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Exploring a cascade Heck-Suzuki reaction based route to kinase inhibitors using Design of Experiments

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1 Experimental procedures

1.1 General procedures for organic synthesis

Reagents and solvents were bought from commercial vendors and used as received, unless otherwise stated. Dry THF and 1,4-dioxane were obtained through distillation over sodium under nitrogen gas. Dry DCM was obtained through distillation over calcium hydride under nitrogen gas. Benzyl benzoate, used as internal standard in quantitative NMR experiments, was bought from Sigma-Aldrich with a certified reference material grade. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60–F_{254}) using a mercury vapor UV-lamp to visualize the analytes. Fisher silica gel (particle size 40-63mm) was used for flash column chromatography. NMR spectra were recorded on samples dissolved in either deuterated chloroform (chloroform-d), DMSO (DMSO-d_6) or acetone (acetone-d_6) using an Agilent 400 MHz (101 MHz for 13C) spectrometer. Residual undeuterated solvent was used as internal reference: chloroform (^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.0 ppm), DMSO (^{1}H δ = 2.50 ppm, ^{13}C δ = 39.52 ppm) and acetone (^{1}H δ = 2.05 ppm, ^{13}C δ = 29.8 ppm). The following abbreviations, or a combination thereof, were used to characterize the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Melting points (mp) were recorded on a Mettler FP 90/82 melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker IFS 66v/S FT-IR spectrometer using KBr pellet sample preparation. Liquid substances were dissolved in DCM and concentrated onto KBr before pellet preparation. HRMS analyses were performed on a QSTAR XL using positive electrospray ionization and a tandem quadropole time-of-flight mass analyzer. HPLC analyses were performed on a Hewlett-Packard 1100 instrument. The system included a vacuum degasser, a binary pump, an autoinjector and a diode array detector. A Hypersil-Keystone HyPurity C18 column (150 mm × 3 mm, 3 µm particles, Thermo Scientific) was used. Mobile phase A consisted of milli-Q water and mobile phase B consisted of acetonitrile. For each sample, 5 µL aliquots were injected onto the column and eluated with a gradient flow of 0.40 mL/min. A linear gradient from 50% to 100% B in 10 min was followed by 10 min of isocratic eluation at 100% B. The column was equilibrated with 50% B for 10 min between each run. The experimental design and statistical analysis were performed with the software MODDE 10, Umetrics AB.

1.1.1 General procedure for the tandem Heck-Suzuki reaction

Indicated amount of substrate **4**, $Pd_2(dba)_3$•$CHCl_3$, P-donor ligand, boronic acid and Cs_2CO_3 were added to an oven dried reaction tube equipped with a cross shaped magnetic stir bar. The reaction vessel was sealed, fitted into a reaction carousel, evacuated of air and refilled with argon (5 cycles). Indicated amount of water (degassed with argon for 60min) was added followed by dry 1,4-dioxane (degassed with argon for 60min). The mixture was heated to 50°C and stirred at that temperature for 24h at 600rpm, then cooled to room temperature, diluted with EtOAc (5 × reaction volume) and run through a column packed with silica gel (10 × substrate mass) in EtOAc. The column was further washed with EtOAc (5 × reaction volume) and the combined filtrate was concentrated under reduced pressure. The relative stereochemistry was determined for compound **5c** by 1D-NOESY. The hydrogens of the TMS-group were saturated with a selective pulse and a NOE was observed at the methylene hydrogens of the ketal. (Fig. S1). The stereochemical assignment was applied to the other compounds in the series, all of which displayed highly conserved ^{1}H-NMR spectra.

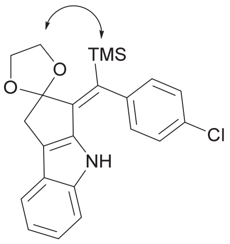


Fig. S1. NOE used to determine the stereochemical outcome of the tandem Heck-Suzuki reaction.

1.1.2 Preparation of NMR samples and evaluation of NMR spectra

The reaction crude product was dissolved in approximately 1ml $CDCl_3$ and benzyl benzoate (V_r) was added as internal standard. NMR was run with 8 transients and 10s relaxation delay. The spectrum was phase corrected, base line corrected and reference adjusted to the residual $CHCl_3$ peak. The benzyl bensoate methylene peak (δ 5.36ppm), the starting material methylene peak (δ 3.34ppm) and the product methylene peak (δ 3.11ppm) were integrated and the amount of starting material and product were calculated according to:

$$n_{s,p} = \frac{I_{s,p}}{I_r} * \frac{V_r * \rho_r}{M_{w,r}}$$

n_s = amount of starting material; n_p = amount of product; I_s = integrated peak area of starting material; I_p = integrated peak area of product; V_r = added volume of benzyl benzoate; ρ_r = density of benzyl benzoate; $M_{w,r}$ = molecular weight of benzyl bensoate.

1.1.3 Preparation of HPLC samples and evaluation of chromatograms

The crude product was dissolved in MeCN (V_1) giving an approximate concentration of 10mM. 150µl (V_2) of this stock solution was diluted to 1ml (V_3) in MeCN and analyzed by HPLC-UV. The peaks corresponding to starting material ($t_R \approx$ 13min) and product ($t_R \approx$ 14min) were integrated and the amount of respective compound was calculated according to:

$$n_{s,p} = \left(\frac{Area - k}{m} * \frac{V_3}{V_2}\right) * V_1$$

n_s = amount of starting material; n_p = amount of product; Area = integrated peak area; m = slope of calibration curve (Fig S7 − S10); k = intercept of calibration curve; V_1, V_2 and V_3 according to above.

1.1.4 Design of experiments

Six factors were investigated at two levels (Table S1). A fractional factorial design of resolution V was used, resulting in totally 41 experiments (Table S1, **No** 1–41). 32 were used for factor variations and 3 for the center point (triplicate). The remaining 6 were triplicate runs for the two axial points of the factor *Ham*, which are *Ham* = -0.27 (i.e. 4-methoxyphenylboronic acid) and *Ham* = 0.54 (i.e. 4-trifluoromethylphenylboronic acid) run in triplicate with intermediate values on all other parameters. We have previously observed problems with certain boronic acid species and the extended procedure of running each in triplicate was used to validate the reproducibility for all three boronic acids. The experiments were run in two blocks, one for *Ham* = -0.27 (i.e. 4-methoxyphenylboronic acid, **No** 1–19) and one for *Ham* = 0.54 (i.e. 4-trifluoromethylphenylboronic acid, **No** 20 – 38) with randomized order within each block. After the initial 41 experiments, 17 additional experiments were included to evolve the initial resolution V fractional factorial design into a central composite face design. Axial runs for *Bor*, *C* and H_2O were introduced in an ordinary manner (**No** 42 – 48). Introduction of axial points for the ligand parameters *t1* and *t2* required four additional ligands. These were run with each of the investigated boronic acids separately (**No** 49 – 52 for *Ham* = -0.27, i.e.4-methoxyphenylboronic acid, and **No** 54 – 57 for *Ham* = 0.54, i.e. 4-trifluoromethylphenylboronic acid). A center point (**No** 48) and axial runs for *Ham* (**No** 53 for *Ham* = -0.27 and **No** 58 for *Ham* = 0.54) were also included to verify that this new set of experiments were comparable with the original experiments.

The reactions were performed according to **1.1.1 General procedure for the tandem Heck-Suzuki reaction** described above using substrate **4** (0.118 mmol), $Pd_2(dba)_3{\bullet}CHCl_3$ (5.9 μmol), P-donor ligand (23.5 μmol). The crude products were analyzed according to **1.1.2 Preparation of NMR samples and evaluation of NMR spectra** and **1.1.3 Preparation of HPLC samples and evaluation of chromatograms** as described above. A representative chromatogram (Fig S2) and NMR-spectrum (Fig S3) are reported for **No** 21, showing both starting material and product. Five of the experiments (**No** 44 – 48) could not be analyzed with HPLC due to apparatus technical problems. Considering the good agreement between NMR- and HPLC-analyses for all other experiments, it was considered reliable to use the NMR-data for the regression analysis.

TABLE S1. Design of Experiments study using a fractional factorial design of resolution V.[a]

No	t1	t2	Bor (equiv.)	C (M)	H_2O (equiv.)	Ham	y/c (NMR)	y/c (HPLC)
1 (11)	-4.215	-5.58	1	0.04	3	-0.27	0.81	0.8
2 (12)	4.744	-6.001	1	0.04	1	-0.27	0.66	0.66
3 (14)	-5.075	2.227	1	0.04	1	-0.27	0.49	0.58
4 (13)	2.431	3.277	1	0.04	3	-0.27	0.74	0.74
5 (11)	-4.215	-5.58	3	0.04	1	-0.27	0.95	0.91
6 (12)	4.744	-6.001	3	0.04	3	-0.27	0.6	0.57
7 (14)	-5.075	2.227	3	0.04	3	-0.27	0.66	0.64
8 (13)	2.431	3.277	3	0.04	1	-0.27	0.74	0.75
9 (11)	-4.215	-5.58	1	0.08	1	-0.27	0.76	0.75
10 (12)	4.744	-6.001	1	0.08	3	-0.27	0.64	0.58
11 (14)	-5.075	2.227	1	0.08	3	-0.27	0.46	0.44
12 (13)	2.431	3.277	1	0.08	1	-0.27	0.74	0.71
13 (11)	-4.215	-5.58	3	0.08	3	-0.27	0.91	0.84
14 (12)	4.744	-6.001	3	0.08	1	-0.27	0.59	0.53
15 (14)	-5.075	2.227	3	0.08	1	-0.27	0.74	0.78

