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Facile synthesis of 4-substituted-4-aminopiperidine derivatives, the key building block of piperazine-based CCR5 antagonists

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Abstract—4-Substituted-4-aminopiperidine is an interesting structural motif found in a number of bioactive compounds. An efficient and convenient method for the synthesis of 4-differently substituted-4-aminopiperidine derivatives was described, employing isonipecotate as a starting material and Curtius rearrangement as a key step. The alkylation of isonipecotate could introduce various substituents at the 4-position of the piperidine ring. With this key building block, we are able to efficiently synthesize piperazino-piperidine based CCR5 antagonist in a highly convergent manner free of using toxic reagents such as diethylaluminum cyanide. The concise synthesis of a potent bioavailable CCR5 antagonist as HIV-1 entry inhibitor, Sch-350634 (**1**) was accomplished in excellent yield using *N*′-Boc-4-methyl-4-aminopiperidine **5a** as a smart building block. The new methodology provides a facile and practical access to the piperazino-piperidine amide analogs as HIV-1 entry inhibitors.

1. Introduction

Interest in 4-subtituted-4-aminopiperidine derives from the varied biological activity of this structural motif containing compounds, which were evaluated as narcotic analgesics,[1] muscarinic M_3 receptor antagonists,[2] neurokinin-1 receptor ligands,[3] 5-HT_{2A} serotonin receptor antagonists,[4] and CCR5 chemokine receptor ligands.[5] Among them, the most attractive pharmacological class is the piperidine-based CCR5 antagonists, as exemplified by the compounds in Figure 1. CCR5, a co-receptor essential for HIV-1 recognition and entry into CD4+ macrophages and T-cells,[6] is a highly validated target for the treatment of HIV-1 infection.[7] A proof of concept for this approach has been provided by Sch-C and Sch-D, two CCR5 receptor antagonists as HIV-1 entry inhibitors under clinical trials.[8]

Currently, piperidine- and piperazine-based compounds disclosed by Schering–Plough Research Institute are an attractive and promising class of potent CCR5 antagonists.[5] As part of our program to further refine compounds in the two families for improved potency, higher selectivity, and good ADME properties, development of convenient synthesis of the structurally diverse piperazino-piperidine amide analogs in laboratory is required. With *N*′-Boc-4-substituted-4-aminopiperidine as a key building block, we established an efficient and short synthesis of the piperazino-piperidine core structure in a convergent manner. Herein we would like to report our newly developed methodology to synthesize 4-subtituted-4-aminopiperidine derivatives and its typical application in the concise synthesis of a potent, orally-active CCR5 antagonist, Sch-350634 (**1**).

2. Results and discussion

According to the literature, three approaches were reported to prepare the 4-substituent-4-aminopiperidine derivatives starting from 4-piperidone. One method involved the Ritter reaction as the key step (large amount of concd H_2SO_4 is needed),[1b,9] the second employed highly toxic cyanide reagent in the Strecker amino nitrile synthesis followed by a hydration,[3a,10] and the third required nucleophilic addition of alkylmagnesium bromide (the type of alkyl group is limited) to the in situ-generated imine from the condensation of the *N*-Boc-4-piperidone with amine.[11]

Keywords: 4-Substituted-4-aminopiperidine; Piperazine-based CCR5 antagonist; Curtius rearrangement; Building block; Convergent synthesis; HIV-1 entry inhibitor.
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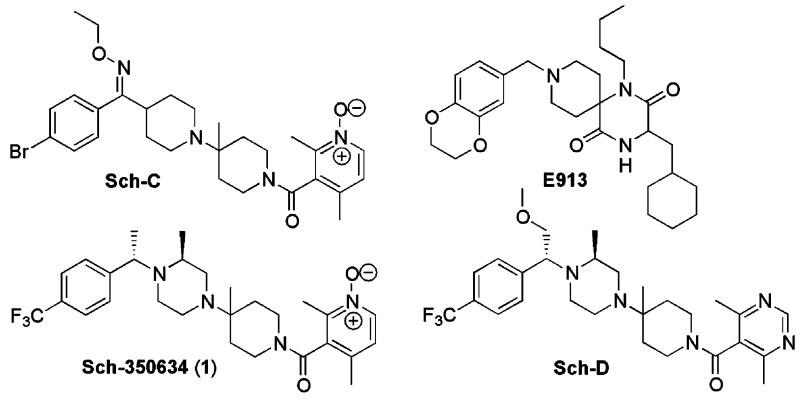


Figure 1. Piperidine- and piperazine-based CCR5 antagonists.

