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DFT-based QSAR study of testosterone and its derivatives

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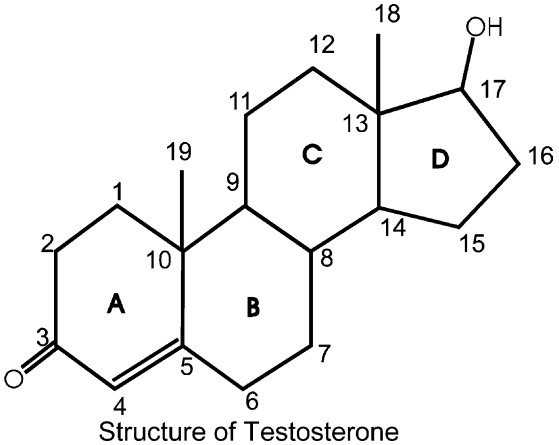
Abstract—QSAR study of derivatives of testosterone has been made with the help of quantum mechanical parameters such as Absolute Hardness (η) and Electronegativity (χ). These two parameters have been derived with the help of density functional theory. The 3-D modeling and geometry optimization of all the compounds have been done with the help of PCMODEL software and semiempirical PM3 calculations performed with the help of WinMOPAC-7.21 software. The absolute hardness provides valuable information due to maximum hardness principle and used in development of QSAR. The information provided by electronegativity is not as clear as in case of absolute hardness.

1. Introduction

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) and the A/B and C/D ring junctions. Testosterone has two primary kinds of activities—androgenic and anabolic.



Structure of Testosterone

There has been a continuous effort to relate the biological activity of any compound with its molecular structure. In recent years, a quantitative basis has been given to this approach called Quantitative Structure Activity Relationship (QSAR). QSAR has been dominating for the last 10–12 years; computational chemistry has given a major boost to this relationship, and a number of reactivity indices have been developed with the help of density functional theory (DFT).[1–3] The survey of the literatures indicates that no QSAR study of testosterone derivatives has been made with the reactivity indices Chemical Potential (μ), Absolute Hardness (η), Global Softness (S) and Electronegativity (χ). Based on these reactivity indices, the QSAR of 75 derivatives of testosterone is presented in this paper.

There are many important applications of DFT in chemistry.[4–11,27] One is the calculation of properties of atom and molecules. Another important use of DFT is in elucidating familiar chemical concept. DFT provides simple but rigorous frameworks to handle complicated systems and, most importantly, it generates intuitive and insightful concepts for understanding chemical changes.

A series of quantities, which are readily used while considering chemical reactivity, appear in a most natural way within the framework of this theory. For example, a new theoretical basis is found for the use of the frontier molecular orbitals (FMO), being the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), as reactivity indices. This concept was introduced by Fukui in the FMO theory.[12]

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In DFT, the ground state energy of an atom or a molecule is written in terms of electron density ρ(r), and the external potential ν(*r*) in the form of following equation.[13]

$$E(\rho) = F(\rho) + \int dr\ \rho(r)\nu(r), \tag{1}$$

where $F(\rho) = T(\rho) + V_{ee}(\rho)$, $T(\rho)$ is the electronic kinetic energy functional, and $V_{ee}(\rho)$ is the electron-electron interaction energy functional. The minimization of the total energy, subject to the condition that the total number of electrons is fixed,

$$N = \int dr\ \rho(r) \tag{2}$$

leads to a Euler–Lagrange equation of the form,

$$\mu = [\partial E/\delta\rho(r)]_v = \nu(r) + \partial F(\rho)/\delta\rho(r), \tag{3}$$

where μ, the Lagrange multiplier, is the chemical potential. The solution of this equation leads to the ground state density, from which one can determine the ground state energy. Parr et al. define the electronegativity is the negative of chemical potential as,[14]

$$\chi = -\mu = -(\partial E/\partial N)\nu(r) \tag{4}$$

The absolute hardness η is defined as[15]

$$\eta = 1/2(\delta\mu/\delta N)\nu(r) = 1/2(\delta^2 E/\delta N^2)\nu(r) \tag{5}$$

where E is the total energy, N the number of electrons of the chemical species and ν(r) the external potential.