16 (13)	2.431	3.277	3	0.08	3	-0.27	0.63	0.52
17 (15)	0.549	-0.56	2	0.06	2	-0.27	0.95	0.94
18 (15)	0.549	-0.56	2	0.06	2	-0.27	0.91	0.86
19 (15)	0.549	-0.56	2	0.06	2	-0.27	0.92	0.88
20 (11)	-4.215	-5.58	1	0.04	3	0.54	0.83	0.8
21 (12)	4.744	-6.001	1	0.04	1	0.54	0.49	0.41
22 (14)	-5.075	2.227	1	0.04	1	0.54	0.69	0.62
23 (13)	2.431	3.277	1	0.04	3	0.54	0.68	0.63
24 (11)	-4.215	-5.58	3	0.04	1	0.54	0.95	0.85
25 (12)	4.744	-6.001	3	0.04	3	0.54	0.7	0.64
26 (14)	-5.075	2.227	3	0.04	3	0.54	0.87	0.76
27 (13)	2.431	3.277	3	0.04	1	0.54	0.7	0.71
28 (11)	-4.215	-5.58	1	0.08	1	0.54	0.88	0.79
29 (12)	4.744	-6.001	1	0.08	3	0.54	0.43	0.36
30 (14)	-5.075	2.227	1	0.08	3	0.54	0.69	0.62
31 (13)	2.431	3.277	1	0.08	1	0.54	0.36	0.33[b]
32 (11)	-4.215	-5.58	3	0.08	3	0.54	0.89	0.84
33 (12)	4.744	-6.001	3	0.08	1	0.54	0.53	0.47
34 (14)	-5.075	2.227	3	0.08	1	0.54	0.81	0.7
35 (13)	2.431	3.277	3	0.08	3	0.54	0.67	0.63
36 (15)	0.549	-0.56	2	0.06	2	0.54	0.84	0.81
37 (15)	0.549	-0.56	2	0.06	2	0.54	0.88	0.81
38 (15)	0.549	-0.56	2	0.06	2	0.54	0.85	0.8
39 (15)	0.549	-0.56	2	0.06	2	0.23	0.88	0.89
40 (15)	0.549	-0.56	2	0.06	2	0.23	0.92	0.92
41 (15)	0.549	-0.56	2	0.06	2	0.23	0.93	0.93
42 (15)	0.549	-0.56	1	0.06	2	0.23	0.84	0.84
43 (15)	0.549	-0.56	3	0.06	2	0.23	0.87	0.88
44 (15)	0.549	-0.56	2	0.04	2	0.23	0.93	-[c]
45 (15)	0.549	-0.56	2	0.08	2	0.23	0.96	-[c]
46 (15)	0.549	-0.56	2	0.06	1	0.23	0.93	-[c]

47 (15)	0.549	-0.56	2	0.06	3	0.23	0.94	-[c]
48 (15)	0.549	-0.56	2	0.06	2	0.23	0.9	-[c]
49 (16)	2.516	-4.169	2	0.06	2	-0.27	0.85	0.92
50 (17)	3.256	-0.642	2	0.06	2	-0.27	0.83	0.85
51 (18)	-0.587	3.813	2	0.06	2	-0.27	0.82	0.79
52 (19)	-3.256	-0.254	2	0.06	2	-0.27	0.84	0.86
53 (15)	0.549	-0.56	2	0.06	2	-0.27	0.89	0.86
54 (16)	2.516	-4.169	2	0.06	2	0.54	0.84	0.8
55 (17)	3.256	-0.642	2	0.06	2	0.54	0.63	0.6
56 (18)	-0.587	3.813	2	0.06	2	0.54	0.8	0.72
57 (19)	-3.256	-0.254	2	0.06	2	0.54	0.94	0.83
58 (15)	0.549	-0.56	2	0.06	2	0.54	0.92	0.88

[a] **No** is the experiment number with ligand number in bracket. **t1** and **t2** are two first latent variables for the P-donor ligand dataset according to Jover et al.[1] **Bor** is the amount of boronic acid. **C** is the reaction concentration. **H_2O** is the amount of water. **Ham** is the Hammet constant, -0.27 correspond to 4-methoxyphenylboronic acid, 0.23 correspond to 4-chlorophenylboronic acid and 0.54 correspond to 4-trifluoromethylphenylboronic acid.[2] **y/c (NMR)** is the ratio between yield and conversion measured by ^{1}H-NMR and **y/c (HPLC)** is the ratio between yield and conversion measured by HPLC. [b] Outlier which was excluded from the model. [c] These experiments could not be analyzed with HPLC due to technical problems with the apparatus.

TABLE S2. Numerical data for model coefficients at 95% confidence.

Yield/Conversion NMR	Coeff. SC	Std. Err.	P	Conf. int(±)
Constant	6.2829	0.101923	0	0.20482
t1	-1.02525	0.099307	6.91E-14	0.199562
t2	-0.854111	0.105793	1.48E-10	0.212596
Bor	0.309149	0.083436	0.00053703	0.16767
Ham	0.020782	0.069272	0.765438	0.139206
t1*t1	-2.87727	0.176685	2.08E-21	0.355058
t1*Bor	-0.348991	0.0989	0.00091863	0.198745
t1*Ham	-0.424018	0.093572	3.78E-05	0.188038

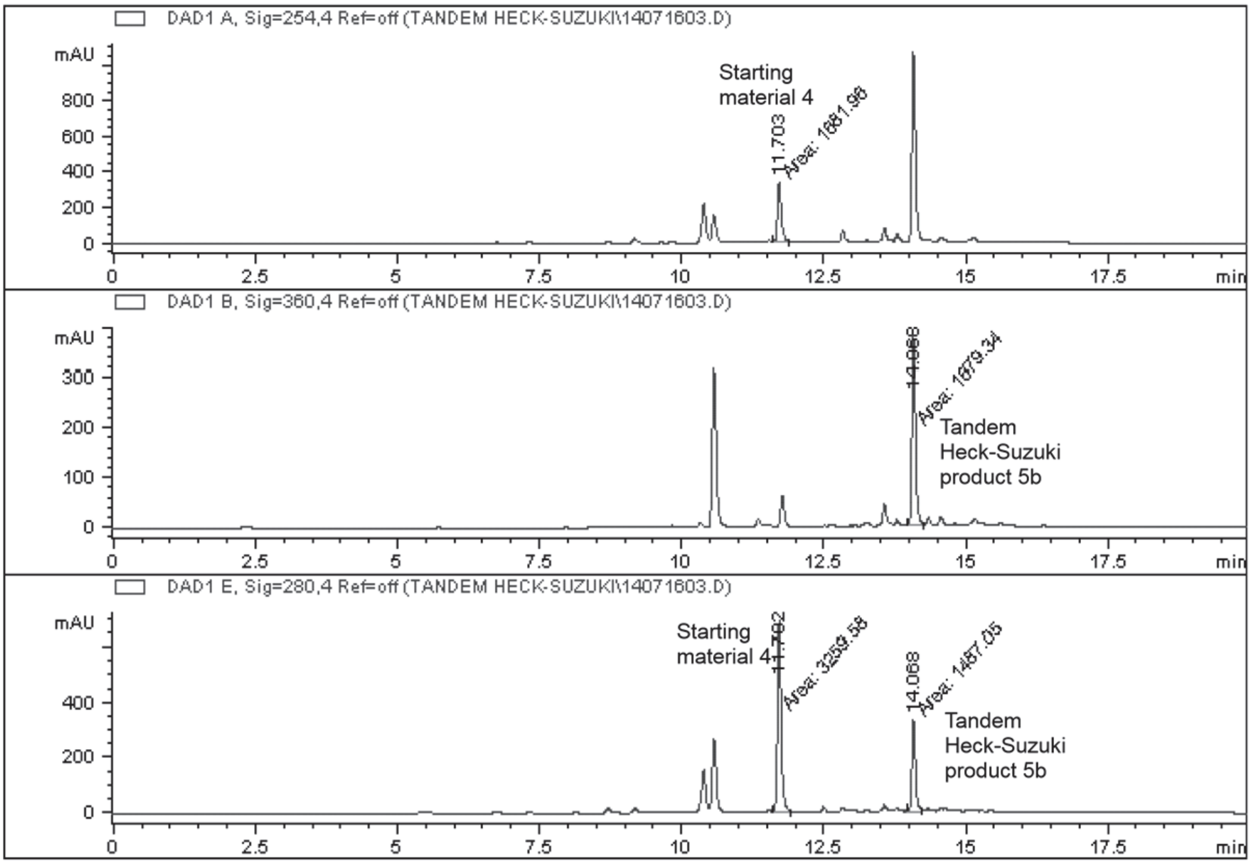


Fig. S2. HPLC chromatogram for the analysis of experiment **No** 21 in the DoE study. Trace analyzed at 254 nm (top), 360 nm (middle) and 280 nm (bottom).

