Supporting Information
for DOI: 10.1055/s-0035-1560582
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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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## Supporting Information

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1. General Details

The $^1$H and $^{13}$C NMR spectra were recorded at 400 and 100 MHz, respectively. The chemical shifts of the $^1$H NMR and $^{13}$C NMR spectra are reported in ppm relative to the residual signals of the solvents (DMSO-d$_6$ @ 2.50 ppm for the $^1$H NMR and 39.5 ppm for the $^{13}$C NMR). All coupling constants ($J$) are reported in Hertz (Hz). The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet; m, multiplet.

Mass spectra were obtained from the High Resolution Mass Spectrometry Unit on a Bruker Waters Micromass LCT-Premier (TOF) in Electrospray Ionization (ESI) by direct infusion. Infrared spectra were obtained from a type of Analect RFX-65A Fourier Transform Infrared spectrometer (KBr tablet). All melting points were obtained using a Thiele apparatus and are uncorrected.

1.1 General procedures

All microwave reactions were carried out in a scientific WBFY-205 microwave reactor. This reactor was a monomode device with a tunable power controller. Reaction temperature was detected using an infrared thermometer. Other reactions were set up with traditional heating in an oil bath. Chromatographic purification of products was accomplished using commercially prepared silica gel (200-300 mesh) with EtOAc-PE as the eluent. For thin layer chromatography (TLC) analysis throughout this work, the commercially prepared TLC plates (silica gel HSGF$_{254}$, 0.20mm) were employed.

1.2 Materials
Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Petroleum ether (PE) used in the experiments refers to the boiling fraction 60-90 °C. (-)-Methyl 3-dehydroshikimate was prepared from (-)-shikimic acid through an improved method based on our previously reported protocol (see General Procedure 2.1).

2. General Procedure for 2-Alkylamino-3-cyanobenzofurans

2.1 Typical procedure for the preparation of 3-MDHS

To a mixture of (-)-shikimic acid (8.7g, 0.05mol) and p-TsOH/SiO$_2$ (1.4g) was added MeOH (100 ml). The mixture was heated at reflux for 5 h. After cooling, the catalyst was filtered off and the filtrate was concentrated under reduced pressure to give crude (-)-methyl shikimate. Then, the crude (-)-methyl shikimate and IBX (16.8g, 0.06mol) was added THF (220 ml). The resulting mixture was stirred at 10-20°C for
the completion of the reaction. The IBA byproduct was filtered off and the filtrate was concentrated under reduced pressure to afford crude 3-MDHS as a white solid. The crude product was recrystallized from EtOAc to give pure 3-MDHS as white crystals.

2.2 Solvent effect for the preparation of methyl 2-amino-3-cyanobenzofuran-5-carboxylate (A) (Step 1)

Solvent effect for step 1 was summarized in Table 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield of A</th>
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<tr>
<td>1</td>
<td>H₂O</td>
<td>97%</td>
</tr>
<tr>
<td>2</td>
<td>EtOH</td>
<td>80%</td>
</tr>
<tr>
<td>3</td>
<td>CH₃CN</td>
<td>78%</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>40%</td>
</tr>
</tbody>
</table>

2.3 General procedure for the preparation of compounds (Table 2, 4a-4j)

To a round bottom flask (25 ml) was added 3-MDHS (0.19 g, 1 mmol), malononitrile (1.5 mmol) and H₂O (10 ml). The flask was then placed into the microwave synthesizer and the mixture was irradiated (240 W) at 85 °C for 10 min. The resulting mixture was filtered under reduced pressure, then the crude intermediate, NaHCO₃ (0.17 g, 2 mmol), bromoalkanes (1 mmol) and DMSO (8 ml) were added to a flask and irradiated (240 W) at 120 °C for 5 min. After cooling, the mixture was poured into brine (40 ml), then extracted with ethyl acetate (3×20 ml) and dried over anhydrous MgSO₄. The organic layer was evaporated and was purified by column chromatography using EtOAc-PE as the eluent to afford the desired products 4a-4j.

2.4 General procedure for the preparation of compounds (Table 2, 4m-4o)

To a round bottom flask (25 ml) was added 3-MDHS (0.19 g, 1 mmol), malononitrile (1.5 mmol) and H₂O (10 ml). The flask was then placed into the microwave synthesizer and the mixture was irradiated (240 W) at 85 °C for 10 min. The resulting mixture was filtered under reduced pressure, then the crude intermediate, NaHCO₃ (0.17 g, 2 mmol), bromoalkanes (1 mmol) and CH₃CN (10 ml) were added to a flask, and the mixture was heated at reflux for 18 h. Then the mixture was concentrated under vacuum and was purified by column chromatography using EtOAc-PE as the eluent to afford the desired products 4m-4o.

2.5 Procedure for the preparation of compounds (Table 2, 5n-5r)

To a round bottom flask (25 ml) was added 3-MDHS (0.19 g, 1 mmol), malononitrile (1.5 mmol) and H₂O (10 ml). The flask was then placed into the microwave synthesizer and the mixture was irradiated (240 W) at 85 °C for 10 min. The resulting mixture was filtered under reduced pressure, then the crude intermediate, NaHCO₃ (0.17 g, 2 mmol), bromoalkanes (2.4 mmol) and CH₃CN (10 ml) were added.
to a flask, the mixture was heated at reflux for 24 h. Then the mixture was concentrated under vacuum and was purified by column chromatography using EtOAc-PE as the eluent to afford the desired products 5n-5r.

