RESEARCH PAPER

Accepted 7 July 2000
Revised 30 June 2000
Received 10 August 1998
Indian J. Pharm. Sci., 2000, 62 (5) 388-392

Quantitative Structure Activity Relationship Analysis of a Series of Antiinflammatory 5-phenyl-3H-imidazo(4,5-c) (1,8) naphthyridin-4-(5H)-ones

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A series of anti-inflammatory 5-phenyl-3H-imidazo(4,5-c) (1,8) naphthyridin-4-(5H)-ones was subjected to quantitative structure activity relationship (QSAR) analysis. The QSAR study showed that the oral antiinflammatory activity, as determined in the carrageenan induced rat paw edema method was highly correlated with thermodynamic (MR) and electronic (Cedensity and Ncharge) parameters. The analysis suggests that lipophilic substituents at third position on the nitrogen atom which increase double bond conjugation within the molecule will enhance the biological activity.

Extensive research is being carried out in our laboratory to find new potent derivatives of non steroidal anti-inflammatory drugs[1,2]. Due to our interest in various structural types and possible mechanisms of action of new potential treatments for inflammatory disorders, we subjected 5-phenyl-3H-imidazo (4,5-c) (1,8) naphthyridine-4-(5H)-ones[3] to quantitative structure activity relationship (QSAR) analysis. They exhibit a broad spectrum of antiinflammatory activity like glucocorticoids in animal models with less actual lethal toxicity. We have used computer-aided molecular modeling to study the QSAR since molecular modeling allow us to estimate a large number of 2D and 3D physicochemical properties. This study may contribute to better understanding between structure and antiinflammatory, activity.

EXPERIMENTAL

The antiinflammatory data was taken from Suzuki *et al.* and the data is expressed as per cent inhibition of carrageenan-induced rat paw edema by the oral route at dosage 50 or 100 mg/kg (AA). For QSAR studies, we have converted the data to per cent paw edema inhibition per micromole of drug per kilogram of body weight (BA). QSAR equation have been derived using log(BA*100) i.e. log(BA') Table 1. For molecular modeling and other related computational studies the software Cerius2 (version 3.5)[4] has been used.

Structures of all compounds (1-33 in Table 1) were sketched using 3D sketcher module of the Cerius2. Energy calculations were done using the universal force field[5]. Every structure was subjected to energy minimization process, in which, first steepest descent (SD) method was used to eliminate bad contacts and then more accurate minimizing methods like Conjugate Gradient[6] (CG) and Truncate Newton-Raphson (N-R) were used. Conformations for each compound were generated and its analysis was performed using GRID method This method was used to perform simple systematic search by varying each specified torsion angle over a grid of equally spaced value. Various possible conformations of each molecule was obtained by setting the limit for maximum number of conformations which can be generated to 150 and using 5 kcal per mole energy cutoff. The most stable conformation of each compound was saved. Geometry of the stable conformation was optimized using a semi-empirical quantum mechanics module, namely, MOPAC (version. 6.0). The AM-1 Hamiltonian has been

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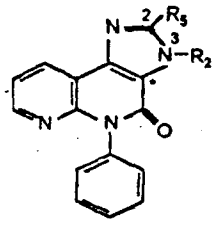
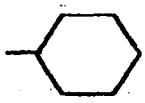
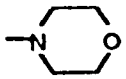
TABLE 1 : STRUCTURES AND BIOLOGICAL ACTIVITY DATA FOR 5-PHENYL-3H-IMIDAZO [4,5-c] [1-8] NAPHTHYRIDIN-4-(5H)-ONES



