Bioorganic & Medicinal Chemistry 21 (2013) 2543–2550

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Design and synthesis of novel chromenone derivatives as interleukin-5 inhibitors

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ARTICLE INFO

Article history:
Received 28 December 2012
Revised 21 February 2013
Accepted 24 February 2013
Available online 5 March 2013

Keywords:
Chromenone analogs
Inhibitor
Interleukin-5
Eosinophils
Asthma

ABSTRACT

A novel series of chromenone analogs were synthesized and evaluated for their inhibitory activity against interleukin-5. Among them 5-(cyclohexylmethoxy)-3-[3-hydroxy-3-(4-hydroxyphenyl)propyl]-4*H*-chromen-4-one (**9b**, 94% inhibition at 30 μM, IC_{50} = 4.0 μM) and 5-(cyclohexylmethoxy)-3-[3-hydroxy-3-(4-methoxyphenyl)propyl]-4*H*-chromen-4-one (**9c**, 94% inhibition at 30 μM, IC_{50} = 6.5 μM) showed the most potent activity. According to the SAR studies introduction of propanone unit in between chromenone and ring B as in 5-(cyclohexylmethoxy)-3-[3-(4-phenyl)-3-oxopropyl]-4*H*-chromen-4-ones (**8**) moderately increased the activity. However, the reduction of these propanones **8** to propanols **9** remarkably enhanced the activity. A small substituent at position 4 of ring B in **9**, especially with hydrogen bonding capability, provides favorable contribution. Disappearance of IL-5 inhibitory activity upon saturation of chroman-4-one of **9** to chroman-4-ones **10** proves the critical importance of planar chromen-4-one unit of this scaffold in the IL-5 inhibition.

1. Introduction

Asthma is the common chronic inflammatory disease of the airways described by variable and periodic symptoms, reversible airflow impediment, and bronchospasm.[1] It is linked with intrusion of T cells and eosinophils, increased levels of pro-inflammatory cytokines such as interleukin-4 (IL-4), IL-5 and IL-13, and shedding of bronchial epithelial cells (ECs).[2] Eosinophils are the major effector cells in allergic inflammation which are produced by the cytokine IL-5. Level of both eosinophil and IL-5 is increased in the circulation and sputum depending upon the severity of the disease.[3–7] As IL-5 is directly involved in the eosinophil production it became an important target in the treatment of asthma.

A numerous synthetic and natural derivatives have been studies for their IL-5 inhibitory activity.[8,9] Among them sophoricoside, a natural product, showed the potent inhibitory activity.[10] Though sophoricoside showed good IL-5 inhibitory activity still the need of potential IL-5 inhibitors persists to treat the disease like asthma. Therefore, in an attempt to find better IL-5 inhibitors, we have investigated a number of isoflavone and chalcone derivatives.[11–14] The SAR studies of these derivatives revealed several important points. We initially observed that the planar chromen-4-one ring as well as phenolic hydroxyl group at 4-position of ring B are crucial for IL-5 inhibitory activity.[11,12] Later the importance of hydrophobic group such as cyclohexylmethoxy group at 5-position of isoflavone (**1b** and **1d**, Fig. 1) was also proven for good IL-5 inhibitory activity. In further exploration of SAR the effect of methylene unit by inserting it between phenyl and chromenone (**2**, Fig. 1) was studied for proving the necessity of isoflavone scaffold.[15] Surprisingly, the results indicate that ring B is not essential for the potent IL-5 activity.[15] To further elaborate this point novel 5-(cyclohexylmethoxy)-3-(1-alkyl-2-hydroxyethylaminomethyl) chromones were investigated (**4**, Fig. 1) and the results established the role of ring B in isoflavone as a simple linker between chromenone and hydroxyl function. Recently, keeping the activity of amino alcohol derivative of chromenone in mind we designed and synthesized a number of *N*-substituted hydroxyethylaminomethylchromenone derivatives (**5**) and tested them for their IL-5 inhibitory activity (Fig. 1).[16] Interestingly, *N*-substituted derivatives (**5**) showed far better activity than the compounds **4** substituted with hydrophobic groups at position 1 of hydroxyethylaminomethylchromenone.[17] In another study we envisioned if the hybrid molecule of isoflavone and chalcone can come up with some good activity against IL-5.[18] Therefore, to exploit their combined structural characteristics novel hybrid chromenone derivatives (**6** and **7**) were studied. These hybrid chromenones did not show good activity but on reducing the α,β-unsaturated ketones of hybrid chromenone (**6**) to the racemic allylic alcohols (**7**), potent IL-5 inhibitory activity was observed. In addition, the activity of these

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http://dx.doi.org/10.1016/j.bmc.2013.02.037

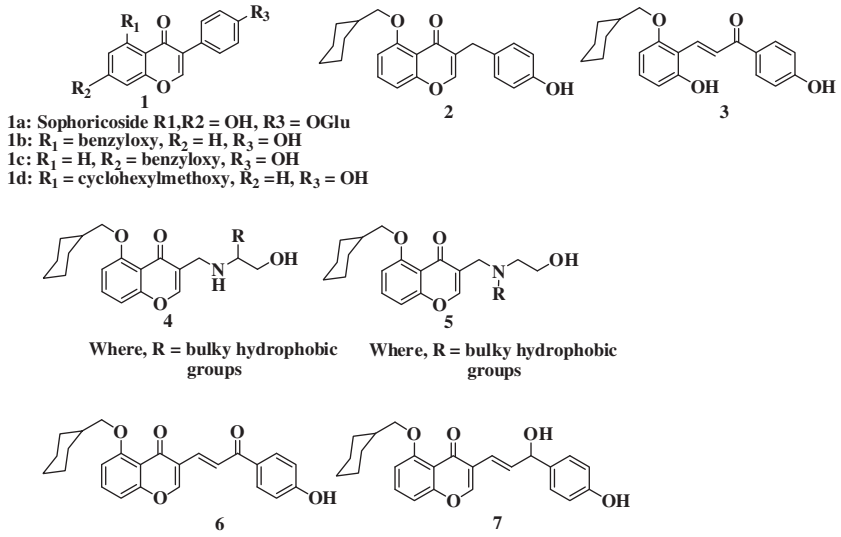


Figure 1. Interleukin-5 inhibitors.

allylic alcohols (**7**) was further increased on introduction of electron withdrawing groups at position 4 of ring B.[18] We additionally studied the conformational analysis and alignment of these derivatives and observed that the carbonyl function of α,β-unsaturated ketones moiety is stretched away from the chromenone ring. However, the corresponding angles of derivatives depicted that hydroxyl group of racemic allylic alcohol moiety is located nearly at right angle position in the chromenone ring plane.[18] These structural characteristics strengthen our view point that there is a need to explore more SAR studies of these hybrid chromenones to understand the correlation between their structure and activity. Therefore, in the current article, we have further modified our previous designs and synthesized newer analogs of chromenones **8**, **9** and **10** (Fig. 2) and studied them for their IL-5 inhibitory activity.