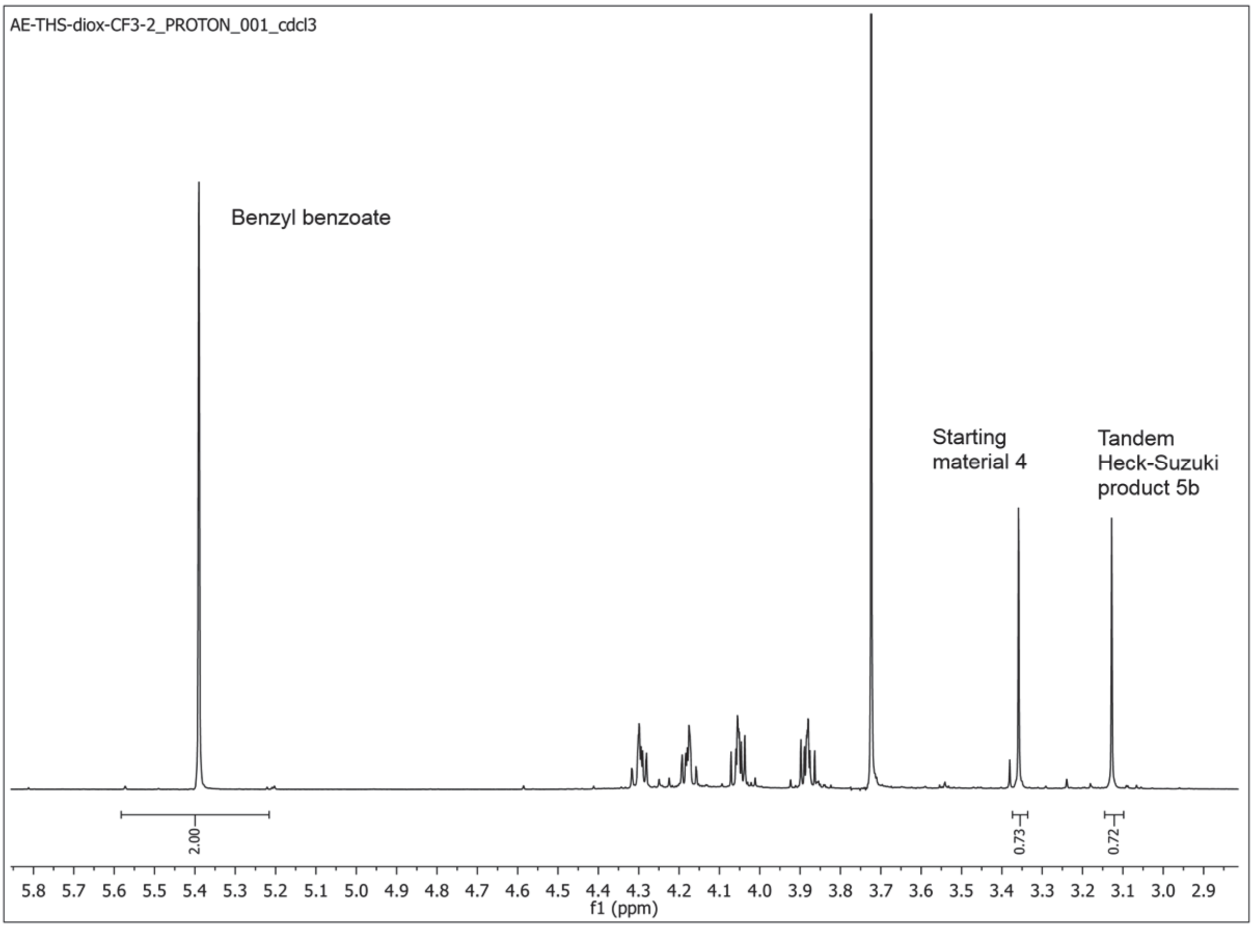
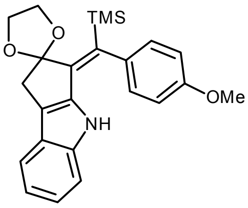


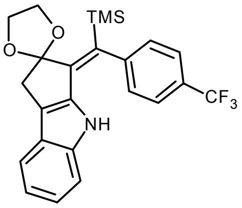
Fig. S3. ^{1}H-NMR spectrum for the analysis of experiment 21 in the DoE study.

1.1.6 Preparation of compounds 5a-t

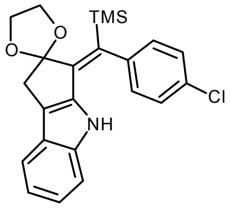
The compounds were prepared according to **1.1.1 General procedure for the tandem Heck-Suzuki reaction** described above. When the reactions have been investigated with two different catalytic loadings, the experiment with the highest loading is reported here. Reaction yields were analyzed by NMR according to **1.1.2 Preparation of NMR samples and evaluation of NMR spectra**. An isolated yield is also given for the majority of compounds.



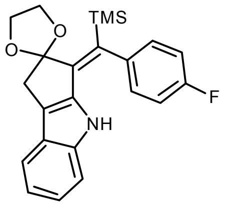
Tandem Heck-Suzuki product 5a. Indole-alkynyl **4** (50 mg, 0.12 mmol), $Pd_2(dba)_3$•$CHCl_3$ (5.9 mg, 5.7 μmol), tris(4-trifluoromethylphenyl)phosphine (11 mg, 24 μmol), Cs_2CO_3 (98 mg, 0.30 mmol), 4-methoxyphenylboronic acid (27 mg, 0.17 mmol), 1,4-dioxane (2.0 ml, 0.06 M), water (4.2 μl, 0.23 mmol). The yield was calculated directly by ^{1}H-NMR analysis of the crude product using benzyl benzoate (20 μl) as internal standard (89%). The compound was not isolated as the analysis agreed with previously reported data.[3]



Tandem Heck-Suzuki product 5b. Indole-alkynyl **4** (51 mg, 0.12 mmol), $Pd_2(dba)_3$•$CHCl_3$ (6.1 mg, 5.9 μmol), tris(4-trifluoromethylphenyl)phosphine (11 mg, 24 μmol), Cs_2CO_3 (94 mg, 0.29 mmol), 4-(trifluoromethyl)phenylboronic acid (34 mg, 0.18 mmol), 1,4-dioxane (2.0 ml, 0.06 M), water (4.2 μl, 0.23 mmol). The yield was calculated directly by ^{1}H-NMR analysis of the crude product using benzyl benzoate (20 μl) as internal standard (89%). It was then combined with the crude products from the Design of Experiments study. The material was purified by column chromatography (ø = 4 cm, 50 g SiO_2, hexane/DCM 1:1) and the obtained solid was recrystallized from boiling EtOH to yield **5b** as white crystals (659 mg); R_f = 0.30 (hexane/DCM 1:1); mp 185°C (EtOH); ν_{max}/cm^{-1} 3458 (NH), 2991, 2976, 2956, 2900, 2887, 2843 (CH); δ_H(400 MHz, Chloroform-d) 7.72 (AA' part of AA'XX' system, 2H), 7.40 (dq, *J* = 7.8, 0.9 Hz, 1H), 7.30 (XX' part of AA'XX' system, 2H), 7.08 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 7.02 (ddd, *J* = 8.0, 7.1, 1.2 Hz, 1H), 6.97 (dt, *J* = 8.1, 1.0 Hz, 1H), 6.14 (s, 1H), 4.34 – 4.23 (m, 2H), 4.22 – 4.12 (m, 2H), 3.11 (s, 2H), 0.09 (s, 9H); δ_C(101 MHz, Chloroform-d) 149.43 (q, *J(F-C)* = 1.2 Hz), 141.28 (q, *J(F-C)* = 0.8 Hz), 140.48, 139.76, 135.93, 128.53 (q, *J(F-C)* = 32,7 Hz), 128.37, 125.73 (q, *J(F-C)* = 3.7 Hz), 124.25 (q, *J(F-C)* = 271.8 Hz), 123.68, 123.45, 121.80, 120.11, 119.58, 117.67, 111.62, 63.06, 36.25, 0.90; HRMS (ESI+ qTOF) calcd for $C_{24}H_{25}F_3NO_2Si$ [M + H] 444.1607, found 444.1605.

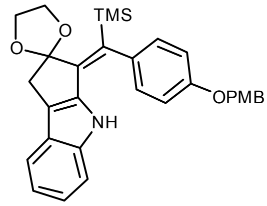


Tandem Heck-Suzuki product 5c. Indole-alkynyl **4** (51 mg, 0.12 mmol), $Pd_2(dba)_3$•$CHCl_3$ (6.1 mg, 5.9 μmol), tris(4-trifluoromethylphenyl)phosphine (11 mg, 24 μmol), Cs_2CO_3 (95 mg, 0.29 mmol), 4-chlorophenylboronic acid (28 mg, 0.18 mmol), 1,4-dioxane (2.0 ml, 0.06 M), water (4.2 μl, 0.23 mmol). The yield was calculated directly by ^{1}H-NMR analysis of the crude product using benzyl benzoate (20 μl) as internal standard (92%). Pure compound was obtained from crude material (150 mg) from the Design of Experiments study. The crude material was dissolved in DCM, concentrated onto SiO_2 (0.5 g) and purified by column chromatography (ø = 2 cm, 20 g SiO_2, hexane/EtOAc 95:5) to yield **5c** as a white crystalline solid (131 mg); R_f = 0.25 (hexanes/EtOAc 95:5); mp 188-190°C (EtOH); ν_{max}/cm^{-1} 3460 (NH), 2958, 2897, 2889 (CH); δ_H(400 MHz, Chloroform-d) 7.44 (AA' part of AA'XX' system, 2H), 7.43 – 7.40 (m, 1H), 7.12 (XX' part of AA'XX' system, 2H), 7.11 – 7.08 (m, 1H), 7.07 – 7.00 (m, 2H), 6.34 (br s, 1H), 4.33 – 4.22 (m, 2H), 4.22 – 4.11 (m, 2H), 3.11 (s, 2H), 0.10 (s, 9H); δ_C(101 MHz, Chloroform-d) 143.6, 141.3, 140.4, 140.0, 136.1, 132.0, 129.3, 129.0, 123.7, 123.3, 121.4, 120.0, 119.5, 117.6, 111.7, 63.0, 36.3, 0.9; HRMS (ESI+ qTOF) calcd for $C_{23}H_{25}ClNO_2Si$ [M + 1] 410.1343, found 410.1372.