Compound No.	R_2	R_5	AA[a]		BA[b]	log (BA')
			100	50		
1	CH_3	H		40.0	0.221	1.3444
2	C_2H_5	H		58.2	0.337	1.5276
3	N-C_3H_7	H		57.3	0.348	1.5416
4	i-C_3H_7	H	43.1		0.131	1.1173
5	CH_2CHCH_2	H		67.8	0.409	1.6117
6	n-C_4H_9	H		45.8	0.291	1.4639
7	i-C_4H_9	H		57.4	0.365	1.5623
8	n-C_6H_{13}	H		35.2	0.243	1.3856
9	$CH_2C_6H_5$	H		63.0	0.443	1.6464
10	$CH(CH_3)C_6H_5$	H	3.5		0.013	0.1139
11	$CH_2CH_2C_6H_5$	H	2.2		0.008	-0.0969
12	$CH_2CHCHC_6H_5$	H	26.3		0.099	0.9956
13	CH_2 	H	34.7		0.124	1.0934
14	CH_2COCH_3	H		41.3	0.263	1.42
15	$CH_2CH_2CH_2OH$	H		42.6	0.273	1.4362
16	$CH_2CH_2OCH_2CH_3$	H		56.7	0.379	1.5786
17	$CH_2CO_2C_2H_5$	H		23.1	0.161	1.2068
18	$CH_2CH_2OCOCH_3$	H		42.2	0.294	1.4683
19	CH_2-4-ClC_6H_4	H	21.3		0.082	0.9138
20	CH_2-4-$NO_2C_6H_4$	H	35.9		0.142	1.1523
21	CH_2-4-$CH_3C_6H_4$	H	39.2		0.143	1.1553
22	CH_2-4-$CH_3OC_6H_4$	H	37.8		0.144	1.1584
23	CH_2-4-$CH_3O_2CC_6H_4$	H		8.7	0.071	0.8513
24	CH_2-3-BrC_6H_4	H	26.9		0.116	1.0645

25	CH_2-3-NO_2 C_6H_4	H	33.1		0.131	1.1173
26	CH_2-3-CH_3 C_6H_4	H		18.4	0.135	1.1303
27	CH_2-3-$CH_3OC_6H_4$	H	13.0		0.049	0.6902
28	CH_2-2-ClC_6H_4	H	14.9		0.057	0.7559
29	CH_2-2,5-$(CH_3)_2$ C_6H_3	H	1.2		0.004	-0.3979
30	$CH_2CH(OH)CH_3$	H		48	0.307	1.4871
31	$CH_2CH_2CH_2N(C_2H_5)_2$	H	7.2		0.027	0.4314
32	$CH_2CH_2CH_2$ 	H		9.7	0.075	0.8751
33	$CH_2C_6H_5$	CH_3		4.7	0.034	0.5315

a : Per cent Inhibition of carrageenan-induced rat paw edema at 50 or 100 mg/kg orally.

b : Per cent paw edema inhibition per μ mole/Kg body weight * At 2 position : Ccharge and Cedensity. — At 3 position : Ncharge and Nedensity and * At this carbon:CNC charge was calculated.

used. The lowest energy of the optimized conformer of each compound is shown in Table 2.

The optimized conformers were used for calculating physicochemical parameters by standard procedures given in QSAR+modules of Cerius2. The AM1-Hamiltonian of MOPAC module was used for calculating atomic charges and electron densities on various atom (shown in Table 1). Connolly surface calculations using water molecule as probe were carried out on all atoms of the molecules with parameters such as probe radius of 1.4 A. dot density of 8.0 A^2, VDW scale factor 1.0.

Following descriptors were calculated for QSAR study (values of only those descriptors occurring in different equations are given in Table 2);

Thermodynamic descriptors calculated were log of partition coefficient (logP)[7] and molecular refractivity (MR)[8]. Spatial descriptors derived were number of rotatable bonds (ROTBONDS), molecular surface area (AREA), density, molecular weight, molecular volume (Vm), principle moment of inertia (PMI)[9], principle moment of inertia-x component (PMIX)[9], principle moment of inertia-y component (PMIY)[9] and principle moment of inertia-z component (PMIZ)[9].

