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Design and synthesis of novel 5-(3,4,5-trimethoxybenzoyl)-4-aminopyrimidine derivatives as potent and selective phosphodiesterase 5 inhibitors: Scaffold hopping using a pseudo-ring by intramolecular hydrogen bond formation

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ABSTRACT

5-(3,4,5-Trimethoxybenzoyl)-4-amimopyrimidine derivatives were found as a novel chemical class of potent and highly selective phosphodiesterase 5 inhibitors. A pseudo-ring formed by an intramolecular hydrogen bond constrained the conformation of 3-chloro-4-methoxybenzylamino and 3,4,5-trimethoxybenzoyl substituents and led to the discovery of T-6932 (**19a**) with a potent PDE5 inhibitory activity (IC_{50} = 0.13 nM) and a high selectivity over PDE6 (IC_{50} ratio: PDE6/PDE5 = 2400). Further modification at the 2-position of T-6932 resulted in the finding of **26**, which exhibited potent relaxant effects on isolated rabbit corpus cavernosum (EC_{30} = 11 nM) with a high PDE5 selectivity over PDE6 (IC_{50} ratio: PDE6/PDE5 = 2800).

In human corpus cavernosum, phosphodiesterase 5 (PDE5) is the primary enzyme to hydrolyze cyclic guanosine monophosphate (cGMP). Inhibition of this enzyme elevates intracellular cGMP level and evoked relaxation of corpus cavernosum.[1] Therefore, orally available PDE5 inhibitors are used for the treatment of male erectile dysfunction as first-line therapy.[2,3] In the USA, sildenafil (**1**), vardenafil, and tadalafil were approved by the FDA in 1998, 2003, and 2003, respectively.[4–6] In addition to these marketed drugs, PDE5 inhibitors having various frameworks, such as phthaladine,[7] quinazoline,[8] quinolone,[9] pyrazolopyrimidine,[10] pyridopyrazinone,[11] and pyrimidine-4(3H)-one[12] have been reported to date.

Ukita et al. have reported the isoquinolinone derivatives (**2**, T-1032) as a prototype PDE5 inhibitor (Fig. 1).[13] Although T-1032 exhibited potent PDE5 inhibitory activity (IC_{50} = 1.0 nM), the selectivity over PDE6 was insufficient (32-fold against trypsin-activated bovine retina PDE6 and 650-fold against light-activated bovine retina PDE6).[14,15] These values were almost equivalent to those of sildenafil which has been reported to cause visual disturbance resulting from PDE6 inhibition in some cases.[16,17] In addition to this, T-1032 showed severe toxicity in dogs; therefore, further evaluation was terminated.

To improve selectivity against PDE6, we started synthetic studies in the search of a novel series of PDE5 inhibitors using T-1032 as a lead compound. First, we investigated whether the carbonyl group of T-1032 plays a crucial role for inhibition of PDE5 and PDE6, since bicyclic rings having a carbonyl group were common frameworks among T-1032, sildenafil, and cGMP. For this purpose, isoquinoline derivatives **B** were designed by deletion of the carbonyl group at the 1-position of the isoquinolinone ring and subsequent introduction of substituents at the 1-position (Fig. 2). Furthermore, the bicyclic framework of **B** was modified aiming to obtain a new chemical class of PDE5 inhibitors with reduced lipophilicity and molecular weight. As shown in Figure 2, a monocyclic series **C** was designed by opening the nitrogen-containing ring of the isoquinoline scaffold. These efforts led to the finding of 5-(3,4,5-trimethoxybenzoyl)-4-amimopyrimidine derivatives as

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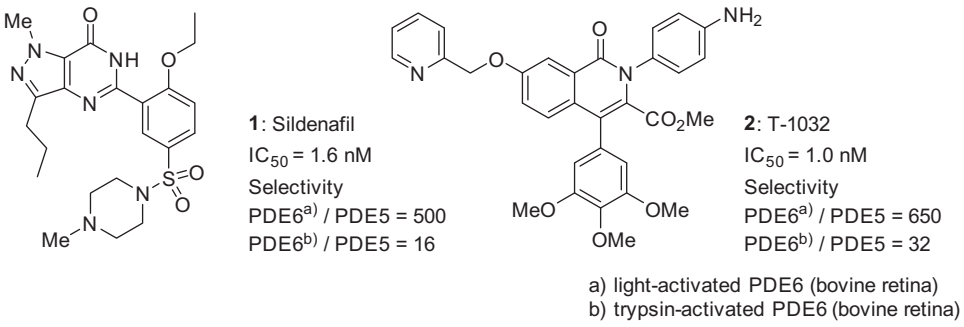


Figure 1. PDE5 inhibitory activity and selectivity against PDE6 of sildenafil (**1**) and T-1032 (**2**).

