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Synthesis and cytotoxic activity of novel tetrahydrobenzodifuran–imidazolium salt derivatives

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ABSTRACT

The synthesis of a series of novel 4-substituted 2,3,6,7-tetrahydrobenzo [1,2-*b*;4,5-*b*′]difuran–1*H*-imidazolium salts is presented. The biological properties of the compounds were evaluated *in vitro* against a panel of human tumor cell lines. Results suggest that the 5,6-dimethyl-benzimidazole or 2-methyl-benzimidazole ring, and substitution of the imidazolyl-3-position with a 2-naphthylmethyl substituent or 2-naphthylacyl substituent, were important to the cytotoxic activity. Notably, 3-(2-Naphthylmethyl)-1-((2,3,6,7-tetrahydrobenzo[1,2-*b*;4,5-*b*′]difuran-4-yl)methyl)-1*H*-5,6-dimethyl-benzimidazol-3-ium bromide (**42**) was found to be the most potent derivative against five human tumor cell lines with IC_{50} values of 1.06–4.34 μM and more selective towards SMMC-7721, A549 and SW480 cell lines. 3-(2-Naphthylacyl)-1-((2,3,6,7-tetrahydrobenzo[1,2-*b*;4,5-*b*′]difuran-4-yl)methyl)-1*H*-2-methyl-benzimidazol-3-ium bromide (**37**) showed higher selectivity to SMMC-7721 and MCF-7 cell lines with IC_{50} values 2.7-fold and 8.4-fold lower than DDP. Study regarding to the antitumor mechanism of action showed that compound **37** could induce cell cycle G1 phase arrest and apoptosis in SMMC-7721 cells.

Tetrahydrobenzodifurans and dihydrobenzofurans represent as important classes of biologically active oxygen-containing heterocycles. Naturally occurring compounds and biologically active agents with dihydrobenzofuran and tetrahydrobenzodifuran moieties exhibit a wide range of remarkable biological activities, especially antitumor activity.[1] As exemplified in Fig. 1, Megapodiol with dihydrobenzofuran moiety is an anti-leukaemic agent,[2] while Mesocyperusphenol A with tetrahydrobenzodifuran moiety showed powerful cytotoxic activity against human *T*-cell leukemia cells.[3] Further study showed that Mesocyperusphenol A was a potent 5-lipoxygenase inhibitor.[4] On the other hand, imidazole and their derivatives have attracted wide attention due to their pharmaceutical potential resulting from their significant biological activities,[5] especially antitumor activity.[6] For instance, natural imidazolium chlorides Lepidiline A and B (Fig. 1) showed potent cytotoxic activity against four human cancer cell lines.[7] However, to the best of our knowledge, no scientific study on the exactly molecular targets of Lepidilines was reported. Considering the value of imidazolium salts, we have previously reported the synthesis of a series of novel imidazolium salts, such as NMIB (Fig. 1), and their potential antitumor activity.[8] Further study of molecular mechanisms showed that the imidazolium salt hybrids can induce the cell cycle arrest and apoptosis in tumor cells.[8c,g] Studies on molecular targets demonstrated that the imidazolium salt hybrids may be the inhibitors of mTOR (mammalian target of rapamycin) signaling.[8i] And the docking calculations also supported this conclusion.[8f,i]

Molecular hybridization is a useful strategy in new drug design and development during the past two decades.[9] Considering the anticancer activities of tetrahydrobenzodifuran, as well as the potent cytotoxic activities of imidazole derivatives, we are interested in the preparation of the hybridizing compounds of 4-substituted 2,3,6,7-tetrahydrobenzo[1,2-*b*;4,5-*b*′]difuran with imidazole moieties. During the past several years, some anticancer agents based on imidazolium salts were reported.[8,10] To the best of our knowledge, no reports concerning antitumor activity of 4-substituted 2,3,6,7-tetrahydrobenzo[1,2-*b*;4,5-*b*′]difuran–imidazole hybrids could be found in the literature.

Herein, a series of novel 4-substituted 2,3,6,7-tetrahydrobenzo [1,2-*b*;4,5-*b*′] difuran imidazolium salts were synthesized to

