Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 1451–1456

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

CDP840. A Prototype of a Novel Class of Orally Active Anti-Inflammatory Phosphodiesterase 4 Inhibitors

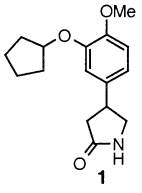
R. P. Alexander,[a,*] G. J. Warrellow,[a] M. A. W. Eaton,[a] E. C. Boyd,[a] J. C. Head,[a] J. R. Porter,[a] J. A. Brown,[a] J. T. Reuberson,[a] B. Hutchinson,[a] P. Turner,[a] B. Boyce,[a] D. Barnes,[a] B. Mason,[a] A. Cannell,[a] R. J. Taylor,[a] A. Zomaya,[a] A. Millican,[a] J. Leonard,[a] R. Morphy,[a] M. Wales,[b] M. Perry,[b] R. A. Allen,[b] N. Gozzard,[b] B. Hughes[b] and G. Higgs[b]

[a]*Department of Medicinal Chemistry, Celltech R&D Ltd., 208 Bath Road, Slough, Berkshire SL1 3WE, UK*
[b]*Department of Biology, Celltech R&D Ltd., 208 Bath Road, Slough, Berkshire SL1 3WE, UK*

Received 20 December 2001; revised 27 February 2002; accepted 26 March 2002

Abstract—The discovery, synthesis and biological activity of a series of triarylethane phosphodiesterase 4 inhibitors is described. Structure–activity relationship studies are presented for CDP840 (**29**), a potent, chiral, selective inhibitor of PDE 4 (IC_{50} 4 nM). CDP840 is non-emetic in the ferret at 30 mg kg^{-1} (po), active in models of inflammation and reverses ozone-induced bronchial hyperreactivity in the guinea pig.

Cyclic nucleotides play a key role in cell function by acting as intracellular secondary messengers, relaying the signals from hormones acting at specific cell-surface receptors.[1] Phosphodiesterases (PDEs) are a superfamily of 11 isoenzymes[2] responsible for the hydrolysis of cAMP and cGMP.[3] Elevation of cAMP levels by stimulation of adenylyl cyclase or by inhibition of PDEs, exerts a broad inhibitory effect on the activity of immune and inflammatory cells.[4] PDE 4, a cAMP specific PDE, has attracted particular attention as a target for the treatment of diseases such as asthma and COPD due to its distribution in most immune and inflammatory cells and airway smooth muscle.[5] The utility of the first generation of PDE 4 inhibitors (e.g., rolipram **1**) has been severely curtailed due to dose limiting side effects such as nausea and vomiting,[6] psychotropic activity[7] and increased gastric secretion.[8]



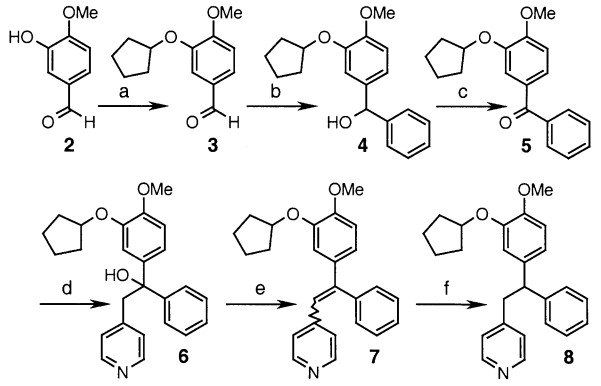
1

*Corresponding author. Tel.: +44-1753-534655; fax: +44-1753-536632; e-mail: rikki.alexander@celltechgroup.com

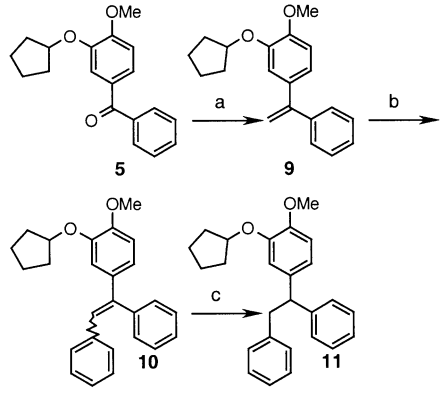
We set out to produce a novel, potent and selective series of inhibitors devoid of these side effects. Exploring the SAR around rolipram (**1**) provided several series of PDE 4 inhibitors,[9] which ultimately led to the triarylethanes. Three approaches (Schemes 1–3) were used to synthesize the triarylethanes. Our initial synthetic efforts were directed towards optimization of the group in the 1 position of the ethane as illustrated by the reaction sequence shown in Scheme 1.[10] Alkylation of isovanillin (**2**) with cyclopentyl bromide in DMF produced the derivative (**3**). Reaction with phenyl lithium furnished the diaryl methanol (**4**) which was subsequently oxidized with activated manganese dioxide yielding the benzophenone (**5**). Reaction with the anion of 4-methyl pyridine gave the alcohol (**6**) which was then converted to the alkene (**7**) by acid catalyzed elimination. Catalytic hydrogenation provided the desired triaryl ethane (**8**).

