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Topological descriptor based study of testosterone derivatives

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ABSTRACT

Five sets of testosterone derivatives have been studied separately in respect of testosterone-receptor interaction and in the development of QSAR models. Derivatives of testosterone have been divided in five sets on the basis of the method of measurement of their biological activity. The study has been made with the help of eight topological descriptors; solvent accessibility surface area (SASA), molar refractivity, valence connectivity index (of order 0, 1 & 2) and shape index (of order 1, 2 & 3). The values of descriptors have been evaluated with the help of CAChe Pro software. QSAR models of the derivatives of first, fourth and fifth sets have high degree of predictive power as the value of correlation coefficient (r^2) is greater than 0.8. The molar refractivity, solvent accessibility surface area (SASA) and shape index (of order 1) are the best descriptors for QSAR models. The results indicate that London dispersive forces appear to play an important role in testosterone-receptor amino acid interaction. Solvent accessibility surface area (SASA) of testosterone is useful in the measurement of extent of interaction of testosterone with environment.

Key Words: Testosterone, SASA, Molar refractivity, Kier shape index, Valence connectivity index.

INTRODUCTION

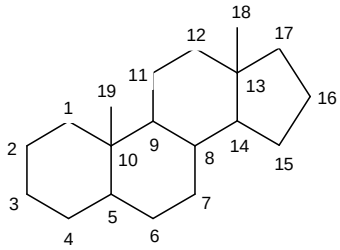
Testosterone is a steroid hormone from the androgen group. It is the principal male sex hormone and an anabolic steroid. It has many physiological and psychological effects in mammals [1-8]. There has been a continuous effort to relate the biological activity of any compound with the quantitative values of descriptors and to develop a mathematical representation of biological activity in terms of structural descriptors of a series of homologous molecules [9-15]. Recently, quantum chemical descriptors such as absolute hardness, electronegativity, ionization potential, electron affinity and atomic softness have been used for examining their relationship with biological activity and also for QSAR study of testosterone derivatives [16, 17].

Very recently, electrophilicity index in combination with atomic softness, global softness, chemical potential and molecular weight has also been used as descriptor for QSAR study [18, 19]. The above studies indicate that search for suitable descriptors for study of relationship with biological activity, for the study of drug-receptor interaction and also for predicting the activity of drugs is matter of interest.

In this paper, we have used a set of topological descriptors, which describe the bulk properties of a molecule, for study of testosterone-receptor interaction and also for examining their relationship with the activity of drugs and for predicting the activity of testosterone derivatives. Recently these descriptors have been noted to provide reliable models in different set of compounds [20-25]. The descriptors used are solvent accessibility surface area (SASA), molar refractivity, valence connectivity index (of order 0, 1 & 2) and shape index (of order 1, 2, & 3).

MATERIALS AND METHODS

The parent skeleton of testosterone is presented in Fig-1. The study materials of this paper are five sets of derivatives of testosterone. The derivatives are divided into five sets on the basis of the method of measurement of their biological activity. These derivatives along with their biological activity are presented in Table-1. The 3D modeling and geometry optimization of all the compounds and evaluation of values of descriptors have been done with the help of CAChe Pro software using the semiemperical PM3 Hamiltonian [26]. The Project Leader program associated with CAChe Pro of Fujitsu has been used for multi linear regression analysis. The values of various descriptors have been evaluated by solving the equations given in theory.



Parent skeleton of Testosterone

Fig-1

Theory:

Solvent Accessibility Surface Area (SASA):

It is the surface area of a biomolecule that is accessible to a solvent and is usually quoted in square angstrom. Lee and Richards first described the solvent accessible surface area (SASA) of a molecular surface [27]. SASA is typically calculated by using the 'rolling ball' algorithm developed by Sharke & Rupley [28].