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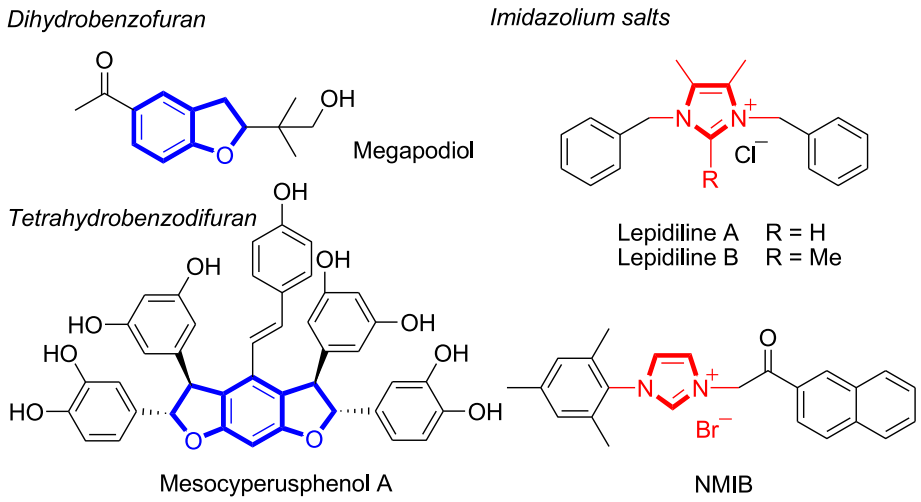
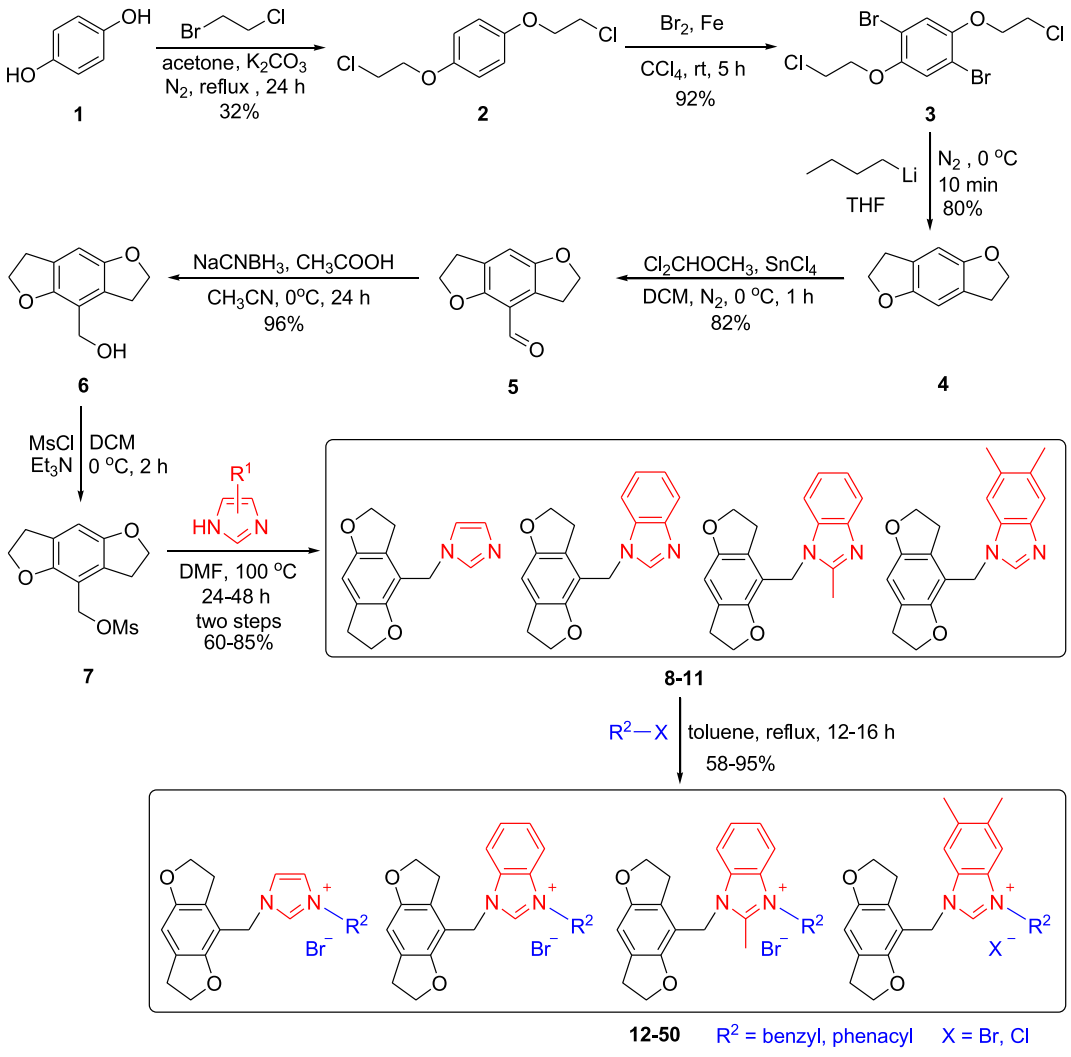


Fig. 1. Representative structures of dihydrobenzofuran, tetrahydrobenzodifuran and imidazolium salts.



Scheme 1. Synthesis of tetrahydrobenzodifuran–1*H*-imidazolium salts **12**–**46**.

explore the cytotoxic activity of tetrahydrobenzodifuran–imidazole hybrids with the ultimate aim of developing potent antitumor agents.

To prepare the tetrahydrobenzodifuran–1*H*-imidazolium salts, hydroquinone **1** was selected as the starting material for the synthese of a series of hybrid derivatives (**12**–**46**, Scheme 1). Hydroquinone **1** was alkylated with 1-bromo-2-chloroethane in acetone to afford 1,4-bis(2-chloroethoxy)benzene **2**. Bromination of bis(2-chloroethyl) ether **2** give the dibromo product **3**. Cyclization of **3** by reacting with *n*-butyllithium in THF afforded tetrahydrobenzodifuran **4** in 80% yield.[11] Formylation of key intermediate **4** with dichloro(methoxy)methane and $SnCl_4$ to afford the 4-formyl product **5**. Reduction of **5** using $NaCNBH_3$ afforded 4-methanol tetrahydrobenzodifuran **6** in 96% yield. Then, 4-methanol compound **6** was treated with the mesylate to afford the respective tetrahydrobenzodifuran–imidazoles (**8**–**11**) bearing various imidazoles (imidazole, benzimidazole, 2-methyl-benzimidazole and 5,6-dimethyl-benzimidazole) by heating under DMF with 60–85% yields (two steps).[12] Finally, thirty-nine tetrahydrobenzodifuran–1*H*-imidazolium salt derivatives (**12**–**50**) were synthesized with good yields via treating tetrahydrobenzodifuran–imidazoles with the various alkyl halides in refluxing toluene (58–95%).[13] The structures and yields of tetrahydrobenzodifuran–1*H*-imidazolium salt derivatives are showed in Table 1.

