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Microwave-assisted synthesis of derivatives of khellinone under phase-transfer catalytic conditions

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Abstract The microwave-assisted synthesis of four new 5-acetyl-4,7-dimethoxy-6-hydroxybenzofuran (khellinone) analogs is described. The structures of the obtained derivatives in the solid state are evaluated on the basis of ^{13}C CP/MAS NMR spectra and theoretical calculations at DFT level. A single crystal X-ray diffraction structure is presented for 8-acetyl-7-hydroxy-4-methylcoumarin. 1,4-Bis(5-acetyl-4,7-dimethoxybenzofuran-6-yloxy)butane was evaluated for potential anticancer activity in an *in vitro* screening panel of 60 human tumor cell lines. Selected leukemia, non-small cell lung cancer, CNS, melanoma, ovarian, and breast cancer cell lines were sensitive to this compound.

Keywords Khellinone; Coumarin; Microwave-assisted synthesis; X-ray diffraction; Anticancer activity.

Introduction

Benzo[b]furan derivatives of plant origin have been the subject of increased interest in recent years due to their diverse biological activities such as anticancer, antioxidant, antimicrobial, and antifungal properties [1]. Cyclopenta[b]benzofuran derivatives isolated from *Aglaia* inhibit protein synthesis and induce apoptosis in several human cancer cell lines [2]. Dihydrobenzofurans of the neolignan type (from *Persea* or *Croton* species) exhibit potent and broad cytotoxicity against different human cancer cell lines [3, 4]. Benzofurans isolated from Brazilian propolis are mildly cytotoxic toward highly metastatic murine colon carcinoma and human fibrosarcoma cells [5]. It has been reported that a Chilean rancher successfully applied an herbal tea from the leaves of *Ammi visnaga* (Apiaceae) for his slow paralysis [6]. Inspired by this case, *Hänsel et al.* isolated khellinone **1** from this plant (Fig. 1), a compound with weak but unusually selective activity as a potassium-channel blocker [7]. Next, symmetrical dimers linked *via* the alkylation of the 6-hydroxy groups of two molecules of khellinone, were discovered as the blockers of the voltage-gated potassium channel Kv1.3 [8].

Coumarins are physiologically active benzo-2-pyron derivatives, used by us previously as intermediates in syntheses of benzofurancarboxylic acids [9]. Their cytotoxic effects, highly dependent on the nature and positions of the functional groups, were most extensively examined in recent years [10]. 7-Hydroxycoumarin (Fig. 1) has been reported to inhibit the proliferation of a number of human malignant cells *in vitro* as well as to demonstrate activity against prostate cancer, malignant melanoma, and metastatic renal cell carcinoma [11–16]. *Lopez-Gonzalez et al.* determined the cytostatic and apoptotic action of 7-hydroxycoumarin on human lung carcinoma cell

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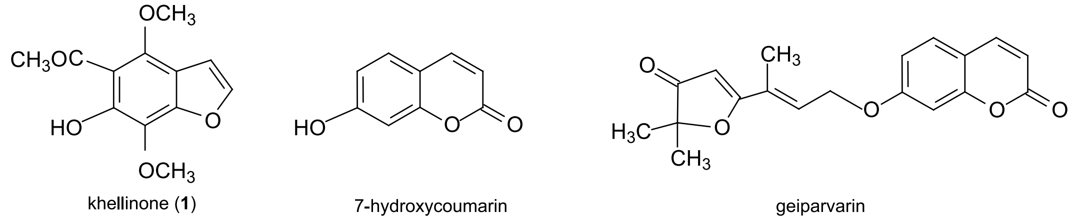
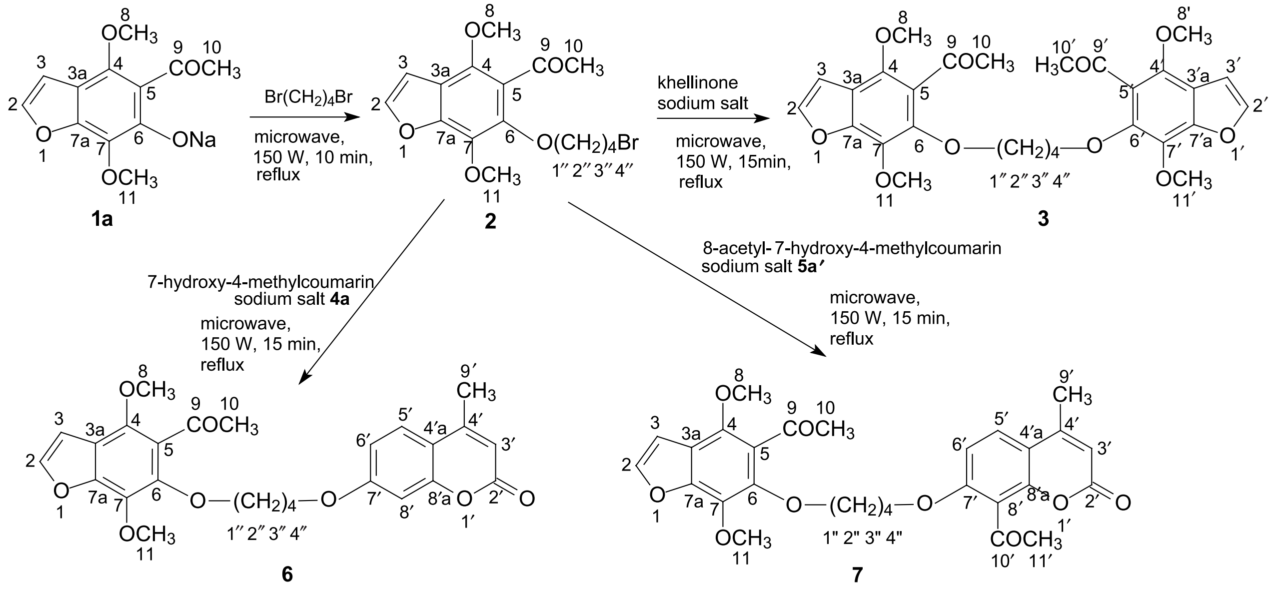


Fig. 1 The structures of khellinone and 7-hydroxycoumarin

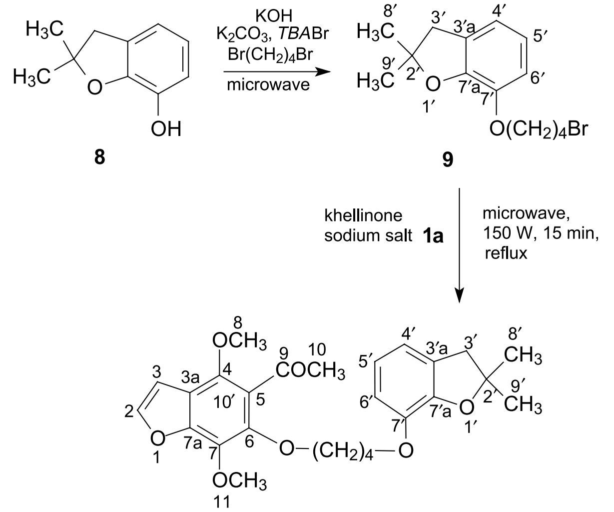


Scheme 1

lines assuming that the coumarins may become new options in treatment of non-small cell lung cancer [17]. Geiparvarin, containing coumarin and furan moieties, isolated from *Geiera parviflora* (Fig. 1) is an antiproliferative compound and may represent a new drug which targets tubulin [10].

