SYNTHESIS OF ANTAGONISTS OF MUSCARINIC (M_3) RECEPTORS

Kenneth J. BROADLEY[a1], Robin H. DAVIES[b], Christine ESCARGUEIL[a2], Alan T. L. LEE[c1], Peter PENSON[a3] and Eric J. THOMAS[c2,*]

[a] *The Welsh School of Pharmacy, Cardiff University, King Edward VII Avenue, Cardiff CF10 3NB, UK; e-mail: [1] broadleykj@cf.ac.uk, [2] escargueilc@cf.ac.uk, [3] P.Penson@ljmu.ac.uk*

[b] *Muscagen Limited, 10, North Road, Cardiff, CF10 3DFY, UK; e-mail: daviesRH@cardiff.ac.uk*

[c] *School of Chemistry, University of Manchester, M13 9PL, UK; e-mail: [1] alan.t.lee@manchester.ac.uk, [2] e.j.thomas@manchester.ac.uk*

Received January 21, 2011
Accepted March 16, 2011
Published online June 8, 2011

Dedicated to Professor Pavel Kočovský on the occasion of his 60th birthday in recognition of his outstanding contributions to the area of organic chemistry.

Several α-hydroxyamides with (2,6-dialkoxyphenoxy)methyl substituents have been prepared and their activities as antagonists of the M_3 muscarinic receptor in guinea pig ileum have been evaluated. *N*-{1-[(Phenyl)methyl]piperidin-4-yl}-2-{2-[(2,6-dimethoxyphenoxy)-methyl]phenyl}-2-hydroxypropanamide and *N*-(1-[{6-amino-4-[(1-propylpiperidin-4-yl)methyl]-pyridin-2-yl}methyl]piperidin-4-yl)-2-cyclopentyl-2-hydroxy-2-phenylacetamide were the most potent compounds prepared, the micromolar potency of the latter indicating that it may be worth further investigation.

Keywords: Muscarinic receptors; Antagonists; Suzuki–Miyaura coupling; α-Hydroxyamides; Alcohols; Amides; Biological activity; Medicinal chemistry.

Muscarinic receptors participate widely in metabolic processes and their selective modulation has significance for many therapeutic applications[1]. Amongst these, regulation of the M_3 receptor, which is found in smooth muscle, has implications for bladder relaxation and treatment of urinary tract incontinence[2]. α-Hydroxyamides, e.g. **1**[3] and **2**[4], are known to be potent and selective inhibitors of M_3 receptors with useful metabolic stabilities, see Fig. 1. Following *ab initio* studies of a model of muscarinic receptors based on the structures of the α-helices of an adapted mammalian bovine rhodopsin receptor, a series of 2-benzazepinones **3** was designed as differently constrained analogues of the α-hydroxyamides **1** and **2**. Representative examples were synthesized and evaluated as selective M_3 antago-

Collect. Czech. Chem. Commun. 2011, Vol. 76, No. 7, pp. 781–801

doi:10.1135/cccc2011017

nists[5]. Further *ab initio* modelling subsequently indicated that the incorporation of a suitably positioned (2,6-dialkoxyphenoxy)methyl substituent could lead to an improvement in selectivity towards M_3 receptors by providing two points of contact with the moiety at position 151 (Ala, M_1, M_3, M_5; Val, M_2, M_4) and led to the design and synthesis of the 2-benzazepinone **4** [6]. The potency of this compound against M_3 receptors in guinea pig ileum was slightly less than that observed for some of the earlier examples, perhaps due to the loss of conformational flexibility when bound to the receptor site. It also showed membrane stabilizing properties at higher doses which suggested that a (2,6-dimethoxyphenyl)methyl substituent in an intrinsically potent compound with its expected high selectivity against M_2 receptors could provide some advantages[6].

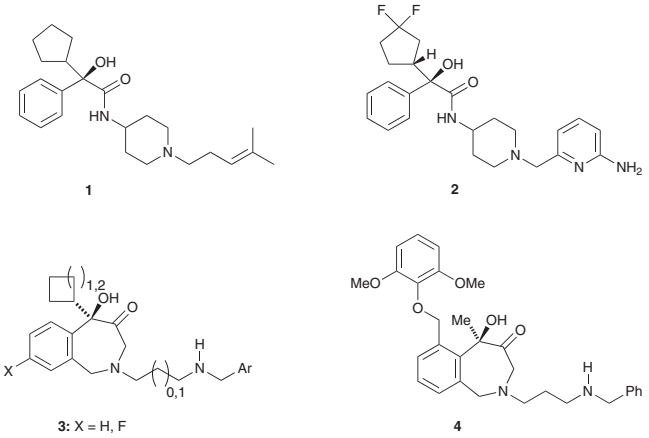


FIG. 1
Representative antagonists of M_3 receptors

It was decided to evaluate analogues of the α-hydroxyamides **1** and **2** with (2,6-dialkoxyphenoxy)methyl substituents at the 2-position in the benzene ring as selective M_3 antagonists. The simpler analogues **5** were prepared first to check procedures for incorporation of the (2,6-dialkoxyphenoxy)methyl substituent. The α-hydroxyamides **6** were then prepared as analogues of the α-hydroxyamide **2** and finally a bis-[(piperidinyl)-methyl]pyridine **7** was prepared to check the effect of further elaboration of the 2-aminopyridine moiety at the 4-position, see Fig. 2.

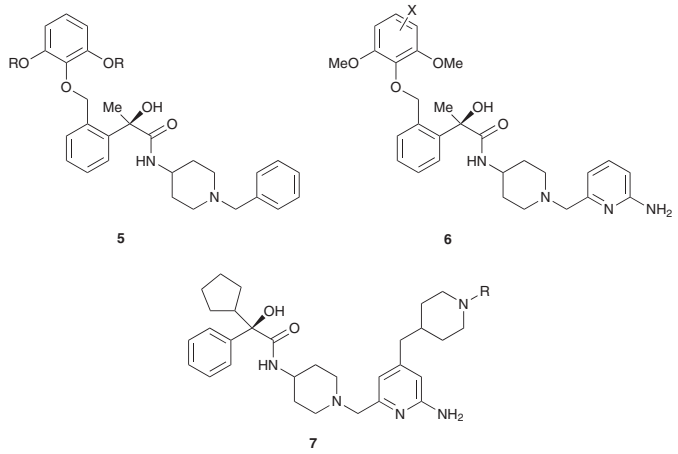


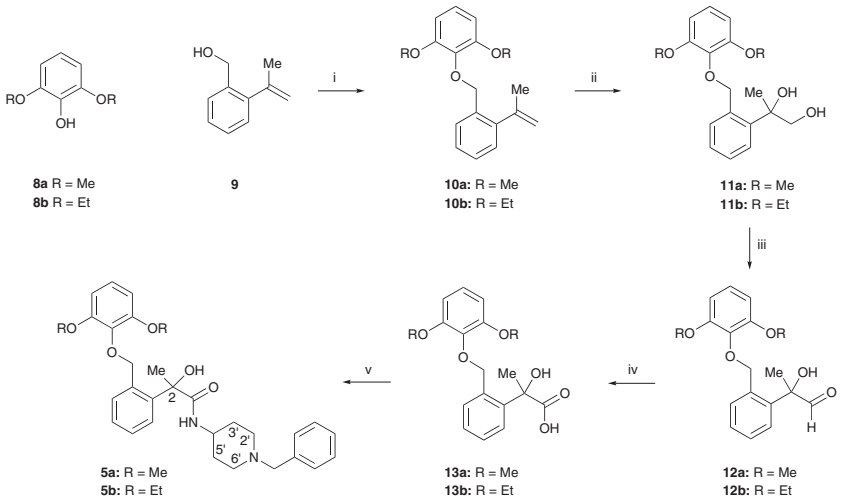
FIG. 2
α-Hydroxyamides to be evaluated as M_3 receptor antagonists

RESULTS AND DISCUSSION

Synthesis of α-Hydroxyamides with (2,6-Dialkoxyphenoxy)methyl Substituents

The racemic α-hydroxyamides **5a**, **5b** were synthesized as outlined in Scheme 1. Following Mitsunobu condensation of the [2-(1-methylethenyl)-phenyl]methyl alcohol **9** [7] with 2,6-dimethoxy- and 2,6-diethoxyphenol (**8a**, **8b**)[8], the resulting ethers **10a**, **10b** were hydroxylated[9] to give the diols **11a**, **11b**. Oxidation of diol **11a** using the Dess–Martin periodinane[10] resulted in C–C bond cleavage to the corresponding acetophenone, but oxidation under Swern conditions[11] gave the required aldehyde **12a** which was oxidized to the acid **13a** using sodium chlorite[12]. The analogous diethoxyphenyl substituted acid **13b** was similarly prepared and the two acids coupled with 4-amino-1-[(phenyl)methyl]piperidine to give the α-hydroxyamides **5a**, **5b**.

Having prepared the α-hydroxyamides **5a**, **5b**, procedures for the incorporation of an additional substituent into the (2,6-dialkoxyphenoxy)methyl moiety, and the (6-aminopyridin-2-yl)methyl substituent, were investigated. 4-Bromo- and 4-chloro-2,6-dimethoxyphenols (**8c** and **8d**) were prepared by regioselective demethylation of the 5-bromo- and 5-chloro-1,2,3-trimethoxybenzenes[13,14], and chlorination of 2,6-dimethoxyphenol gave 3-chloro-2,6-dimethoxyphenol (**8e**)[15]. These 2,6-dialkoxyphenols were



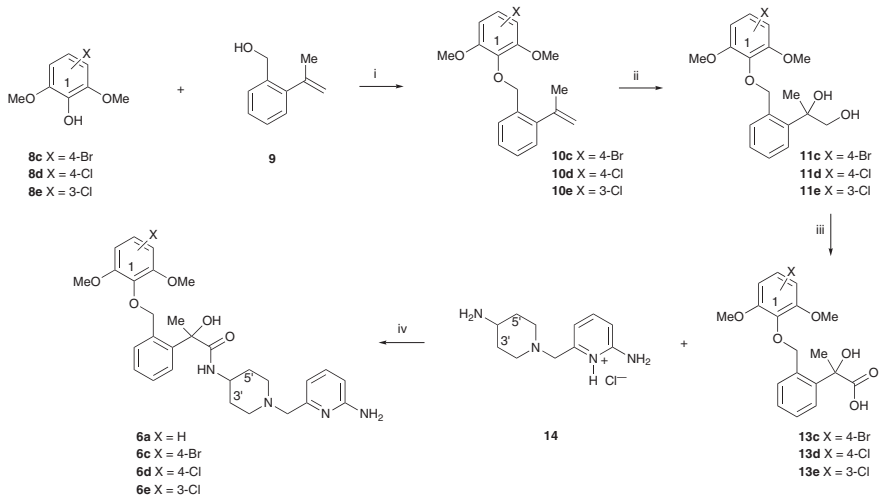
Reagents and conditions: i, 2,6-dialkoxyphenol, Ph_3P, DIAD, r.t., 16 h (**10a**, 75%; **10b**, 43%); ii, OsO_4 (10 mol%), NMO, acetone, water, r.t., (**11a**, **11b**, 93-100%); iii, DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 30 min, Et_3N, r.t., 30 min (**12a**, 68%; **12b**, 50%); iv, 2-methylbut-2-ene, $NaOCl_2$, ^{t}BuOH, water, NaH_2PO_4, 16 h (**13a**, 39%; **13b**, 61%); v, 4-amino-1-benzylpiperidine, HOBt hydrate, 4-methylmorpholine, DMF, 0 °C, then EDCI.HCl, r.t., 16 h (**5a**, 88%; **5b**, 70%).

SCHEME 1

taken through to the α-hydroxy-acids **13c–13e** via a Mitsunobu reaction with the alcohol **9** followed by hydroxylation and oxidation, see Scheme 2. The known 2-amino-6-[(4-aminopiperidin-1-yl)methyl]pyridine hydrochloride (**14**)[4] was then acylated using the hydroxyacids **13a**, **13c–13e** to give the racemic α-hydroxyamides **6a**, **6c–6e**.

Finally, it was decided to investigate the biological activity of α-hydroxyamides **7** which are analogous to the [(6-aminopyridin-2-yl)methyl]-piperidine **2**, but with an additional (piperidin-4-yl)methyl substituent at the 4-position of the pyridine ring. The Suzuki–Miyaura reaction of *N*-Boc-4-methylenepiperidine (**15**) and 4-bromopyridine has been used to access 4-[(piperidin-4-yl)methyl]pyridine (**16**), see Scheme 3 [16]. It was decided to use this approach for the synthesis of the representative α-hydroxyamide **7a**.

