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BMS-813160: A Potent CCR2 and CCR5 Dual Antagonist Selected as a Clinical Candidate

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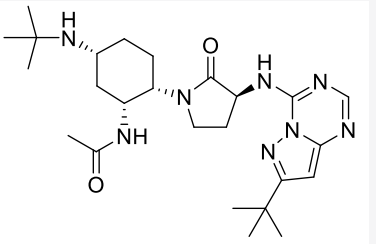
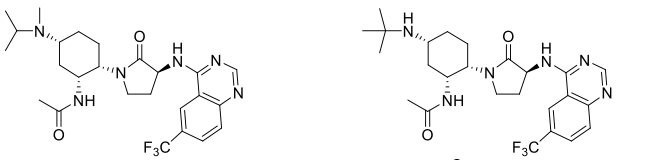
ABSTRACT: BMS-813160 (compound **3**) was identified as a potent and selective CCR2/5 dual antagonist. Compound **3** displayed good permeability at pH = 7.4 in PAMPA experiments and demonstrated excellent human liver microsome stability. Pharmacokinetic studies established that **3** had excellent oral bioavailability and exhibited low clearance in dog and cyno. Compound **3** was also studied in the mouse thioglycollate-induced peritonitis model, which confirmed its ability to inhibit the migration of inflammatory monocytes and macrophages. As a result of this profile, compound **3** was selected as a clinical candidate.



3 (BMS-813160)
CCR2 Bnd IC_{50} = 6.2 ± 2.7 nM
CCR5 Bnd IC_{50} = 3.6 ± 1.8 nM

KEYWORDS: *CCR2 antagonist, CCR5 antagonist, dual antagonist, chemokine, G protein-coupled receptor*

Chemokine receptors are G protein-coupled receptor (GPCR) family members involved in the activation and migration of leukocytes.[1−3] Two chemokine receptors that are often implicated in inflammatory conditions are CC chemokine receptor 2 (CCR2)[4] and CC chemokine receptor 5 (CCR5).[5] The primary ligand for CCR2 is CC chemokine ligand 2 (CCL2);[6] however CCR2 also functions via binding with CCL7, CCL8, CCL13, and CCL16. CCR5 has multiple chemokine ligands,[5] including CCL3, CCL4, CCL5, CCL8, CCL13, and CCL16. CCR2 is the main chemokine receptor expressed on monocytes, but it is also expressed on T cells, immature dendritic cells, and endothelial cells. CCR5 is expressed on monocytes, macrophages, T cells, natural killer cells, and dendritic cells. CCR2 activation initiates the migration of monocytes from the circulation to areas of inflammation within tissues. Overproduction of CCR2 and CCR5 along with their respective ligands is associated with many inflammatory conditions, for example: rheumatoid arthritis,[7,8] multiple sclerosis,[9−11] diabetic nephropathy,[12,13] and fibrosis.[14,15] As such, there has been a tremendous effort over the years to identify antagonists of CCR2 and CCR5.[16−21] Recent findings have also implicated CCR2 and CCR5 in tumor associated immunosuppression[22−24] and the migration of immunosuppressive cells[25−28] to the tumor environment. As a result of these findings, we initiated a program to identify CCR2/5 dual antagonists. Herein we report the results of this effort, which culminated in the identification of BMS-813160 as a clinical candidate.



1
CCR2 Bnd IC_{50} = 1.1 ± 0.5 nM
CCR5 Bnd IC_{50} = 23.6 ± 12 nM

2
CCR2 Bnd IC_{50} = 2.7 ± 1.3 nM
CCR5 Bnd IC_{50} = 6.3 ± 1.5 nM

Figure 1. Our previously reported CCR2 antagonists.

