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QSAR Study of Inhibitors for Human 5α-Reductase of Type-2 by Using Different Descriptors

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Abstract: ***The various QSAR models have been developed to predict the activities in terms of log 1/C for 16 compounds of 5α-Reductase Inhibitors of humans Type-2 derivatives of 4-X-N-Y-6-Azaandrost-ene-3-ones 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(Ƴ) , 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.***

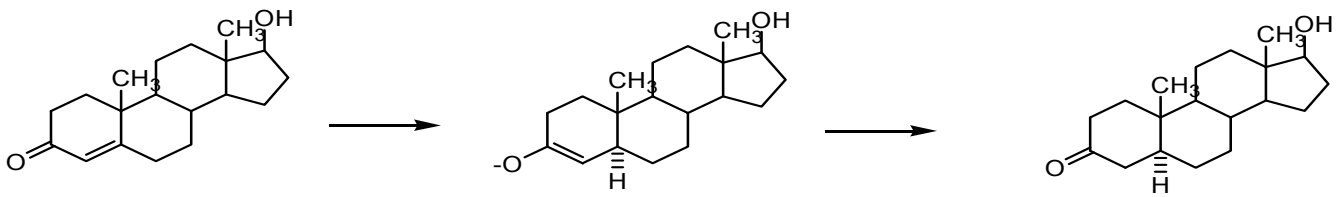
Keywords: Absolute hardness; Chemical potential; electronegativity; Global Softness; HOMO; LUMO, Molar Refractivity (MR). Molecular Volume (MV), Parachor, Refraction Index (n), Surface Tension, Density, Polarizability, Average Mass, PM3

1. 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 dif- ferentiation.[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-X-N-Y-6-Azaandrost-ene-3-ones aryl 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-X-N-Y-6-Azaandrost-ene-3-ones 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.

2. Material and Method

The compounds taken for study are 5α-Reductase Inhibitors of humans Type-2

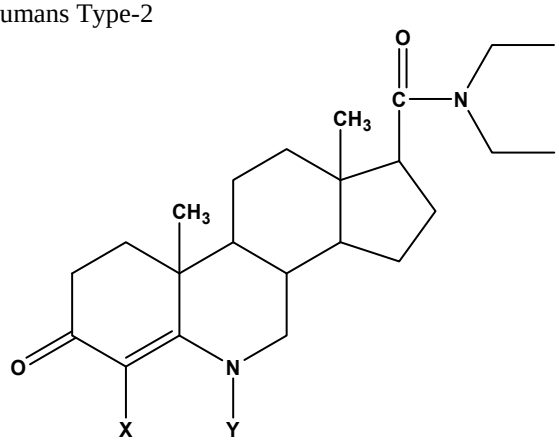


Figure 2: Derivatives of 4-X-N-Y-6-Azaandrost-ene-3-ones

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 2 and 3. Multiple linear regression analysis (MLR) is performed to establish the QSAR. A data set of 5α-Reductase Inhibitors of humans Type-2 Compounds were taken with their observed activity is shown in table 2

3. 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 = 8.05 + 0.491 E LUMO (e.v)
S = 1.03709
PRESS = 19.327
r^2 = 3.7%

Second QSAR model
Obsd log 1/C = 9.02 + 0.078 E LUMO (e.v) + 1.89 E HOMO (e.v)
S = 0.419061
PRESS = 3.95921
r^2= 85.4%

Third QSAR model

Obsd log 1/C = 9.06 + 0.062 E LUMO (e.v) + 1.92 E HOMO (e.v) + 0.0270 S
S = 0.419812
PRESS = 4.0379
r^2= 86.5%

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

First QSAR model
Obsd log 1/C = 10.5 - 0.0228 MR (cm3/mol)
S = 1.04244
PRESS = 18.2156
r^2= 2.7%

Second QSAR model
Obsd log 1/C = 10.4 - 0.055 MR (cm3/mol) + 0.0106 MV (cm3/mol)
S = 1.0777
PRESS = 19.9776
r^2= 3.5%