Therefore we have adopted the substituted benzo[b]furan and 7-hydroxycoumarin systems as pharmacophores and introduced the linker to increase the flexibility of the target compounds.

In this paper we present microwave-assisted synthesis, structural data and 60 cell lines anticancer assay of the khellinone and coumarin derivatives (Schemes 1 and 2). These compounds, except the symmetrical dimer **3** have not been synthesized yet. For the compound **3** we have elaborated the new efficient method of synthesis under microwave-assisted conditions.



Scheme 2

The beneficial effects of microwave irradiation are finding an increased role in the preparation of novel, biologically active compounds. This technique has shown an advantage where processes require forcing conditions or prolonged reaction times, also when sensitive reagents are involved in the synthesis. It usually allows simplifying the operations, resulting in cleaner reaction and increased yield. Using the phase transfer catalysis (PTC) technique under microwave irradiation to carry out the preparation of aromatic ethers by *Williamson* method was found to be highly useful in terms of mildness of conditions, yield, and convenience [18–21].

We have applied a modified method for the O-alkylation of phenols called S-L(ω)-L PTC [22]. It retains the convenience of the solid–liquid PTC technique but is faster and allows optimizing the reaction temperature. The rate of S-L PTC is increased by using a trace amount of water (so called ω-phase) which forms a thin film around the solid particle of a phenolate. It becomes the third, middle phase rich in the catalyst, localized between the solid reactant and organic phase, containing the alkylating agent. Microwave heating under low energy input (*ca.* 100 W) allows the use of the thermally unstable (at temperatures beyond 120–130°C) phase-transfer catalyst tetrabutylammonium bromide.

Systematic examinations of khellinone and coumarin derivatives in solid state are not easy, because of a number of unrelated phenomena: difficulties to obtain single crystals suitable to X-ray diffraction analysis and co-crystallization with solvent. Sometimes they are oils at room temperature. Thus, we decided to use the ^{13}C CP/MAS NMR method and theoretical calculations of shielding constants at DFT level of theory to obtain information about the structure of the solid dimers and relevant components of these dimers.

All attempts to obtain suitable single crystals of the reported new khellinone derivatives failed. Consequently, the X-ray structure of the building block in the synthesis of 1-(5-acetyl-4,7-dimethoxybenzofuran-6-yloxy)-4-(8-acetyl-4-methylcoumarin-7-yloxy)butane (**7**), namely 8-acetyl-7-hydroxy-4-methylcoumarin (**5**) has been solved.

Results and discussion

Syntheses

The khellinone-derived dimers **3**–**5** were synthesized in two steps based on S-L(ω)-L PTC technique (Scheme 1). First, the sodium salt of khellinone **1a** was prepared by heating equimolar amounts of khellinone (**1**) and powdered sodium hydroxide, suspended in toluene, in the monomode microwave oven. Then, the alkylating agent 1,4-dibromobutane, tetrabutylammonium bromide, and water were added to the sodium salt. The mixture was heated in the microwave oven for 10 min to yield 1-(5-acetyl-4,7-dimethoxybenzofuran-6-yloxy)-4-bromobutane (**2**). The bromoalkyl derivative of khellinone **2** was then used as an alkylating agent in the reactions with khellinone sodium salt (**1a**), 7-hydroxy-4-methylcoumarin sodium salt (**4a**), and 8-acetyl-7-hydroxy-4-methylcoumarin sodium salt (**5a**) under the same conditions. The products 1,4-bis(5-acetyl-4,7-dimethoxybenzofuran-6-yloxy)butane (**3**), 1-(5-acetyl-4,7-dimethoxybenzofuran-6-yloxy)-4-(4-methylcoumarin-7-yloxy)butane (**6**), and 1-(5-acetyl-4,7-dimethoxybenzofuran-6-yloxy)-4-(8-acetyl-4-methylcoumarin-7-yloxy) butane (**7**) were isolated by column chromatography on silica gel.

7-Hydroxy-4-methylcoumarin (**4**) was obtained by heating under reflux a mixture of resorcinol, ethyl acetoacetate, and catalytic amounts of *p*-toluenesulfonic acid with azeotropic removal of water and ethanol, according to *Furuta* [23]. Using 2,6-dihydroxyacetophenone instead of resorcinol yielded 8-acetyl-7-hydroxy-4-methylcoumarin (**5**) under the same conditions. Sodium salts **4a** and **5a** of the coumarins **4** and **5** were obtained in the same way as described for khellinone. The khellinone-derived unsymmetrical dimer **10** was prepared in two steps using the S-L(ω)-L PTC technique (Scheme 2). In the first step 2,3-dihydro-2,2-dimethyl-7-benzofuranol (**8**) was subjected to the microwave-assisted alkylation with 1,4-dibromobutane in the presence of anhydrous potassium carbonate, powdered potassium hydroxide, and tetrabutylammonium bromide. The resulting 1-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)-4-bromobutane (**9**) was then used as an alkylating agent in the reaction with khellinone sodium salt **1a**, under the conditions shown in Scheme 1. The product 1-(5-acetyl-4,7-dimethoxybenzofuran-6-yloxy)-4-(2,3-dihydro-2,2-dimethylbenzofuran-7-yloxy)butane (**10**) was isolated by column chromatography on silica gel.

X-Ray structure of 8-acetyl-7-hydroxy-4-methylcoumarin (5)

The molecular and crystal structure of 8-acetyl-7-hydroxy-4-methylcoumarin (**5**) in solid state was analyzed by single crystal X-ray diffraction. All details of the measurements, crystal data, and structure re-

Table 1 Crystal data, data collection, and structure refinement for **5**

Compound	**5**
Empirical formula	$C_{12}H_{10}O_4$
Formula weight	218.20
T/K	293(2)
Wavelength/Å	0.71073
Crystal system, space group	triclinic, P −1
Unit cell dimensions	
a/Å	7.534(3)
b/Å	8.372(3)
c/Å	9.108(3)
α/°	69.03(3)
β/°	72.21(3)
γ/°	89.08(3)
Volume/Å^3	507.9(3)
Z, D_x/Mg · m^{-3}	2, 1.427
μ/mm^{-1}	0.108
F(000)	228
θ range for data collection/°	2.53–27.97
hkl range	$-9 \leq h \leq 9$ $-11 \leq k \leq 10$ $-11 \leq l \leq 11$
Reflections:	
collected	6405
unique (R_{int})	2219(0.013)
observed ($I > 2\sigma(I)$)	1577
Data/restraints/parameters	2219/0/186
Absorption correction	multi-scan
Goodness-of-fit on F^2	1.036
$R(F)$ ($I > 2\sigma(I)$)	0.0371
$wR(F^2)$ (all data)	0.1213
Max/min. $\Delta\rho$/e · Å^{-3}	0.212/−0.146