As shown in Figure 1, our previous efforts in this area were focused on CCR2 selective antagonists and yielded compounds **1**[29] and **2**.[30] Compound **1** was 21-fold more selective for CCR2 compared to CCR5 as measured by our binding assay.[31] Surprisingly, replacement of the isopropylmethylamine of **1** with a *tert*-butyl amine group to provide **2** afforded

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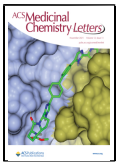
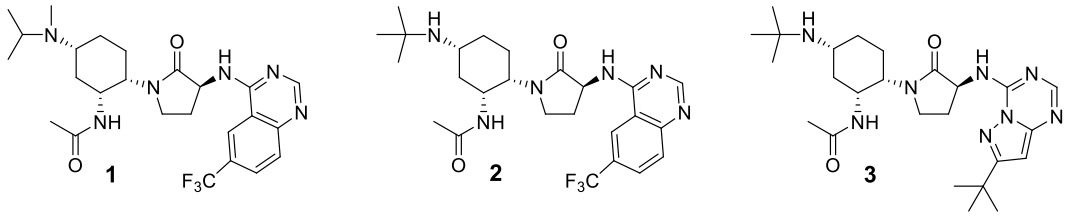


Table 1. Comparison of Compound 3 to Prior Lead Compounds 1 and 2[a]



no.	CCR2 Bnd IC_{50} (nM)	CCR2 CTX IC_{50} (nM)	CCR2 CD11b IC_{50} (nM)	CCR5 Bnd IC_{50} (nM)	CCR5 CTX IC_{50} (nM)	CCR5 CD11b IC_{50} (nM)
1	1.1 ± 0.5	0.7 ± 0.2	NT	23.6 ± 12	NT	NT
2	2.7 ± 1.3	0.8 ± 0.5	2.6 ± 2.2	6.3 ± 1.5	1.1 ± 0.7	34.7 ± 11
3	6.2 ± 2.7	0.8 ± 0.8	4.8 ± 2.7	3.6 ± 1.8	1.1 ± 0.6	5.7 ± 2.4

[a]All assays are reported as means plus or minus standard deviation from two or more determinations. The CCR2 binding (Bnd) assay was performed in human peripheral blood mononuclear cells using labeled ^{125}I-CCL2 as the ligand. CCR5 binding (Bnd) and chemotaxis (CTX) assays were performed using human peripheral T cells using MIP-1β as the ligand (^{125}I-MIP-1β for Bnd). CCR2 chemotaxis was performed using labeled human THP-1 cells and CCL2 as the ligand. CCR2 CD11b and CCR5 CD11b upregulation assays used human whole blood with CCL2 and MIP-1β as the ligands, respectively. For additional details and references on assays, see the Supporting Information. NT = not tested.

Table 2. Compound 3 Profile[a]

assay	result
CCR2 Bnd IC_{50}	6.2 ± 2.7 nM
CCR5 Bnd IC_{50}	3.6 ± 1.8 nM
CCR1 Bnd IC_{50}	>25 μM
CCR4 Bnd IC_{50}	>40 μM
CXCR2 Bnd IC_{50}	>40 μM
mouse CCR2 Bnd IC_{50}	45 ± 22 nM
LM t1/2: h, m, r (min)	146/>200/>200
hERG PC %inhib @ 30 μM	9
protein binding % free h/m/r	71/58/69
PAMPA Pc pH = 5.5 (nm/s)	19
PAMPA Pc pH = 7.4 (nm/s)	336

[a]Liver microsomes (LM) t1/2 reported for human (h), mouse (m), rat (r). Protein binding by equilibrium dialysis with 1 μM conc at 37 °C. For additional details on assays and references see the Supporting Information.

