Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry 12 (2004) 5533–5543
Bioorganic & Medicinal Chemistry

Electrophilicity index as a possible descriptor of biological activity

R. Parthasarathi,[a] V. Subramanian,[a,*] D. R. Roy[b] and P. K. Chattaraj[b,*]

[a]*Chemical Laboratory, Central Leather Research Institute, Adyar, Chennai 600 020, India*
[b]*Department of Chemistry, Indian Institute of Technology, Kharagpur 721 302, India*

Received 28 April 2004; revised 17 July 2004; accepted 10 August 2004
Available online 11 September 2004

Abstract—The purpose of this study is to probe the suitability of DFT based chemical reactivity parameter, electrophilicity index as a possible biological activity descriptor in the development of QSAR. Testosterone derivatives with activity described in terms of various biological activity parameters and the estrogen derivatives by relative binding affinity (RBA) values have been selected as model systems. The implications for the ability of electrophilicity to describe the biological activities are discussed. From the results it is possible to observe that electrophilicity index may be suitable to effectively describe the biological activity.

1. Introduction

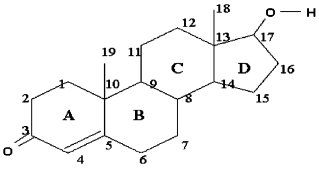
The quantitative structure activity relationship (QSAR) is a mathematical representation of biological activity in terms of structural descriptors of a series of homologue molecules.[1–6] The main objective of QSAR is to look for new molecules with required properties using chemical intuition and experience transformed into a mathematically quantified and computerized form.[6] Once a correlation is established, the structure of any number of compounds with desired properties can be predicted. Thus QSAR methodology saves resources and expedites the process of development of new molecules and drugs.[7] Success of QSAR in the development of new drug molecules and prediction of toxicity of molecules is highly appreciable.[1–6] In the development of QSAR, topology, thermodynamics, quantum chemistry, shape and electronic energy descriptors have been used.[6] Quantum chemical descriptors have been extensively used in QSAR studies in biochemistry. Numerous reviews have been published on the applications of quantum chemical descriptors in QSAR.[6] Recently the uses of quantum chemical descriptors in the development of QSAR have received attention due to reliability and versatility of prediction by these descriptors. In particular, net atomic charges, HOMO–LUMO energies, frontier orbital electron densities and superdelocalizabilities have been used to correlate with various biological activities.[6] Density functional theory based descriptors have found immense usefulness in the prediction of reactivity of atoms and molecules as well as site selectivity.[8–11] The resourcefulness of density functional descriptors in the development of QSAR has been recently reviewed by Chattaraj et al.[12] Chemical hardness (η), chemical potential (μ), polarizability (α) and softness are known as global reactivity descriptors. Fukui function (FF) and local softness are called local reactivity descriptors. Recently Parr et al.[13] have defined a new descriptor to quantify the global electrophilic power of the molecule as electrophilicity index (ω), which defines a quantitative classification of the global electrophilic nature of a molecule within a relative scale. The earlier works of Maynard et al.[14] have formed the strong foundation for the electrophilicity index, which provided the direct relationship between the rates of reaction and the ability to identify the function or capacity of an electrophile and the electrophilic power of the inhibitors. Using the properties of FF, more powerful descriptors of reactivity and site selectivity have been proposed by Chattaraj et al.[15] Subsequently, attempts have been made to probe the expediency of electrophilicity and other global quantities in the QSAR parlance. The usefulness of electrophilicity index in unraveling the toxicity of polychlorinated biphenyls[16,17] and benzidine[18] has been analyzed. It was found that electrophilicity is sufficient enough to describe the toxicity of those molecules. In order to obtain in detail the ability of electrophilicity to

Keywords: Electrophilicity; DFT; Biological activity descriptor; Testosterone; Estrogen; QSAR.
* Corresponding authors. Tel.: +91 04424411630; fax: +91 04424911589; e-mail addresses: subuchem@hotmail.com; pkc@chem.iitkgp.ernet.in

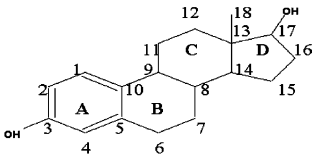
0968-0896/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2004.08.013

predict the biological activity, it is necessary to expand its areas of applications. In this regard several molecules with different biological activities have been chosen to probe the predictive ability of electrophilicity index.

The objective of the present study is to analyze the usefulness of electrophilicity in describing the biological activity of testosterone and estrogen derivatives.



Structure of Testosterone



Structure of Estrogen

Various testosterone derivatives with biological activity quantified in terms of relative binding affinity,[19] androgenic potency,[20] relative androgenic activity,[21] therapeutic index,[22] TeBG affinity,[23,24] relative competition indices,[21,25] binding affinity for rat ventral prostate receptor protein[25] and myotrophic to androgenic potency in temporal have been considered.[26] Biological activity of estrogen derivatives has been described in terms of RBA values.[2] These molecules have been chosen to establish the relationship between the biological activity and the respective electrophilicity index.

2. Theoretical background

2.1. Global and local reactivity descriptors

Based on density functional theory several global chemical reactivity descriptors of molecules such as hardness, chemical potential, softness, electronegativity and electrophilicity index as well as local reactivity descriptors as the Fukui function and the philicity have been defined.[13,15,27–29] It was found that stability of molecules is related to hardness.[29] Pauling[30] introduced the concept of electronegativity as the power of an atom in a molecule to attract electrons to itself. Hardness (η), chemical potential (μ) and electronegativity (χ) are defined as:[9]

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{V(\vec{r})} = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{V(\vec{r})} \tag{1}$$

$$\mu = \left[\frac{\partial E}{\partial N}\right]_{V(\vec{r})} \tag{2}$$

$$\chi = -\mu = -\left[\frac{\partial E}{\partial N}\right]_{V(\vec{r})} \tag{3}$$

where E and $V(\vec{r})$ are electronic energy and external potential of an N-electron system, respectively. Softness is a property of molecules that measures the extent of chemical reactivity. It is the reciprocal of hardness,

$$S = \frac{1}{\eta} \tag{4}$$

Using Koopmans' theorem for closed-shell molecules, η, μ and χ can be redefined as:

$$\eta \approx \frac{1}{2}(I - A) \approx \frac{1}{2}(\varepsilon_{\mathrm{LUMO}} - \varepsilon_{\mathrm{HOMO}}) \tag{5}$$

$$\mu \approx -\frac{1}{2}(I + A) \approx \frac{1}{2}(\varepsilon_{\mathrm{HOMO}} + \varepsilon_{\mathrm{LUMO}}) \tag{6}$$

$$\chi = \frac{I + A}{2} \tag{7}$$

$$I \approx -\varepsilon_{\mathrm{HOMO}} \quad \text{and} \quad A \approx -\varepsilon_{\mathrm{LUMO}} \tag{8}$$

where I and A are the ionization potential and electron affinity of the molecules, respectively. Electron affinity refers to the capability of a ligand to accept precisely one electron from a donor. However in many kinds of bonding viz. covalent, dative or hydrogen bonding, partial charge transfer takes place.

