RESEARCH PAPER

Accepted 8 May 1999
Received 7 August 1998
Indian J. Pharm. Sci., 1999, 61 (4) 206-212

A Quantitative Structure-Activity Relationship Analysis of some Substituted Oxazolopyridines and Benzimidazoles with Antiinflammatory Activity

S.K. CHAKRAVARTI AND S.C. CHATURVEDI*
Department of Pharmacy,
Shri Govindram Seksaria Institute of Technology and Science,
23-Park Road, Indore 452003 (M.P.)
Phone : 91-731-434095 Fax : 91-731-432540

The lowest energy conformations of some antiinflammatory 2-(substituted phenyl)oxazolopyridines, 2-(substituted pyridinyl) benzimidazoles and 1H-benzimidazoles were calculated and quantitative structure-activity relationship analysis was then performed on each category of compounds using thermodynamic, electronic and spatial descriptors.The resulting QSAR equations were validated by leave-one-out cross validation method. Electronic parameter (dipole moment) and spatial parameters (molecular volume and principal moment of inertia) were found to have significant correlationship with antiinflammatory activity.

A large number of arylacetic acids showing antiinflammatory activity has been reported in past few decades[1,2]. Unfortunately, many of these acids have exhibited considerable gastrointestinal intolerance in man. It is generally agreed that gastric irritation is associated, directly or indirectly, with the acidic nature of these drugs[3]. On the other hand, nonacidic antiinflammatory agents, as a class, are generally much less irritating to the gastrointestinal tract[4]. Following these considerations we thought it of importance to study the quantitative structure-activity relationship of some antiinflammatory compounds devoid of acidic functions so that associated molecular properties can be identified and exploited to optimize antiinflammatory activity.

Compounds containing ring structures like benzimidazoles[5] and oxazolopyridines[6] (aryl-fused heterocycles) have been reported to have antiinflammatory activity. Notable examples are 1H-benzimidazoles such as 2-benzyl-1H-benzimidazole, 2-(3-fluorophenyl)1H-benzimidazole, 2-[4-chlorophenyl) methyl]-5-trifluoromethyl-1H-benzimidazole, 1-[(4-fluorophenyl) methyl]-2-([4-propyl-1-piperazinyl)methyl]1H-benzimidazole and thiabendazole[7]. The present paper describes the quantitative structure activity relationships of some 2-phenyl oxazolopyridines, 2-(substituted pyridinyl) benzimidazoles and 1H-benzimidazoles. The structures of the compounds were chosen so that they would cover a wide structural variation.

*For Correspondence

EXPERIMENTAL

The antiinflammatory data of 2-(substituted phenyl) oxazolopyridines (series A and series B, Table 1 and Table 2), 2-(substituted pyridinyl) benzimidazoles (series C, Table 3) and 1H-benzimidazoles (series D, Table 4) were taken from Clark et al[6], Tsukamoto et al[5] and Evans et al[7] respectively. All the biological activity data (AA) has been converted to logarithmic equieffective molar doses (LogBA) for QSAR analysis. The software Cerius2 version 1.6 (Biosym/MSI)[8] on a Silicon Graphics[9] Workstation has been used to perform all molecular modeling functions.

The energy of the molecules were minimized using conjugate gradient algorithm[10] working under Universal Force Field[11]. After energy minimization various possible

conformations of each molecule were searched and the lowest energy conformation amongst these was found. All the descriptor calculations were performed on this lowest energy conformation.

Following descriptors were calculated for QSAR study: Desolvation Free Energy for Water (FH2O)[12], Desolvation Free Energy for Octanol (FOCT)[12], Log of Partition Coefficient (LOGP)[13], Molecular Refractivity (MR)[14], Number of Rotatable Bonds (ROTBONDS)[15], Molecular Surface Area (AREA)[15], Density (DENSITY)[15], Molecular Weight (MW)[15], Molecular Volume (VM)[15,16], Principal Moment of Inertia (PMI)[17], Principal Moment of Inertia-X component (PMIX)[17],Principal Moment of Inertia-Y component (PMLY)[17], Principal Moment of Inertia-Z component (PMIZ)[17], Sum of Atomic Polarizabilities (APOL)[18], Dipole Moment (DIPOLE)[19], Dipole Moment - X component (XDIP)[19], Dipole Moment - Y component (YDIP)[19], Dipole Moment - Z component (ZDIP)[19], Energy of Highest Occupied Molecular Orhital (HOMO)[20], Energy of Lowest Unoccupied Molecular Orbital (LIMO)[20] and Partial Atomic Charges[21].

