High-throughput Screening, Discovery and Optimization to Develop a Benzofuran Class of Hepatitis C Virus Inhibitors

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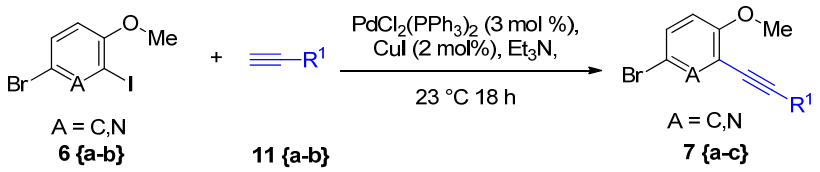
Supporting Information

General experimental section:

All chemicals were used as received from commercial sources. Commercial anhydrous organic solvents (EtOAc, $CHCl_3$, MeOH, EtOH, MeCN, DMF, hexane, toluene, etc.) were used for all reactions. The parallel chemistry reactions were carried out in a Mettler Toledo® Miniblock or sealed microwave vials. Stirring was achieved with oven-dried, magnetic stir bars. Analytical thin layer chromatography (TLC) was performed using commercially prepared polyester backed silica gel plates (200 microns), and visualization was effected with short wavelength UV light (254 nm). Flash column chromatography was carried out using Teledyne Isco CombiFlash R_f employing normal phase disposable columns. Infrared (IR) spectra were acquired as thin films on a PerkinElmer Spectrum 100 FT-IR spectrometer, and the absorptions are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer (400 MHz/500 MHz ^1H and 101/126 MHz ^{13}C). Chemical shifts are reported in parts per million (ppm), and referenced to the solvent: $CDCl_3$ with TMS as internal reference (0.0 ppm for ^1H and 0.0 ppm for ^{13}C) and DMSO-d_6. Coupling constants (*J*) are reported in Hertz (Hz). Purification via preparative HPLC was achieved utilizing a Waters X-Bridge C18 column (19 x 150 mm, 5 μm, with 19 x 10 mm guard column) at a flow rate of 20 mL/min. Samples were diluted in DMSO and purified using an elution mixture of water and MeCN, running a concentration gradient which increased by 20% MeCN over a 4 minute period. The starting and ending points of the corresponding preparative MeCN/water gradient, triggering thresholds, and UV wavelength were selected based on the HPLC analysis of each crude sample. Analytical analysis after preparative chromatography utilized a Waters Acquity system with UV-detection and mass-detection (Waters LCT Premier). The analytical method conditions included a Waters Aquity BEH C18 column (2.1 x 50 mm, 1.7 μm) and elution with a linear gradient of 5% water to 100% MeCN at 0.6 mL/min flow rate. The purity of each sample was determined using UV peak area detected at 214 nm wavelength. High resolution mass spectra for the diversified products were recorded using time-of-flight mass spectrometer.

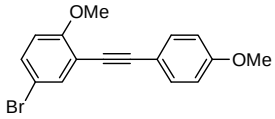
A. Synthetic details and characterization

A.1. General procedure for the Sonogashira coupling: intermediates (7a-7c})



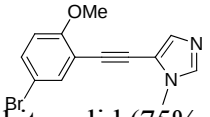
A solution of 4-bromo-2-iodoanisole (**6*a***, 8.0 mmol) or 6-chloro-2-iodo-3-methoxypyridine **6b**, 2 mol % $PdCl_2(PPh_3)_2$ and 3 mol % CuI in Et_3N (6 mL) was stirred at 0 °C and then 12 mmol of appropriate terminal alkyne **11a-11b}** was added to the reaction mixture. The reaction mixture was warmed to room temperature and allowed to proceed under vigorous stirring for *ca*. 18 h under an Ar atmosphere. The resulting mixture was diluted with EtOAc (2 × 200 mL). The separated organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using EtOAc/hexane as the eluent to afford the corresponding products **7{*a-c*}**.

4-Bromo-1-methoxy-2-((4-methoxyphenyl)ethynyl)benzene (7a)



The product was obtained as a clear, colorless oil that solidified upon standing to a white solid (85% yield); MP = 72.5 – 74 °C (uncorrected); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 (d, *J* = 2.5 Hz, 1H), 7.53 – 7.49 (m, 2H), 7.39 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.92 – 6.87 (m, 2H), 6.79 (d, *J* = 8.8 Hz, 1H), 3.92 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.78, 158.92, 135.61, 133.21, 131.99, 115.15, 114.91, 113.96, 112.28, 112.23, 94.72, 82.95, 56.12, 55.32; The obtained data was in accordance with the published literature data.[1]

5-((5-Bromo-2-methoxyphenyl)ethynyl)-1-methyl-1*H*-imidazole (7b)



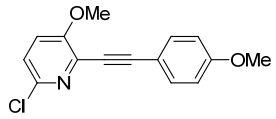
The product was obtained as an off white solid (75% yield); MP = 90.5 – 94 °C (uncorrected); ^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.56 (d, *J* = 2.5 Hz, 1H), 7.53 (s, 1H), 7.41 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.39 – 7.31 (m, 1H), 6.79 (d, *J* = 8.9 Hz, 1H), 3.89 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 159.01, 138.09, 135.17, 132.92, 116.51, 113.58, 112.28, 91.82, 81.71, 56.10, 32.39; HRMS (ESI) *m/z* calcd for $C_{13}H_{12}BrN_2O^+$ $[M+H]^+$: 291.0128, found: 291.0089.

6-Chloro-2-iodo-3-methoxypyridine (**6b**): In an oven dried round bottomed flask, 6-chloro-2-iodopyridin-3-ol (65 mg, 0.254 mmol) was dissolved in THF (1 mL) and then potassium *tert*-

butoxide (0.382 mL, 0.382 mmol) was added slowly to the reaction mixture at room temperature. The resultant reaction mixture was stirred for 15 mins and then iodomethane (0.024 mL, 0.382 mmol) was added slowly to the mixture upon which the colorless solution turned into a white suspension. The reaction was quenched after 8 h with 2 mL of water and extracted with EtOAc. The organic layers were pooled, washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Silica gel column chromatography with EtOAc/hexane provided desired compound as an off white solid.

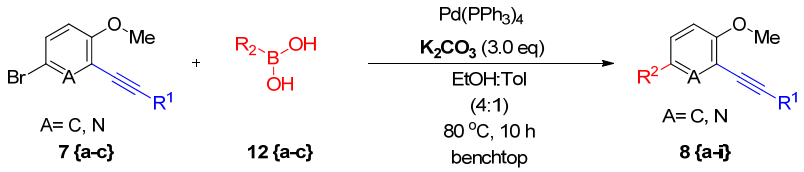
The product was obtained as off white solid (95% yield); MP 64 – 71 °C (uncorrected); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.16 (d, *J* = 8.5 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.04, 141.38, 123.65, 119.26, 108.97, 56.83; HRMS (ESI) *m/z* calcd for $C_6H_6ClINO^+$ $[M+H]^+$: 269.9177, found: 269.9171.

