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C(4)-alkyl substituted furanyl cyclobutenediones as potent, orally bioavailable CXCR2 and CXCR1 receptor antagonists

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Abstract—A novel series of cyclobutenedione centered C(4)-alkyl substituted furanyl analogs was developed as potent CXCR2 and CXCR1 antagonists. Compound **16** exhibits potent inhibitory activities against IL-8 binding to the receptors (CXCR2 *Ki* = 1 nM, IC_{50} = 1.3 nM; CXCR1 *Ki* = 3 nM, IC_{50} = 7.3 nM), and demonstrates potent inhibition against both Gro-α and IL-8 induced hPMN migration (chemotaxis: CXCR2 IC_{50} = 0.5 nM, CXCR1 IC_{50} = 37 nM). In addition, **16** has shown good oral pharmacokinetic profiles in rat, mouse, monkey, and dog.

The recruitment of neutrophil polymorphonuclear (PMN) leukocytes, the most numerous white blood cells, to sites of inflammation is principally mediated by neutrophilic CXC chemokines: IL-8 (Interleukin-8, CXCL8) and related ELR^+ CXC chemokines Gro-α (CXCL1), Gro-β (CXCL-2), and Gro-γ (CXCL3), ENA78 (CXCL5), GCP-2 (CXCL6), and NAP-2 (CXCL7).[1] These CXC chemokines exert their effects through interaction with two G-protein coupled receptors CXCR2 and CXCR1,[2] which are expressed on a number of inflammatory cells including neutrophils, monocytes, and microvascular endothelial cells. Massive infiltration of neutrophils to the lung and increased level of IL-8 are observed with ARDS (Adult Respiratory Distress Syndrome) patients[3] and detected in the sputum of COPD (Chronic Obstructive Pulmonary Disease) patients[4]; increased expression levels of the receptors and IL-8 are also detected in psoriatic tissue[5] and in inflamed gut tissue (inflammatory bowel disease).[6] The existing evidence suggests that effectively blocking the interaction between the neutrophilic chemokines and CXCR2/CXCR1 receptors could conceivably provide new treatments for a number of inflammatory disorders.

Since the mid 1990's, a number of companies have pursued the strategy of CXCR2 and CXCR1 receptor blockade using small molecules.[7] Monoclonal antibodies[8] were explored as an alternative approach. An anti-IL-8 neutralizing antibody has shown positive effects in a Phase III clinical trial in psoriasis,[8b] though no small molecule was currently known to be advanced beyond Phase II clinical studies. Repertaxin (**1**, Fig. 1), a

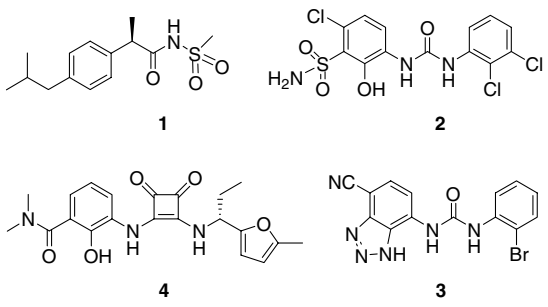

Figure 1. Known CXCR2 and CXCR1 antagonists in clinical trials.

Keywords: CXCR2 receptor; CXCR1 receptor; Dual antagonists.
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CXCR1 allosteric inhibitor by Dompe, is reported to be in Phase II trials for prevention of DGF (delayed graft function) in kidney transplant.[9] *N*,*N*′-Diarylureas **2** and **3**, two CXCR2-selective antagonists from GlaxoSmithKline, are being progressed in Phase I as a potential treatment of COPD.[10] Lastly, diaminocyclobutenedione **4**, a CXCR2 antagonist developed through our own efforts, has been in clinical studies.[11,7a]

Whether selective inhibition of CXCR2 receptor or CXCR1 receptor would be sufficient for complete inhibition of PMN infiltration in humans is still an unanswered question, due partly to the lack of detailed clinical information so far. In addition, the roles of CXCR2 and CXCR1 receptors in various inflammatory diseases are still being investigated. Would a CXCR2 and CXCR1 dual antagonist be ultimately required to achieve the desired therapeutic effects? We were interested in this question and embarked on the exploration of potential dual antagonists.

Among the structurally diverse small molecule CXCR2 or CXCR1 antagonists disclosed, only researchers at GSK recently reported some cyanoguanidines as dual CXCR2 and CXCR1 inhibitors,[7b] including the most potent ones **5** and **6** (Fig. 2). In our SAR studies that led to the discovery of **4**, we have observed that C(4)-alkyl substitution could improve significantly CXCR1 inhibition while maintaining potent CXCR2 inhibition. Herein we report the SAR development and synthesis of a potent class of dual CXCR2 and CXCR1 antagonists bearing a distinct C(4)-alkyl substitution on the furan moiety (**7**).

