Synthesis of Imidazo[1,2-*c*]thiazoles Through the Palladium-Catalyzed Cascade Bicyclization of Isonitriles with Thioamides

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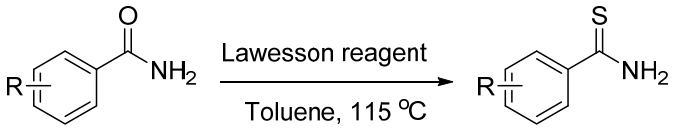
Content

General Information

Unless otherwise specified, commercial reagents and solvents were used without further purification. All manipulations were performed in air at room temperature. For flash column chromatography, 100-200 mesh and 300-400 mesh silica gel were used by eluting with petroleum ether/ethyl acetate. ^{1}H NMR spectra were obtained at 400 MHz and ^{13}C NMR spectra were obtained at 100 MHz by using a Bruker Avance 400 spectrometer. The chemical shifts were given in parts per million relative to $CDCl_3$ (7.26 ppm for ^{1}H) and $CDCl_3$ (77.0 ppm for ^{13}C). Peak multiplicities were reported as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br. s, broad singlet and *J*, coupling constant (Hz). HRMS spectra were reported on the Exactive Mass Spectrometer (Thermo Scientific, USA) followed by ESI or APCI ionization resource.

Experimental Section

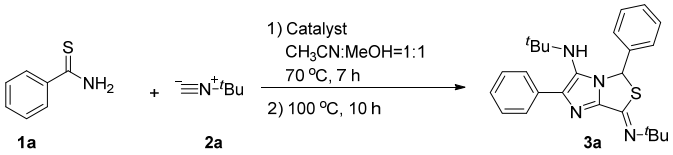
The synthesis of thioamides[1]



A solution of benzamide (1 equiv, 5 mmol), Lawesson reagent (1.1 equiv, 5.5 mmol) and toluene (15 mL) was stirred at 115 °C for 30 min. When the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified through flash column chromatography (petroleum ether/ethyl acetate 10:1) to give benzothioamide.

The screening of reaction conditions

Table S1 Catalyst optimization

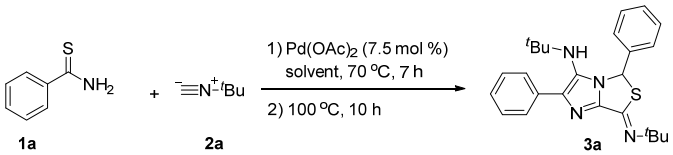


entry[a]	catalyst	Catalyst (mol %)	ligand	yield (%)[b]
1	$CuCl_2$	7.5	-	0
2	CuI	7.5	-	0
3	$PdCl_2$	7.5	-	trace
4	$Cu(OAc)_2$	7.5	-	0
5	$FeCl_3$	7.5	-	0
6	$NiCO_3$	7.5	-	0
7	$CoCl_2$	7.5	-	0
8	$ZnCl_2$	7.5	-	0
9	$Pd(PPh)_4$	7.5	-	trace
12	$Pd(TFA)_2$	7.5	-	0
13	AgOAc	7.5	-	0
14	$AgNO_3$	7.5	-	0
15	$Pd(OAc)_2$	5	-	53
16	**$Pd(OAc)_2$**	**7.5**	**-**	**72**
17	$Pd(OAc)_2$	10	-	72
18	$Pd(OAc)_2$	7.5	dppm	55
19	$Pd(OAc)_2$	7.5	dppe	50

20	$Pd(OAc)_2$	7.5	PPh_3	30
21	$Pd(OAc)_2$	7.5	xantphos	10

[a]Scale: **1a** (1 equiv, 0.3 mmol), **2a** (3 equiv, 0.9 mmol), solvent (3 mL). [b]Isolated yields.

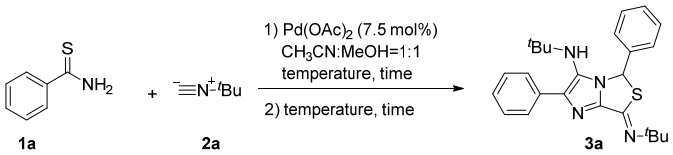
Table S2 solvent optimization



entry[a]	Solvent	yield (%)[b]
1	CH_3CN	15
2	THF	24
3	DMSO	0
4	dioxane	0
5	toluene	0
6	PhCl	0
7	MeOH	7
8	ethanol	3
9	CH_3CN/ethanol=1:1	45
10	CH_3CN/THF=1:1	39
11	CH_3CN/MeOH=3:1	65
12	**CH_3CN/MeOH=1:1**	**72**
13	CH_3CN/MeOH=1:3	62

[a]Scale: **1a** (1 equiv, 0.3 mmol), **2a** (3 equiv, 0.9 mmol), solvent (3 mL). [b]Isolated yields.

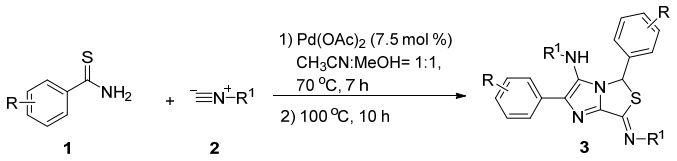
Table S3 temperature and time optimization



entry[a]	step 1	step 2	yield (%)[b]
1	50 °C, 5 h	85 °C, 7 h	trace
2	50 °C, 7 h	85 °C, 10 h	12
3	50 °C, 7 h	100 °C, 10 h	31
4	70 °C, 5 h	85 °C, 10 h	25
5	70 °C, 7 h	85 °C, 4h	20
6	70 °C, 7 h	85 °C, 10 h	43
7	**70 °C, 7 h**	**100 °C, 10 h**	**72**
8	70 °C, 7 h	70 °C, 10 h	0
9	70 °C, 10 h	100 °C, 24 h	53

[a]Scale: **1a** (1 equiv, 0.3 mmol), **2a** (3 equiv, 0.9 mmol), solvent (3 mL). [b]Isolated yields.

The synthesis of product 3



A solution of **1** (1 equiv, 0.3 mmol), **2a** (3 equiv, 0.9 mmol), $Pd(OAc)_2$ (7.5 mol %) in the mixture of CH_3CN and CH_3OH (3 mL, 1:1) was stirred at 70 °C for 7 h. When **1a** was consumed by TLC trace, the reaction continued to reaction at 100 °C for 10 h. Upon completion, the reaction was cooled to room temperature, then the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 15:1 - 10:1) to obtain **3**.

In Vitro Cytotoxicity Assays

The MGC-803, T-24, SK-OV-3, HepG2 cell lines were all obtained from the Institute of Biochemistry and Cell Biology, China Academy of Sciences. Cells were cultured in DMEM, which supplemented with 10% fetal bovine serum in a humidified atmosphere of 5% CO_2/95% air at 37 °C. All compounds and 5-FU were dissolved in the Phosphate Buffered Saline (PBS) with 1% DMSO to give various concentrations to 96-well plates and control wells contained supplemented media with 1% DMSO. Continue incubating for 48 h at 37 °C and in 5% CO_2 atmosphere. MTT (5 $mg \cdot mL^{-1}$) was added into the wells, and the plates were incubated at 37 °C for 4 h. The MTT assay was stopped by adding dimethyl sulfoxide (100 μL per well) and mixed for 10 min vigorously before measuring absorbance at 490 nm in a multi well plate reader. The cytotoxicity was estimated based on the percentage cell survival in a dose dependent manner relative to the negative control. The final IC_{50} (a drug concentration killing 50% cells) values were calculated by the Bliss method. All target compounds were tested against T-24, MGC-803, HepG2 and SK-OV-3 cancer cell lines, respectively.

Apoptosis by flow cytometry

Apoptosis was discriminated with the Annexin V-FITC/propidium iodide (BD, Pharmingen)

test. The HepG2 cells were seeded in 6-well plates (2×106 cells/well) and cultured for 24 h, then treated with compound **3c** for 24 h. The cells were collected and washed twice with cold PBS and then resuspended in 1×Binding Buffer (0.1 M Hepes/NaOH (pH = 7.4), 1.4 M NaCl, 25 mM $CaCl_2$) at a concentration of 1×106 cells/ml. Transfered 100 μL of the solution (1×105 cells) to 1.5 mL culture tube, then added 5 μL of Annexin V- FITC and 5 μL propidium iodide (PI) to each tube. After incubation for 30 minutes in the dark, the specimens were quantified by flow cytometry on a FACS Canto II (BD Biosciences, USA).

Hoechst 33342 staining

HepG2 cells were seeded into 6-well tissue culture plates and incubated for 24 h before the treatment. Cells were treated with compound **3c** for 24 h before incubation with Hoechst 33342. Removed the culture medium containing compounds and fixed the cells in 4% paraformaldehyde for 10 min. The cells were stained with 0.5 mL of Hoechst 33342 for 15 min and then washed twice with PBS. The stained nuclei were observed under a BioTek Cytation microscope fluorescence microscope.

Induction of cell cycle arrest

In the cell cycle analysis, HepG2 cells were respectively treated with indicated concentrations of compound **3c** for 24 h. After treating, cells were harvested by trypsinization and rinsed with PBS. The cells were washed in PBS and fixed with ice-cold 70% ethanol in PBS under violent shaking. The fixed cells were centrifuged and re-suspended in a staining solution (0.5 mL of PBS containing 100 mg/mL RNase A and 1 mg/mL PI) for 30 min at room temperature in the dark and immediately analyzed by flow cytometry. Finally, analysis was performed with the system software.

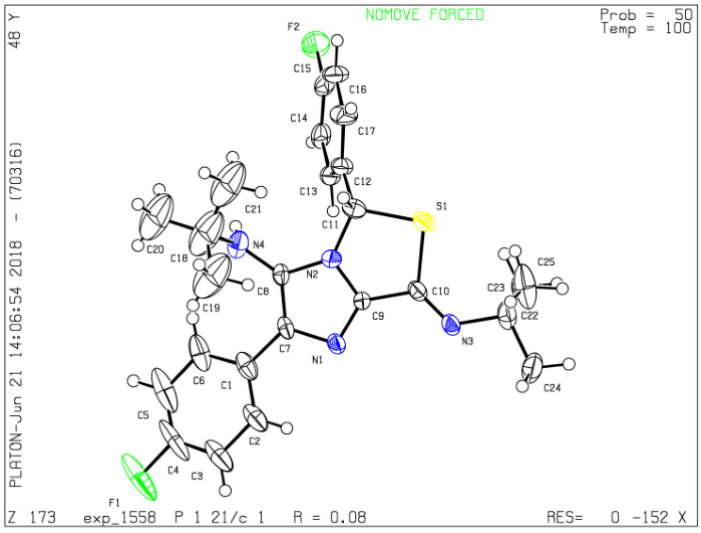
Intracellular ROS

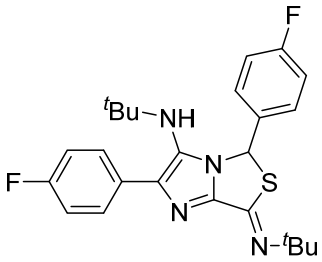
HepG2 cells were seeded into 6-well plates and treated with compound **3c** at 10, 20, 30 μM for 24 h and then were incubated with DCFH-DA (Beyotime, Haimen, China) at 37 °C for 30 min in dark, and then washed three times with PBS. Flow cytometer was used for measuring intracellular ROS generation by detecting the fluorescence intensity and the data analysis was performed with FlowJo software.

Measurement of intracellular Ca^{2+} levels method

HepG2 cells were seeded in 6-well tissue culture plates and incubated with compound **3c** at 10, 20, 30 μM for 24 h. After exposed to compound **3c** for 24 h, HepG2 cells were harvested and washed twice with PBS, then resuspended in Fluo-3 AM for 30 min in dark and washed twice with PBS. Detection of intracellular Ca^{2+} was carried out by flow cytometer and the data analysis was performed with FlowJo software.

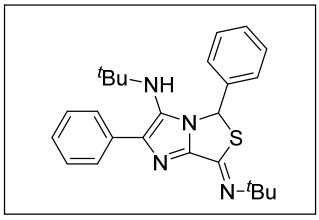
The X-ray Crystal Structure of 3m





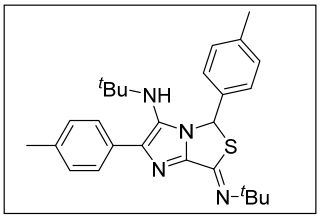
Analytical Data for Compounds

(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-diphenyl-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3a**)



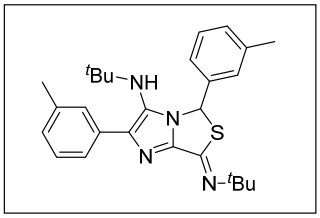
Yellow solid; 45.2 mg (72%); m.p. 81–82 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.5 Hz, 2H), 7.44–7.39 (m, 3H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.24–7.19 (m, 3H), 6.57 (s, 1H), 2.02 (br. s, 1H), 1.42 (s, 9H), 0.97 (s, 9H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.3, 142.5, 141.6, 137.6, 134.8, 131.5, 129.6, 129.5, 127.7, 127.6, 126.8, 126.5, 62.1, 57.1, 56.0, 30.2, 28.3 ppm. **HRMS** (m/z) (ESI): calcd for $C_{25}H_{31}N_4S$ $[M+H]^+$: 419.2264; found 419.2263.

(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-di-p-tolyl-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3b**)



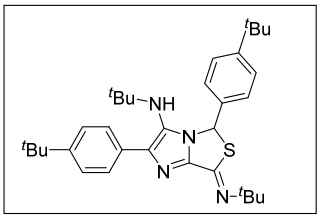
Yellow solid; 48.9 mg (73%); m.p. 72–73 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.12–7.08 (m, 4H), 6.53 (s, 1H), 2.37 (s, 3H), 2.31 (s, 3H), 1.41 (s, 9H), 0.98 (s, 9H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.1, 142.4, 141.9, 139.7, 136.3, 134.5, 131.9, 131.1, 130.2, 128.3, 127.3, 126.3, 61.9, 56.9, 56.0, 30.2, 28.3, 21.3, 21.2 ppm. **HRMS** (m/z) (ESI): calcd for $C_{27}H_{34}N_4NaS$ $[M+Na]^+$: 469.2396; found 469.2398.

(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-di-m-tolyl-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3c**)



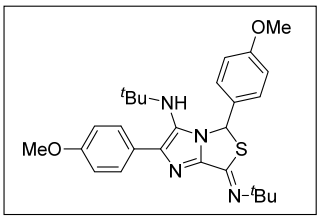
Yellow solid; 40.2 mg (60%); m.p. 67–68 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.22–7.15 (m, 2H), 7.03–6.99 (m, 3H), 6.52 (s, 1H), 2.35 (s, 3H), 2.33 (s, 3H), 1.42 (s, 9H), 0.99 (s, 9H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.2, 142.3, 141.8, 139.6, 137.5, 137.1, 134.7, 131.4, 130.5, 129.3, 128.2, 127.5, 127.4, 126.9, 124.5, 123.5, 62.1, 57.0, 56.0, 30.3, 28.3, 21.4, 21.3 ppm. **HRMS** (m/z) (ESI): calcd for $C_{27}H_{34}N_4NaS$ $[M+Na]^+$: 469.2396; found 469.2397.

