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Design, synthesis and evaluation of dual pharmacology β_2-adrenoceptor agonists and PDE4 inhibitors

Ling Huang [a], Wenjun Shan [c], Qi Zhou [a], Jiaxing Xie [b], Kefang Lai [b,*], Xingshu Li [a,*]

[a] Institute of Drug Synthesis and Pharmaceutical Process, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China
[b] State Key Laboratory of Respiratory Diseases, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510120, China
[c] Jiangsu Hansoh Pharmaceutical Research Institute Co., Ltd, Lianyungang 222000, China

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ABSTRACT

A novel series of formoterol–phthalazinone hybrids were synthesised and evaluated as dual pharmacology β_2-adrenoceptor agonists and PDE4 inhibitors. Most of the hybrids displayed high β_2-adrenoceptor agonist and moderate PDE4 inhibitory activities. The most potent compound, (*R*,*R*)-**11c**, exhibited agonist (EC_{50} = 1.05 nM, pEC_{50} = 9.0) and potent PDE4B2 inhibitory activities (IC_{50} = 0.092 μM).

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease that affects millions of people worldwide. COPD is characterised by limited airflow to and from the lungs, which is not fully reversible.[1] Although the aetiology of COPD remains to be fully understood, smooth muscle dysfunction and chronic inflammation are known to play important roles in the pathophysiology of the disease. Smooth-muscle dysfunction results in exaggerated bronchoconstriction, bronchial hyperresponsiveness, excessive proliferation (hyperplasia), and excessive growth (hypertrophy) of the airway smooth-muscle cells[2] and release of proinflammatory mediators.[3]

β_2-Adrenoceptor agonists induce bronchodilatory effects mediated by the relaxation of airway smooth muscles by increasing cAMP. Thus, inhaled β_2 adrenoceptor agonists are widely used to treat asthma and COPD, providing symptomatic relief by inducing bronchodilation via the relaxation of airway smooth muscle.[4] Currently, salbutamol (a typically short-acting agonist with a rapid onset of action), salmeterol and formoterol (the two most prescribed inhaled long-acting β_2-agonists) are clinically used as β_2-agonists. In addition, a once-daily β_2-agonist indacaterol has been approved in the USA and Europe for the treatment of COPD.

In recent years, PDE4 has been examined as a suitable target for anti-inflammatory therapy to treat respiratory diseases.[5,6] PDE4 inhibitors have been reported to downregulate inflammatory cell activity in vitro[7,8] and exhibit anti-inflammatory and bronchodilatory activity in animal models.[9] These therapeutic effects could be used in the development of new agents, such as steroid-sparing compounds, to treat diseases associated with chronic airway inflammation, particularly in the management of asthma and COPD.[10]

The multifaceted conditions of some diseases have led to the development of multifunctional drugs. These drugs possess two or more complementary biological activities and may represent an important advancement in the treatment of diseases.[11–13] Using a multivalent approach to drug discovery, Hughes et al. designed and synthesised dual pharmacology molecules that function as bronchodilators (Fig. 1, **1**) and target both the M3 muscarinic acetylcholine and β_2-adrenergic receptors.[11] Jones et al. designed and developed of dual pharmacology β_2 agonists–M3 antagonists (Fig. 1, **2**) for the treatment of COPD.[14]

Recently, we used a multivalent approach to synthesise a class of dual pharmacology bronchodilators (Fig. 1, **3**) that target both the β_2-adrenoceptor and PDE4.[15] Here, we present the synthesis and evaluation of a new series of hybrids that in one molecule combine both formoterol, which is one of the two most prescribed inhaled long-acting β_2-agonists, and the PDE4 inhibitor phthalazinone (Fig. 2).

The synthetic route of dual β_2-agonists and PDE4 inhibitors (**11a**–**11c**) is shown in Scheme 1. 1,2-Dimethoxybenzene was reacted with 1,2-cyclohexanedicarboxylic anhydride to afford a ketone acid **4**, which was subsequently reacted with hydrazine to

* Corresponding authors. Tel./fax: +86 20 3994 3050.
E-mail addresses: lixs@mail.sysu.edu.cn, lixsh@mail.sysu.edu.cn (X. Li).

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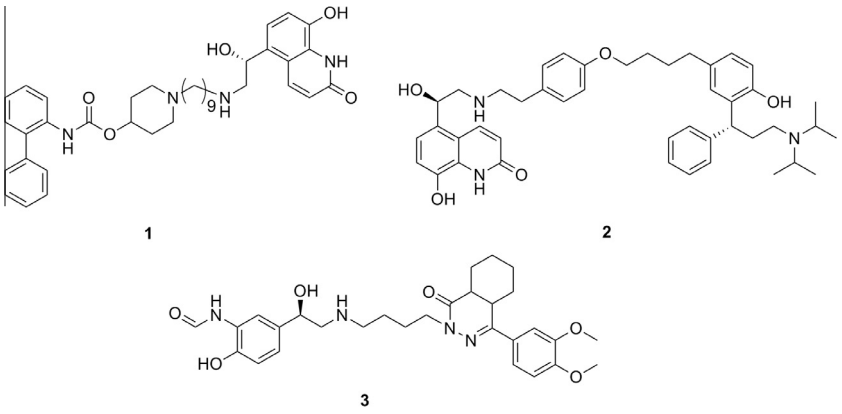


Figure 1. Structures of reported dual pharmacology bronchodilators for the treatment of asthma or COPD.

