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Short communication

A convenient synthesis of new NSAID esters containing amino acid, urea and amide moieties

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A convenient synthetic method for the preparation of novel NSAID twin esters **6a–i** containing amino acid residue, urea and amide moieties has been developed. The synthetic pathway applied for the preparation of target compounds and key intermediates 1-benzotriazolecarboxylic acid chloride (**1**), NSAID benzotriazolides **2a–c** and *N*-(1-benzotriazolecarbonyl)-amino acids **3a–d** involved benzotriazole as a synthetic auxiliary. The final preparation step of esters **6a–i** included the solvent-free reaction of compounds **2a–c** with amino acid derivatives **5a–g**, bearing two hydroxyl groups, one at each terminal, beside urea and amide functionalities.

Keywords: NSAID, ester, amino acid, benzotriazole, urea, amide

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Nonsteroidal anti-inflammatory drugs (NSAIDs) belong to a class of drugs used worldwide for the treatment of pain, fever and inflammatory diseases. Relatively new findings indicating that long-term use of NSAIDs is associated with lower risk of some types of cancer (1, 2) initiated a growing interest in this class of drugs. Numerous NSAID derivatives have been prepared in order to improve analgesic/anti-inflammatory activity, minimize side effects, prolong plasma half-life, increase COX1/COX2 selectivity, cytostatic activity and change water solubility or lipophilicity (3–5). However, our research is directed towards NSAID prodrugs and NSAID derivatives with dual cyclooxygenase/5-lipoxygenase inhibition or potential antioxidative and cytostatic activity. In this light, we have prepared and pharmacologically evaluated numerous amides (6, 7), phosphoramidate derivatives (8), semicarbazides and hydroxycarbamoylcarbazides (9), hydroxamic acid NSAID derivatives (10, 11) and polymer-NSAID conjugates (12, 13). Here, we describe syntheses of novel NSAID esters, derivatives of ibuprofen, ketoprofen and diclofenac, containing amino acid residue, urea and amide moieties, as potential NSAID prodrugs.

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EXPERIMENTAL

Materials and methods

IR spectra were recorded on a FTIR Perkin Elmer Paragon 500 spectrometer (Perkin-Elmer, UK). ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer (Varian, USA), operating at 300 and 75.5 MHz for ^{1}H and ^{13}C nuclei, respectively. Samples were measured in DMSO-d_6 solutions at 20 °C in 5-mm NMR tubes. Chemical shifts (δ) in ppm were referred to TMS. Elemental analyses were performed on a CHNS LECO analyzer (LECO Corporation, USA). Solvent systems cyclohexane/ethyl acetate (1:1), cyclohexane/ethyl acetate/methanol (3:1:0.5), ethyl acetate/cyclohexane/methanol (3:1:0.1) and dichloromethane/methanol (9.5:0.5 and 9:1) and precoated Merck silica gel 60 F_{254} plates (Merck, Germany) were used for thin-layer chromatography (TLC). Spots were visualized by short-wave UV light and iodine vapour. Column chromatography was performed on silica gel (0.063–0.200 mm) (Kemika, Croatia), with dichloromethane/methanol (9.5:0.5), cyclohexane/ethyl acetate/methanol (3:1:0.5) and cyclohexane/ethyl acetate (1:1) as eluents. Benzotriazole (BtH), triphosgene, 2-aminoethanol (ethanolamine), 3-aminopropanol, 5-aminopenthanol and triethylamine (TEA) were purchased from Aldrich (USA). Amino acids were purchased from Kemika, while ibuprofen, ketoprofen and diclofenac were from Pliva and Belupo (Croatia).

Benzotriazole carboxylic acid chloride (**1**) (14), ibuprofen-benzotriazolide (**2a**), ketoprofen-benzotriazolide (**2b**), diclofenac-benzotriazolide (**2c**) (12), *N*-(1-benzotriazolecarbonyl)-L-alanine (**3a**), *N*-(1-benzotriazolecarbonyl)-L-leucine (**3b**), *N*-(1-benzotriazolecarbonyl)-D-phenylglycine (**3c**), *N*-(1-benzotriazolecarbonyl)-L-phenylalanine (**3d**) (15) and L-alanine/3-aminopropanol (**5a**), L-leucine/3-aminopropanol (**5b**), L-leucine/5-aminopenthanol (**5c**), D-phenylglycine/2-aminoethanol (**5d**), D-phenylglycine/5-aminopenthanol (**5e**), L-phenylalanine/2-aminoethanol (**5f**), L-phenylalanine/3-aminopropanol (**5g**) ureidoamides (9) were prepared according to our procedures published earlier.

