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New substituted triaza-benzo[*cd*]azulen-9-ones as promising phosphodiesterase-4 inhibitors

Ingrid Devillers,* Isabelle Pevet, Henry Jacobelli, Corinne Durand, Véronique Fasquelle, Jocelyne Puaud, Bernard Gaudillière, Moulay Idrissi, François Moreau and Roger Wrigglesworth

Pfizer Global Research and Development, Fresnes Laboratories, 3-9 Rue de la Loge, F-94265 Fresnes Cedex, France

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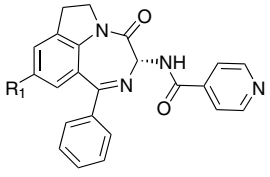
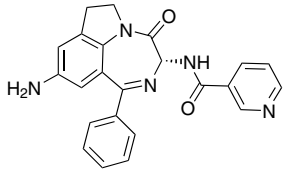
Cyclic nucleotide phosphodiesterases (PDEs) are a broad family of enzymes responsible for the hydrolysis of cyclic c-AMP and c-GMP.[1] PDE4 is a specific c-AMP isoenzyme that is particularly abundant in airway smooth muscle, immune, and inflammatory cells and is therefore considered as a potential molecular target for the development of new immunomodulatory and anti-inflammatory drugs.[2] A number of selective PDE4 inhibitors are under clinical evaluation for the treatment of asthma, chronic obstructive pulmonary disease (COPD), and atopic dermatitis.[3] Although interest has grown steadily, the therapeutic potential of PDE4 inhibitors remains hampered by their dose-limiting side effects such as nausea and emesis.[4]

Recently we reported a novel series of tetrahydrodiazepinoindole PDE4 inhibitors. The initial structure–activity relationship (SAR) studies led to the identification of a first candidate for development, CI-1018 (**1**),[5] which was further improved by the discovery of a new family of 9-amino-tetrahydrodiazepinoindoles. This new series displayed improved in vitro PDE4 activity and selectivity versus other PDEs. One specific compound CI-1044 (**3**) provided efficient in vivo activity in models of antigen-induced eosinophil recruitment and production of LPS-induced TNFα in rats. This compound was registered as a candidate for development.[6]

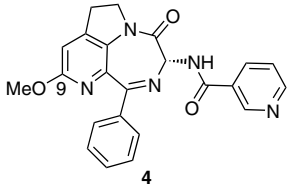




	PDE4 IC_{50}		PDE4 IC_{50}
1 R1 = Me **CI-1018**	1.1 μM	**3 -CI-1044**	0.27 μM
2 R1= OMe	4.4 μM		

Despite its promising pharmacological profile, the aniline structural fragment contained in CI-1044 (**3**) structure was considered as a toxicophore.[7] Aniline fragments have been implicated in two principal metabolic mechanisms of toxicity. Oxidation of the aromatic ring either *ortho* or *para* to the nitrogen or of the aniline nitrogen can lead to reactive metabolites, which are implicated in toxic side effects.

We now report the targeted synthesis and evaluation of the triaza-benzo[*cd*]azulen-9-one system (**4**) containing the substituted azaindoline residue obtained by the replacement of the aniline moiety. Other substituents were chosen based on previous SAR evaluation with a methoxy group at position 9 and nicotinic acyl as an optimized side chain.



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Keywords: PDE4 inhibitor; Azabenzodiazepine; CI-1044; *ortho*-Directed metallation; Pyridine.

* Corresponding author. Tel.: +33-1-45-80-74-86; fax: +33-1-45-60-38-01; e-mail: ingriddevillers@hotmail.com

