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QUATERNARY SUBSTITUTED PDE4 INHIBITORS I : THE SYNTHESIS AND IN VITRO EVALUATION OF A NOVEL SERIES OF OXINDOLES

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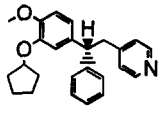
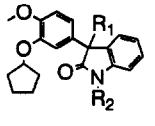
Abstract: The following letter presents the synthesis and in vitro evaluation of a novel quaternary substituted series of phosphodiesterase type (IV) (PDE4) inhibitors. The compounds represent conformationally constrained analogues of the Celltech PDE IV inhibitor, CDP 840. Examples with sub-micromolar IC_{50}'s for PDE4 inhibition are reported.

Recent years have witnessed a resurgence of interest in the potential therapeutic benefits of phosphodiesterase type IV (PDE4) selective inhibitors.[1] Of the seven PDE isoenzymes identified to date,[2] PDE4 is most abundantly found in inflammatory cells such as monocytes and macrophages. Increasing concentrations of the intracellular secondary messenger, cyclic adenosine 3',5'-monophosphate (cAMP) leads to the inhibition of production of the pro-inflammatory cytokine tumor necrosis factor (TNF-α).[3] The role of excessive concentrations of TNF-α in the pathogenesis of a large number of autoimmune disease states, including asthma, septic shock and rheumatoid arthritis is widely documented.[4,5,6] The efficacious effects of antibodies against TNF-α in treatment of rheumatoid arthritis further enhances the appeal of reducing production of this pivotal cytokine.[6] Clearly, the selective inhibition of PDE4 catalysed cAMP to 5'-AMP hydrolysis,[1] with the associated reduction in TNF-α production, represents an attractive target for the treatment of autoimmune and inflammatory diseases.

Much SAR work to date has been performed using the archetypal PDE4 inhibitor rolipram[7] as the lead compound. Rolipram itself elicits both central nervous system and gastrointestinal side effects.[8] To date many potent PDE4 inhibitors have lead to unwanted side effects such as nausea and emesis.[9] It is believed that a high affinity rolipram binding site exists (rolipram, K_d 1-2 nM), in addition to the PDE4 catalytic site (rolipram K_i 1-2 μM), and it has been postulated that rolipram binding is associated with the emetic side effect.[9,10] Potent PDE4 inhibition, coupled with selectivity for the catalytic over the high affinity rolipram binding site, is thus highly sought after in new series of PDE4 inhibitors.


CDP 840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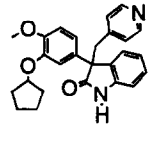
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An example of such selectivity was recently reported by Celltech with CDP 840 (PDE4 IC_{50} 4.5 nM and K_i rolipram binding 60 nM).[11] This letter reveals the synthesis and in vitro evaluation of a novel series of conformationally constrained quaternary substituted oxindole analogues of CDP 840 possessing the general structure shown above 1 and exemplified by 2. It was hoped to produce potent PDE4 inhibitors possessing a similar selectivity profile to CDP 840.

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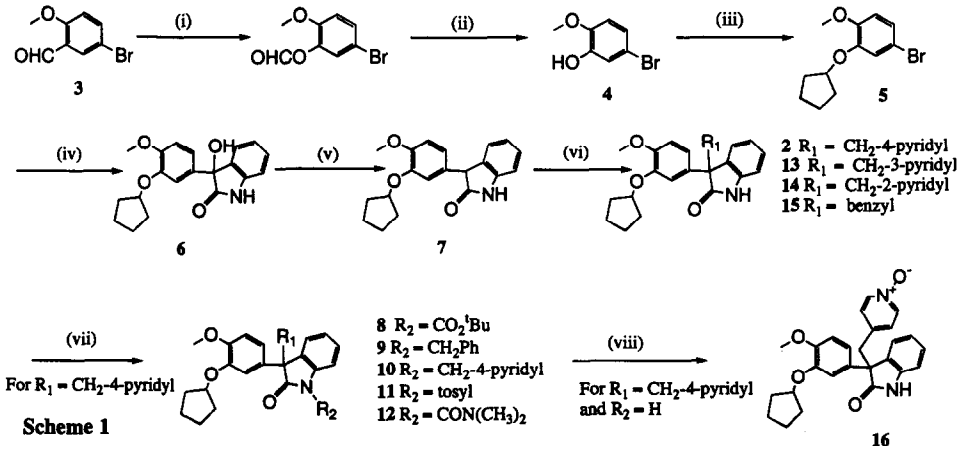
Reports on the PDE4 inhibition of a series of somewhat structurally related 3-norbornyloxy-4-methoxyphenylmethylene oxindoles and spirocyclic indanes have recently appeared.[12] Thus the following synthetic route to the series of compounds of general formula **1** was developed (Scheme 1).