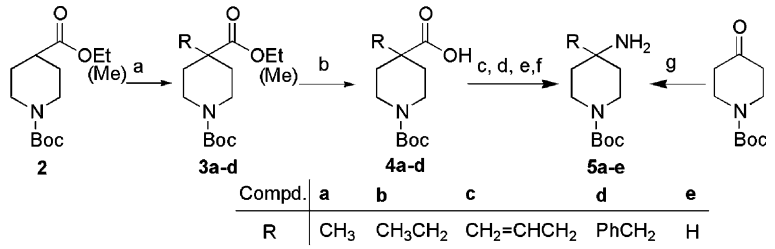
The versatile building block requires a reliable route to an orthogonally-protected piperidine suitably for different synthetic strategy toward various bioactive molecules containing the scaffold of 4-substituent-4-aminopiperidine. Therefore, we developed a new methodology to generate orthogonally-protected 4-substituent-4-aminopiperidine conveniently from commercially available isonipecotic acid, with flexible substitution at the 4-position of the piperidine ring.

As shown in Scheme 1, isonipecotic acid was protected under standard conditions to give *N*-Boc-isonipecotate (**2**) in excellent yield. Introduction of various group at the 4-position was achieved via alkylation of the lithium enolate with either alkyl or aryl halide in THF. The resulting *N*-Boc-4-substituted-isonipecotic acid ethyl ester **3a** was hydrolyzed to give the corresponding acid **4a** using 2 N lithium hydroxide in methanol at room temperature. For the hydrolysis of 4-substituted isonipecotic acid methyl ester **3b–d**, it was found more effective to use 2 N potassium hydroxide in refluxing methanol. Conversion of the acid to the desired product *N*′-Boc-4-substituent-4-aminopiperidine **5** proceeded smoothly via Curtius rearrangement with 4 operations in one pot.[12,13] First, *N*-Boc-4-substituted-isonipecotic acid **4** was activated by forming mixed anhydride with isobutyl chloroformate in basic condition. Then, treatment of the resulting anhydride with sodium azide followed by thermolysis in toluene afforded the *N*-Boc-4-substituent-4-isocyanate, which was hydrolyzed in strong basic conditions to furnish the orthogonally-protected 4-substituent-4-aminopiperidine **5**. The overall yield of the four steps could reach up to 89%. Initial attempts to hydrolyze the isocyanate in 2 N NaOH resulted in the formation of a symmetrical urea as a major product. We increased the concentration of KOH aqueous solution till 10 N and harvested the desired amine product.[13]

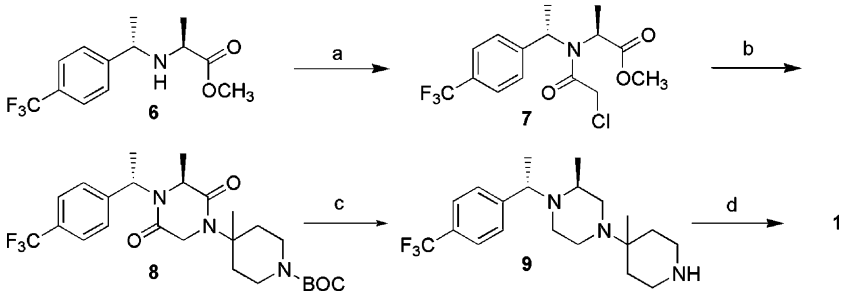
We also developed an operationally simple, high-yield approach for the synthesis of *N*′-Boc-4-aminopiperidine **5e**, not having a 4-substituent. This widely-used synthon was readily prepared by a facile reductive amination of commercially available *N*-Boc-piperidone with H_2 and catalytic 10% Pd–C in the NH_3-saturated methanol in yield of 84%.

