Bioorganic & Medicinal Chemistry Letters 22 (2012) 6694–6699

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Scaffold-hopping with zwitterionic CCR3 antagonists: Identification and optimisation of a series with good potency and pharmacokinetics leading to the discovery of AZ12436092

Ash Bahl [b], Patrick Barton [a], Keith Bowers [b], Moya V. Caffrey [a], Rebecca Denton [c], Peter Gilmour [b], Shaun Hawley [b], Tero Linannen [a], Christopher A. Luckhurst [a], Tobias Mochel [a], Matthew W. D. Perry [a,*], Robert J. Riley [c], Emma Roe [c], Brian Springthorpe [a], Linda Stein [a], Peter Webborn [c]

[a] Department of Medicinal Chemistry, AstraZeneca R&D Charnwood, Bakewell Road, Loughborough LE11 5RH, United Kingdom
[b] Department of Bioscience, AstraZeneca R&D Charnwood, Bakewell Road, Loughborough LE11 5RH, United Kingdom
[c] Department of Discovery DMPK, AstraZeneca R&D Charnwood, Bakewell Road, Loughborough LE11 5RH, United Kingdom

ARTICLE INFO

Article history:
Available online 11 September 2012

Keywords:
Chemokine
Antagonist
Bioavailability

ABSTRACT

The discovery and optimisation of a series of zwitterionic CCR3 antagonists is described. Optimisation of the structure led to AZ12436092, a compound with excellent selectivity over activity at hERG and outstanding pharmacokinetics in preclinical species.

The CCR3 receptor is a seven transmembrane, G-protein-coupled receptor, which belongs to the CC chemokine family.[1] In humans the receptor is expressed on eosinophils,[2] basophils,[3] airway epithelia,[4] airway smooth muscle,[5] dendritic cells,[6] mucosal mast cells[7] and Th2 cells.[8] These cell types are believed to play a key role in the pathophysiology of asthma and rhinitis.[2] Chemokine activation of the CCR3 receptor leads to chemotaxis and activation of cells.[9] The CCR3 receptor is activated by a range of endogenous chemokines, which include eotaxin-1 (CCL11), eotaxin-2 (CCL24), eotaxin-3 (CCL26), MCP-4 (CCL13) and RANTES (CCL5). Levels of these chemokines are raised in allergic diseases such as asthma (atopic and non atopic), allergic rhinitis and atopic dermatitis. As such antagonists of CCR3 are an attractive target for an oral treatment for asthma and other allergic diseases.[10–12]

We have described our earlier work on CCR3/H_1 dual antagonists that lead to the discovery of AZ10565259 (**1**).[13] Activity at hERG was a major issue in this series that was overcome by the addition of an acidic centre making the molecules zwitterionic. The addition of the acidic centre to the molecule resulted in reduced bioavailability that was affected by poor solubility and proved to be dependent on physical form. Whilst **1** progressed into Early Development, work was started to identify an alternate series of compounds, with particular focus on improving bioavailability and pharmacokinetics.

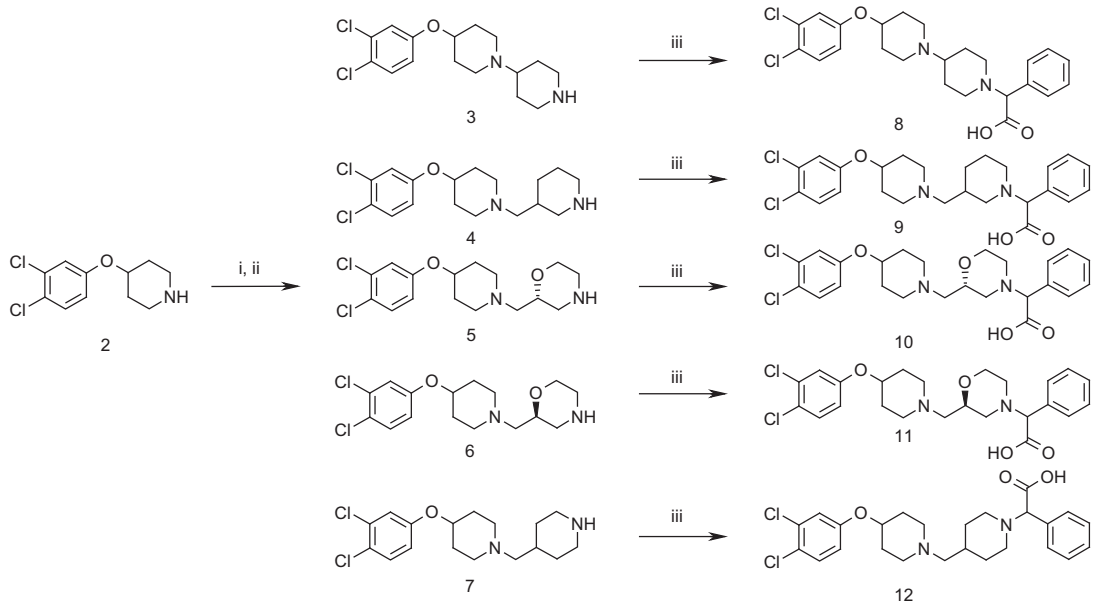
The initial series of compounds were synthesised according to Scheme 1. Thus reductive amination of phenoxypiperidine **2** and an appropriate carbonyl compound gave, after deprotection, the desired diamines **3**–**7** in good yield. Petasis boron-Mannich reaction[14] of the diamines gave racemic amino acids (**8**–**12**).

