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Holographic Quantitative Structure-Activity Relationship (HQSAR) Study of 3,4-Dihydroxychalcone Derivatives as 5-Lipoxygenase Inhibitors

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Abstract

Holographic quantitative structure-activity relationships (HQSAR) is a useful tool to correlates structures with their biological activities. HQSAR is a two dimensional (2D) QSAR methodology, which generates QSAR equations through 2D fingerprint and correlates it with biological activity. Here, we report a 2D-QSAR model for a series of fifty-one 3,4-dihydroxychalcones derivatives utilizing HQSAR methodology. We developed HQSAR model with 6 optimum numbers of components (ONC), which resulted in cross-validated correlation coefficient (q^2) of 0.855 with 0.283 standard error of estimate (SEE). The non-cross-validated correlation coefficient (r2) with 0.966 indicates the model is predictive enough for analysis. Developed HQSAR model was binned in to a hologram length of 257. Atomic contribution map revealed the importance of dihydroxy substitution on phenyl ring.

Key words : HQSAR, 2D-QSAR, 5-Lipoxygenase, Fragment Fingerprint

1. Introduction

The leukotrienes are important mediators of smooth muscle constriction,[1] increased vascular permeability,[2] and leukocyte chemotaxis.[3] The enzyme 5-lipoxygenase catalyzes the initial step in the metabolism of arachidonic acid leading to leukotrienes. Inhibition of the enzyme activity has provided a new therapeutic approach to treating a variety of inflammatory and allergic diseases. Especially, 5-lipoxygenase inhibitors have emerged as an attractive approach to treatment of inflammatory skin diseases, such as psoriasis and contact dermatitis, since these inflammatory dermatoses are not significantly improved by nonsteroidal anti-inflammatory drugs.

Four mechanisms can be considered for 5-lipoxygenase inhibition:[4] (1) antioxidant and/or free radical scavenging, (2) iron chelation, (3) the inhibition of 5-lipoxygenase translocation, and (4) substrate mimicking. In particular, several antioxidant 5-lipoxygenase inhibitors (e.g., DuP 654,[5] lonapalene,[6] and R-68,151[7]) have been shown to be clinically effective against topical inflammatory conditions.

Numerous studies have been undertaken on the 5-lipoxygenase inhibitors. The current status of the research has been reviewed elsewhere.[4,8] Some reports have pointed out toxicological problems associated with nonspecific antioxidants, such as methemoglobinemia.[9] However, clinical trials of lonapalene have demonstrated no side effects to preclude ita administration.[6] It is possible that the efficacy of the antioxidant 5-lipoxygenase inhibitor is independent of its toxicity. For example, 5-lipoxygenase inhibitors readily metabolized by systemic administration would be suitable topical anti-inflammatory agents.

Nakadate et al. have reported that known hydroxychalcones inhibit 12-liipoxygenase and cyclooxygenase in the mouse epidermis.[10] Furthermore, Satoshi et al. found that chalcones with a 3,4-dihydroxy structure strongly inhibited lipid peroxidation in rat liver microsomes.[11]

In this paper, we report a 2D-QSAR study of 3,4-dihydroxychalcone derivatives utilizing HQSAR techniques. With the aim to find out important atoms and groups for 5-lipoxygenase inhibition, present study was carried out with 3,4-dihydroxychaclcone antagonists.

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2. Materials and Methods

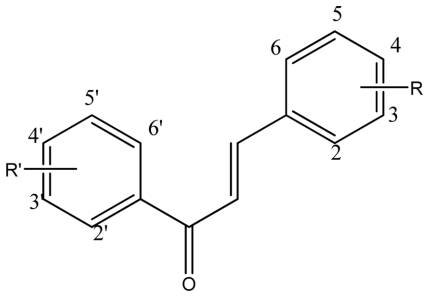
2.1. Data Set

Biological activity containing dataset for 3,4-dihydroxychalcone derivatives was selected from literature for HQSAR study.[11] This dataset consists of 51 molecules. Biological activities were reported in IC_{50} unit. Reported bioactivity values were converted to logarithmic scale to get linear QSAR model using following formula.

$$pIC_{50} = -\log IC_{50}$$

The resultant logarithmic values were utilized as a dependant variable for HQSAR study. All the structures and their biological activities were reported in Table 1.