Compared to those previously reported procedures, the newly developed methodology is flexible and allows for preparing a variety of 4-aminopiperidine derivatives with different functional group at 4-position of the piperidine ring and orthogonal protecting group at the *N*′ position. To our knowledge, this is the most versatile and facile approach to the synthesis of 4-substituent-4-aminopiperidine derivatives reported to date, and the suitably protected *N*′-Boc-4-methyl-4-aminopiperidine is a very useful building block for the syntheses of piperazino-piperidine containing CCR5 antagonists.

The literature-reported synthesis of the aryl piperazino-piperidine amide analogs as CCR5 antagonists was accomplished via S_N2 displacement route or diketopip-



Scheme 1. General synthetic scheme of the versatile building block, *N*′-Boc-4-substituted-4-aminopiperidine. Reagents and conditions: (a) LDA, −78 °C, CH_3I or RBr, THF; (b) 2 N LiOH CH_3OH, rt or 2 N KOH, reflux (for **3b–d**); (c) $ClCOO^iBu$, NMM, THF, −15 °C, 1 h; (d) NaN_3, THF–H_2O, −15 °C, 1 h then rt overnight; (e) toluene, 90 °C, 1.5 h; (f) 10 N KOH, THF–H_2O, 0 °C; (g) H_2, 10% Pd/C, NH_3/CH_3OH, rt, 84.0%.



Scheme 2. Convergent synthesis of Sch-350634 (**1**), a potent and orally active CCR5 antagonist employing *N*′-Boc-4-methyl-4-aminopiperidine (**5a**) as a building block. Reagents and conditions: (a) $ClCH_2COCl$, 1,2-dichloroethane, reflux, 96%; (b) (i) **5a**, DIPEA, CH_3CN, reflux, 80%; (ii) catalytic 2-pyridinol, toluene, 90 °C, 84%; (c) (i) TFA, CH_2Cl_2, rt; (ii) $NaBH_4$, $BF_3{\cdot}Et_2O$, dimethoxy ethane, reflux; (d) 2,4-dimethylnicotinic acid-*N*-oxide, EDCI, HOBT, DIPEA, CH_2Cl_2, rt, overall yield of 47% (three steps for c and d).

erazine route,[14,15] in which the piperazino-piperidine nucleus was constructed by a linear synthetic strategy and the pharmacophore group at 4-position of the piperidine was introduced by a modified Strecker reaction using toxic diethylaluminum cyanide.

With *N*′-Boc-4-substituent-4-aminopiperidine in hand, we envisioned that the backbone of piperazino-piperidine series CCR5 antagonists could be assembled in a highly convergent manner via a nucleophilic substitution followed by a lactamization of chloro-substituted acetyl methyl ester **7** with this key building block **5**. A convergent synthesis of the potent and orally active CCR5 antagonist of Sch-350634 (**1**) (Scheme 2) was taken as an example to demonstrate the general procedure to prepare structurally diverse piperidino-piperazine amides with building block **5**.

According to Scheme 2, compound **6**, which was prepared following a literature precedent,[14,15] was treated with 2-chloroacetyl chloride in refluxing 1,2-dichloroethane to give the corresponding (2-chloroacetyl)-amino-acetic acid methyl ester **7** in yield of 96%. The nucleophilic substitution of **7** with the free amine of the building block **5a** followed by an intramolecular N-acylation reaction in the presence of catalytic 2-pyridinol afforded the aryl diketopiperazino-piperidine **8** in an overall yield of 67.2%.[16] It was noted that the product of the nucleophilic displacement in the refluxing methanol could not undergo the subsequent intramolecular cyclization simultaneously under the same reaction condition. We isolated the intermediate and heated it with catalytic 2-pyridinol in toluene at 90 °C for 6 h to produce the diketopiperazine product **8** as a single stereoisomer.[17] Boc removal with trifluoroacetic acid and subsequent reduction with $NaBH_4$ gave the aryl piperazino-piperidine analog **9**. The coupling of the resulting free amine **9** with the desired aromatic acids proceeded under standard conditions to furnish the desired product **1**.[18] Obviously, by using 4-methyl-piperidin-4-ylamine as a key synthon, we simplify the construction of the nucleus of the piperazino-piperidine amide analogs via one step reaction, furthermore, our developed methodology is devoid of the highly toxic and flammable reagent such as diethylaluminum cyanide employed by the Schering–Plough's modified Strecker reaction, and provides potential for convenient introduction of various substituents at the important 4-position of the piperidine.