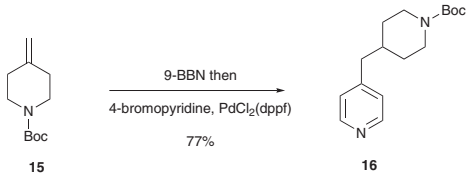
Heating chelidamic acid **17** with phosphorus pentabromide followed by treatment with methanol gave 4-bromo-2,6-bis(methoxycarbonyl)pyridine (**18**), see Scheme 4 [17]. A Suzuki–Miyura reaction with *N-tert*-butoxycarbonyl-4-methylenepiperidine (**15**)[18] then gave the 4-[(piperidin-4-yl)methyl]-



Reagents and conditions: i, **9**, 2,6-dialkoxyphenol, Ph_3P, DIAD, r.t., 16 h (**10c**, 73%; **10d**, 80%; **10e**, 64%); ii, OsO_4 (10 mol%), NMO, acetone, water, r.t., (**11c**, 85%; **11d**, 97%; **11e**, 85%); iii, (a) DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 30 min, Et_3N, r.t., 30 min (b) 2-methylbut-2-ene, $NaOCl_2$, ^{t}BuOH, water, NaH_2PO_4, 16 h (**13c**, 34%; **13d**, 69%; **13e**, 39%); v, **14**, HOBt hydrate, 4-methylmorpholine, DMF, 0 °C, then EDCI.HCl, r.t., 16 h (**6a**, 44%; **6c**, 41%; **6d**, 50%; **6e**, 22%).

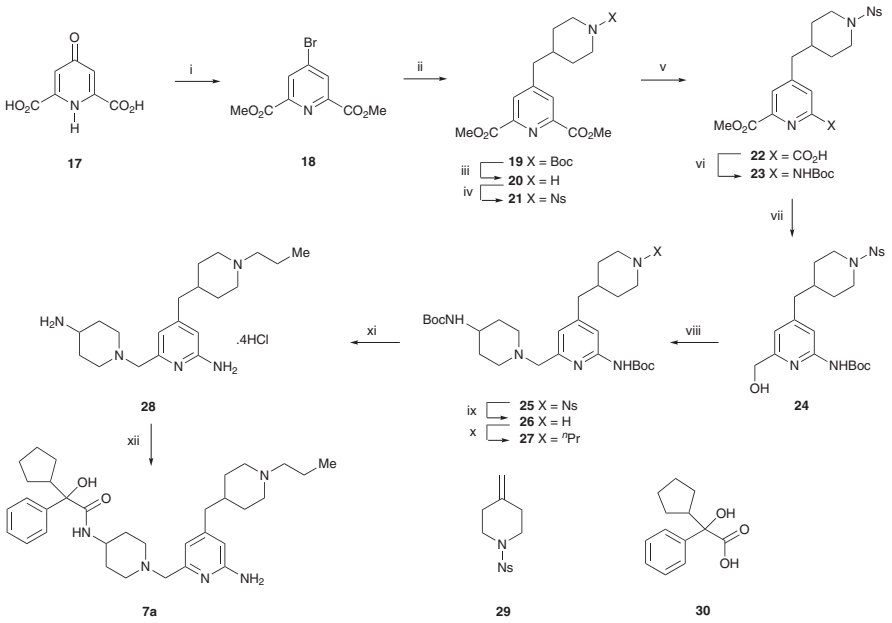
SCHEME 2

pyridine **19**. Removal of the *tert*-butoxycarbonyl group was achieved using trifluoroacetic acid and nosylation of the resulting amine **20** gave the nosyl protected piperidine **21** which was also prepared directly from the bromopyridine **18** via a Suzuki–Miyaura reaction using *N*-nosyl-4-methylenepiperidine (**29**). Monohydrolysis of the bis-ester **21** gave the mono-acid **22** which was converted into the *tert*-butoxycarbonyl protected amine **23** by a Curtius rearrangement. Reduction of the ester gave alcohol **24** which, following conversion into its mesylate, gave the 2-[(*N*-piperidinyl)methyl]-pyridine **25** by displacement using 4-(*tert*-butoxycarbonylamino)piperidine. Selective removal of the nosyl group using thiophenol and potassium car-



SCHEME 3

bonate provided the free piperidine **26** which was subjected to a reductive amination using propanal, triacetoxyborohydride and acetic acid to give the *N*-propyl derivative **27** [19]. Treatment with dilute aqueous hydrogen chloride then gave the amine **28** as its hydrochloride salt and coupling with the racemic α-hydroxyacid **30** gave the α-hydroxyamide **7a**.



Reagents and conditions: i, PBr_5, 90 °C, 3 h, $CHCl_3$, MeOH (84%); ii, **15** or **29**, 9-BBN, THF, heat under reflux, add **18**, K_2CO_3, Pd(dppf)Cl_2.CH_2Cl_2, r.t. 10 - 15 min (**19**, 89%; **21**, 89%); iii, TFA, CH_2Cl_2, r.t., 3 h; iv, NsCl, DMAP, Et_3N, CH_2Cl_2, r.t., 16 h (60% from **19**); v, MeOH, CH_2Cl_2, KOH, r.t., 16 h (91%); vi, $(PhO)_2P(O)N_3$, ^{t}BuOH, toluene, Et_3N, 100 °C, 16 h (66%); vii, $NaBH_4$, $CaCl_2$, EtOH, 0 °C, 2 h (97%); viii, Et_3N, MsCl, EtOAc, 0 °C, 1 h, then K_2CO_3, 4-*tert*-butoxycarbonylaminopiperidine, r.t., 16 h (85%); ix, PhSH, K_2CO_3, MeCN, r.t., 16 h (96%); x, propanal, AcOH, $NaBH(OAc)_3$, CH_2Cl_2, r.t., 16 h (94%); xi, aq. HCl (10%), MeOH, r.t., 24 h; xii, **30**, HOBt hydrate, Et_3N, $CHCl_3$, r.t., 30 min, EDCI hydrochloride, r.t., 16 h (53% from **27**).

SCHEME 4

Evaluation of the Activities of the α-Hydroxyamides as Antagonists of Muscarinic Receptors

The α-hydroxyamides **5a**, **6a**, **6b** and **7a** were screened for biological activity as antagonists of the M_3 receptor which mediates contractions of the guinea pig ileum and the M_2 receptor which mediates negative chrono-

tropic actions in guinea-pig isolated right atria. Tissues were set up in organ baths containing Kreb's bicarbonate buffer gassed with 5% CO_2 in oxygen maintained at 37 °C. Isometric tension was recorded by means of transducers (Ormed, Welwyn Garden City, Hertfordshire, UK) coupled to a PowerLab/4SP computer system (AD Instruments, Charlgrove, Oxfordshire, UK) for data collection. The spontaneous rate of contraction of the right atria was recorded. The data were analysed using Chart v.4.1.1 software (AD Instruments, Charlgrove, Oxfordshire, UK). Cumulative concentration-response curves were obtained for the increases in tension of the ileum and the reduction in rate of the atria in response to the non-selective muscarinic agonist methacholine. Concentration responses were obtained before and repeated in the presence of the compounds dissolved in dimethyl sulfoxide (DMSO). Control experiments were conducted with DMSO alone. Responses were plotted as changes in tension or rate. To determine the dose-ratios for any shifts of the concentration-response curves by the antagonist, curves were plotted as a percentage of the maximum response and dose-ratios calculated at the 50% response. Affinities of the antagonists were calculated as the pA_2 (pK_B) from $pA_2 = \log (DR - 1) - \log B$ where DR is the dose-ratio and B is the molar concentration of agonist. The results are summarised in the Table I.

TABLE I
M_3 and M_2 receptor antagonistic activity of representative hydroxyamides

Compound	M_3 (pK_B)	M_2 (pK_B)
5a	8.05 ± 0.09 (n = 6)	<5.5 (n = 2)
6a	<6.0	–
6b	<6.0	–
7a	7.35 ± 0.45 (n = 4)	<6.0 (n = 4)
Atropine[20]	9.4 ± 0.07 (n = 6)	8.72 ± 0.06 (n = 7)
Darifenacin	9.31 (n = 3)	7.22 (n = 3)

CONCLUSIONS

α-Hydroxyamide **5a** showed competitive muscarinic blocking activity against M_3 receptors of guinea pig ileum in the low nanomolar range but also some membrane stabilizing activity. This latter effect was evident as a depression of the maximum responses as the concentration was increased,

a phenomenon associated with antagonism of ion channels and is advantageous provided no arrhythmic effect is observed. This compound also showed over 100-fold selectivity over atrial M_2 receptors. The hydroxyamides **6a**, **6b** showed disappointing biological activity. However, the high micromolar potency of the α-hydroxyamide **7a** and its selectivity for M_3 over M_2 receptors was promising and may be studied further, the free nitrogen in the piperidinyl ring of the [(piperidinyl)methyl]pyridine **26** providing a site for further elaboration.

EXPERIMENTAL

Flash column chromatography was performed using Merck silica gel (60H; 40–60m, 230–240 mesh). Petrol refers to light petroleum which was redistilled before use and refers to the fraction boiling between 40 and 60 °C. Tetrahydrofuran was dried over sodium-benzophenone and was distilled prior to use. Dichloromethane was dried over CaH_2 and distilled before use. Ether refers to diethyl ether. Reactions under non-aqueous conditions were carried out under an atmosphere of nitrogen or argon.

Electron impact (EI) or chemical ionisation using ammonia (CI) mass spectra were recorded using a Fisons VG Trio 200 spectrometer and high resolution mass spectra on a Kratos Concept IS spectrometer. IR spectra (ν in cm^{-1}) were measured using a Genesis FTIR spectrometer on NaBr plates as evaporated films. NMR spectra were recorded in deuteriated chloroform unless otherwise indicated on either a Varian Unity 500 (500 MHz), Varian INOVA 300 (300 MHz), or a Varian Gemini 200 (200 MHz) spectrometer. Coupling constants (*J*) are given in Hz and chemical shifts in ppm (δ-scale) relative to tetramethylsilane.

4-Chloro-2,6-dimethoxyphenol (**8d**)[13,14]

Aluminium chloride (3.01 g, 22.56 mmol, 7 eq.) was added to 1,2,3-trimethoxy-5-chlorobenzene (653 mg, 3.22 mmol, 1 eq.) in CH_2Cl_2 (218 ml) and the mixture was stirred at ambient temperature for 4 h. After cooling in an ice bath, aqueous hydrogen chloride (2 M, 100 ml) was added and the resulting mixture was stirred for 10 min. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 ml) and the organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to yield the title compound **8d** (608 mg, 100%) as a grey solid used without further purification. R_F 0.09 (50% Et_2O/petrol). IR (film): 3405, 3004, 1611, 1590, 1509, 1463, 1455, 1442, 1423, 1362, 1311, 1239, 1213, 1111, 878, 831, 786. ^{1}H NMR (300 MHz, $CDCl_3$): 6.60 s, 2 H (Ar-H); 5.46 br s, 1 H (OH); 3.89 s, 6 H (OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 147.5, 133.7, 124.6, 105.9, 56.7. MS-CI: 208 (29) [$M^{\bullet+}$ + 18], 206 (100), 191 (12), 189 (40), 190 (11), 188 (26).

Synthesis of 1,3-Dialkoxy-2-{[2-(1-methylethenyl)phenyl]methoxy}benzenes (**10a–10e**). Representative Procedure

Diisopropyl azodicarboxylate (15.12 ml, 76.78 mmol, 3 eq.) was added to the alcohol **9** (3.79 g, 25.59 mmol, 1 eq.), 2,6-alkoxyphenol **8a** (7.89 g, 51.4 mmol, 2 eq.) and triphenylphosphine (20.14 g, 76.78 mmol, 3 eq.) in THF (128 ml) at ambient temperature and the

mixture was stirred for 16 h. After concentration under reduced pressure, chromatography of the residue (5→10–30% Et_2O/petrol) gave the benzyl ether **10a**.

