Available online at www.sciencedirect.com
SCIENCE DIRECT
Bioorganic & Medicinal Chemistry Letters 16 (2006) 1197–1201
Bioorganic & Medicinal Chemistry Letters

Novel lactam NK_1 antagonists with anti-emetic activity

Gregory J. Hollingworth,[a,*] Emma J. Carlson,[b] José L. Castro,[a] Gary G. Chicchi,[c] Natalie Clark,[b] Laura C. Cooper,[a] Olivier Dirat,[a] Jerry Di Salvo,[c] Jason M. Elliott,[a] Ruth Kilburn,[c] Marc M. Kurtz,[c] Wayne Rycroft,[b] F. David Tattersall,[b] Kwei-Lan Tsao[c] and Christopher J. Swain[a]

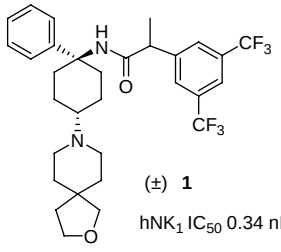
[a]*Department of Medicinal Chemistry, Merck Sharp & Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*
[b]*Department of Pharmacology, Merck Sharp & Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*
[c]*Department of Biochemistry, Merck Research Laboratories, Rahway, NJ 07065, USA*

Received 28 October 2005; revised 23 November 2005; accepted 23 November 2005
Available online 27 December 2005

Abstract—A series of 4,4-disubstituted cyclohexylamine NK_1 antagonists containing a lactam ring is described. The compounds are brain penetrant and activity is demonstrated in a ferret emesis model.

The utility of neurokinin-1 (NK_1) antagonists for the treatment of chemotherapy-induced emesis has now been established; Aprepitant (Emend®) is currently the only commercially available drug in this class.[1] Moreover, their potential utility for a range of therapeutic conditions such as depression, inflammatory bowel disease and asthma has been widely reported.[2] The interest in this receptor, to which the neuropeptide substance P normally binds, has led to the disclosure of selective NK_1 antagonists by several groups including our own.[2,3] In two recent communications, we described a novel structural class of cyclohexylamine NK_1 antagonists exemplified by the lead compound **1**.[4]

The cyclohexyl core of **1** is geminally substituted with a phenyl ring and a 2-[3,5-bis(tri-fluoromethyl)phenyl]propionamide, the key elements of the NK_1 pharmacophore. A pendant amine substituent in the 4-position, *trans* to the amide, locks the cyclohexane ring in the preferred binding conformation with the phenyl ring axially disposed.[4a] The receptor is tolerant of a variety of amine substituents and the 2-oxa-8-azaspiro[5.4]decane group



(±) **1**

hNK_1 IC_{50} 0.34 nM

was developed to give optimal in vitro binding to the NK_1 receptor (hNK_1 IC_{50} 0.34 nM) and binding selectivity over the I_{Kr} cardiac potassium channel (hI_{Kr} K_i 0.8 μM); early compounds in the series had shown poor selectivity over this potassium channel.[4b]

Compound **1** was also shown to be brain penetrant since it was active in the gerbil foot-tapping assay.[5] Central infusion of the NK_1 agonist GR73632 in gerbils causes a foot-tapping response in control animals. Intravenous administration of **1** immediately prior to this infusion showed an inhibition of this centrally mediated response (ID_{50} 1.4 mg/kg iv). Moreover, the compound had similar activity when dosed with a 2 h or 24 h pretreatment time (ID_{50} 1.1 mg/kg iv and 1.6 mg/kg iv, respectively) indicating good central duration of action. The compound was also active after oral dosing at the 24 h time-point (ID_{50} 2.2 mg/kg po).