2.6 Procedure for the preparation of compounds (Table 3, 7a-7g)

To a round bottom flask (25 ml) was added 3-MDHS (0.19 g, 1 mmol), malononitrile (1.5 mmol) and H₂O (10 ml). The flask was then placed into the microwave synthesizer and the mixture was irradiated (240 W) at 85 ºC for 10 min. The result mixture was filtered under reduce pressure, then the crude intermediate, K₂CO₃ (0.27 g, 2 mmol), dibromoalkanes (1.2 mmol) and DMSO (8 ml) were added to a flask and irradiated (240 W) at 120 ºC for 5 min. After cooling, the mixture was poured into brine (40 ml), then extracted with ethyl acetate (3×20 ml) and dried over anhydrous MgSO₄. The organic layer was concentrated under vacuum and was purified by column chromatography using EtOAc-PE as the eluent to afford the desired products 7a-7g.

3. Characterization Data for Products

3.1 Characterization Data for 3-MDHS and intermediate A.

(-)-Methyl-3-dehydroshikimate (3-MDHS)

![3-MDHS structure]

White solid; mp 122-123 ºC; [α]D²⁰ = -55° (c= 0.2, MeOH); ¹H NMR (CD₃COCD₃, 400 MHz) δ: 6.45(d, J= 2.8Hz, 1H, 2-H), 4.57(d, J= 3.6Hz, 1H, 4-OH D₂O exchangeable), 4.47(d, J= 3.6Hz, 1H, 5-OH D₂O exchangeable), 4.57(dd, J₁= 10.4Hz, J₂= 3.6Hz, 1H, 4-H), 3.85(m, 1H, 5-H), 3.81(s, 3H, OCH₃), 3.06(dd, J₁= 18.4Hz, J₂=5.2Hz, 1H, 6α-H), 2.18(ddd, J₁= 18.4Hz, J₂=8.8Hz, J₃= 3.2Hz, 1H, 6β-H); ¹³C NMR(100 MHz, DMSO-d₆), δ: 199.7, 166.0, 145.3, 130.8, 77.6, 70.0, 52.7, 32.6; IR(KBr) νmax/cm⁻¹: 3475, 3394, 3328, 2912, 1730, 1689, 1438, 1249, 1118, 748, 609; MS (EI), m/z: 186(M⁺), 155, 127.

Methyl 2-amino-3-cyanobenzofuran-5-carboxylate (A)

![Methyl 2-amino-3-cyanobenzofuran-5-carboxylate structure]

White needles; mp 260-261 ºC; ¹H NMR (400 MHz,
DMSO-d$_6$ $\delta$: 8.50(s, 2H, NH$_2$), 7.74(d, 1H, $J=1.6$ Hz, 4-ArH), 7.70(dd, 1H, $J_1=8.4$ Hz, $J_2=1.6$ Hz, 6-ArH), 7.48(d, 1H, $J=8.4$ Hz, 7-ArH), 3.86(s, 3H, OCH$_3$); $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$: 166.6, 166.0, 150.5, 128.7, 125.8, 123.2, 116.6, 114.7, 110.0, 60.1, 52.2; IR(KBr) $\nu_{\text{max}}$/cm$^{-1}$: 3409, 3320, 2950, 2212, 1718, 1645, 1583, 1460, 1246, 1186, 1101, 997, 887, 758, 729; MS (EI), m/z: 216(M$^+$), 185, 157, 129, 102, 75.

### 3.2 Characterization Data for Products (Table 2, 4a-4j, 4m-4o and 5n-5r)

**Methyl 3-cyano-2-(ethylamino)benzofuran-5-carboxylate (4a)**

Light yellow solid; yield: 0.20g (82%), mp 189-190°C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$: 8.93(t, $J = 5.60$ Hz, 1H), 7.74(d, $J = 1.60$ Hz, 1H), 7.71(dd, $J_1 = 8.40$ Hz, $J_2 = 1.60$ Hz, 1H), 7.49(d, $J = 8.40$ Hz, 1H), 3.86(s, 3H), 3.47(m, 2H), 1.25(t, $J = 4.00$ Hz, 3H); $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$: 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; IR(KBr) $\nu_{\text{max}}$/cm$^{-1}$: 3442, 3288, 3058, 2972, 2206, 1728, 1712, 1645, 1533, 1448, 1344, 1294, 1248, 1184, 1107, 997, 958, 885, 762, 729, 654, 584; HRMS (ESI-TOF) m/z calcd for C$_{13}$H$_{13}$N$_2$O$_3$ [M+H]$^+$ 245.0921, found 245.0923.

**Methyl 3-cyano-2-(propylamino)benzofuran-5-carboxylate (4b)**

Yellow solid; yield: 0.18g (70%); mp 169-170°C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$: 8.97(t, $J = 6.00$ Hz, 1H), 7.74(d, $J = 1.60$ Hz, 1H), 7.71(dd, $J_1 = 8.40$ Hz, $J_2 = 1.60$ Hz, 1H), 7.49(d, $J = 8.40$ Hz, 1H), 3.86(s, 3H), 3.40(m, 2H), 1.63(m, 2H), 0.94(t, $J = 8.00$ Hz, 3H); $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$: 166.0, 164.8, 150.5, 129.0, 125.9, 123.3, 116.5, 115.2, 110.0, 59.3, 52.2, 44.0, 22.5, 11.0; IR(KBr) $\nu_{\text{max}}$/cm$^{-1}$: 3440, 3282, 3242, 3086, 2949, 2877, 2360, 2204, 1718, 1651, 1462, 1362, 1298, 1242, 1190, 1101, 980, 883, 825, 758, 663, 606; HRMS (ESI-TOF) m/z calcd for C$_{14}$H$_{15}$N$_2$O$_3$ [M+H]$^+$ 259.1077, found 259.1076.