Once we had identified the advantages of the methylene linked bispiperidine skeleton (**7**) we synthesised additional zwitterionic compounds by reductive amination or nucleophilic aromatic substitution (**13**–**25**) (Scheme 2). The nucleophilic aromatic substitution reactions on unactivated halides required copper(I) catalysis,[15] even so yields were moderate to poor.

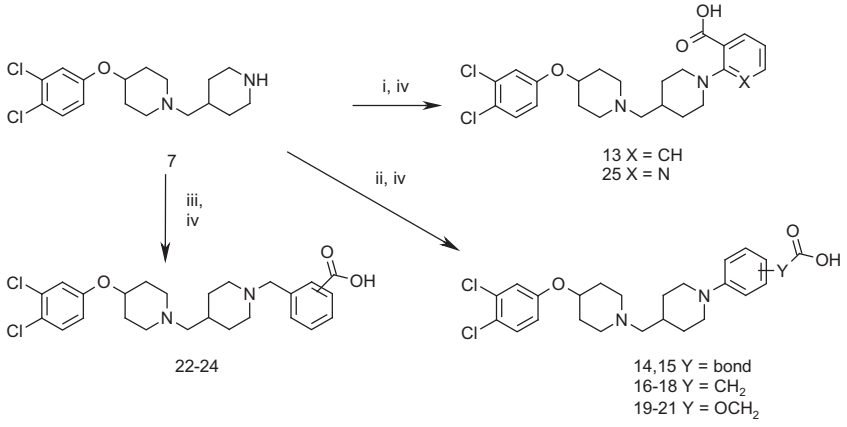
Initially **8**–**12** were synthesised as racemates. Once **12** had been identified as an interesting starting point the enantiomers were separated at the ester stage to give access to the optically pure compounds **26** and **27**. The synthesis of **26** and **27** as single enantiomers required a different approach (Scheme 3). Acylation of amine **2** with cyclopentene carboxylic acid gave amide **28**. Dihydroxylation gave a mixture of diols **29** that could be separated but were normally progressed as a mixture. Reduction of the amide with borane gave diols **30** that could be cleaved to the dialdehyde **31**. The dialdehyde was not isolated but used immediately with an amino acid ester and sodium triacetoxy borohydride to give the esters **32**. Hydrolysis gave acids **26**, **27**, **33**–**63**; it is noteworthy that as the steric bulk around the ester increased the conditions for the

* Corresponding author. Address: AstraZeneca, Innovative Medicines, R&I Chemistry, AstraZeneca R&D Mölndal, Peparedsleden, SE-431 83 Mölndal, Sweden.
E-mail address: matthew.perry@astrazeneca.com (M.W.D. Perry).

