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Bioorganic & Medicinal Chemistry Letters 15 (2005) 1829–1833
Bioorganic & Medicinal Chemistry Letters

Fused pyrimidine based inhibitors of phosphodiesterase 7 (PDE7): synthesis and initial structure–activity relationships

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Received 22 December 2004; revised 5 February 2005; accepted 8 February 2005

Abstract—A series of fused pyrimidine based inhibitors of PDE7 have been derived from an earlier screening lead **1**. The synthesis, structure–activity relationships (SAR) and selectivity against several other PDE family members are described.
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*c*AMP and *c*GMP play pivotal roles in regulating signalling pathways for many essential cellular functions. In the immune system, *c*AMP is a primary regulatory cyclic nucleotide and it is believed that *c*AMP broadly suppresses the functions of immune and inflammatory cells. The reduction of *c*AMP levels is mediated principally by the action of cell-specific phosphodiesterases (PDEs) and as such, an approach to sustain *c*AMP levels through PDE-inhibition would provide a strategy to treat a variety of immune and inflammatory diseases.[1]

The PDEs comprise a family of enzymes, currently known to exist in at least 11 different families some of which (PDE 3, 4, 7, and 8) are specific for *c*AMP, and others (PDE 5, 6, and 9) for *c*GMP. Additional family members (PDE 1, 2, 10, and 11) have dual specificity.

A recent publication indicated a role for PDE7A in the activation and/or proliferation of T cells.[2] Resting T-lymphocytes express mainly PDE3 and PDE4. However, upon activation, T cells dramatically up-regulate PDE7A1 and appear to principally rely on this isozyme for regulation of *c*AMP levels. Suppression of PDE7 up-regulation by anti-sense oligonucleotides inhibited proliferation of IL-2 production, and maintained elevated levels of intracellular *c*AMP in CD3 × CD28 stimulated T cells. PDE7A has also been demonstrated to be

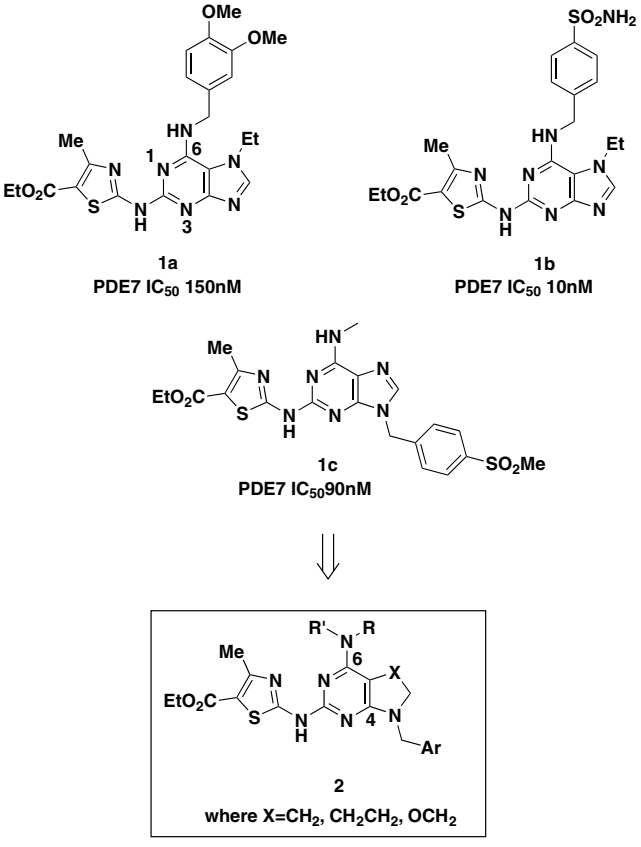

Figure 1. Proposed targets **2**.

Keywords: PDE7; Pyrimidine.
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doi:10.1016/j.bmcl.2005.02.025

Table 1.

