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Synthesis and Profile of SCH351591, a Novel PDE4 Inhibitor

Motasim Billah,[c] Nicola Cooper,[a] Francis Cuss,[c] Richard J. Davenport,[a] Hazel J. Dyke,[a] Robert Egan,[c] Ashit Ganguly,[c] Lewis Gowers,[a] Duncan R. Hannah,[a] Alan F. Haughan,[a] Hannah J. Kendall,[a] Christopher Lowe,[a] Michael Minnicozzi,[c] John G. Montana,[a] Robert Naylor,[b] Janet Oxford,[a] Joanna C. Peake,[a] John J. Piwinski,[c] Karen A. Runcie,[a] Verity Sabin,[a,*] Andrew Sharpe,[a] Neng-Yang Shih[c] and Julie B. H. Warneck[a]

[a]*Celltech Group plc, Granta Park, Abington, Cambridge CB1 6GS, UK*
[b]*Department of Pharmacology, University of Bradford, Bradford BD7 1DP, UK*
[c]*Schering-Plough Corporation, Galloping Hill Road, Kenilworth, NJ 07033-0530, USA*

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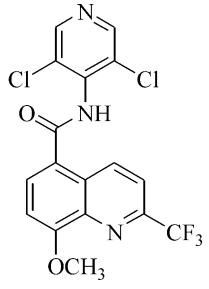
Abstract—The syntheses and pharmacological profiles of some 2-trifluoromethyl-8-methoxyquinoline-5-carboxamides are described. **SCH351591** is a potent selective inhibitor of phosphodiesterase type 4 (PDE4).

PDE4 inhibitors are a class of compounds that have been extensively investigated as a treatment for asthma and other inflammatory disorders.[1] We have recently reported a novel series of 8-methoxyquinoline-5-carboxamide PDE4 inhibitors which had good selectivity for PDE4 and an acceptable therapeutic ratio for binding at the catalytic site over the rolipram binding site.[2] Of this series, one of the most potent compounds in vitro was the 2-trifluoromethyl quinoline **SCH365351**. **SCH365351** was active in a guinea pig lung eosinophilia model[3] when dosed at 10 and 3 mpk and also had good plasma exposure in guinea pigs.



SCH365351

However, a major metabolite was observed in a rat PK study on **SCH365351** (Fig. 1). At time points >3 h, the levels of metabolite were higher than those of the parent compound.

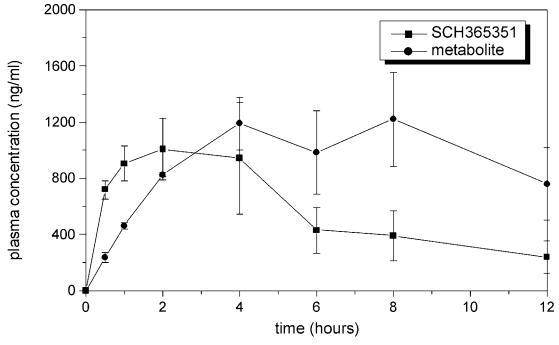


Figure 1. PK profile of **SCH365351** and the major metabolite in rats.

The metabolite was identified as the pyridine *N*-oxide, a discovery which prompted us to investigate the profile of this compound and the SAR around other pyridine *N*-oxides of that type.

SCH365351 was dissolved in chloroform and treated with peracetic acid to give the *N*-oxide **3a** (Scheme 1).

