Supporting Information

Cobalt-Catalyzed and 2-(1-Methylhydrazinyl)pyridine-Assisted Cyclization of Thiophene-2-Carbohydrazides with Maleimides: Efficient Synthesis of Heteroaryl-Fused Pyridones

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1. Materials and methods

All reactions were carried out under Argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. All the chemicals were purchased commercially, and used without further purification. Anhydrous THF was distilled from sodium-benzophenone. Dichloromethane and was distilled from calcium hydride. Thin-layer chromatography (TLC) was conducted with 0.25 mm Tsingdao silica gel plates (60F-254) and visualized by exposure to UV light (254 nm) or stained with potassium permanganate. Flash column chromatography was performed on Tsingdao silica gel (200-300 mesh) and neutral/basic aluminum oxide (200-300mesh). $^1$H NMR spectra were recorded on Bruker spectrometers (at 300, 400 or 500 MHz) and reported relative to deuterated solvent signals or tetramethylsilane internal standard signals. Data for $^1$H NMR spectra were reported as follows: chemical shift (δ/ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.), coupling constant (J/Hz) and integration. $^{13}$C NMR spectra were recorded on Bruker Spectrometers (100 or 125 MHz). Data for $^{13}$C NMR spectra were reported in terms of chemical shift. $^{19}$F NMR spectra were recorded on Bruker Spectrometers (376 MHz). High-resolution mass spectrometry (HRMS) was conducted on Bruker Apex IV RTMS.
2. General procedure for the synthesis of starting materials

Representative Method: (1a-1h)\(^1\)

To a stirred mixture of 2-(1-methylhydrazinyl)pyridine (1.0 equiv, 5 mmol) and Et\(_3\)N (5.0 equiv) in dry CH\(_2\)Cl\(_2\) (0.2 to 0.5 M) was added Thiophene chloride (1.05 equiv) dropwise under Ar atmosphere at 0 °C. Kept the reaction mixture stirred at 0 °C for about 0.5 h, then the resulting mixture was warmed to room temperature and stirred overnight at this temperature. Upon completion of the reaction indicated by TLC, the reaction mixture was washed with H\(_2\)O and extracted with CH\(_2\)Cl\(_2\) (20 mL) for three times. The combined organic phases were washed with brine, dried over with anhydrous Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (n-hexanes/EtOAc = 3:1 to 1:1) to afford the corresponding product. The product gives two sets of NMR signals, owing to the presence of rotamers around the amide.

N'-Methyl-N'-(pyridin-2-yl)thiophene-2-carbohydrazide: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 1a as a solid.

\(^1\)HNMR (400 MHz, DMSO-d\(_6\)) δ 10.82 (s, 1H), 8.16 – 8.15 (m, 1H), 7.91 (d, \(J = 4.0\) Hz, 1H), 3.87 (s, 3H).
Hz, 1H), 7.88 – 7.87 (m, 1H), 7.56 – 7.52 (m, 1H), 7.22 (dd, J = 5.0, 4.0 Hz, 1H), 6.74 – 6.70 (m, 2H), 3.32 (s, 3H). 13C NMR (100 MHz, DMSO-d6) δ 161.1, 160.0, 147.8, 138.0, 137.7, 132.3, 129.5, 128.6, 114.3, 107.2, 38.2. HRMS m/z ([M+H]+) called for C11H12N3OS: 234.0701, found: 234.0696.

N',5-Dimethyl-N'-(pyridin-2-yl)thiophene-2-carbohydrazide: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 1b as a solid.

1H NMR (400 MHz, DMSO-d6) δ 10.68 (s, 1H), 8.15 (d, J = 4.4 Hz, 1H), 7.70 (d, J = 3.6 Hz, 1H), 7.55 – 7.51 (m, 1H), 6.91 (d, J = 3.2 Hz, 1H), 6.72 – 6.69 (m, 2H), 3.30 (s, 3H), 2.49 (s, 3H). 13C NMR (100 MHz, DMSO-d6) δ 161.0, 160.1, 147.8, 146.3, 138.0, 135.1, 129.8, 127.1, 114.2, 107.2, 38.2, 15.7. HRMS m/z ([M+H]+) called for C12H14N3OS: 248.0858, found: 248.0850.

5-Chloro-N'-methyl-N'-(pyridin-2-yl)thiophene-2-carbohydrazide: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 1c as a solid. Spectra for the major rotamer: 1H NMR (400 MHz, DMSO-d6) δ 10.92 (s, 1H), 8.16 (dd, J = 3.6, 1.2 Hz, 1H), 7.80 – 7.77 (m, 1H), 7.55 (dd, J = 8.4, 7.2 Hz, 1H), 7.28 – 7.26 (m, 1H), 6.74 – 6.71 (m, 2H), 3.31 (s, 3H). 13C NMR (100 MHz, DMSO-d6) δ 160.1, 159.8, 147.8, 138.1, 136.9, 134.5, 129.6, 128.8, 114.5, 107.2, 38.2. HRMS m/z ([M+H]+) called for C11H11ClN3OS: 268.0311, found: 268.0305.
5-Bromo-N'-methyl-N'(pyridin-2-yl)thiophene-2-carbohydrazide: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 1d as a solid. 

