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The novel fenoprofenamides – synthesis and spectroscopic characterisation

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Synthesis of a series of new fenoprofenamides (**3a-j**) is described. Amide bonding was achieved by aminolysis of fenoprofen benzotriazolide (**2**) with various amines: primary, secondary, hydroxylamine and amino acids. The structures of synthesised compounds were fully characterised by IR, ^{1}H and ^{13}C NMR spectroscopies and elemental analysis. The synthesised compounds are potential prodrugs of a well known NSAID fenoprofen.

Keywords: fenoprofen, fenoprofenamide, synthesis, benzotriazole, prodrug

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Fenoprofen (α-methyl-3-phenoxybenzeneacetic acid) is a non-steroidal anti-inflammatory drug (NSAID) which is used in the management of mild to moderate pain, fever and inflammation associated with musculoskeletal and joint disorders such as osteoarthritis, rheumatoid arthritis and ankylosing spondylitis (1). The most usual side effects of the chronic use of fenoprofen and other NSAIDs are gastrointestinal disturbances. In addition, since fenoprofen has a rather short plasma half-life (23 h), repeated doses must be given to maintain the therapeutic effect (2). Prodrugs are an approach that can lead to reduced adverse effects as well as to prolonged pharmacological activity. Prodrugs are also used to increase water solubility or lipophilicity, to improve site-specificity and patient acceptance or to decrease toxicity (3). In order to modify fenoprofen pharmacokinetics and bioavailability, a number of derivatives such as aliphatic and aromatic esters and amides (4–6), fatty acyl and alkyl derivatives (7), esters with cyclodextrins (8), compounds with an anti-inflammatory and an anti-oxidant moiety covalently linked by amide or ester bonds (9) and polymer-drug conjugates (10–14) have been synthesised and/or tested for their analgesic/anti-inflammatory activity and gastrointestinal toxicity.

The present paper reports the synthesis and spectroscopic characterisation of a series of fenoprofenamides, as potential fenoprofen prodrugs.

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EXPERIMENTAL

Apparatus and chemicals

Melting points were determined on a Boëtius Microheating Stage (Franz Küstner Nachf. KG, Germany) and remained uncorrected. IR spectra were recorded on a FT-IR 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 the ^{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 are referred to TMS. Coupling constants (*J*) in Hz, are observed through three bonds. For TLC, silica gel plates Kieselgel 60 F_{254} (Merck, Germany) and the following solvent mixtures were used: hexane/ethyl acetate (2:1, 1:1 and 1:3), hexane/acetone (3:1), dichloromethane/methanol (9:1), ethyl acetate/methanol (1:1), dioxane/water (9:1) and butanol/acetic acid/water (8:1:1). Spots were visualised by short-wave UV light and iodine vapour. Preparative TLC was performed on Merck silica gel plates, 2 mm thick, with hexane/ethyl acetate (1:1) as a mobile phase. Column chromatography was performed on silica gel (Kemika, Croatia), 0.063–0.200 mm, with hexane/ethyl acetate (1:3), ethyl acetate/methanol (1:1) or dichloromethane/methanol mixture (9.5:0.5) as eluent. Fenoprofen was kindly obtained from the Faculty of Pharmacy, University of Potchefstroom, South Africa. Amino acids were purchased from Kemika. The amines were distilled and dried prior to use. All solvents were of analytical grade purity and dried.

Chemistry

Synthesis of N-*1-benzotriazole carboxylic acid chloride (1).* – Compound **1** was synthesised according to the procedure published previously (15).

Synthesis of fenoprofen benzotriazolide (2). – Compound **2** was synthesised from fenoprofen and *N*-1-benzotriazole carboxylic acid chloride (**1**) according to the procedure published previously (13).

