Photoredox-catalyzed bisarylation of Bromonitroalkanes enabled by the dual role of nitro functionality: synthesis of bis(indolyl)methanes as promising α-glucosidase inhibitors

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Contents

1. Materials

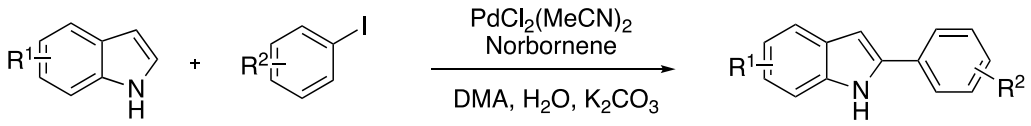
$Ru(bpy)_3Cl_2{\cdot}6H_2O$ was purchased from Adamas-beta ®. R1793896-1g, 98%；α-glucosidase from yeast overproducer (1KU units)、 *p*-nitrophenyl glucopyranoside and acarbose were purchased from Solarbio Inc; Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification.

2. General methods

Reactions were monitored by thin-layer chromatography (TLC) with Haiyang GF 254 silica gel plates (Qingdao Haiyang Chemical Industry Co Ltd, Qingdao, China) using UV light and vanillic aldehyde as visualizing agents. Flash column chromatography was performed using 200-300 mesh silica gel at increased pressure. ^{1}H NMR spectra and ^{13}C NMR spectra were respectively recorded on 400 MHz and 150 MHz NMR spectrometers. Chemical shifts (δ) were expressed in ppm with TMS as the internal standard， and coupling constants (*J*) were reported in Hz. High-resolution mass spectra were obtained with a MALDI-TOF (MALDI-7090, SHIMADZU) and UPLC-Q-TOF-MS (X500B QTOF, SCIEX). Absorbance was measured with an enzyme reader (Spectra max i3, Molecular Devices). The cyclic voltammetry experiments were performed in a three-electrode undivided cell, and were recorded with a CHI 700E potentiostat (CH Instruments, Inc.)

3. Experiment procedures

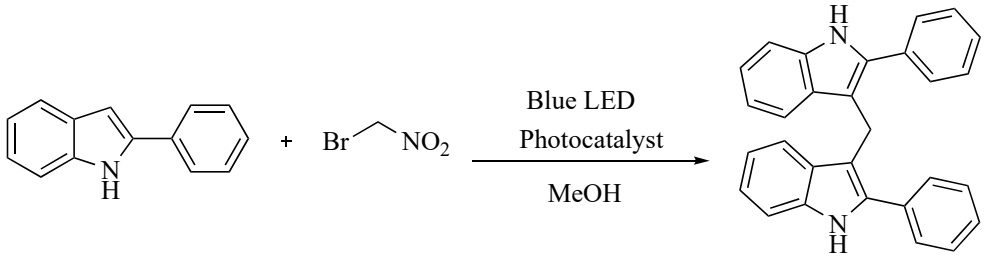
3.1 General procedures for the preparation of 2-arylindoles



The mixture of indole (5.0 mmol), iodobenzene (10 mmol), Pd(OAc)2 (10 mol%), K_2CO_3 (10 mmol), and norbornene (10 mmol) was stirred in N, N-dimethylacetamide (20 mL) with H_2O (1.0 mL) at 70 °C (oil bath)[1]. After completion of the reaction (detected by TLC), the reaction mixture was cooled to room temperature and extracted with EtOAc. The organic layers were combined and washed with H_2O (3 times) and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was first purified by flash chromatography on silica gel using petroleum ether/ethyl acetate as the eluent and then recrystallized to give desired 2-arylindole.

3.2 Extra information for the optimization of reaction conditions

Table S1. Evaluation of Photocatalysts [a]

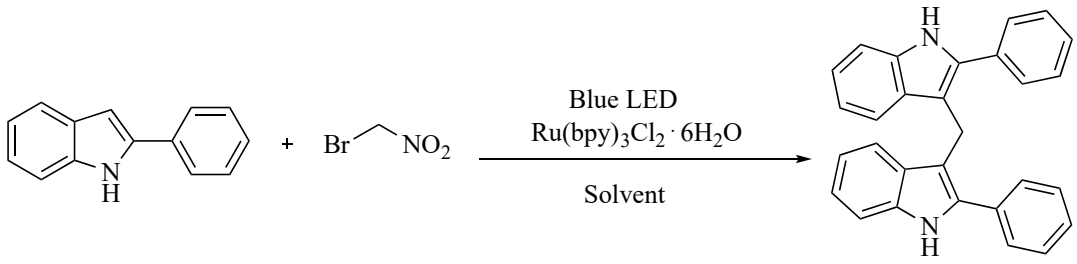


1a **2a** **3a**

Entry	Photocatalyst (2 mol%)	Yield (**3a**) [b]
1	Blank	trace
2	**$Ru(bpy)_3Cl_2 \cdot 6H_2O$**	**28**
3	Esion Y	16
4	Rose Bengal	15
5	Esion B	13
6	Fluorescein	trace
7	Methylene blue	trace

[a] Reaction conditions: A mixture of **1a** (0.5 mmol), **2a** (0.6 mmol), and photocatalyst (2 mol %) in MeOH (1 mL) was under irradiation of 10w Blue LED in the air at 30 °C for 24 h. [b] Yield of the isolated product after silica gel chromatography.

Table S2. Effect of solvents on the model reaction

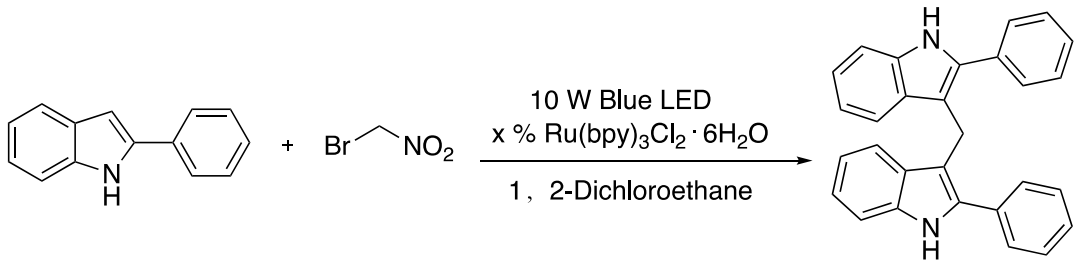


1a **2a** **3a**

Entry	Solvent	Yield (**3a**) % [b]
1	**1, 2-Dichloroethane**	**38**
2	Methanol	28
3	Ethanol	27
4	Dichloromethane	21
5	Acetonitrile	17
6	Tetrahydrofuran	Trace
7	N, N-Dimethylformamide	Trace
8	Dimethyl sulfoxide	Trace

[a] Reaction conditions: A mixture of **1a** (0.5 mmol), **2a** (0.6 mmol), and $Ru(bpy)_3Cl_2·6H_2O$ (2 mol%) in Solvents (1 mL) were under irradiation of 10w Blue LED in the air at 30 °C for 24 h. [b] Yield of the isolated product after silica gel chromatography.

Table S3. Effect of $Ru(bpy)_3Cl_2·6H_2O$ loading on the model reaction[a]

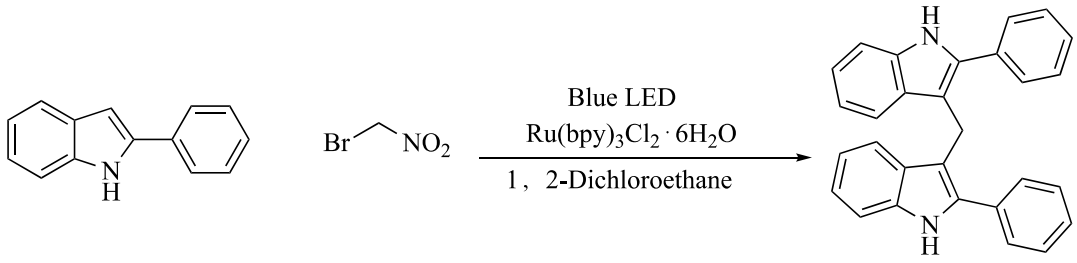


1a **2a** **3a**

Entry	Photocatalyst (x mol%)	Yield (**3a**) %[b]
1	0.5	30
2	1	35
3	**2**	**41**
4	3	32
5	4	34

[a] Reaction conditions: A mixture of **1a** (0.5 mmol), **2a** (0.6 mmol), and $Ru(bpy)_3Cl_2·6H_2O$ (x mol%) in 1,2-Dichloroethane (1 mL) was under irradiation of 10w Blue LED in the air at 30 °C for 24 h. [b] Yield of the isolated product after silica gel chromatography.

Table S4. Effect of the molar ratio of the reaction[a]



1a **2a** **3a**

Entry	**1a:2a**(mmol)	Yield (**3a**) %[b]
1	1:3（0.3:0.9）	50
2	1:2（0.3:0.6）	48
3	1:1（0.3:0.3）	51
4	2:1（0.6:0.3）	59
5	**3:1（0.6:0.2）**	**79**

[a] Reaction conditions: A mixture of **1a**, **2a** and $Ru(bpy)_3Cl_2·6H_2O$ (2 mol %) in 1,2-Dichloroethane (1 mL) was under irradiation of 10w Blue LED in air at 30 °C for 24 h. [b] Yield of the isolated product after silica gel chromatography.

Table S5. Effect of solvent volume on the reaction[a]

Entry	1,2-Dichloroethane (x mL)	Yield (**3a**) %[b]
1	0.5	66
2	**1**	**79**
3	1.5	77
4	2	73
8	2.5	65

[a] Reaction conditions: A mixture of **1a**(0.6mmol), **2a**（0.2mmol）and $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (2 mol %) in 1,2-Dichloroethane (x mL) was under irradiation of 10w Blue LED in air at 30 °C for 24 h. [b] Yield of the isolated product after silica gel chromatography.

Table S6. Effect of time on the reaction[a]

Entry	Reaction time (h)	Yield (**3a**) %[b]
1	6	40
2	12	62
3	18	74
4	24	78
5	**30**	**87**
6	36	85
7	42	84
8	48	85

[a] Reaction conditions: A mixture of **1a** (0.6 mmol), **2a** (0.2 mmol) and $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (2 mol %) in 1,2-Dichloroethane (1 mL) was under irradiation of 10w Blue LED in air at 30 °C. [b] Yield of the isolated product after silica gel chromatography.

4. Mechanism Study

4.1 Fluorescence quenching studies of $Ru(bpy)_3Cl_2{\cdot}6H_2O$

Emission intensities were recorded using a fluorescence spectrophotometer. All $Ru(bpy)_3Cl_2{\cdot}6H_2O$ solutions were excited at 450 nm and the emission intensity was collected at 608 nm (with a 10 nm slit width). The quenching of the excited state of a 0.05 mM solution of $Ru(bpy)_3Cl_2{\cdot}6H_2O$ by various amounts of 2-phenylindole **1a** and bromonitromethane **2a** separately in ethanol. The fluorescence quenching data were measured in the presence of four different concentrations. The emission intensity was collected.

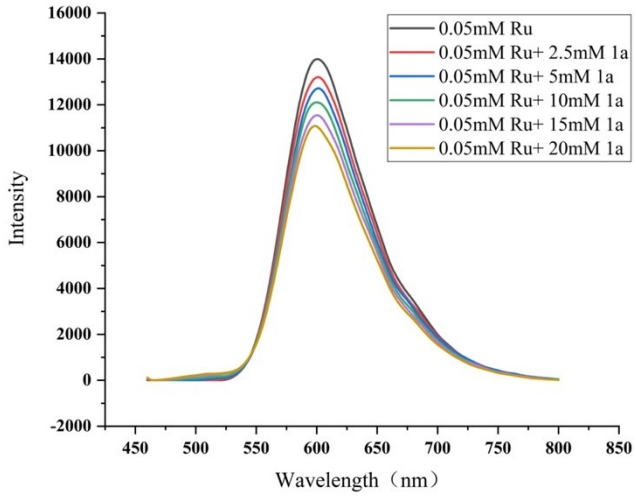


Figure. S1. Fluorescence emission of $Ru(bpy)_3Cl_2.6H_2O$ / 2-phenylindole

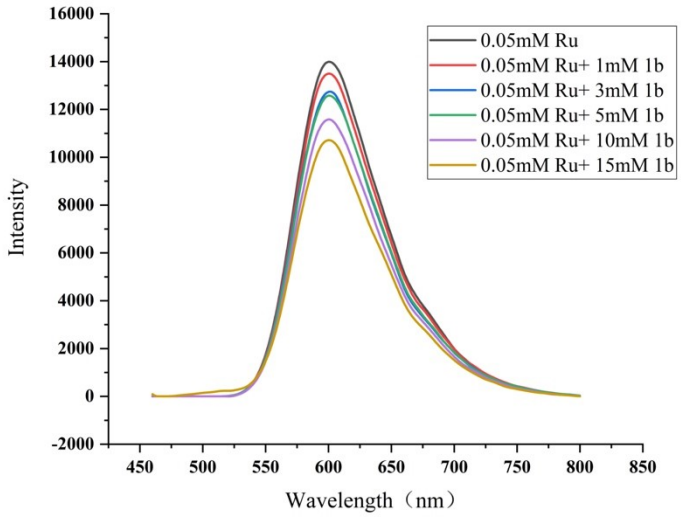
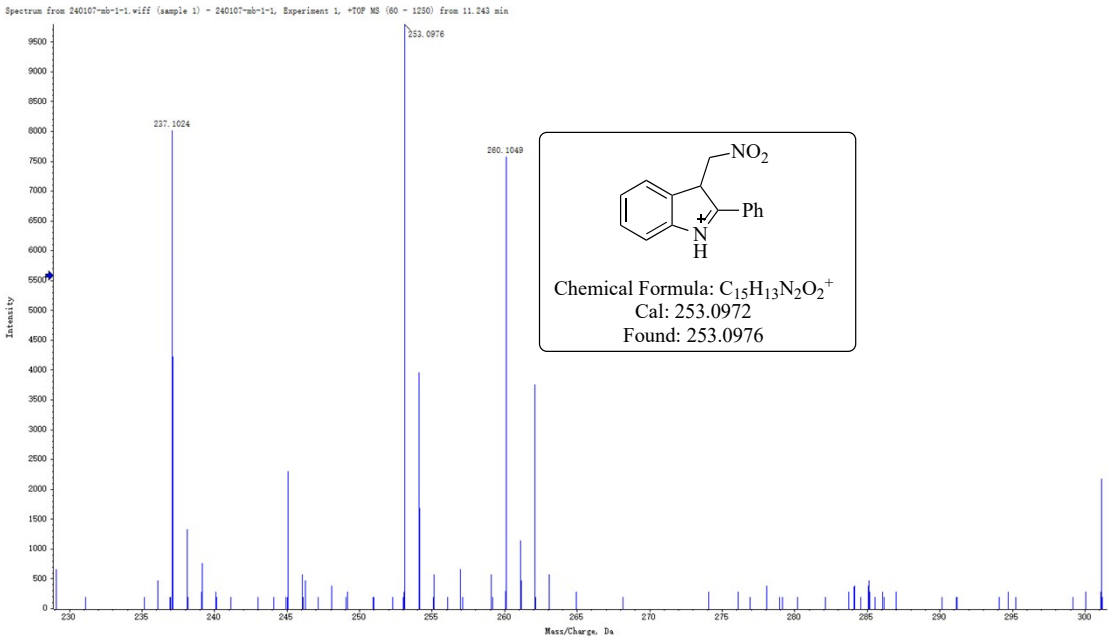


Figure. S2. Fluorescence emission of $Ru(bpy)_3Cl_2.6H_2O$ / bromonitromethane

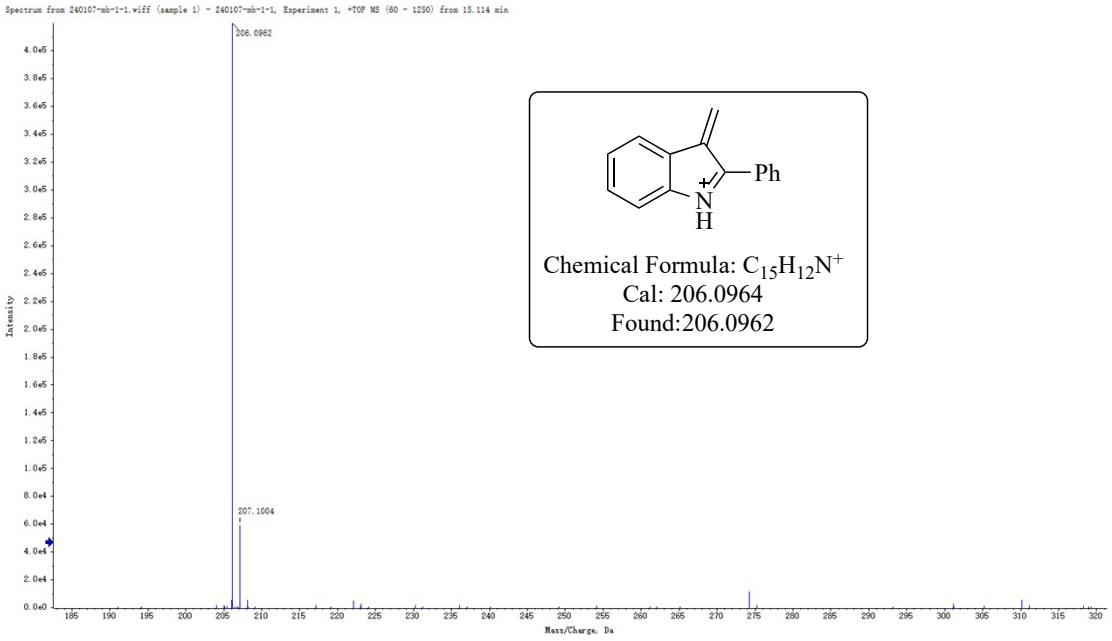
4.2 UPLC-Q-TOF-MS analysis of the reaction

4.2.1 Intermediates V and IV were detected by UPLC-Q-TOF-MS analysis from the reaction mixture of indole and bromonitromethane under the standard reaction conditions.

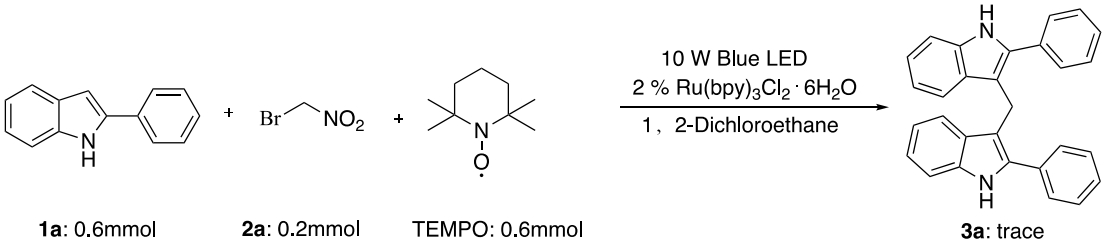
Intermediate V

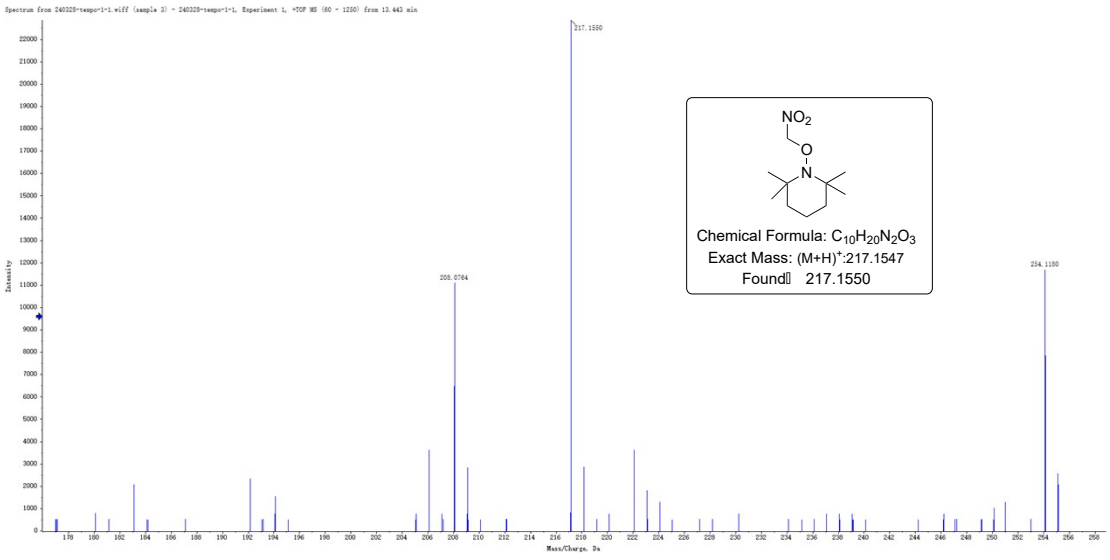


Intermediate IV



4.2.2 Reaction in the presence of TEMPO as the radical scavengers





4.3 Cyclic voltammetry

The cyclic voltammetry experiments were performed, and the reductive potentials of 1b (bromonitromethane) were determined as the onset potential for the reduction of 1b is around -0.625 V, and the E_{red} is approximately -0.975 V (Figure S3). The electrochemical measurements were carried out by a computer-controlled electrochemical analyzer. Cyclic voltammetry was performed in a three-electrode cell (volume 10 mL; acetonitrile as solvent, n-Bu_4NPF_6 0.05 M as the supporting electrolyte, 3 mM concentration of the tested compound) with glassy carbon (diameter 3 mm) as the working electrode, Pt wire as the auxiliary electrode, and Ag/AgCl (3 M KCl) as the reference electrode.3 The scan speed was 100 mV/s. The potential ranges investigated for reductions were 0 to -3.0 V vs. SCE.