**Methyl 3-cyano-2-(isopropylamino)benzofuran-5-carboxylate (4c)**

White solid; yield: 0.20g (78%); mp 168-169°C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$: 8.50(s, 2H, NH$_2$), 7.74(d, 1H, $J=1.6$ Hz, 4-ArH), 7.70(dd, 1H, $J_1=8.4$ Hz, $J_2=1.6$ Hz, 6-ArH), 7.48(d, 1H, $J=8.4$ Hz, 7-ArH), 3.86(s, 3H, OCH$_3$); $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$: 166.6, 166.0, 150.5, 128.7, 125.8, 123.2, 116.6, 114.7, 110.0, 60.1, 52.2; IR(KBr) $\nu_{\text{max}}$/cm$^{-1}$: 3409, 3320, 2950, 2212, 1718, 1645, 1583, 1460, 1246, 1186, 1101, 997, 887. 758, 729; MS (EI), m/z: 216(M$^+$), 185, 157, 129, 102, 75.
MHz, DMSO-d$_6$) δ: 8.89(d, $J = 8.40$ Hz, 1H), 7.75(s, 1H), 7.71(dd, $J_1 = 8.40$ Hz, $J_2 = 1.20$ Hz, 1H), 7.50(d, $J = 8.40$ Hz, 1H), 4.05(m, 1H), 3.86(s, 3H), 1.27(d, $J = 8.00$ Hz, 6H); $^{13}$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; IR(KBr) $v_{\text{max}}$/cm$^{-1}$: 3435, 3288, 3047, 2980, 2200, 1703, 1628, 1531, 1450, 1288, 1250, 1176, 1165, 1101, 976, 766, 731, 644, 600; HRMS (ESI-TOF) $m/z$ calcd for C$_{14}$H$_{15}$N$_2$O$_3$ [M+H]$^+$ 259.1077, found 259.1074.

**Methyl 2-(butylamino)-3-cyanobenzofuran-5-carboxylate (4d)**

White solid; yield: 0.23g (85%); mp 119–120°C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 8.97(t, $J = 5.60$ Hz, 1H), 7.74(d, $J = 1.60$ Hz, 1H), 7.71(dd, $J_1 = 8.80$ Hz, $J_2 = 2.00$ Hz, 1H), 7.50(d, $J = 8.40$ Hz, 1H), 3.86(s, 3H), 3.43(m, 2H), 1.61(m, 2H), 1.39(m, 2H), 0.92(t, $J = 7.20$ Hz, 3H); $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ: 166.0, 164.8, 150.5, 129.0, 125.9, 123.3, 116.5, 115.2, 110.0, 59.3, 52.2, 42.1, 31.2, 19.3, 13.6; IR(KBr) $v_{\text{max}}$/cm$^{-1}$: 3437, 3288, 3242, 3095, 2964, 2214, 1714, 1655, 1531, 1458, 1373, 1296, 1244, 1190, 1155, 1101, 984, 893, 825, 762, 733, 662, 600; HRMS (ESI-TOF) $m/z$ calcd for C$_{15}$H$_{17}$N$_2$O$_3$ [M+H]$^+$ 273.1234, found 273.1237.

**Methyl 2-(sec-butylamino)-3-cyanobenzofuran-5-carboxylate (4e)**

White needles; yield: 0.22g (83%); mp 142–143°C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 8.86(d, $J = 8.80$ Hz, 1H), 7.74(d, $J = 1.60$ Hz, 1H), 7.71(dd, $J_1 = 8.80$ Hz, $J_2 = 2.00$ Hz, 1H), 7.49(d, $J = 8.40$ Hz, 1H), 3.86(s, 3H), 3.82(m, 1H), 1.61(m, 2H), 1.25(d, $J = 6.40$ Hz, 3H), 0.92(t, $J = 7.60$ Hz, 3H); $^{13}$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; IR(KBr) $v_{\text{max}}$/cm$^{-1}$: 3427, 3288, 3242, 2951, 2873, 2204, 1713, 1655, 1531, 1458, 1373, 1296, 1244, 1190, 1155, 1101, 984, 893, 825, 762, 733, 662, 600; HRMS (ESI-TOF) $m/z$ calcd for C$_{15}$H$_{17}$N$_2$O$_3$ [M+H]$^+$ 273.1234, found 273.1236.