Synthesis of amides 3a-j. – Method A: The appropriate amine (0.0135 mol) was added dropwise to a solution of **2** (1.55 g, 0.0045 mol) in toluene (10 mL). The reaction mixture was stirred for 0.5 h at room temperature. After 10 min, precipitation of benzotriazole--amine salt occurred. The precipitation was completed by addition of petroleum ether (10 mL). The salt was filtered off and the mother liquor was extracted 2 times with HCl (c = 0.2 mol L^{-1}), once with water, 3 times with saturated $NaHCO_3$ solution and again 2 times with water. All aqueous solutions were cold. The organic layer was dried (Na_2SO_4), filtered and evaporated under reduced pressure to give the corresponding amide **3**. Products **3f** and **3g** were analytically pure, while **3a** was additionally purified by column chromatography (mobile phase: dichloromethane/methanol 9.5:0.5) and **3h** by recrystallisation (acetone). **3b** was obtained in a similar way, but the reaction proceeded more slowly (2 days). No precipitation occurred during the reaction and benzotriazole and the excess of amine were removed by extraction as described above.

Method B: A solution of **2** (0.52 g, 0.0015 mol) in acetonitrile (3 mL) was added dropwise to a cold mixture of hydroxylamine (0.0045 mol) in acetonitrile (3 mL). The reaction mixture was stirred for 30–45 min at 10 °C and evaporated under reduced pres-

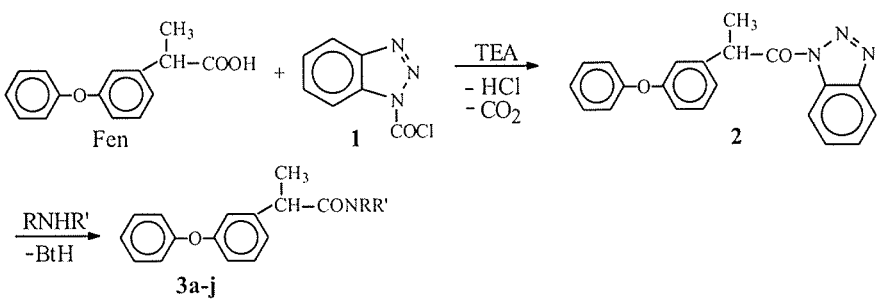
sure. Purification of **3c** and **3d**: the residue was dissolved in dichloromethane (10 mL) and extracted as in method A. The analytically pure sample **3d** was obtained by preparative TLC (mobile phase: hexane/ethyl acetate 1:1). Purification of **3e**: column chromatography with hexane/ethyl acetate 1:3 mobile phase (elution of benzotriazole and amine) and ethyl acetate/methanol 1:1 mixture (elution of the product).

Method C: A solution of **2** (1.03 g, 0.003 mol) in acetone (7 mL) was added dropwise to a solution of amino acid (0.003 mol) and TEA (1.21 g, 0.012 mol) in water (2 mL) and acetone (1 mL). The reaction mixture was stirred for 30 min at room temperature. Acetone was evaporated under reduced pressure. The aqueous solution was acidified to pH 1 (diluted HCl) and extracted 3 times with ethyl acetate. The organic layer was washed with water until neutral, dried (Na_2SO_4) and evaporated under reduced pressure. The analytically pure sample **3i** was obtained by recrystallisation from cyclohexane/ethyl acetate 1:3 mixture and **3j** by column chromatography (mobile phase: dichloromethane/methanol 9.5:0.5).

Detailed reaction conditions and analytical data of **3** are given in Tables I–III.

RESULTS AND DISCUSSION

In our previous paper, a new and convenient method of fenoprofen ester preparation via benzotriazolide was reported (13). The same method was successfully used in the syntheses of various gemfibrozil esters and amides (16). In this paper, an analogous method is applied to fenoprofenamides. In the first step, carboxylic group of fenoprofen reacted with *N*-1-benzotriazolecarboxylic acid chloride (**1**). After decarboxylation, the formed unstable mixed anhydride gave fenoprofen benzotriazolide (**2**). The benzotriazole activated fenoprofen readily reacted with various amino compounds (primary amines, secondary amines, hydroxylamines and amino acids) giving the corresponding amides **3** (Scheme 1).



