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LETTERS

SYNTHESIS AND EVALUATION OF A NOVEL SERIES OF PHOSPHODIESTERASE IV INHIBITORS. A POTENTIAL TREATMENT FOR ASTHMA

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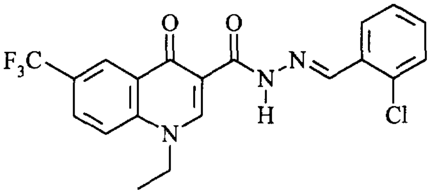
Abstract: The synthesis and pharmacological profile of a novel series of potent and selective phosphodiesterase type IV (PDE IV) inhibitors is described. © 1998 Elsevier Science Ltd. All rights reserved.

Asthma is a chronic, severe and all too often fatal disease the incidence of which is increasing.[1] A range of treatments are currently available based upon inhaled β-agonists[2] and steroids both of which offer only symptomatic relief and have associated side effects. There is an unmet medical need for an orally dosed anti-inflammatory agent, which treats the underlying disease, with a lower side effect profile than current therapies. Over the last decade, the inhibition of phosphodiesterase type IV (PDE IV) has emerged as an anti-inflammatory treatment for asthma.[3] Indeed a vigorous pursuit of selective PDE IV inhibitors has resulted.[4]

A major concern that has arisen from the use of PDE IV inhibitors in clinical trials is the ability of these drugs to induce nausea and emetic side effects.[5] The reasons for emesis have not been proven conclusively but evidence suggests that rolipram,[6] a known PDE IV inhibitor, binds to the PDE IV enzyme at the catalytic site and a rolipram high-affinity binding site[7] which is associated with the nausea and emetic side effects.[4d] Since we believe that a selective PDE IV inhibitor would offer improved therapy with reduced side effects, we accordingly undertook a programme to identify compounds that would have potent PDE IV inhibitory activity but that would exhibit considerably lower inhibitory activity at the rolipram high-affinity binding site.

Compound **1** was identified by directed random screening and provided an exciting non-catechol based lead structure with a reasonably selectivity profile as defined above.[8]

Scheme 1 Initial Lead



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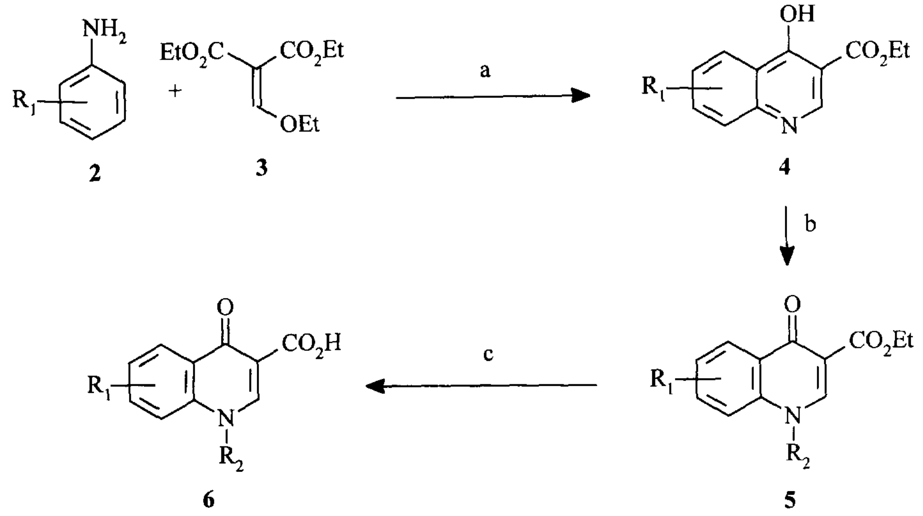
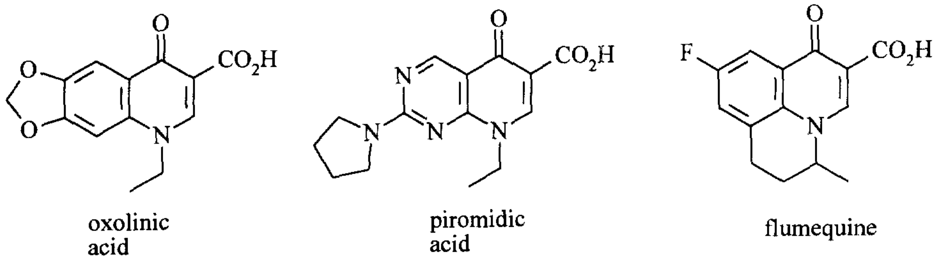
Quinolone-3-carboxylic acids have been utilised as antibacterial agents for some time.[9] A variety of synthetic routes towards their synthesis has been investigated. The method of Kaminsky and Meltzer[10] provided quinolone-3-carboxylic acids **6** as outlined in scheme 2. Condensation of anilines **2** with diethyl ethoxymethylenemalonate **3** followed by thermal cyclisation gave esters **4**, alkylation and hydrolysis of which gave carboxylic acids **6**. Alternatively, a number of these acids such as oxolinic acid, piromidic acid and flumequine, were commercially available, Scheme 3.