*Syntheses of compounds **6a–i**. General procedure*

A solvent free mixture prepared from NSAID benzotriazolide **2a–c** (1 mmol), the corresponding ureidoamide **5a–g** (0.5 mmol) and TEA (0.202 g, 2 mmol) was heated until melting occurred (100–125 °C) and kept at that temperature for 15 minutes. The reaction mixture prepared was cooled, dissolved in 30 mL ethyl acetate and extracted three times with sodium hydroxide solution (3 × 30 mL of water and 10 drops of 5 % NaOH), washed with water, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. Crude products were purified by column chromatography. Analytical and spectral data of synthesized esters **6a–i** are given in Tables I and II.

*2-(4-Isobutyl-phenyl)-propionic acid 5-[2-(3-/5-[2-(4-isobutyl-phenyl)-propionyloxy]-pentyl/-ureido-2-phenyl-acetylamino]-pentyl ester (**6a**)*

A mixture prepared from 0.307 g ibuprofen derivative (**2a**), 0.181 g D-phenylglycine 5-aminopenthanol ureidoamide (**5e**) and TEA was heated at 100 °C. Dichloromethane/methanol 9.5:0.5 was used as eluent for column chromatography.

*2-(4-Isobutyl-phenyl)-propionic acid 3-[2-(3-/3-[2-(4-isobutyl-phenyl)-propionyloxy]--propyl/-ureido-3-phenyl-propionylamino]-propyl ester (**6b**)*

A mixture prepared from 0.307 g ibuprofen derivative (**2a**), 0.162 g L-phenylalanine 3-aminopropanol ureidoamide (**5g**) and TEA was heated at 100 °C. Dichloromethane/methanol 9.5:0.5 was used for column chromatography.

*2-(3-Benzoyl-phenyl)-propionic acid 3-[2-(3-/3-[2-(3-benzoyl-phenyl)--propionyloxy]-propyl/-ureido)-propionylamino]-propyl ester (**6c**)*

Ketoprofen derivative (**2b**, 0.355 g) in a mixture with L-alanine 3-aminopropanol ureidoamide (**5a**, 0.124 g) and TEA was heated at 125 °C. Dichloromethane/methanol 9.5:0.5 was used for column chromatography.

*2-(3-Benzoyl-phenyl)-propionic acid 3-[2-(3-/3-[2-(3-benzoyl-phenyl)-propionyloxy]--propyl/-ureido)-4-methyl-pentanoylamino]-propyl ester (**6d**)*

Ketoprofen derivative (**2b**, 0.355 g) was mixed with L-leucine 3-aminopropanol ureidoamide (**5b**, 0.145 g) and TEA. The mixture was heated at 100 °C. Cyclohexane/ethyl acetate 1:1 was used as eluent for column chromatography.

*2-(3-Benzoyl-phenyl)-propionic acid 5-[2-(3-/5-[2-(3-benzoyl-phenyl)-propionyloxy]--pentyl/-ureido)-4-methyl-pentanoylamino]-pentyl ester (**6e**)*

The titled compound was prepared from a mixture of 0.355 g ketoprofen derivative (**2b**), 0.173 g L-leucine 5-aminopenthanol ureidoamide (**5c**) and TEA heated at 100 °C. Dichloromethane/methanol 9.5:0.5 was used for purification of the crude product by column chromatography.

*2-(3-Benzoyl-phenyl)-propionic acid 2-[2-(3-/2-[2-(3-benzoyl-phenyl)-propionyloxy]--ethyl/-ureido)-2-phenyl-acetylamino]-ethyl ester (**6f**)*

To synthesize the title compound, a mixture of 0.355 g ketoprofen derivative (**2b**), 0.141 g D-phenylglycine 2-aminoethanol ureidoamide (**5d**) and TEA was heated at 115 °C. Ethyl acetate/cyclohexane/methanol 3:1:0.1 was used as eluent for purification of the crude product by column chromatography.