Fen – fenoprofen
TEA – triethylamine
BtH – benzotriazole

Scheme 1

The following amides were synthesised: propyl (**3a**), *N,N*-diethyl (**3b**), 2-hydroxyethyl (**3c**), 3-hydroxypropyl (**3d**), *N,N*-di(2-hydroxyethyl) (**3e**), cyclohexyl (**3f**), benzyl (**3g**), 2-phenylethyl (**3h**) glycine fenoprofenamide (**3i**) and β-alanine fenoprofenamide (**3j**).

Amidation reactions proceeded in mild conditions, at room or even lower temperature. In syntheses of **3a-h**, a three-fold excess of amine was used (Methods A and B). In reactions with lipophilic amines, dry toluene was used as a solvent, which enabled precipitation of the by-product benzotriazole-amine salt (Method A). Quantitative precipitation occurred after addition of petroleum ether into the concentrated reaction mixture. In reactions with hydrophilic bifunctional amines (2-hydroxyethyl amine, 3-hydroxypropyl amine and diethanol amine), acetonitrile was chosen as solvent. To prevent reaction of **2** with hydroxyl group, reactions were performed at a lower temperature (10 °C), adding the benzotriazolide solution to the excess of hydroxylamine. Amino group, as a stronger nucleophile, reacted first and no ester formation occurred. Reactions of benzotriazolide **2** with glycine or β-alanine proceeded in acetone/water mixture, with benzotriazolide/amino acid ratio 1:1, in the presence of triethylamine (TEA) (Method C, synthesis of **3i** and **3j**). The reactions with all primary amines and with diethanol amine were practically instant, while the reaction with diethylamine took much longer. In contrast, **2** did not react at all with dicyclohexyl and diphenyl amines (two weeks at room temperature, 9 h at 70 °C).

Spectral assignment and CHN analysis of all synthesised compounds confirmed their structures. IR spectrum of **3** showed the following absorption maxima: OH at 3371–3400, NH at 3290–3345, COOH carbonyl at 1720 and 1737, and amide carbonyl at 1623–1651 (amide I) and 1581–1591 cm^{-1} (amide II). Reaction conditions, yields, physical, IR spectroscopic and CHN data of compounds **3a-j** are given in Table I. ^1H NMR chemical shifts (δ in ppm), coupling constants (*J* in Hz) and assignments are given in Table II, while ^{13}C NMR chemical shifts and assignments in Table III. ^{13}C NMR spectra were assigned on the basis of substituent effects and comparison with literature data for related compounds. Fenoprofenbenzylamide (**3g**) was previously synthesised (6) but the literature report gives no spectroscopic characterisation. Therefore, its spectroscopic data are reported here, together with the data for the new compounds.

Preliminary hydrolysis studies showed that fenoprofen could be released from the prepared amides, but detailed kinetic studies and evaluation of potential pharmaceutical use still remain to be done.

Acknowledgements. – Financial support of the Ministry of Science and Technology of the Republic of Croatia is highly appreciated (Grant number: 006243).

