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3,4-Diamino-1,2,5-thiadiazole as potent and selective CXCR2 antagonists

Purakkattle Biju *, Arthur G. Taveras, Younong Yu, Junying Zheng, R. William Hipkin, James Fossetta, Xuedong Fan, Jay Fine, Daniel Lundell

Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA

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ABSTRACT

A series of potent and selective 3,4-diamino-1,2,5-thiadiazoles were prepared and found to show excellent binding affinities towards CXCR2 receptor.

The recruitment of inflammatory cells into sites of inflammation is a normal biological response to fight infection. However, excessive recruitment of inflammatory cells exacerbates tissue damage. Uncontrolled leukocyte migration mainly neutrophils to the lungs may be the primary cause of various chronic inflammatory pulmonary conditions like chronic obstructive pulmonary disorder (COPD), which is predicted to be the third most common cause of worldwide death[1] by 2020. Common acute and chronic inflammatory conditions like rheumatoid arthritis, inflammatory bowel disease and psoriasis may also be caused by increased leukocyte migration.

Chemokines[2] are chemoattractant cytokines released by a wide variety of cells that play a major role in leukocyte recruitment to inflammatory sites. These low molecular weight proteins attract a wide range of inflammatory cells such as neutrophils, macrophages, T-cells, eosinophils, and endothelial cells to sites of inflammation and tumor growth. These mediators are divided into four different classes.[3] The CXC chemokines,[4] for example, interleukin-8 (IL-8), GRO-α, neutrophil-activating protein-1 (NAP-1), NAP-2, and ENA-78, are the major mediators of inflammation[5] and joint destruction in both COPD and RA. IL-8 mainly activates neutrophils through the G-protein-coupled receptors, CXCR1 and CXCR2. Due to the obvious relationship between IL-8 and inflammatory diseases, CXCR1 and CXCR2 antagonists[6] have been targets of small-molecule drug discovery. We have recently reported[7] three structural sub-types of CXCR2/CXCR1 dual antagonists. Among them, 3,4-diaminocyclobut-3-ene-1,2-diones (e.g., **1**) represent a very potent class of CXCR2/CXCR1 dual antagonists. We previously reported 1,2,5-thiadiazole-1-oxides **2** and **3**, as replacement for the less known pharmacophore cyclobutenedione. This letter describes the synthesis and SAR development in a new class of selective CXCR2 antagonists, 3,4-diamino derivatives of a heteroaromatic center core 1,2,5-thiadiazole **4** (Fig. 1).

It is noteworthy that the 1,2,5-thiadiazole is a core present in the commercial drug[8] timolol®. Moreover, this is the first report of a class of CXCR2 antagonist with a diamino-heteroaryl core structure. Other known diamino types include urea derivatives **5**,[9a] cyanoguanidines,[9b] **6** and cyclic sulfonamides[9c] **7** from GlaxoSmithKline.

Synthesis of the diamino derivatives of 1,2,5-thiadiazole **4** was very challenging due to the nature of the left and right side amines.

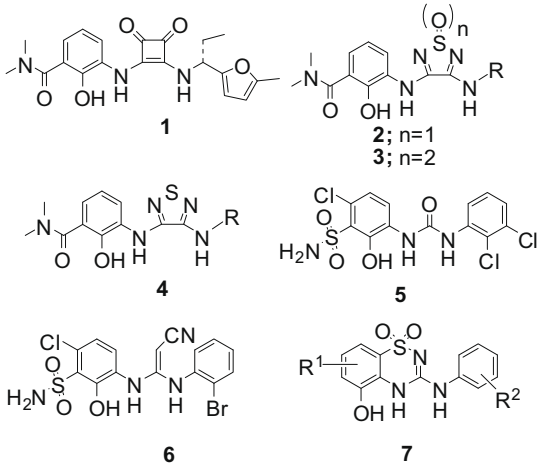

Figure 1. Existing diamino structures as CXCR2/CXCR1 antagonists.

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

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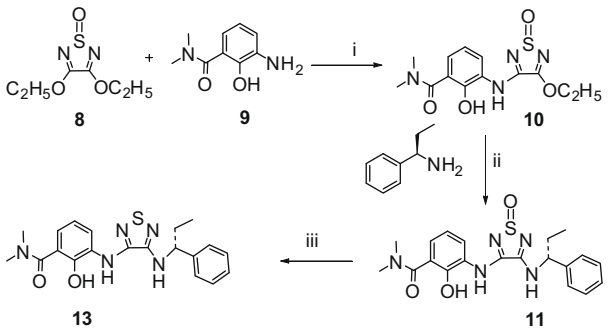
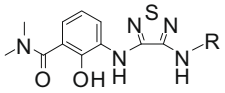


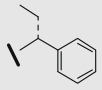
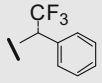
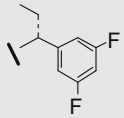
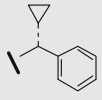
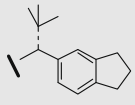
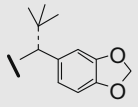
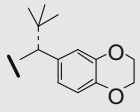
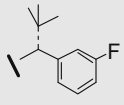
Scheme 1. Synthesis of 3,4-diamino1,2,5-thiadiazole. Reagents and conditions: (i) diisopropylethylamine, C_2H_5OH, rt, 6 h, 90%; (ii) MeOH, diisopropylethylamine, rt, 80%; (iii) PPh_3 (3 equiv), CCl_4, 0 °C–reflux, 3 h; 85%.

