European Journal of Medicinal Chemistry 66 (2013) 423–437

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

# Synthesis and antitumor activities of novel dibenzo[*b*,*d*]furan–imidazole hybrid compounds

Lan-Xiang Liu [a], Xue-Quan Wang [a], Ju-Ming Yan [b], Yan Li [b,*], Cheng-Jun Sun [a], Wen Chen [a], Bei Zhou [a], Hong-Bin Zhang [a], Xiao-Dong Yang [a,*]

[a] *Key Laboratory of Medicinal Chemistry for Natural Resource (Yunnan University), Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming 650091, PR China*

[b] *State Key Laboratory for Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Science, Kunming 650204, PR China*

ARTICLE INFO

*Article history:*
Received 30 January 2013
Received in revised form
4 June 2013
Accepted 7 June 2013
Available online 18 June 2013

*Keywords:*
Hybrid compound
Dibenzo[*b*,*d*]furan
Imidazole
Antitumor activities
Structure–activity relationships

ABSTRACT

A series of novel hybrid compounds between dibenzo[*b*,*d*]furan and imidazole has been prepared and evaluated *in vitro* against a panel of human tumor cell lines. The results suggest that the existence of benzimidazole ring, and the substitution of the imidazolyl-3-position with a naphthylacyl or 4-methoxyphenacyl group, were vital for modulating cytotoxic activity. In particular, hybrid compound **60** was found to be the most potent derivatives against all of human tumor cell lines investigated, while compound **49** was found to be more selective against breast carcinoma (MCF-7) and myeloid liver carcinoma (SMMC-7721). Compound **60** can induce the G1 phase cell cycle arrest and apoptosis in SMMC-7721 cells.



## 1. Introduction

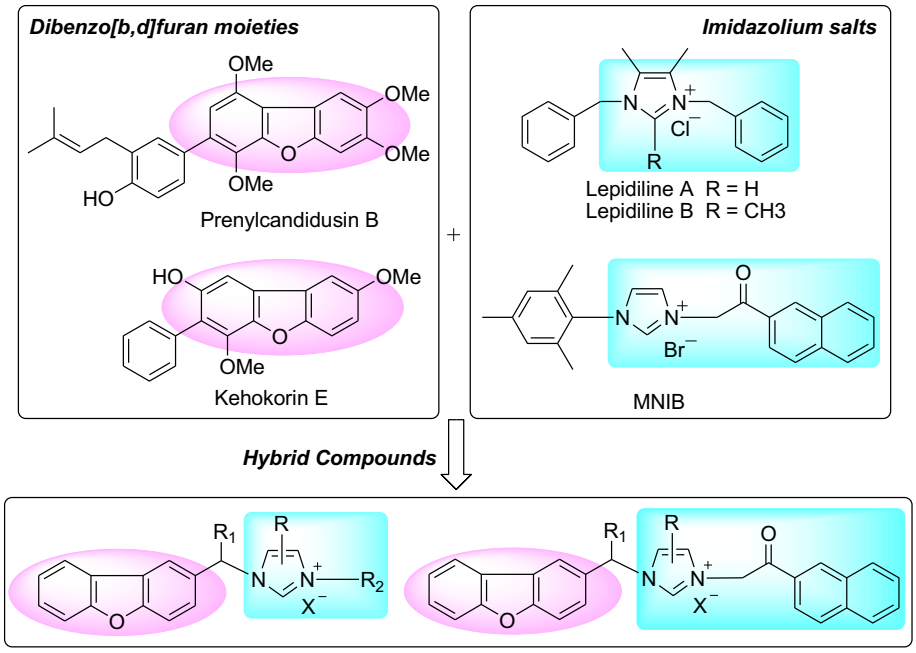
Cancer remains one of the most difficult diseases worldwide to treat and is one of the leading causes of human mortality [1]. Developing new anticancer drugs and more effective treatment strategies for cancer is of great importance. Natural products represent a significant source of inspiration for the design of structural analogs with improved pharmacological profiles [2,3]. Naturally occurring substituted-benzofurans are an important class of biologically active oxygen-containing heterocycles. Natural products possessing the dibenzo[*b*,*d*]furan moiety exhibit a broad range of biological and pharmacological activities [4–7]. Recently, natural occurring benzofurans have been identified to possess antitumor activity [8,9]. As exemplified in Scheme 1, Prenylcandidusin B [8] and Kehokorin E [9] are dibenzo[*b*,*d*]furan derived compounds exhibiting potent cytotoxic activities against human lymphocytic leukemia cells and epithelial carcinoma cells.

Imidazole and its derivatives have attracted considerable interests in recent years for their versatile properties in chemistry and pharmacology. Biological activities of imidazolium salts have been reported [10–13], especially antitumor activity [14,15]. For example, 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 [16]. Recently, we have reported the synthesis of a series of novel hybrid compounds of benzofurans and imidazols moieties and their potential antitumor activities [17–19]. Studies on molecular mechanisms demonstrated that the imidazolium salt hybrids can induce the G1 phase cell cycle arrest and apoptosis in tumor cells [19].

Molecular hybridization is a useful tool in new drug design and development [20]. Design and synthesis of new types of pharmacologically interesting hybrid compounds for drug discovery have received much attention during the past two decades [21,22]. Considering the anticancer activities of naturally occurring dibenzo[*b*,*d*]furans, as well as the potent cytotoxic activities of natural and synthetic imidazole derivatives, we were interested in synthesizing a number of new hybrid compounds bearing dibenzo[*b*,*d*]furan (as shown pink shadows in Scheme 1) and *N*-benzyl or phenacyl substituted imidazole moieties (as shown green shadows in Scheme 1).

* Corresponding author. Tel.: +86 871 65031119; fax: +86 871 65035538.
*E-mail addresses:* liyanb@mail.kib.ac.cn (Y. Li), xdyang@ynu.edu.cn (X.-D. Yang).

0223-5234/$ – see front matter © 2013 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.ejmech.2013.06.011




**Scheme 1.** Design of novel hybrid compounds.

Although dihydrobenzofuran–triazole hybrid compounds were synthesized and found to possess antitubercular activity by Tripathi [23], and some benzofuran-based hybrid compounds were synthesized and found to exhibit cholinesterase inhibitory activity by Rampa [24], to the best of our knowledge, no reports concerning antitumor activity of dibenzo[*b*,*d*]furan–imidazole hybrid compounds have been reported.

In the present research, we designed and synthesized a series of novel hybrid compounds of dibenzo[*b*,*d*]furans with imidazole. The purpose of this study was to investigate the antitumor activity of dibenzo[*b*,*d*]furan–imidazole hybrids, with the ultimate aim of developing novel potent antitumor agents.

## 2. Results and discussion

### 2.1. Chemistry

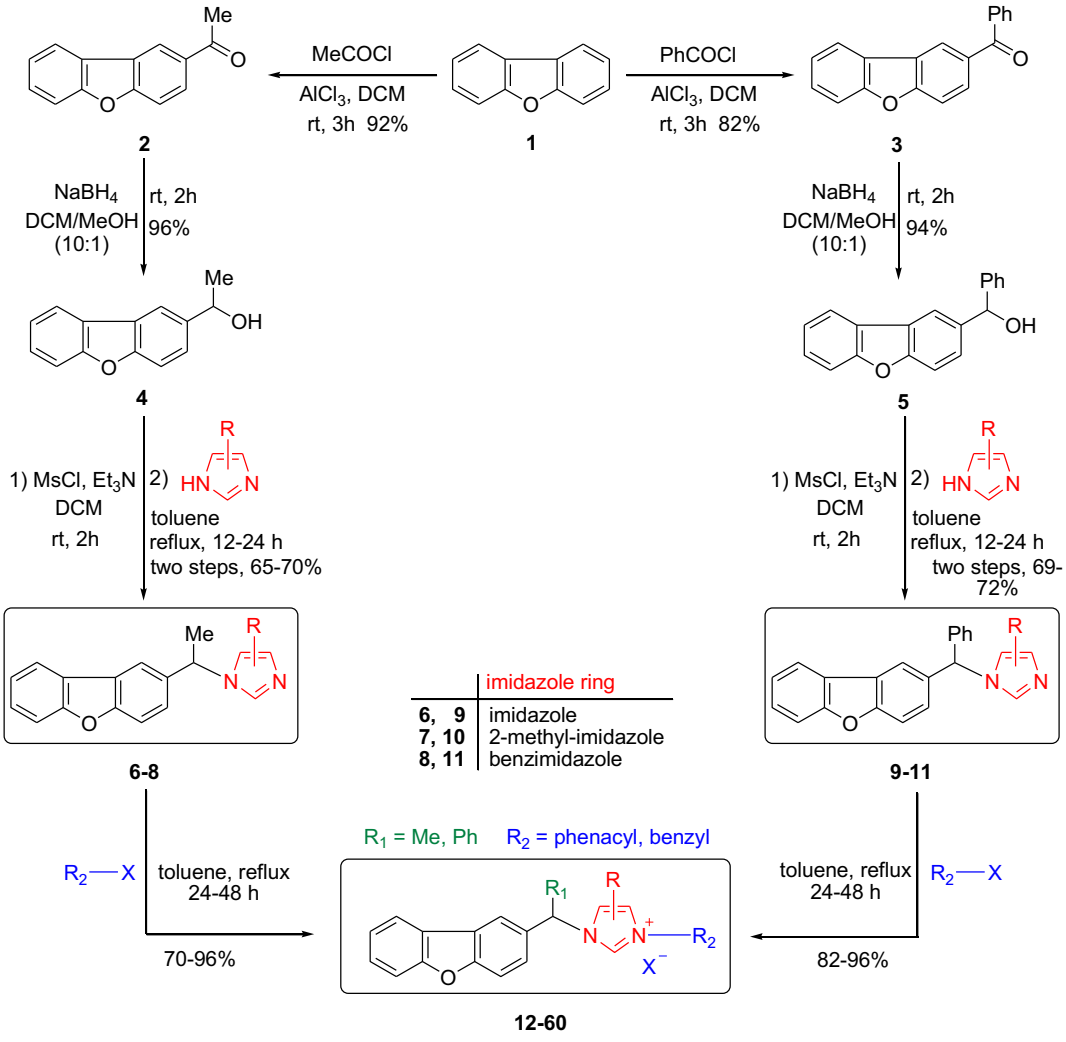
To synthesize the dibenzo[*b*,*d*]furan–imidazole hybrids, we used commercially available imidazole derivatives that were alkylated with dibenzo[*b*,*d*]furan 2-methanol, which was synthesized over two steps from readily available starting materials as shown in Scheme 2. Dibenzo[*b*,*d*]furan **1** was chosen as the starting material for the preparation of a series of dibenzo[*b*,*d*]furan–imidazole hybrids (**6**–**60**). The acetylation and benzoylation of dibenzo[*b*,*d*] furan **1** under Friedel–Craft acylation conditions produced the known compound 1-(dibenzo[*b*,*d*]furan-2-yl)ethanone **2** and 1-(dibenzo [*b*,*d*]furan-2-yl)(phenyl)methanone **3** in 90% and 80% yields [25]. The ketone compounds **2** and **3** were reduced via $NaBH_4$ to the respective 1-(dibenzo[*b*,*d*]furan-2- yl)ethanol (**4**, 96% yield) and 1-(dibenzo[*b*,*d*]furan-2-yl) (phenyl)methanol (**5**, 94% yield). Subsequently, the dibenzo[*b*,*d*]furan 2-methanol compounds **4** and **5** were transformed via the mesylate to the respective six dibenzo [*b*,*d*]furan–imidazole hybrids **6**–**11** with various substituted imidazole (imidazole, 2-methyl-imidazole or benzimidazole) by refluxing under toluene with 65–72% yields (two steps). Finally, forty-nine dibenzo[*b*,*d*]furan-based imidazolium salts (**12**–**60**) were prepared with excellent yields by reaction of dibenzo[*b*,*d*] furan–imidazole hybrids with the corresponding phenacyl and alkyl halides in refluxing toluene (70–96% yields). The structures of hybrid compounds are shown in Table 1.

### 2.2. Biological evaluation and structure–activity relationship analysis

The potential cytotoxicity of all newly synthesized hybrid compounds were evaluated *in vitro* against a panel of human tumor cell lines, according to procedures described in the literature [26,27]. The panel consisted of leukemia (HL-60), breast carcinoma (MCF-7), lung carcinoma (A549), colon carcinoma (SW480) and myeloid liver carcinoma (SMMC-7721). Cisplatin (DDP) was used as the reference drug. The results are summarized in Table 1 ($IC_{50}$ value, defined as the concentrations corresponding to 50% growth inhibition).

As shown in Table 1, the hybrid compounds were more selective toward leukemia cell line (HL-60). Meanwhile, the structures of the hybrid compounds have an obvious influence on the cytotoxic activities. Dibenzo[*b*,*d*]furan–imidazole hybrids **6** and **8** lacked activities against all tumor cell lines investigated at the concentration of 40 μM. At the same time, hybrids **7** and **9**–**11** displayed weak cytotoxic activities. However, their imidazolium salts **12**–**31** exhibited some degree of cytotoxic activities or higher cytotoxic activities. This difference in cytotoxicity between neutral compounds and imidazolium salts may be due to the changes of molecular structure, charge distribution and water solubility [28].

In terms of the various substituted imidazole ring (imidazole, 2-methyl-imidazole or benzimidazole) ring, imidazolium salts **12**–**19** and **37**–**45** with imidazole ring exhibited some degree of cytotoxic activities. Only compound **44** with a 2′-phenyl-phenacyl substituent, as well as compounds **19** and **45** with a naphthylacyl substituent, at position-3 of the imidazole ring displayed higher cytotoxic activity *in vitro* compared with DDP. Meanwhile, imidazolium salt hybrids **20**–**27** and **46**–**52** with 2-methyl-imidazole ring exhibited medium or higher cytotoxic activities. Among them, compounds **27**, **52**, **24** and **49**, bearing a naphthylacyl or 4-methoxyphenacyl substituent at position-3 of the 2-methyl-imidazole, showed higher cytotoxic activities *in vitro* compared




**Scheme 2.** Synthesis of hybrid compounds **6**–**47**.

with DDP. However, imidazolium salt hybrids **28**–**36** and **53**–**60**, with benzimidazole ring, exhibited powerful cytotoxic activities. Most of this kind of derivatives was found to be much more active than DDP, such as compounds **32**–**36**, **53** and **57**–**60**. Among them, compounds **36** and **60**, also bearing a naphthylacyl substituent at position-3 of the benzimidazole, showed potent cytotoxic activitieswith $IC_{50}$ values of 0.93–3.59 μM against five human tumor cell lines investigated.

