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Exploration of benzamidochromenone derivatives with conformational restrictor as interleukin-5 inhibitors

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ABSTRACT

Novel amidochromen-4-one analogs **8a–k** and **9a–f** were prepared and studied for their IL-5 inhibitory activity. Among the synthesized compounds, (6-benzamido-2-cyclohexyl-4-oxo-4*H*-chromen-3-yl)methyl acetate (**8a**, 95% inhibition at 30 μM, IC_{50} = 6.1 μM) exhibited potent IL-5 inhibitory activity. The conformational restrictor at position 2 like bulky cyclohexyl group is favorable for the formation of effective conformer of side chain small ester like acetoxymethyl at position 3 of these chromenone analogs **8**. In addition the hydrophobic planarity of benzamido group at position 6 should be important for the potent IL-5 inhibitory activity. Since replacing acetoxymethyl moiety with hydroxymethyl group at position 3 of chromenone decreases the activity, which indicates that the location of hydrogen bonding group should be near 4 atom distances away from chromenone ring is more optimum for the activity. Therefore, these benzamidochromen-4-one analogs **8** are novel scaffold for finding potent interleukin-5 inhibitors.

1. Introduction

Allergic diseases are the most common chronic diseases among all ages affecting approximately 300 million people worldwide.[1] In these classes, asthma is the leading disease which is caused due to overexpression of interleukin-5 (IL-5). IL-5 is an eosinophil-specific cytokine that stimulates eosinophil production, function and survival which is involved in haematopoiesis and inflammation.[2–5] IL-5 also has the ability to influence inflammatory diseases, such as atopic dermatitis and allergic rhinitis.[6] IL-5 is not only important for the terminal differentiation of eosinophils but is also responsible for the activation of mature eosinophils which are major effectors in allergic inflammation. Eosinophil appears to increase levels of eosinophil granular proteins and production of leukotriene C_4 (LTC_4) and superoxide. Eosinophil granular proteins (such as major basic protein (MBP), eosinophil cationic protein (ECP) and eosinophil peroxidase (EPO)) when combined with H_2O_2 and a halide reportedly damages respiratory epithelium in guinea pigs.[7] Leukotrienes (LTs), in particular LTC_4, LTD_4 and LTE_4, have been proved to participate in the progression of edema formation, mucus secretion, and muscle contraction in the pathogenesis of asthma.[8] Thus inhibition of IL-5 bioactivity could be a good strategy to control allergic diseases.

We have investigated various isoflavonoids (**1**)[9,10] and chalcone derivatives (**2**)[11,12] as inhibitors of IL-5 (Fig. 1). The important features of these isoflavonoid or chalcone derivatives for their potent IL-5 inhibitory activity require the bulky cyclohexylmethyl group at position 5 of ring A and phenolic hydroxy group at 4-position of ring B.[9–12] In addition a number of novel chromenone analogs (**3**, Fig. 1) with insertion of methylene between phenyl and chromenone were prepared and evaluated.[13] Along this line, novel 3-((1-cyclohexyl-3-hydroxypropan-2-ylamino)methyl)-5-(cyclohexylmethoxy)-4*H*-chromen-4-one (**4**, Fig. 1) were also investigated as inhibitors of IL-5.[14] The chromenone with 2-hydroxyethylaminomethyl group did not show any activity. However, the activity was improved on introduction of bulky hydrophobic group at 1-position of 2-hydroxyethylamino moiety. These results confirmed the role of ring B of isoflavone as a simple linker between chromenone and hydroxyl function. Since these hydroxyethylaminomethylchromenone derivatives gave a new direction to our research for finding potent IL-5 inhibitor, we investigated novel N-substituted derivatives **5**[14] with better activity than hydroxyethylaminomethylchromenone[15] **4** but they have poor solubility in water. In order to overcome this limitation as well as enhancing the activity, we had synthesized a series of novel hybrid chromenone[16] derivatives **6** (Fig. 1) for their IL-5 inhibitory activity. However, these hybrid chromenones showed moderate activity. Further modification of hybrid chromenone **6** to allylic alcohol analogs **7** gave more potent inhibition. Comparison of 3D

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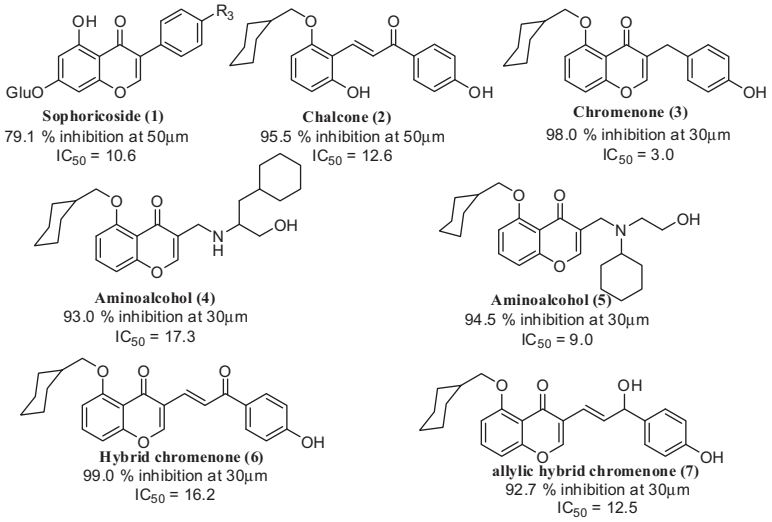


Figure 1. Interleukin-5 inhibitors.

