AMIDES OF 4,4-BIS(4-ETHYLPHENYL)-2,3-DIBROMO-*cis*-2-BUTENOIC ACID*

Jiří HARTL[a], Jaroslava CHOCHOLOUŠOVÁ[a] and † Miroslav SEMONSKÝ[b]

[a] *Faculty of Pharmacy, Charles University, 501 65 Hradec Králové and*
[b] *Research Institute for Pharmacy and Biochemistry, 130 00 Prague 3*

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Amides of 4,4-bis(4-ethylphenyl)-2,3-dibromo-*cis*-2-butenoic acid (*III*—*LI*) have been synthetized and administered to animals with experimental tumours. Their antineoplastic effects did not exceed that of the acid *I*. However, some of the compounds exhibited a more or less selective effect in animals with certain transplantable tumours.

The paper deals with syntheses of amides of 4,4-bis(4-ethylphenyl)-2,3-dibromo--*cis*-2-butenoic acid, *III* – *LI* (Table I), and advances preliminary therapeutic results with some of these compounds, administered to animals with transplanted tumours.

4,4-Bis(4-ethylphenyl)-2,3-dibromo-*cis*-2-butenoic acid (*I*) has been selected for a detailed biological study out of a series of 4,4-diaryl-2,3-dihalogeno-*cis*-2-butenoic acids[1]. In view of the earlier promising results[2] and in an attempt to obtain compounds with a greater, preferably selective, affinity to the tumour tissue we have prepared some of its amides. Selective action was expected mainly with some esters of amino acids and with ethyl ester of glycylglycine or glycylglycylglycine N-acylated by the acid *I* (*cf.* the analogous selectivity of certain esters of N-(β-4-alkoxybenzoyl--β-bromo-2-propeonyl)amino acids[3], see also ref.[4]).

The amides *III* – *LI* were prepared by condensing chloride of 4,4-bis(4-ethylphenyl -2,3-dibromo-*cis*-2-butenoic acid (*II*) with at least two equivalents of the corresponding base (an amine, heterocyclic nitrogenous base or ester of an amino acid) at 0 – 5°C in dichloromethane (method *A*). The amides *XLVIII* and *IL* were prepared in an indifferent medium of N,N-dimethylformamide. The crude amides, obtained generally in good yields, were isolated chromatographically on a column of silica gel and purified, usually by crystallization from a suitable organic solvent. Some physico–chemical data of the compounds *III* – *LI* are listed in Table I. In condensing the chloride *II* with scarce amines, such as an ester of an optically active amino acid, we used only equimolar amounts of this basic component and triethylamine to bind the liberated hydrogen chloride; the yields were much lower in these cases. The chloride *II*

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was obtained by reaction of the acid *I* with approximately the stechiometric amount of thionyl chloride in dichloromethane at about 40°C, N,N-dimethylformamide being used as catalyst.

The amide *XXXIII* was also prepared by condensation of the acid *I* with ethyl ester of glycine in dichloromethane, N,N'-dicyclohexylcarbodiimide being used (method *B*). Analogously, using N,N'-carbonyldiimidazole, condensation of the acid *I* and ethyl ester of glycylglycylglycine in N,N-dimethylformamide gave the amide *IL* (method *C*).

The structures of amides *III – LI* are consistent with their infrared spectra (Table II) and, in the case of amides *III*, *IV*, *XVI*, *XXVIII* and *XXXIII*, also with their ^{1}H-NMR spectra (Table III).

Using the method described previously[5], the prepared compounds were preliminarily tested for a possible therapeutic effect on animals with transplanted tumours. Some interesting results were observed. Compound *IX* administered orally for 12 days, starting on the third day after the transplantation in a daily dose of 100 mg/kg, inhibited growth of sarcoma 37 (tumour S 37) in mice of strain H by 23%. The time length of survival, however, practically did not differ from that of a control group of non-treated mice. Compound *IX*, tested in the same way on strain H mice with the Krebs carcinoma (tumour Kr 2) or mammary adenocarcinoma (tumour HK), had practically no effect whatever. Similarly, administration of compounds *XXXIX* and L, 20 mg/kg *s.c.* daily, to strain H mice with sarcoma 37 (Tumour S 37) reduced the size of the tumour by 21% and 18%, respectively, in either case without any effect on the length of life. With tumours Kr 2 and HK the two compounds had practically no effect either.