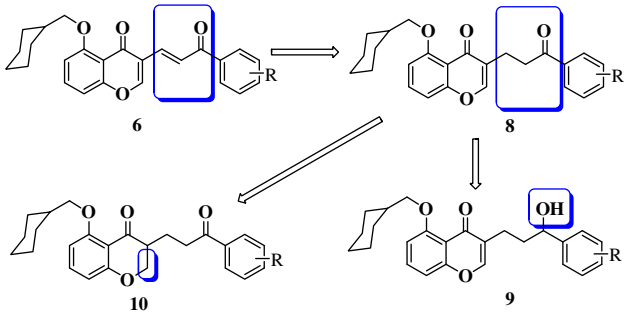
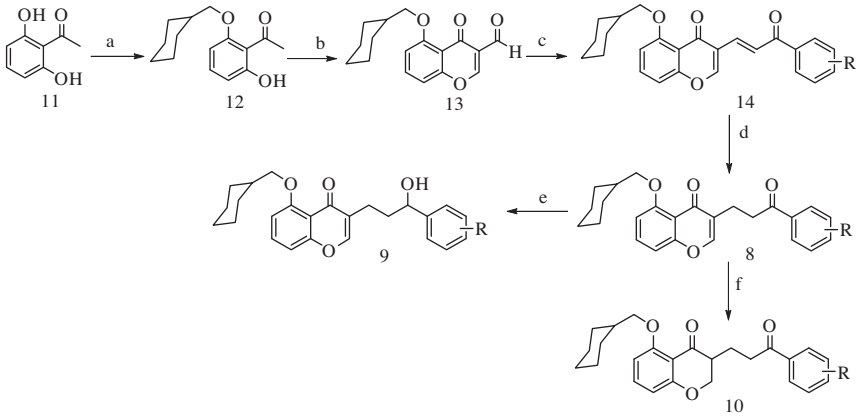


Figure 2. Structural modifications for target IL-5 inhibitors **8**, **9** and **10**.

2. Chemistry

The synthesis of the desired compounds **8a–k** and **9a–k** and **10a–b** were accomplished as outlined in Scheme 1 and the results are listed in Table 1. In brief, the acetophenone **12** was prepared by the partial alkylation of 2,6-dihydroxyacetophenone (**11**).[11] Preparation of **13** was accomplished by the cyclization of **12** using *N*,*N*-dimethylformamide and phosphoryl chloride at ambient temperature.[15] The Wittig reagent was obtained by the reaction of commercially available substituted bromoacetophenone and triphenylphosphine in methylene chloride at ambient temperature.[19,20] The chromenone **14** was prepared by the reaction of compound 3-formyl-5-(cyclohexylmethoxy)-4*H*-chromen-4-one (**13**) with Wittig reagent in methylene chloride at ambient temperature for overnight.[19] To get the compounds **8a–k** initial attempt for the reduction of double bond of propenone linkage in **14** with



Scheme 1. Synthesis of choromone analogs **8a–k**, **9a–k** and **10a–b**. Reagents and conditions: (a) R-Br, CH_3CN, aqueous 95% K_2CO_3, NaI (cat), reflux, overnight, (b) $POCl_3$, DMF, overnight, rt, (c) **13** and Wittig reagent, dichloromethane, overnight, rt, (d) Pd/C, cyclohexene, THF/methanol (1:1), reflux, 5 h, (e) cerium chloride, $NaBH_4$/methanol, 0–5 °C, (f) Pd/C, cyclohexene, THF/methanol (1:1), reflux, 18 h. Note = substituents are located in Table 1.

Table 1
Chromenone analogs **8a–k**, **9a–k** and **10a–b** with their physicochemical properties

Compd	R[a]	Appearance	mp (°C)	Yield (%)
8a	H	White solid	99–101	43.2
8b	OH	White solid	158–160	66.7
8c	OCH_3	White solid	97–99	68.7
8d	CH_3	White solid	106–108	64.6
8e	*t*-Butyl	White solid	150–152	77.8
8f	Cl	White solid	129–131	65.0
8g	F	White solid	98–100	60.4
8h	CF_3	White solid	95–97	56.1
8i	3,4-Cl	White solid	103–105	38.2
8j	CN	White solid	116–118	65.0
8k	Naphthyl[b]	White solid	128–130	52.1
9a	H	White solid	96–98	65.6
9b	OH	White solid	147–149	62.0
9c	OCH_3	White solid	92–94	85.0
9d	CH_3	White solid	102–104	82.0
9e	*t*-Butyl	White solid	187–189	82.0
9f	Cl	White solid	96–98	62.0
9g	F	White solid	109–111	76.0
9h	CF_3	White solid	118–120	88.0
9i	3,4-Cl	White solid	118–120	43.0
9j	CN	White solid	106–108	76.0
9k	Naphthyl[b]	White solid	121–123	62.0
10a	OCH_3	Colorless liquid	—	23.8
10b	3,4-Cl	Colorless liquid	—	33.0

[a] Location of R is position 4 unless noted.
[b] Naphthyl as ring B.

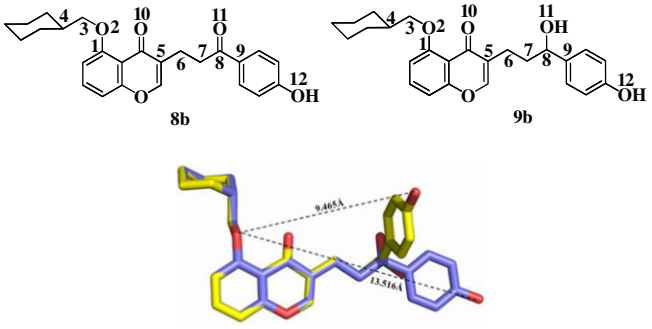


Figure 3. Alignment of compound **8b** (9.651 kcal/mol) and **9b** (10.058 kcal/mol). Slat color (**8b**), Yellow color (**9b**).

the Pd/c with H_2 gas under atmospheric pressure at ambient temperature resulted in a mixture of compounds **8** and **10** with closed R_f values and we could not separate them using column chromatography. Therefore, the reaction condition was changed to Pd/c with cyclohexene in THF/methanol (1:1) under reflux condition. This condition converted **14–8** within 5 h however, on extending the reaction time over 5 h resulted in the formation of mixture therefore the reaction period was fixed up to 5 h to obtain the compounds **8a–k** only. The compounds **9a–k** were prepared by the reduction of **8a–k** in the presence of cerium chloride and sodium borohydride in methanol at 0–5 °C. Finally, the chromanones **10a** and **10b** were obtained by reducing the double bond of chromenone ring of **8c** and **8i**, respectively, using Pd/c with cyclohexene in THF/methanol (1:1) under reflux condition. Prolongation of the reaction time to 18 h completely converted **8** to the chromanones **10**. All these synthesized compounds were characterized by physical and spectral analysis data that confirmed their assigned structures.

3. Conformational analysis and alignment

Molecular model of the compounds **8b** and **9b** were constructed using SYBYL®-X2.0 program package (Tripos Associates Inc.)[21] and their geometry were optimized (Powell conjugate gradient minimization, termination at a gradient of 0.0005 kcal/mol) using the Tripos standard force field[22] and Gasteiger–Hückel atomic partial charges.[23] The 3D structures of the analyzed compounds were assumed to be a bioactive conformation and were aligned according to a chromenone template as shown in Figure 3. The selected dihedral angles and atomic distances are listed in Tables 3 and 4.

