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Pyrrolidinyl phenylurea derivatives as novel CCR3 antagonists

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ABSTRACT

Optimization starting with our lead compound **1** (IC_{50} = 4.9 nM) led to the identification of pyrrolidinyl phenylurea derivatives. Further modification toward improvement of the bioavailability provided (*R*)-1-(1-((6-fluoronaphthalen-2-yl)methyl)pyrrolidin-3-yl)-3-(2-(2-hydroxyethoxy)phenyl)urea **32** (IC_{50} = 1.7 nM), a potent and orally active CCR3 antagonist.

CC chemokine receptor 3 (CCR3) is an eotaxin receptor that appears predominantly on eosinophils. It is believed that antagonism of CCR3 on eosinophils prevents the release of lipid mediators, cytotoxic proteins, oxygen metabolites, and cytokines, all of which have potential to produce the clinical manifestations of inflammatory disease. A selective CCR3 antagonist that suppresses the infiltration of eosinophils into inflammatory sites may have clinical potential for treatment of allergic diseases such as asthma.[1–10]

Previous reports from our joint research project detailed the discovery of potent amide or urea series of CCR3 antagonists with a 6-fluoronaphthalenyl methyl moiety.[11–15] In these studies, the urea-based series displayed different structure–activity relationships from the amide. In our latest Letter,[15] we described the potent lead **1** (IC_{50} = 4.9 nM) as shown in Figure 1,[16] a small molecule CCR3 antagonist with a urea moiety. However, this compound exhibited poor bioavailability in cynomolgus monkeys (1.7%). This Letter will describe the results of our investigation into improvement of the potency and bioavailability of **1**.

To improve bioavailability while maintaining CCR3 inhibitory activity, it is important to identify which part of the molecule is suitable for structural transformation. Our previous research revealed key pharmacophores for CCR3 inhibitory activity, as shown in Figure 1.[13] One pharmacophore is a basic nitrogen atom in the center of the molecule, and the other pharmacophores are two aryl rings, a 6-fluoronaphthalene moiety and nitroaniline ring at the other terminal. To improve the bioavailability of our CCR3 antagonists, the linker part of the molecule, that is, the substructure exclusive of the key pharmacophores, should be changed.

It was considered what structural changes might be acceptable to the linker of the CCR3 antagonist. Based on crystal X-ray analysis of **2**, our potent amide-based CCR3 antagonist,[11] we selected various linkers that might make the molecule take a U-shaped conformation like that of **2** (Fig. 2). The stable conformations of structures designed by chemists were estimated using the conformational search functions of Molecular Operating Environment (MOE): LowModeMD and MMFF94x.[18] Several scaffolds that might take a U-shaped conformation with energy not more than 0.5 kcal/mol above the global minimum energy, were selected and synthesized.

The syntheses of **3**–**5** are displayed in Scheme 1. Alkylation of alpha-position of ester **6**, protecting its amine with a Boc group, yielded **7**. Substitution of chloride in **7** with an azide group and subsequent cyclization with hydrogenation of the azide group

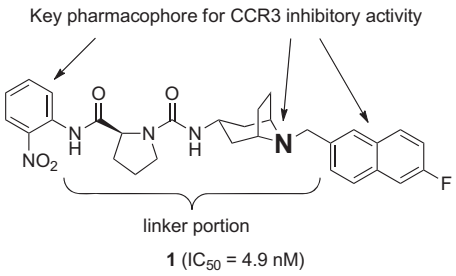

Figure 1. Structure of compound **1**.