While studying the impact of regio-substitutions of the thiophene system on the inhibition of CXCR2 and CXCR1 receptors, it was first realized C(4) substitution could enhance CXCR1 activity. The structures and inhibitory activities of C(5)-methyl (**8**), C(4)-methyl (**9**), and C(3)-methyl (**10**) substituted thienyl analogs are described in Table 1. It is interesting to see that these three methyl substituted analogs had similar inhibitory activities against CXCR2 receptor, however, the C(4)-analog **9** showed a 6-fold more potent CXCR1 inhibition than its regio-analogs **8** and **10**. The same trend was observed with furan system. C(4)-methyl substituted furanyl analog **11** has exhibited an improved CXCR1 activity over its C(5)-methyl (**4**) and C(3)-ethyl (**12**) analogs, while having a similar CXCR2 activity as these analogs (Table 1). In addition, furanyl analogs

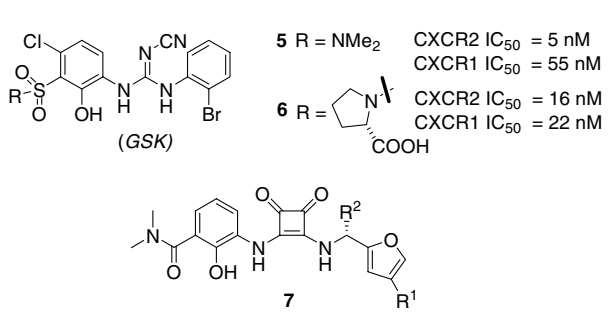
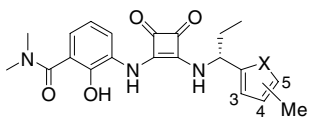
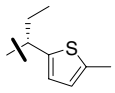
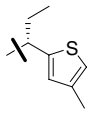
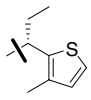
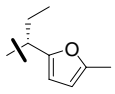
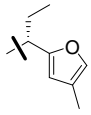


Figure 2. CXCR2–CXCR1 dual inhibitors.

Table 1. Inhibitory activities of substituted thienyl analogs (**8**–**10**) and furanyl analogs (**4**, **11**–**12**)[12]



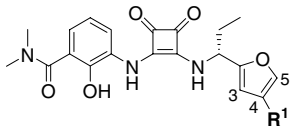
Compound		CXCR2 *Ki*[a] (vs IL-8, nM)	CXCR1 *Ki*[a] (vs IL-8, nM)
8		5	146
9		5	24
10		10	123
4		5	18
11		4	9
12		25	379

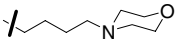
[a] Values are means of at least two experiments.

seem to be more potent CXCR1 inhibitors than their respective thienyl analogs. These early results suggest that the C(4)-position of the thienyl or furanyl systems is advantageous for further CXCR1 activity optimization, thereby leading to potent dual antagonists.

Aiming at further improvement of CXCR1 inhibition, an investigation of C(4)-alkylation of the furan moiety was launched. Straight chain, branched, and/or cyclic alkyl substitutions were introduced, results are summarized in Table 2. All analogs have demonstrated potent CXCR2 inhibition (Ki[12] < 10 nM). Medium sized branched alkyl substituted analogs, 2-butyl (**17**) and 3-pentyl (**18**), displayed the best CXCR2 activities, with *Ki*s of 0.6 and 0.8 nM, respectively. In terms of CXCR1 inhibition, these analogs have a wider range of activities, *Ki* varying from 3 to 283 nM. Smaller sized groups were preferred, and slightly larger cyclic groups led to the reduction of CXCR1 activity (**20**, **21**). The isopropyl substitution appeared to be the best for CXCR1 inhibition, rendering analog **16** with a *Ki* of 3 nM (IC_{50} = 7.3 nM) on CXCR1 receptor. Analog **16** also displayed a potent inhibition against CXCR2 receptor with *Ki* being 1 nM (IC_{50} = 1.3 nM). A brief rat pharmacokinetic evaluation of the C(4)-alkyl analogs (**11**,

Table 2. Inhibitory activities of C4-alkyl substituted furanyl analogs[12]



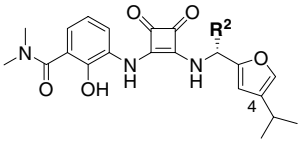
Compound	R^1	CXCR2 *Ki*[a] (vs IL-8, nM)	CXCR1 *Ki*[a] (vs IL-8, nM)	Rat AUC[b] (μM h)
11		4	9	32.6
13		1	7	17.4
14		2	34	NT
15		9	14	0
16[c]		**1**	**3**	5.4
17		0.6	7.6	NT
18		0.8	30	NT
19		4	10	NT
20		3	53	NT
21		4	283	NT

[a] Values are means of at least two experiments.
[b] AUC: area under curve; data were generated based on a 6-h study, po dosing (10 mg/kg), $n = 2$. NT, not tested.
[c] **16**: CXCR2 IC_{50} = 1.3 nM, CXCR1 IC_{50} = 7.3 nM.

