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Design and synthesis of novel hydroxyalkylaminomethylchromones for their IL-5 inhibitory activity

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ABSTRACT

A series of hydroxyalkylaminomethylchromone analogs **3** were prepared and evaluated as inhibitors of interleukin-5. The most active analog **3d** inhibited interleukin-5 activity with an IC_{50} of 17.5 μM. The structural requirements of chromone analogs possessing the inhibitory activity against IL-5 could be summarized as: (i) the cyclohexylmethoxy group at 5th position of the A ring, (ii) the planarity of chromone ring, (iii) hydrophobic unit around the B ring with hydroxyl functional group, (iv) the hydrophobic unit which does not have to be a planar and (v) the length of carbon units between amino and hydroxyl group is limited to two.

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1. Introduction

Inflammatory diseases consist of rheumatoid (arthritis), respiratory (asthma), cutaneous (psoriasis) and inflammatory bowl causes enormous toll on human health.[1] It has been reported that the eosinophil is recognized as a proinflammatory granulocyte involved in various allergic reactions such as in bronchial asthma and atopic dermatitis.[2] Accumulating evidence suggests that eosinophil-activating cytokines, such as interleukin (IL-5), granulocyte macrophage GSF (GM-GSF) and IL-3 are the key molecules implicated in the pathway of inflammatory process associated with eosinophils. However at present, IL-5 is the most predominant chemokine which has the capability of enhancing the activation, differentiation, migration, expansion and survival of eosinophils.[3–5] Thus IL-5 produced by activated Th2 lymphocytes plays a crucial role in allergic disease.[6,7] These eosinophils are a dominant cell type in allergic reactions and this exquisite specificity makes interleukin-5 as an excellent target for attenuating these responses without profound interference with the overall immune system. Glucocorticoids are the most potent agents to treat eosinophilic inflammation and allergic diseases[8] due to its tendency to suppress the inflammatory genes expressing cytokines and inflammatory enzyme.[9] However; their utility is compromised by their metabolic and endocrine side effects.

Recently, some small organic compounds have shown to inhibit the activity of IL-5. Chalcones[10,11] and isothiazolones derived from Cys 66 residue in IL-5 have been identified as IL-5 antagonists.[12] Noteworthy, sophoricoside (**1a,** 92.1% inhibition at 50 μM, IC_{50} = 1.4 μM) and its analogs isolated from *Sophora japonica*, a plant of Leguminosae family, are identified as inhibitors of IL-5 bioactivity.[13] The activity of sophoricoside appears to be more potent than budesonide (70.3% inhibition at 50 μM, IC_{50} = 26.8 μM), which is used for the treatment of chronic asthma. Thus, a number of isoflavonoid analogs of sophoricoside[14,15] have been synthesized and demonstrated to be novel inhibitors of IL-5.

Based on the above observation, the structure–activity relationship of sophoricoside analogs **1a–d** and **2a–b** (Chart 1)[10,11,14,15,18] inferred the necessity of planar chromen-4-one ring and a phenolic hydroxyl group at 4th position on ring B. However, the exact role of ring B in isoflavone analogs in inhibiting IL-5 has not been explored clearly. In continuation of our effort to find more detailed structure–activity relationship (SAR) of isoflavones as IL-5 inhibitor, we have designed and prepared a series of amino alcohol derivatives of chromone **3a–p** as shown in Chart 1 and evaluated their inhibitory activity against interleukin-5.

2. Chemistry

The synthesis of title compound **3** was achieved by the reductive amination[16,17] of **4**[18] as shown in Scheme 1. Thus compound **4** was reacted with various amino alcohols **5** in ethanol at reflux temperature to yield **6**, which was then cooled to ambient condition and subsequently treated with sodium borohydride to obtain the title compounds **3**. The substituents of **3**(**a**–**p**) are indicated in Table 1.