Scheme 2 Preparation of Quinolone-3-carboxylic acids



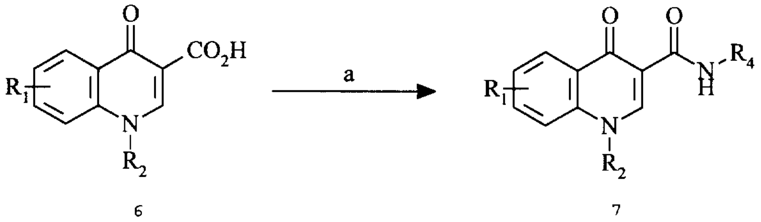
Reagents (a) i. 110°C, 3h ii. Ph_2, Ph_2O, 270°C; (b) NaH, DMF, R_2X; (c) $LiOH.H_2O$, THF, H_2O

Scheme 3 Commercially available Quinolone-3-carboxylic acids



Amides **7** of these quinolone-3-carboxylic acids **6** were then generated via their mixed anhydrides as outlined in Scheme 4.

Scheme 4 Preparation of Amides



Reagents (a) i. isopropenylchloroformate, Et_3N, CH_2Cl_2 ii. H_2NR_4

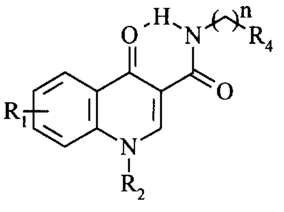
A number of amides **7** were generated in this way, some of which are detailed in Table 1. Compound **8** was produced by direct N-methylation of **7a**. Compound **9**, however, was synthesized by first treating the corresponding ester **5** with phosphorus pentasulfide in refluxing pyridine to give the vinylogous thioamide. Hydrolysis of the ester followed by coupling with an amine as before gave compound **9**.

The compounds were evaluated initially in *in vitro* screens for PDE IV catalytic site activity[11] and high-affinity rolipram binding site activity[12] (RBA). As can be seen from Table 1 this series provides potent PDE IV inhibitors with an excellent PDE IV/RBA ratio.

The chain length linking the amide nitrogen to the aromatic ring could be quite varied with the conformationally constrained bicycles **7c** and **7e** being as active as their non-constrained analogues. Similarily the N-1 substituent could tolerate ethyl, propyl and cyclised flumequine derivatives as depicted by compounds **7b**, **7d** and **7g** respectively.

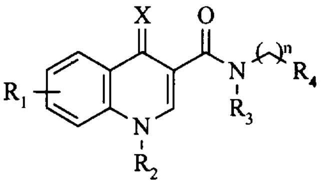
From the ^1H nmr spectra of these compounds it was evident that a strong H-bond existed between the amide N-H and the quinolone carbonyl, as illustrated in Scheme 5.

Scheme 5 Hydrogen Bonding Interaction



This interaction seems to be important since methylation of the amide nitrogen (compound **8**) greatly reduced the PDE IV potency. Exchanging sulfur for oxygen (compound **9**) gave a weaker H-bonding interaction as observed by nmr and one of the best *in vitro* PDE IV potencies in this series.

