Bioorganic & Medicinal Chemistry Letters 19 (2009) 4446–4449

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Diaminocyclobutenediones as potent and orally bioavailable CXCR2 receptor antagonists: SAR in the phenolic amide region

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ARTICLE INFO

Article history:
Received 4 April 2009
Revised 12 May 2009
Accepted 13 May 2009
Available online 18 May 2009

Keywords:
Diaminocyclobutenediones
CXCR2 receptor antagonist
Amide modification

ABSTRACT

A series of potent and orally bioavailable 3,4-diaminocyclobutenediones with various amide modifications and substitution on the left side phenyl ring were prepared and found to show significant inhibitory activities towards both CXCR2 and CXCR1 receptors.

The recruitment of leukocytes into sites of inflammation is a normal biological process to fight infection. However, in diseases such as rheumatoid arthritis, COPD and psoriasis, the uncontrolled leukocyte migration to the site of inflammation may be the leading cause of permanent tissue destruction and further disease progression. As a result of inflammatory stimuli, chemokines[1] released by a wide variety of cells signal the migration of 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[3] include interleukin-8 (IL-8), neutrophil activating protein-1 (NAP-1), NAP-2 and GRO-α as well as many others. These CXC-chemokines 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, rheumatoid arthritis and COPD. IL-8 mainly activates neutrophils through their G-protein coupled receptors, CXCR1 and CXCR2. The increased levels[5] of IL-8, GRO-α and MCP-1 in the sputum from patients with COPD compared to non smokers highlight the importance of chemokine targets for small molecule drug discovery.

Due to the well established relationship between IL-8 and inflammatory diseases, CXCR1 and CXCR2 antagonists[6] have been targets of small molecule drug discovery. Several literature reports are available on the discovery of CXCR2 antagonists.[7,8] We previously reported several publications on the structure–activity relationships of 3,4-diaminocyclobutenedione[8a–e] (e.g., **1**) class of CXCR2 antagonist, 3,4-diaminothiadiazoleoxides[8f] **2** and **3** and 3,4-diamino-1,2,5-thiadiazoles[8g] **4**. Our earlier reports primarily focused on the structure–activity relationships of the right side amine modifications. Herein, we report the R_1 and R_2 modifications on the left side phenolic amide region (Fig. 1).

Structure–activity relationships of the compounds listed in Table 1 shows the basic structural elements required to show CXCR2 receptor antagonism in the 3,4-diaminocyclobutenedione class of compounds. The weaker binding affinity of the benzomorpholine compound **9**, the *N*-methyl compounds **11** and **12** and the methoxy compound **13** established the basic requirement of three critical H-bonding functional groups, the phenolic OH group and the two –NH-groups (Table 1).

The carboxylic acid compound **7,** the unsubstituted amide **8** and the 2-amino phenol compound **10** showed reasonable binding affinity towards the CXCR2 receptor. On the other hand, the *N,N*-dimethyl amide **6** and **17** (Table 2) displayed excellent inhibitory activities. This initial SAR prompted us to explore additional amide modifications, which is depicted in Table 2.

The synthetic procedures for the preparation and coupling of various left and right side amines to the commercially available 3,4-diethoxysquarate can be obtained from our previous publications.[8,9]

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doi:10.1016/j.bmcl.2009.05.049

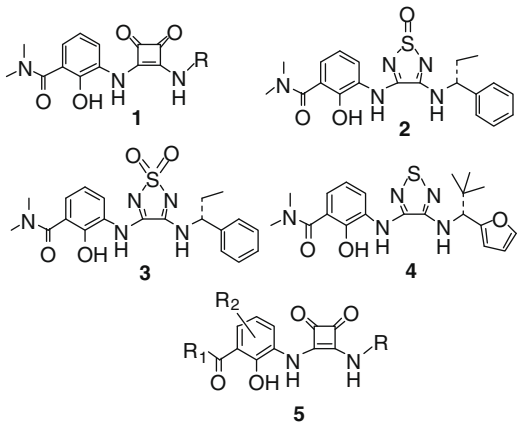


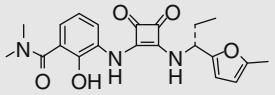
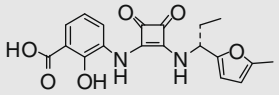
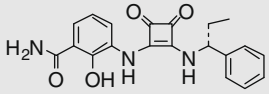
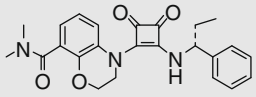
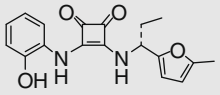
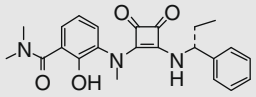
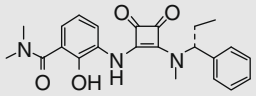
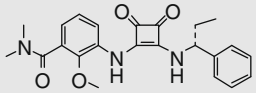
Figure 1. Recently reported diamino structures as CXCR2 antagonists.

While keeping the right side benzylic amine as constant, a number of amides were prepared and evaluated in the membrane binding CXCR2 and CXCR1 assays[10,11] (Table 2). The mono substituted alkyl amides **14**, **15** and **16** showed weaker binding affinity towards the CXCR2 receptor compared to *N*,*N*-dimethyl amide **17** that showed excellent inhibitory activity towards both the receptors. No potency enhancement was seen when we introduced a bulky alkyl group such as an isopropyl group as in compound **18**. The introduction of cyclic amides retained the CXCR2 potency. The notable cyclic amides displayed good potency were the pyrrolidine **19**, the morpholine **20** and the *N*-methyl piperazine **21**. We also explored some of the substituted amides such as hydroxy azetidine **22** and 3-hydroxy pyrrolidine **23**, both showed favorable affinity towards both the receptors. Compound **25**, a pyrrolidine with a carboxylic acid group showed high binding affinity towards both the receptors. When we increased the bulkiness as in *N*-piperazyl compounds, **26** and **27**, no enhancement in potency was observed.