$^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 10.88 (s, 1H), 8.16 – 8.15 (m, 1H), 7.72 (d, $J$ = 4.0 Hz, 1H), 7.57 – 7.53 (m, 1H), 7.37 (d, $J$ = 4.0 Hz, 1H), 6.74 – 6.71 (m, 2H), 3.29 (s, 3H).

$^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 160.0, 159.8, 147.8, 139.5, 138.1, 132.3, 130.3, 118.3, 114.5, 107.2, 38.2. HRMS m/z ([M+H]$^+$) called for C$_{11}$H$_{11}$BrN$_3$OS: 311.9806, found: 311.9803.

5-Acetyl-N'-methyl-N'(pyridin-2-yl)thiophene-2-carbohydrazide: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 1e as a solid.

$^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 11.04 (s, 1H), 8.18 – 8.16 (m, 1H), 7.99 (d, $J$ = 4.0 Hz, 1H), 7.93 (d, $J$ = 4.0 Hz, 1H), 7.58 – 7.54 (m, 1H), 6.76 – 6.73 (m, 2H), 3.32 (s, 3H), 2.59 (s, 3H).

$^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 191.4, 160.1, 159.4, 147.5, 147.2, 143.7, 137.7, 133.9, 129.8, 114.5, 106.9, 37.8, 26.8. HRMS m/z ([M+H]$^+$) called for C$_{13}$H$_{14}$N$_3$O$_2$S: 276.0807, found: 276.0803.

N'-Methyl-N'(pyridin-2-yl)thiophene-3-carbohydrazide: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 1f as a solid.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.83 (s, 1H), 8.13 (d, $J = 3.6$ Hz, 1H), 7.97 (s, 1H), 7.43 – 7.40 (m, 2H), 7.18 (dd, $J = 4.4$, 2.8 Hz, 1H), 6.67 – 6.65 (m, 2H), 3.29 (s, 3H).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 162.5, 159.3, 147.2, 137.8, 135.0, 129.5, 126.5, 126.4, 114.6, 107.2, 38.7. HRMS m/z ([M+H]$^+$) called for C$_{11}$H$_{12}$N$_3$OS: 234.0701, found: 234.0701.

N'-Methyl-N'(pyridin-2-yl)benzo[b]thiophene-2-carbohydrazide: Prepared according to the general procedure, purified by silica gel column chromatography ($n$-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 1g as a solid.

$^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 11.05 (s, 1H), 8.22 (s, 1H), 8.17 – 8.15 (m, 1H), 8.06 – 8.04 (m, 1H), 8.00 – 7.98 (m, 1H), 7.56 – 7.52 (m, 1H), 7.50 – 7.44 (m, 2H), 6.77 (d, $J = 8.8$ Hz, 1H), 6.71 (ddd, $J = 6.8$, 4.8, 0.8 Hz, 1H), 3.33 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 161.6, 159.9, 147.8, 140.8, 139.5, 138.1, 137.7, 127.1, 126.4, 125.9, 125.6, 123.3, 114.4, 107.3, 38.2. HRMS m/z ([M+H]$^+$) called for C$_{15}$H$_{14}$N$_3$OS: 284.0858, found: 284.0852.

N'-Methyl-N'(pyridin-2-yl)benzo[b]thiophene-3-carbohydrazide: Prepared according to the general procedure, purified by silica gel column chromatography ($n$-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 1h as a solid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.80 (s, 1H), 8.45 (d, $J = 8.0$ Hz, 1H), 8.20 (d, $J = 4.4$ Hz, 1H), 8.08 (s, 1H), 7.84 – 7.82 (m, 1H), 7.52 – 7.47 (m, 1H), 7.45 – 7.37 (m, 2H), 6.79 (d, $J = 8.4$ Hz, 1H), 6.73 (t, $J = 6.0$ Hz, 1H), 3.45 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 163.2, 159.2, 147.6, 140.0, 137.8, 136.8, 130.5, 129.4, 125.3, 124.5, 122.4,
114.8, 107.2, 39.1. HRMS m/z ([M+H]^+ ) called for C_{15}H_{14}N_{3}O_{5}S: 284.0858, found: 284.0849.

3. General procedure for cobalt-catalyzed Cyclization of Thiophene-2-Carbohydrazides with Maleimides

A mixture of Thiophene-2-Carbohydrazides (0.20 mmol), maleimide (0.4 mmol), Co(OAc)_2·4H_2O (0.04 mmol), Ag_2CO_3 (0.4 mmol), NaOPiv (0.4 mmol) and DCE (2.0 mL) was added to a 25 mL sealed tube. The tube was stirred at 120 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with 5.0 mL of ethyl acetate and filtered through a plug of celite, followed by washing with 70 mL of ethyl acetate. The combined residue was concentrated under reduced pressure, and then the resulting crude product was purified by column chromatography on to provide the product.