Compounds *IL* and *XLV*, administered to H-strain mice with mammary adenocarcinoma (tumour HK) in the same way and dosage as compound *IX* to the mice with the S 37 tumour, inhibited the tumour growth by 11% and 18% respectively, and prolonged the lives of the mice by 19% and 26%. Again, the two compounds had practically no effect on H-strain mice with sarcoma S 37 (tumour S 37) and the Krebs carcinoma (tumour Kr 2). Compound *XXII*, administered orally in a daily dose of 100 mg/kg *s.c.*, and compound *XXXII*, 20 mg/kg *s.c.*, to H-strain mice with the Krebs carcinoma (tumour Kr 2), inhibited the tumour growth by 19% and 24% respectively, in either case without a significant effect on the life length of the treated animals. To conclude it can be stated that none of the amides *III – LI* attained the antineoplastic effect of the acid *I*. Some of them, however, depending on the nature of the amine residue, differed in their effect on animals with certain types of tumours.

$$(4\text{-}C_2H_5\text{—}C_6H_4)_2CH\text{—}CBr{=}CBr\text{—}CO\text{—}R$$

TABLE I

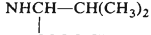
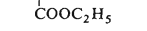
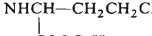
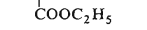
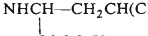
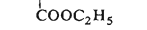
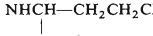
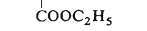
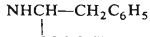
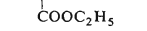
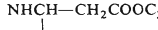
Amides of 4,4-bis(4-Ethylphenyl)-2,3-dibromo-*cis*-2-butenoic Acid (for formula see appendix 1)

Compound	R	Yield, %	M.p., °C, and n_D^{20} (solvent)	Formula (mol.mass)	Calculated/Found			
					% C	% H	% Br	% N
III	NH_2	56	137–138 (hexane)	$C_{20}H_{21}Br_2NO$ (451·2)	53·24 53·36	4·69 4·88	35·42 35·76	3·10 3·31
IV	$NHCH_3$	80	111–113 (cyclohexane)	$C_{21}H_{23}Br_2NO$ (465·2)	54·22 54·40	4·98 5·13	34·36 34·00	3·00 3·12
V	$N(CH_3)_2$	85	87–89 (hexane)	$C_{22}H_{25}Br_2NO$ (479·2)	55·14 54·94	5·25 5·28	33·35 33·46	2·92 2·66
VI	NHC_2H_5	47	125–128 (acetone–hexane)	$C_{22}H_{25}Br_2NO$ (479·2)	55·14 55·18	5·25 5·31	33·35 33·51	2·92 2·97
VII	$N(C_2H_5)_2$	71	46–48 (ethanol–water)	$C_{24}H_{29}Br_2NO$ (507·3)	56·82 57·11	5·76 5·71	31·51 31·75	2·76 2·72
VIII	$NH{-}C_3H_7{-}n$	52	107–109 (cyclohexane)	$C_{23}H_{27}Br_2NO$ (493·3)	56·00 56·05	5·52 5·71	32·39 32·12	2·84 2·61
IX	$NH{-}CH_2CH{=}CH_2$	97	99–101 (acetone–hexane)	$C_{23}H_{25}Br_2NO$ (491·3)	56·23 56·26	5·13 5·17	32·53 32·66	2·85 2·81
X	$NH{-}C_4H_9{-}n$	65	91–93 (cyclohexane)	$C_{24}H_{29}Br_2NO$ (507·3)	56·82 56·84	5·76 5·88	31·51 31·36	2·76 2·60
XI	$NH{-}C_5H_{11}{-}n$	48	96–98 (cyclohexane–hexane)	$C_{25}H_{31}Br_2NO$ (521·3)	57·60 57·72	5·99 6·14	30·66 30·81	2·69 2·73
XII	$NH{-}CH{-}CH_2{-}CH_2$	49	127–129 (n-heptane)	$C_{23}H_{25}Br_2NO$ (491·3)	56·23 56·15	5·13 5·13	32·53 32·62	2·85 2·87
XIII	$NH{-}CH{-}(CH_2)_3{-}CH_2$	50	132–135 (cyclohexane)	$C_{25}H_{29}Br_2NO$ (519·3)	57·82 57·74	5·63 5·77	30·77 30·29	2·70 2·61
XIV	$NH{-}CH{-}(CH_2)_4{-}CH_2$	65	111–113 (cyclohexane)	$C_{26}H_{31}Br_2NO$ (553·4)	58·55 58·53	5·86 5·86	29·97 30·37	2·63 2·90
XV	$NH{-}CH{-}(CH_2)_5{-}CH_2$	85	107–109 (heptane)	$C_{27}H_{33}Br_2NO$ (547·4)	59·25 59·50	6·08 6·13	29·20 29·59	2·56 2·38