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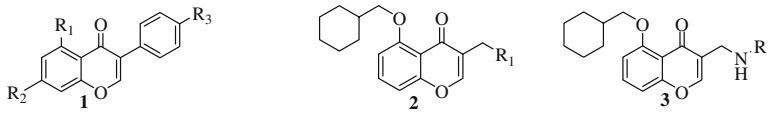
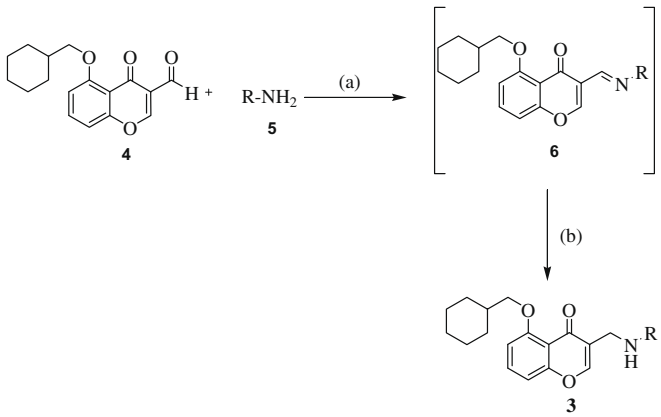


1a: Sophoricoside R1,R_2 = OH, R_3 = OGlu
1b: R_1 = benzyloxy, R_2 = H, R_3 = OH
1c: R_1 = H, R_2 = benzyloxy, R_3 = OH
1d: R_1 = cyclohexylmethoxy, R_2 =H, R_3 = OH

2a, R_1 = 4-(OH)C_6H_4
2b, R_1 = OH

3, R = substituents are located in Table-1

Chart 1. Interleukin-5 inhibitors **1**, **2** and hydroxyalkylaminomethylchromones **3**.



Scheme 1. Synthesis of hydroxyalkylaminomethylchromones **3**(**a**–**p**). Reagents and conditions: (a) ethanol, reflux at 80–90 °C; (b) $NaBH_4$, 10 min, rt. Note = substituents are located in Table 1.

3. Results and discussion

3.1. Pharmacology

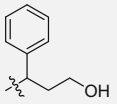
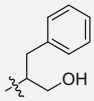
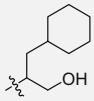
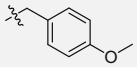
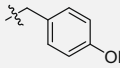
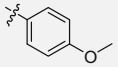
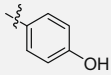
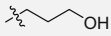
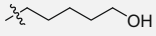
Inhibitory activity of the chromone analogs against IL-5 was evaluated using the IL-5-dependent pro-B Y16 cell line according to the known procedure.[13] The cells were incubated with 3 units/mL mIL-5 for 48 h in the presence or absence of sample, and then cell metabolism was measured as an index of proliferation, using 2-(4-Iodophenyl)-3-(nitrophenyl)-5-(2,4-disulphophenyl)-2*H* tetrazolium sodium salt (WST-1). Effect on the IL-5 bioassay by each test compound is represented as inhibition% at 30 μM samples and also IC_{50} values (Table 2). Data were collected from three independent experiments.

3.2. Structure–activity relationship

In our earlier work,[10,11,13–15] we have emphasized on the importance of a hydrophobic unit at ring A (benzyloxy or cyclohexylmethoxy), planarity of the chromone ring and the hydroxyl group on the ring B for IL-5 inhibitory activity of isoflavones. We have also demonstrated that a simple hydroxyl methyl (without ring B) chromone analog **2b** (85% inhibition at 30 μM, IC_{50} = 7.6 μM)[18] gave good inhibition against IL-5 activity. However, the region around ring B was not fully explored for the structure–activity relationship of isoflavanones. Thus, in the current article we have synthesized a series of chromone derivatives **3a**–**p** by fixing the cyclohexylmethoxy group as a hydrophobic unit on ring A of chromone moiety. The principle is obviously aimed for more effective binding at active site of IL-5 by introducing the amino alcohol unit instead of ring B to get more comparative SAR of these isoflavones.