Topological descriptors were also calculated and tested but they were not found to have any significant correlation and therefore they are not included in the present paper.

Stepwise multiple regression analysis method[22,23] was used to perform QSAR. Following statistical measures were used : n - number of samples in the regression, r-coefficient of correlation, S - standard deviation i.e. $sqrt(\Sigma(Y_{obs}-Y_{calc})^2/n-k-l))$ where k = number of variables and F-F-test for statistical significance. Leave-one-out method was employed for cross validation of the equations.

RESULTS AND DISCUSSION

Series A: 2-(substituted phenyl)oxazolo [4,5-*b*]pyridines[6]

When this series of compounds were subjected to QSAR analysis after excluding compounds with BA=0, Equation [1] resulted :

LOG(BA)= -0.02562(±0.00434)VM-0.62831 (±0.17484)YDIP+0.60517(±0.34634) DENSITY+0.02352(±0.00923)MR+2.74304 (±1.21619)NCHARGE+3.15109 [1]

n = 26 r = 0.831 F = 53.481 S = 0.195

Where NCHARGE is the charge on nitrogen atom of oxazole nucleus.

When parabolic relationships were searched Equation [2] was obtained :

LOG(BA) = -10.02166(±1.38801)HOMO^2-214.02258 (±29.54959)HOMO+1.75339(±0.35163) DENSITY+0.33449(±0.06618)DIPOLE 0.57529(±0.15765)XDIP-1146.18936 [2]

n = 22 r = 0.895 F = 38.283 S = 0.142

In Equation [2] compound with lowest biological activity (Compd. No. 24) and compounds for which the software could not calculate HOMO (Compd. No. 11, 16 and 28) were excluded from the analysis.

The leave-one-out predicted activity by Equation [1] and Equation [2] is given in Table 1. It can be observed from the predicted values that prediction ability of Equation [1] is better than Equation [2].

Series B: 2-(substituted phenyl)oxazolo[5,4-*b*]pyridines[6]

In this series, the compounds with BA=0 were excluded and the remaining compounds were subjected to stepwise multiple regression analysis which resulted in the following Equation :

LOG(BA) = 1.00218(±0.18527)XDIP - 0.02245 (±0.00651)VM+0.28309(±0.14649) YDIP+2.72648 [3]

n = 18 r = 0.879 F = 54.168 S = 0.212

When the compound with lowest activity (No. 17) was excluded and rest of the compounds were subjected to analysis, following Equation was obtained:

LOG(BA) = 0.75775(±0.12079)XDIP-0.00147 (±0.00029)PMI-0.02393(±0.00693) MR+0.36379 [4]

n = 17 r = 0941 F = 116.669 S = 0.129

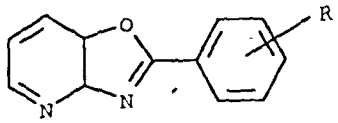
Deletion of only one compound resulted in a significant improvement in r and F-test of Equation [4]. The leave-one-out predicted biological activities by Equation [4] is presented in Table 2. The predictive capability of Equation [4] is good which is evident form Table 2.

