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Development of 3D-QSAR Models for 5-Lipoxygenase Antagonists: Chalcones†

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Abstract—5-Lipoxygenase inhibitors are of current interest for asthma therapy and inflammatory diseases. In order to identify the essential structural and physicochemical requirements in terms of common biophoric sites (pharmacophore) and secondary sites for binding and interacting with 5-lipoxygenase, a series of 51 compounds of chalcones has been used for the development of 3D-QSAR models on APEX-3D expert system. Among several models, the two models have been identified with the statistical criteria $R^2 > 0.75$, Chance < 0.001 and Match > 0.7. Both the models (nos 1 and 2) with three biophoric sites and four secondary sites, showed very good correlation ($r > 0.9$) between the observed and calculated or predicted activities.

Introduction

Asthma, inflammation and allergic diseases are of current interest[1] because there are no selective drugs for the treatment of most of the diseases like rheumatoid arthritis,[2] allergic rhinities, psoriasis,[3,4] ulcerative colitis and asthma.[5] The two major approaches for the design and synthesis of anti-inflammatory agents, are based on the inhibition of two enzymes[6] (i) cyclooxygenase, (ii) lipoxygenase, which are involved in the metabolism of arachidonic acid. Cyclooxygenase has been the common target for most of the anti-inflammatory drugs but due to the association of some side effects such as ulceration and bleeding in gastrointestinal tract with cyclooxygenase inhibitors[7] and implication of leukotrienes in the above inflammatory and allergic disorders,[8,9] the attention is focussed on the 5-lipoxygenase enzyme inhibitors. These inhibitors restrict the synthesis of leukotrienes from arachidonic acid (AA) via peroxidation of AA to 5-hydroperoxyeicoteranoic acid (5-HPETE) followed by dehydration to 5,6-epoxy leukotriene A4 (LTA4). Based on the mechanism of action, the lipoxygenase inhibitors have been classified into four distinct classes: (i) iron chelating inhibitors, (ii) competitive reversible inhibitors, (iii) inhibitors of the 5-lipoxygenase activating protein (FLAP) and (iv) anti-oxidative. Intensive efforts in development of clinically useful drugs from the inhibitors of 5-lipoxygenase enzyme or from leukotrienes inhibitors have led to one marketed drug; Zileuton and others, namely MK-0591, Bay-X-1005 and ABT-761, which are at different stages of drug development, which may provide useful therapy particularly in asthma.[10] However the fear is that these may also suffer with the similar problems related to toxicity, pharmacokinetics and tolerability associated with two leucotriene receptor antagonists, namely Zafraleukast and Montelukast.[11–14] In addition to these agents of the first three classes of 5-LO inhibitors, several antioxidant 5-LO inhibitors such as DUP-654,[15] lonapalene,[16] TMK-688,[17] R-68151,[18] BW-755c,[19] have also shown clinical usefulness as topical anti-inflammatory agents. However these agents are associated with major side effects of methemoglobinemia,[20] as well as other toxic effects, namely Heinz body formation and blood hemolysis due to production of superoxide anion. The clinical trial results of Lonapalene[16] and a report on tetrahydro-1,2,4-triazine-3-ols from Abbott lab,[21] has indicated that these agents are free from methemoglobinemia in human and rat, respectively. Based on these results it was suggested that it might be possible to design inhibitors free from toxicity problem. Among different chemical classes of antioxidant 5-lipoxygenase inhibitors investigated, the

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chalcones have been reported as anti-inflammatory and anti-allergic agents.[22,23] In view of their rapid and extensive metabolism after systemic administration, the chalcones have been identified as promising non toxic topical anti-inflammatory agents. Inspite of being an important area, there are only a few papers on quantitative structure–activity relationship (QSAR) in hydroxamic acid,[24a,b] eicosatetraenoic acids,[24b] benzimidazoles,[24b] (3-pyridyl methyl) benzoquinones,[25] 1-phenyl-3-pyrazolidinones,[26] 2-phenyl hydrazoacetamides,[27] and pyridazinones.[28] In order to gain an insight into the essential structural and physicochemical requirements for design of chalcones, it appeared of interest to identify important pharmacophore by establishing 3D-QSAR models using APEX-3D expert system on chalcones which have exhibited potent 5-lipoxygenase inhibitory activity with anti-oxidative effects. The results of these studies are reported in this paper.

