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Synthesis and structure–activity relationships of heteroaryl substituted-3,4-diamino-3-cyclobut-3-ene-1,2-dione CXCR2/CXCR1 receptor antagonists

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Abstract—Comprehensive SAR studies were undertaken in the 3,4-diaminocyclobut-3-ene-1,2-dione class of CXCR2/CXCR1 receptor antagonists to explore the role of the heterocycle on chemokine receptor binding affinities, functional activity, as well as oral exposure in rat. The nature of the heterocycle as well as the requisite substitution pattern around the heterocycle was shown to have a dramatic effect on the overall biological profile of this class of compounds. The furyl class, particularly the 4-halo adducts, was found to possess superior binding affinities for both the CXCR2 and CXCR1 receptors, functional activity, as well as oral exposure in rat versus other heterocyclic derivatives.

Interleukin-8 or IL-8 (CXCL8) is a proinflammatory member of the CXC chemokine family which plays a critical role in the migration of neutrophils to sites of inflammation and tissue injury.[1] CXCL8 is known to bind to two G-protein coupled, seven transmembrane receptors which were cloned and identified as CXCR1 and CXCR2.[2,3] CXCR2 binds with high affinity to CXCL8 as well as other ELR+ chemokines such as GCP-2 (CXCL6), ENA-78 (CXCL5), and Gro-α (CXCL1), while CXCR1 is less promiscuous and binds to both CXCL8 and CXCL6 with high affinity.[4] When CXCL8 interacts with the CXCR2 and CXCR1 receptors on neutrophils, an intracellular response occurs to include calcium flux, degranulation, and subsequent chemotaxis.[5] In humans, elevated levels of CXCL8 and CXCL1 have been observed in individuals with arthritis, asthma, and COPD, suggestive of the critical role that these chemokines play in such processes.[6] In addition, the importance of small molecule antagonists of CXCL8 receptors has been supported by the normal physiology of mouse gene CXCR2 knockouts.[7]

In 1998, Widdowson and coworkers reported the first small molecule CXCR2 antagonists in the diaryl urea class represented by compound **1**.[8] Several additional series have been reported since[9] and the area has been recently reviewed.[10] The centerpiece of our efforts has been the utilization of the 3,4-diaminocyclobut-3-ene-

Keywords: CXCR2 receptor; CXCR1 receptor; 3,4-Diaminocyclobut-3-ene-1,2-dione class of CXCR2/CXCR1 receptor antagonists; Interleukin-8.
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1,2-dione motif for the preparation of potent CXCR2/CXCR1 receptor antagonists.[11] Recently, we reported[11b] the emergence of several heterocyclic derivatives (thienyl and furyl) in this structural series which culminated in the identification of **2** (SCH 527123), a potent CXCR2/CXCR1 receptor antagonist (Fig. 1) which is currently under clinical investigation.[11c] During the course of those investigations, substitution at the C5-position of the furyl motif was shown to be required to attain good oral exposure in rat albeit at the expense of binding affinity for the CXCR1 receptor.[11b] Based upon these observations, we became interested in further exploring the role of substitution/electronics in the furyl class represented by **2** as well as the possibility of identifying additional heterocyclic motifs that might serve as potent CXCR2/CXCR1 receptor antagonists. Herein, the details of these comprehensive SAR efforts are summarized.[12]

Having previously established the critical elements of the α-side chain in this series of derivatives (as exemplified by **2**) with regard to both stereochemistry [(*R*)-preferred over (*S*)] and length (ethyl) for optimal receptor binding affinities and good oral exposure in rat,[11b] we focused our initial efforts upon the rapid preparation of substituted furyl and heteroaryl derivatives bearing the optimal racemic α-ethyl side chain. The initial SAR generated in the racemic series served to focus followup synthetic efforts of the most interesting analogs with an asymmetric synthesis according to known methodology.[11b,13]

