Turk J Chem
26 (2002) , 955 – 963.

Pyridine and Benzene Templated Potential Peptidomimetics

Kadir DABAK*
İstanbul Technical University, Faculty of Sciences, Department of Chemistry, Maslak, 80626, İstanbul-TURKEY
e-mail: kadird@eczacibasi.com.tr

Received 17.05.2002

This study provides a new approach for the synthesis of pyridine and benzene templated potential peptidomimetics. By the attachment of various amino acid side chains in different combinations on the pyridine template at the 2- and 3- positions and on the benzene core at 1,2,4 positions, different peptidomimetics may be obtained. Arg-10, Leu-11 and Tyr-13 amino acid side chain mimics and their precursors were attached to the pyridine and benzene core with a special arrangement to produce potential peptidomimetics of omega-conotoxin MVIIA.

Introduction

Native peptides are rarely directly usable as drugs due to their inherent limitations. To overcome these limitations, peptides are modified into mimetics. These mimetics, which are also known as peptidomimetics, are derived from peptides by partly or completely removing the amide bonds while retaining essential amino acid side chains in a defined, spatial relationship[1−3]. Heterocycles for the conformational restriction of biologically active peptoids are very often used in pharmacological and medicinal applications[4].

$\omega-$Conotoxin MVIIA, which is also known as "SNX111", from the venom of the cone shell *Conus magus*[5,6] is one of the most promising new drugs for the treatment of severe neuropathic pain[7,8]. SNX-111 works by binding selectively to N-type voltage sensitive calcium channels in mammals. Menzler et al. described an efficient synthesis of an alkylphenyl ether based benzene templated peptidomimetic of SNX111[9].

In this study, the synthesis of pyridine and benzene templated compounds, which can serve as a structural motif able to display different functional groups corresponding to the side chains of amino acids, is described. The synthetic strategy shows a similarity to the dendroid approach to peptidomimetics[10]. Vital amino acids of SNX-111 for binding to the N-type calcium channels are Lys-2, Arg-10, Leu-11, Tyr-13 and Arg-21[11]. In this study, the mimetics of Leu-11, Tyr-13 and Arg-10 amino acid side chains or their precursors were attached to the pyridine and benzene core unit in a special arrangement.

*Author present address: Eczacıbaşı Özgün Kimya, Organize Sanayi Bölgesi, Fatih Cad. No: 12, Çerkezköy, Tekirdağ-TURKEY

Our approach is to attach mimetics of these amino acid mimics to a central core in a special arrangement that allows for some conformational flexibility. Such a system is shown in Figures 1 and 2, where the central core is pyridine and benzene based.

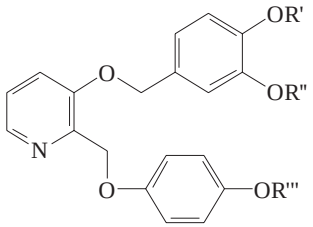


Figure 1

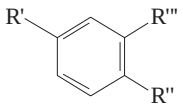


Figure 2

Results and Discussion

The mimetics of Arg-10, Leu-11, Tyr-13 amino acid side chains and their precursors were attached to the pyridine and 1,2,4-trisubstituted benzene core with a special arrangement to produce the potential peptidomimetics of omega-conotoxin MVIIA. The side chains of tyrosine, leucine and arginine were mimicked by *para*-substituted phenol, isopropyl group and *para*-amidino phenyl group.

This study also provides a new approach for the synthesis of pyridine and 1,2,4-trisubstituted benzene templated potential peptidomimetics in general. By the attachment of various amino acid side chains (R′, R″, R‴) in different combinations these templates (Figures 1 and 2), different peptidomimetics may be designed.

The aryl ether linkages were introduced by high-yielding etherifications under mild conditions following Williamson and Mitsunobu protocols.

The synthesis of a leucine and arginine mimetics on the benzene template is shown in Scheme 1.

The synthesis of a leucine mimetic with protected hydroxyl functionality is shown in Scheme 2. This affords 3-isopropoxy-4-methoxy benzylchloride (**10**) in good overall yield from commercially available isovanillin (**3**).

