Bioorganic & Medicinal Chemistry Letters 19 (2009) 1431–1433

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Fluoroalkyl α side chain containing 3,4-diamino-cyclobutenediones as potent and orally bioavailable CXCR2–CXCR1 dual antagonists

Purakkattle Biju *, Arthur G. Taveras, Michael P. Dwyer, Younong Yu, Jianhua Chao, R. William Hipkin, Xuedong Fan, Diane Rindgen, Jay Fine, Daniel Lundell

Schering-Plough Research Institute, Kenilworth, NJ 07033, USA

ARTICLE INFO

Article history:
Received 21 November 2008
Revised 6 January 2009
Accepted 12 January 2009
Available online 15 January 2009

Keywords:
Fluoroalkyl
Cyclobutenediones
CXCR2–CXCR1 dual antagonist

ABSTRACT

A series of potent and orally bioavailable 3,4-diaminocyclobutenediones with various fluoroalkyl groups as α side chain were prepared and found to show significant improvements in the binding affinities towards both CXCR2 and CXCR1 receptors.

© 2009 Elsevier Ltd. All rights reserved.

Chemokines[1] are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T-cells, eosinophils, basophils, neutrophils, and endothelial cells to sites of inflammation and tumor growth. In general, chemokines have been classified[2] into two main classes, the CXC-chemokines and the CC-chemokines. The CXC-chemokines include interleukin-8 (IL-8), neutrophil activating protein-1 (NAP-1), NAP-2, and GRO-α as well as many others. These CXC-chemokines[3] promote the accumulation and activation of neutrophils and hence, they have been implicated in a wide range of acute and chronic inflammatory disorders[4] including psoriasis, RA, and COPD. IL-8 mainly activates neutrophils through their G-protein coupled receptors, CXCR1 and CXCR2. Due to the well established relationship between IL-8 and inflammatory diseases, CXCR1 and CXCR2 antagonists[5] have been targeted for small molecule drug discovery. Several literature reports are available on the discovery of CXCR2 antagonists.[6] We previously reported several publications on the structure–activity relationships of 3,4-diaminocyclobutenedione[6a–d] (e.g., **1**) class of CXCR2 antagonist and two other structures, 3,4-diaminothiadiazoleoxides[6e] **2** and **3** and 3,4-diamino-1,2,5-thiadiazoles[6f] **4**. The other notable CXCR2 antagonists include urea[7a] compounds **5**, cyanoguanidines[7b] **6,** and cyclic sulfonamides[7c] **7** from GlaxoSmithKline. Our previous reports on diaminocyclobutenediones primarily focused on the right side amine modifications, particularly benzyl, substituted furyl, and heteroaryls. Herein, we report our efforts to improve both receptor binding affinities particularly CXCR1 by introducing fluoroalkyl α side chain R_F groups as in **1a** (Fig. 1).

Table 1 summarizes the effect of various fluoroalkyl α-substituents R_F on CXCR2 and CXCR1 binding affinities. A general synthetic procedure[6,8] for the preparation of the right side amines and final coupling to cyclobutenedione can be obtained from our previous

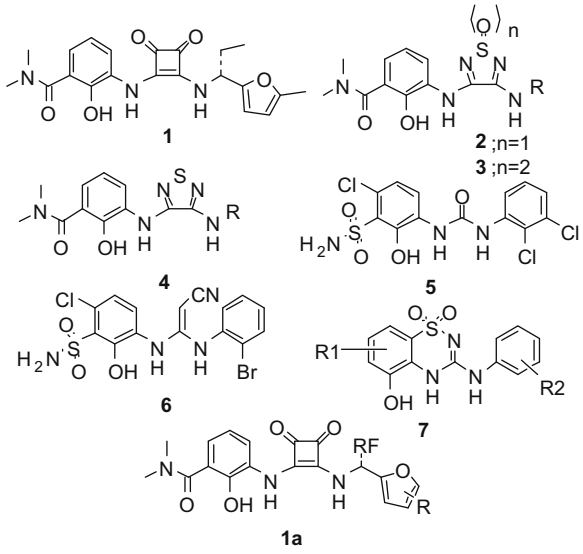
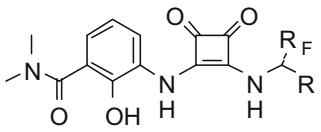


Figure 1. Existing diamino structures as CXCR2 antagonists.

