Electronic Supporting Information

for

Guanidine-Based Azines from N-Heterocyclic Carbene (NHC)-Derived Selenoureas and Diazo Compounds: Synthesis, Structural Diversification, and Biological Evaluation

by

Dimitrios K. Giannopoulos,[a] Ilias Papantzimas,[b] Spyridon A. Ferikoglou,[a] Efstathios Tonis,[a] Nikolaos V. Tzouras,[a,c] Athanasios Pseftogas,[b] Fady Nahra,[c,d] Steven P. Nolan,[c] Aristides G. Eliopoulos,[b]* Georgios C. Vougioukalakis[a]*

[a] Department of Chemistry, National and Kapodistrian University of Athens, Panepistimiopolis, 15771, Athens, Greece

[b] Department of Biology, School of Medicine, National and Kapodistrian University of Athens, Mikras Asias 75, 11527, Athens, Greece

[c] Department of Chemistry and Centre of Sustainable Chemistry, Ghent University, Krijgslaan 281, S-3,9000 Ghent, Belgium.

[d] VITO (Flemish Institute for Technological Research), Boeretang 200, 2400 Mol, Belgium.

*Corresponding authors email addresses: eliopag@med.uoa.gr, vougiouk@chem.uoa.gr

Table of Contents

1. General Information

All reactions were carried out under air, unless otherwise noted. When chemicals were used for experiments under inert atmosphere (Schlenk line), they were either dried under vacuum (solids) or dried and degassed using argon (solvents). Solvents and all other reagents were purchased (Sigma Aldrich, Acros Organics, TCI, Fluorochem) and used without further purification. Purification of compounds by filtration or column chromatography was performed using analytical grade solvents and silica gel 60 (230-400 mesh) purchased from Merck. Thin layer chromatography (TLC) was performed using aluminium sheets (0.2 mm) coated with silica gel 60 with fluorescence material that absorbs at 254 nm (silica gel 60 F254). ^{1}H, ^{13}C, ^{31}P, ^{77}Se NMR spectra were recorded on a 200 MHz Varian Mercury spectrometer, or a Bruker Avance 400 MHz Ultrashield spectrometer, or a Bruker Avance 500 MHz Ultrashield spectrometer at 298 K using the residual solvent peak as reference ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm; DMSO-d_6: δ_H = 2.50 ppm, δ_C = 39.52 ppm). Chemical shifts δ are given in ppm. Peaks are assigned as: s (singlet), d (doublet), t (triplet), q (quadruplet), h (heptaplet), and m

(multiplet). High resolution mass spectra (HRMS) were recorded on a QTOF maxis Impact (Bruker) spectrometer using an Electron Spray Ionization (ESI) source at the Core Facility of the National and Kapodistrian University of Athens

1.1. Materials and Methods

1.1.1. Cell culture

A2780 ovarian and VM-CUB-1 bladder carcinoma cells were cultured in RPMI-1640 and high-glucose DMEM respectively, supplemented with 10% FBS, GlutaMAX and 100 U/mL penicillin/100 μg/mL streptomycin and maintained at 37°C, 5% CO_2. A2780 cells carry wild-type *TP53*,[1] whereas VM-CUB-1 carry a homozygous p53 R175H mutation which results in loss of p53 tumor suppressor function.[2]

1.1.2. Cell viability

Cell viability was tested using MTT conversion assays as previously described.[3] Briefly, cells (7×10^3/well) were seeded in 96-well plates. The next day, compounds were added at the indicated concentrations and 48 h later, 20 μL MTT (5 mg/mL in PBS) was added per well and incubated for 4 h at 37 °C. Supernatants were removed, 200 μL DMSO added, and absorbance recorded at 550 nm. Data were normalized to vehicle controls.

1.1.3. Cell cycle analysis by Flow Cytometry

For cell cycle analysis, 200,000 cells were seeded in 6-well plates and treated with compound **19**, **17**, **11** or **7** (10 or 30 μM), cisplatin (10 μM) as reference, or vehicle control (DMSO) for 24 h. Cells were harvested, fixed in 80% cold ethanol (dropwise) for 30 min at 4 °C, and stained with 50 μg/mL propidium iodide (PI) in the presence of 10 μg/mL RNase A (Invitrogen #AM2271) diluted in staining buffer (100 mM Tris-HCl, pH 7.5, 150 mM NaCl, 1 mM $CaCl_2$, 0.5 mM $MgCl_2$, and 0.1% NP-40). DNA content was analyzed using a FACSCalibur flow cytometer (BD Biosciences).

1.1.4. Annexin-V/propidium iodide (PI) Staining Assay

Apoptosis was assessed using an Annexin-V-FITC apoptosis detection kit (Invitrogen, #V13242). A2780 cells (2×10^5/well, 6-well plates) were treated with compound **19** (10, 30 μM), cisplatin (10 μM) or vehicle control (DMSO) for 36 h. Cell cultures were collected, washed, resuspended in binding buffer, stained with Annexin V-FITC/PI for 10 min in the dark, and analyzed immediately by flow cytometry, according to the instructions of the manufacturer.

1.1.5. Protein extraction and immunoblotting

Protein extraction, quantification and electrophoresis were performed as previously described.[4] For immunoblotting, the following primary antibodies were used: p53 (dilution 1:500, Santa Cruz #47698) and actin (ACTB; dilution 1:500, Sigma Aldrich #MAB1501). Anti-mouse HRP-linked secondary antibody (Sigma Aldrich #A9044) was used at 1:4000 dilution.

2. Experimental Procedures

2.1. Experimental Procedure A: Synthesis of 2-cyano-acetamides

Synthesized according to a published procedure.[5] To a solution of a secondary amine (3 mmol) and 2-cyano acetic acid (280 mg, 3.3 mmol) in CH_2Cl_2 (10 mL) was added a solution of DCC (N,N'-dicyclohexylcarbodiimide, 680 mg, 3.3 mmol) and DMAP [4-(*N*,*N*-dimethylamino)pyridine, 2 mg, 0.05 mmol] in CH_2Cl_2 (20 mL) at 80 ºC. The resulting solution was stirred for 1h. During this period a white solid (1,3-dicyclohexylurea, DCU) precipitated, which was subsequently filtered. After removal of the solvent under reduced pressure, the resulting crude product was recrystallized from EtOH to afford the amides.

2.2. Experimental Procedure B: Synthesis of β-ketoamides

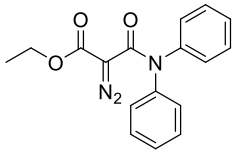
Synthesized according to a published procedure.[6] To a 20 mL Schlenck tube, flame dried and Argon purged, equipped with magnetic stirring bar, were introduced ethylacetoacetate (195 mg, 1.5 mmol), corresponding amine (3 mmol, 2 equiv.), DMAP (25 mg, 0.15 mmol), in 15 mL of dry toluene. The mixture was stirred and heated at reflux overnight. Solvent was removed under vacuo and crude product was purified by column chromatography on silica gel.

2.3. Experimental Procedure C: Synthesis of diazo-compounds

A) Synthesized according to published procedures.[5,7,8] An amide (1 mmol) was dissolved in 2 mL of dry CH_3CN and solution of corresponding azide (triflic azide (2 mL, 2 mmol),[5] 4-acetamidobenzenesulfonyl azide (264 mg, 1.1 mmol),[7] 4-toluenesulfonyl azide – 30% solution in toluene (712 mg, 1.1 mmol)[8]) was added under inert atmosphere at 0 ºC, cooling with an ice-water bath. After the addition of dry triethylamine (202 mg, 2 mmol), the resulting mixture was stirred at room temperature

for 18 h. The solution was concentrated under reduced pressure. The resulting residue was purified by column chromatography to give the pure products. All the diazo-compounds are known in the literature except from diazo-compound **S1**.

2.3.1. ethyl 2-diazo-3-(diphenylamino)-3-oxopropanoate (A)



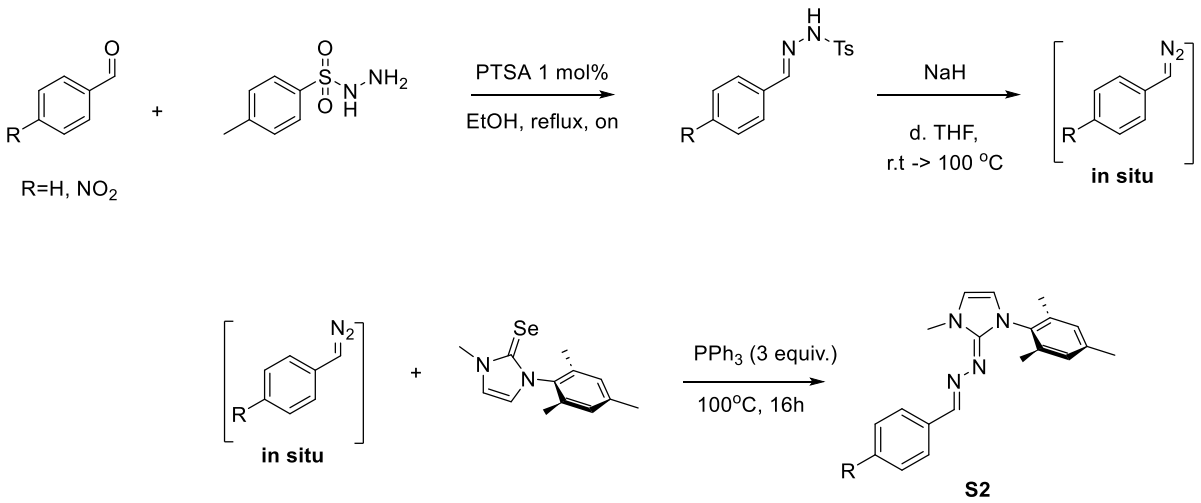
Synthesized according to the general procedure **C**, purified by column chromatography (ethyl acetate / petroleum ether). Isolated as yellow solid in 90 % yield (278.1 mg, 0.9 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37 (m, 4H), 7.27 (m, 2H), 7.21 (m, 4H), 4.05 (q, *J*=7.2, 6.3, 2H), 1.15 (t, *J*=7.1, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.95, 161.53, 143.26, 129.31, 126.78, 126.71, 61.58, 14.28.

HRMS (ESI) m/z cal. for $(M + H)^+$ 310.1147, found 310.1183

B) Experimental procedure for the in-situ generation of diazo-compounds from hydrazones.

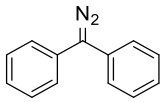


Scheme S1: Azine-product synthesis through in situ generation of diazo-compounds.

Synthesized according to a published procedure.[9] The aldehyde (1 mmol,1 equiv.) was added dropwise/portionwise to a suspension of p-tosylhydrazide (1 mmol, 1.0 equiv.) in MeOH (1 M). A midly exothermic reaction ensued and the hydrazide dissolved. The reaction mixture was then stirred at room temperature until complete conversion was observed by TLC.

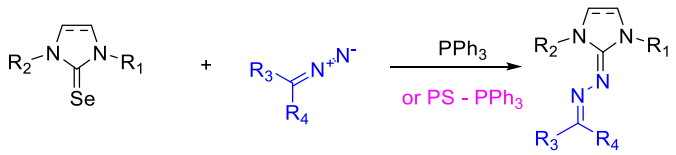
After the corresponding hydrazones were obtained, in a Schlenck tube, under inert atmosphere, sodium hydride (1 mmol, 1 equiv.) and dry THF (1 mL) were added. The reaction was left at room temperature overnight. Because of the instability of these compounds (explosive compounds) the reaction with selenoureas took place in situ.

C) Experimental procedure for benzophenone diazo-compound.



Synthesized according to a published procedure.[10] Hydrazine monohydrate (100 mg, 2 mmol) was added to DMF (1 mL) in a 5 mL round bottom flask equipped with a stir bar and reflux condenser. Benzophenone (182 mg, 1 mmol) was added at once and the solution was stirred and heated to 130 °C for 12 h in an oil bath. Subsequently, water (5 mL) was added followed by extraction with CH_2Cl_2 (2 × 5 mL). The CH_2Cl_2 solution was dried over anhydrous magnesium sulfate and transferred to a 50 mL round bottom flask, placed in an ice bath and allowed to cool to approximately 0 °C. Activated MnO_2 (870 mg, 10 mmol) was added portionwise over 10 min under heavy stirring ensuring the temperature does not exceed 10 °C. The slurry was vigorously stirred at 0 °C for 1 h after which the ice bath was removed and stirring continued for 12 h at room temperature. The solution was filtered through a plug of sodium bicarbonate, plug was washed with additional CH_2Cl_2 (10 mL), and all solvent was removed using a rotary evaporator yielding a crimson liquid. To the residue methanol (0.5 mL) was added, and the solution cooled to -20 °C overnight resulting in the precipitation of a crimson solid which was filtered off and dried under high vacuum to afford the title compound (1.24 g, 64%).

2.4. Experimental Procedure D: Synthesis of Azine Derivatives



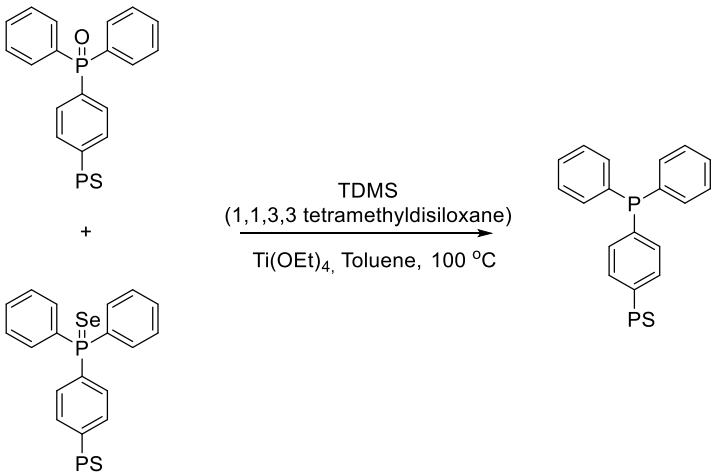
Scheme S2: Synthesis of azine derivatives.

A) Synthesis of Azine-Derivatives using PPh_3:

To a 4 mL vial, equipped with a stirring bar and a septum equipped screw-cap, were introduced NHC-based selenourea (0.125 mmol, 1 equiv.), PPh_3 (0.375 mmol, 3 equiv.), toluene (0.5 mL) and diazo compound (0.15 mmol, 1.2 equiv.). The reaction mixture was stirred at 110 °C for 16 h under air. The solvent was then removed under vacuum. Flash column chromatography on silica gel (ethyl acetate / petroleum ether (5/1 to 1:1)) afforded the pure product.

B) Synthesis of Azine-Derivatives using PS-PPh_3:

Before use, the commercially available PS-PPh_3 resin was filtered and washed with 10 mL of DCM (x3), to remove residual impurities (free PPh_3). To a 4 mL vial, equipped with a stirring bar and septum equipped screw-cap, were introduced NHC-based selenourea (0.125 mmol, 1 equiv.), PS-PPh_3 (0.25 mmol, 2 equiv.), toluene (0.5 mL) and diazo compound (0.15 mmol, 1.2 equiv.). The reaction mixture was stirred at 110 °C for 16 h under air. The resulting mixture was filtered and washed (x3) with DCM. The filtrate was collected and concentrated under vacuum, to afford the pure product. The solid retained on the filter (the oxidized resin) was used in subsequent experiments.



Scheme S3: Recycling reaction of PS-PPh_3

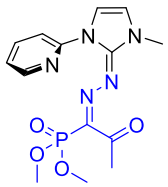
Regeneration of PS-PPh_3 from the oxidized resin was performed following a published procedure by Lemaire and coworkers.[11] To a 4 mL vial, equipped with a stirring bar and septum equipped screw-cap, were introduced the oxidized triphenylphosphine (filtered from the reaction) (0.5 mmol) in 1 mL toluene. Then, TDMS (1.3 mmol, 2.5 equiv.) and $Ti(OEt)_4$ (0.05 mmol, 0.1 equiv.) were added to the vial. The heterogeneous mixture was stirred at 100 °C overnight. After completion of the reaction, the mixture was filtered and washed multiple times with DCM. The recovered resin was further

dried under vacuum to remove residual solvent and used directly in subsequent azine synthesis.

2.5. Experimental Procedure E: Synthesis of halogenated azines

Synthesized according to a published procedure.[12] To a 4 mL vial, equipped with stirring bar and septum equipped screw-cap, were introduced the azine product (0.046 mmol, 1 equiv.), 0.3 mL DCM (0.15 M) and 21 mL of DBU (0.138 mmol, 3 equiv.) and the mixture was cooled at 0 ºC. Then NIS (0.092 mmol, 2 equiv.) or NBS (0.092 mmol, 2 equiv.) were added to the mixture and stirred at room temperatute for 1 hour. The reaction mixture was monitored by TLC (EtOAc 100 %). Upon completion, flash column chromatography (PE: EtOAc 1:1) afforded the pure products.

2.4.1. Dimethyl-((E)-1-(((E)-1-methyl-3-(pyridin-2-yl)-1,3-dihydro-2H-imidazol-2-ylidene)hydrazineylidene)-2-oxopropyl)phosphonate (1)



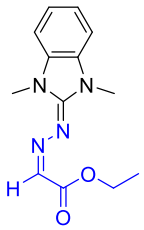
Synthesized according to the general procedure **2.4, A**, purified by column chromatography (ethyl acetate / petroleum ether). Isolated as yellow solid in 90 % yield (39.5 mg, 0.112 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 9.0 Hz, 1H), 8.43 (s, 1H), 7.91 (t, *J* = 3.1 Hz, 1H), 7.66 (t, *J* = 3.1 Hz, 1H), 7.22 (d, *J* = 8.1 Hz 1H), 6.59 (s, 1H), 3.90 (s, 3H), 3.76 (m, 6H), 2.28 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.07, 149.96, 148.73, 147.90, 138.81, 122.46, 119.33, 118.95, 113.66, 52.86, 52.80, 38.45, 27.32.

HRMS (ESI) m/z cal. for $(M + H)^+$ 352.1130, found 352.1180

2.4.2. Ethyl-(Z)-2-((1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-ylidene)hydrazineylidene)acetate (2)



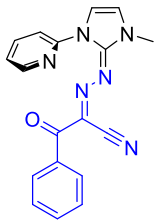
Synthesized according to the general procedure **2.4, A** and **B**. When procedure **A** was used, the product was purified by column chromatography (ethyl acetate / petroleum ether). Isolated as yellow solid in 90 % yield (29 mg, 0.112 mmol). When procedure **B** was used, no column chromatography was used.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (s, 1H), 7.15 (m, 2H), 7.07 (m, 2H), 4.30 (q, *J*=7.1, 2H), 3.80 (s, 6H), 1.35 (t, *J*=7.1, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.63, 154.08, 136.59, 132.45, 122.13, 107.89, 60.42, 31.23, 14.52.

HRMS (ESI) m/z cal. for $(M + H)^+$ 261.1307, found 261.1343

2.4.3. (E)-*N*-((E)-1-methyl-3-(pyridin-2-yl)-1,3-dihydro-2H-imidazol-2-ylidene)-2-oxo-2-phenylacetohydrazonoyl cyanide (3)



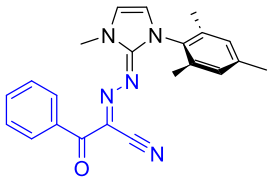
Synthesized according to the general procedure **2.4, A** and **B**. When procedure **A** was used, the product was purified by column chromatography (ethyl acetate / petroleum ether). Isolated as yellow solid in 85 % yield (35 mg, 0.106 mmol). When procedure **B** was used, no column chromatography was used.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 8.4 Hz, 1H), 8.41 (s, 1H), 7.86 (t, *J* = 8.1 Hz, 1H), 7.77 – 7.69 (m, 3H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.22 (s, 1H), 6.60 (s, 1H), 3.58 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 188.94, 149.64, 147.83, 138.63, 137.99, 131.07, 129.12, 127.54, 122.93, 122.68, 119.08, 118.75, 114.35, 37.45.

HRMS (ESI) m/z cal. for $(M + H)^+$ 331.1263, found 331.1285

2.4.4. (E)-*N*-((E)-1-mesityl-3-methyl-1,3-dihydro-2H-imidazol-2-ylidene)-2-oxo-2-phenylacetohydrazonoyl cyanide (4)



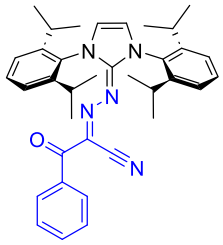
Synthesized according to the general procedure **2.4, A**, purified by column chromatography (ethyl acetate / petroleum ether). Isolated as yellow solid in 90 % yield (41 mg, 0.112 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.32 (m, 3H), 7.26 – 7.20 (m, 2H), 6.82 (s, 1H), 6.50 (s, 2H), 6.47 (s, 1H) 3.76 (s, 3H), 2.07 (s, 3H), 1.87 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 189.70, 149.77, 138.90, 138.54, 134.08, 133.21, 131.12, 129.70, 129.30, 127.79, 122.91, 118.52, 118.20, 34.38, 21.39, 18.35.

HRMS (ESI) m/z cal. for $(M + H)^+$ 372.1780, found 372.1795

2.4.5. (E)-*N*-(1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene)-2-oxo-2-phenylacetohydrazonoyl cyanide (5)



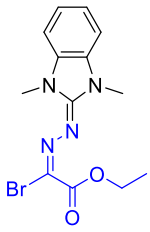
Synthesized according to the general procedure **2.4, A**, purified by column chromatography (ethyl acetate / petroleum ether). Isolated as yellow solid in 84 % yield (59 mg, 0.106 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 1H), 7.25 – 7.19 (m, 2H), 7.18 (s, 1H), 7.09 (s, 2H), 7.07 (s, 2H), 7.05 (d, J = 1.6 Hz, 1H), 6.99 (dd, J = 8.2, 7.2 Hz, 2H), 6.64 (s, 2H), 2.62 (hept, J = 6.9 Hz, 4H), 1.09 (dd, J = 35.2, 6.9 Hz, 24H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 188.62, 150.47, 145.20, 137.84, 132.28, 130.63, 130.57, 129.10, 127.95, 125.26, 124.29, 119.28, 112.65, 29.21, 23.87, 23.24.

HRMS (ESI) m/z cal. for $(M + H)^+$ 560.3345, found 560.3355

2.4.6. Ethyl-(E)-2-bromo-2-((1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-ylidene)hydrazineylidene)acetate (6)



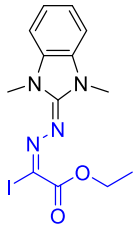
Synthesized according to the general procedure **2.5**, using NBS, purified by column chromatography (ethyl acetate / petroleum ether 1:1). Isolated as yellow solid in 75 % yield (12 mg, 0.035 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37 (m, 4H), 7.27 (m, 2H), 7.21 (m, 4H), 4.05 (q, *J*=7.2, 6.3, 2H), 1.15 (t, *J*=7.1, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.95, 161.53, 143.26, 129.31, 126.78, 126.71, 61.58, 14.28.

HRMS (ESI) m/z cal. for $(M + H)^+$ 340.0358, found 340.0374

2.4.7. Ethyl-(E)-2-((1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-ylidene)hydrazineylidene)-2-iodoacetate (7)



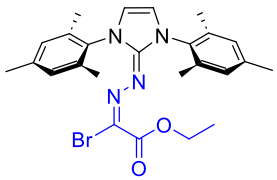
Synthesized according to the general procedure **2.5**, using NIS, purified by column chromatography (DCM 100 %). Isolated as yellow solid in 90 % yield (16 mg, 0.041 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.21 (m, 2H), 7.14 (m, 2H), 4.36 (q, *J*=7.2, 2H), 3.84 (s, 6H), 1.37 (t, *J*=7.3, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.05, 153.38, 132.14, 122.73, 108.49, 101.91, 62.56, 31.12, 14.50.

HRMS (ESI) m/z cal. for $(M + H)^+$ 387.0273, found 387.0292

2.4.8. Ethyl-(E)-2-bromo-2-((1,3-dimesitylimidazolidin-2-ylidene)hydrazineylidene)acetate (8)



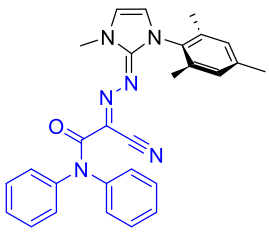
Synthesized according to the general procedure **2.5**, using NBS, purified by column chromatography (ethyl acetate / petroleum ether 1:1). Isolated as yellow solid in 80 % yield (18 mg, 0.036 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.88 (s, 4H), 3.94 (q, *J*=7.2, 2H), 3.86 (s, 4H), 2. 29 (s, 12H), 2.28 (s, 6H), 1.12 (t, *J*=7.3, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.83, 157.19, 137.20, 136.29, 129.18, 115.59, 61.69, 47.86, 21.12, 18.19, 14.17.

HRMS (ESI) m/z cal. for $(M + H)^+$ 500.1610, found 500.1670

2.4.9. (E)-2-(diphenylamino)-*N*-((E)-1-methyl-3-phenyl-1,3-dihydro-2H-imidazol-2-ylidene)-2-oxoacetohydrazonoyl cyanide (9)



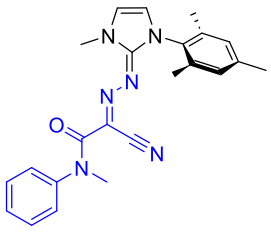
Synthesized according to the general procedure **2.4, A**, purified by column chromatography (ethyl acetate / petroleum ether). Isolated as a yellow solid in 90 % yield (47 mg, 0.112 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.28 (d, J = 8.3 Hz, 4H), 7.16 (d, J = 7.4 Hz, 2H), 6.99 – 6.90 (m, 6H), 6.64 (s, 1H), 6.42 (s, 1H), 3.63 (s, 3H), 2.30 (s, 3H), 1.96 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.38, 149.78, 143.32, 139.72, 138.66, 134.96, 132.98, 128.79, 128.73, 126.90, 125.85, 117.47, 116.90, 115.60, 112.16, 34.48, 29.52, 20.88, 17.89.

