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Identification of novel chromenone derivatives as interleukin-5 inhibitors

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ABSTRACT

A series of (*E*)-5-alkoxy-3-(3-phenyl-3-oxoprop-1-enyl)-4*H*-chromen-4-ones (**4**) and (*E*)-5-alkoxy-3-(3-hydroxy-3-phenylprop-1-enyl)-4*H*-chromen-4-ones (**5**) were synthesized and evaluated for their IL-5 inhibitory activity. Propenone analogs **4** possess some of the structurally important characteristics of isoflavone **2** and chalcone **3** previously known as potent IL-5 inhibitor. However, the inhibitory activity of **4** was weak and therefore this structural hybridization appears to be ineffective for the design of IL-5 inhibitor. Meanwhile the potent activity profile of compounds **5** was discovered. This enhanced activity of **5** compared to **4** could be due to the effective location of hydroxyl group of allylic alcohol moiety of **5** in the 3D structure. The electron withdrawing substituents at position 4 of phenyl ring of **5** enhances the activity possibly due to an increase in the strength of hydrogen bonding property of hydroxyl group of allylic alcohol moiety.

1. Introduction

Millions of people around the world suffer from different types of allergies including hay fever, rhinitis, asthma, eczema, idiopathic eosinophilic syndromes, atopic dermatitis, pet and food allergies. Interestingly, all of them have distinct inflammatory constituents and described by diverse eosinophilic intrusion [1]. Minor allergies can often be treated easily by antihistamines, but makes condition miserable if ignored. One of the serious allergies is asthma, recognized as a chronic inflammatory disease of the airways characterized by edema, decreased mucociliary clearance, epithelial damage, increased neuronal responsiveness, and bronchoalveolar eosinophilia [1].

The precise cause of asthma is still not known but it is believed that both genetic and environmental factors play an important role in the development of the disease. Therefore, it is necessary to study the role of chronic pulmonary inflammation in the pathophysiology of asthma, which involves T cells and eosinophils invasion, 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]. The eosinophils are formed in the bone marrow in response to cytokine activation, and are released into the circulation after proper stimulus. Once in the circulation they accumulate rapidly in the tissue and synthesize various proteins and lipid mediators that cause edema, bronchoconstriction and chemotaxis [3].

The eosinophil is therefore, a perfect target for selectively inhibiting the tissue damage that accompanies allergic diseases, without inducing the immunosuppressive consequences that can arise from systemic use of pleiotropic drugs such as steroids. The development of eosinophils in bone marrow and its release in the circulation requires interleukin-5 [4–7]. Both in humans and animals, inhibiting interleukin-5 with monoclonal antibodies can reduce blood and bronchoalveolar eosinophilia caused by allergic challenges or chronic diseases [8–11]. Therefore, exclusively inhibiting the actions of interleukin-5 can suppress at least one of the alleged causes of asthma, namely tissue damage due to eosinophil accumulation during pulmonary inflammation. In addition, various clinical investigations indicate that the IL-5-regulated eosinophilia plays a vital role in the pathogenesis of asthma [12–15].

The above reports confirm that IL-5 clearly emerges as an important target for the treatment of the asthma. Consequently, a number of IL-5 inhibitors are reported in the literature. Among them, isothiazolones have been synthesized by the modification of Cys 66 residue in IL-5 and reported as its antagonists [16]. However, the most significant discovery is the natural product sophoricoside (**1**, 92.1% inhibition at 50 μM, IC_{50} = 1.4 μM) and its analogs (**2**) which showed potent IL-5 inhibitory activity [17] (Fig. 1). Interestingly, it was also reported as weak IL-3 and GM-CSF inhibitor [18]. While sophoricoside showed promising IL-5 inhibitory activity

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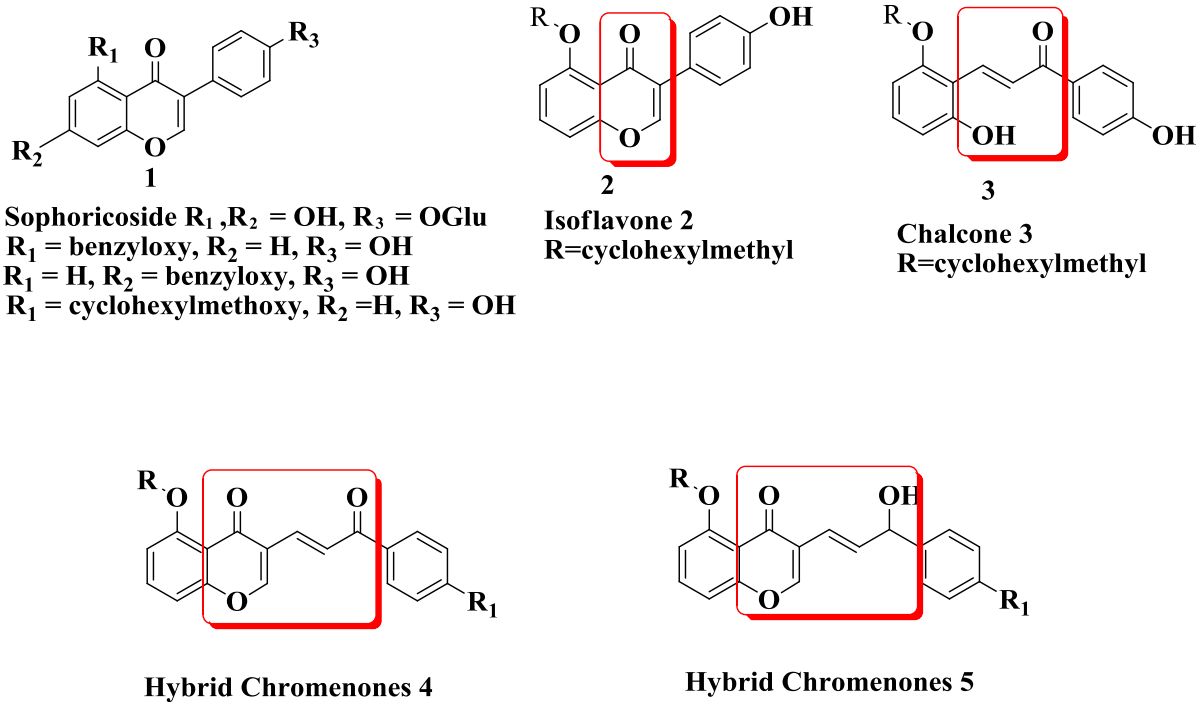


Fig. 1. Structure modifications of chromenones.

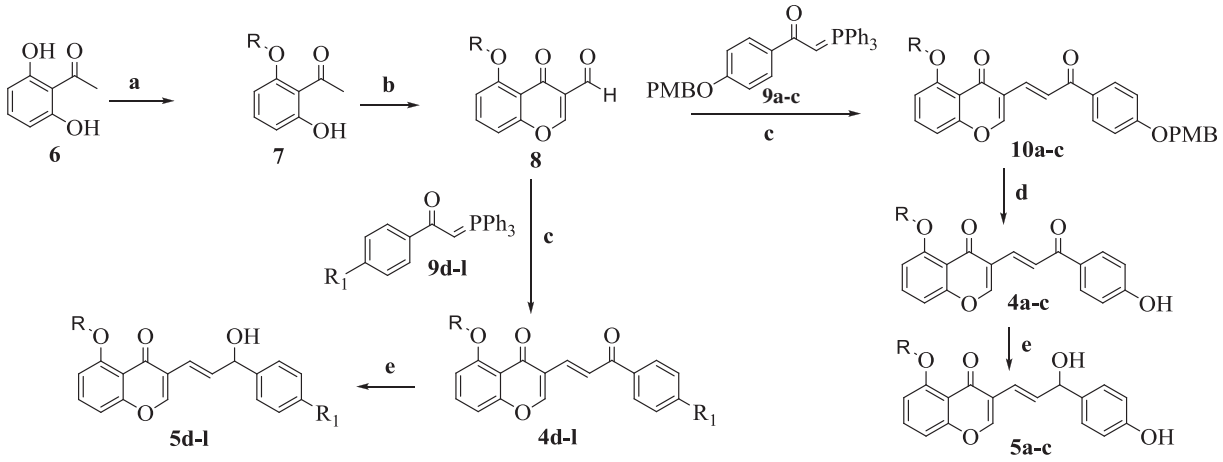
still more diverse and concise structure activity relationship (SAR) studies are needed. Therefore, a number of isoflavonoid analogs (**1** and **2**, Fig. 1) of sophoricoside [19,20] as well as chalcone derivatives (**3**, Fig. 1) [21,22] were investigated as potent IL-5 inhibitors by our group. The SAR studies of isoflavonoid analogs [19] revealed that planar chromen-4-one ring and phenolic hydroxyl group at position 4 of ring B indeed plays an important role in activity. Similarly in chalcone analogs the hydrophobic group such as benzyloxy or cyclohexylmethoxy at position 2 of ring A is necessary [21,22]. In addition, the existence of phenolic hydroxyl at position 6 of ring A is critical. Interestingly, both the isoflavonoid analogs and chalcone derivatives have common structural features such as bulky hydrophobic group at position 5 and 6 of ring A respectively, enhancing their inhibitory activity as compared to the sophoricoside [19,20]. The most important structural features of chalcones are the propenone motif as well as the presence of electron withdrawing groups with hydrogen acceptor property at position 4 of phenyl ring B which subsequently improves their activity. But in case of isoflavone analogs, phenolic hydroxyl group at position 4 of ring B plays an important role for the same. In addition, the possibility of replacement of ring B in isoflavonoid analogs with aliphatic motif was also observed in one of our previous studies [16,23]. Thus after studying all these structural characteristics of isoflavones and chalcones, we hypothesized that combination of their structural characteristics may lead to more active compounds. In this regard, hybrid type target compounds such as chromenone derivatives **4** and **5** were designed, synthesized (Fig. 1) and evaluated for their IL-5 inhibitory activity.

