Bioorganic & Medicinal Chemistry Letters 19 (2009) 837–840

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

New quinoline NK_3 receptor antagonists with CNS activity

Paul W. Smith [a,*], Paul A. Wyman [a], Peter Lovell [a], Caroline Goodacre [a], Halina T. Serafinowska [a], Antonio Vong [a], Frank Harrington [a], Sean Flynn [a], Daniel M. Bradley [a], Rod Porter [a], Sara Coggon [b], Graham Murkitt [b], Kirsten Searle [c], David R. Thomas [c], Jeannette M. Watson [c], William Martin [d], Zining Wu [d], Lee A. Dawson [c]

[a] Medicinal Chemistry, Neuroscience CEDD GlaxoSmithKline Research & Development, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK
[b] Drug Metabolism & Pharmacokinetics, Neuroscience CEDD GlaxoSmithKline Research & Development, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK
[c] Schizophrenia & Bipolar, Neuroscience CEDD GlaxoSmithKline Research & Development, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK
[d] Screening & Compound Profiling, Collegeville, USA

ARTICLE INFO

Article history:
Received 5 November 2008
Revised 28 November 2008
Accepted 2 December 2008
Available online 7 December 2008

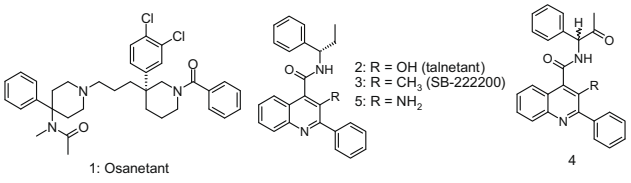
Keywords:
Neurokinin
NK_3 receptor antagonist
Quinoline

ABSTRACT

Lead optimisation starting from the previously reported selective quinoline NK_3 receptor antagonists talnetant **2** (SB-223412) and **3** (SB-222200) led to the identification of 3-aminoquinoline NK_3 antagonist **10** (GSK172981) with excellent CNS penetration. Investigation of a structurally related series of sulfonamides with reduced lipophilicity led to the discovery of **20** (GSK256471). Both **10** and **20** are high affinity, potent NK_3 receptor antagonists which despite having different degrees of CNS penetration produced excellent NK_3 receptor occupancy in an ex vivo binding study in gerbil cortex.

The neurokinin-3 (NK_3) receptor is one of the tachykinin peptide receptor family. It is a seven transmembrane G-protein coupled receptor and is preferentially activated by neurokinin B (NKB). NK_3 receptors are expressed in the mammalian CNS in cortical regions and in basal ganglia structures implicated in psychiatric diseases.[1–3] Pre-clinically it has been demonstrated that NK_3 receptors modulate monoaminergic (noradrenaline and dopamine) and amino acid (GABA) neurotransmission.[4–8] This has led to speculation that modulation of NK_3 receptor activity may have utility in psychiatric disorders such as schizophrenia.[9] Recent reports from preliminary clinical studies with two chemically distinct selective NK_3 receptor antagonists osanetant **1** (SR-142801)[10,11] and talnetant **2** (SB-223412)[12,13] appear to support this possibility and have stimulated further research towards the identification of novel centrally active selective NK_3 receptor antagonists by several research groups, leading to a number of recent publications[14–17] and reviews.[18–21]

At GlaxoSmithKline there has been considerable interest in the quinoline 4-carboxamide series of NK_3 receptor antagonists, with several publications from previous SAR studies in this area.[22–26]



1: Osanetant

4

Of particular relevance to the present study, was the previous identification of SB-222200 **3**, an NK_3 receptor antagonist with CNS activity. Following oral administration **3** was efficacious in a mouse behavioural model (reversed senktide induced head twitches and tail whips).[27] Further analysis, however, also revealed that in vivo **3** generated significant levels of the racemic ketone **4** (R = Me) as a circulating metabolite with low CNS penetration. This raised the possibility of further optimisation to enhance CNS activity. The present study describes new work in the quinoline series directed towards novel NK_3 receptor antagonists with improved metabolic stability and able to occupy receptors in the CNS.

In addition to SB-222200, a related prototype compound with good NK_3 affinity and promising pharmacokinetic profile in rat was the 3-amino quinoline **5**.[24] After oral administration **5** generated similar CNS exposure to SB-222200 (Table 1). Promisingly, **5** also showed reduced in vivo blood clearance and increased NK_3

* Corresponding author. Tel.: +44 01279 875272; fax: +44 01279 644100.
E-mail address: Paul.W.Smith@GSK.com (P.W. Smith).

