Discovery of 2-Hydroxy-*N*,*N*-dimethyl-3-{2-[[(*R*)-1-(5-methylfuran-2-yl)propyl]amino]-3,4-dioxocyclobut-1-enylamino}benzamide (SCH 527123): A Potent, Orally Bioavailable CXCR2/CXCR1 Receptor Antagonist

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Abstract: Structure−activity studies on lead cyclobutenedione **3** led to the discovery of **4** (SCH 527123), a potent, orally bioavailable CXCR2/CXCR1 receptor antagonist with excellent cell-based activity. Compound **4** displayed good oral bioavailability in rat and may be a potential therapeutic agent for the treatment of various inflammatory diseases.

IL-8[a] (CXCL8) is a member of the CXC chemokine family that plays a role in the trafficking of neutrophils to the site of inflammation.[1] In 1990, two chemokine G-protein-coupled, seven-transmembrane receptors (CXCR1 and CXCR2) were cloned and identified and are activated by CXCL8.[2,3] While CXCR2 binds with high affinity to CXCL8 and other ELR+ chemokines such as GCP-2 (CXCL6), ENA-78 (CXCL5), and Gro-α (CXCL1), CXCR1 is less promiscuous and binds only CXCL8 and CXCL6 with high affinity.[4] When CXCL8 interacts with CXCR2 and CXCR1 on neutrophils, an intracellular response occurs, including calcium flux, degranulation, and subsequent chemotaxis.[5] In addition, elevated levels of CXCL8 and CXCL1 have been observed in humans with arthritis, asthma, and COPD, suggestive of the critical role that these CXC chemokines may play in such processes.[6]

Owing to the relevance of CXCL8 and related chemokines in a wide range of inflammatory diseases, CXCR2 and CXCR1 antagonists have attracted attention as targets for small-molecule drug discovery. In 1998, Widdowson and co-workers reported the first small-molecule CXCR2 selective antagonists represented by urea **1** (Figure 1).[7] Analogues in this structural class have been reported to be potent, selective CXCR2 receptor antagonists that possess good bioavailability and in vivo activity in a number of neutrophil animal models.[7] Researchers at Pfizer reported a series of quinoxalines represented by **2**, which showed inhibition of CXCL8 receptor binding and CXCL8-mediated neutrophil chemotaxis.[8] Since these initial disclosures, several other classes of small-molecule CXCR2 antagonists have been disclosed, and this area has been recently reviewed in depth.[9]

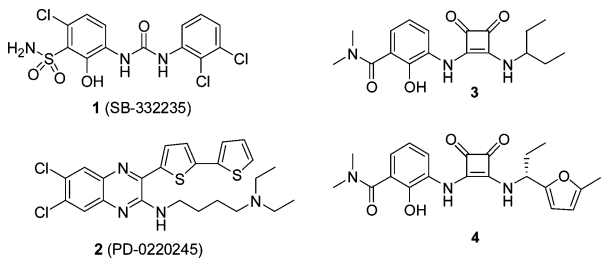

Figure 1. CXCR2-selective and CXCR2/CXCR1 receptor antagonists.

Herein, we report the culmination of our ongoing efforts in the synthesis and SAR development of a series of novel of 3,4-diamino-3-cyclobutene-1,2-dione CXCR2 receptor antagonists.[10] Preliminary studies[11] identified the 3,4-diamino-3-cyclobutene-1,2-dione motif to be central to the development of potent CXCR2 receptor antagonists as represented by **3**. In this Letter, we disclose the design, synthesis, and SAR development of the 3,4-diamino-3-cyclobutene-1,2-dione derivatives from our early lead compound **3**, which led to the discovery of **4**, a potent CXCR2/CXCR1 receptor antagonist (Figure 1).[12] A report[13] has appeared recently on the ability of **4** to inhibit smoke-induced pulmonary neutrophilia in mice, using the designation SCH-N.

The preparation of the 3,4-diamino-3-cyclobutene-1,2-dione derivatives began with the preparation of the requisite optically pure amine fragments utilizing a diastereoselective chiral addition route[14] (Scheme 1). Condensation of substituted aryl or heteroaryl aldehydes **5a**−**f** with *R*-valinol in the presence of $MgSO_4$ followed by TMS protection afforded the protected imines **6a**−**f**. Treatment of imines **6a**−**f** with commercially available organolithium (*i*-PrLi and *t*-BuLi) or in situ generated species (EtLi and cyclopropylLi) afforded the diastereoselective addition products,[15] which were directly subjected to oxidative cleavage conditions to provide amines **7a**−**j**. Nitrosalicyclic acid **8** was converted to the dimethylamide adduct, which upon hydroreduction afforded aniline **9** (Scheme 2). Coupling of **9** with diethyl squarate in EtOH afforded **10**, which upon treatment with commercially available or prepared amines (**7a**−**j**) afforded the final products **3**, **4**, and **11**−**24** as depicted in Tables 1 and 2.

