Bioorganic & Medicinal Chemistry Letters 19 (2009) 1075–1079

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

1-Amido-1-phenyl-3-piperidinylbutanes — CCR5 antagonists for the treatment of HIV. Part 1

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ARTICLE INFO

Article history:
Received 12 December 2008
Revised 5 January 2009
Accepted 6 January 2009
Available online 10 January 2009

Keywords:
HIV
CCR5
Antiviral
Antagonist

ABSTRACT

The development of a new class of CCR5 antagonist replacing the tropane core of maraviroc by piperidine with a branched *N*-substituent is described. Compound **15h** shows good whole cell antiviral activity together with microsomal stability and only weak activity at the hERG ion channel.

The retrovirus HIV (human immunodeficiency virus) can lead to acquired immunodeficiency syndrome (AIDS), a potentially fatal condition resulting from the failure of the immune system. Since its recognition as a disease in 1981,[1] efforts to identify treatments have been frustrated by the rapidity with which mutations which confer resistance can arise, leading to the drive to identify alternative points of intervention in the viral cycle. Maraviroc is the first of a number of CCR5 antagonists that have been developed to block viral entry into cells and was approved by the FDA for the treatment of HIV in 2007.[2,3]

Following the discovery of maraviroc and related tropane-based CCR5 antagonists,[4] we wished to identify a novel chemotype that could capitalise upon different interactions and thereby potentially offer us a different resistance profile.[5] We were particularly interested in replacing the central tropane core since this had been a common feature of all our previous candidates. However, our experience suggested this would be a significant challenge since the tropane offered several key advantages. It had initially been designed to reduce the ability of the central N atom to bind to Asp301 of CYP2D6—activity against this could bring unwanted drug–drug interactions.[6] However, the tropane bridge had also often given a potency increase in our cell-based gp160 fusion assay, and at times, had also proven beneficial for antiviral activity.[7] For example, antiviral activity was lost when this bridge was removed from maraviroc (**1**) to give **2** (Table 1). While the mechanisms for increased fusion potency or for the disproportionate increase in antiviral activity resulting from the incorporation of the tropane bridge are unknown, it is clear that such a modification increases steric hindrance around the central basic centre and restricts the conformational flexibility of the molecule. We proposed that similar steric and conformational effects could also be achieved through the addition of an alpha methyl branch onto the 3-amino-3-phenyl-propyl side chain (Fig. 1). Initially we prepared a series of 4-amido-piperidines as these were readily accessible and previous SAR had demonstrated that these would provide a reasonable level of potency. For example, **3**, a tropane with a simple phenylacetic amide substituent, showed good potency in our cell fusion assay. Removal of the tropane bridge and the ethyl substituent gave **4** which showed a loss of fourfold in potency but still retained some antiviral activity. However, the α-methyl derivative **5** showed a two- to threefold increase in potency in our gp160 fusion assay over the equivalent tropane (**3**) supporting further exploration of this novel core.

Our initial synthesis did not offer any stereochemical control at the newly formed centre in the reductive amination step and compounds were tested as an approximately 1:1 mixture of diastereomers (Scheme 1). The β-amino ester **6** was converted to the cyclobutyl amide by treatment with cyclobutyl carboxylic acid chloride. Direct conversion of the ester to Weinreb amide **8**[8] was followed by reaction with methyl magnesium bromide to afford methyl ketone **9.**

The central fragment was prepared from **10** by reductive amination with ethylamine followed by *N*-Boc protection to give **12**. This

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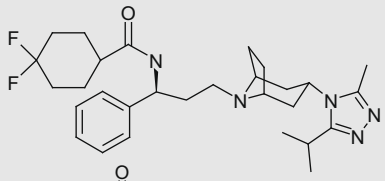
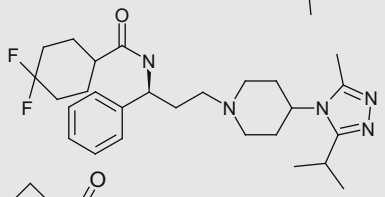
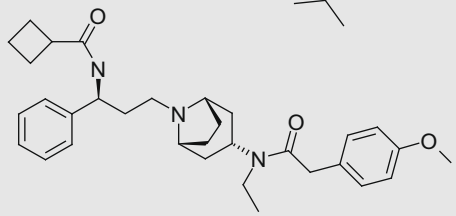
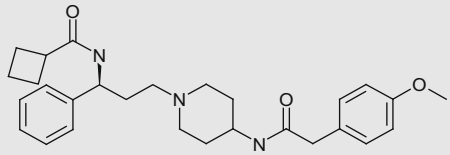
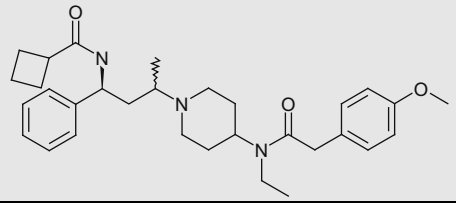
doi:10.1016/j.bmcl.2009.01.009

