Synthesis and Evaluation of the Antitumor Properties of Esters of 2-Furoic Acid and 2-Furylacrylic Acid

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Abstract □ A series of activated and nonactivated esters of 2-furoic and 2-furylacrylic acids were synthesized and examined for antineoplastic activity in the Ehrlich ascites carcinoma screen at 20 mg/kg/d. 2-Furoic acid and 2-furylacrylic acid demonstrated potent activity, as did the methyl and cyanomethyl esters of each series. The vinyl ester of 2-furoic acid possessed antineoplastic activity. However, the ethyl and D,L-tetrahydropyranyl esters of each series were inactive in the tumor screen.

Keyphrases □ 2-Furoic acid—ester derivatives, synthesis, antitumor potential, Ehrlich ascites screen □ 2-Furylacrylic acid—ester derivatives, synthesis, antitumor potential, Ehrlich ascites screen

Activated esters such as vinyl, cyanomethyl, and dihaloethyl esters of amino acids have been shown to have antitumor properties in the Ehrlich ascites screen (1–4). Compounds containing furan moieties have similarly displayed antineoplastic activity (5). It was suggested by Cutting *et al.* (5) that the furan ring may compete for the pentoses in nucleotide synthesis. Such observations have stimulated interest in the synthesis and antineoplastic evaluation of several activated esters of 2-furoic and 2-furylacrylic acids. Reported at this time is the synthesis of vinyl, cyanomethyl, and pyranyl activated esters which were compared with similar nonactivated ethyl and methyl esters of 2-furoic acid and 2-furylacrylic acid for antineoplastic activity.

EXPERIMENTAL

Melting points were determined on an electro-thermal melting point apparatus and are uncorrected. IR spectra were determined in chloroform[1]. NMR spectra were determined in deuterochloroform[2], and chemical shifts are reported in ppm relative to internal tetramethylsilane. Silica gel G[3] was used for TLC, and compounds were visualized by charring with sulfuric acid. Silica gel (AR) CC, 200–325 mesh, was used for column chromatography[4]. 2-Furoic acid[4] (I), 3-furoic acid[4] (XIII), 2-furylacrylic acid[5] (VII), and 3,4-furandicarboxylic acid[4] (XIV) were purchased. Methyl 2-furoate (II), ethyl 2-furoate (III), methyl 2-furylacrylate (VIII), and ethyl 2-furylacrylate (IX) were prepared according to procedures described previously (6–11). Only NMR and IR data pertinent to structure determination are noted below for newly synthesized compounds.

Activated Esters of 2-Furoic Acids—*Vinyl 2-Furoate (IV)*—This compound was prepared by a modification of a procedure described by Weygand and Beryermann (12). To a solution of 1.20 g (10 mmol) of 2-furoic acid in 25 mL of vinyl acetate was added 20 mg of $PdCl_2$-NaCl. The solution was refluxed (70–75°C) for 5 h. After cooling and treating with 30 mg of activated charcoal, the resulting mixture was filtered and solvent was removed *in vacuo*. The residue was dissolved in 20 mg of vinyl acetate, 20 mg of $PdCl_2$-NaCl was added, and the entire procedure was repeated. Chromatography (chloroform) of the crude mixture gave 500 mg (40%) of a colorless oil. IR: 1755 (C=O str), 1648 (C=C str), and 900 cm^{-1} (C=C—H bend); ^{1}H-NMR: δ 4.70 (m, 2, CH_2).

Anal.—Calc. for $C_7H_6O_3$: C, 60.86; H, 4.34. Found: C, 60.90; H, 4.36.

Cyanomethyl 2-Furoate (V)—This material was prepared by treatment of the acid with chloroacetonitrile and triethylamine in ethyl acetate according to a procedure described by Morozova and Zhenodarova (13). The product was crystallized from ether–ligroine, to give ester V (35%), mp 30–31°C. IR: 1755 cm^{-1} (C=O str); ^{1}H-NMR: δ 4.4 (s, 2, OCH_2CN).

