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Macromolecular prodrugs. I. Synthesis of nonsteroidal anti-inflammatory drug esters

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A new method for the preparation of nonsteroidal anti-inflammatory drug esters (derivatives of ibuprofen, ketoprofen, diclofenac, and indomethacin) by means of 1-benzotriazole carboxylic acid chloride (BtcCl) is described. BtcCl reacts with the carboxylic functional group in the drugs forming reactive benzotriazolides. Reactions of the benzotriazolides with hydroxy compounds lead to the corresponding esters. Besides simple alcohols (methanol, ethanol), in esterification reactions, α,β-poly(N-hydroxyethyl)-*DL*-aspartamide (PHEA), a hydrosoluble polymer, previously proposed as plasma expander and a drug carrier, was used. Release of active substances from PHEA-ibuprofen, and PHEA-ketoprofen esters in alkaline medium was studied.

Key words: nonsteroidal anti-inflammatory drug esters, prodrugs, α,β-poly(N-hydroxyethyl)-*DL*-aspartamide, hydrolysis

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally accepted as the first drugs of choice in rheumatic diseases therapy. Their main disadvantages are the relatively short plasma half-lifes and irritation of gastro-enteric mucosa after oral administration, which can lead to ulcer formation (1 – 3). For these reasons, there has been interest in developing prodrug derivatives, biological precursors metabolized to the active compound by hydrolysis or other functionalization reactions. Carboxylic functional group present in NSAIDs offers a number of possibilities for derivative formation and is potentially interesting for the prodrug approach. Ester derivatives should be considered first, since they readily undergo chemical and enzymatic hydrolysis, thus releasing active substances. A variety of ester prodrugs of NSAIDs have been prepared and tested for their analgesic/anti-inflammatory activity and gastrointestinal toxicity (see for example refs. 4 – 8). Several NSAIDs are also covalently bound by ester linkages to a natural or synthetic polymeric matrix, such as dextran (9, 10), α,β-poly(N-hydroxyethyl)-*DL*-aspartamide (PHEA) (11 – 13), and hydroxypropyl cellulose (14). PHEA is a specially interesting and promising drug carrier since it is hydrophilic, nontoxic, nonantigenic and biodegradable when exposed to a complex set of enzymes (11).

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In this paper, we report the ester preparation of ibuprofen [α-methyl-4-(2-methylpropyl)benzeneacetic acid], ketoprofen [3-benzoyl-α-methylbenzeneacetic acid], diclofenac {2-[(2,6-dichlorophenyl)amino]benzeneacetic acid}, and indomethacin [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid] and their binding to PHEA.

EXPERIMENTAL

Melting points are uncorrected. IR- and UV-spectra were recorded on a Perkin-Elmer 457 and a Pye Unicam SP–100 spectrometers, respectively. For thin-layer chromatography, silica gel sheets, Kieselgel 60 F_{254} Merck were used. Solvent systems were ethylacetate/n-heptane 7:3, chloroform/methanol 9:1, and ethylacetate/toluene 2:8. Column chromatography was performed on silica gel 0.063 – 0.200 mm. Ketoprofen was purchased from Lek (Ljubljana), ibuprofen from Belupo (Koprivnica), diclofenac from Pliva (Zagreb), indomethacin and 1,1'-carbonyl-diimidazole (CDI) from Sigma (St. Louis). All solvents were of analytical grade quality and were dried and distilled prior to use.

1-Benzotriazole carboxylic acid chloride (BtcCl) (1). – It was synthesized from benzotriazole and phosgene (15).

*α,β-Poly(N-hydroxyethyl-*DL*-aspartamide (PHEA).* – It was prepared as described earlier (16).

Benzotriazolides ***2a – d****. General procedure.* – 0.91 g (0.005 mol) 1-benzotriazole carboxylic acid chloride (1) in 15 mL toluene was added dropwise to a solution of 0.005 mol of drug (ibuprofen, ketoprofen, diclofenac or indomethacin) and 0.51 g (0.005 mol) triethylamine in 15 mL toluene. The reaction mixture was stirred for 2 hrs at room temperature and then extracted three times with water. The organic layer was dried over anhydrous sodium sulfate and evaporated. A mixture of ether/petrolether was added to the residue and the pure product **2a – d** was filtered off. Yields and analytical data are summarized in Table I.

