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Original article

Benzofuran derivatives as anticancer inhibitors of mTOR signaling

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ABSTRACT

A series of 32 derivatives and isosteres of the mTOR inhibitor **2** were synthesized and compared for their cytotoxicity in radioresistant SQ20B cancer cell line. Several of these compounds, in particular **30b**, were significantly more cytotoxic than **2**. Importantly, **30b** was shown to block both mTORC1 and Akt signaling, suggesting insensitivity to the resistance associated to Akt overactivation observed with rapamycin derivatives currently used in clinic.

1. Introduction

The mammalian Target of Rapamycin (mTOR) is a key protein that controls cell growth, metabolism, autophagy and angiogenesis [1,2]. Its signaling is one of the most frequently altered in cancer cells, which makes mTOR an important target in oncology. In their quest to identify inhibitors of mTOR signaling, William Sellers, Pamela Silver and coworkers at Harvard University identified the hit **1** by high-throughput screening (Fig. 1) [3,4]. We recently reported the first hit to lead optimization of this compound and demonstrated that the replacements of the dimethylamine and benzyl moieties by a 4-piperidino-piperidine and a phenyl (compound **2**) significantly improve cytotoxicity [5]. We also showed that this new class of compounds interacts with the complex mTORC1 to inhibit its activity. Importantly, as far as we know, prior to this study, no benzofuran derivatives had been previously explored as inhibitors of Akt/mTOR signaling. Herein, we report our endeavor to complete the SAR study of this class of compounds and provide new insight on their mechanism of action.

2. Results and discussions

2.1. Chemical synthesis

The 2-phenylbenzofuran derivatives **5a**–**m** were synthesized in a convergent manner from the phosphonium **4** [6] and an acid chloride by a tandem esterification-intramolecular Wittig reaction [7] followed by a saponification (Scheme 1). Next, a Mannich reaction afforded the expected adducts **6a**–**m**. Compound **10** was synthesized similarly, starting from **9**. The adduct **8** was obtained by sulfonylation of the benzofuran derivative **2** [8].

To introduce a methyl in position 3, phenol **11** was condensed with desyl chloride **12** to generate the benzofuran **13** following Hajela's procedure [9]. This adduct was transformed as previously into the Mannich base **14** after phenol deprotection (Scheme 2).

The derivatives and analogues **17a**–**e** were synthesized by a Mannich reaction from easily prepared hydroxyindoles **16a** and **16b** (from known ethers **15a** [10] and **15b** [11]) and from described compounds **16c**,**d** [12] (Scheme 3). Moreover, ester **17d** was quantitatively reduced to alcohol **17e**.

The benzoxazole **20a** and benzimidazole **20b** analogues were prepared from the anilines **18a** and **18b** [13] by a cyclisation/demethylation step followed by a Mannich reaction (Scheme 4).

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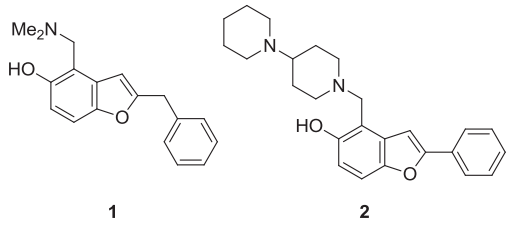


Fig. 1. Structures of HTS hit **1** and lead **2**.

The synthesis of isostere **24** started from pyridone **21**. Optimization of the published iodination conditions (NaOH, I_2) [14] afforded principally a mono-iodinated compound, which upon a Sonogashira reaction with phenylacetylene coupled to a 5-endo-dig ring closure [15] affording directly the furo[3,2-*c*]pyridine **22** (Scheme 5). Metalation of **22** with Fort's procedure (nBuLi/DMAE) [16] followed by a quenching with DMF lead to the aldehyde **23** (15% yield). Finally, expected adduct **24** was obtained by reductive amination of **23**.

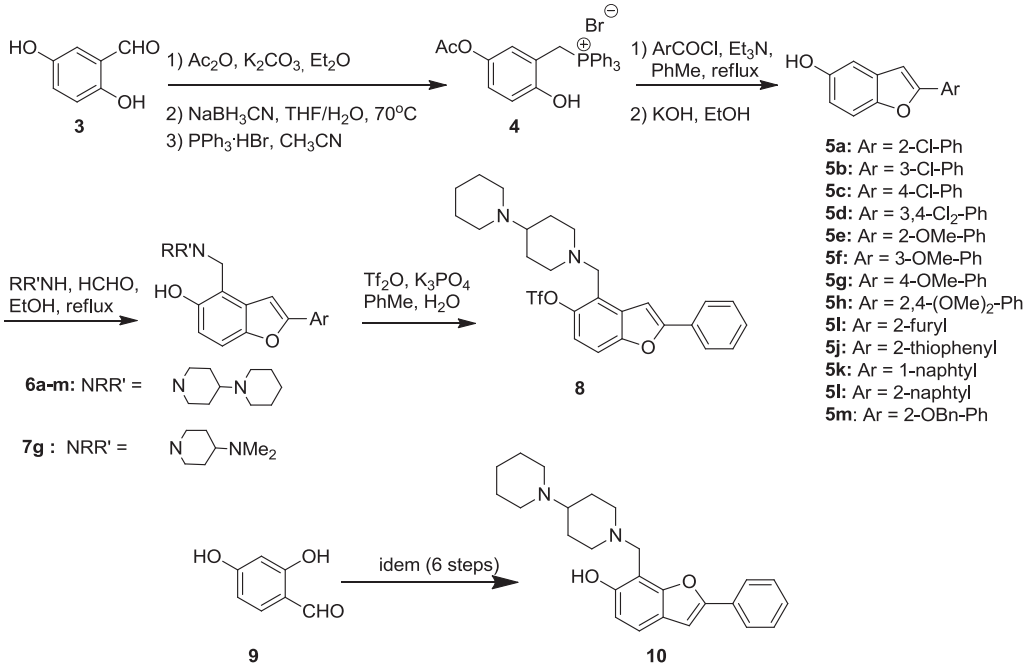
Compound **27**, a bioisostere of benzofuran derivative **2**, was synthesized in three steps from the known 2-phenylbenzofuran-5-amine (**25**) [17] by the introduction of the triflyl moiety followed by a Mannich reaction (Scheme 6). All the attempts to introduce nitrogen in this position by a Pd-cross coupling reaction on the triflate **8** were unsuccessful.

Our approach to *O*-substituted derivatives began with a tandem Sonogashira coupling/5-endo-dig-cyclization [18] using Fu's catalytic system [19] to afford hydroxybenzofurans **29a**,**b** that were alkylated into ethers (Scheme 7). Nucleophilic aromatic substitution displacement of fluoroarene **29b** afforded benzyl ether **29c** [20]. Subsequent reductive amination yielded the expected compounds **30a**,**b**. Dehydroxy analogue **32**, was prepared similarly from bromophenol derivative **31**.

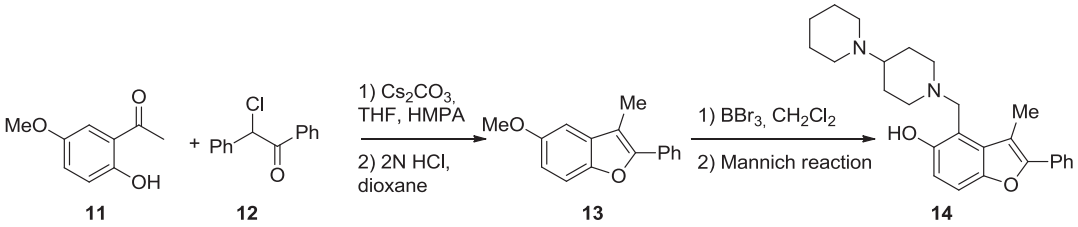
2.2. Biological results

First, we focused our efforts on the substituent on the phenyl moiety (Table 1). The cytotoxicity of benzofuran derivatives was assessed after 72 h of exposure in HNSCC SQ20B cell line and compared to that of everolimus. Overall, chloro- and methoxyphenyl derivatives **6a**–**h** displayed a similar activity as unsubstituted **2**. Replacement of the phenyl by a 2-furyl (**6i**), a 2-thiophenyl (**6j**), a 1-naphtyl (**6k**) or a 2-naphtyl (**6l**) did not change also greatly the activity. Introduction of a methyl (**14**) or a carbethoxy (**17d**) in position 3 was well tolerated, while a more polar hydroxymethyl was slightly detrimental (**17e**).

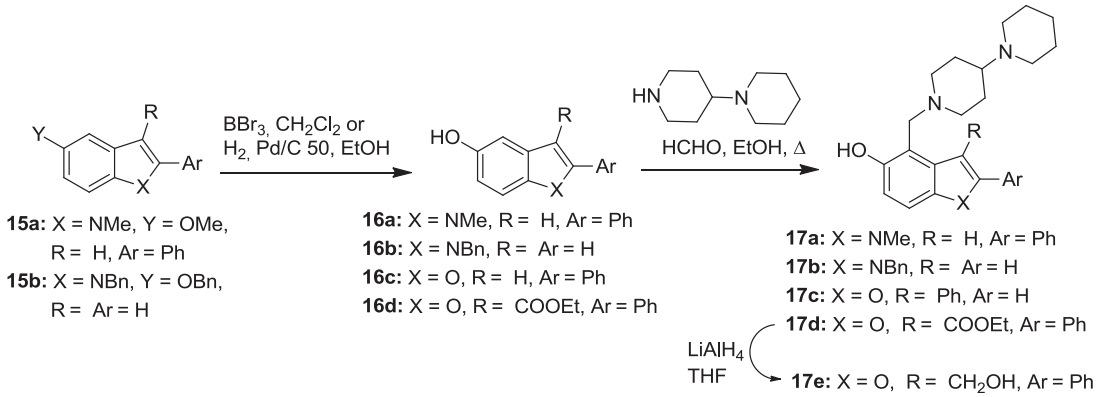
Isosteric modifications of the benzofuran scaffold were next examined. The introduction of a nitrogen atom into the furan ring of **2** to give the oxazole **20a** was less detrimental to the activity than shifting the oxygen within the 5-membered ring to provide **10**. This latter compound was more active than



Scheme 1. Synthesis of 2–phenylbenzofuran derivatives **6a**–**m**, **7g**, **8** and **10**.



