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Synthesis and structure–activity relationship of 7-azaindole piperidine derivatives as CCR2 antagonists

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ABSTRACT

The synthesis and structure–activity relationship of a series of 7-azaindole piperidine derivatives are described. SAR studies led to the discovery of the potent CCR2 antagonists displaying IC_{50} values in the nanomolar range. The representative compound **15** showed reasonable P450 and pharmacokinetics profile.

The monocyte chemoattractant protein-1 (MCP-1), a member of the CC class of chemokines, mediates chemotaxis of monocytes to inflammatory sites through interactions with its CC chemokine receptor-2 (CCR2)[1] and is implicated in various inflammatory diseases.[2–12] The therapeutic potential of CCR2 antagonists for preventing and treating various pathological conditions (such as cockroach allergen-induced asthma, atherosclerosis, rheumatoid arthritis, and multiple sclerosis) has stimulated considerable interest. Several series of CCR2 antagonists have already been described in the literature.[13–27] Recently, we disclosed both the phenyl piperidinyl derivatives as CCR2 antagonists with submicromolar binding affinity and the more potent carboxylic acid/alcohol analogs with IC_{50} in the nanomolar range.[28–30] We now in this communication report the identification of 7-azaindole piperidine derivatives as potent CCR2 antagonists and present the synthesis and structure–activity relationship (SAR) studies.

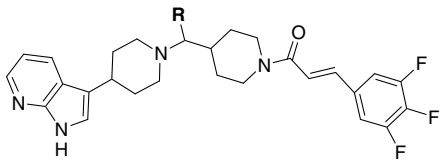
Initial SAR studies on the CH_2 linker between the two piperidines revealed that carboxylic acid derivative **1d** and hydroxymethyl derivative **1e** showed a marked improvement in CCR2 binding affinity relative to the unsubstituted methylene, amide, and ester analogs (Table 1). Hydroxy-methyl derivative was more potent than carboxylic acid derivative. Therefore, we decided to explore more SAR of the hydroxymethyl series. The synthesis of carboxylic acid **1d** is outlined in Scheme 1.

Compound 3-(3,4,5-trifluoro-phenyl)-acryloyl chloride (**2**) was reacted with piperidin-4-yl-acetic acid ethyl ester to give {1-[3,4,5-trifluoro-phenyl)acryloyl]-piperidin-4-yl}-acetic acid ethyl ester (**3**), which was converted to α-bromo-acid **5** through bromination (LHMDS/TMSCl, Br_2) and ester hydrolysis. Bromoacid **5** was refluxed with 3-piperidin-4-yl-1*H*-pyrrolo[2,3-*b*]pyridine in acetonitrile to afford the carboxylic acid compound **1d**.

When the carboxylic acid moiety was replaced with a hydroxylmethyl group the CCR2 binding affinity of the corresponding compound was improved into single digital nanomolar region. Scheme 2 outlines the synthesis of alcohol analogs.

Boc-protected piperidin-4-yl-acetic acid ethyl ester **6** was converted to α-bromo-ester **7** through bromination (LHMDS/TMSCl,

Table 1
Functional group effect on CCR2 binding affinity



Compound	R	CCR2 IC_{50} (nM)
1a	CO_2Et	1900
1b	H	1300
1c	$CONH_2$	960
1d	CO_2H	17
1e	CH_2OH	7

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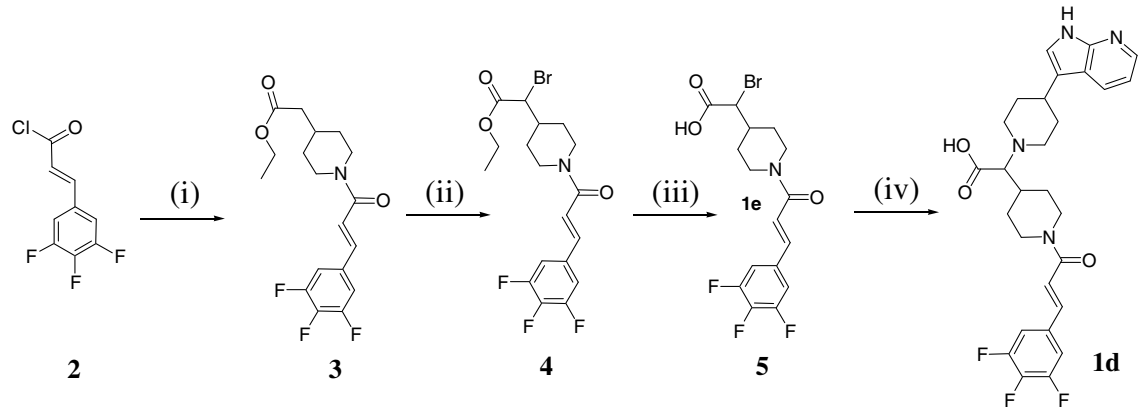
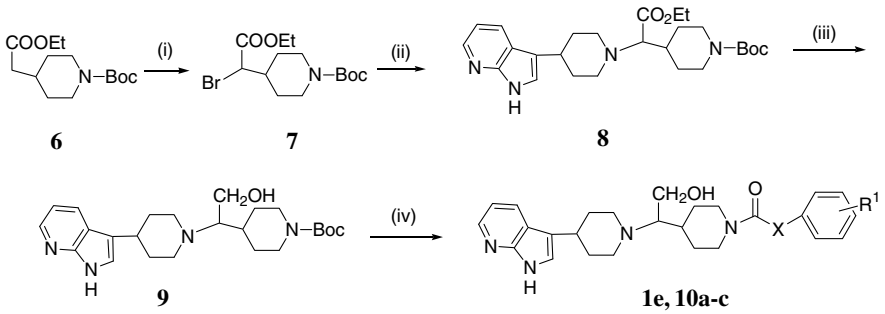