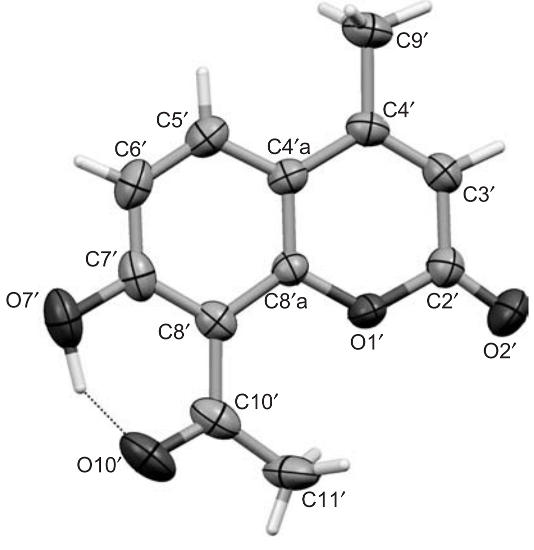


Fig. 2 A view of the molecule of **5**

Table 2 Hydrogen bonding geometry for **5**

D-H····A	$d(D-\mathrm{H})$ Å	$d(\mathrm{H}\cdots A)$ Å	$d(D\cdots A)$ Å	$<(D\mathrm{H}A)$ deg
O7′-H7····O10′	1.07(3)	1.50(3)	2.481(2)	149(2)
C5′–H5····O2′^{i}	0.97(2)	2.42(2)	3.182(2)	135(1)
C9′–H9A····7′^{ii}	0.98(2)	2.73(2)	3.696(2)	168(1)

Symmetry codes: $^{i}x, 1+y, z$; $^{ii}1+x, y, -1+z$

finement are given in Table 1. A view of the molecular structure together with the atomic numbering scheme is shown in Fig. 2 (the drawings were performed with the Mercury program [24]). The results indicate that compound **5** crystallizes in the triclinic space group P-1 with one ordered molecule in the asymmetric unit. Table 2 presents selected bond lengths, valence, and torsion angles. The interatomic distances and bond angles of the coumarin group are, in the majority, in good agreement with published values for other 4-methylcoumarin derivatives [25–29]. But the C7′–C8′ and C8′–C8a′ bond lengths in the benzene ring are rather longer due to the acetyl substituent at C8′ indicating a π-electron delocalization within this fragment of the molecule. Similar structural changes have also been found for o-hydroxyacetophenone derivatives [30].

The coumarin moiety is nearly planar with a maximum deviation of 0.029(1) Å for C7′. The dihedral angle between the least-squares planes of the 2-pyrone and benzene rings is only 1.71(7)°. The methyl C9′ and the hydroxy O7′ atoms are nearly coplanar with the coumarin ring system (the appropriate torsion angles are given in Table 2). The disposition of the acetyl group with respect to the coumarin moiety can be described by the torsion angles C7′–C8′–C10′–C11′ of 174.2(1)° and C7′–C8′–C10′–O10′

Table 3 Selected bond lengths/Å, angles/deg, and selected torsional angles/deg for **5**

C2′–O2′	1.203(2)
C3′–C4′	1.345(2)
C7′–O7′	1.347(2)
C7′–C8′	1.416(2)
C8′–C8′a	1.412(2)
C2′–O1′–C8′a	122.8(1)
C6′–C7′–O7′	117.4(1)
O7′–C7′–C8′	121.2(1)
C2′–C3′–C4′–C9′	178.9(1)
O7′–C7′–C8′–C8′a	−177.8(1)
C7′–C8′–C10′C11′	174.2(1)

of −4.7(2)°. In consequence the O10′, C10′, and C11′ atoms of this group are found to be only marginally out of the plane of the two-ring framework (max deviation of 0.152(2) Å for C11′). Strong intramolecular hydrogen bonding is present between O7′ and O10′ atoms (see Fig. 2 and Table 3) which

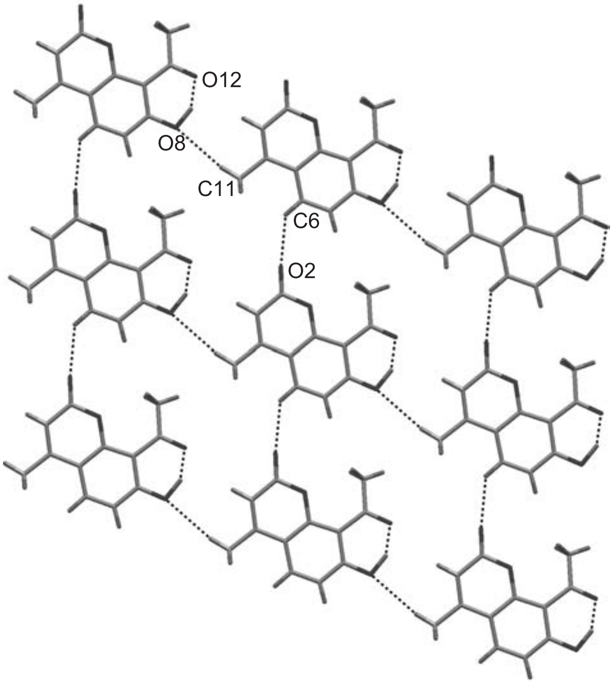


Fig. 3 The interconnections within a sheet for **5**

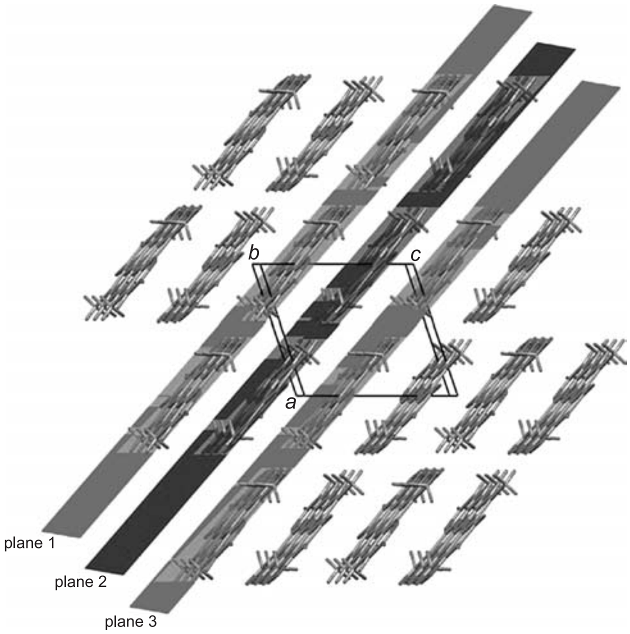


Fig. 4 Projection of the crystal structure of **5** along the *b* axis showing parallel sheets

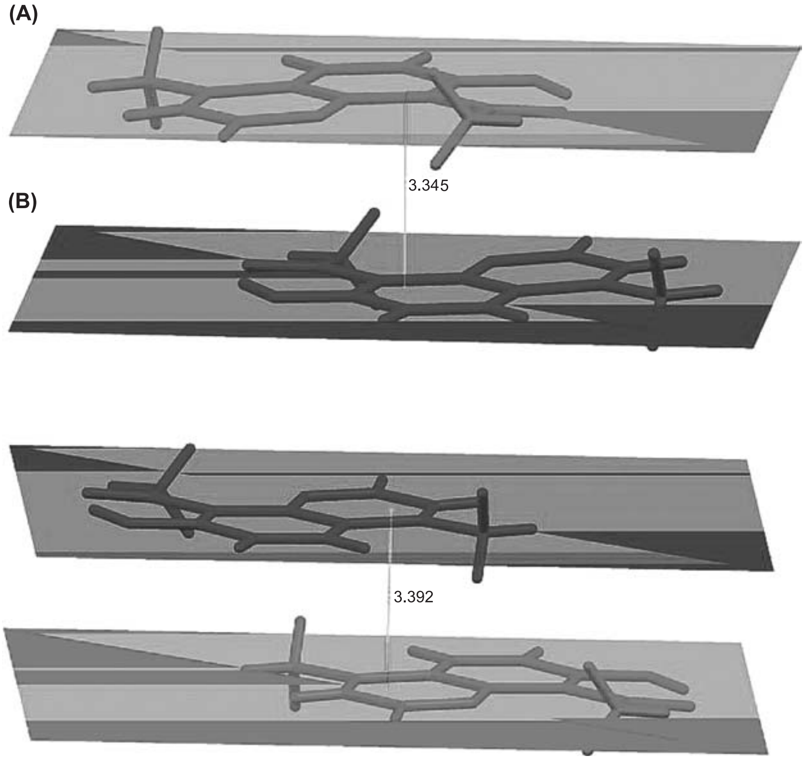


Fig. 5 The distances between stacked benzene rings (A) and between stacked 2-pyrone rings (B) for **5**

is characterized by the disposition of the hydroxyl and acetyl groups in the plane of molecule. The angle between the best planes of the coumarin moiety and the C7′/O7′/H7/O10′/C10′ ring is only 3.4(4)°.

