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8-Methoxyquinoline-5-carboxamides as PDE4 Inhibitors: A Potential Treatment for Asthma

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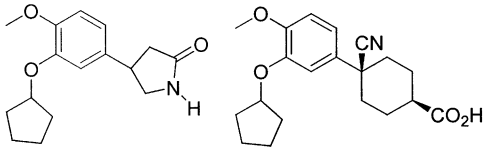
Abstract—A series of bicyclic heteroaryl ring systems was considered as a replacement for the 3-cyclopentyloxy-4-methoxyphenyl moiety in rolipram resulting in the discovery of 8-methoxyquinoline-5-carboxamides as potent inhibitors of phosphodiesterase type 4 (PDE4).

Phosphodiesterase enzymes are responsible for the inactivation of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). Phosphodiesterase 4 (PDE4) is a cAMP specific phosphodiesterase expressed in inflammatory cells, such as eosinophils, and airway smooth muscle. Inhibition of PDE4 results in an elevation of cAMP, which in turn downregulates the inflammatory response.[1] The potential use of PDE4 inhibitors as anti-inflammatory agents for the treatment of asthma has received considerable interest from the pharmaceutical industry.[2] Early PDE4 inhibitors typified by *rolipram*[3] caused dose-limiting side effects, such as nausea and emesis. Recent evidence suggests a correlation between these side effects and the ability to bind at the so-called high affinity rolipram binding site,[4] whilst beneficial effects appear to correlate with binding at the catalytic site.[5] Modifications to the structure of rolipram have been carried out to identify novel PDE4 inhibitors devoid of side effects. To date, the most advanced PDE4 inhibitors are cilomilast (Ariflo, SB-207499) and roflumilast (Byk Gulden), which are now in phase III trials in the clinic.[6]



Rolipram **Cilomilast**

Our objective was to identify PDE4 inhibitors with good selectivity for the catalytic site over the high affinity rolipram binding site. Since inhibition of PDE3 may result in cardiotoxicity, selectivity for PDE4 over the PDE3 isozyme is also important.[7]

Our first replacement for the 3,4-dialkoxyphenyl unit in rolipram was the 7-methoxybenzofuran moiety. To investigate the effect of this change, a series of 2-substituted 7-methoxybenzofuran-4-carboxylic acid (3,5-dichloropyridin-4-yl)amides was prepared and screened in our in vitro assays. These results have been reported in an earlier publication.[8] The best compound from this series in terms of activity and selectivity was the 2-acetyl derivative **1** (Table 1).

As can be seen, a very potent, selective inhibitor of PDE4 was obtained by making this replacement. However, despite being efficacious in the guinea pig skin model,[11] this compound was found to have a poor pharmacokinetic profile. Other examples from this series

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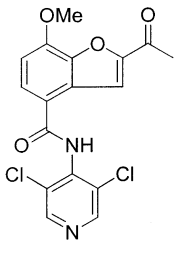
Table 1. Rolipram versus 2-acetylbenzofuran[a]



1

	PDE4 IC_{50}[9]	RBA IC_{50}[10]	PDE4/RBA	PDE3[b] (%)
Rolipram	3.5	0.02	175	27
1	0.001	0.02	0.05	32

[a]Values are shown as IC_{50} (μM) or percent inhibition at 20 μM and are the means of at least two experiments. RBA, rolipram binding assay.
[b]PDE4 was obtained from human U937 cells, rolipram binding protein was obtained from rat brain tissues and PDE3 was obtained from human platelets.

had similar drawbacks. Further modifications to the 2-substituent of the 7-methoxybenzofuran-4-carboxamide series are reported elsewhere.[12] Similarly our attempts to improve the pharmacokinetic profile by incorporation of a nitrogen atom into the benzofuran ring system to give a novel series of 2-ethyl-7-methoxyfuro[2,3-*c*]-pyridine-4-carboxamides are reported in a separate publication.[13]

In view of the disappointing pharmacokinetic properties of the benzofurans, alternative biaryl heterocycles were considered as replacements. It was thought that incorporating one or more nitrogens in the ring system would improve the solubility and hence the pharmacokinetics. Therefore the first replacement considered was the benzimidazole. Various 2- and 3-substituted analogues were prepared giving a series of 7-methoxybenzimidazole-4-carboxylic acid (3,5-dichloropyridin-4-yl)amides **2**.

These compounds were tested in our in vitro assays (Table 2).

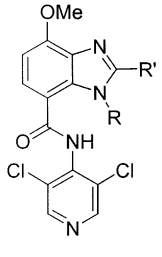
From these results it would appear that a 2-substituent is essential for activity against PDE4. Unfortunately even the 2-substituted 7-methoxybenzimidazoles are only moderately potent PDE4 inhibitors compared to the 2-substituted benzofuran **1**. Also the PDE4 activity to rolipram binding ratio is not acceptable and in many cases favoured rolipram binding. Thus this series of benzimidazoles was not investigated further.

