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Letter

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Discovery of INCB8761/PF-4136309, a Potent, Selective, and Orally Bioavailable CCR2 Antagonist

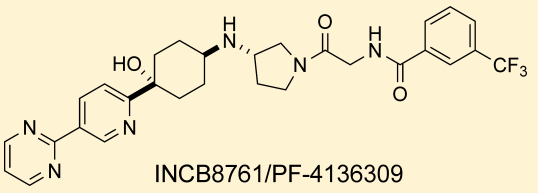
Chu-Biao Xue,*[,†] Anlai Wang,[†] Qi Han,[†] Yingxin Zhang,[†] Ganfeng Cao,[†] Hao Feng,[†] Taisheng Huang,[†] Changsheng Zheng,[†] Michael Xia,[†] Ke Zhang,[†] Lingquan Kong,[†] Joseph Glenn,[†] Rajan Anand,[†] David Meloni,[†] D. J. Robinson,[†] Lixin Shao,[†] Lou Storace,[†] Mei Li,[†] Robert O. Hughes,[‡] Rajesh Devraj,[‡] Philip A. Morton,[‡] D. Joseph Rogier,[‡] Maryanne Covington,[†] Peggy Scherle,[†] Sharon Diamond,[†] Tom Emm,[†] Swamy Yeleswaram,[†] Nancy Contel,[†] Kris Vaddi,[†] Robert Newton,[†] Greg Hollis,[†] and Brian Metcalf[†]

[†]Incyte Corporation, Experimental Station E336, Wilmington, Delaware 19880, United States

[‡]Pfizer Global Research and Development, Chesterfield Parkway West, St. Louis, Missouri 63017, United States

Supporting Information

ABSTRACT: We report the discovery of a new (*S*)-3-aminopyrrolidine series of CCR2 antagonists. Structure−activity relationship studies on this new series led to the identification of **17** (INCB8761/PF-4136309) that exhibited potent CCR2 antagonistic activity, high selectivity, weak hERG activity, and an excellent in vitro and in vivo ADMET profile. INCB8761/PF-4136309 has entered human clinical trials.



INCB8761/PF-4136309

KEYWORDS: *CCR2, chemokine, antagonist, hERG*

CCR2 is a chemokine receptor, a member of the super family of seven-transmembrane G-protein-coupled receptors (GPCRs), and is predominantly expressed on monocytes. Monocyte chemoattractant protein-1 (MCP-1, CCL2) is a specific ligand for CCR2. Binding of MCP-1 to CCR2 induces chemotaxis, resulting in directed migration of monocytes/macrophages to disease sites where MCP-1 expression is elevated. Because macrophages are well-characterized mediators of tissue destruction, accumulation of macrophages at disease sites could lead to morbidity and deterioration of chronic inflammatory and autoimmune diseases.[1] Studies in rodent models have demonstrated the critical role of MCP-1/CCR2 in inflammatory and autoimmune diseases and strongly suggest that CCR2 is an attractive therapeutic target.[2] As a result, antagonism of CCR2 has emerged as a novel therapeutic approach for pharmaceutical research, and a number of potent small molecule CCR2 antagonists have been identified.[3−11]

We have reported the discovery of an (*R*)-3-aminopyrrolidine series of CCR2 antagonists and the identification of a clinical compound INCB3284 (Figure 1) from that series.[11] As a follow-up in our CCR2 project, we tried to identify a second generation of CCR2 antagonist with structural diversity and a better overall profile. On the basis of molecular modeling, we proposed that the connections to the (*R*)-3-aminopyrrolidine core of the left-hand side functional group (4-hydroxy-4-heteroarylcyclohexyl) and the right-hand side functional group (3-trifluoromethylbenzoylaminoacetyl) in the INCB3284 series could be reversed to provide a new series of compounds as shown in I (Figure 1). To test this hypothesis, we synthesized the (*R*)-3-aminopyrrolidine derivative **1** and

