Synthesis and cytotoxicity of novel benzofuran neolignan derivatives

Hua-Fang Fan, Ying-Mei Ren, Xiu-Ling Wu and Qiu-An Wang*

State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, P. R. China

A series of 10 related benzofuran neolignan derivatives were obtained by utilising a biomimetic reaction sequence involving oxidative dimerisation of methyl ferulate, followed by derivatisation reactions. The structures of the new compounds were confirmed by ^{1}H NMR, elemental analysis, MS and IR. All compounds were evaluated for their cytotoxic potential against five human cancer cell lines (HL-60, SMMC-7721, A-549, SK-BR-3 and PAN-1) by the standard MTT method. The results showed that most of them exhibit potent cytotoxicity.

Keywords: benzofuran neolignans, synthesis, cytotoxicity

The benzofuran system, as a significant pharmacophore, is contained in numerous compounds which can be isolated from natural sources as well as in synthetic products. Multiple substituted benzofuran neolignans have received increasing attention due to their excellent biological activities, such as antitumour, antifungal, antimicrobial, antivirus and adenosine aluminium agonist properties.[1,2] Despite many recent reports on benzofuran neolignans and related compounds,[3–7] the full potential of this class of compounds has yet to be realised in terms of both more new molecules and diverse biological activity as drugs.

The present investigation was stimulated by the discovery of some synthetic dihydrobenzofuran neolignans and related benzofuran compounds, which showed potent cytotoxic activity against the human cancer cell lines (HL-60, K-562, NCI-H522, HCT-15, SF-539, M14, OVCAR-3, VO-31, DV-145, MB-435, MDA-N and BT-549).[8] The cytotoxicity of these benzofuran neolignans is strongly dependent on the substitution pattern. Alterations in the chemical structure of benzofuran have significant effects on their biological properties.

With the aim of developing new antitumour-active compounds and investigating structure–activity relationships of benzofuran neolignans derivatives **4–13**, the present study reports the synthesis and cytotoxicity bioassays of a series among which, compounds **5** (herpetol[9]), **6**, **8–13**, were first synthesised.

Results and discussion

The title compounds were synthesised according to the route shown in Scheme 1. With methyl ferulate as the starting material, Ag_2O-catalysed biomimetic oxidative coupling was the crucial step[10] in the reaction sequence, which generated its dimer in 43% yield. The structure of the dimer was found to be the dihydrobenzofuran compound characterised by ^{1}H NMR and MS. Acetylation of the dimer with acetic anhydride and pyridine afforded the compound **1**. This was then dehydrogenated by 2.3-dichloro-5, 6-dicyanobenzoquinone (DDQ) in 1, 4-dioxane to give the compound **2**. Hydrolysis of **2** in the presence of potassium carbonate and methanol under reflux gave the compound **3**. Compound **4** was obtaineded by catalytic hydrogenation of the double bond in the side chain of compound **2** in THF, with 5% Pd/C as catalyst. Compounds **2** and **4** were subjected to reduction by lithium aluminium hydride to afford the corresponding benzofuran neolignan monoalcohol derivatives **6, 7** and diols **5, 8**, respectively.

Prenyl or farnesyl moieties can potentially substitute for conventional lipids as lipophilic carriers of bioactive molecules. The introduction of a prenyl or farnesyl moiety in bioactive molecules is an important post-translational modification centre to many cellular processes.[11,12] Next, we turned our attention to modification of benzofuran neolignans by the prenyl or farnesyl moiety. Compounds **3, 5** and **6**, were reacted with commercially available prenyl bromide or *trans, trans*-farnesyl bromide in the presence of anhydrous potassium carbonate and anhydrous acetone at ambient temperature, to give five *O*-prenyl or *O*-farnesyl substituted benzofuran neolignans derivatives **9–13**.

