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Source / Izvornik: **Croatica Chemica Acta, 2003, 76, 335 - 341**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:163:075831

CROATICA CHEMICA ACTA
CCACAA **76** (4) 335–341 (2003)

ISSN-0011-1643
CCA-2891
Original Scientific Paper

The Novel Ketoprofenamides: Synthesis and Spectroscopic Characterization

Marijana Zovko,[a] Branka Zorc,[a,*] Milena Jadrijević-Mladar Takač,[a] Biserka Metelko,[b] and Predrag Novak[b]

[a]*Faculty of Pharmacy and Biochemistry, A. Kovačića 1, 10 000 Zagreb, Croatia*

[b]*PLIVA Pharm. Ind. Inc., Research Division, Prilaz baruna Filipovića 25, 10 000 Zagreb, Croatia*

RECEIVED FEBRUARY 6, 2003; REVISED APRIL 3, 2003; ACCEPTED JULY 23, 2003

Key words
ketoprofen
amide
benzotriazole
synthesis
FTIR and NMR spectroscopy

Synthesis of a series of new ketoprofenamides (**3a-h**) is described. Amide formation was achieved by aminolysis of ketoprofen benzotriazolide (**2**) with various amines: primary, secondary, hydroxylamine and amino acid β-alanine. The structures of synthesized compounds were characterized by means of IR, ^{1}H and ^{13}C NMR spectroscopies and elemental analysis. The synthesized compounds are potential prodrugs of a well-known NSAID ketoprofen.

INTRODUCTION

Ketoprofen, 2-(3-benzoylphenyl)propionic acid, a non-steroidal anti-inflammatory drug (NSAID), was introduced into therapy in 1986 and so far has gained a wide acceptance. In addition to anti-inflammatory activity, ketoprofen also possesses analgesic and antipyretic properties. It is indicated for long-term management of rheumatoid arthritis and osteoarthritis, for mild to moderate pain and primary dismenorrhea.[1]

Derivatization of carboxylic acid NSAIDs to their amide derivatives has been used for various purposes. Numerous NSAID amides have proved to be useful prodrugs. For example, nepafenac, the amide analogue of amfenac, exhibits enhanced permeation to ocular tissue followed by rapid bioactivation to active compound in posterior segments of the eye.[2] The prodrug approach is also useful in reducing gastrointestinal toxicity of NSAIDs, which is the major side-effect of this class of drugs. Amide derivatives of diclofenac, tolfenamic acid, ibuprofen and indomethacin with a well known antioxidant cysteamine, exhibit good anti-inflammatory and antioxidant activities and show very significant reduction of ulcerogenicity.[3] Glycine amides of ketoprofen and several other well known NSAIDs are significantly less irritating to gastric mucosa, while their anti-inflammatory activities are comparable to their parent drugs.[4,5] Ketoprofen glycinate methyl ester has higher anti-inflammatory and analgesic activity then the parent drug.[6] Ketoprofenamides with heterocyclic residues (2-thiazolinyl, 4-methylpyridyl, 3-hydroxypyridyl, pyridyl, 1,5-dimethyl-2-phenylpyrazolonyl or thiazolyl) also possess significant analgesic and anti-inflammatory activities,[7] while ketoprofen 2-hydroxyethylamide and ketoprofen esters with bis(hydroxyalkylthio)alkanes are useful in the treatment and prevention of atherosclerosis.[8] Some amides possess anti-inflammatory activity independent of the parent compound. Naproxen-lysine derivative is at least as active in inhibiting prostaglandin synthesis as naproxen itself.[9] Primary and

* Author to whom correspondence should be addressed. (E-mail: bzorc@pharma.hr)

secondary amide derivatives of indomethacin and meclofenamic acid are potent and selective cyclooxygenase-2 inhibitors.[10,11] In the indomethacin series, esters and primary and secondary amides are superior to tertiary amides as selective inhibitors. In the meclofenamic acid and 5,8,11,14-eicosatetraynoic acid series, only the amide derivatives inhibit COX-2, while the esters are either inactive or nonselective.[10] Furthermore, enantiomers of ketoprofen and some other chiral NSAIDs can be separated through its diastereomeric amide derivatives by gas,[12] column[13] or liquid chromatography on chiral stationary phases.[14–15]

