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Synthesis and cytotoxic activities of novel hybrid 2-phenyl-3-alkylbenzofuran and imidazole/triazole compounds

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ABSTRACT

A series of novel hybrid compounds of 2-phenyl-3-alkylbenzofuran and imidazole or triazole were prepared and evaluated in vitro against a panel of human tumor cell lines. The results suggest that the 2-ethyl-imidazole ring, and substitution of the imidazolyl-3-position with a 2-bromobenzyl or naphthylacyl group, were vital for modulating inhibitory activity. In particular, hybrid compound **31** was found to be the most potent derivative with IC_{50} values of 0.08–0.55 μM against five strains human tumor cell lines and was found to be more selective against breast carcinoma (MCF-7) and colon carcinoma (SW480) (IC_{50} values 40.8-fold and 40.1-fold lower than cisplatin (DDP)).

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.[2] Natural products represent a significant source of inspiration for the design of structural analogues with improved pharmacological profiles.[3] Naturally occurring substituted-benzofurans are an important class of biologically active oxygen-containing heterocycles. Natural products possessing the 2-phenyl-3-alkylbenzofuran moiety exhibit a broad range of biological and pharmacological activities.[4] Recently, natural occurring benzofurans have been identified to possess antitumor activity. As exemplified in Figure 1, Moracins O[5] and Ebenfuran III[6] are 2-phenyl-3-alkylbenzofuran derived compounds exhibiting potent cytotoxic activities against human hepatocellular cancer cells and breast cancer cells.[5,6]

Imidazole and triazole and their derivatives have attracted considerable interests for their broad range of biological and pharmacological activity,[7] especially antitumor activity.[8] For example, two new imidazolium halides (Fig. 1), Lepidiline A and Lepidiline B, isolated from the roots of *Lepidium meyenii*, showed potent cytotoxic activity against human cancer cell lines.[9] We have previously reported the synthesis of a series of novel imidazolium salts, such as MNIB (Fig. 1), and their potential antitumor activity.[10] Studies on molecular mechanisms demonstrated that the imidazolium salt hybrids can induce the G1 phase cell cycle arrest and apoptosis in tumor cells.[10a]

Molecular hybridization as a drug discovery strategy, involves the rational design of new chemical entities by the fusion of two drugs. The active compounds and/or pharmacophoric units are identified and derived from known bioactive molecules, as shown in the development of new anticancer, anti-Alzheimer, and antimalarial agents.[11] Considering the anticancer activities of naturally occurring 2-phenyl-3-alkylbenzofurans, as well as the potent cytotoxic activities of natural and synthetic imidazole or triazole derivatives, we were interested in synthesizing a number of new hybrid compounds bearing 2-phenyl-3-alkylbenzofuran (as shown pink shadows in Fig. 1) and *N*-benzyl or phenacyl substituted imidazole and triazole moieties (as shown green shadows in Fig. 1).

Although 2-benzylbenzofuran-triazole hybrid molecules were synthesized and found to exhibit CYP26A1 inhibitory activity,[12] to the best of our knowledge, no reports concerning antitumor activity of 2,3-disubstituted benzofuran-imidazole or triazole hybrid compounds have been reported.

In the present research, we designed and synthesized a series of novel hybrid compounds of 2-phenyl-3-alkylbenzofurans with imidazole or triazole. The purpose of this study was to investigate