1,3-Dimethoxy-2-{[2-(1-methylethenyl)phenyl]methoxy}benzene (**10a**) (5.43 g, 75%): a colourless oil, R_F 0.38 (30% Et_2O/petrol). IR (film): 1639, 1596, 1493, 1477, 1437, 1296, 1254, 1219, 1185, 1111, 773, 734. ^{1}H NMR (300 MHz, $CDCl_3$): 7.74 m, 1 H (Ar-H); 7.37–7.27 m, 2 H (Ar-H); 7.22 m, 1 H (Ar-H); 7.04 t, ^3J = 8.4, 1 H (Ar-H); 6.63 t, ^3J = 8.4, 2 H (Ar-H); 5.25 dq, J = 2.1, 1.6, 1 H (1″-H); 5.07 s, 2 H ($ArCH_2$); 4.97 dq, J = 2.1, 1.0, 1 H (1″-H′); 3.85 s, 6 H (2 × OCH_3); 2.15 dd, J = 1.5, 1.0, 3 H (CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 154.2, 144.7, 143.6, 137.6, 134.8, 130.0, 127.8, 127.7, 127.1, 124.0, 115.7, 105.7, 72.5, 56.3, 25.3. MS-ES$^-$: 591 (36), 307 (100). For $C_{18}H_{20}O_3Na$ ($M^{\bullet+}$ + 23) calculated: 307.1305, found: 307.1306.

1,3-Diethoxy-2-{[(2-(1-methylethenyl)phenyl]methoxy}benzene (**10b**) (310 mg, 43%): a colourless oil, R_F 0.58 (50% Et_2O/petrol). IR (film): 1593, 1467, 1392, 1299, 1253, 1212, 1120, 1090, 983, 900, 772, 738. ^{1}H NMR (300 MHz, $CDCl_3$): 7.82 m, 1 H (Ar-H); 7.37–7.27 m, 2 H (Ar-H); 7.23 m, 1 H (Ar-H); 6.99 t, ^3J = 8.4, 1 H (Ar-H); 6.61 t, ^3J = 8.4, 2 H (Ar-H); 5.26 dq, J = 2.1, 1.6, 1 H (1″-H); 5.08 s, 2 H ($ArCH_2$); 5.04–5.00 dq, J = 2.1, 1.0, 1 H (1″-H′); 4.08 q, ^3J = 7.0, 4 H (2 × $OC\mathbf{H}_2CH_3$); 2.17 dd, J = 1.4, 1.0, 3 H (CH_3); 1.46 t, ^3J = 7.0, 6 H (2 × $OCH_2C\mathbf{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$): 153.6, 144.8, 143.7, 138.3, 135.1, 130.3, 127.8, 127.7, 127.1, 123.8, 115.8, 106.8, 72.4, 64.8, 25.5, 15.3. MS-CI: 330 (17) [$M^{\bullet+}$ + 18], 313 (17), 131 (100). For $C_{20}H_{25}O_3$ ($M^{\bullet+}$ + H) calculated: 313.1798, found: 313.1794.

5-Bromo-1,3-dimethoxy-2-{[2-(1-methylethenyl)phenyl]methoxy}benzene (**10c**) (358 mg, 73%; using 2 eq. of Ph_3P and DIAD): a colourless oil, R_F 0.61 (30% Et_2O/petrol). IR (film): 1638, 1587, 1495, 1462, 1442, 1306, 1226, 1185, 1127, 975, 902, 840, 812, 788, 768. ^{1}H NMR (300 MHz, $CDCl_3$): 7.73 m, 1 H (Ar-H); 7.36–7.27 m, 2 H (Ar-H); 7.22 m, 1 H (Ar-H); 6.75 s, 2 H (Ar-H); 5.25 dq, J = 2.0, 1.6, 1 H (1″-H); 5.02 s, 2 H ($ArCH_2$); 4.97 dq, J = 2.1, 1.0, 1 H (1″-H′); 3.83 s, 6 H (2 × OCH_3); 2.14 dd, J = 1.5, 1.0, 3 H (CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 154.6, 144.6, 143.8, 136.6, 134.4, 130.0, 127.9, 127.8, 127.1, 116.5, 115.8, 109.3, 72.6, 56.5, 25.3. MS-ES$^+$: 382 (28) [$M^{\bullet+}$ + 18], 380 (30), 365 (11), 363 (9), 131 (100). For $C_{18}H_{23}NO_3{}^{79}Br$ ($M^{\bullet+}$ + NH_4) calculated: 380.0856, found: 380.0857.

5-Chloro-1,3-dimethoxy-2-{[2-(1-methylethenyl)phenyl]methoxy}benzene (**10d**) (638 mg, 80%; using 1 eq. of Ph_3P and DIAD): a colourless oil, R_F 0.64 (50% Et_2O/petrol). IR (film): 1590, 1495, 1454, 1413, 1225, 1127, 873, 815, 767. ^{1}H NMR (300 MHz, $CDCl_3$): 7.67 m, 1 H (Ar-H); 7.32–7.26 m, 2 H (Ar-H); 7.20 m, 1 H (Ar-H); 6.59 s, 2 H (Ar-H); 5.23 dq, J = 2.1, 1.6, 1 H (1″-H); 5.00 s, 2 H ($ArCH_2$); 4.95 dq, J = 2.1, 1.0, 1 H (1″-H′); 3.80 s, 6 H (2 × OCH_3); 2.12 dd, J = 1.5, 1.0, 3 H (CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 154.3, 144.6, 143.8, 136.1, 134.4, 130.0, 129.2, 127.9, 127.8, 127.1, 115.8, 106.3, 72.6, 56.4, 25.3. MS-CI: 338 (3) [$M^{\bullet+}$ + 18], 336 (7), 321 (1), 319 (3), 131 (100). For $C_{18}H_{19}O_3{}^{35}Cl$ ($M^{\bullet+}$) calculated: 318.1017, found: 318.1017.

1-Chloro-3-{[2-(1-methylethenyl)phenyl]methoxy}-2,4-dimethoxybenzene (**10e**) (277 mg, 64%; using 2 eq. of Ph_3P and DIAD): a colourless oil, R_F 0.58 (30% Et_2O/petrol). IR (film): 1478, 1465, 1439, 1418, 1371, 1297, 1216, 1093, 1013, 981, 900, 794, 760, 698. ^{1}H NMR (300 MHz, $CDCl_3$): 7.74 m, 1 H (Ar-H); 7.40–7.30 m, 2 H (Ar-H); 7.25 m, 1 H (Ar-H); 7.12 and 6.68 each d, ^3J = 9.0, 1 H (Ar-H); 5.28 dq, J = 2.1, 1.6, 1 H (1″-H); 5.10 s, 2 H ($ArCH_2$); 5.00 dq, J = 2.1, 1.0, 1 H (1″-H′); 3.94 and 3.85 each s, 3 H (OCH_3); 2.12 dd, J = 1.5, 1.0, 3 H (CH_3). ^{13}C NMR NMR (75 MHz, $CDCl_3$): 153.4, 150.8, 144.5, 143.8, 143.0, 134.2, 133.9, 129.9, 128.0, 127.3, 124.4, 120.3, 116.0, 108.3, 73.2, 61.6, 56.4, 25.4. MS-CI: 338 (24) [$M^{\bullet+}$ +

18], 336 (73), 321 (5), 319 (16), 131 (100). For $C_{18}H_{23}NO_3{}^{35}Cl$ ($M^{\bullet+}$ + NH_4) calculated: 336.1361, found: 336.1358.

Synthesis of 2-{2-[(2,6-Dialkoxyphenoxy)methyl]phenyl}propane-1,2-diols (**11a–11e**). Representative Procedure

Osmium tetraoxide (483 mg, 1.90 mmol, 10 mole %) followed by *N*-methylmorpholine *N*-oxide (6.68 g, 57.01 mmol, 3 eq.) were added at ambient temperature to the alkene **10a** (5.40 g, 19.00 mmol, 1 eq.) in acetone (304 ml) and water (152 ml). Upon completion of the reaction (monitored by TLC), saturated aqueous sodium sulfite (150 ml) was added. The mixture was stirred for 30 min then extracted with EtOAc (4 × 150 ml). The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give the product that was used without further purification.

2-{2-[(2,6-Dimethoxyphenoxy)methyl]phenyl}propane-1,2-diol (**11a**) (6.05 g, 100%): a pale orange oil, R_F 0.26 (Et_2O). IR (film): 3460, 1597, 1494, 1478, 1372, 1295, 1255, 1210, 1111, 1035, 762. ^{1}H NMR (300 MHz, $CDCl_3$): 7.45 d, ^3J = 7.9, 1 H (Ar-H); 7.34 m, 1 H (Ar-H); 7.18 m, 2 H (Ar-H); 7.04 t, ^3J = 8.4, 1 H (Ar-H); 6.59 d, ^3J = 8.4, 2 H (Ar-H); 5.37 and 5.27 each d, ^2J = 10.4, 1 H (ArHC**H**); 4.75 br s, 1 H (OH); 4.14 and 3.81 each d, ^2J = 11.1, 1 H (HC**H**OH); 3.81 s, 6 H (2 × OCH_3); 2.85 br s, 1 H (OH); 1.66 s, 3 H (CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 153.7, 145.2, 135.8, 134.4, 133.6, 129.1, 127.4, 127.1, 124.4, 105.4, 77.0, 74.8, 71.9, 56.2, 27.7. MS-ES$^+$: 341 (100) ($M^{\bullet+}$ + 23). For $C_{18}H_{22}O_5Na$ ($M^{\bullet+}$ + Na) calculated: 341.1359, found: 341.1356.

2-{2-[(2,6-Diethoxyphenoxy)methyl]phenyl}propane-1,2-diol (**11b**) (412 mg, 93%): a colourless oil, R_F 0.13 (50% Et_2O/petrol). IR (film): 3470, 1594, 1468, 1392, 1298, 1254, 1208, 1118, 1090, 1039, 972, 761, 740. ^{1}H NMR (300 MHz, $CDCl_3$): 7.45 d, ^3J = 7.9, 1 H (Ar-H); 7.36 ddd, ^3J = 7.7, 7.3, ^4J = 1.6, 1 H (Ar-H); 7.28 dd, ^3J = 7.5, ^4J =1.4, 1 H (Ar-H); 7.24 dd, ^3J = 7.3, 7.1, 1 H (Ar-H); 7.00 t, ^3J = 8.4, 1 H (Ar-H); 6.59 d, ^3J = 8.4, 2 H (Ar-H); 5.41 and 5.28 each d, ^2J = 10.0, 1 H (ArHC**H**); 4.13 d, ^2J = 11.3, 1 H (HC**H**OH); 4.13–3.99 m, 4 H (2 × OC**H**$_2$CH$_3$); 3.82 d, ^2J = 11.3, 1 H (**H**CHOH); 1.67 s, 3 H (CH_3); 1.46 t, ^3J = 7.0, 6 H (2 × OCH_2C**H**$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): 153.0, 145.2, 136.4, 134.7, 133.5, 129.0, 127.4, 127.1, 124.2, 106.3, 77.1, 74.7, 71.9, 64.7, 27.8, 15.1. MS-ES$^+$: 369 (100) ($M^{\bullet+}$ + 23), 347 (5), 329 (4). For $C_{20}H_{26}O_5Na$ ($M^{\bullet+}$ + Na) calculated: 369.1672, found: 369.1684.

2-{2-[(4-Bromo-2,6-dimethoxyphenoxy)methyl]phenyl}propane-1,2-diol (**11c**) [331 mg, 85%; after chromatography (50→100% Et_2O/petrol)]: a cloudy oil, R_F 0.10 (50% Et_2O/petrol). IR (film): 3468, 1589, 1494, 1461, 1442, 1409, 1226, 1186, 1127, 1037, 965, 814, 762, 731. ^{1}H NMR (300 MHz, $CDCl_3$): 7.45 dd, ^3J = 8.0, ^2J = 1.2, 1 H (Ar-H); 7.35 ddd, ^3J = 7.9, 6.9, ^4J = 1.9, 1 H (Ar-H); 7.20 ddd, ^3J = 7.5, 7.0, ^4J = 1.3, 1 H (Ar-H); 7.15 dd, ^3J = 7.5, ^4J = 1.9, 1 H (Ar-H); 6.72 s, 2 H (Ar-H); 5.34 and 5.25 each d, ^2J = 10.4, 1 H (ArHC**H**); 4.54 s, 1 H (OH); 4.10 dd, ^2J = 11.1, ^3J = 4.3, 1 H (HC**H**OH); 3.83–3.76 m, 7 H (2 × OCH_3 and HC**H**OH); 3.81 dd, ^3J = 9.2, 4.4, 1 H (OH); 1.64 s, 3 H (CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 154.1, 145.1, 135.0, 134.2, 133.6, 129.2, 127.4, 127.2, 116.9, 109.2, 77.0, 74.8, 71.8, 56.5, 27.6. MS-ES$^+$: 421 (100) [$M^{\bullet+}$ + 23], 419 (93), 416 (18), 414 (20), 399 (6), 397 (6), 381 (10), 379 (9). For $C_{18}H_{21}O_5{}^{79}BrNa$ ($M^{\bullet+}$ + Na) calculated: 419.0465, found: 419.0461.