* Corresponding author. Tel.: +1 908 740 3127; fax: +1 908 740 7152.
E-mail address: purakkattle.biju@spcorp.com (P. Biju).

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.01.033

Table 1
3,4-Diamino-cyclobutenediones: effect of the fluorinated α side chain on CXCR2 and CXCR1 binding versus IL-8



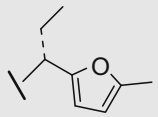
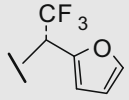
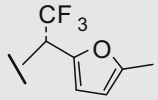
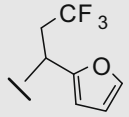
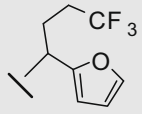
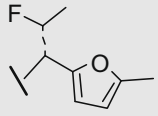
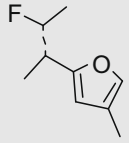
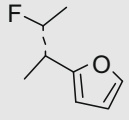
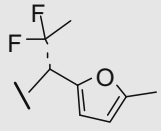
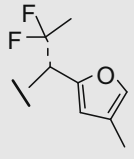
Compounds	–CHR_FR–	CXCR2 K_i (nM)[a]	CXCR1 K_i (nM)[a]
8		4	20
9		2	6
10		5	9
11		5	100
12		400	NT
13		13	16
14		4	5
15		7	43
16		10	6
17		14	6

Table 1 (*continued*)

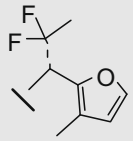
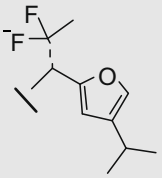
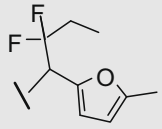
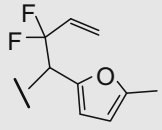
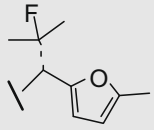
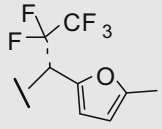
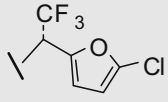
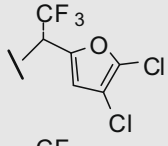
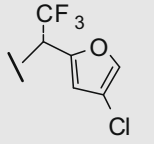
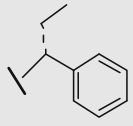
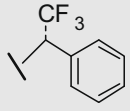
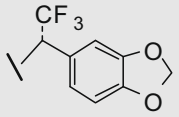
Compounds	–CHR_FR–	CXCR2 K_i (nM)[a]	CXCR1 K_i (nM)[a]
18		12	30
19		2	25
20		5	22
21		9	NT
22		8	24
23		4	10
24		7	34
25		5	103
26		5	20
27		4	40
28		14	40

Table 1 (*continued*)

Compounds	R^1	CXCR2 K_i (nM)[a]	CXCR1 K_i (nM)[a]
29		5	8

NT, not tested.
[a] Values are means of two experiments.