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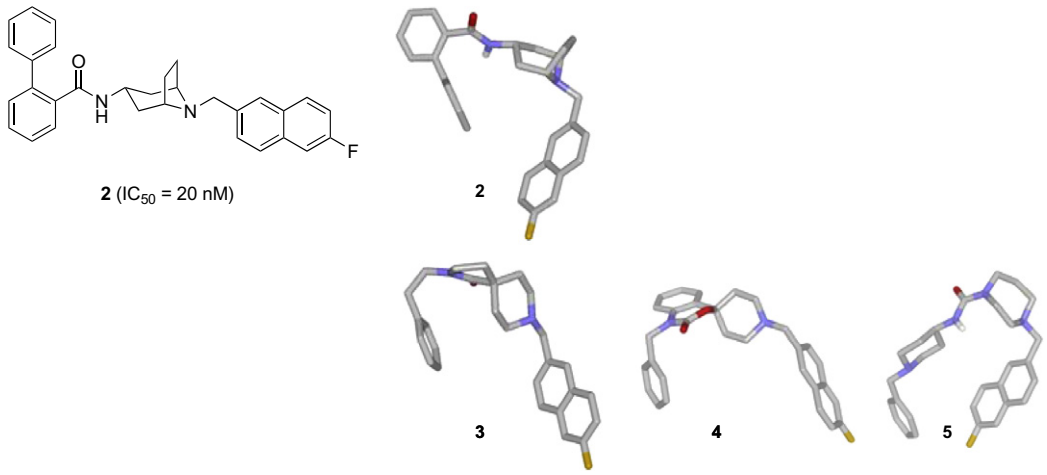
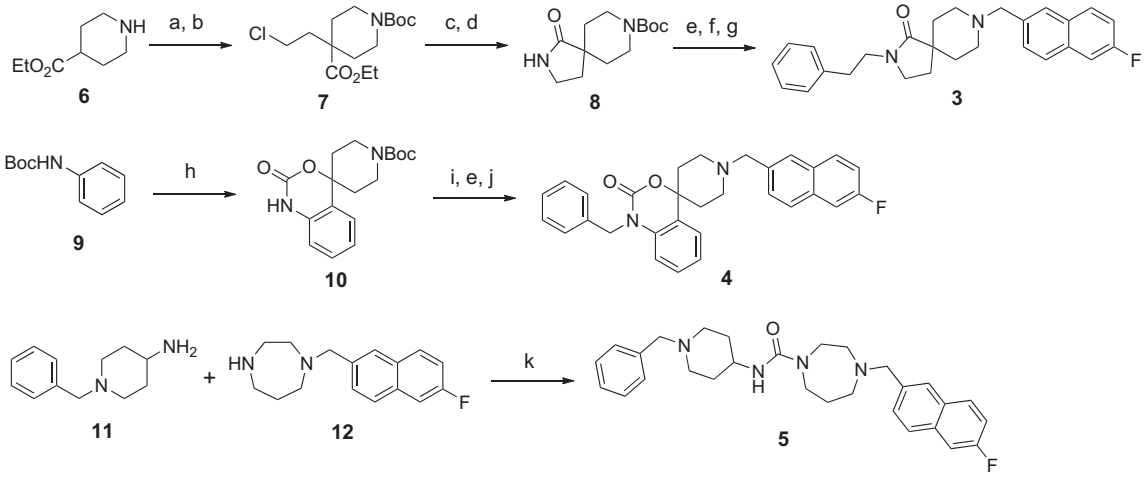
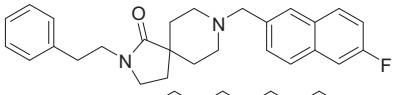
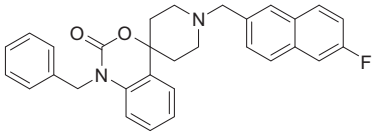
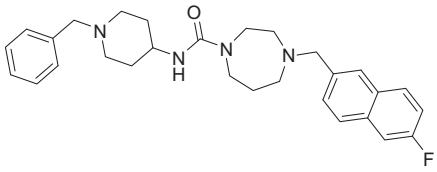


Figure 2. Global minimum structure of compound **2**, and conformations with energy not more than 0.5 kcl/mol above the global minimum energy of **3**–**5**.



Scheme 1. Reagents and conditions: (a) Boc_2O, Et_3N, THF, H_2O, 81%; (b) LDA, THF, −78 °C, then 1-bromo-2-chloroethane, rt, 67%; (c) NaN_3, DMF, 90 °C; (d) H2, 10% Pd-C, EtOH, 73% (2 steps); (e) TFA, CH_2Cl_2; (f) 2-(bromomethyl)-6-fluoronaphthalene, K_2CO_3, DMF, 36% (2 steps); (g) NaH, (2-bromoethyl)benzene, NaI, DMF, 6.0%; (h) *tert*-BuLi in pentane, THF, −78 to −20 °C, then 1-boc-4-piperidone, −78 °C to rt, 45%; (i) NaH, DMF, then BnBr; (j) 2-(bromomethyl)-6-fluoronaphthalene, K_2CO_3, DMF, 43% (3 steps); (k) $ClCO_2p$–NO_2Ph, $NaHCO_3$, CH_2Cl_2, then 12, Et_3N, 83%.

Table 1
CCR3 inhibiting activity of compounds **3**–**5** possessing U-shaped conformation

Compds	Structure	IC_{50} (nM)
3		600
4		20000
5		380

resulted in **8**. Removal of the Boc group of **8**, followed by alkylation with 2-(bromomethyl)-6-fluoronaphthalene and then (2-bromoethyl)benzene, yielded the spiro compound **3**. Spiro-benzoxazine derivative **10** was prepared from **9** using a previously reported method.[19] Compound **10** was converted into **4** via benzylation, followed by deprotection of the amino group and alkylation. Homopiperazine **5** was synthesized by urea coupling of **11** with amine **12**. The CCR3 inhibitory activity data for **3**–**5** are listed in Table 1. Spiro derivative **3** (IC_{50} = 600 nM), spiro-benzoxazine derivative **4** (IC_{50} = 2000 nM), and homopiperazine derivative **5** (IC_{50} = 380 nM), all had U-shaped linkers. Among these, **5** exhibited promising CCR3 inhibitory activity and it was synthesized via a simple method.

The synthetic methods of derivatives of **5** in the following optimization are shown in Scheme 2. Sulfonamidation of amine **14** with sulfonyl chloride **13**, followed by dechlorination by hydrogenation yielded deprotected product **15** and protected product **16** at 20% and 33%, 'respectively'. Urea coupling of **15** with amines **12** or **18** afforded **17** or **19**.[14] Compound **21** was converted from **20** via urea coupling with **18** and subsequent deprotection and mesylation of the amino group. Amine **22** and aniline **24** were used in place of **20** as the starting materials for compounds **23** and **25**, 'respectively'.

First, the benzyl moiety of **5** was modified to improve inhibitory activity (Table 2). Consequently, **17**, bearing a hydroxyphenyl