HRMS (ESI) m/z cal. for $(M + H)^+$ 463.2202, found 463.2240

2.4.10. (E)-2-(methyl(phenyl)amino)-*N*-((E)-1-methyl-3-phenyl-1,3-dihydro-2H-imidazol-2-ylidene)-2-oxoacetohydrazonoyl cyanide (10)



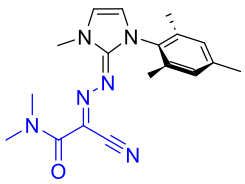
Synthesized according to the general procedures **2.4, A** and **B**. When procedure **A** was used, the product was purified by column chromatography (ethyl acetate). Isolated as yellow oil in 90 % yield (40 mg, 0.112 mmol). When procedure **B** was used, no column chromatography was used.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.7 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 7.7 Hz, 2H), 6.91 (s, 2H), 6.61 (s, 1H), 6.38 (s, 1H), 3.60 (s, 3H), 3.16 (s, 3H), 2.29 (s, 3H), 1.98 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.90, 150.09, 144.14, 138.53, 135.26, 134.90, 133.24, 131.97, 131.87, 131.76, 128.84, 128.71, 128.51, 128.42, 128.38, 128.26, 126.18, 126.06, 125.65, 117.21, 116.63, 115.44, 112.45, 38.18, 34.27, 20.81, 17.82, 17.74.

HRMS (ESI) m/z cal. for $(M + H)^+$ 401.2045, found 401.2085

2.4.11. (E)-2-(dimethylamino)-*N*-((E)-1-mesityl-3-methyl-1,3-dihydro-2H-imidazol-2-ylidene)-2-oxoacetohydrazonoyl cyanide (11)



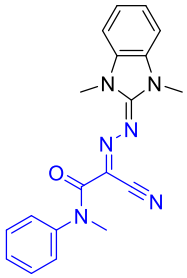
Synthesized according to the general procedure **2.4, A**, purified by column chromatography (ethyl acetate / petroleum ether). Isolated as yellow solid in 90 % yield (38 mg, 0.112 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.87 (s, 2H), 6.71 (s, 1H), 6.33 (s, 1H), 3.68 (s, 3H), 2.77 (d, J = 15.7 Hz, 3H), 2.41 – 2.22 (m, 3H), 1.98 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.96, 150.09, 138.97, 135.26, 134.74, 129.39, 129.05, 117.68, 117.51, 117.33, 113.83, 33.83, 30.12, 21.35, 18.38.

HRMS (ESI) m/z cal. for $(M + H)^+$ 339.1889, found 339.1895

2.4.12. (E)-*N*-(1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-ylidene)-2-(methyl(phenyl)amino)-2-oxoacetohydrazonoyl cyanide (12)



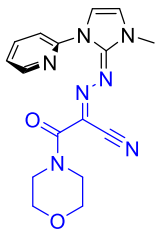
Synthesized according to the general procedure **2.4, A**, purified by column chromatography (ethyl acetate / petroleum ether). Isolated as yellow solid in 90 % yield (39 mg, 0.112 mmol).

^{1}H NMR (400 MHz, CDCl3) δ 7.38 (t, *J* = 8.0 Hz, 3H), 7.26 – 7.22 (m, 3H), 7.14 (m, 3H), 3.63 (s, 6H), 3.49 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.34, 144.33, 131.74, 131.69, 129.49, 129.10, 126.79, 126.62, 125.81, 123.11, 122.79, 119.05, 112.16, 108.82, 108.45, 38.79, 30.98.

HRMS (ESI) m/z cal. for $(M + H)^+$ 347.1576, found 347.1593

2.4.13. (E)-*N*-((E)-1-methyl-3-(pyridin-2-yl)-1,3-dihydro-2H-imidazol-2-ylidene)-2-morpholino-2-oxoacetohydrazonoyl cyanide (13)



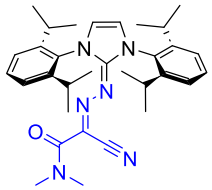
Synthesized according to the general procedure **2.4, A**, purified by column chromatography (ethyl acetate / petroleum ether). Isolated as yellow solid in 87 % yield (36.8 mg, 0.108 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 8.4 Hz, 1H), 8.46 – 8.41 (m, 1H), 7.87 (t, *J* = 8.0 Hz, 1H), 7.64 (s, 1H), 7.28 – 7.24 (m, 1H), 6.57 (s, 1H), 5.29 (DCM), 3.80 (s, 3H), 3.68 (m, 8H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.45, 150.06, 148.50, 147.76, 138.52, 122.14, 118.44, 116.13, 113.54, 113.45, 77.16, 77.04, 76.84, 76.52, 66.70, 37.32, 29.50.

HRMS (ESI) m/z cal. for $(M + H)^+$ 340.1477, found 340.1490

2.4.14. (E)-*N*-(1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene)-2-(dimethylamino)-2-oxoacetohydrazonoyl cyanide (14)



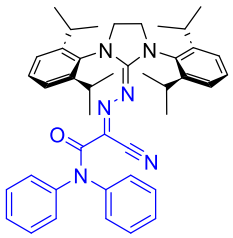
Synthesized according to the general procedure **2.4, A**, purified by column chromatography (ethyl acetate / petroleum ether). Isolated as yellow solid in 84 % yield (55.2 mg, 0.105 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 4H), 6.62 (s, 1H), 2.76 (m, 6H), 2.06 (s, 2H), 1.27 – 1.21 (m, 12H), 1.20 – 1.14 (m, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.55, 151.13, 145.98, 133.23, 132.90, 130.07, 124.18, 123.91, 118.32, 117.69, 112.58, 37.09, 33.88, 29.17, 29.15, 24.22, 23.89, 23.35, 23.08.

HRMS (ESI) m/z cal. for $(M + H)^+$ 527.3454, found 527.3484

2.4.15. (E)-*N*-(1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene)-2-(diphenylamino)-2-oxoacetohydrazonoyl cyanide (15)



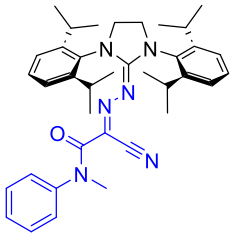
Synthesized according to the general procedure **2.4, A**, purified by column chromatography (ethyl acetate / petroleum ether). Isolated as yellow solid in 70 % yield (57 mg, 0.087 mmol), when 2 equiv. of diazo compound were used.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (t, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 7.6 Hz, 4H), 7.13 (d, *J* = 4.6 Hz, 6H), 6.98 – 6.54 (m, 4H), 3.97 (s, 4H), 3.06 (m, 3H), 1.32-1.27 (m, 12H), 1.15-1.08 (m, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.78, 159.71, 146.63, 135.01, 129.15, 129.02, 128.92, 127.25, 126.52, 124.18, 123.73, 116.23, 50.37, 29.85, 29.18, 24.77, 23.82.

HRMS (ESI) m/z cal. for $(M + H)^+$ 653.3923, found 653.3931

2.4.16. (E)-N-(1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene)-2-(methyl(phenyl)amino)-2-oxoacetohydrazonoyl cyanide (16)



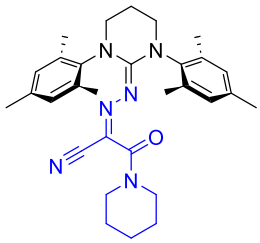
Synthesized according to the general procedure **2.4, A**, purified by column chromatography (ethyl acetate / petroleum ether). Isolated as yellow oil in 75 % yield (55 mg, 0.093 mmol), when 2 equiv. of diazo compound were used.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 16.3, 8.0 Hz, 2H), 7.27 (q, *J* = 10.3, 9.3 Hz, 5H), 7.09 (d, *J* = 7.9 Hz, 2H), 6.62 (d, *J* = 8.4 Hz, 2H), 4.09 – 3.96 (m, 4H), 3.19 – 2.76 (m, 8H), 1.40 – 1.34 (m, 12H), 1.22 (m, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.20, 146.69, 146.25, 141.44, 134.51, 128.85, 128.73, 128.60, 128.48, 126.97, 126.01, 125.58, 123.92, 123.69, 115.96, 110.97, 49.59, 36.19, 28.88, 28.84, 24.35, 24.02, 23.72, 23.49, 23.31.

HRMS (ESI) m/z cal. for $(M + H)^+$ 591.3767, found 591.3787

2.4.17. (E)-*N*-(1,3-dimesityltetrahydropyrimidin-2(1H)-ylidene)-2-oxo-2-(piperidin-1-yl)acetohydrazonoyl cyanide (17)



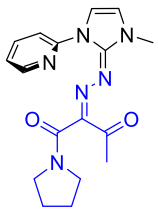
Synthesized according to the general procedure **2.4, A**, purified by column chromatography (ethyl acetate / petroleum ether). Isolated as yellow solid in 87 % yield (54 mg, 0.108 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 1H), 3.60 (t, *J* = 6.1 Hz, 4H), 3.46 (s, 2H), 3.23 – 3.19 (m, 2H), 2.39 (s, 2H) 2.26 (m, 24H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.87, 154.85, 139.72, 137.08, 134.37, 130.06, 129.31, 129.22, 117.85, 112.27, 66.92, 49.06, 30.44, 23.06, 21.03, 18.90, 18.42, 18.29.

HRMS (ESI) m/z cal. for $(M + H)^+$ 499.3141, found 499.3150

2.4.18. (E)-2-(((E)-1-methyl-3-(pyridin-2-yl)-1,3-dihydro-2H-imidazol-2-ylidene)hydrazineylidene)-1-(pyrrolidin-1-yl)butane-1,3-dione (18)



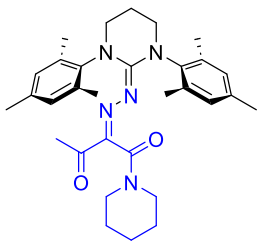
Synthesized according to the general procedure **2.4, A**, purified by column chromatography (ethyl acetate / petroleum ether). Isolated as yellow solid in 90 % yield (38 mg, 0.112 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.47 (d, *J*=8.4, 1H), 8.41 (d, *J*=4.8, 1H), 7.72 (t, *J*=8.1, 1H), 7.54 (s, 1H), 7.17 (t, *J*=6.2, 1H), 6.44 (s, 1H), 4.12 (q, *J*=7.9, 7.3, 2H), 3.90 (s, 3H), 3.68 (m, 2H), 3.20 (m, 2H), 2.32 (s, 3H), 2.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.51, 166.74, 150.64, 149.48, 149.28, 147.90, 137.98, 121.61, 118.40, 118.08, 112.29, 45.74, 45.09, 38.30, 25.83, 25.22, 24.66.

HRMS (ESI) m/z cal. for $(M + H)^+$ 341.1681, found 341.1692

2.4.19. (E)-2-((1,3-dimesityltetrahydropyrimidin-2(1H)-ylidene)hydrazineylidene)-1-morpholinobutane-1,3-dione (19)



Synthesized according to the general procedure **2.4, A**, purified by column chromatography (ethyl acetate / petroleum ether). Isolated as yellow solid in 90 % yield (58 mg, 0.112 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 2H), 6.85 (s, 2H), 3.72 (m, 2H), 3.62 – 3.49 (m, 2H), 3.43 – 3.37 (m, 4H), 3.14 (t, *J* = 9.8 Hz, 1H), 2.87 (m, 2H), 2.65 – 2.49 (m, 1H), 2.33 – 2.16 (m, 23H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.90, 166.32, 155.10, 147.00, 140.92, 136.76, 135.59, 133.39, 129.43, 129.32, 129.24, 66.58, 66.21, 49.09, 44.99, 40.63, 24.16, 23.32, 20.93, 18.60, 18.46, 18.21.

HRMS (ESI) m/z cal. for $(M + H)^+$ 518.3086, found 518.3092

2.4.20. (E)-2-((1,3-dicyclohexyl-1,3-dihydro-2H-imidazol-2-ylidene)hydrazineylidene)-1-(piperidin-1-yl)butane-1,3-dione (20)

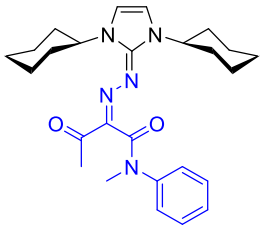
Synthesized according to the general procedure **2,4 A**, purified by column chromatography (ethyl acetate / petroleum ether). Isolated as yellow solid in 85 % yield (45 mg, 0.106 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (s, 2H), 4.76 (td, *J* = 11.6, 3.6 Hz, 2H), 3.83 – 3.43 (m, 2H), 3.19 (q, *J* = 4.6 Hz, 2H), 2.37 (s, 2H), 2.13 – 1.29 (m, 24H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.25, 166.84, 148.66, 144.88, 113.85, 111.39, 54.81, 46.84, 41.49, 32.92, 32.50, 29.47, 29.43, 26.63, 25.47, 25.37, 25.34, 25.06, 24.69.

HRMS (ESI) m/z cal. for $(M + H)^+$ 428.2981, found 428.2991

2.4.21.(E)-2-((1,3-dicyclohexyl-1,3-dihydro-2H-imidazol-2-ylidene)hydrazineylidene)-*N*-methyl-3-oxo-N-phenylbutanamide (21)



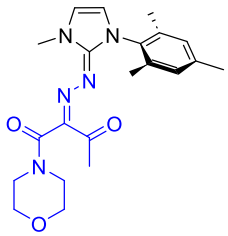
Synthesized according to the general procedure **2.4, A**, purified by column chromatography (ethyl acetate / petroleum ether). Isolated as yellow solid in 90 % yield (50 mg, 0.112 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.23 (m, 2H), 7.19 – 7.15 (m, 3H), 6.56 (s, 2H), 4.59 – 4.49 (m, 2H), 3.39 (d, *J* = 2.8 Hz, 3H), 2.12 – 2.02 (m, 3H), 1.96 – 1.74 (m, 6H), 1.44 – 1.21 (m, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.01, 168.64, 148.95, 145.78, 143.40, 128.28, 127.18, 125.85, 111.74, 55.24, 35.75, 33.22, 32.82, 25.67, 25.58, 25.38, 24.59.

HRMS (ESI) m/z cal. for $(M + H)^+$ 450.2824, found 450.2840

2.4.22.(E)-2-(((E)-1-mesityl-3-methyl-1,3-dihydro-2H-imidazol-2-ylidene)hydrazineylidene)-1-morpholinobutane-1,3-dione (22)



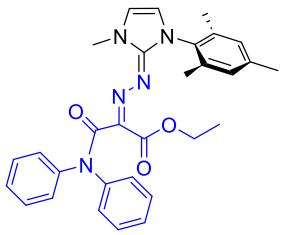
Synthesized according to the general procedure **2.4, A**, purified by column chromatography (ethyl acetate / petroleum ether). Isolated as yellow solid in 90 % yield (44 mg, 0.112 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 2H), 6.65 (s, 1H), 6.36 (s, 1H), 3.72 – 3.30 (m, 12H), 3.10 (s, 2H), 2.28 (s, 3H), 2.04 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.88, 166.49, 145.75, 138.65, 134.94, 134.73, 129.59, 129.07, 116.87, 116.46, 67.45, 66.82, 46.40, 41.45, 34.01, 29.79, 23.95, 21.00, 18.05.

HRMS (ESI) m/z cal. for $(M + H)^+$ 398.2147, found 398.2162

2.4.23. Ethyl-(Z)-3-(diphenylamino)-2-(((E)-1-mesityl-3-methyl-1,3-dihydro-2H-imidazol-2-ylidene)hydrazineylidene)-3-oxopropanoate (23)



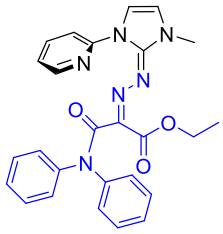
Synthesized according to the general procedure **2.4, A**, purified by column chromatography (ethyl acetate / petroleum ether). Isolated as yellow solid in 85 % yield (54 mg, 0.106 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.22 (t, *J*=7.7, 2H), 7.13 (t, *J*=7.5, 2H), 7.08 (t, *J*=7.4, 2H), 7.00 (d, *J*=7.3, 2H), 6.95 (m, 4H), 6.44 (d, *J*=2.4, 1H), 6.35 (d, *J*=2.4, 1H), 4.21 (m, *J*=27.3, 2H), 3.75 (s, 3H), 2.27 (s, 3H), 2.10 (s, 6H), 1.26 (t, *J*=7.1, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.07, 163.97, 150.87, 142.48, 142.13, 138.79, 136.83, 135.36, 133.14, 129.22, 128.67, 128.35, 127.49, 127.43, 126.93, 126.06, 118.00, 114.91, 60.18, 36.78, 29.81, 21.18, 18.23, 15.05.

HRMS (ESI) m/z cal. for $(M + H)^+$ 510.2427, found 510.2435

2.4.24.Ethyl-(Z)-3-(diphenylamino)-2-(((E)-1-methyl-3-(pyridin-2-yl)-1,3-dihydro-2H-imidazol-2-ylidene)hydrazineylidene)-3-oxopropanoate (24)



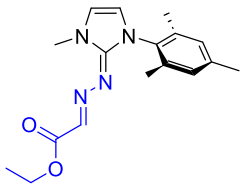
Synthesized according to the general procedures **2.4, A** and **B**. When procedure **A** was used, the product was purified by column chromatography (ethyl acetate / petroleum ether). Isolated as yellow solid in 90 % yield (52 mg, 0.112 mmol). When procedure **B** was used, no column chromatography was used.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 – 8.56 (m, 1H), 8.33 – 8.27 (m, 1H), 7.67 – 7.48 (m, 3H), 7.48 – 7.41 (m, 2H), 7.40 – 7.28 (m, 3H), 7.28 – 7.16 (m, 2H), 7.16 – 6.97 (m, 4H), 6.27 (d, *J* = 2.7 Hz, 1H), 4.15 – 4.11 (m, 2H), 3.55 (s, 3H), 1.22 – 1.09 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.75, 163.30, 151.07, 149.26, 147.87, 142.40, 141.77, 138.99, 138.42, 132.27, 132.06, 128.92, 128.78, 128.67, 128.58, 128.03, 127.53, 126.05, 121.46, 118.40, 117.92, 111.89, 60.61, 38.16, 29.82, 14.55.

HRMS (ESI) m/z cal. for $(M + H)^+$ 469.1943, found 469.1952

2.4.25. Ethyl (E)-2-(((E)-1-mesityl-3-methyl-1,3-dihydro-2H-imidazol-2-ylidene)hydrazineylidene)acetate (25)



Synthesized according to the general procedure **2.4, B**. This product is already published in our group's previous work.[13] Isolated as a yellow solid in 90 % yield (42 mg, 0.135 mmol).

^{1}H NMR (400 MHz $CDCl_3$) δ 7.24 (s, 1H,) 6.90 (s, 2H), 6.48 (d, J = 2.5 Hz, 1H), 6.27 (d, J = 2.5 Hz, 1H), 3.73 (s, 3H), 3.60 (s, 3H), 2.31 (s, 3H), 2.04 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 152.1, 138.2, 135.5, 134.1, 132.1, 128.9, 117.1, 115.4, 51.0, 35.4, 21.2, 18.1

3. NMR Spectra

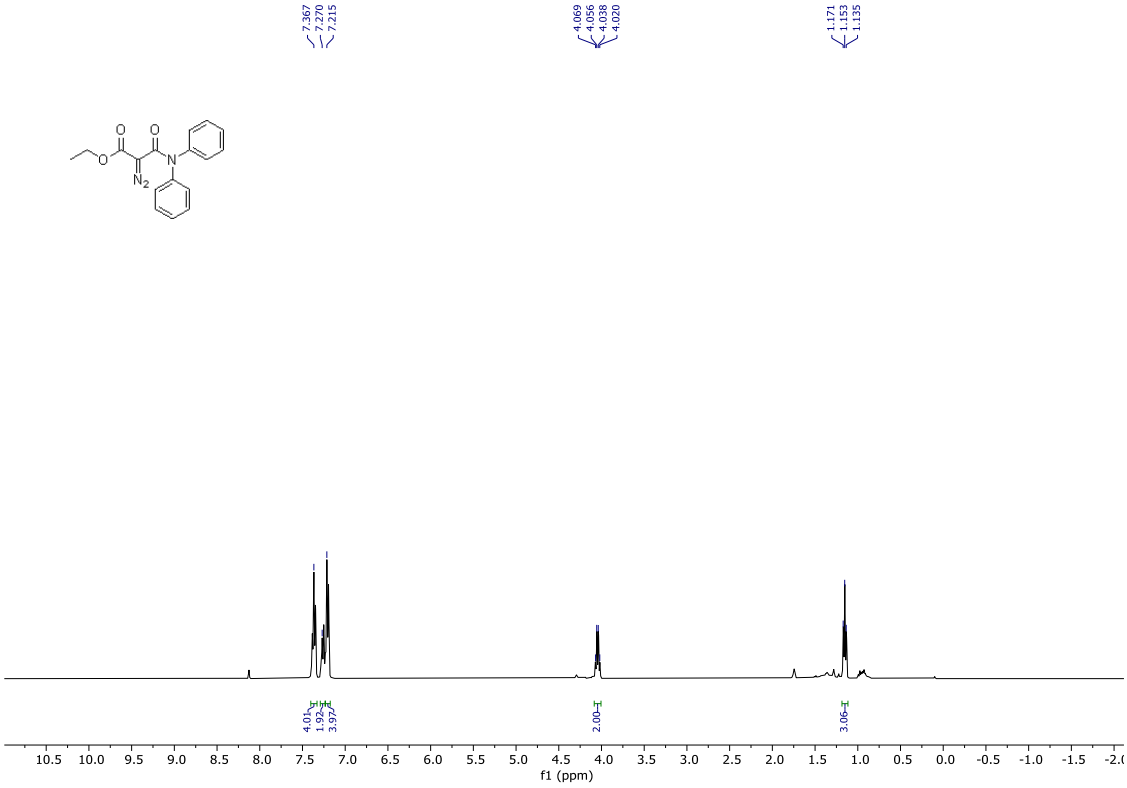


Figure S1. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **A**.

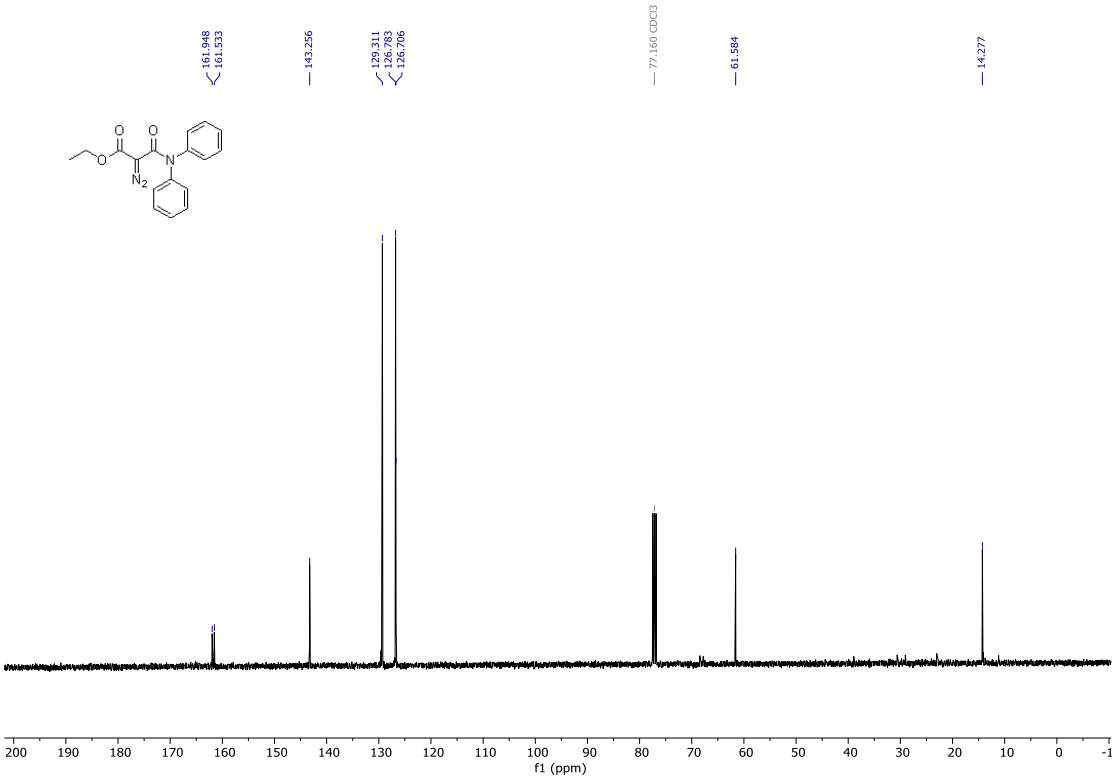


Figure S2. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **A**.

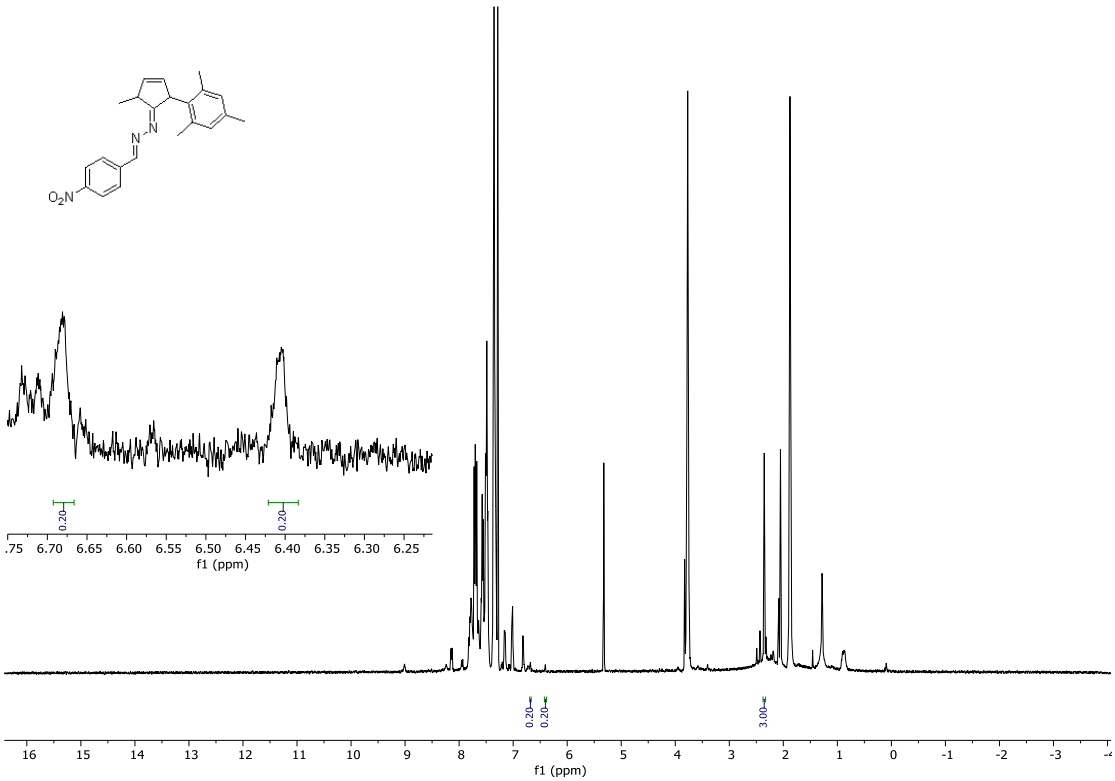


Figure S3. Crude ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **S2**.