*2-(3-Benzoyl-phenyl)-propionic acid 2-[2-(3-/2-[2-(3-benzoyl-phenyl)-propionyloxy]--ethyl/-ureido)-3-phenyl-propionylamino]-ethyl ester (**6g**)*

A mixture prepared from 0.355 g ketoprofen derivative (**2b**), 0.148 g L-phenylalanine 2-aminoethanol ureidoamide (**5f**) and TEA was heated at 100 °C. Ethyl acetate/cyclohexane/methanol 3:1:0.1 was used for column chromatography purification.

*Table I. Analytical and spectral data of compounds **6a–i***

Compd.	Yield (%)	IR (film): ν_{max} (cm^{-1})	Molecular formula (M_r)	Analysis (calcd./found) (%)		
				C	H	N
6a	80	3302, 2915, 1732, 1650, 1570, 1460, 1378, 1365, 1265, 1173, 735	$C_{45}H_{63}N_3O_6$ (742.00)	72.84/72.92	8.56/8.27	5.66/5.95
6b	74	3300, 2916, 1732, 1644, 1568, 1464, 1378, 1366, 1262, 1168, 748	$C_{42}H_{57}N_3O_6$ (699.92)	72.07/72.56	8.21/8.05	6.00/5.55
6c	82	3302, 3065, 2927, 2869, 1731, 1659, 1635, 1569, 1556, 1449, 1380, 1318, 1284, 1250, 1206, 1173, 1079, 960, 719, 644	$C_{42}H_{45}N_3O_8$ (719.82)	70.08/69.77	6.30/5.94	5.84/5.95
6d	90	3300, 3060, 2950, 1736, 1650, 1558, 1448, 1378, 1284, 1176, 1076, 954, 704, 642	$C_{46}H_{55}N_3O_8$ (777.94)	71.02/70.79	7.13/7.00	5.40/5.75
6e	73	3291, 3064, 2932, 2869, 1732, 1659, 1633, 1566, 1556, 1448, 1378, 1318, 1283, 1206, 1176, 1077, 954, 721, 706, 643	$C_{49}H_{59}N_3O_8$ (818.01)	71.95/72.16	7.27/7.54	5.14/5.44
6f	65	3296, 3064, 2980, 1735, 1633, 1564, 1449, 1374, 1284, 1172, 1077, 698, 643	$C_{45}H_{43}N_3O_8$ (753.84)	71.70/72.01	5.75/5.34	5.57/5.50
6g	79	3302, 3063, 2979, 2938, 1732, 1663, 1646, 1569, 1554, 1451, 1380, 1284, 1205, 1177, 1078, 956, 823, 722, 644	$C_{46}H_{45}N_3O_8$ (767.86)	71.95/72.31	5.91/6.04	5.47/5.78
6h	68	3300, 3050, 2940, 1736, 1654, 1560, 1448, 1282, 1166, 1076, 954, 700, 642	$C_{48}H_{49}N_3O_8$ (795.92)	72.43/71.99	6.21/6.42	5.28/5.66
6i	77	3300, 3090, 2850, 1718, 1650, 1566, 1508, 1452, 1238, 1142, 1092, 775, 744, 700	$C_{44}H_{43}Cl_4N_5O_6$ (879.65)	60.08/60.41	4.93/4.52	7.96/7.61

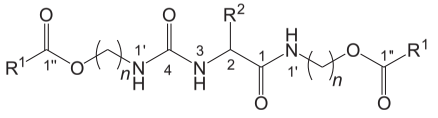
*2-(3-Benzoyl-phenyl)-propionic acid 3-[2-(3-/3-[2-(3-benzoyl-phenyl)-propionyloxy]--propyl/-ureido)-phenyl-propionylamino]-propyl ester (**6h**)*

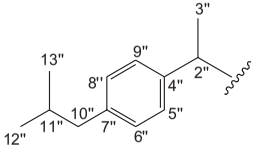
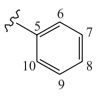
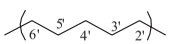
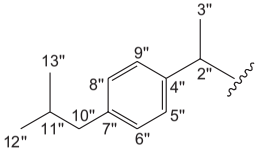
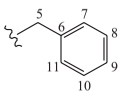
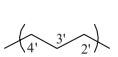
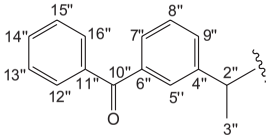
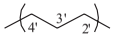
Ketoprofen derivative (**2b**, 0.355 g) was mixed with 0.162 g L-phenylalanine 3-aminopropanol ureidoamide (**5g**) and TEA. The mixture was heated at 120 °C. The crude product was purified on the chromatographic column using ethyl acetate/cyclohexane/methanol 3:1:0.1 as eluent.