Scheme 2. Synthesis of 2–phenylbenzofuran derivative **14**.



Scheme 3. Synthesis of indole and 2–phenyl-3-subtituted benzofuran derivatives **17a**–**e**.

benzimidazole **20b** and *N*-methylindole **17a**. Interestingly, isosteric replacement coupled to a migration of the phenyl moiety yielded indole **17b** that was as cytotoxic as **17a**. Migration of the phenyl ring from the 2- to the 3-position (**14c**) decreased also cytotoxicity.

Next, we examined the contribution of the phenolic hydroxy to cytotoxicity. Replacing the phenol moiety of **2** by a H-bond acceptor to give the furo[3,2-*c*]pyridine **24** altered the activity. Exchanging the phenolic hydroxyl by another H-bond donor such as a triflylamide (**27**) conserved the cytotoxicity. Surprisingly, the introduction of a triflate ester (**8**), which cannot donate an H-bond, was also well tolerated, while the deletion of the phenolic hydroxy reduced cytotoxicity (**32**). Next, we showed that the piperidinopiperidine moiety can be replaced by a dimethylamino moiety (**7g**) without loss of activity, resulting in a significant gain in ligand efficiency.

In the following experiments we observed a drift in the sensitivity of the cells toward the cytotoxicity induced by this class of agents, probably because of origin of the cells or of the culture medium. To meaningfully compare our compounds, we tested one more time the most significant compounds and observed the same trends of activities (Table 2). Finally, we observed that the introduction of a hydrophobic benzyloxy moiety on the phenyl ring (**6m**) significantly improves cytotoxicity. Methylation of the phenolic hydroxy (**30a**) did not alter the activity but gratefully enhanced solubility. We combined all these data to design **30b**, which displayed an enhanced cytotoxicity. We then compared this optimized lead compound **30b** with **2**, **6m**, everolimus and OZI027 on a panel of cell lines (Fig. 2). The pattern of sensitivity of **30b** is close to **6m** as expected, but significantly different from everolimus or OZI027. Interestingly, HOP62 HNSCC cell line was the most sensitive to **30b**, **2**, **6m** and OZI027 but not to everolimus, whereas Colo205 colon cancer cell line was resistant to all tested compounds. Next, we examined the effect of **30b** on inhibition of mTOR signaling. We observed a decrease in phosphorylation of S6 ribosomal protein and 4-EBP1 protein, the main targets of mTORC1. In contrast to mTORC1 specific inhibitor everolimus, we did not see the recurrent Akt hyperactivation (Fig. 3). Indeed, mTOR exerts its activity through two functional complexes, mTORC1 and mTORC2 (Fig. 3) [1,2]. Akt, also known as protein kinase B (PKB) activates mTORC1 and is activated by mTORC2. Rapamycin and its analogues selectively inhibit mTORC1, which decreases the phosphorylation of downstream proteins, such as S6, and also increases Akt activity through a feed-back mechanism, resulting in resistance to treatment. In fact, inhibition of mTORC1 induces a compensatory activation of mTORC2 which stimulates Akt through its phosphorylation at serine 473 [21].

3. Conclusion

In a previous study, we performed the first hit to lead optimization of **1** discovered by William Sellers, Pamela Silver and coworkers at Harvard [3]. We found that **2** displayed an enhanced cytotoxicity compared to **1** and demonstrated that, this new family of anticancer agents interacts with the complex mTORC1 to inhibit its activity [5]. Herein, we continued our optimization program based on **2**. The seven isosteric replacement of the benzofuran scaffold that we examined were detrimental to the activity. We also showed that methylation of the phenolic hydroxyl and replacement of the 4–piperidinopiperidine by a 4-dimethylaminopiperidine is well tolerated. Importantly, substitution of the phenyl by a benzyloxy significantly improved the cytotoxicity in cancer cells. Combination of these data resulted in **30b**, which has an IC50 10 fold lower than **2**. Both compounds display a similar profile of cytotoxicity on a panel of human cancer cell lines, suggesting a related mechanism of action. Importantly, **30b** was shown to inhibit both mTORC1 and Akt signaling, suggesting that it should overcome the resistance associated to Akt overactivation observed with rapamycin derivatives.

4. Experimental protocol

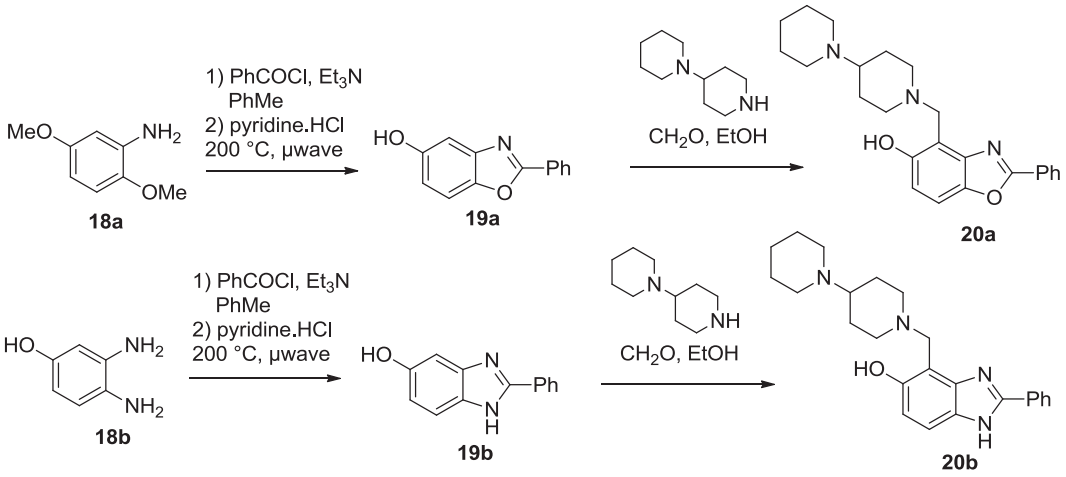
4.1. Biology

4.1.1. Cell lines

Hepatocarcinoma SK-HEP1, prostate DU145, renal CAKI1 and ovarian OVCAR3 cell lines were obtained from the ATCC (Rockville, MD). Colon Colo205, HCT116, HT29, and HSCLC HOP62 cell lines were purchased from NCI cell line bank. SQ20B was kindly provided by Prof. E. Deutsch (Institute Gustave Roussy, France). ColoR was developed in our laboratory. Cells were grown as monolayers in RPMI medium supplemented with 10% fetal calf serum (Invitrogen, Cergy-Pontoise, France), 2 mM glutamine, 100 units/ml penicillin and 100 μg/ml streptomycin at 37 °C in a humidified 5% CO_2 atmosphere, and regularly checked for the absence of *Mycoplasma*.

4.1.2. Cell cytotoxicity assay

Cell survival was determined using the MTT assay (3–(4,5–dimethylthiazol–2–yl)–2,5–diphenyltetrazolium bromide; Sigma, Saint-Quentin Fallavier, France). The conversion of yellow water-soluble tetrazolium MTT into purple insoluble formazan is catalyzed by mitochondrial dehydrogenases and used to estimate the number of viable cells. In brief, cells were seeded in 96-well tissue culture plates at a density of 2×10^3 cells/well. After drug exposure, cells were incubated with 0.4 mg/ml MTT for 4 h at 37 °C. After



Scheme 4. Synthesis of benzoxazole and benzimidazole derivatives **20a**–**b**.

incubation, the supernatant was discarded, insoluble formazan precipitates were dissolved in 0.1 mL of DMSO and the absorbance was measured at 560 nm by use of a microplate reader (Thermo, France). Wells with untreated cells or with drug-containing medium without cells were used as positive and negative controls respectively. Everolimus and OZI027 were purchased from Selleck Chemicals (Munich, Germany).

4.1.3. Western blot analysis

Cells were lysed in buffer containing 50 mM HEPES (pH 7.6), 150 mM NaCl, 1% Triton X-100, 2 mM sodium vanadate, 100 mM NaF, and 0.4 mg/ml phenylmethylsulfonyl fluoride. Equal amounts of protein (30 μg/lane) were subjected to SDS-PAGE and transferred to nitrocellulose membranes. Membranes were blocked with 5% milk in 0.05% Tween 20/phosphate-buffered saline and then incubated with the primary antibody overnight. Membranes were then washed and incubated with the secondary antibody conjugated to horseradish peroxidase. Bands were visualized by using the enhanced chemiluminescence Western blotting detection system. Densitometric analysis was performed under conditions that yielded a linear response.

4.2. Chemistry

All reagents and solvents for synthesis were purchased from Sigma–Aldrich, Fluka, or Acros and used without further purification. Column chromatography was carried out on silica gel 60 (Merck, 70–230 mesh). ^{1}H NMR spectra at 300 MHz or 400 MHz and ^{13}C NMR spectra at 75 MHz or 100 MHz were recorded with Brucker spectrometers 300 and 400 with the deuterated solvent as the lock and residual solvent as the internal reference. All chemical shift values, coupling constants *J* and the multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad) are quoted in ppm, in Hz and in Hz, respectively. High resolution mass spectra (HRMS) were obtained using a Agilent Q-TOF (time of flight) 6520 and low resolution mass spectra using an Agilent MSD 1200 SL (ESI/APCI). Analytical RP-HPLC-MS was performed using a C18 column (30 mm × 1 mm; 1.9 μm) using the following parameters: (1) the solvent system A (acetonitrile) and B (0.05% TFA in H_2O); (2) the linear gradient $t = 0$ min with 98% B, $t = 5$ min with 5% B, $t = 6$ min with 5% B, $t = 7$ min with 98% B, and $t = 9$ min with 98% B; (3) flow rate of 0.3 mL/min; (4) column temperature 50 °C; (5) ratio of products determined by integration of spectra recorded at 210 or 254 nm; (6) ionization mode ESI.

