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DRUG SYNTHESIS

SYNTHESIS AND CHARACTERIZATION OF SELECTED METHYL 5-METHOXY-2-METHYL-1-BENZOFURAN-3-CARBOXYLATE DERIVATIVES WITH POTENTIAL ANTIMICROBIAL ACTIVITY

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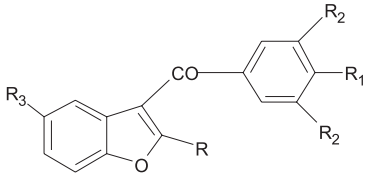
Abstract: Halogen and aminoalkyl derivatives of methyl 5-methoxy-2-methyl-1-benzofuran-3-carboxylate were prepared using 5-hydroxy-2-methyl-3-benzofuranocarboxylic acid as starting material. ^{1}H-NMR spectra were obtained for all of the synthesized structures, and for compounds **1** and **2** X-ray crystal structures were obtained too. All derivatives were tested for antimicrobial activity against a selection of Gram-positive cocci, Gram-negative rods and yeasts.

Keywords: methyl 5-methoxy-2-methyl-1-benzofuran-3-carboxylate, antimicrobial activity, antifungal activity, X-ray diffraction

Heterocyclic compounds containing benzofuran ring in their structures display a variety of pharmacological properties such as antiarrhytmic, spasmolitic, antiviral, anticancer, antifungal and anti-inflammatory activity (1–7). Compounds with high biological activity can be isolated from natural sources as well as obtained in chemical synthesis. The most recognized benzofurans are khellinone and visnaginone which are naturally occurring benzofuran derivatives isolated from *Ammi visnaga* (Apiaceae). They have been known for centuries to possess antispasmodic activity (8). Recently, it has been found that some their derivatives showed antibacterial activity on Gram negative and Gram positive microorganisms (9), immunosuppressive (10, 11) and anticancer activity (12). Other very important and recognized benzofurans are amiodarone, bufuralol, benzbromarone (Fig. 1). Amiodarone is a highly effective antiarrhythmic agent and it also possesses antifungal activity (1, 13–16). Bufuralol is

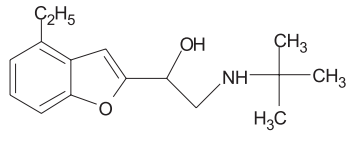


AMIODARONE:

R=Bu, R_1 =$OCH_2CH_2N(C_2H_5)_2$, R_2= I, R_3=H

BENZBROMARONE:

R=Et, R_1=OH, R_2= Br, R_3=H



BUFURALOL

Figure 1. The structures of amiodarone, bufuralol and benzbromarone

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nonselective β-adrenoreceptor antagonist (17) and benzbromarone is effective in lowering uric acid levels, as well as reducing the number of acute gout attacks in patients for whom other treatments are ineffective (18, 19).

Other examples of compounds with related structures showing biological activity can also be found in the literature. What is more, can be found derivatives containing halogens in their structure e.g.,: methyl 5-chloro-1-benzofuran-2-carboxylate which shows high affinity for adrenergic receptors and possesses antidepressive activity (20) or 5-bromo-3-hydroxy-1-benzofuran-2-yl)(4-methoxyphenyl)methanone which inhibits absorption of biogenic amines (21).

Widespread pharmacological profile of benzofurans has caused for many years a research in the field of synthesis of new biologically active benzofurans. We obtained a large group of compounds which show biological activity and some of them contain halogens in their structure (22–24). Generally, our research shows that brominated compounds display higher activity than the corresponding precursor compounds before bromination (23–25).

