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Predicting pharmacophore signals for post-coital antifertility activity of 1-trifluoromethyl-1,2,2-triphenylethylene derivatives: a statistical approximation using E-state index

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Abstract—Considering the worth of developing non-steroidal estrogen analogues, the present research explores the pharmacophores of 1-trifluoromethyl-1,2,2-triphenylethylenes (Fig. 1) for post-coital antifertility activity using electrotopological state atom (E-state) index. The study shows the efficacy of E-state index in developing statistically acceptable model, which explains the electronic environment and topological states of different atoms in a molecule. The exploration concluded that phenyl ring attached to an ethylenic moiety, *para* substitution by nucleophilic group on the phenyl ring and presence of strong electronegative group as the 4th substituent on the 1st carbon of the ethylenic moiety might be crucial for activity.

Estrogens are sex hormones that regulate the neuroendocrine actions involved in the control of ovulation, the cyclical preparation of the reproductive tract for fertilization and implantation.[1] The mechanism of estrogenic action is thought to act predominantly by regulating gene expression after binding with the estrogen receptor, the binding sites of which are located in the nucleus of target cells.[2] There are two isoforms of human estrogen receptors (α and β) with subtle differences in their respective character.[3] Antiestrogens are compounds that impede estrogen action. Most compounds in this category are structural derivatives of the non-steroidal estrogen analogues, triphenylethylenes. The pharmacology of nonsteroidal antiestrogens is extremely complicated and a unifying theory for their mechanism of action is challenging to define. Tamoxifen, a familiar nonsteroidal antiestrogenic triphenylethylene exhibits diverse actions in different species.[1,4] Studies with ^{3}H antiestrogens have identified a microsomal binding site with high affinity for the triphenylethylene-type antiestrogens.[5] The binding site has been found in all tissues (unlike the estrogen receptor, found only in estrogen targeted tissues), although the maximum concentration is found in the liver.[6] The high binding affinities of these group of compounds contribute to their long biological half-life.[4] Incidences of endometriosis, endometrial and breast cancer are elevated with the use of steroidal estrogens alone or in combination.[7,8] However, toremifene and tamoxifen have shown reduced prevalence of such side effects.[9]

Structural requirements have been defined for substituted triphenylethylenes to inhibit estrogen action.[10] Substitution of a basic side chain in the triphenylethylene nucleus yield estrogen receptor ligands with amplified antagonistic efficacy when the unsubstituted rings are in *trans* relationship.[11–13] Several estrogenic triphenylethylenes having an NO_2, Cl or ethyl fragment as a fourth substituent on the ethylene have been investigated as antifertility agents.[10,14,15] Numerous triphenylethylenes bearing CF_3 substituents in various positions on the aromatic rings have been prepared, but their estrogenicity was determined to be appreciably less than that of the equivalent unsubstituted compounds.[16] The present investigation is based on a series of triphenylethylenes with CF_3 groups placed directly on the ethylene moiety for post-coital antifertility activity.[17] An attempt has been undertaken to study the electronic character and topological environment of atoms responsible for pharmacophoric foundation of these group of compounds for post-coital antifertility activity using the electrotopological state atom (E-state) index developed by Kier and Hall.[18,19]

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Topological models directly give structural information to guide design of new molecules[20] and it has been demonstrated to predict 3-D structural parameters, as well.[21] Atom-level parts of molecules are the critical ingredients in meaningful drug-receptor interaction. An atom in a molecule is part of a field of information relating to electronic influences and topological environment.[18,19,22–24] This field produces change in the state of an atom or group, when changes in the molecule are introduced. By quantification of the influence of this field on any atom, one gets the opportunity to associate this influence to the biological performance of a molecule. This quantification is dependent upon three components:

(i) The attribute associated with each atom called the intrinsic state (I), which is quantitation of the composition, hybrid state, topology and hydride state of the atoms or groups in isolation. It is derived from molecular connectivity calculations[26] as, $I=[(2/N)^2\delta^v+1]\ /\ \delta$, where N is the principal quantum number, δ is the number of sigma electrons from the atom (excluding those bonding to hydrogen) and δ^v is the number of valence electrons.
(ii) The quantification of the field effect, which is the influence of one atom on another within the molecule. It is called the perturbation which is numerically expressed as, $\Delta I=\Sigma(I_i-I_j)$, where i and j are serial numbers of atoms.
(iii) Distance or separation between any two atoms in a convenient metric. This is expressed as the graph distance, r. The final expression of the field perturbation of the intrinsic state is considered as, $\Delta I=\Sigma(I_i-I_j)/r^2$.