Material and Methods

All molecular modelling and 3D-QSAR studies were performed on a Silicon Graphics *INDY* R-4000 workstation employing Molecular Simulation Incorporation (MSI) software[29] (Insight-II, Builder, Search-compare, Discover, and APEX-3D). All structures of chalcone derivatives (Table 1) were constructed using the sketch program in builder module of Insight II software[30] and minimized for the energy using steepest descent, conjugative gradient and Newton–Raphson algorithms in sequence followed by Quasi Newton–Raphson (Va09a),[31] optimization techniques implemented in the Discover module by using energy tolerence value of 0.001 kcal/mol and maximum number of iteration set to 1000. In view of our earlier findings that the total energy of the molecular conformation obtained through above standard energy minimization procedure do not differ much with the near global minimum energy conformations,[32,33] these molecules were stored in MDL format and were used for the computational calculation of different physicochemical properties including atomic charges, π-population, electron donor and acceptor indexes, HOMO and LUMO coefficient, hydrophobicity and molar refractivity based on atomic contributions[34,35] by the MOPAC 6.0 (MNDO Hamiltonian)[36] version. The compounds were classified into following three classes:[36b] (i) most active ($-\mathrm{LogIC}_{50} > -0.5$), (ii) active ($-\log\mathrm{IC}_{50} < -0.5$ and > -2.5), (iii) less active ($-\log\mathrm{IC}_{50} < -2.5$). The data were used by APEX-3D program for automated biophore (pharmacophore) identification and 3D-QSAR model building.[37,38] The automatically identified biophore (pharmacophore) by APEX-3D in terms of structural and electronic pattern, the local array of descriptor centres (like user defined atoms, pseudo atoms like ring centres, hydrophobic regions or hydrogen binding sites) which are common to a class of molecules in their bioactive conformation, responsible for activity through interaction with the receptor were used to derive 3D-QSAR equations with the setting of, the site radius at 0.80, the occupancy at 10, the sensitivity at 0.80 and the randomization at 100. The global properties, (total hydrophobicity and total refractivity) the biophoric site properties (π-population, charge, HOMO, LUMO, hydrogen acceptor, (hydrogen donor, and hydrophobicity) and the secondary site parameters hydrogen acceptor, presence; hydrogen donor, presence; heteroatom, presence; hydrophobic, hydrophobicity; steric, refractivity; ring, presence) were used as independent variables and biological activity as dependent variable, to derive equations for 3D-QSAR models.

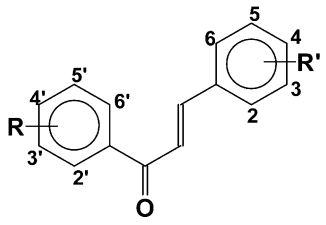
Quality of each model was estimated from the observed R^2 (the fraction of the total explained variance of the observed activity data by the model), RMSA (calculated root mean square error based on all compounds with degrees of freedom correction), RMSP (root mean square error based on 'leave one out' with no degrees of freedom correction), chance statistics (evaluated as the ratio of the equivalent regression equation to the total number of randomized sets; a chance value of 0.01 corresponds to 1% chance of fortuitous correlation) and match parameter (evaluated for the quality of superimposition for molecules having common biophores; a value of 1 corresponding to the best possible fit 100%).

Results and Discussion

Out of 53 3,4-dihydroxy chalcons reported as 5-lipoxygenase inhibitors by Sogawa et al.,[39] only 51 compounds were considered for analysis because of non-availability of IC_{50} values for two compounds. Several biophoric models were obtained with different size and arrangement. Among several biophoric models for all 51 compounds, only two models (Fig. 1) were considered based on the statistical criteria ($R^2 > 0.75$, Chance < 0.001, Superimposition match > 0.7). Both these models with three biophoric sites showed very good superimposition (Figs 2 and 3) as indicated by the high match value > 0.70 with, high squared correlation co-efficient value ($r^2 = 0.88$), high reliability (chance value 0.00) and low difference in RMSA and RMSP value (< 0.03) (Table 2).