2. Chemistry

The synthesis of the desired compounds **4a**–**l** and **5a**–**l** was accomplished as outlined in Scheme 1. In brief, the acetophenone **7** was prepared by the partial alkylation of 2, 6-dihydroxyacetophenone (**6**) [19]. Preparation of **8** was accomplished by the cyclization of **7** using *N*, *N*-dimethylformamide and phosphoryl chloride at ambient temperature [23]. The Wittig reagents (**9a**–**c**, **9d**–**l**) were obtained by the reaction of commercially available substituted bromoacetophenones and triphenylphosphine in methylene chloride at ambient temperature [24,25]. The reaction of 5-alkoxy-4-oxo-4H-chromene-3-carbaldehydes (**8**) [23] with Wittig reagents **9a**–**c** in methylene chloride at ambient temperature for overnight produced the chromenone **10a**–**c** and the following deprotection of **10a**–**c** with trifluoroacetic acid at ambient temperature for 3 h gave compounds **4a**–**c**. The reaction of **8** with Wittig reagents **9d**–**l** in methylene chloride at ambient temperature for overnight produced the desired chromenone **4d**–**l** [24]. These analogs could be prepared by simple aldol condensation with aldehyde **8** and substituted acetophenones in the presence of base. However, these attempts gave the multiple products. The reasons were inferred due to the instability of aldehyde **8** under basic condition. Finally, the racemic allylic alcohols **5a**–**l** were obtained by the reduction of ketone function of **4a**–**l** using sodium borohydride in presence of cerium chloride at 0–5 °C. The synthesized chromenones **4** and **5** may exist as either the *Z* or *E* isomer. The coupling constants of protons on α,β-unsaturated ketone unit appears as 12–16 Hz. Thus the compounds **4** and **5** have *E* stereochemistry around double bond. All these synthesized compounds were listed in Table 1 and characterized by physical and spectral analysis data that confirmed their assigned structures.

3. Pharmacology

Inhibitory activity of the chromenone analogs **4** and **5** against IL-5 was evaluated using the IL-5-dependent pro-B Y16 cell line according to the known procedure [17]. 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)-2H tetrazolium sodium salt (WST-1). The effect of test compounds on the IL-5 bioassay is represented as inhibition % at 30 μM samples and also IC_{50} values (Table 2). Data were collected from three independent experiments.



Scheme 1. Synthesis of choromone analogs. (a) R–Br, CH_3CN, aqueous 95% K_2CO_3, NaI (cat), reflux, overnight, (b) $POCl_3$, DMF, overnight, rt. (c) dichloromethane, overnight (d) TFA, dichloromethane, 3 h, rt. (e) $NaBH_4$, $CeCl_3$, Dichloromethane/methanol. Note* = substitution are located in Table 1.

4. Conformational analysis and alignment

Molecular models of compounds **4c** and **5c** were constructed using SYBYL®-X1.3 program package (Tripos Associates Inc.) [26] and their geometry were optimized (Powell conjugate gradient minimization, termination at a gradient of 0.0005 kcal/mol.) using the Tripos standard force field [27] and Gasteiger-Hückel atomic partial charges [28]. 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 Fig. 2. The selected dihedral angles and atomic distances are listed in Tables 3 and 4.

5. Results and discussion

Designed (*E*)-3-(3-phenyl-3-oxoprop-1-enyl)-4*H*-chromen-4-ones **4** possess chromenone and phenylpropenone moieties (Fig. 1), which have been recognized as the effective structural motifs of isoflavone **2** and chalcone **3** for the inhibition of IL-5. Thus the chromenones **4** could be considered as the hybrid structure.

Table 1
Chromenone analogs **4a**–**l** and **5a**–**l** with their physicochemical properties.

Compd.	R	R_1	Appearance	m.p (°C)	Yield (%)
4a	Methyl	OH	White solid	220–222	52.2
4b	Isobutyl	OH	Brown Solid	141–143	44.0
4c	Cyclohexylmethyl	OH	Yellow solid	288–290	55.7
4d	Cyclohexylmethyl	H	White solid	176–178	66.2
4e	Cyclohexylmethyl	OCH_3	White solid	185–187	48.8
4f	Cyclohexylmethyl	CH_3	White solid	200–202	45.3
4g	Cyclohexylmethyl	t-butyl	White solid	236–238	49.2
4h	Cyclohexylmethyl	Cl	White solid	219–221	58.4
4i	Cyclohexylmethyl	F	White solid	190–192	72.3
4j	Cyclohexylmethyl	CF_3	White solid	204–206	52.6
4k	Cyclohexylmethyl	NO_2	Yellow solid	280–282	64.3
4l	Cyclohexylmethyl	CN	Yellow solid	265–267	55.9
5a	Methyl	OH	White solid	174–176	44.8
5b	Isobutyl	OH	Brown solid	139–141	65.0
5c	Cyclohexylmethyl	OH	Yellow solid	284–286	90.2
5d	Cyclohexylmethyl	H	Yellow solid	170–172	85.4
5e	Cyclohexylmethyl	OCH_3	Yellow solid	175–177	80.7
5f	Cyclohexylmethyl	CH_3	Yellow solid	190–192	79.3
5g	Cyclohexylmethyl	t-butyl	Yellow solid	230–232	83.5
5h	Cyclohexylmethyl	Cl	Yellow solid	210–212	80.2
5i	Cyclohexylmethyl	F	Yellow solid	182–184	79.7
5j	Cyclohexylmethyl	CF_3	Yellow solid	190–192	79.3
5k	Cyclohexylmethyl	NO_2	Yellow solid	275–277	83.5
5l	Cyclohexylmethyl	CN	Yellow solid	259–261	79.0

As shown in Table 1, the size of alkoxy substituents of hybrid analogs **4** and **5** at position 5 of chromenone ring was varied with methoxy, isobutoxy, or cyclohexylmethoxy to investigate the effect of size or lipophilicity of hybrid chromenones **4** and **5**. For finding the effective substitution at position 4 of phenyl ring of **4** and **5** various substituents such as hydrogen bonding group (OH), hydrophobic electron donating groups (CH_3, *t*-butyl), electron donating group (OCH_3) and electron withdrawing group (F, Cl, CF_3, NO_2, CN) were studied for the inhibitory activity.

Comparison of the activity of hybrid analog **4c** (IC_{50} = 16.2 μM) with those of corresponding isoflavone **2** (IC_{50} = 5.8 μM) and chalcone **3** (IC_{50} = 12.6 μM) revealed decrement in the activity (Table 2). The activity of all other analogs of **4** did not exceed the activity of compared compounds. Thus hybridization with characteristics of both isoflavone and chalcone did not give any advantage.

However, some of structure activity relationship could be extracted from the results. Considering the activity of **4a**–**c**, increasing the bulkiness on position 5 of ring A increases the activity, thus making **4c** the most active one. Regarding the effect of substituents on position 4 of phenyl ring of compounds **4**, the hydroxyl group (as shown in compounds **4b** and **4c**) plays an essential role for the activity. These findings are consistent with our previous studies where the bulky hydrophobic groups at positions 5 and 6 of ring A in isoflavone and chalcones, respectively and hydroxyl group on ring B had positive effect on the activity [21,22].

Table 2
Inhibitory activity of chromone analogs **4a**–**l** and **5a**–**l** against Interleukin-5.

Compd.	% Inhibition at 30 μM[a]	IC_{50} (μM)[a]	Compd.	% Inhibition at 30 μM[a]	IC_{50} (μM)[a]
4a	32.3	>30	**5a**	21.3	>30
4b	87.5	19.1	**5b**	20.6	>30
4c	99.0	16.2	**5c**	92.7	12.5
4d	17.2	>30	**5d**	93.9	15.0
4e	9.3	>30	**5e**	93.6	16.0
4f	57.5	25.1	**5f**	93.2	15.0
4g	99.2	18.1	**5g**	15.7	>30
4h	46.3	>30	**5h**	94.5	7.0
4i	15.4	>30	**5i**	93.2	6.4
4j	42.7	>30	**5j**	92.7	13.2
4k	11.8	>30	**5k**	93.8	7.0
4l	9.2	>30	**5l**	94.4	6.7
2[20]	91.7[b]	5.8	**3**[22]	99.0[b]	12.6
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.