Table 2
Rapid rat pharmacokinetic results for a selected list of compounds

Compound	R rat AUC (po) (μM h)[a]
8	49.0
10	19.8
13	3.6
14	3.6
16	3.0
27	17.4
29	9.17

[a] Values are means of three experiments.

reports. Compound **9** with a trifluoromethyl group showed threefold improvement in CXCR1 and twofold in CXCR2 binding affinities compared to the ethyl compound **8**. However, a trifluoroethyl group as found in compound **11**, showed weaker binding affinity towards CXCR1 receptor while retaining excellent CXCR2 affinity. Introduction of 1,1,1-trifluoropropyl group as in compound **12** further weakened the CXCR2 affinity. Based on these results, we focused our attention on trifluoromethyl and fluoroethyl side chains. Compound **14** with a 2-fluoroethyl side chain on 4-methyl furan was one of the most potent duel CXCR2–CXCR1 antagonists. It is interesting to note that a difluoroethyl substituted compound **16** and **17** had a threefold improvement towards CXCR1 binding affinity over the compound **8**. 3,3-Difluoropropyl substitution as in compound **20** did not improve the CXCR1 potency. Compound **23** with a pentafluoroethyl substitution showed twofold improvements in CXCR1 affinity compared to the ethyl side chain. A 2-fluoroisopropyl substitution as in compound **22** was well tolerated on both the receptor affinities. We also incorporated the fluoroalkyl side chain in the right side benzyl series. Compound **29** with a trifluoromethyl group in phenylmethylenedioxy motif showed single digit nanomolar affinity towards both the receptors. Most of these compounds showed excellent blood levels in the rapid rat pharmacokinetic screen as shown in Table 2.

In summary, the fluoroalkyl modifications significantly improved binding affinities towards both CXCR1 and CXCR2 receptor. Moreover, fluoroalkyl α side chain modifications produced compounds with excellent blood levels. Compounds **9**, **10**, and **14** were identified as the most potent compounds.

Acknowledgments

We thank Dr. Robert Aslanian, Dr. John Piwinski, Dr. Viyyoor Girijavallabhan, and Dr. Christopher Boyce from Schering-Plough Research Institute.