4.2.1. General procedure for the Mannich reaction (Method A)

The secondary amine (2 eq) was added to an EtOH (0.1–0.2 M) solution of 5–hydroxy–benzofuran derivative (1 eq) and formaldehyde (37% in water, 2 eq). The solution was stirred at reflux (3 h–16 h) and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel or by recrystallization in EtOH.

4.2.2. 4–([1,4′–Bipiperidin]–1′–ylmethyl)–2–(2–chlorophenyl) benzofuran–5–ol (**6a**)

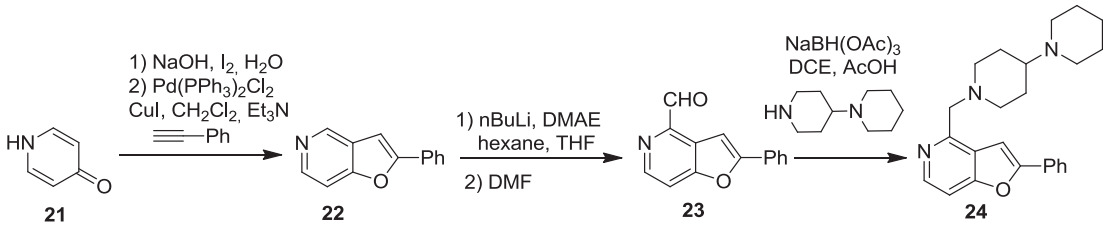
Using Method A, formaldehyde (37% in water, 54 μL, 0.7 mmol), 4–piperidinopiperidine (120 mg, 0.7 mmol) and 5–hydroxy–2–(2–chlorophenyl)benzofuran **5a** (86 mg, 0.3 mmol) gave 105 mg (70%) of **6a** as a white solid after recrystallization in ethanol: $R_f = 0.16$ (acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34–1.37 (m, 2H), 1.51–1.64 (m, 6H), 1.79 (d, $J = 12.8$ Hz, 2H), 2.06–2.12 (br m, 2H), 2.26 (t, $J = 11.6$ Hz, 1H), 2.40–2.45 (m, 4H), 3.06 (d, $J = 12.0$ Hz, 2H), 3.84 (s, NCH_2), 6.75 (d, $J = 8.8$ Hz, 1H), 7.16–7.32 (m, 4H), 7.40 (d, $J = 8.0$ Hz, 1H), 7.94 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 26.4, 29.7, 50.3, 53.2, 57.9, 62.3, 105.0, 110.4, 111.8, 114.5, 127.0, 128.4, 128.9, 129.0, 130.8, 131.0, 148.2, 152.2, 153.8, 1 peak is missing and believed to overlap with peaks nearby; HRMS (M + H^+)(ESI^+) 425.2007 [M + H^+] (calcd for $C_{25}H_{29}ClN_2O_2H^+$ 425.1990).

4.2.3. 4–([1,4′–Bipiperidin]–1′–ylmethyl)–2–(3–chlorophenyl) benzofuran–5–ol (**6b**)

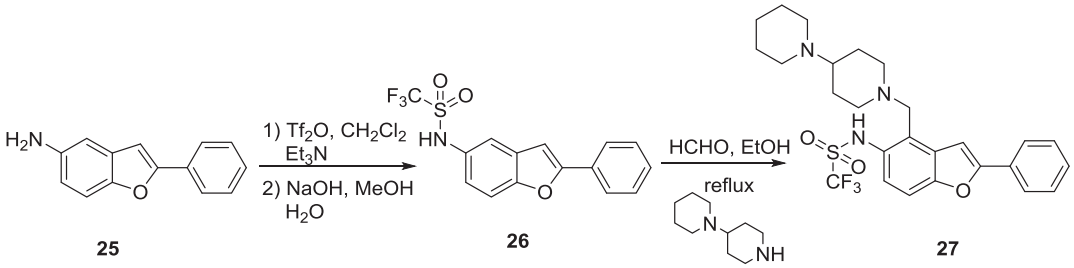
Using Method A, formaldehyde (37% in water, 56 μL, 0.7 mmol), 4–Piperidinopiperidine (121 mg, 0.7 mmol) and 5–hydroxy–2–(3–chlorophenyl)benzofuran **5b** (90 mg, 0.4 mmol) gave 90 mg (58%) of **6b** as a white solid after recrystalisation in ethanol: $R_f = 0.15$ (acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35–1.39 (m, 2H), 1.50–1.65 (m, 6H), 1.79 (d, $J = 12.4$ Hz, 2H), 2.06–2.11 (m, 2H), 2.28 (m, 1H), 2.42–2.45 (m, 4H), 3.05 (d, $J = 12.0$ Hz, 2H), 3.82 (s, NCH_2), 6.74 (d, $J = 8.8$ Hz, 1H), 6.86 (s, 1H), 7.21–7.31 (m, 3H), 7.62 (d, $J = 7.6$ Hz, 1H), 7.74 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 26.3, 27.9, 50.3, 53.2, 57.9, 62.3, 100.2, 110.6, 111.5, 114.3, 122.8, 124.8, 128.2, 128.3, 130.1, 132.3, 134.9, 149.1, 153.9, 154.7; HRMS (M + H^+)(ESI^+) 425.2003 [M + H^+] (calcd for $C_{25}H_{29}ClN_2O_3H^+$ 425.1990).

4.2.4. 4–([1,4′–Bipiperidin]–1′–ylmethyl)–2–(4–chlorophenyl) benzofuran–5–ol (**6c**)

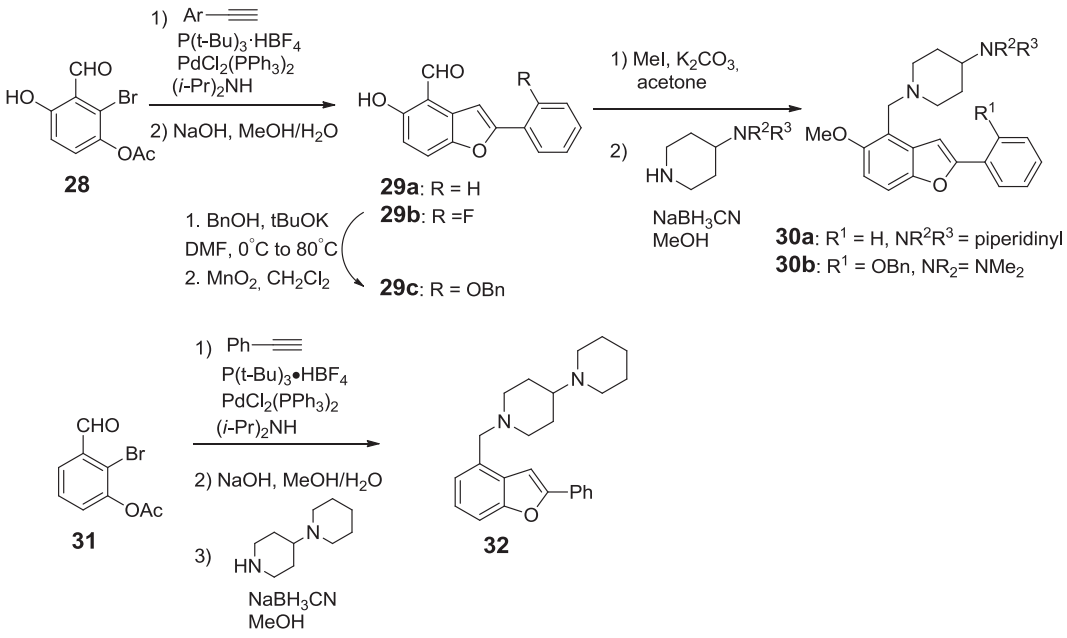
Using Method A, formaldehyde (37% in water, 62 μL, 0.8 mmol), 4–piperidinopiperidine (138 mg, 0.8 mmol) and 5–hydroxy–2–(4–chlorophenyl)benzofuran **5c** (100 mg, 0.4 mmol) gave 110 mg (63%) of **6c** as a white solid after recrystalisation in ethanol:



Scheme 5. Synthesis of the furopyridine derivative **24**.



Scheme 6. Synthesis of the bioisostere **27**.



Scheme 7. Synthesis of *O*-substituted derivatives **30a–b** and **32**.

$R_f = 0.12$ (acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.38 (m, 2H), 1.49–1.64 (m, 6H), 1.79 (d, $J = 12.8$ Hz, 2H), 2.05–2.11 (br m, 2H), 2.23–2.30 (m, 1H), 2.42–2.45 (m, 4H), 3.05 (d, $J = 12.0$ Hz, 2H), 3.81 (s, NCH_2), 6.72 (d, $J = 8.8$ Hz, 1H), 6.82 (s, 1H), 7.19–7.22 (m, 1H), 7.32 (d, $J = 8.6$ Hz, 2H), 7.67 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 26.2, 27.8, 50.2, 53.1, 57.8, 62.4, 99.5, 110.5, 111.4, 114.1, 126.0, 128.4, 129.0, 129.1, 134.2, 149.0, 153.9, 155.1; HRMS ($M + H^+$)(ESI^+) 425.2011 [$M + H^+$] (calcd for $C_{25}H_{29}ClN_2O_3H^+$ 425.1990).