13, **15**, and **16**) has revealed that these compounds in general have good oral pharmacokinetic profile, except **15**; and less branched alkyl group R^1 is better.

Having identified the isopropyl group as the best C4-substitution we further evaluated the combination effect of this group with a number of pseudo-benzylic substitutions R^2 (Table 3). In both the exploration of the C(4) position (R^1, Table 2) and the pseudo-benzylic site (R^2), we have observed a general trend that the binding pocket of the CXCR1 receptor is much more restrictive than the CXCR2 receptor's. All of these pseudo-benzylic analogs, methyl (**22**), isopropyl (**23**), cyclopropyl (**24**), *tert*-butyl (**25**), trifluoro-methyl (**26**), and ethyl (**16**), have shown similarly potent CXCR2 inhibition ($Ki < 6$ nM), however, only ethyl analog **16** exhibited a potency below 10 nM CXCR1 inhibition. Groups slightly larger than the ethyl reduced moderately CXCR1 activity (3- to 5-fold), while the smaller methyl group (**22**) resulted in a 17-fold decrease of CXCR1 activity. Taken together, the combination of iPr (R^1)/Et (R^2) was recognized as being optimal thus far.

Table 3. Inhibitory activities of C(4)-isopropyl substituted furan analogs[12]



Compound	R^2	CXCR2 *Ki*[a] (vs IL-8, nM)	CXCR1 *Ki*[a] (vs IL-8, nM)
22	Me	2	50
16	Et	**1**	**3**
23	iPr	4	11
24	cPr	3	10
25	tBu	4	14
26	CF_3	6	16

[a] Values are means of at least two experiments.

Furanyl analog **16** has emerged as the most potent CXCR2–CXCR1 dual antagonist to date. It has been evaluated further in a wide range of in vitro and in vivo studies. In the chemotaxis assays, it demon-

Table 4. Oral pharmacokinetic parameters of compound **16**

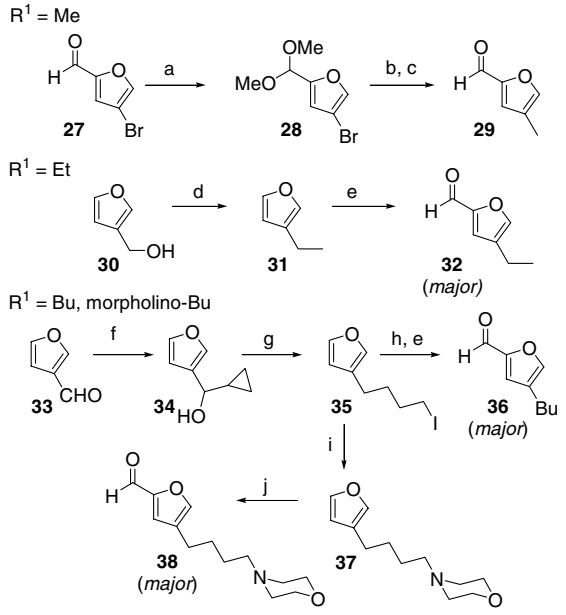
Species	Dose (po)	AUC (μM h)	C_{max} (μM)
Rat	10 mg/kg, 6 h	5.4	3.8
Mouse	25 mg/kg, 7 h	4.6	4.6
Monkey	3 mg/kg, 48 h	4.2	0.38
Dog	2 mg/kg, 48 h	7.1	5.3

strated potent inhibition against both Gro-α and IL-8 induced human neutrophil migration (chemotaxis IC_{50} = 0.5 nM, against 30 nM of Gro-α; chemotaxis IC_{50} = 37 nM, against 3 nM of IL-8).[13] When profiled in vivo, **16** achieved an ED_{50} of 0.9 mg/kg in the rat LPS (lipopolysaccharide) challenged model[14] and an ED_{50} of 1 mg/kg in the mouse cigarette smoke induced neutrophilic inflammatory model.[15]

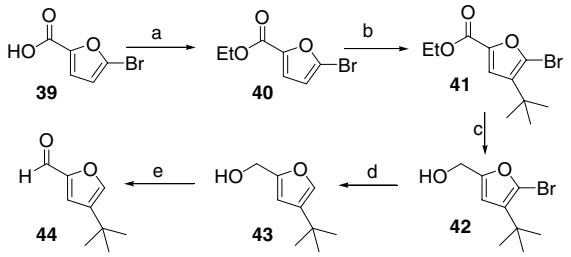
Evaluated in four different animal species, compound **16** has shown good oral pharmacokinetic profiles in general. Results are described in Table 4.