The field effect, ΔI modifies the intrinsic state, producing a configuration or state value which is called the electrotopological state,[25] $S=I+\Delta I$.

Antifertility activities of 1-trifluoromethyl-1,2,2-triphenylethylenes,[17] expressed as pED_{50} (μg) are shown in Table 1. The electrotopological states of various atoms were calculated by means of a JAVA 2 based program ETSA-CS,[27] which was standardized using established sets of data. The program STATISTICA 5.0[28] was used to correlate biological activity with S-values of different atoms. Statistical parameters of the regression equation considered were 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[29] was performed that generated PRESS (predictive residual sum of squares), SDEP (standard deviation of error of predictions) and $Pres_{av}$ (average of absolute value of predicted residuals). A compound was considered as an outlier in the equation when the residual value exceeded twice the standard error of estimate. Efforts have also been taken to draw a relationship with the pED_{50} of these sets of molecules using first order molecular connectivity index ($^1\chi^v$),[26] hydrophobicity parameters (Log P[25], π[30,31]), steric factor (molecular refractivity)[32] and atomic charges[33] along with E-state index to develop better models, but did not produce any satisfactory correlation. The hydrophobicity parameters, molecular refractivity and atomic charges were calculated using CS MOPAC Pro 5.0 and CS Chem3D Pro 5.0.[34]

The best relation involving all the 18 compounds with E-state index was found to be

$$pED_{50} = 2.768\ (\pm0.423)S_3-1.419(\pm0.360)S_5 + 0.735(\pm0.229)\ S_{22}-10.294\ (\pm4.882) \quad (1)$$

$n=18$, $R=0.870$, $R^2=0.757$, $EV=70.451\%$, $F=14.510$ (df 3,14), $s=0.337$, AVRES = 0.220, PRESS = 4.014, SDEP = 0.472, $Pres_{av}=0.324$

Compound **15** was considered as an outlier and was removed, the resultant equation was

$$pED_{50} = 2.724(\pm0.342)\ S_3 - 1.487(\pm0.292)\ S_5 + 0.749(\pm0.185)\ S_{22} - 10.572(\pm3.942) \quad (2)$$

$n=17$, $R=0.913$, $R^2=0.834$, $EV=79.590\%$, $F=21.798$ (df 3,13), $s=0.272$, AVRES = 0.195, PRESS = 5.057, SDEP = 0.545, $Pres_{av}=0.377$

The 95% confidence intervals are shown in parentheses and the F- values are significant at 99% confidence level. The independent variables used are not intercorrelated ($|r|\leq0.5$). The predicted activities obtained from the eqs 1 and 2 are delineated in Table 1.

Phenyl ring constitutes one of the imperative structural features of non-steroidal estrogen analogues, triphenylethylenes for its binding to estrogen receptors.[11,35] From the regression analysis it appears that C3, C5 and F22 atoms of the molecule constitute the most significant role for post-coital antifertility activity. Importance of the phenyl ring fragment attached to the 2nd ethylenic carbon can thus be envisaged.[11,35] Saturation of the ethylenic double bond (Compound **18**) causes increase of S-value at C3 atom that resulted in marked decrease of activity[17] and in fact exhibited the least activity among the set of 18 molecules. Hence, not only the phenyl ring but also that being attached to an

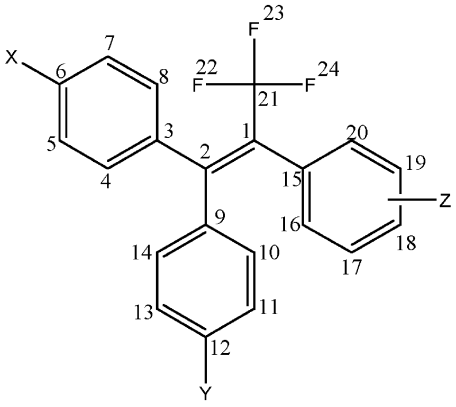
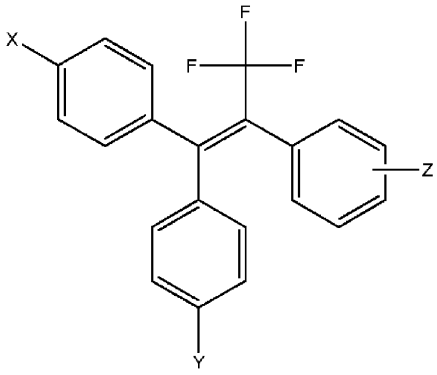


Figure 1. General structure of 1-trifluoromethyl-1,2,2-triphenylethylenes: the common atoms have been numbered 1 through 24.