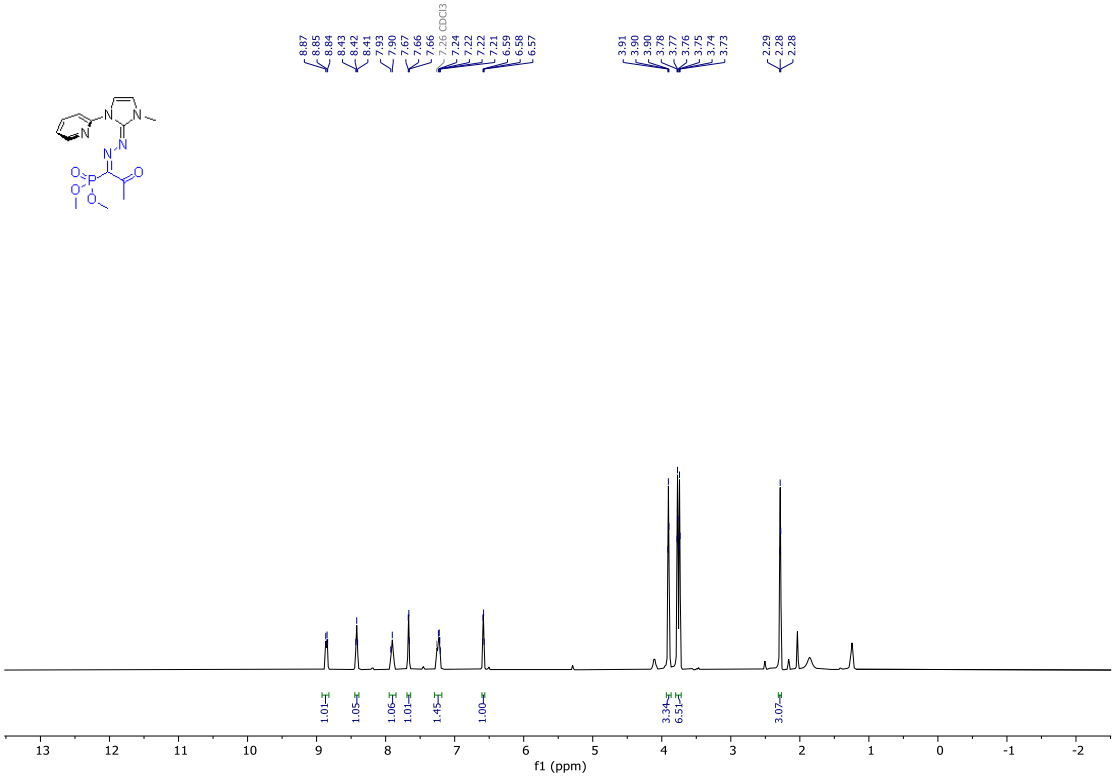


Figure S4. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **1**.

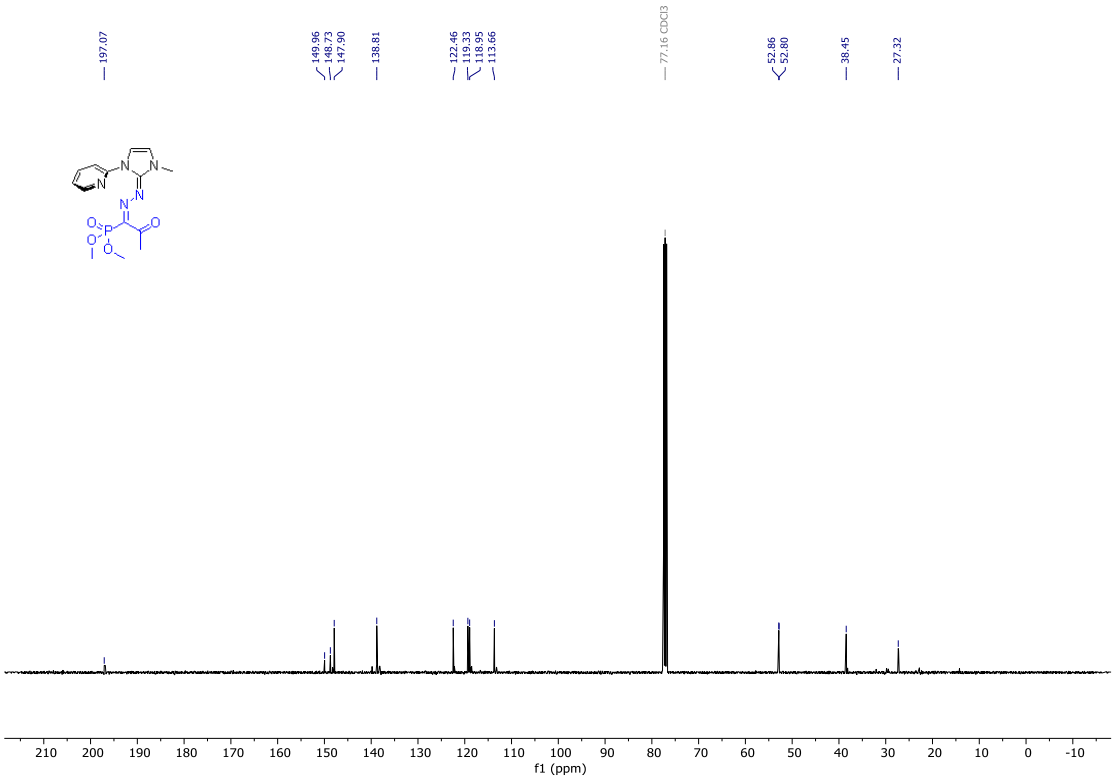


Figure S5. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **1**.

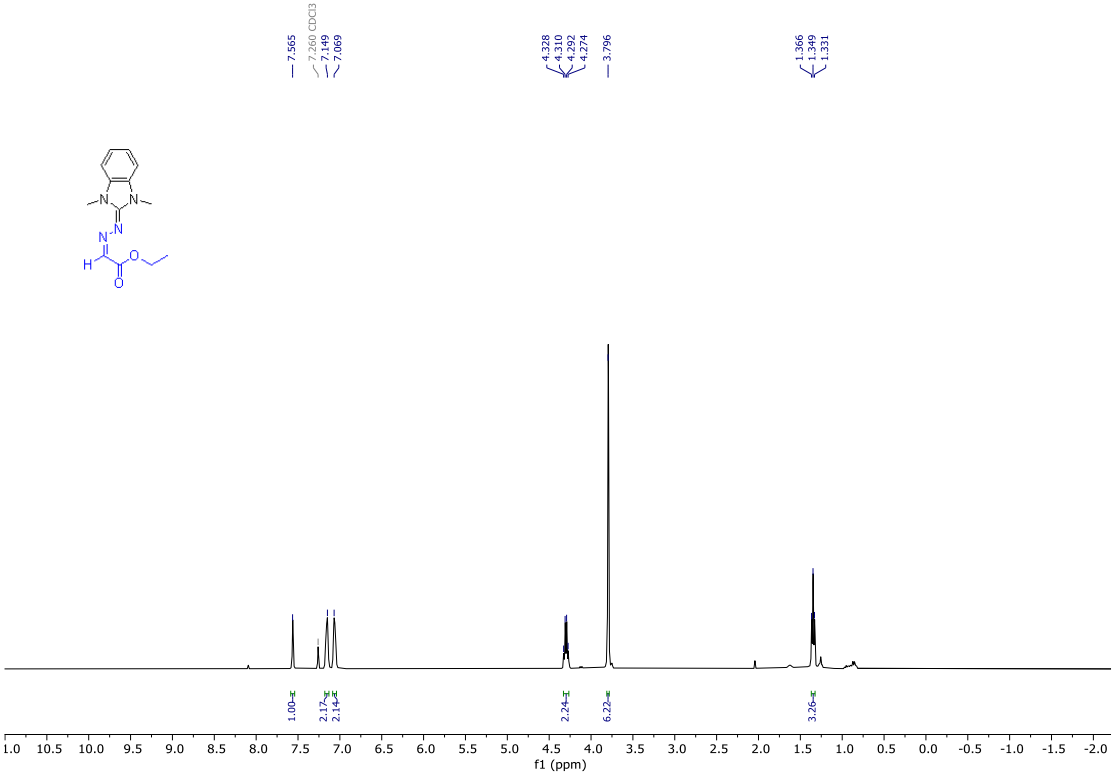


Figure S6. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **2**.

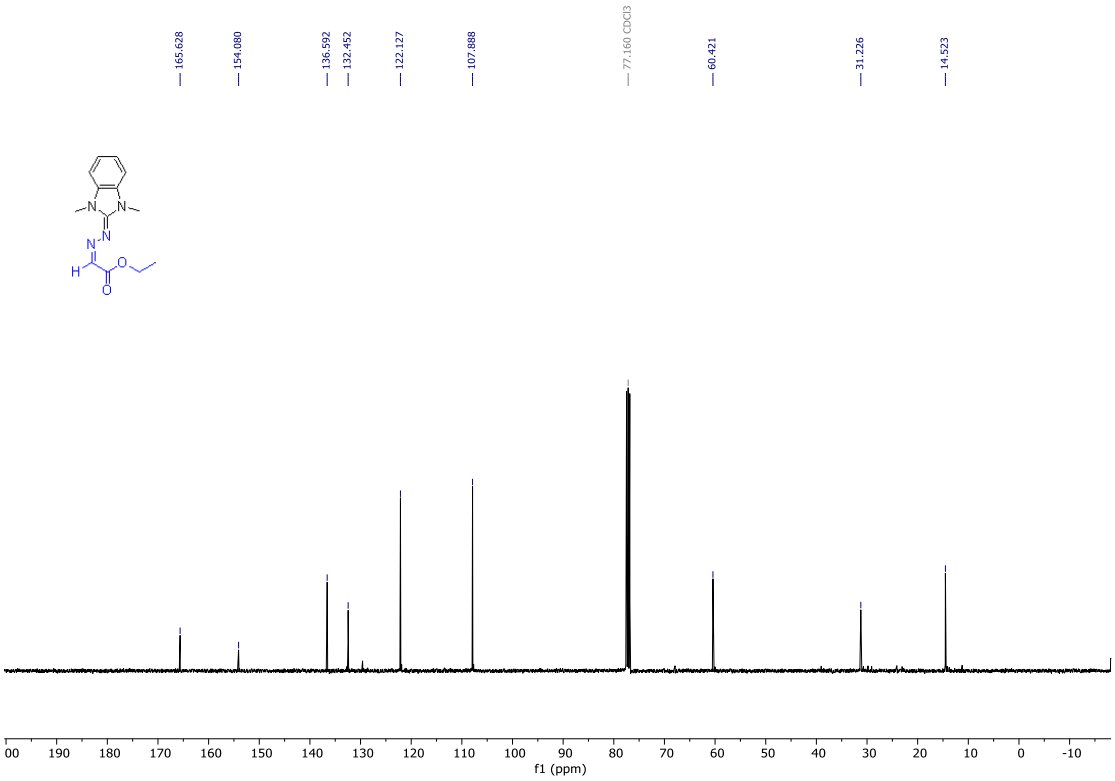


Figure S7. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **2**.

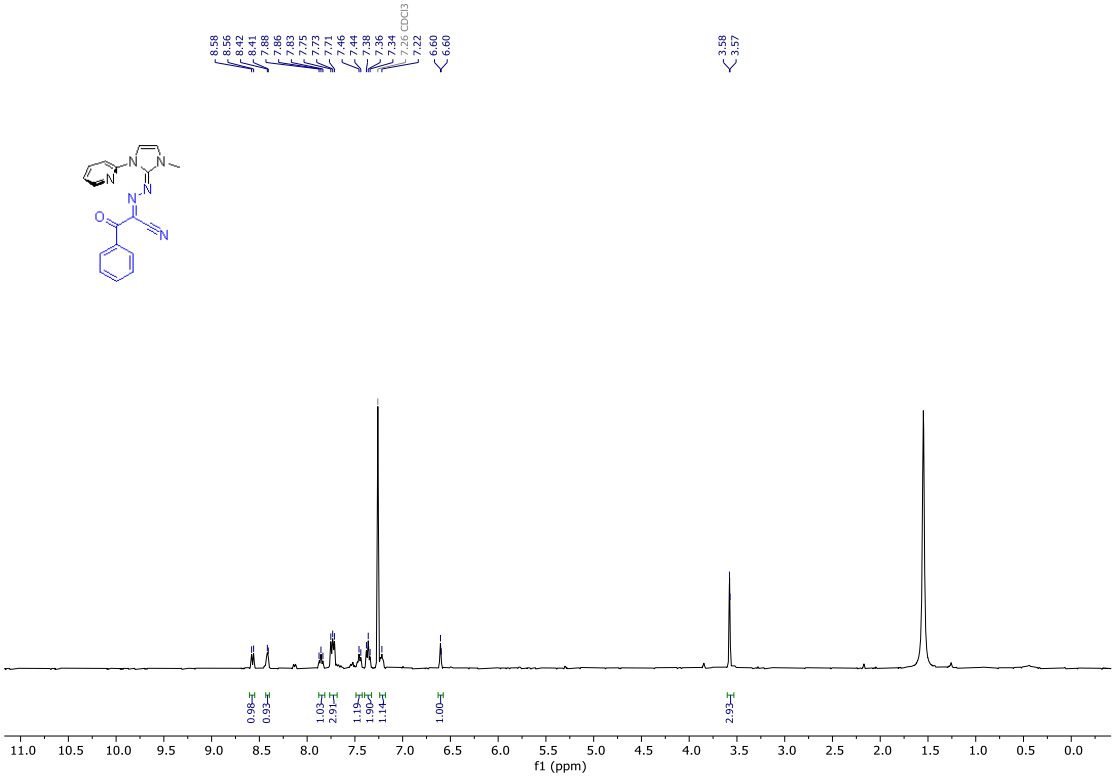


Figure S8. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **3**.

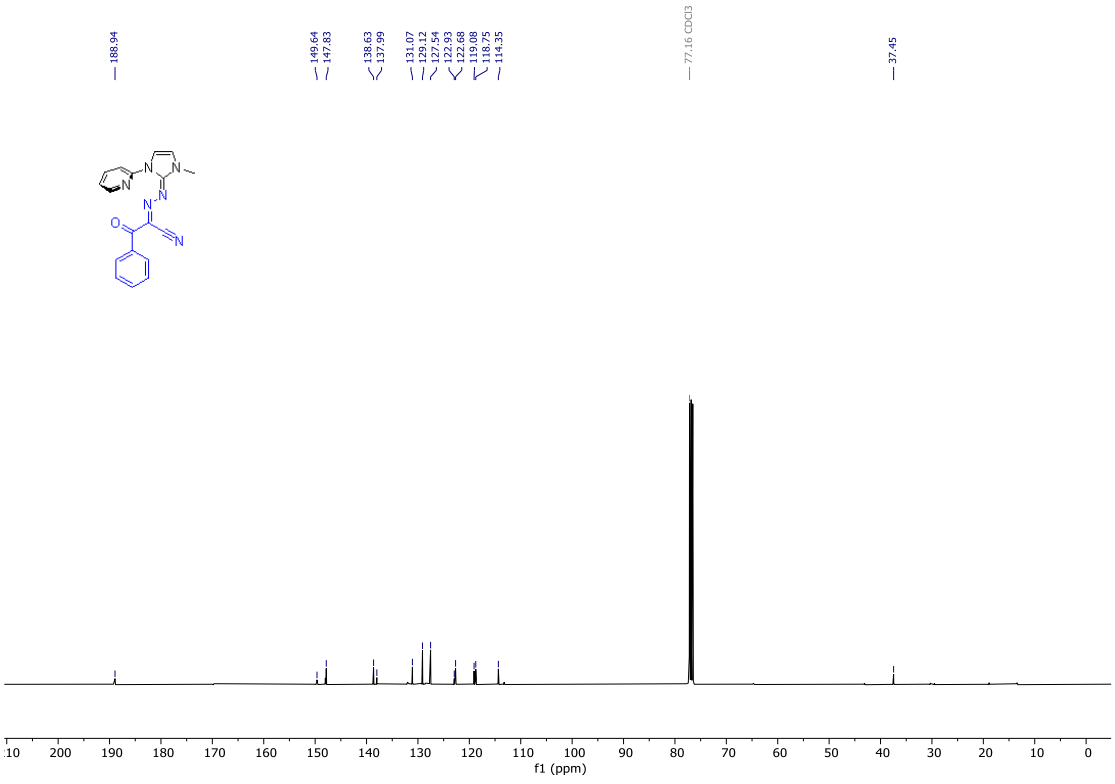


Figure S9. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **3**.

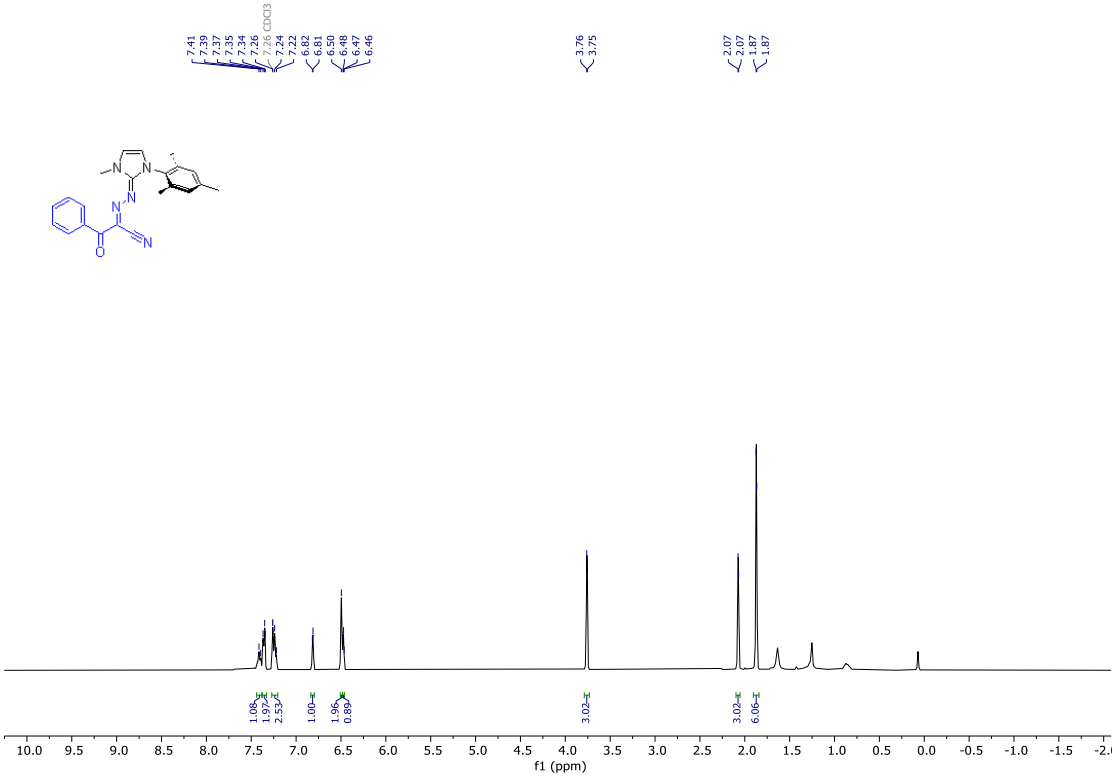


Figure S10. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **4**.

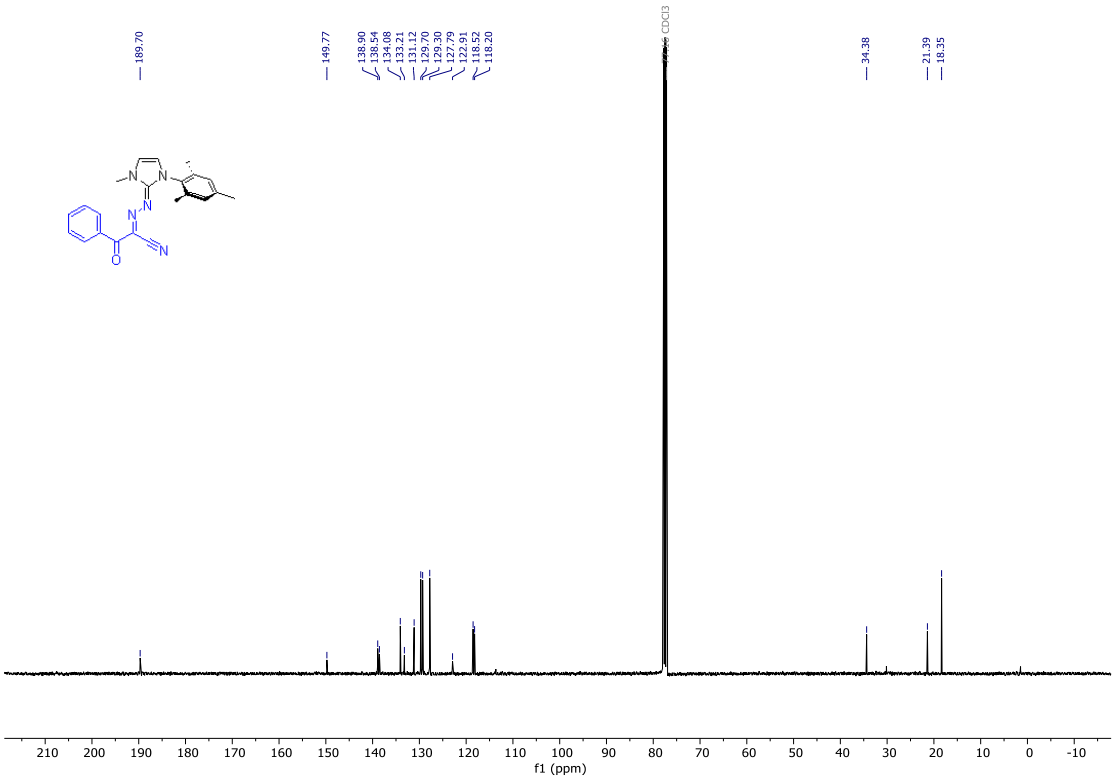


Figure S11. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **4**.

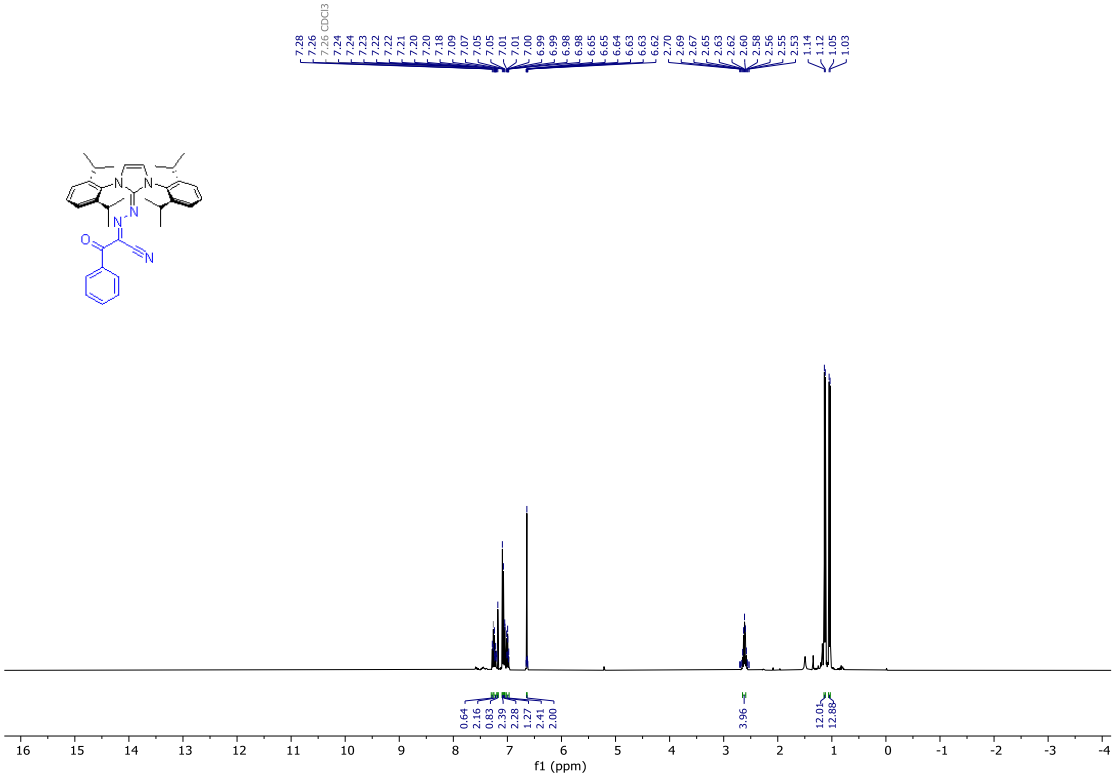


Figure S12. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5**.