In the first set of experiment, analog **3a** (88% inhibition at 30 μM, IC_{50} = 18.5 μM, *C* log *P* = 3.958) gave moderate inhibitory activity as compared to **2a** (98% inhibition at 30 μM, IC_{50} <3.0 μM).

Table 1
Structures and *C* log *P* values of **3**(**a**–**p**)

Compd No.	R	*C* log *P*[a]
3a		3.9589
3b		4.2635
3c		4.7913
3d		5.8733
3e		4.6645
3f		4.5835
3g		3.9975
3h		5.0855
3i		5.1881
3j		4.4185
3k		2.9143
3l		3.2435
3m		3.6355
3n		4.2813
3o		3.6223
3p		4.5503

[a] *C* log *P* values were calculated by Chem. draw version 9.0.

This suggests that the hydroxyphenyl ring (ring B) of **2a** can be replaced by hydroxyethylaminomethyl group to maintain the activity of isoflavanones. To confirm the optimum size of amino alcohol moiety, we increased one carbon unit between amino (NH) and hydroxyl (OH) function in **3a**. As a result, complete loss of activity was observed in analog **3b** (30% inhibition at 30 μM, IC_{50} >50 μM, *C* log *P* = 4.2635). This outcome supports that chain length of amino alcohol plays a critical role in inhibitory activity against IL-5.

Table 2
Interleukin-5 inhibitory activity of **3**(**a**–**p**)

Compd No.	Inhibition[a] at 30 μM (%)	IC_{50}
3a	88	18.5
3b	30	>50
3c	72	25.7
3d	93	17.3
3e	32	>50
3f	43	>30
3g	50	28.5
3h	14	>50
Sophoricoside	79.1[b]	10.6
3i	31	>50
3j	57	27.3
3k	13	>50
3l	15	>50
3m	20	>50
3n	13	>50
3o	63	26.4
3p	65.0	26.2
Budesonide	70.2[b]	26.2

[a] IC_{50} values are taken as a mean from three experiments.
[b] Inhibition at 50 μM.

Conversely, the analog **3c** (72% inhibition at 30 μM, IC_{50} <25.7 μM, *C* log *P* = 4.7913) inserted with one methylene unit between amino alcohol chain and phenyl group in **3a** shows comparable activity to **3a**. On the other hand, the replacement of phenyl group of **3c** with cyclohexyl moiety, as shown in **3d** (93% inhibition at 30 μM, IC_{50} <17.5 μM, *C* log *P* = 5.8733) led to enhancement of activity. Thus the bulky hydrophobic group in this region should be more important than the shape.

In order to explore the role of amino (–NH) group as hydrogen bonding source, when we removed hydroxymethyl group from **3a**, there was a complete loss of activity in the resulting analogs **3e** (32% inhibition at 30 μM, IC_{50} >50 μM, *C* log *P* = 4.6645) and **3f** (43% inhibition at 30 μM, IC_{50} >30 μM, *C* log *P* = 4.5835). This result indicates that the alcoholic –OH group is very essential for the inhibition than amino (–NH) group. However, introduction of phenolic hydroxyl group as shown in analogs **3g** (55% inhibition at 30 μM, IC_{50} = 28.5 μM, *C* log *P* = 3.9975) and **3j** (57% inhibition at 30 μM, IC_{50} 27.3 μM, *C* log *P* = 4.4185) rejuvenates the activity, though their levels are moderate. Such trend appears in the series of **3h** (14% inhibition at 30 μM, IC_{50} >50 μM, *C* log *P* = 5.0855), **3i** (31% inhibition at 30 μM, IC_{50} >50 μM, *C* log *P* = 5.1881) and **3j** (57% inhibition at 30 μM, IC_{50} = 27.3 μM, *C* log *P* = 4.4185). The more potent activity of **3a**, **3c**, and **3d** than those of **3g** and **3j** implies that the alcoholic hydroxyl is better than the phenolic one.

