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QSAR STUDY OF TESTOSTERONE DERIVATIVES USING QUANTUM CHEMICAL AND TOPOLOGICAL DESCRIPTORS

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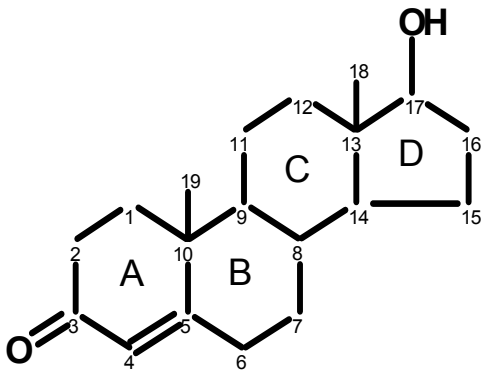
ABSTRACT

QSAR models of testosterone derivatives, whose receptor binding affinity is known, have been developed by using maximum of four descriptors. The descriptors are heat of formation, log P, molecular weight, shape index (basic kappa, order 1), connectivity index (order 0, standard), valence connectivity index (order 0, standard), solvent accessibility surface area and molar refractivity**.** The best QSAR model has correlation coefficient above 0.99 and has been developed by combination of four descriptors viz. heat of formation, shape index order 1, valence connectivity index order 0 and solvent accessibility surface area. This QSAR model is very reliable and can efficiently be used for the prediction of receptor binding affinity.

Keywords: Testosterone, topological descriptor, quantum chemical descriptor, QSAR.

INTRODUCTION

Androgens are steroids that are responsible for the development and maintenance of the male phenotype. Androgens affect the development, growth and function of a wide variety of cell types and tissues, and these effects are due to the interaction of androgens with an intracellular component, the androgen receptor [1, 2]. An androgen or male sex hormone is defined as a substance capable of developing and maintaining masculine sexual characteristics (including the genital tract, secondary sexual characteristics and fertility) and the anabolic status of somatic tissues. Testosterone is the principal androgen (male sex hormone) in the circulation of mature male mammals. The general chemical structure of testosterone is based upon the androstane C19 steroid, consisting of the fused four ring steroid nucleus (17 carbon atoms, rings A-D) and the two axial methyl groups (carbon 18 and 19) at the A/B and C/D ring junctions.



Structure of testosterone

A hormone has definite chemical structure. The physiological or therapeutic action of hormone depends entirely on its chemical structure. Slight modification or alteration in the chemical structure may result in the change of its activity drastically. In case of testosterone and its derivatives the chemical structure has also been related to androgenic activity [3]. Most of the investigators are interested in structure-activity relationship. 17β-hydroxyl group is an important feature for androgenic and anabolic activity, loss of this 17β-hydroxyl group abolishes androgenic activity [4]. Reduction of A-ring functional groups has variable effects on activity e.g. conversion of

T to DHT has little effect or may increase potency in a variety of bioassay system [5, 6].

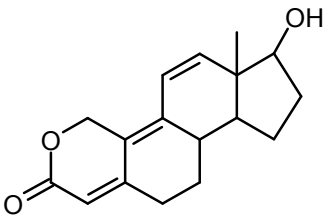
Atomic softness and quantum mechanical parameters based QSAR study of testosterone derivatives have been made [7, 8]. Using the same descriptors the study have been extended on estrogen derivatives also [9, 10]. The results of these studies have successfully described high quality of predictive power. In the present paper, quantum chemical and topological descriptors have been used for QSAR study of testosterone derivatives [11].

MATERIAL AND METHOD

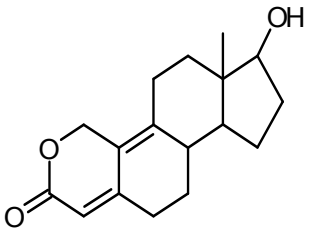
Ten testosterone derivatives have been chosen for QSAR studies [12, 13] which are included in Table-1. Structures of testosterone derivatives are given in Figure-1. QSAR studies of these derivatives have been made with the help of following quantum chemical and topological descriptors:

Table -1: ***Testosterone derivatives with their biological activity in terms of Receptor Binding Affinity***

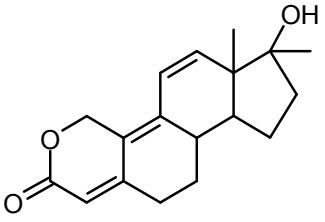
No	Name of Compound	Receptor Binding Affinity
1	2-oxa-17β -hydroxy-estra-4, 9,11-triene-3-one	1.40
2	2-oxa-17β -hydroxy-estra-4, 9-diene-3-one	3.20
3	2-oxa-17β -hydroxy,17 α -methyl-estra-4,9,11-triene-3-one	3.80
4	17β -hydroxy,17 α -methyl-4,9,11-triene-3-one	2.30
5	3α,17 β -dihydroxy-5α -androstane	2.10
6	5α -androstane-3,17-dione	2.60
7	5α -androstane	0.02
8	5α -androstane-3-one	0.50
9	17β -hydroxy-5α -androstane	0.08
10	3α -hydroxy-5α -androstane-17-one	2.70



