Eur. J. Med. Chem. 33 (1998) 47–53

Short communication

Quantitative structure–activity relationship analysis of a series of *trans*-octahydro-11-oxodibenzo-[*b*,*e*]-thiepin propionic acid derivatives

Subhash Ajmani*, Subhash Chandra Chaturvedi

Department of Pharmacy, Shri Govindram Seksaria Institute of Technology and Science, 23 Park Road, Indore – 452 003 (M.P.), India

(Received 21 April 1997; accepted 10 September 1997)

Abstract – The structures of a series of antiinflammatory *trans*-octahydro-11-oxodibenzo-[*b*,*e*]-thiepin propionic acid ester and amide derivatives were submitted to molecular modeling software, and after energy minimization of the structures, a number of electronic, spatial and thermodynamic descriptors were calculated. After quantitative structure–activity relationship (QSAR) analysis the result showed that the electronic descriptors, especially partial atomic charges on C15 and C18, have important effects on the oral anti-inflammatory activity. © Elsevier, Paris

quantitative structure–activity relationship analysis / antiinflammatory activity / thiepin propionic acid esters and amides

1. Introduction

Extensive research is being carried out in our laboratory to find new potent derivatives of non-steroidal antiinflammatory drugs belonging to the aryl propionic acid category. This category of drugs suffers from gastrointestinal complications ranging from mild dyspepsia, gastric discomfort to nausea, vomiting and gastric bleeding [1]. In order to minimize these side effects the free carboxylic acid group is generally masked by derivatization, but apart from changing its physicochemical properties, it also alters the pharmacological activity of the drug to a considerable extent. To investigate the effects of esterification and amidation on various physicochemical properties of the molecule, a series of antiinflammatory *trans*-octahydro-11-oxo-dibenzo-[*b*,*e*]-thiepin propionic acid ester and amide derivatives (*table I*) was subjected to quantitative structure–activity relationship (QSAR) analysis. Kurokawa et al. have synthesized this series to reduce ulcerogenicity of the parent acid [2]. Computer-aided molecular modeling was used for this study as it offers the opportunity to estimate a great number of physicochemical properties based on 3D and detailed electronic structure of a molecule. This study may contribute to a better understanding of the relationship between structure and antiinflammatory activity [3].

2. Method and data

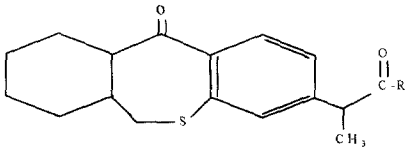
The antiinflammatory activity data were taken from Kurokawa et al. [2]. These data were expressed as 'Percent inhibition of carageenan-induced hind paw edema in the rat caused by 5 mg/kg of drug (AA)'. The data were converted to 'Percent paw edema inhibition per micromole of drug per kilogram body weight (BA)' (*table I*) for QSAR analysis.

For molecular modeling and for the calculation of various descriptors different modules provided in molecular modeling software Cerius^2 version 1.6 were used [4].

The structures of the compounds (**1–33**, *table I*) were built using the molecular sketching facilities provided in the molecular modeling environment of Cerius^2. The energy of the molecules was minimized using a conjugate gradient algorithm [5]. The force field energy expressions were the bonds, angles, torsions, inversions and van der Waals terms. The minimization terminates where the root mean square (RMS) force on the model is less than 0.1000 kCal/

*Correspondence and reprints

Table I. Structures and carageenan-induced edema data for *trans*-octahydro-11-oxodibenzo-[*b*,*e*]-thiepin propionic acid ester and amide derivatives used in this study.



