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Sequential C–C, C–O, and C–N Bond-Forming Reaction of Methyl (–)-3-Dehydroshikimate, Malononitrile, and Bromoalkanes: Simple Synthesis of 2-(Alkylamino)-3-cyanobenzofurans from a Biomass-Derived Substrate

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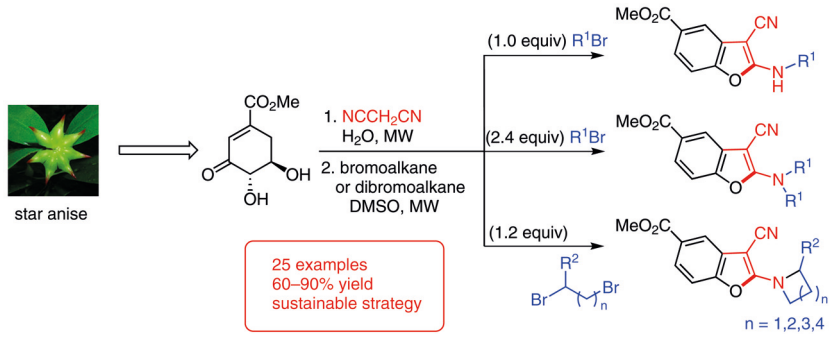

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Abstract An interesting and simple method was developed for the synthesis of 2-(alkylamino)-3-cyanobenzofurans by consecutive C–C, C–O, and C–N coupling reaction of methyl (–)-3-dehydroshikimate with malononitrile and a bromoalkane or dibromoalkane under microwave conditions. This process represents a metal-free sustainable strategy for the construction of 2-(alkylamino)-3-cyanobenzofurans from a biomass-derived starting material.

Key words benzofurans, coupling, nitriles, bromoalkanes, cascade reaction, green-chemistry

The benzofuran scaffold is an important privileged structure that occurs in various natural products and synthetic molecules that show interesting biological and pharmaceutical activities.[1] For instance, the antiviral and antifungal agent ailanthoidol,[2] the antitumor natural product obovaten,[3] the cardiac arrhythmia drug dronedarone, and the H_3 receptor antagonist ABT-239 are all characterized by a benzofuran motif (Figure 1).[4,5] Studies have also shown that benzofurans can serve as protein phosphatase 1B inhibitors,[6] 5-lipoxygenase inhibitors,[7] antimicrobial agents,[8] antioxidants,[9] antidepressants, and antidementia agents.[10,11]

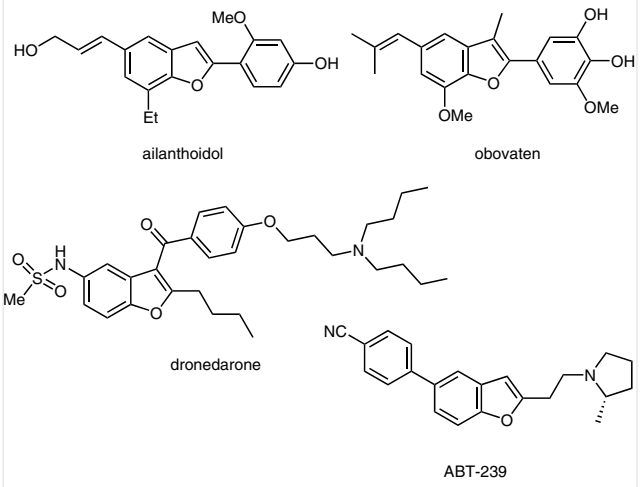


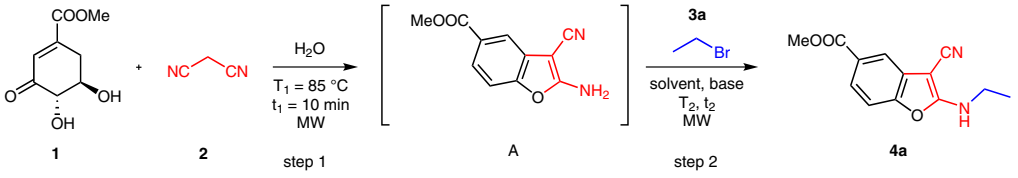
Figure 1 Examples of biologically active benzofuran derivatives