Table 1
Cell fusion and antiviral activities for maraviroc and related analogues

Compound	Structure	Fusion IC_{50}[a]	AV IC_{90}[b]	log$D_{7.4}$	pK_a	HLM Cl[c]	hERG inhibition[d]
1		0.2 nM	0.7 nM	2.0	7.7	22	0% @ 300 nM
2[9]		7.5 nM	Inactive	1.7	7.2	<8	0% @ 300 nM
3		14 nM	—	2.9	8.7	183	IC_{50} = 248 nM
4[10]		48 nM	310 nM	2.2	8.2	—	Not tested
5		5 nM	—	—	7.8	137	Not tested

[a] Cell fusion assay.[7]
[b] Antiviral activity—concentration required to inhibit replication of HIV_{Bal} in PM-1 cells by 90%.
[c] Human liver microsome stability (μl/min/mg of microsomal protein).
[d] The concentration required to inhibit [^{3}H]dofetilide binding to hERG stably expressed on HEK-293 cells.

was reductively coupled to ketone **9** in the presence of $Ti(O^iPr)_4$ providing **13** as a mixture of isomers. Deprotection and acylation gave analogues **14** as an approximate 1:1 mixture of isomers.

A series of analogues were prepared (Table 2). Changes in the aryl substituent of phenyl acetic acid moiety (examples **14a**–**14j**) gave a 3-log unit spread in activity in our cell fusion assay. While substitution at the 2-position was less favoured, potency increased with lipophilicity in the 3 or 4-position and also with electron withdrawing substituents in the 4-position. A similar trend was observed in a related series by Burrows.[11] In particular 3,4-diCl (**14a**) and 4-CF_3 (**14c**) showed particularly high potencies that translated into excellent levels of activity in our whole cell antiviral assay with IC_{90}'s of 0.20 and 0.24 nM, respectively. Substitution at the benzylic carbon (**14k**) was not tolerated, however the amide could be replaced with a urea, and to a lesser extent with a carbamate. Urea **14l** showed pM activity in our cell fusion assay, but this 10-fold increase over the activity seen with **14a** did not translate into higher efficacy in the antiviral assay. Such a non-linear relationship between cell fusion-based assays and whole cell antiviral assays has previously been reported.[12] Additional substitution to give a tetrasubstituted urea was not tolerated (**14n**). Benzyl or phenyl carbamates **14o** and **14q** showed equivalent potency in the cell fusion assay, although again the antiviral activities were significantly different with only **14o** showing good activity.

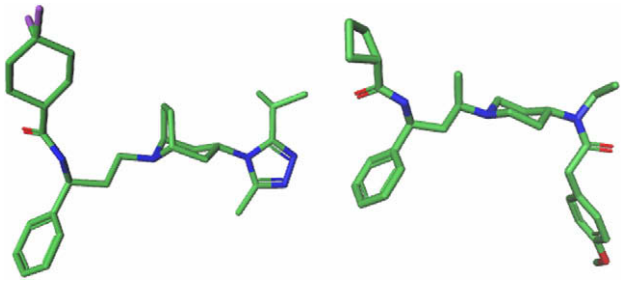
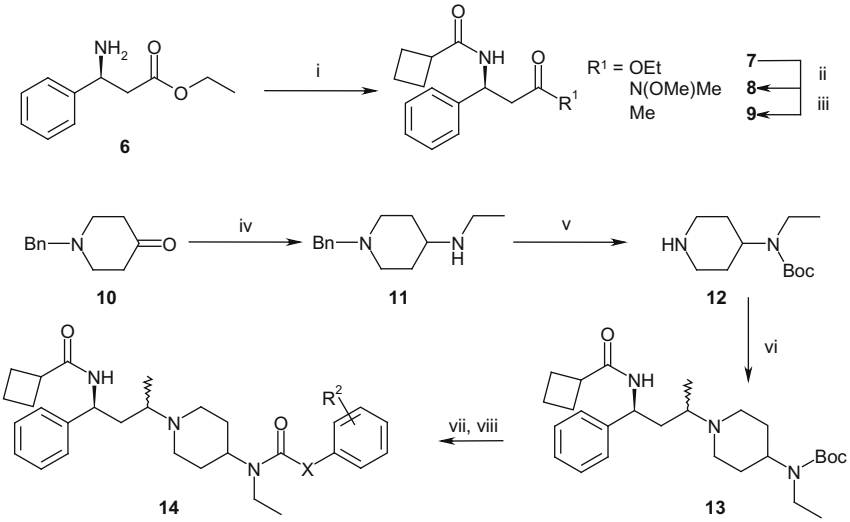


Figure 1. Low energy conformations of **1** and **5**.

