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Correlation of activity of 2-(X-benzyloxy)-4,6-dimethoxyacetophenones with topological indices and with the Hansch equation

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Abstract

The antispasmodic activities of the 2-(X-benzyloxy)-4,6-dimethoxyacetophenones (X = H, 4′-F, 4′-NO_2, 4′-CH_3, 4′-Cl, 3′,4′-$(CH_3)_2$, 4′-OCH_3, 4′-Br, 4′-$C(CH_3)_3$, 4′-$OCH_2C_6H_5$) against acetylcholine-induced contraction of the guinea pig ileum were correlated with different topological indices. Good correlations were obtained through a simple regression equation with electrotopological state indices (S_i) for the carbon atoms $S(C_1)$ and $S(C_6)$. Using multiple linear regression with two variables the best correlations were obtained with carbons in the 6- and 1-positions with σ. Such results indicate that the corresponding carbon atoms play an important role in the biological activity. The equation of Hansch showed that the activity of these compounds increases when the ring substituent in the benzyloxy group are more highly electron-releasing and hydrophobic.

Keywords: Xanthoxyline derivatives; Topological indices; QSAR

1. Introduction

A number of graph-based topological indices and electrotopological indices (with electronic attributes) have been proposed in an attempt to quantify the structural and electronic attributes of molecules for use in quantitative structure–activity relationship (QSAR) studies [1–21].

In previous works [22–24], we have compared the experimentally-determined order of potency of the antispasmodic activity of 2-(X-benzyloxy)-4,6-dimethoxyacetophenones (X = H, 4′-F, 4′-NO_2, 4′-CH_3, 4′-Cl, 3′,4′-$(CH_3)_2$, 4′-OCH_3) with the order corresponding to parameters suggested by the manual method of Topliss [25]. It was shown that the parameters $\pi - 2\sigma$ and $\pi - 3\sigma$ correlated in a better way with the activity of the compounds, indicating that both the electronic and the hydrophobic effects of the substituents participate in the activity, the electronic effects (σ) being predominantly responsible for the activity's determination. In accordance with these Topliss parameters, other substituent electron donors which increase the hydrophobicity in general were introduced into the molecules.

In this work, the activity of ten 2-(X-benzyloxy)-4,6-dimethoxyacetophenones were correlated with molecular connectivity indices, κ values and electrotopological indices, etc., in order to obtain more information about the structural factors of these molecules which determine their antispasmodic activities. Moreover, the equation of Hansch was applied in order to observe whether the parameters of the molecules that gave good correlation with the activity were the same as those indicated by the manual method of Topliss.

2. Experimental

2.1. Methods and calculation

The isolation of xanthoxyline, the methods of synthesis and identification of their derivatives and also the

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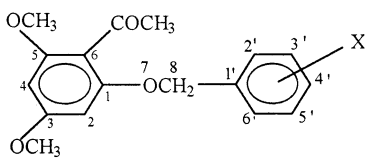
pharmacological experiments have been described already [22–24].

The topological indices taken into consideration were calculated using the computational program MOLCONN-X, developed by Kier and Hall [27].

In order to test the quality of the regression equation, the following statistical parameters were used: correlation coefficient (r), determination coefficient (r^2) and test of the null hypothesis (F-test). All the single and multiple linear regression analysis calculations were carried out using the ORIGIN computer program.

3. Results and discussion

The molecular skeleton with different substituents studied is illustrated below:



X = H; 3′,4′-$(CH_3)_2$; 4′-CH_3; 4′-OCH_3; 4′-Cl; 4′-F; 4′-NO_2; 4′-Br; 4′-$OCH_2C_6H_5$; 4′-C $(CH_3)_3$.

3.1. Correlation using topological indices

The values of biological activity of different 2-(X-benzyloxy)-4,6-dimethoxyacetophenones and calculated topological indices such as molecular connectivity, Wiener and κ indices related with the topology of the molecules are given in Table 1.

