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Synthesis of 3-(4-Isopropoxyphenyl)-3-(2-methoxyphenyl)propionamides

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Abstract—Hydrolysis of 3-(4-isopropoxyphenyl)-3-(2-methoxyphenyl)propionitrile results in 3-(4-isopropoxyphenyl)-3-(2-methoxyphenyl)propionic acid, which after reaction with thionyl chloride is turned into acyl-chloride. By acylation of a number of amines by 3-(4-isopropoxyphenyl)-3-(2-methoxyphenyl)propionyl chloride, synthesized the corresponding propionamides. The results of biological tests showed that the obtained compounds possess week antibacterial activity .

Keywords: acylation, propionamides, hydrolysis, 3-(4-isopropoxyphenyl)-3-(2-methoxyphenyl)propionic acid

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Amides have received great attention both due to their synthetic versatility and a wide range of biological activity [1–5]. Extending our earlier studies, we synthesized 3-(4-isopropoxyphenyl)-3-(2-methoxyphenyl)propionic acid (**II**) via hydrolysis of the previously obtained 3-(4-isopropoxyphenyl)-3-(2-methoxyphenyl)propionitrile (**I**) [6]. Reaction of acid (**II**) with thionyl chloride gave acyl chloride (**A**), which was used for acylation of various amines to yield the corresponding propionamides **III**–**XIV** (Scheme 1).

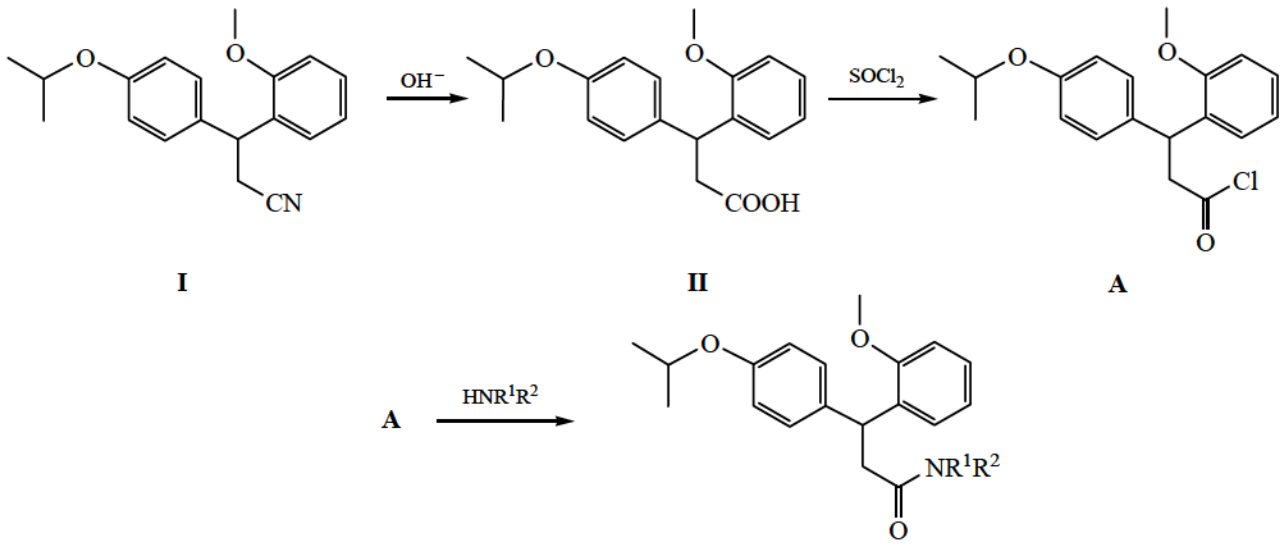
Antibacterial activity of compounds **III**–**XIV** towards Gram-positive staphylococcus (*Staphylococcus aureus* 209 p, 1) and Gram-negative rods (*Sh. dysenteriae Flexneri* 6858 and *E. Coli* 0-55) was studied as described elsewhere [7] at the bacteria load of 20 million of microbes per 1 mL of the nutrient medium. The compounds were studied in the 1 : 20 dilution with DMSO. All compounds showed low antibacterial activity with respect to the Gram-negative strains, suppressing the growth of microorganisms over the 10–14 mm (diameter) area. Variation of the substituent did not influence the activity. Furazolidon (with the growth suppression area of d = 24–25 mm) was used as reference [8].