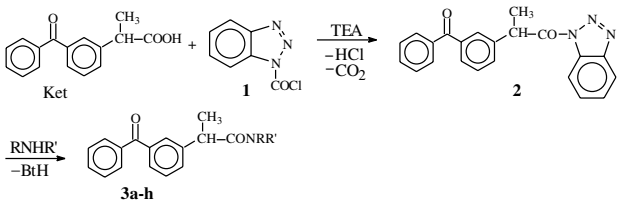
The present paper reports the synthesis and spectroscopic characterization of several ketoprofenamides, as potential NSAID drugs or prodrugs.

RESULTS AND DISCUSSION

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

The following ketoprofenamides were synthesized: propyl (**3a**), *N,N*-diethyl (**3b**), cyclohexyl (**3c**), 2-aminoethyl (**3d**), β-alanine (**3e**), 2-hydroxyethyl (**3f**), 3-hydroxypropyl (**3g**) and *N,N*-di(2-hydroxyethyl) (**3h**). All amides, except amide **3f**, are new compounds. Compound **3f** was previously synthesised, but the literature report[8] gave no spectroscopic characterisation. Therefore, its spectroscopic data are reported here, together with the data for the new compounds. In addition, our method provides product **3f** in significantly higher yield (88 %), in comparison with the previously reported method (40.6 %).

The amide preparation proceeded in mild conditions, at room or even lower temperature. In syntheses of **3a–c** and **3f–h**, a five-fold excess of amine was added (Methods A and D). Even higher excess of amine was used in preparation of amide **3d** (Method B), in order to avoid bis-product formation. Preparation of amide **3e** was performed with equimolar ratio of benzotriazolide **2** and β-alanine, in the presence of triethylamine, which formed a salt with by-product benzotriazole and prevented its reaction with the starting amino compound (Method C). Reactions with lipophilic amines (propylamine, diethylamine, cyclohexylamine, ethylenediamine) were performed in dry toluene, reaction with β-alanine in water/acetone mixture and reactions with hydrophilic bifunctional amines (2-hydroxyethylamine, 3-hydroxypropylamine and diethanolamine) in acetonitrile. To prevent reaction of **2** with hydroxyl group, reactions were performed at a lower temperature (10 °C), by addition of the benzotriazolide solution to the excess of hydroxylamine. Amino group, as a stronger nucleophile, reacted first and no ester formation occurred. The reactions with all primary amines and with diethanolamine were practically instant, while the reaction with diethylamine lasted much longer.



3a R = $CH_2CH_2CH_3$ R' = H
3b R = R' = CH_2CH_3
3c R = C_6H_{11} R' = H
3d R = $CH_2CH_2NH_2$ R' = H
3e R = CH_2CH_2COOH R' = H
3f R = CH_2CH_2OH R' = H
3g R = $CH_2CH_2CH_2OH$ R' = H
3h R = R' = CH_2CH_2OH

Scheme 1.

Spectral assignment and CHN analysis of all synthesized compounds confirmed their structures. FTIR spectra of **3** showed the characteristic absorbtion bands for OH at ν 3308–3390 cm^{-1} (compounds **3f-h**), ν NH at 3296–3310 cm^{-1} (all compounds), COOH carbonyl at ν 1715 cm^{-1} (**3e**) and amide group at ν 1644–1660 cm^{-1} (amide I) and ν 1537–1598 cm^{-1} (amide II) (all compounds). The stretching vibration of ketone carbonyl moiety in most cases overlapped with amide I carbonyl absorption. The parallel display of FTIR spectra of ketoprofen, ketoprofen benzotriazolide (**2**) and one of the synthesised amide (**3a**) is presented in Figure 1. Reaction conditions, yields, physical, IR spectroscopic and CHN data of compounds **3a-h** are given in Table I.