The corresponding global softness S, which bears an inverse relationship with the absolute hardness, is defined as

$$S = 1/2\eta = (\partial N/\partial\mu)\nu(r) \tag{6}$$

The operational definition of absolute hardness and global softness are obtained by finite difference approximation of eq 1

$$\eta = 1/2(\text{IP-EA}) \tag{7}$$

$$S = 1/(\text{IP-EA}) \tag{8}$$

Where IP and EA are the Ionization Potential and Electron Affinity respectively, of the chemical species according to the Koopman's theorem, the IP is simply the eigen value of HOMO with change of sign and EA is the eigen value of LUMO with change of sign [14] hence the equations 7 and 8 can be written as

$$\eta = 1/2(\varepsilon\text{LUMO} - \varepsilon\text{HOMO}) \tag{9}$$

$$S = 1/(\varepsilon\text{LUMO} - \varepsilon\text{HOMO}) \tag{10}$$

The absolute hardness and global softness are the property of the molecule.

2. Result and discussion

The biological activity of testosterone derivatives has been evaluated by eight different parameters. The testosterone derivatives are accordingly divided in eight different sets, which along with their biological activity are presented in Tables 2–9. Each table excepting Table 8 has been divided into A and B subgroups in order to demonstrate better and sequential relationship between the biological activity and reactivity parameters. The different terms of activity measurements are mentioned at the bottom of each table and the activity in each table has been arranged in increasing order. The reactivity indices such as absolute hardness (η),[16] and electronegativity (χ)[17] of the corresponding testosterone derivatives are also presented in the table. The QSAR study of each set has been discussed as below.

2.1. First Set

The first set consists of ten testosterone derivatives and their biological activity has been measured in terms of relative binding affinity.[18] The reactivity indices along with biological activity of this set of compounds are placed in Table 2. A close look at this table indicates that addition of 1–2 double bond or 17α-methyl group and removal of 1α-methyl group or 19-methyl group increases the activity. Removal of 9–10 and 11–12 double bond or addition of 11β-hydroxy group decreases the activity.

The examination of Table 2 also indicates that there is inverse relationship between absolute hardness and relative binding affinity. Although there is an inverse relationship but there is no sequential rise or fall. In order to provide sequential relationship we divided the set into two subgroups—A and B. In Subgroup A, compounds **1**, **3**, **4** and **8** and in Subgroup B, compounds **6**, **7** and **9** show the sequential relationship very clearly. Compounds **2**, **5** and **10** do not follow the sequential trend.

2.2. Second Set

Second set of derivatives contains 12 compounds and their biological activity is shown in terms of androgenic potency.[19] The biological activity and the reactivity indices of these derivatives are given in Table 3. A close

Table 1. Containing 8 sets of testosterone derivatives with their observed biological activity