The rapid progress in biological research on benzofurans has stimulated recent interest in the synthesis of various functionalized benzofuran derivatives.[12] Wang, Kumaraswamy, and Sakai and their respective co-workers used the coupling reaction of activated phenols with α-bromo ketones to provide an array of 2-carbonylated benzofurans in high yields.[13] Liu, Hu, and Ragauskas and their re-

spective co-workers have reported consecutive coupling and cyclization reactions of *O*-arylhydroxylamines, aryl triflates, or catechols to give 3-carbonylated benzofurans in good yields and excellent regioselectivities.[14] Others have developed cross-coupling strategies that exploit the reactions of alkynes with *o*-substituted phenolics in the presence of transition metals and ligands to give various 2,3-disubstituted benzofurans in moderate to good yields.[15] More recently, several groups have demonstrated a hypervalent iodine-mediated oxidative dearomatization and palladium-catalyzed domino reaction to provide access to multifunctionalized benzofurans from 2-alkynylphenols, terminal alkenes, and aromatic amines in the presence of (diacetoxyiodo)benzene and palladium(II) bromide.[16] Although these methods represent workable approaches to syntheses of particular types of benzofurans and show considerable potential for medicinal chemistry research, there remains a need to expand the chemical diversity and range of synthetic strategies for the benzofuran motif. As far as we are aware, there have been no previous reports on the synthesis and biological properties of 2-(alkylamino)-3-cyanobenzofurans, a novel group of multifunctionalized benzofurans. As a part of our continuing efforts on biomass conversion and the utilization of methyl 3-dehydroshikimate (3-MDHS) as an interesting platform compound derived from shikimic acid,[17] we report a novel and efficient method for the synthesis of 2-(alkylamino)-3-cyanobenzofurans by sequential C–C, C–O, and C–N coupling reactions, starting from 3-MDHS.

Initially, we chose the reaction of 3-MDHS (**1**), readily obtained from renewably sourced shikimic acid as previously described,[17] with malononitrile (**2**) and bromoethane (**3a**) as a model reaction for the optimization of the reaction conditions, the results are summarized in Table 1. Interestingly, when 3-MDHS (**1**, 1 mmol) was treated with malononitrile (**2**, 1.5 mmol) in water (10 mL) at 85 °C for ten minutes under catalyst-free microwave conditions, the novel multifunctional intermediate methyl 2-amino-3-cyanobenzofuran-5-carboxylate (**A**) was precipitated and could be isolated quantitatively by filtration of the reaction mixture (step 1). The formation of intermediate **A** probably occurs through highly consecutive and thermodynamically favorable processes that include Knoevenagel condensation, dehydrative aromatization, intramolecular addition, and

Table 1 Optimization of the Reaction Conditions[a]