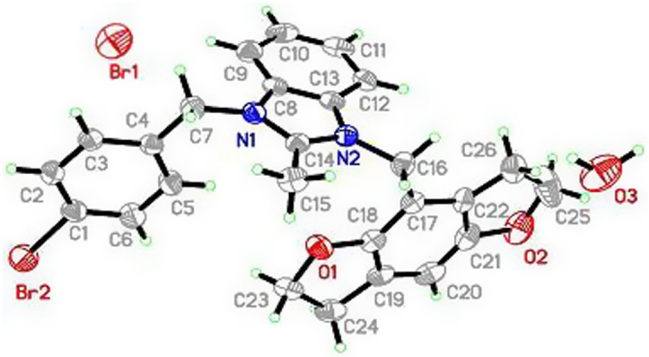


Fig. 2. X-ray crystal structures of compound **30**.

To confirm the structures of the tetrahydrobenzodifuran–1*H*-imidazolium salts, compound **30** was selected as representative compounds and characterized by X-ray crystallography (CCDC 1507586),[14] as shown in Fig. 2.

The potential cytotoxicity of all above synthesized tetrahydrobenzodifuran–1*H*-imidazolium salts were evaluated *in vitro* against a panel of human tumor cell lines, including leukaemia (HL-60), myeloid liver carcinoma (SMMC-7721), lung carcinoma

Table 1
Structures and yields of compounds **8**–**50**.

Entry	Compound	Imidazole ring	R^2	X	Molecular formula	Yields (%)
1	**8**	Imidazole	–	Br	$C_{14}H_{14}N_2O_2$	65
2	**9**	Benzimidazole	–	Br	$C_{18}H_{16}N_2O_2$	76
3	**10**	2-Methyl-benzimidazole	–	Br	$C_{19}H_{18}N_2O_2$	73
4	**11**	5,6-Dimethyl-benzimidazole	–	Br	$C_{20}H_{20}N_2O_2$	80
5	**12**	Imidazole	4-Methylbenzyl	Br	$C_{22}H_{23}BrN_2O_2$	90
6	**13**	Imidazole	4-Bromobenzyl	Br	$C_{21}H_{20}Br_2N_2O_2$	87
7	**14**	Imidazole	2-Bromobenzyl	Br	$C_{21}H_{20}Br_2N_2O_2$	75
8	**15**	Imidazole	4-Nitrobenzyl	Br	$C_{21}H_{20}BrN_3O_4$	81
9	**16**	Imidazole	2-Naphthylmethyl	Br	$C_{25}H_{23}BrN_2O_2$	78
10	**17**	Imidazole	4-Methoxyphenacy	Br	$C_{23}H_{23}BrN_2O_4$	73
11	**18**	Imidazole	4-Bromophenacyl	Br	$C_{22}H_{20}Br_2N_2O_3$	64
12	**19**	Imidazole	Naphthylacyl	Br	$C_{26}H_{23}BrN_2O_3$	76
13	**20**	Benzimidazole	4-Methylbenzyl	Br	$C_{26}H_{25}BrN_2O_2$	79
14	**21**	Benzimidazole	4-Bromobenzyl	Br	$C_{25}H_{22}Br_2N_2O_2$	58
15	**22**	Benzimidazole	2-Bromobenzyl	Br	$C_{25}H_{22}Br_2N_2O_2$	74
16	**23**	Benzimidazole	4-Nitrobenzyl	Br	$C_{25}H_{22}BrN_3O_4$	82
17	**24**	Benzimidazole	2-Naphthylmethyl	Br	$C_{29}H_{25}BrN_2O_2$	64
18	**25**	Benzimidazole	Phenacyl	Br	$C_{26}H_{23}BrN_2O_3$	65
19	**26**	Benzimidazole	4-Methoxyphenacy	Br	$C_{27}H_{25}BrN_2O_4$	71
20	**27**	Benzimidazole	4-Bromophenacyl	Br	$C_{26}H_{22}Br_2N_2O_3$	63
21	**28**	Benzimidazole	Naphthylacyl	Br	$C_{30}H_{25}BrN_2O_3$	71
22	**29**	2-Methyl-benzimidazole	4-Methylbenzyl	Br	$C_{27}H_{27}BrN_2O_2$	71
23	**30**	2-Methyl-benzimidazole	4-Bromobenzyl	Br	$C_{26}H_{24}Br_2N_2O_2$	73
24	**31**	2-Methyl-benzimidazole	2-Bromobenzyl	Br	$C_{26}H_{24}Br_2N_2O_2$	80
25	**32**	2-Methyl-benzimidazole	4-Nitrobenzyl	Br	$C_{26}H_{24}BrN_3O_4$	66
26	**33**	2-Methyl-benzimidazole	2-Naphthylmethyl	Br	$C_{30}H_{27}BrN_2O_2$	67
27	**34**	2-Methyl-benzimidazole	Phenacyl	Br	$C_{27}H_{25}BrN_2O_3$	78
28	**35**	2-Methyl-benzimidazole	4-Methoxyphenacy	Br	$C_{28}H_{27}BrN_2O_4$	64
29	**36**	2-Methyl-benzimidazole	4-Bromophenacyl	Br	$C_{27}H_{24}Br_2N_2O_3$	86
30	**37**	2-Methyl-benzimidazole	Naphthylacyl	Br	$C_{31}H_{27}BrN_2O_3$	62
31	**38**	5,6-Dimethyl-benzimidazole	4-Methylbenzyl	Br	$C_{28}H_{29}BrN_2O_2$	64
32	**39**	5,6-Dimethyl-benzimidazole	4-Bromobenzyl	Br	$C_{27}H_{26}Br_2N_2O_2$	72
33	**40**	5,6-Dimethyl-benzimidazole	2-Bromobenzyl	Br	$C_{27}H_{26}Br_2N_2O_2$	93
34	**41**	5,6-Dimethyl-benzimidazole	4-Nitrobenzyl	Br	$C_{27}H_{26}BrN_3O_4$	95
35	**42**	5,6-Dimethyl-benzimidazole	2-Naphthylmethyl	Br	$C_{31}H_{29}BrN_2O_2$	68
36	**43**	5,6-Dimethyl-benzimidazole	Phenacyl	Br	$C_{28}H_{27}BrN_2O_3$	74
37	**44**	5,6-Dimethyl-benzimidazole	4-Methoxyphenacy	Br	$C_{29}H_{29}BrN_2O_4$	84
38	**45**	5,6-Dimethyl-benzimidazole	4-Bromophenacyl	Br	$C_{28}H_{26}Br_2N_2O_3$	70
39	**46**	5,6-Dimethyl-benzimidazole	Naphthylacyl	Br	$C_{32}H_{29}BrN_2O_3$	67
40	**47**	5,6-Dimethyl-benzimidazole	4-Methylbenzyl	Cl	$C_{28}H_{29}ClN_2O_2$	76
62	**48**	5,6-Dimethyl-benzimidazole	4-Bromobenzyl	Cl	$C_{27}H_{26}BrClN_2O_2$	62
42	**49**	5,6-Dimethyl-benzimidazole	2-Naphthylmethyl	Cl	$C_{31}H_{29}ClN_2O_2$	80
43	**50**	5,6-Dimethyl-benzimidazole	4-Bromophenacyl	Cl	$C_{28}H_{26}BrClN_2O_3$	78

