Chinese Chemical Letters Vol. 16, No. 10, pp 1283-1286, 2005 1283
http://www.imm.ac.cn/journal/ccl.html

Design and Synthesis of Pyrido[1,2-e]purin-4(3H)-one Derivatives as Potential PDE 5 Inhibitors

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Abstract: A novel series of pyrido[1,2-e]purin-4(3H)-one derivatives containing polar substituents on 5'-position were designed and prepared as potential PDE5 inhibitors. This paper reports the synthetic routes, ^{1}H-NMR data, and the PDE5 inhibitory activities of the target compounds. The polar piperazinyl group contained (on 5'-position) compound, **3B2**, showed the highest activity among the tested derivatives but less potency than sildenafil **1**.

Keywords: Pyrido[1,2-e]purin-4(3H)-one, PDE5 inhibitor, sildenafil, erectile dysfunction (ED).

The phosphodiesterases (PDEs) regulate physiological processes by the hydrolysis of intracellular second messengers, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) to their biologically inactive 5'-derivatives. In human corpus carvernosum tissue, type V phosphodiesterase (PDE5) is the major enzyme to degrade cGMP and plays a key role in the control of penile erection[1,2]. Sildenafil **1**, as a PDE5 inhibitor for treatment of erectile dysfunction (ED), increases the half-life of cGMP, eventually cause a decrease in intracellular calcium concentration, resulting in the relaxation of smooth muscle in the corpus cavernosum. This relaxation leaded to increased arterial blood flow to the penis and ultimately erection. Despite the efficacy and commercial success, **1** has shown clinically significant adverse reactions such as headache, flushing, dyspepsia and visual disturbances, which may be linked to insufficient selectivity *versus* other PDEs[3, 4]. Therefore, both potencies toward PDE5 and selectivities against other PDEs are important for the successful development of new PDE5 inhibitors[1,5]. Herein, we report the design and synthesis of novel pyrido[1,2-e]-purin-4(3H)-one derivatives as potential PDE5 inhibitors.

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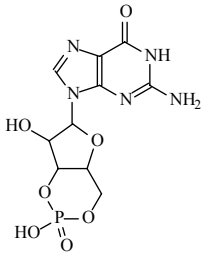

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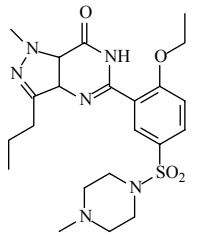

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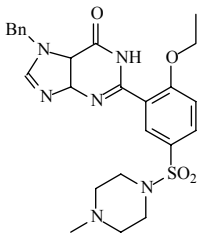

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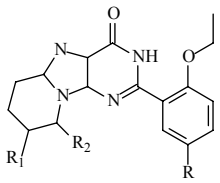
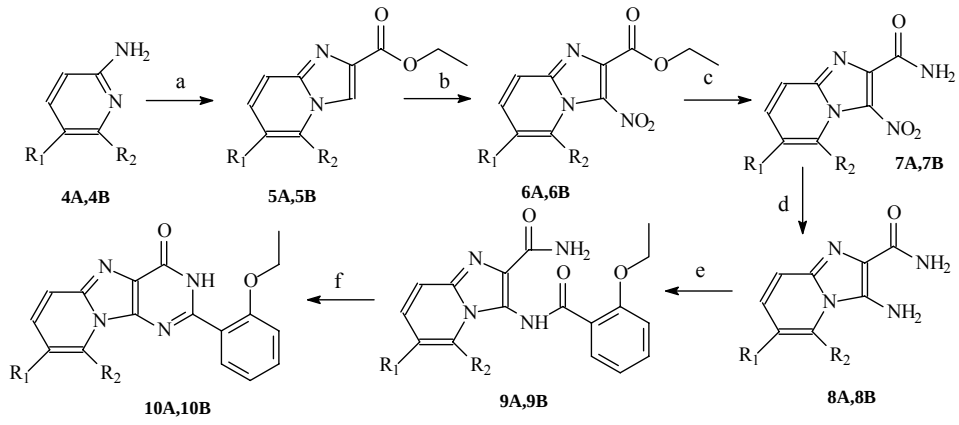