A complimentary synthesis is exemplified by the reaction sequence shown in Scheme 2. Olefination of benzophenone (**5**) gave the alkene (**9**). Heck reaction with an aryl halide yielded the trisubstituted alkene (**10**), as a mixture of double bond isomers. Catalytic hydrogenation provided the triarylethane (**11**). The 1-ethane substituent was varied to ascertain the optimal group. Table 1 shows that the 4-pyridyl group is optimal of the groups studied. Removal of the aromaticity to give compound **14** leads to a complete loss of activity. Attempts to

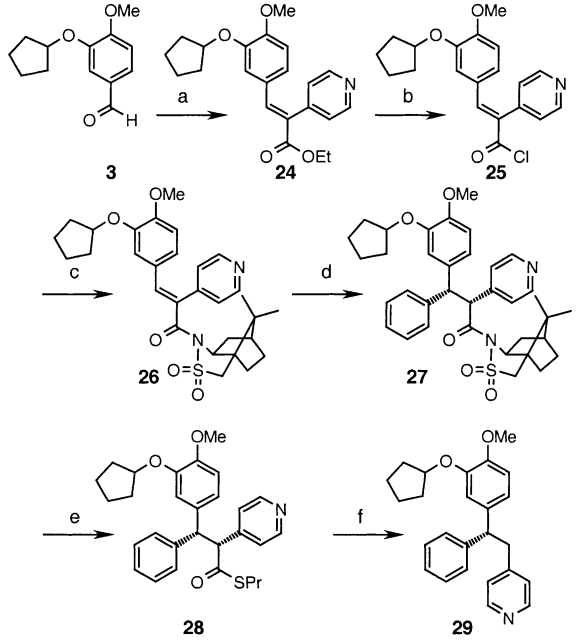
0960-894X/02/$ - see front matter
PII: S0960-894X(02)00202-0



Scheme 1. Reagents and conditions: (a) c-C_5H_9Br, Cs_2CO_3, DMF, 95%; (b) PhLi, THF, 99%; (c) MnO_2, CH_2Cl_2, 85%; (d) LDA, 4-MePy, THF, 90%; (e) TsOH, PhMe, 100%; (d) Pd/C, H_2, EtOH, 90%.

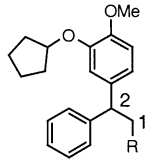


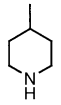
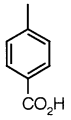
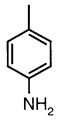
Scheme 2. Reagents and conditions: (a) $MePPh_3Br$, LDA, THF, 97%; (b) $Pd(OAc)_2$, (*o*-Tolyl)$_3$P, Et_3N, PhBr; 35%; (c) Pd/C, H_2, EtOH, 95%.



Scheme 3. Reagents and conditions: (a) Ethyl 4-pyridylacetate, TsOH, piperidine, PhMe, 58%; (b) (1) NaOH, (2) $SOCl_2$; (c) Sultam, THF, 67% (2 steps); (d) PhMgBr, THF, 76%; (e) LiSPr, THF; (f) NaOH, HCl, 82% (2 steps).

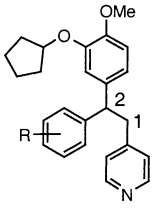
Table 1. SAR for the 1-ethane group



Compd	R	Inhibition of PDE 4A (yeast) IC_{50} (nM)
8		17.5
11		1170[a]
12		172
13		40
14		> 8000[a]
15		40
16		389
17		423[a]

[a]Inhibition of PDE 4A (yeast), K_i (nM).