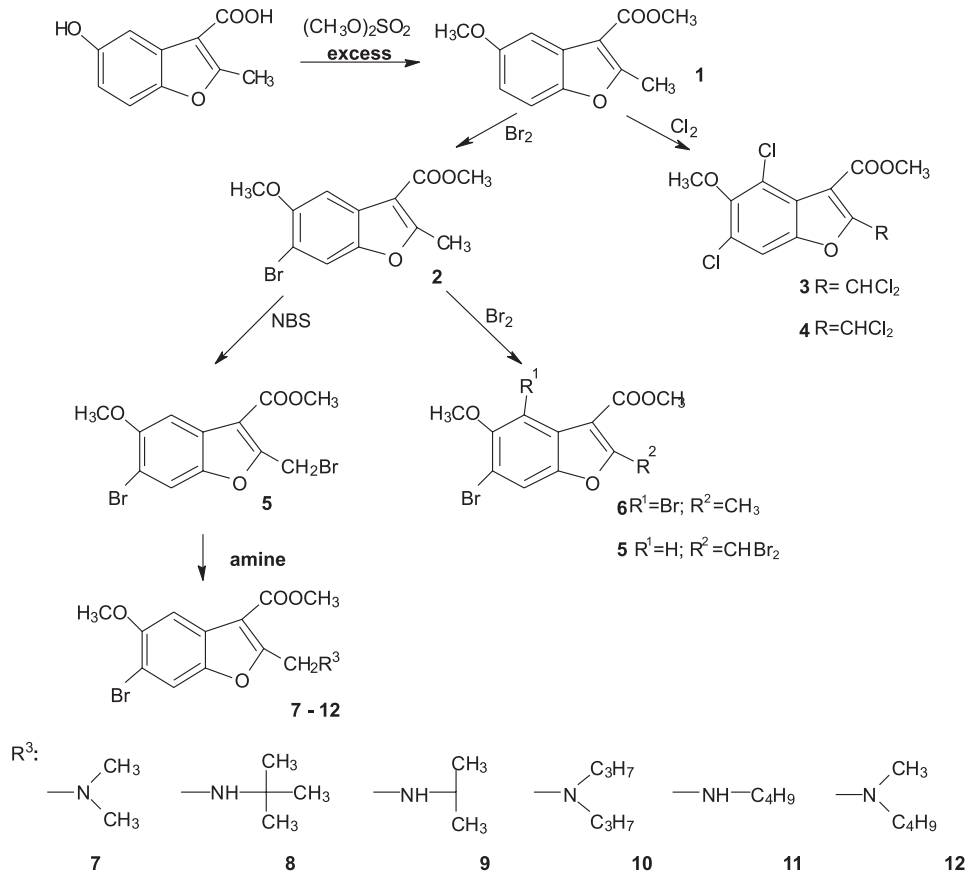
It is worth to notice that (3-amino-2-hydroxypropyl) derivatives of 4,5,6-tribromo-2,3-dihydro-2,2-dimethyl-7-benzofuranol and its analogues are the topic of a patent application (26). These compounds exhibit synergistic antifungal activity in combination with the antifungal compound – amiodarone. They are further useful as antifungal agents for the prevention and/or treatment of fungal infections in plants.

In light of this information, we have decided to continue our research, and thus design and synthesize some new compounds that might show antimicrobial activity (Scheme 1).

EXPERIMENTAL

Chemistry

Melting points were determined in capillaries in Electrothermal 9100 apparatus and are uncorrect-



Scheme 1. Method of preparation of compounds **1**–**12**.

ed. The proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded in $CDCl_3$ on a Varian UNITY-plus 300 spectrometer operating at 300 MHz. Chemical shift values are expressed in ppm (parts per million) in relation to tetramethylsilane as an internal standard. Elemental analyses were recorded with CHN model 2400 Perkin-Elmer apparatus. Chromatographic columns were filled with Merck 0.05–0.2 mm (70–325 mesh ASTM) silica gel. Reactions were monitored by TLC on silica gel G (plates with fluorescent indicator 254 nm, layer thickness 0.2 mm, Merck), using chloroform-methanol 98:2 and 95:5 (v/v) as eluents. The starting compound – 5-hydroxy-2-methyl-1-benzofuran-3-carboxylic acid was prepared according to a previous procedure (27).

Methyl 5-methoxy-2-methyl-1-benzofuran-3-carboxylate (**1**)

A mixture of 5-hydroxy-2-methyl-1-benzofuran-3-carboxylic acid (20 mmol), K_2CO_3 (20 mmol) and excess $(CH_3O)_2SO_2$ (60 mmol) in acetone (30 mL) was refluxed for 48 h. When the reaction was completed, the boiling mixture was filtered and the solvent was evaporated. The residue was purified by column chromatography on silica gel, eluent: chloroform.

White powder, (78%), m.p. 54–55°C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 7.44 (d, 1H, *J* = 2.7 Hz, Ar-H), 7.33 (d, 1H, *J* = 9 Hz, Ar-H), 6.85 (m, 1H, Ar-H), 3.94 (s, 3H, $COOCH_3$), 3.87 (s, 3H, OCH_3), 2.74 (s, 3H, CH_3). Analysis: calcd. for $C_{12}H_{12}O_4$ (220.221): C, 65.45; H, 5.49%; found C, 65.41; H, 5.54%.

Methyl 6-bromo-5-methoxy-2-methyl-1-benzofuran-3-carboxylate (**2**)

Ester **1** (20 mmol) was dissolved in $CHCl_3$ (20 mL), then a solution of bromine (20 mmol) in $CHCl_3$ (10 mL) was added dropwise with stirring for 0.5 h. Stirring was continued for 8 h at room temperature. When the reaction was completed, the solvent was evaporated. The residue was purified by column chromatography on silica gel (eluent: chloroform and chloroform:methanol 50:0.1, v/v) and finally recrystallized from ethanol to produce yellow powder (70%); m.p. 123–124°C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 7.61 (s, 1H, Ar-H), 7.45 (s, 1H, Ar-H), 3.95 (m, 6H, $COOCH_3$, OCH_3), 2.72 (s, 3H, CH_3). Analysis: calcd. for $C_{12}H_{11}BrO_4$ (299.1173): C, 48.18; H, 3.71%; found C, 47.98; H, 3.86%.