The in vitro affinities of these compounds for the CXCR2 and CXCR1 receptors were determined by a membrane binding assay,[16,17] while the functional activity was assessed in a human neutrophil (hPMN) chemotaxis assay in the presence of various chemoattractants (CXCL8 or CXCL1).[18] The blood levels in rats after oral administration were determined according to a rapid rat pharmacokinetic screen.[19]

With our initial early lead compound **3** in hand, we focused our discovery program upon improving the in vitro potencies for the chemokine receptors, functional activity, and oral bioavailability in rat of this class of compounds. Initial SAR studies[11] in this structural series established the importance of the three key H-bonding elements (two −NH and one −OH) and the dimethylamide phenol aniline in **3** as essential for CXCR2 receptor affinity. While **3** displayed reasonable affinity

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[a] Abbreviations: IL-8, interleukin-8; COPD, chronic obstructive pulmonary disease; CXC, cysteine (C)-X-C motif; ELR+, glutamic acid−leucine−arginine; GCP-2, human granulocyte chemotactic protein-2; ENA-78, epithelial-derived neutrophil attractant-78; Gro-α, growth-related protein-α; hPMN, human polymorphonuclear leukocyte; AUC, area under curve; HPBCD, hydroxypropyl-*β*-cyclodextrin.

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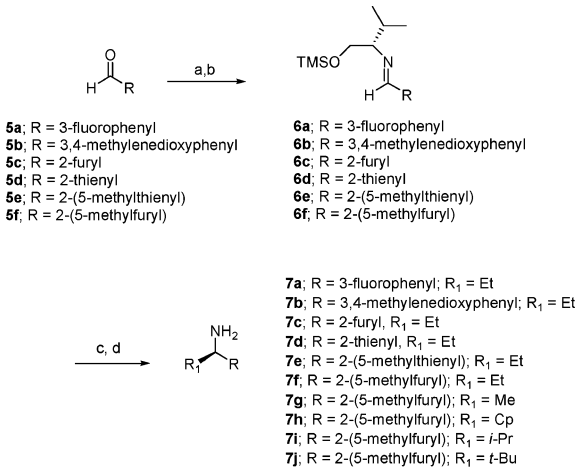
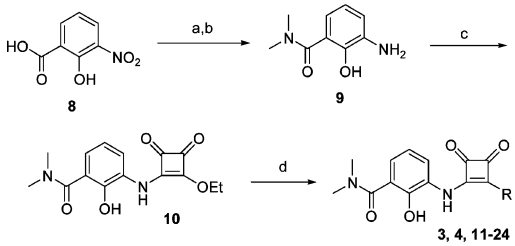
Scheme 1. Preparation of Chiral Amines **7a**−**j**[a]



[a] Reagents and conditions: (a) *R*-valinol, $MgSO_4$, CH_2Cl_2; (b) TMSCl, Et_3N (90% two steps); (c) R_1Li, Et_2O, −40 °C; (d) H_5IO_6, $MeNH_2$ (40% in H_2O) or $Pd(OAc)_4$.

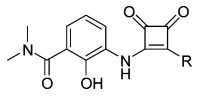
Scheme 2. Preparation of 3,4-Diamino-3-cyclobutene-1,2-dione Derivatives **3**, **4**, **11**−**24**[a]

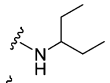
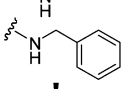
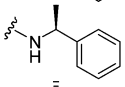
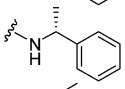
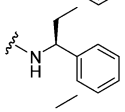
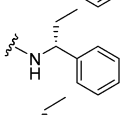
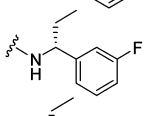
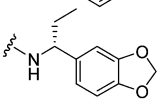
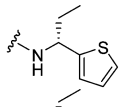
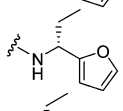
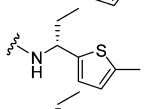
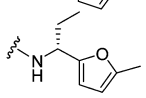


[a] Reagents and conditions: (a) $(COCl)_2$, DMF, then $HNMe_2$, 93%; (b) Pd/C (10%), H_2 (40 psi), 97%; (c) diethyl squarate, EtOH, room temp, 70%; (d) **7a**−**j**, EtOH, room temp or reflux, 41−96%.