Molar Refractivity [29]:

The molar refractivity is a constitutive-additive property that is calculated by the Lorenz-Lorentz formula,

$$MR = \frac{n^2 - 1}{n^2 + 2} * \frac{M}{p}$$

Where M is the molecular weight, n is the refraction index and ρ is the density and its value depends only of the wave longitude of the light used to measure the refraction index. For a radiation of infinite wavelength, the molar refractivity represents the real volume of the

molecules. Molar refractivity is related, not only to the volume of the molecule but also to the London dispersive forces that act in the drug-receptor interaction.

Valence Connectivity Index (χ):

This index, originally defined by Randic [30] and subsequently refined by Kier & Hall [31], was calculated from the hydrogen suppressed molecular graph. It is defined as follows,

$$ {}^{m}\chi^{v} = \sum_{i=1}^{NS} \prod_{k=1}^{m+1} \left[\frac{1}{\delta_k^v} \right]^{1/2} $$

Where, $\delta_k^v = \frac{(Z_k^v - H_k)}{(Z_k - Z_k^v - 1)}$ - valence connectivity for the k-th atom in the molecular graph, Z_k - the total number of electrons in the k-th atom, Z^v_k- the number of valence electrons in the k-th atom, H_k - the number of hydrogen atoms directly attached to the kth non-hydrogen atom, m = 0 - atomic valence connectivity indices (called order-0), m = 1 - one bond path valence connectivity indices (called order-1), m = 2 - two bond fragment valence connectivity indices (called order-2)

m = 3- three contiguous bond fragment valence connectivity indices etc.

Shape Index (κn):

Kier [32, 33] was first to propose shape indices for molecular graphs, the so called kappa shape indices. The first order kappa shape index (1 κ or k1) is given by,

$$ {}^{1}\kappa = \frac{A(A-1)^2}{({}^{1}P)^2} $$

Where, iP = Length of paths of bond length i in the hydrogen suppressed molecule and A is the number of non hydrogen atoms in the molecule. The second order kappa shape index (2 κ or k2) and third order kappa shape index (3 κ or k3) is given by

$$ {}^{2}\kappa = \frac{(A-1)(A-2)^2}{({}^{2}P)^2} $$

$$ {}^{3}\kappa = \frac{(A-1)(A-3)^2}{({}^{3}P)^2} \quad \text{if A is odd} $$

$$ {}^{3}\kappa = \frac{(A-3)(A-2)^2}{({}^{3}P)^2} \quad \text{if A is even} $$

Table-1: Name and biological activities of five sets of testosterone derivatives

No.	Name of Compound	Receptor Binding Affinity
1	2-oxa-17β-hydroxy-estra-4, 9,11-triene-3-one	1.4
2	2-oxa-17β-hydroxy-estra-4, 9-diene-3-one	3.2
3	2-oxa-17β-hydroxy,17α-methyl-estra-4,9,11-triene-3-one	3.8
4	17β-hydroxy,17α-methyl- estra-4,9,11-triene -3-one	2.3
5	3α,17β-dihydroxy-5α-androstane	2.1
6	5α-androstane-3,17-dione	2.6
7	5α-androstane	0.02
8	5α-androstane-3-one	0.5
9	17β-hydroxy-5α-androstane	0.08
10	3α-hydroxy-5α-androstane-17-one	2.7

First set of derivatives containing 10 compounds and their biological activity in terms of "Receptor Binding Affinity"

No.	Name of Compound	Androgenic Potency
1	17β-hydroxy,17α-methyl-5α-androst-1-en-3-one	25
2	17β-hydroxy-5α-androst-1-en-3-one	100
3	17β-hydroxy,17α-ethyl-5α-androst-1-en-3-one	2
4	17β-hydroxy,2-methyl-5α-androst-1-en-3-one	50
5	17β-hydroxy,2,17α-dimethyl-5α-androst-1-en-3-one	25
6	17β-hydroxy,2-methyl,17α-ethyl-5α-androst-1-en-3-one	1
7	5α-androst-1-en-3β,17β-diol	50
8	17α-methyl-5α-androst-1-ene-3β,17β-diol	100
9	17α-ethyl-5α-androst-1-ene-3β,17β-diol	5
10	17β-hydroxy,6β-methyl-5α-androst-1-en-3-one	10
11	17β-hydroxy,6β,17α-dimethyl-5α-androst-1-en-3-one	10
12	17β-hydroxy,6β-methyl, 17α-ethyl-5α-androst-1-en-3-one	1.5

