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PAPER

Design, synthesis and cytotoxic activities of novel hybrid compounds between dihydrobenzofuran and imidazole†

Wen Chen,‡[a,b] Xiao-Dong Yang,‡[a] Yan Li,[c] Li-Juan Yang,[b] Xue-Quan Wang,[a] Gao-Lan Zhang[a] and Hong-Bin Zhang*[a]

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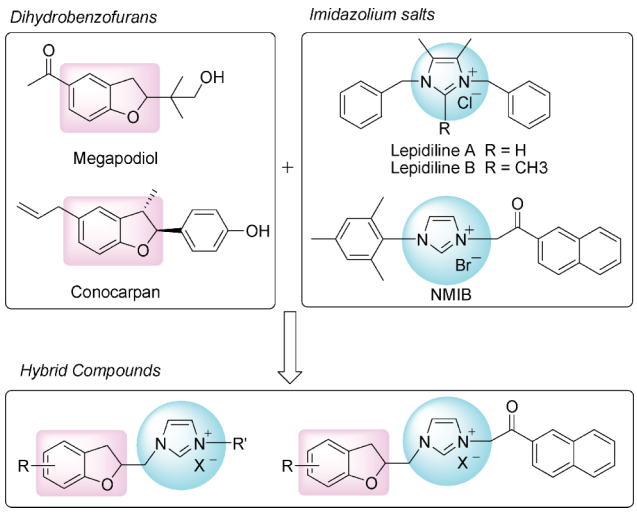
A series of novel hybrid compounds between dihydrobenzofuran and imidazole has been prepared and evaluated *in vitro* against a panel of human tumor cell lines. The results suggest that substitution of the imidazolyl-1-position with an electron-donating dihydrobenzofuran, and the imidazolyl-3-position with a naphthylacyl or electron-rich phenacyl group, were vital for modulating cytotoxic activity.

Introduction

Design and synthesis of new types of pharmacologically interesting hybrid compounds for drug discovery have received much attention during the past two decades.[1] Naturally occurring substituted-2,3-dihydrobenzofurans are an important class of biologically active oxygen-containing heterocycles. Natural products possessing the dihydrobenzofuran moiety exhibit a broad range of biological and pharmacological activities.[2] Recently, natural occurring dihydrobenzofurans have been identified to possess antitumor activity. As exemplified in Scheme 1, Megapodiol is an anti-leukaemic agent[3] and Conocarpan is an anticancer agent.[4] There are also dihydrobenzofuran derived compounds exhibiting potent cytotoxic activity and presenting the effect on cell cycle and apoptosis.[5,6]

Imidazolium salts have attracted considerable interest in recent years for their versatile properties in chemistry and pharmacology. Biological activities of imidazolium salts have been reported,[7] especially antitumor activity.[8] For example (Scheme 1), two new imidazolium halides (Scheme 1), Lepidiline A and Lepidiline B, isolated from the roots of *Lepidium meyenii*, showed potent cytotoxic activity against the human cancer cell lines.[9] Recently, we have reported the synthesis of a series of novel phenacylimidazolium bromides such as NMIB (Scheme 1) and their potential antitumor activity.[10,11]



Scheme 1 Design of novel hybrid compounds.

Considering the anticancer activities of naturally occurring substituted-2,3-dihydrobenzofurans as well as the potent cytotoxic activities of natural and synthetic imidazolium derivatives, we were interested in synthesizing a number of new hybrid compounds bearing dibenzofuran and imidazolium moieties (Scheme 1).

Although dihydrobenzofuran-triazole hybrid compounds were synthesized and found to possess antitubercular activity by Tripathi,[12] and some benzofuran-based hybrid compounds were synthesized and found to exhibit cholinesterase inhibitory activity by Rampa,[13] to the best of our knowledge, no reports concerning antitumor activity for hybrid compounds between dihydrobenzofuran and imidazole have been reported.