4. Pharmacology

Inhibitory activity of the chromenone analogs (**8a–k**, **9a–k** and **10a–b)** against IL-5 was evaluated using the IL-5-dependent pro-B Y16 cell line according to the previously reported procedure.[24] The cells were incubated with 3 U/mL mIL-5 for 48 h, in the presence or absence of sample, and then measured cell metabolism as an index of proliferation, using 2-(4-iodophenyl)-3-(nitrophenyl)-5-(2,4-disulphophenyl)-2*H* tetrazolium sodium salt (WST-1). Data were collected from three independent experiments. The effect of test compounds on the IL-5 bioassay is represented as per cent inhibition at 30 μM samples and IC_{50} values were calculated (Table 2).

5. Results and discussion

We have previously described that compound **6** possesses effective structural motifs of isoflavone **2**[15] and chalcone **3**[14] that is both

Table 2
Inhibitory activity of chromone analogs **8a–k**, **9a–k** and **10a–b** against Interleukin-5

Compd	% Inhibition at 30 μM[a]	IC_{50}[a](μM)	Compd	% Inhibition at 30 μM[a]	IC_{50}[a] (μM)
8a	12.3	>30	**9c**	94.0	6.5
8b	80.0	15.0	**9d**	13.5	>30
8c	91.0	16.0	**9e**	6.6	>30
8d	70.0	>30	**9f**	94.0	9.0
8e	6.7	>30	**9g**	94.0	9.0
8f	94.0	14.0	**9h**	55.0	>30
8g	93.0	20.0	**9i**	94.0	7.9
8h	5.3	>30	**9j**	94.0	15.0
8i	68.0	22.0	**9k**	86.0	17.0
8j	93.0	17.0	**10a**	34.0	>30
8k	10.0	>30	**10b**	40.0	>30
9a	94.0	12.0			
9b	94.0	4.0			
1d[12]	91.7[b]	5.8	2[15]	98.0	3.0
Budesonide	55.3	27.1	Sophoricoside	79.1	10.6

[a] % Inhibitions and IC_{50} values are taken as mean from 3 experiments.
[b] Inhibition at 50 μM.

Table 3
Torsion angle (°) and Total energy of compound **8b** and **9b**

Compound **8b**[a] (9.651 kcal/mol)[b]		Compound **9b**[a] (10.058 kcal/mol)[b]	
$<C_1–O_2–C_3–C_4$	182.5	$<C_1–O_2–C_3–C_4$	182.5
$<C_5–C_6–C_7–C_8$	180.0	$<C_5–C_6–C_7–C_8$	176.6
$<C_6–C_7–C_8–O_{11}$	359.8	$<C_6–C_7–C_8–O_{11}$	183.5
$<C_6–C_7–C_8–C_9$	179.8	$<C_6–C_7–C_8–C_9$	58.1

[a] Numbers on the atoms of **8b** and **9b** are presented in Figure 3.
[b] Total energy.

Table 4
Distance (Å) in compounds **8b** and **9b**

Compound **8b**[a]		Compound **9b**[a]	
$O_2–O_{10}$	2.706	$O_2–O_{10}$	2.706
$O_2–O_{11}$	7.612	$O_2–O_{11}$	9.187
$O_2–O_{12}$	13.516	$O_2–O_{12}$	9.465
$O_{10}–O_{11}$	4.907	$O_{10}–O_{11}$	6.552
$O_{10}–O_{12}$	10.894	$O_{10}–O_{12}$	7.338
$O_{11}–O_{12}$	6.393	$O_{11}–O_{12}$	6.439

[a] Numbers on the atoms of **8b** and **9b** are presented in Figure 3.

chromenone and phenylpropenone moieties (Fig. 1) for effective IL-5 inhibition.[18] However, chromenones **6** show weak IL-5 inhibitory activity. We hypothesized that it could be the planarity of sterically strained *trans* α,β-unsaturated ketone of chromenones **6** which restricts the conformation and thus the compound failed to show IL-5 activity. Therefore, we further designed various analogs (**8**–**10**, Fig. 2) of **6** by reducing the unsaturated ketone to saturated ketone and studied the effect of various substituents such as hydrogen bonding group, hydrophobic electron donating groups (CH_3, *t*-butyl), electron donating group (OCH_3) and electron withdrawing group (F, Cl, CF_3, CN) at position 4 of ring B for their IL-5 inhibitory activity.

Accordingly, the compounds **8a–k** were prepared and studied for their IL-5 inhibitory activity and the compounds **8b–c**, **8f–g** and **8i–j** showed good IL-5 inhibitory activity while the compounds **8a**, **8d–e**, **8h** and **8k** did not turn up with any activity. These results indicate that the compounds containing relatively small functional groups regardless their electronic properties at position 4 of ring B showed IL-5 inhibitory activity. However, the compounds having bulky hydrophobic groups at the same position did not show any activity. On comparing the activity of these saturated ketones **8** with their counterpart α,β-unsaturated ketone (**14**),[18] the former showed far better activity most probably due to their flexibility of saturated ketone moiety of **8** to form an effective conformation fitting to the active site of the target IL-5. However, these chromenones exerted still lower activity compared to isoflavone **2**[15] though it was better than isoflavone **1d**.[12]

Considering the point that reduction of α,β-unsaturated ketone of **6** to allylic alcohol of **7** dramatically increased the activity,[18] in another set of experiment the carbonyl function of ketone moiety of **8** was reduced to the alcohol. Accordingly, compounds **9a–k** were prepared and tested for their IL-5 inhibitory activity as shown in Table 2. Although the activity was lost in the compounds with bulky groups such as methyl, *tert*-butyl and trifluoromethyl at position 4 of ring B (compounds **9d**, **9e** and **9h**), other alcoholic compounds **9a–c**, **9f**, **9g** and **9i–k** were better inhibitors than the corresponding ketones **8**. Exceptionally, **9b** (94% inhibition at 30 μM, IC_{50} = 4.0 μM) and **9c** (94% inhibition at 30 μM, IC_{50} = 6.5 μM) with hydrogen bonding capable electron donating group at 4-position of ring B showed highly potent inhibition. In addition the compounds containing electron withdrawing group at position 4 of ring B such as **9f–g** and **9i** also showed quite good inhibition against IL-5. Analog **9j** with cyano at this position and **9k** with planar naphthyl as ring B showed fairly good inhibition. However, analogs **9d–e** and **9h** with bulky functional groups still did not show any activity. Therefore, the above results support the importance of hydrogen bond characteristics of hydroxyl group and small size of substituent at position 4 of ring B for the activity.

In another set of experiment, the effect of saturation in chromenone ring of **8** was investigated. Accordingly, chroman-4-ones **10a** and **10b** were synthesized and tested for their IL-5 inhibitory activity but their activity was very low (Table 2). Upon saturation of conjugate system in chromen-4-one ring, the conformational change is obviously enormous and their conjugation of pyrenone system is demolished. Thus the increased bulkiness of chroman-4-one compared to chromen-4-one would block its fitting into the binding site of the putative receptor or the loss of the resonance within the pyrenone unit of chromen-4-one of **8** in chroman-4-ones **10** would diminish the power of binding capability of chromen-4-one moiety remarkably. Therefore, these results again prove the critical importance of chromen-4-one structural unit of this scaffold in their IL-5 inhibition.