General procedure for synthesis of chloro derivatives of esters (3 and 4)

Ester **1** (20 mmol) was dissolved in $CHCl_3$ (20 mL). Next, chlorine, obtained in the reaction of $KMnO_4$ with concentrated HCl, was passed through the solution. When the reaction was completed, the solvent was evaporated. The residue was purified by column chromatography on silica gel (eluents: chloroform and chloroform/methanol 100:0.5, v/v). Finally, two compounds **3** and **4** were obtained with 20 and 30% yields, respectively.

Methyl 4,6-dichloro-2-(chloromethyl)-5-methoxy-1-benzofuran-3-carboxylate (**3**)

White powder (20%); m.p. 98–99°C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 7.54 (s, 1H, Ar-H), 4.88 (s, 2H, CH_2Cl), 4.00 (s, 3H, $COOCH_3$), 3.93 (s, 3H, OCH_3). Analysis: calcd. for $C_{12}H_8Cl_3O_4$ (323.556): C, 44.55; H, 2.80%; found C, 44.58; H, 2.78%.

Methyl 4,6-dichloro-2-(dichloromethyl)-5-methoxy-1-benzofuran-3-carboxylate (4)

White powder (30%); m.p. 121–122°C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 7.55 (s, 1H, Ar-H), 7.22 (s, 1H, $CHCl_2$), 3.94 (s, 3H, $COOCH_3$), 3.85 (s, 3H, OCH_3). Analysis: calcd. for $C_{12}H_8Cl_4O_4$ (358.001): C, 40.26; H, 2.25%; found C, 40.31; H, 2.30%.

Methyl 6-bromo-2-(bromomethyl)-5-methoxy-1-benzofuran-3-carboxylate (**5**)

To a solution of **2** (20 mmol) in dry carbon tetrachloride (50 mL) was added N-bromosuccinimide (NBS) (20 mmol) and catalytic amount of benzoyl peroxide. The reaction mixture was refluxed for 8 h. When the reaction was completed, the mixture was filtered and the solvent was evaporated. The residue was purified by a column chromatography (eluent: chloroform).

Yellow powder (70%); m.p. 153–155°C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 7.66 (s, 1H, Ar-H), 7.41 (s, 1H, Ar-H), 4.84 (s, 2H, CH_2Br), 3.94 (s, 3H, $COOCH_3$), 3.90 (s, 3H, OCH_3). Analysis: calcd. for $C_{12}H_{10}Br_2O_4$ (378.0134): C, 38.13; H, 2.67%; found C, 37.90; H, 2.57%.

General procedure for synthesis of bromo derivatives using Br_2 (5 and 6)

Compound **2** (20 mmol) was dissolved in $CHCl_3$ (20 mL). Next, the solution of bromine (40 mmol) in $CHCl_3$ (10 mL) was added dropwise with stirring for 0.5 h. Stirring was continued for 8 h at room temperature. When the reaction was completed, the mixture was filtered and the solvent was evaporated. The mixture of derivatives was purified by a column chromatography (eluent: chloroform). Next, obtained compounds were crystallized from ethanol. Finally, two compounds **5** and **6** have been isolated.

Methyl 6-bromo-2-(bromomethyl)-5-methoxy-1-benzofuran-3-carboxylate (5)

Yellow powder (30%); m.p. 153–155°C.

Methyl 4,6-dibromo-5-methoxy-2-methyl-1-benzofuran-3-carboxylate (6)

Yellow powder (40%); m.p. 119–121°C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 7.55 (s, 1H, Ar-H), 3.88 (s, 3H, $COOCH_3$), 3.83 (s, 3H, OCH_3), 2.51 (s, 3H, CH_3). Analysis: calcd. for $C_{12}H_{10}Br_2O_4$ (378.0134): C, 38.13; H, 2.67%. Found C, 38.12; H, 2.68%.

General procedure for synthesis of amino derivatives (7–12)

Compound **5** (20 mmol) was dissolved in acetone (20 mL). Next, an appropriate amine (20 mmol) and powdered anhydrous K_2CO_3 (20 mmol) were added. The reaction mixture was refluxed for 16–24 h, respectively. When the reaction was completed, the mixture was filtered and the solvent was evaporated. The residue was purified by a column chromatography (eluents: chloroform, chloroform/methanol 100:0.2, chloroform/methanol 100:0.5, v/v). In the next step, compounds were crystallized from ethanol. The amino derivatives were converted to their hydrochlorides and crystallized from methanol.

Methyl 6-bromo-2-[(dimethylamino)methyl]-5-methoxy-1-benzofuran-3-carboxylate (7)

White powder (60%); m.p. 184–185°C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 12.12 (br. s, 1H, NH^+), 8.13 (s, 1H, Ar-H), 7.88 (s, 1H, Ar-H), 4.17 (m, 2H, CH_2), 3.75 (s, 3H, $COOCH_3$), 3.69 (s, 3H, OCH_3), 3.22 (m, 6H, N-$(CH_3)_2$). Analysis calcd. for $C_{14}H_{17}BrClNO_4$ (378.646): C, 44.41; H, 4.53; N, 3.70%; found C, 44.30; H, 4.41; N, 3.60%.