Second set of derivatives containing 12 compounds and their biological activity in terms of "Androgenic Potency"

No.	Name of Compound	TeBG Affinity
1	Aldosterone	-5.32
2	Androstanediol	-9.11
3	Androstenediol	-9.17
4	Androstenedione	-7.46
5	Androsterone	-7.14
6	Corticosterone	-6.34
7	Cortisol	-6.2
8	Cortisone	-6.41
9	Dehydroepiandrosterone	-7.81
10	Deoxycorticosterone	-7.38

11	Deoxycortisol	-7.2
12	17-β-hydroxy-5α-androstan-3-one	-9.74
13	Estradiol	-8.83
14	Estriol	-6.63
15	Estrone	-8.17
16	Etiocholanolone	-6.14
17	Pregnenolone	-7.14
18	17-hydroxy,pregnenolone	-6.36
19	Progesterone	-6.94
20	17-hydroxy progesterone	-6.99
21	17-β-hydroxy-4-androsten-3-one	-9.2

Third set of derivatives containing 21 compounds and their biological activity in terms of "TeBG Affinity"

No.	Name of Compound	Androgenic Potency in Rat
1	5α-androstane-3,17-dione	0.2
2	Testosterone	0.4
3	7α-methyl testosterone	0.4
4	5α-dihydro testosterone	1
5	7α-methyl-5α-dihydro testosterone	1.2
6	19-nor testosterone	0.2
7	17α-methyl-19-nor testosterone	0.3
8	19-nor dihydrotestosterone	0.1
9	7α-methyl-19-nor-5α-dihydro testosterone	0.3

Fourth set of derivatives containing 9 compounds and their biological activity in terms of "Androgenic Potency in Rat"

No.	Name of Compound	Mytotrophic to Androgenic Potency in Temporal
1	3α,17β-dihydroxy-5α-androstane	1.4
2	5α-androstane-3,17-dione	1.3
3	17β-hydroxy,17α-methyl-5α-androstan-3-one	0.9
4	Androst-4-ene-3,17-dione	0.6
5	Testosterone	1
6	17α-methyl testosterone	0.5
7	5α-dihydro testosterone	1.5
8	Dehydroepiandrosterone	0.8
9	Epiandrosterone	0.7
10	17α-methyl-5α-androstane-3α,17β-diol	1.3

Fifth set of derivatives containing 10 compounds and their biological activity in terms of "Myotrophic to Androgenic Potency in Temporal"

RESULTS AND DISCUSSION

1-QSAR models:

The values of descriptors of five sets of compounds have been calculated. QSAR models using different combinations of descriptors were tried, but the models which provided best correlation coefficient for each set are described below.

First Set: The first set contains 10 derivatives of testosterone where biological activity has been measured in terms of "receptor binding affinity" [34, 35]. The values of eight descriptors alongwith their biological activities are given in Table-2. The best QSAR model for this set of derivatives has been obtained by using molar refractivity as first descriptor, SASA as second descriptor; shape index (order-1) as third descriptor and shape index (order-2) as fourth descriptor. The predicted activity (PA1) of compounds have been obtained by the following regression equation,

$$PA1=-0.799355*MR+0.578433*SASA+3.58624*{}^1\kappa - 11.468*{}^2\kappa +3.44635$$

$$rCV^2=0.530998,\ r^2=0.899788$$

The predicted activities obtained from above regression equation are listed in Table-3 alongwith their observed activity.

Table-2: Values of descriptors and observed activities of first set of derivatives containing 10 compounds.