Table 1. Structures and biological activities of 3,4-dihydroxychalcone derivatives



Sr. No.	R'	R	Actual Activity	Predicted Activity	Residual Value
1	4'-OH	-	3.64	3.89	-0.25
2	2',4'-OH	-	3.40	3.69	-0.29
3	2',4',6'-OH	-	3.85	3.26	0.59
4	2'-OH	4-OH	4.38	4.13	0.25
5	2',4'-OH	4-OH	4.46	4.56	-0.10
6	2',4',6'-OH	4-OH	4.00	4.12	-0.12
7	-	3,4-OH	7.37	7.30	0.07
8	2'-OH	3,4-OH	7.64	7.41	0.23
9	3'-OH	3,4-OH	8.38	8.31	0.07
10	4'-OH	3,4-OH	8.40	8.04	0.36
11	2',4'-OH	3,4-OH	8.34	7.85	0.49
12	2',4',6'-OH	3,4-OH	6.85	7.40	-0.55
13	2-thienyl	3,4-OH	7.66	7.50	0.16
14	3-pyridyl	3,4-OH	6.68	6.52	0.16
15	2'-OH	3-OCH_3, 4-OH	4.77	4.60	0.17
16	4'-Cl	3-OCH_3, 4-OH	5.05	5.05	0.00
17	4'-OCH_3	3-OCH_3, 4-OH	4.92	5.14	-0.22
18	2'-Cl	3,4-OH	7.04	7.32	-0.28
19	4'-Cl	3,4-OH	8.07	7.75	0.32
20	4'-NO_2	3,4-OH	7.64	7.85	-0.21
21	2'-CF_3	3,4-OH	7.24	7.41	-0.17
22	3'-CH_3	3,4-OH	7.57	7.62	-0.05
23	4'-CH_3	3,4-OH	7.12	7.71	-0.59
24	2'-OCH_3	3,4-OH	7.57	7.47	0.10
25	3'-OCH_3	3,4-OH	8.19	7.88	0.31

Table 1. Continued

Sr. No.	R'	R	Actual Activity	Predicted Activity	Residual Value
26	4'-OCH_3	3,4-OH	7.70	7.83	-0.13
27	3'-$N(CH_3)_2$	3,4-OH	8.01	7.90	0.11
28	4'- $N(CH_3)_2$	3,4-OH	8.33	8.10	0.23
29	4'-$OCH(CH_3)_2$	3,4-OH	8.39	8.06	0.33
30	2'-OH,4'-OCH_3	3,4-OH	7.82	7.89	-0.07
31	2'-OH, 5'-OCH_3	3,4-OH	7.39	7.54	-0.15
32	4'-OH,3'-OCH_3	3,4-OH	8.05	8.30	-0.25
33	2'-CH_3,4'-CH3	3,4-OH	7.77	7.67	0.10
34	2'-OCH_3, 4'-OCH_3	3,4-OH	8.00	7.90	0.10
35	2'-OCH_3,5'-OCH_3	3,4-OH	8.11	7.80	0.31
36	2'-OCH_3,6'-OCH_3	3,4-OH	6.43	6.66	-0.23
37	3'-OCH_3, 4'-OCH_3	3,4-OH	7.74	7.85	-0.11
38	2'-CH_3, 4'-CH_3, 6'-CH_3	3,4-OH	6.40	6.77	-0.37
39	3'-OCH_3, 4'-OCH_3, 5'-OCH_3	3,4-OH	7.80	7.82	-0.02
40	2',5'-OH	3,4-OH	7.19	7.59	-0.40
41	2'-OH,5'-CH_3	3,4-OH	7.41	7.48	-0.07
42	2'-OH,5'-OC_2H_5	3,4-OH	8.28	8.10	0.18
43	2'-OH,5'-$CH(CH_3)_2$	3,4-OH	8.40	8.40	0.00
44	2'-OH,5'-$OCH(CH_3)_2$	3,4-OH	7.96	7.96	0.00
45	2'-OH,5'-OC_4H_9	3,4-OH	7.00	6.91	0.09
46	2',5'-CH_3	3,4-OH	7.80	7.72	0.08
47	2'-OCH_3, 5'-CH_3	3,4-OH	7.62	7.29	0.33
48	2'-OCH3, 5'-OC_2H_5	3,4-OH	8.42	8.12	0.30
49	2'-OCH_3, 5'-$OCH(CH_3)_2$	3,4-OH	7.85	7.93	-0.08
50	2'-OC_2H_5, 5-OCH_3	3,4-OH	7.57	8.16	-0.59
51	2'-OC_2H_5, 5-OC_2H_5	3,4-OH	8.62	8.60	0.02

2.2. Molecular Modeling

All the molecular modeling study was performed by SYBYL 8.1[12] molecular modeling package. Sketching of all structures was performed by SYBYL sketching program. The most active compound (**51**) of datasets was drawn using SYBYL and minimized with Tripos force field with distance dependant dielectric functions. Similarly, other compounds of dataset were drawn based on template compound by constraining common substructure. Gasteiger-Marsilli charges were applied to all the molecules.