In the next set of experiment, we removed hydrophobic phenyl group in **3a**. The resulting compound **3k** (13% inhibition at 30 μM, IC_{50} >50 μM, *C* log *P* = 2.9143) showed complete loss of activity, even though it has the hydroxyl group. This was another important result which implies that the hydrophobic side chain branched on amino alcohol is critical for the activity. By increasing number of methylene groups in amino alcohol as shown in **3l** (one methylene unit) and **3m** (two methylene units) did not turn up with any inhibition as indicated in **3b**. Interestingly, the increment of the size of alkyl group as a branch in **3k** as in propyl analog **3n** (13% inhibition at 30 μM, IC_{50} >50 μM, *C* log *P* = 4.2813), dimethyl analog **3o** (63% inhibition at 30 μM, IC_{50} 26.4 μM, *C* log *P* = 3.6223) and *tert*-butyl analog **3p** (65% inhibition at 30 μM, IC_{50} 26.2 μM, *C* log *P* = 4.5503) showed gradual increment in their inhibition. Thus, the bulky hydrophobic group as a branch in amino ethanol is critical moiety for the activity.

Considering *C* log *P* values of **3a**, **3c**, **3n**, **3o** and **3p**, it was observed that increasing the hydrophobicity by introduction of branched groups is not correlated to the activity but instead the size of these groups is more important for the IL-5 inhibition. Thus, these groups are highly participating in binding hydrophobic zone of the putative receptor. This also supports that planarity is not necessary for their effective inhibition around ring B of **1d**.

4. Conclusion

On the basis of our previous[18] and current studies, we can conclude that the structural requirements of chromones analogs for their IL-5 activity should be considered as the following; (i) the cyclohexylmethyl group at 5th position of the ring A for their hydrophobic region,[18] (ii) the planarity of chromone ring,[18] (iii) hydrophobic unit is must with hydroxyl functional group around the ring B for activity and both should be inter-related to each other (iv) the hydrophobic unit does not have to be a planar and (v) the two methylene unit between amino and hydroxyl group are important.

5. Materials and method

5.1. Chemistry

Melting points (mp) 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[19] to use. Thin layer chromatography was performed on E Merck Silica Gel GF-254 per-coated plates and the identification was done with UV light and colorization with 10% phosphomolybdic acid spray followed by heating. Flash column chromatography was performed with E Merck silica gel (230–400 mesh). Infra red spectrum was recorded by using sample (neat sample without solvent or KBr) as such on FT-IR spectrum with Nicolet—380 models. NMR spectra were measured against the peak of tetramethylsilane by Varian Unity Inova 400 NMR (400 MHz) spectrometers. High resolution mass spectrum (HRMS) was recorded on API2000 mass spectrometer (PE Sciex, Toronto, Canada).

5.1.1. General synthetic procedure for the preparation of 3(a–d)

A solution of 3-formyl chromone **4**(**a**–**p**) (1 mmol) in ethanol (50 ml) was treated with appropriate amine **5** (1 equiv). The reaction mixture was cooled to room temperature after stir at reflux temperature for 4 h to obtain an intermediate **6** which was consequently treated with sodium borohydride (2 mmol) portion wise over a period of 10 min and allowed to stir for 2 h at the same condition. The reaction mixture was concentrated, partitioned between water and ethylacetate. The organic layer was washed with brine solution, dried over Na_2SO_4 and concentrated under reduced pressure to give a expected product. The purification was done by flash silica gel chromatography.