Compound	R	AA[a]	BA[b]	log(BA)
1	OCH_3	21.6	1.3756	0.1385
2	OC_2H_5	38.3	2.5466	0.4060
3	O–nC_3H_7	25.4	1.7601	0.2455
4	O–iC_3H_7	25.6	1.7740	0.2489
5	O–nC_4H_9	26.0	1.8747	0.2729
6	O–iC_4H_9	29.3	2.1126	0.3248
7	O–nC_5H_{11}	22.1	1.6555	0.2189
8	O–nC_6H_{13}	28.3	2.1992	0.3423
9	O–	15.6	1.2060	0.0814
10	O–Ph	22.0	1.6742	0.2238
11	OCH_2Ph	25.6	2.0200	0.3053
12	$O(CH_2)_2Ph$	39.1	3.1949	0.5045
13	$O(CH_2)_3Ph$	26.0	2.1974	0.3419
14	OCH_2–CH=CH_2	33.5	2.3079	0.3632
15	OCH_2–CH=CHPh	20.3	1.7075	0.2324
16	OCH_2COPh	26.6	2.2481	0.3518
17	$OCH_2COOC_2H_5$	20.2	1.5776	0.1980
18	$O(CH_2)_2OC_2H_5$	34.6	2.6054	0.4159
19	$O(CH_2)_2O(CH_2)_2OH$	28.1	2.2059	0.3436
20	$O(CH_2)_2$– 	22.2	1.8540	0.2681
21	OCH_2-2-Py	30.6	2.4205	0.3839
22	OCH_2-3-Py	29.9	2.3651	0.3739
23	$O(CH_2)_2$-2-Py	25.5	2.0887	0.3199
24	NH_2	30.5	1.8509	0.2674
25	NHOH	29.9	1.9101	0.2811
26	$NHCH_3$	14.6	0.9269	–0.0330
27	$N(CH_3)_2$	2.7	0.1790	–0.7472
28[c]	$N(CH_2)_2Ph$	–5.5	–0.4329	–
29	$N(CH_2)_2OH$	22.3	1.5497	0.1903
30	$NHCH_2COOH$	29.7	2.1470	0.3318
31	–	5.3	0.3938	–0.4047
32	–	7.1	0.5304	–0.2754
33	– 	5.3	0.4097	–0.3875

[a]Percent inhibition of carageenan-induced paw edema in the rat at 5 mg/kg orally; [b]percent inhibition of paw edema per micromole of drug per kilogram of body weight; [c]compound not included in the study.

mol/Å. The non-bond and the hydrogen-bond lists were updated every 50 steps and the model was updated every 5 steps.

After energy minimization of the structures, the following descriptors were calculated for the QSAR study using the facilities provided in 'Drug Discovery Workbench QSAR+' of Cerius² (values only of those descriptors occurring in different equations are given in *table II*).

2.1. Thermodynamic descriptors

a. Desolvation free energy for water **(FH_2O)** [6–8]
b. Desolvation free energy for octanol **(FOCT)** [6–8]
c. Log of partition coefficient **(LOGP)** [6–8]
d. Molecular refractivity **(MR)** [9, 10]

2.2. Spatial descriptors

a. Molecular surface area **(AREA)** [11, 12]
b. Density **(DENSITY)** [11, 12]
c. Molecular weight **(MW)** [11, 12]
d. Principal moment of inertia **(PMI)** [13]
e. Principal moment of inertia *x*-component **(PMIX)** [13]
f. Principal moment of inertia *y*-component **(PMIY)** [13]
g. Principal moment of inertia *z*-component **(PMIZ)** [13]
h. Number of rotatable bonds **(ROTBONDS)** [13]
i. Molecular volume **(VM)** [11, 12]

2.3. Electronic descriptors

a. Sum of atomic polarizibilities **(APOL)** [7, 14]
b. Dipole moment **(DIPOLE)** [15–18]
c. Dipole moment *x*-component **(XDIP)** [15–18]
d. Dipole moment *y*-component **(YDIP)** [15–18]
e. Dipole moment *z*-component **(ZDIP)** [15–18]
f. Energy of highest occupied molecular orbital **(HOMO)** [19, 20]
g. Energy of lowest unoccupied molecular orbital **(LUMO)** [19, 20]
h. Partial atomic charges [21, 22]

The HOMO, LUMO and partial atomic charges were calculated using the CNDO2 method. Dipole moments were then calculated using partial atomic charges and atomic coordinates. The atomic numbering scheme used in the charge calculation is shown in *figure 1*.