The 10 benzofuran neolignans derivatives **4–13** were tested for cytotoxic activity against myeloid leukaemia (HL-60), liver carcinoma (SMMC-7721), lung carcinoma (A-549), breast tumour cells (SK-BR-3) and pancreatic cancer (PANC-1) cell line by standard MTT method. The results showed that most of them have good activity. IC_{50} values (μg/mL) of synthetic novel benzofuran neolignans derivatives on five human caner cell lines were plotted in Table 1. Compounds **5, 6** and **12** exhibited potent cytotoxicity against the PANC-1 cancer cell line with IC_{50} values of 10.83, 12.32 and 19.84 μg/mL respectively. Compounds **7** and **12** showed cytotoxicity against cancer cell line A-549 with IC50 values of 7.2 and 3.65 μg/mL. Compound **12** showed cytotoxicity against cancer cell line SMMC-7721 with IC_{50} values of 7.61 μg/mL. Biological activities of all the compounds mentioned above are similar or even improved compared with the positive control, cisplatin (DPP).

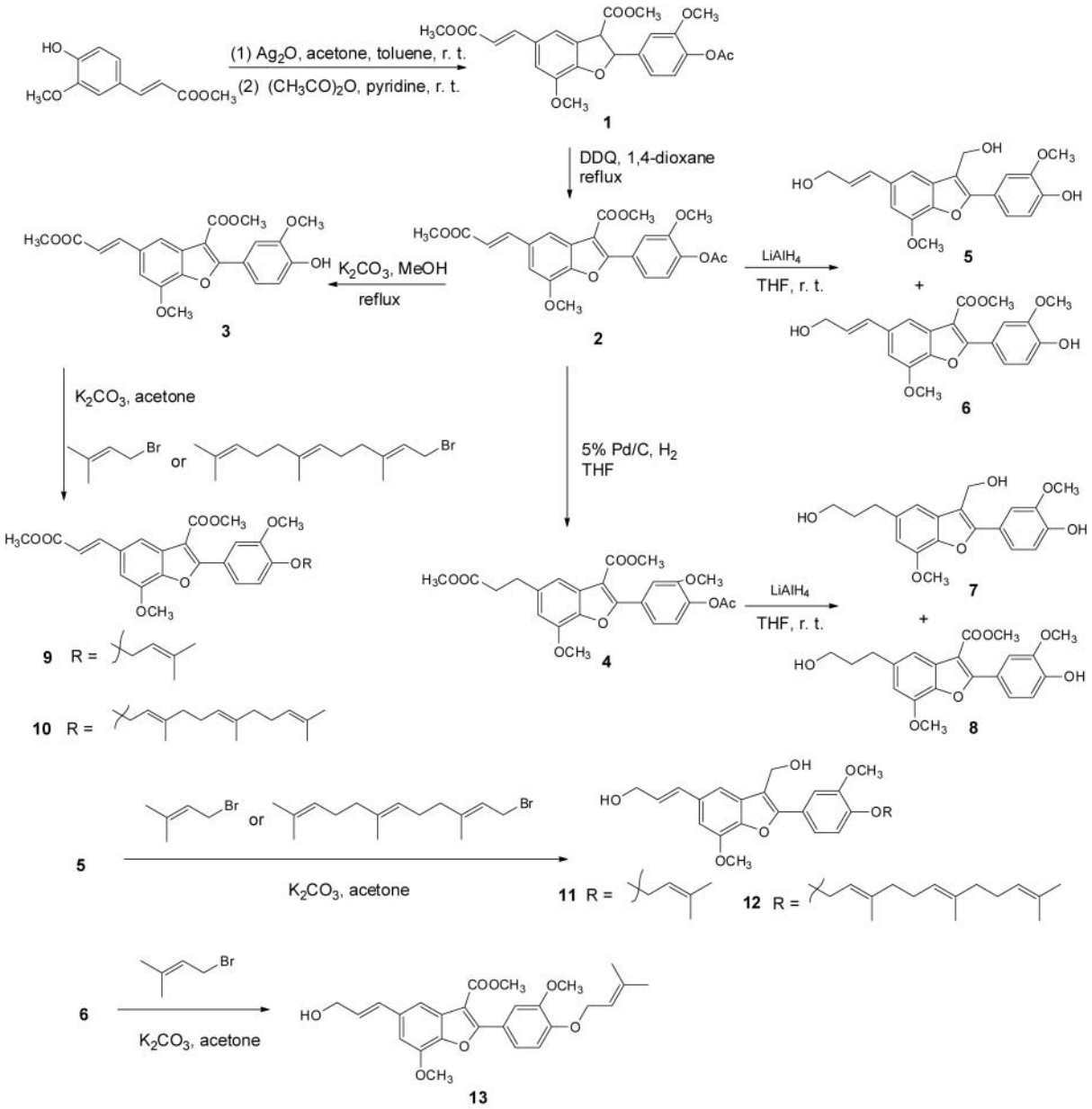
Experimental

Melting points were measured on a XRC-I apparatus and were uncorrected. IR spectra were recorded on a Bruker Tensor-27 spectrometer, ^{1}H NMR spectra were recorded on a Bruker AM-400 instrument, using tetramethylsilane as an internal standard, chemical shifts (δ) in ppm, coupling constants (*J*) in Hz, Mass spectra were determined with ZAB-HS spectrometer by the EI or FAB method. Elemental analyses were carried out on a Perkin-Elmer 240B microanalyser. All solvents were dried by standard procedures. Methyl ferulate was prepared from vanillin and malonic acid by the reported procedure[13]. 