Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 1617–1619

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

8-Methoxyquinolines as PDE4 Inhibitors

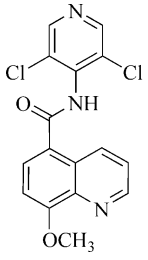
Motasim Billah,[c] George M. Buckley,[a] Nicola Cooper,[a] Hazel J. Dyke,[a] Robert Egan,[c] Ashit Ganguly,[c] Lewis Gowers,[a] Alan F. Haughan,[a] Hannah J. Kendall,[a] Christopher Lowe,[a] Michael Minnicozzi,[c] John G. Montana,[a] Janet Oxford,[a] Joanna C. Peake,[a] C. Louise Picken,[a] John J. Piwinski,[c] Robert Naylor,[b] Verity Sabin,[a,*] Neng-Yang Shih[c] and Julie B. H. Warneck[a]

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

Received 8 March 2002; accepted 4 April 2002

Abstract—The synthesis and pharmacological profile of a novel series of 2-substituted 8-methoxyquinolines is described. The 2-trifluoromethyl compound was found to be a potent inhibitor of phosphodiesterase type 4 (PDE4).

Inhibitors of PDE4 (a cAMP specific phosphodiesterase found in inflammatory cells and airway smooth muscle) have been investigated extensively as a potential treatment for asthma.[1] We have previously reported novel methoxybenzo-fused heterocycles (such as 7-methoxybenzofurans,[2] 7-methoxybenzimidazoles,[3] 8-methoxyquinolines[3] and 7-methoxyfuro-[2,3-*c*]-pyridines[4]) as PDE4 inhibitors. The most efficacious of these compounds in vivo was the 8-methoxyquinoline **D4418**.[3] Because the in vitro and in vivo profiles of **D4418** were so promising, we next prepared a series of 8-methoxyquinoline-5-carboxamides with a variety of substitutents at the 2-position. Our objective was to improve in vitro potency, in vivo efficacy and plasma exposure and half life.



D4418

The 8-methoxyquinolines **2a** and **2b** were prepared by methylation of commercially available 8-hydroxyquinolines (Scheme 1).

2c was prepared by Skraup quinoline synthesis starting with 2-methoxyaniline (Scheme 2).

o-Anisidine was reacted with ethyl 1,1,1-trifluoroacetate in the presence of polyphosphoric acid to give a quinolone which was chlorinated at the 4-position with phosphorous pentachloride in phosphorous oxychloride. The 4-chloro substituent was removed by hydrogenation to give **2d** (Scheme 3).

2e was prepared from **2a** using butyllithium followed by iodomethane (Scheme 4).

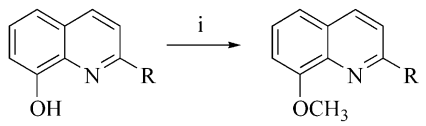
The 8-methoxyquinolines **2a**–**2e** were brominated *para* to the methoxy group and then carbonylated to give 8-methoxyquinoline-5-carboxylic acids **3a**–**3e** (Scheme 5).

3a–**3e** were activated as acid chlorides or *p*-nitrophenyl esters and then reacted with the sodium salt of 4-amino-3,5-dichloropyridine to give the 8-methoxyquinoline-5-carboxamides **4a**–**4e** (Scheme 6).

4b was reacted with methylmagnesium bromide to give the 2-acetyl compound **4f** which was itself reacted with sodium borohydride to give **4g** and with *O*-methylhydroxylamine to give **4h** (Scheme 7).