Esters ***3a – d****. General procedure.* – A solution of 0.002 mol benzotriazolide **2a – d** and 0.81 g (0.008 mol) triethylamine in 10 mL alcohol was refluxed for 3 hrs.* The solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel column (the eluent for **3a** and **3c**: chloroform/methanol 9.5:0.5; the eluent for **3b** and **3d**: ethylacetate/n-heptane 7:3) or it was dissolved in 10 mL ethylacetate and extracted three times with a small amount of ice-cold 10% NaOH, washed several times with water, dried over anhydrous sodium sulfate and evaporated. Yields and analytical data are summarized in Table II.

*PHEA-drug esters (****4a – d****). General procedure.* – Method A: A solution of 1.00 g PHEA, 0.0021 mol benzotriazolide **2a – d**, and 1.41 g (0.014 mol) triethylamine in 30 mL DMF was left for three days at room temperature with occasional shaking. The solvent was evaporated in vacuo to a small volume and the polymeric product precipitated by adding acetone. The product was filtered off and washed several times with a small amount of acetone until benzotriazole was completely washed off (TLC control).

* Preparation of esters **3c** and **3d** was run under a nitrogen atmosphere in the presence of sodium dithionite.

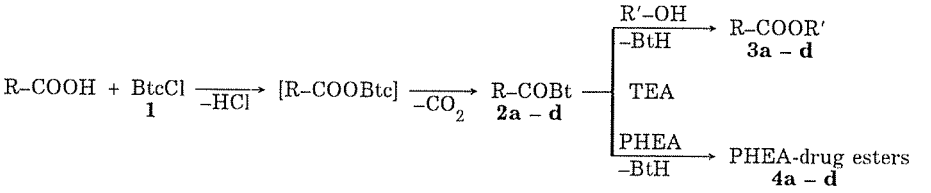
Method B: A solution of 0.50 g (0.003 mol) CDI in 3 mL DMF was added dropwise at 0 °C to a solution of 0.0022 mol of drug dissolved in 30 mL DMF. The reaction mixture was stirred at 0 °C for 30 min. and then a solution of 1.00 g PHEA in 30 mL DMF was added dropwise. The reaction mixture was stirred 20 min. at 0 °C and then maintained at room temperature for three days with occasional shaking. The isolation of products **4a** – **d** was the same as in method A. Yields and spectral data of products **4a** – **d** are summarized in Table III.

Release of drugs from PHEA-ibuprofen (4a) and PHEA-ketoprofen (4b) at pH 11. – A solution of adduct **4a** (γ = 1.71 mg mL^{-1}) or adduct **4b** (γ = 24.94 mg mL^{-1}) in 5×10^{-2} mol L^{-1} NaOH in a well stoppered silica cell was thermostated at 37 ± 0.1 °C. The drug release from adduct by hydrolysis was measured by UV-spectrometry (264 nm and 260 nm, respectively) at appropriate time intervals. Rate constants were computed using a nonlinear least-square fitting program.