In the crystal of **5**, the packing of the molecules is stabilized by intermolecular C–H···O hydrogen bonds and stacking forces. The molecules are linked by C6–H6···O2 and C11–H11A···O8 interactions forming sheets parallel to the (101) plane (Figs. 3 and 4). Cohesion between sheets results in $\pi\cdots\pi$ stacking interactions by partly overlapping molecules from neighboring parallel sheets. The benzene and 2-pyrone rings overlap alternately; for example benzene rings between plane 1 and 2 and 2-pyrone rings between plane 2 and 3, according to Fig. 4. The perpendicular distance between stacked benzene rings from neighboring parallel sheets is 3.35 Å and between stacked 2-pyrone rings is 3.39 Å, as shown in Fig. 5. The geometric parameters of all intra- and intermolecular hydrogen bonds are given in Table 3.

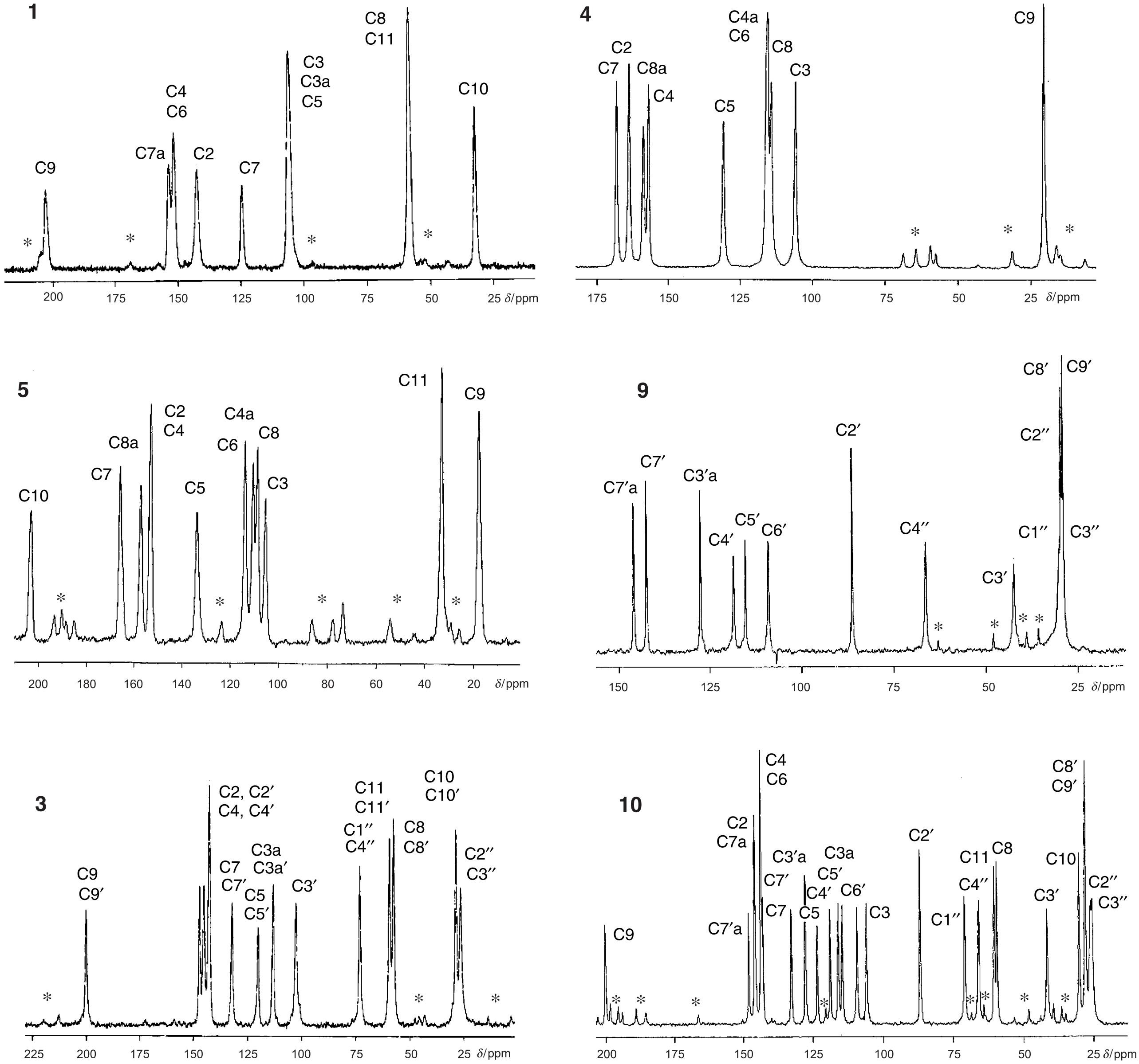


Fig. 6 The ^{13}C CP/MAS NMR spectra of 5-acetyl-6-hydroxy-4,7-dimethoxybenzofuran (**1**), 1,4-bis(5-acetyl-4,7-dimethoxybenzofuran-6-yloxy)butane (**3**), 7-hydroxy-4-methylcoumarin (**4**), 8-acetyl-7-hydroxy-4-methylcoumarin (**5**), 1-(2,3-dihydro-2,2-dimethylbenzofuran-7-yloxy)-4-bromobutane (**9**), and 1-(5-acetyl-4,7-dimethoxybenzofuran-6-yloxy)-4-(2,3-dihydro-2,2-dimethylbenzofuran-7-yloxy)butane (**10**) in solid state. Sidebands are marked with an asterisk

NMR spectra and molecular modeling

Theoretical computations provided two types of information: the shielding constants of ^{1}H and ^{13}C atoms of the molecules, and structural data of those conformations, which correspond to the NMR experimental resonances. In the case of NMR solution spectra, the calculation helped us to assign properly resonances of those ^{13}C atoms for which 1D and 2D dimensional NMR experiments gave unclear information, while the theoretical analysis of ^{13}C NMR resonances for the solid state allowed us to propose chemical shifts derived stable conformations. Theoretical shielding constants were computed employing the DFT $B3LYP/6\text{-}31G^{**}$ method using CHF-GIAO approach for geometries optimized at $PM3$ level of theory for all analyzed compounds, and additionally for X-ray derived atomic coordinates of **5**.