Methyl 6-bromo-2-[(*tert*-butylamino)methyl]-5-methoxy-1-benzofuran-3-carboxylate (8)

White powder (55%); m.p. 115–116°C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 10.92 (br. s, 1H, NH^+),7.92 (s, 1H, Ar-H), 7.58 (s, 1H, Ar-H), 4.75 (m, 2H, CH_2), 4.04 (s, 3H, $COOCH_3$), 3.96 (s, 3H, OCH_3), 1.50 (m, 9H, N-$C(CH_3)_3$). Analysis: calcd. for $C_{16}H_{21}BrClNO_4$ (406.69): C, 47.25; H, 5.20; N, 3.44%; found C, 47.15; H, 5.37; N, 3.42%.

Methyl 6-bromo-5-methoxy-2-[(prop-2-ylamino) methyl]-1-benzofuran-3-carboxylate (9)

White powder (47%); m.p. 193–194°C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 12.10 (br. s, 1H, NH^+), 7.67 (m, 2H, Ar-H), 4.26 (m, 2H, CH_2), 3.91 (s, 3H, $COOCH_3$), 3.81 (s, 3H, OCH_3), 1.32 (m, 7H, N-$CH(CH_3)_2$). Analysis: calcd. for $C_{15}H_{19}BrClNO_4$ (392.673): C, 45.88; H, 4.88; N, 3.57%; found C, 45.53; H, 4.55; N, 3.05%.

Methyl 6-bromo-2-[(diprop-2-ylamino)methyl]-5-methoxy-1-benzofuran-3-carboxylate (10)

White powder (56%); m.p. 188–189°C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 10.08 (br. s, 1H, NH^+), 8.13 (s, 1H, Ar-H), 7.54 (s, 1H, Ar-H), 4.88 (m, 2H, CH_2), 3.98 (s, 3H, $COOCH_3$), 3.94 (s, 3H, OCH_3), 3.82 (m, 2H, CH), 1.40 (d, 6H, J = 6.6 Hz, $(CH_3)_2$), 1.34 (d, 6H, J = 6.3 Hz, $(CH_3)_2$). Analysis: calcd. for $C_{18}H_{25}BrClNO_4$ (434.75): C, 49.73; H, 5.80; N, 3.22%; found C, 49.64; H, 5.84; N, 3.24%.

Methyl 6-bromo-2-[(butylamino)methyl]-5-methoxy-1-benzofuran-3-carboxylate (11)

White powder (44%); m.p. 203–204°C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 9.29 (br. s, 1H, NH^+), 8.13 (s, 1H, Ar-H), 7.53 (s, 1H, Ar-H), 4.66 (m, 2H, CH_2), 3.95 (s, 3H, $COOCH_3$), 3.94 (s, 3H, OCH_3), 3.02 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 1.34 (m, 2H, CH_2), 0.89 (m, 2H, CH_3). Analysis: calcd. for $C_{16}H_{21}BrClNO_4$ (406.69): C, 47.25; H, 5.20; N, 3.44%; found C, 47.52; H, 5.35; N, 3.51%.

Methyl 6-bromo-2-{[butyl(methyl)amino]methyl}-5-methoxy-1-benzofuran-3-carboxylate (12)

White powder (48%); m.p. 167–168°C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 10.92 (br. s, 1H, NH^+), 8.14 (s, 1H, Ar-H), 7.55 (s, 1H, Ar-H), 4.80 (m, 2H, CH_2), 3.96 (s, 3H, $COOCH_3$), 3.94 (s, 3H, OCH_3), 3.16 (m, 3H, CH_3), 2.80 (m, 2H, CH_3), 1.73 (m, 2H, CH_2), 1.34 (m, 2H, CH_2). Analysis: calcd. for $C_{17}H_{23}BrClNO_4 \times H_2O$ (438.73): C, 46.54; H, 5.74; N, 3.19%; found C, 46.41; H, 5.72; N, 3.27%.

Crystallography

Crystals suitable for X-ray analysis were grown by slow evaporation from ethanol solution (**1**) and ethyl acetate solution (**2**). All details of the measurements, crystal data and structure refinement are given in Table 1. The data were collected on an Oxford Diffraction KM4CCD diffractometer (28), using graphite-monochromated MoK_α radiation at 293 K. The unit cells parameters were determined by least-squares treatment of setting angles of the highest-intensity reflections chosen from the whole experiments. Intensity data were corrected for the Lorentz and polarization effects (29). The structures were solved by direct methods by use the SHELXS97 program (30) and refined by the full-matrix least-squares method with the SHELXL97 program (31). The function $\Sigma w(|F_o|^2 - |F_c|^2)^2$ was minimized with w^{-1} =

$[\sigma^2(F_o)^2 + (0.0823)^2]$ for **1** and $w^{-1} = [\sigma^2(F_o)^2 + (0.0437P)^2]$ for **2**, where $P = (F_o^2 + 2F_c^2)/3$. All non-hydrogen atoms were refined with anisotropic thermal parameters. The coordinates of the hydrogen atoms were calculated in idealized positions and refined as a riding model with their thermal parameters calculated as 1.2 (1.5 for methyl group) times U_{eq} of the respective carrier carbon atom.

