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Original article

Synthesis and structural characterization of derivatives of 2- and 3-benzo[b]furan carboxylic acids with potential cytotoxic activity

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Abstract

Derivatives of 2- and 3-benzo[b]furancarboxylic acids were prepared and evaluated for their cytotoxic potential in the National Cancer Institute, Bethesda, USA. Six compounds: 7-acetyl-6-hydroxy-3-methyl-2-benzofurancarboxylic acid (**2**), 6-hydroxy-7-(*p*-methoxycinnamoyl)-3-methyl-2-benzofurancarboxylic acid (**4**), 5-bromo-7-hydroxy-6-methoxy-2-benzofurancarboxylic acid methyl ester (**6a**), 6-acetyl-5-(*O*-ethyl-2′-diethylamino)-2-methyl-3-benzofurancarboxylic acid methyl ester (**1f**), 6-(*O*-ethyl-2′-diethylamino)-7-*p*-methoxycinnamoyl)-3-methyl-2-benzofurancarboxylic acid methyl ester hydrochloride (**4b**), 5-bromo-7-(*O*-ethyl-2′-diethylamino)-6-methoxy-2-benzofurancarboxylic acid methyl ester (**6b**) showed significant cytotoxic activities against human cancer cell lines. In addition the crystal structures of 7-methoxy-2-benzofurancarboxylic acid methyl ester (**7a**) has been solved by X-ray structure analysis of single crystals.

Keywords: 2-Benzofurancarboxylic acid; 3-Benzofurancarboxylic acid; Cytotoxic activity; Crystal structure of 7-methoxy-2-benzofurancarboxylic acid methyl ester

1. Introduction

It is widely known that numerous compounds containing the benzo[b]furan system, isolated from natural sources as well as synthetic, show cytostatic and/or cytotoxic activity. Cyclopenta[b]benzofuran lignans found in *Aglaia* showed broadly potent growth inhibitory activity with a panel of cultured cell lines (IC50 values of 1–30 ng ml^{-1}) [1–7]. Neolignans isolated from *Persea* species are cytotoxic to human cancer cell lines: mouth epidermoid carcinoma, lung adenocarcinoma and colon adenocarcinoma in vitro [8]. 2-Aryl and 2-aroyl benzofurans show varied biological activity as antibacterial, cytotoxic, antiproliferative and potential immunosuppressant agents [9–12]. Recently, it was proved that esters of substituted 2-benzofurancarboxylic acids showed selective cytotoxicity against human tumorigenic cell line VA13 (CCL-75.1) [13].

Inspired by these reports, in a continuation of our research in the field of synthesis of new, biologically active benzo[b]-furans [14] we have designed and prepared derivatives of 2- and 3-benzo[b]furancarboxylic acids **1–7** (Fig. 1) with the aim of finding new cytotoxic compounds. The acids **1–6** were synthesized according to previously published papers [15–22], however, neither ^{1}H NMR nor ^{13}C NMR spectra of the acids were reported earlier. Having in mind that the potential therapeutic application of the acids **1–7** is limited by their aqueous insolubility, we prepared appropriate, water-soluble ammonium salts. We also describe in details the synthesis of alkyl esters of the acids **1–7**, and *O*-ethyl-*N,N*-diethyl derivatives of the selected esters as well as their cytotoxicities in a variety of cancer cell cultures. To complete the structural characterization of benzofuran-derived compounds we report results of the X-ray crystallographic studies for methyl ester of 7-methoxy-2-benzofurancarboxylic acid (**7a**).

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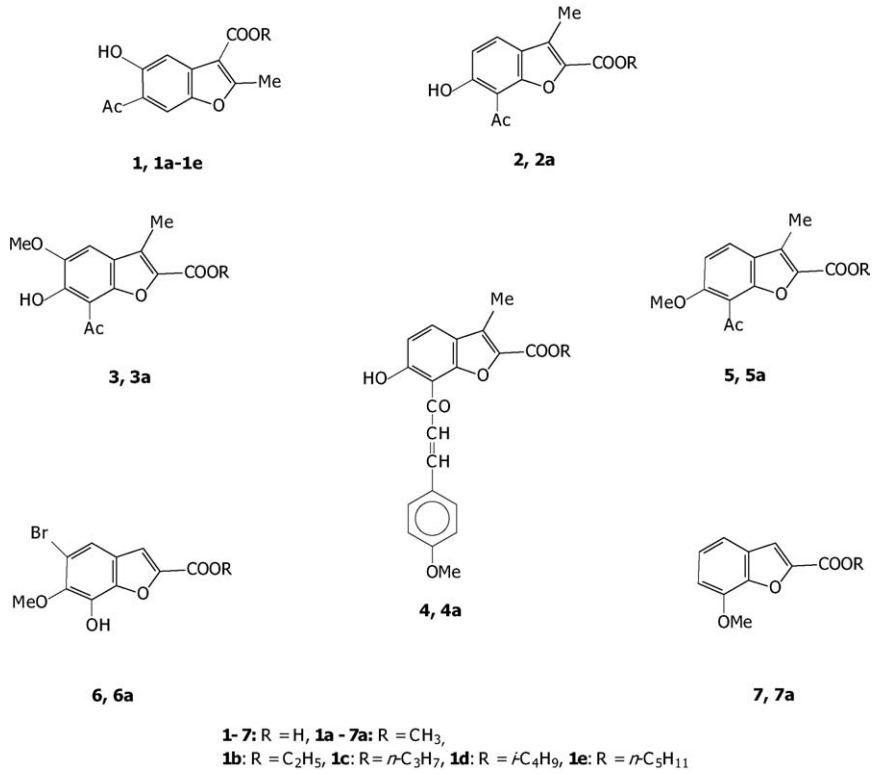
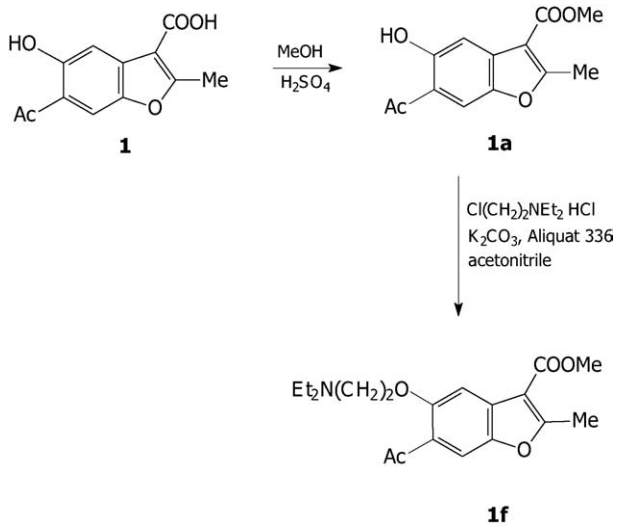


Fig. 1. 2- and 3-Benzofurancarboxylic acids and esters.