In the present research, we have designed and synthesized a series of novel dihydrobenzofuran-imidazole hybrids. The

[a]*Key Laboratory of Medicinal Chemistry for Natural Resource, Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming, 650091, P. R. China. E-mail: zhanghb@ynu.edu.cnorzhanghbyd@gmail.com; Fax: +86-871-5035538; Tel: +86-871-5031119*

[b]*Key Laboratory of Ethnic Medicine Resource Chemistry, State Ethnic Affairs Commission & Ministry of Education, School of Chemistry and Biotechnology, Yunnan University of Nationalities, Kunming, 650031, P. R. China*

[c]*State Key Laboratory for Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Science, Kunming, 650204, P. R. China*

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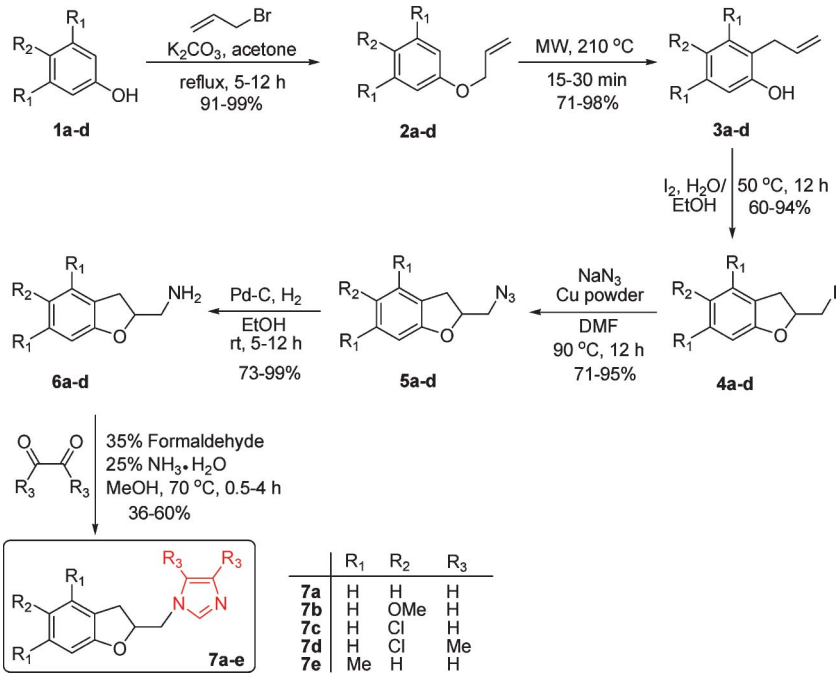
‡ These authors contributed equally to this paper.



Scheme 2 Synthesis of hybrid compounds **7a–e**.

purpose of this study was to investigate the antitumor activity of dihydrobenzofuran-based imidazole hybrid compounds, with the ultimate aim of developing novel potent antitumor agents.

Results and discussion

Chemistry

As shown in Scheme 2, *o*-allylphenols **3a–d** were readily prepared in a two-step sequence from allyl bromide and substituted-phenol **1**. Thus, allylation of phenols **1a–d** to allyl phenyl ethers **2a–d**, and subsequent Claisen rearrangement prompted by microwave irradiation provided **3a–d** in good yield. *o*-Allylphenols **3a–d** reacted with iodine (1.1 eq.) in water at 50 °C to give the required intermediate 2-(iodomethyl)-2,3-dihydrobenzofurans **4a–d** in 60–94% yields.[14] Then, we attempted to treat compound **4** with imidazole to prepare substituted imidazole **7**. Unfortunately, we failed to effect this conversion and a 2-methylbenzofuran was formed.[14] We next focused on the construction of imidazole ring of compound **7** by subsequent azido reaction, reduction, and our earlier reported method.[15] The reaction of these iodomethyl-dihydrobenzofurans **4a–d** with sodium azide in the presence of Cu powder (as catalyst) at 90 °C in *N*,*N*-dimethylformamide yielded the desired 2-(azidomethyl)-dihydrobenzofuran derivatives **5a–d** in good yields.[12] Subsequently, the reduction of compounds **5a–d** by catalytic hydrogenation in methanol gave the corresponding amines **6a–d**.

Base on our previous synthesis,[15] 1-(2-methyl-dihydrobenzofuran)-substituted imidazoles **7a–e** were prepared by treatment of 2-(aminomethyl)-dihydrobenzofurans **6a–d** with ammonia, formaldehyde and glyoxal. Finally, thirty dihydrobenzofuran-based imidazolium salts (**8–37**) were prepared with excellent yields by reaction of 1-dihydrobenzofuran-substituted imidazoles **7a–e** with the corresponding phenacyl and alkyl bromides in refluxing toluene. The structures and yields of hybrid compounds are shown in Tables 1.

