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ORIGINAL ARTICLE

Synthesis of potentially bioactive PABA-related *N*-(aminoalkyl)lactamic amino acids and esters via selective S_NAr reactions

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Abstract Potentially bioactive *N*-(aminoalkyl)lactamic amino acids and esters were synthesized in satisfactory to good yields by S_NAr reactions of aromatic acids with *N*-(3-aminopropyl)lactams followed by esterification with tertiary amino alcohols. The addition–elimination S_NAr mechanism was confirmed by NMR and MS measurements.

Keywords PABA derivatives · Lactams · Potential bio-activity · S_NAr reaction

Introduction

Derivatives of *p*-aminobenzoic acid (PABA) have shown interesting pharmacological properties (Kabbani et al. 2007; Furuya et al. 1995; Saavedra et al. 2006). Some of such derivatives are used as acetylcholinesterase inhibitors in palliative treatment of the Alzheimer's disease (Correa-Basurto et al. 2005). PABA analogs such as procaine and lidocaine are anesthetics which interact with sodium channels reducing their sensibility, motion and autonomic function (Löfström 1960; Pateromichelakis 2008; Heath et al. 1984). PABA itself is a water soluble non-poisonous drug and is easily absorbed by intestinal treatment. It has also been used against typhus and other rickettsial diseases (Little 2002) and as a common ingredient in sunscreen agents (Bruze et al. 1990; Gennaro 1991). PABA has also shown antioxidant properties and is also a component of the vitamin B-complex (John et al. 1995; Vo-Dinh et al. 2005).

On the other hand, molecules containing *N*-(3-aminopropyl)-2-azepanone (APA) or *N*-(3-aminopropyl)-2-pyrrolidone (APP) moieties have been reported as inhibitors of the human tryptase, an important mediator in the asthma pathology (Zhao et al. 2004), whereas APP derivatives were found to be active against H2N2 and H3N2 strains of the influenza virus (Stamatiou et al. 2001). APP derivatives have also been reported as HIV-1 protease inhibitors (Ghosh et al. 2009).

Herein we describe the results of synthesis of several PABA derivatives **5**–**6** and analogs **7**–**8** by a selective nucleophilic aromatic substitution reaction (S_NAr) (Gierczyk et al. 2003; Terrier 1991; Bunnett and Zahler 1951; Buncel et al. 1995) of 4-chloro-3-nitrobenzoic acid (**1**) and 4-chloro-3-nitrobenzenesulfonic acid (**2**) with APA (**3**) and APP (**4**) amino-lactams.

We have also note that PABA derivatives (**5** and **6**) can be easily transformed via Fischer's esterification to potentially bioactive procaine-like compounds (Paramus and Rutherford 1972; Waukegan 1960). Hence this reaction with the aminoalcohols 3-(dimethylamino)propan-1-ol (**9**) and 3-(diethylamino)propan-1-ol (**10**) afforded the

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corresponding PABA-related *N*-(3-aminoalkyl)lactamic aminoesters (**11**–**14**) in good yields. This simple and relatively facile and efficient synthesis may lead to a great variety of such procaine-like compounds with potential toxicological and pharmacological properties. Biological activity of amino acids (**5**–**8**) and aminoesters (**11**–**14**) is under current investigation and the results will be opportunely communicated.

Materials and methods

Commercial DBU, DBN, 4-chloro-3-nitrobenzoic acid, 4-chloro-3-nitrobenzenesulfonic acid, 3-dimethylamino-1-propanol and 3-diethylamino-1-propanol were used without previous purification. Thin layer chromatography (TLC) was performed on Macherey–Nagel silica gel plates and visualized using iodine reagent. ^{1}H NMR spectra were obtained on Varian Inova instrument at 500 MHz. ^{13}C NMR spectra were obtained on Bruker Avance DPX at 250 MHz. Chemical shifts for ^{1}H NMR and ^{13}C NMR were referenced to residual solvent ($CDCl_3$ $\delta = 7.27$ ppm for ^{1}H NMR, $\delta = 77.23$ ppm for ^{13}C NMR; DMSO-d_6 $\delta = 2.50$ ppm for ^{1}H NMR, $\delta = 39.5$ ppm for ^{13}C NMR; D_2O $\delta = 4.8$ ppm for ^{1}H NMR) were reported in ppm, and were observed at 25°C. TSP4 was used as reference for ^{13}C NMR spectra in D_2O solvent. Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublet, t = triplet, qua = quadruplet, qu = quintuplet, m = multiplet, br s = broad singlet), integration, and coupling constants (in Hertz). GC–MS spectra were obtained using a Shimadzu QP-2010plus. The column inside the GC was a capillary column coated with 5% diphenyl–95% dimethyl polysiloxane. The injection port of the GC was set at 250°C. The GC column was initially set up at 80°C and held there for 2 min after run was started. A heating rate of 10°C/min was used to heat the column to 280°C, where the temperature was held for 5 min. The energy used for electron ionization (EI) was 70 eV. The carrier gas used for the GC–MS was helium. MS spectra were also obtained by direct insertion in the mass spectrometer. ESI(+)-MS spectra were obtained using a Micromass QTof hybrid quadrupole time-of-flight mass spectrometer operating at 7,000 mass resolution and 5 ppm mass accuracy. The solutions were infused directly into the ESI source by means of syringe pump at a flow rate of 10 μL/min (Becke 1993). The gaseous protonated molecules display rather clean tandem mass spectra with fragment ions formed upon 15–20 eV collisions with argon that are fully compatible with their proposed structures. ESI–MS and ESI–MS/MS were acquired in a QTof Waters Micromass mass spectrometer using positive ion mode from 1:1 H_2O–MeOH solution with addition of a few microlitres of formic acid, and using the following basic operation conditions: capillary and cone voltages were set to 3,500 and 45 V, respectively, with a desolvation temperature of 100°C. For the tandem MS experiments, 15–20 eV collisions with argon were used. FTIR measurements were conducted in a spectrometer Bruker, model Vector 22, and the spectra were collected at room temperature (23°C) with 124 scans, 4 cm^{-1} spectral resolution in the form of KBr pellets. All melting points (mp) were obtained using a Quimis Q-340 M apparatus. Microwave synthesis was realized using a CEM Focused Microwave Synthesis System, model Discover. For normal pressure operations standard glassware (25 mL two-necked Pirex round-bottomed flask) with a water-cooled reflux condenser fitted on top of the cavity was used. The microwave power and reaction temperature were set to 70 W and 120°C.