An important aspect of the development of this C(4)-alkyl substituted furyl series is the synthesis of key intermediates C(4)-alkyl substituted 2-furaldehydes. Multiple synthetic approaches (Schemes 1–3) have been developed to allow access to these not readily available aldehydes.

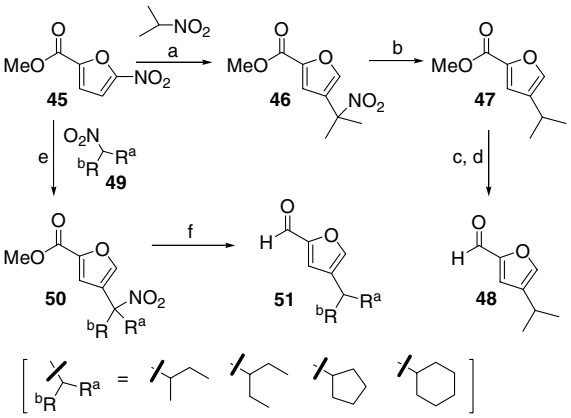
Straight chain substituted 2-furaldehydes, 4-methyl (**29**), 4-ethyl (**32**),[16] 4-butyl (**36**), and 4-morpholino-butyl



Scheme 1. Reagents and conditions: (a) $(MeO)_3CH$, pTsOH (cat), MeOH, 60 °C, 80%; (b) *n*BuLi, THF, −78 °C; MeI, −78 °C to −60 °C, >95%; (c) acetone, pTsOH (cat), 70 °C, >95%; (d) TsCl, Et_2O, NaOH, −20 °C, 3 h; Me_2CuLi, −20 °C[16]; (e) *t*BuLi, Et_2O, rt; DMF, rt, low yield, isomeric aldehyde also formed (minor); (f) *t*BuLi, cPrBr, Et_2O, −78 °C, 10 min, then rt, 1.5 h; addition of **33**, −78 °C, 1 h, 92%; (g) NaI, TMSCl, CH_3CN, rt, 5 min, 47%; (h) *t*BuLi, Et_2O, −78 °C, 20 min; rt, 2.5 h, >95%; (i) K_2CO_3, morpholine, acetone, rt, 2 d, 73%; (j) *t*BuLi, Et_2O, −78 °C to rt, 4 h; DMF, rt, 4 h, 66% of **38** and its regio isomer (3-substituted-2-aldehyde) in 1:0.6 ratio.



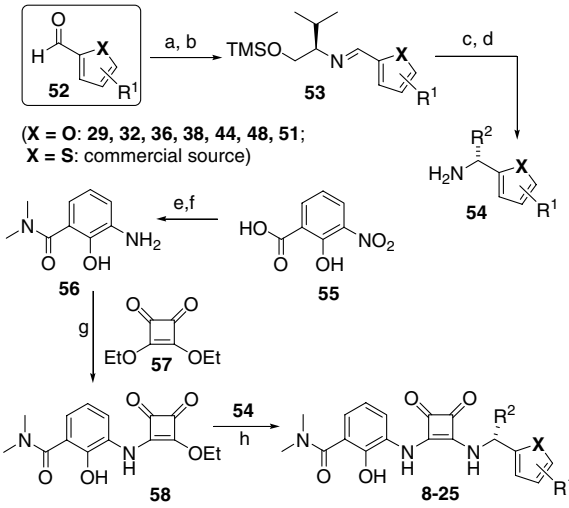
Scheme 2. Reagents and conditions: (a) $(ClC{=}O)_2$, DMF(cat), CH_2Cl_2, rt, 1 h; EtOH, NEt_3, rt, 15 h, 93%; (b) $nC_{18}H_{37}Br$, $AlCl_3$, CS_2, rt, 37%; (c) $LiAlH_4$, THF, −10 °C to rt, 3.5 h, Q; (d) *n*BuLi, THF, −78 °C, 15 min, Q; (e) CH_2Cl_2, Dess-Martin periodinane, rt, 1.5 h, 74% over three steps.