Models 1 and 2 also have high statistical significance $> 99.9\%$, with F values $F_{(4,46)} = 84$ against the value for 99.9% significance ($F_{4,46\ \alpha\ 0.001} = 5.5$). The three biophoric sites A_1, B_1, C_1, common to all molecules in model no. 1 correspond to the carbonyl oxygen, its lone pair and centre of the phenyl ring bearing the R_1 substituents, respectively. The spatial disposition of these sites, in terms of inter site distances, is $A_1-B_1 = 3.00$ (± 0.001), $A_1-C_1 = 3.74$ (± 0.02), $B_1-C_1 = 6.30$ (± 0.40) A^0 for model no. 1. The physicochemical characteristics of the biophore centres corresponding to sites are A_1 [Charge_ het ($-0.29 + 0.013$) and Don_01 (68.50 ± 0.05)], C_1 [cycle size (6) and π-electron (6)] and site B_1 for H-site (1). In addition to this pharmacophore with three biophoric centres the model has four secondary sites 1a–1d. The two secondary sites, 1b and 1c, are in terms of molar refractivity (MR) parameter in the vicinity of the carbon atom at 6′ and 3 positions, respectively, which may be involved in steric interactions.

Table 1. 5-Lipoxygenase inhibitory activity data of chalcones



S. No.	R′	R	5-LO inhibitory activity					
			Experimentally observed[a]		Model no. 1 ($-\log IC_{50}$)		Model no. 2 ($-\log IC_{50}$)	
			IC_{50} (μM)	$-\log IC_{50}$ (μM)	Calculated[b]	Predicted[c]	Calculated[d]	Predicted[e]
1	4′-OH	H	230	−2.36	−2.13	−2.07	−1.80	−1.67
2	2′,4′-OH	H	400	−2.60	−2.13	−2.01	−1.80	−1.61
3	2′,4′,6′-OH	H	142	−2.15	−2.13	−2.13	−2.54	−2.67
4	2′-OH	4-OH	42	−1.62	−1.22	−1.09	−1.80	−1.84
5	2′,4′-OH	4-OH	35	−1.54	−2.13	−2.28	−1.80	−1.86
6	2′,4′,6′-OH	4-OH	100	−2.00	−2.13	−2.16	−2.54	−2.72
7	H	3,4-OH	0.043	1.37	1.81	1.83	1.93	2.12
8	2′-OH	3,4-OH	0.023	1.64	1.81	1.82	1.93	2.03
9	3′-OH	3,4-OH	0.0042	2.37	1.81	1.78	1.70	1.68
10	4′-OH	3,4-OH	0.0040	2.39	1.81	1.78	1.93	1.78
11	2′,4′-OH	3,4-OH	0.0046	2.33	1.81	1.78	1.93	1.80
12	2′,4′,6′-OH	3,4-OH	0.14	0.85	1.38	1.41	0.96	0.98
13	2-Thienyl	3,4-OH	0.022	1.65	1.81	1.82	1.70	1.70
14	3-Pyridyl	3,4-OH	0.21	0.68	0.69	0.70	1.70	1.73
15	2′-OH	3-OMe, 4-OH	17	−1.23	−1.22	−1.22	−1.09	−1.01
16	4′-Cl	3-OMe, 4-OH	8.9	−0.95	−1.22	−1.31	−1.09	−1.15
17	4′-OCH_3	3-OMe, 4-OH	12	−1.08	−1.22	−1.27	−1.09	−1.09
18	H	2′-Cl	0.092	1.04	1.81	1.85	1.70	1.72
19	H	4′-Cl	0.0085	2.07	1.81	1.79	1.70	1.69
20	H	4′-NO_2	0.023	1.64	1.81	1.82	1.70	1.70
21	H	2′-CF_3	0.058	1.24	0.97	0.91	1.70	1.71
22	H	3′-CH_3	0.027	1.57	1.81	1.82	1.70	1.70
23	H	4′-CH_3	0.076	1.12	1.81	1.84	1.70	1.71
24	H	2′-OCH_3	0.027	1.57	1.42	1.42	1.70	1.70
25	H	3′-OCH_3	0.0065	2.19	1.81	1.79	1.70	1.68
26	H	4′-OCH_3	0.020	1.70	1.81	1.81	1.70	1.70
27	H	3′-$N(CH_3)_2$	0.0098	2.01	1.81	1.80	1.70	1.69
28	H	4′-$N(CH_3)_2$	0.0047	2.33	1.81	1.78	1.70	1.68
29	H	4′-$OCH(CH_3)_2$	0.0041	1.39	1.81	1.83	1.70	1.71
30	H	2′-OH, 4′-OCH_3	0.015	1.82	1.38	1.35	1.70	1.69
31	H	2′-OH, 5′-OCH_3	0.041	1.39	1.64	1.65	1.70	1.71
32	H	4′-OH, 3′-OCH_3	0.0090	2.05	1.81	1.80	1.70	1.69
33	H	2′-CH_3, 4′-CH_3	0.017	1.77	1.42	1.41	1.70	1.70
34	H	2′-OCH_3, 4′-OCH_3	0.010	2.00	1.42	1.39	1.70	1.69
35	H	2′-OCH_3, 5′-OCH_3	0.0078	2.10	1.68	1.66	1.70	1.69
36	H	2′-OCH_3, 6′-OCH_3	0.370	0.43	1.42	1.47	0.96	1.08
37	H	3′-OCH_3, 4′-OCH_3	0.018	1.74	1.81	1.81	1.70	1.70
38	H	2′-CH_3, 4′-CH_3, 6′-CH_3	0.400	0.40	0.97	1.09	0.59	0.72
39	H	3′-OCH_3, 4′-OCH_3, 5′-OCH_3	0.016	1.79	2.07	2.09	1.70	1.69
40	2′,5′-OH	H	0.064	1.19	1.67	1.69	1.70	1.71
41	2′OH, 5′-CH_3	H	0.039	1.40	1.94	2.05	1.70	1.71
42	2′OH, 5′-OC_2H_5	H	0.0053	2.27	1.64	1.61	1.70	1.68
43	2′OH, 5′-$CH(CH_3)_2$	H	0.004	2.39	1.91	1.83	1.70	1.68
44	2′OH, 5′-$OCH(CH_3)_2$	H	0.011	1.95	1.64	1.62	1.70	1.69
45	2′OH, 5′-OC_4H_9	H	0.10	0.00	1.64	1.70	1.70	1.75
46	2′,5′-CH_3	H	0.016	1.79	1.53	1.46	1.70	1.69
47	2′OCH_3, 5′-CH_3	H	0.024	1.62	1.98	2.06	1.70	1.70
48	2′OCH_3, 5′-OC_2H_5	H	0.0038	2.42	1.68	1.65	1.70	1.68
49	2′OCH_3, 5′-$OCH(CH_3)_2$	H	0.014	1.85	1.68	1.67	1.70	1.69
50	2′OC_2H_5, 5′-OCH_3	H	0.027	1.56	1.68	1.68	1.70	1.70
51	2′,5′-OC_2H_5	H	0.0024	2.61	1.68	1.64	1.70	1.67