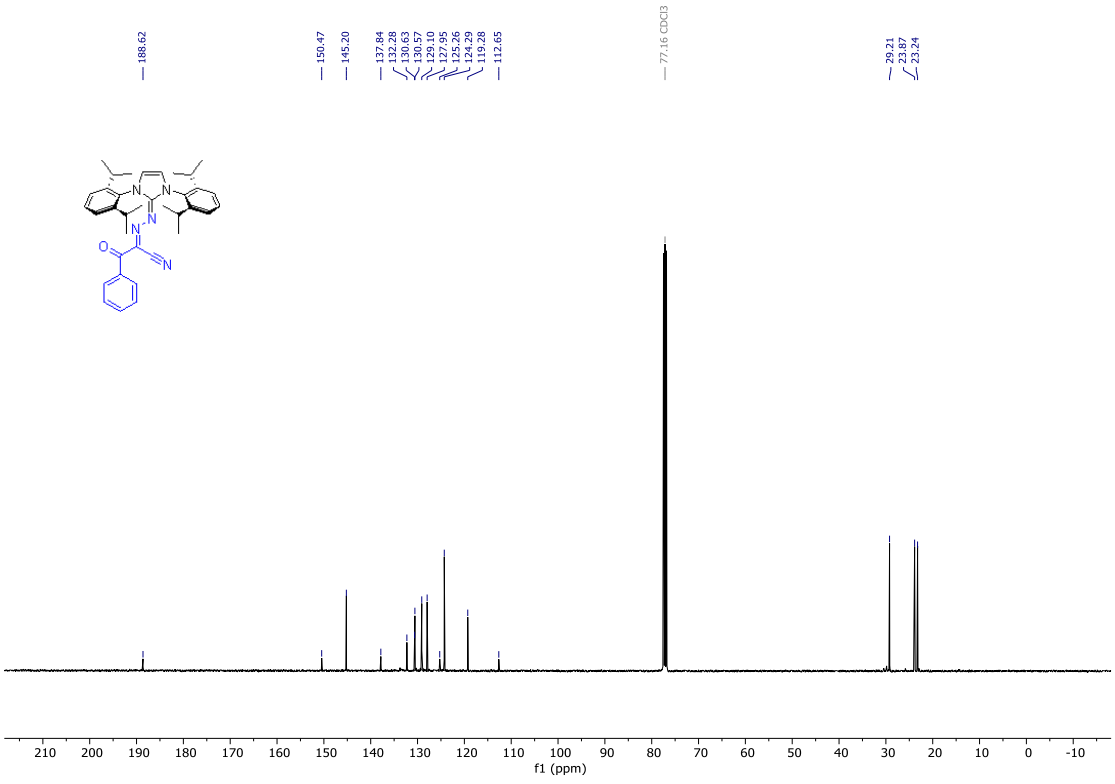


Figure S13. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5**.

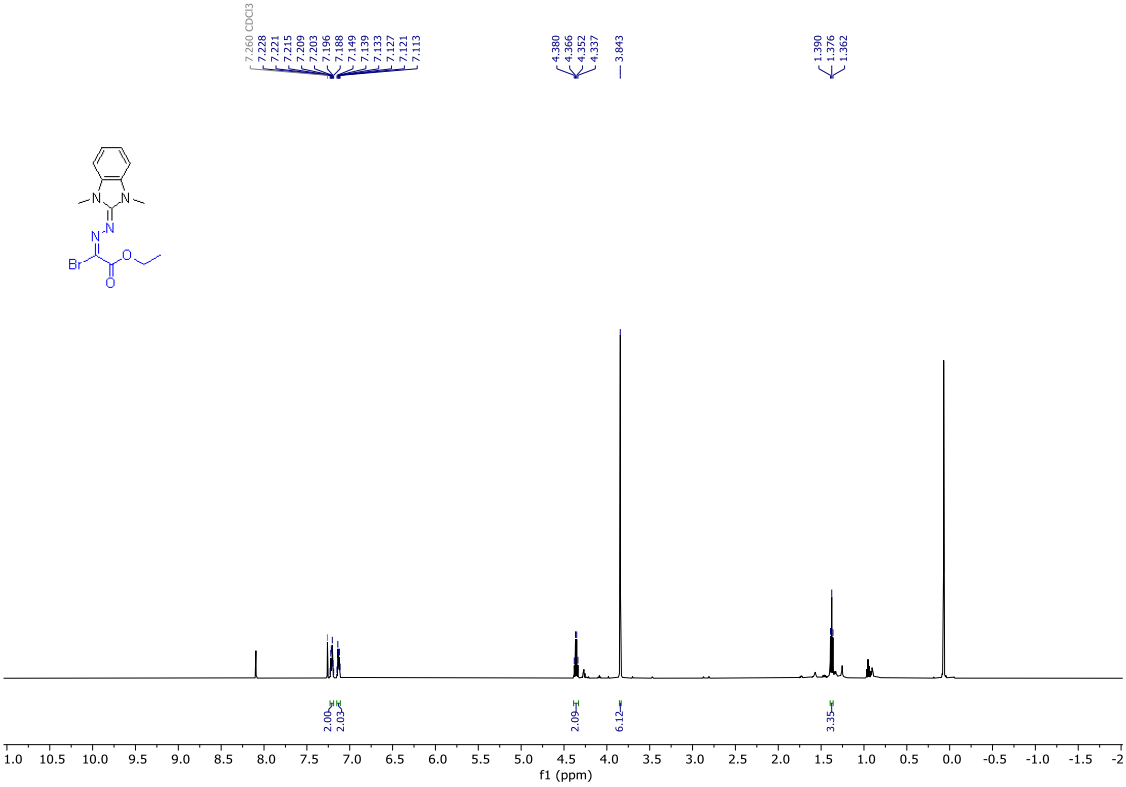


Figure S14. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **6**.

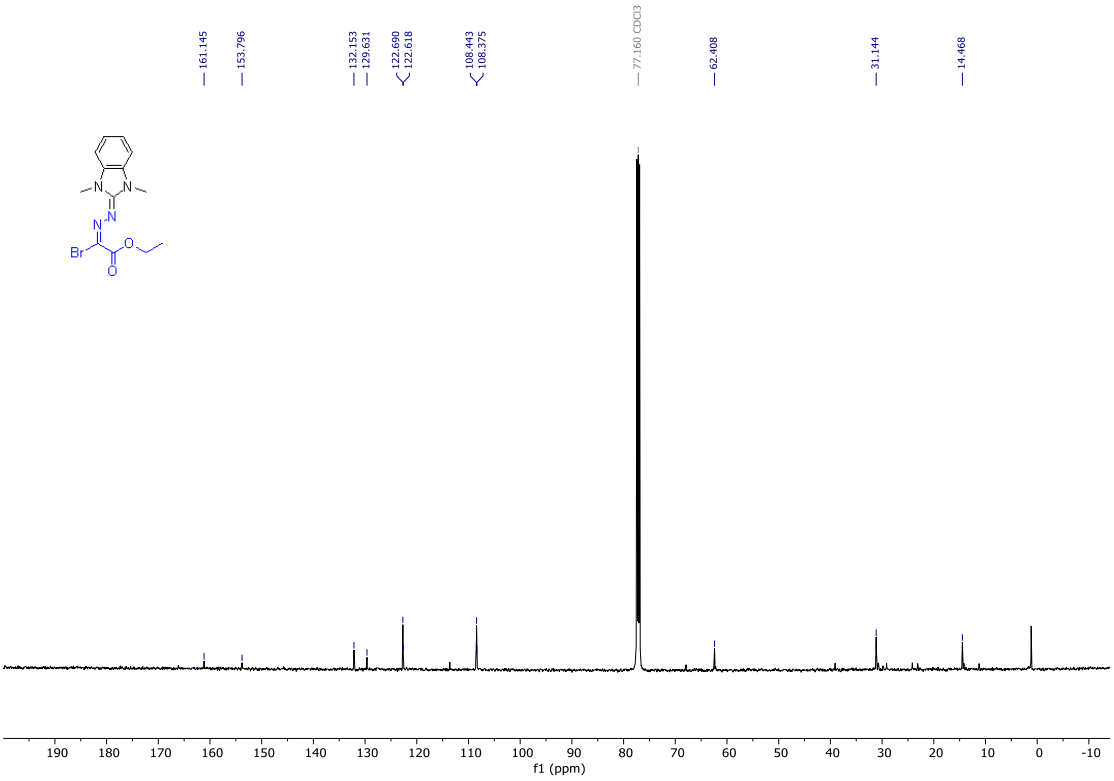


Figure S15. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **6**.

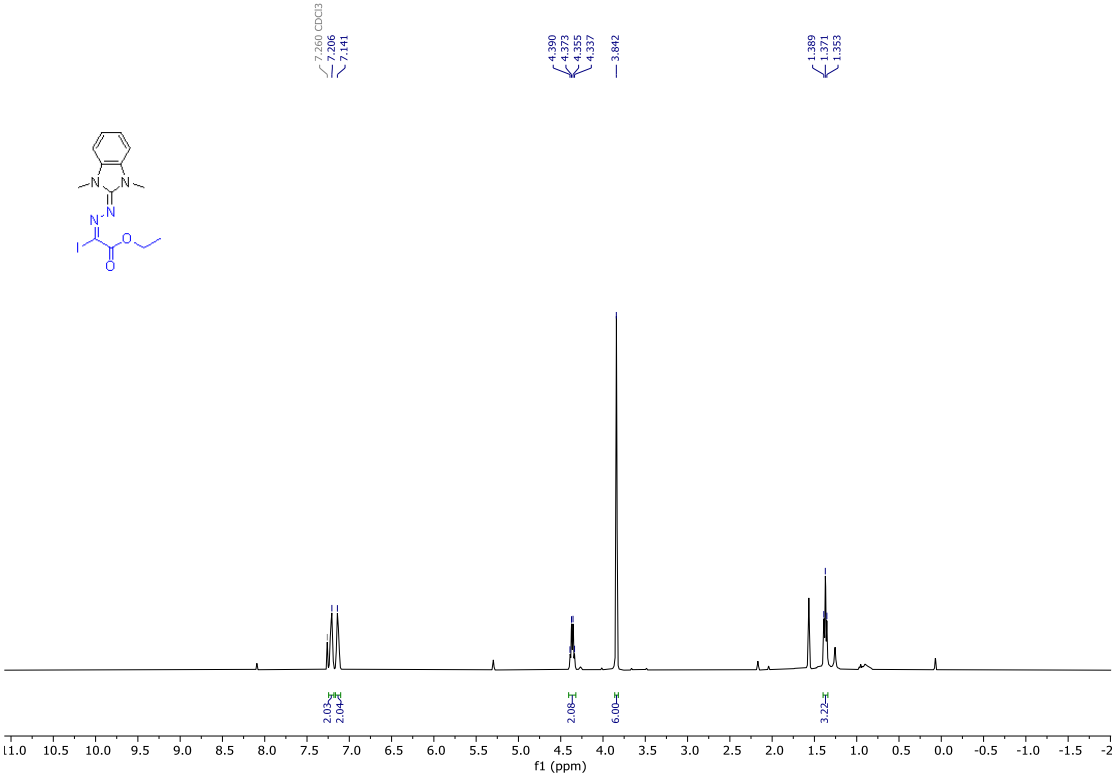


Figure S16. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7**.

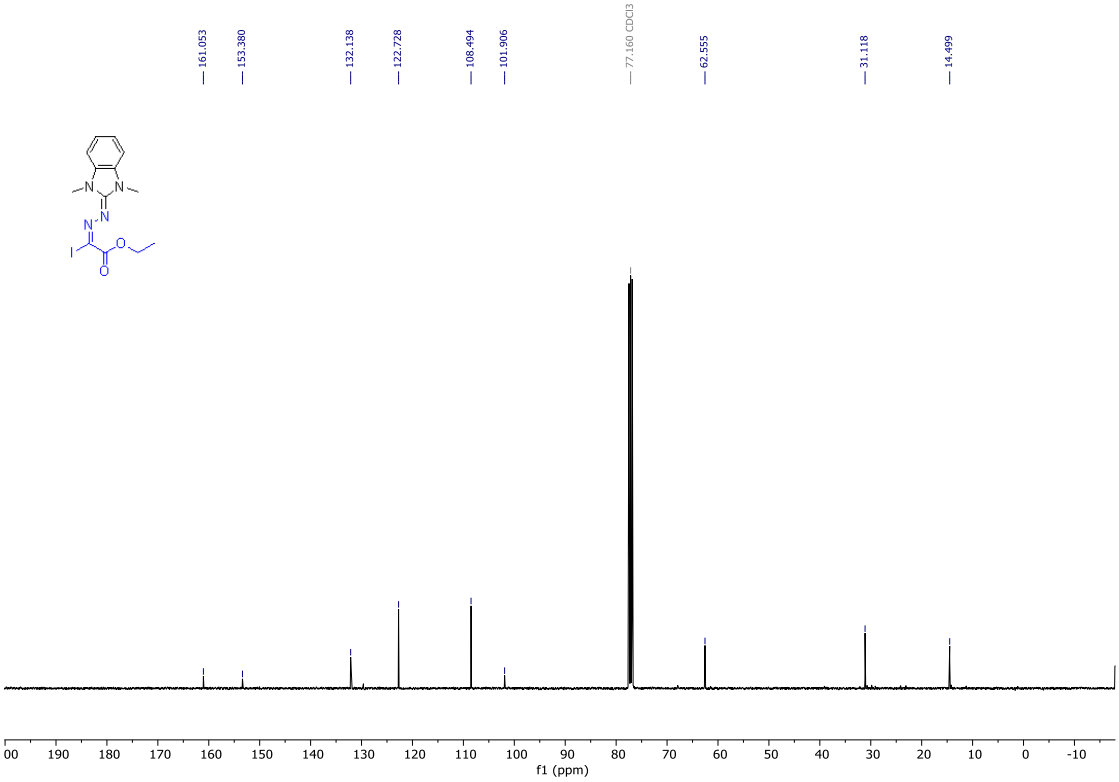


Figure S17. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **7**.

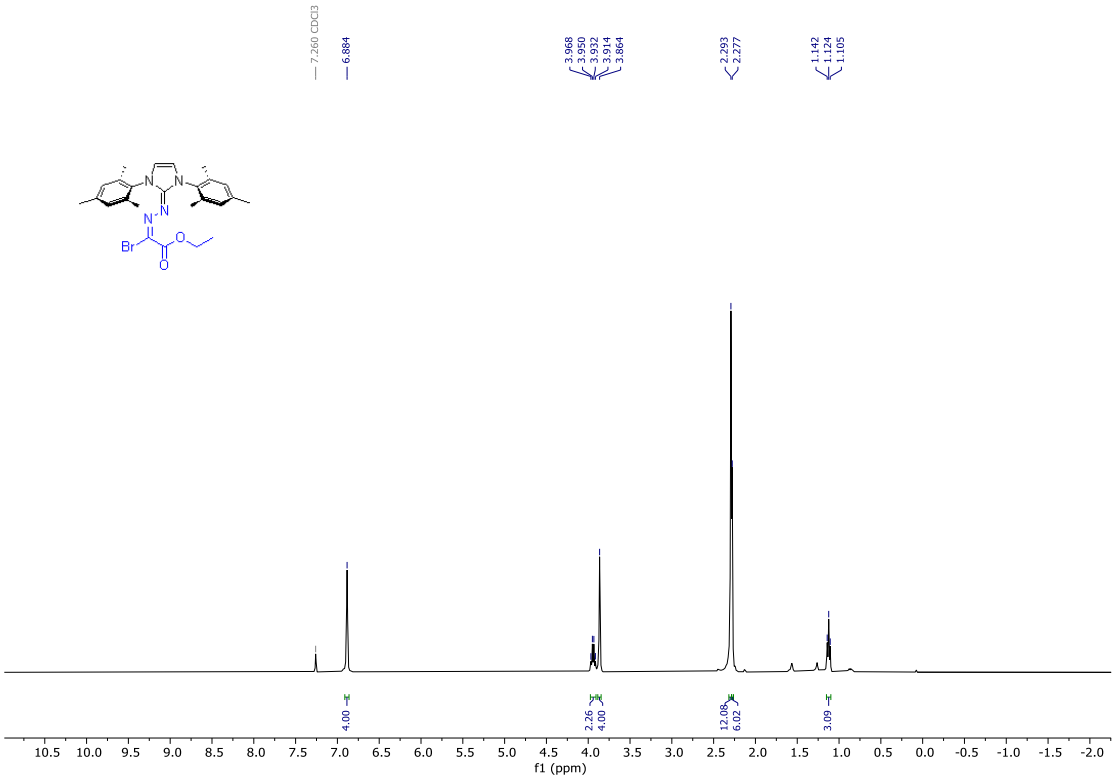


Figure S18. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **8**.

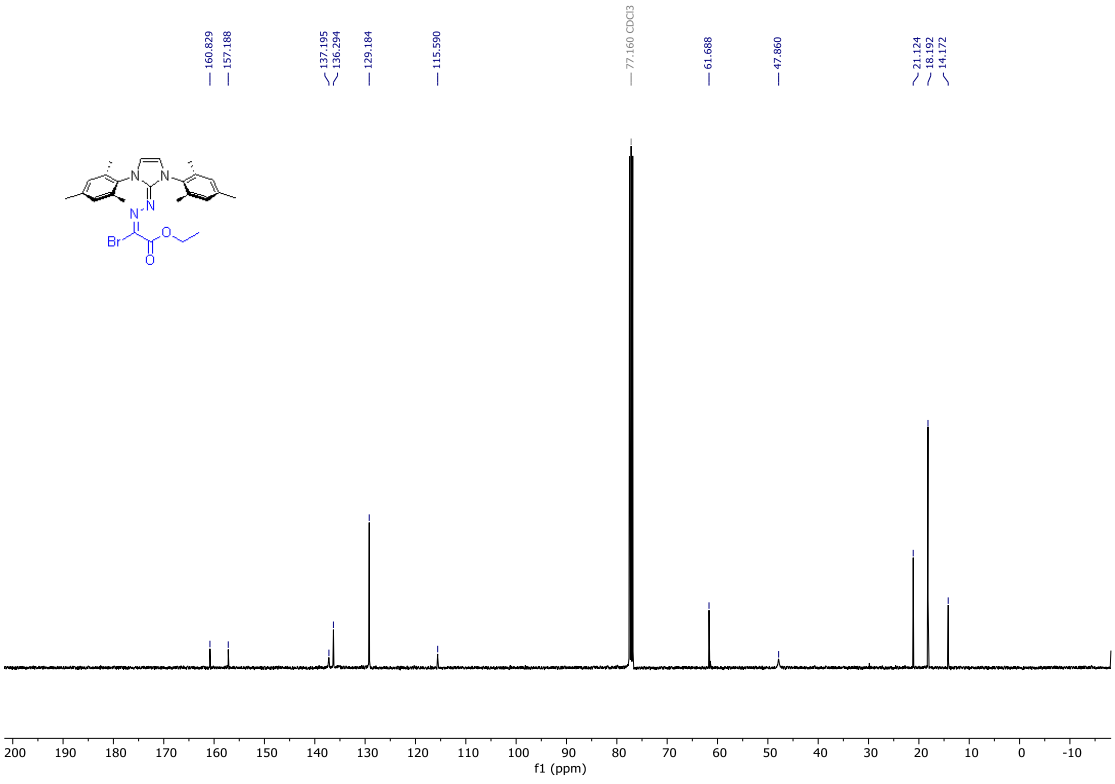


Figure S19. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **8**.

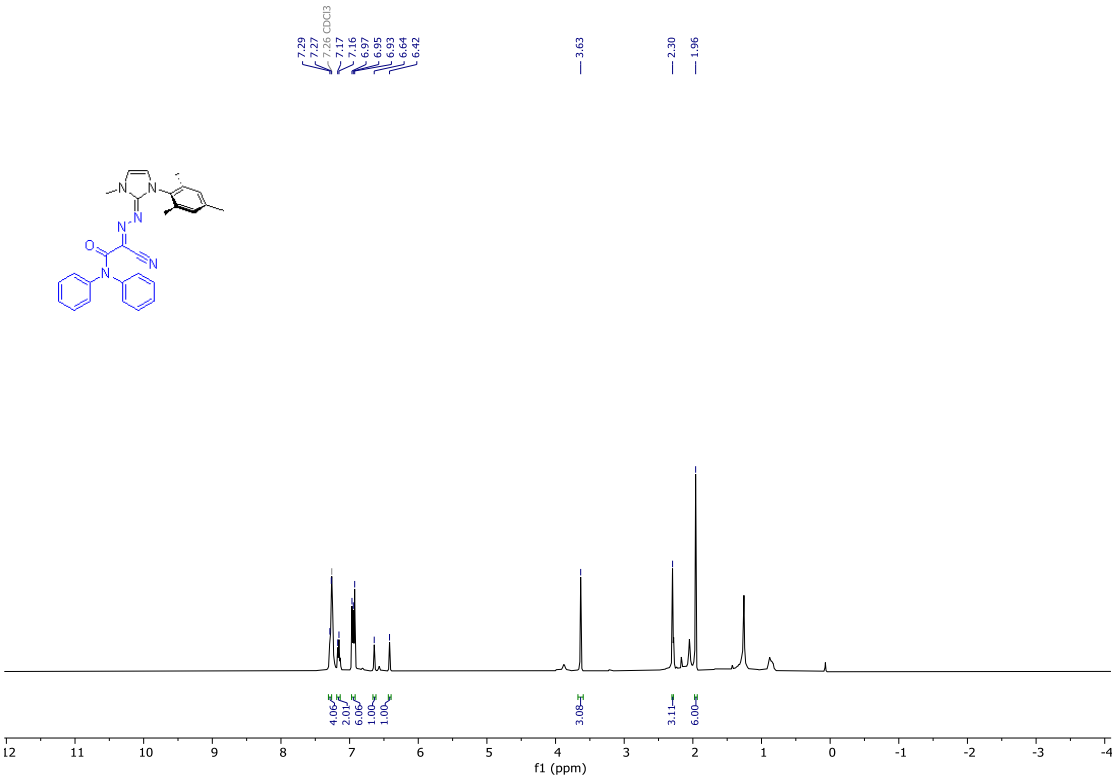


Figure S20. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **9**.

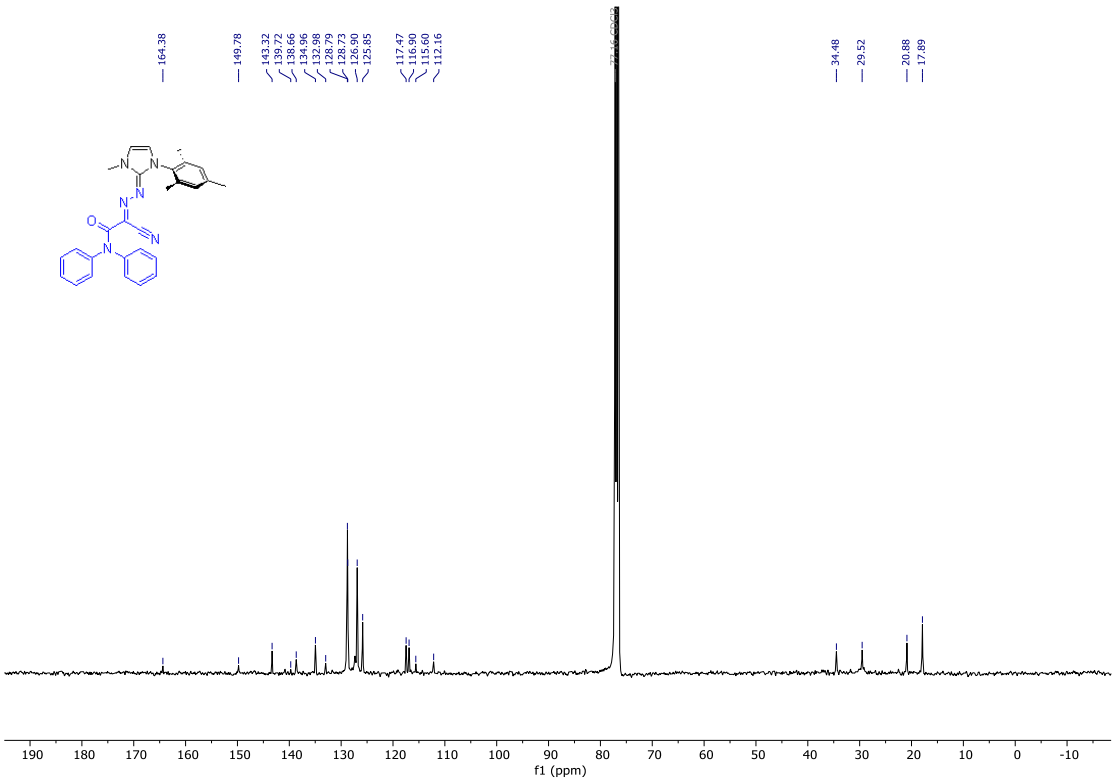


Figure S21. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **9**.

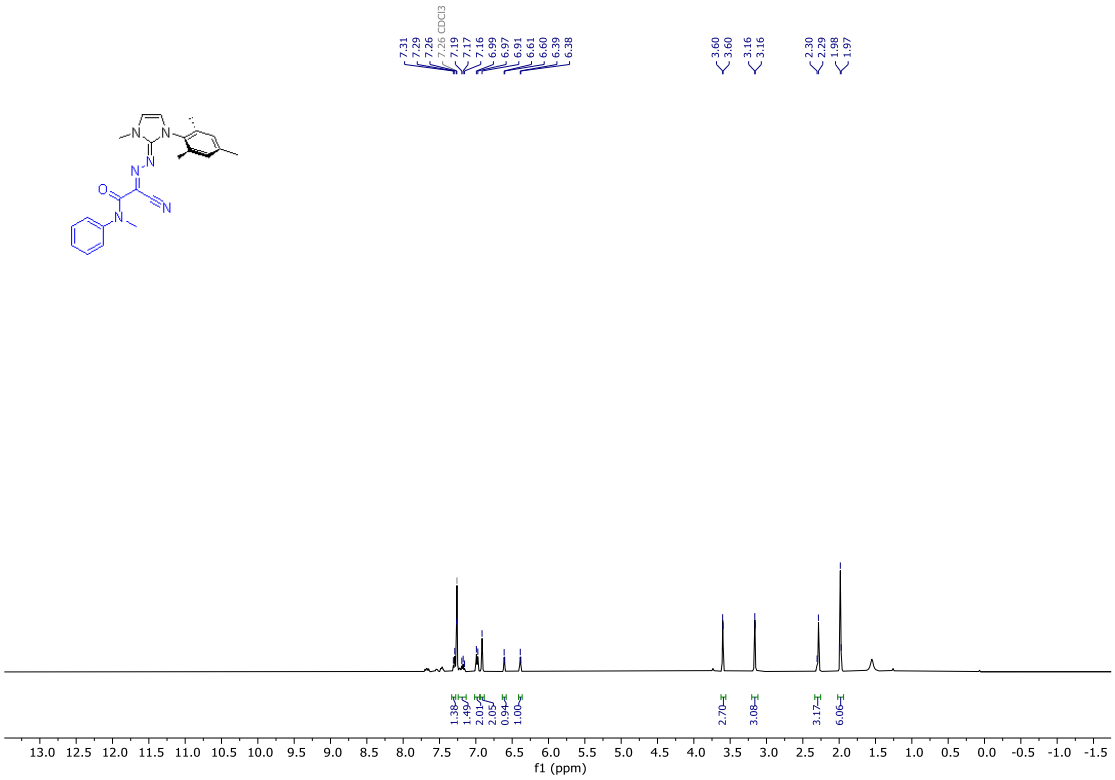


Figure S22. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **10**.

