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8-(3-Chloro-4-methoxybenzyl)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one derivatives as potent and selective phosphodiesterase 5 inhibitors

Toshiaki Sakamoto [a], Yuichi Koga [a], Masataka Hikota [a], Kenji Matsuki [a], Hideki Mochida [b], Kohei Kikkawa [b], Kotomi Fujishige [c], Jun Kotera [c], Kenji Omori [c,d], Hiroshi Morimoto [a,*], Koichiro Yamada [a]

[a] *Medicinal Chemistry Research Laboratories II, Mitsubishi Tanabe Pharma Corporation, 2-2-50 Kawagishi, Toda, Saitama 335-8505, Japan*
[b] *Pharmacology Research Laboratories II, Mitsubishi Tanabe Pharma Corporation, 2-2-50 Kawagishi, Toda, Saitama 335-8505, Japan*
[c] *Advanced Medical Research Laboratories, Mitsubishi Tanabe Pharma Corporation, 2-2-50 Kawagishi, Toda, Saitama 335-8505, Japan*
[d] *Industry and Academia Cooperation Research Project, Laboratory of Target and Drug Discovery, Graduate School of Pharmaceutical Sciences, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8601, Japan*

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ABSTRACT

A novel series of highly selective phosphodiesterase 5 (PDE5) inhibitors was found. 8*H*-Pyrido[2,3-*d*]pyrimidin-7-one derivatives bearing an (*S*)-2-(hydroxymethyl)pyrrolidin-1-yl group at the 2-position and a 3-chloro-4-methoxybenzyl group at the 8-position exhibited potent PDE5 inhibitory activities and high PDE5 selectivity over PDE6. Among the synthesized compounds, the 5-methyl analogue (**5b**) showed the most potent relaxant effect on isolated rabbit corpus cavernosum with an EC_{30} value of 0.85 nM.

Phosphodiesterase 5 (PDE5) is a cyclic guanosine monophosphate (*c*GMP)-specific hydrolytic enzyme, and the inhibitors of PDE5 are used for the treatment of erectile dysfunction (ED)[1,2] and pulmonary arterial hypertension (PAH).[3] The first approved orally active PDE5 inhibitor, sildenafil showed high efficacy, but visual side effects such as cyanopsia and visual disturbance were reported in some cases.[4,5] These adverse effects are indicated to be attributed to inhibition of PDE6.[6] After the launch of sildenafil, PDE5-selective inhibitors having various frameworks, such as tetrahydro-β-carboline,[7,8] phthaladine,[9] quinazoline,[10] quinolone,[11] pyrazolopyrimidine,[12] pyridopyrazinone,[13] and pyrimidin-4(3*H*)-one[14] have been reported to date.

In previous Letters, we reported findings of 5-(3,4,5-trimethoxybenzoyl)-pyrimidine derivatives **2** as a novel chemical class of highly PDE5-selective inhibitors by a scaffold hopping strategy using isoquinolin-1-one derivative T-1032 (**1**) as a lead compound.[15] Furthermore, transformation to pyrimidine-5-carboxamide derivatives and subsequent optimization of the substituents led to the discovery of avanafil (**3**), which has been approved by the FDA for the treatment of ED (Fig. 1).[16] In the course of this study, 5-benzoylpyrimidine derivative **2a** was found to show a potent PDE5 inhibitory activity (IC_{50} = 0.21 nM) and a high PDE5 selectivity over PDE6 (PDE6/PDE5 = 5700), but its relaxant effect on isolated rabbit corpus cavernosum was insufficient (EC_{30} >100 nM) owing to its high lipophilicity (*c*Log*P* = 4.01). Aiming to potentiate the relaxant effect, further synthetic study was carried out using **2a** as a lead compound. First, the trimethoxybenzene moiety was modified to reduce the lipophilicity (compounds **4**). As a next step, the substituents at the 4- and 5-positions of the pyrimidine ring were bound to potentiate PDE5 inhibitory activity (compounds **5**). These efforts led to the finding of a novel chemical series of highly selective PDE5 inhibitors which exhibit potent relaxant effect on isolated rabbit corpus cavernosum. In this Letter, we report the detail of the synthesis and biological activities of novel 8*H*-pyrido[2,3-*d*]pyrimidin-7-one derivatives **5**.