6-Chloro-3-methoxy-2-((4-methoxyphenyl)ethynyl)pyridine (7c)



6-Chloro-2-iodo-3-methoxypyridine **6b** was reacted according to the general Sonogashira protocol above to afford the product **7c** as a yellow semisolid (93% yield);^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 – 7.54 (m, 2H), 7.27 – 7.18 (m, 2H), 6.95 – 6.86 (m, 2H), 3.96 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.31, 155.90, 141.65, 133.76, 133.43, 123.67, 120.73, 114.23, 114.02, 95.60, 83.33, 56.39, 55.34; HRMS (ESI) *m/z* calcd for $C_{15}H_{13}ClNO_2^+$ $[M+H]^+$: 274.0629, found: 274.0602.

A.2. Suzuki-Miayura cross coupling intermediates



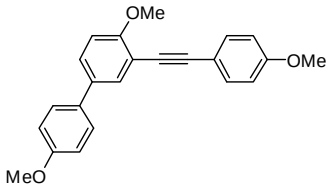
General procedure for the preparation of alkynes 8 by Suzuki-Miyaura coupling

Procedure A: To a solution of bromoalkyne ***7a-7b*** (1.66 mmol) and 5 mol % $Pd(PPh_3)_4$ in toluene (10 mL) was added K_2CO_3 (5.0 mmol) under an Ar atmosphere. To the resulting mixture

was added arylboronic acid (2.5 mmol) dissolved in ethanol:toluene (4:1) (5 mL). The reaction mixture was heated at 80 °C for 10 h with vigorous stirring. Upon cooling to room temperature, the reaction mixture was extracted with EtOAc (2 × 40 mL). The combined extracts were dried over Na_2SO_4, concentrated, and purified by silica gel flash column chromatography using EtOAc/hexane as the eluent to afford the corresponding product.

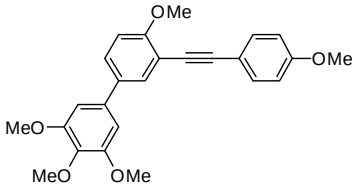
Procedure B for pyrido analogs: To a solution of chloroalkyne **7c** (370 mg, 1.35 mmol), X-PHOS (129 mg, 0.27 mmol, 20 mol%) and $Pd(OAc)_2$ (30 mg, 0.135 mmol, 10 mol %) in Dioxane (10 mL):Water(2 mL) was added K_3PO_4 (860mg, 4.0 mmol) under an argon atmosphere in 20 mL microwave vial. To the resulting mixture was added boronic acid **12b** (2.7 mmol) and vaccum purged thrice. The reaction mixture was heated at 100 °C for 120 mins under microwave irradiation. Upon cooling to room temperature, the reaction mixture was extracted with EtOAc (2 × 40 mL). The combined organic extracts were dried over Na_2SO_4, concentrated, and purified by silica gel flash column chromatography using EtOAc/hexane as the eluent to afford the corresponding product.

4,4'-Dimethoxy-3-((4-methoxyphenyl)ethynyl)-1,1'-biphenyl (8a)



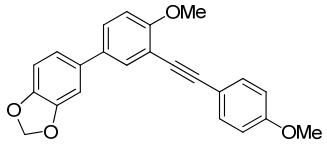
Procedure A .The product was obtained as a pale yellow solid (72% yield): MP = 132 – 137 °C (uncorrected);[1]H NMR (400 MHz, Chloroform-*d*) δ 7.61 (d, *J* = 2.4 Hz, 1H), 7.47 – 7.41 (m, 4H), 7.38 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.91 – 6.85 (m, 3H), 6.83 – 6.77 (m, 2H), 3.86 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H). The obtained data was in accordance with the published literature data.[1]

3,4,4',5-Tetramethoxy-3'-((4-methoxyphenyl)ethynyl)-1,1'-biphenyl (8b)



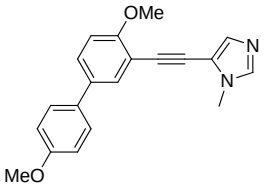
Procedure A. The product was obtained as a yellow oil (52% yield); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.76 (s, 3H), 3.82 (s, 3H), 3.86 (d, *J* = 1.1 Hz, 9H), 3.88 (s, 3H), 6.66 (d, *J* = 12.0 Hz, 4H), 6.77 – 6.84 (m, 2H), 6.88 (d, *J* = 8.6 Hz, 1H), 7.40 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.43 – 7.47 (m, 2H), 7.61 (d, *J* = 2.4 Hz, 1H); HRMS (ESI) *m/z* calcd for $C_{25}H_{25}O_5^+$ $[M+H]^+$: 405.1697, found: 405.1663. The obtained data was in accordance with the published literature data.[1]

5-(4-Methoxy-3-((4-methoxyphenyl)ethynyl)phenyl)benzo[*d*][1,3]dioxole (8c)



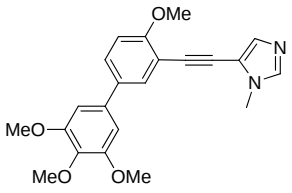
Procedure A.The product was obtained as a white solid (67% yield); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.86 (s, 3H), 3.97 (s, 3H), 6.02 (s, 2H), 6.87 – 6.94 (m, 3H), 6.96 (d, *J* = 8.6 Hz, 1H), 7.03 – 7.09 (m, 2H), 7.45 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.52 – 7.58 (m, 2H), 7.68 (d, *J* = 2.4 Hz, 1H). The obtained data was in accordance with the published literature data.[1]

5-((4,4'-Dimethoxy-[1,1'-biphenyl]-3-yl)ethynyl)-1-methyl-1*H*-imidazole (8d)



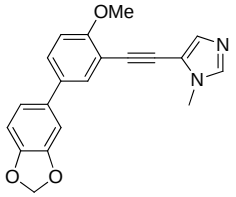
Procedure A. The product was obtained as an off-white solid (93% yield); mp 146-148 °C (uncorrected); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.48 (s, 1H), 7.69 (d, *J* = 2.4 Hz, 1H), 7.59 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.47 (s, 1H), 7.03 – 6.96 (m, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.34, 159.13, 136.36, 133.68, 132.07, 131.33, 129.52, 128.49, 127.75, 125.73, 114.36, 114.32, 111.80, 111.13, 110.52, 95.41, 56.04, 55.40, 33.68; HRMS (ESI) *m/z* calcd for $C_{20}H_{19}N_2O_2^+$ $[M+H]^+$: 319.1441, found: 319.1429.

1-Methyl-5-((3',4,4',5'-tetramethoxy-[1,1'-biphenyl]-3-yl)ethynyl)-1*H*-imidazole (8e)



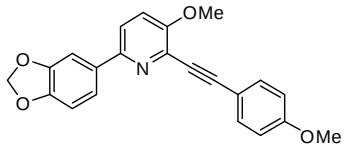
Procedure A.The product was obtained as a white fluffy solid (80% yield); mp 125-128 °C (uncorrected); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.73 (s, 1H), 7.58 (d, J = 2.3 Hz, 1H), 7.46 (dd, J = 8.6, 2.4 Hz, 1H), 7.32 (s, 1H), 6.91 (d, J = 8.7 Hz, 1H), 6.66 (s, 2H), 3.89 (s, 3H), 3.87 (s, 6H), 3.82 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.99, 153.59, 137.67, 135.40, 134.22, 131.70, 130.38, 111.13, 110.49, 109.96, 109.53, 104.04, 61.26, 61.20, 61.02, 56.29, 56.11, 56.07; HRMS (ESI) *m/z* calcd for $C_{22}H_{23}N_2O_4^+$ $[M+H]^+$: 379.1652, found: 379.1642.