The deposition numbers CCDC 828195 for **1** and 828196 for **2** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Microbiology

The standard strains of *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922 and *Candida albicans* ATCC 14053 and one clinical isolate *Stenotrophomonas maltophilia* CO2275 were used.

The bacteria were cultured on the plates Columbia agar with 5% sheep blood, at temperature

Table 1. Crystal data, data collection and structure refinement for compounds **1** and **2**.

Compound	**1**	**2**
Empirical formula	$C_{12}H_{12}O_4$	$C_{12}H_{11}O_4Br$
Formula weight	220.22	299.12
T (K)	293 (2)	293 (2)
Wavelength (Å)	0.71073	0.71073
Crystal system, space group	triclinic, P –1	triclinic, P –1
Unit cell dimensions		
a (Å)	8.811 (1)	7.4068 (4)
b (Å)	9.824 (1)	8.4760 (4)
c (Å)	13.383 (2)	10.7129 (6)
α (°)	101.65 (1)	80.856 (4)
β (°)	95.96 (1)	78.984 (4)
γ (°)	102.05 (1)	65.474 (5)
Volume (Å^3)	1096.6 (3)	598.21 (5)
Z, D_x (Mg/m^3)	4, 1.334	2, 1.661
μ (mm^{-1})	0.100	3.435
F(000)	464	300
θ range for data collection (°)	4.13 – 26.37	1.94 – 27.91
hkl range	–11 = h = 10	–9 = h = 9
	–12 = k = 12	–10 = k = 10
	–16 = l = 16	–13 = l = 13
Reflections:		
collected	17663	7702
unique (R_{int})	4467 (0.038)	2605(0.021)
observed ($I > 2\sigma(I)$)	2383	1921
Data / restraints / parameters	4467 / 0 / 289	2605 / 0 / 154
Absorption correction	multi-scan	multi-scan
Goodness-of-fit on F^2	0.936	1.022
$R(F)$ ($I > 2\sigma(I)$)	0.0445	0.0273
$wR(F^2)$ (all data)	0.1390	0.0744
Max/min. $\Delta\rho$ (e/Å^3)	0.257/ – 0.268	0.264 / –0.300

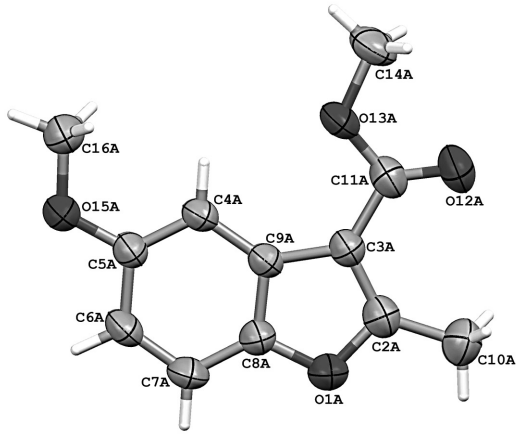
35–37°C, in an aerobic atmosphere, for 24 h. The fungal strain was cultured in the Sabouraud agar, incubated at 30°C, in the same atmosphere, for at least 24 h. The method according to CLSI (Clinical and Laboratory Standards Institute) directives was applied [32]. The compounds **1**–**12** were tested to their bacteriostatic activity at the high concentrations (512 mg/L).

Screening for the antimicrobial activity

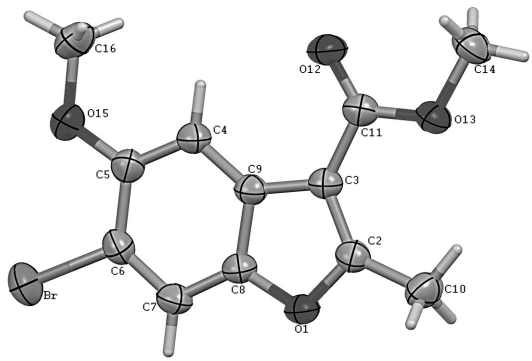
The tested substances were dissolved in DMSO and then the solutions were added to brain heart infusion broth (BHI) medium to the final concentration of 512 mg/L.

The cultures, which were in mid-logarithmic phase of growth, were suspended in 0.9% NaCl solution to obtain 0.5 McFarland's optical density. 1.0–9.0 × 10^5 cells (0.1 mL of the prepared suspension) were added to sample tubes with 3 mL of BHI broth medium containing the tested substances. Samples were incubated at appropriate temperature for 24–48 h. If after 48 h, the growth was absent, the substance was noticed as potentially possessing antimicrobial activity.

In all experiments strains vitality controls and a DMSO antimicrobial activity controls in the applied concentrations were performed.



a) A view of the molecule of **1**. Only molecule *A* is presented.



b) A view of the molecule of **2**.

Figure 2. The molecular structues of **1** (a) and **2** (b) with the atom numbering scheme

Table 2. Selected bond lengths [Å] and angles [deg] and selected torsional angles [deg] for **1** and **2**.