2. Results and discussion

2.1. Chemistry

The exemplary synthesis of 6-acetyl-5-(*O*-ethyl-2′-diethylamino)-2-methyl-3-benzofurancarboxylic acid methyl ester (**1f**) is presented in Scheme 1. The starting material was 6-acetyl-5-hydroxy-2-methyl-3-benzofurancarboxylic acid (**1**), which was esterified with methanol to protect the carboxylic group against *O*-alkylation, yielding the ester **1a**.



Scheme 1. An exemplary synthesis of the methyl ester **1a** and the O-aminoalkyl derivative **1f** of 6-acetyl-5-hydroxy-2-methyl-3-benzofurancarboxylic acid **1**.

6-acetyl-5-hydroxy-2-methyl-3-benzofurancarboxylic acid methyl ester (**1a**) was subjected to the reaction with 2-chloroethyl-*N,N*-diethylamine under phase transfer catalysis conditions. The reaction proceeded in acetone with Aliquat 336, in the presence of anhydrous potassium carbonate to give *O*-ethyl-2′-diethylamino derivative **1f**. The acids **2**–**7** were esterified under the same conditions. The esters **2a**, **3a**, **4a** and **6a** were *O*-alkylated in the same way as the compound **1a** to yield *O*-ethyl-2′-diethylamino derivatives **2b**, **3b**, **4b** and **6b**. Then, the more lipophilic esters of the acid **1**—ethyl **1b**, *n*-propyl **1c**, isobutyl **1d** and amyl **1e** were prepared for future biological evaluation. O-Alkylation of the phenolic function of the esters **1b** and **1c** under the same conditions as the methyl ester **1a** resulted in their *O*-diethylamino derivatives **1g** and **1h**. The compounds prepared according to the scheme are presented in Fig. 2.

Resulting *O*-ethyl-2-diethylamino derivatives of the esters (**1f, 1g, 1h, 2b, 3b, 4b, 6b**) were then converted to hydrochloride salts to improve water solubility and protect against decomposition.

2.2. Cytotoxicity against cancer cell lines

6-Acetyl-5-hydroxy-2-methyl-3-benzofurancarboxylic acid (**1**), the methyl ester **1a** and *O*-ethyl-2′-diethylamino derivative **1f**; 7-acetyl-6-hydroxy-3-methyl-2-benzofurancarboxylic acid (**2**), the methyl ester **2a** and *O*-ethyl-2′-diethylamino derivative **2b**; 7-acetyl-6-hydroxy-5-methoxy-3-methyl-2-benzofurancarboxylic acid (**3**), the methyl ester **3a** and *O*-ethyl-2′-diethylamino derivative **3b**; 6-hydroxy-7-

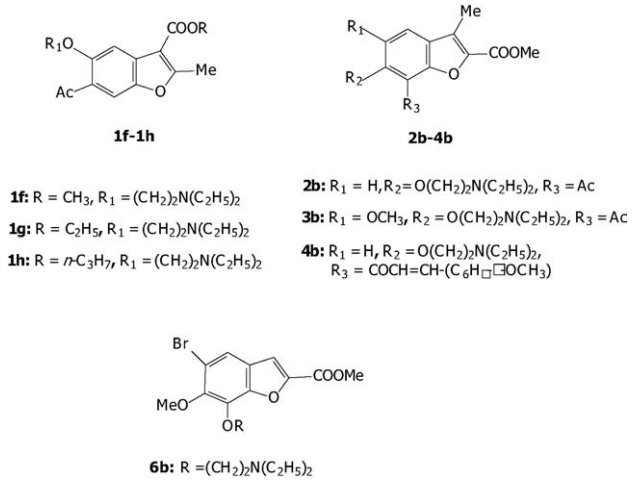


Fig. 2. *O*-Aminoalkyl derivatives of 2- and 3-benzofurancarboxylic acids esters.

(*p*-methoxycinnamoyl)-3-methyl-2-benzofurancarboxylic acid (**4**), the methyl ester **4a** and *O*-ethyl-2′-diethylamino derivative **4b**; 7-acetyl-6-methoxy-3-methyl-2-benzofurancarboxylic acid (**5**), the methyl ester **5a**; 5-bromo-7-hydroxy-6-methoxy-2-benzofurancarboxylic acid (**6**) the methyl ester **6a** and *O*-ethyl-2′-diethylamino derivative **6b**; and the methyl ester of 7-methoxy-2-benzofurancarboxylic acid (**7a)** were submitted for cytotoxicity testing in the National Cancer Institute 's in vitro drug discovery screen. Initially they had been evaluated in the three-cell line panel consisting of the MCF-7 (Breast), NCI-H460 (Lung) and SF-268 (CNS).

Compounds **1**, **1a**, **2a**, **2b**, **3**, **3a**, **3b**, **4a**, **5**, **5a**, **6**, **7a** were considered inactive in the primary screen. The acids **2** and **4,** the ester **6a** and *O*-ethyl-2′-diethylamino derivatives **1f, 4b** and **6b** were relatively potent in the screens. They were passed on for evaluation in the full panel of 60 different cell lines, representing human leukemia, non-small cell lung cancer, colon cancer, central nervous system (CNS) cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer cell lines. Results from representative cell lines are listed in Table 1, along with mean graph midpoint (MGM) values for all 60 lines.