[a]From ref 39.
[b]From eq 1.
[c]From eq 1 using 'leave one out method'.
[d]From eq 2.
[e]From eq 2 using 'leave one out' method.

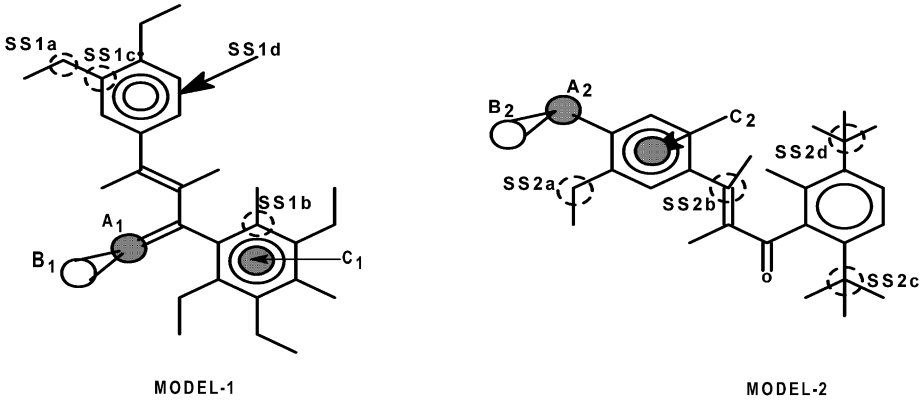


Figure 1. Pictorial representation of biophoric sites (A, B and C) and secondary sites (SS) in models 1 and 2.