Since analogs **9** were more active than the corresponding **8** in spite of their structural similarity, the detailed structural requirements of compounds **8b** and **9b** were also studied for their potent IL-5 inhibitory activity. We compared the three dimensional structural sketches of compounds **8b** and **9b** and observed that there was much difference not only in their torsional angles (Table 3) but also in the distance (Å) from oxygen of cyclohexylmethoxy group to oxygen at *para*-position of phenyl ring (Table 4). Specially, comparison in the region of side chain at position 8 of chromenone scaffolds of saturated ketone (**8b**) and alcohol (**9b**) is illustrated in Figure 3. As mentioned in Table 3 the dihedral angle ($<C_6–C_7–C_8–C_9$) of compound **8b** is 179.8° which indicates that the propanone side chain of **8b** is stretched away from the chromenone ring. In addition, the distance (13.516 Å, Table 4, Fig. 3) from oxygen of cyclohexylmethoxy to oxygen at *para*-position of phenyl ring of **8b** also confirms this stretched conformation. Meanwhile the corresponding angles ($<C_6–C_7–C_8–C_9$ = 58.1°, Table 3) of **9b** depicts that its propanol side chain is more folded and the alcoholic hydroxyl group is located nearly at right angle position in the chromenone ring plane. The much shorter distance (9.465 Å, Fig. 3) from oxygen of cyclohexylmethoxy to oxygen at *para*-position of phenyl ring in **9b** compared to **8b** also implies the folded conformation. Such conformational changes might cause the enhancement of the activity in analogs **9** compared to those of the corresponding compounds **8**. Therefore, the folded conformation as shown in **9b** could be much closer to the effective conformation for binding to the putative receptor.

6. Conclusion

A series of 5-(cyclohexylmethoxy)-3-[3-(4-phenyl)-3-oxopropyl]-4*H*-chromen-4-ones (**8**) and 5-(cyclohexylmethoxy)-3-[3-hydroxy-3-(4-phenyl)propyl]-4*H*-chromen-4-ones (**9**) and 5-(cyclohexylmethoxy)-3-[3-(phenyl)-3-oxopropyl]chroman-4-ones (**10**) were synthesized and evaluated for their IL-5 inhibitory activity. Among the synthesized compounds, the inhibitory activity of saturated ketones **8** was relatively weak and therefore this structural modification is not sufficient for the design of IL-5 inhibitor. However, the alcohols **9** showed potent inhibition, especially the compounds **9b** and **9c** containing hydroxyl in propyl linkage and a small electron donating group with hydrogen bonding capability at position 4 of ring B. In addition, the IL-5 inhibitory activity of compounds **9f–g** and **9i** also prove the importance of small substituents at position 4 of ring B. Disappearance of IL-5 inhibitory activity upon saturation of chroman-4-one of **9** to chroman-4-ones **10** again demonstrates the importance of planar chromen-4-one unit.

7. Materials and methods

7.1. Chemistry

Melting points were determined on Electro thermal 1A 9100 MK2 apparatus and are uncorrected. All commercial chemicals were used as obtained and all solvents were purified by the standard procedures prior to use.[25] Thin layer chromatography was performed on E Merck silica gel GF-254 precoated plates and the identification was done with UV light and colorization with spray 10% phosphomolybdic acid followed by heating. Flash column chromatography was performed with E Merck silica gel (230–400 mesh). Infra-red spectrum was recorded by using sample as such on FT-IR spectrum with Nicolet — 380 models. NMR spectra were measured against the peak of tetramethylsilane by JEOL JNM-EX90 NMR (89.45 MHz) and Varain Unity Inova 400 NMR (400 MHz) spectrometers. High resolution mass spectra (HRMS) were measured by using Shimadzu LCMS-IT-TOF spectrometer.

7.1.1. General procedure for preparation of compounds (8)

The mixture of compound (**14**) (1 equiv) and cyclohexene (2 equiv) was added to THF/methanol (1:1) and 20% Pd/c and the reaction mixture was refluxed for 5 h. After the reaction mixture was filtered using celite and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography to afford the compound **8**.

7.1.1.1. 5-(Cyclohexylmethoxy)-3-(3-oxo-3-phenylpropyl)-4*H*-chromen-4-one (8a). Yield 43.2%; white solid; mp 99.0 °C; IR 2923, 1697, 1676, 832, 811 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.66 (s, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.38–7.24 (m, 5H), 6.95 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 8.0, 1H), 3.87 (d, J = 8.0 Hz, 2H), 3.33 (t, J = 4.0 Hz, 2H), 2.85 (t, J = 4.0 Hz, 2H), 2.05–2.02 (m, 3H), 1.80–1.71 (m, 2H), 1.40–1.21 (m, 3H), 1.27–1.21 (m, 1H), 1.14–1.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 185.5, 177.7, 159.7, 158.7, 151.5, 143.79, 133.4, 129.2, 128.2 124.3, 114.9, 109.7, 106.9, 37.2, 36.9, 29.8, 26.4, 25.7, 21.5, 20.7; HRMS: calcd for $C_{25}H_{26}O_4$ m/z 390.1831, found: 390.1825.

7.1.1.2. 5-(Cyclohexylmethoxy)-3-[3-(4-hydroxyphenyl)-3-oxopropyl]-4*H*-chromen-4-one (8b). Yield 66.7%; white solid; mp 158.0 °C; IR 3428, 2923, 1659, 1453, 1243, 1066 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.93 (s, 1H), 7.72 (d, J = 4.0 Hz, 2H), 7.51 (t, J = 8.0 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.0, 2H), 3.89 (d, J = 4.0 Hz, 2H), 3.22 (t, J = 4.0 Hz, 2H), 2.84 (t, J = 4.0 Hz, 2H), 2.39 (s, 3H), 2.05–2.02 (m, 3H), 1.80–1.71 (m, 2H), 1.36 (s, 9H) 1.40–1.21 (m, 3H), 1.27–1.21 (m, 1H), 1.14–1.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 199.4, 177.7, 162.7, 158.7, 151.4, 143.7, 134.4, 133.3, 129.2, 128.2, 124.3, 114.9, 109.7, 106.9, 99.1, 91.7, 89.6, 50.1, 37.3, 29.8, 21.5, 20.7; HRMS: calcd for $C_{25}H_{26}O_5$ m/z 406.1780, found: 406.1773.

7.1.1.3. 5-(Cyclohexylmethoxy)-3-[3-(4-methoxyphenyl)-3-oxopropyl]-4*H*-chromen-4-one (8c). Yield 68.7%; white solid; mp 97.0 °C; IR 2931, 1632, 1453, 1243, 833 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.86 (d, J = 8.0 Hz), 7.84 (s, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 8.0, 1H), 3.87 (d, J = 4.0 Hz, 2H), 3.24 (t, J = 4.0 Hz, 2H), 2.83 (t, J = 4.0 Hz, 2H), 2.39 (s, 3H), 2.05-2.02 (m, 3H), 1.80–1.71 (m, 2H), 1.40–1.21 (m, 3H), 1.27–1.21 (m, 1H), 1.14–1.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 178.3, 160.1, 159.2, 159.0, 150.9, 137.1, 133.8, 127.5, 125.5, 115.1, 114.1, 109.7, 107.3, 75.2, 72.7, 55.5, 38.8, 37.6, 30.1, 26.7, 26.0, 22.2; HRMS: calcd for $C_{26}H_{28}O_5$ m/z 420.1937, found: 420.1932.

