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Identification of chemokine receptor CCR4 antagonist

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Abstract—The present study reports the identification and hits to leads optimization of chemokine receptor CCR4 antagonists. Compound **12** is a high affinity, non-cytotoxic antagonist of CCR4 that blocks the functional activity mediated by the receptor.

Chemokines are a group of small (~8–14 kDa), mostly basic, structurally related cytokine peptides that regulate cell trafficking of various types of leukocytes through interactions with a subset of seven transmembrane G-protein coupled receptors.[1] CCR4 is a chemokine receptor that partners with the ligands MDC (macrophage derived chemokine, CCL22) and TARC (thymus and activation-regulated chemokine, CCL17), both of which are members of the beta or CC class of chemokines.[2] The CCR4 chemokine receptor is important in facilitating the migration of selected CD4 + thymocytes to the thymus and through the compartments of the thymus, as a part of the process of T cell maturation and differentiation. MDC, TARC, and CCR4 expressing Th2 cells are found in asthmatic lungs, arthritic joints, and inflamed skin. A CCR4 antagonist is expected to prevent recruitment of CD4 + Th2 polarized T cells to sites of inflammation by blocking chemotaxis and cellular activation. Anti-MDC and anti-TARC antibodies are each separately reported to have efficacy in murine asthma models.[3] Additional in vivo studies in animal models have demonstrated utility of these antibodies in preventing other immunological responses.[4] CCR4 antagonists are expected to have therapeutic potential in the treatment of diseases such as asthma, rheumatoid arthritis, and psoriasis.[1] Small molecule antagonists of CCR4 were recently disclosed.[5] Herein we report identification of a small molecule CCR4 antagonist, which blocks the functional response mediated through the receptor.

During the screening of the corporate compound collection, a series of closely related quinazoline, quinoline, and isoquinoline derivatives were identified as 'hits' with modest activity in the CCR4 binding assay (Fig. 1).[11] The compounds also inhibited chemotaxis. However, these hits were found to be cytotoxic to the cells. The observed inhibition of chemotaxis may be due to cytotoxicity and not because of receptor antagonism.

The foremost goal for the program was to determine if cytotoxicity and CCR4 antagonist activity could be diverged by structural modification of our initial hits. SAR from the screening suggested that the position of the ring nitrogen atoms in the central ring made little difference to the CCR4 activity. We embarked upon systematic exploration of linkers that separated the central aromatic core and the terminal aromatic moiety ($\mathbf{R^1}$). These analogs were synthesized from 2-aminobenzamide using a known approach as shown below (Scheme 1).[6] The overall yields of products varied from 35% to 60%.

As shown in Table 1, the two atoms tether either in the form of a straight chain (**4d**) or as a part of an aryl ether (**4f**) or as a part of a constrained ring (as in naphthalene,

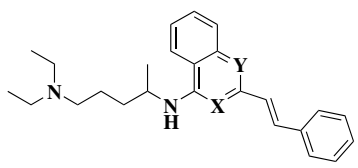

Figure 1. Either X or Y = N or both N; CCR4 (MDC binding) IC_{50} = 3.6–6.1 μM; cell cytotoxicity CC_{50} = 3–5 μM; chemotaxis Inh = 12–20 μM.

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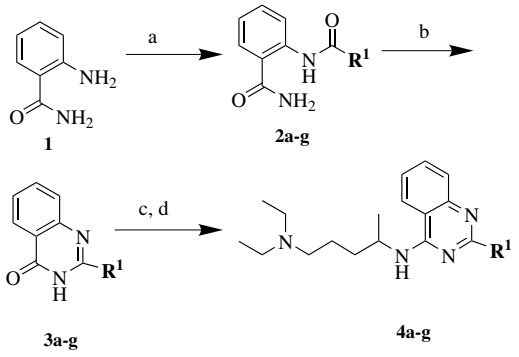
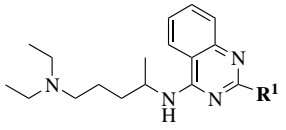


Scheme 1. Reagents and conditions: (a) R_1CO_2H, EDCI, CH_2Cl_2, 85%; (b) NaOEt, H_2O_2, 65%; (c) $POCl_3$, 100 °C; (d) N^1,N^1-diethyl-pentane-1,4-diamine, 95 °C, $(i\text{-Pr})_2$EtN, NMP, 50%.

