CODEN IEJMAT *Internet Electronic Journal of Molecular Design* **2005**, *4*, 270–278 ISSN 1538–6414
BioChem Press http://www.biochempress.com

Inter*net* Electronic Journal of Molecular Design

April 2005, Volume 4, Number 4, Pages 270–278

Editor: Ovidiu Ivanciuc

Exploring Pharmacophore Patterns for Uterotrophic Activity of Bromotriphenylethylene Derivatives

Subhendu Mukherjee, Arup Mukherjee, and Achintya Saha

Department of Chemical Technology, University of Calcutta, 92 A.P.C. Road, Kolkata–700009, India

Received: March 19, 2004; Revised: August 6, 2004; Accepted: October 27, 2004; Published: April 30, 2005

Citation of the article:
S. Mukherjee, A. Mukherjee, and A. Saha, Exploring Pharmacophore Patterns for Uterotrophic Activity of Bromotriphenylethylene Derivatives, *Internet Electron. J. Mol. Des.* **2005**, *4*, 270–278, http://www.biochempress.com.

Inter*net* Electronic Journal of Molecular Design

BioChem Press
http://www.biochempress.com

Exploring Pharmacophore Patterns for Uterotrophic Activity of Bromotriphenylethylene Derivatives

Subhendu Mukherjee, Arup Mukherjee, and Achintya Saha *

Department of Chemical Technology, University of Calcutta, 92 A.P.C. Road, Kolkata–700009, India

Received: March 19, 2004; Revised: August 6, 2004; Accepted: October 27, 2004; Published: April 30, 2005

Internet Electron. J. Mol. Des. **2005**, *4* (4), 270–278

Abstract

Motivation. Taking into consideration the worth of developing non–steroidal estrogen analogs, the present study explores the pharmacophore of bromotriphenylethylenes for uterotrophic activity using physicochemical and topological parameters.

Method. Multiple linear regression techniques were employed in the modeling of experimental uterotrophic activity (*Log* UC) of bromotriphenylethylene derivatives. The statistical quality of the model has been judged by parameters such as correlation coefficient R, explained variance EV, predicted variance Q^2 and variance ratio F.

Results. A linear regression model with $R = 0.761$ that explained 50.523% uterotrophic activity of a set of 21 nos. of bromotriphenylethylene derivatives was obtained with E–State indices of 2 atoms, hydrophobic substituent constant and configuration of the bromine atom of the molecule. Considering the outliers of the QSAR model, a relationship was established that explained 85.340% variation in activity with $R = 0.939$.

Conclusions. This exploration concludes that phenyl ring attached to an ethylenic moiety, substitution by electron withdrawing group in the phenyl ring, α–configuration of the bromine atom and hydrophobicity of bromotriphenylethylenes might be essential for activity. The study also shows the efficacy of E–State indices and hydrophobicity factors in developing statistically acceptable model of consistent predictive ability that explains the electronic environment and topological states of different atoms in a molecule along with hydrophobicity contribution of substituents.

Keywords. Pharmacophore search; bromotriphenylethylenes; uterotrophic activity; E–State indices; hydrophobic factor.

Abbreviations and notations

π, Hydrophobic substituent constant	Pred., Predicted value
I_β, Indicator variable used to designate configuration of Br_{21}	Pred. Res., Predicted residual
Cal., Calculated value	QSAR, Quantitative structure–activity relationships
Cal. Res., Calculated residual	SERM, Selective Estrogen Receptor Modulators
E–State, Electrotoplogical state	UC, Uterine change
Obs., Observed value	

* Correspondence author; phone: 91–33–2350–8386; fax: 91–33–2351–9755; E–mail: achintya_saha@yahoo.com.