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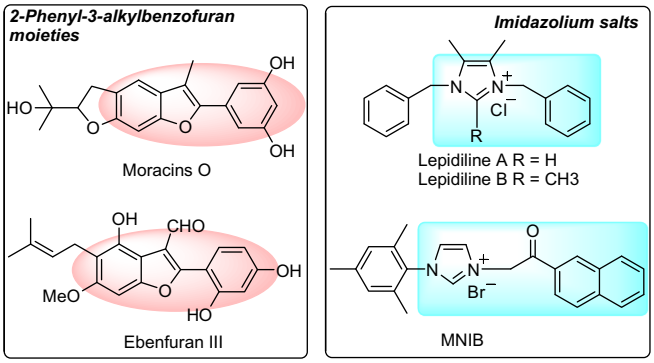
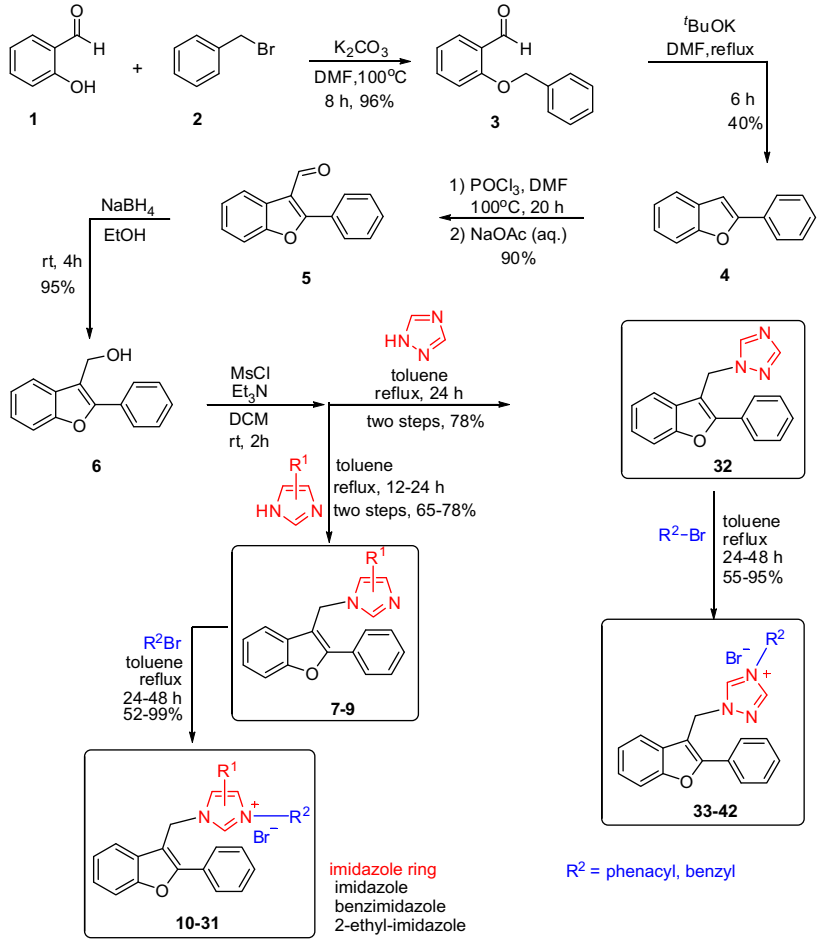


Figure 1. Representative structures of natural 2-phenyl-3-alkylbenzofurans and imidazolium salts.

the antitumor activity of 2-phenyl-3-alkylbenzofuran- imidazole/triazole hybrids, with the ultimate aim of developing novel potent antitumor agents.

To synthesize the 2-phenyl-3-alkylbenzofuran-imidazole hybrids, we used commercially available imidazole and triazole derivatives that were alkylated with 2-phenylbenzofuran 3-methanol, which was synthesized over four steps from readily available starting materials as shown in scheme 1. Salicylaldehyde **1** was chosen as the starting material for the preparation of a series of 2-phenyl-3-alkylbenzofuran-imidazole/triazole hybrids (**7**–**42**). Salicylaldehyde **1** was reacted with benzyl bromide **2** in DMF at 100 °C to give ether the ether **3** in 96% yields. The key step in the formation of the 2-phenylbenzofuran backbone was achieved by heating benzyl salicylaldehyde ether **3** in a base-mediated condensation to produce the intermediate 2-phenylbenzofuran (**4**, 40% yield). The formylation of 2-phenylbenzofuran **4** under Vilsmeier–Haack conditions followed by hydrolysis produced the known compound 2-phenylbenzofuran-3-carbaldehyde **5** in 90% yield. The 2-phenylbenzofuran-3-carbaldehyde **5** was reduced via $NaBH_4$ to the respective 2-phenylbenzofuran 3-methanol compound (**6**, 95% yields). Subsequently, the 2-phenylbenzofuran 3-methanol compound **6** was transformed via the mesylate to give the respective 2-phenyl-3-alkylbenzofuran–imidazole hybrids (**7**–**9**) and 2-phenyl-3-alkylbenzofuran–triazole hybrid **32** by refluxing under toluene with 65–78% yields (two steps).[13] Finally, thirty 2-phenyl-3-alkylbenzofuran-based imidazolium salts (**9**–**31**) and 2-phenyl-3-alkyl-benzofuranbased triazolium salts (**33**–**42**) were prepared with excellent yields by reaction of 2-phenyl-3-alkylbenzofuran–imidazole/triazole hybrids with the corresponding phenacyl and alkyl halides in refluxing toluene (52–99% yields).[14] The structures and yields of hybrid compounds are shown in Table 1.