Scheme 3. Reagents and conditions: (a) KO*t*Bu, 2-nitropropane, HMPA, rt, 18 h, 86%; (b) nBu_3SnH, AIBN (cat), Tol, 90 °C, 4 h, 78%; (c) $LiAlH_4$, THF, 0 °C to rt, 3 h, Q; (d) CH_2Cl_2, Dess-Martin periodinane, rt, 3 h, 78%; (e) KO^{t}Bu, **49**, HMPA, rt, overnight (NaH, when $R^a = R^b$ = Et); (f) applying conditions used in (b–d).

(**38**), were prepared using the approaches described in Scheme 1. Fully branched *tert*-butyl substituted 2-furaldehyde **44** was synthesized via a 5-step sequence starting from furyl carboxylic acid **39** (Scheme 2). Acid **39** was first transformed to ester **40**, the *tert*-butyl group was then installed to the C4 position via the Friedel-Crafts alkylation,[17] providing the necessary intermediate **41**. Upon a further three-step manipulation, **41** was converted to the 4-*tert*-butyl-2-furaldehyde **44**.

A common synthetic route that could be used to introduce various branched C4-alkyl substitutions was developed (Scheme 3). Utilizing a method by Ono,[18] the commercially available methyl-5-nitro-2-furoate (**45**) reacted with 2-nitro propane under basic conditions to provide **46** via a regioselective cine-substitution. The nitro group in **46** was removed by radical reduction to afford **47**. Subsequent reduction of the ester **47** and oxidation of the resultant alcohol generated 4-isopropyl-2-furaldehyde **48** in good yield. This sequence has been successfully applied to the synthesis of several 2-furaldehydes with branched alkyl substitution at C4 position (**51**), just replacing 2-nitro propane with appropriate nitro-alkanes (**49**) at the start of the route. Secondary nitro-alkanes **49**, cyclic or acyclic, reacted with nitro-furoate **45** in a manner similar to 2-nitropro-



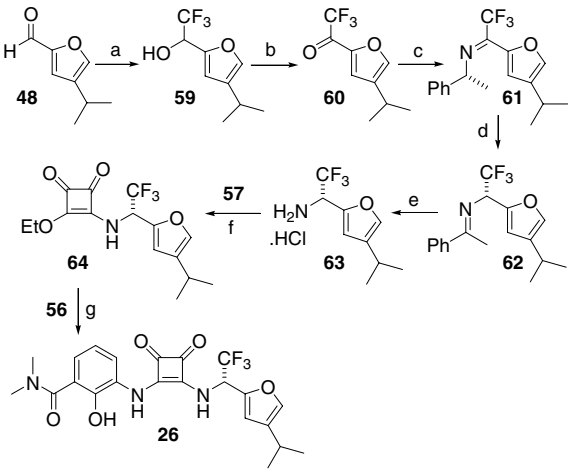
Scheme 4. Reagents and conditions: (a) (*R*)-Valinol, $MgSO_4$, CH_2Cl_2, rt, 2d, 95–100%; (b) TMSCl, NEt_3, CH_2Cl_2, 5 h to overnight, 80–90%; (c) R^2Li, ether, −78 °C to −30 °C, 3–5 h; aq. HCl, rt, 60–90%; (d) for R^2 = Me, Et, iPr, cPr, the oxidative cleavage conditions: H_5IO_6, $MeNH_2$, MeOH, H_2O, rt, overnight; for R^2 = tBu, the oxidative cleavage conditions: $Pb(OAc)_4$, CH_2Cl_2–MeOH, 0 °C, 1 h; NaOH, 0 °C, 2 h, 20–50%; (e) $(ClC{=}O)_2$, DMF(cat), CH_2Cl_2, rt, 1 h; Me_2NH, NEt_3, 2 h, 90%; (f) 10% Pd/C, EtOH, H_2, rt, overnight, 90%; (g) EtOH, 0 °C to rt, overnight, >60%; (h) EtOH, rt, or heat, 30–90%.

pane to produce key intermediates **50**, which were converted in three steps to the corresponding 2-furaldehydes **51** in good yields.

The conversion of the C4-alkyl-2-furyl aldehydes (Schemes 1–3), or the commercially available thienyl aldehydes, to the final targets was straightforward using a general synthetic process developed in our group.[7a] As depicted in Scheme 4, aryl aldehyde **52** was first condensed with (*R*)-valinol, and the resulting alcohol was silylated to afford imine **53**.[19] Various organolithium reagents were added to **53**,[20] and the adducts were subjected to oxidative cleavage conditions to reveal chiral amines **54**. Separately a cyclobutenedione intermediate **58** was prepared in three steps from nitro salicylic acid (**55**). Under mild conditions, chiral amines **54** condensed with intermediate **58** to produce the targeted analogs **8**–**25**.