	PDE1 IC_{50} (μM) (PDE1/PDE7)	PDE2 IC_{50} (μM) (PDE2/PDE7)	PDE3 IC_{50} (μM) (PDE3/PDE7)	PDE4 IC_{50} (μM) (PDE4/PDE7)	PDE5 IC_{50} (μM) (PDE5/PDE7)	PDE7 IC_{50} (μM)
Rolipram	>10	>10	>10	0.74	>10	>10
Sidenafil	>10	>10	7.0	4.6	0.011	>10
1a	0.22 (1.5)	1.7 (11)	0.58 (3.8)	1.1 (7.3)	0.27 (1.8)	0.15
1b	0.95 (86)	0.95 (86)	2.97 (270)	0.55 (50)	0.011 (1.0)	0.011
1c	50.0 (556)	(NT)	23.3 (259)	0.27 (3)	0.72 (8)	0.09

up-regulated in human B-lymphocytes.[3] PDE7A3, a splice variant of PDE7A1, is also reported to be up-regulated in activated $CD4^+$ T cells.[4] This expression profile suggests inhibitors of PDE7A would have broad application as immunosuppressants. It has recently been shown that PDE7A deficient mice show no deficiencies in T cell function, which calls the original hypothesis into question.[5] Identification of a small molecule inhibitor of PDE7, which could be evaluated in animal models could shed light on the current understanding of the relevance of this target.

Several groups have reported the preparation of potent inhibitors of PDE7.[6a–d] We recently reported a focused chemistry effort around our purine-based deck-hit **1a**.[6e] Variations around the purine core at C-6 demonstrated that the potency and PDE selectivity could be improved over the initial lead (e.g., Table 1, **1b**). As part of a study to investigate the selectivity (Table 1) and improve physical properties of this series, the regiochemistry around the purine scaffold was used to examine the preferred spatial orientation of the C-6 substituent (Fig. 1). In general, these purine analogs displayed poor aqueous solubility (<5 μg/mL @ pH 6.5) and were not sufficiently permeable to membranes to permit gastrointestinal absorption (PAMPA[7] 0–5 nm/s). This in turn impeded their evaluation in vivo.

Hence, our first objective was to identify a novel scaffold with improved permeability as measured by PAMPA. More specifically, we sought to explore systems other than **1c** in an effort to increase either solubility or permeability. As part of this strategy, we needed a synthetic route that would allow for diversity at the pyrimidine 4- and 6-positions of our target **2**, to be installed at a late stage in order to permit efficient analog preparation. With this in mind, a synthetic route was devised to the fused-pyrimidine systems **2**, which relied upon a novel reductive amination–cyclization protocol from a common aldehyde intermediate (Fig. 2).

The synthetic pathway utilized in the preparation of the tetrahydropyrrolopyrimidine system is outlined in Scheme 1.

Thiazole guanidine **5** was prepared through the condensation of 2-imino-4-thiobiuret **3** with 2-chloroacetoacetate **4** in the presence of pyridine. Guanidine **5** was readily condensed with commercially available diethyl allyl malonate under basic conditions in refluxing ethanol to give the desired pyrimidone **6** in 67% yield. Dichloropyrimidine **7** was formed in 74% yield after

