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Conformationally Restricted Indolopiperidine Derivatives as Potent CCR2B Receptor Antagonists

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Abstract—The preparation and biological evaluation of a series of indolopiperidine CCR2B receptor antagonists possessing a conformationally restricted C-5 linker chain in combination with a restricted piperidine ring are described. Compared to the parent compound **1**, analogue **8** shows a dramatic improvement in selectivity against a range of 5-HT and dopaminergic receptors.

Over recent years, there has been a rapid growth in the number of isolated low molecular weight proteins called chemokines (*chemo*tactic cyto*kines*).[1] These proteins are involved in a variety of inflammatory responses via interaction with chemokine receptors located on the cell surface of leukocytes followed by chemotaxis and infiltration into the adjacent tissue. The chemotactic proteins can be divided into four families dependent on the arrangement of conserved cysteine residues near the N-terminus.[1] Monocyte chemotactic protein-1 (MCP-1) is a member of the CC class of chemokines, and has been strongly implicated in various inflammatory diseases.[2] The effects of MCP-1 are mediated primarily via the CCR2B receptor,[3] and it has been widely recognised that antagonists of this receptor are potential therapeutic agents for various pathological conditions, for example, atherosclerosis[4] and rheumatoid arthritis.[5] This hypothesis has been recently validated by studies using MCP-1[6] and CCR2[7] knockout mice.

Recently, we described the identification of indolopiperidine **1** as a potent MCP-1 receptor antagonist, which displayed selectivity over the closely related CCR5 receptor.[8] Due to its structural similarity with 5-hydroxytryptamine (5-HT), we decided to further profile **1** against a number of 5-HT and dopaminergic receptors. Unfortunately, cross screening of **1** showed this chemokine selective antagonist to be promiscuous against a number of 5-HT and dopaminergic receptors (Table 1).

In order to improve the selectivity profile of **1**, we decided to explore conformational restriction of the indolopiperidine nucleus and the flexible C-5 linker chain. Recently, we proposed that conformational restriction of an indolopiperidine nucleus via a tropane moiety may lead to a more selective tryptamine template due to conformational restriction of the piperidine ring and increased steric bulk around the basic nitrogen.[10] To explore this hypothesis, we prepared the closely related tropane analogues **2** and **3**. Whilst both isomers display a reduction in MCP-1 receptor affinity, activity is greater in the equatorial isomer **3**. Interestingly, although the tropane moiety had led to a reduction in CCR2B affinity, a more significant reduction in a number of 5-HT and dopaminergic receptor affinities had also been achieved (Table 2).

Previous SAR studies had identified the C-5 alkyl chain as an optimal spacer between the basic nitrogen and the cinnamide. These studies had also identified the amide as an important H-bond acceptor. In order to retain the structural features responsible for CCR2B affinity whilst investigating conformational restriction of the flexible

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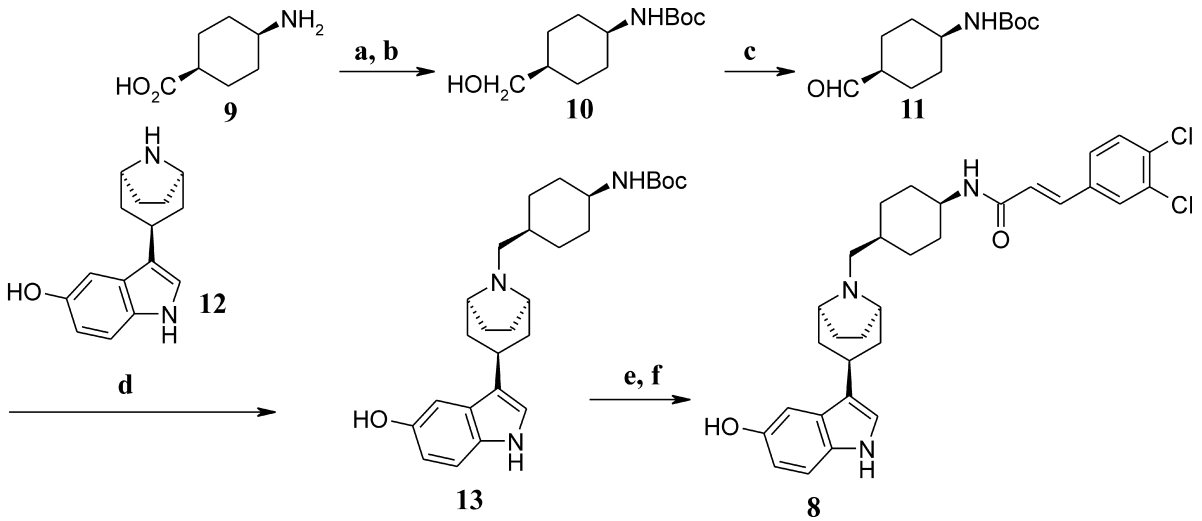


Scheme 1. Preparation of conformationally restricted analogue **8**. Reagents: (a) Boc_2O, TEA (100%); (b) $MeCO_2Cl$, TEA, $NaBH_4$ (95%); (c) DMSO, $(COCl)_2$, TEA (96%); (d) **12**, $NaHB(OAc)_3$ (40%); (e) HCl–EtOH (100%); (f) 3,4-diCl-cinnamic acid, EDC, HOBT (73%).