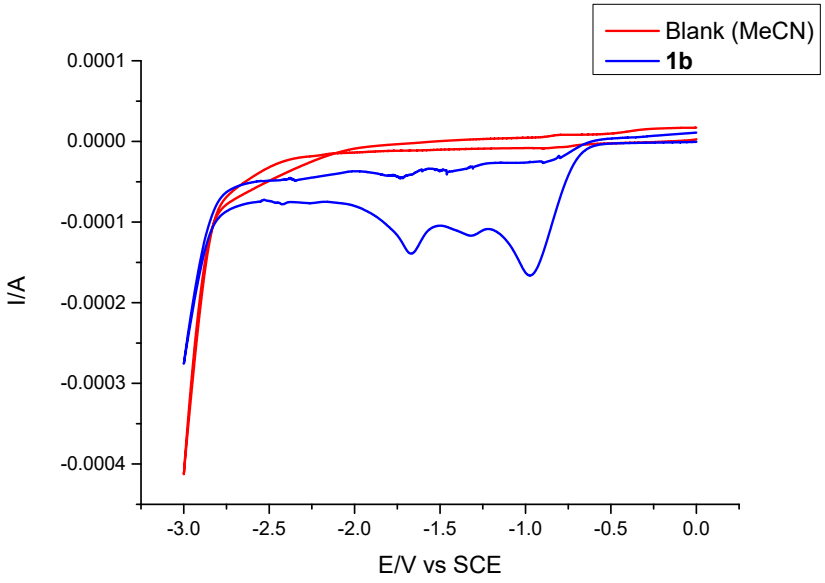


Figure S3. Cyclic voltammograms of background and 1b (3 mM) in an electrolyte of n-Bu_4NPF_6 (0.05 mM) in MeCN from 0 to -3.0 V. The onset potential for the reduction of 1b is around -0.625 V and the Ered is approximately-0.975 V.

5. α-Glucosidase inhibitory assay

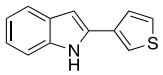
The α-glucosidase inhibition activity was performed with slight modifications as given by Rahim et al.[2] The total volume of 200 µL reaction mixture contained, Add 140 µL of phosphate buffer (pH=6.8) to the 96-well plate, add 20 µL of α-glucosidase (2.5 units, Solarbio Inc) and add 20 µL of different concentrations of bisindolylmethanes compounds (70% DMSO as solvent) to the wells and incubate for 10 min at 37°C in an incubator; then add 20 µL of the *p*-nitrophenyl glucopyranoside (pNPG, Solarbio Inc). After 20 min of incubation at 37 °C, the reaction was terminated by adding 100 µL of Na_2CO_3, and the absorbance value was read at 405 nm with an enzyme reader. The control group was replaced by 20µl of 70% DMSO, Acarbose was used as the positive control. All experiments were carried out in triplicates (mean ± SEM, n = 3). The inhibition rate was calculated as follows:

$$Inhibition(\%) = \frac{Abs\ of\ control - Abs\ of\ sample}{Abs\ of\ control} \times\ 100$$

Active compound solutions were suitably diluted, and their inhibition studies were determined. Data obtained was used for the determination of IC_{50} values (concentration at which there is 50% enzyme inhibition).

Table 7 Inhibitory IC_{50} values of indoles derivatives against α-glucosidase enzyme [a]

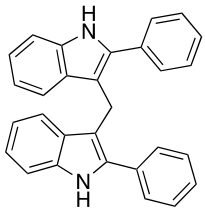
Entry	R1	R2	Product	IC_{50} ± SEM (µM)
1	H	H	3a	12.11 ± 0.39
2	4-CF3	H	3b	11.36 ± 0.90
3	4-F	H	3c	18.31 ± 0.94
4	4-Cl	H	3d	28.06 ± 0.40
5	4-Br	H	3e	5.45 ± 0.64
6	4-Me	H	3f	11.56 ± 0.12
7	4-MeO	H	3g	10.97 ± 0.59
8	3-F	H	3h	13.0 ± 0.30
9	3-Cl	H	3i	9.87 ± 0.57
10	3-Br	H	3j	7.22 ± 0.27
11	3-Me	H	3k	9.08 ± 0.94
12	3-MeO	H	3l	14.85 ± 0.73
13	H	5-F	3m	11.93 ± 0.81
14	H	5-Cl	3n	8.75 ± 0.66
15	H	5- Br	3o	6.61 ± 0.18
16	H	5-Me	3p	8.74 ± 0.16

17	H	6-F	3q	7.76 ± 0.41
18	H	6-Me	3r	10.05 ±0.14
19			3s	7.05±0.10

SEM[a] (Standard error mean)

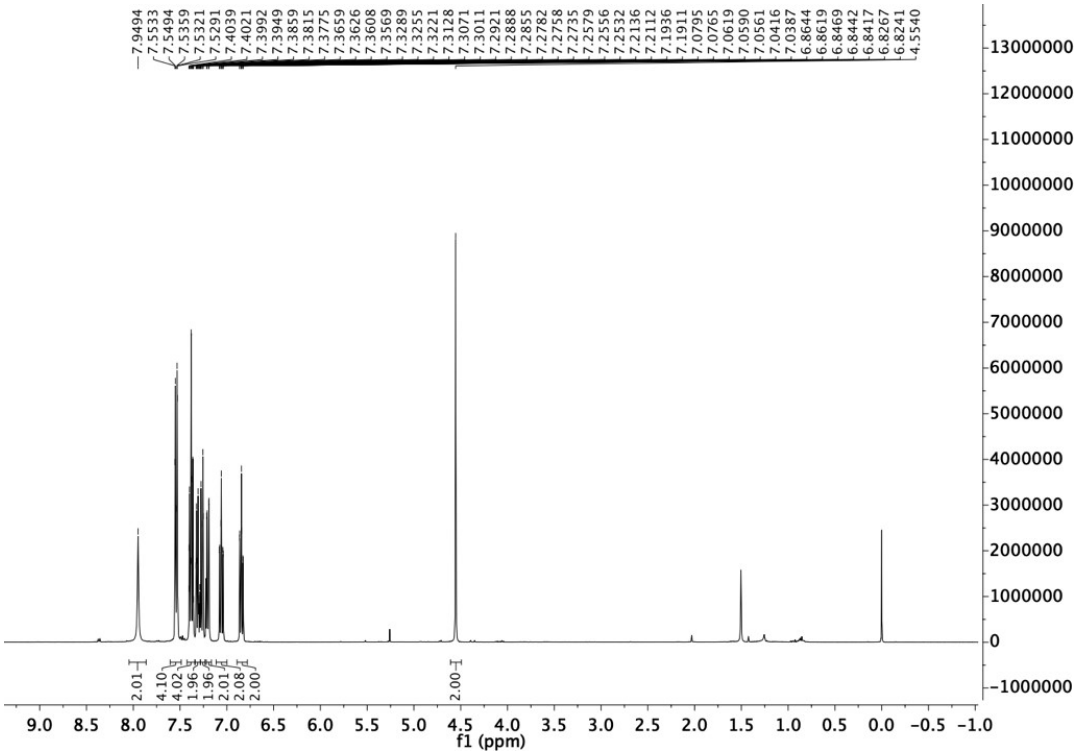
6. Characterization of products.

(3a) Bis(2-phenyl-1*H*-indol-3-yl)methane[3]

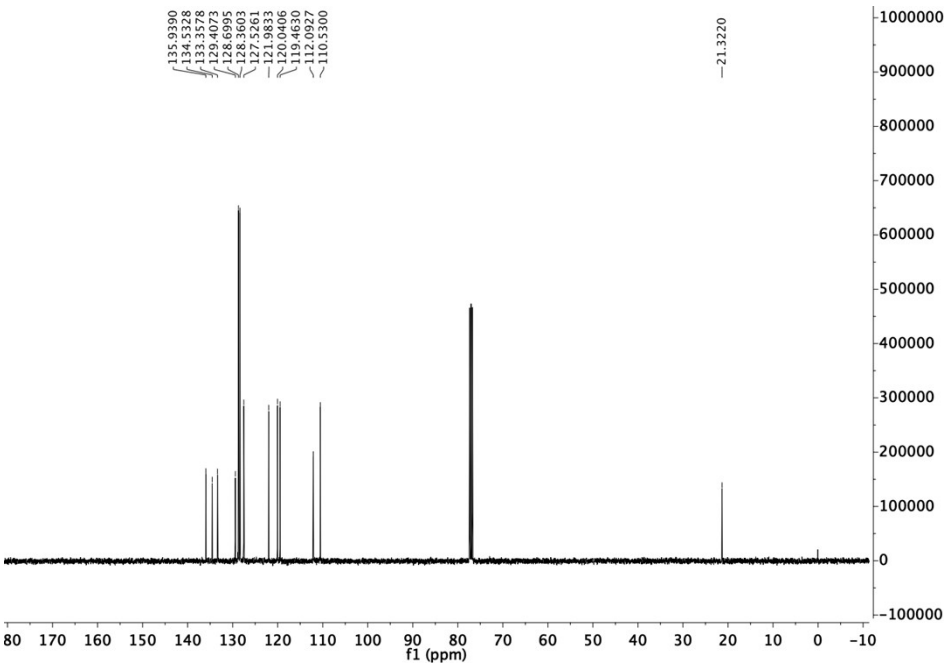


R_f = 0.25 (PE/EtOAc, 10:1). 87% yield. Pale yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 (s, 2H), 7.60 - 7.49 (m, 4H), 7.43 - 7.34 (m, 4H), 7.34 - 7.28 (m, 2H), 7.33 - 7.29 (m, 2H), 7.29 - 7.25 (m, 2H), 7.21 - 7.19 (m, 2H), 6.86 - 6.82(m, 2H), 4.55 (s, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 135.94, 134.53, 133.36, 129.41, 128.70, 128.36, 127.53, 121.98, 120.04, 119.46, 112.09, 110.53, 21.32. MALDI-TOF-MS: m/z: calcd for $C_{29}H_{22}N_2$ $(M+H)^+$: 399.1856; found 399.1852.

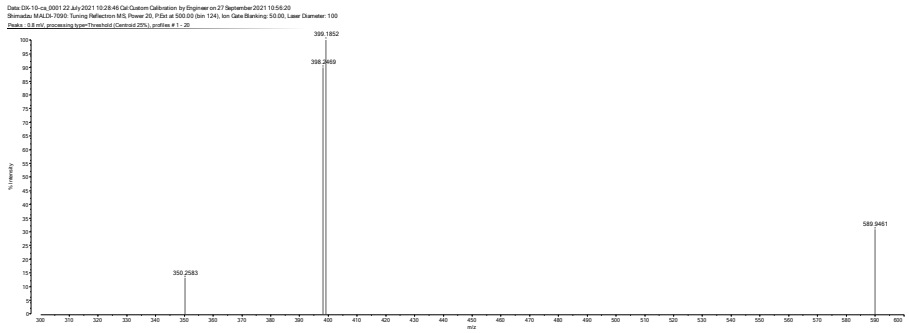
^{1}H NMR Spectrum ($CDCl_3$) of **3a**



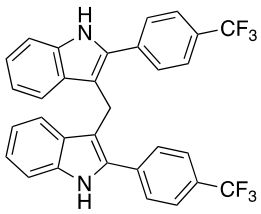
^{13}C NMR Spectrum ($CDCl_3$) of **3a**



HRMS of **3a**

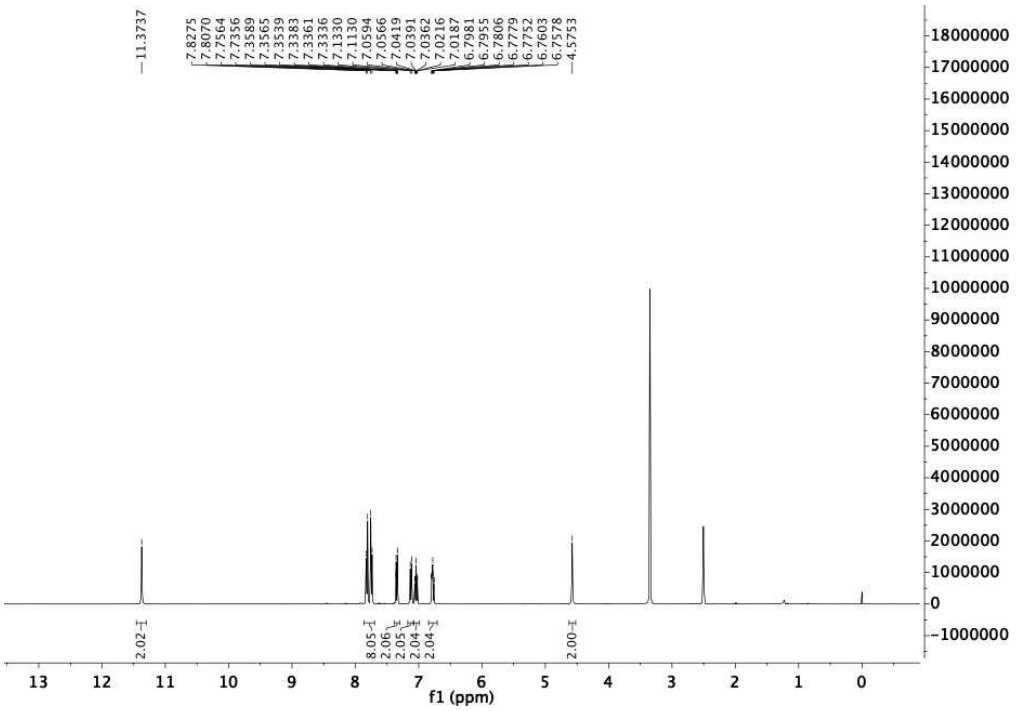


(3b) Bis(2-(4-(trifluoromethyl)phenyl)-1*H*-indol-3-yl)methane）

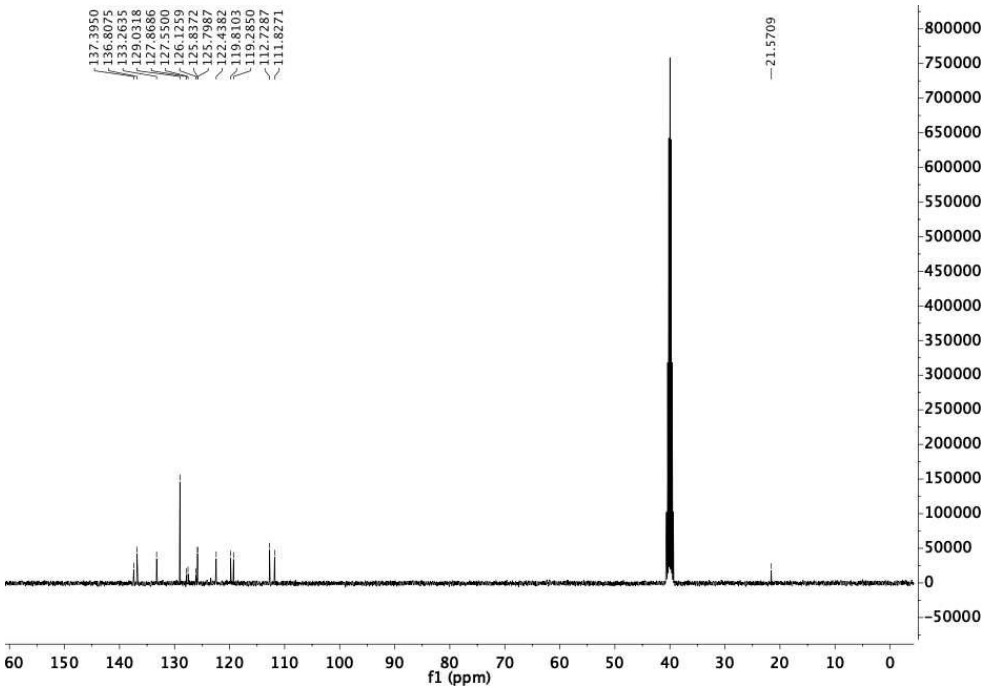


Rf = 0.25 (PE/EtOAc, 10:1). 54% yield. Light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.37 (s, 2H), 7.86 - 7.70 (m, 8H), 7.38 - 7.29(m, 2H), 7.12 - 7.08(m, 2H), 7.07 - 6.98(m, 2H), 6.84 - 6.70(m, 2H), 4.58 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 137.40, 136.81, 133.26, 129.03, 127.87, 127.55, 126.13, 125.84, 125.80, 122.44, 119.81, 119.28, 112.73, 111.83, 21.57. ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.91. MALDI-TOF-MS: m/z: calcd for $C_{31}H_{20}F_6N_2$ $(M+H)^+$: 535.1531; found 534.1533.

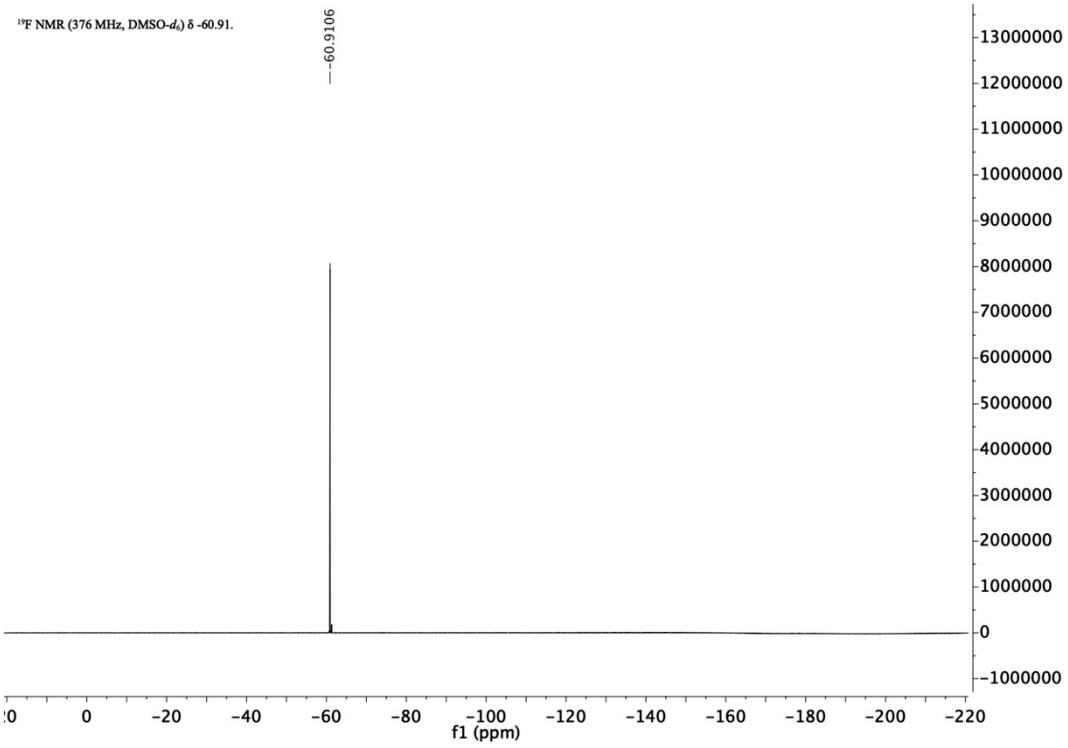
^{1}H NMR Spectrum (DMSO) of **3b**



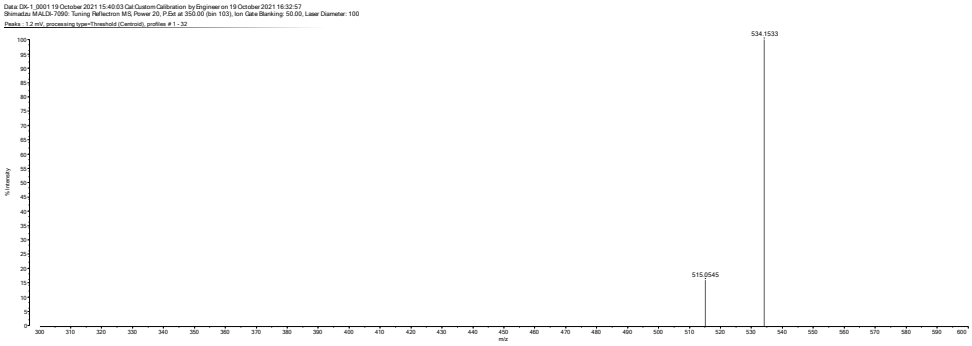
^{13}C NMR Spectrum ($CDCl_3$) of **3b**