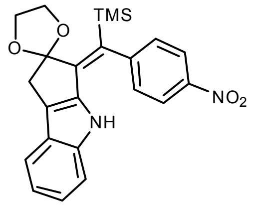


Tandem Heck-Suzuki product 5d. Two batches were made: **1)** Indole-alkynyl **4** (51 mg, 0.12 mmol), $Pd_2(dba)_3$•$CHCl_3$ (6.4 mg, 6.2 μmol), tris(4-trifluoromethylphenyl)phosphine (11 mg, 24 μmol), Cs_2CO_3 (99 mg, 0.30 mmol), 4-fluorophenylboronic acid (25 mg, 0.18 mmol), 1,4-dioxane (2.0 ml, 0.06 M), water (4.3 μl, 0.24 mmol). The yield was calculated by ^{1}H-NMR analysis of the crude product using benzyl benzoate (20 μl) as internal standard (86%). **2)** Indole-alkynyl **4** (130 mg, 0.31 mmol), $Pd_2(dba)_3$•$CHCl_3$ (16 mg, 15 μmol), triphenylphosphine (18 mg, 68 μmol), Cs_2CO_3 (250 mg, 0.77 mmol), 4-fluorophenylboronic acid (86 mg, 0.62 mmol), 1,4-dioxane (5.0 ml, 0.06 M), water (11 μl, 0.61 mmol). The crude product from batch 2 was purified by column chromatography (ø = 2 cm, 22 g SiO_2, hexane/EtOAc 95:5) to yield **5d** as a white crystalline solid (103 mg, 85%); R_f = 0.15 (hexanes/EtOAc 95:5); mp 151-152°C (hexane/EtOAc 95:5); ν_{max}/cm^{-1} 3464 (NH), 2974, 2956, 2922, 2898 (CH); δ_H(400 MHz, Acetone-d6) 7.40 (ddt, *J* = 7.7, 1.5, 0.8 Hz, 1H), 7.39(br s, 1H), 7.21 (AA' part of a AA'BB' system, *J(F-H)* = 8.9 Hz, 2H), 7.16 – 7.09 (m, 3H), 7.02 (ddd, *J* = 8.2, 7.0, 1.4 Hz, 1H), 6.97 (ddd, *J* = 7.7, 7.0, 1.3 Hz, 1H), 4.31 – 4.23 (m, 2H), 4.23 – 4.15 (m, 2H), 3.08 (s, 2H), 0.06 (s, 9H); δ_C(101 MHz, Acetone-d6) 162.3 (d, *J(F-C)* = 242.7 Hz), 142.8, 141.9, 141.8 (d, *J(F-C)* = 3.7 Hz), 140.9, 136.5, 130.1

(d, *J(F-C)* = 7.6 Hz), 124.6, 123.8, 122.1, 120.6, 120.0, 118.4, 116.5 (d, *J(F-C)* = 21.3 Hz), 113.0, 63.6, 36.6, 1.3; HRMS (ESI+ qTOF) calcd for $C_{23}H_{25}FNO_2Si$ [M + 1] 394.1639, found 394.1640.

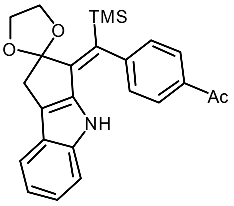


Tandem Heck-Suzuki product 5e. Two batches were made: **1)** Indole-alkynyl **4** (50 mg, 0.12 mmol), $Pd_2(dba)_3$•$CHCl_3$ (5.9 mg, 5.7 µmol), tris(4-trifluoromethylphenyl)phosphine (11 mg, 24 µmol), Cs_2CO_3 (96 mg, 0.29 mmol), (4-(OPMB)phenyl)boronic acid (46 mg, 0.18 mmol), 1,4-dioxane (2.0 ml, 0.06 M), water (4.2 µl, 0.23 mmol). The yield was calculated by ^{1}H-NMR analysis of the crude product using benzyl benzoate (20 µl) as internal standard (93%). **2)** Indole-alkynyl **4** (150 mg, 0.35 mmol), $Pd_2(dba)_3$•$CHCl_3$ (18 mg, 17 µmol), tris(4-trifluoromethylphenyl)phosphine (34 mg, 72 µmol), Cs_2CO_3 (284 mg, 0.87 mmol), (4-(OPMB)phenyl)boronic acid (136 mg, 0.53 mmol), 1,4-dioxane (5.9 ml, 0.06 M), water (13 µl, 0.72 mmol). The crude products from the two batches were combined, purified by column chromatography (ø = 4 cm, 25 g SiO_2, hexane/DCM 3:1 → 0:1) and recrystallized from boiling EtOH to yield **5e** as a light yellow crystalline solid (217 mg, 90%); R_f = 0.15 (hexane/DCM 1:1); mp 135-136°C (EtOH); ν_{max}/cm^{-1} 3431 (NH), 2947, 2893 (CH); δ_H(400 MHz, Chloroform-d) 7.46 – 7.41 (AA' part of AA'XX' system, 2H), 7.39 (dq, *J* = 7.8, 1.0 Hz, 1H), 7.07 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 7.05 (s, 4H), 7.02 – 6.94 (m, 4H), 6.35 (br s, 1H), 5.08 (s, 2H), 4.32 – 4.21 (m, 2H), 4.21 – 4.10 (m, 2H), 3.84 (s, 3H), 3.09 (s, 2H), 0.09 (s, 9H); δ_C(101 MHz, Chloroform-d) 159.5, 157.1, 141.3, 140.6, 140.2, 137.5, 137.3, 129.3, 128.9, 128.8, 123.8, 122.9, 120.5, 119.8, 119.4, 117.6, 115.3, 114.0, 111.6, 69.9, 63.0, 55.3, 36.4, 0.9; HRMS (ESI+ qTOF) calcd for $C_{31}H_{34}NO_4Si$ [M + 1] 512.2257, found 512.2240.

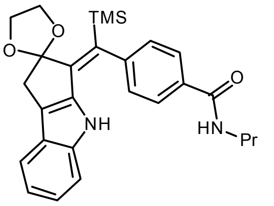


Tandem Heck-Suzuki product 5f. Indole-alkynyl **4** (51 mg, 0.12 mmol), $Pd_2(dba)_3$•$CHCl_3$ (25 mg, 24 µmol), tris(4-trifluoromethylphenyl)phosphine (43 mg, 93 µmol), Cs_2CO_3 (101 mg, 0.31 mmol), 4-nitrophenylboronic acid (30 mg, 0.18 mmol), 1,4-dioxane (2.0 ml, 0.06 M), water (4.2 µl, 0.23 mmol). The yield was calculated by ^{1}H-NMR analysis of the crude product using benzyl benzoate (20 µl) as internal standard (64%). The crude product was purified by column chromatography (ø = 2 cm, 10 g SiO_2, hexane/DCM 1:3) to yield **5f** as an orange crystalline solid (30 mg, 60%); R_f = 0.2 (hexanes/EtOAc 9:1); mp decompose ~260°C (concentrated from hexanes/EtOAc 9:1); ν_{max}/cm^{-1} 3464 (NH), 2954, 2904, 2889 (CH), 1508 (NO_2); δ_H(400 MHz, Chloroform-d) 8.34 (AA' part of AA'XX' system, 2H), 7.41 (ddt, *J* = 7.8, 1.4, 0.8 Hz, 1H), 7.35, (XX' part of AA'XX' system, 2H), 7.10 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 7.03

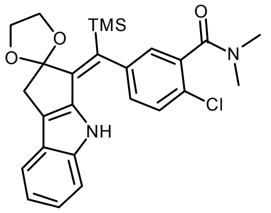
(ddd, *J* = 7.9, 7.1, 1.2 Hz, 1H), 7.01 (dt, *J* = 8.1, 0.9 Hz, 1H), 6.23 (br s, 1H), 4.34 – 4.23 (m, 2H), 4.23 – 4.12 (m, 2H), 3.11 (s, 2H), 0.09 (s, 9H); δ_C(101 MHz, Chloroform-d) 153.2, 146.3, 141.2, 140.7, 139.3, 135.1, 128.9, 124.2, 123.8, 123.7, 122.6, 120.3, 119.7, 117.7, 111.8, 63.1, 36.1, 1.0; HRMS (ESI+ qTOF) calcd for $C_{23}H_{25}N_2O_4Si$ [M + 1] 421.1584, found 421.1525.



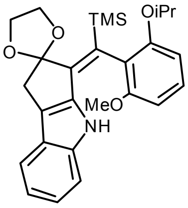
Tandem Heck-Suzuki product 5g. Indole-alkynyl **4** (51 mg, 0.12 mmol), $Pd_2(dba)_3{\bullet}CHCl_3$ (24 mg, 23 μmol), tris(4-trifluoromethylphenyl)phosphine (45 mg, 96 μmol), Cs_2CO_3 (95 mg, 0.29 mmol), 4-acetylphenylboronic acid (29 mg, 0.18 mmol), 1,4-dioxane (2.0 ml, 0.06 M), water (4.2 μl, 0.23 mmol). The yield was calculated by ^{1}H-NMR analysis of the crude product using benzyl benzoate (20 μl) as internal standard (24%). Purification of the crude product was not pursued due to the limited amount of product.



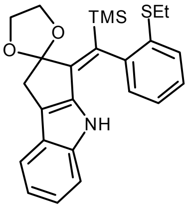
Tandem Heck-Suzuki product 5h. Indole-alkynyl **4** (51 mg, 0.12 mmol), $Pd_2(dba)_3{\bullet}CHCl_3$ (24 mg, 23 μmol), tris(4-trifluoromethylphenyl)phosphine (43 mg, 93 μmol), Cs_2CO_3 (100 mg, 0.31 mmol), 4-(propylcarbamoyl)phenylboronic acid (37 mg, 0.18 mmol), 1,4-dioxane (2.0 ml, 0.06 M), water (4.3 μl, 0.24 mmol). The yield was calculated by ^{1}H-NMR analysis of the crude product using benzyl benzoate (20 μl) as internal standard (7%). Purification of the crude product was not pursued due to the limited amount of product.



