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ARTICLE

Expanding the chemical space: Discovery of new anticancer 3-arylbenzofuran derivatives

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Abstract

A new chemical space was generated via C_2-functionalization of 3-arylbenzofurans. Mannich reaction of 3-arylbenzofurans with secondary amines and formaldehyde allowed for installation of aminomethyl unit at C_2 position of benzofurans. A formyl group at C_2 site introduced as a result of Vilsmeier-Haack formylation of 3-arylbenzofurans was employed as a reacting partner for three-component Kabachnik-Fields reaction with various amines and triethyl phosphite to give a wide variety of aminomethylphosphonates. Furthermore, several benzo[*d*]oxazoles and pyrrolo[1,2-*a*]quinoxalines were prepared by using the formyl group. Biological screening of the synthesized compounds revealed that the benzofuran bearing a pyrrolo[1,2-*a*]quinoxaline moiety (**5b**) most potently inhibited the viability of human blood cancer cells, but not solid tumor cells. Caspase activity assay, analysis of Annexin V-positive cells, and Western blot analysis indicated that **5b**-induced death of human lymphoma U937 cells could result from its potential to induce the caspase-dependent apoptotic death of blood cancer cells with inhibition of ERK activation.

1 | INTRODUCTION

Despite extensive use of the privileged structures in medicinal chemistry for drug discovery, there are still many rooms to generate new chemical spaces[1] based on them as numerous substitution patterns around the core framework are possible. As shown in Figure 1, 3-arylbenzofuran moiety, a subclass of benzofurans, has been frequently observed in many natural products as well as unnatural medicinal agents.

Notably, 3-arylbenzofuran skeleton represents a key pharmacophore in a number of medicinal research areas by having a distinctive functional moiety at C_2 position, exhibiting antibacterial, anticancer, or antihyperglycemic activity.[2] Thus, expansion of this heterocyclic chemical space via generation of new 3-arylbenzofurans with unique substitution patterns would offer opportunities for biological exploration associated with these chemical entities, which would deliver discovery of useful therapeutic agents for the treatment of diseases. These

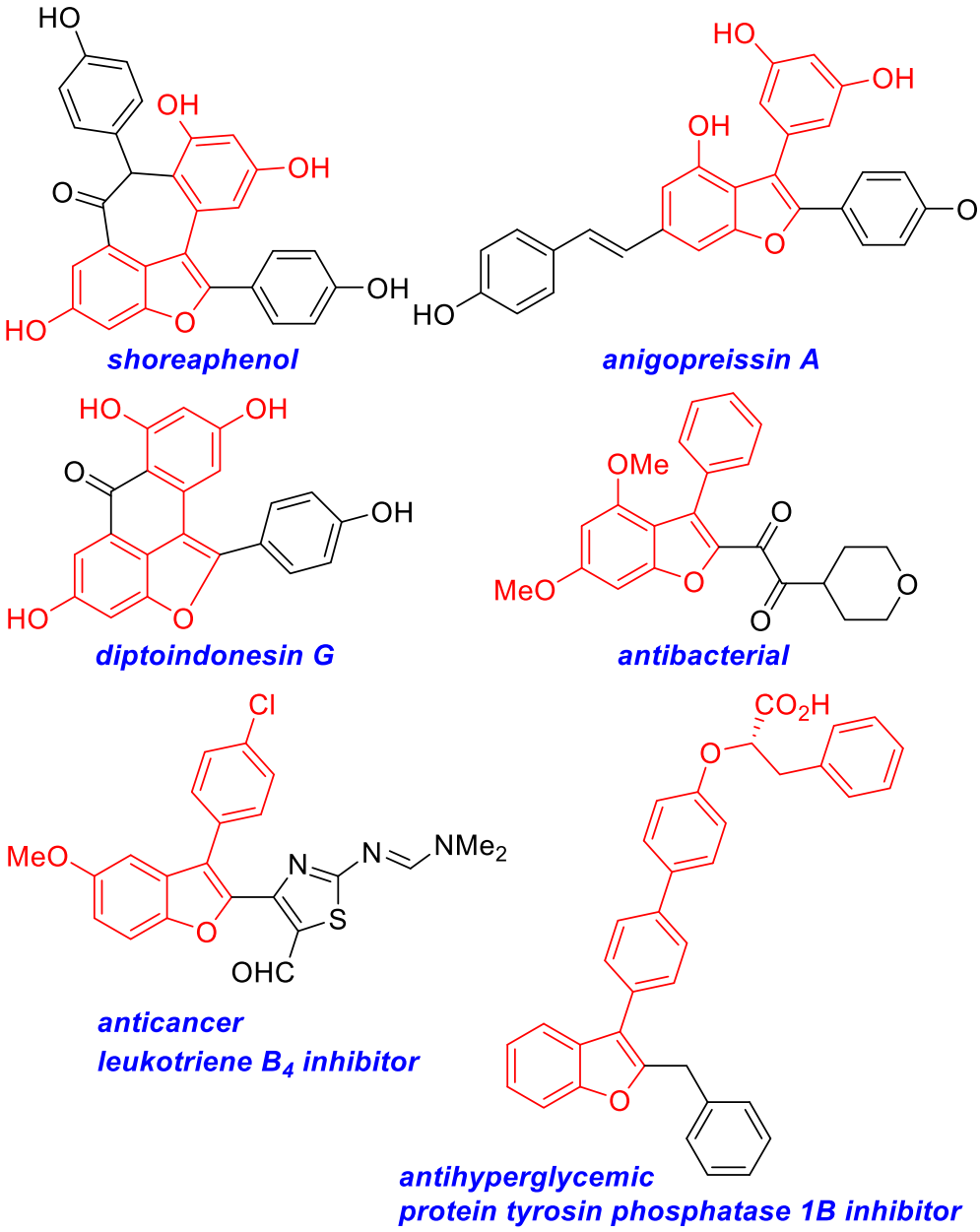


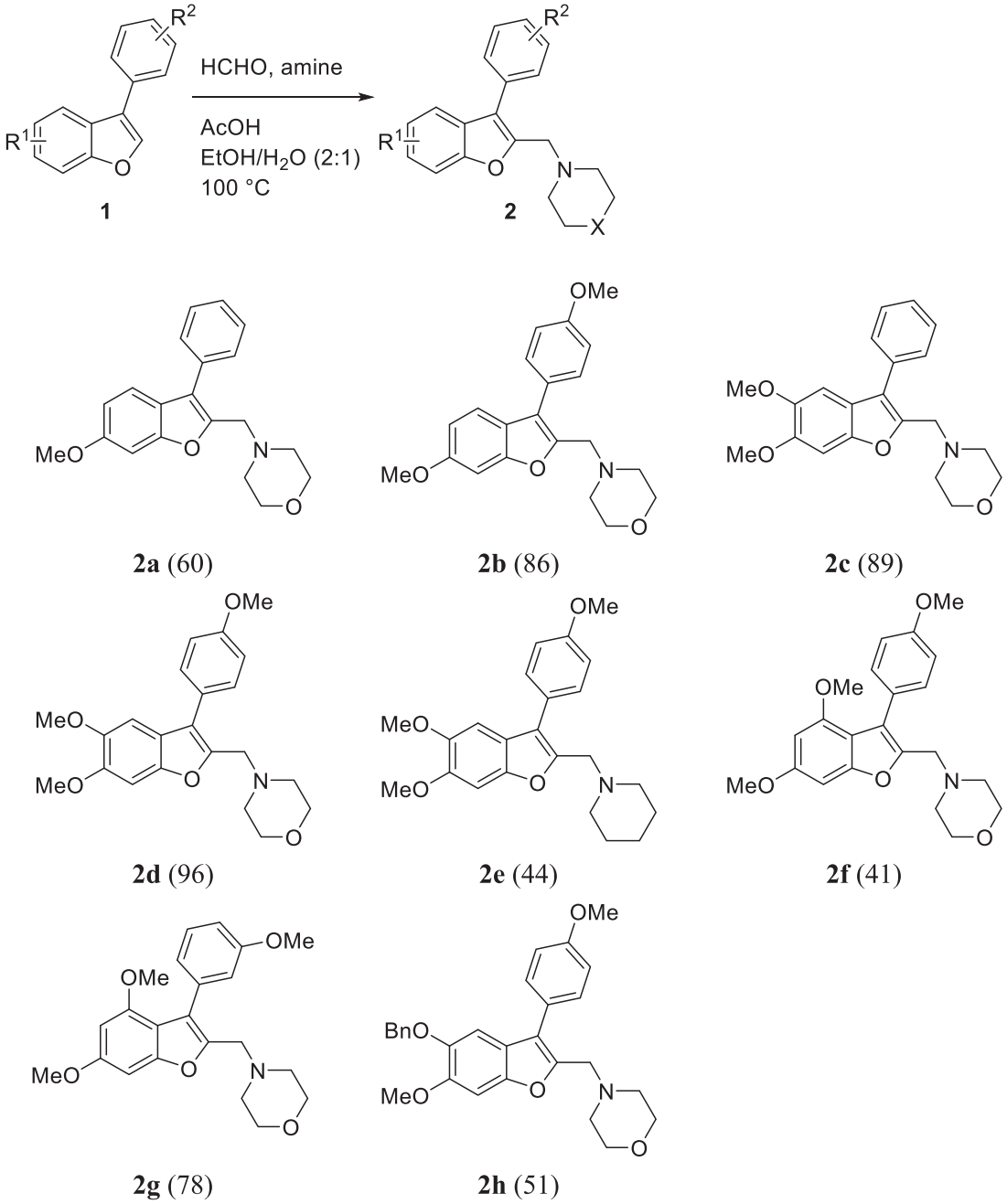
FIGURE 1 Some bioactive natural and unnatural compounds bearing a 3-arylbenzofuran unit

observations as well as our continued research interest on benzofurans[3] led us to design and synthesize novel 3-arylbenzofuran compounds by installing new functional groups at C_2 site for biological evaluation. Here, we wish to report our strategy to extend new chemical territory based on 3-arylbenzofuran and their biological activity.

2 | RESULTS AND DISCUSSION

As a means to introduce novel substituents at C_2 position of 3-arylbenzofurans, we first used the Mannich aminomethylation method as some benzofurans with an aminomethyl moiety at C_2 site were reported to display intriguing biological activities.[4] Thus, several 3-arylbenzofurans **1**[5] were treated with formaldehyde and amine in the presence of acetic acid at 100°C to give the corresponding aminomethylated benzofurans **2** (Scheme 1).