2.2. Electrophilicity index

Parr et al.[13] have proposed electrophilicity index as a measure of energy lowering due to maximal electron flow between donor and acceptor. They defined electrophilicity index (ω) as follows:

$$\omega = \frac{\mu^2}{2\eta} \tag{9}$$

When two molecules react, which one will act as an electrophile (nucleophile) will depend on, which has a higher (lower) electrophilicity index. This new reactivity index measures the stabilization in energy when the system acquires an additional electronic charge ΔN from the environment. The electrophilicity is a descriptor of reactivity that allows a quantitative classification of the global electrophilic nature of a molecule within a relative scale. The usefulness of this new reactivity quantity has been recently demonstrated in understanding the toxicity of various pollutants in terms of their reactivity and site selectivity.[16–18]

3. Computational details

Testosterone derivatives with biological activity characterized in terms of various activity parameters[19–26] and estrogen derivatives with RBA values[2] are considered. All the geometries of testosterone and estrogen derivatives are minimized using the *Gaussian 03*[31] package with semi-empirical AM1 Hamiltonian. Single point calculation has also been made at the B3LYP/6-31G* level with the AM1 geometry. Using the Koopmans' theorem for closed-shell system, the ionization potential (I) and electron affinity (A) are calculated using Eq. 8. Employing Eqs. 5, 6 and 9, all the global chemical reactivity descriptors are obtained. Standard linear regression analyses are performed to find the relationship between the various biological activity indices with the electrophilicity of testosterone and estrogen derivatives.

4. Results and discussion

Biological activity is the result of chosen molecular species interacting with a biological entity. In clinical studies, human organism represents biological entity and in pre-clinical trials, it is the experimental animals (in vivo) or experimental models (in vitro). Biological activity depends on the nature of compound (structure and physico-chemical properties), biological entity (species, sex, age, etc.) and mode of treatment (dose, route, etc.).[32] There exists the hierarchy in biological activities, which corresponds to the natural biological sequence. The biological activities can be defined and determined in organism, organ/tissue and cellular and molecular levels. If the molecule is found to have several activities at different levels, the activities of additional levels can be considered as the cause (mechanism).[32] Approaches to evaluate the compounds with similar activity are conceptually based on the idea that significant similarities in molecular structure and properties are responsible for the same biological activity. However, structure and activity can be obtained in many different ways/sources and it is difficult to generate general molecular representations that capture structure–activity relationships for diverse sets of molecules. Since there are several descriptors employed to build structure–activity relationship, the selection of appropriate descriptors for such generalized QSAR model is a mammoth task and in general a large number of descriptors are to be used to get a satisfactory correlation. In order to obtain a generalized model for QSAR, the structure–activity relationship has been developed in the present work for testosterone and estrogen derivatives with the help of a conceptually simpler single descriptor; namely the electrophilicity index.

In this study the linear relationship between eight different types (sets 1–8) of biological activity[19–26] and respective electrophilicity indices of various testosterone derivatives has been considered. The experimental and calculated (both AM1 and B3LYP) results for various cases are presented in Tables 1–8. The calculated

Table 1. Electrophilicity index of testosterone derivatives with their observed and calculated biological activity in terms of relative binding affinity (RBA)[19]

No	Set-1	Electrophilicity (AM1)	Electrophilicity (B3LYP)	Expt. RBA	Calculated RBA	
					AM1	B3LYP
1	19-Nortestosterone	0.092	0.099	0.40	0.689	0.735
2	Fluoxymesterone	0.090	0.096	0.77	0.754	0.819
3	17α-Methyltestosterone	0.091	0.100	0.85	0.701	0.732
4	Oxymetholone	0.076	0.080	1.54	1.314	1.159
5	Ethylestrenol	0.055	0.037	2.00	2.102	2.114

Table 2. Electrophilicity index of testosterone derivatives with their observed and calculated biological activity in terms of androgenic potency (AP)[20]

No	Set-2	Electrophilicity (AM1)	Electrophilicity (B3LYP)	Expt. AP	Calculated AP	
					AM1	B3LYP
1	17β-Hydroxy,17α-methyl-5α-androst-1-en-3-one	0.094	0.109	25	7.747	9.234
2	17β-Hydroxy,17α-ethyl-5α-androst-1-en-3-one	0.093	0.108	2	7.913	9.603
3	17β-Hydroxy,2,17α-dimethyl-5α-androst-1-en-3-one	0.090	0.106	25	16.758	12.185
4	17β-Hydroxy,2-methyl,17α-ethyl-5α-androst-1-en-3-one	0.090	0.106	1	16.894	12.515
5	5α-Androst-1-en-3β,17β-diol	0.065	0.049	50	74.359	74.878
6	17α-Methyl-5α-androst-1-ene-3β,17β-diol	0.064	0.049	100	74.518	74.867
7	17β-Hydroxy,6β-methyl-5α-androst-1-en-3-one	0.093	0.108	10	8.530	10.257
8	17β-Hydroxy,6β,17α-dimethyl-5α-androst-1-en-3-one	0.093	0.108	10	8.815	10.297
9	17β-Hydroxy,6β-methyl,17α-ethyl-5α-androst-1-en-3-one	0.093	0.107	1.5	8.964	10.665

Table 3. Electrophilicity index of testosterone derivatives with their observed and calculated biological activity in terms of relative androgenic activity (RAA)[21]

No	Set-3	Electrophilicity (AM1)	Electrophilicity (B3LYP)	Expt. RAA	Calculated RAA	
					AM1	B3LYP
1	Testosterone	0.092	0.100	0.4	0.585	−0.601
2	7α-Methyltestosterone	0.091	0.100	0.4	2.114	0.326
3	17α-Methyltestosterone	0.091	0.100	0.4	0.978	0.326
4	7α,17α-Dimethyltestosterone	0.091	0.100	0.6	2.525	0.844
5	19-Nortestosterone	0.092	0.099	0.2	0.218	2.154
6	7α-Methyl-19-nor-testosterone	0.091	0.099	2.6	1.718	2.712
7	7α,17α-Dimethyl-19-nor-testosterone	0.091	0.099	5.7	2.161	4.538