Comp. No.	Molar Refractivity	SASA	Shape Index (Order1)	Shape Index (Order2)	Shape Index (Order3)	Valence Conne-ctivity Index (Order 0)	Valence Conne-ctivity Index (Order 1)	Valence Conne-ctivity Index (Order 2)	Obs. Act-ivity
1	78.162	115.04	13.648	4.75	1.961	11.763	7.574	6.755	1.4
2	77.045	114.59	13.648	4.75	1.961	12.023	7.871	7.132	3.2
3	82.8	119.17	14.583	4.747	1.994	12.686	7.946	7.391	3.8
4	86.385	120.69	14.583	4.747	1.994	12.985	8.307	7.75	2.3
5	84.63	117.99	14.583	4.747	1.926	13.722	9.311	9.223	2.1
6	82.781	116.28	14.583	4.747	1.926	13.49	9	8.818	2.6
7	81.446	111.23	12.719	4.247	1.704	13.088	9.135	8.988	0.02
8	82.088	113.18	13.648	4.497	1.889	13.289	9.046	8.985	0.5
9	82.961	114.56	13.648	4.497	1.756	13.405	9.236	9.04	0.08
10	83.808	118.15	14.583	4.747	1.926	13.606	9.163	9.003	2.7

Second Set: The second set contains 12 derivatives of testosterone where biological activity has been measured in terms of "androgenic potency" [36]. The values of eight descriptors alongwith their biological activities are given in Table-4. The best QSAR model for this set of derivatives has been developed by using SASA as first descriptor, shape index (order-1) as second descriptor and shape index (order-3) as third descriptor. The predicted activity (PA2) of compounds have been obtained by the following regression equation,

$$PA2=20.7907*SASA-63.3028*{}^1\kappa -652.621*{}^3\kappa -189.922$$

$$rCV^2=0.209106,\ r^2=0.685813$$

The predicted activities obtained from this regression equation are listed in Table-5 alongwith their observed activity.

Table-3: Observed & predicted activity of first set of compounds.

Comp. No.	Observed Activity	Predicted activity (PA-1)
1	1.4	1.982
2	3.2	2.615
3	3.8	4.051
4	2.3	2.065
5	2.1	1.906
6	2.6	2.395
7	0.02	-0.41
8	0.5	0.67
9	0.08	0.77
10	2.7	2.656

Table-4: Values of descriptors and observed activities of second set of derivatives containing 12 compounds

Comp. No.	Molar Refractivity	SASA	Shape Index (Order1)	Shape Index (Order2)	Shape Index (Order3)	Valence Connectivity Index (Order 0)	Valence Connectivity Index (Order 1)	Valence Connectivity Index (Order 2)	Obs. Activity
1	89.427	120.95	15.523	4.762	1.977	14.269	9.223	9.29	25
2	84.789	117.04	14.583	4.747	1.926	13.347	8.851	8.659	100
3	93.951	124.77	16.467	5.247	2.083	14.976	9.784	9.401	2
4	89.146	122.74	15.523	4.997	2.042	14.269	9.268	9.109	50
5	93.784	126.14	16.467	5.011	2.083	15.192	9.64	9.74	25
6	98.308	130.7	17.416	5.497	2.198	15.899	10.2	9.852	1
7	85.593	117.61	14.583	4.747	1.926	13.463	9.004	8.817	50
8	90.231	121.78	15.523	4.762	1.977	14.386	9.376	9.448	100
9	94.755	124.53	16.467	5.247	2.083	15.093	9.937	9.559	5
10	89.338	121.7	15.523	4.997	2.042	14.217	9.262	9.204	10
11	93.976	126.14	16.467	5.011	2.083	15.14	9.634	9.835	10
12	98.5	131	17.416	5.497	2.198	15.847	10.19	9.946	1.5

Table-5: Observed & predicted activity of second set of compounds

Comp. No.	Observed Activity	Predicted activity (PA-2)
1	25	51.832
2	100	63.329
3	2	2.317
4	50	46.627
5	25	30.8
6	1	-9.52
7	50	75.179
8	100	69.088
9	5	-2.673
10	10	25.005
11	10	30.8
12	1.5	-3.283

Third Set: The third set contains 21 derivatives of testosterone and their biological activity is reported in terms of "TeBG Affinity" [37, 38]. The values of descriptors alongwith their biological activities are placed in Table-6. The best QSAR model obtained for this set of derivatives is given by following regression equation,

$$PA3=-0.547033*SASA+10.7657*3\kappa +5.75132*0\chi -6.99964 *1\chi +20.6758$$
$$rCV^2=0.566535,\ r^2=0.768848$$

This regression equation contains SASA as first descriptor, shape index (order-3) as second descriptor, valence connectivity index (order-0) as third descriptor and valence connectivity index (order-1) as fourth descriptor. Compound No. – 16 and 21 are outlier in the MLR analysis. The predicted activities obtained from above regression equation are listed in Table-7 alongwith their observed activity.