5-((5-(Benzo[*d*][1,3]dioxol-5-yl)-2-methoxyphenyl)ethynyl)-1-methyl-1*H*-imidazole (8f)



Procedure A.The product was obtained as a yellow solid (84% yield); mp 154-157 °C (uncorrected);^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (s, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.65 (dd, J = 8.7, 2.4 Hz, 1H), 7.29 (dd, J = 7.2, 1.4 Hz, 2H), 7.16 (d, J = 8.8 Hz, 1H), 7.15 (dd, J = 8.1, 1.9 Hz, 1H), 6.99 (d, J = 8.1 Hz, 1H), 6.06 (s, 2H), 3.90 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.74, 148.29, 147.19, 135.24, 133.88, 133.69, 131.59, 130.27, 121.85, 120.22, 119.02, 111.19, 110.52, 110.22, 109.77, 108.71, 107.27, 102.01, 101.29, 96.65, 56.05, 34.53; HRMS (ESI) *m/z* calcd for $C_{20}H_{17}N_2O_3^+$ $[M+H]^+$: 333.1234, found: 333.122.

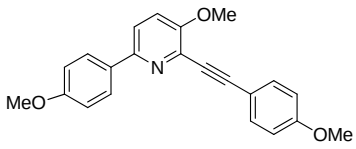
6-(Benzo[*d*][1,3]dioxol-5-yl)-3-methoxy-2-((4-methoxyphenyl)ethynyl)pyridine(8g)



Procedure B. The product was obtained as a yellow solid (69% yield); mp 188-192 °C (uncorrected);^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.55 – 7.50 (m, 2H), 7.47 (d, J = 8.7 Hz, 1H), 7.43 (d, J = 1.7 Hz, 1H), 7.38 (dd, J = 8.1, 1.8 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 6.83 (s, 1H), 6.83 – 6.76 (m, 2H), 5.93 (s, 2H), 3.88 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.03, 155.63, 149.59, 148.16, 147.92, 133.71, 133.26, 133.20, 120.48, 119.86, 118.50, 114.81,

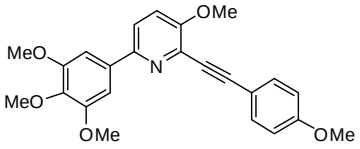
113.93, 108.35, 107.30, 101.22, 93.93, 84.57, 56.06, 55.32; HRMS (ESI) *m/z* calcd for $C_{22}H_{18}NO_4^+$ $[M+H]^+$: 360.1230, found: 360.1199.

3-Methoxy-6-(4-methoxyphenyl)-2-((4-methoxyphenyl)ethynyl)pyridine(8h)



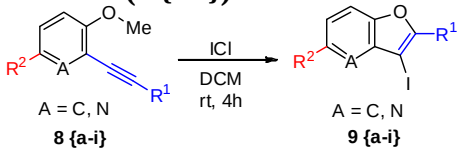
Procedure B.The product was obtained as a yellow solid (42% yield); mp 178-182 °C (uncorrected); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 – 8.09 (m, 2H), 7.81 (dd, J = 14.7, 8.8 Hz, 3H), 7.50 (d, J = 8.7 Hz, 1H), 7.24 – 7.15 (m, 2H), 7.10 (dq, J = 8.8, 2.3, 1.8 Hz, 2H), 4.17 (s, 3H), 4.06 (s, 3H), 4.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.99, 159.96, 155.50, 149.83, 133.71, 133.22, 131.45, 127.89, 119.70, 118.54, 114.88, 114.00, 113.92, 93.83, 84.67, 56.06, 55.32; HRMS (ESI) *m/z* calcd for $C_{22}H_{20}NO_3^+$ $[M+H]^+$: 346.1438, found: 346.1442.

3-Methoxy-2-((4-methoxyphenyl)ethynyl)-6-(3,4,5-trimethoxyphenyl)pyridine (8i)



Procedure B.The product was obtained as a yellow semisolid (67% yield); mp 152-158 °C (uncorrected);^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 – 7.55 (m, 2H), 7.53 (s, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.13 (s, 2H), 6.86 – 6.79 (m, 2H), 3.91 (s, 3H), 3.91 (s, 6H), 3.82 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.09, 155.85, 153.44, 149.78, 138.54, 134.53, 133.70, 133.29, 120.32, 118.41, 114.73, 113.97, 103.97, 94.17, 84.54, 60.97, 56.30, 56.08, 55.33; HRMS (ESI) *m/z* calcd for $C_{24}H_{24}NO_5^+$ $[M+H]^+$: 406.1649, found: 406.1592.

A.3. Iodocyclization: intermediates (9 {a-i})

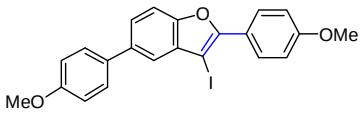


General procedure for the iodocyclization of compounds 8*a-8i*}

To a solution of 1.0 eq. of alkyne **8a-8i** and 15 mL of CH_2Cl_2 was added gradually 1.5 eq. of ICl dissolved in 10 mL of CH_2Cl_2. The reaction mixture was allowed to stir at room temperature for 1- 2 h. The reaction was monitored by TLC to establish completion. (Note: reaction were divided

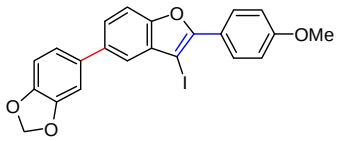
in 50mg batches to optimize the yield. Product was decomposing with the higher concentration). The excess ICl was removed by washing with satd aq $Na_2S_2O_3$. The mixture was then extracted by EtOAc (2 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel using EtOAc/hexanes as the eluent.

3-Iodo-2,5-bis(4-methoxyphenyl)benzofuran (9a)



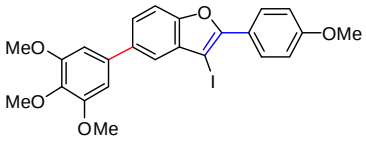
Reaction was carried out on 1.16 mmol scale.The product was obtained as a white solid (340mg, 0.745 mmol, 64% yield); mp 174-178 °C (uncorrected); HRMS (ESI) *m/z* calcd for $C_{22}H_{18}IO_3^+$ $[M+H]^+$: 457.0295, found: 457.0284. The obtained data was in accordance with the published literature data.[1]

5-(3-Iodo-2-(4-methoxyphenyl)benzofuran-5-yl)benzo[*d*][1,3]dioxole (9b)



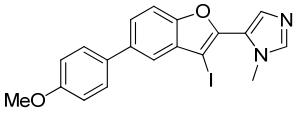
Reaction was carried out on 1.12 mmol scale.The product was obtained as a white solid (250 mg, 0.53 mmol,48% yield); **HRMS** (ESI) *m/z* calcd for $C_{22}H_{16}IO_4^+$ $[M+H]^+$: 471.0088, found: 471.0039. The obtained data was in accordance with the published literature data.[1]