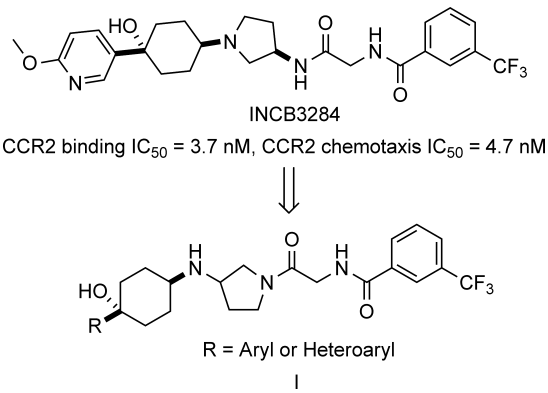


Figure 1.

(*S*)-3-aminopyrrolidine derivative **2** utilizing 4-phenylcyclohexyl as the left-hand side moiety (Figure 2). As drawn in **1** and **2** (Figure 2), the stereochemistry at the cyclohexyl was presumed to be cis by analogy to that in the INCB3344 and INCB3284 series.[9,11] This was later confirmed by the X-ray crystal structure of **17** (vide infra). In contrast to the INCB3284 series where an R configuration at the pyrrolidine is critical to CCR2 activity, **1** with an R configuration is a very weak CCR2 antagonist with an IC_{50} of 860 nM in antagonism of MCP-1 binding to human CCR2 (hCCR2), while **2** with an S

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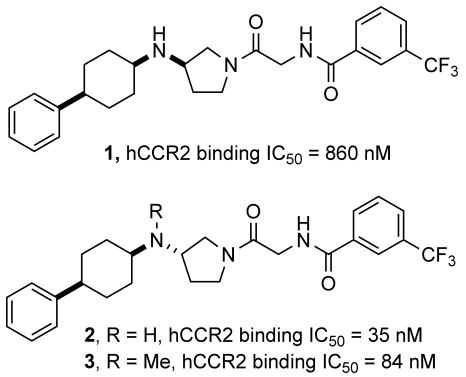
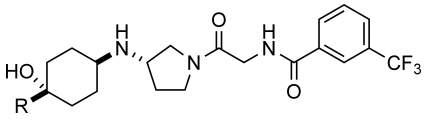


Figure 2.

configuration is 25-fold more potent than **1**, with an IC_{50} of 35 nM. Methylation of the secondary basic amine in **2** resulted in a slight loss in binding affinity (**3**, IC_{50} = 84 nM).

Encouraged by the decent binding affinity of **2**, structure–activity relationship (SAR) studies were initiated at the 4-position of cyclohexyl on the left-hand side (Table 1). Our previous SAR studies in the INCB3344 series[9] and INCB3284 series[11] have demonstrated that a hydroxyl group and a heteroaryl at the 4-position of cyclohexyl were consistent with weak hERG activity and low intrinsic clearance. Thus, we first added a hydroxyl at the 4-position of cyclohexyl in **2** to provide analogue **4**. This resulted in a slight loss in CCR2 binding affinity (IC_{50} = 65 nM). We next replaced the phenyl at the 4-position of cyclohexyl in **4** with different heteroaryls. Disappointingly, replacement of the phenyl at the 4-position of cyclohexyl in **4** with 6-methoxy-3-pyridyl, the left-hand side heteroaryl in INCB3284, provided analogue **5**, which is not as potent as **4** and is 26-fold weaker than INCB3284 in binding affinity. The 26-fold loss in binding affinity resulting from reversing the connections to the 3-aminopyrrolidine of the left-hand side moiety and the right-hand side moiety in INCB3284 reflects the changes around the pyrrolidine ring from a secondary amide, a tertiary amine, and an R configuration in INCB3284 to a tertiary amide, a secondary amine, and an S configuration in **5**, respectively, as the left-hand side moiety and the right-hand side moiety in both compounds are the same. However, it is likely that these changes may cause a twisted orientation of the 4-hydroxy-4-(6-methoxy-2-pyridyl)cyclohexyl moiety on the left-hand side that is now not an optimal residue for effective interaction with the receptor. Thus, we continued to explore other heteroaryls. Removal of the methoxy group in **5** afforded the 3-pyridyl analogue **6** that is not as active as **5**. Strikingly, replacement of the 3-pyridyl in **6** with 2-pyridyl improved the binding affinity from an IC_{50} of 126 nM for **6** to an IC_{50} of 11 nM for **7**, a 12-fold enhancement. The 12-fold improvement in binding affinity of **7** over **6** is not merely the result of polarity alteration from the barely exposed 3-pyridyl nitrogen in **6** to the sterically shielded 2-pyridyl nitrogen in **7** as **7** is 6-fold more active than the more hydrophobic phenyl analogue **4**. It is likely that the 2-pyridyl nitrogen places the 2-pyridyl residue in a favorable orientation for more effective interaction with the receptor. Attempts to add one more nitrogen at the 3-position within the 2-pyridyl ring in **7** to provide the more polar 2-pyrimidinyl (**8**) resulted in a 6-fold loss in binding affinity. However, the binding affinity is less affected when the 2-pyridyl in **7** is replaced with 2-thiazolyl (**9**).