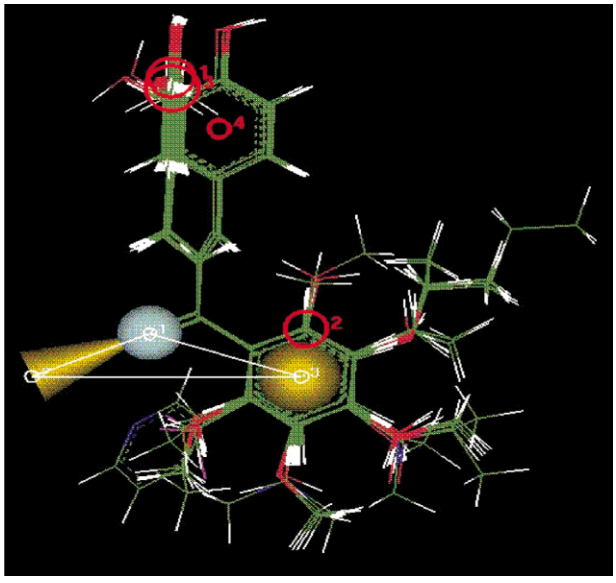


Figure 2. Superimposition of the compounds **1**–**51** with biophoric sites (solid spheres) and secondary sites (red circles) for model no. 1.

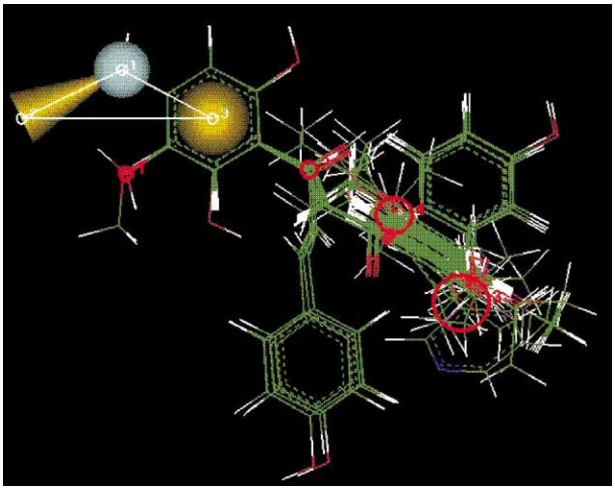


Figure 3. Superimposition of the compounds **1**–**51** for pictorial representation of biophoric sites (A, B and C), sites (solid spheres) and secondary sites (SS) (red circles) in model no. 2.

Among the other two secondary sites, the site 1a is the hydrogen-bonding site in the vicinity of the oxygen atom attached to carbon atom at the 3-position and site 1d as the centre of the phenyl ring bearing R-substituent (Fig. 1) possibly involved in π–π interaction. The distances of different secondary sites from biophoric centres are: SS1a (7.34±0.03, 9.06±0.084, 9.06±0.05 from the biophoric centres A_1, B_1 and C_1, respectively), SS1b (3.67±0.02, 6.56±0.05 and 1.391±0.003 from the biophoric centres A_1, B_1 and C_1, respectively, SS1c (7.04±0.31,8.85±0.30 and 8.70±0.27 from the biophoric centres A_1, B_1 and C_1, respectively), SS1d (6.00±0.02, 8.22±0.04 and 7.21±0.020 from the biophoric centres A_1, B_1 and C_1, respectively) in model no. 1.

The 3D QSAR equation for the biophore model no. 1 (eq 1) describes the 5-lipoxygenase activity (log $1/IC_{50}$) as a dependent variable and above four secondary sites parameters (Table 3) as independent variables. The equation with high correlation coefficient value ($r=0.94$) and r cross-validated ($r_{cv}=0.87$) is of high statistical significance >99.9% ($F_{4,46\alpha0.001}=5.54$; $F_{4,46}=85.19$) and shows a reasonable good agreement between the observed and calculated values (Table 1). This equation indicates that secondary sites 1a–1d contribute positively for 5-LO inhibitory activity suggesting that interactions due to the presence of H-donor group at site 1a, presence of bulkier group at site 1c and of six-membered ring at site 1d, are favourable for activity in the order of 1:4:1 while the steric interactions at secondary site 1b are not favourable for the activity.