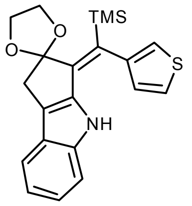
Tandem Heck-Suzuki product 5i. Two batches were made: **1)** Indole-alkynyl **4** (50 mg, 0.12 mmol), $Pd_2(dba)_3{\bullet}CHCl_3$ (5.9 mg, 5.7 μmol), tris(4-trifluoromethylphenyl)phosphine (11 mg, 24 μmol), Cs_2CO_3 (100 mg, 0.31 mmol), 4-chloro-3-(dimethylcarbamoyl)phenylboronic acid (40 mg, 0.18 mmol), 1,4-dioxane (2.0 ml, 0.06 M), water (4.2 μl, 0.23 mmol). The yield was calculated by ^{1}H-NMR analysis of the crude product using benzyl benzoate (20 μl) as internal standard (84%). **2)** Indole-alkynyl **4** (150 mg, 0.35 mmol), $Pd_2(dba)_3{\bullet}CHCl_3$ (18 mg, 18 μmol), tris(4-trifluoromethylphenyl)phosphine (33 mg, 71 μmol), Cs_2CO_3 (290 mg, 0.89 mmol), 4-chloro-3-(dimethylcarbamoyl)phenylboronic acid (120 mg, 0.53 mmol), 1,4-dioxane (5.9 ml, 0.06 M), water (13 μl, 0.72 mmol). The crude product from batch 2 was purified by column chromatography (ø = 4 cm, 32 g SiO_2, DCM/MeOH 1:0 → 99:1) to yield a mixture of **5i** and a major contaminant. An analytical sample was prepared by the following recrystallization procedure: an oil was formed in minimal amount of EtOAc and a layer of hexane was added on top, the biphasic system was left at -20°C for 48h to yield crystals. The motherliquid was removed with a pipette. The recrystallization procedure was repeated twice to give pure **5i** as a tan crystalline solid (60 mg, 36%); The compound exist as a complex mixture of rotamers, complicating NMR analysis; $R_f = 0.2$ (DCM/MeOH 99:1); mp 89-99°C (EtOAc); ν_{max}/cm^{-1} 3464 (NH), 2958, 2943, 2927, 2893 (CH), 1624 (CO); δ_H(400 MHz, Chloroform-d) 7.55 – 7.43 (m, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.24 – 6.97 (m, 4H), 7.02 (t, *J* = 7.7 Hz, 1H), 6.96 – 6.67 (m, 0.9H), 6.18 (br s, 0.3H), 4.32 – 4.20 (m, 2H), 4.20 – 4.09 (m, 2H), 3.20 – 3.01 (m, 5H), 2.90 (br s, 3H), 0.09 (s, 9H); δ_C (101 MHz, Chloroform-d) 167.9, 144.4, 141.8, 140.8, 137.0, 130.01, 129.95, 129.7, 129.5, 128.1, 127.7, 127.1, 127.1, 123.5, 122.0, 120.1, 119.3, 117.7, 112.4, 63.0, 38.0, 36.1, 34.7, 1.1; HRMS (ESI+ qTOF) calcd for $C_{26}H_{30}ClN_2O_3Si$ [M + 1] 481.1714, found 481.1719.



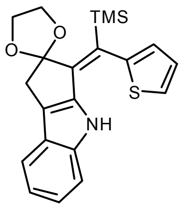
Tandem Heck-Suzuki product 5j. Indole-alkynyl **4** (50 mg, 0.12 mmol), $Pd_2(dba)_3$•$CHCl_3$ (24 mg, 23 μmol), tris(4-trifluoromethylphenyl)phosphine (44 mg, 94 μmol), Cs_2CO_3 (95 mg, 0.29 mmol), 4-methoxy-6-isopropoxy-phenylboronic acid (38 mg, 0.18 mmol), 1,4-dioxane (2.0 ml, 0.06 M), water (4.2 μl, 0.23 mmol). The yield was calculated by ^{1}H-NMR analysis of the crude product using benzyl benzoate (20 μl) as internal standard (20%). Purification of the crude product was not pursued due to the limited amount of product.



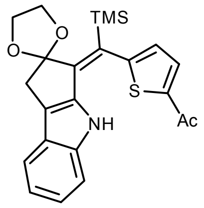
Tandem Heck-Suzuki product 5k. Indole-alkynyl **4** (49 mg, 0.12 mmol), $Pd_2(dba)_3$•$CHCl_3$ (6.0 mg, 5.8 μmol), tris(4-trifluoromethylphenyl)phosphine (11 mg, 24 μmol), Cs_2CO_3 (96 mg, 0.29 mmol), 2-ethynylthiophenylboronic acid (27 mg, 0.15 mmol), 1,4-dioxane (2.0 ml, 0.06 M), water (4.2 μl, 0.23 mmol). The yield was calculated by ^{1}H-NMR analysis of the crude product using benzyl benzoate (20 μl) as internal standard (1%). Purification of the crude product was not pursued due to the limited amount of product.



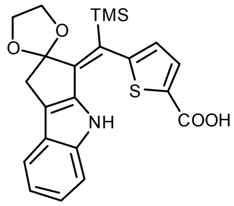
Tandem Heck-Suzuki product 5l. Two batches were made: **1)** Indole-alkynyl **4** (50 mg, 0.12 mmol), $Pd_2(dba)_3$•$CHCl_3$ (6.3 mg, 6.1 μmol), tris(4-trifluoromethylphenyl)phosphine (11 mg, 24 μmol), Cs_2CO_3 (98 mg, 0.30 mmol), 3-thienylboronic acid (23 mg, 0.18 mmol), 1,4-dioxane (2.0 ml, 0.06 M), water (4.2 μl, 0.23 mmol). The yield was calculated by ^{1}H-NMR analysis of the crude product using benzyl benzoate (20 μl) as internal standard (84%) **2)** Indole-alkynyl **4** (150 mg, 0.35 mmol), $Pd_2(dba)_3$•$CHCl_3$ (19 mg, 18 µmol), tris(4-trifluoromethylphenyl)phosphine (33 mg, 71 µmol), Cs_2CO_3 (285 mg, 0.87 mmol), 3-thienylboronic acid (67 mg, 0.52 mmol), 1,4-dioxane (5.8 ml, 0.06 M), water (13 µl, 0.72 mmol). The crude products from the two batches were combined, purified by column chromatography (ø = 4 cm, 27 g SiO_2, hexane/DCM 3:1 → 1:1). The obtained solid was recrystallized from boiling EtOH to yield **5l** as a white crystalline solid (143 mg, 79%); $R_f = 0.35$ (hexane/DCM 1:1); mp 122-123°C (EtOH); ν_{max}/cm^{-1} 3444 (NH), 2954, 2904, 2887 (CH); δ_H(400 MHz, Chloroform-d) 7.47 (dd, *J* = 4.8, 3.0 Hz, 1H), 7.41 (dq, *J* = 7.8, 0.8 Hz, 1H), 7.12 – 7.07 (m, 1H), 7.06 – 7.00 (m, 2H), 6.96 (dd, *J* = 3.0, 1.3 Hz, 1H), 6.93 (dd, *J* = 4.8, 1.3 Hz, 1H), 6.55 (br s, 1H), 4.33 – 4.21 (m, 2H), 4.21 – 4.10 (m, 2H), 3.10 (s, 2H), 0.11 (s, 9H); δ_C(101 MHz, Chloroform-d) 144.9, 141.9, 140.39, 140.36, 132.3, 128.7, 126.0, 123.8, 123.1, 121.0, 119.8, 119.5, 119.3, 117.5, 111.6, 63.0, 36.4, 0.6; HRMS (ESI+ qTOF) calcd for $C_{21}H_{24}NO_2SSi$ [M + 1] 382.1297, found 382.1313.



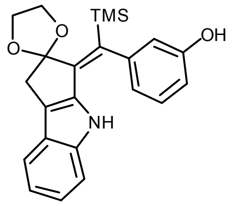
Tandem Heck-Suzuki product 5m. Indole-alkynyl **4** (51 mg, 0.12 mmol), $Pd_2(dba)_3$•$CHCl_3$ (6.3 mg, 6.1 µmol), tris(4-trifluoromethylphenyl)phosphine (11 mg, 24 µmol), Cs_2CO_3 (99 mg, 0.30 mmol), 2-thienylphenylboronic acid (23 mg, 0.17 mmol), 1,4-dioxane (2.0 ml, 0.06 M), water (4.2 µl, 0.23 mmol). The yield was calculated by ^{1}H-NMR analysis of the crude product using benzyl benzoate (20 µl) as internal standard (88%). Purification of this compound was not pursued.



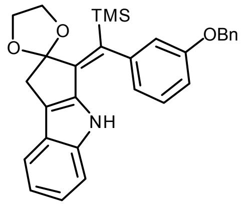
Tandem Heck-Suzuki product 5n. Two batches were made: **1)** Indole-alkynyl **4** (50 mg, 0.12 mmol), $Pd_2(dba)_3$•$CHCl_3$ (19 mg, 18 µmol), tris(4-trifluoromethylphenyl)phosphine (33 mg, 70 µmol), Cs_2CO_3 (97 mg, 0.30 mmol), (5-acetylthiophen-2-yl)boronic acid (31 mg, 0.18 mmol), 1,4-dioxane (2.0 ml, 0.06 M), water (4.2 µl, 0.23 mmol).The yield was calculated by ^{1}H-NMR analysis of the crude product using benzyl benzoate (20 µl) as internal standard (54%). **2)** Indole-alkynyl **4** (150 mg, 0.35 mmol), $Pd_2(dba)_3$•$CHCl_3$ (55 mg, 53 µmol), tris(4-trifluoromethylphenyl)phosphine (99 mg, 0.21 mmol), Cs_2CO_3 (286 mg, 0.88 mmol), (5-acetylthiophen-2-yl)boronic acid (90 mg, 0.53 mmol), 1,4-dioxane (5.9 ml, 0.06 M), water (13 µl, 0.72 mmol). The crude product from batch 2 was purified by column chromatography (ø = 4 cm, 35 g SiO_2, hexane/DCM 1:1 → 1:3) to yield **5n** as a light yellow crystalline solid (77 mg, 52%); $R_f = 0.15$ (hexane/DCM 1:3); mp 190-191°C (concentrated from hexane/DCM 1:3); ν_{max}/cm^{-1} 3383 (NH), 2972, 2951, 2925, 2902 (CH), 1658 (CO); δ_H(400 MHz, Chloroform-d) 7.75 (d, *J* = 3.7 Hz, 1H), 7.43 (dq, *J* = 7.9, 1.0 Hz, 1H), 7.17 – 7.09 (m, 2H), 7.04 (ddd, *J* = 8.0, 6.6, 1.5 Hz, 1H), 6.86 (br s, 1H), 6.83 (d, J = 3.7 Hz, 1H), 4.32 – 4.21 (m, 2H), 4.21 – 4.09 (m, 2H), 3.11 (s, 2H), 2.61 (s, 3H), 0.14 (s, 9H); δ_C(101 MHz, Chloroform-d) 190.4, 156.4, 144.2, 143.2, 140.9, 139.4, 133.0, 128.0, 125.9, 124.0, 123.6, 123.3, 120.2, 119.8, 117.4, 111.9, 63.1, 36.2, 26.8, 0.5; HRMS (ESI+ qTOF) calcd for $C_{23}H_{26}NO_3SSi$ [M + 1] 424.1403, found 424.1393.