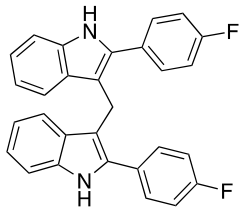
^{19}F NMR Spectrum (DMSO) of **3b**



HRMS of **3b**

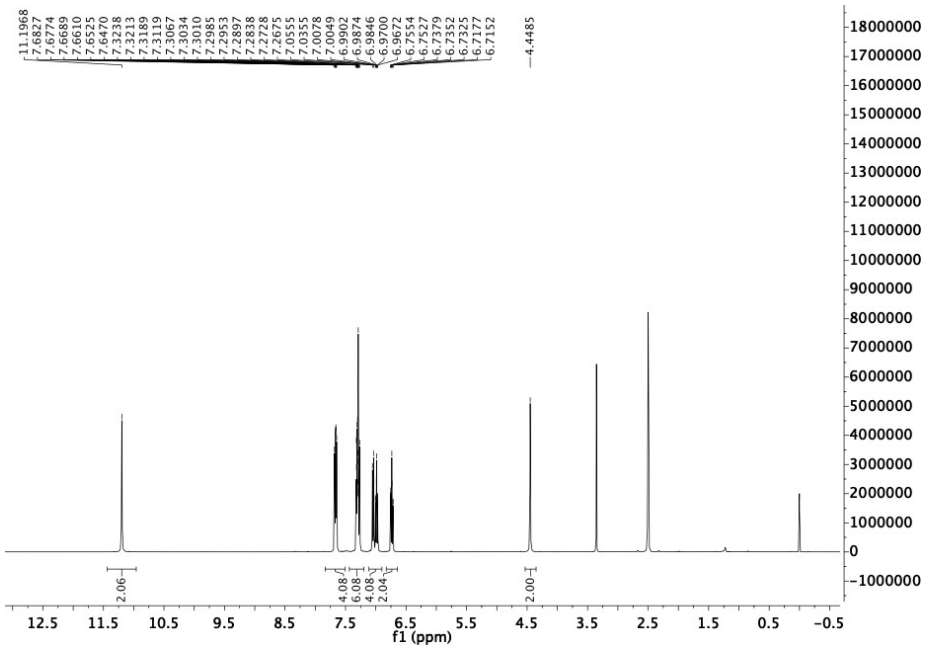


(3c) Bis(2-(4-fluorophenyl)-1*H*-indol-3-yl)methane

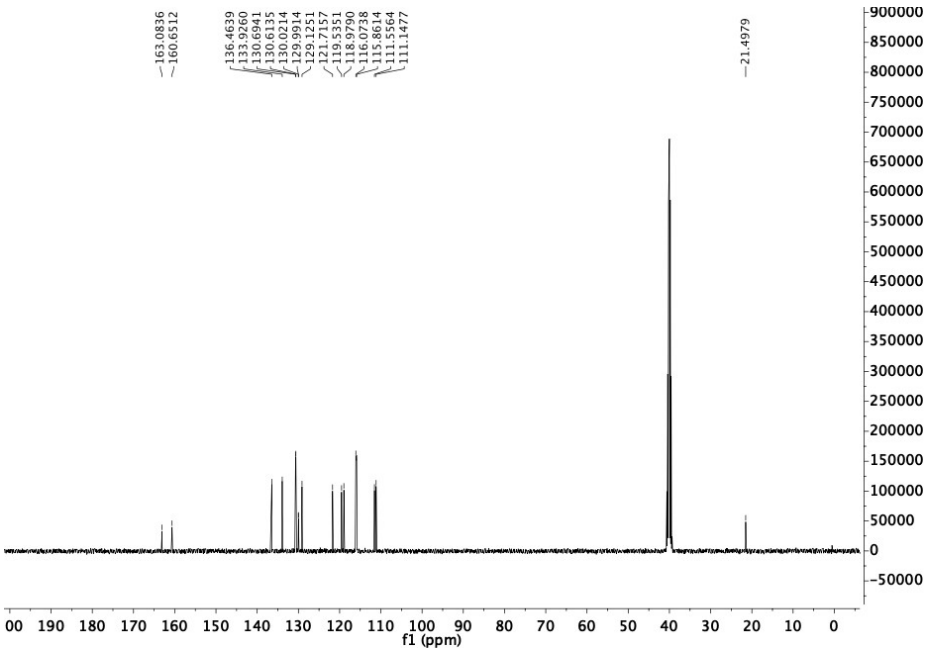


Rf = 0.25 (PE/EtOAc, 10:1). 76% yield. Light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (s, 2H), 7.84 - 7.51 (m, 4H), 7.44 - 7.20 (m, 6H), 7.11 - 6.90 (m, 4H), 6.76 - 6.72(m, 2H), 4.45 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.08, 136.46, 133.93, 130.69, 130.61, 130.02, 129.99, 129.13, 121.72, 119.54, 118.98, 116.07, 115.86, 111.56, 111.15, 21.50. ^{19}F NMR (376 MHz, DMSO-d_6) δ -114.60. MALDI-TOF-MS: m/z: calcd for $C_{29}H_{20}F_2N_2$ (M): 434.1595; found: 434.1594.

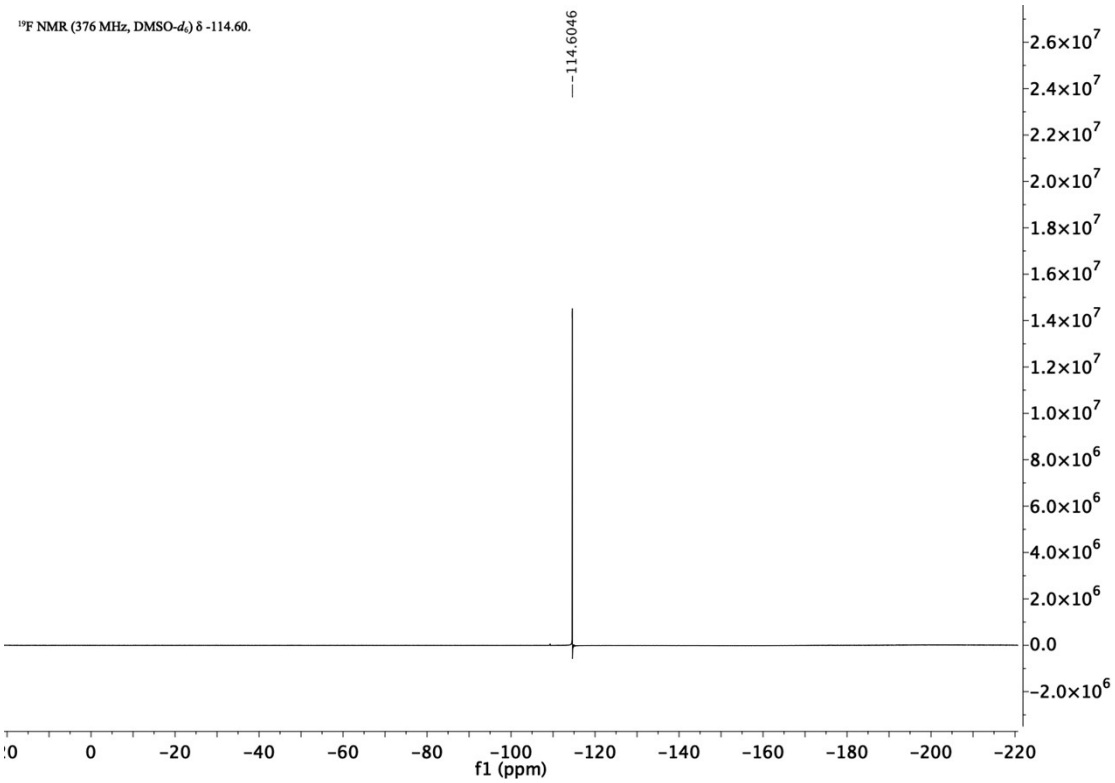
^{1}H NMR Spectrum (DMSO) of **3c**



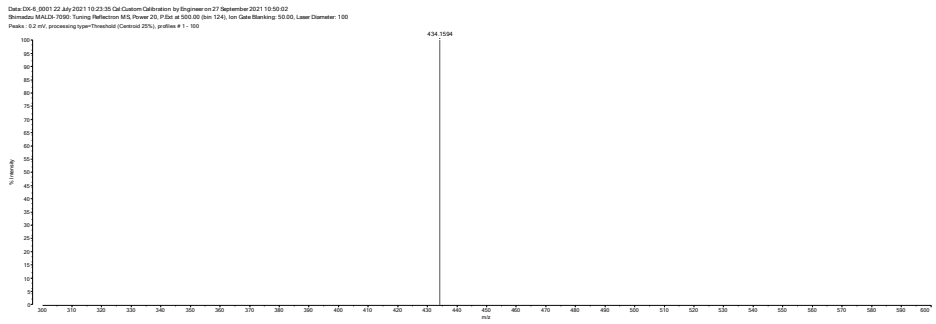
^{13}C NMR Spectrum (DMSO) of **3c**



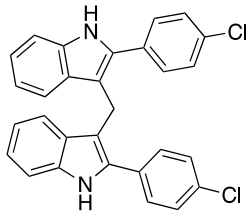
^{19}F NMR Spectrum (DMSO) of **3c**



HRMS of **3c**

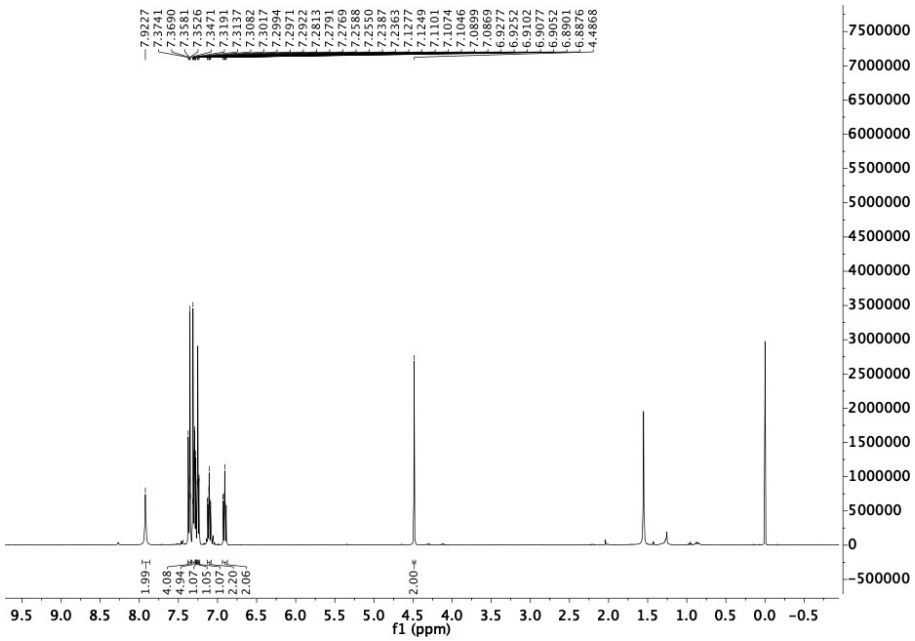


(3d) Bis(2-(4-chlorophenyl)-1*H*-indol-3-yl)methane [3]

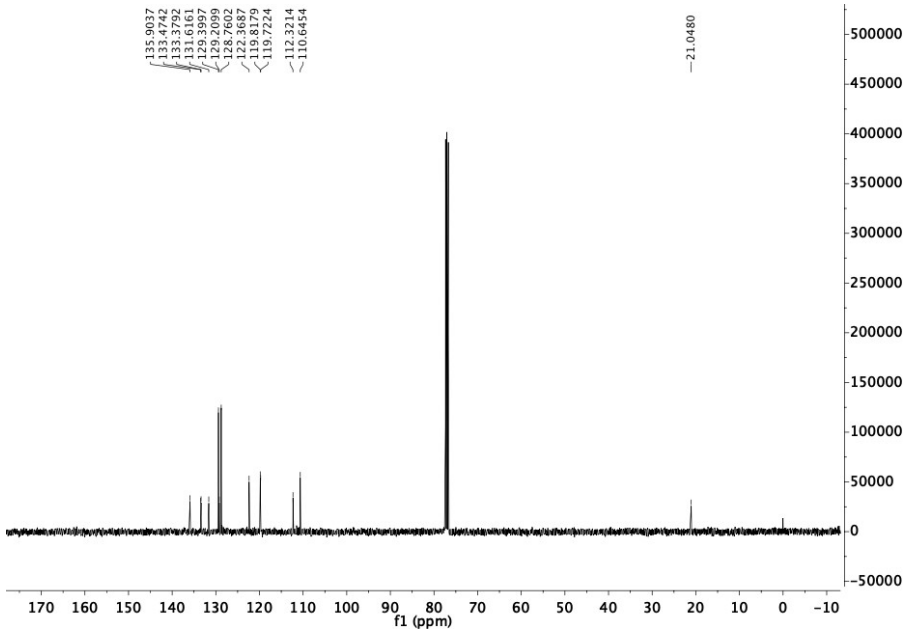


R_f = 0.25 (PE/EtOAc, 10:1). 58% yield. Light yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92 (s, 2H), 7.40 - 7.34 (m, 4H), 7.33 - 7.26 (m, 6H), 7.26 (d, J = 1.5 Hz, 1H), 7.24 (d, J = 1.0 Hz, 1H), 7.13 - 7.09 (m, 2H), 6.93 - 6.89(m, 2H), 4.49 (s, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 135.90, 133.47, 133.38, 131.62, 129.40, 129.21, 128.76, 122.37, 119.82, 119.72, 112.32, 110.65, 21.05; MALDI-TOF-MS: m/z: calcd for $C_{29}H_{20}Cl_2N_2$ (M): 466.1004; found: 466.1000.

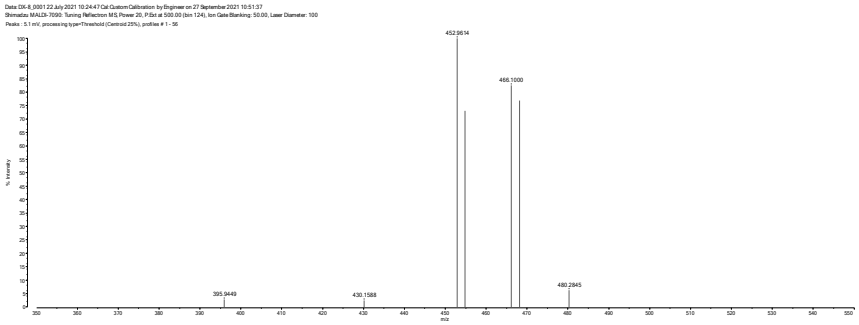
^{1}H NMR Spectrum ($CDCl_3$) of **3d**



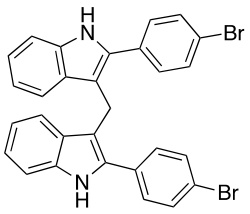
^{13}C NMR Spectrum ($CDCl_3$) of **3d**



HRMS of **3d**

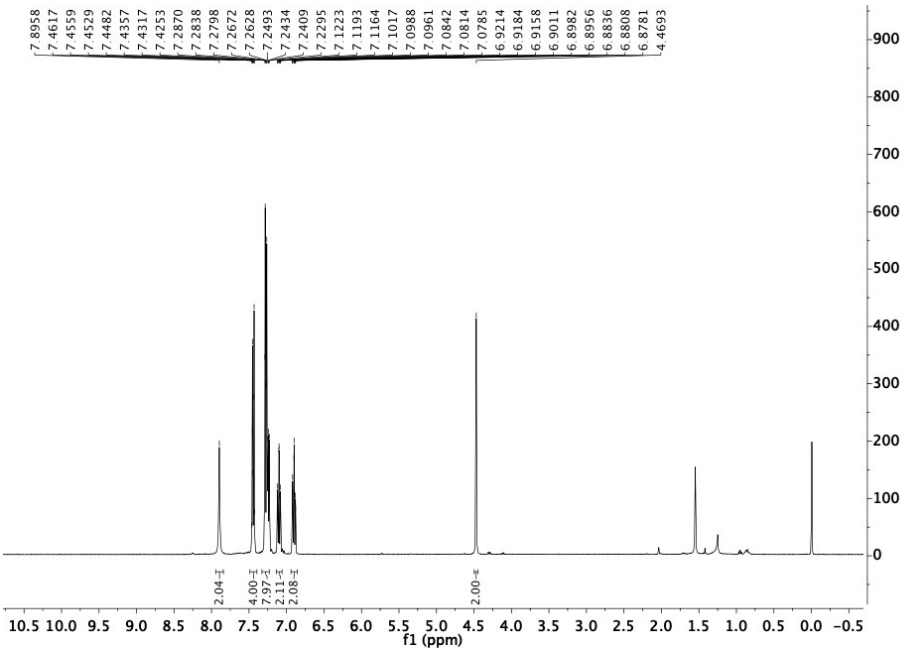


(3e) Bis(2-(4-bromophenyl)-1*H*-indol-3-yl)methane

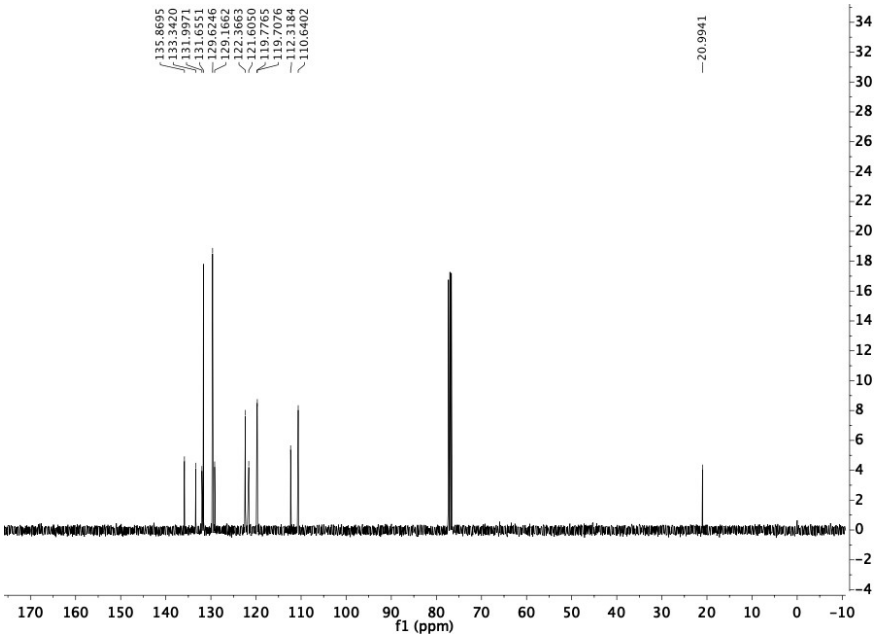


R_f = 0.25 (PE/EtOAc, 12:1). 56% yield. yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 (s, 2H), 7.46 - 7.43 (m, 4H), 7.29 - 7.28(m, 8H), 7.12 - 7.08 (m, 2H), 6.92 - 6.89(m, 2H), 4.47 (s, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 135.87, 133.34, 132.00, 131.66, 129.62, 129.17, 122.37, 121.60, 119.78, 119.71, 112.32, 110.64, 20.99. MALDI-TOF-MS $(M+H)^+$: m/z: calcd for $C_{29}H_{20}Br_2N_2$ (M): 555.0066; found: 555.0063.