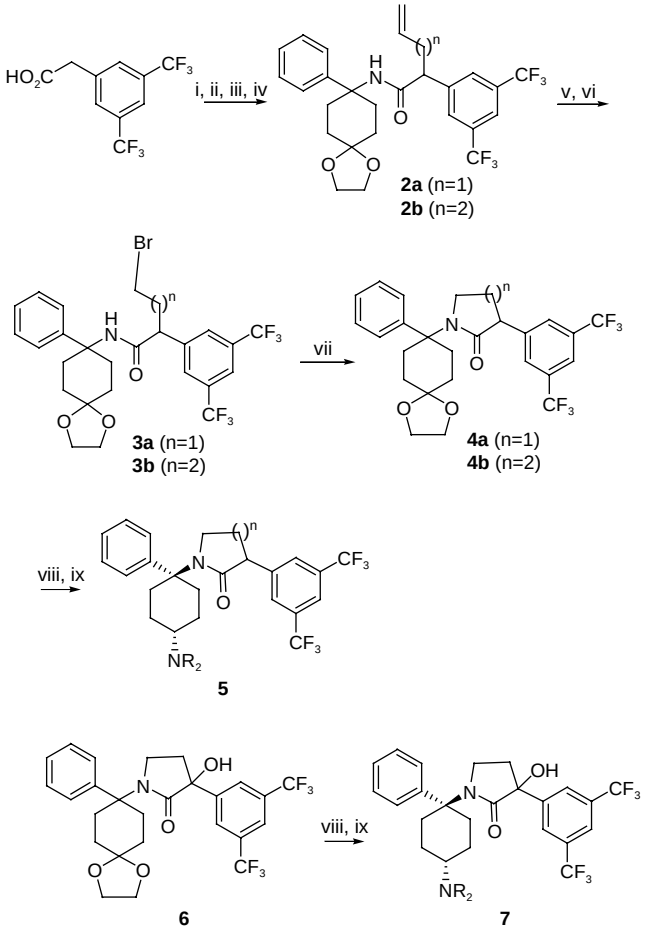
Keywords: NK_1; Neurokinin; Tachykinin; Substance P; Emesis; Anti-emetic; Lactam.
* Corresponding author. Tel.: +44 1279 440468; e-mail: greg_hollingworth@merck.com

0960-894X/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.11.111

While this is a good profile, the activity in the gerbil assay at early time-points is weaker than expected by comparison with other series of NK_1 antagonists. It was reasoned that reducing the high polarity of the amide might confer better brain penetration on these compounds and improve activity in this key in vivo assay.

A series of lactams was therefore proposed which do not have an amide N–H bond and as a result are less polar. Whilst the formation of a lactam also limits the conformational degrees of freedom, modelling studies had suggested that these molecules could adopt a suitable conformation for binding to the NK_1 receptor. Analogues containing five- and six-membered lactam rings were synthesised according to Scheme 1.

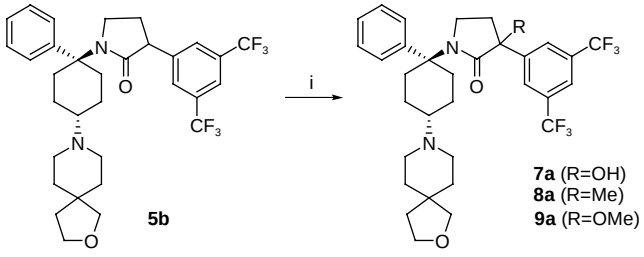
Mono-alkylation of the dianion derived from 3,5-bis(trifluoromethyl)phenylacetic acid using either allyl bromide or 4-bromobut-1-ene as electrophile was followed by amide coupling of the acid product with 4-amino-4-phenylcyclohexan-1-one.[4] Ketone protection under standard conditions led to amides **2a** and **2b**, respectively. Ozonolysis with reductive work-up then bromination of the resulting alcohol led to the bromides **3a/3b**. Cyclisation of the bromides to the lactams **4a/4b** was achieved using sodium hydride as base in moderate yield. Ketal deprotection then reductive amination and removal of the less active *cis*-isomer by chromatography furnished the final compounds **5** as the pure *trans*-isomers.[6] The cyclisation reaction of the bromides **3a/3b** using sodium hydride was complicated by the propensity of the lactam to hydroxylate at the benzylic position, presumably by reaction of the anion (produced in the presence of excess base) with trace amounts of oxygen. This side reaction, particularly problematic on a small scale, could be suppressed by rigorous degassing with argon, although a more convenient and reproducible cyclisation was found to occur using one equivalent of sodium hexamethyldisilazide as base at room temperature, producing a 86% yield of **4a** from **3a**. The oxidation could be used to advantage if allowed to run to completion, the oxidised product **6** allowing synthesis of hydroxylated analogues **7**.