When series A and series B are combined and subjected to stepwise multiple regression analysis after deletion of compounds with low activities (AA=3 and AA=5), following Equation was obtained :

LOG(BA) = -0.2106(±0.00354)VM+0.08859 (±0.03076)DIPOLE+0.25212(0.08738) XDIP-0.16834(±0.08072)LUMO- 0.45905(±0.33874)ZDIP- 0.13691(±0.10515) YDIP+2.72538 [5]

n = 40 r = 0.762 F = 52.559 S = 0.185

Table I - Structure and antiinflammatory activity for 2-(substituted phenyl) oxazolo [4,5-b] pyridines (Series A)

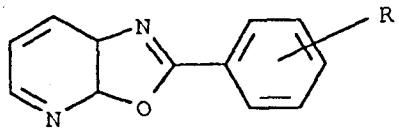


No.	R	AA*	BA**	LOG(BA)	Predicted activity (leave-one-out)	
					Eq [1]	Eq [2]
1	H	41	0.2682	-0.5716	-0.6543	0.6912
2	4-F	28	0.1999	-0.6991	-0.7767	-0.6131
3	4-OMe	14	0.1056	-0.9764	-0.7161	-1.4856
4	4-Cl	24	0.1845	-0.7339	-0.8866	-0.7093
5	4-OCF_3	0	0.0000	-	-	-
6	4-Me	5	0.0350	-1.4554	-1.0687	-1.0391
7	3-NO_2	21	0.1688	-0.7725	-0.4709	-1.4474
8	3-Me	14	0.0981	-1.0083	-0.8559	-0.8485
9	3-Cl	32	0.2460	-0.6090	-0.5791	-0.6473
10	3-CN	21	0.1549	-0.8101	-0.7161	-0.6169
11	3-Br	23	0.2109	-0.6759	-0.9834	-
12	2-Cl	38	0.2922	-0.5344	-0.5919	-0.7242
13	2-F	64	0.4569	-0.3401	-0.3623	-0.7091
14	2-OMe	9	0.0679	-1.1683	-0.9154	-1.1988
15	2-Me	0	0.0000	-	-	-
16	2-Br	24	0.2201	-0.6574	-0.5169	-
17	2-CF_3	19	0.1673	-0.7764	-0.7879	-0.7686
18	2-SMe	21	0.1696	-0.7706	-1.3479	-1.1750
19	2-CN	62	0.4572	-0.3399	-0.7683	-0.6716
20	2-F,4-Cl	19	0.1575	-0.8028	-0.9698	-0.6207
21	2,5-F_2	18	0.1393	-0.8560	-0.7172	-0.4179
22	2,6-F_2	66	0.5108	-0.2917	-0.2256	-0.4949
23	2,4-F_2	23	0.1780	-0.7496	-0.7366	-0.5114
24	2-CN,5-OMe	3	0.0251	-1.5999	-1.2521	-
25	2,6-CN_2	19	0.1559	-0.8070	-0.9520	-0.5923
26	2,6-Cl_2	14	0.1237	-0.9076	-0.6810	-0.7061
27	2-Cl,6-F	50	0.4144	-0.3826	-0-5700	-0.6408
28	2-Br,5-OMe	8	0.0814	-1.0895	-1.1264	-

* *Percent inhibition of paw edema by 30.0 mg/kg of drug*

** *Percent paw edema inhibition per micromolecule of drug per kg of body weight*

Table II - Structure and antiinflammatory activity for 2-(substituted phenyl) oxazolo[5,4-b] pyridines (Series B)



No.	R	AA*	BA**	LOG(BA)	Predicted activity (leave-one-out)Eq[4]
1	H	55	0.3597	-0.4440	-0.61835
2	4-F	27	0.1928	-0.7149	-0.70097
3	4-OMe	29	0.2187	-0.6602	-0.88026
4	4-Cl	14	0.1076	-0.9680	-1.18251
5	4-Me	0	0.0000	-	-
6	3-OMe	0	0.0000	-	-
7	3-Cl	8	0.0615	-1.2111	-1.11676
8	2-F	61	0.4355	-0.3609	-0.44018
9	2-Br	31	0.2843	-0.5463	-0.28308
10	2-CN	61	0.4498	-0.3469	-0.33563
11	4-CN	17	0.1254	-0.9019	-0.66475
12	3-CF_3	7	0.0616	-1.2101	-1.38254
13	3-Me	14	0.0981	-1.0083	-0.93134
14	2-NO_2	57	0.4583	-0.3389	-0.40319
15	2-NH_2	13	0.0915	-1.0384	-0.84135
16	3-CN	50	0.3687	-0.4333	-0.48135
17	2-Me	3	0.0210	-1.6773	-
18	2,6-F_2	50	0.3869	-0.4123	-0.5137
19	3-F	35	0.2499	-0.6022	-0.59044
20	4-No_2	5	0.0402	-1.3958	-1.16191