Table 4. Electrophilicity index of testosterone derivatives with their observed and calculated biological activity in terms of therapeutic index (TI)[22]

No	Set-4	Electrophilicity (AM1)	Electrophilicity (B3LYP)	Expt. TI	Calculated TI	
					AM1	B3LYP
1	Methylandrostenediol	0.060	0.040	0.28	0.274	0.277
2	19-Nor-17α-ethyltestosterone	0.092	0.099	0.55	0.561	0.530
3	4-Fluro testosterone acetate	0.100	0.118	0.58	0.641	0.613
4	4-Chloro testosterone acetate	0.099	0.124	0.68	0.630	0.636
5	4-Chloro testosterone propionate	0.096	0.118	0.56	0.600	0.613
6	4-Hydroxy testosterone acetate	0.093	0.113	0.52	0.570	0.590
7	4-Hydroxy-19-nor-testosterone acetate	0.093	0.112	0.55	0.571	0.586
8	4-Chloro-17α-methyl-19-nor-testosterone	0.096	0.116	0.73	0.603	0.604

Table 5. Electrophilicity index of testosterone derivatives with their observed and calculated biological activity in terms of TeBG affinity (TeBG)[23,24]

No	Set-5	Electrophilicity (AM1)	Electrophilicity (B3LYP)	Expt. TeBG	Calculated TeBG	
					AM1	B3LYP
1	Androstanediol	0.035	0.026	−9.11	−9.321	−9.240
2	Androstenediol	0.060	0.040	−9.17	−8.238	−8.782
3	Androsterone	0.068	0.070	−7.14	−7.891	−7.822
4	Corticosterone	0.091	0.098	−6.34	−6.874	−6.933
5	Cortisol	0.090	0.108	−6.20	−6.914	−6.596
6	Cortisone	0.096	0.110	−6.41	−6.621	−6.539
7	Dehydroepiandrosterone	0.064	0.072	−7.81	−8.053	−7.745
8	Deoxycorticosterone	0.093	0.103	−7.38	−6.774	−6.767
9	Deoxycortisol	0.085	0.106	−7.20	−7.141	−6.675
10	17β-Estradiol	0.070	0.050	−8.83	−7.782	−8.467
11	Estrone	0.074	0.068	−8.17	−7.625	−7.891
12	Pregnenolone	0.065	0.071	−7.14	−8.021	−7.803
13	Progesterone	0.092	0.101	−6.94	−6.816	−6.828
14	17-Hydroxy progesterone	0.093	0.103	−6.99	−6.758	−6.743

Table 6. Electrophilicity index of testosterone derivatives with their observed and calculated biological activity in terms of relative competition indices (RCI)[25,21]

No	Set-6	Electrophilicity (AM1)	Electrophilicity (B3LYP)	Expt. RCI	Calculated RCI	
					AM1	B3LYP
1	Testosterone	0.092	0.100	0.1	0.150	0.149
2	17α-Methyltestosterone	0.091	0.100	0.2	0.153	0.150
3	7α-Methyl-5α-dihydrotestosterone	0.070	0.069	0.4	0.507	0.499
4	19-Nor dihydrotestosterone	0.071	0.069	0.5	0.492	0.499
5	7α-Methyl-19-nor-5α-dihydrotestosterone	0.071	0.069	0.6	0.498	0.502

Table 7. Electrophilicity index of testosterone derivatives with their observed and calculated biological activity in terms of binding affinity for rat ventral prostate receptor protein (BARVPRP)[25]

No	Set-7	Electrophilicity (AM1)	Electrophilicity (B3LYP)	Expt. BARVPRP	Calculated BARVPRP	
					AM1	B3LYP
1	17α-Methyltestosterone	0.091	0.100	4.2	4.533	4.927
2	5α-Dihydrotestosterone	0.071	0.069	6.9	6.949	6.852
3	14-Dehydro-17α-methyl-19-nor-testosterone	0.088	0.101	4.4	4.986	4.819
4	14-Dehydro-19-nor-testosterone	0.088	0.102	5.9	4.931	4.802

electrophilicity index of testosterone derivatives and their relationship with various biological activities have been presented in Figure 1. Respective correlation coefficients and the regression equations are inserted in the respective plots. In Figure 1, a–h represent the relationship between the electrophilicity using AM1 and plots i–p represent the electrophilicity index in B3LYP/6-31G* method with relative binding affinity, androgenic

Table 8. Electrophilicity index of testosterone derivatives with their observed and calculated biological activity in terms of myotrophic to androgenic potency in temporal (MAPT)[26]

No	Set-8	Electrophilicity (AM1)	Electrophilicity (B3LYP)	Expt. MAPT	Calculated MAPT	
					AM1	B3LYP
1	3α,17β-Dihydroxy-5α-androstane	0.034	0.028	1.4	1.318	1.321
2	17β-Hydroxy-17α-methyl-5α-androst-3-one	0.071	0.069	0.9	0.815	0.877
3	Androst-4-ene-3,17-dione	0.095	0.107	0.6	0.486	0.465
4	17α-Methyltestosterone	0.091	0.100	0.5	0.535	0.545
5	Dehydroepiandrosterone	0.064	0.072	0.8	0.907	0.841
6	Epiandrosterone	0.069	0.072	0.7	0.840	0.849