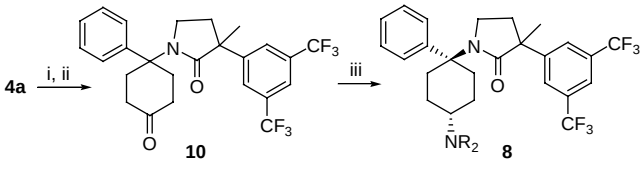
Scheme 1. Reagents and conditions: (i) 2 equiv *n*-BuLi, $Br(CH_2)_nCH{=}CH_2$, THF, 79%; (ii) $(COCl)_2$ 100%; (iii) 4-amino-4-phenylcyclohexan-1-one, py, CH_2Cl_2, 60%; (iv) ethylene glycol, *p*-TSA, $PhCH_3$, 98%; (v) O_3, then $NaBH_4$, $MeOH/CH_2Cl_2$, 83%; (vi) CBr_4, PPh_3, 2,6-di-*tert*-butyl-4-picoline, CH_2Cl_2, rt, 76%; (vii) NaH, THF, 88% or NaHMDS, THF, 86%; (viii) HCl, acetone-water, 97%; (ix) HNR_2, $NaBH(OAc)_3$, DCE, ca. 80%, then separate *cis*- and *trans*-isomers (Notes: yields quoted are for $n = 1$ sequence; all numbered compounds are racemic).

In the lead series, the α-methyl substituent had been shown to be important.[4b] For this reason, the α-methylated lactam was also targeted. Simple methylation of **5b** on a small scale was again complicated by the propensity of the benzylic anion to oxidise. Thus, in addition to the desired product, the corresponding hydroxylated and methoxylated compounds were produced (Scheme 2).

A more satisfactory synthesis, amenable to analogue production, was developed to obviate this problem (Scheme 3). A slurry of sodium hydride in DMF was added to a mixture of lactam **4a** and iodomethane in DMF. Under these conditions, the sole product in 97% yield was the desired methylated compound which

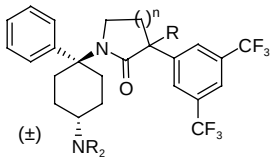


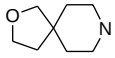
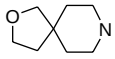
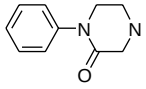
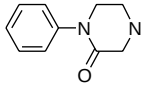
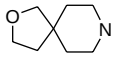
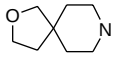
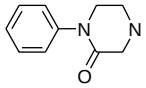
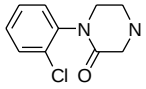
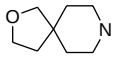
Scheme 2. Reagents: (i) NaH, MeI, DMF, combined yield 90%.

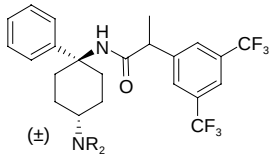


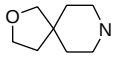
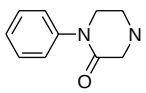
Scheme 3. Reagents: (i) MeI, DMF, then NaH, DMF; (ii) HCl, acetone–water; (iii) HNR_2, $NaBH(OAc)_3$, DCE, ca. 80% then separate isomers.

Table 1. NK_1 receptor binding affinity, gerbil foot-tapping results and I_{Kr} channel activity for the lactam series. Selected α-methyl amides are shown for comparison



Compound	NR_2	*n*	R	hNK_1[a] IC_{50} (nM)	Gerbil FT[b] ID_{50} (mg/kg)		hI_{Kr}[c] K_i (nM)
					t = 0	*t* = 24 h	
5a		1	H	6.2	—	—	984
5b		1	H	0.50	0.35	62% at 3	327
5c		2	H	0.80	—	34% at 3	798
5d		1	H	1.1	0.09	2.10	1996
5e		2	H	1.5	—	—	6529
7a		1	OH	0.66	—	5% at 3	862
8a		1	Me	0.33	—	0.24	364
8b		1	Me	0.48	0.22	0.60	1946
8c		1	Me	0.48	—	57% at 3	2987
9a		1	OMe	0.48	—	29% at 3	947