Table-6: Values of descriptors and observed activities of third set of derivatives containing 21 compounds

Comp. No.	Molar Refractivity	SASA	Shape Index (Order1)	Shape Index (Order2)	Shape Index (Order3)	Valence Conne-ctivity Index (Order 0)	Valence Conne-ctivity Index (Order 1)	Valence Conne-ctivity Index (Order 2)	Obs. Act-ivity
1	96.885	136.86	19.322	6.805	2.704	15.317	9.89	9.144	-5.32
2	84.63	118.16	14.583	4.747	1.926	13.722	9.311	9.223	-9.11
3	85.326	118.62	14.583	4.747	1.926	13.515	9.023	8.769	-9.17
4	83.701	118.89	14.583	4.747	1.926	13.283	8.722	8.387	-7.46
5	83.808	115.72	14.583	4.747	1.926	13.606	9.163	9.003	-7.14
6	96.093	134.46	18.367	6.27	2.588	15.332	9.865	9.42	-6.34
7	97.492	136.65	19.322	6.25	2.486	15.702	9.957	9.557	-6.2
8	96.568	136.15	19.322	6.25	2.486	15.585	9.804	9.381	-6.41
9	84.658	117.58	14.583	4.747	1.926	13.399	8.859	8.574	-7.81
10	94.501	131.88	17.416	6.021	2.481	15.014	9.774	9.268	-7.38
11	95.9	132.06	18.367	6	2.371	15.384	9.866	9.405	-7.2
12	83.603	117.48	14.583	4.747	1.926	13.606	9.147	9.037	-9.74
13	79.618	116.21	13.648	4.75	1.961	12.179	8.093	7.436	-8.83
14	80.979	118.15	14.583	5	2.066	12.496	8.184	7.591	-6.63
15	78.796	116.05	13.648	4.75	1.961	12.062	7.945	7.217	-8.17
16	83.808	118.31	14.583	4.747	1.926	13.606	9.163	9.003	-6.14
17	93.756	129.07	16.467	5.5	2.289	14.976	9.741	9.441	-7.14
18	95.156	129.33	17.416	5.497	2.198	15.346	9.832	9.567	-6.36
19	92.799	128.3	16.467	5.5	2.289	14.86	9.604	9.254	-6.94
20	94.128	129.78	17.416	5.497	2.198	15.23	9.669	9.386	-6.99
21	84.523	116.33	14.583	4.747	1.926	13.399	8.87	8.607	-9.2

Fourth Set: The fourth set of derivatives contains 9 compounds and their biological activity is reported in terms of "androgenic potency in rat" [29]. The values of descriptors alongwith their biological activities are placed in Table-8.The best QSAR model obtained for this set of derivatives contains molar refractivity as first descriptor, shape index (order-1) as second descriptor; shape index (order-3) as third descriptor and valence connectivity index (order-2) as

fourth descriptor; the predicted activity (PA4) of compounds have been obtained by the following regression equation,

$$PA4=0.407501*MR-2.74595*1\kappa -2.52755*3\kappa +1.89628*2\chi -5.34263$$
$$rCV^2=0.456895,\ r^2=0.804219$$

The predicted activities obtained from the above regression equation are listed in Table-9 alongwith their observed activity.

Table-7: Observed & predicted activity of third set of compounds.