**Methyl 3-cyano-2-(isobutylamino)benzofuran-5-carboxylate (4f)**

Yellow solid; yield: 0.24g (87%); mp 136–137°C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 9.04(t, $J = 6.00$ Hz, 1H), 7.74(d, $J = 1.20$ Hz, 1H), 7.71(dd,
$J_1 = 8.40 \text{ Hz, } J_2 = 1.60 \text{ Hz, } 1\text{H}$), 7.48(d, $J = 8.40 \text{ Hz, } 1\text{H}$), 3.86(s, 3H), 3.24(t, $J = 6.40 \text{ Hz, } 2\text{H}$), 1.93(m, 1H), 0.95(d, $J = 6.40 \text{ Hz, } 6\text{H}$); $^1$C NMR (100 MHz, DMSO-d$_6$) δ: 165.9, 164.8, 150.3, 128.9, 125.8, 123.2, 116.4, 115.1, 109.9, 59.2, 52.1, 49.6, 28.2, 19.6; IR(KBr) $\nu_{\max}$/cm$^{-1}$: 3429, 3292, 3248, 3097, 2960, 2212, 1711, 1657, 1460, 1300, 1248, 1186, 1099, 1063, 985, 887, 822, 766, 660; HRMS (ESI-TOF) $m/z$ calcd for C$_{13}$H$_{17}$N$_2$O$_3$ [M+H]$^+$ 273.1239, found 273.1239.

**Methyl 3-cyano-2-(pentylamino)benzofuran-5-carboxylate (4g)**

White crystals; yield: 0.24g (85%); mp 120–121°C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 8.96(t, $J = 5.60 \text{ Hz, } 1\text{H}$), 7.74(d, $J = 1.20 \text{ Hz, } 1\text{H}$), 7.71(dd, $J_1 = 8.40 \text{ Hz, } J_2 = 1.60 \text{ Hz, } 1\text{H}$), 7.49(d, $J = 8.40 \text{ Hz, } 1\text{H}$), 3.86(s, 3H), 3.41(m, 2H), 1.62(m, 2H), 1.33(m, 4H), 0.88(t, $J = 6.80 \text{ Hz, } 3\text{H}$); $^1$C NMR (100 MHz, DMSO-d$_6$) δ: 166.0, 164.8, 150.5, 129.0, 125.9, 123.3, 116.5, 115.2, 110.0, 59.3, 52.2, 42.3, 28.8, 28.2, 21.8, 13.9; IR(KBr) $\nu_{\max}$/cm$^{-1}$: 3431, 3280, 3232, 3091, 2947, 2872, 2208, 1718, 1668, 1464, 1356, 1302, 1244, 1190, 1153, 1101, 985, 891, 827, 762, 733, 623; HRMS (ESI-TOF) $m/z$ calcd for C$_{16}$H$_{19}$N$_2$O$_3$ [M+H]$^+$ 287.1396, found 287.1395.

**Methyl 3-cyano-2-(isopentylamino)benzofuran-5-carboxylate (4h)**

White needles; yield: 0.23g (81%); mp 136–137°C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 8.94(t, $J = 6.00 \text{ Hz, } 1\text{H}$), 7.74(d, $J = 1.20 \text{ Hz, } 1\text{H}$), 7.70(dd, $J_1 = 8.40 \text{ Hz, } J_2 = 1.60 \text{ Hz, } 1\text{H}$), 7.49(d, $J = 8.40 \text{ Hz, } 1\text{H}$), 3.86(s, 3H), 3.44(m, 2H), 1.69(m, 1H), 1.52(m, 2H), 0.92(d, $J = 6.40 \text{ Hz, } 6\text{H}$); $^1$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; IR(KBr) $\nu_{\max}$/cm$^{-1}$: 3429, 3224, 3086, 2986, 2951, 2879, 2214, 1718, 1662, 1460, 1369, 1294, 1248, 1190, 1119, 1101, 991, 957, 895, 822, 764, 669, 623; HRMS (ESI-TOF) $m/z$ calcd for C$_{16}$H$_{19}$N$_2$O$_3$ [M+H]$^+$ 287.1396, found 287.1397.

**Methyl 3-cyano-2-(hexylamino)benzofuran-5-carboxylate (4i)**

Yellow needles; yield: 0.27g (89%); mp 121–122°C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 8.96(t, $J = 5.60 \text{ Hz, } 1\text{H}$), 7.74(d, $J = 1.60 \text{ Hz, } 1\text{H}$),
7.71(dd, $J_1 = 8.40$ Hz, $J_2 = 1.60$ Hz, 1H), 7.49(d, $J = 8.80$ Hz, 1H), 3.86(s, 3H), 3.41(m, 2H), 1.61(m, 2H), 1.33(m, 6H), 0.87(t, $J = 6.80$ Hz, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 166.0, 164.7, 150.5, 129.0, 125.9, 123.2, 116.5, 115.2, 110.0, 59.3, 52.2, 42.4, 30.8, 29.1, 25.7, 22.0, 13.9; IR(KBr) $\nu_{\text{max}}$/cm$^{-1}$: 3423, 3280, 3240, 3091, 2941, 2870, 2204, 1716, 1664, 1616, 1464, 1367, 1356, 1302, 1246, 1190, 1151, 1103, 1059, 985, 891, 827, 762, 733, 667, 606; HRMS (ESI-TOF) $m/z$ calcd for C$_{17}$H$_{21}$N$_2$O$_3$ [M+H]$^+$ 301.1547, found 301.1549.

**Methyl 3-cyano-2-(3-hydroxypropylamino)benzofuran-5-carboxylate (4j)**

Brown solid; yield: 0.16g (60%); mp 150–151°C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.89(t, $J = 5.60$ Hz, 1H), 7.74(d, $J = 1.20$ Hz, 1H), 7.70(dd, $J_1 = 8.40$ Hz, $J_2 = 2.00$ Hz, 1H), 7.49(d, $J = 8.40$ Hz, 1H), 4.59(s, 1H), 3.86(s, 3H), 3.50(m, 4H), 1.78(m, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 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; IR(KBr) $\nu_{\text{max}}$/cm$^{-1}$: 3469, 3286, 3242, 3084, 2947, 2881, 2202, 1713, 1651, 1456, 1363, 1302, 1244, 1190, 1144, 1099, 1063, 978, 885, 829, 760, 698, 658, 590; HRMS (ESI-TOF) $m/z$ calcd for C$_{14}$H$_{15}$N$_2$O$_4$ [M+H]$^+$ 275.1032, found 275.1031.