Table 2. Effect of substituent position on 2-phenyl group



Compd	R	Inhibition of PDE 4A (yeast) IC_{50} (nM)
18	*ortho*-OMe	259
19	*meta*-OMe	58
20	*para*-OMe	17
21	*ortho*-F	158
22	*meta*-F	8
23	*para*-F	47

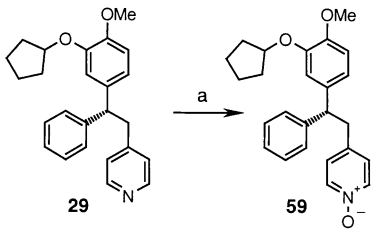
replace the 4-pyridine with other heterocycles leads to a loss in activity, the 4-pyrimidine, (**13**) and the 5-(1-methyl) imidazole (**15**) being the next most active. Attempts to mimic the pyridine ring with a substituted benzene ring leads to a significant loss in potency. Table 2 shows the effect of moving a substituent around the phenyl group in the 2 position of the ethane. Whilst *meta* and *para* substitution retain potency, substitution in the *ortho* position leads to a loss of activity, for both the methoxy and the fluorine substituents. This suggested that the *meta* and *para* positions were more tolerant of substitution and an exploration of the SAR associated with these positions could be useful in the pursuit of more potent compounds.

An asymmetric synthesis of this class of compounds was required, (Scheme 3).[11] Knovenagel condensation of ethyl 4-pyridylacetate with aldehyde **3** gave the cinnamate **24**. Base hydrolysis of the ester resulted in the acid, which was converted to the acid chloride **25** with thionyl chloride. Reaction with the sodium salt of (2*S*)-bornane-2,10-sultam gave the acyl sultam **26**. Michael reaction[12] with phenylmagnesium bromide gave, after crystallization, the product **27** as a single diastereoisomer.[11] Removal of the sultam was achieved using lithium thiopropiolate. The thioester **28** was hydrolyzed with base and the acid removed by decarboxylation to give the triarylethane **29**, CDP840, in greater than 99.5% ee. This chiral synthesis of the eutomer of **8**, **29**, allowed assignment of its stereochemistry as *R* by X-ray analysis of the intermediate **27**.

This synthetic route facilitated an exploration of the SAR associated with the phenyl group and a comparison of the enantiomers of **8**. The potency against PDE 4 and ability to inhibit the LPS-stimulated TNF-α production in human whole blood,[13] a measure of cellular efficacy, of this series is reported in Table 3. CDP840, **29**, has an IC_{50} against PDE 4 of 4 nM, but its ability to inhibit LPS-induced TNF-α production in human whole blood is 8.5 μM, representing a 2125-fold drop of in activity. CDP840, **29**, is an exceptionally selective PDE 4 inhibitor, having an IC_{50} against PDEs 1, 2, 3, 5 and 7 of greater than 10,000 nM. The distomer of **8**, **30**, is over 30-fold less active against PDE 4, although this differential is reduced to 3-fold when inhibiting LPS-stimulated TNF-α formation in human whole blood when compared to the eutomer, **29**. PDE 4 is tolerant of a wide range of groups in the 2 position of the ethane. Both aromatic and heteroaromatic groups give potent compounds. A series of *para* substituted sulfonamides was synthesized, compounds **36** to **42**. The cyclic sulfonamide, **42**, was the most potent compound against the isolated enzyme. However, the pentafluorophenyl sulfonamide **41** is the most potent inhibitor of TNF-α production in that series, showing only a 19-fold drop off in activity in the whole blood assay. Other functionality was accommodated in the *para* position. Ureas and amides gave potent compounds. A series of *meta* substituted ureas was synthesized, compounds **47** to **56**. Compound **49** (CT 2450) is the most potent inhibitor of the isolated enzyme, having an IC_{50} of 0.3 nM. However, compounds that are disubstituted on the terminal nitrogen of the urea show the least drop off in activity between isolated enzyme assay and human whole blood assay. Whilst **54** and **56** are equipotent in inhibiting LPS-stimulated TNF-α in human whole blood, **56** shows only a 16-fold differential between the two assays. Other functionality is tolerated at the *meta* position as illustrated by the sulfuric diamide **57** and the ether **58**. Peracetic acid oxidation of CDP840, **29**, Scheme 4, gives the pyridine *N*-oxide, **59**, in 97% yield. **59** showed similar activity to the parent compound in inhibiting PDE 4 (IC_{50} 7 nM) and TNF-α production (IC_{50} 6.6 μM). Whilst the pyridine ring is required for activity, the basic nitrogen atom is not.