2-(3-methoxy-4-acetyloxyphenyl)-3-methoxycarbonyl-5-(3-methoxycarbonylvinyl)-7-methoxy-2,3-dihydrobenzo[b]furan (**1**)[14], 2-(3-methoxy-4-acetyloxyphenyl)-3-methoxycarbonyl-5-(3-methoxycarbonylvinyl)-7-methoxybenzo[b]furan (**2**)[14], 2-(3-methoxy-4-hydroxyphenyl)-3-methoxycarbonyl-5-(3-methoxycarbonylvinyl)-7-methoxybenzo[b]furan (**3**)[14] and 2-(3-methoxy-4-acetyloxyphenyl)-3-methoxycarbonyl-5-(3-methoxycarbonylethyl)-7-methoxybenzo[b]furan (**4**)[8] were prepared according to previous methods.

*Synthesis of herpetol (**5**) and 2-(3-methoxy-4-hydroxyphenyl-3-methoxycarbonyl-5-(3-hydroxypropenyl)-7-methoxybenzo [b]furan (**6**)*: To a solution of compound **2** (115 mg, 0.25 mmol) in THF (10 mL) $LiAlH_4$ (45 mg, 1.19 mmol) was added at 0°C. After stirring at room temperature for 5 h, the reaction mixture was decomposed with 5% H_2SO_4 (5 mL), then water (10 mL) was added. The aqueous solution was extracted with EtOAc (3 × 15 mL), and the organic layer was washed with brine (2 × 15 mL), dried over anhydrous $mgSO_4$. The solvent was removed in a vacuum, the residue was chromatographed on a silica gel with petroleum ether/ethyl acetate (1:1) to give herpetol (**5**) as white solid 57 mg, yield 50.5%, and compound **6** as white solid 23 mg, yield 15.2%.

Herpetol (**5**): M.p. 167–168°C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.49 (s, ^{1}H, 4′-OH), 7.40 (d, *J* = 2.0 Hz, ^{1}H, H-2′), 7.31 (s, ^{1}H, H-4),

* Correspondent. E-mail: wangqa@hnu.cn



Scheme 1 Synthetic route of benzofuran neolignans derivatives **4–13**.