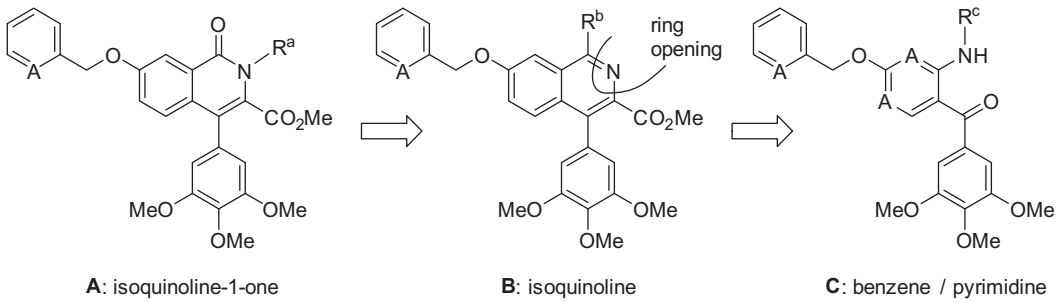
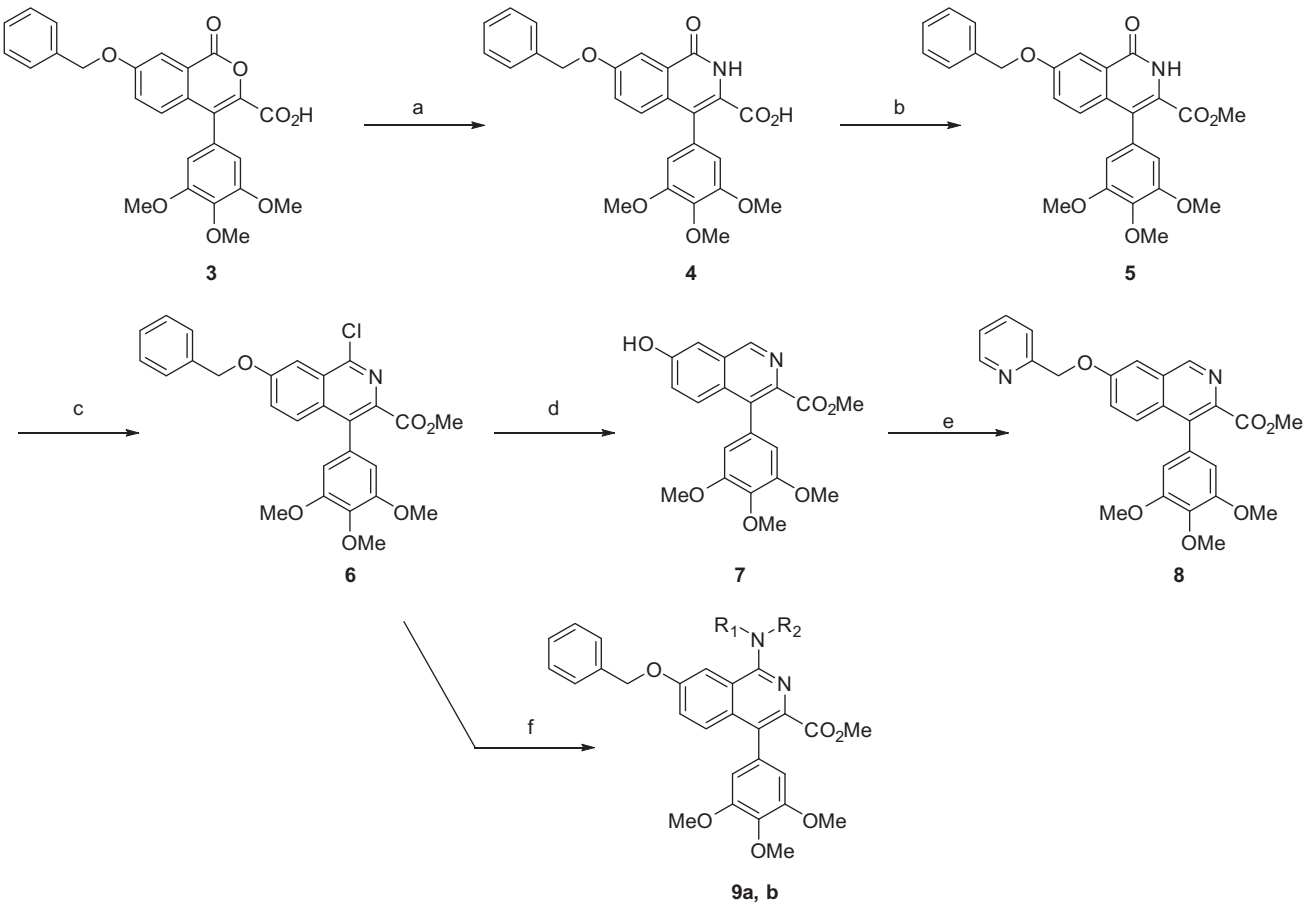


Figure 2. Transformation of bicyclic leads into monocyclic compounds.



Scheme 1. Reagents and conditions: (a) NH_3–MeOH, rt (84%); (b) $SOCl_2$, MeOH, reflux (75%); (c) $POCl_3$, reflux (quant.); (d) Pd-C, H_2, Et_3N, EtOH, rt; (e) 2-chloromethylpyridine, K_2CO_3, DMF, 50 °C (53% from **6**); (f) R^1R^2NH, CuO, pyridine, 100 °C (**9a** 22%) or R^1R^2NH, *i*-PrOH, reflux (**9b** 50%).