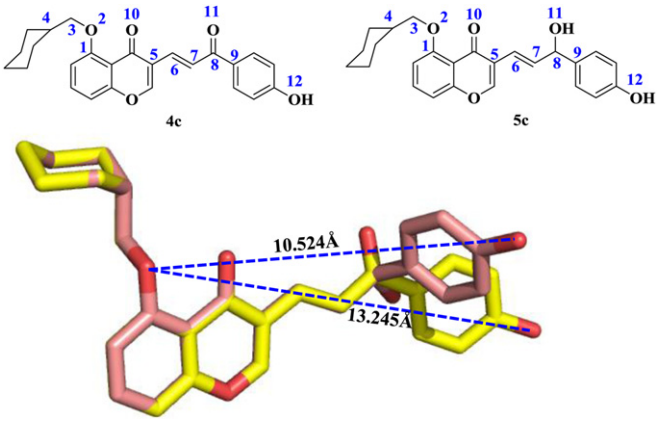


Fig. 2. Alignment of compound **4c** (11.471 kcals/mol) and **5c** (10.849 kcals/mol). Yellow color (**4c**), Pink color (**5c**). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Analogs substituted on position 4 of phenyl ring of compounds **4** with methoxy (**4e**), chloro (**4h**), fluoro (**4i**), trifluoromethyl (**4j**), nitro (**4k**), or cyano (**4l**) did not show any activity. However, hydrophobic substitution such as methyl or *tert*-butyl group as shown in **4f** (57.5% inhibition at 30 μM, IC_{50} = 25.1 μM) and **4g** (99.2% inhibition at 30 μM, IC_{50} = 18.1 μM) still possessed the moderate level of activity, presumably due to their bulkiness and electron donating properties.

As α,β-unsaturated ketone of (*E*)-3-(3-phenyl-3-oxoprop-1-enyl)-4*H*-chromen-4-ones **4** seemed to be the reason for the loss of activity of these chromenones, in another set of experiment the carbonyl function of α,β-unsaturated ketones was reduced to the racemic allylic alcohols. Accordingly, compounds **5a**–**l** were prepared and tested for their IL-5 inhibitory activity as shown in Table 2. Although the activity was lost in the compounds with less bulky groups such as methoxy and isobutoxy at position 5 of ring A (compounds **5a** and **5b**), other cyclohexylmethoxy compounds (**5c**–**f** and **5h**–**l**) were better inhibitors than the corresponding α,β-unsaturated ketones (**4c**–**f** and **4h**–**l**). Exceptionally, the bulky *tert*-butyl **5g** (15% inhibition at 30 μM, IC_{50} > 30 μM) did not turn up with any inhibitory activity. The above results indicate the importance of hydrogen bond characteristic of allylic hydroxyl group for the activity.

Interestingly, the activity of 3-(3-hydroxy-3-phenylprop-1-enyl)-4*H*-chromen-4-ones **5** was further improved by introducing the electron withdrawing group at *p*-position of ring B such as chloro (**5h**, 93.5% inhibition at 30 μM, IC_{50} = 7.0 μM), fluoro (**5i**, 93.2% inhibition at 30 μM, IC_{50} = 6.4 μM), trifluoro (**5j**, 92.7% inhibition at 30 μM, IC_{50} = 13.2 μM), nitro (**5k**, 93.8% inhibition at 30 μM, IC_{50} = 7.0 μM) and cyano analogs (**5l**, 94.4% inhibition at 30 μM, IC_{50} = 6.7 μM). These electron withdrawing groups on position 4 of phenyl ring in **5** obviously increases hydrogen bonding power of hydroxyl group of allylic alcohol moiety of **5** and therefore the activity of these analogs should be increased.

To further investigate the detailed structural requirements for the potent IL-5 inhibitor we compared the structural sketches of the compound **4c** and **5c** and observed a dramatic difference in the region of side chain of hybrid chromenone scaffolds **4c** and **5c** (Fig. 2). The dihedral angle ($\angle C_6{-}C_7{-}C_8{-}C_9$) of compound **4c** is 192.3° (Table 3). This indicates that the carbonyl function of α,β-unsaturated ketones moiety of **4c** is stretched away from the chromenone ring. In addition, the distance (13.245 Å, Table 4, Fig. 2) from oxygen of methoxy group to oxygen at position 4 of phenyl ring of **4c** also confirms this stretch conformation. Meanwhile the corresponding angles ($\angle C_6{-}C_7{-}C_8{-}C_9$ = 108.3°, Table 3) of **5c** depict that hydroxyl group of racemic allylic alcohol moiety of **5c** is located nearly at right angle position in chromenone ring plane. The much shorter distance (10.523 Å, Fig. 2) of methoxy group to oxygen at position 4 of phenyl ring in **5c** than in **4c** also implies the folded conformation of racemic allylic alcohol moiety. Such conformational change might cause the enhancement of the activity in analogs **5** compared to those of the corresponding compounds **4**. Therefore, the folded conformation as shown in **5c** could be much closer to the effective conformation for binding to the putative receptor.

Table 3
Torsion angle (°) and total energy of compound **4c** and **5c**.

Compound **4c**[a] (11.471 kcals/mol)[b]		Compound **5c**[a] (10.849 kcals/mol)[b]	
$\angle C_1{-}O_2{-}C_3{-}C_4$	182.4°	$\angle C_1{-}O_2{-}C_3{-}C_4$	182.5°
$\angle C_5{-}C_6{-}C_7{-}C_8$	179.5°	$\angle C_5{-}C_6{-}C_7{-}C_8$	188.3°
$\angle C_6{-}C_7{-}C_8{-}C_9$	192.3°	$\angle C_6{-}C_7{-}C_8{-}C_9$	108.3°

[a] Numbers on the atoms of **4c** and **5c** are presented in Fig. 2.
[b] Total energy.

Table 4
Bond distances (Å) in compounds **4c** and **5c**.

Compound **4c**[a]		Compound **5c**[a]	
$O_2{-}O_{12}$	13.245	$O_2{-}O_{13}$	10.523
$O_2{-}O_{11}$	7.544	$O_2{-}O_{12}$	8.863
$O_{10}{-}O_{12}$	10.669	$O_{11}{-}O_{13}$	8.451
$O_{10}{-}O_{11}$	4.856	$O_{11}{-}O_{12}$	6.327
$O_{11}{-}O_{12}$	6.389	$O_{12}{-}O_{13}$	6.413
$O_2{-}O_{12}$	13.245	$O_2{-}O_{13}$	10.523

[a] Numbers on the atoms of **4c** and **5c** are presented in Fig. 2.

6. Conclusion

A series of (*E*)-5-alkoxy-3-(3-phenyl-3-oxoprop-1-enyl)-4*H*-chromen-4-ones (**4**) and (*E*)-5-alkoxy-3-(3-hydroxy-3-phenylprop-1-enyl)-4*H*-chromen-4-ones (**5**) were synthesized and evaluated for their IL-5 inhibitory activity. Propenone analogs **4** possess some of the structurally important characteristics of isoflavone **2** and chalcone **3**, known potent IL-5 inhibitors. However, the inhibitory activity of **4** was weak and therefore this structural hybridization appears to be ineffective for the design of IL-5 inhibitor. Hydrogen bonding acceptor property of carbonyl oxygen of propenone scaffold of (*E*)-3-(3-phenyl-3-oxoprop-1-enyl)-4*H*-chromen-4-ones **4** did not contribute for the inhibition of IL-5. However hydroxyl function on ring B of **4** still acts as an important functional group. Meanwhile the potent activity profile of compounds **5** was discovered. This enhanced activity of **5** compared to **4** could be due to the effective location of hydroxyl group of allylic alcohol moiety of **5** in the 3D structure. The electron withdrawing substituents at position 4 of phenyl ring of **5** enhances the activity possibly due to an increase in the strength of hydrogen bonding property of hydroxyl group in allylic alcohol moiety of 3-(3-hydroxy-3-phenylprop-1-enyl)-4*H*-chromen-4-ones (**5a**–**l**).

7. Materials and methods

7.1. Chemistry

Melting points (m.p.) were determined on Electrothermal 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 [29]. 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). Infrared 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 Varain Unity Inova 400 NMR (400 MHz) spectrometer. High resolution mass spectra (HRMS) were measured by using Shimadzu LCMS-IT-TOF spectrometer.

*7.1.1. Procedure for the preparation of compounds **6**, **7** and **8***

The synthetic procedures for all compounds **6**, **7** and **8** are followed as described previously [19–22].

*7.1.2. Procedure for the preparation of compounds **9a**, **9d**–**l** [24,25]*

Solution of substituted bromoacetophenone (1.0 equivalent) in methylene chloride (10 mL) was added to a solution of triphenylphosphine (1.2 equivalent) in methylene chloride (10 mL) under nitrogen. The mixture was stirred overnight and then added 100 mL ether. After stirred for 1 h, the resulting phosphonium salt was filtered and the precipitate was washed with ether and dried under vacuum. The dried phosphonium salt was suspended in a mixture of water (50 mL) and methanol (50 mL), and the mixture was stirred for 1 h. Aqueous sodium hydroxide (2 M) was added to the mixture until pH reached between 7 and 8. The mixture was then stirred vigorously for 5 h. After evaporated methanol, the aqueous layer was extracted with methylene chloride. Organic layer was dried over Na_2SO_4 and evaporated to obtain the compounds **9a**, **9d**–**l**.