7.1.1.4. 5-(Cyclohexylmethoxy)-3-(3-oxo-3-*p*-tolylpropyl)-4*H*-chromen-4-one (8d). Yield 64.6%; white solid; mp 106.0 °C; IR 2922, 1650, 1494, 1092, 815, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.86 (d, J = 8 Hz, 2H), 7.84 (s, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.23 (d, J = 8 Hz, 2H), 6.93 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 8.0, 1H), 3.87 (d, J = 4.0 Hz, 2H), 3.33 (t, J = 4.0 Hz, 2H), 2.85 (t, J = 4.0 Hz, 2H), 2.39 (s, 3H), 2.05–2.02 (m, 3H), 1.80–1.71 (m, 2H), 1.40–1.21 (m, 3H), 1.27–1.21 (m, 1H), 1.14–1.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 178.5, 177.7, 159.7, 158.7, 151.5, 140.8, 133.4, 129.2, 128.2 124.3, 114.9, 109.7, 106.9, 37.2, 36.9, 29.8, 26.4, 24.8, 22.5, 21.5, 20.7; HRMS: calcd for $C_{26}H_{28}O_4$ m/z 404.1988, found: 404.1983.

7.1.1.5. 3-[3-(4-*tert*-Butylphenyl)-3-oxopropyl]-5-(cyclohexylmethoxy)-4*H*-chromen-4-one (8e). Yield 77.8%; white solid; mp 150.0 °C; IR 2924, 1635, 1454, 1266, 1066, 833 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65 (s, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.0 Hz, 1H), 6.74 (d, J = 8.0, 1H), 3.93 (d, J = 4.0 Hz, 2H), 3.24 (t, J = 4.0 Hz, 2H), 2.83 (t, J = 4.0 Hz, 2H), 2.39 (s, 3H), 2.05–2.02 (m, 3H), 1.80–1.71 (m, 2H), 1.36 (s, 9H) 1.40–1.21 (m, 3H), 1.27–1.21 (m, 1H), 1.14–1.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 199.3, 160.1, 159.2, 159.0, 150.9, 137.1, 133.8, 128.6, 125.1, 109.7, 107.3, 75.2, 72.7, 55.5, 40.3, 38.8, 37.6, 31.4, 26.7, 26.0, 22.2; HRMS: calcd for $C_{29}H_{34}O_4$ m/z 446.2457, found: 446.2451.

7.1.1.6. 3-[3-(4-Chlorophenyl)-3-oxopropyl]-5-(cyclohexylmethoxy)-4*H*-chromen-4-one (8f). Yield 65.0%; white solid; mp 129.0 °C; IR 2933, 1632, 1266, 833, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.06 (d, J = 8.0 Hz, 2H), 7.84 (s, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.49 (t, J = 8.0 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.74 (d, J = 8.0, 1H), 3.87 (d, J = 4.0 Hz, 2H), 3.38 (t, J = 4.0 Hz, 2H), 2.85 (t, J = 4.0 Hz, 2H), 2.39 (s, 3H), 2.05–2.02 (m, 3H), 1.80–1.71 (m, 2H), 1.36 (s, 9H) 1.40–1.21 (m, 3H), 1.27–1.21 (m, 1H), 1.14–1.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 198.4, 179.1, 158.2, 159.0, 150.8, 138.1, 137.7, 134.8, 133.0, 128.6, 125.1, 118.8, 110.7, 109.3, 78.2, 38.8, 37.6, 31.4, 26.7, 26.0, 22.2; HRMS: calcd for $C_{26}H_{25}ClO_4$ m/z 424.1441, found: 424.1435.

7.1.1.7. 5-(Cyclohexylmethoxy)-3-[3-(4-fluorophenyl)-3-oxopropyl]-4*H*-chromen-4-one (8g). Yield 60.4%; white solid; mp 98.0 °C; IR 2923, 1697, 1676, 832, 811 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.01 (t, J = 8.0 Hz, 2H), 7.84 (s, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.10 (t, J = 8 Hz, 2H), 6.94 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 8.0, 1H), 3.87 (d, J = 8.0 Hz, 2H), 3.33 (t, J = 4.0 Hz, 2H), 2.85 (t, J = 4.0 Hz, 2H), 2.05-2.02 (m, 3H), 1.80–1.71 (m, 2H), 1.40–1.21 (m, 3H), 1.27–1.21 (m, 1H), 1.14–1.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 198.48, 177.7, 169.0, 159.7, 158.7, 151.5, 143.8, 133.4, 129.2, 128.2 124.3, 115.9, 109.7, 106.9, 37.2, 36.9, 29.8, 26.4, 25.7, 21.5, 20.7; HRMS: calcd for $C_{25}H_{25}FO_4$ m/z 408.1737, found: 408.1733.

7.1.1.8. 5-(Cyclohexylmethoxy)-3-{3-[4-(trifluoromethyl)phenyl]-3-oxopropyl}-4*H*-chromen-4-one (8h). Yield 56.1%; white solid; mp 95.0 °C IR 2924, 1660 1453, 1250, 1293, 833 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.07 (s, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.51 (t, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.0 Hz, 1H), 6.74 (d, J = 8.0, 1H), 3.87 (d, J = 4.0 Hz, 2H), 3.38 (t, J = 4.0 Hz, 2H), 2.85 (t, J = 4.0 Hz, 2H), 2.39 (s, 3H), 2.05–2.02 (m, 3H), 1.80–1.71 (m, 2H), 1.36 (s, 9H) 1.40–1.21 (m, 3H), 1.27–1.21 (m, 1H), 1.14–1.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 198.5, 177.7, 169.0 159.7, 158.7, 151.5, 143.8, 133.4, 129.2, 128.2 124.3, 115.9, 109.7, 106.9, 37.2, 36.9, 29.8, 26.4, 25.7, 21.5, 20.7; HRMS: calcd for $C_{26}H_{25}F_3O_4$ m/z 458.1705, found: 458.1697.

7.1.1.9. 3-[3-(3,4-Dichlorophenyl)-3-oxopropyl]-5-(cyclohexylmethoxy)-4*H*-chromen-4-one (8i). Yield 38.2%; white solid; mp 103.0 °C; IR 2931, 1653, 1453, 1243, 833,776 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.00 (s, 1H), 8.07 (d, J = 4.0 Hz, 2H), 7.81 (dd, J = 8.0,

4.0 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 6.49 (d, *J* = 8.0, 1H), 3.87 (d, *J* = 4.0 Hz, 2H), 3.38 (t, *J* = 4.0 Hz, 2H), 2.85 (t, *J* = 4.0 Hz, 2H), 2.39 (s, 3H), 2.05–2.02 (m, 3H), 1.80–1.71 (m, 2H), 1.36 (s, 9H) 1.40–1.21 (m, 3H), 1.27–1.21 (m, 1H), 1.14–1.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 199.4, 177.7, 159.7, 158.7, 151.4, 143.7, 134.4, 133.3, 129.2, 128.2, 124.3, 114.9, 109.7, 106.9, 99.1, 91.7, 89.6, 51.0, 37.3, 29.8, 21.5, 20.7; HRMS: calcd for $C_{25}H_{24}Cl_2O_4$ *m*/*z* 458.1052, found: 458.1047.