In the exploration of the optimal substituent at the 2-position of the pyrimidine derivatives **2**, we found that incorporation of polar substituents to reduce the lipophilicity of the compounds led to an improvement of the relaxant effect.[15] Therefore, we focused on modification of the 3,4,5-trimethoxybenzene moiety at the 5-position, to which high lipophilicity of **2a** (*c*Log*P* = 4.01) is attributed, and pyrimidine-5-carbaldehyde **4a** (*c*Log*P* = 2.78) and 5-acetylpyrimidine **4b** (*c*Log*P* = 3.25) were designed by deletion of the 3,4,5-trimethoxyphenyl group. In addition, **4c** (*c*Log*P* = 3.79), **4e** (*c*Log*P* = 3.07), and **4f** (*c*Log*P* = 3.48) were designed by replacement of the 3,4,5-trimethoxybenzene with N-containing heterocycles.

* Corresponding author. Tel.: +81 045 963 7164; fax: +81 045 963 7165.
E-mail address: morimoto.hiroshi@md.mt-pharma.co.jp (H. Morimoto).

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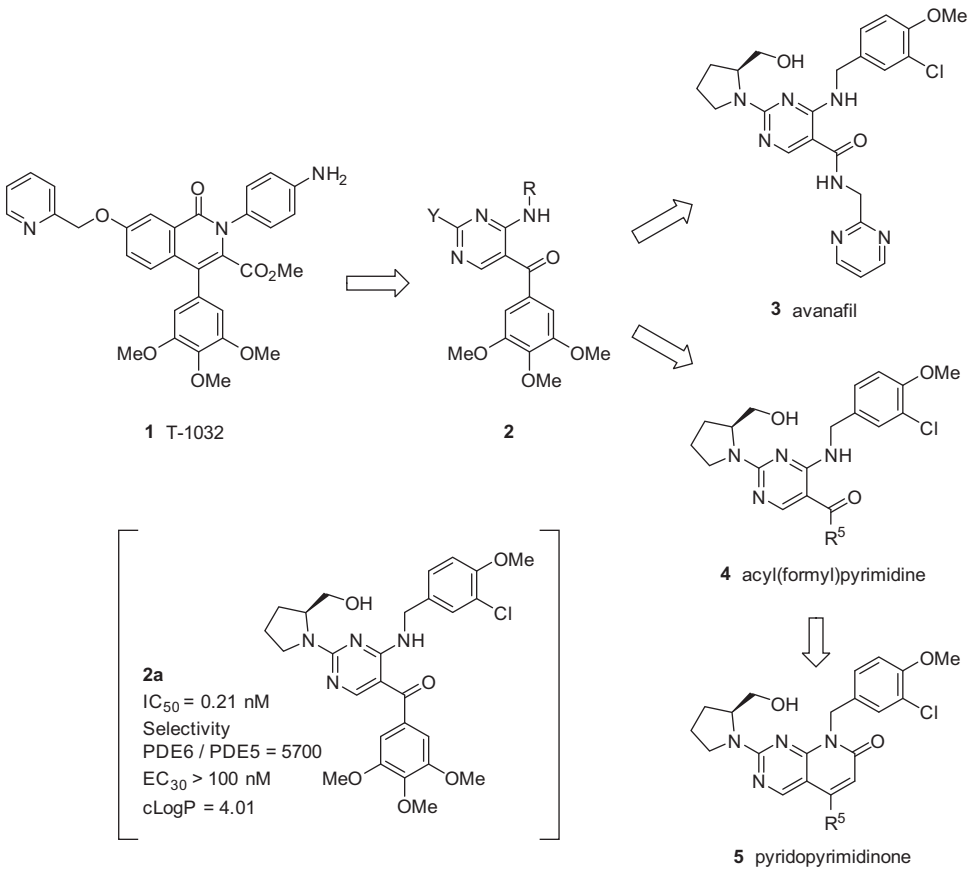

Figure 1. Structures of pyrimidine derivatives (**2**, **3**, **4**) and pyridopyrimidinone derivatives **5**.