Third QSAR model
Obsd log 1/C = 11.5 - 0.086 MR (cm3/mol) + 0.0177 MV (cm3/mol)+ 0.000052 Parachor (cm3/mol)
S = 1.11815
PRESS = 1129878
r^2 = 4.1%

Fourth QSAR model
Obsd log 1/C = - 3063 - 12.0 MR (cm3/mol) + 3.79 MV (cm3/mol) + 0.00141 Parachor (cm3/mol) + 1989 Refraction Index
S = 0.26664
S = 0.617435

r^2 = 73.2%

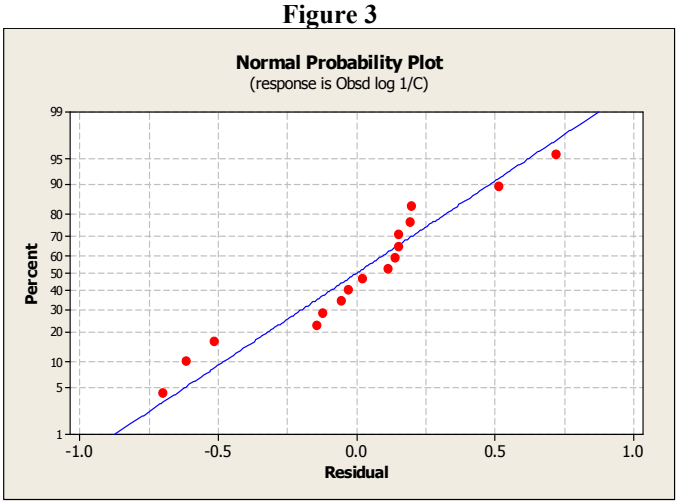
Fifth QSAR model
Obsd log 1/C = - 2513 - 9.69 MR (cm3/mol) + 3.06 MV (cm3/mol) + 0.00111 Parachor (cm3/mol) + 1639 Refraction Index- 0.209 Surface T (dyne/cm)
S = 0.592264
PRESS = 3052699
r^2 = 77.6%

Sixth QSAR model
Obsd log 1/C = - 3194 - 11.7 MR (cm3/mol) + 3.71 MV (cm3/mol)+ 0.00103 Parachor (cm3/mol) + 2089 Refraction Index- 0.272 Surface T (dyne/cm) - 14.0 Density (g/cm3)
S = 0.560793
PRESS = 31106670
r^2 = 81.9%

Seventh QSAR model
Obsd log 1/C = - 3169 - 16.2 MR (cm3/mol) + 3.68 MV (cm3/mol)+ 0.00102 Parachor (cm3/mol) + 2074 Refraction Index- 0.277 Surface T (dyne/cm) - 14.0 Density (g/cm3)+ 11.6 Polarizability (cm3)
S = 0.592869
PRESS = 32700990
r^2 = 82.0%

Eighth QSAR model
Obsd log 1/C = - 2991 - 31.8 MR (cm3/mol) + 3.38 MV (cm3/mol)+ 0.00118 Parachor (cm3/mol) + 2037 Refraction Index- 0.238 Surface T (dyne/cm) - 129 Density (g/cm3)+ 50.3 Polarizability (cm3) + 0.349 Average Mass (Da)
S = 0.602197
PRESS = 81644417
r^2 = 83.8%

Figure 3



4. Conclusion

The quantum mechanical descriptor and physicochemical parameters Values of the descriptors of the Derivatives of 4-X-N-Y-6-Azaandrost-ene-3-ones derivatives have been calculated using PM3 method and are given in table-2 and 3. With the help of these values of quantum QSAR descriptors of models third 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 physicochemicalQSAR models are the model third and eighth respectively listed below-

Obsd log 1/C = 9.06 + 0.062 E LUMO (e.v) + 1.92 E HOMO (e.v) + 0.0270 S
S = 0.419812
PRESS = 4.0379
r^2= 86.5%

Fourth QSAR model
Obsd log 1/C = - 3063 - 12.0 MR (cm3/mol) + 3.79 MV (cm3/mol) + 0.00141 Parachor (cm3/mol) + 1989 Refraction Index
S = 0.26664
S = 0.617435
r^2 = 73.2%

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-3, which is clearly illustrates the high predictive power of the QSAR model third.

