DOI: 10.1002/cmdc.200600182

Synthesis and Biological Evaluation of 1,3,3,4-Tetrasubstituted Pyrrolidine CCR5 Receptor Antagonists. Discovery of a Potent and Orally Bioavailable Anti-HIV Agent

Dawei Ma,*[a] Shanghai Yu,[a] Ben Li,[b] Li Chen,[c] Renhai Chen,[c] Kunqian Yu,[d] Linqi Zhang,[e, f] Zhiwei Chen,[e] Dafang Zhong,[g] Zheng Gong,[d] Renxiao Wang,[a] Hualiang Jiang,[d] and Gang Pei[b]

*A series of 1,3,3,4-tetrasubstituted pyrrolidine containing CCR5 receptor antagonists were designed, which were elaborated either by condensation of a lithium salt of 3-(*N,N*-dibenzyl)aminopropionic acid methyl ester with ethyl benzoformate or by Baylis–Hillman reaction of ethyl acrylate with ethyl benzoformate and subsequent 1,4-addition of benzylamine, in the key steps. These compounds bearing 4-(*N,N*-disubstituted)amino piperidine units showed low nanomolar potency against the CCR5 receptor, whereas molecules with a 4-phenylpiperidine moiety displayed poor activity. Asymmetric synthesis of the most potent compound* ***23a*** *gave rise to the (3*R*,4*S*)-enantiomer* ***30*** *and the (3*S*,4*R*)-enantiomer* ***31****, which showed IC_{50} values of 2.9 and 385.9 nM, respectively. These results indicated that (3*R*,4*S*)-configuration in the series of compounds is favored for their interaction with the CCR5 receptor. The possible binding mode of these antagonists with the CCR5 receptor was discussed using a computer-modeling method. Compound* ***30*** *displayed excellent replication inhibition of seven genetically diverse R5 HIV-1 strains in the PBMC model, in a concentration-dependent manner with EC_{50} values ranging from 0.3 nM to 30 nM. This molecule showed oral bioavailabilities of 41.2% and 21.6% in rats and dogs, respectively. Thus, compound* ***30*** *is a promising candidate for the treatment of HIV-1 infection.*

Introduction

As a perfect therapy has not been established for the Type 1 Human Immunodeficiency Virus (HIV-1) infection, discovery of new anti-HIV agents, particularly those acting by novel mechanisms, is still an urgent task for scientists worldwide.[1] The β-chemokine receptor CCR5, a member of the G-protein-coupled receptor (GPCRs) subfamily, has been identified as an essential coreceptor for HIV-1 to dock and gain entry into $CD4^+$ macrophages and T-cells. Consequently, inhibition of its activity holds promise for the treatment and/or prevention of HIV-1 infection.[1,2] This concept has led to intense research efforts directed toward the development of potent CCR5 antagonists.[2] As a result, several classes of compounds were found possessing excellent affinity for the human CCR5 receptor, and some of them have shown promising anti-HIV action in either cellular models or clinical trials. For example, TAK-779 (**1**, Figure 1),[3] a quaternary ammonium derivative, is the first nonpeptide molecule shown to block the replication of the M-tropic R5 HIV-1 strains in low nanomolar concentrations by interaction with CCR5. Three compounds entered phase II and III clinical trials, namely, UK-427,857 (**2**), a triazol-containing compound developed by Pfizer,[4] Sch-417690 (**3**), a piperazino-piperidine embodied molecule discovered by Schering-Plough,[5] and spirodiketopiperazine GW-873140 (**4**) developed by GlaxoSmithKline.[6] Recently, Takeda scientists disclosed that the CCR5 antagonist,

[a] *Prof. Dr. D. Ma, Dr. S. Yu, Dr. R. Wang*
State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032 (China)
Fax: (+86) 21-64166128
E-mail: madw@mail.sioc.ac.cn

[b] *B. Li, Prof. Dr. G. Pei*
Shanghai Institute of Biological Chemistry & Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, 319 Yueyang Lu, Shanghai 200031 (China)

[c] *Dr. L. Chen, R. Chen*
Shanghai Targetdrug CO., LTD, 500 Caobao Lu, Shanghai 20023 (China)

[d] *Dr. K. Yu, Z. Gong, Prof. Dr. H. Jiang*
Drug Discovery and Design Center, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai 201203 (China)

[e] *Prof. Dr. L. Zhang, Z. Chen*
Modern Virology Research Center and AIDS Center, State Key Laboratory of Virology, College of Life Sciences, Wuhan University, Wuhan 430072 (China)

[f] *Prof. Dr. L. Zhang*
The AIDS Research Center, Chinese Academy of Medical Sciences, Peking Union Medical School, Beijing 100730 (China)

[g] *Prof. Dr. D. Zhong*
Drug Metabolism and Pharmacokinetics Research Center, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 646 Songtao Road, Shanghai 201203 (China)

Supporting information for this article is available on the WWW under http://www.chemmedchem.org or from the author.

