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Investigation of the pyrazinones as PDE5 inhibitors: Evaluation of regioisomeric projections into the solvent region

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ABSTRACT

We describe the design, synthesis and profiling of a novel series of PDE5 inhibitors. We take advantage of an alternate projection into the solvent region to identify compounds with excellent potency, selectivity and pharmacokinetic profiles.

Expressed in vascular smooth muscle cells phosphodiesterase type 5 (PDE5) hydrolyzes cGMP to the inactive metabolite 5′-GMP. Over the last decade, significant clinical and commercial experience has demonstrated the safety, tolerance and efficacy of PDE5 inhibitors, such as sildenafil, for the treatment of male erectile dysfunction (MED).[1] Recently, preclinical studies as well as clinical trials have suggested that PDE5 inhibitors could be/are effective in the treatment of various other diseases such as Raynaud's disease, gastrointestinal disorders and stroke.[2] Against this backdrop, we initiated a program directed toward the discovery of long-acting, selective inhibitors of PDE5.

We recently described the design, synthesis and evaluation of a series of aminopyridopyrazinones as novel PDE5 inhibitors (Fig. 1).[3] Optimization of the pharmacokinetic (PK) profile of advanced lead compound **1**, a highly potent and selective inhibitor of PDE5, led to cyclohexanol[4] **2** which had a favorable preclinical PK profile but attrited during rodent toxicological studies. Subsequent refinement led to the basic piperazine derivative **3** which is currently in clinical trials.[5] Herein, we describe our efforts to further examine the SAR of this series of compounds and develop alternate approaches to effectively balance the potency, selectivity and PK profiles. Examination of crystal structure of **1** (Fig. 4) bound to PDE5 suggested the geometric isomers envisioned in Figure 2 would project substituents into the solvent region and be well tolerated from the potency perspective. Furthermore, we speculated that the 1,4 relationship between the propyloxy ether and the solvent region may confer improved solubility as compared to the 1,3 derived compounds.

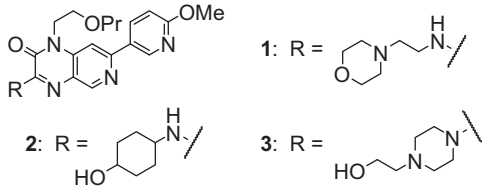

Figure 1. Key 1,3 aminopyrazinone lead structures: advanced lead **1**, pre-clinical candidate **2** and clinical candidate **3**.

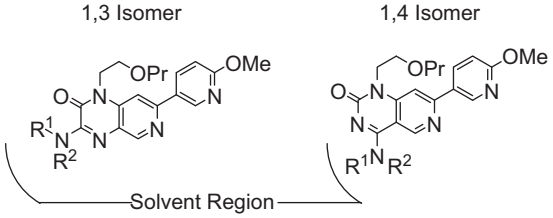

Figure 2. Proposed, novel 1,4 isomer compared to the 1,3 isomer. The southeastern pyridine[6] version of both cores is illustrated.

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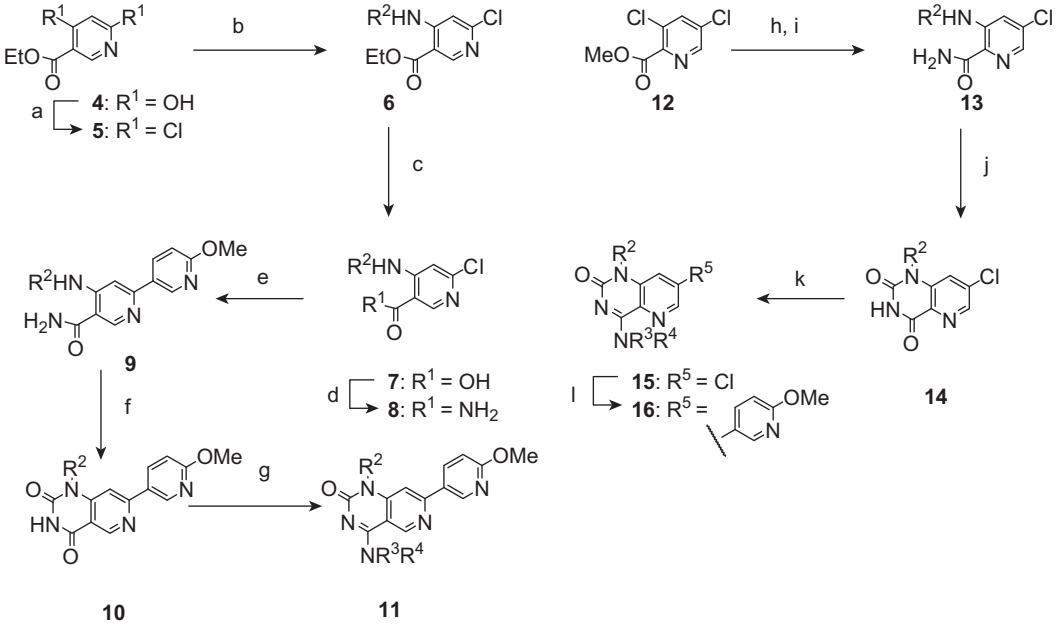
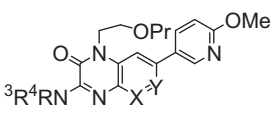