When pseudo-benzylic substitution R^2 was a CF_3 group, an alternative approach is utilized to generate the final target. The sequence was illustrated in Scheme 5 with the preparation of **26**. Aldehyde **48** was converted to a CF_3-alcohol **59** under the conditions of trifluoromethyl trimethylsilane and a catalytic amount of cesium fluoride. Subsequent oxidation of **59** produced ketone **60**, which was condensed with (*R*)-methyl benzyl amine to afford imine **61**. A DBU induced hydride migration converted **61** to **62**, upon acid hydrolysis, producing the amine hydrochloride salt **63**.[21] Treatment of salt **63** with diethyl squarate **57**, followed by coupling with aniline **56**, provided the CF_3-analog **26**.

In summary, we have discovered a novel and potent class of dual CXCR2 and CXCR1 antagonists exemplified by C4-isopropylfuranyl **16**. This compound demonstrates potent inhibition of IL-8 and Gro-α-stimulated human neutrophil migration, is orally bioavailable in mouse, rat, dog, and monkey; and demonstrates potent inhibition of neutrophil infiltration in rat and mouse lungs in LPS- or smoke-induced animal models, respectively.



Scheme 5. Reagents and conditions: (a) CF_3TMS, CsF (cat), rt, 14 h; HCl, rt, 5 h, 90%; (b) TPAP, NMO, CH_2Cl_2, rt, 12 h, 98%; (c) (*R*)-methyl benzylamine, $TiCl_4$, tol, rt, 2.5 h, 55%; (d) DBU, 0 °C, 3 h, 100%; (e) Et_2O, HCl, rt, 2 h, 77%; (f) EtOH, NEt_3, rt, 15 h, 48%; (g) EtOH, DIEA, 70 °C, 39 h, 82%.

References and notes

1. Murphy, P. M.; Baggiolini, M.; Charo, I. F.; Hebert, C. A.; Horuk, R.; Matsushima, K. *Pharmacol. Rev.* **2000**, *52*, 145.
2. (a) Holmes, W. E.; Lee, J.; Kuang, W. J.; Rice, G. C.; Wood, W. I. *Science* **1991**, *253*, 1278; (b) Murphy, P. M.; Tiffany, H. L. *Science* **1991**, *253*, 1280.
3. (a) Miller, E. J.; Cohen, A. B.; Nagao, S.; Griffith, D.; Maunder, R. J.; Martin, T. R.; Weiner-Kronish, J. P.; Sticherling, M.; Christophers, E.; Matthay, M. A. *Am. Rev. Respir. Dis.* **1992**, *146*, 427; (b) Strieter, R. M.; Keane, M. P.; Burdick, M. D.; Sakkour, A.; Murray, L. A.; Belperio, J. A. *Curr. Drug Targets Inflamm. Allergy* **2005**, *4*, 299.
4. (a) Barnes, P. J. *Pulmon. Pharm. Ther.* **1999**, *12*, 67; (b) Keatings, V. M.; Collins, P. D.; Scott, D. M.; Barnes, P. J. *Am. J. Respir. Crit. Care Med.* **1996**, *153*, 530.
5. (a) Kulke, R.; Bornscheuer, E.; Schluter, C.; Bartels, J.; Rowert, J.; Sticherling, M.; Christophers, E. *J. Invest. Dermatol.* **1998**, *110*, 90; (b) Homey, B. *Curr. Drug Targets Inflamm. Allergy* **2004**, *3*, 169.
6. Williams, E. J.; Haque, S.; Banks, C.; Johnson, P.; Sarsfield, P.; Sheron, N. *J. Pathol.* **2000**, *192*, 533.
7. Small molecule CXCR2 or CXCR1 antagonists: (a) Dwyer, M. P.; Yu, Y.; Chao, J.; Aki, C.; Chao, J.; Purakkattle, B.; Girijavallabhan, V.; Rindgen, D.; Bond, R.; Mayer-Ezel, R.; Jakway, J.; Hipkin, R. W.; Fosetta, J.; Gonsiorek, W.; Bian, H.; Fan, X.; Terminelli, C.; Fine, J.; Lundell, D.; Merritt, J. R.; Rokosz, L. L.; Kaiser, B.; Li, G.; Wang, W.; Stauffer, T.; Ozgur, L.; Baldwin, J.; Taveras, A. G. *J. Med. Chem.* **2006**, *49*, 7603; (b) Nie, H.; Widdowson, K. L.; Palovich, M. R.; Fu, W.; Elliott, J. D.; Bryan, D. L.; Burman, M.; Schmidt, D. B.; Foley, J.

