Supporting Information

for

2-Phenylbenzothiazolyl Iridium Complexes as Inhibitors and Probes of Amyloid β Aggregation

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I. Experimental Procedures

General methods. All reagents were purchased from commercial sources and used as received unless stated otherwise. Solvents were purified prior to use by passing through a column of activated alumina using an MBRAUN SPS. All solutions and buffers were prepared using metal-free Millipore water that was treated with Chelex overnight and filtered through a 0.22 μm nylon filter. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a Bruker 500 spectrometer (500 MHz). Chemical shifts are reported in ppm downfield from tetramethylsilane. UV-visible spectra were recorded on a Varian Cary 50 Bio spectrophotometer and are reported as λ_{max}, nm (ε, M^{-1} cm^{-1}). **HN-1** to **HN-8** were dissolved in DMSO to prepare 5.0 mM stock solutions.

Aβ peptide preparation. All Aβ$_{42}$ monomeric films were prepared following a literature protocol. Briefly, the Aβ$_{42}$ peptide (GLBio) was dissolved in hexafluoroisopropyl alcohol (HFIP, 1 mM) and incubated for 1 h at room temperature. The clear solution was transferred into low-binding Eppendorf tubes and allowed to evaporate overnight. The aliquots were dried by vacuum centrifugation for 10 min, and the resulting films of monomeric Aβ$_{42}$ were stored at -80 °C. Aβ fibrils were generated by dissolving monomeric Aβ films in DMSO, diluting into the appropriate buffer, and incubating for 24 h at 37 °C with continuous agitation (final DMSO concentration was < 2%). For preparation of Aβ$_{42}$ oligomers, peptides were suspended in PBS buffer and incubated overnight at 4 °C.[1] For preparation of Aβ$_{42}$ monomers, peptides were suspended in PBS buffer and utilized for measurements within 1 hour of suspension.

Fluorescence measurements. All fluorescence measurements were performed using a SpectraMax M2e plate reader (Molecular Devices). For the ThT-based kinetic studies, complexes **HN-1** to **HN-8** were diluted to a final concentration of 10 μM along with Aβ (10 μM) in PBS containing 10 μM of ThT, and the fluorescence was measured at 485 nm (λ_{ex} = 435 nm) for 40 hours.

Histological staining of 5xFAD mice brain sections. Eight-month-old 5xFAD transgenic mice brain sections were blocked with bovine serum albumin (2% BSA in PBS, pH 7.4, 10 min) and covered with a PBS solution of compound and Congo Red (5 μM) for 60 min. The sections were treated with BSA again (4 min) to remove any compound non-specifically bound to the tissue. Finally, the sections were washed with PBS (3 × 2 min), DI water (2 min), and mounted with non-fluorescent mounting media. For antibody staining, the brain sections were incubated with CF594-conjugated HJ3.4 anti-Aβ antibody (CF594-HJ3.4) solution (1:1000 dilution in blocking solution)

at room temperature for 1 h instead of Congo Red. The HJ3.4 antibody was purchased from the Holtzman laboratory, Washington University, St Louis, USA. The brain sections were then washed with PBS (3 × 2 min) and mounted with mounting media. The stained brain sections were imaged using an Invitrogen™ EVOS™ FL Auto 2 Imaging System equipped with the following LED cubes: DAPI channel (357/44 ex, 447/60 em), GFP channel (470/22 ex, 525/50 em), and Texas Red channel (585/29 ex, 628/32 em).

Log D measurements. The compound (80 μM) in 0.5 mL octanol was subjected to partition with 0.5 mL octanol-saturated PBS (pH 7.4). The resulting mixture was stirred vigorously for 5 min, and centrifuged at 2,000 rpm for 5 min. The octanol layer was separated from PBS layer, and its fluorescence spectrum was recorded (excited at 305 nm). The above PBS layer was partitioned with PBS-saturated octanol 0.5 mL, and the octanol layer was separated after 5 min. vigorous stirring and 5 min. centrifuge at 2,000 rpm, and its spectrum was recorded. The Log D value was calculated by the fluorescence intensity ratio at 400 nm for the above two octanol extractions.

K_i measurements. A 96-well plate was equipped with compound (at varying concentrations), Thioflavin T (4 μM), and $A\beta_{42}$ fibrils (10 μM) in triplicate in 100 μL total volume. For each concentration of compound, a corresponding control well was equipped with compound and $A\beta_{42}$ aggregates (10 μM). The fluorescence was measured following 15 minutes of shaking at 485 nm (λex = 435 nm) using a SpectraMax M2e plate reader (Molecular Devices, USA).

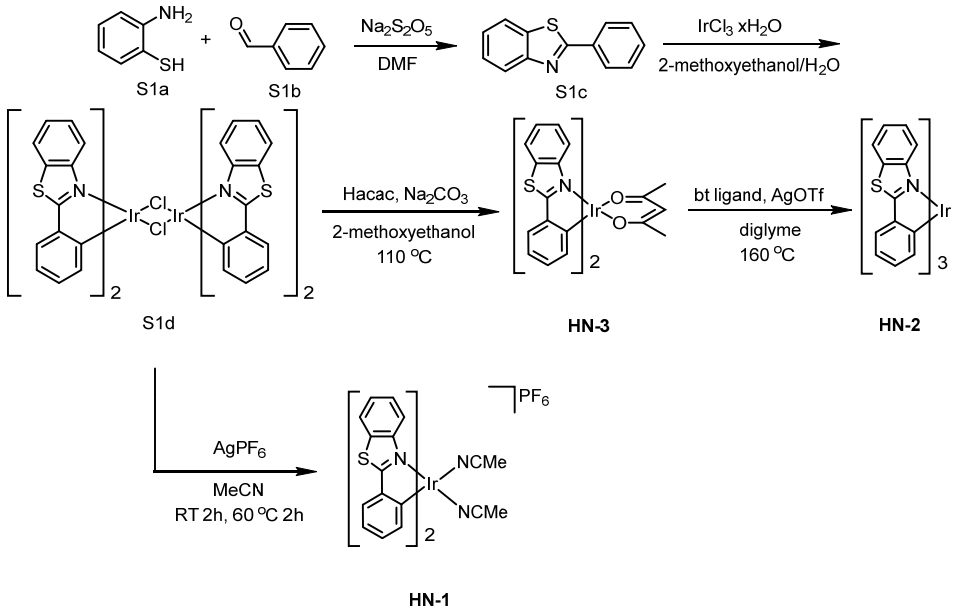
Kd measurements. A 96-well plate was equipped with compound (at varying concentrations) and $A\beta_{42}$ oligomers in triplicate in 100 uL total volume. For each concentration of compound, a corresponding control well was equipped with compound. The fluorescence was measured following 15 min of shaking using a SpectraMax M2e plate reader (Molecular Devices, USA).

Cell viability studies. The N2A cells (American Type Culture Collection Line CCL-131™) were seeded (2.5×10^4 cells/well) onto 96-well plates with DMEM/10% FBS and incubated for 24 h. The media was replaced with serum-free medium containing N_2 supplement. After 1 h, the $A\beta_{42}$ peptide [20 μM], $CuCl_2$ [20 μM], and Iridium complexes [2 μM] were added into each well in different conditions ($A\beta_{42}$ only, Iridium complexes only, $A\beta_{42}$ only, $A\beta_{42}$ + Iridium complexes), followed by incubation at 37 °C. The final volume in each well was 100 μL, with up to 1% DMSO. After 40 h, each well was treated with 10 μL of Alamar blue reagent and the cells were incubated for 1.5 h. Absorbance was measured at 570 nm (control OD = 600 nm) using a SpectraMax M2e plate reader (Molecular Devices, USA).

Animal studies. Experiments involving animals were performed in compliance with the Institutional Animal Care and Use committee of the University of Illinois at Urbana-Champaign. Eleven-month-old 5xFAD mice were divided into three groups[2]. The three groups of 2 mice each were treated daily with freshly prepared solutions of **HN-2**, **HN-3**, and **HN-8** via intraperitoneal injection (1 mg/kg of body weight in 200 µL of PBS, pH 7.4, 1% DMSO). After 10 days, all mice were sacrificed under deep anaesthesia for perfusion and the brains were harvested.

Determination of complex stability in injection media. Solutions of complex in PBS (500 µM, pH 7.4) were incubated at room temperature for 0 or 24 hr. Samples were diluted to 50 µM in MeCN prior to HPLC analysis (Agilent Technologies 1260 Infinity II).

II. Synthesis and characterization of Iridium complexes



Scheme S1. Synthesis of Iridium complexes **HN-1-3**.

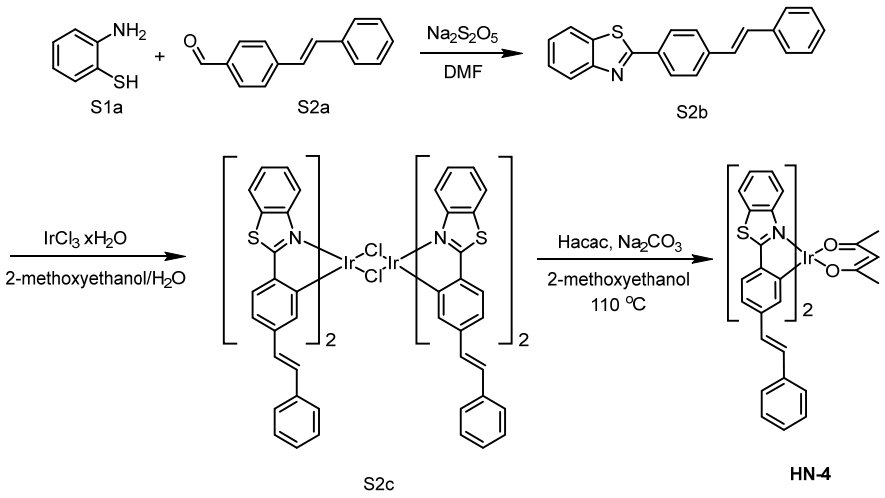
S1c. $Na_2S_2O_5$ (2.56 g) was added to a stirring mixture of **S1a** (1.41 mL, 13.2 mmol) and **S1b** (1.48 mL, 13.2 mmol) in DMF (42 mL). The reaction mixture was then refluxed for 2h. After completion of the reaction, the mixture was allowed to cool to room temperature. After addition of water (150 mL), the product **S1c** (2.44 g, 82%) was precipitated as a solid.

S1d $[Ir(bt)_2(\mu\text{-}Cl)]_2$. A mixture of $IrCl_3 \cdot xH_2O$ (248 mg, 0.83 mmol, 1 equiv) and ligand **S1c** (bt, 369 mg, 1.74 mmol, 2.1 equiv) in 40 mL of 2-methoxyethanol/H_2O (v:v=3:1) was refluxed under N_2 for 24 h. After the resulting solution was cooled down to room temperature, cold DI water was added. The precipitate was filtered and washed with DI water and a minimum amount of acetone. The solid was dried under vacuum to give the orange colored chloro-bridged dimer. The resulting dimer was used without further purification or characterization.

HN-1. This compound was synthesized by modification of a previously reported procedure.[3] In the glovebox, **S1d** (150 mg, 1 equiv) was dissolved in 50 mL of acetonitrile and to the reaction mixture was added $AgPF_6$ (66 mg, 2.2 equiv). The reaction mixture was stirred at room temperature for 2 h and then was taken outside of glovebox and heated to 60 °C for an additional 2 h. The resulting solution was cooled down and filtered through Celite to remove AgCl. The solvent volume was reduced, and the product was precipitated by addition of hexane. The yellow precipitate was collected, washed with hexane and dried under vacuum. Yield: 188 mg, 90%. A suitable crystal for X-ray crystallography was grown using the BF_4 salt of **HN-1**. ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.49 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.1 Hz, 1H), 7.82 (dd, J = 8.4, 7.2 Hz, 1H), 7.66 (t, J = 7.8 Hz, 2H), 6.99 (t, J = 7.5 Hz, 1H), 6.80 (t, J = 7.6 Hz, 1H), 6.20 (d, J = 7.7 Hz, 1H), 2.43 (d, J = 0.9 Hz, 3H). ^{19}F NMR (470 MHz, $CDCl_3$) δ −72.25 (3F), −73.76 (3F). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 147.7, 141.3, 138.5, 130.4, 129.4, 128.9, 124.7, 123.8, 121.2, 121.0, 119.7, 118.7. 27.8, 1.5. Calcd for $[M\text{-}(MeCN)_2]^+$, 613.0384; Found 613.0383.

HN-3. $[Ir(bt)_2(\mu\text{-}Cl)]_2$ (200 mg, 0.15 mmol, 1 equiv) and Na_2CO_3 (100 mg, 0.943 mmol, 6.3 equiv) were dissolved in 0.03 mL of acetylacetone and 10 mL of 2-methoxyethanol. The resulting reaction mixture was refluxed under N_2 overnight. After cooling the reaction mixture to room temperature, DI water was added. The orange precipitate was collected and washed with DI water and then hexane. The crude product was purified by flash column on silica using CH_2Cl_2. The solid was dried under vacuum to give the product. Yield: 146 mg, 72%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.31-8.22 (m, 2H), 8.04-7.87 (m, 2H), 7.75 (d, J = 7.7 Hz, 2H), 7.66-7.49 (m, 4H), 6.86 (t, J = 7.4 Hz, 2H), 6.61 (t, J = 7.4 Hz, 2H), 6.21 (d, J = 7.8 Hz, 2H), 5.19 (d, J = 1.1 Hz, 1H), 1.72 (d, J = 1.1 Hz, 6H). The ^{1}H NMR spectrum matches those in the literature.[4] Calcd for $[M]^+$, 712.0830; Found 712.0840.

HN-2. A mixture of $Ir(bt)_2(acac)$ **HN-3** (82 mg, 0.12 mmol, 1 equiv), ligand **S1c** (100 mg, 0.47 mmol, 4 equiv), AgOTf (61 mg, 0.24 mmol, 2 equiv), and diglyme (5 mL) was refluxed under N_2 at 160 °C overnight. The resulting reaction mixture was cooled down to room temperature and DI water was added. The precipitation was collected and washed with water. The resulting solid was extracted with CH_2Cl_2 and the orange solution was filtered through silica and then the solvent was removed under vacuum. The crude solid was washed with a minimum amount of acetone and dried under vacuum to give a bright orange product. Yield: 50 mg, 53%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.7 Hz, 3H), 7.66 (dd, J = 7.6, 1.5 Hz, 3H), 7.23-7.16 (m, 3H), 6.90 (dtd, J = 8.4, 7.1, 6.7, 1.3 Hz, 6H), 6.81 (td, J = 7.5, 1.5 Hz, 3H), 6.68 (d, J = 8.3 Hz, 3H), 6.64-6.59 (m, 3H). The ^{1}H NMR spectrum matches those in the literature.[5] Calcd for $[M]^+$, 823.0762; Found 823.0769.



