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7-Methoxyfuro[2,3-*c*]pyridine-4-carboxamides as PDE4 Inhibitors: A Potential Treatment for Asthma

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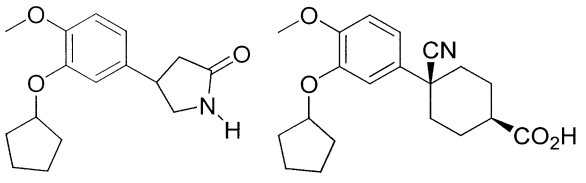
Abstract—The synthesis and pharmacological profile of a novel series of 7-methoxy-furo[2,3-*c*]pyridine-4-carboxamides is described. Some of these compounds were found to be potent inhibitors of phosphodiesterase type 4 (PDE4). Initial

Phosphodiesterase type 4 (PDE4) is a cAMP-specific phosphodiesterase present in inflammatory cells and airway smooth muscle. It catalyses deactivation of cAMP by hydrolysis of the phosphodiester bond. The elevated levels of cAMP which result from inhibition of PDE4 cause activation of the protein kinases responsible for decreasing inflammatory cell activity and airway smooth muscle tone. This leads to suppression of inflammatory cell functions and relaxation of airway smooth muscle.[1] These effects have prompted the investigation of PDE4 inhibitors as a potential treatment for asthma.[2] The first selective PDE4 inhibitor to be identified was *rolipram*,[3] which also caused side effects of nausea and emesis. It has been postulated that in addition to binding to the catalytic site on the enzyme, rolipram also binds to a high affinity site (known as the rolipram binding site)[4] and it is believed that the emetic side effects correlate with this binding.[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 inhibitor is *cilomilast* (Ariflo, SB-207499), which is 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 rolipram binding site. Since inhibition of PDE3 may result in cardiotoxicity, selectivity for PDE4 over the PDE3 isozyme is also important.[7]

The preparation of a series of PDE4 inhibitors in which the 3,4-dialkoxyphenyl unit is replaced with a 7-methoxybenzofuran has been previously reported.[8,9] Here we describe the replacement of the 7-methoxybenzofuran with 7-methoxyfuro[2,3-*c*]pyridine to generate a novel series of inhibitors. Incorporation of the nitrogen atom was intended to improve the pharmacokinetic properties of this series over the benzofurans. A variety of substituents have been incorporated at the 2-position of the furopyridine to investigate their effect on potency and selectivity. Some work has also been undertaken to investigate the effect of replacing the 3,5-dichloropyridyl with other six-membered aromatic rings.

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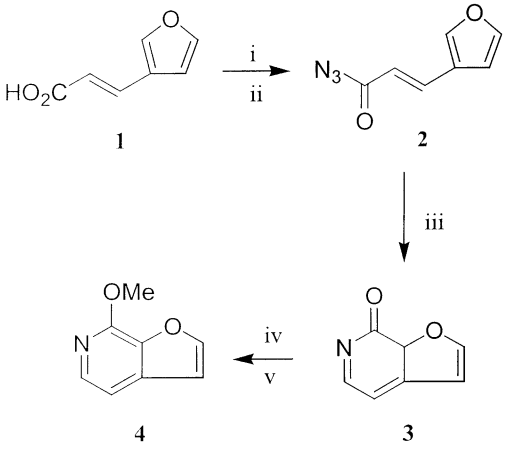
Following the procedure of Shiotani and Morita,[10] commercially available furan-3-acrylic acid **1** was treated with isobutyl chloroformate and triethylamine in acetone to give a mixed anhydride, which was converted to acyl azide **2** by reaction with sodium azide. Heating acyl azide **2** with tributylamine in diphenylmethane at 180 °C afforded furo[2,3-*c*]pyridin-7(6*H*)-one **3**. This was converted to the desired 7-methoxyfuro[2,3-*c*]pyridine **4** via the 7-chloro derivative by refluxing with phosphorus oxychloride followed by treatment with sodium methoxide in 1,4-dioxane (Scheme 1).