It is known that the molecular connectivity indices of valence give information about unsaturation, the presence of heteroatoms, the branching, the cyclicity and the size of the chain. The simple linear correlation between the biological activity ($\log 1/C$) and the connectivity indices (^1X, ^2X, ^3X_p, ^4X_p,...) do not give significant correlations, showing that these parameters give no information about the biological activity studied. The same case occurs with Wiener and κ indices.

The analysis with two-variable regression equations that give a more complete information of the molecules, using the molecular connectivity indice, is not sufficient to give a good correlation. This led us to test the correlation with the electrotopological state indices (E-state values) of the different atoms that encode information about the topological and electronical factors of a molecule [14].

The values of the electrotopological indices for the more important carbon atoms in the molecules are shown in Table 2. Some of them gave good simple linear correlation with the activity of the compounds. The best simple linear correlations were obtained with $S(C_{3'})$ (the E-state value for the 3′-position carbon atom, $r = 0.8988$—see the molecular skeleton above), with $S(C_6)$ (6-position carbon atom, $r = 0.8778$), and with $S(C_1)$ ($r = 0.8700$), for the ten compounds studied. These results indicate that the electronic and topological states of these carbon atoms give important information about the biological activity of these compounds.

It is clear that the E-state index gives some information about the inductive effects on the atom. The colinearity between the E-state index $S(C_6)$ and σ is not high ($r = 0.689$) showing that information of the inductive effect is not completely encoded in the E-state index.

Thus, applying a multiple linear regression equation of two variables, using the E-state indices $S(C_6)$ and $S(C_1)$ with σ, the correlation is significantly better as can be observed in Eqs. (1) and (2):

$$\text{Log}\,(1/C) = 9.9063S(C_6) - 1.1234\sigma + 1.0489 \quad (1)$$

$$r^2 = 0.9252 \quad r = 0.9619 \quad n = 10$$

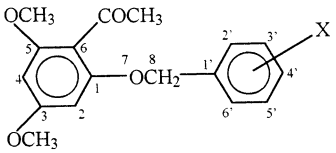
$$F_{S(C_6)} = 12.16 \ (\text{prob} > F = 0.0102) \quad \text{SD} = 2.8406$$

$$F_{\sigma} = 14.47 \ (\text{prob} > F = 0.0067) \quad \text{SD} = 0.2952$$

Table 1
Biological activity ($\log 1/C$) and topological indices (X, molecular connectivity indices; W, Wiener indices; κ, kappa indices) of different substituted 2-(X-benzyloxy)-4,6-dimethoxyacetophenones [X = H, 4′-F, 4′-NO_2, 4′-CH_3, 4′-Cl, 3′,4′-$(CH_3)_2$, etc...]

Obs.	Compounds	Log $1/C$	$^1X^v$	$^2X^v$	$^3X_p^v$	$^4X_p^v$	$^5X_p^v$	$^3X_c^v$	$^4X_{pc}^v$	W	$^1\kappa$	$^2\kappa$	$^3\kappa$
1	3′,4′-$(CH_3)_2$	5.55	7.4180	5.4663	3.8128	2.3599	1.5764	0.7570	1.5127	1230	19.3264	8.9091	4.9887
2	4′-CH_3	5.48	7.0013	5.0333	3.3621	2.1509	1.4971	0.6350	1.1034	1094	18.3403	8.7409	4.9967
3	4′-OCH_3	5.23	7.1137	4.8957	3.4006	2.1884	1.4385	0.5363	1.0575	1264	19.3264	9.4761	5.2350
4	4′-Cl	4.99	7.0682	5.1106	3.4068	2.1732	1.5258	0.6573	1.1291	1094	18.3403	8.7409	4.9967
5	H	4.94	6.5906	4.5333	3.0843	2.0408	1.3268	0.4683	0.9109	946	17.3554	8.5850	4.7334
6	4′-F	4.63	6.6903	4.6741	3.1548	2.0472	1.3640	0.5313	0.9837	1094	18.3403	8.7409	4.9967
7	4′-NO_2	3.15	7.0900	4.9712	3.3887	2.1805	1.4397	0.5801	1.1009	1436	20.3136	9.6298	5.4970
8	4′-Br	5.20	7.4833	5.5898	3.6834	2.3116	1.7035	0.7956	1.2889	1094	18.3403	8.7409	4.9967
9	4′-$OCH_2C_6H_5$	5.58	9.2583	6.4659	4.4132	2.8894	1.9376	0.6542	1.2218	2656	23.6587	12.1428	7.000
10	4′-$C(CH_3)_3$	5.34	8.2513	6.9946	4.0615	2.5676	1.6401	1.8016	2.1232	1610	21.3018	9.2739	5.7363