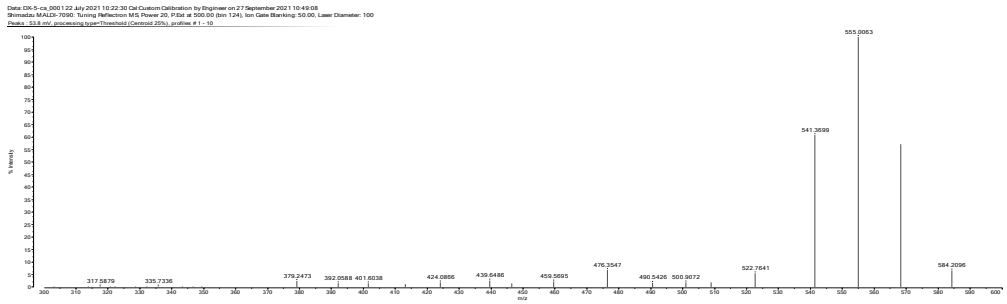
^{1}H NMR Spectrum ($CDCl_3$) of **3e**



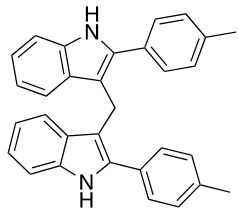
^{13}C NMR Spectrum ($CDCl_3$) of **3e**



HRMS of **3e**

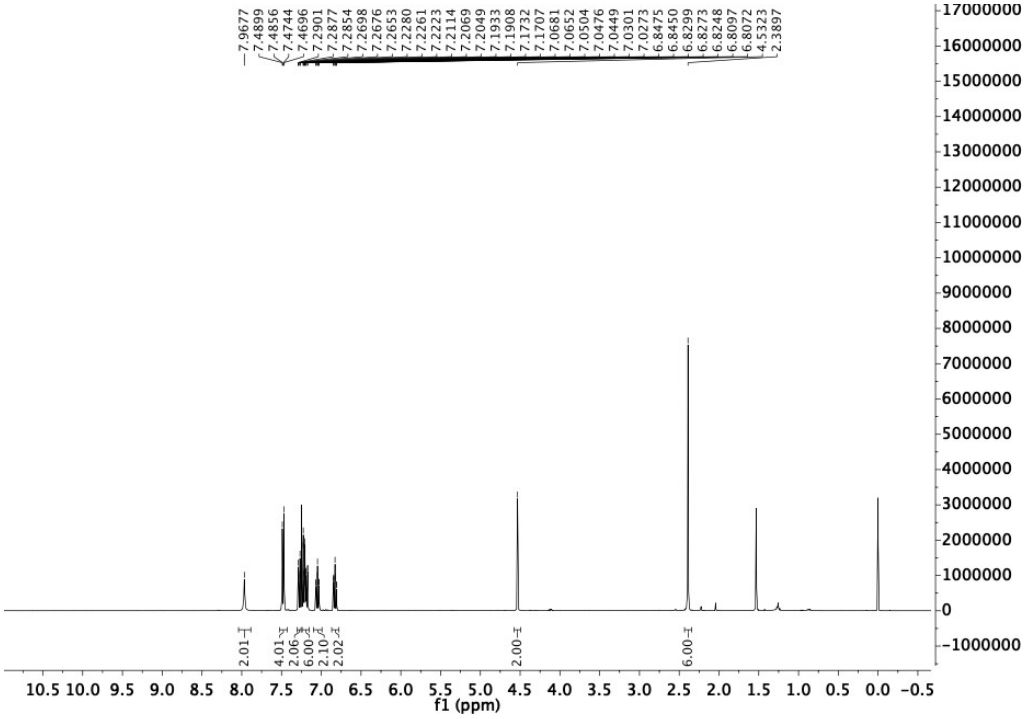


(3f) Bis(2-(*p*-tolyl)-1*H*-indol-3-yl)methane[3]

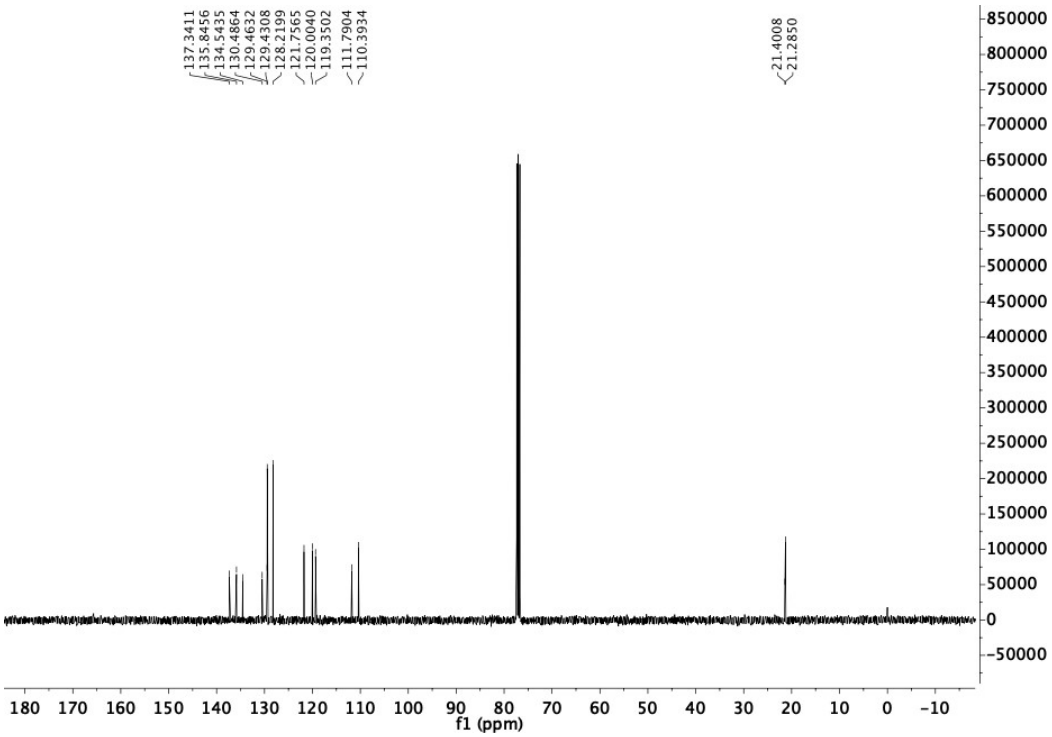


R_f = 0.25 (PE/EtOAc, 10:1). 76% yield. yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.97 (s, 2H), 7.53 - 7.43 (m, 4H), 7.29 - 7.26 (m, 2H), 7.24 - 7.15 (m, 6H), 7.07 - 7.03 (m, 2H), 6.84 - 6.80 (m, 2H), 4.53 (s, 2H), 2.39 (s, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 137.34, 135.85, 134.54, 130.49, 129.46, 129.43, 128.22, 121.76, 120.00, 119.35, 111.79, 110.39, 21.40, 21.29. MALDI-TOF-MS: m/z: calcd for $C_{30}H_{26}N_2$ $(M+H)^+$: 427.2169; found: 427.2168.

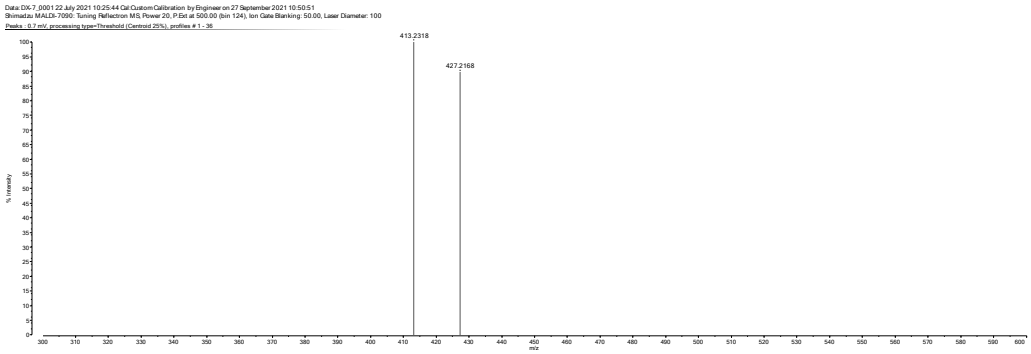
^{1}H NMR Spectrum ($CDCl_3$) of **3f**



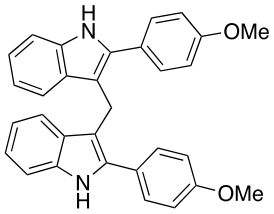
^{13}C NMR Spectrum ($CDCl_3$) of **3f**



HRMS of **3f**

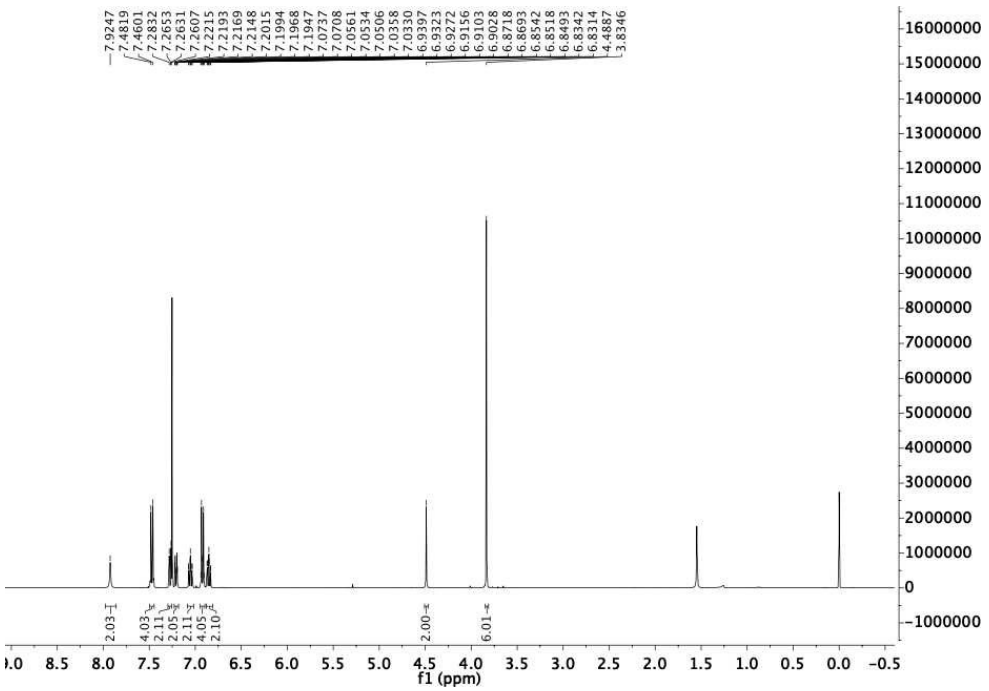


(3g) Bis(2-(4-methoxyphenyl)-1*H*-indol-3-yl)methane[3]

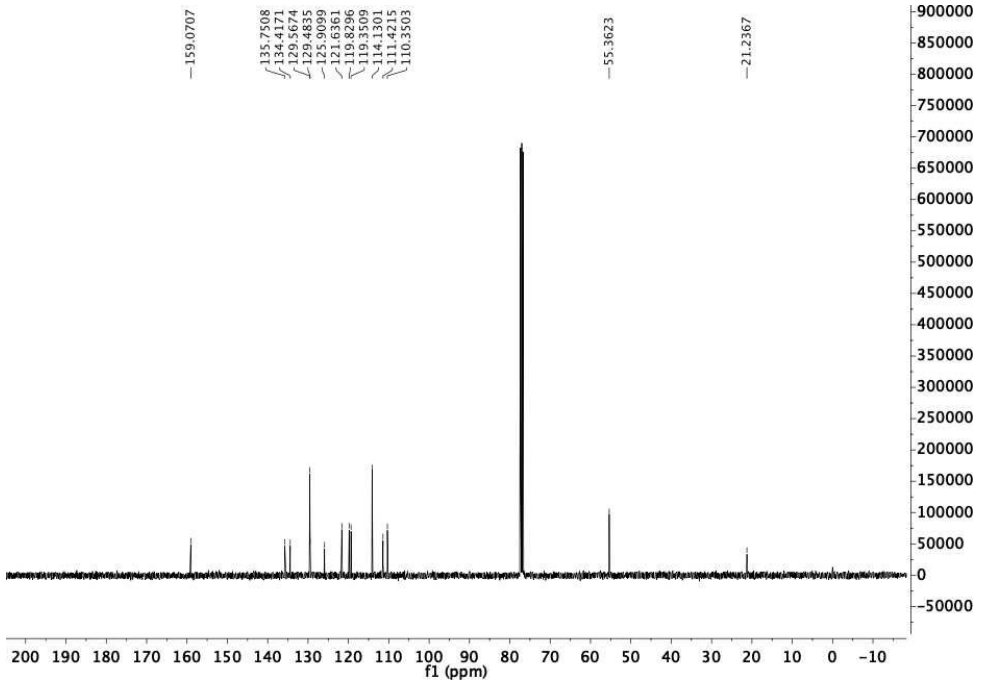


R_f = 0.25 (PE/EtOAc, 6:1). 67% yield. yellow solid. ^{11}H NMR (400 MHz, Chloroform-*d*) δ 7.92 (s, 2H), 7.49 - 7.7.44 (m, 4H), 7.30 - 7.26 (m, 2H), 7.23 - 7.18 (m, 2H), 7.05 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 2H), 6.95 - 6.90 (m, 4H), 6.85 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 2H), 4.49 (s, 2H), 3.83 (s, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.07, 135.75, 134.42, 129.57, 129.48, 125.91, 121.64, 119.83, 119.35, 114.13, 111.42, 110.35, 55.36, 21.24. MALDI-TOF-MS: m/z: calcd for $C_{31}H_{26}N_2O_2$ (M): 458.1994; found: 458.1997.

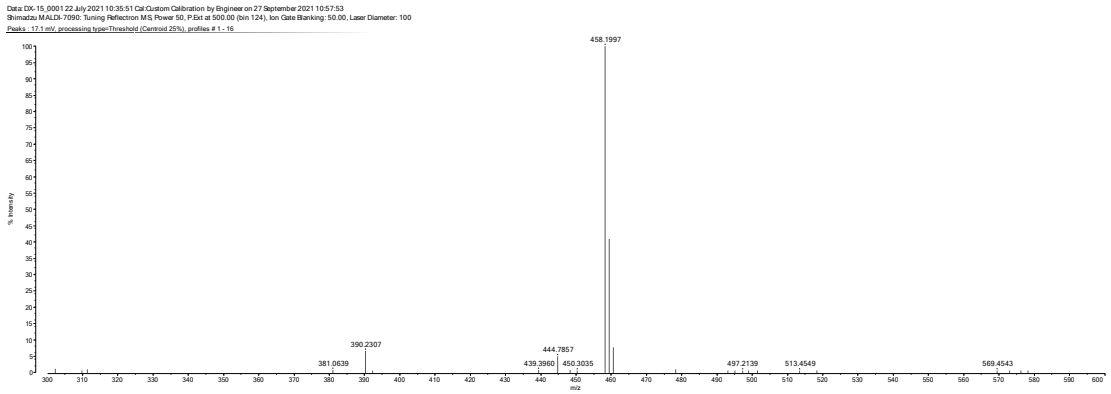
^{1}H NMR Spectrum ($CDCl_3$) of **3g**



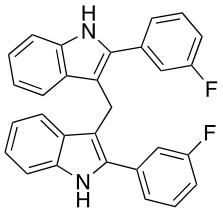
^{13}C NMR Spectrum ($CDCl_3$) of **3g**



HRMS of **3g**

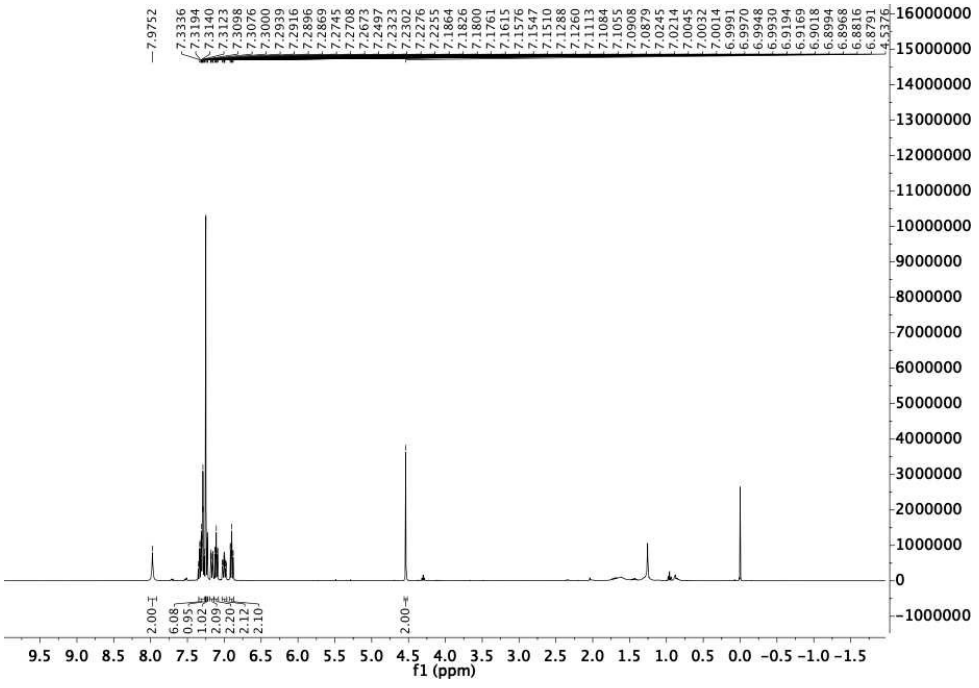


(3h) Bis(2-(3-fluorophenyl)-1*H*-indol-3-yl)methane

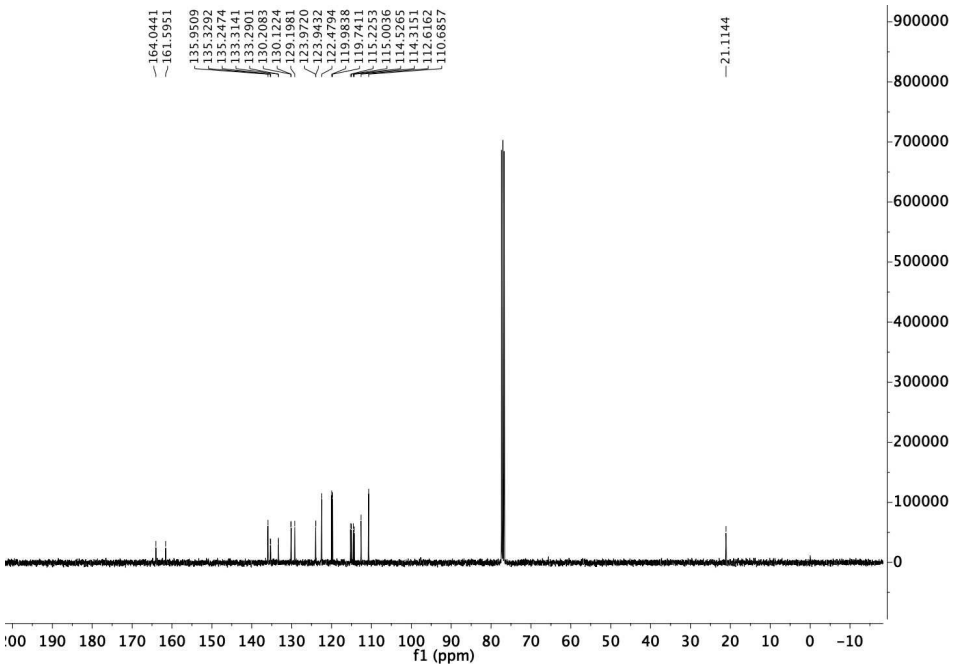


R_f = 0.25 (PE/EtOAc, 10:1). 55% yield. white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 (s, 2H), 7.35 - 7.26 (m, 6H), 7.25 (m, 1H), 7.23 (m, 1H), 7.20 - 7.14 (m, 2H), 7.13 - 7.07 (m, 2H), 7.03 - 6.97 (m, 2H), 6.90 (m, 2H), 4.54 (s, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.60, 135.95, 135.33, 135.25, 133.31, 133.29, 130.21, 130.12, 129.20, 123.97, 123.94, 122.48, 119.98, 119.74, 115.23, 115.00, 114.53, 114.32, 112.62, 110.69, 21.11. ^{19}F NMR (376 MHz, Chloroform -*d*) δ -112.32. MALDI-TOF-MS: m/z: calcd for $C_{31}H_{26}N_2O_2$ $(M+H)^+$: 435.1667; found: 435.1672

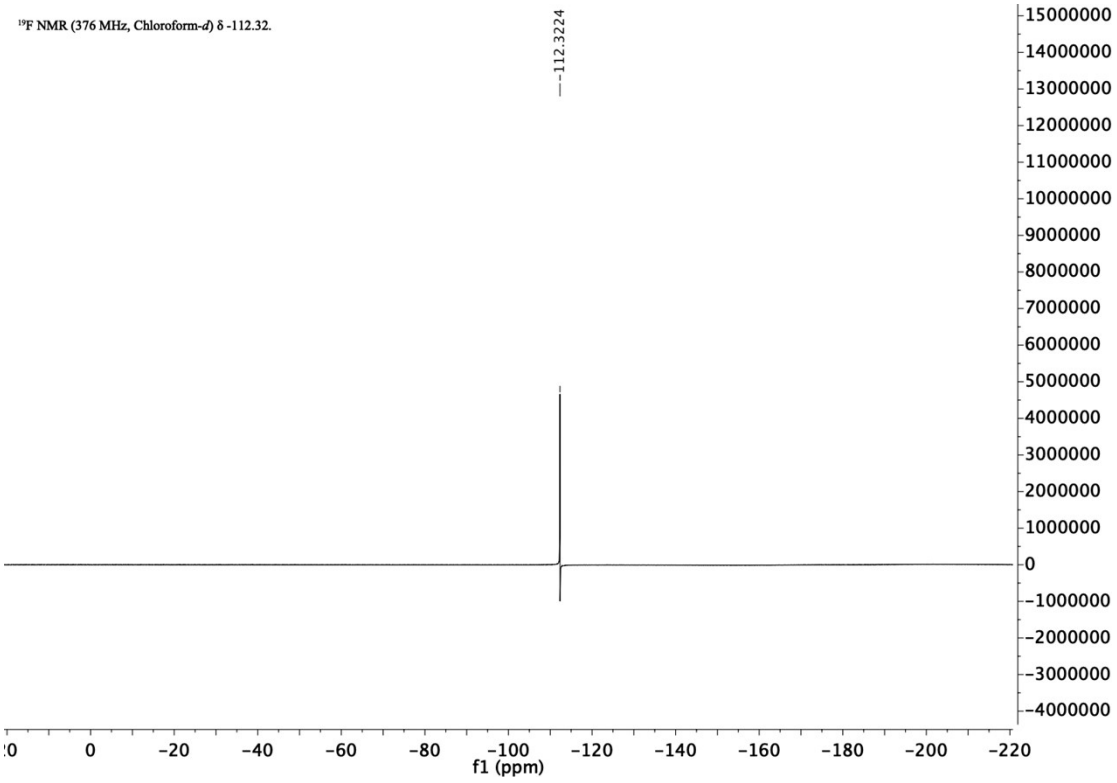
^{1}H NMR Spectrum ($CDCl_3$) of **3h**



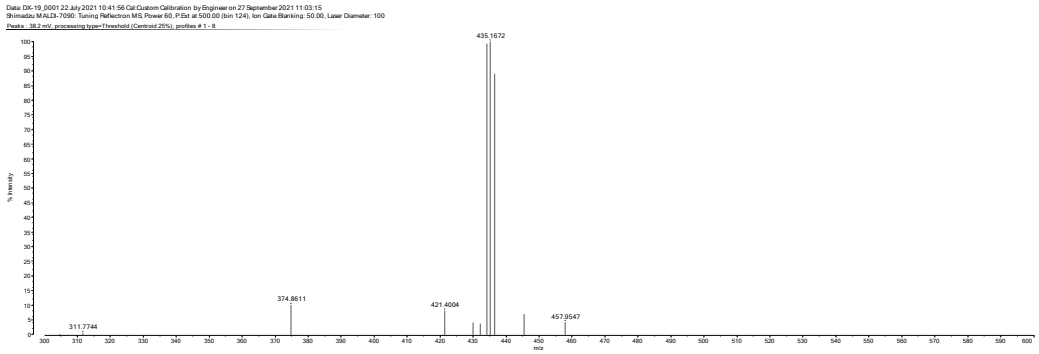
^{13}C NMR Spectrum ($CDCl_3$) of **3h**