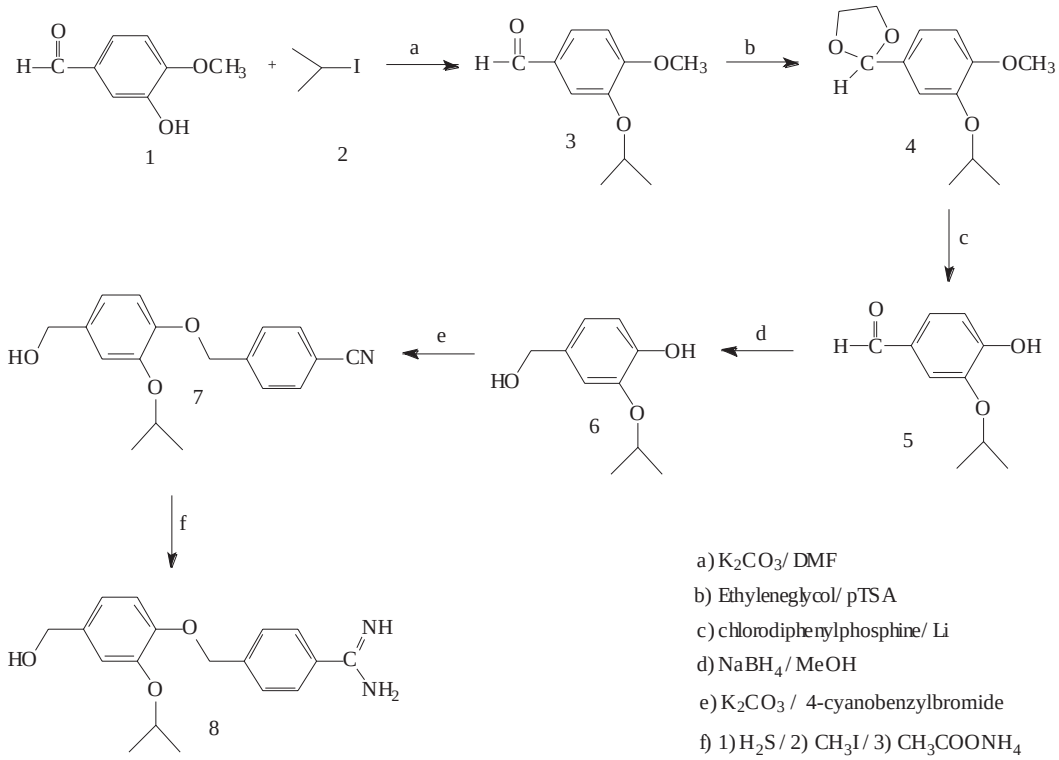
2-hydroxymethyl-3-hydroxypyridine hydrochloride (**11**) was readily synthesised by the literature procedure[12].

In Scheme 3, synthesis of the tyrosine mimetic on the pyridine template is shown.

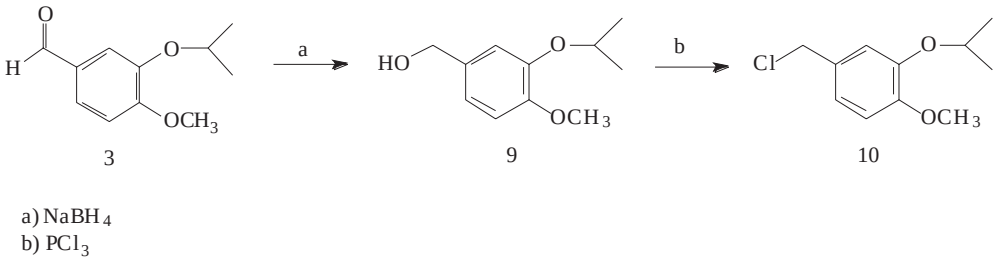
The deprotection of allyl group was performed on the compound (**16**) and tyrosine and leucine mimetics were obtained on the pyridine template (Scheme 4).

Experimental

^{1}H NMR spectra were recorded at 300 MHz on a Varian Gemini-2000 NMR spectrometer and at 270 MHz on a Jeol JNM EX270 machine; ^{13}C spectra were recorded at 75.4 MHz on the Varian instrument and at 67.8 MHz on the Jeol. Me_4Si was used as an internal reference. Mass spectra were produced on a Kratos model MS25 magnetic sector mass spectrometer using electron impact ionisation (70eV), and infra-red spectra were recorded on a Perkin Elmer 298 spectrometer.