After exploring the amide modifications, we turned our attention to various alkyl, aryl and halo substitution on the left side benzene ring at positions 4**,** 5 and 6 as in Table 3. The 4-bromo **28**, 5-cyano **32** and 6-methyl **34** compounds retained high affinity towards CXCR2 receptor. On the other hand, 5-methyl compound **29** was much weaker than the corresponding 6-methyl compound. No enhancement in potency was observed with the more bulkier 4-phenyl **30** and 4-(2-pyridyl) **31** compounds compared to the unsubstituted compound **17**. The 5-phenyl substitution was not tolerated may be due to steric reasons. Overall, an electron withdrawing and relatively small groups at positions 4 and 5 were found to show high binding affinity towards CXCR2 receptor.

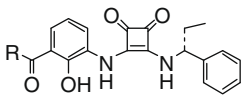
Table 4 shows list of compounds with substitution at position 5 and its effect on CXCR2 binding affinity with a thiophene right side motif. We learned that the 5-cyano substitution brought the best

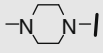
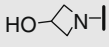
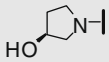
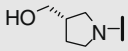
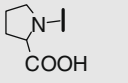
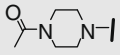
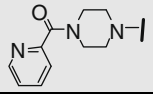
Table 1
SAR on the left side phenolic amide: The key structural requirements, the phenolic OH and two –NH-functional groups

Compound #	Compound structure	CXCR2 Ki (nM)[a] (vs ^{125}I- hIL-8)
6		5
7		12
8		25
9		>270
10		22
11		>270
12		>270
13		>270

[a] Values are means of two experiments.

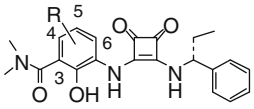
Table 2
3,4-Diaminocyclobutene diones: SAR in the amide region



Compounds	R	CXCR2 Ki (nM)[a] (vs ^{125}I- hIL-8)	CXCR1 Ki (nM)[a] (vs ^{125}I- hIL-8)
14		28	NT
15		219	NT
16		34	NT
17		4.4	40
18		11	123
19		9	NT
20		10	NT
21		12	41
22		20	NT
23		18	21
24		20	NT
25		5	30
26		27	NT
27		20	NT

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

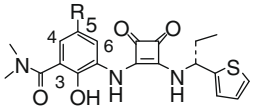
Table 3
Right side benzylic series: substitution in the phenyl ring



Compounds	R	CXCR2 Ki (nM)[a] (vs ^{125}I- hIL-8)	CXCR1 Ki (nM)[a] (vs ^{125}I- hIL-8)
17	H	4.4	40
28	4-Bromo	4	NT[a]
29	5-Methyl	203	NT
30	4-Phenyl	17	NT
31	4-(2-Pyridyl)	15	>1000
32	5-Cyano	3	NT
33	5-Phenyl	>2000	NT
34	6-Methyl	4.5	381

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

Table 4
Right side thiophene series: substitution in the phenyl ring



Compounds	R	CXCR2 Ki (nM)[a] (vs ^{125}I- hIL-8)	CXCR1 Ki (nM)[a] (vs ^{125}I- hIL-8)
35	H	5	210
36	Cyano	5	54
37	Chloro	50	1221
38	Bromo	61	2068
39	Methyl	76	2797

[a] Values are means of two experiments.

Table 5
Rat pharmacokinetic results for a selected list of compounds: dosed @ 10mpk

Compounds	Rat PK (AUC) (p.o) (μM.h)[a]
8	2.2
14	0.4
17	17.4
18	1.4
19	1.0
22	0.5
24	0.44
28	0.06
34	2.3
35	2.5
37	2.2
38	1.4

[a] Values are means of two experiments.

overall profile compared to chloro, bromo or methyl substitution. The 5-cyano compound **36** not only retained high affinity towards CXCR2 receptor but also showed improvement in inhibitory activities towrds CXCR1 receptor. Some of the compounds listed in the above Tables 2–4 showed decent plasma levels in the rat pharmacokinetic analysis. The *N*,*N*-dimethyl amide compound **17** had an excellent plasma levels, which suggest the better in vivo stability of dimethyl amide motif compared to other amides in Table 2. It is noteworthy that substitution at positions 4, 5 and 6 did not improve the exposure level as seen with compounds **28**, **34**, **37**, and **38** (Table 5).

In summary, the left side SAR in the 3,4-diaminocyclobutenedione class of compounds clearly established the requirement of the key Phenol and the two –NH-functionalities. Moreover, slight improvement in CXCR1 affinity can be accomplished by introducing certain amide functionalities like 3-hydroxy pyrrolidine or pyrrolidine-3-carboxylic acid. The substitution at 3, 4 and 5 positions with a small electron withdrawing group also showed improvement in receptor affinities.

Acknowledgments

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

References and notes

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9. For the detailed preparation procedures of the left side amines, refer to the patents WO 2002076926, WO 2002076926, WO 2005068460.

10. Competition binding analyses at hCXCR1 and hCXCR2 using radio labeled **6** has shown that compound infact is an allosteric antagonist. Since compound **6** is an allosteric antagonist, the Ki values reported in this paper for a similar class of compounds can be better viewed as IC_{50} values, although these values were measured in the presence of ^{125}I-hIL-8. SAR studies have been conducted by using Ki (Technically IC_{50}) values and we have seen good correlation with cell based assays. We have not done any competition binding experiments on any of the compounds presented in this paper, except compound **6**.
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