2-{2-[(4-Chloro-2,6-dimethoxyphenoxy)methyl]phenyl}propane-1,2-diol (**11d**) [664 mg, 97%; after chromatography (40→100% Et_2O/petrol]: a white foam, R_F 0.13 (50% Et_2O/petrol). IR (film): 3468, 1592, 1496, 1463, 1455, 1445, 1415, 1312, 1226, 1187, 1127, 1037, 873, 817, 763, 733. ^{1}H NMR (300 MHz, $CDCl_3$): 7.42 dd, ^3J = 7.9, ^4J = 1.0, 1 H (Ar-H); 7.32 td,

^3J = 7.8, 7.1, ^4J = 1.9, 1 H (Ar-H); 7.17 ddd, ^3J = 7.5, 7.0, ^4J = 1.2, 1 H (Ar-H); 7.12 dd, ^3J = 7.6, ^4J = 1.7, 1 H (Ar-H); 6.55 s, 2 H (Ar-H); 5.30 and 5.22 d, ^2J = 10.4, each 1 H (ArHC**H**); 4.08 and 3.77 each d, ^2J = 11.3, 1 H (HC**H**OH); 3.75 s, 6 H (2 × OCH_3); 1.61 s, 3 H (CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 153.8, 145.0, 134.4, 134.1, 133.5, 129.6, 129.1, 127.4, 127.1, 106.2, 76.9, 74.8, 71.8, 56.4, 27.6. MS-ES$^+$: 377 (6) [$M^{\bullet+}$ + 23], 375 (21), 372 (28), 370 (100), 355 (0.3), 353 (1). For $C_{18}H_{25}NO_5{}^{35}Cl$ ($M^{\bullet+}$ + NH_4] calculated: 370.1416, found: 370.1413.

2-{2-[(3-Chloro-2,6-dimethoxyphenoxy)methyl]phenyl}propane-1,2-diol (**11e**) [331 mg, 85%; after chromatography (50→100% Et_2O/petrol)]: a white foam, R_F 0.10 (50% Et_2O/petrol). IR (film): 3468, 1580, 1478, 1465, 1418, 1373, 1296, 1230, 1091, 1037, 972, 795, 762. ^{1}H NMR (300 MHz, $CDCl_3$): 7.43 dd, ^3J = 7.8, ^4J = 1.5, 1 H (Ar-H); 7.35 ddd, ^3J = 8.0, 6.9, ^4J = 1.8, 1 H (Ar-H); 7.29 dd, ^3J = 7.6, ^4J = 1.7, 1 H (Ar-H); 7.22 td, ^3J = 7.2, ^4J = 1.5, 1 H (Ar-H); 7.10 d, ^3J = 9.0, 1 H (Ar-H); 6.61 d, ^3J = 9.0, 1 H (Ar-H); 5.43 and 5.38 each d, ^2J = 10.4, 1 H (ArHC**H**); 4.46 s, 1 H (OH); 4.09 dd, ^2J = 11.2, ^3J = 3.6, 1 H (HC**H**OH); 3.91 s, 3 H (OCH_3); 3.78 dd, ^2J = 11.4, ^3J = 2.3, 1 H (HC**H**OH); 3.75 s, 3 H (OCH_3); 2.70 dd, ^3J = 8.9, 4.6, 1 H (OH); 1.66 s, 3 H (CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 152.8, 150.5, 144.8, 141.5, 134.3, 133.4, 129.2, 127.4, 127.4, 124.8, 120.5, 108.1, 77.0, 75.1, 71.7, 61.4, 56.3, 27.6. MS-ES$^+$: 377 (35) [$M^{\bullet+}$ + 23], 375 (100), 372 (3), 370 (9), 355 (0.6), 353 (1). For $C_{18}H_{21}O_5{}^{35}ClNa$ ($M^{\bullet+}$ + Na) calculated: 375.0970, found: 375.0968.

2-{2-[(2,6-Dimethoxyphenoxy)methyl]phenyl}-2-hydroxypropanal (**12a**)

Dimethyl sulfoxide (3.60 ml, 50.26 mmol, 4 eq.) in CH_2Cl_2 (25 ml) was added dropwise to oxalyl chloride (2.20 ml, 25.13 mmol, 2 eq.) in CH_2Cl_2 (25 ml) at –78 °C and the mixture stirred for 30 min before adding the alcohol **11a** (4.00 g, 12.56 mmol, 1 eq.) in CH_2Cl_2 (25 ml). The reaction was stirred for a further 30 min then Et_3N (10.50 ml, 75.39 mmol, 6 eq.) was added dropwise and the mixture was allowed to warm to 0 °C and stirred for 30 min. Water (80 ml) was added and the mixture was extracted with CH_2Cl_2 (3 × 80 ml). The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (30→70% Et_2O/petrol) gave the title compound **12a** (2.71 g, 68%) as an orange oil, R_F 0.55 (Et_2O). IR (film): 3456, 2360, 2342, 1733, 1598, 1494, 1479, 1296, 1256, 1210, 1185, 1111, 773. ^{1}H NMR (300 MHz, $CDCl_3$): 9.84 s, 1 H (CHO); 7.44–7.33 m, 3 H (Ar-H); 7.28 m, 1 H (Ar-H); 7.03 t, ^3J = 8.5, 1 H (Ar-H); 6.59 d, ^3J = 8.5, 2 H (Ar-H); 5.51 br s, 1 H (OH); 5.19 and 5.13 d, ^2J = 10.7, each 1 H (ArHC**H**); 3.85 s, 6 H (2 × OCH_3); 1.77 s, 3 H, s (CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 201.6, 153.7, 139.8, 135.8, 135.5, 133.0, 129.0, 128.3, 127.7, 124.5, 105.4, 80.7, 74.2, 56.2, 24.8. MS-CI: 339 (100) [$M^{\bullet+}$ + 23]. For $C_{18}H_{20}O_5Na$ ($M^{\bullet+}$ + Na) calculated: 339.1203, found: 339.1204.

2-{2-[(2,6-Diethoxyphenoxy)methyl]phenyl}-2-hydroxypropanal (**12b**)

Following the procedure outlined for the synthesis of the aldehyde **12a**, using dimethyl sulfoxide (0.44 ml, 5.95 mmol, 5 eq.) in CH_2Cl_2 (5 ml) and oxalyl chloride (0.31 ml, 3.57 mmol, 3 eq.) in CH_2Cl_2 (5 ml), the diol **11b** (412 mg, 1.19 mmol, 1 eq.) in CH_2Cl_2 (22 ml) with Et_3N (0.99 ml, 7.14 mmol, 6 eq.) gave, after chromatography (20→30% Et_2O/petrol) the title compound **12b** (206 mg, 50%) as a pale yellow oil, R_F 0.34 (50% Et_2O/petrol). IR (film): 3465, 1734, 1595, 1468, 1372, 1299, 1255, 1208, 1118, 1090, 975, 767, 738. ^{1}H NMR (300 MHz, $CDCl_3$): 9.91 s, 1 H (CHO); 7.46–7.29 m, 4 H (Ar-H); 7.01 t, ^3J = 8.4, 1 H (Ar-H); 6.59 d, ^3J = 8.4, 2 H (Ar-H); 5.44 br s, 1 H (OH); 5.21 s, 2 H ($ArCH_2$);

4.10 m, 4 H (OCH_2CH_3); 1.80 s, 3 H (CH_3); 1.48 t, ^3J = 7.0, 6 H (OCH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 201.9, 153.1, 139.9, 136.4, 135.7, 132.9, 129.0, 128.3, 127.7, 124.4, 106.3, 80.8, 74.1, 64.7, 25.0, 15.2. MS-ES$^+$: 367 (60) [$M^{\bullet+}$ + 23], 345 (22), 327 (16). For $C_{20}H_{24}O_5Na$ ($M^{\bullet+}$ + Na) calculated: 367.1516, found: 367.1516.

2-{2-[(2,6-Dimethoxyphenoxy)methyl]phenyl}-2-hydroxypropanoic Acid (**13a**)

2-Methyl-2-butene (105 ml, 209.63 mmol, 30 eq.), sodium chlorite (3.98 g, 44.02 mmol, 6.3 eq.) and sodium dihydrogen phosphate (10.90 g, 69.88 mmol, 10 eq.) were added to the aldehyde **12a** (2.21 g, 6.99 mmol, 1 eq.) in *tert*-butanol (87 ml) and water (87 ml) and the mixture stirred for 16 h. Saturated aqueous sodium sulfite (87 ml) was added and the mixture stirred for 30 min then extracted with ethyl acetate (3 × 100 ml). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (50→100% Et_2O/petrol) to give the title compound **13a** (894 mg, 39%) as a pale yellow oil, R_F 0.39 (Et_2O). IR (film): 3438, 1732, 1645, 1598, 1479, 1465, 1419, 1374, 1296, 1257, 1217, 1112, 1092, 1007, 760 and 733. ^1H NMR (300 MHz, $CDCl_3$): 7.68 dd, ^3J = 7.9, ^4J = 1.2, 1 H (Ar-H); 7.41 td, ^3J = 7.6, ^4J = 1.6, 1 H (Ar-H); 7.30 td, ^3J = 7.4, ^4J = 1.3, 1 H (Ar-H); 7.23 dd, ^3J = 7.5, ^4J = 1.6, 1 H (Ar-H); 7.05 t, ^3J = 8.4, 1 H (Ar-H); 6.59 d, ^3J = 8.4, 2 H (Ar-H); 5.28 and 5.02 each d, ^2J = 11.3, 1 H (ArHC**H**); 3.80 s, 6 H (2 × OCH_3); 2.00 s, 3 H (CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 177.7, 153.5, 140.9, 135.2, 134.5, 133.3, 129.3, 128.7, 127.6, 124.8, 105.5, 77.2, 73.9, 56.2, 27.4. MS-ES$^-$: 331 (100) [$M^{\bullet+}$ – 1]. For $C_{18}H_{19}O_6$ ($M^{\bullet+}$ – H) calculated: 331.1187, found: 331.1178.

2-{2-[(2,6-Diethoxyphenoxy)methyl]phenyl}-2-hydroxypropanoic Acid (**13b**)

Following the procedure outlined for the synthesis of the acid **13a**, aldehyde **12b** (206 mg, 0.60 mmol, 1 eq.), after chromatography (50→60% Et_2O/petrol) gave the title compound **13b** (132 mg, 61%) as a pale oil, R_F 0.11 (50% Et_2O/petrol). IR (film): 3434, 1724, 1595, 1468, 1392, 1298, 1254, 1212, 1118, 1090, 737. ^1H NMR (300 MHz, $CDCl_3$): 7.69 dd, ^3J = 7.9, ^4J = 0.7, 1 H (Ar-H); 7.42 td, ^3J = 7.5, ^4J = 1.7, 1 H (Ar-H); 7.30 ddd, ^3J = 7.6, 7.1, ^4J = 1.0, 1 H (Ar-H); 7.25 dd, ^3J = 7.4, ^4J = 1.7, 1 H (Ar-H); 7.01 t, ^3J = 8.4, 1 H (Ar-H); 6.57 d, ^3J = 8.4, 2 H (Ar-H); 6.30 br s, 1 H (OH); 5.27 and 5.09 each d, ^2J = 11.4, 1 H (ArHC**H**); 4.06 m, 4 H (OCH_2CH_3); 2.00 s, 3 H (CH_3); 1.44 t, ^3J = 7.0, 6 H (2 × OCH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 177.2, 152.7, 140.9, 135.4, 134.6, 133.4, 129.4, 128.8, 127.7, 127.8, 106.2, 77.2, 73.9, 64.7, 27.3, 15.0. MS-ES$^+$: 361 (23) [$M^{\bullet+}$ + 1], 136 (100). For $C_{20}H_{25}O_6$ ($M^{\bullet+}$ + H) calculated: 361.1646, found: 361.1656.