In Fig. 6 we have shown ^{13}C CP/MAS NMR spectra of those compounds, which are solid at room temperature: 1,4-bis(5-acetyl-4,7-dimethoxybenzofuran-6-yloxy)butane (**3**), 1-(5-acetyl-4,7-dimethoxybenzofuran-6-yloxy)-4-(2,3-dihydro-2,2-dimethylbenzofuran-7-yloxy)butane (**10**), and three of their components 5-acetyl-6-hydroxy-4,7-dimethoxybenzofuran (**1**), 7-hydroxy-4-methylcoumarin (**4**), 8-acetyl-7-hydroxy-4-methylcoumarin (**5**), as well as 1-(2,3-dihydro-2,2-dimethylbenzofuran-7-yloxy)-4-bromobutane (**9**). The notation used in the discussion of NMR results is shown in Schemes 1 and 2. The most probably assignment of signals is also given in Fig. 6 and Table 4.

The methoxy groups at aromatic rings affected the conformational variability in the solid state. We could even determine by X-ray crystallography non-averaged two or more structures in the asymmetric unit or multiple resonances in NMR solid state spectra for such compounds [31, 32]. These differences are predominantly caused by different dihedral angles between the planes of methoxy groups and the planes of the aromatic rings. An analogical phenomenon could take place for acetyl groups [33]. Surprisingly, the solid state ^{13}C NMR spectra of **1**, **3**, **4**, **5**, **9**, and **10** are simple and resemble the solution ones. Small differences between the values of the chemical shifts in solution and in solid state could be interpreted by intermolecular and intramolecular interactions. We calculated the theoretical shielding constants σ/ppm for various conformations of

Table 4 ^{13}C CP/MAS chemical shift in solid state ppm

No.	^{13}C chemical shifts in solid state for components/ppm						
	C2,C2′	C3,C3′	C4,C4′	C4a/C3a*	C5,C5′	C6,C6′	C7,C7′
1	142.3	105.9	151.6	*105.8	105.9	151.6	124.5
4	163.9	105.9	157.0	115.5	131.0	115.5	168.2
5	153.0	105.4	153.0	110.9	133.7	113.8	165.7
9	86.3	42.4	118.5	127.5	115.3	109.0	142.3
	C8,C8′	C8a/C7a*	C9	C10	C11	Linker	
1	58.1	*153.5	202.9	32.1	58.1		
4	114.2	158.8	20.5	–	–	–	
5	108.8	157.0	17.9	203.1	33.0	–	
9	–	*145.9	29.7			29.1, 30.2	
	^{13}C chemical shifts in solid state for dimers/ppm						
	C2,C2′	C3,C3′	C4,C4′	C3a, 3a′	C5,C5′	C6,C6′	C7,C7′
3	142.6	102.5	142.6	113.2	120.2	145.1	132.1
10	148.1	105.9	143.6	114.5	123.4	143.6	132.8
	87.4	41.5	120.5	127.6	115.9	109.3	143.0
	C8,C8′	C7a,C7′a	C9	C10	C11	Linker	
3	57.5	147.1	200.2	28.6	59.3	73.0, 26.4	
10	59.4	145.9	200.1	30.1	60.4	70.9, 65.9	
	–	*148.1				26.0, 25.5	

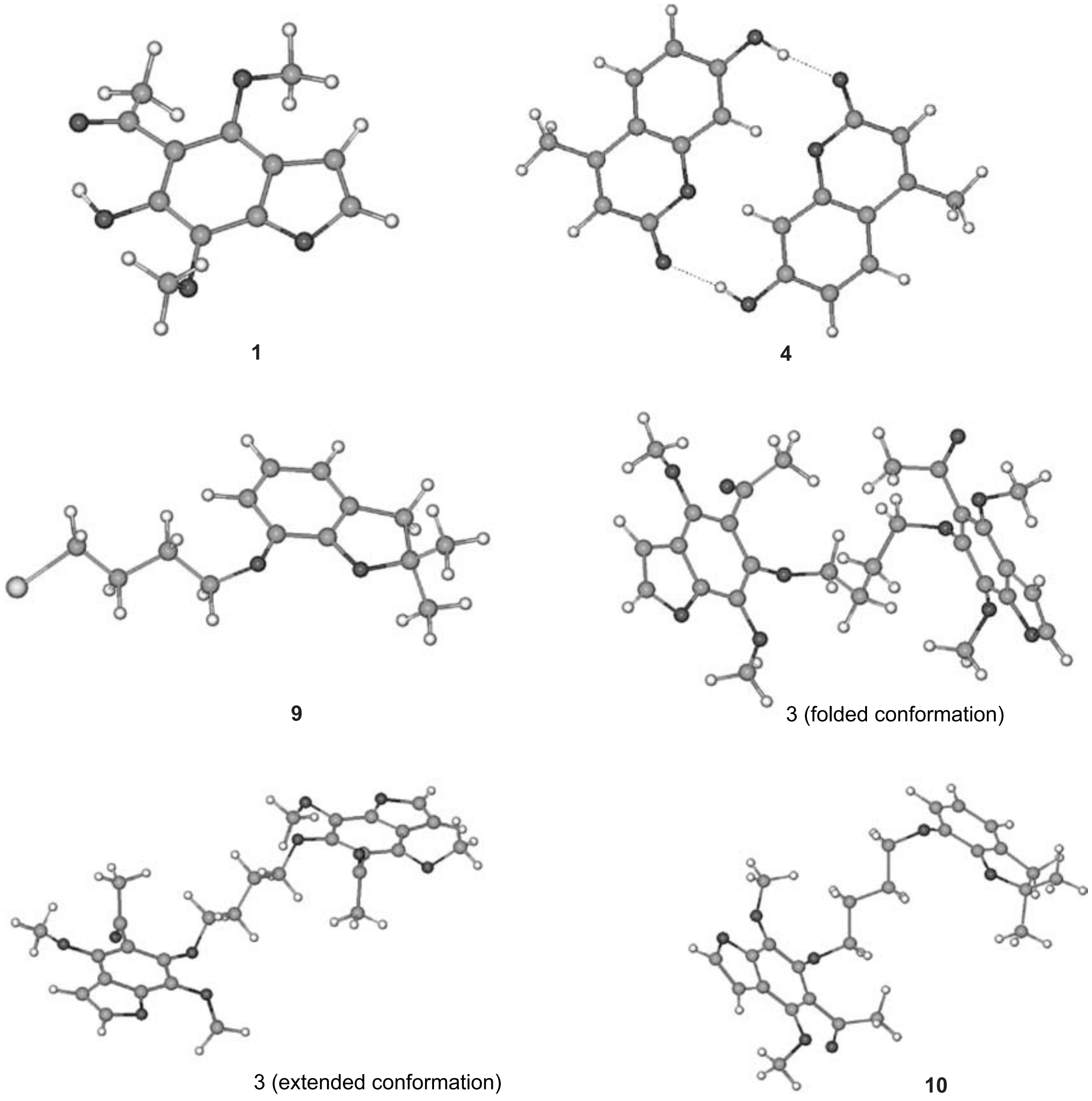


Fig. 7 Proposed and analyzed conformations in solid state of **1**, **3**, **3a**, **4**, **9**, and **10**

analyzed compounds of **1**, **3**, **4**, **5**, **9**, and **10** and compared them with the experimental chemical shifts δ/ppm. If we found the linear correlation between theoretical σ and experimental δ data, we proposed the probable structure of the most stable conformer in solid state. In the spectrum of 5-acetyl-6-hydroxy-4,7-dimethoxybenzofuran (khellinone) (**1**) we observed less resonances than carbon atoms in the molecule. The values of shielding constants are strongly dependent on locations of methoxy groups in different examined conformations. The best agreement with experimental chemical shifts we obtained for the structure shown in Fig. 7, with the intramolecular hydrogen bond between OH···O=C groups, and almost perpendicular orientation of both methoxy group planes to the benzene ring plane. The solid state spectrum of 7-hydroxy-4-methylcoumarin (**4**) represents a more classic example. All resonances are shifted to higher frequencies, what is in good agreement with a single pattern of shielding constants calculated for a dimer stabilized by the intermolecular interactions OH···O type also shown in Fig. 7. In the analysis of 8-acetyl-7-hydroxy-4-methylcoumarin (**5**) we used the X-ray derived atomic coordinates and optimized at the *PM*3 level of theory. For both types of coordinates we have obtained very good linear correlations between the theoretical and experimental values ($r^2 = 0.998$ and 0.996). It should mean that our conclusions concerning the solid state structures of the compounds