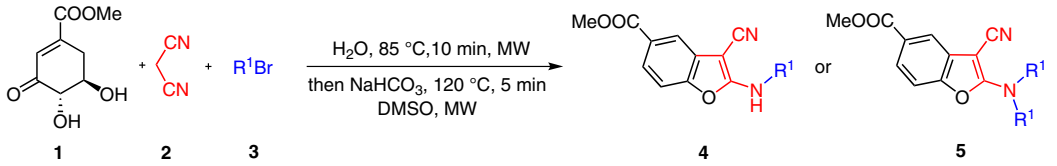


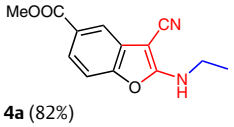
Entry	Solvent	Base	T_2 (°C)	t_2[b] (min)	Yield[c] (%)
1	DMF	K_2CO_3	90	6	62
2	EtOH	K_2CO_3	78	15	trace
3	MeCN	K_2CO_3	80	10	53
4	1,4-dioxane	K_2CO_3	100	10	trace
5	THF	K_2CO_3	66	15	–
6	DMSO	K_2CO_3	110	5	77
7	DMSO	Cs_2CO_3	110	5	64
8	DMSO	Na_2CO_3	110	6	75
9	DMSO	$NaHCO_3$	110	5	81
10	DMSO	Et_3N	110	6	60
11	DMSO	$NaHCO_3$	90	8	54
12	DMSO	$NaHCO_3$	120	5	82
13	DMSO	$NaHCO_3$	130	5	78
14	DMSO	$NaHCO_3$	140	5	74
15	DMSO	$NaHCO_3$	120[d]	300	65

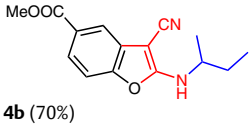
[a] Reaction conditions (unless otherwise noted): Step1: **1** (1 mmol), **2** (1.5 mmol), H_2O (10.0 mL), 85 °C, MW; Step 2: intermediate A (without further purification); **3a** (1 mmol), base (2 mmol), solvent (8 mL), 120 °C, MW, 5 min.
[b] The ramp time is included as part of the reaction time.
[c] Isolated yield.
[d] Oil bath.

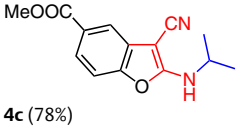
isomerization, leading to the construction of the new C–C and C–O bonds in **A**. Note that water was the optimal solvent for step 1; other solvents such as ethanol, acetonitrile, or tetrahydrofuran gave **A** in much lower yields (see Supporting Information). Subsequent N-alkylation of **A** with bromoethane (**3a**) in the presence of potassium carbonate in *N*,*N*-dimethylformamide under microwave conditions gave benzofuran **4a** in 62% yield. When other solvents were screened, dimethyl sulfoxide gave the best result (77% yield; Table 1, entries 1–6). We also explored the effect of the

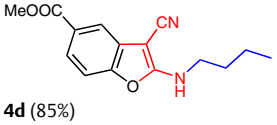
Table 2 Scope of the Reaction[a,b]

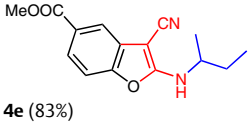


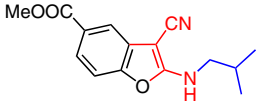

4a (82%)

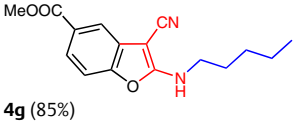

4b (70%)

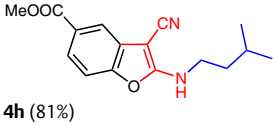

4c (78%)

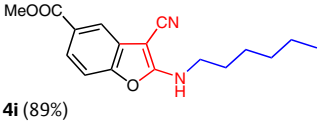

4d (85%)

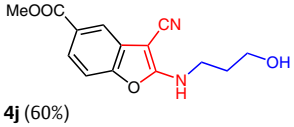

4e (83%)

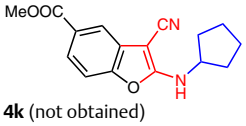

4f (87%)

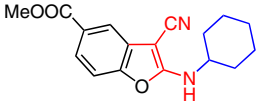

4g (85%)

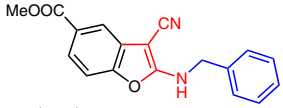

4h (81%)

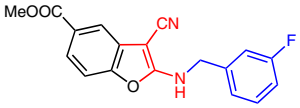

4i (89%)

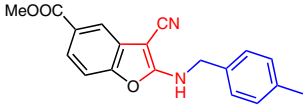

4j (60%)

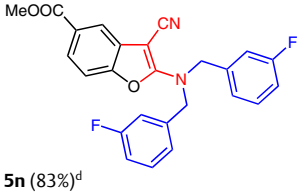

4k (not obtained)