1 INTRODUCTION

Estrogen is responsible for growth and development of reproductive tract, breast and other secondary sex organs. The growth response produced in the uterus by estrogens is transitory, and the maintenance of such growth requires the hormone to be available more or less continuously. When estrogen is withdrawn atrophy of the uterus occurs [1]. Estrogens produce localized, selective and vivid responses in female reproductive tissues. The search for a biochemical mechanism of action of estrogen focused on these regions. It was shown that the uptake of estradiol is rapid, being retained to a high degree in the uterus and vagina [2]. Binding sites in the uterus exhibit both high affinity (K_D 10^{-11} to 10^{-10} M) and low capacity. These binding protein(s) have been identified in both the cytoplasmic and nuclear fractions of the target cells [3–4]. Estrogens produce their effects upon the mammalian uterus by increasing synthesis of RNA in target cells [4]. Antiestrogens hinder estrogen–stimulated activity in uterine wet weight in immature or ovariectomized rats. Most antiestrogens are structural derivatives of triphenylethylene [5] and are known as Selective Estrogen Receptor Modulators (SERM), as their activity depends on the target organ. These characteristics have generated interest in their potential clinical use, and current research focuses on the finding an ideal SERM [6]. At the sub cellular level, antiestrogens check the binding of ^{3}H estradiol to estrogen receptors. Studies with ^{3}H antiestrogens have confirmed the direct binding to estrogen receptors [7]. Binding to the active sites has been found to be stereospecific in nature [8] and there is also geometrical requirement for substituted triphenylethylenes to exert antiestrogenic action [9].

The antigonadotropic activity of triphenylethylenes is closely dependent upon maintaining integrity of the basic triphenylethylene structure [10]. Several triphenylethylenes having an NO_2, Cl or ethyl fragment as fourth substituent have been investigated as antifertility agents [9,11–12]. The present exploration is based on a series of triphenylethylenes with the hydrogen on the ethylene moiety replaced by bromine for uterotrophic activity [13]. An endeavor has been undertaken to investigate the electronic character and topological environment of atoms as well as the hydrophobicity contribution of different substituents responsible for pharmacophoric basis of these group of compounds.

Atomic features of molecules are the vital ingredients in significant drug–receptor interaction. According to Kier and Hall (1990), an atom in a molecule is part of a field of information with regard to electronic influences and topological surrounding [14–15]. Quantification of influence of this field on any atom can correlate to the biological performance of a molecule. This quantification is based upon three components:

(1) The attribute associated with each atom called the intrinsic state, which quantifies the organization, hybrid state, topology and hydride state of the atoms or groups in isolation,

(2) The quantification of the field effect that influences one atom on another within the molecule

and

(3) Distance or separation between any two atoms in a convenient matrix.

The overall contribution on any atom is articulated as the electrotoplogical state (E–State) [16], mathematically defined as

$$S_i = I_i + \Delta I_i \tag{1}$$

where

$$I = [(2/N)^2\delta^v + 1]/\delta \tag{2}$$

and

$$\Delta I_i = \sum_{i \neq j} (I_i - I_j)/r^2 \tag{3}$$

where I is derived from molecular connectivity calculations [17] and called the intrinsic state of an atom, ΔI_i is the perturbation factor, N is the principal quantum number, δ is the number of sigma electrons from the atom (excluding those bonding to hydrogen), δ^v is the number of valence electrons, i and j are serial numbers of atoms and r is the shortest graph distance between two atoms.

An outgrowth of the receptor concept of drug action is increased emphasis on the magnitude of physico–chemical properties of the molecules and relation of such properties to biological action. A consideration of such properties is fundamental in discussing several important aspects of the overall drug effect, *i.e*., accessibility of drugs to their site of action across various membranes. The properties must contribute favorably to absorption and distribution phenomena for increasing drug concentration at the active site [18]. Thus, hydrophobicity of drug molecules plays key role in getting transported to their active sites. When working on a set of derivatives, the hydrophobicity of the compounds in the series can be represented on a relative scale with the hydrophobic substituent constant, π [19]. The value for the substituent X is defined as:

$$\pi_X = \log P_{RX} - \log P_{RH} \tag{4}$$

where P_{RX} and P_{RH} are the partition coefficients of the derivatives and the parent compound respectively. The variable π_X expresses the variation in lipophilicity, which results when a substituent X replaces H in RH.

