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Ligand-based CoMFA and CoMSIA studies on chromone derivatives as radical scavengers

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ABSTRACT

The antioxidant activity for a series of chromone compounds, evaluated by DPPH free radical scavenging assay, were subjected to 3D-QSAR studies using comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA). All 48 chromone derivatives were geometry optimized by AM1 and HF/6-31G* calculations. The CoMFA and CoMSIA results were compared between different alignment strategies. The best CoMFA model obtained from HF/6-31G* optimization with field fit alignment gave cross-validated r^2 (q^2) = 0.821, noncross-validated r^2 = 0.987, S = 0.095, and F = 388.255. The best CoMSIA model derived from AM1 optimized structures and superimposition alignment gave q^2 = 0.876, noncross-validated r^2 = 0.976, S = 0.129, and F = 208.073, including electrostatic, hydrophobic, hydrogen bond donor and acceptor fields. The contour maps provide the fruitful structure–radical scavenging activity relationships which are useful for designing new compounds with higher activity.

1. Introduction

Flavonoids are natural phenyl substituted chromones which show many biological and pharmacological activities [1] such as anti-inflammatory [2,3], anti-allergic [3], antimicrobial [2], estrogenic [2,4], anti-HIV [5,6] and anticancer activities [7,8]. Recent interests in natural antioxidants have been stimulated by potential health benefits arising from the antioxidant activity of flavonoids [9–11]. Flavonoids like many other polyphenols are very effective radical scavengers (chain-breaking antioxidants) because they are highly reactive hydrogen or electron donors [12–14]. Structure–activity relationship (SAR) studies of flavonoids have indicated the importance of the number and location of the phenolic OH groups for effective radical scavenging activity [15–17].

In the previous study, we have designed and synthesized a series of chromone derivatives and evaluated for their radical scavenging activity using 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging activity (Table 1). 7,8-Dihydroxy-2-(3′-trifluoromethylphenyl)-3-(3″-trifluoromethylbenzoyl) chromone, **32**, was found to be the most active antioxidant with the IC_{50} = 4.95 ± 0.02 μM [18]. Chromone **32** was more potent than the known antioxidant flavonoids, quercetin (IC_{50} = 10.89 μM), luteolin (IC_{50} = 11.0 μM) and fisetin (IC_{50} = 14.06 μM) [19]. To explore the relationships between the structures of these compounds and their antioxidant activity, a three-dimensional quantitative structure–activity relationship (3D-QSAR) study using comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) were performed in this study. In the absence of information regarding the biological target, indirect ligand-based approaches 3D-QSAR such as CoMFA and CoMSIA can assist in clarifying the SARs.

CoMFA is a versatile and powerful tool in rational drug design and related applications. CoMFA samples the steric (Lennard–Jones) and electrostatic (Coulombic) fields surrounding a set of ligands and constructs a 3D-QSAR model by correlating these 3D steric and electrostatic fields with the corresponding observed activities. Partial least squares (PLS) analysis, with a cross validation procedure, is employed to select relevant components from the large set of CoMFA data to build up the best QSAR equation [20]. CoMSIA is an extension of the CoMFA methodology and differs only in the implementation of the fields [21,22]. In CoMSIA approach, hydrophobic, hydrogen bond donor and hydrogen bond acceptor similarity fields are calculated in addition to the steric and electrostatic fields, which provides a better interpretation of the correlations between the 3D structures of the studied molecules and their activities. The fields are evaluated by a PLS analysis similar to CoMFA. The obtained CoMFA and CoMSIA contour maps results are used as visual guides for design of the new and more potent radical scavenging compounds.

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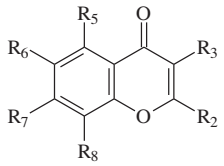
Table 1
Structures and the radical scavenging activity of the studied chromone derivatives.