8-Methoxy-2-trifluoromethylquinoline-5-carboxylic acid was activated by conversion either to the acid chloride or to the *p*-nitrophenyl ester and then reacted with the

*Corresponding author. Tel.: +44-1223-896513; fax: +44-1223-896400; e-mail: verity.sabin@celltechgroup.com

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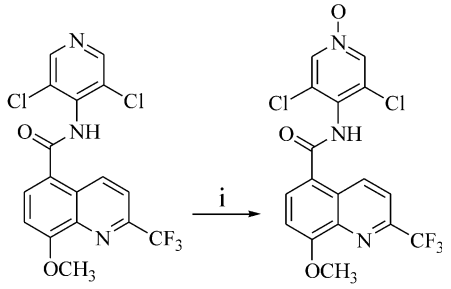
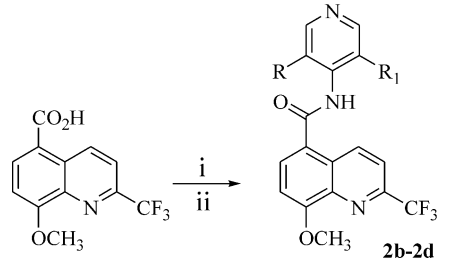
sodium salts of various substituted 4-amino pyridines to give amides such as **2b**–**2d** (Scheme 2).

These were oxidised to the *N*-oxides **3b**–**3d** using peracetic acid as described above. **2b**–**2d** and **3a**–**3d** were screened in vitro against PDE4 and in a rolipram binding assay (RBA) (Table 1).



Scheme 1. Reagents and conditions: (i) peracetic acid (36–40% in acetic acid), 50 °C, 7 days, $CHCl_3$.



Scheme 2. Reagents and conditions: (i) $C_2Cl_2O_2$, DMF, DCM or *p*-nitrophenol, Et_3N, DMAP, DCM; (ii) sodium salt of appropriate amino pyridine, DMF.

Table 1. 2-Trifluoromethylquinoline-5-carboxamides[a]

	R	R_1	PDE4 IC_{50}[4]	RBA IC_{50}[5]	PDE4:RBA
SCH365351	Cl	Cl	0.051	0.077	0.66
2b	Cl	H	1.12	0.11	10
2c	Me	Me	0.12	0.058	2.1
2d	F	F	0.035	0.038	0.94
3a (SCH351591)	Cl	Cl	0.06	0.15	0.40
3b	Cl	H	0.24	0.37	0.65
3c	Me	Me	0.15	0.38	0.39
3d	F	F	0.07	0.06	1.17

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

Table 2. In vitro profile of **SCH351591**[a]

PDE4	0.06
PDE1	15%
PDE2	0%
PDE3	31%
PDE5	5%
PDE7	10%

[a]Values are shown as IC_{50} (μM) or percent inhibition at 10 μM and are the means of at least two experiments. PDE1 was recombinant enzyme, PDE2, 3 and 5 were obtained from human platelets, PDE7 was obtained from a human T-lymphocyte cell line.

The activities of the *N*-oxides **3a**–**3d** against PDE4 were similar to or improved over those of the parent pyridines **SCH365351** and **2b**–**2d**. The PDE4:RBA ratios were improved except in the case of **3d**. Both the monochloro and dimethyl compounds **3b** and **3c** were significantly less active against PDE4 than **3a**; the difluoro compound **3d**, though of similar activity to **3a** against PDE4, had a much poorer ratio. The dichloropyridine-*N*-oxide **3a** was therefore selected for further studies and given the number **SCH351591**.

SCH351591 was screened against other PDE isozymes and was found to be selective for PDE4 over PDE1, 2, 3, 5 and 7 (Table 2).

Pharmacokinetic studies[6] in the rat (Fig. 2), dosing orally at 3 mg/kg, showed **SCH351591** to have a C_{max} of 3058 ng/mL and an $AUC_{0\text{-}t}$ of 50503 ng h/mL, a considerable improvement over **SCH365351** (C_{max} = 1008 ng/mL, $AUC_{0\text{-}t}$ = 6860 ng h/mL).

The guinea pig PK profile (Fig. 3), was also greatly improved over **SCH365351**. (C_{max} of 1393 ng/mL and an $AUC_{0\text{-}t}$ of 15757 ng h/mL when dosed orally at 3 mg/kg compared with C_{max} = 380 ng/mL and $AUC_{0\text{-}t}$ = 1174 ng h/mL for **SCH365351**.)