* *Percent inhibition of paw edema by 30.0 mg/kg of drug*

** *Percent paw edema inhibition per micromolecule of drug per kg of body weight*

Although the correlation coefficient of Equation [5] is less, it should be noted that VM, DIPOLE, and components of DIPOLE found place in Equation [5].

Series C: 2-(Substituted pyridinyl)benzimidazoles[5]

When this series was subjected to stepwise regression after deletion of compounds with AA<0, no statistically significant equation was obtained, but when compounds having AA<=10 were deleted from space then Equation [6] resulted :

LOG(BA) = 0.16711(±0.10766) YDIP +0.00611(±0.00197) VM +0.02238 (±0.00838) FH2O-0.12376(±0.16007) HOMO -3.18513 [6]

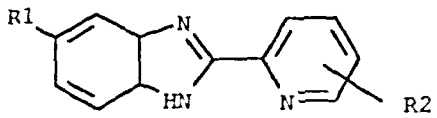
n = 24 r = 0.759 F = 29.886 S = 0.120

Again in Equation [6] YDIP and VM alongwith FH2O and HOMO is required to explain the variation in activity.

Series D: 1H-Benzimidazoles[7]

In this series some 1H-benzimidazoles which are

Table III - Structure and antiinflammatory activity for 2-(substituted pyridinyl) benzimidazole (Series C)

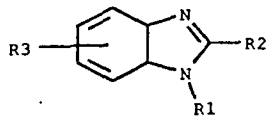


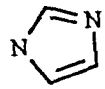
No.	R1	R2	AA*	BA**	LOG(BA)
1	H	H	22	0.0429	-1.3671
2	H	3-Me	17	0.0356	-1.4489
3	H	4-Me	-4	-0.0084	-
4	H	5-Me	19	0.0398	-1.4006
5	H	6-Me	44	0.0921	-1.0359
6	H	5-Et	44	0.0982	-1.0077
7	H	6-Et	41	0.0915	-1.0383
8	H	5-n-Bu	-16	-0.0402	-
9	H	5-CH_2OH	-10	-0.0225	-
10	H	6-CH_2OH	-13	-0.0293	-
11	H	5-COOEt	-16	-0.0428	-
12	H	6-COOEt	31	0.0829	-1.0817
13	H	6-Cl	30	0.0689	-1.1618
14	H	6-OMe	47	0.1059	-0.9752
15	H	6-$CONH_2$	13	0.0309	-1.5090
16	H	6-OH	-7	-0.0148	-
17	Me	H	35	0.0732	-1.1353
18	OMe	H	34	0.0766	-1.1159
19	Cl	H	36	0.0827	-1.0826
20	Me	5-Me	7	0.0156	-1.8061
21	Cl	5-Me	-5	-0.0122	-
22	Me	6-Me	42	0.0938	-1.0279
23	OMe	6-Me	40	0.0957	-1.0190
24	Cl	6-Me	39	0.0950	-1.0221
25	OH	6-Me	6	0.0135	-1.8692
26	Me	5-Et	35	0.0831	-1.0806
27	OMe	5-Et	58	0.1469	-0.8329
28	Cl	5-Et	-2	-0.0052	-
29	OH	5-Et	25	0.0598	-1.2232
30	NO_2	5-Et	-5	-0.0134	-
31	NH_2	5-Et	25	0.0596	-1.2249
32	NHAc	5-Et	5	0.0140	-1.8534
33	Me	6-Et	10	0.0237	-1.6247
34	OMe	6-Et	52	0.1317	-0.8804
35	Cl	6-Et	3	0.0077	-2.1117
36	H	5,6-$(Me)_2$	37	0.0826	-1.0829
37	Me	5,6-$(Me)_2$	-19	-0.0451	-
38	Me	6-OMe	32	0.0766	-1.1159
39	Me	6-Cl	36	0.0877	-1.1159
40	Me	6-OH	-6	-0.0135	-