Table 1. Identification of Aryl/Heteroaryl Ring at the 4-Position of Cyclohexyl



		CCR2, IC_{50} (nM)[a]	
compd	R	binding[b]	CTX[c]
4	phenyl	65 (2)	
5	6-methoxy-3-pyridyl	95 (2)	
6	3-pyridyl	126 (2)	
7	2-pyridyl	11 (8)	52 (8)
8	2-pyrimidinyl	66 (2)	
9	2-thiazolyl	18 (2)	
10	4-methyl-2-pyridyl	305 (2)	
11	6-methyl-2-pyridyl	51 (2)	
12	5-methyl-2-pyridyl	6.9 (12)	15 (12)

[a]Numbers in parentheses represent numbers of determinations. Standard deviations were less than 30% of the measured value. For assay protocols, see ref 9. [b]Antagonism of MCP-1 binding to hCCR2. [c]Antagonism of chemotaxis activity.

Because the 2-pyridyl is superior to other heterocycles at the 4-position of cyclohexyl, **7** was taken forward for further SAR exploration. To improve the CCR2 activity of **7**, we considered extending the left-hand side moiety by substitution on the 2-pyridyl ring. A simple methyl group substitution was first attempted (Table 1). Substitution at 4-position (**10**) or 6-position (**11**) resulted in about 28- and 5-fold loss, respectively, in binding affinity while substitution at 5-position (**12**) slightly improved the binding affinity. More importantly, the methyl group in **12** improved the chemotaxis activity from an IC_{50} of 52 nM in **7** to an IC_{50} of 15 nM in **12**. These results demonstrated that substitution at the 4- or 6-position is detrimental, while CCR2 binding affinity and especially chemotaxis activity can be improved by attachment of an extra group at the 5-position of the 2-pyridyl.

Although **7** and **12** did not meet our criteria in CCR2 activity, they were subjected to dofetilide binding assay[12] and patch clamp assay to understand the hERG activity of this series of compounds (Table 2). Compound **7** was a weak hERG inhibitor, displaying an IC_{50} of >30 μM in the dofetilide assay and 34% inhibition at 10 μM in the patch clamp assay. In contrast, **12** was a potent hERG inhibitor, exhibiting an IC_{50} of 24 μM in the dofetilide assay and 71% inhibition at 10 μM in the patch clamp assay. These results prompted us to investigate polar heteroaryl groups at the 5-position of the 2-pyridyl in **7** in an attempt to improve the CCR2 activity while concurrently minimizing the hERG activity.