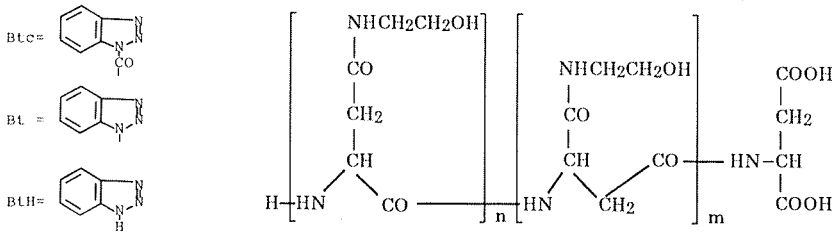
RESULTS AND DISCUSSION

A new method for the preparation of NSAIDs esters has been developed (Scheme 1). In the first step, the starting acidic NSAIDs (ibuprofen, ketoprofen, diclofenac, and indomethacin) react with 1-benzotriazole carboxylic acid chloride (**1**) forming N-acyl benzotriazoles, the so-called benzotriazolides **2a** – **d**. The structures of compounds **2a** – **d** are confirmed by elemental analysis and IR-spectroscopy (Table I). The IR-spectra show a carbonyl band between 1745 and 1720 cm^{-1}, which is characteristic of reactive N-acyl azoles (17, 18). If alcohols are used as nucleophiles in the reaction with benzotriazolides, the corresponding esters are formed. The reaction is accelerated with triethylamine (TEA). The list of synthesized esters **3a** – **d** and their spectral characteristics are given in Table II. Benzotriazolides also react with the polyhydroxy polymer PHEA. The products of these reactions, PHEA-drug esters (adducts) **4a** – **d** are shown in Table III. Polymer esters **4c** and **4d** are also prepared via 1,1'-carbonyldiimidazole (CDI) (11). The existence of an ester bond in PHEA-drug adducts is confirmed by IR- and UV-spectroscopy. The IR-spectra of adducts **4a** – **d**, besides absorption bands characteristic of hydroxyl, amide I and amide II, exhibited an ester carbonyl band at 1720 or 1750 cm^{-1}. Their UV-spectra show the absorptions in the range where PHEA itself does not absorb (the absence of free drugs is checked by TLC).

The drug loading in PHEA-drug esters depended on the applied molar ratio of the reactants **2a** – **d** and PHEA. The molar ratio allowing a substitution of approximately 33% of the available hydroxyl groups of PHEA was chosen. The content of ibuprofen and ketoprofen was determined by hydrolysis in alkaline medium. Polymeric ester **4a** contained 28% of ibuprofen and ester **4b** 30% of ketoprofen. The percentage of drugs in polymeric esters **4c** and **4d** was estimated by UV-absorption spectroscopy using the molar absorption coefficient for diclofenac methyl ester ε_{276} = 8644 in ethanol and for indomethacin ethyl ester ε_{318} = 1266 in ethanol. The load of diclofenac in **4c** was 12% (10%), and the amount of indomethacin in **4d** was 17% (20%).



TEA = triethylamine
PHEA = α,β-poly(N-hydroxyethyl)-*DL*-aspartamide



Scheme 1

*Table I. Benzotriazolides R—COBt (**2a — d**)*

Compds. **2a – d**	R	Yield (%)	M.p. (°C)	Molecular formula	Elemental analysis C H N calcd./found (%)			IR (KBr): ν_{max} (cm^{-1})
a	Ibu	76	56 – 59	$C_{19}H_{21}N_3O$ (307.40)	74.24 74.29	6.89 6.79	13.67 13.70	2960,1745,1385, 955,755
b	Ket	83	96 – 98	$C_{22}H_{17}N_3O_2$ (355.40)	74.35 74.29	4.82 4.97	11.82 11.99	1730,1660,1455, 1385,1325,1290, 970,950,755,720
c	Dic	85	162 – 164	$C_{20}H_{14}Cl_2N_4O$ (397.27)	60.47 60.30	3.55 3.68	14.10 14.35	3335,1720,1595, 1455,1380,1000, 750
d	Ind	86	105 – 107	$C_{25}H_{19}ClN_4O_3$ (458.90)	65.43 65.64	4.17 4.15	12.21 12.25	2940,1735,1680, 1480,1380,1330, 1220,980,750

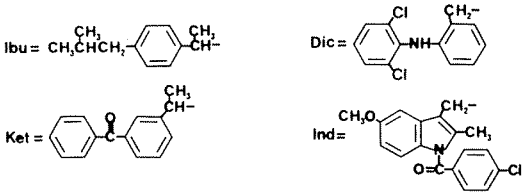


*Table II. Esters R—COOR' (**3a — d**)*

Compds. **3a – d**	R	R'	Yield (%)	M.p. (°C)	Lit. m. p. (°C)	IR (KBr or 100%): ν_{max} (cm^{-1})	UV: λ_{max} (nm)
a	Ibu	Me	100	oil	oil (19)	2960,1745,1460, 1210,1170,865,850	–
b	Ket	Et	89	oil	oil (20)	2980,1735,1660,1450, 1285,1180,725,710	255[a]
c	Dic	Me	95	101 – 102	101 – 102 (21)	3350,1740,1450,1295, 1145,785,750	276[b]
d	Ind	Et	94	96 – 97	96 – 98 (4)	2990,2920,1730,1675 1605,1465,1360,1325, 1235,1185,805,755	318[c]

Me = methyl, Et = ethyl
c (mol L^{-1}, EtOH): a = 10^{-5}, b = 4.5×10^{-5}, c = 2.2×10^{-4}.