The results show that 7-substituted 6-hydroxy-3-methyl-2-benzofurancarboxylic acid system possesses some cytotoxic activity (see the acids **2** and **4**). The cytotoxicity testing results for compounds **6a**, **1f**, **4b** and **6b** demonstrate the importance of substitutions on both carboxyl and phenolic moieties. Esterification of the carboxylic group in the acid **6** followed by the *O*-aminoalkylation of the phenolic moiety led to significant increase of the cytotoxicity. Considering the derivatives **4b** and **6b**, the introduction of ethyl-2-diethylamino group seems to have more pronouncing effect on the cytotoxicity. Hydrochlorides of *O*-aminoalkylated esters appear to be promising candidates for further development.

2.3. X-Ray structure analysis

The molecular structure of **7a** in solid state was analyzed by single crystal X-ray diffraction technique. Only for this compound we have obtained suitable crystals. The crystallographic data, together with data collection and structure refinement details are listed in Table 2. Selected bond lengths, bond angles and torsion angles are listed in Table 3.

Additional crystallographic data have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 248344. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 33 6033 or e-mail: deposit@ccdc.cam.ac.uk].

The displacement ellipsoid representation of the molecule, together with the atomic numbering scheme, is shown in Fig. 3. They compare well with those observed in other benzofuran derivatives [24–26].

The benzofuran system is essentially planar with no atomic deviation greater than 0.018(2) Å (for C9 atom) from its least-squares plane. The methoxycarbonyl group is planar to within 0.004 Å and makes an angle of 4.8(2)° with the best plane of the planar benzofuran moiety. The methoxy group at C8 is almost coplanar with the benzofuran fragment. The orientation of this substituent with respect to the benzofuran moiety

Table 1
Cytotoxicities of derivatives of benzofurancarboxylic acids

Compound	Cytotoxicity (GI_{50} in μM)[a]							
	Leukemia		Lung NCI-H226	Colon HCT-15	Renal		Breast T-47D	MGM[b]
	SR	MOLT-4			A498	SN12C		
2	NT	> 100	0.0188	> 100	> 100	NT	> 100	4.08
4	19.2	31.0	45.1	28.2	14.9	27.5	64.7	4.25
6a	0.35	22.4	29.0	17.6	32.7	NT	NT	4.64
1f	2.58	3.02	11.4	10.5	53.0	1.64	2.25	5.00
4b	0.18	0.78	25.3	0.92	22.6	0.012	NT	5.42
6b	0.54	0.37	1.16	0.86	7.39	0.92	0.19	5.92

NT, not tested.

[a] The cytotoxicity GI_{50} values are the concentrations corresponding to 50% growth inhibition.

[b] Mean graph midpoint for all human cancer cell lines (ca. 60) tested. The panels and cells employed included the following: leukemia CCRF-CEM, K-562, MOLT-4, RPMI-8226, HL60(TB), SR; non-small cell lung cancer: A549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322 M, NCI-H460, NCI-H522; colon cancer: COLO 205, HCC-2998, HCT-116, HCT-15, HT-29, KM12, SW-620; CNS cancer: SF-268, SF-295, SF-539, SNB-19, SNB-75, U251; Melanoma: LOX IMVI, MALME-3 M, M14, SK-MEL-2, SK-MEL-5, SK-MEL-28, UACC-257, UACC-62; Ovarian cancer: IGROV1, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, SK-OV-3; Renal cancer: 786-0, A498, ACHN, CAKI-1, RXF 393, SN12C, TK-10, UO-31; Prostate cancer: PC-3, DU-145; Breast cancer: MCF-7, NCI/ADR-RES, MDA-MB-231/ATCC, HS 578T, MDA-MB-435, BT-549, T-47D.

Table 2
Crystal data, data collection and structure refinement for compound **7a**

Empirical formula	$C_{11}H_{10}O_4$
Formula weight	206.19
T (K)	293(2)
Wavelength (Å)	0.71073
Crystal system, space group	monoclinic, $P\,2_1/c$
Unit cell dimensions	
A (Å)	7.214(1)
B (Å)	19.982(4)
C (Å)	7.491(1)
β (°)	110.85(3)
Volume (Å^3)	1009.1 (3)
Z, D_x (Mg m^{-3})	4, 1.357
μ (mm^{-1})	0.104
F(000)	432
θ Range for data collection (°)	3.08–26.50
hkl Range	$-8 \le h \le 9$
	$-25 \le k \le 22$
	$-8 \le l \le 9$
Reflections	
Collected	6568
unique (R_{int})	2090 (0.0394)
Data/restraints/parameters	2090/0/166
Goodness-of-fit on F^2	0.874
$R(F)$ ($I > 2\sigma(I)$)	0.0392
w$R(F^2)$ (all data)	0.1018
Max/min. $\Delta\rho$ (e Å^{-3})	0.141/–0.168

Table 3
Selected bond lengths, bond angles and torsion angles (Å, °) for **7a**

O1–C2	1.386(2)
O1–C9	1.374(2)
C2–C3	1.340(3)
C8–O10	1.361(3)
C12–O13	1.206(2)
C2–O1–C9	105.0(2)
O1–C2–C3	111.3(2)
C7–C8–C10	127.0(2)
C8–O10–C11	117.1(2)
C3–C2–C12–O13	–176.7(2)
C3–C2–C12–O14	4.0(4)
C2–C12–O14–C15	–179.6(2)

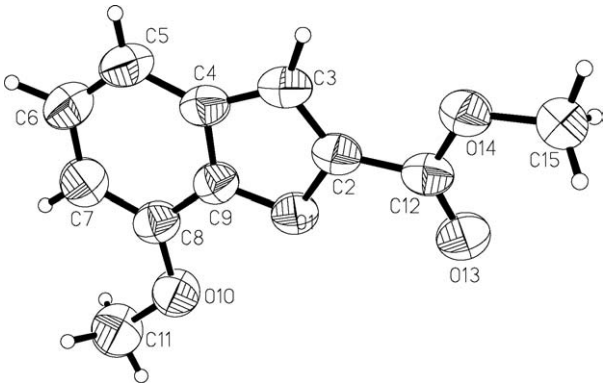


Fig. 3. A view of the molecule **7a** showing the labeling scheme. Displacement ellipsoids are drawn at the 50% probability level [23].