2-Methyl-4-(methyl(pyridin-2-yl)amino)-1H-pyrrolo[3,4-b]thieno[3,2-d]pyridine-1,3,5(2H,4H)-trione: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 3aa as a solid. ^1H NMR (400 MHz, CDCl_3) δ 8.09 (ddd, J = 4.8, 2.0, 0.8 Hz, 1H), 7.94 (d, J = 5.2 Hz, 1H), 7.83 (d, J = 5.2 Hz, 1H), 7.58 – 7.54 (m, 1H), 6.75 (ddd, J = 7.2, 4.8, 0.8 Hz, 1H), 6.62 (d, J = 8.4 Hz, 1H), 3.58 (s, 3H), 3.07 (s, 3H). ^13C NMR (100 MHz, CDCl_3) δ 165.9, 161.9, 157.5, 157.0, 148.1, 138.7, 138.1, 137.2, 137.1, 134.9, 123.1, 115.7, 109.7, 106.0, 38.2, 24.0. HRMS m/z ([M+H]^+ ) called for C_{16}H_{12}ClN_{4}O_{5}S: 341.0708, found: 341.0710.
2,7-Dimethyl-4-(methyl(pyridin-2-yl)amino)-1H-pyrrolo[3,4-b]thieno[3,2-d]pyridine-1,3,5(2H,4H)-trione: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 3ba as a solid. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.10 (d, \(J = 5.0\) Hz, 1H), 7.57 – 7.53 (m, 1H), 7.51 (d, \(J = 1.0\) Hz, 1H), 6.75 (ddd, \(J = 7.0, 5.0, 0.5\) Hz, 1H), 6.59 (d, \(J = 8.0\) Hz, 1H), 3.57 (s, 3H), 3.07 (s, 3H), 2.68 (d, \(J = 1.0\) Hz, 3H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 176.6, 166.1, 161.9, 157.1, 153.4, 148.1, 138.6, 138.0, 137.9, 133.3, 121.2, 115.5, 109.4, 106.0, 38.2, 23.9, 16.4. HRMS m/z ([M+H]\(^+\)) called for C\(_{17}\)H\(_{15}\)N\(_4\)O\(_3\)S: 355.0865, found: 355.0862.

7-Chloro-2-methyl-4-(methyl(pyridin-2-yl)amino)-1H-pyrrolo[3,4-b]thieno[3,2-d]pyridine-1,3,5(2H,4H)-trione: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 3ca as a solid. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.06 (dd, \(J = 5.0, 1.0\) Hz, 1H), 7.68 (s, 1H), 7.60 – 7.56 (m, 1H), 6.76 (ddd, \(J = 7.5, 5.0, 1.0\) Hz), 6.65 (d, \(J = 8.5\) Hz, 1H), 3.56 (s, 3H), 3.07 (s, 3H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 165.5, 161.6, 156.8, 156.4, 148.1, 143.4, 139.6, 138.1, 136.9, 133.0, 122.2, 115.8, 108.8, 106.0, 38.3, 24.0. HRMS m/z ([M+H]\(^+\)) called for C\(_{16}\)H\(_{12}\)ClN\(_4\)O\(_3\)S: 375.0319, found: 375.0313.
7-Bromo-2-methyl-4-(methyl(pyridin-2-yl)amino)-1H-pyrrolo[3,4-b]thieno[3,2-d]pyridine-1,3,5(2H,4H)-trione: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 3da as a solid. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.06 (d, $J = 4.0$ Hz, 1H), 7.83 (s, 1H), 7.59 – 7.56 (m, 1H), 6.76 (dd, $J = 7.0$, 5.0 Hz, 1H), 6.65 (d, $J = 8.5$ Hz, 1H), 3.56 (s, 3H), 3.07 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 165.5, 161.6, 156.8, 156.3, 148.1, 139.4, 138.1, 137.6, 135.7, 126.8, 125.9, 115.8, 108.5, 106.0, 38.2, 24.0. HRMS m/z ([M+H]$^+$) called for C$_{16}$H$_{12}$BrN$_4$O$_3$: 418.9813, found: 418.9806.

7-Acetyl-2-methyl-4-(methyl(pyridin-2-yl)amino)-1H-pyrrolo[3,4-b]thieno[3,2-d]pyridine-1,3,5(2H,4H)-trione: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 3ea as a solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.30 (s, 1H), 8.06 (d, $J = 4.4$ Hz, 1H), 7.63 – 7.59 (m, 1H), 6.79 (dd, $J = 7.2$, 5.2 Hz, 1H), 6.70 (d, $J = 8.4$ Hz, 1H), 3.59 (s, 3H), 3.11 (s, 3H), 2.73 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 191.0, 165.7, 161.6, 157.6, 156.7, 153.2, 148.1, 139.6, 138.8, 138.2, 136.9, 126.3, 115.9, 106.1, 38.3, 27.2, 24.1. HRMS m/z ([M+H]$^+$) called for C$_{18}$H$_{15}$N$_4$O$_4$: 383.0814, found: 383.0814.
7-Methyl-5-(methyl(pyridin-2-yl)amino)-4H-pyrrolo[3,4-b]thieno[2,3-d]pyridine-4,6,8(5H,7H)-trione: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 3fa as a solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.10 (d, $J$ = 4.0 Hz, 1H), 7.77 (d, $J$ = 5.2 Hz, 1H), 7.63 (d, $J$ = 5.2 Hz, 1H), 7.60 – 7.56 (m, 1H), 6.77 (dd, $J$ = 6.4, 4.8 Hz, 1H), 6.64 (d, $J$ = 8.4 Hz, 1H), 3.58 (s, 3H), 3.10 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.4, 161.6, 157.9, 157.0, 148.1, 138.0, 137.8, 136.7, 134.7, 130.0, 126.2, 115.6, 109.8, 106.0, 38.2, 24.1. HRMS m/z ([M+H]$^+$) called for C$_{16}$H$_{12}$ClN$_4$O$_3$S: 341.0708, found: 341.0712.