No.	Name of Compound	Relative binding affinity
First set of deriviatives containing 10 compounds and their biological activity in terms of relative binding affinity[18]		
01	1α-Methyldihydrotestosterone	0.03
02	19-Nortestosterone	0.40
03	Stanazolol	0.60
04	Metahnedienone	0.75
05	Fluoxymesterone	0.77
06	17α-methyltestosterone	0.85
07	Methyltrienolone	1.00
08	Oxymetholone	1.54
09	Methenolone	1.67
10	Ethylestrenol	2.00
Second set of derivatives containing 12 compounds and their biological activity in terms of androgenic potency (19)		
		Androgenic potency
11	17β-Hydroxy,17α-methyl-5α-androst-1-en-3-one	25
12	17β-Hydroxy-5α-androst-1-en-3-one	100
13	17β-Hydroxy,17α-ethyl-5α-androst-1-en-3-one	2
14	17β-Hydroxy,2-methyl-5α-androst-1-en-3-one	50
15	17β-Hydroxy,2,17α-dimethyl-5α-androst-1-en-3-one	25
16	17β-Hydroxy,2-methyl,17α-ethyl-5α-androst-1-en-3-one	1
17	5α-Androst-1-en-3β,17β-diol	50
18	17α-Methyl-5α-androst-1-ene-3β,17β-diol	100
19	17α-Ethyl-5α-androst-1-ene-3β,17β-diol	5
20	17β-Hydroxy,6β-methyl-5α-androst-1-en-3-one	10
21	17β-Hydroxy,6β,17α-dimethyl-5α-androst-1-en-3-one	10
22	17β-Hydroxy,6β-methyl, 17α-ethyl-5α-androst-1-en-3-one	1.5
Third set of derivatives containing 15 compounds and their biological activity in terms of relative androgenic activity (20)		
		Relative androgenic activity
23	Testosterone	0.4
06	7α-Methyl testosterone	0.4
24	17α-Methyl testosterone	0.4
25	7α,17α-Dimethyl testosterone	0.6
26	5α-Dihydrotestosterone	1.0
27	7α-Methyl-5α-dihydrotestosterone	1.2
28	7α,17α-Dimethyl-5α-dihydrotestosterone	1.5
29	17α-Methyl-5α-dihydrotestosterone	0.8
02	19-Nor testosterone	0.2
30	7α-Methyl-19-nor testosterone	2.6
31	17α-Methyl-19-nor testosterone	0.3
32	19-Nor dihydrotestosterone	0.1
33	7α-Methyl-19-nor-5α-dihydro testosterone	0.3
34	7α,17α-Dimethyl-19-nor-5α-dihydro testosterone	0.3
35	7α,17α-Dimethyl-19-nor- testosterone	5.7
Fourth set of derivatives containing 12 compounds and their biological activity in terms of therapeutic index (21)		
		Therapeutic index
36	Testosterone propionate	0.26
37	Methylandrostenediol	0.28
38	19-Nor-17α-ethyl testosterone	0.55
39	4-Fluro testosterone acetate	0.58
40	4-Chloro testosterone acetate	0.68
41	4-Chloro testosterone propionate	0.56
42	4-Bromo testosterone	0.34
43	4-Chloro-17β-hydroxy testosterone acetate	0.39
44	4- Hydroxy testosterone acetate	0.52
45	4-Chloro-19-nor testosterone acetate	1.13
46	4- Hydroxy-19-nor testosterone acetate	0.55
47	4-Chloro-17α-mehyl-19-nor testosterone	0.73
Fifth set of derivatives containing 21 compounds and their biological activity in terms of TeBG affinity (22, 23)		
		TeBG affinity
48	Aldosterone	−5.32
49	Androstanediol	−9.11
50	Androstenediol	−9.17
51	Androstenedione	−7.46
52	Androsterone	−7.14
53	Corticosterone	−6.34

(*continued on next page*)

Table 1 (*continued*)