Table 4
Hydrogen-bonding geometry (Å, °) for **7a**

D–H···A	D–H	H···A	D···A	< (DHA)
C11–H11A...O13^{i}	1.02(2)	2.58(3)	3.471(4)	146(2)
C15–H15B...O14^{ii}	0.93(2)	2.50(2)	3.359(4)	153(2)
C11–H11C...O10^{iii}	0.93(3)	2.82(3)	3.418(3)	123(2)
C15–H15A···O1^{iv}	0.93(2)	2.62(2)	3.467(4)	151(2)
C6–H6...O10^{v}	1.00(2)	2.73(2)	3.610(3)	148(2)

Symmetry codes: (i) $x, y, -1 + z$; (ii) $1 - x, 1 - y, 3 - z$; (iii) $x, 0.5 - y, -0.5 + z$; (iv) $-x, 1 - y, 2 - z$; (v) $1 + x, y, z$.

can be described by the torsion angle C7–C8–O10–C11 of –2.3(3)°.

The structure is stabilized by C–H···O hydrogen bonds. The geometric parameters of all these bonds are listed in Table 4 and the scheme of these bonds is shown in Fig. 4. In the crystal the molecules are arranged in a herringbone pattern forming molecular layers along the c (Fig. 5) axis. Within the layer the molecules are linked by C11–H11A···O13 (x, y, $-1 + z$) and C6–H6···O10 ($1 + x$, y, z) hydrogen bonds to form infinite chains along the c and a axis, respectively. Centrosymmetric dimers are formed by means of C15–H15B···O14 ($1 - x$, $1 - y$, $3 - z$) and C15–H15A···O1 ($-x$, $1 - y$, $2 - z$) hydrogen bonds, which connect adjacent chains. Neighboring layers are linked via C11–H11C···O10 (x, $0.5 - y$, $-0.5 + z$) contact. Some of these intermolecular hydrogen bonds are shown in Fig. 5.

3. Experimental

3.1. General

All chemicals were obtained from Sigma-Aldrich. All reactions were monitored by thin layer chromatography on aluminium-backed silica gel 60 F_{254} plates (Merck), developing system: $CHCl_3$–MeOH = 9:1 and visualized with ultraviolet light. Melting points were determined in a capillary on Kofler 's apparatus and are uncorrected. The ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian UNITYplus-200 spectrometer, operating at 199.97 MHz for ^{1}H and at 50.28 MHz for ^{13}C. The chemical shift values, expressed in ppm, were referenced downfield to TMS at ambient temperature. IR spectra [$CHCl_3$, cm^{-1}] were recorded on a Specord 75 IR spectrophotometer. Microanalyses were performed at the Microanalysis Laboratory of Warsaw Technical University and all values were within ± 0.4% of the calculated compositions.

3.2. Substituted benzofurancarboxylic acids ***1–6*** and their ammonium salts

General procedure. 50 mg sample of each acid was dissolved in aqueous ammonia (1–2 ml) and left at ambient temperature overnight. Then the excess of ammonia was evaporated and the solid residue was dried in vacuo.

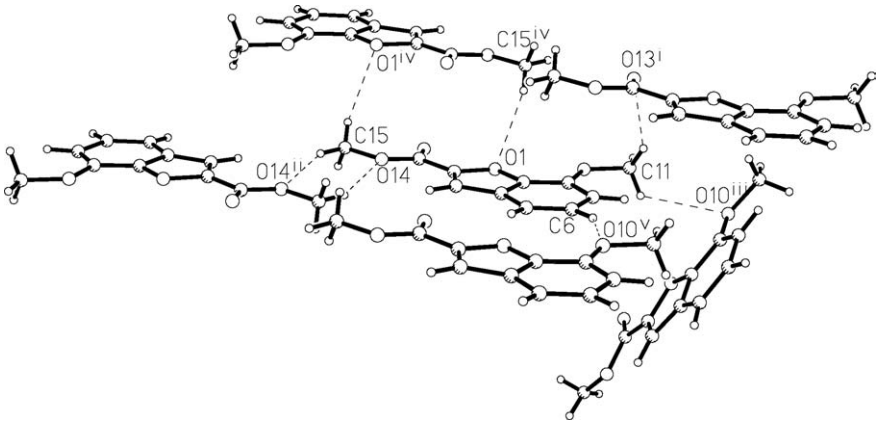


Fig. 4. The scheme of intermolecular hydrogen bonds C–H···O for **7a**.
The dashed lines represent the hydrogen bonds (the symmetry codes are the same as those given in Table 4).

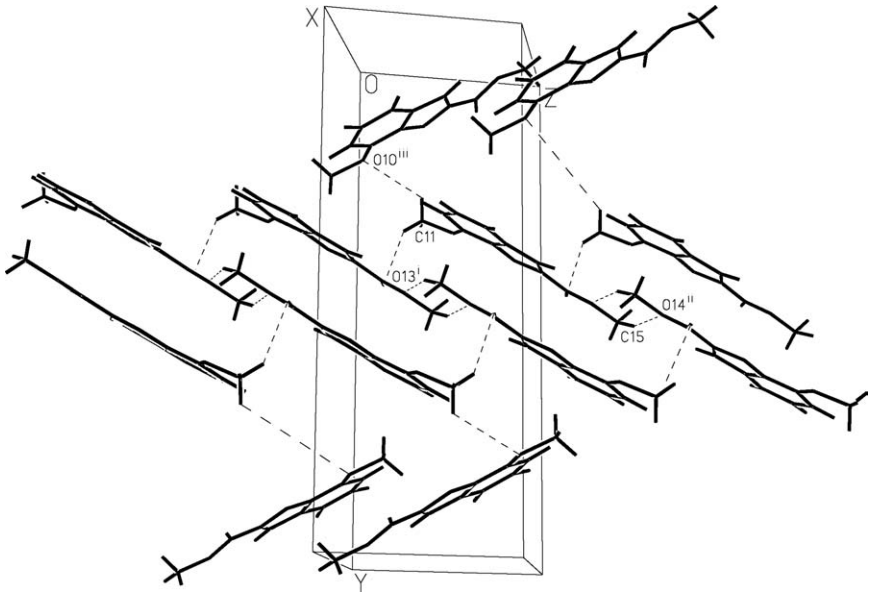


Fig. 5. The packing arrangement of **7a** with dashed lines indicating some of the intermolecular hydrogen bonds C–H···O (the symmetry codes are the same as those given in Table 4).