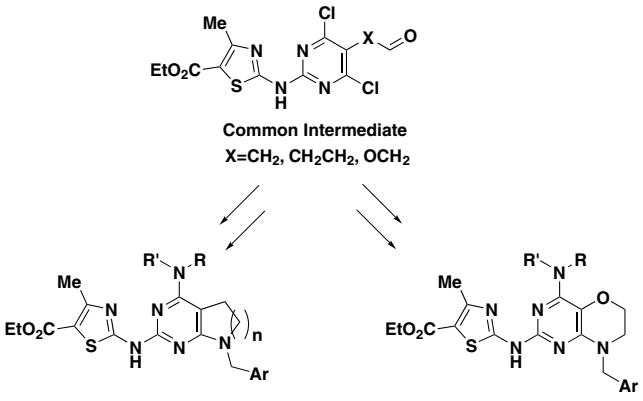


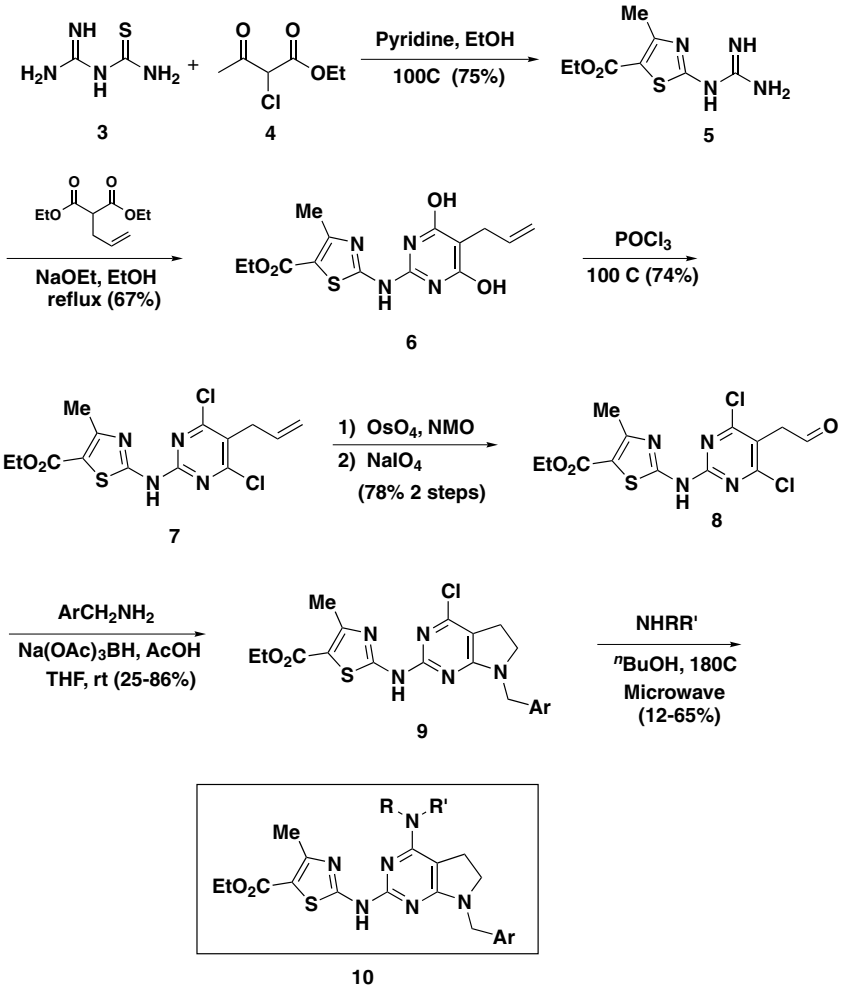
Figure 2.

treatment of **6** with $POCl_3$. The olefin of **7** was oxidized in a two step procedure using catalytic osmium tetroxide to give the diol, which was subsequently cleaved using sodium periodate to give a 78% yield of the aldehyde **8** in two steps. With the aldehyde in hand, the reductive amination/cyclization step was performed with a variety of amines to provide the tetrahydropyrrolopyrimidine system **9**. Diversity at C-6 was obtained by carrying out the subsequent reaction in a microwave with a variety of amines to provide compounds of ring system **10**.

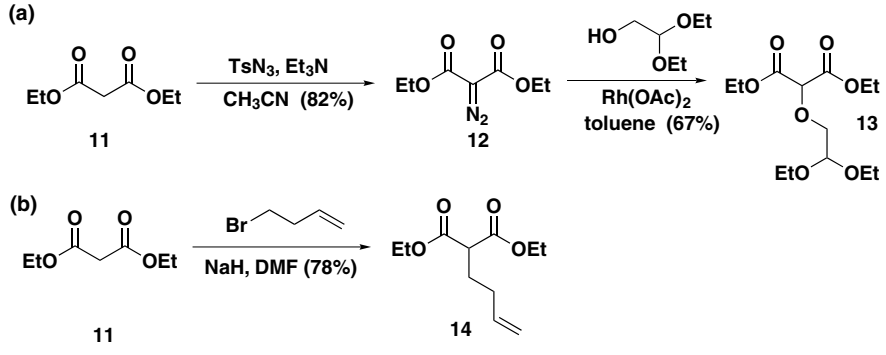
Analogous [6,6]-fused systems were synthesized in a similar manner using **13** and **14** as the coupling partners in the condensation with guanidine **5**. Scheme 2 illustrates the synthesis of each of these coupling partners.

The structure–activity relationships for the inhibition of PDE catalytic activity are summarized in Table 2.