Table 5 Cytotoxicity of **3** ($GI_{50}/\mu M$)[a]

Leukemia	Non-small cell lung cancer	CNS cancer	Melanoma	Ovarian cancer	Prostate cancer	Breast cancer
CCRF-CEM 2.10 MOLT-4 1.86 RPMI-8226 2.06	EKVX 2.72 NCI-H23 5.66	SF-295 2.74	UACC-257 2.90	OVCAR-4 3.99	PC-3 2.14	NCI/ADR-RES 2.24 T47D 2.75

MGM[b] 4.59

[a] The cytotoxicity GI50 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, HL-60 (TB), K-562, MOLT-4, RPMI-8226, SR; non-small cell lung cancer: A549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, NCI-H460; 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-3M, M14, SK-MEL-2, SK-MEL-5, SK-MEL-28, UACC-257, UACC-62; Ovarian cancer: OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, SK-OV-3; Renal cancer: 786-0, A498, ACHN, CAKI-1, 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, I-47D

obtained by us based on molecular modeling and the experimental ^{13}C CP/MAS NMR chemical shifts are justified. We considered the solid 1-(2,3-dihydro-2,2-dimethylbenzofuran-7-yloxy)-4-bromobutane (**9**), because the unsubstituted 2,3-dihydro-2,2-dimethyl-7-benzofuranol is liquid at room temperature. Satisfying agreement of the theoretical *versus* the experimental values of resonances was obtained for the conformation shown in Fig. 7, in which the butyl linker exhibits an extended *zig-zag* conformation, and the butyloxy group is not placed within the benzene ring plane. Atom C4$''$ is pointed at the C6$'$ atom, what is reflected by low frequency shift of C6$'$ atom resonance by 4.1 ppm as compared to the solution spectrum. Separate, sharp resonances of *gem*-methyl groups at C2$'$ atom (29.6 and 29.1 ppm) show that there are no dynamics at C-2$'$ in the solid state. The discussion presented above helped us to carry out the conformational analysis of dimers **3** and **10**. We considered two orientations of the heterocyclic systems: the first one with O1 and O1$'$ atoms at the same side of the aliphatic linker with a folded conformation of the linker, and the second with O1 and O1$'$ atoms turned in opposite direction and a *zig-zag* conformation of the aliphatic linker (see Fig. 7). The latter conformations are more stable, by average 15 kJ/mol. Such conformations are compatible with the X-ray structure of another khellinone dimer [34]. For both types of conformations of **3** and **10** we calculated the theoretical shielding constants. We found better linear correlations between the experimental chemical shifts and those theoretical values which correspond to lower energy conformations ($r^2 \sim 0.98$). On this basis we were encouraged to propose extended conformations for both compounds **3** and **10** (see Fig. 7). The separations between the aromatic parts (C6$\cdots$C6$'$ and C6$\cdots$C7$'$) are close to 7.60 Å, and in each molecule both aromatic systems are almost parallel to each other. The methoxy groups 8 and 8$'$ in **3** show smaller deviations from the benzofuran ring plane than the other two methoxy groups 11 and 11$'$, and both acetyl groups which are almost perpendicular to them. The benzofuran system in compound **10** demonstrates the same features. Both methyl groups at C2$'$ atom in 1,2-dihydrobenzofuran system show only one signal of double intensity.

Anticancer assay

Compound **3** was accepted for evaluation by the Division of Cancer Treatment and Diagnosis National Cancer Institute (Bethesda, USA) 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. The details are available at the web site http://dtp.nci.nih.gov. Results from representative cell lines are listed in Table 5, along with mean graph midpoint (MGM) values for all 60 lines.

Conclusions

An efficient method of microwave-assisted synthesis was worked out for a series of benzofuran and coumarin derivatives. 1,4-*Bis*(5-acetyl-4,7-dimethoxybenzofuran-6-yloxy)butane (**3**) at micromolar concentrations reduces the growth of human leukemia, non-small cell lung cancer, CNS, melanoma, ovarian, and breast cancer cells.

The stable solid state conformations of 1,4-bis(5-acetyl-4,7-dimethoxybenzofuran-6-yloxy)butane (**3**), 1-(5-acetyl-4,7-dimethoxybenzofuran-6-yloxy)-4-(2,3-dihydro-2,2-dimethylbenzofuran-7-yloxy)butane (**10**), and their three components: 5-acetyl-6-hydroxy-4,7-dimethoxybenzofuran (**1**), 7-hydroxy-4-methylcoumarin (**4**), 8-acetyl-7-hydroxy-4-methylcoumarin (**5**) as well as 1-(2,2-dimethyl[2,3]dihydrobenzofuran-7-yloxy)-4-bromobutane (**9**) were proposed on the basis of ^{13}C CP/MAS NMR solid state spectra and molecular modeling at DFT level of theory.

The conformation of the molecule of 8-acetyl-7-hydroxy-4-methylcoumarin (**5**) was confirmed by X-ray analysis. The crystal structure of **5** is stabilized by intermolecular C–H$\cdots$O hydrogen bonds and stacking forces between parallel sheets.

Experimental

All chemicals were purchased from the major chemical suppliers as high or highest purity grade and used without any further purification. Microwave oven Plazmatronika 1000 W (http://www.plazmatronika.pl) equipped with a single mode cavity suitable for microscale synthesis and microwave choked outlet connected to external condenser, was used at its 50, 30, and 15% power. Melting points were determined with a Digital Melting Point Apparatus 9001. ^{1}H and ^{13}C NMR spectra in solution were recorded at 25°C with a Varian Unity plus-200, and standard Varian software was employed. Several (as indicated) ^{1}H and ^{13}C NMR spectra in solution were recorded with a Bruker Avance DMX 400. The solid state ^{13}C CP/MAS NMR spectra were measured using a Bruker Avance DMX 400. The powdered samples were spun at 8–10 kHz. Contact time of 6 ms, repetition time of 10 s, and spectral width of 24 kHz were used for accumulation of 4000 scans. Chemical shifts δ [ppm] were referenced to *TMS*. IR spectra were recorded on a FT IR Perkin Elmer instrument. High resolution mass spectra were recorded on Quattro LCT (TOF). Theoretical shielding constants were computed at DFT level of theory (*B3LYP*/6-31G** hybrid functional and CHF-GIAO approach) for geometries optimized at *PM*3 level of theory for all analyzed compounds, and additionally for X-ray derived atomic coordinates of **5**.

*Preparation of sodium salts of phenols **1**, **4**, **5**, and **8***

Phenolates **1a**, **4a**, **5a**, and **8a** were prepared by heating equimolar amounts of the appropriate phenol and powdered sodium hydroxide (3 mmol) in 2 cm^3 toluene under reflux in the monomode microwave oven (300 W, 10 min). The products were used without further purification.

