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Synthesis, biological evaluation and quantitative structure-activities relationship of flavonoids as vasorelaxant agents

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ABSTRACT

A series of flavonoid derivatives were designed, synthesized. Their vasorelaxant activities were evaluated experimentally against rat aorta rings pretreated with phenylephrine (PE). Among them, 6-hydroxy-8-allyl-4′-chloro-flavanone **8q** exhibited the highest vasodilatory activity (EC_{50} = 4.6 μM, E_{max} = 95.1%). The 3D-QSAR analysis was carried out by comparative molecular field analysis (CoMFA) method, and a statistically reliable model with good predictive power (r^2 = 0.872 and q^2_{cv} = 0.496) was established. The contour plots of CoMFA model provide a good insight into the structure-activity relationships of these compounds and may be used to design more potent flavonoids derivatives as vasorelaxant agents.

1. Introduction

Flavonoids, important components of a variety of traditional Chinese medicines and phytomedicines, are compounds bearing a C_6–C_3–C_6 skeleton with diverse pharmacological properties, such as anticancer, antioxidant, anti-aging and antibacterial effect.[1–3] And their cardiovascular protective effects have been reported recently.[4,5] The epidemiological reports demonstrated that people can lower incidence of heart diseases if they have a high dietary intake of flavonoids.[6,7] As we know, one of the main reasons in cardiovascular diseases is involvement of increasing tonicity or losing relaxation capacity of vascular tissues. Many studies have demonstrated some flavonoids produced concentration-dependent relaxation responses on isolated aorta rings and antihypertensive effect on animal models.[8–10] The relaxation is in part mediated by stimulation of nitric oxide released from the endothelium, while the majority of the relaxation is attributed to direct action of the flavonoids on the vascular smooth.[11–13] Although structure-activity relationships (SAR) studies of flavonoids are hampered by their structural diversity and different effect mechanisms, several structural features have been found to be involved in the endothelium-dependent vasodilatory activity:[9,10] (1) 4-carbonyl group is required as well as the double bond between C_2–C_3; (2) the pattern of hydroxylation in B-ring is important for the activity, (3) the presence of glycosylation group greatly reduce relaxation effect.

In our previous studies, some quercetin derivatives (or analogs) were prepared, and their vasodilatory activities had positive correlation with their log *P* values. Among them, 5,7-dihydroxy-3′-bromo-flavone exhibited the highest vasodilatory activity.[14] These prompted us to design a novel series of lipophilic flavonoid derivatives in attempt to improve vasodilatory activity. In the course of an analog generation program, introduction of allyl group as well as decreasing the number of hydroxyl groups in A-ring were taken into consideration, and the effect of structural skeletons (chalcone, flavanone, flavone and aurone) and substituents on B-ring on vasodilatory activities were also investigated. According to the analyses above, in present paper, we described the synthesis of a series of flavonoids derivatives, and the evaluation of these compounds as vasorelaxant agents. In addition, a comparative molecular field analysis (CoMFA) was performed to probe the quantitative structure-activity relationships (QSAR) of these compounds.

2. Results and discussion

2.1. Chemistry

The synthetic route of compounds **7**–**10** is illustrated in Scheme 1. Acetophenone **1** was treated with chloromethoxymethyl ether and potassium carbonate in acetone at room temperature to produce compounds **2**, which were allylated by allyl bromide and successively heated at 220 °C to afford Claisen rearrange products **3**. Intermediates **4** were prepared by Claisen–Schmidt condensation of **2** or **3** with appropriate aromatic aldehyde. Flavanones **5** were obtained by cyclization of 2-hydroxy-chalcones **4** in a solution of

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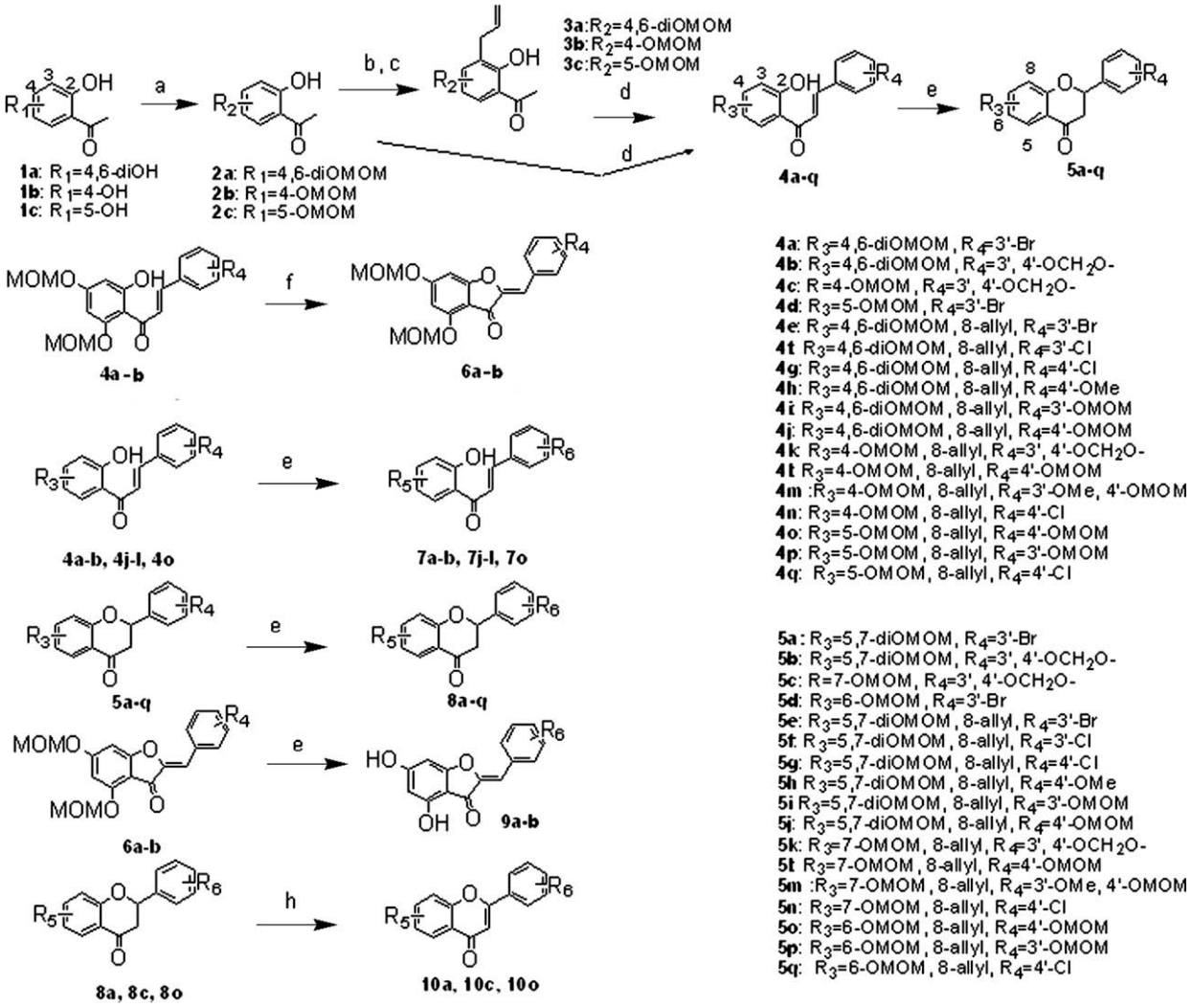


Scheme 1. Synthesis of flavonoids **7a–b, 7j–l, 7o**, **8a–q**, **9a–b**, **10a**, **10c** and **10o.** Reagents and conditions: (a) MOMCl, K_2CO_3, acetone 0 °C to rt.; (b) Allyl bromide, K_2CO_3, DMF, 100 °C; (c) 220 °C, *N,N*-dimethylaniline, N_2; (d) appropriate benzaldehyde, 10% KOH, Ethanol/H_2O, rt; (e): NaOAc, EtOH, reflux; (f): $Hg(OAc)_2$, pyridine, 60 °C (g): 5% HCl, MeOH/THF (1/1, v/v), reflux; (h) I_2, pyridine, 90 °C.

NaOAc in ethanol at 80 °C, while aurones **6** were obtained by reaction of **4** in a solution of $Hg(OAc)_2$ in pyridine at 60 °C, respectively. Demethoxymethylation of **4**, **5** and **6** were carried out in 5% HCl MeOH/THF (1/4, v/v) at reflux temperature to afford compounds **7**, **8** and **9** in good yield, respectively. Finally, flavones **10** were obtained by dehydrogenation of the corresponding flavanones **8** in presence of iodine and pyridine. Structures of all synthesized compounds were elucidated by ^{1}H NMR and ESI-MS.

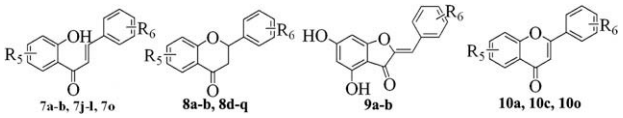
2.2. Vasorelaxation activity and SAR

Vasodilatory activity was evaluated in aortic rings with endothelium pre-contracted with 1 μM phenylephrine (PE). Quercetin, a well known vasodilator, was used as the positive control. All the tested compounds promoted relaxation in a dose-dependent manner and their maximal effects was observed at 300 μM. According to their ability to induce vasorelaxation (Table 1 and Fig. 1), tested compounds are classified into three categories based on their potency (EC_{50}) and efficacy (E_{max}). Compounds inducing 50% relaxation at small concentration (less than 50 μM) with good efficacy (more than 90%) are considered to be good relaxing agents, and the compounds inducing moderate E_{max} (70–90%) with low EC_{50} values (less than 100 μM) are moderate relaxing agents. Weak vasodilators are the compounds whose EC_{50} values are more than 100 μM and E_{max} values are limited (less than 70%).

As shown in Table 1, chalcone and flavanone derivatives showed higher activities than flavone and aurone derivatives bearing same substituents (**7a**, **8a** > **10a** > **9a**; **7b, 8b** > **9b**).

Though the result of our previous studies showed that flavonoids had higher activity with the augment of log *P* values,[14] unfortunately, it was observed that the vasodilatory activity of flavonoids was not just connected with lipophilicity when allyl group was introduced and the number of hydroxyl groups in A-ring was decreased in present studies. For example, Compound **8e** bearing 8-allyl group (more lipophilic), exhibited weaker activity than that of compound **8a** without allyl group (less lipophilic). However, 6-hydroxy-8-allyl-4′-chloro-flavanone **8q** exhibited the highest vasodilatory activity (EC_{50} = 4.6 μM, E_{max} = 95.1%), and it is more potent than compound of **8d** without of allyl group (EC_{50} = 38.5 μM, E_{max} = 91.8%). In allylated flavonoid derivatives, the effects on vasodilatory activities of different substituents of flavonoids were further investigated. Hydroxyl substituent on B-ring could significantly increase the vasorelaxant activity (**7j**, **7l** > **7k**; **8i**, **8j** > **8e–h**) when they were bearing hydroxyl group on C-5 position of A-ring. But it did not seem to have any effect of hydroxyl group on B-ring for the flavonoids without hydroxyl group