In terms of the substituent at position-3 of imidazole ring, imidazolium salt hybrids **12**, **13**, **21**, **29**, **38** and **47** with butyl or 4-nitrobenzyl substituent, as well as hybrids **15**, **23**, **31** and **48** with 4-hydroxyphenacyl substituent at position-3 of imidazole ring, showed lacked or decreased activities against five tumor cell lines. However, compared with above alkyl substituent (butyl or 4-nitrobenzyl) imidazolium salt derivatives, hybrid compounds with phenacyl or substituted phenacyl substituent at position-3 of imidazole ring exhibited moderate or potent cytotoxic activities. Most of this kind of derivatives showed moderate or potent activities (except 4-hydroxyphenacyl substituent). Especially, compounds **19**, **27**, **36**, **45**, **52** and **60** with a naphthylacyl substituent, as well as compounds **16**, **24**, **32**, **41**, **49** and **57** with a 4-methoxyphenacyl substituent at position-3 of the imidazole ring, displayed higher cytotoxic activities *in vitro* compared with DDP. Interestingly, hybrid compounds **60**, **27** and **44**, bearing a naphthylacyl or 2′-phenyl-phenacyl substituent at position-3 of imidazole ring, were found to be the most potent derivative with $IC_{50}$ values of 0.52–3.86 μM against all of human tumor cell lines investigated and more active than DDP. Notably, hybrids **49**, bearing a 4-methoxyphenacyl substituent at position-3 of 2-methyl-imidazole, exhibited cytotoxic activity selectively against lung carcinoma (A549) and myeloid liver carcinoma (SMMC-7721), with $IC_{50}$ value 7.2-fold and 5.9-fold lower than DDP, respectively. The results show that steric and electronic effects have an important role in the cytotoxic activity of imidazolium salt hybrids. Generally, a bulkier naphthylacyl substituent at position-3 of imidazole ring, as well as an electron-donating methoxy group at position-4 of phenacyl substituent, exhibit higher cytotoxic activity against tumor cells [17,18]. Compared with hybrid compounds between 2-benzylbenzofuran and imidazole reported in the previous work [17], the new hybrids prepared in this work exhibited more potent cytotoxic activities against five human tumor cell lines, especially against HL-60 and MCF-7 with $IC_{50}$ value over 2.0-fold.

This finding suggests that the existence of benzimidazole ring and substitution of the imidazolyl-3-position with a naphthylacyl or 4-methoxyphenacyl group were important for modulating cytotoxic activity. The structure–activity relationship (SAR) results are summarized in Scheme 3.

**Table 1**
Structures and cytotoxic activities of hybrid compounds **6**–**60** *in vitro*[b] ($IC_{50}$, μM[a]).

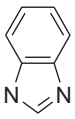
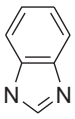
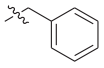
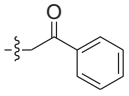
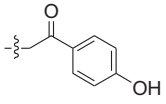
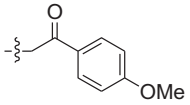
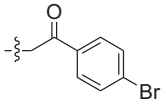
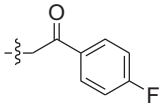
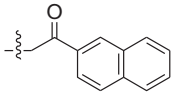
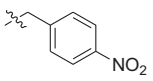
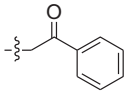
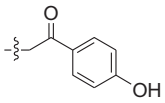
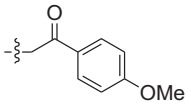
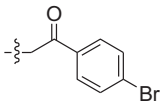
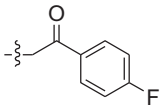
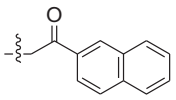
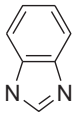
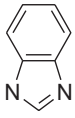
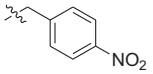
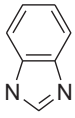
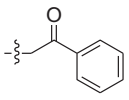
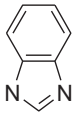
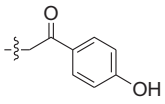
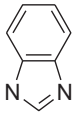
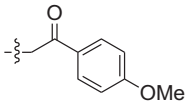
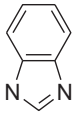
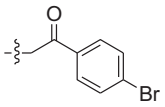
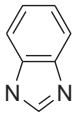
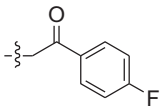
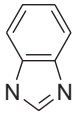
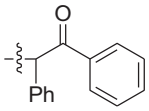
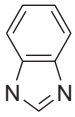
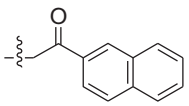
| Compound | $R_1$ | Imidazole ring | $R_2$ | X | HL-60 | MCF-7 | A-549 | SW480 | SMMC-7721 |
|---|---|---|---|---|---|---|---|---|---|
| **6** | Me |  | – | – | >40 | >40 | >40 | >40 | >40 |
| **7** | Me |  | – | – | 10.86 | 18.74 | 16.17 | 21.35 | >40 |
| **8** | Me |  | – | – | >40 | >40 | >40 | >40 | >40 |
| **9** | Ph |  | – | – | 20.98 | >40 | 24.63 | >40 | 33.67 |
| **10** | Ph |  | – | – | 14.50 | 23.51 | 18.18 | >40 | 30.21 |
| **11** | Ph |  | – | – | 17.22 | 20.88 | 23.39 | >40 | 25.43 |
| **12** | Me |  |  | I | 5.63 | 9.11 | 12.81 | 24.11 | 14.17 |
| **13** | Me |  |  | Br | 11.35 | 13.80 | >40 | >40 | 22.48 |
| **14** | Me |  |  | Br | 2.55 | 14.09 | 27.01 | 14.43 | 12.05 |
| **15** | Me |  |  | Br | >40 | >40 | >40 | >40 | >40 |
| **16** | Me |  |  | Br | 3.45 | 9.02 | 12.21 | 12.68 | 9.98 |
| **17** | Me |  |  | Br | 2.95 | 4.08 | 13.74 | 6.85 | 11.02 |
| **18** | Me |  |  | Br | 2.64 | 16.74 | 22.64 | 16.41 | 17.51 |
| **19** | Me |  |  | Br | 2.46 | 3.50 | 8.46 | 3.69 | 6.43 |
| **20** | Me |  |  | I | 3.08 | 6.60 | 12.96 | 10.04 | 7.98 |
| **21** | Me |  |  | Br | 14.55 | >40 | >40 | >40 | >40 |
| **22** | Me |  |  | Br | 2.85 | 4.49 | 17.89 | 10.07 | 3.02 |

**Table 1** (*continued*)

| Compound | $R_1$ | Imidazole ring | $R_2$ | X | HL-60 | MCF-7 | A-549 | SW480 | SMMC-7721 |
|---|---|---|---|---|---|---|---|---|---|
| **23** | Me |  |  | Br | 12.19 | 26.42 | 28.58 | 37.45 | 13.33 |
| **24** | Me |  |  | Br | 0.70 | 1.29 | 3.02 | 5.78 | 1.43 |
| **25** | Me |  |  | Br | 2.67 | 6.77 | 12.85 | 11.80 | 6.40 |
| **26** | Me |  |  | Br | 2.96 | 16.24 | 15.41 | 12.28 | 4.70 |
| **27** | Me |  |  | Br | 0.60 | 1.65 | 3.86 | 3.09 | 2.15 |
| **28** | Me |  |  | I | 1.67 | 9.41 | 8.55 | 11.06 | 3.78 |
| **29** | Me |  |  | Br | 5.93 | 13.75 | 32.30 | 13.42 | 18.41 |
| **30** | Me |  |  | Br | 2.46 | 12.51 | 18.10 | 14.55 | 8.51 |
| **31** | Me |  |  | Br | 2.35 | 14.15 | 20.06 | 16.27 | 24.07 |
| **32** | Me |  |  | Br | 2.05 | 3.42 | 5.95 | 3.18 | 2.95 |
| **33** | Me |  |  | Br | 0.66 | 3.08 | 3.54 | 3.18 | 2.62 |
| **34** | Me |  |  | Br | 1.67 | 3.85 | 13.65 | 9.77 | 6.31 |
| **35** | Me |  |  | Br | 2.79 | 9.35 | 12.71 | 10.52 | 5.40 |
| **36** | Me |  |  | Br | 1.65 | 3.14 | 3.46 | 2.95 | 2.24 |

(*continued on next page*)

**Table 1** (*continued*)

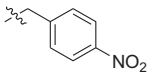
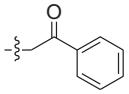
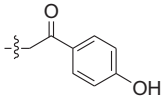
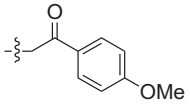
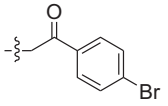
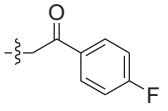
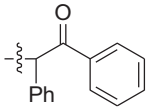
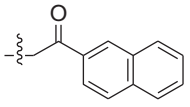
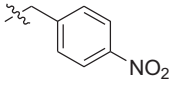
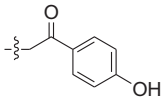
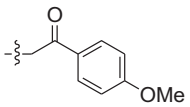
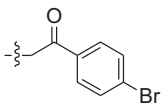
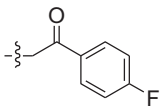
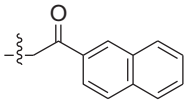
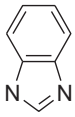
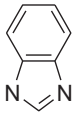
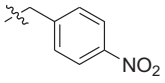
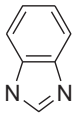
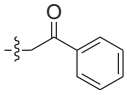
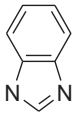
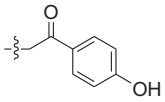
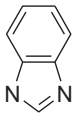
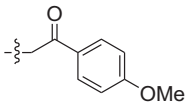
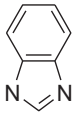
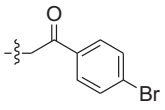
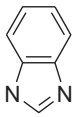
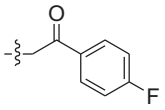
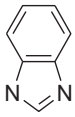
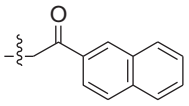
| Compound | $R_1$ | Imidazole ring | $R_2$ | X | HL-60 | MCF-7 | A-549 | SW480 | SMMC-7721 |
|---|---|---|---|---|---|---|---|---|---|
| **37** | Ph |  |  | I | 1.10 | 6.03 | 11.44 | 13.05 | 8.13 |
| **38** | Ph |  |  | Br | 10.82 | 10.32 | 28.55 | 19.07 | 15.32 |
| **39** | Ph |  |  | Br | 2.14 | 6.29 | 17.66 | 9.05 | 11.41 |
| **40** | Ph |  |  | Br | 2.61 | 7.05 | 6.80 | 15.16 | 6.28 |
| **41** | Ph |  |  | Br | 2.09 | 4.12 | 7.27 | 3.76 | 5.59 |
| **42** | Ph |  |  | Br | 2.13 | 3.32 | 7.70 | 2.11 | 10.83 |
| **43** | Ph |  |  | Br | 3.00 | 4.00 | 10.15 | 5.16 | 14.49 |
| **44** | Ph |  |  | Br | 0.52 | 1.46 | 3.75 | 2.36 | 2.38 |
| **45** | Ph |  |  | Br | 1.91 | 2.78 | 5.86 | 2.57 | 3.61 |
| **46** | Ph |  |  | I | 3.81 | 11.89 | 21.37 | 28.43 | 13.05 |
| **47** | Ph |  |  | Br | 8.74 | 15.30 | >40 | 18.22 | 18.50 |
| **48** | Ph |  |  | Br | 3.92 | 11.76 | 26.21 | 14.33 | 8.84 |
| **49** | Ph |  |  | Br | 0.59 | 2.42 | 1.90 | 3.73 | 2.08 |
| **50** | Ph |  |  | Br | 2.25 | 3.45 | 9.46 | 1.98 | 3.93 |
| **51** | Ph |  |  | Br | 2.13 | 3.23 | 4.88 | 1.89 | 4.22 |

**Table 1** (*continued*)

| Compound | $R_1$ | Imidazole ring | $R_2$ | X | HL-60 | MCF-7 | A-549 | SW480 | SMMC-7721 |
|---|---|---|---|---|---|---|---|---|---|
| **52** | Ph |  |  | Br | 0.98 | 2.31 | 3.78 | 2.62 | 2.57 |
| **53** | Ph |  |  | I | 1.12 | 3.37 | 4.61 | 8.00 | 2.93 |
| **54** | Ph |  |  | Br | 4.60 | 9.26 | 21.68 | 16.70 | 13.18 |
| **55** | Ph |  |  | Br | 2.30 | 2.50 | 13.58 | 3.54 | 4.61 |
| **56** | Ph |  |  | Br | 2.89 | 9.15 | 17.71 | 15.61 | 10.84 |
| **57** | Ph |  |  | Br | 0.64 | 4.78 | 3.34 | 5.56 | 2.10 |
| **58** | Ph |  |  | Br | 2.10 | 2.91 | 3.80 | 3.83 | 3.36 |
| **59** | Ph |  |  | Br | 2.18 | 1.87 | 12.11 | 3.60 | 3.57 |
| **60** | Ph |  |  | Br | 0.93 | 1.04 | 3.54 | 3.59 | 2.86 |
| DDP | – | – | – | – | 3.10 | 10.64 | 13.61 | 14.75 | 12.32 |

[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.

### 2.3. Compound **60** induces G1 phase arrest and apoptosis in cancer cells

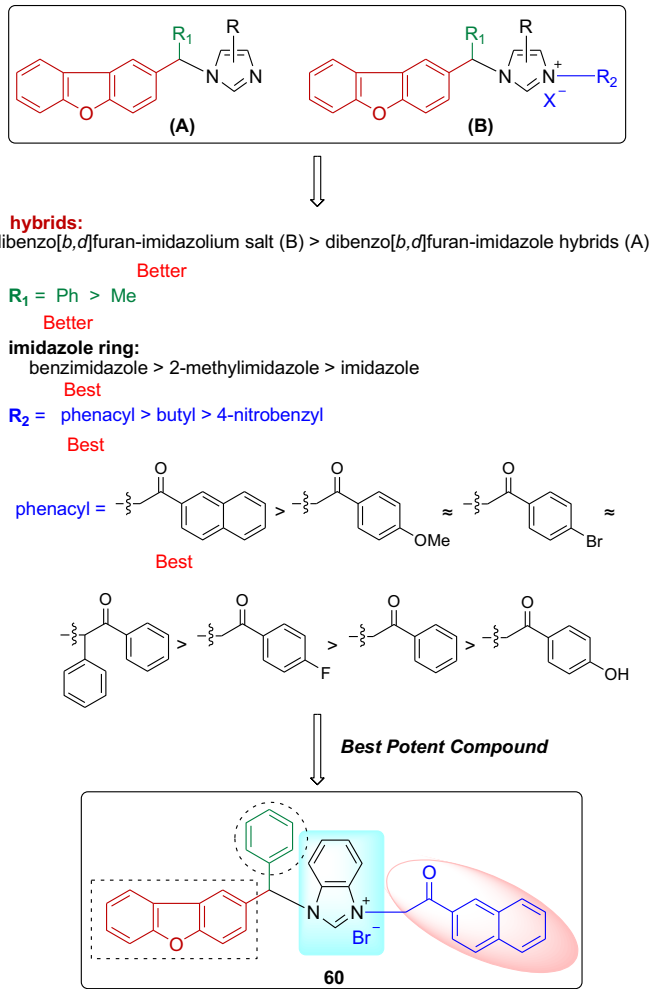
SMMC-7721 cells were exposed to increasing concentrations of compound **60** and cell apoptosis was determined with Annexin V-FITC/PI double-labeled cell cytometry. As shown in Fig. 1, after treatment of cells with compound **60** at 3, 6, 9 μM for 48 h, the apoptotic cell rate was 7.60 ± 2.76%, 43.60 ± 1.70% and 50.80 ± 1.63%, respectively, which were statistically different from the control (2.73 ± 0.69%).

The results of cell cycle analysis on SMMC-7721 cells treated with compound **60** are summarized in Fig. 2. Compared with the control cells, the percentage of cells of G1 phase was significantly increased in the cells incubated with compound **60** with a dose dependent manner. In the meanwhile, the fraction of cells in G2/M phase decreased accordingly, while the proportion of S phase cells showed no obvious change. Our data suggest that compound **60** may induce cancer cell apoptosis via arresting the cells at G1 phase in the cell cycle.

Disruption or malfunction of cell cycle control within the G1 phase has been recognized as the most important biochemical phenomenon for tumor progression and tumorigenesis. The ability of certain small molecules to control cell cycle machinery within the G1 phase has provided exciting new opportunities with hopes of developing new types of drugs efficacious against refractory cancers [29].