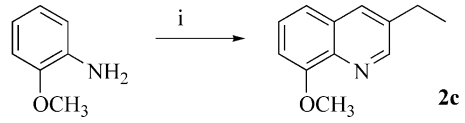
*Corresponding author. Tel.: +44-1223-896513; fax: +44-1223-896400; e-mail: verity.sabin@celltechgroup.com

0960-894X/02/$ - see front matter
PII: S0960-894X(02)00224-X

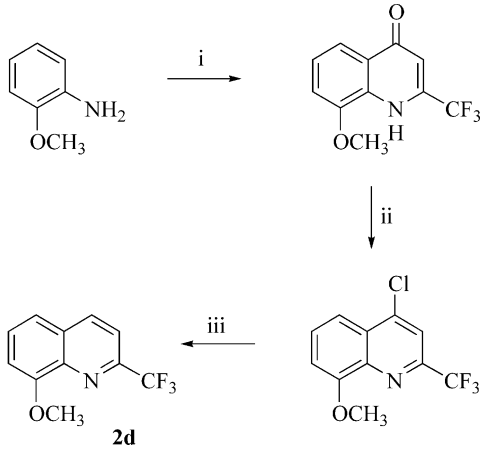


2a R = CH_3
2b R = CN

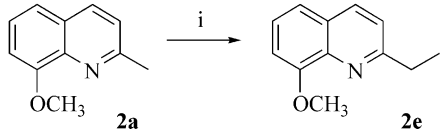
Scheme 1. Reagents and conditions: (i) MeI, NaOH, TBAI, THF, H_2O.



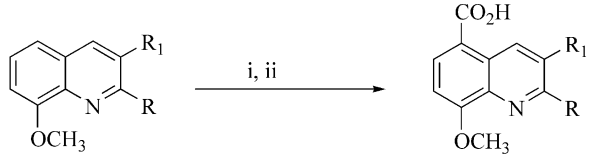
Scheme 2. Reagents and conditions: (i) H_2SO_4, I_2, 2-ethyl acrolein.



Scheme 3. Reagents and conditions: (i) $EtO_2CCH_2COCF_3$, PPA; (ii) PCl_5, $POCl_3$; (iii) H_2, Pd/C.



Scheme 4. Reagents and conditions: (i) BuLi, THF then MeI.

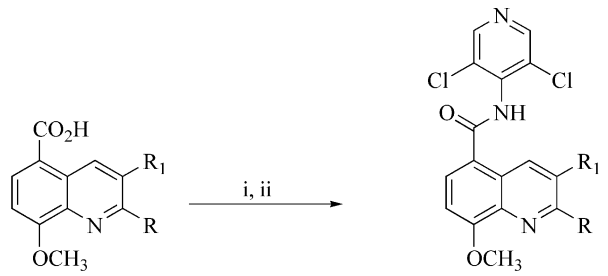


3a R = CH_3, R_1 = H **3b** R = CN, R_1 = H **3c** R = H, R_1 = Et
3d R = CF_3, R_1 = H **3e** R = Et, R_1 = H

Scheme 5. Reagents and conditions: (i) Br_2, MeOH; (ii) CO, $PdCl_2(PPh_3)_2$, Et_3N, THF or DMF, H_2O.

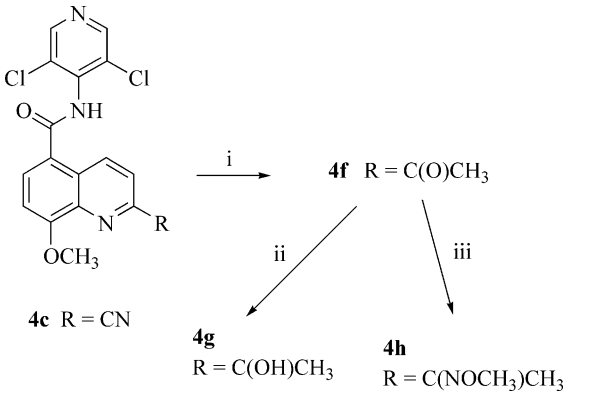
The 8-methoxyquinoline-5-carboxamides **4a**–**4h** were screened in vitro against PDE4 and PDE3, and in a rolipram binding assay (RBA) (Table 1).