2-Methyl-4-(methyl(pyridin-2-yl)amino)-1H-benzo[4,5]thieno[3,2-d]pyrrolo[3,4-b]pyridine-1,3,5(2H,4H)-trione: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 3ga as a solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.52 – 9.48 (m, 1H), 8.09 (dt, $J$ = 4.8, 1.2 Hz, 1H), 8.00 – 7.97 (m, 1H), 7.67 – 7.63 (m, 2H), 7.62 – 7.58 (m, 1H), 6.78 (ddd, $J$ = 7.2, 4.8, 0.8 Hz, 1H), 6.68 (d, $J$ = 8.4 Hz, 1H), 3.64 (s, 3H), 3.16 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.2, 161.5, 157.8, 156.8, 148.1, 142.8, 139.2, 138.1, 135.9, 134.9, 134.1, 129.0, 128.6, 126.0, 123.0, 115.7, 110.7, 106.0, 38.2, 24.2. HRMS m/z ([M+H]$^+$) called for C$_{20}$H$_{15}$N$_4$O$_3$S: 391.0865, found: 391.0861.
2-Methyl-4-(methyl(pyridin-2-yl)amino)-1H-benzo[4,5]thieno[2,3-d]pyrrolo[3,4-b]pyridine-1,3,5(2H,4H)-trione: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product \(3\text{ha}\) as a solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.86 – 8.84 (m, 1H), 8.10 – 8.09 (m, 1H), 7.99 – 7.97 (m, 1H), 7.62 – 7.55 (m, 3H), 6.79 (dd, \(J = 7.2\), 4.8 Hz, 1H), 6.70 (d, \(J = 8.4\) Hz, 1H), 3.65 (s, 3H), 3.14 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 165.4, 161.3, 157.7, 157.0, 148.1, 140.5, 140.2, 138.4, 138.1, 135.4, 127.5, 127.3, 126.2, 125.5, 122.5, 115.8, 109.2, 106.0, 38.3, 24.2. HRMS m/z ([M+H]\(^+\)) called for \(\text{C}_{20}\text{H}_{15}\text{N}_{4}\text{O}_{3}\text{S}\): 391.0865, found: 391.0866.

7-Chloro-2-ethyl-4-(methyl(pyridin-2-yl)amino)-1H-pyrrolo[3,4-b]thieno[3,2-d]pyridine-1,3,5(2H,4H)-trione: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product \(3\text{cb}\) as a solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.08 (d, \(J = 4.0\) Hz, 1H), 7.69 (s, 1H), 7.61 – 7.56 (m, 1H), 6.77 (dd, \(J = 6.8, 4.8\) Hz, 1H), 6.66 (d, \(J = 8.4\) Hz, 1H), 3.64 (qd, \(J = 7.2, 1.6\) Hz, 2H), 3.57 (s, 3H), 1.22 (t, \(J = 7.2\) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 165.3, 161.3, 156.8, 156.4, 148.0, 143.3, 139.3, 138.1, 136.9, 132.9, 122.2, 115.8, 108.7, 106.0, 38.3, 33.2, 13.9. HRMS m/z ([M+H]\(^+\)) called for \(\text{C}_{17}\text{H}_{14}\text{ClN}_{4}\text{O}_{3}\text{S}\): 389.0475, found: 389.0470.
7-Chloro-2-isobutyl-4-(methyl(pyridin-2-yl)amino)-1H-pyrrolo[3,4-b]thieno[3,2-d]pyridine-1,3,5(2H,4H)-trione: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 3cc as a solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.06 (dd, $J = 5.2$, 2.0 Hz, 1H), 7.69 (s, 1H), 7.60 – 7.58 (m, 1H), 6.76 (dd, $J = 7.2$, 4.8 Hz, 1H), 6.66 (d, $J = 8.4$ Hz, 1H), 3.57 (s, 3H), 3.37 (d, $J = 7.2$ Hz, 2H), 2.06 – 1.96 (m, 1H), 0.89 (d, $J = 6.4$ Hz, 3H), 0.87 (d, $J = 6.8$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.8, 161.8, 156.8, 156.5, 148.0, 143.3, 139.2, 138.1, 138.0, 136.9, 133.0, 122.3, 115.8, 108.6, 106.0, 45.5, 38.3, 27.9, 20.0, 19.9. HRMS m/z ([M+H]$^+$) called for C$_{19}$H$_{18}$ClN$_4$O$_3$S: 417.0788, found: 417.0781.