Compound	NR_2	hNK_1[a] IC_{50} (nM)	Gerbil FT[b] ID_{50} (mg/kg)		hI_{Kr}[c] K_i (nM)
			t = 0	*t* = 24 h	
1		0.34	1.44	1.62	787
11		0.62	0.13	1.20	3706

[a] Displacement of [^{125}I]-labelled substance P from the cloned hNK_1 receptor expressed in CHO cells (mean, $n = 3$).[8]
[b] Inhibition of GR73632-induced foot-tapping in gerbils.[5] All NK_1 antagonists given intravenously. Where ID_{50} value is not determined, % inhibition at 3 mg/kg is quoted.
[c] Displacement of labelled MK-499 from the cloned channel expressed in HEK cells (mean, $n = 3$).[9]

underwent deketalisation in 99% yield to give ketone **10**. This was elaborated to final compounds **8** as before.

A series of lactams was synthesised predominantly where the pendant amine substituent is a piperidine spiroether (as is the case for the lead compound **1**) or a 1-aryl-piperazin-2-one. The latter are based on the related, more potent lead **11**.[7] The biological data for these lactams are shown in Table 1.

It was pleasing to find that high NK_1 receptor binding affinity was observed across the whole series. As seen for the α-methyl amide series,[4,7] the piperidine spiroethers and 1-arylpiperazin-2-ones do give a real benefit over the simple dimethylamino group of **5a**. Both five- and six-membered lactam rings are well tolerated (**5b–e**) and hydroxy, methyl, and methoxy substituents all appear to be acceptable at the benzylic position (**7a**, **8a–c** and **9a**).

The lactams were also tested for their binding selectivity for NK_1 over the hERG cardiac potassium channel responsible for the I_{Kr} current. The selectivities are similar to those observed for the secondary amide analogues and range from modest (650-fold for **5b**) to excellent (4300-fold for **5e**). The piperazinones appear to give a slightly better selectivity than the corresponding piperidine spiroether analogues, however, it would be desirable to improve further upon this selectivity window.

Several compounds were profiled in the gerbil foot-tapping assay at the $t = 0$ time-point. The piperidine spiroether **5b** showed improved activity over the lead **1**, indicating improved brain penetration in agreement with the original hypothesis. For the inherently more brain penetrant aryl piperazinone series, it was pleasing that the lactams **5d** and **8b** retained the good activity of the lead **11**.

Having demonstrated good brain penetration for the lactam series, several NK_1 antagonists were tested in the gerbil assay after 24 h pretreatment to assess their central duration of action. Both **5b** and **5d** were interesting compounds, with activity being observed, although they were poorer in this protocol than their analogous amides **1** and **11**, respectively. Substitution at the benzylic position with hydroxy or methoxy groups (**7a** and **9a**) was detrimental, no improvement over the lead being seen. In contrast, substitution with a methyl group gave compounds (**8a** and **8b**) that did show a significantly improved central duration of action over their non-methylated counterparts (**5b** and **5d**) and also over the lead compounds **1** and **11**, respectively.

The excellent activity of these compounds in the gerbil assay was an extremely encouraging result, and two compounds (**5b** and **8a**) were further evaluated in our ferret emesis model.[10] In this assay, the inhibition by an NK_1 antagonist of *cis*-platin-induced emesis is measured. This functional assay is clearly relevant to the use of an NK_1 antagonist for the treatment of chemotherapy-induced nausea and vomiting. The emetic response is centrally mediated and in our experience only highly active, rapidly brain penetrant compounds show activity in this assay. It was therefore gratifying to find that both of these compounds did show a positive effect.