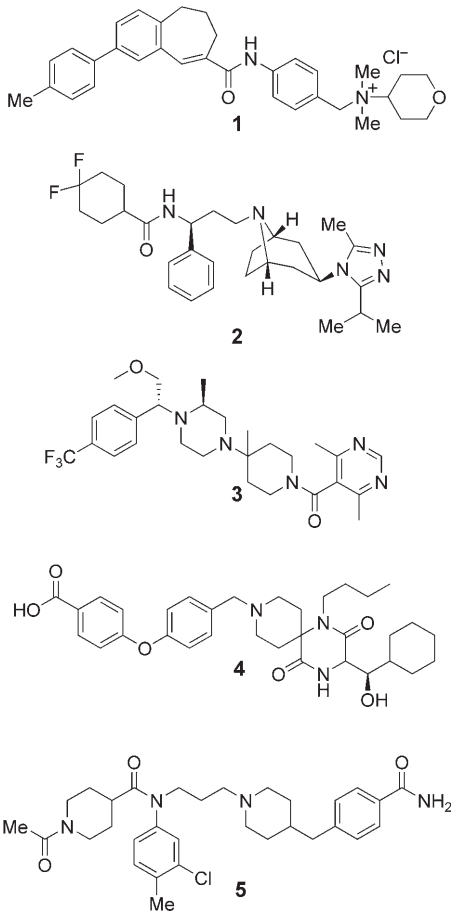


Figure 1. Structures of some CCR5 antagonists with potent anti-HIV activity.

TAK-220 (**5**), was an orally bioavailable anti-HIV agent and holds promise for further development.[7]

In 2001, research groups at Merck reported that a series of 1,3,4-trisubstituted pyrrolidines (**A**, Figure 2), such as **6**, possessed high affinity for CCR5 and exhibited anti-HIV activity.[8] Unfortunately, these compounds showed poor oral bioavailability in pharmacokinetic evaluations. Further optimization was thus undertaken and it was revealed that compound **7**, a (pyrrolidin-1-yl)acetic acid embodied compound, displayed better pharmacokinetic properties yet retained excellent inhibition activities toward CCR5.[9] However, this modification introduced an additional chiral center, which made the chemical synthesis more difficult.

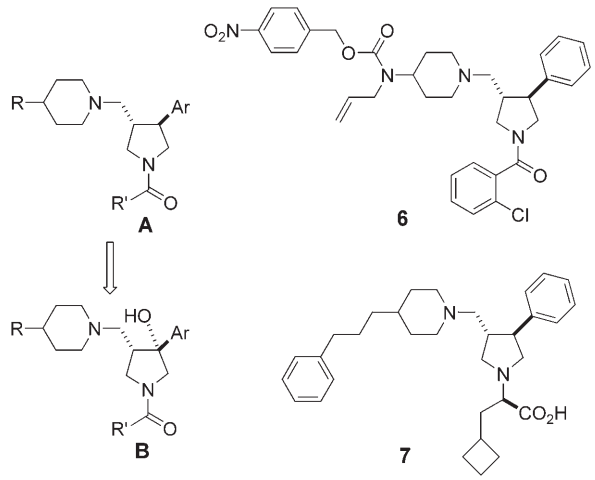
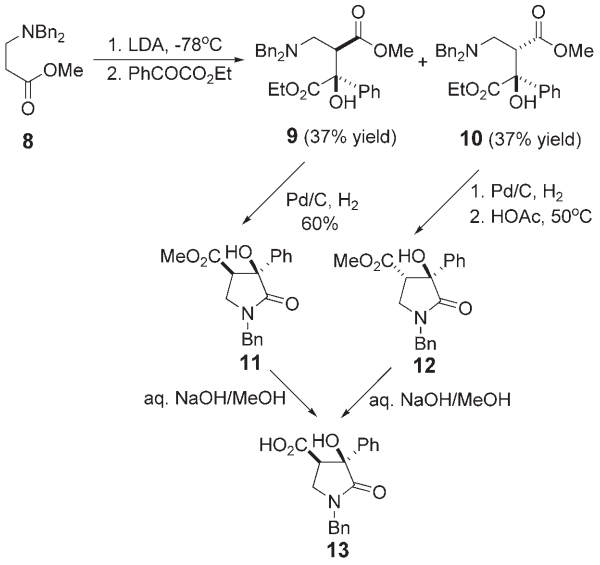


Figure 2. Structures of the Merck CCR5 antagonists and our designed molecules.

Based on Merck's studies,[8,9] we designed a series of 1,3,3,4-tetrasubstituted pyrrolidines **B** as potential new CCR5 antagonists. The crucial change in structure was the introduction of a hydroxy group at the 3 position of the pyrrolidine ring. During subsequent studies, it was found that this modification not only made enantioselective synthesis of the core structure easier, but also resulted in compounds with good binding affinity, potent anti-HIV activity, and promising oral bioavailability. Herein, we report these results in detail.

Results and Discussion

The initial approach to our designed core structure is illustrated in Scheme 1. Treatment of 3-(*N*,*N*-dibenzyl)aminopropionic

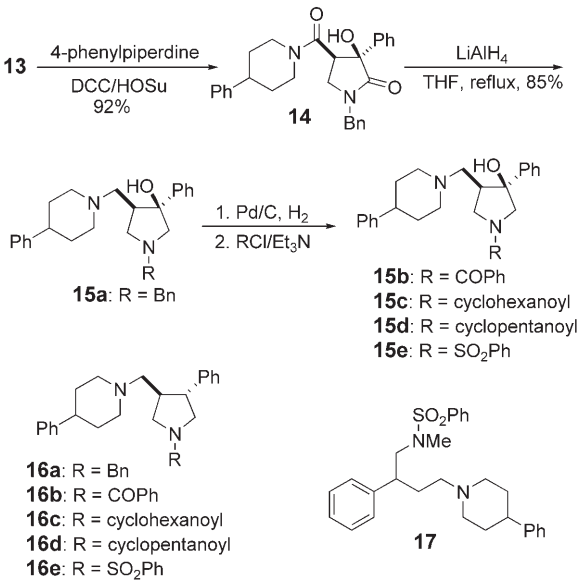


Scheme 1. The initial approach to our designed core structure.