5.1.1.1. 5-(Cyclohexylmethoxy)-3-((2-hydroxy-1-phenylethylamino)methyl)-4*H*-chromen-4-one (3a). Yield 52%; Yellow crystal; mp 124–126 °C; IR(neat): 3403, 2924, 2853, 1645, 1593 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05–2.04 (m, 11H), 3.66 (t, *J* = 6.8 Hz 1H), 3.68 (t, *J* = 6.8 Hz, 1H), 3.84 (d, *J* = 6.4 Hz, 2H), 4.41 (t, *J* = 6.0 Hz, 1H), 4.62 (s, 2H), 6.41 (d, *J* = 8.4 Hz, 1H), 6.54–6.61 (m, 2H), 6.74 (d, *J* = 8.4 Hz, 1H), 7.18 (t, *J* = 8.4 Hz, 1H), 7.21–7.37 (m, 4H). HRMS calcd for $C_{25}H_{29}NO_4$ *m*/*z* 407.2097, found 407.2091.

5.1.1.2. 5-(Cyclohexylmethoxy)-3-((3-hydroxy-1-phenylpropylamino)methyl)-4*H*-chromen-4-one (3b). Yield 54%; viscous yellow solid; IR(neat): 3398, 2925, 1650, 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82–2.00 (m, 11H), 2.10 (q, *J* = 6.0 Hz, 2H), 3.67 (t, *J* = 5.6 Hz, 2H), 3.84 (d, *J* = 6.0 Hz, 2H), 4.41 (t, *J* = 5.6 Hz, 1H), 4.60 (s, 2H), 6.49 (d, *J* = 8.4 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 7.20–7.40 (m, 7H). HRMS calcd for $C_{26}H_{31}NO_4$ *m*/*z* 421.2253, found 421.2248.

5.1.1.3. 5-(Cyclohexylmethoxy)-3-((1-hydroxy-3-phenylpropan-2-ylamino)methyl)-4*H*-chromen-4-one (3c). Yield 48%; yellow crystal; mp 123–125 °C; IR(neat): 3403, 2925, 1650, 1578 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08–2.05 (m, 11H), 2.51(d, J = 6.0 Hz, 1H), 2.72 (d, J = 6.0 Hz, 1H) 3.10 (m, 1H), 3.61–3.67 (m, 2H), 3.86 (d, J = 6.0 Hz, 2H), 4.57 (s, 2H), 6.49–6.57 (m, 2H), 7.20–7.34 (m, 7H). HRMS calcd for $C_{26}H_{31}NO_4$ m/z 421.2253, found 421.2249.

5.1.1.4. 3-((1-Cyclohexyl-3-hydroxypropan-2-ylamino)methyl)-5-(cyclohexylmethoxy)-4*H*-chromen-4-one (3d). Yield 45%; yellow crystal; mp 103–105 °C; IR(neat): 3408, 2922, 1650, 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81–1.98 (m, 24H), 2.98 (m, 1H), 3.45 (d, J = 6.0 Hz, 1H), 3.68 (d, J = 5.6 Hz, 1H), 3.87 (d, J = 5.6 Hz, 2H), 4.62 (s, 2H), 5.20 (s, 1H), 6.45 (d, J = 8.0 Hz), 6.61 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 8.4 Hz, 1H), 7.32 (s, 1H). HRMS calcd for $C_{26}H_{37}NO_4$ m/z 427.2723, found 427.2718.

5.1.1.5. 3-((Benzylamino)methyl)-5-(cyclohexylmethoxy)-4*H*-chromen-4-one (3e). Yield 54%; colorless crystal; mp 115–117 °C; IR(neat): 2410, 2925, 1650, 1598, 1579 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82–2.01 (m, 11H), 3.87 (d, J = 6.0 Hz, 2H), 4.40 (s, 2H), 4.62 (s, 2H), 6.42 (d, J = 8.0 Hz, 1H), 6.54 (d, J = 8.0 Hz, 1H), 7.17 (t, J = 8.4 Hz, 1H), 7.21–7.38 (m, 6H). HRMS calcd for $C_{24}H_{27}NO_3$ m/z 377.1991, found 377.1984.