3-Iodo-2-(4-methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)benzofuran (9c)



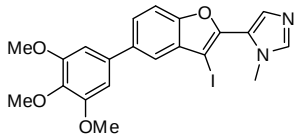
Reaction was carried out on 0.86 mmol scale.The product was obtained as an off-white solid (330 mg, 0.64 mmol,74% yield); HRMS (ESI) *m/z* calcd for $C_{24}H_{22}IO_5^+$ $[M+H]^+$: 517.0506, found: 517.0473. The obtained data was in accordance with the published literature data.[1]

5-(3-Iodo-5-(4-methoxyphenyl)benzofuran-2-yl)-1-methyl-1*H*-imidazole (9d)



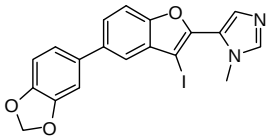
Reaction was carried out on 1.34 mmol scale. The product was obtained as an off-white solid (430 mg, 1.0 mmol, 78% yield); MP = 151 – 171 °C (uncorrected); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 (s, 1H), 7.55 – 7.50 (m, 3H), 7.49 (td, *J* = 4.4, 1.9 Hz, 2H), 7.45 – 7.41 (m, 1H), 6.98 – 6.92 (m, 2H), 3.84 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.22, 153.40, 147.29, 138.29, 137.45, 133.55, 133.36, 131.78, 128.50, 125.11, 119.69, 114.33, 111.29, 64.47, 55.41, 33.87; **HRMS** (ESI) *m/z* calcd for $C_{19}H_{16}IN_2O_2^+$ $[M+H]^+$: 431.0251, found: 431.0245.

5-(3-Iodo-5-(3,4,5-trimethoxyphenyl)benzofuran-2-yl)-1-methyl-1*H*-imidazole (9e)



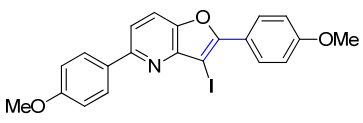
Reaction was carried out on 0.54 mmol scale. The product was obtained as a white solid (172 mg, 0.35 mmol, 66% yield); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.94 (s, 1H), 7.73 (s, 1H), 7.62 – 7.51 (m, 3H), 6.85 (s, 2H), 3.99 (s, 6H), 3.96 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.67, 153.54, 147.26, 138.06, 137.69, 137.03, 131.71, 125.53, 120.15, 111.37, 104.90, 64.62, 61.03, 56.34, 29.72; HRMS (ESI) *m/z* calcd for $C_{21}H_{20}IN_2O_4^+$ $[M+H]^+$: 491.0462, found: 491.0462.

5-(5-(Benzo[*d*][1,3]dioxol-5-yl)-3-iodobenzofuran-2-yl)-1-methyl-1*H*-imidazole (9f)



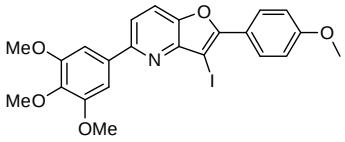
Reaction was carried out on 0.22 mmol scale.The product was obtained as an off-white to light brown solid (80 mg, 0.18 mmol,80% yield); MP = 182 – 186 °C (uncorrected);^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.74 – 7.62 (m, 3H), 7.53 (d, *J* = 1.8 Hz, 1H), 7.33 (d, *J* = 1.8 Hz, 1H), 7.21 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.04 (d, *J* = 8.1 Hz, 1H), 6.10 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.44, 147.16, 146.35, 146.08, 139.32, 136.49, 134.31, 132.38, 130.74, 124.17, 119.95, 118.87, 110.29, 107.62, 107.01, 100.21, 63.36, 28.68; HRMS (ESI) *m/z* calcd for $C_{19}H_{14}IN_2O_3^+$ $[M+H]^+$: 445.0044, found: 445.0036.

3-Iodo-2,5-bis(4-methoxyphenyl)furo[3,2-*b*]pyridine (9g)



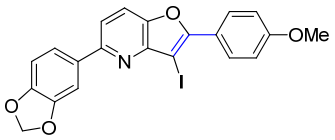
Reaction was carried out on 0.85 mmol scale.The product was obtained as a light brown solid (220 mg, 0.481mmol,56% yield); MP = 164 – 172 °C (uncorrected); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15 (d, *J* = 8.9 Hz, 2H), 8.01 (d, *J* = 8.8 Hz, 2H), 7.67 – 7.54 (m, 2H), 6.97 (t, *J* = 9.4 Hz, 4H), 3.83 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.90, 160.32, 156.64, 154.38, 149.34, 145.90, 132.20, 129.25, 128.48, 122.35, 118.33, 116.73, 114.14, 114.08, 77.33, 77.01, 76.70, 63.16, 55.43, 55.40; HRMS (ESI) *m/z* calcd for $C_{21}H_{17}INO_3^+$ $[M+H]^+$: 458.0248, found: 458.0242.

3-Iodo-2-(4-methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)furo[3,2-*b*]pyridine (9h)



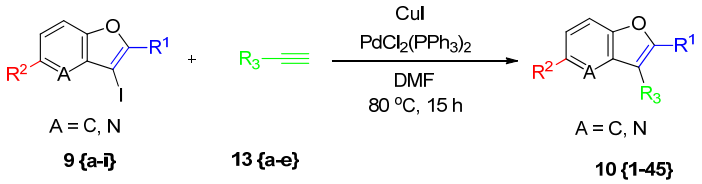
Reaction was carried out on 0.88mmol scale.The product was obtained as offwhite solid (290 mg, 0.561mmol,63% yield); mp 162-167 °C (uncorrected); ^{1}H NMR (500 MHz, Chloroform-*d*) *δ* 8.18 – 8.12 (m, 2H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.28 (s, 2H), 7.01 – 6.95 (m, 2H), 3.93 (s, 6H), 3.84 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.97, 156.97, 154.34, 153.50, 149.40, 146.17, 138.93, 135.16, 129.36, 129.29, 122.16, 118.41, 117.33, 114.13, 114.10, 104.64, 62.85, 61.00, 56.29, 55.46; HRMS (ESI) *m/z* calcd for $C_{23}H_{21}INO_5^+$ $[M+H]^+$: 518.0459, found: 518.0454.

5-(Benzo[*d*][1,3]dioxol-5-yl)-3-iodo-2-(4-methoxyphenyl)furo[3,2-*b*]pyridine (9i)



Reaction was carried out on 1.0 mmol scale.The product was obtained as an off-white solid (350 mg, 0.743 mmol,74% yield); MP = 178 – 182 °C (uncorrected); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.23 – 8.21 (m, 2H), 7.73 – 7.68 (m, 2H), 7.63 – 7.58 (m, 2H), 7.08 – 7.01 (m, 2H), 6.96 – 6.88 (m, 1H), 6.04 (d, *J* = 2.7 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.89, 156.78, 154.10, 149.28, 148.25, 146.00, 133.90, 129.25, 122.22, 121.18, 118.43, 116.94, 114.06, 110.14, 108.42, 107.85, 101.26, 62.92, 55.44; HRMS (ESI) *m/z* calcd for $C_{21}H_{15}INO_4^+$ $[M+H]^+$: 472.0040, found: 472.0038.