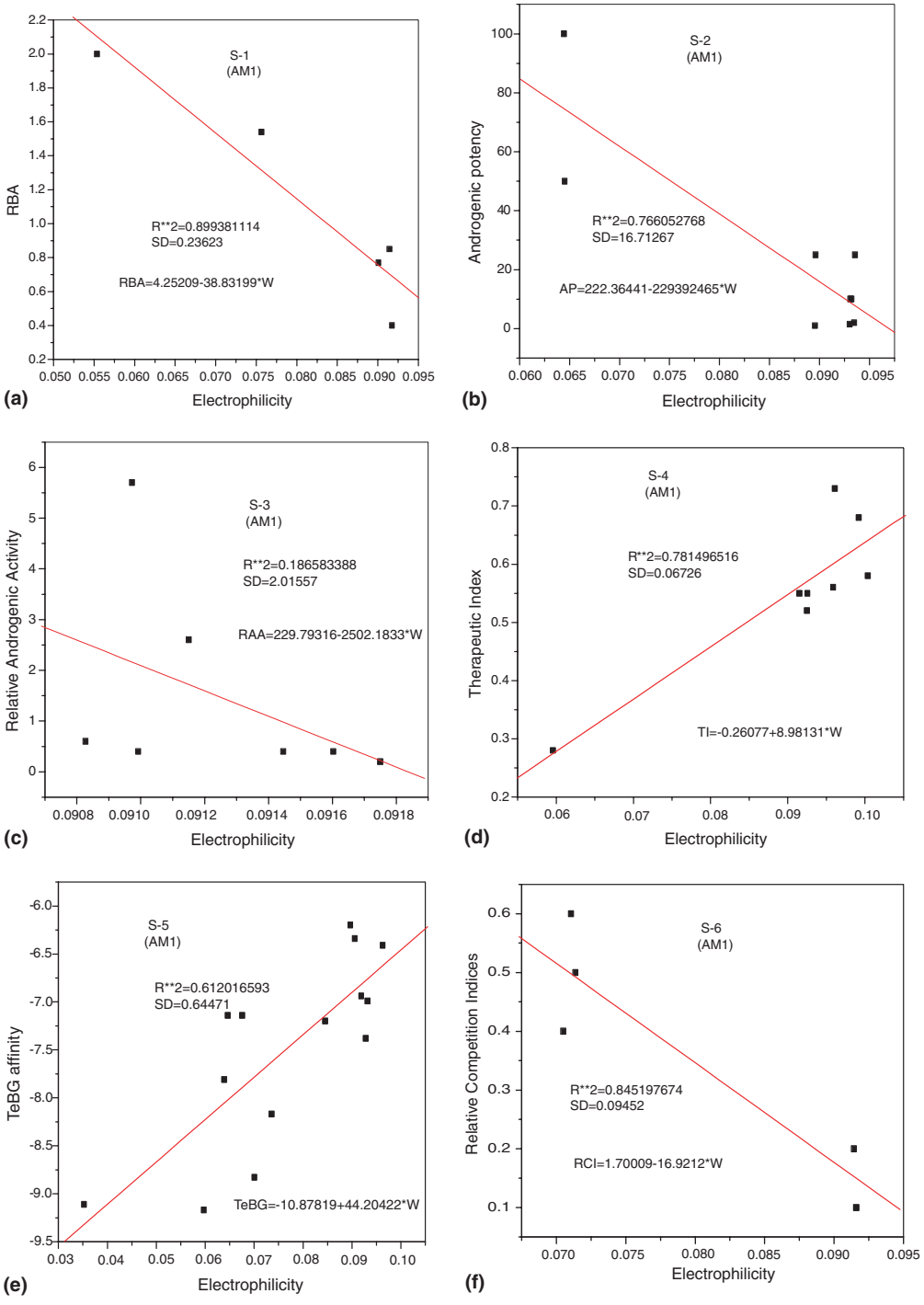


Figure 1. Relationship between various biological activities of testosterone derivatives with electrophilicity index.

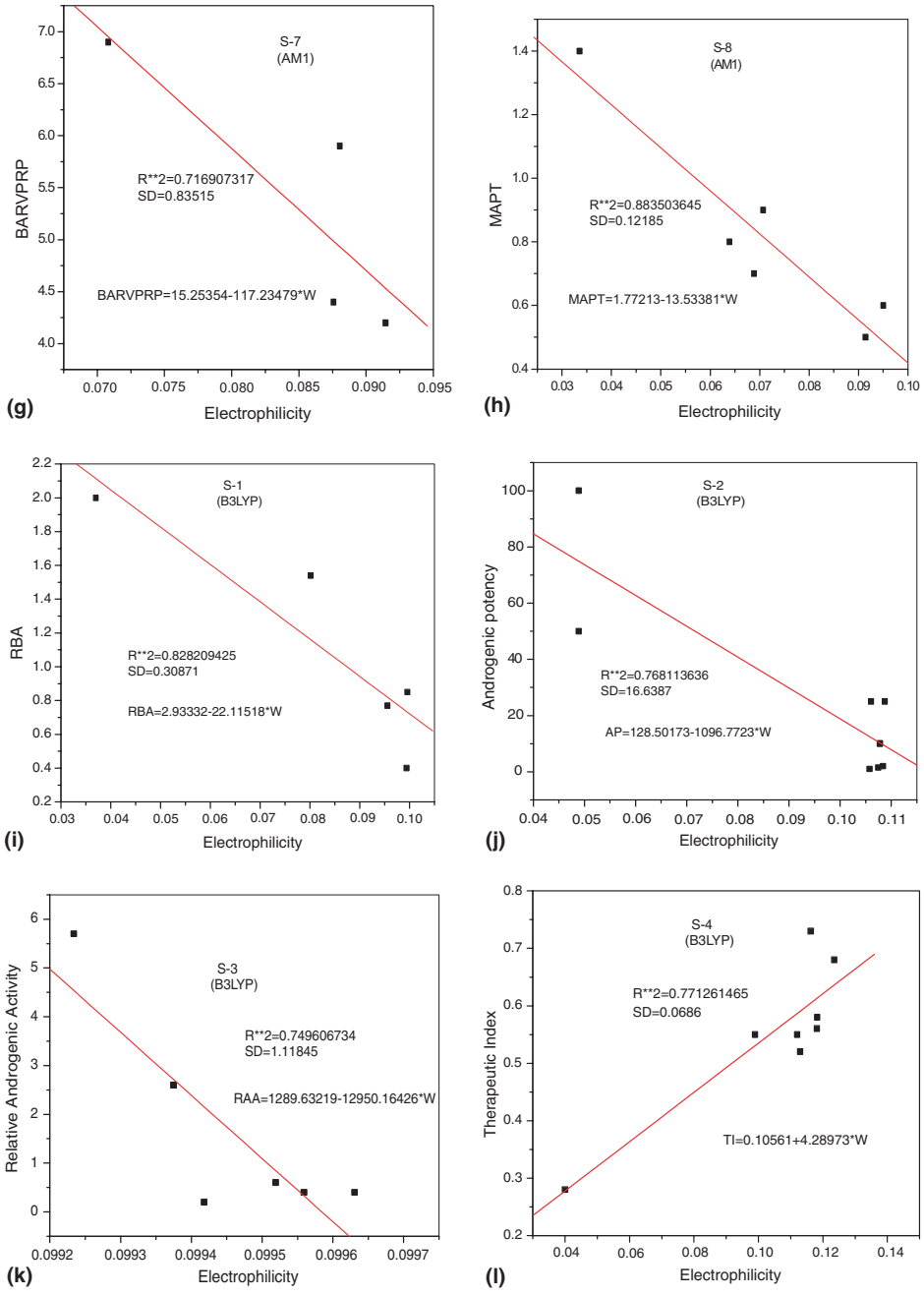


Figure 1 (*continued*)