No.	Name of Compound	Relative binding affinity
54	Cortisol	−6.20
55	Cortisone	−6.41
56	Dehydroepiandrosterone	−7.81
57	Deoxycorticosterone	−7.38
58	Deoxycortisol	−7.20
26	Dihydrotestosterone	−9.74
59	Estradiol	−8.83
60	Estriol	−6.63
61	Estrone	−8.17
62	Etiocholanolone	−6.14
63	Pregnenolone	−7.14
64	17-Hydroxy pregnenolone	−6.36
65	Progesterone	−6.94
66	17-Hydroxy progesterone	−6.99
23	Testosterone	−9.20
	Sixth set of derivatives containing nine compounds and their biological activity in terms of relative competition indices (24, 20)	
		Relative Competition Indices
67	5α-Androstane-3,17-dione	0
23	Testosterone	0.1
06	7α-Methyl testosterone	0.2
26	5α-Dihydro testosterone	1.0
27	7α-Methyl-5α-dihydro testosterone	0.4
02	19-Nor testosterone	0.9
31	17α-Methyl-19-nor testosterone	1.2
32	19-Nor dihydrotestosterone	0.5
33	7α-Methyl-19-nor-5α-dihydro testosterone	0.6
	Seventh set of derivatives containing six compounds and their biological activity in terms of binding affinity for rat ventral prostate receptor protein (24)	
		Binding affinity for rat ventral prostate receptor protein
06	7α-Methyl testosterone	4.2
26	5α-Dihydro testosterone	6.9
02	19-Nor testosterone	8.6
68	14-Dehydro-17α-methyl-19-nor testosterone	4.4
69	14-Dehydro-19-nor testosterone	5.9
70	14-Dehydro testosterone	5.0
	Eights set of derivatives containing 10 compounds and their biological activity in terms of myotrophic to androgenic potency in temporal (25)	
		Myotrophic to androgenic potency in temporal
71	3α,17β-Dihydroxy-5α-androstane	1.4
67	5α-Androstane-3,17-dione	1.3
72	17β-Hydroxy,17α-methyl-5α-androst-3-one	0.9
73	Androst-4-ene-3,17-dione	0.6
23	Testosterone	1.0
24	17α-Methyl testosterone	0.5
26	5α-Dihydro testosterone	1.5
56	Dehydroepiandrosterone	0.8
74	Epiandrosterone	0.7
75	17α-Methyl-5α-androstane-3α,17β-diol	1.3

look at this table indicates that addition of ethyl, methyl or ethyl and methyl group at any position in 17β-hydroxy-5α-androst-1-en-3-one decreases the androgenic potency. While replacement of 3-keto group by 3β-hydroxy group with an additional methyl group increases the androgenic potency. The discussion also indicates that there is a direct relationship between absolute hardness and androgenic potency of testosterone derivatives. We have divided the compounds of this table in two different subgroups-A and B. subgroup-A contains six compounds, and subgroup-B contains four compounds. If the relationship is examined in these two sets separately the sequence is also exhibited clearly. In Subgroup-A, compounds-16, 22, 13, 20, 21 and 18 and in Subgroup-B, compounds-11, 14, 17 and 12 show the direct relationship very clearly. Compounds-15 and 19 do not follow the trend.

2.3. Third Set

Third set of derivatives contains 15 compounds and their observed biological activity is shown in terms of

Table 2. Calculation of global parameters of first set of derivatives containing 10 compounds

No.	χ	η	A
Subgroup A			
01	4.85113	5.67494	0.03
03	3.79732	4.92248	0.6
04	5.329455	4.854215	0.75
08	4.644895	4.854175	1.54
Subgroup B			
06	4.82809	5.61455	0.85
07	5.199665	5.021585	1
09	5.099895	4.995765	1.67

η is absolute hardness, χ is electronegativity and A is observed biological activity in terms of ratio of Relative binding affinities for rat skeletal muscle and rat prostate. The RBA value was as competitors for the receptor binding of Methyltrienolone in cytosol from rat skeletal muscle and rat prostate and calculated from logit-log plots.[18]

Table 3. Calculation of global parameters of second set of derivatives containing 12 compounds

No.	χ	η	A
Subgroup A			
16	4.71756	4.02969	1
22	4.844341	4.09157	1.5
13	5.245165	5.158005	2
20	5.276145	5.174015	10
21	5.280445	5.174236	10
18	4.423925	5.468085	100
Subgroup-B			
11	5.647085	4.711485	25
14	5.08136	5.02631	50
17	4.044945	5.101615	50
12	5.26146	5.15861	100