The synthesis of the racemic heteroaryl derivatives[14] is depicted in Schemes 1 and 2. Beginning with the commercially available or prepared heterocyclic aldehydes **3**, treatment with $LiN(TMS)_2$ followed by addition of EtMgBr afforded the desired racemic amine adducts **4** according to the procedure of Hart in a single step.[15] Alternatively, aldehydes **3** were converted to the amine via a three-step protocol which relied upon an alcohol to azide transformation[17] followed by treatment with PPh_3/H_2O (Scheme 1). Coupling with the previously described dimethyl amide cyclobutenedione adduct **5**,[11b] which was prepared in three steps from nitrosalicyclic acid, afforded the final adducts **6**–**40**. The aryl and heteroaryl 4-substituted furyl derivatives (**22**–**25**) were prepared by Suzuki coupling of various boronic acids with the Boc-protected 4-Br adduct **42** followed by deprotection and coupling with intermediate **5** (Scheme 2).[16]

Table 1 summarizes the SAR studies for the substituted furyl derivatives. At the C5 position, the CXCR2 binding affinity was well maintained with increasing size of substitution (H vs Me vs Et, etc.) however the CXCR1 receptor was less tolerant with the binding affinity drop-

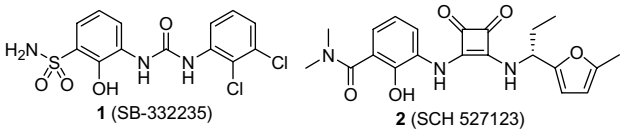
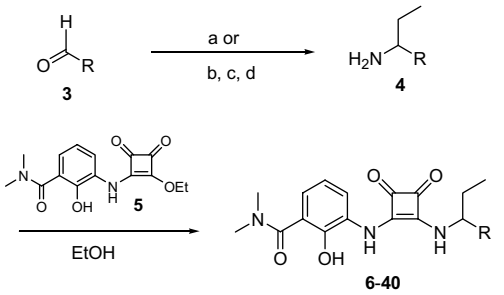
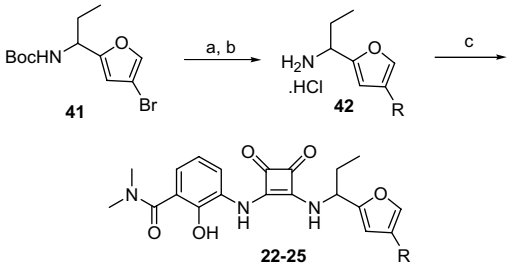


Figure 1. CXCR2 and CXCR2/CXCR1 receptor antagonists.

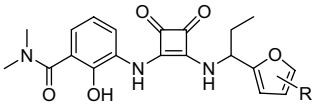


Scheme 1. Reagents and conditions: (a) $LiN(TMS)_2$ then EtMgBr or (b) EtMgBr, Et_2O; (c) DPPA, DBU; (d) PPh_3, H_2O.



Scheme 2. Reagents and conditions: (a) $RB(OH)_2$, $Pd(PPh_3)_4$, K_3PO_4, DME/H_2O; (b) 4 N HCl/dioxane; (c) **5**, EtOH, Et_3N, rt.

Table 1. Receptor binding affinities for racemic furyl derivatives



Compound	R	IC_{50} of CXCR2[a] (nM)	IC_{50} of CXCR1[a] (nM)
6	5-H	5.0	67
7	5-Me	5.7	99
8	5-Et	4.1	854
9	5-Br	4.7	463
10	5-Cl	4.8	275
11	$5\text{-}CF_3$	17.2	6062
12	$5\text{-}CF_2H$	6.8	568
13	$5\text{-}CH_2OH$	2.8	182
14	$5\text{-}CH_2N(Me)_2$	94	na[b]
15	$5\text{-}CON(Me)_2$	171	na[a]
16	5-(2-Cl)Ph	49	4870
17	$5\text{-}(2\text{-}CF_3)Ph$	150	na[a]
18	5-(3-Cl)Ph	58	3376
19	$5\text{-}(3\text{-}CF_3)Ph$	87	3434
20	4-Cl	4.5	100
21	4-Br	5.0	93
22	4-Ph	6.1	150
23	4-(4-Pyridyl)	9.5	526
24	4-(3-Thienyl)	8.2	221
25	4-(3,5-Dimethyl-4-isoxazolyl)	7.6	345
26	2,3-Benzofuran	3.5	412
27	3-Br	16.5	1023

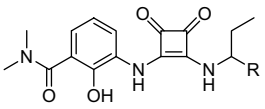
[a] Values are means of two ($n = 2$) runs. See Ref. 11b for assay details.
[b] na, not active at >10,000 nM.