Next, Vilsmeier-Haack formylation[6] of **1** was carried out to afford aldehyde **3** as an intermediate for further diversification at C_2 site (Scheme 2).[7] The resulting aldehyde of **3** was used to make aminomethylphosphonates[8] by three-component Kabachnik-Fields reaction[9] with amines and triethyl phosphite under $FeCl_3$ catalysis.[10] A new benzofuran chemical library **4** bearing diverse

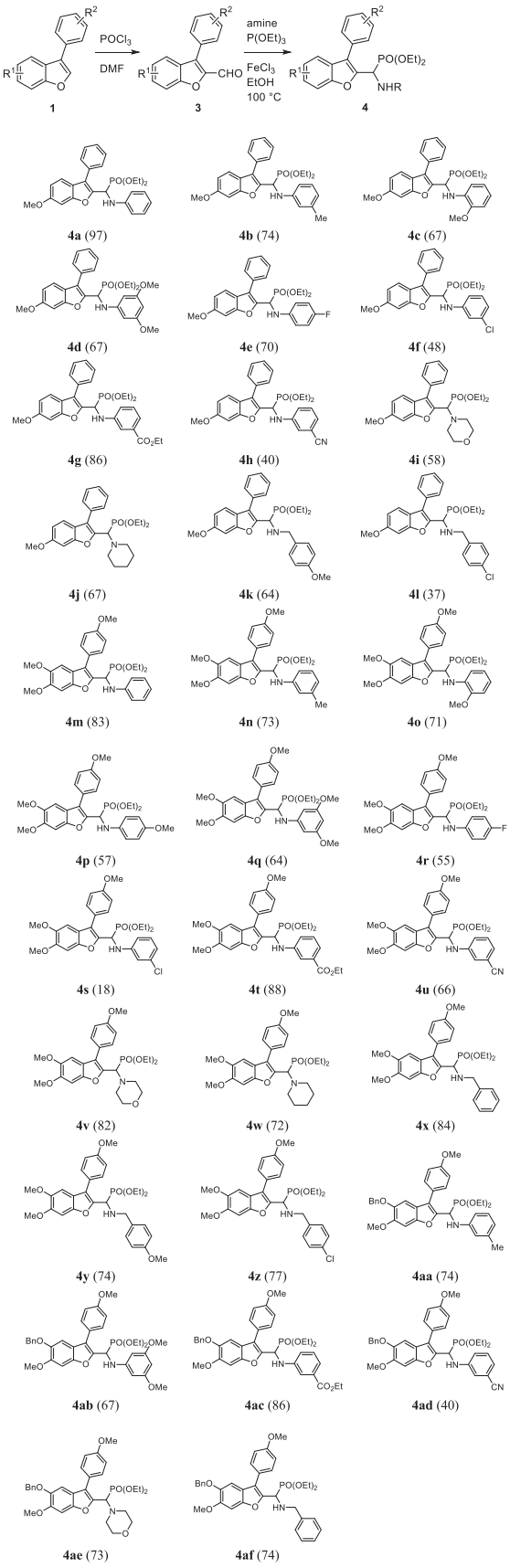


SCHEME 1 Synthesis of New 3-Arylbenzofurans 2. [a]Reaction conditions: **1**, formaldehyde (3.0 equiv), amine (4.0 equiv), and AcOH (19.0 equiv) in EtOH/H_2O (2:1), 100°C. [b]Isolated yield (%)

aminomethylphosphonates was constructed under optimized conditions.

Furthermore, as shown in Scheme 3, the formyl group of **3** was utilized to form pyrrolo[1,2-*a*]quinoxaline[11] and benzo[*d*]oxazole[12] as these two heteroaromatic moieties have been known to display interesting pharmacological functions including antibacterial and anticancer activities.[13,14]

Having established a novel chemical library (**2**, **4**, **5**, and **6**) starting from 3-arylbenzofurans, we turn our attention to evaluate the biological activity of the compounds. Anticancer screening results revealed that the benzofuran bearing a pyrrolo[1,2-*a*]quinoxaline moiety **(5b)** exhibited the most potent activity among the compounds evaluated; IC_{50} of **5b** on the viability of human acute myeloid leukemia (AML) U937 cells was 9.34 μM (Figure 2A). Cytarabine, one of the major regimens in the treatment of AML, was used as a reference.[15] Benzofurans having a morpholinomethyl **(2d)** or piperidinomethyl group **(2e)** at C_2 position displayed weak potency.



SCHEME 2 Synthesis of New 3-Arylbenzofurans 4. [a]Reaction conditions: From **1** to **3**: **1**, $POCl_3$ (3.0 equiv), DMF (3.0 equiv), CH_2Cl_2, 0°C. From **3** to **4**: **3**, amine (1.2 equiv), triethyl phosphite (1.5 equiv), $FeCl_3$ (0.1 equiv), EtOH, 100°C. [b]Isolated yield (%)

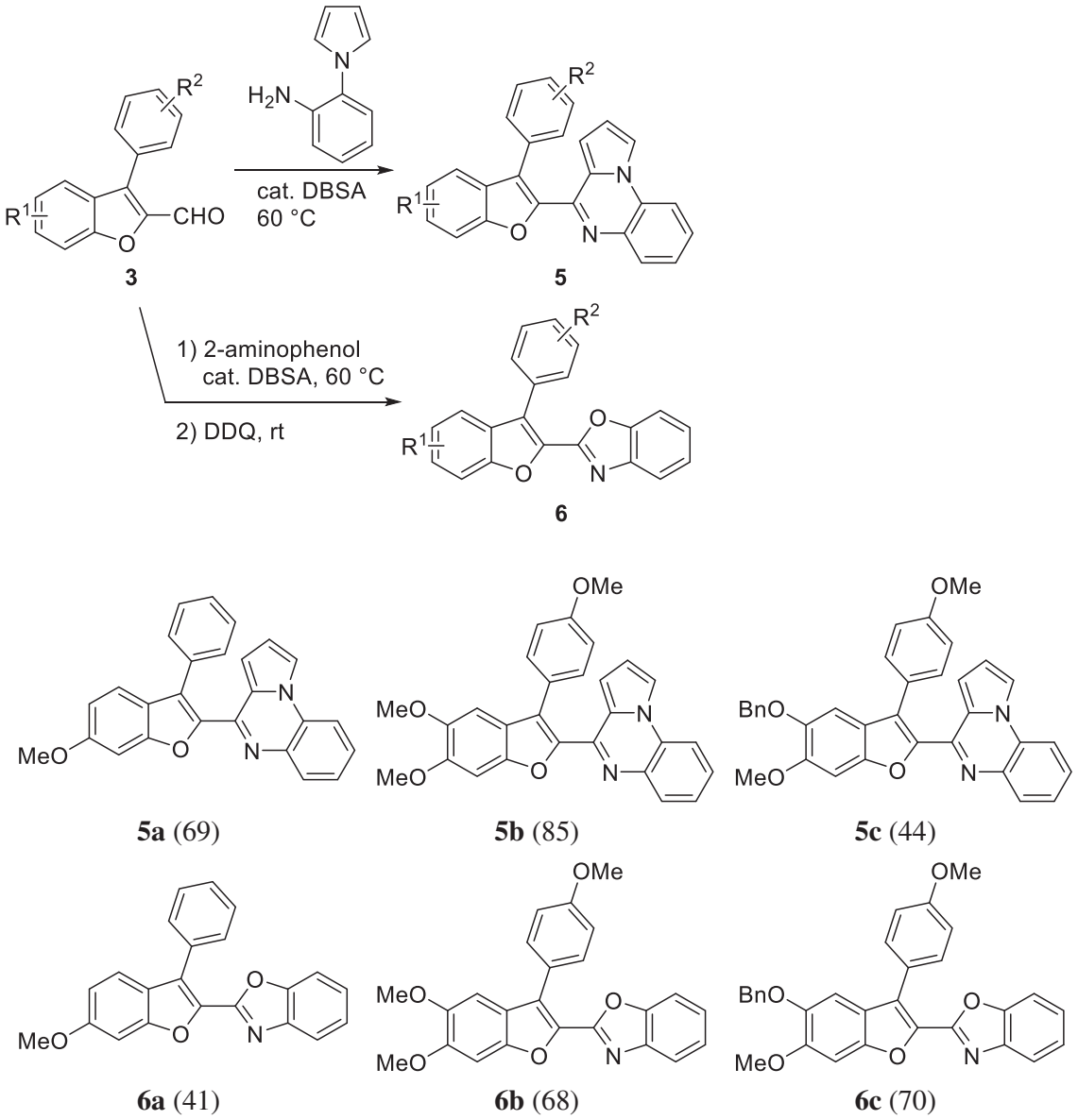
Likewise, decreased anticancer activities were observed with compounds possessing an aminomethylphosphonate **(4)**. Decreased potency of **5c** implied that a big substituent such as benzyl had a negative impact on anticancer activity. Interestingly, benzofuran-benzo[*d*]oxazole hybrid **(6b)** showed less anticancer potency than **5b**, indicating the importance of the nitrogen-containing heterocycles on anticancer activity. In addition, the caspase activity assay and the analysis of Annexin V-positive cells revealed that the caspase-dependent apoptosis could result in the **5b**-induced death of U937 cells as done by cytarabine (Figure 2B,C).[16]

Furthermore, anticancer activity of **5b** compared with those of **5a** and **5c** was investigated in other blood cancer cells such as human T-lymphoblastic leukemia Jurkat cells and human leukemia HL-60 cells, and solid tumor cell lines such as human hepatoblastoma HepG2 cells and human gastric cancer Hs746T cells. As shown in U937 cells, **5b** exhibited the potential anticancer activity in Jurkat and HL-60, but not in solid tumor cells (Table 1). Both **5a** and **5c** did not show any cytotoxic activity in cancer cells used in this study. This result suggested that anticancer activity of **5b** could be specific in blood cancer cells. This hypothesis might be evaluated in a further study using several blood cancer cells and NCI-60 tumor cell lines screen.

Since activation of caspase-3 requires its proteolytic processing, the caspase-dependent cell death by **5b** was confirmed by Western blot analysis; the cleaved form of caspase-3 was increased by **5b** (Figure 3).[17] The nuclear enzyme poly(ADP-ribose) polymerase (PARP) is one of the main targets of caspase-3 and its cleavage serves as a marker of apoptotic cells.[18] The **5b**-mediated induction of cleaved PARP was also confirmed by Western blot analysis using anti-PARP antibody and anti-cleaved PARP antibody as shown in the second image and the third image in Figure 3, respectively. Cleavages of both caspase-3 and PARP by **5a** or **5c** were not observed here. In addition, the effect of **5b** on the activation of survival-related ERK and stress-responsive-JNK was investigated.[19] As shown in Figure 3, **5b**, not **5a** or **5c**, strongly inhibited the phosphorylation of ERK, but not JNK. This result suggested that ERK signaling pathway could be associated with **5b**-mediated induction of caspase-dependent apoptosis in U937 cells.

3 | CONCLUSIONS

In conclusion, with an aim to expand the chemical space based on 3-arylbenzofuran core skeleton, C_2-



SCHEME 3 Synthesis of New 3-Arylbenzofurans 5 and 6. [a]Reaction conditions: From **3** to **5**: **3**, 2-(1*H*-pyrrol-1-yl)aniline (1.2 equiv), and DBSA (0.2 equiv), THF, 60°C. From **3** to **6**: **3**, 2-aminophenol (2.0 equiv), and DBSA (0.2 equiv), EtOH, 60°C. DDQ (1.5 equiv), THF, rt. [b]Isolated yield (%)

functionalization of 3-arylbenzofuran was carried out, thereby leading to a new 3-arylbenzofuran chemical library having a number of nitrogen-containing groups at C_2 site. Biological screening of the synthesized compounds showed that benzofuran-pyrrolo[1,2-*a*] quinoxaline hybrid (**5b**) strongly inhibit the viability of human blood cancer cells, but not solid tumor cell lines. Furthermore, the caspase activity assay, the analysis of Annexin V-positive cells, and Western blot analysis revealed that **5b**-induced death of U937 cells could result from its potential to induce the caspase-dependent apoptotic death of blood cancer cells with the inhibition of ERK activation. More structural optimization based on these results and evaluation of these compounds under different biological settings as well as further extension of chemical space are underway and the results will be reported soon.