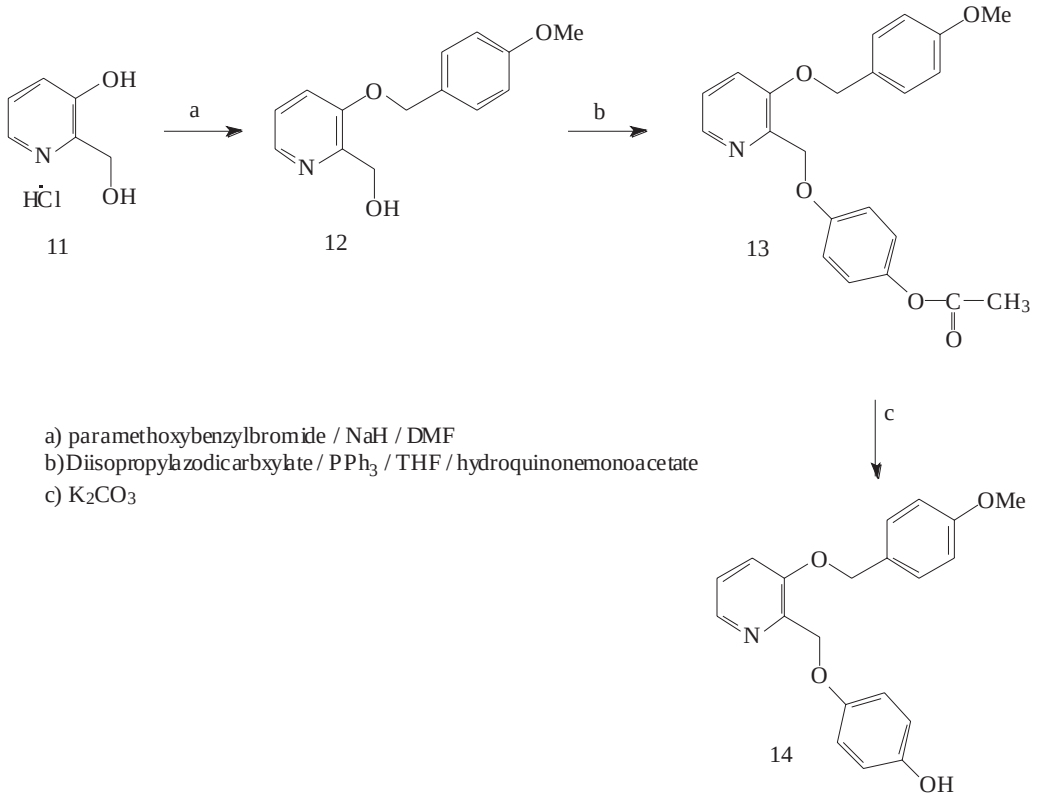
Scheme 1



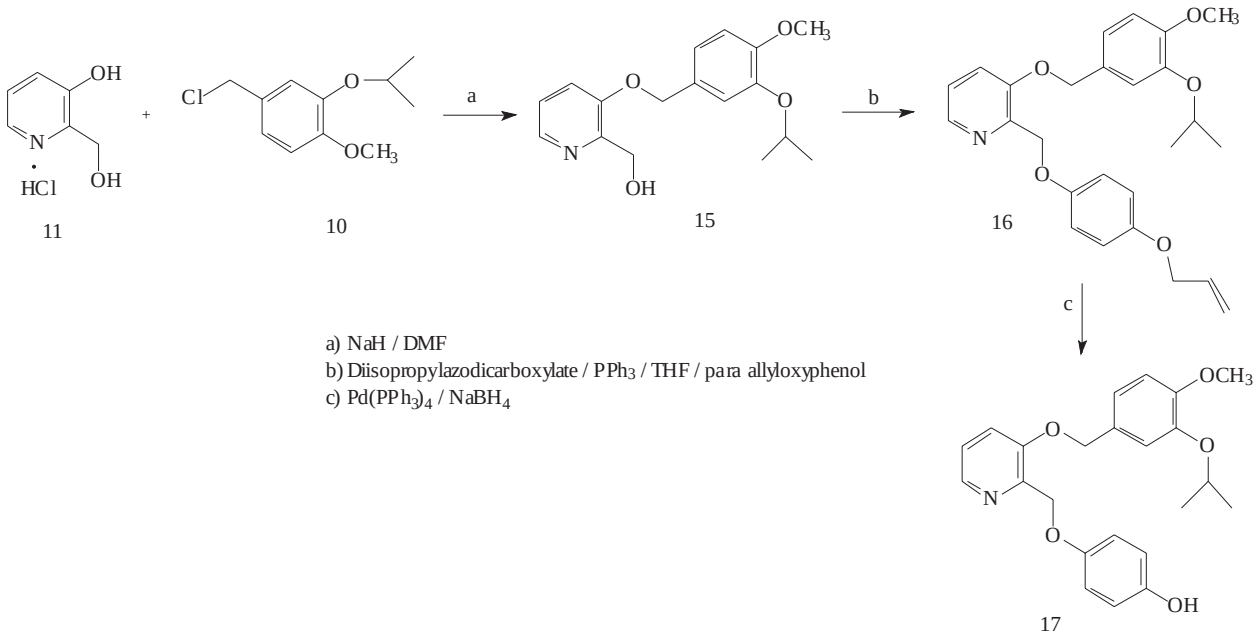
Scheme 2

Synthesis of 3-Isopropoxy-4-methoxybenzaldehyde (3)

To a solution of 3-hydroxy-4-methoxybenzaldehyde (isovanillin) (**1**) (10.0 g, 65.7 mmol) in DMF (200 mL) under a nitrogen atmosphere was added anhydrous potassium carbonate (18.3 g, 131.7 mmol). To this stirred mixture was added 2-iodopropane (11.7 g, 131.4 mmol) and stirring continued for 4 h at which time further iodopropane was added (4 mL) and the reaction continued for 1 h. The reaction mixture was poured into water (400 mL) and extracted with ethyl acetate. The combined organic phase was washed with water and then 100 mL aqueous 2M NaOH solution. A final wash with water (100 mL) and by sat. aqueous NaCl (100 mL) followed by drying over Na_2SO_4 gave a pale yellow oil on evaporation *in vacuo* (12.08 g, 95%): ^{1}H NMR (270 MHz, $CDCl_3$) 1.40 (d, 6H, J = 6.2 Hz), 3.94 (s, 3H), 4.65 (septet, 1H, J = 6.2 Hz), 6.99 (dd, 1H, J = 7.9 Hz), 7.41-7.48 (m, 2H), 9.87 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 21.7, 55.9, 71.2, 110.9, 112.6, 126.4, 130.0, 147.8, 155.7, 191.0; IR (film) 2970, 2930, 2840, 1690, 1510, 1440 cm^{-1}; MS (EI) m/e (relative intensity) 194 (M^+, 28), 152 (100); Anal. calc. for $C_{11}H_{14}O_3$: C, 68.04; H, 7.22. Found C, 67.65; H, 7.52%.