Table 1
Structure and vasorelaxant activities of tested flavonoids



No.	R_5	R_6	EC_{50} (10μM)	pEC_{50}	E_{max}	Activity class[b]	ComFA model	
							Pred. pEC_{50}	Res.
Quercetin	/	/	24.4	3.61	91.3	++	/	/
7a	4,6-DiOH	3′-Br	2.13	4.67	99.8	+++	4.70	0.03
7b	4,6-DiOH	3′,4′-OCH_2O-	2.25	4.65	104.1	+++	4.69	0.04
7j	3-Allyl-4,6-diOH	4′-OH	2.40	4.62	108.1	+++	4.52	−0.10
7k	3-Allyl-4-OH	3′,4′-OCH_2O–	N.D.[c]	/	71.8	+	/	/
7l[a]	3-Allyl-4-OH	4′-OH	8.91	4.05	73.4	++	4.19	0.14
7o	3-Allyl-5-OH	4′-OH	N.D.[c]	/	59.8	+	/	/
8a	5,7-DiOH	3′-Br	4.24	4.36	93.5	+++	4.38	0.02
8b	5,7-DiOH	3′,4′-OCH_2O–	2.01	4.70	97.2	+++	4.75	0.05
8d	6-OH	3′-Br	3.85	4.42	91.8	+++	4.70	0.28
8e	5,7-DiOH-8-Allyl	3′-Br	N.D.[c]	/	78.8	+	/	/
8f	5,7-DiOH-8-Allyl	3′-Cl	N.D.[c]	/	76.7	+	/	/
8g	5,7-DiOH-8-Allyl	4′-Cl	N.D.[c]	/	77.6	+	/	/
8h	5,7-DiOH-8-Allyl	4′-OMe	N.D.[c]	/	81.0	+	/	/
8i	5,7-DiOH-8-Allyl	3′-OH	3.70	4.44	97.8	+++	4.68	0.24
8j	5,7-DiOH-8-Allyl	4′-OH	3.21	4.49	9.86	+++	4.57	0.08
8k	7-OH-8-Allyl	3′,4′-OCH_2O–	0.94	5.03	96.6	+++	4.88	−0.15
8l	7-OH-8-Allyl	4′-OH	2.69	4.57	87.2	++	4.58	0.01
8m	7-OH-8-Allyl	3′-OMe,4′-OH	N.D.[c]	/	85.0	+	/	/
8n	7-OH-8-Allyl	4′-Cl	14.2	3.84	70.8	+++	3.78	−0.06
8o[a]	6-OH-8-Allyl	4′-OH	3.45	4.47	95.3	+++	4.66	0.19
8p	6-OH-8-Allyl	3′-OH	1.02	4.99	90.2	+++	4.89	−0.10
8q	6-OH-8-Allyl	4′-Cl	0.46	5.33	95.1	+++	4.97	−0.36
9a	H	3′-Br	N.D.[c]	/	59.2	+	/	/
9b	H	3′,4′-OCH_2O–	22.0	3.65	58.4	+	3.57	−0.08
10a[a]	5,7-DiOH	3′-Br	3.68	4.44	84.3	++	4.06	−0.38
10c	7-OH	3′,4′-OCH_2O–	8.17	4.09	82.1	++	4.09	0.00
10o	6-OH-8-Allyl	4′-OH	5.13	4.29	67.3	+	4.33	0.04

[a] The compounds were used as test set.
[b] Activity scale: +++ (highly active); ++ (moderately active); + (weakly active).
[c] N.D. means not determined.

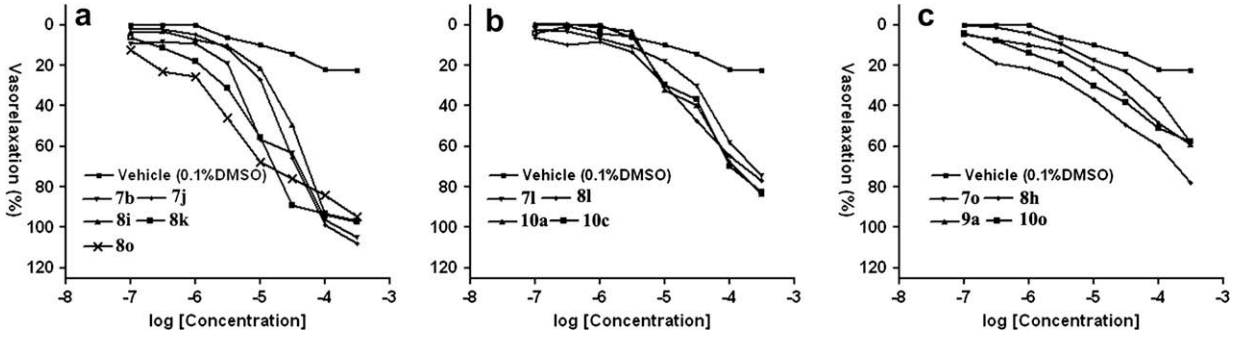


Figure 1. Effects of flavonoids on relaxation in aortic rings with endothelium pre-contracted with 1 μM phenylephrine. Flavonoids were added cumulatively to achieve the appropriate concentrations. Results are expressed as means ± standard error of mean in terms of percentage relaxation of the contraction to PE ($n = 4$). (a) Representative flavonoids (**7b**, **7j**, **8i**, **8k** and **8o**) with good relaxation effect; (b) representative flavonoids (**7l**, **8l**, **10a** and **10c**) with moderate relaxation effect; and (c) representative flavonoids (**7o**, **8h**, **9a** and **10o**) with weak relaxation effect.

on C-5 position of A-ring. For example, the compounds **8l, 8o** and **8p** which bearing hydroxyl group on B-ring displayed slightly weaker vasorelaxant activity than compounds **8k** and **8q**.

2.3. CoMFA analysis

3D-QSAR methods,[15–17] especially CoMFA,[16] are widely used in drug design, because they allow rapid generation of QSAR models, from which biological activity of newly designed molecules can be predicted. Herein, the compounds with available EC_{50} (**7a–b, 7j–l, 8a–b**, **8d, 8i–l, 8n–q**, **9b**, **10a**, **10c** and **10o)** were selected for development a 3D-QSAR model using CoMFA method, and divided into training set ($n = 16$) and test set ($n = 3$). The pEC_{50} values of these compounds were used as dependent variables. As shown in Table 2, a CoMFA model was developed with conventional correlation coefficient $r^2 = 0.872$ and LOO cross-validated coefficient

Table 2
Summary of CoMFA analysis

CoMFA model	Result
R^2 cross-validated (q^2)	0.496
Number of components	3
Non cross-validated r^2	0.872
Standard error of estimate	0.170
F	27.224
Steric contribution	51.8%
Electrostatic contribution	48.2%

q^2_{cv} = 0.496, the contribution of steric and electrostatic fields are 51.8% and 48.2%, respectively. Furthermore, we applied a test set to verify if the model can also estimate the activity of compounds that are structurally distinct from those included in the training set. The theoretical results of three compounds from test set were in good agreement with the experimental values, except for compound **10a** whose deviation between experimental and calculated pEC_{50} is 0.38. The actual and calculated activity values for training and test set compounds are shown in Table 1 and Figure 2.

The steric contour plot was shown in Figure 3a. It was found that a medium-sized yellow colored contour was surrounding *ortho*- and *meta*-positions of the B-ring of flavone and aurone derivatives. This meant that the bulky substituents at *ortho*- and *meta*-positions on B-ring of flavone and aurone derivatives would decrease the potency of vasorelaxant activities. For example, compounds **9b** and **10c** displayed weaker potency of vasorelaxant activity, which might due to the fact that methlenedioxyl groups on B-ring of these two compounds are too bulky. In addition, a medium-sized green colored contour was surrounding *ortho*- and *meta*-positions of the B-ring of flavanone derivatives. So, the bulky substituents at *ortho*- and *meta*-positions on B-ring would increase the potency of vasorelaxant activities. For instance, flavanones **8b** and **8k** exhibited more potent than **8a** and **8m**, respectively.

The electrostatic contour plot is shown in Figure 3b. The blue contour defines a region where an increase in the positive charge will result in enhanced activity, whereas the red contour defines a region of space where increasing electron density is favorable. As shown in Figure 3b, the flavanones bearing 6-hydroxyl group displayed higher potency of vasorelaxant activity (**8q** > **8n**, **8g**), which might due to the fact that hydroxyl group is associated with electronegative substituents. The similar results were observed in the weakly active chalcone derivatives **7k**, **7l** and **7o** which have a negatively charged allyl group inside red contour region. It was found that three medium-sized blue colored contour was surrounding the bond between C-2 and C-3 position of flavanone, flavone and aurone derivatives. This meant that the negative negatively charged double bond between C-2 and C-3 would result in decreased activity. In addition, the compounds with high activity (**8b**, **8p**, **8q** and **8k**) usually have a methylene group of allyl or methylenedioxyl group to occupy another two big blue contour regions. The contours in both cases are seen mainly close to the basic skeleton, which is important for designing new chemistries.

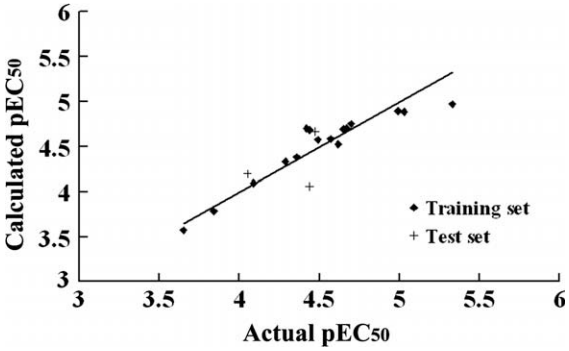


Figure 2. CoMFA calculated vs actual pEC_{50} values.

3. Conclusion

By optimizing the formerly discovered lead compound and carrying out structure-activity relationship analysis, a series of chalcone and flavanone derivatives with high vasodilatory activity (EC_{50}, E_{max}) were developed. 3D-QSAR analysis using CoMFA was performed to explore comprehensive structure-activity relationships and a statistically reliable model with good predictive power (r^2 = 0.872, q^2_{cv} = 0.496) was established on the basis of the common substructure-based alignment. According to the CoMFA contours, the details on the relationship linking structure and activity as well as clues for structural modifications that can improve the activity are provided. The model would be used to design more potent flavonoids derivatives as vasorelaxant agents and predict their activity prior to synthesis.

4. Experiment

4.1. Chemistry

Melting points were obtained on a B-540 Büchi melting-point apparatus and are uncorrected. ^{1}H NMR spectra was recorded on a Brüker AM 400 instrument at 400 MHz (chemical shifts are expressed as δ values relative to TMS as internal standard). ESI (positive) was recorded on an Esquire-LC-00075 spectrometer.

Compounds **2a–c** were obtained by selective methoxymethylation of **1a–c** with chloromethoxylmethyl ether in K_2CO_3/acetone, respectively, according to the approach in Ref. 18.

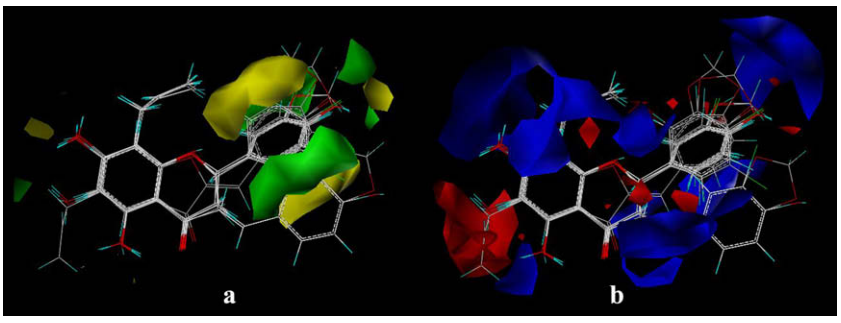


Figure 3. Electrostatic map and steric map from the CoMFA model. Compounds **7j**, **8q**, **9a** and **10a** were shown inside the field. (a) The favorable steric areas with more bulk are indicated by green isopleths, where as the disfavorable steric areas are shown by yellow isopleths. (b) The favorable electrostatic areas with positive charges are indicated by blue isopleths, whereas the favorable electrostatic areas with negative charges are show by red isoplet.

4.2. General procedure for synthesis of allylated acetophenone (3a–c)

A solution of compound **2**, allyl bromide and K_2CO_3 in 100 mL DMF was heated at 100 °C under N_2 atmosphere for 6 h, then poured into cold water and extracted with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was dissolved in *N*,*N*-dimethylaniline and then heated at 220 °C for 2.5 h. The mixture was concentrated in vacuum, and the residue was purified over silicon gel column using petroleum ether/ethyl acetate (30:1, v/v) as eluent gave **3**.

4.2.1. 2-Hydroxy-3-allyl-4,6-dimethoxymethoxy-acetophenone (3a)

Reagent: compound **2a** (10.0 g, 39.1 mmol), allyl bromide (14.2 g, 117 mmol). Yellow oil (5.8 g, 51%); ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 2.60 (s, 3H), 3.41 (d, 1H, J = 6.0 Hz), 3.45 (s, 3H), 3.51 (s, 3H), 4.95 (dd, 1H, J = 1.6, 9.6 Hz), 5.02 (dd, 1H, J = 1.6, 16.8 Hz), 5.95 (m, 1H), 5.22 (s, 2H), 5.25 (s, 2H), 6.40 (s, 1H), 13.85 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 297.