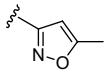
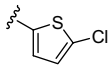
ping off with increasing size of substitution (**6**–**10**). The 5-H analog (**6**) displayed the best affinity for the CXCR1 receptor indicative of the tight SAR at this position. Interestingly, trifluoromethyl analog **11** demonstrated a substantial loss in binding affinity for both chemokine receptors compared both to the CF_2H analog **12** and Me derivative **7** suggestive of potential electronic considerations at this site. While methanol derivative **13** was well tolerated at the C5 position, incorporation of basic funtionality, dimethylamido, or substituted phenyl motifs resulted in a dramatic loss in binding affinity for both receptors (**15**–**19**). The C4 position of the furyl motif was found to be much more tolerant of functionality as demonstrated by the comparable CXCR2 affinities with improved CXCR1 binding affinity of the 4-halo derivatives (**20** and **21**) and phenyl derivative (**22**) versus the corresponding C5 adducts (**9**, **10**, and **16**–**19**). In addition, a variety of heteroaryl motifs were found to be tolerated at this position albeit with slightly poorer affinity for both receptors versus the 4-halo derivatives. Owing to concern over potential C5 oxidation in this series, 4,5-disubstituted analogs such as **26** were prepared and found to be reasonably well tolerated for both chemokine receptors. However, substitution at the C3 position of the furan ring was not well tolerated by either receptor as demonstrated by the 3-Br analog (**27**).

Having completed the rapid survey of racemic substituted furyl derivatives, attention was turned toward the preparation of other heterocyclic derivatives to explore the feasibility of replacing the furan ring. These analogs were prepared according to the general synthetic route laid out in Scheme 1 and the receptor binding data are summarized in Table 2. In general, the heterocyclic compounds showed reduced binding affinity toward the CXCR2 receptor versus the furyl derivatives in Table 1 with variable affinity for the CXCR1 receptor based upon structure. While the 2- and 3-thienyl analogs (**35** and **36**) displayed comparable binding affinities for both chemokine receptors, the analogous furyl derivatives (**6** and **34**) displayed divergent profiles illustrating the sensitivity of the chemokine receptors to the placement of the heteroatom within the ring. Interestingly, the 2-thienyl series (**36**–**38**) demonstrated analogous SAR trends to the corresponding furyl derivatives while basic heterocycles such as **39** or **40** were not well tolerated by either the CXCR2 or CXCR1 receptor. A couple of five-membered heterocyclic analogs (**32** and **35**) emerged from these efforts which displayed reasonable potency to merit further investigation.

Based upon the broad SAR screen of racemic derivatives from Tables 1 and 2, a focused series of optically pure (*R*)-ethyl substituted heteroaryl analogs[17] were prepared according to our previously disclosed route[11b] (Scheme 3). The binding affinities for the CXCR2 and CXCR1 receptors as well as oral exposure data in rat[18] are summarized in Table 3. The 4-substituted furans **45** and **46** demonstrated an excellent combination of superior CXCR2 and CXCR1 receptor binding affinities as well as oral exposure in rat consistent with previous observations for this series. While heterocyclic

Table 2. Receptor binding affinities for racemic heterocyclic derivatives

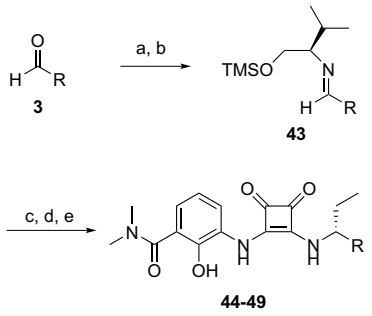


Compound	R	IC_{50} for CXCR2[a] (nM)	IC_{50} for CXCR1[a] (nM)
28		8.6	795
29		10.9	805
30		9.8	703
31		9.8	302
32		7.5	224
33		8.2	289
34		8.0	812
35		5.8	165
36		6.2	179
37		6.2	1110
38		21	1372
39		815	na[b]
40		50	2856

[a] Values are means of two ($n = 2$) runs. See Ref. 11b for assay details.
[b] na, not active at >10,000 nM.

derivatives such as **47** and **48** showed good receptor binding affinities, modest oral exposure in rat precluded further progression of these compounds. Interestingly, the 2-pyridyl analog **49** showed improved binding affinities for both receptors versus the 4-pyridyl analog **40** suggestive of a key role that the placement of the heteroatom in the ring plays on the profile.