Comp. No.	Observed Activity	Predicted activity (PA-3)
1	-5.32	-6.214
2	-9.11	-9.481
3	-9.17	-8.907
4	-7.46	-8.282
5	-7.14	-7.778
6	-6.34	-5.889
7	-6.2	-6.701
8	-6.41	-6.03
9	-7.81	-7.858
10	-7.38	-6.822
11	-7.2	-6.62
12	-9.74	-8.628
13	-8.83	-8.386
14	-6.63	-7.131
15	-8.17	-7.936
17	-7.14	-7.339
18	-6.36	-6.97
19	-6.94	-6.626
20	-6.99	-6.742

Table-8: Values of descriptors and observed activities of fourth set of derivatives containing 9 compounds

Comp. No.	Molar Refractivity	SASA	Shape Index (Order1)	Shape Index (Order2)	Shape Index (Order3)	Valence Connectivity Index (Order 0)	Valence Connectivity Index (Order 1)	Valence Connectivity Index (Order 2)	Obs. Activity
1	82.781	116.28	14.583	4.747	1.926	13.49	9	8.818	0.2
2	84.523	118.06	14.583	4.747	1.926	13.399	8.87	8.607	0.4
3	89.071	121.42	15.523	4.997	2.042	14.269	9.28	9.163	0.4
4	83.603	116.05	14.583	4.747	1.926	13.606	9.147	9.037	1
5	88.151	120.1	15.523	4.997	2.042	14.476	9.558	9.587	1.2
6	80.048	116.3	13.648	4.75	1.961	12.476	8.508	7.941	0.2
7	84.685	118.57	14.583	4.747	1.994	13.399	8.88	8.572	0.3
8	79.128	114.31	13.648	4.75	1.961	12.684	8.791	8.355	0.1
9	83.676	117.4	14.583	5	2.066	13.554	9.202	8.904	0.3

Table-9: Observed & predicted activity of fourth set of compounds.

Comp. No.	Obs. Activity	Predicted activity (PA-4)
1	0.2	0.2
2	0.4	0.51
3	0.4	0.543
4	1	0.95
5	1.2	0.972
6	0.2	-0.098
7	0.3	0.337
8	0.1	0.312
9	0.3	0.374

Fifth Set: The fifth set of derivatives contains 10 compounds with their biological activity reported in terms of "mytotrophic to androgenic potency in temporal" [39]. The values of eight descriptors alongwith their biological activities are placed in Table-10. The best QSAR model obtained for this set of derivatives contains SASA as first descriptor, shape index (order-3) as second descriptor, valence connectivity index (order-1) as third descriptor and valence connectivity index (order-2) as fourth descriptor; the predicted activity (PA5) of compounds have been obtained by the following regression equation,

$$PA5=0.0896599*SASA-43.0685*3\kappa -9.73304*1\chi +7.98287 *2\chi +90.9205$$

$$rCV^2=0.437643,\ r^2=0.926944$$

The predicted activities obtained from the above regression equations are listed in Table-11 alongwith their observed activity.

Analysis of variance (ANOVA):

In order to assess the gravity of regression, analysis of variance of the best QSAR model of each set has been performed. The statistical parameters have been obtained by STATISTICA 8.0 version software and are included in Table-12.

Table-10: Values of descriptors and observed activities of fifth set of derivatives containing 10 compounds.

Comp. No.	Molar Refractivity	SASA	Shape Index (Order1)	Shape Index (Order2)	Shape Index (Order3)	Valence Connectivity Index (Order 0)	Valence Connectivity Index (Order 1)	Valence Connectivity Index (Order 2)	Obs. Activity
1	84.63	117.99	14.583	4.747	1.926	13.722	9.311	9.223	1.4
2	82.781	116.28	14.583	4.747	1.926	13.49	9	8.818	1.3
3	88.24	119.22	15.523	4.762	1.977	14.529	9.519	9.668	0.9
4	83.701	118.66	14.583	4.747	1.926	13.283	8.722	8.387	0.6
5	84.523	118.06	14.583	4.747	1.926	13.399	8.87	8.607	1
6	89.16	122.55	15.523	4.762	1.977	14.322	9.242	9.238	0.5
7	83.603	116.05	14.583	4.747	1.926	13.606	9.147	9.037	1.5
8	84.658	117.58	14.583	4.747	1.926	13.399	8.859	8.574	0.8
9	84.658	117.58	14.583	4.747	1.926	13.399	8.859	8.574	0.7
10	89.268	122.24	15.523	4.762	1.977	14.645	9.683	9.854	1.3

Table-11: Observed & predicted activity of fifth set of compounds.