A direct comparison between compounds **1c** and **2a** shows a nearly fourfold loss in activity for the saturated system. However, replacing the methylamine moiety at C-6 with a piperazine group (compound **2b**) improves the PDE7 activity to 20 nM. A further improvement is made in this first system by replacing the aryl portion with trimethoxybenzylamine, a modification which also improves the selectivity against PDE1–5. For the fused six-membered compounds (**2f–i**), the same trend is observed again, with the compound bearing the trimethoxybenzylamine- and piperazine-residues possessing the best PDE7 activity and selectivity. For the final fused system, which incorporates an oxygen into the saturated ring (**2j**,**k**), the same trend again holds, but this time producing a compound with a far superior PDE selectivity profile.



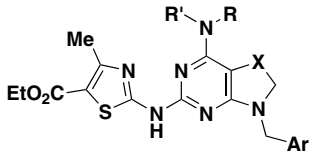
Scheme 1.

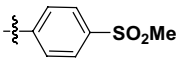
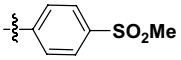
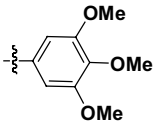
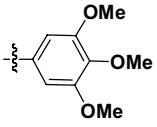
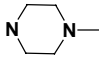
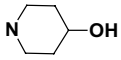
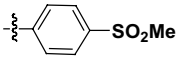
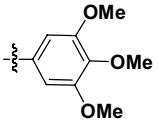
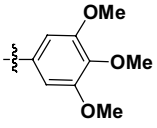
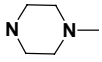
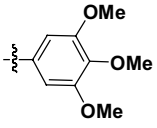
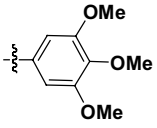
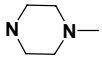


Scheme 2.

In addition to improvements in PDE7 potency and selectivity, PAMPA and solubility data was used as a guide to the improvements made in the physicochemical properties of these newly synthesized molecules. While significant improvements in acid solubility for compounds with basic amines was noted (>1 mg/mL), **2a**–**k** did not show a significant improvement in solubility at pH 6.5 (5–20 μg/mL) compared to the purines **1a**–**c**. Gratifyingly, compounds **2a**–**k** showed significant improvements over their purine counterparts (PAMPA range = 0–5 nm/s) with respect to membrane permeability as measure by PAMPA.[8] The [6,4]-fused system **2a**–**e**, displayed a significant improvement in permeability (PAMPA range = 90–110 nm/s). The [6,6]-fused systems, **2f**–**k**, also displayed a significant improvement in permeability (PAMPA range = 135–298 nm/s) over the purines **1a**–**c**. In our assays compounds with a permeability of >100 nm/s are considered reasonable candidates for oral evaluation in vivo. Promising plasma exposures were seen for compound **2c** when administered orally to mice

Table 2. SAR with respect to PDE inhibition, PDE#/PDE7 represents the IC_{50} ratio [data is the average of two experimental determinations]



Compound	X	Ar	NRR′	PDE7 IC_{50} (nM)	PDE1/ PDE7	PDE2/ PDE7	PDE3/ PDE7	PDE4/ PDE7	PDE5/ PDE7
2a	CH_2			340	NT	NT	NT	6	NT
2b	CH_2			20	352	NT	1031	94	1
2c	CH_2			6	576	NT	1879	795	362
2d	CH_2			20	156	NT	315	189	104
2e	CH_2			150	35	NT	154	13	7
2f	CH_2CH_2			60	157	27	392	54	8
2g	CH_2CH_2			100	162	33	390	35	13
2h	CH_2CH_2			30	166	114	734	105	182
2i	CH_2CH_2			150	39	NT	174	27	9
2j	OCH_2			5	1173	NT	3852	1200	1236
2k	OCH_2			70	64	NT	206	67	64

at a dose of 10 mg/kg in a 1:1 PEG–H_2O vehicle. Drug levels >1 μM were observed at $t = 1$ h.

In summary, we have reported the generation of several chemotypes with improvements in physical characteristics, which could lead to compounds useful for in vivo evaluation. Additionally these new scaffolds produced compounds with improvements in potency and PDE selectivity compared to the initial purine lead molecules.

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