acid methyl ester **8** with LDA followed by trapping the generated anion with ethyl benzoformate produced two separable diastereoisomers **9** and **10**.[10] Hydrogenolysis of the diester **9** catalyzed by Pd/C in methanol gave rise to lactam **11** directly. However, under the same conditions, diester **10** only provided a debenzylated product. The desired lactam **12** was obtained upon heating the debenzylated intermediate at 50 °C in the presence of acetic acid. Interestingly, product **13** was isolated from pyrrolidinones **11** and **12** upon hydrolysis with 1 N NaOH in methanol at room temperature. This result clearly indicated that the acid **13** was more thermodynamically stable in comparison with its *trans*-isomer.

Acid **13** was further converted to the target molecules **15**, the 3-hydroxy analogues of Merck's CCR5 antagonists **16**, as

depicted in Scheme 2. Coupling of **13** with 4-phenylpiperidine afforded amide **14**, which was reduced with LAH to provide diamine **15a**. Pd/C catalyzed hydrogenolysis of **15a** in methanol yielded a secondary amine, which was exposed to the corresponding acid chlorides and to phenylsulfonic chloride to furnish amides **15b**–**15d**, and phenylsulfonamide **15e**, respectively.



Scheme 2. Target molecules **15**, the 3-hydroxy analogues of the Merck CCR5 antagonists **16**, also shown is **17** another of Merck's compounds.

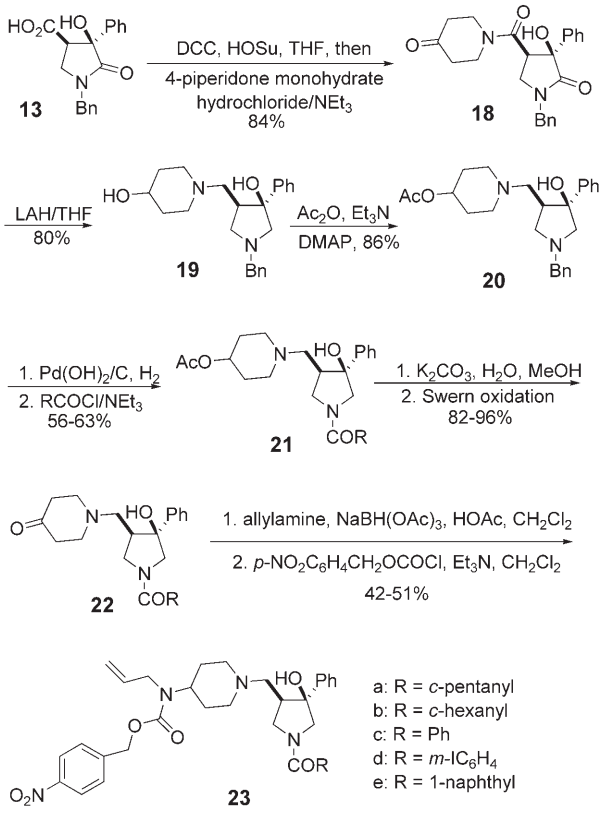
The synthesized compounds were tested using a biological assay for inhibition of RANTES-stimulated [^{35}S]-GTPγS binding to CCR5-expressing CHO cell membranes,[11] the results are summarized in Table 1. For comparison, the IC_{50} values for Merck's compounds **16a**–**16e** are also listed although a different biological assay (displacement of ^{125}I-labeled MIP-1α from the CCR5 receptor expressed on CHO cell membranes)[8] was used. Our compounds showed apparent inhibitory activity toward the CCR5 receptor. However, their potencies were considerably lower compared to Merck's corresponding compounds, whereas another Merck compound **17**,[12] showed similar potency in these two biological assays. These results implied that the 3-hydroxy group might play some role in the interaction of **15** with the CCR5 receptor. From the data, we observed that the trend in the structure–activity relationship for **15** and **16** is identical; that is, N1-acylated compounds (**15b**–**15d**) displayed better activity than the corresponding N1-alkyl or N1-phenylsulfonyl compounds. Thus, in further modifications we chose acyl groups as substituents at the 1-position of the pyrrolidine ring and used other SAR results released by Merck scientists to guide our molecular design.

Table 1. Potencies for CCR5 antagonists **15** and **16**.

Compound	IC_{50} [nM][a]	Compound	IC_{50} [nM][b]
15a	>10000	**16a**	152±16
15b	2855±860	**16b**	67±7
15c	~2000	**16c**	34±3
15d	1895±615	**16d**	19±2
15e	~10000	**16e**	152±16
17	30	**17**	120

[a] Inhibition of RANTES-stimulated [^{35}S]-GTPγS binding to CCR5-expressing CHO cell membranes. [b] Displacement of ^{125}I-labeled MIP-1α from the CCR5 receptor expressed on CHO cell membranes.