However, the pharmacokinetic profile of the benzimidazoles had been found to be an improvement over that of the benzofurans. Therefore we were encouraged to consider other nitrogen-containing systems, such as quinolines. A series of 8-methoxyquinoline-4-carboxamides **3** was prepared and screened in our in vitro assays to examine the effect of this replacement and to explore substitution on the pyridin-4-yl moiety (Table 3).

Clearly, the unsubstituted pyridine analogue **3a** does not reach the required levels of potency against PDE4. However, despite not being as potent as many of the benzofurans, both the mono- and dichloro-substituted 8-methoxyquinoline-4-carboxylic acid (pyridyl-4-yl)amides **3b**,**3c** have acceptable levels of activity against PDE4. In addition, although the absolute potency is very similar to that of the best of the benzimidazoles, the ratio of activity against PDE4 to rolipram binding is far more suitable.

The preparation of 8-methoxyquinoline-4-carboxylic acid (3,5-dichloropyridyl-4-yl)amide **3c** was achieved via a simple three-step synthesis. Thus commercially available 3-amino-4-methoxybenzoic acid **4** is subjected to the usual Skraup conditions resulting in 8-methoxyquinoline-4-carboxylic acid **5**. This acid is converted to acid chloride **6** using thionyl chloride, which on treatment with the anion of 4-amino-3,5-dichloropyridine (preformed using sodium hydride in DMF) resulted in formation of the desired amide **3c** (Scheme 1).

Table 2. Benzimidazoles[a]



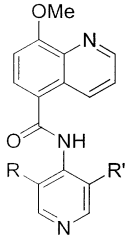
2

a R=Me, R'=$COCH_3$
b R=Me, R'=CF_3
c R=Me, R'=H
d R=H, R'=CF_3

	PDE4 IC_{50}[9]	RBA IC_{50}[10]	PDE4/RBA	PDE3 (%)
2a	0.48	0.20	2.4	NT
2b	0.29	0.46	0.63	11
2c	IA	NT	NA	NT
2d	0.12	0.02	6	43

[a]Values are shown as IC_{50} (μM) or percent inhibition at 20 μM and are the means of at least two experiments. RBA, rolipram binding assay; IA, inactive; NT, not tested; NA, not applicable.

Table 3. Quinolines[a]

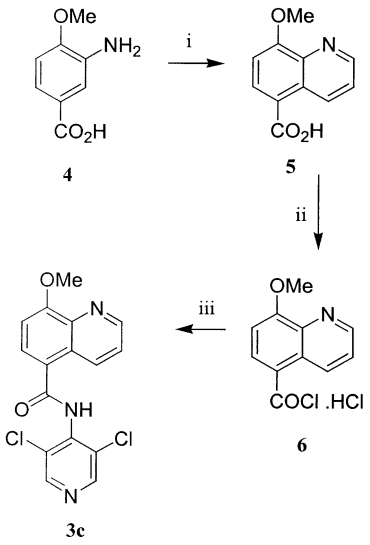


3

a R=H, R'=H
b R=H, R'=Cl
c R=Cl, R'=Cl

	PDE4 IC_{50}[9]	RBA IC_{50}[10]	PDE4/RBA	PDE3 (%)
3a	1.9	6.3	0.30	NT
3b	0.11	0.48	0.23	NT
3c	0.17	0.53	0.32	10

[a]Values are shown as IC_{50} (μM) or percent inhibition at 20 μM and are the means of at least two experiments. RBA, rolipram binding assay.



Scheme 1. Reagents and conditions: (i) glycerol, concd H_2SO_4, I_2, reflux; (ii) $SOCl_2$; (iii) 4-amino-3,5-dichloropyridine, NaH, DMF.

Given the potency and selectivity achieved, the dichloro-substituted compound **3c** was selected for in vivo studies. Pharmacokinetic studies in the guinea pig dosing at 5 mg/kg po showed a C_{max} of 473 ng/mL and an AUC of 925 ng h/mL. The oral bioavailability was found to be 62% and the iv half-life was 0.6 h.

The compound was then evaluated in a guinea pig lung eosinophilia model.[14] When administered orally at 30 mg/kg, the compound showed significant levels of inhibition of eosinophil influx and hyper-reactivity.

The compound was also assessed for emetic and CNS side effects in a ferret emesis model.[15] Neither emesis nor CNS effects were observed when the compound was dosed orally at 60 mg/kg indicating a significant difference between the efficacious and emetic doses.

In summary, we have identified 8-methoxyquinoline-4-carboxylic acid (3,5-dichloropyridyl-4-yl)amide **3c** as a potent, selective PDE4 inhibitor. The compound has a good pharmacokinetic profile and shows reasonable levels of oral activity in a functional model of inflammation. Compared to some of the early PDE4 inhibitors such as rolipram, it has reduced liability for emetic and CNS side effects. In view of its attractive in vitro and in vivo profiles, the compound was selected for further development and assigned the number **D4418**. Further optimisation work based on this template is described in the following paper.

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