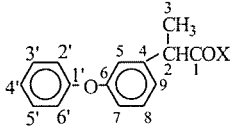
Compd. No.	R	R'	Solvent	Temp. (°C)	Time (h)	Yield (%)	M.p. (°C)	Molecular formula (M_r)	Analysis (%) Calculated/found C	H	N	IR (KBr) ν_{max} (cm^{-1})
3a	$CH_2CH_2CH_3$	H	Toluene	20	0.5	75	oil	$C_{18}H_{21}NO_2$ (283.37)	76.29 75.72	7.47 7.43	4.94 4.94	3296, 2966, 2933, 2875, 1646, 1582, 1551, 1488, 1443, 1248, 1210, 1163, 937, 756, 692
3b	CH_2CH_3	CH_2CH_3	Toluene	20	48.0	76	oil	$C_{19}H_{23}NO_2$ (297.39)	76.73 76.12	7.79 7.36	4.71 4.73	2974, 2932, 1641, 1582, 1487, 1466, 1448, 1430, 1257, 1240, 1140, 930, 790, 752, 692
3c	CH_2CH_2OH	H	Acetonitrile	10	0.8	86	oil	$C_{17}H_{19}NO_3$ (285.34)	71.56 70.53	6.71 6.76	4.91 4.91	3400, 3308, 2935, 1651, 1582, 1548, 1487, 1444, 1247, 1209, 1163, 1071, 933, 757, 693
3d	$CH_2CH_2CH_2OH$	H	Acetonitrile	10	0.5	93	oil	$C_{18}H_{21}NO_3$ (299.36)	72.22 71.44	7.07 7.12	4.68 4.56	3400, 3298, 2937, 1648, 1582, 1486, 1443, 1246, 1209, 1071, 926, 757, 693
3e	CH_2CH_2OH	CH_2CH_2OH	Acetonitrile	10	0.5	64	oil	$C_{19}H_{23}NO_4$ (329.39)	69.28 69.80	7.04 6.94	4.25 4.30	3371, 2934, 1623, 1583, 1487, 1444, 1243, 1216, 1070, 931, 756, 694
3f	C_6H_{11}	H	Toluene	20	0.5	92	102–103	$C_{21}H_{25}NO_2$ (323.43)	77.99 77.50	7.79 7.62	4.33 4.24	3295, 2928, 2855, 1641, 1581, 1552, 1485, 1446, 1242, 1211, 1155, 694
3g	$CH_2C_6H_5$	H	Toluene	20	0.5	94	66–67	$C_{22}H_{21}NO_2$ (331.41)	79.73 79.42	6.38 6.45	4.22 3.97	3290, 3064-2874, 1648, 1582, 1545, 1487, 1454, 1246, 1210, 1164, 1023, 928, 753, 694
3h	$CH_2CH_2C_6H_5$	H	Toluene	20	0.5	83	64–65	$C_{23}H_{23}NO_2$ (345.44)	79.97 79.75	6.71 6.61	4.05 4.08	3292, 3064-2874, 1647, 1582, 1560, 1544, 1487, 1454, 1246, 1210, 931, 752, 695
3i	CH_2COOH	H	Acetone/ water	20	0.5	71	132–133	$C_{17}H_{17}NO_4$ (299.32)	68.22 68.18	5.72 5.85	4.68 4.88	3345, 2987, 1737, 1708, 1648, 1591, 1585, 1484, 1257, 1240, 1212, 939, 872, 752, 688
3j	CH_2CH_2COOH	H	Acetone/ water	20	0.5	70	oil	$C_{18}H_{19}NO_4$ (313.35)	68.99 68.80	6.11 5.99	4.47 4.52	3298, 2927, 1720, 1651, 1582, 1448, 1443, 1188, 1246, 1209, 1074, 933, 758, 693

