-0.691	0.681	7.28
-1.452	-0.841	-1.147	-0.306	0.152	1.147	7.13
-1.565	-0.042	-0.804	-0.762	-0.597	0.804	6.89
-1.352	-0.132	-0.742	-0.610	-0.608	0.742	7.03
-0.602	-0.423	-0.513	-0.090	-1.238	0.513	7.92
-0.602	-0.602	-0.602	0.000	-1.059	0.602	7.72

Table 3- Values of Physicochemical descriptors predicted with biological activities of series 'A

Obsd log 1/C	MR (cm3/mol)	MV (cm3/mol)	Parachor (cm3/mol)	Refraction Index	Surface T (dyne/cm)	Density (g/cm^3)	Polarizability (cm^3)	Average Mass (Da)
7.7	113.990	338.500	883.800	1.588	46.400	1.159	45.190	392.534
8.1	113.990	342.700	891.100	1.579	45.700	1.197	45.180	410.524
7.64	113.990	342.700	891.100	1.579	45.700	1.197	45.180	410.524
7.65	113.990	342.700	891.100	1.579	45.700	1.197	45.180	410.524
8.25	118.970	372.000	945.800	1.552	41.700	1.237	47.160	460.532
7.9	118.970	372.000	945.800	1.552	41.700	1.237	47.160	460.532
7.68	118.970	372.000	945.800	1.552	41.700	1.237	47.160	460.532
8.24	123.950	405.500	1007.800	1.523	38.100	1.303	49.140	528.530
7.84	118.890	350.500	920.900	1.593	47.600	1.218	47.130	426.979
7.74	118.890	350.500	920.900	1.593	47.600	1.218	47.130	426.979
8.17	118.890	350.500	920.900	1.593	47.600	1.218	47.130	426.979
7.69	121.680	354.700	934.900	1.602	48.200	1.328	48.240	471.430
7.52	118.820	354.800	922.100	1.584	45.600	1.145	47.100	406.560
7.61	118.820	354.800	922.100	1.584	45.600	1.145	47.100	406.560
7.76	118.820	354.800	922.100	1.584	45.600	1.145	47.100	406.560
7.85	123.640	371.000	960.300	1.580	44.800	1.133	49.010	420.587
7.96	120.670	362.500	942.400	1.580	45.600	1.191	47.830	422.560
7.72	120.670	362.500	942.400	1.580	45.600	1.191	47.830	422.560
7.59	120.670	362.500	942.400	1.580	45.600	1.191	47.830	422.560
7.42	138.590	403.800	1055.900	1.602	46.700	1.191	54.940	468.630
7.85	138.590	403.800	1055.900	1.602	46.700	1.191	54.940	468.630
7.46	138.590	403.800	1055.900	1.602	46.700	1.191	54.940	468.630
7.89	115.870	336.900	899.000	1.603	50.600	1.191	45.930	408.533
7.28	115.870	336.900	899.000	1.603	50.600	1.191	45.930	408.533
7.13	115.870	336.900	899.000	1.603	50.600	1.191	45.930	408.533
6.89	118.230	340.800	911.800	1.610	51.200	1.191	46.870	407.548
7.03	118.230	340.800	911.800	1.610	51.200	1.191	46.870	407.548
7.92	143.790	416.600	1101.100	1.606	48.700	1.191	57.000	496.640
7.72	143.790	416.600	1101.100	1.606	48.700	1.191	57.000	496.640

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