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A Quantitative Structure-Activity Relationship Analysis of some Nimesulide Analogues using Computer-Aided Molecular Modeling

S. K. CHAKRAVARTI, S. AJMANI, MEENA TIWARI AND S. C. CHATURVEDI*
Department of Pharmacy, Shri Govindram Seksaria Institute of Technology and Science, 23-Park Road, Indore-452003 (M.P.)

The structures of a series of antiinflammatory 2'-(2, 4-difluorophenoxy)-4'substituted methanesulfonilides were submitted to a molecular modeling software and after energy minimization and conformational analysis of the structures, a number of electronic, spatial and thermodynamic descriptors were calculated. The result of the quantitative structure-activity relationship (QSAR) analysis showed that the oral antiinflammatory activity, as determined in the rat adjuvant arthritis model, was highly correlated with the X-component of the principal moment of inertia. Dipole moment of the molecules and energy of the highest occupied molecular orbital were also important in determining the activity of the molecules.

THE work published by Wilkerson[1] on the QSAR analysis of 2'-(2, 4-difluorophenoxy)-4' substituted methanesulfonilides directed us to investigate the finer details of the quantitative structure-activity relationship of the above said series of 2'-(2, 4-difluorophenoxy)-4'-substituted methanesulfonilides (Fig. 1). This series was reported by Tsuji et al[2]. These methanesulfonilides are analogues of nimesulide, which has been reported to have antiinflammatory and analgesic activity without gastrointestinal side effects as determined in animal models[2,3]. Wilkerson[1] reported that the antiinflammatory activity of this series was highly correlated with the electronic (σ) and steric (Sterimol B1) effects exhibited by the 4'-substitution(R1). We have used computer-aided molecular modeling to study the QSAR relationship of this series as molecular modeling offers opportunities to estimate a great number of physicochemical properties based on the 3D and detailed electronic structure of the molecule. This study may contribute to a better understanding of the relationship between structure and antiinflammatory activity[4].

*For correspondence

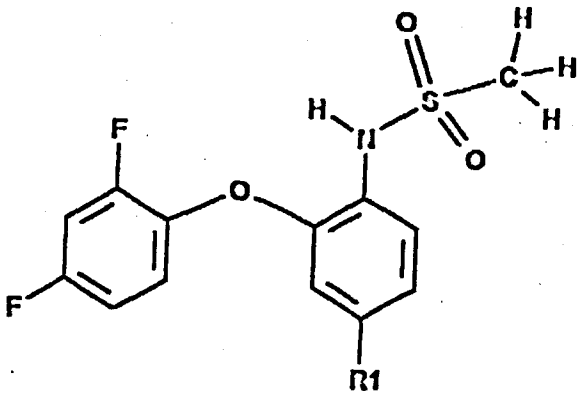

Fig. 1: 2'-(2,4-Difluorophenoxy)-4'-substituted Methanesulfonilides used in this study

MATERIAL AND METHODS

The antiinflammatory data were taken from Tsuji et al[2], and the data were expressed as percent inhibition of adjuvant-induced paw edema in the rat caused by 10 mg/kg of drug (AA). We have converted the data to percent paw edema inhibition per micromole of drug per kilogram of body weight (BA) (Table 1). For molecular modeling and

Table 1 : RAT ADJUVANT-ARTHRITIS DATA FOR 2'-(2, 4-DIFLUOROPHENOXY)-4' SUBSTITUTED METHANESULFONILIDES USED IN THIS STUDY

Compound	RI	AA[a]	BA[b]	Log BA
1	NO_2	100	3.44	0.5369
2	CN	85	2.76	0.4404
3	COMe	79	2.70	0.4308
4	CONHMe	65	2.32	0.3648
5	$CONH_2$	59	2.02	0.3053
6	$CONMe_2$	59	2.19	0.3395
7	CF_3	58	2.13	0.3284
8	SO_2Me	58	2.19	0.3402
9	CH=CHCOMe	55	2.02	0.3055
10	SMe	49	1.69	0.2285
11	CH=NOMe	48	1.71	0.2331
12	COOEt	28	1.04	0.0169
13	S-iPr	23	0.86	-0.0661
14	CH=NOH	22	0.75	-0.1231
15	SOMe	21	0.76	-0.1198
16	COEt	20	0.71	-0.1483
17	SH	20	0.66	-0.1787
18	SEt	14	0.50	-0.2983
19	Me	11	0.35	-0.4626
20	H	3	0.09	-1.0468

[a]Inhibition of paw edema in the rat adjuvant arthritis model at 10.0 mg/kg orally. [b]Percent paw edema inhibition per micromolecule of drug per kilogram of body weight.

calculation of various descriptors we have used different modules provided in molecular modeling software Cerius2 version 3.5[5].