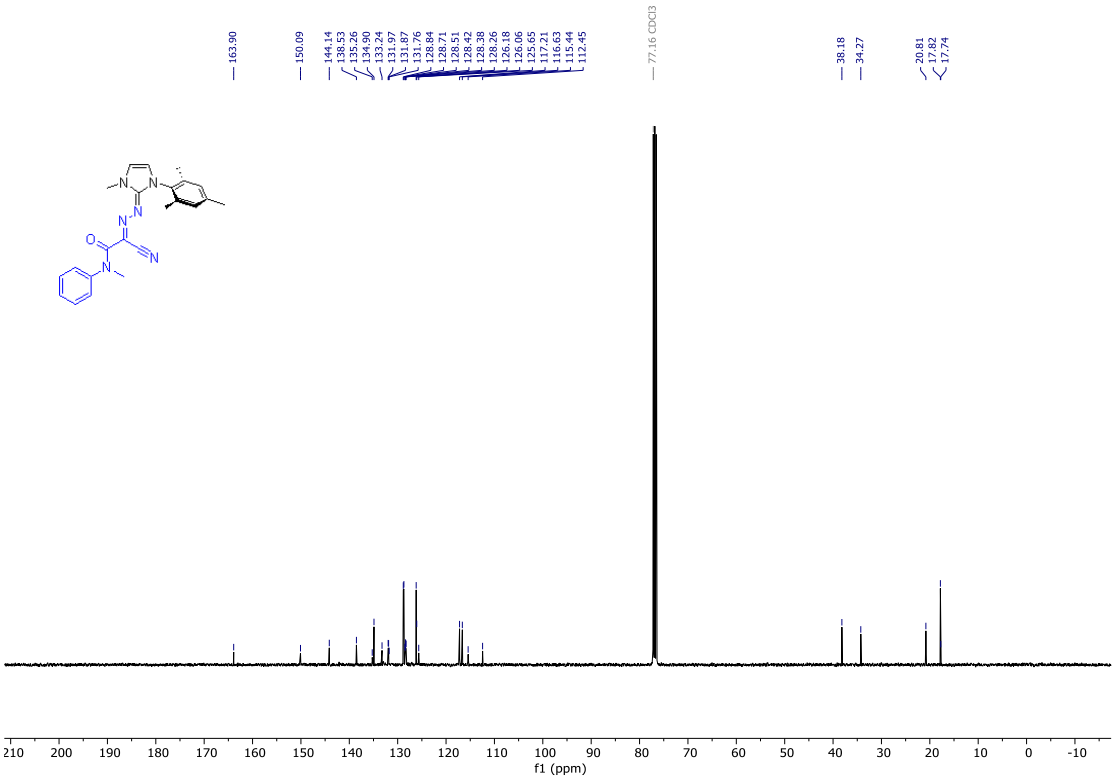


Figure S23. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **10**.

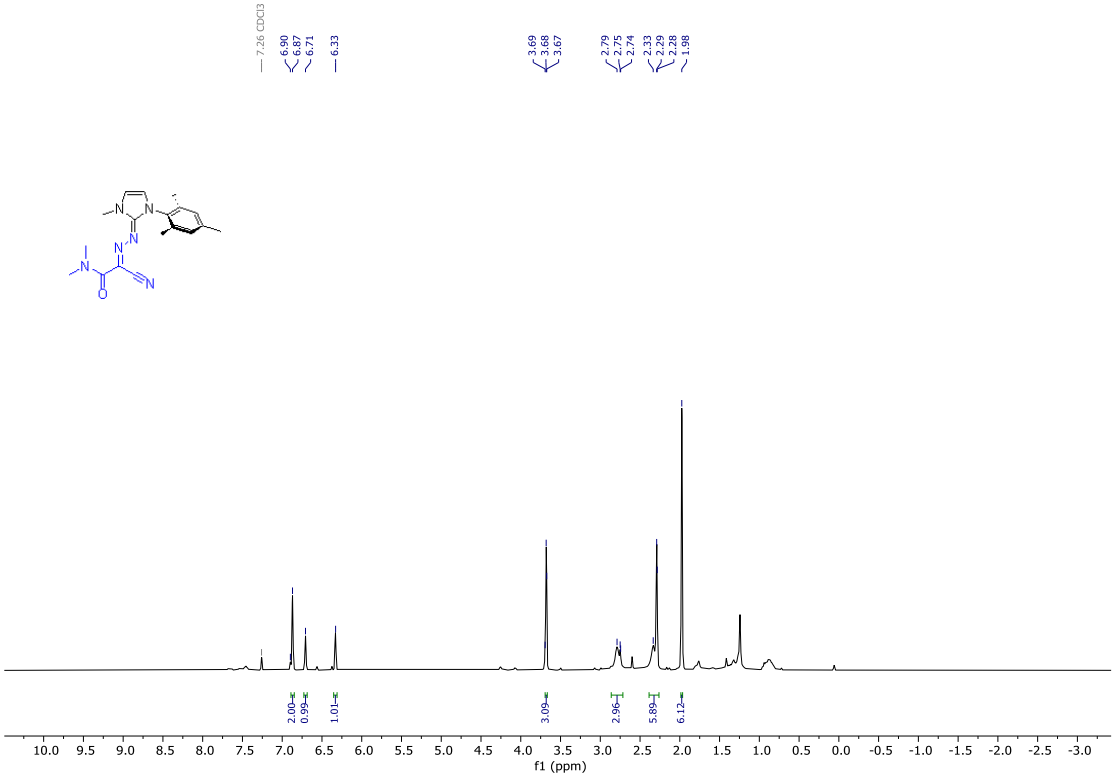


Figure S24. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **11**.

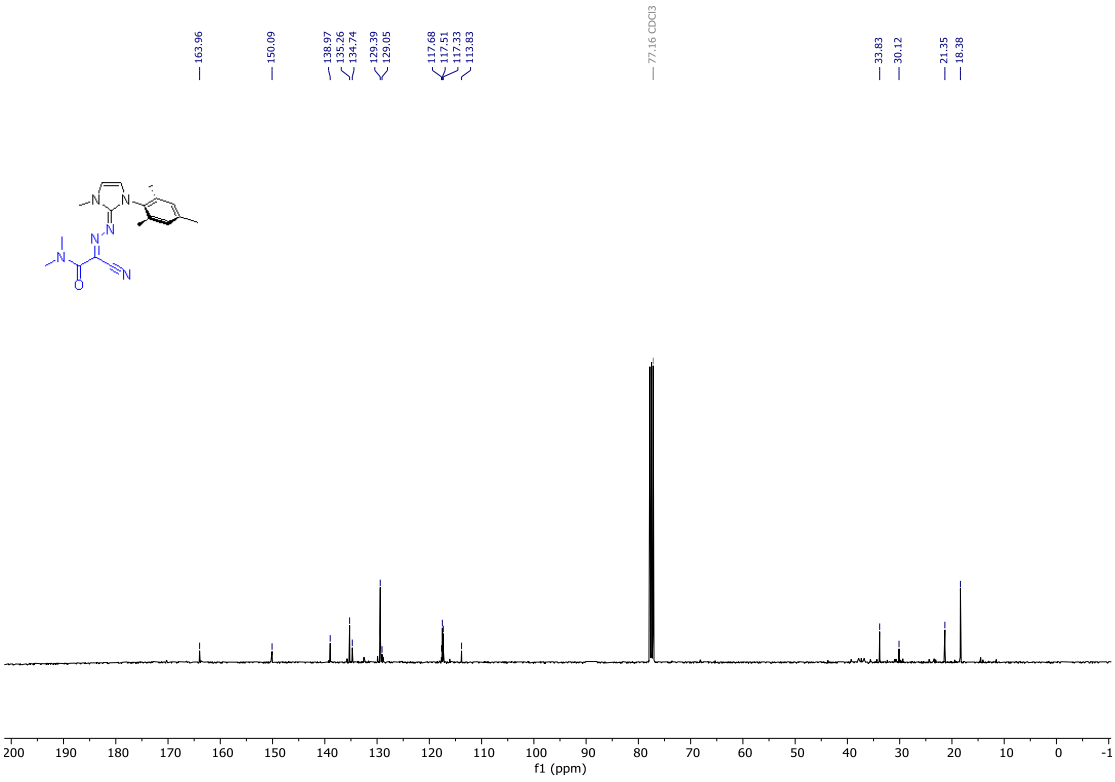


Figure S25. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **11**.

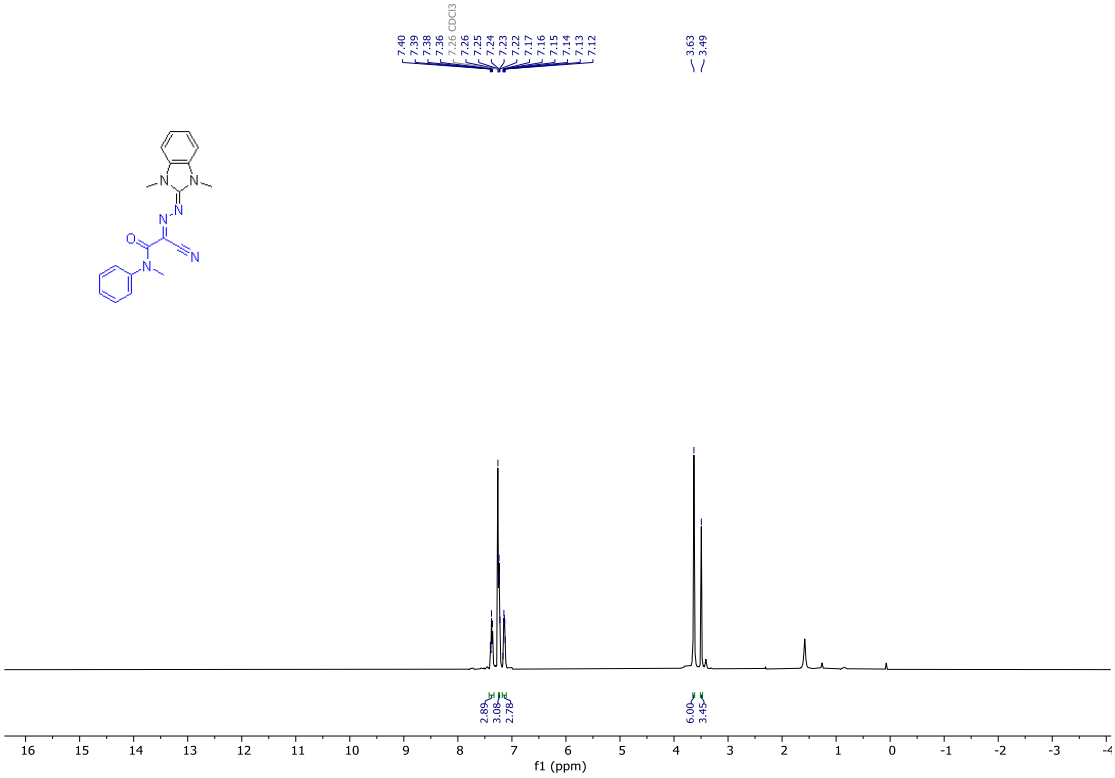


Figure S26. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **12**.

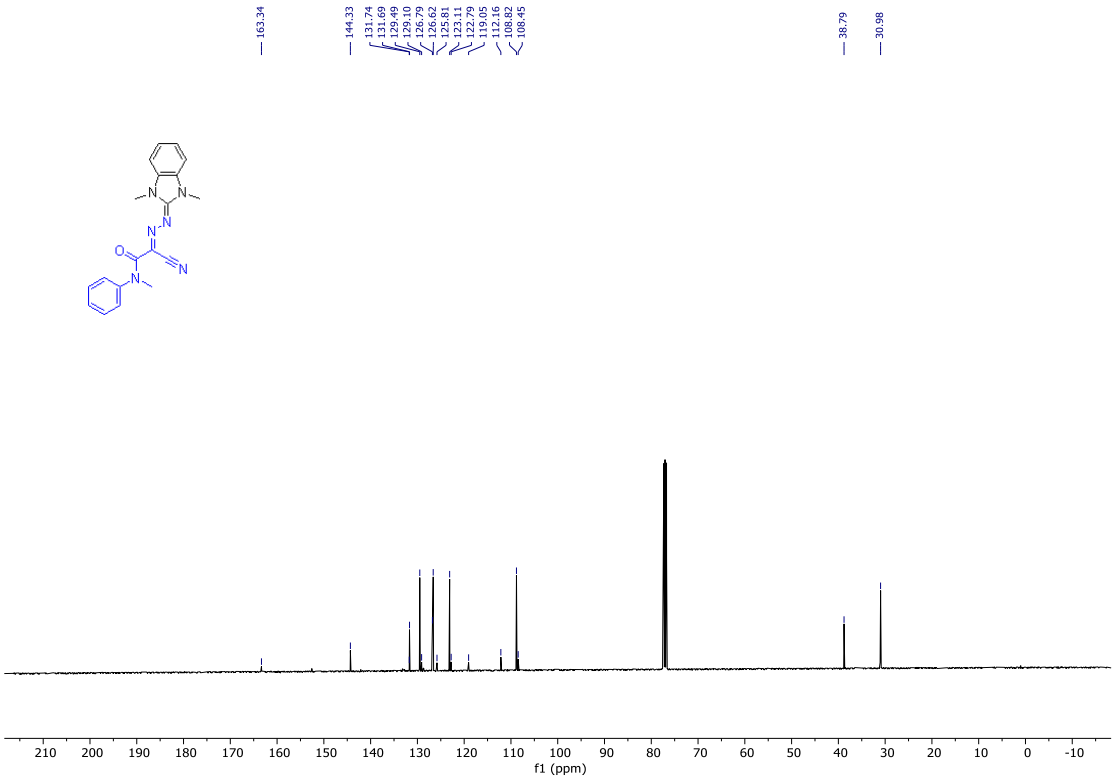


Figure S27. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **12**.

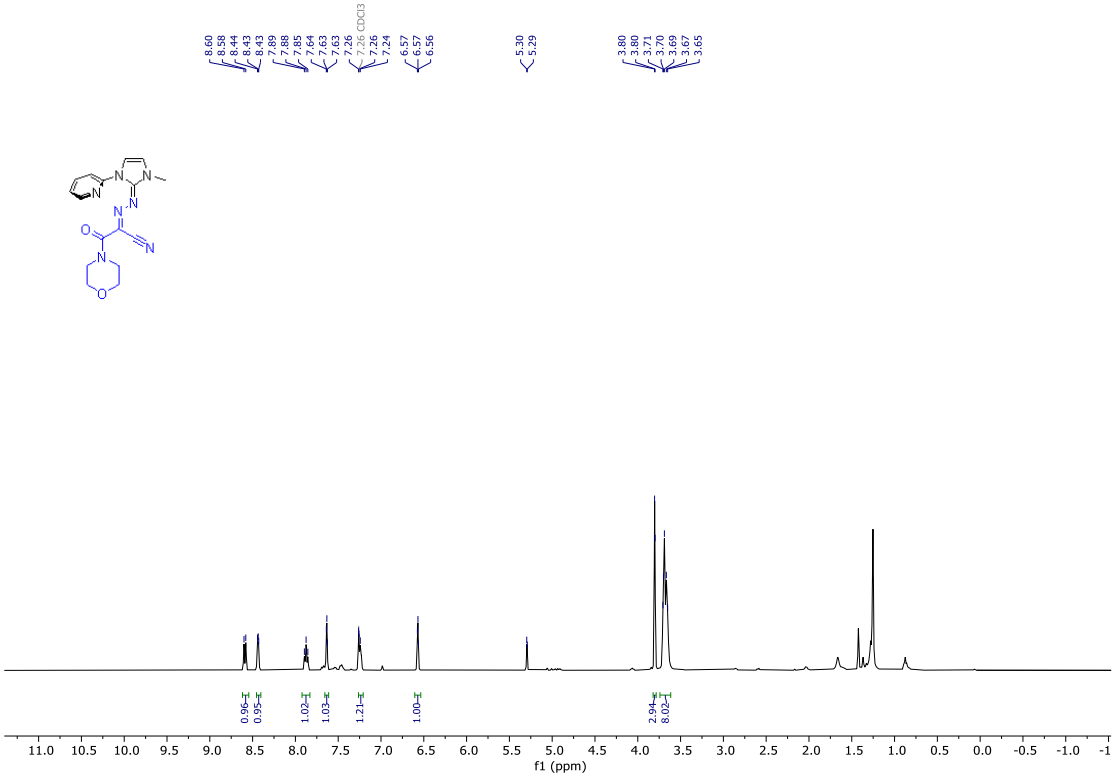


Figure S28. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **13**.

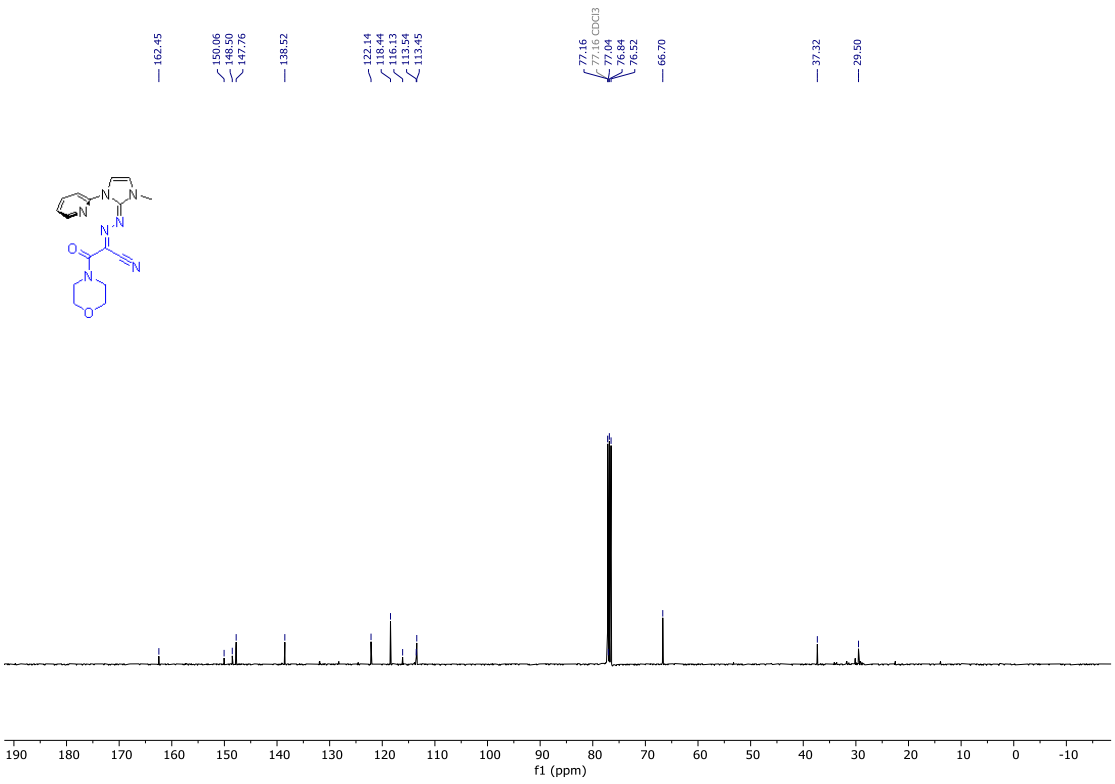


Figure S29. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **13**.

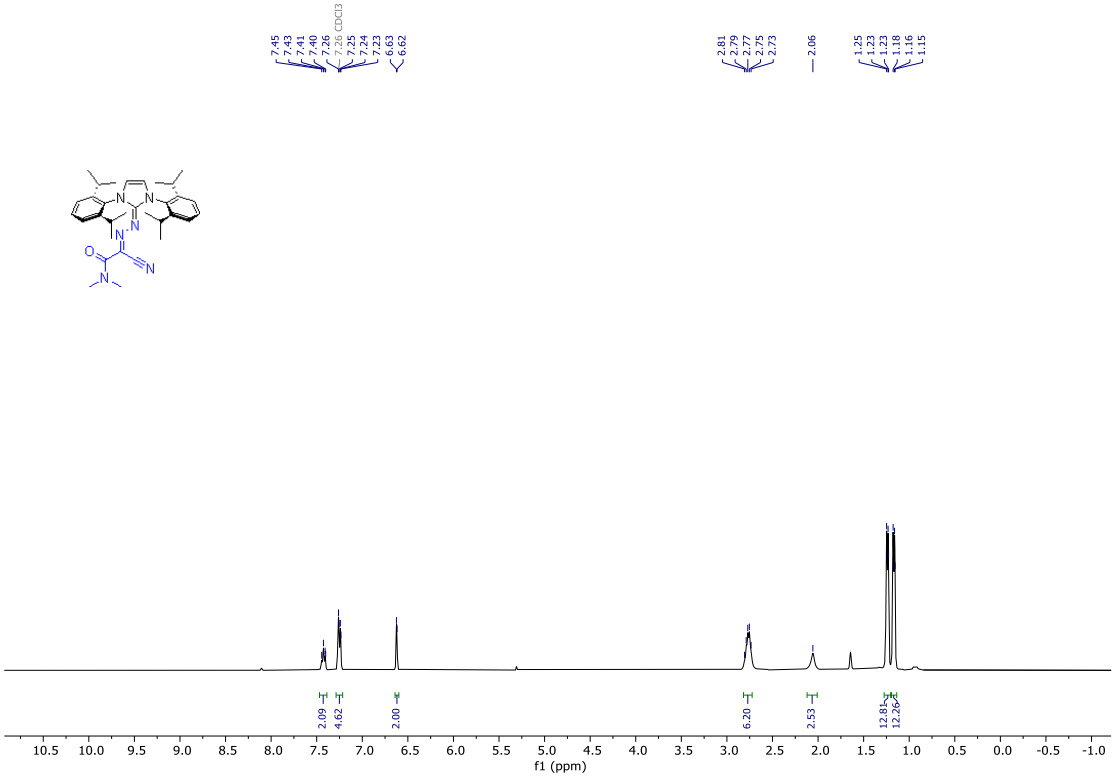


Figure S30. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **14**.

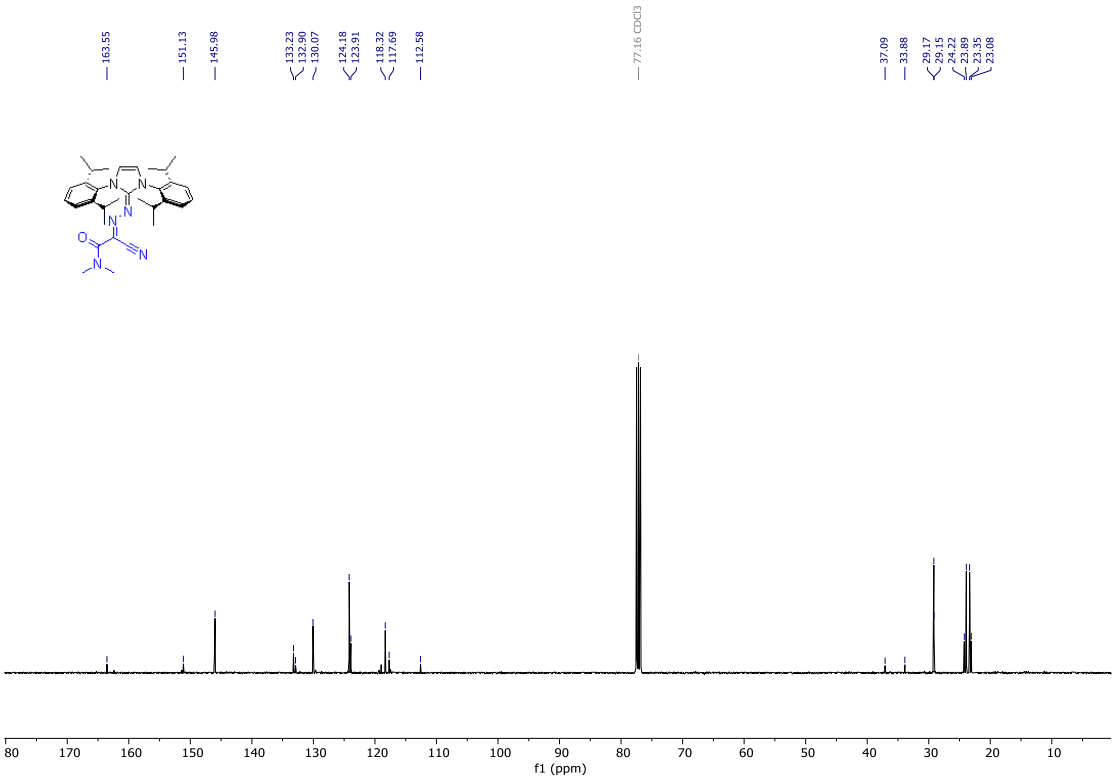


Figure S31. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **14**.

