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Substituted 2-Pyridinemethanol Derivatives as Potent and Selective Phosphodiesterase-4 Inhibitors

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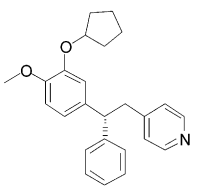
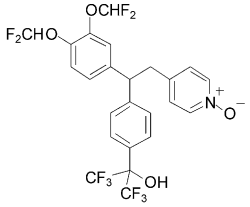
Abstract—The synthesis and the phosphodiesterase-4 (PDE4) inhibitory activity of 2-pyridinemethanol derivatives is described. The evaluation of the structure–activity relationship (SAR) in this series of novel PDE4 inhibitors led to the identification of compound **9** which exhibits excellent in vitro activity, desirable pharmacokinetic parameters and good efficacy in animal models of bronchoconstriction.

Cyclic nucleotide phosphodiesterases (PDEs) constitute a broad family of enzymes responsible for the hydrolysis and consequent deactivation of the second messengers cAMP and cGMP.[1] The cAMP specific PDE4 isozymes,[2] encoded by four genes (A–D), are particularly abundant in inflammatory and immune cells and in airway smooth muscles.[3] It is now well established that inhibition of PDE4 results in antiinflammatory and immunomodulatory activities, both in vitro and in animal models.[4] A number of PDE4 inhibitors are under clinical evaluation for the treatment of asthma, chronic obstructive pulmonary disease (COPD) and atopic dermatitis.[5] Despite promising results, the therapeutic potential of PDE4 inhibitors remains hampered by their dose-limiting side effects such as nausea and emesis.[6] Therefore, the search for novel PDE4 inhibitors with superior therapeutic index remains a very active field of research.[5,7]

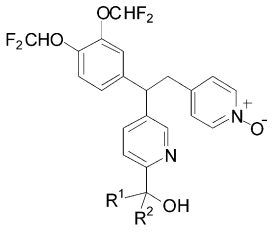


CDP840



L-791,943

Recently, we reported how a SAR study directed toward the improvement of the metabolic stability of PDE4 inhibitor CDP840[8] led to the discovery of compound L-791,943.[9] The development of L-791,943 was precluded, despite an otherwise favorable pharmacological profile, by an excessively long half-life in a variety of animal species. The introduction of a soft metabolic site[10] to the structure of L-791,943 and the substitution of the metabolically resistant bis(trifluoromethyl)carbinolbenzene moiety by an aminopyridine residue[11] both produced inhibitors with improved pharmacokinetic profiles. We now report on the optimization of a novel series of triarylethane derivatives of general structure **1**, bearing a 2-pyridinemethanol residue.[12]



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The synthesis of PDE4 inhibitors **1** is presented in Scheme 1. Palladium catalyzed methoxycarbonylation[13] of bromopyridine **2**[11] afforded in 95% yield the ester **3**, which was transformed to the Weinreb amide[14] **4**.

Addition of a variety of organometallic reagents to this intermediate gave access to ketones **5a–e**. Selective

