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QSAR Comparative Molecular Field Analysis of Substituted Benzamides as Antiinflammatory Agents

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A series of N-(4,6-dimethyl-2-pyridinyl)benzamides as non-acidic antiinflammatory drugs was subjected to a 3D-quantitative structure activity relationship using Comparative Molecular Field Analysis. The series was studied with an attempt to derive a co-relationship between biological activity as dependent variable and descriptors as independent variables. The statistical method used was partial least square analysis to ascertain a co-relationship.

Gastric irritation, the most prominent side effect to the widely used non-steroidal antiinflammatory drugs, compels the medicinal chemists to discover novel category of non acidic antiinflammatory drugs which are partially or fully devoid of gastrointestinal toxic effects such as ulceration, hemorrhage and perforation. Novel categories of drugs are being developed based on new mechanism of action and pathogenesis of inflammation.

The non acidic antiinflammatory compounds of the previously reported benzamides prompted us to establish QSAR[1] in the given series having N-(4,6-dimethyl 2-pyridinyl) moiety as a basic nucleus (fig.1). The observed antiinflammatory activity elicited by the inhibition of carrageenan- induced rat paw edema in shown in Table 1.

The compounds were reported in the publications[2,3]. The compounds containing substitution at position-2 (ortho) were omitted since they showed no or very minimal activity. The compounds having di-substituted benzamide nucleus were also omitted from the series as they were found to be outliers.

MATERIALS AND METHODS

Comparative Molecular Field Analysis (CoMFA)[4,5] technique applied for studying quantitative structure activity relationship provides steric and electrostatic field representation, field fitting to optimize mutual alignment within a series of molecules, cross validation to indicate the predictive validity of the correlations, and graphic representation of the results are shown in the form of contour maps. The positioning of molecular model relative to the template within a fixed lattice is the most important variable in CoMFA.

The studies were performed on Silicon Graphics, Photon SX-Workstation, Model-Octane, CPU (1,300 MHz), MIPS, 812000 (IP30), processor (MIPSR 12010), Min Memory (128 MB), Data Cache (32 KB), Instruction Cache (32 KB), Secondary Instruction Data Cache (2 MB), Operating System IRIX 64 Release 65, Graphics (IEI). The software used was Sybyl 6.6. The TRIPOS molecular mechanics force field[6] was applied in this technique. Powell's method was employed for energy minimization. Conformational Analysis was not performed due to the rigidity of –CO-NH amide linkage.

The resolution level of parameterization in Cartesian lattice was set to 2 A. The sp^3 carbon probe with a change of +1 and Vander Waals radius of 1.52 A was used for ligand energy interaction in an equidistant lattice. Cartesian standard fields were truncated to 30 Kcal/mol, 1.5 Kcal/mol for electrostatic and steric energy fields respectively. The MOPAC atomic charges[7] were calculated on given sets of compounds. A total of 23 compounds were sketched, en-

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TABLE 1: SERIES OF COMPOUNDS N-(4,6- DIMETHYL – 2-PYRIDINYL) BENZAMIDES

Compound No.	R	% Inhibition of Carragenan induced rat paw edema (P)[a] Dose = 200 mg/ kg body weight
1	H	84.7±5.4
2	4-NO	54.4±12.5
3	3-NH_2	53.8±8.9
4	4-NH_2	63.6±6.4
5	3-$NHCOCH_3$	44.5±7.5
6	4-$NHCOCH_3$	53.3±7.7
7	2-OH	0
8	4-F	60.4±8.4
10	3-Cl	61.1±2.5
11	-Cl	54.5±5.5
12	3-Br	78.3±3.4
13	4-Br	38.3±8.6
14	3-CH_3	47.5±8.4
15	3-CF_3	65.8±6.2
16	2-OCH_3	33.0±5.7
17	3-OCH_3	61.3±7.0
18	4-OCH_3	48.3±8.2
19	4-OC_2H_5	45.0±6.1
20	4-SCH_3	45.0±8.4
24	4-CN	57.3±5.5
25	3-NO_2	78.8±8.9
27	4-CN	57.3±5.5
28	3-F	91.4±2.9
29	$(CH_2)_2$-C_6H_6	29.2±11.0

[a]In order to scale the values the percentage inhibition (P) was taken as log (P/100-P) on molecular spreadsheet while performing CoMFA. [b]0.8 mol/ kg.

ergy minimized and exported to QSAR Module of Sybyl Version 6.6 software. The CoMFA electrostatic energy interaction (the crude molecular volume=No. of lattice intersection points in electrostatic energy field, column I in Table 2), CoMFA steric energy interaction (the crude molecular volume=No. of lattice intersection points in steric energy field., Column II), C lop P, lipophillic parameter CMR, Computational Molecular Refractivity[8,9] (a thermodynamic parameter, which is a combined measure of its size and polarisability) and X, Y and Z component[10,11] (a electronic descriptor that indicates strength and behaviour of a molecule in an electrostatic field) were computed.