F.; Sarau, H. M.; Busch-Petersen, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5513; (c) Merritt, J. R.; Rokosz, L. L.; Nelson, K. H., Jr.; Kaiser, B.; Wang, W.; Stauffer, T. M.; Ozgur, L. E.; Schilling, A.; Li, G.; Baldwin, J. J.; Taveras, A. G.; Dwyer, M. P.; Chao, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4107; (d) Ho, K.-K.; Auld, D. S.; Bohnstedt, A. C.; Conti, P.; Dokter, W.; Erickson, S.; Feng, D.; Inglese, J.; Kingsbury, C.; Kultgen, S. G.; Liu, R.-Q.; Masterson, C. M.; Ohlmeyer, M.; Rong, Y.; Rooseboom, M.; Roughton, A.; Samama, P.; Smit, M.-J.; Son, E.; van der Louw, J.; Vogel, G.; Webb, M.; Wijkmans, J.; You, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2724; (e) Allegretti, M.; Bertini, R.; Cesta, M. C.; Bizzarri, C.; Bitondo, R. D.; Cioccio, V. D.; Galliera, E.; Berdini, V.; Topai, A.; Zampella, G.; Russo, V.; Bello, N. D.; Nano, G.; Nicolini, L.; Locati, M.; Fantucci, P.; Florio, S.; Colotta, F. *J. Med. Chem.* **2005**, *48*, 4312; (f) Widdowson, K. L.; Elliott, J. D.; Veber, D. F.; Nie, H.; Rutledge, M. C.; McCleland, B. W.; Xiang, J.-N.; Jurewicz, A. J.; Hertzberg, R. P.; Foley, J. J.; Griswold, D. E.; Martin, L.; Lee, J. M.; White, J. R.; Sarau, H. M. *J. Med. Chem.* **2004**, *47*, 1319; (g) Jin, Q.; Nie, H.; McCleland, B. W.; Widdowson, K. L.; Palovich, M. R.; Elliott, J. D.; Goodman, R. M.; Burman, M.; Sarau, H. M.; Ward, K. W.; Nord, M.; Orr, B. M.; Gorycki, P. D.; Busch-Petersen, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4375; (h) Weidner-Wells, M. A.; Henninger, T. C.; Fraga-Spano, S. A.; Boggs, C. M.; Matheis, M.; Ritchie, D. M.; Argentieri, D. C.; Wachter, M. P.; Hlasta, D. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4307; (i) Baxter, A.; Bennion, C.; Bent, J.; Boden, K.; Brough, S.; Cooper, A.; Kinchin, E.; Kindon, N.; McInally, T.; Mortimore, M.; Roberts, B.; Unitt, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2625; (j) Li, J. J.; Carson, K. G.; Trivedi, B. K.; Yue, W. S.; Ye, Q.; Glynn, R. A.; Miller, S. R.; Connor, D. T.; Roth, B. D.; Luly, J. R.; Low, J. E.; Heilig, D. J.; Yang, W.; Qin, S.; Hunt, S. *Bioorg. Med. Chem.* **2003**, *11*, 3777.