While good levels of antiviral activity were observed, we felt that this series was flawed. With the notable exception of sulphone **14e,** we appeared to be locked into relatively lipophilic series with significant metabolic vulnerability. Even **14e** with a modest log$D_{7.4}$ of 1.8 was rapidly turned over in HLM (Cl = 379 μl/min/mg microsomal protein) which we propose is as a result of *N*-de-ethylation since the dealkylated derivative showed considerably better microsomal stability (data not shown). While potency was not significantly reduced when the *N*-ethyl group was removed, previous experience had suggested that the removal of the ethyl group would expose a second



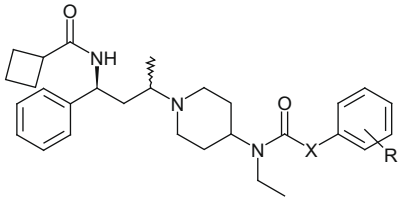
Scheme 1. Preparation of 1-amido-1-phenyl-3-piperidinylbutanes. Reagents and conditions: i—cBuCOCl, Et_3N, CH_2Cl_2, 0 °C, 98%; ii—MeNHOMe.HCl, ^iPrMgCl, THF, <4 °C, 77%; iii—MeMgBr, THF, −68 °C, 74%; iv—(a) $EtNH_2$, THF; (b) $Na(OAc)_3BH$, RT, 100%; v—(a) Boc_2O, CH_2Cl_2, RT, 100%; (b) 10% Pd/C, H_2 50 psi, 50 °C, EtOH, 97%; vi—**9**, $Ti(O^iPr)_4$, $NaBH_3CN$, CH_2Cl_2, MeOH, 67%; vii—HCl, Et_2O; viii—X = CH_2 or CMe_2: phenylacetic acid, CDI, Et_3N, CH_2Cl_2, 87–100%; X = NCH_2: ArNCO, CH_2Cl_2, 59–95%; X = NHMe: (a) PhNHMe, triphosgene, Et_3N, CH_2Cl_2; (b) Et_3N, THF, **13**, reflux, 78%; X = OCH_2 or O: carbamoyl chloride, Et_3N, CH_2Cl_2, RT, 51–84%; X = bond: benzoic acid, HOBT, Et_3N, CH_2Cl_2, 45–65%.

H-bond acceptor which would limit the potential for oral absorption. An analysis of 215 project compounds with similar molecular weights and numbers of H-bond acceptors and for which caco-2 flux had been measured, showed the probability of good caco-2 flux decreased significantly with increasing number of H-bond donors (Table 3). With 2 or more H-bond donors, the probability of a level of caco-2 flux predictive for good oral absorption was reduced to 10%. Removal of the amidic proton on the propyl side chain was not tolerated. For example *N*-methylation of **1** resulted in a >1000-fold fall-of in activity. Consequently we wished to identify alternative structures that would avoid *N*-dealkylation but not introduce a second H-bond donor (see Table 4).

Table 3
Percentage of compounds with caco-2 flux (apical–basal) P_{app} >2 × 10^{-6} cm/s (supportive of good oral absorption[13])

No. of H-bond donors	0	1	> 2
*c*log*P* > 2.5	86%, *n* = 35	35%, *n* = 60	20%, *n* = 5
*c*log*P* < 2.5	33%, *n* = 49	7%, *n* = 61	0%, *n* = 5