3-(4-Isopropoxyphenyl)-3-(2-methoxyphenyl)-propionic acid (II). 33.6 g (0.6 mol) of KOH was dissolved at heating in 120 mL of ethylene glycol; the obtained solution was added to 44.2 g (0.15 mol) of nitrile **I**; the mixture was refluxed during 6 h and cooled; 120 mL of water was added; the mixture was extracted with diethyl ether; the aqueous layer acidified with 60 mL of conc. HCl to acidic reaction, extracted with benzene (3 × 150 mL), washed with water and, dried. After removal of benzene, the residue was distilled under vacuum. Yield 41 g (88%), bp 220–223°C (1 mmHg). IR spectrum, ν, cm^{-1}: 3400–3200 (OH), 1710 (C=O), 1610, 1590 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.29 d (6H, $2CH_3$, J 6.0 Hz); 2.84 d.d (1H, CH^A, J 15.7, 8.5 Hz), 2.85 d.d (1H, CH^B, J 15.7, 7.4 Hz); 3.82 s (3H, OCH_3); 4.48 sept. (1H, OCH, J 6.0 Hz); 4.76 d.d (1H, CH, J 8.5, 7.4 Hz); 6.68-6.73 m (2H), 6.81–6.87 m (2H) and 7.07–7.15 m (4H, $2C_6H_4$); 11.52 br.s (1H, OH). Found, %: C 73.00; H 7.67. $C_{19}H_{22}O_4$. Calculated, %: C 72.59; H 7.05.

3-(4-Isopropoxyphenyl)-3-(2-methoxyphenyl)-propionyl chloride (A). A mixture of 31.4 g (0.1 mol) of acid **II**, 13.1 g (0.11 mol) of $SOCl_2$, and 50 mL of benzene was refluxed during 2 h; benzene was removed, the viscous residue was used without purification for further transformations.

3-(4-Isopropoxyphenyl)-3-(2-methoxyphenyl)-*N*-propionamides (III–XIV). Equimolar amount of

Scheme 1.



R^1 = H, R^2 = 4-$MeOC_6H_4$ (**III**), phenethyl (**IV**), Bn (**V**), 4-ClC_6H_4 (**VI**), 4-*i*-PrOBn (**VII**), C_6H_{11} (**VIII**), 2-$MeOC_6H_4$ (**IX**), thiazol-2-yl (**X**), 3-MeC_6H_4 (**XI**); NR^1R^2 = piperidin-1-yl (**XII**), *N,N*-dipropyl (**XIII**), morpholin (**XIV**).

compound **A** was added dropwise under stirring to a solution of 0.01 mol of the amine and 0.01 mol of triethylamine in dry benzene; the mixture was refluxed during 3 h, cooled, acidified with HCl solution to slightly acidic reaction, extracted with benzene, washed with water, and dried; benzene was removed. Compounds **III–XI** were crystalline compounds (recrystallized from ethanol), compounds **XII–XIV** were viscous liquids (distilled under vacuum).

3-(4-Isopropoxyphenyl)-3-(2-methoxyphenyl-*N*-(4-methoxyphenyl)propionamide (III). Yield 63%, mp 153–155°C. IR spectrum, ν, cm^{-1}: 3276 (NH); 1644 (C=O). ^1H NMR spectrum, δ, ppm: 1.27 d (6H, $\underline{CH_3}CH\underline{CH_3}$, *J* 6.0 Hz); 2.90 d (2H, CH_2, *J* 7.8 Hz); 3.72 s (3H, OCH_3); 3.79 s (3H, OCH_3); 4.47 sept. (1H, OCH, *J* 6.0 Hz); 4.87 t (1H, CH, *J* 7.8 Hz); 6.65–6.75 m (4H); 6.81–6.89 m (2H); 7.07–7.15 m (3H); 7.17–7.22 m (1H) and 7.33–7.40 m (2H, $2C_6H_4$); 9.44 s (1H, NH). Found, %: C 74.90; H 7.58; N 3.78. $C_{26}H_{29}NO_4$. Calculated, %: C 74.44; H 6.97; N 3.34.