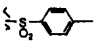
Scheme 1

Reagents and Conditions: (i) *m*-CPBA (1.5 equiv), CH_2Cl_2, 25 °C, 3 h, > 90%. (ii) KOH (2 equiv), MeOH : H_2O, 4 : 1, 25 °C, 1 h, > 90%. (iii) K_2CO_3 (1.5 equiv), cyclopentylbromide (1.5 equiv), DMF, 50 °C, 20 h, 93%. (iv) Mg (2 equiv), I_2 (cat.), THF, reflux, 0.5 h, followed by isatin addition (1 equiv.), 25 °C, 2 h, 30%. (v) Et_3SiH (2 equiv), $BF_3.Et_2O$ (0.2 equiv), CH_2Cl_2, reflux, 2 h, 53%. (vi) NaH (2.2 equiv), R_1Cl (1.1 equiv), DMF, 0 °C, 60-90%. (vii) NaH (1.1 equiv), R_2Cl or $(BOC)_2O$ (1.1 equiv), DMF, 0 °C, 70-90%. (viii) *m*-CPBA (1.25 equiv), CH_2Cl_2, 25 °C, 3 h, 82%.

Baeyer-Villiger oxidation of 2-methoxy-4-bromo-benzaldehyde **3** followed by hydrolysis gave the desired phenol **4** in good yield (> 90%). Alkylation produced **5** containing the 3-methoxy-4-cyclopentoxyphenyl moiety commonly seen in PDE4 inhibitors. Formation of the Grignard reagent of **5** followed by coupling with isatin[11] gave **6** containing the desired oxindole core. The hydroxyl group was subsequently removed by treatment with the triethylsilane/$BF_3.Et_2O$ reagent combination[14] to give **7**. Alkylation occurred preferentially at the benzylic position, as opposed to the oxindole nitrogen, giving **2, 13, 14, 15** with only small amounts of the bis-alkylated product being detected. *N*-alkylation using similar conditions gave **8, 9, 10, 11, 12** and generally proceeded in good yield (70-90%). Oxidation of **2** to its corresponding *N*-oxide **16** proceeded smoothly with *m*-CPBA (82%). Compounds were evaluated for PDE4 inhibition (IC_{50}, μM) and rolipram displacement (K_i, μM) using the methods reported by Thompson and Schmeichen respectively.[15] The results are summarized in Table 1. Activities of the two standards CDP 840 (PDE4 IC_{50} 9 nM and K_i rolipram binding 52 nM) and rolipram (PDE4 IC_{50} 320 nM and K_i rolipram binding 4.5 nM) were determined in-house using these procedures. The parent unsubstituted oxindole intermediate **7** showed weak signs of PDE4 inhibitory activity (IC_{50} 6 μM). Subsequent alkylation with chloropicoline, resulted in a ten-fold increase in PDE4 activity (**2**, IC_{50} 0.6 μM), but high affinity for the

rolipram binding site (K_i 0.2 μM). A brief exploration of *N*-functionalized derivatives **8, 9, 10, 11, 12** resulted in noticeable decreases in PDE4 activity for compounds **9, 10, 11, 12.** Only the BOC derivative **8** maintained its PDE4 activity, which perhaps parallels the potent PDE4 series of BOC-pyrrolidines reported by Stafford et al.[16] A slight improvement in PDE4 activity (IC_{50} 0.4 μM) was observed for the 3-pyridyl derivative **13.** Selectivity for the catalytic over the rolipram binding site was similar to that observed for **8.**

Table 1

Compound	R_1	R_2	PDE4 IC_{50} μM	K_i rolipram binding μM[100]
7	H	H	6	>3.7
2		H	0.6	0.2
8			0.7	2.8
9			2	>3.7
10			1	>3.7
11			2.4	>3.7
12			1.7	2.4
13		H	0.4	2.6
14		H	0.7	>3.7
15		H	1	>3.7
16		H	1.2	>3.7

The analogous 2-pyridyl **14** and benzyl **15** derivatives both possessed slightly lower PDE4 activities than **13.** Conversion of **8** to its *N*-oxide derivative also lead to reductions in both PDE4 activity and rolipram binding. In summary, the above quaternary substituted oxindole series represents a structurally novel class of PDE4 inhibitors. Sub-micromolar PDE4 activity is observed for the most promising compounds **2, 8, 13, 14** and reasonable selectivity for the catalytic binding site over the rolipram binding site for both **8** and **13** suggests potential for addressing the emetic side effect

commonly observed with potent PDE4 inhibitors. Efforts at improving in vitro potency with alternative quaternary substituted compounds will be presented in due course.

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