## 3. Conclusion

In summary, a number of novel dibenzo[*b*,*d*]furan–imidazole hybrid compounds proved to be potent antitumor agents. The results show that the hybrid compounds were more selective toward leukemia cell line (HL-60) and suggest that the imidazolium salt hybrids **24**, **27**, **36**, **49**, **52** and **60**, bearing a benzimidazole or 2-methyl-imidazole ring, and naphthylacyl or 4-methoxyphenacyl substituent at position-3 of the imidazole ring, were found to be the most potent activity. Compounds **60**, **27** and **44** were found to




**Scheme 3.** Structure–activity relationships of hybrid compounds.

be the most potent derivative with $IC_{50}$ values of 0.52–3.86 μM against all of human tumor cell lines investigated, and compound **49** exhibited cytotoxic activity selectively against lung carcinoma (A549) and myeloid liver carcinoma (SMMC-7721), with $IC_{50}$ value 7.2-fold and 5.9-fold lower than DDP. Compound **60** can induce the G1 phase cell cycle arrest and apoptosis in SMMC-7721 cells. Further SARs and target identification studies of the dibenzo[*b*,*d*]furan-based imidazolium salts are in progress.

## 4. Experimental section

### 4.1. Chemistry

#### 4.1.1. General

Melting points were obtained on an XT-4 melting-point apparatus and were uncorrected. NMR spectra were recorded on a Bruker Avance 300 spectrometer (300 MHz for $^1$H and 75 M HZ for $^{13}$C). Chemical shifts are reported as $\delta$ values in parts per million (ppm) relative to tetramethylsilane (TMS) and $J$ values are expressed in Hertz. 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 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.

#### 4.1.2. Synthesis of compounds **2** and **3**

Anhydrous $AlCl_3$ (8.64 g, 65.45 mmol) in chloroform (50 mL) was added to acetyl chloride (5.11 g, 65.45 mmol) or benzoyl chloride (9.16 g, 65.45 mmol) and then dibenzo[*b*,*d*]furan **1** (10.0 g, 59.50 mmol) in chloroform (100 mL) slowly and left at RT for 3 h. After the reaction (TLC) was completed, the reaction mixture was quenched with 1 N HCl and extracted with chloroform (3 × 100 mL). The combined organic extracts were washed with $H_2O$, dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuum. The residue was chromatographed on silica gel (petroleum ether 60–90 °C:ethyl acetate = 10:1) to afford the product **2** or **3** as white powder.

*4.1.2.1. 1-(Dibenzo[b,d]furan-2-yl)ethanone (**2**).* Yield 92%, white powder. $^1$H NMR ($CDCl_3$): $\delta$ 8.54 (1H, d, $J$ = 1.2), 8.08 (1H, d, $J$ = 7.5), 7.97 (1H, d, $J$ = 7.5), 7.58–7.54 (2H, m), 7.51–7.45 (1H, m), 7.37 (1H, t, $J$ = 7.5), 1.75 (3H, s). $^{13}$C NMR ($CDCl_3$): $\delta$ 197.3, 158.9, 156.9, 132.5, 128.0, 124.6, 123.7, 121.6, 120.9, 111.9, 111.6, 26.8.

*4.1.2.2. 1-(Dibenzo[b,d]furan-2-yl)(phenyl)methanone (**3**).* Yield 82%, white powder. $^1$H NMR ($CDCl_3$): $\delta$ 8.43 (1H, s), 7.97–7.93 (2H, m), 7.85–7.82 (2H, m), 7.62–7.57 (3H, m), 7.53–7.46 (3H, m), 7.38–7.33 (1H, m). $^{13}$C NMR ($CDCl_3$): $\delta$ 196.2, 158.6, 156.9, 138.1, 132.6, 132.3, 130.0, 129.8, 128.6, 128.4, 128.0, 125.0, 124.4, 123.7, 123.4, 121.4, 120.3, 111.9, 111.5.

#### 4.1.3. Synthesis of compounds **4** and **5**

To a stirred solution of compound **2** (3.15 g, 15 mmol) or **3** (4.08 g, 15 mmol) in MeOH (25 mL) at 0 °C was added $NaBH_4$ (0.28 g, 7.5 mmol) in small portions over a period of 20 min, and then at ambient temperature for 4 h. Reaction progress was monitored by TLC. A small amount of water was added and the mixture was stirred for 15 min before rotary evaporation. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 60–90 °C:ethyl acetate = 5:1) to afford the product **4** or **5** as white powder.

*4.1.3.1. 1-(Dibenzo[b,d]furan-2-yl)ethanol (**4**).* Yield 96%, white powder. $^1$H NMR ($CDCl_3$): $\delta$ 7.89–7.84 (2H, m), 7.53–7.50 (1H, m), 7.47–7.34 (3H, m), 7.29–7.26 (1H, m), 2.60–2.29 (1H, m), 1.54–1.51 (3H, m). $^{13}$C NMR ($CDCl_3$): $\delta$ 156.6, 155.6, 140.6, 127.2, 124.8, 122.7, 120.7, 117.5, 111.7, 111.5, 70.5, 25.7.

*4.1.3.2. 1-(Dibenzo[b,d]furan-2-yl)(phenyl)methanol (**5**).* Yield 94%, white powder. $^1$H NMR ($CDCl_3$): $\delta$ 8.43 (1H, s), 7.97–7.93 (2H, m), 7.85–7.82 (2H, m), 7.62–7.57 (3H, m), 7.53–7.46 (3H, m), 7.38–7.33 (1H, m). $^{13}$C NMR ($CDCl_3$): $\delta$ 196.2, 158.6, 156.9, 138.1, 132.6, 132.3, 130.0, 129.8, 128.6, 128.4, 128.0, 125.0, 124.4, 123.7, 123.4, 121.4, 120.3, 112.0, 111.5.

#### 4.1.4. General procedure for the preparation of 1-dibenzo[b,d]furan-substituted imidazoles (**6**–**11**)

To a solution of compound **4** (212 mg, 1 mmol) or **5** (274 mg, 1 mmol) in dichloromethane (50 mL) was added methanesulfonyl chloride (1.2 mmol) and triethylamine (2 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 12 h. After quenching the reaction with water (50 mL), the layers were separated. The organic phase was dried over anhydrous $Na_2SO_4$ and concentrated, and used for the next synthetic step. A mixture of the previous methanesulfonate and imidazole or substituted imidazole (3 mmol) was stirred in acetonitrile (20 mL) at reflux for 24–48 h

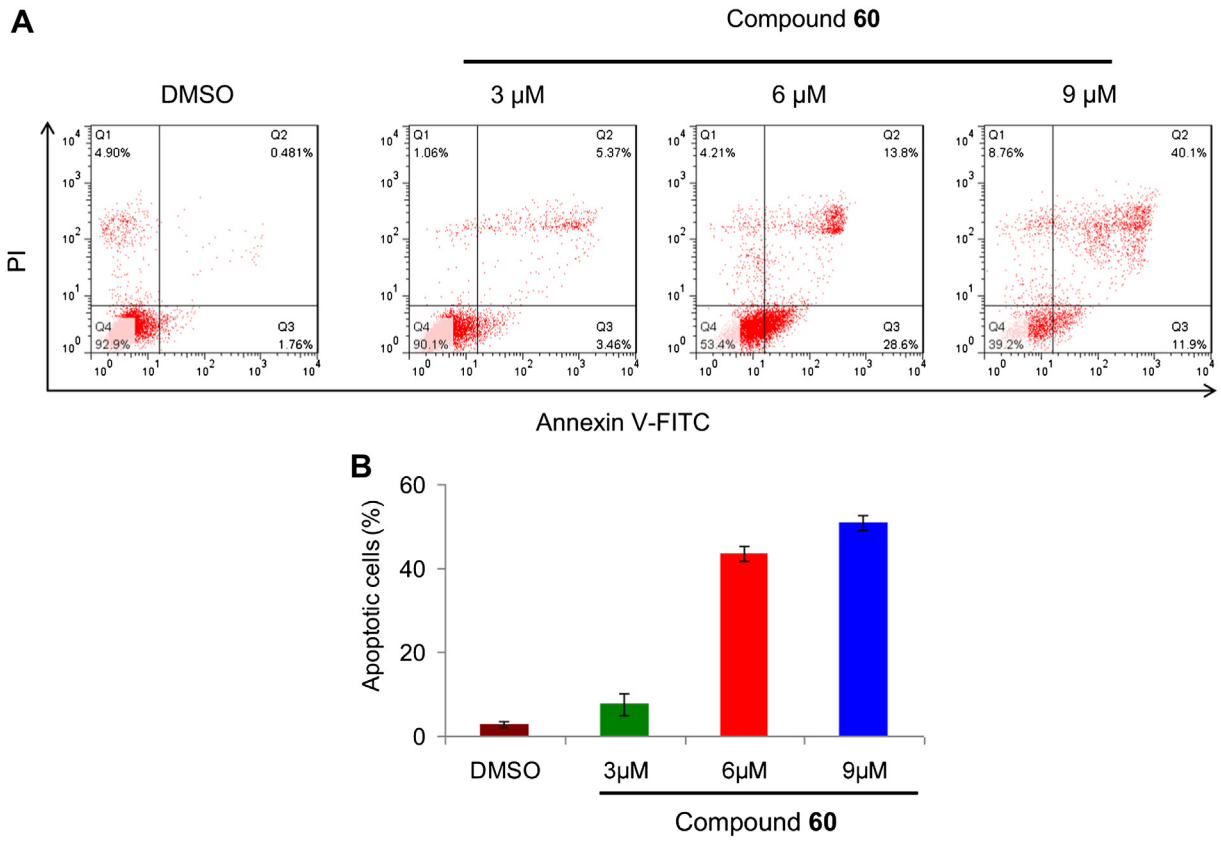
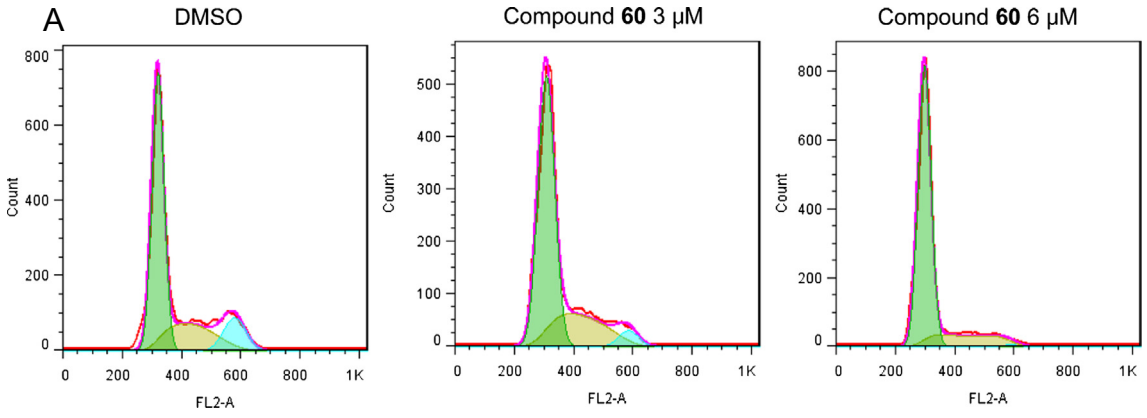



**Fig. 1.** Compound **60** caused significant apoptosis of SMMC-7721 cells. (A) Cells were treated with 3, 6 and 9 μM compound **60** for 48 h. Cell apoptosis was determined by Annexin V-FITC/PI double-staining assay. (B) The quantification of cell apoptosis. Data represents the mean ± S.D. of three independent experiments.




B

| Treatment | Cells (%) | | |
|---|---|---|---|
| | G1 | S | G2/M |
| DMSO | 60.29 | 24.41 | 12.84 |
| Compound **60** (3 μM) | 67.74 | 26.80 | 4.96 |
| Compound **60** (6 μM) | 80.14 | 17.80 | 0.75 |

**Fig. 2.** Compound **60** induces G1 phase arrest in SMMC-7721 cells. (A) Cells were treated with 3 and 6 μM of compound **60** for 24 h. Cell cycle was determined by PI staining and cell cytometry. (B) The percentages of cells in different phases were quantified. At least three independent experiments were performed and data of one representative experiment is shown.

(monitored by TLC). After cooling to room temperature, the solvent was concentrated, and the residue was diluted with EtOAc (20 mL). The organic layer was washed with water (20 mL) and brine (20 mL), dried over anhydrous $Na_2SO_4$ and concentrated. The residue was purified by column chromatography (silica gel, petroleum ether 60–90 °C:ethyl acetate = 3:1→1:1) to afford **6**–**11** in 65–72% yield (two steps) as yellow oil or powder.

*4.1.4.1. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-1H-imidazole (**6**).* Yield 65%, yellow powder, mp 92–94 °C. IR $\nu_{max}$ ($cm^{-1}$): 3432, 3094, 2982, 1638, 1487, 1295, 1200, 1087, 1019, 823, 763, 663. $^1H$ NMR ($CDCl_3$): $\delta$ 7.84 (1H, d, $J$ = 7.8), 7.63 (2H, d, $J$ = 7.4), 7.49 (1H, d, $J$ = 9.6), 7.44–7.37 (2H, m), 7.28 (1H, t, $J$ = 14.7), 7.18–7.15 (1H, m), 7.10 (1H, s), 6.92 (1H, s), 5.43–5.36 (1H, m), 1.85 (3H, d, $J$ = 7.2). $^{13}C$ NMR ($CDCl_3$): $\delta$ 156.6, 155.6, 136.2, 136.0, 129.4, 127.6, 125.2, 124.6, 123.7, 122.9, 120.7, 118.1, 118.0, 111.9, 111.7, 56.4, 22.3. HRMS (ESI-TOF) $m/z$ Calcd for $C_{17}H_{15}N_2O$ $[M + 1]^+$ 263.1184, found 263.1176.

*4.1.4.2. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-2-methyl-1H-imidazole (**7**).* Yield 70%, yellow oil. IR $\nu_{max}$ ($cm^{-1}$): 3374, 2974, 1883, 1637, 1592, 1481, 1430, 1281, 1193, 1134, 1026, 986, 931, 879, 824, 751, 678. $^1H$ NMR ($CDCl_3$): $\delta$ 7.71 (1H, d, $J$ = 7.5), 7.42 (1H, s), 7.38–7.35 (1H, m), 7.31–7.24 (2H, m), 7.17–7.12 (1H, m), 6.98–6.95 (1H, m), 6.88 (2H, s), 5.26–5.23 (1H, m), 2.14 (3H, s), 1.67 (3H, d, $J$ = 6.9). $^{13}C$ NMR ($CDCl_3$): $\delta$ 156.6, 155.4, 144.7, 136.5, 127.5, 127.2, 126.9, 125.0, 123.7, 122.9, 120.7, 117.7, 116.48, 111.9, 111.7, 55.0, 22.7, 13.5. HRMS (ESI-TOF) $m/z$ Calcd for $C_{18}H_{17}N_2O$ $[M + 1]^+$ 277.1341, found 277.1327.