Tandem Heck-Suzuki product 5o. Indole-alkynyl **4** (51 mg, 0.12 mmol), $Pd_2(dba)_3$•$CHCl_3$ (6.1 mg, 5.9 μmol), tris(4-trifluoromethylphenyl)phosphine (11 mg, 24 μmol), Cs_2CO_3 (97 mg, 0.30 mmol), (5-carboxythiophen-2-yl)boronic acid (31 mg, 0.18 mmol), 1,4-dioxane (2.0 ml, 0.06 M), water (4.2 μl, 0.23 mmol). The yield was calculated by ^{1}H-NMR analysis of the crude product using benzyl benzoate (25 μl) as internal standard (0%). Purification of the crude product was not pursued as no product could be detected in NMR.

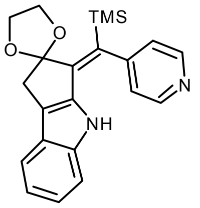


Tandem Heck-Suzuki product 5p. Indole-alkynyl **4** (51 mg, 0.12 mmol), $Pd_2(dba)_3$•$CHCl_3$ (24 mg, 23 μmol), tris(4-trifluoromethylphenyl)phosphine (44 mg, 95 μmol), Cs_2CO_3 (100 mg, 0.31 mmol), 3-hydroxyphenylboronic acid (25 mg, 0.18 mmol), 1,4-dioxane (2.0 ml, 0.06 M), water (4.3 μl, 0.24 mmol). The yield was calculated by ^{1}H-NMR analysis of the crude product using benzyl benzoate (20 μl) as internal standard (26%). Purification of the crude product was not pursued due to the limited amount of product.

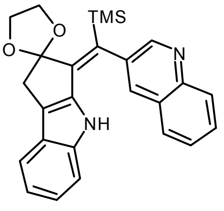


Tandem Heck-Suzuki product 5q. Two batches were made: **1)** Indole-alkynyl **4** (51 mg, 0.12 mmol), $Pd_2(dba)_3$•$CHCl_3$ (6.1 mg, 5.9 μmol), tris(4-trifluoromethylphenyl)phosphine (11 mg, 24 μmol), Cs_2CO_3 (96 mg, 0.29 mmol), 3-(benzyloxy)phenylboronic acid (40 mg, 0.18 mmol), 1,4-dioxane (2.0 ml, 0.06 M), water (4.2 μl, 0.23 mmol). The yield was calculated by ^{1}H-NMR analysis of the crude product using benzyl benzoate (25 μl) as internal standard (94%). **2)** Indole-alkynyl **4** (150 mg, 0.35 mmol), $Pd_2(dba)_3$•$CHCl_3$ (19 mg, 18 μmol), tris(4-trifluoromethylphenyl)phosphine (33 mg, 70 μmol), Cs_2CO_3 (289 mg, 0.89 mmol), 3-(benzyloxy)phenylboronic acid (121 mg, 0.53 mmol), 1,4-dioxane (5.9 ml, 0.06 M), water (13 μl, 0.72 mmol). The crude products from the two batches were combined, purified by column chromatography (ø = 4 cm, 25 g SiO_2, hexane/DCM 1:1) to yield **5q** as an uncolored oil (198 mg, 87%) having a negligible amount contaminant. 20% of isolated material was used for preparing an analytical sample by additional column chromatography (ø = 2 cm, 14 g SiO_2, hexane/DCM 1:1). R_f =

0.2 (hexane/DCM 1:1); ν_{max}/cm^{-1} 3450 (NH), 2954, 2895 (CH); δ_H(400 MHz, Chloroform-d) 7.45 – 7.28 (m, 7H), 7.08 (ddd, *J* = 8.1, 7.1, 1.3 Hz, 1H), 7.04 – 6.94 (m, 3H), 6.79 – 6.74 (m, 2H), 6.40 (br s, 1H), 5.14 – 5.06 (m, 2H), 4.33 – 4.22 (m, 2H), 4.22 – 4.11 (m, 2H), 3.11 (s, 1H), 0.08 (s, 9H); δ_C(101 MHz, Chloroform-d) 158.8, 146.7, 140.8, 140.4, 140.3, 137.5, 136.8, 129.8, 128.6, 127.9, 127.4, 123.8, 122.9, 120.7, 120.3, 119.8, 119.4, 117.7, 113.8, 113.4, 111.7, 69.9, 63.0, 36.4, 0.8; HRMS (ESI+ qTOF) calcd for $C_{30}H_{32}NO_3Si$ [M + 1] 482.2151, found 482.2133.

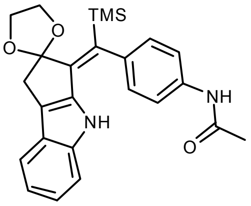


Tandem Heck-Suzuki product 5r. Two batches were made: **1)** Indole-alkynyl **4** (51 mg, 0.12 mmol), $Pd_2(dba)_3$•$CHCl_3$ (24 mg, 23 µmol), tris(4-trifluoromethylphenyl)phosphine (45 mg, 95 µmol), Cs_2CO_3 (99 mg, 0.30 mmol), 4-pyridinylboronic acid (22 mg, 0.18 mmol), 1,4-dioxane (2.0 ml, 0.06 M), water (4.2 µl, 0.23 mmol). The yield was calculated by ^{1}H-NMR analysis of the crude product using benzyl benzoate (20 µl) as internal standard (78%). **2)** Indole-alkynyl **4** (149 mg, 0.35 mmol), $Pd_2(dba)_3$•$CHCl_3$ (73 mg, 70 µmol), tris(4-trifluoromethylphenyl)phosphine (132 mg, 0.28 mmol), Cs_2CO_3 (285 mg, 0.87 mmol), 4-pyridinylboronic acid acid (66 mg, 0.53 mmol), 1,4-dioxane (5.9 ml, 0.06 M), water (13 µl, 0.72 mmol). The crude products from the two batches were dissolved in acetone, combined and concentrated onto SiO_2 (3.5 g). The silica bound crude product was purified by column chromatography (ø = 4 cm, 30 g SiO_2, hexane/DCM/MeOH 1:3:0 → 0:1:0 → 0:97:3). The obtained solid was triturated with boiling EtOH (5 ml) for 5 min then cooled to -20°C for 2 h to yield **5r** as a white crystalline solid (136 mg, 77%); R_f = 0.45 (DCM/MeOH 95:5); mp decompose ~285°C (EtOH); ν_{max}/cm^{-1} 3465 (NH), 2981, 2970, 2951, 2900 (CH); δ_H(400 MHz, Chloroform-d) 8.69 – 8.66 (m, 2H), 7.42 – 7.39 (m, 1H), 7.15 – 7.12 (m, 2H), 7.12 – 7.07 (m, 1H), 7.05 – 6.99 (m, 2H), 6.40 (br s, 1H), 4.33 – 4.22 (m, 2H), 4.22 – 4.11 (m, 2H), 3.10 (s, 2H), 0.10 (s, 9H); δ_C(101 MHz, Chloroform-d) 154.0, 150.3, 140.9, 140.6, 139.4, 134.2, 123.7, 123.6, 123.3, 122.3, 120.2, 119.6, 117.7, 111.8, 63.1, 36.1, 1.0; HRMS (ESI+ qTOF) calcd for $C_{22}H_{25}N_2O_2Si$ [M + 1] 377.1685, found 377.1636.



Tandem Heck-Suzuki product 5s. Two batches were made: **1)** Indole-alkynyl **4** (50 mg, 0.12 mmol), $Pd_2(dba)_3$•$CHCl_3$ (24 mg, 23 µmol), tris(4-trifluoromethylphenyl)phosphine (43 mg, 93 µmol), Cs_2CO_3 (96 mg, 0.29 mmol), 3-quinolineboronic acid (31 mg, 0.18 mmol), 1,4-dioxane (2.0 ml, 0.06 M), water (4.2 µl, 0.23 mmol). The yield was calculated by ^{1}H-NMR analysis of the crude product using benzyl benzoate (20 µl) as internal standard (73%). **2)** Indole-alkynyl **4** (150 mg, 0.35 mmol), $Pd_2(dba)_3$•$CHCl_3$

(73 mg, 70 μmol), tris(4-trifluoromethylphenyl)phosphine (132 mg, 0.28 mmol), Cs_2CO_3 (285 mg, 0.87 mmol), 3-quinolineboronic acid (92 mg, 0.53 mmol), 1,4-dioxane (5.9 ml, 0.06 M), water (13 μl, 0.72 mmol). The crude products from the two batches were combined purified by column chromatography (ø = 4 cm, 30 g SiO_2, hexane/DCM/MeOH 1:3:0 → 0:1:0 → 0:97:3), then triturated with boiling EtOH (3 ml) for 5 min and cooled to -20°C for 2 h to yield **5s** as a white crystalline solid (132 mg, 66%) containing a negligible amount of a contaminant; An analytical sample was obtained by repeating the triturating procedure; R_f = 0.65 (DCM/MeOH 95:5); mp 219-220°C (EtOH); ν_{max}/cm^{-1} 3471 (NH), 2956, 2893 (CH); δ_H(400 MHz, Chloroform-d) 8.78 (d, *J* = 2.2 Hz, 1H), 8.18 (dq, *J* = 8.5, 1.0 Hz, 1H), 7.94 (dd, *J* = 2.2, 1.0 Hz, 1H), 7.85 – 7.81 (m, 1H), 7.76 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.61 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.41 – 7.38 (m, 1H), 7.04 – 6.96 (m, 2H), 6.86 – 6.80 (m, 1H), 6.27 (br s, 1H), 4.37 – 4.26 (m, 2H), 4.25 – 4.14 (m, 2H), 3.17 (d, *J* = 14.8 Hz, 1H), 3.12 (d, *J* = 14.8 Hz, 1H), 0.11 (s, 9H); δ_C(101 MHz, Chloroform-d) 150.9, 146.7, 142.7, 140.6, 139.8, 138.1, 133.5, 133.0, 129.4, 129.3, 127.8, 127.7, 127.2, 123.6, 123.5, 122.4, 120.2, 119.6, 117.7, 111.8, 63.14, 63.07, 36.2, 1.1; HRMS (ESI+ qTOF) calcd for $C_{26}H_{27}N_2O_2Si$ [M + 1] 427.1842, found 427.1814.