	R_1	R_2
3A1-A3	CH_3	H
3B1-B4	H	CH_3

Design and Synthesis

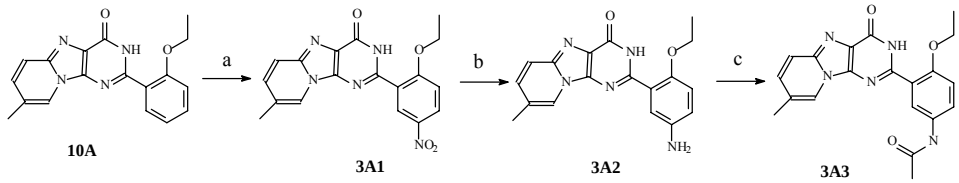
In the wide variety of PDE5 inhibitors reported recent years, imidazoquinazolinones **2** are more potent and selective than **1**[6]. Both **1** and **2** contain polar sulfonamide group on the 2-phenyl ring, and this substituent may fill the space occupied by the phosphate of cGMP in the PDE5 active site and improve PDE5 inhibitory activity distinctly[7,8]. The new skeleton **3** designed by us, is a purine based structure and possesses some resemblance between cGMP and **2**. Polar groups also introduced on to the 5'- position of the 2-phenyl ring in the designed tricyclic pyridopurinone molecules to generate the compounds of pyrido[1,2-e]purin-4(3H)-one family. Following the known procedures in the literature[9,10], the intermediates **10A** and **10B** were obtained from commercially available 2-aminopicolines (**Scheme 1**). The synthetic routes of target compounds **3A1-A3** and **3B1-B4** were shown in **Scheme 2** and **Scheme 3** respectively. ^{1}H-NMR data of representative compounds were listed in **Table 1**.

Scheme 1 The synthetic routes of compounds **10A** and **10B**



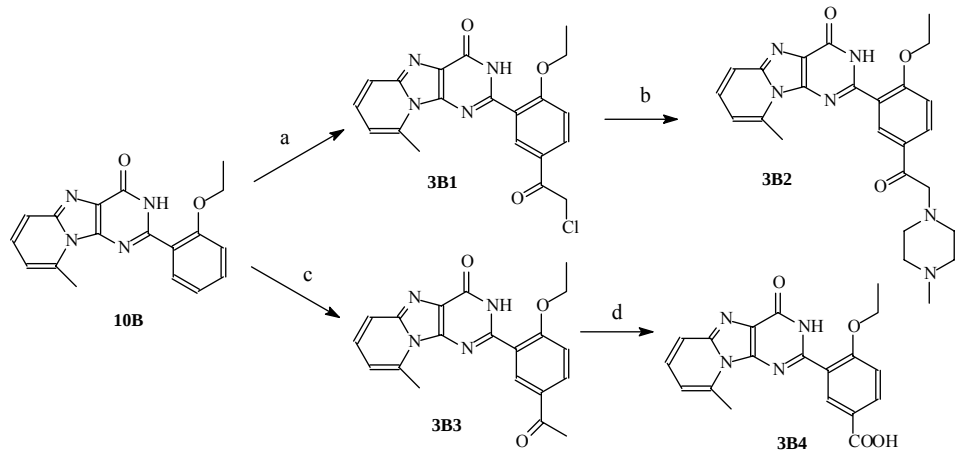
a: ethyl bromopyruvate, EtOH; b HNO_3, H_2SO_4; c: NH_4OH, H_2O, THF; d: H_2, Pt/C, MeOH; e: 2-ethoxybenzoyl chloride, pyridine, DMAP, CH_2Cl_2; f: *t*-BuOK, *t*-BuOH, reflux. (Notes: **A**: R_1 = CH_3, R_2=H; **B**: R_1= H, R_2= CH_3)

Scheme 2 The synthesis of target compounds **3A1-3A3**



a: HNO_3, H_2SO_4; b: H_2, Raney-Ni, MeOH; c: CH_3COCl, NEt_3, THF.

Scheme 3 The synthesis of target compounds **3B1-3B4**



a: $ClCH_2COCl$, $AlCl_3$, CH_2Cl_2; b: N-methylpiperazine, K_2CO_3, DMF; c: CH_3COCl, $AlCl_3$, CH_2Cl_2; d: 2mol/L NaOH, Br_2.

