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Urea based CCR3 antagonists employing a tetrahydro-1,3-oxazin-2-one spacer

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ABSTRACT

Conformational restriction of open chain analogs with a more polar tetrahydro-1,3-oxazin-2-one spacer led to the identification of potent urea-based CCR3 antagonists that exhibited excellent selectivity over binding to CYP2D6. The in vitro binding and eosinophil shape change data are presented. Compound **19b** exhibited similar selectivity and potency to our development candidate BMS-639623.

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Accumulation of pulmonary eosinophils is one of the hallmarks of allergic asthma,[1] and the number of eosinophils is often correlated with disease severity.[1,2] Although the pathophysiological role of the eosinophil remains enigmatic, studies in both humans[3] and mice[4] have suggested that this leukocyte likely participates in remodeling of the asthmatic airway. CC Chemokine Receptor 3 (CCR3) serves as the primary chemokine receptor[5] on eosinophils and, together with its ligands, mediates both the migration and activation of eosinophils.[6] Several independent studies with CCR3-deficient mice have confirmed the central role of CCR3 in governing eosinophilia in murine models of asthma.[7] Moreover, human genetic studies have suggested that the primary CCR3 ligand (eotaxin-1) plays a role in human asthma.[8] Given these results, numerous researchers have pursued the discovery and development of selective CCR3 antagonists for the treatment of allergic asthma.[9]

Colleagues in our laboratories recently described the discovery of DPC168 (**A**, Fig. 1) as a picomolar antagonist of CCR3 with pharmacokinetics suitable for clinical development.[10] Subsequent to this, we described our efforts to improve the selectivity of this series of urea-based CCR3 antagonists relative to inhibition of the 2D6 isoform of human cytochrome P-450 (CYP2D6) by reducing the lipophilicity of the central ring (see piperidine **B**, Fig. 1)[11] or by replacing the central ring with an acyclic chain substituted with polar groups (**C** and **D**, Fig. 1).[12] These latter studies led to the identification of BMS-639623 (**C**, Fig. 1) as a backup candidate for clinical development in asthma. We reasoned that combining the structural features inherent in the central linking moieties of **A**–**D** in the form of tetrahydro-1,3-oxazin-2-ones (hereafter 'oxazolidinones'; see **E**, Fig. 1) should provide an alternative series of urea-based CCR3 antagonists with improved selectivity over CYP2D6 inhibition. In this Letter, we describe the synthesis, in vitro binding and functional profiles of this new oxazolidinone-linked series of CCR3 antagonists.

We envisioned that oxazolidinones of type **E** (Fig. 1) can be synthesized from the known[13] ethyl ester **3a**. However, attempted hydrolysis of **3a** under mild conditions did not yield the desired acid **4** (Scheme 1), presumably due to the base-lability of **3a**.[14] In order to avoid base-mediated decomposition, the *tert*-butyl ester **3b** was prepared in a fashion analogous to literature protocol, starting with *t*-Bu acrylate (Scheme 1). The relative stereochemistry of the vinyl and ester moieties in **3b** was assigned based on the literature precedent,[13] and was not unambiguously confirmed (vide infra). Deprotection of the *tert*-butyl ester provided the racemic acid **4** in high yield. However, Curtius rearrangement proceeded in poor yield, presumably due to the basic conditions and high temperature employed during the reaction.[15] Ozonolysis of the double bond, followed by reductive workup, afforded the aldehyde, which was subjected to reductive amination with known amines (**6**, **7a**, **7b**)[10,16] to provide the amino-oxazolidinones **8**. Carbamate deprotection, followed by coupling of the nascent amine with known phenyl carbamates (**9**, **10**)[10,12] afforded the original target compounds **11–13**.