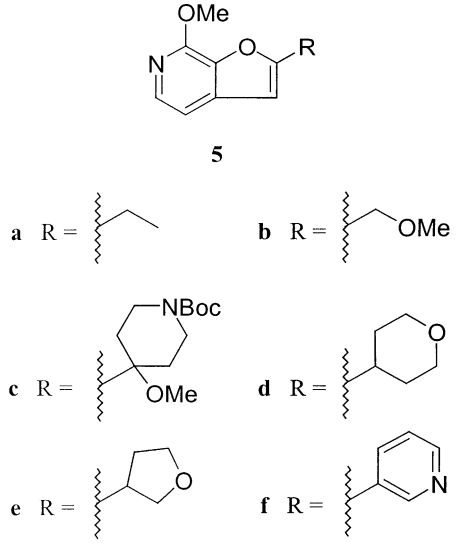


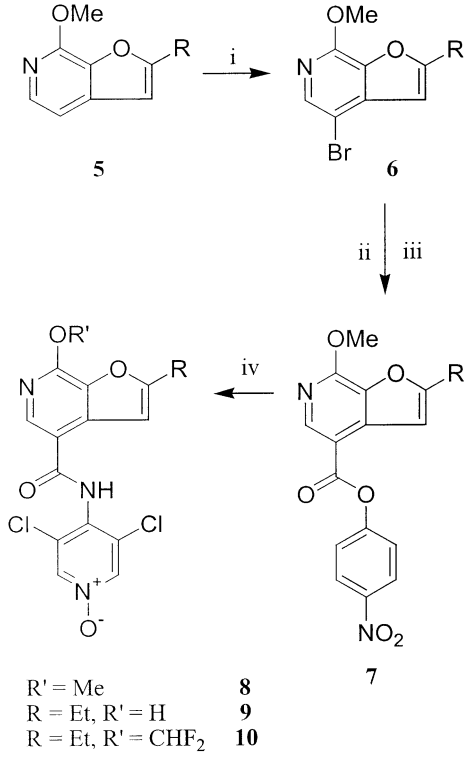
Scheme 1. Reagents and conditions: (i) $ClCO_2CH_2CH_2(CH_3)_2$, NEt_3, acetone; (ii) NaN_3, H_2O; (iii) NBu_3, Ph_2CH_2, 180 °C; (iv) $POCl_3$: (v) NaOMe, 1,4-dioxane.

The preparation of the required 2-substituted furopyridines was achieved in a variety of ways. Treatment of 7-methoxyfuro[2,3-*c*]pyridine **4** with *n*-butyl lithium and ethyl iodide afforded 2-ethyl-7-methoxyfuro[2,3-*c*]pyridine **5a**. Forming the anion at the 2-position of the furopyridine in the same way and subsequent treatment with formaldehyde followed by reaction with methyl iodide and sodium hydride gave the methoxymethyl analogue **5b**. Similarly using *N*-Boc-protected 4-piperidinone as the electrophile resulted in 4-methoxy-4-(7-methoxyfuro[2,3-*c*]pyridin-2-yl)-piperidine-1-carboxylic acid *tert*-butyl ester **5c**. The cyclic ethers **5d** and **5e** were prepared using tetrahydro-4*H*-pyran-4-one and dihydrofuran-3-one respectively in the initial anion reaction. Treatment with mesyl chloride and triethylamine followed by hydrogenation using Raney nickel gave the desired products. 2-Bromofuro[2,3-*c*]pyridine was prepared by reaction of the anion with bromine. This intermediate was converted to the 2-pyridyl derivative **5f** via a palladium-catalysed Suzuki reaction with (3-pyridyl)-borane.

Once the 2-substituent was in place, the various intermediates were further elaborated to the desired final compounds using the same set of reaction conditions. Thus, the 4-bromo-7-methoxy-furo[2,3-*c*]pyridines **6** were prepared by treatment of compounds **5** with *N*-bromosuccinimide. Carbonylation followed by 4-nitrophenyl ester formation afforded key intermediates **7**. These were coupled with the anion of 4-amino-3,5-dichloropyridine-*N*-oxide (preformed using sodium hydride in DMF) to give our novel series of test compounds **8** (Scheme 2).

These were screened in our in vitro assay (Table 1).





R' = Me **8**
R = Et, R' = H **9**
R = Et, R' = CHF_2 **10**

Scheme 2. Reagents and conditions: (i) NBS, MeCN; (ii) CO, $Pd(OA_c)_2$, bis-diphenylphosphinopropane, NEt_3, THF, H_2O; (iii) *p*-nitrophenol, EDC·HCl, DMAP, CH_2Cl_2; (iv) 4-amino-3,5-dichloropyridine-*N*-oxide, NaH, DMF.

Table 1. 2-Substituted furo[2,3-*c*]pyridines[a]

	PDE4 IC_{50}[11]	RBA IC_{50}[12]	PDE4/RBA	PDE3[b] (%)
Rolipram	3.5	0.02	175	27
8a	0.014	0.084	0.16	32
8b	0.047	0.280	0.17	IA
8c	0.048	1.01	0.05	IA
8d	0.047	0.295	0.16	3
8e	0.023	0.151	0.15	NT
8f	0.062	0.621	0.10	NT

[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.

As can be seen, a wide variety of substituents are tolerated at the 2-position of the furo[2,3-*c*]pyridine giving a novel series of potent and selective PDE4 inhibitors. The most potent compound with acceptable selectivity over binding at the rolipram site was found to be 2-ethyl-7-methoxyfuro[2,3-*c*]pyridine-4-carboxylic acid (3,5-dichloro-1-oxopyridin-4-yl)amide **8a**.