General procedure for the synthesis of *N*-(3-aminopropyl)-2-azepanone (**3**) and *N*-(3-aminopropyl)-2-pyrrolidone (**4**)

1,5-Diazabicyclo[4.3.0]non-5-ene (1.86 g, 15 mmol) or 1,8-diazabicyclo[5.4.0]undec-7-ene (2.28 g, 15 mmol) and water (0.27 g, 15 mmol) were mixed in a round flask coupled to a reflux condenser and the mixture was heated for 12 h at 85°C. The corresponding amino-lactams were obtained as a colorless oil after chromatography ($CHCl_3$–MeOH–conc. NH_3, 9:1:1, then $CHCl_3$–MeOH, 4:1) in agreement with reported procedure (Kraft 1999). The reaction was monitored by TLC and GC–MS.

General procedure for the synthesis of PABA-related *N*-(3-aminoalkyl)lactamic amino acids (**5**–**6**) and analogs (**7**–**8**)

To a solution of 4-chloro-3-nitrobenzoic acid (1.6 g, 8 mmol) **1** or 4-chloro-3-nitrobenzenosulfonic acid (1.89 g, 8 mmol) **2** in acetonitrile (30 mL) or DMSO (10 mL) was added slowly *N*-(3-aminopropyl)-2-azepanone (1.42 g, 10 mmol) **4** or *N*-(3-aminopropyl)-2-pyrrolidone (1.7 g, 10 mmol) **3** and the mixture was stirred and heated at 85°C for 8–12 h. The solvent was removed under vacuum and the product was treated with dilute HCl (5%) for removal excess of amino-lactam. The crude product was filtered off and recrystallized from 1:1 H_2O–EtOH. The purity of product was checked by TLC using a toluene–acetone–ethanol mixture as an eluent.

General procedure for the synthesis of PABA-related *N*-(3-aminoalkyl)lactamic esters (**11**–**14**)

Compound **5** (2.45 g, 8 mmol) or **6** (2.68 g, 8 mmol) was dissolved in a toluene (30 mL) and DMF (5 mL) solution.

Catalytic amount of H_2SO_4 or $H_3PW_{12}O_{40}$ (molar relation carboxylic acid:catalyst was 10 and 1, respectively) was added and the resulting mixture was stirred with dropwise addition of 3-(dimethylamino)propan-1-ol (1.03 g, 10 mmol) or 3-(diethylamino)propan-1-ol (1.31, 10 mmol) followed by heating at 130°C for 10 h under reflux conditions and using a Dean–Stark water separator. Then the reaction mixture was washed with dilute solution (5%) of $NaHCO_3$. The organic layer was filtered off and the residual organic solvent was removed under vacuum given the corresponding esters **11–14** as oily products. The purity was checked by TLC using 45:45:7:3 toluene–acetone–ethanol–NH_4OH (conc.).

General procedure for study of selectivity on esterification of aminoalcohols with benzoic acid **1** (compounds **15–17**)

The procedure was the same as used for **11–14**. After washing with dilute $NaHCO_3$ the organic layer is filtered off and the solvent was removed under vacuum given a yellow solid from starting aminoalcohols **9** and **10**. The crude products (compounds **15–17**) were recrystallized from 1:1 ethylether–petroleum ether (bp 60–80°C) and analyzed by GC–MS.