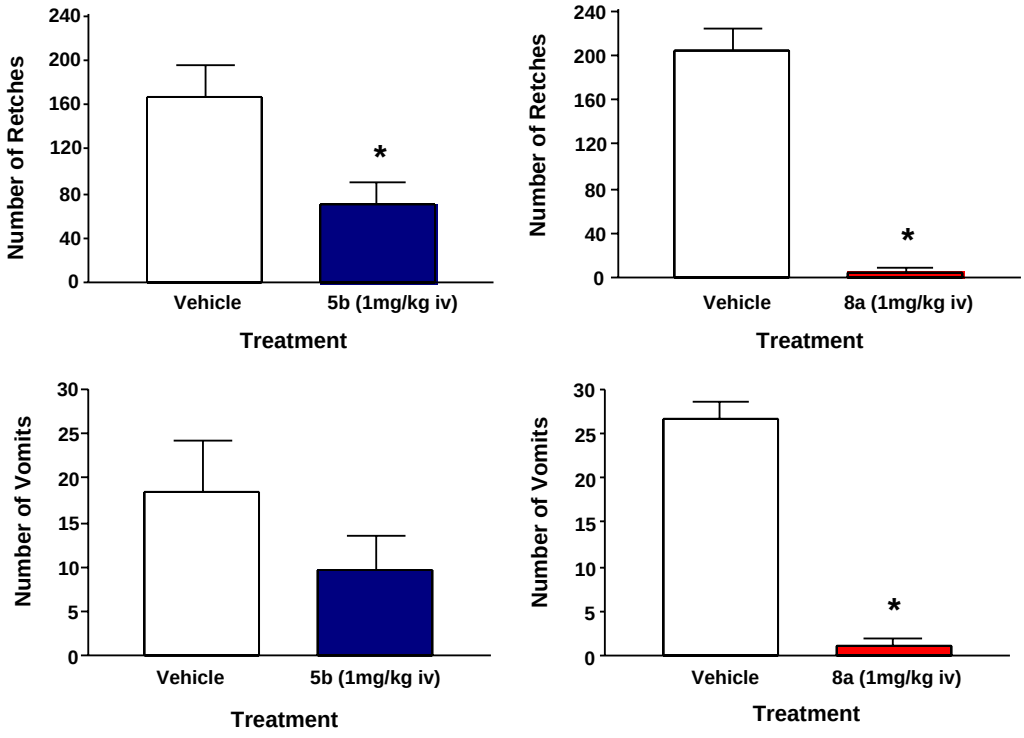


Figure 1. Effects of **5b** (blue) and **8a** (red) on *cis*-platin induced emesis in ferrets.

Ferrets were dosed intravenously with either 1 mg/kg of NK_1 antagonist or vehicle immediately prior to administration of 10 mg/kg iv *cis*-platin. The animals were then observed over a 4 h period and the retching and vomiting recorded. The results are shown in Figure 1.

It can be seen that a 50% inhibition of both retching and vomiting was observed for **5b**, which is an encouraging result. Methylation, however, appears to make a significant difference, compound **8a** being superior in this assay with an excellent 90% block of the emesis.[11]

In summary, a new class of high affinity cyclohexylamine NK_1 antagonists containing five- or six-membered lactam rings has been identified, with modest to excellent binding selectivity over the hI_{Kr} potassium channel. These compounds are brain penetrant (demonstrated by activity in a gerbil foot-tapping assay) and by judicious choice of substitution at the benzylic position, a long central duration of action can be achieved. The most promising compound **8a** shows good activity in a ferret emesis model when dosed intravenously with ID_{90} of $\approx$1 mg/kg.