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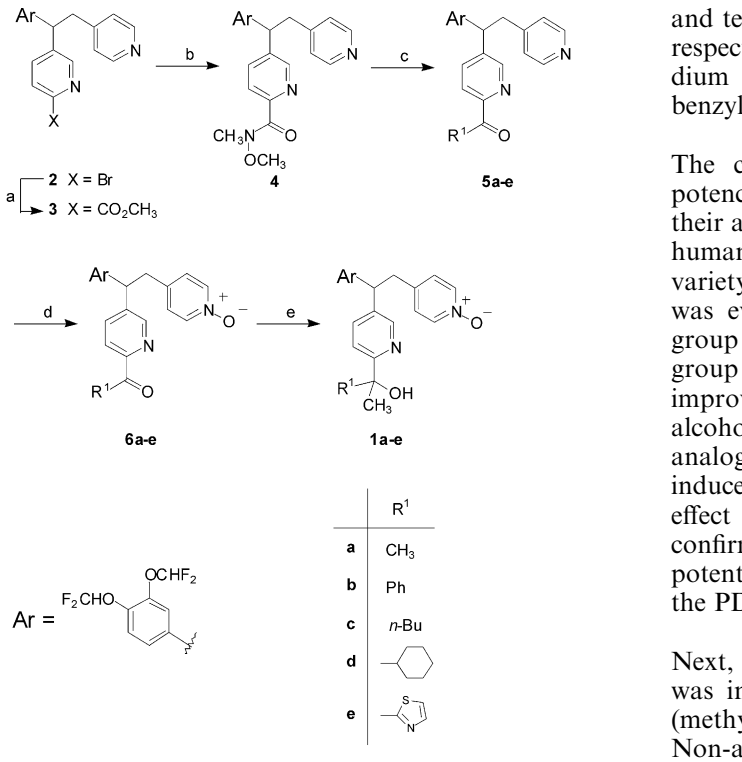
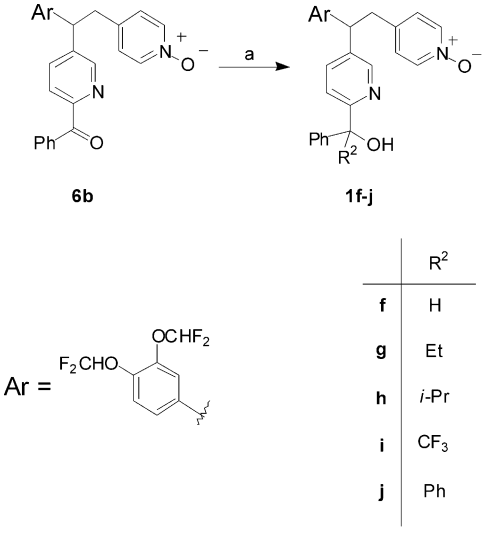


Scheme 1. Reagents and conditions: (a) CO, CH_3OH, $Pd(OAc)_2$, dppf, Et_3N, DMF, 60 °C, 95%; (b) $CH_3O(CH_3)NH{\cdot}HCl$, CH_3MgBr, THF, −78–0 °C, 91%; (c) **5a**: CH_3MgBr, THF, 0 °C, 100%; **5b**: PhMgCl, THF, −78–0 °C; **5c**: *n*-BuLi, THF, −78 °C, 51%; **5d**: cyclohexylmagnesium chloride, THF, 0 °C; **5e**: thiazole, *n*-BuLi, THF, −78 °C, 98%; (d) MMPP, CH_2Cl_2/CH_3OH (9/1), rt; (e) CH_3MgBr, CH_2Cl_2, −78 °C, 50–80%.

oxidation of the monosubstituted pyridine ring was then accomplished by treatment with magnesium monoperoxyphthalate (MMPP) to afford pyridine-*N*-oxides **6a–e**. Addition of methylmagnesium bromide to these ketones gave the desired tertiary alcohols **1a–e**. Analogues **1f–j** were obtained by the addition of the requisite organometallic reagents to phenylketone **6b** (Scheme 2). Use of ethylmagnesium bromide gave access to secondary and tertiary alcohols **1f** and **1g** in yields of 35 and 50% respectively. Benzyl derivative **8** was obtained by palladium catalyzed coupling of bromopyridine **7**[11] with benzylmagnesium bromide in 73% yield (Scheme 3).

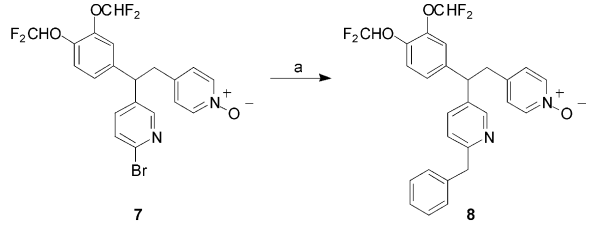


Scheme 2. Reagents and conditions: (a) **1f** and **1g**: EtMgBr, CH_2Cl_2, −78 °C, 35 and 50%; **1h**: *i*-PrMgBr, CH_2Cl_2, −78 °C, 47%; **1i**: $TMSCF_3$/TBAF, THF, 0 °C, 71%; **1j**: PhMgCl, CH_2Cl_2, −78 °C, 39%.