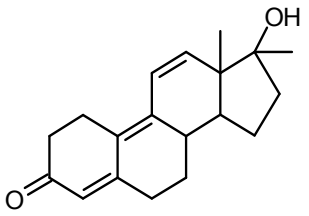
(1)-2-oxa-17β-hydroxy, estra-4, 9,11-triene-3-one.



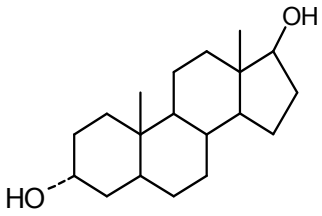
(2)-2-oxa-17β-hydroxy Estra-4, 9-diene-3-one.



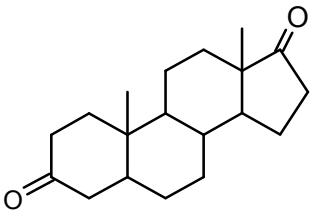
(3)-2-oxa-17β-hydroxy, 17α-methyl, estra-4, 9, 11-triene-3-one.



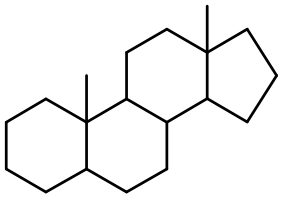
(4)-17β-hydroxy, 17α-methyl,



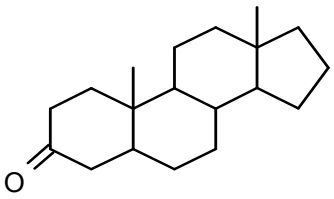
(5)-3α, 17β-dihydroxy, Estra-4, 9, 11-triene-3-one.



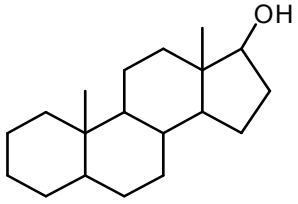
(6)-5α-androstane-3, 17-dione.



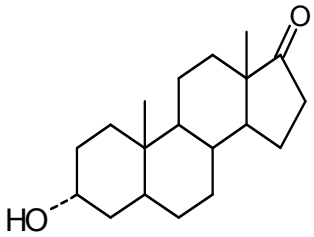
(7)-5α-androstane.



(8)-5α-androstane-3-one.



(9)-17β-hydroxy, 5α-androstane.



(10)-3α-hydroxy, 5α-androstane-17-one.

Figure -1: ***Structures of Testosterone derivatives***

1. Heat of Formation (kcal/mole)	ΔH_f
2. Log P	LP
3. Molecular Weight	MW
4. Shape Index (basic kappa, order 1)	SI1
5. Connectivity Index (order 0, standard)	CI0
6. Valence Connectivity Index (order 0, standard)	χ_0
7. Solvent Accessibility Surface Area	SASA
8. Molar Refractivity	MR

Descriptors in different combinations have been used for Multilinear Regression Analysis (MLR). The predicted activity obtained by regression equation has been examined for selecting QSAR models, which have high degree of predictive power; the correlation coefficient and cross validation coefficient of all the regression equation have been evaluated and listed in decreasing order of the predictive power.

The best QSAR model and the combination of descriptors providing that model have been identified. On the basis of such models new derivatives can be proposed which may have better hormonal activity. Cache software has been used for the calculation of descriptors of testosterone derivatives. At first, we have optimized the geometry by using PM3 Hamiltonian and then calculated the values of descriptors with the help of procedures given in Table-2. Values of quantum chemical and topological descriptors of testosterone derivatives are included in Table-3. Outlier compound is the compound 1.