3. Conclusion

In summary, we have developed a new method to synthesize a series of 4-substituted-4-aminopiperidine derivatives employing commercially available isonipecotate as a starting material and Curtius rearrangement as a key step. The key building block was successfully applied to an efficient synthesis of piperazino-piperidine based CCR5 antagonist in a highly convergent manner free of using toxic reagents such as diethylaluminum cyanide. The concise synthesis of a potent bioavailable CCR5 antagonist as HIV-1 entry inhibitor, Sch-350634 (**1**) was accomplished in excellent yield using *N*′-Boc-4-methyl-4-aminopiperidine **5a** as a smart building block. The newly developed methodology provides us with a facile and practical access to the structurally diverse piperazino-piperidine compounds as CCR5 antagonists, thus potentially benefits the development of the HIV-1 entry inhibitors into new anti-AIDS drugs.

Acknowledgements

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16. The typical procedure to prepare the key intermediate **8**: Compound **7** (0.221 g, 0.63 mmol), *N*′-Boc-4-methyl-4-aminopiperidine (0.148 g, 0.69 mmol), and DIPEA (0.20 mL, 1.16 mmol) in CH_3CN (5.0 mL) was refluxed overnight and the solvent was removed under reduced pressure. The residue was purified by chromatography using PE/EtOAc (1:1) as eluent to give the mono-substituted product as oil (0.265 g, yield 80.0%). The mono-substituted intermediate (0.265 g, 0.50 mmol) and 2-hydroxy-pyridine (0.04 g, 0.36 mmol) were dissolved in dry toluene (1.5 mL) and stirred at 90 °C for 6 h. After the removal of the solvent, the residue was purified by chromatography using PE/EtOAc (1:1) as eluent to give compound **8** as white solid (0.209 g, yield 84%). $[\alpha]_D^{20}$ −19 (*c* 0.565, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, 2H, $J = 8.0$ Hz); 7.36 (d, 2H, $J = 8.0$ Hz); 5.82 (q, 1H, $J = 6.8$ Hz); 4.06 (AB, 1H, $J = 16.8$ Hz); 3.91 (AB, 1H, $J = 16.8$ Hz); 3.64 (q, 1H, $J = 7.2$ Hz); 3.59–3.48 (m, 2H); 3.26–3.11 (m, 2H); 2.44–2.39 (m, 1H); 2.26–2.21 (m, 1H); 1.79–1.68 (m, 2H); 1.65 (d, 3H, $J = 6.8$ Hz); 1.47 (d, 3H, $J = 7.0$ Hz); 1.46 (s, 9H); 1.36 (s, 3H). EI-MS (*m*/*z*, %): 497 (M^+, 6.0). IR (KBr): 3400, 2980, 2862, 1684, 1653, 1414, 1327, 1140, 1173 cm^{-1}.
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18. The physicochemical data for the synthetic **1**: $[\alpha]_D^{20}$ +9.08 (*c* 0.93, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (d, 1H, $J = 6.6$ Hz); 7.53 (m, 4H); 7.00 (d, 1H, $J = 6.9$ Hz); 4.22 (br t, 1H); 3.98 (br s, 1H); 3.40 (m, 2H); 2.99 (m, 2H); 2.64–2.57 (m, 1H); 2.46 (d, 3H, $J = 9.9$ Hz); 2.41–2.27 (m, 3H); 2.26 (d, 3H, $J = 9.0$ Hz); 2.01 (br t, 1H); 1.82–1.72 (m, 2H); 1.46–1.25 (m, 3H); 1.29 (d, 3H, $J = 6.9$ Hz); 1.14 (d, 3H, $J = 6.3$ Hz); 0.93 (s, 3H). ESI-MS (*m*/*z*, %): 519.2 (M^++H, 100.0), 541.3 (M^++Na, 37.0).