Biological evaluation and structure–activity relationship analysis

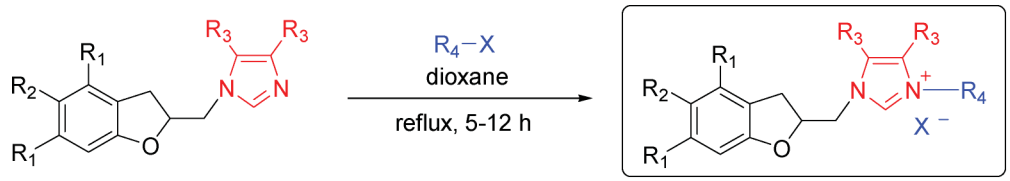
The cytotoxic potential of all newly synthesized hybrid compounds was evaluated *in vitro* against a panel of human tumor cell lines according to procedures described in the literature.[16] The panel consisted of myeloid leukaemia (HL-60), liver carcinoma (SMMC-7721), lung carcinoma (A549), breast carcinoma (MCF-7), and colon carcinoma (SW480). Cisplatin (DDP) was used as the reference drug. The results are summarized in Table 2 (IC_{50} value, defined as the concentrations corresponding to 50% growth inhibition).

As shown in Table 2, the structures of the hybrid compounds have an obvious influence on the cytotoxic activities. Dihydrobenzofuran-imidazole hybrids **7a–e** lacked activity against all tumor cell lines investigated at the concentration of 40 μM. Meanwhile, their imidazolium salts **8–15** with no substituent at dihydrobenzofuran ring and **16–22** with a methoxy group (–OMe) on the dihydrobenzofuran ring were inactive (except compound **8**).

However, hybrid compounds **23–30** with a halogen substituent (–Cl) on the dihydrobenzofuran ring exhibited some degree of cytotoxic activities. Among them, compound **23**, bearing a naphthylacyl substituent at position-3 of imidazole, was the most active compound.

Compared with above, no substituent and methoxy or halogen substituent derivatives, hybrid compounds **31–37** with a methyl group (R_1=Me) at position-4 and -6 of the dihydrobenzofuran ring exhibited higher cytotoxic activity. Most of this kind of

Table 1 Synthesis of hybrid compounds **8–37** from **7a–e**



7a-e **8-37** 65-96%

Entry	Compound no.	R_1	R_2	R_3	R_4	X	Yields (%)
1	**7a**	H	H	H	—	—	60
2	**7b**	H	OMe	H	—	—	55
3	**7c**	H	Cl	H	—	—	47
4	**7d**	H	Cl	Me	—	—	36
5	**7e**	Me	H	H	—	—	45
6	**8**	H	H	H	Naphthylacyl	Br	66
7	**9**	H	H	H	4-Bromophenacyl	Br	68
8	**10**	H	H	H	4-Methoxyphenacyl	Br	87
9	**11**	H	H	H	2-Bromobenzyl	Br	92
10	**12**	H	H	H	Pentyl	I	93
11	**13**	H	H	H	Allyl	Br	96
12	**14**	H	H	H	2′-Phenyl-phenacyl	Br	65
13	**15**	H	H	H	Benzyl	Br	95
14	**16**	H	OMe	H	Naphthylacyl	Br	81
15	**17**	H	OMe	H	Benzyl	Br	85
16	**18**	H	OMe	H	4-Bromophenacyl	Br	83
17	**19**	H	OMe	H	2′-Phenyl-phenacyl	Br	65
18	**20**	H	OMe	H	2-Bromobenzyl	Br	80
19	**21**	H	OMe	H	Pentyl	I	84
20	**22**	H	OMe	H	4-Methoxyphenacyl	Br	84
21	**23**	H	Cl	H	Naphthylacyl	Br	80
22	**24**	H	Cl	H	4-Bromophenacyl	Br	82
23	**25**	H	Cl	H	Allyl	Br	95
24	**26**	H	Cl	H	2-Bromobenzyl	Br	90
25	**27**	H	Cl	H	Benzyl	Br	93
26	**28**	H	Cl	H	4-Methoxyphenacyl	Br	82
27	**29**	H	Cl	Me	4-Bromophenacyl	Br	77
28	**30**	H	Cl	Me	4-Methoxyphenacyl	Br	77
29	**31**	Me	H	H	Naphthylacyl	Br	77
30	**32**	Me	H	H	4-Bromophenacyl	Br	78
31	**33**	Me	H	H	Pentyl	I	90
32	**34**	Me	H	H	2-Bromobenzyl	Br	78
33	**35**	Me	H	H	Allyl	Br	94
34	**36**	Me	H	H	4-Methoxyphenacyl	Br	80
35	**37**	Me	H	H	Benzyl	Br	91

