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3,4-Diamino-2,5-thiadiazole-1-oxides as potent CXCR2/CXCR1 antagonists

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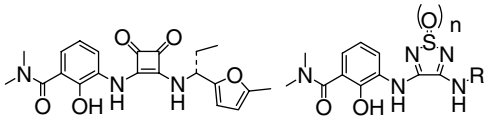
Abstract—A series of novel and potent 3,4-diamino-2,5-thiadiazole-1-oxides were prepared and found to show excellent binding affinities for CXCR2 and CXCR1 receptors and excellent inhibitory activity of Gro-α and IL-8 mediated in vitro hPMN MPO release of CXCR2 and CXCR1 expressing cell lines. On the other hand, a closely related 3,4-diamino-2,5-thiadiazole-dioxide did not show functional activity despite its excellent binding affinities for CXCR2 and CXCR1 in membrane binding assays. A detailed SAR has been discussed in these two closely related structures.

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 tumour 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, GRO-α and many more. 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 obvious relationship between IL-8 and inflammatory diseases, CXCR1 and CXCR2 antagonists[5] are targets of small molecule drug discovery. Several literature reports are available for the discovery of CXCR2 antagonists.[6]

We have previously reported[6] several 3,4-diaminocyclobut-3-ene-1,2-diones (e.g. **1**) as potent CXCR2/CXCR1 antagonists. We envisaged that 2,5-thiadiazole-1-oxides could be a viable replacement for the less known pharmacophore cyclobutenedione. Several literature reports[7] are available for the use of thiadiazole oxides in drug discovery. Herein, we would like to disclose the medicinal chemistry efforts in replacing the centre pharmacophore cyclobutenedione with 2,5-thiadiazole-1-oxides and its structure–activity relationships with various right side alkyl, aryl and heteroaryl motifs (R) as in structures **2** and **3**.



1 **2**; n=1 **3**; n=2

The preparation of the 3,4-diaminothiadiazole dioxides of general structure **3** was commenced with the readily available 3,4-diethoxy-2,5-thiadiazoledioxide **4**. A standard procedure for the synthesis of the left side phenolic-aniline and the right side amines was described in our previous publications.[6] Coupling of the phenolic amine **5** with the 3,4-diethoxythiadiazoledioxide **4** in ethanol afforded the intermediate **6**, which upon

Keywords: CXCR2 and CXCR1 receptor; Thiadiazole-1-oxide; Antagonist.
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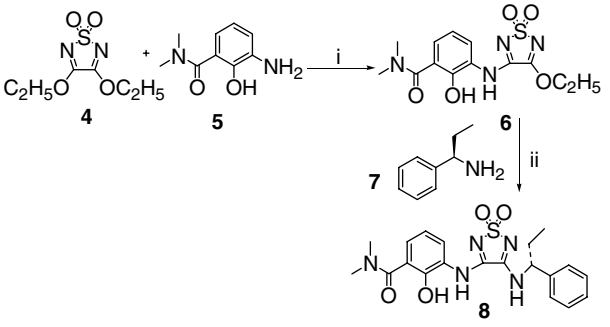


Scheme 1. Reagents and conditions: (i) diisopropylethylamine, CH_3OH, rt, 6 h, 90%; (ii) CH_3OH, diisopropylethyl amine, rt, 12 h, 80%.

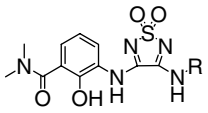
subsequent treatment with commercially available amine **7** or prepared amines resulted in the final products (**8**–**17**) in excellent yield, as depicted in Scheme 1. We kept the left side phenolic amine **5** constant throughout our studies and explored the SAR with right side amines. Both aryl and heteroaryl substitutions were tolerated on the right side. Alkyl compounds were not as potent as the aryl substituted ones. Binding affinities[6] for compounds **8**–**17** are shown in Table 1. Compounds **12** and **15** showed excellent binding affinity for both CXCR2 and CXCR1 receptors.

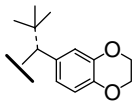
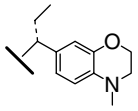
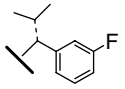
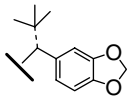
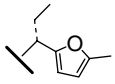
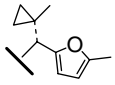
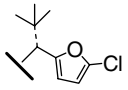
After identifying a series of potent compounds in the membrane binding assays, in vitro cell based functional activity was determined in a human neutrophil (hPMN) MPO release assay[8] in the presence of various chemoattractants (IL-8 or GRO-α). We were surprised to notice that none of these compounds exhibited functional activity in in vitro cell based assays. The functional data are shown in Table 2. The blood levels in rats following oral administration were determined according to a rapid rat pharmacokinetic screen.