4a was 2-fold more potent against PDE4 than **D4418**. Incorporating nitrile at the 2-position (**4b**) not only decreased activity against PDE4 but also increased activity at the rolipram binding site, leading to a very poor ratio. However, replacing the methyl group of **4a** with trifluoromethyl (**4d**) improved activity against PDE4. Of the two ethyl compounds **4c** and **4e**, the 2-isomer **4e** was significantly more potent and had a better ratio than the 3-isomer **4c**. The 2-acetyl compound **4f** was less potent against PDE4 than **D4418**, and had a similar ratio. Reduction of the acetyl group in **4f** to give the alcohol **4g** improved activity against PDE4 and maintained the ratio, while converting **4f** to the methoxy oxime **4h** improved activity against both PDE4 and in the RBA and was therefore detrimental to the ratio.



4a R = CH_3, R_1 = H **4b** R = CN, R_1 = H **4c** R = H, R_1 = Et
4d R = CF_3, R_1 = H **4e** R = Et, R_1 = H

Scheme 6. Reagents and conditions: (i) $C_2Cl_2O_2$, DMF, DCM or *p*-nitrophenol, Et_3N, DMAP, DCM; (ii) sodium salt of 4-amino-3,5-dichloropyridine, DMF.



Scheme 7. Reagents and conditions: (i) MeMgBr, THF; (ii) $NaBH_4$, EtOH; (iii) $MeONH_2$, pyridine, toluene.

On the basis of its potency against PDE4 and selectivity for the catalytic site over the rolipram binding site, **4d** was selected for evaluation in guinea pig pharmacokinetic studies[7] and in a guinea pig lung eosinophilia study.[8] Pharmacokinetic studies in the guinea pig (Fig. 1), dosing orally at 5 mg/kg, showed **4d** to have a C_{max} of 380 ng/mL, an AUC of 1174 ng h/mL and an oral bioavailability of 78%.

In a guinea pig lung eosinophilia model, **4d** caused significant levels of inhibition of eosinophil influx when administered orally at 10 and 3 mg/kg (Fig. 2).

4d was assessed for emetic side effects in a ferret emesis model.[9] No emesis was observed when the compound was dosed orally at 6 mg/kg to a group of four animals.

Table 1. 2-Substituted quinoline-5-carboxamides[a]

	R	R_1	PDE4 IC_{50}[5]	RBA IC_{50}[6]	PDE 4:RBA	PDE 3 (%)
D4418	H	H	0.17	0.53	0.32	10
4a	CH_3	H	0.088	0.074	1.19	21
4b	CN	H	0.70	0.043	16.28	38
4c	H	CH_2CH_3	0.21	0.16	1.31	12
4d	CF_3	H	0.051	0.077	0.66	15
4e	CH_2CH_3	H	0.043	0.0753	0.57	35
4f	$C(O)CH_3$	H	0.44	1.5	0.29	27
4g	$C(OH)CH_3$	H	0.18	0.79	0.22	30
4h	$C(NOCH_3)CH_3$	H	0.21	0.14	1.5	22

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

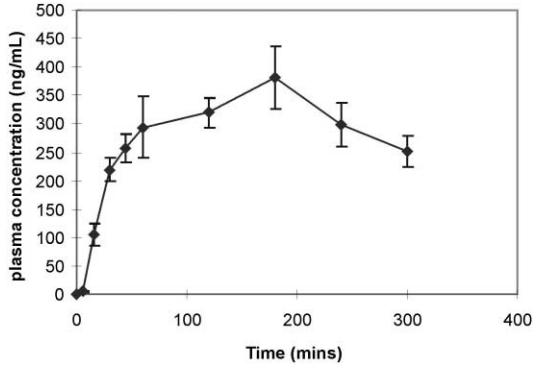


Figure 1. PK profile of **4d** in guinea pig dosing orally at 5 mg/kg ($n=4$).