As shown in Table 2, attachment of 3-pyridyl (**13**) or 4-pyridyl (**14**) at the 5-position of the 2-pyridyl in **7** had little effect on the CCR2 binding affinity but remarkably improved the chemotaxis activity by 10- and 20-fold, respectively. Surprisingly, these polar groups also increased the hERG activity. Compounds **13** and **14** were more potent than **7** in the dofetilide assay. For this reason, attempts were made to further increase the polarity of the left-hand side moiety by replacing the distal pyridyl with 2-heteroatom containing heterocycles (**15**–**19**). The 5-pyrimidinyl analogue **15** was not potent

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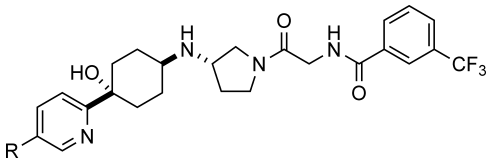
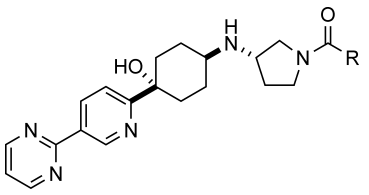
Table 2. Modification at the 5-Position on the 2-Pyridyl[a]

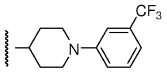
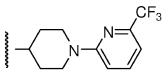
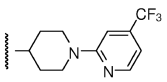
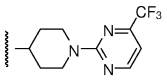
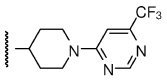
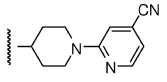
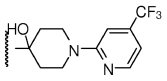


compd	R	CCR2, IC_{50} (nM) binding[b]	CCR2, IC_{50} (nM) CTX[c]	Alexa[d] IC_{50} (nM)	dofetilide[e] IC_{50} (μM)	patch clamp[f] inh. at 10 μM (%)
7	H	11 (8)	52 (8)		>30 (2)	34
12	methyl	6.9 (12)	15 (12)		24 (2)	71
13	3-pyridyl	9.0 (2)	5.4 (2)		30 (2)	
14	4-pyridyl	5.7 (2)	2.6 (2)		13 (2)	
15	5-pyrimidinyl	10 (2)	36 (2)			
16	2-pyrazinyl	6.0 (4)	3.8 (4)	6.5 (2)	>30 (2)	70
17	2-pyrimidinyl	5.2 (42)	3.9 (42)	19 (12)	>30 (2)	35
18	2-thiazolyl	6.0 (4)	1.8 (4)	67 (2)	>30 (2)	85
19	2-oxazolyl	5.6 (4)	3.4 (4)	31 (2)	>30 (2)	72

[a]Numbers in parentheses represent numbers of determinations. Standard deviations were less than 30% of the measured value. [b]Antagonism of MCP-1 binding to hCCR2. [c]Antagonism of chemotaxis activity. [d]Alexa whole blood activity (see ref 10 for assay protocol). [e]Dofetilide hERG binding activity. [f]Inhibition of hERG potassium current at 10 μM from single determination of patch clamp assay.

Table 3. Modification on the Right-Hand Side Moiety[a]



compd	R	CCR2, IC_{50} (nM) Binding	CCR2, IC_{50} (nM) CTX	Alexa IC_{50} (nM)	Dofetilide IC_{50} (μM)
20		3.6(2)	6.1(2)	37(3)	9
21		4.5(4)	8.8(4)	88(2)	10
22		3.3(12)	1.9(12)	12(4)	28
23		5.4(6)	4.3(6)	29(2)	26
24		10(2)		40(2)	>30
25		11(6)	18(4)	33(6)	>30
26		3.3(2)	23(2)	33(2)	>30

[a]See the Table 2 footnotes.

enough to meet our criteria, especially in chemotaxis. However, moving one of the 5-pyrimidinyl nitrogen atoms one-atom closer to the 2-pyridyl ring provided the 2-pyrazinyl analogue **16**, which was potent in CCR2 binding affinity (IC_{50} = 6 nM) and chemotaxis activity (IC_{50} = 3.8 nM). Equally important, **16** was very potent in a human whole blood assay (Alexa assay),[10] with an IC_{50} of 6.5 nM. Unfortunately, **16** exhibited 70% inhibition of the hERG potassium current at 10 μM in the