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.[15] The panel consisted of leukemia (HL-60), myeloid liver carcinoma (SMMC-7721), lung carcinoma (A549), breast carcinoma (MCF-7), and colon carcinoma (SW480). Cisplatin (DDP) was used as the reference drug. The results are summarized in Table 2 (IC_{50} value, defined as the concentrations corresponding to 50% growth inhibition).



Scheme 1. Synthesis of hybrid compounds **7**–**42**.

Table 1
Structures and yields of hybrid compounds **7–42**

Entry	Compound	Imidazole/ triazole ring	R^2	Molecular formula	Yields (%)
1	**7**	Imidazole	—	$C_{18}H_{14}N_2O$	70
2	**8**	Benzimidazole	—	$C_{22}H_{16}N_2O$	65
3	**9**	2-Ethyl-imidazole	—	$C_{20}H_{18}N_2O$	78
4	**10**	Imidazole	Phenacyl	$C_{26}H_{21}BrN_2O_2$	81
5	**11**	Imidazole	4-Hydroxyphenacyl	$C_{26}H_{21}BrN_2O_3$	83
6	**12**	Imidazole	4-Methoxyphenacyl	$C_{27}H_{23}BrN_2O_3$	84
7	**13**	Imidazole	4-Fluorophenacyl	$C_{26}H_{20}BrFN_2O_2$	87
8	**14**	Imidazole	4-Bromophenacyl	$C_{26}H_{20}Br_2N_2O_2$	75
9	**15**	Imidazole	Naphthylacyl	$C_{30}H_{23}BrN_2O_2$	55
10	**16**	Imidazole	2-Bromobenzyl	$C_{25}H_{20}BrN_2O$	52
11	**17**	Benzimidazole	Phenacyl	$C_{30}H_{23}BrN_2O_2$	93
12	**18**	Benzimidazole	4-Hydroxyphenacyl	$C_{30}H_{23}BrN_2O_3$	52
13	**19**	Benzimidazole	4-Methoxyphenacyl	$C_{31}H_{25}BrN_2O_3$	92
14	**20**	Benzimidazole	4-Fluorophenacyl	$C_{30}H_{22}BrFN_2O_2$	68
15	**21**	Benzimidazole	4-Bromophenacyl	$C_{30}H_{22}Br_2N_2O_2$	76
16	**22**	Benzimidazole	Naphthylacyl	$C_{35}H_{25}BrN_2O_2$	96
17	**23**	Benzimidazole	Benzyl	$C_{29}H_{23}BrN_2O$	99
18	**24**	Benzimidazole	2-Bromobenzyl	$C_{29}H_{22}BrN_2O$	53
19	**25**	2-Ethyl-imidazole	Phenacyl	$C_{28}H_{25}BrN_2O_2$	95
20	**26**	2-Ethyl-imidazole	4-Hydroxyphenacyl	$C_{28}H_{25}BrNO_3$	91
21	**27**	2-Ethyl-imidazole	4-Methoxyphenacyl	$C_{29}H_{27}BrN_2O_3$	82
22	**28**	2-Ethyl-imidazole	4-Fluorophenacyl	$C_{28}H_{24}BrFN_2O_2$	91
23	**29**	2-Ethyl-imidazole	4-Bromophenacyl	$C_{28}H_{24}Br_2N_2O_2$	99
24	**30**	2-Ethyl-imidazole	Naphthylacyl	$C_{32}H_{27}BrN_2O_2$	93
25	**31**	2-Ethyl-imidazole	2-Bromobenzyl	$C_{27}H_{24}Br_2N_2O$	84
26	**32**	1,2,4-Triazole	—	$C_{17}H_{13}N_3O$	78
27	**33**	1,2,4-Triazole	Phenacyl	$C_{25}H_{20}BrN_3O_2$	90
28	**34**	1,2,4-Triazole	4-Hydroxyphenacyl	$C_{25}H_{20}BrN_3O_3$	92
29	**35**	1,2,4-Triazole	4-Methoxyphenacyl	$C_{26}H_{22}BrN_3O_3$	95
30	**36**	1,2,4-Triazole	4-Fluorophenacyl	$C_{25}H_9BrFN_3O_2$	86
31	**37**	1,2,4-Triazole	4-Bromophenacyl	$C_{25}H_{19}Br_2N_3O_2$	85
32	**38**	1,2,4-Triazole	Naphthylacyl	$C_{29}H_{22}BrN_3O_2$	88
33	**39**	1,2,4-Triazole	2′-Phenyl-phenacyl	$C_{31}H_{24}BrN_3O_2$	77
34	**40**	1,2,4-Triazole	Benzyl	$C_{24}H_{20}BrN_3O$	88
35	**41**	1,2,4-Triazole	2-Bromobenzyl	$C_{24}H_{19}Br_2N_3O$	75
36	**42**	1,2,4-Triazole	Butyl	$C_{21}H_{22}BrN_3O$	55