4.2.2. 2-Hydroxy-3-allyl-4-methoxymethoxy-acetophenone (3b)

Reagent: compound **2b** (10.0 g, 51.0 mmol), allyl bromide (18.5 g, 153 mmol). Yellow oil (4.6 g, 38%); 2.57 (s, 3H), 3.42 (d, 1H, J = 6.0 Hz), 3.49 (s, 3H), 4.96 (dd, 1H, J = 1.6, 9.6 Hz), 5.04 (dd, 1H, J = 1.6, 16.8 Hz), 5.21 (s, 2H), 5.98 (m, 1H), 6.68 (d, 1H, J = 8.4 Hz), 7.61 (d, 1H, J = 8.4 Hz), 13.87 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 237.

4.2.3. 2-Hydroxy-3-allyl-5-methoxymethoxy-acetophenone (3c)

Reagent: compound **2c** (10.0 g, 51.0 mmol), allyl bromide (18.5 g, 153 mmol). Yellow oil (6.7 g, 56%); 2.59 (s, 3H), 3.41 (d, 1H, J = 6.0 Hz), 3.48 (s, 3H), 5.01 (dd, 1H, J = 1.6, 9.6 Hz), 5.12 (dd, 1H, J = 1.6, 16.8 Hz), 5.22 (s, 2H), 5.96 (m, 1H), 7.06 (d, 1H, J = 2.0 Hz), 7.33 (d, 1H, J = 2.0 Hz), 13.85 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 237.

4.3. General procedure for synthesis of chalcones (4a–q)

To a cold solution of the 2-hydroxy-acetophenone **2** or **3** and appropriate benzaldehyde in 3 mL H_2O–EtOH (1/4, v/v), 3 mL 20% KOH solution (H_2O–EtOH 1/4, v/v) was added. The resulting mixture was stirred at room temperature for 24 h. The mixture was poured into ice–water, acidified to pH ~ 5 with 1 N HCl, and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified on silica gel column using petroleum ether/ethyl acetate (20:1 ~ 10:1, v/v) as eluent gave chalcone **4**.

4.3.1. 2-Hydroxy-4,6-dimethoxymethoxy-3′-bromo-chalcone (4a)

Reagent: compound **2a** (500.1 mg, 1.95 mmol), 3-bromo-benzaldehyde (379.4 mg, 2.05 mmol). Yellow solid (586 mg, 71%), mp: 73–75 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 3.50 (s, 3H), 3.57 (s, 3H), 5.21 (s, 2H), 5.31 (s, 2H), 6.25 (d, 1H, J = 2.4 Hz), 6.34 (d, 1H, J = 2.4 Hz), 7.29 (t, 1H, J = 8.0 Hz), 7.52 (t, 2H, J = 8.0 Hz), 7.69 (d, 1H, J = 16.0 Hz), 7.76 (s, 1H), 7.92 (d, 1H, J = 16.0 Hz), 13.75 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 423.

4.3.2. 2-Hydroxy-4,6-dimethoxymethoxy-3′,4′-methylenedioxy-chalcone (4b)

Reagent: compound **2a** (500.0 mg, 1.95 mmol), 3,4-methylenedioxy-benzaldehyde (307.6 mg, 2.05 mmol). Yellow solid (515.3 mg, 68%), mp: 105–107 °C; ^{1}H NMR ($CDCl_3$, 400 M, δ): 3.50 (s, 3H), 3.56 (s, 3H), 5.20 (s, 2H), 5.30 (s, 2H), 6.04 (s, 2H), 6.26 (d, 1H, J = 2.4 Hz), 6.33 (d, 1H, J = 2.4 Hz), 6.86 (d, 1H, J = 8.0 Hz), 7.11 (dd, 1H, J = 2.0, 8.0 Hz), 7.12 (d, 1H, J = 2.0 Hz), 7.74 (d, 1H, J = 15.6 Hz), 7.79 (d, 1H, J = 15.6 Hz), 13.90 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 389.

4.3.3. 2-Hydroxy-4-methoxymethoxy-3′,4′-methylenedioxy-chalcone (4c)

Reagent: compound **2b** (500.3 mg, 2.55 mmol), 3,4-methylenedioxy-benzaldehyde (402.0 mg, 2.68 mmol). Yellow solid (544.2 mg, 65%), mp: 130–133 °C; ^{1}H NMR ($CDCl_3$, 400 M, δ): 3.51 (s, 3H), 5.24 (s, 2H), 6.06 (s, 2H), 6.60 (dd, 1H, J = 2.0, 8.0 Hz), 6.65 (d, 1H, J = 2.0 Hz), 6.87 (d, 1H, J = 8.4 Hz), 7.16 (d, 1H, J = 8.4 Hz), 7.19 (s, 1H), 7.42 (d, 1H, J = 15.2 Hz), 7.82 (d, 1H, J = 15.2 Hz), 7.85 (d, 1H, J = 8.0 Hz), 13.35 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 329.

4.3.4. 2-Hydroxy-5-methoxymethoxy-3′-bromo-chalcone (4d)

Reagent: compound **2c** (500.1 mg, 2.55 mmol), 3-bromo-benzaldehyde (495.6 mg, 2.68 mmol). Yellow solid (620.5 mg, 67%), mp: 101–103 °C; ^{1}H NMR ($CDCl_3$, 400 M, δ): 3.49 (s, 3H), 5.22 (s, 2H), 6.90 (dd, 1H, J = 2.4, 8.0 Hz), 6.96 (d, 1H, J = 8.0 Hz), 7.30 (d, 1H, J = 2.4 Hz), 7.34 (t, 1H, J = 8.0 Hz), 7.51 (d, 1H, J = 16.0 Hz), 7.64 (d, 2H, J = 8.0 Hz), 7.73 (d, 1H, J = 2.0 Hz), 7.90 (d, 1H, J = 16.0 Hz), 12.95 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 363.

4.3.5. 2-Hydroxy-4,6-dimethoxymethoxy-3-allyl-3′-bromo-chalcone (4e)

Reagent: compound **3a** (499.8 mg, 1.69 mmol), 3-bromo-benzaldehyde (328.0 mg, 1.77 mmol). Yellow syrup (492.5 mg, 63%); ^{1}H NMR ($CDCl_3$, 400 M, δ): 3.43 (d, 2H, J = 6.0 Hz), 3.51 (s, 3H), 3.54 (s, 3H), 4.95 (dd, 1H, J = 1.2, 9.6 Hz), 5.06 (dd, 1H, J = 1.2, 16.8 Hz), 5.22 (s, 2H), 5.26 (s, 2H), 5.98 (m, 1H), 6.40 (s, 1H), 7.27 (t, 1H, J = 8.0 Hz), 7.50 (t, 2H, J = 8.0 Hz), 7.70 (d, 1H, J = 16.0 Hz), 7.72 (s, 1H), 7.90 (d, 1H, J = 16.0 Hz), 13.74 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 463.

4.3.6. 2-Hydroxy-4,6-dimethoxymethoxy-3-allyl-3′-chloro-chalcone (4f)

Reagent: compound **3a** (500.4 mg, 1.69 mmol), 3-chloro-benzaldehyde (249.4 mg, 1.78 mmol). Yellow syrup (424.5 mg, 60%); ^{1}H NMR ($CDCl_3$, 400 M, δ): 3.42 (d, 2H, J = 6.0 Hz), 3.51 (s, 3H), 3.53 (s, 3H), 4.98 (dd, 1H, J = 1.2, 9.6 Hz), 5.01 (dd, 1H, J = 1.2, 16.8 Hz), 5.21 (s, 2H), 5.25 (s, 2H), 5.99 (m, 1H), 6.41 (s, 1H), 7.21 (t, 1H, J = 8.0 Hz), 7.50 (t, 2H, J = 8.0 Hz), 7.65 (d, 1H, J = 16.0 Hz), 7.73 (s, 1H), 7.87 (d, 1H, J = 16.0 Hz), 13.75 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 419.

4.3.7. 2-Hydroxy-4,6-dimethoxymethoxy-3-allyl-4′-chloro-chalcone (4g)

Reagent: compound **3a** (500.2 mg, 1.69 mmol), 4-chloro-benzaldehyde (249.3 mg, 1.77 mmol). Yellow solid (410.2 mg, 58%), mp: 89–91 °C; ^{1}H NMR ($CDCl_3$, 400 M, δ): 3.41 (d, 2H, J = 6.0 Hz), 3.50 (s, 3H), 3.53 (s, 3H), 4.97 (dd, 1H, J = 1.6, 10.0 Hz), 5.04 (dd, 1H, J = 1.6, 16.8 Hz), 5.26 (s, 2H), 5.30 (s, 2H), 5.97 (m, 1H), 6.42 (s, 1H), 7.39 (d, 2H, J = 8.0 Hz), 7.54 (d, 2H, J = 8.0 Hz), 7.72 (d, 1H, J = 16.0 Hz), 7.88 (d, 1H, J = 16.0 Hz), 13.79 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 419.

4.3.8. 2-Hydroxy-4,6-dimethoxymethoxy-3-allyl-4′-methoxy-chalcone (4h)

Reagent: compound **3a** (499.9 mg, 1.69 mmol), 4-methoxy-benzaldehyde (241.2 mg, 1.77 mmol). Yellow solid (384.6 mg, 55%), mp: 80–82 °C; ^{1}H NMR ($CDCl_3$, 400 M, δ): 3.42 (d, 2H, J = 6.0 Hz), 3.49 (s, 3H), 3.53 (s, 3H), 3.76 (s, 3H), 4.99 (dd, 1H, J = 1.6, 10.0 Hz), 5.07 (dd, 1H, J = 1.6, 17.2 Hz), 5.22 (s, 2H), 5.28

(s, 2H), 5.98 (m, 1H), 6.40 (s, 1H), 7.02 (d, 2H, J = 8.4 Hz), 7.59 (d, 2H, J = 8.4 Hz), 7.71 (d, 1H, J = 16.0 Hz), 7.82 (d, 1H, J = 16.0 Hz), 13.86 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 415.

4.3.9. 2-Hydroxy-3′,4,6-trimethoxymethoxy-3-allyl-chalcone (4i)

Reagent: compound **3a** (500.0 mg, 1.69 mmol), 3-methoxymethoxy-benzaldehyde (294.4 mg, 1.77 mmol). Yellow syrup (457.5 mg, 61%). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 3.43 (d, 2H, J = 6.0 Hz), 3.48 (s, 3H), 3.49 (s, 3H), 3.52 (s, 3H), 4.96 (dd, 1H, J = 1.6, 10.0 Hz), 5.05 (dd, 1H, J = 1.6, 17.2 Hz), 5.19 (s, 2H), 5.22 (s, 2H), 5.28 (s, 2H), 6.41 (s, 1H), 7.08 (dd, 1H, J = 2.0, 8.0 Hz), 7.21 (d, 1H, J = 8.0 Hz), 7.30 (t, 1H, J = 8.0 Hz), 7.31 (s, 1H), 7.71 (d, 1H, J = 16.0 Hz), 7.88 (d, 1H, J = 16.0 Hz), 13.75 (s, 1H). ESI-MS: m/z $[M+H]^+$ 445.

4.3.10. 2-Hydroxy-4,4′,6-trimethoxymethoxy-3-allyl-chalcone (4j)

Reagent: compound **3a** (500.2 mg, 1.69 mmol), 4-methoxymethoxy-benzaldehyde (294.5 mg, 1.77 mmol). Yellow syrup (442.7 mg, 59%). ^{1}H NMR ($CDCl_3$, 400 M, δ): 3.40 (d, 2H, J = 5.6 Hz), 3.48 (s, 3H), 3.49 (s, 3H), 3.52 (s, 3H), 4.96 (dd, 1H, J = 1.2, 10.0 Hz), 5.02 (dd, 1H, J = 1.2, 17.2 Hz), 5.22 (s, 2H), 5.24 (s, 2H), 5.28 (s, 2H), 5.96 (m, 1H), 6.41 (s, 1H), 7.06 (d, 2H, J = 8.4 Hz), 7.55 (d, 2H, J = 8.4 Hz), 7.77 (d, 1H, J = 16.0 Hz), 7.83 (d, 1H, J = 16.0 Hz), 13.89 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 445.