5.1.1.6. 5-(Cyclohexylmethoxy)-3-((4-methoxybenzylamino)-methyl)-4*H*-chromen-4-one (3f). Yield 50%; yellow crystal; mp 96–98 °C; IR(neat): 3403, 2922, 1650, 1598, 1579 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80–2.00 (m, 11H), 3.86 (d, J = 6.0 Hz, 2H), 3.91 (s, 3H), 4.39 (s, 2H), 4.60 (s, 2H), 6.45–6.51 (m, 2H), 6.82 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 8.0 Hz, 2H), 7.23 (t, J = 8.4 Hz, 1H), 7.38 (s, 1H). HRMS calcd for $C_{25}H_{29}NO_4$ m/z 407.2097, found 407.2092.

5.1.1.7. 5-(Cyclohexylmethoxy)-3-((4-hydroxybenzylamino)methyl)-4*H*-chromen-4-one (3g). Yield 48%; yellow crystal; mp 121–123 °C; IR(neat): 3381, 2926, 1650, 1598, 1578 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84–2.03 (m, 11H), 3.90 (d, J = 5.6 Hz, 2H), 4.42 (s, 2H), 4.58 (s, 2H), 6.46 (d, J = 8.0 Hz, 1H), 6.57–6.81 (m, 3H), 7.01–7.16 (m, 3H), 7.37 (s, 1H). 10.9 (s, 1H). HRMS calcd for $C_{24}H_{27}NO_4$ m/z 393.1940, found 393.1933.

5.1.1.8. 5-(Cyclohexylmethoxy)-3-((phenylamino)methyl)-4*H*-chromen-4-one (3h). Yield 57%; viscous yellow oil; IR(neat): 3410, 2922, 1650, 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06–2.01 (m, 11H), 3.88 (d, J = 6.0 Hz, 2H), 4.77 (s, 2H), 6.44 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 8.4 Hz, 1H), 7.10–7.33 (m, 7H). HRMS calcd for $C_{23}H_{25}NO_3$ m/z 363.1834, found 363.1831.

5.1.1.9. 5-(Cyclohexylmethoxy)-3-((4-methoxyphenylamino)-methyl)-4*H*-chromen-4-one (3i). Yield 45%; yellow crystal; mp 121–123 °C; IR(neat): 3410, 2922, 1650, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02–2.00 (m, 11H), 3.86 (d, J = 6.0 Hz, 2H), 3.93 (s, 3H), 4.57 (s, 2H), 6.45 (d, J = 8.0 Hz, 2H), 6.51–6.78 (m, 3H), 6.96 (d, J = 8.0 Hz, 2H), 7.21 (t, J = 8.4 Hz, 1H), 7.33 (s, 1H). HRMS calcd for $C_{24}H_{27}NO_4$ m/z 393.1940, found 393.1936.

5.1.1.10. 5-(Cyclohexylmethoxy)-3-((4-hydroxyphenylamino)-methyl)-4*H*-chromen-4-one (3j). Yield 52%; yellow crystal; mp 104–106 °C; IR(neat): 3409, 2926, 1650, 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02–2.00 (m, 11H), 3.87 (d, J = 6.0 Hz, 2H), 4.80 (s, 2H), 6.49 (d, J = 8.4 Hz, 2H), 6.75 (d, J = 8.0 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 7.19 (t, J = 8.0 Hz, 1H), 7.31 (s, 1H), 10.81 (s, 1H). HRMS calcd for $C_{23}H_{25}NO_4$ m/z 379.1784, found 379.1781.

5.1.1.11. 5-(Cyclohexylmethoxy)-3-((2-hydroxyethylamino)-methyl)-4*H*-chromen-4-one (3k). Yield 51%; viscus yellow oil; IR(neat): 3403, 2925, 1650, 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92–2.08 (m, 11H), 3.53 (t, J = 5.6 Hz, 2H), 3.67 (t, J = 5.6 Hz, 2H), 3.88 (d, J = 6.0 Hz, 2H), 4.82 (s, 2H), 6.38 (d, J = 8.0 Hz, 1H), 6.59 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 7.34 (s, 1H). HRMS calcd for $C_{19}H_{25}NO_4$ m/z 331.1784, found 331.1779.