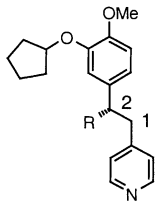
CDP840, **29**, was profiled in models of pulmonary eosinophilic inflammation and antigen-induced bronchoconstriction. CDP840, **29**, caused a dose dependent reduction of IL-5-induced pleural eosinophilia in rats ($ED_{50} = 0.03\ mg\ kg^{-1}$) when dosed orally. The eosinophils in pleural exudates from CDP840-treated animals contained higher levels of eosinophil peroxidase (EPO) than cells from control animals, suggesting a stabilizing effect on eosinophil degranulation.[14] Antigen-induced pulmonary eosinop-hilia in sensitized guinea pigs was reduced in a dose-dependent way by CDP840, ($ED_{50} = 0.1\ mg\ kg^{-1}$) and intracellular EPO levels were significantly higher.[15] In sensitized guinea pigs, aerosols of the antigen ovalbumin caused a dose-dependent bronchoconstriction demonstrated by an increase in pulmonary inflation pressure. Administration of CDP840, ($ED_{50} = 1.0\ mg\ kg^{-1}$, ip), 1 h before antigen challenge, resulted in a dose-dependent reduction in response to antigen.[14] CDP840 ($ED_{50} = 0.01\ mg\ kg^{-1}$ ip) dose relatedly inhibited ozone-induced hyperreactivity to histamine in guinea pigs.[15] CDP840 was non-emetic in ferrets at doses up to $30\ mg\ kg^{-1}$ (po). CDP840 when dosed at 15 mg *b.i.d.* to asthmatic patients for 9.5 days attenuated the late phase asthmatic response to allergen challenge by 30% in the absence of any bronchodilatory or histamine antagonist effect.[16] This suggests that CDP840 may exert its effects via an anti-inflammatory mechanism. It was also shown to be devoid of the side effects normally associated with PDE 4 inhibitors at single oral doses of up to 64 mg.

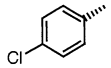
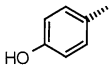
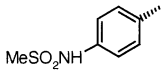
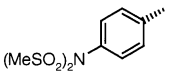
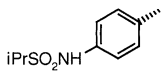
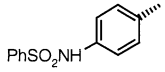
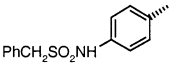
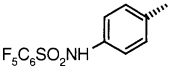
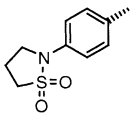
In summary a novel triarylethane series of potent, selective PDE 4 inhibitors was discovered. The prototype member of this series, CDP840, **29**, was shown to reduce antigen-induced bronchoconstriction and pulmonary eosinophilic inflammation in animal models and attenuate the late phase asthmatic response to allergen challenge in patients. These results suggest that



Scheme 4. Reagents and conditions: (a) CH_3CO_3H, CH_2Cl_2, 97%.

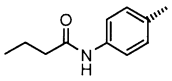
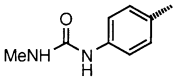
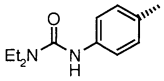
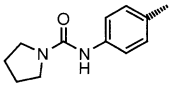
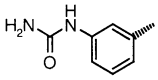
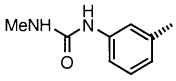
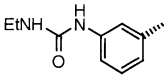
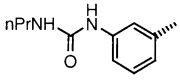
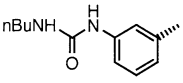
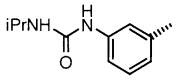
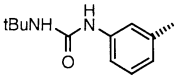
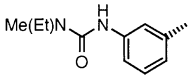
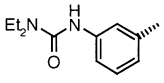
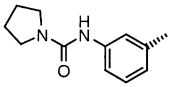
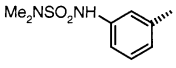
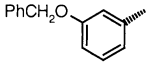
Table 3. SAR for group in ethane 2 position



Compd	R[a]	Inhibition of PDE 4A (yeast) IC_{50} (nM)	HWB (TNF-α) IC_{50}, μM[b]
29		4	8.5
30		148	27.6
31		8	6.5
32		5	5.9
33		3	11.8
34		68	6.9
35		5	6.9
36		2.5	2.2
37		9	2.2
38		7	1.8
39		7	4.7
40		8	2.5
41		7.5	0.14
42		0.8	0.51