*[2-(2,6-Dichloro-phenylamino)-phenyl]-acetic acid 3-/2-[3-(3-/2-[2-(2,6-dichloro--phenylamino)-phenyl]-acetoxy/-propyl)-ureido]-3-phenyl-propionylamino/-propyl ester (**6i**)*

A mixture of 0.397 g diclofenac derivative (**2c**), 0.162 g L-phenylalanine 3-aminopropanol ureidoamide (**5g**) and TEA was heated at 100 °C. Column chromatography with dichloromethane/methanol 9.5:0.5 as eluent was used for purification of the crude product.

*Table II. ^1H and ^{13}C NMR spectra of NSAID esters **6a–i***



Compd.	R^1	R^2		^1H NMR (DMSO-d_6, δ ppm)	^{13}C NMR (DMSO-d_6, δ ppm)
6a				8.21 (t, 1H, 1′ (amide), J = 5.50 Hz), 7.46–7.08 (m, 13H, arom.), 6.57 (t, 1H, 1′ (urea), J = 5.64 Hz), 6.20–6.17 (m, 1H, 3), 5.27–5.24 (m, 1H, 2), 4.00–3.91 (m, 2H, 2″), 3.73–3.58 (m, 4H, 6′), 3.00–2.89 (m, 4H, 2′), 2.42–2.39 (m, 4H, 10″), 1.83–1.76 (m, 2H, 11″), 1.50–1.05 (m, 18H, 3′–5′, 3″), 0.86–0.83 (m, 12H, 12″, 13″)	175.91, 174.36 (1″), 170.92 (1), 157.47 (4), 141.21, 140.20, 140.00, 138.95, 138.40 (5, 4″, 7″), 129.49, 129.41, 128.56, 127.56, 127.48, 126.94 (6–10, 5″, 6″, 8″, 9″), 64.44 (6′), 61.06 (2′), 56.97 (2), 44.75 (2″), 44.68 (10″), 30.02 (11″), 29.90, 28.19, 28.04, 22.92, 22.69 (3′–5′), 22.63, 22.59 (12″, 13″), 18.99, 18.84 (3″)
6b				7.91 (t, 1H, 1′ (amide), J = 5.50 Hz), 7.45–7.43, 7.23–7.09 (2m, 13H, arom.), 6.06 (t, 1H, 1′ (urea), J = 5.60 Hz), 6.00 (m, 1H, 3), 4.30 (m, 1H, 2), 3.98–3.88 (m, 4H, 4′), 3.73 (q, 2H, 2″, J = 6.99 Hz), 3.03–2.83, 2.75–2.70 (2m, 6H, 5, 2′), 2.41 (d, 4H, 10″, J = 3.57 Hz), 1.81–1.78 (m, 2H, 11″), 1.58–1.54, 1.48–1.45, 1.37–1.33 (3m, 10H, 3′, 3″), 0.84 (d, 12H, 12″, 13″, J = 3.51 Hz)	—
6c		$^5CH_3$		7.91 (t, 1H, 1′ (amide), J = 5.62 Hz), 7.74–7.50 (m, 18H, arom.), 6.08 (t, 1H, 1′ (urea), J = 5.62 Hz), 6.01 (d, 1H, 3, J = 7.79 Hz), 4.10–3.90 (m, 7H, 2, 4′, 2″), 3.06–2.93 (2q, 4H, 2′), 1.70–1.59 (m, 4H, 3′), 1.43 (d, 6H, 3″, J = 7.07 Hz), 1.11 (d, 3H, 5, J = 6.89 Hz)	196.07 (10″), 174.00, 173.95 (1″), 173.60 (1), 157.72 (4), 141.58, 137.65, 137.41 (4″, 8″, 11″), 133.20, 132.22, 129.30, 128.95, 128.90, (5″–7″, 9″, 14″), 130.05, 129.04 (12″, 13″, 15″, 16″), 62.82, 62.73 (4′), 49.01 (2), 44.71 (2″), 36.23, 35.57 (2′), 29.61, 28.70 (3′), 20.19 (5), 18.91 (3″)