As shown in Table 2, the structures of the hybrid compounds have an obvious influence on the inhibitory activities. 2-Phenyl-3-alkylbenzofuran–imidazole hybrids **7–9** and the 2-phenyl-3-alkylbenzofuran–triazole hybrid **32** lacked activities against all tumor cell lines investigated at the concentration of 40 μM. However, their imidazolium salts **10–31** and triazolium salts **33–42** exhibited some degree of inhibitory activities.

In terms of the imidazole ring (imidazole, benzimidazole, or 2-ethyl-imidazole) and triazole ring, imidazolium salts **10–16** with imidazole and triazolium salts **33–42** displayed some inhibitory activities. Meanwhile, hybrid compounds **17–24**, with benzimidazole, exhibited medium inhibitory activities. Among them, compounds **15**, **16**, **22**, **24**, and **38**, bearing a naphthylacyl or 2-bromobenzyl substituent at position-3/4 of the imidazole/triazole, showed similar or higher inhibitory activity in vitro than DDP. Compounds **22** and **24**, also bearing a naphthylacyl or 2-bromobenzyl at position-3 of the imidazole ring, displayed higher inhibitory activity than DDP. However, imidazolium salt hybrids **25–31**, with 2-ethyl-imidazole, exhibited powerful inhibitory activities. Most of these derivatives were found to be much more active than DDP (compounds **27**, **28**, **29**, **30** and **31**). Compared with the triazolium salts **33–42**, the imidazolium salts **10–31** displayed higher inhibitory activity. This difference of imidazolium and triazolium salts in inhibition may be largely due to the changes of molecular structure and charge distribution (electron rich) between imidazole ring and triazole ring. Recently, it has also been proved that the imidazole derivatives exhibited more potent inhibitory activity than triazole derivatives by Oyama's group.[16]

In terms of the substituent at position-3 of imidazole or position-4 of triazole ring, hybrids **11**, **18**, **26**, **34**, and **42**, with 4-hydroxyphenacyl or butyl substituent at position-3/4 of imidazole/triazole ring, showed decreased activities against five tumor cell lines. However, hybrid compounds with phenacyl or substituted phenacyl substituents exhibited moderate or potent inhibitory activities. Among them, compounds **15**, **22**, **30**, and **38**, bearing a naphthylacyl substituent, were the most active compounds with similar or higher inhibitory activities than DDP.