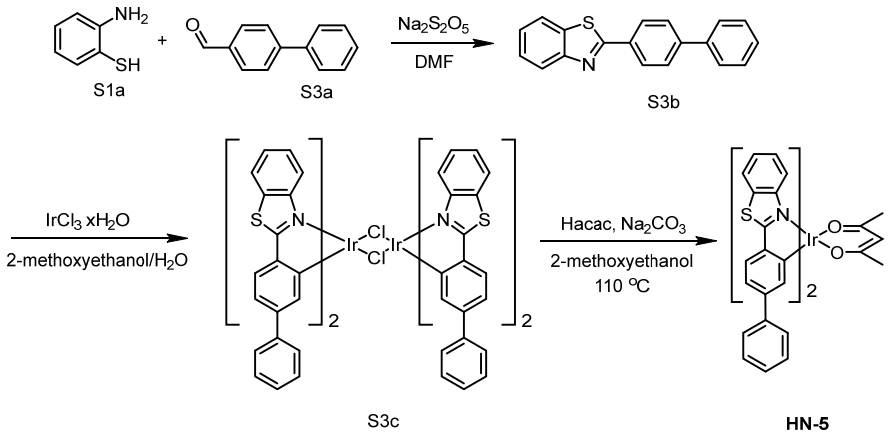
Scheme S2. Synthesis of Iridium complexes **HN-4**.

S2b. $Na_2S_2O_5$ (210 mg) was added to a stirring mixture of **S1a** (1.8 g, 14.4 mmol) and **S2a** (3.0 g, 14.4 mmol) in DMF (50 mL). The reaction mixture was then refluxed at 130 °C for 6 h, and then the reaction mixture was poured into ice water and the solid product was filtered. Crystallization of crude product from ethanol gave pure product **S2b** (3.4 g, 75%).

S2c. A mixture of $IrCl_3{\cdot}xH_2O$ (248 mg, 0.81 mmol, 1 equiv) and ligand **S2b** (650 mg, 2.07 mmol, 2.5 equiv) in 40 mL of 2-methoxyethanol/H_2O (v:v=3:1) was refluxed under N_2 for 24 h. After resulting solution was cooled down to room temperature, cold DI water was added. The

precipitation was filtered and washed with DI water and a minimum amount of acetone. The solid was dried under vacuum to give the orange colored chloro-bridged dimer **S2c**. The resulting complex was used without further purification or characterization.

HN-4. S2c (284 mg, 0.17 mmol, 1 equiv) and Na_2CO_3 (118 mg, 1.11 mmol, 6.6 equiv) were dissolved in 0.03 mL of acetylacetone and 10 mL of 2-methoxyethanol. The resulting reaction mixture was refluxed under N_2 overnight. After cooling the reaction mixture to room temperature, DI water was added. The orange precipitate was collected and washed with DI water and then hexane. The crude product was purified by flash column on silica using CH_2Cl_2. The solid was dried under vacuum to give pure product **HN-4** (38 mg, 12%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.20-8.13 (m, 2H), 7.99-7.94 (m, 2H), 7.68 (d, J = 8.0 Hz, 2H), 7.48 (s, 4H), 7.30 (dt, J = 13.1, 7.8 Hz, 10H), 7.21 (d, J = 7.1 Hz, 2H), 7.12 (d, J = 9.2 Hz, 2H), 6.73 (d, J = 5.4 Hz, 2H), 6.53 (s, 2H), 5.19 (s, 1H), 1.82 (s, 6H). Calcd for $[M]^+$,916.1769; 916.1787.



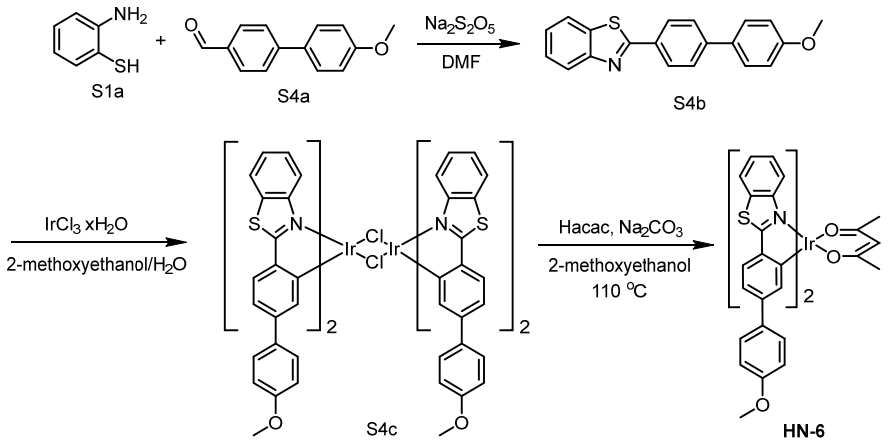
Scheme S3. Synthesis of Iridium complexes **HN-5**.

S3b. $Na_2S_2O_5$ (240 mg) was added to a stirring mixture of **S1a** (2.1 g, 16.5 mmol) and **S3a** (3.0 g, 16.5 mmol) in DMF (50 mL). The reaction mixture was then refluxed at 130 °C overnight. Then the reaction mixture was poured into ice water and the solid product was filtered. Crystallization of crude product from ethanol gave pure product **S3b** (2.4 g, 51%).

S3c. A mixture of $IrCl_3 \cdot xH_2O$ (242 mg, 0.80 mmol) and ligand **S3b** (608 mg, 2.12 mmol) in 40 mL of 2-methoxyethanol/H_2O (v:v = 3:1) was refluxed under N_2 for 24 h. After resulting solution was cooled down to room temperature, cold DI water was added. The precipitation was filtered and washed with DI water and minimum amount of acetone. The solid was dried under vacuum to

give orange colored chloro-bridged dimer **S3c**. The resulting dimer was used without further purification or characterization.

HN-5. S3c (224 mg, 0.14 mmol) and Na_2CO_3 (148 mg, 1.39 mmol) were dissolved in the solution of 42 mg of acetylacetone in 10 mL of 2-methoxyethanol. The resulting reaction mixture was refluxed under N_2 overnight. After cooling the reaction mixture to room temperature, DI water was added. The orange precipitate was collected and washed with DI water, ethanol and then hexane. The crude product was purified by flash column on silica using hexane and ethyl acetate (hexane:ethyl acetate = 2:1). The solid was dried under vacuum to give product **HN-5** (52 mg, 21%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.21 (d, *J* = 9.2 Hz, 2H), 7.94 (d, *J* = 9.1 Hz, 2H), 7.74 (d, *J* = 7.9 Hz, 2H), 7.49 (dd, 4H), 7.32-7.21 (m, 6H), 7.11-7.13 (m, 6H), 6.67 (s, 2H), 5.20 (s, 1H), 1.83 (s, 6H). Calcd for $[M]^+$, 864.1456; Found 864.1470.



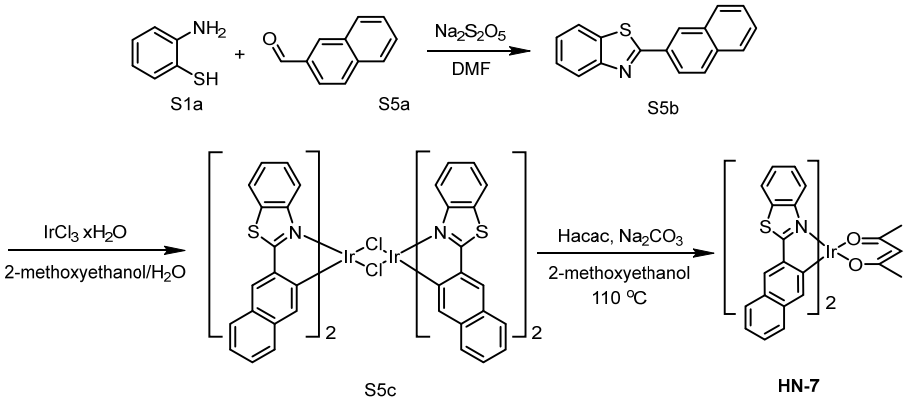
Scheme S4. Synthesis of Iridium complexes **HN-6**.

S4b. $Na_2S_2O_5$ (69 mg) was added to a stirring mixture of **S1a** (588 mg, 4.7 mmol) and **S5a** (1.0 g, 4.7 mmol) in DMF (20 mL). The reaction mixture was then refluxed overnight. After completion of the reaction, the mixture was allowed to cool to room temperature. After addition of water (100 mL), the crude product precipitated as a solid. After crystallization from ethanol, pure product **S4b** (955 mg, 64%) was obtained.

S4c. A mixture of $IrCl_3{\cdot}xH_2O$ (242 mg, 0.81 mmol, 1 equiv) and ligand **S4b** (658 mg, 2.07 mmol, 2.5 equiv) in 40mL of 2-methoxyethanol/H_2O (v:v=3:1) was refluxed under N_2 for 24 h. After resulting solution was cooled down to room temperature, cold DI water was added. The

precipitation was filtered and washed with DI water and minimum amount of acetone. The solid was dried under vacuum to give the orange colored chloro-bridged dimer **S4c**. The resulting dimer was used without further purification or characterization.

HN-6. S4c (241 mg, 0.14 mmol) and Na_2CO_3 (148 mg, 1.39 mmol) were dissolved in the solution of 42 mg of acetylacetone in 10 mL of 2-methoxyethanol. The resulting reaction mixture was refluxed under N_2 overnight. After cooling the reaction mixture to room temperature, DI water was added. The orange precipitate was collected and washed with DI water, ethanol and then hexane. The crude product was purified by flash column on silica using hexane and ethyl acetate (hexane:ethyl acetate = 2:1). The solid was dried under vacuum to give product **HN-6** (37 mg, 14%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.25-8.16 (m, 2H), 8.00-7.88 (m, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.52-7.44 (m, 4H), 7.17-7.05 (m, 6H), 6.76 (d, J = 8.7 Hz, 4H), 6.63 (d, J = 1.6 Hz, 2H), 5.19 (s, 1H), 3.77 (s, 6H), 1.83 (s, 6H). ESI-MS: Calcd for $[M+H]^+$, 925.1746; Found, 925.1711.



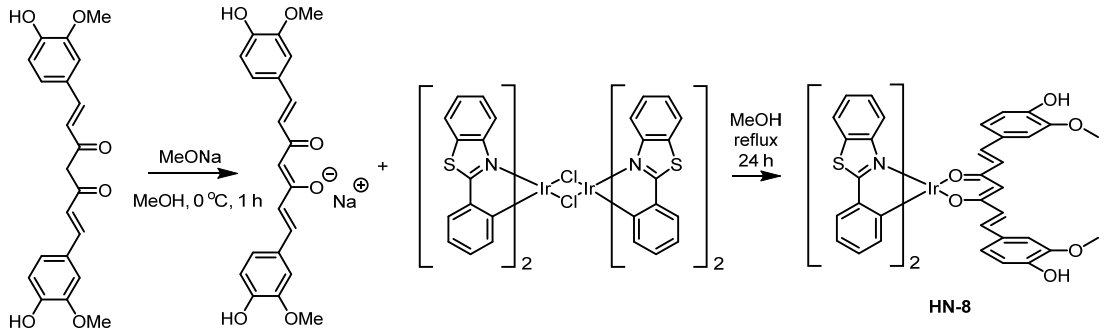
Scheme S5. Synthesis of Iridium complexes **HN-7**.

S5b. $Na_2S_2O_5$ (280 mg) was added to a stirring mixture of **S1a** (2.4 g, 19.2 mmol) and **S5a** (3.0 g, 19.2 mmol) in DMF (40 mL). The reaction mixture was then refluxed for 2h. After completion of the reaction, mixture was allowed to cool to room temperature. After addition of water (150 mL), the crude product precipitated as a solid. After recrystallization from ethanol, pure product **S1c** (1.5 g, 30%) was acquired.

S5c. A mixture of $IrCl_3 \cdot xH_2O$ (242 mg, 0.81 mmol, 1 equiv) and ligand **S5b** (541 mg, 2.07 mmol, 2.5 equiv) in 40mL of 2-methoxyethanol/H_2O (v:v=3:1) was refluxed under N_2 for 24 h. After resulting solution was cooled down to room temperature, cold DI water was added. The

precipitation was filtered and washed with DI water and minimum amount of acetone. The solid was dried under vacuum to give the orange colored chloro-bridged dimer **S5c**. The resulting dimer was used without further purification or characterization.

HN-7. S5c (250 mg, 0.17 mmol) and Na_2CO_3 (118 mg, 1.11 mmol) were dissolved in the solution of 33 mg of acetylacetone in 10 mL of 2-methoxyethanol. The resulting reaction mixture was refluxed under N_2 overnight. After cooling the reaction mixture to room temperature, DI water was added. The orange precipitate was collected and washed with DI water, ethanol and then hexane. The crude product was purified by flash column on silica using hexane and ethyl acetate (hexane:ethyl acetate = 2:1). The solid was dried under vacuum to give product **HN-7** (176 mg, 64%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.4 Hz, 4H), 7.99 (d, *J* = 8.1 Hz, 2H), 7.71-7.63 (m, 2H), 7.54-7.42 (m, 4H), 7.22-7.08 (m, 6H), 6.73 (s, 2H), 5.16 (s, 1H), 1.75 (s, 6H). ESI-MS: Calcd for $[M+H]^+$, 813.1221; Found, 813.1171.



Scheme S6. Synthesis of Iridium complexes **HN-8**.