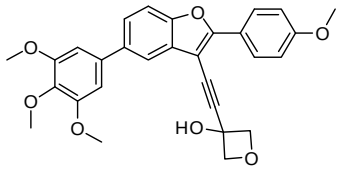
A.4. Parallel Synthesis of New Analogues



General procedure for Sonogashira coupling to prepare 10{*1-45*}

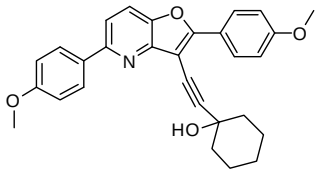
To a 4 dram vial was added the appropriate 3-iodobenzofuran **9** (0.09 mmol), the alkyne **13** (2.0 equiv), 5 mol % $PdCl_2(PPh_3)_2$, 5 mol % CuI, DMF (1 mL) and Et_2NH (0.5 mL). The solution was stirred and flushed with argon, and then heated to 80 °C until TLC revealed complete conversion of the starting material. The solution was allowed to cool and diluted with EtOAc (3 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by preparative HPLC to afford the corresponding product in 1-74% yield. The actual yields, purities and quantities of the library compounds are compiled in Table S1.

3-((2-(4-Methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)benzofuran-3-yl)ethynyl)oxetan-3-ol (10{*14*})



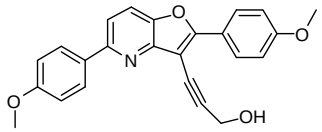
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.26 – 8.19 (m, 1H), 7.88 – 7.83 (m, 1H), 7.75 – 7.69 (m, 1H), 7.60 – 7.54 (m, 1H), 7.54 – 7.48 (m, 1H), 7.09 – 7.01 (m, 2H), 6.82 (d, *J* = 9.8 Hz, 2H), 5.07 (dd, *J* = 6.7, 0.7 Hz, 1H), 4.95 (dd, *J* = 7.1, 0.6 Hz, 1H), 4.92 (dd, *J* = 6.7, 0.6 Hz, 1H), 4.89 – 4.84 (m, 1H), 3.98 (s, 3H), 3.98 (s, 3H), 3.93 (s, 3H), 3.91 (d, *J* = 5.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.77, 160.71, 158.39, 153.80, 153.00, 152.80, 137.61, 133.45, 130.14, 128.92, 127.75, 124.77, 122.46, 121.74, 118.13, 117.84, 114.32, 114.26, 111.33, 104.97, 95.96, 94.86, 84.73, 83.79, 78.90, 73.39, 68.05, 61.02, 56.35, 55.44; HRMS (ESI) *m/z* calcd for $C_{29}H_{27}O_7^+$ $[M+H]^+$: 487.1752, found: 487.1759.

1-((2,5-Bis(4-methoxyphenyl)furo[3,2-*b*]pyridin-3-yl)ethynyl)cyclohexanol (10{*16*})



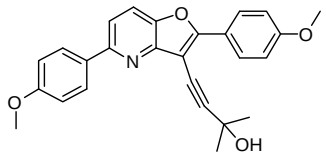
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.37 – 8.27 (m, 2H), 8.01 (d, *J* = 8.7 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.15 – 6.94 (m, 4H), 3.92 (s, 3H), 3.88 (s, 3H), 2.27 – 2.12 (m, 2H), 1.91 – 1.71 (m, 6H), 1.67 (d, *J* = 9.8 Hz, 1H), 1.40 – 1.31 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.36, 160.79, 160.58, 153.57, 147.20, 146.05, 129.32, 128.18, 121.88, 119.96, 117.26, 114.25, 114.18, 103.11, 97.64, 74.19, 69.15, 55.51, 55.41, 41.00, 39.91, 25.40, 23.58; HRMS (ESI) *m/z* calcd for $C_{29}H_{28}NO_4^+$ $[M+H]^+$: 454.2014, found: 454.2049.

3-(2,5-Bis(4-methoxyphenyl)furo[3,2-*b*]pyridin-3-yl)prop-2-yn-1-ol (10{*17*})



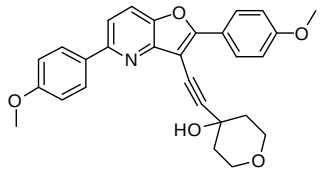
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.23 (d, *J* = 9.0 Hz, 2H), 7.99 – 7.92 (m, 2H), 7.74 (d, *J* = 8.6 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.08 – 6.94 (m, 4H), 4.65 (s, 2H), 3.89 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.17, 160.45, 160.29, 154.29, 148.08, 145.76, 131.27, 128.97, 128.00, 121.96, 119.05, 117.04, 114.26, 114.10, 97.70, 97.07, 76.00, 55.45, 55.38, 51.85; HRMS (ESI) *m/z* calcd for $C_{24}H_{20}NO_4^+$ $[M+H]^+$: 386.1388, found: 386.1419.

4-(2,5-Bis(4-methoxyphenyl)furo[3,2-*b*]pyridin-3-yl)-2-methylbut-3-yn-2-ol (10{*18*})



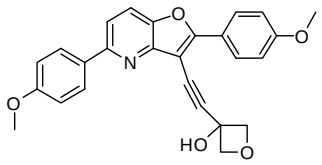
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.34 – 8.29 (m, 2H), 8.03 (d, *J* = 8.7 Hz, 2H), 7.97 (d, *J* = 8.9 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.13 – 7.00 (m, 4H), 3.93 (s, 3H), 3.88 (s, 3H), 1.76 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.81, 161.36, 152.95, 146.37, 145.79, 130.03, 128.43, 121.37, 117.96, 114.41, 104.82, 96.73, 71.59, 65.28, 55.55, 31.13; HRMS (ESI) *m/z* calcd for $C_{26}H_{24}NO_4^+$ $[M+H]^+$: 414.1701, found: 414.1728.

4-((2,5-Bis(4-methoxyphenyl)furo[3,2-*b*]pyridin-3-yl)ethynyl)tetrahydro-2*H*-pyran-4-ol (10{*20*})



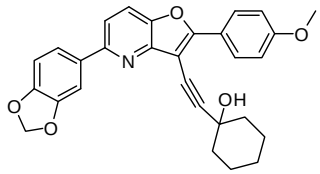
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.33 – 8.22 (m, 2H), 7.99 (d, *J* = 8.6 Hz, 2H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.04 (d, *J* = 9.0 Hz, 4H), 4.04 (dt, *J* = 11.6, 4.3 Hz, 2H), 3.93 (s, 3H), 3.88 (s, 3H), 3.88 – 3.82 (m, 2H), 2.21 (d, *J* = 13.3 Hz, 2H), 2.05 (ddd, *J* = 12.9, 9.0, 3.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.66, 161.07, 153.52, 146.62, 146.18, 133.78, 129.61, 128.28, 128.02, 121.48, 120.57, 117.68, 114.38, 114.28, 114.03, 113.94, 102.07, 96.89, 74.62, 66.05, 65.02, 55.56, 55.44, 39.83; HRMS (ESI) *m/z* calcd for $C_{28}H_{26}NO_5^+$ $[M+H]^+$: 456.1806, found: 456.1837.