η is absolute hardness, χ is electronegativity and A is observed biological activity in term of Androgenic potency. Androgenic potency is percent of activity of testosterone propionate and was determined from the minimal levels at which significant increases in seminal vesicle or levator ani muscle weights were obtained.[19]

relative androgenic activity.[20] The activities along with reactivity indices are given in Table 4. Examination of this table shows that the biological activity is inversely proportional to absolute hardness. It is further observed that the addition of 17α-methyl group, 7α-methyl group and 4–5 double bond in 19-nor dihydrotestosterone always increases the activity. The inverse relationship can be better represented if the compounds of the Table 4 are divided into two subgroup—A and B. Subgroup A includes the compounds-**32**, **33**, **34**, **23**, **06**, **24**, **25** and **30** and Subgroup B includes compounds **26**, **27** and **35**. Compounds **02**, **31**, **28** and **29** do not follow the sequential relationship.

2.4. Fourth Set

Fourth set of derivatives contains 12 compounds and their observed biological activity is in terms of therapeutic index.[21] The activities along with reactivity indices are given in Table 5. A close look at this table indicates inverse relationship of activity with absolute hardness. The QSAR of various compounds of this set indicates that addition of 17α-methyl group decreases the therapeutic index and removal of 19-methyl group increases the therapeutic index. The presence of 4-chloro group increases while addition of 11β-hydroxy group decreases the therapeutic index. It is also obvious that the therapeutic index is inversely proportional to absolute hardness. The inverse relationship can be sequentially demonstrated if we divide the compounds of Table 5 in two subgroups—A and B. In Subgroup A, the compounds **36**, **38**, **46**, **40**, **47** and **45** and in Subgroup B, compounds **37**, **42**, **43** and **44** are included for better representation of relationship. Compounds **41** and **39** do not follow the trend.

Table 4. Calculation of global parameters of third set of derivatives containing 15 compounds

	Subgroup-A		
No.	χ	η	A
Subgroup A			
32	4.842175	5.669855	0.1
33	4.848035	5.663955	0.3
34	4.839425	5.663475	0.3
23	5.08402	4.98521	0.4
06	5.06769	4.98425	0.4
24	5.057306	4.983285	0.4
25	5.04855	4.982981	0.6
30	5.039875	4.961685	2.6
Subgroup B			
26	4.82193	5.65811	1
27	4.805115	5.655255	1.2
35	5.01999	4.960161	5.7

η is absolute hardness, χ is electronegativity and A is observed biological activity in terms of Relative androgenic activity and were calculated by the results with 5α-dihydrotestosterone taken as 1.0. The test steroids were injected subcutaniously into castrated rats daily for seven days and the wet weights of the ventral prostate were compared[20]

2.5. Fifth Set

The fifth set of derivatives has 21 compounds, their observed biological activity is shown in terms of TeBG affinity.[22,23] The activities along with reactivity indices are given in Table 6. A reference to the table indicates direct relationship between absolute hardness and biological activity. It is also observed that addition of 17α-hydroxy group increases while addition of 4–5 or 5–6 double bond decreases the TeBG affinity. Replacement of 17β-hydroxy group by 17-ketone group increases the TeBG affinity. Table 6 also indicates that there is an inverse relationship between absolute hardness and TeBG affinity. The relationship can be shown in sequence also, if the compounds of Table 6 are placed in two subgroups A and B. In Subgroup A, the compounds **26**, **49**, **56**, **57**, **58**, **55**, **53**, **54** and **48** and in Subgroup B, compounds **50**, **63**, **65** and **60** are included for sequential representation. Compounds **51**, **52**, **59**, **61**, **62**, **64**, **66** and **23** do not follow the sequential trend.