Electronic descriptors such as sum of atomic polarizibilities (APOL)[10], dipole moment (DIPOLE)[11], dipole moment-x component (XDIP)[11], dipole moment-y component (YDIP)[11], dipole moment-z component (ZDIP)[11], super delocalizibility (Sr) and partial atomic charges, were derived.

Shape descriptors calculated were difference volume (DIFFV), common overlap steric volume (COSV), non common overlap steric volume (NCOSV), common overlap volume ratio (Fo) and RMS to shape reference (ShapeRMS).

Quantum mechanical descriptors: These descriptors were calculated by MOPAC module. Lowest unoccupied molecular orbital energy (LUMO_MO)[12], highest occupied molecular orbital energy (HOMO_MO)[13], heat of formation (HF_MO). Conformational descriptors such as radius of gyration (ROG) and Indicator variables: Like hydrogen bond acceptor (HBA), hydrogen bond donor (HBD) and Connolly surface (Connolly)[14] were also derived.

The correlation between biological activity and physicochemical parameters was found through stepwise multiple regression analysis using the method of least squares. The limit of cross correlations has been given as 0.5. Linear and quadratic (parabolic) QSAR equations have been generated. The statistical measures used were: number of compounds (n), correlation coefficient (r), squared correlation coefficient (R^2), fischer's value (F) and standard deviation (s).

TABLE 2 : CALCULATED VALUES OF DESCRIPTORS FOR COMPOUNDS OF THE SERIES AND LOWEST ENERGY OF THE CONFORMATIONS

Compd. No.	Lowest Energy (kcal/mole)	Vm	Connolly	logP	MR	CNCcharge	Cedensity	Ncharge	Sr
1	99.8323	238.7405	243.12	2.4808	78.3766	0.2046	3.841	-0.421	0.7534
2	95.6074	255.5582	265.705	2.8233	83.1246	0.2025	3.845	-0.4017	2.9688
3	106.3825	272.5686	273.694	3.2919	87.6488	0.1963	3.848	-0.393	3.7422
4	53.7169	271.9867	279.465	3.2364	87.5428	0.1894	3.839	-0.3801	3.7607
5	94.3409	266.9711	271.442	3.2214	87.5393	0.206	3.86	-0.4038	2.1485
6	111.3402	289.7536	295.477	3.6882	92.2498	0.1979	3.856	-0.4149	1.7208
7	75.6223	289.4085	291.318	3.6947	92.1206	1.1915	3.857	-0.4092	1.7236
8	112.4371	323.6012	330.752	4.4808	101.4518	0.1948	3.851	-0.3994	1.6728
9	102.9965	310.7914	308.502	4.2574	102.9892	0.2043	3.87	-0.4126	1.3269
10	98.3394	327.4764	324.318	4.6705	107.4074	0.1931	3.863	-0.3939	0.4904
11	99.9371	327.591	321.038	4.5091	107.7438	0.1934	3.835	-0.3967	0.4904
12	100.182	337.52	333.87	4.7898	113.3078	0.215	3.854	-0.3952	1.6173
13	111.6527	329.2559	319.487	4.3796	104.1214	0.1916	3.863	-0.4124	0.4903
14	76.8172	274.8892	279.606	2.5698	88.0123	0.1878	3.866	-0.442	2.9455
15	101.3331	280.9966	289.759	2.0898	89.5343	0.2017	3.842	-0.4087	0.6929
16	84.7717	297.7785	308.603	2.6585	94.1681	0.1845	3.863	-0.4513	1.7713
17	102.9707	300.3908	318.447	2.3968	93.9783	0.1867	3.834	-0.426	0.4864
18	74.2457	300.7218	312.728	2.1668	93.8204	0.1861	3.852	-0.4499	0.4867
19	91.4488	324.6537	320.399	4.7754	107.794	0.205	3.859	-0.415	1.5544
20	110.0984	334.2742	332.387	4.211	110.3139	0.2048	3.857	-0.4142	1.5677
21	91.0115	327.7883	330.66	4.7246	108.0304	0.2048	3.868	-0.4076	0.4904
22	116.0116	336.5811	339.879	4.0047	109.4524	0.2044	3.867	-0.4105	1.6599
23	139.5044	355.8998	355.594	3.9875	114.5167	0.2048	3.864	-0.4133	1.6317
24	90.3947	328.5642	325.5	5.0492	110.612	0.204	3.86	-0.4129	1.6317
25	100.956	334.7982	335.28	4.211	110.3139	0.2041	3.858	-0.4138	1.5334
26	93.0085	327.9847	325.69	4.7246	108.0304	0.2049	3.868	-0.4098	0.4904
27	111.9346	336.6165	335.751	4.0047	109.4524	0.2048	3.866	-0.4098	1.6551
28	109.9149	324.3482	319.272	4.7754	107.794	0.2024	3.784	-0.3973	1.5831
29	95.9317	344.6109	341.126	5.1918	113.0716	0.2	3.875	-0.4213	1.5494
30	64.3216	280.7828	282.994	2.4508	89.0871	0.1849	3.862	-0.4435	0.6929
31	98.6921	352.8064	352.713	3.197	110.7571	0.1972	3.857	-0.4145	0.6988
32	102.2842	350.4511	349.779	2.1694	110.3356	0.2016	3.855	-0.4055	0.4885
33	69.7743	327.5132	319.105	5.1828	105.555	0.1923	3.74	-0.397	0.4904