Table -2: Descriptors and the procedures by which they have been evaluated

S. No.	Descriptor	Procedure
1	Heat of Formation	PM3 geometry
2	Log P	PLevalLogPGC
3	Molecular Weight	Extracted from Compound
4	Shape Index (basic kappa, order 1)	PLevalKappa1
5	Connectivity Index (order 0, standard)	PLevalMolChi0
6	Valence Connectivity Index (order 0, standard)	PLevalMolChi0V
7	Solvent Accessibility Surface Area	PM3-H2O_Geo
8	Molar Refractivity	PLevalMRGC

Table -3: ***Values of quantum chemical and topological descriptors of testosterone derivatives***

CMP	ΔH_f	LP	MW	SI1	CI0	χ_0	SASA	MR	RBA
1	-96.171	1.547	272.343	13.648	13.905	11.763	115.279	78.162	1.40
2	-121.779	1.807	274.359	13.648	13.905	12.023	115.017	77.045	3.20
3	-101.864	1.625	286.370	14.583	14.828	12.686	118.942	82.800	3.80
4	-66.064	1.669	284.397	14.583	14.828	12.985	120.691	86.385	2.30
5	-129.478	3.725	292.461	14.583	14.828	13.722	116.909	84.630	2.10
6	-113.046	4.461	288.429	14.583	14.828	13.490	117.590	82.781	2.60
8	-81.796	4.847	274.445	13.648	13.958	13.289	113.279	82.088	0.50
9	-91.488	4.783	276.461	13.648	13.958	13.405	114.179	82.961	0.08
10	-120.587	4.253	290.445	14.583	14.828	13.606	116.775	83.808	2.70

CMP= Compound, ΔH_f = Heat of Formation (kcal/mole), LP = Log P, MW = Molecular Weight, SI1 = Shape Index (basic kappa, order 1), CI0 = Connectivity Index (order 0, standard), χ_0= Valence Connectivity Index (order 0, standard), SASA = Solvent Accessibility Surface Area, MR = Molar Refractivity, RBA = Receptor Binding Affinity

RESULT AND DISCUSSION

QSAR models using different combinations of descriptors have been tried. The maximum number of descriptors in one QSAR model is limited to four. Best 10 QSAR models, in decreasing order of predictive power, are described here whose MLR equations are as under-

1. PA1=-0.00602933*ΔH_f+4.01066 *SI1-2.36409*χ_0-0.355332*SASA + 17.0018
   rCV^2=0.464047
   r^2=0.993292
2. PA2=11.765*SI1-7.81151*CI0-2.30498*χ_0-0.427744*SASA +28.1591
   rCV^2=0.777301
   r^2=0.993214
3. PA3=0.172905*LP+4.67446*SI1-2.90109*χ_0-0.416837*SASA +21.8273
   rCV^2=0.867744
   r^2=0.992979
4. PA4=-0.00864797*ΔH_f+4.08864 *CI0-2.41009*χ_0-0.326343*SASA + 11.7713
   rCV^2=0.301226
   r^2=0.992317

5. PA5=0.0280614*MW+4.07541*SI1-2.57935*χ_0-0.430606*SASA +20.363
   rCV^2=0.805288
   r^2=0.991157
6. PA6=4.64688*SI1-2.56613*χ_0-0.471711*SASA+24.8044
   rCV^2=0.959914
   r^2=0.990325
7. PA7=0.0512961*MW+3.9318*CI0-2.71512*χ_0-0.415418*SASA +14.8034
   rCV^2=0.709115
   r^2=0.988698
8. PA8=0.165713*LP+5.08824*CI0-3.04475*χ_0-0.441554*SASA +19.4003
   rCV^2=0.786027
   r^2=0.987784
9. PA9=1.69166*SI1+1.40573*CI0-1.06467*χ_0-0.287281*MR-4.50155
   rCV^2=0.23807
   r^2=0.987016
10. PA10=2.99642*SI1-1.04687*χ_0-0.281067*MR-3.44436
    rCV^2=0.876794
    r^2=0.986947

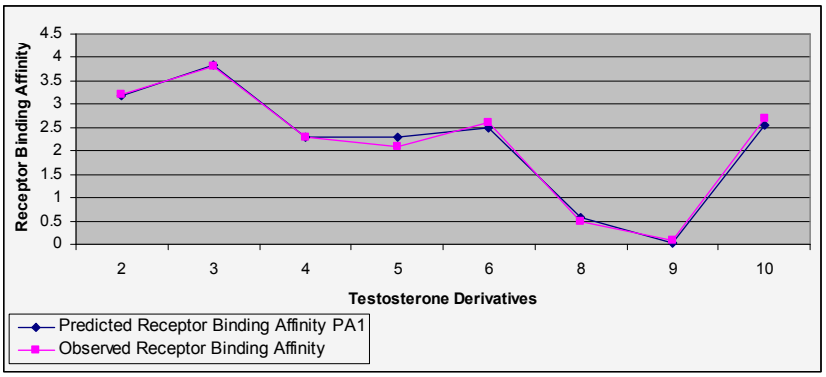
We have also calculated the predicted receptor binding affinity of testosterone derivatives PA1-PA10 by substituting the values of descriptors in MLR equations. These values are listed in Table-4.

