QUATERNARY SUBSTITUTED PDE IV INHIBITORS II : THE SYNTHESIS AND IN VITRO EVALUATION OF A NOVEL SERIES OF γ-LACTAMS

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Abstract: This communication describes the synthesis and in vitro evaluation of a novel potent series of phosphodiesterase type (IV) (PDE IV) inhibitors. Several of the quaternary substituted lactams presented possess low nanomolar IC_{50}'s for PDE IV inhibition. © 1998 Elsevier Science Ltd. All rights reserved.

PDE IV, the major PDE isozyme found within inflammatory cells, regulates levels of the secondary messenger cyclic adenosine monophosphate (cAMP) via hydrolysis to its acyclic analogue 5'-adenosine monophosphate (5'-AMP).[1] The pivotal role that increased cAMP levels play in retarding production of the pro-inflammatory cytokine tumor necrosis factor (TNF-α)[2] has pushed the cAMP specific PDE IV to the forefront of molecular targets for the potential treatment of autoimmune diseases. Early inhibitors of PDE IV include the anti-depressant rolipram **1** and analogs thereof.[3] Of more recent note are the 3,4-disubstituted pyrrolidine derivatives **4** reported by Stafford et al.[4] and the Celltech inhibitor CDP 840.[5] The latter has been shown to possess selectivity for the catalytic binding site over the rolipram binding site, a highly desirable property for overcoming the emetic side effect often seen with potent PDE IV inhibitors.[6] This letter reports the synthesis and PDE IV inhibitory activity of a novel series of quaternary substituted γ-lactams with the general structure **2**.

Rolipram 1   2   3   4   CDP840
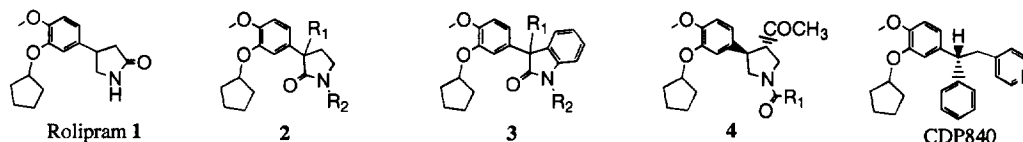
The structural resemblance of **2** to the series of quaternary substituted oxindoles **3**, originally designed as conformationally constrained analogs of CDP 840 and reported in a earlier communication,[7] is clear. From a design aspect, we hoped to increase the PDE IV potency of the latter series by maintaining the novel spirocyclic feature, while accessing compounds which were similar to the pyrrolidine series **4**.

The following synthetic scheme was therefore developed to access lactams of type **2** amenable to straightforward SAR studies at R_1 and R_2. Commercially available 3-hydroxy-4-methoxyphenylacetic acid was methylated giving **5** and alkylated with cyclopentyl bromide to afford the rolipram-like 3-methoxy-4-cyclopentoxy moiety **6**. Treatment with base and bromoacetonitrile produced **7**, followed by reduction with Raney Nickel to access the desired lactam core structure **8**.[8] BOC protection of the lactam nitrogen proved facile

and subsequent *C*-alkylation with 4-picolyl chloride gave **10** in modest yield. Ring opened products **11** and **12**, presumably formed via cleavage by adventitious NaOH, were also detected in the reaction mixture. BOC removal and reaction with a variety of alkylating/acylating/sulfonylating agents (R_2Cl) gave final products **16** to **28**. *N*-oxide formation proceeded smoothly with *m*-CPBA giving **29** and **30** respectively. Reduction of the lactam **13** and acylation afforded products **14** and **15**, respectively.

Scheme 1

Reagents & conditions :- (i) HCl (g), MeOH, rt, 20 h, 95%. (ii) cyclopentylbromide (1.5 equiv), K_2CO_3 (1.5 equiv), DMF, 70 °C, 20 h, 56%. (iii) KHMDS (1 equiv), dimethoxyethane, -78 °C, then $BrCH_2CN$ (1 equiv), 3 h, -78 °C, mono-alkylated product (17%), di-alkylated product (39%). (iv) Ra-Ni (xs), MeOH, H_2, 50 °C, 20 h, 57%. (v) $(BOC)_2O$ (1.2 equiv), Et_3N (1.2 equiv), DMAP (cat), rt, 20 h, 63%. (vi) 4-picolyl chloride (3 equiv), NaH (3 equiv), DMF, rt, 20 h, 48%. (vii) TFA, CH_2Cl_2, rt, 2 h, 90%. (viii) R_2Cl, NaH (1.1 equiv), DMF, 60-90%. (ix) *m*-CPBA (1 equiv), CH_2Cl_2, rt, 4 h, 90%. (x) Red-Al, toluene, 80 °C, 2 h. (xi) BOC_2O, Et_3N, DMAP (cat), CH_2Cl_2, rt, 3 h, 40% for (x) and (xi) combined.