Table 2
Activity of 1-amido-1-phenyl-3-piperidinylbutanes



Compound	R	X	Fusion IC_{50}, nM	*c*log*P*	AV IC_{90}, nM
14a	3,4-diCl	CH_2	0.05	5.17	0.20
14b	4-Cl	CH_2	0.34	4.58	
14c	4-CF_3	CH_2	0.48	4.75	0.24
14d	4-F	CH_2	0.94	4.01	2.81
14e	4-SO_2Me	CH_2	0.07	2.22	
14f	3-Cl	CH_2	1.54	4.58	
14g	2,4-diCl	CH_2	2.33	5.29	
14h	4-Me	CH_2	3.76	4.36	
14i	H	CH_2	13.4	3.78	
14j	2-OMe	CH_2	17.9	3.86	
14k	H	CMe_2	>25,000	4.57	
14l	3,4-diCl	$NHCH_2$	0.003	5.24	0.236
14m	H	$NHCH_2$	0.16	3.93	
14n	H	NMe	6,430	4.16	
14o	H	OCH_2	3.16	5.1	0.322
14p	4-Cl	O	3.4	5.18	
14q	4-F	O	3.63	4.61	61.4
14r	4-F	—	4.83	3.72	1630
14s	4-Cl	—	25.3	4.29	
14t	3,4-diCl	—	33.7	4.91	
14u	4-OMe	—	64.4	3.72	
14v	H	—	73.5	3.50	

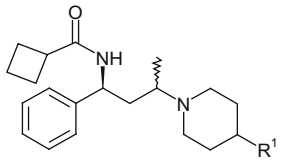
Heterocycles have been investigated as bioisosteres of amides and with some success against the CCR5 receptor.[14]

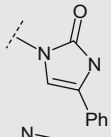
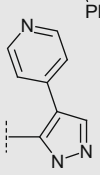
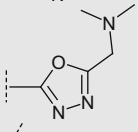
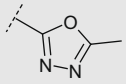
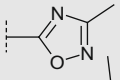
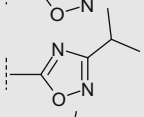
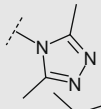
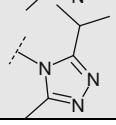
The 4-heterocycle substituted piperidines **15** were prepared by reductive amination of imines formed via $Ti(O^iPr)_4$-mediated dehydration of ketone **9** and the appropriate piperidine as shown in Scheme 2.

While our first example, **15a**, a cyclic analogue of the open-chained urea **14i** showed little activity, further examples without the additional phenyl ring were more encouraging. Pyrazole **15b** showed modest levels of activity with improved metabolic stability. The 1,3,4-oxadiazoles **15c** and **15d** retained some cell fusion activity, exhibited no observable turnover in human liver microsomes and also benefited from a significant drop in hERG activity. The latter gave us confidence that we would be able to design out this unwanted activity. Isomeric 1,2,4-oxadiazole **15e** although more potent than **15d** was significantly more lipophilic and reintroduced metabolic vulnerability. Switching to the 1,3,4-triazoles **15g** and **15h** gave us potency, metabolic stability and, in the case of **15h**, only weak activity against the hERG ion channel.

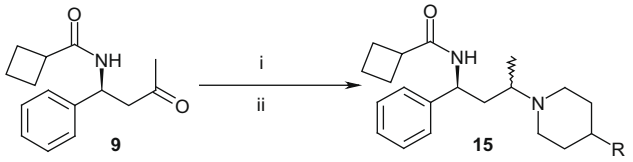
Since these 4-heterocyclic piperidines were still un-resolved at the α-methyl stereocentre, the diastereomeric isomers of **15h** were separated by column chromatography. As expected, both isomers showed no measurable turnover in HLM. There was a 15-fold split in their relative activities in the cell fusion assay (IC_{50} = 4.3 and 60 nM). The more active isomer showed the higher level of activity at the hERG channel (IC_{50} = 2.1 vs 7.1 μM) but was still sufficiently weak to give us confidence that this series merited further investigation. This work will be described in a subsequent paper along with the stereochemical assignment of the more active species.

Table 4
Activity of key 4-heterocyclic piperidines



Compound[a]	R^1	Fusion IC_{50}, nM	log $D_{7.4}$	HLM[b]	hERG IC_{50}, nM
15a[15]		2310	3.5	35	4.7
15b		382	2.4	38	117
15c[16]		540	1.1	<7	3100
15d[17]		1849	1.3	<7	<5280
15e[18]		21.4	2.1	56	Not tested
15f[19]		94.6	3.2	204	1650
15g[9]		37.5	1.2	<7	849
15h[9]		2.0	1.9	<7	4000

[a] Precursor 4-heterocyclepiperidine.
[b] (μl/min/mg of microsomal protein).



Scheme 2. Preparation of 4-heterocyclic piperidines. Reagents: i—4-substituted piperidine, $Ti(O^iPr)_4$, CH_2Cl_2; ii—$NaBH_3CN$, MeOH, 8–41%.

We have developed a replacement to the tropane core which is a key feature to the profile exhibited by maraviroc. Sterically encumbering the central nitrogen with an α-methyl group gave a series with good whole cell antiviral activity, metabolic stability and a significant window over activity at the hERG ion channel.

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