Scheme 3



Scheme 4

3-Isopropoxy-4-methoxybenzaldehyde ethylene acetal (4)

To a mixture of 3-isopropoxy-4-methoxybenzaldehyde (**3**) (18.8 g, 0.097 mol) in toluene (350 mL) was added ethylene glycol (100 mL, 1.8 mol) and *p*-toluene sulphonic acid (300 mg). The mixture was heated

under reflux with a Dean and Stark apparatus for 4.5 h and then allowed to cool. The reaction mixture was poured into 10% aq. potassium carbonate (700 mL) and the toluene layer was separated and washed sucessively with two 250 mL portions of 10% aq. K_2CO_3 and one 250 mL portion of brine and K_2CO_3 (25 mL 10% K_2CO_3 + 225 mL sat. NaCl aq.). The organic phase was dried over sodium sulphate, filtered and evaporated to give an off-white crystalline solid (21.25 g, 92%). mp 49-51°C; ^{1}H NMR (270 MHz, $CDCl_3$) 1.37 (dd, 6H, J = 6.1 Hz), 3.85 (s, 3H), 3.91-4.15 (m, 4 H), 4.57 (septet, 1H, J = 6.1 Hz), 5.74 (s, 1H), 6.87 (d, 1H, J = 8.8 Hz), 7.02-7.04 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 21.9, 55.9, 59.7, 65.1, 71.4, 103.7, 111.6, 113.7, 119.5, 130.3, 147.4, 151.2; IR(nujol) 1605, 1520, 1450, 1130 cm^{-1}; MS (EI) *m/e* (relative intensity) 238 (M^+, 26), 196 (21), 195 (54), 151 (22), 124 (31), 73 (100). Anal. calc. for $C_{13}H_{18}O_4$: C, 65.54; H, 7.61. Found C, 65.62; H, 7.54%.

3-Isopropoxy-4-hydroxybenzaldehyde (5)

To solution of chlorodiphenylphosphine (9.88 g, 44 mmol) in dry THF (50 mL) under an inert atmosphere was added small segments of lithium wire (3-5 mm long, cut directly into a flask) (0.77 g, 0.11 mole-washed prior to addition with hexane and dried with a paper towel). After approx. 5 min a fine ppt. started to form and after 10-15 min a deep red colour persisted. This mixture was stirred for 1 h and then a solution of 3-isopropoxy-4-methoxybenzaldehyde ethylene acetal (**4**) (7.65 g, 32 mmol) in dry THF (20 mL) was added and the reaction mixture was stirred for 2 h. The reaction mixture was then poured into water (300 mL) (through a plug of glass wool to remove unreacted Li) and 15 mL 10% aq. NaOH solution was added. The mixture was extracted with diethyl ether and the combined organic phases were washed with 10% aq. NaOH and all combined aqueous phases were cooled in an ice bath and acidified by dropwise addition of conc. HCl. A milky ppt. formed and the mixture was extracted with diethyl ether, and combined organic layers were washed with water, sat. aq. NaCl solution and dried over sodium sulphate. Filtration and evaporation gave the product (5.1 g, 88%) as a colourless oil: ^{1}H NMR (270 MHz, $CDCl_3$) 1.40 (d, 6H, J = 6.3 Hz), 4.72 (septet, 1H, J = 6.1 Hz), 7.04 (d, 1H, J = 8.6 Hz), 7.38-7.42 (m, 2H), 9.81 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 21.7, 71.7, 111.1, 114.6, 127.1, 129.7, 145.4, 152.7, 191.2; IR (nujol) 3400 (br), 1690, 1590 cm^{-1}; MS (EI) *m/e* (relative intensity) 180 (M^+, 34), 138 (90), 137 (100); Anal. calc. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found C, 66.50; H, 6.77%.