*Table III. PHEA-drug esters (**4a — d**)*

Compound **4a – d**	R	Method	Yield (%)	Drug loading (%)	IR (KBr): ν_{max} (cm^{-1})	UV: λ_{max} (nm)
a	Ibu	A	65	28	3700–2700,1720,1655, 1535,1405,1170,1060	264[a]
b	Ket	A	70	30	3700–2500,1720,1655, 1535,1400,1065	257[b]
c	Dic	A	66	12	3700–2700,1720,1650,	278[c]
		B	65	10	1530,1050	
d	Ind	A	66	17	3700–2700,1750,1650,	277[d]
		B	68	20	1525	

γ(μg mL^{-1}, H_2O): a = 1990; b = 45; c = 366; d = 323.

Giammona *et al.* (13) described the release of drugs from PHEA-ibuprofen **4a** and PHEA-ketoprofen **4b** in simulated gastric juice. In the same publication, hydrolysis of adducts **4a** and **4b** in pH 10 buffer solution (H_3BO_3, KCl and 0.1 mol L^{-1} NaOH) was performed (70 °C, 20 hrs) in order to determine the drug loading. Since no kinetic measurements in alkaline medium were described, we studied the kinetics of the drug release from these adducts at pH 11. The results are presented in Figs. 1 and 2. The data fit (pseudo) first-order kinetics and the rate constants $k = 1.68 \times 10^{-2}$ min^{-1} ($t_{1/2}$ = 41.3 min.) for ibuprofen and $k = 9.32 \times 10^{-2}$ min^{-1} ($t_{1/2}$ = 7.4 min.) for ketoprofen were obtained, showing that the alkaline catalyzed hydrolysis proceeded very quickly.

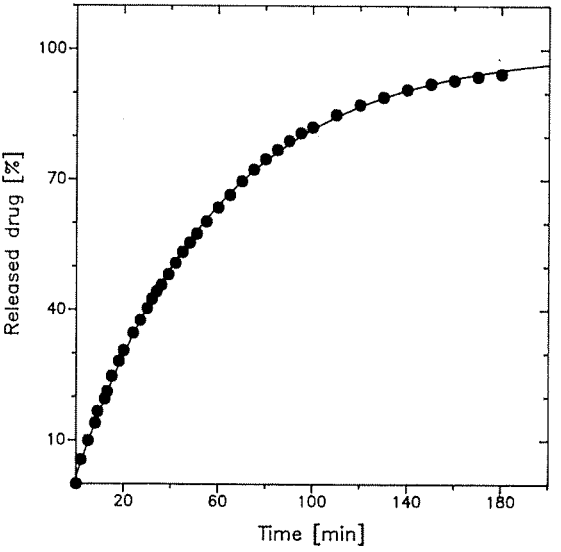


Fig. 1. Release of ibuprofen from ester **4a** in 5×10^{-2} mol L^{-1} NaOH at 37 ± 0.1 °C.

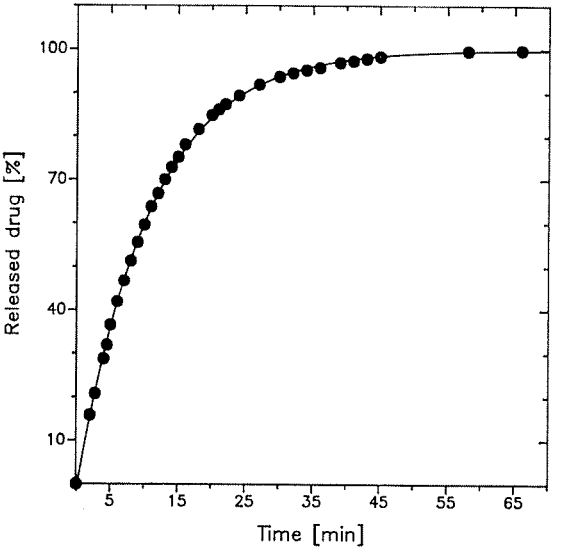


Fig. 2. Release of ketoprofen from ester **4b** in 5×10^{-2} mol L^{-1} NaOH at 37 ± 0.1 °C.