^{13}C and ^{1}H NMR chemical shifts of compounds **3a-h** were assigned by the combined use of one- and two-dimensional NMR spectra. Proton resonances were deduced

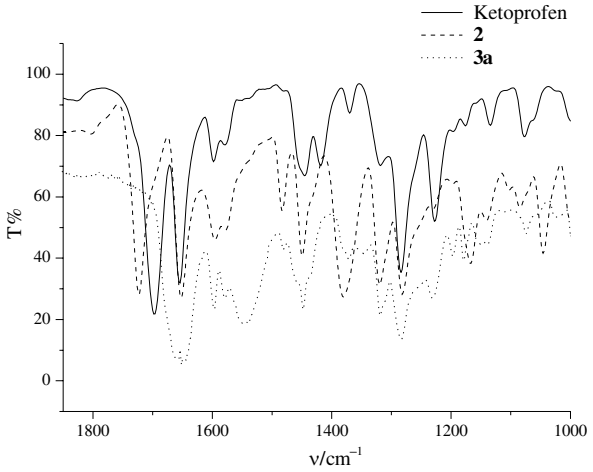
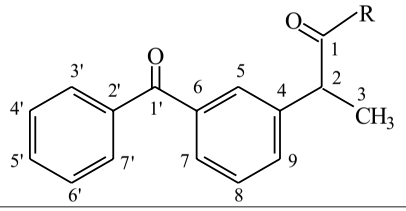


Figure 1. Parallel display of FTIR spectra of ketoprofen, ketoprofen benzotriazolide (**2**) and ketoprofen propylamide (**3a**).

TABLE I. Preparation and analytical data of ketoprofen amides **3a-h**

Compd. No.	R	R'	Solvent	Temp. °C	Time h	Yield %	M.p. °C	Molecular formula (M_r)	Anal. cald. (found) / % C	H	N	IR (KBr) ν_{max} / cm^{-1}
3a	$CH_2CH_2CH_3$	H	toluene	20	0.25	87	oil	$C_{19}H_{21}NO_2$ (295.38)	77.26 (77.06	7.16 7.51	4.74 4.94)	3302, 2966, 2933, 2874, 1660, 1650, 1598, 1547, 1448, 1318, 1284, 1231, 1178, 954, 722, 704, 642
3b	CH_2CH_3	CH_2CH_3	toluene	20	24	65	oil	$C_{20}H_{23}NO_2$ (309.40)	77.64 (77.25	7.49 7.85	4.52 4.45)	2973, 2932, 1659, 1642, 1580, 1481, 1461, 1447, 1430, 1282, 1245, 1144, 954, 720, 701, 646
3c	C_6H_{11}	H	toluene	20	0.25	93	120–121	$C_{22}H_{25}NO_2$ (335.44)	78.77 (78.75	7.51 7.60	4.17 4.07)	3300, 2931, 2854, 1659, 1642, 1597, 1537, 1481, 1448, 1283, 1224, 954, 722, 705, 642
3d	$CH_2CH_2NH_2$	H	toluene	20	0.75	57	oil	$C_{18}H_{20}N_2O_2$ (296.36)	72.95 (72.80	6.80 7.00	9.45 9.75)	3296, 3058, 2872, 1656, 1596, 1545, 1446, 1283, 1231, 1178, 1074, 954, 703, 641
3e	CH_2CH_2COOH	H	acetone/water	20	0.5	73	65–66	$C_{19}H_{19}NO_4$ (325.36)	70.14 (69.90	5.89 5.99	4.31 4.63)	3310, 2932, 1715, 1652, 1596, 1557, 1447, 1319, 1284, 1234, 1196, 1076, 906, 721, 705, 642
3f	CH_2CH_2OH	H	acetonitrile	10	0.75	86	oil	$C_{18}H_{19}NO_3$ (297.35)	72.71 (71.85	6.44 6.68	4.71 4.95)	3316, 2934, 2877, 1652, 1597, 1544, 1448, 1317, 1285, 1235, 1168, 956, 722, 706, 642
3g	$CH_2CH_2CH_2OH$	H	acetonitrile	10	0.5	93	oil	$C_{19}H_{21}NO_3$ (311.38)	73.29 (72.99	6.80 7.02	4.50 4.55)	3308, 2934, 2876, 1658, 1597, 1547, 1447, 1284, 1236, 1180, 1071, 956, 722, 705, 642
3h	CH_2CH_2OH	CH_2CH_2OH	acetonitrile	10	0.5	64	oil	$C_{20}H_{23}NO_4$ (341.40)	70.36 (69.80	6.79 6.49	4.10 3.43)	3390, 2975, 2934, 1644, 1632, 1557, 1446, 1284, 1212, 1058, 954, 721, 702, 694