Tandem Heck-Suzuki product 5t. Two batches were made: **1)** Indole-alkynyl **4** (50 mg, 0.12 mmol), $Pd_2(dba)_3$•$CHCl_3$ (25 mg, 24 μmol), tris(4-trifluoromethylphenyl)phosphine (44 mg, 93 μmol), Cs_2CO_3 (94 mg, 0.29 mmol), 4-(acetamido)phenylboronic acid (32 mg, 0.18 mmol), 1,4-dioxane (2.0 ml, 0.06 M), water (4.3 μl, 0.24 mmol). The yield was calculated by ^{1}H-NMR analysis of the crude product using benzyl benzoate (20 μl) as internal standard (87%). **2)** Indole-alkynyl **4** (150 mg, 0.35 mmol), $Pd_2(dba)_3$•$CHCl_3$ (73 mg, 70 μmol), tris(4-trifluoromethylphenyl)phosphine (131 mg, 0.28 mmol), Cs_2CO_3 (288 mg, 0.88 mmol), 4-(acetamido)phenylboronic acid (96 mg, 0.53 mmol), 1,4-dioxane (5.9 ml, 0.06 M), water (13 μl, 0.72 mmol). The crude products from the two batches were combined, purified by column chromatography (ø = 4 cm, 33 g SiO_2, DCM/MeOH 98:2 → 97:3). The obtained solid was triturated with EtOH (1.5 ml) at 50°C for 50 min then cooled to 4°C for 3 h to yield **5t** as a white crystalline solid (181 mg, 89%) having a minor contaminant. An analytical sample was made by triturating with DCM; R_f = 0.35 (DCM/MeOH 95:5); mp decompose ~265°C (DCM); ν_{max}/cm^{-1} 3452 (NH), 3300 (NH), 2898 (CH), 1658 (CO); δ_H(400 MHz, Chloroform-d) 7.62 – 7.56 (AA' part of AA'XX' system, 2H), 7.38 (dq, *J* = 7.8, 0.9 Hz, 1H), 7.27 (br s, 1H), 7.13 – 7.09 (AA' part of AA'XX' system, 2H), 7.08 – 7.03 (m, 1H), 7.02 – 6.97 (m, 2H), 6.40 (br s, 1H), 4.32 – 4.22 (m, 2H), 4.21 – 4.10 (m, 2H), 3.09 (s, 2H), 2.24 (s, 3H), 0.08 (s, 9H); δ_C(101 MHz, Chloroform-d) 168.3, 141.2, 141.1, 140.36, 140.34, 137.0, 136.2, 128.4, 123.8, 123.0, 120.9, 120.0, 119.8, 119.4, 117.7, 111.7, 63.0, 36.3, 24.7, 0.9; HRMS (ESI+ qTOF) calcd for $C_{25}H_{29}N_2O_3Si$ [M + 1] 433.1947, found 433.1998.

1.1.7 Preparation of compound 6a-t

To a round bottom flask equipped with a magnetic stir bar was added substrate (**5b-t**) and acetone. HCl (5M, aq.) was added dropwise and a yellow color change could be observed. The reaction was stirred at ambient temperature for indicated amount of time and then diluted with water to twice the volume. The mixture was extracted with EtOAc (3 times à 1 × reaction volume) and the combined extracts were washed with brine (1 × reaction volume), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude hydrolysis product was transferred to a oven dried round bottom flask equipped with a magnetic stir bar. The flask was sealed, evacuated of air and refilled with argon (3 cycles). Dry THF was added and the resulting mixture was cooled to -5°C. TBAF (1M in THF) was added dropwise and a color change from yellow to deep red was observed. The mixture was stirred at -5°C for indicated amount of time, then diluted with EtOAc (5 × reaction volume), warmed to room temperature and washed with water (5 × reaction volume). The aqueous phase was in some cases extracted with EtOAc, see below. The organic phase(s) were washed with brine (5 × reaction volume), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The relative stereochemistry was in all cases determined by 1D-NOESY. The N-**H** of the indole ring was saturated with a selective pulse and NOE was observed at substituents of the exocyclic double bond (Fig. S4).

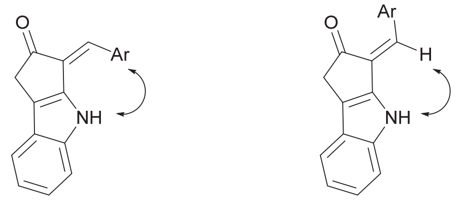
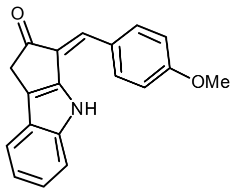
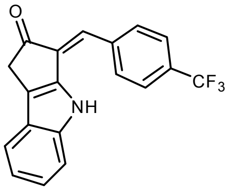


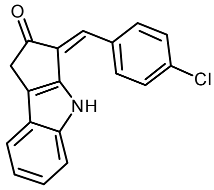
Fig. S4. NOE used to determine the stereochemistry around the exocyclic double bond.



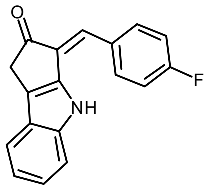
Compound 6a. Prepared according to previously described method.[3]



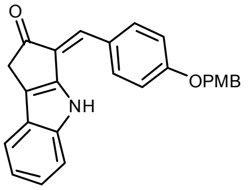
Compound 6b. Ketal **5b** (425 mg, 0.96 mmol), acetone (24 ml, 0.04 M) and HCl (2.9 ml, 14.4 mmol) were stirred for 15 min. Crude hydrolysis product, THF (8.0 ml, 0.12 M) and TBAF (1.9 ml, 1.9 mmol) were stirred for 30 min. The crude product was dissolved in acetone, concentrated onto SiO_2 (2 g) and purified by column chromatography (ø = 4 cm, 22 g SiO_2, hexane/DCM 1:1). DCM (5 ml) was added to the product and the resulting slurry was heated to boiling. Hexane (20 ml) was added and the mixture was cooled to 4°C for 18 h. The motherliquid was removed with a pipette, leaving **6b** as a yellow crystalline solid (237 mg, 75%); R_f = 0.30 (hexane/DCM 1:1); mp decompose ~220°C (precipitated from hexane/DCM); ν_{max}/cm^{-1} 3323 (NH), 1714 (CO); δ_H(400 MHz, DMSO-d6) 10.99 (br s, 1H), 7.94 – 7.90 (AA' part of AA'XX' system, 2H), 7.87 – 7.82 (XX' part of AA'XX' system, 2H), 7.56 (dq, *J* = 7.9, 1.0 Hz, 1H), 7.51 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.25 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.05 (s, 1H), 3.59 (s, 2H); δ_C(101 MHz, DMSO-d6) 203.8, 140.5, 139.3 (q, *J(F-C)* = 1.4 Hz), 138.9, 129.6, 129.0, 128.3 (q, *J(F-C)* = 31.8 Hz), 126.1 (q, *J(F-C)* = 3.9 Hz), 124.6, 124.3 (q, *J(F-C)* = 272 Hz), 123.4, 122.7, 120.9, 120.3, 119.9, 113.0, 35.7; HRMS (ESI+ qTOF) calcd for $C_{19}H_{13}F_3NO$ [M + 1] 328.0949, found 328.0933.



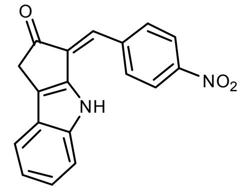
Compound 6c. Ketal **5c** (145 mg, 0.35 mmol), acetone (8.9 ml, 0.04 M) and HCl (1.1 ml, 5.3 mmol) were stirred for 10 min. The crude hydrolysis product, THF (3.0 ml, 0.12 M) and TBAF (0.7 ml, 0.7 mmol) were stirred for 20 min. The crude product was directly after workup concentrated onto SiO_2 (1.5 g), purified by column chromatography (ø = 2 cm, 22 g SiO_2, hexane/EtOAc 5:1) and triturated with EtOAc to yield **6c** as a yellow crystalline solid (91 mg, 87%); R_f = 0.45 (hexanes/EtOAc 4:1); mp decompose ~230°C (concentrated from hexane/EtOAc 5:1); ν_{max}/cm^{-1} 3323 (NH), 1714 (CO); δ_H(400 MHz, DMSO-d6) 10.94 (br s, 1H), 7.77 – 7.72 (AA' part of AA'BB' system, 2H), 7.59 – 7.54 (BB' part of AA'BB' system, 2H), 7.55 – 7.52 (m, 1H), 7.51 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.23 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.09 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.00 (s, 1H), 3.56 (s, 2H); δ_C(101 MHz, DMSO-d6) 203.9, 140.3, 139.1, 134.0, 133.1, 130.2, 129.3, 128.6, 124.2, 123.5, 121.7, 121.7, 120.2, 119.7, 113.0, 35.8; HRMS (ESI+ qTOF) calcd for $C_{18}H_{13}ClNO$ [M + 1] 294.0686, found 294.0687.