Scheme 1. Reagents and conditions: (a) $POCl_3$, 100 °C; (b) R_2NH_2, dichloroethane, 23 °C; (c) LiOH, 1,2-dimethoxyethane, water, 23 °C; (d) $SOCl_2$, cat. DMF, CH_2Cl_2, 23 °C then NH_4OH (aq), 23 °C; (e) 6-methoxypyridin-3-ylboronic acid, $Pd(Ph_3P)_4$, Na_2CO_3, dioxane, water, reflux; (f) NaH, di(1*H*-imidazol-1-yl)methanone, DMF, 0→75 °C; (g) $POCl_3$, 100 °C then R_3R_4NH, CH_2Cl_2, 23 °C; (h) 7 N NH_3, MeOH, 23 °C; (i) R_2NH_2, *i*Pr_2NEt, DMSO, 120 °C; (j) NaH, di(1*H*-imidazol-1-yl)methanone, DMF, 0→75 °C; (k) $SOCl_2$, cat. DMF, CH_2Cl_2, 23 °C then R_3R_4NH, CH_2Cl_2, 23 °C; (l) 6-methoxypyridin-3-ylboronic acid, $Pd(Ph_3P)_4$, Na_2CO_3, dioxane, water, reflux.

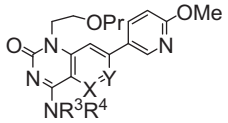
To examine the potential of this geometry we synthesized several prototype compounds in both the southeastern and southern pyridine core ring systems. The syntheses of these rings systems are illustrated in Scheme 1. Synthesis of 1,4 southeastern pyridines (general structure **11**) commenced with the chlorination of dihydroxy pyridine **4** in neat $POCl_3$ to yield **5**. Displacement of the 4-chloro group in **5** with various primary amines proceeded smoothly and in good yield to give **6**. Saponification followed by formation of the primary amide gave **8** in nearly quantitative yield. Suzuki cross coupling between **8** and 6-methoxypyridin-3-ylboronic acid yielded **9** in 65% yield. Treatment of **9** with CDI and sodium hydride provided the penultimate dione, **10**, in excellent yield. Finally, chlorination of **10** with $POCl_3$ provided the highly reactive intermediate chloropyrimidinone which was immediately reacted with the requisite amines to give **11**. The synthesis of the southern pyridine derived isomers (**16**) proceeded along a similar synthetic route. We began from the known intermediate **12** which was converted to the analogous amide by the action of 7 N NH_3. Treatment of this compound with primary amines in DMSO at 120 °C proceeded in modest yield to provide **13**. Treatment of amino amide **13** with CDI and sodium hydride provided **14**. Chlorination with $SOCl_2$ followed by displacement with amines afforded the aminopyrimidinones, **15**. The synthesis of **16** was completed via a Suzuki cross coupling (42% yield).

Table 1 summarizes the PDE5 potency and PDE6 and PDE11 selectivity and compares the characteristics of the 1,3 and 1,4 geometries in both the southeastern and southern pyridine cores. The PDE5 potency of the 1,4 geometry was similar to what we had determined for the 1,3 system. For instance, morpholines **1** (PDE5 IC_{50} = 0.07 nM) and **17** (PDE5 IC_{50} = 0.08 nM) were equipotent against PDE5 as were southeastern cyclohexanols **2** (PDE5 IC_{50} = 0.05 nM) and **18** (PDE5 IC_{50} = 0.05 nM). For both piperazine pairs (**3** and **21** and **22** and **23**) there was approximately a fivefold loss in potency in the 1,4 geometry as compared to the 1,3 geometry; however, both **21** and **23** possess nanomolar potency against PDE5 (IC_{50} = 1.38 and 1.64 nM, respectively). We were further encouraged by the suggestion from this early set of compounds that the 1,4 geometry might afford more selectivity, particularly over PDE6, than the analogous 1,3 compound. For example, **20** is significantly more selective than **19** (1020-fold vs 48-fold).[7]

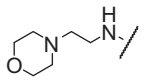
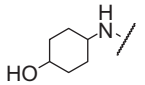
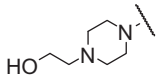
Table 1
Comparison of the PDE5 potency and PDE6 and PDE11 selectivity of 1,3 southeastern and southern pyridines to 1,4 southeastern and southern pyridines



1,3SE: X = CH_2, Y = N
1,3S : X = N, Y = CH_2



1,4SE: X = CH_2, Y = N
1,4S: X = N, Y = CH_2

	X	Core	$-NR^3R^4$	PDE5[a]	6x/11x[b]
1		1,3SE		0.07	158/4860
17		1,4SE		0.08	334/9050
2		1,3SE		0.05	200/1316
18		1,4SE		0.05	675/3950
19		1,3S		0.32	48/675
20		1,4S		0.10	1020/3830
3		1,3SE		0.20	157/2463
21		1,4SE		1.38	181/>1450
22		1,3S		0.35	245/1771
23		1,4S		1.64	381/>1220

[a] PDE IC_{50} (nM).
[b] 6x = PDE6 IC_{50}/PDE5 IC_{50}; 11x = PDE11 IC_{50}/PDE5 IC_{50}.

Encouraged by these early results we designed and synthesized a diverse library of compounds to rapidly establish the key features