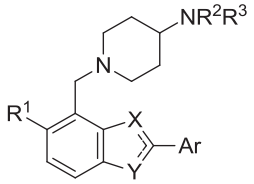
4.2.5. 4–([1,4′–Bipiperidin]–1′–ylmethyl)–2–(3,4–dichlorophenyl)benzofuran–5–ol (**6d**)

Using Method A, formaldehyde (37% in water, 55 μL, 0.7 mmol), 4–piperidinopiperidine (118 mg, 0.7 mmol) and 5–hydroxy–2–(3,4–dichlorophenyl)benzofuran **5d** (100 mg, 0.35 mmol) gave 95 mg (73%) of **6d** as a white solid after column (acetone): $R_f = 0.14$ (acetone); IR (cm^{-1}) 2933, 2809, 1602, 1498, 1443, 1145, 1105; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44–1.48 (m, 2H), 1.59–1.72 (m, 6H), 1.88 (d, $J = 12.8$ Hz, 2H), 2.13–2.19 (br m, 2H), 2.32–2.38 (m, 1H), 2.50–2.53 (m, 4H), 3.14 (d, $J = 12.0$ Hz, 2H), 3.88 (s, NCH_2), 6.83 (d, $J = 8.8$ Hz, 1H), 6.93 (s, 1H), 7.29 (m, 1H), 7.49 (d, $J = 8.4$ Hz, 1H), 7.63 (dd, $J = 2.0$, 8.4 Hz, 1H), 7.90 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 26.6, 28.1, 50.5, 53.4, 58.0, 62.4, 100.7, 110.8, 111.7, 114.8, 124.0, 126.6, 128.4, 130.7, 131.0, 132.3, 133.3, 149.3, 153.8, 154.2; HRMS ($M + H^+$)(ESI^+) 459.16148 [$M + H^+$] (calcd for $C_{25}H_{28}Cl_2N_2O_2H^+$ 459.16006).

4.2.6. 4–([1,4′–Bipiperidin]–1′–ylmethyl)–2–(2–methoxyphenyl) benzofuran–5–ol (**6e**)

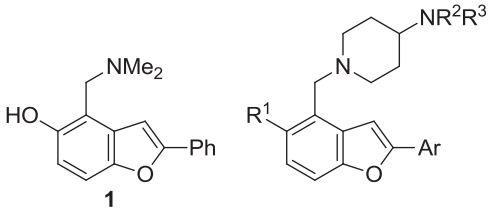
Using Method A, formaldehyde (37% in water, 64 μL, 0.8 mmol), 4–piperidinopiperidine (71 mg, 0.4 mmol) and 5–hydroxy–2–(2–

Table 1
Cytotoxicity of benzofuran derivatives in SQ20B cancer cells (72 h treatment).



cpd	R^1	Ar	X	Y	NR^2R^3	IC50 (μM)
2	OH	Ph	CH	O	Piperidine	1.4 ± 0.24
6a	OH	2-Cl-Ph	CH	O	Piperidine	2.6 ± 0.49
6b	OH	3-Cl-Ph	CH	O	Piperidine	0.92 ± 0.21
6c	OH	4-Cl-Ph	CH	O	Piperidine	0.86 ± 0.44
6d	OH	3,4-Cl_2-Ph	CH	O	Piperidine	2.3 ± 0.47
6e	OH	2-OMe-Ph	CH	O	Piperidine	1.3 ± 0.51
6f	OH	3-OMe-Ph	CH	O	Piperidine	2.0 ± 0.33
6g	OH	4-OMe-Ph	CH	O	Piperidine	0.85 ± 0.28
6h	OH	2,6-$(OMe)_2$-Ph	CH	O	Piperidine	1.1 ± 0.44
6i	OH	2-Furyl	CH	O	Piperidine	4.0 ± 1.4
6j	OH	2-Thiophenyl	CH	O	Piperidine	2.7 ± 0.63
6k	OH	1-Naphtyl	CH	O	Piperidine	0.86 ± 0.08
6l	OH	2-Naphtyl	CH	O	Piperidine	2.8 ± 0.73
14	OH	Ph	CMe	O	Piperidine	1.2 ± 0.14
17d	OH	Ph	C–COOEt	O	Piperidine	1.5 ± 0.22
17e	OH	Ph	C–CH_2OH	O	Piperidine	3.4 ± 0.38
20a	OH	Ph	N	O	Piperidine	6.5 ± 0.56
10	OH	Ph	O	CH	Piperidine	11 ± 2.7
20b	OH	Ph	N	NH	Piperidine	21 ± 5.2
17a	OH	Ph	CH	NMe	Piperidine	19 ± 4.5
17b	OH	H	CH	NBn	Piperidine	17 ± 4.9
14c	OH	H	C-Ph	O	Piperidine	11 ± 3.6
24	2-Phenyl-furo[3,2-*c*]pyridine				Piperidine	18 ± 4.2
27	NHTf	Ph	CH	O	Piperidine	2.1 ± 0.44
8	OTf	Ph	CH	O	Piperidine	2.8 ± 0.28
32	H	Ph	CH	O	Piperidine	7.5 ± 2.1
7g	OH	4-OMe-Ph	CH	O	NMe_2	1.2 ± 0.38

Table 2
Cytotoxicity of benzofuran derivatives in SQ20B cancer cells (72 h treatment).



cpd	R^1	Ar	NR^2R^3	IC50 (μM)
RAD001 (everolimus)				7.3 ± 3.1
1	OH			32 ± 1.7
2	OH	Ph	Piperidine	2.5 ± 1.3
6g	OH	4-OMe-Ph	Piperidine	0.72 ± 0.48
7g	OH	4-OMe-Ph	NMe_2	1.5 ± 0.9
6m	OH	2-OBn-Ph	Piperidine	0.38 ± 0.22
30a	OMe	Ph	Piperidine	2.5 ± 1.7
30b	OMe	2-OBn-Ph	NMe_2	0.46 ± 0.25

methoxyphenyl)benzofuran **5e** (100 mg, 0.4 mmol) gave 105 mg (60%) of **6e** as a white solid after recrystalisation in ethanol: R_f = 0.36 (acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46–1.78 (m, 2H), 1.61–1.74 (m, 6H), 1.88 (d, J = 12.4 Hz, 2H), 2.17–2.23 (br m, 2H), 2.37 (t, J = 11.2 Hz, 1H), 2.52–2.55 (m, 4H), 3.17 (d, J = 11.6 Hz, 2H), 3.95 (s, NCH_2), 4.04 (s, OCH_3), 6.80 (d, J = 8.4 Hz, 1H), 7.02–7.11 (m, 2H), 7.28–7.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 26.4, 27.9, 50.1, 53.2, 55.5; 57.9, 62.4, 104.0, 110.1, 111.0, 111.5, 113.5, 119.4, 120.9, 127.1, 129.1, 129.2, 147.9, 152.5, 153.5, 156.3; HRMS (M + H^+)(ESI^+) 421.2503 [M + H^+] (calcd for $C_{26}H_{32}N_2O_3H^+$ 421.2485).

4.2.7. 4–([1,4′–Bipiperidin]–1′–ylmethyl)–2–(3–methoxyphenyl) benzofuran–5–ol (**6f**)

Using Method A, formaldehyde (37% in water, 54 μL, 0.7 mmol), 4–piperidinopiperidine (120 mg, 0.7 mmol) and 5–hydroxy–2–(3–methoxyphenyl)benzofuran **5f** (85 mg, 0.35 mmol) gave 120 mg (82%) of **6f** as a white solid after flash column chromatography on silica gel: R_f = 0.33 (acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.38 (m, 2H), 1.49–1.65 (m, 6H), 1.79 (d, J = 12.4 Hz, 2H), 2.06–2,12 (br m, 2H), 2.23–2.30 (m, 1H), 2.42–2.45 (m, 4H), 3.07 (d, J = 12.4 Hz, 2H), 3.81 (s, NCH_2), 3.82 (s, OCH_3), 6.71 (d, J = 8.8 Hz, 1H), 6.80–6.83 (m, 2H), 7.19–7.35 (m, 3H), 8.05 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 26.4, 27.9, 50.1, 53.2, 55.5; 57.9, 62.4, 104.0, 110.1, 111.0, 111.5, 113.5, 119.4, 120.9, 127.1, 129.1, 129.2, 147.9, 152.5, 153.5, 156.3; HRMS (M + H^+)(ESI^+) 421.2503 [M + H^+] (calcd for $C_{26}H_{32}N_2O_3H^+$ 421.2485).