derivatives showed moderate activity. Compounds **31**, **32** and **36**, bearing a phenacyl substituent at position-3 of the imidazole ring, displayed similar cytotoxic activity *in vitro* compared with DDP. Interestingly, compound **31**, a naphthylacyl substituent at position-3 of imidazole, was found to be the most potent derivative with IC_{50} values lower than 16.0 μM against all of human tumor cell lines investigated and more active than DDP (except against HL-60 and SW480 cells).

In terms of the imidazole ring, the cytotoxic activities of hybrid compounds with phenacyl substituent at position-3 of imidazole were higher than those of hybrid compounds with the other alkyl substituent. Especially, the hybrid compounds with naphthylacyl or electron-rich phenacyl substituents displayed higher cytotoxic activities, such as compounds **23**, **28**, **30**, **31** and **36**. Notably, compound **23** exhibited cytotoxic activity selectively against breast carcinoma (MCF-7) with IC_{50} value 2.2-fold more sensitive to DDP.

The results suggest that substitution of the imidazolyl-1-position with an electron-donating dihydrobenzofuran, and the 3-position with a naphthylacyl or electron-rich phenacyl group, were vital for modulating cytotoxic activity. The structure–activity relationship (SAR) results were summarized in Scheme 3.

Conclusion

A number of novel dihydrobenzofuran-imidazole hybrids prepared in this research proved to be potent antitumor agents. The hybrid compounds **31** and **36**, bearing a methyl substituted dihydrobenzofuran at position-1 and a naphthylacyl or electron-rich phenacyl at position-3 of imidazole ring, were found to be the most potent compounds. Compound **31** was found to be the most potent derivative against all human tumor cell lines investigated and more active than DDP, while compound **23** was more selective

Table 2 Cytotoxic activities of hybrid compounds *in vitro*[b] (IC_{50}, μM[a])

Entry	Compound no.	MCF-7	HL-60	SMMC-7721	A549	SW480
1	**7a**	>40	>40	>40	>40	>40
2	**7b**	>40	>40	>40	>40	>40
3	**7c**	>40	>40	>40	>40	>40
4	**7d**	>40	>40	>40	>40	>40
5	**7e**	>40	>40	>40	>40	>40
6	**8**	25.67	18.18	>40	35.17	>40
7	**9**	>40	>40	>40	>40	>40
8	**10**	>40	>40	>40	>40	>40
9	**11**	>40	>40	>40	>40	>40
10	**12**	>40	>40	>40	>40	>40
11	**13**	>40	>40	>40	>40	>40
12	**14**	>40	>40	>40	>40	>40
13	**15**	>40	>40	>40	>40	>40
14	**16**	>40	>40	>40	>40	>40
15	**17**	>40	>40	>40	>40	>40
16	**18**	>40	>40	>40	>40	>40
17	**19**	>40	>40	>40	>40	>40
18	**20**	>40	>40	>40	>40	>40
19	**21**	>40	>40	>40	>40	>40
20	**22**	>40	>40	>40	>40	>40
21	**23**	5.78	10.86	27.18	17.60	16.55
22	**24**	>40	>40	>40	>40	>40
23	**25**	>40	>40	>40	>40	>40
24	**26**	>40	>40	>40	>40	>40
25	**27**	>40	>40	>40	>40	>40
26	**28**	13.97	23.90	30.92	23.52	>40
27	**29**	14.75	12.97	27.62	24.68	23.11
28	**30**	7.70	8.95	20.02	10.69	>40
29	**31**	7.95	6.18	15.23	12.35	14.63
30	**32**	14.13	11.96	>40	21.35	17.81
31	**33**	>40	>40	>40	>40	>40
32	**34**	20.62	35.74	37.51	28.99	>40
33	**35**	>40	>40	>40	>40	>40
34	**36**	15.02	8.40	22.41	17.89	33.02
35	**37**	>40	>40	>40	>40	>40
41	**DDP**	12.99	5.52	18.77	16.51	12.61