*Synthesis of 4-[N-(3′-aminopropyl)-2-pyrrolidone]-3-nitrobenzoic acid (**5**)*

The 4-chloro-3-nitrobenzoic acid (**1**) and *N*-(3-aminopropyl)-2-pyrrolidone (**3**) were reacted according to the general procedure yielding a yellow solid (2.18 g, 89%): mp = 219–224°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, 1H, $^4J_{HH}$ = 1.9 Hz), 8.22 (dd, 1H, $^4J_{HH}$ = 1.9, $^3J_{HH}$ = 8.2 Hz), 7.53 (d, 1H, $^3J_{HH}$ = 8.2 Hz), 5.28 (s, 1H), 3.62 (t, 2H), 3.51 (t, 2H), 3.40 (t, 2H), 3.13 (t, 2H), 2.16 (qu, 2H), 2.04 (qu, 2H) ppm; ^{13}C NMR (250 MHz, D_2O) δ 170.6, 164.5, 146.5, 136.6, 133.7, 131.6, 128.3, 125.8, 41.9, 37.7, 31.1, 29.7, 17.9 ppm; FTIR (KBr) ν 3,214, 1,608, 1,683 cm^{-1}; ESI(+)-MS *m/z* found: 308.141, *m/z* calculated for $[C_{14}H_{17}N_3O_5 + H]^+$: 308.125, Fragment ions were also observed: $[M + H–H_2O]^+$ of *m/z* 290, $[M + H–H_2O–C_2H_4]^+$ of *m/z* 262 and $[M + H–C_7H_6N_2O_4]^+$ of *m/z* 126 (5-member ring).

*Synthesis of 4-[N-(3′-aminopropyl)-2-azepanone]-3-nitrobenzoic acid (**6**)*

The 4-chloro-3-nitrobenzoic acid (**1**) and *N*-(3-aminopropyl)-2-azepanone (**4**) were reacted according to the general procedure yielding a yellow solid (1,74 g, 86%): mp = 157–159°C; ^{1}HNMR (500 MHz, DMSO-d_6) δ 8.47 (d, 1H, $^4J_{HH}$ = 1.9 Hz), 8.16 (dd, 1H, $^4J_{HH}$ = 1.9, $^3J_{HH}$ = 8,3 Hz), 7.87 (d, 1H, $^3J_{HH}$ = 8.3 Hz), 3.55 (t, 2H), 3.47 (t, 2H), 3.37 (m, 2H), 3.25 (m, 2H), 1.90 (qu, 2H), 1.60 (m, 6H) ppm; ^{13}C NMR (250 MHz, D_2O) δ 174.4, 168.6, 149.6, 139.3, 136.5, 134.5, 131.5, 128.8, 50.8, 40.6, 35.4, 31.1, 28.5, 26.0, 21.8, 17,7 ppm; FTIR (KBr) ν 3,220, 1,605, 1,680 cm^{-1}; ESI(+)-MS *m/z* found: 336.201, *m/z* calculated for $[C_{16}H_{22}N_3O_5 + H]^+$: 336.156, fragment ions were also observed: $[M + H–H_2O]^+$ of *m/z* 318, $[M + H–H_2O–C_2H_4]^+$ of *m/z* 290 and $[M + H–C_7H_6N_2O_4]^+$ of *m/z* 154 (7-member ring).

*Synthesis of 4-[N-(3′-aminopropyl)-2-pyrrolidone]-3-nitrobenzenesulfonic acid (**7**)*

The 4-chloro-3-nitrobenzenesulfonic acid (**2**) and *N*-(3-aminopropyl)-2-pyrrolidone (**3**) were reacted according to the general procedure yielding a brown solid (1.7 g, 82%): mp >310°C; ^{1}H NMR (500 MHz, D_2O) δ 8.25 (d, 1H, $^4J_{HH}$ = 2.1 Hz), 7.76 (dd, 1H, $^4J_{HH}$ = 2.1, $^3J_{HH}$ = 8.3 Hz), 6.92 (d, 1H, $^3J_{HH}$ = 8.3 Hz), 3.55 (t, 2H), 3.31 (m, 2H), 2.87 (t, 2H), 2.72 (t, 2H), 2.30 (m, 2H), 1.91 (m, 2H) ppm; ^{13}C NMR (250 MHz, DMSO-d_6) δ 178.6, 146.5, 142.6, 132.9, 130.5, 124.5, 123.2, 53.3, 47.9, 42.0, 39.3, 29.8, 18.1 ppm; FTIR (KBr) ν 3,570, 1,653, 1,269 cm^{-1}; ESI(+)-MS *m/z* found: 344.099, *m/z* calculated for $[C_{13}H_{17}N_3O_6S + H]^+$: 344.092, fragment ions were also observed: $[M + H–H_2O]^+$ of *m/z* 326, $[M + H–C_2H_4]^+$ of *m/z* 298 and $[M + H–C_6H_6N_2O_5S]^+$ of *m/z* 126 (5-member ring).