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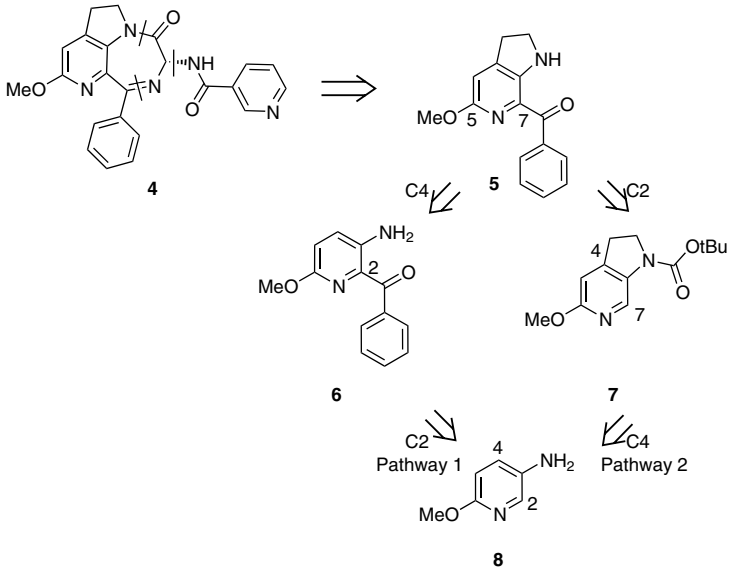
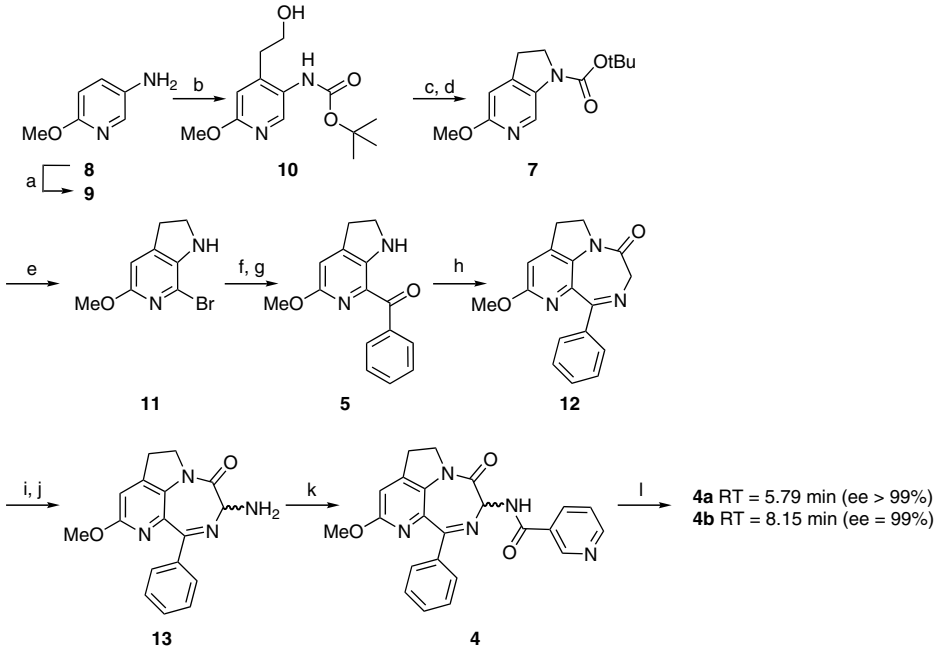


Scheme 1. Retrosynthetic analysis of 2,3-dihydro-pyrrolo[2,3-*c*]pyridine.

The retrosynthetic analysis we envisaged is described in Scheme 1. The key step in the synthesis was the preparation of 5-methoxy-7-benzoyl substituted 6-azaindoline (2,3-dihydro-pyrrolo[2,3-*c*]pyridine) (**5**). To the best of our knowledge only few examples of a 2,4-substituted-3-aminopyridine synthesis are described in the literature.[8] Most of the methodologies concerned 4-aminopyridine.[9] In this context, we investigated different pathways based on the *ortho*-lithiation at halogenated C2 then C4 (pathway 1) or directed *ortho*-metallation at C4 then C2 (pathway 2), respectively (Scheme 1).

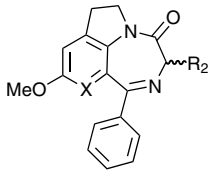
We initially started with our attempts to introduce both substituent following a general *ortho*-lithiation strategy. Unfortunately, in each pathway, the reaction with the second electrophile failed.[10] Therefore we focussed our attention to the functionalization at position 7 of the 6-azaindoline in the second pathway (step C2, Scheme 1), which ultimately lead to the successful synthesis of PDE4 inhibitor (**4**) described in Scheme 2.