potency, relative androgenic activity, therapeutic index, TeBG affinity, relative competition indices, binding affinity for rat ventral prostate receptor protein and myotrophic to androgenic potency in temporal, respectively.[19–26] It is clear from Figure 1 that the electrophilicity exhibits linear correlation with all the biological activities. For RBA, relative competition indices and myotrophic to androgenic potency in temporal activity have shown higher correlation with electrophilicity index as evident from the linear regression analysis. Generally toxins appear to act as electron acceptors in a charge transfer complex with a receptor in biological environment.[33,34] In this regard electron affinity is used as a descriptor to understand the toxicity. Although electron affinity could be able to establish the toxicity of several compounds, it is not possible to accurately describe the toxic potential of various chemical compounds. This has been evident from the recent study on the[3,4,33,35] tetrachlorodibenzo-*p*-dioxin using DFT.[36,37] The planarity and the electron affinity are known to be two important factors governing the toxicity of polychlorinated biphenyls and benzidine and their correlation with the electrophilicity has been analyzed in recent years.[16–18] Since the transfer of electrons (or a nucleophile in a general sense) between a toxin and a receptor is the crux of the toxicity, electron affinity,

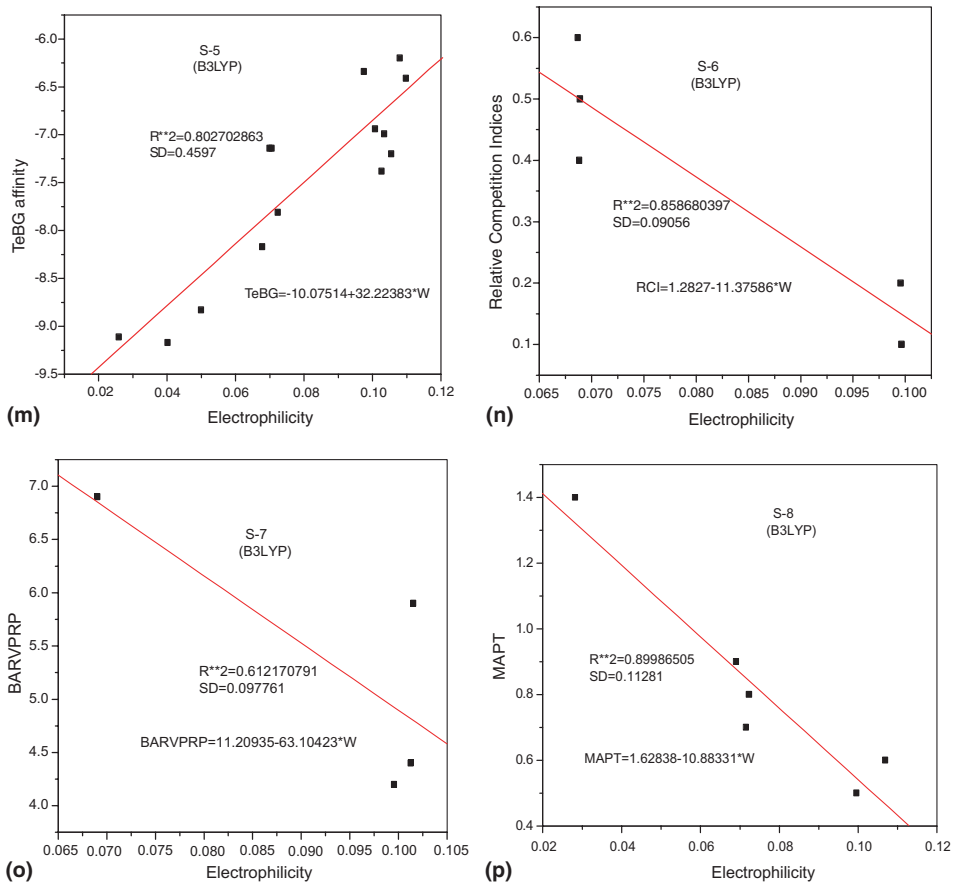


Figure 1 (*continued*)

Table 9. Electrophilicity index of 16α-substituted estradiol derivatives with their observed and calculated biological activity[2]

No	Set-1	Electrophilicity (AM1)	Electrophilicity (B3LYP)	Expt. RBA	Calculated RBA	
					AM1	B3LYP
1	H	0.07	0.05	2	1.696	1.989
2	CH_2Br	0.07	0.05	1.97	1.539	1.829
3	OH	0.071	0.051	1.28	0.899	1.515
4	$CH_2CH{=}CHCH_2OC_6H_5$	0.07	0.054	0.85	1.708	0.420
5	$CH_2CH_2CH_2CN$	0.072	0.054	−0.05	0.206	0.294

Table 10. Electrophilicity index of 17α-substituted estradiol derivatives with their observed and calculated biological activity[2]

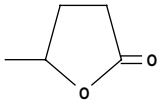
No	Set-2	Electrophilicity (AM1)	Electrophilicity (B3LYP)	Experimental RBA	Calculated RBA	
					AM1	B3LYP
1	$C{\equiv}CMe$	0.069	0.049	1.51	1.381	1.398
2	$CH_2CH{=}CH_2$	0.070	0.050	1.26	1.285	1.316
3	C_6H_5	0.072	0.054	1.08	0.984	0.977
4		0.074	0.055	0.92	0.713	0.854
5		0.071	0.052	0.90	1.074	1.105
6	$CH_2C_6H_5$	0.073	0.057	0.63	0.863	0.649

Table 11. Electrophilicity index of 11β-, 16α-, 17α-substituted estradiol derivatives with their observed and calculated biological activity[2]