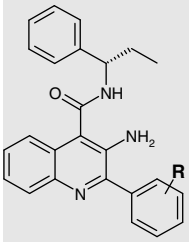
0960-894X/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2008.12.005

Table 1
NK_3 receptor binding and rat pharmacokinetics of SB-222200 **3** and amine **5**[a,27]

Compound	NK_3 pK_i	Brain C_{max} ng/g*	Brain AUC_{0-8h}* (ng h/g)	CLb** (ml/min/kg)
SB-222200 **3**	8.1	107	507	62
5	8.7	80	577	27

* Sprague–Dawley male rats. Dose = 3 mg/kg po formulated as methyl cellulose suspension.
** Dose = 1 mg/kg iv. In all studies blood and brain samples were measured between 0.5 and 12 h post-dose. Blood samples and brain homogenates were extracted by protein precipitation and the extracts analysed by LC–MS/MS. Brain exposures determined from exsanguinated homogenate. ND, not determined.
[a] Binding affinity pK_i is mean from at least 2 determinations. SD ⩽ 0.3 for all compounds.

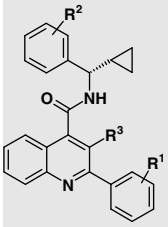
Table 2
NK_3 receptor antagonist binding and rat pharmacokinetics of 3-amino-2-(fluorophenyl)-*N*-[(1*S*)-1-phenylpropyl]-4-quinolinecarboxamides



	R	NK_3 pK_i	Brain C_{max}* (ng/g)	Brain AUC_{0-8h}* (ng h/g)	CLb** (ml/min/kg)
6	*o*-F	7.8	ND	ND	ND
7	*m*-F	8.4	223	1388	28
8	*p*-F	8.1	137	880	30

* Sprague–Dawley male rats. Dose = 3 mg/kg po formulated as methyl cellulose suspension.
** Dose = 1 mg/kg iv. In all studies blood and brain samples were measured between 0.5 and 12 h post-dose. Blood samples and brain homogenates were extracted by protein precipitation and the extracts analysed by LC–MS/MS. Brain exposures determined from exsanguinated homogenate. ND, not determined.

Table 3
NK_3 receptor antagonist binding and rat pharmacokinetics of *N*-[cyclopropyl(halophenyl) methyl]-3-amino and 3-methyl-2-halophenyl-4-quinoline carboxamides



	R^1	R^2	R^3	NK_3 pK_i	Brain C_{max}* (ng/g)	Brain AUC_{0-t}* (ng h/g)
9	H	H	NH_2	8.3	104	539
10 (GSK172981)	*m*-F	H	NH_2	8.0	464	2537
11 (*R*-enantiomer)[a]	*m*-F	H	NH_2	6.6	ND	ND
12	H	*m*-F	NH_2	8.5	237	1328
13	H	*o*-F	NH_2	8.3	ND	ND
14	*m*-F	*m*-F	NH_2	8.2	408	2524
15	*m*-F	H	CH_3	8.0	70	457

* Sprague–Dawley male rats. Dose = 3 mg/kg po formulated as methyl cellulose suspension.
[a] Prepared by chiral hplc resolution of racemate (generated from racemic amine).

affinity. Thus an SAR investigation was initiated to further optimise this compound.

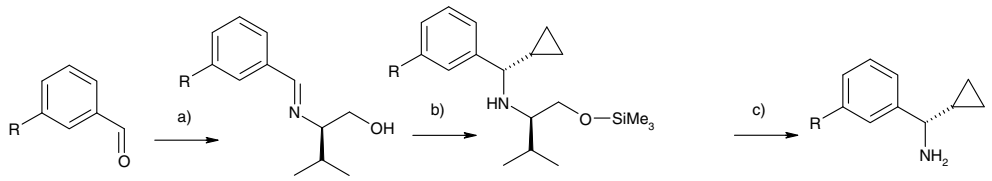
Previous SAR studies in the quinoline series had revealed little scope for introducing large substituents onto the C-2 Ph ring whilst maintaining high NK_3 affinity.[24,26] Hence only a limited investigation was carried out at this position (Table 2). Introduction of fluorine at the ortho position of the C-2 phenyl ring led to a marked reduction in NK_3 receptor affinity (compound **6**). By contrast, however, only a modest (~2- to 4-fold) reduction in affinity was observed on introduction of either *m*- or *p*-F (compounds **7–8**). Furthermore, when dosed orally in rats, **7** and **8** both produced excellent brain exposure.