Using amide **6**, one of the most potent antagonists discovered by Merck researchers, as a template,[8b] we tried to tune the pyrrolidine part of **15** to improve the potency. Accordingly, compounds **23a**–**23e** became our new targets, their synthesis is outlined in Scheme 3. After transformation of acid **13** into its activated ester, amide formation was performed with 4-piperidone to afford diamide **18**. LAH-reduction of the amide **18** provided diamine **19**, which was treated with acetic anhydride to selectively protect the secondary alcohol. Hydrogenolysis of the resultant amine **20** followed by acylation of the liberated secondary amine with several acyl chlorides gave rise to amides **21** in 53–63% yields. After hydrolysis of **21** with aqueous K_2CO_3 in methanol, Swern oxidation was carried out to afford ketones **22**. Finally, reductive amination of **22** with alyl amine and subsequent condensation with 4′-nitrobenzyl chloroformate furnished carbamates **23a**–**23e**.



Scheme 3. Synthesis of compounds **23a**–**23e**.

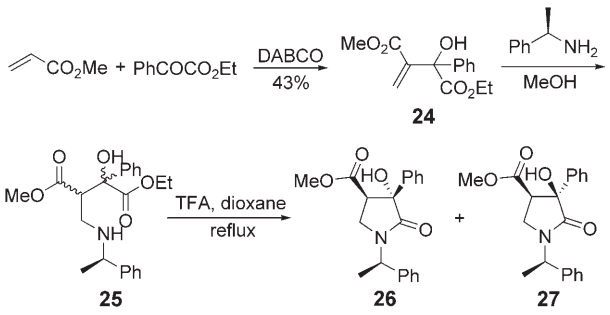
The binding affinity of these newly assembled compounds was examined, the data are shown in Table 2. We were grati-

Table 2. Inhibition of RANTES-stimulated [^{35}S]-GTPγS binding to CCR5-expressing CHO cell membranes by compounds **23**.

Compound	IC_{50} [nM]
23a	5.3 ± 0.6
23b	7.3 ± 0.6
23c	9.7 ± 0.7
23d	24.9 ± 8.9
23e	26.8 ± 2.0

fied to find that all these compounds had low nanomolar potency against the CCR5 receptor. It appears that larger substituents at the 1-position led to less potent compounds. The most potent compound in this series is carbamate **23a**, with an IC_{50} of 5.3 nM, which is almost identical to that displayed by the structurally related Merck antagonist **6**.[8b] As our previous compounds showed much lower potencies than the corresponding Merck antagonists (Table 1), this result implied that introducing suitable substituents at the 4-position of the piperidine unit could attenuate the influence of the 3-hydroxy group of the pyrrolidine ring on activity.

In a further attempt to optimize this new series of compounds we developed a facile and enantioselective synthesis of the 1,3,3,4-tetrasubstituted pyrrolidine core. As outlined in Scheme 4, DABCO-catalyzed Baylis–Hillman reaction of methyl



Scheme 4. Outline of the synthesis of 1,3,3,4-tetrasubstituted pyrrolidine core.

acrylate and ethyl benzoformate provided diester **24** in 43% yield,[13] which was reacted with (*R*)-α-methylbenzylamine in methanol to afford the 1,4-addition product **25** as a mixture of four diastereomers. Lactamization of **25** occurred upon refluxing in dioxane containing TFA, producing enantiopure pyrrolidone **26** in 27% overall yield (35% yield by chromatography) after direct crystallization from the reaction solution. The stereochemistry of **26** was established by X-ray structure analysis as indicated in Figure 3. Pyrrolidone **27** was isolated from the mother liquor by column chromatography. This process was proven successful even in a hundred kilogram scale. In Merck's report,[8b] asymmetric dipolar cycloaddition of an azomethine ylide to a cinnamate bearing a chiral oxazolidione was employed to elaborate the required enantiopure 1,3,4-trisubstituted pyrrolidine core. Apparently, our approach for assembling