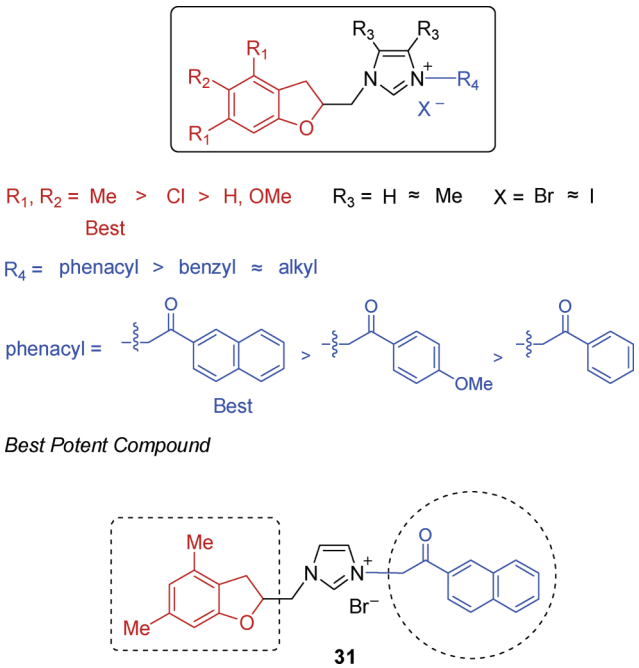
[a] Cytotoxicity as IC_{50} for each cell line, is the concentration of compound which reduced by 50% the optical density of treated cells with respect to untreated cells using the MTT assay. [b] Data represent the mean values of three independent determinations.

towards breast carcinoma (MCF-7). The dihydrobenzofuran-based imidazolium salts **31** and **23** can serve as valuable leads for further structural modifications.

Experimental Section

General procedures

Melting points were obtained on a XT-4 melting-point apparatus and were uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Bruker Avance 300 spectrometer at 300 MHz. Carbon-13 nuclear magnetic resonance (^{13}C-NMR) was recorded on Bruker Avance 300 spectrometer at 75 MHz. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS) for all recorded NMR spectra. Low resolution mass spectra were recorded on a VG Auto Spec-3000 magnetic sector MS spectrometer. High resolution mass spectra were taken on AB QSTAR Pulsar mass spectrometer. Silica gel (200–300 mesh) for column chromatography and silica GF_{254} for TLC were produced by Qingdao Marine Chemical Company (China). All air- or moisture-sensitive



Scheme 3 Structure–activity relationship of hybrid compounds.

reactions were conducted under an argon atmosphere. Starting materials and reagents used in reactions were obtained commercially from Acros, Aldrich, Fluka and were used without purification, unless otherwise indicated.

Synthesis of 2a–2d. To a solution of phenols **1** (0.1 mol) and potassium carbonate (0.2 mmol) in acetone (250 mL) was added allyl bromide (0.12 mol). The resulting mixture was then stirred at reflux for 5–12 h. After filtration through Celite and washed with ethyl acetate, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 60–90 °C : ethyl acetate = 10 : 1) to afford the products **2** (91–99%) as colorless oil. See ESI file for characterization data.†

Synthesis of compounds 3a–3d. The allyl phenyl ethers **2** (3 mol) was put in a vial (CEM Discover). The sealed vial was then heated at 210 °C under microwave irradiation (CEM Discover) for 15–30 min. After cooling to room temperature, the residue was diluted with AcOEt (1–2 mL) and chromatographed on silica gel (petroleum ether 60–90 °C : ethyl acetate = 20 : 1) to afford the products **3** (70–98%) as pale yellow oil. See ESI file for characterization data.†