Table 5. Calculation of global parameters of forth set of derivatives containing 12 compounds

No.	χ	η	A
Subgroup A			
36	5.138775	4.994685	0.3
38	5.063335	4.961845	0.55
46	4.723921	4.62534	0.6
40	4.95226	4.57517	0.7
47	4.89323	4.56062	0.7
45	4.879705	4.559175	1.1
Subgroup B			
37	4.30599	5.28762	0.28
42	5.17029	4.804691	0.34
43	4.8114	4.59367	0.39
44	4.806515	4.542405	0.52

η is absolute hardness, χ is electronegativity and A is observed biological activity in term of Therapeutic index. Myotrophic and androgenic activity for levator ani muscle and ventral prostrate were determined by using groups of seven or more previously castrated albino rats weighing 30–40 g. The steroids were either prepared in oil or as aqueous suspension with 0.5% carboxymethyl cellulose, 0.4% Tween 80, 09% benzyl alcohol and physiological salt solution are injected subcutaniously daily for seven days. Twenty-four h after last injection the animal were autopsied and levator ani muscle, ventral prostate and seminal vesicle were removed and their wet weight recorded. The therapeutic index is ratio of levator ani muscle and ventral prostate.[21]

Table 6. Calculation of global parameters of fifth set of derivatives containing 21 compounds

No.	χ	η	A
Subgroup A			
26	4.82193	5.65811	−9.7
49	5.277875	5.277875	−9.1
56	4.41238	5.22355	−7.8
57	5.175465	5.040375	−7.4
58	5.093291	5.03942	−7.2
55	5.30929	5.02899	−6.4
53	5.120166	5.028895	−6.3
54	5.073545	5.017915	−6.2
48	5.202055	5.005555	−5.3
Subgroup B			
50	4.26343	5.20307	−9.2
63	4.368275	5.176035	−7.2
65	5.136465	5.004265	−6.9
60	4.27823	4.612901	−6.6

η is absolute hardness, χ is electronegativity and A is observed biological activity in terms of testosterone binding globulin (TeBG) affinity. The binding affinity of 21 endogenous steroids for TeBG was determined under equilibrium conditions using a solid phase method at physiological pH and temperature.[22–23,29]

2.6. Sixth Set

The sixth set has nine compounds, their biological activity has been presented in terms of relative competition indices.[24,20] The biological activities along with reactivity indices are given in Table 7. Table 7 indicates that biological activity and absolute hardness are inversely related. The QSAR shows that addition of 7α-methyl group always increases the androgenicity while removal of 19-methyl group always decreases the androgenicity. In case of addition of 4-5 double bond

Table 7. Calculation of global parameters of sixth set of derivatives containing nine compounds

No.	χ	η	A
Subgroup A			
67	4.82809	5.61455	0
23	5.08402	4.98521	0.1
06	5.06769	4.98425	0.2
02	5.04687	4.958335	0.9
31	5.01739	4.956395	1.2
Subgroup B			
32	4.84218	5.669855	0.5
33	4.84804	5.663955	0.6
26	4.82193	5.65811	1

η is absolute hardness, χ is electronegativity and A is observed biological activity in terms of relative competition indices (RCI) and was calculated by receptor binding affinity of compounds and receptor binding affinity of DHT (RCI = A-comp/A-DHT).[24,20]

the androgenicity increase when any additional methyl group is not present in 5α-dihydrotestosterone nucleus. Examination of Table 7 also indicates that there is inverse relationship between androgenicity and absolute hardness. In order to provide a sequential relationship the compounds of Table 7 are divided in two subgroup-A and B. In Subgroup A, compounds **67**, **23**, **06**, **02** and **31** and in Subgroup B, compounds **32**, **33** and **26** show this inverse relationship very clearly. Compounds **27** do not follow the sequence.

2.7. Seventh Set

The seventh set has six compounds, their biological activity has been presented in terms of binding affinity for rat ventral prostate receptor protein.[24] The activities along with reactivity indices are given in Table 8. This table indicates that there is direct relationship between absolute hardness and biological activity. The QSAR shows that the addition of 14–15 double bond decreases while removal of 19-methyl group increases the affinity. Addition of 7-methyl group also decreases while addition of 4-5 double bond increases the affinity. A reference to Table 8 shows that there is direct relationship between absolute hardness and affinity. Compounds **06** and **02** do not follow the sequential trend.