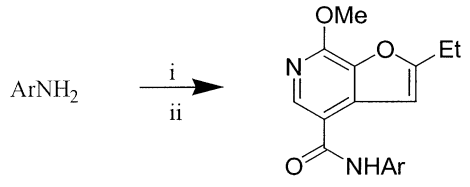
Having identified the 2-ethyl derivative **8a** as a potent, selective inhibitor of PDE4 we investigated the effect of the 7-methoxy substituent. Removing the methyl group to give the furo[2,3-*c*]pyridin-7(*6H*)-one analogue **9** resulted in a dramatic decrease in activity. However replacing the 7-methoxy moiety with a 7-difluoromethoxy substituent to give compound **10** enhanced the potency of this series of inhibitors (Table 2).

Table 2. 7-Substituted furo[2,3-*c*]pyridines[a]

	PDE4 IC_{50}[11]	RBA IC_{50}[12]	PDE4/RBA	PDE3
8a	0.014	0.084	0.16	32%
9	22%	61%	NA	NT
10	0.0037	0.028	0.13	NT

[a]Values are shown as IC_{50} (μM) or percent inhibition at 1 μM and are the means of at least two experiments. RBA, rolipram binding assay.

Moving on to investigate the effect of replacing the 3,5-dichloropyridyl-*N*-oxide moiety with other substituted six-membered aromatic rings, a variety of aromatic amines were coupled with 2-ethyl-7-methoxyfuro[2,3-*c*]pyridine-4-carboxylic acid 4-nitrophenyl ester **7a** in the way previously described (Scheme 3). A series of compounds **11** were thus prepared (Scheme 3) and tested in our in vitro assay (Table 3).



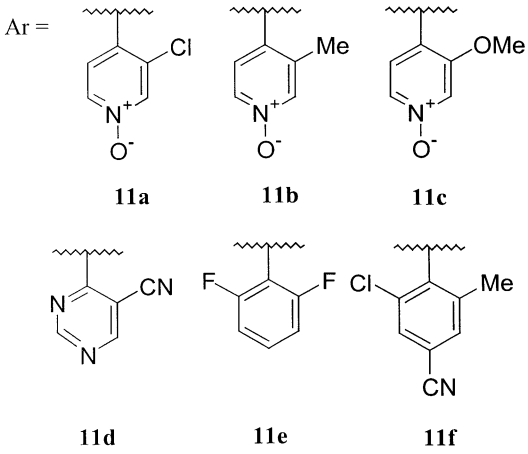
11

Scheme 3. Reagents and conditions: (i) NaH or NaHMDS, DMF; (ii) 2-ethyl-7-methoxfuro[2,3-*c*]pyridine-4-carboxylic acid 4-nitropheyl ester **7a**.

Table 3. *N*-Heterocyclo-2-ethylfuro[2,3-*c*]pyridinyl-4-carboxamides[a]

	PDE4 IC_{50}[11]	RBA IC_{50}[12]	PDE4/RBA	PDE3[b] (%)
8a	0.014	0.084	0.16	32%
11a	0.12	0.28	0.45	39%
11b	0.12	0.35	0.33	NT
11c	21%	NT	NA	NT
11d	0.14	0.27	0.49	IA
11e	0.066	0.27	0.24	NT
11f	0.23	0.58	0.39	NT

[a]Values are shown as IC_{50} (μM) or percent inhibition at 1 μM for PDE4 and 20 μM for PDE3 and are the means of at least two experiments. RBA, rolipram binding assay.



Removal of one chloro substituent from the parent compound to give **11a** resulted in a 10-fold drop in activity against PDE4 as well as reducing the selectivity for catalytic activity over binding to the rolipram site. A similar effect was seen by replacing the chloro substituent with a methyl group as in compound **11b**. However the 3-methoxy analogue **11c** had dramatically reduced potency against PDE4. Incorporating a second nitrogen in the ring as in the 5-cyanopyrimidin-4-yl example **11d** gave a compound with a very similar activity and selectivity profile to the mono-substituted pyridines **11a** and **11b**. Reasonably potent and selective inhibition could be achieved after removing the pyridine nitrogen as exemplified by **11e** and **11f**. However, 2-ethyl-7-methoxy-furo[2,3-*c*]pyridine-4-carboxylic acid (3,5-dichloro-1-oxopyridin-4-yl)amide **8a** remained our most potent and selective compound in this series.

Given this high potency and selectivity, this compound was selected for in vivo studies. Pharmacokinetic studies in the guinea pig dosing at 3 mg/kg po showed a C_{max} of 1411 ng/mL and an AUC of 4942 ng h/mL. The bioavailability was found to be 54%. Using the same dosing, the corresponding benzofuran analogue showed a C_{max} of 311 ng/mL and an AUC of 1394 ng h/mL. Thus incorporation of the ring nitrogen has improved the pharmacokinetics as predicted. The compound was then evaluated in a guinea pig lung eosinophilia model.[13] Administering po at 10 mg/kg, the compound showed 40% inhibition of lung eosinophilia (mean result of three experiments).

In summary, we have identified a series of novel furo[2,3-*c*]pyridines as potent and selective PDE4 inhibitors with a good pharmacokinetic profile. Significant levels of oral activity were demonstrated in a functional model of inflammation.

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