**Methyl 2-(benzylamino)-3-cyanobenzofuran-5-carboxylate (4m)**

White crystals; yield: 0.24g (80%); mp 202–203°C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 9.50(t, $J = 6.40$ Hz, 1H), 7.76(s, 1H), 7.71(dd, $J_1 = 8.40$ Hz, $J_2 = 1.60$ Hz, 1H), 7.51(d, $J = 8.40$ Hz, 1H), 7.38(m, 4H), 7.31(m, 1H), 4.65(d, $J = 6.40$ Hz, 2H), 3.86(s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 166.0, 164.8, 150.5, 137.9, 128.8, 128.6, 127.5, 127.2, 126.0, 123.4, 116.8, 114.9, 110.2, 60.2, 52.2, 45.6; IR(KBr) $\nu_{\text{max}}$/cm$^{-1}$: 3433, 3286, 3234, 3091, 2941, 2210, 1714, 1655, 1460, 1354, 1304, 1244, 1184, 1140, 1092, 985, 879, 818, 750, 698, 640; HRMS (ESI-TOF) calcd for C$_{18}$H$_{15}$N$_2$O$_3$ [M+H]$^+$ 307.1083, found 307.1085.

**Methyl 3-cyano-2-(3-fluorobenzylamino)benzofuran-5-carboxylate (4n)**

White solid; yield: 0.20g (61%); mp 167–168°C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 9.49(t, $J = 4.00$ Hz, 1H), 7.76(d, $J = 1.20$ Hz, 1H), 7.72(dd, $J_1 =$
8.40 Hz, $J_2 = 1.60$ Hz, 1H), 7.51(d, $J = 8.40$ Hz, 1H), 7.42(m, 1H), 7.23(m, 2H), 7.14(m, 1H), 4.67(d, $J = 8.00$ Hz, 2H), 3.86(s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 165.8, 164.6, 163.4, 160.9(d, $^{3}$J$_{FC} = 250$ Hz), 150.4, 140.9, 140.8, 130.6, 130.5(d, $^{3}$J$_{FC} = 10$ Hz), 128.6, 125.9, 123.4, 123.0, 116.7, 114.6, 114.3, 114.1(d, $^{2}$J$_{FC} = 20$ Hz), 114.0, 113.8(d, $^{2}$J$_{FC} = 20$ Hz), 110.2, 60.3, 52.1, 45.0; IR(KBr) $\nu_{max}$/cm$^{-1}$: 3435, 3284, 3251, 3076, 2953, 2214, 1720, 1649, 1591, 1473, 1444, 1350, 1300, 1254, 1192, 1144, 1103, 1066, 987, 791, 760, 737, 523; HRMS (ESI-TOF) m/z calcd for C$_{18}$H$_{14}$FN$_2$O$_3$ [M+H]$^+$ 325.0983, found 325.0985.

**Methyl 3-cyano-2-(4-methylbenzylamino)benzofuran-5-carboxylate (4o)**

![Chemical Structure](image)

White needles; yield: 0.22g (70%); mp 169-170°C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 9.46(t, $J = 6.40$ Hz, 1H), 7.75(d, $J = 2.00$ Hz, 1H), 7.71(dd, $J_1 = 8.80$ Hz, $J_2 = 2.00$ Hz, 1H), 7.50(d, $J = 8.40$ Hz, 1H), 7.28(d, $J = 8.00$ Hz, 2H), 7.18(d, $J = 8.00$ Hz, 2H), 4.59(d, $J = 6.40$ Hz, 2H), 3.86(s, 3H), 2.28(s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 165.9, 164.7, 150.5, 136.6, 134.8, 129.1, 128.8, 127.2, 126.0, 123.4, 116.7, 114.9, 110.2, 60.1, 52.2, 45.3, 20.7; IR(KBr) $\nu_{max}$/cm$^{-1}$: 3284, 3234, 3091, 2958, 2926, 2216, 1722, 1653, 1514, 1464, 1437, 1352, 1304, 1255, 1184, 1097, 1028, 883, 804, 754, 667, 563; HRMS (ESI-TOF) m/z calcd for C$_{19}$H$_{16}$N$_2$NaO$_3$ [M+Na]$^+$ 343.1059, found 343.1059.