2.3. HQSAR

HQSAR is a technique that employs fragment fingerprints as predictive variables of biological activity or other structural related data.[13] HQSAR does not require a 3D structure of bioactive conformation or molecular alignments. HQSAR model generation deals with the 2D structure directed fragment fingerprints.[14] These molecular fingerprints are broken into strings at fixed intervals as specified by a hologram length (HL) parameter. The HL determines the number of bins in the hologram into which the fragments are hashed. The optimal HQSAR model was derived from screening through the 12 default HL values, which were a set of 12 prime numbers ranging from 53-401. The model development was performed using the following parameters: atom (A), bond (B), connection (C), chirality (Ch), hydrogen (H) and donor/acceptor (DA). The validity of the model depends on statistical parameters such as r^2, q^2 by LOO, and standard error.

3. Results

3.1. HQSAR Model Analysis

We derived a HQSAR model with good predictivity. Model was obtained with A/B/C/H/DA parameters with the atom counts 4-7, and it produced good results. Developed model showed q^2=0.838 with 0.607 standard error of prediction (SDEP). The r^2=0.937 with 0.379 standard error of estimate. Higher r2 value reflects the model predictivity. The obtained model hashed into a bin of 257 with 5 optimum numbers of components (ONC). The entire developed models are listed in Table 2. To check further robustness of developed model, the atom count parameter was explored. Different atom counts (1-9) was used to check whether it affect the predictivity of model. With the atom counts 6-9, we obtained a more robust model with q^2=0.855, SDEP=0.581, r^2=0.966, SEE=0.283, BHL=257 and ONC=6. This model was used for final analysis. These models are listed in Table 3. The graph of predicted versus actual activities of molecules under study is shown in Figure 1.

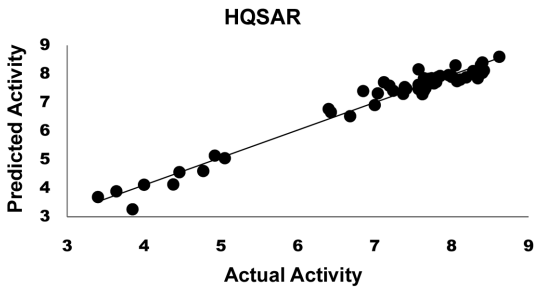


Fig. 1. Graph plot of predicted versus actual activities of molecules.

Table 2. Statistical summary of HQSAR models

Parameters	ONC	q^2	SDEP	r^2	SEE	BHL
A	6	0.681	0.861	0.859	0.573	307
B	6	0.721	0.806	0.887	0.513	257
C	6	0.704	0.830	0.858	0.575	199
H	6	0.736	0.784	0.831	0.627	97
Ch	6	0.736	0.784	0.831	0.627	97
DA	6	0.830	0.629	0.933	0.396	353
A/B	5	0.688	0.843	0.868	0.547	353
A/B/C	4	0.741	0.758	0.881	0.515	353
A/B/DA	5	0.806	0.665	0.929	0.401	353
A/B/C/H	6	0.751	0.761	0.889	0.508	257
A/B/C/DA	6	0.822	0.644	0.948	0.347	257
A/B/C/H/DA	**5**	**0.838**	**0.607**	**0.937**	**0.379**	**257**

A=Atom, B=Bond, C=Connection, H=Hydrogen, Ch=Chirality, DA=Donor and acceptor, ONC=Optimum number of components, q^2=Cross-validated correlation coefficient, r^2=Non-cross-validated correlation coefficient, SDEP=Standard error of prediction, SEE=Standard error of estimate, BHL=best hologram length. Model chosen for analysis is highlighted in bold font. All the models were generated with default atom counts (4-7).