The field fit procedure is one of the alignment rules that can be used to increase field similarity within a series of molecules. The PLS method[12] (partial least squares) was used to derive a linear relationship, and cross validation was performed using N leave out method, with a 2 Kcal/mol column filter to check for consistency and predictiveness. The optimum number of components used to derive a non-validated model was defined as the number of components leading to the highest cross validation r^2 (called q^2) and lowest standard errors of prediction (SEP). Only model of 0.46 and above and a fraction of variance r^2 over 0.85 for the optimum number of components were further considered.

RESULTS AND DISCUSSION

The best CoMFA results were obtained using a sp^3 carbon probe carrying a charge of +I, for a grid spacing of 2 A and when the steric and electrostatic energies were truncated to 1.5 Kcal/mol and 30 Kcal/ mol respectively. The compounds 3, 4, 6, 8, 10, 11, 14, 15, 17, 18, 20, 24, 25, 27, 28 were included in the training set. The remaining compounds 1, 2, 5, 12, 13, 19, 26, 29 comprised the test set were used to evaluate the predictive power.

As shown in Table 3, the electrostatic contributions were found to be the highest of all parameters, and combined electrostatic and steric fields as well as calculated molar refractivity and Z component when studied together showed ($r^2_{cv} = q^2$=0.465 and a r^2=0.976) the best predictions.

The 3D QSAR contour maps figs.2 and 3 illustrate clearly the electrostatic and steric interactions in Comparative Molecular Field Analysis respectively. In the contour maps electrostatically unfavorable region correspond to blue areas and electrostatically favorable region correspond to red areas[13-15]. The red polyhedral near the meta position suggests the biological activity can be enhanced by introduction of more electronegative groups for strong electrostatic field interactions. The vice versa is the case with blue region. Since the steric contribution was too low for the given set of compounds, it did not show any appreciable enhancement in biological activity with inclusion of bulky groups.

The above study suggests that the, electronegative character of the substituents preferably at meta position of benzamide moiety result in significant enhancement of

TABLE 2: CALCULATION OF PARAMETERS FOR THE GIVEN SERIES OF COMPOUNDS

Compound No.	CoMFA both	CoMFA steric	CoMFA Electro-static	C log P[a]	CMR[b]	Dip. X[c]	Dip. Y[d]	Dip. Z[e]
1	104	52	16	2.98	6.78	-1.64	-4.36	-0.8
2	119	59	22	3.45	7.26	1.03	-0.90	-3.39
3	109	63	21	2.07	7.15	-0.79	-5.28	-1.13
4	110	62	22	0.10	8.12	-0.68	-5.22	1.00
5	127	48	31	2.29	8.12	3.22	-0.72	-0.23
6	129	52	32	2.29	8.12	0.26	-4.08	-6.91
7	100	58	29	3.6	6.94	1.44	-2.19	-3.56
8	124	42	51	3.18	6.80	2.64	-2.91	-1.71
10	106	53	20	3.75	8.28	0.64	7.91	-2.19
11	108	54	20	3.75	7.28	-0.22	-1.52	-2.48
12	106	53	18	3.90	7.56	-0.62	-1.92	-2.22
13	112	56	19	3.90	7.56	-0.23	-1.74	-2.47
14	111	55	21	3.40	7.25	0.18	-1.85	-4.05
15	113	56	38	3.90	7.29	1.90	-2.06	2.28
16	118	58	26	3.02	7.40	1.22	-0.32	-3.84
17	120	60	23	3.09	7.40	-1.39	-3.43	-2.73
18	115	57	22	3.09	7.87	0.00	-3.58	-3.45
19	125	62	23	3.62	7.40	0.05	-3.58	-3.54
20	109	54	23	2.85	8.05	-1.85	-3.65	-0.44
24	109	52	27	2.55	7.40	1.03	-0.90	-3.39
25	111	61	23	2.85	7.23	-0.51	-1.44	3.48
26	107	52	29	2.55	8.19	-3.64	-0.14	-4.35
27	122	74	23	0.0	6.80	-3.00	-3.48	-2.58
28	104	52	20	3.18	10.22	0.77	-2.01	-1.68
29	148	54	26	5.43	7.40	-0.42	-2.61	-3.14