5.1.1.12. 5-(Cyclohexylmethoxy)-3-((3-hydroxypropylamino)-methyl)-4*H*-chromen-4-one (3l). Yield 59%; yellow crystal; mp 110–112 °C; IR(neat): 3390, 2924, 1650, 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04–2.04 (m, 13H), 3.34 (t, J = 5.6 Hz, 2H), 3.63 (t, J = 5.6 Hz, 2H), 3.85 (d, J = 6.0 Hz, 2H), 4.67 (s, 2H), 6.51 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 7.20 (t, J = 8.4 Hz, 1H), 7.37 (s, 1H). HRMS calcd for $C_{20}H_{27}NO_4$ m/z 345.1940, found 345.1931.

5.1.1.13. 5-(Cyclohexylmethoxy)-3-((5-hydroxypentylamino)-methyl)-4*H*-chromen-4-one (3m). Yield 44%; viscus yellow oil; IR(neat): 3398, 2924, 1650, 1598, 1453 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03–2.04 (m, 17H), 3.31 (t, J = 6.0 Hz. 2H), 3.70 (t, J = 5.6 Hz, 2H), 3.85 (d, J = 5.6 Hz, 2H), 4.69 (s, 2H), 6.49 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 8.4 Hz, 1H), 7.38 (s, 1H). HRMS calcd for $C_{22}H_{31}NO_4$ m/z 373.2253, found 373.2245.

5.1.1.14. 5-(Cyclohexylmethoxy)-3-((1-hydroxypentan-2-ylamino)methyl)-4*H*-chromen-4-one (3n). Yield 59%; viscus yellow oil; IR(neat): 3409, 2923, 1650, 1578, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88–2.07 (m, 18H), 3.10 (m, 1H), 3.42 (d, J = 5.6 Hz, 1H), 3.70 (d, J = 5.6 Hz, 1H), 3.88 (d, J = 6.0 Hz, 2H), 4.56 (s, 2H), 6.44–5.53 (m, 2H), 7.20 (t, J = 8.4 Hz, 1H), 7.36 (s, 1H). HRMS calcd for $C_{22}H_{31}NO_4$ m/z 373.2253, found 373.2248.

5.1.1.15. 5-(Cyclohexylmethoxy)-3-((1-hydroxy-2-methylpropan-2-ylamino)methyl)-4*H*-chromen-4-one (3o). Yield 55%; yellow crystal; mp 93–95 °C; IR(neat): 3381, 2924, 1647, 1581 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82–2.01 (m, 17H), 3.72 (s, 2H), 3.87 (d, J = 6.0 Hz, 2H), 4.54 (s, 2H), 6.46–6.55 (m, 2H), 7.23 (t, J = 8.0 Hz, 1H), 7.38 (s, 1H). HRMS calcd for $C_{21}H_{29}NO_4$ m/z 359.2097, found 359.2093.

5.1.1.16. 5-(Cyclohexylmethoxy)-3-((1-hydroxy-3,3-dimethylbutan-2-ylamino)methyl)-4*H*- chromen-4-one (3p). Yield 50%; Yellow crystal; mp 70–71 °C; IR(neat): 3402, 2925, 2855, 1646, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (s, 6H), 1.07–2.04 (m, 11H), 2.80 (m, 1H), 3.56 (m, 1H), 3.85 (d, J = 5.6 Hz, 2H), 4.14 (m, 1H), 4.62 (q, 1H), 6.43–6.57 (m, 2H), 7.19 (t, J = 8.4 Hz, 1H), 7.26 (s, 1H). HRMS calcd for $C_{23}H_{33}NO_4$ m/z 387.2410, found 387.2403.

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