*7.1.2.1. 1-(4-Methoxybenzyloxy-phenyl)-2-(triphenylphosphosphanylidene)-ethanone (**9a**).* Yield 90.2%; White color solid; ^{1}H NMR ($CDCl_3$) δ 8.43 (d, J = 8.0 Hz, 2H), 7.96–7.91 (m, 6H), 7.77–7.65 (m, 4H), 7.67–7.62 (m, 6H), 7.48–7.42 (m, 5H), 5.21 (s, 2H), 4.46 (d, J = 24.0 Hz, 1H), 3.82 (s, 3H).

*7.1.2.2. 1-Phenyl-2-(triphenylphosphanylidene)-ethanone (**9d**).* Yield 71.3%; White color solid; ^{1}H NMR ($CDCl_3$) δ 8.00–7.97 (m, 2H), 7.75–7.69 (m, 6H), 7.56–7.45 (m, 9H), 7.36–7.34 (m, 3H), 4.44 (d, J = 24.0 Hz, 1H).

*7.1.2.3. 1-(4-Methoxy-phenyl)-2-(triphenylphosphosphanylidene)-ethanone (**9e**).* Yield 82.3%; White color solid; ^{1}H NMR ($CDCl_3$) δ 8.42 (d, J = 8.0 Hz, 2H), 7.96–7.91 (m, 6H), 7.73–7.63 (m, 9H), 6.99–6.97 (d, J = 8.0 Hz, 2H), 4.45 (d, J = 24.0 Hz, 1H), 3.86 (s, 3H).

*7.1.2.4. 1-p-Tolyl-2-(triphenylphosphosphanylidene)-ethanone (**9f**).* Yield 91.5%; White color solid; ^{1}H NMR ($CDCl_3$) δ 8.00–7.97 (m, 2H), 7.75–7.69 (m, 6H), 7.56–7.45 (m, 9H), 7.36–7.34 (m, 2H), 4.46 (d, J = 24.0 Hz, 1H), 2.35(s 3H).

*7.1.2.5. 1-(4-tert-Butyl-phenyl)-2-(triphenylphosphosphanylidene)-ethanone (**9g**).* Yield 89.3%; White color solid; ^{1}H NMR ($CDCl_3$) δ 8.32 (d, J = 8.0 Hz, 2H), 7.96–7.91 (m, 6H), 7.74–7.63 (m, 9H), 7.52 (d, J = 8.0 Hz, 2H), 4.46 (d, J = 24.0 Hz, 1H), 1.29 (s, 9H).

*7.1.2.6. 1-(4-Chloro-phenyl)-2-(triphenylphosphosphanylidene)-ethanone (**9h**).* Yield 87.7%; White color solid; ^{1}H NMR ($CDCl_3$) δ 8.32 (d, J = 8.0 Hz, 2H), 7.96–7.91 (m, 6H), 7.67–7.63 (m, 9H), 7.49 (d, J = 8.0 Hz, 2H), 4.46 (d, J = 24.0 Hz, 1H).

*7.1.2.7. 1-(4-Fluoro-phenyl)-2-(triphenylphosphosphanylidene)-ethanone (**9i**).* Yield 85.6%; White color solid; ^{1}H NMR ($CDCl_3$) δ 8.46 (d, J = 8.0 Hz, 2H), 7.96–7.91 (m, 6H), 7.76–7.65 (m, 9H), 7.14(t, J = 8.0 Hz, 2H), 4.46 (d, J = 24.0 Hz, 1H).

*7.1.2.8. 1-(4-Trifluoromethyl-phenyl)-2-(triphenylphosphosphanylidene)-ethanone (**9j**).* Yield 86.8%; White color solid; ^{1}H NMR ($CDCl_3$) δ 8.05 (d, J = 8.0 Hz, 2H), 7.74–7.69 (m, 6H), 7.61–7.56 (m, 5H), 7.51–7.47 (m, 6H), 4.45 (d, J = 24.0 Hz, 1H).

*7.1.2.9. 1-(4-Nitro-phenyl)-2-(triphenylphosphosphanylidene)-ethanone (**9k**).* Yield 94.3%; White color solid; ^{1}H NMR ($CDCl_3$) δ 8.43 (d, J = 8.0 Hz, 2H), 7.96–7.91 (m, 6H), 7.77–7.65 (m, 5H), 7.67–7.62 (m, 6H), 4.46 (d, J = 24.0 Hz, 1H).

*7.1.2.10. 4-[2-(Triphenylphosphosphanylidene)-acetyl]-benzonitrile (**9l**).* Yield 89.8%; White color solid; ^{1}H NMR ($CDCl_3$) δ 8.52 (d, J = 16.0 Hz, 2H), 7.58–7.45 (m, 15H), 7.02 (d, J = 8.0 Hz, 2H), 3.95 (d, J = 24.0 Hz, 1H).

*7.1.3. General procedure for the preparation for compound **4a**–**c***

Compound **8a**, **b** or **c** (1.0 equivalent) was added slowly to a mixture of 1-(4-methoxybenzyloxy-phenyl)-2-(triphenylphosphosphanylidene) ethanone (**9a**, 1.25 equivalent) in methylene chloride (25 mL) and then the reaction mixture was stirred overnight at ambient temperature. After evaporating the solvent under reduced pressure, ether (100 mL) was added to the residue and the resulted crystals were filtered and washed with ether. The above crystals were recrystallized from methanol and dried under vacuum to obtain the compound **10a**–**c**. Compounds **10a**, **b** or **c** were dissolved in dry methylene chloride and TFA (2 equivalent) was added at ambient temperature. The reaction mixture was stirred for 3 h, then washed with water and evaporated the solvent under reduced pressure. The crude residue was further purified by column chromatography to obtain **4a**–**c**.

*7.1.3.1. (E)-5-Methoxy-3-(3-(4-(4-methoxybenzyloxy)phenyl)-3-oxoprop-1-enyl)-4H-chromen-4-one(**10a**).* Yield 73.2%; Off-White solid; m.p. 212–216 °C; ^{1}H NMR ($CDCl_3$) δ 8.28 (d, J = 15.4 Hz, 1H), 8.20 (d, J = 8.8 Hz, 2H), 8.33 (s, 1H), 7.54 (t, J = 8.4 Hz, 1H), 7.35–7.48 (m, 5H), 7.06 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.3 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 5.16 (s, 2H), 4.02 (s, 3H), 3.82 (s, 3H).

*7.1.3.2. (E)-5-Isobutoxy-3-(3-(4-(4-methoxybenzyloxy)phenyl)-3-oxoprop-1-enyl)-4H-chromen-4-one (**10b**).* Yield 71.2%; Off-White solid; m.p. 128–130 °C; ^{1}H NMR ($CDCl_3$) δ 8.56 (d, J = 15.4 Hz, 1H), 8.12 (d, J = 8.8 Hz, 2H), 8.03 (s, 1H), 7.54 (t, J = 8.4 Hz, 1H), 7.35–7.48 (m, 5H), 7.06 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.3 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 5.16 (s, 2H), 3.90 (d, J = 6.8 Hz, 2H), 3.84 (s, 3H), 2.32 (m, 1H), 1.15 (d, J = 6.8 Hz, 6H).

*7.1.3.3. (E)-5-(Cyclohexylmethoxy)-3-(3-(4-(4-methoxybenzyloxy) phenyl)-3-oxoprop-1-enyl)-4H-chromen-4-one(**10c**).* Yield 41.4%; Off-white solid; m.p. 170–174 °C; ^{1}H NMR ($CDCl_3$) δ 8.55 (d, J = 16.0 Hz, 1H), 8.12 (d, J = 8.0 Hz, 2H), 8.04 (s, 1H), 7.55 (t, J = 8.0 Hz, 1H), 7.43 (d, J = 12.0 Hz, 1H), 7.38 (d, J = 8.0, Hz, 2H), 7.06–6.99 (m, 3H), 6.96–6.91 (m, 2H), 6.85 (d, J = 8.0 Hz, 1H), 5.08 (s, 2H), 3.94 (d, J = 4.0 Hz, 2H), 3.83 (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).

*7.1.3.4. (E)-3-(3-(4-Hydroxyphenyl)-3-oxoprop-1-enyl)-5-methoxy-4H-chromen-4-one (**4a**).* Yield 52.2.%; off white solid; m.p. 220–222 °C; R_f 0.28 (1:1 Ethyl acetate:Hexane); IR 3429, 3160, 1666, 1640, 1470, 1268, 775 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.44 (s, 1H), 8.84 (s, 1H), 8.32 (d, J = 16.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.72 (t, J = 8.0 Hz, 1H), 7.50 (d, J = 16.0 Hz, 1H), 7.19 (dd, J = 4.0, 8.0 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 8.0 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 187.56, 174.76, 162.34, 159.82, 158.00, 157.15, 134.80, 134.78, 131.03, 129.20, 123.10, 119.82, 115.60, 113.94, 110.00, 107.95, 56.26; HRMS: calculated for $C_{19}H_{14}O_5$ m/z 322.0841, Found: 322.0836.