Table 1 IC_{50} values (μg/mL) of benzofuran neolignans derivatives on the human cancer cell lines

Compound	HL-60	SMMC-7721	A-549	SK-BR-3	PANC-1
4	4.03	23.37	22.68	>30	>30
5	2.31	13.49	>30	11.62	10.83
6	2.30	13.61	>30	>30	12.32
7	>30	>30	>30	>30	>30
8	3.88	18.90	7.20	>30	>30
9	>30	>30	>30	>30	>30
10	>30	>30	>30	>30	>30
11	>30	>30	>30	>30	>30
12	3.6	7.61	3.65	21.93	19.84
13	3.09	22.05	>30	>30	>30
DDP (MW300)	0.51	5.87	9.00	5.27	19.84

7.29 (dd, J = 8.0, 2.0 Hz, ^{1}H, H-6′), 7.03 (s, ^{1}H, H-6), 6.94 (d, J = 8.0 Hz, ^{1}H, H-5′), 6.64 (d, J = 16.0 Hz, ^{1}H, H-8), 6.41 (m, ^{1}H, H-9), 5.28 (t, J = 5.2 Hz, ^{1}H, 11-OH), 4.88 (t, J = 5.6 Hz, ^{1}H, 10-OH, 4.70 (d, J = 4.8 Hz, 2H, H-11), 4.16 (m, J = 5.6, 5.2 Hz, 5.2 Hz, 2H, H-10), 3.99, 3.86 (s, 3H/each, -OCH_3). IR (KBr) cm^{-1}: 3473, 3455, 3001, 2937, 2852, 1654, 1609, 1514, 1465, 1429, 1377, 1312, 1272, 1221, 1146, 1102, 1056, 994, 886, 859; MS: *m/z* 356 [M$^+$]. Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66. Found: C, 67.28; H, 5.42%. The spectral data are in agreement with those reported previously for this compound.[9]

6: M.p 169–170°C, ^{1}H NMR (DMSO-d_6, 400 MHz):δ9.77 (s, ^{1}H, 4′-OH), 7.64 (d, J = 2.0 Hz, ^{1}H, H-2′), 7.51 (s, ^{1}H, H-4), 7.45 (dd, J = 8.0, 2.0 Hz, ^{1}H, H-6′), 7.14 (s, ^{1}H, H-6), 6.92 (d, J = 8.0 Hz, ^{1}H, H-5′), 6.66 (m, J = 16.0 Hz, ^{1}H, H-8), 6.64 (m, ^{1}H, H-9), 4.89 (t, ^{1}H, 10-OH), 4.16 (m, 2H, H-10), 3.99, 3.88, 3.84 (s, 3H/each, -OCH_3). IR (KBr)cm^{-1}:3540, 3481, 3414, 3017, 2946, 2849, 1712, 1598, 1570, 1511, 1469, 1451, 1424, 1378, 1320, 1276, 1236, 1222, 1148, 1098, 1048, 963, 852, 812, 788, 735, 696, 603. MS: *m/z* 384 [M$^+$]. Anal. Calcd for $C_{21}H_{20}O_7$: C, 65.62; H, 5.24. Found: C, 65.33; H, 5.43%.

*Synthesis of 2-(3-methoxy-4-hydroxyphenyl)-3-methoxycarbonyl-5-(3-hydroxypropyl)-7-methoxy benzo [b] furan (***7***) and 2-(3-methoxy-4-hydroxyphenyl)-3-hydroxymethyl-5-(3-hydroxypropyl)-7-methoxy benzo[b] furan (***8***)*: To a solution of compound **4** (542 mg, 1.19 mmol) in THF (10 mL) was added $LiAlH_4$ (90 mg, 2.38 mmol) at 0°C. After stirring at room temperature for 12 h, the reaction mixture was quenched with 5% H_2SO_4 (160 mL), then water (10 mL) was added. The aqueous solution was extracted with EtOAc (3 × 20 mL), the organic layer was washed with brine (2 × 20 mL), dried over anhydrous

$MgSO_4$. The solvent was evaporated and purified by silica gel chromatography with petroleum ether/ethyl acetate (1:1) as eluent to afford compound **7** as white solid 140 mg, yield: 33%; and compound **8** as white solid 200 mg, yield: 44%.