*4.1.4.3. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-1H-benzo[d]imidazole (**8**).* Yield 68%, yellow powder, mp 115–117 °C. IR $\nu_{max}$ ($cm^{-1}$): 3435, 3105, 3051, 2976, 2896, 1948, 1895, 1772, 1599, 1477, 1446, 1375, 1287, 1231, 1202, 1126, 1025, 980, 879, 743, 628. $^1H$ NMR ($CDCl_3$): $\delta$ 7.88 (1H, s), 7.67 (1H, d, $J$ = 7.8), 7.42–7.39 (2H, m), 7.16 (1H, d, $J$ = 7.8), 7.06–6.99 (2H, m), 6.97–6.80 (5H, m), 5.27–5.24 (1H, m), 1.58 (3H, d, $J$ = 6.6). $^{13}C$ NMR ($CDCl_3$): $\delta$ 156.5, 155.5, 144.3, 141.1, 135.4, 133.7, 127.5, 125.1, 124.6, 123.6, 122.3, 120.7, 120.4, 118.0, 111.9, 111.6, 110.8, 55.1, 21.8. HRMS (ESI-TOF) $m/z$ Calcd for $C_{21}H_{17}N_2O$ $[M + 1]^+$ 313.1341, found 313.1313.

*4.1.4.4. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-1H-imidazole (**9**).* Yield 70%, yellow powder, mp 117–119 °C. IR $\nu_{max}$ ($cm^{-1}$): 3415, 3159, 3060, 2982, 2925, 1598, 1522, 1438, 1343, 1196, 1105, 1030, 960, 816, 768, 671. $^1H$ NMR ($CDCl_3$): $\delta$ 7.86 (1H, d, $J$ = 9.0), 7.66 (1H, d, $J$ = 0.9), 7.55 (2H, d, $J$ = 9.0), 7.48–7.46 (2H, m), 7.38–7.32 (4H, m), 7.23–7.20 (1H, m), 7.16–7.13 (3H, m), 6.89 (1H, s), 6.70 (1H, s). $^{13}C$ NMR ($CDCl_3$): $\delta$ 156.7, 155.9, 139.4, 137.5, 133.9, 129.5, 129.0, 128.5, 128.0, 127.7, 127.2, 124.8, 123.7, 123.0, 120.9, 120.3, 119.4, 112.0, 111.8, 65.0. HRMS (ESI-TOF) $m/z$ Calcd for $C_{22}H_{17}N_2O$ $[M + 1]^+$ 325.1341, found 325.1352.

*4.1.4.5. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-2-methyl-1H-imidazole (**10**).* Yield 69%, yellow oil. IR $\nu_{max}$ ($cm^{-1}$): 3378, 3055, 2922, 1962, 1893, 1730, 1593, 1481, 1423, 1257, 1195, 1127, 1029, 984, 842, 744, 687. $^1H$ NMR ($CDCl_3$): $\delta$ 7.84 (1H, d, $J$ = 7.8), 7.57 (1H, s), 7.52 (2H, t, $J$ = 7.8), 7.45 (1H, t, $J$ = 7.5), 7.37–7.28 (4H, m), 7.16 (1H, d, $J$ = 7.8), 7.10–7.08 (2H, m), 6.94 (1H, s), 6.63 (1H, s), 6.56 (1H, s), 2.36 (3H, s). $^{13}C$ NMR ($CDCl_3$): $\delta$ 156.7, 155.8, 145.2, 139.3, 133.8, 128.9, 128.3, 128.2, 127.7, 127.4, 126.9, 124.8, 123.7, 123.0, 120.9, 120.4, 118.8, 112.0, 111.8, 63.6, 13.6. HRMS (ESI-TOF) $m/z$ Calcd for $C_{23}H_{19}N_2O$ $[M + 1]^+$ 339.1497, found 339.1493.

*4.1.4.6. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-1H-benzo[d]imidazole (**11**).* Yield 70%, yellow oil. IR $\nu_{max}$ ($cm^{-1}$): 3409, 3053, 1893, 1721, 1602, 1480, 1446, 1323, 1201, 1123, 1020, 880, 843, 745, 643. $^1H$ NMR ($CDCl_3$): $\delta$ 7.86 (1H, d, $J$ = 7.8), 7.78 (1H, d, $J$ = 7.8), 7.71 (1H, s), 7.66 (1H, s), 7.55–7.50 (2H, m), 7.45–7.42 (1H, m), 7.36–7.34 (3H, m), 7.29–7.22 (3H, m), 7.19–7.16 (4H, m), 6.91 (1H, s). $^{13}C$ NMR ($CDCl_3$): $\delta$ 156.7, 155.9, 144.3, 142.7, 138.4, 134.2, 132.9, 129.1, 128.7, 128.6, 128.3, 128.2, 127.8, 127.3, 125.0, 123.6, 123.1, 123.0, 122.9, 122.6, 120.9, 120.5, 112.2, 111.8, 110.9, 63.7. HRMS (ESI-TOF) $m/z$ Calcd for $C_{26}H_{19}N_2O$ $[M + 1]^+$ 375.1497, found 375.1471.

*4.1.5. General procedure for the preparation of 2-benzylbenzofuran-based imidazolium salts (**10**–**47**)*

A mixture of 1-dibenzo[*b*,*d*]furan-substituted imidazole **6**–**11** (1 mmol) and phenacyl bromides or alkyl halides (1.2 mmol) was stirred in acetone (10 mL) at reflux toluene or DMF (10 mL) at room temperature for 8–24 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 **12**–**60** in 70–96% yields.

*4.1.5.1. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-butyl-1H-imidazol-3-ium iodide (**12**).* Yield 70%, yellow oil. IR $\nu_{max}$ ($cm^{-1}$): 3438, 3121, 3047, 2957, 2866, 1881, 1723, 1560, 1444, 1325, 1261, 1191, 1164, 1104, 1015, 821, 748, 631. $^1H$ NMR ($CDCl_3$): $\delta$ 10.12 (1H, s), 8.25 (1H, s), 7.97–7.95 (1H, m), 7.54 (2H, s), 7.45–7.33 (4H, m), 7.14–7.11 (1H, m), 6.08–6.04 (1H, m), 4.20 (2H, t, $J$ = 7.5), 2.00–1.98 (3H, m), 1.75–1.74 (2H, m), 1.20–1.18 (2H, m), 0.75 (3H, t, $J$ = 7.5). $^{13}C$ NMR ($CDCl_3$): $\delta$ 156.4, 155.9, 134.9, 132.7, 127.7, 126.3, 125.0, 123.4, 123.0, 122.4, 121.6, 121.3, 120.1, 112.2, 111.5, 59.9, 49.8, 32.0, 21.8, 19.3, 13.4. HRMS (ESI-TOF) $m/z$ Calcd for $C_{21}H_{23}N_2O$ $[M - I]^+$ 319.1805, found 319.1816.

*4.1.5.2. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(4-nitrobenzyl)-1H-imidazol-3-ium bromide (**13**).* Yield 70%, yellow powder, mp 118–119 °C. IR $\nu_{max}$ ($cm^{-1}$): 3416, 3055, 2847, 2196, 1603, 1519, 1442, 1344, 1263, 1195, 1147, 1017, 920, 841, 729, 620. $^1H$ NMR ($CDCl_3$): $\delta$ 10.89 (1H, s), 8.16 (1H, s), 8.03–7.96 (3H, m), 7.83–7.81 (2H, m), 7.69 (1H, s), 7.48–7.41 (3H, m), 7.38–7.36 (2H, m), 7.28–7.24 (1H, m), 5.99–5.89 (2H, m), 5.30 (1H, s), 2.11 (3H, d, $J$ = 5.7). $^{13}C$ NMR ($CDCl_3$): $\delta$ 156.6, 156.2, 148.1, 140.3, 136.4, 132.3, 130.3, 128.0, 126.0, 125.2, 124.2, 123.3, 123.2, 122.7, 121.3, 119.8, 111.8, 60.5, 51.9, 21.8. HRMS (ESI-TOF) $m/z$ Calcd for $C_{24}H_{20}N_3O_3$ $[M - Br]^+$ 398.1499, found 398.1506.

*4.1.5.3. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(2-oxo-2-phenylethyl)-1H-imidazol-3-ium bromide (**14**).* Yield 70%, white powder, mp 200–201 °C. IR $\nu_{max}$ ($cm^{-1}$): 3427, 3116, 3053, 2953, 1698, 1558, 1444, 1337, 1235, 1193, 997, 827, 750, 685. $^1H$ NMR (MeOD): $\delta$ 9.30 (1H, s), 8.24 (1H, s), 8.13–8.07 (3H, m), 7.84 (1H, s), 7.74–7.65 (3H, m), 7.62–7.50 (5H, m), 7.40 (1H, t, $J$ = 7.2), 6.08–6.03 (3H, m), 2.12 (3H, d, $J$ = 6.9). $^{13}C$ NMR (MeOD): $\delta$ 192.1, 158.2, 157.6, 138.2, 135.7, 135.1, 135.0, 130.2, 129.4, 129.1, 127.3, 126.4, 125.8, 124.9, 124.4, 122.3, 122.2, 120.7, 113.4, 112.8, 61.5, 56.8, 21.8. HRMS (ESI-TOF) $m/z$ Calcd for $C_{25}H_{21}N_2O_2$ $[M - Br]^+$ 381.1598, found 381.1585.

*4.1.5.4. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(2-(4-hydroxyphenyl)-2-oxoethyl)-1H-imidazol-3-ium bromide (**15**).* Yield 70%, white powder, mp 204–205 °C. IR $\nu_{max}$ ($cm^{-1}$): 3418, 3118, 1678, 1599, 1441, 1345, 1238, 1155, 986, 835, 750, 642. $^1H$ NMR (DMSO): $\delta$ 10.70 (1H, s), 9.39 (1H, s), 8.39 (1H, s), 8.18 (1H, d, $J$ = 6.9), 8.07 (1H, s), 7.93 (2H, d, $J$ = 7.8), 7.78 (2H, s), 7.73 (1H, d, $J$ = 8.1), 7.65 (1H, t, $J$ = 8.1), 7.56 (1H, t, $J$ = 6.9), 6.96 (2H, d, $J$ = 7.8), 6.13–6.12 (1H, m), 5.94 (2H, s), 2.03 (3H, d, $J$ = 5.4). $^{13}C$ NMR (DMSO): $\delta$ 189.1, 163.2, 155.9, 155.3, 136.7, 134.2, 130.7, 128.1, 126.6, 125.0, 124.5, 124.1, 123.4, 123.1, 121.3, 120.7, 119.8, 115.7, 112.2, 111.8, 58.7, 55.0, 20.8. HRMS (ESI-TOF) $m/z$ Calcd for $C_{25}H_{21}N_2O_3$ $[M - Br]^+$ 397.1547, found 397.1558.

*4.1.5.5. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(2-(4-methoxyphenyl)-2-oxoethyl)-1H-imidazol-3-ium bromide (**16**).* Yield 70%, white powder, mp 213–214 °C. IR $\nu_{max}$ ($cm^{-1}$): 3416, 3039, 2837, 1689, 1600, 1438, 1321, 1245, 1172, 1026, 828, 751, 630. $^1$H NMR (DMSO): $\delta$ 9.48 (1H, s), 8.43 (1H, s), 8.19 (1H, d, $J$ = 7.5), 8.11 (1H, s), 8.03 (2H, d, $J$ = 8.7), 7.82–7.80 (2H, m), 7.77–7.65 (2H, m), 7.54 (1H, t, $J$ = 8.1), 7.45 (1H, t, $J$ = 7.5), 7.14 (2H, d, $J$ = 8.7), 6.16–6.14 (1H, m), 6.06 (2H, s), 3.86 (3H, s), 2.04 (3H, d, $J$ = 6.9). $^{13}$C NMR (DMSO): $\delta$ 189.5, 164.1, 155.9, 155.3, 136.7, 134.2, 130.6, 128.1, 126.6, 126.4, 124.5, 124.1, 123.3, 123.2, 121.3, 120.8, 119.9, 114.3, 112.2, 111.8, 58.7, 55.7, 55.2, 20.9. HRMS (ESI-TOF) $m/z$ Calcd for $C_{26}H_{23}N_2O_3$ $[M - Br]^+$ 411.1703, found 411.1698.

*4.1.5.6. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(2-(4-bromophenyl)-2-oxoethyl)-1H-imidazol-3-ium bromide (**17**).* Yield 70%, white powder, mp 239–241 °C. IR $\nu_{max}$ ($cm^{-1}$): 3397, 3125, 3041, 2962, 1701, 1580, 1482, 1441, 1395, 1198, 1161, 991, 818, 754, 625. $^1$H NMR (DMSO): $\delta$ 9.37 (1H, s), 8.39 (1H, s), 8.17 (1H, d, $J$ = 6.0), 8.08 (1H, s), 7.97 (2H, d, $J$ = 9.0), 7.86–7.76 (4H, m), 7.73 (1H, d, $J$ = 8.1), 7.65 (1H, d, $J$ = 8.1), 7.56 (1H, t, $J$ = 6.9), 7.44 (1H, t, $J$ = 6.9), 6.14–6.12 (1H, m), 6.05 (2H, s), 2.04 (3H, d, $J$ = 6.0). $^{13}$C NMR (DMSO): $\delta$ 190.7, 155.9, 155.3, 136.7, 134.1, 132.6, 132.2, 130.0, 128.6, 128.1, 126.6, 124.5, 124.1, 123.4, 123.1, 121.3, 120.8, 119.8, 112.2, 111.8, 58.7, 55.5, 20.8. HRMS (ESI-TOF) $m/z$ Calcd for $C_{25}H_{20}BrN_2O_2$ $[M - Br]^+$ 459.0708, found 459.0678.

*4.1.5.7. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(2-(4-fluorophenyl)-2-oxoethyl)-1H-imidazol-3-ium bromide (**18**).* Yield 70%, white powder, mp 209–210 °C. IR $\nu_{max}$ ($cm^{-1}$): 3419, 3116, 3049, 2966, 1695, 1598, 1485, 1441, 1333, 1235, 1195, 1157, 995, 836, 756, 631. $^1$H NMR (DMSO): $\delta$ 9.46 (1H, s), 8.43 (1H, s), 8.20–8.12 (4H, m), 7.83–7.78 (2H, m), 7.73 (1H, d, $J$ = 7.8), 7.67 (1H, d, $J$ = 7.8), 7.56 (1H, t, $J$ = 7.5), 7.50–7.42 (3H, m), 6.18–6.12 (1H, m), 6.12 (2H, s), 2.05 (3H, d, $J$ = 6.9). $^{13}$C NMR (DMSO): $\delta$ 190.0, 155.9, 155.3, 136.7, 134.1, 131.3, 131.2, 130.4, 128.1, 126.6, 124.5, 124.1, 123.3, 123.2, 121.3, 120.8, 119.9, 116.4, 116.1, 112.2, 111.8, 58.7, 55.5, 20.9. HRMS (ESI-TOF) $m/z$ Calcd for $C_{25}H_{20}FN_2O_2$ $[M - Br]^+$ 399.1503, found 399.1480.

*4.1.5.8. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(2-(naphthalen-2-yl)-2-oxoethyl)-1H-imidazol-3-ium bromide (**19**).* Yield 70%, white powder, mp 261–262 °C. IR $\nu_{max}$ ($cm^{-1}$): 3370, 3122, 3041, 2918, 1687, 1445, 1360, 1266, 1165, 814, 714, 696. $^1$H NMR (DMSO): $\delta$ 9.44 (1H, s), 8.83 (1H, s), 8.41 (1H, s), 8.19 (1H, d, $J$ = 7.5), 8.13–8.11 (2H, m), 8.07–8.01 (2H, m), 7.85–7.80 (2H, m), 7.75–7.66 (4H, m), 7.60–7.57 (1H, m), 7.47 (1H, t, $J$ = 7.5), 6.22 (2H, s), 6.17–6.15 (1H, m), 2.06 (3H, d, $J$ = 6.6). $^{13}$C NMR (DMSO): $\delta$ 191.2, 155.9, 155.2, 136.8, 135.5, 134.1, 132.0, 130.9, 130.5, 129.6, 129.3, 128.8, 128.1, 127.8, 127.4, 126.6, 124.6, 124.1, 123.4, 123.1, 121.2, 120.9, 119.9, 112.2, 111.8, 58.8, 55.5, 20.8. HRMS (ESI-TOF) $m/z$ Calcd for $C_{29}H_{23}N_2O_2$ $[M - Br]^+$ 431.1754, found 431.1736.