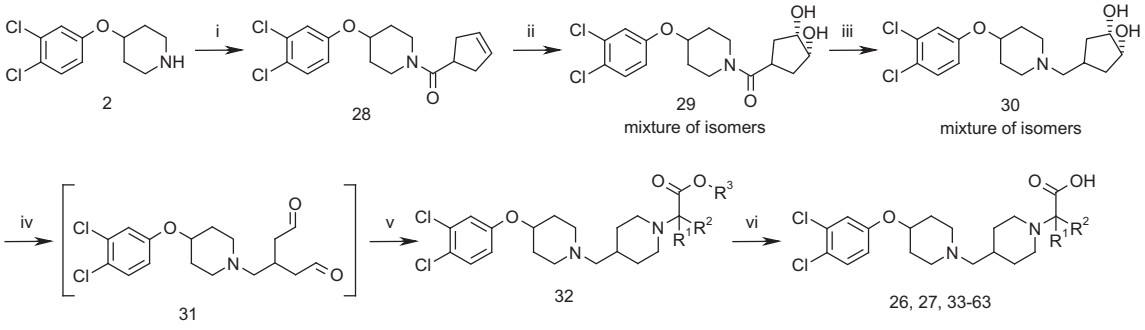
0960-894X/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2012.08.103



Scheme 1. Syntheses of compounds **8**–**12.** (i) RCHO or RCOR, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, rt, 18 h; (ii) TFA, CH_2Cl_2, rt, 16 h; (iii) $PhB(OH)_2$, OHCCOOH, EtOH, 100 °C μwave.



Scheme 2. Syntheses of compounds **13**–**25.** (i) ArF, K_2CO_3, DMF, 90 °C; (ii) ArI, CuI, K_2CO_3, L-proline, DMSO, 85 °C; (iii) ArCHO, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, rt, 18 h; (iv) LiOH–MeOH–THF, H_2O, rt, 16 h.



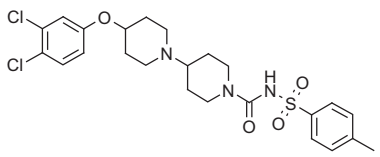
Scheme 3. Chiral synthesis of **26**, **27**, **33**–**63**. (i) Cyclopentene carbonyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt 2 h; (ii) $K_2OsO_4{\cdot}2H_2O$, NMO, acetone–water, rt, 18 h; (iii) BH_3.THF, THF, reflux, 2 h; (iv) $NaIO_4$, AcOH, H_2O, rt, 1 h; (v) amino acid ester, $NaBH(OAc)_3$, AcOH, CH_2Cl_2 or THF, rt, 18 h (vi) R^1 = H, R^3 = Me LiOH, MeOH–THF–H_2O, rt, 18 h or 6 M aq HCl, *i*-PrOH, 80 °C, 24 h; R^1 = Me, R^3 = Me 48% aq HBr, reflux, 48 h; R^1 = Me, R^3 = *t*-Bu HCl, dioxan-THF, rt, 16 h.

hydrolysis of methyl esters changed from mild to forcing; fortunately the most hindered cases with an α-methyl were not susceptible to racemisation. Ultimately we switched to using *t*-butyl esters to simplify this step. The synthetic sequence was high-yielding and required few chromatographic steps and was thus an ideal method to explore these systems.

Many amino acids are available commercially and there are many methods for their synthesis, thus this route enabled a wide range of substitution to be investigated. α-Methyl amino acids were purchased or synthesised by Schöllkopf methodology[16,17] and then esterified.

Changes to the phenoxy group had to be made at the start of the synthetic sequence. Synthesis of the phenoxypiperidines was carried out as previously described; however the 2-methyl analogue **69** required a previously unknown fluorobenzene. Lithiation of 3,4-dichlorofluorobenzene **66**, with careful control of the base stoichiometry, gave the desired 3,4-dichloro-2-methylfluorobenzene **67** contaminated by small amounts of residual **66** and dimethylated product **68**. Switching from iodomethane to dimethyl sulfate as methylating agent and carefully controlling the temperature maximised the yield of **67** that was then purified by fractional distillation. Displacement of fluoride with the potassium alkoxide of 4-hydroxypiperidine proceeded uneventfully to give **69** (see Scheme 4).