TABLE II. ^{13}C NMR chemical shifts, δ in ppm, for ketoprofen and amides **3a-3h**, recorded in DMSO-d_6 solution



	R								
	OH	1'' 2'' 3'' NHCH$_2$CH$_2$CH$_3$	1'' 2'' CH$_2$CH$_3$ N 3'' 4'' CH$_2$CH$_3$	2'' 3'' 1'' NH 4'' 6'' 5''	1'' 2'' NHCH$_2$CH$_2$NH$_2$	1'' 2'' 3'' NHCH$_2$CH$_2$COOH	1'' 2'' NHCH$_2$CH$_2$OH	1'' 2'' 3'' NHCH$_2$CH$_2$CH$_2$OH	1'' 2'' CH$_2$CH$_2$OH N 3'' 4'' CH$_2$CH$_2$OH
C \ Compd.	Ketoprofen	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**
1	175.08	172.20	171.69	171.75	172.98	172.72	172.92	172.76	173.27
2	44.45	44.34	41.15	44.59	44.97	44.61	44.66	44.78	41.15
3	18.43	17.98	21.00	18.42	18.67	18.52	18.58	18.44	20.97
4	141.81	142.35	143.21	142.86	142.88	142.67	142.76	142.75	143.17
5	128.39	127.50	128.34	128.35	128.13	128.36	128.42	128.36	128.62
6	136.93	136.31	137.38	136.74	136.92	136.72	136.75	136.77	137.44
7	128.20	127.90	128.08	127.85	128.96	127.94	128.95	127.94	128.19
8	128.59	127.97	129.03	128.43	127.38	128.40	128.42	128.43	129.10
9	131.79	131.04	131.85	131.45	132.76	131.59	131.57	131.48	132.10
1'	195.55	195.24	195.81	195.69	195.80	195.65	195.65	195.66	195.90
2'	136.87	136.53	137.11	137.00	137.12	136.94	136.97	136.97	137.23
3'	129.50	129.06	129.69	129.52	129.68	129.52	129.53	129.51	129.86
4'	128.49	128.04	128.69	128.48	128.61	128.48	128.49	128.48	128.81
5'	132.63	132.17	132.86	132.60	131.70	132.58	132.60	132.59	132.95
6'	128.49	128.04	128.69	128.48	128.61	128.48	128.49	128.48	128.81
7'	129.50	129.06	129.69	129.52	129.68	129.52	129.53	129.51	129.86
1''		39.79	41.32	47.39	44.97	35.31	41.48	35.71	50.57
2''		21.75	14.42	32.26	40.42	34.85	59.72	32.25	59.49
3''		10.75	39.72	24.39		174.11		58.22	48.80
4''			12.88	24.47					58.91
5''				25.13					
6''				32.26					

TABLE III. ^{1}H NMR chemical shifts, δ in ppm, for ketoprofen and amides **3a-3h**, recorded in DMSO-d_6 solution

Compd. / H	Ketoprofen	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**
	12.5(COOH)	8.04 (NH)		7.93 (NH)	8.05 (NH) 1.65 (NH_2)	8.10 (NH)	8.07 (NH) 4.66 (OH)	8.02 (NH) 4.39 (OH)	4.16 (OH)
2	3.82	3.70	4.14	3.69	3.71	3.70	3.74	3.70	4.29
3	1.40	1.35	1.30	1.34	1.36	1.33	1.32	1.35	1.30
4									
5	7.68	7.73	7.66	7.73	7.73	7.72	7.73	7.72	7.67
6									
7	7.60	7.59	7.60	7.58	7.59	7.56	7.59	7.59	7.59
8	7.52	7.50	7.52	7.50	7.50	7.48	7.50	7.50	7.52
9	7.60	7.63	7.62	7.61	7.62	7.60	7.63	7.62	7.61
1'									
2'									
3'	7.74	7.73	7.70	7.73	7.73	7.72	7.73	7.73	7.72
4'	7.57	7.57	7.56	7.55	7.57	7.58	7.57	7.57	7.57
5'	7.69	7.69	7.68	7.69	7.69	7.68	7.69	7.69	7.69
6'	7.57	7.57	7.56	7.55	7.57	7.58	7.57	7.57	7.57
7'	7.74	7.73	7.70	7.73	7.73	7.72	7.73	7.73	7.72
1"		2.99	3.27	3.48	3.61–3.58	3.15–3.26	3.09	3.08	3.23–3.28 3.42–3.51
2"		1.36	0.93	1.16–1.19 1.75	3.28–3.13	2.26	3.36	1.51	3.30–3.52
3"		0.78	3.16 3.35	1.19–1.25 1.67				3.35	3.16–3.23 3.43–3.52
4"			0.97	1.19–1.25 1.67					3.30–3.52
5"				1.08–1.14 1.52					
6"				1.01–1.08 1.60					