(Z)-*N*-(*tert*-butyl)-2,5-bis(4-(*tert*-butyl)phenyl)-7-(*tert*-butylimino)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3d**)



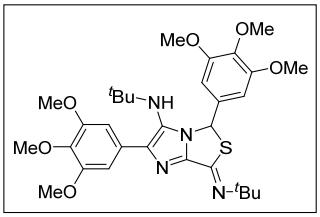
Yellow solid; 62.1 mg (78%); m.p. 140–141 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H), 6.54 (s, 1H), 1.42 (s, 9H), 1.33 (s, 9H), 1.30 (s, 9H), 1.00 (s, 9H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.9, 149.6, 144.1, 142.3, 142.1, 134.4, 131.8, 131.2, 126.9, 126.4, 126.1, 124.5, 61.9, 56.9, 55.9, 34.8, 34.4, 31.3, 31.2, 30.2, 28.3 ppm. **HRMS** (m/z) (ESI): calcd for $C_{33}H_{47}N_4S$ $[M+H]^+$: 531.3516; found 531.3514.

(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-bis(4-methoxyphenyl)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine(**3e**)



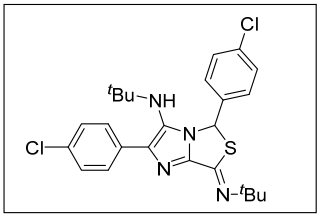
Green solid; 48.8 mg (68%); m.p. 64–65 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.8 Hz, 2H), 7.15 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 6.52 (s, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 1.41 (s, 9H), 0.97 (s, 9H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.4, 158.5, 143.9, 142.3, 142.2, 130.7, 129.1, 128.7, 127.9, 127.6, 114.9, 113.1, 61.9, 56.9, 56.0, 55.4, 55.1, 30.2, 28.3 ppm. **HRMS** (m/z) (ESI): calcd for $C_{27}H_{35}O_2N_4S$ $[M+H]^+$: 479.2475; found 479.2480.

(Z) -*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-bis(3,4,5-trimethoxyphenyl)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3f**)



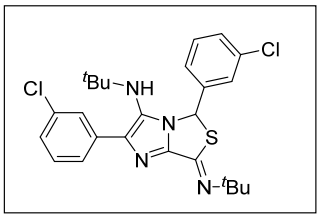
Brown solid; 49.4 mg (55%); m.p. 78–79 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (s, 2H), 6.50 (s, 1H), 6.37 (s, 2H), 3.87 (s, 9H), 3.84 (s, 3H), 3.79 (s, 6H), 1.99 (br. s, 1H), 1.43 (s, 9H), 1.05 (s, 9H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.2, 152.6, 144.0, 142.1, 142.0, 138.9, 137.1, 132.6, 131.2, 130.3, 104.6, 103.1, 62.4, 60.9, 60.8, 57.1, 56.4, 56.2, 56.1, 30.4, 28.2 ppm. **HRMS** (m/z) (ESI): calcd for $C_{31}H_{42}O_6N_4S$ $[M+H]^+$: 599.2898; found 599.2899.

(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-bis(4-chlorophenyl)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3g**)



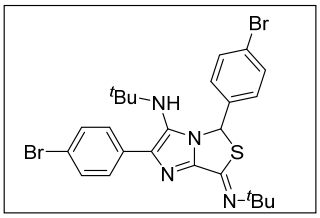
Brown solid; 59.9 mg (82%); m.p. 103–104 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.7 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.53 (s, 1H), 1.41 (s, 9H), 0.98 (s, 9H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.4, 141.7, 141.1, 136.1, 135.6, 133.1, 132.6, 131.3, 129.9, 128.8, 128.0, 127.7, 61.4, 57.2, 56.2, 30.2, 28.3 ppm. **HRMS** (m/z) (ESI): calcd for $C_{25}H_{28}N_4Cl_2NaS$ $[M+Na]^+$: 509.1304; found 509.1308.

(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-bis(3-chlorophenyl)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3h**)



Yellow solid; 47.5 mg (65%); m.p. 82–83 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.41–7.35 (m, 2H), 7.29–7.17 (m, 3H), 7.08 (d, *J* = 6.9 Hz, 1H), 6.53 (s, 1H), 2.05 (br. s, 1H),1.44 (s, 9H), 1.02 (s, 9H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.4, 141.3, 140.9, 139.6, 136.3, 135.5, 133.7, 131.6, 130.9, 129.9, 129.1, 127.4, 126.9, 126.6, 125.5, 124.4, 61.3, 57.2, 56.3, 30.3, 28.3 ppm. **HRMS** (m/z) (ESI): calcd for $C_{25}H_{28}N_4Cl_2NaS$: 509.1304 $[M+Na]^+$; found 509.1308.

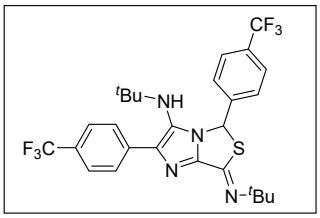
(Z)-2,5-bis(4-bromophenyl)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3i**)



Yellow solid; 71.8 mg (83%); m.p. 176–177 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.50 (s, 1H), 1.97 (br. s, 1H), 1.39 (s, 9H), 0.96 (s, 9H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.3, 141.5, 141.1, 136.5, 133.5, 132.7, 131.2, 130.8, 129.0, 127.9, 123.7, 120.8, 61.4, 57.1, 56.2, 30.2, 28.2 ppm. **HRMS** (m/z) (ESI): calcd for $C_{25}H_{28}N_4Br_2NaS$: 597.0293 $[M+Na]^+$; found 597.0291.

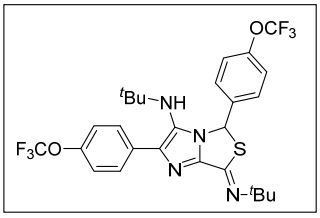
(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-bis(4-(trifluoromethyl)phenyl)-5*H*,7*H*-imidazo[1,2-*c*]thi

azol-3-amine (**3j**)



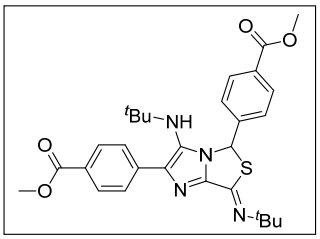
Yellow solid; 70.7 mg (85%); m.p. 156–157 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 6.62 (s, 1H), 1.42 (s, 9H), 1.00 (s, 9H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.7, 141.7, 141.5, 140.6, 138.0, 131.9 (q, *J* = 3.7 Hz), 131.8 (q, *J* = 32.9 Hz), 128.7 (q, *J* = 32.3 Hz), 128,3 (q, *J* = 3.3 Hz), 127.5, 126.5 (q, *J* = 3.6 Hz), 124.8 (q, *J* = 3.7 Hz), 124.3 (q, *J* = 272.0 Hz), 123.5 (q, *J* = 272.3 Hz), 61.3, 57.3, 56.4, 30.2, 28.2 ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) *δ* -62.39, -62.80 ppm. **HRMS** (m/z) (ESI): calcd for $C_{27}H_{29}N_4F_6S$ $[M+H]^+$: 555.2012; found 555.2013.

(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-bis(4-(trifluoromethoxy)phenyl)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3k**)



Yellow solid; 76.5 mg (87%); m.p. 119–120 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 1.9 Hz, 4H), 7.18 (d, *J* = 8.3 Hz, 2H), 6.60 (s, 1H), 2.02 (br. s, 1H), 1.44 (s, 9H), 1.01 (s, 9H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.8, 148.1, 144.4, 141.5, 141.0, 136.1, 133.3, 131.3, 128.8, 128.0, 121.8, 120.4 (q, *J* = 256.8 Hz), 120.3 (q, *J* = 258.3 Hz), 120.2, 61.3, 57.2, 56.2, 30.2, 28.2 ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) *δ* -57.79, -57.82 ppm. **HRMS** (m/z) (ESI): calcd for $C_{27}H_{29}O_2N_4F_6S$ $[M+H]^+$: 587.1910; found 587.1907.

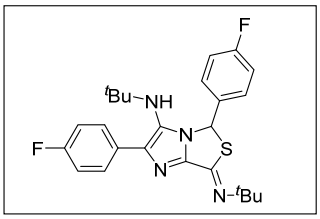
Dimethyl 4,4'-(3-(*tert*-butylamino)-7-(*tert*-butylimino)-5*H*,7*H*-imidazo[1,2-*c*]thiazole-2,5-diyl) (Z)-dibenzoate (**3l**)



Yellow solid; 42.8 mg (80%); m.p. 83–84 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.0 Hz, 4H), 7.96 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 5.9 Hz, 2H), 6.59 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 2.01 (br. s, 1H), 1.39 (s, 9H), 0.96 (s, 9H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.2, 166.1, 144.8, 142.5, 141.8, 140.9, 139.3, 132.3, 131.5, 131.0, 129.3, 128.4, 127.3, 126.4, 61.6, 57.4, 56.5,

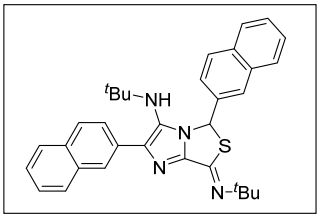
52.5, 52.0, 30.3, 28.4 ppm. **HRMS** (m/z) (ESI): calcd for $C_{29}H_{34}O_4N_4NaS$ $[M+Na]^+$: 557,2193; found 557.2185.

(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-bis(4-fluorophenyl)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3m**)



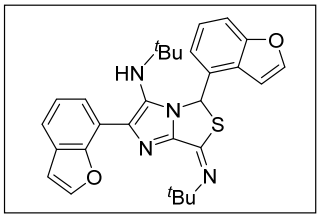
Brown solid; 54.5 mg (80%); m.p. 161–162 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98–7.92 (m, 2H), 7.23–7.18 (m, 2H), 7.14–7.08 (m, 2H), 7.02–6.95 (m, 2H), 6.55 (s, 1H), 1.41 (s, 9H), 0.96 (s, 9H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.1 (d, *J* = 250.8 Hz), 161.9 (d, *J* = 246.0 Hz), 144.2, 141.9, 141.3, 133.4 (d, *J* = 3.3 Hz), 131.0, 130.8 (d, *J* = 3.1 Hz), 129.3 (d, *J* = 7.9 Hz), 128.4 (d, *J* = 8.5 Hz), 116.7 (d, *J* = 22.1 Hz), 114.6 (d, *J* = 21.3 Hz), 61.4, 57.1, 56.1, 30.2, 28.3 ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) *δ* -110.47, -115.05 ppm. **HRMS** (m/z) (ESI): calcd for $C_{25}H_{28}N_4F_2NaS$ $[M+Na]^+$: 477.1895; found 477.1898.

(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-di(naphthalen-2-yl)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3n**)



Yellow solid; 52.9 mg (68%); m.p. 75–76 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.23 (d, *J* = 8.6 Hz, 1H), 7.95–7.74 (m, 7H), 7.59–7.55 (m, 2H), 7.44–7.39 (m, 2H), 7.23 (d, *J* = 8.5 Hz, 1H), 6.79 (s, 1H), 2.09 (br. s, 1H), 1.47 (s, 9H), 1.00 (s, 9H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.5, 142.3, 141.8, 134.6, 133.6, 133.2, 132.9, 132.5, 132.3, 131.9, 130.3, 128.2, 128.0, 127.9, 127.5, 127.3, 127.1, 127.0, 126.2, 126.1, 125.8, 125.7, 125.4, 122.9, 62.4, 57.1, 56.2, 30.3, 28.3 ppm. **HRMS** (m/z) (ESI): calcd for $C_{33}H_{35}N_4S$ $[M+H]^+$: 519.2577; found 519.2579.

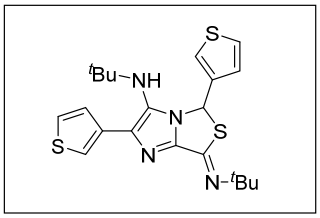
(E)-4-(benzofuran-4-yl)-2-(benzofuran-7-yl)-*N*-(*tert*-butyl)-6-(*tert*-butylimino)-3a,6-dihydro-4*H*-thieno[3,4-b]pyrrol-3-amine (**3o**)



Brown solid; 39.6 mg (53%); m.p. 51–52 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63–7.56 (m, 2H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.42 (t, *J* = 9.9 Hz, 1H), 7.37–7.31 (m, 1H), 7.29 (d, *J* = 9.9 Hz, 1H),

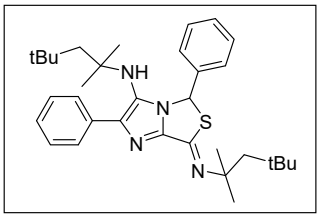
7.27–7.23 (m, 3H), 6.87 (s, 1H), 6.72 (s, 1H), 1.48 (s, 9H), 1.21 (s, 9H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.1, 154.0, 151.8, 150.9, 145.2, 140.9, 134.0, 133.2, 128.8, 127.5, 125.2, 123.7, 123.3, 122.9, 121.5, 120.9, 111.7, 110.5, 105.5, 102.9, 57.4, 56.0, 55.9, 29.9, 28.3 ppm. **HRMS** (m/z) (ESI): calcd for $C_{29}H_{30}O_2N_4NaS$ $[M+Na]^+$: 521.1982; found 521.1987.

(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-di(thiophen-3-yl)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3p**)



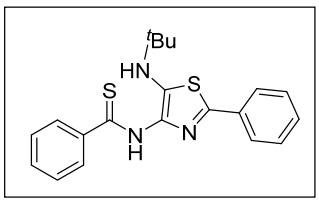
Brown solid; 54.9 mg (85%); m.p. 74–75 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81–7.78 (m, 1H), 7.70–7.67 (m, 1H), 7.40–7.37 (m, 1H), 7.35–7.32 (m, 1H), 7.23–7.20 (m, 1H), 6.87–6.84 (m, 1H), 6.70 (s, 1H), 1.41 (s, 9H), 1.04 (s, 9H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.9, 141.7, 139.7, 138.3, 135.6, 130.8, 128.6, 127.2, 125.1, 124.2, 123.8, 121.9, 57.6, 57.0, 55.9, 30.2, 28.3 ppm. **HRMS** (m/z) (ESI): calcd for $C_{21}H_{26}N_4NaS_3$ $[M+Na]^+$: 453.1212; found 453.1215.

(Z)-2,5-diphenyl-*N*-(2,4,4-trimethylpentan-2-yl)-7-((2,4,4-trimethylpentan-2-yl)imino)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3q**)



Tawny solid; 69.3 mg (87%); m.p. 80–81 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.9 Hz, 2H), 7.41 (d, *J* = 7.1 Hz, 3H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.23–7.17 (m, 3H), 6.56 (s, 1H), 1.87 (d, *J* = 14.6 Hz, 1H), 1.71 (d, *J* = 14.6 Hz, 1H), 1.48 (s, 3H), 1.43 (s, 3H), 1.33 (d, *J* = 14.5 Hz, 1H), 1.26 (d, *J* = 14.5 Hz, 1H), 1.09 (s, 3H), 1.01 (s, 9H), 0.83 (s, 3H), 0.79 (s, 9H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.3, 142.4, 140.2, 137.7, 135.1, 131.3, 129.6, 129.5, 127.8, 127.7, 126.8, 126.3, 61.9, 60.8, 60.1, 56.7, 52.7, 31.8, 31.6, 31.5, 30.1, 28.9, 28.5, 28.3 ppm. **HRMS** (m/z) (ESI): calcd for $C_{33}H_{47}N_4S$ $[M+H]^+$: 531.3516; found 531.3517.