The compounds prepared were evaluated for their potency to inhibit the PDE4A enzyme in vitro[15] and for their ability to inhibit LPS-induced TNF-α formation in human whole blood (HWB).[16] Initially, the effect of a variety of substituents at position 2 of the pyridine ring was evaluated (Table 1). Replacement of the methyl group present in compound **6a** by a lipophilic phenyl group produces ketone **6b**, an inhibitor showing a 4-fold improvement in potency. The analogous secondary alcohol **1f** is even more potent, while the reduced benzyl analogue **8** shows a decreased ability to inhibit LPS-induced TNF-α formation in HWB. The favorable effect brought by a hydroxyl group at this position is confirmed by the fact that tertiary alcohol **1b** is the most potent inhibitor in this series with an IC_{50} of 0.6 nM in the PDE4A assay and 0.35 μM in the HWB assay.

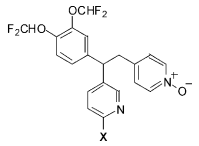
Next, the effect of substitution at the carbinol position was investigated (Table 2). Reduction of lipophilicity (methyl derivative **1a**) has a negative effect on potency. Non-aromatic analogues **1c** and **1d** are equipotent to phenyl derivative **1b** in the HWB assay despite lower potencies in the enzyme assay. Replacement of the phenyl group by heterocycles (e.g., thiazole **1e**) did not improve the inhibitory profile. The phenyl analogue **1b** remains the best PDE4 inhibitor in this series. Substitution of the methyl group (R^2), at the carbinol position, by larger alkyl (**1g** and **1h**), trifluoromethyl (**1i**) or phenyl (**1j**) units did not have significant effects on potency (Table 3). Tertiary alcohol **1b** was selected for further evaluation.

Pure diastereomers of inhibitor **1b** were obtained in the following way (Scheme 4). First, the enantiomers of ketone **6b** were resolved by chromatography, using a Chiralpak AD HPLC column (25% *i*-PrOH in hexanes). Under these conditions, the PDE4 inhibitory activity resides mainly in the fast-eluting enantiomer (−)-**6b** (data not shown). Enantiomer (−)-**6b** was then converted to **1b** diastereomers 1 and 2 by treatment with methylmagnesium bromide. A second chromatographic separation on the Chiralpak AD HPLC column (25% EtOH in hexanes) yielded the fast-eluting diastereomer 1 (**9**) and the slow-eluting diastereomer 2 (**10**). The same procedure applied to enantiomer (+)-**6b** afforded diastereomers 3 and 4 (**11**), which were not separated.



Scheme 3. Reagents and conditions: (a) BnMgBr, $ZnBr_2$, $Pd(PPh_3)_4$, THF, −78 °C to rt, 73%.

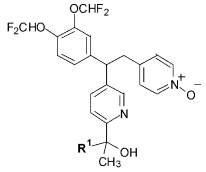
Table 1. SAR at position 2 of the pyridine ring



Compd	X	PDE 4A IC_{50} (nM)[a]	HWB (TNF-α) IC_{50} (μM)[a]
6a		102	2.2
6b		23	0.60
1f		6	0.36
8		3	0.77
1b		0.6	0.35
CDP840	—	4	16

[a]Each IC_{50} value is an average of at least three experiments.

Table 2. SAR on substituent $\mathbf{R^1}$ of the carbinol moiety



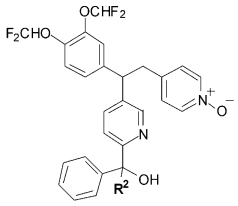
Compd	R^1	PDE 4A IC_{50} (nM)[a]	HWB (TNF-α) IC_{50} (μM)[a]
1b		0.6	0.35
1a	CH_3	40	0.89
1c	*n*-Bu	6	0.34
1d		1.2	0.30
1e		6	0.49

[a]Each IC_{50} value is an average of at least three experiments.

As observed previously in the triarylethane class of PDE4 inhibitors,[8,10,11] a major stereochemical effect on inhibitory potency is observed at the chiral methine carbon. Diastereomers 3 and 4 (**11**) are significantly less potent than diastereomers 1 (**9**) and 2 (**10**) (Table 4). In contrast, the stereochemistry at the chiral carbinol center does not influence significantly the biological activity since both diastereomers **9** and **10** are essentially equipotent in vitro.