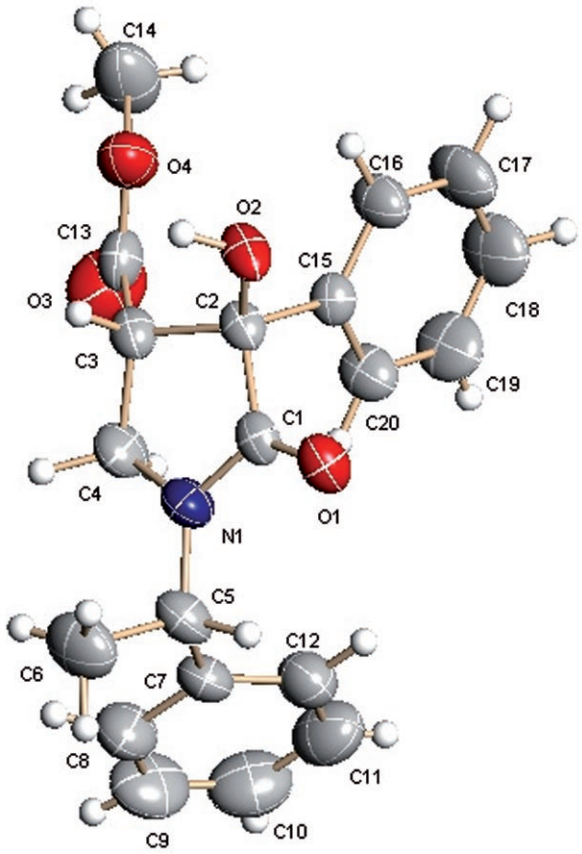


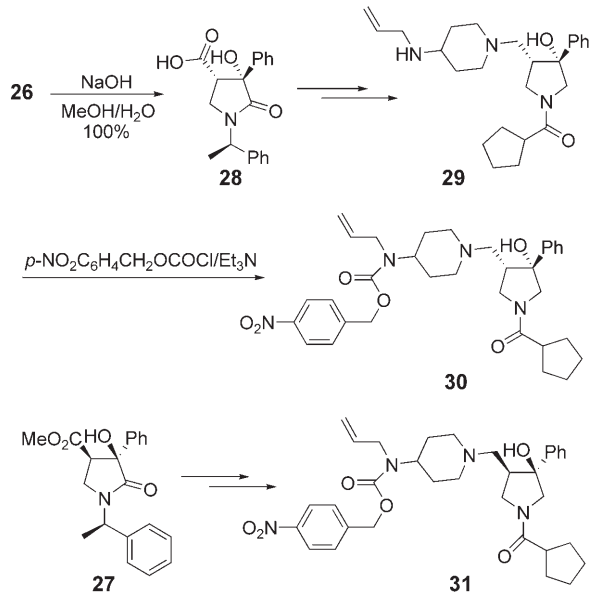
Figure 3. X-ray structure of lactam **26**.

the enantiopure pyrrolidine core is more practical because of the inexpensive starting materials and convenient procedures.

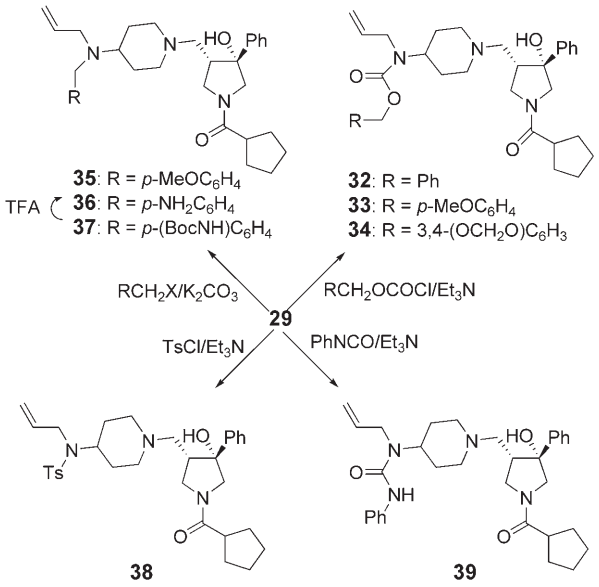
Hydrolysis of **26** with aqueous NaOH in methanol produced amino acid **28**, which was transformed to amide **29** according to the reaction sequence indicated in Scheme 3 (Scheme 5). Condensation of the secondary amine **29** with 4′-nitrobenzyl chloroformate produced carbamate **30**, the (3*R*,4*S*)-enantiomer of **23a**. Following the same procedure, carbamate **31**, the (3*S*,4*R*)-enantiomer of **23a**, was synthesized from the lactam **27**. This synthesis offered an opportunity to explore the stereochemical requirement for interaction of the present antagonists with CCR5.

To probe if the substituents on the 4-amino group of the piperidine unit could alter the antagonist activity, several analogues of **30** were assembled from the secondary amine **29** (Scheme 6). Coupling of **29** with three other chloroformates provided carbamates **32**–**34**. In addition, alkylative amination of **29** gave rise to diamines **35**–**37**. Furthermore, sulfonamide **38** and urea **39** were elaborated by reacting **29** with tosyl chloride and phenyl isocyanate, respectively.

The potencies against the CCR5 receptor of these enantiopure compounds are summarized in Table 3. Compound **30** showed the best result, having an IC_{50} of 2.9 nM, whereas its enantiomer **31** displayed much poorer activity towards the CCR5 receptor, indicated by an IC_{50} of 385.9 nM. These results clearly illustrated that the (3*R*,4*S*)-configuration of this series of



Scheme 5. Synthesis of compounds **28, 29**, **30**, and **31. 29** was synthesized according to Scheme 3



Scheme 6. Synthesis of several analogues of **30**.

Table 3. Inhibition of RANTES-stimulated [^{35}S]-GTPγS binding to CCR5-expressing CHO cell membranes by compounds **30**–**39**.

Compound	IC_{50} [nM]
30	2.9 ± 0.3
31	385.9 ± 140
32	8.75
33	4.33
34	122
35	> 1000
36	26.0
37	16.1
38	53.4
39	6.46

compounds is favored for their interaction with the CCR5 receptor.

N-Benzoxycarbonyl and *N*-(4-methyoxy)-benzoxycarbonyl-substituted compounds **32** and **33** showed slightly lower potencies compared to **30**. However, the IC_{50} value increased dramatically for *N*-(3,4-methylenedioxy)benzoxycarbonyl substituted compound **34**, indicating that the size of the carbamate moiety at the 4-aminopiperidine position is also critical for inhibition activity towards the CCR5 receptor.

Besides the carbamate substituents, attachment of substituted benzyl or tosyl groups, or a urea unit at the 4-aminopiperidine position of **29**, also led to potent antagonists (**36**–**39**). Interestingly, compound **35**, having a *N*-(4-methoxy)benzyl group, displayed poor binding affinity, whereas replacing this group with either an amino (**36**) or a *tert*-butoxycarbonylamino group (**37**), resulted in potent compounds. The existence of an additional hydrogen bond between the NH moiety and CCR5 receptor was proposed to tentatively rationalize this difference.