4.2.8. 4–([1,4′–Bipiperidin]–1′–ylmethyl)–2–(4–methoxyphenyl) benzofuran–5–ol (**6g**)

Using Method A, formaldehyde (37% in water, 54 μL, 0.7 mmol), 4–piperidinopiperidine (120 mg, 0.7 mmol) and 5–hydroxy–2–(4–methoxyphenyl)benzofuran **5g** (85 mg, 0.35 mmol) gave 105 mg (72%) of **6g** as a white solid after flash column chromatography on silica gel: R_f = 0.37 (acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34–1.37 (m, 2H), 1.48–1.60 (m, 6H), 1.77 (d, J = 12.8 Hz, 2H), 2.04–2.10 (br m, 2H), 2.23–2.30 (m, 1H), 2.41–2.45 (m, 4H),

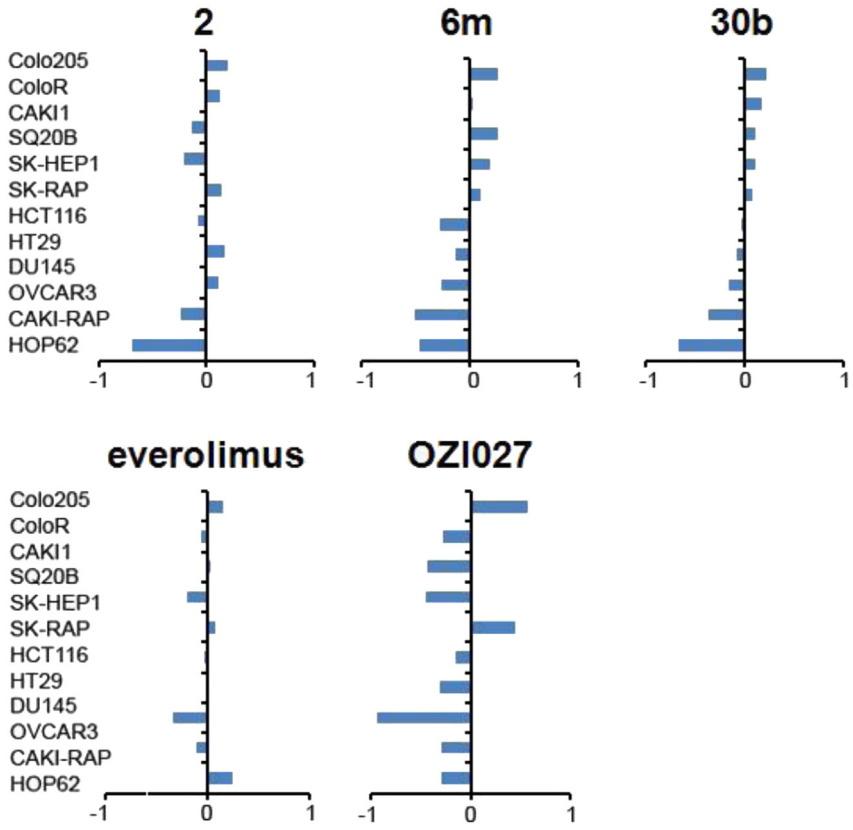


Fig. 2. Cytotoxicity of benzofuran derivatives in a panel of cancer cell lines. The indicated values are calculated as follows: log(IC_{50} individual cell line) - mean (log IC_{50}). Negative values indicate that the cell line is more sensitive than the average, whereas positive values indicate that the cell line is more resistant than the average.

3.05 (d, J = 12.0 Hz, 2H), 3.77 (s, OCH_3), 3.80 (s, NCH_2), 6.66–6.70 (m, 2H), 6.88 (d, J = 9.0 Hz, 2H), 7.18–7.20 (d, J = 8.8 Hz, 1H), 7.67 (d, J = 9.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 26.4, 27.9, 50.3, 53.1, 55.4; 57.9, 62.3, 97.5, 110.3, 111.2, 113.1, 114.2, 123.5, 126.3, 148.8, 153.7, 156.4, 159.9, 1 carbon peak is missing and believed to overlap with peaks nearby; HRMS (M + H^+)(ESI^+) 421.2502 [M + H^+] (calcd for $C_{26}H_{32}N_2O_3H^+$ 421.2485).

*4.2.9. 4–([1,4′–Bipiperidin]–1′–ylmethyl)–2–(2,4–methoxyphenyl)benzofuran–5–ol (**6h**)*

Using Method A, formaldehyde (37% in water, 140 μL, 1.5 mmol), 4–piperidinopiperidine (125 mg, 0.5 mmol) and 5–hydroxy–2–(2,4–dimethoxyphenyl)benzofuran **5h** (200 mg, 0.75 mmol) gave 195 mg (56%) of **6h** as a white solid after column (acetone): R_f = 0.14 (acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34–1.36 (m, 2H), 1.48–1.60 (m, 6H), 1.76 (d, J = 12.4 Hz, 2H), 2.04–2.10 (m, 2H), 2.22–2.28 (m, 1H), 2.41–2.44 (m, 4H), 3.04 (d, J = 12.0 Hz, 2H), 3.77 (s, OCH_3), 3.82 (s, NCH_2), 3.90 (s, OCH_3), 6.47 (d, J = 2.0 Hz, 1H), 6.52 (dd, J = 2.0, 8.4 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 6.97 (s, 1H), 7.18 (d, J = 9.6 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 26.4, 27.9, 50.2, 53.1, 55.5, 55.6 (2 OCH_3), 57.9, 62.4, 98.8, 102.0, 104.9, 109.8, 111.3, 112.9, 128.0, 129.3, 147.7, 152.8, 153.5, 157.6, 160.9, 1 carbon peak is missing and believed to overlap with peaks nearby; HRMS (M + H^+)(ESI^+) 451.2608 [M + H^+] (calcd for $C_{27}H_{34}N_2O_4H^+$ 451.2591).

*4.2.10. 4–([1,4′–Bipiperidin]–1′–ylmethyl)–2–(furan–2–yl) benzofuran–5–ol (**6i**)*

Using Method A, formaldehyde (37% in water, 130 μL, 1.6 mmol), 4–piperidinopiperidine (270 mg, 1.6 mmol) and 5–hydroxy–2–(furan–2–yl)benzofuran **5i** (200 mg, 0.8 mmol) gave 170 mg (56%) of **6i** as a white solid after flash chromatography on silica gel (acetone): R_f = 0.15 (acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44–1.46 (m, 2H), 1.58–1.68 (m, 6H), 1.85 (d, J = 12.8 Hz, 2H), 2.11–2.17 (m, 2H), 2.30–2.36 (m, 1H), 2.48–2.53 (br m, 4H), 3.12 (d, J = 11.6 Hz, 2H), 3.87 (s, NCH_2), 6.51 (dd, J = 1.6, 3.2 Hz, 1H), 6.76–6.80 (s, 3H), 7.27 (d, J = 9.2 Hz, 1H), 7.49 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 26.4, 27.9, 50.3, 53.1, 57.8, 62.3, 99.0, 107.4, 110.4, 111.5, 111.7, 113.8, 128.1, 142.9, 146.3, 148.4, 148.6, 154.0; LC–MS (M + H^+)(ESI^+) 381.21877 [M + H^+] (calcd for $C_{23}H_{28}N_2O_2SH^+$ 381.21726).

*4.2.11. 4–([1,4′–Bipiperidin]–1′–ylmethyl)–2–(thiophen–2–yl) benzofuran–5–ol (**6j**)*

Using Method A, formaldehyde (37% in water, 200 μL, 2.1 mmol), 4–piperidinopiperidine (358 mg, 2.1 mmol) and 5–hydroxy–2–(thiophen–2–yl)benzofuran **5j** (230 mg, 1.1 mmol) gave 130 mg (50%) of **6j** as a white solid after flash chromatography on silica gel (acetone): R_f = 0.15 (acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43–1.47 (m, 2H), 1.57–1.71 (m, 6H), 1.86 (d, J = 12.4 Hz, 2H), 2.10–2.18 (br m, 2H), 2.30–2.36 (m, 1H), 2.48–2.54 (br m, 4H), 3.12 (d, J = 12.4 Hz, 2H), 3.56 (s, NCH_2), 6.75 (s, 1H), 6.79 (d, J = 8.4 Hz, 1H), 7.09 (dd, J = 3.6, 5.2 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.32 (dd, J = 1.2, 5.2 Hz, 1H), 7.45 (dd, J = 1.2, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 26.4, 27.9, 50.3, 53.1, 57.9, 62.3, 99.0, 110.3, 111.3, 113.7, 124.4, 125.6, 127.9, 128.5, 133.5, 148.6, 151.6, 153.9; LC–MS (M + H^+)(ESI^+) 397.19574 [M + H^+] (calcd for $C_{23}H_{28}N_2O_2SH^+$ 397.19442).

*4.2.12. 4–([1,4′–Bipiperidin]–1′–ylmethyl)–2–(naphthalen–1–yl)benzofuran–5–ol (**6k**)*

Using Method A, formaldehyde (37% in water, 108 μL, 1.4 mmol), 4–piperidinopiperidine (240 mg, 1.4 mmol) and 5–hydroxy–2–

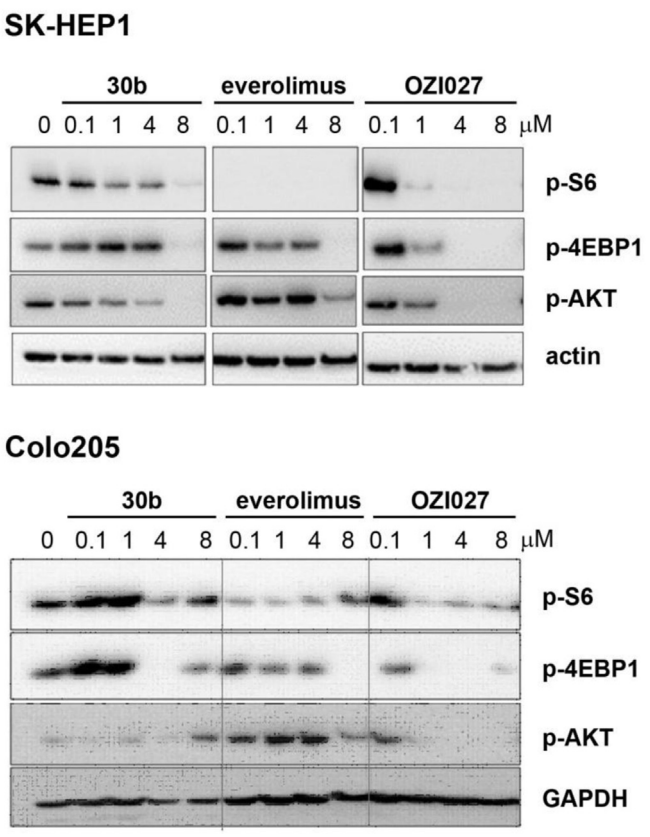


Fig. 3. Inhibition of mTORC1 and Akt signaling. SK-HEP1 and Colo205 cells were treated with **30b**, everolimus or OZI027 for 24 h and were immunoblotted with antibodies against p-S6, p-4EBP1 (downstream targets of mTORC1) and p-Akt (S473).