N-{1-[(Phenyl)methyl]piperidin-4-yl}-2-{2-[(2,6-dimethoxyphenoxy)methyl]phenyl}-2-hydroxypropanamide (**5a**)

A mixture of the hydroxyacid **13a** (150 mg, 0.45 mmol, 1.0 eq.), 4-amino-1-benzylpiperidine (0.9 ml, 0.45 mmol, 1.0 eq.), HOBt hydrate (67 mg, 0.50 mmol, 1.1 eq.) and 4-methylmorpholine (0.199 ml, 1.81 mmol, 4 eq.) in DMF (2.25 ml) was stirred at 0 °C for 30 min then EDCI hydrochloride salt (87 mg, 0.45 mmol, 1.0 eq.) was added. The reaction mixture was allowed to stir for 16 h at ambient temperature then Et_2O (15 ml) was added. The organic layer was washed with saturated aqueous sodium hydrogen carbonate (15 ml) and the aqueous phase was extracted with Et_2O (3 × 15 ml). The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatogra-

phy of the residue (70% EtOAc/petrol; 1% Et_3N) gave the title compound **5a** (200 mg, 88%) as a colourless oil, R_F 0.54 (10% MeOH/CH_2Cl_2). IR (film): 3400, 2360, 1660, 1597, 1495, 1478, 1367, 1296, 1255, 1221, 1113 and 744. ^{1}H NMR (300 MHz, C_6D_6): 7.68 dd, ^3J = 7.9, ^4J = 1.1, 1 H (Ar-H); 7.34–7.25 m, 4 H (Ar-H and NH); 7.22–7.04 m, 4 H (Ar-H); 6.97 td, ^3J = 7.4, ^4J = 1.3, 1 H (Ar-H); 6.76 t, ^3J = 8.4, 1 H (Ar-H); 6.23 d, ^3J = 8.4, 2 H (Ar-H); 5.84 br s, 1 H (OH); 5.66 and 5.22 each d, ^2J = 11.4, 1 H (ArHC**H**); 3.93 m, 1 H (4′-H); 3.24 s, 6 H (2 × OCH_3); 3.20 s, 2 H ($ArCH_2N$); 2.59–2.43 m, 2 H; 2.06 s, 3 H (CH_3); 1.90–1.69 m, 4 H; 1.45–1.26 m, 2 H. ^{13}C NMR (75 MHz, C_6D_6): 175.1, 153.8, 143.4, 139.5, 136.2, 135.5, 132.7, 129.0, 128.6, 128.4, 128.1, 127.5, 127.1, 124.1, 105.6, 77.5, 73.9, 63.0, 55.6, 52.3, 52.2, 46.6, 32.2, 32.1, 28.5. MS-ES$^+$: 527 (100) [$M^{\bullet+}$ + 23], 505 (75). For $C_{30}H_{37}N_2O_5$ ($M^{\bullet+}$ + H) calculated: 505.2697, found: 505.2701.

N-{1-[(Phenyl)methyl]piperidin-4-yl}-2-{2-[(2,6-diethoxyphenoxy)methyl]phenyl}-2-hydroxypropanamide (**5b**)

Following the procedure outlined for the synthesis of the amide **5a**, the hydroxyacid **13b** (132 mg, 0.37 mmol, 1.0 eq.) and 4-amino-1-benzylpiperidine (0.75 ml, 0.37 mmol, 1.0 eq.) gave, after chromatography (50→80% EtOAc/petrol; 1% Et_3N), the title compound **5b** (137 mg, 70%) as a colourless oil, R_F 0.40 (10% MeOH/CH_2Cl_2). IR (film): 3459, 3399, 1670, 1595, 1493, 1468, 1392, 1367, 1298, 1253, 1207, 1090, 1090, 741. ^{1}H NMR (300 MHz, C_6D_6): 7.69 dd, ^3J = 7.7, ^4J = 1.0, 1 H (Ar-H); 7.38 d, ^3J = 8.1, 1 H (NH); 7.32 dd, ^3J = 7.5, ^4J = 1.4, 1 H (Ar-H); 7.30–7.24 m, 2 H (Ar-H); 7.22–7.07 m, 4 H (Ar-H); 7.01 td, ^3J = 7.4, ^4J = 1.1, 1 H (Ar-H); 6.81 t, ^3J = 8.3, 1 H (Ar-H); 6.30 d, ^3J = 8.3, 2 H (Ar-H); 5.78 br s, 1 H (OH); 5.65 and 5.26 each d, ^2J = 11.5, 1 H (ArHC**H**); 3.93 m, 1 H (4′-H); 3.56 m, 4 H ($OC\mathbf{H}_2CH_3$); 3.20 s, 2 H ($ArCH_2N$); 2.58–2.46 m, 2 H; 2.04 s, 3 H (CH_3); 1.91–1.70 m, 4 H; 1.45–1.27 m, 2 H; 1.11 t, ^3J = 7.0, 6 H (2 × $OCH_2C\mathbf{H}_3$). ^{13}C NMR (75 MHz, C_6D_6): 175.2, 153.1, 143.5, 139.5, 136.8, 135.7, 132.6, 129.0, 128.6, 128.5, 128.4, 128.0, 127.1, 124.0, 106.5, 77.6, 74.0, 64.4, 63.0, 52.3, 46.6, 32.2, 32.0, 28.4, 14.8. MS-ES$^+$: 553 (100) [$M^{\bullet+}$ + 1]. For $C_{32}H_{41}N_2O_5$ ($M^{\bullet+}$ + H) calculated: 533.3010, found: 533.3018.

Preparation of 2-{2-[(2,6-Dimethoxyphenoxy)methyl]phenyl}-2-hydroxypropanoic Acids (**13c–13e**). Representative Procedure

Dimethyl sulfoxide (0.30 ml, 4.18 mmol, 5 eq.) in CH_2Cl_2 (5 ml) was added dropwise to oxalyl chloride (0.22 ml, 2.51 mmol, 3 eq.) in CH_2Cl_2 (11 ml) at –78 °C and the mixture stirred for 30 min before adding the diol **11c** (331 mg, 0.84 mmol, 1 eq.) in CH_2Cl_2 (7 ml). The reaction was stirred for a further 30 min then Et_3N (0.70 ml, 5.02 mmol, 6 eq.) was added dropwise and the mixture was allowed to warm to 0 °C and stirred for 30 min. Saturated aqueous ammonium chloride (20 ml) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 ml). The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford the corresponding aldehyde (498 mg) as a yellow oil used without further purification.

2-Methyl-2-butene (12.50 ml, 25.09 mmol, 30 eq.), sodium chlorite (378 mg, 4.18 mmol, 5 eq.) and sodium dihydrogen phosphate (1.30 g, 8.36 mmol, 10 eq.) were added to the aldehyde (330 mg, 0.84 mmol, 1 eq.) in *tert*-butanol (10.5 ml) and water (10.5 ml). The mixture was stirred for 16 h then saturated aqueous sodium sulfite (11 ml) was added. The mixture stirred for 30 min then extracted with ethyl acetate (5 × 20 ml). The organic ex-

tracts were dried (Na_2SO_4) and concentrated under reduced presure. Chromatography of the residue (40→50% Et_2O/petrol) gave the product.

2-{2-[(4-Bromo-2,6-dimethoxyphenoxy)methyl]phenyl}-2-hydroxypropanoic acid (**13c**) (91 mg, 34%): a colourless oil, R_F 0.10 (50% Et_2O/petrol). IR (film): 3437, 1725, 1589, 1494, 1459, 1409, 1226, 1186, 1127, 815, 761. ^{1}H NMR (300 MHz, $CDCl_3$): 7.63 dd, ^3J = 7.9, ^4J = 1.2, 1 H (Ar-H); 7.39 ddd, ^3J = 7.7, 7.5, ^4J = 1.6, 1 H (Ar-H); 7.28 ddd, ^3J = 7.5, 7.4, ^4J = 1.3, 1 H (Ar-H); 7.20 dd, ^3J = 7.5, ^4J = 1.6, 1 H (Ar-H); 6.69 s, 2 H (Ar-H); 5.95 br s, 1 H (OH); 5.21 and 4.98 each d, ^2J = 11.3, 1 H (ArHC**H**); 3.75 s, 6 H (2 × OCH_3); 1.96 s, 3 H (CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 177.5, 153.9, 140.8, 134.4, 134.2, 133.3, 129.5, 128.7, 127.6, 117.4, 109.1, 77.2, 74.0, 56.5, 27.4. MS-ES$^+$: 435 (58) [$M^{\bullet+}$ + 23], 433 (58), 430 (5), 428 (5), 413 (3), 411 (3), 395 (8), 393 (8), 269 (100). For $C_{18}H_{19}O_6{}^{79}$BrNa ($M^{\bullet+}$ + Na) calculated: 433.0257, found: 433.0253.

2-{2-[(4-Chloro-2,6-dimethoxyphenoxy)methyl]phenyl}-2-hydroxypropanoic acid (**13d**) (252 mg, 69%; after chromatography using 40→70% Et_2O/petrol): a pale yellow oil, R_F 0.09 (50% Et_2O/petrol). IR (film): 3441, 1728, 1592, 1496, 1462, 1447, 1414, 1312, 1226, 1186, 1127, 874, 816, 762. ^{1}H NMR (300 MHz, $CDCl_3$): 7.63 dd, ^3J = 7.9, ^4J = 1.0, 1 H (Ar-H); 7.38 ddd, ^3J = 7.7, 7.5, ^4J = 1.6, 1 H (Ar-H); 7.27 td, ^3J = 7.4, ^4J = 1.2, 1 H (Ar-H); 7.18 dd, ^3J = 7.5, ^4J = 1.5, 1 H (Ar-H); 6.54 s, 2 H (Ar-H); 5.99 br s, 1 H (OH); 5.21 and 4.96 each d, ^2J = 11.3, 1 H (ArHC**H**); 3.74 s, 6 H (2 × OCH_3); 1.95 s, 3 H (CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 177.2, 153.6, 140.8, 134.2, 133.8, 133.3, 130.2, 129.5, 128.7, 127.6, 106.2, 77.2, 74.1, 56.4, 27.4. MS-ES$^+$: 391 (40) [$M^{\bullet+}$ + 23], 389 (100), 386 (11), 384 (25). For $C_{18}H_{19}O_6{}^{35}$ClNa ($M^{\bullet+}$ + Na) calculated: 389.0762, found: 389.0763.

2-{2-[(3-Chloro-2,6-dimethoxyphenoxy)methyl]phenyl}-2-hydroxypropanoic acid (**13e**) (102 mg, 39%): a colourless oil, R_F 0.51 (Et_2O). IR (film): 3434, 1726, 1582, 1477, 1465, 1419, 1375, 1295, 1231, 1091, 1011, 810. ^{1}H NMR (300 MHz, $CDCl_3$): 7.62 d, ^3J = 7.6, 1 H (Ar-H); 7.43–7.29 m 3 H (Ar-H); 7.09 d, ^3J = 9.0, 1 H (Ar-H); 6.58 d, ^3J = 9.0, 1 H (Ar-H); 5.69 br s, 1 H (OH); 5.27 and 5.15 each d, ^2J = 11.3, 1 H (ArHC**H**); 3.85 and 3.73 each s, 3 H (OCH_3); 1.96 s, 3 H (CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 178.1, 152.6, 150.3, 141.0, 140.7, 134.3, 133.0, 129.4, 128.8, 127.6, 125.1, 120.5, 108.1, 77.2, 74.4, 61.5, 56.3 and 27.5. MS-ES$^+$: 391 (39) [$M^{\bullet+}$ + 23], 389 (100), 386 (2), 384 (7). For $C_{18}H_{19}O_6{}^{35}$ClNa ($M^{\bullet+}$ + Na) calculated: 389.0762, found: 389.0761.

Preparation of *N*-{1-[(6-Aminopyridin-2-yl)methyl]piperidin-4-yl}-2-{2-[(2,6-dimethoxyphenoxy)methyl]phenyl}-2-hydroxypropanamides (**6a**, **6c–6e**). Representative Procedure

The hydroxy acid **13a** (70 mg, 0.21 mmol, 1.0 eq.), 2-amino-6-(4-aminopiperidinyl)methylpyridine hydrochloride (87 mg, 0.28 mmol, 1.3 eq.), HOBt hydrate (48 mg, 0.35 mmol, 1.7 eq.) and Et_3N (0.205 ml, 1.48 mmol, 7 eq.) were stirred in in $CHCl_3$ (4 ml) at 0 °C for 30 min. EDCI·hydrochloride salt (52 mg, 0.27 mmol, 1.3 eq.) was added and the mixture stirred for 16 h at ambient temperature. EtOAc (15 ml) was added and the organic layer was washed with saturated aqueous sodium hydrogen carbonate (15 ml). The aqueous phase was extracted with EtOAc (3 × 15 ml) and the organic extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (0→2% MeOH/CH_2Cl_2; 1% Et_3N) gave the product.