XVI	NH—C_6H_5	69	130–132 (cyclohexane)	$C_{26}H_{25}Br_2NO$ (527·3)	59·22 59·41	4·77 4·84	30·31 29·89	2·66 2·70
XVII	NH—CH_2—C_6H_5	40	99–101 (hexane)	$C_{27}H_{27}Br_2NO$ (541·3)	59·91 60·15	5·02 5·17	29·52 29·31	2·59 2·42
XVIII	NH—C_6H_4—CH_3—3	72	103–105 (cyclohexane)	$C_{27}H_{27}Br_2NO$ (541·3)	59·91 60·02	5·02 5·18	29·52 29·10	2·99 2·38
XIX	NH—C_6H_4—CH_3—4	83	47–49 (cyclohexane)	$C_{27}H_{27}Br_2NO$ (541·3)	59·91 60·16	5·02 5·20	29·52 29·57	2·59 2·34
XX	NH—C_6H_4—OCH_3—2	80	90–92 (hexane)	$C_{27}H_{27}Br_2NO_2$ (557·4)	58·19 58·04	4·88 4·92	28·67 28·79	2·51 2·66
XXI	NH—C_6H_4—OCH_3—3	88	93–94 (hexane)	$C_{27}H_{27}Br_2NO_2$ (557·4)	58·19 58·18	4·88 4·79	28·67 28·81	2·51 2·45
XXII	NH—C_6H_4—OCH_3—4	85	61–64 (cyclohexane)	$C_{27}H_{27}Br_2NO_2$ (557·4)	58·19 58·08	4·88 5·01	28·67 28·49	2·51 2·56
XXIII	NH—C_6H_4—Cl—2	91	96–98 (light petroleum)	$C_{26}H_{24}Br_2ClNO$ (561·8)	55·59 55·60	4·31 4·27	28·47 28·33	2·50 2·59
XXIV	NH—C_6H_4—Cl—3	86	149–151 (cyclohexane)	$C_{26}H_{24}Br_2ClNO$ (561·8)	55·59 55·71	4·31 4·33	28·47 28·35	2·50 2·47
XXV	NH—C_6H_4—Cl—4	88	127–130 (acetone–light petroleum)	$C_{26}H_{24}Br_2ClNO$ (561·8)	55·59 55·42	4·31 4·32	28·47 28·61	2·50 2·44
XXVI	NH—$C_6H_3(CH_3)_2$—2,6	49	105–107 (cyclohexane–hexane)	$C_{28}H_{29}Br_2NO$ (555·4)	60·54 60·62	5·26 5·25	28·78 28·95	2·52 2·55
XXVII	N—$(CH_2)_3$—CH_2	55	134–136 (cyclohexane)	$C_{24}H_{27}Br_2NO$ (505·3)	57·05 57·14	5·38 5·38	31·63 31·86	2·77 3·08
XXVIII	N—$(CH_2)_4$—CH_2	79	101–103 (cyclohexane)	$C_{25}H_{29}Br_2NO$ (519·3)	57·82 58·06	5·62 5·77	30·77 30·92	2·69 2·72
XXIX	N—$(CH_2)_5$—CH_2	75	78–79 (methanol)	$C_{26}H_{31}Br_2NO$ (533·4)	58·55 58·46	5·86 5·97	29·96 29·81	2·62 2·62
XXX	N—$(CH_2)_2$—O—CH_2—CH_2	75	102–104 (cyclohexane–hexane)	$C_{24}H_{27}Br_2NO$ (521·3)	55·30 55·34	5·22 5·05	30·66 30·42	2·68 2·51
XXXI	N—$(CH_2)_2$—N(CH_3)—CH_2—CH_2	45	105–107 (methanol–water)	$C_{25}H_{30}Br_2N_2O$ (534·4)	56·19 56·22	5·66 5·64	29·91 30·11	5·24 5·29