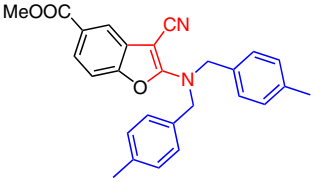

4l (not obtained)

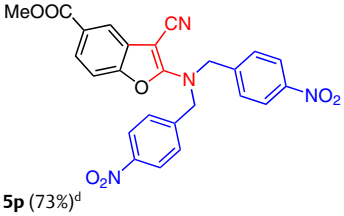

4m (80%)[c]

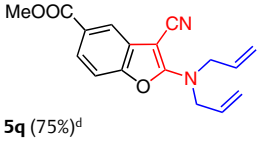

4n (61%)[c]

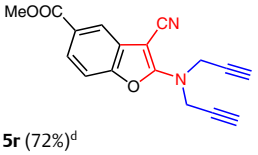

4o (70%)[c]


5n (83%)[d]


5o (78%)[d]


5p (73%)[d]


5q (75%)[d]


5r (72%)[d]

[a] Reaction conditions: Step1: **1** (1 mmol), **2** (1.5mmol), H_2O (10.0 mL), 85 °C, MW, 10 min; Step2: **3** (1 mmol), $NaHCO_3$ (2 mmol), DMSO (8 mL), 120 °C, MW, 5 min.18

[b] All yields are isolated yields.

[c] Step 2: **3** (1 mmol), $NaHCO_3$ (2 mmol), MeCN (8 mL), 80 °C (conventional heating), 18 h.

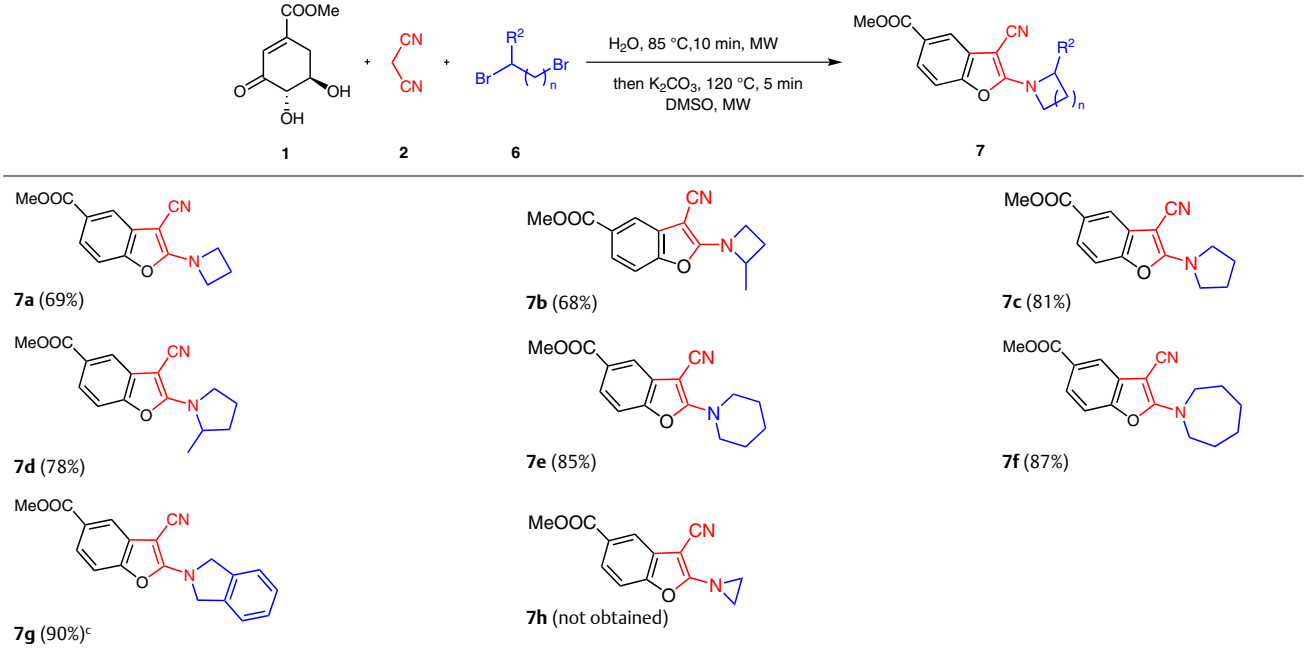
[d] Step 2: **3** (2.4 mmol), $NaHCO_3$ (4 mmol), MeCN (8 mL), 80 °C (conventional heating), 18 h.