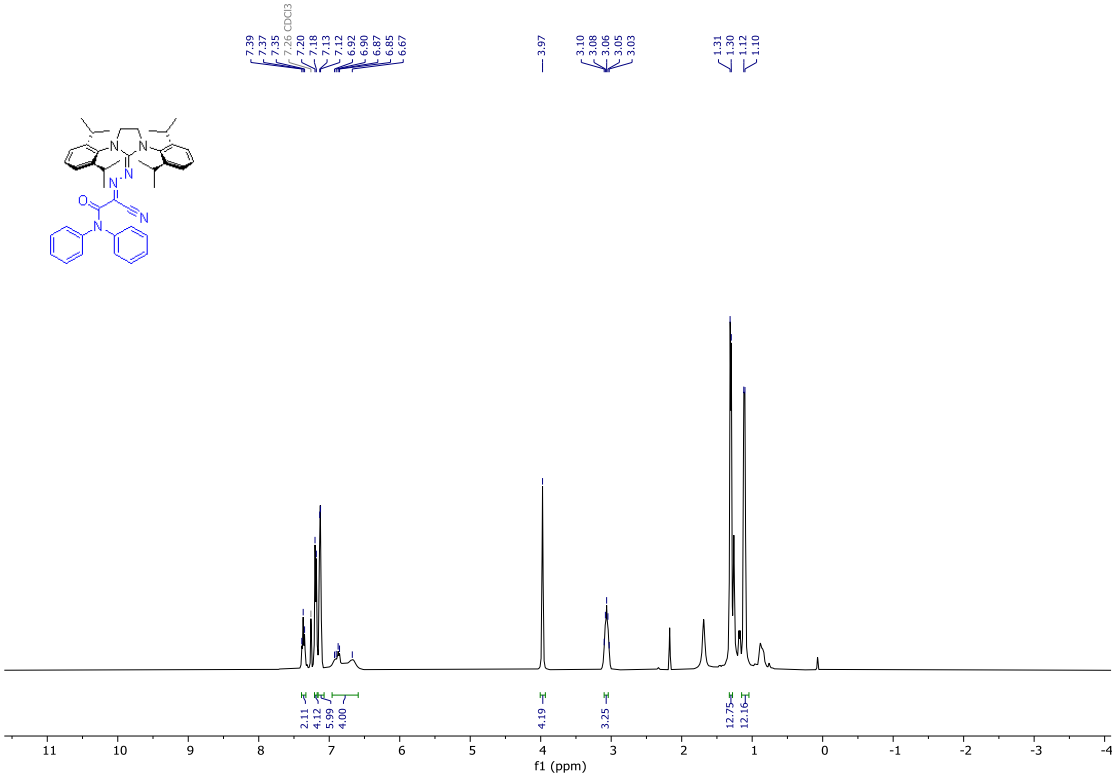


Figure S32. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **15**.

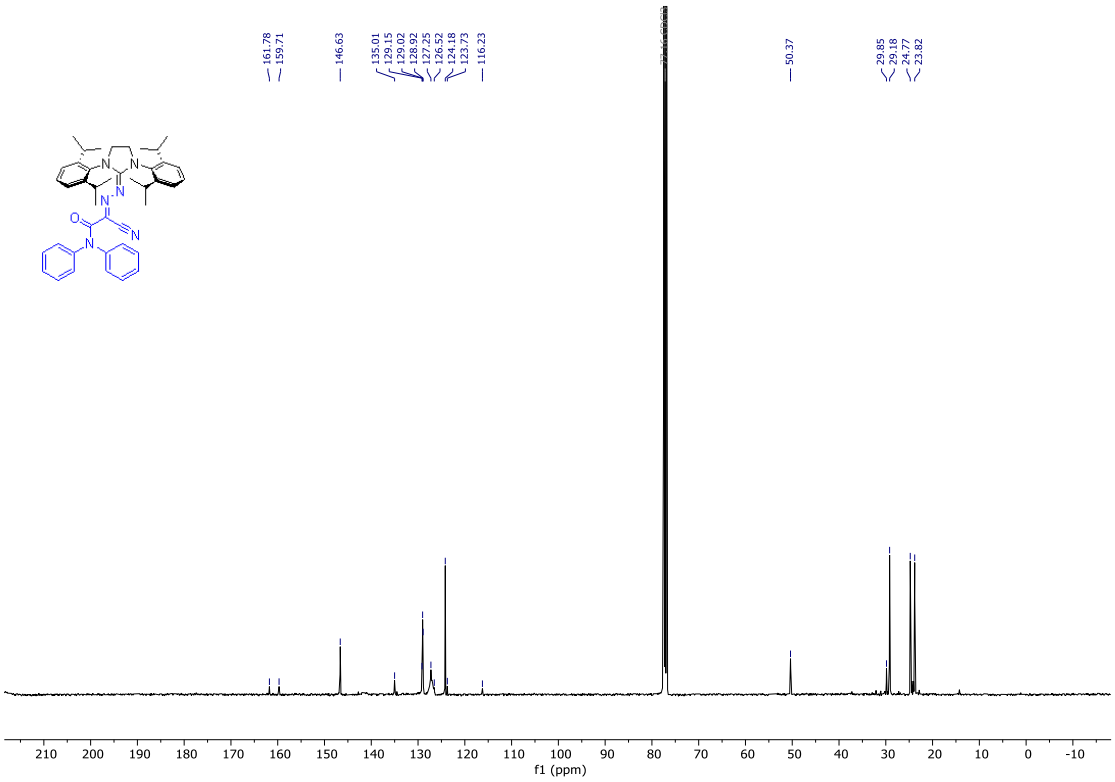


Figure S33. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **15**.

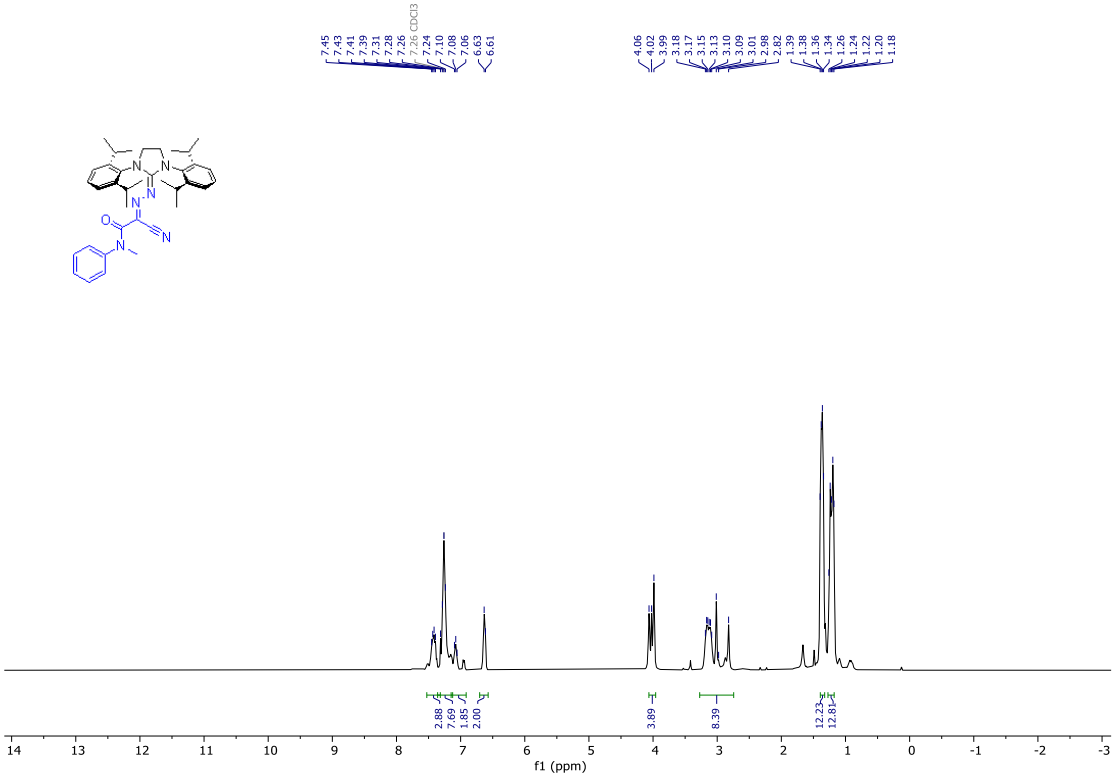


Figure S34. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **16**.

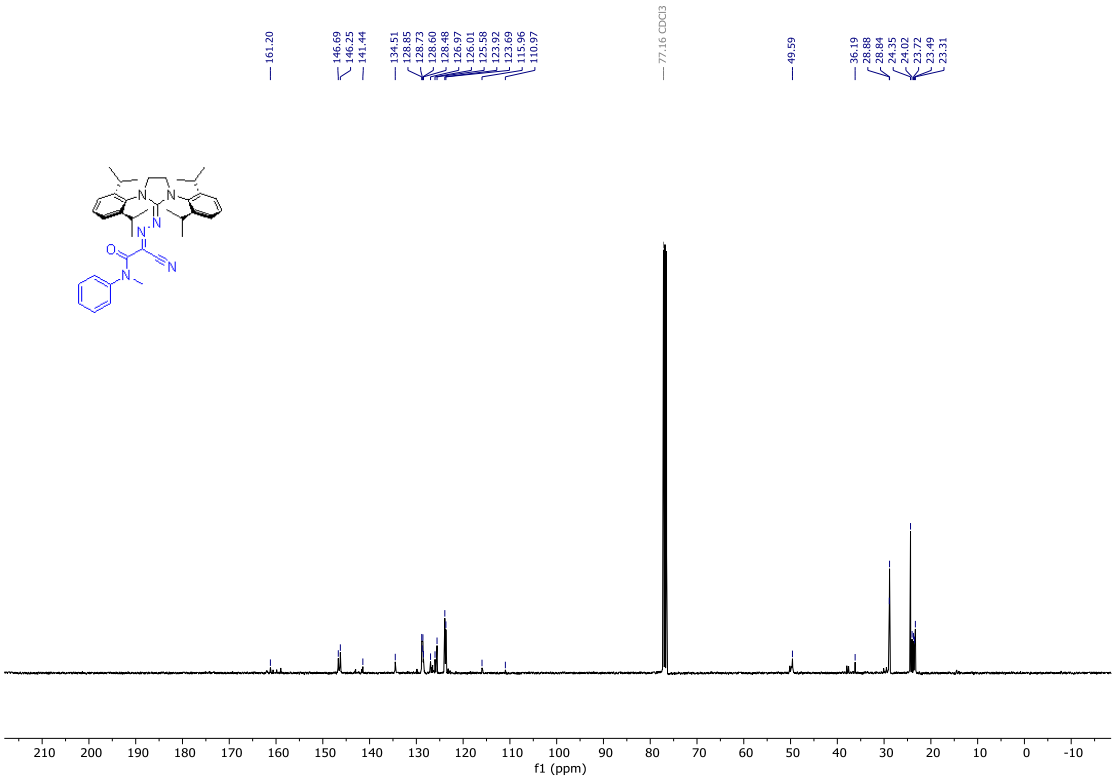


Figure S35. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **16**.

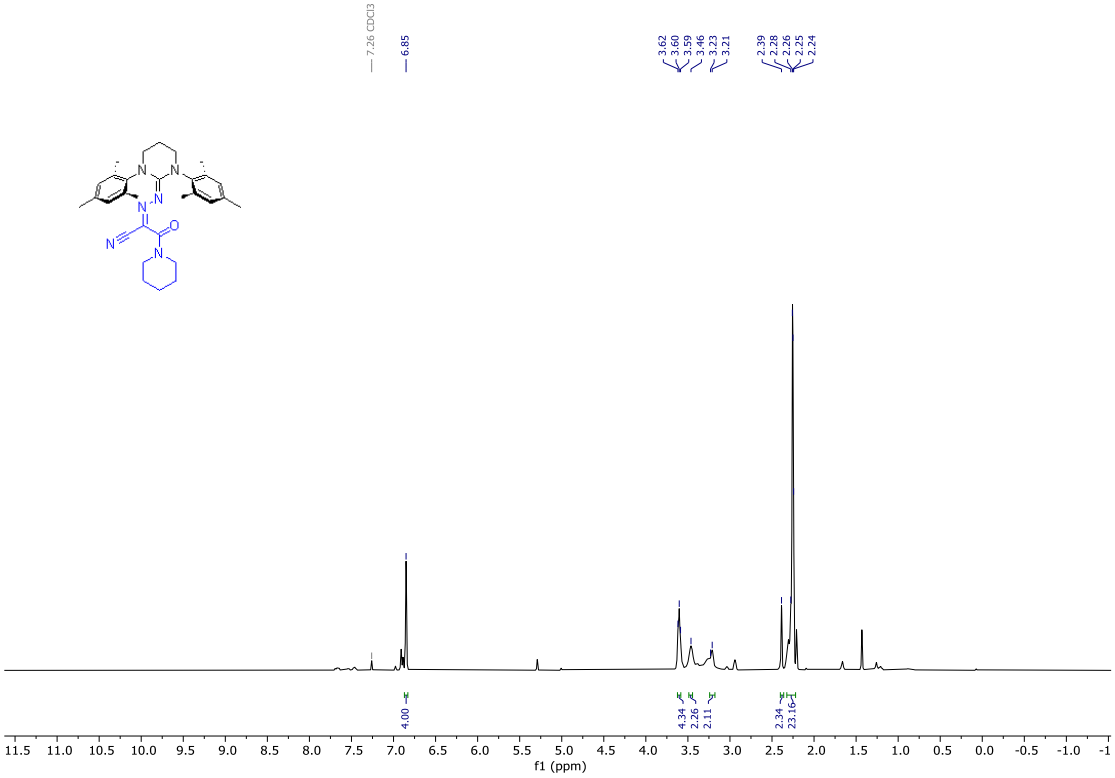


Figure S36. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **17**.

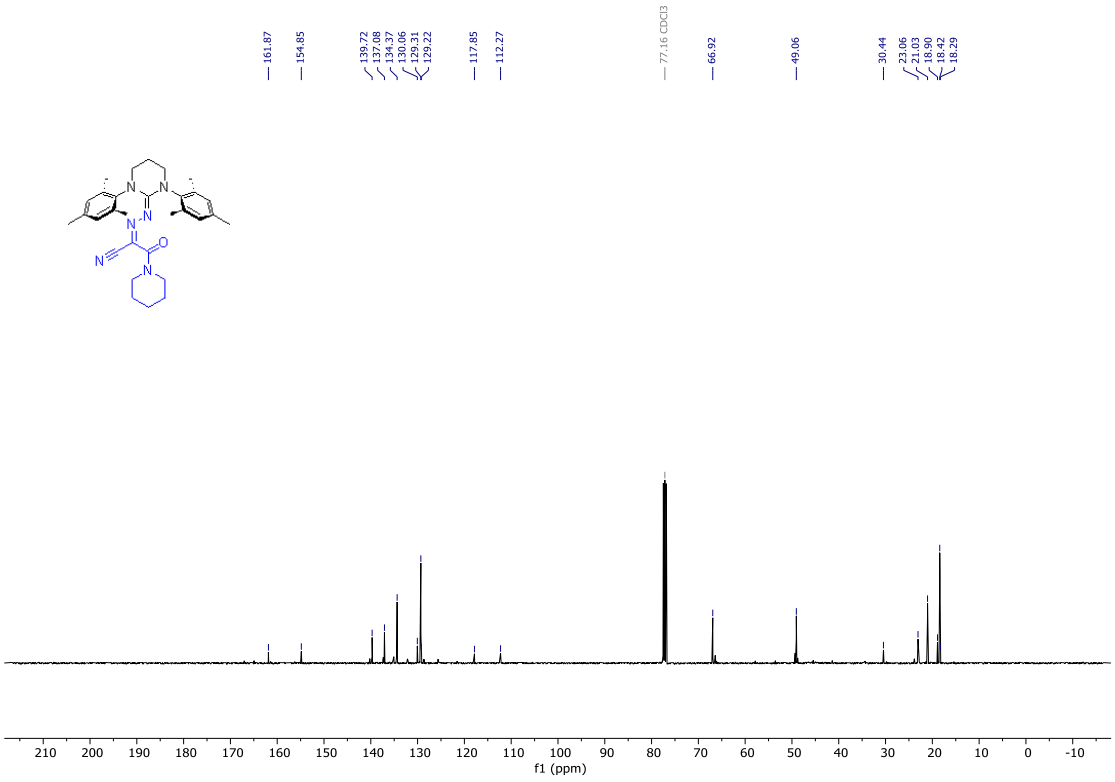


Figure S37. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **17**.

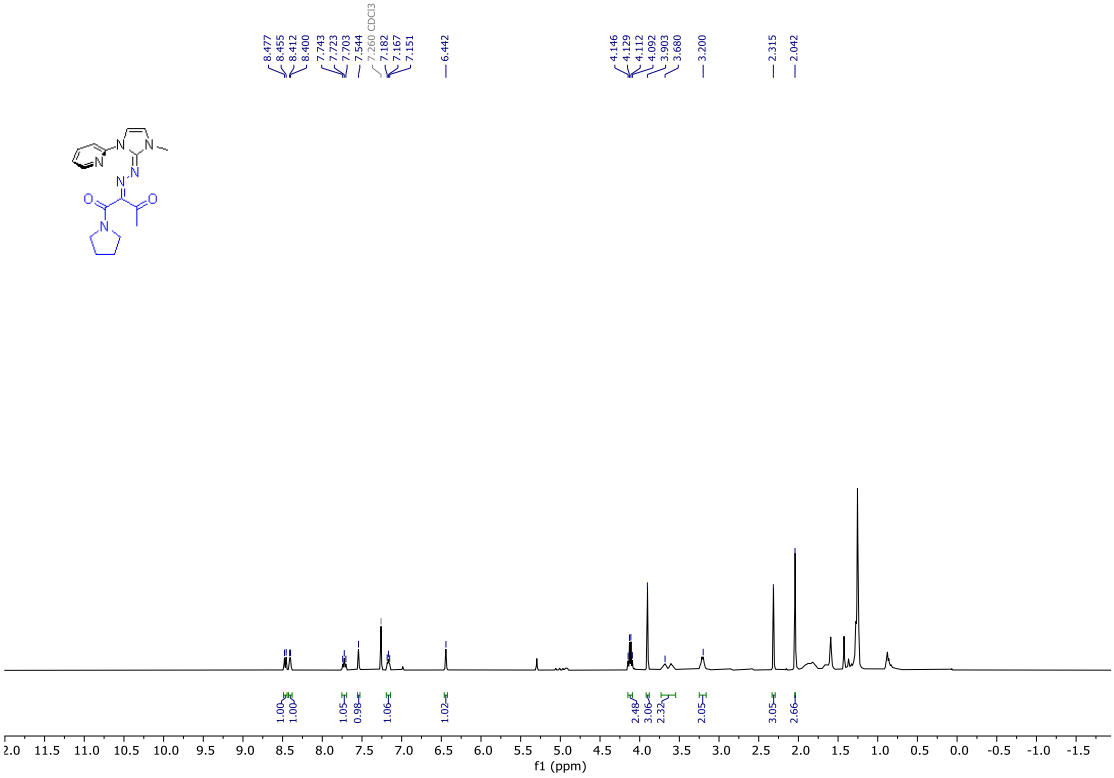


Figure S38. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **18**.

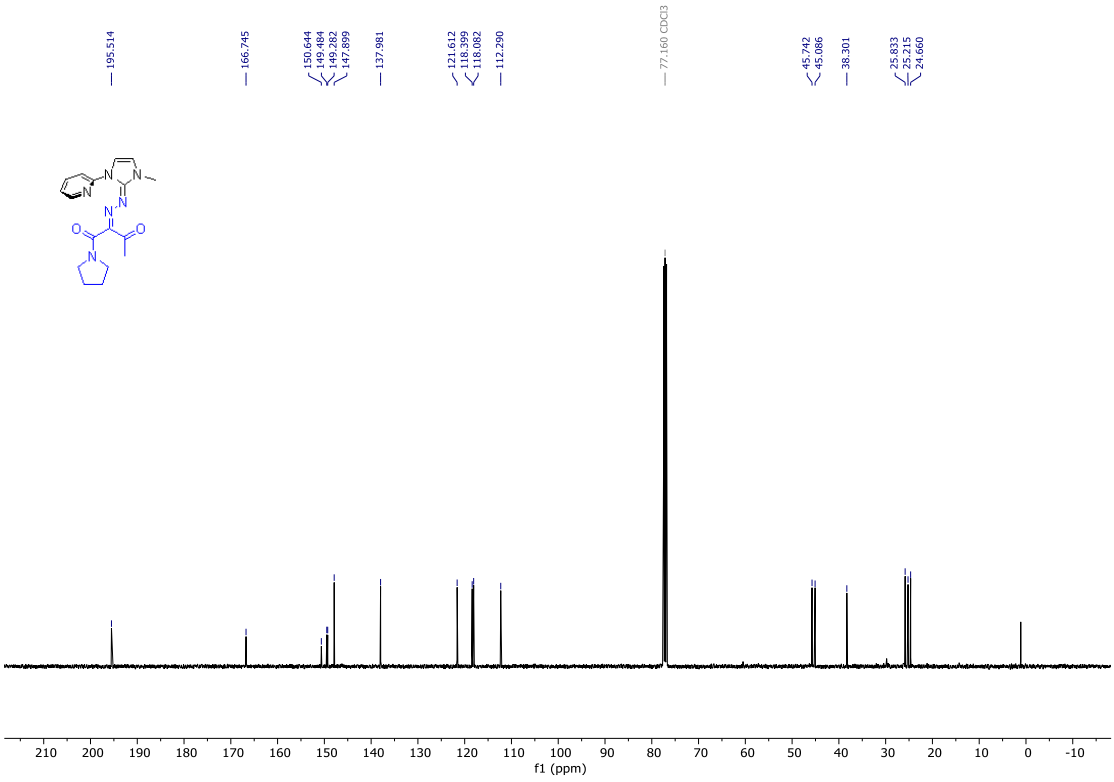


Figure S39. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **18**.

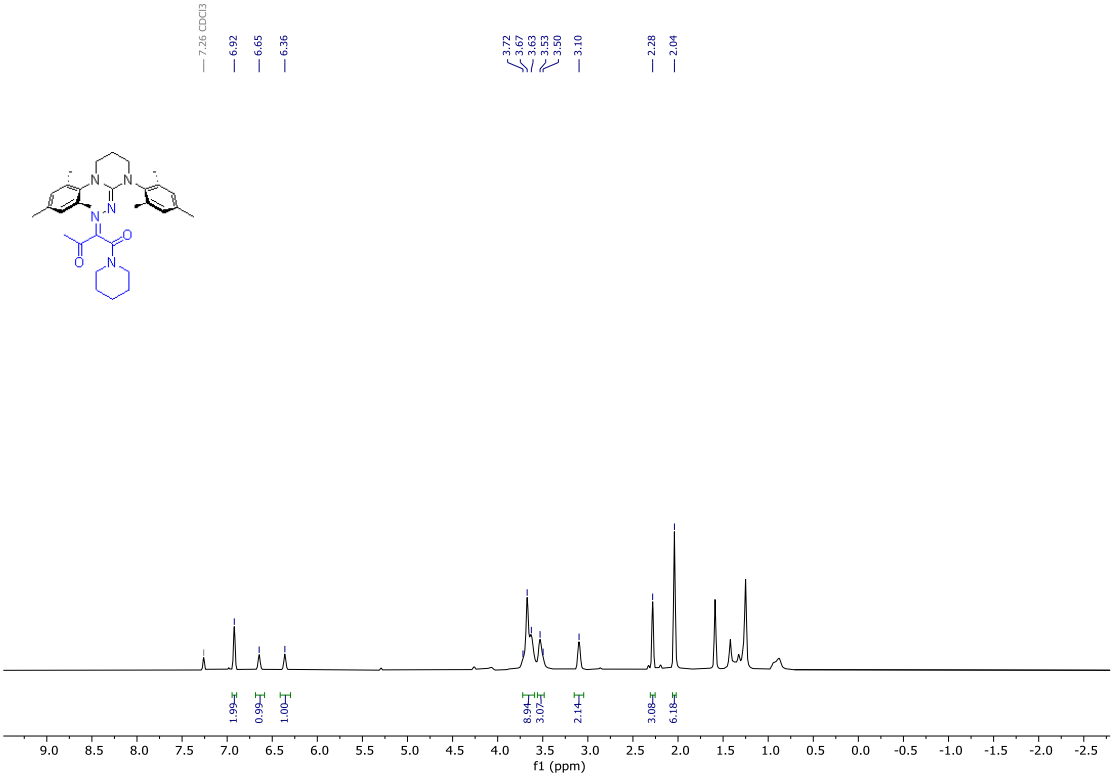


Figure S40. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **19**.

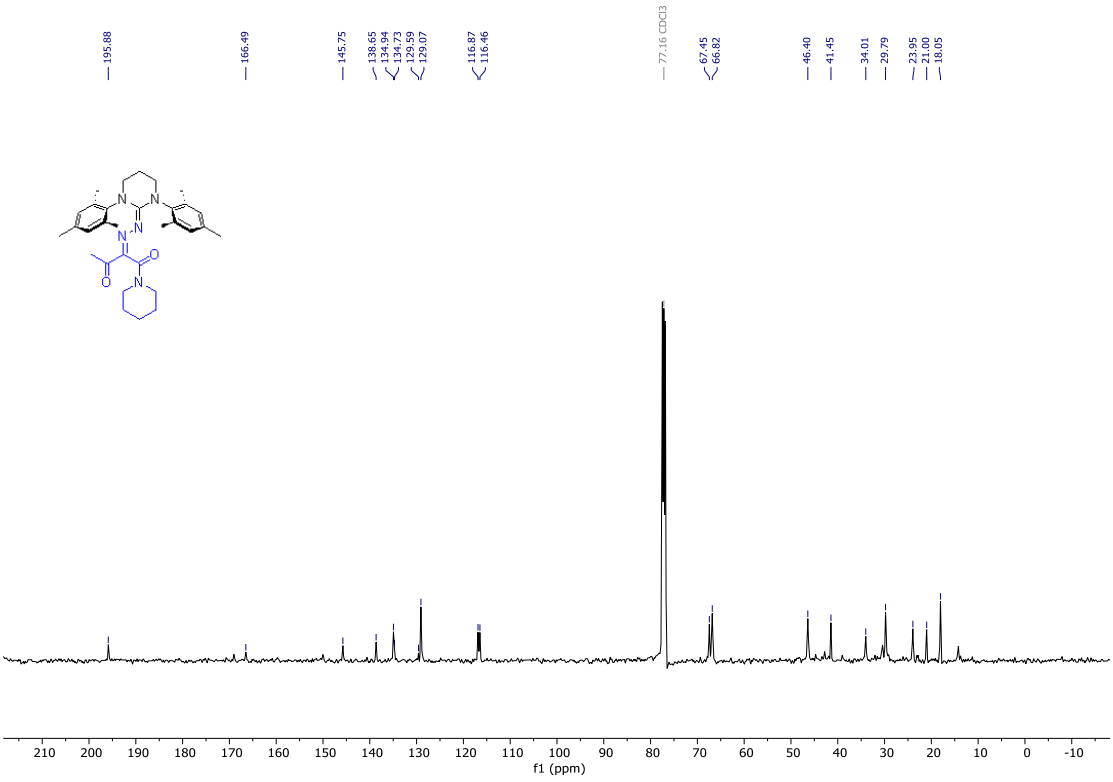


Figure S41. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **19**.