Table II. ^1H NMR data of fenoprofen amides 3a-j

Compd. No.	^1H NMR, δ (ppm)[a]
3a	7.97 (t, 1H, *J* = 5.0 Hz, CONH), 7.38 (t, 2H, *J* = 7.8 Hz, H-2',6'), 7.30 (t, 1H, *J* = 8.0 Hz, H-4'), 7.13 (t, 1H, *J* = 7.0 Hz, H-8), 7.08 (d, 1H, *J* = 7.6 Hz, H-7), 6.99 (s, 1H, H-5), 6.98 (d, 2H, *J* = 7.6 Hz, H-3',5'), 6.83 (dd, 1H, ^3J = 8.0 Hz, ^4J = 2.3 Hz, H-9), 3.57 (q, 1H, *J* = 6.9 Hz, H-2), 2.99 (m, 2H, H-1''), 1.35 (t, 2H, *J* = 7.1 Hz, H-2''), 1.29 (d, 3H, *J* = 7.0 Hz, H-3) and 0.76 (t, 3H, *J* = 7.3 Hz, H-3'')
3b	7.40-7.29 (m, 3H, H-2',4',6'), 7.12 (t, 1H, *J* = 7.4 Hz, H-8), 7.06 (d, 1H, *J* = 7.4 Hz, H-7), 6.98 (s, 1H, H-5), 6.94 (d, 2H, *J* = 9.7 Hz, H-3',5'), 6.85 (dd, 1H, ^3J = 8.1 Hz, ^4J = 1.4 Hz, H-9), 3.99 (q, 1H, *J* = 6.8 Hz, H-2), 3.34-3.04 (m, 4H, H-1'',3''), 1.25 (d, 3H, *J* = 6.8 Hz, H-3), 0.92 and 0.89 (2 t, 6H, *J* = 7.1 Hz, H-2'',4'')
3c	8.02 (t, 1H, *J* = 5.2 Hz, CONH), 7.37 (t, 2H, *J* = 8.0 Hz, H-2',6'), 7.28 (t, 1H, *J* = 7.9 Hz, H-4'), 7.12 (t, 1H, *J* = 7.4 Hz, H-8), 7.05 (d, 1H, *J* = 8.5 Hz, H-7), 6.99 (s, 1H, H-5), 6.98 (d, 2H, *J* = 7.7 Hz, H-3',5'), 6.81 (dd, 1H, ^3J = 8.2 Hz, ^4J = 1.3 Hz, H-9), 4.69 (s, 1H, OH), 4.00 (q, 1H, *J* = 7.1 Hz, H-2), 3.35 (t, 2H, *J* = 5.7 Hz, H-2''), 3.30-3.02 (m, 2H, H-1'') and 1.28 (d, 3H, *J* = 7.1 Hz, H-3)
3d	8.01 (bs, 1H, CONH), 7.38 (t, 2H, *J* = 7.6 Hz, H-2',6'), 7.29 (t, 1H, *J* = 7.8 Hz, H-4'), 7.13 (t, 1H, *J* = 7.1 Hz, H-8), 7.07 (d, 1H, *J* = 7.8, H-7), 6.98 (s, 3H, H-3',5,5'), 6.83 (d, 1H, *J* = 7.8 Hz, H-9), 4.48 (bs, 1H, OH), 3.57 (q, 1H, *J* = 7.1 Hz, H-2), 3.34 (t, 2H, *J* = 6.0 Hz, H-3''), 3.06 (d, 2H, *J* = 5.8 Hz, H-1''), 1.49 (t, 2H, *J* = 6.5 Hz, H-2'') and 1.28 (d, 3H, *J* = 6.8 Hz, H-3)
3e	7.38 (t, 2H, *J* = 7.5 Hz, H-2',6'), 7.31 (t, 1H, *J* = 8.0 Hz, H-4'), 7.13 (t, 1H, *J* = 7.8 Hz, H-8), 7.05 (d, 1H, *J* = 7.5 Hz, H-7), 7.05 (d, 2H, *J* = 7.7 Hz, H-3',5'), 6.93 (s, 1H, H-5'), 6.84 (d, 1H, *J* = 8.0 Hz, H-9), 4.88 (bs, 1H, OH), 4.68 (bs, 1H, OH), 4.15 (q, 1H, *J* = 6.4, H-2), 3.54-3.39 (m, 2H, H-2'',4''), 3.26-3.13 (m, 2H, H-1'',3'') and 1.25 (d, 3H, *J* = 6.7 Hz, H-3)