from high-resolution ^{1}H and COSY spectra, while those of carbon from APT, HMQC and HMBC spectra. ^{13}C and ^{1}H NMR chemical shifts are listed in Table II and III, respectively. HMBC NMR spectrum of **3j** is shown in Figure 2. Ketoprofen 2-hydroxyethylamide (**3f**) was previously synthesised,[8] but the literature report gives no spectroscopic characterization. Therefore, its spectroscopic data are reported here, together with the data for the new compounds.

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

EXPERIMENTAL

Melting points were determined on a Boëtius Microheating Stage (Franz Küstner Nachf. KG, Germany) and remained uncorrected. IR spectra (KBr pellets) were recorded on a FT-IR Perkin Elmer Paragon 500 spectrometer (Perkin Elmer, UK).

NMR experiments were carried out on a Bruker Avance DRX500 spectrometer operating at 500.13 MHz for ^{1}H, with a 5 mm diameter inverse detection probe and a *z*-axis gradient coil. The solvent was DMSO-d_6 and all experiments were performed at ambient temperature. TMS was used as the internal standard. ^{1}H NMR experiments were performed with spectral width of 10000 Hz, 65 K data points and 8–16 scans.

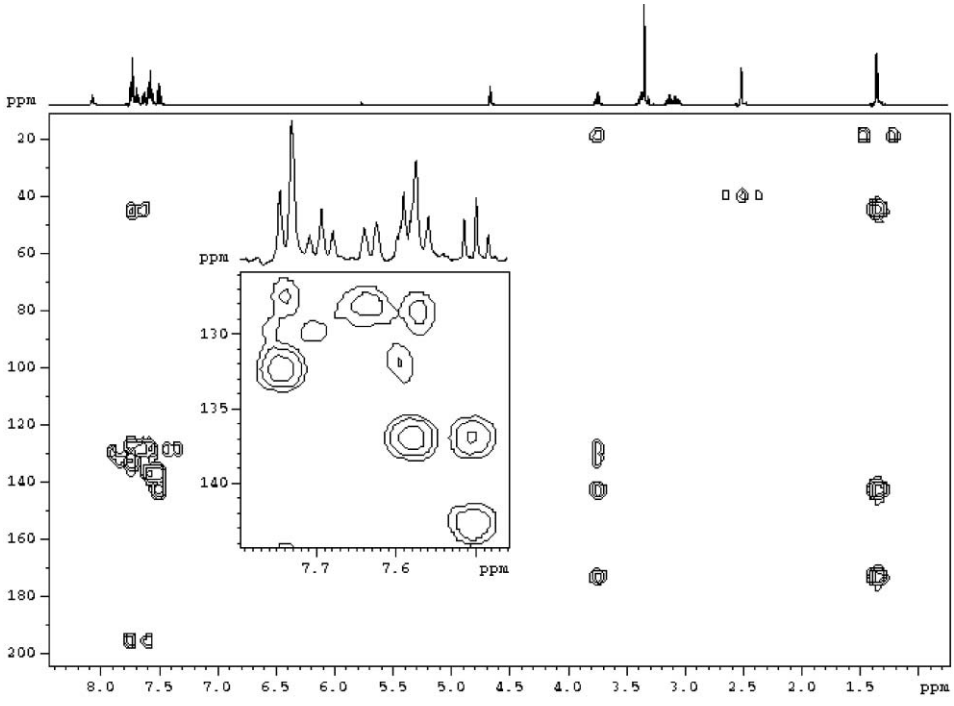


Figure 2. HMBC NMR spectrum of compound **3f**.