Anal.—Calc. for $C_7H_5NO_3$: C, 55.63; H, 3.31; N, 9.27. Found: C, 55.69; H, 3.34; N, 9.30.

Tetrahydropyranyl 2-Furoate (VI)—To a solution of 1.12 g (10 mmol) of 2-furoic acid in 30 mL of dry ether were added 50 mg of *p*-toluenesulfonic acid and 1.4 mL (20 mmol) 3,4-dihydropyran. The mixture was stirred at room temperature for ~4 h, filtered, and the filtrate was washed with 5% $NaHCO_3$ (3 × 5 mL) and water (3 × 5 mL) and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure, to give 400 mg (20%) of an oily product. Chromatography ($CHCl_3$–EtOH, 95:5) on silica gel gave 250 mg (13%) of a colorless oil. IR: 1755 cm^{-1} (C=O str); ^{1}H-NMR: δ 1.4–2.0 (m, 6, C-3,-4,-5 tetrahydropyranyl protons).

Anal.—Calc. for $C_{10}H_{12}O_4$: C, 61.22; H, 6.12. Found: C, 61.22; H, 6.12.

Activated Esters of 2-Furylacrylic Acid—The vinyl (X), cyanomethyl (XI), and tetrahydropyranyl esters (XII) were synthesized according to the same procedures described for the analogous 2-furoic acid derivatives.

Vinyl 2-Furylacrylate (X)—Yield of 30%; chromatography ($CHCl_3$) on silica gel gave an oil.

Anal.—Calc. for $C_9H_8O_3$: C, 65.85; H, 4.87. Found: C, 65.90; H, 4.91.

Cyanomethyl 2-Furylacrylate (XI)—mp 46°C; 40% yield (ether–ligroine). IR: 2080 (C≡N str) and 1740 cm^{-1} (C=O str).

Anal.—Calc. for $C_9H_7NO_3$: C, 61.02; H, 3.98; N, 7.91. Found: C, 60.86; H, 4.06; N, 7.85.

Tetrahydropyranyl 2-Furylacrylate (XII)—Yield of ~10%; column chromatography, Florisil (ether), gave a colorless oil.

Anal.—Calc. for $C_{12}H_{14}O_4$: C, 64.86; H, 6.30. Found: C, 65.98; H, 6.35.

Repeated attempts at obtaining correct elemental analyses for chromatographically pure XII were unsuccessful. The structure was confirmed by ^{1}H- and ^{13}C-NMR spectra. ^{13}C-NMR: δ 20, 25, 28, 65 (C_3, C_4, C_5 and C_6 of tetrahydropyranyl), 95 (C_2), 165 (ester carbonyl), 125, 135 (C=C), 140, 118, 112, and 145 (C_2, C_3, C_4, C_5 of furyl). ^{1}H-NMR: 5.72 (s, 1, O_2CH), 3.69 (m, 2, C-6 tetrahydropyranyl protons), and 1.15–1.8 ppm (m, 6, C-3,-4,-5 tetrahydropyranyl protons).

Pharmacological Studies—The compounds were tested for antitumor activity in the Ehrlich ascites carcinoma screen in CF_1 male mice using a procedure described by Piantadosi *et al.* (14), with certain modifications. Eight days after tumor transplantation, donor mice were sacrificed, and ascites fluid was collected and diluted with isotonic saline. An aliquot was placed in a hemocytometer chamber, and the number of cells per milliliter was calculated. Then, 10^6 cells were injected intraperitoneally into each test animal using an 18-gauge needle. 6-Mercaptopurine was used as internal standard in the test. The test drugs were homogenized in 0.05% polysorbate 80 and administered intraperitoneally at 20 mg/kg/d for 9 d. After 10 d, the inoculated mice were sacrificed, and the ascitic fluid was collected. The volume (mL) of the ascitic fluid was measured, and the total packed ascites cell volume for each group was measured utilizing nonheparinized capillary tubes centrifuged at 3000

[1] With a PYE-Unicam SP/100 grating spectrophotometer.
[2] With a Varian T 60A spectrometer or JEOL FX-60 spectrometer.
[3] Merck.
[4] Elemental analyses were performed by Dorni U. Kolbe, West Germany.
[5] Aldrich Chemical Co.