To interpret the structure–activity relationship of our compounds, we have studied the binding of compound **30**, the most potent one of all, to CCR5 by molecular modeling. A structural model of antagonist-bound human CCR5 has been obtained through homology modeling in our previous studies.[14,15] Experimental results from site-directed mutagenesis suggest that the binding pocket on CCR5 is located at the extracellular side of the transmembrane domain. Our model of CCR5 reveals that this binding pocket is mainly composed of conserved residues, including Tyr 37, Trp 86, Tyr 108, Phe 112, Trp 248, Tyr 251, and Glu 283, and conservatively variable residues, including Thr 105, Leu 107, Phe 112, Gly 115, Lys 197, and Met 287, on transmembrane helices 1, 2, 3, and 7 (Figure 4), which is consistent with experimental observations.[16–18]

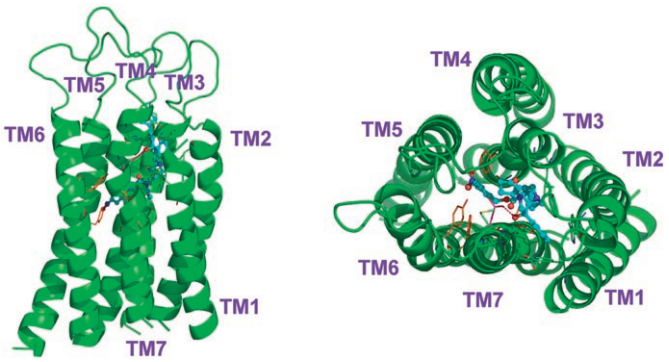


Figure 4. Compound **30** bound to CCR5: a) side view, b) top view.

In this study, binding modes of compound **30** and one of the Merck compounds (compound **6**) were predicted based on this CCR5 model through molecular docking using the Glide program.[19] Figure 5 illustrates the interactions between **30** and CCR5 in detail. Our model suggests that **30** binds to CCR5 in a basically extended conformation. Its binding to CCR5 is characterized by significant hydrophobic interactions (Figure 5 A). The nitrobenzene group on **30**, which points to the inner-cellular end of the binding pocket, is surrounded by

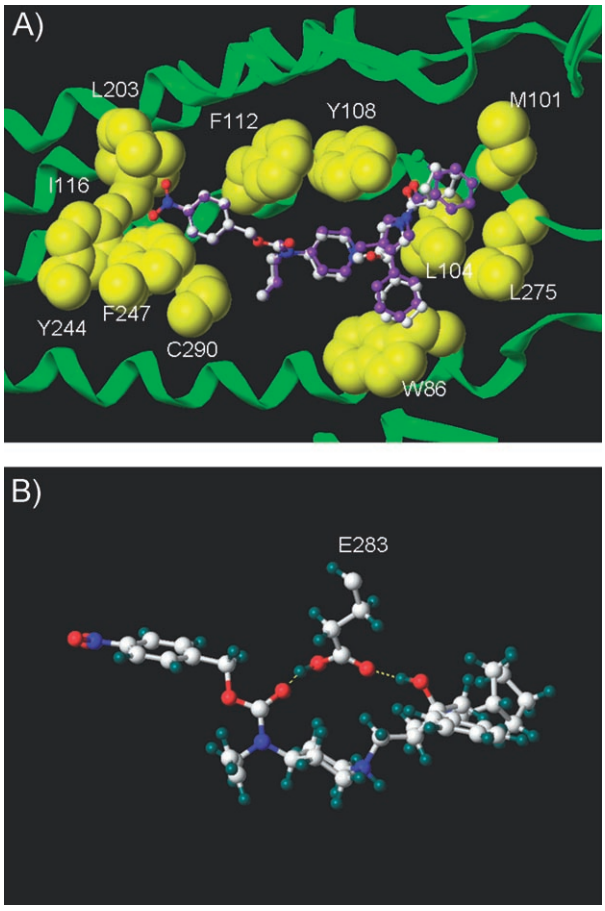


Figure 5. Interactions between compounds **30** and **6** with CCR5. a) Carbon atoms on **30** and **6** are colored in white and purple, respectively. Surrounding hydrophobic residues are presented in space-filling models in yellow. Several residues are concealed in this figure to give a clear view of **30** and **6**. b) The conserved residue Glu 283 may form a coordinated hydrogen bonding network with **30**. Hydrogen bonds are presented as dashed yellow lines.

Phe 112, Val 199, Leu 203, Phe 247, Tyr 251, and Cys 290. This explains the significantly poorer potency of compounds **15a** to **15e** as such a chemical moiety is completely missing in those compounds. Another phenyl moiety on **30** contacts with Tyr 37, Trp 86, and Met 287. Our model suggests that this phenyl moiety is basically parallel to the indole ring on Trp 86. The distance between the centers of these two ring systems is approximately 4 Å, indicating the formation of favorable π-π stacking. This explains the preference to an aromatic moiety at this position on both our compounds and the Merck compounds. Note that our model suggests that compound **30** binds to CCR5 in a basically identical manner to compound **6** as they are close analogues. A terminal cyclopentyl group on **30**, however, has replaced the original *o*-chlorophenyl group on **6**, which form favorable hydrophobic contacts with Met 100, Leu 104, Tyr 108, Leu 275, and Met 279.