Scheme 1. Synthesis of carboxylic acid **1d**. Reagents and conditions: (i) Piperidin-4-ylacetic acid ethyl ester, TEA, 75%; (ii) LiHMDS, TMSCl, −78 °C, then Br_2, 60%; (iii) LiOH, 98%; (iv) 3-piperidin-4-yl-1*H*-pyrrolo[2,3-*b*]pyridine, CH_3CN, TEA, reflux, 38%.

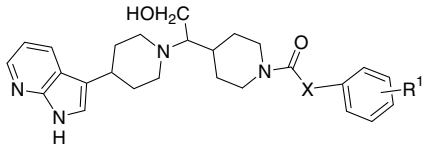


Scheme 2. Synthesis of alcohol analogs. Reagent and conditions: (i) LHMDS, TMSCl, −78 °C, then Br_2, 82%; (ii) 3-piperidin-4-yl-1*H*-pyrrolo[2,3-*b*]pyridine, CH_3CN, $N(i\text{-}Pr)_2Et$, reflux, 44%; (iii) LAH, 0 °C, 95%; (iv) a—TFA; b—ArCH=CHCOCl, or ArNCO, 22–87%.

Br_2). Compound **7** was then refluxed with 3-piperidin-4-yl-1*H*-pyrrolo[2,3-*b*]pyridine in acetonitrile to afford ester **8**, which was reduced to alcohol **9** with lithium aluminum hydride. Alcohol **9** was converted to the target compounds **1e** and **10a–c** via deprotection of the Boc group with TFA, and acylation with appropriate acid chloride or isocyanate.

The 7-azaindole piperidine series showed similar SAR with that of the previously reported indole piperidine series,[29,30] but was found to have improved solubility. Table 2 lists CCR2 membrane binding affinities for the most potent analogs. Halogen substitution on the 3-, 4-, or 5-position of the cinnamoyl phenyl ring was preferred. The urea-containing compound **10c** also possessed significant affinity for the CCR2.

Table 2
CCR2 binding affinities of alcohol analogs



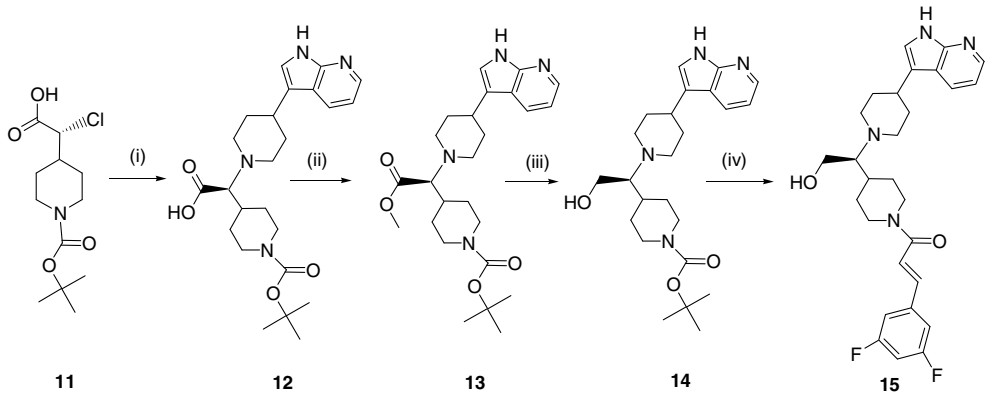
Compound	X	R^1	CCR2 IC_{50} (nM)
1e	CH=CH	3,4,5-TriF	7
10a	CH=CH	3,5-DiF	6
10b	CH=CH	3,4-DiCl	6
10c	NH	3,4-DiCl	14

Compounds **1e** and **10a–c** were initially prepared as their racemates. In order to determine if there was a difference in binding affinity between the two enantiomers of **10a**, the (*S*) enantiomer was prepared from the chiral chloro-acid **11** through the synthetic route outlined in Scheme 3.