6d

8.02 (t, 1H, 1′ (amide), J = 5.53 Hz), 7.74–7.50 (m, 18H, arom.), 6.31–6.29 (m, 2H, 3, 1′), 4.08–3.92 (m, 7H, 2, 4′, 2″), 3.05–2.95 (m, 4H, 2′), 1.68–1.24 (m, 13H, 5, 6, 3′, 3″), 0.83 (2d, 6H, 7, 8)

196.06 (10″), 173.97, 173.93 (1″), 173.67 (1), 158.14 (4), 141.59, 137.67, 137.44 (6, 4″, 6″, 11″), 133.17, 132.21, 130.03, 129.29, 129.03, 128.94, 128.86 (5″, 7″– 9″, 12″–16″), 62.88 (4′), 52.20 (2), 44.72 (2″), 42.77 (5), 36.30, 35.58 (2′), 29.64, 28.68 (3′), 24.72, 23.38, 22.44 (6–8), 18.88 (3″)

6e

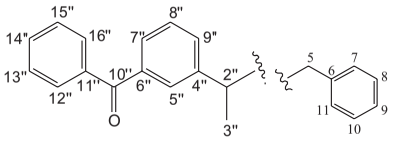
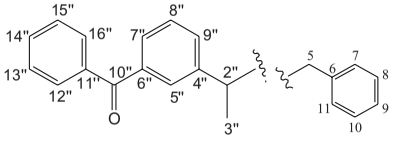
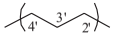
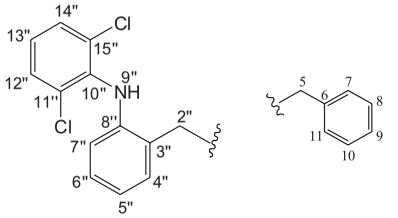
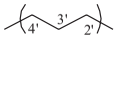
7.87 (t, 1H, 1′ (amide), J = 5.50 Hz), 7.73–7.50 (m, 18H, arom.), 5.92 (t, 1H, 1′ (urea), J = 5.50 Hz), 5.87 (d, 1H, 3, J = 8.84 Hz), 4.13–3.89 (m, 7H, 2, 6′, 2″), 3.02–2.86 (m, 4H, 2′), 1.54–1.13 (m, 21H, 5, 6, 3′–5′, 3″), 0.84 (2d, 6H, 7, 8)

196.04 (10″), 173.95 (1″), 173.30 (1), 157.95 (4), 141.62, 137.63, 137.41 (4″, 8″, 11″), 133.21, 132.20, 129.36, 128.92, (5″–7″, 9″, 14″), 130.03, 129.04 (12″, 13″, 15″, 16″), 64.75 (6′), 51.89 (2), 44.75 (2″), 43.00 (5), 39.43, 38.56 (2′), 29.95, 28.95, 28.18, 28.09, 23.05, 23.00 (3′–5′), 24.73, 23.38, 22.54 (6–8), 18.82 (3″)

6f

8.47 (t, 1H, 1′ (amide), J = 4.34 Hz), 7.75–7.49 (m, 18H, arom.), 7.37–7.22 (m, 5H, arom.), 6.84 (d, 1H, 3, J = 8.31 Hz), 6.36 (t, 1H, 1′ (urea), J = 5.54 Hz), 5.32 (d, 1H, 2, J = 8.01 Hz), 4.10–3.78 (m, 6H, 3′, 2″), 3.32–3.21 (m, 4H, 2′), 1.43, 1.37 (2d, 6H, 3″, J = 7.39 Hz)