To generate QSAR equations a stepwise multiple parameter regression analysis method was used [23]. The following statistical measures were used:

n: the number of samples in the regression
r: coefficient of correlation
r^2: coefficient of determination
s: standard deviation
t: t-test for statistical significance

where

$s = \mathrm{SQRT}[\mathrm{SUM}(y_{calc} - y_{obs})^2/(n - k - 1)]$
k = number of variables in the equation

3. Results and discussion

All calculated descriptors and log(BA) of compounds **1–33** were subjected to stepwise multiple parameter regression analysis, and the following equations were obtained:

$$\log(BA) = 10.8424(2.0567)C15 + 0.9758(0.2015), \quad (1)$$

$n = 32$, $r = 0.693$, $r^2 = 0.481$, $t = 5.272$, $s = 0.0368$;

$$\log(BA) = 10.7711(1.9003)C15 - 0.7021(0.2831)XDIP + 0.8255(0.1861), \quad (2)$$

$n = 32$, $r = 0.756$, $r^2 = 0.572$, $t = 4.400$, $s = 0.0346$;

$$\log(BA) = 9.8093(1.8080)C15 - 0.8448(0.2693)XDIP - 0.0250(0.0105)FOCT + 0.4123(0.1727), \quad (3)$$

$n = 32$, $r = 0.803$, $r^2 = 0.644$, $t = 4.111$, $s = 0.0326$;

$$\log(BA) = 8.2057(1.7527)C15 - 1.0018(0.2519)XDIP - 0.0313(0.0098)FOCT - 0.2754(0.1048)ZDIP + 0.1222(0.1569), \quad (4)$$

$n = 32$, $r = 0.845$, $r^2 = 0.717$, $t = 4.132$, $s = 0.0302$;

$$\log(BA) = 7.2509(1.7488)C15 - 1.0261(0.2478)XDIP - 0.0365(0.0106)FOCT - 0.3144(0.1077)ZDIP - 0.2707(0.1807)C19 - 4.6844(3.2926)C11 - 0.7855(0.1502), \quad (5)$$

$n = 32$, $r = 0.872$, $r^2 = 0.760$, $t = 3.629$, $s = 0.0300$.

Out of equations (1)–(5), equation (4) is statistically significant and has a good correlation coefficient. The independent variables of equations (1)–(5) are not significantly cross-correlated which is evident from the correlation matrix (*table III*). In equations (1)–(5) C15 has the highest correlation with log(BA). The plot of log(BA) as a function of C15 is given in *figure 2*.

No significant improvement was observed when parabolic relationships were searched including all the descriptors and the following equation was obtained:

$$\log(BA) = -265.98(90.95)C15^2 - 28.9836(13.3384)C15 - 0.0231(0.0093)FOCT - 0.6705(0.2674)XDIP - 0.2752(0.1788)C19 - 28.1545(21.4024)C2 + 3.8698(3.3977)C13 - 7.8745(0.1473), \quad (6)$$

$n = 32$, $r = 0.882$, $r^2 = 0.778$, $t = 3.468$, $s = 0.0300$.

Table II. Calculated values of descriptors for compounds **1–33**.

Compound	DENSITY (g/mL)	FOCT (kcal/mol)	DIPOLE (Debyes)	ROTBONDS	XDIP (Debyes)	ZDIP (Debyes)
1	1.1059	–8.6299	2.9609	3	–0.3137	–0.4421
2	1.0929	–9.1499	2.2303	4	–0.2749	–0.3533
3	1.0699	–9.6700	2.1762	5	–0.2879	–0.2404
4	1.0750	–9.3499	2.1194	4	–0.2088	–0.2943
5	1.0576	–10.1900	2.2108	6	–0.3081	–0.2313
6	1.0565	–9.8699	2.2998	5	–0.2534	–0.4063
7	1.0468	–10.7100	2.1790	7	–0.3010	–0.1642
8	1.0335	–11.2300	2.2130	8	–0.2788	–0.1503
9	1.0606	–11.6300	2.8329	4	–0.3164	–0.3154
10	1.1416	–12.7899	2.7494	4	–0.3589	–0.3421
11	1.1231	–13.2499	2.5456	5	–0.4004	–0.3038
12	1.1033	–13.7699	2.2394	6	–0.0780	–0.4557
13	1.0831	–14.2899	2.0752	7	–0.2105	–0.3744
14	1.0984	–10.0600	2.9138	5	–0.1055	–0.5953
15	1.1148	–14.6700	2.2801	6	–0.1067	–0.4566
16	1.1524	–11.6399	3.5096	6	0.0034	–0.7061
17	1.1306	–9.8099	3.7516	7	–0.2556	–0.7375
18	1.0850	–12.0000	2.3009	7	–0.1513	–0.4308
19	1.1081	–19.6400	1.9766	8	–0.1571	–0.3772
20	1.0843	–13.3800	3.2132	6	–0.2328	–0.6272
21	1.1363	–13.9200	2.9264	5	–0.4500	0.2301
22	1.1414	–13.9200	2.8782	5	–0.2904	0.5175
23	1.1257	–14.4200	2.5805	6	–0.1818	–0.0933
24	1.1079	–14.9399	2.7735	2	–0.2181	0.1128
25	1.1374	–18.7299	2.0309	3	–0.0914	0.1642
26	1.0873	–11.6099	2.0364	3	–0.1845	0.0947
27	1.0688	–8.2799	1.9028	3	–0.0827	0.0829
28	1.1014	–12.4400	1.8696	4	–0.0107	–0.3879
29	1.0953	–19.7699	2.6038	5	0.0549	–0.5289
30	1.1481	–17.7700	2.6425	5	–0.3026	–0.0369
31	1.0588	–10.5600	1.7683	3	–0.0801	0.0794
32	1.0971	–11.8500	2.2255	3	–0.0390	0.0440
33	1.0602	–10.1800	1.9392	3	–0.1514	–0.0248