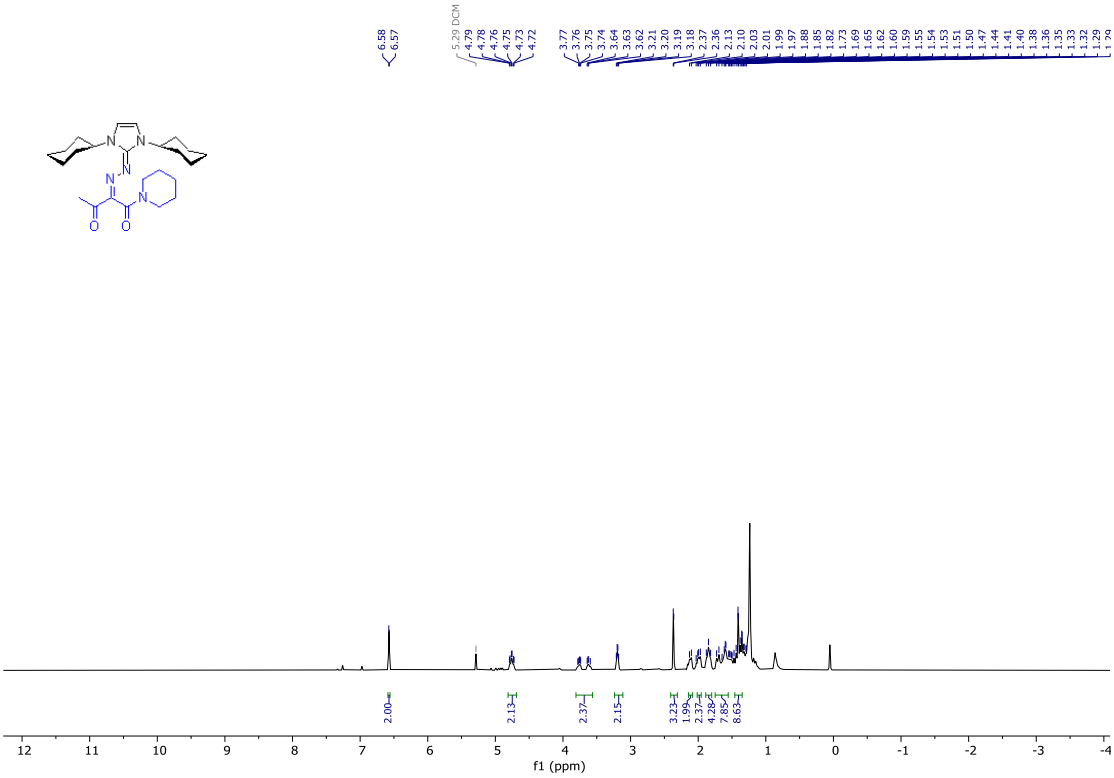


Figure S42. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **20**.

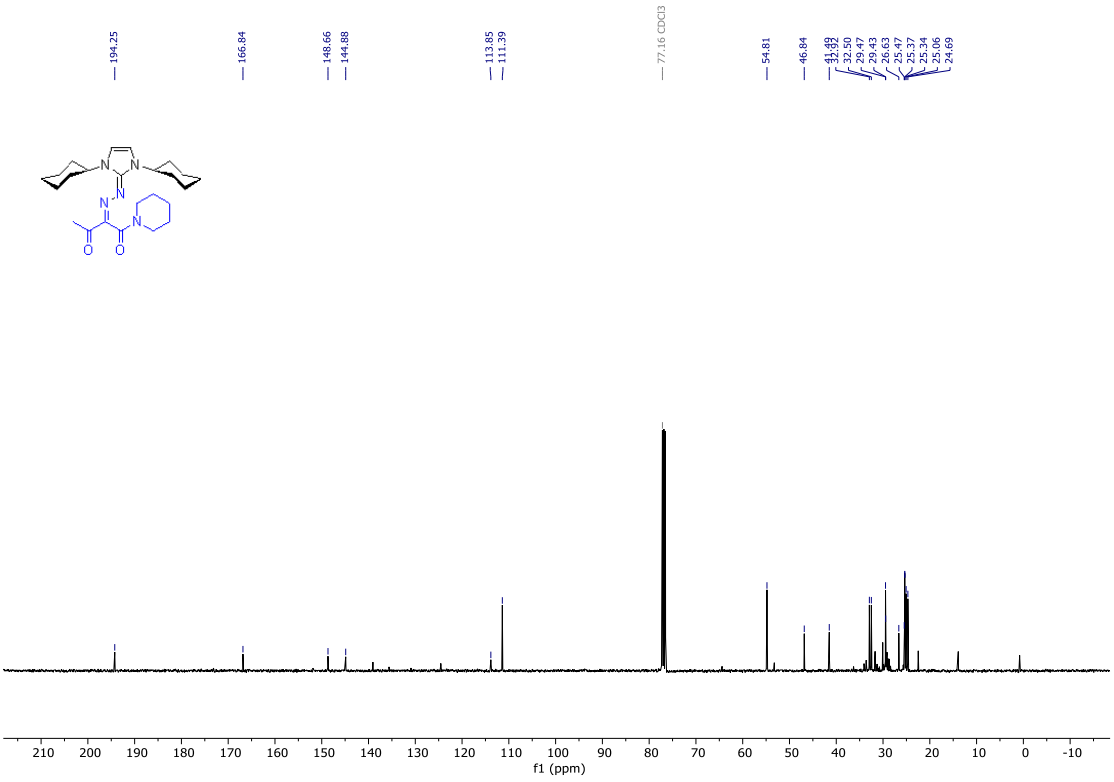


Figure S43. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **20**.

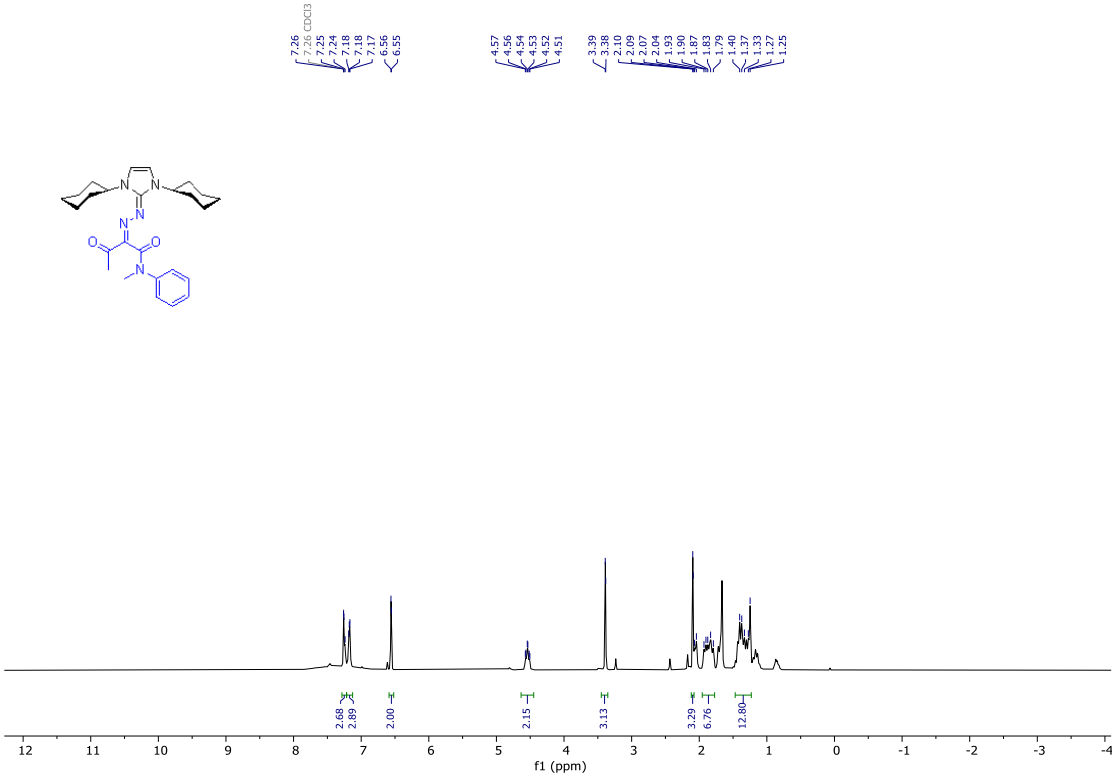


Figure S44. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **21**.

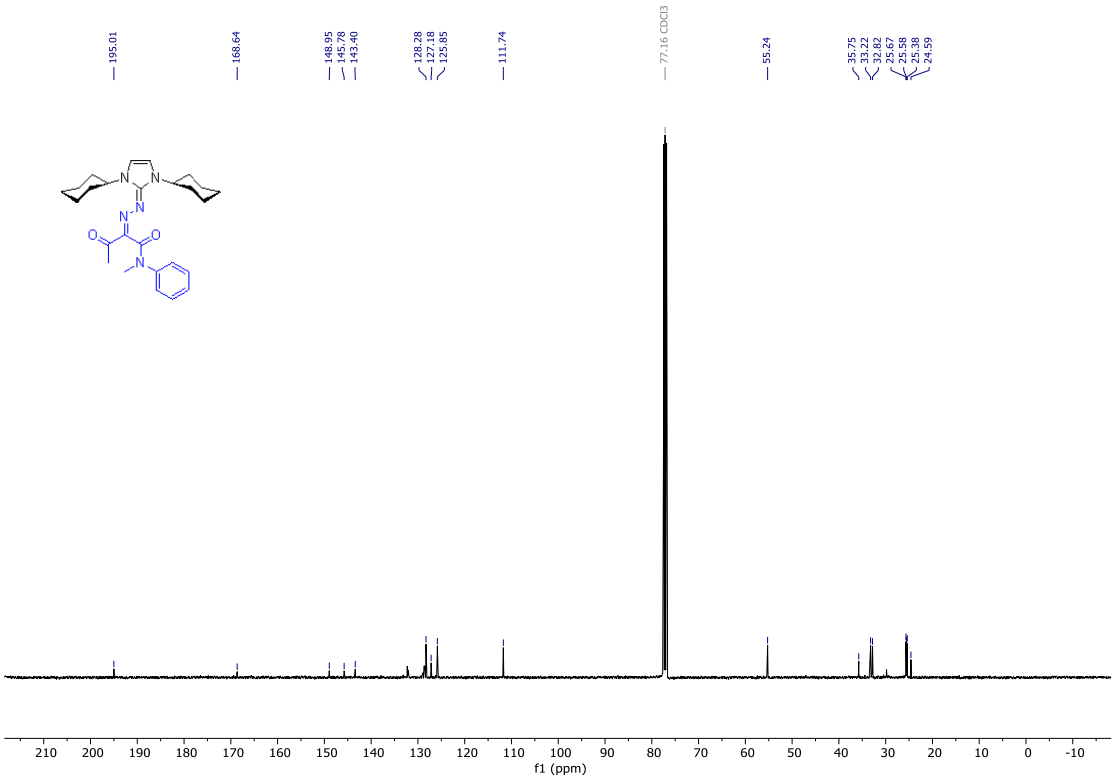


Figure S45. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **21**.

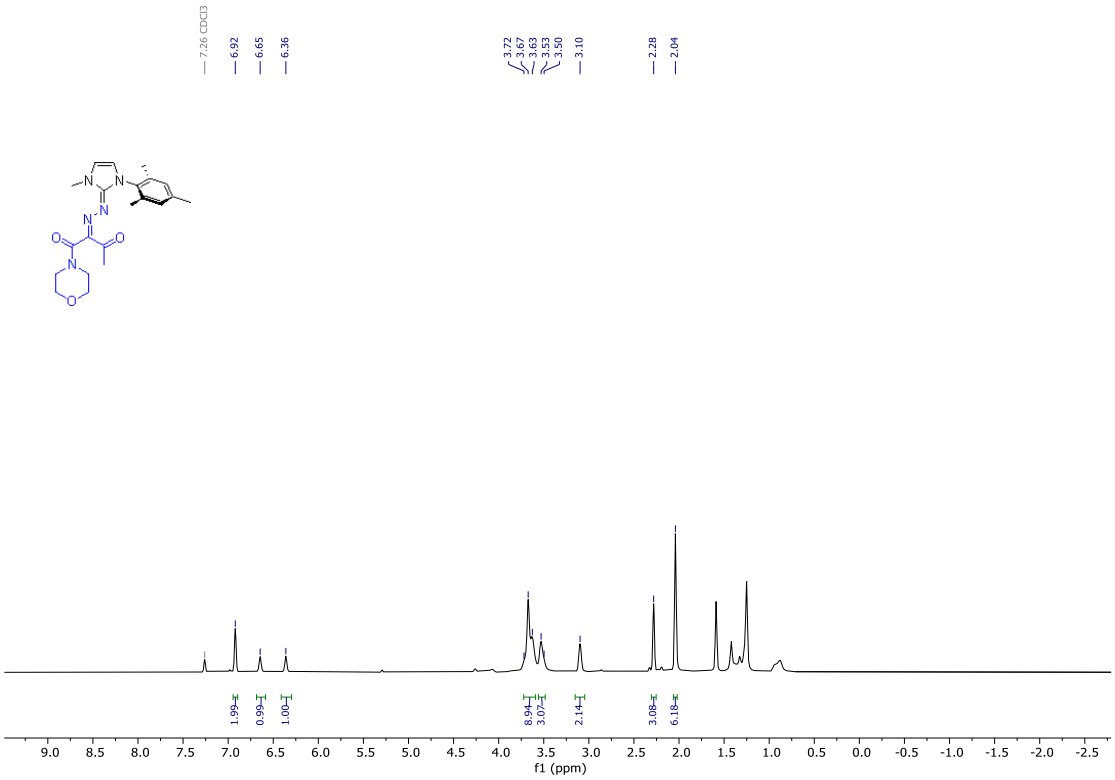


Figure S46. ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **22**.

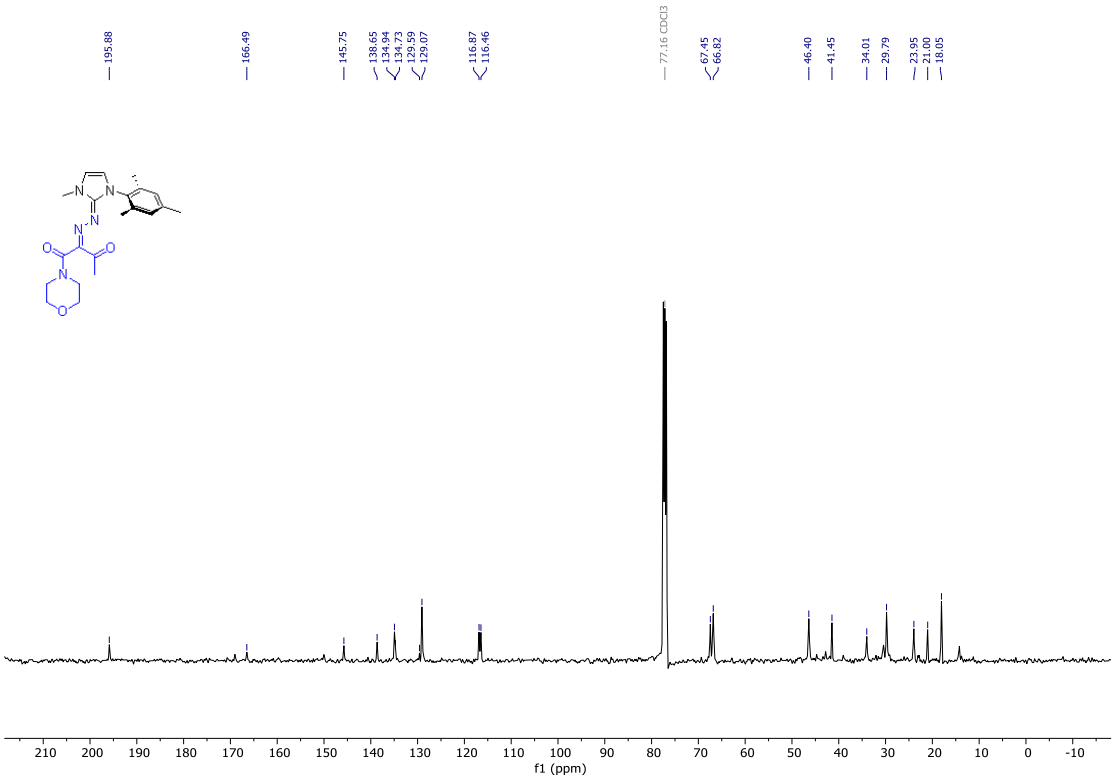


Figure S47. ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **22**.

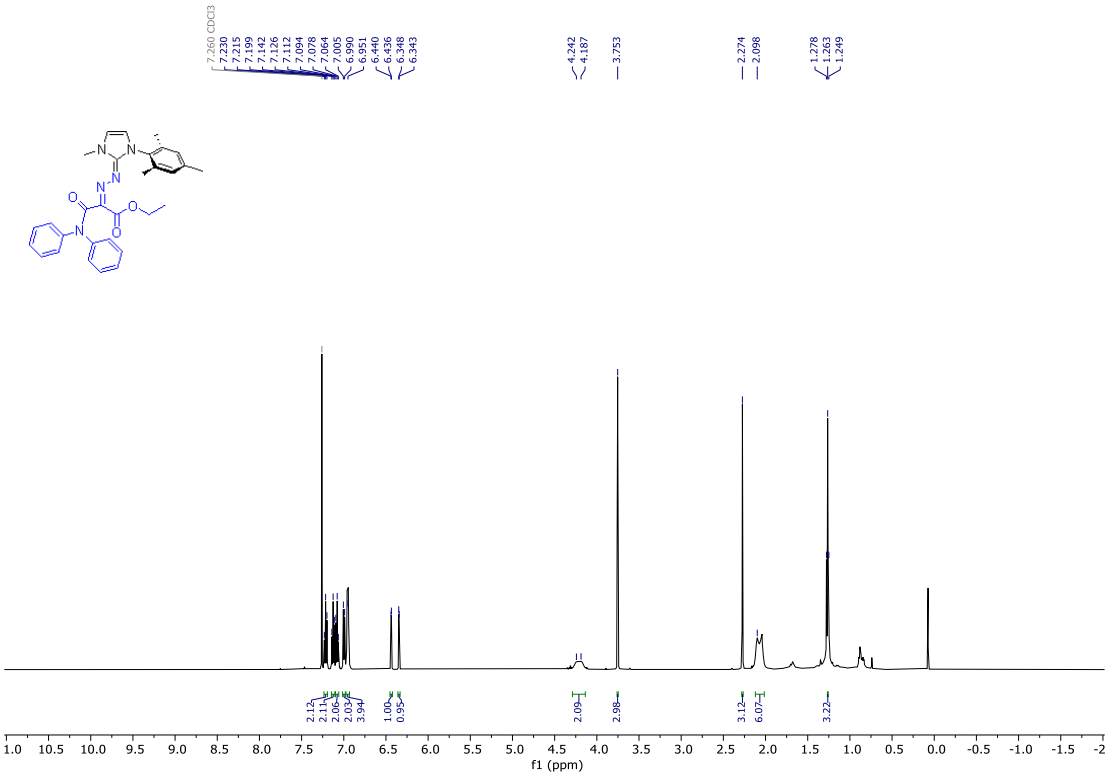


Figure S48. ^{1}H-NMR (500 MHz, $CDCl_3$) of compound **23**.

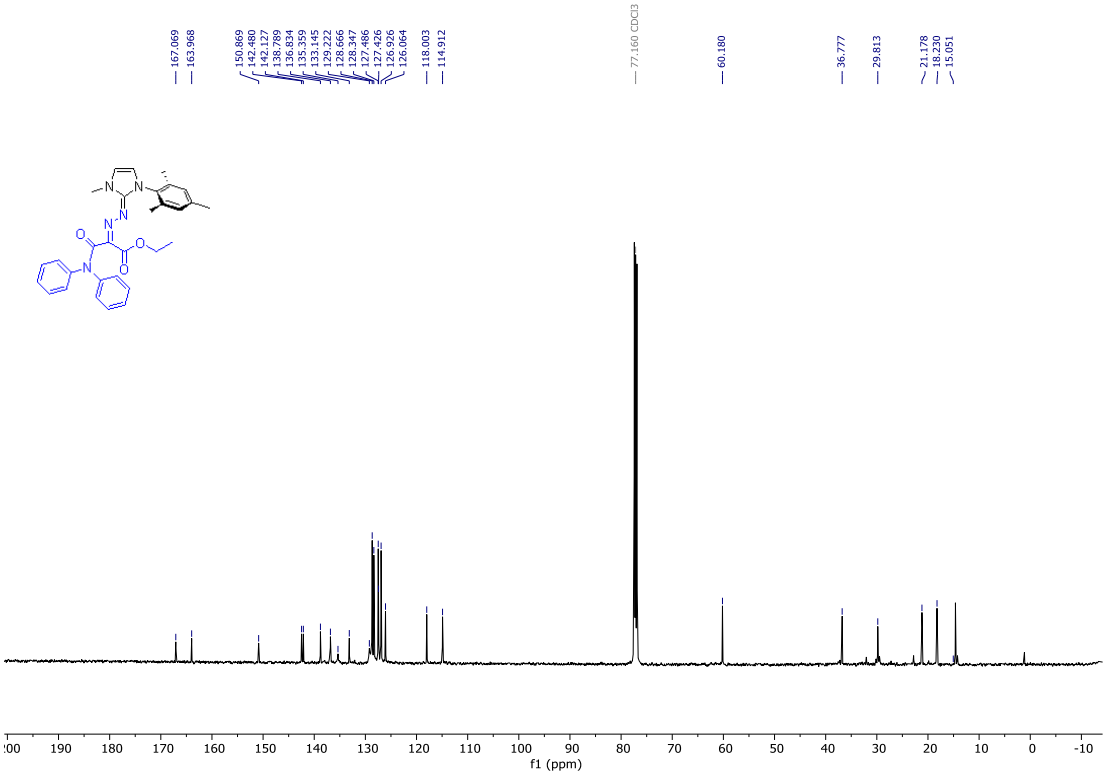


Figure S49. ^{13}C-NMR (126 MHz, $CDCl_3$) of compound **23**.

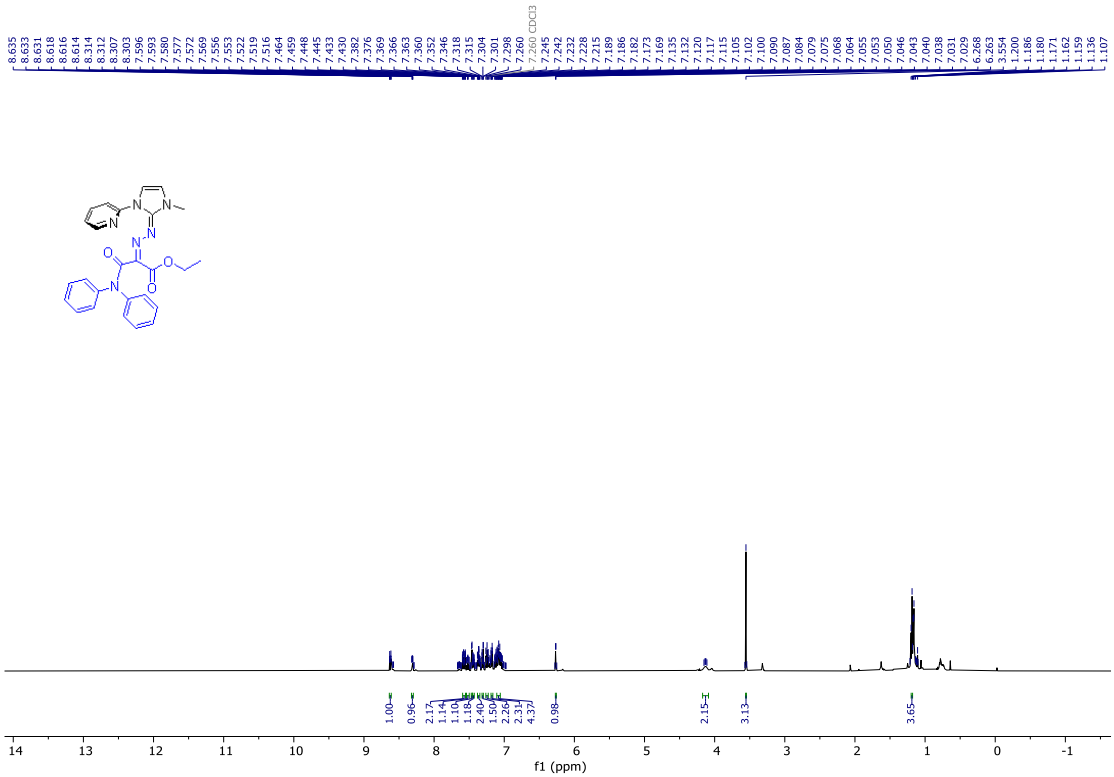


Figure S50. ^{1}H-NMR (500 MHz, $CDCl_3$) of compound **24**.