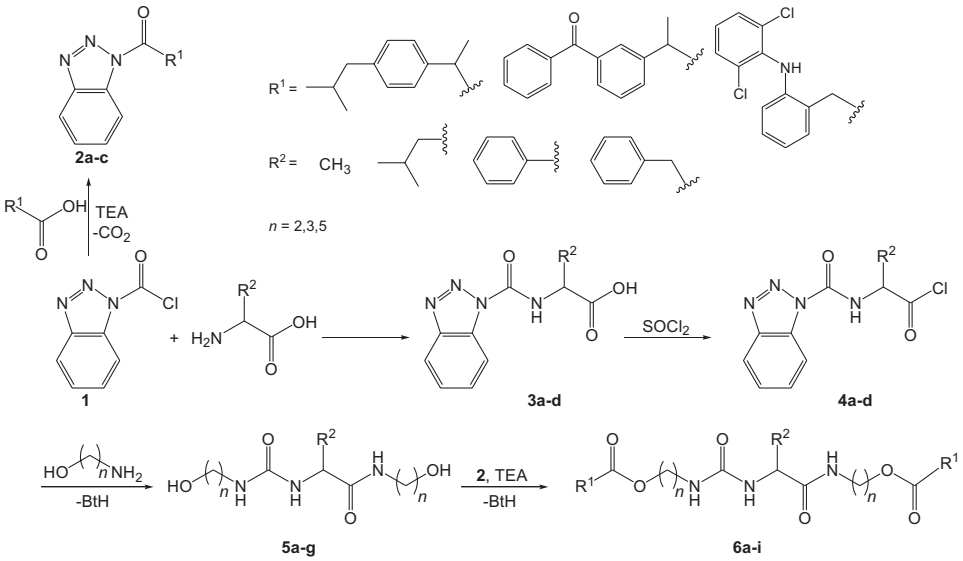
196.04 (10″), 173.93, 173.85 (1″), 171.40 (1), 157.44 (4), 141.47, 141.39, 140.72, 140.70, 140.66, 137.62, 137.39 (5, 4″, 8″, 11″), 133.20, 132.31, 132.27, 129.28, 128.94, (5″–7″, 9″, 14″), 130.08, 129.04 (12″, 13″, 15″, 16″), 127.64, 127.01 (6, 7, 9, 10), 127.68 (8), 64.59, 63.32 (3′), 56.97 (2), 44.75, 44.68 (2″), 38.59, 38.03 (2′), 18.99, 18.89 (3″)

6g			8.14 (t, 1H, 1′ (amide), *J* = 5.25 Hz), 7.74–7.48 (m, 18H, arom.), 7.22–7.09 (m, 5H, arom.), 6.22–6.18 (d+t, 2H, 3, 1′ (urea), 4.36 (q, 1H, 2), 4.07–3.88 (m, 6H, 3′, 2″), 3.31–3.14 (m, 4H, 5, 2′), 2.88–2.66 (m, 2H, 2′), 1.44, 1.41 (2d, 6H, 3″)	196.04, 196.01 (10″), 173.93 (1″), 172.59 (1), 157.73 (4), 141.48, 141.46, 138.17, 138.14, 137.62, 137.61, 137.39 (6, 4″, 8″, 11″), 133.20, 132.30, 129.29, 128.96 (5″–7″, 9″, 14″), 130.07, 129.03 (12″, 13″, 15″, 16″), 129.67, 128.39 (7, 8, 10, 11), 126.59 (9), 64.54 63.54, 63.40 (3′), 54.69 (2), 44.74 (2″), 39.34 (5), 38.55, 37.90 (2′), 19.00 (3″)
6h			7.91 (t, 1H, 1′ (amide), *J* = 5.54 Hz), 7.74–7.50 (m, 18H, arom.), 7.21–7.11 (m, 5H, arom.), 6.61 (t, 1H, 1′ (urea), *J* = 5.70 Hz), 6.00 (d, 1H, 3, *J* = 4.23 Hz), 4.30 (q, 1H, 2, *J* = 7.11 Hz), 4.02–3.91 (m, 6H, 4′, 2″), 3.07–2.70 (m, 6H, 5, 2′), 1.62–1.54 (m, 4H, 3′), 1.44 (d, 6H, 3″, *J* = 7.08 Hz)	195.50 (10″), 173.41, 173, 34 (1″), 171.62 (1), 157.17 (4), 141.02, 137.65, 137.12, 136.87 (6, 4″, 6″, 11″), 132.62, 131.64, 129.47, 129.08, 128.73, 128.47, 128.38, 128.32, 127.81, 125.99 (7–11, 5″, 7″–9″, 12″–16″), 62.20 (4′), 54.21 (2), 44.17 (2″), 38.92 (5), 35.66, 34.98 (2′), 29.00, 28.08 (3′), 18.33 (3″)
6i			7.93 (t, 1H, 1′ (amide), *J* = 5.55 Hz), 7.53 (d, 4H, arom., *J* = 8.07 Hz), 7.24–7.04, 6.88–6.84 (2m, 13H, arom.), 6.28 (d, 2H, arom., *J* = 8.07 Hz), 6.11 (t, 1H, 1′ (urea), *J* = 5.72 Hz), 6.03 (d, 1H, 3, *J* = 8.49 Hz), 4.33 (q, 1H, 2, *J* = 6.63 Hz), 4.06, 3.99 (2t, 4H, 4′, *J* = 6.57 Hz), 3.81 (s, 4H, 2″), 3.18–2.99, 2.91–2.84, 2.79–2.71 (3m, 6H, 5, 2′), 1.70–1.62 (m, 4H, 3′)	172.09 (1″), 172.04 (1), 157.78 (4), 143.27, 138.23, 137.58, 131.12, 131.08, 123.74 (6, 3″, 8″, 10″, 11″, 15″), 131.34, 129.66, 129.62, 128.41, 128.17, 126.57, 126.33, 121.15, 116.41 (7–11, 4″–7″, 12″–14″), 63.06 (4′), 54.81 (2), 39.76 (5), 37.51 (2″), 36.41, 35.73 (2′), 29.59, 28.66 (3′)