(naphthalen−1−yl)benzofuran **5k** (185 mg, 0.7 mmol) gave 155 mg (50%) of **6k** as a yellow solid after flash column chromatography on silica gel: $R_f = 0.17$ (acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40−1.52 (m, 2H), 1.59−1.77 (m, 6H), 1.90 (d, J = 12.8 Hz, 2H), 2.17−2.23 (m, 2H), 2.33−2.39 (m, 1H), 2.50−2.56 (br m, 4H), 3.18 (d, J = 12.0 Hz, 2H), 3.97 (s, NCH_2), 6.87 (d, J = 8.8 Hz, 1H), 6.97 (s, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.54−7.60 (m, 3H), 7.86−7.94 (m, 3H), 8.49 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 26.5, 28.0, 50.3, 53.2, 58.0, 62.3, 103.6, 110.6, 111.5, 113.8, 125.3, 125.6126.1, 126.8, 127.2, 128.4, 128.5, 128.6, 129.4, 130.7, 134.0, 149.1, 153.8, 156.1; HRMS (M + H$^+$)(ESI$^+$) 441.25504 [M + H$^+$] (calcd for $C_{29}H_{32}N_2O_2H^+$ 441.25365).

*4.2.13. 4−([1,4′−Bipiperidin]−1′−ylmethyl)−2−(naphthalen−2−yl)benzofuran−5−ol (**6l**)*

Using Method A, formaldehyde (37% in water, 75 μL, 0.8 mmol), 4−piperidinopiperidine (134 mg, 0.8 mmol) and 5−hydroxy−2−(naphthalen−2−yl)benzofuran **5l** (100 mg, 0.4 mmol) gave 65 mg (50%) of **6l** as a white solid after recrystallization in ethanol: R_f = 0.16 (acetone); IR (cm^{-1}) 2938, 2814, 1599, 1444, 1419, 1101, 788; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45−1.49 (m, 2H), 1.59−1.72 (m, 6H), 1.90 (d, J = 12.4 Hz, 2H), 2.17−2.11 (br m, 2H), 2.33−2.41 (m, 1H), 2.51−2,57 (br m, 4H), 3.18 (d, J = 12.4 Hz, 2H), 3.95 (s, NCH_2), 6.84 (d, J = 8.8 Hz, 1H), 7.05 (s, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.49−7.56 (m, 2H), 7.85−7.96 (m, 4H), 8.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 26.4, 27.8, 50.3, 53.2, 57.9, 62.4, 99.7, 110.5, 111.4, 113.9, 122.7, 123.7, 126.4, 126.6, 127.8, 127.9, 128.4, 128.5, 128.6, 133.2, 133.5, 149.1, 153.8, 156.3; HRMS (M + H$^+$)(ESI$^+$) 441.25497 [M + H$^+$] (calcd for $C_{29}H_{32}N_2O_2H^+$ 441.25365).

*4.2.14. 4−([1,4′−Bipiperidin]−1′−ylmethyl)−2−(2−benzyloxy) benzofuran−5−ol (**6m**)*

Using Method A, formaldehyde (37% in water, 47 μL, 0.5 mmol), 4−piperidinopiperidine (84 mg, 0.5 mmol) and 5−hydroxy−2−(2−benzyloxy)benzofuran **5m** (80 mg, 0.25 mmol) gave 70 mg (56%) of **6m** as a colorless oil after column (acetone): R_f = 0.20 (acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45−1.49 (m, 2H), 1.61−1.73 (m, 6H), 1.88 (d, J = 12.4 Hz, 2H), 2.05−2.11 (br m, 2H), 2.33−2.41 (m, 1H), 2.53−2.56 (m, 4H), 3.12 (d, J = 12.0 Hz, 2H), 3.75 (s, NCH_2), 5.28 (s, OCH_2), 6.79 (d, J = 8.8 Hz, 1H), 7.06−7.13 (m, 2H), 7.24 (s, 1H), 7.28−7.34 (m, 2H), 7.40−7.48 (m, 3H), 7.54−7.58 (m, 2H), 8.07 (dd, J = 1.6, 8.0 Hz, H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 26.3, 27.8, 50.2, 53.2, 57.7, 62.4, 70.6 (OCH_2), 104.5, 110.1, 111.5, 112.4, 113.5, 119.8, 121.2, 127.0, 127.7, 128.2, 128.7, 129.1, 129.1, 136.8, 147.9, 152.4, 153.4, 155.5; HRMS (M + H$^+$)(ESI$^+$) 405.25482 [M + H$^+$] (calcd for $C_{26}H_{32}N_2O_2H^+$ 405.25365).

*4.2.15. 4−((4−(Dimethylamino)piperidin−1−yl)methyl)−2−(4−methoxyphenyl)benzofuran−5−ol (**7g**)*

Using Method A, formaldehyde (37% in water, 70 μL, 0.7 mmol), N,N−dimethylpiperidin−4−amine (85 mg, 0.7 mmol) and 5−hydroxy−2−(4−methoxyphenyl)benzofuran (**5g**) (80 mg, 0.35 mmol) gave 90 mg (72%) of **7g** as a white solid after flash chromatography on silica gel (acetone): R_f = 0.15 (acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54−1.60 (m, 2H), 1.77−1.82 (m, 2H), 2.08−2.23 (m, 9H), 3.05 (d, J = 12.0 Hz, 2H), 3.79 (s, OCH_3), 3.82 (s, NCH_2), 6.66−6.70 (m, 2H), 6.89 (d, J = 8.8 Hz, 2H), 7.18−7.22 (m, 1H), 7.69 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 41.6, 52.7, 55.4 (OCH_3), 57.9 (CH_2N), 61.8, 110.3, 111.1, 113.1, 114.2, 114.3, 123.5, 126.3, 128.8, 148.7, 153.7, 156.4, 159.9; LC−MS (M + H$^+$)(ESI$^+$) 381.21877 [M + H$^+$] (calcd for $C_{23}H_{28}N_2O_3H^+$ 381.21726).

*4.2.16. 4-([1,4′-Bipiperidin]-1′-ylmethyl)-2-phenylbenzofuran-5-yl trifluoromethanesulfonate (**8**)*

At 0 °C, Tf_2O (97 μL, 0.58 mmol) was added to a toluene (1 mL) solution of 5-hydroxybenzofuran derivative **2** (125 mg, 0.32 mmol) and an aqueous solution of K_3PO_4 (30% w/w, 0.7 mL, 0.96 mmol). The biphasic solution was stirred vigorously at room temperature (6 h). H_2O was added and the layers were separated. The aqueous layer was washed with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried and concentrated under vacuum to obtain 180 mg (33%) of a white solid corresponding to the trifluoromethanesulfonate **8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44−1.44 (m, 2H), 1.56−1.68 (m, 6H), 1.78 (d, J = 12.0 Hz, 2H), 2.04 (t, J = 11.8 Hz, 2H), 2.47−2.50 (m, 5H), 2.90 (d, J = 12.0 Hz, 2H), 3.70 (s, CH_2N), 7.07 (d, J = 8.8 Hz, 1H), 7.16−7.21 (m, 2H), 7.32−7.42 (m, 3H), 7.81 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 25.0, 27.0, 50.3, 52.9, 54.7, 63.5, 100.8, 111.2, 117.3, 118.7 (q, J = 316.8 Hz, CF_3), 124.5, 125.2, 128.9, 129.3, 129.7, 131.3, 144.4, 153.0, 158.1; MS (M + H$^+$)(ESI$^+$) 523.2 [M + H$^+$] (calcd for $C_{26}H_{29}F_3N_2O_4SH^+$ 523.2).

*4.2.17. 7−([1,4′−Bipiperidin]−1′−ylmethyl)−2−phenylbenzofuran−6−ol (**10**)*

Employing Method A, using 2−phenylbenzofuran−6−ol (**S-1**) (65 mg, 0.31 mmol), 4−piperidinopiperidine (104 mg, 0.62 mmol), formaldehyde (50 μL, 0.62 mmol, 40% in water) gave 40 mg (33%) of a white solid corresponding to the **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43−1.49 (m, 2H), 1.60−1.74 (m, 6H), 1.89 (d, J = 12.8 Hz, 2H), 2.25 (t, J = 12.2 Hz, 2H), 2.34−2.41 (m, 1H), 2.50−2.55 (m, 4H), 3.18 (d, J = 12.2 Hz, 2H), 4.10 (s, CH_2N), 6.79 (d, J = 8.4 Hz, 1H), 6.94 (s, 1H), 7.28−7.34 (m, 2H), 7.44 (t, J = 7.8 Hz, 2H), 7.80 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 26.4, 28.0, 50.3, 53.2, 54.4, 62.3, 101.7, 104.7, 113.0, 119.9, 121.1, 124.3, 127.9, 128.7, 130.9, 153.7, 154.3, 156.3; HRMS (M + H$^+$)(ESI$^+$) 391.23800 [M + H$^+$] (calcd for $C_{25}H_{30}N_2O_2H^+$ 391.23855).