*4.1.5.9. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-butyl-2-methyl-1H-imidazol-3-ium iodide (**20**).* Yield 70%, yellow oil. IR $\nu_{max}$ ($cm^{-1}$): 3420, 3059, 2959, 2871, 1582, 1444, 1376, 1247, 1197, 1123, 1037, 882, 832, 747, 675. $^1$H NMR ($CDCl_3$): $\delta$ 8.03–7.98 (2H, m), 7.56 (2H, s), 7.43–7.41 (2H, m), 7.36 (2H, s), 7.23–7.21 (1H, m), 6.11–6.08 (1H, m), 4.09 (2H, t, $J$ = 7.5), 2.72 (3H, s), 1.92 (3H, d, $J$ = 6.0), 1.69–1.66 (2H, m), 1.26–1.12 (2H, m), 0.80 (3H, t, $J$ = 7.5). $^{13}$C NMR ($CDCl_3$): $\delta$ 156.5, 155.8, 143.3, 132.8, 127.8, 125.6, 125.1, 123.4, 123.1, 121.9, 121.5, 119.5, 119.2, 112.4, 111.6, 58.4, 48.8, 31.6, 22.3, 19.5, 13.5, 12.3. HRMS (ESI-TOF) $m/z$ Calcd for $C_{22}H_{25}N_2O$ $[M - I]^+$ 333.1961, found 333.1969.

*4.1.5.10. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(4-nitrobenzyl)-2-methyl-1H-imidazol-3-ium bromide (**21**).* Yield 70%, white powder, mp 244–245 °C. IR $\nu_{max}$ ($cm^{-1}$): 3415, 3159, 3060, 2982, 2925, 1598, 1522, 1438, 1343, 1196, 1105, 1030, 960, 816, 768, 671. $^1$H NMR (DMSO): $\delta$ 8.39 (1H, s), 8.23–8.19 (4H, m), 7.79 (1H, s), 7.71–7.54 (6H, m), 7.42 (1H, s), 6.09–6.07 (1H, m), 5.67 (2H, s), 2.76 (3H, s), 1.99 (3H, s). $^{13}$C NMR (DMSO): $\delta$ 155.9, 155.1, 147.3, 144.5, 141.7, 134.0, 129.2, 128.0, 126.5, 123.9, 123.2, 122.4, 121.4, 119.9, 119.4, 112.0, 111.7, 57.0, 49.9, 21.0, 10.3. HRMS (ESI-TOF) $m/z$ Calcd for $C_{25}H_{22}N_3O_3$ $[M - Br]^+$ 412.1656, found 412.1669.

*4.1.5.11. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(2-oxo-2-phenylethyl)-2-methyl-1H-imidazol-3-ium bromide (**22**).* Yield 70%, white powder, mp 246–247 °C. IR $\nu_{max}$ ($cm^{-1}$): 3420, 3125, 3013, 2925, 2353, 1696, 1604, 1561, 1481, 1441, 1345, 1204, 1131, 1069, 990, 831, 754, 687. $^1$H NMR (MeOD): $\delta$ 8.13–8.09 (4H, m), 7.92 (1H, s), 7.72–7.59 (6H, m), 7.56–7.50 (2H, m), 7.40 (1H, t, $J$ = 7.2), 6.11–6.07 (1H, m), 6.06 (2H, m), 2.61 (3H, s), 2.09 (3H, d, $J$ = 6.9). $^{13}$C NMR (MeOD): $\delta$ 191.9, 158.1, 157.4, 147.3, 135.8, 135.1, 130.2, 129.6, 129.1, 126.9, 126.3, 124.9, 124.4, 122.2, 120.1, 120.1, 113.4, 112.7, 59.5, 55.9, 21.8, 10.6. HRMS (ESI-TOF) $m/z$ Calcd for $C_{26}H_{23}N_2O_2$ $[M - Br]^+$ 395.1754, found 395.1758.

*4.1.5.12. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(2-(4-hydroxyphenyl)-2-oxoethyl)-2-methyl-1H-imidazol-3-ium bromide (**23**).* Yield 70%, white powder, mp 252–253 °C. IR $\nu_{max}$ ($cm^{-1}$): 3129, 2930, 2582, 2430, 1680, 1590, 1510, 1442, 1351, 1223, 1170, 1112, 1040, 990, 838, 748, 677. $^1$H NMR (DMSO): $\delta$ 10.68 (1H, s), 8.39 (1H, s), 8.20 (1H, d, $J$ = 7.5), 8.14 (1H, s), 7.94 (2H, d, $J$ = 8.7), 7.79 (2H, s), 7.76–7.70 (1H, m), 7.62–7.52 (2H, m), 7.43 (1H, t, $J$ = 7.5), 6.98 (2H, d, $J$ = 8.7), 6.17–6.14 (1H, m), 6.06 (2H, s), 2.65 (3H, s), 2.01 (3H, d, $J$ = 6.6). $^{13}$C NMR (DMSO): $\delta$ 188.9, 163.3, 155.9, 155.1, 145.3, 134.1, 131.1, 128.0, 126.2, 125.1, 124.1, 123.2, 121.4, 119.7, 118.6, 115.6, 112.1, 111.8, 56.9, 54.1, 21.0, 10.0. HRMS (ESI-TOF) $m/z$ Calcd for $C_{26}H_{23}N_2O_3$ $[M - Br]^+$ 411.1703, found 411.1689.

*4.1.5.13. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(2-(4-methoxyphenyl)-2-oxoethyl)-2-methyl-1H-imidazol-3-ium bromide (**24**).* Yield 70%, white powder, mp 231–232 °C. IR $\nu_{max}$ ($cm^{-1}$): 3401, 3051, 2927, 2835, 1686, 1597, 1511, 1433, 1318, 1239, 1175, 1030, 821, 745, 590. $^1$H NMR (MeOD): $\delta$ 8.12–8.07 (4H, m), 7.89 (1H, s), 7.63–7.52 (5H, m), 7.40–7.38 (1H, m), 7.09–7.06 (2H, m), 6.07–6.00 (1H, m), 5.99 (2H, m), 3.89 (3H, s), 2.59 (3H, s), 2.08 (3H, s). $^{13}$C NMR (MeOD): $\delta$ 190.2, 166.4, 158.1, 157.3, 147.3, 135.0, 132.1, 129.1, 127.8, 126.9, 126.3, 124.9, 124.4, 122.3, 120.1, 120.0, 115.4, 113.4, 112.8, 59.4, 56.3, 55.5, 21.8, 10.7. HRMS (ESI-TOF) $m/z$ Calcd for $C_{27}H_{25}N_2O_3$ $[M - Br]^+$ 425.1865, found 425.1865.

*4.1.5.14. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(2-(4-bromophenyl)-2-oxoethyl)-2-methyl-1H-imidazol-3-ium bromide (**25**).* Yield 70%, white powder, mp 259–260 °C. IR $\nu_{max}$ ($cm^{-1}$): 3430, 3109, 3044, 2926, 1696, 1631, 1583, 1484, 1441, 1343, 1204, 1069, 989, 815, 755, 628. $^1$H NMR (DMSO): $\delta$ 8.18 (1H, s), 8.20 (1H, d, $J$ = 6.0), 8.14 (1H, s), 7.85 (2H, d, $J$ = 8.4), 7.78 (2H, d, $J$ = 8.7), 7.74–7.71 (3H, m), 7.62–7.53 (2H, m), 7.44 (1H, t, $J$ = 7.5), 6.16–6.13 (3H, m), 2.68 (3H, s), 2.02 (3H, d, $J$ = 6.6). $^{13}$C NMR (DMSO): $\delta$ 190.5, 155.9, 155.1, 145.4, 134.1, 132.7, 132.0, 130.3, 128.6, 128.1, 126.3, 124.1, 123.3, 123.2, 121.4, 119.7, 118.7, 112.2, 111.8, 57.0, 54.5, 21.0, 9.9. HRMS (ESI-TOF) $m/z$ Calcd for $C_{26}H_{22}BrN_2O_2$ $[M - Br]^+$ 473.0865, found 473.0843.

*4.1.5.15. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(2-(4-fluorophenyl)-2-oxoethyl)-2-methyl-1H-imidazol-3-ium bromide (**26**).* Yield 70%, white powder, mp 240–242 °C. IR $\nu_{max}$ ($cm^{-1}$): 3416, 3052, 2920, 1693, 1595, 1505, 1428, 1342, 1279, 1231, 1196, 1156, 990, 839, 758, 681. $^1$H NMR (DMSO): $\delta$ 8.37 (1H, s), 8.21–8.13 (4H, m), 7.80–7.72 (3H, m), 7.63–7.42 (5H, m), 6.15–6.13 (3H, m), 2.68 (3H, s), 2.02 (3H, d, $J$ = 6.6). $^{13}$C NMR (DMSO): $\delta$ 189.8, 155.9, 155.1, 145.4, 134.1, 131.6, 131.4, 130.5, 128.1, 126.3, 124.1, 123.3, 123.2, 121.3, 119.7, 118.7, 112.2,

111.8, 57.0, 54.5, 21.0, 9.9. HRMS (ESI-TOF) *m/z* Calcd for $C_{26}H_{22}FN_2O_2$ $[M - Br]^+$ 413.1660, found 413.1669.

*4.1.5.16. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(2-(naphthalen-2-yl)-2-oxoethyl)-2-methyl-1H-imidazol-3-ium bromide (**27**).* Yield 70%, white powder, mp 220–221 °C. IR $\nu_{max}$ ($cm^{-1}$): 3387, 3069, 2973, 2896, 2349, 1687, 1626, 1520, 1441, 1380, 1274, 1196, 1041, 869, 814, 747. $^1H$ NMR ($CDCl_3$): $\delta$ 8.91 (1H, s), 8.06–7.91 (5H, m), 7.73 (2H, t, $J = 7.8$), 7.54–7.39 (6H, m), 7.32–7.28 (2H, m), 6.59 (2H, s), 5.98–5.94 (1H, m) 2.67 (3H, s), 1.96 (3H, d, $J = 6.6$). $^{13}C$ NMR ($CDCl_3$): $\delta$ 190.6, 156.7, 155.9, 145.7, 136.1, 132.5, 132.4, 131.9, 130.6, 130.2, 129.3, 128.8, 127.9, 127.6, 127.0, 125.3, 123.8, 123.4, 123.3, 123.2, 121.4, 119.0, 118.3, 112.6, 111.7, 58.3, 56.1, 21.9, 11.7. HRMS (ESI-TOF) *m/z* Calcd for $C_{30}H_{25}N_2O_2$ $[M - Br]^+$ 445.1911, found 445.1902.

*4.1.5.17. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-butyl-1H-benzo[d] imidazol-3-ium iodide (**28**).* Yield 70%, yellow Powder, mp 215–217 °C. IR $\nu_{max}$ ($cm^{-1}$): 3423, 3136, 3026, 2954, 2864, 1969, 1896, 1775, 1603, 1555, 1435, 1331, 1254, 1198, 1198, 1133, 1069, 1020, 947, 833, 756, 626. $^1H$ NMR (DMSO): $\delta$ 10.19 (1H, s), 8.45 (1H, s), 8.14 (2H, d, $J = 7.5$), 7.89 (1H, d, $J = 6.0$), 7.76–7.51 (6H, m), 7.41 (1H, t, $J = 7.5$), 6.38–6.36 (1H, m), 4.58 (2H, t, $J = 7.5$), 2.16 (3H, d, $J = 6.0$), 2.00–1.96 (2H, m), 1.41–1.39 (2H, m), 0.97–0.92 (3H, t, $J = 7.5$). $^{13}C$ NMR (DMSO): $\delta$ 155.9, 155.1, 141.1, 134.0, 131.4, 130.6, 128.0, 126.6, 126.3, 123.3, 123.1, 121.4, 119.8, 114.2, 113.9, 112.2, 111.8, 57.3, 46.9, 30.6, 21.3, 19.2, 13.4. HRMS (ESI-TOF) *m/z* Calcd for $C_{25}H_{25}N_2O_2$ $[M - I]^+$ 369.1961, found 369.1954.

*4.1.5.18. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(4-nitrobenzyl)-1H-benzo[d] imidazol-3-ium bromide (**29**).* Yield 70%, white powder, mp 156–157 °C. IR $\nu_{max}$ ($cm^{-1}$): 3434, 3119, 3056, 2974, 1687, 1607, 1552, 1436, 1198, 1130, 1063, 1017, 842, 750, 624. $^1H$ NMR (DMSO): $\delta$ 10.35 (1H, s), 8.43 (1H, s), 8.28 (2H, d, $J = 9.0$), 8.13 (1H, d, $J = 7.5$), 7.89–7.82 (3H, m), 7.79–7.76 (1H, s), 7.74–7.70 (3H, m), 7.59–7.54 (3H, m), 7.42 (1H, t, $J = 7.5$), 6.40–6.37 (1H, m), 6.01 (2H, s), 2.18 (3H, d, $J = 6.6$). $^{13}C$ NMR (DMSO): $\delta$ 155.9, 155.2, 147.6, 142.2, 141.3, 133.7, 131.2, 129.4, 128.1, 126.9, 126.3, 123.9, 123.3, 121.2, 119.8, 114.5, 113.9, 112.2, 111.8, 57.6, 49.4, 21.2. HRMS (ESI-TOF) *m/z* Calcd for $C_{28}H_{22}N_3O_3$ $[M - Br]^+$ 448.1565, found 448.1641.

*4.1.5.19. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(2-oxo-2-phenylethyl)-1H-benzo[d] imidazol-3-ium bromide (**30**).* Yield 70%, white powder, mp 160–161 °C. IR $\nu_{max}$ ($cm^{-1}$): 3420, 3125, 3013, 2925, 2353, 1696, 1604, 1561, 1481, 1441, 1345, 1204, 1131, 1069, 990, 831, 754, 687. $^1H$ NMR (300 MHz, DMSO): $\delta$ 10.32 (1H, s), 8.54 (1H, s), 8.18–8.11 (4H, m), 8.04 (1H, d, $J = 7.8$), 7.80–7.56 (8H, m), 7.52 (1H, t, $J = 7.8$ Hz), 7.41 (1H, t, $J = 7.5$ Hz), 6.56–6.52 (3H, m), 2.17 (3H, d, $J = 6.3$ Hz). $^{13}C$ NMR (75 MHz, DMSO): $\delta$ 191.2, 155.9, 155.2, 142.6, 134.6, 133.7, 132.4, 130.2, 129.1, 128.4, 128.1, 126.8, 126.6, 126.3, 124.2, 123.3, 123.1, 121.4, 119.8, 114.2, 112.3, 111.8, 57.3, 53.5, 21.3. HRMS (ESI-TOF) *m/z* Calcd for $C_{29}H_{23}N_2O_2$ $[M - Br]^+$ 431.1754, found 431.1766.