HN-8. This compound was synthesized by modification of a previously reported procedure.[6] Curcumin (20 mg, 0.054 mmol) was dissolved in methanol (11 mL) and NaOMe (3 mg, 0.054 mmol) was added. The mixture was stirred for 1 h at 0 °C and then $[Ir(bt)_2(\mu\text{-}Cl)]_2$ (39 mg, 0.027 mmol) was added. The resulting orange solution was stirred at reflux for 24 h. The orange-red precipitate was purified through flash chromatography (hexane:ethyl acetate = 5:1) to give pure product **HN-8** (36 mg, 68%) as an orange solid. ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.2 Hz, 2H), 7.87 (d, *J* = 7.7 Hz, 2H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.38-7.29 (m, 4H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.99 (s, 2H), 6.92 (t, *J* = 7.4 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 2H), 6.71 (t, *J* = 7.5 Hz, 2H), 6.51 (d, *J* = 7.7 Hz, 2H), 6.45 (d, *J* = 15.7 Hz, 2H), 5.77 (s, 2H), 5.54 (s, 1H), 3.88 (s, 6H). ^{13}C NMR

(125 MHz, $CDCl_3$) δ 180.5, 177.7, 151.2, 149.2, 146.9, 146.8, 142.3, 136.5, 135.3, 131.6, 130.1, 129.3, 128.3, 127.7, 125.9, 125.3, 122.4, 122.0, 121.2, 120.7, 114.9, 109.5, 104.8, 56.2. ESI-MS: Calcd for $[M+H]^+$, 981.1644; Found, 981.1647.

III. UV-vis and emission spectra of Iridium complexes

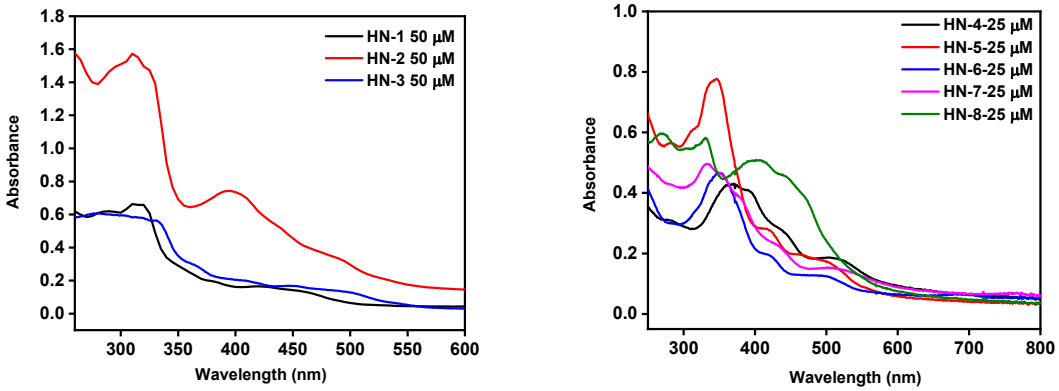


Figure S1. UV-vis spectra of investigated Iridium complexes in PBS with 0.5% DMSO.

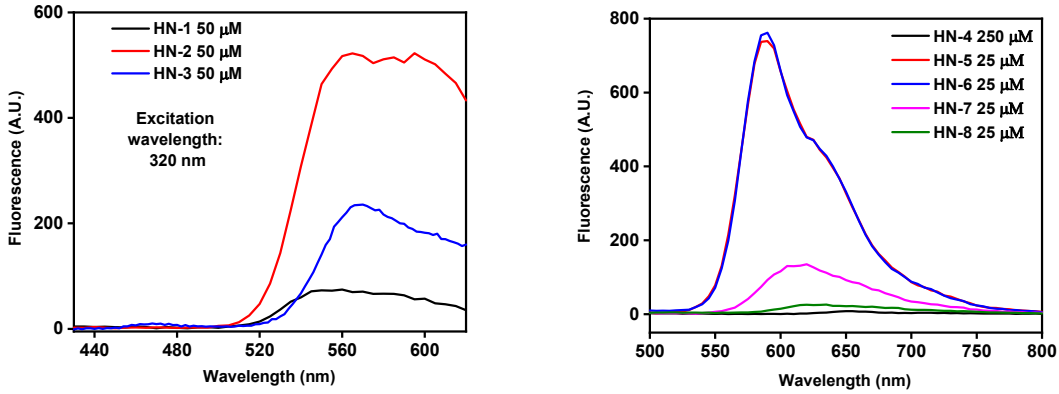


Figure S2. Fluorescence spectra of investigated Iridium complexes in PBS with 0.5% DMSO.

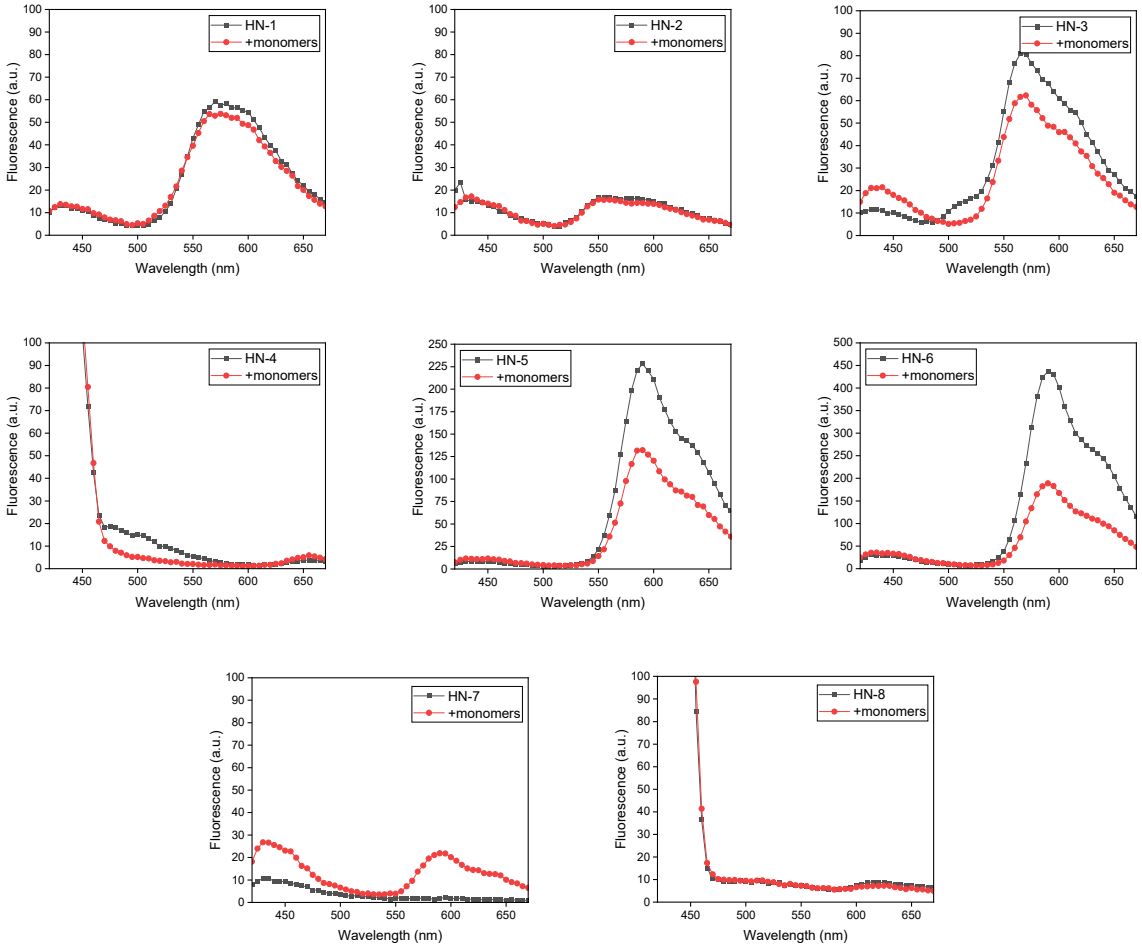


Figure S3. Fluorescence changes of complexes **HN-1** to **HN-8** upon incubation with $A\beta_{42}$ monomers. Complexes **HN-1**, **HN-2**, and **HN-3** were tested at 10 μM. Complexes **HN-4**, **HN-5**, **HN-6**, **HN-7**, and **HN-8** were tested at 20 μM. [$A\beta_{42}$] = 10 μM. Excitation wavelengths listed in table S1.

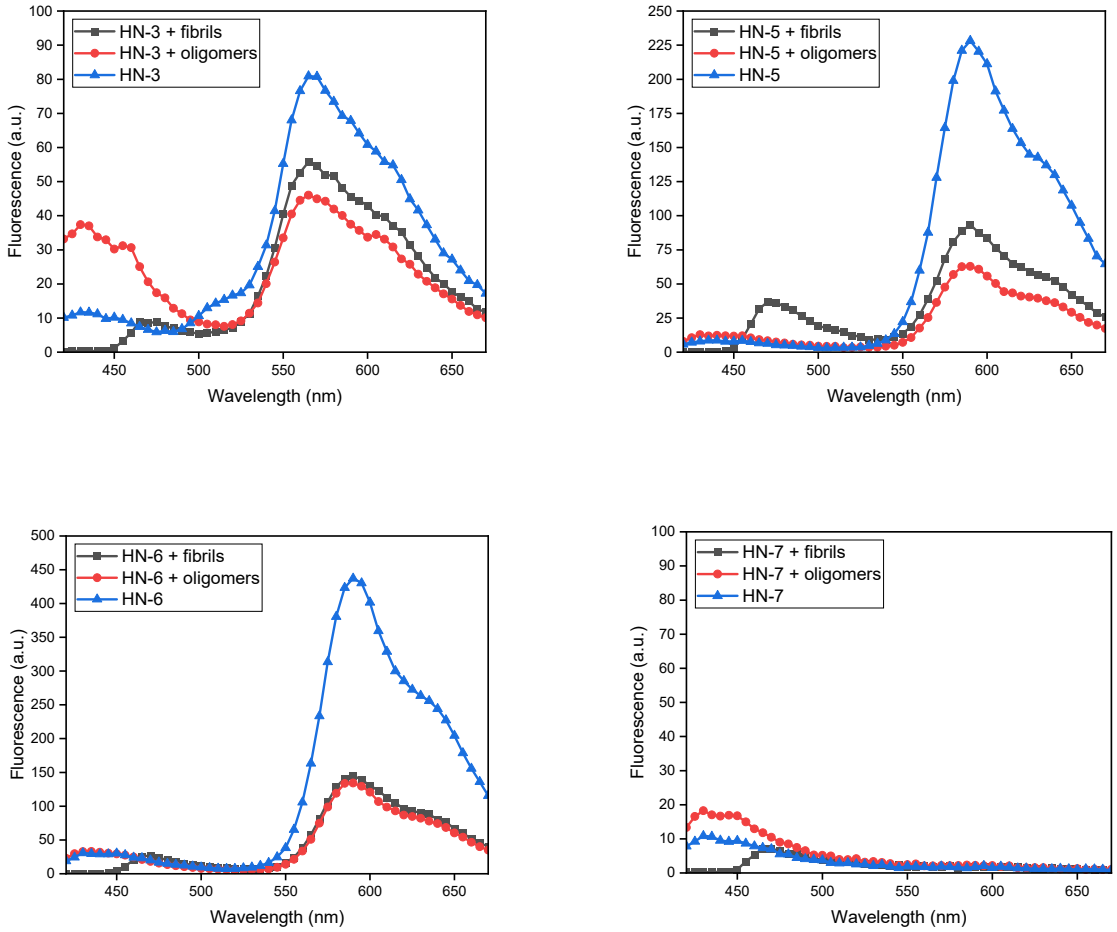


Figure S4. Fluorescence changes of complexes **HN-3**, **HN-5**, **HN-6**, and **HN-7** (blue) upon incubation with Aβ$_{42}$ oligomers (red) and fibrils (black). [**HN-3**] = 10 μM, [**HN-5**] = [**HN-6**] = [**HN-7**] = 20 μM. [Aβ$_{42}$] = 10 μM. Excitation wavelengths listed in table S1.

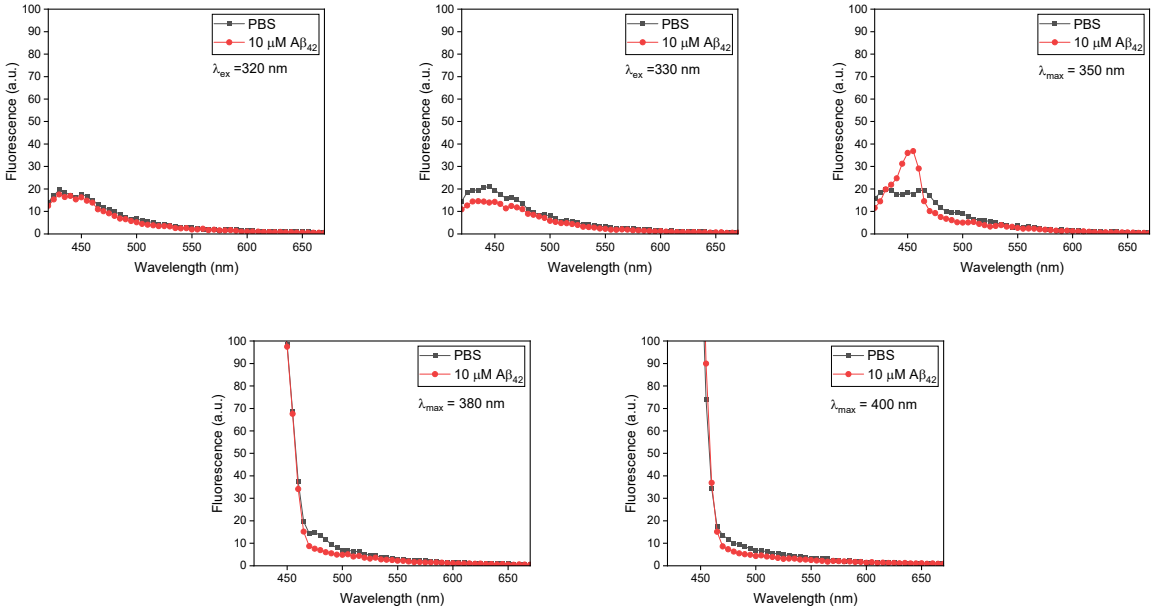


Figure S5. Fluorescence of $A\beta_{42}$ fibrils in PBS following excitation at wavelengths listed in table S1. pH 7.4. [$A\beta_{42}$] = 10 μM.

Table S1. Excitation and emission wavelengths of investigated Ir complexes.