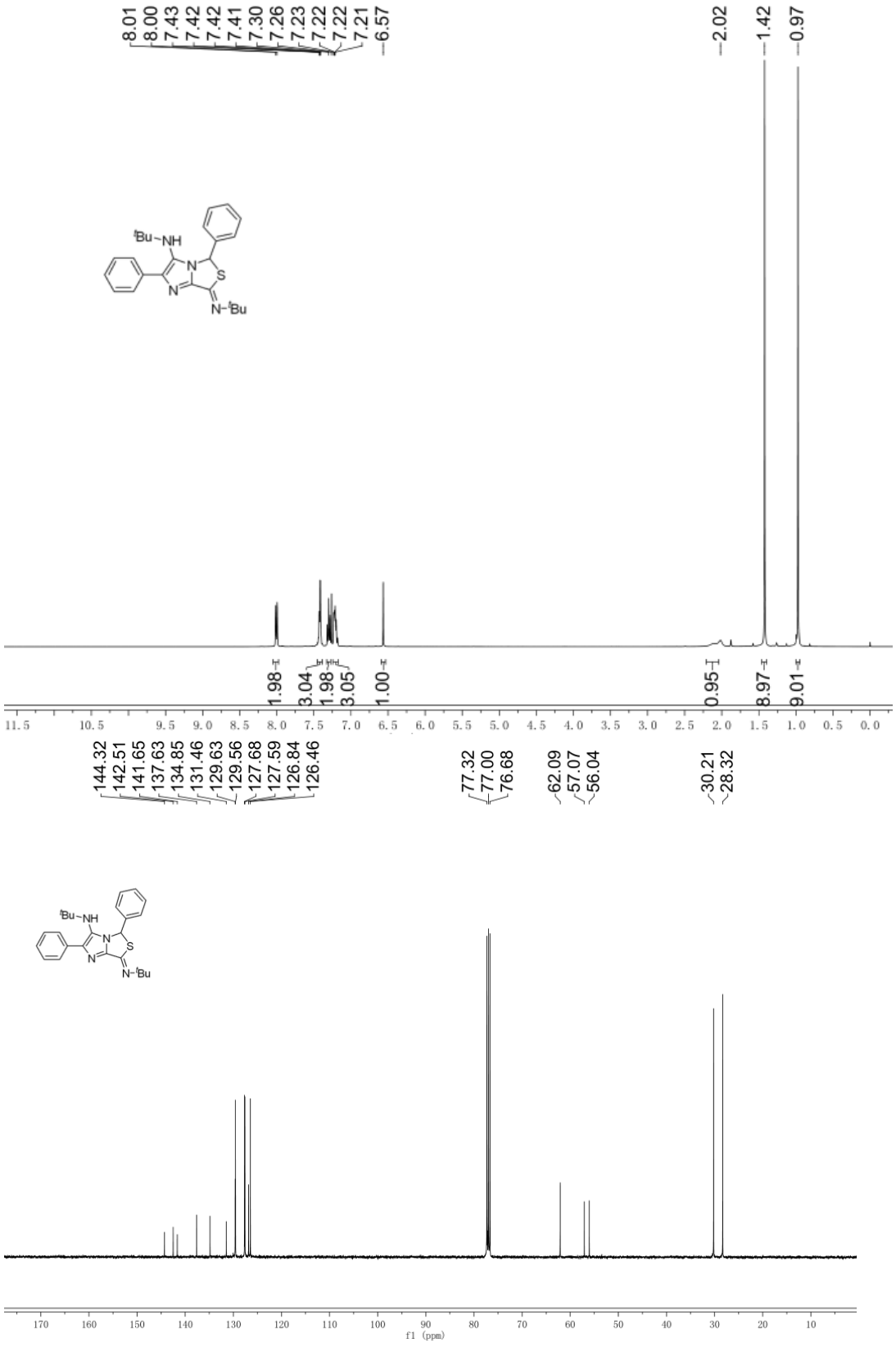
N-(5-(*tert*-butylamino)-2-phenylthiazol-4-yl)benzothioamide (intermediate **H**)[2]



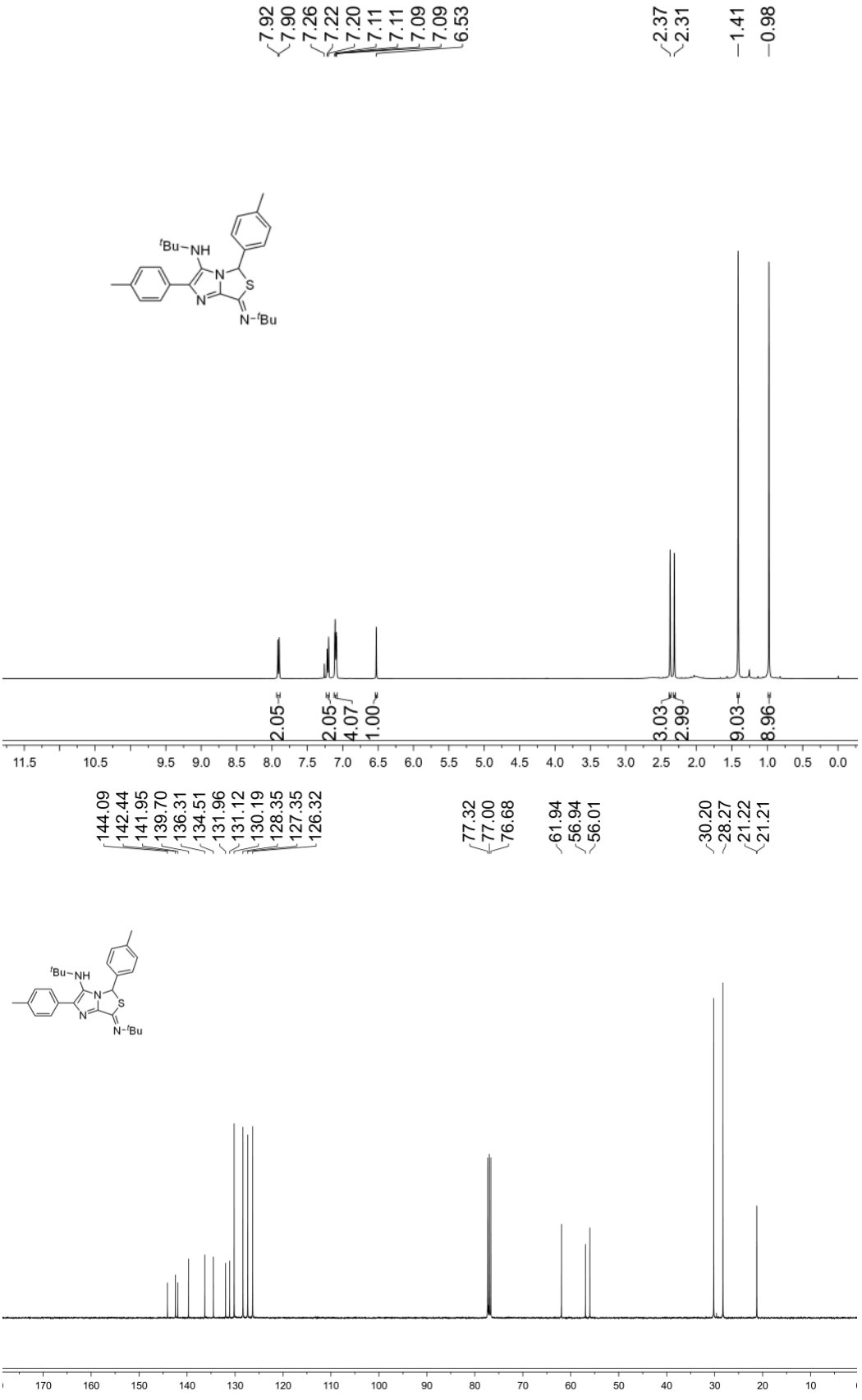
Yellow oil (90% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.22 (br. s, 1H), 7.93 – 7.87 (m, 2H), 7.73 – 7.67 (m, 2H), 7.48 – 7.44 (m, 1H), 7.40 – 7.32 (m, 5H), 4.54 (br. s, 1H), 1.36 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.2, 153.3, 141.0, 137.9, 133.5, 132.7, 131.5, 129.1, 128.8, 128.5, 127.1, 125.1, 53.3, 29.3 ppm.

Copies of ^{1}H NMR, ^{19}F NMR and ^{13}C NMR Spectra for All Compounds

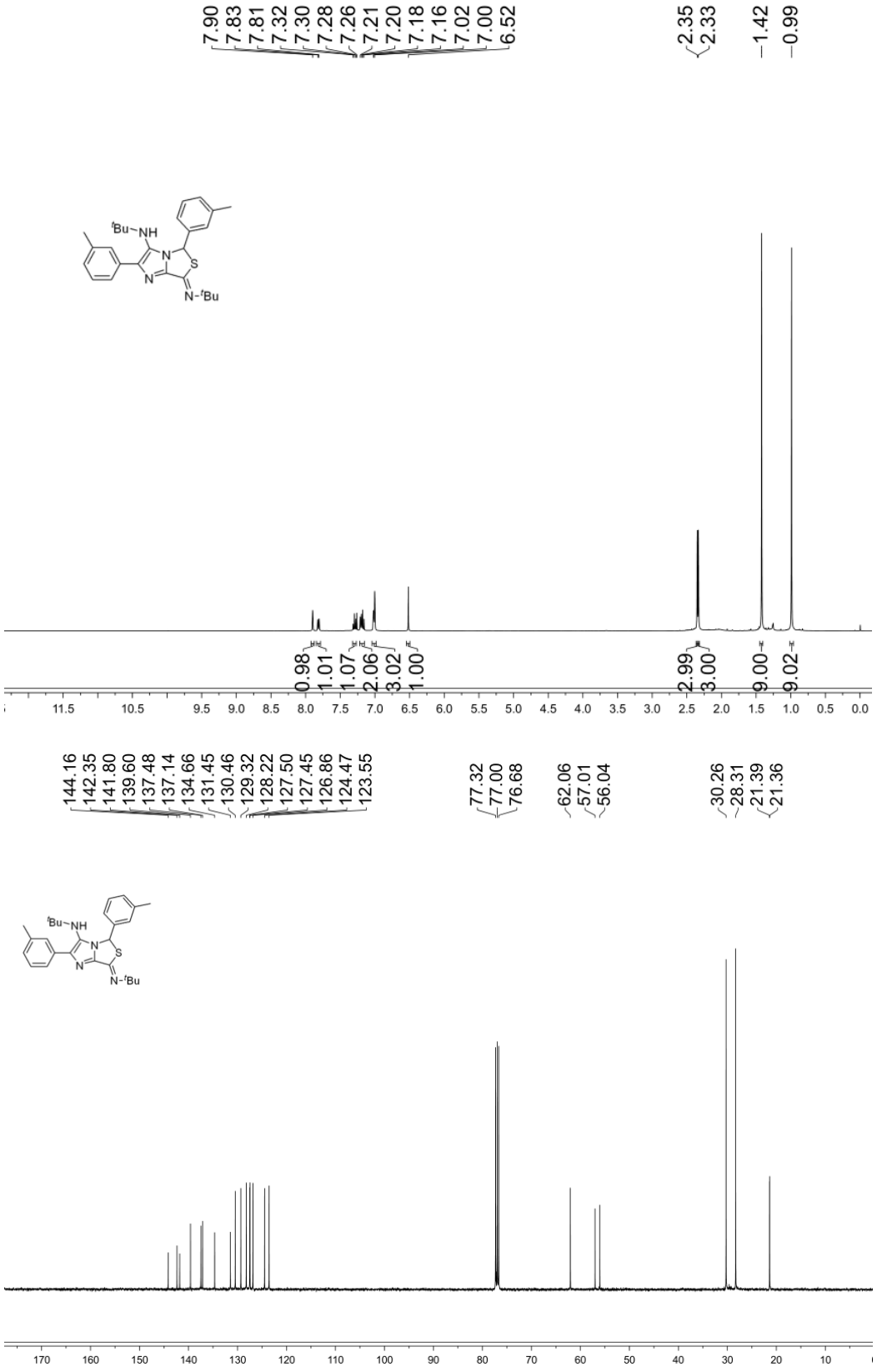
(Z) -*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-diphenyl-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3a**)



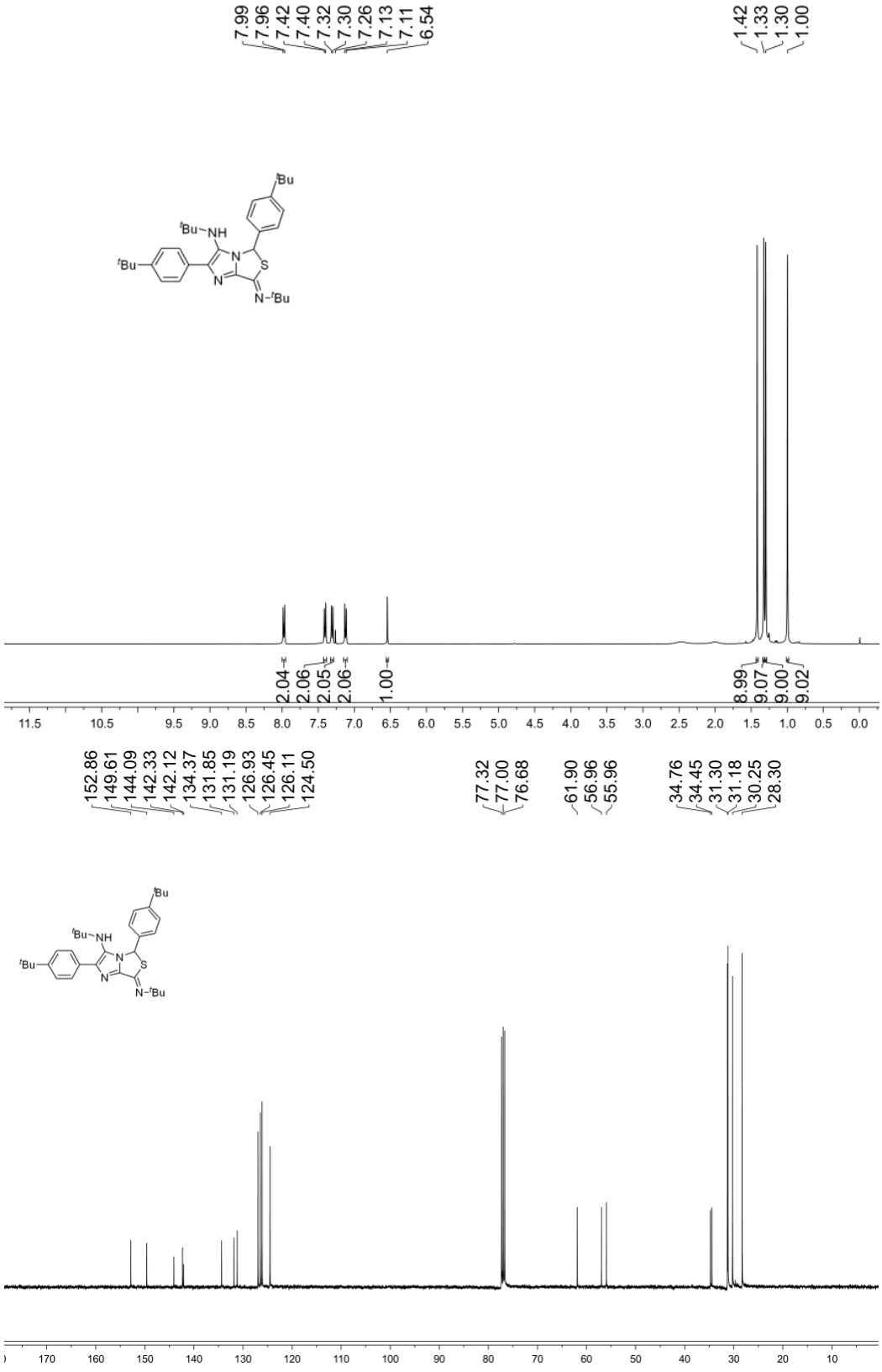
(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-di-p-tolyl-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3b**)