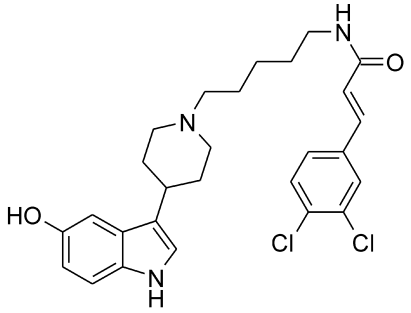
C-5 alkyl chain, we explored a number of cyclohexyl and aromatic linkers (Table 3).

Interestingly, while the *cis* analogues **5a** and **5b** showed comparable affinity to the flexible C-5 analogue **1**, the related *trans* isomers **7a** and **7b** showed a significant decrease in CCR2B affinity. The dramatic loss of affinity with the aromatic analogues **4** and **6** is presumably due to an adverse conformational effect. Although the *cis* analogue **5b** had not given an increase in MCP-1 receptor affinity, suggesting the conformational restriction of the C-5 chain was far from optimal, we decided to profile this analogue further to elucidate whether we had achieved our primary goal of reducing 5-HT and dopaminergic affinity (Table 4).

Importantly, conformational restriction of the flexible C-5 chain gave up to a 400-fold decrease in 5-HT receptor affinities, although potency against a number of receptors still remained high.

Although we had shown incorporation of a tropane into the piperidine ring of **1** gave a 6-fold decrease in CCR2B affinity, we decided to incorporate this structural modification into analogue **5b** to see if an additive effect on selectivity could be achieved. To our surprise, analogue **8**, incorporating the tropane modification together with the *cis* linker, gave a modest improvement in CCR2B affinity in contrast to the 6-fold decrease observed previously. Interestingly, cross screening of analogue **8** showed that conformational restraint of both the

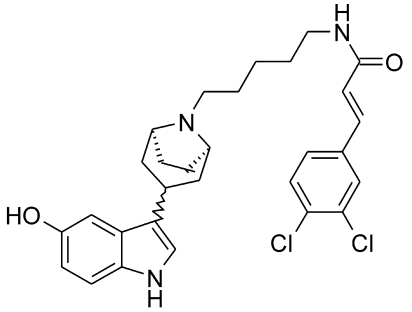
Table 1. Receptor binding profile of **1**



1, CCR2B K_i 50 nM, (pK_i 7.3)[9]

Receptor	pK_i	Receptor	pK_i
CCR2B	7.3[9]	5-HT_{2B}	7.6
5-HT_{1A}	7.0	5-HT_{2C}	7.1
5-HT_{1B}	7.9	5-HT_6	7.1
5-HT_{1E}	8.2	5-HT_7	7.2
5-HT_{1F}	8.5	D_2	7.8
5-HT_{2A}	7.7	D_3	8.1

Table 2. Receptor ΔpK_i of equatorial tropane **3** relative to indolopiperidine **1**

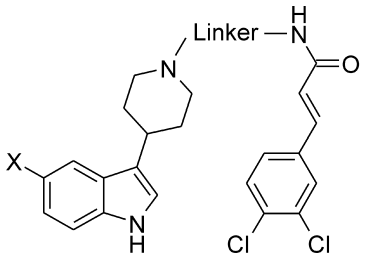


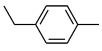
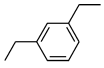
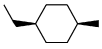
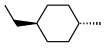
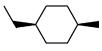
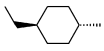
2, axial isomer, K_i 630 nM, (pK_i 6.2)

3, equatorial isomer, K_i 251 nM, (pK_i 6.6)

Receptor	ΔpK_i	Receptor	ΔpK_i
CCR2B	−0.7	5-HT_{2B}	−1.5
5-HT_{1A}	−1.1	5-HT_{2C}	−0.5
5-HT_{1B}	−1.6	5-HT_6	−0.9
5-HT_{1E}	−3.2	5-HT_7	−1.5
5-HT_{1F}	−2.7	D_2	−1.7
5-HT_{2A}	−0.9	D_3	−1.4

