Bioorganic & Medicinal Chemistry Letters 18 (2008) 4642–4646

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

4-Amino-2-cyanopyrimidines: Novel scaffold for nonpeptidic cathepsin S inhibitors

Osamu Irie [a,*], Fumiaki Yokokawa [a], Takeru Ehara [a], Atsuko Iwasaki [a], Yuki Iwaki [a], Yuko Hitomi [a], Kazuhide Konishi [a], Masashi Kishida [a], Atsushi Toyao [a], Keiichi Masuya [a], Hiroki Gunji [a], Junichi Sakaki [a], Genji Iwasaki [a], Hajime Hirao [a], Takanori Kanazawa [a], Keiko Tanabe [a], Takatoshi Kosaka [a], Terance W. Hart [b], Allan Hallett [b]

[a] Global Discovery Chemistry, Novartis Institutes for BioMedical Research, Ohkubo 8, Tsukuba, Ibaraki 300-2611, Japan
[b] Novartis Institutes for BioMedical Research, 5 Gower Place, London WC1E 6BS, UK

ARTICLE INFO

Article history:
Received 30 May 2008
Revised 1 July 2008
Accepted 5 July 2008
Available online 10 July 2008

Keywords:
Pyrimidine
Cathepsin S inhibitors
Nitrile
Cysteine protease

ABSTRACT

We describe here a novel 4-amino-2-cyanopyrimidine scaffold for nonpeptidomimetic cathepsin S selective inhibitors. Some of the synthesized compounds have sub-nanomolar potency and high selectivity toward cathepsin S along with promising pharmacokinetic and physicochemical properties. The key structural features of the inhibitors consist of a combination of a spiro[2.5]oct-6-ylmethylamine P2 group at the 4-position, a small or polar P3 group at the 5-position and/or a polar group at the 6-position of the pyrimidine.

Eleven members of the cysteine cathepsin family have been identified in the human genome (cathepsins B, C, H, F, K, L, O, S, V, W, and X).[1] Lysosomal cysteine proteases are important enzymes for processing proteins such as prohormones. Recent studies on their genes revealed that these cathepsins have specific individual functions which are important for the normal functioning of an organism. These functions are often associated with the restricted tissue localization of the cathepsins, as demonstrated for cathepsins S, V, and K. Cathepsin S (Cat S) is predominantly expressed in spleen, professional antigen presenting cells (APC), such as dendritic cells, B lymphocytes, and macrophages. The major role of Cat S in these cells is the processing of the major histocompatibility complex (MHC) class II associated invariant chain, which is essential for the normal functioning of the immune system. Cat S is largely responsible for the last proteolytic cleavage step of the invariant chain that produces class II-associated leupeptin induced peptide (CLIP). Due to its role in the immunological system, Cat S is an attractive therapeutic target and selective Cat S inhibitors[2] may also modulate a number of other diseases such as rheumatoid arthritis, multiple sclerosis, myasthenia gravis, asthma, atherosclerosis, and neuropathic pain.[3]

We have recently reported a novel Cat K inhibitor **1** and its analogs having a 2-cyanopyrimidine scaffold.[4] However, 2-cyanopyrimidine derivatives were rapidly cleared from the circulation in

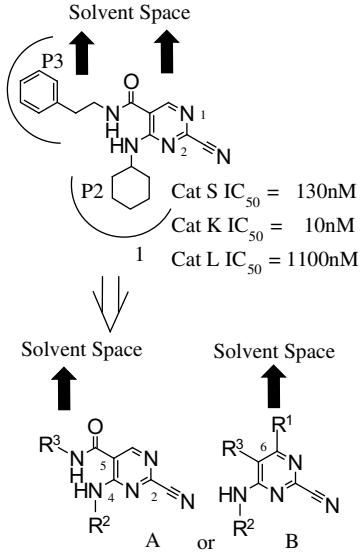
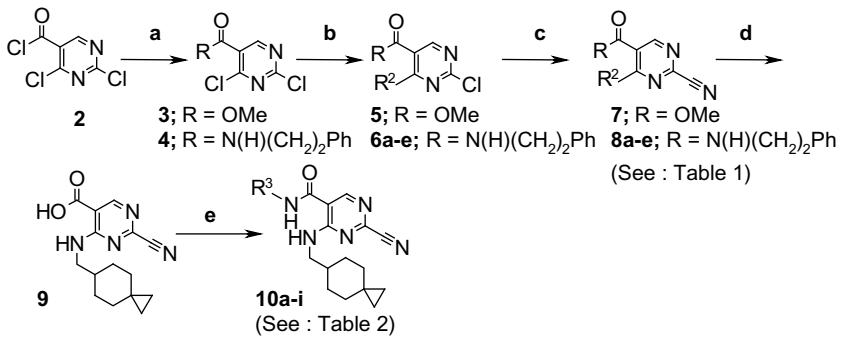


Figure 1. Design of new 2-cyanopyrimidine Cat S inhibitors.

