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Discovery of triazines as potent, selective and orally active PDE4 inhibitors

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ABSTRACT

Expanding on HTS hit **4** afforded a series of [1,3,5]triazine derivatives as novel PDE4 inhibitors. The SAR development and optimization process with the emphasis on ligand efficiency and physicochemical properties led to the discovery of compound **44** as a potent, selective and orally active PDE4 inhibitor.

Hydrolyzing the key secondary messengers adenosine and guanosine 3′,5′-cyclic monophosphates (cAMP and cGMP) into their corresponding 5′-monophosphate nucleotides and, thus, decreasing concentrations of cAMP and cGMP, phosphodiesterase enzymes (PDEs) play an important role in various biological processes.[1] Based on primary structure, substrate specificity and sensitivity to cofactors or inhibitory drugs, eleven isoenzymes of mammalian cyclic nucleotide phosphodiesterase have been identified so far.[2] Among them, PDE4 is responsible for the degradation of cAMP in many cell types and has been proposed as an attractive target in various diseases including asthma and chronic obstructive pulmonary disease (COPD).[3]

First generation PDE4 inhibitors represented by rolipram **1** (Fig. 1) demonstrated severe side effects of nausea and emesis at effective anti-inflammatory doses. Whilst second generation PDE4 inhibitors such as cilomilast **2** (Fig. 1) and roflumilast **3** (Fig. 1) have shown improved side effect profiles in clinical trials, the maximum dose is still limited by adverse events.[4] After numerous compounds not having advanced past the clinic, roflumilast **3** was recently launched for the treatment of COPD.[5] The side effect profiles of many PDE4 inhibitors structurally related to compounds **1**-**3** have triggered interest in the development of novel, sometimes sub-type selective chemotypes, that may exhibit an improved therapeutic window, lacking the dialkoxyphenyl group and also avoiding the aminodichloropyridine moiety that has recently come under scrutiny by public health authorities because of its carcinogenic metabolites (ADCP-*N*-oxide and its epoxide).[4,6] As in many instances an increased therapeutic index in animal models was achieved only at the expense of accepting unfavorable physicochemical properties for the inhibitor molecule, our aim was therefore to control molecular weight and focus on ligand efficiency during the optimization process.

In this context, screening of our in-house compound library resulted in the identification of [1,3,5]triazine derivative **4** exhibiting inhibitory activity in the sub-micromolar range (Fig. 2). PDE4 inhibitors based on the *s*-triazine scaffold, exemplified by **5** (Fig. 2) with an IC_{50} value of 140 nM, have been reported before but were not tested in vivo.[7] This communication describes our efforts to optimize hit compound **4** into a potent, selective and orally active PDE4 inhibitor.

The synthesis of the triazine derivatives, outlined in Scheme 1, proceeded via sequential substitution of cyanuric chloride under standard reaction conditions. Starting with the bulkier component the two amino groups were introduced via a one-pot method without isolating the intermediate. Replacement of the remaining chloro atom at elevated temperatures led to the final products. Some α-aminonitriles used as building blocks were not commercially available and prepared by treating the corresponding ketones in the presence of ammonia or methylamine with potassium cyanide.[8] A different synthetic route was applied to obtain **21** following an established procedure.[9]

The compounds described in this paper were assessed against PDE4A, PDE4B and PDE4D isoforms.[10] As no selectivity was observed, only the PDE4A inhibitory activities will be presented herein.

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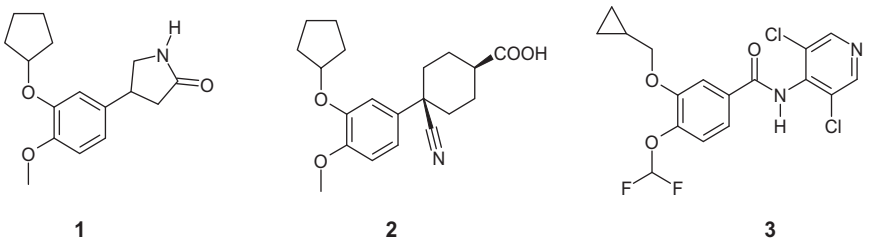


Figure 1. Structures of PDE4 inhibitors rolipram **1**, cilomilast **2**, and roflumilast **3**.