for the CXCR2 receptor, functional activity,[11] and modest oral bioavailability in rat (Table 1), additional SAR work focused upon optimization of the diethylamino fragment of **3** to improve the biological profile of this series of compounds. Toward this end, initial incorporation of a benzylic functionality was not impressive (**11**−**13**); however, a trend in terms of preferred stereochemistry was observed (Table 1). While benzylic derivative (**11**) and the enantiomeric α-methyl derivatives (**12** and **13**) showed reduced binding affinity to the CXCR2 receptor versus the branched alkyl derivative **3**, the ethyl-substituted derivatives (**14** and **15**) revealed a significant difference in the overall biological profile between the (*R*)- and (*S*)-enantiomers with respect to both chemokine receptor affinity (CXCR2 and CXCR1) and rat pharmacokinetics (Table 1). Compound **15** demonstrated an improvement in affinity for the CXCR2 and CXCR1 receptor and improved oral exposure in rat versus lead compound **3**. In addition, the corresponding (*S*)-enantiomer (**14**) showed a reduced affinity for the CXCR2 receptor and very poor rat pharmacokinetics. Having established the critical importance of the (*R*)-ethyl derivative side chain for improved CXCR2 and CXCR1 receptor affinity and rat pharmacokinetics, a brief survey of substitution around the phenyl motif of **15** was conducted. Incorporation of electron-withdrawing (**16**) and electron-donating substituents (**17**) on the phenyl ring displayed affinities comparable to those of the CXCR2 receptor and CXCR1 receptor while maintaining reasonable oral drug exposure in rat (Table 1). Bioisosteric replacement of the phenyl ring of **15** with a 2-thienyl (**18**) or 2-furyl (**19**) motif yielded derivatives with improved CXCR2 and CXCR1 receptor affinities compared to **15**. While these heteroaryl derivatives

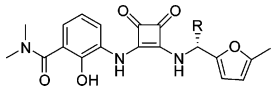
Table 1. Aryl and Heteroaryl Derivatives **3**, **4**, and **11**−**20**



compd	R	IC_{50} for CXCR2 (nM)[a]	IC_{50} for CXCR1 (nM)[a]	Rat AUC (PO) (uM·hr)[20]
3		15 ± 1	910 ± 66	6.4
11		236 ± 10	na[b]	---
12		244 ± 19	na[b]	---
13		17 ± 1	3058 ± 313	---
14		234 ± 20	na[b]	1.0
15		6.8 ± 1.2	254 ± 4	17.4
16		4.9 ± 0.7	197 ± 17	18.3
17		5.0 ± 1.2	145 ± 13	31.7
18		6.0 ± 0.2	81 ± 5	2.5
19		3.8 ± 0.2	26 ± 2	1.4
20		5.3 ± 0.2	235 ± 2	14.1
4		2.6 ± 0.3	36 ± 5	49.0

[a] Values reported are the mean ± range ($n = 2$) except **4** (mean ± SEM, $n = 4$). [b] na = not active at >10000 nM.

Table 2. 5-Methylfuryl Derivatives **4** and **21**−**24**



compd	R	IC_{50} for CXCR2 (nM)[a]	IC_{50} for CXCR1 (nM)[a]	rat AUC (po) (μM·h)[20]
21	Me	5.4 ± 1.0	775 ± 27	34.0
4	Et	2.6 ± 0.3	36 ± 5	49.0
22	Cp	3.6 ± 0.5	55 ± 3	1.4
23	*i*-Pr	6.2 ± 1.4	34 ± 2	3.2
24	*t*-Bu	3.8 ± 0.4	11 ± 1	2.6

[a] Values reported are the mean ± range ($n = 2$) except **4** (mean ± SEM, $n = 4$).

displayed excellent affinity for the CXCR2 and CXCR1 receptors, poor oral bioavailability in rat limited their utility (Table 1). Because of concerns about the metabolic liability of the 5-H substitution in **18** and **19**, a 5-methyl substituent was introduced to provide thiophene **20** and furyl derivative **4**. These derivatives displayed comparable affinity for the CXCR2

Table 3. hPMN Chemotaxis Assay for **4**, **21**, and **15**

	chemotaxis inhibition IC_{50} (nM);[a] $n = 2$			
	CXCL8		CXCL1	
compd	mean	range	mean	range
4	16	1.5	<1.0	
21	251	1.4	2.4	1.2
15	398	1.2	48	1.6

[a] Derived by testing the effect of increasing concentrations of compound on the chemotaxis AUC in response to CXCL8 (0.03−30 nM) or CXCL1 (0.1−100 nM). Therefore, IC_{50} is the compound concentration (nM) at which the chemotaxis AUC was inhibited 50%.

receptor as the 5-H analogues in addition to a slightly decreased affinity for the CXCR1 receptor (Table 1). More importantly, **20** and **4** displayed vastly improved rat plasma levels after oral administration compared to the 5-H analogues **18** and **19** (Table 1). The 5-methylfuryl derivative **4** emerged from these efforts possessing excellent affinity for the CXCR2 and CXCR1 receptors and having excellent oral exposure in the rapid rat pharmacokinetic screen.