Because of the apparent base sensitivity of oxazolidinone **4**—presumably due to the labile hydrogen atom alpha to the acid moiety—we decided to quarternize this carbon atom by incorporating a methyl group, with the aim of increasing the yield during the

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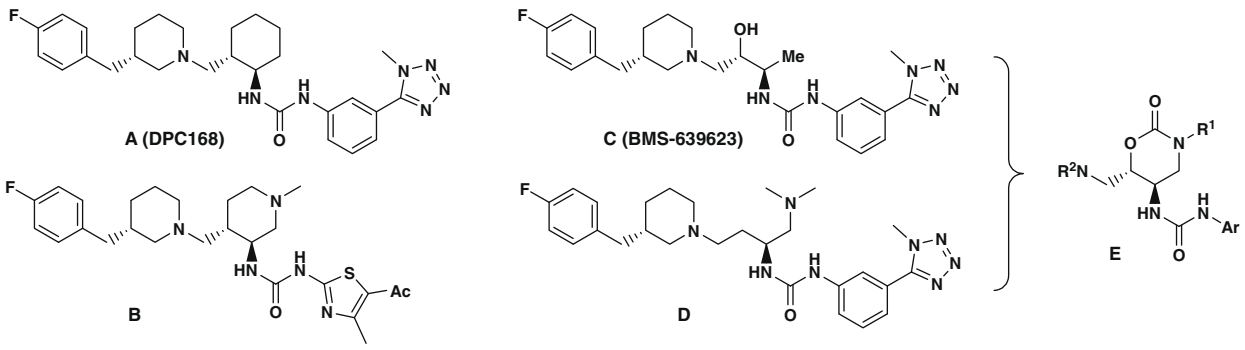
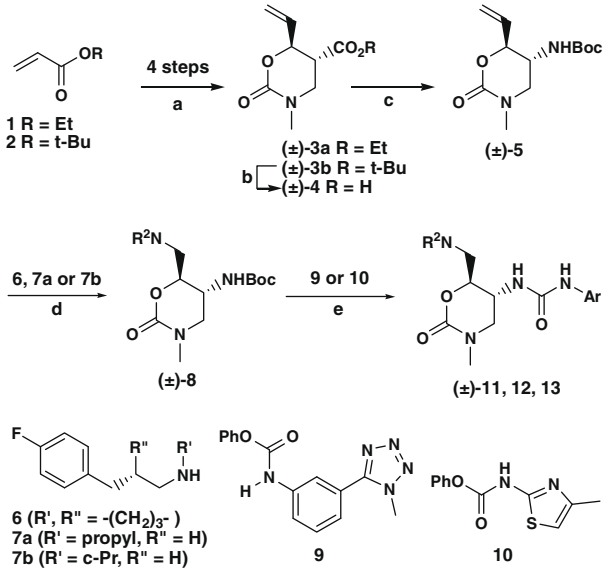


Figure 1. Previous members of the urea-based class of CCR3 antagonists provide precedent for the use of tetrahydro-1,3-oxazin-2-one as a spacer.

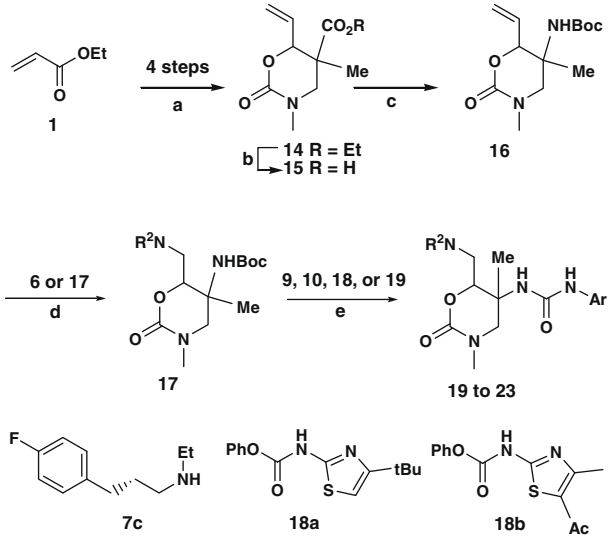
Curtius rearrangement sequence. Although structure–activity relationships (SAR) in the acyclic series of CCR3 antagonists suggested that quarternizing the carbon atom adjacent to the urea nitrogen could be tolerated by the receptor,[17] it was of interest to see if this trend would continue in the oxazolidinone series. The key methyl-oxazolidinone precursor **14** was synthesized following the aforementioned literature protocol,[13] and its conversion to the target compounds is outlined in Scheme 2. Hydrolysis of the *tert*-butyl ester in **14** employing 6 N HCl provided the racemic acid **15** in good yield. In order to establish the relative stereochemistry of the acid and vinyl moieties, a single crystal X-ray analysis of **15** was performed.[18]