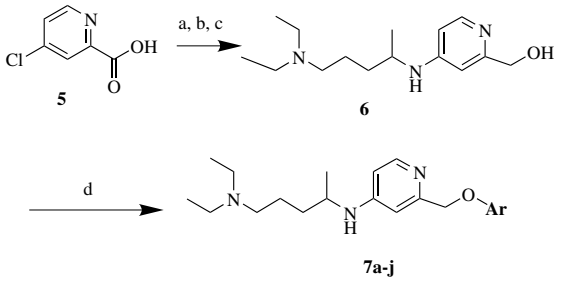
Table 1.



Compd #	R^1	CCR4 IC_{50} (μM)[11]
4a	Ph	> 25
4b	2-Naphthyl	**2.5**
4c	$-CH_2Ph$	10
4d	$-CH_2CH_2Ph$	**2.4**
4e	$-CH_2CH_2CH_2Ph$	>10
4f	$-CH_2OPh$	**2**
4g	–CONHPh	>10

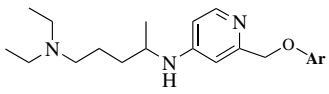
4b) was preferred.[7,11] On the contrary, an amide linker was not tolerated.

In addition to these changes, removal of the fused phenyl ring was also tolerated (data not shown). Since the position of the core nitrogen atoms did not affect the activity (observed from original hits), we decided to examine the nature of substitution pattern in the terminal aromatic group using a pyridine scaffold with benzyl ether system. The required pyridine scaffold was prepared in two steps from commercially available 4-chloro-pyridine-2-carboxylic acid (Scheme 2).[8] A parallel synthesis of aryl ether analogs was carried out using modified Mitsunobu conditions.[9] The summary of results is as shown in Table 2. 2,4-Dichlorophenyl was found to be the preferred terminal aromatic group (compound **7b**). These compounds were devoid of the cell toxicity (at 100 μM) observed in the original hits.



Scheme 2. Reagents and conditions: (a) EtOH, H_2SO_4, 90%; (b) N^1,N^1-diethyl-pentane-1,4-diamine, 95 °C, $(i\text{-Pr})_2$ EtN, NMP, 62%; (c) LAH, THF, 60 °C, 85%; (d) ArOH, ^{n}Bu$_3$P, 1,1′-(azodicarbonyl)-dipiperidine, CH_2Cl_2, 62%.

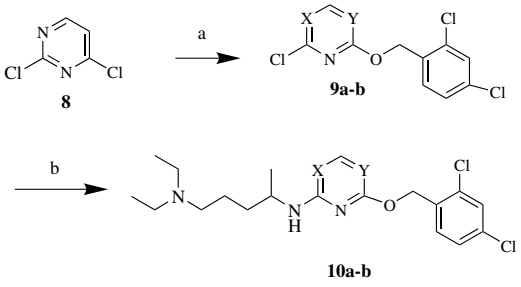
Table 2.



Compd #	Ar	CCR4 IC_{50} (μM)[11]
7a	2-Cl-Ph	17
7b	2,4-Di-Cl-Ph	**1.2**
7c	4-Cl-Ph	20
7d	3-Cl-Ph	25
7e	3,4-Di-Cl-Ph	4
7f	3,5-Di-Cl-Ph	25
7g	Ph	>30
7h	2,4-Di-OMe-Ph	>30
7i	3-OMe-Ph	>30
7j	4-F-Ph	18

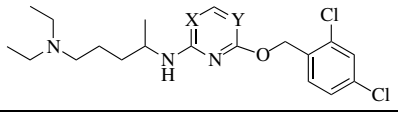
We then embarked on further examination of the linkage while keeping the Ar group constant (2,4-di-Cl-Ph). These compounds were synthesized by sequential displacement of chlorines from 4,6 dichloro-pyrimidine[10] (Scheme 3). As seen with compounds (**10a** vs **7b**), reversal of the ether linkage was tolerated. In addition, no dramatic difference in the activity of two regioisomers (**10a** and **b**) was observed (Table 3).

We subsequently explored the chain length that separates the terminal amino group and the core as well as the requirement of the amino group. As shown in the table, a linker with more than three atoms was required.



Scheme 3. Reagents and conditions: (a) 2,4-di-Cl-benzyl alcohol, ^{n}Bu$_4$NOH, chlorobenzene, separate regioisomers, 60% major; (b) N^1,N^1-diethyl-pentane-1,4-diamine, 95 °C, $(i\text{-Pr})_2$ EtN, NMP, 73%.

Table 3.



Compd #	X	Y	CCR4 IC_{50} (μM)[11]
10a	N	CH	1.5
10b	CH	N	2.8