**Methyl 2-(bis(3-fluorobenzyl)amino)-3-cyanobenzofuran-5-carboxylate (5n)**

![Chemical Structure](image)

White crystals; yield: 0.36g (83%); mp 120-121°C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 7.81(s, 1H), 7.77(dd, $J_1 = 8.40$ Hz, $J_2 = 1.60$ Hz, 1H), 7.59(d, $J = 8.80$ Hz, 1H), 7.42(m, 2H), 7.22(t, $J = 7.60$ Hz, 4H), 7.15(m, 2H), 4.94(s, 4H), 3.87(s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 165.9, 163.6(d, $^{3}$J$_{FC} = 242.3$ Hz, 2C), 163.3, 161.2, 150.4, 139.0, 138.9(d, $^{3}$J$_{FC} = 10$ Hz, 2C), 130.8, 130.7(d, $^{3}$J$_{FC} = 10$ Hz, 2C), 129.2, 126.2, 124.0, 123.1, 117.1, 114.9, 114.6, 114.4(d, $^{2}$J$_{FC} = 20.8$ Hz, 2C), 114.2, 113.9(d, $^{2}$J$_{FC} = 21.8$ Hz, 2C), 110.6, 62.1, 52.3, 52.1; IR(KBr) $\nu_{max}$/cm$^{-1}$: 3439, 3068, 2947, 2202, 1720, 1620, 1591, 1485, 1446, 1311, 1246, 1182, 1149, 1099, 960, 906, 870, 835, 797, 756, 698, 619, 528; HRMS (ESI-TOF) m/z calcd for C$_{25}$H$_{18}$F$_2$N$_2$NaO$_3$ [M+Na]$^+$ 455.1178, found 455.1179.

**Methyl 2-(bis(4-methylbenzyl)amino)-3-cyanobenzofuran-5-carboxylate (5o)**
White crystals; yield: 0.33g (78%); mp 122–123°C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 8.15(dd, $J_1 = 8.40$ Hz, $J_2 = 1.60$ Hz, 1H), 8.03(d, $J = 2.00$ Hz, 1H), 7.53(d, $J = 8.80$ Hz, 1H), 7.51(d, $J = 8.00$ Hz, 2H), 7.26(d, $J = 7.60$ Hz, 2H), 7.13(d, $J = 7.60$ Hz, 2H), 7.04(d, $J = 8.00$ Hz, 2H), 5.42(s, 2H), 3.85(s, 3H), 3.68(s, 2H), 2.34(s, 3H), 2.29(s, 3H); $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ: 165.0, 158.7, 137.8, 137.7, 133.3, 132.3, 130.3, 129.8, 129.1, 128.9, 128.7, 128.4, 122.2, 118.5, 114.3, 113.9, 71.1, 52.3, 41.5, 20.8, 20.7; IR(KBr) $v_{\text{max}}$/cm$^{-1}$: 3425, 3091, 3020, 2943, 2202, 1714, 1610, 1510, 1443, 1404, 1311, 1275, 1234, 1190, 1130, 987, 874, 810, 798, 766, 725, 656, 488; HRMS (ESI-TOF) m/z calcd for C$_{27}$H$_{24}$N$_2$NaO$_3$ [M+Na]$^+$ 447.1679, found 447.1680.

**Methyl 2-(bis(4-nitrobenzyl)amino)-3-cyanobenzofuran -5-carboxylate (5p)**

White needles; yield: 0.35g (73%); mp 194–195°C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 8.31(d, $J = 1.60$ Hz, 1H), 8.26(d, $J = 8.80$ Hz, 2H), 8.04(m, 3H), 7.70(d, $J = 8.80$ Hz, 2H), 7.26(q, 3H), 4.85(d, $J = 3.20$ Hz, 2H), 4.02(d, $J = 13.2$ Hz, 1H), 3.89(s, 3H), 3.82(d, $J = 12.8$ Hz, 1H); $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ: 165.1, 157.3, 155.0, 147.0, 146.6, 146.6, 140.6, 133.3, 131.8, 128.8, 126.5, 126.0, 124.0, 123.5, 123.0, 117.2, 111.1, 52.4, 50.4, 46.0, 42.7; IR(KBr) $v_{\text{max}}$/cm$^{-1}$: 3440, 3078, 2852, 2208, 1728, 1608, 1518, 1485, 1439, 1344, 1292, 1255, 1225, 1099, 1043, 976, 849, 837, 760, 729, 588; HRMS (ESI-TOF) m/z calcd for C$_{25}$H$_{19}$N$_4$O$_7$ [M+H]$^+$ 487.1254, found 487.1254.

**Methyl 3-cyano-2-(diallylamino)benzofuran-5-carboxylate (5q)**

White needles; yield: 0.22g (75%); mp 69–70°C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 7.78(d, $J = 1.60$ Hz, 1H), 7.75(dd, $J_1 = 8.40$ Hz, $J_2 = 1.60$ Hz, 1H), 7.54(d, $J = 8.40$ Hz, 1H), 5.96(m, 2H), 5.30(m, 4H), 4.24(d, $J = 4.00$ Hz, 4H), 3.87(s, 3H); $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ: 165.9, 162.9, 150.4, 132.2, 129.2, 126.1, 123.7, 118.0, 116.9, 115.4, 110.3, 61.0, 52.2, 51.2; IR(KBr) $v_{\text{max}}$/cm$^{-1}$: 3431, 3078, 3016, 2951, 2195, 1714, 1645, 1614, 1589, 1447, 1302, 1248, 1186, 1120, 1095, 1063, 999, 933, 895, 829, 760, 700, 569; HRMS (ESI-TOF) m/z calcd for C$_{17}$H$_{17}$N$_2$O$_3$
[M+H]$^+$ 297.1239, found 297.1240.