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patch clamp assay despite its weak activity in the dofetilide assay (IC_{50} > 30 μM). Moving the nitrogen atom at the 4-position of the pyrazinyl one-atom closer to the 2-pyridyl provided the 2-pyrimidinyl analogue **17**. This analogue is as potent as **16** in CCR2 binding affinity (IC_{50} = 5.2 nM) and chemotaxis activity (IC_{50} = 3.9 nM) but about 3-fold weaker than **16** in the whole blood assay (IC_{50} = 19 nM). In contrast to **16**, **17** exhibited weak hERG activity in the patch clamp assay, with 35% inhibition of the potassium current. The two five-membered heteroaryl analogues **18** (2-thiazolyl) and **19** (2-oxazolyl) were potent in the CCR2 binding and chemotaxis assays, although they were slightly less active than **17** in the whole blood assay. Despite their weak hERG activity in the dofetilide assay, they were potent in the patch clamp assay (72−85% inhibition at 10 μM).

Having identified 4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexyl as the preferred left-hand side moiety, we extended our SAR studies to the right-hand side moiety of **17**. On the basis of the extended conformation of the right-hand side moiety of **17** from its X-ray crystal structure (Figure 3), we considered replacing the three-atom linker between the middle carbonyl and the trifluoromethylphenyl in **17** with a carbocycle. Because piperidine possesses a length of about three atoms counting from the 1-position to the 4-position, it was chosen for our exploration (Table 3). Thus, replacement of the three-atom linker in **17** with a piperidine afforded compound **20**. Strikingly, **20** is as potent as **17** in the CCR2 binding and chemotaxis assays and is only 2-fold less active than **17** in the whole blood assay. Unfortunately, this replacement led to an enhancement in hERG binding activity as reflected by an IC_{50} of 9 μM in the dofetilide assay. To modulate the hERG activity, we sought to adjust the polarity of the 3-trifluoromethylphenyl in **20** by replacing it with trifluoromethylpyridyl to provide 6-trifluoromethyl-2-pyridyl analogue **21** and 4-trifluoromethyl-2-pyridyl analogue **22**. With the pyridyl nitrogen sterically shielded by both the piperidine ring and the trifluoromethyl, **21** showed no improvement in hERG activity. With the pyridyl nitrogen at the 4-position of the trifluoromethyl that is more solvent exposed, **22** exhibited weaker hERG activity (IC_{50} = 28 μM) in the dofetilide assay than **20** but is still not weak enough to meet our criteria. Of special note on **22** is its potent chemotaxis and whole blood activity, with an IC_{50} of 1.9 nM in the chemotaxis assay and an IC_{50} of 12 nM in the whole blood assay. Replacement of 4-trifluoromethyl-2-pyridyl in **22** with 4-trifluoromethyl-2-pyrimidinyl to further increase polarity did not improve the hERG activity (**23**, IC_{50} = 26 μM), while replacement of 4-trifluoromethylpyridyl in **22** with 6-trifluoromethyl-4-pyrimidinyl (**24**) reduced the hERG activity to an IC_{50} of >30 μM but resulted in a 3-fold loss in CCR2 binding affinity. The hERG binding activity of **22** can also be reduced by replacing the trifluoromethyl in **22** with cyano (**25**) or by introducing a hydroxyl group at the 4-position of the piperidine (**26**), but both compounds exhibited 10−12 times weaker chemotaxis activity than **22**.

Given its superior profile, **17** was further evaluated in vitro and in vivo. In addition to being a potent human CCR2 antagonist (Table 2), **17** is also a potent murine CCR2 antagonist, exhibiting IC_{50} values of 17 and 13 nM in mouse