The single crystal X-ray analysis of compound **15** revealed it to be a mixture of *cis* and *trans* isomers.[19] Since separation of diastereomers of the acid-oxazolidinone **15** was difficult, it was carried over to the next step without further purification. Curtius rearrangement of **15** led to the desired Boc-protected amine **16** in good yield after recrystallization from ethyl ether. Reductive amination with amines (**6, 7c**), followed by Boc deprotection and coupling with phenyl carbamates (**9, 10, 18a, 18b**) led to oxazolidinones **19–23**. Fortuitously, the *cis*- and *trans*-diastereomers could be easily separated via silica gel column chromatography at this stage. The relative stereochemistry of the individual diastereomers was not established.[20]

The binding and cellular functional data for selected compounds is listed in Table 1. From these data, it is clear that (i) quarternizing the carbon atom adjacent to the urea functionality did not lead to significant changes in binding potency (compare compounds **11** with **19a** and **19b**); (ii) the *m*-(methyltetrazolyl)phenyl moiety is the favored tail-piece in terms of binding (for example, compare the diasteromeric pairs **19a,b** with **20a,b**); (iii) the binding potency of the open chain amines **23a** and **23b** are similar to that of the cyclic piperidine analogs **19a** and **19b;** (iv) in terms of cellular shape change, one diastereomer is approximately an order of magnitude more potent than the other diastereomer (compare **19a** with **19b** and **23a** with **23b**); and (iv) most of the compounds show better selectivity over CYP2D6 compared to **B** (Fig. 1, IC_{50} = 7200 nM)**,** BMS-639623 (**C**, Fig. 1, K_i = 2600 nM) and excellent selectivity compared to DPC168 (**A**, Fig. 1, IC_{50} = 30 nM). Compound **19b** appeared to be the best compound in the series, as it exhibited comparable binding, functional and CYP2D6 potency to clinical candidate BMS-639623 (**C**). The compound also exhibited excellent selectivity over the hERG channel (IC_{50} = 15,700 nM in a Ca^{2+}-flux assay). However, like all of the compounds in this oxazolidinone series, it was not stable when incubated in vitro with human liver microsomes, and so it was not advanced into detailed in vivo evaluation.



Scheme 1. Reagents and conditions: (a) see Ref. 13; (b) 6 N HCl, dioxane, 50 °C, 30 min, 85%; (c) DPPA, *t*-BuOH, toluene, Et_3N, 110 °C, 18 h, 9%; (d) i—O_3, CH_2Cl_2, −78 °C, DMS; ii—CH_2Cl_2, $Na(OAC)_3BH$, 10–36% over two steps; (e) i—3 N HCl, dioxane, 50 °C, 1 h, quantitative; ii—CH_3CN, rt, 18 h, 70%.



Scheme 2. Reagents and conditions: (a) see Ref. 13; (b) 6 N HCl, dioxane, 50 °C, 30 min, 79%; (c) DPPA, *t*-BuOH, toluene, Et_3N, 110 °C, 18 h, 46%; (d) i—O_3, CH_2Cl_2, −78 °C, DMS; ii—CH_2Cl_2, $Na(OAc)_3BH$, 44–59% over two steps; (e) i—3 N HCl, dioxane, 50 °C, 1 h, quantitative; ii—CH_3CN, rt, 18 h.

Table 1
Binding and shape change data for urea-based CCR3 antagonists employing a tetrahydro 1,3-oxazin-2-one spacer[21,22]