No	Set-3			Electrophilicity (AM1)	Electrophilicity (B3LYP)	Experimental RBA	Calculated RBA	
	11β	16α	17α				AM1	B3LYP
1	Et	H	C≡CH	0.070	0.050	1.94	1.037	1.318
2	Et	OH	Me	0.071	0.051	1.93	1.478	1.744
3	Et	OH	C≡CH	0.071	0.051	1.90	1.560	1.880
4	H	OH	H	0.071	0.051	1.32	1.717	1.718
5	H	OH	C_6H_5	0.071	0.050	0.90	1.520	1.298
6	OMe	OH	C_6H_5	0.069	0.049	0.70	0.635	0.415
7	OMe	OH	C≡CH	0.069	0.049	0	0.742	0.317

Table 12. Electrophilicity index of 2, 4, 7α-, 11β-, 17α-substituted estradiol derivatives with their observed and calculated biological activity[2]

No	Set-4					Electrophilicity (AM1)	Electrophilicity (B3LYP)	Expt. RBA	Calculated RBA	
	2	4	7α	11β	17α				AM1	B3LYP
1	H	H	H	H	H	0.070	0.050	2	1.961	1.987
2	H	H	H	H	C≡CH	0.070	0.050	2	1.962	1.975
3	H	H	H	Et	H	0.070	0.050	1.89	1.965	1.944
4	H	F	H	H	$CH=CH_2$	0.079	0.052	1.87	1.835	1.843
5	H	F	Me	H	C≡CH	0.079	0.052	1.8	1.837	1.810

Table 13. Electrophilicity index of 2, 4, 7α-, 11β-, 16α-, 17α-substituted estradiol derivatives with their observed and calculated biological activity[2]

No	Set-5						Electrophilicity (AM1)	Electrophilicity (B3LYP)[a]	Expt. RBA	Calculated RBA	
	2	4	7α	11β	16α	17α				AM1	B3LYP
1	H	H	H	H	I	H	0.08	0.06	1.90	1.668	1.890
2	F	H	H	H	H	CH=CHI(*Z*)	0.08	0.06	1.73	1.737	1.746
3	H	H	H	H	H	CH=CHI(*Z*)	0.07	0.06	1.70	1.619	1.651
4	H	H	Me	H	H	CH=CHI(*Z*)	0.07	0.06	1.65	1.616	1.658
5	H	H	H	Et	H	CH=CHI(*E*)	0.07	0.06	1.63	1.608	1.569
6	H	H	H	H	H	CH=CHI(*E*)	0.07	0.05	1.60	1.609	1.545
7	H	H	Me	H	H	CH=CHI(*E*)	0.07	0.06	1.57	1.611	1.565
8	H	F	Me	H	H	CH=CHI(*E*)	0.08	0.06	1.56	1.706	1.643
9	H	H	H	OMe	H	CH=CHI(*E*)	0.07	0.05	1.44	1.606	1.513

[a] Molecules contains iodine atom are calculated at B3LYP/3-21G*.

planarity and electrophilicity have been turned out to be natural descriptors of the toxic nature of these compounds. For biological activities, electrophilicity exhibits a satisfactory linear relationship[38] with correlation coefficient (R^2) ranging from 0.61 to 0.90. Although some variation exists in the relative androgenic activity correlation using AM1 level of calculation, B3LYP method shows better performance in terms of prediction of activities. Biological activities of many of these compounds are correlated with electronegativity and hardness.[39] Although electronegativity fails to correlate with the biological activity a meaningful correlation, albeit without any regression analysis, is obtained in terms of the hardness, which has been rationalized in the light of the maximum hardness principle.[29] It has been discussed in the previous QSAR studies that it is difficult to obtain SAR with any single property descriptor. However it is evident from the present study that electrophilicity index provides reliable relationship between various biological activities thereby enabling us to develop SAR based on electrophilicity index only.

In the case of estrogen derivatives (sets 1–5), SAR studies have been made between relative binding affinity (RBA)[2] and electrophilicity indices and the results for both AM1/B3LYP are presented in Tables 9–13. The linear regression analyses are shown in Figure 2. It is understandable from the results that it is possible to obtain meaningful SAR for estrogen derivatives by describing the activity with the help of electrophilicity index. It can be noted from the results (B3LYP) that R^2-values for various cases range between 0.73 and 0.87 thereby confirming the fact that the electrophilicity properly quantifies the biological activity. Although there is no one-to-one agreement between AM1 and B3LYP values, the B3LYP method in general provides better estimates of biological activity when compared to the corresponding AM1 values. It is important to note from all the tables and Figure 3 that the calculated