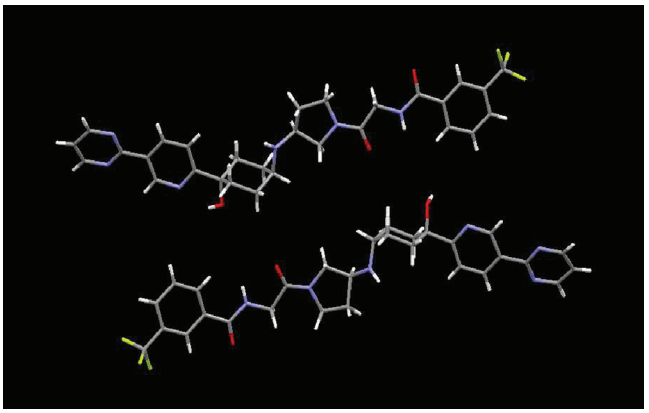
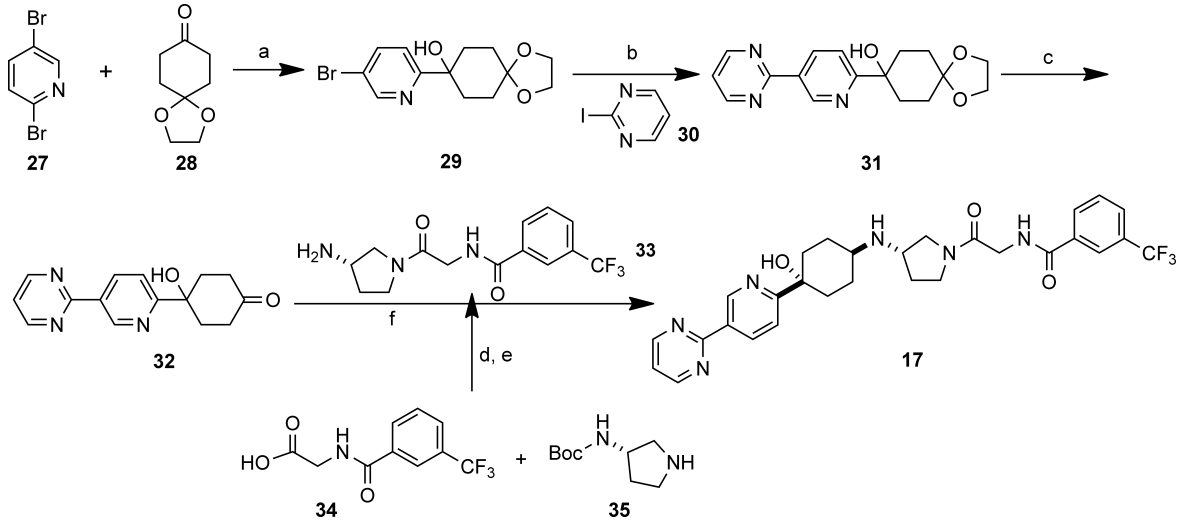


Figure 3. X-ray crystal structure of two molecules of compound **17**. Gray, carbon atoms; white, hydrogen atoms; blue, nitrogen atoms; red, oxygen atoms; and green, fluorine atoms.

Scheme 1. Synthesis of 17[a]



[a]Reagent and conditions: (a) *n*-BuLi, toluene, −78 °C to room temperature, 79%. (b) iPrMgCl, THF, nickel(II) acetylacetonate, 1,2-bis(diphenylphosphino)ethane. (c) 4 N HCl, THF, H_2O, 58% for two steps. (d) Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, DMF, Et_3N, 96%. (e) 4 N HCl in dioxane, MeOH, 100%. (f) $NaBH(OAc)_3$, iBuOH, 66%.

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and rat binding assays and 16 and 2.8 nM in mouse and rat chemotaxis assays. In signaling assays, **17** is potent in inhibiting CCR2 mediated signaling events such as intracellular calcium mobilization and ERK (extracellular signal-regulated kinase) phosphorylation with IC_{50} values of 3.3 and 0.5 nM, respectively. Cerep screens revealed that **17** is a selective CCR2 inhibitor, showing no significant inhibitory activity at a concentration of 1 μM when tested against a panel of >50 ion channels, transporters, chemokine receptors including CCR1, CCR3, CCR5, CXCR3, and CXCR5, and additional GPCRs. In hERG patch clamp assay, **17** inhibited hERG potassium current with an IC_{50} of 20 μM.