At the start of this programme we decided to continue to make zwitterions in order to maintain the required selectivity against the hERG channel, thus we started to evaluate other zwitterionic compounds we had made during the programme that led to **1**. One such compound was the racemic amino acid **8**. This compound had moderate CCR3 potency,[18] good in vitro metabolic stability, a respectable half-life in rat and measurable bioavailability; it was also only weakly active at the hERG channel (pIC_{50} 5.3 in an ion flux assay) (Table 1). Our previous experience that led to the discovery of (**1**) had shown that the anionic centre was tolerated in only a limited range of positions without a significant negative impact on the CCR3 potency and that small changes could have large effects. We decided to evaluate related ring-systems to investigate the effects on potency. 3-Piperidinyl methyl **9** (racemic mixture of diastereomers), showed no advantage. The morpholine analogues **10**, **11**, (both a mixture at the carboxylate centre) showed differing effects on CCR3 and H_1 potencies with (**11**) being more potent at CCR3 and having moderate bioavailability in rats. The 4-piperidinyl methyl **12** showed the best potency at CCR3, close to the levels obtained for **1**. H_1 activity was broadly consistent across the series with the most potent compound being the weakest at CCR3 (**10**). The compounds from these series were only weakly active at the hERG channel, encouraging the belief that zwitterions could provide a general solution to this problem. The separated enantiomers of **12 (26**, **27)** showed again a divergent effect on CCR3 and H_1 potencies. The enantiomer with the higher CCR3 potency **27** (stereochemistry initially unknown) was taken to in vivo rat PK and had a good half-life but poor bioavailability. The factors that governed bioavailability were not clear to us as, although **8** and **27** were poorly bioavailable, the closely related compound **11** was acceptably bioavailable (target >30%). We chose to explore the chemistry further with the hope of discovering alternate structures where good CCR3 potency and acceptable bioavailability were combined. Unlike **1** solubility did not seem to be a limiting factor for bioavailability (data not shown).



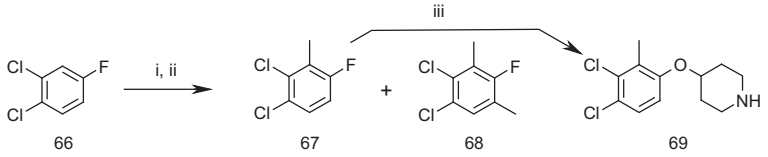
1

Synthetically the 4-piperidinylmethyl-4-piperidinyl system was attractive because of the simplicity of the achiral core. We had previously shown that carboxylate groups on the piperidine rings were disfavoured so we investigated alternative positions that a carboxylate could be attached close to the second (right-hand as drawn) aromatic ring (Table 2). This table shows that most of these compounds had CCR3 potencies in the 7.0–7.7 range with one notable exception; compound **13** is a log unit more potent at CCR3 (pK_i 8.7) and also has high potency at H_1 (pK_i 8.2). Additionally **13** had a reasonable half-life and good bioavailability when dosed to rats ($t_{1/2}$ 4.1 h; F = 58%). Unfortunately hERG activity was also much higher. It is noticeable that **13** has higher lipophilicity than the other compounds shown, we attributed this to charge-pairing between the adjacent positive and negative ions in the zwitterion reducing the hydrophilicity (it is also noteworthy that **13** is doubly basic implying that the aromatic ring is not coplanar with the piperidine; data not shown). We synthesised the pyridine analogue **25** which indeed was much weaker at hERG, however the CCR3 activity was almost abolished though H_1 activity was little changed. Extensive further studies on this series failed to deliver a compound with both good CCR3 potency and low hERG activity.

Our breakthrough came when we made the homologated analogues of **12**; **33** & **34**; the CCR3 and H_1 potency values for **33** compare favourably to those of **12** and **27**; interestingly S stereochemistry was now favoured for potency at CCR3. More importantly **33** showed excellent bioavailability (62%) and long half-life (12 h) in rat whilst retaining only weak activity at hERG.

Exploration of substitution on the phenyl ring **33** showed only small effects on CCR3 and H_1 activity with *meta* substitution being generally disfavoured and *ortho* substitution having a small potency boost (**43**, **46**). Amongst substituted phenyl groups lipophilicity did not appear to be a significant factor driving potency against either CCR3 or H_1. Heterocyclic analogues showed a reduction in potency at both CCR3 and H_1 and had poorer metabolic stability in general (data not shown) (Table 3, Chart 1).