Compound	C2	C3	C5	C11	C13	C14
1	–0.26375	–0.06462	–0.26212	–0.14286	–0.13043	0.00093
2	–0.26339	–0.06406	–0.26196	–0.14417	–0.13090	0.01897
3	–0.26304	–0.06311	–0.26219	–0.14301	–0.13567	0.00783
4	–0.26306	–0.06277	–0.26228	–0.14283	–0.13324	0.00718
5	–0.26272	–0.06199	–0.26234	–0.14274	–0.14051	0.00691
6	–0.26248	0.06186	–0.26249	–0.14186	–0.12629	0.01171
7	–0.26302	–0.06249	–0.26202	–0.14297	–0.12983	0.01602
8	–0.26293	–0.06150	–0.26233	–0.14303	–0.13558	0.01177
9	–0.26199	–0.05954	–0.26307	–0.13934	–0.14654	–0.01275
10	–0.26309	–0.06306	–0.26246	–0.14260	–0.13724	–0.00856
11	–0.26219	–0.06064	–0.26275	–0.13977	–0.14984	–0.01793
12	–0.26281	–0.06180	–0.26168	–0.14776	–0.12961	0.02065
13	–0.26131	–0.05645	–0.26287	–0.13908	–0.11891	0.02384
14	–0.26362	–0.06341	–0.26216	–0.14275	–0.13354	–0.00137
15	–0.26969	–0.05283	–0.26382	–0.13455	–0.13044	–0.00179
16	–0.26408	–0.06633	–0.26186	–0.14435	–0.11917	0.01118
17	–0.26358	–0.06376	–0.26269	–0.14106	–0.13909	–0.01248
18	–0.26316	–0.06281	–0.26228	–0.14291	–0.13451	0.00240
19	–0.26411	–0.06309	–0.26286	–0.10469	–0.13353	–0.00130
20	–0.26299	–0.06086	–0.26267	–0.10419	–0.14125	–0.00767
21	–0.26296	–0.06164	–0.26256	–0.14008	–0.13454	0.00161
22	–0.26269	–0.06149	–0.26245	–0.14165	–0.13349	0.00651
23	–0.26256	–0.05993	–0.26242	–0.14128	–0.14894	0.00345
24	–0.26382	–0.06559	–0.26215	–0.14163	–0.11656	–0.00366
25	–0.26408	–0.06667	–0.26177	–0.14479	–0.12114	0.03363
26	–0.26296	–0.06311	–0.26268	–0.13936	–0.12750	–0.01556
27	–0.26288	–0.06293	–0.26258	–0.14053	–0.12126	–0.01744
28	–0.26208	–0.05902	–0.26295	–0.13882	–0.12705	–0.00291
29	–0.26379	–0.06515	–0.26201	–0.14303	–0.14232	–0.00558
30	–0.26408	–0.06678	–0.26235	–0.13959	–0.11652	–0.02499
31	–0.26249	–0.06055	–0.26281	–0.14027	–0.12576	–0.00727
32	–0.26326	–0.06404	–0.26254	–0.14133	–0.11387	–0.01127
33	–0.26215	–0.06059	–0.26299	–0.14026	–0.12746	–0.00277