Synthesis of compounds 4a–4d. A mixture of *o*-allylphenols **3** (1.0 mmol) and iodine (1.2 mmol) in ethanol/water (20 mL, 1 : 9) was stirred at 50 °C for 12 h. After completion, the reaction mixture was extracted with ethyl acetate and washed with water. The organic fraction was washed with aqueous sodium thiosulphate, dried (anhyd. Na_2SO_4) and evaporated to furnish the crude product, which was chromatographed on silica gel (petroleum ether 60–90 °C : ethyl acetate = 20 : 1) to afford the products **4** (60–94%) as yellow powder. See ESI file for characterization data.†

Synthesis of compounds 5a–5d. To a magnetically stirred solution of the 2-(iodomethyl)-2,3-dihydrobenzofuran **4** (1.0 mmol) in DMF, NaN_3 (1.2 mmol) and Cu-powder (catalyst, 10 mol%) was cautiously added and reaction mixture was stirred for 6–8 h at

90 °C. Reaction progress was monitored by TLC. The reaction mixture was diluted with water and extracted by ethylacetate; organic layer was washed by water and brine, dried (anhyd. Na_2SO_4) and evaporated under reduced pressure to yield crude product, which was chromatographed on silica gel (petroleum ether 60–90 °C : ethyl acetate = 20 : 1) to afford the products **5** (71–90%) as yellow oil. See ESI file for characterization data.†

Synthesis of compounds 6a–6d. Pd/C (10 wt% Pd on carbon; 15 mol%) was added to a solution of 2-(azidomethyl)-dihydrobenzofuran derivatives **5** (1 mmol) in ethanol (50 ml) and the reaction mixture was stirred at room temperature under hydrogen atmosphere for 5–12 h. Reaction progress was monitored by TLC. The catalyst was filtered off and the solvent was evaporated to give a residue, which was purified by short silica gel column (ethyl acetate : methanol : Et_3N = 10 : 1 : 0.1) to afford the products **6** (73–99%) as a colorless oil. See ESI file for characterization data.†

Synthesis of compounds 7a–7d. To a magnetically stirred solution of the 30% aq. glyoxal or 2,3-butanedione (1.2 mmol) and 37% aq. formaldehyde (1.2 mmol) in methanol (30 mL) at 70 °C, 2-(aminomethyl)-dihydrobenzofurans **6** (1.0 mmol) and 25% aq. ammonia (1.2 mmol) was added and reaction mixture was stirred for 4 h at the same temperature. Reaction progress was monitored by TLC. After removed the solvent, the dark residue was poured into ice water (20 mL) and extracted by ethylacetate; organic layer was washed by water and brine, dried (anhyd. Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (ethyl acetate : methanol : Et_3N = 20 : 1 : 0.1) to afford the products **7** (36–60%) as yellow oil or powder.

Compound 7a. Yield 60%. Yellow oil. IR (KBr) 3105, 2929, 2852, 1597, 1475, 1230, 1020, 865, 750 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.50 (1H, s), 7.08 (2H, t, J = 7.8 Hz), 7.01 (1H, s), 6.98 (1H, s), 6.84–6.74 (2H, m), 4.97–4.88 (1H, m), 4.16–4.05 (2H, m), 3.24 (H, dd, J = 15.7, 9.3 Hz), 2.82 (1H, dd, J = 15.7, 7.1 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 158.58, 137.60, 129.38, 128.30, 125.38, 124.96, 120.93, 119.63, 109.57, 80.97, 50.53, 32.53. HRMS (ESI-TOF) m/z Calcd for $C_{12}H_{13}N_2O$ $[M+H]^+$ 201.1028, found 201.1020.

Compound 7b. Yield 55%. Yellow powder, mp 66–67 °C. IR (KBr) 3104, 2989, 2944, 2839, 1604, 1493, 1438, 1240, 1195, 1024, 844, 802 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.53 (1H, s), 7.04 (1H, s), 7.01 (1H, s), 6.71–6.63 (3H, m), 4.99–4.96 (1H, m), 4.16 (2H, d, J = 5.3 Hz), 3.72 (3H, s), 3.27 (1H, dd, J = 15.4, 9.2 Hz), 2.84 (1H, dd, J = 15.8, 7.2 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 154.53, 152.76, 137.68, 129.54, 126.42, 119.70, 113.34, 111.33, 109.61, 81.23, 56.00, 50.63, 33.12. HRMS (ESI-TOF) m/z Calcd for $C_{13}H_{15}N_2O_2$ $[M+H]^+$ 231.1134, found 231.1133.