Substitution on the phenoxy ring was investigated through a series of analogues **49–57** (Table 4, Chart 2). As was observed with previous compounds there was a general trend of the potency at both CCR3 and H_1 having a significant relationship with lipophilicity (Chart 1). Thus the two similar trisubstituted phenoxy compounds **55** and **56** are very similar in potencies at CCR3 and H_1. Further profiling of these compounds showed that the 2-methyl



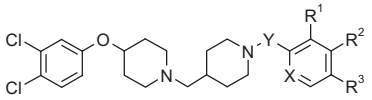
Scheme 4. Synthesis of 4-(2-methyl-3,4-dichlorophenoxy)piperidine; (i) LDA (1.05 equiv), THF, −60 °C then warm to −40 °C for 30 min; (ii) MeI or Me_2SO_4, −60 °C, 30 min then to ry 16 h; (iii) 4-hydroxypiperidine, KOBu-*t*, NMP, 67 °C, 18 h.

Table 1
Data for Data for boron Mannich products **1**, **8**–**12**, **26**, **27**

Compound	CCR3 binding pK_i	H1 binding pK_i	hERG binding pIC_{50}[19]	Human microsomes CL_{int} ml/min/kg	Rat $t_{1/2}$ iv (h)	Ratbioavailability F (%)
1	8.2	7.5	4.6	1	2.7	30
8[a]	7.4	7.2		6	2.4	13
9[b]	7.1	7.2	4.6	<3		
10[c]	6.9	7.7		<3		
11[c]	7.5	7.0	<4.5		1.9	36
12[a]	7.9	7.3	<4.5	<3		
26[d]	7.5	7.6	4.6	<3		
27[e]	8.0	7.0	4.8	<3	4.8	5

[a] Racemic.
[b] Racemic mixture of diastereomers.
[c] Chiral morpholine, mixture of isomers at amino acid.
[d] Later shown to be S.
[e] Later shown to be R (**26** & **27** are the **2** enantiomers of **12**).

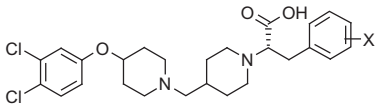
Table 2
Data for benzoic and phenylacetic acids **13**–**25**



Compound	R^1	R^2	R^3	X	Y	CCR3 binding pK_i	H_1 binding pK_i	hERG binding pIC_{50}	Log$D_{7.4}$
13	CO_2H	H	H	CH	Bond	8.7	8.2	5.8	2.8
14	H	CO_2H	H	CH	Bond	7.0	8.3	4.5	2.2
15	H	H	CO_2H	CH	Bond	6.8	7.2	4.5	2.3
16	CH_2CO_2H	H	H	CH	Bond	7.7	7.8	4.9	
17	H	CH_2CO_2H	H	CH	Bond	7.4	8.3	4.5	1.6
18	H	H	CH_2CO_2H	CH	Bond	7.6	7.7	4.5	1.8
19	OCH_2CO_2H	H	H	CH	Bond	7.5	7.8	4.5	2
20	H	OCH_2CO_2H	H	CH	Bond	7.4	8.3	5	2
21	H	H	OCH_2CO_2H	CH	Bond	7.0	7.4	5	
22	CO_2H	H	H	CH	CH_2	7.7	7.2	4.9	2.5
23	H	CO_2H	H	CH	CH_2	6.6	7.3	4.7	1.3
24	H	H	CO_2H	CH	CH_2	6.2	6.9	4.5	1.1
25	CO_2H	H	H	N	Bond	6.2	8.0	4.5	1.7

of **56** was much less susceptible to metabolism than the 3-methyl of **55** (rat hepatocyte CL_{int} <3 vs 13 μL/ml/10^6 cells; rat in vivo $t_{1/2}$ 10 vs 0.8 h). The four disubstituted compounds **49**, **51**, **52** and **54** with similar lipophilicities are very similar in profile; the less lipophilic **53** is however markedly more potent than the monosubstituted **50**. Cyano substitution on the phenoxy ring (**57**) resulted in the only compound with a significant deviation from the lipophilic trend exhibiting good potency at CCR3 and only weak