Complexes	λ_{ex} *(nm)*	λ_{em} *(nm)*
HN-1	320	550
HN-2	320	565
HN-3	320	565
HN-4	380	650
HN-5	350	585
HN-6	350	585
HN-7	330	625
HN-8	400	625

IV. TEM figures of $A\beta_{42}$ oligomers and fibrils

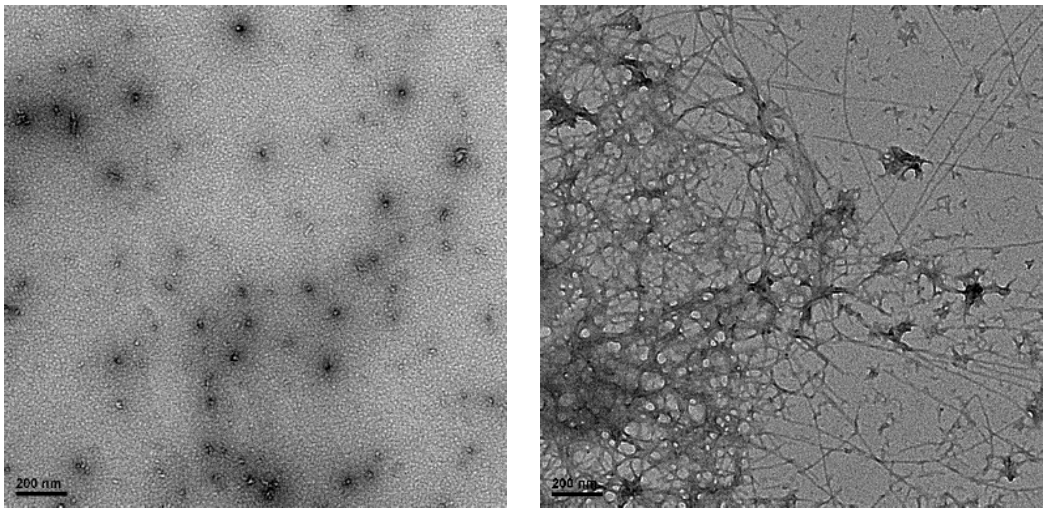


Figure S6. TEM images of $A\beta_{42}$ oligomers (left) and fibrils (right). Scale bar: 200 nm.

V. Complex affinity values with $A\beta_{42}$ species

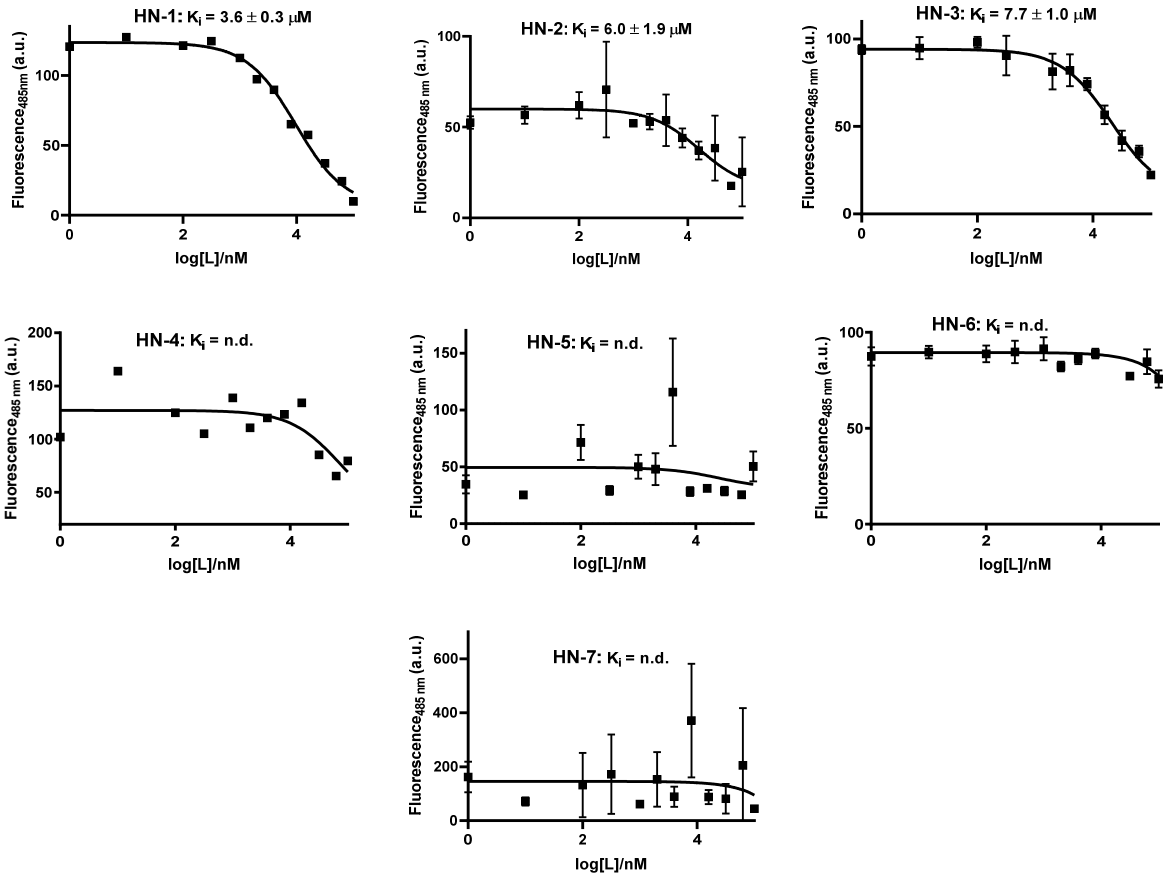


Figure S7. K_i determination of **HN-1 to HN-7** with $A\beta_{42}$ fibrils. Poor solubility of **HN-4** to **HN-7** limited concentrations at the ligands could be tested and K_i could not be determined for those ligands.

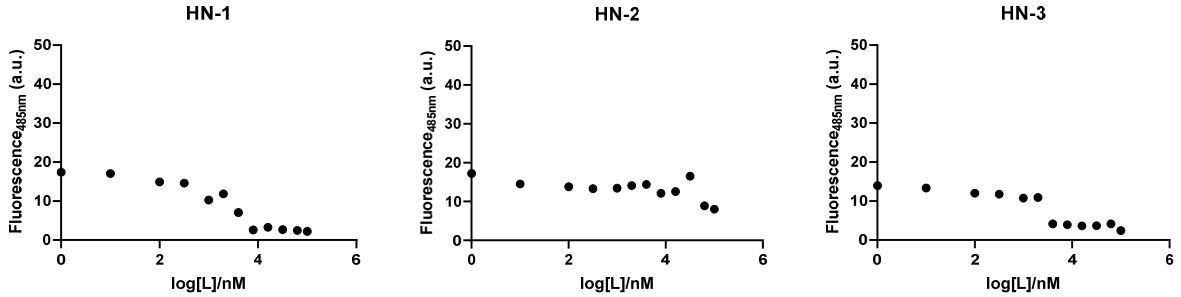


Figure S8. K_i control well values of **HN-1 to HN-3** loaded with various concentrations of complex and 2 μM Thioflavin T (λex = 435 nm, λem = 485 nm).

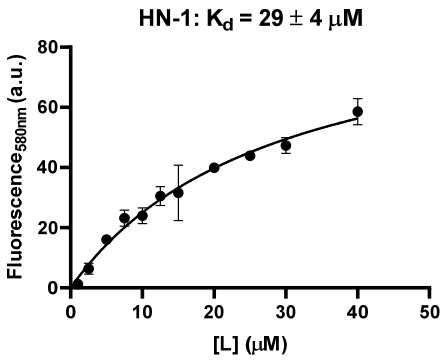


Figure S9. Determination of complex affinity with Aβ$_{42}$ oligomers. K_d determination of **HN-1** with Aβ$_{42}$ oligomers at various concentrations of complex. [Aβ$_{42}$] = 5 μM, (λex = 320 nm, λem = 580 nm).

VI. Inhibition of Amyloid β Aggregation

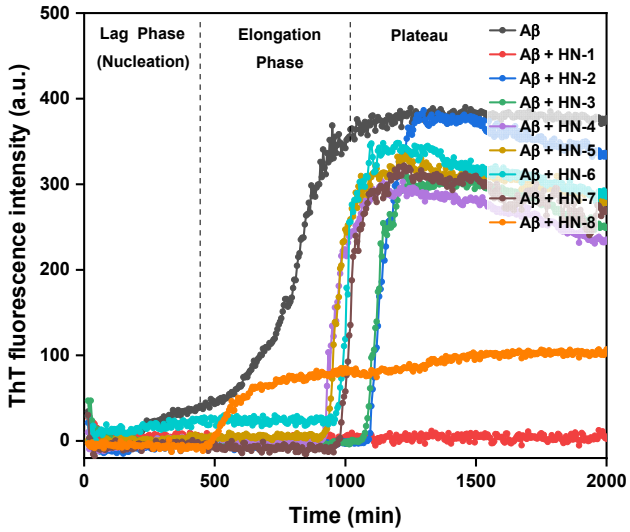


Figure S10. Time-resolved measurements of the aggregation of Aβ$_{42}$ through determination of ThT emission at 485 nm (ex = 435 nm) for monomeric Aβ$_{42}$ incubated with ligands **HN-1** to **HN-8**. [Aβ$_{42}$] = 10 μM; [ThT] = 10 μM; [ligand] = 10 μM.

Note: The abnormal time-resolved aggregation curve of Aβ$_{42}$ incubated with **HN-8** may be due to the decomposition of **HN-8**, since curcumin derivatives are proposed to undergo decomposition under physiological conditions.[7]

VII. Cytotoxicity studies of curcumin and curcumin with $A\beta_{42}$

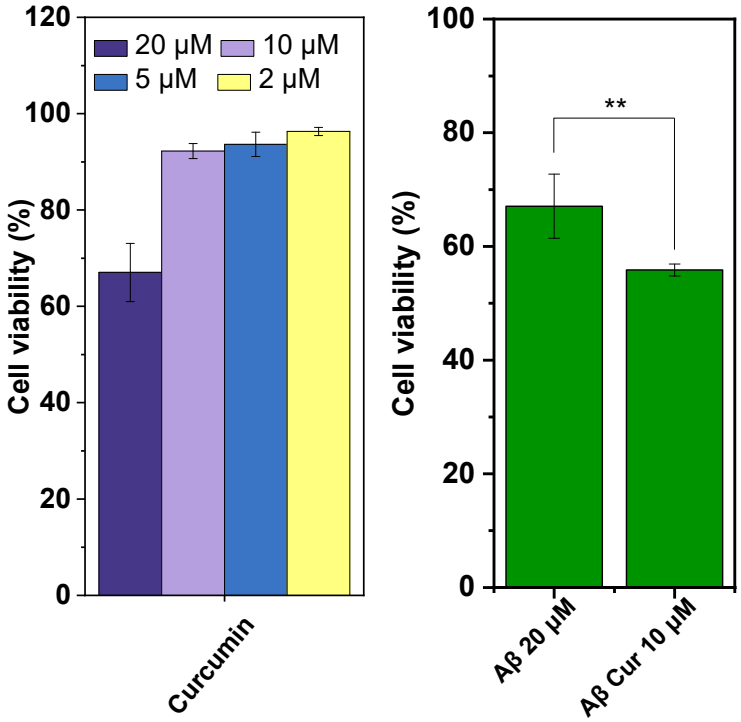


Figure S11. Cytotoxicity studies of curcumin (left) and curcumin with $A\beta_{42}$ (right).

VIII. In vivo blood-brain barrier permeability

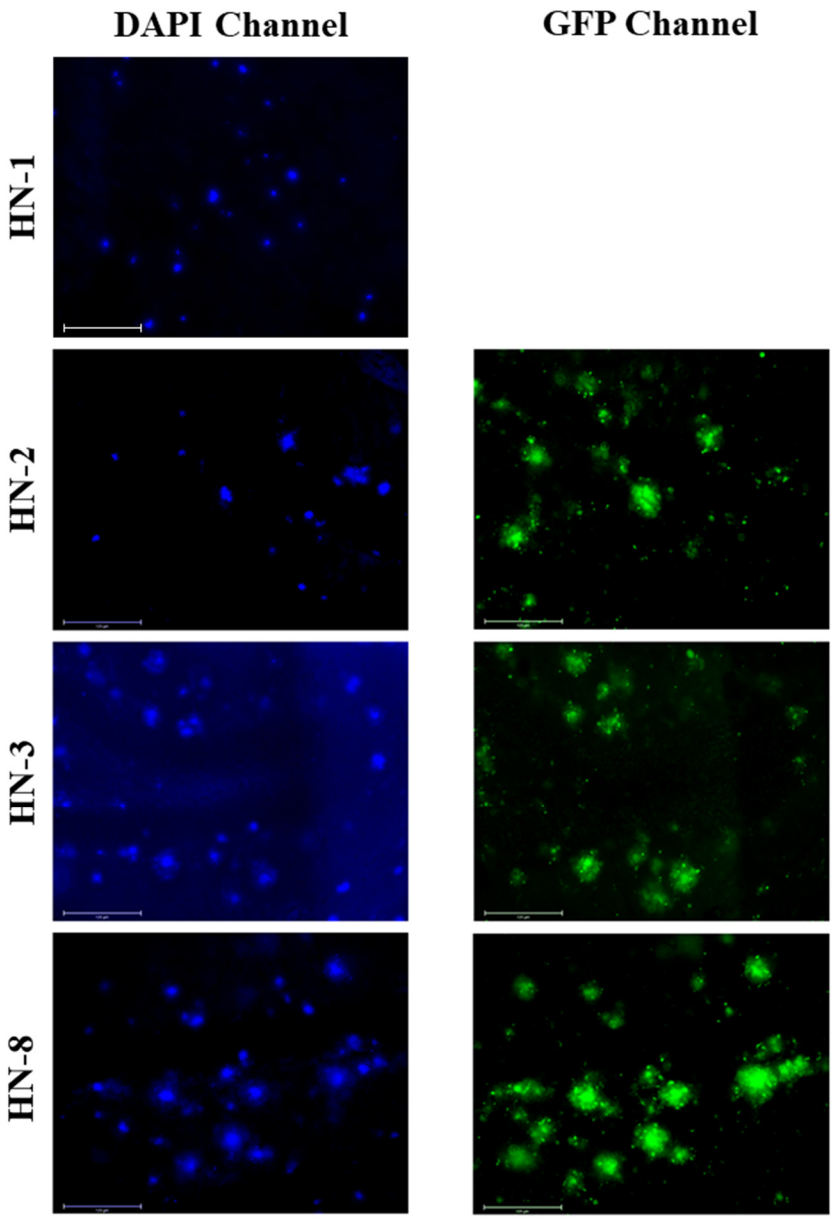


Figure S12. Representative fluorescence microscopy images of brain sections from 11-month old 5xFAD mice administrated with iridium complexes for 10 days i.p. Scale bar = 125 μm. No GFP image of HN-1 was obtained due to an observed lack of fluorescence.