Table 2
Biological activity (log $1/C$) and electrotopological-state indices, $S(C_i)$ of different substituted 2-(X-benzyloxy)-4,6-dimethoxyacetophenones [X = 4′-H, 4′-F, 4′-NO_2, 4′-CH_3, 4′-Cl, 3′,4′-$(CH_3)_2$, etc…]



Obs.	Substituents	Log $1/C$	$S(C_1)$	$S(C_6)$	$S(C_{3'})$
1	3′,4′-$(CH_3)_2$	5.55	0.4647	0.4279	2.0616
2	4′-CH_3	5.48	0.4623	0.4263	2.0245
3	4′-OCH_3	5.23	0.4347	0.4044	1.8579
4	4′-Cl	4.99	0.4293	0.4002	1.7900
5	H	4.94	0.4607	0.4252	1.9412
6	4′-F	4.63	0.3685	0.3522	1.3579
7	4′-NO_2	3.15	0.3306	0.3196	1.3995
8	4′-Br	5.20	0.4506	0.4170	1.9412
9	4′-$OCH_2C_6H_5$	5.58	0.4288	0.3992	1.9024
10	4′-$C(CH_3)_3$	5.34	0.4617	0.4256	2.1079
11	4′-NH_2	–	0.4310	0.4016	1.8023
12	4′-OH	–	0.3998	0.3769	1.5801
13	4′-$OCH(CH_3)_2$	–	0.4363	0.4056	1.8995
14	4′-$N(CH_3)_2$	–	0.4541	0.4196	2.0245
15	4′-$N(C_2H_5)_2$	–	0.4597	0.4241	2.0870
16	3′-CH_3	–	0.4632	0.4268	1.9782
17	4′-$(CH_2)_3CH_3$	–	0.4711	0.4332	2.1313
18	4′-$O(CH_2)_3CH_3$	–	0.4416	0.4100	1.9230
19	4′-$CH(CH_3)CH_2CH_3$	–	0.4673	0.4301	2.1299
20	4′-$CH_2CH(CH_3)_2$	–	0.4676	0.4303	2.1218
21	4′-C_6H_5[a]	–	0.4498	0.4159	2.0616
22	4′-N=NC_6H_5	–	0.4181	0.3904	1.8643
23	4′-OC_6H_5	–	0.4244	0.3957	1.8787
24	4′-C_6H_{11}	–	0.4815	0.4418	2.2150
25	4′-$C_6H_4(CH_3)$p	–	0.4503	0.4163	2.0708
26	4′-C≡C–C_6H_5	–	0.4321	0.4015	1.9511
27	4′-CH=CH–C_6H_5	–	0.4461	0.4127	2.0379
28	4′-CH_2CH_2–C_6H_5	–	0.4600	0.4239	2.1247
29	4′-$C_6H_4(C_6H_5)$p	–	0.4438	0.4106	2.0776
30	4′-$N(C_6H_5)_2$	–	0.4333	0.4021	2.0662

[a] Cyclohexyl.

$$\text{Log}\,(1/C) = 7.8728S(C_1) - 1.1345\sigma + 1.6301 \quad (2)$$

$r^2 = 0.9234$ $r = 0.\ 9609$ $n = 10$
$F_{S(C_1)} = 69.83$ (prob $> F = 0.0001$) SD = 2.3008
$F_\sigma = 14.53$ (prob $> F = 0.0066$) SD = 0.2976

Considering all the information encoded in the two variables of Eqs. (1) and (2), the importance of the inductive effect of substituents on the activity of these compounds is evident.