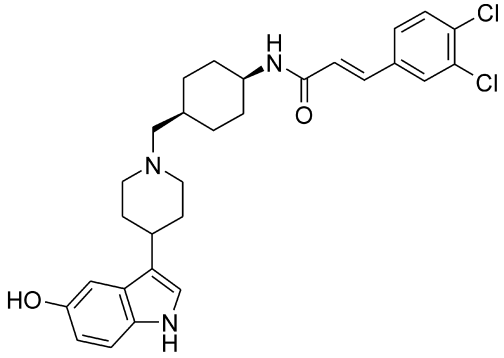
Table 3. CCR2B affinity for constrained C-5 chain analogues



Compd	Linker	X	K_i (nM)	Compd	Linker	X	K_i (nM)
4		H	i.a.	**6**		H	i.a.
5a		H	126	**7a**		H	631
5b		OH	79	**7b**		OH	316

i.a., inactive.

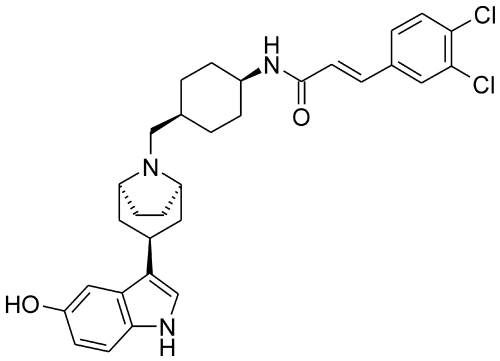
Table 4. Receptor ΔpK_i of **5b** relative to indolopiperidine **1**



5b, CCR2B K_i 126 nM, (pK_i 7.1)

Receptor	ΔpK_i	Receptor	ΔpK_i
CCR2B	−0.2	5-HT_{2B}	−0.5
5-HT_{1A}	−0.7	5-HT_{2C}	−0.4
5-HT_{1B}	−1.2	5-HT_6	−0.9
5-HT_{1E}	−1.4	5-HT_7	−0.4
5-HT_{1F}	−2.6	D_2	−0.8
5-HT_{2A}	−0.1	D_3	−0.9

Table 5. Receptor ΔpK_i of **8** relative to indolopiperidine **1**



8, CCR2B K_i 40nM, (pK_i 7.4)

Receptor	pK_i	ΔpK_i relative to **1**	Receptor	pK_i	ΔpK_i relative to **1**
CCR2B	7.4	+0.1	5-HT2B	6.3	−1.3
5-HT1A	5.1	−1.9	5-HT2C	<5.5	>−1.6
5HT1B	6.0	−1.9	5HT-6	5.7	−1.4
5-HT1E	<5.2	>−3.2	5-HT7	<6.1	>−1.9
5HT1F	<5.5	>−3.0	D2	5.9	−1.9
5-HT2A	<4.7	−3.0	D3	5.6	−2.5

piperidine ring and the C-5 alkyl chain gave a further increase in selectivity. Constrained analogue **8** displays comparable CCR2B affinity relative to the flexible analogue **1**; however, a dramatic 1000-fold increase in selectivity has been achieved against a number of 5-HT and dopaminergic receptors (Table 5).

Chemistry[11]

The cyclohexyl-linked indolotropane analogue **8** was prepared as outlined in Scheme 1. Protection of the *cis* amino-acid **9** with Boc anhydride followed by reaction with methyl chloroformate and reduction of the resulting mixed anhydride with sodium borohydride afforded alcohol **10**. Swern oxidation gave aldehyde **11** which was reductively aminated with amine **12**[10] to afford amine **13**. Removal of the Boc protecting group with ethanolic HCl followed by coupling of the resulting amine with 3,4-dichlorocinnamic acid yielded the desired conformationally restricted analogue **8**.

Summary

In summary, starting from the promiscuous CCR2B antagonist **1**, we have explored the possibility of introducing selectivity against a range of problematic 5-HT

and dopaminergic receptors via a programme of conformational restriction. This study demonstrated that significant improvements in selectivity could be achieved through restriction of both the tryptamine-like indolopiperidine ring and the flexible C-5 chain. Restriction of the piperidine ring as a tropane moiety and introduction of a *cis* cyclohexyl linker afforded constrained analogue **8**, which displays a modest improvement in CCR2B affinity but, importantly, has led to 1000-fold improvement in its selectivity profile against a number of 5-HT and dopaminergic receptors.

References and Notes

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9. All K_i values represent the mean of at least two determinations for the inhibition of [^{125}I]-MCP-1 binding to the cloned human CCR2B receptor expressed in CHO cells, using 10-point displacement curves.
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11. All novel compounds gave satisfactory analytical data in full agreement with their proposed structures.