base. Whereas inorganic bases (such as potassium, cesium, or sodium carbonate or sodium bicarbonate) and the organic base triethylamine were all suitable for this N-alkylation process (entries 6–10), sodium bicarbonate proved to be the optimal base, affording the desired product in 82% yield. In addition, a study on the reaction temperature showed that 120 °C was most favorable for step 2; lower or higher temperatures gave lower yields (entries 11–14). In contrast to microwave heating, when the reaction was performed with conventional heating, a prolonged reaction time (300 min) was needed to give a 65% yield of **4a** (entry 15). Therefore, the optimal conditions for the synthesis of 2-(alkylamino)-3-cyanobenzofurans are as follows: 3-MDHS (**1**, 1 mmol) and malononitrile (**2**, 1.5 mmol) in water (10 mL) at 85 °C for 10 minutes (step 1), then **A**, **3a** (1 mmol), and sodium bicarbonate (2.0 mmol) in dimethyl sulfoxide (8 mL) at 120 °C for 5 minutes (step 2). Both steps are performed under microwave conditions (entry 12).

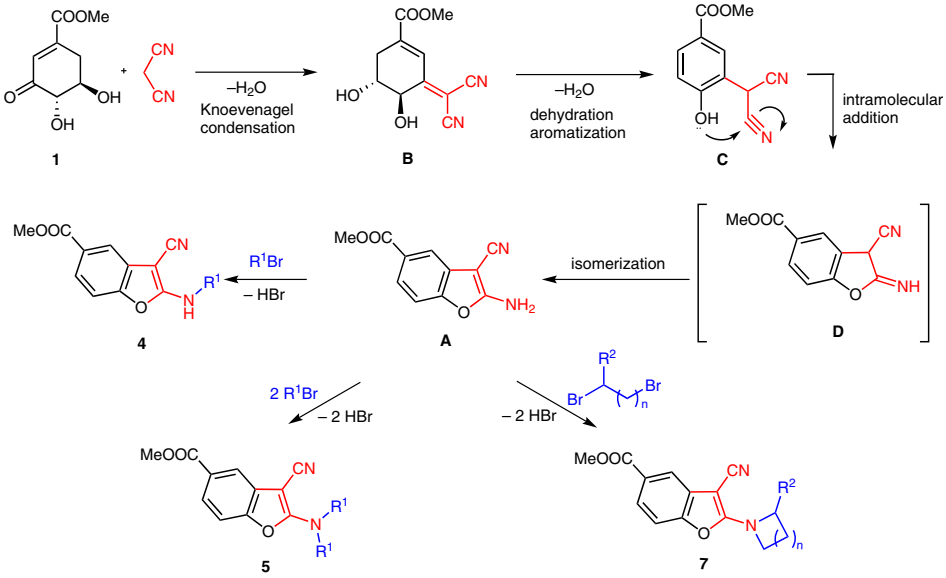
Having established the optimal reaction conditions, we screened a variety of bromoalkanes **3** to explore the generality and limitations of this cascade process. As shown in Table 2, the coupling reactions of intermediate **A** with various linear or branched saturated bromoalkanes proceeded under the optimized conditions to give the corresponding 2-(alkylamino)-3-cyanobenzofurans in satisfactory yield (70–89%). The hydroxylated alkyl bromide **3j** also gave the expected product **4j** in 60% yield (Table 2). We were disappointed to note that the desired products (**4k**, **4l**) were not detected when bromocyclopentane **3k** or bromocyclohexane **3l** was used as the reactant, indicating that the steric hindrance in **3** has a significant effect on the course of step 2. Interestingly, the reaction worked well under the standard reaction conditions when reactive benzylated bromides **3m**–**o** were used, affording the corresponding products **4m**–**o** in 61–80% yield. Note that when an excess (2.4 equiv) of a reactive bromoalkane, such as the benzylated bromides **3n**–**p**, allyl bromide (**3q**), or propargyl bromide (**3r**), was used as the reactant, the corresponding *N*,*N*-(dialkylamino)-3-cyanobenzofuran **5n**–**r** was obtained in good to high yield.