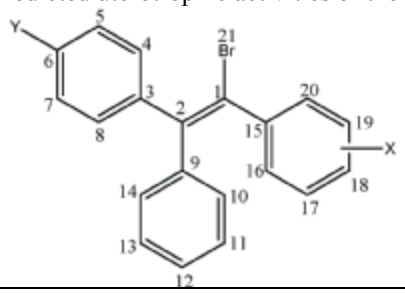
2 MATERIALS AND METHODS

2.1 Chemical and Statistical Data

In the present study a set of 21 molecules belonging to bromotriphenylethylenes (Table 1) exhibiting uterotrophic activity [13] were selected. Biological activity (estrogenic activity) was expressed in terms of logarithm of percentage change in uterus (*Log* UC) [13]. Statistical

parameters of the regression equation considered are: *r* or *R* (correlation coefficient), *EV* (explained variance), *F* (variance ratio), *df* (degree of freedom), *s* (standard error of estimate) and *AVRES* (average of absolute values of residuals). Leave–one–out cross–validation [20] was performed that generated *PRESS* (predictive residual sum of squares), *SDEP* (standard deviation of error of predictions), $Pres_{av}$ (average of absolute value of predicted residuals) and Q^2 (Cross–validated variance).

Table 1. Observed, calculated and predicted uterotrophic activities of the bromotriphenylethylene derivatives



Compound	Substituents			Biological activity (*Log* UC)				
	X	Y	Br_{21} configuration	Obs.[a]	Cal.[b]	Cal. Res.[c]	Pred.[d]	Pred. Res.[c]
1	*p*–Cl	H	*β*	1.544	1.674	–0.130	1.767	–0.223
2	*m*–CF3	H	*β*	2.140	2.114	0.026	2.109	0.031
3	*m*–F	H	*β*	1.898	1.883	0.015	1.878	0.020
4	*o*–F	H	*β*	2.340	–	–	1.976	0.364
5	*p*–F	H	*β*	2.117	–	–	1.824	0.293
6	*o*–F	CH_3O	Mix.	2.346	2.235	0.111	2.224	0.122
7	*o*–F	CH_3O	*α*	2.283	2.334	–0.051	2.347	–0.064
8	*p*–F	CH_3O	*α*	2.033	2.182	–0.149	2.219	–0.186
9	*p*–F	CH_3O	*β*	2.090	1.983	0.107	1.959	0.131
10	*p*–Cl	CH_3O	*α*	2.193	2.032	0.161	1.989	0.204
11	*p*–Cl	CH_3O	*β*	2.176	–	–	1.832	0.344
12	*m*–F	CH_3O	Mix.	2.117	2.141	–0.024	2.144	–0.027
13	*m*–F	CH_3O	*α*	2.250	2.241	0.009	2.239	0.011
14	*m*–F	$C_6H_5CH_2O$	*α*	2.391	–	–	2.073	0.318
15	*m*–F	$C_6H_5CH_2O$	*β*	1.919	1.873	0.046	1.854	0.065
16	*p*–F	$C_6H_5CH_2O$	*α*	1.973	2.014	–0.041	2.032	–0.059
17	*o*–F	$C_6H_5CH_2O$	*α*	2.193	2.166	0.027	2.152	0.041
18	*o*–F	$C_6H_5CH_2O$	*β*	1.914	1.966	–0.052	1.989	–0.075
19	*m*–F	HO	*β*	2.408	2.419	–0.011	2.423	–0.015
20	*p*–F	HO	*β*	2.360	2.361	–0.001	2.361	–0.001
21	*o*–F	HO	*β*	2.468	2.513	–0.045	2.536	–0.068

[a] Observed value [13]; [b] Calculated as per Eq. (8)
[c] Residual value; [d] Predicted from Eq. (8)
The common atoms have been numbered 1 through 21

2.2 Computer Software

The electrotopological states of various atoms were calculated using a JAVA2 based program *ETSA–CS* [21], which was standardized using established sets of data. The hydrophobicity of the molecules was computed with *CS Chem3D Pro 5.0* [22]. Statistical analysis was performed by *Statistica version 5*.0 [23] using standard and forward stepwise multiple regression methods. In the

present study, QSAR model generation was performed by correlation analysis.