Table II. *Continued.*

Compound	C15	C18	C19	O20	S10
1	–0.05959	0.62466	–0.42294	–0.52313	–0.40745
2	–0.04519	0.60991	–0.41798	–0.53608	–0.41140
3	–0.06979	0.60821	–0.41889	–0.54519	–0.41665
4	–0.07028	0.61972	–0.42439	–0.55640	–0.41911
5	–0.07002	0.60861	–0.41876	–0.54480	–0.41943
6	–0.07604	0.59605	–0.40979	–0.53808	–0.42223
7	–0.07129	0.60555	–0.41920	–0.54629	–0.42003
8	–0.07246	0.60646	–0.41952	–0.54749	–0.42264
9	–0.08468	0.59564	–0.42217	–0.53903	–0.44316
10	–0.06833	0.59211	–0.41596	–0.52201	–0.41692
11	–0.08557	0.62392	–0.41869	–0.50079	–0.42666
12	–0.04522	0.60461	–0.42568	–0.54739	–0.44262
13	–0.06721	0.60059	–0.41969	–0.54647	–0.48963
14	–0.05839	0.61106	–0.42092	–0.53350	–0.41598
15	–0.08976	0.60031	–0.41894	–0.54581	–0.45461
16	–0.06728	0.59623	–0.42455	–0.54146	–0.40664
17	–0.06857	0.61252	–0.41405	–0.49514	–0.41269
18	–0.05385	0.60732	–0.42283	–0.50450	–0.41288
19	–0.05707	0.60973	–0.41769	–0.52989	–0.41035
20	–0.07299	0.60853	–0.41882	–0.52647	–0.43055
21	–0.06578	0.60559	–0.42037	–0.52970	–0.43969
22	–0.06338	0.60828	–0.42255	–0.53580	–0.42329
23	–0.05127	0.60296	–0.40812	–0.49508	–0.43554
24	–0.08551	0.48888	–0.42978	–0.47709	–0.41152
25	–0.03728	0.55081	–0.40649	–0.52503	–0.39894
26	–0.10026	0.49896	–0.42243	–0.50326	–0.42291
27	–0.10275	0.51634	–0.43618	–0.53073	–0.42777
28	–0.08492	0.48508	–0.38758	–0.51980	–0.42990
29	–0.06273	0.47539	–0.38181	–0.49948	–0.39667
30	–0.09804	0.48147	–0.41678	–0.48688	–0.39396
31	–0.09902	0.48605	–0.44688	–0.53982	–0.43799
32	–0.10178	0.48831	–0.44418	–0.53689	–0.42537
33	–0.09338	0.48572	0.44764	–0.53403	–0.44535

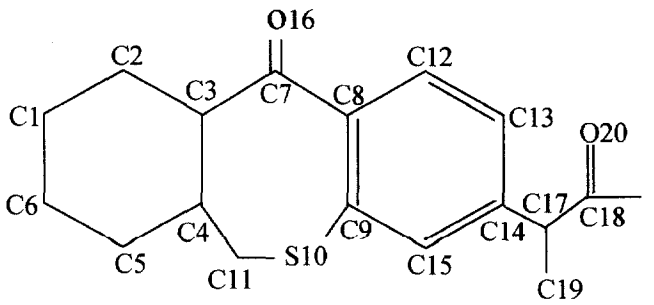


Figure 1. Atomic numbering scheme used for the charge calculation of compounds **1–33**.

To investigate other relationships, C15 was eliminated and the remaining descriptors were subjected to stepwise multiple parameter regression analysis. The following equations were obtained:

$$\log(BA) = 3.2599(0.7581)C18 - 1.6861(0.2199), \quad (7)$$

$n = 32$, $r = 0.618$, $r^2 = 0.381$, $t = 4.300$, $s = 0.0402$;

$$\log(BA) = 3.9431(0.6075)C18 - 0.0464(0.0102)FOCT - 2.6622(0.1708), \quad (8)$$

$n = 32$, $r = 0.800$, $r^2 = 0.639$, $t = 5.070$, $s = 0.0317$;

$$\log(BA) = 3.8667(0.5361)C18 - 0.0462(0.0090)FOCT + 191.45(62.69)C5 + 47.63(0.15), \quad (9)$$

$n = 32$, $r = 0.854$, $r^2 = 0.729$, $t = 5.017$, $s = 0.0285$;

Table III. Correlation matrix for the parameters in equations (1)–(5).