3-Isopropoxy-4-hydroxybenzylalcohol (6)

To a solution of 3-isopropoxy-4-hydroxybenzaldehyde (**5**) (5.1 g, 28 mmol) in methanol (75 mL) was added sodium borohydride (1.07 g, 28 mmol) in portions over 10 min. The reaction mixture was allowed to reach room temperature and was stirred over a period of 2 h. 2M HCl (aq.) (2 mL) was added and the methanol was evaporated *in vacuo*. The residue was partitioned between water and ethyl acetate and the organic phase washed with water, sat. aq. NaCl and dried over sodium sulphate. Evaporation gave a brown oil which was purified by flash chromatography on silica gel (eluting 1:1 EtOAc-hexane) to afford the required product as a colourless oil (3.8 g, 75%): ^{1}H NMR (270 MHz, $CDCl_3$) 1.36 (d, 6H, J = 5.9 Hz), 1.65 (br s, 1H), 4.58 (s, 2H),4.60 (septet, 1H, J = 5.9 Hz), 5.73 (s, 1H), 6.8-6.9 (m, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 22.0, 65.0, 71.6, 112.6, 114.3, 120.1, 132.7, 144.6, 146.0; IR (nujol) 3400 (br), 1690, 1590 cm^{-1}; MS (EI) *m/e* (relative intensity) 182 (M^+, 53), 141 (9), 140 (100), 139 (31); Anal. calc. for $C_{10}H_{14}O_3$: C, 65.93; H, 7.69. Found C, 65.54; H, 7.91%.

3-Isopropoxy-4-(*p*-cyanobenzyloxy)benzyl alcohol (7)

To a solution of 3-isopropoxy-4-hydroxybenzyl alcohol (**6**) (2.16 g, 11.8 mmol) in anhydrous DMF (20 mL) under an inert atmosphere was added potassium carbonate (3.27 g, 24 mmol) and stirring was continued for 10 min. A solution of 4-cyanobenzyl bromide (2.32 g, 11.8 mmol) in DMF (10 mL) was added via a syringe and the reaction mixture was then stirred for 4 h at room temperature. Water (200 mL) was added the and reaction mixture was extracted with EtOAc (2 x 100 mL). The combined organic phases were washed with water and sat. aq. NaCl solution and then dried over sodium sulphate to give an off-white solid on evaporation of solvents. Trituration with petroleum ether (60-80°C) gave the title compound (3.05 g, 87%) as a colourless solid: mp 72-73°C; ^{1}H NMR (300 MHz, $CDCl_3$) 1.37 (d, 6H, J = 6.1 Hz), 2.10 (s, 1H), 4.59 (septet, 1H, J = 6.1 Hz), 5.01 (s, 2H), 5.12 (s, 2H), 6.82 (s, 2H), 6.98 (s, 1H), 7.57 (d, 2H, J = 8.0 Hz), 7.64 (d, 2H, J = 8.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) 22.0, 64.8, 70.4, 71.7, 111.4, 115.6, 118.6, 119.9, 127.5, 132.3, 135.3, 143.1, 148.3, 148.5; IR (nujol) 3300, 2220, 1615, 1590, 1515 cm^{-1}; MS (EI) *m/e* (relative intensity) 297 (M^+4), 255 (1), 197 (6); Anal. calc. for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71. Found C, 72.57; H, 6.35; N, 4.71%.

p-(4-hydroxymethyl-3-isopropoxy)phenoxy benzamidine acetic acid salt (8)

Hydrogen sulphide was bubbled through a solution of the benzonitrile (**7**) (1.02 g) in pyridine-triethylamine (20 ml-2 ml) for 20 min. at room temperature. After 24 h at room temperature in a stoppered flask, the reaction mixture was concentrated under a steady stream of nitrogen. The residue was diluted with ethyl acetate, washed with $KHSO_4$ and brine, and dried over sodium sulphate. Concentration *in vacuo* afforded a quantitative yield of thioamide derivative. (Hexane/ethyl acetate= 1/1, Rf=0.3). The thioamide derivative was dissolved in a solution of acetone-iodomethane (150 ml-4 ml). The reaction mixture was warmed to achieve reflux for 5 h. Concentration in vacuo afforded the thioimidate as the HI salt. A solution of the thioimidate and ammomium acetate (0.77 g) in methanol (150 ml) was warmed to achieve reflux for 8 h. After cooling to room temperature, the reaction mixture was concentrated under a steady stream of nitrogen, and then acetone (200 ml) was added and the precipitated product was filtrated. 0.6 g, 50% overall. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.37 (d, 6H, J = 6.1 Hz), 1.72 (s, 3H), 3.35 (broad), 4.35 (s, 2H), 4.59 (septet, 1H), 5.20 (s, 2H), 6.78 (d, 1H), 6.85 (d, 2H), 7.61 (d, 2H, J = 8 Hz), 7.78 (d, 2H, J = 8 Hz). MS (EI) m/e (relative intensity) 311 (9), 297 (28), 139 (58), 116 (100), 93 (40), 43 (35).