Table 1

Comp.No.	*X*	*Y*	*Obsd log 1/C*
1	H	-COMe	5.52
2	H	$-CH_2COOH$	5.82
3	H	-Me	8.64
4	H	$-C_2H_5$	8.46
5	H	$(CH_2)_2CH_3$	8.38
6	H	$CHMe_2$	8.31
7	H	$(CH_2)_3CH_3$	7.54
8	H	$-C_2H_{13}$	7.92
9	H	$-CH_2C_6H_5$	7.40
10	Cl	H	8.70
11	Br	H	8.68
12	I	H	8.22
13	CH_2NMe_2	H	6.77
14	-Me	H	8.41
15	C_2H_5	H	6.75
16	-Me	-Me	8.35

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

Obsd log 1/C	E LUMO (e.v)	E HOMO (e.v)	μ	η	S	χ
5.52	-0.914	-1.452	-1.183	0.269	0.358	1.183
5.82	-1.024	-1.587	-1.306	0.281	0.611	1.306
8.64	-0.228	-0.228	-0.228	0.000	-4.158	0.228
8.46	0.084	-0.471	-0.194	0.278	12.376	0.194
8.38	-1.007	-0.412	-0.710	-0.298	-0.581	0.710
8.31	-1.007	-0.425	-0.716	-0.291	-0.568	0.716
7.54	-0.828	-0.828	-0.828	0.000	-0.379	0.828
7.92	-0.995	-0.564	-0.779	-0.215	-0.441	0.779
7.4	-0.890	-0.890	-0.890	0.000	-0.234	0.890
8.7	-1.001	-0.245	-0.623	-0.378	-0.754	0.623
8.68	-0.908	-0.123	-0.515	-0.392	-0.979	0.515
8.22	-0.264	-0.314	-0.289	0.025	-3.474	0.289
6.77	-0.24	-1.521	-0.881	0.641	-2.646	0.881
8.41	-0.252	-0.548	-0.400	0.148	-3.420	0.400
6.75	-0.24	-0.825	-0.533	0.293	-3.342	0.533
8.35	-0.179	-0.014	-0.097	-0.083	-5.573	0.097

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

Obsd log 1/C	MR (cm3/mol)	P RO FP 9	Parachor (cm3/mol)	Refraction Index	Surface T (dyne/cm)	Density (g/cm^3)	Polarizability (cm^3)	Average Mass (Da)
5.52	117.350	363.100	950.000	1.559	46.800	1.140	46.520	414.581
5.82	118.890	360.400	967.000	1.573	51.800	1.190	47.130	430.580
8.64	112.600	350.100	904.800	1.556	44.500	1.100	44.640	386.571
8.46	117.240	366.300	944.800	1.553	44.200	1.090	46.470	400.597
8.38	121.870	382.400	984.900	1.550	43.900	1.080	48.310	414.624
8.31	121.840	383.000	982.900	1.549	43.300	1.080	48.300	414.624
7.54	126.500	398.500	1025.000	1.547	43.700	1.070	50.140	428.651
7.92	135.760	430.700	1105.100	1.542	43.300	1.060	53.820	456.704
7.4	137.320	408.700	10786.000	1.586	48.500	1.130	54.430	462.667
8.7	112.350	346.300	901.800	1.562	45.900	1.170	44.540	406.989
8.68	115.240	348.200	915.700	1.576	47.800	1.290	45.680	451.440
8.22	120.450	354.800	938.600	1.594	48.900	1.400	47.750	498.441
6.77	120.660	373.600	969.300	1.559	45.300	1.110	47.830	415.612
8.41	112.150	351.100	903.000	1.551	43.700	1.100	44.460	386.571
6.75	116.780	367.300	943.000	1.548	43.400	1.090	46.290	400.597
8.35	117.010	366.100	941.100	1.552	43.600	1.090	46.380	400.597

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