The synthesis of the pyrimidine derivatives (**4a**–**c**, **4e**, **4f**) was illustrated in Scheme 1. 4-Aminopyrimidine derivative **7** was obtained by condensation of commercially available **6** with 3-chloro-4-methoxybenzylamine. Reduction of the ester group in **7** with $LiAlH_4$ and subsequent oxidation of the resulting alcohol with MnO_2 gave pyrimidine-5-carbaldehyde **8**. The 2-position of the pyrimidine ring was substituted with (*S*)-prolinol after oxidation of the methylsulfanyl group with *m*CPBA to give **4a**. 5-Acylpyrimidine derivatives **4b**–**d** were obtained by addition of the corresponding R^5-metal reagents to the formyl group of **4a** and the following oxidation with MnO_2. The 1-methylimidazol-2-yl analogue **4e** was synthesized via **9** which was prepared from **8** in the same manner as that described above. **4f** was obtained by 1,4-addition of morpholine to 5-acryloylpyrimidine **4d**.

PDE5 inhibitory activities of the synthesized compounds were evaluated using the enzyme isolated from canine lung.[17] As shown in Table 1, the pyrimidine-5-carbaldehyde derivative **4a** showed a moderate PDE5 inhibitory activity (IC_{50} = 33 nM), and the modification of the formyl group into an acetyl group led to the improvement of the potency (**4b**, IC_{50} = 5.2 nM). Although the N-containing heterocycles were tolerated on the acyl groups, all of the synthesized 5-position variants were more than ten times less potent than **2a**.

Aiming to improve their PDE5 inhibitory activity, we planned the construction of a bicyclic framework by cyclization between the substituents at the 4- and 5-positions of the pyrimidine ring. Ring closure modifications reduce the flexibility of the molecules and sometimes achieve dramatic changes in potency, selectivity permeability, and so on.[18,19] Based on this idea, 8*H*-pyrido[2,3-*d*]pyrimidin-7-one derivatives were designed and synthesized as described in Scheme 2.

Pyrimidine-5-carbaldehyde **8** was converted into α,β-unsaturated ester **10** by Horner–Wadsworth–Emmons reaction, and **10** was cyclized in the presence of NaH to give pyridopyrimidinone derivative **11a**. Alternatively, **11e** was prepared from 5-acetylpyrimidine **9** by treatment with trimethylphosphonoacetate and excess NaH in toluene at 100 °C.[20] The 2-methylsulfanyl groups of these compounds were substituted with (*S*)-prolinol in the same manner as that described above to give **5a** and **5e**. 1,4-Addition of a cuprate, which was prepared from MeLi and CuCN, to **10** and concomitant cyclization gave **12**. After substitution of the 2-position, resulting **13** was treated with DDQ to give **5b**. Compound **5c** was obtained from **4c** in 17% yield, accompanied by recovery of 48% of starting material. In the synthesis of **5f**, methyl trimethylsilylacetate was used instead of the Horner–Wadsworth–Emmons reagent,[21] since **5f** was not obtained by the same procedure as used for preparation of **5c**.

PDE5 inhibitory activities of these compounds were evaluated, and the light-activated bovine retina PDE6 was used for evaluation of PDE6 inhibitory activity. As summarized in Table 2, pyridopyrimidinone derivatives (**5a**–**c**, **5e**, **5f**) showed high potency, which were superior to the corresponding cyclization precursors, pyrimidine derivatives (**4a**–**c**, **4e**, **4f**), respectively. These results may be attributed to the restriction of the molecule into a bioactive conformation. Among the synthesized compounds, the 5-methyl analogue (**5b**) showed the most potent PDE5 inhibitory activity (IC_{50} = 0.86 nM) and the highest selectivity over PDE6 (PDE6/PDE5 = 2300).