*O-Alkylation of sodium salts of phenols **1a**, **4a**, **5a**, and **8a***

The alkylating agent (1,4-dibromobutane or bromoalkyl component **2** or **9**, 3 mmol), 193 mg tetrabutylammonium bromide (0.6 mmol), and 0.15 cm^3 water were added to the appropriate sodium salt. The mixture was heated under reflux in the microwave oven for 10–15 min (150 W). The products were purified by column chromatography on silica gel (eluent $CHCl_3$-*AcOEt* or cyclohexane-*AcOEt*).

1-(5-Acetyl-4,7-dimethoxybenzofuran-6-yloxy)-4-bromobutane (**2**, $C_{16}H_{19}O_5Br$)

This compound was prepared according to the methods described above using 0.709 g khellinone (3 mmol) and 0.12 g sodium hydroxide (3 mmol). The resulting sodium salt of khellinone, 0.36 cm^3 1,4-dibromobutane (3 mmol, 0.65 g), 0.194 g tetrabutylammonium bromide (0.6 mmol), and 0.15 cm^3 water were combined and heated under reflux in the microwave oven. The reaction was monitored on TLC on silica gel plates (eluent $CHCl_3$:*AcOEt*, 10:1, $R_f = 0.68$). The reaction mixture was dissolved in 10 cm^3 chloroform and the inorganic salts were filtered off. Solvent was evaporated and the residue purified by column chromatography on silica gel (eluent $CHCl_3$:*AcOEt*, 20:1). Yield 0.476 g, 43%, oil; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.84$ (m, 2 H, 3″-H_2), 1.98 (m, 2 H, 2″-H_2), 2.47 (s, 3 H, 10-H_3), 3.44 (t, $J = 6.6$ Hz, 2 H, 4″-H_2), 3.93 (s, 3 H, 8-H_3), 4.01 (m, 5 H, 11-H_3, 1″-H_2), 6.82 (d, $J = 2.2$ Hz, 1 H, 3-H), 7.52 (d, $J = 2.2$ Hz, 1 H, 2-H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 28.69$ (3″-C), 29.30 (2″-C), 32.86 (10-C), 33.60 (4″-C), 61.13 (8-C), 61.18 (11-C), 74.02 (1″-C), 105.04 (3-C), 116.43 (3a-C), 124.39 (5-C), 134.38 (7-C), 143.98 (6-C), 144.47 (4-C), 144.61 (2-C), 148.62 (7a-C), 202.06 (9-C) ppm; IR (neat): $\bar{\nu} = 2939$, 1703, 1604, 1477, 1346, 1265, 1136, 1068, 746 cm^{-1}; TOF MS ES+: $m/z = 393.0314$ [$C_{16}H_{19}O_5{}^{79}Br + Na$].

1,4-Bis(5-acetyl-4,7-dimethoxybenzofuran-6-yloxy)butane (***3***) [8]

Yield 1.34 g, 85%, mp 119–120°C (Ref. [8] 119–120°C); TLC: eluent $CHCl_3$:*AcOEt*, 10:1, $R_f = 0.51$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.89$ (m, 4 H, 2″, 3″-H_2), 2.54 (s, 6 H, 10, 10′-H_3), 3.99 (s, 6 H, 8,8′-H_3), 4.07 (s, 6 H, 11, 11′-H_3), 4.12 (m, 4 H, 1″, 4″-H_2), 6.87 (d, $J = 1.8$ Hz, 2 H, 3, 3′-H), 7.58 (d, $J = 1.8$ Hz, 2 H, 2, 2′-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 26.85$ (2″, 3″-C), 33.01 (10, 10′-C), 61.29 (8, 8′-C) 61.40 (11, 11′-C), 74.96 (1″, 4″-C), 105.17 (3, 3′-C), 116.53 (3a, 3′a-C), 124.68 (5, 5′-C), 134.59 (7, 7′-C), 144.10 (6, 6′-C), 144.70 (2, 2′), 144.88 (4, 4′-C), 148.53 (7a, 7′a -C), 202.24 (9, 9′-C) ppm; IR (KBr): $\bar{\nu} = 3157$, 3127, 3000–2841 (multiple bands), 1702, 1593, 1478, 1440, 1378, 1348, 1270, 1194, 1171, 1140, 1072, 1005, 988, 956, 921, 879, 843, 755 cm^{-1}.

1-(5-Acetyl-4,7-dimethoxybenzofuran-6-yloxy)-4-(4-methylcoumarin-7-yloxy)butane (**6**, $C_{26}H_{26}O_8$)

Yield 0.84 g, 60%, oil; TLC: eluent $CHCl_3$:*AcOEt*, 10:1, $R_f = 0.54$; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.96$ (m, 4 H, 2″,3″-H_2), 2.40 (d, $J = 1.2$ Hz, 3 H, 9′-H_3), 2.54 (s, 3 H, 10-H_3), 4.00 (s, 3H, 11-H_3), 4.08 (s, 3 H, 8-H_3,), 4.07 (m, 4 H, 1″-H_2, 4″-

H_2), 6.12 (d, $J = 1.2$ Hz, 1 H, 3′-H), 6.83 (d, $J = 2.2$ Hz, 3-H), 6.86 (d, $J = 8.7$ Hz, 1 H, 6′-H), 6.89 (m, 1 H, 8′-H), 7.50 (d, $J = 8.7$ Hz, 1 H, 5′-H), 7.59 (d, $J = 2.2$ Hz, 1 H, 2-H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 18.68$ (9′-C), 25.67 (2″-C), 26.68 (3″-C), 32.89 (10-C), 61.13 (8-C), 61.19 (11-C), 68.13 (4″-C), 74.56 (1″-C), 101.44 (6′-C), 105.06 (3-C), 111.84 (8′-C), 112.60 (3′-C), 113.47 (4′a -C), 116.40 (3a-C), 124.41 (5-C), 125.51 (5′-C), 134.40 (7-C), 144.00 (6-C), 144.60 (2-C, 4-C), 148.65 (7a-C), 152.61 (4′-C), 155.28 (2′-C), 161.38 (8′a-C), 162.16 (7′-C), 202.12 (9-C); IR (neat): $\bar{\nu} = 2943$, 1715, 1614, 1477, 1431, 1386, 1347, 1265, 1200, 1140, 1070, 989, 878, 846, 748 cm^{-1}; TOF MS ES+: $m/z = 489.1525$ [$C_{26}H_{26}O_8 + Na$].

1-(5-Acetyl-4,7-dimethoxybenzofuran-6-yloxy)-4-(8-acetyl-4-methylcoumarin-7-yloxy)butane (**7**, $C_{28}H_{28}O_9$)

Yield 0.82 g, 54%, oil; TLC: eluent $CHCl_3$:*AcOEt*, 10:1, $R_f = 0.36$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.84$ (m, 2 H, 2″-H_2), 1.97 (m, 2 H, 3″-H_2), 2.37 (s, 3 H, 9′-H_3), 2.50 (s, 3 H, 11′-H_3), 2.56 (s, 3 H, 9-H_3), 3.97, 4.04 (2 s, 6 H, 8, 11-H_3), 4.08 (t, $J = 6.0$ Hz, 2 H, 4″-H_2), 4.13 (t, $J = 6.0$ Hz, 2 H, 1″-H_2), 6.10 (s, 1 H, 3′-H), 6.85 (d, $J = 3.0$ Hz, 1 H, 3-H), 6.89 (d, $J = 9.2$ Hz, 1 H, 6′-H), 7.54 (d, $J = 9.2$ Hz, 1 H, 5′-H), 7.59 (d, $J = 3.0$ Hz, 2-H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 18.92$ (9′-C), 25.81 (2″-C), 26.66 (3″-C), 32.56 (11′-C), 33.06 (10-C), 61.28 (8,11-C), 68.95 (1″, 4″-C), 105.22 (3-C), 108.58 (6′-C), 112.63 (3′-C), 114.05 (4′a-C), 116.51 (3a-C), 119.73 (8′-C), 124.42 (5-C), 126.57 (5′-C), 134.49 (7-C), 144.14 (6-C), 144.58 (4-C), 144.80 (2-C), 148.81 (7a-C), 150.76 (4′-C), 152.38 (8′a-C), 158.13 (2′-C), 160.23 (7′-C), 199.50 (9-C), 202.34 (10′-C) ppm; TOF MS ES+: $m/z = 531.1631$ [$C_{28}H_{28}O_9 + Na$].