Table 1 *In Vitro* Biological Data



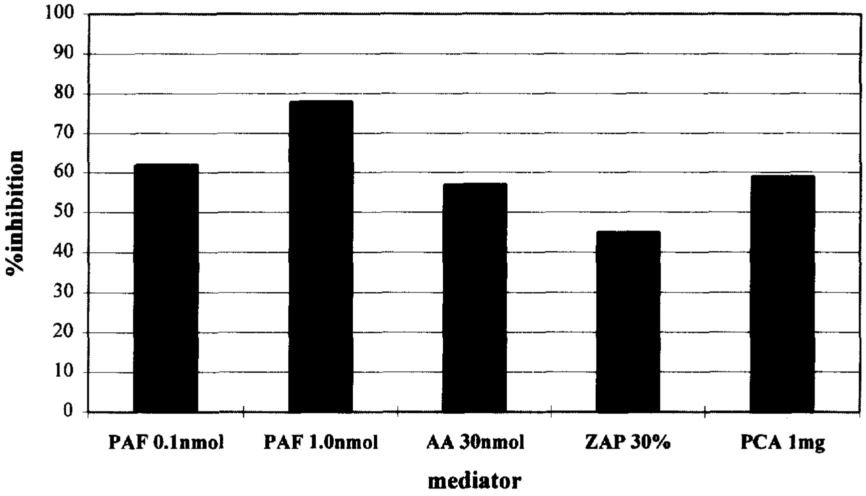
Compound	X	n	R$_1$	R$_2$	R$_3$	R$_4$	PDE IV *IC$_{50}$	RBA IC$_{50}$	Ratio PDE IV/RBA
7a	O	2	6-CF$_3$	Et	H	Ph	0.6μM	8% @ 1μM	<0.6
7b	O	2	6-CF$_3$	Et	H	4-Pyridyl	1.5μM	24% @ 10μM	<0.15
7c	O	0	6-CF$_3$	Et	H	1-(5,6-Dimethoxy indanyl)	0.9μM	22% @ 1μM	<0.9
7d	O	2	6-CF$_3$	Pr	H	4-Pyridyl .HCl	1.7μM	10μM	0.17
7e	O	0	P*	Et	H	1-(5-Acetamido indanyl)	1.8μM	17% @ 1μM	<1
7f	O	2	P*	Et	H	4-Pyridyl	1.2μM	11% @ 1μM	<1
7g	O	2	F*	F*	H	4-Pyridyl	7μM	8% @ 10μM	<0.7
7h	O	2	O*	Et	H	4-Pyridyl	23μM	31% @ 10μM	~1
8	O	2	6-CF$_3$	Et	Me	Ph	49μM	15% @ 100μM	<0.49
9	S	2	6-CF$_3$	Et	H	4-Pyridyl	0.46μM	15% @ 1μM	<0.46

O* = oxolinic acid derivative.
F* = flumequine derivative.
P* = piromidic acid derivative.

Rolipram was used as an assay standard for the PDE IV (3.5μM) and RBA (25nM) assays. Initial lead compound **1** had a PDE IV IC$_{50}$ of 1.1μM and was inactive in the RBA assay at 10μM.

In order to investigate the *in vivo* efficacy of this series of compounds a number of the compounds were dosed in a guinea pig skin eosinophilia model.[13] Compounds **7c**, **7e**, **7f**, **7g**, **7h** and **9** were each administered at 10mg/Kg po in this model. Each showed good activity across the range of mediators,[14] as illustrated for compound **7g** in Table 2.

Table 2 **Inhibition of Eosinophilia in the Guinea Pig by Oral Dosing of Compound 7g at 10mg/Kg**



Compounds were also assessed for emetic and CNS side effects in a ferret emesis model.[15] After oral administration of the compounds the animals were observed for signs of vomiting, retching, head burrowing, mouth scratching or salivation. Compound **7g** was clear of all side effects at 20mg/Kg. This compares favourably with rolipram which when administered orally shows inhibition of eosinophilia in the guinea pig skin model at 0.5 mg/Kg but is emetic in the ferret emesis model at 0.3mg/Kg.

Conclusions

We have identified a novel series of non-catechol based PDE IV inhibitors displaying good oral activity in a functional model of inflammation utilising a range of key mediators at doses which we have shown have no emetic side effects. Our strategy to further improve the enzyme potency and oral activity of this and other series of compounds will be the subject of future publications.

Acknowledgement

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