REFERENCES

1. A. L. Blower and C. P. Armstrong, *Br. J. Surg.* **74** (1987) 759.
2. K. D. Rainsford, *Agents Actions* **5** (1975) 326.

3. T. Y. Shen and C. H. Winter, in *Advances in Drug Research* (Eds. N. J. Harper and A. B. Simmonds), Academic Press, London 1977, Vol. 12, pp. 114–124.
4. L. Fišnerova, J. Grimova, V. Rabek, and Z. Roubal, *Česk. Farm.* **26** (1977) 227.
5. K. H. Boltze, O. Brendler, H. Jacobi, W. Opitz, S. Raddatz, P. R. Seidel, and D. Vollbrecht, *Arzneim.-Forsch.* **30** (1980) 1314.
6. V. R. Shanbhag, A. M. Crider, R. Gokhale, A. Harpalani, and R. M. Dick, *J. Pharm. Sci.* **81** (1992) 149.
7. M. W. Whitehouse and K. D. Rainsford, *J. Pharm. Pharmacol.* **32** (1980) 795.
8. H. Honda, S. Sato, K. Isomae, J. Ookawa, and T. Kuwamura, Ger. Offen. DE 3,407,806, 1984; ref. *Chem. Abstr.* **102** (1985) 78574j.
9. C. Larsen, *Int. J. Pharm.* **52** (1989) 55.
10. a) C. Larsen and M. Johansen, *Acta Pharm. Nord.* **1** (1989) 57; b) C. Larsen and B. H. Jensen, *ibid.* **3** (1991) 41, 71.
11. G. Giammona, B. Carlisi, and S. Palazzo, *J. Polym. Sci., Part A. Polym. Chem.* **25** (1987) 2813.
12. G. Giammona, G. Puglisi, B. Carlisi, R. Pignatello, A. Spadaro, and A. Caruso, *Int. J. Pharm.* **57** (1989) 55.
13. G. Giammona, B. Carlisi, G. Pitarresi, and G. Fontana, *J. Bioact. Compat. Polym.* **6** (1991) 129.
14. G. A. Meyer, R. T. Lostritto, and J. F. Johnson, *J. Appl. Polym. Sci.* **42** (1991) 2247.
15. I. Butula, M. V. Prošteník, and V. Vela, *Croat. Chem. Acta* **49** (1977) 837.
16. B. Zorc, M. Ljubić, S. Antolić, J. Filipović-Grčić, D. Maysinger, T. Alebić-Kolbah, and I. Jalšenjak, *Int. J. Pharm.*, in press.
17. a) H. A. Staab, *Chem. Ber.* **89** (1956) 1927; b) H. A. Staab, *ibid.* **90** (1957) 1320.
18. a) H. A. Staab, *Ann. Chem.* **609** (1957) 75, 83; b) H. A. Staab and G. Seel, *ibid.* **612** (1958) 187.
19. K. Ogura, S. Mitamura, K. Kishi, and G. Tsuchihashi, *Synthesis* **1979**, 880.
20. N. Blažević, M. Žinić, T. Kovač, V. Šunjić, and F. Kajfež, *Acta Pharm. Jugosl.* **25** (1975) 155.
21. J. R. Geigy, Neth. Appl. 6,604,752, 1966; ref. *Chem. Abstr.* **67** (1967) 81925p.

SAŽETAK

Makromolekularni prolijekovi. I. Sinteza estera nesteroidnih protuupalnih lijekova

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Opisana je nova metoda priprave estera nesteroidnih protuupalnih lijekova iz skupine karboksilnih kiselina (ibuprofen, ketoprofen, diklofenak i indometacin) upotrebom klorida 1-benzotriazol karboksilne kiseline (BtcCl). BtcCl reagira s ovim kiselinama tvoreći benzotriazolide koji s hidroksi spojevima daju odgovarajuće estere. Osim jednostavnih alkohola (metanol, etanol) za esterifikaciju je upotrebljen i α,β-poli(N-hidroksietil)-*DL*-aspartamid (PHEA), vodotopljivi polimer ranije predložen kao plazma ekspander i makromolekularni nosač lijekova. Proučavana je kinetika otpuštanja farmakološki aktivne supstancije iz PHEA-ibuprofen i PHEA-ketoprofen estera u lužnatom mediju.

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