3-(4-Isopropoxyphenyl)-3-(2-methoxyphenyl)-*N*-phenethylpropionamide (IV). Yield 60 %, mp 113–115°C. IR spectrum, ν, cm^{-1}: 3293 (NH); 1636 (C=O). ^1H NMR spectrum, δ, ppm: 1.28 d (6H, $\underline{CH_3}CH\underline{CH_3}$, *J*6.0 Hz); 2.58 t (2H, $\underline{CH_2}$Ph, *J* 7.2 Hz); 2.69 d (2H, CH_2, *J* 7.9 Hz); 3.12–3.29 m (2H, NCH_2); 3.79 s (3H, OCH_3); 4.47 sept. (1H, OCH, *J* 6.0 Hz); 4.79 t (1H, CH, *J*7.9 Hz); 6.65–6.70 m (2H); 6.80–6.87 m (2H) and 7.02–7.23 m (9H, $3C_6H_4$); 7.45 br.t (1H, NH, *J* 5.5 Hz). Found, %: C 88.04; H 6.98; N 2.97. $C_{27}H_{31}NO_3$. Calculated, %: C 77.67; H 7.48; N 3.35.

***N*-Benzyl-3-(4-isopropoxyphenyl)-3-(2-methoxyphenyl)propionamide (V).** Yield 68%, mp 163–165°C. IR spectrum, ν, cm^{-1}: 3246 (NH); 1638 (C=O). ^1H NMR spectrum, δ, ppm: 1.30 d (6H, $\underline{CH_3}CH\underline{CH_3}$, *J* 6.0 Hz); 2.80 d (2H, CH_2, *J* 8.0 Hz); 3.80 s (3H, OCH_3); 4.16 d.d (1H, NCH_2, *J* 15.2, 5.7 Hz); 4.25 d.d (1H, NCH_2, *J*15.2, 6.0 Hz); 4.48 sept. (1H, OCH, *J* 6.0 Hz); 4.85 t (1H, CH, *J*8.0 Hz); 6.66–6.72 m (2H); 6.81–6.88 m (2H); 6.90–6.95 m (2H) and 7.08–7.23 m (7H, H-Ar); 7.96 d.d (1H, NH, *J*6.0, 5.7 Hz). Found, %: C 77.87; H 7.67; N 3.96. $C_{26}H_{29}NO_3$. Calculated, %: C 77.39; H 7.24; N 3.47.

***N*-(4-Chlorophenyl)-3-(4-isopropoxyphenyl)-3-(2-methoxyphenyl)propionamide (VI).** Yield 64 %, mp 158–160°C. IR spectrum, ν, cm^{-1}: 3277 (NH); 1656 (C=O). ^1H NMR spectrum, δ, ppm: 1.27 d (6H, $\underline{CH_3}CH\underline{CH_3}$, *J* 6.0 Hz); 2.92 d.d (1H, CH_2, *J* 15.0, 7.5 Hz); 2.94 d.d (1H, CH_2, *J*15.0, 8.2 Hz); 3.79 s (3H, OCH_3); 4.46 sept. (1H, OCH, *J* 6.0 Hz); 4.88 d.d (1H, CH, *J* 8.2, 7.5 Hz); 6.65–6.71 m (2H); 6.81–6.88 m (2H); 7.07–7.20 m (6H) and 7.48–7.54 m (2H, $3C_6H_4$); 9.71 s (1H, NH). Found, %: C 71.27; H 6.95; N 3.89. $C_{25}H_{26}ClNO_3$. Calculated, %: C 70.83; H 6.18; N 3.30.

***N*-(4-Isopropoxybenzyl)-3-(4-isopropoxyphenyl)-3-(2-methoxyphenyl)propionamide (VII).** Yield 63%, mp 123–124°C. IR spectrum, ν, cm^{-1}: 3308 (NH); 1648 (C=O). ^1H NMR spectrum, δ, ppm: 1.29 d (6H, $\underline{CH_3}CH\underline{CH_3}$, *J* 6.0 Hz); 2.75 d.d (1H, CH_2, *J* 14.5, 7.6 Hz); 2.78 d.d (1H, CH_2, *J* 14.5, 8.5 Hz); 3.80 s (3H, OCH_3); 4.06 d.d (1H, NCH_2, *J* 15.0, 5.7 Hz); 4.17 d.d (1H, NCH_2, *J* 15.0, 6.0 Hz); 4.48 sept. (1H, OCH, *J* 6.0 Hz); 4.49 sept. (1H, OCH, *J* 6.0 Hz); 4.83 d.d (1H, CH, *J* 8.5, 7.6 Hz); 6.62–6.70 m (4H); 6.78–6.87 m (4H) and 7.07–7.22 m (4H, $3C_6H_4$); 7.84 br.d.d (1H, NH, *J* 6.0, 5.5 Hz). Found, %: C 76.00; H 8.15; N 3.68. $C_{29}H_{35}NO_4$. Calculated, %: C 75.46; H 7.64; N 3.03.