* Corresponding author. Tel.: +81 29 865 2384; fax: +81 29 865 2308.
E-mail address: osamu.irie@novartis.com (O. Irie).

0960-894X/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2008.07.011

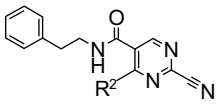


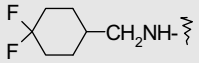
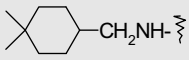
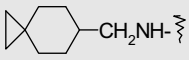
Scheme 1. Reagents and conditions: (a) MeOH or phenethylamine, NEt_3, CH_2Cl_2, 0 °C–rt, 69–86%; (b) R^2XH (X = NH or NMe), MeOH, rt–60 °C, 88–98%, or cyclohexylmethanol, NaH, THF, 0 °C–rt, 32%; (c) NaCN, DABCO, DMSO–H_2O, rt–80 °C, 62–96%; (d) LiOH, THF–H_2O, 0 °C, 1 h, 33–98%; (e) R^3NH_2, EDC–HCl, HOAt, DMF, 0 °C–rt, 10 h, 19–88%.

rat pharmacokinetic experiments (PK), and showed low aqueous solubility. The low solubility is largely due to the lipophilic nature of compounds that were designed to attractively interact with the lipophilic active site of cathepsins. There are, however, some regions in cathepsins that accept polar functional groups. The effective use of such regions is expected to afford water soluble Cat S specific inhibitors. After switching the selectivity preference to Cat S, we thus focused on improving the physicochemical properties, especially the thermodynamic solubility and the PK profiles, starting from the 2-cyanopyrimidine compound **1**.[4] Our strategy was to add a polar functional group at the 5- or the 6-position on the pyrimidine ring (Fig. 1). Herein, we describe the details of the novel scaffold, some of which turned out to be potent and orally bioavailable Cat S inhibitors with suitable PK and physicochemical properties.

The synthesis of 5-substituted pyrimidines, type A analogs in Figure 1, is shown in Scheme 1. Condensation of commercially available 2,4-dichloropyrimidine-5-carbonyl chloride **2** with methanol, as a protecting group, or phenethylamine as a P3 part gave a methyl ester **3** and an amide **4**. Treatment of P2 amines or sodium cyclohexylmethoxide with pyrimidine **3** or **4** followed by addition of sodium cyanide provided methyl ester **7** and compounds **8a–f** (Table 1). Hydrolysis of **7** under basic conditions provided a

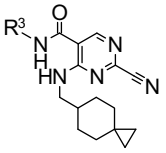
Table 1
Optimization of the P2 moiety

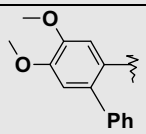
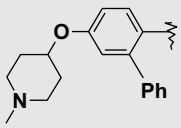
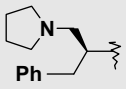
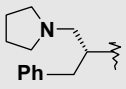
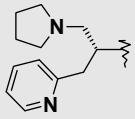
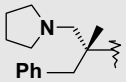
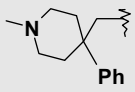
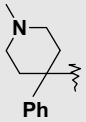
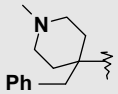


Compound	R^2	IC_{50}[a] (nM)		
		Cat S	Cat K	Cat L
1	Cyclohexyl-NH–	130	10	1100
8a	Cyclohexyl-CH_2NH–	22	15	>2000
8b	Cyclohexyl-$CH_2N(Me)$--	32	36	2000
8c	Cyclohexyl-CH_2O–	14	9	780
8d		22	130	>3000
8e		93	>3000	>3000
8f		15	>3000	>3000

[a] Inhibition profiles were determined by a fluorometric assay with recombinant human Cat K, L, and S, employing Z-Phe-Arg-AMC (Cat K and L) and L-Leu-Leu-Arg-AMC (Cat S) as synthetic substrates.[4]

Table 2
Optimization of the P3 moiety



Compound	R^3	IC_{50}[a] (nM)		
		Cat S	Cat K	Cat L
10a		24	>1000	>3000
10b		3	–	840
10c		23	200	1500
10d		<1	44	150
10e		4	–	480
10f		21	–	840
10g		6	170	700
10h		7	–	510
10i		2	140	180

[a] Inhibition profiles were determined by a fluorometric assay with recombinant human Cat K, L, and S, employing Z-Phe-Arg-AMC (Cat K and L) and L-Leu-Leu-Arg-AMC (Cat S) as synthetic substrates.[4]