RESULTS AND DISCUSSION

Synthesis of novel NSAID twin esters **6a–i** containing amino acid residue, urea and amide moieties is described. The synthetic pathway applied for the preparation of target compounds is presented in Scheme 1. The key intermediates 1-benzotriazolecarboxylic acid chloride (**1**), NSAID benzotriazolides **2a–c**, *N*-(1-benzotriazolecarbonyl)-amino acids **3a–d** and ureidoamides **5a–g** were prepared according to our procedures reported elsewhere (9, 12, 14, 15). 1-Benzotriazolecarboxylic acid chloride (**1**) was synthesized from benzotriazole and triphosgene (14) and further used in the preparation of *N*-(1-benzotriazolecarbonyl)-amino acids **3a–d** (15). Two aliphatic (L-alanine, L-leucine) and two aromatic (D-phenylglycine, L-phenylalanine) amino acids were used in experiments. The prepared amino acid derivatives **3a–d** were transformed to the corresponding chlorides **4a–d** by means of thionyl chloride. In the reaction with aminoalcohols (2-aminoethanol, 3-aminopropanol or 5-aminopenthanol), they gave ureidoamides **5a–g** (9). 1-Benzotriazolecarboxylic acid chloride (**1**) was also used in the preparation of ibuprofen (**2a**), ketoprofen (**2b**) and diclofenac benzotriazolide (**2c**) (12). The benzotriazole moiety in compounds **2a–c** activated the nucleophilic substitution of molecules with hydroxyl groups present in ureido amides **5a–g**, allowing preparation of the final esters **6a–i**.

Structures of compounds **6a–i** were deduced from analyses of their IR, ^{1}H and ^{13}C NMR spectra and were confirmed by elemental analysis (Table I). Chemical shifts were consistent with the proposed structures of novel compounds. IR spectra of esters **6a–i** showed characteristic bands for NH at 3302–3291 cm^{-1} and three different carbonyl groups at 1736–1718, 1663–1633 and 1570–1556 cm^{-1}, respectively. In ^{1}H NMR spectra, carbamide



Scheme 1

NH-1′ appeared as triplets between 6.61 and 5.92 ppm, while the NH-3 proton appeared as a doublet between 6.84 and 5.87 ppm. Amide NH-1′ appeared as a triplet between 8.47 and 7.87 ppm. All three NH groups were exchangeable with D_2O. Ester carbonyls C-1« in ^{13}C NMR spectra appeared as only one or two very close signals between 175.91 and 172.09 ppm. Amide C-1 atom was located between 173.67 and 170.92 ppm, while urea carbonyl C-4 appeared between 158.14 and 157.17 ppm. Ketoprofen derivatives **6c–h** showed additional carbonyl C-10« uniformly located at 196 ppm. Detailed NMR data of all new compounds are given in Table II.

CONCLUSIONS

The environmentally friendly solvent-free protocol for synthesis of novel NSAID esters containing amino acid residue, urea and amide moieties has been described. The prepared esters are potential NSAID prodrugs. Their analgesic, anti-inflammatory and antioxidative activities still remain to be evaluated.

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