8. (a) Mahler, D. A.; Huang, S.; Tabrizi, M.; Bell, G. M. *Chest* **2004**, *126*, 926; (b) http://www.anogen.ca/antibodies_abcream.htm.
9. Bizzarri, C.; Beccari, A. R.; Bertini, R.; Cavicchia, M. R.; Giorgini, S.; Allegretti, M. *Pharmacol. Ther.* **2006**, *112*, 139.
10. Busch-Petersen, J.; Jin, Q.; McCleland, B. W.; Nie, H.; Palovich, M. R.; Davis, R. S.; Fu, W.; Elliott, J. D.; Burman, M.; Foley, J. J.; Schmidt, D. B.; Podolin, P.; Bolognese, B. J.; Underwood, D. C.; Osborn, R. R.; Dehaas, C. J.; Salmon, M.; Carpenter, D. C.; Killian, D. J.; Sarau, H. M.; Widdowson, K. L. In *Abstracts of Papers*, 228th National Meeting of the American Chemical Society, Philadelphia, PA, United States, August 22–26, 2004; American Chemical Society: Washington, DC, 2004; MEDI-192.
11. Dwyer, M. P.; Yu, Y.; Chao, J.; Aki, C.; Chao, J.; Purakkattle, B.; Rindgen, D.; Bond, R.; Jakway, J.; Hipkin, R. W.; Fosetta, J.; Gonsiorek,W.; Bian, H.; Fine, J.; Merritt, J. R.; Rokosz, L. L.; Kaiser, B.; Li, G.; Wang, W.; Stauffer, T.; Ozgur, L.; Taveras, A. In *Abstract of Papers*, 231st National Meeting of the American Chemical Society, Atlanta, GA, United States, March 26–30, 2006; American Chemical Society: Washington, DC, 2006; MEDI-019.
12. *CXCR2 SPA assay*. For each well of a 96-well plate, a reaction mixture of 4 μg hCXCR2-CHO overexpressing membranes (biosignal) and 200 μg/well WGA-SPA beads (Amersham) in 100 uL was prepared in a CXCR2 assay buffer (25 mM Hepes, pH 7.4, 2 mM CaCl2, and 1 mM $MgCl_2$). A 0.4 nM stock of ligand, [^{125}I]-IL-8 (NEN), was prepared in the CXCR2 assay buffer. 20× stock solutions of test compounds were prepared in DMSO (Sigma). A 6× stock solution of Gro-α (R&D) was prepared in CXCR2 assay buffer. The above solutions were added to a 96-well assay plate (Perkin-Elmer or Corning) as follows: 10 μL test compound or DMSO, 40 μL CXCR2 assay buffer or Gro-α stock, 100 μL of reaction mixture, 50 μL of ligand stock (Final [ligand] = 0.1 nM). The assay plates were shaken for 5 min on a plate shaker and then incubated for 2–8 h before cpm/well were determined in Microbeta Trilux counter (Perkin-Elmer). %Inhibition of total binding minus non-specific binding (250 nM Gro-α or 50 μM antagonists) was determined for IC_{50} values. *Ki* values were generated from binding IC_{50} by correcting for the radioligand concentration used in the binding assay.
CXCR1 SPA assay. For each well of a 96-well plate, a reaction mixture of 10 μg hCXCR1–CHO overexpressing membranes (Biosignal) and 200 μg/well WGA-SPA beads (Amersham) in 100 μL was prepared in a CXCR1 assay buffer {(25 mM Hepes, pH 7.8, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 125 mM NaCl, and 0.1% BSA (Sigma)}. A 0.4 nM stock of ligand, [^{125}I]-IL-8 (NEN), was prepared in the CXCR1 assay buffer. 20× stock solutions of test compounds were prepared in DMSO (Sigma). A 6× stock solution of IL-8 (R&D) was prepared in CXCR2 assay buffer. The above solutions were added to a 96-well assay plate (Perkin-Elmer) as follows: 10 μL test compound or DMSO, 40 μL CXCR1 assay buffer or IL-8 stock, 100 μL of reaction mixture, 50 μL of ligand stock (Final [ligand] = 0.1 nM). The assay plates were shaken for 5 min on a plate shaker and then incubated for 8 h before cpm/well were determined in Microbeta Trilux counter (Perkin-Elmer). %Inhibition of total binding minus non-specific binding (250 nM IL-8) was determined for IC_{50} values. *Ki* values were generated from binding IC_{50} by correcting for the radioligand concentration used in the binding assay.
13. In vitro data have shown that this class of antagonists is non-competitive against Gro-α, but seems to be competitive against IL-8. For example, against 0.3 nM of IL-8, chemotaxis IC_{50} of **16** is 3.7 nM.
14. for assay conditions, refer to: Spond, J.; Billah, M. M.; Chapman, R. W.; Egan, R. W.; Hey, J. A.; House, A.; Kreutner, W.; Minnicozzi, M. *Pulmon. Pharm. Ther.* **2004**, *17*, 133.
15. for assay conditions, refer to: Thatcher, T. H.; McHugh, N. A.; Egan, R. W.; Chapman, R. W.; Hey, J. A.; Turner, C. K.; Redonnet, M. R.; Seweryniak, K. E.; Sime, P. J.; Phipps, R. P. *Am. J. Physiol. Lung Cell Mol. Physiol.* **2005**, *289*, L322.
16. Wiley, R. A.; Choo, H.-Y.; McClellan, D. *J. Org. Chem.* **1983**, *48*, 1106.
17. Gilman, H.; Turck, J. A. V., Jr. *J. Am. Chem. Soc.* **1939**, *61*, 473.
18. Ono, N.; Jun, T. X.; Kaji, A. *Synthesis* **1987**, 821.
19. Alvaro, G.; Martelli, G.; Savoia, D.; Zoffoli, A. *Synthesis* **1998**, 1773.
20. In most cases, the addition of organolithium reagents to imine **53** produced one diastereomer detectable by Hnmr.
21. (a) Soloshonok, V.; Ono, T. *J. Org. Chem.* **1997**, *62*, 3030; (b) Chiral amine salt **63** was derivatized with (*R*)-(−)-Mosher's acid chloride, and the *de* of the diastereomeric amides was determined to be 83% based on Hnmr analysis of the crude product mixture.