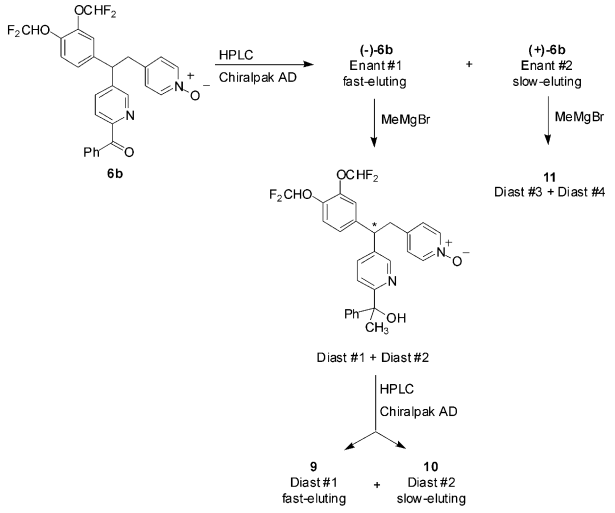
Despite similar intrinsic potencies, diastereomer **9** presents a slightly superior in vivo profile compared to **10**.

Table 3. SAR on substituent $\mathbf{R^2}$ of the carbinol moiety



Compd	R^2	PDE 4A IC_{50} (nM)[a]	HWB (TNF-α) IC_{50} (μM)[a]
1b	CH_3	0.6	0.35
1g	Et	1.0	0.16
1h	*i*-Pr	0.8	0.37
1i	CF_3	2.4	0.46
1j	Ph	0.8	0.55

[a]Each IC_{50} value is an average of at least three experiments.



Scheme 4. Resolution of tertiary alcohol **1b**.

Table 4. Biological activity of diastereomers **9**, **10** and **11**

Compd		PDE 4A IC_{50} (nM)[a]	HWB (TNF-α) IC_{50} (μM)[a]
1b	Racemic Mixture	0.6	0.35
9	Diastereomer 1	2	0.16
10	Diastereomer 2	1	0.11
11	Diastereomers 3 and 4	48	3.5

[a]Each IC_{50} value is an average of at least three experiments.

For example, inhibitors **9** and **10** inhibit ovalbumin induced bronchoconstriction in conscious guinea pigs[17] by 62 and 34% respectively when administered ip at 0.3 mg/kg (0.5 h pre-treatment). This behavior may correlate with the fact that diastereomer **9** presents a superior pharmacokinetic profile in various animal species. For this reason, compound **9** was selected for further evaluation. Inhibitor **9** is highly selective against the PDE4 enzyme ($IC_{50}=2$ nM); no inhibitory activity was detected against other phosphodiesterases at concentrations up to 5 μM. In contrast to its predecessor L-791,943,[9] compound **9** presents suitable half-lives of 1.5 h in rats and 2.2 h in squirrel monkeys following intravenous administration at 5 mg/kg. The compound is also well

absorbed in both species, following oral dosage, with bioavailabilities of 57 and 73% respectively. Induction of emesis in squirrel monkeys is observed at an oral dose of 10 mg/kg. Under these conditions, the maximal concentration (C_{max}) of **9** measured in plasma is 2.2 μM. Knowing that compound **9** inhibits LPS-induced TNF-α production in squirrel monkey whole blood with an IC_{50} of 0.11 μM, an estimation of the emetic window can be made by taking the ratio of these two concentrations. In the case of **9**, this ratio is 20, while for CDP840 and L-791,943 the same analysis provides ratios of 8 and >20 respectively. Inhibitor **9** is also effective for the inhibition of ascaris-induced bronchoconstriction in conscious sheep,[18] exhibiting 33% and 91% inhibition of the early and late-phase responses respectively, at a dose of 0.5 mg/kg iv (4 days of dosing) given 2 h prior to challenge. On the whole, the data indicates that inhibitor **9** shows good in vivo efficacy in pulmonary function models while maintaining an improved window with respect to emesis.

In conclusion, we have developed a novel series of potent PDE4 inhibitors by replacing the metabolically resistant bis(trifluoromethyl)carbinolbenzene moiety found in L-791,943 by substituted 2-pyridinemethanol residues. The results of the SAR study in this series led to the identification of PDE4 inhibitor **9**, which exhibits excellent in vitro activity (HWB IC_{50} = 0.16 μM). Furthermore, compound **9** is well absorbed and presents a shorter half-life than L-791,943 in rats and squirrel monkeys. Compound **9** is active in the guinea pig model of ovalbumin-induced bronchoconstriction (0.3 mg/kg) and in the sheep model of ascaris-induced bronchoconstriction (0.5 mg/kg).

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