At the outset of our SAR studies we focused on modifying the *tert*-butyl group (Table 1). Increased steric bulkiness by extending two of the methyl groups (**6**) or introducing a cyclohexyl ring (**7**) led to an improvement in potency. Interestingly, the attachment of a cyano function (**8**-**10**) yielded the first double digit nanomolar inhibitors in the series. A smaller or larger size of the cycle and further prolongation of the ethyl chains showed barely any influence on inhibitory activity (**11**-**13**). The fourfold less active ethinyl derivative **14** indicated a weak interaction of the cyano nitrogen with the enzyme serving as an hydrogen bond acceptor.

Next we moved on to explore the structure-activity relationship of the methylamino substituent (Table 2). While a sharp drop in potency was caused by omitting the methyl group (**15**), adding size at this position (**16**-**18**) was not well tolerated either. In addition, the two hydrogen bond donor elements were identified as crucial structural features required for potent inhibition (**19** and **20**).

Based on our initial lead **10** the SAR studies were finally centered on the chloro position (Table 3). At this point we also started to pay attention to issues encountered during the course of our investigations like a lack of selectivity over PDE7 and weak stability in rat liver microsomes.

Small carbon linked groups slightly improved (**21**) or maintained (**22**) inhibitory activity. Although the impact of a methoxy substituent (**23**) was less pronounced, a ninefold increase in potency was detected for methylthio derivative **24**. But unfortunately, despite achieving single digit nanomolar PDE4 inhibition,

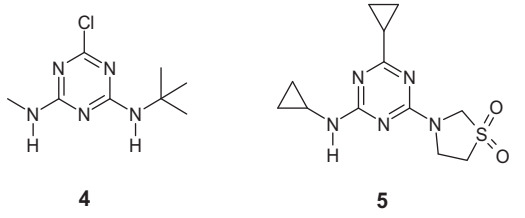
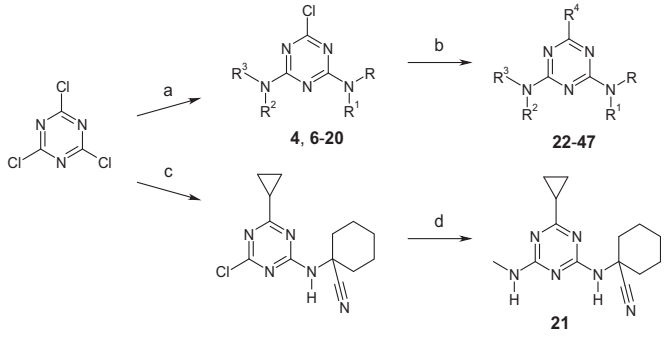
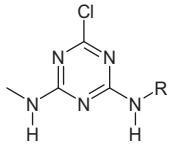


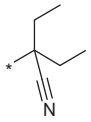
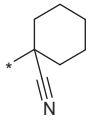
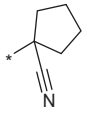
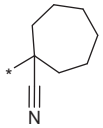
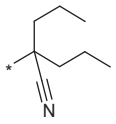
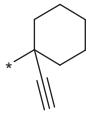
Figure 2. Structures of hit **4** and triazine **5**.



Scheme 1. Reagents and conditions: (a) (i) RR^1NH, THF, H_2O, NaOH, 0 °C, 1 h, (ii) R^2R^3NH, THF, H_2O, NaOH, 10–15 °C, 1 h, 52–88% yield; (b) For **22**–**24**: R^4Na, THF, 50 °C, 6 h, 33–61% yield; For **25**–**30**: R^4H, THF, pyridine, reflux, 2 h, 50–67% yield; For **31**–**47**: R^4H, DMF, pyridine, 35–62% yield; (c) (i) c-PrMgBr, THF, toluene, 10–15 °C, 1 h, (ii) 1 N HCl, 0 °C, 1 h, (iii) 1-aminocyclohexylcarbonitrile, CH_2Cl_2, H_2O, K_2CO_3, 0 °C, 1 h, 25% yield; (d) methylamine, THF, reflux, 4 h, 74% yield.

Table 1
Inhibitory activity of triazine derivatives **4** and **6**–**14**



Compd	R	PDE4A4[10] IC_{50} (nM)
4		245
6		156
7		104
8		160
9		87
10		40
11		54
12		44
13		60
14		149