***N*-Cyclohexyl-3-(4-isopropoxyphenyl)-3-(2-methoxyphenyl)propionamide (VIII).** Yield 58 %, mp 146–148°C. IR spectrum, ν, cm^{-1}: 3281 (NH); 1629 (C=O). ^1H NMR spectrum, δ, ppm: 0.93–1.37 m (5H) and 1.48–1.69 m (5H, C_6H_{11});1.28 d (6H, $\underline{CH_3}CH\underline{CH_3}$, *J* 6.0 Hz); 2.66 d.d (2H, CH_2, *J* 8.0 Hz); 3.38–3.51 m (1H, NCH); 3.79 s (3H, OCH_3); 4.46 sept. (1H, OCH, *J* 6.0 Hz); 4.76 t (1H, CH, *J* 8.0 Hz); 6.64–6.69 m (2H); 6.79–6.87 m (2H) and 7.03-7.19 m (5H, $2C_6H_4$, and NH). Found, %: C 76.47; H 8.92; N 3.94. $C_{25}H_{33}NO_3$. Calculated, %: C 75.91; H 8.41; N 3.54.

3-(4-Isopropoxyphenyl)-3-*N*-bis(2-methoxyphenyl)-propionamide (IX). Yield 62%, mp 133–135°C. IR spectrum, ν, cm^{-1}: 3265 (NH); 1664 (C=O). ^1H NMR spectrum, δ, ppm: 1.28 d (6H, $\underline{CH_3}CH\underline{CH_3}$, *J* 6.0 Hz); 2.97–3.11 m (2H, CH_2); 3.82 s (6H, $2CH_3O$); 4.47 sept. (1H, OCH, *J* 6.0 Hz); 4.86 t (1H, CH, *J* 7.9 Hz); 6.67–6.73 m (2H); 6.77–6.96 m (5H); 7.08–7.23 m (4H) and 8.02 d (1H, $3C_6H_4$, *J* 7.8 Hz); 8.36 s (1H, NH). Found, %: C 74.90; H 6.66; N 3.12. $C_{26}H_{29}NO_4$. Calculated, %: C 74.44; H 6.97; N 3.34.

[3-(4-Isopropoxyphenyl)-3-(2-methoxyphenyl)-*N*-thiazol-2-yl]propionamide (X). Yield 65 %, mp 152–154°C. IR spectrum, ν, cm^{-1}: 3269 (NH); 1670 (C=O). ^1H NMR spectrum, δ, ppm: 1.27 d (6H, $\underline{CH_3}CH\underline{CH_3}$, *J* 6.0 Hz); 3.05 d.d (1H, CH^A, *J* 15.1, 7.3 Hz), 3.09 d.d (1H, CH^B, *J* 15.1, 8.3 Hz); 3.80 s (3H, OCH_3); 4.46 sept. (1H, OCH, *J* 6.0 Hz); 4.92 d.d (1H, CH, *J* 8.3, 7.3 Hz); 6.66–6.72 m (2H) and 6.81–6.88 m (2H, C_6H_4); 6.89 d (1H, CHS, *J* 3.5); 7.08–7.19 m (4H, C_6H_4); 7.31 d (1H, =CHN, *J* 3.5 Hz); 11.93 s (1H, NH). Found, %: C 66.25; H 6.73; N 7.66. $C_{22}H_{24}N_2O_3S$. Calculated, %: C 66.64; H 6.10; N 7.06.

[3-(4-Isopropoxyphenyl)-3-(2-methoxyphenyl)-*N*-tolyl]propionamide (XI). Yield 60 %, mp 142–143°C. IR spectrum, ν, cm^{-1}: 3272 (NH); 1645 (C=O). ^1H NMR spectrum, δ, ppm: 1.27 d (6H, $\underline{CH_3}CH\underline{CH_3}$, *J* 6.0 Hz); 2.29 s (3H, $CH_3C_6H_4$); 2.92 d (2H, CH_2C=O, *J* 7.9 Hz); 3.80 s (3H, OCH_3); 4.46 sept. (1H, OCH, *J* 6.0 Hz); 4.88 t (1H, CH, *J* 7.9 Hz); 6.66–6.75 m (3H) and 6.81–6.88 m (2H); 7.01–7.14 m (4H); 7.17–7.26 m (2H) and 7.33 t (1H, $3C_6H_4$, *J* 2.0 Hz); 9.45 s (1H, NH). Found, %: C 77.23; H 7.52; N 3.26. $C_{26}H_{29}NO_3$. Calculated, %: C 77.39; H 7.24; N 3.47.