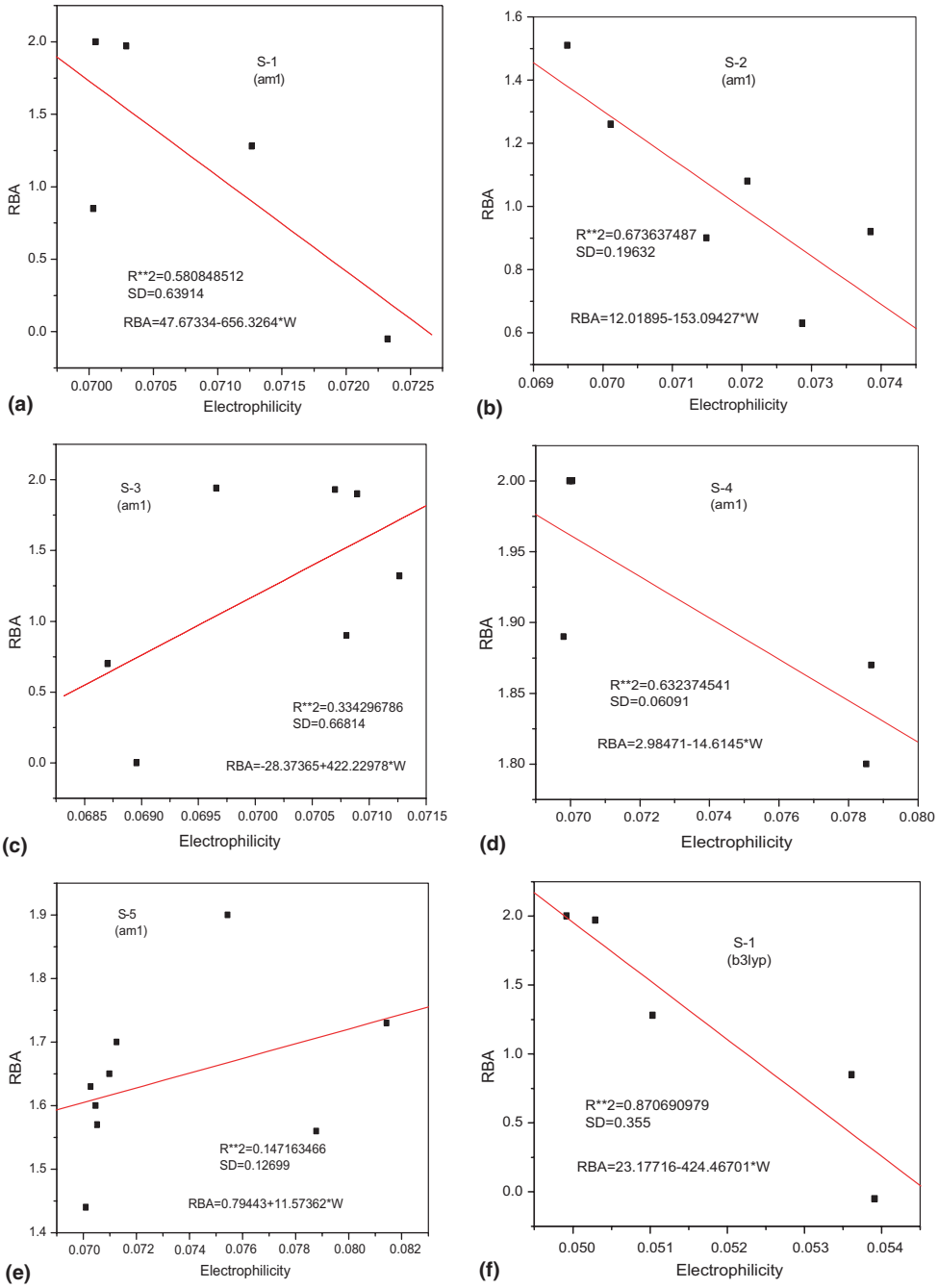


Figure 2. Relationship between RBA values of estrogen derivatives with electrophilicity index.

biological activities are in good agreement with the experimental biological activities. Results provide a reasonably good correlation with a single parameter and hence a compelling evidence that electrophilicity is a suitable descriptor of biological activity.

5. Conclusion

It is evident from the present investigation that electrophilicity index properly describes the biological activity of testosterone and estrogen derivatives. It is known from the earlier studies on QSAR that it is necessary to use various possible combinations of structural descriptors. In this context, the SAR based on electrophilicity is shown to be promising. Since the electrophilicity index is a chemical reactivity descriptor and its definition has strong foundation from the density functional theory, it is appropriate to make use of this descriptor in the QSAR parlance and the usefulness of such application is evident from the present investigation. Results emanated from this study show that the electrophilicity can be used as a descriptor of biological activity.

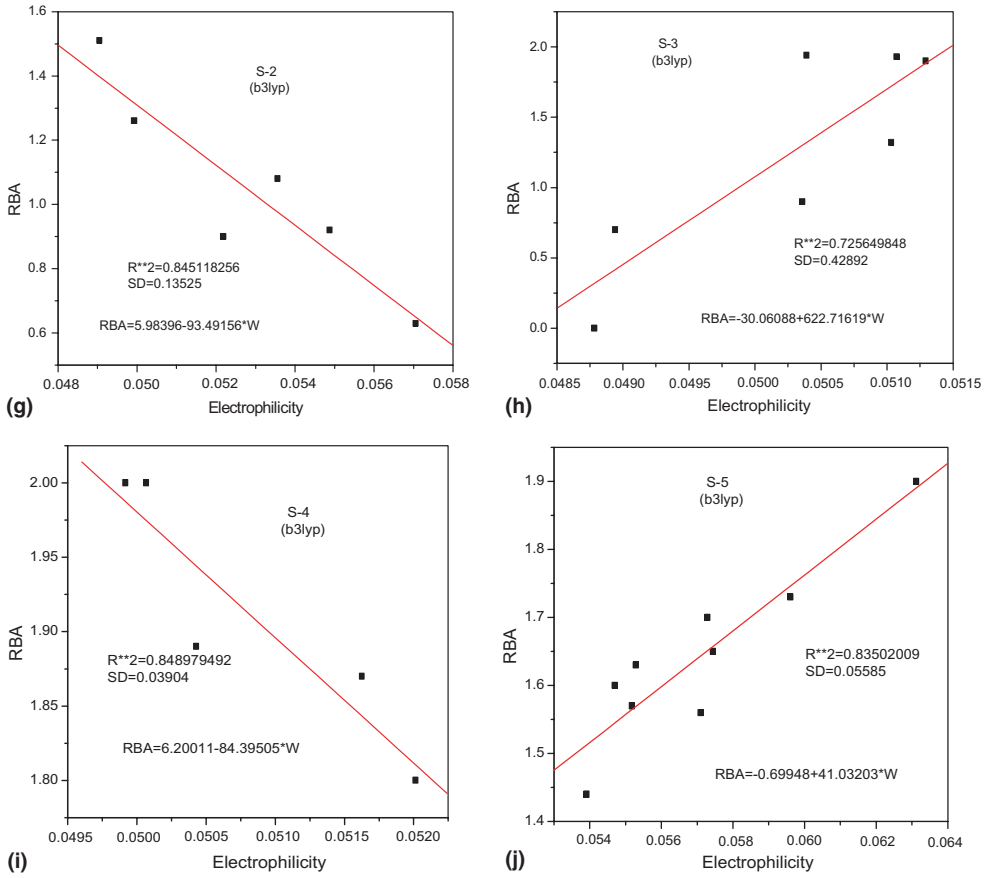


Figure 2 (*continued*)

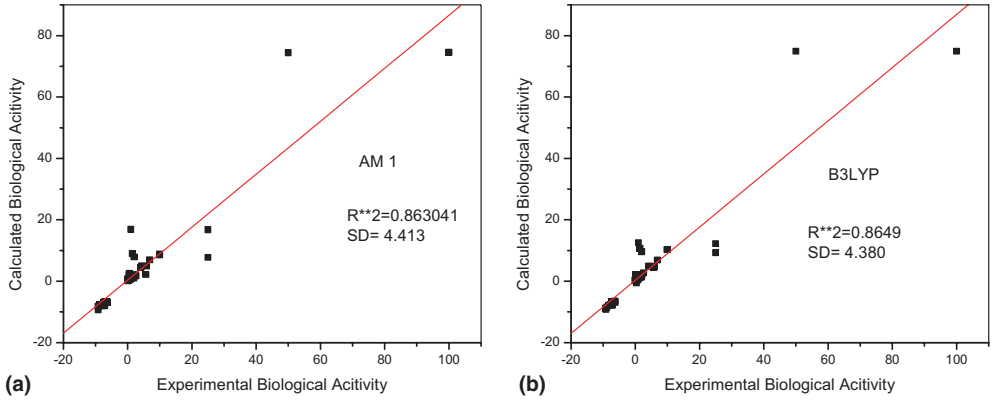


Figure 3. Relationship between calculated biological activity with experimental biological activity: (a) AM1 level and (b) B3LYP level.