TABLE I
(*Continued*)

Compound	R	Yield, %	M.p., °C, and n_D^{20} (solvent)	Formula (mol.mass)	Calculated/Found			
					% C	% H	% Br	% N
XXXII	$NH-CH_2COOCH_3$	76	108–110 (acetone–hexane)	$C_{23}H_{25}Br_2NO_3$ (523·3)	52·79 52·57	4·82 4·89	30·54 30·31	2·67 2·64
XXXIII	$NHCH_2COOC_2H_5$	69	84–86 (cyclohexane)	$C_{24}H_{27}Br_2NO_3$ (537·3)	53·65 53·68	5·06 5·14	29·74 29·80	2·61 2·61
XXXIV	$NHCH_2COOC_3H_7$—n	84	65–67 (hexane)	$C_{25}H_{29}Br_2NO_3$ (551·3)	54·46 54·45	5·30 5·18	28·99 28·81	2·54 2·56
XXXV	$NHCH_2COOC_4H_9$—n	80	63–65 (hexane)	$C_{26}H_{31}Br_2NO_3$ (565·4)	55·24 55·25	5·53 5·57	28·27 28·11	2·48 2·39
XXXVI[a]	$NHCH(CH_3)COOC_2H_5$ L	63	71–73 (hexane)	$C_{25}H_{29}Br_2NO_3$ (551·3)	54·46 54·17	5·30 5·41	28·99 29·15	2·54 2·80
XXXVII	$NHCH(CH_3)COOC_2H_5$ DL	55	93–95 (ethanol–water)	$C_{25}H_{29}Br_2NO_3$ (551·3)	54·46 54·16	5·30 5·26	28·99 29·19	2·54 2·37
XXXVIII	$NHC(CH_3)_2COOC_2H_5$	64	68–70 (hexane)	$C_{26}H_{31}Br_2NO_3$ (565·4)	55·24 55·12	5·53 5·77	28·27 28·41	2·48 2·44
XXXIX[b]	N-(CH$_2$)$_2$-CH$_2$ L CH $COOC_2H_5$	67	65–67 (hexane)	$C_{27}H_{31}Br_2NO_3$ (577·4)	56·17 56·24	5·41 5·52	27·68 27·83	2·42 2·22
XL[c]	$NHCH(CH(CH_3)_2)COOC_2H_5$ L	68	1·5666 —	$C_{27}H_{33}Br_2NO_3$ (579·4)	55·97 55·84	5·74 5·80	— —	2·42 2·40

XLI	 D	52	1·5676 —	$C_{27}H_{33}Br_2NO_3$ (579·4)	55·97 56·17	5·74 5·92	— —	2·42 2·21
XLII	 DL	83	66—68 (hexane)	$C_{27}H_{33}BrNO_3$ (579·4)	55·97 56·10	5·74 5·70	27·58 27·78	2·42 2·64
XLIII	 DL	65	63—66 (hexane)	$C_{28}H_{35}Br_2NO_3$ (593·4)	56·67 56·93	5·94 6·12	26·93 26·81	2·36 2·20
XLIV[e]	 L	76	1·5592	$C_{28}H_{35}Br_2NO_3$ (593·4)	56·67 56·66	5·94 6·12	— —	2·36 2·30
XLV	 DL	51	80—83 (cyclohexane–hexane)	$C_{31}H_{33}Br_2NO_3$ (627·4)	59·34 59·50	5·30 5·39	25·47 25·83	2·23 2·17
XLVI[f]	 L	68	1·5636 —	$C_{28}H_{33}Br_2NO_5$ (623·4)	53·95 54·13	5·34 5·51	— —	2·25 2·29
XLVII	 L	80	1·5577 —	$C_{29}H_{35}Br_2NO_5$ (637·4)	54·65 54·55	5·53 5·64	— —	2·20 2·22
XLVIII		65	125—127 (ethanol–water)	$C_{26}H_{30}Br_2N_2O_4$ (594·4)	52·54 52·70	5·09 5·12	26·89 26·97	4·71 4·60
IL		88	139—141 (ethanol)	$C_{28}H_{33}Br_2N_3O_5$ (651·4)	51·63 51·60	5·11 5·04	24·53 24·67	6·45 6·51
L		63	72—75 (acetone–hexane)	$C_{28}H_{33}Br_2NO_3$ (591·4)	56·87 57·00	5·62 5·74	27·02 27·08	2·37 2·21
LI		77	88—90 (hexane)	$C_{29}H_{35}Br_2NO_3$ (605·4)	57·53 57·68	5·83 5·97	26·40 26·73	2·31 2·25