7: M.p. 122–123°C; ^{1}H NMR ($DMSO_3$-d_6, 400 MHz): δ 9.47 (s, ^{1}H, 4′-OH), 7.39 (d, *J* = 1.2 Hz, ^{1}H, H-2′), 7.28 (dd, *J* = 8.0, 1.2 Hz, ^{1}H, H-6′), 7.10 (s, ^{1}H, H-4), 6.91 (d, *J* = 8.0 Hz, ^{1}H, H-5′), 6.76 (s, ^{1}H, H-6), 5.25 (t, *J* = 4.8 Hz, ^{1}H, 11-OH), 4.68 (d, *J* = 4.8 Hz, 2H, H-11), 4.52 (s, ^{1}H, 10-OH), 3.95, 3.86 (s, 3H/each, OCH_3), 3.48–3.43 (m, 2H, H-10), 2.70 (t, *J* = 8.0 Hz, 2H, H-8), 1.83–1.76 (m, 2H, H-9). MS: *m/z* 358 [M$^+$]. Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19. Found: C, 66.62; H, 5.85%. The spectral data are in agreement with those reported previously for this compound.[15]

8: M.p. 119–120°C, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (d, *J* = 2.0 Hz, ^{1}H, H-2′), 7.60 (dd, *J* = 8.0, 2.0 Hz, ^{1}H, H-6′), 7.42 (d, *J* = 0.8 Hz, ^{1}H, H-4), 6.99 (d, *J* = 8.0 Hz, ^{1}H, H-5′), 6.68 (d, *J* = 0.8 Hz, ^{1}H, H-6), 6.46(s, ^{1}H, 4′-OH), 3.98, 3.93, 3.92 (s, 3H/each,-OCH_3), 3.72, 2.80 (m, 2H, H-10), 2.70 (t, *J* = 8.0 Hz, 2H, H-8), 1.83–1.76 (m, 2H, H-9), IR (KBr) cm^{-1}: 3454, 3311, 3086, 2950, 2840, 1710, 1597, 1521, 1477, 1434, 1287, 1242, 1138, 1092, 1046, 877, 821. MS: *m/z* 384 [M$^+$]. Anal. Calcd for $C_{2}{}^{1}{}_{H}{}_{22}O_7$: C, 65.28; H, 5.74. Found: C, 64.91; H, 5.52%.

*Synthesis of 2-(3-methoxy-4-O-prenylphenyl)-3-methoxycarbonyl-5-(3-hydroxypropenyl)-7-methoxy benzo [b] furan (***9**): To a mixture of compound **3** (50 mg, 0.12 mmol) and anhydrous K_2CO_3 (165 mg, 1.2 mmol) in dry acetone, a solution of prenyl bromide (0.04 mL, 0.12 mmol) in acetone (2 mL) was added dropwise with stirring. The reaction was allowed to proceed at room temperature for 3 h, and then the reaction mixture was filtered and evaporated. The residue was subjected to chromatography on silica gel with petroleum ether/ethyl acetate (3:1) as eluent to give compound **9** as a light yellow solid 30 mg, yield 52%; m. p. 135–136°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ7.82 (s, ^{1}H, H-4), 7.72 (d, *J* = 2.0 Hz, ^{1}H, H-2′), 7.70 (dd, *J* = 8.0 Hz, ^{1}H, H-5′), 6.47 (d, *J* = 16.0 Hz, ^{1}H, H-9), 5.54 (t, *J* = 6.8 Hz, ^{1}H, H-2′), 4.68 (d, *J* = 6.8 Hz, 2H, H-1′), 4.06, 3.97, 397, 3.84 (s, 3H/each,-OCH_3), 1.69 (s, 3H, –CH_3), 1.60 (s, 3H, –CH_3). IR (KBr)cm^{-1}: 3092, 2948, 1723, 1912, 1602, 1511, 1478, 1246, 1148, 1088, 1055, 846. MS (FAB$^+$): *m/z* 483 (M+1)$^+$. Anal. Calcd for $C_{27}H_{28}O_8$: C, 67.49; H, 5.87. Found: C, 67.62; H, 5.96%.