	log(BA)	C15	XDIP	FOCT	ZDIP	C19	C11
log(BA)	1.000						
C15	0.693	1.000					
XDIP	0.312	0.015	1.000				
FOCT	0.340	0.214	0.213	1.000			
ZDIP	0.334	0.293	0.172	0.115	1.000		
C19	0.349	0.183	0.084	0.105	0.104	1.000	
C11	0.029	0.052	0.015	0.338	0.194	0.016	1.000

Table IV. Correlation matrix for the parameters in equations (7)–(10).

	log(BA)	C18	FOCT	C5	O20	C3	C11
log(BA)	1.000						
C18	0.617	1.000					
FOCT	0.340	0.247	1.000				
C5	0.333	0.046	0.003	1.000			
O20	0.060	0.377	0.385	0.063	1.000		
C3	0.082	0.106	0.167	0.115	0.144	1.000	
C11	0.029	0.114	0.338	0.405	0.021	0.024	1.000

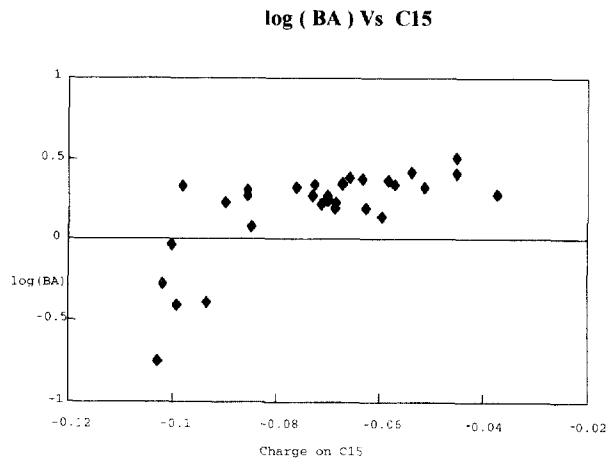


Figure 2. Activity log(BA) as a function of the charge on C15.

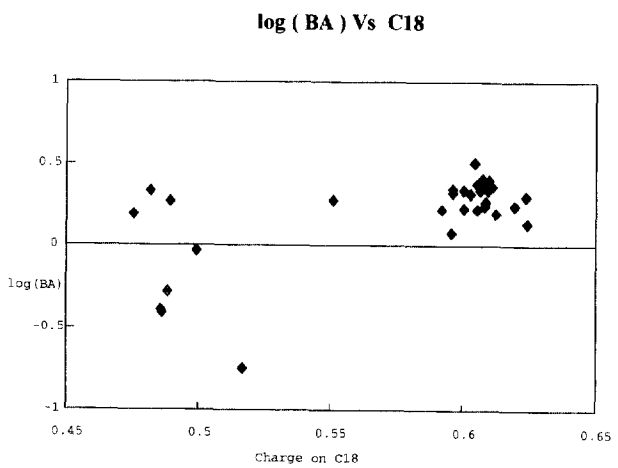


Figure 3. Activity log(BA) as a function of the charge on C18.

$$\log(BA) = 4.2511(0.5557)C18 - 0.0489(0.0099)FOCT + 153.69(67.47)C5 + 2.1104(1.4341)O20 + 1.6851(1.1929)C3 - 4.4235(3.3257)C11 + 38.06(0.14), \quad (10)$$

$n = 32$, $r = 0.884$, $r^2 = 0.781$, $t = 3.860$, $s = 0.0286$.

Out of equations (7)–(10), equation (9) is statistically significant and has a good correlation coefficient. The independent variables of equations (7)–(10) are not significantly cross-correlated which is evident from the correlation matrix (*table IV*). In equations (7)–(10) C18 has the highest correlation with log(BA). The plot of log(BA) as a function of C18 is given in *figure 3*. Equation (7) and equation (8) also reflects that when FOCT is added with C18 then the correlation coefficient and t-test are improved significantly.

No significant improvement was observed when parabolic relationships were searched after the elimination of C15 and the following equation was obtained:

$$\log(BA) = 36.04(21.06)C18^2 - 35.76(23.10)C18 - 0.0546(0.0092)FOCT + 146.64(64.94)C5 + 2.1236(1.1664)C3 - 5.2716(3.2046)C11 + 0.0734(0.0558)DIPOLE + 45.74(0.14), \quad (11)$$

$n = 32$, $r = 0.898$, $r^2 = 0.807$, $t = 3.786$, $s = 0.0280$.