Compounds were evaluated for PDE IV inhibition (IC_{50}, nM) and rolipram displacement (K_i, nM) using the methods reported by Thompson and Schmeichen respectively.[9] The results are summarized in Table 1. Weak signs of PDE IV activity were observed at an early stage with the evaluation of intermediates **8** (IC_{50} (PDE IV) 5000 nM, K_i (rolipram binding) > 3745 nM) and **9** (IC_{50} 700 nM, K_i 337 nM). This immediately highlighted the importance of the BOC group, which provided almost a ten fold increase in PDE IV potency. A similar occurrence was previously observed in the pyrrolidine series **4** by Stafford et al.[4] Formation of the quarternary
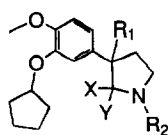
General Structure

Table 1

Cmpd #	X,Y	R_1	R_2	PDEIV IC$_{50}$ nM	K$_i$ rolipram bind. nM
8	O	H	H	5000	>3745
9	O	H	$CO_2(CH_3)_3$	700	337
10	O	[pyridylmethyl]	$CO_2(CH_3)_3$	6.3	7.5
13	O	[pyridylmethyl]	H	800	210
15	H,H	[pyridylmethyl]	$CO_2(CH_3)_3$	807	470
16	O	[pyridylmethyl]	$CO_2CH(CH_3)_2$	44	113
17	O	[pyridylmethyl]	$CO_2CH_2CH_3$	137	139
18	O	[pyridylmethyl]	CO_2CH_3	293	822
19	O	[pyridylmethyl]	[benzyl]	56	51
20	O	[pyridylmethyl]	[pyridylmethyl]	401	443
21	O	[pyridylmethyl]	$SO_2C_6H_4$p-CH_3	61	217
22	O	[pyridylmethyl]	$CON(CH_3)_2$	319	274
23	O	[pyridylmethyl]	$COCH_3$	461	367
24	O	[pyridylmethyl]	[butyl]	123	137
25	O	[pyridylmethyl]	[isopentyl]	81	80
26	O	[pyridylmethyl]	[cyclohexylmethyl]	48	43
27	O	[pyridylmethyl]	[naphthylmethyl]	17	4.3
28	O	[pyridylmethyl]	[benzofuranylmethyl]	293	822
29	O	[pyridyl N-oxide methyl]	H	1600	2247
30	O	[pyridyl N-oxide methyl]	$CO_2(CH_3)_3$	59	217
31	O	[benzyl]	H	1000	787
32	O	[benzyl]	$CO_2(CH_3)_3$	220	2996
33	O	[CH$_2$CN]	$CO_2(CH_3)_3$	82	476

centre via alkylation of **9** with picolyl chloride giving **10** produced an excellent 100-fold increase in potency (IC$_{50}$ 6.3 nM, K$_i$ 7 nM).[10] However, neither of the two ring opened side products **11** and **12** possessed PDE IV activity.

The high potency of the γ-lactam **10**, when compared to its analogue in the related oxindole series (For **3** where $R_1=$ 4-CH_2py, $R_2 =$ BOC, IC_{50} (PDE IV) 700 nM, K_i (rolipram binding) 2800 nM), exemplifies the dramatic improvement in PDE IV activity on removal of the fused phenyl ring.[7] BOC removal from **10** to give **13** resulted, as expected, in a corresponding drop in activity (IC_{50} 800 nM, K_i 210 nM). Reduction of lactam **13** to the corresponding pyrrolidine **14** and BOC protection to give **15** showed the existence of an important lactam carbonyl interaction with a >100-fold drop in PDE IV activity (IC_{50} 800 nM, K_i 470 nM). Interesting decreases in PDE IV activity on going from butyloxy-isopropyloxy-ethoxy-methoxy **10, 16, 17, 18** clearly indicates a preference for larger lipophilic groups in this region of space. A further drop in activity was also observed for the N-acetyl analog **23** (IC_{50} 461 nM, K_i 367 nM) and the N-dimethyl urea derivative **22** (IC_{50} 319 nM, K_i 274 nM). The benzyl derivative **19** showed it was possible to deviate from carbamate protection while still maintaining good PDE IV potency (IC_{50} 56 nM, K_i 51 nM). A preference for such bulky non polar groups in this position could again be seen via the subsequent drop in activity for the analogous and more polar 4-pyridyl derivative **20** (IC_{50} 401 nM, K_i 403 nM). Good activity was also observed for the sulfonamide **21** (IC_{50} 61 nM, K_i 217 nM). Based on these observations a variety of lipophilic groups were investigated for their PDE IV potency at R_2. Once again increasing the size and lipophilicity of the substituents **24, 25, 26** from butyl - isopentyl - methylcyclohexyl gave gradual increases in PDE IV potency. A similar trend was observed with affinity for the rolipram binding site. The 2-napthyl derivative **27**[11] possessed excellent PDE IV inhibitory activity (IC_{50} 17 nM) with the highest recorded rolipram binding affinity in the series (K_i 4.3 nM). Interestingly, the 1-napthyl analog **28** showed a drop in PDE IV activity (IC_{50} 293 nM) and an even greater reduction in rolipram binding affinity (K_i 822 nM). This perhaps suggests a definite shape to the binding pocket that exists around the lactam nitrogen. Encouraged with the potent inhibitors **10** and **27**, a brief SAR study was undertaken around R_1, maintaining R_2 as t-butyloxycarbonyl. A drop in activity was observed for the N-oxide derivative **30** (IC_{50} 59 nM, K_i 217 nM). Removal of the pyridyl nitrogen **32** showed a 30-fold decrease in activity (IC_{50} 220 nM, K_i 2996 nM) when compared to **10**. This compound showed highest selectivity (ten fold greater) for the catalytic over the rolipram binding site in the above series. Again BOC removal for the latter two compounds giving **29** (IC_{50} 1600 nM, K_i 2247 nM) and **31** (IC_{50} 1000 nM, K_i 787 nM) lead to dramatic decreases in PDE IV activity. Interestingly it was possible to replace the pyridyl functionality with a nitrile group **33** and still maintain good PDE IV activity (IC_{50} 82 nM, K_i 476 nM). Related nitrile functionality at a similarly positioned quarternary centre has been previously reported by Barnette et al in their series of cyanocyclohexylcarboxylic acid PDE IV inhibitors.[12]