Compound 7c. Yield 47%. Yellow powder, mp 92–93 °C. IR (KBr) 3113, 2938, 2848, 1597, 1475, 1429, 1293, 1234, 1165, 1071, 1007, 811, 747, 667 cm^{-1}. ^{1}H-NMR (300 MHz, CDCl3) δ: 7.52 (1H, s), 7.07–7.04 (3H, m), 7.00 (1H, s), 6.69 (1H, d, J = 8.4 Hz), 5.06–4.98 (1H, m), 4.25–4.16 (2H, m), 3.28 (1H, dd, J = 15.9, 9.3 Hz), 2.86 (1H, dd, J = 15.9, 7.2 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 157.37, 137.69, 129.69, 128.33, 127.40, 125.74, 125.13, 119.69, 110.58, 81.73, 50.48, 32.50. HRMS (ESI-TOF) m/z Calcd for $C_{12}H_{12}ClN_2O$ $[M+H]^+$ 235.0638, found 235.0588.

Compound 7d. Yield 36%. Yellow oil. IR (KBr) 3120, 2924, 2852, 1708, 1601, 1475, 1303, 1234, 1168, 1017, 809, 678 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.36 (1H, s), 7.06–7.01 (2H, m), 6.65 (1H, d, J = 8.4 Hz), 4.97–4.90 (1H, m), 3.99 (2H, d, J = 5.7 Hz), 3.25 (1H, dd, J = 15.9, 9.2 Hz), 2.84 (1H, dd, J = 16.0, 7.0 Hz), 2.11 (6H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 157.36, 135.42, 133.83, 128.30, 127.42, 125.70, 125.16, 122.22, 110.57, 81.76, 48.30, 32.67, 12.72, 8.58. HRMS (ESI-TOF) m/z Calcd for $C_{14}H_{15}ClN_2O$ $[M+H]^+$ 263.0951, found 263.0946.

Compound 7e. Yield 45%. Yellow oil. IR (KBr) 3050, 2923, 2852, 1675, 1601, 1500, 1445, 1289, 1227, 1027, 833 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.54 (1H, s), 7.05 (1H, s), 7.02 (1H, s), 6.50 (1H, s), 6.46 (1H, s), 5.02–4.92 (1H, m), 4.16 (2H, d, J = 5.4 Hz), 3.16 (1H, dd, J = 15.5, 9.3 Hz), 2.72 (1H, dd, J = 15.6, 7.2 Hz), 2.29 (3H, s), 2.25 (3H, s). ^{13}C-NMR (75 MHz, CDCl3) δ: 158.65, 138.57, 137.70, 134.47, 129.54, 122.79, 121.42, 119.70, 107.72, 81.13, 50.79, 31.44, 21.39, 18.82. HRMS (ESI-TOF) m/z Calcd for $C_{14}H_{17}N_2O$ $[M+H]^+$ 229.1341, found 229.1301.

Synthesis of compounds 8–37. A mixture of 1-dihydrobenzofuran-substituted imidazoles **7** (1 mmol) and phenacyl bromides or alkyl bromides (1.2 mmol) was stirred in dioxane (10 mL) at reflux for 8–16 h. An insoluble substance was formed. After completion of the reaction as indicated by TLC, the precipitate was filtered through a small pad of Celite, and washed with toluene (3 × 10 mL), then dried to afford imidazolium salts **8–37** in 65–96% yields. See ESI file for characterization data.†

Cytotoxicity assay. The assay was in five kinds of cell lines (HL-60, SMMC-7721, A549, MCF-7 and SW480). Cells were cultured at 37 °C under a humidified atmosphere of 5% CO_2 in RPMI 1640 medium supplemented with 10% fetal serum and dispersed in replicate 96-well plates. Compounds were then added. After 48 h exposure to the compounds, cells viability were determined by the [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] (MTT) cytotoxicity assay by measuring the absorbance at 570 nm with a microplate spectrophotometer. Each test was performed in triplicate.

Acknowledgements

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