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Table 2
Cytotoxic activities of compounds **8**–**50** *in vitro*[b] (IC_{50}, μM[a]).

Entry	Compound	HL-60	SMMC-7721	A-549	MCF-7	SW480
1	**8**	>20	>20	>20	>20	>20
2	**9**	>20	>20	>20	>20	>20
3	**10**	>20	>20	>20	>20	>20
4	**11**	>20	>20	>20	>20	>20
5	**12**	>20	>20	>20	>20	>20
6	**13**	>20	>20	>20	>20	>20
7	**14**	>20	>20	>20	>20	>20
8	**15**	>20	>20	>20	>20	>20
9	**16**	>20	>20	>20	>20	>20
10	**17**	>20	>20	>20	>20	>20
11	**18**	>20	>20	>20	>20	>20
12	**19**	>20	>20	>20	>20	>20
13	**20**	>20	>20	>20	>20	>20
14	**21**	4.12	17.81	>20	5.40	10.05
15	**22**	4.90	>20	>20	8.30	8.95
16	**23**	>20	>20	>20	>20	>20
17	**24**	2.30	5.66	10.67	2.62	4.11
18	**25**	>20	>20	>20	>20	>20
19	**26**	5.99	>20	>20	6.60	13.95
20	**27**	5.81	5.95	16.12	5.12	5.11
21	**28**	1.88	5.25	7.73	2.20	5.42
22	**29**	>20	>20	>20	>20	>20
23	**30**	3.63	7.42	>20	4.86	7.22
24	**31**	>20	>20	>20	>20	>20
25	**32**	>20	>20	>20	>20	>20
26	**33**	1.76	5.50	9.14	3.40	4.10
27	**34**	>20	>20	>20	>20	>20
28	**35**	5.14	>20	>20	7.87	10.12
29	**36**	4.70	11.75	>20	6.43	8.29
30	**37**	0.80	4.52	6.10	1.65	4.49
31	**38**	1.58	4.43	5.82	7.39	6.15
32	**39**	0.49	4.72	6.90	6.85	10.13
33	**40**	3.18	5.96	8.64	7.29	7.87
34	**41**	>20	>20	>20	>20	>20
35	**42**	1.06	2.99	4.34	3.94	3.48
36	**43**	5.68	17.43	>20	7.80	11.87
37	**44**	2.71	6.87	15.37	9.87	13.70
38	**45**	4.04	6.23	8.00	12.66	16.27
39	**46**	1.95	5.64	7.77	8.67	13.97
40	**47**	0.38	6.49	4.06	7.98	6.31
41	**48**	0.57	6.61	9.01	8.05	7.76
42	**49**	0.29	2.98	3.62	8.34	6.84
43	**50**	2.38	12.98	15.26	17.97	15.18
44	DDP	2.06	12.36	7.61	13.93	8.17

[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.