Despite the excellent profiles of **7** and **8**, further analysis revealed that both molecules still underwent extensive oxidation of the C-4 amide sidechain (in a manner analogous to SB-222200). The ethyl group on the C-4 substituent was therefore replaced by cyclopropyl. Simultaneously the effects of fluorine substitution in the C-4 aryl ring were probed (Table 3).

The (*S*)-cyclopropanated amines utilised in this work were prepared as shown in Scheme 1. Reaction of the appropriate benzaldehyde with D-valinol generated chiral imine intermediates. The hydroxyl group was protected with TMS-chloride and the desired chiral centre generated by nucleophilic addition of cyclopropyl lithium. Finally the silyl group was removed and valinol auxiliary cleaved with aqueous periodate.[28] In all cases, preparation of intermediate quinoline acids and amide coupling reactions were carried out as previously reported.[24,26†]

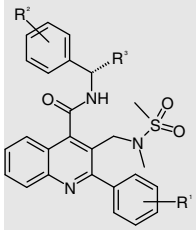
The NK_3 binding affinity and rat CNS exposure of **9** are both similar to **5**. Introduction of fluorine onto the C-2 phenyl ring (*m*-F compound **10**) resulted in a modest reduction in NK_3 receptor binding affinity but this was offset by a marked increase in expo-

† Diastereomeric excess for cyclopropanation reactions was not determined. However, chiral hplc on final compounds showed virtually undetectable levels of *R*-enantiomer.



Scheme 1. Synthesis of chiral amines. Reagents and conditions: R=H: (a) D-valinol, CH_2Cl_2, 87%; (b) Me_3SiCl, Et_3N, CH_2Cl_2 91% then cyclopropyl-Li, −40 °C, 87%; (c) MeOH, aq H_5IO_6 74%.

Table 4
C-3 sulfonamide analogues



	R^1	R^2	R^3	NK_3 pK_i	Brain C_{max}* (ng/g)	Brain AUC_{0-t}* (ng h/g)	Calc logP
16	H	*m*-F	Ethyl	8.9	ND	ND	4.6
17	*m*-F	H	Ethyl	8.9	ND	ND	4.6
18	*m*-F	*m*-F	Cyclopropyl	8.2	ND	ND	4.7
19	H	H	Cyclopropyl	8.8	ND	ND	4.4
20 (GSK256471)	H	*m*-F	Cyclopropyl	9.0	43	172	4.5 (3.2)[a]

* Sprague–Dawley male rats. Dose = 3 mg/kg po formulated as methyl cellulose suspension.
[a] Measured log*D* pH 7.4.

sure (rat blood clearance 24 ml/min/kg, brain concentrations increased 4- to 5-fold). As observed in previous studies, the *R*-enantiomer of **10** (compound **11**) had low NK_3 receptor affinity.[25]

Introduction of fluorine onto the C-4 phenyl ring was also well tolerated with minimal loss in NK_3 receptor affinity (compounds **12–14**). Compounds **12** and **14** also displayed excellent in vivo pharmacokinetic profiles in rat, reaching levels in brain much higher than **5.** Somewhat surprisingly, when similar structural modifications were applied to the C-3 methyl quinolines a corresponding increase in CNS exposure did not occur (compound **15**).

Whilst the NK_3 and pharmacokinetic profiles of **5–15** are promising, all these molecules are highly lipophilic (Daylight *clogP* all >6) and it is well recognised that this undesirable property potentially increases the risk of attrition in drug development.[29] Furthermore, it is apparent from previous SAR studies that modification of the quinoline C-2 and C-4 substituents to reduce lipophilicity generally produces a marked reduction in NK_3 receptor affinity. By contrast, however, previous SAR studies revealed tolerance for structural variation at the quinoline C-3 position maintaining high NK_3 receptor affinity.[24,26] Hence alternative substituents were also introduced at this position.