*4.1.5.20. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(2-(4-hydroxyphenyl)-2-oxoethyl)-1H-benzo[d]imidazol-3-ium bromide (**31**).* Yield 70%, white powder, mp 174–175 °C. IR $\nu_{max}$ ($cm^{-1}$): 3386, 3061, 2447, 1916, 1789, 1682, 1593, 1478, 1439, 1343, 1230, 1067, 986, 836, 752, 691. $^1H$ NMR (DMSO): $\delta$ 10.72 (1H, s), 10.24 (1H, s), 8.48 (1H, s), 8.17 (1H, d, $J = 7.5$), 8.06–8.03 (4H, m), 7.78–7.69 (3H, m), 7.62–7.51 (3H, m), 7.43 (1H, t, $J = 7.5$), 7.04 (2H, d, $J = 8.1$), 6.54–6.52 (1H, m), 6.47 (2H, s), 2.16 (3H, d, $J = 6.0$). $^{13}C$ NMR (DMSO): $\delta$ 189.0, 163.3, 155.9, 155.2, 142.6, 133.7, 132.4, 131.1, 130.2, 128.1, 126.8, 126.5, 126.2, 125.1, 124.1, 123.3, 123.1, 121.3, 119.7, 115.7, 114.2, 114.1, 112.3, 111.8, 57.3, 52.9, 21.2. HRMS (ESI-TOF) *m/z* Calcd for $C_{29}H_{23}N_2O_3$ $[M - Br]^+$ 447.1703, found 447.1683.

*4.1.5.21. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(2-(4-methoxyphenyl)-2-oxoethyl)-1H-benzo[d]imidazol-3-ium bromide (**32**).* Yield 70%, yellow powder, mp 168–169 °C. IR $\nu_{max}$ ($cm^{-1}$): 3410, 3109, 2937, 2835, 1683, 1599, 1564, 1436, 1262, 1185, 1128, 1069, 1021, 998, 834, 754, 691. $^1H$ NMR ($CDCl_3$): $\delta$ 11.09 (1H, s), 8.24 (1H, s), 8.13 (2H, $J = 8.4$ Hz), 8.07 (1H, $J = 7.8$), 7.63 (1H, $J = 7.8$), 7.57–7.52 (4H, m), 7.49–7.35 (3H, m), 7.32–7.27 (1H, m), 6.88 (2H, d, $J = 8.4$), 6.64–6.62 (2H, m), 6.14–6.12 (1H, m), 3.78 (3H, s), 2.25 (3H, d, $J = 6.6$). $^{13}C$ NMR ($CDCl_3$): $\delta$ 188.7, 164.7, 156.6, 156.0, 142.4, 132.6, 131.2, 130.5, 127.8, 127.1, 126.8, 126.4, 125.5, 125.3, 123.4, 123.1, 121.6, 119.3, 114.3, 114.0, 113.6, 112.4, 111.5, 59.2, 55.6, 53.6, 22.4. HRMS (ESI-TOF) *m/z* Calcd for $C_{30}H_{25}N_2O_3$ $[M - Br]^+$ 461.1860, found 461.1839.

*4.1.5.22. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(2-(4-bromophenyl)-2-oxoethyl)-1H-benzo[d]imidazol-3-ium bromide (**33**).* Yield 70%, white powder, mp 231–233 °C. IR $\nu_{max}$ ($cm^{-1}$): 3386, 3061, 2447, 1916, 1789, 1682, 1593, 1478, 1439, 1343, 1230, 1067, 986, 836, 752, 691. $^1H$ NMR ($CDCl_3$): $\delta$ 11.09 (1H, s), 8.20 (1H, s), 8.05 (3H, d, $J = 6.9$), 7.73 (1H, d, $J = 6.9$), 7.74–7.42 (9H, m), 7.29 (1H, d, $J = 6.9$), 6.80 (2H, s), 6.10–6.08 (1H, m), 2.26 (3H, s). $^{13}C$ NMR ($CDCl_3$): $\delta$ 190.0, 156.6, 156.1, 142.4, 132.6, 132.5, 132.3, 132.2, 130.5, 130.3, 130.1, 127.9, 127.3, 126.9, 125.4, 123.4, 123.1, 121.5, 119.1, 114.0, 113.8, 112.5, 111.6, 59.3, 54.2, 22.4. HRMS (ESI-TOF) *m/z* Calcd for $C_{29}H_{22}BrN_2O_2$ $[M - Br]^+$ 509.0859, found 509.0868.

*4.1.5.23. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(2-(4-fluorophenyl)-2-oxoethyl)-1H-benzo [d]imidazol-3-ium bromide (**34**).* Yield 70%, white powder, mp 163–164 °C. IR $\nu_{max}$ ($cm^{-1}$): 3423, 3136, 3026, 2954, 2864, 1969, 1896, 1775, 1603, 1555, 1435, 1331, 1254, 1198, 1198, 1133, 1069, 1020, 947, 833, 756, 626. $^1H$ NMR (DMSO): $\delta$ 10.31 (1H, s), 8.52 (1H, s), 8.28–8.24 (2H, m), 8.20 (1H, d, $J = 6.6$), 8.15 (1H, d, $J = 7.5$), 8.05–8.02 (1H, m), 7.79–7.71 (3H, m), 7.68–7.61 (2H, m), 7.58–7.52 (3H, m), 7.45 (1H, d, $J = 7.5$), 6.60–6.54 (3H, m), 2.17 (3H, d, $J = 6.9$). $^{13}C$ NMR (DMSO): $\delta$ 189.9, 155.9, 155.2, 142.6, 133.7, 132.3, 131.6, 131.5, 130.6, 130.2, 128.1, 126.8, 126.6, 126.3, 124.2, 123.3, 123.1, 121.3, 119.8, 116.3, 116.1, 114.2, 112.2, 111.8, 57.4, 53.4, 21.2. HRMS (ESI-TOF) *m/z* Calcd for $C_{29}H_{22}FN_2O_2$ $[M - Br]^+$ 449.1660, found 449.1642.

*4.1.5.24. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(2-oxo-1,2-diphenylethyl)-1H-benzo[d]imidazol-3-ium bromide (**35**).* Yield 70%, yellow Powder, mp 143–145 °C. IR $\nu_{max}$ ($cm^{-1}$): 3420, 3125, 3013, 2925, 2353, 1696, 1604, 1561, 1481, 1441, 1345, 1204, 1131, 1069, 990, 831, 754, 687. $^1H$ NMR (DMSO): $\delta$ 10.13 (1H, s), 8.44 (1H, s), 8.19–8.13 (3H, m), 8.03 (1H, d, $J = 8.4$), 7.96 (1H, d, $J = 7.5$), 7.83–7.80 (1H, m), 7.77–7.69 (6H, m), 7.63–7.42 (9H, m), 6.50–6.46 (1H, s), 2.40 (3H, s). $^{13}C$ NMR (DMSO): $\delta$ 199.9, 155.9, 155.2, 142.2, 133.7, 132.0, 130.1, 129.5, 129.5, 129.1, 128.1, 126.8, 126.6, 126.3, 124.1, 123.3, 123.1, 121.3, 119.7, 114.2, 114.1, 112.2, 111.8, 57.3, 55.6, 21.2. HRMS (ESI-TOF) *m/z* Calcd for $C_{35}H_{27}N_2O_2$ $[M - Br]^+$ 507.2067, found 507.2052.

*4.1.5.25. 1-(1-(Dibenzo[b,d]furan-2-yl)ethyl)-3-(2-(naphthalen-2-yl)-2-oxoethyl)-1H-benzo[d]imidazol-3-ium bromide (**36**).* Yield 70%, white powder, mp 228–229 °C. IR $\nu_{max}$ ($cm^{-1}$): 3414, 3130, 3052, 2986, 2761, 1692, 1623, 1559, 1479, 1435, 1355, 1262, 1196, 1019, 940, 822, 755, 689. $^1H$ NMR (DMSO): $\delta$ 10.13 (1H, s), 8.94 (1H, s), 8.46 (1H, s), 8.25 (1H, d, $J = 7.8$), 8.18–8.07 (5H, m), 8.03 (1H, d, $J = 6.9$), 7.81–7.64 (7H, m), 7.56 (1H, t, $J = 7.5$), 7.45 (1H, t, $J = 7.5$), 6.58 (2H, s), 6.54–6.52 (1H, m), 2.17 (3H, d, $J = 6.6$). $^{13}C$ NMR (DMSO): $\delta$ 191.1, 155.9, 155.3, 142.7, 135.6, 133.6, 132.4, 132.0, 131.0, 130.8, 130.3, 129.7, 129.4, 128.8, 128.1, 127.9, 127.4, 126.9, 126.6, 126.3, 124.2, 123.3, 121.2, 119.8, 114.1, 112.3, 111.8, 57.4, 53.4, 21.1. HRMS (ESI-TOF) *m/z* Calcd for $C_{33}H_{25}N_2O_2$ $[M - Br]^+$ 481.1911, found 481.1885.

*4.1.5.26. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-butyl-1H-imidazol-3-ium iodide (**37**).* Yield 70%, yellow oil. IR $\nu_{max}$ ($cm^{-1}$): 3426, 3056, 2957, 2868, 1726, 1599, 1549, 1445, 1321, 1247, 1193, 1141, 1024, 838, 745, 659. $^1H$ NMR ($CDCl_3$): $\delta$ 9.69 (1H, s), 8.04 (1H, s), 7.95 (1H, d, $J = 7.5$), 7.74 (2H, s), 7.54–7.51 (2H, m), 7.49–7.46 (2H, m), 7.44–7.31 (6H, m) 7.26 (1H, t, $J = 7.5$), 4.33 (2H, t, $J = 7.5$), 1.92–1.82 (2H, m), 1.37–1.29 (2H, m), 0.89 (3H, t, $J = 7.5$). $^{13}C$ NMR ($CDCl_3$): $\delta$ 156.6, 156.1, 136.6, 136.0, 130.9, 129.3, 129.2, 128.1, 127.9, 127.5, 125.1, 123.3, 123.1, 122.9, 121.9, 121.4, 121.3, 112.4, 111.6, 66.6, 50.3, 31.8, 19.4, 13.4. HRMS (ESI-TOF) *m/z* Calcd for $C_{26}H_{25}N_2O$ $[M - I]^+$ 381.1961, found 381.1972.

*4.1.5.27. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-(4-nitrobenzyl)-1H-imidazol-3-ium bromide (**38**).* Yield 70%, white powder, mp 120–121 °C. IR $\nu_{max}$ ($cm^{-1}$): 3403, 3055, 1604, 1522, 1442, 1339, 1248, 1195, 1139, 1023, 845, 730, 661. $^1H$ NMR (DMSO): $\delta$ 9.61 (1H, s), 8.25 (2H, s), 8.23 (1H, s), 8.13 (1H, d, $J = 7.5$), 8.08 (1H, s), 7.93 (1H, s), 7.80–7.76 (3H, m), 7.69 (1H, d, $J = 8.1$), 7.54–7.36 (9H, m), 5.73 (2H, s). $^{13}C$ NMR (DMSO): $\delta$ 155.9, 155.3, 147.5, 142.0, 137.4, 137.1, 132.0, 129.7, 129.2, 128.9, 128.1, 128.0, 124.3, 123.9, 123.3, 123.0, 121.5, 112.3, 111.7, 66.0, 51.2. HRMS (ESI-TOF) *m/z* Calcd for $C_{29}H_{22}N_3O_3$ $[M - Br]^+$ 460.1656, found 460.1663.

*4.1.5.28. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-(2-oxo-2-phenylethyl)-1H-imidazol-3-ium bromide (**39**).* Yield 70%, yellow oil. IR $\nu_{max}$ ($cm^{-1}$): 3388, 3056, 1700, 1589, 1548, 1442, 1343, 1234, 1204, 1149, 990, 837, 750, 689. $^1H$ NMR ($CDCl_3$): $\delta$ 9.58 (1H, s), 7.93–7.87 (5H, m), 7.52–7.40 (6H, m), 7.36–7.16 (9H, m), 6.30 (2H, s). $^{13}C$ NMR ($CDCl_3$): $\delta$ 190.6, 156.6, 156.1, 138.0, 136.6, 134.5, 133.3, 131.0, 129.4, 128.9, 128.5, 128.1, 127.9, 127.4, 125.1, 124.6, 123.4, 123.1, 121.4, 120.9, 112.5, 111.7, 67.0, 56.2. HRMS (ESI-TOF) *m/z* Calcd for $C_{30}H_{23}N_2O_2$ $[M - Br]^+$ 443.1754, found 443.1760.

*4.1.5.29. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-(2-(4-hydroxyphenyl)-2- oxoethyl)-1H-imidazol-3-ium bromide (**40**).* Yield 70%, white powder, mp 166–168 °C. IR $\nu_{max}$ ($cm^{-1}$): 3411, 3080, 1682, 1596, 1442, 1343, 1237, 1156, 1035, 989, 839, 745, 658. $^1H$ NMR (DMSO): $\delta$ 10.67 (1H, s), 9.16 (1H, s), 8.16 (2H, d, $J = 9.6$), 7.94–7.90 (4H, m), 7.83 (1H, d, $J = 8.7$), 7.73 (1H, d, $J = 8.1$), 7.58–7.42 (6H, m), 7.39–7.35 (3H, m), 6.98 (2H, d, $J = 8.7$), 6.00 (2H, s). $^{13}C$ NMR (DMSO): $\delta$ 189.1, 163.2, 156.0, 155.4, 137.9, 137.4, 132.0, 130.7, 129.2, 128.9, 128.2, 127.9, 125.1, 124.9, 124.3, 123.4, 123.0, 122.1, 121.4, 121.2, 115.7, 112.4, 111.8, 65.8, 55.2. HRMS (ESI-TOF) *m/z* Calcd for $C_{30}H_{23}N_2O_3$ $[M - Br]^+$ 459.1709, found 459.1693.

*4.1.5.30. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-(2-(4-methoxyphenyl)-2-oxoethyl)-1H-imidazol-3-ium bromide (**41**).* Yield 70%. White powder, mp 156–157 °C. IR $\nu_{max}$ ($cm^{-1}$): 3400, 3057, 2963, 2917, 1684, 1598, 1442, 1320, 1249, 1185, 1028, 836, 748, 658. $^1H$ NMR (MeOD): $\delta$ 8.98 (1H, s), 8.05–8.02 (4H, m), 7.73 (2H, d, $J = 8.4$), 7.68 (1H, d, $J = 8.7$), 7.60 (1H, d, $J = 8.4$), 7.49–7.41 (5H, m), 7.39–7.34 (4H, m), 7.06 (2H, d, $J = 8.4$), 5.96 (2H, s), 3.32 (3H, s). $^{13}C$ NMR (MeOD): $\delta$ 190.4, 166.3, 158.2, 157.6, 139.6, 138.5, 132.9, 131.9, 130.6, 130.5, 129.3, 129.3, 128.9, 127.8, 126.5, 126.0, 124.8, 124.4, 123.5, 122.2, 115.4, 113.5, 112.8, 68.7. HRMS (ESI-TOF) *m/z* Calcd for $C_{31}H_{25}N_2O_3$ $[M - Br]^+$ 473.1865, found 473.1857.

*4.1.5.31. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-(2-(4-bromophenyl)-2-oxoethyl)-1H-imidazol-3-ium bromide (**42**).* Yield 70%, white powder, mp 163–165 °C. IR $\nu_{max}$ ($cm^{-1}$): 3390, 3145, 3074, 2964, 2904, 1670, 1583, 1482, 1442, 1350, 1200, 1148, 1072, 991, 812, 753, 665. $^1H$ NMR (DMSO): $\delta$ 9.04 (1H, s), 8.15–8.14 (2H, m), 7.98–7.92 (3H, m), 7.87–7.83 (4H, m), 7.75 (1H, d, $J = 8.1$), 7.60–7.43 (7H, m), 7.34 (2H, d, $J = 6.9$), 6.01 (2H, s). $^{13}C$ NMR (DMSO): $\delta$ 190.6, 153.4, 152.9, 136.9, 134.9, 131.5, 130.4, 129.9, 129.3, 129.1, 128.7, 128.2, 127.4, 127.3, 126.8, 125.1, 124.0, 123.1, 122.6, 121.7, 119.2, 110.9, 107.9, 55.1, 43.0. HRMS (ESI-TOF) *m/z* Calcd for $C_{30}H_{22}BrN_2O_2$ $[M - Br]^+$ 521.0859, found 521.0847.