3f	7.84 (d, 1H, *J* = 7.7 Hz, CONH), 7.37 (t, 2H, *J* = 7.6 Hz, H-2',6'), 7.29 (t, 1H, *J* = 7.9 Hz, H-4'), 7.12 (t, 1H, *J* = 7.8 Hz, H-8), 7.08 (d, 1H, *J* = 8.1 Hz, H-7), 6.99 (s, 1H, H-5), 6.98 (d, 2H, *J* = 7.7 Hz, H-3',5'), 6.83 (d, 1H, *J* = 8.1 Hz, H-9), 3.57 (q, 1H, *J* = 6.9 Hz, H-2), 3.48-3.45 (m, 1H, H-1''), 1.74-1.50 and 1.21-0.99 (2m, 10H, H-2'-6'') and 1.28 (d, 3H, *J* = 7.0 Hz, H-3)
3g	8.50 (t, 1H, *J* = 5.5 Hz, CONH), 7.36 (d, 2H, *J* = 7.9 Hz, H-2',6'), 7.32 (t, 1H, *J* = 7.8 Hz, H-4'), 7.25 (d, 2H, *J* = 7.7 Hz, H-3'',7''), 7.21 (t, 1H, *J* = 7.0 Hz, H-5''), 7.19 (d, 1H, *J* = 7.4 Hz, H-7), 7.15 (s, 1H, H-5), 7.12 (t, 2H, *J* = 7.0 Hz, H-3',5'), 7.00 (t, 3H, *J* = 8.1 Hz, 4'',6'',9), 6.86 (dd, 1H, ^3J = 7.2 Hz, ^4J = 1.4 Hz, H-8), 4.24 (t, 2H, *J* = 4.9 Hz, H-1''), 3.67 (q, 1H, *J* = 7.0 Hz, H-2) and 1.34 (d, 3H, *J* = 6.9 Hz, H-3)
3h	8.05 (t, 1H, *J* = 5.4 Hz, CONH), 7.39 (t, 2H, *J* = 7.4 Hz, H-2',6'), 7.31 (t, 1H, *J* = 8.0 Hz, H-4'), 7.23 (t, 2H, *J* = 7.2 Hz, H-4'',8''), 7.21 (t, 1H, *J* = 6.4 Hz, H-6''), 7.16 (t, 1H, *J* = 7.4 Hz, H-7), 7.12 (d, 2H, *J* = 8.01 Hz, H-5'',7''), 7.07 (d, 1H, *J* = 8.7 Hz, H-7), 7.01 (s, 1H, H-5), 6.99 (s, 2H, H-3',5'), 6.85 (d, 1H, *J* = 7.8 Hz, H-9), 3.56 (q, 1H, *J* = 6.8 Hz, H-2), 3.28-3.16 (m, 2H, H-1''), 2.64 (t, 2H, *J* = 7.1 Hz, H-2'') and 1.28 (d, 3H, *J* = 6.9 Hz, H-3)
3i	12.53 (s, 1H, COOH), 8.30 (t, 1H, *J* = 5.5 Hz, NH), 7.35 (t, 2H, *J* = 7.8 Hz, H-2',6'), 7.27 (t, 1H, *J* = 8.0 Hz, H-4'), 7.09 (dd, 2H, *J* = 7.5 Hz, H-3',5'), 6.99 (d, 2H, *J* = 8.6 Hz, H-7), 6.96 (m, 2H, H-5,8), 6.80 (dd, 1H, *J* = 7.8, H-9), 3.71 (t, 2H, *J* = 5.5 Hz, H-1''), 3.66 (q, 2H, *J* = 7.0 Hz, H-2) and 1.26 (d, 3H. *J* =7.0 Hz, H-3)
3j	11.00 (s, 1H, COOH), 8.06 (t, 1H, *J* = 5.0 Hz, NH), 7.39 (t, 2H, *J* = 7.8 Hz, H-3',5'), 7.29 (t, 1H, *J* = 7.9 Hz, H-8), 7.13 (t, 1H, *J* = 7.4 Hz, H-4'), 7.06 (d, 1H, *J* = 8.7 Hz, H-7), 7.01 (s, 1H, H-5), 6.98 (d, 2H, *J* = 7.8 Hz, H-2',6'), 6.82 (d, 1H, *J* = 8.2 Hz, H-9), 3.57 (q, 1H, *J* = 6.8 Hz, H-2), 3.24-3.11 (m, 2H, H-1''), 2.26 (t, 2H, *J* = 6.8 Hz, H-2'') and 1.27 (d, 3H, *J* = 6.9 Hz, H-3)