Table 2. E–state and hydrophobic substituent constant values of bromotriphenylethylene derivatives

	E–State index (Common atoms 1–21)																	π
No.	C_1	C_2	C_3	C_4	C_5	C_6	C_9	C_{10}	C_{11}	C_{12}	C_{15}	C_{16}	C_{17}	C_{18}	C_{19}	C_{20}	Br_{21}	
1	–0.002	0.700	0.443	2.433	2.123	2.055	0.443	2.433	2.123	2.055	0.269	0.255	1.922	–1.695	1.922	2.255	5.225	1.220
2	–0.621	0.264	0.121	2.203	1.940	1.906	0.121	2.203	1.940	1.906	–0.673	1.771	1.160	0.576	–3.578	0.925	4.893	1.590
3	–0.283	0.522	0.321	2.346	2.057	2.003	0.321	2.346	2.057	2.003	–0.236	2.069	1.535	0.889	–5.581	1.237	5.060	0.820
4	–0.545	0.395	0.251	2.306	2.030	1.985	0.251	2.306	2.030	1.985	–0.868	1.823	1.781	1.475	0.949	–5.415	4.958	0.820
5	–0.157	0.592	0.364	2.373	2.075	2.016	0.364	2.373	2.075	2.016	0.026	1.823	0.949	–5.584	0.949	1.823	5.117	0.820
6	–0.590	0.334	0.160	2.222	1.985	–1.254	0.207	2.285	2.014	1.972	–0.901	1.806	1.768	1.464	0.936	–5.441	4.964	0.700
7	–0.590	0.334	0.160	2.222	1.985	–1.254	0.207	2.285	2.014	1.972	–0.901	1.806	1.768	1.464	0.936	–5.441	4.964	0.700
8	–0.201	0.530	0.273	2.288	2.030	–1.222	0.319	2.351	2.058	2.003	–0.008	1.806	0.936	–5.601	0.936	1.806	5.123	0.700
9	–0.201	0.530	0.273	2.288	2.030	–1.222	0.319	2.351	2.058	2.003	–0.008	1.806	0.936	–5.601	0.936	1.806	5.123	0.700
10	–0.046	0.638	0.352	2.349	2.078	–1.183	0.399	2.412	2.106	2.042	0.235	2.238	1.908	–1.712	1.908	2.238	5.231	1.100
11	–0.046	0.638	0.352	2.349	2.078	–1.183	0.399	2.412	2.106	2.042	0.235	2.238	1.908	–1.712	1.908	2.238	5.231	1.100
12	–0.328	0.460	0.230	2.262	2.011	–1.235	0.277	2.325	2.040	1.990	–0.269	2.052	1.522	0.878	–5.601	1.220	5.066	0.700
13	–0.328	0.460	0.230	2.262	2.011	–1.235	0.277	2.325	2.040	1.990	–0.269	2.052	1.522	0.878	–5.601	1.220	5.066	0.700
14	–0.335	0.452	0.222	2.307	2.088	–1.187	0.269	2.337	2.049	1.997	–0.276	2.062	1.530	0.884	–5.606	1.230	5.120	2.430
15	–0.335	0.452	0.222	2.307	2.088	–1.187	0.269	2.337	2.049	1.997	–0.276	2.062	1.530	0.884	–5.606	1.230	5.120	2.430
16	–0.209	0.522	0.265	2.333	2.106	–1.173	0.312	2.363	2.067	2.010	–0.014	1.816	0.944	–5.605	0.944	1.816	5.176	2.430
17	–0.597	0.326	0.152	2.266	2.062	–1.206	0.200	2.297	2.023	1.979	–0.908	1.816	1.775	1.470	0.944	–5.446	5.017	2.430
18	–0.597	0.326	0.152	2.266	2.062	–1.206	0.200	2.297	2.023	1.979	–0.908	1.816	1.775	1.470	0.944	–5.446	5.017	2.430
19	–0.391	0.369	0.087	1.984	1.387	–3.653	0.214	2.274	2.001	1.959	–0.315	2.013	1.491	0.853	–5.629	1.181	5.003	0.440
20	–0.264	0.439	0.130	2.011	1.405	–3.639	0.257	2.300	2.019	1.972	–0.053	1.767	0.905	–5.623	0.905	1.767	5.060	0.440
21	–0.652	0.243	0.017	1.944	1.360	–3.672	0.144	2.234	1.975	1.941	–0.947	1.767	1.737	1.439	0.905	–5.476	4.901	0.440