The structures of the compounds (1-20 in Table 1) were built using the molecular sketching facilities provided in the modeling environment of Cerius2.The energy of the molecules were minimized using conjugate gradient algorithm[6] working under Universal Force Field[7]. The minimization terminates where the root mean square (RMS) force on the model is less than 0.0001 kcal/mole/A°. After energy minimization various possible conformations of each molecule were calculated by setting the limit for the maximum number of conformations which can be generated to 150. The number of conformations generated for each molecule and their corresponding energy can be seen in Table 2. After this, the lowest energy conformation of each was found. All the descriptor calculations were performed

Table 2 : CALCULATED VALUES OF DESCRIPTORS FOR COMPOUNDS 1-20 AND THE NUMBER OF CONFORMATIONS GENERATED AND THE LOWEST ENERGY OF THE CONFORMATIONS

Compd. No.	No. of conformations	Lowest Energy kcal/mol	PMIX[c]	PMIZ[d]	DIPOLE Debyes	ZDIP[e] Debyes	XDIP[f] Debyes	HOMO
1	126	68.00	322.966	777.549	11.328	-4.5152	3.5807	-9.6558
2	124	83.78	255.771	715.523	8.418	-4.9983	2.0613	-9.2649
3	124	68.09	314.012	785.458	8.324	-5.5668	-0.6903	-9.1519
4	102	116.48	379.626	876.333	8.380	-3.9631	0.0277	-9.1132
5	108	67.79	314.902	788.322	8.614	-4.8428	0.5105	-9.1400
6	79	134.29	400.701	907.559	8.085	2.6107	1.1332	-9.0883
7	139	101.30	398.289	845.941	7.695	0.3575	11.7148	-9.3368
8	112	120.72	452.855	910.902	8.085	-0.6112	4.2776	-9.4160
9	119	59.49	417.281	878.780	4.493	-3.2484	-2.2886	-8.7123
10	133	71.73	302.506	783.369	6.952	-1.2559	2.7805	-8.3925
11	106	94.04	421.636	864.301	5.138	-2.7782	2.5539	-8.8767
12	99	94.36	424.496	960.249	7.462	-2.7346	-5.0911	-9.1936
13	120	34.50	393.042	895.827	6.734	-1.1346	1.2068	-8.3638
14	95	98.97	260.879	763.862	7.530	-2.6379	6.3947	-9.0916
15	130	66.52	364.986	842.039	8.541	1.2721	-5.3303	-9.0469
16	84	105.75	344.406	837.994	8.239	2.7195	-2.5808	-9.1211
17	121	65.01	270.594	729.099	7.007	-5.3858	0.9963	-8.3872
18	123	74.03	343.328	816.303	6.839	-2.3165	0.1646	-8.3657
19	142	69.69	198.443	663.110	5.171	-4.3278	1.3975	-8.7670
20	127	86.96	146.526	609.817	5.371	-4.4033	2.3587	-8.9273

[c]x-component of principal moment of inertia, [d]z-component of principal moment of inertia, [e]z-component of dipole moment, [f]x-component of dipole moment

on this lowest energy conformation.

Following descriptors were calculated for QSAR study (values of only those descriptors which found place in the equations are given in Table 2).

1. Thermodynamic descriptors

a) Desolvation free energy for water (FH20)[8, 9]

b) Desolvation free energy for octanol (FOCT)[8, 9]

c) Log of partition coefficient (LOGP)[8, 9]

d) Molecular refractivity (MR)[9, 10]

2. Spatial descriptors

a) Number of rotatable bonds (ROTBONDS)[9]

b) Molecular surface area (AREA)[11]

c) Density (DENSITY)[11]

d) Molecular weight (MW)[11]

e) Molecular volume (VM)[11]

f) Principal moment of inertia (PMI)[12]

g) Principal moment of inertia - X component (PMIX)[12]

h) Principal moment of inertia - Y component (PMIY)[12]

j) Principal moment of inertia - Z component (PMIZ)[12]

3. Electronic descriptors

a) Sum of atomic polarizabilities (APOL)[13]

b) Dipole moment (DIPOLE)[14, 15]

c) Dipole moment - X component (XDIP)[14,15]

d) Dipole moment - Y component (YDIP)[14,15]

e) Dipole moment - Z component (ZDIP)[14,15]

f) Energy of highest occupied molecular orbital (HOMO)[16]

g) Energy of lowest unoccupied molecular orbital (LUMO)[16]

h) Partial atomic charges[17]

The HOMO, LUMO and dipole moments were calculated using MOPAC method. Partial charges were calculated using charge equilibration[17] (QEq) method.