In summary, a novel series of potent spirocyclic γ-lactam PDE IV inhibitors has been discovered with improved PDE IV activity over the spirocyclic oxindole series reported earlier.[7] A sterically large lipophilic group at R_2 gives optimal PDE IV activity, exemplified by inhibitors **10** and **27**. The lactam carbonyl also plays a key role in maintaining PDE IV activity. The pyrrolidine **15** showed a ten fold decrease in PDE IV potency.

Substitution at R_1 is a definite prerequisite for PDE IV activity with 4-picolyl substitution proving most advantageous. Several compounds possessed selectivity for the catalytic over the rolipram binding site.[13] Most encouraging was the 10-fold selectivity observed for compound **32**. In vivo studies and emesis data will be reported in the near future.

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10.   Compound **10** : 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-2-oxo-3-pyridin-4-ylmethyl-pyrrolidine-1 carboxylic acid *tert*-butyl ester, mp 148-149 °C, white solid. For $C_{27}H_{34}O_5N_2$ calcd C 69.51 H 7.34 N 6.0. Found C 69.37 H 7.33 N 5.86. MS (FAB). Exact mass measurement- Theoretical $(M+H^+)$ 467.2546, measured 467.2560. ^{1}H (CDCl$_3$) 1.5 (9H, s, 3x C$\underline{H}_3$), 1.55-1.60, 1.75-1.95 (8H, 2xm, cyclopentyl), 2.0-2.1, 2.3-2.4, 3.35-3.45, 3.6-3.7 (4H, 3xm, C$\underline{H}_2$C$\underline{H}_2$), 3.05-3.25 (2H, s, C$\underline{H}_2$py), 3.8 (3H, s, OC$\underline{H}_3$), 4.7-4.75 (1H, m, C$\underline{H}$), 6.75-6.80, 7.0 (5H, m, s, C$_6\underline{H}_3$, 2 from C$_5\underline{H}_4$N), 8.35-8.40 (2H, br m, 2 from C$_5\underline{H}_4$N).

11.   Compound **17** : 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-naphthalen-2-ylmethyl-3-pyridin-4-ylmethyl-pyrrolidin-2-one, an oil. MS (FAB) 507 (MH^+), 414. Exact mass measurement- Theoretical $(M+H^+)$ 507.2648, measured 507.2679. ^{1}H (CDCl$_3$)1.55-1.65, 1.75-2.0 (8H, 3xm cyclopentyl), 2.05-2.2, 2.25-2.4, 2.9-3.0, 3.05-3.1 (4H, m, C$\underline{H}_2$C$\underline{H}_2$), 3.15-3.30 (2H, m, C$\underline{H}_2$py), 3.7 (3H, s, OC$\underline{H}_3$), 4.75-4.80 (1H, m, C$\underline{H}$), 4.5-4.7 (2H, m, C$\underline{H}_2$napth), 6.75-6.8, 6.85-6.9, 6.9-6.95, 7.1-7.2, 7.4-7.5, 7.6-7.65, 7.65-7.7, 7.75-7.8 (12H, 8xm, C$_6\underline{H}_3$, 2 from C$_5\underline{H}_4$N, C$_{10}\underline{H}_7$), 8.35-8.45 (2H, br m, 2 from C$_5\underline{H}_4$N).

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