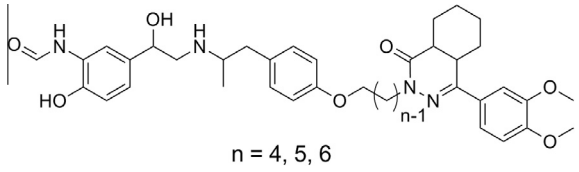


Figure 2. The synthesised β_2-adrenoceptor agonists-PDE4 inhibitors.

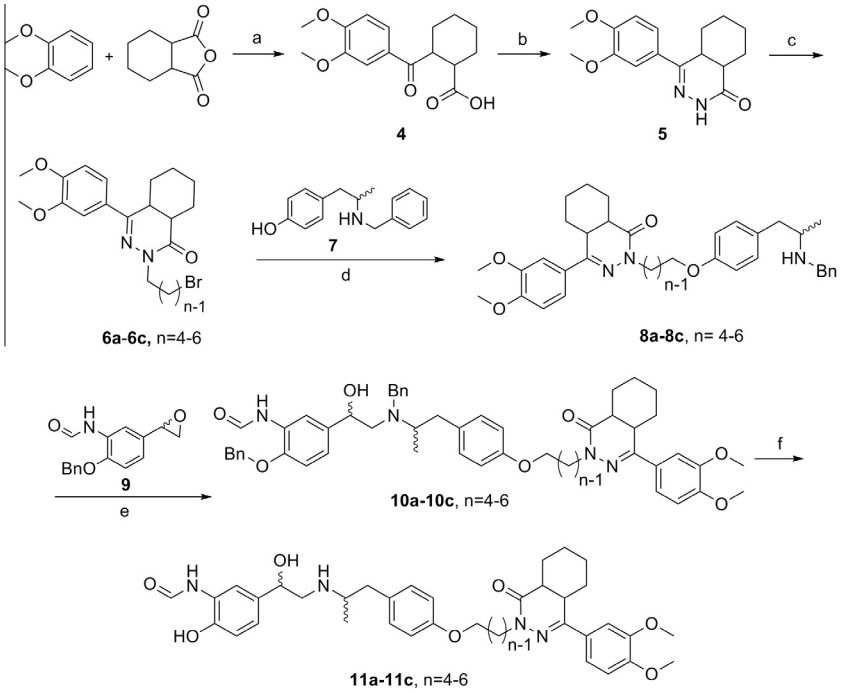
yield the known PDE4 inhibitor 4-(3,4-dimethoxyphenyl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (**5**).[16,17] *N*-Alkyl phthalazinones **6a–6c** were obtained by treating compound **5** with dibromoalkanes and NaH in DMF. The intermediates were then reacted with 4-(2-(benzylamino)propyl)phenol (**7**) to provide compounds **8a–8c**. Finally, the target compounds (**11a–11c**) were obtained by coupling epoxide **9** with compounds **8a–8c** followed by deprotection via hydrogenation in the presence of Pd/C.

The racemic secondly amine **7** was synthesised in a one-pot reaction reductive hydrogenation and subsequent O-demethylation reaction in an overall yield of 72% (Scheme 2).

Epoxide intermediate **9**, the intermediate containing the pharmacophore of the β_2-adrenoceptor agonist, was prepared using commercially available 4-hydroxy-3-nitro-acetophenone in several steps according to previously reported procedures (Scheme 3).[18]

In order to investigate the relationship between the chiral center of the compounds and the activity of the β_2-adrenoceptor, an enantiomer of **11c**, (*R*,*R*)-**11c**, was synthesized using enantiopure secondly amine (*R*)-**7** and enantiopure epoxide (*R*)-**9** as the intermediates according to the synthetic route shown in Scheme 1. (*R*)-**7** and (*R*)-**9** were prepared according to procedures reported previously.[18]

For studying the in vitro β_2-adrenoceptor agonist activity of target compounds, The effects of **11a–11c** and (*R*,*R*)-**11c** on the tracheal rings of guinea pigs were assessed using (*R*,*R*)-formoterol according to a previously described protocol.[19,20] The concentration–response curves are showen in Figure 3 and the EC_{50} and pEC_{50} values are summarized in Table 1. The maximum relaxant effect exhibited by Isoproterenol was considered to be 100%. The EC_{50} values were estimated from the concentration–response



Scheme 1. Synthetic scheme for synthesis of dual β_2-adrenoceptor agonists-PDE4 inhibitors. Reagents and conditions: (a) $AlCl_3$, CH_2CH_2, reflux, 76%; (b) NH_2NH_2, EtOH, reflux, 32%; (c) $Br(CH_2)_nBr$, NaH, DMF, rt, 80–88%; (d) **7**, K_2CO_3, DMF, 60 °C, 60–65%; (e) **9**, neat, 120 °C, 55–61%; (f) 10% Pd/C, H_2, MeOH, rt, 58–65%.