The sample concentration was 30 mg ml^{-1}. The digital resolution was 0.15 Hz per point. In ^{13}C NMR spectra the spectral width was 31440 Hz, number of data points 65 K and number of scans 500–1000 per spectrum. The digital resolution was 0.5 Hz per point. Two-dimensional absolute value gradient selected COSY spectra were recorded under the following conditions. Spectral width was 6660 Hz in both domains, 2 K data points were applied in time domain and 256 increments were collected for each data set with linear prediction and zero filling to 1 K. A relaxation delay was 1.5 s. Spectra were processed with sine window functions. The digital resolution was 3.3 Hz per point in f1 and 26.0 Hz per point in f2 domain. The number of scans was 4. Absolute value HSQC and HMBC spectra were recorded with a relaxation delay of 1.5 s and 8-16 scans per increment. The spectral width was 6600 Hz in acquisition domain f2 and 31000 Hz in time domain f1. Data were collected into 2048 × 256 acquisition matrix and processed using a 2K × 1K transformed matrix with zero filling in f1 domain. Sine multiplication was performed prior to Fourier transformations. In HMBC spectra the delay for long-range couplings was set to 60 ms.

For TLC, silica gel plates Kieselgel 60 F_{254} (Merck, Germany) and the following solvents and solvent mixtures were used: ethyl acetate, methanol, cyclohexane/ethyl acetate (1:1), ethyl acetate/methanol (1:1 and 9:1) and butanol/acetic acid/water (8:1:1). Spots were visualized by short-wave UV light and iodine vapor. Column chromatography was performed on silica gel (Kemika, Croatia), 0.063-0.200 mm, with ethyl acetate, ethyl acetate/methanol (1:1), cyclohexane/ethyl acetate (1:3), dichloromethane/methanol (1:1) as eluent. Ketoprofen was kindly obtained from Belupo, Croatia. The amines were distilled and dried prior to use. All solvents were of analytical grade purity and dried.

N-*1-Benzotriazole carboxylic acid chloride (BtcCl) (**1**)*

Compound **1** was synthesized from benzotriazole and 20 % phosgene solution in toluene following the published procedure.[17]

*Ketoprofen benzotriazolide (Ket-Bt) (**2**)*

Compound **2** was synthesized from ketoprofen and *N*-1-benzotriazole carboxylic acid chloride (**1**) according to the procedure published previously.[16]

*Ketoprofen amides (**3a**-**h**)*

Method A (amides **3a**-**c**): The appropriate amine (0.0113 mol) dissolved in 5 ml toluene was added dropwise to a solution of **2** (0.817 g, 0.0023 mol) in toluene (10 ml). After 15 min (**3a**,**3c**) or 24 h (**3b**), reaction mixture was extracted 4 times with water. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to give the corresponding amide **3**. Products **3a** and **3c** were analytically pure while **3b** was additionally purified by column chromatography (mobile phase cyclohexane/ethyl acetate 1:3).

Method B (amide **3d**): A solution of **2** (0.817 g, 0.0023 mol) in 20 ml toluene was added dropwise to a solution of 2-aminoethylamine (6.760 g, 0.1125 mol) in toluene (50 ml). After 45 min, reaction mixture was extracted 5 times with water. Aqueous layers were collected and extracted 5 times with dichloromethane. Organic extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure to give amide **3d**. Crude product was purified by column chromatography using dichloromethane/methanol 1:1 as a mobile phase.

Method C (amide **3e**): To a solution of β-alanine (0.205 g, 0.0023 mol) and TEA (0.465 g, 0.0046 mol) in water/acetone mixture (2 ml + 1 ml), a solution of **2** (0.817 g, 0.0023 mol) in acetone (7 ml) was added dropwise. 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 and extracted 3 times with dichloromethane. The organic layer was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The analytically pure sample **3e** was obtained by column chromatography with ethyl acetate as a mobile phase (elution of benzotriazole) and ethyl acetate/methanol 1:1 mixture (elution of the product).