4 | EXPERIMENTAL SECTION

4.1 | General methods

Unless specified, all reagents and starting materials were purchased from commercial sources and used as received without purification. "Concentrated" refers to

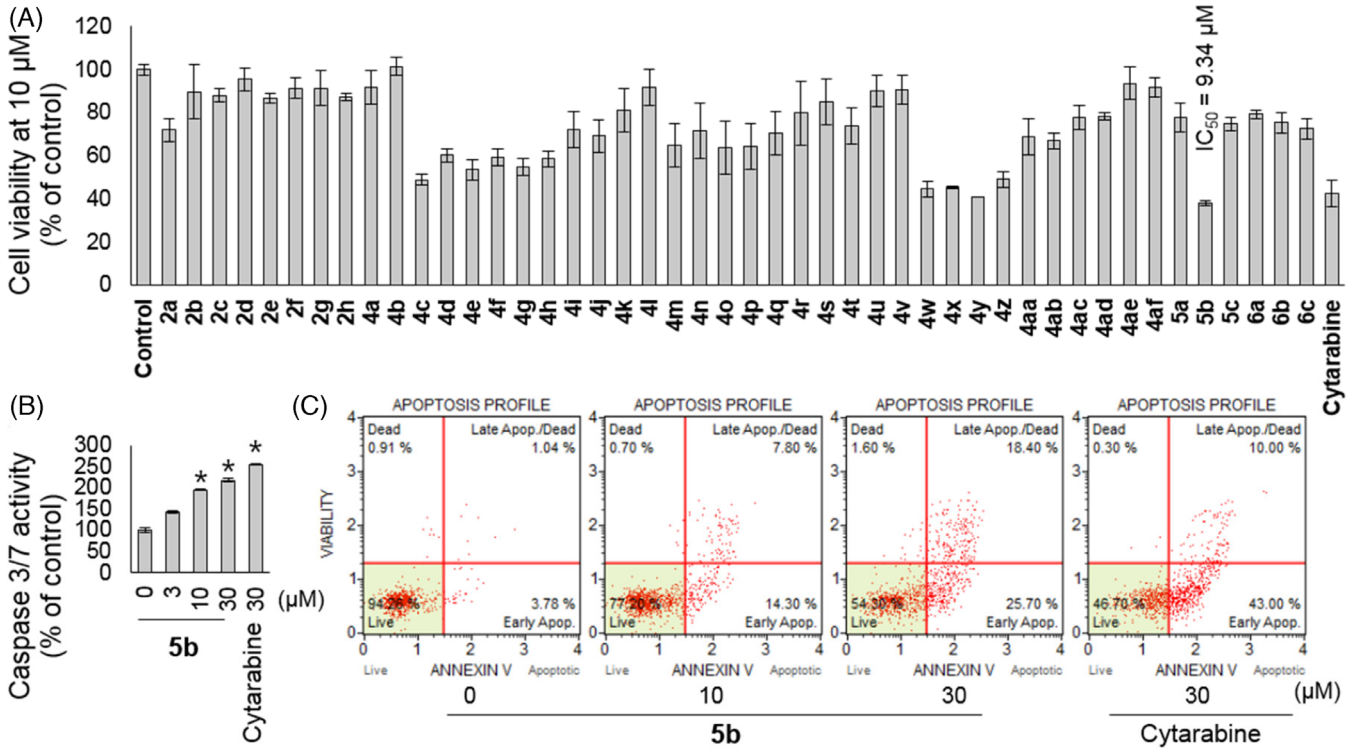


FIGURE 2 The effect of compounds on the viability of U937 cells was evaluated at 10 μM using CCK-8 assay A. Apoptotic activity of **5b** was evaluated by measuring capspase-3/7 activity B, and counting Annexin V-positive cells C. *, $P < 0.001$

	5a (μM)	5b (μM)	5c (μM)	Cytarabine (μM)
U937	>30	9.34	>30	0.19
Jurkat	>30	8.90	>30	0.15
HL-60	>30	7.52	>30	0.16
HepG2	>30	>30	>30	6.50
Hs746T	>30	>30	>30	19.78

TABLE 1 IC_{50} of **5a**, **5b**, and **5c** in viability of cancer cells

the removal of volatile solvents via distillation using a rotary evaporator. "Dried" refers to pouring onto, or passing through, anhydrous magnesium sulfate followed by filtration. Flash chromatography was performed using silica gel (230-400 mesh) with hexanes, ethyl acetate, and dichloromethane as the eluents. All reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (F-254) visualizing with UV light. Melting points were measured using a capillary melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz NMR spectrometer and were described as chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet), coupling constant in hertz (Hz), and number of protons. HRMS were measured with electrospray ionization (ESI) and Q-TOF mass analyzer.

4.1.1 | General procedure for the synthesis of 2

To a vial charged with **1** (0.089 mmol), amine (4.0 equiv), and formaldehyde (3.0 equiv) in ethanol (1 mL) and H_2O (0.5 mL) was added acetic acid (19.0 equiv) at room temperature. After being stirred at 100°C for 3 hours, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane: ethyl acetate:dichloromethane) to give **2**.

4-((6-Methoxy-3-phenylbenzofuran-2-yl)methyl) morpholine (2a)

White solid, mp: 131°C-132°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 to 7.51 (m, 2*H*), 7.51 to 7.42 (m, 3*H*),

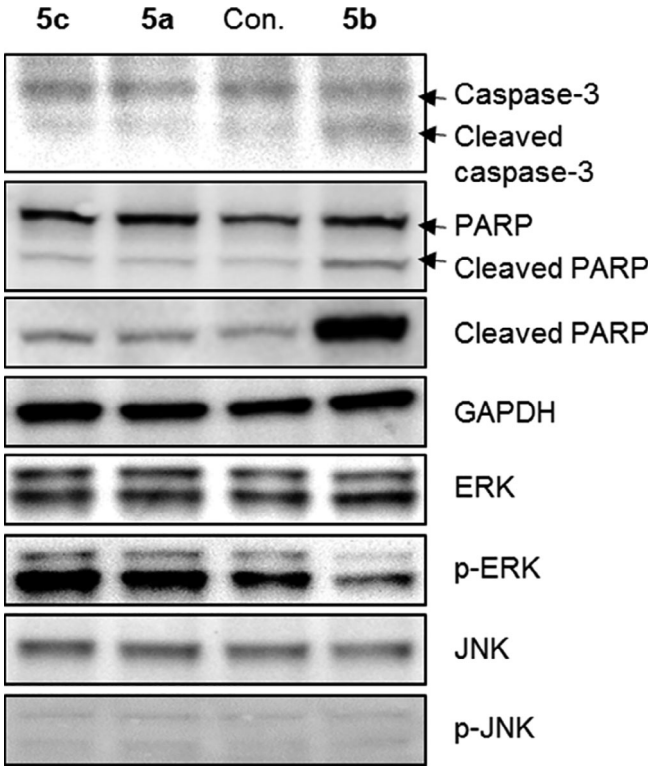


FIGURE 3 The effect of compounds on the levels of proteins related to apoptosis and signaling cascades. U937 cells were incubated with 10 μM of each compound for 1 day, and then protein expression levels were determined by Western blot analysis

7.39 (t, J = 7.2 Hz, 1*H*), 7.08 (d, J = 2.0 Hz, 1*H*), 6.88 (dd, J = 2.4, 8.8 Hz, 1*H*), 3.86 (s, 3*H*), 3.75 to 3.70 (m, 6*H*), 2.51 (br s, 4*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.3, 155.5, 132.3, 129.4, 128.9, 127.6, 121.8, 120.3, 111.9, 96.2, 67.0, 55.9, 54.0, 53.5; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{20}H_{22}NO_3$ 324.1594, found 324.1593.

4-((6-Methoxy-3-(4-methoxyphenyl)benzofuran-2-yl) methyl)morpholine (2b)

White solid, mp: 106°C to 107°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.8 Hz, 2*H*), 7.42 (d, J = 8.8 Hz, 1*H*), 7.07 (d, J = 2.4 Hz, 1*H*), 7.02 (d, J = 8.8 Hz, 2*H*), 6.87 (dd, J = 2.4, 8.4 Hz, 1*H*), 3.88 (s, 3*H*), 3.86 (s, 3*H*), 3.72 (t, J = 4.8 Hz, 4*H*), 3.69 (s, 2*H*), 2.50 (br s, 4*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.1, 158.2, 155.4, 148.6, 130.5, 124.6, 122.0, 120.3, 120.27, 114.3, 111.8, 96.2, 67.0, 55.9, 55.5, 54.0, 53.6; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{21}H_{24}NO_4$ 354.1700, found 354.1704.[20]

4-((5,6-Dimethoxy-3-phenylbenzofuran-2-yl)methyl) morpholine (2c)

White solid, mp: 106°C to 108°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 to 7.47 (m, 4*H*), 7.40 (t, J = 6.8 Hz, 1*H*), 7.10 (s, 1*H*), 6.98 (s, 1*H*), 3.94 (s, 3*H*), 3.88 (s, 3*H*), 3.75 to 6.69 (m, 6*H*), 2.50 (br s, 4*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.1, 148.3, 146.9, 132.5, 129.4, 129.0, 127.6, 20.2, 101.4, 95.6, 67.0, 56.6, 56.4, 54.0, 53.5; **HRMS** (ESI-QTOF) *m/z* $[M + Na]^+$ calcd for $C_{21}H_{23}NNaO_4$ 376.1519, found 376.1515.

4-((5,6-Dimethoxy-3-(4-methoxyphenyl)benzofuran-2-yl) methyl)morpholine (2d)

Light yellow solid, mp: 114°C to 115°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.4 Hz, 2*H*), 7.09 (s, 1*H*), 7.04 (d, J = 8.4 Hz, 2*H*), 6.96 (s, 1*H*), 3.93 (s, 3*H*), 3.88 (s, 6*H*), 3.72 (t, J = 4.4 Hz, 4*H*), 3.68 (s, 2*H*), 2.49 (br s, 4*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.1, 149.0, 148.2, 146.8, 130.5, 124.7, 120.5, 114.4, 101.4, 95.6, 67.0, 56.6, 56.4, 55.5, 54.0, 53.5; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{22}H_{26}NO_5$ 384.1805, found 384.1801.

1-((5,6-Dimethoxy-3-(4-methoxyphenyl)benzofuran-2-yl) methyl)piperidine (2e)

Orange solid, mp: 101°C to 102°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.8 Hz, 2*H*), 7.10 (s, 1*H*), 7.03 (d, J = 8.4 Hz, 2*H*), 6.95 (s, 1*H*), 3.93 (s, 3*H*), 3.88 (s, 3*H*), 3.87 (s, 3*H*), 3.65 (s, 2*H*), 2.41 (br s, 4*H*), 1.65 to 1.53 (m, 4*H*), 1.40 (br s, 2*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.9, 149.7, 149.0, 148.0, 146.6, 130.5, 124.9, 120.6, 120.2, 114.3, 101.4, 95.7, 56.6, 56.4, 55.4, 54.5, 54.3, 26.0, 24.3; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{23}H_{28}NO_4$ 382.2013, found 382.2011.

4-((4,6-Dimethoxy-3-(4-methoxyphenyl)benzofuran-2-yl) methyl)morpholine (2f)

White solid, mp: 122°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.0 Hz, 2*H*), 6.94 (d, J = 8.4 Hz, 2*H*), 6.69 (d, J = 1.6 Hz, 1*H*), 6.30 (d, J = 1.6 Hz, 1*H*), 3.87 (s, 3*H*), 3.84 (s, 3*H*), 3.73 to 3.68 (m, 7*H*), 3.60 (s, 2*H*), 2.45 (br s, 4*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.1, 158.8, 156.4, 154.7, 131.7, 125.0, 113.2, 111.4, 94.5, 88.4, 67.0, 55.9, 55.6, 55.4, 53.5, 53.4; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{22}H_{26}NO_5$ 384.1805, found 384.1805.

4-((4,6-Dimethoxy-3-[3-methoxyphenyl]benzofuran-2-yl) methyl)morpholine (2g)

White solid, mp: 84°C to 85°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (t, J = 7.6 Hz, 1*H*), 7.09 to 7.04 (m, 2*H*), 6.90 (d, J = 7.2 Hz, 1*H*), 6.69 (d, J = 1.6 Hz, 1*H*), 6.32 (d, J = 1.6 Hz, 1*H*), 3.85 (s, 3*H*), 3.84 (s, 3*H*), 3.74 to 3.68 (m, 7*H*), 3.62 (s, 2*H*), 2.47 (br s, 4*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.2, 159.0, 156.4, 154.6, 148.1, 134.1, 128.6, 123.1, 120.6, 116.1, 113.0, 111.1, 95.6, 88.4, 67.0, 55.9, 55.5, 55.4, 53.6, 53.4; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{22}H_{26}NO_5$ 384.1805, found 384.1800.