To generate QSAR equations, stepwise multiple regression analysis method[18] was used. The following statistical measures were used:

n the number of samples in the regression

r coefficient of correlation

r^2 coefficient of determination

std standard deviation

t t-test for statistical significance

RESULTS AND DISCUSSION

When all the calculated parameters and log(BA) of compounds 1-20 were subjected to stepwise multiple parameter regression analysis, the following equations were obtained:

BA = 0.002847 (0.000907) PMIX-0.8863 (0.3181) .... (1)
n = 20 r = 0.595 r^2 = 0.354 t = 3.139 STD = 0.039

BA = 0.00258 (0.000795) PMIX+0.1057 (0.0406) DIPOLE
– 1.5823 (0.2766) ..... (2)
n = 20 r = 0.734 r^2 = 0.539 t = 4.581 STD = 0.033

BA = 0.00344 (0.000818) PMIX+0.1096(0.0367)DIPOLE
-0.0559(0.0255) ZDIP-2.0331(0.2500) ..... (3)
n = 20 r = 0.803 r^2 = 0.645 t = 5.719 STD = 0.029

BA = 0.00359 (0.000799) PMIX + 0.1073 (0.0356) DIPOLE
-0.0574(0.0247)ZDIP+0.0211(0.0148)XDIP
-2.0968(0.2422) ..... (4)
n = 20 r = 0.829 r^2 = 0.687 t = 6.296 STD = 0.027

Statistically Eq. (4) is significant and have a good correlation coefficient. The independent variables of Eq. (1)-(4) are not significantly cross correlated which is evident from the correlation matrix (Table 3). Calculated and observed log (BA) for Eq. (4) can be seen in Table 4.

To investigate other relationships, PMIX was deleted from the space and the remaining descriptors were subjected to stepwise regression analysis, Eq. (5) was resulted which is statistically less significant than Eq. (4).

BA = 0.00321 (0.000847) PMIZ+0.1033 (0.0391) DIPOLE
0.0602 (0.0279) ZDIP+0.0289 (0.0166) XDIP
-3.4890 (0.2648) ..... (5)
n = 20 r = 0.792 r^2 = 0.627 t = 5.498 STD = 0.029

When parabolic relationships were searched the following two equations were obtained:

BA = -0.0000223 (0.00000861) $PMIX^2$+0.0166 (0.00539) PMIX
-2.8693 (0.2773) ..... (6)

Table 3 : CORRELATION MATRIX FOR THE PARAMETERS IN EQUATION [1-4]

	Log (BA)	PMIX	DIPOLE	ZDIP	XDIP
Log (BA)	1.000				
PMIX	0.595	1.000			
DIPOLE	0.502	0.129	1.000		
ZDIP	0.021	0.484	0.105	1.000	
XDIP	0.138	0.123	0.031	0.022	1.000

Table 4 : FOUND AND CALCULATED ACTIVITY VALUES FOR COMPOUNDS 1-20

Compound	R	Found Log(BA)	Calcd. Log(BA) Eq.4	Calcd. Log(BA) Eq.7	Found AA	Calcd. AA Eq.4	Calcd. AA Eq.7
1	NO_2	0.5369	0.6121	0.5851	100	118.9	111.7
2	CN	0.4404	0.0544	0.1389	85	34.9	42.5
3	COMe	0.4308	0.2278	0.3457	79	49.5	64.9
4	CONHMe	0.3648	0.3923	0.3754	65	69.3	66.6
5	$CONH_2$	0.3053	0.2459	0.3319	59	51.5	62.7
6	$CONMe_2$	0.3395	0.0822	0.0497	59	32.6	30.2
7	CF_3	0.3284	0.3848	0.4642	58	66.0	79.3
8	SO_2Me	0.3402	0.5208	0.2741	58	87.9	49.8
9	CH=CHCOMe	0.3055	0.0204	0.1184	55	28.5	35.8
10	SMe	0.2285	-0.1348	-0.1129	49	21.2	22.3
11	CH=NOMe	0.2331	0.1806	0.2418	48	42.5	48.9
12	COOEt	0.0169	0.2760	0.1944	28	50.8	42.1
13	S-iPr	-0.0661	0.1263	-0.0136	23	35.8	25.9
14	CH=NOH	-0.1231	-0.0664	0.0757	22	25.1	34.8
15	SOMe	-0.1198	-0.0246	-0.0236	21	26.1	26.2
16	COEt	-0.1483	-0.1879	-0.0413	20	18.3	25.6
17	SH	-0.1787	-0.0440	-0.0906	20	27.3	24.5
18	SEt	-0.2983	0.0051	-0.0056	14	28.2	27.5
19	Me	-0.4626	-0.5521	-0.5163	11	8.9	9.7
20	H	-1.0468	-0.6923	-0.9649	3	6.8	3.6

n = 20 r = 0.732 r^2 =0.536 t = 3. 134 STD = 0.035

BA = -0.0000244 (0.00000624) $PMIX^2$ + 0.0186 (0.00391) PMIX

-0.3565 (0.1286) HOMO-0.05011 (0.0204) ZDIP

+0.0199 (0.0125) XDIP-6.6178 (0.1995).....(7)

n = 20 r = 0.896 r^2 = 0.802 t = 5.872 STD = 0.023

It can be seen that there is a significant improvement in Eq. (1) after adding the square term of PMIX. Eq. (7) is statistically significant and it has a good prediction capability. Calculated and observed log(BA) for Eq. (7) can be seen in Table 4.

On the basis of the above studies it can be concluded that the x-component of principal moment of inertia and dipole moments of the molecules have important effects on the oral antiinflammatory activity. This also indicates that a particular spatial charge distribution and mass distribution in the molecules is required for good antiinflammatory activity.

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