When administered orally in a guinea pig lung eosinophilia model,[7] **SCH351591** caused significant levels of inhibition of eosinophil influx at 10, 3 and 1 mg/kg (Fig. 4).

SCH351591 was assessed for emetic side effects in a ferret emesis model.[8] No emesis was observed when the

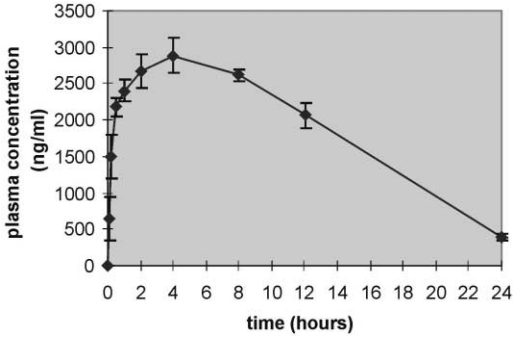


Figure 2. PK profile of **SCH351591** in rats dosed orally at 3 mg/kg (n = 3).

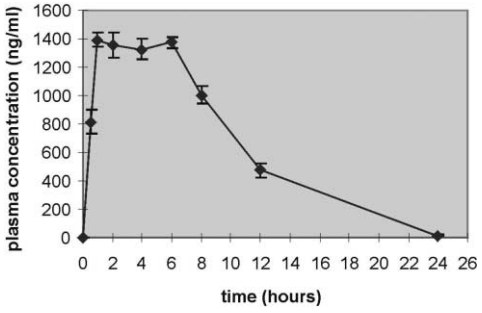


Figure 3. PK profile of **SCH351591** in guinea pigs dosed orally at 3 mg/kg (n = 3).

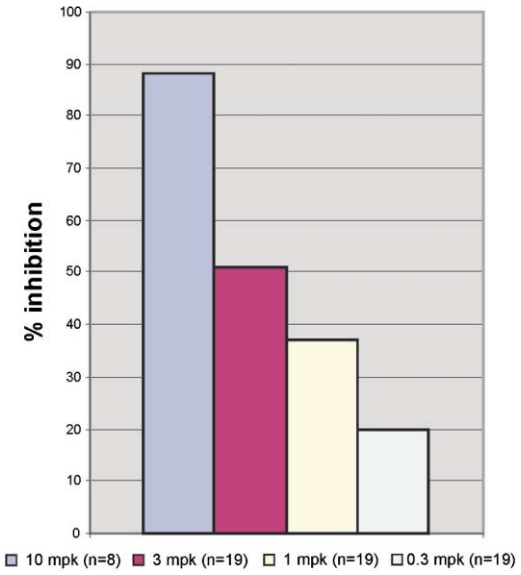


Figure 4. Inhibition of guinea pig lung eosinophilia by oral dosing of **SCH351591**.

compound was dosed orally to a group of four animals at 5 mg/kg each, despite appreciable plasma levels ($C_{max} = 3500$ ng/mL, $AUC_{0\text{-}t} = 26700$ ng h/mL) at this dose.

In summary, **SCH351591** is a potent selective inhibitor of PDE4 with an excellent PK profile and significant activity in an in vivo model at doses which showed no emetic side effects. It was therefore selected for further studies, and details on the outcome of these will be disclosed in subsequent publications.

References and Notes

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6. The pharmacokinetic profiles of the selected compounds were determined in animals cannulated in the right carotid artery for blood collection. For oral dosing, the compound was prepared in 0.4% w/v methylcellulose in water. Samples were collected at 0.5, 1, 2, 4, 6, 8 and 12 h post-dosing. Plasma was obtained by centrifugation of the blood sample and the drug concentration was then determined using liquid chromatography–mass spectrometry following protein precipitation.
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