Table - 4: ***Values of predicted receptor binding affinity PA1 to PA10***

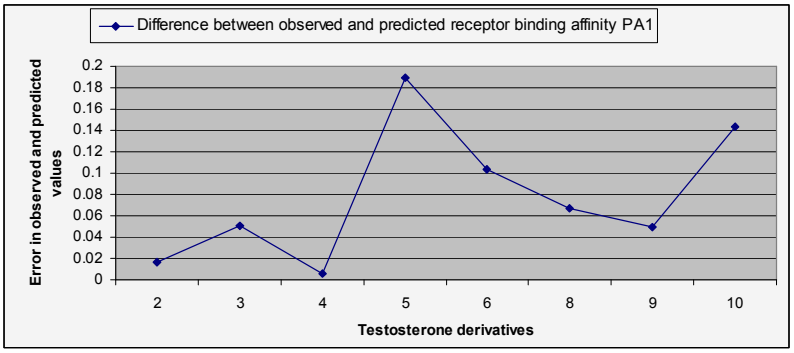
Comp	PA1	PA2	PA3	PA4	PA5	PA6	PA7	PA8	PA9	PA10
2	3.183	3.200	3.116	3.167	3.146	3.120	3.126	3.061	3.200	3.211
3	3.850	3.785	3.895	3.889	3.893	3.911	3.939	3.973	3.719	3.701
4	2.306	2.348	2.307	2.288	2.314	2.319	2.300	2.298	2.371	2.380
5	2.289	2.266	2.099	2.293	2.266	2.211	2.282	2.063	2.090	2.101
6	2.497	2.510	2.617	2.489	2.460	2.486	2.424	2.593	2.869	2.864
8	0.567	0.617	0.694	0.552	0.632	0.692	0.622	0.745	0.477	0.468
9	0.030	-0.037	-0.030	0.062	0.001	-0.031	0.036	-0.017	0.103	0.101
10	2.557	2.591	2.583	2.540	2.567	2.572	2.550	2.564	2.450	2.454

BEST QSAR MODEL

Best QSAR model has been obtained using the descriptors heat of formation, shape index order 1, valence connectivity index order 0 and solvent accessibility surface area. The value of correlation coefficient is 0.993292 and cross-validation coefficient is 0.464047. These values of correlation and cross-validation coefficients indicate very good predictive power of QSAR model PA1. Graph-1 shows the values of observed and predicted receptor binding affinity PA1 of testosterone derivatives. Difference between observed receptor binding affinity and predicted receptor binding affinity PA1 is shown in Graph-2.



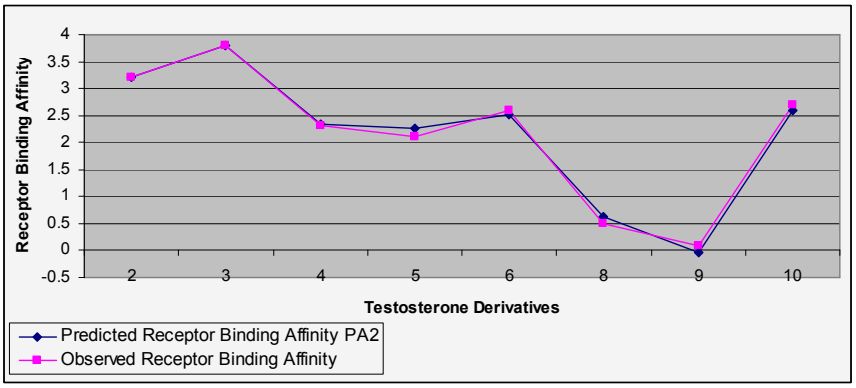
Graph -1: ***Graph between observed and predicted receptor binding affinity PA1 of testosterone derivatives.***



Graph -2: ***Difference between observed receptor binding affinity and predicted receptor binding affinity PA1***

SECOND BEST QSAR MODEL

Second best QSAR model has been obtained using the descriptors shape index order 1, connectivity index order 0, valence connectivity index order 0 and solvent accessibility surface area. The value of correlation coefficient is 0.993214 and cross-validation coefficient is 0.777301. These values of correlation and cross-validation coefficients indicate very good predictive power of QSAR model PA2. Graph-3 shows the values of observed and predicted receptor binding affinity PA2 of testosterone derivatives.



Graph - 3: Graph between observed and predicted receptor binding affinity PA2 of testosterone derivatives.

CONCLUSION

Heat of formation, shape index order 1, valence connectivity index order 0 and solvent accessibility surface area are the best combination of descriptors to provide best QSAR model. The descriptor valence connectivity order 0 is also a good descriptor of receptor binding affinity of testosterone derivatives as is present in most of the combinations of descriptors providing the QSAR models having good predictive power.

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