	1		**2**
	A	B	
O1-C2	1.366(2)	1.367(2)	1.371(2)
O1-C8	1.382(2)	1.388(2)	1.384(2)
C5-O15	1.375(2)	1.374(2)	1.376(2)
C5-C6	1.400(3)	1.402(3)	1.414(3)
C2-O1-C8	107.0(2)	106.4(1)	106.4(1)
C3-C11-O13	110.6(2)	111.6(2)	113.3(2)
C4-C5-O15	124.1(2)	123.5(2)	124.4(2)
C9-C3-C2-C10	-179.7(2)	179.9(2)	-178.5(2)
C4-C5-O15-C16	-2.7(3)	7.9(3)	1.3(3)
C2-C3-C11-O12	4.1(4)	7.7(3)	-171.8(2)
C2-C3-C11-O13	-175.7(2)	-171.8(2)	8.7(3)
C3-C11-O13-C14	-178.1(2)	179.1(2)	177.2(2)

RESULTS AND DISCUSSION

Chemistry

The chosen starting material was 5-hydroxy-2-methyl-1-benzofuran-3-carboxylic acid, which was dimethylated by using dimethyl sulfate to give compound **1**. Next, halogen derivatives were synthesized by using Br_2 or Cl_2. In the reaction of Cl_2 we received a mixture of products in which the substitution was a benzofuran ring in positions C4 and C6, and a methyl group. Thus, we obtained methyl 4,6-dichloro-2-(chloromethyl)-5-methoxy-1-benzofuran-3-carboxylate (**3**) and methyl 4,6-dichloro-2-(dichloromethyl)-5-methoxy-1-benzofuran-3-carboxylate (**4**).

The introduction of bromine was made in two steps. In the first step, we received monobromo derivative: methyl 6-bromo-5-methoxy-2-methyl-1-benzofuran-3-carboxylate (**2**) by using an equimolar amount of Br_2. The second step was performed in two ways. Firstly, wishing to substitute the hydrogen in the methyl group, we acted on the compound **2** with NBS and obtained methyl 6-bromo-2-(bromomethyl)-5-methoxy-1-benzofuran-3-carboxylate (**5**) with high yield.

Secondly, wishing to substitute halogen in benzofuran ring on C6, we used an excess amount of Br_2. As a result, we received a mixture of products: the expected product – methyl 4,6-dibromo-5-methoxy-2-methyl-1-benzofuran-3-carboxylate (**6**) and the additional product: methyl 6-bromo-2-(bromomethyl)-5-methoxy-1-benzofuran-3-carboxylate (**5**). We noted that compound **5** we also obtained using the first method but with higher yield than on second way.

Finally, methyl 6-bromo-(2-bromomethyl)-5-methoxy-1-benzofuran-3-carboxylate (**5**) was condensed with appropriate amines. The obtained aminoalkyl derivatives we converted into their hydrochlorides. ^{1}H-NMR and elemental analyses spectra were obtained for all of the synthesized structures, and for compounds **1** and **2** an X-ray crystal structure was obtained too.

X-ray structure analysis

The molecular and crystal structures of **1** and **2** in the solid state were analyzed by single crystal X-ray diffraction. The results indicate that both compounds crystallize in the triclinic space group P-1. The asymmetric unit contains two independent molecules *A* and *B* for **1** and one ordered molecule for **2**. A view of the molecular structures together with the atomic numbering scheme is shown in Figure 2 (the drawings were performed with Mercury program (33)). The molecules *A* and *B* of **1** do not differ significantly in their bond lengths or bond angles and for this reason only molecule *A* is depicted. Selected bond lengths, bond angles and torsion angles are listed in Table 2.

The molecular structures of both compounds are very similar. The benzofuran moieties are nearly planar with a maximum deviation of 0.007 (2) Å for C8A, –0.008 (2) Å for C5B of **1** and 0.011 (2) Å for C8 of **2**. The methoxycarbonyl groups are also planar within 0.009 Å and 0.002 Å for mole-