Due to the unexpected lack of functional activity, efforts were further focused on the modification of thiadiazole-oxide centre core. We decided to follow up a structurally closely related 3,4-diamino-2,5-thiadiazole-1-oxide[9] **2**. Following a similar procedure, coupling of the phenolic aniline **5** with 3,4-diethoxy-2,5-thiadiazole-1-oxide **4a** in methanol afforded **6a**, which upon subsequent treatment with commercially available or prepared amines like **7a**, resulted in the final products (**18**–**28**) in excellent yield as depicted in Scheme 2 and Table 3.

3,4-Diamino-2,5-thiadiazole-1-oxides (**18**–**28**) showed excellent binding affinities for the CXCR2 receptor irrespective of the nature of right side substitution. In general, compounds with a bulky substitution, like an isopropyl or *tert*-butyl, showed better affinity towards the CXCR1 receptor. After exploring a detailed SAR with the right side amines, compound **27**, with a *tert*-butyl side chain containing furan, showed excellent binding affinity towards both the receptors. Moreover, compounds **18** and **25** showed excellent blood levels in the rapid rat pharmacokinetic screen. Unlike the thiadiazole-dioxide **3** series, this series of compounds showed excel-

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



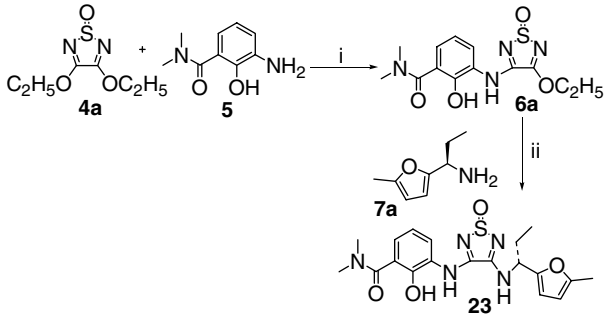
Compound	R	CXCR2 K_i[a] (nM)	CXCR1 K_i[a] (nM)
8		NT	8990
9		24	2000
10		9	2800
11		11	652
12		4.7	46
13		NT	5950
14		184	1100
15		11	61
16		16	188
17		9	129

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

Table 2. In vitro hPMN MPO release and rapid rat pharmacokinetic results for selected list of compounds

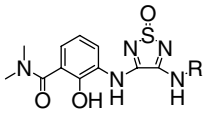
Compound	hPMN MPO release-10 nM IL-8 IC_{50} (μM)	hPMN MPO release 100 nM GRO-α IC_{50} (μM)	r rat pK (po) (μM h)
8	8.99	−39% at 1	2.3
9	NT	−12% at 1	1.87
14	NT	−11% at 1	
15	NT	3% at 1	
16	NT	−19% at 1	

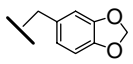
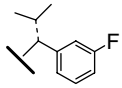
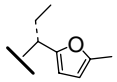
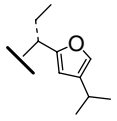
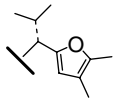
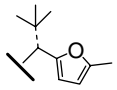
NT, not tested.



Scheme 2. Reagents and conditions: (i) diisopropylethylamine, CH_3OH, rt, 10 h, 90%; (ii) CH_3OH, diisopropylethyl amine, rt, 12 h, 80%.

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



Compound	R	$CXCR_2$ K_i[a] (nM)	CXCR1 K_i[a] (nM)
18		58	484
19		15	10000
20		5	1220
21		8	4010
22		4	130
23		3	234
24		9	61
25		2.7	50
26		12	375
27		2.3	21
28		5	38

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

Table 4. In vitro hPMN MPO release and rapid rat pharmacokinetic results for selected list of compounds

Compound	hPMN MPO release 10 nM IL-8 IC_{50} (μM)	hPMN MPO release, 100 nM GRO-α IC_{50} (μM)	r rat p*K* (po) (μM h)
18	0.684	0.038	5.28
20	NT	0.331	
22	0.142	0.028	
23	0.539	0.133	
24	0.015	0.008	
25	0.054	0.013	119
26	0.400	0.132	
27	0.020	0.008	
28	0.080	0.027	

NT, not tested.

lent functional activity in in vitro human neutrophil (hPMN) MPO release assay[8] (Table 4). Compounds **24** and **27** were identified as the most potent compounds in the hPMN MPO release assay.

In summary, we have discovered a novel series of potent 3,4-diamino-2,5-thiadiazole-1-oxides as CXCR2/CXCR1 receptor antagonists.

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