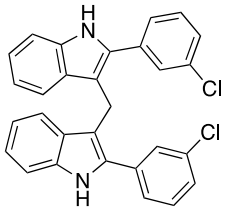
^{19}F NMR Spectrum (DMSO) of **3h**



HRMS of **3h**

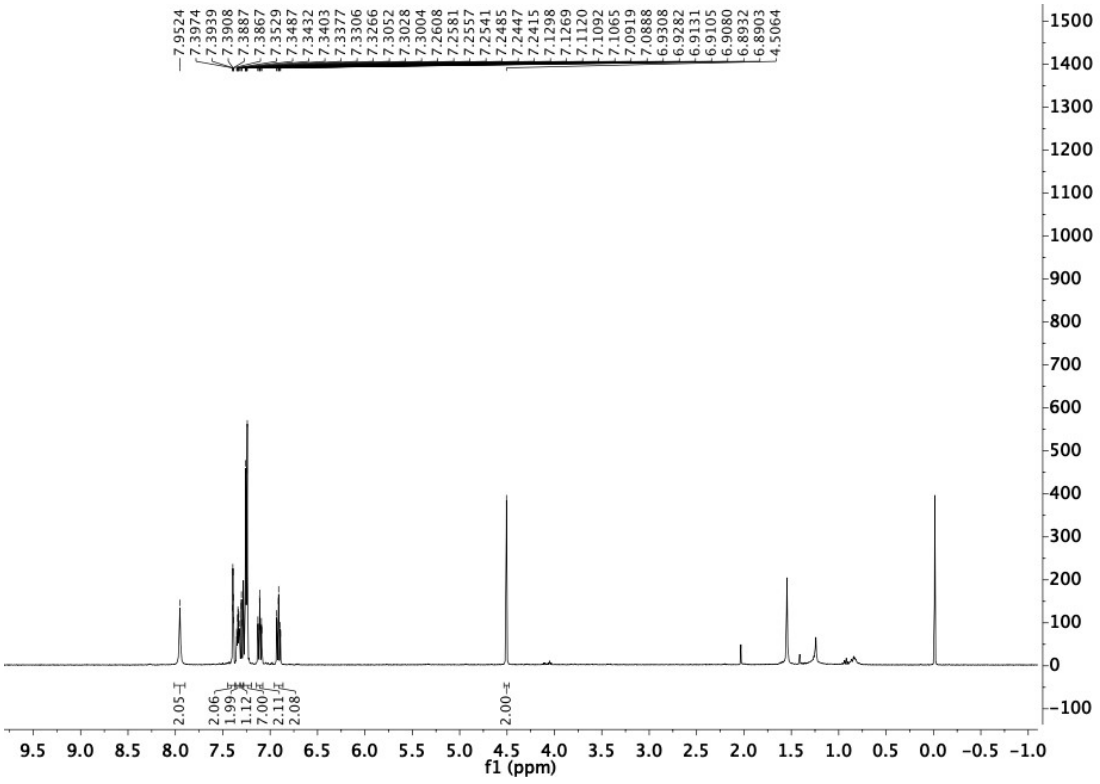


(3i) Bis(2-(3-chlorophenyl)-1*H*-indol-3-yl)methane

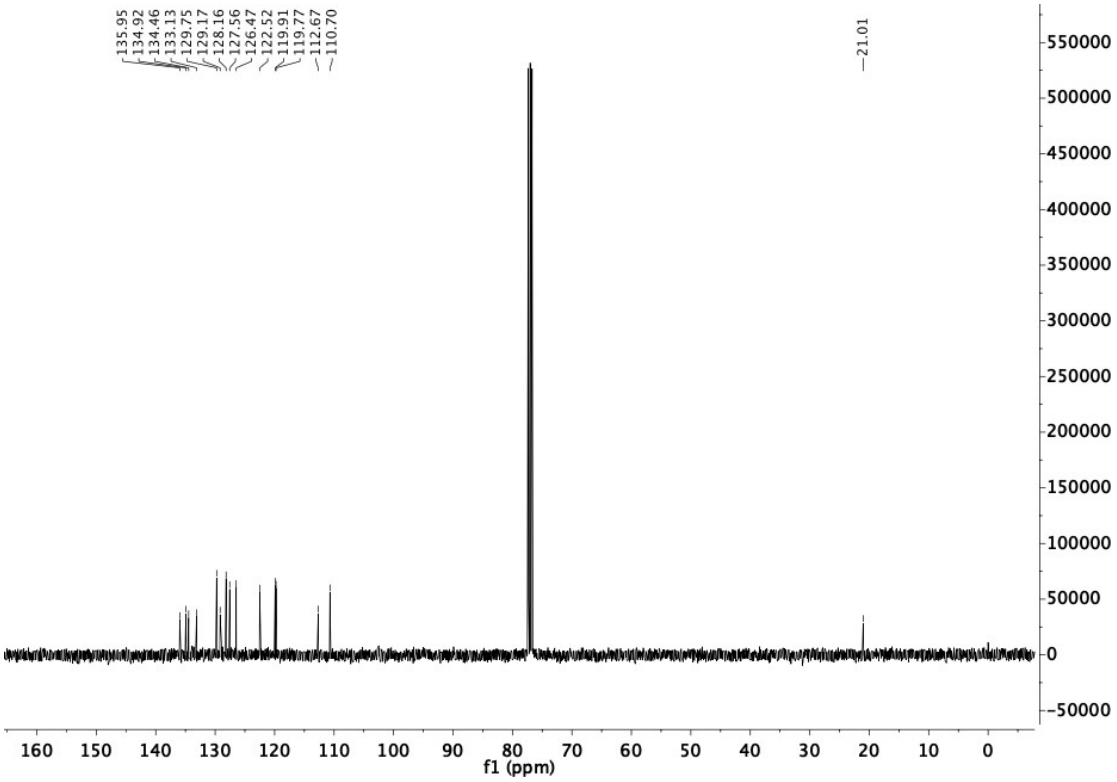


Rf = 0.25 (PE/EtOAc, 10:1). 54% yield. Pale yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 (s, 2H), 7.41 - 7.40 (m, 2H), 7.38 - 7.33 (m, 2H), 7.31 - 7.28 (m, 2H), 7.25 - 7.21 (m, 6H), 7.13 - 7.08 (m, 2H), 6.93 - 6.89 (m, 2H), 4.52 (s, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 135.95, 134.92, 134.46, 133.13, 129.75, 129.17, 128.16, 127.56, 126.47, 122.52, 119.91, 119.77, 112.67, 110.70, 21.01. MALDI-TOF-MS: m/z: calcd for $C_{29}H_{20}Cl_2N_2$ (M): 466.1004; found: 466.1005.

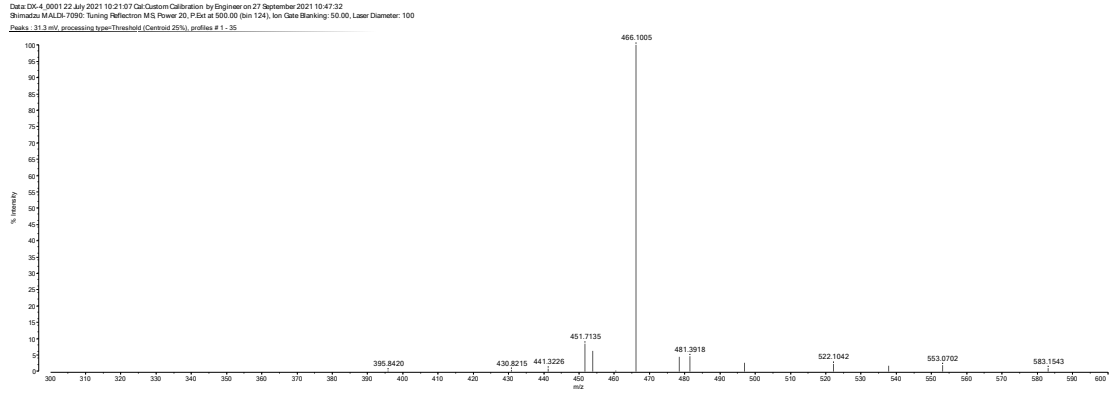
^{1}H NMR Spectrum ($CDCl_3$) of **3i**



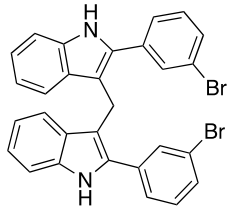
^{13}C NMR Spectrum ($CDCl_3$) of **3i**



HRMS of **3i**

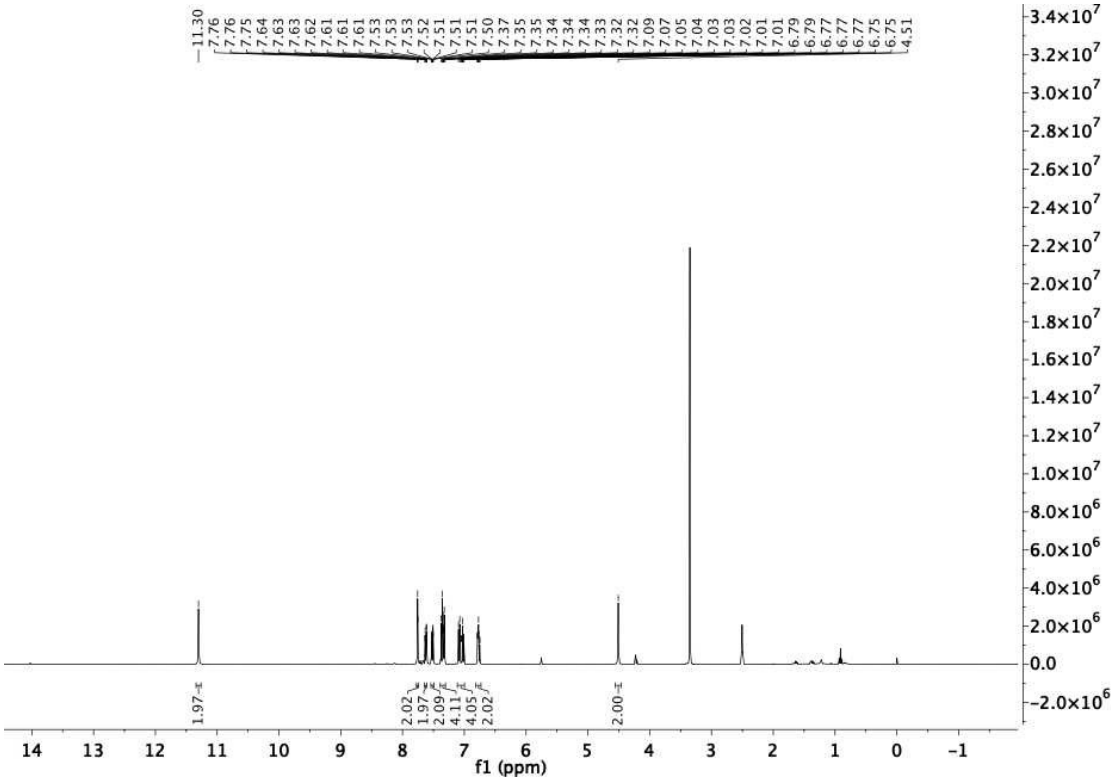


(3j) Bis(2-(3-bromophenyl)-1*H*-indol-3-yl)methane

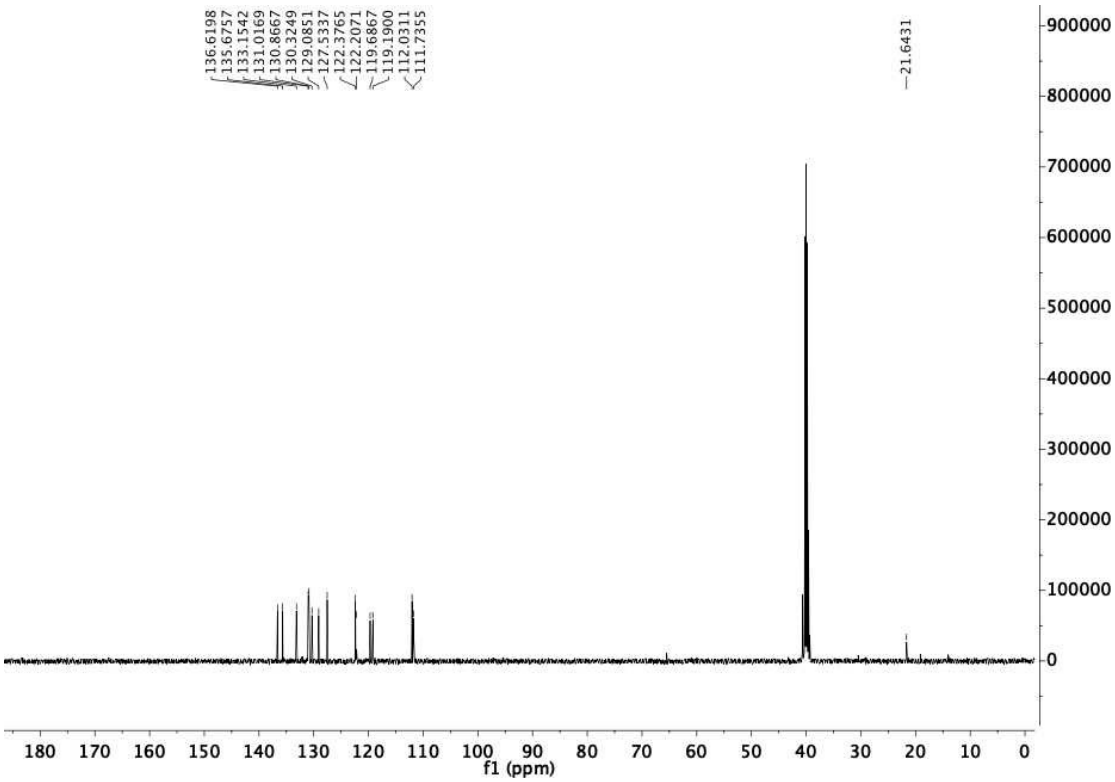


Rf = 0.25 (PE/EtOAc, 12:1). 62% yield. Pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.30 (s, 2H), 7.76 (t, *J* = 1.8 Hz, 2H), 7.64 - 7.60 (m, 2H), 7.54 - 7.49 (m, 2H), 7.39 - 7.30 (m, 4H), 7.11 - 7.00 (m, 4H), 6.81 - 6.73 (m, 2H), 4.51 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 136.62, 135.68, 133.15, 131.02, 130.87, 130.32, 129.09, 127.53, 122.38, 122.21, 119.69, 119.19, 112.03, 111.74, 21.64. MALDI-TOF-MS: m/z: calcd for $C_{29}H_{20}Br_2N_2$ (M): 555.0066; found: 555.0065.

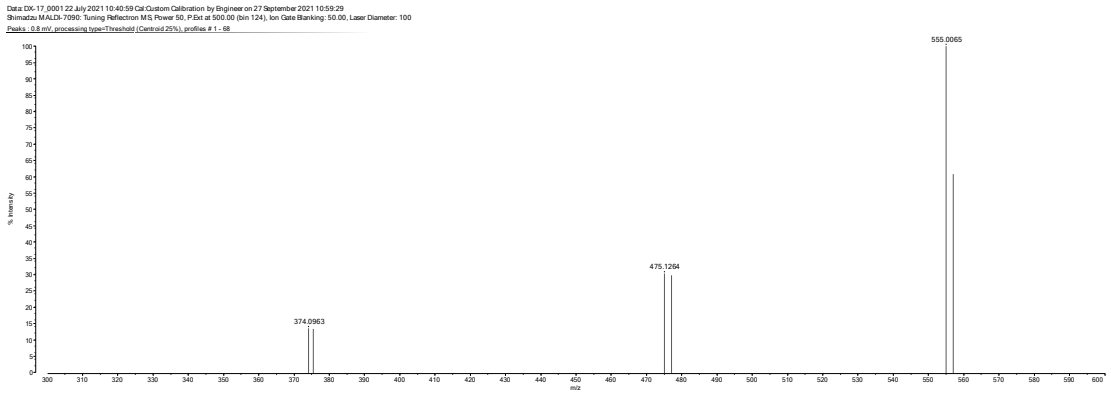
^{1}H NMR Spectrum (DMSO) of **3j**



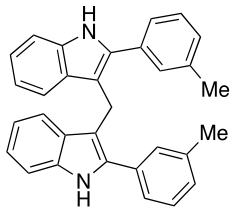
^{13}C NMR Spectrum (DMSO) of **3j**



HRMS of **3j**

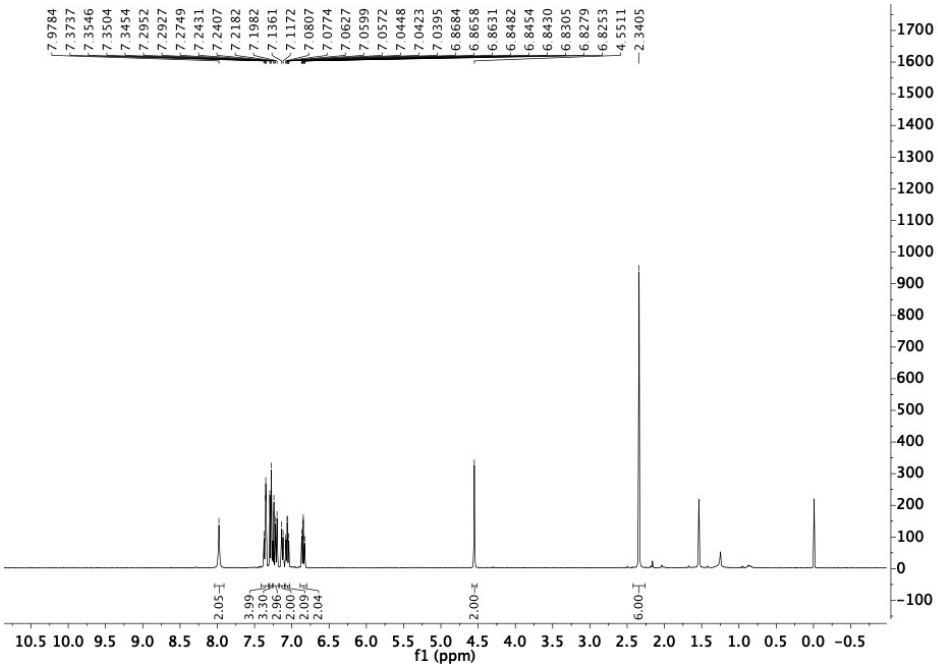


(3k) Bis(2-(*m*-tolyl)-1*H*-indol-3-yl)methane

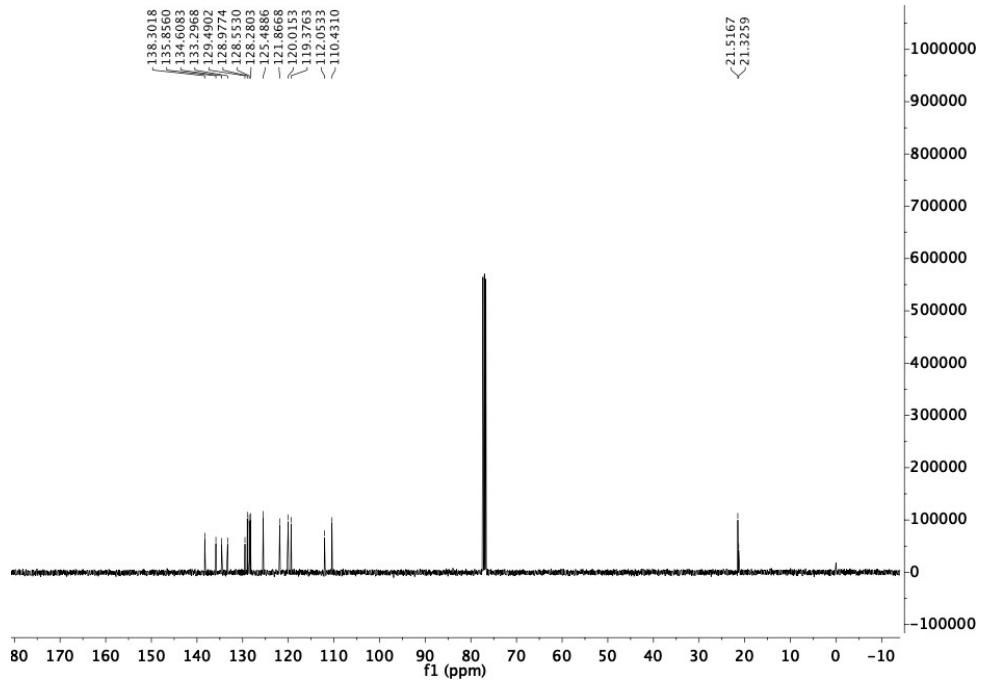


Rf = 0.25 (PE/EtOAc, 8:1). 51% yield. Pale yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 (s, 2H), 7.41 - 7.31 (m, 4H), 7.30 -7.27 (m, 3H), 7.25 - 7.17 (m, 3H), 7.16 - 7.10 (m, 2H), 7.09 - 7.03 (m, 2H), 6.89 - 6.80 (m, 2H), 4.55 (s, 2H), 2.34 (s, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 138.30, 135.86, 134.61, 133.30, 129.49, 128.98, 128.55, 128.28, 125.49, 121.87, 120.02, 119.38, 112.05, 110.43, 21.52, 21.33. MALDI-TOF-MS: m/z: calcd for $C_{31}H_{26}N_2$ $(M+H)^+$: 427.2169; found: 427.2164.