Having optimized the heterocyclic portion of this class of molecules as demonstrated in furyl derivative **4**, attention turned toward optimization of the α-side chain with regard to potency and pharmacokinetics. Since SAR work in the 3,4-diamino-3-cyclobutene-1,2-dione structural series revealed a limited tolerance for polar functionality in the side chain region,[21] a focused effort incorporating alkyl and branched alkyl derivatives was undertaken. The synthesis of these analogues was performed according to the routes in Schemes 1 and 2 and is summarized in Table 2. The α-methyl derivative **21** showed excellent affinity for the CXCR2 receptor with over 100-fold selectivity versus the CXCR1 receptor. In addition, α-methyl derivative **21** displayed comparable pharmacokinetics in rat versus **4** and was identified as a CXCR2-selective candidate for further evaluation in cell-based assays. The affinity for the CXCR2 and CXCR1 receptors was maintained with increasing β-branching of the side chain (Cp < *i*-Pr < *t*-Bu), as demonstrated in **22**−**24**, but at the expense of oral rat exposure (Table 2). Having achieved improved chemokine receptor affinity and oral exposure in rat versus our initial lead **3**, several compounds were selected for functional evaluation in a human neutrophil chemotaxis assay.

In a human neutrophil (hPMN) chemotaxis assay,[18] **4** displayed superior inhibition of chemotaxis in vitro induced by CXCL1 or CXCL8 versus **15** or **21** (Table 3). Compound **4** demonstrated complete inhibition of CXCL1-mediated neutrophil chemotaxis at 2 nM, while inhibition of CXCL8-mediated chemotaxis was less potent.[18] In addition, **4** was equipotent in blocking CXCL1 and CXCL8 binding (and receptor signaling) in CXCR2 recombinants (data not shown). Experiments with CXCR2-selective compounds such as **15**, **21**, and **1** indicate that CXCL8 stimulates chemotaxis of isolated hPMN primarily through activation of CXCR1.[22] The effect of **4** was specific in that chemotaxis of human neutrophils induced by other neutrophil activating agents such as C5a and fMLP was not affected (data not shown). In an extensive counterscreen assay, concentrations of 2−20 μM of **4** showed less than 15% inhibition of other closely related chemokine receptors (CXCR3, CCR5, etc.), indicative of its overall selectivity for the CXCR2 and CXCR1 receptors.[22]

In summary, we have identified a series of potent, orally bioavailable substituted 3,4-diamino-3-cyclobutene-1,2-dione CXCR2/CXCR1 receptor antagonists with excellent functional activity. Subsequent optimization of receptor affinities and pharmacokinetics resulted in the discovery of furyl derivative **4**, a potent inhibitor of human neutrophil chemotaxis with good pharmacokinetics in rat. This compound should be appropriate for exploring the role of these receptors in human disease.

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Supporting Information Available: Experimental procedures and characterization data for **3**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The diastereoselectivities of the organometallic additions were determined to be consistently >15:1 by ^{1}H NMR analysis of the corresponding *β*-amino alcohol in accordance with ref 14.

(16) The CXCR2 binding data for **3** depicted in Table 1 is 3-fold higher than the reported value in ref 11. Different assay conditions were employed for the compounds in Tables 1 and 2 leading to subtle differences in the binding affinities. The complete assay conditions are found in Supporting Information.

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(18) Full experimental details for this assay and subsequent data analysis can be found in Supporting Information.

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(20) Rats ($n = 2$) were orally administered with 10 mg/kg of compound in 20% HPBCD. Blood was drawn at intervals over a 6 h period. Plasma from the two animals was pooled at each sampled time point. AUC was calculated over a 0−6 h period. See ref 19 for a detailed description of this protocol.

(21) Dwyer, M. P.; Yu, Y.; Chao, J.; Aki, C.; Chao, J.; Purakkattle, B.; Taveras, A. G. Unpublished results.

(22) A detailed description of the pharmacology and in vivo properties of **4** will be reported in due course.

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