[a] DMSO-d_6 solution

Table III. ^{13}C *NMR data of fenoprofen amides 3a-j*[a]



X

	OH	1" 2" 3" NHCH2CH2CH3	1" 2" CH2CH3 N 3" 4" CH2CH3	1" 2" NHCH2CH2OH	1" 2" 3" NHCH2CH2CH2OH	1" 2" CH2CH2OH N 3" 4" CH2CH2OH	2" 3" 1" NH 4" 6" 5"	1" 2" 3" 4" NHCH2 5" 7" 6"	1" 2" 3" 4" 5" NHCH2CH2 6" 8" 7"	1" 2" NHCH2COOH	1" 2" 3" NHCH2CH2COOH
C atom	Fen	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	**3j**
1	175.67	172.89	171.67	173.23	173.06	173.15	171.96	173.05	172.90	171.39	172.98
2	45.08	45.06	41.37	44.95	45.02	41.18	44.80	45.06	45.01	44.74	44.82
3	18.80	18.58	21.03	18.73	18.57	20.69	18.48	18.53	18.53	18.72	18.65
4	143.99	144.80	145.06	144.75	144.77	144.86	144.84	144.59	144.61	144.36	144.62
5	117.98	117.65	117.36	117.70	117.63	117.41	117.53	117.80	117.69	117.92	117.59
6	156.97	156.73	156.89	156.70	156.72	156.85	156.73	156.75	156.70	156.72	156.65
7	116.91	116.71	116.85	116.65	116.70	116.75	116.65	116.87	116.68	116.73	116.61
8	130.13	129.85	130.33	129.85	129.87	130.28	129.77	129.91	129.84	129.16	129.83
9	122.77	122.49	122.53	122.51	122.48	122.59	122.37	122.56	122.52	122.65	122.47
1'	156.78	156.55	156.70	156.58	156.56	156.63	156.51	156.54	156.55	156.56	156.55
2'	118.91	118.64	118.62	118.69	118.67	118.67	118.60	118.54	118.66	118.69	118.68
3'	130.24	130.14	130.56	130.16	130.16	130.17	130.07	130.15	130.15	130.16	130.14
4'	123.68	123.49	123.55	123.51	123.51	123.56	123.42	123.48	123.51	123.50	123.50
5'	130.24	130.14	130.56	130.16	130.16	130.17	130.07	130.15	130.15	130.16	130.14
6'	118.91	118.64	118.62	118.69	118.67	118.67	118.60	118.54	118.66	118.69	118.68
1"		40.42	39.67	59.96	35.86	50.34	47.52	42.15	40.38	40.84	40.43
2"		22.44	12.84	41.69	32.46	59.38	32.43	139.58	40.17	173.52	40.15
3"		11.43	41.27		58.41	48.62	24.67	128.35	139.53		173.42
4"			14.33			58.73	25.32	127.13	128.78		
5"							24.59	126.84	128.34		
6"							32.43	127.13	126.12		
7"								128.35	128.34		
8"									128.78		

[a] DMSO-d_6 solution, δ (ppm)

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S A Ž E T A K

Novi amidi fenoprofena – sinteza i spektroskopska karakterizacija

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U radu je opisana sinteza novih amida fenoprofena (**3a-j**). Amidna veza je ostvarena aminolizom benzotriazolida fenoprofena (**2**) s primarnim i sekundarnim aminima, hidroksilaminom i amino kiselinama. Strukture sintetiziranih spojeva u potpunosti su karakterizirane IR, ^{1}H i ^{13}C NMR spektroskopijom i elementarnom analizom. Sintetizirani spojevi su potencijalni prolijekovi nesteroidnog protuupalnog lijeka fenoprofena.

Ključne riječi: fenoprofen, amid fenoprofena, sinteza, benzotriazol, prolijek

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