4.3.11. 2-Hydroxy-4-methoxymethoxy-3-allyl-3′,4′-methylenedioxy-chalcone (4k)

Reagent: compound **3b** (500.1 mg, 2.12 mmol), 3,4-methylenedioxy-benzaldehyde (333.8 mg, 2.23 mmol). Yellow solid (506.9 mg, 65%), mp: 110–112 °C. ^{1}H NMR ($CDCl_3$, 400 M, δ): 3.45 (d, 2H, J = 6.0 Hz), 3.51 (s, 3H), 5.10 (dd, 1H, J = 1.6, 9.6 Hz), 5.13 (dd, 1H, J = 1.6, 16.8 Hz), 5.20 (s, 2H), 6.00 (m, 1H), 6.06 (s, 2H), 6.71 (d, 1H, J = 8.4 Hz), 6.85 (d, 1H, J = 8.4 Hz), 7.14 (dd, 1H, J = 2.0, 8.4 Hz), 7.18 (d, 1H, J = 2.0 Hz), 7.48 (d, 1H, J = 15.2 Hz), 7.78 (d, 1H, J = 8.4 Hz), 7.85 (d, 1H, J = 15.2 Hz), 13.49 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 369.

4.3.12. 2-Hydroxy-4,4′-dimethoxymethoxy-3-allyl-chalcone (4l)

Reagent: compound **3b** (500.1 mg, 2.12 mmol), 4-methoxymethoxy-benzaldehyde (369.4 mg, 2.23 mmol). Yellow solid (471.9 mg, 58%), mp: 74–75 °C. ^{1}H NMR ($CDCl_3$, 400 M, δ): 3.48 (d, 2H, J = 6.4 Hz), 3.49 (s, 3H), 3.50 (s, 3H), 4.98 (dd, 1H, J = 1.6, 9.6 Hz), 5.04 (dd, 1H, J = 1.6, 16.4 Hz), 5.23 (s, 2H), 5.28 (s, 2H), 5.99 (m, 1H), 6.70 (d, 1H, J = 8.4 Hz), 7.08 (d, 2H, J = 8.8 Hz), 7.49 (d, 1H, J = 15.2 Hz), 7.60 (d, 2H, J = 8.8 Hz), 7.79 (d, 1H, J = 8.4 Hz), 7.86 (d, 1H, J = 15.2 Hz), 13.52 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 385.

4.3.13. 2-Hydroxy-4,4′-dimethoxymethoxy-3-allyl-3′-methoxy-chalcone (4m)

Reagent: compound **3b** (500.3 mg, 2.12 mmol), 3-methoxy-4-methoxymethoxy-benzaldehyde (436.3 mg, 2.23 mmol). Yellow syrup (482.7 mg, 55%); ^{1}H NMR ($CDCl_3$, 400 M, δ): 3.45 (d, 2H, J = 6.0 Hz), 3.52 (s, 3H), 3.55 (s, 3H), 3.90 (s, 3H), 5.11 (dd, 1H, J = 1.6, 9.6 Hz), 5.15 (dd, 1H, J = 1.6, 16.8 Hz), 5.20 (s, 2H), 5.25 (s, 2H), 6.01 (m, 1H), 6.73 (d, 1H, J = 8.0 Hz), 6.85 (d, 1H, J = 8.0 Hz), 7.11 (dd, 1H, J = 2.0 8.0 Hz), 7.13 (d, 1H, J = 2.0 Hz), 7.48 (d, 1H, J = 16.0 Hz), 7.78 (d, 1H, J = 8.0 Hz), 7.81 (d, 1H, J = 16.0 Hz), 13.49 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 415.

4.3.14. 2-Hydroxy-4-methoxymethoxy-3-allyl-4′-chloro-chalcone (4n)

Reagent: compound **3b** (499.9 mg, 2.12 mmol), 4-chloro-benzaldehyde (312.5 mg, 2.22 mmol). Yellow solid (470.8 mg, 62%), mp: 115–117 °C; ^{1}H NMR ($CDCl_3$, 400 M, δ): 3.42 (d, 2H, J = 6.0 Hz), 3.51 (s, 3H), 5.10 (dd, 1H, J = 1.6, 9.6 Hz), 5.14 (dd, 1H, J = 1.6, 16.8 Hz), 5.20 (s, 2H), 6.00 (m, 1H), 6.76 (d, 1H, J = 8.0 Hz), 7.38 (d, 2H, J = 8.4 Hz), 7.48 (d, 1H, J = 16.0 Hz), 7.53 (d, 2H, J = 8.4 Hz), 7.80 (d, 1H, J = 8.0 Hz), 7.81 (d, 1H, J = 16.0 Hz), 13.49 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 359.

4.3.15. 2-Hydroxy-4′,5-dimethoxymethoxy-3-allyl-chalcone (4o)

Reagent: compound **3c** (500.2 mg, 2.12 mmol), 4-methoxymethoxy-benzaldehyde (369.4 mg, 2.22 mmol). Yellow solid (431.4 mg, 53%), mp: 90–92 °C; ^{1}H NMR ($CDCl_3$, 400 M, δ): 3.46 (d, 2H, J = 6.0 Hz), 3.51 (s, 3H), 3.54 (s, 3H), 5.11 (dd, 1H, J = 1.6, 9.6 Hz), 5.14 (dd, 1H, J = 1.6, 16.8 Hz), 5.17 (s, 2H), 5.25 (s, 2H), 6.03 (m, 1H), 7.11 (d, 2H, J = 8.0 Hz), 7.16 (d, 1H, J = 2.4 Hz), 7.47 (d, 1H, J = 2.4 Hz), 7.51 (d, 1H, J = 16.0 Hz), 7.64 (d, 2H, J = 8.0 Hz), 7.90 (d, 1H, J = 16.0 Hz), 12.96 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 385.

4.3.16. 2-Hydroxy-3′,5-dimethoxymethoxy-3-allyl-chalcone (4p)

Reagent: compound **3c** (500.0 mg, 2.12 mmol), 3-methoxymethoxy-benzaldehyde (369.3 mg, 2.22 mmol). Yellow solid (463.7 mg, 57%), mp: 86–87 °C; ^{1}H NMR ($CDCl_3$, 400 M, δ): 3.46 (d, 2H, J = 6.0 Hz), 3.50 (s, 3H), 3.52 (s, 3H), 5.13 (dd, 1H, J = 1.2, 9.6 Hz), 5.13 (dd, 1H, J = 1.2, 16.8 Hz), 5.18 (s, 2H), 5.25 (s, 2H), 6.03 (m, 1H), 7.14 (dd, 1H, J =2.0, 8.0 Hz), 7.17 (d, 1H, J = 2.0 Hz), 7.33 (d, 1H, J = 8.0 Hz), 7.34 (s, 1H), 7.37 (t, 1H, J = 8.0 Hz), 7.46 (d, 1H, J = 2.0 Hz), 7.57 (d, 1H, J = 15.6Hz), 7.88 (d, 1H, J = 15.6 Hz), 12.84 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 385.

4.3.17. 2-Hydroxy-5-methoxymethoxy-3-allyl-4′-chloro-chalcone (4q)

Reagent: compound **3c** (500.1 mg, 2.12 mmol), 4-chloro-benzaldehyde (312.6 mg, 2.23 mmol). Yellow solid (455.8 mg, 60%), mp: 100–102 °C; ^{1}H NMR ($CDCl_3$, 400 M, δ): 3.47 (d, 2H, J = 6.0 Hz), 3.52 (s, 3H), 5.12 (dd, 1H, J = 1.6, 9.6 Hz), 5.15 (dd, 1H, J = 1.6, 16.8 Hz), 5.24 (s, 2H), 6.02 (m, 1H), 7.16 (d, 1H, J = 2.4 Hz), 7.38 (d, 2H, J = 8.4 Hz), 7.45 (d, 1H, J = 2.4 Hz), 7.52 (d, 1H, J = 16.0 Hz), 7.56 (d, 2H, J = 8.4 Hz), 7.88 (d, 1H, J = 16.0 Hz), 12.60 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 359.

4.4. General procedure for synthesis of compounds 5a–q

A solution of **4** and 500 mg sodium acetate in 5 mL ethanol containing 3 drops of water was refluxed for 24 h. The mixture was poured into cold water and extracted with ethyl acetate. The organic phase was washed with saturated NaCl solution, dried (Na_2SO_4). After removing the solvent, the residue was purified on silica gel column using petroleum ether/ethyl acetate (15:1 ~ 10:1, v/v) as eluent afforded flavanone **5**.

4.4.1. (±)5,7-Dimethoxymethoxy-3′-bromo-flavanone (5a)

Reagent: compound **4a** (400.1 mg, 0.95 mmol), sodium acetate (500 mg). Pale yellow solid (260.1 mg, 65%), mp: 101–103 °C; ^{1}H NMR ($CDCl_3$, 400 M, δ): 2.80 (dd, 1H, J = 2.4, 16.8 Hz), 2.97 (dd, 1H, J = 12.8, 16.8 Hz), 3.50 (s, 3H), 3.55 (s, 3H), 5.20 (s, 2H), 5.30 (s, 2H), 5.40 (dd, 1H, J = 2.4, 16.8 Hz), 6.42 (d, 1H, J = 2.4 Hz), 6.46 (d, 1H, J = 2.4 Hz), 7.30 (t, 1H, J = 8.4 Hz), 7.37 (d, 1H, J = 8.0 Hz), 7.51 (d, 1H, J = 8.0 Hz), 7.66 (s, 1H). ESI-MS: m/z $[M+H]^+$ 423.

4.4.2. (±)5,7-Dimethoxymethoxy-3′,4′-methylenedioxy-flavanone (5b)

Reagent: compound **4b** (400.0 mg, 1.03 mmol), sodium acetate (500 mg). Pale yellow solid (248.0 mg, 62%), mp: 142–144 °C; ^{1}H NMR ($CDCl_3$, 400 M, δ): 2.82 (dd, 1H, J = 2.0, 16.8 Hz), 2.99 (dd, 1H, J = 12.4, 16.8 Hz), 3.51 (s, 3H), 3.54 (s, 3H), 5.22 (s, 2H), 5.38

(s, 2H), 5.41 (dd, 1H, J = 2.0, 12.4 Hz), 6.01 (s, 2H), 6.41 (d, 1H, J = 2.4 Hz), 6.48 (d, 1H, J = 2.4 Hz), 6.81 (d, 1H, J = 8.0 Hz), 6.85 (dd, 1H, J = 2.0, 8.0 Hz), 6.94 (d, 1H, J = 2.0 Hz). ESI-MS: m/z $[M+H]^+$ 389.

4.4.3. (±)7-Methoxymethoxy-3′,4′-methylenedioxy-flavanone (5c)

Reagent: compound **4c** (399.7 mg, 1.22 mmol), sodium acetate (500 mg). Pale yellow syrup (271.8 mg, 68%); ^{1}H NMR ($CDCl_3$, 400 M, δ): 2.83 (dd, 1H, J = 2.8, 16.8 Hz), 2.96 (dd, 1H, J = 12.8, 16.8 Hz), 3.51 (s, 3H), 5.22 (s, 2H), 5.43 (dd, 1H, J = 2.8, 12.8 Hz), 6.03 (s, 2H), 6.72 (d, 1H, J = 2.4 Hz), 6.75 (dd, 1H, J = 2.4, 8.4 Hz), 6.75 (d, 1H, J = 8.0 Hz), 6.86 (dd, 1H, J = 2.0, 8.0 Hz), 6.98 (d, 1H, J = 2.0 Hz), 7.89 (d, 1H, J = 8.4 Hz). ESI-MS: m/z $[M+H]^+$ 329.

4.4.4. (±)6-Methoxymethoxy-3′-bromo-flavanone (5d)

Reagent: compound **4d** (400.3 mg, 1.10 mmol), sodium acetate (500 mg). white solid (220.2 mg, 55%), mp: 95–96 °C. ^{1}H NMR ($CDCl_3$, 400 M, δ): 2.87 (dd, 1H, J = 2.8, 16.8 Hz), 3.01 (dd, 1H, J = 13.2, 16.8 Hz), 3.48 (s, 3H), 5.17 (s, 2H), 5.41(dd, 1H, J = 2.8, 13.2 Hz), 7.02 (d, 1H, J = 8.4 Hz), 7.23 (dd, 1H, J = 2.4, 8.4 Hz), 7.31 (t, 1H, J = 8.4 Hz), 7.38 (d, 1H, J = 8.4 Hz), 7.52 (dd, 1H, J = 2.4, 8.4 Hz), 7.56 (d, 1H, J = 8.4 Hz), 7.67 (s, 1H). ESI-MS: m/z $[M+H]^+$ 329.