[a] $[\alpha]_D^{20}$ +6·7° (*c* 0·35); [b] $[\alpha]_D^{20}$ −19·6° (*c* 0·37); [c] $[\alpha]_D^{20}$ +6·5° (*c* 0·27); [d] $[\alpha]_D^{20}$ −10·4° (*c* 0·41); [e] $[\alpha]_D^{20}$ +1·8° (*c* 0·32); $[\alpha]_D^{20}$ −16·4° (*c* 0·43).

TABLE II

Stretching Vibrations of Functional Groups in the IR Spectra of Amides *III*—*LI* (peaks in cm^{-1})

Compound	C=O (amide)	NH (amide)	C=O (ester)
III	1 690	3 520, 3 410	
IV, VI, VIII—XV, XVII	1 655—1 660	3 420—3 450	
XVI	1 680	3 420	
XVIII—XXVI	1 665—1 670	3 380—3 410	
V, VII, XXVII—XXXI	1 620—1 640		
XXXIX	1 630		1 725
XXXII—XXXVIII, XL—LI	1 660—1 680	3 380—3 420	1 720—1 745

TABLE III

Chemical Shifts (in δ scale, ppm) and the Interaction Constants (Hz) in ^{1}H-NMR Spectra

Compound	CH_3CH_2—	CH_3CH_2—	Phenyl	=CH—	—NH_2
III	1·17 t(6 H) $J = 8·0$	2·60 q(4 H) $J = 8·0$	7·20 s(8 H)	6·14 s(1 H)	6·25 d(2 H)
IV[a]	1·20 t(6 H) $J = 8·0$	2·61 q(4 H) $J = 8·0$	7·20 s(8 H)	6·10 s(1 H)	—
XVI[b]	1·21 t(6 H) $J = 8·0$	2·65 q(4 H) $J = 8·0$	7·20—7·60 m (14 H)	6·01 s(1 H)	—
XXVIII[c]	1·20 t(6 H) $J = 8·0$	2·60 q(4 H) $J = 8·0$	7·16 m(8 H)	5·39 s(1 H)	
XXXIII[d]	1·21 t(6 H) $J = 8·0$	2·65 q(4 H) $J = 8·0$	7·20 s(8 H)	6·16 s(1 H)	—

[a] —NH— 6·10 (1 H) overlapped by =CH—, —$NHCH_3$ 2·83 d (3 H); [b] —NH— overlapped by the aromatic H; [c] —N—$(CH_2)_4$—CH_2 3·50 m (2 H) H_{eq}, 3·10 m (2 H) H_{ax}, 1·50 m (6 H); [d] —NH—6·62 t (1 H), $J = 5·0$ Hz, —CH_2COO— 4·04 d (2 H), $J = 5·0$ Hz, —$COOCH_2$— 4·20 q (2 H), $J = 7·0$ Hz, —$COOCH_2CH_3$ y,y 1·25 t (3 H), $J = 7·0$.

EXPERIMENTAL

The melting points, determined on the Kofler block, are not corrected. The samples for elemental analyses were dried *in vacuo* (10 Pa) over phosphorus pentoxide, at temperatures chosen with regard to their melting points. The crude products were purified on a column of silica gel, particle size 40—100 nm, the ratio of the adsorbent to the compound being 1 : 30. The purities of the compounds and the course of the column chromatography were checked by thin-layer chromatography on Silufol plates UV_{254}, impregnated with a 10% solution of formamide in acetone. The eluant was usually benzene or benzene–chloroform (9 : 1). With plates Lucefol Quick paraffin oil (5%) in benzene was used as the stationary phase and a methanol–water mixture (7 : 3) as the mobile phase. The spots on the plates were detected by fluorescence quenching, using UV light 254 nm, or by spraying them with a solution of mercury(II) acetate and diphenylcarbazone. The refraction indices were read on an Abbe refractometer (Zeiss, model G). The optical rotations were measured in methanol, using a polarimeter Perkin–Elmer 141. The IR spectra of the compounds were measured with a spectrophotometer Perkin–Elmer 577 in 5% chloroform solutions and a 0·1 mm NaCl cell. The ^{1}H-NMR spectra were determined with a spectrometer ZKR 60 (Zeiss), using 6% solutions of the compounds in deuterochloroform and tetramethylsilane as internal standard. The reaction components employed were practically anhydrous.