*Synthesis of 4-[N-(3′-aminopropyl)-2-azepanone]-3-nitrobenzenesulfonic acid (**8**)*

The 4-chloro-3-nitrobenzenesulfonic acid (**2**) and *N*-(3-aminopropyl)-2-azepanone (**4**) were reacted according to the general procedure yielding a brown solid (2.55 g, 86%): mp >310°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.41 (d, 1H, $^4J_{HH}$ = 1.9 Hz), 8.12 (dd, 1H, $^4J_{HH}$ = 1.9, $^3J_{HH}$ = 8,3 Hz), 7.79 (d, 1H, $^3J_{HH}$ = 8,3 Hz), 3.54 (t, 2H), 3.47 (t, 2H), 3.26 (t, 2H), 2.68 (m, 2H), 1.91 (qu, 2H), 1.63 (m, 6H) ppm; ^{13}C NMR (250 MHz, $CDCl_3$) δ 170.7, 152.5, 142.1, 139.4, 136.9, 132.5, 131.3, 58.8, 53.3, 43.1, 36.9, 33.7, 31.4, 28.8, 24.4 ppm; FTIR (KBr) ν 3,600, 1,703, 1,270 cm^{-1}; ESI(+)-MS *m/z* found: 372.110, *m/z* calculated for $[C_{15}H_{22}N_3O_6S + H]^+$: 372.123, fragment ions were also observed: $[M + H–H_2O]^+$ of *m/z* 354, $[M + H–C_2H_4]^+$ of *m/z* 326 and $[M + H–C_6H_6N_2O_5S]^+$ of *m/z* 154 (7-member ring).

*Synthesis of N,N-dimethylaminopropyl-4-[N-(3′-aminopropyl)-2-pyrrolidone]-3-nitrobenzoate (**11**)*

The 4-[N-(3′-aminopropyl)-2-pyrrolidone]-3-nitrobenzoic acid (**5**) and 3-(dimethylamino)propan-1-ol were reacted

according to the general procedure yielding a yellow oily (2.03 g, 65%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (d, 1H, $^{4}J_{HH} = 2.9$ Hz), 8.50 (br s, 1H), 8.26 (dd, 1H, $^{4}J_{HH} = 2.9$, $^{3}J_{HH} = 9.2$ Hz), 6.91 (d, 1H, $^{3}J_{HH} = 9.2$ Hz), 4.43 (t, 2H), 3.47-3.38 (m, 8H), 2.84 (t, 6H), 3.16 (m, 2H), 2.43 (m, 2H) ppm; ^{13}C NMR (250 MHz, $CDCl_3$) δ 176.1, 165.0, 148.3, 136.6, 130.5, 129.9, 116.6, 113.8, 61.7, 55.7, 47.7, 43.3, 41.3, 40.6, 31.1, 26.9, 24.6, 18.2 ppm; ESI(+)-MS *m/z* found: 393.224, *m/z* calculated for $[C_{19}H_{28}N_4O_5 + H]^+$: 393.213, fragment ions were also observed: $[M + H–C_2H_7N]^+$ of *m/z* 348, $[M + H–C_5H_{13}NO]^+$ of *m/z* 290 and $[M + H–C_{12}H_{17}N_3O_4]^+$ of *m/z* 126 (5-member ring).

*Synthesis of N,N-diethylaminopropyl-4-[N-(3′-aminopropyl)-2-pyrrolidone]-3-nitrobenzoate (**12**)*

The 4-[N-(3′-aminopropyl)-2-pyrrolidone]-3-nitrobenzoic acid (**5**) and 3-(diethylamino)propan-1-ol were reacted according to the general procedure yielding an orange oily (2.41 g, 72%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (d, 1H, $^{4}J_{HH} = 2.4$ Hz), 8.20 (t, 1H), 8.03 (dd, 1H, $^{4}J_{HH} = 2.4$, $^{3}J_{HH} = 8.7$ Hz), 6.86 (d, 1H, $^{3}J_{HH} = 8.7$ Hz), 4.37 (t, 2H), 3.47-3.37 (m, 8H), 2.89 (m, 4H), 2.41 (t, 2H), 2.16 (qu, 2H), 2.06 (qu, 2H), 1,94 (qu, 2H), 1.25 (t, 6H) ppm; ^{13}C NMR (250 MHz, $CDCl_3$) δ 175.8, 165.1, 147.8, 136.5, 131.6, 129.8, 117.1, 113.7, 62.8, 49.1, 47.6, 46.8, 41.0, 40.5, 31.0, 26.9, 18.1, 10.1 ppm; ESI(+)-MS *m/z* found: 421.239, *m/z* calculated for $[C_{21}H_{33}N_4O_5 + H]^+$: 421.245, fragment ions were also observed: $[M + H–C_4H_{11}N]^+$ of *m/z* 348, $[M + H–C_7H_{17}NO]^+$ of *m/z* 290 and $[M + H–C_{14}H_{21}N_3O_4]^+$ of *m/z* 126 (5-member ring).