7.92
7.90
7.26
7.22
7.20
7.11
7.11
7.09
7.09
6.53
2.37
2.31
1.41
0.98
tBu–NH
N–tBu
2.05
2.05
4.07
1.00
3.03
2.99
9.03
8.96
144.09
142.44
141.95
139.70
136.31
134.51
131.96
131.12
130.19
128.35
127.35
126.32
77.32
77.00
76.68
61.94
56.94
56.01
30.20
28.27
21.22
21.21

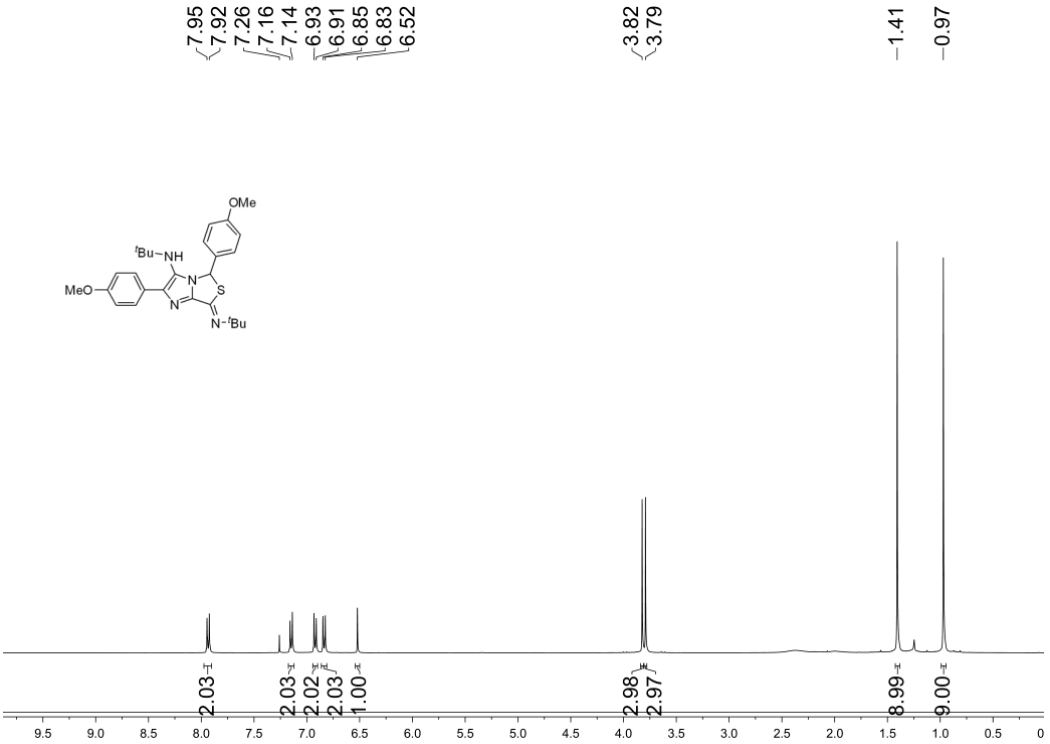
(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-di-m-tolyl-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3c**)

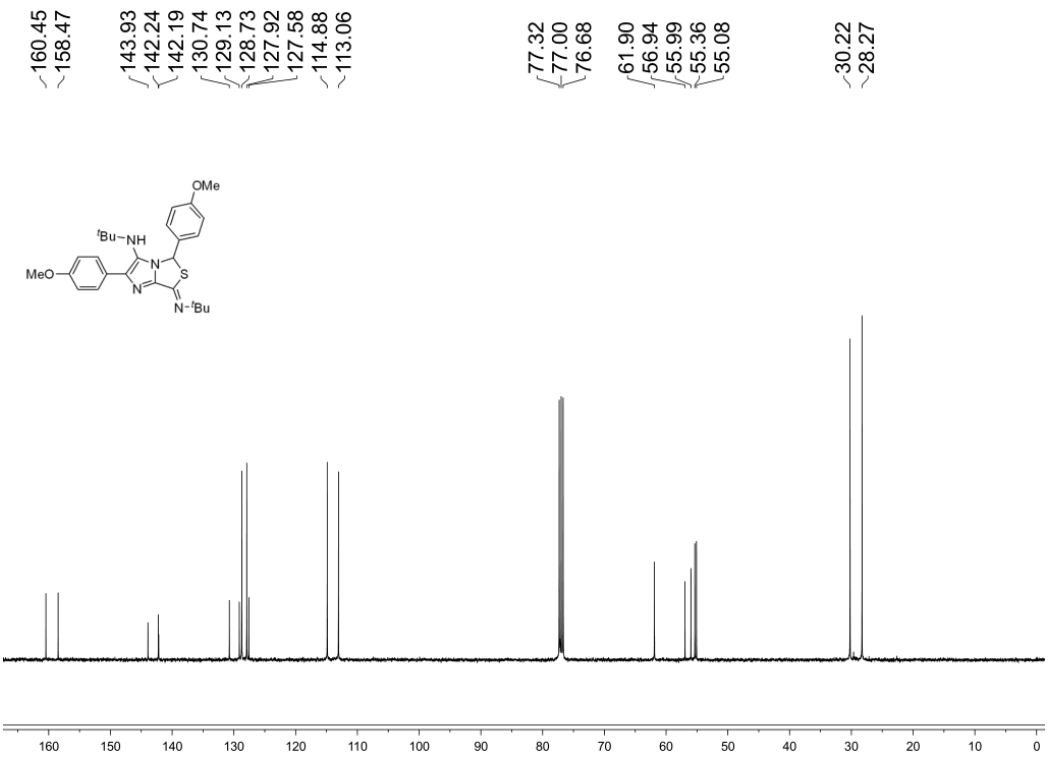


(Z)-*N*-(*tert*-butyl)-2,5-bis(4-(*tert*-butyl)phenyl)-7-(*tert*-butylimino)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3d**)

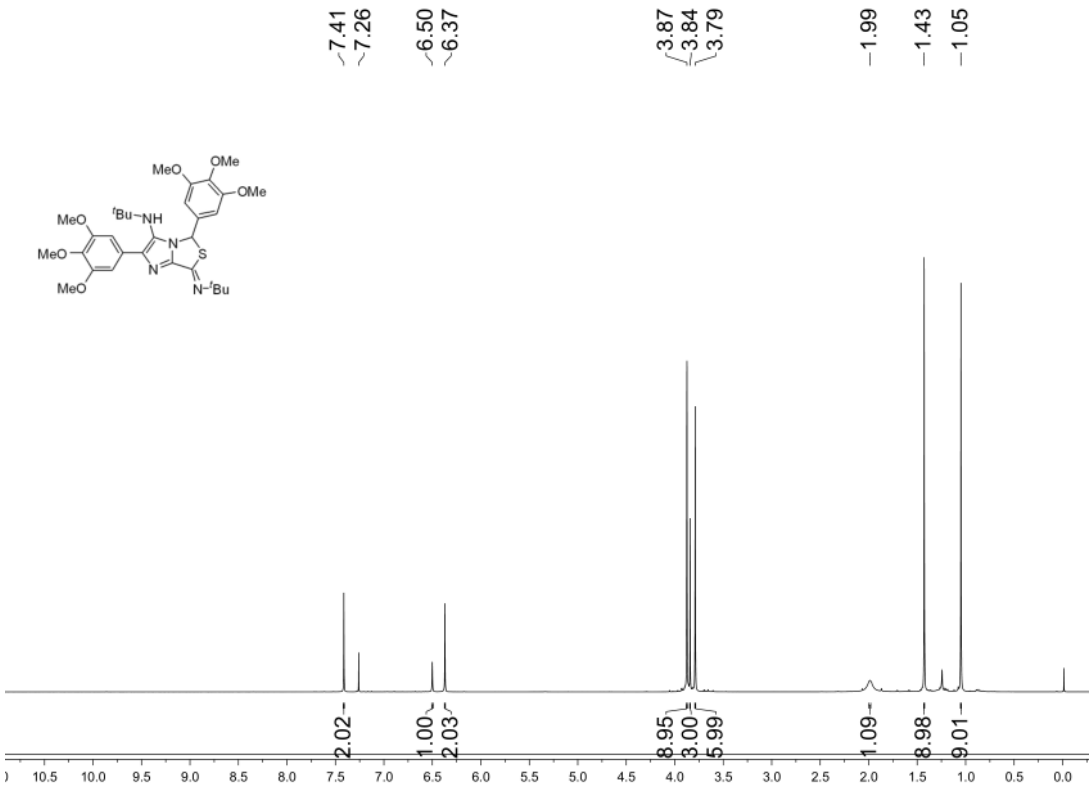


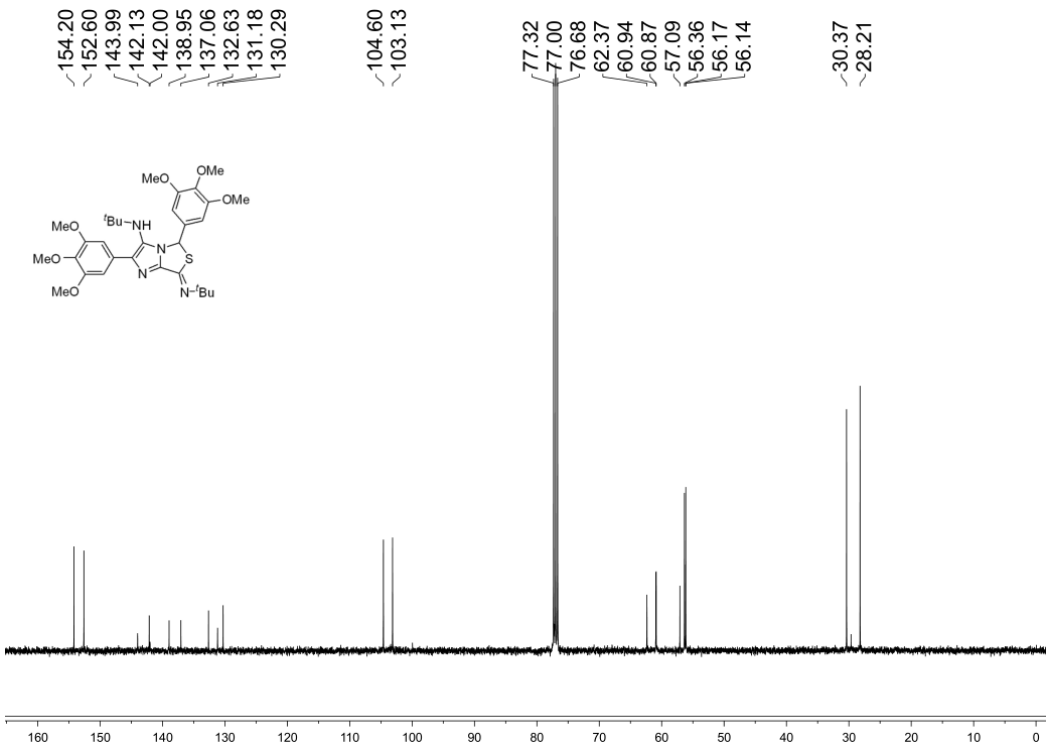
(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-bis(4-methoxyphenyl)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine(**3e**)



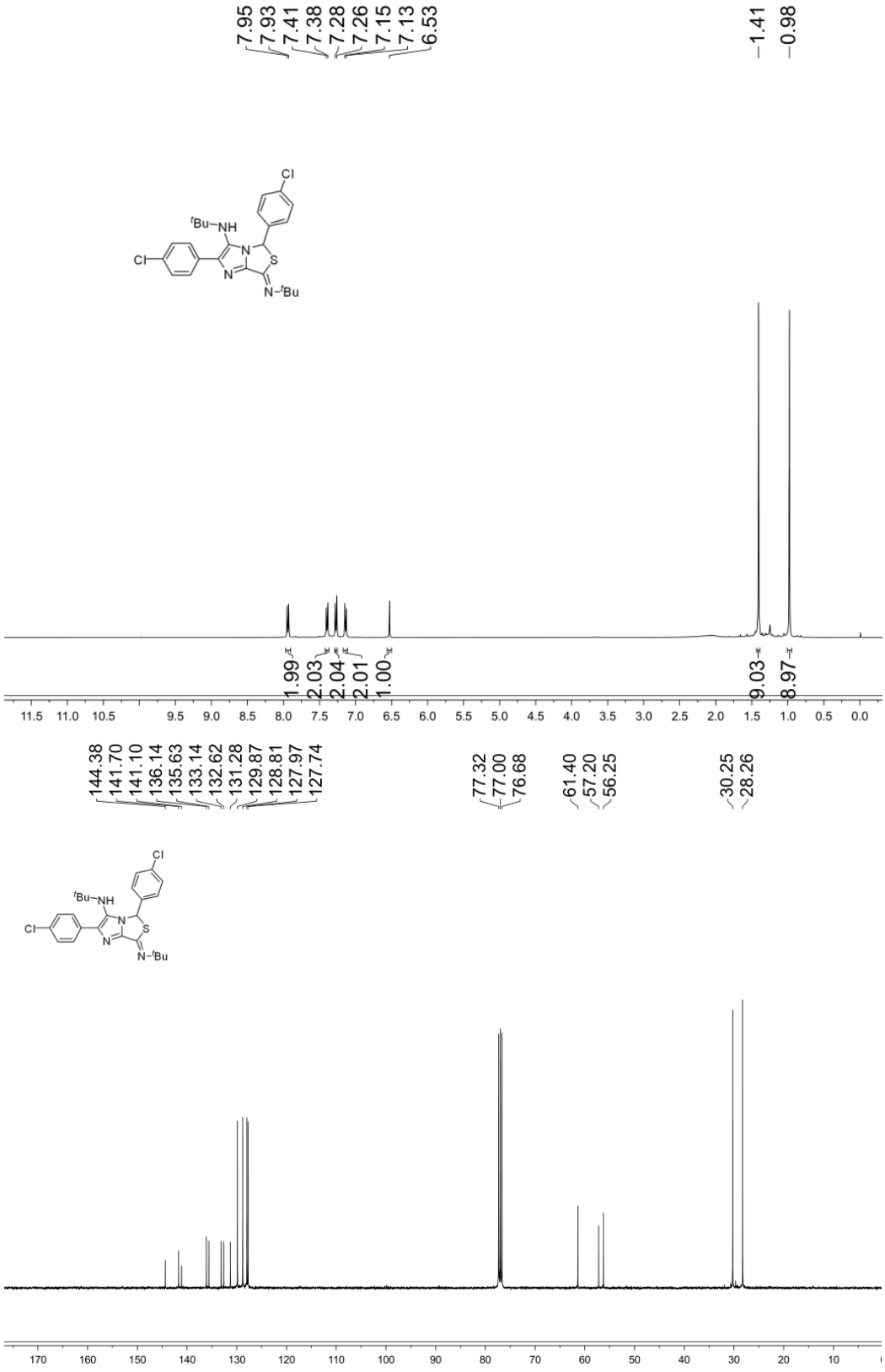


(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-bis(3,4,5-trimethoxyphenyl)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3f**)