N-{1-[(6-Aminopyridin-2-yl)methyl]piperidin-4-yl}-2-{2-[(2,6-dimethoxyphenoxy)methyl]phenyl}-2-hydroxypropanamide (**6a**) (48 mg, 44%): a colourless oil, R_F 0.19 (10% MeOH/CH_2Cl_2).

IR (film): 3390, 1656, 1620, 1598, 1517, 1494, 1476, 1295, 1255, 1109 and 734. ^{1}H NMR (300 MHz, $CDCl_3$): 7.61 d, ^3J = 7.9, 1 H (Ar-H); 7.40–7.27 m, 3 H (Ar-H and NH); 7.18 dd, ^3J = 7.6, 7.2, 1 H (Ar-H); 7.13 dd, ^3J = 7.5, ^4J = 1.6, 1 H (Ar-H); 6.98 dd, ^3J = 8.5, 8.4, 1 H (Ar-H); 6.68 d, ^3J = 7.3, 1 H (Ar-H); 6.53 d, ^3J = 8.4, 2 H (Ar-H); 6.35 d, ^3J = 8.1, 1 H (Ar-H); 5.67 br s, 1 H (OH); 5.26 and 4.93 each d, ^2J = 11.1, 1 H (PhHC**H**); 4.47 br s, 2 H ($ArNH_2$); 3.78 m, 1 H (4′-H); 3.74 s, 6 H (2 × OCH_3); 3.43 s, 2 H ($ArCH_2N$); 2.83 m, 2 H; 2.22–2.08 and 1.98–1.92 each m, 2 H; 1.88 s, 3 H (CH_3); 1.67–1.46 m, 2 H. ^{13}C NMR (75 MHz, $CDCl_3$): 175.7, 158.4, 157.3, 153.5, 142.5, 138.2, 135.3, 134.5, 133.1, 129.1, 128.0, 127.9, 127.5, 113.5, 107.1, 105.5, 77.3, 73.8, 64.8, 56.2, 52.8, 46.7, 32.2, 32.0, 28.2. MS-ES$^+$: 543 (12) [$M^{\bullet+}$ + 23], 521 (100). For $C_{29}H_{37}N_4O_5$ ($M^{\bullet+}$ + H) calculated: 521.2758, found: 521.2776.

N-{1-[(6-Aminopyridin-2-yl)methyl]piperidin-4-yl}-2-{2-[(4-bromo-2,6-dimethoxyphenoxy)methyl]-phenyl}-2-hydroxypropanamide (**6c**) (64 mg, 41%): a white gum, R_F 0.19 (10% MeOH/CH_2Cl_2). IR (film): 3468, 3391, 1659, 1620, 1589, 1514, 1495, 1463, 1409, 1226, 1127, 731. ^{1}H NMR (300 MHz, $CDCl_3$): 7.62 dd, ^3J = 8.0, ^4J = 0.9, 1 H (Ar-H); 7.39 dd, ^3J = 8.1, 7.4, 1 H (Ar-H); 7.34 ddd, ^3J = 7.8, 7.5, ^4J = 1.6, 1 H (Ar-H); 7.25–7.17 m, 2 H (Ar-H and NH); 7.12 dd, ^3J = 7.5, ^4J = 1.5, 1 H (Ar-H); 6.71 d, ^3J = 7.3, 1 H (Ar-H); 6.67 s, 2 H (Ar-H); 6.38 d, ^3J = 8.2, 1 H (Ar-H); 5.41 br s, 1 H (OH); 5.25 and 4.88 each d, ^2J = 11.4, 1 H (PhHC**H**); 4.54 br s, 2 H ($ArNH_2$); 3.82 m, 1 H (4′-H); 3.73 s, 6 H (2 × OCH_3); 3.47 s, 2 H ($ArCH_2N$); 2.93–2.80, 2.27–2.14 and 1.98–1.85 each m, 2 H; 1.88 s, 3 H (CH_3); 1.68–1.50 m, 2 H. ^{13}C NMR (75 MHz, $CDCl_3$): 175.6, 158.3, 156.7, 153.9, 142.2, 138.4, 134.6, 134.4, 133.0, 129.2, 128.2, 128.0, 117.1, 113.6, 109.2, 107.4, 77.3, 73.8, 64.5, 56.5, 52.7, 46.6, 32.0, 31.9, 28.2. MS-ES$^+$: 623 (4) [$M^{\bullet+}$ + 23], 621 (4), 601 (100), 599 (100). For $C_{29}H_{36}N_4O_5{}^{79}Br$ ($M^{\bullet+}$ + H) calculated: 599.1864, found: 599.1859.

N-{1-[(6-Aminopyridin-2-yl)methyl]piperidin-4-yl}-2-{2-[(4-chloro-2,6-dimethoxyphenoxy)methyl]-phenyl}-2-hydroxypropanamide (**6d**) (190 mg, 50%): a white foam, R_F 0.19 (10% MeOH/CH_2Cl_2). IR (film): 3463, 3390, 3199, 1660, 1621, 1592, 1515, 1496, 1464, 1414, 1226, 1124, 732. ^{1}H NMR (300 MHz, $CDCl_3$) 7.61 d, ^3J = 7.9, 1 H (Ar-H); 7.38 dd, ^3J = 8.1, 7.3, 1 H (Ar-H); 7.34 td, ^3J = 7.7, ^4J = 1.3, 1 H (Ar-H); 7.25–7.16 m, 2 H (Ar-H and NH); 7.11 dd, ^3J = 7.5, ^4J = 1.2, 1 H (Ar-H); 6.70 d, ^3J = 7.3, 1 H (Ar-H); 6.53 s, 2 H (Ar-H); 6.37 d, ^3J = 8.2, 1 H (Ar-H); 5.42 br s, 1 H (OH); 5.24 and 4.87 each d, ^2J = 11.3, 1 H (PhHC**H**); 4.48 br s, 2 H ($ArNH_2$); 3.83 m, 1 H (4′-H); 3.72 s, 6 H (2 × OCH_3); 3.45 s, 2 H ($ArCH_2N$); 2.90–2.78, 2.24–2.10 and 1.98–1.84 each m, 2 H; 1.87 s, 3 H (CH_3); 1.66–1.48 m, 2 H. ^{13}C NMR (75 MHz, $CDCl_3$): 175.6, 158.3, 157.1, 153.7, 142.3, 138.3, 134.4, 134.0, 133.0, 129.8, 129.2, 128.1, 128.0, 113.6, 107.2, 106.2, 77.3, 73.9, 64.7, 56.4, 52.8, 46.7, 32.1, 32.0, 28.2. MS-ES$^+$: 579 (17) [$M^{\bullet+}$ + 23], 577 (27), 557 (69), 555 (100). For $C_{29}H_{36}N_4O_5{}^{35}Cl$ ($M^{\bullet+}$ + H) calculated: 555.2369, found: 555.2370.

N-{1-[(6-Aminopyridin-2-yl)methyl]piperidin-4-yl}-2-{2-[(3-chloro-2,6-dimethoxyphenoxy)methyl]-phenyl}-2-hydroxypropanamide (**6e**) (33 mg, 22%): a colourless oil, R_F 0.40 (10% MeOH/CH_2Cl_2). IR (film): 3352, 1659, 1651, 1619, 1580, 1513, 1464, 1092, 1009. ^{1}H NMR (300 MHz, $CDCl_3$): 7.64 d, ^3J = 7.6, 1 H (Ar-H); 7.42–7.34 and 7.32–7.22 each m, 2 H (Ar-H); 7.18 d, ^3J = 8.2, 1 H (NH); 7.08 d, ^3J = 9.1, 1 H (Ar-H); 6.70 d, ^3J = 7.3, 1 H (Ar-H); 6.59 d, ^3J = 9.1, 1 H (Ar-H); 6.38 d, ^3J = 8.2, 1 H (Ar-H); 5.31 br s, 1 H (OH); 5.30 and 5.02 each d, ^2J = 11.3, 1 H (PhHC**H**); 4.52 br s, 2 H ($ArNH_2$); 3.83 m, 1 H (4-H); 3.84 and 3.72 each s, 3 H (OCH_3); 3.46 s, 2 H ($ArCH_2N$); 2.84 m, 2 H; 2.27–2.13 and 1.98–1.82 each m, 2 H; 1.89 s, 3 H (CH_3); 1.68–1.47 m, 2 H. ^{13}C NMR (75 MHz, $CDCl_3$): 175.5, 158.3, 156.9, 152.6, 150.3, 142.2, 141.2, 138.4, 134.4, 132.8, 129.3, 128.4, 128.0, 125.0, 120.5, 113.6, 108.3, 107.3,

77.3, 74.5, 64.6, 61.4, 56.4, 52.7, 46.6, 32.1, 31.9, 28.1. MS-ES$^+$: 579 (2) [$M^{\bullet+}$ + 23], 577 (6), 557 (72), 555 (100). For $C_{29}H_{36}N_4O_5{}^{35}Cl$ ($M^{\bullet+}$ + H) calculated: 555.2369, found: 555.2374.

Dimethyl 4-[(1-*tert*-Butoxycarbonylpiperidin-4-yl)methyl]pyridine-2,6-dicarboxylate (**19**)

9-Bicycloboranonane (1.67 ml, 0.5 M in THF, 0.84 mmol, 1.7 eq.) was added to the 4-methylenepiperidine **15** (100 mg, 0.51 mmol, 1.1 eq.) in THF (3.3 ml) and the solution heated under reflux for 3 h. After cooling to room temperature, water (0.10 ml), DMF (1.04 ml), K_2CO_3 (293 mg, 1.38 mmol, 3.0 eq.) and the bromide **18** (126 mg, 0.46 mmol, 1.0 eq.) were added and the resulting mixture degassed under a stream of N_2 for 15 min. Pd(dppf)Cl_2·CH_2Cl_2 (19 mg, 0.02 mmol, 5 mole %) was added and the resulting mixture was stirred for 10 min. Water (20 ml) was added and the mixture extracted with EtOAc (3 × 20 ml). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (25→100% Et_2O/petrol) gave the title compound **19** (177 mg, 89%) as a white solid, R_F 0.32 (Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$): 8.11 s, 2 H (Ar-H); 4.10 m, 2 H; 4.03 s, 6 H (2 × CO_2CH_3); 2.71 d, ^3J = 7.2, 2 H (4-CH_2); 2.63 m, 2 H; 1.80 m, 1 H (4'-H); 1.59 m, 2 H; 1.45 s, 9 H [$C(CH_3)_3$]; 1.30–1.11 m, 2 H. ^{13}C NMR (75 MHz, $CDCl_3$): 165.5, 155.0, 152.7, 148.47, 128.9, 79.7, 53.5, 43.9, 42.6, 37.6, 32.0, 28.7. MS-ES$^+$: 393 (65) [$M^{\bullet+}$ + 1], 216 (30), 177 (12), 160 (48), 116 (100).

Dimethyl 4-{[1-(2-Nitrobenzenesulfonyl)piperidin-4-yl]methyl}pyridine-2,6-dicarboxylate (**21**)

The *tert*-butyloxycarbonylamine **19** (251 mg, 0.64 mmol) was stirred in CH_2Cl_2 (4.2 ml) and trifluoroacetic acid (2.1 ml) for 3 h at ambient temperature. The reaction mixture was concentrated under reduced pressure and the residue was washed with saturated aqueous sodium bicarbonate (20 ml) and CH_2Cl_2 (3 × 20 ml). The organic extracts were wash with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the amine **20**. This was dissolved in CH_2Cl_2 (8 ml), and NsCl (170 mg, 0.77 mmol, 1.2 eq.), Et_3N (133 μm^3, 0.96 mmol, 1.5 eq.) and DMAP (1.6 mg, 2 mole %) were added. The mixture was stirred for 16 h at ambient temperature and water (20 ml) and CH_2Cl_2 (20 ml) were added. The aqueous phase was washed with CH_2Cl_2 (3 × 20 ml) and the organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (0→10% MeOH/Et_2O) gave the title compound **21** (183 mg, 60%) as a white foam, R_F 0.09 (Et_2O). IR (film): 3091, 1727, 1601, 1549, 1443, 1367, 1250, 1217, 1163, 1126, 998, 940, 913, 852, 781, 748, 734. ^{1}H NMR (300 MHz, $CDCl_3$): 8.12 s, 2 H (Ar-H); 8.00 m, 1 H (Ar-H); 7.72 m, 2 H (Ar-H); 7.65 m, 1 H (Ar-H); 4.05 s, 6 H (2 × CO_2CH_3); 3.88 m, 2 H; 2.81–2.68 m, 4 H; 1.90–1.60 m, 3 H; 1.50–1.32 m, 2 H. ^{13}C NMR (75 MHz, $CDCl_3$): 165.5, 152.2, 148.6, 133.9, 131.9, 131.8, 131.2, 128.8, 124.4, 53.5, 46.2, 42.1, 36.8, 31.6. MS-ES$^+$: 500 (100) [$M^{\bullet+}$ + 23], 495 (23). For $C_{21}H_{23}N_3O_8Na$ ($M^{\bullet+}$ + Na) calculated: 500.1098, found: 500.1101.