To further investigate the applicability of our protocol, we examined the coupling reactions of an array of dibromoalkanes **6a**–**h** (Table 3). The reaction was found to accommodate a variety of dibromoalkanes **6a**–**g**, giving the corresponding four- to seven-membered nitrogen-containing alicyclic-substituted benzofurans **7a**–**g** in good to high yields (68–90%), regardless of whether a linear or branched dibromoalkane was used. Note that when 1,2-bis(bromomethyl)benzene (**6g**) was used, the reaction with intermediate **A** led to the corresponding benzofuran **7g** in excellent yield, probably owing to the high reactivity of the benzylic bromide groups in the substrate. Unfortunately, the

Table 3 Scope of Dibromoalkane Substrates[a,b]



[a] Reaction conditions: Step1: **1** (1 mmol), **2** (1.5 mmol), H_2O (10.0 mL), 85 °C, MW, 10 min; Step 2: **6** (1.2 mmol), K_2CO_3 (2 mmol), DMSO (8 mL), 120 °C (MW).18
[b] All yields are isolated yields.
[c] Step 2: MeCN, 80 °C (conventional heating), 18 h.



Scheme 1 Proposed reaction pathway for the formation of 2-(alkylamino)-3-cyanobenzofurans

use of 1,2-dibromoethane (**6h**) did not give the expected benzofuran **7h**, possibly due to the immense strain that has to be overcome for the formation of the aziridine motif.

On the basis of our previous studies and the results discussed above, we propose a plausible reaction pathway for the formation of the benzofurans (Scheme 1).[17] The reaction starts with the Knoevenagel condensation of 3-MDHS (**1**) with malononitrile to generate the olefin **B** with loss of water. Olefin **B** is then readily transformed by dehydrative aromatization into intermediate **C**, which undergoes subsequent intramolecular cycloaddition to give imine **D**. The driving force of forming a conjugated product then results in isomerization of **D** to give intermediate **A**. Finally, nucleophilic substitution of **A** with various bromoalkanes or dibromoalkanes gives the corresponding 2-(alkylamino)-3-cyanobenzofurans **4**, **5**, or **7**.

In summary, we have developed a novel and straightforward protocol for the assembly of multifunctional benzofurans through a cascade reaction of 3-MDHS, malononitrile, and a bromoalkane involving C–C, C–O, and C–N bond-forming processes. Notable features of this strategy, such as the use of a biomass-derived starting material, metal-free reaction conditions, controllable selectivity, and operational simplicity make the protocol synthetically useful. It is worth mentioning that the presence in the benzofuran products of readily transformable methoxycarbonyl, cyano, and alkylamino functional groups should facilitate further transformations and might be useful in medicinal chemistry research.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560582.