3-((2,5-Bis(4-methoxyphenyl)furo[3,2-*b*]pyridin-3-yl)ethynyl)oxetan-3-ol (10{*19*})



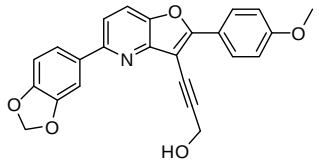
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.29 – 8.24 (m, 2H), 7.94 (d, *J* = 8.7 Hz, 2H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.08 – 7.03 (m, 4H), 5.02 (d, *J* = 6.8 Hz, 2H), 4.92 (d, *J* = 6.8 Hz, 2H), 3.93 (d, *J* = 1.7 Hz, 3H), 3.89 (s, 3H); ^{13}C NMR (126 MHz, CDCl3) δ 161.83, 161.33, 161.15, 153.71, 146.53, 146.20, 129.71, 128.59, 128.34, 121.24, 120.72, 117.95, 114.52, 114.31, 98.71, 96.24, 84.77, 75.88, 67.19, 55.56, 55.45; HRMS (ESI) *m/z* calcd for $C_{26}H_{22}NO_5^+$ $[M+H]^+$: 428.1493, found: 428.1533.

1-((5-(Benzo[*d*][1,3]dioxol-5-yl)-2-(4-methoxyphenyl)furo[3,2-*b*]pyridin-3-yl)ethynyl)cyclohexanol (10{*21*})



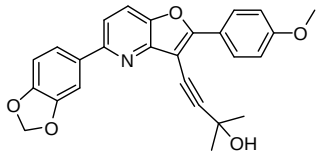
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.32 – 8.21 (m, 2H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.58 – 7.49 (m, 3H), 7.05 – 6.98 (m, 2H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.04 (s, 2H), 3.91 (s, 3H), 2.19 (d, *J* = 12.3 Hz, 2H), 1.88 – 1.73 (m, 6H), 1.71 – 1.61 (m, 2H), 1.45 – 1.28 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.20, 160.31, 153.61, 148.58, 148.19, 147.78, 145.98, 128.05, 122.01, 121.89, 119.28, 117.07, 114.19, 108.45, 108.06, 102.73, 101.40, 97.93, 74.40, 69.19, 55.48, 40.98, 39.94, 25.38, 23.55; HRMS (ESI) *m/z* calcd for $C_{29}H_{26}NO_5^+$ $[M+H]^+$: 468.1806, found: 468.1843.

3-(5-(Benzo[*d*][1,3]dioxol-5-yl)-2-(4-methoxyphenyl)furo[3,2-*b*]pyridin-3-yl)prop-2-yn-1-ol (10{*22*})



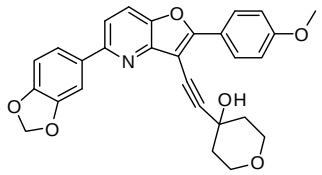
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.28 – 8.19 (m, 2H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.53 (d, *J* = 1.7 Hz, 1H), 7.50 (dd, *J* = 8.3, 2.2 Hz, 2H), 7.04 – 6.98 (m, 2H), 6.91 (d, *J* = 8.1 Hz, 1H), 6.03 (s, 2H), 4.66 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.18, 160.42, 154.07, 148.44, 148.17, 148.13, 145.81, 133.16, 128.00, 121.92, 121.74, 118.94, 117.09, 114.25, 108.44, 108.08, 101.38, 97.72, 97.05, 75.91, 55.45, 51.85; HRMS (ESI) *m/z* calcd for $C_{24}H_{18}NO_5^+$ $[M+H]^+$: 400.1180, found: 400.1216.

4-(5-(Benzo[*d*][1,3]dioxol-5-yl)-2-(4-methoxyphenyl)furo[3,2-*b*]pyridin-3-yl)-2-methylbut-3-yn-2-ol (10{*23*})



^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.32 – 8.25 (m, 2H), 7.83 (d, *J* = 8.6 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.61 – 7.52 (m, 3H), 7.09 – 7.01 (m, 2H), 6.05 (s, 2H), 3.92 (s, 3H), 1.76 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.40, 160.90, 153.44, 148.84, 148.22, 147.17, 146.09, 128.14, 122.28, 121.82, 119.81, 117.32, 114.27, 108.52, 108.26, 103.68, 101.46, 97.50, 72.28, 65.54, 55.50, 31.28; HRMS (ESI) *m/z* calcd for $C_{26}H_{22}NO_5^+$ $[M+H]^+$: 428.1493, found: 428.1533.

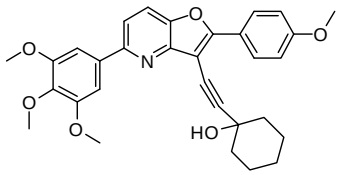
4-((5-(Benzo[*d*][1,3]dioxol-5-yl)-2-(4-methoxyphenyl)furo[3,2-*b*]pyridin-3-yl)ethynyl)tetrahydro-2*H*-pyran-4-ol (10{*25*})



^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.26 (d, *J* = 8.8 Hz, 2H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.57 – 7.50 (m, 3H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 1H), 6.06 (s, 2H), 4.06 – 3.99 (m, 2H), 3.92 (s, 3H), 3.85 (ddd, *J* = 11.7, 9.1, 2.7 Hz, 2H), 2.21 (d, *J* = 13.3 Hz, 2H), 2.05 (ddd, *J* = 12.9, 8.9, 3.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.66, 161.18, 153.33, 149.12, 148.27,

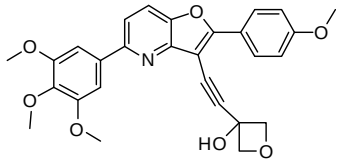
146.76, 146.23, 128.27, 122.64, 121.46, 120.39, 117.72, 108.59, 108.37, 102.04, 101.58, 96.94, 74.62, 66.07, 64.99, 55.56, 39.82; HRMS (ESI) *m/z* calcd for $C_{28}H_{24}NO_6^+$ $[M+H]^+$: 470.1599, found: 470.1640.

1-((2-(4-Methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)furo[3,2-*b*]pyridin-3-yl)ethynyl)cyclohexanol (10{*26*})



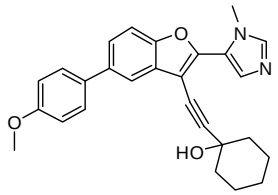
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.41 – 8.13 (m, 2H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.62 (d, *J* = 8.6 Hz, 1H), 7.33 (s, 2H), 7.11 – 6.90 (m, 2H), 4.00 (s, 6H), 3.93 (s, 3H), 3.91 (s, 3H), 2.27 – 2.07 (m, 2H), 1.88 – 1.69 (m, 6H), 1.64 (d, *J* = 13.5 Hz, 1H), 1.44 – 1.21 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.17, 160.28, 153.76, 153.41, 148.15, 146.06, 139.00, 134.20, 127.99, 122.04, 118.97, 117.13, 114.19, 104.80, 102.43, 98.03, 74.64, 69.31, 61.00, 56.26, 55.48, 39.99, 25.35, 23.59; HRMS (ESI) *m/z* calcd for $C_{31}H_{32}NO_6^+$ $[M+H]^+$: 514.2225, found: 514.2228.