**Methyl 3-cyano-2-(diprop-2-ynylamino)benzofuran-5-carboxylate (5r)**

White solid; yield: 0.21 g (72%); mp 112–113 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$: 7.89 (d, $J = 1.20$ Hz, 1H), 7.83 (dd, $J_1 = 8.40$ Hz, $J_2 = 1.60$ Hz, 1H), 7.64 (d, $J = 8.40$ Hz, 1H), 4.54 (s, 4H), 3.88 (s, 3H), 3.50 (s, 2H); $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$: 165.8, 162.0, 150.6, 128.5, 126.4, 124.5, 117.6, 114.2, 110.7, 77.7, 76.9, 64.3, 52.3; IR(KBr) $\nu_{max}$/cm$^{-1}$: 3415, 3238, 3093, 2953, 2218, 2116, 1713, 1612, 1589, 1475, 1444, 1350, 1248, 1182, 1103, 1059, 953, 897, 833, 760, 727, 683, 546; HRMS (ESI-TOF) m/z calc for C$_{17}$H$_{13}$N$_2$O$_3$ [M+H]$^+$ 293.0926, found 293.0926.

3.3 Characterization Data for Products (Table 3, 7a-7g)

**Methyl 2-(azetidin-1-yl)-3-cyanobenzofuran-5-carboxylate (7a)**

White needles; yield: 0.18 g (69%); mp 158–159 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$: 7.74 (d, $J = 1.60$ Hz, 1H), 7.71 (dd, $J_1 = 8.80$ Hz, $J_2 = 2.00$ Hz, 1H), 7.50 (d, $J = 8.80$ Hz, 1H), 4.37 (t, $J = 8.00$ Hz, 4H), 3.86 (s, 3H), 2.50 (m, 2H); $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$: 165.9, 164.3, 151.0, 128.5, 126.1, 123.5, 116.9, 114.6, 110.3, 60.7, 52.2, 17.3; IR(KBr) $\nu_{max}$/cm$^{-1}$: 3419, 3016, 2953, 2881, 2206, 1722, 1641, 1458, 1446, 1429, 1356, 1300, 1246, 1184, 1163, 1095, 1057, 974, 883, 798, 758, 731, 656; HRMS (ESI-TOF) m/z calc for C$_{14}$H$_{13}$N$_2$O$_3$ [M+H]$^+$ 257.0926, found 257.0927.

**Methyl 3-cyano-2-(2-methylazetidin-1-yl)benzofuran-5-carboxylate (7b)**

White solid; yield: 0.18 g (68%); mp 136–137 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$: 7.75 (d, $J = 1.60$ Hz, 1H), 7.72 (dd, $J_1 = 8.40$ Hz, $J_2 = 1.60$ Hz, 1H), 7.50 (d, $J = 8.40$ Hz, 1H), 4.76 (m, 1H), 4.27 (m, 2H), 3.87 (s, 3H), 2.62 (m, 1H), 2.13 (m, 1H), 1.56 (d, $J = 8.00$ Hz, 3H); $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$: 165.9, 164.3, 151.0, 128.4, 126.0, 123.5, 116.9, 114.7, 110.3, 61.3, 60.8, 52.2, 48.6, 25.0, 21.7; IR(KBr) $\nu_{max}$/cm$^{-1}$: 3425, 3010, 2960, 2881, 2199, 1728, 1624, 1591, 1452, 1419, 1348, 1298, 1236, 1186, 1161, 1097, 1065, 1016, 962, 889, 814, 760, 733, 658, 519;
HRMS (ESI-TOF) m/z calcd for C_{15}H_{15}N_{2}O_{3} [M+H]^+ 271.1083, found 271.1081.

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

White needles; yield: 0.22g (81%); mp 185–186°C; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\): 7.71(d, \(J = 1.20\) Hz, 1H), 7.69(dd, \(J_1 = 8.40\) Hz, \(J_2 = 2.00\) Hz, 1H), 7.48(d, \(J = 8.40\) Hz, 1H), 3.87(s, 3H), 3.68(t, \(J = 6.00\) Hz, 4H), 2.00(t, \(J = 6.40\) Hz, 4H); \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\): 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; IR(KBr) \(v_{\text{max}}/\text{cm}^{-1}\): 3431, 3064, 2960, 2879, 2191, 1724, 1637, 1450, 1352, 1300, 1246, 1178, 1097, 960, 881, 858, 818, 764, 733, 662, 517; HRMS (ESI-TOF) m/z calcd for C_{15}H_{15}N_{2}O_{3} [M+H]^+ 271.1083, found 271.1085.

**Methyl 3-cyano-2-(2-methylpyrrolidin-1-yl)benzofuran-5-carboxylate (7d)**

White solid; yield: 0.22g (78%); mp 144–145°C; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\): 7.75(d, \(J = 1.60\) Hz, 1H), 7.70(dd, \(J_1 = 8.40\) Hz, \(J_2 = 1.60\) Hz, 1H), 7.50(d, \(J = 8.40\) Hz, 1H), 4.31(t, \(J = 4.00\) Hz, 1H), 3.87(s, 3H), 3.83(m, 1H), 3.65(m, 1H), 2.09(m, 3H), 1.74(m, 1H), 1.30(d, \(J = 4.00\) Hz, 3H); \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\): 165.9, 161.5, 150.7, 129.2, 125.9, 123.2, 116.5, 115.7, 110.0, 60.2, 55.4, 52.1, 32.1, 22.7, 19.8; IR(KBr) \(v_{\text{max}}/\text{cm}^{-1}\): 3423, 2964, 2875, 2721, 2195, 1888, 1726, 1624, 1593, 1452, 1354, 1296, 1238, 1178, 1095, 1030, 976, 881, 831, 798, 762, 735, 687, 658, 519; HRMS (ESI-TOF) m/z calcd for C_{16}H_{17}N_{2}O_{3} [M+H]^+ 285.1234, found 285.1235.