Synthesis of 3-Isopropoxy-4-methoxybenzylalcohol (9)

To a solution of 3-isopropoxy-4-methoxybenzaldyde (**3**) (11.9 g, 61.3 mmol) in methanol (130 mL) was added sodium borohydride (2.2 g, 61.3 mmol) in small portions over a period of 10 min. After stirring for 3.5 h 2M HCl solution (10 mL) was added cautiously to quench excess $NaBH_4$ and methanol was removed *in vacuo*. The residue was partitioned between water and ethyl acetate and organic phase was separated and washed with water (100 mL) and sat. aq. NaCl solution (100 mL). Drying the organic phase over sodium sulphate and evaporation gave a yellow oil (11.04g, 91%), which was homogeneous by ^{1}H NMR. Further purification if necessary could be achieved by flash chromatography (eluting with EtOAc-hexane, 1:1): ^{1}H NMR (270 MHz, $CDCl_3$) 1.34 (d, 6H, J = 6.0 Hz), 3.80 (s, 3H), 4.52 (septet, 1H, J = 6.2 Hz), 4.52 (s, 2H) 6.81 (s, 1H), 6.82 (dd, 1H, J = 8.1 and 1.4 Hz), 6.91 (d, 1H, J = 1.4 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) 21.8, 55.7, 64.6, 71.2, 111.7, 114.9, 119.7, 133.6, 147.1, 149.7; IR (film) 3410 br, 2980, 1605, 1515 cm^{-1}; MS (EI) *m/e* (relative intensity) 196 (M^+, 30), 154 (100), 137 (28).

Synthesis of 3-isopropoxy-4-methoxybenzylchloride (10)

To a solution of 3-Isopropoxy-4-methoxybenzylalcohol (**9**) (1.68 g, 8.6 mmol) in dry toluene (20 mL) was added phosphorous trichloride (0.75 mL, 8.6 mmol). The reaction mixture was stirred for 45 min and then partitioned between ethyl acetate and water. The organic phase was washed with sat. NaCl solution and then dried over sodium sulphate. Filtration and evaporation gave the product as a colourless oil, which was purified by flash chromatography on silica gel (eluting with ethyl acetate-hexane 1:3) to afford the product as a colourless oil (1.23 g; 67%): ^{1}H NMR (270 MHz, $CDCl_3$) 1.35 (d, 6H, J = 5.9 Hz), 3.81 (s, 3H), 4.52 (s, 2H), 4.52 (septet, 1H, J = 5.9 Hz), 6.79 (d, 1H, J = 8.3 Hz), 6.89-6.92 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 21.8, 46.4, 55.7, 71.2, 111.5, 115.9, 121.3, 129.7, 147.1, 150.3; IR (film) 2980, 2840, 1610, 1590, 1515, 1470, 1445, 1430, 1385 cm^{-1}; MS (EI) m/e (relative intensity) 216 (5), 214 (M^+, 15), 179 (9), 174 (9), 173 (3), 172 (28), 137 (100).

Synthesis of 2-Hydroxymethyl-3-hydroxypyridine Hydrochloride (11)

To a solution of 3-hydroxypyridine (15.0 g, 0.156 mole) in aqueous sodium hydroxide (6.3 g, 0.158 mole in 63 mL H_2O) was added 38% aq. formaldehyde solution (12.6 mL, 0.156 mole). The reaction mixture was heated at 90-100° for 3 h and then allowed to cool to ambient temperature. Acetic acid (9.47 mL, 0.156 mole) was added and water was removed *in vacuo* and the solid obtained was stirred with acetone (200 mL) and the ppt. sodium acetate was filtered off, and then washed with acetone (2 x 50 mL). The combined organic phase was treated with HCl gas and the off-white ppt. that formed was washed with acetone the then HCl (g) saturated ethanol and filtered. Drying *in vacuo* afforded the title compound (5.3 g, 23%) as an off-white solid: mp 180°C, ^{1}H NMR (270 MHz, DMSO-d_6) 4.92 (s, 2H), 7.90 (m, 1H), 8.04 (m, 1H), 8.38 (m, 1H); ^{13}C NMR (67.8 MHz, DMSO-d_6) 56.3, 126.3, 130.0, 131.3, 145.0, 153.6 IR (nujol) 3490 br, 1590, 1520 cm^{-1}; MS (EI) m/e (relative intensity) 125 (M^+100).

Synthesis of 2-Hydroxymethyl-3-(p-methoxybezyloxy) pyridine (12)

To a solution (suspn.) of 2-hydroxymethyl-3-hydroxy pyridine hydrochloride (**11**) (6.21 g, 38.5 mmol) in DMF (70 ml) under nitrogen and cooled with an ice-bath was added NaH in portions over 6 min. The mixture was stirred for 45 min. at room temperature and then a solution of the 4-methoxybenzylbromide (7.04 g, 35 mmol) was added in 50 ml DMF via a syringe. The and then stirred for 4 h. Reaction mixture was poured into ice-cooled water (500 ml) and extracted with ethyl acetate. The organic phase was washed with water and saturated NaCl and dried over Na_2SO_4. Evaporation gave a dark solid, which was purified by column chromatography on silica gel (hexane/ethyl acetate = 1/1) (2.59 g, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 3H), 4.83 (s, 2H), 5.08 (s, 2H), 6.85 (d, 2H), 7.24 (s, 2H), 7.30 (d, 2H), 8.2 (d, 2H).