2-(tert-Butyl)-7-chloro-4-(methyl(pyridin-2-yl)amino)-1H-pyrrolo[3,4-b]thieno[3,2-d]pyridine-1,3,5(2H,4H)-trione: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 3cd as a solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.10 (d, $J = 4.4$ Hz, 1H), 7.69 (s, 1H), 7.60 – 7.55 (m, 1H), 6.77 (dd, $J = 7.2$, 5.2 Hz, 1H), 6.62 (d, $J = 8.4$ Hz, 1H), 3.56 (s, 3H), 1.61 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.8, 162.3, 156.9, 156.6, 148.0, 143.2, 138.0, 136.9, 133.0, 122.2, 115.6, 108.7, 106.0, 58.5, 38.3, 29.0. HRMS m/z ([M+H]$^+$) called for C$_{19}$H$_{18}$ClN$_4$O$_3$S: 417.0788, found: 417.0784.
7-Chloro-2-cyclohexyl-4-(methyl(pyridin-2-yl)amino)-1H-pyrrolo[3,4-b]thieno[3,2-d]pyridine-1,3,5(2H,4H)-trione: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 3ce as a solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.10 – 8.09 (m, 1H), 7.69 (s, 1H), 7.62 – 7.57 (m, 1H), 6.78 (dd, $J = 6.8$, 5.2 Hz, 1H), 6.65 (d, $J = 8.4$ Hz, 1H), 3.98 (tt, $J = 12.4$, 4.0 Hz, 1H), 3.58 (s, 3H), 2.14 – 1.99 (m, 2H), 1.84 (d, $J = 11.2$ Hz, 2H), 1.71 (d, $J = 14.0$ Hz, 2H), 1.34 – 1.24 (m, 4H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.6, 161.4, 156.8, 156.5, 148.0, 143.3, 138.8, 138.1, 137.0, 132.9, 122.2, 115.7, 108.6, 106.0, 51.3, 38.3, 30.0, 25.9, 25.0. HRMS m/z ([M+H]$^+$) called for C$_{21}$H$_{20}$ClN$_4$O$_3$: 443.0945, found: 443.0937.

7-Chloro-4-(methyl(pyridin-2-yl)amino)-2-phenyl-1H-pyrrolo[3,4-b]thieno[3,2-d]pyridine-1,3,5(2H,4H)-trione: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 3cf as a solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.09 (d, $J = 4.4$ Hz, 1H), 7.75 (s, 1H), 7.62 – 7.58 (m, 1H), 7.46 (t, $J = 7.6$ Hz, 2H), 7.39 – 7.35 (m, 3H), 6.78 (dd, $J = 6.8$, 4.8 Hz, 1H), 6.71 (d, $J = 8.8$ Hz, 1H), 3.60 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 164.4, 160.4, 156.7, 156.5, 148.0, 143.6, 139.0, 138.2, 136.9,
133.5, 130.8, 129.1, 128.2, 126.3, 122.4, 115.9, 108.6, 106.1, 38.4. **HRMS m/z ([M+H]^+)** called for C_{21}H_{13}ClN_{4}O_{3}S: 437.0475, found: 437.0466.

7-Chloro-4-(methyl(pyridin-2-yl)amino)-2-(p-tolyl)-1H-pyrrolo[3,4-b]thieno[3,2-d]pyridine-1,3,5(2H,4H)-trione: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 3cg as a solid. **^1H NMR** (400 MHz, CDCl_3) δ 8.09 (d, J = 4.0 Hz, 1H), 7.75 (s, 1H), 7.63 – 7.54 (m, 1H), 7.26 (d, J = 7.6 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 6.78 (dd, J = 7.2, 5.6 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 3.60 (s, 3H), 2.38 (s, 3H). **^13C NMR** (100 MHz, CDCl_3) δ 164.5, 160.5, 156.7, 156.5, 148.0, 143.5, 139.0, 138.3, 138.1, 136.9, 133.4, 129.7, 128.1, 126.2, 122.4, 115.9, 108.6, 106.1, 38.4, 21.2. **HRMS m/z ([M+H]^+)** called for C_{22}H_{16}ClN_{4}O_{3}S: 451.0632, found: 451.0622.

7-Chloro-2-(4-fluorophenyl)-4-(methyl(pyridin-2-yl)amino)-1H-pyrrolo[3,4-b]thieno[3,2-d]pyridine-1,3,5(2H,4H)-trione: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 3ch as a solid. **^1H NMR** (400 MHz, CDCl_3) δ 8.08 (dd, J = 4.8, 0.8 Hz, 1H), 7.74 (s, 1H), 7.63 – 7.58 (m, 1H), 7.36 – 7.32 (m,
2H), 7.17 – 7.12 (m, 2H), 6.79 (dd, \( J = 6.8, 5.2 \) Hz, 1H), 6.71 (d, \( J = 8.4 \) Hz, 1H), 3.59 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 164.3, 163.2, 160.5 (d, \( J = 36 \) Hz), 156.6 (d, \( J = 22.0 \) Hz), 148.0, 143.7, 139.0, 138.2, 136.8, 133.5, 128.2 (d, \( J = 8.0 \) Hz), 126.7, 122.3, 116.2, 116.0, 115.9, 108.5, 106.1, 38.4. \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \( \delta \) -112.6. HRMS m/z ([M+H]^+) called for C\(_{21}\)H\(_{13}\)ClFN\(_4\)O\(_3\)S: 455.0381, found: 455.0376.