*4.2.18. 4–([1,4′–bipiperidin]–1′–ylmethyl)–3–methyl–2–phenylbenzofuran–5–ol (**14**)*

Employing Method A, using benzofuran derivative **13** (70 mg, 0.31 mmol), 4–piperidinopiperidine (105 mg, 0.62 mmol), formaldehyde (48 μL, 0.62 mmol, 40% in water) gave 65 mg (52%) of **14** as a white solid after column (acetone): $R_f = 0.18$ (Acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46–1.49 (m, 2H), 1.60–1.75 (m, 6H), 1.91 (d, $J = 12.8$ Hz, 2H), 2.16–2.23 (m, 2H), 2.38–2.45 (m, 1H), 2.51–2.56 (m, 7H), 3.19 (d, $J = 11.6$ Hz, 2H), 4.16 (s, CH_2N), 6.82 (d, $J = 8.8$ Hz, 1H), 7.27–7.31 (m, 1H), 7.39 (t, $J = 7.4$ Hz, 1H), 7.49 (t, $J = 7.4$ Hz, 2H), 7.69 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 13.0 (CH_3), 24.7, 26.3, 27.8, 50.2, 53.1, 56.5, 62.4 (NCH), 110.6, 110.9, 113.0, 114.0, 127.8, 128.1, 128.5, 131.2, 148.5, 154.2, 2 peaks are missing and believed to overlap nearby; HRMS (M + H$^+$)(ESI$^+$) 405.2557 [M + H$^+$] (calcd for $C_{26}H_{32}N_2O_2H^+$ 405.2536).

*4.2.19. 4–([1,4′–Bipiperidin]–1′–ylmethyl)–1–methyl–2–phenyl–1H–indol–5–ol (**17a**)*

Employing Method A, using 5–hydroxy–1–methyl–2–phenyl–1H–indole (**16a**) (25 mg, 0.11 mmol), 4–piperidinopiperidine (21 mg, 0.22 mmol), formaldehyde (18 μL, 0.22 mmol, 40% in water) gave 10 mg (33%) of a brown solid corresponding to the **17a**: $R_f = 0.48$ (Acetone/MeOH 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44–1.49 (m, 2H), 1.57–1.71 (m, 6H), 1.87 (d, $J = 12.8$ Hz, 2H), 2.15 (t, $J = 11.2$ Hz, 2H), 2.36–2.42 (m, 1H), 2.52–2.56 (m, 4H), 3.18 (d, $J = 12.6$ Hz, 2H), 3.70 (s, NCH_3), 3.95 (s, CH_2N), 6.40 (s, 1H), 6.83 (d, $J = 8.7$ Hz, 1H), 7.17 (d, $J = 8.7$ Hz, 1H) 7.40–7.53 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 24.9, 26.3, 28.5, 31.6 (CH_3), 49.7, 51.3, 57.7, 62.3, 99.7, 110.6, 112.9, 128.9, 129.2, 129.6, 130.3, 134.3, 134.8143.3, 152.1, 1 carbon peak is missing and believed to overlap with peaks nearby; HRMS (M + H$^+$)(ESI$^+$) 404.2702 [M + H$^+$] (calcd for $C_{26}H_{33}N_3OH^+$ 404.2696).

*4.2.20. 4-([1,4′-Bipiperidin]-1′-ylmethyl)-1-benzyl-1H-indol-5-ol (**17b**)*

Using Method A with formaldehyde (80 μL, 0.90 mmol), **16b** (100 mg, 0.45 mmol) and 4–piperidinopiperidine (152 mg, 0.90 mmol), **17b** [23] (79 mg, 44%) was obtained as a white solid after purification by column chromatography on silica gel using CH_2Cl_2/MeOH (7/3) as solvent; $R_f = 0.43$ (EtOAc/MeOH 8/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47–1.51 (m, 2H), 1.62–1.75 (m, 6H), 1.91 (d, $J = 12.3$ Hz, 2H), 2.13–2.21 (m, 2H), 2.40–2.60 (m, 5H), 3.16 (d, $J = 12.0$ Hz, 2H), 3.96 (s, NCH3), 5.24 (s, NCH2), 6.38 (d, $J = 3.0$ Hz, 1H), 6.75 (d, $J = 8.7$ Hz, 1H), 7.04–7.16 (m, 4H), 7.25–7.33 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 26.2, 27.7, 50.2, 53.1, 57.8, 62.2, 70.5, 101.6, 110.6, 111.7, 113.6, 126.8, 127.4, 128.2, 128.6, 140.7, 149.1, 153.6, 159.4.

*4.2.21. 4–([1,4′–Bipiperidin]–1′–ylmethyl)–3–phenylbenzofuran–5–ol (**17c**)*

Using Method A, formaldehyde (37% in water, 205 μL, 2.2 mmol), 4–piperidinopiperidine (370 mg, 2.2 mmol) and 5–hydroxy–3–phenylbenzofuran (**16c**) [24] (230 mg, 1.1 mmol) gave 170 mg (56%) of **17c** as a white solid after flash chromatography on silica gel (acetone): $R_f = 0.16$ (acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40–1.46 (m, 2H), 1.54–1.63 (m, 6H), 1.78 (d, $J = 12.4$ Hz, 2H), 1.88 (m, 2H), 2.21–2.29 (m, 1H), 2.45–2.49 (m, 4H), 3.01 (d, $J = 12.0$ Hz, 2H), 3.59 (s, NCH_2), 6.87 (d, $J = 8.8$ Hz, 1H), 7.33–7.48 (s, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 26.4, 27.7, 50.2, 52.7, 56.3, 62.2, 111.0, 112.8, 114.3, 122.5, 125.9, 127.7, 128.2, 130.2, 133.8, 143.0, 154.7.

*4.2.22. Ethyl 4–([1,4′–bipiperidin]–1′–ylmethyl)–5–hydroxy–2–phenylbenzofuran–3–carboxylate (**17d**)*

Employing Method A, using ethyl 5–hydroxy–2–phenylbenzofuran–3–carboxylate [25] (**16d**) (1.00 g, 3.5 mmol), 4–piperidinopiperidine (1.2 g, 7.1 mmol), formaldehyde (535 μL, 7.1 mmol, 40% in water) gave 1.20 g (75%) of **17d** as an orange oil after column (acetone): $R_f = 0.32$ (Acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, $J = 7.2$ Hz, OCH_2CH_3), 1.42–1.48 (m, 2H), 1.57–1.73 (m, 6H), 1.86 (d, $J = 12.9$ Hz, 2H), 2.14–2.23 (m, 2H), 2.31–2.36 (m, 1H), 2.39–2.53 (m, 4H), 3.13 (d, $J = 12.0$ Hz, 2H), 3.99 (s, CH_2N), 4.35 (q, $J = 7.2$ Hz, OCH_2CH_3), 6.82 (d, $J = 8.8$ Hz, 1H), 7.32 (d, $J = 8.8$ Hz, 1H), 7.43–7.47 (m, 3H), 7.72–7.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 24.8, 26.4, 27.9, 50.3, 53.0, 57.2, 61.4, 62.2, 110.1, 110.8, 112.3, 115.2, 125.4, 127.9, 128.3, 129.5, 130.0, 148.2, 155.4, 156.9, 166.3; HRMS (M + H$^+$)(ESI$^+$) 463.2607 [M + H$^+$] (calcd for $C_{28}H_{34}N_2O_4H^+$ 463.2591).

*4.2.23. 4–([1,4′–Bipiperidin]–1′–ylmethyl)–3–(hydroxymethyl)–2–phenylbenzofuran–5–ol (**17e**)*

A THF solution (3 mL) of ethyl 4–([1,4′–bipiperidin]–1′–ylmethyl)–5–hydroxy–2–phenylbenzofuran–3–carboxylate (**17d**) (140 mg, 0.3 mmol) was added dropwisely to a THF suspension (10 mL) of $LiAlH_4$ (80 mg, 2.1 mmol). The mixture was stirred at room temperature (3 h). 625 μL of H_2O was added dropwisely at 0 °C followed by 625 μL of a 1 M NaOH solution and 625 μL of H_2O. CH_2Cl_2 (10 mL) was added and the mixture was filtered. The filtrate was concentrated under vacuum to obtain the alcohol **17e** (125 mg, quant.) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42–1.48 (m, 2H), 1.57–1.73 (m, 6H), 1.85 (d, $J = 12.0$ Hz, 2H), 2.20–2.27 (m, 2H), 2.35–2.42 (m, 1H), 2.51–2.54 (m, 4H), 3.14 (d, $J = 12.0$ Hz, 2H), 4.19 (s, CH_2N), 4.8 (s, OCH_2), 6.83 (d, $J = 8.6$ Hz, 1H), 7.31 (d, $J = 8.6$ Hz, 1H), 7.42–7.53 (m, 3H), 7.72–7.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 26.0, 29.7, 50.1, 52.6, 56.0, 62.4, 70.6, 110.8, 113.2, 114.2, 115.1, 127.5, 128.1, 128.7, 129.0, 130.3, 148.8, 154.1, 155.0; HRMS (M + H$^+$)(ESI$^+$) 421.2510 [M + H$^+$] (calcd fo $C_{26}H_{32}N_2O_3H^+$ 421.2485).

*4.2.24. 4–([1,4′–Bipiperidin]–1′–ylmethyl)–2–phenylbenzo[d]oxazol–5–ol (**20a**)*

Employing Method A, using 5–hydroxy–2–phenylbenzoxazole (**19a**) (100 mg, 0.47 mmol), 4–piperidinopiperidine (160 mg, 0.95 mmol), formaldehyde (72 μL, 0.95 mmol, 40% in water) gave 140 mg (75%) of a white solid corresponding to the **20a**: $R_f = 0.10$ (acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44–1.47 (m, 2H), 1.58–1.74 (m, 6H), 1.90 (d, $J = 13.2$ Hz, 2H), 2.24–2.40 (m, 3H), 2.52–2.55 (m, 4H), 3.16 (d, $J = 12.0$ Hz, 2H), 4.19 (s, CH_2N), 6.85 (d, $J = 8.8$ Hz, 1H), 7.35 (d, $J = 8.8$ Hz, 1H), 7.51–7.54 (m, 3H), 8.21–8.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 26.4, 28.0, 50.3, 53.1, 55.7, 62.2, 109.3, 111.7, 113.8, 127.5, 127.5, 128.8, 131.2, 141.3, 144.3, 155.4, 163.2; HRMS (M + H$^+$)(ESI$^+$) 392.23389[M + H$^+$] (calcd for $C_{24}H_{29}N_3O_2H^+$ 392.23380).