3 RESULTS AND DISCUSSION

In the present study QSAR models were developed using a set of 21 molecules. Biological activity (estrogenic activity) is expressed in terms of logarithm of percentage change in uterus (*Log* UC). The observed and calculated biological activity datasets of bromotriphenylethylene derivatives [13] are delineated in Table 1. Table 2 shows the various E–state (common atoms 1–21), and hydrophobic substituent constants of bromotriphenylethylene derivatives.

The important univariate relations developed for uterotrophic activity of bromotriphenylethylenes were with

1. E–state index of atom C_3 (S_3)

$$Log\ \mathrm{UC} = 4.734(\pm 0.672) - 1.147(\pm 0.298) S_3$$
$$r = 0.662,\ EV = 40.883\%,\ F = 14.831(df\ 1,19),\ AVRES = 0.130\ (n=21),\ PRESS = 0.660,\ Pres_{av} = 0.143,\ SDEP = 0.177,\ Q^2 = 0.319 \quad (5)$$

2. E–state index of atom C_4 (S_4)

$$Log\ \mathrm{UC} = 2.456(\pm 0.093) - 1.343(\pm 0.375) S_4$$
$$r = 0.635,\ EV = 37.159\%,\ F = 12.826(df\ 1,19),\ AVRES = 0.137\ (n=21),\ PRESS = 0.747,\ Pres_{av} = 0.154,\ SDEP = 0.189,\ Q^2 = 0.228 \quad (6)$$

S_3 and S_4 are highly intercorrelated ($|r| > 0.8$). Hence, a new S_{3+4} variable was introduced that defined the summation of E–state values of C_3 and C_4 atoms, which explains 42.351% variance in

the activity (r = 0.673). Additional parameters, I_β indicating configuration pattern to designate β (1) / α (0) / mixed (0.5) configuration of Br_{21} atom along with hydrophobic substituent constant (π) were introduced with S_{3+4} to obtain the best relation that explained 50.5% variance with 76.1% correlation.

$$Log\ \text{UC} = 3.925(\pm 0.398) - 0.642(\pm 0.160) S_{3+4} - 0.076(\pm 0.048)^{\#}\pi - 0.145(\pm 0.076)^{\#} I_\beta$$
$$R = 0.761,\ EV = 50.523\%,\ F = 7.808(df\ 3,17),\ AVRES = 0.104,\ s = 0.155,\ n = 21,\ PRESS = 0.632,\ Pres_{av} = 0.129,\ SDEP = 0.174,\ Q^2 = 0.347 \quad (7)$$

Compounds **4**, **5**, **11** and **14** behaved as outliers and excluded, the resultant equation was

$$Log\ \text{UC} = 4.413(\pm 0.257) - 0.849(\pm 0.104) S_{3+4} - 0.079(\pm 0.030)\pi - 0.200(\pm 0.048) I_\beta$$
$$R = 0.939,\ R^2 = 0.881,\ EV = 85.340\%,\ F = 32.037(df = 3,13),\ s = 0.089,\ n = 17,\ AVRES = 0.059,\ PRESS = 0.184,\ Pres_{av} = 0.079,\ SDEP = 0.104,\ Q^2 = 0.787 \quad (8)$$

The correlation matrix of Eq. (8) shows orthogonality: S_{3+4} vs. π / I_β = 0.301 / 0.268 and π vs. I_β=0.091.

