Bioorganic & Medicinal Chemistry Letters 25 (2015) 649–653

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Discovery and SAR study of 2-(4-pyridylamino)thieno[3,2-*d*]pyrimidin-4(3*H*)-ones as soluble and highly potent PDE7 inhibitors

Yusuke Endo *, Kentaro Kawai, Takeshi Asano, Seiji Amano, Yoshihito Asanuma, Keisuke Sawada, Keiji Ogura, Naoya Nagata, Noriko Ueo, Nobuaki Takahashi, Yo Sonoda, Noriyuki Kamei *

Drug Research Center, Kaken Pharmaceutical Co. Ltd, 14, Shinomiya Minamigawara-cho, Yamashina, Kyoto 607-8042, Japan

ARTICLE INFO

Article history:
Received 18 November 2014
Revised 28 November 2014
Accepted 29 November 2014
Available online 6 December 2014

Keywords:
Phosphodiesterase
Thienopyrimidinone
T-cell
Aqueous solubility

ABSTRACT

The discovery and SAR study of a new series of soluble and highly potent phosphodiesterase (PDE) 7 inhibitors are described herein. We explored a new lead compound with improved solubility, which led to the discovery of a 2-(4-pyridylamino)thieno[3,2-*d*]pyrimidin-4(3*H*)-one series. The introduction of 3-piperidines at the 7-position resulted in the significant enhancement of PDE7 activity. In particular, compound **32** also showed strong PDE7 inhibitory activity; good selectivity against PDE3, 4, and 5; and good aqueous solubility.

Phosphodiesterases (PDEs) hydrolyze the second messenger molecules 3′,5′-cyclic adenosine monophosphate (cAMP) and 3′,5′-cyclic guanosine monophosphate (cGMP) to affect cellular signaling. Among the 11 PDEs, the inhibitors of PDE3, PDE4, and PDE5 have been developed for clinical use; therefore, the PDE family is recognized as a druggable target.[1–3] PDE7 selectively catalyzes the degradation of cAMP to AMP, and the inhibition of PDE7 results in increased levels of cAMP. In addition, PDE7 is upregulated in activated T-cells[4] and in B-lymphocytes.[5] The PDE7 inhibitors will have broad application as treatment for T-cell related diseases, autoimmune diseases,[5] CNS disorders,[6] and airway diseases.[7] Considering the clinical utility, discovery of selective PDE7 inhibitors is desired for avoiding side effects caused by inhibiting other PDE enzymes.

Several groups have reported potent PDE7 inhibitors.[8–12] We recently reported the identification of a novel series of 2-(cyclopentylamino)thieno[3,2-*d*]pyrimidin-4(3*H*)-one derivatives (Fig. 1).[13] We obtained a hit compound **1**, and the preliminary modifications resulted in the discovery of the fragment-sized compound **2** with highly improved ligand efficiency.[14,15] Computational modeling and a structure–activity relationship (SAR) study led to 7-substituted derivatives as selective PDE7 inhibitors, including the initial lead compound **3**, which showed single nanomolar potency for PDE7 with 170-fold selectivity over PDE4 and <100 nM inhibitory activity of IL-2 production from mouse activated lymphocytes. However, compound **3** and its derivatives had poor solubility in the aqueous neutral solution compared to compound **2**. We considered that the introduction of substituents at the 7-position drastically decreased aqueous solubility. Therefore, we needed to discover another lead compound with a 7-substituent that had good physicochemical properties as well as good biological activity and enzyme selectivity.

In this Letter, we describe how we investigated the modifications of a previous series and obtained an alternative lead compound with improved aqueous solubility and potency.

We thought that the modification of substituents at the 2- and 7-positions would lead to increase both of solubility and potency. Therefore, our first approach was the modification of substituents at the 2-position of thieno[3,2-*d*]pyrimidin-4(3*H*)-one. In our previous study, the bulky cyclopentyl group of 2-(cyclopentylamino)thieno[3,2-*d*]pyrimidin-4(3*H*)-ones was considered to fit the hydrophobic binding subpocket to increase PDE7 activity. We assumed that an aromatic amino group was suitable for the 2-position and prepared analogues with an aromatic amino group at the 2-position (**7**–**17**) as shown in Scheme 1.

Methyl 3-aminothiophene-2-carboxylate (**4**) was treated with ethyl isothiocyanate to generate the fused ring product **5**. The methylation of **5** with iodomethane followed by the oxidation of the sulfur generated sulfone **6**. The methanesulfonyl moiety of **6** was substituted with various amines to produce **7**–**17**.