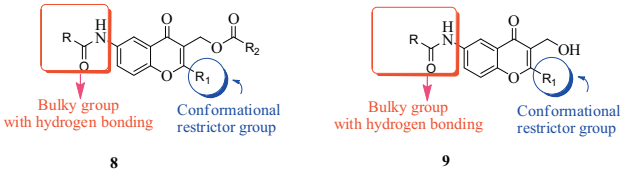


Figure 2. Current design of benzamidochromenones.

conformation of **6** and **7** showed much differences.[17] The carbonyl function of α,β-unsaturated ketones moiety of **6** is stretched away from the chromenone ring. Meanwhile the corresponding angles of **7** depict that hydroxy group allylic alcohol moiety of **7** is located nearly at right angle position in chromenone ring plane. Thus the twisted form as shown in **7** appears as effective conformation.

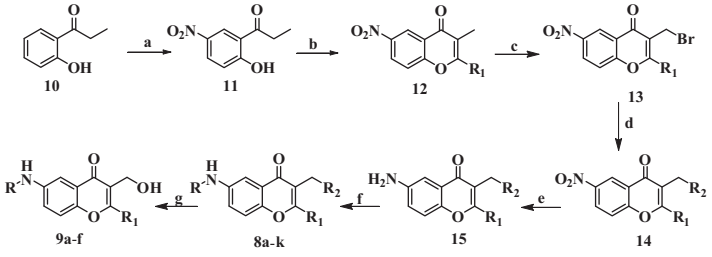
In this regard, introduction of bulky substituent on position 2 of chromenone ring might enforce to locate hydrogen bonding group of side chain at position 3 of chromenone ring into effective position. Additionally, location of hydrophobic group at position 5 of chromenones was proved to move to position 7 without affecting the activity.[14] Hydrophobic amide groups at position 6 for more effective structural variation were considered in design of new analogs. Therefore we designed and synthesized a series of novel amidochromen-4-one analogs (**8** and **9**) as shown in Figure 2 and tested their IL-5 inhibitory activity using Y-16 cell based assay.

2. Chemistry

The syntheses of the designed compounds **8a–k** and **9a–f** were accomplished as outlined in Scheme 1. The nitration of commercially available 2-hydroxypropiophenone (**10**) using nitric acid in acetic acid at ambient temperature yielded compound **11**, which was reacted with appropriate acid chloride in DMF at 60–70 °C gave chromen-4-ones **12**. The chromenone **12** was then brominated using *N*-bromosuccinimide (NBS) in presence of 2,2′-azobis(2-methylpropionitrile) (AIBN) as a catalyst in carbon tetrachloride at reflux temperature gave bromomethyl compounds **13** in excellent yield. The bromo compounds **13** were then treated with various potassium salts of appropriate acids in DMF at room temperature produced chromenone esters **14** with good yield. Subsequent treatment of compounds **14** with hydrogen in the presence of Pd/C in THF and methanol provided the key intermediates amine derivatives **15**, which were further used without purification. The amine intermediates **15** were treated with benzoyl chloride to produce compounds **8a–f** and **8j–k**. Compound **8g** was prepared by reacting of amine **15** with benzyl bromide. Compound **8h** was obtained by treating of **15** with phenylisocynate and **8i** was produced by reacting of **15** with benzenesulfonyl chloride. All the above amidochromen-4-one esters were treated with aqueous LiOH solution in methanol at room temperature for 1 h to yield chromenone alcohols **9a–f**. All compounds obtained are listed in Table 1.

3. Pharmacology

Inhibitory activity of the chromenone analogs (**8a–k** and **9a–f**) against IL-5 was evaluated using the IL-5-dependent pro-B Y16 cell line according to the previously reported procedure.[18] The cells were incubated with 3 units/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-



Scheme 1. Synthesis of chromenone analogs **8a–k** and **9a–f**. Reagents and conditions: (a) Nitric acid, CH_3COOH, rt; (b) RCOCl, K_2CO_3, DMF 80–90 °C; (c) NBS, CCl_4, AIBN, reflux; (d) R_2COONa, DMF; (e) 10% Pd/C, H_2 gas, MeOH, rt; (f) RCOCl, benzenesulfonyl chloride or phenylisocynate, TEA, methylene chloride, 0–5 °C; (g) LiOH, MeOH, rt. Substituents are listed in Table 1.