2-Benzyl-7-chloro-4-(methyl(pyridin-2-yl)amino)-1H-pyrrolo[3,4-b]thieno[3,2-d]pyridine-1,3,5(2H,4H)-trione: Prepared according to the general procedure, purified by silica gel column chromatography (\( n \)-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 3ci as a solid. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.06 (dd, \( J = 4.5, 0.5 \) Hz, 1H), 7.68 (s, 1H), 7.60-7.57 (m, 1H), 7.37 – 7.35 (m, 2H), 7.33 – 7.28 (m, 3H), 6.77 (dd, \( J = 6.5, 5.0 \) Hz, 1H), 6.66 (d, \( J = 8.5 \) Hz, 1H), 4.75 (d, \( J = 14.5 \) Hz, 1H), 4.68 (d, \( J = 15.0 \) Hz, 1H), 3.56 (s, 3H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 165.2, 161.2, 156.8, 156.4, 148.0, 143.4, 139.5, 138.1, 136.9, 135.9, 133.1, 128.7, 128.6, 128.0, 122.2, 115.8, 108.7, 106.1, 41.8, 38.3. HRMS m/z ([M+H]^+) called for C\(_{22}\)H\(_{16}\)ClN\(_4\)O\(_3\)S: 451.0632, found: 451.0623.

7-Chloro-4-(methyl(pyridin-2-yl)amino)-2-(4-methylbenzyl)-1H-pyrrolo[3,4-b]thieno[3,2-d]pyridine-1,3,5(2H,4H)-trione: Prepared according to the general
procedure, purified by silica gel column chromatography ($n$-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 3cj as a solid. **$^1$H NMR** (400 MHz, CDCl$_3$) δ 8.08 (dd, $J = 4.8$, 0.8 Hz, 1H), 7.69 (s, 1H), 7.62-7.58 (m, 1H), 7.31 (d, $J = 8.4$ Hz, 2H), 6.84 (d, $J = 8.8$ Hz, 2H), 6.79 (dd, $J = 7.2$, 5.2 Hz, 1H), 6.66 (d, $J = 8.4$ Hz, 1H), 4.70 (d, $J = 14.8$ Hz, 1H), 4.63 (d, $J = 14.8$ Hz, 1H), 3.78 (s, 3H), 3.57 (s, 3H). **$^{13}$C NMR** (100 MHz, CDCl$_3$) δ 165.2, 161.2, 159.3, 156.8, 156.4, 148.0, 143.4, 139.4, 138.1, 136.9, 133.0, 132.9, 128.1, 128.2, 115.8, 114.1, 108.7, 106.1, 55.3, 41.3, 38.3. **HRMS** m/z ([M+H]$^+$) called for C$_{23}$H$_{18}$ClN$_4$O$_4$S: 465.0788, found: 465.0784.

7-Chloro-2-(4-methoxybenzyl)-4-(methyl(pyridin-2-yl)amino)-1H-pyrrolo[3,4-b]thieno[3,2-d]pyridine-1,3,5(2H,4H)-trione: Prepared according to the general procedure, purified by silica gel column chromatography ($n$-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 3ck as a solid. **$^1$H NMR** (400 MHz, CDCl$_3$) δ 8.08 (d, $J = 4.0$ Hz, 1H), 7.69 (s, 1H), 7.62 – 7.58 (m, 1H), 7.31 (d, $J = 8.4$ Hz, 2H), 6.84 (d, $J = 8.8$ Hz, 2H), 6.79 (dd, $J = 7.2$, 5.2 Hz, 1H), 6.66 (d, $J = 8.4$ Hz, 1H), 4.70 (d, $J = 14.8$ Hz, 1H), 4.63 (d, $J = 14.8$ Hz, 1H), 3.78 (s, 3H), 3.57 (s, 3H). **$^{13}$C NMR** (100 MHz, CDCl$_3$) δ 165.2, 161.2, 159.3, 156.8, 156.4, 148.0, 143.4, 139.4, 138.1, 136.9, 133.0, 132.9, 128.1, 128.2, 115.8, 114.1, 108.7, 106.1, 55.3, 41.3, 38.3. **HRMS** m/z ([M+H]$^+$) called for C$_{23}$H$_{18}$ClN$_4$O$_4$S: 481.0737, found: 481.0734.
eno[3,2-d]pyridine-1,3,5(2H,4H)-trione: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 3cl as a solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.07 (dd, J = 4.8, 0.8 Hz, 1H), 7.69 (s, 1H), 7.63-7.58 (m, 1H), 7.32 – 7.28 (m, 4H), 6.79 (dd, J = 6.8, 5.2 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 4.73 (d, J = 14.8 Hz, 1H), 4.66 (d, J = 14.8 Hz, 1H), 3.57 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.1, 161.1, 156.8, 156.4, 148.0, 143.5, 139.4, 138.2, 136.8, 134.3, 134.0, 133.2, 130.1, 128.9, 122.2, 115.9, 108.6, 106.1, 41.1, 38.4. HRMS m/z ([M+H]$^+$) called for C$_{22}$H$_{15}$Cl$_2$N$_4$O$_3$: 485.0242, found: 485.0237.