Figure S13. Representative fluorescence microscopy images of brain sections from untreated 14-month old 5xFAD mice, stained with the CF594-HJ3.4 antibody. Scale bar = 125 μm.

Determination of complex stability in injection media.

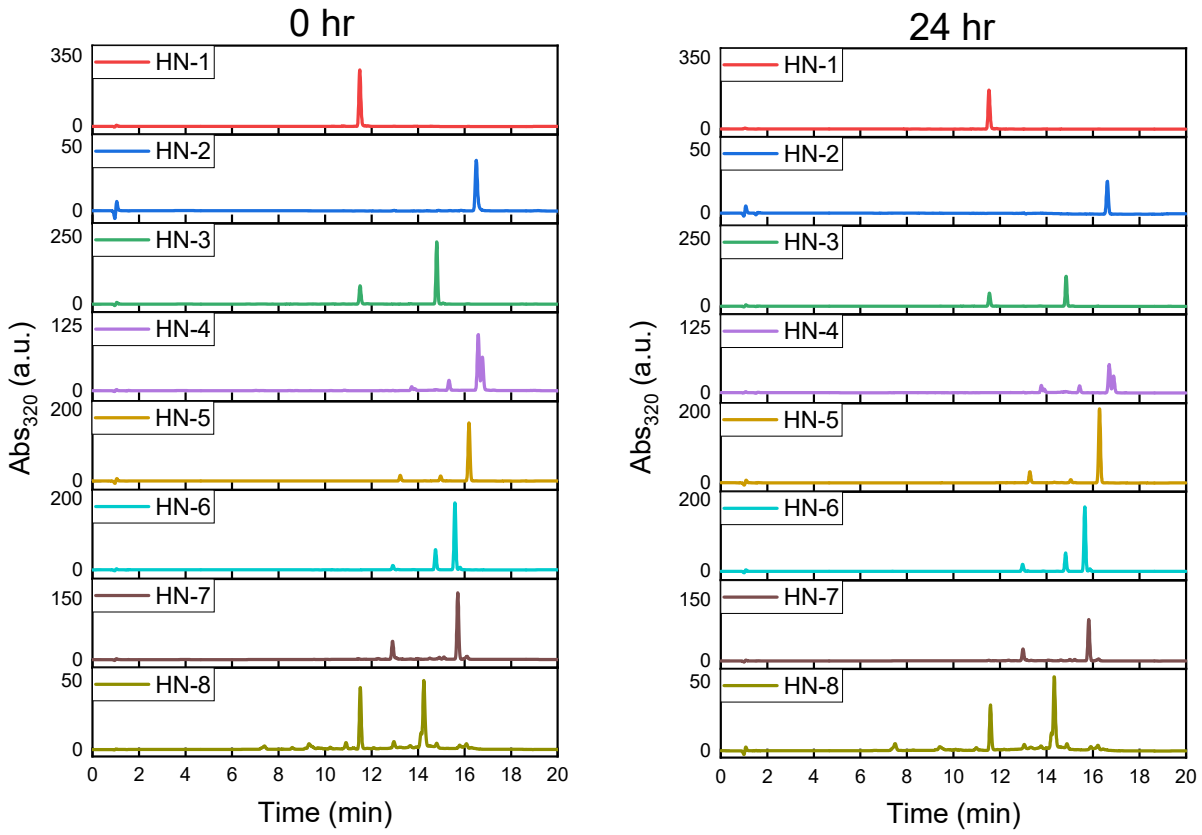


Figure S14. HPLC traces of complexes incubated in PBS for up to 24 hr.

Table S2. Complex peak areas and percent of peak remaining following 24 hr incubation in PBS for HPLC traces shown in Figure S14.

Complexes	*Retention Time*	*Peak Area (0 hr)*	*Peak Area (24 hr)*	*% Remaining (24 hr)*
HN-1	*11.5*	*1716*	*1147*	*97*
HN-1	*16.6*	*291*	*163*	*56*
HN-3	*11.5* *14.8*	*412* *1251*	*292* *589*	*71* *47*
HN-4	*16.8*	*1059*	*552*	*52*
HN-5	*16.2*	*992*	*1251*	*126*
HN-6	*15.6*	*1062*	*1008*	*95*
HN-7	*15.8*	*956*	*608*	*64*
HN-8	*11.5* *14.3*	*259* *375*	*210* *398*	*81* *106*

IX. X-ray structure determination of complex HN-1

General information. Single crystals were grown by layering solution of pentane over the concentrated solution of CH_2Cl_2 and $CHCl_3$. Crystals were mounted on a Bruker D8 Venture kappa diffractometer equipped with a Photon II CPAD detector. An Iμs microfocus Mo source (λ = 0.71073 Å) coupled with a multi-layer mirror monochromator provided the incident beam. The sample was mounted on a 0.3 mm nylon loop with the minimal amount of Paratone-N oil. Data was collected as a series of φ and/or ω scans. Data was collected at 100 K using a cold stream of N2(g). The collection, cell refinement, and integration of intensity data was carried out with the APEXIII software. (Bruker 2018 APEXIII. Bruker AXS, Inc.: Madison, Wisconsin, USA) A multiscan absorption correction was performed with SADABS.[8] The structure was phased with intrinsic methods using SHELXT and refined with the full-matrix leastsquares program SHELXL.[9] Hydrogen atoms were placed in calculated positions using the standard riding model and refined isotropically; all non-hydrogen atoms were refined anisotropically.

Table S3. Crystal data and structure refinement for **HN-1** (*CCDC deposition number 2070088*)

Crystal data	
Chemical formula	$C_{30}H_{22}IrN_4S_2 \cdot CHCl_3 \cdot BF_4$
M_r	901.01
Crystal system, space group	Triclinic, $P\bar{1}$
Temperature (K)	100
a, *b*, *c* (Å)	8.7808 (2), 11.9226 (3), 15.5911 (4)
α, β, γ (°)	94.55, 92.96, 93.46
V (Å^3)	1621.51 (7)
Z	2
Radiation type	Mo *K*α
μ (mm^{-1})	4.55
Crystal size (mm)	0.34 × 0.30 × 0.21
Data collection	
Diffractometer	Bruker Kappa/PhotonII CCD
Absorption correction	Multi-scan *SADABS2016*/2 (Bruker,2016/2) was used for absorption correction. wR2(int) was 0.1001 before and 0.0498 after correction. The Ratio of minimum to maximum transmission is 0.6739. The λ/2 correction factor

	is Not present.
T_{min}, T_{max}	0.502, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	119223, 8069, 7935
R_{int}	0.033
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.667
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.026, 0.072, 1.07
No. of reflections	8069
No. of parameters	454
No. of restraints	64
H-atom treatment	H-atom parameters constrained
$\Delta\rangle_{max}$, $\Delta\rangle_{min}$ (e Å^{-3})	1.24, -1.68

Table S4. Bond length (Å) and angles (°) for **HN-1**

Ir1—N2	2.064 (3)	C2—H2	0.9500
Ir1—N4	2.143 (3)	C2—C3	1.388 (5)
Ir1—N3	2.128 (3)	C5—H5	0.9500
Ir1—N1	2.061 (3)	C5—C4	1.377 (6)
Ir1—C14	2.008 (3)	C18—H18	0.9500
Ir1—C1	2.007 (3)	C25—H25	0.9500
S2—C20	1.724 (3)	C25—C24	1.386 (5)
S2—C21	1.740 (4)	C3—H3	0.9500
S1—C7	1.715 (3)	C3—C4	1.396 (6)
S1—C8	1.743 (4)	C8—C13	1.410 (5)
Cl1—C31	1.741 (5)	C8—C9	1.396 (5)
Cl2—C31	1.761 (5)	C13—C12	1.385 (6)
Cl3—C31	1.753 (6)	C4—H4	0.9500
N2—C26	1.398 (4)	C27—C28	1.452 (6)
N2—C20	1.320 (4)	C24—H24	0.9500
N4—C29	1.143 (5)	C24—C23	1.399 (5)
N3—C27	1.137 (5)	C28—H28A	0.9800
N1—C7	1.328 (5)	C28—H28B	0.9800
N1—C13	1.397 (5)	C28—H28C	0.9800
F1—B1	1.379 (8)	C22—H22	0.9500
C14—C19	1.412 (5)	C22—C23	1.386 (6)
C14—C15	1.402 (5)	C23—H23	0.9500
F3—B1	1.393 (9)	C30—H30A	0.9800
C1—C6	1.409 (5)	C30—H30B	0.9800

C1—C2	1.403 (5)	C30—H30C	0.9800
C19—C20	1.449 (5)	B1—F2	1.492 (7)
C19—C18	1.396 (5)	B1—F4	1.340 (6)
C6—C7	1.447 (5)	B1—F4A	1.527 (8)
C6—C5	1.396 (5)	B1—F2A	1.273 (9)
C26—C21	1.405 (5)	B1—F1A	1.378 (12)
C26—C25	1.390 (5)	B1—F3A	1.385 (13)
C15—H15	0.9500	C12—H12	0.9500
C15—C16	1.391 (5)	C12—C11	1.390 (6)
C16—H16	0.9500	C10—H10	0.9500
C16—C17	1.396 (6)	C10—C9	1.370 (7)
C29—C30	1.442 (5)	C10—C11	1.400 (7)
C17—H17	0.9500	C9—H9	0.9500
C17—C18	1.383 (5)	C11—H11	0.9500
C21—C22	1.389 (5)	C31—H31	1.0000

N2—Ir1—N4	102.11 (11)	C17—C18—H18	120.6
N2—Ir1—N3	84.20 (11)	C26—C25—H25	120.9
N3—Ir1—N4	86.14 (12)	C24—C25—C26	118.1 (3)
N1—Ir1—N2	171.77 (11)	C24—C25—H25	120.9
N1—Ir1—N4	84.46 (11)	C2—C3—H3	119.5
N1—Ir1—N3	101.34 (12)	C2—C3—C4	120.9 (4)
C14—Ir1—N2	80.10 (12)	C4—C3—H3	119.5
C14—Ir1—N4	177.53 (12)	C13—C8—S1	110.6 (3)
C14—Ir1—N3	93.02 (12)	C9—C8—S1	128.1 (3)
C14—Ir1—N1	93.44 (12)	C9—C8—C13	121.3 (4)
C1—Ir1—N2	94.26 (12)	N1—C13—C8	112.5 (3)
C1—Ir1—N4	92.62 (12)	C12—C13—C8	120.4 (3)
C1—Ir1—N3	177.77 (12)	C5—C4—C3	119.6 (3)
C1—Ir1—N1	80.37 (13)	C5—C4—H4	120.2
C1—Ir1—C14	88.29 (13)	C3—C4—H4	120.2
C20—S2—C21	89.83 (16)	N3—C27—C28	178.2 (4)
C7—S1—C8	89.45 (18)	C25—C24—H24	119.4
C26—N2—Ir1	133.9 (2)	C25—C24—C23	121.2 (4)
C20—N2—Ir1	113.6 (2)	C23—C24—H24	119.4
C20—N2—C26	112.4 (3)	C27—C28—H28A	109.5
C29—N4—Ir1	166.5 (3)	C27—C28—H28B	109.5
C27—N3—Ir1	168.8 (3)	C27—C28—H28C	109.5
C7—N1—Ir1	113.4 (2)	H28A—C28—H28B	109.5
C7—N1—C13	111.9 (3)	H28A—C28—H28C	109.5
C13—N1—Ir1	134.7 (2)	H28B—C28—H28C	109.5
C19—C14—Ir1	114.9 (2)	C21—C22—H22	121.2
C15—C14—Ir1	128.5 (3)	C23—C22—C21	117.7 (3)
C15—C14—C19	116.7 (3)	C23—C22—H22	121.2
C6—C1—Ir1	114.9 (2)	C24—C23—H23	119.4
C2—C1—Ir1	128.5 (3)	C22—C23—C24	121.2 (3)
C2—C1—C6	116.6 (3)	C22—C23—H23	119.4
C14—C19—C20	112.8 (3)	C29—C30—H30A	109.5
C18—C19—C14	122.9 (3)	C29—C30—H30B	109.5

C18—C19—C20	124.3 (3)	C29—C30—H30C	109.5
C1—C6—C7	112.9 (3)	H30A—C30—H30B	109.5
C5—C6—C1	122.5 (3)	H30A—C30—H30C	109.5
C5—C6—C7	124.5 (3)	H30B—C30—H30C	109.5
N2—C26—C21	112.8 (3)	F1—B1—F3	110.3 (12)
C25—C26—N2	126.7 (3)	F1—B1—F2	97.0 (8)
C25—C26—C21	120.4 (3)	F3—B1—F2	100.6 (9)
C14—C15—H15	119.6	F4—B1—F1	125.0 (7)
C16—C15—C14	120.9 (3)	F4—B1—F3	113.6 (10)
C16—C15—H15	119.6	F4—B1—F2	105.7 (5)
C15—C16—H16	119.5	F2A—B1—F4A	107.9 (8)
C15—C16—C17	121.0 (3)	F2A—B1—F1A	117.4 (14)
C17—C16—H16	119.5	F2A—B1—F3A	128.1 (18)
N2—C20—S2	114.7 (2)	F1A—B1—F4A	86.1 (11)
N2—C20—C19	118.0 (3)	F1A—B1—F3A	110.7 (19)
C19—C20—S2	127.3 (3)	F3A—B1—F4A	93.3 (15)
N1—C7—S1	115.5 (3)	C13—C12—H12	120.9
N1—C7—C6	118.2 (3)	C13—C12—C11	118.2 (4)
C6—C7—S1	126.3 (3)	C11—C12—H12	120.9
N4—C29—C30	179.0 (4)	C9—C10—H10	119.1
C16—C17—H17	120.1	C9—C10—C11	121.8 (4)
C18—C17—C16	119.8 (3)	C11—C10—H10	119.1
C18—C17—H17	120.1	C8—C9—H9	121.2
C26—C21—S2	110.3 (3)	C10—C9—C8	117.5 (4)
C22—C21—S2	128.3 (3)	C10—C9—H9	121.2
C22—C21—C26	121.4 (3)	C12—C11—C10	120.8 (4)
C1—C2—H2	119.5	C12—C11—H11	119.6
C3—C2—C1	121.0 (3)	C10—C11—H11	119.6
C3—C2—H2	119.5	Cl1—C31—Cl2	109.8 (3)
C6—C5—H5	120.3	Cl1—C31—Cl3	110.7 (3)
C4—C5—C6	119.3 (3)	Cl1—C31—H31	108.7
C4—C5—H5	120.3	Cl2—C31—H31	108.7
C19—C18—H18	120.6	Cl3—C31—Cl2	110.2 (3)
C17—C18—C19	118.8 (3)	Cl3—C31—H31	108.7