In vitro ADME (absorption, distribution, metabolism, and excretion) profiling revealed that **17** has a moderate permeability across Caco-2 monolayers with a value of 3.1×10^{-6} cm/s. In protein binding, **17** had a free fraction of 23% in human serum. When incubated with human liver microsomes, **17** exhibited a moderate intrinsic clearance, with a half-life ($t_{1/2}$) of 89 min. When **17** was incubated with human S9 with or without NADPH and the cofactor glutathione, no glutathione adducts were detected. Compound **17** is not a cytochrome P450 (CYP) inhibitor, with IC_{50} values of >30 μM against five major CYP isozymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Compound **17** is not a CYP inducer at concentrations up to 30 μM.

The pharmacokinetics of **17** was assessed in rats and dogs (Table 4). Following iv administration of **17**, the total systemic clearance was moderate in rats but low in dogs. The apparent steady-state volume of distribution (Vss) followed the same trend as in clearance, with high Vss in rats and low Vss in dogs. As a result, **17** exhibited a moderate half-life in both species after iv administration (2.5 and 2.4 h). When administered orally, **17** was absorbed rapidly, with peak concentration time (T_{max}) at 1.2 h for rats and 0.25 h for dogs. A similar half-life was observed in both species between iv dosing and po dosing. Compound **17** was well absorbed, with an oral bioavailability of 78% in both species.

Table 4. Pharmacokinetic Parameters of 17

	rats[a]	dogs[a]
iv		
dose (mg/kg)	2	2
CL (L/h/kg)	1.41	0.46
Vss (L/kg)	7.0	0.62
$t1/2$ (h)	2.5	2.4
po		
dose (mg/kg)	10	10
C_{max} (nM)	610	20039
T_{max} (h)	1.2	0.25
AUC (nM h)	2723	35560
$t1/2$ (h)	2.5	3.2
F %	78	78

[a]Three animals per study.

The synthesis of this series of compounds is exemplified by compound **17** as illustrated in Scheme 1. Selective lithiation at the 2-bromine of 2,5-dibromopyridine **27** with *n*-butyl lithium in toluene followed by addition of 1,4-cyclohexanedione monoethylene ketal **28** produced the adduct **29**. Treatment of **29** with isopropylmagnesium chloride followed by addition of nickel(II) acetylacetonate, 1,2-bis(diphenylphosphino)-ethane, and 2-iodopyrimidine (**30**) provided the coupling product **31**. The ketal in **31** was converted to a ketone (**32**) by treatment with 4 N HCl in THF. Reductive amination of **32** with **33**, which was generated by coupling of **34** with **35** followed by removal of the Boc group, gave rise to a mixture of two isomers with a ratio of about 2:1 that was separated by silica gel chromatography. The major isomer was the active isomer **17**, while the minor isomer was inactive at a concentration of 1 μM in the CCR2 binding assay. The stereochemistry at the cyclohexyl in **17** was illustrated by X-ray crystallography (Figure 3), with the hydroxyl trans to the amino. In the crystal structure, the cyclohexyl assumes a chair conformation with 5-(2-pyrimidinyl)-2-pyridinyl at the equatorial position and the amino and hydroxyl at the axial positions.

In summary, we discovered a new series of CCR2 antagonists by reversing the connections of the left-hand side moiety and the right-hand side moiety to the 3-aminopyrrolidine core structure in the INCB3284 series. In contrast to the INCB3284 series in which an R configuration on pyrrolidine is critical to binding to CCR2, an S configuration on pyrrolidine in the new series is superior to an R configuration. SAR studies at the 4-position of cyclohexyl on the left-hand side led to the identification of a potent CCR2 antagonist **17** (INCB8761/PF-4136309) with high selectivity, weak hERG activity, high free fraction in protein binding, and an excellent in vitro and in vivo ADMET (ADME and toxicology) profile. INCB8761/PF-4136309 has entered human clinical trials.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures for the synthesis of compound **17** and characterization data for compounds **1**–**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: 302-498-6706. Fax: 302-425-2750. E-mail: cxue@incyte.com.

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