[3-(4-Isopropoxyphenyl)-3-(2-methoxyphenyl)-1-piperidin-1-yl]propan-1-one (XII). Yield 64 %, bp 235-238°C (1 mmHg). IR spectrum, ν, cm^{-1}: 1654 (C=O). ^1H NMR spectrum, δ, ppm: 1.28 d (6H, $\underline{CH_3}CH\underline{CH_3}$, *J* 6.0 Hz); 1.34–1.46 m (4H) and 1.54–1.63 m (2H, *N*-3,3',4-CH_2–$C_5H_{10}N$); 2.82 d.d (1H, CH^A, *J* 6.4 Hz), 2.93 d.d (1H, CH^B, *J* 15.1, 8.5 Hz); 3.34–3.42 m (4H, CH_2NCH_2); 3.79 s (3H, OCH_3); 4.47 sept. (1H, OCH, *J* 6.0 Hz); 4.77 d.d (1H, CH, *J* 8.5, 6.4 Hz); 6.64–6.70 m (2H), 6.80–6.86 m (2H) and 7.03–7.14 m (4H, $2C_6H_4$). Found, %: C 75.21; H 8.78; N 4.00. $C_{24}H_{31}NO_3$. Calculated, %: C 75.56; H 8.19; N 3.67.

[3-(4-Isopropoxyphenyl)-3-(2-methoxyphenyl)-*N*,*N*-dipropyl]propionamide (XIII). Yield 62 %, bp 223–225°C (2 mmHg). IR spectrum, ν, cm^{-1}: 1640 (C=O). ^1H NMR spectrum, δ, ppm: 0.78 t (3H, *J* 7.4 Hz) and 0.91 t (3H, $\underline{CH_3}CH_2NCH_2\underline{CH_3}$, *J* 7.4 Hz); 1.29 d (6H, $\underline{CH_3}CH\underline{CH_3}$, *J* 6.0 Hz); 1.32–1.60 m (4H, $2NCH_2\underline{CH_2}$); 2.85 d.d (1H, CH^A *J* 15.0, 6.5 Hz), 2.91 d.d (1H, CH^B, *J* 15.0, 8.6 Hz); 3.06–3.24 m (4H, CH_2NCH_2); 3.79 s (3H, OCH_3); 4.48 sept. (1H, OCH, *J* 6.0 Hz); 4.83 d.d (1H, CH, *J* 8.6, 6.5 Hz); 6.65–6.71 m (2H); 6.81–6.87 m (2H) and 7.03–7.15 m (4H, $2C_6H_4$). Found, %: C 76.08; H 8.66; N 3.92. $C_{25}H_{35}NO_3$. Calculated, %: C 75.53; H 8.87; N 3.52.

3-(4-Isopropoxyphenyl)-3-(2-methoxyphenyl)-1-morpholin-4-yl-propan-1-one (XIV). Yield 65 %, bp 237–240°C (1 mmHg). IR spectrum, ν, cm^{-1}: 1644 (C=O). ^1H NMR spectrum, δ, ppm: 1.28 d (6H, $\underline{CH_3}CH\underline{CH_3}$, *J* 6.0 Hz); 2.86 d.d (1H, CH^A, *J* 15.0, 6.6 Hz), 2.96 d.d (1H, CH^B, *J* 15.0, 8.6 Hz); 3.32–3.49 m (8H, C_4H_8NO); 3.79 s (3H, OCH_3); 4.47 sept. (1H, OCH, *J* 6.0 Hz); 4.77 d.d (1H, CH, *J* 8.6, 6.6 Hz); 6.65–6.71 m (2H); 6.81–6.87 m (2H) and 7.04–7.15 m (4H, $2C_6H_4$). Found, %: C 72.43; H 8.00; N 3.96. $C_{23}H_{29}NO_4$. Calculated, %: C 72.04; H 7.62; N 3.65.

IR spectra were recorded using a NICOLET AVATAR 330 FT-IR spectrophotometer. ^1H NMR spectra were registered with a Mercury VX-300 (300.08 MHz) spectrometer in DMSO-d_6–CCl_4 solution, with TMS as internal reference.

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