RESULTS AND DISCUSSION

On stepwise multiple regression analysis some significant QSAR equations obtained are as follows:

$$\log(BA') = -0.00120^{*} MR^2 + 0.207355^{*} MR - 7.42947 \quad [1]$$

$n=33$, $r=0.662$, $r^2=0.438$, $F=11.681$, $s=0.388$

$$\log(BA') = -0.00302^{*} MR^2 + 0.553022^{*} MR + 34.15645^{*} CNCcharge + 3.725210^{*} Cedensity - 44.7702 \quad [2]$$

TABLE 3 : SQUARED CROSS CORRELATION MATRIX

	log (BA')	MR	CNCcharge	Cedensity	Ncharge	Sr
log(BA')	1.000					
MR	0.398	1.000				
CNCcharge	0.007	0.178	1.000			
Cedensity	0.027	0.004	0.023	1.000		
Ncharge	0.080	0.042	0.180	0.100	1.000	
Sr	0.101	0.137	0.001	0.010	0.053	1.000

n=33, r=0.796, r^2=0.633, F=12.080, s=0.324

log (BA')= -0.00337* MR^2+0.626659* MR +46.47269 * CNCcharge -12.20119 * Ncharge+0.100169*Sr-41.8219 [3]

n=33, r=0.846, r^2=0.716, F=13.640, s=0.290

It can be seen from equation 1 that MR shows parabolic relationship with log (BA'). It depicts that an optimum steric bulk is needed for better action of drug molecules. It can be seen that the statistical significance of the equation is increased by adding electronic parameters CNCcharge, Ncharge, Cedensity, Sr. The parameters in equation 2 and 3 are not significantly cross correlated Table 3.

From the equation it can be suggested that for enhancement of biological activity, substitution on nitrogen atom on 3rd position (R_2 substituents) with electron donating groups or atoms (like N, S and O) which result in electron delocalization.

From the above analysis, it can be concluded that lipophilic substituents on the nitrogen atom at 3rd position of 5-phenyl-3H-imidazo(4,5-c)(1,8) naphthyridine-4-(5H)-ones which increase double bond conjugation within the molecule will enhance the biological activity. Also the generated QSAR equations can be used in designing of new anti-inflammatory molecules.

ACKNOWLEDGEMENTS

Authors wish to thank M/s Torrent Pharmaceutical Ltd. Bhat, Gandhinagar for providing access to molecular modeling software facilities. They are also thankful to the Director. SGSITS, for providing facilities for this work. Nirantar, A., is thankful to the Ministry of Human Resource Development, New Delhi, for providing a research fellowship for this project.

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