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N-Arylsulfonyl-α-amino carboxamides are potent and selective inhibitors of the chemokine receptor CCR10 that show efficacy in the murine DNFB model of contact hypersensitivity

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ABSTRACT

Compound **1** ((4-amino-3,5-dichlorophenyl)-1-(4-methylpiperidin-1-yl)-4-(2-nitroimidazol-1-yl)-1-oxobutane-2-sulfonamido) was discovered to be a 690 nM antagonist of human CCR10 Ca^{2+} flux. Optimization delivered (2*R*)-4-(2-cyanopyrrol-1-yl)-*S*-(1*H*-indol-4-yl)-1-(4-methylpiperidin-1-yl)-1-oxobutane-2-sulfonamido (**eut-22**) that is 300 fold more potent a CCR10 antagonist than **1** and eliminates potential toxicity, mutagenicity, and drug–drug-interaction liabilities often associated with nitroaryls and anilines. **eut-22** is highly selective over other GPCR's, including a number of other chemokine receptors. Finally, **eut-22** is efficacious in the murine DNFB model of contact hypersensitivity. The efficacy of this compound provides further evidence for the role of CCR10 in dermatological inflammatory conditions.

The control of T cell homing to different tissues during inflammation is the result of the interplay of selectins, integrins and chemokine receptors (CCRs), resulting in the direction of distinct T cell subsets to specific inflammatory sites[1,2] The chemokine receptor CCR10 plays an important role in the migration of skin-homing memory T-cells to the skin[3,4] through activation by the chemokine CCL27/CTACK or to mucosal epithelia through activation of CCL28.[5] Both CCR10 and CCL27 are associated with inflammatory skin diseases such as allergic contact dermatitis and psoriasis.[6–8] Notably, interruption of the CCL27–CCR10 interaction with anti-CCL27 antibodies suppresses allergen-induced skin inflammation.[6] These reports suggest disruption of the CCL27–CCR10 interaction may be a promising treatment for inflammatory skin diseases. However, the impact of blocking CCR10 directly on inflammation in the skin has not been reported. Indeed, there are contradictory reports of whether CCR10 antagonism is sufficient for a robust anti-inflammatory response, or whether intervention at other signaling pathways is also required.[9–12] We embarked on a program to discover and optimize selective small molecule antagonists of CCR10 and to elucidate the role of CCR10 in inflammatory skin diseases. Herein we describe the discovery and optimization of potent CCR10 antagonists that further demonstrate efficacy in a murine model of contact hypersensitivity.

We began by screening for inhibitors of the CCL27 dependent Ca^{2+} flux in CHO-K cells stably transfected with both human CCR10 and aequorin.[13] Our screen identified compound **1** with a CCR10 IC_{50} of 690 nM. Compound **1** (Fig. 1) also demonstrated further functional CCR10 antagonism by inhibiting the CCL27 dependent chemotaxis of Ba/F3 cells stably transfected with human CCR10 with an IC_{50} of 53 nM. However, 20 μM of **1** exhibited no

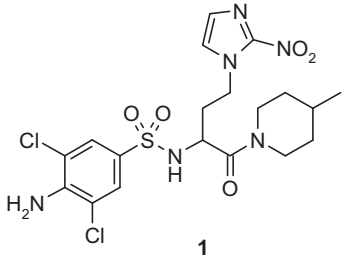

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Figure 1.

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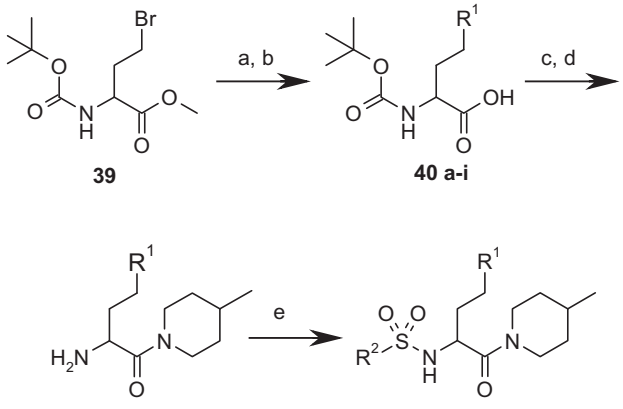
antagonism of murine CCL27 dependent Ca^{2+} flux in CHO-K cells stably transfected with murine CCR10 despite 88% sequence identity (90% homology) between human and murine CCR10.

Compound **1** also contains at least two structural alerts associated with toxicity in the nitro group and the aniline.[14] We began optimization efforts by establishing SAR trends that could avoid the nitro and aniline. Meanwhile, we tracked our progress against the murine receptor to establish whether functional probes for murine models of skin inflammation would emerge.