* *Percent inhibition of paw edema by 100.0 mg/kg of drug*

** *Percent paw edema inhibition per micromolecule of drug per kg of body weight*

Table IV - Structure and antiinflammatory activity for 1H-benzimidazole (Series D)



No.	R1	R2	R3	AA*	BA**	LOG(BA)	Predicted activity (leave-one-out) Eq[7]
1	H	4-ClC_6H_4	5(6)-MeO	2	0.0157	-1.8037	-1.4645
2	H	4-ClC_6H_4	5(6)-OH	4	0.0296	-1.5293	-1.6091
3	Me	4-ClC_6H_4	5-O-$(CH_2)_2$- 	6	0.0671	-1.1731	-1.4683
4	Me	4-ClC_6H_4	5-O-CH(OMe)Me	33	0.3006	-0.5220	-1.1742
5	C_6H_5	4-ClC_6H_4	6-O-$(CH_2)_2NEt_2$	43	0.5474	-0.2617	-0.4829
6	C_6H_5	4-ClC_6H_4	6-NH-$(CH_2)_2OH$	10	0.1098	-0.9593	-1.4141
7	C_6H_5	4-ClC_6H_4	6-NH-$(CH_2)_3Me$	2	0.0229	-1.6408	-0.7225
8	C_6H_5	4-ClC_6H_4	6- 	0	0.0000	-	-
9	C_6H_5	4-ClC_6H_4	5-CH(NHEt)Me	21	0.2209	-0.6558	-0.8296

** Percentage improvement in the joint of the paw compared to controls by 33.0 mg/kg of drug*

*** Percent improvement in the joint of the paw micromolecule of drug per kg of body weight*

substituted on various positions of benzimidazole ring (Table 4) were considered. The compound with BA=0 was deleted and then the analysis was carried out. It resulted in the following Equation :

LOG(BA) = 0.00502(±0.00176)PMIX-1.61539 (±76524) XDIP-1.97594

n = 8 r = 0.799 F = 10.604 S = 0.401 [7]

Leave-one-out prediction of Equation [7] is shown in Table 4.

The above studies revealed that electronic and steric parameters are associated with antiinflammatory activity of substituted oxazolopyridines and benzimidazoles. Amongst the steric parameters, mainly molecular volume which is indicative of steric bulk and principal moment of inertia which describes the mass distribution over the molecules, are found to be of significance. Amongst the electronic parameters, components of dipole moment were found to be associated with activity.

In series A, it has been observed that substituents on the phenyl ring which produce a less value of VM and high negative value of YDIP generally result in high activity. For example, 2-F (AA=64, VM=153.26, YDIP=-0.416), 2,6-F_2 (AA=66, VM=156.40, YDIP=-0.347) have high activity. Bulky substituents results in low activity for example, 2-Me (AA=0, VM-167.72, YDIP=-0.125), 4-Me (AA=5, VM=168.03, YDIP=0.345), 2-CN, 5-OMe (AA=3, VM=186.89, YDIP=-0.274) and 2-Br, 5-OMe (AA=8, VM=195.84, YDIP=-0.514).

In Series B, it has been observed that substituents on the phenyl ring which produce a high value of XDIP result in high activity, for example, 3-CN (AA=50, XDIP=0.315) and 2-NO_2 (AA=57, XDIP=0.622), whereas, substituents which produce a low XDIP value result in low activity, for example 3-Cl (AA=8, XDIP=-0.242) and 3-CE_3 (AA=7, XDIP=-0.215).

When both Series A and Series B were combined and analyzed, then once again dipole moment and its components were found to be associated with activity. In Series C, YDIP, VM, FH20 and HOMO were found to influence the activity and in Series D, PMIX and XDIP are associated with antiinflammatory activity.