Table 1 The ^{1}H-NMR data of target compounds *

Cpd.	^{1}H-NMR (δ ppm)
3A2	11.98 (br s, 1H, NH), 8.45 (d, 1H, J=1.6Hz), 7.62 (d, 1H, J=9.4Hz), 7.39 (dd, 1H, J=9.4, 1.6Hz), 7.36 (dd, 1H, J=6.0, 2.9Hz), 6.96 (d, 1H, J=8.8Hz), 6.78 (dd, 1H, J=8.8, 2.9Hz), 4.90 (br s, 2H, NH_2), 4.09 (q, 2H, J=7.0Hz), 2.50 (s, 3H), 1.35 (t, 3H, J=7.0Hz) (DMSO-d_6)
3A3	12.19 (br s, 1H, NH), 10.00 (br s, 1H, NHCO), 8.45 (s, 1H), 8.06 (s, 1H), 7.71 (d, 1H, J=9.1Hz), 7.63 (d, 1H, J=9.3Hz), 7.40 (dd, 1H, J=9.3, 1.4Hz), 7.14 (d, 1H, J=9.1Hz), 4.13 (q, 2H, J=7.0Hz), 2.35 (s, 3H), 2.03 (s, 3H, $COCH_3$), 1.35 (t, 3H, J=7.0Hz) (DMSO-d_6)
3B2	11.41 (br s, 1H, NH), 9.17 (d, 1H, J=2.2Hz), 8.17 (dd, 1H, J=8.8, 2.2Hz), 7.62 (d, 1H, J=9.2Hz), 7.34 (dd, 1H, J=9.21, 6.8Hz), 7.14 (d, 1H, J=8.8Hz), 6.70 (d, 1H, J=6.8Hz), 4.43 (q, 2H, J=7.1Hz), 3.85 (s, 2H, $COCH_2N$), 3.23 (s, 3H), 2.70 (br s, 4H, CH_2 of piperazine), 2.59 (br s, 4H, CH_2 of piperazine), 2.35 (s, 3H, NCH_3) , 1.66 (t, 3H, J=7.1Hz) ($CDCl_3$)
3B3	12.36 (br s, 1H, NH), 8.40 (d, 1H, J=2.4Hz), 8.13 (dd, 1H, J=8.8, 2.4Hz), 7.59 (d, 1H, J=9.0Hz), 7.46 (dd, 1H, J=9.0, 6.8Hz), 7.32 (d, 1H, J=8.8Hz), 6.88 (d, 1H, J=6.8Hz), 4.28 (q, 2H, J=6.9Hz), 3.09 (s, 3H), 2.60 (s, 3H, $COCH_3$), 1.41 (t, 3H, J=6.9Hz) (DMSO-d_6)
3B4	12.32 (br s, 1H, NH), 8.37 (d, 1H, J=2.3Hz), 8.07 (dd, 1H, J=8.8, 2.3Hz), 7.57 (d, 1H, J=9.2Hz), 7.44 (dd, 1H, J=9.2, 6.8Hz), 7.30 (d, 1H, J=8.8Hz), 6.87 (d, 1H, J=6.8Hz), 4.25 (q, 2H, J=6.8Hz), 3.07 (s, 3H), 1.39 (t, 3H, J=7.0Hz) (DMSO-d_6)

* ^{1}H-NMR spectra were taken on a Varian Mercury 300 spectrometer. Tetramethylsilane was used as an internal standard.

PDE5 inhibitory activities

Using [^{3}H]-cGMP SPA kit, the compounds were evaluated for the inhibitory activities against PDE5 isolated from human platelet[11,12]. The results indicated that the polar piperazinyl group contained (on 5'- position) compound, **3B2**, shows the highest activity among the tested derivatives but less potency than **1** (**Table 2**). Extensive SAR exploration of this pyridopurinone template will be reported in due course.

Table 2 *In vitro* PDE5 inhibitory activities of target compounds*****

Cpd.	Inhibition (%)	Cpd.	Inhibition (%)
3A1	36.6	**3B2**	77.8▲
3A2	32.4	**3B3**	40.5
3A3	68.1	**3B4**	10.3
10A	59.3	Sildenafil **1**	98.7▪

***** Inhibition (%) data was tested at 1 μ mol/L. ▲IC_{50} = 0.102 μ mol/L. ▪IC_{50} = 0.004 μ mol/L.

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13. The ^{1}H-NMR data of **3A1**, **3B1** were deposited in editorial office of CCL.

Received 21 December, 2004