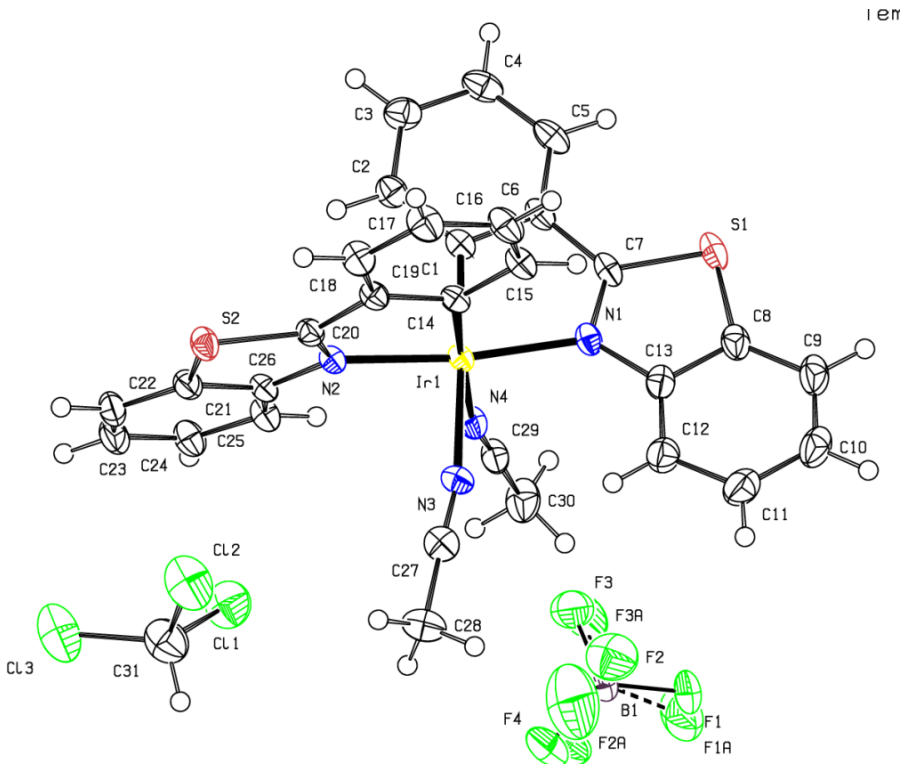
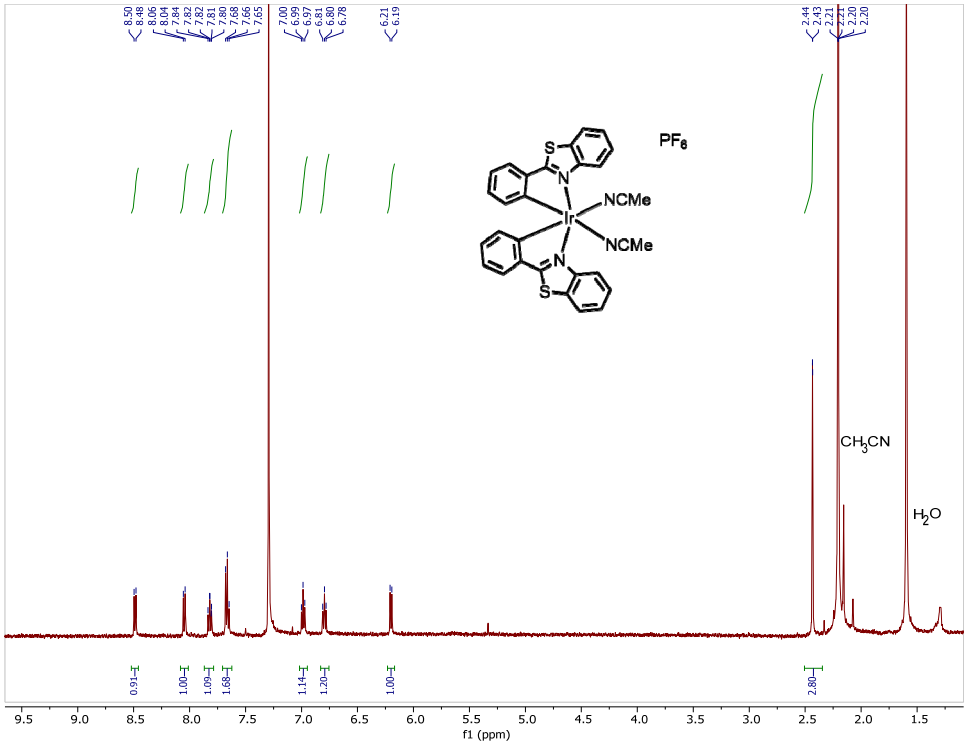


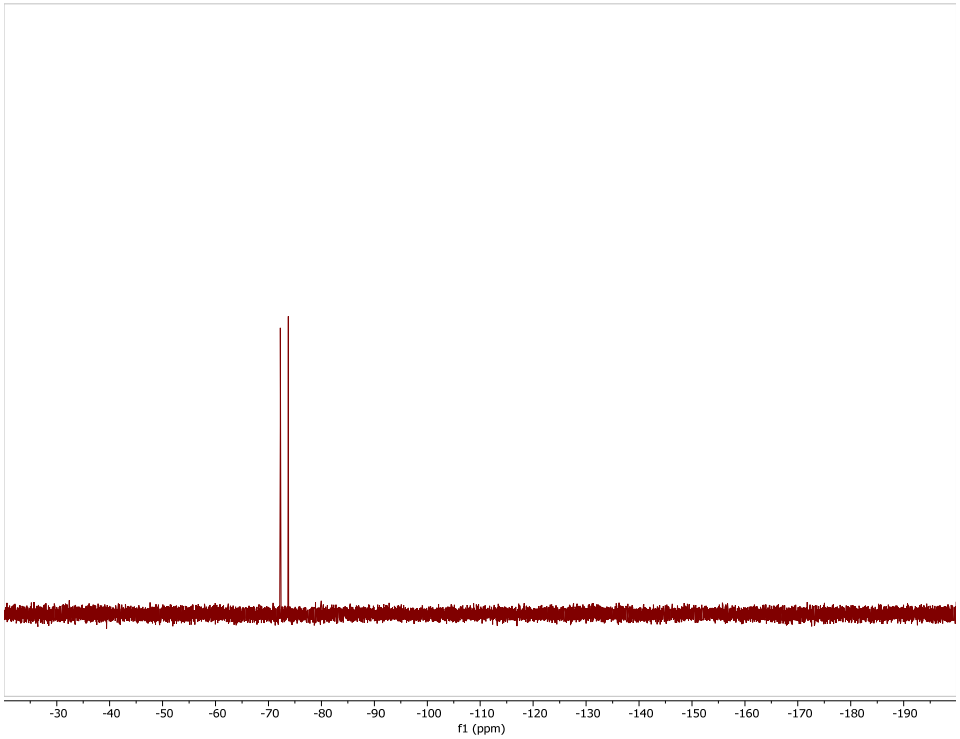
Figure S15. Projection view of **HN-1** with 50% probability ellipsoids.