Comp. No.	Observed Activity	Predicted activity (PA-5)
1	1.4	1.551
2	1.3	1.192
3	0.9	0.993
4	0.6	0.67
5	1	0.932
6	0.5	0.555
7	1.5	1.489
8	0.8	0.733
9	0.7	0.733
10	1.3	1.152

Table-12: Correlation summary of best QSAR model of each set.

S. No.	rCV^2	r^2	F value	P Value	Variable count
Set-1	0.530998	0.899788	11.22351	0.010330	4
Set-2	0.209106	0.685813	5.820852	0.020737	3
Set-3	0.566535	0.768848	11.64156	0.000225	4
Set-4	0.456895	0.804219	4.107738	0.099982	4
Set-5	0.437643	0.926944	15.86006	0.004786	4

2-Testosterone-Receptor interaction:

Androgens act on target cells to regulate gene expression through the formation of a steroid-receptor complex. Testosterone acts directly or as 5α-dihydrotestosterone (DHT) or by conversion into estradiol. DHT is formed in the cytoplasm, enters the nucleus of the cell, and binds to the steroid receptor protein. The steroid receptor protein has a large number of amino acid and amide group, hence act as nucleophile, the action of testosterone is accordingly reported to be electrophylic towards the receptor [16].

The nature of drug-receptor interaction may be covalent, hydrophobic, hydrogen bonded, van der Wall type interaction, dispersive forces. Factors such as steric effect, substitution of different groups, shape and size of the molecule also play an important role in drug-receptor interaction. The bulk properties of a molecule such as surface area, bonding of groups and substituents, volume of the molecule, shape related properties etc have been recently used successfully for QSAR study of different compounds [20, 23].But no study of these properties have been made in respect of drug-receptor interaction or for the study of their relationship with biological activity. In this paper, a study on the factors responsible for bulk property in testosterone-receptor interaction and also their relationship with biological activity of testosterone derivatives has been made. The testosterone derivatives have been described under five sets, on the basis of mode of biological activity measurement; hence the relationship has been examined separately for each set.

The first set contains 10 derivatives of testosterone where biological activity has been measured in terms of "receptor binding affinity". The values of eight descriptors alongwith their biological activities are given in Table-2. A close look at Table-2 indicates that there is a direct relationship between solvent accessibility surface area (SASA) and biological activity as shown by the values given against each compound. 2-oxa-17β-hydroxy,17α-methyl,estra-4,9,11-triene-3-one

(SASA=119.17 & Bio. Act.= 3.8) > 3α-hydroxy,5α-androstane-17-one (SASA=118.15 & Bio. Act.= 2.7) > 5α-androstane-3,17-dione (SASA=116.28 & Bio. Act.= 2.6) > 2-oxa-17β-hydroxy-estra-4, 9,11-triene-3-one (SASA=115.04 & Bio. Act.= 1.4) > 5α-androstane-3-one (SASA=113.18 & Bio. Act.= 0.5) > 5α-androstane (SASA=111.23 & Bio. Act.= 0.02).

The second set contains 12 derivatives of testosterone where biological activity has been measured in terms of "androgenic potency". The values of eight descriptors alongwith their biological activities are given in Table-4. A close look of Table-4 indicates that there is an inverse relationship between molar refractivity and biological activity as shown by the values given against each compound in decreasing order of biological activity. 17β-hydroxy,5α-androst-1-en-3-one (MR=84.789 & Bio. Act.= 100) > 17β-hydroxy,2-methyl-5α-androst-1-en-3-one (MR=89.146 & Bio. Act.= 50) > 17β-hydroxy,17α-methyl,5α-androst-1-en-3-one (MR=89.427 & Bio. Act.= 25) > 17β-hydroxy,6β,17α-dimethyl,5α-androst-1-en-3-one (MR=93.976 & Bio. Act.= 10) > 17α-ethyl,5α-androst-1-ene-3β,17β-diol (MR=94.755 & Bio. Act.= 5) > 17β-hydroxy,6β-methyl, 17α-ethyl,5α-androst-1-en-3-one (MR=98.5 & Bio. Act.= 1.5).