Method D (amides **3f-h**): A solution of **2** (0.817 g, 0.0023 mol) in acetonitrile (10 ml) was added dropwise to a cold mixture of the appropriate hydroxylamine (0.0113 mol) in acetonitrile (5 ml). The reaction mixture was stirred for 30–45 min at 10 °C and evaporated under reduced pressure. The residue was dissolved in dichloromethane and extracted 3 times with water. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The analytically pure samples **3f-h** were obtained by triturating with petrolether/cyclohexane 1:1 and column chromatography with ethyl acetate/methanol 1:1 mobile phase, respectively.

Acknowledgement. – This work was supported by Grant 0006543 of the Ministry of Science and Technology of the Republic of Croatia.

REFERENCES

1. W. O. Foye, T. L. Lemke, and D. A. Williams, *Nonsteroidal Anti-inflammatory Drugs*, in: *Principles of Medicinal Chemistry*, 4th Ed., Lippincott Williams & Wilkins, Philadelphia, 1995, p 562.
2. T. L. Ke, G. Graff, J. M. Spellman, and J. M. Yanni, *Inflammation* **24** (2000) 371–384.
3. P. N. Kourounakis, K. Tsiakitzis, A. P. Kourounakis, and D. Galanakis, *Toxicology* **144** (2000) 205–210.
4. V. R. Shanbhag, A. M. Crider, R. Gokhale, A. Harpalani, and R. M. Dick, *J. Pharm. Sci.* **81** (1992) 149–154.
5. P. Singh, L. L. Hingorani and G. K. Trivedi, *Indian J. Chem., Sect. B* **29** (1990) 551–555.
6. S. S. Dhaneshwar and S. C. Chaturvedi, *Indian Drugs* **31** (1994) 374–377.
7. R. G. W. Spickett, A. V. Noverola, and J. P. Soto, Brit. 1,436,502, 19 May 1976, Spain. Appl. 419,319, 04 Oct 1973; ref. *Chem. Abstr.* **86** (1977) 43691u.
8. L. Lafon, Belg. Pat. 853,321,07, Oct 1977; Brit. Appl. 76/14,395, 08 Apr 1976; ref. *Chem. Abstr.* **88** (1978) 190403w.
9. E. J. F. Franssen, F. Moolenaar, D. Dezeeuw, and D. K. F. Meijer, *Advan. Drug Deliv. Rev.* **14** (1994) 67–88.
10. A. S. Kalgutkar, B. C. Crews, S. W. Rowlinson, A. B. Marnett, K. R. Kozak, R. P. Remmel, and L. J. Marnett, *Proc. Natl. Acad. Sci. USA* **97** (2000) 925–930.
11. A. S. Kalgutkar, A. B. Marnett, B. C. Crews, R. P. Remmel, and L. J. Marnett, *J. Med. Chem.* **43** (2000) 2860–2870.
12. B. Blessington, N. Crabb, S. Karkee, and A. Northage, *J. Chromatogr.* **469** (1989) 183–190.
13. N. Blažević, M. Žinić, T. Kovač, V. Šunjić, and F. Kajfež, *Acta Pharm. Jugosl.* **23** (1975) 155–164.
14. A. Van Overbeke, W. Baeyens, and C. Dewaele, *J. Liq. Chromatogr.* **18** (1995) 2427–2443.
15. M. H. Hyun, J. J. Ryoo, Y. J. Cho, and J. S. Jin, *J. Chromatogr.* **692** (1995) 91–96.
16. B. Zorc, S. Antolić, and I. Butula, *Acta Pharm.* **43** (l993) 127–133.
17. I. Butula and M. Jadrijević-Mladar Takač, *Croat. Chem. Acta* **73** (2000) 569–574.

SAŽETAK

Novi amidi ketoprofena: priprava i spektroskopska karakterizacija

Marijana Zovko, Branka Zorc, Milena Jadrijević-Mladar Takač, Biserka Metelko i Predrag Novak

Opisana je priprava novih amida ketoprofena aminolizom benzotriazolida ketoprofena s primarnim i sekundarnim aminima, hidroksilaminima i β-alaninom. Pripravljeni spojevi karakterizirani su pomoću IR, ^1H i ^{13}C NMR spektroskopija i elementarne analize, a predstavljaju potencijalne prolijekove nesteroidnoga protuupalnoga lijeka ketoprofena.