Table 1. Structural features, observed and predicted post-coital antifertility activities of trifluoromethyl triphenylethylenes



Compd	Substituents			Biological activity [Post-coital antifertility oral pED_{50} (μg)]				
No.	X	Y	Z	Obs.[ψ]	Calcd[x]	Pred.[x]	Calcd[y]	Pred.[y]
1	H	H	H	2.079	1.822	1.797	1.759	1.725
2	CH_3O	H	H	1.114	1.746	1.791	1.692	1.736
3	H	CH_3O	H	1.602	1.835	1.851	1.777	1.790
4	H	H	*p*-CH_3O	2.079	1.893	1.879	1.835	1.815
5	CH_3O	CH_3O	H	2.079	1.758	1.735	1.710	1.681
6	F	H	H	2.491	2.494	2.604	2.527	4.017
7	H	H	*p*-F	1.602	1.595	1.593	1.542	1.535
8	CH_3O	H	*p*-F	1.301	1.518	1.538	1.475	1.491
9	H	H	*m*-F	1.204	1.506	1.536	1.456	1.482
10	H	H	*o*-F	1.204	1.355	1.375	1.310	1.325
11	H	H	*p*-CF_3	1.477	1.394	1.386	1.356	1.344
12	H	H	*m*-CF_3	1.477	1.256	1.222	1.225	1.186
13	H	H	*p*-$CF(CF_3)_2$	1.204	1.065	1.024	1.053	1.008
14	H	H	*p*-Cl	1.477	1.805	1.830	1.747	1.769
15	H	H	*p*-CH_3	2.681	1.919	1.857	—	—
16	H	H	[a]	2.914	2.939	2.953	2.852	2.810
17[b]	H	H	H	2.301	2.383	3.762	2.371	3.553
18[c]	H	H	H	2.991	2.995	2.999	2.911	2.862

Obs. = Observed values, Calcd = Calculated values, Pred. = Predicted values.
[ψ] Observed values are taken from ref. 17.
[x] From Eq. (1); [y] From Eq. (2).
[a] Phenyl group replaced by 2-thienyl group in compound **16**.
[b] One fluorine atom has been substituted by trifluoromethyl group in compound **17**.
[c] Ethylene moiety replaced by ethane in compound **18**.

ethylenic carbon seems to be crucial. From Figure 1, it can be observed that C3 is the point of attachment of the phenyl ring to an ethylenic carbon, which has been demonstrated to be one of the principal contributor for activity. Substitution by hydroxyl group[35] and alkyl ether analogue[2] at C6 or C12 of non-steroidal estrogen analogues increases affinity for the receptor. Substitution by a *p*-CH_3O group (e^- donating) in the phenyl ring causing an increase of e^- density around adjacent atoms of the ring (particularly at C5, C7, C11 or C13 which have negative contribution) resulted in marked increase of activity. However the same substitution, with an additional *p*-fluoro substitution in the phenyl ring also caused increase in activity but to a lesser extent, possibly due to the electronegative effect of fluorine (encoded in its *I* value) which diminished the enhanced e^- density around C5 by some degree. It is also worthwhile to note that presence of thienyl moiety instead of the third phenyl ring (Compound **16**) significantly decreased the potency, this is probably because of thienyl fragment which has more -*I* effect compared to the resonance stabilized phenyl ring. It appears from the regression analysis that S_3 and S_{22} have positive contribution, so decrease in *S*-value of these descriptors will increase activity. Replacement of the 1-CF_3 groups by a C_2F_5 (Compound **17**) decreased the potency. Substitution of one of the fluorine atoms by CF_3 group caused increase of e^- density around C21, which is responsible for generation of more electronegativity on existing fluorine atoms attached to C21.

In view of these observations, the present study could account for some of the structural requirements of 1-trifluoromethyl-1,2,2-triphenylethylenes for post-coital antifertility activity. The study supports that phenyl ring attached to an ethylenic carbon, *para* substitution by a nucleophilic group in the phenyl ring and presence of highly electronegative group (like the fluoro groups) as fourth substituent in the 1st carbon of ethylenic moiety could be important for activity. The potential of the E-State index to converge attention on the fragment(s) of a series of congeneric bioactive molecules essential for activity makes it an informative contrivance in QSAR studies.

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