The third set contains 21 derivatives of testosterone and their biological activity is reported in terms of "TeBG Affinity". The values of descriptors alongwith their biological activities are placed in Table-6. A close look at Table-6 indicates that there is a direct relationship between solvent accessibility surface area (SASA) and biological activity as shown by the values given against each compound. 17-β-hydroxy,5α-androstan-3-one (SASA=117.48 & Bio. Act.= -9.74) < Androstenediol (SASA=118.62 & Bio. Act.= -9.17) < Androstenedione (SASA=118.89 & Bio. Act.= -7.46) < Deoxycorticosterone (SASA=131.88 & Bio. Act.= -7.38) < Deoxycortisol (SASA=132.06 & Bio. Act.= -7.2) < Cortisone (SASA=136.15 & Bio. Act.= -6.41) < Cortisol (SASA=136.65 & Bio. Act.= -6.2) < Aldosterone (SASA=136.86 & Bio. Act.= -5.32).

The fourth set of derivatives contains 9 compounds and their biological activity is reported in terms of "androgenic potency in rat". The values of descriptors alongwith their biological activities are placed in Table-8. A close look at Table-8 indicates that there is a direct relationship between molar refractivity and biological activity as shown by the values given against each compound. 19-nor dihydrotestosterone (MR=79.128 & Bio. Act.= 0.1) < 19-nor testosterone (MR=80.048 Bio. Act.= 0.2) < 7α-methyl,19-nor-5α-dihydro testosterone (MR=83.676 & Bio. Act.= 0.3) < Testosterone (MR=84.523 & Bio. Act.= 0.4) < 7α-methyl,5α-dihydro testosterone (MR=88.151 & Bio. Act.= 1.2).

The fifth set of derivatives contains 10 derivatives with their biological activity reported in terms of "mytotrophic to androgenic potency in temporal". The values of eight descriptors alongwith their biological activities are placed in Table-10. A close look at Table-10 indicates that there is an inverse relationship between molar refractivity and biological activity as shown by the values given against each compound in decreasing order of biological activity. 5α-dihydro testosterone (MR=83.603 & Bio. Act.= 1.5) > 3α,17β-dihydroxy,5α-androstane (MR=84.63 & Bio. Act.= 1.4) > 17β-hydroxy,17α-methyl,5α-androstan-3-one (MR=88.24 & Bio. Act.= 0.9) > 17α-methyl, testosterone (MR=89.16 & Bio. Act.= 0.5).

From the above discussion it can be inferred that, biological activity of testosterone derivatives is either directly or inversely related to molar refractivity or solvent accessibility surface area (SASA). Molar refractivity is related to the London dispersive forces that act in the drug-receptor interaction. London dispersive forces appear to play an important role in testosterone-

receptor binding. This type of intermolecular forces arises due to induced dipole-induced dipole interactions.

The extent to which a biomolecule interacts with its environment (the solvent) is naturally proportional to the degree to which it is exposed to these environments. SASA is the measure of this exposure. Therefore, SASA of testosterone has an important role in the study of its interaction with receptor.

CONCLUSION

1-QSAR models of the derivatives of first, fourth and fifth sets have high degree of predictive power as the value of correlation coefficient (r^2) is greater than 0.8.
2-The molar refractivity and solvent accessibility surface area (SASA) are either directly or inversely related to the biological activity of testosterone derivatives.
3-London dispersive forces appear to play an important role in testosterone-receptor amino acid interaction.
4- Solvent accessibility surface area (SASA) of testosterone is useful in the measurement of extent of interaction of testosterone with environment.

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