Table 3
Effects of substitution on phenyl ring



Compound	X	CCR3 binding pK_i	H1 binding pK_i	hERG binding pIC_{50}	Log$D_{7.4}$	Human microsomes CL_{int} μl/min/mg
33	H	8.0	7.3	4.8	2.5	<3
34[a]	H	7.5	7.0	5.2	2.5	<3
35	2-Cl	8.0	7.3	<5		<5
36	4-Cl	7.7	7.5	5.4	2.9	<3
37	2-F	8.0	7.3	<4.5	2.6	4
38	3-F	7.6	6.9	<5	2.7	8
39	4-F	8.1	7.3	5	3	10
40	2-CN	8.3	7.8	4.6	2.1	6
41	3-CN	7.7	7.6	4.9	2.3	<5
42	4-CN	8.1	7.8	5.3	2.2	<3
43	2-Me	8.3	7.5	<4.6	2.5	<3
44	3-Me	7.7	7.8	5.2	2.8	<6
45	4-Me	7.7	7.1	5.2	3	14
46	2-MeO	8.4	7.2	5	2.8	8
47	4-MeO	7.6	7.2	5		
48	3-CF_3	7.7	6.8	5.2		7

[a] R stereochemistry.

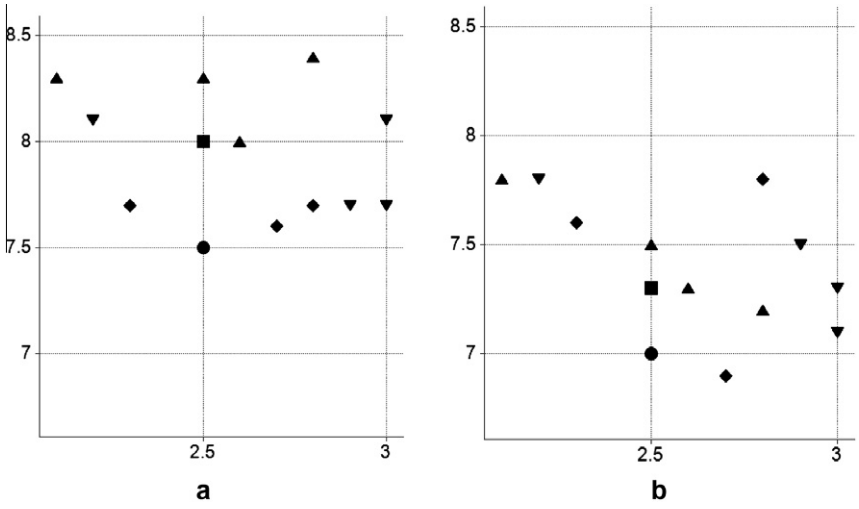
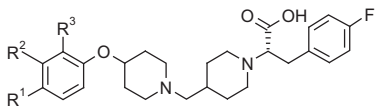


Chart 1. (a) pK_i CCR3 versus Log$D_{7.4}$; (b) pK_i H_1 versus Log$D_{7.4}$ for compounds from Table 3 with measured Log$D$ values; shape by substitution position H (■); H (R stereochemistry, (●), ortho (▲), meta (♦), para (▼).

Table 4
Effects of phenoxy substitution



Compound	R^1	R^2	R^3	CCR3 binding pK_i	H_1 binding pK_i	hERG binding pIC_{50}	Log$D_{7.4}$	Human microsomes CL_{int} µl/min/mg
49	Cl	Cl	H	8.0	7.3	<4.5	2.6	4
50	Cl	H	H	7.3	6.4	<4	1.9	<3
51	Cl	H	Cl	8.3	7.0	<4.5	2.6	<3
52	Cl	H	Me	8.4	7.1	<4.5	2.5	<3
53	F	H	Me	7.9	6.8	<4	1.8	<3
54	Cl	Me	H	8.1	7.0	<4	2.5	<3
55	Cl	Me	Cl	9.3	7.4	<4.5	3.2	<3
56	Cl	Cl	Me	9.3	7.5	<4.3	3.5	<3
57	CN	Cl	Me	8.9	6.3	4.8	2.2	6

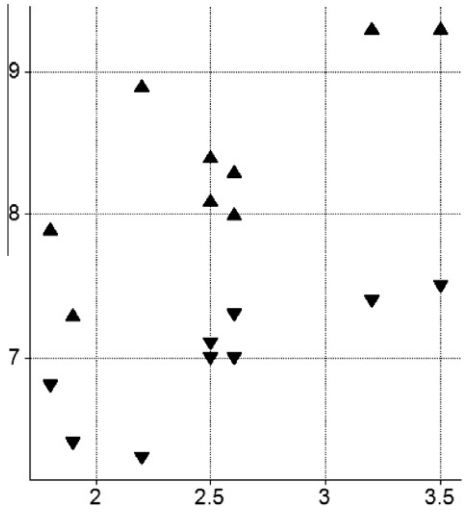


Chart 2. pK_i (CCR3 (▲) or H_1 (▼)) versus Log$D_{7.4}$ for the compounds of Table 4.