Acknowledgements

We are thankful to CSIR, New Delhi for financial assistance and the referee for constructive criticism.

References and notes

1. Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
2. Gao, H.; Katzenellenbogen, J. A.; Garg, R.; Hansch, C. *Chem. Rev.* **1999**, *99*, 723.
3. Franke, R. *Theoretical Drug Design Methods*; Elsevier: Amsterdam, New York, 1984; p 115.
4. Gupta, S. P.; Singh, P.; Bindal, M. C. *Chem. Rev.* **1983**, *83*, 633.
5. Gupta, S. P. *Chem. Rev.* **1991**, *91*, 1109.
6. Karelson, M.; Lobanov, V. S.; Katritzky, A. R. *Chem. Rev.* **1996**, *96*, 1027.
7. Cronin, M. T. D. *Current Opinion in Drug Discovery and Development* **2000**, *3*, 292.
8. Parr, R. G. *Annu. Rev. Phys. Chem.* **1983**, *34*, 631.
9. Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: Oxford, UK, 1989.
10. Chermette, H. *J. Comput. Chem.* **1999**, *20*, 129.

11. Geerlings, P.; De Proft, F.; Langenaeker, W. *Chem. Rev.* **2003**, *103*, 1793.
12. Chattaraj, P. K.; Nath, S.; Maiti, B. Reactivity Descriptors. In *Computational Medicinal Chemistry for Drug Discovery*; Tollenaere, J., Bultinck, P., Winter, H. D., Langenaeker, W., Eds.; Marcel Dekker: New York, 2003, pp 295–322, Chapter 11.
13. Parr, R. G.; Szentpaly, L. V.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922.
14. Maynard, A. T.; Huang, M.; Rice, W. G.; Covell, D. G. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 11578.
15. Chattaraj, P. K.; Maiti, B.; Sarkar, U. *J. Phys. Chem. A* **2003**, *107*, 4973.
16. Parthasarathi, R.; Padmanabhan, J.; Subramanian, V.; Maiti, B.; Chattaraj, P. K. *J. Phys. Chem. A* **2003**, *107*, 10346; Thanikaivelan, P.; Subramanian, V.; Raghava Rao, J.; Nair, B. U. *Chem. Phys. Lett.* **2000**, *323*, 59; Parthasarathi, R.; Padmanabhan, J.; Elango, M.; Subramanian, V.; Chattaraj, P. K. *Chem. Phys. Lett.* **2004**, *394*, 225.
17. Parthasarathi, R.; Padmanabhan, J.; Subramanian, V.; Maiti, B.; Chattaraj, P. K. *Curr. Sci.* **2004**, *86*, 535.
18. Parthasarathi, R.; Padmanabhan, J.; Subramanian, V.; Sarkar, U.; Maiti, B.; Chattaraj, P. K. *Internet Electron J. Mol. Des.* **2003**, *2*, 798.
19. Saartok, T.; Dahlberg, E.; Gustafsson, J. A. *Endocrinology* **1984**, *114*, 2100.
20. Counsell, R. E.; Klimstra, P. D.; Colton, F. B. *Endocrinology* **1962**, *27*, 248.
21. Liao, S.; Liang, T.; Fang, S.; Castenada, E.; Shao, T. C. *J. Biol. Chem.* **1973**, *248*, 6154.
22. Sala, G.; Baldratti, G. *Proc. Soc. Exptl. Biol. Med. (N.Y.)* **1957**, *95*, 22.
23. Cramer, R. D., III; Patterson, D. E.; Bunse, J. D. *J. Am. Chem. Soc.* **1988**, *110*, 5959.
24. Good, A. C.; So, S. S.; Richards, W. G. *J. Med. Chem.* **1993**, *36*, 433.
25. Wolff, M. E. In *Burger's Medicinal Chemistry and Drug Discovery* In *Therapeutic Agents*; John Wiley & Sons: New York, 1995; Vol. 4, p 472.
26. Kochakian, C. D. *Anabolic-Androgenic Steroids*; Springer: Berlin, Heidelberg, New York, 1976.
27. Parr, R. G.; Donnelly, R. A.; Levy, M.; Palke, W. E. *J. Chem. Phys.* **1978**, *68*, 3801.
28. Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512.
29. Parr, R. G.; Chattaraj, P. K. *J. Am. Chem. Soc.* **1991**, *113*, 1854.
30. Pauling, L. *The Nature of the Chemical Bond*, 3rd ed.; Cornell University Press: Ithaca, New York, 1960.
31. *Gaussian 03*, Revision B.03; Gaussian, Inc.: Pittsburgh, PA, 2003.
32. Filimonov, D. A.; Poroikov, V. V. PASS: *Computerized Prediction of Biological Activity Spectra for Chemical Substances*. In *Bioactive Compound Design: Possibilities for Industrial Use*; BIOS Scientific: Oxford, 1996; pp 47–56.
33. Miller, G.; Sontum, S.; Glosby, D. G. *Bull. Environ. Contam. Toxicol.* **1977**, *18*, 611.
34. Cheney, B. V.; Timothy, T. *Int. J. Quantum Chem.* **1979**, *16*, 87.
35. Arulmozhiraja, S.; Selvin, P. C.; Fujii, T. *J. Phys. Chem. A* **2002**, *106*, 1765.
36. Arulmozhiraja, S.; Fujii, T.; Sato, G. *Mol. Phys.* **2002**, *100*, 423.
37. Arulmozhiraja, S.; Fujii, T.; Tokiwa, H. *J. Phys. Chem. A* **2000**, *104*, 7068.
38. Ravichandran, S. *QSAR*, Adv. Biomed. Comput. Center, NCI-Frederick, MD 21702 (06/10/2003).
39. Singh, P. P.; Srivastava, H. K.; Pasha, F. A. *Biorg. Med. Chem.* **2004**, *12*, 171.