7.1.1.10. 4-{3-[5-(Cyclohexylmethoxy)-4-oxo-4*H*-chromen-3-yl] propanoyl}benzonitrile (8j). Yield 65.0%; white solid; mp 116.0 °C; IR 2930, 2245, 1649, 1453, 833 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.06 (d, *J* = 8.0 Hz, 2H), 7.84 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.49 (t, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 8.0, 1H), 3.87 (d, *J* = 4.0 Hz, 2H), 3.38 (t, *J* = 4.0 Hz, 2H), 2.85 (t, *J* = 4.0 Hz, 2H), 2.39 (s, 3H), 2.05–2.02 (m, 3H), 1.80–1.71 (m, 2H), 1.36 (s, 9H) 1.40–1.21 (m, 3H), 1.27–1.21 (m, 1H), 1.14–1.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 198.4, 179.1, 158.2, 159.0, 150.8, 139.1, 134.8, 133.0, 128.6, 125.1, 118.8, 117.6, 110.7, 109.3, 78.2, 38.8, 37.6, 31.4, 26.7, 26.0, 22.2; HRMS: calcd for $C_{26}H_{25}NO_4$ *m*/*z* 415.1784, found: 415.1778.

7.1.1.11. 5-(Cyclohexylmethoxy)-3-[3-(naphthalen-3-yl)-3-oxopropyl]-4*H*-chromen-4-one (8k). Yield 52.1%; white solid; mp 128.0 °C; IR 2928, 1650, 1454, 1243, 833 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.56 (s, 1H), 8.04 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H),7.90–7.85 (m, 3H), 7.61–7.52 (m, 2H), 7.47 (t, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 3.88 (d, *J* = 4.0 Hz, 2H), 3.52 (t, *J* = 4.0 Hz, 2H), 2.92 (t, *J* = 4.0 Hz, 2H), 2.39 (s, 3H), 2.05–2.02 (m, 3H), 1.80–1.71 (m, 2H), 1.36 (s, 9H) 1.40–1.21 (m, 3H), 1.27–1.21 (m, 1H), 1.14–1.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 199.4, 177.7, 162.7, 158.7, 151.4, 143.7, 135.6, 134.3, 132.5, 129.5, 128.2, 124.3, 114.9, 111.4, 109.7, 106.9, 99.1, 91.7, 89.6, 51.0, 37.3, 29.8, 21.5, 20.7; HRMS: calculated for $C_{29}H_{28}O_4$ m/z 440.1988, found: 440.1981.

7.1.2. General procedure for preparation of compounds (9)

$CeCl_3{\cdot}7H_20$ (1.1 equiv) was added to a solution of chromen-4-one (**8**) (1.0 equiv) in a 1:1 mixture of methanol and THF and stirred for 10 min at ambient temperature then cooled to 0–5 °C and then $NaBH_4$ (1.0 equiv) was added at once. The reaction was continued stirred until disappearance of the starting material on TLC analysis. After reaction mixture was evaporated, the residue was dissolved in methylene chloride and washed with water followed by brine solution. After dehydration with anhydrous sodium sulfate, the organic layer was evaporated and the residue purified by column chromatography to afford **9**.

7.1.2.1. 5-(Cyclohexylmethoxy)-3-(3-hydroxy-3-phenylpropyl)-4*H*-chromen-4-one (9a). Yield 65.6%; white solid; mp 96.0 °C; IR 3388, 2923, 1650, 1264, 659 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.66 (s, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.38–7.30 (m, 5H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 4.68–4.65 (m, 1H), 3.87 (d, *J* = 4.0 Hz, 2H), 3.36 (br s, 1H), 2.73–2.66 (m, 1H), 2.55–2.49 (m, 1H), 2.05–1.88 (m, 5H), 1.79–1.69 (m, 3H), 1.38–1.23 (m, 3H), 1.15–1.06 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 178.8, 159.5, 158.4, 150.3, 144.3, 133.1, 128.0, 125.5, 124.8, 114.4, 109.2, 106.7, 74.5, 38.5, 36.9, 29.4, 25.4, 21.5; HRMS: calcd for $C_{25}H_{28}O_4$ *m*/*z* 392.1988, found: 392.1982.

7.1.2.2. 3-[3-(4-Hydroxyphenyl)-3-hydroxypropyl]-5-(cyclohexylmethoxy)-4*H*-chromen-4-one (9b). Yield 62.0%; white solid; mp 147.0 °C; IR 3424, 2923, 1659, 1454, 1266, 1066 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55 (s, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.0, 2H), 4.66 (dd, *J* = 4.5, 8.9 Hz, 1H), 3.86 (d, *J* = 6.1 Hz, 2H), 3.07 (br s, 1H), 2.59–2.70 (m, 1H), 2.45–2.55 (m, 1H), 1.95–2.06 (m, 4H), 1.73–1.82 (m, 3H), 1.18–1.37 (m, 3H), 1.03–1.16 (m, 3H); ^{13}C NMR (CDCl3) δ 177.1, 159.5, 158.4, 150.2, 141.3, 136.6, 133.1, 128.8, 125.5, 124.9, 114.4, 109.3, 106.7, 76.9, 76.7, 76.4, 74.6, 72.3, 38.3, 37.0, 29.5, 29.5, 26.1, 25.4, 21.5, 20.7; HRMS: calcd for $C_{25}H_{28}O_5$ *m*/*z* 408.1937, found: 408.1933.

7.1.2.3. 5-(Cyclohexylmethoxy)-3-[3-hydroxy-3-(4-methoxyphenyl)propyl]-4*H*-chromen-4-one (9c). Yield 85%; white solid; mp 92.0 °C; IR 3398, 2919, 1644, 1245, 827 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.64 (s, 1H), 7.49 (t, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.76 (d, *J* = 8.2 Hz, 1H), 4.62 (dd, *J* = 4.5, 8.9 Hz, 1H), 3.86 (d, *J* = 6.1 Hz, 2H), 3.79 (s, 3H), 3.07 (br s, 1H), 2.59–2.70 (m, 1H), 2.45–2.55 (m, 1H), 1.95–2.06 (m, 4H), 1.73–1.82 (m, 3H), 1.18–1.37 (m, 3H), 1.03–1.16 (m, 3H); ^{13}C NMR (CDCl3) δ 176.1, 160.1, 159.3, 159.1, 150.9, 137.1, 133.8, 127.5, 125.5, 115.1, 114.1, 109.9, 107.3, 77.6, 77.5, 77.3, 75.2, 72.7, 55.5, 38.9, 37.6, 30.1, 30.1, 26.8, 26.0, 22.2; HRMS: calcd for $C_{29}H_{30}O_5$ *m*/*z* 422.2093, found: 422.2088.