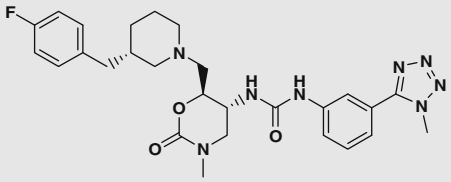
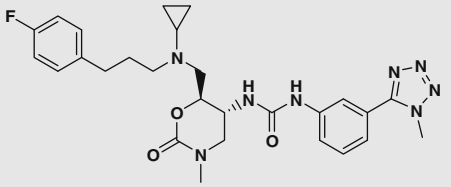
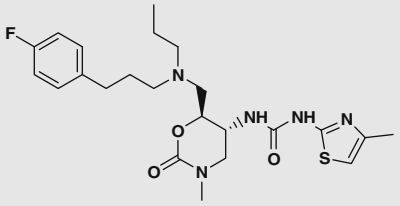
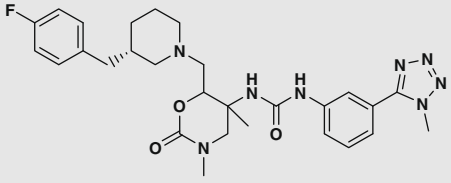
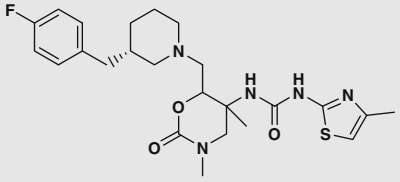
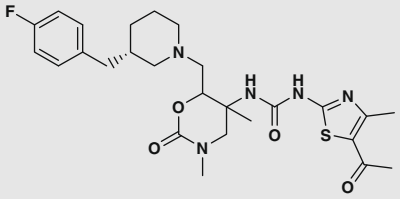
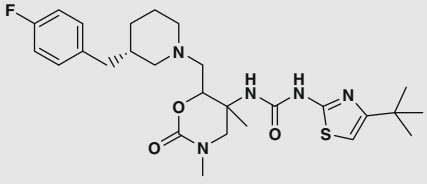
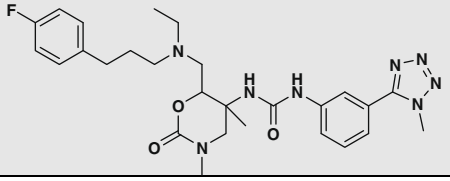
Compound	Structure	CCR3 binding (IC_{50}, nM)	Shape change (IC_{50}, nM)	CYP2D6 (IC_{50}, nM)
A	See Figure 1	2	ND	30
B	See Figure 1	1.2	ND	7400
C	See Figure 1	0.3	0.038	K_i = 2600
11		0.23	ND	4300
12		2.1	2.2, 2.9	ND
13		9.2	ND	ND
19a		0.12	2.4, 6.3	33,000
19b		0.15	0.13, 0.12	17,000
20a		5.4	ND	ND
20b		0.37	3.4	2100
21a		13	ND	ND
21b		1.1	ND	21,000
22a		44	ND	ND
22b		5.5	ND	40,000

Table 1 (*continued*)

Compound	Structure	CCR3 binding (IC_{50}, nM)	Shape change (IC_{50}, nM)	CYP2D6 (IC_{50}, nM)
23a		0.18	4.4	5900
23b		0.47	>3, >10	14,000

ND, not determined.

In conclusion, a series of urea-based CCR3 antagonists with a tetrahydro-1,3-oxazin-2-one linker have been identified. Quarternizing the carbon atom adjacent to the urea functionality of the tetrahydro-1,3-oxazin-2-one core was critical to obtaining good yields during the Curtius rearrangement reaction en route to the final products. Of the compounds shown, the potency and selectivity of analog **19b** was similar to that of our development candidate BMS-639623. We will report our additional efforts towards generating potent, selective, and bioavailable CCR3 antagonists in subsequent manuscripts.

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19. The authors in Ref. 13 observe that the threo aldol product undergoes cyclization to the *trans*-oxazolidinone within 10 min, whereas the mesylate of the erythro isomer gives the *cis*-oxazolidinone when kept at room temperature for 3 days. When we subjected the diasteromeric mixture of the aldol products to the cyclization conditions reported in Ref. 13 and stirred the reaction mixture for 18 h at room temperature, a mixture of *cis*–*trans*-oxazolidinone isomers (**15**) was obtained along with erythromesylate in a ratio of ~1:1.5.
20. Chiral HPLC analysis (Chiracel OD, 250 × 4.6 mm 10 u, CO2/MeOH, 70:30) of **19a** indicated the presence of a set of enantiomers, in a 1:1 ratio, as expected.
21. For a description of the human CCR3 binding assay please see Ref. 12, and references cited therein.
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