4.4.5. (±)5,7-Dimethoxymethoxy-8-allyl-3′-bromo-flavanone (5e)

Reagent: compound **4e** (400.1 mg, 0.86 mmol), sodium acetate (500 mg). Pale yellow syrup (240.1 mg, 60%); ^{1}H NMR ($CDCl_3$, 400 M, δ): 2.84 (dd, 1H, J = 2.8, 16.8 Hz), 2.94 (dd, 1H, J = 12.8, 16.8 Hz), 3.43 (d, 2H, J = 6.0 Hz), 3.49 (s, 3H), 3.55 (s, 3H), 4.99 (dd, 1H, J = 1.6, 10.0 Hz), 5.02 (dd, 1H, J = 1.6, 16.8Hz), 5.25 (s, 2H), 5.29 (s, 2H), 5.38 (dd, 1H, J = 2.8, 12.8 Hz), 5.93 (m, 1H), 6.62 (s, 1H), 7.30 (t, 1H, J = 8.0 Hz), 7.38 (d, 1H, J = 8.0 Hz), 7.51 (d, 1H, J = 8.0 Hz), 7.65 (s, 1H). ESI-MS: m/z $[M+H]^+$ 463.

4.4.6. (±)5,7-Dimethoxymethoxy-8-allyl-3′-chloro-flavanone (5f)

Reagent: compound **4f** (400.1 mg, 0.96 mmol), sodium acetate (500 mg). Pale yellow solid (220.1 mg, 55%), mp: 84–86 °C; ^{1}H NMR ($CDCl_3$, 400 M, δ): 2.88 (dd, 1H, J = 2.8, 16.8 Hz), 2.93 (dd, 1H, J = 12.8, 16.8 Hz), 3.42 (d, 2H, J = 6.0 Hz), 3.46 (s, 3H), 3.53 (s, 3H), 4.96 (dd, 1H, J = 2.0, 9.6 Hz), 5.01 (dd, 1H, J = 2.0, 16.4 Hz), 5.22 (s, 2H), 5.28 (s, 2H), 5.40 (dd, 1H, J = 2.8, 12.8 Hz), 5.94 (m, 1H), 6.62 (s, 1H), 7.25 (t, 1H, J = 8.0 Hz), 7.36 (d, 1H, J = 8.0 Hz), 7.49 (d, 1H, J = 8.0 Hz), 7.69 (s, 1H). ESI-MS: m/z $[M+H]^+$ 419.

4.4.7. (±)5,7-Dimethoxymethoxy-8-allyl-4′-chloro-flavanone (5g)

Reagent: compound **4g** (400.0 mg, 0.96 mmol), sodium acetate (500 mg). Pale yellow solid (240.0 mg, 60%), mp: 89–91 °C; ^{1}H NMR ($CDCl_3$, 400 M, δ): 2.85 (dd, 1H, J = 2.8, 16.8 Hz), 2.93 (dd, 1H, J = 12.8, 16.8 Hz), 3.43 (d, 2H, J = 6.0 Hz), 3.48 (s, 3H), 3.52 (s, 3H), 4.97 (dd, 1H, J = 2.0, 9.6 Hz), 5.02 (dd, 1H, J = 2.0, 16.4 Hz), 5.21 (s, 2H), 5.26 (s, 2H), 5.42 (dd, 1H, J = 2.8, 12.8 Hz), 5.94 (m, 1H), 6.60 (s, 1H), 7.43 (d, 2H, J = 8.4 Hz), 7.52 (d, 2H, J = 8.4 Hz). ESI-MS: m/z $[M+H]^+$ 419.

4.4.8. (±)5,7-Dimethoxymethoxy-8-allyl-4′-methoxy-flavanone (5h)

Reagent: compound **4h** (400.2 mg, 0.97 mmol), sodium acetate (500 mg). Pale yellow syrup (252.1 mg, 63%); ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 2.81 (dd, 1H, J = 16.4, 2.8 Hz), 2.96 (dd, 1H, J = 13.4, 16.4 Hz), 3.40 (d, 2H, J = 6.0 Hz), 3.48 (s, 3H), 3.53 (s, 3H), 3.89 (s, 3H), 4.95 (dd, 1H, J = 2.0, 9.6 Hz), 5.01 (dd, 1H, J = 2.0, 16.8 Hz), 5.20 (s, 2H), 5.24 (s, 2H), 5.34 (dd, 1H, J = 2.8, 13.4 Hz), 5.93 (m, 1H), 6.60 (s, 1H), 7.05 (d, 2H, J = 8.4 Hz), 7.41 (d, 2H, J = 8.4 Hz). ESI-MS: m/z $[M+H]^+$ 415.

4.4.9. (±)3′,5,7-Trimethoxymethoxy-8-allyl-flavanone (5i)

Reagent: compound **4i** (400.0 mg, 0.90 mmol), sodium acetate (500 mg). Pale yellow solid (212.0 mg, 53%), mp: 72–74 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 2.80 (dd, 1H, J = 16.8, 2.8 Hz), 2.95 (dd, 1H, J = 13.4, 16.8 Hz), 3.44 (d, 2H, J = 6.0 Hz), 3.45, (s, 3H), 3.48 (s, 3H), 3.53 (s, 3H), 4.96 (dd, 1H, J = 2.0, 9.6 Hz), 5.01 (dd, 1H, J = 2.0, 16.4 Hz), 5.20 (s, 2H), 5.24 (s, 2H), 5.26 (s, 2H), 5.35 (dd, 1H, J = 2.8, 13.4 Hz), 5.92 (m, 1H), 6.58 (s, 1H), 7.06 (d, 1H, J = 8.0 Hz), 7.10 (d, 1H, J = 8.0 Hz), 7.19 (s, 1H), 7.38 (1H, d, J = 8.0 Hz). ESI-MS: m/z $[M+H]^+$ 445.

4.4.10. (±)4′,5,7-Trimethoxymethoxy-8-allyl-flavanone (5j)

Reagent: compound **4j** (400.3 mg, 0.90 mmol), sodium acetate (500 mg). Pale yellow solid (208.2 mg, 52%), mp: 77–79 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 2.82 (dd, 1H, J = 16.4, 2.8 Hz), 2.98 (dd, 1H, J = 13.4, 16.4 Hz), 3.41 (d, 2H, J = 6.0 Hz), 3.48 (s, 3H), 3.49 (s, 3H), 3.55 (s, 3H), 4.96 (dd, 1H, J = 2.0, 9.6 Hz), 5.02 (dd, 1H, J = 2.0, 16.4 Hz), 5.21 (s, 2H), 5.24 (s, 2H), 5.26 (s, 2H), 5.94 (m, 1H), 6.60 (s, 1H), 7.06 (d, 2H, J = 8.4 Hz), 7.40 (d, 2H, J = 8.4 Hz). ESI-MS: m/z $[M+H]^+$ 445.

4.4.11. (±)7-Methoxymethoxy-8-allyl-3′,4′-methylenedioxy-flavanone (5k)

Reagent: compound **4k** (400.1 mg, 1.09 mmol), sodium acetate (500 mg). Pale yellow syrup (232.1 mg, 58%); ^{1}H NMR ($CDCl_3$, 400 M, δ): 2.85 (dd, 1H, J = 2.8, 16.8 Hz), 3.02 (dd, 1H, J = 12.8, 16.8 Hz), 3.43 (d, 2H, J = 6.0 Hz), 3.48 (s, 3H), 4.98 (dd, 1H, J = 1.6, 9.6 Hz), 5.03 (dd, 1H, J = 1.6, 16.4 Hz), 5.23 (s, 2H), 5.42 (dd, 1H, J = 2.8, 12.8 Hz), 5.95 (m, 1H), 6.02 (s, 2H), 6.78 (d, 1H, J = 8.0 Hz), 6.81 (d, 1H, J = 8.0 Hz), 6.84 (dd, 1H, J = 2.0, 8.0 Hz), 6.96 (d, 1H, J = 2.0 Hz), 7.85 (d, 1H, J = 8.0 Hz). ESI-MS: m/z $[M+H]^+$ 369.

4.4.12. (±)4′,7-Dimethoxymethoxy-8-allyl-flavanone (5l)

Reagent: compound **4l** (399.8 mg, 1.04 mmol), sodium acetate (500 mg). Pale yellow solid (239.9 mg, 60%), mp: 64–66 °C; ^{1}H NMR ($CDCl_3$, 400 M, δ): 2.86 (dd, 1H, J = 2.8, 16.8 Hz), 3.01 (dd, 1H, J = 12.8, 16.8 Hz), 3.46 (d, 2H, J = 6.0 Hz), 3.49 (s, 3H), 3.51 (s, 3H), 4.97 (dd, 1H, J = 2.0, 10.0 Hz), 5.01 (dd, 1H, J = 2.0, 16.8Hz), 5.22 (s, 2H), 5.28 (s, 2H), 5.43 (dd, 1H, J = 2.8, 12.8 Hz), 5.93 (m, 1H), 6.84 (d, 1H, J = 8.4 Hz), 7.11 (d, 2H, J = 8.4 Hz), 7.41 (d, 2H, J = 8.4 Hz), 7.83 (d, 1H, J = 8.4 Hz). ESI-MS: m/z $[M+H]^+$ 385.

4.4.13. (±)4′,7-Dimethoxymethoxy-8-allyl-3′-methoxy-flavanone (5m)

Reagent: compound **4m** (400.2 mg, 0.97 mmol), sodium acetate (500 mg). Pale yellow solid (236.1 mg, 59%), mp: 92–93 °C; ^{1}H NMR ($CDCl_3$, 400 M, δ): 2.86 (dd, 1H, J = 2.8, 16.8 Hz), 3.00 (dd, 1H, J = 12.8, 16.8 Hz), 3.46 (d, 2H, J = 6.0 Hz), 3.47 (s, 3H), 3.53 (s, 3H), 3.91(s, 3H), 4.96 (dd, 1H, J = 1.6, 9.6 Hz), 5.02 (dd, 1H, J = 1.6, 16.4 Hz), 5.26 (s, 2H), 5.27 (s, 2H), 5.40 (dd, 1H, J = 2.8, 12.8 Hz), 5.93 (m, 1H), 6.83 (d, 1H, J = 8.4 Hz), 6.94 (d, 1H, J = 8.0 Hz),7.08 (dd, 1H, J = 2.0, 8.4 Hz), 7.32 (d, 1H, J = 2.0 Hz), 7.82 (d, 1H, J = 8.0 Hz). ESI-MS: m/z $[M+H]^+$ 415.

4.4.14. (±)7-Methoxymethoxy-8-allyl-4′-chloro-flavanone (5n)

Reagent: compound **4n** (400.1 mg, 1.12 mmol), sodium acetate (500 mg). Pale yellow syrup (212.1 mg, 53%); ^{1}H NMR ($CDCl_3$, 400 M, δ): 2.83 (dd, 1H, J = 2.8, 16.8 Hz), 3.00 (dd, 1H, J = 12.8, 16.8 Hz), 3.41 (d, 2H, J = 6.0 Hz), 3.48 (s, 3H), 4.96 (dd, 1H, J = 1.6, 9.6 Hz), 5.01 (dd, 1H, J = 1.6, 16.4 Hz), 5.23 (s, 2H), 5.42 (dd, 1H, J = 2.8, 12.8 Hz), 5.95 (m, 1H), 6.69 (d, 1H, J = 8.0 Hz), 7.15 (d, 2H,

J = 8.4 Hz), 7.44 (d, 1H, J = 8.4 Hz), 7.83 (d, 1H, J = 8.0 Hz). ESI-MS: m/z $[M+H]^+$ 359.

4.4.15. (±)4′,6-Dimethoxymethoxy-8-allyl-flavanone (5o)

Reagent: compound **4o** (400.0 mg, 1.04 mmol), sodium acetate (500 mg). Pale yellow solid (220.1 mg, 55%), mp: 96–97 °C. ^{1}H NMR ($CDCl_3$, 400 M, δ): 2.85 (dd, 1H, J = 2.8, 16.8 Hz), 3.02 (dd, 1H, J = 13.2, 16.8 Hz), 3.43 (d, 2H, J = 6.0 Hz), 3.48 (s, 3H), 3.51 (s, 3H), 5.06 (dd, 1H, J = 1.6, 9.6 Hz), 5.10 (dd, 1H, J = 1.6, 16.4 Hz), 5.18 (s, 2H), 5.25 (s, 2H), 5.40 (dd, 1H, J = 2.8, 13.2), 5.98 (m, 1H), 7.08 (d, 2H, J = 8.4 Hz), 7.11 (d, 1H, J = 2.0 Hz), 7.40 (d, 1H, J = 2.0 Hz), 7.45 (d, 2H, J = 8.4 Hz). ESI-MS: m/z $[M+H]^+$ 385.