(*continued on next page*)

Table 3 (*continued*)

Compd	R[a]	Inhibition of PDE 4A (yeast) IC_{50} (nM)	HWB (TNF-α) IC_{50}, μM[b]
43		4.8	22.9
44		4	7.3
45		11	8.7
46		10	10.5
47		22	2.7
48		19	5.2
49		0.3	2.5
50		54.6	8.1
51		113	12.8
52		31	3.1
53		137	4.3
54		16	0.3
55		27	2.3
56		5	0.3
57		12	6.4
58		102	6.4

[a]All compounds are chiral, ee >99.5%.
[b]Inhibition of LPS-induced TNF-α in human whole blood (HWB).[13]

the triarylethane series could be the basis of an orally active prophylactic treatment for asthma or other inflammatory diseases.

Acknowledgements

We are indebted to Dr D. J. Williams of Imperial College London for the crystal structure of **27**.

References and Notes

1. Robinson, G. A.; Butcher, R. W.; Sutherland, E. W. *Ann. Rev. Biochem.* **1968**, *37*, 149.
2. Francis, S.; Turko, I.; Corbin, V. J. D. *Progress in Nucleic Acid Research* **2000**, *65*, 1.
3. (a) Yuasa, K.; Kanoh, Y.; Okumura, K.; Omori, K. *Eur. J. Biochem.* **2001**, *268*, 168. (b) Soderling, S. H.; Beavo, J. A. *Curr. Opin. Cell Biol.* **2000**, *12*, 174.
4. (a) Giembycz, M. A.; Dent, G. *Clin. Exp. Allergy* **1993**, *22*, 19. (b) Kammer, G. M. *Immunol. Today* **1988**, *9*, 39. (c) Nicholson, C. D.; Challiss, R. A.; Shahid, M. *Trends Pharmacol. Sci.* **1991**, *12*, 19. (d) Torphy, T. J.; Undem, B. J. **1991**, *46*, 512.
5. Christensen, S. B.; Torphy, T. J. In *Annual Reports in Medicinal Chemistry*, Bristol, A. J. Ed.; Academic Press: New York, 1994; Vol. 29, p 185.
6. Horowski, R.; Sastre-y-Herandez, M. *Curr. Ther. Res.* **1985**, *38*, 23.
7. Zeller, E.; Stief, H. J.; Pflug, B.; Satre, Y.; Herandez, M. *Pharmacopsychiatry* **1984**, *17*, 188.
8. Puurunen, J.; Lucke, C.; Schwabe, U. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1978**, *304*, 69.
9. (a) Beeley, N. R. A.; Millican, T. A. 1993, WO 93/25517. (b) Boyd, E. C.; Eaton, M. A. W.; Warrellow, G. J. 1994, WO 94/10118.
10. Warrellow, G. W.; Boyd, E. C.; Alexander, R. P. 1994, WO 94/14742.
11. Alexander, R. P.; Warrellow, G. J.; Head, J. C.; Boyd, E. C.; Porter, J. R. 1995, WO 95/17386.
12. Oppolzer, W.; Poli, G.; Starkemann, C.; Bernardinelli, G. *Helv. Chim. Acta* **1987**, *70*, 2201.
13. Brideau, C.; Van Staden, C.; Sthyler, A.; Rodger, I. W.; Chan, C.-C. *Br. J. Pharmacol.* **1999**, *126*, 979.
14. Hughes, B.; Howat, D.; Lisle, H.; Holbrook, M.; James, T.; Gozzard, N.; Blease, K.; Hughes, P.; Kingaby, R.; Warrellow, G.; Alexander, R.; Eaton, M.; Perry, M.; Wales, M.; Smith, B.; Owens, R.; Catterall, C.; Lumb, S.; Russell, A.; Allen, R.; Merriman, M.; Bloxham, D.; Higgs, G. *Br. J. Pharmacol.* **1996**, *118*, 1183.
15. Holbrook, M.; Gozzard, N.; James, T.; Higgs, G.; Hughes, B. *Br. J. Pharmacol.* **1996**, *118*, 1192.
16. Harbinson, P. L.; MacLeod, D.; Hawksworth, R.; O'Toole, S.; Sulivan, P. J.; Heath, P.; Kilfeather, S.; Page, C. P.; Costello, J.; Holgate, S. T.; Lee, T. H. *Eur. Respir. J.* **1997**, *10*, 1008.