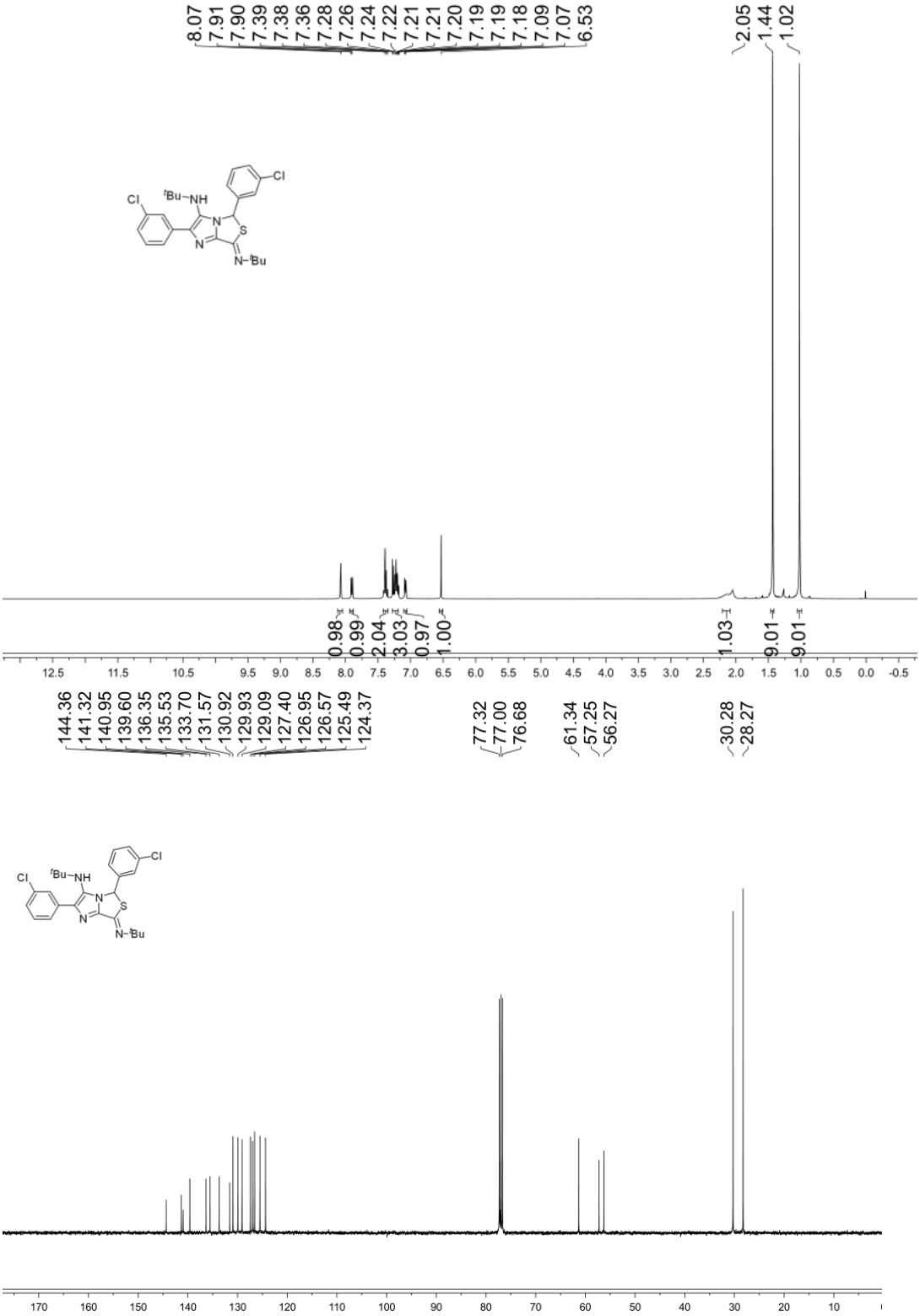




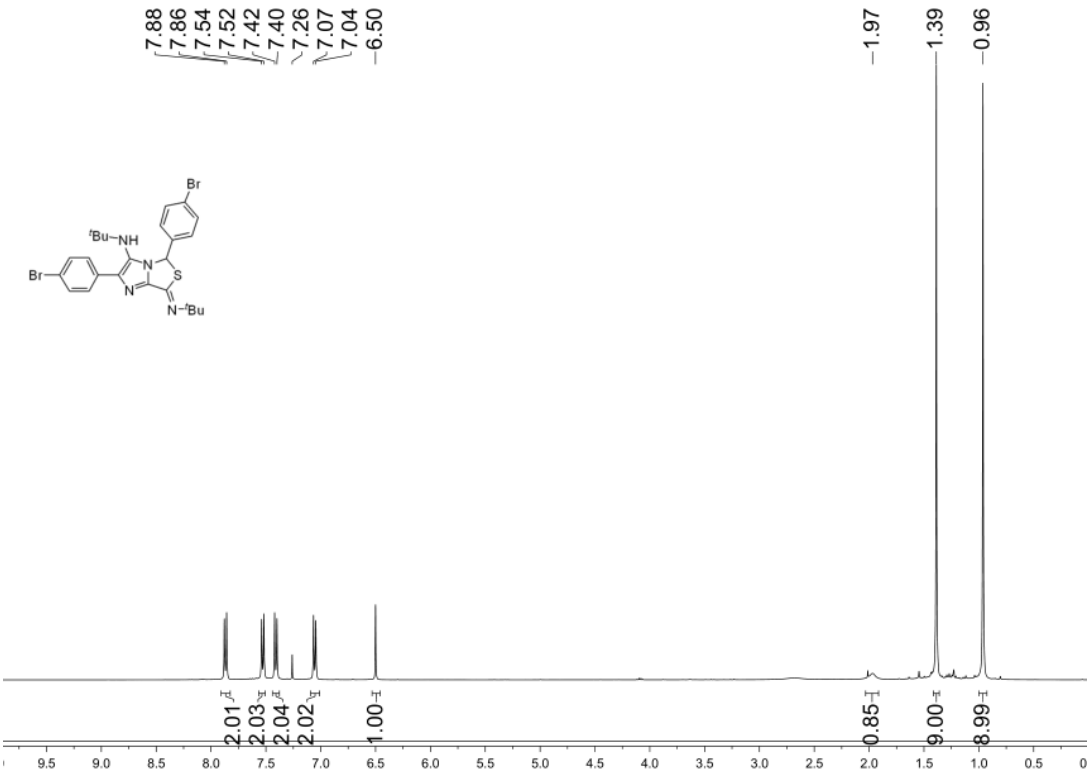
(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-bis(4-chlorophenyl)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3g**)

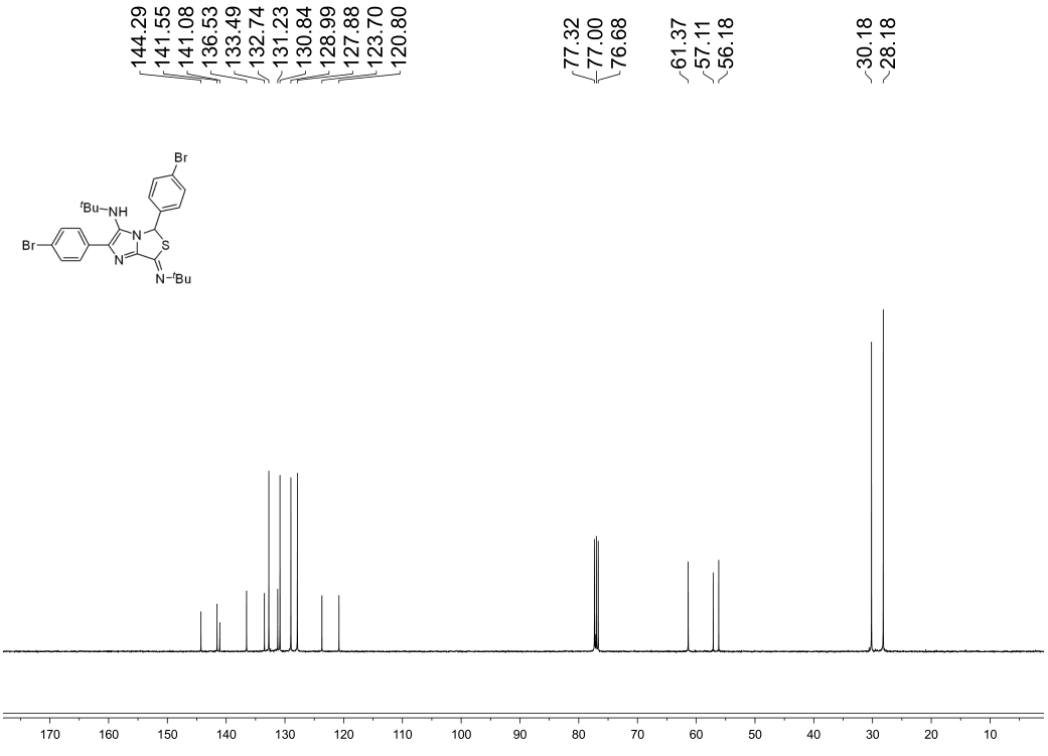


(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-bis(3-chlorophenyl)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3h**)

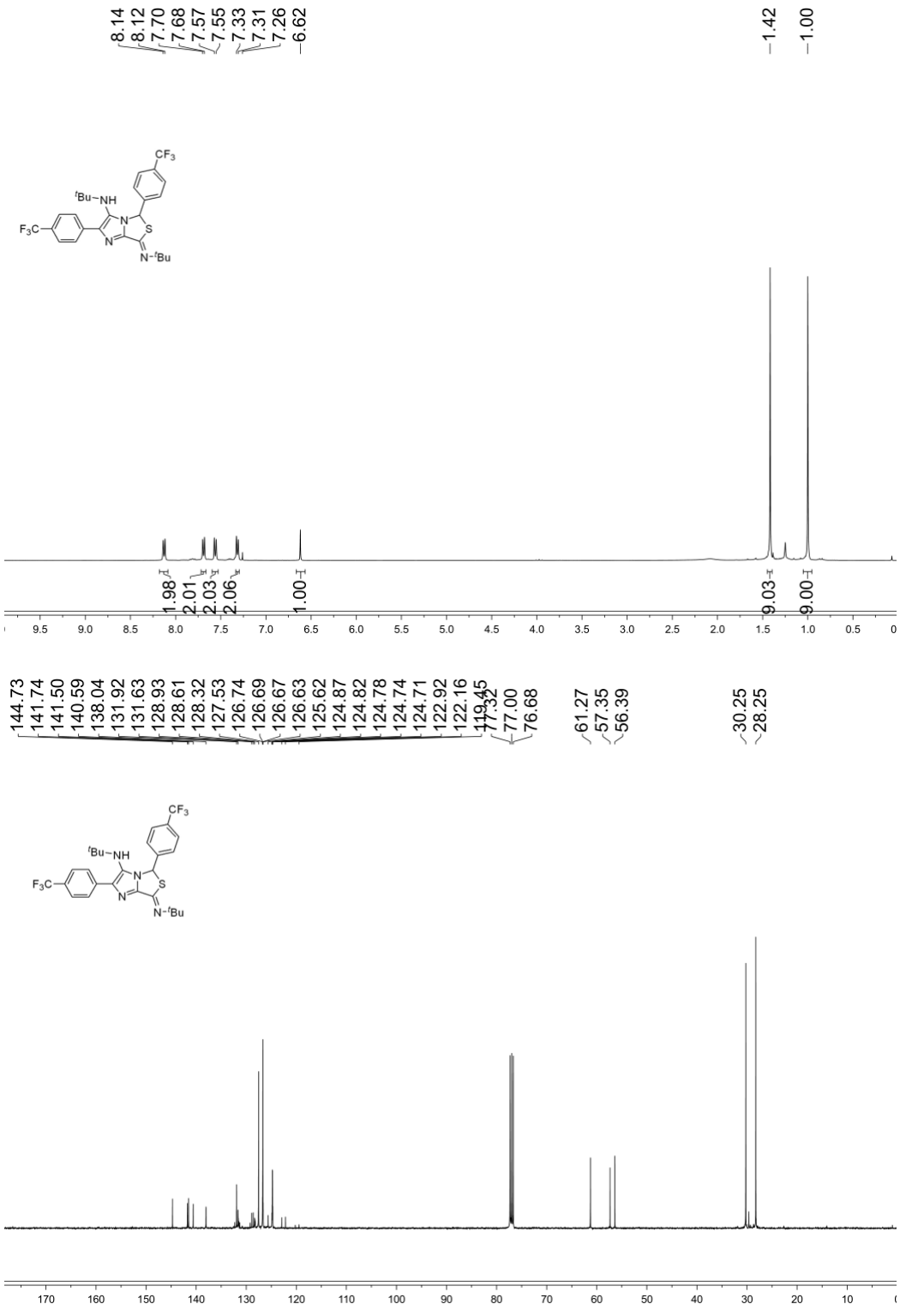


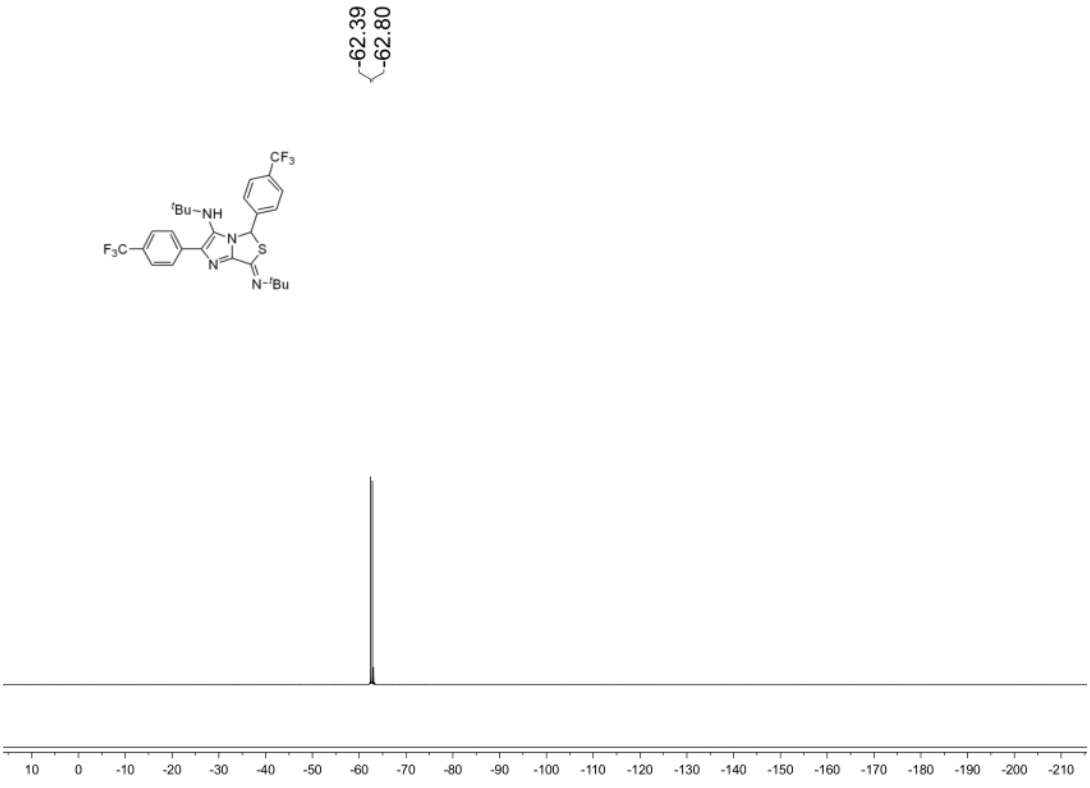
(Z)-2,5-bis(4-bromophenyl)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3i**)