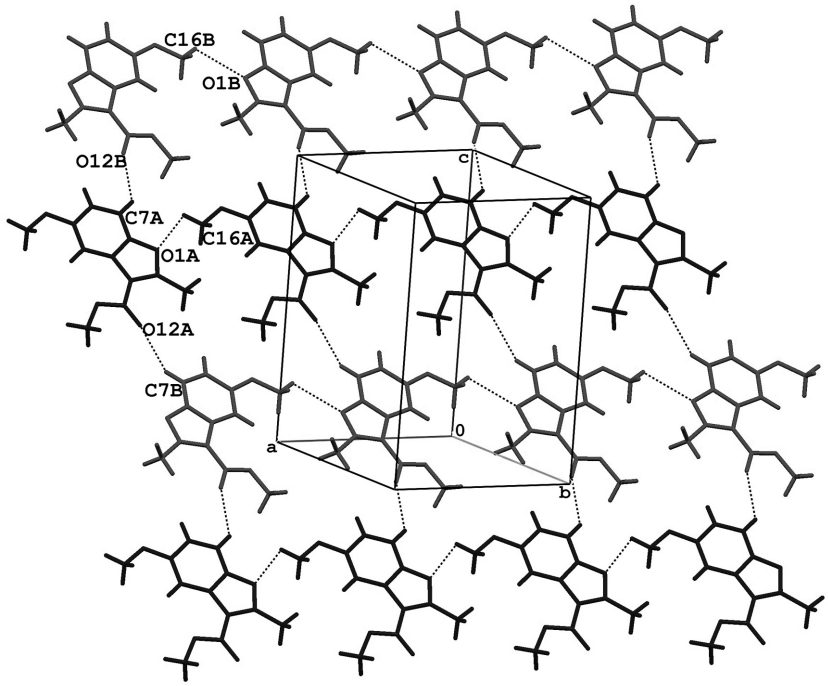


Figure 3. The interconnections within a sheet for **1**

Table 3. Intermolecular interactions in crystals (Å, deg).

D-H···A	D-H	H···A	D···A	<(D-H···A)
		1		
C7A-H7A···O12B^{i}	0.93	2.56	3.251(3)	131
C7B-H7B···O12A^{ii}	0.93	2.63	3.429(2)	145
C16A-H16A···O1A^{iii}	0.96	2.73	3.044(3)	100
C16B-H16D···O1B^{iv}	0.96	2.75	3.054(3)	99
C16A-H16C···O1B^{v}	0.96	2.70	3.415(3)	132
C10B-H10E···O15A^{v}	0.96	2.77	3.534(3)	137
C14B-H14E···O12B^{vi}	0.96	2.76	3.488(3)	133
C14A-H14C···O13A^{vii}	0.96	2.75	3.598(3)	148
C10B-H10F···O15B^{viii}	0.96	2.80	3.588(3)	140
Symmetry codes: (i) x, y, z – 1; (ii) x, y + 1, z; (iii) x – 1, y, z; (iv) x + 1, y, z; (v) –x, –y + 1, –z + 1; (vi) –x + 1, –y + 1, –z + 2; (vii) –x, –y, –z + 1; (viii) –x + 1, –y + 2, –z + 2				
C7-H7A···O12^{i}	0.93	2.47	3.379(2)	165
C14-H14B···O1^{ii}	0.96	2.62	3.247(2)	123
C14-H14C···O12^{iii}	0.96	2.64	3.584(3)	167
Br···Br			3.611(1)	
Symmetry codes: (i) x, y + 1, z; (ii) x, y – 1, z; (iii) –x + 1, –y, –z + 1; (iv) –x, –y + 2, –z + 2				