[a]Computational log of Partition Coefficient. [b]Computational Molecular Refractivity. [c]Dipole for X Component. [d]Dipole for Y Component. [e]Dipole for Z Component

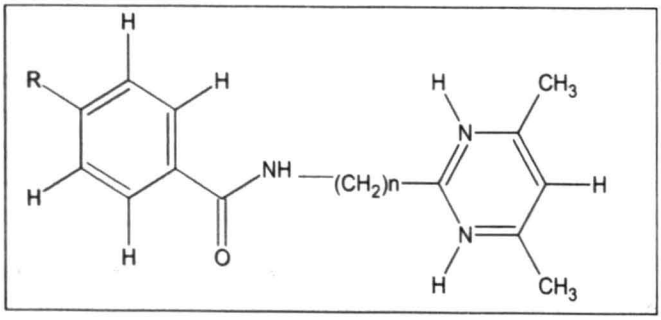

Fig. 1: N- (4,6-dimethyl-2-pyrinyl) benzamide

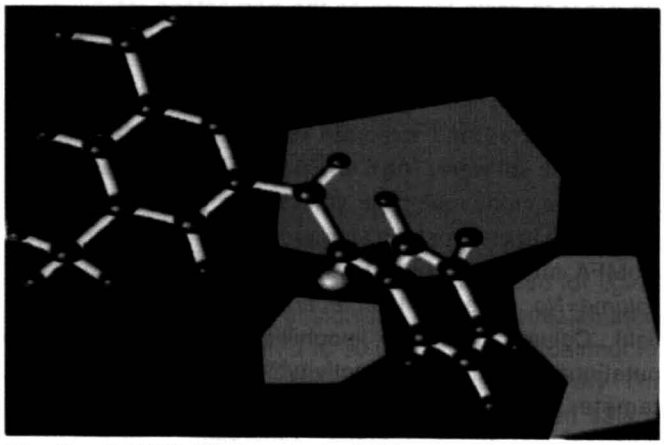

Fig. 2: CoMFA Electrostatic field

TABLE 3: RESULT OF COMFA PARTIAL LEAST SQUARE ANALYSIS RUN

Parameter	Value
No. of compounds	23
Principal components[a]	5
r^2cv^b	0.465
F test[c]	54.38
r^2d	0.976
P Value	0.000
SEE	0.072
Steric Contribution (Normal Coif, Fraction)[e]	(1.331, .316)
Electrostatic contribution	(2.044, 0.486)
CMR	(0.723, 0.172)
Z component	(0.109, 0.0260

[a]Optimal no. of components. [b]Cross validated r^2 after N leave out procedure. [c]r^2 =(SD-PRESS)/SD = (^{Y}Actual-^{Y}Mean)^2. [d]Ratio of r^2 explained to unexplained = $r^2/1-r^2$. [e]Values of Normal Coefficient and Fraction given in the parenthesis.

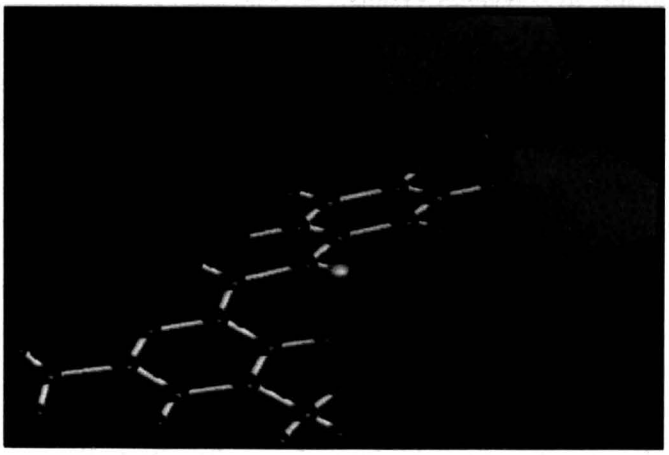

Fig. 3: CoMFA steric fields

biological activity. It suggests that an inclusion of electronegative groups (at meta position) like -SCH_3, -CHF_2, -CF_2CH_3, -$CHFCH_2$, affect the electron distribution and will improve pharmacological activity of the molecule.

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