7-Chloro-2-(4-fluorobenzyl)-4-(methyl(pyridin-2-yl)amino)-1H-pyrrolo[3,4-b]thi eno[3,2-d]pyridine-1,3,5(2H,4H)-trione: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 3cm as a solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.05 (d, J = 4.0 Hz, 1H), 7.67 (s, 1H), 7.61 – 7.57 (m, 1H), 7.34 (dd, J = 8.8, 5.6 Hz, 2H), 6.98 (t, J = 8.8 Hz, 2H), 6.78 (dd, J = 6.8, 4.8 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H), 4.71 (d, J = 14.8 Hz, 1H), 4.65 (d, J = 14.8 Hz, 1H), 3.56 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.1, 163.7, 161.1, 156.6 (d, J = 39.0 Hz), 148.0, 143.5, 139.4, 138.2, 136.8, 133.1, 131.7, 130.5 (d, J = 8.0 Hz), 122.2, 115.9, 115.7, 115.5, 108.6, 106.1, 41.1, 38.4. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -113.8. HRMS m/z ([M+H]$^+$) called for C$_{22}$H$_{15}$ClF$_2$N$_4$O$_3$: 469.0537, found: 469.0533.
**7-Chloro-2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)phenyl)-4-(methyl(pyridin-2-yl)amino)-1H-pyrrolo[3,4-b]thieno[3,2-d]pyridine-1,3,5(2H,4H)-trione:**

Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 3cn as a solid. **1H NMR** (400 MHz, CDCl₃) δ 8.09 (d, J = 4.0 Hz, 1H), 7.75 (s, 1H), 7.63-7.59 (m, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.51 (t, J = 2.0 Hz, 1H), 7.44 – 7.39 (m, 2H), 6.87 (s, 2H), 6.80 – 6.77 (m, 1H), 6.71 (d, J = 8.4 Hz, 1H), 3.60 (s, 3H). **13C NMR** (100 MHz, CDCl₃) δ 169.0, 163.9, 160.0, 156.6, 156.5, 148.1, 143.7, 138.9, 138.2, 136.7, 134.3, 133.6, 131.9, 131.6, 129.5, 125.0, 124.9, 123.0, 122.4, 116.0, 108.5, 106.0, 38.4. **HRMS** m/z ([M+H]+) called for C₂₅H₁₅ClN₅O₅S: 532.0482, found: 532.0476.

**7-Chloro-2-(4-(4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzyl)phenyl)-4-(methyl (pyridin-2-yl)amino)-1H-pyrrolo[3,4-b]thieno[3,2-d]pyridine-1,3,5(2H,4H)-trione:**

Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 3co as a solid. **1H NMR** (400 MHz, CDCl₃) δ 8.08 (dd, J = 4.8, 0.8 Hz, 1H),
7.74 (s, 1H), 7.61 – 7.57 (m, 1H), 7.28 – 7.26 (m, 8H), 6.83 (s, 2H), 6.77 (ddd, J = 7.2, 4.8, 0.8 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 4.03 (s, 2H), 3.59 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 169.5, 164.4, 160.4, 156.7, 156.5, 148.0, 143.6, 140.6, 140.30, 139.0, 138.1, 136.9, 134.2, 133.4, 129.7, 129.4, 129.0, 126.4, 126.2, 122.4, 115.9, 108.6, 106.0, 41.1, 38.4. HRMS m/z ([M+H]\(^+\)) called for C\(_{32}\)H\(_{21}\)ClN\(_5\)O\(_5\)S: 622.0952, found: 622.0944.

4. Synthetic Applications of thiophene-fused pyridones

Procedure for the Pd-catalyzed Sonogashira coupling reaction: To an oven-dried flask (10 mL) charged with the bromide 3da (83.4 mg, 0.2 mmol), bis(triphenylphosphine)palladium(II) chloride (14.0 mg, 10 mol %), CuI (7.6 mg, 20 mol %) was added anhydrous THF (1.5 mL), propargyl alcohol 4 (56.0 mg, 5.0 equiv) and Et\(_3\)N (0.4 mL) under N\(_2\) atmosphere. After being stirred for 6 h at 40 °C, the reaction mixture was concentrated under reduced pressure and purified by column chromatography on silica gel, eluting with n-hexanes/EtOAc (4:1 ~ 2:1, v/v), to afford corresponding product 5.

7-(3-Hydroxyprop-1-yn-1-yl)-2-methyl-4-(methyl(pyridin-2-yl)amino)-1H-pyrrolo[3,4-b]thieno[3,2-d]pyridine-1,3,5(2H,4H)-trione: Prepared according to the general procedure, purified by silica gel column chromatography (n-hexanes/EtOAc = 20:1 to 10:1) to afford the corresponding product 5 as a solid. \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) 8.08 (s, 1H), 7.80 (s, 1H), 7.61 (t, J = 7.6 Hz, 1H), 6.81 (dd, J = 6.8, 5.2 Hz, 1H), 6.75 (s, 1H), 5.57 (t, J = 6.0 Hz, 1H), 4.40 (d, J = 6.0 Hz, 2H), 3.46 (s, 3H), 2.96 (s, 3H). \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) 165.9, 161.9, 157.4, 156.4, 148.0, 140.3, 138.7, 137.3, 133.5, 133.4, 130.2, 126.6, 115.8, 106.8, 100.5, 76.0, 50.0, 37.7, 24.2. HRMS m/z ([M+H]\(^+\)) called for C\(_{19}\)H\(_{15}\)N\(_4\)O\(_4\)S: 395.0714, found: 395.0809.
General experiment procedure for reductive removal of the directing group: An oven-dried 25 mL two-neck round bottom flask was charged with 3 (0.1 mmol). After purging with Ar three times, 5 mL fresh distilled THF and 1 mL MeOH was added, followed by SmI$_2$ (0.1M in THF, 20 equiv) was added dropwise at 0 °C. After 5 minutes, the mixture was stirred overnight. After that the mixture was quenched with 5 mL saturated aqueous Na$_2$S$_2$O$_3$ and extracted with DCM, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure and the product was obtained via column chromatography.