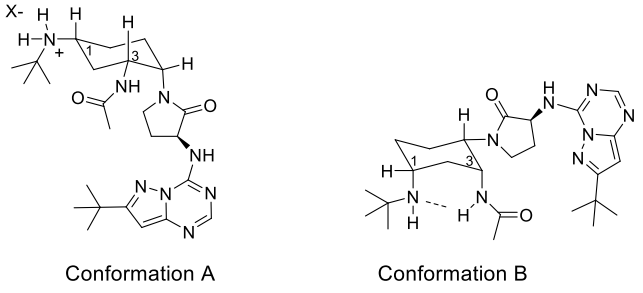
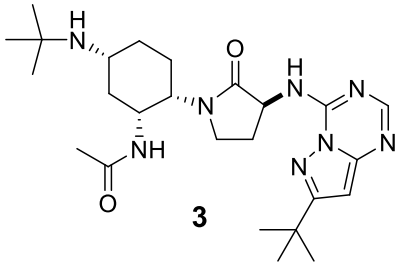


Figure 2. Conformations of compound **3**.

Table 3. Pharmacokinetic Data for Compound 3[a]



species	dose (mpk) *iv/po*	CL_{iv} (mL/min/kg)	F%	oral AUC (nM·h)
mouse	2/10	85	100%	5406
rat	2/10	50	94%	6500
dog	1/1	17	61%	1230
monkey	1/1	16	63%	1300

[a]Values are means obtained from three or more animals.

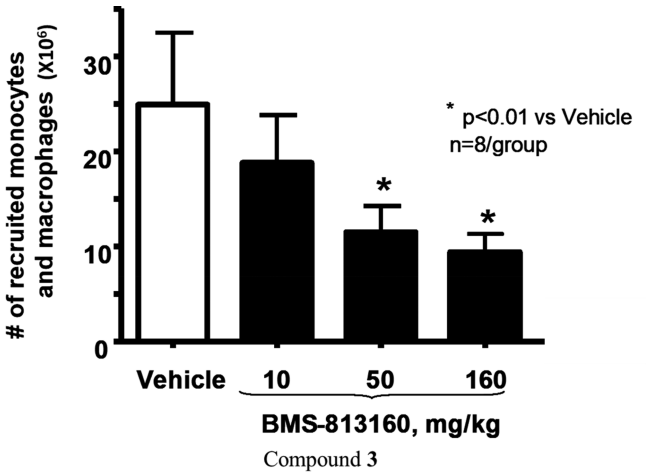


Figure 3. Oral efficacy of compound **3** in the 48 h peritonitis mouse model.

improved CCR5 affinity. In fact, compound **2** was only 2-fold selective for CCR2 over CCR5 in binding affinity. As we initiated our search for CCR2/5 dual antagonists, we continued to incorporate the *tert*-butyl amine group as a way to ensure CCR5 activity. The *tert*-butyl amine group also conferred superior metabolic stability when compared to the isopropylmethylamine group, which suffered from lower metabolic stability due to a demethylation. However, compound **2** was not an optimized CCR2/5 dual antagonist as a result of its activity in our CD11b human whole blood assay.[31] As shown in Table 1, compound **2** had a CCR5 CD11b human whole blood IC_{50} = 34.7 nM. We viewed the CCR5 CD11b human whole blood assay (and the CCR2 version) as our most physiologically relevant assay and sought to optimize compound **2** for CD11b assay activity. Hoping for