4.4.16. (±)3′,6-Dimethoxymethoxy-8-allyl-flavanone (5p)

Reagent: compound **4p** (400.3 mg, 1.04 mmol), sodium acetate (500 mg). Pale yellow solid (244.2 mg, 61%), mp: 62–64 °C; ^{1}H NMR ($CDCl_3$, 400 M, δ): 2.87 (dd, 1H, J = 2.8, 16.8 Hz), 3.03 (dd, 1H, J = 13.2, 16.8 Hz), 3.42 (d, 2H, J = 6.0 Hz), 3.48 (s, 3H), 3.53 (s, 3H), 5.07 (dd, 1H, J = 1.6, 9.6 Hz), 5.12 (dd, 1H, J = 1.6, 16.4 Hz), 5.20 (s, 2H), 5.22 (s, 2H), 5.43 (dd, 1H, J = 2.8, 13.2 Hz), 5.99 (m, 1H), 7.03 (dd, 1H, J = 8.0 Hz), 7.05 (d, 1H, J = 8.0 Hz), 7.09 (d, 1H, J = 2.0 Hz), 7.19 (s, 1H), 7.37 (d, 1H, J = 8.0 Hz), 7.43 (d, H, J = 2.0 Hz). ESI-MS: m/z $[M+H]^+$ 385.

4.4.17. (±)6-Methoxymethoxy-8-allyl-4′-chloro-flavanone (5q)

Reagent: compound **4q** (400.0 mg, 1.12 mmol), sodium acetate (500 mg). Pale yellow solid (232.0 mg, 58%), mp: 100–101 °C; ^{1}H NMR ($CDCl_3$, 400 M, δ): 2.88 (dd, 1H, J = 2.4, 16.4 Hz), 2.98 (dd, 1H, J = 12.8, 16.4 Hz), 3.40 (d, 2H, J = 6.4 Hz), 3.48 (s, 3H), 5.07 (dd, 1H, J = 1.6, 9.6 Hz), 5.09 (dd, 1H, J = 1.6, 16.4 Hz), 5.15 (s, 2H), 5.41 (dd, 1H, J = 2.4, 12.8 Hz), 5.95 (m, 1H), 7.11 (d, 1H, J = 2.4 Hz), 7.41 (s, 4H), 7.44 (s, 1H, J = 2.4 Hz). ESI-MS: m/z $[M+H]^+$ 359.

4.5. General procedure for synthesis of compounds 6a–b

A solution of **5** and mercuric acetate in 1 mL anhydrous pyridine was heated at 60 °C for 2 h. The mixture was poured into cold water. The precipitate was separated and purified on silica gel column using petroleum ether/ethyl acetate (12:1, v/v) as eluent afforded **6**.

4.5.1. 5,7-Methoxymethoxy-3′-bromo-aurone (6a)

Reagent: compound **4a** (100.0 mg, 0.24 mmol), mercuric acetate (150.6 mg, 0.48 mmol). Yellow solid (69.7 mg, 70%), mp: 136–138 °C; ^{1}H NMR ($CDCl_3$, 400 M, δ): 3.52 (s, 3H), 3.54 (s, 3H), 5.27 (s, 2H), 5.37 (s, 2H), 6.53 (1H, J = 1.6 Hz), 6.66 (1H, J = 1.6 Hz), 6.67 (s, 1H), 7.30 (t, 1H, J = 8.0 Hz), 7.49 (dt, 1H, J = 8.0, 1.6 Hz), 7.74 (d, 1H, J = 8.0 Hz), 8.06 (t, 1H, J = 1.6 Hz). ESI-MS: m/z $[M+H]^+$ 421.

4.5.2. 5,7-Methoxymethoxy-3′,4′-methylenedioxy-aurone (6b)

Reagent: compound **4b** (100.0 mg, 0.26 mmol), mercuric acetate (164.2 mg, 0.52 mmol). Yellow solid (74.6 mg, 75%), mp: 164–165 °C; ^{1}H NMR ($CDCl_3$, 400 M, δ): 3.53 (s, 3H), 3.54 (s, 3H), 5.26 (s, 2H), 5.37 (s, 2H), 6.04 (s, 2H), 6.53 (1H, J = 2.0 Hz), 6.64 (1H, J = 2.0 Hz), 6.71 (s, 1H), 6.87 (d, 1H, J = 8.0 Hz), 7.28 (dd, 1H, J = 2.0, 8.0 Hz), 7.54 (d, 1H, J = 2.0 Hz). ESI-MS: m/z $[M+H]^+$ 387.

4.6. General procedure for synthesis of compounds 7a–b, 7j–l, 7o, 8a–q and 9a–b

To a solution of **4a–b, 4j–l, 4o, 5a–q or 6a–b** in 10 mL methanol/THF(1/1, v/v), 2 mL 3 N HCl was added. The resulting mixture was refluxed for 45 min, then poured into cold water and extracted with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified over silicon gel column using petroleum ether/ethyl acetate as eluent gave **7a–b, 7j–l, 7o**, **8a–q** or **9a–b**.

4.6.1. 2,4,6-Trihydroxy-3′-bromo-chalcone (7a)

Reagent: compound **4a** (100 mg, 0.24 mmol). Yellow amorphous powder (63.4 mg, 80%), mp: 168–170 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 5.98 (s, 2H), 7.41 (t, 1H, J = 8.0 Hz), 7.59 (dd, 1H, J = 1.6, 8.0 Hz), 7.68 (d, 1H, J = 8.0 Hz), 7.70 (d, 1H, J = 15.6 Hz), 7.87 (t, 1H, J = 1.6 Hz), 8.24 (d, 1H, J = 15.6 Hz), 9.38 (s, 1H, OH), 11.96 (s, 2H, OH). ESI-MS: m/z $[M+H]^+$ 335.

4.6.2. 2,4,6-Trihydroxy-3′,4′-methylenedioxy-chalcone (7b)

Reagent: compound **4b** (100 mg, 0.26 mmol). Yellow amorphous powder (57.2 mg, 74%), mp: 198–200 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 5.97 (s, 2H), 6.08 (s, 2H), 6.91 (d, 1H, J = 8.4 Hz), 7.20 (d, 1H, J = 1.2, 8.4 Hz), 7.21 (d, 1H, J = 1.2 Hz), 7.72 (d, 1H, J = 15.6 Hz), 8.10 (d, 1H, J = 15.6 Hz), 9.27 (s, 1H, OH), 11.99 (s, 2H, OH). ESI-MS: m/z $[M+H]^+$ 301.

4.6.3. 2,4,4′,6-Tetra-hydroxy-3-allyl-chalcone (7j)

Reagent: compound **4j** (100 mg, 0.23 mmol). Yellow amorphous powder (46.4 mg, 66%), mp: 185–187 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 3.28 (td, 2H, J = 1.6, 6.0 Hz), 4.83 (qd, 1H, J = 2.0, 12.0 Hz), 4.94 (qd, 1H, J = 2.0, 16.0 Hz), 5.87 (m, 1H), 6.06 (s, 1H), 6.85 (d, 2H, J = 8.4 Hz), 7.52 (d, 2H J = 8.4 Hz), 7.71 (d, 1H, J = 15.6 Hz), 8.08 (d, 1H, J = 15.6 Hz), 8.82 (s, 1H, OH), 9.03 (s, 1H, OH), 9.61 (s, 1H, OH), 14.39 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 313.

4.6.4. 2,4-Dihydroxy-3-allyl-3′,4′-methylenedioxy-chalcone (7k)

Reagent: compound **4k** (100 mg, 0.27 mmol). Yellow amorphous powder (67.8 mg, 77%), mp: 174–175 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 3.53 (td, 2H, J = 1.6, 6.0 Hz), 5.16 (qd, 1H, J = 1.6, 10.0 Hz), 5.20 (qd, 1H, J = 1.6, 16.8 Hz), 6.10 (m, 1H), 6.04 (s, 2H), 6.44 (d, 1H, J = 8.4 Hz), 6.85 (d, 1H, J = 8.4 Hz), 7.13 (dd, 1H, J = 1.6, 8.0 Hz), 7.42 (d, 1H, J = 16.0 Hz), 7.75 (d, 1H, J = 8.4 Hz), 7.80 (d, 1H, J = 16.0 Hz), 9.26 (s, 1H, OH), 13.82 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 325.

4.6.5. 2,4,4′-Trihydroxy-3-allyl-chalcone (7l)

Reagent: compound **4l** (100 mg, 0.52 mmol); Yellow amorphous powder (53.9 mg, 70%), mp: 179–182 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): ^{1}H NMR (acetone-d_6, 400 M, δ): 3.39 (td, 2H, J = 1.6, 6.0 Hz), 4.86 (qd, 1H, J = 1.6, 10.0 Hz), 4.97 (qd, 1H, J = 1.6, 16.8 Hz), 5.95 (m, 1H), 6.51 (d, 1H, J = 8.4 Hz), 6.90 (d, 2H, J = 8.4 Hz), 7.71 (d, 2H, J = 8.4 Hz), 7.72 (d, 1H, J = 16.0 Hz), 7.81 (d, 1H, J = 16.0 Hz), 7.97 (d, 1H, J = 8.4 Hz), 8.98 (s, 1H, OH), 9.31 (s, 1H, OH), 13.95 (s, 1H, OH).

4.6.6. 2,4′,5-Trihydroxy-3-allyl-chalcone (7o)

Reagent: compound **4o** (100 mg, 0.26 mmol). Yellow amorphous powder (56.3 mg, 73%), mp: 152–154 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 3.38 (td, 2H, J = 1.6, 6.0 Hz), 5.04 (qd, 1H, J = 1.6, 10.0 Hz), 5.11 (qd, 1H, J = 1.6, 17.2 Hz), 5.99 (m, 1H), 6.95 (d, 2H, J = 8.4 Hz), 7.02 (d, 1H, J = 2.4 Hz), 7.48 (d, 1H, J = 2.4 Hz), 7.76 (d, 1H, J = 15.2 Hz), 7.79 (d, 2H, J = 8.4 Hz), 7.88 (d, 1H, J = 15.2 Hz), 8.00 (s, 1H, OH), 9.06 (s, 1H, OH), 12.93 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 325.

4.6.7. (±)5,7-Dihydroxy-3′-bromide-flavanone (8a)

Reagent: compound **5a** (200 mg, 0.47 mmol). White amorphous powder (134.6 mg, 85%), mp: 217–218 °C. ^{1}H NMR (acetone-d_6,

400 M, δ): 2.85 (dd, 1H, J = 3.2, 17.2 Hz), 3.18 (dd, 1H, J = 12.8, 17.2 Hz), 5.61 (dd, 1H, J = 3.2, 17.2 Hz), 5.98 (d, 1H, J = 2.4 Hz), 6.02 (d, 1H, J = 2.4 Hz), 7.42 (t, 1H, J = 8.0 Hz), 7.57–7.59 (m, 2H), 7.78 (t, 1H, J = 2.4 Hz), 9.68 (s, 1H, OH), 12.13 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 335.

4.6.8. (±)5,7-Dihydroxy-3′,4′-methylenedioxy-flavanone (8b)

Reagent: compound **5b** (100 mg, 0.26 mmol). White amorphous powder (63.4 mg, 82%), mp: 215–216 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 2.75 (dd, 1H, J = 2.4, 16.4 Hz), 3.18 (dd, 1H, J = 12.4, 16.4 Hz), 5.48 (dd, 1H, J = 2.4, 16.4 Hz), 5.95 (d, 1H, J = 2.0 Hz), 5.97 (d, 1H, J = 2.0 Hz), 6.04 (s, 2H), 6.89 (d, 1H, J = 7.6 Hz), 7.03 (dd, 1H, J = 1.6, 7.6 Hz), 7.10 (d, 1H, J = 1.6 Hz), 9.67 (s, 1H, OH), 12.15 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 301.