4-((5-(Benzyloxy)-6-methoxy-3-(4-methoxyphenyl) benzofuran-2-yl)methyl)morpholine (2h)

White solid, mp: 103°C to 104°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, J = 7.2 Hz, 2*H*), 7.41 to 7.28 (m, 5*H*), 7.10 (s, 1*H*), 7.05 to 6.96 (m, 3*H*), 5.11 (s, 2*H*), 3.93 (s, 3*H*), 3.88 (s, 3*H*), 3.76 to 3.62 (m, 6*H*), 3.50 (s, 4*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.0, 149.5, 145.7, 137.4, 130.4, 128.6, 128.0, 127.7, 120.5, 114.4, 105.2, 96.0, 72.2, 67.0, 56.5, 55.5, 54.0, 53.5; **HRMS** (ESI-QTOF) *m/z* [M + H]$^+$ calcd for $C_{28}H_{30}NO_5$ 460.2118, found 460.2114.

4.1.2 | General procedure for the synthesis of 3

In a vial charged with anhydrous *N,N*-dimethylformamide (3.0 equiv) was dropwise added phosphoryl chloride (3.0 equiv) at 0°C and the reaction mixture was stirred for 20 minutes. To this mixture was dropwise added a solution of **1** (2.23 mmol) in CH_2Cl_2 (7.5 mL) at 0°C. After being stirred at room temperature for 15 hours, the reaction mixture was quenched with H_2O. After evaporation of organic solvent, the resulting suspended solid was filtered and dried to give **3**, which was used for the next step without further purification.

6-Methoxy-3-phenylbenzofuran-2-carbaldehyde (3a)

Light yellow solid, mp: 108°C to 110°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.77 (s, 1*H*), 7.65 to 7.60 (m, 3*H*), 7.59 to 7.51 (m, 3*H*), 7.09 (d, J = 2.0 Hz, 1*H*), 6.99 (dd, J = 2.0, 8.8 Hz, 1*H*), 3.91 (s, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 179.1, 162.4, 157.3, 147.6, 135.2, 130.0, 129.53, 129.5, 129.3, 123.2, 120.5, 115.1, 95.7, 56.0; **HRMS** (ESI-QTOF) *m/z* [M + H]$^+$ calcd for $C_{16}H_{13}O_3$ 253.0859, found 253.0860.

5,6-Dimethoxy-3-(4-methoxyphenyl)benzofuran-2-carbaldehyde (3b)

Light yellow solid, mp: 183°C to 186°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.71 (s, 1*H*), 7.56 (d, J = 8.4 Hz, 2*H*), 7.12 to 7.07 (m, 3*H*), 7.05 (s, 1*H*), 3.99 (s, 3*H*), 3.91 (s, 6*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.6, 160.7, 152.9, 151.6, 148.2, 147.6, 135.1, 131.2, 121.9, 119.3, 114.9, 101.9, 95.3, 56.5, 56.5, 55.6; **HRMS** (ESI-QTOF) *m/z* [M + H]$^+$ calcd for $C_{18}H_{17}O_5$ 313.1071, found 313.1070.

5-(Benzyloxy)-6-methoxy-3-(4-methoxyphenyl) benzofuran-2-carbaldehyde (3c)

Light yellow solid, mp: 139°C to 140°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.70 (s, 1*H*), 7.49 to 7.43 (m, 4*H*), 7.42 to 7.30 (m, 3*H*), 7.10 (d, J = 6.8 Hz, 2*H*), 7.06 (d, J = 8.4 Hz, 2*H*), 5.14 (s, 2*H*), 3.98 (s, 3*H*), 3.91 (s, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.7, 160.6, 153.7, 151.9, 147.5, 147.1, 136.7, 131.2, 128.7, 128.2, 127.7, 121.8, 119.2, 114.8, 105.4, 95.4, 71.9, 56.5, 55.6; **HRMS** (ESI-QTOF) *m/z* [M+Na]$^+$ calcd for $C_{24}H_{20}NaO_5$ 411.1203, found 411.1207.

4.1.3 | General procedure for the synthesis of 4

To a solution of **3** (0.12 mmol) in ethanol (1 mL) were added amine (1.2 equiv), triethyl phosphite (1.5 equiv), and $FeCl_3$ (0.1 equiv) at room temperature. After being stirred at 100°C for 16 hours, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane: ethyl acetate: dichloromethane) to give **4**.

Diethyl ((6-methoxy-3-phenylbenzofuran-2-yl) (phenylamino)methyl)phosphonate (4a)

White solid, mp: 96°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 to 7.42 (m, 5*H*), 7.37 (d, J = 8.4 Hz, 1*H*), 7.04 (s, 1*H*), 6.98 (t, J = 7.6 Hz, 2*H*), 6.85 (d, J = 8.4 Hz, 1*H*), 6.65 (t, J = 6.8 Hz, 1*H*), 6.36 (d, J = 8.0 Hz, 2*H*), 5.07 (dd, J = 9.6, 24.0 Hz, 1*H*), 4.67 (br s, 1*H*), 4.32 to 4.20 (m, 2*H*), 4.19 to 4.10 (m, 1*H*), 4.02 to 3.91 (m, 1*H*), 3.84 (s, 3*H*), 1.34 (t, J = 7.0 Hz, 3*H*), 1.19 (t, J = 7.0 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.5, 155.5, 146.1, 146.0, 145.8, 145.6, 131.8, 131.76, 129.33, 129.3, 129.13, 129.1, 128.0, 120.4, 119.1, 114.2, 112.2, 96.2, 63.9, 63.8, 63.5, 63.4, 55.9, 49.6, 48.0, 16.7, 16.6, 16.5, 16.4; **HRMS** (ESI-QTOF) *m/z* [M + H]$^+$ calcd for $C_{26}H_{29}NO_5P$ 466.1778, found 466.1773.

Diethyl ((6-methoxy-3-phenylbenzofuran-2-yl)(m-tolylamino)methyl)phosphonate (4b)

White solid, mp: 102°C to 105°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 to 7.51 (m, 4*H*), 7.46 (t, J = 6.8 Hz, 1*H*), 7.38 (d, J = 8.4 Hz, 1*H*), 7.04 (d, J = 2.0 Hz, 1*H*), 6.90 to 6.82 (m, 2*H*), 6.46 (d, J = 7.6 Hz, 1*H*), 6.22 (d, J = 8.0 Hz, 1*H*), 6.08 (s, 1*H*), 5.06 (dd, J = 10.4, 24.8 Hz, 1*H*), 4.64 (dd, J = 5.2, 10.0 Hz, 1*H*), 4.33 to 4.22 (m, 2*H*), 4.19 to 4.09 (m, 1*H*), 4.04 to 3.91 (m, 1*H*), 3.83 (s, 3*H*), 2.04 (s, 3*H*), 1.35 (t, J = 7.0 Hz, 3*H*), 1.19 (t, J = 7.0 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.5, 155.5, 146.3, 146.2, 145.7, 145.6, 138.9, 129.4, 129.36, 129.1, 128.9, 128.0, 120.3, 119.9, 114.6, 112.2, 111.7, 96.2, 63.9, 63.85, 63.5, 63.4, 55.8, 49.3, 47.7, 21.5, 16.7, 16.65, 16.5, 16.4; **HRMS** (ESI-QTOF) *m/z* [M + H]$^+$ calcd for $C_{27}H_{31}NO_5P$ 480.1934, found 480.1931.

Diethyl ((6-methoxy-3-phenylbenzofuran-2-yl) ((2-methoxyphenyl)amino)methyl)phosphonate (4c)

Light yellow solid, mp: 143°C to 144°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 to 7.48 (m, 4*H*), 7.44 (t, J = 7.2 Hz, 1*H*), 7.36 (d, J = 8.4 Hz, 1*H*), 7.06 (d, J = 2.0 Hz, 1*H*), 6.84 (dd, J = 2.4, 8.8 Hz, 1*H*), 6.67 (d,

J = 7.2 Hz, 1*H*), 6.60 (t, *J* = 7.6 Hz, 1*H*), 6.54 (t, *J* = 7.6 Hz, 1*H*), 6.10 (d, *J* = 7.2 Hz, 1*H*), 5.22 (dd, *J* = 5.2, 10.0 Hz, 1*H*), 5.10 (dd, *J* = 10.4, 23.6 Hz, 1*H*), 4.32 to 4.20 (m, 2*H*), 4.19 to 4.10 (m, 1*H*), 4.04 to 3.95 (m, 1*H*), 3.84 (s, 3*H*), 3.77 (s, 3*H*), 1.33 (t, *J* = 7.0 Hz, 3*H*), 1.20 (t, *J* = 7.0 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.5, 155.6, 147.7, 146.3, 146.2, 131.84, 131.8, 129.4, 129.37, 129.1, 127.9, 120.8, 120.3, 118.3, 112.1, 111.4, 109.8, 96.3, 63.8, 63.78, 63.45, 63.4, 55.9, 55.5, 49.2, 47.6, 16.7, 16.6, 16.5, 16.45; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{27}H_{31}NO_6P$ 496.1884, found 496.1887.

Diethyl (((3,5-dimethoxyphenyl)amino)(6-methoxy-3-phenylbenzofuran-2-yl)methyl)phosphonate (4d)

Light yellow solid, mp: 140°C to 142°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 to 7.58 (m, 2*H*), 7.52 (t, *J* = 7.6 Hz, 2*H*), 7.45 to 7.39 (m, 2*H*), 7.05 (d, *J* = 2.0 Hz, 1*H*), 6.86 (dd, *J* = 2.0, 8.4 Hz, 1*H*), 5.80 (s, 1*H*), 5.57 (d, *J* = 2.0 Hz, 2*H*), 5.08 (dd, *J* = 10.0, 24.4 Hz, 1*H*), 4.73 (dd, *J* = 5.6, 10.0 Hz, 1*H*), 4.33 to 4.21 (m, 2*H*), 4.19 to 4.09 (m, 1*H*), 4.01 to 3.89 (m, 1*H*), 3.84 (s, 3*H*), 3.49 (m, 6*H*), 1.36 (t, *J* = 7.2 Hz, 3*H*), 1.18 (t, *J* = 7.2 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.5, 158.5, 155.5, 147.8, 147.7, 146.1, 146.1, 131.7, 129.3, 129.27, 129.1, 128.0, 120.4, 112.2, 96.2, 92.4, 92.1, 64.0, 63.9, 63.6, 63.5, 55.8, 55.1, 49.5, 47.9, 16.7, 16.6, 16.5, 16.4; **HRMS** (ESI-QTOF) *m/z* $[M + Na]^+$ calcd for $C_{28}H_{32}NNaO_7P$ 548.1809, found 548.1809.

Diethyl (((4-fluorophenyl)amino)(6-methoxy-3-phenylbenzofuran-2-yl)methyl)phosphonate (4e)

White solid, mp: 96°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 to 7.49 (m, 4*H*), 7.48 to 7.42 (m, 1*H*), 7.37 (d, *J* = 8.8 Hz, 1*H*), 7.04 (d, *J* = 1.6 Hz, 1*H*), 6.87 (dd, *J* = 2.0, 8.8 Hz, 1*H*), 6.67 (t, *J* = 8.6 Hz, 2*H*), 6.28 (dd, *J* = 4.4, 8.8 Hz, 2*H*), 4.98 (dd, *J* = 10.4, 24.4 Hz, 1*H*), 4.59 to 4.51 (m, 1*H*), 4.33 to 4.20 (m, 2*H*), 4.20 to 4.10 (m, 1*H*), 4.02 to 3.91 (m, 1*H*), 3.84 (s, 3*H*), 1.35 (t, *J* = 7.2 Hz, 3*H*), 1.20 (t, *J* = 7.2 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.6, 157.9, 155.5, 145.8, 141.9, 131.7, 129.3, 129.27, 129.1, 128.1, 121.5, 120.4, 115.7, 115.5, 115.45, 115.4, 112.3, 96.2, 63.9, 63.8, 63.6, 63.5, 55.9, 50.5, 48.8, 16.7, 16.6, 16.5, 16.4; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{26}H_{28}FNO_5P$ 484.1684, found 484.1685.