*4.2.25. 4–([1,4′–Bipiperidin]–1′–ylmethyl)–2–phenyl–1H–benzo[d]imidazol–5–ol (**20b**)*

Employing Method A, using benzimidazole tautomers (**19b**) (105 mg, 0.50 mmol), 4–piperidinopiperidine (168 mg, 1.00 mmol), formaldehyde (76 μL, 1.00 mmol, 40% in water) gave 60 mg (31%) of a white solid corresponding to the **20b**: $R_f = 0.05$ (acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43–1.46 (m, 2H), 1.58–1.71 (m, 6H), 1.83 (d, $J = 11.6$ Hz, 2H), 2.14–2.34 (m, 3H), 2.48–2.53 (m, 4H), 3.11 (d, $J = 9.2$ Hz, 2H), 4.09–4.33 (s, CH_2N), 6.80 (d, $J = 8.8$ Hz, 1H), 7.05–7.29 (br m, 1H), 7.42–7.47 (m, 3H), 7.98–8.08 (m, 2H); HRMS (M + H$^+$)(ESI$^+$) 391.24932 [M + H$^+$] (calcd for $C_{24}H_{30}N_4OH^+$ 391.24978).

*4.2.26. 4-([1,4′-Bipiperidin]-1′-ylmethyl)-2-phenylfuro[3,2-c]pyridine (**24**)*

$NaBH(OAc)_3$ (94 mg, 0.4 mmol) was added to an anhydrous DCE (1 mL) solution of aldehyde **23** (45 mg, 0.2 mmol) and 4–

piperidinopiperidine (37 mg, 0.22 mmol). The mixture was stirred at room temperature (24 h). The volatiles were evaporated under vacuum. H_2O and CH_2Cl_2 were added and the layers were separated. The aqueous layer was washed with CH_2Cl_2 (30 mL). The organic layers were combined and concentrate under vacuum. The crude residue was purified by flash column chromatography on silica gel with CH_2Cl_2/MeOH (7/3) as eluant to obtain **24** as a white solid (7 mg, 10%): $R_f = 0.16$ (CH_2Cl_2/MeOH; 2/8); ^{1}H NMR (300 MHz, CD_3OD) δ 1.55–1.60 (m, 2H), 1.70–1.80 (m, 4H), 1.92–2.01 (m, 4H), 2.19–2.27 (br m, 2H), 2.68–2.76 (m, 1H), 2.86–2.96 (m, 4H), 3.09 (d, J = 10.0 Hz, 2H), 3.96 (s, CH_2N), 7.45–7.59 (m, 5H), 7.97 (d, J = 8.0 Hz, 2H), 8.37 (d, J = 5.2 Hz, 1H); HRMS (M + H$^+$)(ESI$^+$) 376.2395 [M + H$^+$] (calcd for $C_{24}H_{29}N_3OH^+$ 376.2383).

*4.2.27. N–(4–([1,4′–Bipiperidin]–1′–ylmethyl)–2–phenylbenzofuran–5–yl)methanesulfonamide (**27**)*

In a sealed tube, *N*–(2–phenylbenzofuran–5–yl)methanesulfonamide (**26**) (130 mg, 0.46 mmol), 4–piperidinopiperidine (306 mg, 1.82 mmol), formaldehyde (175 μL, 2.28 mmol, 37% in water) were added followed by EtOH (1 mL). The mixture was stirred at 110 °C (3 days). H_2O and CH_2Cl_2 were added. The layers were separated and the aqueous layer was washed with CH_2Cl_2. The organic layers were combined, and concentrated under vacuum. The crude residue was purified by flash column chromatography on silica gel with acetone/MeOH (10/0 to 8/2) as the eluant to obtain **27** as a white solid (80 mg, 38%): R_f = 0.09 (acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43–1.47 (m, 2H), 1.57–1.70 (m, 6H), 1.86 (d, J = 12.4 Hz, 2H), 2.12–2.20 (m, 2H), 2.31–2.36 (m, 1H), 2.51–2.54 (m, 4H), 3.00–3.05 (m, 5H), 3.86 (s, CH_2N), 7.03 (s, 1H), 7.39–7.51 (m, 5H), 7.88 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 26.2, 27.8, 40.1, 50.3, 53.0, 57.7, 62.4, 99.2, 110.8, 117.2, 118.3, 128.9, 129.0, 129.9, 130.0, 133.7, 151.7, 157.0, 1 carbon peak is missing and believed to overlap with peaks nearby; HRMS (M + H$^+$)(ESI$^+$) 468.2341 [M + H$^+$] (calcd for $C_{26}H_{33}N_3O_3SH^+$ 468.2315).

*4.2.28. 1′-((5-Methoxy-2-phenylbenzofuran-4-yl)methyl)-1,4′-bipiperidine (**30a**)*

$NaBH_3CN$ (27 mg, 0.4 mmol) was added to an anhydrous MeOH (5 mL) solution of aldehyde **S-13** (see supporting information) (50 mg, 0.2 mmol), AcOH (cat., 1 drop) and 4–piperidinopiperidine (37 mg, 0.2 mmol). The mixture was stirred at room temperature (16 h), then evaporated under vacuum. The crude residue was purified by flash column chromatography on silica gel with acetone/MeOH (10/0 to 8/2) as the eluant to obtain a yellow oil corresponding to **30a** (40 mg, 50%): R_f = 0.10 (acetone/MeOH; 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73–1.99 (m, 10H), 2.15–2.22 (m, 2H), 2.86–3.12 (m, 5H·), 3.12 (d, J = 12.0 Hz, 2H), 3.86 (s, CH_2N), 3.88 (s, CH_3O), 6.92 (d, J = 9.2 Hz, 1H), 7.19 (s, 1H), 7.35–7.48 (m, 4H), 7.88 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 24.6, 26.9, 49.9, 52.9, 53.5, 57.4, 63.3, 101.1, 109.4, 110.3, 117.2, 125.0, 128.8, 129.0, 130.5, 131.1, 149.9, 154.2, 156.7; HRMS (M + H$^+$)(ESI$^+$) 405.2542 [M + H$^+$] (calcd for $C_{26}H_{32}N_2O_2H^+$ 405.2542).

*4.2.29. 1-((2-(2-(Benzyloxy)phenyl)-5-methoxybenzofuran-4-yl)methyl)-N,N-dimethylpiperidin-4-amine (**30b**)*

$NaBH_3CN$ (13 mg, 0.2 mmol) was added to an anhydrous MeOH (2.5 mL) solution of aldehyde **S-14** (described in supporting information) (37 mg, 0.1 mmol), AcOH (cat., 1 drop) and *N,N*-dimethylpiperidin-4-amine (14 mg, 0.1 mmol). The mixture was stirred at room temperature (5 h) then evaporated under vacuum. The crude residue was purified by flash column chromatography on silica gel with acetone/MeOH (10/0 to 8/2) as the eluant to obtain a colorless oil of **30b** (43 mg, 91%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37–1.42 (m, 2H), 1.61–1.64 (br d, J = 11.9 Hz, 2H), 1.84–1.91 (m, 2H), 2.26 (s, 2NCH_3), 2.30–2.40 (m, 1H), 2.71–2.77 (br d, J = 11.9 Hz, 2H), 3.61 (s, 2H), 3.75 (s, 3H), 5.12 (s, 2H), 6.78 (d, J = 8.9 Hz, 1H), 6.98–7.03 (br m, 2H), 7.18–7.27 (m, 2H), 7.33–7.39 (m, 3H), 7.44–7.49 (br d, J = 7.2 Hz, 2H), 7.98 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 39.9, 52.2, 53.1, 57.3, 61.9, 70.8, 106.4, 109.5, 110.1, 112.3, 117.3, 119.8, 121.2, 127.2, 128.3, 128.6, 128.9, 129.4, 132.0, 136.7, 148.9, 153.0, 154.3, 155.8; LRMS (M + H$^+$)(ESI$^+$) 471.2 [M + H$^+$] (calcd for $C_{30}H_{34}N_2O_3H^+$ 471.2).

*4.2.30. 1′-((2-Phenylbenzofuran-4-yl)methyl)-1,4′-bipiperidine (**32**)*

$NaBH_3CN$ (33 mg, 0.46 mmol) was added to an anhydrous MeOH (1 mL) solution of aldehyde **S-15** (see supporting information) (50 mg, 0.23 mmol), AcOH (cat., 1 drop) and 4–piperidinopiperidine (42 mg, 0.25 mmol). The mixture was stirred at room temperature (16 h) then evaporated under vacuum. The crude residue was purified by flash column chromatography on silica gel with acetone/MeOH (10/0 to 9/1) as the eluant to obtain a white solid corresponding to **32** (42 mg, 50%): R_f = 0.20 (acetone/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32–1.36 (m, 2H), 1.48–1.55 (m, 6H), 1.72 (d, J = 12.4 Hz, 2H), 1.90–1.97 (m, 2H), 2.15–2.26 (m, 1H), 2.41–2.45 (m, 4H), 2.92 (d, J = 11.6 Hz, 2H), 3.66 (s, CH_2N), 7.07 (d, J = 7.2 Hz, 1H), 7.13–7.18 (m, 2H), 7.25–7.29 (m, 1H), 7.33–7.40 (m, 3H), 7.90 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 26.3, 28.2, 50.3, 53.7, 60.9, 62.9, 101.0, 110.0, 123.4, 124.1, 125.2, 128.6, 129.0, 129.3, 130.8, 132.0, 155.2, 155.6; HRMS (M + H$^+$)(ESI$^+$) 375.2436 [M + H$^+$] (calcd for $C_{25}H_{30}N_2OH^+$ 375.2436).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.05.014.

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