7.1.2.4. 5-(Cyclohexylmethoxy)-3-(3-hydroxy-3-*p*-tolylpropyl)-4*H*-chromen-4-one (9d). Yield 82%; white solid; mp 102.0 °C; IR 3389, 2928, 1666, 1264, 659 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.65 (s, 1H), 7.49 (t, *J* = 8.41 Hz, 1H), 7.25 (d, *J* = 8.05 Hz, 2H), 7.13 (d, *J* = 8.05 Hz, 2H), 6.94 (d, *J* = 8.54 Hz, 1H), 6.76 (d, *J* = 8.29 Hz, 1H), 4.63 (dd, *J* = 4.15, 8.78 Hz, 1H), 3.86 (d, *J* = 6.10 Hz, 2H), 3.16 (br s, 1H), 2.61–2.71 (m, 1H), 2.52 (dd, *J* = 5.12, 8.05 Hz, 1H), 2.32 (s, 3H), 1.89–2.07 (m, 5H), 1.73–1.82 (m, 2H), 1.18–1.40 (m, 5H), 1.03–1.16 (m, 1H); ^{13}C NMR (CDCl3) δ 177.1, 159.5, 158.4, 150.2, 141.3, 136.6, 133.1, 128.8, 125.5, 124.9, 114.4, 109.3, 106.7, 76.9, 76.7, 76.4, 74.6, 72.3, 38.3, 37.0, 29.5, 29.5, 26.1, 25.4, 21.5, 20.7; HRMS: calcd for $C_{26}H_{30}O_4$ *m*/*z* 406.2144, found: 406.2139.

7.1.2.5. 3-[3-(4-*tert*-Butylphenyl)-3-hydroxypropyl]-5-(cyclohexylmethoxy)-4*H*-chromen-4-one (9e). Yield 82%; white solid; mp 187.0 °C; IR 3402, 2850, 1644, 1266, 1066 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.65 (s, 1H), 7.49 (t, *J* = 8.41 Hz, 1H), 7.33–7.37 (m, 2H), 7.27–7.32 (m, 2H), 6.94 (dd, *J* = 0.73, 8.54 Hz, 1H), 6.76 (d, *J* = 8.29 Hz, 1H), 4.64 (dd, *J* = 4.39, 8.78 Hz, 1H), 3.86 (d, *J* = 5.85 Hz, 2H), 3.09 (br s, 1H), 2.60–2.71 (m, 1H), 2.47–2.58 (m, 1H), 1.89–2.09 (m, 5H), 1.67–1.84 (m, 4H), 1.24–1.37 (m, 13H), 1.07–1.15 (m, 2H); ^{13}C NMR (CDCl3) δ 178.2, 160.0, 158.8, 150.6, 150.4, 141.7, 133.6, 125.8, 125.4, 125.3, 114.9, 109.7, 107.1, 77.4, 77.1, 76.8, 75.0, 72.8, 38.5, 37.4, 34.5, 31.4, 29.9, 29.9, 26.6, 25.9, 22.0; HRMS: calcd for $C_{29}H_{36}O_4$ *m*/*z* 448.2614, found: 448.2610.

7.1.2.6. 3-[3-(4-Chlorophenyl)-3-hydroxypropyl]-5-(cyclohexylmethoxy)-4*H*-chromen-4-one (9f). Yield 62%; white solid; mp 96.0 °C; IR 3402, 2928, 1652, 767, 659 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.70 (s, 1H), 7.46–7.54 (m, 1H), 7.27–7.40 (m, 5H), 6.93–6.99 (m, 1H), 6.74–6.82 (m, 1H), 4.65 (ddd, *J* = 4.39, 9.45, 13.96 Hz, 1H), 3.87 (d, *J* = 6.34 Hz, 2H), 3.69 (br s, 1H), 2.64–2.77 (m, 1H), 2.43–2.57 (m, 1H), 2.05–1.88 (m, 5H), 1.79–1.69 (m, 3H), 1.38–1.23 (m, 3H), 1.15–1.06 (m, 2H); ^{13}C NMR (CDCl3) δ 187.9, 177.0, 166.0, 163.5, 158.9, 157.5, 135.9, 134.4, 134.0, 131.0, 131.1, 127.1, 124.3, 115.7, 113.6, 109.3, 108.3, 74.6, 72.0, 38.5, 38.4, 29.7, 26.4, 27.3, 21.0; HRMS: calcd for $C_{25}H_{27}ClO_4$ *m*/*z* 426.1598, found: 426.1593.

7.1.2.7. 5-(Cyclohexylmethoxy)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4*H*-chromen-4-one (9g). Yield 76%; white solid; mp 109.0 °C; IR 3402, 2848, 1635, 1460, 1064, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.67 (s, 1H), 7.50 (t, *J* = 8.41 Hz, 1H), 7.30–7.35 (m, 2H), 7.00 (t, *J* = 8.78 Hz, 2H), 6.96 (dd, *J* = 0.73, 8.54 Hz, 1H), 6.77 (d, *J* = 8.29 Hz, 1H), 4.63 (dd, *J* = 3.90, 9.27 Hz, 1H), 3.86 (d, *J* = 4.00 Hz, 2H), 3.53 (br s, 1H), 2.66–2.76 (m, 1H), 2.44–2.53 (m,

1H), 1.89–2.03 (m, 5H), 1.67–1.82 (m, 4H), 1.22–1.37 (m, 3H), 1.03–1.16 (m, 2H); ^{13}C NMR (CDCl3) δ 187.9, 174.1, 166.0, 163.5, 158.9, 157.5, 135.9, 134.4, 134.0, 131.0, 130.9, 122.1, 119.3, 115.7, 113.6, 109.3, 108.3, 74.6, 72.0, 38.5, 38.4, 29.8, 29.7, 26.4, 27.3, 21.0, 18.6; HRMS: calcd for $C_{25}H_{27}FO_4$ *m*/*z* 410.1893, found: 410.1887.

7.1.2.8. 5-(Cyclohexylmethoxy)-3-{3-[4-(trifluoromethyl)phenyl]-3-hydroxypropyl}-4*H*-chromen-4-one (9h). Yield 88%; white solid; mp 118.0 °C; IR 3399, 2919, 1650, 1255, 833 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.69 (s, 1H), 7.57 (d, *J* = 8.29 Hz, 2H), 7.52–7.46 (m, 3H), 6.99–6.94 (m, 1H), 6.78 (d, *J* = 8.05 Hz, 1H), 4.76–4.65 (m, 1H), 4.02 (d, *J* = 3.66 Hz, 1H), 3.99 (d, *J* = 3.6, 2H), 2.77 (d, *J* = 6.10 Hz, 1H), 2.50 (s, 1H), 2.02–1.92 (m, 4H), 1.82–1.69 (m, 4H), 1.36–1.25 (m, 3H), 1.11 (br s, 3H); ^{13}C NMR ($CDCl_3$) δ 187.9, 174.1, 166.0, 163.5, 158.9, 157.5, 135.9, 134.4, 134.0, 131.0, 130.9, 127.1, 124.3, 115.7, 113.6, 109.3, 108.3, 74.6, 72.0, 38.5, 38.4, 29.8, 29.7, 26.4, 27.3, 21.0, 19.2; HRMS: calcd for $C_{26}H_{27}F_3O_4$ *m*/*z* 460.1861, found: 460.1855.