One of the most promising novel, polar C-3 substituents found in this investigation was the methyl[(methylsulfonyl)amino]methyl group. Thus compounds **16–20** were prepared using optimised C-2 and C-4 substituents (Table 4). In general these compounds showed excellent NK_3 receptor binding affinity, although, in contrast to the 3-amino quinolines, the whole brain concentration produced by **20** in a rat pharmacokinetic study was moderate.

From these studies compounds **10** and **20** were selected for further profiling. Both were confirmed as NK_3 receptor antagonists in a functional assay using FLIPR (fluorometric imaging plate reader) technology to determine their ability to inhibit intracellular NKB induced calcium release (human U2OS cells transiently transduced with recombinant BacMan virus expressing NK_3 receptor[30]). Functional pK_i values for **10** and **20** were similar to binding affinities (7.7 and 8.9, respectively).[‡]

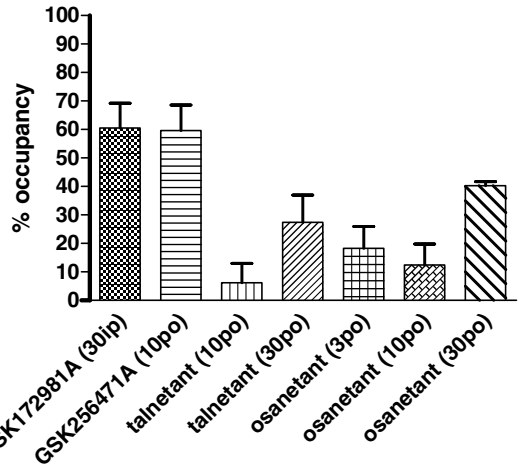


Figure 1. Ex vivo receptor binding study comparing GSK172981 **10** and GSK256471 **20** with talnetant **2** and osanetant **1.** Figure demonstrates increase in cortical NK_3 receptor occupancy ($n = 5$, mean value ± SEM). Compounds administered are illustrated on *x*-axis followed by dose in mg/kg and route of administration.

The ability of these two compounds to occupy NK_3 receptors in the CNS was then measured and compared directly against talnetant and osanetant in an ex vivo NK_3 receptor occupancy study in gerbil (Fig. 1 and Table 5).[31]

In this experiment, at similar doses, the cortical NK_3 receptor occupancy of both **10** and **20** exceeded that of talnetant and osanetant. It is noteworthy that despite very large differences in brain exposure, the measured NK_3 receptor occupancy of **10** and **20** is similar. This can be explained if unbound brain concentration

‡ IC_{50} values were determined from an inhibition dose-response curve. The potency of each antagonist (functional pK_i) was calculated from pIC_{50} by the Cheng–Prusoff equation using EC_{50} of NKB determined in a separate experiment.

Table 5
Exposure data generated in gerbil cortex NK_3 occupancy study

Compound	Calc log*P* (measured log$D_{7.4}$)	Dose (mg/kg) route	NK_3 pK_i gerbil[31]	Mean total brain ng/ml (nM)	Measured tissue binding % gerbil brain	Free brain conc (nM)	Measured mean receptor occupancy (RO) %
GSK172981 **10**	6.8	30 ip	8.3	2062 (5011)	99.3	35	61
GSK256471 **20**	4.5 (3.2)	10 po	8.9	61 (118)	96.7	4	60
SB223412	7.4	10 po	7.7	9 (24)	98.8	0.3	6
(talnetant, **2**)		30 po		42 (110)		1.3	27
SB236984	5.9	10 po	8.7	6 (10)	99.8	0.02	12
(osanetant, **1**)		30 po		10 (16)		0.03	40

and receptor affinity are considered rather than total brain concentration (Table 5). Equilibrium dialysis measurement of the brain tissue binding of **10**, perhaps unsurprisingly, revealed very high non-specific binding and a very low proportion of unbound drug (F_{ub} 0.7%).[33,34] Compound **20**, with reduced lipophilicity, has an increased proportion of free drug (F_{ub} 3.3%, ~5-fold higher than **10**). This difference, together with higher affinity for the NK_3 receptor, offsets the fact that the total brain concentration of **20** is much lower than **10** (118 nM vs 5 μM).

In light of the excellent brain receptor occupancy profiles of **10** and **20**, these compounds have been progressed for further in vivo evaluation which will be reported in due course.[35]

In summary, new SAR studies within the established quinoline series of NK_3 receptor antagonists has led to the discovery of two promising new compounds which both produce excellent NK_3 receptor occupancy in gerbil brain.