2.8. Eighth Set

This set has 10 derivatives and their biological activity is shown in terms of ratio of myotrophic to androgenic activity in temporal.[25] The activities along with reactivity indices are given in Table 9. Table 9 indicates direct relationship between biological activity and absolute hardness. The QSAR shows that addition of 4–5 or 5–6 double bond in 5α-androstan nucleus always decreases the activity. It also shows that the addition of 17α-methyl group causes adverse effect on activity. The replacement of 17-ketone group by 17β-hydroxy group increases the activity. The above discussion also shows that absolute hardness increases with increase of activity. The direct relationship is better demonstrated even in sequential manner if the compounds of this table are divided in two subgroups—A and B as shown in Table

Table 8. Calculation of global parameters of seventh set of derivatives containing six compounds

No.	χ	η	A
68	4.865	4.739485	4.4
70	4.87245	4.746095	5
69	4.88383	4.749285	5.9
26	4.82193	5.65811	6.9

η is absolute hardness, χ is electronegativity and A is observed biological activity in terms of rat ventral prostate receptor protein.[24]

Table 9. Calculation of Global Parameters of Eights Set of Derivatives Containing 10 Compounds

No.	χ	η	A
Subgroup A			
73	5.14874	4.98405	0.6
74	4.39463	5.243025	0.7
72	4.76234	5.610465	0.9
67	4.82809	5.61455	1.3
75	3.80377	6.69597	1.3
Subgroup B			
24	5.05731	4.983285	0.5
56	4.41238	5.22355	0.8
26	4.82193	5.65811	1.5

η is absolute hardness, χ is electronegativity and A is observed biological activity in terms of ratio of myotrophic to androgenic (seminal vesicle and prostate) activity of several C−19 steroids. The respective values are compared to those of testosterone set at 1.00.[25]

9. In Subgroup A, compounds **73**, **74**, **72**, **67** and **75** and in Subgroup B, compounds **24**, **56** and **26** show this direct relationship clearly. Compounds **71** and **23** do not follow the sequential trend.

3. Conclusion

From the above structure activity relationship discussion it is clear that the absolute hardness is an important parameter for QSAR study. On the basis of this we can build up theoretical base for demonstrating relative activity of compounds. Since the observed biological activities have been measured by different methods hence trends are also different. The direct or inverse relationship depends on the nature of the activity, which is elaborated at the bottom of each table. Besides absolute hardness (η), we have evaluated another DFT based reactivity indices electronegativity (χ), which is also included in Tables 2–9. Hardness provides a better relationship because of maximum hardness principle.[5,28] The close examination of tables shows that the trend of relationship between biological activity and electronegativity is not as clear as in case of absolute hardness.

4. Experimental

The biological activity of testosterone derivatives has been measured by eight different methods: Receptor Binding Affinity, Androgenic Potency, Relative Androgenic Activity, Myotrophic Potency, TeBG Affinity, Androgenic Potency in Rat, Binding Affinity for Rat Ventral Prostate Receptor Protein and Androgenic Potency in Temporal.[18–25] The derivatives accordingly have been studied in eight sets. The name of all the derivatives are given in Table 1.

For QSAR prediction, the 3-D modeling and geometry optimization of all the compounds have been done with the help of PCMODEL software, using PM3 hamiltonian.[26] The MOPAC calculations have been performed with WINMOPAC 7.21 software, by applying keywords PM3 Charge = 0 Gnorm = 0.1, Bonds, Geo-OK, Vectors Density and all the values required for the determination of the value of absolute hardness and electronegativity have been obtained from this software by solving the equations given in theory and the result are reported in Tables 2–9.

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