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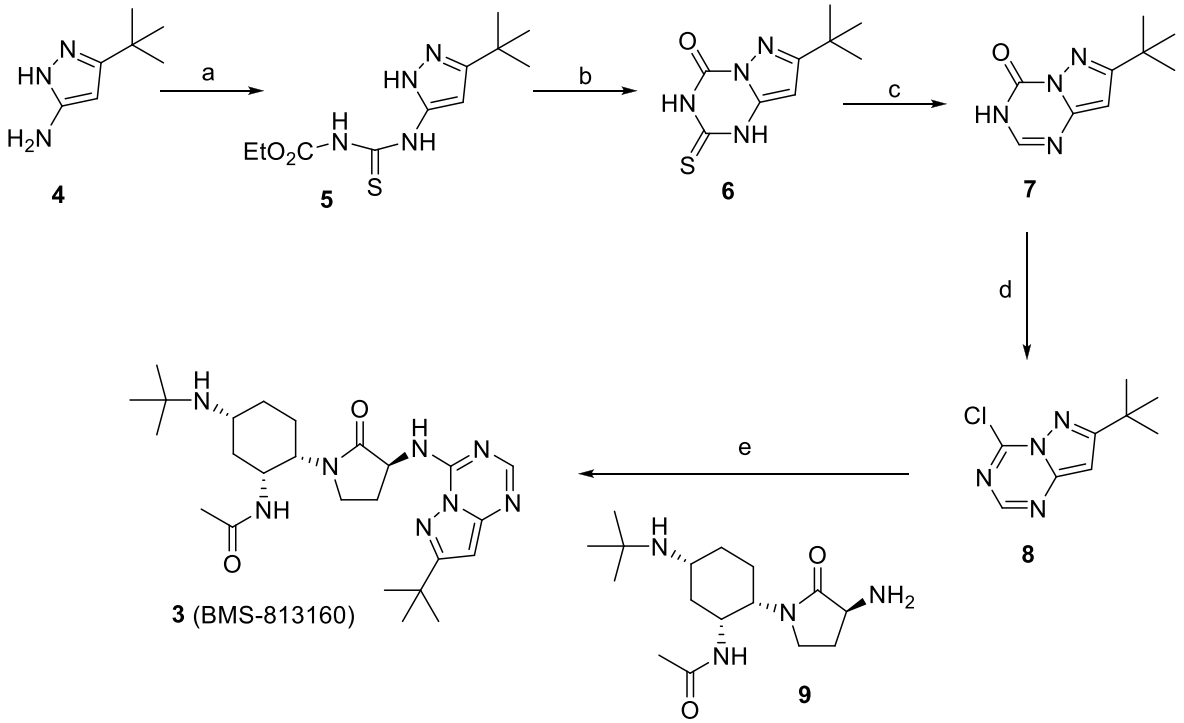
Scheme 1. Synthesis of Compound 3[a]



[a]Reagents and conditions: (a) EtO_2C-NCS, EtOAc, benzene, 90%; (b) NaOH, 95%; (c) Ra-Ni, NH_4OH, MeOH, 100 °C, 50%; (d) $POCl_3$, Δ; (e) **9**, Et_3N, *i*PrOH, 15%.

improved potency in this assay, we examined replacement of the right-hand side quinazoline moiety by a number of other heterocycles. This effort yielded the *tert*-butyl pyrazolotriazine compound **3**, which displayed excellent binding affinity for both CCR2 and CCR5. In fact, **3** had 2-fold better binding affinity for CCR5 over CCR2; however, it was equipotent in the functional chemotaxis assay dependent on either CCR5 or CCR2. Importantly, compound **3** had excellent activity in the CCR2 CD11b human whole blood assay and the CCR5 CD11b human whole blood assay, making it a potent dual antagonist worthy of additional profiling.

As shown in Table 2, selectivity profiling was performed on compound **3**, and it proved to be selective against chemokine family member assays we had in-house: CCR1, CCR4, and CXCR2 (**3** was also inactive in a broad GPCR panel—data not shown). As was the case with many of our antagonists, the human CCR2 activity did not translate to mouse, as the binding affinity in mouse was moderate (mouse CCR2 binding IC_{50} = 45 nM). Compound **3** had excellent human liver microsome stability, which translated well into other species. Although ion channel liabilities are known to be problematic for chemokine antagonists,[32] compound **3** was not potent in a hERG patch clamp assay. Our cyclohexylamine antagonist class has historically had high plasma free fraction, and compound **3** continued this trend. Also inherent in this class is pH-dependent permeability that is controlled by two conformations.[29] As shown in Figure 2, at low pH the 1,3-diequatorial conformation A predominates, which has poor permeability as reflected in the PAMPA Pc of 19 nm/s at pH = 5.5. Conformation A is also the bioactive conformation observed in a CCR2 crystal structure of the close analogue BMS-687681.[33] However, at higher pH (as in pH = 7.4) some of the free base is available which will predominately have the 1,3-diaxial conformation B stabilized by the hydrogen bond between the free *tert*-butyl amine and the "NH" of the acetamide. This 1,3-diaxial conformation shields the polar groups beneath the cyclohexane and increases the cLogP.[29] The result is excellent permeability for the free base (Pc 336 nm/s), as the 1,3-diaxial conformation shuttles the compound through the membrane.