References and notes

1. (a) Adams, D. H.; Lioyd, A. R. *Lancet* **1997**, *349*, 490; (b) Saunders, J.; Tarby, C. M. *Drug Discovery Today* **1999**, *4*, 80; (c) Gura, T. *Science* **1996**, *272*, 954.
2. (a) Skelton, N. J.; Quan, C.; Reilly, D.; Lowman, H. *Structure* **1999**, *7*, 157. and references cited therein; (b) Rahman, A.; Harvey, K.; Siddiqui, R. *Curr. Pharm. Des.* **1999**, *5*, 241. and references cited therein.
3. Traves, S. L.; Smith, S. J.; Barnes, P. J.; Donnelly, L. E. *J. Leukocyte Biol.* **2004**, *76*, 1.
4. (a) Luster, A. D. N. *Eng. J. Med.* **1998**, *338*, 436; (b) Barnes, P. J.; Shapiro, S. D.; Pauwels, R. A. *Eur. Respir. J.* **2003**, *4*, 672; (c) Donnely, L. E.; Rogers, D. F. *Drugs* **2003**, *63*, 1973; (d) Feldmann, M.; Brennan, F. M.; Maini, R. N. *Annu. Rev. Immunol.* **1996**, *14*, 397; (e) Kucharzik, T.; Walsh, S. V.; Chen, J.; Parkos, C. A.; Nusrat, A. *Am. J. Pathol.* **2001**, *159*, 2001; (f) Cummings, C. J.; Martin, T. R.; Frevert, C. W.; Quan, J. M.; Wong, V. A.; Mongovin, S. M.; Hagen, T. R.; Steinberg, K. P.; Goodman, R. B. *J. Immunol.* **1999**, *162*, 2341; (g) Glinski, W.; Jablonska, S. *J. Invest. Dermatol.* **1984**, *82*, 386.
5. (a) Wu, L.; Ruffing, N.; Shi, X.; Newman, W.; Soler, D.; Mackay, C.; Quin, S. *J. Biol. Chem.* **1996**, *271*, 31202; (b) Jones, S. A.; Dewald, B.; Lewis, I. C.; Baggiolini, M. *J. Biol. Chem.* **1997**, *272*, 16166; (c) Shibata, F.; Konishi, K.; Nakagawa, H. *Biol. Pharm. Bull.* **2002**, *25*, 1217.
6. (a) Merritt, J. R.; Rokosz, L. L.; Nelson, K. H.; Kaiser, B.; Wang, W.; Stauffer, T. M.; Ozgur, L. E.; Schilling, A.; Li, G.; Baldwin, J.; Taveras, A. G.; Dwyer, M. P.; Chao, J. *J. Bioorg. Med. Chem. Lett.* **2006**, *16*, 4107; (b) Dwyer, M. P.; Yu, Y.; Chao, J. P.; Aki, C.; Chao, J. H.; Biju, P.; Girijavallabhan, V.; Rindgen, D.; Bond, R.; Mayer-Ezel, R.; Jakway, J.; Hipkin, R. W.; Fossetta, J.; Gonsiorek, W.; Bian, H.; Fan, X.; Terminelli, C.; Fine, J.; Lundell, D.; Merritt, J. R.; Rokosz, L. L.; Kaiser, B.; Li, G.; Wang, W.; Stauffer, T. M.; Ozgur, L. E.; Taveras, A. G. *J. Med. Chem.* **2006**, *49*, 7603; (c) Chao, J. H.; Taveras, A. G.; Chao, J. P.; Aki, C.; Dwyer, M. P.; Yu, Y.; Biju, P.; Rindgen, D.; Jakway, J.; Hipkin, W.; Fossetta, J.; Fan, X.; Lundell, D.; Fine, J.; Minnicozzi, M.; Phillips, J.; Merritt, J. R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3778. and references cited therein; (d) Yu, Y.; Dwyer, M. P.; Chao, J.; Aki, C.; Chao, J.; Purakkattle, B.; Rindgen, D.; Bond, R.; Mayer-Ezel, R.; Jakway, J.; Qiu, H.; Hipkin, R. W.; Fossetta, J.; Gonsiorek, W.; Bian, H.; Fan, X.; Terminelli, C.; Fine, J.; Lundell, D.; Merritt, J. R.; He, Z.; Lai, G.; Wu, W.; Taveras, A. G. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1318; (e) Biju, P.; Taveras, A.; Yu, Y.; Zheng, Z.; Chao, J.; Rindgen, D.; Jakway, J.; Hipkin, R. W.; Fossetta, J.; Fan, X.; Fine, J.; Qiu, H.; Merritt, J. R.; Baldwin, J. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 228; f Biju, P. et al. Unpublished results.
7. (a) Nie, H.; Widdowson, K. L.; Palovich, M. R.; Fu, W.; Elliot, J. D.; Bryan, D. L.; Burman, M.; Scmidt, D. B.; Foley, J. F.; Sarau, H. M.; Busch-Petersen, J. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5513; b Busch-Petersen, J.; Jin, Q.; McCleland, B. W.; Nie, H.; Palovich, M. R.; Davis, R. S.; Fu, W.; Elliot, J. D.; Burman, M.; Foley, J. J.; Schmidt, D. B.; Podolin, P.; Bolognese, B. J.; Underwood, D.C.; Osborn, R. R.; Dehaas, C. J.; Salmon, M.; Carpenter, D. C.; Kilian, D. J.; Sarau, H. M.; Widdowson, K. L. *Abstracts of Papers*, 228th National Meeting of the American Chemical Society, Philadelphia, PA, United States, August 22–26, 2004; American Chemical Society: Washington, DC, 2004; MEDI-192.; (c) Wang, Y.; Busch-Petersen, J.; Wang, F.; Ma, L.; Fu, W.; Kerns, J. K.; Jin, J.; Palovich, M. R.; Shen, J.-K.; Burman, M.; Foley, J. J.; Scmidt, D. B.; Hunsberger, G. E.; Sarau, H. M.; Widdowson, K. L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3864.
8. Biju, Purakkattle *Synth. Commun.* **2008**, *38*(12), 1940.