3-((2-(4-Methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)furo[3,2-*b*]pyridin-3-yl)ethynyl)oxetan-3-ol (10{*29*})



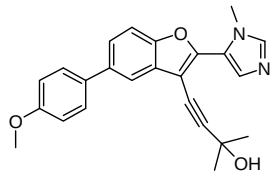
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.32 – 8.23 (m, 2H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.61 (d, *J* = 8.6 Hz, 1H), 7.22 (s, 2H), 7.10 – 7.04 (m, 2H), 5.03 (d, *J* = 7.1 Hz, 2H), 4.90 (d, *J* = 7.0 Hz, 2H), 4.00 (s, 6H), 3.93 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.69, 161.14, 154.25, 153.48, 147.49, 146.27, 139.34, 133.35, 128.34, 128.22, 121.45, 119.85, 118.10, 114.49, 114.33, 105.33, 98.16, 96.66, 84.77, 76.33, 72.39, 67.31, 61.02, 56.41, 55.55; HRMS (ESI) *m/z* calcd for $C_{28}H_{26}NO_7^+$ $[M+H]^+$: 488.1705, found: 488.1709.

1-((5-(4-Methoxyphenyl)-2-(1-methyl-1*H*-imidazol-5-yl)benzofuran-3-yl)ethynyl) cyclohexanol (10{*31*})



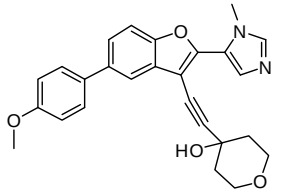
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.21 (s, 1H), 8.14 (s, 1H), 7.73 (d, *J* = 1.5 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.51 – 7.42 (m, 2H), 7.05 – 7.00 (m, 2H), 4.08 (s, 3H), 3.89 (s, 3H), 2.19 – 2.11 (m, 2H), 1.87 – 1.76 (m, 4H), 1.74 – 1.58 (m, 4H), 1.40 – 1.29 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.14, 152.85, 147.99, 139.31, 137.31, 133.52, 128.96, 128.85, 128.46, 124.91, 123.46, 118.09, 114.29, 111.30, 102.70, 100.89, 74.04, 69.22, 55.41, 40.99, 39.90, 35.19, 25.23, 23.36; HRMS (ESI) *m/z* calcd for $C_{27}H_{27}N_2O_3^+$ $[M+H]^+$: 427.20174, found: 427.2019.

4-(5-(4-Methoxyphenyl)-2-(1-methyl-1*H*-imidazol-5-yl)benzofuran-3-yl)-2-methylbut-3-yn-2-ol (10{*33*})



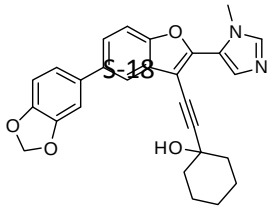
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.92 (s, 1H), 7.73 (s, 1H), 7.62 – 7.52 (m, 3H), 7.52 – 7.43 (m, 3H), 7.03 – 6.97 (m, 2H), 3.96 (s, 3H), 3.86 (s, 3H), 2.61(s, 1H) 1.71 (s, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.09, 152.77, 149.66, 137.18, 133.69, 129.14, 128.48, 127.73, 124.47, 123.19, 118.07, 114.25, 111.16, 102.29, 99.39, 72.75, 65.77, 55.40, 34.33, 31.58; HRMS (ESI) *m/z* calcd for $C_{24}H_{23}N_2O_3^+$ $[M+H]^+$: 387.1704, found: 387.1723.

4-((5-(4-Methoxyphenyl)-2-(1-methyl-1*H*-imidazol-5-yl)benzofuran-3-yl)ethynyl) tetrahydro-2*H*-pyran-4-ol (10{*35*})



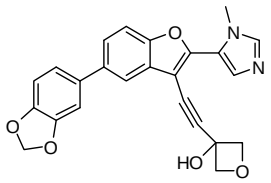
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.07 (s, 1H), 7.89 (s, 1H), 7.72 (s, 1H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.51 (q, *J* = 8.6 Hz, 2H), 7.03 (d, *J* = 8.6 Hz, 2H), 4.05 (s, 3H), 4.01 (dd, *J* = 10.9, 5.7 Hz, 2H), 3.89 (s, 3H), 3.79 (td, *J* = 15.2, 13.2, 7.7 Hz, 2H), 2.18 (d, *J* = 13.2 Hz, 3H), 2.01 (dd, *J* = 12.7, 3.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.19, 152.83, 149.08, 139.81, 137.45, 133.51, 130.77, 128.92, 128.49, 124.88, 123.21, 117.99, 114.32, 111.33, 100.52, 99.84, 75.14, 66.39, 64.82, 55.43, 39.93, 34.78; HRMS (ESI) *m/z* calcd for $C_{26}H_{25}N_2O_4^+$ $[M+H]^+$: 429.1810, found: 429.1831.

1-((5-(Benzo[*d*][1,3]dioxol-5-yl)-2-(1-methyl-1*H*-imidazol-5-yl)benzofuran-3-yl)ethynyl)cyclohexanol (10{*36*})



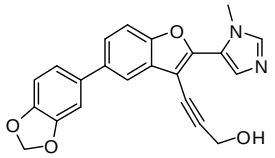
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.30 (s, 1H), 8.09 (s, 1H), 7.70 (s, 1H), 7.50 (s, 2H), 7.11 – 7.03 (m, 2H), 6.89 (d, *J* = 7.9 Hz, 1H), 6.00 (s, 2H), 4.10 (s, 3H), 2.05 (d, *J* = 11.8 Hz, 2H), 1.82 – 1.68 (m, 4H), 1.66 – 1.50 (m, 4H), 1.30 (d, *J* = 10.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.15, 148.14, 147.11, 137.67, 135.20, 128.71, 125.54, 120.93, 118.50, 111.44, 108.65, 107.94, 103.32, 102.30, 101.22, 73.31, 68.74, 40.38, 39.60, 35.49, 25.15, 23.28; HRMS (ESI) *m/z* calcd for $C_{27}H_{25}N_2O_4^+$ $[M+H]^+$: 441.1810, found: 441.1840.

3-((5-(Benzo[*d*][1,3]dioxol-5-yl)-2-(1-methyl-1*H*-imidazol-5-yl)benzofuran-3-yl)ethynyl)oxetan-3-ol (10{*39*})



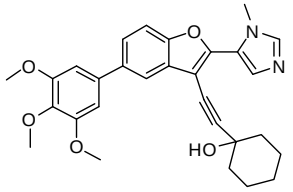
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.06 (s, 1H), 7.97 (s, 1H), 7.69 (d, *J* = 4.4 Hz, 1H), 7.46 (d, *J* = 3.5 Hz, 2H), 7.09 – 6.99 (m, 2H), 6.90 – 6.80 (m, 1H), 5.95 (d, *J* = 4.9 Hz, 2H), 4.93 (d, *J* = 5.6 Hz, 2H), 4.88 – 4.69 (m, 2H), 4.03 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.04, 148.10, 147.08, 137.75, 135.04, 128.39, 125.42, 120.91, 118.36, 111.42, 108.55, 107.88, 101.16, 100.82, 97.78, 84.86, 75.25, 66.80, 35.11; HRMS (ESI) *m/z* calcd for $C_{24}H_{19}N_2O_5^+$ $[M+H]^+$: 415.1289, found: 415.1310.