As shown in Table 3, compound **3** had excellent oral bioavailability across the four species studied. This confirms the excellent permeability observed for **3** as predicted by the *in vitro* PAMPA measurements. Compound **3** displayed mixed clearances *in vivo*, significantly higher in rodents, whereas dog and cyno displayed low clearances. The oral 24-h AUC was very good across all four species. This excellent oral bioavailability prompted us to study compound **3** in a mouse model of inflammatory cellular recruitment.

As mentioned above, CCR2 and CCR5 play an important role in the migration of inflammatory monocytes and macrophages, and this can be modeled in the 48 h mouse thioglycollate (TG) induced peritonitis model.[34] However, since compound **3** only has moderate mouse activity, we performed this study in a human-CCR2 knock-in mouse.[35] As shown in Figure 3, compound **3** was dosed orally BID, because of its high clearance in mouse, over 48 h at three different doses (10, 50, and 160 mg/kg). The thioglycollate challenge was administered only once, which was 1 h after the first dose of compound **3** (preventative mode). The results show that compound **3** significantly reduced inflammatory monocyte and macrophage infiltration in the peritoneum in a dose-dependent fashion.

Compound **3** was synthesized starting from 3-(*tert*-butyl)-1*H*-pyrazol-5-amine **4** as shown in Scheme 1. Compound **4** was treated with ethoxycarbonyl isothiocyanate overnight to yield the thiourea **5**.[36] Base treatment of **5** initiated a

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cyclization to give compound **6**. Desulfurization of **6** was accomplished with Raney nickel (Ra-Ni) and afforded compound **7**. Treatment of **7** with refluxing $POCl_3$ gave compound **8**, which was used without purification. In the final step, our previously reported amine **9**[30] was coupled to compound **8** and provided the desired compound **3**.

In summary, we have identified compound **3** (BMS-813160) as a potent and selective CCR2/5 dual antagonist. *In vitro* experiments indicated that **3** had good permeability at pH = 7.4 and excellent metabolic stability. These measurements were confirmed *in vivo*, as compound **3** displayed excellent oral bioavailability and had low clearance in dog and cyno. Compound **3** proved to be efficacious in the mouse TG-induced peritonitis model, which validated its ability to inhibit the migration of inflammatory monocytes and macrophages. As a result of the above profile, compound **3** was selected as a clinical candidate and was advanced into clinical trials.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.1c00373.

Compound characterization data and additional assay details/references (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

AUC, area under the curve; BID, twice a day; BMS, Bristol Myers Squibb; Bnd, binding; BSA, bovine serum albumin; C, concentration; CCL2, CC chemokine ligand 2; CCR2, CC chemokine receptor 2; CCR5, CC chemokine receptor 5; CL, clearance; CTX, chemotaxis; EDTA, ethylenediaminetetraacetic acid; F, bioavailability; GPCR, G protein-coupled receptors; h, hour; hERG, human ether-a-go-go-related gene; hWB, human whole blood; iv, intravenous; LM, liver microsome; M, molar; NADPH, dihydronicotinamide-adenine dinucleotide phosphate; ND, not determined; NMP, *N*-methylpyrrolidinone; PC, patch clamp; PD, pharmacodynamics; PK, pharmacokinetic; po, per os, oral dose; qd, once a day; Ra-Ni, Raney nickel; SAR, structure activity relationship; SFC, supercritical fluid chromatography; TG, thioglycollate

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