*Synthesis of N,N-dimethylaminopropyl-4-[N-(3′-aminopropyl)-2-azepanone]-3-nitrobenzoate (**13**)*

The 4-[N-(3′-aminopropyl)-2-azepanone]-3-nitrobenzoic acid (**6**) and 3-(dimethylamino)propan-1-ol were reacted according to the general procedure yielding an orange oily (2.01 g, 60%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 (t, 1H), 8.6 (d, 1H, $^{4}J_{HH} = 1.9$ Hz), 7.95 (dd, 1H, $^{4}J_{HH} = 1.9$, $^{3}J_{HH} = 9.2$ Hz), 7.1 (d, 1H, $^{3}J_{HH} = 9.2$ Hz), 3.44 (t, 2H, $J_{HH} = 5.8$) Hz 3.35–3.40 (m, 10H), 2.45 (m, 6H), 2.41 (t, 2H), 1.74 (t, 2H), 1.65–1.62 (m, 2H), 1.55–1.52 (m, 6H) ppm; ^{13}C NMR (250 MHz, DMSO-d_6) δ 175.7, 166.7, 147.8, 136.7, 131.1, 129.1, 118, 115, 59.2, 56, 49.2, 45.4, 44.1, 41.1, 40.6, 37.1, 29.9, 29, 27.4, 23,7 ppm; ESI(+)-MS *m/z* found: 421.278, *m/z* calculated for $[C_{21}H_{33}N_4O_5 + H]^+$: 421.245, fragment ions were also observed: $[M + H–C_2H_7N]^+$ of *m/z* 376, $[M + H–C_5H_{11}NO]^+$ of *m/z* 318 and $[M + H–C_7H_6\ N_2O_4]^+$ of *m/z* 154 (7-member ring).

*Synthesis of N,N-diethylaminopropyl-4-[N-(3′-aminopropyl)-2-azepanone]-3-nitrobenzoate (**14**)*

The 4-[N-(3′-aminopropyl)-2-azepanone]-3-nitrobenzoic acid (**7**) and 3-(diethylamino)propan-1-ol were reacted according to the general procedure yielding a yellow oily (2.47 g, 69%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 (t, 1H), 8.58 (d, 1H, $^{4}J_{HH} = 1.8$ Hz), 7.93 (dd, 1H, $^{4}J_{HH} = 1.8$, $^{3}J_{HH} = 9.1$ Hz), 7.1 (d, 1H, $^{3}J_{HH} = 9.1$ Hz), 3.79 (t, 2H, $J_{HH} = 5.6$ Hz), 3.47–3.29 (m, 10H), 2.99 (m, 4H), 1.46–1.89 (m, 10H), 1.05–1.17 (m, 6H) ppm; ^{13}C NMR (250 MHz, DMSO-d_6) δ 175.4, 166.4, 136.4, 130.8, 128.9, 117.7, 114.8, 100, 63.5, 58.6, 48.9, 46.8, 45.1, 36.9, 29.7, 28.7, 27.2, 24.5, 23.4, 9.4 ppm; ESI(+)-MS *m/z* found: 449.272, *m/z* calculated for $[C_{23}H_{36}N_4O_5 + H]^+$: 449.276, fragment ions were also observed: $[M + H–C_2H_7N]^+$ of *m/z* 376, $[M + H–C_5H_{11}NO]^+$ of *m/z* 318 and $[M + H–C_7H_6\ N_2O_4]^+$ of *m/z* 154 (7-member ring).

*Characterization of intermediate 4-N,N-dimethylamino-3-nitrobenzoic acid (**15**)* Yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, 1H); 8.04 (dd, 1H), 7.0 (d, 1H), 3.01 (s, 6H); DEPT ^{13}C NMR (250 MHz, $CDCl_3$) δ 169.7, 49.0, 136.7, 134.1, 130.1, 116.9, 116.5, 42.1 ppm; ESI(+)-MS *m/z* found: 211.068, *m/z* calculated for $[C_{14}H_{21}N_3O_4 + H]^+$: 211.071, fragment ions were also observed: $[M + H–H_2O]^+$ of *m/z* 193, $[M + H–H_2O–CH_3]^+$ of *m/z* 177, $[M + H–H_2O–C_2H_6]^+$ of *m/z* 163 and $[M + H–H_2O–C_2H_6–CO]^+$ of *m/z* 135.

*Synthesis of N,N-dimethylaminopropyl-4′-(N,N-dimethylamino)-3′-nitrobenzoate (**16**)*

The 4-chloro-3-nitrobenzoic acid (**1**) and 3-(dimethylamino)propan-1-ol were reacted according to the general procedure yielding an orange oily (1.69 g, 60%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, 1H), 8.0 (dd, 1H), 6.97 (d, 1H), 4,34 (t, 2H), 2.98 (s, 6H), 2.45 (t, 2H), 2.27 (s, 6H), 1.94 (qu, 2H) ppm; DEPT ^{13}C NMR (250 MHz, $CDCl_3$) δ 162.5, 145.8, 134.6, 131.1, 126.5, 115.8, 114.0, 60.7, 53.5, 42.6, 39.5, 24.3 ppm; ESI(+)-FTMS *m/z* found: 296.160, *m/z* calculated for $[C_{14}H_{21}N_3O_4 + H]^+$: 296.161, fragment ions were also observed: $[M + H–C_2H_6N]^+$ of *m/z* 251 and $[M + H–C_5H_{12}NO]^+$ of *m/z* 193.