X. Characterizations of Iridium complexes

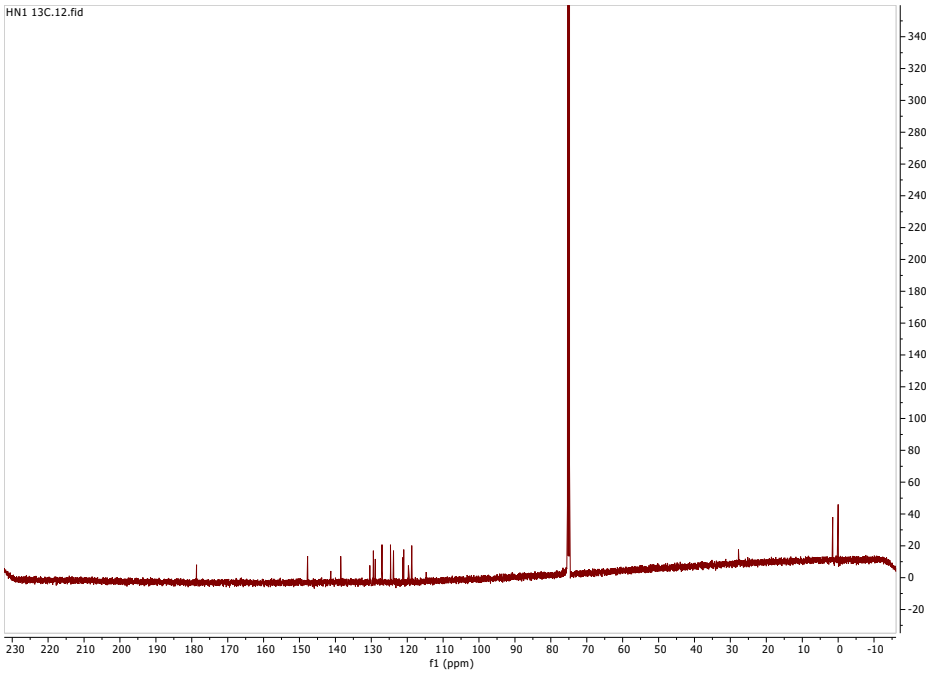
HN-1 ^{1}H NMR



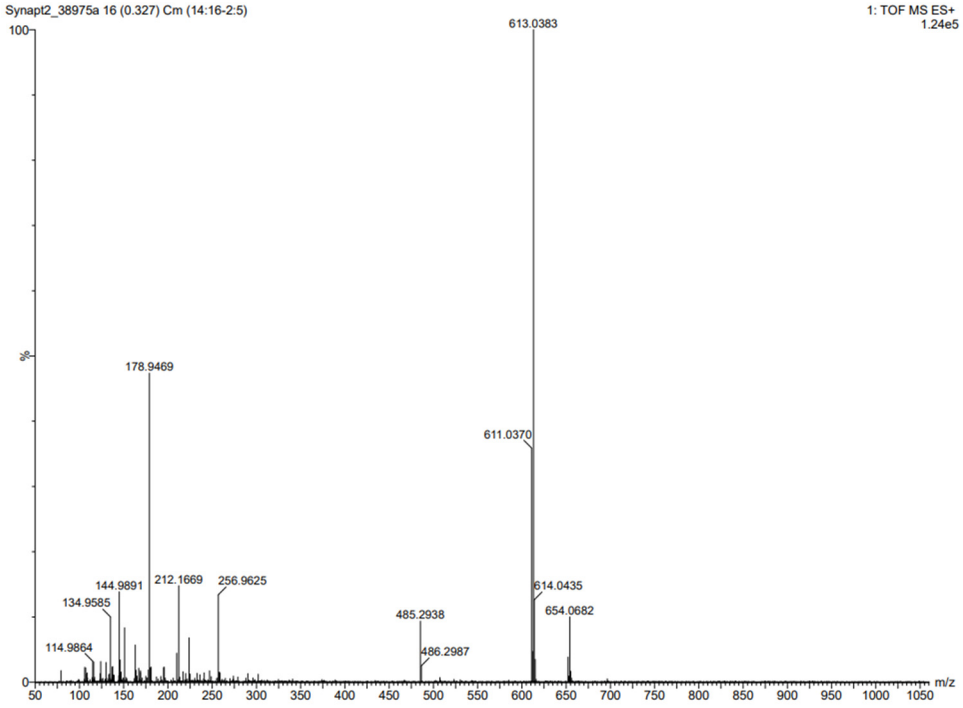
HN-1 ^{19}F NMR



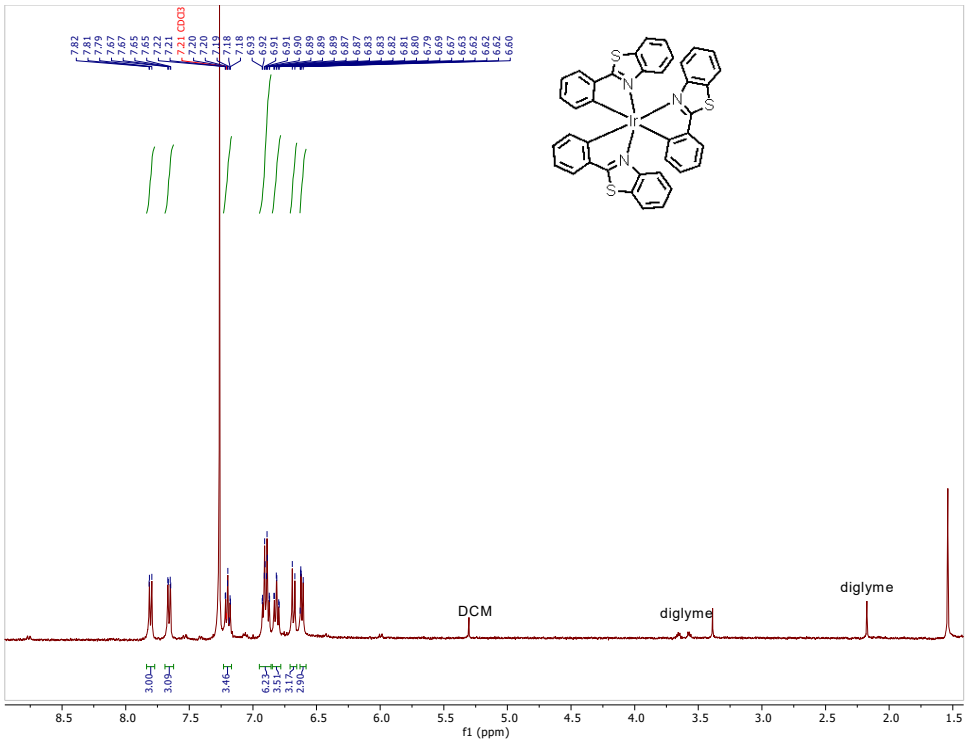
HN-1 ^{13}C NMR



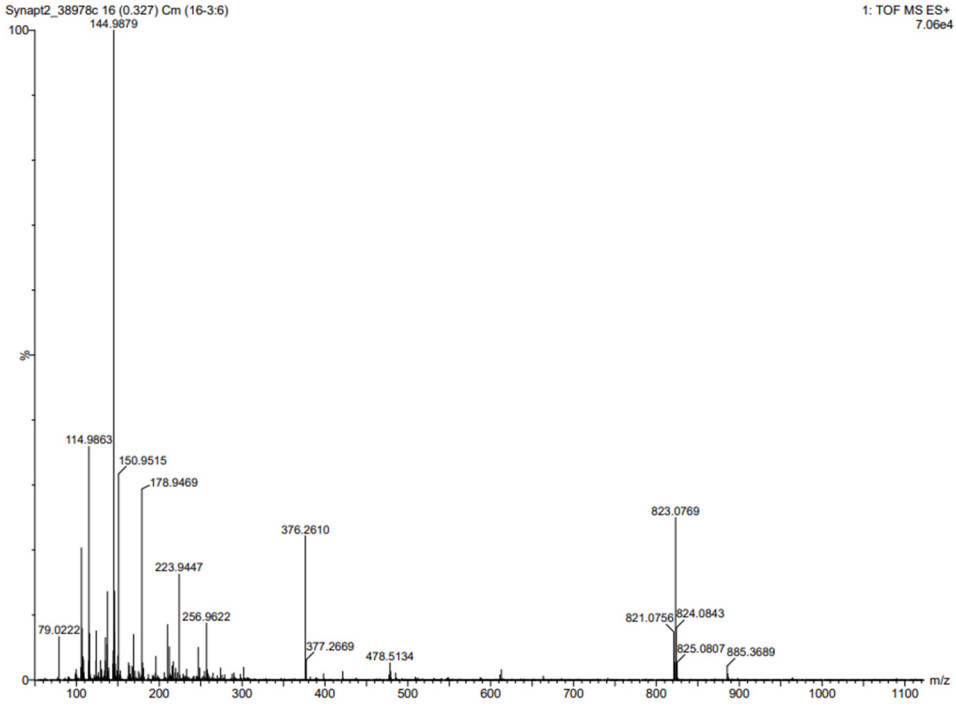
HN-1 High Resolution Mass Spectrum



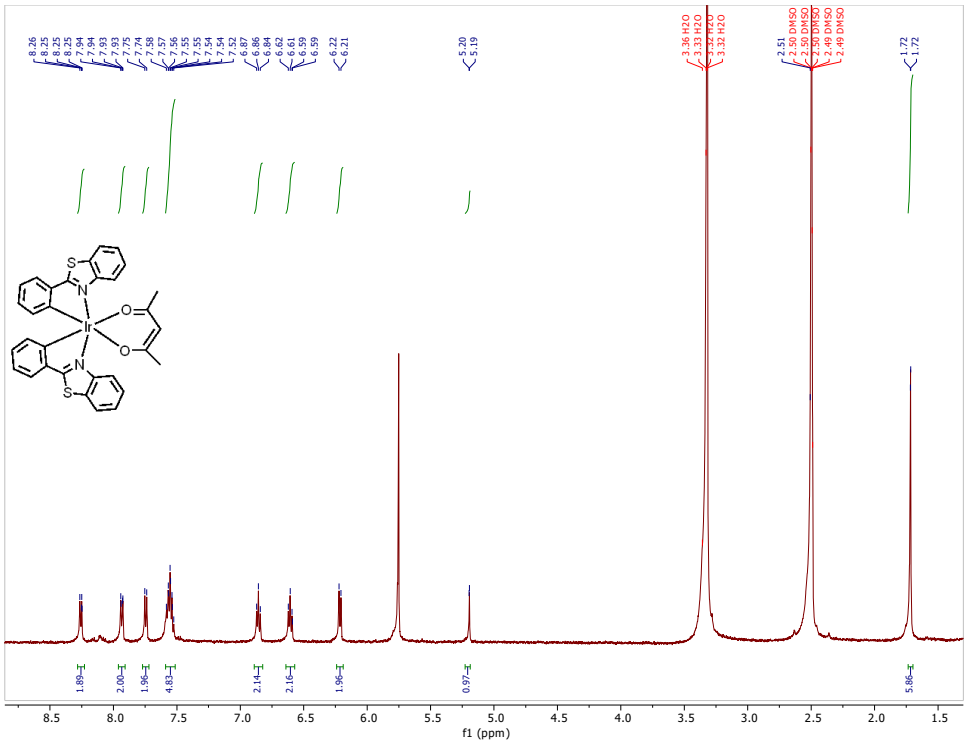
HN-2 ^{1}H NMR



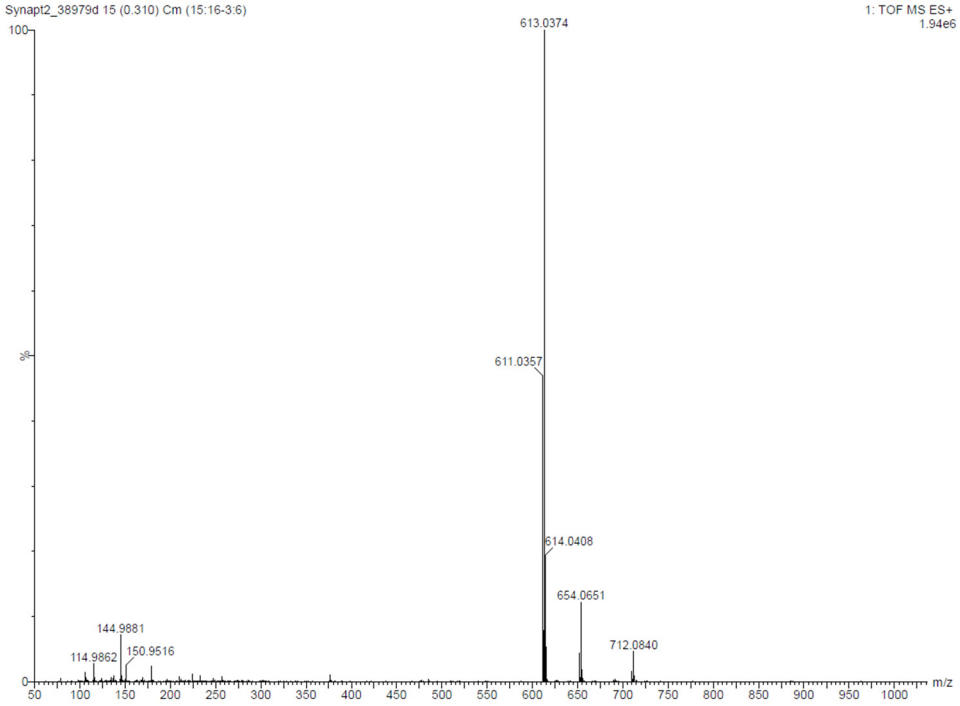
HN-2 High Resolution Mass Spectrum



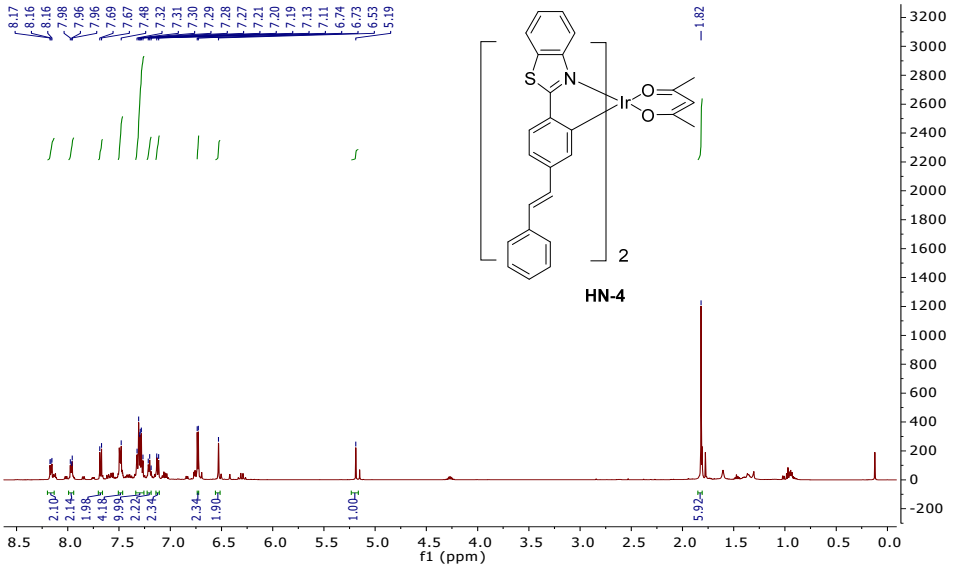
HN-3 ^{1}H NMR



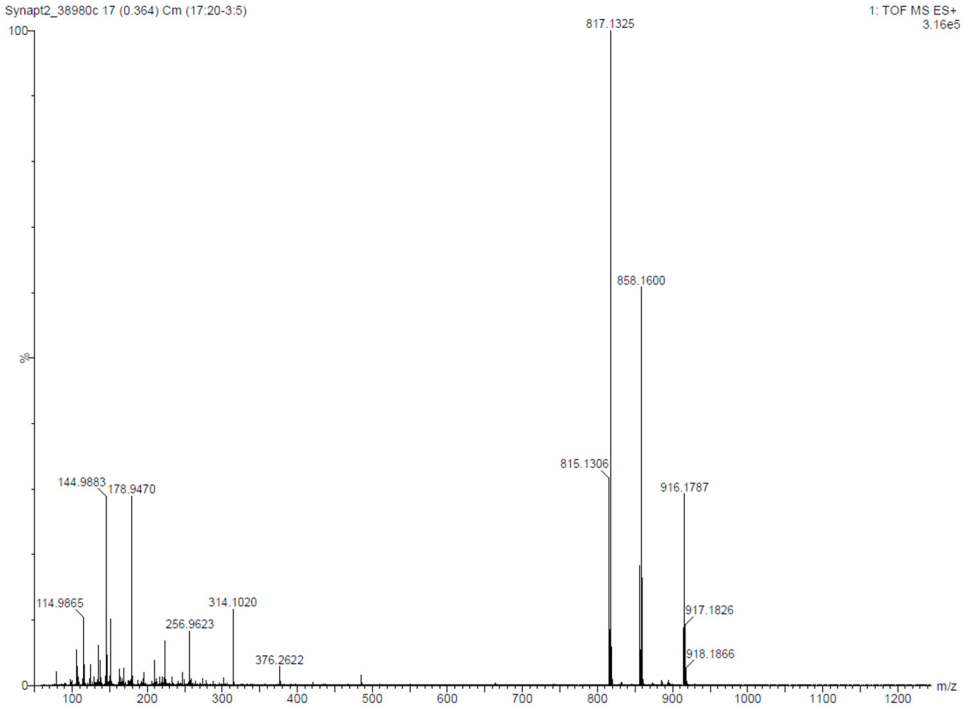
HN-3 High Resolution Mass Spectrum



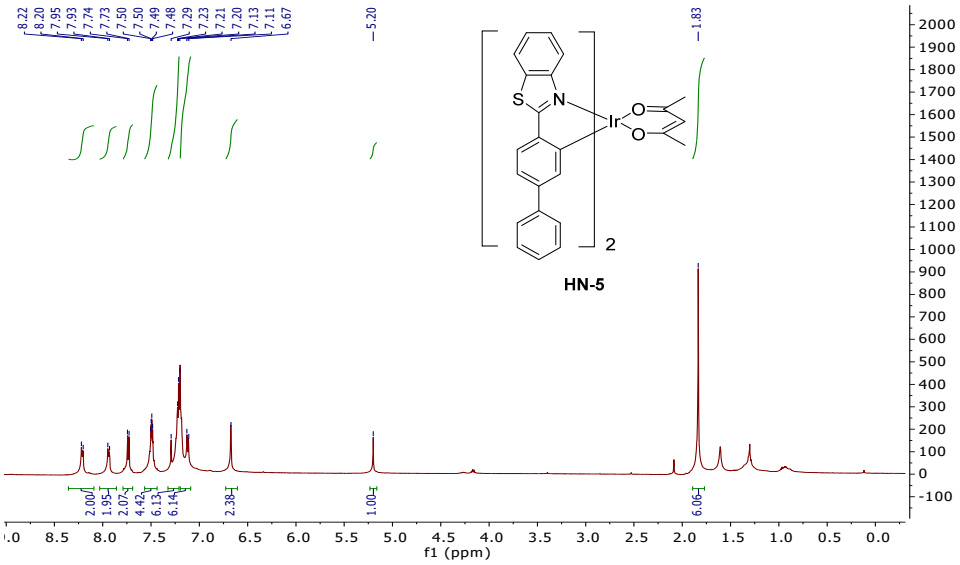
HN-4 ^{1}H NMR