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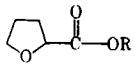
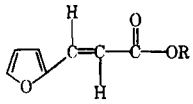
Table I—Antineoplastic Activity of 2-Furoic and 2-Furanacrylic Acids and Ester Derivatives in the Ehrlich Ascites Screen in CF_1 Male Mice at 20 mg/kg/d

Compound	R	mM/kg	Survival on Day 10	Ascrit (Packed Cell Volume), mL	Volume Ascites Fluid, mL	Inhibition, %
						
I	—H	0.179	6/6	41.6	0.77	89.7
II	$-CH_3$	0.158	2/6	2.0	0.25	99.7
III	$-CH_2CH_3$	0.144	6/6	39.7	3.70	52.9
IV	$CH{=}CH_2$	0.145	7/8	25.1	0.21	98.3
V	CH_2CN	0.132	7/8	44.0	0.50	85.7
VI		0.075	6/6	505.6	3.73	39.5
						
VII	—H	0.145	6/6	28.4	0.08	99.3
VIII	$-CH_3$	0.132	6/6	28.3	0.66	94.0
IX	$-CH_2CH_3$	0.121	6/6	43.5	3.05	57.5
X	$CH{=}CH_2$	0.122	6/6	39.0	2.03	74.6
XI	CH_2CN	0.113	4/6	36.3	0.58	93.2
XII		0.090	4/6	37.5	3.58	56.1
XIII	—H	0.179	5/6	40.5	2.81	72.7
XIV	—H	0.128	5/6	38.9	2.10	72.7
6-Mercaptopurine	—	—	6/6	0.70	0.30	99.9
0.05% Polysorbate 80	—	—	6/6	32.4	9.62	—

rpm for 3–5 min. The control (C) value for the volume of tumor was 9.62 ± 0.48 (*SD*) mL; the ascrit (total packed cell volume) was 32.4 ± 1.69 mL at day 10. Percent inhibition of tumor growth was calculated by the following formula for the treated animals (T):

$$\% \text{ inhibition} = 100 - \frac{\text{volume}_T \times \text{ascrit}_T}{\text{volume}_C \times \text{ascrit}_C} \times 100$$

Any compound that exhibited 80% inhibition of tumor growth was considered significantly active (Table I).

RESULTS AND DISCUSSION

The 2-furoic and 2-furylacrylic acid derivatives that demonstrated potent activity in the Ehrlich ascites screen at 20 mg/kg/d were I, II, IV, V, VII, VIII, XI, and the standard (6-mercaptopurine). In the 2-furoic acid series, the methyl ester (II) derivative demonstrated the most potent activity demonstrating 99.7% inhibition. The activated vinyl (IV) and cyanomethyl esters (V) were also active, *i.e.*, 98.3% and 85.7% inhibition, respectively. The methyl ester (VIII) of the furylacrylic acid series, as well as the cyanomethyl ester (XI), demonstrated potent activity, *i.e.*, 94.0% and 93.2% inhibition of Ehrlich ascites carcinoma growth, respectively. The ethyl and tetrahydropyranyl esters of both series of acids proved to be inactive as antineoplastic agents in the Ehrlich ascites screen. Movement of the acid side chain on the furan ring from the 2-position (XIII and XIV) resulted in compounds which were not active in the Ehrlich ascites screen. These results suggest that activated esters of 2-furoic acid and 2-furylacrylic acid were not as active as the nonactivated methyl ester, but were more active than the ethyl ester derivatives.

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