Chloride of 4,4-Bis(4-ethylphenyl)-2,3-dibromo-*cis*-2-butenoic Acid (*II*)

To a solution of the acid[6] *I* (9·0 g, 20 mmol) in dichloromethane (35 ml) was added N,N-dimethylformamide (0·2 ml), then excluding the aerial moisture, thionyl chloride (2·60 g, 22 mmol) was added dropwise. After 2 hours' boiling the dichloromethane was distilled off *in vacuo* (water aspirator) and 25 ml of benzene was added. The mixture was distilled again *in vacuo* to remove the remaining thionyl chloride. The residue was the chloride *II* used for the reaction.

Amides of 4,4-Bis(4-ethylphenyl)-2,3-dibromo-*cis*-2-butenoic Acid, *III*—*LI* (method A)

Forty mmol of a basic component, of 20 mmol of an amino acid ester and 20 mmol of triethylamine, in 35 ml of dichloromethane was treated with 20 mmol of the chloride *II*, added dropwise under stirring at such a rate that the temperature of the reaction mixture did not exceed +5°C. After 24 hours' standing at room temperature the hydrochloride of the basic component was collected on a filter and washed on the filter with a little portion of dichloromethane; the filtrate was shaken with two 20 ml portions of water. The dichloromethane solution was freed from water with magnesium sulphate and taken to dryness by evaporation *in vacuo* (water aspirator). After drying to constant weight the residue (an oil as a rule) was purified chromatographically (1%) of methanol. The products were crystallized from suitable solvents (see Table I). Compounds *XL*, *XLI*, *XLIV*, *XLVI* and *XLVII* obtained as oily liquids, were re-purified on a column of silica gel that had been freed from extractants by chloroform, also used as eluant. The yields and some physico-chemical properties of compounds *III*—*LI* are given in Table I.

Amide *XXXIII* (method *B*)

The acid *I* (2·26 g, 5 mmol), glycine ethyl ester (0·57 g, 5·5 mmol) and N,N′-dicyclohexylcarbodiimide (1·13 g, 5·5 mmol) were dissolved in 30 ml of dichloromethane and the solution was left standing at 10°C for 24 h. The separated N,N′-dicyclohexylurea was filtered off (1·5 g) and the filtrate was taken to dryness *in vacuo*. The residue was purified chromatographically, chloroform being used as eluant. The combined fractions gave 1·23 g (46)% of the amide *XXXIII*. After repeated crystallization from cyclohexane its m.p. was 84—85·5°C. On mixing with an authentic sample the m.p. was undepressed.

Amide *IL* (method *C*)

A solution of the compound *I* (0·45 g, 1 mmol) in N,N-dimethylformamide (5 ml) was treated with N,N'-carbonyldiimidazol (0·177 g, 1·1 mmol). After 2 hours standing at 20°C a solution of glycylglycylglycine ethyl ester (0·24 g, 1·1 mmol) in N,N-dimethylformamide (5 ml) was added and the mixture was left standing for 24 h at room temperature. The solvent was distilled off *in vacuo*. The residue was dried at 100°C *in vacuo* to constant weight and purified on a column of silica gel, chloroform with 1% of methanol being used as eluant. The combined fractions contained 0·30 g (46%) of a substance, which after repeated crystallization from ethanol melted at 138—141°C. The mixed m.p. with the same compound obtained by method *A* was undepressed.

The elemental analyses were performed by Mrs D. Karlíčková, the IR *spectra were determined by Mrs J. Žižková, both of the Faculty of Pharmacy, Charles University. The polarometric measurements were carried out by Mrs I. Bendová, the* ^{1}H-NMR *spectra were interpreted by Dr B. Kakáč and the antineoplastic effects were assessed by Dr K. Řežábek, all of the Research Institute for Pharmacy and Biochemistry.*

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