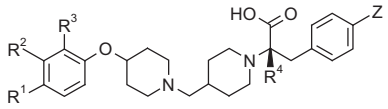
activity at H_1. This cyano substituted compound however was less stable to metabolism (human liver microsomes) than other compounds.

Substitution on the aliphatic chain of the phenylalanine had mixed effects; β-substituted compounds were less active than the parent (data not shown) but the α-methyl compounds gained potency at CCR3 and the selectivity over H_1 activity was increased (Table 5). The most potent CCR3 antagonist **62** was highly lipophilic (log$D_{7.4}$ 3.0), but given the potency of this α-methylated system we were able to attenuate lipophilicity within the phenoxy ring (**63**–**65**) whilst retaining potency (Table 6).

Antagonism of the H_1 receptor is a feature of the phenoxypiperidine moiety that characterises this series of CCR3 antagonists. Since many asthmatics take H_1 antagonist drugs there is a potential benefit to a dual antagonist. The SAR of H_1 antagonism however did not parallel that for CCR3; in particular the changes that improved activity at CCR3, 2-substitution on the phenoxy ring and α-methylation of the amino acid, had little effect on H_1 antagonism which appeared to be largely driven by lipophilicity. Many later compounds had >100-fold selectivity for CCR3 over H_1 and thus could no longer be considered to be dual antagonists.

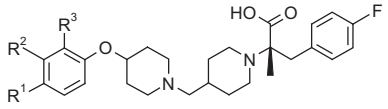
Several α-methylated compounds from this series received extended evaluation; ultimately **63** (AZ12436092) was selected for development as a CCR3 selective antagonist. **63** has subnanomolar CCR3 potency but only very weak activity at the hERG channel thereby removing any cardiac liability via this mechanism. The pharmacokinetics in rat and dog are excellent with long half lives and high bioavailability (**63** dog PK iv $t_{1/2}$ 12 h, oral F 83%). Further

Table 5
Matched pairs showing effect of α-alkylation on CCR3 and H1 binding



Compound	R^1	R^2	R^3	Z	R^4	CCR3 pK_i	H_1 pK_i	Selectivity (CCR3−H_1)
33	Cl	Cl	H	H	H	8.0	7.3	0.7
58					Me	8.5	7.0	1.5
39	Cl	Cl	H	F	H	8.1	7.3	0.7
59					Me	9.1	7.1	2.0
60	Cl	Cl	Me	H	H	8.7	7.2	1.5
61					Me	8.8	6.7	2.1
56	Cl	Cl	Me	F	H	9.3	7.5	1.8
62					Me	9.7	7.5	2.2

Table 6
Optimised compounds with moderate log$D_{7.4}$ and balanced properties



Compound	R^1	R^2	R^3	CCR3 binding pK_i	H_1 binding pK_i	hERG binding pIC_{50}	Log$D_{7.4}$	Rat $t_{1/2}$ iv (h)	Rat bioavailability F (%)
63	Cl	H	Me	9.2	6.8	4.5	2.6	8.7	52
64	Cl	Me	H	8.9	7.3	<4	2.1	7.3	84
65	F	H	Me	8.7	7.1	<4	2.0	4.5	24

screening of **63** in a panel of >140 other assays (MDS Pharma), of which >100 were other GPCR receptors showed no additional activities at 10 μM. Compound **63** was shown to inhibit CCL-24 (eotaxin-2) induced shape-change of eosinophils[20] in human blood (pA_2 7.9); this represented a significant improvement over AZ0565259 (**1**) and, coupled with the significantly improved pharmacokinetics meant that this compound was suitable for further evaluation.

In conclusion we took a moderately active starting point and investigated a series of changes to the core scaffold which identified that the addition of 2 methylene units, one between the 2 piperidine rings, the other between the amino acid and the phenyl ring that made a marked difference to the potency, pharmacokinetics and bioavailability of these compounds. Optimisation of the substitution patterns generated compounds with excellent potency at CCR3, very good pharmacokinetics, including high and consistent bioavailability, and low hERG risk.