Similar to model 1, model 2 also contains three common biophoric site A_2, B_2, C_2 corresponding to 4-hydroxyl oxygen, its lone pair, and centre of phenyl ring bearing R substitution, respectively, for all the 51 compounds. The mean site distances between these biophoric centres are, $A_2-B_2=3.00$ (±0.001), $A_2-C_2=2.77$ (±0.003), $B_2-C_2=5.14$ (±0.008). The physicochemical characteristics corresponding to these biophoric centres are A_2 in terms of DON_01 (8.40±0.05), electron donor capability in the presence of H-site (1) for site B_2 and site C_2 in terms of π-electron (6) and cycle size (6). In addition, model 2 also has four secondary sites. The first secondary site 2a is the hydrogen-bonding site in the vicinity of the oxygen atom attached to carbon atom at position 3. Among the other three secondary sites, the sites 2b–2d are in terms of molar refractivity (MR)

Table 2. Statistical details of the two best-selected models (model nos 1 and 2)

Model no.	RMSA[a]	RMSP[b]	R^2	Chance	Size	Match	Variable	No. of compounds
1	0.51	0.53	0.88	0.00	3	0.75	4	51
2	0.52	0.53	0.88	0.00	3	0.73	4	51

[a]RMSA, root mean square error of approximation.
[b]RMSP, root mean square error of prediction 'leave one out'.

Table 3. Parameter values for the secondary sites (SS) in model nos. 1 and 2 for the compounds described in Table 1

Compound no.	Model no. 1				Model no. 2			
	H-Donor Presence at SS1a	Steric Refractivity at SS1b	Steric Refractivity at SS1c	Ring Presence at SS1d	H-Donor Presence at SS2a	Steric Refractivity at SS2b	Steric Refractivity at SS2c	Steric Refractivity at SS2d
1	—	3.450	3.450	1.000	—	4.000	—	—
2	—	3.450	3.450	1.000	—	4.000	—	—
3	—	3.750	3.450	1.000	—	4.000	—	—
4	—	3.450	3.450	1.000	—	4.250	—	—
5	—	3.450	3.450	1.000	—	4.000	—	—
6	—	3.750	3.450	1.000	—	4.000	—	—
7	—	3.450	3.750	1.000	1.000	4.250	—	—
8	—	3.450	3.750	1.000	1.000	4.250	—	—
9	1.000	3.450	3.750	—	1.000	4.250	—	—
10	—	3.450	3.750	1.000	1.000	4.250	—	—
11	—	3.450	3.750	1.000	1.000	4.250	—	—
12	—	3.450	3.450	1.000	—	4.000	—	—
13	—	3.450	3.450	1.000	—	4.000	—	—
14	—	3.750	3.450	1.000	—	4.000	—	—
15	—	3.450	3.450	1.000	—	4.250	—	—
16	—	3.450	3.450	1.000	—	4.000	—	—
17	—	3.450	3.450	1.000	—	4.000	—	—
18	1.000	3.450	3.750	—	1.000	4.250	—	—
19	1.000	3.450	3.750	—	1.000	4.250	—	—
20	1.000	3.450	3.750	—	1.000	4.250	—	—
21	1.000	3.450	3.750	—	1.000	4.250	2.950	—
22	1.000	3.450	3.750	—	1.000	4.250	—	—
23	1.000	3.450	3.750	—	1.000	4.250	—	—
24	1.000	3.450	3.750	—	1.000	4.250	1.350	—
25	1.000	3.450	3.750	—	1.000	4.250	—	—
26	1.000	3.450	3.750	—	1.000	4.250	—	—
27	1.000	3.450	3.750	—	1.000	4.250	—	—
28	1.000	3.450	3.750	—	1.000	4.250	—	—
29	1.000	3.450	3.750	—	1.000	4.250	—	—
30	1.000	3.450	3.750	—	1.000	4.250	1.500	—
31	1.000	3.450	3.750	—	1.000	4.250	1.500	1.350
32	1.000	3.450	3.750	—	1.000	4.250	—	—
33	1.000	3.450	3.750	—	1.000	4.250	1.350	—
34	1.000	3.450	3.750	—	1.000	4.250	1.350	—
35	1.000	3.450	3.750	—	1.000	4.250	1.350	1.350
36	1.000	3.750	3.750	—	1.000	4.250	1.350	—
37	1.000	3.450	3.750	—	1.000	4.250	—	—
38	1.000	3.900	3.750	—	1.000	4.250	2.950	—
39	1.000	3.450	3.750	—	1.000	4.250	—	1.350
40	1.000	3.450	3.750	—	1.000	4.250	1.500	1.500
41	1.000	3.450	3.750	—	1.000	4.250	1.500	2.950
42	1.000	3.450	3.750	—	1.000	4.250	1.500	1.350
43	1.000	3.450	3.750	—	1.000	4.250	1.500	2.800
44	1.000	3.450	3.750	—	1.000	4.250	1.500	1.350
45	1.000	3.450	3.750	—	1.000	4.250	1.500	1.350
46	1.000	3.450	3.750	—	1.000	4.250	2.950	2.950
47	1.000	3.450	3.750	—	1.000	4.250	1.350	2.950
48	1.000	3.450	3.750	—	1.000	4.250	1.350	1.350
49	1.000	3.450	3.750	—	1.000	4.250	1.350	1.350
50	1.000	3.450	3.750	—	1.000	4.250	1.350	1.350
51	1.000	3.450	3.750	—	1.000	4.250	1.350	1.350