Alternatively, 9-bicycloboranonane (0.5 M in THF, 10.63 ml, 5.31 mmol, 1.7 eq.) was added to the 4-methylenepiperidine **29** (1.00 g, 3.54 mmol, 1.1 eq.) in THF (3.3 ml) and the solution was heated under reflux for 1 h. After cooling to room temperature, water (0.70 ml), DMF (7.28 ml), K_2CO_3 (1.34 g, 9.66 mmol, 3.0 eq.) and bromide **18** (883 mg, 42 mmol) were added and the resulting mixture degassed under a stream of N_2 for 15 min. Pd(dppf)Cl_2·CH_2Cl_2 (131 mg, 0.16 mmol, 5 mole %) was added and the resulting mixture was stirred for 30 min. Water (70 ml) was added and the mixture extracted with EtOAc (3 ×

70 ml). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (0→10% MeOH/Et_2O) gave the product **21** (1.37 g, 89%) as a white foam.

6-Methoxycarbonyl-4-{[1-(2-nitrobenzenesulfonyl)piperidin-4-yl]methyl}pyridine-2-carboxylic Acid (**22**)

Diester **21** (727 mg, 1.52 mmol, 1 eq.) in CH_2Cl_2 (17 ml) and MeOH (17 ml) was cooled to 0 °C and KOH pellets (86 mg, 1.52 mmol, 1 eq.) were added. The reaction mixture was stirred at ambient temperature for 16 h then concentrated under reduced pressure and the residue was suspended in ethyl acetate. After filtration, the precipitated potassium salt was dissolved in water (20 ml) and the solution acidified to pH 3 with concentrated aqueous hydrogen chloride. The solution was extracted with CH_2Cl_2 (3 × 20 ml) and the organic extracts were washed with water, brine and dried ($MgSO_4$). Concentration under reduced pressure gave the title compound **22** (642 mg, 91%) as a white foam, R_F 0.20 (10% MeOH/CH_2Cl_2). IR (film): 3469, 1729, 1603, 1544, 1438, 1373, 1349, 1244, 1165, 732. ^{1}H NMR (300 MHz, $CDCl_3$): 8.21 and 8.14 each d, ^4J = 1.5, 1 H (Ar-H); 8.00 m, 1 H (Ar-H); 7.79–7.69 m, 2 H (Ar-H); 7.65 m, 1 H (Ar-H); 4.06 s, 3 H (CO_2CH_3); 3.87 m, 2 H; 2.81–2.69 m, 4 H; 1.75 m, 1 H (4'-H); 1.73 m, 2 H; 1.50–1.34 m, 2 H. ^{13}C NMR (75 MHz, $CDCl_3$): 164.7, 164.2, 153.8, 148.5, 147.0, 134.0, 131.9, 131.8, 131.1, 129.7, 128.9, 127.6, 124.4, 53.5, 46.1, 42.2, 36.8, 31.6. MS-ES$^+$: 464 (12) [$M^{\bullet+}$ + 1], 454 (100), 445 (74). For $C_{20}H_{22}N_3O_8S$ ($M^{\bullet+}$ + H) calculated: 464.1122, found: 464.1124.

Methyl 6-*tert*-Butoxycarbonylamino-4-{[1-(2-nitrobenzenesulfonyl)piperidin-4-yl]methyl}-pyridine-2-carboxylate (**23**)

Diphenylphosphoryl azide (510 ml, 2.37 mmol, 1.2 eq.) was added at room temperature to the acid **22** (914 mg, 1.97 mmol, 1.0 eq.) and Et_3N (0.55 ml, 3.94 mmol, 2.0 eq.) in toluene (11.6 ml) and *t*-BuOH (1.2 ml) and the mixture heated at 100 °C for 16 h. After being cooled to room temperature, the reaction mixture was diluted with EtOAc (50 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate (50 ml) and brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue (50→90% Et_2O/petrol) gave the title compound **23** (695 mg, 66%) as a white foam, R_F 0.46 (Et_2O). IR (film): 3219, 1725, 1610, 1571, 1546, 1449, 1432, 1369, 1247, 1161, 912, 733. ^{1}H NMR (300 MHz, $CDCl_3$): 7.99 and 7.72 each m, 2 H (Ar-H); 7.66–7.59 m, 3 H (Ar-H and ArNH); 4.00 s, 3 H (CO_2CH_3); 3.92–3.82 m, 2 H; 2.80–2.68 m, 2 H; 2.64 d, ^3J = 6.7, 2 H (4-CH_2); 1.78–1.68 m, 3 H; 1.53 s, 9 H [$C(CH_3)_3$]; 1.48–1.28 m, 2 H. ^{13}C NMR (75 MHz, $CDCl_3$): 165.7, 152.8, 152.6, 152.4, 148.6, 146.1, 133.9, 131.9, 131.7, 131.1, 124.3, 121.2, 116.4, 81.6, 53.2, 46.2, 42.4, 36.8, 31.7, 28.4. MS-ES$^+$: 557 (100) [$M^{\bullet+}$ + 23], 535 (1). For $C_{24}H_{30}N_4O_8SNa$ ($M^{\bullet+}$ + Na) calculated: 557.1677, found: 557.1687.

[6-*tert*-Butoxycarbonylamino-4-{[1-(2-nitrobenzenesulfonyl)piperidin-4-yl]methyl}-pyridin-2-yl]methanol (**24**)

Sodium borohydride (150 mg, 3.96 mmol, 5 eq.) was added to the ester **23** (423 mg, 0.79 mmol, 1 eq.) and $CaCl_2$ (176 mg, 1.58 mmol, 2 eq.) in EtOH (9 ml). The mixture was stirred at 0 °C for 2 h then poured into water (20 ml) and extracted with EtOAc (3 × 20 ml). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give the

title compound **24** (358 mg, 97%) as a white foam, R_F 0.12 (Et_2O). IR (film): 3364, 3235, 2360, 1725, 1614, 1570, 1545, 1436, 1370, 1232, 1161, 1097, 732. ^{1}H NMR (300 MHz, $CDCl_3$): 7.99 m, 1 H (Ar-H); 7.72 m, 2 H (Ar-H); 7.68 s, 1 H (Ar-H); 7.63 m, 1 H (Ar-H); 7.48 br s, 1 H (ArNH); 6.72 s, 1 H (Ar-H); 4.65 s, 2 H (CH_2O); 3.86 m, 2 H; 2.73 m, 2 H; 2.56 d, ^3J = 6.6, 2 H (4′-CH_2); 1.79–1.67 m, 3 H; 1.55 s, 9 H [$C(CH_3)_3$]; 1.45–1.27 m, 2 H. ^{13}C NMR (75 MHz, $CDCl_3$): 157.6, 152.7, 152.5, 151.5, 148.6, 133.9, 131.9, 131.8, 131.1, 124.3, 116.2, 111.1, 81.6, 64.0, 46.3, 42.6, 36.8, 31.8, 28.5. MS-ES$^+$: 1035 (20), 529 (100) [$M^{\bullet+}$ + 23], 507 (1). For $C_{23}H_{30}N_4O_7SNa$ ($M^{\bullet+}$ + Na) calculated: 529.1727, found: 529.1730.

4-*tert*-Butoxycarbonylamino-1-[6-*tert*-butoxycarbonylamino-4-([{[1-(2-nitrobenzenesulfonyl)piperidin-4-yl]methyl}pyridin-2-yl]methyl)piperidine (**25**)

Methanesulfonyl chloride (0.27 ml, 3.48 mmol, 3.0 eq.) was added to the alcohol **24** (586 mg, 1.16 mmol, 1.0 eq.) and Et_3N (0.50 ml, 3.59 mmol, 3.1 eq.) in EtOAc (6.70 ml) and the mixture stirred at 0 °C for 1 h. Saturated aqueous sodium hydrogen carbonate (50 ml) was added and the organic layer washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to leave the mesylate (682 mg) as a white foam. This was taken up in CH_3CN (7.8 ml) and K_2CO_3 (497 mg, 3.59 mmol, 3.1 eq.) and 4-*tert*-butoxycarbonylaminopiperidine (255 mg, 1.27 mmol, 1.1 eq.) were added. The mixture was stirred at room temperature for 16 h then poured into water (50 ml) and extracted with CH_2Cl_2 (3 × 50 ml). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (0→5% MeOH/Et_2O; 1% Et_3N) gave the title compound **25** (682 mg, 85%) as a white foam, R_F 0.20 (Et_2O). IR (film): 3357, 3209, 1713, 1611, 1569, 1547, 1438, 1368, 1234, 1163, 1047, 937, 736. ^{1}H NMR (300 MHz, $CDCl_3$): 7.99 m, 1 H (Ar-H); 7.72 and 7.63 each m, 2 H (Ar-H); 7.34 s, 1 H (ArNH); 6.80 s, 1 H (Ar-H); 4.50 br d, ^3J = 6.6, 1 H (NH); 3.86 m, 2 H; 3.50 m, 1 H (4-H); 3.47 s, 2 H (2′-CH_2); 2.87–2.75 and 2.78–2.67 each m, 2 H; 2.55 d, ^3J = 6.7, 2 H (4′-CH_2); 2.15 m, 2 H; 1.93 m, 2 H; 1.78–1.66 m, 3 H; 1.57–1.47 m, 2 H; 1.53 and 1.47 each s, 9 H [$C(CH_3)_3$]; 1.50–1.25 m, 2 H. ^{13}C NMR (75 MHz, $CDCl_3$): 157.0, 155.5, 152.7, 151.9, 151.8, 148.6, 133.8, 131.9, 131.7, 131.2, 124.3, 119.4, 110.8, 81.1, 79.5, 64.5, 52.9, 47.9, 46.3, 42.5, 36.9, 32.7, 31.8, 28.7, 28.6. MS-ES$^+$: 711 (100) [$M^{\bullet+}$ + 23], 689 (21). For $C_{33}H_{49}N_6O_8S$ ($M^{\bullet+}$ + H) calculated: 689.3327, found: 689.3339.

4-*tert*-Butoxycarbonylamino-1-[6-*tert*-butoxycarbonylamino-4-{[(piperidin-4-yl)methyl]-pyridin-2-yl}methyl]piperidine (**26**)

Benzenethiol (0.17 ml, 1.76 mmol, 3 eq.) was added to a suspension of the nosylate **25** (394 mg, 0.58 mmol, 1 eq.) and K_2CO_3 (316 mg, 2.29 mmol, 4 eq.) in acetonitrile (10 ml). The mixture was stirred at ambient temperature for 16 h then concentrated under reduced pressure. The residue was extracted with water (20 ml) and CH_2Cl_2 (20 ml) and the aqueous phase extracted with CH_2Cl_2 (3 × 20 ml). The organic extracts were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue (0→30% MeOH/CH_2Cl_2; 1% Et_3N) gave the title compound **26** (276 mg, 96%) as a pale foam, R_F 0.23 (30% MeOH/CH_2Cl_2). IR (film): 3314, 1712, 1611, 1568, 1520, 1435, 1391, 1367, 1288, 1237, 1163, 1046, 733. ^{1}H NMR (300 MHz, $CDCl_3$): 7.65 d, ^4J = 1.0, 1 H (Ar-H); 7.31 s, 1 H (ArNH); 6.82 d, ^4J = 1.2, 1 H (Ar-H); 4.49 br d, ^3J = 6.6, 1 H (NH); 3.50 m, 1 H (4-H); 3.49 s, 2 H (2′-CH_2); 3.11 m, 2 H; 2.83 m, 2 H; 2.60 m, 2 H; 2.54 d, ^3J = 7.0, 2 H

(4′-CH_2); 2.16 m, 2 H; 1.99–1.86 m, 2 H; 1.78–1.66 m, 3 H; 1.57–1.47 m, 2 H; 1.55 and 1.48 each s, 9 H [$C(CH_3)_3$]; 1.38–1.16 m, 2 H. ^{13}C NMR (75 MHz, $CDCl_3$): 156.8, 155.5, 152.7, 152.3, 151.8, 119.5, 111.0, 81.0, 79.5, 64.5, 52.9, 48.0, 46.0, 43.4, 37.4, 32.7, 32.5, 28.7, 28.5. MS-ES$^+$: 526 (8) [$M^{\bullet+}$ + 23], 504 (100). For $C_{27}H_{46}N_5O_4$ ($M^{\bullet+}$ + H) calculated: 504.3544, found: 504.3535.