Synthesis of 2-((p-acetoxy) phenoxy) methy-3-(p-methoxybezyloxy) pyridine (13)

To a solution of hydroquinon monoacetate (6.12 mmol) in THF (50 ml) under a nitrogen atmosphere was added PPh_3 (6.12 mmol) followed by diisopropylazodicarboxylate (6.37 mmol). After stirring for 5 min. to this mixture was added a solution of 2-hydroxmetyl-3-(p-methoxy)benzyloxy pyridine (**12**) (6.12 mmol) in THF (30 ml) and the solution was allowed to stand for 20 h at room temperature. The solvent was removed under reduced pressure and purified by column chromatography on silica gel (hexane/ethylacetate = 1/3 Rf = 0.6). ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.18 (s, 3H), 3.72 (s, 3H), 4.98 (s, 2H), 5.20 (s, 2H), 6.8-7.2 (m, 10H), 8.16 (d, 1H, J = 2Hz), ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.7, 21.7, 54.9, 67.1, 69.7, 113.47, 113.8, 115.3, 117.9, 119.3, 121.9, 123.8, 127.7, 128.6, 129.5, 140.8, 144.0, 145.5, 153.0, 156.4, 159.2, 169.4.

Synthesis of 2-((p-hydroxy) phenoxy) methy-3-(p-methoxybezyloxy) pyridine (14)

A methanol (15 ml) solution of 2-((p-acetoxy) phenoxy) methy-3-(p-methoxy-bezyloxy) pyridine (**13**) (0.5 g, 1.31 mmol) was treated with K_2CO_3 (1.05 g, 7.64 mmol)/water (10 ml). The solution was allowed to stand for 1 h at room temperature. It was then acidified with 10% HCl to neutral and extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4 and evaporated. The product was obtained as pure foam (0.35 g, 78%) (hexane/ethyl acetate = 1/3, Rf = 0.55) ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.75 (s, 3H), 5.02 (s, 2H), 5.16 (s, 2H), 6.75-6.88 (m, 5H), 7.19-7.31 (m, 5H), 8.16 (d, 1H, 2Hz). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.6, 54.9, 67.0, 69.9, 113.8, 115.9, 116.0, 118.3, 119.7, 122.7, 124.0, 127.7, 128.7, 129.6, 140.3, 145.9, 150.9, 152.0, 153.1, 159.

Synthesis of 2-Hydroxymethyl-3-[(3'isopropoxy-4'methoxy)benzyloxy]pyridine (15)

To a suspension of 3-hydroxy-2-hydroxymethylpyridine hydrochloride (**11**) (0.78 g, 4.57 mmol) in anhydrous DMF (15 mL) under a nitrogen atmosphere and cooled with an ice-water bath was added sodium hydride (60 wt. % , 0.365 g, 9.14 mmol) in portions over 8-10 min. After stirring at the ice-bath temperature for 10 min, a solution of 3-isopropoxy-4-methoxybenzyl chloride (**10**) (1.09 g, 4.57 mmol) in DMF (15 mL) was added. The reaction mixture was allowed to warm to room temperature and after 1 h heated at 50-60°C for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate and the combined organic phases were washed with water and sat. aq. NaCl and dried over sodium sulphate. Purification by flash chromatography (1:1 EtOAc-hexane) gave the product as a white crystalline solid (0.77 g, 56%): mp 111-113 ° C; ^{1}H NMR (300 MHz, $CDCl_3$) 1.37 (d, 6H, J = 6.2 Hz), 3.87 (s, 3H), 4.32 (t, 1H, J = 4.8 Hz), 4.51 (septet, 1H, J = 6.2 Hz), 4.79 (d, 2H, 4.5 Hz), 5.03 (s, 2H), 6.80-6.90 (m, 3H), 7.18 (m, 2H), 8.17 (dd, 1H, 3.0 and 3.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) 21.9, 55.9, 60.1, 69.9, 71.5, 111.9, 115.2, 118.1, 120.4, 122.6, 128.4, 139.8, 147.6, 148.8, 150.6, 151.5; IR (nujol) 3150, 2910, 1595, 1598, 1515 cm^{-1}; MS (EI) m/e (relative intensity) 303 (M^+5), 273 (2), 196 (21), 180 (13), 179 (100); Anal. calc. for $C_{19}H_{21}NO_4$: C, 67.39; H, 7.98; N, 4.62. Found C, 67.39; H, 7.06; N, 4.50%.