*7.1.3.5. (E)-3-(3-(4-Hydroxyphenyl)-3-oxoprop-1-enyl)-5-isobutoxy-4H-chromen-4-one (**4b**).* Yield 44.0%; Brown solid; m.p. 141–143 °C; R_f 0.36 (4:6 Ethyl acetate:Hexane); IR 3212, 2923, 1697, 1676, 1244, 811 cm^{-11}; H NMR (DMSO-d_6) δ 8.62 (d, J = 16.0 Hz, 1H), 8.21 (s, 1H),

8.10 (s, 1H), 8.07 (d, J = 8.0 Hz, 2H), 7.59 (t, J = 8.0 Hz, 1H), 7.44 (d, J = 16.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.05 (dd, J = 4.0, 8.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 3.93 (d, J = 8.0 Hz, 2H), 2.34–2.38 (m, 1H), 1.07 (d, J = 4.0 Hz, 6H); ^{13}C NMR (DMSO-d_6) δ 187.20, 174.20, 161.90, 158.92, 156.91, 156.85, 134.34, 134.30, 130.61, 128.77, 122.47, 119.54, 115.17, 113.60, 109.31, 108.18, 74.56, 27.33, 18.64; HRMS: calculated for $C_{22}H_{20}O_5$ m/z 364.1311, Found: 364.1304.

*7.1.3.6. (E)-5-(Cyclohexylmethoxy)-3-(3-(4-hydroxyphenyl)-3-oxoprop-1-enyl)-4H-chromen-4-one (**4c**).* Yield 55.7%; Yellow color solid; m.p. 288–290 °C; R_f = 0.38 (2:8 Ethyl acetate:Hexane); IR (cm^{-1}): 3233, 2918, 2853, 1665, 1248, 788; ^{1}H NMR ($CDCl_3$) δ 8.54 (d, J = 15.4 Hz, 1H), 8.05–8.03 (m, 3H), 7.57–7.43 (m, 4H), 7.01 (d, J = 8.3 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H) 3.93 (d, J = 6.4 Hz, 2H), 2.05–2.02 (m, 3H), 1.82–1.72(m, 3H), 1.41–1.10 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 189.74, 175.90, 160.36, 157.64, 150.30, 143.01, 137.87, 134.41, 129.87, 124.55, 123.95, 120.37, 115.02, 109.79, 108.52, 75.15, 37.29, 29.90, 26.55, 25.79; HRMS: calculated for $C_{25}H_{24}O_5$: m/z 404.1624, Found: 404.1618.

*7.1.4. General procedure for the preparation for compounds **4b–j** [17]*

Compound **8c** (1.0 equivalent) were added slowly to a mixture of substituted triphenylphosphorane (**9d–l**) (1.2 equivalent) in dichloromethane (25 mL) and then the reaction mixture was stirred overnight at room temperature. After the reaction mixture was evaporated, ether (100 mL) was added to the crude residue. The resulted crystals were filtered and washed with ether again. The above crystals were recrystallized from methanol and dried under vacuum to obtain the compound **4d–l**.

*7.1.4.1. (E)-5-(Cyclohexylmethoxy)-3-(3-oxo-3-phenylprop-1-enyl)-4H-chromen-4-one (**4d**).* Yield 66.2%; White color solid; m.p. 176–178 °C; R_f = 0.4 (2:8 Ethyl acetate:Hexane); IR (cm^{-1}): 2918, 2853, 1653, 1234, 709; ^{1}H NMR ($CDCl_3$) δ 8.52 (d, J = 15.4 Hz, 1H), 8.10–8.08 (m, 2H), 8.04 (s, 1H), 7.59–7.44 (m, 4H), 7.01 (d, J = 8.3 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 3.93 (d, J = 6.4 Hz, 2H), 2.05–2.02 (m, 3H), 1.82–1.79 (m, 3H), 1.41–1.07 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 191.16, 160.15, 157.53, 156.7, 138.06, 135.77, 133.96, 132.79, 128.81, 128.53, 125.35, 120.68, 109.61, 108.19, 75.04, 37.26, 29.87, 26.55, 25.77; HRMS: calculated for $C_{25}H_{24}O_4$: m/z 388.1675, Found: 388.1670.

*7.1.4.2. (E)-5-(Cyclohexylmethoxy)-3-(3-(4-methoxyphenyl)-3-oxoprop-1-enyl)-4H-chromen-4-one (**4e**).* Yield 48.8%; White color solid; m.p. 185–187 °C; R_f = 0.38 (2:8 Ethyl acetate:Hexane); IR (cm^{-1}): 2920, 1655, 1212, 1140, 722; ^{1}H NMR ($CDCl_3$) δ 8.55(d, J = 15.4 Hz, 1H), 8.12 (d, J = 8.8 Hz, 2H), 8.03 (s, 1H), 7.54 (t, J = 8.3 Hz, 1H), 7.44 (d, J = 15.4 Hz, 1H), 7.01–6.96 (m, 1H), 6.85 (d, J = 8.3 Hz, 1H), 3.93 (d, J = 6.4 Hz, 2H), 3.89 (s, 3H), 2.06–2.01 (m, 3H), 1.82–1.70(m, 3H), 1.39–1.09 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 189.43, 175.80, 163.42, 160.42, 157.51, 156.63, 134.96, 133.90, 131.15, 131.00, 125.30, 120.73, 115.01, 113.73, 109.62, 108.12, 75.02, 55.48, 37.23, 29.86, 26.55, 25.77; HRMS calculated for $C_{26}H_{26}O_5$: m/z 418.1780, Found: 418.1775.

*7.1.4.3. (E)-5-(Cyclohexylmethoxy)-3-(3-oxo-3-p-tolylprop-1-enyl)-4H-chromen-4-one (**4f**).* Yield 45.3%; White color solid; m.p. 200–202 °C; R_f = 0.4 (2:8 Ethyl acetate:Hexane); IR (cm^{-1}): 2928, 1665, 1210, 801; ^{1}H NMR ($CDCl_3$) δ 8.84 (d, J = 8.0 Hz, 2H), 8.5 (d, J = 16.0 Hz, 1H), 8.7 (s, 1H), 7.86 (d, J = 8.0 Hz, 2H) 7.59–7.51 (m, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H) 3.94 (d, J = 8.0 Hz, 2H), 2.05–2.02 (m, 3H), 1.82–1.72(m, 3H), 1.39–1.11 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 190.90, 175.97, 160.31, 157.72, 156.84, 143.79, 135.64, 135.51, 134.09, 125.58, 120.86, 115.13, 109.75, 108.27, 75.10, 37.28, 29.90, 26.58, 25.80, 21.73; HRMS calculated for $C_{26}H_{26}O_4$: m/z 404.1831, Found: 404.1825.

*7.1.4.4. (E)-3-(3-(4-tert-Butylphenyl)-3-oxoprop-1-enyl)-5-(cyclohexylmethoxy)-4H-chromen-4-one (**4g**).* Yield 49.2%; White color solid; m.p. 236–238 °C; R_f = 0.5 (2:8 Ethyl acetate:Hexane); IR (cm^{-1}): 2918, 2853, 1665, 1653, 1220, 794; ^{1}H NMR ($CDCl_3$) δ 8.50 (d, J = 12.0 Hz, 1H), 8.06–8.03 (m, 3H), 7.55–7.50 (m, 4H), 7.00 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H) 3.93 (d, J = 8.0 Hz, 2H), 2.06–2.03 (m, 3H), 1.82–1.79(m, 3H), 1.39–1.13 (m, 16H); ^{13}C NMR ($CDCl_3$) δ 190.95, 175.93, 160.31, 157.71, 156.77, 156.71, 135.55, 134.08, 128.95, 125.65, 120.88, 115.13, 109.75, 108.25, 75.10, 37.30, 35.17, 31.18, 29.90, 26.58, 25.81; HRMS calculated for $C_{29}H_{32}O_4$: m/z 444.2301, Found: 444.2294.

*7.1.4.5. (E)-3-(3-(4-Chlorophenyl)-3-oxoprop-1-enyl)-5-(cyclohexylmethoxy)-4H-chromen-4-one (**4h**).* Yield 58.4%; White color solid; m.p. 219–221 °C; R_f = 0.4 (2:8 Ethyl acetate:Hexane); IR (cm^{-1}): 2920, 2853, 1653, 1265, 734; ^{1}H NMR ($CDCl_3$) δ 8.54 (d, J = 15.4 Hz, 1H), 8.05–8.03 (m, 3H), 7.57–7.43 (m, 4H), 7.01 (d, J = 8.3 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H) 3.93 (d, J = 6.4 Hz, 2H), 2.05–2.02 (m, 3H), 1.82–1.72(m, 3H), 1.41–1.10 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 189381, 175.73, 160.12, 157.47, 157.14, 139.21, 136.35, 136.29, 134.05, 130.23, 128.85, 124.78, 120.46, 114.93, 109.61, 108.23, 75.03, 7.23, 29.86, 26.53, 25.76; HRMS calculated for $C_{25}H_{23}ClO_4$: m/z 422.1285, Found: 422.1280.