Although a single equation was not found to be describing the antiinflammatory activity of all the four series of compounds and some equations are poor in prediction capability, this study identified some common factors responsible for variation in activity in the group of antiinflammatory molecules having oxazolopyridine and benzimidazole ring structure. Consequently this study may prove to be helpful in development and optimization of non-acidic antiinflammatory agents having similar ring structures.

ACKNOWLEDGMENTS

Authors wish to thank M/s Torrent Pharmaceuticals Ltd., Ahmedabad for providing access to computational and molecular modeling software facilities. Authors are also thankful to Director, S.G.S.I.T.S., Indore for providing facilities for this project. S.K. Chakravarti is thankful to CSIR, New Delhi for providing research fellowship for this project.

REFERENCES

1. Moser, P., Sallman, A. and Wiesenberg, I., **J. Med. Chem.,** 1990, 33, 2358.
2. Atkinson, D.C., Godfrey, K.E., Meek, B., Saville, J.F., and Stillings, M.R., **J. Med. Chem.,** 1982, 26, 1353.
3. Price, A.H. and Fletcher, M., **Drugs,** 1990, Suppl. 5, 1.
4. Shen, T.Y., **Drugs Exp. Clin. Res.,** 1977, 2, 1.
5. Tsukamoto, G., Yoshino, K., Kohno, T., Ohtaka, H., Hajime, K. and Ito, K., **J. Med. Chem.,** 1980, 23, 734.
6. Clark, R.L., Pessolano, A.A. Witzel, B., Lanza, T. and Shen, T.Y., **J. Med. Chem.,** 1978, 21, 1158.
7. Evans, D., Hicks, T.A., Williamson, W.R.N., Dawson, W., Meacock, S.C.R. and Kitchen, E.A., **Eur. J. Med. Chem.,** 1996, 31, 635.
8. Cerius2 Version 1.6, Biosym/Molecular Simulations Inc., 9685 Scranton Road, California, USA 92121-3752.
9. Silicon Graphics, Inc., 2011 N. Shoreline Blvd., Mountain View, CA, 94043, USA.
10. Fletcher, R. and Reeves, C.M., **Comput. J.,** 1964, 7, 149.
11. Rappe, A.K., Casewit, C.J., Colwell, K.S., Goddard III, W.A. and Skiff, W.M., **J. Am. Chem. Soc.,** 1992, 114, 10024.
12. Pearlman, R.S., In; Yalkowsky Sh, Sinkula AA, Valvani YC Eds, Physical Chemistry Properties of Drug Dekker, New York, 1980.
13. Hansch, C. and Leo, A., In: Substituent Constants for Correlation Analysis in Chemistry and Biology, John Wiley and Sons, New York, 1979.
14. Dunn, W.J. III, **Eur. J. Med. Chem.,** 1977, 12, 109.
15. van de Waterbeemd, H. and Testa, B., **Adv. Drug. Res.,** 1987, 16, 85.
16. James, K.C., In: Smith, H.J. Eds., Smith and Williams' Introduction to the Principles of Drug Design Wright Publishers, 1988.
17. Hill, T.L., In: Introduction to Statistical Thermodynamics, Addision Wesley, Reading MA, 1960.
18. Marsili, M. and Gasteiger, J., **Croatica. Chemica. Acta.,** 1980, 53, 601.
19. Gasteiger, J. and Marsili, M., **Tel. Letters.,** 1978, 34, 3181.
20. Pople, J.A. and Segal, G.A., **J. Chem. Phys.,** 1966, 44, 3289.
21. Rappe, A.K. and Goddard III, W.A., **J. Chem. Phys.,** 1991, 95, 3358.
22. Draper, N.R., and Smith, H., In: Applied Regression Analysis, John Wiley & Sons, New york, 1966.
23. Chakravarti, S.K., Ajmani, S. and Chaturvedi, S.C., **Ind., J. Pharm. Sci.,** 1998, 60, 371.