Diethyl (((3-chlorophenyl)amino)(6-methoxy-3-phenylbenzofuran-2-yl)methyl)phosphonate (4f)

White solid, mp: 138°C to 139°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 to 7.51 (m, 4*H*), 7.47 (br s, 1*H*), 7.38 (d, *J* = 8.8 Hz, 1*H*), 7.03 (s, 1*H*), 6.93 to 6.82 (m, 2*H*), 6.60 (d, *J* = 7.6 Hz, 1*H*), 6.30 to 6.22 (m, 2*H*), 4.99 (dd, *J* = 10.4, 24.8 Hz, 1*H*), 4.79 to 4.73 (m, 1*H*), 4.32 to 4.21 (m, 2*H*), 4.21 to 4.10 (m, 1*H*), 4.03 to 3.91 (m, 1*H*), 3.84 (s, 3*H*), 1.36 (t, *J* = 7.0 Hz, 3*H*), 1.20 (t, *J* = 7.0 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.6, 155.6, 151.1, 146.9, 145.5, 134.9, 130.1, 129.42, 129.4, 129.3, 128.2, 122.0, 121.5, 120.5, 119.0, 113.8, 112.6, 112.3, 96.2, 63.9, 63.86, 63.7, 63.6, 55.9, 49.3, 47.7, 16.7, 16.7, 16.5, 16.4; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{26}H_{28}ClNO_5P$ 500.1388, found 500.1384.

Ethyl 3-(((diethoxyphosphoryl)(6-methoxy-3-phenylbenzofuran-2-yl)methyl)amino)benzoate (4g)

Yellow solid, mp: 139°C to 140°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 to 7.50 (m, 4*H*), 7.45 (t, *J* = 7.0 Hz, 1*H*), 7.37 (d, *J* = 8.8 Hz, 1*H*), 7.34 (d, *J* = 7.6 Hz, 1*H*), 7.15 (br s, 1*H*), 7.06 to 7.00 (m, 2*H*), 6.85 (dd, *J* = 2.0, 8.4 Hz, 1*H*), 6.49 (dd, *J* = 1.6, 8.0 Hz, 1*H*), 5.12 (dd, *J* = 10.0, 24.0 Hz, 1*H*), 4.82 (dd, *J* = 5.2, 10.0 Hz, 1*H*), 4.32 to 4.20 (m, 3*H*), 4.17 to 4.08 (m, 2*H*), 4.02 to 3.92 (m, 1*H*), 3.83 (s, 3*H*), 1.37 to 1.29 (m, 6*H*), 1.20 (t, *J* = 7.0 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.6, 158.6, 155.5, 145.9, 145.7, 145.6, 145.5, 131.4, 129.32, 129.3, 129.1, 129.06, 128.1, 120.4, 120.2, 118.1, 115.2, 112.3, 96.1, 63.9, 63.8, 63.77, 63.7, 63.6, 63.5, 60.9, 55.8, 49.7, 48.1, 16.7, 16.6, 16.5, 16.4, 16.3, 16.2; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{29}H_{33}NO_7P$ 538.1989, found 538.1985.

Diethyl (((3-cyanophenyl)amino)(6-methoxy-3-phenylbenzofuran-2-yl)methyl)phosphonate (4h)

Yellow solid, mp: 59°C to 61°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 to 7.47 (m, 5*H*), 7.39 (d, *J* = 8.8 Hz, 1*H*), 7.05 (t, *J* = 7.8 Hz, 1*H*), 7.00 (d, *J* = 1.6 Hz, 1*H*), 6.90 (d, *J* = 7.6 Hz, 1*H*), 6.87 (dd, *J* = 2.4, 8.8 Hz, 1*H*), 6.60 (dd, *J* = 1.6, 8.4 Hz, 1*H*), 6.42 (s, 1*H*), 5.05 to 4.92 (m, 2*H*), 4.35 to 4.23 (m, 2*H*), 4.30 to 4.09 (m, 1*H*), 4.03 to 3.88 (m, 1*H*), 3.82 (s, 3*H*), 1.37 (t, *J* = 7.2 Hz, 3*H*), 1.21 (t, *J* = 7.2 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.8, 155.6, 146.2, 146.0, 144.9, 144.8, 131.3, 129.8, 129.5, 129.3, 129.26, 128.5, 122.5, 122.4, 122.3, 121.3, 120.5, 118.9, 118.8, 116.2, 113.0, 112.5, 96.2, 63.9, 63.85, 63.8, 55.9, 49.1, 47.5, 16.7, 16.6, 16.5, 16.4; **HRMS** (ESI-QTOF) *m/z* $[M + Na]^+$ calcd for $C_{27}H_{27}N_2NaO_5P$ 513.1550, found 513.1558.

Diethyl ((6-methoxy-3-phenylbenzofuran-2-yl)(morpholino)methyl)phosphonate (4i)

White solid, mp: 84°C to 86°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 to 7.44 (m, 4*H*), 7.40 (d, *J* = 8.8 Hz, 2*H*), 7.14 (s, 1*H*), 6.90 (d, *J* = 7.2 Hz, 1*H*), 4.34 to 4.18 (m, 3*H*), 4.18 to 4.06 (m, 1*H*), 4.05 to 3.91 (m, 1*H*), 3.88 (s, 3*H*), 3.71 to 3.57 (m, 4*H*), 2.91 (br s, 2*H*), 2.48 (br s, 2*H*), 1.35 (t, *J* = 7.0 Hz, 3*H*), 1.18 (t, *J* = 7.0 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.7, 155.6, 145.5, 132.0, 129.4, 129.1, 127.9, 121.4, 120.4, 112.5, 96.2, 67.5, 63.5, 63.4, 62.8, 62.7, 60.6, 59.0, 55.9, 52.2, 16.8, 16.7, 16.6, 16.5;

HRMS (ESI-QTOF) *m/z* $[M+Na]^+$ calcd for $C_{24}H_{30}NNaO_6P$ 482.1703, found 482.1707.

Diethyl ((6-methoxy-3-phenylbenzofuran-2-yl)(piperidin-1-yl)methyl)phosphonate (4j)

White solid, mp: 115°C to 117°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 to 7.44 (m, 4*H*), 7.42 to 7.36 (m, 2*H*), 7.16 (d, *J* = 2.0 Hz, 1*H*), 6.89 (dd, *J* = 2.0, 8.4 Hz, 1*H*), 4.36 to 4.18 (m, 3*H*), 4.15 to 4.05 (m, 1*H*), 4.03 to 3.93 (m, 1*H*), 3.87 (s, 3*H*), 2.89 (br s, 2*H*), 2.36 (br s, 2*H*), 1.59 to 1.42 (m, 4*H*), 1.37 to 1.25 (m, 5*H*), 1.16 (t, *J* = 7.2 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.4, 155.5, 146.54, 146.5, 132.3, 129.4, 129.0, 127.7, 122.6, 122.5, 121.5, 120.3, 112.3, 96.3, 63.5, 63.45, 62.5, 62.4, 61.1, 59.5, 55.9, 53.1, 53.06, 26.7, 24.1, 16.74, 16.7, 16.5, 16.48; **HRMS** (ESI-QTOF) *m/z* $[M + Na]^+$ calcd for $C_{25}H_{32}NNaO_5P$ 480.1910, found 480.1914.

Diethyl ((6-methoxy-3-phenylbenzofuran-2-yl)((4-methoxybenzyl)amino)methyl)phosphonate (4k)

White solid, mp: 91°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 to 7.46 (m, 3*H*), 7.43 (t, *J* = 7.4 Hz, 2*H*), 7.37 (t, *J* = 7.2 Hz, 1*H*), 7.11 (d, *J* = 2.0 Hz, 1*H*), 6.94 to 6.86 (m, 3*H*), 6.62 (d, *J* = 8.4 Hz, 2*H*), 4.30 to 4.15 (m, 3*H*), 4.13 to 4.05 (m, 1*H*), 4.04 to 3.93 (m, 1*H*), 3.88 (s, 3*H*), 3.75 to 3.67 (m, 4*H*), 3.34 (d, *J* = 12.8 Hz, 1*H*), 1.32 (t, *J* = 7.0 Hz, 3*H*), 1.18 (t, *J* = 7.0 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.7, 158.5, 155.7, 146.7, 146.6, 131.8, 130.7, 129.8, 129.2, 129.1, 129.0, 127.6, 122.0, 121.5, 120.4, 113.6, 112.1, 96.3, 63.6, 63.5, 63.0, 62.9, 55.9, 55.3, 52.1, 50.8, 50.6, 50.4, 16.7, 16.6, 16.5, 16.4; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{28}H_{33}NO_6P$ 510.2040, found 510.2045.

Diethyl (((4-chlorobenzyl)amino)(6-methoxy-3-phenylbenzofuran-2-yl)methyl)phosphonate (4l)

White solid, mp: 89°C to 90°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 to 7.35 (m, 6*H*), 7.11 (d, *J* = 1.2 Hz, 1*H*), 7.05 (d, *J* = 8.4 Hz, 2*H*), 6.95 to 6.88 (m, 3*H*), 4.28 to 4.16 (m, 3*H*), 4.14 to 4.04 (m, 1*H*), 4.02 to 3.93 (m, 1*H*), 3.88 (s, 3*H*), 3.72 (d, *J* = 13.2 Hz, 1*H*), 3.37 (d, *J* = 13.2 Hz, 1*H*), 1.33 (t, *J* = 7.0 Hz, 3*H*), 1.19 (t, *J* = 7.0 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.6, 155.7, 146.3, 137.1, 132.8, 131.6, 129.9, 129.1, 128.3, 127.8, 120.5, 112.3, 96.3, 63.6, 63.5, 63.1, 63.0, 55.9, 52.1, 50.6, 50.5, 16.7, 16.6, 16.5, 16.4; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{27}H_{30}ClNO_5P$ 514.1545, found 514.1542.

Diethyl ((5,6-dimethoxy-3-(4-methoxyphenyl)benzofuran-2-yl)(phenylamino)methyl)phosphonate (4m)

Yellow solid, mp: 130°C to 131°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2*H*), 7.09 (d, *J* = 8.4 Hz, 2*H*), 7.06 (s, 1*H*), 7.00 (t, *J* = 8.4 Hz, 2*H*), 6.88 (s, 1*H*), 6.65 (t, *J* = 7.2 Hz, 1*H*), 6.38 (d, *J* = 7.6 Hz, 2*H*), 5.02 (d, *J* = 24.4 Hz, 1*H*), 4.66 (br s, 1*H*), 4.31 to 4.20 (m, 2*H*), 4.18 to 4.08 (m, 1*H*), 4.00 to 3.89 (m, 7*H*), 3.84 (s, 3*H*), 1.34 (t, *J* = 6.8 Hz, 3*H*), 1.18 (t, *J* = 6.8 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.5, 149.2, 148.4, 146.9, 145.8, 145.7, 130.5, 130.48, 129.1, 124.1, 121.4, 120.3, 119.0, 114.6, 114.2, 101.3, 95.7, 63.9, 63.8, 63.5, 63.4, 56.6, 56.4, 55.5, 49.6, 48.0, 16.7, 16.6, 16.5, 16.4; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{28}H_{33}NO_7P$ 526.1989, found 526.1991.