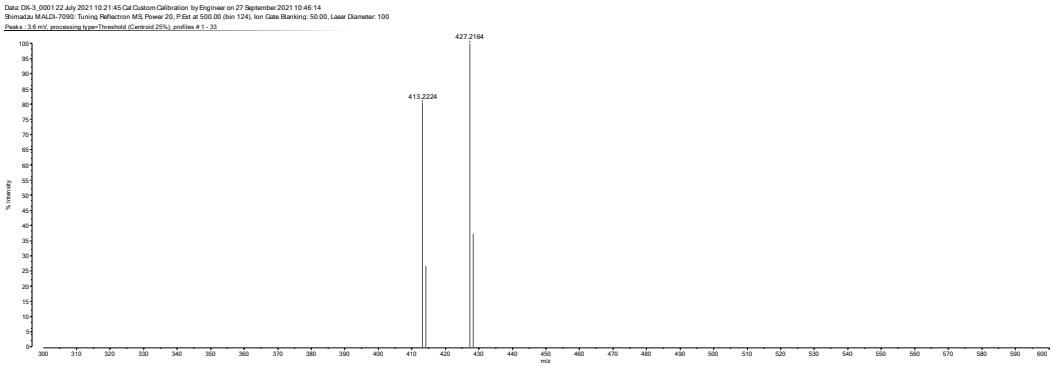
^{1}H NMR Spectrum ($CDCl_3$) of **3k**



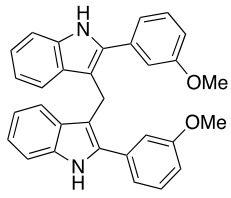
^{13}C NMR Spectrum ($CDCl_3$) of **3k**



HRMS of **3k**

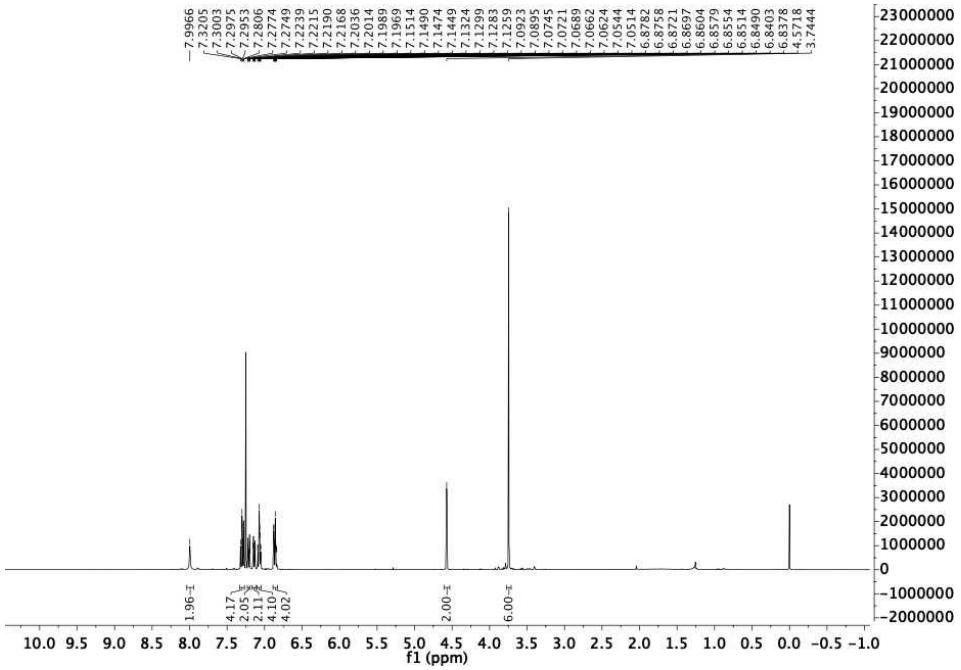


(3l) Bis(2-(3-methoxyphenyl)-1*H*-indol-3-yl)methane

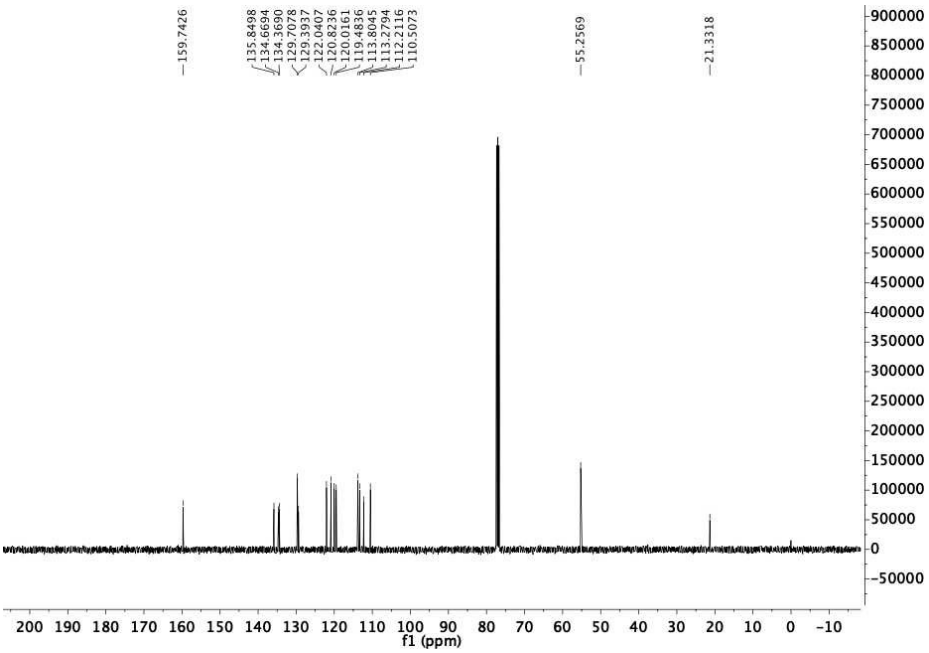


Rf = 0.25 (PE/EtOAc, 8:1). 46% yield. yellow solid.^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (s, 2H), 7.33 - 7.27 (m, 4H), 7.23 - 7.19 (m, 2H), 7.16 - 7.12 (m, 2H), 7.10 - 7.04 (m, 4H), 6.89 - 6.83 (m, 4H), 4.57 (s, 2H), 3.74 (s, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.74, 135.85, 134.67, 134.37, 129.71, 129.39, 122.04, 120.82, 120.02, 119.48, 113.80, 113.28, 112.21, 110.51, 55.26, 21.33. MALDI-TOF-MS: m/z: calcd for $C_{31}H_{26}N_2O_2$ (M): 458.1994; found: 458.1994.

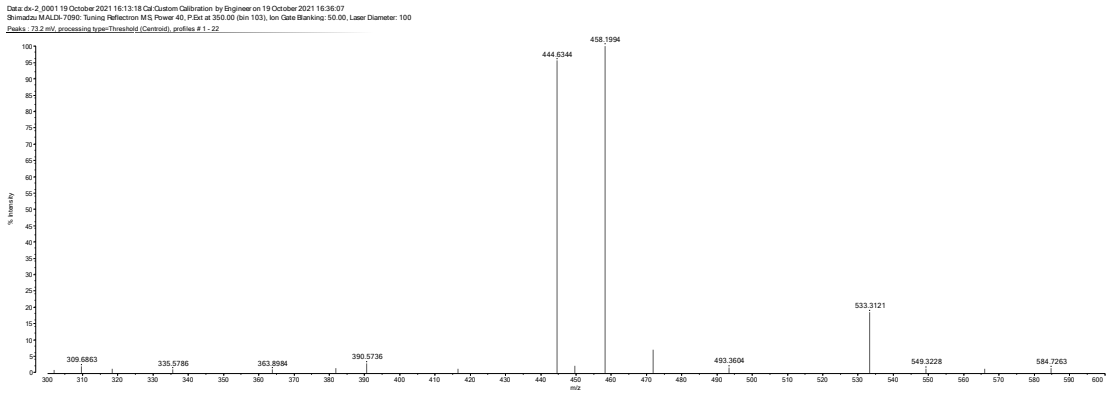
^{1}H NMR Spectrum ($CDCl_3$) of **3l**



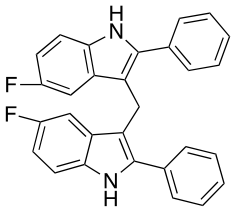
^{13}C NMR Spectrum ($CDCl_3$) of **3l**



HRMS of **3l**

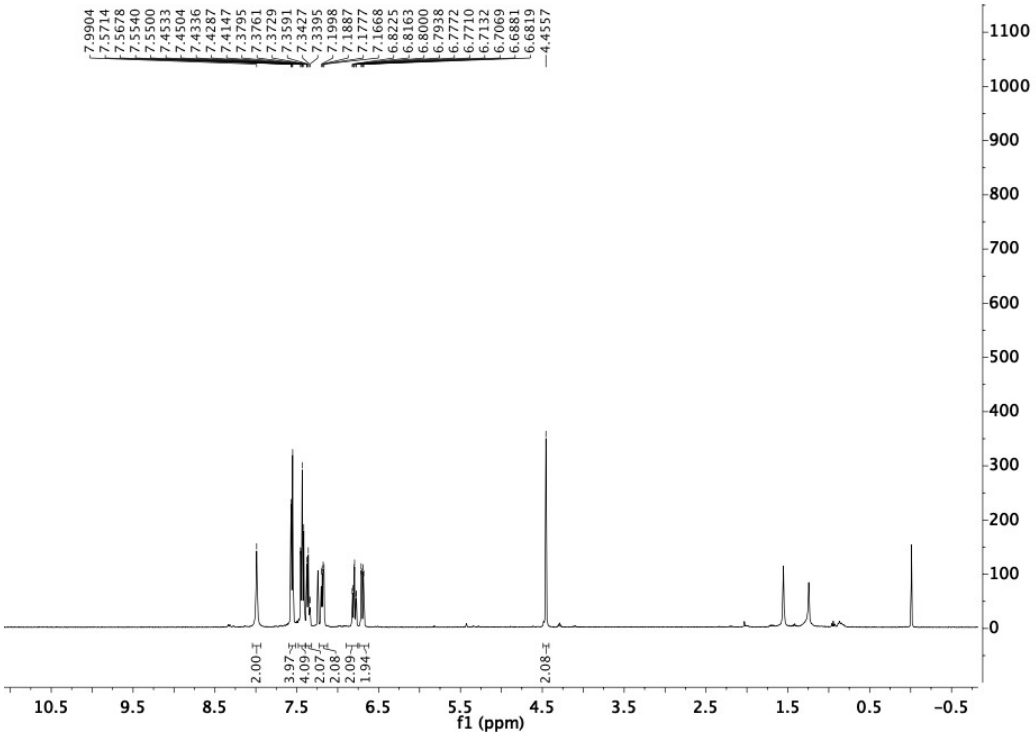


(3m) Bis(5-fluoro-2-phenyl-1*H*-indol-3-yl)methane

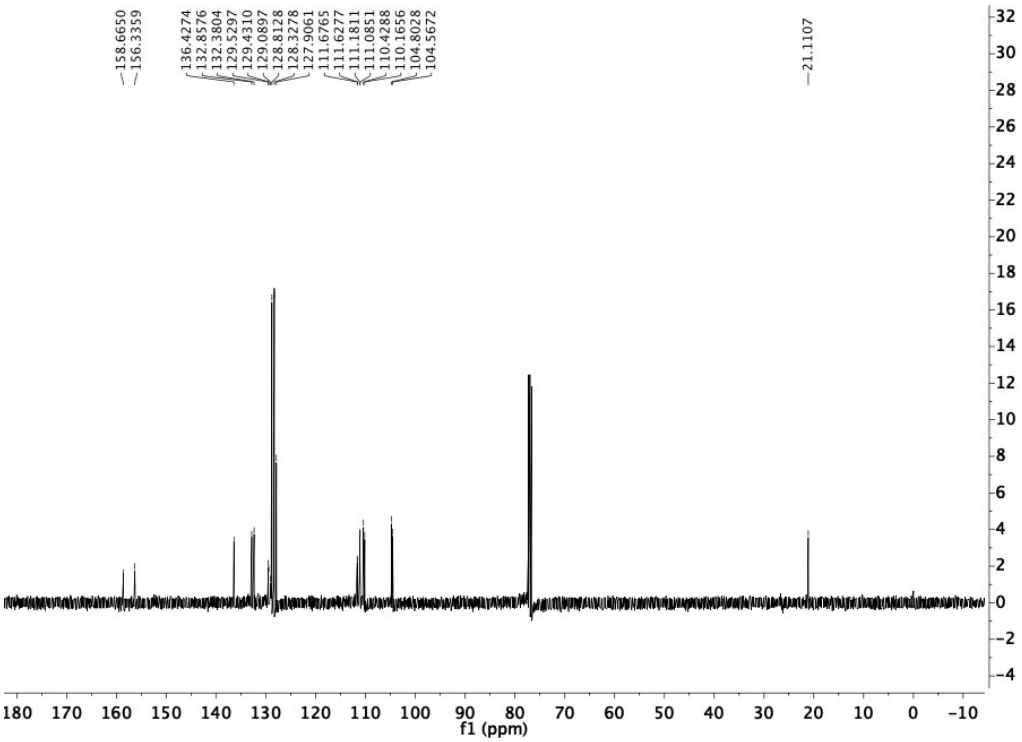


Rf = 0.25 (PE/EtOAc, 8:1). 41% yield. Pale yellow solid.^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (s, 2H), 7.61 - 7.52(m, 4H), 7.48 - 7.39 (m, 4H), 7.39 - 7.31 (m, 2H), 7.21 - 7.12(m, 2H), 6.86 - 6.75(m, 2H), 6.74 - 6.60(m, 2H), 4.46 (s, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.67, 156.34, 136.43, 132.86, 132.38, 128.81, 128.33, 127.91, 111.63, 111.18, 111.09, 110.43, 110.17, 104.80, 104.57, 21.11. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -124.30. MALDI-TOF-MS: m/z: calcd for $C_{29}H_{20}F_2N_2$ $(M+H)^+$: 435.1667; found: 435.1662.

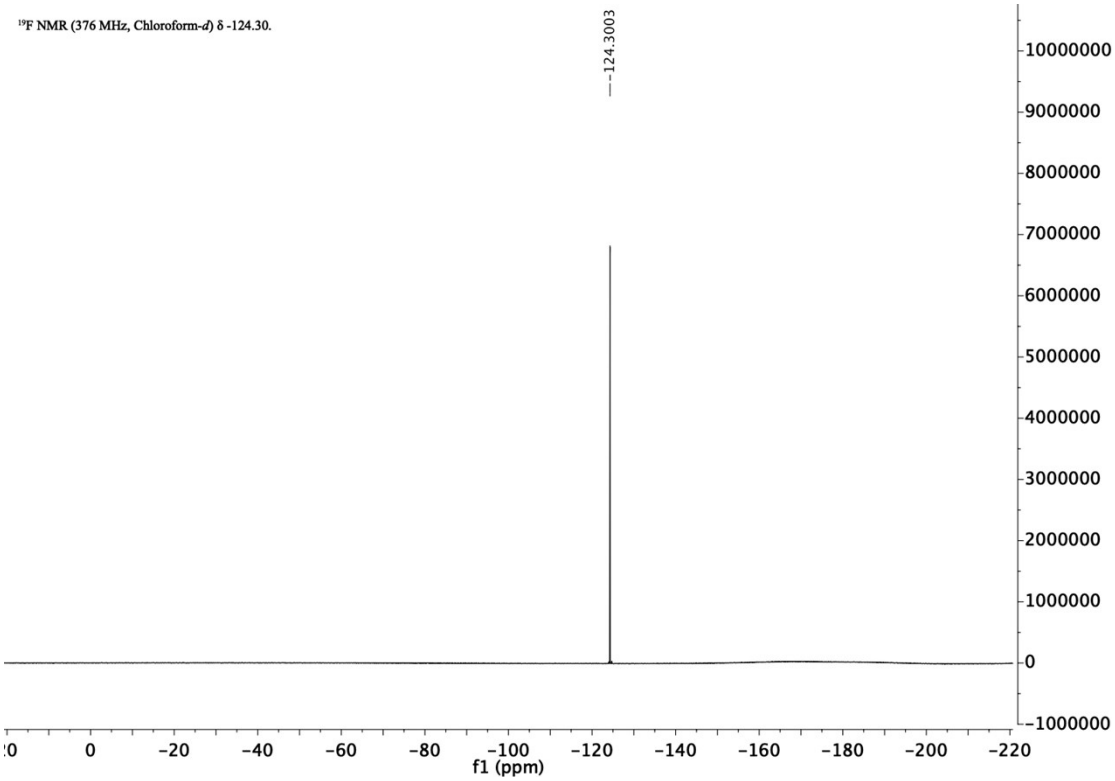
^{1}H NMR Spectrum ($CDCl_3$) of **3m**



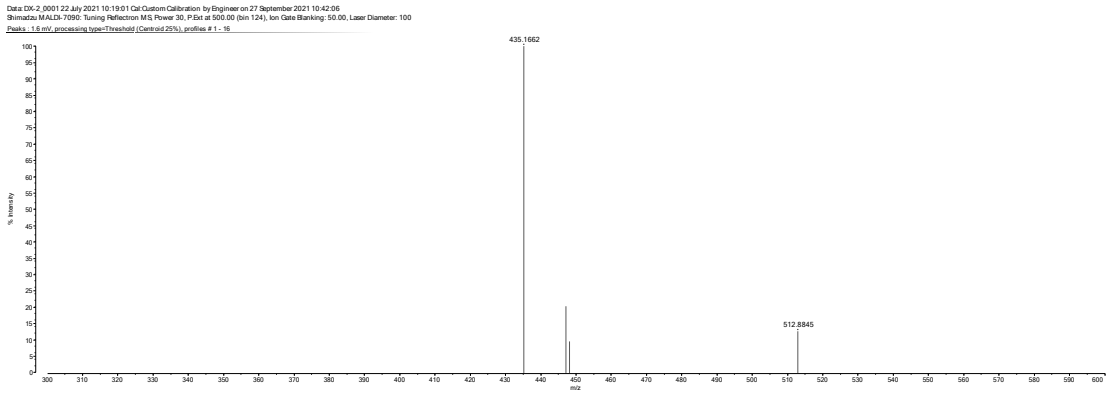
^{13}C NMR Spectrum ($CDCl_3$) of **3m**