The 95% confidence intervals are shown in parentheses and the F– values are significant at 99% confidence level. The regression constants for all relations are significant at 95% (except those superscripted with $^{\#}$). The independent variables used are not intercorrelated ($|r| < 0.3$). Statistically significant QSAR model is regarded as consistent when $Q^2 > 0.6$ [24]. Thus the Eq. (8) with cross–validated variances satisfying above condition was employed for predicting activities of the compounds.

This model generated through the studies brought into picture the importance of E–State indices of atoms C_3 and C_4, the hydrophobicity of the molecule and configuration of the bromine atom at C_1 of triphenylethylenes for uterotrophic activity. Aryl ring constitutes one of the crucial features of non–steroidal estrogen analogs, triphenylethylenes for binding to estrogen receptors [25,26]. From the regression analysis, it appears that atoms C_3 and C_4 of the molecule constitute substantial role for uterotrophic activity of these compounds. Worth of the phenyl ring fragment attached to the 2nd ethylenic carbon can thus be envisaged. The hydrophobic substituent constant in the model has a negative coefficient; therefore decrease in value of hydrophobicity parameter will actually have a tendency to increase the uterotrophic activity of the molecule. As such, substitution of the parent compound (hydrophobic) by moieties that imparts a measurable polarity to drug components (e.g., halogens, halogenated methyl, methoxy, hydroxy and nitro groups), should increase the uterotrophic activity of this series. This can be perceived among the existing set of compounds as substitutions with methoxy [4] and/or hydroxy [26] groups generally resulted in more active compounds. Binding to the active site has been found to be stereospecific in nature for substituted triphenylethylenes [9]. α–Bromo substitution at C_1 of ethylene moiety increases the activity since the indicator variable I_β used in the equation has negative coefficient.

4 CONCLUSIONS

In view of these observations, the present study could account for some of the fundamental structural requirements of bromotriphenylethylenes for uterotrophic activity. Eq. (8) with cross–validated variance of 0.787 could explain 85.3% variation in activity. A correlation of 93.9% has been achieved with a standard error of estimate 0.089 and all coefficients have been found to be significant at 95%. This work supports that a phenyl ring attached to C_2, substitution by an electron–withdrawing group in the phenyl ring, configuration of the bromine atom at C_1 and hydrophobicity [2] of the molecule could be important for estrogenic activity. Analogs of bromotriphenylethylenes have been found to be superior with regard to uterine growth stimulation in comparison to non–halogen substituted and iodo–substituted analogs [27]. Thus, the relation developed in this study can assist in design of further potent analogs taking bromotriphenylethylene as lead molecule. QSAR models have been established for diverse triphenylethylenes using CoMFA, Classical and Hologram QSAR approaches where correlations in the range 75–99% were achieved [28]. Structure–activity relationships have also been drawn for distinct triphenylethylenes with estrogen receptor ligands using MultiCASE expert system [29] where a minimum distance requirement between binding features along with importance of a phenolic hydroxyl group and hydrophobicity have been established with a correlation of 93.9% within datasets. Pharmacophore signals of diverse series of trifluoromethyl triphenylethylenes have been established through structure–activity relationship models with 91% correlation that explained importance of strong electronegative groups as fourth substituent on triphenylethylene [30]. In comparison this work demonstrates assembling of structure–activity relationship model through regressional analysis using E–state indices and hydrophobic substituent constant for defining pharmacophore of estrogenic triphenylethylenes, by which a statistically significant and superior relationship has been achieved with 94% correlation that explained 85% variance in activity. Distinct features of bromotriphenylethylenes for uterotrophic activity have also been identified in the process. The potential of E–state indices to converge attention on the fragment(s) of a series of congeneric bioactive molecules essential for activity makes them informative tools in QSAR studies.

5 REFERENCES

[1] E. V. Jensen, On the Mechanism of Estrogen action, *Perspect. Biol. Med.* **1962**, *6*, 47–59.

[2] R. W. Brueggemeier, D. D. Miller and J. T. Dalton, Estrogens, Progestins and Androgens; in: *Foye's Principles of Medicinal Chemistry*; Eds. D. A. Williams and T. L. Lemke, Lippincott Williams & Wilkins, Philadelphia, 2002, pp 692–695.