Compared with the above imidazolium salt derivatives with phenacyl or butyl substituents, hybrid compounds **16**, **24**, and **31**, with a 2-bromobenzyl substituent at position-3 of the imidazole ring, exhibited higher inhibitory activities. These hybrid compounds displayed more potent inhibitory activities than DDP. Interestingly, hybrid compound **31**, with a 2-bromobenzyl

Table 2
Cytotoxic activities of hybrid compounds **7–42** in vitro[a] (IC_{50}, μM[b])

Entry	Compound	HL-60	SMMC-7721	A549	MCF-7	SW480
1	**7**	>40	>40	>40	>40	>40
2	**8**	>40	>40	>40	>40	>40
3	**9**	>40	>40	>40	>40	>40
4	**10**	2.49	9.83	>40	15.45	15.49
5	**11**	>40	>40	>40	>40	>40
6	**12**	2.28	16.49	16.27	10.27	11.92
7	**13**	2.98	13.44	>40	14.62	15.54
8	**14**	1.57	17.77	13.76	3.65	3.36
9	**15**	2.06	9.42	13.97	3.68	3.48
10	**16**	1.86	6.61	11.23	5.58	10.35
11	**17**	1.97	8.46	12.21	3.92	3.44
12	**18**	13.04	20.66	33.99	16.22	18.16
13	**19**	0.61	16.60	9.12	23.78	>40
14	**20**	2.03	9.41	11.79	3.13	3.29
15	**21**	2.11	2.94	5.25	4.08	4.37
16	**22**	2.34	2.63	4.50	3.24	3.61
17	**23**	1.96	4.81	7.09	3.49	3.26
18	**24**	0.64	2.10	3.34	4.78	5.56
19	**25**	2.09	5.01	12.50	7.53	11.89
20	**26**	13.15	13.13	27.08	17.39	>40
21	**27**	0.58	11.81	12.90	3.17	5.69
22	**28**	0.99	8.13	14.56	5.03	11.33
23	**29**	0.72	6.07	12.76	2.89	3.58
24	**30**	0.61	2.30	5.35	3.03	3.14
25	**31**	0.08	0.52	0.55	0.51	0.47
26	**32**	>40	>40	>40	>40	>40
27	**33**	3.51	5.76	13.74	14.67	17.09
28	**34**	>40	>40	>40	>40	>40
29	**35**	3.22	5.76	13.68	14.92	17.20
30	**36**	9.67	9.21	15.08	16.36	16.75
31	**37**	9.71	10.82	14.58	10.44	14.63
32	**38**	2.33	1.86	2.06	3.11	2.89
33	**39**	15.90	16.12	16.80	20.71	20.92
34	**40**	>40	>40	>40	>40	>40
35	**41**	9.00	21.90	33.06	16.34	18.89
36	**42**	>40	>40	>40	>40	>40
37	**DDP**	1.69	12.49	14.09	20.82	18.85

[a] Data represent the mean values of three independent determinations.
[b] 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.