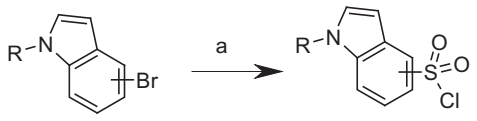
The synthesis of compounds **1**–**38** are summarized in Schemes 1–3, and have been described elsewhere.[15] Bromide **39** was prepared from γ-aminobutyrolactone via the published procedure.[16] Imidazole, 2-nitroimidazole, 2-chloroimidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, 2-cyanopyrrole, and pyrrole were alkylated with **39** to provide **40a**–**i**, with 1,2,3-triazole generating a separable mixture of **40e** and **40f** in a 2:1 ratio. The final products were prepared from *N*-Boc-amino acids **41a**–**o** via amide coupling with 4-methylpiperidine, followed by Boc removal, and treatment of the resulting amine with the appropriate sulfonyl chloride in the presence of an acid scavenger. The homophenylalanine compounds *R*-**10** and *S*-**10** were respectively prepared from commercially available (*R*)- and (*S*)-Boc-homophenylalanine. **41l**, **41m**, and **41n** were prepared via Strecker chemistry as described previously.[17]

The sulfonyl chlorides used to prepare **15**, **16**, **17**, **23**, and **24** were obtained from commercial vendors. 4-Amino-3,5-dichlorobenzene-sulfonyl chloride and 3-amino-2,4-dimethylbenzenesulfonyl chloride were prepared by chlorosulfonylation of 2,6-dichloroaniline and 2,6-dimethylanline respectively. The indolesulfonyl chlorides (**43a**–**f**) were prepared from the corresponding bromoindole via bromine-halogen exchange with *t*-butyllithium followed by quenching with saturated SO_2 in THF (Scheme 2). The resulting lithium sulfinate was then oxidized to the sulfonyl chloride with NCS. In some cases, the indole was protected as a Boc carbamate. In these cases, the final sulfonamide product was treated with HCl in dioxane to provide the product.



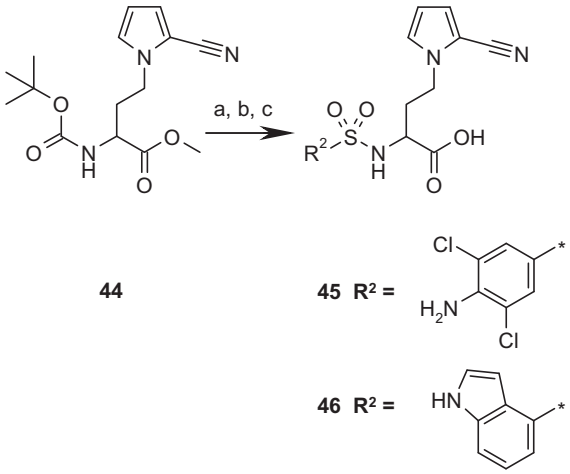
41 a R^1 = 2-nitroimidazol-1-yl
b R^1 = imidazol-1-yl
c R^1 = 2-cyanoimidazol-1-yl
d R^1 = 2-chloroimidazol-1-yl
e R^1 = 1,2,3-triazol-1-yl
f R^1 = 1,2,3-triazol-2-yl
g R^1 = 1,2,4-triazol-1-yl
h R^1 = pyrazol-1-yl
i R^1 = pyrrol-1-yl
j R^1 = R-phenyl
k R^1 = S-phenyl
l R^1 = 2-chlorophenyl
m R^1 = 5-cyanopyrazol-1-yl
n R^1 = 5-chloropyrazol-2-yl
o R^1 = 2-cyanopyrrol-1-yl

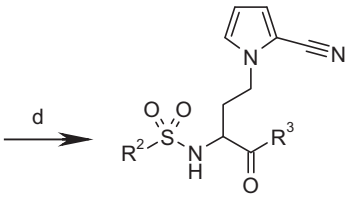
Scheme 1. Reagents and conditions: (a) R^1-H, NaH (40–100%); (b) NaOH, water, MeOH/dioxane (48–100%); (c) 4-methylpiperidine, EDC, HOBt, or 4-methylpiperidine, HATU, trialkylamine (30–100%); (d) HCl or TFA (73–100%); (e) R^2SO_2Cl, trialkylamine (20–100%).



42 a **R** = H; 6-substituted
b **R** = H; 4-substituted
c **R** = Me; 4-substituted
d **R** = Boc; 7-substituted
e **R** = H; 5-substituted
f **R** = Boc; 5-substituted

Scheme 2. Reagents and conditions: (a) NaH (R = H only), -*t*BuLi, saturated SO_2 in THF, then NCS (23–78%).





45: **25, 27, 30, 32, 34, 36, 37**
46: **26, 28, 29, 31, 33, 35, 38**

Scheme 3. Reagents and conditions: (a) HCl (66–100%); (b) R^2-SO_2Cl, base (**45**: 67%, **46**: 66%); (c) NaOH; (d) HATU, base, R^3-amine; or EDC, HOBt, R^3-amine (23–51%).

The synthesis of amide analogues is illustrated in Scheme 3. The Boc group of **44** is removed under acidic conditions, and reaction with sulfonyl chlorides followed by saponification delivered **45** and **46**. Amide coupling with HATU or EDC/HOBt then delivered amide analogues **25**–**38**.

We began to find replacements for the nitroimidazole by assessing whether the nitro group was necessary for CCR10 potency (Table 1). While the nitro group improves potency over the unsubstituted imidazole **2**, it can be replaced with either cyano or chloro (cf. **3** and **4** to **1**). By exploring replacements to the imidazole, we also discovered that the imidazole is not ideal. In the absence of a 2-subtituent, a distally disposed aza group (analogous to the imidazole 3-position as with **2**, **5** and **7**) is detrimental to