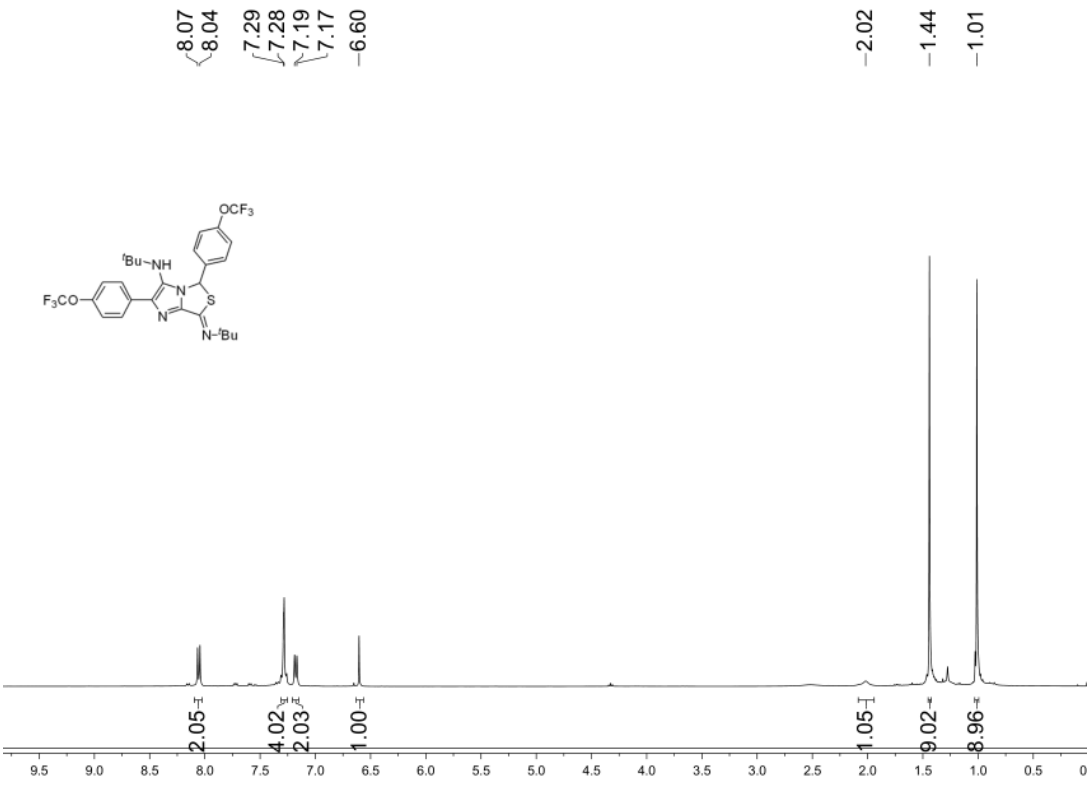


(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-bis(4-(trifluoromethyl)phenyl)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3j**)





(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-bis(4-(trifluoromethoxy)phenyl)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3k**)



149.84
149.83
148.10
148.08
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141.51
141.03
136.14
133.29
131.30
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128.00
124.24
124.12
121.81
121.69
121.55
120.16
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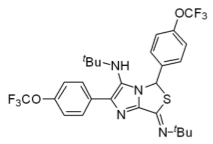
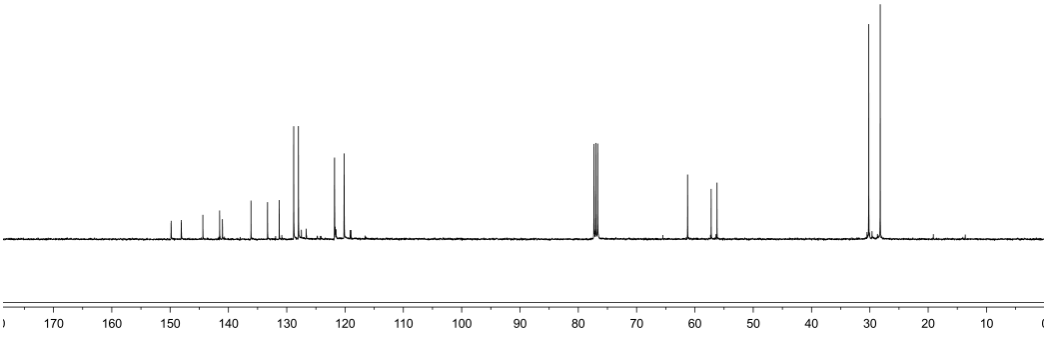
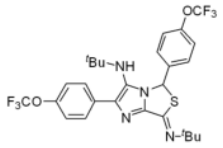
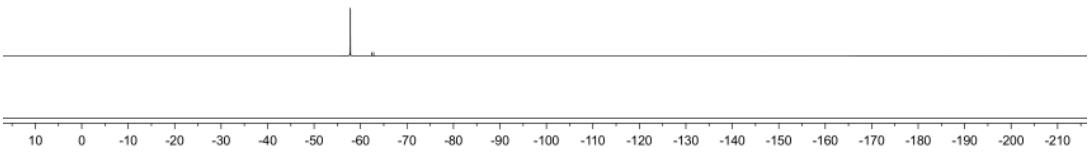
76.68
61.26
57.21
56.21
30.19
28.23