The colinearity between the E-state index ($S(C_6)$ and $S(C_1)$) and the hydrophobic parameter π is low ($r = 0.4671$ and $r = 0.4693$). The multiple linear regression equation between the activity and E-state indices $S(C_6)$ and $S(C_1)$ together with the parameter π give a less significant correlation:

$$\text{Log}\,(1/C) = 12.2231S(C_1) + 0.2226\pi - 0.3744 \quad (3)$$

$r^2 = 0.8046$ $r = 0.8970$ $n = 10$ SD = 0.3599

$$\text{Log}\,(1/C) = 15.2920S(C_6) + 0.2224\pi - 1.2413 \quad (4)$$

$r^2 = 0.8108$ $r = 0.9005$ $n = 10$ SD = 0.3541

Kier and Hall [3], using the E-state values of the ring atoms of barbiturates, have explored the possibility of a specific atom involvement in the stability constants of their complex with cyclodextrins. The results indicate that the electrotopological state of the carbonyl oxygen atom gives the information that they are highly influential in the binding of barbiturates with β-cyclodextrin.

In the same way, Hall et al. [21] have computed the E-state values of the nine skeletal atoms in the benzimidazole ring system, showing that the two nitrogen atoms and the carbon atom of the 2-position play an important role in the biological activity against the flu virus. In our case, it is possible to observe that the E-state value for the carbon atom of the 1- and 6-positions gives good correlations in single-variable and also in the two-variable equations together with the σ parameter. Thus, it is possible to conclude that the electronic and topological states of the carbon atoms in the 1- and 6-positions, near the carbonyl group, give important information about the activity of these compounds. This ability to focus on atoms or regions in a molecule as principal areas related to the activity is a major advantage in approaching drug design in a quantitative way.

3.2. Correlation using Hansch equation

The values of activity of different 2-(X-benzyloxy)-4,6-dimethoxyacetophenones were correlated using the equation of Hansch of two variables σ and π [26], thus obtaining a good correlation coefficient ($r = 0.9055$) according to Eq. (5):

$$\text{Log}\,(1/C) = 0.1784\pi - 1.6466\sigma + 4.8989 \quad (5)$$

$$r = 0.9055 \quad r^2 = 0.8199 \quad n = 10 \quad \text{SD} = 0.3455$$

The coefficients of this equation indicate that the most important contribution is made by σ values, and the negativity of the σ values is proportional to the increase in activity. The contribution of π is secondary, showing that when the value of π increases the activity will increase too.

In accordance with these observations, using electrotopological indices of carbon atoms in the 6- and 1-positions and the parameters σ and π, it is possible to predict the substituents which should be tested in order to obtain a better activity, as may be observed in Table 3. They are fundamentally substituent electron-donors which increase the hydrophobicity of the molecule.

Table 3
Experimental (log $1/C$) and calculated (Eqs. (1), (2) and (5)) biological activity of different 2-(X-benzyloxy)-4,6-dimethoxyacetophenones [X = H, 4′-F, 4′-NO_2, 4′-CH_3, 4′-Cl, 3′,4′-$(CH_3)_2$, etc.] substituted and residual values (RV = log $1/C$ − Calc. Eq.)