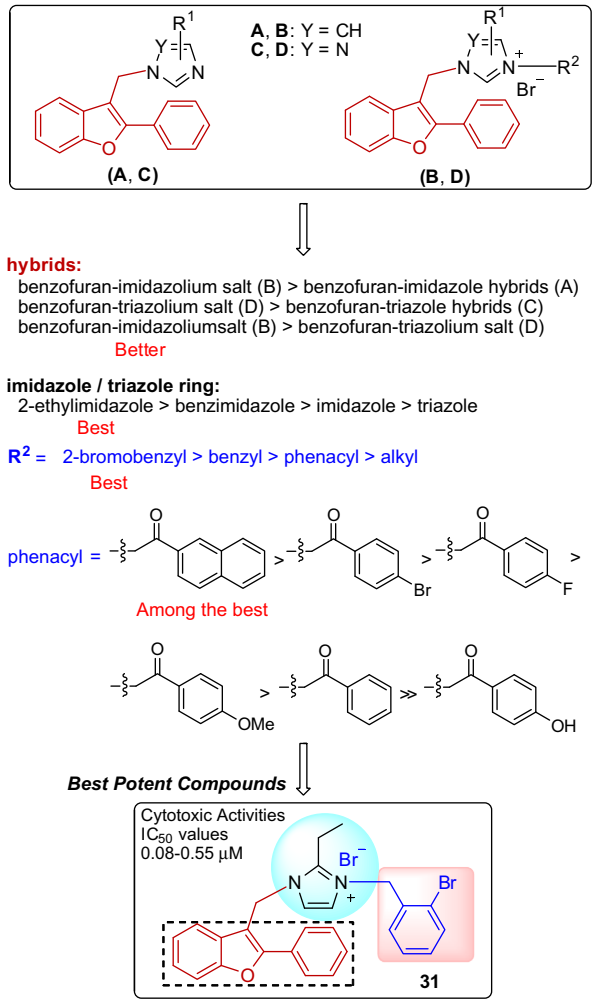


Figure 2. Structure–activity relationships of hybrid compounds.

substituent at position-3 of 2-ethyl-imidazole, was found to be the most potent derivative with IC_{50} values of 0.08–0.55 μM against all of human tumor cell lines investigated, and much more active than DDP. Notably, this compound exhibited inhibitory activity selectively against breast carcinoma (MCF-7) and colon carcinoma (SW480), with IC_{50} values 40.8-fold and 40.1-fold lower than DDP.

This finding suggests that the existence of 2-ethyl-imidazole ring, and substitution of the imidazolyl-3-position with a 2-bromobenzyl or naphthylacyl group, were important for modulating inhibitory activity. The structure–activity relationship (SAR) results are summarized in Figure 2.

In addition, the inhibition of mTOR (mammalian target of rapamycin) signaling of some newly synthesized hybrid compounds were evaluated according to procedures described in the literature.[17] Rapamycin was used as the reference drugs. The results are summarized in Table 3 (Ratio, defined as Eukaryotic initiation factor 4E (eIF4E) Cytoplasmic-to-Nuclear). In order to rationalize the observed SARs for this series of compound, we attempted to

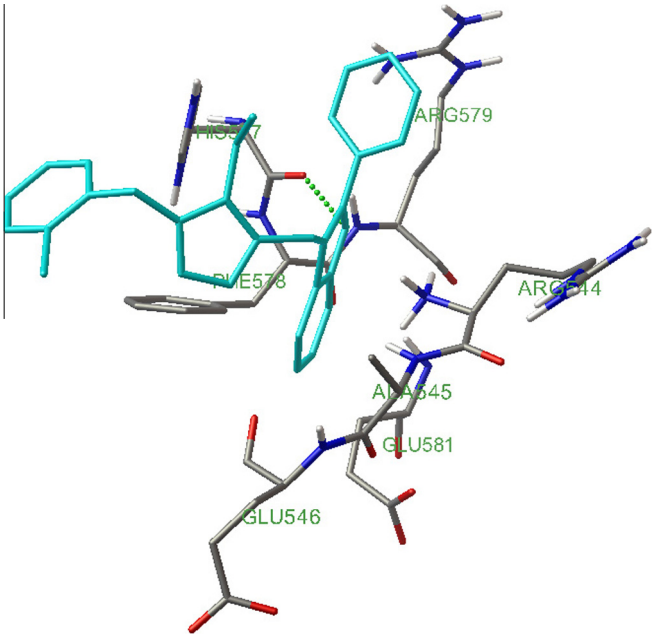


Figure 3. Model of hybrid compound **31** docked into PI3Kγ.