The synthesis started with the conversion of the 2-methoxy-5-aminopyridine to the corresponding car-



Scheme 2. Reagents and conditions: (a) Boc_2O, dioxane, 96%; (b) *n*-BuLi, TMEDA, ethylene oxide, ether, −78 °C, 57%; (c) MsCl, CH_2Cl_2, 90%; (d) LiHMDS, THF, −78 °C, 91%; (e) HBr, H_2O_2, 75%; (f) $Zn(CN)_2$, $Pd_2(dba)_3$, dppf, DMF, 74%; (g) PhMgBr, THF, 55%; (h) methyl glycinate hydrochloride, pyridine, 48 h, 43%; (i) *t*-BuOK, trisyl azide, CH_3CO_2H, THF, −78 °C, 26%; (j) PPh_3, H_2O, THF, 69%; (k) TOTU, DIPEA, nicotinic acid, CH_2Cl_2, 84%; (l) chiral preparative chromatography Chiralcel OD-H, 17 mL/min, 100% CH_3CN, 220 nM.

Table 1. Phosphodiesterase inhibitory activities for compounds



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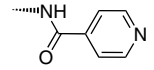
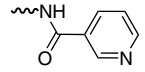
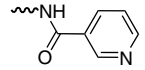
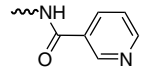
Entry	Compounds	X	R2	PDE4 IC_{50}[a], μM[a]	PDE1	PDE3	PDE5
1	**14a**	C	H	40	52	77	ND[b]
2	**12**	N	H	23	>100	>100	91
3	**2**[c,c]	C		4.4	16	41	ND
4	**4** (*rac*)	N		6.1	14	12	>100
5	**4a**[d]	N		4.3	5.8	31	95
6	**4b**[d]	N		73	28	>100	>100

[a] Values are means of three experiments.
[b] Not determined.
[c] See Ref. 6.
[d] Single enantiomer.

bamate (**9**). The *ortho*-lithiation of the carbamate at C4 on the pyridine ring using BuLi followed by addition of ethylene oxide afforded the 4-(2-hydroxyethyl) substituted amino pyridine (**10**). The amino alcohol was then cyclized by conversion to the methylsulfonate. Although this primary mesylate derivative underwent direct in situ cyclization, we improved yields by treatment with Li-HMDS to furnish the pyrrolidino–pyridine compound (**7**) as previously described in the literature.[9] Again, all attempts to introduce the substituent at C2 on the pyridine ring failed using the *ortho*-lithiation reaction. Therefore we then performed aromatic functionalization of the pyridine ring. Bromination using HBr in H_2O_2 gave the *N*-deprotected 2-brominated pyrrolidino–pyridine compound (**11**) in one step in good yield.[11] Subsequent cyanation[12] was performed with an optimized palladium catalyzed reaction and introduction of the benzoyl group was achieved by the Grignard reaction[13] with phenylmagnesium bromide giving the desired phenylmethanone compound (**5**). The latter was converted to the seven-membered ring (**12**) using methylglycinate hydrochloride following the procedure previously described.[6] The introduction of the primary amino function was first investigated via oxime conversion but the subsequent reduction failed or gave a poor yield for the two steps. Then we turned our attention to the direct azidation[14] using trisyl azide to favor the azide transfer under carefully controlled reaction conditions.[15] Mild reduction to the primary amine was accomplished using triphenylphosphine in THF/H_2O[16] to provide intermediate (**13**) while catalytic hydrogenation led to overreduction of the diazepine ring. Classical condensation with the appropriate acid provided final targeted compound (**4**). Pure enantiomers (**4a** and **4b**) were obtained after resolution of the racemic mixture by chiral chromatography.

Inhibitory activities of these compounds have been determined on different PDE isoenzymes following procedures previously described.[6] Results are presented in Table 1.

Based on our previous SAR studies, we were interested to compare whether the introduction of a nitrogen atom on the benzodiazepine ring would affect the PDE4 activity and selectivity versus other PDEs. Synthetic intermediates (**12** and **14a**) already showed weak activity (entries 1 and 2). According to known SAR, introduction of the aromatic side chain R2 led to improved activities for pyridino compounds. Furthermore the activity range was conserved with the replacement of the aniline moiety (entries 3 and 4) and only one single enantiomer (**4a**) was shown to be active (entry 5).

These promising data open large perspectives for the preparation of corresponding 9-amino-triaza-benzo-[*cd*]azulen-9-one, which remains to be investigated.

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