[3] E.V. Jensen, T. Suzuki and T. Kawashima, A Two–step Mechanism for the Interaction of Estradiol with Rat Uterus, *Proc. Natl. Acad. Sci.* **1968**, *59*, 632–638.

[4] L. Chan and B. W. O'Malley, Mechanism of Action of the Sex Steroid Hormones, *N. Engl. J. Med.* **1976**, *294*, 1322–1328,1372–1381,1430–1437.

[5] V. C. Jordan, Selective Estrogen Receptor Modulators; in: *Foye's Principles of Medicinal Chemistry*; Eds. D. A. Williams and T. L. Lemke, Lippincott Williams & Wilkins, Philadelphia, 2002, pp 1059–1061.
[6] A. B. González, J. A. Martínez, and I. C. Romero, Antiestrogens: Mechanism of Action and Clinical Applications, *Salud pública de méxico* **2001**, *43*, 1–7.
[7] V. C. Jordan, Biochemical Pharmacology of Antiestrogen Action, *Pharmacol. Rev.* **1984**, *36*, 245–276.
[8] W. P. Noteboom and J. Gorski, Stereospecific Binding of the Estrogens in the Rat Uterus, *Arch. Biochem. Biophys*. **1965**, *111*, 559–568.
[9] M. J. K. Harper and A. L. Walpole, Contrasting Endocrine Activities of *cis* and *trans* Isomers in a Series of Substituted Triphenylethylenes, *Nature* **1966**, *212*, 87.
[10] H. H. Fox, J. T. Gibas, H.L. Lee and A. Boris, Synthetic Antigonadotrophins. II, *J. Med. Chem*. **1964**, *7*, 790–792.
[11] M. R. Callantine, R. R. Humphrey, S. L. Lee, B. L. Windsor, N. H. Scholtin and O. P. O'Brien, Action of an Estrogen Antagonist on Reproductive Mechanisms in the Rat, *Endocrinology* **1966**, *79*, 153–167.
[12] D. E. Holtkamp, J. G. Greslin, G. A. Root and L. J. Lerner, Gonadotrophin Inhibiting and Anti–Fecundity Effects of Chloramiphene, *Proc. Soc. Exp. Biol. Med*. **1960**, *105*, 197–201.
[13] H. H. Fox, J. T. Gibas, H. L. Lee and A. Boris, Synthetic Antigonadotrophins. IV. Bromotriphenylethylenes, *J. Med. Chem*. **1965**, *8*, 415–416.
[14] L. B. Kier and L. H. Hall, An Electrotopological State Index for Atoms in Molecules, *Pharm. Res*. **1990**, *7*, 801–807.
[15] L. H. Hall, B. Mohney and L. B. Kier, The Electrotopological State: An Atom Index for QSAR, *Quant. Struct. – Act. Relat*. **1991**, *10*, 43–51.
[16] L. B. Kier, Atom–Level Descriptors for QSAR Analyzes; in: *Chemometric Methods in Molecular Design* (*Methods and Principles in Medicinal Chemistry*), Ed. H. V. de Waterbeemd, VCH Verlagsgesellschaft Mbh, Weinheim, 1995, pp 39–44.
[17] L. B. Kier and L. H. Hall, Derivation and Significance of Valence Molecular Connectivity, *J. Pharm. Sci*. **1981**, *70*, 583–589.
[18] J. Knittel and R. Zavod, Drug Design and Relationship of Functional Groups to Pharmacologic Activity; in: *Foye's Principles of Medicinal Chemistry*; Eds. D. A. Williams and T. L. Lemke, Lippincott Williams & Wilkins, Philadelphia, 2002, pp 37–55.
[19] H. V. de Waterbeemd and B. Testa, The Parameterization of Lipophilicity and Other Structural Properties in Drug Design; in: *Advances in Drug Research. Vol. 16*, Ed. B. Testa, Academic Press, New York, 1987, pp 85–225.
[20] S. Wold and L. Eriksson, Statistical Validation of QSAR Results; in: *Chemometric Methods in Molecular Design* (*Methods and Principles in Medicinal Chemistry*), Ed. H. V. de Waterbeemd, VCH Verlagsgesellschaft mbh, Weinheim, 1995, pp 312–318.
[21] ETSA–CS, 2003, Cyber–Mate, Srirampur, Hooghly, W. Bengal, INDIA.
[22] CS Chem3D Pro version 5.0, 1999, CambridgeSoft, Corp., Cambridge, US. http://www.camsoft.com
[23] Statistica, version 5.0, 1995, StatSoft, inc., Tulsa, US. http://www.statsoftinc.com
[24] S. Clementi and S. Wold, How to Choose the Proper Statistical Method; in: *Chemometric Methods in Molecular Design* (*Methods and Principles in Medicinal Chemistry*), Ed. H. V. de Waterbeemd, VCH Verlagsgesellschaft mbh: Weinheim, 1995, pp 325.
[25] M. Pons, A. Michel, A. Crastes de Paulet, J. Gilbert, J. F. Miquel, G. Précigoux, M. Hospital, T. Ojasoo and J. P. Raynaud, Influence of New Hydroxylated Triphenylethylene (TPE) Derivatives on Estradiol Binding to Uterine Cytosol, *J. Steroid Biochem*. **1984**, *20*, 137–145.
[26] V. C. Jordan, S. Mittal, B. Gosdon, R. Koch and M. E. Lieberman, Structure–Activity Relationships of Estrogens, *Environ. Health Perspect*. **1985**, *61*, 97–110.
[27] E. R. Desombre, R. C. Mease, J. Sanghavi, T. Singh, R. H. Seevers and A. Hughes. Estrogen Receptor Binding Affinity and Uterotrophic Activity of Triphenylhaloethylenes, *J. Steroid Biochem*. **1988**, *29*, 583–590.
[28] W. Tong, D. R. Lowis, R. Perkins, Y. Chen, W. J. Welsh, D. W. Goddette, T. W. Heritage and D. M. Sheehan. Evaluation of Quantitative Structure–Activity Relationship Methods for Large–Scale Prediction of Chemicals Binding to the Estrogen Receptor, *J. Chem. Inf. Comput. Sci*. **1998**, *38*, 669–677.
[29] G. Klopman and S. K. Chakravarti, Structure Activity Relationship Study of a Diverse Set of Estrogen Receptor Ligands (I) Using MultiCASE Expert System, *Chemosphere* **2003**, *51*, 445–459.
[30] S. Mukherjee, A. Mukherjee and A. Saha, Predicting Pharmacophore Signals for Post–Coital Antifertility Activity