References and notes

1. Langlois, X.; Wintmolders, C.; te Riele, P.; Leysen, J. E.; Jurzak, M. *Neuropharmacology* **2001**, *40*, 242.
2. Mussap, C. J.; Geraghty, D. P.; Burcher, E. *J. Neurochem.* **1993**, *60*, 1987.
3. Tooney, P. A.; Au, G. G.; Chahl, L. A. *Clin. Exp. Pharmacol. Physiol.* **2000**, *27*, 947.
4. Bert, L.; Rodier, D.; Bougault, I.; Allouard, N.; Le Fur, G.; Soubrie, P.; Steinberg, R. *Synapse* **2002**, *43*, 62.
5. Furuta, T.; Koyano, K.; Tomioka, R.; Yanagawa, Y.; Kaneko, T. *J. Comp. Neurol.* **2004**, *473*, 43.
6. Gueudet, C.; Santucci, V.; Soubrie, P.; Le Fur, G. *Synapse* **1999**, *33*, 71.
7. Marco, N.; Thirion, A.; Mons, G.; Bougault, I.; Le Fur, G.; Soubrie, P.; Steinberg, R. *Neuropeptides* **1998**, *32*, 481.
8. Preston, Z.; Richardson, P. J.; Pinnock, R. D.; Lee, K. *Neurosci. Lett.* **2000**, *284*, 89.
9. Spooren, W.; Riemer, C.; Meltzer, H. *Nat. Rev. Drug Discov.* **2005**, *4*, 967.
10. Kamali, F. *Curr. Opin. Investig. Drugs* **2001**, *2*, 950.
11. Kronenberg, G.; Berger, P.; Tauber, R. F.; Bandelow, B.; Henkel, V.; Heuser, I. *Pharmacopsychiatry* **2005**, *38*, 24.
12. Evangelista, S. *Curr. Opin. Investig. Drugs* **2005**, *6*, 717.
13. Dawson, L. A.; Cato, K. J.; Scott, C.; Watson, J. M.; Wood, M. D.; Foxton, R.; de la Flor, R.; Jones, G. A.; Kew, J. N.; Cluderay, J. E.; Southam, E.; Murkitt, G. S.; Gartlon, J.; Pemberton, D. J.; Jones, D. N.; Davies, C. H.; Hagan, J. *Neuropsychopharmacology* **2008**, *33*, 1642.
14. Borioni, A.; Mustazza, C.; Sestili, I.; Sbraccia, M.; Turchetto, L.; Del Giudice, M. R. *Arch. Pharm. (Weinheim)* **2007**, *340*, 17.
15. Elliott, J. M.; Carling, R. W.; Chicchi, G. G.; Crawforth, J.; Hutson, P. H.; Jones, A. B.; Kelly, S.; Marwood, R.; Meneses-Lorente, G.; Mezzogori, E.; Murray, F.; Rigby, M.; Royo, I.; Russell, M. G.; Shaw, D.; Sohal, B.; Tsao, K. L.; Williams, B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5752.
16. Elliott, J. M.; Carling, R. W.; Chambers, M.; Chicchi, G. G.; Hutson, P. H.; Jones, A. B.; MacLeod, A.; Marwood, R.; Meneses-Lorente, G.; Mezzogori, E.; Murray, F.; Rigby, M.; Royo, I.; Russell, M. G.; Sohal, B.; Tsao, K. L.; Williams, B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5748.
17. Yan, H.; Kerns, J.; Jin, Q., et al *Synthetic Commun.* **2005**, *35*, 3105.
18. Smith, P. W.; Dawson, L. A. *Recent Patents CNS Drug Discov.* **2008**, *3*, 1.
19. Meltzer, H. *Drug Discov. Today* **2006**, *3*, 555.
20. Albert, J.; Potts, W. *Expert Opin. Ther. Patents* **2006**, *16*, 925.
21. Rumsey, W.; Kerns, J. K. *Handbook Exp. Pharmacol.* **2004**, *164*, 273.
22. Blaney, F. E.; Raveglia, L. F.; Artico, M.; Cavagnera, S.; Dartois, C.; Farina, C.; Grugni, M.; Gagliardi, S.; Luttmann, M. A.; Martinelli, M.; Nadler, G. M.; Parini, C.; Petrillo, P.; Sarau, H. M.; Scheideler, M. A.; Hay, D. W.; Giardina, G. A. *J. Med. Chem.* **2001**, *44*, 1675.