*4.1.5.32. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-(2-(4-fluorophenyl)-2-oxoethyl)-1H-imidazol-3-ium bromide (**43**).* Yield 70%, white powder, mp 172–173 °C. IR $\nu_{max}$ ($cm^{-1}$): 3407, 3154, 3084, 2970, 2917, 1697, 1597, 1554, 1443, 1350, 1231, 1149, 1041, 993, 838, 751, 660. $^1H$ NMR (DMSO): $\delta$ 9.08 (1H, s), 8.15–8.11 (4H, m), 7.93 (1H, s), 7.87–7.83 (2H, m), 7.75 (1H, d, $J = 8.1$), 7.65–7.41 (9H, m), 7.35 (2H, d, $J = 6.9$), 6.04 (2H, s). $^{13}C$ NMR (DMSO): $\delta$ 190.0, 156.0, 155.4, 137.9, 137.4, 132.0, 131.3, 131.2, 129.3, 129.0, 128.2, 127.9, 124.9, 124.3, 123.4, 123.0, 122.2, 121.4, 121.2, 116.4, 116.1, 112.4, 111.8, 65.9, 55.6. HRMS (ESI-TOF) *m/z* Calcd for $C_{30}H_{22}FN_2O_2$ $[M - Br]^+$ 461.1660, found 461.1668.

*4.1.5.33. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-(2-oxo-1,2-diphenylethyl)-1H-imidazol-3-ium bromide (**44**).* Yield 70%, white powder, mp 159–160 °C. IR $\nu_{max}$ ($cm^{-1}$): 3398, 3056, 1691, 1595, 1541, 1446, 1324, 1197, 1139, 1030, 842, 751, 696. $^1H$ NMR (DMSO): $\delta$ 9.40 (1H, s), 8.18–8.12 (2H, m), 8.03–7.98 (3H, m), 7.91 (1H, s), 7.84–7.80 (2H, m), 7.75–7.72 (1H, m), 7.63–7.58 (3H, m), 7.51–7.48 (12H, m), 7.35–7.33 (2H, m). $^{13}C$ NMR (DMSO): $\delta$ 191.8, 156.0, 155.4, 137.5, 137.2, 134.3, 133.4, 132.2, 132.0, 131.8, 130.2, 129.9, 129.5, 129.2, 129.0, 128.2, 128.0, 127.7, 124.3, 123.4, 123.3, 123.0, 122.0, 121.5, 121.4, 121.2, 112.4, 111.8, 67.0, 66.0. HRMS (ESI-TOF) *m/z* Calcd for $C_{36}H_{27}N_2O_2$ $[M - Br]^+$ 519.2073, found 519.2062.

*4.1.5.34. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-(2-(naphthalen-2-yl)-2- oxoethyl)-1H-imidazol-3-ium bromide (**45**).* Yield 70%, white powder, mp 180–181 °C. IR $\nu_{max}$ ($cm^{-1}$): 3414, 3056, 2907, 2353, 1691, 1626, 1557, 1479, 1357, 1196, 1143, 1030, 942, 805, 747, 657. $^1H$ NMR (DMSO): $\delta$ 9.21 (1H, s), 8.83 (1H, s), 8.21–8.11 (4H, m), 8.07–7.98 (4H, m), 7.85 (1H, d, $J = 8.7$), 7.76–7.70 (3H, m), 7.67–7.52 (6H, m) 7.48–7.43 (1H, m), 7.40–7.38 (2H, m), 6.25 (2H, s). $^{13}C$ NMR (DMSO): $\delta$ 191.2, 156.0, 155.4, 137.9, 137.4, 135.5, 132.0, 130.9, 130.4, 129.6, 129.3, 129.0, 128.2, 127.9, 127.3, 124.9, 124.3, 123.4, 123.1, 121.3, 112.4, 65.9, 55.8. HRMS (ESI-TOF) *m/z* Calcd for $C_{34}H_{25}N_2O_2$ $[M - Br]^+$ 493.1916, found 493.1912.

*4.1.5.35. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-butyl-2-methyl-1H-imidazol-3-ium iodide (**46**).* Yield 70%, yellow Powder, mp 108–110 °C. IR $\nu_{max}$ ($cm^{-1}$): 3420, 3050, 2957, 1585, 1447, 1248, 1192, 1122, 1031, 902, 841, 749, 700. $^1H$ NMR (DMSO): $\delta$ 7.98–7.96 (1H, m), 7.68 (2H, d, $J = 7.8$), 7.60 (2H, d, $J = 8.1$), 7.46–7.40 (1H, m), 7.37–7.28 (6H, m), 7.19–7.15 (3H, m), 4.06 (2H, t, $J = 7.2$), 2.57 (3H, s), 1.68–1.58 (2H, m), 1.24–1.07 (2H, m), 0.78 (3H, t, $J = 7.2$). $^{13}C$ NMR (DMSO): $\delta$ 155.9, 155.2, 144.4, 136.9, 131.6, 129.2, 128.8, 128.2, 128.1, 128.0, 124.2, 123.4, 123.0, 121.7, 121.4, 120.1, 112.3, 111.8, 64.0, 47.6, 30.9, 18.9, 13.4, 10.1. HRMS (ESI-TOF) *m/z* Calcd for $C_{27}H_{27}N_2O$ $[M - I]^+$ 395.2118, found 395.2124.

*4.1.5.36. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-(4-nitrobenzyl)-2-methyl-1H-imidazol-3-ium bromide (**47**).* Yield 70%, white powder, mp 241–242 °C. IR $\nu_{max}$ ($cm^{-1}$): 3401, 3058, 2916, 1596, 1515, 1447, 1343, 1261, 1193, 1107, 1032, 841, 748, 658. $^1H$ NMR (DMSO): $\delta$ 8.26 (2H, d, $J = 8.1$), 8.15 (1H, s), 8.11 (1H, d, $J = 7.8$), 7.98 (1H, s), 7.80 (1H, d, $J = 8.4$), 7.72–7.66 (3H, m), 7.57–7.37 (8H, m), 7.34–7.32 (2H, m), 5.75 (2H, s), 2.72 (3H, s). $^{13}C$ NMR (DMSO): $\delta$ 155.9, 155.3, 147.4, 145.4, 141.6, 136.8, 131.5, 129.2, 128.8, 128.2, 124.2, 124.0, 123.3, 123.0, 121.5, 121.4, 120.7, 112.3, 111.8, 64.2, 50.1, 10.5. HRMS (ESI-TOF) *m/z* Calcd for $C_{30}H_{24}N_3O_3$ $[M - Br]^+$ 474.1812, found 474.1824.

*4.1.5.37. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-(2-(4-hydroxyphenyl)-2-oxoethyl)-2-methyl-1H-imidazol-3-ium bromide (**48**).* Yield 70%, white powder, mp 239–241 °C. IR $\nu_{max}$ ($cm^{-1}$):

3412, 3098, 1678, 1598, 1502, 1441, 1343, 1237, 1036, 986, 836, 749, 697. $^1$H NMR (DMSO): δ 10.67 (1H, s), 8.21–8.19 (2H, m), 8.12 (2H, d, $J$ = 6.3), 7.95 (1H, d, $J$ = 8.4), 7.85–7.82 (2H, m), 7.76–7.40 (9H, m), 7.32 (1H, d, $J$ = 6.9), 6.99 (2H, d, $J$ = 8.4), 6.10 (2H, s), 2.61 (3H, s). $^{13}$C NMR (DMSO): δ 188.8, 163.3, 156.0, 155.3, 146.4, 136.9, 131.6, 131.1, 129.2, 128.9, 125.1, 124.3, 123.4, 123.2, 123.0, 121.4, 119.9, 115.6, 112.3, 111.8, 64.1, 54.2, 10.2. HRMS (ESI-TOF) $m/z$ Calcd for $C_{31}H_{25}N_2O_3$ $[M - Br]^+$ 473.1865, found 473.1871.

*4.1.5.38. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-(2-(4-methoxyphenyl)-2-oxoethyl)-2-methyl-1H-imidazol-3-ium bromide (**49**).* Yield 70%, white powder, mp 271–273 °C. IR $\nu_{max}$ ($cm^{-1}$): 3413, 3051, 2905, 1683, 1600, 1502, 1436, 1249, 1187, 1119, 1030, 985, 840, 751, 703. $^1$H NMR (DMSO): δ 8.04–8.02 (2H, m), 7.97–7.95 (2H, m), 7.79–7.76 (1H, m), 7.67–7.64 (1H, m), 7.44–7.37 (8H, m), 7.26–7.23 (2H, m), 7.09 (2H, d, $J$ = 6.0), 6.01 (2H, s), 3.81 (3H, s), 2.52 (3H, s). $^{13}$C NMR (DMSO): δ 189.0, 163.3, 155.9, 155.2, 142.6, 133.7, 132.4, 131.1, 130.2, 128.1, 126.8, 126.5, 126.2, 125.1, 124.1, 123.3, 123.1, 121.3, 119.7, 115.7, 114.2, 114.1, 112.3, 111.8, 57.3, 52.9, 21.2. HRMS (ESI-TOF) $m/z$ Calcd for $C_{32}H_{27}N_2O_3$ $[M - Br]^+$ 487.2022, found 487.2005.

*4.1.5.39. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-(2-(4-bromophenyl)-2-oxoethyl)-2-methyl-1H-imidazol-3-ium bromide (**50**).* Yield 70%, white powder, mp 270–271 °C. IR $\nu_{max}$ ($cm^{-1}$): 3404, 3047, 2914, 1696, 1582, 1488, 1444, 1394, 1278, 1199, 1071, 986, 902, 759, 705, 657. $^1$H NMR (DMSO): δ 8.11 (2H, s), 7.99 (2H, d, $J$ = 7.2), 7.88–7.83 (3H, m), 7.77 (1H, d, $J$ = 7.5), 7.70 (1H, s), 7.58–7.44 (8H, m), 7.33–7.31 (2H, m), 6.11 (2H, s), 2.61 (3H, s). $^{13}$C NMR (DMSO): δ 190.4, 156.0, 155.3, 146.4, 136.8, 132.7, 132.1, 131.5, 130.3, 129.2, 128.9, 128.6, 128.3, 128.1, 124.4, 123.1, 123.0, 121.3, 120.0, 112.4, 111.8, 64.2, 54.6, 10.0. HRMS (ESI-TOF) $m/z$ Calcd for $C_{31}H_{24}BrN_2O_2$ $[M - Br]^+$ 535.1021, found 535.1007.

*4.1.5.40. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-(2-(4-fluorophenyl)-2-oxoethyl)-2-methyl-1H-imidazol-3-ium bromide (**51**).* Yield 70%, white powder, mp 271–273 °C. IR $\nu_{max}$ ($cm^{-1}$): 3420, 3056, 2913, 1695, 1595, 1497, 1442, 1235, 1198, 1157, 1092, 987, 844, 751, 702, 658. $^1$H NMR (DMSO): δ 8.13 (4H, s), 7.85 (1H, d, $J$ = 7.8), 7.75–7.73 (2H, m), 7.53–7.49 (10H, m), 7.34–7.32 (2H, m), 6.16 (2H, s), 2.63 (3H, s). $^{13}$C NMR (DMSO): δ 189.7, 156.0, 146.4, 136.8, 131.6, 129.2, 128.2, 128.1, 124.3, 123.4, 123.1, 121.4, 120.0, 116.3, 116.0, 112.4, 111.8, 64.2, 54.6, 10.0. HRMS (ESI-TOF) $m/z$ Calcd for $C_{31}H_{24}FN_2O_2$ $[M - Br]^+$ 475.1822, found 475.1811.

*4.1.5.41. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-(2-(naphthalen-2-yl)-2-oxoethyl)-2- methyl-1H-imidazol-3-ium bromide (**52**).* Yield 70%, white powder, mp 206–208 °C. IR $\nu_{max}$ ($cm^{-1}$): 3393, 3040, 2909, 1687, 1628, 1448, 1355, 1268, 1195, 1039, 1030, 939, 847, 746, 701, 655. $^1$H NMR (DMSO): δ 8.88 (1H, s), 8.22–8.11 (4H, m), 8.07–8.03 (2H, m), 7.86 (2H, d, $J$ = 7.8), 7.77–7.66 (3H, m), 7.62–7.52 (6H, m), 7.49–7.41 (2H, m) 7.35 (2H, d, $J$ = 6.9), 6.36 (2H, s), 2.69 (3H, s). $^{13}$C NMR (DMSO): δ 191.0, 156.0, 155.3, 146.5, 136.9, 135.5, 131.9, 131.6, 131.0, 130.9, 129.6, 129.2, 128.9, 128.6, 128.2, 128.1, 127.8, 127.3, 124.3, 123.4, 123.0, 121.5, 120.0, 112.4, 111.8, 64.2, 54.9, 10.2. HRMS (ESI-TOF) $m/z$ Calcd for $C_{35}H_{27}N_2O_2$ $[M - Br]^+$ 507.2073, found 507.2053.

*4.1.5.42. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-butyl-1H-benzo[d]imidazol-3-ium iodide (**53**).* Yield 70%, yellow powder, mp 198–200 °C. IR $\nu_{max}$ ($cm^{-1}$): 3414, 3105, 3037, 2961, 2868, 1600, 1553, 1476, 1437, 1326, 1246, 1192, 1127, 1017, 843, 755, 697. $^1$H NMR (DMSO): δ 9.49 (1H, s), 8.27 (1H, s), 8.18 (1H, d, $J$ = 8.4), 8.10 (1H, d, $J$ = 7.5), 7.83 (1H, d, $J$ = 8.1), 7.78–7.72 (4H, m), 7.69–7.61 (3H, m) 7.58–7.43 (5H, m), 7.41–7.38 (1H, m), 4.53 (2H, t, $J$ = 7.2), 1.90–1.83 (2H, m), 1.36–1.27 (2H, m), 0.89 (3H, t, $J$ = 7.2). $^{13}$C NMR (DMSO): δ 156.0, 155.5, 141.9, 136.4, 131.6, 131.2, 131.0, 129.3, 129.0, 128.2, 126.8, 124.3, 123.0, 121.7, 121.4, 114.5, 114.1, 112.5, 111.8, 64.2, 47.0, 30.7, 19.1, 13.4. HRMS (ESI-TOF) $m/z$ Calcd for $C_{30}H_{27}N_2O$ $[M - I]^+$ 431.2123, found 431.2110.

*4.1.5.43. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-(4-nitrobenzyl)-1H-benzo[d] imidazol-3-ium bromide (**54**).* Yield 70%, yellow powder, mp 160–162 °C. IR $\nu_{max}$ ($cm^{-1}$): 3411, 3016, 2953, 1605, 1522, 1438, 1344, 1195, 1120, 1016, 847, 806, 749, 653. $^1$H NMR (DMSO): δ 9.81 (1H, s), 8.37 (1H, s), 8.25 (2H, d, $J$ = 8.4), 8.13 (1H, d, $J$ = 7.8), 7.90–7.80 (3H, m), 7.77–7.67 (5H, m), 7.58–7.38 (9H, m), 6.02 (2H, s). $^{13}$C NMR (DMSO): δ 156.0, 155.5, 147.4, 143.0, 141.5, 136.3, 131.4, 131.0, 129.3, 129.2, 128.4, 127.1, 126.9, 124.4, 123.9, 123.4, 123.1, 121.8, 121.4, 114.8, 114.1, 112.5, 111.8, 64.6, 49.5. HRMS (ESI-TOF) $m/z$ Calcd for $C_{33}H_{24}N_3O_3$ $[M - Br]^+$ 510.1812, found 510.1820.