7.1.2.9. 3-[3-(3,4-Dichlorophenyl)-3-hydroxypropyl]-5-(cyclohexylmethoxy)-4*H*-chromen-4-one (9i). Yield 43.0%; white solid; mp 118.0 °C; IR 3387, 2921, 1643, 750, 620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.64 (s, 1H), 7.48 (t, *J* = 8.41 Hz, 1H), 7.25 (d, *J* = 8.05 Hz, 2H), 7.13 (d, *J* = 7.80 Hz, 2H), 6.94 (dd, *J* = 0.98, 8.54 Hz, 1H), 6.76 (d, *J* = 8.29 Hz, 1H), 4.60–4.67 (m, 1H), 3.86 (d, *J* = 5.85 Hz, 2H), 3.06–3.11 (m, 1H), 2.61–2.71 (m, 1H), 2.46–2.55 (m, 1H), 1.95–2.06 (m, 4H), 1.73–1.80 (m, 2H), 1.21–1.37 (m, 3H), 1.04–1.16 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 188.2, 179.0, 166.3, 163.5, 158.0, 158.9, 157.5, 135.9, 134.4, 134.0, 131.0, 131.1, 127.1, 124.3, 115.7, 113.6, 109.3, 108.3, 74.6, 72.0, 38.5, 38.4, 29.7, 26.4, 27.3, 21.0; HRMS: calcd for $C_{25}H_{26}Cl_2O_4$ *m*/*z* 460.1208, found: 460.1204.

7.1.2.10. 3-[3-(4-Cyano)-3-hydroxypropyl]-5-(cyclohexylmethoxy)-4*H*-chromen-4-one (9j). Yield 76%; white solid; mp 106.0 °C; IR 3394, 2923, 2245, 1650, 1260, 655 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.71 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.41 Hz, 1H), 7.48 (d, *J* = 8.29 Hz, 2H), 6.97 (dd, *J* = 0.73, 8.54 Hz, 1H), 6.79 (d, *J* = 7.81 Hz, 1H), 4.68 (m, 1H) 4.35 (d, *J* = 3.66 Hz, 2H), 3.91–3.84 (m, 2H), 2.75–2.87 (m, 1H), 2.42–2.53 (m, 1H), 1.93–2.04 (m, 3H), 1.86–1.93 (m, 2H), 1.71–1.82 (m, 2H), 1.24–1.37 (m, 3H), 1.05–1.17 (m, 2H); ^{13}C NMR (CDCl3) δ 177.9, 174.1, 166.0, 163.5, 158.9, 157.5, 135.9, 134.4, 134.0, 131.0, 130.9, 122.1, 119.3, 115.7, 113.6, 109.3, 74.6, 72.0, 38.5, 38.4, 29.8, 29.7, 26.4, 27.3, 21.0, 18.6; HRMS: cald for $C_{26}H_{27}NO_4$ *m*/*z* 417.1940, found: 417.1932.

7.1.2.11. 5-(Cyclohexylmethoxy)-3-[3-hydroxy-3-(naphthalen-3-yl)propyl]-4*H*-chromen-4-one (9k). Yield 62.0%; light yellow solid; mp 121.0 °C; IR 3392, 2928, 1650, 1264, 659 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.77–7.85 (m, 4H), 7.66 (s, 1H), 7.41–7.48 (m, 4H), 6.94 (d, *J* = 8.29 Hz, 1H), 6.76 (d, *J* = 8.29 Hz, 1H), 4.83 (dd, *J* = 4.27, 8.90 Hz, 1H), 3.86 (d, *J* = 6.10 Hz, 2H), 3.54 (br s, 1H), 2.68–2.78 (m, 1H), 2.49–2.58 (m, 1H), 1.97–2.06 (m, 4H), 1.73–1.81 (m, 3H), 1.24–1.37 (m, 3H), 1.04–1.16 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 178.8, 159.5, 158.4, 157.3, 156.2, 154.3, 154.2, 150.3, 144.3, 133.1, 128.0, 127.8, 127.6, 127.4, 127.1, 125.5, 124.8, 114.4, 109.2, 106.7, 74.5, 38.5, 36.9, 29.44, 25.4, 21.5, 19.2; HRMS: calcd for $C_{29}H_{30}O_4$ *m*/*z* 442.2144, found: 442.2138.

7.1.3. General procedure for preparation of compounds (10)

The mixture of compound (**8**) (1 equiv) and cyclohexene (2 equiv) was added to THF/methanol (1:1) and 20% Pd/c and the resulted mixture was refluxed for 18 h. After the reaction was completed, the reaction mixture was filtered using celite and the fitrate was evaporated under reduced pressure. The residue was purified by column chromatography to afford the compound **10**.

7.1.3.1. 5-(Cyclohexylmethoxy)-2,3-dihydro-3-[3-(4-methoxyphenyl)-3-oxopropyl]chromen-4-one (10a). Yield 23.8%; color less liquid; IR 2931, 1632, 1602, 1453, 1243, 833 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.96 (d, *J* = 8.0 Hz, 2H), 7.31 (t, *J* = 8.29 Hz, 1H), 6.90–6.96 (m, 2H), 6.45–6.54 (m, 2H), 4.53–4.49 (m, 1H), 4.29–4.24 (m, 1H), 3.86–3.88 (m, 3H), 3.81 (d, *J* = 6.34 Hz, 2H), 3.14 (t, *J* = 7.32 Hz, 2H), 2.67–2.78 (m, 1H), 2.23–2.28 (m, 1H), 1.99–1.90 (m, 3H), 1.77 (d, *J* = 12.68 Hz, 2H), 1.23–1.37 (m, 4H), 1.05–1.15 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 199.3, 197.0, 160.1, 159.2, 159.0, 150.9, 137.1, 133.8, 127.5, 125.5, 115.0, 114.1, 109.7, 107.3, 75.2, 72.7, 55.5, 38.8, 37.6, 30.1, 26.7, 26.0, 22.2; HRMS: calcd for $C_{26}H_{30}O_5$ *m*/*z* 422.2093, found: 422.2089.

7.1.3.2. 3-[3-(3,4-Dichlorophenyl)-3-oxopropyl]-5-(cyclohexylmethoxy)-2,3-dihydrochromen-4-one (10b). Yield 33.0%; color less liquid; IR 2921, 1666, 1645, 750, 620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.07 (d, *J* = 1.4 Hz, 1H), 7.81 (dd, *J* = 1.3, 8.41 Hz, 1H), 7.54 (d, *J* = 8.29 Hz, 1H), 7.33 (t, *J* = 8.29 Hz, 1H), 6.49 (d, *J* = 8.54 Hz, 1H), 6.52 (d, *J* = 8.29 Hz, 1H), 4.52–4.48 (m, 1H), 4.29–4.24 (m, 1H), 3.81 (d, *J* = 6.34 Hz, 2H), 3.11–3.22 (m, 2H), 2.66–2.76 (m, 1H), 2.19 (d, *J* = 7.80 Hz, 1H), 1.86–2.01 (m, 4H), 1.77–1.69 (m, 3H), 1.17–1.39 (m, 4H), 1.04–1.14 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 199.4, 196.7, 177.65, 159.7, 158.7, 151.4, 143.7, 134.4, 133.3, 129.2, 128.2, 124.3, 114.9, 109.7, 106.9, 99.1, 91.7, 89.6, 51.0, 37.3, 29.8, 21.5, 20.7; HRMS: calcd for $C_{25}H_{26}Cl_2O_4$ *m*/*z* 460.1208, found: 460.1203.

Acknowledgment

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (Grant number 2011-0014889).

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