*7.1.4.6. (E)-5-(Cyclohexylmethoxy)-3-(3-(4-fluorophenyl)-3-oxoprop-1-enyl)-4H-chromen-4-one (**4i**).* Yield 72.3%; White color solid; m.p. 190–192 °C; R_f = 0.4 (2:8 Ethyl acetate:Hexane); IR (cm^{-1}): 2900, 2853, 1665, 1653, 1201, 810; ^{1}H NMR ($CDCl_3$) δ 8.55(d, J = 15.4 Hz, 1H), 8.15–8.11 (m, 2H), 8.04 (s, 1H), 7.54 (t, J = 8.3 Hz, 1H), 7.45 (d, J = 15.4 Hz, 1H), 7.19–7.14 (m, 2H), 7.01 (d, J = 8.3 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H) 3.93 (d, J = 6.4 Hz, 2H), 2.05–2.01 (m, 3H), 1.82–1.70(m, 3H), 1.41–1.07 (m, 5H); ^{13}C NMR ($CDCl_3$) 190.15, 175.68, 160.12, 157.44, 157.37, 140.81, 136.99, 134.11, 129.04, 125.58, 125.54, 124.68, 120.34, 114.88, 109.60, 108.27, 75.02, 37.23, 29.84, 26.50, 25.74; HRMS calculated for $C_{25}H_{23}FO_4$: m/z 406.1580, Found: 406.1574.

*7.1.4.7. (E)-5-(Cyclohexylmethoxy)-3-(3-oxo-3-(4-(trifluoromethyl)phenyl)prop-1-enyl)-4H-chromen-4-one (**4j**).* Yield 52.6%; White color solid; m.p. 204–206 °C; R_f = 0.4 (2:8 Ethyl acetate:Hexane); IR (cm^{-1}): 2934, 2840, 1665, 1653, 1198. 703; ^{1}H NMR ($CDCl_3$) δ 8.52 (d, J = 15.4 Hz, 1H), 8.19 (d, J = 8.0 Hz, 2H), 8.06 (s, 1H) 7.77 (d, J = 8.3 Hz, 2H), 7.54 (t, J = 8.3 Hz, 1H), 7.48 (d, J = 15.4 Hz, 1H), 7.02 (dd, J = 1.0, 8.0 Hz, 1H) 6.87 (d, J = 7.8 Hz, 1H) 3.93 (d, J = 6.4 Hz, 2H), 2.05–2.02 (m, 3H), 1.82–1.72(m, 3H), 1.38–1.10 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 190.15, 175.68, 160.12, 157.44, 157.37, 140.81, 136.99, 134.11, 129.58, 125.54, 124.68, 120.34, 114.88, 109.60, 108.27, 75.02, 37.23, 29.84, 26.50, 25.74; HRMS calculated for $C_{26}H_{23}F_3O_4$: m/z 456.1548, Found: 456.1544.

*7.1.4.8. (E)-5-(Cyclohexylmethoxy)-3-(3-(4-nitrophenyl)-3-oxoprop-1-enyl)-4H-chromen-4-one (**4k**).* Yield 64.3%; Yellow color solid; mp. : 280–282 °C; R_f = 0.37 (2:8 Ethyl acetate:Hexane); IR (cm^{-1}): 2918, 1665, 1510, 1201, 751; ^{1}H NMR ($CDCl_3$) δ 8.60 (d, J = 15.4 Hz, 1H), 8.35 (d, J = 8.8 Hz, 2H), 8.23 (d, J = 8.8 Hz, 2H), 7.54 (t, J = 8.3 Hz, 1H), 7.49 (d, J = 15.4 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 3.94 (d, J = 6.3 Hz, 2H), 2.05–2.02 (m, 3H), 1.82–1.72 (m, 3H), 1.42–1.07 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 189.50, 175.68, 160.16,157.78, 157.44, 150.11, 142.83,137.70, 134.24, 129.71, 124.39, 123.79, 120.22, 114.87, 109.63, 108.39, 37.25, 29.86, 26.52, 25.76; HRMS calculated for $C_{25}H_{23}NO_6$: m/z 433.1525, Found: 433.1520.

*7.1.4.9. (E)-4-(3-(5-(Cyclohexylmethoxy)-4-oxo-4H-chromen-3-yl) acryloyl)benzonitrile (**4l**).* Yield 55.9%; Yellow color solid; m.p. 265–267 °C; R_f = 0.4 (2:8 Ethyl acetate:Hexane); IR (cm^{-1}): 2956, 2248, 1665, 1245, 706; ^{1}H NMR ($CDCl_3$) δ 8.56(d, J = 16.0 Hz, 1H), 8.17(d,

J = 8.0 Hz, 2H), 8.07 (s, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.59–7.46 (m, 2H), 7.03 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H) 3.94 (d, J = 8.0 Hz, 2H), 2.05–2.02 (m, 3H), 1.82–1.73 (m, 3H), 1.42–1.07 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 189.95, 175.91, 160.34, 157.88, 141.45, 137.66, 134.37, 132.60, 129.30, 124.47, 120.39, 118.33, 116.06, 115.02, 109.76, 108.48, 75.14, 37.27, 29.89, 26.54, 25.78; HRMS calculated for $C_{26}H_{23}NO_4$: m/z 413.1627, Found: 413.1623.

*7.1.5. General procedure for preparation of compounds (**5a–l**)*

Compound (**4**) (1.0 equivalent) was added to a mixture of methanol/THF (1:1) and then added $CeCl_3.7H_20$ (1.1 equivalent) and stirred the reaction mixture for 10 min at ambient temperature. Now cooled the reaction mixture to 0–5 °C and added $NaBH_4$ (1.0 equivalent) and further stirred the reaction mixture for 1 h at room temperature. The reaction solvent was evaporated under reduced pressure and the obtained crude residue was dissolved in methylene chloride and washed with water followed by brine solution. The organic layer was dried with anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography to afford the compounds **5**.

*7.1.5.1. (E)-3-(3-Hydroxy-3-(4-hydroxyphenyl)prop-1-enyl)-5-methoxy-4H-chromen-4-one(**5a**).* Yield 44.8.%; off white solid; m.p. = 174–176 °C; R_f 0.25 (4:6 Ethyl acetate:Hexane); IR 3215, 2978, 1655, 1471, 1236, 1090, 701 cm^{-1}; H NMR (DMSO-d_6) δ 7.85 (s, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 16.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.50 (m, 1H), 7.19 (dd, J = 6.5, 15.8 Hz 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 8.0 Hz, 2H), 4.63–4.67 (m, 1H), 3.91 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 187.56, 174.76, 162.34, 159.82, 158.00, 157.15, 134.80, 134.78, 131.03, 129.20, 123.10, 119.82, 115.60, 113.94, 110.00, 73.09, 56.26; HRMS: calculated for $C_{19}H_{16}O_5$ m/z 324.0998, Found: 324.0992.

*7.1.5.2. (E)-3-(3-Hydroxy-3-(4-hydroxyphenyl)prop-1-enyl)-5-isobutoxy-4H-chromen-4-one (**5b**).* Yield 65.0.%; Brown solid; m.p. = 139–141 °C; R_f 0.30 (4:6 Ethyl acetate:Hexane); IR 3212, 2961, 1655, 1478, 1236, 1098, 715 cm^{-1}; H NMR ($CDCl_3$) δ ^{1}H NMR ($CDCl_3$) δ 7.85 (s, 1H), 7.51 (t, J = 8.4 Hz, 1H), 7.18–7.25 (m, 2H), 6.96 (d, J = 8.5 Hz, 1H), 6.82–6.86 (m, 2H), 6.80 (d, J = 7.8 Hz, 1H), 6.72 (dd, J = 6.1, 15.8 Hz, 1H), 6.58 (d, J = 15.8 Hz, 1H), 5.26 (d, J = 3.6 Hz, 1H), 3.93 (d, J = 6.8 Hz, 2H), 2.24–2.38 (m, 1H), 1.06 (d, J = 6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 177.19, 161.89, 160.40, 157.94, 135.12, 134.72, 131.75, 130.50, 125.78, 120.95, 116.40, 115.98, 110.01, 108.51, 76.32, 75.71, 27.99, 19.54; HRMS: calculated for $C_{22}H_{22}O_5$ m/z 366.1467, Found: 366.1462.

*7.1.5.3. (E)-5-(Cyclohexylmethoxy)-3-(3-hydroxy-3-phenylprop-1-enyl)-4H-chromen-4-one (**5c**).* Yield 90.2%; Yellow color solid; m.p. 170–172 °C; R_f = 0.5 (3:7 Ethyl acetate:Hexane); IR (cm^{-1}): 3290, 2920, 2854, 2343, 1065, 705; ^{1}H NMR ($CDCl_3$) δ 7.82 (s, 1H), 7.50–7.41 (m, 3H), 7.37–7.34 (m, 2H), 7.29 (d, J = 4 Hz, 1H), 6.93 (dd, J = 6.1, 15.8 Hz, 1H), 6.76 (d, J = 15.8 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 5.36 (d, J = 8.0 Hz, 1H), 3.86 (d, J = 6.9 Hz, 2H), 2.03–1.95 (m, 3H), 1.79–1.69 (m, 3H), 1.39–1.06 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 176.28, 160.12, 158.25, 142.79, 133.94, 133.67, 128.72, 127.84, 126.52, 122.56, 121.23, 114.91, 109.67, 107.38, 75.43, 74.91, 37.41, 29.88, 26.57, 25.83; HRMS calculated for $C_{25}H_{26}O_4$: m/z 390.1831, Found: 390.1824.