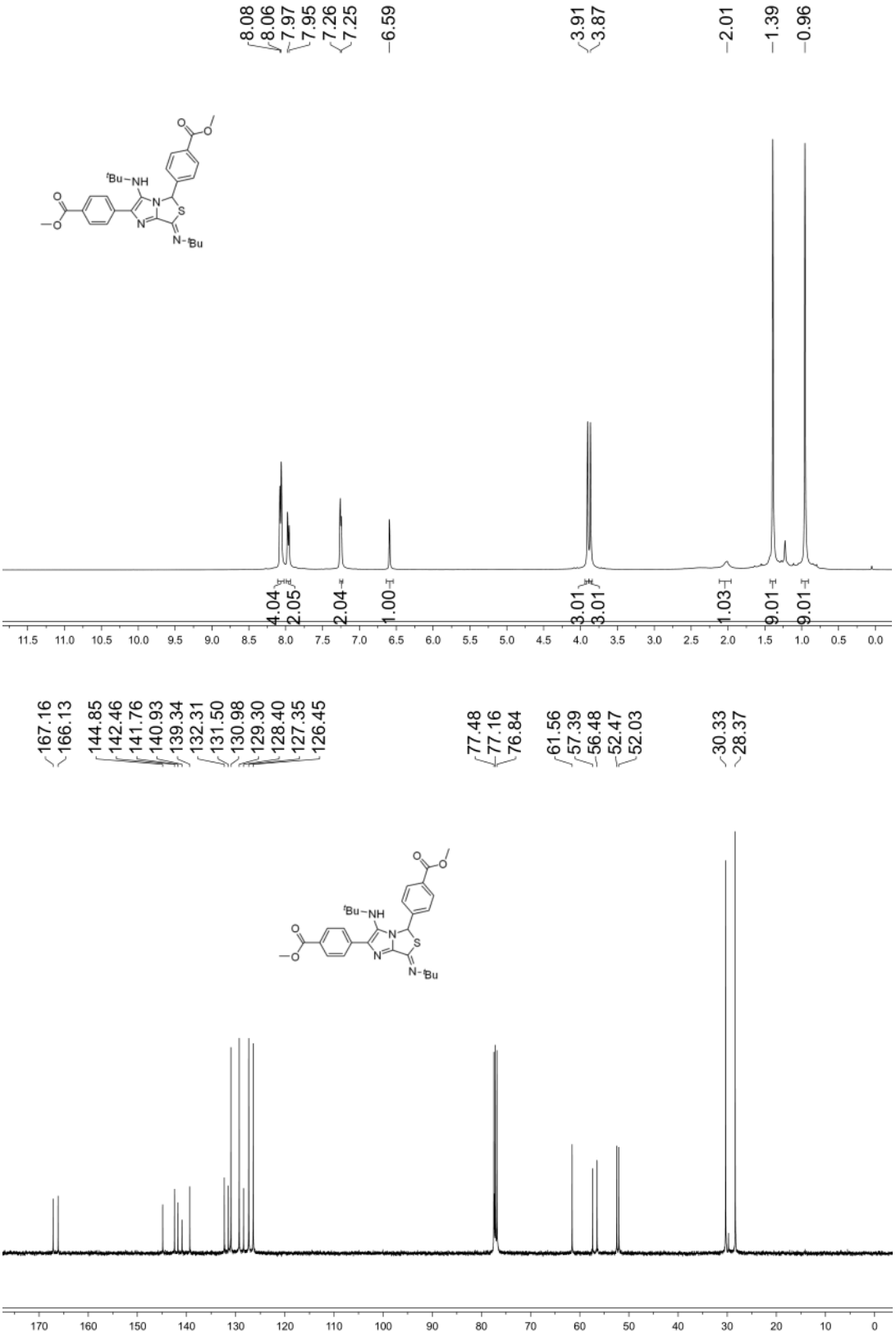


-57.79
-57.82

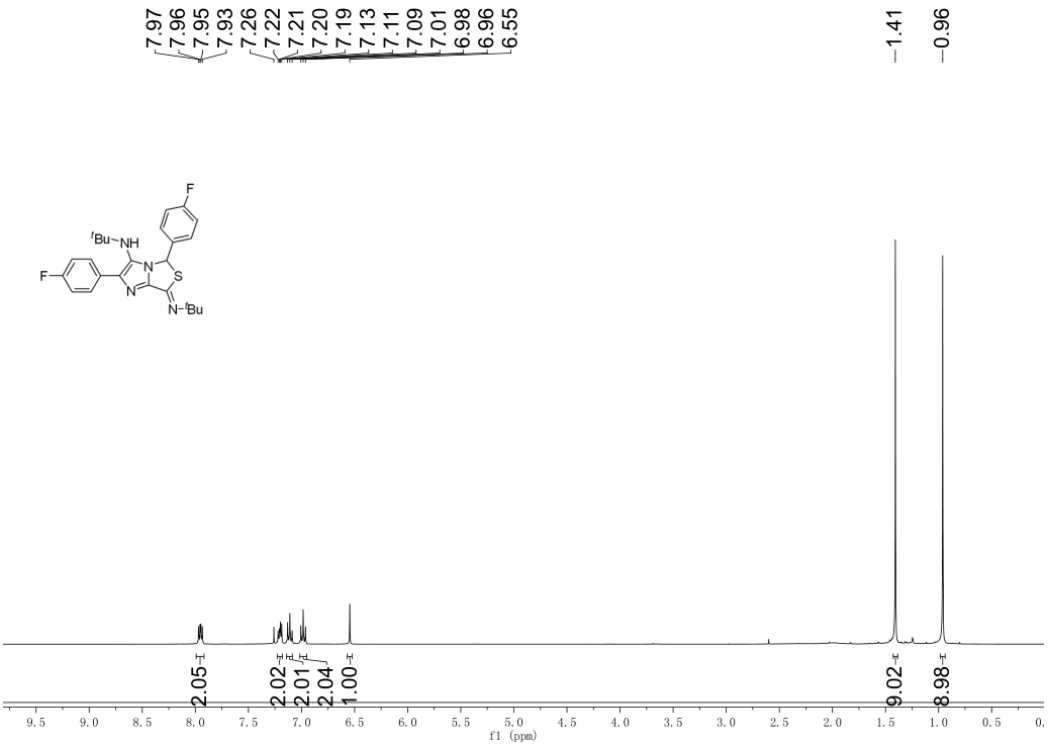


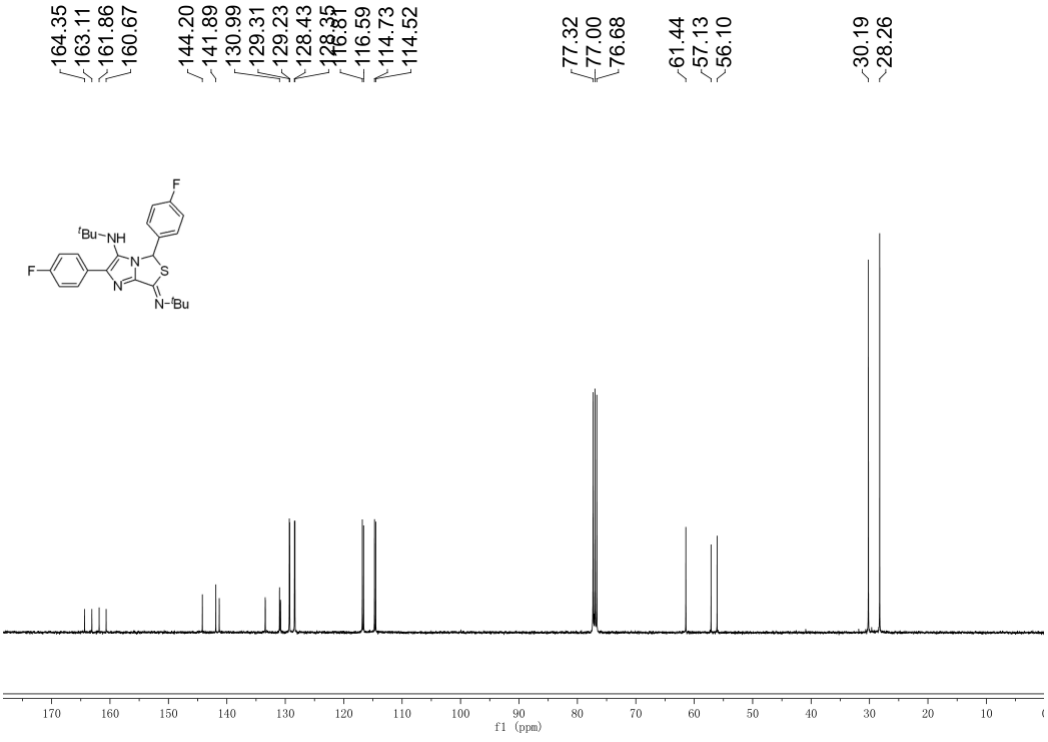


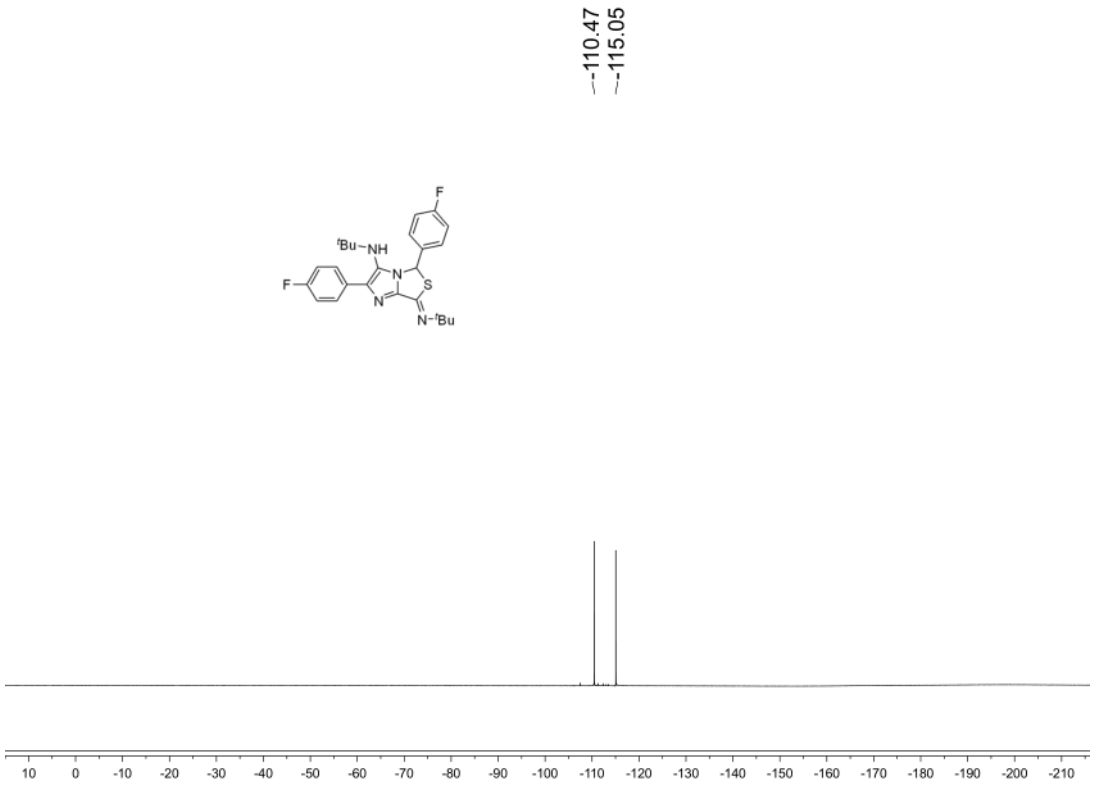
Dimethyl 4,4'-(3-(tert-butylamino)-7-(*tert*-butylimino)-5*H*,7*H*-imidazo[1,2-*c*]thiazole-2,5-diyl) (Z)-dibenzoate (**3l**)



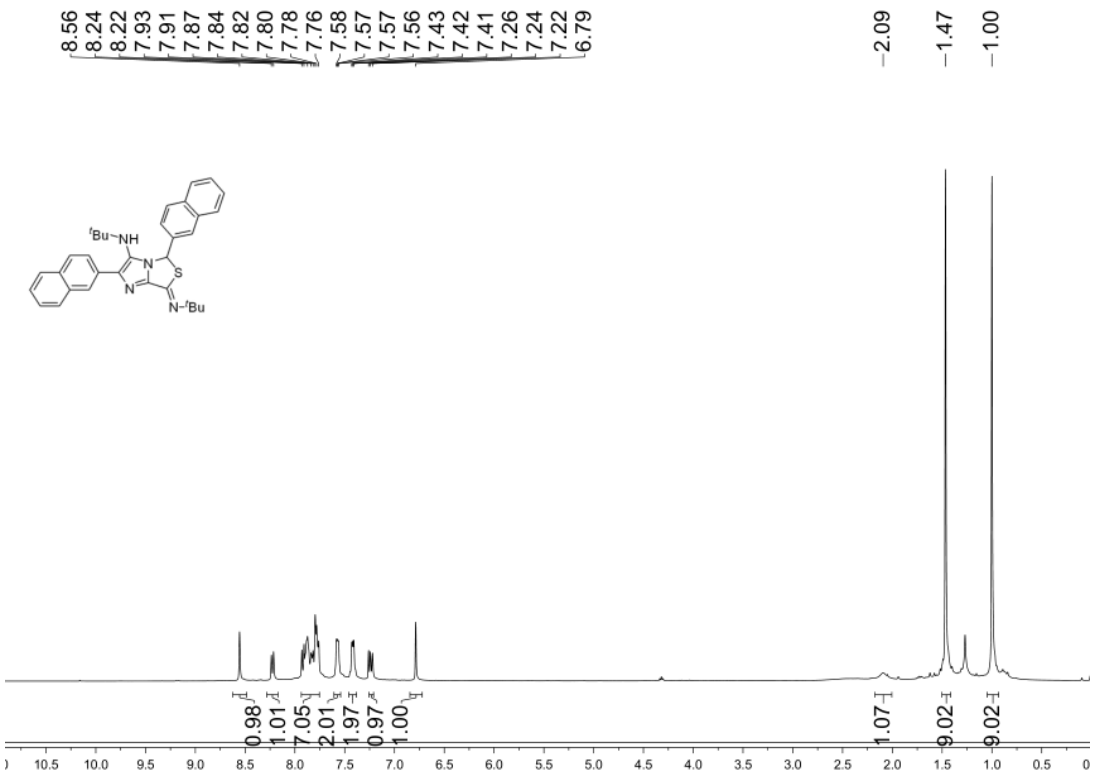
(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-bis(4-fluorophenyl)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3m**)

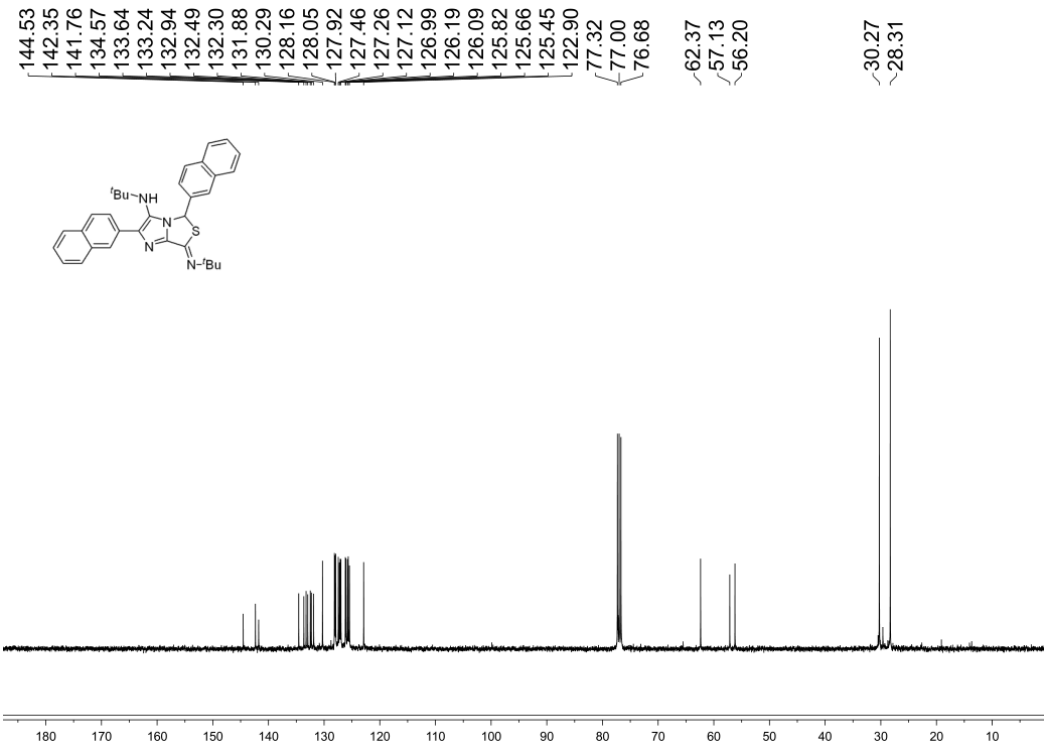




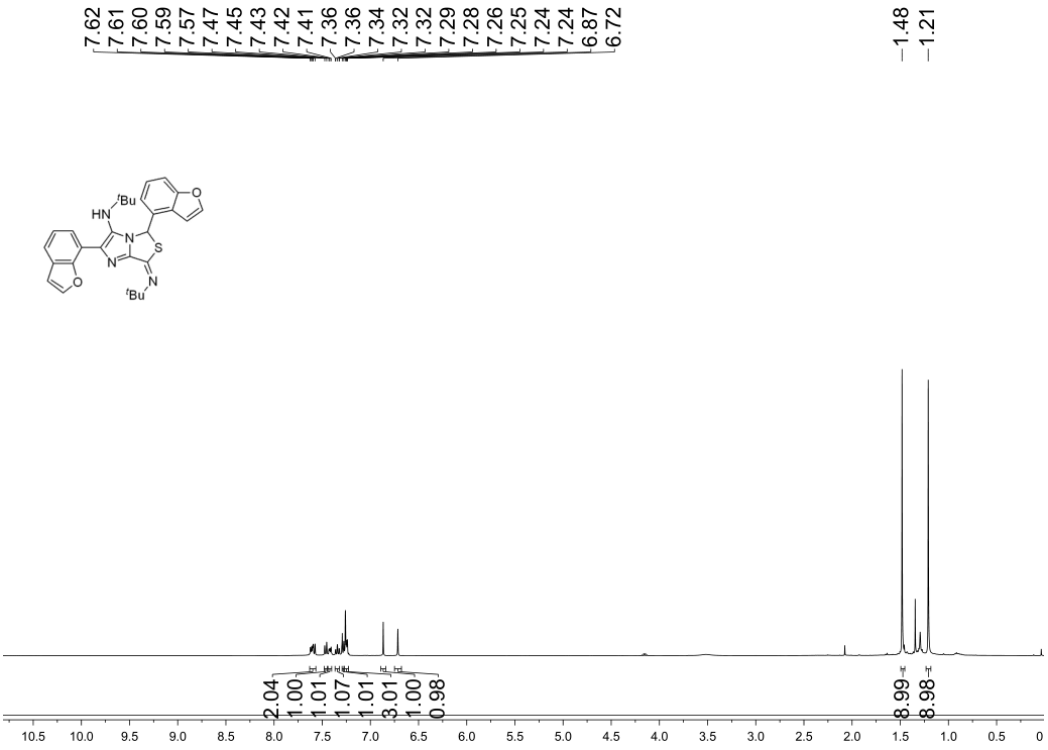


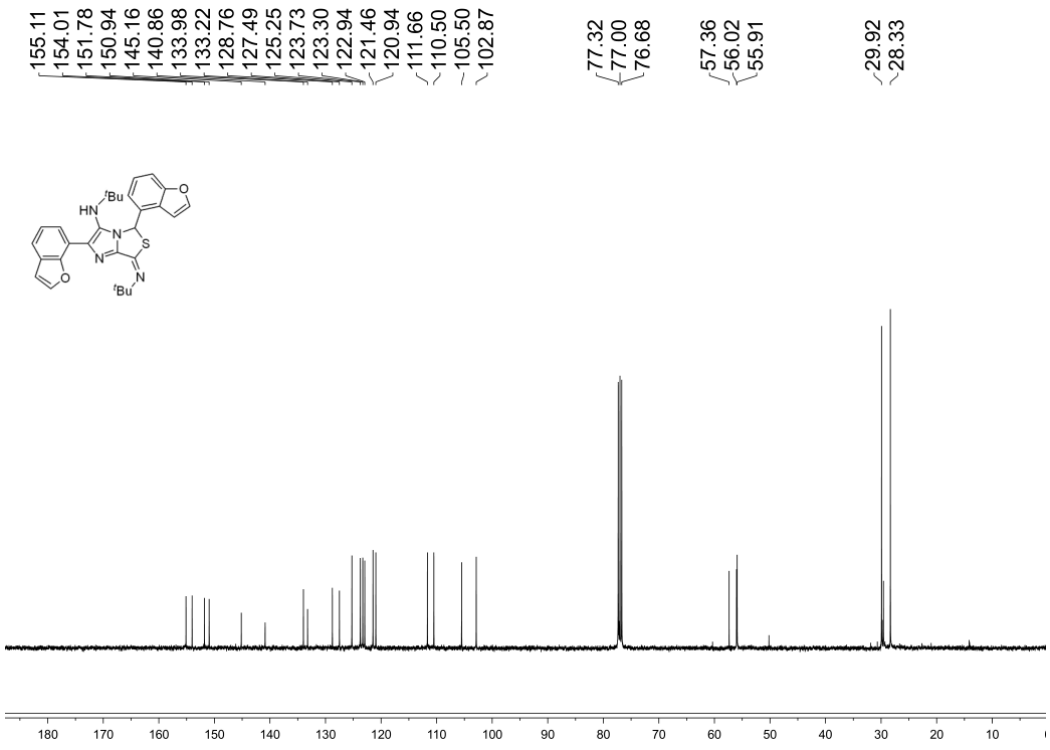
(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-di(naphthalen-2-yl)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3n**)