Compound **11** was refluxed with 3-piperidin-4-yl-1*H*-pyrrolo[2,3-*b*]pyridine in acetonitrile to give the amino acid **12**, which was converted to ester **13** with (trimethylsilyl)diazomethane. Ester **13** was reduced to alcohol **14** with LAH. Alcohol **14** was converted to the target compound **15** via removal of the Boc group with TFA, and acylation with appropriate acid chloride.

Compound **15** possessed an hCCR2 membrane binding IC_{50} of 4 nM and was selected for further evaluation. During the CYP450 study (using cDNA expressed human enzymes), it showed relatively clean profile with IC_{50}s of >40 μM for 1A2, 27.1 μM for 2C19, 13.3 μM for 2D6, 25.2 μM for 3A4(BFC), >40 μM for 3A4(BQ) and 20.6 μM for 3A4 (DBF). The bioavailability of compound **15** in rats was 36% with po (C_{max} 341 ng/ml, $T_{1/2}$ 5.6 h) at 10 mg/kg dosage (vehicle 20% HPBCD in water).

In summary, a series of 7-azaindole piperidine derivatives have been synthesized and the carboxylic acid **1d** and alcohol **1e** have been identified as potent CCR2 antagonists. Those compounds were found to possess significantly higher affinity for the human CCR2 receptor than the ester **1a**, amide **1c**, and unsubstituted analog **1b**. Alcohol analogs **1e**, **10a**, and **10b** showed IC_{50} values in the nanomolar range. Compound **15** showed reasonable P450 and pharmacokinetics profiles. Further studies in this series that address pharmacology profile will be reported in due course.



Scheme 3. Synthesis of chiral alcohol. Reagents and conditions: (i) 3-Piperidin-4-yl-1*H*-pyrrolo[2,3-*b*]pyridine, CH_3CN, Na_2CO_3, reflux; (ii) $TMSCHN_2$, MeOH, 22% for two steps; (iii) LAH, 0 °C, 97%; (iv) a—TFA; b—3-(3,5-difluoro-phenyl)-acryloyl chloride, 50%.