*7.1.5.4. (E)-5-(Cyclohexylmethoxy)-3-(3-hydroxy-3-(4-hydroxyphenyl) prop-1-enyl)-4H-chromen-4-one (**5d**).* Yield 85.4%; Yellow color solid; m.p. 284–286 °C; R_f = 0.38 (3:7 Ethyl acetate:Hexane); IR(cm^{-1}): 3398, 3070, 2854, 2358, 1070; ^{1}H NMR ($CDCl_3$) δ 8.22 (d, J = 8.0 Hz, 2H), 7.83 (s, 1H), 7.62 (d, J = 15.0 Hz, 2H), 7.51 (t, J = 8.0 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.67–6.60 (m, 2H), 5.47 (d, J = 4.0 Hz, 1H), 3.88 (d, J = 8.0 Hz, 2H), 2.03–1.96 (m, 3H), 1.80–1.65 (m, 3H), 1.39–1.07 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 175.90, 160.36, 157.64, 150.30, 143.01, 137.87, 134.41, 129.87, 124.55, 123.95, 120.37, 115.02, 109.79, 108.52, 75.63, 75.15, 37.29, 29.90, 26.55, 25.79; HRMS calculated for $C_{25}H_{26}O_5$: m/z 406.1780, Found: 406.1776.

*7.1.5.5. (E)-5-(Cyclohexylmethoxy)-3-(3-hydroxy-3-(4-methoxyphenyl)prop-1-enyl)-4H-chromen-4-one (**5e**).* Yield 80.7%; Yellow color solid; m.p. 175–177 °C; R_f : 0.4 (3:7 Ethyl acetate:Hexane); IR(cm^{-1}): 3298, 3070, 2920, 2860, 2358, 1077; ^{1}H NMR ($CDCl_3$) δ 7.83 (s, 1H), 7.51–7.49 (m, 1H), 7.41–7.39 (m, 2H), 7.04 (t, J = 8.0 Hz, 2H), 6.95 (d, J = 15.4 Hz, 1H), 6.78 (dd, J = 6.9, 15.0 Hz, 1H), 6.62 (t, J = 8.0 Hz, 2H), 5.35 (d, J = 4.0 Hz, 1H), 3.87 (d, J = 4.0 Hz, 2H), 2.03–1.98 (m, 3H), 1.79–1.70 (m, 3H), 1.36–1.08 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 176.03, 163.63, 160.31, 157.71, 157.71, 156.83, 135.13, 134.07, 131.32, 131.17, 125.46, 120.46, 120.88, 115.15, 113.87, 109.76. 108.76. 108.26. 76.03. 75.11. 55.55. 37.28. 29.90. 26.58. 25.80; HRMS calculated for $C_{26}H_{28}O_5$: m/z 420.1937, Found: 420.1932.

*7.1.5.6. (E)-5-(Cyclohexylmethoxy)-3-(3-hydroxy-3-p-tolylprop-1-enyl)-4H-chromen-4-one (**5f**).* Yield 79.3%; Yellow color solid; m.p. 190–192 °C; R_f = 0.4 (3:7 Ethyl acetate:Hexane); IR(cm^{-1}): 3390, 3070, 2920, 2854, 2358, 1049; ^{1}H NMR ($CDCl_3$) δ 7.85 (s, 1H), 7.51 (t, J = 8.4 Hz, 1H), 7.18–7.25 (m, 2H), 6.96 (dd, J = 0.7, 8.5 Hz, 1H), 6.82–6.86 (m, 2H), 6.80 (d, J = 7.8 Hz, 1H), 6.72 (dd, J = 6.1, 15.8 Hz, 1H), 6.56 (d, J = 15.8 Hz, 1H), 5.41 (d, J = 4.0 Hz, 1H), 3.87 (d, J = 4.0 Hz, 2H), 2.03–1.96 (m, 3H), 1.80–1.73 (m, 3H), 1.36–1.09 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 175.97, 160.31, 157.72, 156.84, 143.79, 135.64, 135.51, 134.09, 125.58, 120.86, 115.13, 109.75, 108.27, 76.02, 75.10, 37.28, 29.90, 26.58, 25.80, 21.73; HRMS calculated for $C_{26}H_{28}O_4$: m/z 404.1988, Found: 404.1981.

*7.1.5.7. (E)-3-(3-(4-tert-Butylphenyl)-3-hydroxyprop-1-enyl)-5-(cyclohexylmethoxy)-4H-chromen-4-one (**5g**).* Yield 83.5%; Yellow color solid; m.p. 230–232 °C; R_f = 0.5 (3:7 Ethyl acetate:Hexane); IR (cm^{-1}): 3390, 3077, 2920, 2854, 2358, 1109; ^{1}H NMR ($CDCl_3$) δ 7.83 (s, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.40–7.34 (m, 4H), 6.93 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 15.4 Hz, 1H), 6.71–6.56 (m, 2H), 5.34 (d, J = 8.0 Hz, 1H), 3.86 (d, J = 8.0 Hz, 2H), 2.04–1.98 (m, 3H), 1.80–1.66 (m, 3H), 1.36–1.06 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 175.93, 160.31, 157.71, 156.77, 156.71, 135.55, 134.08, 128.95, 125.65, 120.88, 115.13, 109.75, 108.25, 76.11 75.10, 37.30, 35.17, 31.18, 29.90, 26.58, 25.81; HRMS calculated for $C_{29}H_{34}O_4$: m/z 446.2457, Found: 446.2451.

*7.1.5.8. (E)-3-(3-(4-Chlorophenyl)-3-hydroxyprop-1-enyl)-5-(cyclohexylmethoxy)-4H-chromen-4-one (**5h**).* Yield 80.2%; Yellow color solid; m.p. 210–212 °C; R_f = 0.4 (3:7 Ethyl acetate:Hexane); IR(cm^{-1}): 3398, 3070, 2920, 2854, 2358, 2343; ^{1}H NMR ($CDCl_3$) δ 7.82 (s, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.37–7.31 (m, 5H), 6.95 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 15.0 Hz, 1H), 6.61 (dd, J = 6.1, 15.0 Hz, 1H), 5.34 (d, J = 8.0 Hz, 1H), 3.87 (d, J = 4.0 Hz, 2H), 2.03–1.97 (m, 3H), 1.80–1.70 (m, 3H), 1.36–1.08 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 176.95, 160.32, 157.67, 157.34, 139.39, 136.46, 134.22, 130.39, 129.01, 124.94, 120.62, 115.08, 109.75, 108.37, 76.08, 75.12, 37.28, 29.89, 26.56, 25.79; HRMS calculated for $C_{25}H_{25}ClO_4$: m/z 424.1441, Found: 424.1436.

*7.1.5.9. (E)-5-(Cyclohexylmethoxy)-3-(3-(4-fluorophenyl)-3-hydroxyprop-1-enyl)-4H-chromen-4-one (**5i**).* Yield 79.7%; Yellow color solid; m.p. 182–184 °C; R_f = 0.4 (3:7 Ethyl acetate:Hexane); IR(cm^{-1}): 3398, 3070, 2920, 2854, 2358, 2343; ^{1}H NMR ($CDCl_3$) δ 7.83 (s, 1H), 7.51–7.49 (m, 1H), 7.41–7.39 (m, 2H), 7.04 (t, J = 8.0 Hz, 2H), 6.95 (d, J = 15.0 Hz, 1H), 6.78 (d, J = 15.0 Hz, 1H), 6.62 (t, J = 8.0 Hz, 2H), 5.35 (d, J = 4.0 Hz, 1H), 3.87 (d, J = 4.0 Hz, 2H), 2.03–1.98 (m, 3H), 1.79–1.70 (m, 3H), 1.36–1.08 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 175.93, 160.35, 157.67, 157.59, 141.01, 137.18, 134.31, 129.23, 125.77, 124.86, 120.52, 109.76, 108.43, 76.06, 75.14, 37.30, 29.90,

26.56, 25.79; HRMS calculated for $C_{25}H_{25}FO_4$: *m*/*z* 408.1737, Found: 408.1734.

*7.1.5.10. (E)-5-(Cyclohexylmethoxy)-3-(3-hydroxy-3-(4-(trifluoromethyl)phenyl)prop-1-enyl)-4H-chromen-4-one (**5j**).* Yield 79.3%; Yellow color solid; m.p. 190–192 °C; R_f = 0.4 (3:7 Ethyl acetate:-Hexane); IR(cm^{-1}): 3398, 3070, 2920, 2854, 2358, 2343; ^{1}H NMR ($CDCl_3$) δ 7.83 (s, 1H), 7.52–7.47 (m, 2H), 7.42–7.39 (m, 1H), 7.24 (d, *J* = 15.2 Hz, 1H), 6.96 (d, *J* = 15.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 2H), 6.62–6.58 (m, 2H), 5.31 (d, *J* = 8.0 Hz, 1H), 3.87 (d, *J* = 8.0 Hz, 2H) 2.03–1.99 (m, 3H), 1.79–1.70 (m, 3H), 1.39–1.06 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 175.95, 167.12, 164.59, 160.32, 157.67, 157.22, 136.18, 134.18, 131.62, 131.53, 125.03, 120.65, 115.87, 120.65, 115.87, 115.65, 115.08, 109.75, 108.34, 75.19, 75.11, 37.28, 29.89, 26.56, 25.79; HRMS calculated for $C_{26}H_{25}F_3O_4$: *m*/*z* 458.1705, Found: 458.1700.