(A549), breast carcinoma (MCF-7) and colon carcinoma (SW480), on the basis of the procedures in the literature.[15] DDP (Cisplatin) was chosen as positive control. The results were listed in Table 2.

As shown in Table 2, the structures of tetrahydrobenzodifuran–imidazole derivatives have an evident influence on the inhibitory activities. Tetrahydrobenzodifuran–imidazoles **8**–**11** and tetrahydrobenzodifuran–imidazolium salts **12**–**19** lacked activities against all tumor cell lines investigated at the concentration of 20 μM. However, their benzimidazolium salts **20**–**50** displayed some degree or high cytotoxicity. This difference in inhibitory activities between neutral molecules and their salts may be introduced by the changes of molecular structure, charge distribution and water solubility.[16]

For the imidazole rings (imidazole, benzimidazole, 2-methylbenzimidazole or 5,6-dimethyl-benzimidazole), imidazolium salts **12**–**19** with imidazole rings lacked activities against all tumor cell lines. Meanwhile, compounds **20**–**28** with benzimidazole rings showed medium inhibitory activities. Among them, only compounds **24** and **28**, bearing a 2-naphthylmethyl or 2-naphthylacyl substituent at position-3 of the benzimidazole ring, exhibited higher inhibitory activity compared with DDP. However, compounds **30**–**37** with 2-methyl-benzimidazole ring and **38**–**46** with 5,6-dimethyl-benzimidazole ring displayed powerful inhibitory activities. Among them, compounds **33**, **37** and **42**, with a 2-naphthylmethyl or 2-naphthylacyl group at position-3 of the substituted benzimidazole ring, showed potent higher inhibitory activity *in vitro* than DDP.

For the substituents of imidazolium salts, a 4-nitrobenzyl substituent at position-3 of imidazole rings, such as **15**, **23**, **32** and **41**, lacked activities against all tumor cell lines. A 2-bromobenzyl, 4-methylbenzyl, or phenacyl substituent at position-3 of imidazole rings, such as **20**, **22**, **25**, **29**, **31** and **34**, decreased the inhibitory activities, while a 4-bromobenzyl, 4-bromophenacyl or 4-methoxyphenacyl substituent, such as **21**, **26**, **27**, **30**, **35**, **36** and **39**, could slightly improve the inhibitory activities. Especially, compound **39** was more selective to HL-60 cell lines with IC_{50} values of 0.49 μM. Interestingly, compared with above substituents, a 2-naphthylmethyl substituent in **24**, **33** and **42** or 2-naphthylacyl substituent in **28**, **37** and **46** could cause obvious improvement of the inhibitory activities against tumor cell lines. Most of these kinds

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of slats exhibited strong cytotoxic activities and were more active than DDP. Notably, compound **42**, with a 2-naphthylmethyl substituent at position-3 of 5,6-dimethyl-benzimidazole, was found to be the most potent derivative against five human tumor cell lines investigated with IC_{50} values below 4.34 μM, and exhibited inhibitory activity selectively against SMMC-7721, A549 and SW480 cell lines compared with DDP. Meanwhile, compound **37** with a 2-naphthylacyl substituent was more selective to MCF-7 cell lines with IC_{50} value 8.4-fold lower than DDP.

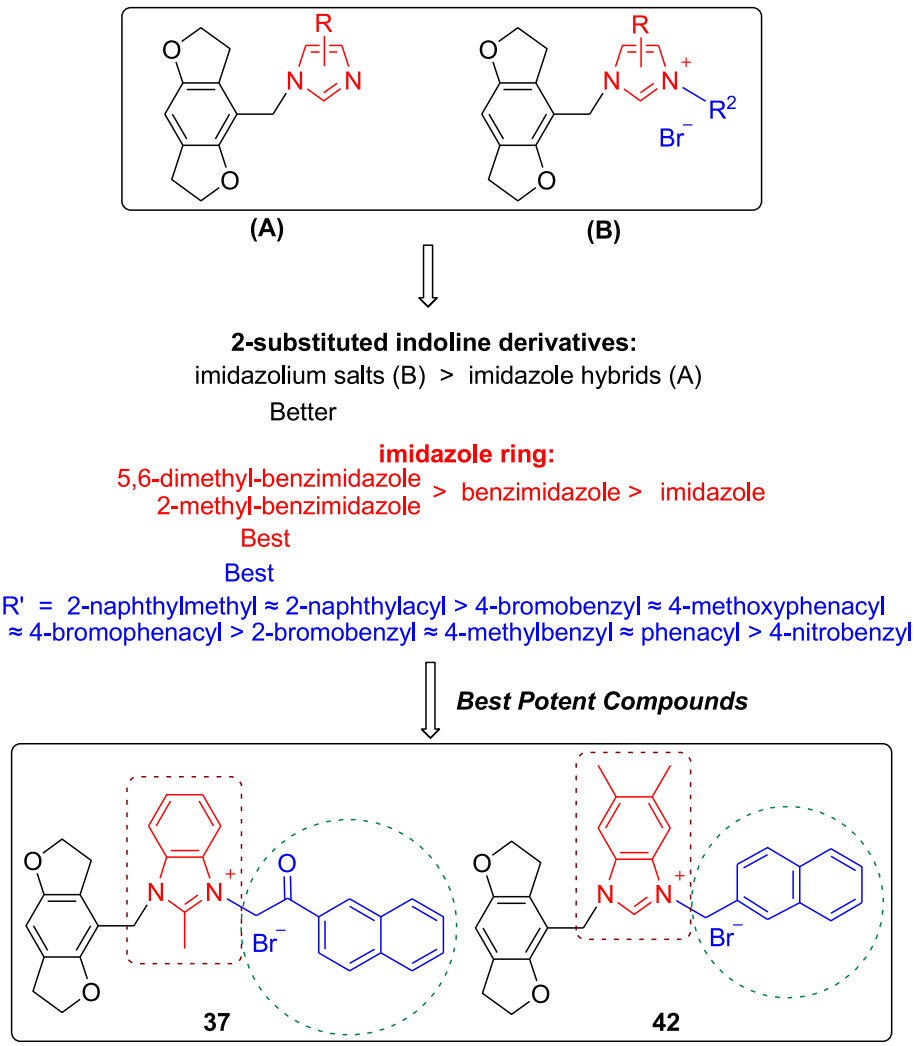
For the different salts, imidazolium chlorides **47**, **48**, **49** and **50** displayed similar inhibitory activities to imidazolium bromides **38**, **39**, **42** and **45**, respectively. Salt effect of different halides had little effect on the cytotoxic activities of imidazolium salt derivatives.