References and notes

1. Dando, T. M.; Perry, C. M. *Drugs* **2004**, *64*, 777.
2. (a) Leroy, V.; Mauser, P.; Gao, Z.; Peet, N. P. *Expert Opin. Investig. Drugs* **2000**, 9; (b) Seward, E. M.; Swain, C. J. *Exp. Opin. Ther. Patents* **1999**, 9; (c) Swain, C. J.; Rupniak, N. M. J. *Annu. Rep. Med. Chem.* **1999**, *33*, 51; (d) Holzer, P.; Holzer-Petsche, U. *Curr. Opin. Pharm.* **2001**, *1*, 583, and references cited therein.
3. (a) Cooper, L. C.; Chicchi, G. G.; Dinnell, K.; Elliott, J. M.; Hollingworth, G. J.; Kurtz, M. M.; Locker, K. L.; Morrison, D.; Shaw, D. E.; Tsao, K.-L.; Watt, A. P.; Williams, A. R.; Swain, C. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1233; (b) Dinnell, K.; Chicchi, G. G.; Dhar, M. J.; Elliott, J. M.; Hollingworth, G. J.; Kurtz, M. M.; Ridgill, M. P.; Rycroft, W.; Tsao, K.-L.; Williams, A. R.; Swain, C. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1237; (c) Williams, B. J.; Cascieri, M. A.; Chicchi, G. G.; Harrison, T.; Owens, A. P.; Owen, S. N.; Rupniak, N. M. J.; Tattersall, F. D.; Williams, A. R.; Swain, C. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2719; (d) Seward, E. M.; Carlson, E.; Harrison, T.; Haworth, K. E.; Herbert, R.; Kelleher, F. J.; Kurtz, M. M.; Moseley, J.; Owen, S. N.; Owens, A. P.; Sadowski, S. J.; Swain, C. J.; Williams, B. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2515.
4. (a) Elliott, J. M.; Castro, J. L.; Chicchi, G. G.; Cooper, L. C.; Dinnell, K.; Hollingworth, G. J.; Ridgill, M. P.; Rycroft, W.; Kurtz, M. M.; Shaw, D. E.; Swain, C. J.; Tsao, K.-L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1755; (b) Cooper, L. C.; Carlson, E. J.; Castro, J. L.; Chicchi, G. G.; Dinnell, K.; Di Salvo, J.; Elliott, J. M.; Hollingworth, G. J.; Kurtz, M. M.; Ridgill, M. P.; Rycroft, W.; Tsao, K-L.; Swain, C. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1759.
5. Rupniak, N. M. J.; Tattersall, F. D.; Williams, A. R.; Rycroft, W.; Carlson, E.; Cascieri, M. A.; Sadowski, S.; Ber, E.; Hale, J. J.; Mills, S. G.; MacCoss, M.; Seward, E.; Huscroft, I.; Owen, S.; Swain, C. J.; Hill, R. G.; Hargreaves, R. J. *Eur. J. Pharmacol.* **1997**, *326*, 201.
6. Reductive amination reactions were typically unselective or slightly *trans*-selective (ratios 1:1 to 2.5:1). ^{1}H NMR experiments (400 MHz, CD_3OD) show that, in both isomers, the cyclohexyl ring adopts a chair conformation with the C-1 hydrogen axial. In *cis*-isomers, NOEs are seen from the *o*-hydrogens of the 4-phenyl group to both axial and equatorial C-3 hydrogens, indicating that the 4-phenyl group is equatorial. In trans-isomers, NOEs are seen from the *o*-hydrogens of the 4-phenyl group to the equatorial C-3 hydrogens and to the axial C-2 hydrogens, indicating that the 4-phenyl group is axial.
7. Ridgill, M. P., manuscript in preparation.
8. Cascieri, M. A.; Ber, E.; Fong, T. M.; Sadowski, S.; Bansal, A.; Swain, C. J.; Seward, E. M.; Frances, B.; Burns, D.; Strader, C. D. *Mol. Pharmacol.* **1992**, *42*, 458.
9. I_{Kr} affinity is measured using the MK-499 binding assay which is performed on membrane preparations from human embryonic kidney (HEK) cells constitutively expressing hERG. For a detailed protocol, see Ref. 4b.
10. Tattersall, F. D.; Rycroft, W.; Francis, B.; Pearce, D.; Merchant, K.; MacLeod, A. M.; Ladduwahetty, T.; Keown, L.; Swain, C.; Baker, R.; Cascieri, M.; Ber, E.; Metzger, J.; MacIntyre, E.; Hill, R. G.; Hargreaves, R. J. *Neuropharmacology* **1996**, *35*, 1121.
11. Spectroscopic data for compound **8a**: *m/z* (ES^+) 609 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (2H, s), 7.71 (1H, s), 7.51 (2H, d, *J* 6), 7.34 (2H, t, *J* 6), 7.25 (1H, t, *J* 6), 3.80 (2H, t, *J* 7), 3.48 (2H, s), 3.27–3.18 (1H, m), 3.15–3.08 (1H, m), 3.00–2.85 (2H, m), 2.50–2.20 (6H, m), 2.06–1.97 (1H, m), 1.87–1.75 (2H, m), 1.70–1.50 (8H, m), 1.47–1.32 (2H, m), 1.40 (3H, s).