dock hybrids **31** and **38** with some crystal structure of proteins in this signaling pathway, for example, mTORC1, mTORC2, and PI3K using Autodock 4.0 (see Supplementary data for a detailed description of the docking experiments). Although these two compounds could not dock with mTORC1 or mTORC2, they could dock well with PI3Kγ (PDB code 3PRZ). Figure 3 shows hybrid **31** is predicted to engage a hydrogen bond with HIS577 using furan oxygen, and it also shows 2-ethyl-imidazole ring and benzofuran ring can foster van der Waals interactions with the gap bounded by PHE578, ALA545, and GLU546. Similarly, hybrid **38** establishes a hydrogen bond with ARG579 using carbonylic oxygen, and its 2-phenyl-3-alkylbenzofuran moiety can interact with the gap bounded by PHE578, GLU546, GLU584, and ALA545, while its triazole ring placed in the pocket bounded by PHE578, HIS577, TRP576, and ARG579 (Fig. 4). All these favorable interactions contribute to achieve a good docking score (AutoDock binding energy of **31** is—4.48 kcal/mol, and AutoDock binding energy of **38** is—4.84 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 conclusion, a number of novel 2-phenyl-3-alkylbenzofuran-imidazole/triazole hybrid compounds proved to be potent antitumor agents. Hybrids **22**, **24**, **30**, and **31**, bearing a 2-ethyl-imidazole or benzimidazole ring, and 2-bromobenzyl or naphthylacyl substituent at position-3 of the imidazole ring, were found to be the most potent activity. Compound **31** was found to have the most potent derivative, with IC_{50} values of 0.08–0.55 μM against all human tumor cell lines investigated and more selective towards breast carcinoma (MCF-7) and colon carcinoma (SW480), with IC_{50} values 40.8-fold and 40.1-fold lower than DDP. The 2-phenyl-3-alkylbenzofuran-based imidazolium salts **22**, **24**, **30**, and **31** are

Table 3
Eukaryotic initiation factor 4E (eIF4E) Cytoplasmic-to-Nuclear of representative hybrid compounds

Entry	1	2	3	4	5	6	7	8	9	10
Compound	Control	**12**	**19**	**23**	**24**	**30**	**31**	**33**	**38**	Rapamycin
Ratio[a]	0.85	1.12	1.32	1.54	1.52	1.55	1.07	1.11	0.96	1.59

[a] Ratio, defined as Eukaryotic initiation factor 4E (eIF4E) Cytoplasmic-to-Nuclear.

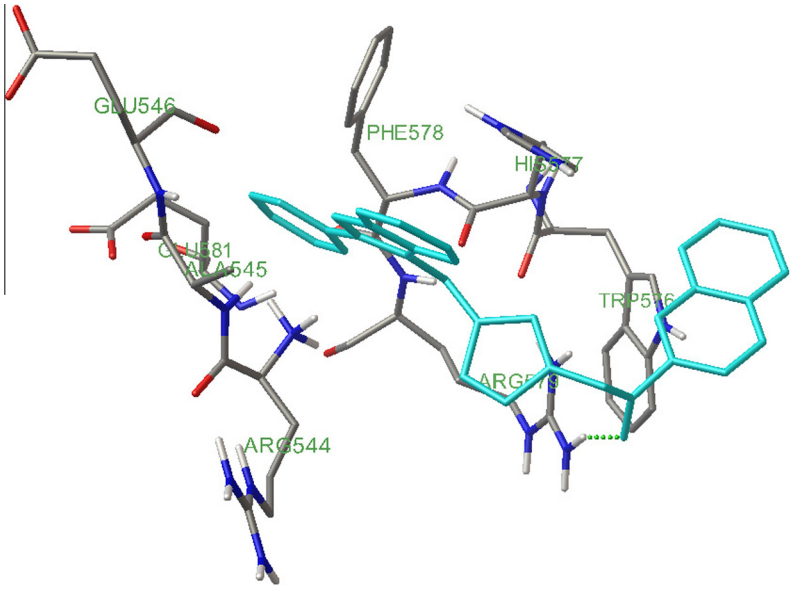


Figure 4. Model of hybrid compound **38** docked into PI3Kγ.

promising leads for further structural modifications, guided by the valuable information obtained from our SARs.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.06.001.