*3.2.1. 6-Acetyl-5-hydroxy-2-methyl-3-benzofurancarboxylic acid (**1**)*

M.p. 275–278 °C (methanol), lit. 265–268 °C (methanol) [15], ammonium salt, m.p. 170–171 °C; IR (cm^{-1}) 3000–2600, 1720, 1640, 1240; ^{1}H NMR (200 MHz, DMSO-d_6): δ 13.09 (s, 1 H, 3-COOH), 11.91 (s, 1 H, 5-OH), 8.06 (s, 1 H, 7-H), 7.26 (s, 1 H, 4-H), 2.73 (s, 3 H, 6-$COCH_3$), 2.68 (s, 3 H, 2-CH_3); ^{13}C NMR (DMSO-d_6) δ 203.9 (7-$COCH_3$), 168.3 (2-COOH), 164.4, 157.6, 146.1, 133.3, 116.7, 112.7, 108.9, 107.6, 27.6, 14.4 (2-CH_3).

*3.2.2. 7-Acetyl-6-hydroxy-3-methyl-2-benzofurancarboxylic acid (**2**)*

M.p. 252–253 °C (acetic acid), lit. 247 °C [18,19], 252 °C [16,17]; ammonium salt, m.p. 199–200 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 13.25 (br.s, 1 H, 2-COOH), 12.91 (s, 1 H, 6-OH), 7.86 (d, J = 8.8 Hz, 1 H, 4-H), 6.88 (d, J = 8.8 Hz, 1 H, 5-H), 2.80 (s, 3 H, 7-$COCH_3$), 2.45 (s, 3 H, 3-CH_3); ^{13}C NMR (DMSO-d_6): δ 202.2 (7-$COCH_3$), 160.5 (2-COOH), 163.1, 152.6, 140.7, 128.9, 124.9, 121.2, 114.5, 106.3, 31.2 (7-$COCH_3$), 8.8 (3-CH_3).

*3.2.3. 7-Acetyl-6-hydroxy-5-methoxy-3-methyl-2-benzofurancarboxylic acid (**3**)*

M.p. 247–248 °C (acetic acid), lit. 265–267 °C (acetic acid) [20], ammonium salt, m.p. 210–211 °C; IR(cm^{-1}) 3300–2450, 1700, 1640; ^{1}H NMR (200 MHz, DMSO-d_6): δ 13.15 (s, 2 H, 2-COOH, 6-OH), 7.36 (s, 1 H, 4-H), 3.85 (s, 3 H, 5-OCH_3), 2.77 (s, 3 H, 7-$COCH_3$), 2.44 (s, 3 H, 3-CH_3); ^{13}C NMR (DMSO-d_6): δ 202.5 (7-$COCH_3$), 160.5 (2-COOH), 154.3, 146.3, 145.8, 140.2, 125.1, 119.2, 108.0, 106.2, 56.1 (5-OCH_3), 31.1 (7-$COCH_3$), 8.9 (3-CH_3).

*3.2.4. 6-Hydroxy-7-(p-methoxycinnamoyl)-3-methyl-2-benzofurancarboxylic acid (**4**)*

M.p. 234–236 °C (acetic acid), lit. 275–276 °C (acetic acid) [22], ammonium salt, m.p. 224–225 °C; IR (cm^{-1}) 3300–2400, 1700, 1600; ^{1}H NMR (200 MHz, DMSO-d_6): δ 13.49

(s, 1 H), 8.10 (d, J = 15.6 Hz, 1 H, 1′-H), 7.80 (m, 4 H, 4-H, 2′-H 5′-H, 6′-H), 6.98 (m, 3 H, 5-H, 3′-H, 4′-H), 3.85 (s, 3 H, phenyl-OC$\underline{H}_3$), 2.48 (s, 3 H, 3-C$\underline{H}_3$); ^{13}C NMR (DMSO-d_6): δ 190.8.

(7-$\underline{C}$O–), 163.9, 161.8, 160.5 (2-$\underline{C}$OOH), 152.2, 145.0, 140.5, 130.7, 128.6, 124.8, 122.3, 121.3, 114.8, 114.5, 106.8, 55.3 (7′-O$\underline{C}H_3$), 8.8 (3-$\underline{C}H_3$).

*3.2.5. 7-Acetyl-6-methoxy-3-methyl-2-benzofurancarboxylic acid (**5**)*

M.p. 232–235 °C (acetic acid), lit. 234 °C [16], ammonium salt, m.p. 150–152 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.84 (d, J = 8.8 Hz, 1 H, 4-H), 7.22 (d, J = 8.6 Hz, 1 H, 5-H), 3.95 (s, 3 H, 6-OC$\underline{H}_3$), 2.61 (s, 3 H, 7-COC$\underline{H}_3$), 2.51 (s, 3 H, 3-C$\underline{H}_3$); ^{13}C NMR (DMSO-d_6): δ 197.3 (7-$\underline{C}$OCH$_3$), 160.8 (2-$\underline{C}$OOH), 157.5, 151.1, 141.3, 124.4, 123.1, 113.9, 109.2, 56.8 (6-O$\underline{C}H_3$), 32.2 (7-CO$\underline{C}H_3$), 9.0 (3-$\underline{C}H_3$).

*3.2.6. 5-Bromo-7-hydroxy-6-methoxy-2-benzofurancarboxylic acid (**6**)*

M.p. 218–220 °C (acetic acid), ammonium salt, m.p. 230–231 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.35 (s, 1 H, 4-H), 7.31 (s, 1 H, 3-H), 3.91 (s, 3 H, 6-OC$\underline{H}_3$); ^{13}C NMR (DMSO-d_6): δ = 159.9 (2-$\underline{C}$OOH), 147.6, 147.2, 144.6, 131.9, 123.1, 113.8, 112.1, 101.7, 57.3 (6-O$\underline{C}H_3$). $C_{10}H_7BrO_5$ (287.1): calc. C 41.84, H 2.46; found C 41.70, H 2.32.

3.3. Synthesis of esters of substituted 2- and 3-benzofurancarboxylic acids

General procedure. A mixture of an acid (**1**–**7**) (4 mmol), appropriate alcohol (250 ml) and concentrated sulfuric acid (1.0 ml) was refluxed for 35–40 h. When the conversion was complete, the solvent was evaporated. The oily residue was dissolved in chloroform (10 ml), washed with 10% NaOH (5 ml) and water (5 ml) and dried over anh. $MgSO_4$. The drying agent was removed by filtration and the solvent was evaporated. The solid residue was crystallized from appropriate solvent.