Log $1/IC_{50} = 2.78(\pm 0.31)$ H-donor presence (at SS1a) -2.46 (± 0.75) steric refractivity (at SS1b) $+ 12.44$ (± 1.13) steric refractivity (at SS1c) $+ 3.02$ (± 0.40) ring presence (at SS1d) -39.24

$N = 51$, $r = 0.94$, $F = 85.19$, RMSA $= 0.52$, RMSP $= 0.53$ (1)

Log $1/IC_{50} = 3.03$ $(\pm 0.28$H-donor. Presence (at SS2a) $+ 3.64$ (± 1.38) steric referactivity (at SS2b) -0.29 (± 0.09) steric refractivity (at SS2c) $+ 0.19$ (± 0.09) steric refractivity(at SS2d) -16.70

$N = 51$, $r = 0.94$, $F = 84.19$, RMSA $= 0.52$, RMSP $= 0.53$ (2)

parameter in the vicinity, of the olefinic carbon atom attached to carbon at position 1, carbon atom attached to the carbon atoms at 2′-carbon and 5′-carbon positions respectively (Fig. 1) which may be involved in steric interactions. The other secondary site 2a is the hydrogen-bonding site in the vicinity of the oxygen atom at position 3. The distance of these secondary sites from biophoric centre are SS2a (2.82 ± 0.008, 3.20 ± 0.008, 2.77 ± 0.002 from the biophoric centres A_2, B_2 and C_2, respectively), SS2b (5.69 ± 0.004, 7.86 ± 0.01 and 3.00 ± 0.006 from the biophoric centres A_2, B_2 and C_2, respectively), SS2c ($11.02\pm0.0.08$, $12.87\pm0.0.08$ and 8.29 ± 0.18 form the biophoric centres A_2, B_2 and C_2, respectively), SS2d (10.12 ± 0.07, 11.89 ± 0.054 and 8.01 ± 0.06 from the biophore centres A_2, B_2 and C_2, respectively) in model no. 2.

The 3D-QSAR equation for the biophore model 2 (eq 2) describes the 5-LO inhibitory activity (log $1/IC_{50}$) as a dependent variable and above four secondary site parameters as independent variables. According to it the secondary sites 2a, 2b, 2d contribute positively for 5-LO inhibitory activity suggesting that interactions due to the presence of H-donor group at site 2a, presence of π-electrons at site 2b and bulkier group at site 2d, are favourable for activity in the order of 1:1.2:0.6 while the steric interactions at secondary site 2c is not favourable for the activity. The equation with high correlation coefficient value ($r=0.94$) and r cross-validated ($r_{cv}=0.87$) is of high statistical significance $>99.9\%$ ($F_{4,46\alpha0.001}=5.54$; $F_{4,46}=84.19$) and shows a reasonable good agreement between the observed and calculated values (Table 1).

Conclusion

A close examination of both these models reveal that there is a common biophore (pharmacophore) comprising of three similar biophoric sites present in both models with almost similar spatial disposition as indicated by mean inter-biophoric distances, one of the sites is involved in hydrogen bonding, second site is for electrostatic and ionic interactions and the third is involved in π–π interactions. The identification of common pattern comprising the phenyl rings bearing R,R' substitution may be useful for designing new molecules with good 5-LO inhibitory activity. Judicious modulation by substituents keeping in view the secondary site contributions may lead to desired 5-lipoxygenase inhibitors.

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