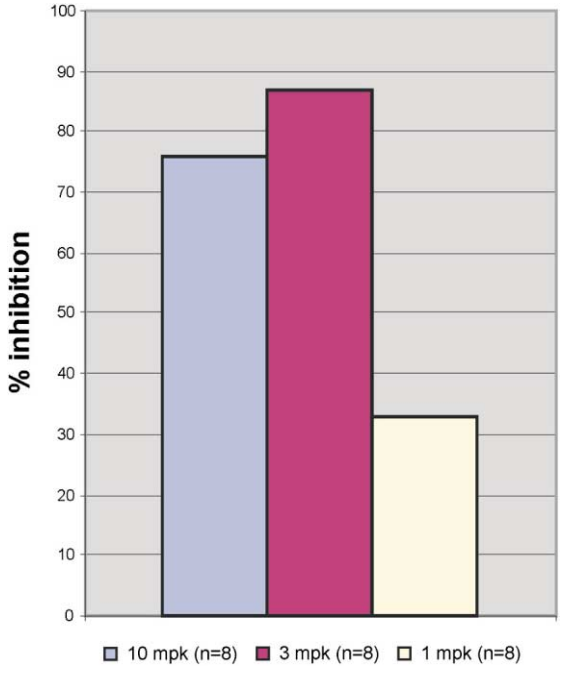


Figure 2. Inhibition of guinea pig lung eosinophilia by oral dosing of **4d** at 1, 3 and 10 mg/kg.

In conclusion, **4d** is a novel, potent and selective inhibitor of PDE4. Compared with **D4418**, it had an improved plasma half life in vivo when dosed orally to guinea pigs, and significantly improved activity in a guinea pig lung eosinophilia model. Further studies on compounds in this series will be reported in due course.

References and Notes

1. (a) Karlsson, J.-A.; Aldous, D. *Exp. Opin. Ther. Pat.* **1997**, *7*, 989. (b) Dyke, H. D.; Montana, J. G. *Exp. Opin. Invest. Drugs* **1999**, *8*, 1301.
2. Buckley, G. M.; Cooper, N.; Dyke, H. J.; Galleway, F.; Gowers, L.; Gregory, J. C.; Hannah, D. R.; Haughan, A. F.; Hellewell, P. G.; Kendall, H. J.; Lowe, C.; Maxey, R.; Montana, J. G.; Naylor, R.; Picken, C. L.; Runcie, K. A.; Sabin, V.; Tuladhar, B. R.; Warneck, J. B. H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2137.
3. Buckley, G. M.; Cooper, N.; Dyke, H. J.; Galleway, F.; Gowers, L.; Haughan, A. F.; Kendall, H. J.; Lowe, C.; Maxey, R.; Montana, J. G.; Naylor, R.; Oxford, J.; Peake, J. C.; Picken, C. L.; Runcie, K. A.; Sabin, V.; Sharpe, A.; Warneck, J. B. H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1613.
4. Buckley, G. M.; Cooper, N.; Davenport, R. J.; Dyke, H. J.; Galleway, F. P.; Gowers, L.; Haughan, A. F.; Kendall, H. J.; Lowe, C.; Montana, J. G.; Oxford, J.; Peake, J. C.; Picken, C. L.; Richard, M. D.; Sabin, V.; Sharpe, A.; Warneck, J. B. H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 509.
5. Thompson, W. J.; Terasaki, W. L.; Epstein, P. M.; Strada, S. *J. Adv. Cyclic Nucleotide Res.* **1979**, *10*, 69.
6. Schneider, H. H.; Schmeichen, R.; Brezinski, M.; Seidler, J. *Eur. J. Pharmacol.* **1997**, *127*, 105.
7. 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.
8. (a) Mauser, P. J.; Pitman, A.; Witt, A.; Fernandez, X.; Zurcher, J.; Kung, T.; Jones, H.; Watnick, A. S.; Egan, R. W.; Kreutner, W.; Adams, G. K. III *Am. Rev. Respir. Dis.* **1993**, *148*, 1623. (b) Mauser, P. J.; Pitman, A. M.; Fernandez, X.; Foran, S. K.; Adams, G. K. III; Kreutner, W.; Egan, R. W.; Chapman, R. W. *Am. J. Respir. Crit. Care Med.* **1995**, *152*, 467.
9. Costall, B.; Domeney, A. M.; Naylor, R. J.; Tattersall, F. D. *Neuropharmacology* **1987**, *26*, 1321.