*3.3.1. 6-Acetyl-5-hydroxy-2-methyl-3-benzofurancarboxylic acid methyl ester (**1a**)*

Yield 95%; m.p. 178–179 °C (methanol) lit. 168–170 °C (methanol) [15]; IR (cm^{-1}) 1720, 1650, 1240; ^{1}H NMR (200 MHz, $CDCl_3$): δ 12.18 (s, 1 H, 5-O$\underline{H}$), 7.77 (s, 1 H, 7-$\underline{H}$), 7.47 (s, 1 H, 4-$\underline{H}$), 3.95 (s, 3 H, 3-COOC$\underline{H}_3$), 2.79 (s, 3 H, 6-COCH_3), 2.68 (s, 3 H, 2-C$\underline{H}_3$).

*3.3.2. 6-Acetyl-5-hydroxy-2-methyl-3-benzofurancarboxylic acid ethyl ester (**1b**)*

Yield 87%. m.p. 146–147 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 12.18 (s, 1 H, 5-O$\underline{H}$), 7.75 (s, 1 H, 7-$\underline{H}$), 7.45 (s, 1 H, 4-$\underline{H}$), 4.40 (q, J = 7.2 Hz, 2 H, 3-COOC$\underline{H}_2$), 2.78 (s, 3 H, 6-COCH_3), 2.67 (s, 3 H, 2-C$\underline{H}_3$), 1.44 (t, J = 7.2 Hz, 3 H, 3-COOCH$_2$C$\underline{H}_3$). $C_{14}H_{14}O_5$ (262.26): calc. C 64.12, H 5.38; found C 64.50, H 5.60.

*3.3.3. 6-Acetyl-5-hydroxy-2-methyl-3-benzofurancarboxylic acid n-propyl ester (**1c**)*

Yield 85%; m.p. 94–95 °C (*n*-propanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.20 (br.s, 1 H, 5-O$\underline{H}$), 7.76 (s, 1 H, 7-$\underline{H}$), 7.46 (s, 1 H, 4-$\underline{H}$), 4.32 (t, J = 6.6 Hz, 2 H, 3-COOC$\underline{H}_2$), 2.79 (s, 3 H, 6-COCH_3), 2.68 (s, 3 H, 2-C$\underline{H}_3$), 1.84 (m, 2 H, 3-COOCH$_2$C$\underline{H}_2$), 1.07 (t, J = 7.4 Hz, 3 H, 3-COOCH$_2$CH$_2$C$\underline{H}_3$); $C_{15}H_{16}O_5$ (276.29): calc. C 65.24, H 5.79; found C 65.50, H 5.80.

*3.3.4. 6-Acetyl-5-hydroxy-2-methyl-3-benzofurancarboxylic acid isobutyl ester (**1d**)*

Yield 88%; Oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.19 (br.s, 1 H, 5-O$\underline{H}$), 7.77 (s, 1 H, 7-$\underline{H}$), 7.47 (s, 1 H, 4-$\underline{H}$), 4.15 (t, J = 5.0 Hz, 2 H, 3-COOC$\underline{H}_2$), 2.79 (s, 3 H, 6-COCH_3), 2.68 (s, 3 H, 2-C$\underline{H}_3$), 2.14 (m, 1 H, 3-COOCH$_2$C$\underline{H}$), 1.07, 1.05 (2 s, 6 H, 3-COOCH$_2$CH(C$\underline{H}_3$)$_2$); $C_{16}H_{18}O_5$ (298.95): calc. C 64.22, H 6.02; found C 64.85, H 6.34.

*3.3.5. 6-Acetyl-5-hydroxy-2-methyl-3-benzofurancarboxylic acid n-pentyl ester (**1e**)*

Yield 87%; Oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.19 (s, 1 H, 5-O$\underline{H}$), 7.77 (s, 1 H, 7-$\underline{H}$), 7.46 (s, 1 H, 4-$\underline{H}$), 4.34 (t, J = 6.8 Hz, 2 H, 3-COOC$\underline{H}_2$), 2.79 (d, J = 7.6 Hz, 3 H, 6-COCH_3), 2.68 (s, 3 H, 2-C$\underline{H}_3$), 1.82 (m, 2 H, 3-COOCH$_2$C$\underline{H}_2$), 1.43 (m, 4 H, 3-COO(CH$_2$)$_2$C$\underline{H}_2$C$\underline{H}_2$), 0.94 (t, J = 7.0 Hz, 3 H, 3-COO(CH$_2$)$_4$C$\underline{H}_3$); $C_{17}H_{20}O_5$ (303.95): calc. C 67.12, H 6.58; found C 67.43, H 6.12.

*3.3.6. 7-Acetyl-6-hydroxy-3-methyl-2-benzofurancarboxylic acid methyl ester (**2a**)*

Yield 93%; m.p. 110–112 °C (methanol), lit. 156 °C [16]; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.68 (d, J = 8.8 Hz, 1 H, 4-H), 6.96 (d, J = 8.8 Hz, 1 H, 5-H), 3.96 (s, 3 H, 2-COOC$\underline{H}_3$), 2.96 (s, 3 H, 7-COC$\underline{H}_3$), 2.56 (s, 3 H, 3-C$\underline{H}_3$); $C_{13}H_{12}O_5$ (248.24): calc. C 62.90, H 4.87; found C 62.54, H 4.47.

*3.3.7. 7-Acetyl-6-hydroxy-5-methoxy-3-methyl-2-benzofurancarboxylic acid methyl ester (**3a**)*

Yield 97%; m.p. 140–142 °C (hexane), lit. 180–181 °C (methanol) [21]; IR(cm^{-1}) 1710, 1690; ^{1}H NMR (200 MHz, $CDCl_3$): δ 13.62 (s, 1 H, 6-O$\underline{H}$), 7.16 (s, 1 H, 4-H), 3.98 (s, 3 H, 5-OC$\underline{H}_3$), 3.96 (s, 3 H, 2-COOC$\underline{H}_3$), 2.97 (s, 3 H, 7-COC$\underline{H}_3$), 2.57 (s, 3 H, 3-C$\underline{H}_3$).