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(18) **Methyl 2-(Alkylamino)-3-cyanobenzofuran-5-carboxylates 4a–j and 7a–g; General Procedure**
A 25 mL round-bottomed flask was charged with 3-MDHS (**1**; 0.19 g, 1 mmol), malononitrile (**2**; 1.5 mmol), and H_2O (10 mL). The flask was placed in a microwave synthesizer, and the mixture was irradiated (240 W) at 85 °C for 10 min. The mixture was then filtered under reduced pressure to give the crude intermediate **A**, which was used in step 2 without further purification.
Intermediate **A**, inorganic base [$NaHCO_3$ (2 mmol) for **4a–j**; K_2CO_3 (2 mmol) for **7a–g**], bromoalkane **3** [monobromoalkane (2 mmol) for **4a–4**; dibromoalkane for **7a–g**], and DMSO (8 mL) were added to a flask and irradiated (240 W) at 120 °C for 5 min then cooled. The mixture was then poured into brine (40 mL), extracted with EtOAc (3 × 20 mL), and dried ($MgSO_4$). The organic layer was concentrated and the residue was purified by column chromatography (silica gel, EtOAc–PE).
Methyl 3-Cyano-2-(ethylamino)-1-benzofuran-5-carboxylate (4a)
Light-yellow solid; yield: 82%; mp 189–190 °C. IR (KBr): 3442, 3288, 3058, 2972, 2206, 1728, 1712, 1645, 1533, 1448, 1344, 1294, 1248, 1184, 1107, 997, 958, 885, 762, 729, 654, 584 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.93 (t, *J* = 5.60 Hz, 1 H), 7.74 (d, *J* = 1.60 Hz, 1 H), 7.71 (dd, J_1 = 8.40 Hz, J_2 = 1.60 Hz, 1 H), 7.49 (d, *J* = 8.40 Hz, 1 H), 3.86 (s, 3 H), 3.47 (m, 2 H), 1.25 (t, *J* = 4.00 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.9, 164.6, 150.4, 128.9, 125.8, 123.2, 116.5, 115.1, 110.0, 59.3, 52.1, 37.1, 14.8. HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{13}H_{13}N_2O_3$: 245.0921; found: 245.0923.
Methyl 3-Cyano-2-(propylamino)-1-benzofuran-5-carboxylate (4c)
White solid; yield: 70%; mp 168–169 °C. IR (KBr): 3435, 3288, 3047, 2980, 2200, 1703, 1628, 1531, 1450, 1288, 1250, 1176, 1165, 1101, 976, 766, 731, 644, 600 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.89 (d, *J* = 8.40 Hz, 1 H), 7.75 (s, 1 H), 7.71 (dd, J_1 = 8.40 Hz, J_2 = 1.20 Hz, 1 H), 7.50 (d, *J* = 8.40 Hz, 1 H), 4.05 (m, 1 H), 3.86 (s, 3 H), 1.27 (d, *J* = 8.00 Hz, 6 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.0, 163.9, 150.5, 129.0, 125.9, 123.3, 116.5, 115.2, 110.0, 59.3, 52.2, 45.0, 22.6. HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{14}H_{15}N_2O_3$: 259.1077; found: 259.1074.
Methyl 2-(*sec*-Butylamino)-3-cyano-1-benzofuran-5-carboxylate (4e)
White needles; yield: 83%; mp 142–143 °C. IR (KBr): 3427, 3278, 3224, 3095, 2964, 2214, 1714, 1649, 1460, 1298, 1246, 1184, 1082, 991, 899, 822, 764, 656 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.86 (d, *J* = 8.80 Hz, 1 H), 7.74 (d, *J* = 1.60 Hz, 1 H), 7.71 (dd, J_1 = 8.80 Hz, J_2 = 2.00 Hz, 1 H), 7.49 (d, *J* = 8.40 Hz, 1 H), 3.86 (s, 3 H), 3.82 (m, 1 H), 1.61 (m, 2 H), 1.25 (d, *J* = 6.40 Hz, 3 H), 0.92 (t, *J* = 7.60 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.0, 164.2, 150.4, 129.1, 125.9, 123.3, 116.5, 115.3, 110.0, 59.1, 52.2, 50.6, 29.0, 20.4, 10.3. HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{15}H_{17}N_2O_3$: 273.1234; found: 273.1236.
Methyl 3-Cyano-2-[(3-methylbutyl)amino]-1-benzofuran-5-carboxylate (4h)
White needles; yield: 81%; mp 136–137 °C. IR (KBr): 3429, 3224, 3086, 2951, 2879, 2214, 1718, 1662, 1460, 1369, 1294, 1248, 1190, 1119, 1101, 991, 957, 895, 822, 764, 669, 623 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.94 (t, *J* = 6.00 Hz, 1 H), 7.74 (d, *J* = 1.20 Hz, 1 H), 7.70 (dd, J_1 = 8.40 Hz, J_2 = 1.60 Hz, 1 H), 7.49 (d, *J* = 8.40 Hz, 1 H), 3.86 (s, 3 H), 3.44 (m, 2 H), 1.69 (m, 1 H), 1.52 (m, 2 H), 0.92 (d, *J* = 6.40 Hz, 6 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.0, 164.7, 150.5, 129.0, 125.9, 123.3, 116.5, 115.2, 110.0, 59.3, 52.2, 40.7, 37.9, 25.1, 22.3. HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{16}H_{19}N_2O_3$: 287.1396; found: 287.1397.
Methyl 3-Cyano-2-[(3-hydroxypropyl)amino]-1-benzofuran-5-carboxylate (4j)
Brown solid; yield: 60%; mp 150–151 °C. IR (KBr): 3469, 3286, 3242, 3084, 2947, 2881, 2202, 1713, 1651, 1456, 1363, 1302, 1244, 1190, 1144, 1099, 1063, 978, 885, 829, 760, 698, 658, 590 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.89 (t, *J* = 5.60 Hz, 1 H), 7.74 (d, *J* = 1.20 Hz, 1 H), 7.70 (dd, J_1 = 8.40 Hz, J_2 = 2.00 Hz, 1 H), 7.49 (d, *J* = 8.40 Hz, 1 H), 4.59 (s, 1 H), 3.86 (s, 3 H), 3.50 (m, 4 H), 1.78 (m, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.0, 164.8,