3-(5-(Benzo[*d*][1,3]dioxol-5-yl)-2-(1-methyl-1*H*-imidazol-5-yl)benzofuran-3-yl)prop-2-yn-1-ol (10{*37*)



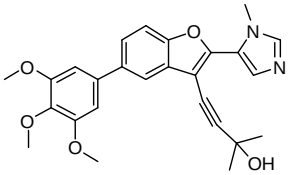
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.93 (s, 1H), 7.82 – 7.73 (m, 1H), 7.62 (s, 1H), 7.55 – 7.35 (m, 3H), 7.20 – 7.07 (m, 2H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.03 (d, *J* = 1.8 Hz, 2H), 4.59 (s, 2H), 4.03 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.83, 152.05, 150.93, 141.28, 139.28, 133.01, 128.61, 124.78, 122.18, 115.15, 112.45, 111.81, 105.09, 103.87, 100.30, 79.02, 54.75, 44.05, 38.28; HRMS (ESI) *m/z* calcd for $C_{22}H_{17}N_2O_4^+$ $[M+H]^+$: 373.1184, found: 373.1209.

1-((2-(1-Methyl-1*H*-imidazol-5-yl)-5-(3,4,5-trimethoxyphenyl)benzofuran-3-yl)ethynyl)cyclohexanol (10{*41*})



^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.11 (s, 1H), 8.06 (s, 1H), 7.74 (s, 1H), 7.50 (s, 2H), 6.81 (s, 2H), 4.10 (s, 0H), 4.07 (s, 3H), 3.96 (s, 6H), 3.91 (s, 3H), 2.11 (d, *J* = 8.5 Hz, 2H), 1.83 – 1.58 (m, 8H), 1.33 (d, *J* = 11.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.51, 153.14, 148.42, 139.50, 137.87, 137.60, 137.09, 129.68, 129.07, 125.15, 123.39, 118.60, 111.34, 104.79, 102.46, 100.72, 74.15, 69.28, 61.03, 56.29, 40.97, 39.91, 35.03, 25.22, 23.39; HRMS (ESI) *m/z* calcd for $C_{29}H_{31}N_2O_5^+$ $[M+H]^+$: 487.2228, found: 487.2263.

2-Methyl-4-(2-(1-methyl-1*H*-imidazol-5-yl)-5-(3,4,5-trimethoxyphenyl)benzofuran-3-yl)but-3-yn-2-ol (10{*43*})



^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.03 (s, 1H), 7.94 (s, 1H), 7.66 (s, 1H), 7.44 – 7.39 (m, 2H), 6.73 (s, 2H), 3.99 (s, 3H), 3.89 (s, 7H), 3.84 (s, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.48, 153.09, 148.88, 139.65, 137.94, 137.60, 137.17, 130.06, 128.83, 125.14, 123.33, 118.62, 111.29, 104.90, 103.16, 100.31, 72.26, 65.74, 61.03, 56.34, 40.97, 34.95, 31.55. HRMS (ESI) *m/z* calcd for $C_{26}H_{26}N_2O_5^+$ $[M+H]^+$: 447.1915, found: 447.1950.

B. Data for Library Compounds (HRMS, Purity, Quantity and Yield Summary)

Compound Lot Number	Calculated Exact Mass	[3] High Resolution Mass Found	[2] Final Purity (UV Area %)	[1] Final Weight	Yield (%)
10{1}	453.2062	453.2047	97.9%	13.1mg	32%
10{2}	385.1436	385.1422	98.5%	11.0mg	32%
10{3}	413.1749	413.1745	98.8%	23.0mg	62%
10{4}	427.1541	427.1533	98.9%	28.2mg	74%
10{5}	455.1854	455.1847	99.3%	25.1mg	61%

10{6}	467.1854	467.1859	98.4%	24.6mg	59%
10{7}	399.1228	399.1216	99.1%	16.9mg	47%
10{8}	427.1541	427.1552	99.1%	23.0mg	60%
10{9}	441.1334	441.1335	99.4%	24.4mg	62%
10{10}	469.1647	469.1624	98.8%	29.0mg	69%
10{11}	513.2273	513.2277	98.9%	0.9 mg	2%
10{12}	445.1647	445.1624	98.4%	16.1mg	40%
10{13}	473.196	473.1956	92.8%	24.4mg	57%
10{14}	487.1753	487.1759	98.8%	22.1mg	51%
10{15}	515.2066	515.2090	99.3%	25.1mg	54%
10{16}	454.2014	454.2049	96.2%	12.7mg	31%
10{17}	386.1388	386.1419	96.1%	10.5mg	30%
10{18}	414.1701	414.1728	98.7%	10.5mg	28%
10{19}	428.1494	428.1533	95.0%	21.3mg	55%
10{20}	456.1807	456.1837	100.0%	19.3mg	47%
10{21}	468.1807	468.1843	93.9%	18.5mg	44%
10{22}	400.1181	400.1216	97.0%	22.2mg	62%
10{23}	428.1494	428.1533	96.4%	12.4mg	32%
10{24}	442.1286	442.1315	99.4%	10.0mg	25%
10{25}	470.1599	470.1640	97.1%	20.7mg	49%
10{26}	514.2225	514.2228	100.0%	28.4mg	61%
10{27}	446.1599	446.1612	100.0%	3.7 mg	9%
10{28}	474.1912	474.1918	100.0%	17.1mg	40%
10{29}	399.1228	488.1709	99.5%	24.7mg	56%
10{30}	467.1854	516.2025	98.5%	19.3mg	42%
10{31}	427.2017	427.2019	99.7%	18.7mg	49%
10{32}	359.1391	359.1377	97.7%	7.9mg	19%[a]
10{33}	387.1704	387.1723	98.8%	6.6mg	19%
10{34}	401.1497	401.1520	90.2%	0.5mg	1%
10{35}	429.181	429.1831	98.3%	13.6mg	35%
10{36}	441.181	441.1840	95.8%	14.0mg	35%

10{37}	373.1184	373.1209	95.4%	6.9mg	21%
10{38}	401.1497	401.1523	97.1%	20.0mg	56%
10{39}	415.129	415.1310	94.8%	11.5mg	31%
10{40}	443.1603	443.1624	95.1%	9.5mg	24%
10{41}	487.2229	487.2263	92.9%	6.4mg	15%
10{42}	419.1603	419.1637	94.0%	17.3mg	46%
10{43}	447.1916	447.1950	94.4%	10.9mg	27%
10{44}	461.1708	461.1741	94.6%	5.3mg	13%
10{45}	489.2021	489.2052	95.7%	7.6mg	17%

[a]: Reaction was run on 0.11 mmol scale.

Reference:

1. Cho, C.-H.; Neuenswander, B.; Lushington, G. H.; Larock, R. C.*J. Comb. Chem.* **2008**, *10* (6), 941-947.