Synthesis of 2-(3-methoxy-4-O-farnesylphenyl)-3-methoxy carbonyl-5-(3-hydroxypropenyl)-7-methoxybenzo [b] furan (**10**): Prepared from compound **3** and *trans, trans*-farnesyl bromide by the same procedure as for **9** synthesis. Yield: 52%; White solid; m. p. 100–101°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, *J* = 16.0 Hz, ^{1}H, H-8), 7.80 (s, ^{1}H, H-4), 7.73 (d, *J* = 1.6 Hz, ^{1}H, H-2), 7.70 (dd, *J* = 8.41, 1.6 Hz, ^{1}H, H-6′), 7.02 (s, ^{1}H, H-6), 6.97 (d, *J* = 8.4 Hz, ^{1}H, H-5′), 6.47 (d, *J* = 16.0 Hz, ^{1}H, H-9), 5.54 (t, ^{1}H, H-2′), 5.13–5.06 (m, 2H, H-6″, H-10″), 4.67 (d, *J* = 16.0 Hz, 2H, H-1″), 4.05 (s, 3H, 11-OCH_3), 3.97 (s, 6H, 10, 3′-OCH_3), 3.84 (s, 3H, 7-OCH_3), 2.15–1.94 (m, 8H,-CH_2-4″, 5″, 8″, 9″). IR (KBr)cm^{-1}: 3093, 2948, 2920, 1716, 1632, 1601, 1510, 1475, 1247, 1232, 1149, 1084, 1039, 845, 785; MS (FAB$^+$): *m/z* 615 (M+1)$^+$. Anal. Calcd for $C_{37}H_{42}O_8$: C, 72.29; H, 6.89. Found: C, 72.55; H, 6.68%.

*Synthesis of 2-(3-methoxy-4-O-prenylphenyl)-3-hydroxymethyl-5-(3-hydroxypropenyl)-7-methoxy benzo[b] furan (***11**): Prepared from herpetol (**5**) and prenyl bromide as described for the preparation of compound **9** from compound **3** and prenyl bromide. White solid, yield: 23%; m.p. 98–99°C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.41 (d, *J* = 5.0 Hz, ^{1}H, H-2′), 7.38 (dd, *J* = 8.4, 2.0 Hz, ^{1}H, H-6′), 7.32 (s, ^{1}H, H-4), 7.14 (d, *J* = 8.8 Hz, ^{1}H, H-5′), 7.05 (s, ^{1}H, H-6), 6.64 (d, *J* = 16.0 Hz, ^{1}H, H-8), 6.41 (m, ^{1}H, H-9), 5.47 (t, *J* = 6.8 Hz, ^{1}H, H-2″), 5.3 (t, *J* = 5.2 Hz, ^{1}H, 11-OH), 4.88 (t, *J* = 5.6 Hz, ^{1}H, 10-OH), 4.70 (d, *J* = 4.8 Hz, 2H, H-11), 4.59 (d, *J* = 6.4 Hz, 2H, H-1′), 4.15 (dd, *J* = 5.6, 5.2 Hz, 2H, H-10), 3.99, 3.84 (s, 3H/each,-OCH_3), 1.77, 1.73 (s, 3H/each,-CH_3). MS (FAB$^+$): *m/z* 425 (M+1)$^+$, Anal. Calcd for $C_{25}H_{28}O_6$: C, 70.7; H, 6.65. Found: C, 70.49; H, 6.42%.