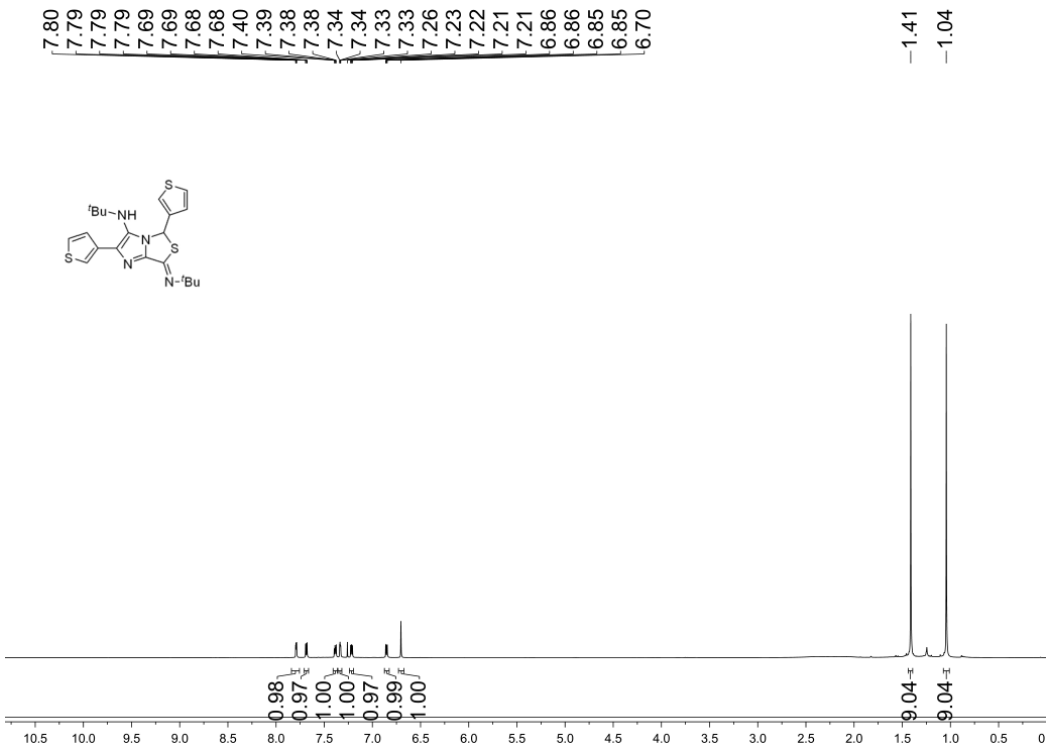


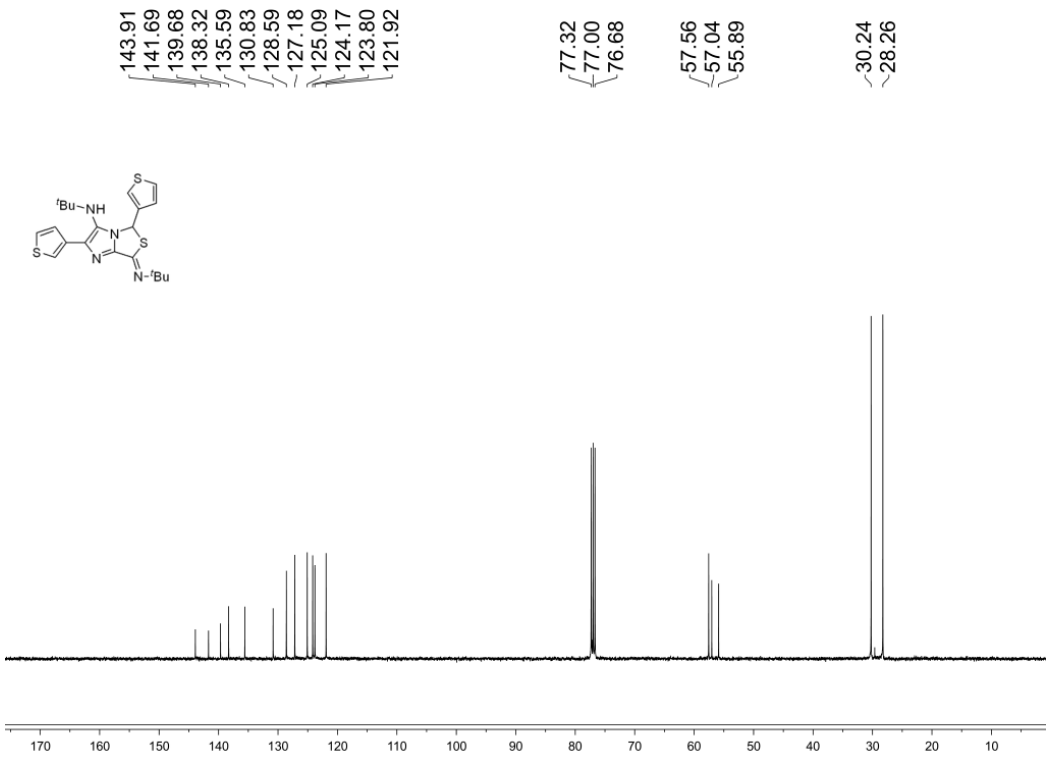
(E)-4-(benzofuran-4-yl)-2-(benzofuran-7-yl)-*N*-(*tert*-butyl)-6-(*tert*-butylimino)-3a,6-dihydro-4*H*-thieno[3,4-b]pyrrol-3-amine (**3o**)



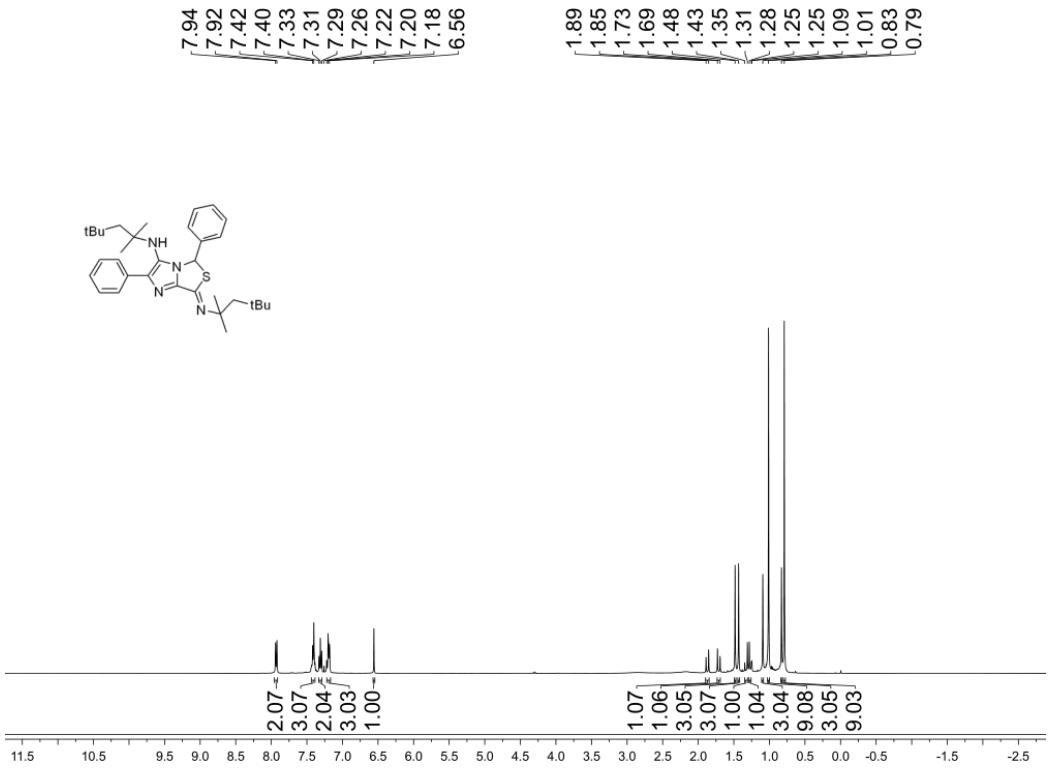


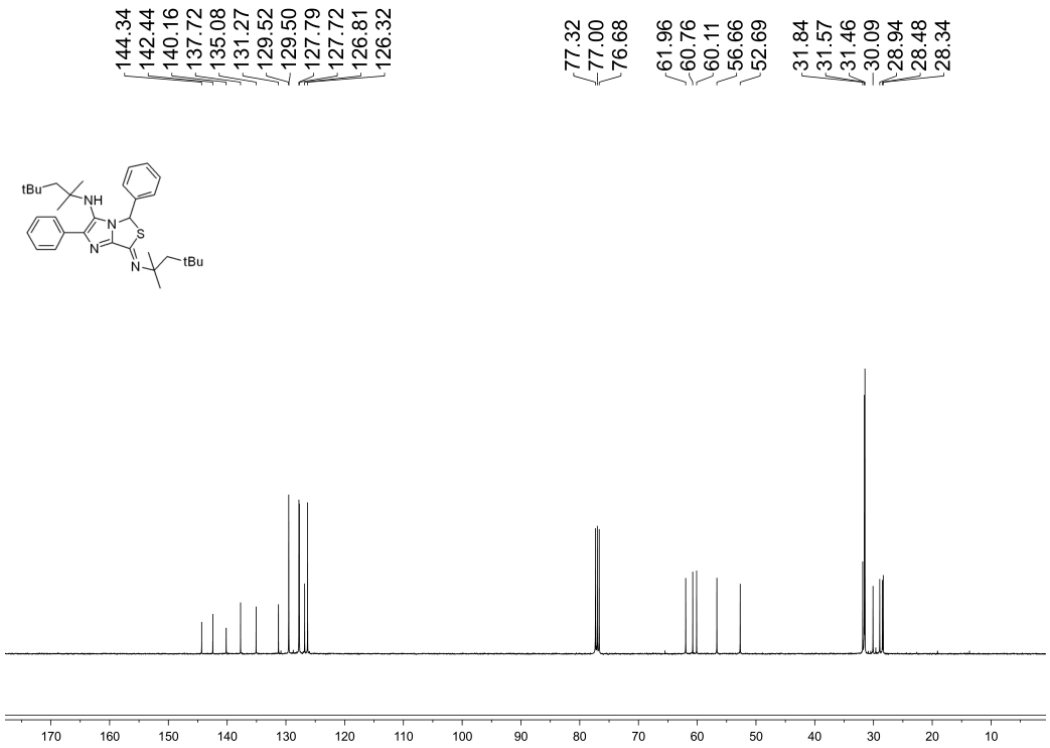
(Z)-*N*-(*tert*-butyl)-7-(*tert*-butylimino)-2,5-di(thiophen-3-yl)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3p**)



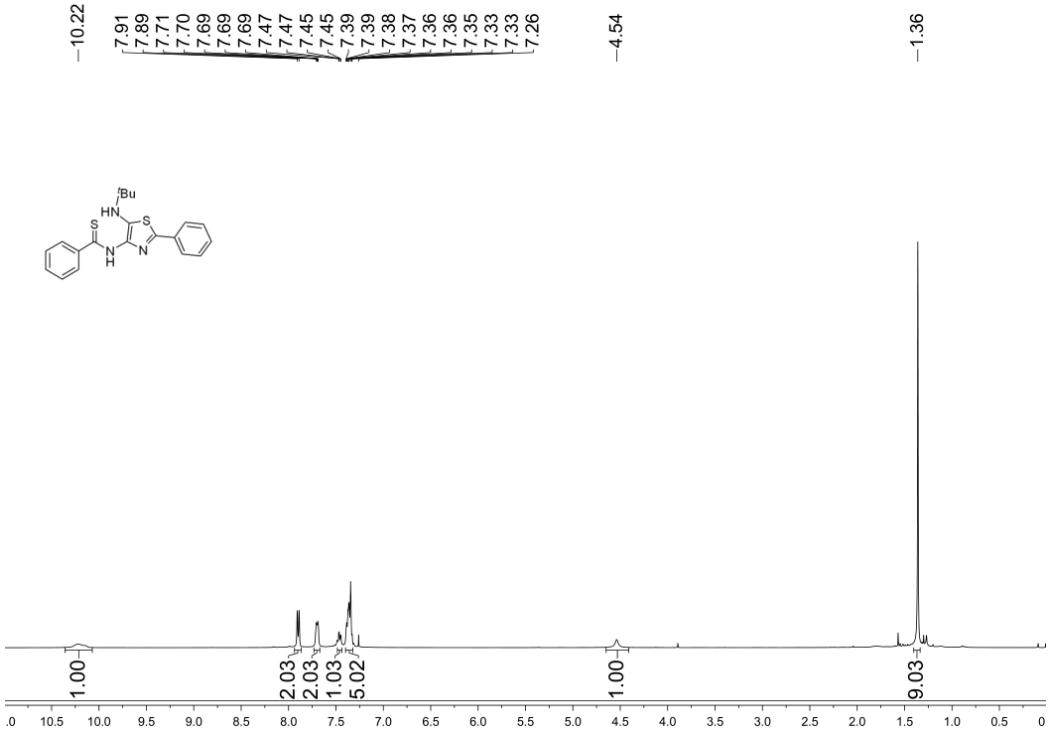


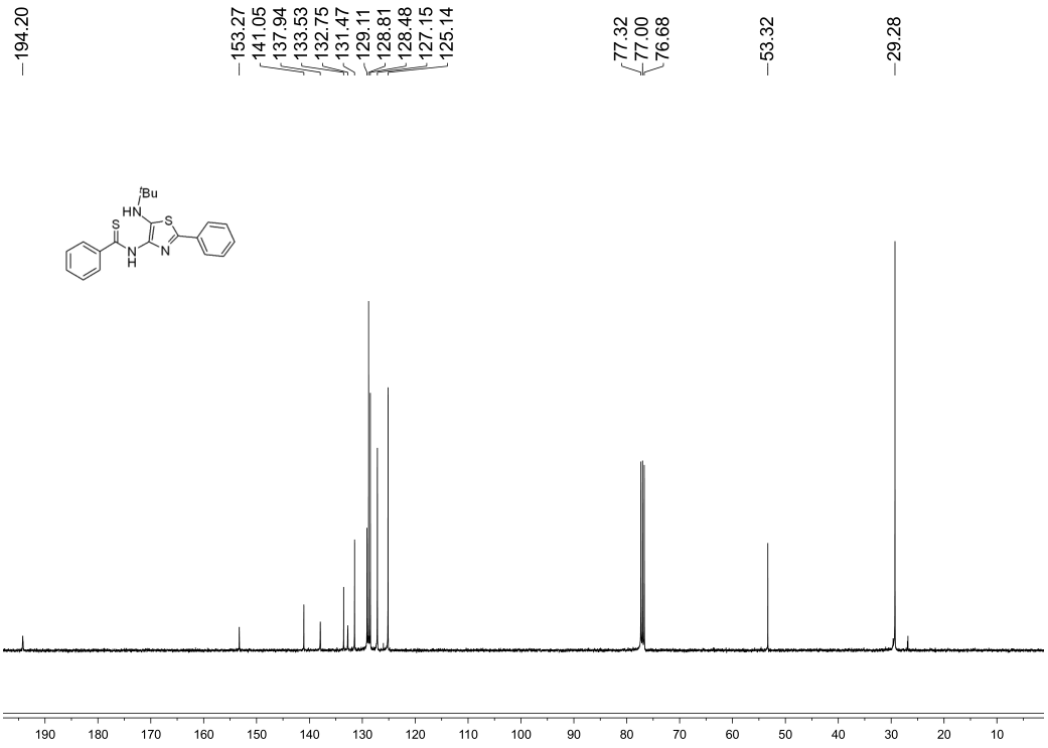
(Z)-2,5-diphenyl-*N*-(2,4,4-trimethylpentan-2-yl)-7-((2,4,4-trimethylpentan-2-yl)imino)-5*H*,7*H*-imidazo[1,2-*c*]thiazol-3-amine (**3q**)



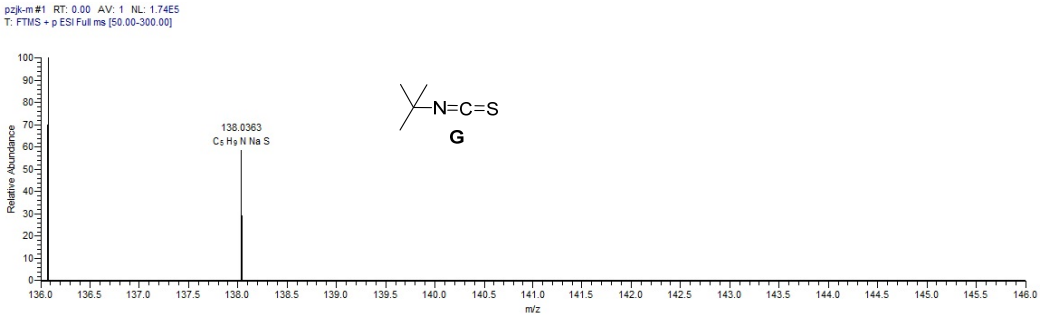


N-(5-(*tert*-butylamino)-2-phenylthiazol-4-yl)benzothioamide (intermediate **H**)





HRMS Spectra of isothiocyanate **G**



Reference

[1] R. S. Varma and D. Kumar, *Org*. *Lett*. **1999**, *1*, 697–700.

[2] W. Tong, W. H. Li, Y. He, Z. Y. Mo, H. T. Tang, H. S. Wang and Y. M. Pan, *Org. Lett.* **2018**, *20*, 2494−2498.