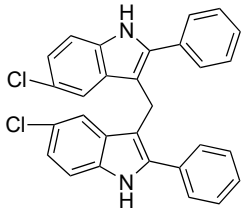
^{19}F NMR Spectrum (DMSO) of **3m**



HRMS of **3m**

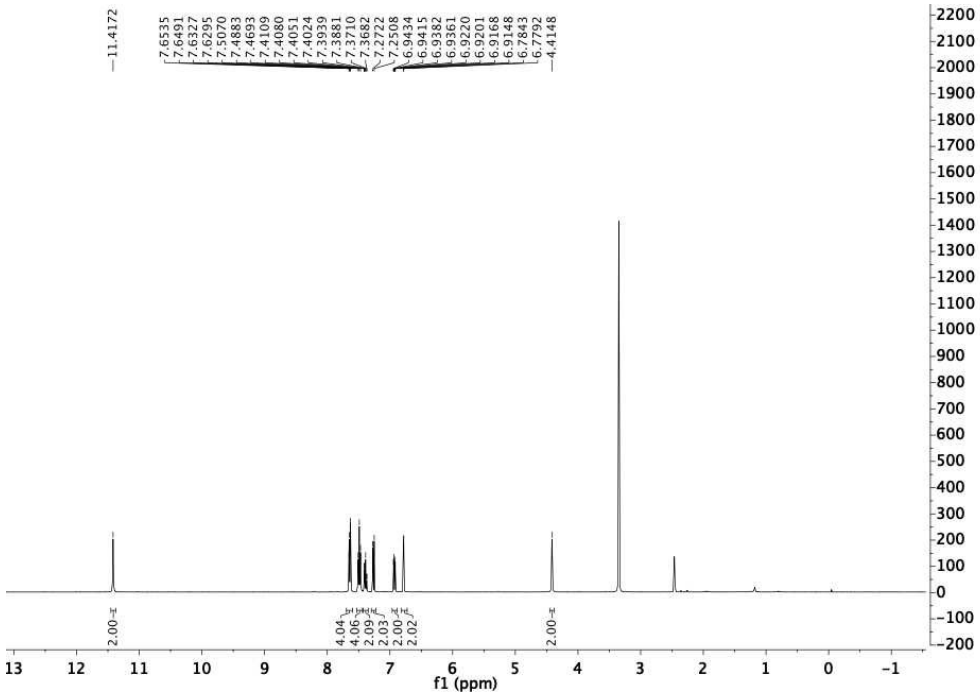


(3n) Bis(5-chloro-2-phenyl-1*H*-indol-3-yl)methane

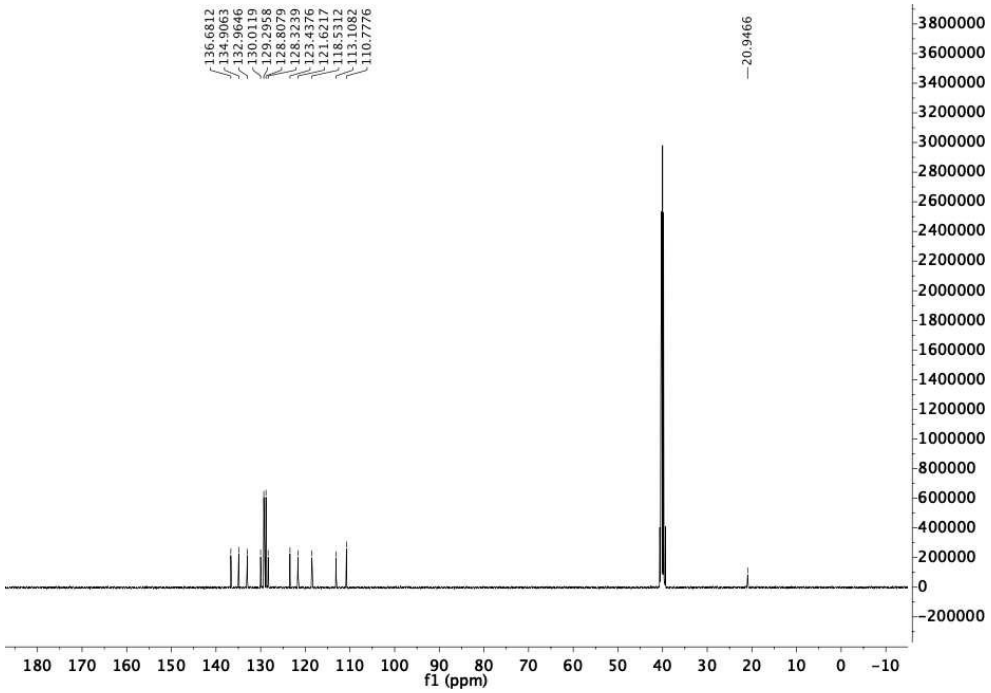


R_f = 0.25 (PE/EtOAc, 10:1). 39% yield. yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.42 (s, 2H), 7.69 - 7.60 (m, 4H), 7.52- 7.43 (m, 4H), 7.43 - 7.35 (m, 2H), 7.29 - 7.23 (m, 2H), 6.96- 6.88 (m, 2H), 6.78 (d, *J* = 2.1 Hz, 2H), 4.41 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 136.68, 134.91, 132.96, 130.01, 129.30, 128.81, 128.32, 123.44, 121.62, 118.53, 113.11, 110.78, 20.95. MALDI-TOF-MS: m/z: calcd for $C_{29}H_{20}Cl_2N_2$ (M): 466.1004; found:466.1002.

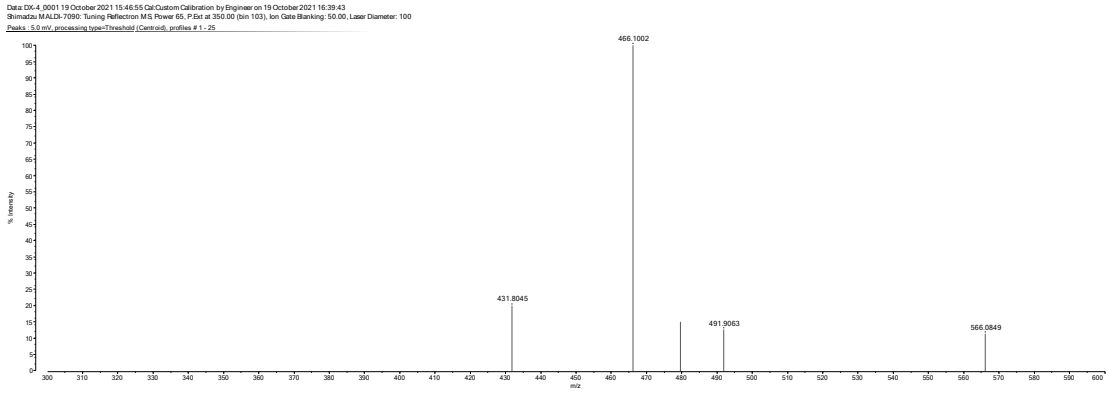
^{1}H NMR Spectrum (DMSO) of **3n**



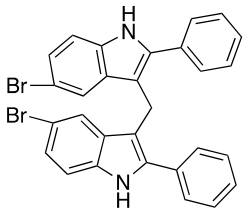
^{13}C NMR Spectrum (DMSO) of **3n**



HRMS of **3n**

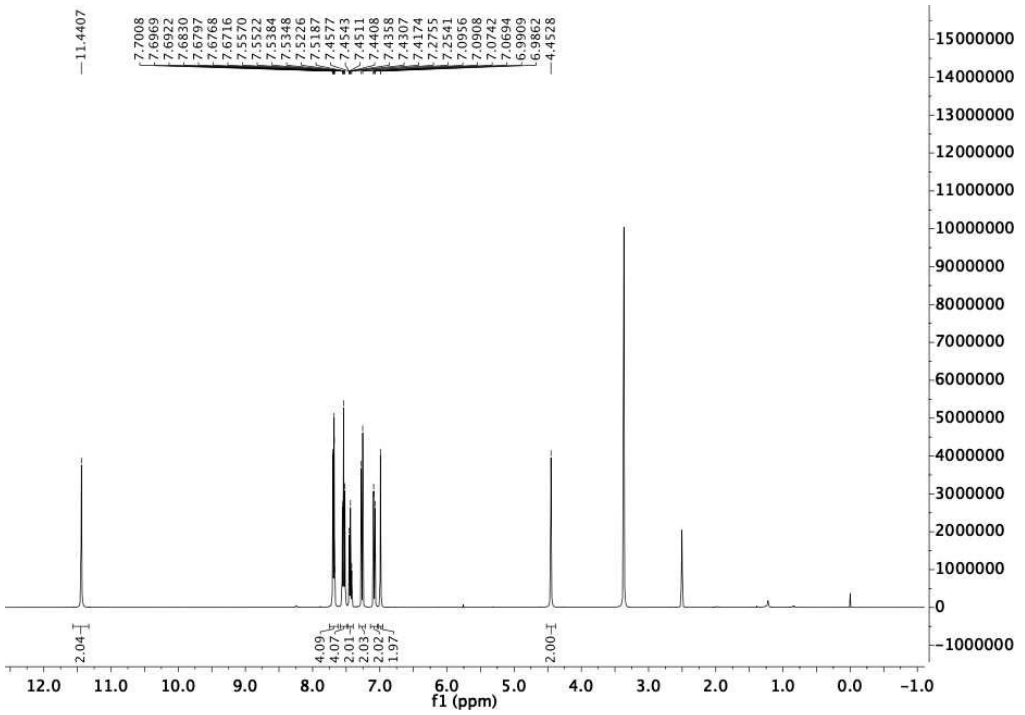


(3o) Bis(5-bromo-2-phenyl-1*H*-indol-3-yl)methane

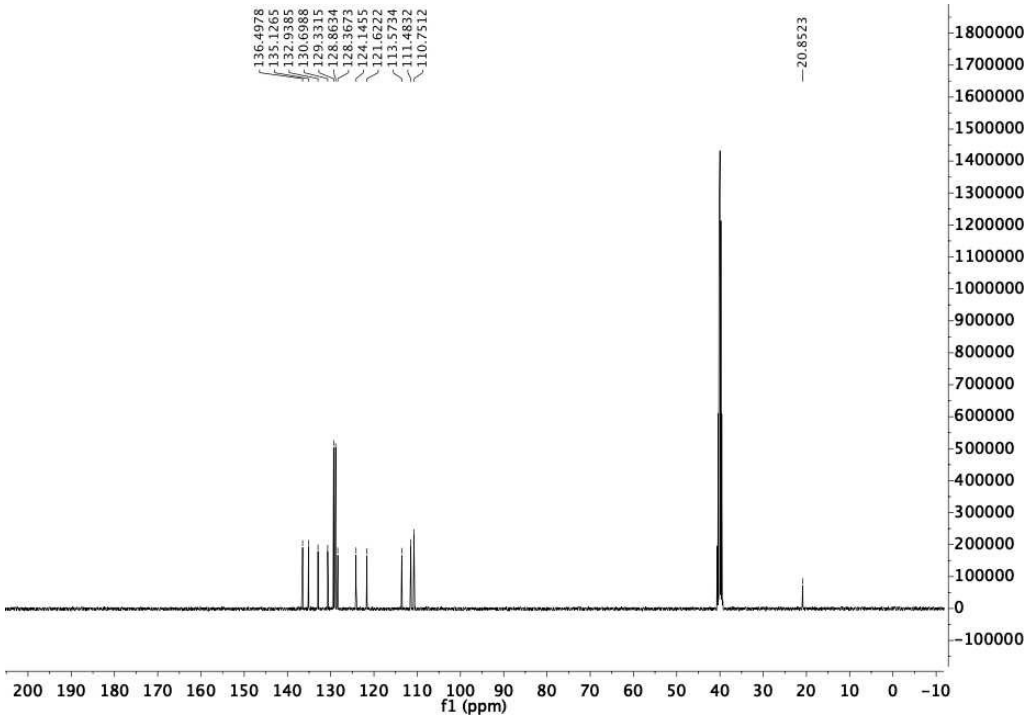


Rf = 0.25 (PE/EtOAc, 8:1). 28% yield. Pale yellow solid.^{1}H NMR (400 MHz, DMSO-d_6) δ 11.44 (s, 2H), 7.75 - 7.62 (m, 4H), 7.75 - 7.62 (m, 4H), 7.47 - 7.40 (m, 2H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.08 (dd, *J* = 8.6, 1.9 Hz, 2H), 6.99 (d, *J* = 1.9 Hz, 2H), 4.45 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 136.50, 135.13, 132.94, 130.70, 129.33, 128.86, 128.37, 124.15, 121.62, 113.57, 111.48, 110.75, 20.85. MALDI-TOF-MS: m/z: calcd for $C_{29}H_{20}Br_2N_2$ $(M+H)^+$: 553.9993; found:553.9996.

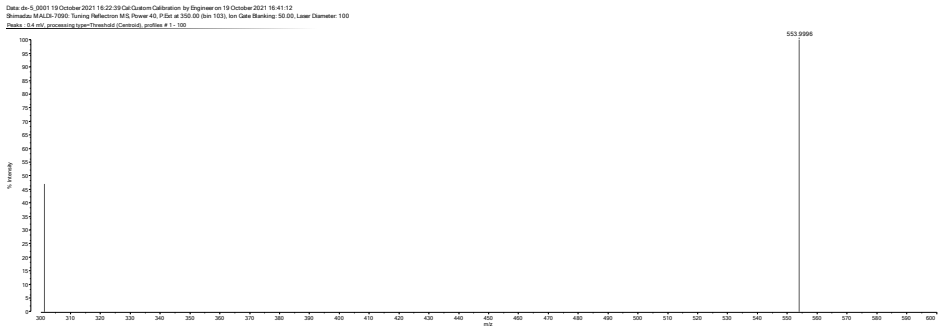
^{1}H NMR Spectrum (DMSO) of **3o**



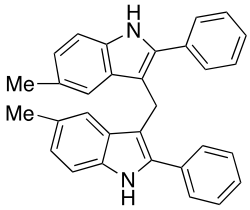
^{13}C NMR Spectrum (DMSO) of **3o**



HRMS of **3o**



(3p) Bis(5-methyl-2-phenyl-1*H*-indol-3-yl)methane

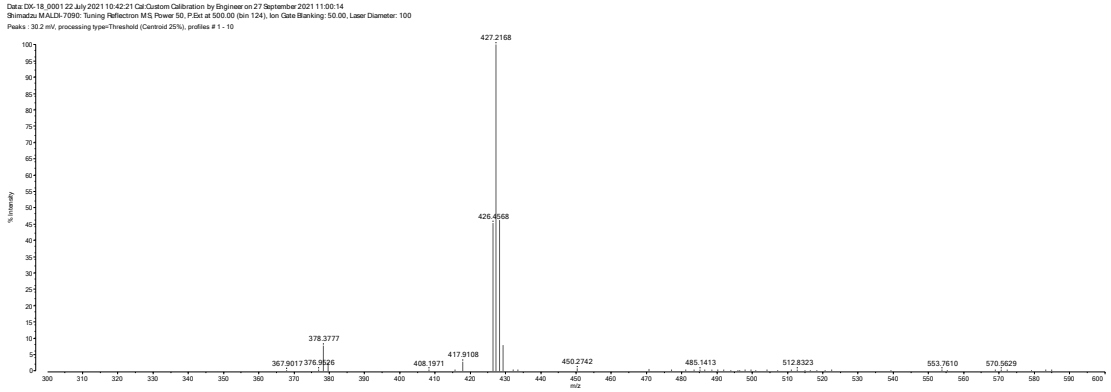


Rf = 0.25 (PE/EtOAc, 12:1). 83% yield. Pale yellow solid.^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 (s, 2H), 7.63 - 7.55(m, 4H), 7.50 - 7.41 (m, 4H), 7.40 - 7.32 (m, 2H), 7.14 (dd, *J* = 8.6, 1.2 Hz, 2H), 6.93 - 6.82 (m, 4H), 4.52 (s, 2H), 2.19 (s, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 134.53, 134.21, 133.78, 129.54, 128.72, 128.71, 128.47, 128.27, 127.45, 123.47, 119.80, 111.98, 110.06, 21.44, 20.69. MALDI-TOF-MS: m/z: calcd for $C_{31}H_{26}N_2$ $(M+H)^+$: 427.2169; found: 427.2168.

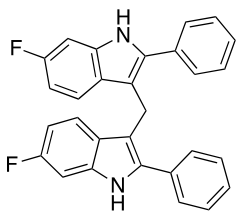
^{1}H NMR Spectrum ($CDCl_3$) of **3p**

^{13}C NMR Spectrum ($CDCl_3$) of **3p**

HRMS of **3p**

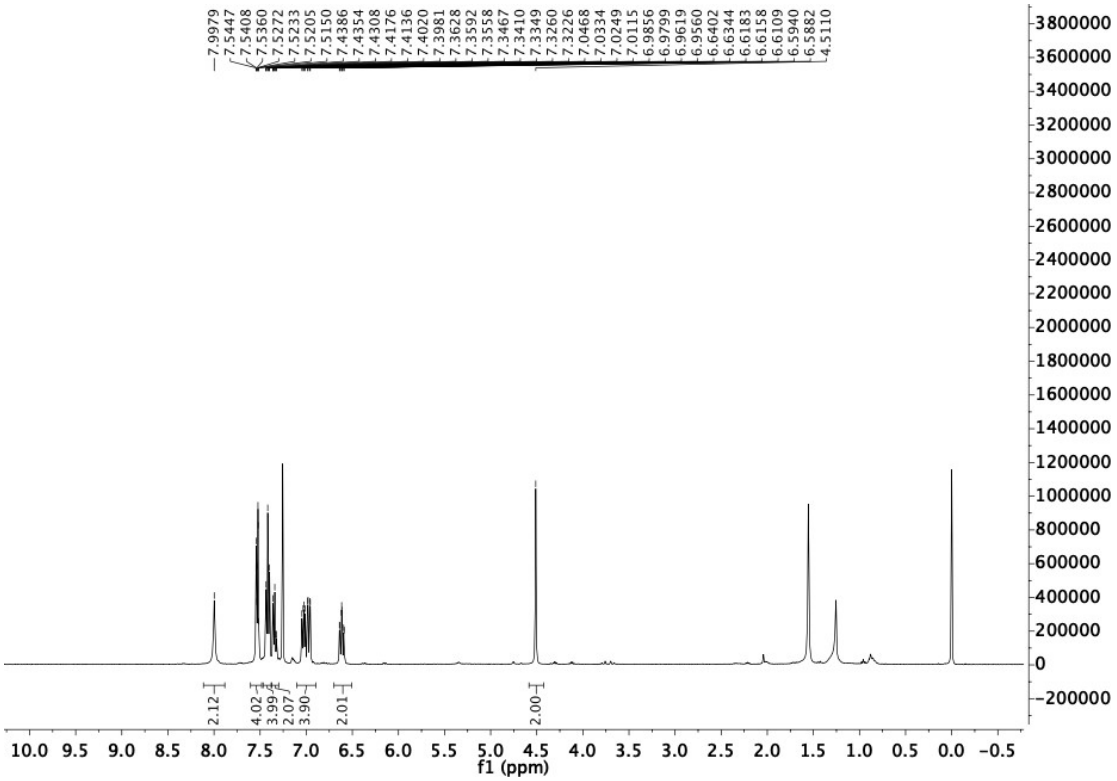


(3q) Bis(6-fluoro-2-phenyl-1*H*-indol-3-yl)methane

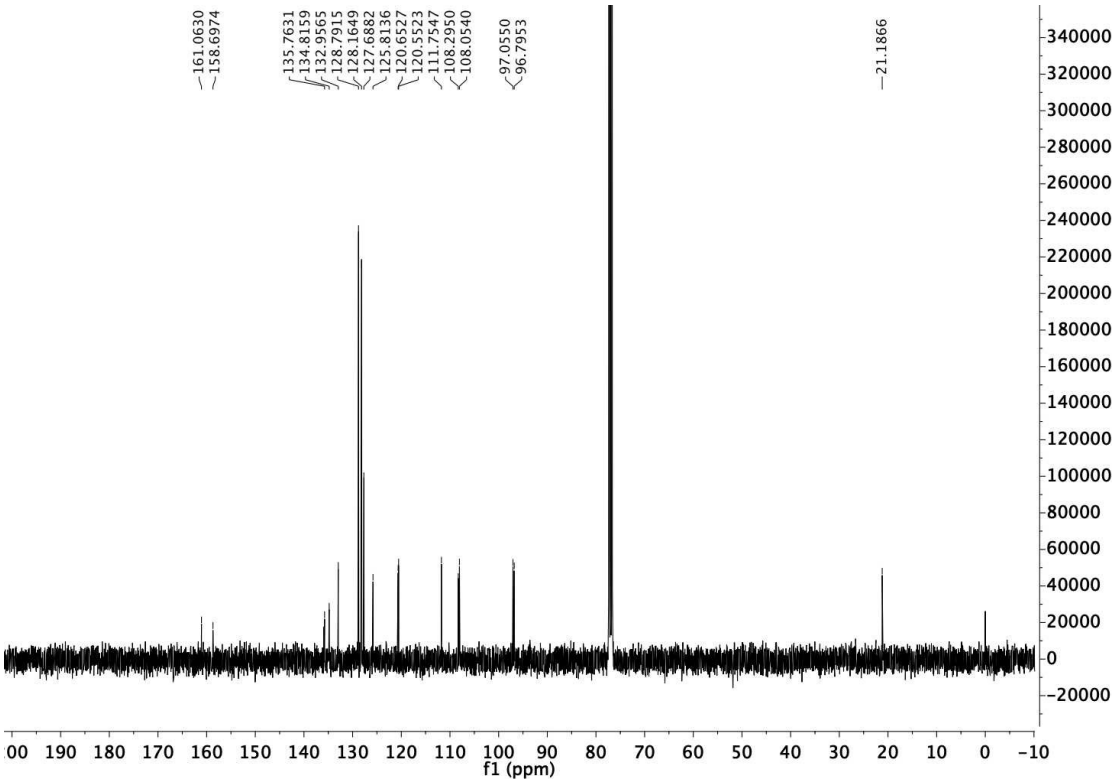


Rf = 0.25 (PE/EtOAc, 10:1). 48% yield. Pale yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (s, 2H), 7.60 - 7.48(m, 4H), 7.47 - 7.38 (m, 4H), 7.38- 7.30 (m, 2H), 7.10 - 6.90 (m, 4H), 6.70 - 6.51 (m, 2H), 4.51 (s, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.07, 158.70, 135.77, 134.82, 132.97, 128.80, 128.17, 127.70, 125.82, 120.66, 120.56, 111.76, 108.30, 108.06, 97.06, 96.80, 21.20. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -112.34. MALDI-TOF-MS: m/z: calcd for $C_{29}H_{20}F_2N_2$ (M): 434.1595; found: 434.1595.