4.6.9. (±)7-Hydroxy-3′,4′-methylenedioxy-flavanone (8c)

Reagent: compound **5c** (100 mg, 0.30 mmol). White amorphous powder (67.5 mg, 78%), mp: 181–183 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 2.78 (dd, 1H, J = 2.8, 16.8 Hz), 3.03 (dd, 1H, J = 12.8, 16.8 Hz), 5.60 (dd, J = 2.8, 12.8 Hz), 6.48 (d, 1H, J = 2.0 Hz), 6.60 (dd, J = 2.0, 8.4 Hz), 7.01 (d, 1H, J = 8.0 Hz), 7.05 (dd, 1H, J = 1.2, 8.0 Hz), 7.08 (d, J = 1.2 Hz), 9.46 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 285.

4.6.10. (±)6-Hydroxy-3′-bromide-flavanone (8d)

Reagent: compound 5 d (100 mg, 0.28 mmol). White amorphous powder (70.3 mg, 80%), mp: 174–175 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 2.85 (dd, 1H, J = 2.8, 16.8 Hz), 3.08 (dd, 1H, J = 12.8, 16.8 Hz), 5.57 (dd, J = 2.8, 12.8 Hz), 6.99 (d, 1H, J = 8.4 Hz), 7.11 (dd, J = 2.4, 8.4 Hz), 7.25 (d, 1H, J = 2.4 Hz), 7.41 (t, 1H, J = 8.4 Hz), 7.58 (t, 2H, J = 8.4 Hz), 7.80 (s, 1H), 8.38 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 319.

4.6.11. (±)5,7-Dihydroxy-8-allyl-3′-bromide-flavanone (8e)

Reagent: compound **5e** (100 mg, 0.22 mmol); White amorphous powder (59.1 mg, 73%), mp: 151–153 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 2.82 (dd, 1H, J = 16.8, 2.8 Hz), 3.09 (d, 1H, J = 12.4, 16.8 Hz), 3.32 (t, 2H, J = 6.0 Hz), 4.84 (dd, 1H, J = 2.0, 9.6 Hz), 4.95 (dd, 1H, J = 2.0, 16.8 Hz), 5.56 (dd, 1H, J = 2.8, 12.4 Hz), 6.05 (s, 1H), 7.37 (t, 1H, J = 8.0 Hz), 7.53 (d, 2H, J = 8.0 Hz), 7.75 (s, 1H), 9.59 (s, 1H, OH), 12.08 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 375.

4.6.12. (±)5,7-Dihydroxy-3′-chloro-8-allyl-flavanone (8f)

Reagent: compound **5f** (100 mg, 0.24 mmol). White amorphous powder (59.2 mg, 75%), mp: 135–136 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 2.93 (dd, 1H, J = 16.8, 3.6 Hz), 3.17 (d, 1H, J = 12.4, 16.8 Hz), 3.33 (d, 2H, J = 6.0 Hz), 4.91 (dd, 1H, J = 1.6, 10.0 Hz), 4.97 (dd, 1H, J = 1.6, 16.8 Hz), 5.65 (dd, J = 3.6, 12.4 Hz), 5.89 (m, 1H), 6.10 (s, 1H), 7.43 (d, 1H, J = 8.0 Hz), 7.49 (t, 1H, J = 8.0 Hz), 7.55 (d, 1H, J = 8.0 Hz), 7.65 (s, 1H), 9.65 (s, 1H, OH), 12.01 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 331.

4.6.13. (±)5,7-Dihydroxy-4′-chloro-8-allyl-flavanone (8g)

Reagent: compound **5g** (100 mg, 0.24 mmol). White amorphous powder (55.2 mg, 70%), mp: 157–158 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 2.80 (dd, 1H, J = 16.4, 2.4 Hz), 3.11 (d, 1H, J = 12.4, 16.8 Hz), 3.30 (t, 2H, J = 6.0 Hz), 4.88 (dd, 1H, J = 2.0, 9.6 Hz), 4.96 (dd, 1H, J = 2.0, 16.8 Hz), 5.61 (dd, J = 2.4, 12.4 Hz), 5.88 (m, 1H), 6.06 (s, 1H), 7.49 (d, 2H, J = 8.0 Hz), 7.61 (d, 2H, J = 8.0 Hz), 9.67 (s, 1H, OH), 12.11 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 331.

4.6.14. (±)5,7-Dihydroxy-4′-methoxy-8-allyl-flavanone (8h)

Reagent: compound **5h** (100 mg, 0.24 mmol). White amorphous powder (55.9 mg, 71%), mp: 142–143 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 2.80 (dd, 1H, J = 17.2, 2.8 Hz), 3.13 (d, 1H, J = 12.4, 16.8 Hz), 3.28 (t, 2H, J = 6.0 Hz), 3.83 (s, 3H, OMe), 4.87 (dd, 1H, J = 2.0, 10.4 Hz), 4.95 (dd, 1H, J = 2.0, 16.8 Hz), 5.50 (dd, J = 2.8, 12.4 Hz), 5.88 (m, 1H), 6.04 (s, 1H), 7.00 (d, 2H, J = 8.0 Hz), 7.50 (d, 2H, J = 8.0 Hz), 9.60 (s, 1H, OH), 12.15 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 297.

4.6.15. (±)3′,5,7-Trihydroxy-8-allyl-flavanone (8i)

Reagent: compound **5i** (100 mg, 0.23 mmol). White amorphous powder (45.7 mg, 65%), mp: 188–190 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 2.79 (dd, 1H, J = 2.8, 16.8 Hz), 3.02 (dd, 1H, J = 12.4, 16.8 Hz), 3.26 (d, 2H, J = 6.0 Hz), 4.84 (dd, 1H, J = 2.0, 9.6 Hz), 4.93 (dd, 1H, J = 2.0, 16.8 Hz), 5.46 (dd, J = 2.8, 12.4 Hz), 5.85 (m, 1H), 6.00 (s, 1H), 6.80 (dd, J = 2.0, 8.0 Hz), 6.97 (d, 1H, J = 8.0 Hz), 7.01 (d, 1H, J = 2.0 Hz), 7.21 (t, 1H, J = 8.0 Hz), 8.45 (s, 1H, OH), 9.54 (s,1H, OH), 12.09 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 313.

4.6.16. (±)4′,5,7-Trihydroxy-8-allyl-flavanone (8j)

Reagent: compound **5j** (100 mg, 0.23 mmol). White amorphous powder (47.8 mg, 68%), mp: 195–196 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 2.75 (dd, 1H, J = 16.4, 2.8 Hz), 3.03 (d, 1H, J = 12.0, 16.4 Hz), 3.26 (d, 2H, J = 6.0 Hz), 4.88 (dd, 1H, J = 2.0, 9.6 Hz), 4.88 (dd, 1H, J = 2.0, 9.6 Hz), 4.95 (dd,1H, J = 2.0, 12.0 Hz), 5.44 (dd, J = 2.8, 12.4 Hz), 6.01 (s, 1H), 7.05 (d, 2H, J = 8.0 Hz), 7.35 (d, 2H, J = 8.0 Hz), 8.65 (s, 1H, OH), 9.58 (s, 1H, OH), 12.11 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 313.

4.6.17. (±)7-Hydroxy-8-allyl-3′,4′-methylenedioxy-flavanone (8k)

Reagent: compound **5k** (100 mg, 0.27 mmol). White amorphous powder (66.1 mg, 75%), mp: 171–173 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 2.80 (dd, 1H, J = 3.6, 16.8 Hz), 2.98 (dd, 1H, J = 12.8, 16.8 Hz), 3.47 (d, 2H, J = 6.4 Hz), 5.10–5.16 (m, 2H), 5.37 (dd, 1H, J = 3.6, 12.8 Hz), 5.96 (m, 1H), 6.00 (d, 2H, J = 0.8 Hz), 6.57 (d, 1H, J = 8.0 Hz), 6.84 (d, 1H, J = 8.0 Hz), 6.90 (dd, 1H, J = 1.2, 8.0 Hz), 6.98 (d, 1H, J = 1.2 Hz), 7.77 (d, 1H, J = 8.0 Hz), 9.22 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 325.

4.6.18. (±)4′,7-Dihydroxy-8-allyl-flavanone (8l)

Reagent: compound **5l** (100 mg, 0.26 mmol); White amorphous powder (56.3 mg, 73%), mp: 178–181 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 2.68 (dd, 1H, J = 2.8, 16.0 Hz), 2.94 (dd, 1H, J = 12.4, 16.0 Hz), 3.34 (d, 2H, J = 6.8 Hz), 4.88 (m, 1H), 4.93 (m, 1H), 5.40 (dd, 1H, J = 2.8, 12.4 Hz), 5.87 (m, 1H), 6.59 (d, 1H, J = 8.4 Hz), 6.85 (d, 2H, J = 8.4 Hz), 7.37 (d, 2H, J = 8.4 Hz), 7.57 (d, 1H, J = 8.4), 8.41 (s, 1H, OH), 9.18 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 297.

4.6.19. (±) 4′,7-Dihydroxy-8-allyl-3′-methoxy-flavanone (8m)

Reagent: compound **5m** (100 mg, 0.24 mmol). White amorphous powder (54.3 mg, 69%), mp: 179–180 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 2.72 (dd, 1H, J = 16.8, 2.4 Hz), 2.97 (d, 1H, J = 13.2, 16.8 Hz), 3.40 (d, 2H, J = 6.4 Hz), 3.86 (s, 3H, OMe), 4.91 (dd, 1H, J = 2.0, 10.0 Hz), 4.99 (dd, 1H, J = 2.0, 16.8 Hz), 5.44 (dd, J = 2.4, 13.2 Hz), 5.93 (m, 1H), 6.62 (d, 1H, J = 8.4 Hz), 6.99 (s, 2H), 7.07 (s, 1H), 7.61 (d, 1H, J = 8.4 Hz), 7.73 (s, 1H, OH), 9.29 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 327.

4.6.20. (±)7-Hydroxy-8-allyl-4′-chloro-flavanone (8n)

Reagent: compound **5n** (100 mg, 0.28 mmol). White amorphous powder (67.6 mg, 77%) mp: 148–150 °C. ^{1}H NMR ($CDCl_3$, 400 M, δ): 2.81 (dd, 1H, J = 2.4, 16.8 Hz), 2.97 (dd, 1H, J = 12.8, 16.8 Hz), 3.43 (d, 1H, J = 6.0 Hz), 4.92 (dd, 1H, J = 2.0, 10.0 Hz), 5.00 (dd, 1H, J = 2.0, 16.8 Hz), 5.60 (dd, 1H, J = 2.4, 12.8 Hz), 5.94 (m, 1H), 5.67 (d, 1H, J = 8.0 Hz), 7.50 (d, 2H, J = 8.4 Hz), 7.63 (d, 3H, J = 8.4 Hz). ESI-MS: m/z $[M+H]^+$ 315.

4.6.21. (±)4′,6-Dihydroxy-8-allyl-flavanone (8o)

Reagent: compound **5o** (100 mg, 0.26 mmol). White amorphous powder (57.8 mg, 75%), mp: 176–177 °C. ^{1}H NMR ($CDCl_3$, 400 M, δ): 2.86 (dd, 1H, J = 2.8, 16.8 Hz), 3.01 (dd, 1H, J = 13.2, 16.8 Hz), 3.37 (d, 1H, J = 6.8 Hz), 5.06 (m, 1H), 5.10 (m, 1H), 5.36 (dd, 1H, J = 2.8, 13.2 Hz), 5.94 (m, 1H), 6.88 (d, 2H, J = 8.4 Hz), 6.97 (d, 1H, J = 2.8 Hz), 7.20 (d, 1H, J = 2.8 Hz), 7.35 (d, 2H, J = 8.4 Hz). ESI-MS: m/z $[M+H]^+$ 297.

4.6.22. (±)3′,6-Dihydroxy-8-allyl-flavanone (8p)

Reagent: compound **5p** (100 mg, 0.26 mmol). White amorphous powder (60.1 mg, 78%), mp: 160–162 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 2.82 (dd, 1H, J = 16.4, 3.6 Hz), 2.99 (d, 1H, J = 12.8, 16.4 Hz), 3.39 (d, 2H, J = 6.4 Hz), 5.03 (dd, 1H, J = 1.6, 10.0 Hz), 5.09 (dd, 1H, J = 1.6, 16.8 Hz), 5.47 (dd, J = 3.6, 12.8 Hz), 5.99 (m, 1H), 6.83 (dd, 1H, J = 1.6, 8.0 Hz), 6.98 (d, 1H, J = 2.4 Hz), 7.02 (d, 1H, J = 8.0 Hz), 7.07 (s, 1H), 7.14 (d, 1H, J = 2.4 Hz), 7.25 (t, 1H, J = 8.0 Hz), 8.25 (s, 1H, OH), 8.49 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 297.