Synthesis of 2-[(*p*-allyloxy)phenoxy]methyl-3-[(3'-isopropoxy-4'-methoxy)benzyl oxy] pyridine (16)

To a solution of 2-hydroxymethyl-3-[(3'-isopropoxy-4'-methoxy) benzyl oxy] pyridine (**15**) (1.5 g, 4.95 mmol) and triphenyl phosphine (1.29g, 4.95 mmol) in dry THF (50 mL) was added diisopropyl azodicarboxylate (1.01 ml, 5.17 mmol) causing yellow coloration. After stirring for 10 min 4-allyloxyphenol (4.95 mmol) was added and the reaction mixture was allowed to stand under an argon atmosphere for 20 h. The THF was evaporated and the residue purified by column chromatography on silica gel (gradient elution; ethyl acetate-hexane = 1/2 Rf = 0.57) followed by recrystallisation from ethyl acetate-hexane to afford the title compound (1.18g, 55%) as a white solid.^{1}H NMR (270 MHz, $CDCl_3$) δ 1.28 (d, 6 H, J = 6 Hz), 3.84 (s, 3H), 4.43 (septet, 1H, J = 6 Hz) 4.46-4.49 (m, 2H), 5.05 (s, 2H), 5.20 (s, 2H), 5.39 (dd, 2H, J = 17 Mhz), 5.99-6.11 (m, 1 H), 6.80-6.90 (m, 3H), 6.92-7.0 (m, 4H), 8.26 (dd, 1H, J = 4.3 and 1.8 Hz), ^{13}C NMR (67.8 Mhz, $CDCl_3$) δ 21.9, 22.6, 55.9, 677.7, 69.3, 69.9, 70.2, 71.2, 76.5, 77.0, 77.4, 111.77, 114.8, 115.1, 115.4, 115.9, 120.0, 123.9, 128.3, 133.5, 141.2, 147.4, 150.2, 153.3

Synthesis of 2-((p-hydroxy)methoxy)methyl-3-((3′-isopropoxy-4′-methoxy benzyl) oxy) pyridine (17)

To a solutuion of (**16**) (0.3 g, 0.69 mmol) in 50 ml THF was added a catalytic amount of $Pd(PPh_3)_4$ (0.00159 g, 0.02 eq). The yellow solution was stirred for 5 min. and $NaBH_4$(0.038 g, 1.034 mmol) was introduced. The mixture became black over time. After 1 h, excess $NaBH_4$was destroyed by addition of 1 N HCl. The solvent was removed and the aqueous solution extracted with ethyl acetate. The organic phase was washed with water, dried over sodium sulphate and the solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane/ ethyl acetate = 1/1 Rf = 0.42) and an oily compound was obtained (20%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.28 (d, 6H, J = 6 Hz), 3.84 (s, 3H), 4.43 (septet, 1H, J = 6 Hz), 5.06 (s, 2H), 5.16 (s, 2H), 6.67-6.83 (dd, 4H, J = 25 and 7 Hz), 6.86-6.96 (m, 3H), 7.26 (m, 2H), 8.26 (dd, 1H, J = 4 and 1.8 Hz). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.0, 20.18, 21.92, 29.6, 55.9, 67.6, 70.3, 71.3, 111.8, 114.8, 116.11, 116.17, 119.8, 120.1, 124.1, 128.3, 136.5, 141.0, 146.3, 147.4, 150.2, 152.8, 153.4, 183.3.

Acknowledgements

The author thanks his PhD supervisor Prof. Dr. Ahmet Akar (İstanbul Technical University), TÜBİTAK, İTÜ and Prof. A. McCillop (University of East Anglia, England).

References

1. A.E.P. Adang, P.H.H. Hermkens, J.T.M. Linders, H.C.J. Ottenheijm, C.J. Staveren, **Recl. Trav. Chim. Pays-Bas, 113**, 63-78 (1994).
2. A. Giannis, T. Kolter, **Angew. Chem. Int. Ed. Eng., 32**, 1244-1267 (1993).
3. J. Gante, **Angew. Chem. Int. Ed. Eng., 33**, 1699-1720 (1993).
4. a) R. Paul, Halfpenny; David C. Horwell; John Hughes; John C. Hunter; David C. Rees, **J.Med.Chem**, **33: 1** 286-291 (1990).
   b) Zhao-Xia Guo; Andrew N. Cammidge; David C. Horwell, **Tetrahedron 56: 29** 5169 – 5176 (2000).
5. B.M. Olivera, W.R. Gray, R. Zeikus, J.M. McIntosh, J. Varga, J. Rivier, V. de Santos, L.J. Cruz, **Science, 230**, 1338-1343 (1985).
6. B.M. Olivera, J. Rivier, J.K. Scott, D.R. Hillyard, LJ.J. Cruz, **Biol. Chem., 266,** 22067-22070, (1991).
7. A.B. Malmberg, T.L. Yaksh, **Pain, 60**, 83-90 (1995).
8. D. Wemeling, B. Pfeifer, J. Berger, L. Piecoro, R. Luther, D.J. McGuire, **Neurovirol, 2,** 52 (1996).
9. S. Menzler, J.A. Bikker, D.C. Horwell, **Tetrahedron Lett., 39,** 7619-7622 (1998).
10. V.A. Joanne, D.C. Horwell, J.A.H. Lainton, J.A. O'Neil, G.S. Ratcliffe, **Chem. Commun., 21,** 2121-2122 (1997).
11. L. Nadashi, D. Yamashiro, D. Chung, K.T. Hornoch, P. Adriaenssens, J. Ramachandran, **Biochemistry, 34,** 8076-8081 (1995).
12. D. Heinert, A.E. Millar, **Tetrahedron,** 54 (1985).