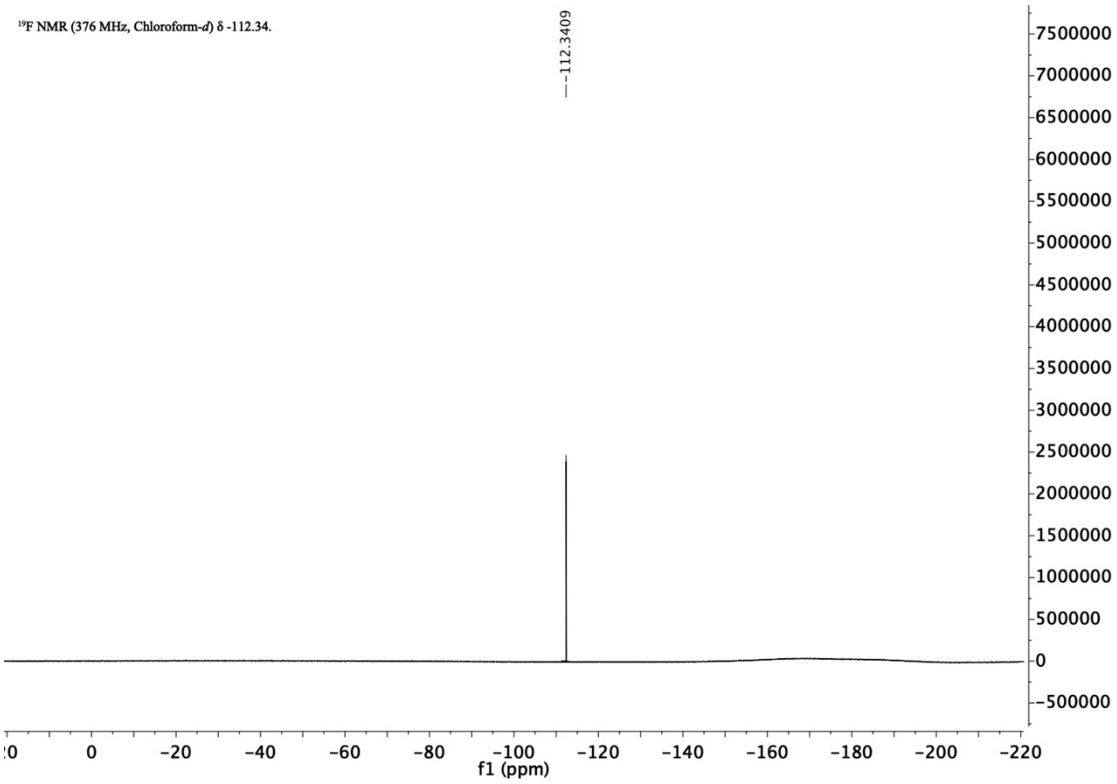
^{1}H NMR Spectrum ($CDCl_3$) of **3q**



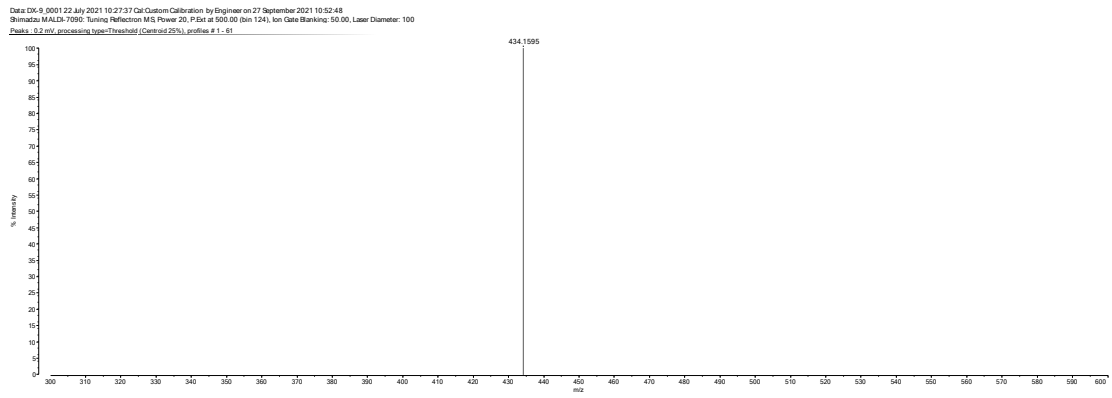
^{13}C NMR Spectrum ($CDCl_3$) of **3q**



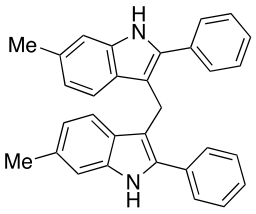
^{19}F NMR Spectrum (DMSO) of **3q**



HRMS of **3q**

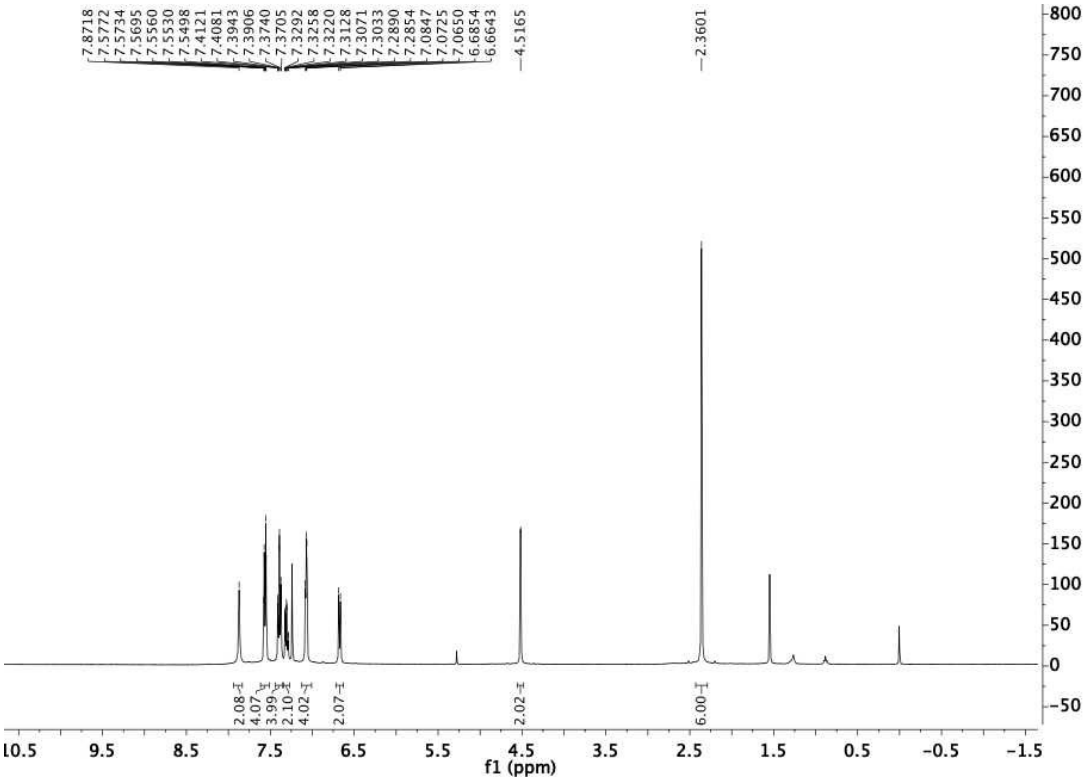


(3r) Bis(6-methyl-2-phenyl-1*H*-indol-3-yl)methane

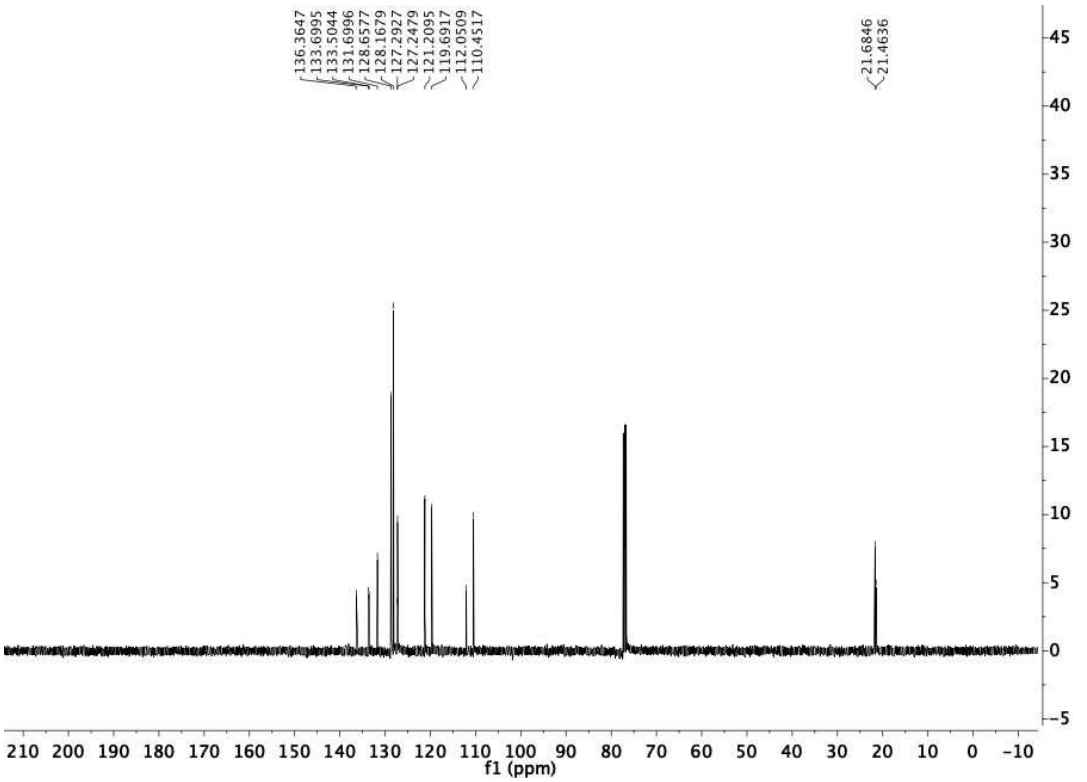


Rf = 0.25 (PE/EtOAc, 10:1). 84% yield. Pale yellow solid.^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (s, 2H), 7.62 - 7.51 (m, 4H), 7.44 - 7.36 (m, 4H), 7.34 - 7.27 (m, 2H), 7.12 - 7.01 (m, 4H), 6.72 – 6.63 (m, 2H), 4.51 (s, 2H), 2.36 (s, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 136.36, 133.70, 133.50, 131.70, 128.66, 128.17, 127.29, 127.25, 121.21, 119.69, 112.05, 110.45, 21.68, 21.46. MALDI-TOF-MS: m/z: calcd for $C_{29}H_{20}F_2N_2$ (M): 426.2096; found: 426.2099

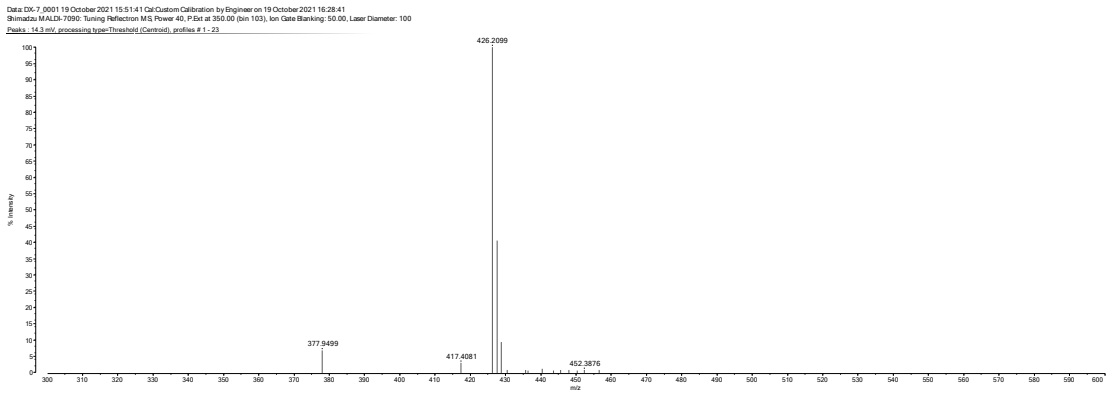
^{1}H NMR Spectrum ($CDCl_3$) of **3r**



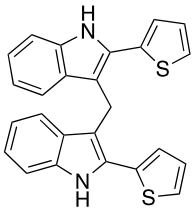
^{13}C NMR Spectrum ($CDCl_3$) of **3r**



HRMS of **3r**

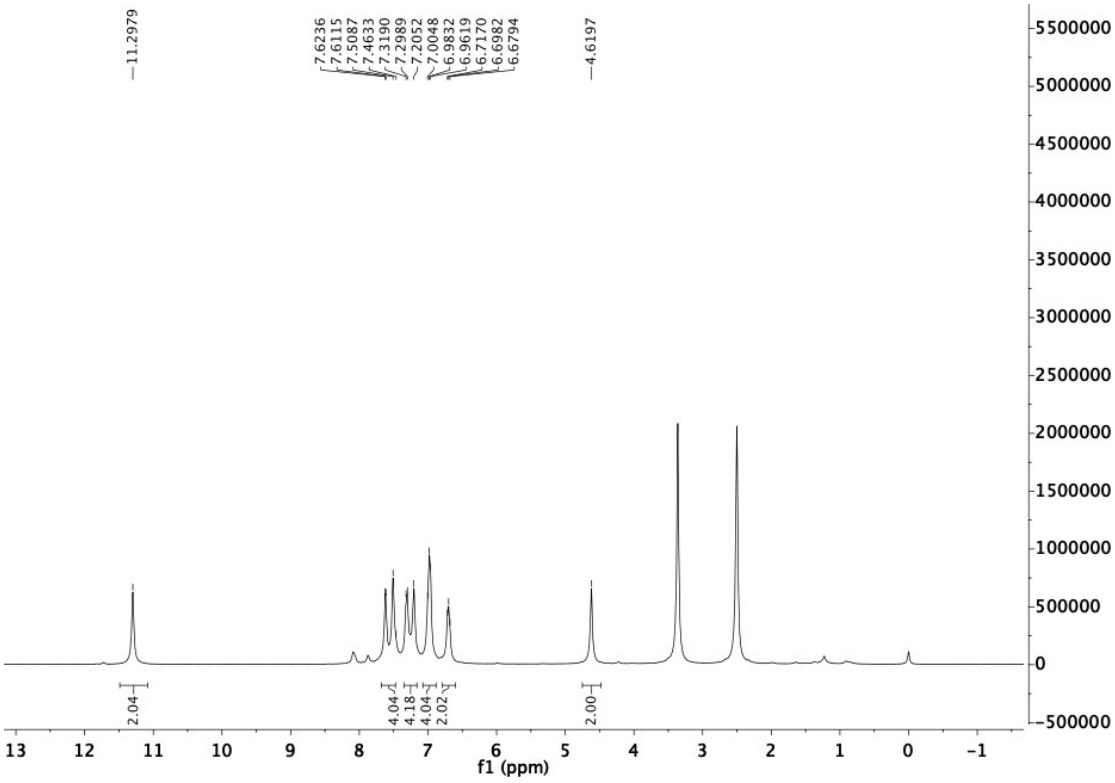


(3s) Bis(2-(thiophen-2-yl)-1*H*-indol-3-yl)methane(3s)

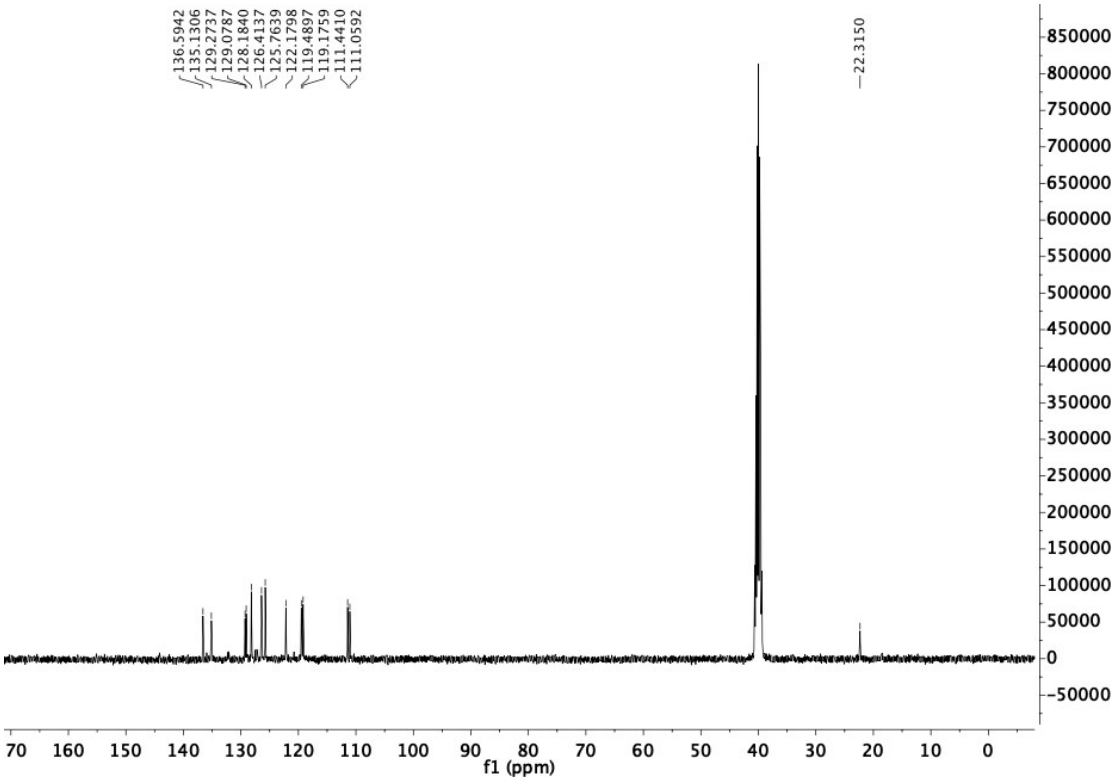


R_f = 0.25 (PE/EtOAc, 9:1). 58% yield. Orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.30 (s, 2H), 7.68 - 7.47 (m, 4H), 7.34 - 7.16 (m, 4H), 7.07 - 6.88(m, 4H), 6.79 - 6.60(m, 2H), 4.62 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 136.59, 135.13, 129.27, 129.08, 128.18, 126.41, 125.76, 122.18, 119.49, 119.18, 111.44, 111.06, 22.31. MALDI-TOF-MS: m/z: calcd for $C_{25}H_{18}N_2S_2$ M: 410.0911; found 410.0912.

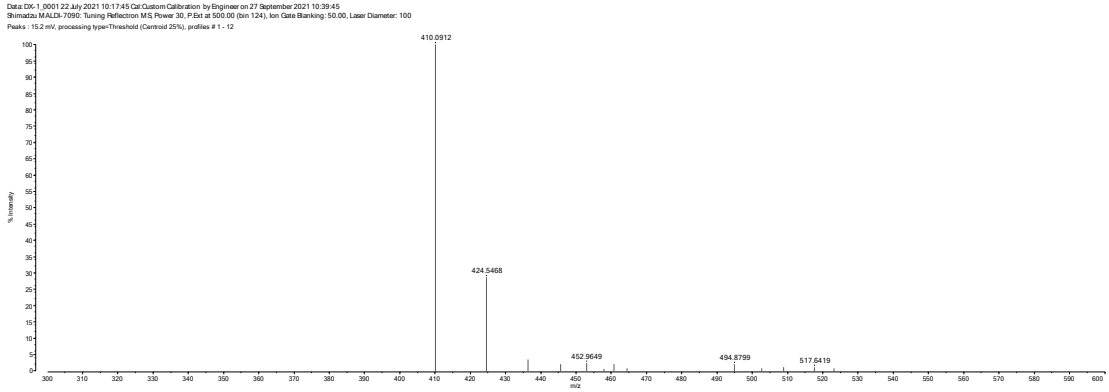
^{1}H NMR Spectrum (DMSO) of **3s**



^{13}C NMR Spectrum (DMSO) of **3s**



HRMS of **3s**



7. References

[1] Y. Gao, W. Zhu, L. Yin, B. Dong, J. Fu, Z. Ye, F. Xue, C. Jiang, Palladium-catalyzed direct C2-arylation of free (N-H) indoles via norbornene-mediated regioselective C-H activation. *Tetrahedron Lett*, 2017, **58 (23)**, 2213-2216.

[2] M. Taha, N. H. Ismail, K. Javaid, S. Imran, H. Anouar el, A. Wadood, W. Atia Tul, M. Ali, K. M. Khan, S. M. Saad, F. Rahim and M. I. Choudhary, Evaluation of 2-indolcarbohydrazones as potent α-glucosidase inhibitors, in silico studies and DFT based stereochemical predictions. *Bioorg Chem*, 2015, **63**, 24-35.

[3] P. Kaswan, N.K. Nandwana, B. DeBoef, and A. Kumar. Vanadyl acetylacetonate catalyzed methylenation of imidazo[1,2-a]pyridines by using dimethylacetamide as a methylene source: direct access to bis(imidazo[1,2-a]pyridin-3-yl)methanes. *Adv. Synth. Catal*, 2016, **358**, 2108-2115.