This observation suggests that the existence of 5,6-dimethyl-benzimidazole or 2-methyl-benzimidazole ring, and substitution of the imidazolyl-3-position with a 2-naphthylmethyl or 2-naphthylacyl group, were important for the antitumor activity. In general, the structure-activity relationship (SAR) results were summarized in Scheme 2.

SMMC-7721 cells were exposed to increasing concentrations of compound **37** and cell apoptosis was determined with Annexin V-FITC/PI double-labeled cell cytometry. As shown in Fig. 2, after treatment of cells with compound **37** at 4, 8, 12, 16 μM for 48 h, the apoptotic cell rate was 4.96 ± 0.49%, 5.83 ± 0.47%, 38.30 ± 0.03% and 91.23 ± 2.26%, respectively, which were statistically significantly different from the control (4.61 ± 0.52%).

The results of cell cycle analysis on SMMC-7721 cells treated with compound **37** were presented in Fig. 3. Compared with the control cells, the percentage of cells of G1 phase increased during the cells incubated with compound **37** with a dose dependent manner. Compound **37** treatment caused 79.59 ± 0.75% cells in G0/G1 phase as compared to control showing 70.12 ± 0.18%. On the contrary, the fraction of cells in S and G2/M phase decreased slightly accordingly from 14.85 ± 0.21% to 8.75 ± 1.48% and 4.37 ± 0.04% to 0.94 ± 0.65%, respectively. The data showed that compound **37** may induce G1 phase arrest in the cell cycle (Fig. 4).

In our previous work, we found that imidazolium salts which were synthesized might be potential inhibitors of mTOR signaling.[8k] In order to rationalize the observed SARs for this series of compound, we attempted to dock compound **42** with some crystal structure of proteins in this signaling pathway, e. g. mTORC1, mTORC2, and PI3K, using Autodock 4.2. Although this compound could not dock with mTORC1 or mTORC2, it could dock well with PI3Kγ (PDB code 3PRZ). Fig. 5 shows that compound **42** is predicted to engage a hydrogen bond with ARG690 using furan oxygen, and it also shows that hybrid z1-c6 can foster van der Waals interactions with the gap bounded by HIS295, ARG849, GLU846, TRP292, LEU657, ARG690, ARG277,



Scheme 2. Structure analysis of tetrahydrobenzodifuran–1*H*-imidazolium salts.