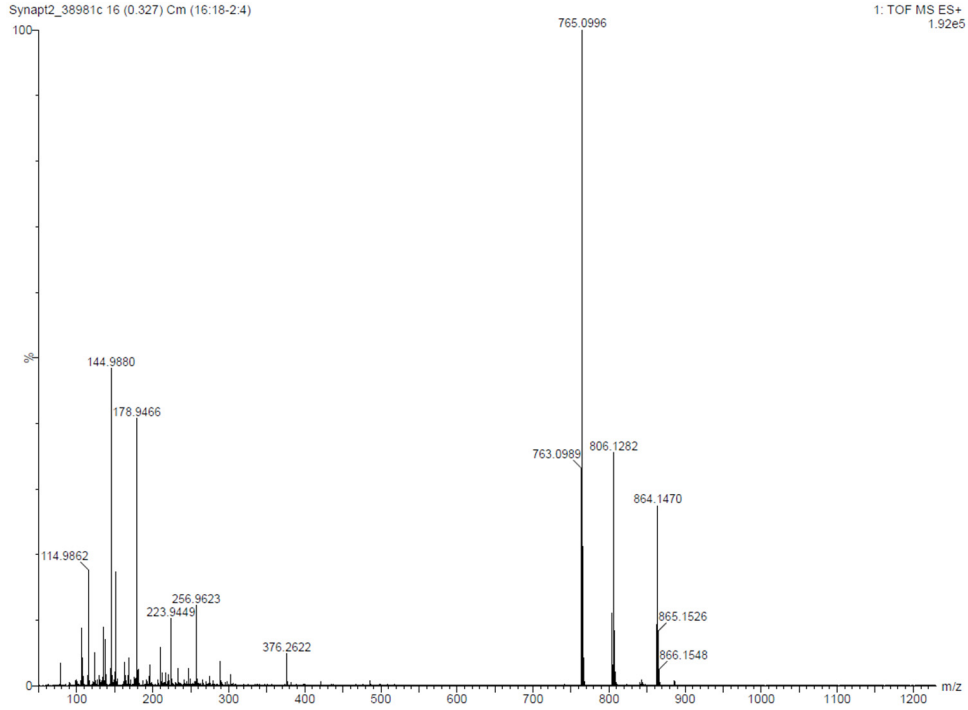
HN-4 High Resolution Mass Spectrum



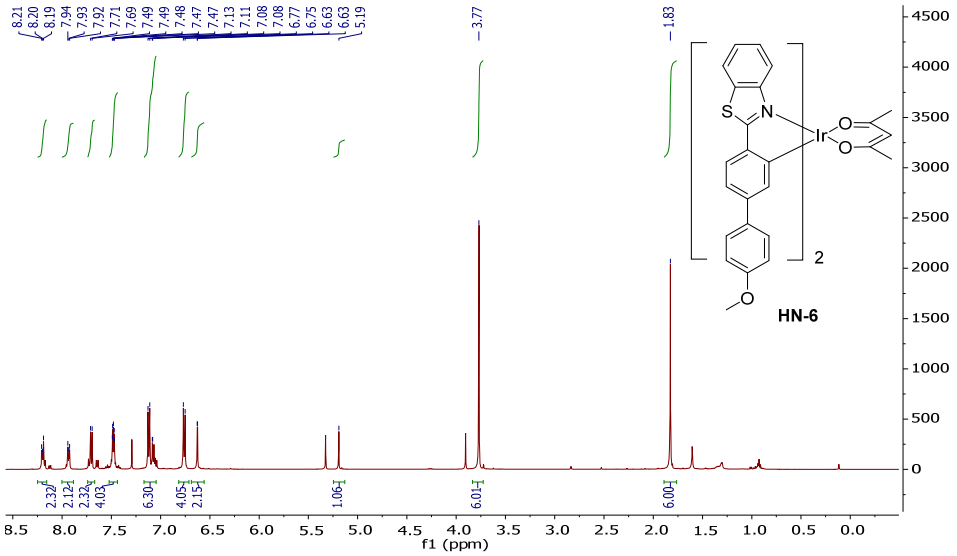
HN-5 ^{1}H NMR



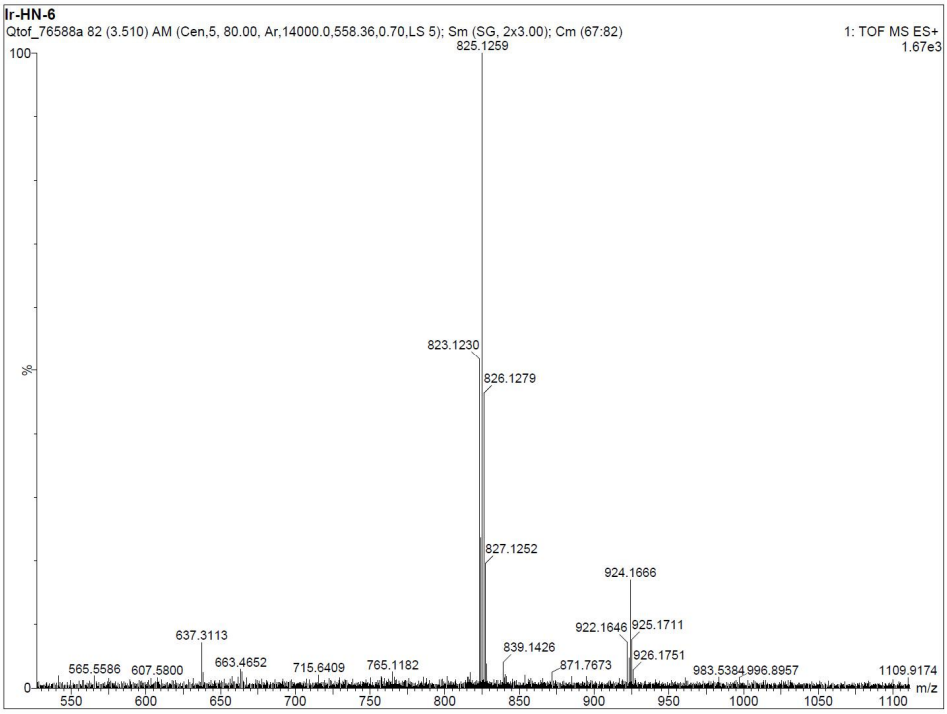
HN-5 High Resolution Mass Spectrum



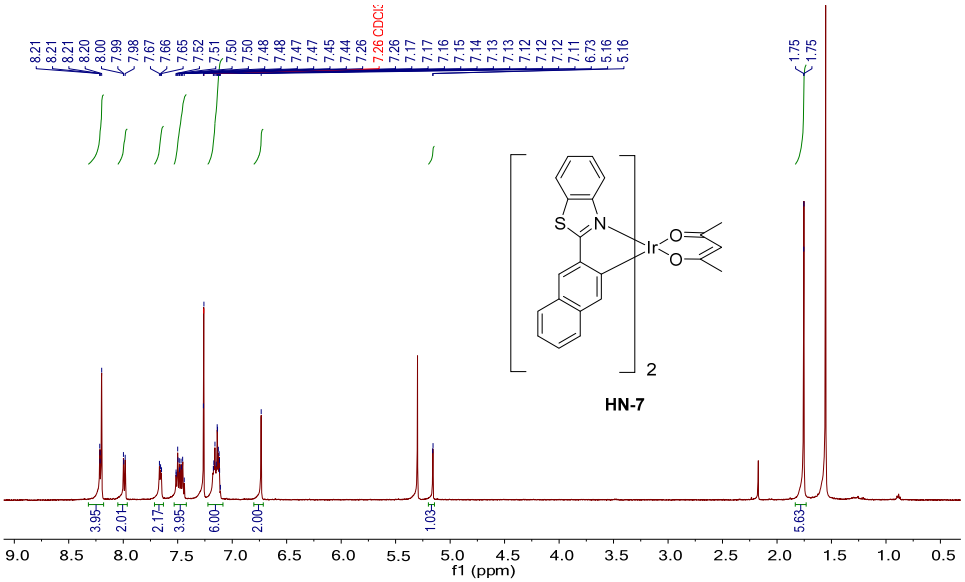
HN-6 ^{1}H NMR



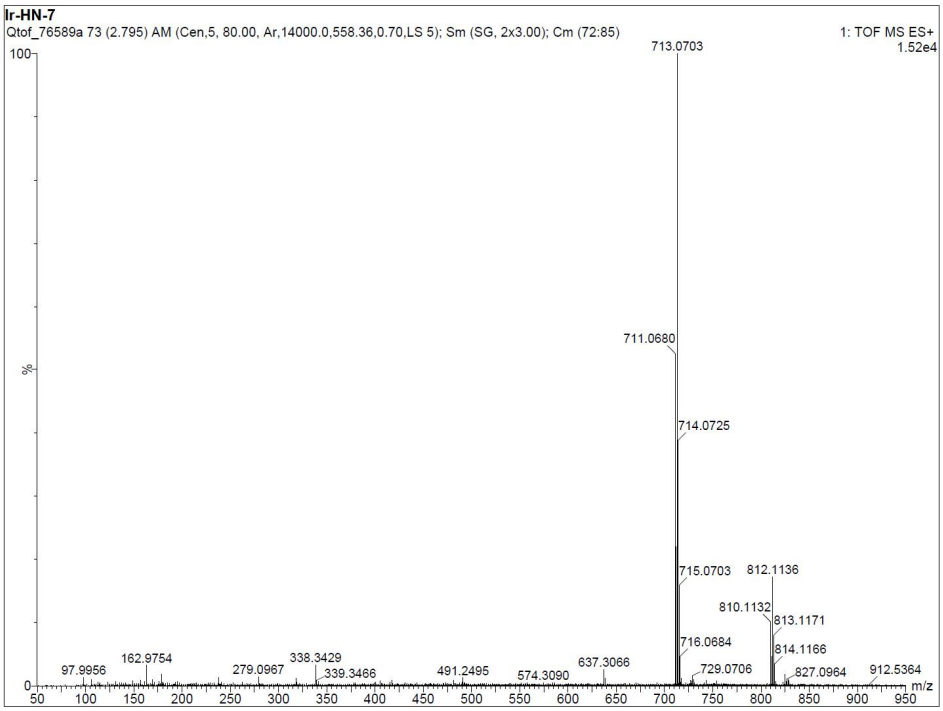
HN-6 High Resolution Mass Spectrum



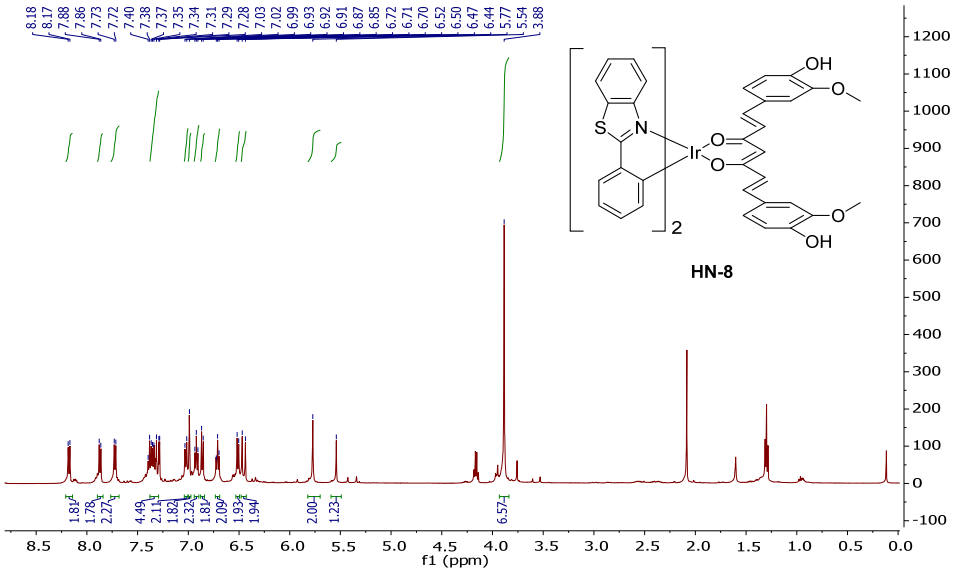
HN-7 ^{1}H NMR



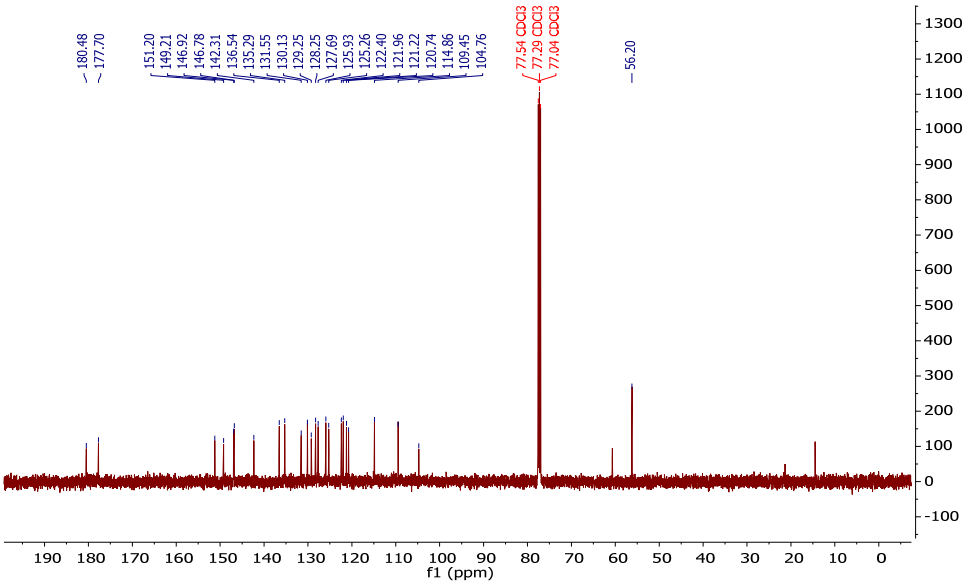
HN-7 High Resolution Mass Spectrum



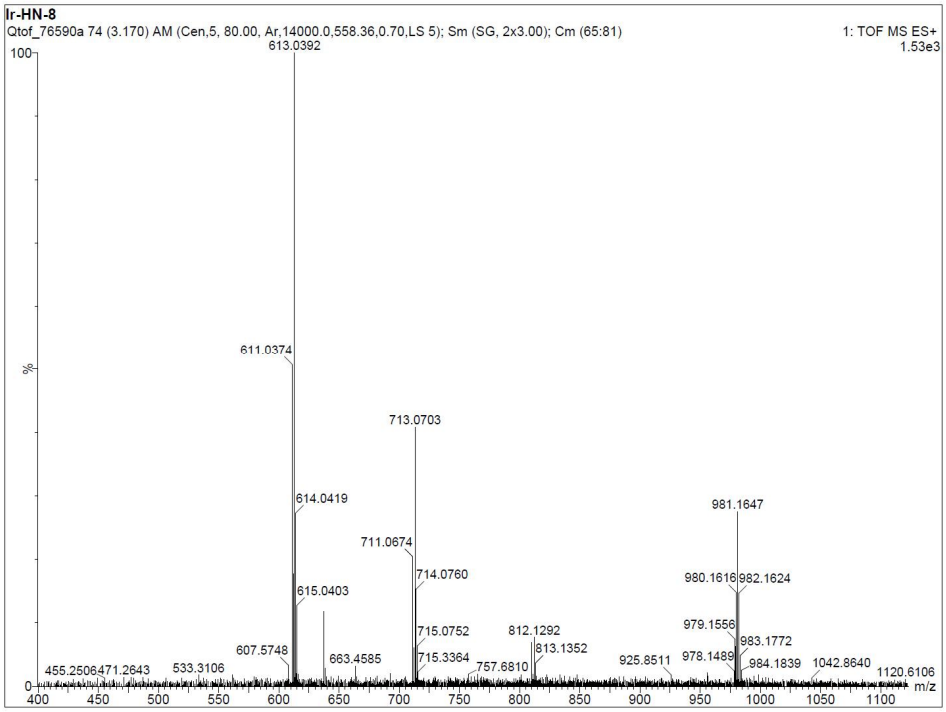
HN-8 ^{1}H NMR



HN-8 ^{13}C NMR



HN-8 High Resolution Mass Spectrum



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