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13. *General procedure for the preparation of hybrids **7–9** and **32**.* To a solution of 2-phenyl-benzofuran 3-methanol **6** (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 2 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 carried over to the next synthetic step. To the resulting, methanesulfonate was added imidazole, or substituted imidazole or 1,2,4-triazole (3 mmol), and the mixture was stirred in toluene (20 mL) at reflux for 12–24 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 = 1:1) to afford **7–9** and **32** in 65–78% yield (two steps).
*Compound **7**:* yellow powder, yield 70%, mp 102–104 °C. IR ν_{max} (cm^{-1}): 3101, 3055, 1601, 1501, 1449, 1283, 1221, 1112, 1074, 806, 750, 687. ^1H NMR (300 MHz, $CDCl_3$): δ 7.63 (2H, ddd, J = 6.6, 2.1, 1.2 Hz), 7.56 (1H, s), 7.51–7.36 (4H, m), 7.31–7.25 (1H, m), 7.23–7.14 (2H, m), 7.04 (1H, s), 6.89 (1H, s), 5.29 (2H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.91 (C), 153.72 (C), 136.73 (CH), 129.69 (CH), 129.45 (C), 129.31 (CH), 128.91 (CH),128.49 (C), 127.25 (CH), 125.06 (CH), 123.30 (CH), 118.96 (CH), 118.73 (CH), 111.30 (CH), 109.69 (C), 41.20 (CH_2). HRMS (ESI-TOF) m/z Calcd for $C_{18}H_{14}N_2ONa$ $[M+Na]^+$ 297.0998, found 297.1015.
14. *General procedure for the preparation hybrids **10–31** and **33–42**.* A mixture of hybrids **7–9** or **32** (1 mmol), and phenacyl bromides or alkyl bromides (1.2 mmol), was stirred in toluene (10 mL) at reflux for 24–48 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 **10–31** and **33–42** in 52–99% yields.
*Compound **31**:* yellow oil, yield 84%. IR ν_{max} (cm^{-1}): 3049, 2935, 2864, 1618, 1583, 1513, 1445, 1244,1194, 1105, 1031, 754, 700. ^1H NMR (300 MHz, $CDCl_3$): δ 7.85 (2H, d, J = 6.0 Hz), 7.79 (1H, s), 7.76–7.68 (2H, m), 7.65–7.53 (4H, m), 7.53–7.24 (5H, m), 7.04 (1H, d, J = 6.3 Hz), 5.93 (2H, s), 5.53 (2H, s), 3.06 (2H, q, J = 7.5 Hz), 0.88 (3H, t, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.29 (C),152.94 (C), 148.01 (C), 132.80 (C), 132.59 (CH), 130.17 (CH), 129.33 (CH), 129.05 (CH), 128.64 (CH), 128.15 (C), 127.83 (CH), 127.07 (CH), 124.99 (CH), 122.99 (CH), 121.98 (C), 121.44 (CH), 119.13 (CH), 110.99 (CH), 107.96 (CH), 50.52 (CH_2), 42.11 (CH_2), 16.29 (CH_2), 9.99 (CH_3). HRMS (ESI-TOF) m/z Calcd for $C_{27}H_{24}BrN_2O$ $[M-Br]^+$ 471.1067, found 471.1070.
*Compound **38**:* white powder, yield 88%, mp 232–234 °C. IR ν_{max} (cm^{-1}): 3050, 2958, 2865, 1698, 1560, 1450, 1364, 1262, 1161, 818, 716, 698. ^1H NMR (300 MHz, $CDCl_3$): δ 10.62 (1H, s), 8.95 (1H, s), 8.72 (1H, s), 8.06 (1H, d, J = 7.8 Hz), 8.00 (1H, d, J = 8.7 Hz), 7.93–7.86 (4H, m), 7.75 (1H, d, J = 6.3 Hz), 7.67–7.51 (6H, m), 7.37 (2H, s), 6.38 (2H, s), 5.92 (2H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.02 (C), 159.62 (C), 157.71 (C), 149.23 (CH), 147.29 (CH), 139.95

(C), 136.03 (C), 134.89 (CH), 133.89 (C), 133.60 (CH), 133.17 (CH), 132.83 (CH), 132.68 (CH), 131.45 (CH), 130.91 (CH), 129.18 (CH), 127.51 (CH), 126.65 (CH), 122.90 (CH), 115.13 (CH), 110.00 (C), 58.06 (CH_2), 51.31 (CH_2). HRMS (ESI-TOF) *m/z* Calcd for $C_{29}H_{22}N_3O_2$ $[M-Br]^+$ 444.1707, found 444.1718.

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