*4.1.5.44. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-(2-oxo-2-phenylethyl)-1H-benzo[d]imidazol-3-ium bromide (**55**).* Yield 70%, yellow powder, mp 179–180 °C. IR $\nu_{max}$ ($cm^{-1}$): 3386, 3021, 1693, 1598, 1554, 1440, 1340, 1229, 1195, 1028, 986, 812, 751, 693. $^1$H NMR (DMSO): δ 9.44 (1H, s), 8.29 (1H, s), 8.16 (1H, dd, $J$ = 12.9, 7.2), 8.12 (2H, s), 8.09 (1H, s), 7.98 (1H, s), 7.85 (2H, t, $J$ = 8.4), 7.79–7.72 (2H, m), 7.68–7.60 (5H, m) 7.57–7.51 (5H, m), 7.45–7.38 (2H, m), 6.42 (2H, s). $^{13}$C NMR (DMSO): δ 191.3, 156.0, 155.5, 143.4, 136.3, 134.5, 133.7, 132.7, 130.9, 130.7, 129.4, 129.1, 129.0, 128.3, 128.2, 127.1, 126.8, 124.4, 123.4, 123.0, 121.6, 121.4, 114.5, 114.3, 112.6, 111.8, 64.1, 53.6. HRMS (ESI-TOF) $m/z$ Calcd for $C_{34}H_{25}N_2O_2$ $[M - Br]^+$ 493.1916, found 493.1888.

*4.1.5.45. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-(2-(4-hydroxyphenyl)-2-oxoethyl)-1H-benzo[d]imidazol-3-ium bromide (**56**).* Yield 70%, white powder, mp 182–184 °C. IR $\nu_{max}$ ($cm^{-1}$): 3400, 3056, 1680, 1595, 1481, 1439, 1237, 1196, 984, 840, 751, 654. $^1$H NMR (DMSO): δ 10.69 (1H, s), 9.41 (1H, s), 8.26 (1H, s), 8.12 (2H, d, $J$ = 7.8 Hz), 7.97 (2H, d, $J$ = 8.7), 7.94 (1H, s), 7.83 (2H, t, $J$ = 9.6), 7.80–7.39 (11H, m), 6.99 (2H, d, $J$ = 8.7), 6.28 (2H, s). $^{13}$C NMR (DMSO): δ 189.1, 163.2, 156.0, 155.5, 143.5, 136.3, 132.7, 131.0, 130.7, 129.4, 129.1, 128.1, 127.0, 126.7, 124.4, 123.4, 123.0, 121.5, 115.6, 114.4, 114.2, 112.6, 111.8, 64.1, 53.0. HRMS (ESI-TOF) $m/z$ Calcd for $C_{34}H_{25}N_2O_3$ $[M - Br]^+$ 509.1860, found 509.1869.

*4.1.5.46. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-(2-(4-methoxyphenyl)-2-oxoethyl)-1H-benzo[d]imidazol-3-ium bromide (**57**).* Yield 70%, white powder, mp 250–252 °C. IR $\nu_{max}$ ($cm^{-1}$): 3386, 3021, 1693, 1598, 1554, 1440, 1340, 1229, 1195, 1028, 986, 812, 751, 693. $^1$H NMR (DMSO): δ 9.42 (1H, s), 8.27 (1H, s), 8.15–8.06 (4H, m), 7.95 (1H, s), 7.85 (2H, t, $J$ = 7.5), 7.78–7.75 (1H, m), 7.72–7.70 (1H, m) 7.68–7.65 (1H, m), 7.62–7.44 (7H, m), 7.41–7.39(1H, m), 7.17 (2H, d, $J$ = 8.7), 6.34 (2H, s), 3.89 (3H, s). $^{13}$C NMR (DMSO): δ 189.5, 164.1, 156.0, 155.5, 143.5, 136.3, 132.7, 130.9, 130.8, 129.40, 129.1, 128.3, 128.1, 127.1, 126.7, 126.5, 124.4, 123.4, 123.0, 121.5, 121.4, 114.4, 114.3, 112.6, 111.8, 64.1, 55.8, 53.6. HRMS (ESI-TOF) $m/z$ Calcd for $C_{35}H_{27}N_2O_3$ $[M - Br]^+$ 523.2016, found 523.2023.

*4.1.5.47. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-(2-(4-bromophenyl)-2-oxoethyl)-1H-benzo[d]imidazol-3-ium bromide (**58**).* Yield 70%, white powder, mp 251–253 °C. IR $\nu_{max}$ ($cm^{-1}$): 3394, 3149, 3019, 2902, 1698, 1562, 1483, 1441, 1335, 1194, 1128, 1070, 983, 810, 756, 701, 656. $^1$H NMR (DMSO): δ 9.40 (1H, s), 8.28 (1H, s), 8.17 (1H, d, $J$ = 8.1), 8.12 (1H, d, $J$ = 8.1), 8.03 (2H, d, $J$ = 8.4), 7.96 (1H, s), 7.88–7.81 (4H, m), 7.74 (1H, d, $J$ = 8.4), 7.67 (1H, d, $J$ = 8.7), 7.62 (1H, d, $J$ = 3.0), 7.58 (1H, d, $J$ = 8.7), 7.53–7.50 (6H, m), 7.42 (1H, t, $J$ = 7.5), 6.39 (2H, s). $^{13}$C NMR (DMSO): δ 190.6, 156.0, 155.5, 143.4, 136.2, 132.8, 132.6, 132.1, 130.9, 130.7, 130.3, 129.4,

129.1, 128.6, 128.2, 127.1, 126.8, 124.4, 123.4, 123.0, 121.6, 121.4, 114.5, 114.3, 112.6, 111.8, 64.2, 53.6. HRMS (ESI-TOF) *m/z* Calcd for $C_{34}H_{24}BrN_2O_2$ $[M - Br]^+$ 571.1021, found 571.0993.

*4.1.5.48. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-(2-(4-fluorophenyl)-2-oxoethyl)-1H-benzo[d]imidazol-3-ium bromide (**59**).* Yield 70%, white powder, mp 167–169 °C. IR $\nu_{max}$ ($cm^{-1}$): 3382, 3024, 2968, 1695, 1598, 1555, 1439, 1440, 1233, 11.98, 1039, 987, 838, 752, 708, 654. $^1H$ NMR (DMSO): $\delta$ 9.40 (1H, s), 8.32 (1H, s), 8.27–8.15 (3H, m), 8.12 (1H, d, $J = 7.8$), 7.95 (1H, s), 7.86 (1H, d, $J = 8.7$), 7.82 (1H, d, $J = 8.1$), 7.79 (1H, d, $J = 5.7$), 7.74 (1H, d, $J = 8.1$), 7.67–7.72 (2H, m), 7.69–7.66 (1H, m), 7.63–7.44 (7H, m), 7.42 (1H, t, $J = 7.5$), 6.39 (2H, s). $^{13}C$ NMR (DMSO): $\delta$ 189.9, 164.0, 156.0, 155.5, 143.4, 136.2, 132.7, 131.5, 131.4, 130.9, 130.7, 130.5, 129.4, 128.3, 128.1, 127.1, 126.8, 124.5, 123.4, 123.0, 121.6, 121.4, 116.3, 116.0, 114.5, 114.2, 112.6, 111.8, 64.2, 53.5. HRMS (ESI-TOF) *m/z* Calcd for $C_{34}H_{23}FN_2O_2$ $[M - Br]^+$ 511.1816, found 511.1825.

*4.1.5.49. 1-(Dibenzo[b,d]furan-2-yl(phenyl)methyl)-3-(2-(naphthalen-2-yl)-2-oxoethyl)-1H-benzo[d]imidazol-3-ium bromide (**60**).* Yield 70%, white powder, mp 267–269 °C. IR $\nu_{max}$ ($cm^{-1}$): 3393, 3160, 3021, 2896, 1963, 1690, 1558, 1481, 1260, 1187, 1126, 1018, 939, 807, 752, 705, 649. $^1H$ NMR (DMSO): $\delta$ 9.53 (1H, s), 8.93 (1H, s), 8.34 (1H, s), 8.24 (2H, d, $J = 6.0$), 8.16–8.13 (2H, m), 8.08–8.02 (3H, m), 7.88 (2H, d, $J = 8.4$), 7.75–7.66 (6H, m), 7.64–7.44 (6H, m), 7.42 (1H, t, $J = 7.5$), 6.59 (2H, s). $^{13}C$ NMR (DMSO): $\delta$ 191.2, 156.0, 155.5, 143.5, 136.3, 135.5, 132.7, 132.0, 131.0, 131.0, 130.8, 129.7, 129.4, 129.3, 129.1, 128.7, 128.2, 127.8, 127.3, 127.1, 126.8, 124.5, 123.4, 123.3, 123.0, 121.6, 121.4, 114.5, 114.3, 112.6, 111.8, 64.2, 53.7. HRMS (ESI-TOF) *m/z* Calcd for $C_{38}H_{27}N_2O_2$ $[M - Br]^+$ 543.2073, found 543.2050.

### 4.2. 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.

### 4.3. Cell apoptosis analysis

Cell apoptosis was analyzed using the Annexin V-FITC/PI Apoptosis kit (BD Biosciences, Franklin Lakes, NJ) according to the manufacturer's protocols. Cells were seeded in 6-well plates at a density of $1.2 \times 10^6$ cells/well. After 48 h of compound treatment at the indicated concentrations, cells were collected and then washed twice with cold PBS, and then resuspended in a binding buffer containing Annexin V-FITC and propidium iodine (PI). After incubation for 15 min at room temperature in the dark, the fluorescent intensity was measured using a FACSCalibur flow cytometer (BD Biosciences, Franklin Lakes, NJ).

### 4.4. Cell cycle analysis

To analyze the DNA content by flow cytometry, cells were collected and washed twice with PBS. Cells were fixed with 70% ethanol overnight. Fixed cells were washed with PBS, and then stained with a 50 μg/ml propidium iodide (PI) solution containing 50 μg/ml RNase A for 30 min at room temperature. Fluorescence intensity was analyzed by FACSCalibur flow cytometer (BD Biosciences, San Jose, CA, USA). The percentages of the cells distributed in different phases of the cell cycle were determined using ModFIT LT 2.0.

## Acknowledgments

This work was supported by Natural Science Foundation of China (30960460, 20925205 and 21062026), Natural Science Foundation of Yunnan Province (2012FB113 and 2010GA014), National Basic Research Program of China (973 Program, 2009CB522300), Project of Recruited Top Talent of Sciences and Technology of Yunnan Province (2009C1120), and 100 Talents Program of CAS.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.06.011.

## References

[1] H. Varmus, Science 312 (2006) 1162–1165.
[2] D.J. Newman, J. Med. Chem. 51 (2008) 2589–2599.
[3] I. Ojima, J. Med. Chem. 51 (2008) 2587–2588.
[4] H. Huang, X. Feng, Z. Xiao, L. Liu, H. Li, L. Ma, Z. She, Y. Lin, J. Ju, Y. Lu, J. Nat. Prod. 74 (2011) 997–1002.
[5] A. Kaneko, M. Tsukada, M. Fukai, K. Miki, K. Kinoshita, K. Takahashi, K. Koyama, T. Suzuki, K. Nishio, J. Nat. Prod. 73 (2010) 1002–1004.
[6] C.H. Lin, T.H. Ou, I.S. Chen, I.L. Tsai, H.S. Chang, C.H. Liao, J. Nat. Prod. 73 (2010) 1628–1631.
[7] W.K.P. Shiu, S. Gibbons, Phytochemistry 70 (2009) 403–406.
[8] S. Cai, S. Sun, H. Zhou, X. Kong, T. Zhu, D. Li, Q. Gu, J. Nat. Prod. 74 (2011) 1106–1110.
[9] K. Watanabe, T. Ohtsuki, Y. Yamamoto, M. Ishibashi, Heterocycles 71 (2007) 1807–1814.
[10] C. Pardin, A.R. Schmitzer, L. Leclercq, Chem. Eur. J. 16 (2010) 4686–4692.
[11] J.Z. Vlahakis, C. Lazar, I.E. Crandall, W.A. Szarek, Bioorg. Med. Chem. 18 (2010) 6184–6196.
[12] A. Vik, E. Hedner, C. Charnock, L.W. Tangen, Ø. Samuelsen, R. Larsson, L. Bohlinb, L.L. Gundersen, Bioorg. Med. Chem. 15 (2007) 4016–4037.
[13] S.J. Dominianni, T.T. Yen, J. Med. Chem. 32 (1989) 2301–2306.
[14] C.G. Fortuna, V. Barresi, G. Berellini, G. Musumarra, Bioorg. Med. Chem. 16 (2008) 4150–4159.
[15] M.R. Saberi, T.K. Vinh, S.W. Yee, B.J.N. Griffiths, P.J. Evan, C. Simsons, J. Med. Chem. 49 (2006) 1016–1022.
[16] B. Cui, B.L. Zheng, K. He, Q.Y. Zheng, J. Nat. Prod. 66 (2003) 1101–1103.
[17] X.Q. Wang, L.X. Liu, Y. Li, C.J. Sun, W. Chen, L. Li, H.B. Zhang, X.D. Yang, Eur. J. Med. Chem. 62 (2013) 111–121.
[18] W. Chen, X.D. Yang, Y. Li, L.J. Yang, X.Q. Wang, G.L. Zhang, H.B. Zhang, Org. Biomol. Chem. 9 (2011) 4250–4255.
[19] X.H. Zeng, X.D. Yang, Y.L. Zhang, C. Qing, H.B. Zhang, Bioorg. Med. Chem. Lett. 20 (2010) 1844–1847.
[20] C. Viegas Jnr, A. Danuello, V.S. Bolzani, E.J. Barreiro, C.A.M. Fraga, Curr. Med. Chem. 14 (2007) 1829–1852.
[21] V.K. Vladimir, G.B. Alicia, Eur. J. Med. Chem. 44 (2009) 3091–3113.
[22] M. Getlik, C. Grütter, J.R. Simard, S. Klüter, M. Rabiller, H.B. Rode, A. Robubi, D. Rauh, J. Med. Chem. 52 (2009) 3915–3926.
[23] R.P. Tripathi, A.K. Yadav, A. Ajay, S.S. Bisht, V. Chaturvedi, S.K. Sinha, Eur. J. Med. Chem. 45 (2010) 142–148.
[24] S. Rizzo, C. Rivière, L. Piazzi, A. Bisi, S. Gobbi, M. Bartolini, V. Andrisano, F. Morroni, A. Tarozzi, J.P. Monti, A. Rampa, J. Med. Chem. 51 (2008) 2883–2886.
[25] S.R. Hanson, L.J. Whalen, C.H. Wong, Bioorg. Med. Chem. 14 (2006) 8386–8395.
[26] R. Cao, Q. Chen, X. Hou, H. Chen, H. Guan, Y. Ma, W. Peng, A. Xu, Bioorg. Med. Chem. 12 (2004) 4613–4623.
[27] D.K. Kim, D.H. Ryu, J.Y. Lee, N. Lee, Y.W. Kim, J.S. Kim, K. Chang, G.J. Im, T.K. Kim, W.S. Choi, J. Med. Chem. 44 (2001) 1594–1602.
[28] J. Ranke, S. Stolte, R. Störmann, J. Arning, B. Jastorff, Chem. Rev. 107 (2007) 2183–2206.
[29] J. Massague, Nature 432 (2004) 298–306.