Synthesis of 2-(3-methoxy-4-O-farnesylphenyl)-3-hydroxylmethyl-5-(3-hydroxyl-propenyl)-7-methoxy benzo[b] furan (**12**): Prepared from herpetol (**5**) and *trans, trans*-farnesyl bromide as described for the preparation of compound **9** from compound **3** and prenyl bromide. Light yellow solid, yield: 46%; m. p. 68–69°C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.41 (d, *J* = 2.0 Hz, ^{1}H, H-2′), 7.36 (m, ^{1}H, H-6′), 7.31 (s, ^{1}H, H-4), 7.12 (d, *J* = 8.4 Hz, ^{1}H, H-5′), 7.04 (d, *J* = 1.2 Hz, ^{1}H, H-6), 6.64 (d, *J* = 16.4 Hz, ^{1}H, H-8), 6.41 (m, ^{1}H, H-9), 5.45 (t, *J* = 6.0, ^{1}H, H-2″), 5.30 (t, *J* = 5.2 Hz, ^{1}H, OH-11), 5.07 (m, 2H, H-6″, 10″), 4.87 (t, *J* = 5.2 Hz, ^{1}H, OH-10), 4.69 (d, *J* = 5.2 Hz, 2H, H-11), 4.61 (d, *J* = 6.8 Hz, 2H, H-1″),4.15 (dd, *J* = 5.2 Hz, 2H, H-10), 3.98, 3.84 (s, 3H/each,-OCH_3), 2.10-1.89 (m, 8H, H-4″, 5″, 8″, 9″), 1.72, 1.61, 1.60, 1.54 (s, 3H/each, –CH_3). IR (KBr) cm^{-1}: 3376, 2965, 2920, 1670, 1599, 1514, 1479, 1381, 1344, 1310, 1254, 1221, 1189, 1148, 1091, 1038, 993, 965, 854, 802, 778, 702; MS (FAB$^+$): *m/z* 559 (M+1)$^+$. Anal. Calcd for $C_{35}H_{42}O_6$: C, 75.24; H, 7.58. Found: C, 75.51; H, 7.42%.

Synthesis of 2-(3-methoxy-4-O-prenylphenyl)-3-methoxy carbonyl-5-(3-hydroxypropenyl)-7-methoxybenzo [b] furan (**13**): Prepared from compound **6** and prenyl bromide as described for the preparation of compound **9** from compound **3** and prenyl bromide. White solid, yield: 26%; m. p. 104–105°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69 (d, *J* = 2.0 Hz, ^{1}H, H-2′), 7.67 (dd, *J* = 8.4, 2.4 Hz, ^{1}H, H-6′), 7.60 (d, *J* = 1.2 Hz, ^{1}H, H-4), 6.963 (d, *J* = 8.4 Hz, ^{1}H, H-5′), 6.92 (d, *J* = 1.2 Hz, ^{1}H, H-6), 6.73 (d, *J* = 16.0 Hz, ^{1}H, H-8), 6.39 (m, ^{1}H, H-9), 5.54 (m, ^{1}H, H-2″), 4.67 (d, *J* = 6.4 Hz, 2H, H-1″), 4.37 (m, 2H, H-10), 4.03, 3.96, 3.95 (s, 3H/each, –OCH_3), 1.79, 1.76 (s, 3H/each, –CH_3). IR (KBr) cm^{-1}: 3429, 2939, 2858, 2598, 2031, 1712, 1599, 1509, 1468, 1383, 1314, 1262, 1181, 1143, 1093, 1048, 990, 887, 861, 790, 738. MS (FAB$^+$): *m/z* 453 (M+1)$^+$. Anal. Calcd for $C_{26}H_{28}O_7$: C, 69.01; H, 6.24. Found: C, 69.29; H, 6.38%.

Assay for cytotoxic activity

The cytotoxic assay was performed by using the (4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay method, cisplatin (DDP, MW300) as a positive control. Five different human cancer cell lines, myeloid leukaemia (HL-60), liver carcinoma (SMMC-7721), lung carcinoma (A-549), breast tumour cell (SK-BR-3) and pancreatic cancer (PANC-1), were cultured on DMEM or RPMI-1640 medium supplemented with foetal bovine serum (10%). A suspension of the cells was added to each well ($1 \times 10^4 - 2 \times 10^4$ cells/well, 100 μL) of 96-microwell plate and incubated for 12 h. Test compounds were dissolved in DMSO at various concentrations (30, 10, 1 and 0.1 μg/mL) and 10 μL of the test solutions or DMSO (control) was added to each well. The plate was incubated at 37°C for 48 h. After termination of the cell culture by adding 5% MTT in PBS (20 μL) to each well, the plate was kept in the incubator for 4 h. To each well was added 100 μL of 20% SDS, the formazan crystals were dissolved and the plate was read on a microplate reader (Bio-Rad 680) at 595 nm. A dose–response curve was plotted for each compound, and the half maximal inhibitory concentration (IC_{50}) for cancer cell lines was recorded.

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