Diethyl ((5,6-dimethoxy-3-(4-methoxyphenyl)benzofuran-2-yl)(m-tolylamino)methyl)phosphonate (4n)

White solid, mp: 128°C to 130°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.4 Hz, 2*H*), 7.10 (d, *J* = 8.8 Hz, 2*H*), 7.06 (s, 1*H*), 6.92 to 6.85 (m, 2*H*), 6.47 (d, *J* = 7.6 Hz, 1*H*), 6.23 (d, *J* = 7.6 Hz, 1*H*), 6.12 (s, 1*H*), 5.01 (dd, *J* = 10.0, 24.4 Hz, 1*H*), 4.68 to 4.59 (m, 1*H*), 4.31 to 4.21 (m, 2*H*), 4.19 to 4.09 (m, 1*H*), 4.01 to 3.87 (m, 7*H*), 3.84 (s, 3*H*), 2.07 (s, 3*H*), 1.35 (t, *J* = 7.0 Hz, 3*H*), 1.19 (t, *J* = 7.0 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.5, 149.2, 148.4, 146.8, 145.8, 145.6, 138.9, 130.5, 128.9, 124.1, 121.3, 120.2, 119.8, 114.6, 111.6, 101.2, 95.7, 63.9, 63.8, 63.4, 63.36, 56.5, 56.4, 55.5, 49.3, 47.7, 21.5, 16.7, 16.6, 16.5, 16.4; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{29}H_{35}NO_7P$ 540.2146, found 540.2142.

Diethyl ((5,6-dimethoxy-3-(4-methoxyphenyl)benzofuran-2-yl)((2-methoxyphenyl)amino)methyl)phosphonate (4o)

Orange solid, mp: 106°C to 108°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2*H*), 7.10 to 7.04 (m, 3*H*), 6.87 (s, 1*H*), 6.70 to 6.54 (m, 3*H*), 6.12 (d, *J* = 7.6 Hz, 1*H*), 5.21 (dd, *J* = 5.6, 10.0 Hz, 1*H*), 5.04 (dd, *J* = 10.4, 24.0 Hz, 1*H*), 4.30 to 4.20 (m, 2*H*), 4.19 to 4.09 (m, 1*H*), 4.02 to 3.94 (m, 1*H*), 3.91 (s, 6*H*), 3.84 (s, 3*H*), 3.78 (s, 3*H*), 1.33 (t, *J* = 7.0 Hz, 3*H*), 1.20 (t, *J* = 7.0 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.4, 149.2, 148.4, 147.7, 146.8, 135.7, 135.5, 130.54, 130.5, 124.1, 120.8, 118.2, 114.6, 111.4, 109.8, 101.3, 95.7, 63.8, 63.7, 63.4, 63.3, 56.6, 56.4, 55.5, 55.49, 49.2, 47.6, 16.7, 16.6, 16.5, 16.45; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{29}H_{35}NO_8P$ 556.2095, found 556.2096.

Diethyl ((5,6-dimethoxy-3-(4-methoxyphenyl)benzofuran-2-yl)((4-methoxyphenyl)amino)methyl)phosphonate (4p)

Brown solid, mp: 115°C to 116°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2*H*), 7.10 to 7.05 (m, 3*H*), 6.87 (s, 1*H*), 6.58 (d, *J* = 8.8 Hz, 2*H*), 6.35 (d, *J* = 8.8 Hz, 2*H*), 4.92 (dd, *J* = 10.4, 24.4 Hz, 1*H*), 4.44 to 4.36 (m, 1*H*), 4.31 to 4.20 (m, 2*H*), 4.18 to 4.06 (m, 1*H*), 4.01 to 3.88 (m,

7*H*), 3.84 (s, 3*H*), 2.07 (s, 3*H*), 1.35 (t, *J* = 7.2 Hz, 3*H*), 1.19 (t, *J* = 7.2 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.3, 153.0, 149.0, 148.2, 146.7, 145.8, 139.6, 139.5, 130.3, 123.9, 123.89, 121.3, 120.2, 120.1, 115.7, 114.45, 114.4, 101.1, 95.5, 63.7, 63.6, 63.2, 63.15, 56.4, 56.2, 55.6, 55.3, 50.6, 49.0, 16.5, 16.48, 16.3, 16.28; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{29}H_{35}NO_8P$ 556.2095, found 556.2095.

Diethyl ((5,6-dimethoxy-3-(4-methoxyphenyl) benzofuran-2-yl)((3,5-dimethoxyphenyl)amino)methyl) phosphonate (4q)

Yellow solid, mp: 75°C to 77°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.8 Hz, 2*H*), 7.10 to 7.04 (m, 3*H*), 6.91 (s, 1*H*), 5.81 (s, 1*H*), 5.61 to 5.57 (m, 2*H*), 5.02 (dd, *J* = 10.0, 24.4 Hz, 1*H*), 4.74 to 4.65 (m, 1*H*), 4.30 to 4.21 (m, 2*H*), 4.17 to 4.09 (m, 1*H*), 3.97 to 3.87 (m, 7*H*), 3.85 (s, 3*H*), 3.54 (s, 6*H*), 1.35 (t, *J* = 7.0 Hz, 3*H*), 1.18 (t, *J* = 7.0 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.5, 159.5, 149.2, 148.5, 147.9, 147.8, 146.9, 130.5, 124.0, 123.98, 121.0, 120.9, 120.2, 120.18, 114.6, 101.4, 95.7, 92.6, 92.0, 63.9, 63.8, 63.5, 63.4, 56.6, 56.4, 55.5, 55.1, 49.6, 48.0, 16.7, 16.65, 16.5, 16.4; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{30}H_{37}NO_9P$ 586.2200, found 586.2205.

Diethyl ((5,6-dimethoxy-3-(4-methoxyphenyl) benzofuran-2-yl)((4-fluorophenyl)amino)methyl) phosphonate (4r)

White solid, mp: 116°C to 118°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 6.8 Hz, 2*H*), 7.13 to 7.03 (m, 3*H*), 6.88 (s, 1*H*), 6.69 (t, *J* = 8.4 Hz, 2*H*), 6.31 (br s, 2*H*), 4.93 (dd, *J* = 10.4, 24.4 Hz, 1*H*), 4.54 (br s, 1*H*), 4.32 to 4.08 (m, 3*H*), 4.02 to 3.87 (m, 7*H*), 3.85 (s, 3*H*), 1.35 (t, *J* = 6.8 Hz, 3*H*), 1.19 (t, *J* = 6.8 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.5, 157.9, 155.5, 149.2, 148.5, 146.9, 145.4, 130.4, 123.9, 120.2, 115.7, 115.5, 115.4, 114.7, 101.3, 95.6, 63.8, 63.76, 63.5, 63.45, 56.6, 56.4, 55.5, 50.4, 48.8, 16.7, 16.6, 16.5, 16.45; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{28}H_{32}FNO_7P$ 544.1898, found 5444.1893.

Diethyl (((3-chlorophenyl)amino)(5,6-dimethoxy-3-(4-methoxyphenyl)benzofuran-2-yl)methyl) phosphonate (4s)

White solid, mp: 142°C to 143°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2*H*), 7.10 (d, *J* = 8.4 Hz, 2*H*), 7.05 (s, 1*H*), 6.94 to 6.86 (m, 2*H*), 6,61 (d, *J* = 8.0 Hz, 1*H*), 6.31 to 6.25 (m, 2*H*), 4.94 (dd, *J* = 10.4, 24.4 Hz, 1*H*), 4.75 (dd, *J* = 6.0, 9.6 Hz, 1*H*), 4.30 to 4.20 (m, 2*H*), 4.19 to 4.09 (m, 1*H*), 4.00 to 3.89 (m, 7*H*), 3.85 (s, 3*H*), 1.36 (t, *J* = 7.2 Hz, 3*H*), 1.19 (t, *J* = 7.2 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.6, 148.6, 147.0, 146.95, 146.9, 145.2, 134.9, 130.61, 130.6, 130.1, 118.9, 114.8, 113.8, 112.7, 101.3, 95.6, 63.9, 63.8, 63.6, 63.56, 56.6, 56.4, 55.5, 49.3, 47.7, 16.7, 16.65, 16.5, 16.45; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{28}H_{32}ClNO_7P$ 560.1599, found 560.1597.

Ethyl 3-(((diethoxyphosphoryl)(5,6-dimethoxy-3-(4-methoxyphenyl)benzofuran-2-yl)methyl)amino) benzoate (4t)

White solid, mp: 74°C to 77°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2*H*), 7.34 (d, *J* = 7.6 Hz, 1*H*), 7.16 (s, 1*H*), 7.12 to 7.00 (m, 4*H*), 6.88 (s, 1*H*), 6.50 (d, *J* = 7.2 Hz, 1*H*), 5.07 (dd, *J* = 10.4, 24.4 Hz, 1*H*), 4.83 to 4.74 (m, 1*H*), 4.35 to 4.20 (m, 4*H*), 4.19 to 4.08 (m, 1*H*), 4.01 to 3.87 (m, 7*H*), 3.84 (s, 3*H*), 1.40 to 1.28 (m, 6*H*), 1.20 (t, *J* = 6.8 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.6, 159.5, 149.2, 148.5, 146.9, 145.9, 145.8, 131.4, 130.5, 130.48, 129.1, 123.8, 120.2, 118.1, 115.3, 114.7, 101.3, 95.6, 63.8, 63.77, 63.54, 63.5, 60.9, 56.5, 56.4, 55.5, 49.7, 48.1, 16.7, 16.6, 16.5, 16.4, 14.4; **HRMS** (ESI-QTOF) *m/z* $[M + Na]^+$ calcd for $C_{31}H_{36}NNaO_9P$ 620.2020, found 620.2028.

Diethyl (((3-cyanophenyl)amino)(5,6-dimethoxy-3-(4-methoxyphenyl)benzofuran-2-yl)methyl) phosphonate (4u)

Yellow solid, mp: 144°C to 146°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2*H*), 7.14 (d, *J* = 8.4 Hz, 2*H*), 7.06 (t, *J* = 8.0 Hz, 1*H*), 7.00 (s, 1*H*), 6.91 (d, *J* = 7.6 Hz, 1*H*), 6.89 (s, 1*H*), 6.63 (d, *J* = 8.4 Hz, 1*H*), 6.43 (s, 1*H*), 5.00 to 4.88 (m, 2*H*), 4.32 to 4.21 (m, 2*H*), 4.21 to 4.11 (m, 1*H*), 4.01 to 3.90 (m, 4*H*), 3.89 (s, 3*H*), 3.85 (s, 3*H*), 1.37 (t, *J* = 6.8 Hz, 3*H*), 1.20 (t, *J* = 6.8 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.8, 149.2, 148.7, 147.0, 146.3, 146.1, 130.5, 130.46, 129.8, 123.5, 122.5, 119.0, 118.9, 116.1, 115.0, 112.9, 101.3, 95.6, 63.9, 63.8, 63.7, 56.5, 56.4, 55.6, 49.1, 47.5, 16.7, 16.6, 16.5, 16.4; **HRMS** (ESI-QTOF) *m/z* $[M + Na]^+$ calcd for $C_{29}H_{31}NNaO_7P$ 573.1767, found 573.1763.

Diethyl ((5,6-dimethoxy-3-(4-methoxyphenyl) benzofuran-2-yl)(morpholino)methyl) phosphonate (4v)

White solid, mp: 143°C to 145°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2*H*), 7.17 (s, 1*H*), 7.04 (d, *J* = 8.4 Hz, 2*H*), 6.90 (s, 1*H*), 4.28 to 4.20 (m, 3*H*), 4.15 to 4.07 (m, 1*H*), 4.01 to 3.92 (m, 4*H*), 3.91 to 3.85 (m, 6*H*), 3.71 to 3.58 (m, 4*H*), 2.90 (br s, 2*H*), 2.47 (br s, 2*H*), 1.35 (t, *J* = 7.0 Hz, 3*H*), 1.17 (t, *J* = 7.0 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.3, 149.3, 148.6, 146.9, 145.3, 145.2, 130.52, 130.5, 124.3, 123.1, 123.0, 120.1, 114.6, 101.2, 95.8, 67.5, 63.4, 63.35, 62.7, 62.67, 60.6, 58.9, 56.6, 56.4, 55.5, 52.2, 52.1, 16.8, 16.7, 16.6, 16.5; **HRMS** (ESI-QTOF) *m/z* $[M + Na]^+$ calcd for $C_{26}H_{34}NNaO_8P$ 542.1914, found 542.1911.