23. Giardina, G. A.; Artico, M.; Cavagnera, S.; Cerri, A.; Consolandi, E.; Gagliardi, S.; Graziani, D.; Grugni, M.; Hay, D. W.; Luttmann, M. A.; Mena, R.; Raveglia, L. F.; Rigolio, R.; Sarau, H. M.; Schmidt, D. B.; Zanoni, G.; Farina, C. *Farmaco* **1999**, *54*, 364.
24. Giardina, G. A.; Raveglia, L. F.; Grugni, M.; Sarau, H. M.; Farina, C.; Medhurst, A. D.; Graziani, D.; Schmidt, D. B.; Rigolio, R.; Luttmann, M.; Cavagnera, S.; Foley, J. J.; Vecchietti, V.; Hay, D. W. *J. Med. Chem.* **1999**, *42*, 1053.
25. Giardina, G. A.; Sarau, H. M.; Farina, C.; Medhurst, A. D.; Grugni, M.; Foley, J. J.; Raveglia, L. F.; Schmidt, D. B.; Rigolio, R.; Vassallo, M.; Vecchietti, V.; Hay, D. W. *J. Med. Chem.* **1996**, *39*, 2281.
26. Giardina, G. A.; Sarau, H. M.; Farina, C.; Medhurst, A. D.; Grugni, M.; Raveglia, L. F.; Schmidt, D. B.; Rigolio, R.; Luttmann, M.; Vecchietti, V.; Hay, D. W. *J. Med. Chem.* **1997**, *40*, 1794.
27. Sarau, H. M.; Griswold, D. E.; Bush, B.; Potts, W.; Sandhu, P.; Lundberg, D.; Foley, J. J.; Schmidt, D. B.; Webb, E. F.; Martin, L. D.; Legos, J. J.; Whitmore, R. G.; Barone, F. C.; Medhurst, A. D.; Luttmann, M. A.; Giardina, G. A.; Hay, D. W. *J. Pharmacol. Exp. Ther.* **2000**, *295*, 373.
28. Bradley, D. M., Porter, R. A., Smith, P. W., Stead, R. E. A., Vong, A. K. K. WO2006050991, 2006.
29. Leeson, P. D.; Springthorpe, B. *Nat. Rev. Drug Discov.* **2007**, *6*, 881.
30. Ames, R.; Fornwald, J.; Nuthulaganti, P.; Trill, J.; Foley, J.; Buckley, P.; Kost, T.; Wu, Z.; Romanos, M. *Receptors Channels* **2004**, *10*, 99.
31. There are considerable species differences in NK_3 receptor expression and sequence and many NK_3 ligands have reduced affinity for rodent homologues of the receptor. Gerbil was selected as a suitable species for the occupancy study since quinoline antagonists generally show similar affinities between gerbil and human NK_3 (Table 5). Gerbils were pre-dosed with test ligand and cortical tissue harvested following a 1-h pre-treatment time. Ex vivo receptor occupancy was determined using a modified version of previously reported homogenate binding techniques.[32]
32. Thomas, D. R.; Nelson, D. R.; Johnson, A. M. *Psychopharmacology (Berl)* **1987**, *93*, 193.
33. Wan, H.; Rehngren, M.; Giordanetto, F.; Bergstrom, F.; Tunek, A. *J. Med. Chem.* **2007**, *50*, 4606.
34. Watson, J. M.; Coggon, S.; Lucas, A.; Clarke, K. L.; Viggers, J.; Cheetham, S.; Jeffrey, P.; Porter, R. A., Read, K. D. *Drug Metab. Dispos.*, submitted for publication.
35. Dawson, L. A.; Dada, S.; Langmead, C. J.; Watson, J. M.; Wu, Z.; de la Flor, R.; Jones, G. A.; Kew, J. N.; Cluderay, J. E.; Southam, E.; Murkitt, G. S.; Hill, M. D.; Jones, D. N.; Davies, C. H.; Hagan, J.; Smith, P. W. In vitro and in vivo comparison of two non-peptide NK_3 receptor antagonists: improvements in efficacy achieved through enhanced brain penetration or altered pharmacological characteristics, in preparation.