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References and notes

1. Charo, I. F.; Myers, S. J.; Herman, A.; Franci, C.; Connolly, A. J.; Coughlin, S. R. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 2752.
2. Ruth, J. H.; Rottman, J. B.; Katschke, K. J., Jr.; Qin, S.; Wu, L.; LaRosa, G.; Ponath, P.; Pope, R. M.; Koch, A. E. *Arthritis Rheum.* **2001**, *44*, 2750.
3. Carulli, M. T.; Ong, V. H.; Ponticos, M.; Xu, S.; Abraham, D. J.; Black, C. M.; Denton, C. P. *Arthritis Rheum.* **2005**, *52*, 3772.
4. Boring, L.; Gosling, J.; Cleary, M.; Charo, I. F. *Nature* **1998**, *394*, 894.
5. Dawson, T. C.; Kuziel, W. A.; Osahar, T. A.; Maeda, N. *Atherosclerosis* **1999**, *143*, 205.
6. Weisberg, S. P.; Hunter, D.; Huber, R.; Lemieux, J.; Slaymaker, S.; Vaddi, K.; Charo, I.; Leibel, R. L.; Ferrante, A. W., Jr. *J. Clin. Invest.* **2006**, *116*, 115.
7. Lloyd, C. M.; Minto, A. W.; Dorf, M. E.; Proudfoot, A.; Wells, T. N. C.; Salant, D. J.; Gutierrez-Ramos, J. C. *J. Exp. Med.* **1997**, *185*, 1371.
8. Kitagawa, K.; Wada, T.; Furuichi, K.; Hashimoto, H.; Ishiwata, Y.; Asano, M.; Takeya, M.; Kuziel, W. A.; Matsushima, K.; Mukaida, N.; Yokoyama, H. *Am. J. Pathol.* **2004**, *165*, 237.
9. Izikson, L.; Klein, R. S.; Luster, A. D.; Weiner, H. L. *Clin. Immunol.* **2002**, *103*, 125.
10. Kurihara, T.; Warr, G.; Loy, J.; Bravo, R. *J. Exp. Med.* **1997**, *186*, 1757.
11. Ross, R. *New Engl. J. Med.* **1999**, *147*, 213.
12. Boring, L.; Gosling, J.; Chensue, S. W.; Kunkel, S. L.; Farese, R. V., Jr.; Broxmeyer, H. E.; Charo, I. F. *J. Clin. Invest.* **1997**, *100*, 2552.
13. Moree, W. J.; Kataoka, K.; Ramirez-Weinhouse, M. M.; Shiota, T.; Imai, M.; Tsutsumi, T.; Sudo, M.; Endo, N.; Muroga, Y.; Hada, T.; Fanning, D.; Saunders, J.; Kato, Y.; Myers, P. L.; Tarby, C. M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1869.
14. Pasternak, A.; Goble, S. D.; Vicario, P. P.; Di Salvo, J.; Ayala, J. M.; Struthers, M.; DeMartino, J. A.; Mills, S. G.; Yang, L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 994.
15. Cherney, R. J.; Mo, R.; Meyer, D. T.; Nelson, D. J.; Lo, Y. C.; Yang, G.; Scherle, P. A.; Mandlekar, S.; Wasserman, Z. R.; Jezak, H.; Solomon, K. A.; Tebben, A. J.; Carter, P. H.; Decicco, C. P. *J. Med. Chem.* **2008**, *51*, 721.
16. Lagu, B.; Gerchak, C.; Pan, M.; Hou, C.; Singer, M.; Malaviya, R.; Matheis, M.; Olini, G.; Cavender, D.; Wachter, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4382.
17. Butora, G.; Jiao, R.; Parsons, W. H.; Vicario, P. P.; Jin, H.; Ayala, J. M.; Cascieri, M. A.; Yang, L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3636.
18. Yang, L.; Butora, G.; Jiao, R. X.; Pasternak, A.; Zhou, C.; Parsons, W. H.; Mills, S. G.; Vicario, P. P.; Ayala, J. M.; Cascieri, M. A.; MacCoss, M. *J. Med. Chem.* **2007**, *50*, 2609.
19. Pinkerton, A. B.; Huang, D.; Cube, R. V.; Hutchinson, J. H.; Struthers, M.; Ayala, J. M.; Vicario, P. P.; Patel, S. R.; Wisniewski, T.; DeMartino, J. A.; Vernier, J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 807.
20. Brodmerkel, C. M.; Huber, R.; Covington, M.; Diamond, S.; Hall, L.; Collins, R.; Leffet, L.; Gallagher, K.; Feldman, P.; Collier, P.; Stow, M.; Gu, X.; Baribaud, F.; Shin, N.; Thomas, B.; Burn, T.; Hollis, G.; Yeleswaram, S.; Solomon, K.; Friedman, S.; Wang, A.; Xue, C. B.; Newton, R. C.; Scherle, P.; Vaddi, K. *J. Immunol.* **2005**, *175*, 5370.
21. Van Lommen, G.; Doyon, J.; Coesemans, E.; Boeckx, S.; Cools, M.; Buntinx, M.; Hermans, B.; Van Wauwe, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 497.
22. Moree, W. J.; Kataoka, K.; Ramirez-Weinhouse, M. M.; Shiota, T.; Imai, M.; Sudo, M.; Tsutsumi, T.; Endo, N.; Muroga, Y.; Hada, T.; Tanaka, H.; Morita, T.; Greene, J.; Barnum, D.; Saunders, J.; Kato, Y.; Myers, P. L.; Tarby, C. M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5413.
23. Kettle, J. G.; Faull, A. W.; Barker, A. J.; Davies, D. H.; Stone, M. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 405.
24. Gao, Z.; Metz, W. A. *Chem. Rev.* **2003**, *103*, 3733.
25. Witherington, J.; Bordas, V.; Cooper, D. G.; Forbes, I. T.; Gribble, A. D.; Ife, R. J.; Berkhout, T.; Gohil, J.; Groot, P. H. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2177.
26. Forbes, I. T.; Cooper, D. G.; Dodds, E. K.; Hickey, D. M. B.; Ife, R. J.; Meeson, M.; Stockley, M.; Berkhout, T. A.; Gohil, J.; Groot, P. H. E.; Moores, K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1803.
27. Mirzadegan, T.; Diehl, F.; Ebi, B.; Bhakta, S.; Polsky, I.; McCarley, D.; Mulkins, M.; Weatherhead, G. S.; Lapierre, J.-M.; Dankwardt, J.; Morgans, D., Jr.; Wilhelm, R.; Jarnagin, K. *J. Biol. Chem.* **2000**, *275*, 25562.
28. Xia, M.; Hou, C.; DeMong, D.; Pollack, S.; Pan, M.; Brackley, J.; Singer, M.; Matheis, M.; Cavender, D.; Wachter, M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3562.
29. Xia, M.; Hou, C.; DeMong, D. E.; Pollack, S. R.; Pan, M.; Brackley, J. A.; Jain, N.; Gerchak, C.; Singer, M.; Malaviya, R.; Matheis, M.; Olini, G.; Cavender, D.; Wachter, M. *J. Med. Chem.* **2007**, *50*, 5561.
30. Xia, M.; Hou, C.; Pollack, S.; Brackley, J.; DeMong, D.; Pan, M.; Singer, M.; Matheis, M.; Olini, G.; Cavender, D.; Wachter, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5964.