4.6.23. (±)6-Hydroxy-4′-chloro-8-allyl-flavanone (8q)

Reagent: compound **5q** (100 mg, 0.28 mmol). White amorphous powder (62.3 mg, 71%), mp: 150–151 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 2.85 (dd, 1H, J = 16.8, 2.8 Hz), 3.02 (d, 1H, J = 13.2, 16.8 Hz), 3.38 (d, 2H, J = 6.4 Hz), 5.03 (dd, 1H, J = 1.6, 10.0 Hz), 5.08 (dd, 1H, J = 1.6, 16.8 Hz), 5.57 (dd, J = 2.8, 13.2 Hz), 5.97 (m, 1H), 6.99 (d, 1H, J = 2.4 Hz), 7.14 (d, 1H, J = 2.4 Hz), 7.48 (d, 2H, J = 8.4 Hz), 7.63 (d, 2H, J = 8.4 Hz), 8.28 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 315.

4.6.24. 5,7-Dihydroxy-3′-bromo-aurone (9a)

Reagent: compound **6a** (100 mg, 0.24 mmol). Yellow powder (52.2 mg, 66%), mp: 271–273 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 6.17 (d, 1H, J = 1.6 Hz), 6.38 (d, 1H, J = 1.6 Hz), 6.60 (s, 1H), 7.44 (t, 1H, J = 8.0 Hz), 7.59 (m, 1H), 7.93 (d, 1H, J = 8.0 Hz), 8.13 (t, 1H, J = 2.0 Hz), 9.29 (s, 1H, OH), 9.93 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 333.

4.6.25. 5,7-Hydroxy-3′,4′-methylenedioxy-aurone (9b)

Reagent: compound **6b** (100 mg, 0.26 mmol). White amorphous powder (44.8 mg, 58%), mp: 275–277 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 6.10 (s, 2H), 6.14 (d, 1H, J = 1.6 Hz), 6.38 (d, 1H, J = 1.6 Hz), 6.59 (s, 1H), 6.96 (d, 1H, J = 8.0 Hz), 7.41 (1H, dd, J = 1.6, 8.0 Hz), 7.55 (d, 1H, J = 1.6 Hz), 9.08 (s, 1H, OH), 9.83 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 299.

4.7. General procedure for synthesis of compounds 10a, 10c, 10o

A stirred solution of corresponding flavanones **8a, 8c** or **8o** and iodine in dry pyridine (1 mL) was heated to 90 °C for 6 h. The mixture was cooled and poured into cold water. The precipitate was separated and the mixture was extracted with ethyl acetate. The combined organic phase was washed with saturated sodium thiosulfate and water, successively. Then the organic layer was dried with sodium sulfate and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (5:1 ~ 1:1, v/v) as eluent afforded **10a, 10c** or **10o**.

4.7.1. 5,7-Dihydroxy-3′-bromo-flavone (10a)

Reagent: compound **8a** (60 mg, 0.18 mmol), iodine (45.5 mg, 0.18 mmol). Yellow amorphous powder (41.7 mg, 70%), mp: 270–272 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 6.29 (d, 1H, J = 2.0 Hz), 6.62 (d, 1H, J = 2.0 Hz), 6.87 (s, 1H), 7.56 (t, 1H, J = 8.0 Hz), 7.79 (dd, 1H, J = 2.0, 8.0 Hz), 8.07 (d, 1H, J = 8.0 Hz), 8.25 (t, 1H, J = 2.0 Hz), 9.76 (s, 1H, OH), 12.82 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 333.

4.7.2. 7-Hydroxy-3′,4′-methylenedioxy-flavone (10c)

Reagent: compound **8c** (100 mg, 0.21 mmol), iodine (43.7 mg, 0.21 mmol). White amorphous powder (40.5 mg, 68%), mp: 250–253 °C. ^{1}H NMR (acetone-d_6, 400 M, δ): 6.70 (s, 1H), 6.95 (dd, 1H, J = 2.0, 8.0 Hz), 7.01 (d, 1H, J = 8.0 Hz), 7.06 (d, 1H, J = 2.0 Hz), 7.50 (dd, 1H, J = 1.6, 8.0 Hz), 7.69 (d, 1H, J = 1.6 Hz), 7.94 (d, 1H, J = 8.0 Hz), 9.70 (s, 1H, OH). ESI-MS: m/z $[M+H]^+$ 283.

4.7.3. 6,4′-Hydroxy-8-allyl-flavone (10o)

Reagent: compound **8o** (60 mg, 0.20 mmol), iodine (51.5 mg, 0.20 mmol). White amorphous powder (35.8 mg, 60%), mp: 275–276 °C. ^{1}H NMR (MeOH-d_4, 400 M, δ): 3.73 (d, 2H, J = 6.0 Hz), 5.14 (m, 1H), 5.17 (m, 1H), 6.09 (m, 1H), 6.71 (s, 1H), 6.94 (d, 2H, J = 8.0 Hz), 7.12 (d, 1H, J = 2.8 Hz), 7.30 (d, 1H, J = 2.8 Hz), 7.87 (d, 2H, J = 8.0 Hz). ESI-MS: m/z $[M+H]^+$ 295.

4.8. Vasodilatory effect assay

Vascular rings were prepared from the aorta of male Male Sprague-Dawley rats (four to six months old and weighing on average 250 g), and contraction studies were performed following the general procedure detailed in the literature.[19] After an equilibration period of at least 1 h, isometric contractions induced by PE (1 μM) were obtained. When contraction of the tissue in response to this vasoconstrictor agent had stabilized (after about 20 min), cumulatively increasing concentrations of the tested compounds were added to the bath at 15–20 min intervals (the time needed to obtain steady-state relaxation). Control tissues were simultaneously subjected to the same procedures, but omitting the compounds and adding the vehicle. The flavonoids-induced maximal relaxation (E_{max}) in aortic rings was calculated as a percentage of the contraction in response to PE (1 μM). The half maximum effective concentration (EC_{50}) was defined as the concentration of the flavonoids that induced 50% of maximum relaxation from the contraction elicited by PE (1 μM) and was calculated from the concentration–response curve by nonlinear regression (curve fit) using GraphPad Prism (Version 4.0).

4.9. Molecular modeling and alignment

The 3D structures of all compounds were built and minimized using SYBYL 6.9.[20] The geometries of all molecules involved in this study were optimized by Powell's method using the tripos force field. Conformation analyses were also carried out using the SYBYL/GRID search module. The lowest-energy conformations were considered as the bioactive conformations. Compound **8q** with the most potent activity was selected as the reference molecule. Then, all the common oxygen atoms in all skeletons of flavonoids were selected as the atoms to superimpose all the compounds using SYBYL/Fit-atom module.

4.10. CoMFA analysis

The steric and electrostatic fields in CoMFA were calculated using an sp^3 carbon atom with +1.0 charge as the probe atom. The both field energies were truncated to ±30 kcal/mol. And The CoMFA fields generated automatically were scaled by the CoMFA-STD method. In order to investigate the effect of grid spacing, initially the CoMFA models were developed at varying grid spacing values (i.e., 0.5, 1.0 and 2.0 Å), and the best q^2 values were obtained when the grid spacing was set to 1.0 Å.

4.11. Partial least squares (PLS) analysis

The PLS method[21] was used to set up a correlation between the molecular fields and the pEC_{50} of vasorelaxant activities of tested compounds. The optimal number of components was determined using cross-validation (leave-one-out) method. To speed up the analysis and reduce noise, columns with an σ value below 2.0 kcal/mol were filtered off. The cross-validated q^2 that resulted in optimum number of components and lowest standard error of prediction were taken. Then, final analysis was performed to calculate conventional r^2 and standard error using the optimum number of components.

4.12. CoMFA contour maps

Contour maps were generated as a scalar product of coefficients and standard deviation (StDev * Coeff) associated with each column. Favored and disfavored levels, fixed at 80% and 20%, respectively, were used to display the steric and the electrostatic fields. The contours for steric fields are shown in green (more bulk favored) and yellow (less bulk favored), while the electrostatic field contours are displayed in red (electronegative substituents favored) and blue (electropositive substituents favored) colors.

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References and notes

1. Ren, W.; Qiao, Z.; Wang, H.; Zhu, L.; Zhang, L. *Med. Res. Rev.* **2003**, *23*, 519–534.
2. Carlo, G. D.; Mascolo, N.; Izzo, A. A.; Capasso, F. *Life Sci.* **1999**, *65*, 337–353.
3. Tripoli, E.; Guardia, M. L.; Giammanco, S.; Majo, D. D.; Giammanco, M. *Food Chem.* **2007**, *104*, 466–479.
4. Yochum, L.; 1 Kushi, L. H.; Meyer, K.; Folsom, A. R. *Am. J. Epidemiol.* **1999**, *149*, 943–949.
5. Jenkins, D. J. A.; Kendall, C. W. C.; D'Costa, M. A.; Jackson, C. J. A.; Vidgen, E.; Singer, W.; Silverman, J. A.; Koumbridis, G.; Honey, J.; Rao, A. V.; Fleshner, N.; Klotz, L. *J. Urol.* **2003**, *169*, 507–511.
6. Harborne, J. B.; Williams, C. A. *Phytochemistry* **2000**, *55*, 481–504.
7. Knekt, P.; Kumpulainen, J.; Jarvinen, R.; Rissanen, H.; Heliovaara, M.; Reunanen, A.; Hakulinen, T.; Aromaa, A. *Am. J. Clin. Nutr.* **2002**, *76*, 560–568.
8. Fusi, F.; Saponara, S.; Pessina, F.; Gorelli, B.; Sgaragli, G. *Eur. J. Nutr.* **2003**, *42*, 10–17.
9. Xu, Y. C.; Leung, S. W. S.; Yeung, D. K. Y.; Hu, L. H.; Chen, G. H.; Che, C. M.; Man, R. Y. K. *Phytochemistry* **2007**, 1179–1188.
10. Duarte, J.; Perez-vizcaino, F.; Jimenez, J.; Tamargo, J.; Zarzuelo, A. *Stud. Nat. Prod. Chem.* **2001**, *25*, 565–605.
11. Mishra, S. K.; Abbot, S. E.; Choudhury, A.; Cheng, M.; Khatab, N.; Maycock, N. J. R.; Zavery, A.; Aaronson, P. I. *Cardiovasc. Res.* **2000**, *46*, 539–546.
12. Zhang, Y. H.; Park, Y. S.; Kim, T. J.; Fang, L. H.; Ahn, H. Y.; Hong, J. T.; Kim, Y.; Lee, C. K.; Yun, Y. P. *Gen. Pharmacol.* **2002**, *35*, 341–347.
13. Ajar, M.; Gilani, A. H.; Mustafa, M. R. *Life Sci.* **2003**, *74*, 603–612.
14. Chen, Z.; Hu, Y.; Wu, H.; Jiang, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3949–3952.
15. Yang, G. F.; Huang, X. Q. *Curr. Pharm. Des.* **2006**, *12*, 4601–4611.
16. Cramer, R. D.; Patterson, D. E.; Bunce, J. D. *J. Am. Chem. Soc.* **1988**, *110*, 5959–5967.
17. Fatemi, M. H.; Gharaghani, S. *Bioorg. Med. Chem.* **2007**, *15*, 7746–7754.
18. Dong, X.; Fan, Y.; Yu, L.; Hu, Y. *Arch. Pharm. Chem. Life Sci.* **2007**, *340*, 372–376.
19. Qian, L.; Wang, H.; Qiu, W.; Huang, H.; Bruce, I. C.; Xia, Q. *Vascul. Pharmacol.* **2006**, *45*, 374–382.
20. SYBYL Molecular Modeling System, Versions 5 and 6, TRIPOS Assoc., St. Louis, MO, U.S.A.
21. Wold, S.; Albano, C.; Dunn, W.; Edlund, U.; Esbensen, K.; Geladi, P.; Hellberg, S.; Johansson, E.; Lindberg, W.; Sjosstrom, M.. In *Chemometrics*; Kolwalski, B., Ed.; Reidel: Dordrecht, 1987; Vol. 1, p 17.