*3.3.8. 6-Hydroxy-7-(p-methoxycinnamoyl)-3-methyl-2-benzofurancarboxylic acid methyl ester (**4a**)*

Yield 90%; m.p. 180–182 °C (methanol), lit. 213–215 °C [22]; ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.04 (s, 1 H, 6-O$\underline{H}$), 8.42 (d, J = 15.2 Hz, 1 H, 1′-H), 7.99 (d, J = 15.4 Hz, 1 H, 2′-H), 7.73 (m, 3 H, 4-H, 5′-H, 6′-H), 6.99 (m, 3 H, 5-H, 3′-H, 4′-H), 4.03 (s, 3 H, 2-COOC$\underline{H}_3$), 3.89 (s, 3 H, phenyl-OC$\underline{H}_3$), 2.25 (s, 3 H, 3-C$\underline{H}_3$).

*3.3.9. 7-Acetyl-6-methoxy-3-methyl-2-benzofurancarboxylic acid methyl ester (**5a**)*

Yield 90%; m.p. 124–125 °C lit. 132 °C [16]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, J = 8.7 Hz, 1 H, 4-H), 6.93

(d, J = 8.8 Hz, 1 H, 5-H), 3.89, 3.86 (2 s, 6 H, 6-OC$\underline{H}_3$, 2-COOC$\underline{H}_3$), 2.63 (s, 3 H, 7-COC$\underline{H}_3$), 2.48 (s, 3 H, 3-C$\underline{H}_3$).

*3.3.10. 5-Bromo-7-hydroxy-6-methoxy -2-benzofurancarboxylic acid methyl ester (**6a**)*

Yield 92%; m.p. 133–134 °C (methanol); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.47 (s, 1 H, 3-H), 7.12 (s, 1 H, 4-H), 3.97 (s, 6 H, 6-OC$\underline{H}_3$, 2-COOC$\underline{H}_3$); $C_{11}H_9BrO_5$ (301.1): calc. C 43.88, H 3.01; found C 43.85, H 3.02.

*3.3.11. 7-Methoxy-2-benzofurancarboxylic acid methyl ester (**7a**)*

Yield 95%; m.p. 72–73 °C (methanol), lit. 79 °C [27], ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.53 (s, 1 H, 3-H), 7.25–7.20 (m, 2 H, 4,6-H), 6.92 (d, J = 7.6 Hz, 1 H, 5-H), 4.02 (s, 3 H, 2-COOC$\underline{H}_3$).

3.4. Synthesis of O-*(ethyl*-N,N-*diethylamino)substituted esters of benzofurancarboxylic acids*

General procedure. A mixture of an appropriate benzofurancarboxylic acid ester, with free phenolic OH group (1.8 mmol), *N*,*N*-diethyl-2-chloroethylamine hydrochloride (7.2 mmol), anhydrous potassium carbonate (10 mmol) and Aliquat 336® (0.4 mmol) was suspended in anhydrous acetone (20 ml) and refluxed with stirring for 16–20 h. When the ester was alkylated, inorganic salts were removed by filtration. The solvent was evaporated. The residue was purified by column chromatography on silica gel (eluent: chloroform) and/or crystallized from appropriate solvent to give a base. It was dissolved in methanol saturated with gaseous HCl. The hydrochloride was precipitated by addition of diethyl ether. The crude product was crystallized from methanol/ethyl ether.

*3.4.1. 6-Acetyl-5-(*O*-ethyl-2′-diethylamino)-2-methyl-3-benzofurancarboxylic acid methyl ester (**1f**)*

Yield 62%; m.p. 129–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (s, 1 H, 7-$\underline{H}$), 7.56 (s, 1 H, 4-$\underline{H}$), 4.72 (m, 2 H, 5-OC$\underline{H}_2$), 3.99 (s, 3 H, 3-COOC$\underline{H}_3$), 3.34 (m, 6 H, N(C$\underline{H}_2$)$_3$), 2.80 (s, 3 H, 6-COCH_3), 2.63 (s, 3 H, 2-C$\underline{H}_3$), 1.48 (m, 6 H, 2 × CH_2C$\underline{H}_3$); $C_{19}H_{26}ClNO_5$ (383.9): calc. C 59.44, H 6.83, N 3.65; found C 59.54, H 6.97, N 3.70.

*3.4.2. 6-Acetyl-5-(*O*-ethyl-2′-diethylamino)-2-methyl-3-benzofurancarboxylic acid ethyl ester (**1g**)*

Yield 57%. Oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (s, 1 H, 7-$\underline{H}$), 7.53 (s, 1 H, 4-$\underline{H}$), 4.43 (t, J = 6.4 Hz, 2 H, 5-OC$\underline{H}_2$), 4.19 (t, J = 6.2 Hz, 2 H, 3-COOC$\underline{H}_2$), 2.85 (m, 6 H, N(C$\underline{H}_2$)$_3$), 2.76 (s, 3 H, 6-COCH_3), 2.65 (s, 3 H, 2-C$\underline{H}_3$), 1.25 (m, 6 H, 2 × CH_2C$\underline{H}_3$), 1.06 (t, J = 6.6 Hz, 3 H, 5-OCH_2C$\underline{H}_3$); $C_{20}H_{27}NO_5$ (361.4): calc. C 66.46, H 7.53, N 3.88; found C 66.44, H 7.32, N 3.78.

*3.4.3. 6-Acetyl-5-(*O*-ethyl-2′-diethylamino)-2-methyl-3-benzofurancarboxylic acid n-propyl ester (**1h**)*

Yield 60%; Oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 1 H, 7-$\underline{H}$), 7.45 (s, 1 H, 4-$\underline{H}$), 4.08 (m, 2 H, 5-OC$\underline{H}_2$), 3.66 (m, 2 H, 3-COOC$\underline{H}_2$), 3.58–3.14 (m, 6 H, N(C$\underline{H}_2$)$_3$), 2.87 (t, J = 6.0 Hz, 2H, 3-COOCH_2C$\underline{H}_2$), 2.59 (s, 3 H, 6-COCH_3), 2.58 (s, 3 H, 2-C$\underline{H}_3$), 1.39 (m, 6 H, 2 × CH_2C$\underline{H}_3$), 1.04 (t, J = 7.0 Hz, 3 H, 5-OCH_2CH_2C$\underline{H}_3$); $C_{21}H_{29}NO_5$ (375.4): calc. C 67.19, H 7.79, N 3.73; found C 67.44, H 7.94, N 3.95.