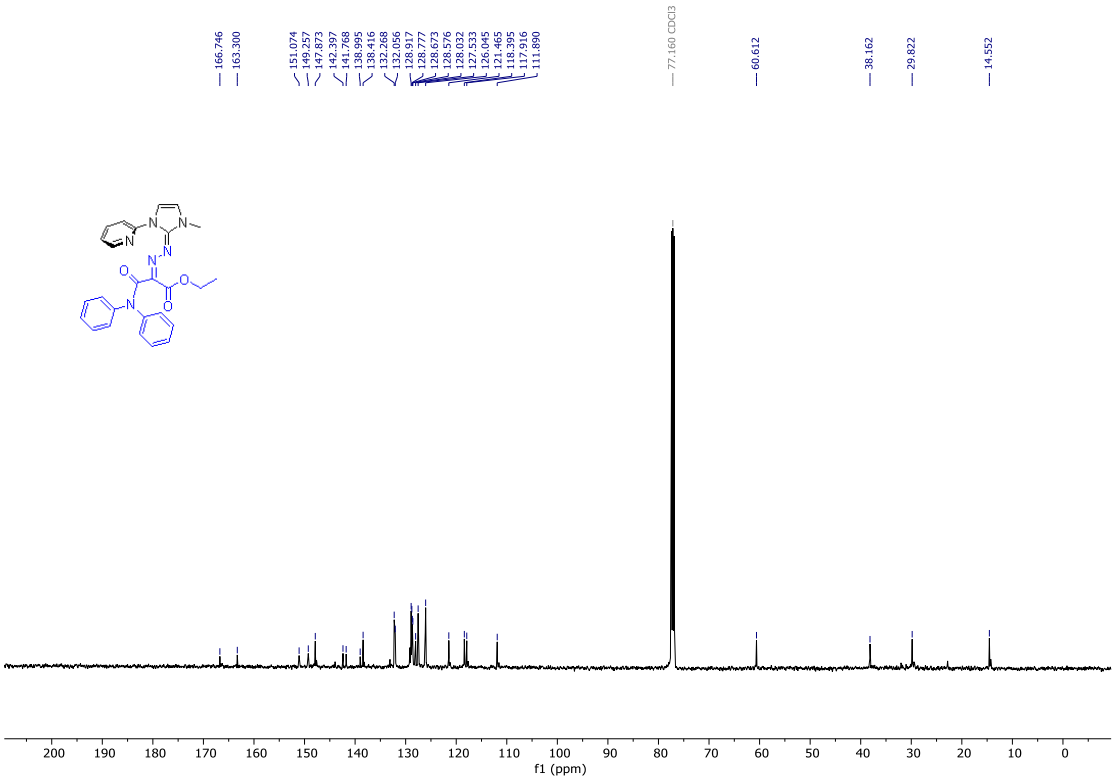


Figure S51. ^{13}C-NMR (126 MHz, $CDCl_3$) of compound **24**.

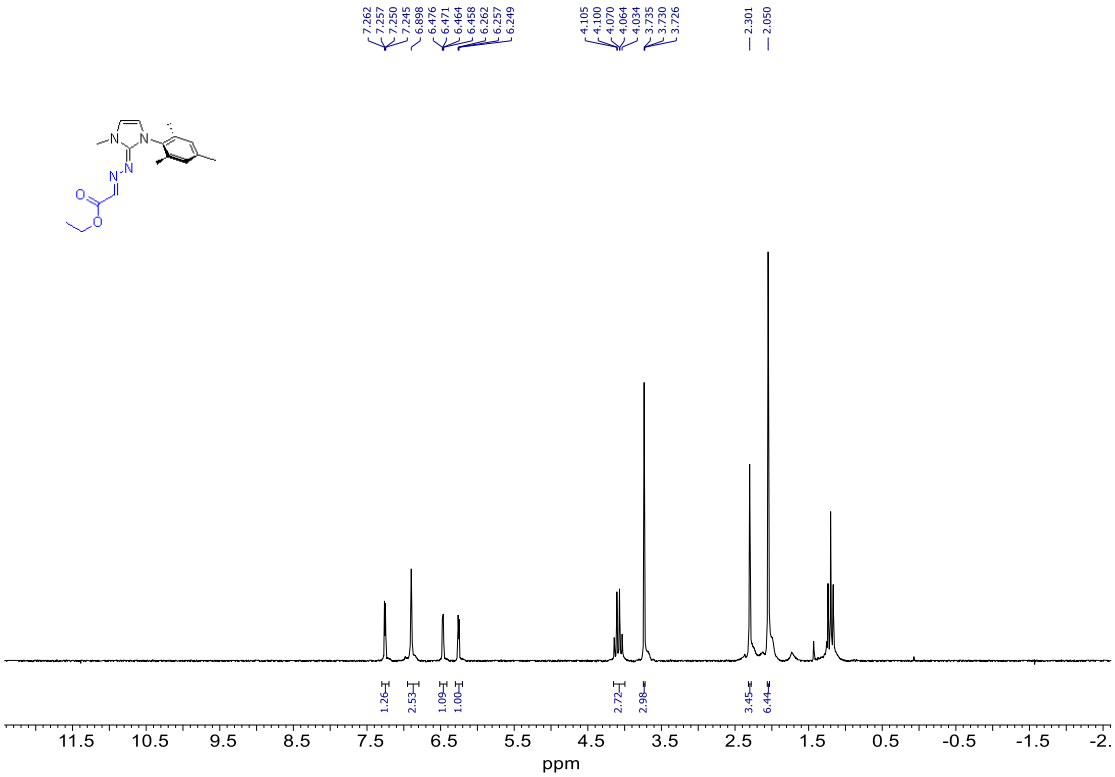


Figure S52: ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **25** obtained using PS-PPh_3, recorded from the concentrated filtrate after removal of the resin.

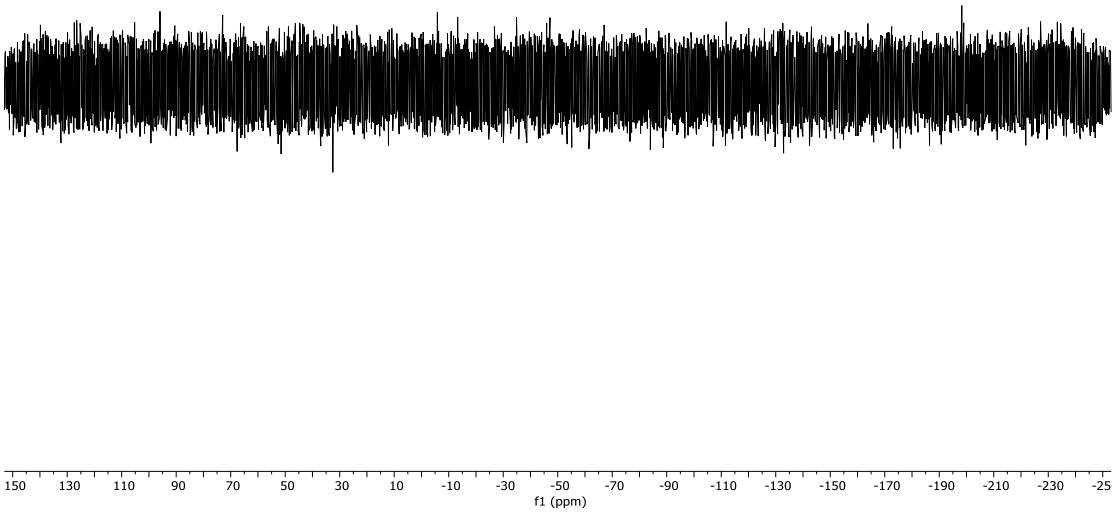


Figure S53: ^{31}P-NMR (162 MHz, $CDCl_3$) of the concentrated filtrate from the synthesis of compound **25** using PS-PPh_3.

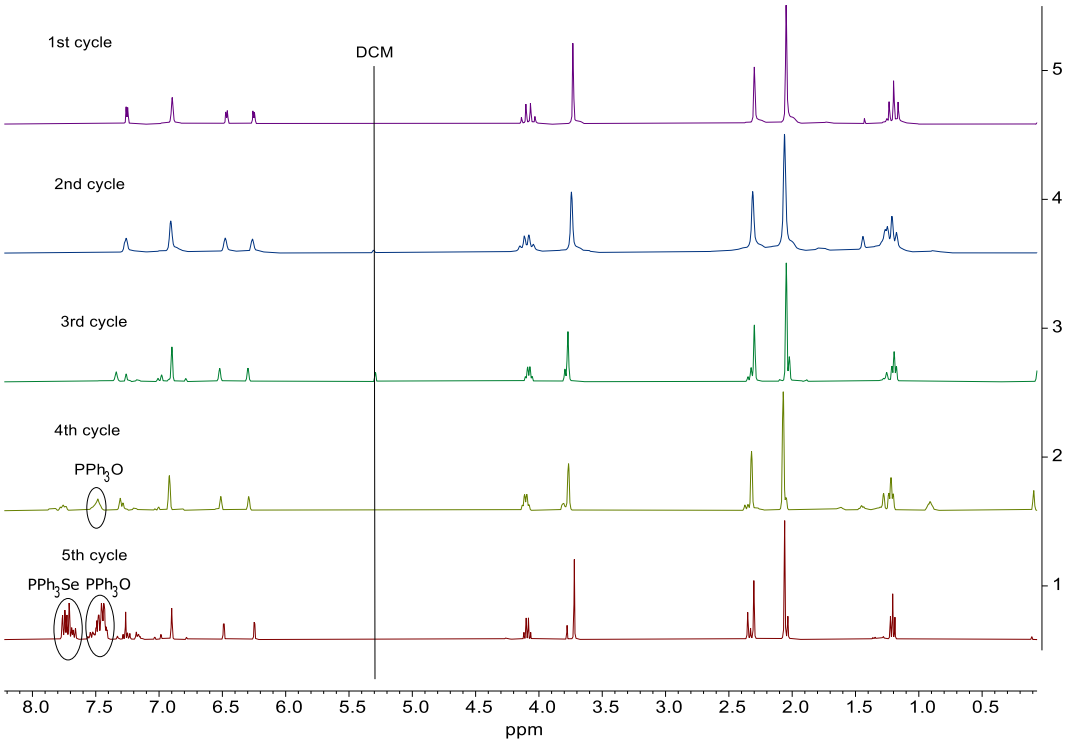


Figure S54: ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **25** obtained using recycled PS-PPh_3, recorded from the concentrated filtrate after removal of the resin.

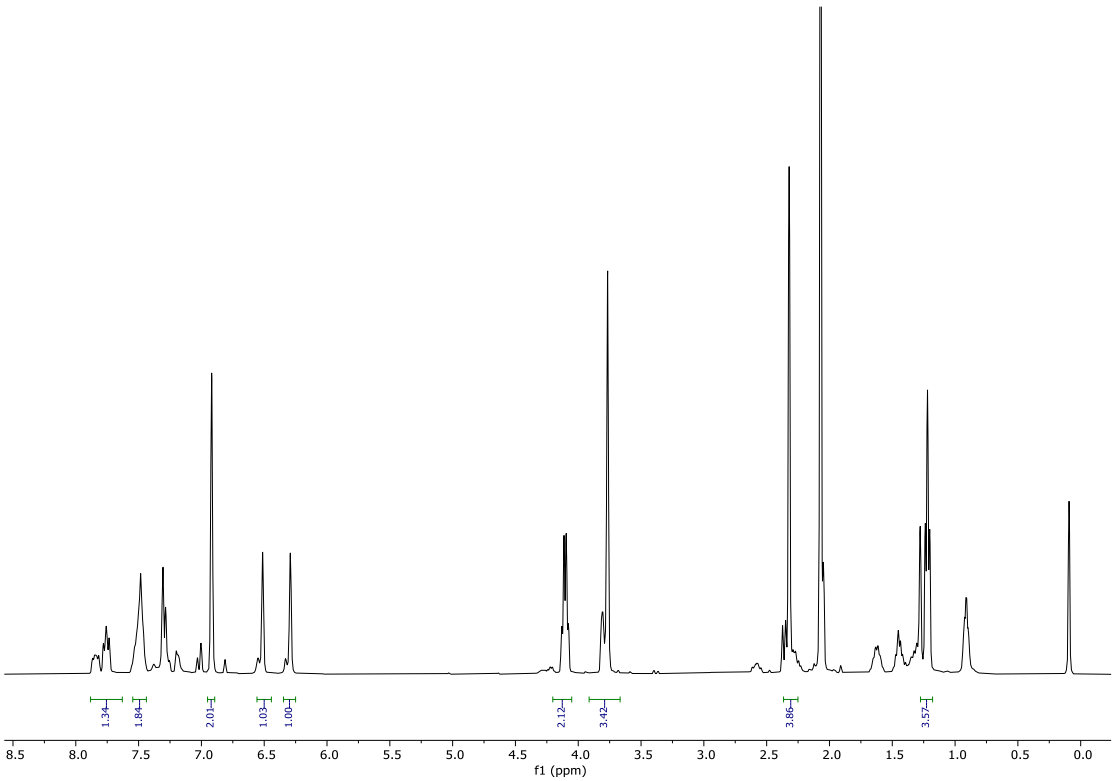


Figure S55: ^{1}H-NMR (400 MHz, $CDCl_3$) of compound **25** obtained recycled PS-PPh_3 after 4 cycles, recorded from the concentrated filtrate after removal of the resin.

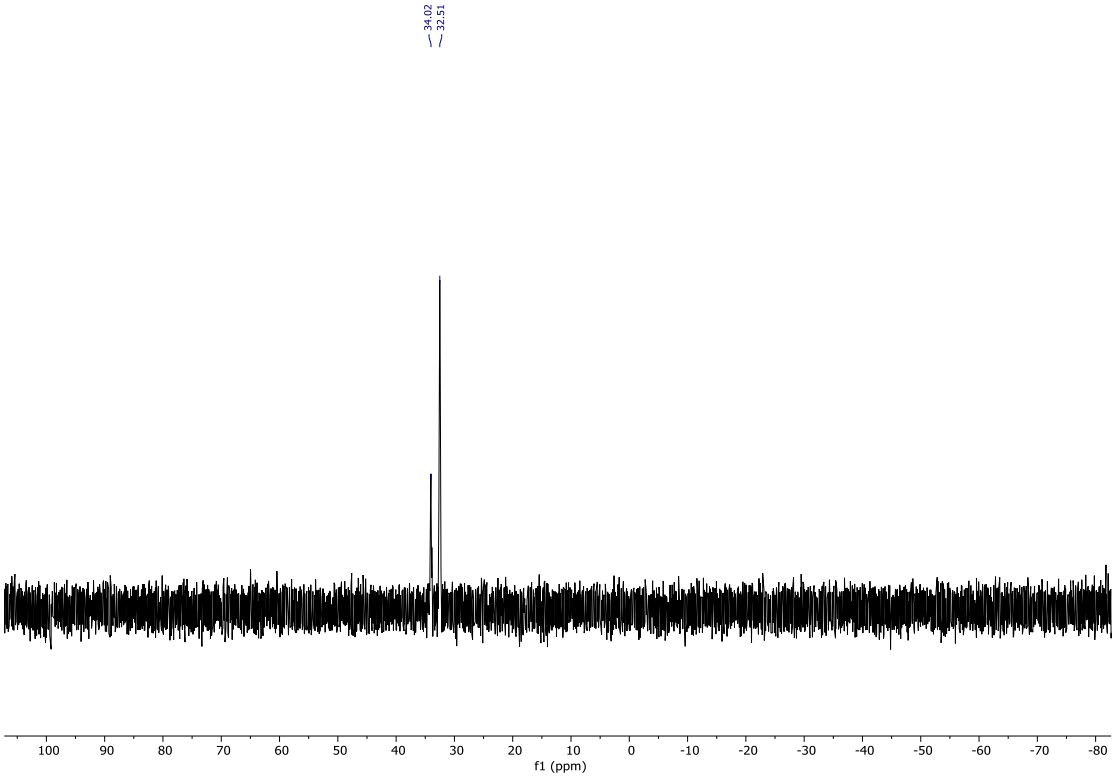


Figure S56: ^{31}P-NMR (162 MHz, $CDCl_3$) of the concentrated filtrate from the synthesis of compound **25**, using recycled PS-PPh_3 after 4 cycles.

4. Biological Evaluation - Figures

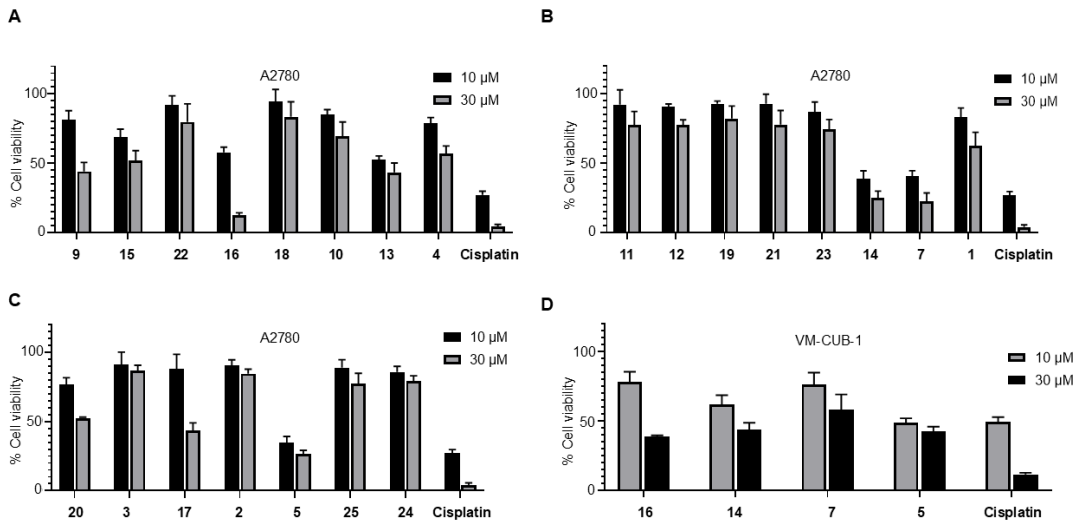


Figure S57: A,B,C) Initial screening for compounds in A2780 cells, D) MTT for 4 most promising compounds in VM-CUB-1 cells.

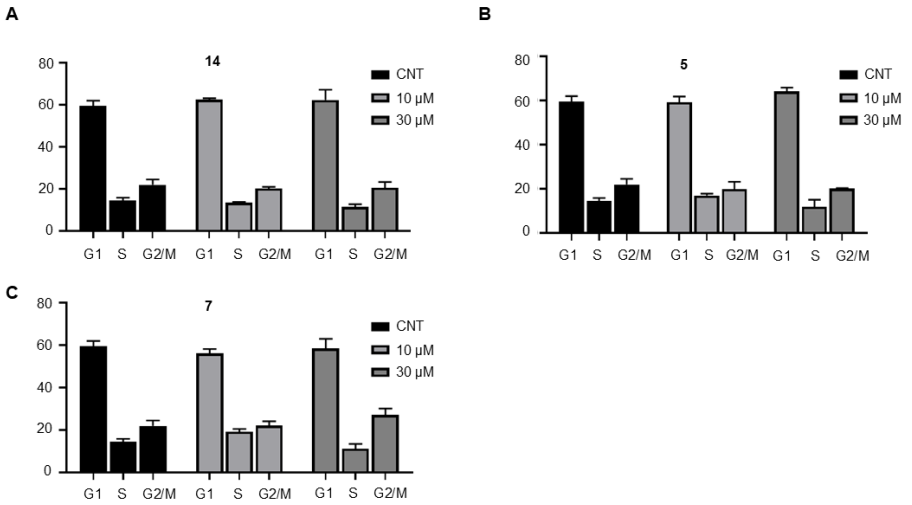


Figure S58: A) Cell cycle analysis for compound **14**, B) Cell cycle analysis for compound **5**, C) Cell cycle analysis for compound **7**.

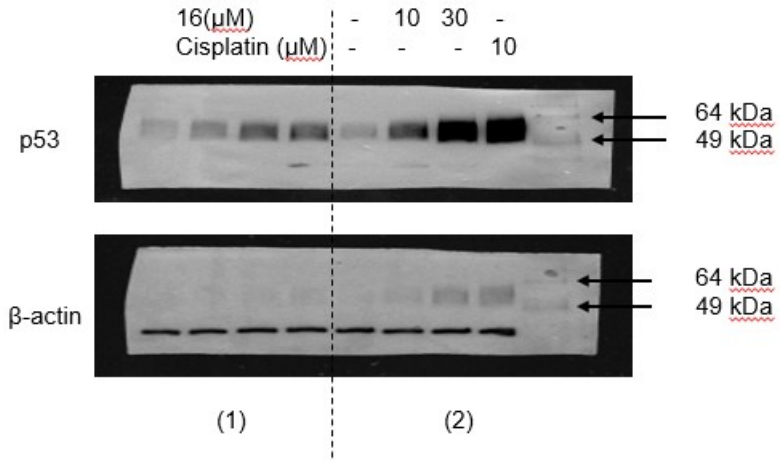


Figure S59: Whole blot images of Western-blot experiment. Both p53 and b-actin were blotted on the same membrane. Molecular mass markers are shown. Part (2) of the whole blot image is used in Figure 2E.

4. References.

(1) Eliopoulos, A. G.; Kerr, D. J.; Herod, J.; Hodgkins, L.; Krajewski, S.; Reed, J. C.; Young, L. S. The Control of Apoptosis and Drug Resistance in Ovarian Cancer: Influence of P53 and Bcl-2. *Oncogene* **1995**, *11* (7), 1217–1228.

(2) Nickerson, M. L.; Witte, N.; Im, K. M.; Turan, S.; Owens, C.; Misner, K.; Tsang, S. X.; Cai, Z.; Wu, S.; Dean, M.; Costello, J. C.; Theodorescu, D. Molecular Analysis of Urothelial Cancer Cell Lines for Modeling Tumor Biology and Drug Response. *Oncogene* **2017**, *36* (1), 35–46. https://doi.org/10.1038/onc.2016.172.

(3) Vardouli, L.; Lindqvist, C.; Vlahou, K.; Loskog, A. S. I.; Eliopoulos, A. G. Adenovirus Delivery of Human CD40 Ligand Gene Confers Direct Therapeutic

Effects on Carcinomas. *Cancer Gene Ther.* **2009**, *16* (11), 848–860. https://doi.org/10.1038/cgt.2009.31.
(4) Gkirtzimanaki, K.; Gkouskou, K. K.; Oleksiewicz, U.; Nikolaidis, G.; Vyrla, D.; Liontos, M.; Pelekanou, V.; Kanellis, D. C.; Evangelou, K.; Stathopoulos, E. N.; Field, J. K.; Tsichlis, P. N.; Gorgoulis, V.; Liloglou, T.; Eliopoulos, A. G. TPL2 Kinase Is a Suppressor of Lung Carcinogenesis. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110* (16), E1470-1479. https://doi.org/10.1073/pnas.1215938110.
(5) Mo, S.; Xu, C.; Xu, J. Expeditious and Convenient Synthesis of Polycyclic Difluoroboron Complexes of 2-Oxoindoline-3-Carboxamides by Tandem Reaction. *Adv. Synth. Catal.* **2016**, *358* (11), 1767–1777. https://doi.org/10.1002/adsc.201600118.
(6) Allais, C.; Constantieux, T.; Rodriguez, J. Use of β,γ-Unsaturated α-Ketocarbonyls for a Totally Regioselective Oxidative Multicomponent Synthesis of Polyfunctionalized Pyridines. *Chem. – Eur. J.* **2009**, *15* (47), 12945–12948. https://doi.org/10.1002/chem.200902491.
(7) Döben, N.; Yan, H.; Kischkewitz, M.; Mao, J.; Studer, A. Intermolecular Acetoxyaminoalkylation of α-Diazo Amides with (Diacetoxyiodo)Benzene and Amines. *Org. Lett.* **2018**, *20* (24), 7933–7936. https://doi.org/10.1021/acs.orglett.8b03504.
(8) Chan, W.-W.; Kwong, T.-L.; Yu, W.-Y. Ruthenium-Catalyzed Intramolecular Cyclization of Diazo-β-Ketoanilides for the Synthesis of 3-Alkylideneoxindoles. *Org. Biomol. Chem.* **2012**, *10* (18), 3749–3755. https://doi.org/10.1039/C2OB06985G.
(9) Crespin, L.; Biancalana, L.; Morack, T.; Blakemore, D. C.; Ley, S. V. One-Pot Acid-Catalyzed Ring-Opening/Cyclization/Oxidation of Aziridines with *N* -Tosylhydrazones: Access to 1,2,4-Triazines. *Org. Lett.* **2017**, *19* (5), 1084–1087. https://doi.org/10.1021/acs.orglett.7b00101.
(10) Klimovica, K.; Heidlas, J. X.; Romero, I.; Le, T. V.; Daugulis, O. "Sandwich" Diimine-Copper Catalysts for C−H Functionalization by Carbene Insertion. *Angew. Chem. Int. Ed.* **2022**, *61* (31), e202200334. https://doi.org/10.1002/anie.202200334.
(11) Berthod, R.; Favre-Réguillon, A.; Mohamad, J.; Mignani, G.; Docherty, G.; Lemaire, M. A Catalytic Method for the Reduction of Secondary and Tertiary Phosphine Oxides. *N. Y.* **2007**, No. 10.
(12) Bonge, H. T.; Pintea, B.; Hansen, T. Highly Efficient Formation of Halodiazoacetates and Their Use in Stereoselective Synthesis of Halocyclopropanes. *Org. Biomol. Chem.* **2008**, *6* (20), 3670. https://doi.org/10.1039/b814374a.
(13) Tonis, E.; Tzouras, N. V.; Bracho Pozsoni, N.; Saab, M.; Bhandary, S.; Van Hecke, K.; Nelson, D. J.; Nahra, F.; Nolan, S. P.; Vougioukalakis, G. C. Modular Synthesis of Azines Bearing a Guanidine Core from N-Heterocyclic Carbene (NHC)-Derived Selenoureas and Diazo Reagents. *Chem. – Eur. J.* **2024**, *30* (53), e202401816. https://doi.org/10.1002/chem.202401816.