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

White crystals; yield: 0.24g (85%); mp 147–148°C; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\): 7.76(d, \(J = 1.20\) Hz, 1H), 7.73(dd, \(J_1 = 8.40\) Hz, \(J_2 = 1.60\) Hz, 1H), 7.50(d, \(J = 8.40\) Hz, 1H), 3.87(s, 3H), 3.73(s, 4H), 1.67(s, 6H); \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\): 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; IR(KBr) \(v_{\text{max}}/\text{cm}^{-1}\): 3448, 3425, 3107, 2939, 2856, 2197, 1724, 1610, 1585, 1450, 1383, 1363, 1302, 1234, 1186, 1142, 1097, 962, 851, 800,
Methyl 2-(azepan-1-yl)-3-cyanobenzofuran-5-carboxylate (7f)

White needles; yield: 0.26g (87%); mp 132–133°C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\): 7.76(d, \(J = 1.20\) Hz, 1H), 7.72(dd, \(J_1 = 8.40\) Hz, \(J_2 = 1.60\) Hz, 1H), 7.51(d, \(J = 8.80\) Hz, 1H), 3.87(s, 3H), 3.75(t, \(J = 6.00\) Hz, 4H), 1.82(s, 4H), 1.57(t, \(J = 2.80\) Hz, 4H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\): 165.9, 163.0, 150.4, 129.5, 126.0, 123.4, 116.6, 115.8, 110.1, 59.8, 52.2, 48.8, 27.5, 26.3; IR(KBr) \(v_{\text{max}}/\text{cm}^{-1}\): 3427, 3070, 2927, 2860, 2195, 1726, 1622, 1591, 1450, 1358, 1304, 1236, 1178, 1097, 984, 887, 818, 758, 669, 517; HRMS (ESI-TOF) m/z calcd for C\(_{16}\)H\(_{17}\)N\(_2\)O\(_3\) [M+H]\(^+\) 285.1239, found 285.1238.

Methyl 3-cyano-2-(isoindolin-2-yl)benzofuran-5-carboxylate(7g)

White needles; yield: 0.29g (90%); mp >210°C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\): 7.83(s, 1H), 7.75(d, \(J = 8.40\) Hz, 1H), 7.56(d, \(J = 8.40\) Hz, 1H), 7.47(s, 2H), 7.37(s, 2H), 5.10(s, 4H), 3.87(s, 3H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\): 166.0, 161.9, 151.0, 135.4, 129.3, 127.8, 126.2, 123.7, 123.0, 117.0, 115.6, 110.5, 53.9, 52.3; IR(KBr) \(v_{\text{max}}/\text{cm}^{-1}\): 3034, 2943, 2864, 2206, 1713, 1633, 1579, 1458, 1358, 1286, 1244, 1178, 1090, 962, 906, 835, 744, 673, 517; HRMS (ESI-TOF) m/z calcd for C\(_{19}\)H\(_{15}\)N\(_2\)O\(_3\) [M+H]\(^+\) 319.1077, found 319.1072.
4. $^1$H-NMR and $^{13}$C-NMR spectra of compounds 4a-4j, 4m-4o, 5n-5r and 7a-7g

[$^1$H NMR and $^{13}$C NMR spectrum of 4a in DMSO-$d_6$]
[^1H NMR and ^13C NMR spectrum of 4b in DMSO-d$_6$]
[$^1$H NMR and $^{13}$C NMR spectrum of 4c in DMSO-d$_6$]
[^1H NMR and ^13C NMR spectrum of 4d in DMSO-d_6]
[\textbf{\textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectrum of 4f in DMSO-d_6}]
[\(^1\)H NMR and \(^{13}\)C NMR spectrum of 4g in DMSO-\(d_6\)]
$[^1H \text{NMR and } ^{13}\text{C NMR spectrum of } 4h \text{ in } \text{DMSO-}d_6]$
[1H NMR and 13C NMR spectrum of 4i in DMSO-d6]
[\textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectrum of 4j in DMSO-\textit{d}_6]
[\textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectrum of 4m in DMSO-d\textsubscript{6}]
[\textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectrum of 4n in DMSO-d\textsubscript{6}]
$[^1\text{H NMR and } ^{13}\text{C NMR spectrum of 4o in DMSO-d}_6]$
[\textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectrum of 5n in DMSO-d\textsubscript{6}]
[\textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectrum of 5o in DMSO-\textit{d}_6]
[^1H NMR and ^13C NMR spectrum of 5p in DMSO-d₆]
[\textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectrum of 5q in DMSO-d\textsubscript{6}]
[^1H NMR and ^13C NMR spectrum of 7a in DMSO-d_6]
[\textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectrum of 7b in DMSO-\textit{d}_6]
[\text{\textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectrum of 7c in DMSO-d_6}]
[\textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectrum of 7d in DMSO-d_{6}]
[\(^1\)H NMR and \(^{13}\)C NMR spectrum of 7e in DMSO-d6]
[^H NMR and ^13C NMR spectrum of 7f in DMSO-d_6]
[^1H NMR and ^13C NMR spectrum of 7g in DMSO-d_6]
$^{13}$C NMR spectrum of sample 0-MWJ318

H$_2$COOC$_2$F$_2$N$_2$C$_6$H$_4$