Table 3. Statistical parameters obtained for model A/B/C/H/DA using different atom counts

Atom Counts	ONC	q^2	SDEP	r^2	SEE	BHL
1-4	6	0.703	0.832	0.879	0.531	151
2-5	5	0.793	0.689	0.903	0.471	151
3-6	5	0.832	0.618	0.953	0.389	199
4-7	5	0.838	0.607	0.937	0.379	257
5-8	6	0.849	0.593	0.948	0.348	257
6-9	**6**	**0.855**	**0.581**	**0.966**	**0.283**	**257**

Model chosen for final analysis is shown in bold font

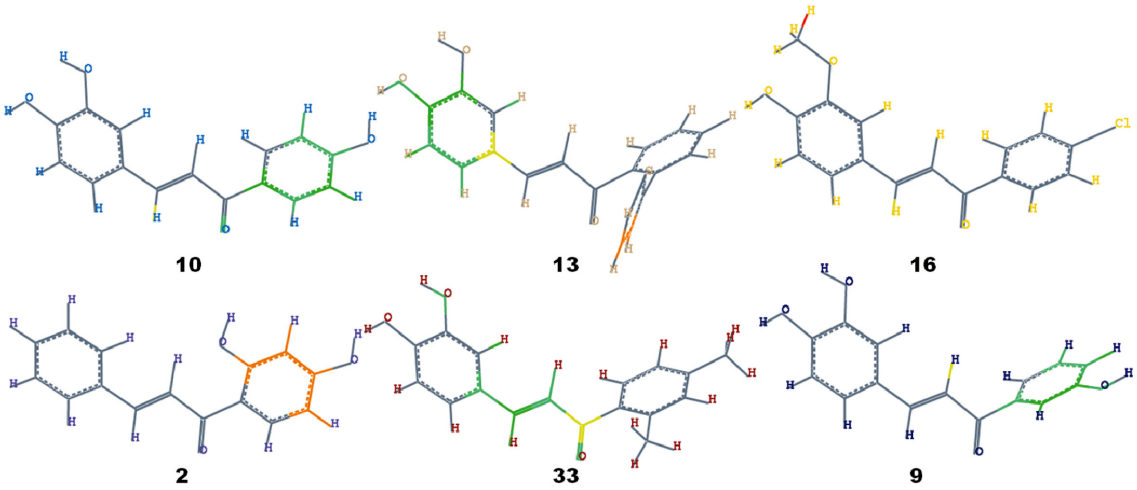


Fig. 2. Atomic contribution maps for few molecules.

3.2. Atomic Contribution Map Analysis

Atomic contribution map analysis was done to check the importance of atoms and groups for 5-lipoxygenase inhibitory effect. In SYBYL, standard color coding was employed for atomic contribution maps. Red, redorange and orange designated unfavorable and negative contribution to the activity, while yellow, green-blue and green denoted favorable or positive contribution to the activity. White indicated an intermediate contribution to activity. For study of atomic contribution, molecules were selected randomly. Atomic contribution maps for few molecules are shown in Figure 2.

For molecule **16** (pIC_{50}=5.05), the atomic contribution map shows intermediate contribution which is denoted by white color (On white background gray color). It indicated that for developed HQSAR model it showed intermediate contribution. In case of molecule **10** (pIC_{50}=8.40), the contribution map was obtained with favorable white and green contour map. The R' substituted phenyl ring showed higher contribution for inhibitory activity, whereas left hand side of molecule showed intermediate contribution for inhibitory effect. The contribution map for molecule **33** (pIC_{50}=7.77) showed its higher contribution towards HQSAR model development. The green and yellow color coding for linker between two phenyl rings indicated that this part of molecule is the most important for 5-lipoxygenase inhibitory activity and all the molecules in dataset has this scaffold structure. The contribution map for compound 2 (pIC_{50}=3.40) indicated that right hand side of molecule showed negative contribution for model development. This happens because of all the molecules have 3,4-dihydroxy substitution at left hand side phenyl ring, but unfortunately in this molecule it is absent, and this might be the reason why this molecule is lower active.

4. Discussion

In this study, we derived a HQSAR model with good predictivity in terms of q^2 and r^2 statistics. The advantage of HQSAR technique in QSAR model development is that it doesn't require bioactive conformations of molecules as well as it is alignment independent.

Atomic contribution maps revealed that, there is higher requirement of dihydroxy substitutions on left side phenyl ring for inhibitory activity. There could be chances that this dihydroxy groups might interacts with receptor through hydrogen bond interactions. This is why in our developed models (Table 2), model with single DA parameter showed higher q^2 (0.830) value. Through atomic contribution we could find out atom and groups important for 5-lipoxygenase antagonism.

5. Conclusions

In summary, we developed predictive HQSAR model in terms of q^2 and r^2 for 3,4-dihydroxychalcone deriv-

atives. Higher statistical values for both q^2 and r^2 reflect models robustness and internal predictivity. Analysis of atomic contribution map helps us to find out the atoms as well as groups which are important for inhibitory potency.

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