Diethyl ((5,6-dimethoxy-3-(4-methoxyphenyl) benzofuran-2-yl)(piperidin-1-yl)methyl) phosphonate (4w)

Orange solid, mp: 162°C to 163°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.4 Hz, 2*H*), 7.18 (s, 1*H*), 7.03 (d, *J* = 8.4 Hz, 2*H*), 6.91 (s, 1*H*), 4.31 to 4.20 (m, 3*H*), 4.14 to 4.04 (m, 1*H*), 4.00 to 3.92 (m, 4*H*), 3.88 (s, 3*H*), 3.87 (s, 3*H*), 2.89 (br s, 2*H*), 2.35 (br s, 2*H*), 1.60 to 1.44 (m, 4*H*), 1.38 to 1.27 (m, 5*H*) 1.16 (t, *J* = 7.2 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.2, 149.2, 148.4, 146.8, 146.3, 146.3, 130.5, 124.6, 122.5, 122.4, 120.2, 114.5, 101.2, 95.9, 63.5, 63.4, 62.5, 62.4, 61.1, 59.5, 56.6, 56.4, 55.4, 53.2, 53.1, 26.7, 24.1, 16.7, 16.69, 16.5, 16.48; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{27}H_{37}NO_7P$ 518.2302, found 518.2305.

Diethyl ((benzylamino)(5,6-dimethoxy-3-(4-methoxyphenyl)benzofuran-2-yl)methyl) phosphonate (4x)

White solid, mp: 141°C to 142°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.8 Hz, 2*H*), 7.16 to 7.09 (m, 4*H*), 7.06 to 7.01 (m, 2*H*), 7.01 to 6.95 (m, 3*H*), 4.28 to 4.14 (m, 3*H*), 4.12 to 4.04 (m, 1*H*), 3.99 to 3.91 (m, 4*H*), 3.89 (s, 3*H*), 3.87 (s, 3*H*), 3.76 (d, *J* = 13.0 Hz, 1*H*), 3.42 (d, *J* = 13.0 Hz, 1*H*), 2.43 (br s, 1*H*), 1.33 (t, *J* = 7.2 Hz, 3*H*), 1.18 (t, *J* = 7.2 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.3, 149.3, 149.32, 148.4, 146.9, 138.8, 130.3, 130.2, 128.6, 128.2, 127.1, 124.1, 124.07, 120.2, 114.5, 101.4, 95.7, 63.5, 63.46, 63.0, 62.9, 56.6, 56.4, 55.5, 52.4, 51.4, 51.3, 50.8, 16.7, 16.6, 16.5, 16.4; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{29}H_{35}NO_7P$ 520.2095, found 520.2096.

Diethyl ((5,6-dimethoxy-3-(4-methoxyphenyl) benzofuran-2-yl)((4-methoxybenzyl)amino)methyl) phosphonate (4y)

Yellow solid, mp: 92°C to 94°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2*H*), 7.13 (s, 1*H*), 7.02 to 6.96 (m, 3*H*), 6.92 (d, *J* = 8.4 Hz, 2*H*), 6.64 (d, *J* = 8.4 Hz, 2*H*), 4.27 to 4.15 (m, 3*H*), 4.13 to 4.05 (m, 1*H*), 4.00 to 3.91 (m, 4*H*), 3.90 (s, 3*H*), 3.87 (s, 3*H*), 3.81 (d, *J* = 9.6 Hz, 1*H*), 3.75 to 3.67 (m, 4*H*), 3.34 (d, *J* = 12.8 Hz, 1*H*), 1.33 (t, *J* = 7.2 Hz, 3*H*), 1.18 (t, *J* = 7.2 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.1, 158.5, 149.2, 148.3, 146.7, 146.1, 130.6, 130.1, 130.09, 129.7, 124.0, 123.99, 120.0, 114.4, 113.7, 113.4, 101.2, 95.6, 63.4, 63.3, 62.8, 62.7, 56.4, 56.3, 55.3, 55.1, 51.9, 50.6, 50.4, 50.3, 16.5, 16.46, 16.3, 16.27; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{30}H_{37}NO_8P$ 570.2251, found 570.2251.

Diethyl (((4-chlorobenzyl)amino)(5,6-dimethoxy-3-(4-methoxyphenyl)benzofuran-2-yl)methyl) phosphonate (4z)

Yellow solid, mp: 153°C to 154°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.0 Hz, 2*H*), 7.13 (s, 1*H*), 7.07 (d, *J* = 8.4 Hz, 2*H*), 7.02 to 6.90 (m, 5*H*), 4.27 to 4.17 (m, 3*H*), 4.14 to 4.06 (m, 1*H*), 4.01 to 3.92 (m, 4*H*), 3.89 (s, 3*H*), 3.88 (s, 3*H*), 3.73 (d, *J* = 13.6 Hz, 1*H*), 3.38 (d, *J* = 13.6 Hz, 1*H*), 1.34 (t, *J* = 7.2 Hz, 3*H*), 1.19 (t, *J* = 7.2 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.3, 149.3, 148.5, 146.9, 145.9, 137.2, 132.7, 130.1, 129.9, 128.3, 123.94, 123.9, 122.0, 120.0, 114.6, 101.4, 95.7, 63.5, 63.4, 63.0, 62.9, 56.6, 56.4, 55.5, 52.1, 50.6, 50.5, 50.4, 16.7, 16.6, 16.5, 16.4; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{29}H_{34}ClNO_7P$ 574.1756, found 574.1754.

Diethyl ((5-(benzyloxy)-6-methoxy-3-(4-methoxyphenyl) benzofuran-2-yl)(m-tolylamino)methyl) phosphonate (4aa)

White solid, mp: 71°C to 72°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 to 7.27 (m, 7*H*), 7.10 to 7.02 (m, 3*H*), 6.95 (s, 1*H*), 6.88 (t, *J* = 7.6 Hz, 1*H*), 6.46 (d, *J* = 7.2 Hz, 1*H*), 6.21 (d, *J* = 7.6 Hz, 1*H*), 6.10 (s 1*H*), 5.12 to 4.95 (m, 3*H*), 4.63 (br s, 1*H*), 4.30 to 4.20 (m, 2*H*), 4.18 to 4.07 (m, 1*H*), 4.01 to 3.87 (m, 7*H*), 2.06 (s, 3*H*), 1.35 (t, *J* = 7.0 Hz, 3*H*), 1.18 (t, *J* = 7.0 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.4, 149.7, 149.3, 145.8, 145.6, 138.9, 137.3, 130.4, 128.9, 128.6, 128.0, 127.7, 124.1, 119.8, 114.6, 111.5, 105.0, 96.1, 72.1, 63.9, 63.8, 63.4, 63.38, 56.5, 55.5, 49.3, 47.7, 21.5, 16.7, 16.65, 16.5, 16.4; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{35}H_{39}NO_7P$ 616.2459, found 616.2459.

Diethyl ((5-(benzyloxy)-6-methoxy-3-(4-methoxyphenyl) benzofuran-2-yl)((3,5-dimethoxyphenyl)amino)methyl) phosphonate (4ab)

Yellow solid, mp: 150°C to 151°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 to 7.39 (m, 4*H*), 7.39 to 7.27 (m, 3*H*), 7.07 (s, 1*H*), 7.04 (d, *J* = 8.4 Hz, 2*H*), 6.98 (s, 1*H*), 5.80 (s, 1*H*) 5.57 (s, 2*H*), 5.12 to 4.95 (m, 3*H*), 4.70 (dd, *J* = 5.6, 9.6 Hz, 1*H*), 4.30 to 4.20 (m, 2*H*), 4.17 to 4.07 (m, 1*H*), 3.97 to 3.86 (m, 7*H*), 3.51 (s, 6*H*), 1.35 (t, *J* = 7.2 Hz, 3*H*), 1.18 (t, *J* = 7.2 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.5, 159.4, 149.7, 147.9, 147.7, 145.8, 137.3, 130.4, 128.6, 128.0, 127.7, 123.9, 120.9, 120.2, 114.6, 105.2, 96.1, 92.5, 92.0, 72.2, 63.9, 63.8, 63.5, 63.46, 56.5, 55.5, 55.1, 49.6, 48.0, 16.7, 16.66, 16.5, 16.4; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{36}H_{41}NO_9P$ 662.2513, found 662.2512.

Ethyl 3-(((5-(benzyloxy)-6-methoxy-3-(4-methoxyphenyl) benzofuran-2-yl)(diethoxyphosphoryl)methyl)amino) benzoate (4ac)

Yellow solid, mp: 144°C to 146°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 to 7.27 (m, 8*H*), 7.15 (s, 1*H*), 7.08 to 7.00 (m, 4*H*), 6.95 (s, 1*H*), 6.48 (dd, *J* = 1.6, 8.0 Hz, 1*H*), 5.13 to 5.00 (m, 3*H*), 4.79 (dd, *J* = 5.2, 10.0 Hz, 1*H*), 4.33 to 4.19 (m, 4*H*), 4.17 to 4.07 (m, 1*H*), 4.01 to 3.87 (m, 7*H*), 1.35 (t, *J* = 6.0 Hz, 3*H*), 1.31 (t, *J* = 6.0 Hz, 3*H*), 1.19 (t, *J* = 7.0 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.6,

159.5, 149.7, 149.4, 145.9, 145.88, 145.8, 130.4, 130.39, 129.1, 128.6, 128.0, 127.7, 120.2, 115.3, 114.6, 105.0, 96.0, 72.1, 63.9, 63.8, 63.6, 63.5, 60.9, 56.5, 55.5, 49.7, 48.1, 16.7, 16.6, 16.5, 16.4, 14.4; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{37}H_{41}NO_9P$ 674.2513, found 674.2515.

Diethyl ((5-(benzyloxy)-6-methoxy-3-(4-methoxyphenyl) benzofuran-2-yl)((3-cyanophenyl)amino)methyl) phosphonate (4ad)

Yellow solid, mp: 68°C to 70°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 to 7.29 (m, 7*H*), 7.11 (d, *J* = 8.4 Hz, 2*H*), 7.08 to 7.01 (m, 2*H*), 6.96 (s, 1*H*), 6.90 (d, *J* = 7.6 Hz, 1*H*), 6.60 (d, *J* = 8.0 Hz, 1*H*), 6.41 (s, 1*H*), 5.13 to 5.03 (m, 2*H*), 5.00 to 4.88 (m, 2*H*), 4.31 to 4.20 (m, 2*H*), 4.20 to 4.11 (m, 1*H*), 4.01 to 3.91 (m, 4*H*), 3.89 (s, 3*H*), 1.37 (t, *J* = 7.0 Hz, 3*H*), 1.20 (t, *J* = 7.0 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.7, 149.7, 149.6, 146.1, 146.0, 130.4, 130.37, 129.8, 128.6, 128.0, 127.7, 122.5, 116.2, 115.0, 104.9, 96.0, 72.1, 63.9, 63.81, 63.8, 56.5, 55.6, 49.1, 47.5, 16.7, 16.6, 16.5, 16.4; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{35}H_{36}NO_7P$ 627.2255, found 627.2254.

Diethyl ((5-(benzyloxy)-6-methoxy-3-(4-methoxyphenyl) benzofuran-2-yl)(morpholino)methyl)phosphonate (4ae)

White solid, mp: 101°C to 103°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 to 7.43 (m, 2*H*), 7.40 to 7.28 (m, 5*H*), 7.17 (s, 1*H*), 7.00 (d, *J* = 8.4 Hz, 2*H*), 6.98 (s, 1*H*), 5.14 to 5.06 (m, 2*H*), 4.29 to 4.19 (m, 3*H*), 4.16 to 4.06 (m, 1*H*), 4.01 to 3.92 (m, 4*H*), 3.88 (s, 3*H*), 3.71 to 3.57 (m, 4*H*), 2.88 (br s, 2*H*), 2.46 (br s, 2*H*), 1.35 (t, *J* = 7.0 Hz, 3*H*), 1.17 (t, *J* = 7.0 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.3, 149.7, 149.5, 145.9, 145.2, 137.3, 130.4, 128.6, 128.0, 127.7, 124.2, 123.0, 120.1, 114.6, 105.0, 96.2, 72.1, 67.5, 63.4, 63.35, 62.8, 62.7, 60.6, 58.9, 56.5, 55.5, 52.1, 52.06, 16.8, 16.7, 16.6, 16.5; **HRMS** (ESI-QTOF) *m/z* $[M + Na]^+$ calcd for $C_{32}H_{38}NNaO_8P$ 618.2227, found 618.2231.