Acknowledgments

We acknowledge the skilled experimental contributions of our colleagues in the analytical chemistry and bioscience departments at AstraZeneca R&D Charnwood that enabled this work.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.08.103. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Kunkel, S. L.; Standiford, T. J.; Strieter, R. M.; Kasama, T. *Lung Biol. Health Dis.* **1995**, *80*, 579.
2. Heath, H.; Qin, S.; Rao, P.; Wu, L.; LaRosa, G.; Kassam, N.; Ponath, P. D.; Mackay, C. R. *J. Clin. Invest.* **1997**, *99*, 178.
3. Uguccioni, M.; Mackay, C. R.; Ochensberger, B.; Loetscher, P.; Rhis, S.; LaRosa, G. J.; Rao, P.; Ponath, P. D.; Baggiolini, M.; Dahinden, C. A. *J. Clin. Invest.* **1997**, *100*, 1137.
4. Stellato, C.; Brummet, M. E.; Plitt, J. R.; Shahabuddin, S.; Baroody, F. M.; Liu, M. C.; Ponath, P. D.; Beck, L. A. *J. Immunol.* **2001**, *166*, 1457.
5. Joubert, P.; Lajoie-Kadoch, S.; Labonté, I.; Gounni, A. S.; Maghni, K.; Wellemans, V.; Chakir, J.; Laviolette, M.; Hamid, Q.; Lamkhioued, B. *J. Immunol.* **2005**, *175*, 2702.
6. Ayehunie, S.; Garcia-Zepeda, E. A.; Hoxie, J. A.; Horuk, R.; Kupper, T. S.; Luster, A. D.; Ruprecht, R. M. *Blood* **1997**, *90*, 1379.
7. Sutcliffe, A.; Kaur, D.; Page, S.; Woodman, L.; Armour, C. L.; Baraket, M.; Bradding, P.; Hughes, J. M.; Brightling, C. E. *Thorax* **2006**, *61*, 657.
8. Gerber, B. O.; Zanni, M. P.; Uguccioni, M.; Loetscher, M.; Mackay, C. R.; Pichler, W. J.; Yawalkar, N.; Baggiolini, M.; Moser, B. *Curr. Biol.* **1997**, *7*, 836.
9. Griffiths-Johnson, D. A.; Collins, P. D.; Jose, P. J.; Williams, T. J. *Methods Enzymol.* **1997**, *288*, 241–266.
10. Lukacs, N. W., 1; Hogaboam, C. M., 1; Kunkel, S. L. *Curr. Drug Targets Inflamm. Allergy* **2005**, *4*, 313.
11. Nakamura, H.; Weiss, S. T.; Israel, E.; Luster, A. D.; Drazen, J. M.; Lilly, C. M. *Am. J. Respir. Crit. Care Med.* **1952**, *1999*, 160.
12. Wise, E.; Pease, J. E. In *Asthma: Modern Therapeutic Targets*; Polosa, R., Holgate, S. T., Eds.; Clinical Publishing: Oxford, UK, 2007; p 171.
13. Bahl, A.; Barton, P.; Bowers, K.; Brough, S.; Evans, R.; Luckhurst, C. A.; Mochel, T.; Perry, M. W. D.; Rigby, A.; Riley, R. J.; Sanganee, H.; Sisson, A., Springthorpe, B. *Biorog. Med. Chem. Lett.* (2012), http://dx.doi.org/10.1016/j.bmcl.2012.08.124.
14. Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583.
15. Ma, D.; Cai, Qian; Zhang, Hui *Org. Lett.* **2003**, *5*, 2453.
16. Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem., Int. Ed.* **1981**, *93*, 793.
17. Schöllkopf, U.; Groth, U.; Westphalen, K. O.; Deng, C. *Synthesis* **1981**, 969.
18. Unless otherwise noted biological assays were run as previously reported.[13]
19. Springthorpe, B.; Strandlund, G. WO2005037052; *Chem. Abstr.* **2005**, *142*, 426388.
20. Sabroe, I.; Hartnell, A.; Jopling, L. A.; Bel, S.; Ponath, P. D.; Pease, J. E.; Collins, P. D.; Williams, T. J. *J. Immunol.* **1999**, *162*, 2946.