The most notable polar interaction between **30** and CCR5 involves the conserved residue Glu 283. Our model suggests that the terminal carboxyl group on the side chain of Glu 283 may form hydrogen bonds simultaneously with the carbamate group and the hydroxyl group on **30** (Figure 5B). This is possible as this carboxyl group is likely to stay in neutral form because of the nonpolar environment inside the binding pocket of CCR5. According to our model, these two donor–acceptor atom pairs shown in Figure 5B are 2.5 Å and 2.8 Å long, respectively, both of which fall in a typical hydrogen bonding range. Our model indicates that changing the carbamate group to a urea group will not disturb the ligand from binding as the changed oxygen atom is not directly involved in hydrogen bonding. This can be validated by the similar potency exhibited by **32** and **39**. Compared to the Merck compounds, the hydroxyl group is a new feature on our compounds. Apparently, Glu 283 may form at most one hydrogen bond with **6**. Thus, the introduction of an additional hydroxyl group not only leads to new chemistry, but also serves nicely for the binding to CCR5 if introduced in an appropriate chirality.

The in vitro potency of compound **30** to inhibit HIV-1 entry and replication was investigated in a replication assay using PBMC (peripheral blood mononuclear cells) cultures. As summarized in Table 4, **30** inhibited the replication of seven genetically diverse, R5 HIV-1 isolates or laboratory strains in PBMC in a concentration-dependent manner with EC_{50} values ranging from 0.3 nM to 30 nM. It is noteworthy that **30** exhibited wide-spectrum potency against the replication of CCR5-using (R5) HIV-1, but had no effect on viral replication of CXCR4-using (X4) HIV-1 strain, NL4-3, in PBMC. This is similar with that shown by the other known CCR5 antagonists possessing anti-HIV activity. Importantly, **30** also showed potent antiviral activity against a multidrug-resistant strain named J18. Besides 5 subtype A and B strains, both subtype C strain 93IN109 and subtype O strain CA9 were sensitive to **30** with EC_{50} values of less than 2 nM. Thus, we concluded that the compound **30** was a potent inhibitor against CCR5-dependent HIV-1 replication.

Table 4. Antiviral activity of compound **30** against different HIV-1 subtypes in PBMC[a]

HIV-1 strain	HIV-1 subtype Clade/ origin	Coreceptor use	EC_{50} [nM]
JRFL	B	R5	30.6 ± 11.0
HNz2	B	R5	4.70 ± 1.20
20678	B	R5	2.80 ± 1.50
NL4-3	B	X4	>1000
J18[b]	B	R5	0.76 ± 0.03
TK1135		R5	8.40 ± 5.10
93IN109	C	R5	1.90 ± 1.20
CA9	O	R5	0.30 ± 0.10

[a] The EC_{50} of compound **30** was calculated from the inhibition of p24 Ag production, as measured by p24 ELISA on the cell culture supernatant at the day 7 after infection. [b] J18 is a R5 tropic multi-resistant strain: resistant to PI (L10I, M36I, L63P, A71T, L90M) and RTI (M41L, E44D, T69D, V108I, V118I, L210W, T215D).

In pharmacokinetic studies in rat and dog, compound **30** was found to possess a favorable pharmacokinetic profile. The pharmacokinetic properties are summarized in Table 5. Compound **30** was administered orally to rats (10 mg kg^{-1}) and dogs (3.0 mg kg^{-1}) and was absorbed well by both species. In

Table 5. Rat and dog pharmacokinetics.

	Rat[a]	Dog[b]
Dose [mg kg^{-1}]	10	3
CL/F [mL min^{-1} kg^{-1}]	244.6	220.4
V_z/F [L kg^{-1}]	37.7	68.4
C_{max} [ng mL^{-1}]	305	83.3
$t_{1/2}$ [h]	1.58	3.62
% F	41.2	21.6

[a] Average data generated after 10 mg kg^{-1} po and 10 mg kg^{-1} iv doses in $n=8$ animals/dose. [b] Average data generated after 3 mg kg^{-1} po and 3 mg kg^{-1} iv doses in $n=8$ animals/dose.

both animals, oral bioavailability of compound **30** was assessed and determined to be 41.2% and 21.6%, respectively. The difference in bioavailability was probably due to the different oral absorption of the two species. The maximum plasma concentrations achieved in both species were in excess of the antiviral activity, with EC_{50} values ranging from 0.177 ng mL^{-1} (0.3 nM) to 17.7 ng mL^{-1} (30 nM), determined by replication assays in vitro.

In conclusion, we have found a class of 1,3,3,4-tetrasubstrituted pyrrolidines, which are potent CCR5 antagonists. Compound **30** was selected for further evaluation. The molecule displayed highly potent and selective inhibition of CCR5-dependant HIV-1 replication. Pharmacokinetic studies revealed that this compound was orally available in both rats and dogs. Taken together, we concluded that compound **30** should be a promising drug candidate for treatment of HIV-1 infection. Its clinical studies are being pursued and the results will be disclosed in due course.

Acknowledgements

The authors are grateful to the Minstry of Sciences, Chinese Academy of Sciences, National Natural Science Foundation of China (grant 20321202), and Science and Technology Commission of Shanghai Municipality for their financial support.

Keywords: antagonists · anti-HIV · CCR5 receptor · enantioselectivity · heterocycles

[1] For reviews, see: a) D. C. Meadows, J. Gervay-Hague, *ChemMedChem* **2006**, *1*, 17 – 29; b) E. D. Clercq, *J. Med. Chem.* **2005**, *48*, 1297 – 1313.