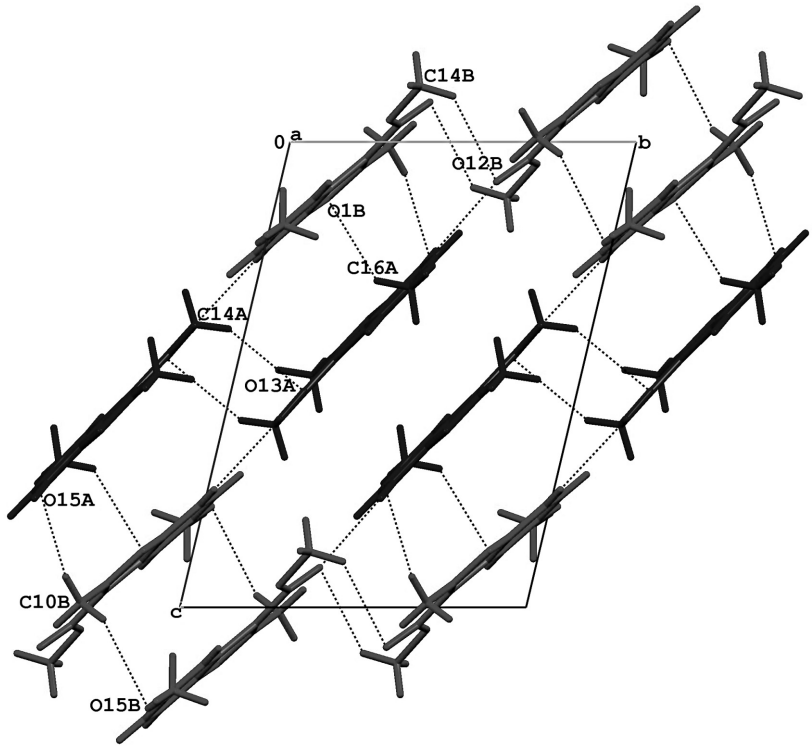


Figure 4. Projection of the crystal structure of **1** along the *a* axis

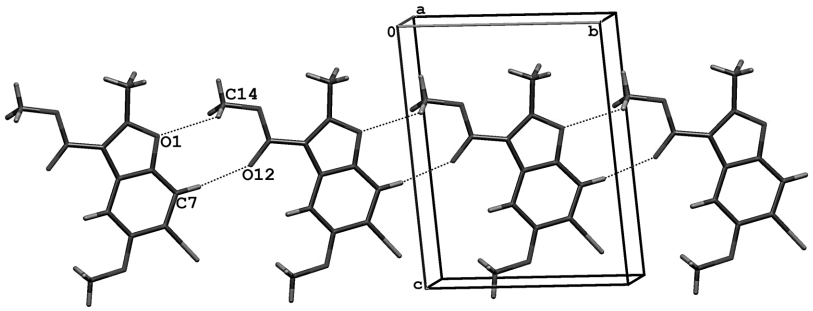


Figure 5. The interconnections within a tape for **2**

cule *A* and *B* of **1** and 0.010 Å for **2**. These groups make an angle of 3.9 (2)°, 7.4 (2)° and 7.9 (1)° with the best plane of the benzofuran system (*A* and *B* of **1** and **2**, respectively). In **1**, the C10, O15 atoms are almost coplanar with the benzofuran fragment and the C16 atoms are found to be only marginally out of the plane of this fragment (max deviation of 0.149 (3) Å for C16B). In **2**, the C10, O15, C16 and Br atoms are practically coplanar with the two-ring framework (max deviation of 0.077 (2) Å for Br). The disposition of the methoxy and methoxycarbonyl groups with respect to the benzofuran part can be described by the appropriate torsion angles (Table 2).

In crystals, the main driving forces for the supramolecular structures formation are C-H···O intermolecular interactions. The geometric parameters of all contacts are given in Table 3.

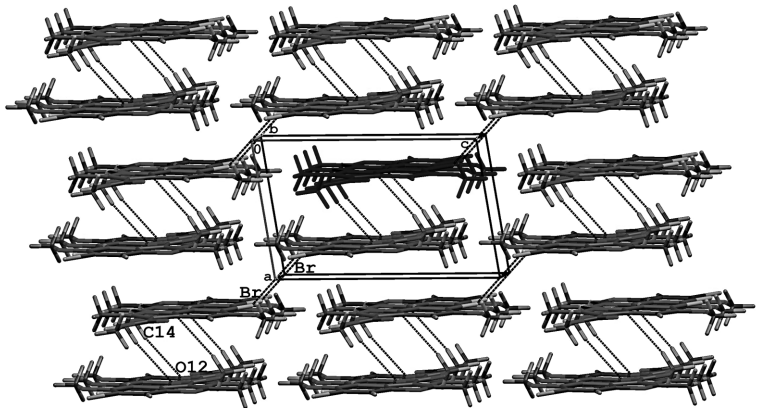


Figure 6. The packing arrangement of **2** along the *b* axis

In **1**, the molecules *A* and *B* are linked by C7B-H7B···O12A and C7A-H7A···O12B hydrogen bonds forming chains, then adjacent chains interact *via* C16B-H16D···O1B and C16A-H16A···O1A contacts to create sheets parallel to the (011) plane (Fig. 3).

Three-dimensional supramolecular structure results from remaining C-H···O interactions (see Table 3) and weak p×××p forces (Fig. 4).

In **2**, the molecules are joined by C7-H7A···O12 and C14-H14B···O1 hydrogen bonds to form tapes which expand in the [010] direction (Fig. 5).

The adjoining tapes are organized into layers parallel to the (101) plane *via* C14-H14C···O12 and Br···Br contacts (Fig. 6).

Antimicrobial activity

All halogen derivatives were tested for their antimicrobial activity against four microbial species: *Staphylococcus aureus, Escherichia coli, Stenotrophomonas maltophilia and Candida albicans*.

The chosen set of species provides a good model for screening of newly synthesized chemical compounds for antimicrobial activity. They differ in cell wall structure, mechanism of the patogenicity and susceptibility to antimicrobial drugs. These microorganisms are the cause of many hospital infection.

Staphylococcus aureus is a Gram-positive coccus, it is found in the nose and skin of humans and animals. *Staphylococcus aureus* infections usually cause purulent skin and food poisoning through the production of toxins. *Escherichia coli* is a Gram-negative bacillus, which is the part of the physiological bacterial flora of the colon. It may cause urinary tract infections, abscesses, nosocomial infections and food poisoning. *S. aureus* and *E. coli* are resistant to many antibiotics, because they synthesize enzymes that degrade drugs. In the case of *S. aureus* is also a modification of the antibiotic-binding proteins (MRSA). *Stenotrophomonas maltophilia* is a Gram-negative bacillus, which causes opportunistic infections. It is responsible for infection in immunosuppressed patients. It is characterized by a natural resistance to many antibiotics (34).

Candida albicans is a fungus (a form of yeast). It is causal agent of opportunistic infections oral cavity and genital in humans. Systemic fungal infections (fungemias) have emerged as important causes of morbidity in immunocompromised patients. Under normal circumstances, *C. albicans* lives in 80% of the human population with no harmful effects, although overgrowth results in candidiasis (35).

Our earlier study shows that brominated compounds display higher antimicrobial activity than the corresponding precursor compounds before bromination. In addition, many reports indicate that the aminoalkyl derivatives show similar activity. Described compounds include both these fragments and some activity was expected.. Therefore, the received result seem surprising. None of the tested compounds showed any microbial activity. It is not possible to point out undoubtedly that these compounds do not possess antibacterial activity because these studies are based on a selected and limited number of bacterial strains.

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