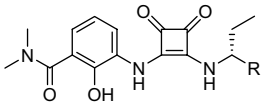
In an effort to further characterize and prioritize the derivatives found in Table 3, several analogs were examined for their ability to inhibit CXCR2- and CXCR1-mediated chemotaxis using recombinant cells

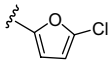
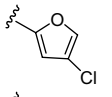
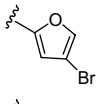
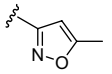
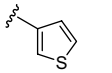
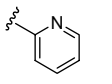


Scheme 3. Reagents and conditions: (a) *R*-valinol, $MgSO_4$, CH_2Cl_2; (b) TMSCl, Et_3N; (c) EtLi, Et_2O; (d) H_5IO_6, $MeNH_2$ (40% in H_2O); (e) **5**, EtOH, rt.

(Ba/F3-hCXCR2 and Ba/F3-hCXCR1).[19] From Table 4, furyl derivative **46** displayed superior potency to inhibit both CXCR2- and CXCR1-mediated chemotaxis versus the other heterocyclic analogs **47** and **49**. As one might expect based on their binding activity (Table 3), these derivatives more potently inhibited CXCR2-mediated chemotaxis relative to their activity at CXCR1 (Table 4). However, the relative binding potencies of compounds **46**, **47**, and **49** at CXCR1 did not effectively capture differences in the compounds functional potency in blocking chemotaxis through this receptor.[20] The implementation of this cell-based assay was critical in differentiating derivatives based upon functional activity versus that otherwise look comparable based upon the receptor binding affinities reported in Table 3. The functional data presented in Table 4 are in excellent agreement with the pharmacological characterization of compound **2** as an allosteric antagonist of both the CXCR2 and CXCR1 receptors but whose functional effects are mediated primarily through the CXCR2 receptor.[20]

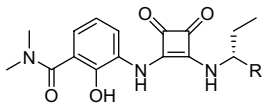
Table 3. Receptor binding affinities and rat exposure data for optically pure derivatives



Compound	R	IC_{50} for CXCR2[a] (nM)	IC_{50} for CXCR1[a] (nM)	Rat AUC[b] (10 mpk, po) (μM h)
44		4.6	244	—
45		3.8	62	21.5
46		3.5	55	33.4
47		6.3	171	3.7
48		3.4	104	—
49		3.3	148	—

[a] Values are means of two ($n = 2$) runs. See Ref. 11b for assay details.
[b] Procedure for assay found in Ref. 18.

Table 4. Ba/F3 chemotaxis data[19] for **46**, **47**, and **49**



Compound	IC_{50} for hCXCR2[a] (nM)	IC_{50} for hCXCR1[a] (nM)
46	2.0	917
47	12.2	na[b]
49	4.5	na[b]

[a] Values are means of at least two ($n = 2$) runs.
[b] na, not active at >10,000 nM.

In conclusion, this work has illustrated the critical role of the heterocycle and requisite substitution around heterocycle plays on the overall biological profile of the 3,4-diaminocyclobut-3-ene-1,2-dione CXCR2/CXCR1 receptor antagonists. These SAR studies have illustrated the tolerant nature of the CXCR2 receptor versus the more sensitive CXCR1 receptor to both structural and electronic considerations. While several heterocyclic replacements of the furyl motif found in **2** demonstrated reasonable receptor binding affinities, modest oral exposure in rat and lack of suitable functional activity precluded further advancement of these derivatives. The furyl series, particularly the 4-halo analogs, was found to possess superior chemokine receptor binding affinities, functional activity, and oral exposure in rat compared to the broad panel of other heterocyclic derivatives. Additional studies[21] profiling the further utility of the furyl class of 3,4-diaminocyclobut-3-ene-1,2-dione CXCR2/CXCR1 receptor antagonists will be reported in due course.

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