[2] For reviews, see: a) A. Palani, J. R. Tagat, *J. Med. Chem.* **2006**, *49*, 2851 – 2857; b) Z. Gao, W. A. Metz, *Chem. Rev.* **2003**, *103*, 3733 – 3752.

[3] M. Baba, O. Nishimura, N. Kanzaki, M. Okamoto, H. Sawada, Y. Iizawa, M. Shiraishi, Y. Aramaki, K. Okonogi, Y. Ogawa, K. Meguro, M. Fujino, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 5698 – 5703.

[4] A. Wood, D. Armour, *Prog. Med. Chem.* **2005**, *43*, 239 – 271.

[5] J. M. Strizki, C. Tremblay, S. Xu, L. Wojcik, N. Wagner, W. Gonsiorek, R. W. Hipkin, C.-C. Chou, C. Pugliese-Sivo, Y. Xiao, J. R. Tagat, K. Cox, T. Priestley, S. Sorota, W. Huang, M. Hirsch, G. R. Reyes, B. M. Baroudy, *Antimicrob. Agents Chemother.* **2005**, *49*, 4911 – 4919.

[6] K. Maeda, K. Yoshimura, S. Shibayama, H. Habashita, H. Tada, H. Sagwa, T. Miyakawa, M. Aoki, D. Fukushima, H. Mitsuya, *J. Biol. Chem.* **2001**, *276*, 35 194 – 35 200.

[7] K. Takashima, H. Miyake, N. Kanzaki, Y. Tagawa, X. Wang, Y. Sugihara, Y. Iizawa, M. Baba, *Antimicrob. Agents Chemother.* **2005**, *49*, 3474 – 3482.

[8] a) J. J. Hale, R. J. Budhu, S. G. Mills, M. MacCoss, L. Malkowitz, S. L. Gould, M. S. Springer, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1437 – 1440; b) J. J. Hale, R. J. Budhu, E. B. Holson, P. E. Finke, B. Oates, S. G. Mills, M. MacCoss, S. L. Gould, J. A. DeMartino, M. S. Springer, S. Siciliano, L. Malkowitz, W. A. Schleif, D. Hazuda, M. Miller, J. Kessler, R. Danzeisen, K. Holmes, J. Lineberger, A. Carella, G. Carver, E. Emini, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2741 – 2745.

[9] C. L. Lynch, J. J. Hale, R. J. Budhu, A. L. Gentry, S. G. Mills, K. T. Chapman, M. MacCoss, L. Malkowitz, M. S. Springer, S. L. Gould, J. A. DeMartino, S. Siciliano, M. A. Cascieri, A. Carella, G. Carver, K. Holmes, W. A. Schleif, R. Danzeisen, D. Hazuda, J. Kessler, J. Lineberger, M. Miller, E Emini, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3001 – 3004.

[10] D. Ma, J. Jiang, *Tetrahedron: Asymmetry* **1998**, *9*, 575 – 579.

[11] W. Zhang, J. Naveno, B. Haribadu, H. Tamamura, K. Hiramatu, A. Omagari, G. Pei, J. P. Manfredi, N. Fujii, J. R. Broach, S. C. Peiper, *J. Biol. Chem.* **2002**, *277*, 24 515 – 24 521.

[12] P. E. Finke, L. C. Meurer, B. Oates, S. G. Mills, M. MacCoss, L. Malkowitz, M. S. Springer, B. L. Daugherty, S. L. Gould, J. A. DeMartino, S. Siciliano, A. Carella, G. Carver, K. Holmes, R. Danzeisen, D. Hazuda, J. Kessler, J. Lineberger, M. Miller, W. A. Schleif, E. Emini, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 265 – 270.

[13] D. Basavaaiah, T. K. Bharathi, V. V. L. Gowriswari, *Tetrahedron Lett.* **1987**, *28*, 4351 – 4352.

[14] Y. Xu, H. Liu, C. Niu, C. Luo, X. Luo, J. Shen, K. Chen, H. Jiang, *Bioorg. Med. Chem.* **2004**, *12*, 6193 – 6208.

[15] X. Huang, H. Jiang, X. M. Luo, K. X. Chen, R. Y. Ji, Y. Cao, G. Pei, *Acta Pharmacol. Sin.* **2000**, *21*, 521 – 528.

[16] T. Dragic, A. Trkola, D. A. Thompson, E. G. Cormier, F. A. Kajumo, E. Maxwell, S.-W. Lin, W, Ying, S. O. Smith, T. P. Sakmar, J. P. Moore, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 5639 – 5644.

[17] F. Tsamis, S. Gavrilov, F. Kajumo, C. Seibert, S. Kuhmann, T. Ketas, A. Trkola, A. Palani, J. W. Clader, J. R. Tagat, S. McCombie, B. Baroudy, J. P. Moore, T. P. Sakmar, T. Dragic, *J. Virol.* **2003**, *77*, 5201 – 5208.

[18] M. Nishikawa, K. Takashima, T. Nishi, R. A. Furuta, N. Kanzaki, Y. Yamamoto, J. Fujisawa, *Antimicrob. Agents Chemother.* **2005**, *49*, 4708 – 4715.

[19] Glide (version 2.5) in the First Discovery suite, Schrödinger Inc., New York, **2003**.

Received: July 23, 2006
Published online on December 13, 2006