We developed a three step synthesis[10] from the readily available 3,4-diethoxy-2,5-thiadiazole-1-oxide **8** by employing a novel reduction of the thiadiazole oxide. Coupling of the phenolic aniline **9** with 3,4-diethoxy-2,5-thiadiazole-1-oxide **8** in methanol afforded **10,** which upon subsequent treatment with commercially available (R)-(+)-α-ethylbenzylamine gave the diamino-thiadiazole oxide **11**. A novel reduction of the compound **11** with Ph_3P and CCl_4 in dichloromethane gave the corresponding 1,2,5-thiadiazole **13** in good yield (Scheme 1). By following a similar procedure, a number of thiadiazoles were prepared with different left and right side amines (Tables 1–3). A general procedure for the preparation of various left- and right-side amines can be obtained from our previous reports.[7]

Table 1 shows the structure–activity relationship of 3,4-diamino-1,2,5-thiadiazole compounds. We kept the left-side phenolic amine as constant and studied the effect of various right side benzylic-substituted amines towards CXCR2-binding affinity. It is interesting to note that this class of compounds is less potent compared to the corresponding cyclobutenediones[7a–d] or thiadiazole-1-oxides.[7e] However, compounds **13** and **16** showed good binding affinity towards the CXCR2 receptor. Moreover, these compounds behaved as selective CXCR2 antagonists with micromolar activity towards CXCR1 receptor. Compound **18**, with a methylenedioxy substitution and a *tert*-butyl side chain, showed reasonable CXCR1-binding affinity.

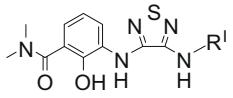
Table 1
(3,4-Diamino-1,2,5-thiadiazole): effect of right-side substituents R on CXCR2 and CXCR1 binding versus IL-8

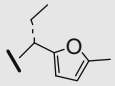
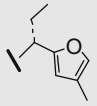
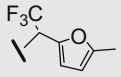
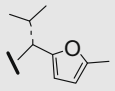
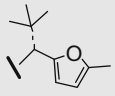
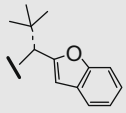
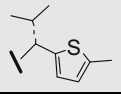


Compound	R	CXCR2 K_i[a] (nM)	CXCR1 K_i[a] (nM)
12		43	10,000
13		21	5110
14		36	4300
15		20	4100
16		16	2030
17		44	10,000
18		52	330
19		126	10,000
20		78	1300

[a] Values are reported as means of two experiments.

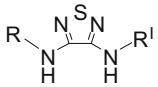
Table 2
(3,4-Diamino-1,2,5-thiadiazole): effect of right-side hetero-aryl substituents R^1 on CXCR2 and CXCR1 binding versus IL-8

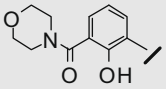
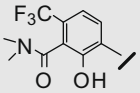
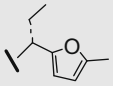
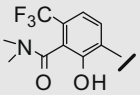
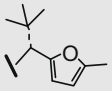
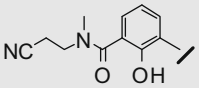
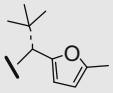
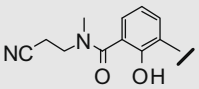
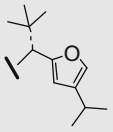
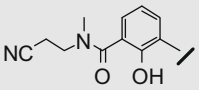


Compound	R^1	CXCR2 K_i[a] (nM)	CXCR1 K_i[a] (nM)
21		13	3000
22		35	2280
23		53	10,000
24		15	2400
25		14	91
26		15	381
27		76	2360
28		14	1300

[a] Values are reported as means of two experiments.

Table 3
(3,4-Diamino-1,2,5-thiadiazole): effect of right-side heteroaryl substituents R^1 and left-side subtituent R on CXCR2 and CXCR1 binding versus IL-8



Compound	R	R^1	CXCR2 K_i[a] (nM)	CXCR1 K_i[a] (nM)
29			18	1270
30			7.5	749
31			38	168
32			13	114
33			34	79
34			14	44

[a] Values are reported as means of two experiments.

Table 4
In vitro hPMN MPO release for selected list of compounds

Compound	hPMN MPO release 10 nM IL-8 IC_{50}[a] (nm)	hPMN MPO release 100 nM GRO-α IC_{50}[a] (nm)
24	3910	36
25	143	21

[a] Values are reported as means of two experiments.

Table 2 shows the effect of various right-side heteroaryl amine modifications on both CXCR2 and CXCR1 inhibitory activities. In general, the furyl amine-substituted thiadiazoles showed similar activity profiles to the right-side phenyl compounds. Most of these compounds showed weaker binding affinity towards the CXCR1 receptor with the exception of compound **25** that showed reasonable inhibitory activity towards both receptors.

Table 3 summarizes our efforts to further improve both CXCR2 and CXCR1 receptor-binding affinities. Table 4 summarizes limited functional data in in vitro human neutrophil (hPMN) MPO release assay[11] for compounds **24** and **25.**

In summary, we have discovered a novel series of 3,4-diamino-1,2,5-thiadiazoles as potent and selective CXCR2 receptor antagonists.

Acknowledgments

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