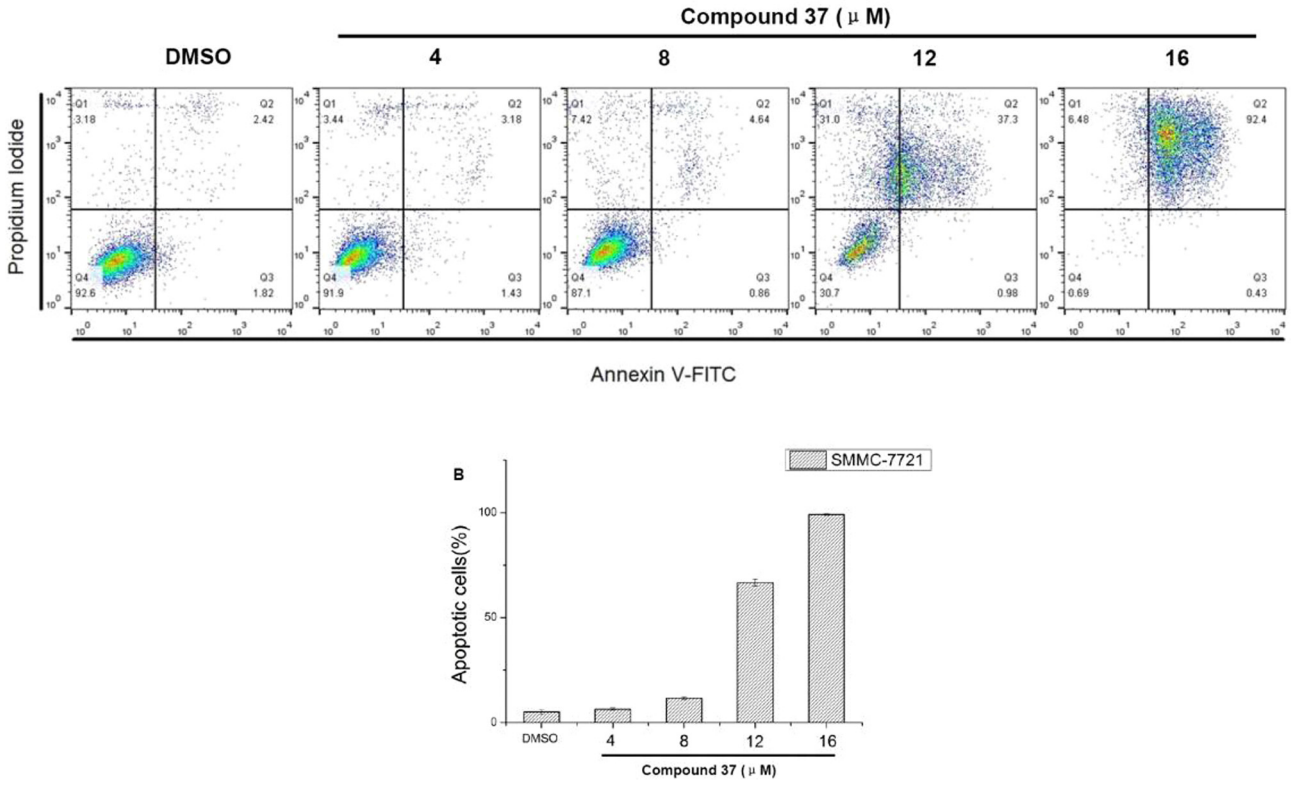
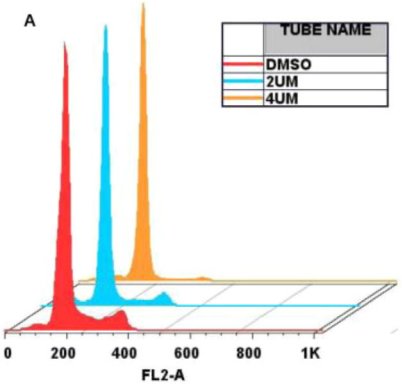


Fig. 3. Compound **37** caused significant apoptosis of SMMC-7721 cells. (A) Cells were treated with 4, 8, 12, 16 μM compound **37** for 48 h. Cell apoptosis was determined by Annexin V-FITC/PI double-staining assay. (B) The quantification of cell apoptosis. Data represents the mean ± S.D. of three independent experiments.



B

Treatment	SMMC 7721 (%)		
	G0/G1	S	G2/M
DMSO	70.12±0.18	20.18±0.02	3.12±0.02
37 (2 μ M)	70.58±0.11	14.85±0.21	4.37±0.04
37 (4 μ M)	79.57±0.75	8.75±1.48	0.94±0.65

Fig. 4. Compound **37** induces G1 phase arrest in SMMC-7721 cells. (A) Cells were treated with 2 and 4 μM of compound **37** 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.

ASP788, GLY868, TYR867, and PRO866. All these favorable interactions contribute to achieve a good docking score (AutoDock binding energy is −10.41 kcal/mol) and an excellent inhibitory activity as it results from the experimental data. These interesting findings would be helpful for our further research.

In summary, a series of novel 4-substituted 2,3,6,7-tetrahydrobenzo[1,2-b;4,5-b′] difuran–1*H*-imidazolium salts were synthesized and proved to potent cytotoxic activity. Compounds **24**, **28**, **33**, **37**, **42** and **46**, with a 5,6-dimethyl-benzimidazole or 2-methyl-benzimidazole ring, and 2-naphthylmethyl substituent or 2-naphthylacyl substituent at position-3 of the benzimidazole ring, were found to be the most potent derivatives. Notably, Compound **42** was found to possess the most potent derivative against five human tumor cell lines with IC_{50} values below 4.34 μM and showed more selective towards SMMC-7721, A549 and SW480 cell lines. Compound **37** was more selective to SMMC-7721 and MCF-7 cell lines with IC_{50} values 2.7-fold and 8.4-fold lower than DDP. Study on the antitumor mechanism of action showed that compound **37** could induce cell cycle G1 phase arrest and apoptosis in SMMC-7721 cells. The 4-substituted 2,3,6,7-tetrahydrobenzo[1,2-*b*;4,5-*b*′]difuran–1*H*-imidazolium salts **24**, **28**, **33**, **37**, **42** and **46** are promising leads for further structural modifications, guided by the valuable information obtained from our SARs.

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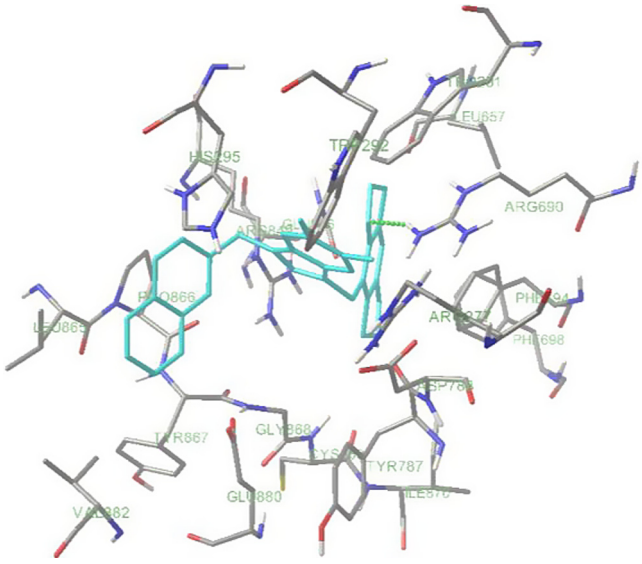

Fig. 5. Model of compound **42** docked into PI3Kγ.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2017.02.053.