To investigate other relationships, C15 and C18 were eliminated and remaining descriptors were subjected to stepwise multiple parameter regression analysis. The best equation obtained was equation (12) which is statistically less significant than the previous equations:

$$\log(BA) = 0.0686(0.0204)ROTBONDS + 3.1957(0.9395)DENSITY + 9.6326(2.3588)C14 - 0.6274(0.2663)XDIP + 2.7556(1.6339)S10 - 4.2662(3.6793)C13 - 3.1854(0.1619), \quad (12)$$

$n = 32$, $r = 0.849$, $r^2 = 0.721$, $t = 3.280$, $s = 0.0324$.

Equations (1)–(12) reveal that the electronic descriptors were the important factors in determining the antiinflammatory activity.

4. Conclusion

The above study allows to conclude that the electronic descriptors, especially partial atomic charges on C15 and C18, have an important effect in determining the oral antiinflammatory activity. It suggests that esterification and amidation of the carboxylic acid group of the molecule affects the electron density distribution and are responsible for the change in pharmacokinetic behaviour which ultimately affects the pharmacological activity of the molecule. This study pleads for careful considerations to be observed during the masking of carboxylic acid groups to minimize gastrointestinal disturbances.

Acknowledgements

The authors wish to thank M/s Torrent Pharmaceuticals Ltd., Ahmedabad, India, for providing access to molecular modeling software facilities and to Director S.G.S.I.T.S., Indore, India, for providing the necessary facilities for this work. S.A. is grateful to the Ministry of Human Resource Development, New Delhi, India, for providing a research fellowship for this project.

References

[1] Flower R.J., Moncade S., Vane J.R., in: Gilman A.G., Goodman L.S., Gilman A. (Eds.), The Pharmacological Basis of Therapeutics (6th ed.), MacMillan, New York, 1980, p. 712.
[2] Kurokawa M., Uno H., J. Med. Chem. 33 (1990) 504.
[3] Gund P., Jensen N.P., Non-Steroidal Antiinflammatory and Antiarthritic Drugs. In: Topliss J.G. (Ed.), Quantitative Structure–Activity Relationship of Drugs, Academic Press, New York, 1983, p. 285.
[4] Cerius² version 1.6, Biosym/Molecular Simulations Inc., 9685 Scranton Road, California, USA.
[5] Fletcher R., Reeves C.M., Comput. J. 7 (1964) 149.
[6] Pearlman R.S., in: Yalkowsky S.H., Sinkula A.A., Valvani Y.C. (Eds.), Physical Chemistry Properties of Drugs, Dekker, New York, 1964.
[7] Hopfinger A.J., Conformational Properties of Macromolecules, Academic Press, New York, 1973.
[8] Leffler J.E., Grunwald E., Rates and Equilibrium Constants of Organic Reactions, Wiley, New York, 1963.
[9] Hansch C., Leo A., Substituent Constants for Correlation Analysis in Chemistry and Biology, Wiley, New York, 1979.
[10] Dunn III W.J., Eur. J. Med. Chem. 12 (1977) 109.
[11] Van de Waterbeemd H., Testa B., Adv. Drug. Res. 16 (1987) 85.
[12] James K.C., in : Smith H.J. (Ed.), Smith and Williams 'Introduction to the Principles of Drug Design', Wright, 1988, ch. 8.
[13] Hill T.L., Introduction to Statistical Thermodynamics, Addison Wesley, Reading, MA, 1960.
[14] Marsili M., Gasteiger J., Croat. Chem. Acta 53 (1980) 601.
[15] Bottcher C.J.F., Theory of Electric Polarization, Elsevier, Amsterdam, 1952.
[16] Del Re G., Biophys. Acta 75 (1963) 153.
[17] Gasteiger J., Marsili M., Tetrahedron Lett. 34 (1978) 3181.
[18] Gasteiger J., Marsili M., Tetrahedron 36 (1980) 3219.
[19] Pople J.A., Beveridge D.L., Approximate Molecular Orbital Theory, McGraw Hill, New York, 1970.
[20] Pople J.A., Segal G.A., J. Chem. Phys. 44 (1966) 3289.
[21] Stane A.J., Alderton M., Mol. Phys. 56 (1985) 1047.
[22] Williams D.E., in: Lipowitz K.B., Boyd D.B. (Eds.), Review of Computer Chemistry, VCH, New York, 1991, p. 219.
[23] Draper N.R., Smith H., Applied Regression Analysis, Wiley, New York, 1966.