*Synthesis of 3-diethylaminopropyl-4′-(N,N-dimethylamino)-3′-nitrobenzoate (**17**)*

The 4-chloro-3-nitrobenzoic acid (**1**) and 3-(diethylamino)propan-1-ol were reacted according to the general procedure yielding an orange oily (1.42 g, 55): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, 1H), 7.99 (dd, 1H), 6.98 (d, 1H), 4.35 (t, 2H), 2.99 (s, 5H), 2.6 (m, 6H), 1,93 (t, 2H); 1.05 (qua, 6H); DEPT ^{13}C NMR (250 MHz, $CDCl_3$)

δ 165.0, 148.4, 137.2, 133.7, 129.1, 118.5, 116.7, 63.5, 49.2, 46.8, 42.1, 26.3, 11.5 ppm; ESI(+)-FTMS *m/z* found: 324.191, *m/z* calculated for $[C_{16}H_{25}N_3O_4 + H]^+$: 324.192, fragment ions were also observed: $[M + H–C_4H_{10}N]^+$ of *m/z* 251 and $[M + H–C_7H_{16}NO]^+$ of *m/z* 193.

Results and discussion

Synthesis

Hydrolysis of amidines DBU and DBN were performed by reported methods (Kraft 1999; Shi and Shen 2002). We have also investigated DBU and DBN hydrolysis under microwave irradiation with a dramatic improvement of reaction times (Table 1).

Some works have reported in situ preparation of the APA and APP lactams in the presence of chloropentafluorbenzene for one-pot S_NAr reaction (Gierczyk et al. 2003). However, we did not have good results using this procedure for *N*-arylation of APA and APP with benzoic and benzenesulfonic acids **1** and **2**. Therefore, we have carried out the S_NAr reactions by a two-step procedure with improved yields (Scheme 1).

The solvent effect on the S_NAr reaction was studied for synthesis of intermediates **5** and **6** in acetonitrile and DMSO (Table 2).

Both the higher solvating strength and dielectric constant of DMSO (Jorgensen and Acevedo 2004) seems to favor reaction by stabilizing the ionic intermediate of an addition–elimination S_NAr reaction (Table 2). Therefore, we have carried out the synthesis of analogs **7** and **8** (Table 2, entries 5 and 6) using DMSO as solvent.

The synthesis of procaine-like PABA-related aminoesters (**11–14**) was performed according to Scheme 2 below.

DMF was used as a co-solvent for improvement of interfacial reaction and for a more efficient bulk heating of the reaction mixture. Esterification was also performed using $H_3PW_{12}O_{40}$ (HPW) as catalyst with similar yields of the esters. Yield (%) of product **12** was 72 and 75% using H_2SO_4 and $H_3PW_{12}O_{40}$ as catalysts, respectively. Thus, sulfuric acid can be replaced by a more eco-friendly HPW catalyst.

NMR and MS characterization

The ^{1}H NMR spectra of amino acids **5–8** and aminoesters **11–14** showed the methylenic protons signals bonded to heteroatoms in the aliphatic chain in the range of 3.13–4.43 ppm. The chemical shifts of aromatic protons were observed in the range of 7.50–8.53 ppm. The ^{1}H NMR coupling constants of aromatic protons $^3J_{HH}$ = 8.2–9.1 Hz and $^4J_{HH}$ = 1.9–2.1 Hz have been measured supporting the formation of addition–elimination S_NAr products.

The ^{13}C NMR spectra of compounds **5–8** and **11–14** have shown the signals corresponding to aromatic carbon atoms in the range of 123.2–152.5 ppm. The chemical shifts for carbon atom bonded to chlorine in the starting compounds **1** and **2** are usually observed at about 132.8–134.1 ppm. However, ^{13}C NMR spectra of **5–8** and **11–14** showed chemical shifts

Table 1 Microwave-assisted and classical hydrolysis results for DBN and DBU

Amidine	Microwave-assisted	Classical heating
DBN	80–89% and 15 min	85–94% and 12 h
DBU	70–80% and 15 min	75–82% and 12 h