Obs.	Substituents	Exp.[a]	Calc.[b] (Eq. (1))	RV	Calc.[b] (Eq. (2))	RV	Calc.[b] (Eq. (5))	RV
1	3′,4′-$(CH_3)_2$	5.55	5.56	0.01	5.56	0.01	5.39	0.16
2	4′-CH_3	5.48	5.46	0.02	5.46	0.02	5.28	0.20
3	4′-OCH_3	5.23	5.36	0.13	5.36	0.13	5.34	0.11
4	4′-Cl	4.99	4.76	0.23	4.75	0.14	4.65	0.34
5	4′-H	4.94	5.26	0.32	5.26	0.32	4.90	0.04
6	4′-F	4.63	4.47	0.16	4.46	0.17	4.82	0.19
7	4′-NO_2	3.15	3.34	0.19	3.35	0.20	3.56	0.41
8	4′-Br	5.20	4.92	0.28	4.92	0.28	4.67	0.53
9	4′-$OCH_2C_6H_5$	5.58	5.48	0.10	5.48	0.10	5.89	0.31
10	4′-$C(CH_3)_3$	5.34	5.49	0.15	5.49	0.15	5.58	0.24
11	4′-NH_2	–	5.21	–	5.21	–	4.94	–
12	4′-OH	–	4.65	–	4.64	–	4.58	–
13	4′-$OCH(CH_3)_2$	–	5.57	–	5.58	–	5.70	–
14	4′-$N(CH_3)_2$	–	6.14	–	6.15	–	6.30	–
15	4′-$N(C_2H_5)_2$	–	6.06	–	6.07	–	6.29	–
16	3′-CH_3	–	5.36	–	5.36	–	5.11	–
17	4′-$(CH_2)_3CH_3$	–	5.52	–	5.52	–	5.54	–
18	4′-$O(CH_2)_3CH_3$	–	5.47	–	5.47	–	5.75	–
19	4′-$CH(CH_3)CH_2CH_3$	–	5.44	–	5.44	–	5.46	–
20	4′-$CH_2CH(CH_3)_2$	–	5.45	–	5.45	–	5.40	–
21	4′-C_6H_5[c]	–	5.18	–	5.18	–	5.26	–
22	4′-N=NC_6H_5	–	4.48	–	4.48	–	4.56	–
23	4′-OC_6H_5	–	5.00	–	5.01	–	5.32	–
24	4′-C_6H_{11}	–	5.59	–	5.59	–	5.64	–
25	4′-$C_6H_4(CH_3)p$	–	5.21	–	5.21	–	5.43	–
26	4′-C≡C–C_6H_5	–	4.85	–	4.85	–	5.11	–
27	4′-CH=CH–C_6H_5	–	5.22	–	5.22	–	5.49	–
28	4′-CH_2CH_2–C_6H_5	–	5.38	–	5.39	–	5.57	–
29	4′-$C_6H_4(C_6H_5)p$	–	5.09	–	5.10	–	5.60	–
30	4′-$N(C_6H_5)_2$	–	5.28	–	5.29	–	5.91	–

[a] Experimental values for activity (log $1/C$).
[b] Values computed for activity from Eqs. (1), (2) and (5).
[c] Cyclohexyl.

Some substituents that could be able to increase the activity in accordance with these equations are: 4′-$OCH(CH_3)_2$, 4′-$N(CH_3)_2$, 4′-$N(C_2H_5)_2$, 4′-$(CH_2)_3CH_3$, 4′-$O(CH_2)_3CH_3$, 4′-$CH(CH_3)CH_2CH_3$, 4′-$CH_2CH(CH_3)_2$ and 4′-C_6H_{11} (cyclohexyl).

4. Conclusion

The correlation between the activity of 2-(X-benzyloxy)-4,6-dimethoxyacetophenones and the electrotopological state indices indicate that the carbon atoms in the 1- and 6-positions of the molecules give important information about the biological activity of these compounds.

The application of the Hansch equation shows that the most electron-releasing and hydrophobic substituents in the benzyloxy ring increase the activity of these compounds in accordance with the results obtained from the application of the simple manual Topliss method.

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