Investigation of substituents at the 2-position of the thienopyrimidinone started by replacing the cyclopentylamino group with a phenylamino group (Table 1). The activity of phenyl analogue **7**

* Corresponding authors.

http://dx.doi.org/10.1016/j.bmcl.2014.11.090
0960-894X/

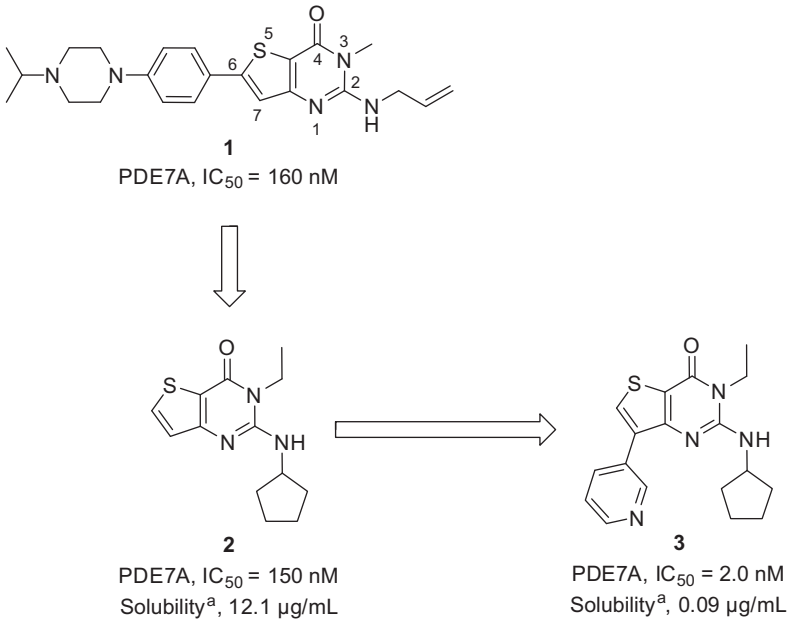
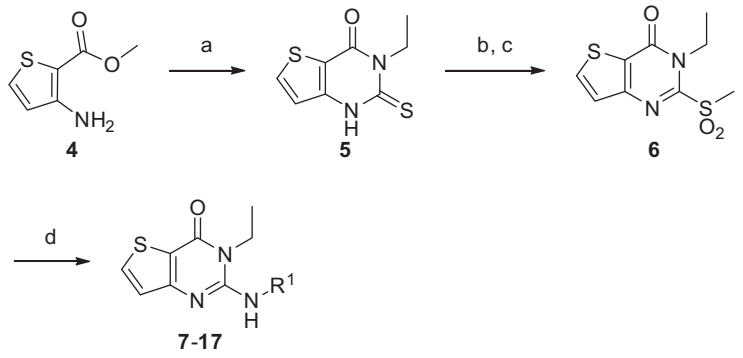


Figure 1. 2-(Cyclopentylamino)thieno[3,2-*d*]pyrimidin-4(3*H*)-one series. [a]Measured by the weight dissolved in phosphate buffer (pH 6.8).

dropped slightly, but the aqueous solubility improved compared to compound **2**. This finding encouraged us to further examine the SAR study at the 2-position. Next, compounds **8**–**10** were prepared to verify the effect of substituents on the aromatic ring. The introduction of methyl group at the *ortho* position (**8**) was well tolerated with regard to PDE7 activity, whereas *meta*- and *para*-substituted analogues (**9** and **10**) showed significantly decreased potency. Because compound **8** additionally displayed good aqueous solubility, the *ortho* position was found to be suitable for incorporating the substituents. While the introduction of a larger ethyl (**11**) and an electron-withdrawing cyano (**12**) group resulted in low potency, fluoro and chloro derivatives (**13** and **14**) showed higher potency than **7**. Additionally, **13** showed improved solubility. These results revealed that only small substituents at the *ortho* position would be tolerated for PDE7 activity and that the fluoro group would be the most effective substituent with regard to both PDE7 activity and aqueous solubility.

Replacing the phenyl moiety with a more polar pyridyl group was carried out to improve the solubility (**15** and **16**). These compounds showed considerably improved aqueous solubility; however, both compounds displayed decreased activity. Although 4-pyridine **16** was 2-fold less active compared to **7**, we tried to introduce the substituent to the pyridyl ring. Compound **17** with the fluoro group at the pyridine 3-position showed more improved PDE7 activity than expected while maintaining aqueous solubility. The fluoro group, as a substituent on the pyridine, was also suitable for potency, as was the benzene group. Thus, screening at the 2-position revealed that the 3-fluoro-4-pyridylamino group contributed to the improved activity and solubility. With respect to the PDE4 activity, compounds (**8**, **13**, **14**, and **17**) with substituents at the *ortho* position showed slightly increased PDE7 selectivity.

In our previous study,[13] aromatic rings at the 7-position were suitable for improving potency; however, the incorporation led to markedly decreased aqueous solubility. Therefore, we needed to explore favorable substituents at the 7-position of thienopyrimidinone. The introduction of various substituents at the 7-position into **17** was carried out to examine whether the PDE7 activity and aqueous solubility were compatible. Compounds **19**, **21**–**22**, and **24** were synthesized as shown in Scheme 2. Iodination of sulfone **6** with NIS followed by substitution of methanesulfonyl group with 4-amino-3-fluoropyridine generated the iodide **18**. Cyanide **19** was obtained by the displacement of iodine. Compound **18** was functionalized by Heck reaction with ethylene glycol monovinyl ether followed by ketonization to generate compound **20**. The reduction and Grignard reaction of **20** gave the alcohols **21** and **22**, respectively. The alcohol **24** was obtained via Heck reaction of **18** and hydrogenation followed by reduction with LAH.



Scheme 1. Reagents and conditions: (a) ethyl isothiocyanate, pyridine, reflux; (b) NaH, MeI, DMF, 0 °C; (c) *m*CPBA, DCM, rt; (d) R^1-NH_2, LiHMDS, DMSO, rt or THF, 60 °C.