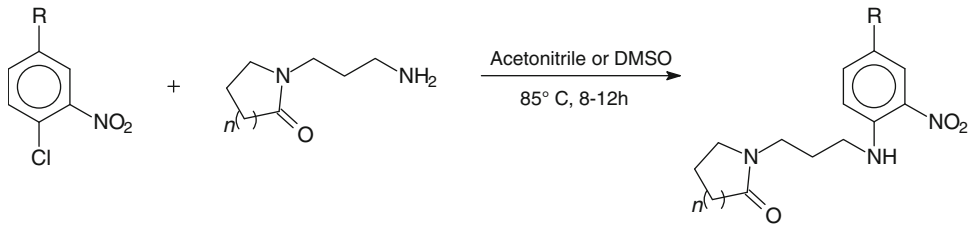
Out put power 70 W, reaction temperature 120°C for both methods

Table 2 Solvent effect in the S_NAr – formation of PABA derivatives **5–6**

Entry	Solvent	Compound	Time (h)	Yield[a] (%)
1	Acetonitrile	5	12	59
2	DMSO	5	8	89
3	Acetonitrile	6	12	60
4	DMSO	6	8	86
5	DMSO	7	8	82
6	DMSO	8	8	87

[a] Isolated product

Scheme 1 Synthesis of PABA-related *N*-(3-aminopropyl)lactamic amino acids

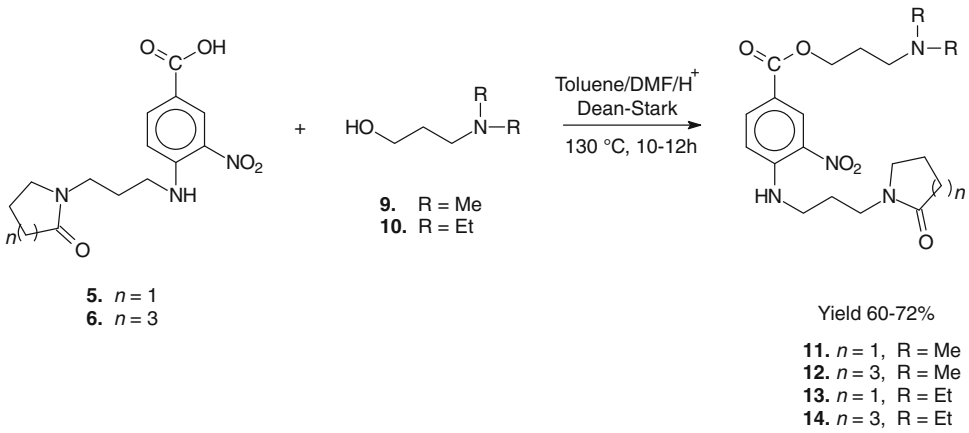


1. R = COOH
2. R = SO_3H

3. *n* = 1
4. *n* = 3

5. *n* = 1, R = COOH
6. *n* = 3, R = COOH
7. *n* = 1, R = SO_3H
8. *n* = 3, R = SO_3H

Scheme 2 Synthesis of procaine-like derivatives **11–14**



5. $n = 1$
6. $n = 3$

9. R = Me
10. R = Et

11. $n = 1$, R = Me
12. $n = 3$, R = Me
13. $n = 1$, R = Et
14. $n = 3$, R = Et

for this carbon nucleus in the range of 146.5–152.5 ppm indicating the substitution of chlorine atom for nitrogen atom of the amino terminal group of the amino-lactams **3** and **4**. The observation of typical lactamic carbonyl resonances (Terrier 1991; Bunnett and Zahler 1951) at 170.0–174.4 ppm has proved the presence of (aminoalkyl)lactamic moieties in the structures of **5–8** and **11–14**. For **5** and **6**, chemical shifts of carboxylic carbon have been observed at 163.8 and 168.7 ppm, respectively. Finally, ^{13}C NMR spectra of carboxylic esters **11–14** showed signals in the range of 164.8–166.8 ppm which were attributed to ester carbonyl groups.

Compounds **5–8** and **11–14** were also characterized by tandem mass spectrometry using electrospray ionization in the positive ion mode (ESI(+)-MS/MS). The most favored structurally diagnostic dissociation channel involves the neutral loss of the respective aniline R–Ph–NH_2 to form the major fragment ion corresponding to protonated form of *N*-allyl(five-member)lactamic ring of *m/z* 126 for **5**, **7**, **11** and **13** and seven-member ring of *m/z* 154 for **6**, **8**, **12** and **14**, respectively. Loss of water (*m/z* 290, 318, 326 and 354) followed by C_2H_2 (*m/z* 262, 290, 298 and 326) now involving most likely the lactamic ring is also an important dissociation channel for the gaseous protonated molecules of **5–8**. In the ESI–MS/MS of procaine-like derivatives **11** and **12,** the fragment ions of *m/z* 348 and 290 are formed by loss of $C_5H_{13}N$ and $C_5H_{11}NO$ respectively, whereas for **13** and **14** the fragment ions of *m/z* 376 and 318 are formed by respective loss of C_3H_9N and $C_7H_{15}NO$.