*3.4.4. 7-Acetyl-6-(*O*-ethyl-2′-diethylamino)-3-methyl-2-benzofurancarboxylic acid methyl ester hydrochloride (**2b**)*

Yield 75%; m.p. 161–163 °C (methanol/ethyl ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 12.37 (br.s, 1 H, N$\underline{H}$), 7.67 (d, J = 8.6 Hz, 1 H, 4-H), 7.09 (d, J = 8.8 Hz, 1 H, 5-H), 4.71 (t, J = 4.4 Hz, 2 H, 6-OC$\underline{H}_2$), 3.96 (s, 3 H, 2-COOC$\underline{H}_3$), 3.52–3.32 (m, 6 H, N(C$\underline{H}_2$)$_3$), 2.78 (s, 3 H, 7-COC$\underline{H}_3$), 2.57 (s, 3 H, 3-C$\underline{H}_3$), 1.46 (m, 6 H, 2 × CH_2C$\underline{H}_3$); $C_{19}H_{26}ClNO_5$ × H_2O (401.9): calc. C 56.78, H 6.52, N 3.48; found C 56.62, H 6.83, N 3.57.

*3.4.5. 7-Acetyl-6-(*O*-ethyl-2′-diethylamino)-5-methoxy-3-methyl-2-benzofurancarboxylic acid methyl ester hydrochloride (**3b**)*

Yield 78%; m.p. 137–138 °C (methanol/ethyl ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.07 (br.s, 1 H, N$\underline{H}$), 7.15 (s, 1 H, 4-H), 4.54 (m, 2 H, 6-OC$\underline{H}_2$), 3.99 (s, 3 H, 5-OC$\underline{H}_3$), 3.97 (s, 3 H, 2-COOC$\underline{H}_3$), 3.53–3.24 (m, 6 H, N(C$\underline{H}_2$)$_3$), 2.79 (s, 3 H, 7-COC$\underline{H}_3$), 2.58 (s, 3 H, 3-C$\underline{H}_3$), 1.47 (m, 6 H, 2 × CH_2C$\underline{H}_3$); $C_{20}H_{28}ClNO_6$ (413.9): calc. C 58.06, H 6.77, N 3.38; found C 58.07, H 6.52, N 3.49.

*3.4.6. 6-(*O*-ethyl-2′-diethylamino)-7-(p-methoxy-cinnamoyl)-3-methyl-2-benzofurancarboxylic acid methyl ester hydrochloride (**4b**)*

Yield 60%; m.p. 160–161 °C (methanol/ethyl ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 12.38 (br.s, 1 H, N$\underline{H}$), 7.68 (d, J = 8.8 Hz, 1 H, 4-H), 7.52 (m, 2 H, 5′-H, 6′-H), 7.40 (d, J = 15.8 Hz, 1 H, 1′-H), 7.08 (m, 2 H, 2′-H, 5′-H), 6.91 (d, J = 8.8 Hz, 2 H, 3′-H, 4′-H), 4.71 (m, 2 H, 6-OC$\underline{H}_2$), 3.90 (s, 3 H, 2-COOC$\underline{H}_3$), 3.85 (s, 3 H, phenyl-OC$\underline{H}_3$), 3.42–3.18 (m, 6 H, N(C$\underline{H}_2$)$_3$), 2.59 (s, 3 H, 3-C$\underline{H}_3$), 1.33 (t, J = 7.0 Hz, 6 H, 2 × CH_2C$\underline{H}_3$); $C_{27}H_{32}ClNO_6$ (502.1): calc. C 64.60, H 6.38, N 2.79; found C 64.79, H 6.36, N 3.03.

*3.4.7. 5-Bromo-7-(*O*-ethyl-2′-diethylamino)-6-methoxy-2-benzofurancarboxylic acid methyl ester (**6b**)*

Yield 58%; Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 (s, 1 H, 3-H), 7.06 (s, 1 H, 4-H), 4.45 (s, 2 H, 7-OC$\underline{H}_2$), 3.87 (d, J = 9.2 Hz, 6 H, N(C$\underline{H}_2$)$_3$), 1.19 (s, 6 H, 2 × CH_2C$\underline{H}_3$); $C_{17}H_{22}BrNO_5$ (400.3): calc. C 51.01, H 5.54, N 3.51; found C 51.16, H 5.57, N 3.35.

3.5. Cytotoxicity

The in vitro cell line screening utilizing 60 different human tumor cell lines was carried out in National Institute of Health, National Cancer Institute, Bethesda, USA. A 48 h continuous drug exposure protocol was used and a sulforhodamine

B protein assay was used to estimate cell growth. Additional details concerning the NCI 's drug discovery and development program are available at http://dtp.nci.nih.gov.

3.6. X-ray diffraction measurements

Crystals suitable for X-ray analysis were grown from methanol solution by slow evaporation. Diffraction data were collected on an Oxford Diffraction KM4CCD diffractometer [28] at room temperature, using graphite-monochromated MoK_α radiation. A total of 612 frames were measured in four separate runs in order to cover the symmetry-independent part of the reciprocal space. The ω-scan was used with a step of 0.75°, two reference frames were measured after every 50 frames, they did not show any systematic changes either in peaks positions or in their intensities. The unit-cell parameters were determined by the least-squares treatment of setting angles of 1712 highest-intensity reflections, chosen from the whole experiment. Intensity data were corrected for the Lorentz and polarization effects [29]. The structure was solved by direct methods with the SHELXS-97 program [30] and refined with full-matrix least squares by the SHELXL-97 [31] program. The function $\Sigma w(|F_o|^2-|F_c|^2)^2$ was minimized with $w^{-1} = [\sigma^2(F_o)^2 + (0.0423\ P)^2]$, where $P = (F_o^2 + 2\ F_c^2)/3$. All non-hydrogen atoms were refined anisotropically, positions of hydrogen atoms were generated geometrically and than refined, U_{iso} parameters set at 1.2 (1.5 for methyl groups) times U_{eq} of the appropriate carrier atom.

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