150.5, 129.0, 125.9, 123.2, 116.5, 115.2, 110.0, 59.4, 57.8, 52.2, 32.2. HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{14}H_{15}N_2O_4$: 275.1032; found: 275.1031.

Methyl 3-Cyano-2-pyrrolidin-1-yl-1-benzofuran-5-carboxylate (7c)

White needles; yield: 81%; mp 185–186 °C. IR (KBr): 3431, 3064, 2960, 2879, 2191, 1724, 1637, 1450, 1352, 1300, 1246, 1178, 1097, 960, 881, 858, 818, 764, 733, 662, 517 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.71 (d, J = 1.20 Hz, 1 H), 7.69 (dd, J_1 = 8.40 Hz, J_2 = 2.00 Hz, 1 H), 7.48 (d, J = 8.40 Hz, 1 H), 3.87 (s, 3 H), 3.68 (t, J = 6.00 Hz, 4 H), 2.00 (t, J = 6.40 Hz, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.0, 161.8, 150.7, 129.3, 126.0, 123.3, 116.6, 115.8, 110.1, 60.2, 52.2, 48.1, 24.9. HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{15}H_{15}N_2O_3$: 271.1083; found: 271.1085.

Methyl 3-Cyano-2-piperidin-1-yl-1-benzofuran-5-carboxylate (7e)

White crystals; yield: 87%; mp 147–148 °C. IR (KBr): 3448, 3425, 3107, 2939, 2856, 2197, 1724, 1610, 1585, 1450, 1383, 1363, 1302, 1234, 1186, 1142, 1097, 962, 851, 800, 760, 665, 609 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.76 (d, J = 1.20 Hz, 1 H), 7.73 (dd, J_1 = 8.40 Hz, J_2 = 1.60 Hz, 1 H), 7.50 (d, J = 8.40 Hz, 1 H), 3.87 (s, 3 H), 3.73 (s, 4 H), 1.67 (s, 6 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.9, 162.8, 150.2, 129.2, 126.0, 123.7, 116.7, 115.6, 110.2, 61.0, 52.2, 47.0, 24.8, 23.1. HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{16}H_{17}N_2O_3$: 285.1239; found: 285.1238.