Diethyl ((benzylamino)(5-(benzyloxy)-6-methoxy-3-(4-methoxyphenyl)benzofuran-2-yl)methyl) phosphonate (4af)

White solid, mp: 82°C to 83°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.2 Hz, 2*H*), 7.38 (t, *J* = 7.4 Hz, 2*H*), 7.35 to 7.29 (m, 3*H*), 7.16 to 7.08 (m, 4*H*), 7.05 (s, 1*H*), 7.03 to 6.98 (m, 2*H*), 6.94 (d, *J* = 8.4 Hz, 2*H*), 5.17 to 5.07 (m, 2*H*), 4.27 to 4.14 (m, 3*H*), 4.12 to 4.03 (m, 1*H*), 3.99 to 3.09 (m, 4*H*), 3.87 (s, 3*H*), 3.74 (d, *J* = 13.2 Hz, 1*H*), 3.39 (d, *J* = 13.2 Hz, 1*H*), 1.32 (t, *J* = 7.2 Hz, 3*H*), 1.17 (t, *J* = 7.2 Hz, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.1, 149.7, 149.1, 146.0, 145.96, 145.6, 138.6, 137.2, 130.02, 130.0, 128.5, 128.4, 128.0, 127.6, 114.3, 105.0, 96.0, 72.0, 63.4, 63.3, 62.8, 62.76, 56.4, 55.3, 52.3, 51.3, 51.1, 50.6, 16.5, 16.45, 16.3, 16.26; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{35}H_{39}NO_7P$ 616.2459, found 616.2458.

4.1.4 | General procedure for the synthesis of 5

To a solution of **3** (0.12 mmol) in tetrahydrofuran (1 mL) were added 2-(1*H*-pyrrol-1-yl)aniline (1.2 equiv) and DBSA (0.2 equiv) at room temperature. After being stirred at 60°C for 48 hours, the reaction mixture was concentrated under reduced pressure. The reaction mixture was basified with aq. $NaHCO_3$ solution and extracted with ethyl acetate (1 mL × 3). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane:ethyl acetate:dichloromethane) to give **5**.

4-(6-Methoxy-3-phenylbenzofuran-2-yl)pyrrolo[1,2-a] quinoxaline (5a)

Orange solid, mp: 228°C to 229°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (s, 1*H*), 7.85 (d, *J* = 8.0 Hz, 1*H*), 7.81 (d, *J* = 8.0 Hz, 1*H*), 7.66 to 7.58 (m, 3*H*), 7.49 (t, *J* = 7.8 Hz, 1*H*), 7.43 to 7.31 (m, 4*H*), 7.20 (s, 1*H*), 7.03 (d, *J* = 3.2 Hz, 1*H*), 6.97 (d, *J* = 8.4 Hz, 1*H*), 6.81 (s, 1*H*), 3.92 (s, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.5, 155.9, 147.2, 144.9, 130.5, 130.1, 128.3, 127.7, 125.3, 121.5, 114.4, 114.2, 113.7, 113.1, 109.3, 96.0, 55.9; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{26}H_{19}N_2O_2$ 391.1441, found 391.1445.

4-(5,6-Dimethoxy-3-(4-methoxyphenyl)benzofuran-2-yl) pyrrolo[1,2-a]quinoxaline (5b)

Brown solid, mp: 140°C to 141°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (br s, 1*H*), 7.82 (t, *J* = 7.2 Hz, 2*H*), 7.59 (d, *J* = 8.8 Hz, 2*H*), 7.47 (t, *J* = 7.0 Hz, 1*H*), 7.39 (t, *J* = 7.0 Hz, 1*H*), 7.21 (s, 1*H*), 7.11 to 7.05 (m, 2*H*), 6.97 (d, *J* = 8.8 Hz, 2*H*), 6.82 (dd, *J* = 2.8, 4.0 Hz, 1*H*), 4.00 (s, 3*H*), 3.93 (s, 3*H*), 3.86 (s, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.3, 149.8, 149.79, 147.4, 145.0, 131.4, 130.5, 127.8, 125.4, 125.0, 114.4, 114.2, 113.9, 113.7, 109.5, 101.8, 95.5, 56.6, 56.5, 55.5; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{28}H_{23}N_2O_4$ 451.1652, found 451.1656.

4-(5-(Benzyloxy)-6-methoxy-3-(4-methoxyphenyl) benzofuran-2-yl)pyrrolo[1,2-a]quinoxaline (5c)

Yellow solid, mp: 128°C to 129°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (s, 1*H*), 7.83 (t, *J* = 7.2 Hz, 2*H*), 7.52 to 7.45 (m, 5*H*), 7.39 (t, *J* = 7.4 Hz, 3*H*), 7.33 (t, *J* = 7.0 Hz, 1*H*), 7.22 (s, 1*H*), 7.16 (s, 1*H*), 7.05 (d, *J* = 4.0 Hz, 1*H*), 6.93 (d, *J* = 8.8 Hz, 2*H*), 6.81 (dd, *J* = 2.8, 4.0 Hz, 1*H*), 5.16 (s, 2*H*), 4.00 (s, 3*H*), 3.86 (s, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.2, 150.5, 150.2, 146.2, 145.0, 131.3, 130.4,

128.7, 128.1, 127.8, 127.7, 125.3, 114.3, 114.1, 113.8, 113.6, 109.4, 105.5, 95.7, 72.1, 56.5, 55.4; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{34}H_{27}N_2O_4$ 527.1965, found 527.1967.

4.1.5 | General procedure for the synthesis of 6

To a solution of **3** (0.12 mmol) in ethanol (1 mL) were added 2-aminophenol (2.0 equiv) and DBSA (0.2 equiv) at room temperature. After being stirred at 60°C for 12 hours, the reaction mixture was concentrated in vacuo. The reaction mixture was basified with aq. $NaHCO_3$ solution and extracted with ethyl acetate (1 mL × 3). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was suspended in ethanol and filtered to give the intermediate as a yellow solid. To a solution of this intermediate (0.042 mmol) in tetrahydrofuran (1 mL) was added DDQ (1.5 equiv) at room temperature. After being stirred at room temperature for 1 hour, the reaction mixture was concentrated under reduced pressure. The reaction mixture was basified with aq. $NaHCO_3$ solution and extracted with ethyl acetate (1 mL × 3). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane:ethyl acetate:dichloromethane) to give **6**.

2-(6-Methoxy-3-phenylbenzofuran-2-yl)benzo[d] oxazole (6a)

White solid, mp: 171°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 6.8 Hz, 1*H*), 7.72 (d, *J* = 7.2 Hz, 2*H*), 7.59 to 7.48 (m, 4*H*), 7.44 (d, *J* = 8.0 Hz, 1*H*), 7.36 to 7.29 (m, 2*H*), 7.17 (s, 1*H*), 6.96 (d, *J* = 8.8 Hz, 1*H*), 3.91 (s, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.5, 156.6, 156.1, 150.3, 141.7, 130.6, 130.1, 128.7, 128.6, 126.3, 125.5, 125.0, 122.1, 122.0, 120.4, 113.8, 110.8, 95.9, 55.9; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{22}H_{16}NO_3$ 342.1125, found 342.1130.

2-(5,6-Dimethoxy-3-(4-methoxyphenyl)benzofuran-2-yl) benzo[d]oxazole (6b)

Yellow solid, mp: 164°C to 165°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 6.8 Hz, 1*H*), 7.66 (d, *J* = 8.4 Hz, 2*H*), 7.46 (d, *J* = 8.4 Hz, 1*H*), 7.36 to 7.28 (m, 2*H*), 7.18 (s, 1*H*), 7.11 (d, *J* = 8.4 Hz, 2*H*), 7.00 (s, 1*H*), 4.00 (s, 3*H*), 3.94 (s, 3*H*), 3.91 (s, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.9, 156.3, 150.9, 150.6, 150.3, 147.8, 141.7, 137.6, 131.3, 126.3, 125.3, 124.9, 122.9, 120.9, 120.3, 114.2, 110.7, 101.7, 95.3, 56.6, 56.5, 55.5; **HRMS** (ESI-QTOF) *m/z* $[M + Na]^+$ calcd for $C_{24}H_{19}NNaO_4$ 424.1155, found 424.1156.

2-(5-(Benzyloxy)-6-methoxy-3-(4-methoxyphenyl) benzofuran-2-yl)benzo[d]oxazole (6c)

Yellow solid, mp: 166°C to 167°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 6.8 Hz, 1*H*), 7.58 (d, *J* = 8.8 Hz, 2*H*), 7.49 to 7.44 (m, 3*H*), 7.39 (t, *J* = 7.2 Hz, 2*H*), 7.36 to 7.28 (m, 3*H*), 7.18 (s, 1*H*), 7.10 to 7.04 (m, 3*H*), 5.14 (s, 2*H*), 3.98 (s, 3*H*), 3.93 (s, 3*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.9, 151.6, 150.9, 150.3, 146.6, 141.8, 137.0, 131.3, 128.7, 128.1, 127.8, 126.2, 125.3, 124.9, 122.8, 120.8, 120.3, 114.1, 110.7, 105.3, 95.5, 72.0, 56.5, 55.5; **HRMS** (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{30}H_{24}NO_5$ 478.1649, found 478.1640.

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[15] Cell viability assay – All cell culture materials were purchased from HyClone (South Logan, UT, USA). Human lymphoma U937, human T-lymphoblastic leukemia Jurkat (American Type Culture Collection, Manassas, VA, USA) and human leukemia HL-60 (Korean Cell Line Bank, Seoul, Korea) were maintained in RPMI-1640 containing 10% fetal bovine serum, 100 U/ml of penicillin, and 100 μg/ml streptomycin. Human hepatoblastoma HepG2 and human gastric cancer cells Hs746T (Korean Cell Line Bank) were maintained in MEM and RPMI-1640 containing 10% fetal bovine serum, 100 U/ml of penicillin, and 100 μg/ml streptomycin, respectively. Cells were seeded in a 96-well plate at 2 × 103 cells/well and incubated with compounds for 3 days. Then, cell viability was evaluated in triplicate using Cell Counting Kit-8 (Dojindo Molecular Technologies, Rockville, MD, USA) according to the manufacturer's protocol. Absorbance was measured at 450 nm using HIDEX sense microplate reader (Turku, Finland). Cytarabine (Sigma-Aldrich, St. Louis, MO, USA) was used as the reference compound. Compounds used in this study were dissolved with DMSO and prepared to 30 mM stock solutions that were further diluted with cell culture medium. Therefore, 0.1% DMSO was used for the control in all experiments. All quantitative values are presented as mean ± SD.

[16] Caspase-3/7 activity assay & Apoptosis assay—Cells were seeded in a 96-well plate at 4 × 103 cells/well and incubated with 5b or cytarabine for 6 h. Then, caspase-3/7 activity was evaluated in triplicate using Apo-ONE Homogeneous Caspase-3/7 Assay (Promega, WI) according to the manufacturer's protocol. All quantitative values are presented as mean ± SD. Statistical differences were analyzed using Student's t-test. A value of $P < 0.05$ was considered significant. Apoptosis was evaluated by counting Annexin V-positive cells. Briefly, cells were seeded in a 96-well plate at 2 × 103 cells/well and incubated with compounds for three days. Then, cells were incubated with Muse Annexin V & Dead Cell Reagent (Millipore) according to the manufacturer's protocol and analyzed in Muse Cell Analyzer (Millipore).

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