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Compd.	R_2	R_3	R_5	R_6	R_7	R_8	IC_{50} (μM)
1	Phenyl	H	H	H	H	OH	371.78 ± 1.87
2	CH_3	H	H	H	OH	OH	17.50 ± 0.41
3	Benzyl	H	H	H	OH	OH	5.93 ± 0.07
4	Phenyl	H	H	H	OH	OH	13.62 ± 1.23
5	CH_3	H	H	H	OH	H	199.15 ± 0.97
6	Benzyl	H	H	H	OH	H	77.15 ± 0.77
7	Benzyl	CH_3	H	H	OH	H	911.92 ± 8.36
8	Phenyl	H	H	H	OH	H	1518.51 ± 11.31
9	Phenyl	CH_3	H	H	OH	H	1202.82 ± 12.16
10	4′-(NO_2)-Phenyl	H	H	H	OH	H	1103.52 ± 13.00
11	3′-(CF_3)-Phenyl	H	H	H	OH	H	381.01 ± 3.56
12	4′-(F)-Phenyl	H	H	H	OH	H	696.20 ± 3.90
13	3′,5′-(diNO_2)-Phenyl	H	H	H	OH	H	1145.89 ± 13.09
14	3′-(Cl)-Phenyl	H	H	H	OH	H	697.51 ± 9.30
15	3′,4′-(diCl)-Phenyl	H	H	H	OH	H	518.49 ± 8.30
16	4′-(*t*-butyl)-Phenyl	H	H	H	OH	H	517.12 ± 7.99
17	3′-(CF_3)-Phenyl	H	OH	H	OH	H	993.04 ± 14.11
18	4′-(F)-Phenyl	H	OH	H	OH	H	481.64 ± 6.21
19	3′,4′-(diF)-Phenyl	H	OH	H	OH	H	340.16 ± 4.49
20	4′-(*t*-butyl)-Phenyl	H	OH	H	OH	H	353.09 ± 5.74
21	4́-(NO_2)-Phenyl	H	OH	H	OH	H	491.74 ± 8.04
22	3′,5′-(diNO_2)-Phenyl	H	OH	H	OH	H	409.66 ± 2.29
23	3′-(Cl)-Phenyl	H	OH	H	OH	H	550.50 ± 7.73
24	3′,4′-(diCl)-Phenyl	H	OH	H	OH	H	742.82 ± 10.75
25	4′-(OCH_3)-Phenyl	H	OH	H	OH	H	516.47 ± 516.47
26	3′-(OCH_3)-Phenyl	H	OH	H	OH	H	678.67 ± 28.26
27	3′-(OCH_3)-Phenyl	H	H	OH	H	H	1106.21 ± 4.59
28	3′-(Cl)-Phenyl	H	H	OH	H	H	1112.54 ± 27.15
29	4′-(F)-Phenyl	H	H	OH	H	H	981.07 ± 11.36
30	3′-(CF_3)-Phenyl	H	H	OH	H	H	935.71 ± 26.59
31	4′-(*t*-butyl)-Phenyl	H	H	OH	H	H	2476.91 ± 24.63
32	3′-(CF_3)-Phenyl	3″-(CF_3)-benzoyl	H	H	OH	OH	4.95 ± 0.02
33	3′-(Cl)-Phenyl	3″-(Cl)-benzoyl	H	H	OH	OH	11.82 ± 0.04
34	3′-(OCH_3)-Phenyl	3″-(OCH_3)-benzoyl	H	H	OH	OH	10.24 ± 0.15
35	4′-(F)-Phenyl	4″-(F)-benzoyl	H	H	OH	OH	13.95 ± 0.03
36	4′-(NO_2)-Phenyl	4″-(NO_2)-benzoyl	H	H	OH	OH	11.49 ± 0.17
37	4′-(OCH_3)-Phenyl	4″-(OCH_3)-benzoyl	H	H	OH	OH	12.15 ± 0.07
38	3′,4′-(diF)-Phenyl	3″,4″-(diF)-benzoyl	H	H	OH	H	553.95 ± 1.70
39	3′-(CF_3)-Phenyl	3″-(CF_3)-benzoyl	H	H	OH	H	405.32 ± 4.45
40	3′-(Cl)-Phenyl	3″-(Cl)-benzoyl	H	H	OH	H	523.11 ± 4.42
41	3′-(OCH_3)-Phenyl	3″-(OCH_3)-benzoyl	H	H	OH	H	597.11 ± 0.85
42	4′-(F)-Phenyl	4″-(F)-benzoyl	H	H	OH	H	572.53 ± 5.42
43	4′-(NO_2)-Phenyl	4″-(NO_2)-benzoyl	H	H	OH	H	362.25 ± 6.26
44	4′-(OCH_3)-Phenyl	4″-(OCH_3)-benzoyl	H	H	OH	H	559.49 ± 4.68
45	4′-(*t*-butyl)-Phenyl	4″-(*t*-butyl)-benzoyl	H	H	OH	H	408.18 ± 4.97
46	3′-(OCH_3)-Phenyl	3″-(OCH_3)-benzoyl	OH	H	OH	H	531.59 ± 4.28
47	4′-(NO_2)-Phenyl	4″-(NO_2)-benzoyl	OH	H	OH	H	353.40 ± 11.37
48	4′-(*t*-butyl)-Phenyl	4″-(*t*-butyl)-benzoyl	H	OH	H	H	1217.90 ± 27.79

2. Materials and methods

2.1. Biological activity data of chromone derivatives

The radical scavenging activity of chromone derivatives was determined by DPPH assay [18]. The IC_{50} values (μM) from DPPH assay (Table 1) were expressed as pIC_{50} ($-\log IC_{50}$). The total of 48 molecules was divided into a training set and a test set (38 molecules in training set and 10 molecules in the test set). The training and test set compounds were chosen manually such that low, moderate, and high activity compounds were present in approximately equal proportions in both sets. The test set was used to evaluate the predictive power of the CoMFA and CoMSIA models.

2.2. Generating the 3D structures

The 3D structures of all studied compounds were modeled with SYBYL 8.1 molecular modeling program (Tripos Associates, Saint Louis, MO) on Indigo Elan workstation (Silicon Graphics Inc., Mountain View, CA) using sketch approach. The fragment libraries in SYBYL database containing of small molecules were used as building blocks for the construction of larger ones. Each structure was first energy minimized using the standard Tripos force field with a distance-dependent dielectric function and the Powell conjugate gradient algorithm. Convergence criteria of 0.01 kcal/(mol Å) was used for energy minimization. The partial atomic charges were calculated using the Gasteiger–Hückel method.