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12. *General procedure for the preparation of tetrahydrobenzodifuran–imidazoles* **8**–**11**. To a solution of compound **6** (1 mmol) in dichloromethane (30 mL) was added methanesulfonyl chloride (1.5 mmol) and triethylamine (2 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2 h. After quenching the reaction with water (30 mL), the layers were separated. The organic phase was dried over anhydrous Na_2SO_4 and concentrated, and carried over to the next synthetic step. To the resulting, methanesulfonate was added imidazole, or substituted imidazole (3 mmol), and the mixture was stirred in DMF (15 ml) at reflux for 24–48 h (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 using column chromatography (silica gel, petroleum ether 60–90 °C: ethyl acetate = 2:1 to 1:1) to afford **8**–**11** in 65–80% yield (two steps). *Compound* **11**: white powder, yield 80%. IR ν_{max} (cm^{-1}): 3435, 3072, 2963, 2887, 1629, 1452, 1329, 1223, 1160, 1010, 941, 860, 754. ^1H NMR (400 MHz, DMSO) δ: 8.11 (1H, s), 7.39 (1H, s), 7.25 (1H, s), 6.62 (1H, s), 5.26 (2H, s), 4.58 (2H, t, *J* = 8.4 Hz), 4.39 (2H, t, *J* = 8.4 Hz), 3.13 (2H, t, *J* = 8.4 Hz), 2.85 (2H, t, *J* = 8.4 Hz), 2.28 (3H, s), 2.27 (3H, s). ^{13}C NMR (100 MHz, DMSO) δ: 154.42 (C), 152.26 (C), 143.88 (CH), 142.39 (C), 132.67 (C), 131.37 (C), 130.37 (CH), 126.96 (C), 125.49 (CH), 119.91(CH), 114.69 (C), 110.86 (CH), 106.30 (CH), 71.89 (CH_2), 71.49 (CH_2), 41.31 (CH_2), 30.30 (CH_2), 28.49 (CH_2), 20.79 (CH_3), 20.29 (CH_3). HRMS (ESI-TOF) *m*/*z* Calcd for $C_{20}H_{20}N_2O_2$ $[M+1]^+$ 321.1598, found 321.1592.
13. *General procedure for the preparation tetrahydrobenzodifuran–1H-imidazolium salts* **12**–**46**. A mixture of compound **8**–**11** (0.2 mmol), and phenacyl bromides or alkyl bromides (0.24 mmol), was stirred in toluene (5 ml) at reflux for 12–16 h. An insoluble substance was formed. After completion of the reaction, as indicated by TLC, the precipitate was filtered through a small pad of Celite, and washed with toluene (3 × 10 ml), then dried to afford imidazolium salts **12**–**46** in 58–95% yields. *Compound* **37**: white powder, yield 62%. Mp 217–219 °C. IR ν_{max} (cm^{-1}): 3432, 3019, 2897, 1688, 1527, 1476, 1359, 1221, 1192, 1020, 979, 857, 747. ^1H NMR (400 MHz, DMSO) δ: 8.96 (1H, s), 8.22 (1H, d, *J* = 8.0 Hz), 8.16 (1H, d, *J* = 8.7 Hz), 8.11-8.05 (3H, m), 7.85 (1H, d, *J* = 7.2 Hz), 7.80-7.71 (2H, m), 7.65-7.59 (2H, m), 6.73 (1H, s), 6.62 (2H, s), 5.75 (2H, s), 4.52 (2H, t, *J* = 4.4 Hz), 4.49 (2H, t, *J* = 4.4 Hz), 3.11 (2H, t, *J* = 8.5 Hz), 3.03 (2H, t, *J* = 8.5 Hz), 2.51 (3H, s). ^{13}C NMR (100 MHz, DMSO) δ: 191.40 (C), 154.5 (C), 154.10 (C), 152.11 (C), 136.10 (C), 132.44 (C), 131.85 (C), 131.74 (CH), 131.54 (C), 131.33 (C), 130.16 (CH), 129.91 (CH), 129.07 (CH), 128.39 (CH), 127.94 (CH), 127.64 (C), 126.86 (CH), 126.76 (CH), 125.16 (C), 124.00(CH), 113.69 (CH), 113.52 (CH), 112.07 (C), 107.01 (CH), 72.32 (CH_2), 71.66 (CH_2), 52.39 (CH_2), 43.53 (CH_2), 30.02 (CH_2), 28.76 (CH_2), 11.34 (CH_3). HRMS (ESI-TOF) *m*/*z* Calcd for $C_{31}H_{27}N_2O_3$ $[M-Br]^+$ 475.2016, found 475.2019.
14. CCDC 1507586 contains the supplementary crystallographic data for compound **30**. The data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
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