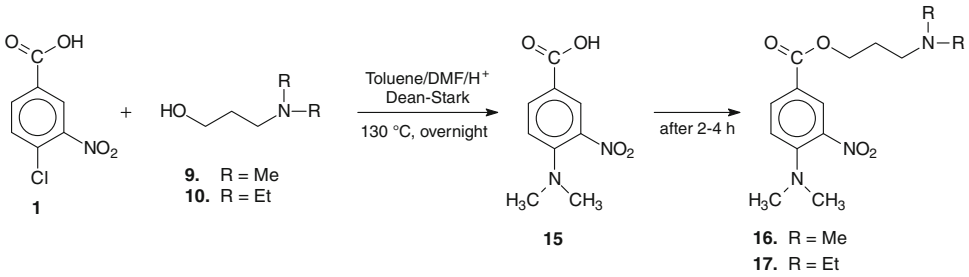
Reaction selectivity

We have also investigated the direct esterification of **9** and **10** with the benzoic acid **1** and we have been observed that amination with DMF (Scheme 3) has also occurred leading to the formation of ester-S_NAr adducts **16–17** and the possible intermediate **15.**

Full-scan FTMS spectra of the reaction mixture have shown $[M + H]^+$ ions of *m/z* 296 for compound **16** and *m/z* 324 for compound **17**. High-resolution MS data have shown that the elemental composition of these ions is $C_{14}H_{22}O_4N_3$ and $C_{16}H_{26}O_4N_3$, respectively. ESI(+)-FTMS/MS spectra were also acquired showing the most abundant ions of *m/z* 251 and 193 for **16** and **17** corresponding to the neutral loss of the $(CH_3)_2NH$ (45 g mol^{-1}) or $(C_2H_5)_2NH$ (73 g mol^{-1}) leading to the fragment ion of *m/z* 251 and neutral loss of the aminoalcohols $(CH_3)_2N$-$(CH_2)_3$-OH (103 g mol^{-1}) and $(C_2H_5)_2N$-$(CH_2)_3$-OH (131 g mol^{-1}) leading to the fragment ion of *m/z* 193.

Reactions illustrated in Scheme 3 above, have been monitored by GC–MS. The total ion chromatograms show sharp peaks for **16** and **17** at retention time of 21.0 and 22.0 min, respectively. Moreover, both chromatograms show the broad peaks corresponding to the same

Scheme 3 Formation ester – S_NAr adducts **16** and **17**



1

9. R = Me
10. R = Et

15

16. R = Me
17. R = Et

intermediate product (*m*/*z* 210), the 4-(*N*,*N*-dimethylamino)-3-nitrobenzoic acid **15.** This is in agreement with amination of benzoic acid **1** with DMF used as co-solvent. Similar reaction has been reported in a recent work (Tsai et al. 2008).

The ^{1}H NMR spectra of compounds **15–17** showed signals of aromatic protons (C2, C6 and C5) in the range of 6.9–8.4 ppm. In the ^{1}H NMR spectra of **16** and **17** the chemical shifts of protons of methylene groups bonded to oxygen or nitrogen atoms of aliphatic chain are observed at 4.3 and 2.3 ppm, respectively. The ^{1}H NMR spectra of **15–17** showed the signals of methylic protons of dimethylamino group (at C7 position) observed at 3.0 ppm. In the ^{1}H spectrum of **17** the chemical shift observed at 1.0 ppm was assigned to methyl signals of terminal *N*,*N*-diethylamino group of esterified aminoalcohol (C11). The ^{1}H-^{13}C COSY spectra of **15–17** using HMBC showed the correlation of proton signals at 3.0 ppm with C4 carbon signal at around 150 ppm indicating the presence of *N*,*N*-dimethylamino group in the C4 position. Moreover, in the ^{1}H–^{1}H COSY spectra of **15–17** non-coupling was observed for the proton signal at 3.0 ppm confirming the presence of methylic protons. The ^{13}C NMR spectrum of **15–17** showed the chemical shift of aromatic carbons in the range of 114–148 ppm. DEPT ^{13}C NMR spectrum of **16** has showed chemical shifts of methylenic carbon atoms C8, C10 and C9 at 60.7, 53.5 and 24.3 ppm, respectively, at the same time for **17** the methylenic carbon atoms C8, C10, C10′ and C9 are observed at 63.5, 49.2, 46.8 and 26.3 ppm, respectively. In the ^{13}C NMR spectrum of **16** the methylic carbon atoms C7 and C11 are observed at 42.6 and 39.5 ppm, respectively, while that for **17** are observed at 42.1 and 11.5 ppm, respectively. The ^{13}C NMR spectra of **15** showed the signal at 166 ppm indicating the presence of carboxylic acid group. Spectra of **16** and **17** have showed resonance of carboxylic ester groups at 162 and 165 ppm respectively.

Conclusions

PABA derivatives and sulfonic analogs containing lactamic moieties are synthesized in good yields via S_NAr reactions. Carboxylic esters of tertiary aminoalcohols are also prepared. Other interesting adducts are obtained through amination of DMF opening a combinatorial route for additional PABA derivatives by *N*-arylation of amides. Important spectroscopic data is available for all compounds useful for QSAR studies.

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