1-(2,2-Dimethyl[2,3]dihydrobenzofuran-7-yloxy)-4-bromobutane (**9**, $C_{14}H_{19}BrO_2$)

2,3-Dihydro-2,2-dimethyl-7-benzofuranol (Aldrich) (3 mmol, 0.493 g), 0.12 g sodium hydroxide (3 mmol), 2.073 g anhydrous potassium carbonate (15 mmol), 1.8 cm^3 1,4-dibromobutane (15 mmol, 3.25 g), 0.1 g tetrabutylammonium bromide (0.3 mmol) were combined and heated under reflux in the microwave oven (500 W). The reaction was monitored on TLC on silica gel plates (eluent cyclohexane:*AcOEt*, 5:1, $R_f = 0.78$). The reaction mixture was dissolved in $CHCl_3$ (10 cm^3), the inorganic salts were filtered off. Solvent was evaporated and the residue purified by column chromatography on silica gel (eluent cyclohexane:*AcOEt*, 10:1). Yield 0.74 g, 82%, mp 40–41°C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.51$ (s, 6 H, 8′, 9′-H_3), 1.96 (q, $J = 6.8$ Hz, 2 H, 2″-H_2), 2.05 (q, $J = 6.8$ Hz, 2 H, 3″-H_2), 3.02 (s, 2 H, 3′-H), 3.49 (t, $J = 6.4$ Hz, 2 H, 1″-H_2), 4.094 (t, $J = 6.4$ Hz, 2 H, 4″-H_2), 6.76 (m, 3 H, 4′, 5′, 6′-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.20$ (3″-C), 28.40 (8′,9′-C), 29.58 (2″-C), 33.72 (1″-C), 43.46 (3′-C), 68.30 (4″-C), 87.36 (2′-C), 113.44 (6′-C), 117.94 (5′-C), 120.40 (4′-C), 128.48 (3′a-C), 143.73 (7′-C), 148.04 (7′a-C) ppm; IR (KBr): $\bar{\nu} = 3070$, 3049, 2969–2872 (multiple bands), 1614, 1592, 1471, 1492, 1436, 1369,1303, 1281, 1243,1199, 1129, 1075, 955, 877, 846, 775, 755, 720, 627 cm^{-1}.

1-(5-Acetyl-4,7-dimethoxybenzofuran-6-yloxy)-4-(2,3-dihydro-2,2-dimethylbenzofuran-7-yloxy)butane (**10**, $C_{26}H_{30}O_7$)

Yield 0.54 g, 40%, mp 64–66°C; TLC: eluent $CHCl_3$:*AcOEt*, 10:1, $R_f = 0.78$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.50$ (s, 6 H, 8′,9′-H_3), 1.94 (m, 4 H, 2″, 3″-H_2), 2.52 (s, 3 H, 10-H_3), 3.01 (s, 1 H, 3′-H), 3.98 (s, 3 H, 11-H_3), 4.06 (s, 3 H, 8-H_3), 4.10 (m, 2 H, 1″-H_2), 4.12 (m, 2 H, 4″-H_2), 6.76 (s, 3 H, 4′,5′,6′-H), 6.87 (s,1 H, 3-H), 7.57 (s, 1 H, 2-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 26.02$ (3″-C), 26.94 (2″-C), 28.50 (8′, 9′-C), 33.14 (10-C), 43.59 (3′-C), 61.40 (8-C), 61.51 (11-C), 68.91 (4″-C), 75.06 (1″-C), 87.40 (2′-C), 105.29 (3-C), 113.21 (6′-C), 116.61 (3a-C), 117.74 (5′-C), 120.52 (4′-C), 124.75 (5-C), 128.59 (3′a-C), 134.65 (7-C), 144.05 (7′-C), 144.20 (4-C) 144.79 (2-C), 144.98 (6-C), 148.03 (7a-C), 148.94 (7′a-C), 202.43 (9-C) ppm; IR (KBr): $\bar{\nu} = 3153$, 3129, 2964–2848 (multiple bands), 1704, 1614, 1592, 1542, 1478, 1491, 1374, 1346, 1303, 1283, 1269, 1198, 1170, 1139, 1075, 954, 871, 776, 759, 723, 632 cm^{-1}; TOF MS ES+: $m/z = 477.1889$ [$C_{26}H_{30}O_7 + Na$].

7-Hydroxy-4-methylcoumarin (***4***)

A mixture of 2.2 g resorcinol (20 mmol), 4.0 cm^3 ethyl acetoacetate (30 mmol) and 0.417 g *p*-toluenesulfonic acid (2.2 mmol) in 35 cm^3 toluene was heated at reflux for 8 h with azeotropic removal of water and ethanol by use of a *Dean-Stark* trap. The reaction mixture was left overnight. Then 50 cm^3 ice–water were added and the mixture was stirred for 45 min. The precipitate was filtered off and dried. Crystallization (*Me*OH) yielded a colorless solid, 3.17 g (90%), mp 187–188°C (Ref. [35] 188°C (*Me*OH, H_2O)).

8-Acetyl-7-hydroxy-4-methylcoumarin (***5***)

Using of 2,6-dihydroxyacetophenone (Aldrich) instead of resorcinol resulted in yellow solid, yield 80%, mp 174–175°C (*Et*OH) (Ref. [36] 172–175°C (*Et*OH)).

X-Ray diffraction studies

Crystals of **5** suitable for X-ray analysis were grown by slow evaporation from ethanol solution. The data were collected on an Oxford Diffraction KM4CCD diffractometer [37] at 293 K, using graphite-monochromated MoK_α radiation. The unit cell parameters were determined by least-squares treatment of setting angles of highest-intensity reflections chosen from the whole experiment. Intensity data were corrected for the *Lorentz* and polarization effects [37]. The structures were solved by direct methods by use of the SIR2004 program [38] and refined by the full-matrix least-squares method with the SHELXL97 program [39]. The function $\Sigma w(|F_o|^2 - |F_c|^2)^2$ was minimized with $w^{-1} = [\sigma^2(F_o)^2 + (0.0655P)^2 + 0.0654P]$, where $P = (F_o^2 + 2F_c^2)/3$. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in the calculated positions and then their positional and thermal parameters were refined. An empirical extinction correction was also applied according to the formula $F_c' = kF_c[1 + (0.001\chi F_c^2\lambda^3/\sin 2\theta)]^{-1/4}$ [39], and the extinction coefficient χ was equal to 0.071(9).

The deposition number CCDC 678518 for **5** contains 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.

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