of 1–Trifluoromethyl–1,2,2–Triphenylethylene Derivatives: A Statistical Approximation Using E–State Index, *Bioorg*. *Med*. *Chem*. *Lett*. **2004**, *14*, 897–900.

Biographies

Subhendu Mukherjee is PhD candidate in Chemical Technology at the University of Calcutta, Kolkata, India. He completed Master of Pharmacy degree with specialization in Pharmaceutical Chemistry from Birla Institute of Technology, Mesra, Ranchi, India. He has published and presented a number of research papers on pharmacology and drug design. His research interests are: molecular modeling, molecular pharmacology and natural products chemistry.

Arup Mukherjee is Professor of Chemical Technology and erstwhile Head of the Department of Chemical Technology, University of Calcutta. He has contributed extensively towards research on drug design and synthetic chemistry both in India and United States. He also published more than 30 research papers in the field of molecular modeling and synthetic chemistry. His recent research interests are development of novel synthetic schemes for bioactive polymers and non–steroidal estrogens and nanoparticle drug delivery system.

Achintya Saha is Senior Lecturer in Pharmaceutical & Fine Chemical Technology at the Department of Chemical Technology, University of Calcutta. He has published more than 25 research papers in the subject of molecular modeling, blood–lipid interaction studies on diverse contraceptives and biochemical pharmacology. He is a member of the board of Associate Editors (2003-06) of *Journal of the Indian Chemical Society*, India. His current research are molecular modeling and development of non–steroidal estrogen analogs.