*7.1.5.11. (E)-5-(Cyclohexylmethoxy)-3-(3-hydroxy-3-(4-nitrophenyl) prop-1-enyl)-4H-chromen-4-one (**5k**).* Yield 83.5%; Yellow color solid; m.p. 275–277 °C; R_f : 0.37 (3:7 Ethyl acetate:Hexane); IR(cm^{-1}): 3398, 3070, 2920, 2854, 2358, 2343; ^{1}H NMR ($CDCl_3$) δ 8.21 (d, *J* = 8.0 Hz, 2H), 7.82 (s, 1H), 7.61 (d, *J* = 15.2 Hz, 2H), 7.50 (t, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.66–6.59 (m, 2H), 5.46 (d, *J* = 4 Hz, 1H), 3.87 (d, *J* = 8.0 Hz, 2H), 2.02–1.95 (m, 3H), 1.79–1.64 (m, 3H), 1.38–1.06 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 175.90, 160.36, 157.98, 157.64, 150.30, 143.01, 137.87, 134.41, 137.87, 134.41, 129.87, 124.55, 123.95, 120.37, 115.02, 109.77, 108.52, 76.65, 75.15, 37.29, 29.90, 26.55, 25.79; HRMS calculated for $C_{25}H_{25}NO_6$: *m*/*z* 435.1682, Found: 435.1678.

*7.1.5.12. (E)-4-(3-(5-(Cyclohexylmethoxy)-4-oxo-4H-chromen-3-yl)-1-hydroxyallyl)benzonitrile (**5l**).* Yield 79.0%; Yellow color solid; m.p. 259–261 °C; R_f = 0.4 (3:7 Ethyl acetate:Hexane); IR (cm^{-1}): 3398, 3070, 2920, 2854, 2358, 2343; ^{1}H NMR ($CDCl_3$) δ 7.83 (s, 1H), 7.66–7.64 (m, 2H), 7.56–7.48 (m, 3H), 6.95 (d, *J* = 15.0 Hz, 1H), 6.79 (d, *J* = 15.0 Hz, 1H), 6.63 (t, *J* = 8.0 Hz, 2H), 5.41 (d, *J* = 4.0 Hz, 1H), 3.87 (d, *J* = 8.0 Hz, 2H) 2.03–1.96 (m, 3H), 1.80–1.70 (m, 3H), 1.36–1.09 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 189.95, 175.91, 160.34, 157.88, 141.45, 137.66, 134.37, 132.60, 129.30, 124.47, 120.39, 118.33, 116.06, 115.02, 109.76, 108.48, 75.14, 37.27, 29.89, 26.54, 25.78; HRMS calculated for $C_{26}H_{25}NO_4$: *m*/*z* 415.1784, Found: 415.1780.

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References

[1] A.B. Kay, J. Allergy Clin. Immunol. 87 (1991) 893–910.
[2] A. Trautmann, P. Schmid-Grendelmeier, K. Krüger, R. Crameri, M. Akdis, A. Akkaya, E.–B. Bröcker, K. Blaser, C.A. Akdis, J. Allergy Clin. Immunol. 109 (2002) 329–337.
[3] G.J. Gleich, H. Kita, C.R. Adolphson, Eosinophils, in: M. N.Frank, K.F. Austen, H.N. Cloman, E.R. Inanue (Eds.), Samters Immunologic Diseases, fifth ed., Little Brown Co., Boston, 1995, pp. 205–245.
[4] E. Clutterbuck, J.G. Shields, J. Gorden, S.H. Smith, A. Boyd, R.E. Callard, H.D. Campbell, I.G. Young, C.J. Sanderson, Eur. J. Immunol. 17 (1987) 1743–1750.
[5] E.J. Clutterbuck, E.M.A. Hirst, C.J. Sanderson, Blood 73 (1989) 1504–1512.
[6] E.J. Clutterbuck, C.J. Sanderson, Blood 75 (1990) 1774–1779.
[7] A.N.J. Mckenzie, B. Ely, C.J. Sanderson, Mol. Immunol. 28 (1991) 155–158.
[8] A.R. Gulbenkian, R.W. Egan, X. Fernandez, H. Jones, W. Kreutner, T.T. Kung, F. Payvandi, L. Sullivan, J.A. Zurcher, A.S. Watnick, Am. Rev. Respir. Dis. 146 (1992) 263–265.
[9] T.T. Kung, D. Stelts, J.A. Zurcher, A.S. Watnick, H. Jones, P.J. Mauser, X. Fernandez, S. Umland, W. Kreutner, R.W. Chapman, R.W. Egan, J. Allergy Clin. Immunol 94 (1994) 1217–1224.
[10] P.J. Mauser, A. Pitman, A. Witt, X. Fernandez, J. Zurcher, T.T. Kung, H. Jones, A.S. Watnick, R.W. Egan, W. Kreutner, G.K. Adams III, Am. Rev. Respir. Dis. 148 (1993) 1623–1627.
[11] P.J. Mauser, A.M. Pitman, X. Fernandez, S.K. Foran, G.K. Adams III, W. Kreutner, R.W. Egan, R.W. Chapman, Am. J. Respir. Crit. Care Med. 152 (1995) 467–472.
[12] G.J. Gleich, C. Adolphson, Agents Actions Suppl. 43 (1993) 223–230.
[13] M. Azzawi, B. Bradley, P.K. Jeffery, A.J. Frew, A.J. Wardlaw, G. Knowles, B. Assoufi, J.V. Collins, S. Durham, A.B. Kay, Am. Rev. Respir. Dis. 142 (1990) 1407–1413.
[14] M. Azzawi, P.W. Johnston, S. Majumdar, A.B. Kay, P.K. Jeffery, Am. Rev. Respir. Dis. 145 (1992) 1477–1482.
[15] A.M. Bentley, G. Menz, C. Storz, D.S. Robinson, B. Bradley, P.K. Jeffery, S.R. Durham, A.B. Kay, Am. Rev. Respir. Dis. 146 (1992) 500–506.
[16] R. Devos, Y. Guisez, G. Plaetinck, S. Cornelis, J. Traverier, J. Van der Heyden, C.H. Florey, J.E. Scheffler, Eur. J. Biochem 225 (1994) 635–640.
[17] B. Min, S.H. Oh, H.K. Lee, K. Takatsu, I.M. Chang, K.R. Min, Y. Kim, Planta Med. 65 (1999) 408–412.
[18] J. Yun, C.K. Lee, I.M. Chang, K. Takatsu, T. Hirano, K.R. Min, M.K. Lee, Y. Kim, Life Sci. 67 (2000) 2855–2863.
[19] S.H. Jung, S.H. Cho, T.H. Dang, J.H. Lee, J.H. Ju, M.K. Kim, S.H. Lee, J.C. Ryu, Y. Kim, Eur. J. Med. Chem. 38 (2003) 537–545.
[20] H.M. Yang, H.R. Shin, S.C. Bang, K.C. Lee, L.T.A. Hoang, I.J. Lee, Y. Kim, S.H. Jung, Arch. Pharmacal. Res. 30 (2007) 950–954.
[21] H.M. Yang, H.R. Shin, S.H. Cho, G.Y. Song, I.J. Lee, M.K. Kim, S.H. Lee, J.C. Ryu, Y. Kim, S.H. Jung, Arch. Pharmacal. Res. 29 (2006) 969–976.
[22] H.M. Yang, H.R. Shin, S.H. Cho, G.Y. Song, I.J. Lee, M.K. Kim, S.H. Lee, J.C. Ryu, Y. Kim, S.-H. Jung, Bioorg. Med. Chem. 15 (2007) 104–111.
[23] P. Thanigaimalai, T.A.-L. Hoang a, K.-C. Lee, V.K. Sharma, S.-C. Bang, J.H. Yun, E. Roh, Y. Kim, S.-H. Jung, Eur. J. Med. Chem. 45 (2010) 2531–2536.
[24] H. Kuroda, E. Hanaki, H. Izawa, M. Kano, H. Itahashi, Tetrahedron 60 (2004) 1913–1920.
[25] S. Lopes, C.M. Nunes, A. Gomez-Zavaglia, T.M.V.D. Pinho e Melo, R. Fausto, Tetrahedron 67 (2011) 7794–7804.
[26] Tripos Associates, SYBYL®-X1.3, Molecular Modeling Software, Tripos Associates, St. Louis, MO, 2011.http://www.tripos.com.
[27] M. Clark, R.D. Cramer III, N. van Opdenbosch, J. Comput. Chem. 10 (1989) 982–1012.
[28] W.P. Purcell, J.A. Singer, J. Chem. Eng. Data 12 (1967) 235–246.
[29] D.D. Perrin, W.L.F. Armarego, D.R. Perrin, Purification of Laboratory Chemicals, second ed., Pergamon Press, Oxford, England, 1982.