![Chemical structure of 6](image)

**7-Chloro-2-methyl-1H-pyrrolo[3,4-b]thieno[3,2-d]pyridine-1,3,5(2H,4H)-trione:** Prepared according to the general procedure, purified by silica gel column chromatography (DCM/MeOH = 20:1 to 10:1) to afford the corresponding product 6 as a solid. Spectra for the major rotamer:

**$^1$H NMR** (400 MHz, DMSO-$d_6$) $\delta$ 12.91 (s, 1H), 7.62 (s, 1H), 6.91 (d, $J$ = 9.6 Hz, 1H), 5.60 (d, $J$ = 8.8 Hz, 1H), 2.87 (s, 3H).

**$^{13}$C NMR** (100 MHz, DMSO-$d_6$) $\delta$ 164.9, 158.2, 153.6, 139.9, 139.5, 128.5, 122.1, 105.2, 80.3, 25.9. **HRMS** m/z ([M+H]$^+$) called for C$_{10}$H$_8$ClN$_2$O$_3$S: 270.9944, found: 270.9909.

![Chemical structure of 7](image)
(3aR,8bS)-7-Chloro-2-(4-methoxybenzyl)-3a,8b-dihydro-1H-pyrrolo[3,4-b]thieno[3,2-d]pyridine-1,3,5(2H,4H)-trione: Prepared according to the general procedure, purified by silica gel column chromatography (DCM/MeOH = 20:1 to 10:1) to afford the corresponding product 7 as a solid. Spectra for the major rotamer: $^1$H NMR (500 MHz, DMSO-d$_6$) δ 12.89 (s, 1H), 7.64 (s, 1H), 7.22 (d, $J = 8.5$ Hz, 2H), 7.05 (d, $J = 9.0$ Hz, 1H), 6.87 (d, $J = 8.5$ Hz, 2H), 5.47 (d, $J = 8.5$ Hz, 1H), 4.75 (d, $J = 15.5$ Hz, 1H), 4.18 (d, $J = 15.5$ Hz, 1H), 3.70 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-d$_6$) δ 164.9, 159.0, 158.2, 153.7, 139.9, 139.6, 130.1, 129.6, 122.2, 114.6, 114.4, 105.0, 78.6, 55.6, 41.8. HRMS m/z ([M+H]$^+$) called for C$_{17}$H$_{14}$ClN$_2$O$_4$S: 377.0363, found: 377.0360.

5. References


6. $^1$H, $^{13}$C and $^{19}$F NMR Spectra

$^1$H, $^{13}$C NMR spectra of compound 1a
$^{1}$H, $^{13}$C NMR spectra of compound 1b
$^1$H, $^{13}$C NMR spectra of compound 1c
\( ^1\text{H}, ^{13}\text{C} \) NMR spectra of compound \( \text{Id} \)
$^1$H, $^{13}$C NMR spectra of compound 1e
$^1$H, $^{13}$C NMR spectra of compound 1f
$^1$H, $^{13}$C NMR spectra of compound 1g

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$^{1}H, ^{13}C$ NMR spectra of compound 1h
$^1$H, $^{13}$C NMR spectra of compound 3aa
$^{1}H, ^{13}C$ NMR spectra of compound 3ba
$^{1}H$, $^{13}C$ NMR spectra of compound 3ca
$^{1}H, ^{13}C$ NMR spectra of compound 3da
$^1$H, $^{13}$C NMR spectra of compound 3ea
$^1$H, $^{13}$C NMR spectra of compound 3fa
\( ^1H, ^{13}C \) NMR spectra of compound 3ga
$^{1}\text{H}$, $^{13}\text{C}$ NMR spectra of compound 3ha
$^1$H, $^{13}$C NMR spectra of compound 3cb
$^{1}{H}, ^{13}{C}$ NMR spectra of compound 3ce

[Chemical structure and NMR spectra images]

S40
$^{1}H$, $^{13}C$ NMR spectra of compound 3cd

![NMR Spectra Image]
$^1$H, $^{13}$C NMR spectra of compound 3ce
$^{1}H, {^{13}C}$ NMR spectra of compound 3ef
$^1$H, $^{13}$C NMR spectra of compound 3cg
$^1$H, $^{13}$C, $^{19}$F NMR spectra of compound 3ch
$^1$H, $^{13}$C NMR spectra of compound 3ei
$^1$H, $^{13}$C NMR spectra of compound 3cj
$^1$H, $^{13}$C NMR spectra of compound 3ek
$^1$H, $^{13}$C NMR spectra of compound 3cl
$^{1}H, ^{13}C, ^{19}FNMR$ spectra of compound 3cm
$^1$H, $^{13}$C NMR spectra of compound 3cn
$^{1}H, ^{13}C$ NMR spectra of compound 3co
$^1$H, $^{13}$C NMR spectra of compound 5
$^1\text{H}, ^{13}\text{C}$ NMR spectra of compound 6
$^1$H, $^{13}$C NMR spectra of compound 7