4-*tert*-Butoxycarbonylamino-1-[{6-*tert*-butoxycarbonylamino-4-[(1-propylpiperidin-4-yl)-methyl]pyridin-2-yl}methyl]piperidine (**27**)

Sodium triacetoxyborohydride (348 mg, 1.64 mmol, 3 eq.) was added to the amine **26** (276 mg, 0.55 mmol, 1.0 eq.), propionaldehyde (395 μm^3, 5.48 mmol, 10.0 eq.), and acetic acid (35 μm^3, 0.60 mmol, 1.1 eq.) in CH_2Cl_2 (5.5 ml) and the mixture stirred for 16 h. Aqueous sodium hydroxide (20 ml, 1 M) was added and the mixture was extracted with CH_2Cl_2 (4 × 20 ml). The organic extracts were wash with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (0→10% MeOH/Et_2O; 1% Et_3N) gave the title compound **27** (280 mg, 94%) as a colourless oil, R_F 0.37 (30% MeOH/CH_2Cl_2). IR (film): 3358, 1713, 1611, 1568, 1519, 1435, 1367, 1288, 1235, 1162, 1046, 733. ^{1}H NMR (300 MHz, $CDCl_3$): 7.64 s, 1 H (Ar-H); 7.33 s, 1 H (ArNH); 6.82 s, 1 H (Ar-H); 4.49 br d, ^3J = 6.8, 1 H (NH); 3.50 m, 1 H (4-H); 3.48 s, 2 H (2′-CH_2); 2.99 m, 2 H; 2.83 m, 2 H; 2.55 d, ^3J = 6.3, 2 H (4′-CH_2); 2.35 m, 2 H (1″-CH_2); 2.16 m, 2 H; 2.06–1.88 m, 4 H; 1.73–1.32 m, 9 H; 1.54 and 1.48 each s, 9 H [$C(CH_3)_3$]; 0.93 t, ^3J = 7.5, 3 H ($NCH_2CH_2C\mathbf{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$): 156.6, 155.5, 152.9, 152.7, 151.7, 119.6, 111.0, 80.9, 79.5, 64.5, 61.4, 54.0, 52.8, 47.9, 43.1, 37.5, 32.7, 32.4, 28.7, 28.5, 20.4, 12.3. MS-ES$^+$: 568 (19) [$M^{\bullet+}$ + 23], 546 (100). For $C_{30}H_{52}N_5O_4$ ($M^{\bullet+}$ + H) calculated: 546.4014, found: 546.4020.

4-Amino-1-[{6-amino-4-[(1-propylpiperidin-4-yl)methyl]pyridin-2-yl}methyl]piperidine (**28**)

The bis-*tert*-butoxycarbonyl amine **27** (280 mg, 0.51 mmol) in methanolic hydrogen chloride (5.8 ml, 10%) was stirred at room temperature for 24 h. Concentration under reduced pressure gave the title compound **28** (254 mg, 100%) as a pale highly hygroscopic foam, m.p. > 350 °C (decomposition). IR (film): 3662, 3332, 1665, 1453, 1395, 1230, 1049, 943, 870. ^{1}H NMR (500 MHz, CD_3OD): 7.12 and 6.89 each s, 1 H (Ar-H); 4.46 s, 2 H (2′-CH_2); 3.65 m, 2 H; 3.47 m, 3 H; 3.33 m, 2 H; 2.93 m, 4 H; 2.62 d, ^3J = 6.0, 2 H (4′-CH_2); 2.25 m, 2 H; 2.07 m, 3 H; 1.86 m, 2 H; 1.69 m, 2 H ($NCH_2C\mathbf{H}_2CH_3$); 1.55 m, 2 H; 0.92 t, ^3J = 7.3, 3 H ($NCH_2CH_2C\mathbf{H}_3$). ^{13}C NMR (75 MHz, CD_3OD): 158.1, 155.1, 135.8, 118.4, 114.7, 58.7, 55.5, 52.6, 51.0, 45.3, 41.1, 33.6, 29.1, 27.1, 17.5, 10.6. MS-ES$^+$: 346 (100). For $C_{20}H_{36}N_5$ ($M^{\bullet+}$ – H_3Cl_4) calculated: 346.2965, found: 346.2969.

N-(1-[{6-Amino-4-[(1-propylpiperidin-4-yl)methyl]pyridin-2-yl}methyl]piperidin-4-yl)-2-cyclopentyl-2-hydroxy-2-phenylacetamide (**7a**)

The acid **30** (37 mg, 0.17 mmol, 1.3 eq.), amine hydrochloride **28** (64 mg, 0.13 mmol, 1.0 eq.), HOBt hydrate (35 mg, 0.26 mmol, 2.0 eq.) and Et_3N (0.15 ml, 1.04 mmol, 10.0 eq.) in $CHCl_3$ (3.4 ml) were stirred at ambient temperature for 30 min then EDCI hydrochloride salt (40 mg, 0.21 mmol, 1.6 eq.) was added. The reaction mixture was allowed to stir for 16 h at ambient temperature before EtOAc (15 ml) was added. The organic layer was washed with saturated aqueous sodium bicarbonate (15 ml) and the aqueous phase was extracted

with EtOAc (3 × 15 ml). The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (0→20% MeOH/Et_2O; 1% Et_3N) gave the title compound **7a** (38 mg, 53%) as a pale oil, R_F 0.11 (30% MeOH/CH_2Cl_2). IR (film): 3393, 1652, 1621, 1567, 1516, 1447, 1376, 1335, 1287, 910, 732. ^{1}H NMR (500 MHz, $CDCl_3$): 7.53 d, ^3J = 7.4, 2 H (Ar-H); 7.28–7.16 m, 3 H (Ar-H); 6.40 s, 1 H (Ar-H); 6.32 d, ^3J = 8.2, 1 H (CONH); 6.07 s, 1 H, s (Ar-H); 4.37 br s, 2 H (NH_2); 3.64 m, 1 H (4′-H); 3.31 s, 2 H (2″-CH_2); 3.24 m, 2 H; 3.00–2.86 m, 3 H; 2.72–2.62, 2.32–2.22, 2.10–2.00, 1.93–1.80 and 1.79–1.68 each m, 2 H; 1.66–1.33 m, 14 H; 1.31–1.20 m, 3 H; 0.80 t, ^3J = 7.4, 3 H ($NCH_2CH_2C\mathbf{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$): 173.6, 158.4, 156.7, 151.9, 143.0, 128.6, 127.7, 125.8, 114.9, 107.7, 79.8, 64.6, 53.8, 52.6, 46.7, 42.6, 37.0, 32.1, 31.9, 27.0, 26.9, 26.4, 26.2, 12.2. MS-CI: 570 (19) [$M^{\bullet+}$ + 23], 548 (100). For $C_{33}H_{50}N_5O_2$ ($M^{\bullet+}$ + H) calculated: 548.3959, found: 548.3966.

4-Methylene-1-(2-nitrophenylsulfonyl)piperidine (**29**)

Butyllithium (1.6 M in hexanes, 14.71 ml, 23.74 mmol, 1.5 eq.) was added dropwise to a suspension of methyltriphenylphosphonium bromide (8.48 g, 23.74 mmol, 1.5 eq.) in THF (100 ml) at 25 °C. After 30 min, 1-(2-nitrophenylsulfonyl)-4-oxopiperidine (4.50 g, 15.82 mmol, 1.0 eq.) in THF (30 ml) was added and the mixture stirred for 16 h. MeOH was added and the mixture concentrated under reduced pressure. Chromatography of the residue (10→100% Et_2O/petrol) gave the title compound **29** (2.68 g, 60%) as a yellow solid, m.p. 143–145 °C, R_F 0.64 (Et_2O). IR (film): 1655, 1588, 1555, 1373, 1344, 1168, 1152, 931, 898, 789, 747, 732. ^{1}H NMR (300 MHz, $CDCl_3$): 8.03 m, 1 H (Ar-H); 7.78–7.68 m, 2 H (Ar-H); 7.64 m, 1 H (Ar-H); 4.81 s, 2 H (4-CH_2); 3.37 and 2.35 each t, ^3J = 5.8, 4 H (2 × CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): 143.4, 133.9, 132.2, 131.8, 131.1, 124.4, 110.8, 47.8, 34.5. MS-CI: 300 (16) [$M^{\bullet+}$ + 18], 283 (9), 253 (100). For $C_{12}H_{15}N_2O_4S$ ($M^{\bullet+}$ + H) calculated: 283.0747, found: 283.0742.

REFERENCES

1. Eglen R. M. (Ed.): *Muscarinic Receptor Subtypes in Smooth Muscle*. CRC, Boca Raton, Florida 1997; ISBN-10 0849385490.
2. Abrams P., Anderson K. E., Buccafusco J. J., Chapple C., Chet de Groat W., Fryer A. D., Kay G., Laties A., Nathanson N. M., Pasricka P. J., Wein A. J.: *Br. J. Pharmacol.* **2006**, *148*, 565.
3. Mitsuya M., Mase T., Tsuchiya Y., Kawakami K., Hattori H., Kobayashi K., Ogino Y., Fujikawa T., Satoh A., Kimura T., Noguchi K., Ohtake N., Tomimoto K.: *Bioorg. Med. Chem.* **1999**, *7*, 2555.
4. Mitsuya M., Kobayashi K., Kawakami K., Satoh A., Ogino Y., Kakikawa T., Ohtake N., Kimura T., Hirose H., Sato A., Numazawa T., Hasegawa T., Noguchi K., Mase T.: *J. Med. Chem.* **2000**, *43*, 5017.
5. Bradshaw B., Evans P., Fletcher J., Lee A. T. L., Mwashimba P. G., Oehlrich D., Thomas E. J., Davies R. H., Allen P. C. P., Broadley K. J., Hamrouni A., Escargueil C.: *Org. Biomol. Chem.* **2008**, 2138.
6. Evans P., Lee A. T. L., Thomas E. J.: *Org. Biomol. Chem.* **2008**, 2158.
7. Jiménez-Estrada M., Navarro A., Flores M. V., Chilpa R. R., Hernández B., Anaya A. L., Lotina-Hennsen B.: *J. Agric. Food Chem.* **1996**, *44*, 2839.

8. Hoffmann A. W.: *Chem. Ber.* **1878**, *11*, 797.
9. VanRheenen L., Cha D. Y., Hartley W. M.: *Org. Synth.* **1978**, *58*, 43.
10. Dess D. B., Martin J. C.: *J. Am. Chem. Soc.* **1991**, *113*, 7277.
11. Mancuso A. J., Huang S.-L., Swern D.: *J. Org. Chem.* **1978**, *43*, 2480.
12. Bal B. S., Childers W. E., Jr., Pinnick H. W.: *Tetrahedron* **1981**, *37*, 2091.
13. Kohn M., Steiner L.: *J. Org. Chem.* **1947**, *12*, 30.
14. Horner L., Göwecke S.: *Chem. Ber.* **1961**, *94*, 1267.
15. Varhanícková D., Lee S. C., Shiu W.-Y., Mackay D.: *J. Chem. Eng. Data* **1995**, *40*, 620.
16. Vice S., Bara T., Bauer A., Evans C. A., Ford J., Josien H., McCombie S., Miller M., Nazareno D., Palani A., Tagat J.: *J. Org. Chem.* **2001**, *66*, 2487.
17. Lundgren S., Lutsenko S., Jönsson C., Moberg C.: *Org. Lett.* **2003**, *5*, 3663.
18. Aissa C.: *J. Org. Chem.* **2006,** *71*, 360.
19. Gribble G. W., Ferguson D. C.: *J. Chem. Soc., Chem. Commun.* **1975**, 535.
20. Alabaster V. A.: *Life Sci.* **1997**, *60*, 1053.