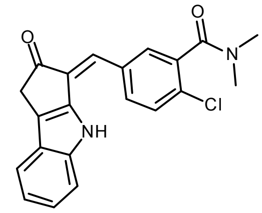
Compound 6d. Ketal **5d** (63 mg, 0.16 mmol), acetone (4.0 ml, 0.04 M) and HCl (0.48 ml, 2.4 mmol) were stirred for 10 min. Crude hydrolysis product, THF (1.3 ml, 0.12 M) and TBAF (0.3 ml, 0.3 mmol) were stirred for 20 min. The workup included extraction of the aqueous phase with EtOAc (5 ml). The crude product was dissolved in DCM, concentrated onto SiO$_2$ (1.5 g) and purified by column chromatography (ø = 2 cm, 10 g SiO$_2$, hexane/EtOAc 4:1). DCM (1 ml) was added to the product and to the resulting slurry was added hexane (5 ml). The motherliquid was removed with a pipette, leaving **6d** as a yellow crystalline solid (31 mg, 70%); R$_f$ = 0.45 (hexanes/EtOAc 3:1); mp decompose ~235°C (precipitated from hexane/DCM); ν_{max}/cm^{-1} 3321 (NH), 1714 (CO); δ_H(400 MHz, DMSO-d6) 10.93 (br s, 1H), 7.80 (d of AA' of AA'XX' spin system, *J(H-F)* = 5.6 Hz, 2H), 7.55 – 7.52 (m, 1H), 7.51 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.35 (d of XX' of AA'XX' spin system, *J(H-F)* = 8.9 Hz, 2H), 7.22 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 7.09 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.03 (s, 1H), 3.55 (s, 2H); δ_C(101 MHz, DMSO-d6) 204.0, 162.2 (d, *J(C-F)* = 246.9 Hz), 140.2, 139.2, 131.6 (d, *J(C-F)* = 3.2 Hz), 130.8 (d, *J(C-F)* = 8.4 Hz), 128.0 (d, *J(C-F)* = 1.7 Hz), 124.0, 123.5, 122.1, 121.2, 120.2, 119.6, 116.3 (d, *J(C-F)*= 21.8 Hz), 113.0, 35.8; HRMS (ESI+ qTOF) calcd for $C_{18}H_{13}FNO$ [M + 1] 278.0981, found 278.0985.



Compound 6e. Ketal **5e** (200 mg, 0.39 mmol), acetone (9.8 ml, 0.04 M) and HCl (1.2 ml, 6.0 mmol) were stirred for 10 min. Crude hydrolysis product, THF (3.2 ml, 0.12 M) and TBAF (0.8 ml, 0.8 mmol) were stirred for 20 min. The crude mixture still contained starting material and was treated with THF (3.2 ml, 0.12 M) and TBAF (0.8 ml, 0.8 mmol) for another 20 min. The crude product was dissolved in DCM, concentrated onto SiO$_2$ (3 g) and purified by column chromatography (ø = 2 cm, 14 g SiO$_2$, hexane/DCM 1:3 → 0:1). DCM (5 ml) was added to the product and the resulting slurry was heated to boiling. Hexane (15 ml) was added and the motherliquid was removed to yield **6e** as a yellow crystalline precipitate (123 mg, 80%); R$_f$ = 0.40 (DCM); mp 212-214°C (precipitated from hexane/DCM); ν_{max}/cm^{-1} 3319 (NH), 1712 (CO); δ_H(400 MHz, DMSO-d6) 10.95 (br s, 1H), 7.72 (AA' part of AA'XX' system, 2H), 7.53 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.53 – 7.50 (m, 1H), 7.42 (XX' part of AA'XX' system, 2H), 7.20 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.16 (AA' part of AA'XX' system, 2H), 7.08 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 7.01 (s, 1H), 6.97 (XX' part of AA'XX' system, 2H), 5.12 (s, 2H), 3.77 (s, 3H), 3.53 (s, 2H); δ_C(101 MHz, DMSO-d6) 204.2, 159.11, 159.08, 140.1, 139.6, 130.4, 129.5, 128.6, 127.6, 126.4, 123.62, 123.58, 123.57, 120.1, 120.0, 119.3, 115.6, 113.9, 113.0, 69.2, 55.1, 35.8; HRMS (ESI+ qTOF) calcd for $C_{26}H_{22}NO_3$ [M + 1] 396.1600, found 396.1615.

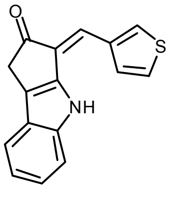


Compound 6f. Ketal **5f** (220 mg, 0.52 mmol), acetone (14 ml, 0.04 M) and HCl (1.6 ml, 8.0 mmol) were stirred for 15 min. Crude hydrolysis product, THF (4.5 ml, 0.12 M) and TBAF (1.1 ml, 1.1 mmol) were stirred for 20 min. The crude product was directly after workup concentrated onto SiO_2 (6 g) and purified by column chromatography (ø = 4 cm, 20 g SiO_2, hexane/EtOAc 3:1). DCM (5 ml) was added to the product and the resulting slurry was heated to boiling. Hexane (10 ml) was added and the motherliquid was removed from the precipitate which was redisolved in acetone (5 ml). The addition of hexane (10 ml) precipitated **6f** as a red crystalline solid (95 mg, 60%); The compound exists as a mixture of E/Z isomers (7:6 in DMSO-d6); mp decompose ~260°C (precipitated from hexane/acetone); R_f = 0.2 and 0.4 (hexanes/EtOAc 3:1); ν_{max}/cm^{-1} 3340 (NH), 1730 (CO), 1504 (NO_2), 1336 (NO_2); δ_H(400 MHz, DMSO-d6) **E-isomer:** 10.99 (br s, 1H), 8.32 (AA' part of AA'XX' system, 2H), 7.94 (XX' part if AA'XX' system, 2H), 7.56 (dq, *J* = 8.0, 1.0 Hz, 1H), 7.51 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.26 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.05 (s, 1H), 3.59 (s, 2H). **Z-isomer:** 11.71 (br s, 1H), 8.22 (AA' part of AAXX' system, 2H), 8.14 (XX' part of AA'XX' system, 2H), 7.51 (dq, *J* = 8.0, 0.9 Hz, 1H), 7.46 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.23 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.07 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.07 (s, 1H), 3.55 (s, 2H). δ_C(101 MHz, DMSO-d6) **Both E- and Z-isomer:** 203.5, 203.0, 146.5, 146.4, 143.5, 142.2, 141.3, 140.6, 140.2, 138.9, 131.2, 130.9, 130.5, 129.4, 124.9, 124.4, 124.3, 123.9, 123.8, 123.3, 123.3, 122.9, 120.4, 120.1, 120.1, 120.0, 119.4, 113.0, 112.3, 37.4, 35.6; HRMS (ESI+ qTOF) calcd for $C_{18}H_{13}N_2O_3$ [M + 1] 305.0926, found 305.0943.

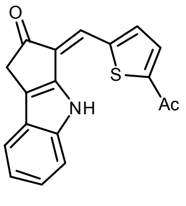


Compound 6i. Ketal **5i** (154 mg, 0.32 mmol) in mixture with an unknown contaminant from previous step, acetone (8.0 ml, 0.04 M) and HCl (1.0 ml, 5.0 mmol) were stirred for 25 min. Crude hydrolysis product, THF (2.7 ml, 0.12 M) and TBAF (0.6 ml, 0.6 mmol) were stirred for 40 min. The workup included extraction of the aqueous phase with EtOAc (3 × 10 ml). The crude product was purified by column chromatography (ø = 2 cm, 10 g SiO_2, DCM/MeOH 99:1). DCM (2 ml) was added to the product followed by hexane (8 ml) and the resulting mixture was cooled to -20°C for 12 h. The motherliquid was removed to yield **6i** as a yellow crystalline solid precipitate (47 mg, 40%); R_f = 0.25 (DCM/MeOH 99:1); mp decompose ~220°C (precipitated from hexane/DCM); ν_{max}/cm^{-1} 3255 (NH), 1732 (CO), 1637 (CO); δ_H(400 MHz, DMSO-d6) 10.91 (br s, 1H), 7.86 (ddd, *J* = 8.4, 2.2, 0.7 Hz, 1H), 7.66 (dt, *J* = 8.4, 0.5 Hz, 1H), 7.58 – 7.57 (m, 1H), 7.54 (ddt, *J* = 7.9, 1.3, 0.7 Hz, 1H), 7.48 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.24 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.09 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.99 (q, *J* = 0.7 Hz, 1H), 3.57 (s,

2H), 3.03 (s, 3H), 2.86 (s, 3H); δ_C(101 MHz, DMSO-d6) 203.8, 166.6, 140.4, 139.2, 136.9, 134.7, 130.5, 129.1, 129.0, 128.8, 128.7, 124.3, 123.5, 122.1, 121.0, 120.3, 119.8, 113.0, 37.6, 35.8, 34.1; HRMS (ESI+ qTOF) calcd for $C_{21}H_{18}ClN_2O_2$ [M + 1] 365.1057, found 365.1063.

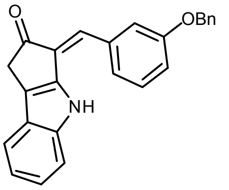


Compound 6l. Ketal **5l** (135 mg, 0.35 mmol), acetone (9.0 ml, 0.04 M) and HCl (1.1 ml, 5.5 mmol) were stirred for 15 min. Crude hydrolysis product, THF (3.0 ml, 0.12 M) and TBAF (0.7 ml, 0.7 mmol) were stirred for 60 min. The workup included extraction of the aqueous phase with EtOAc (15 ml). The crude product was dissolved in DCM, concentrated onto SiO_2 (2 g) and purified by column chromatography (ø = 2 cm, 14 g SiO_2, hexane/DCM 1:1 → 1:3). DCM (2 ml) was added to the product and the resulting slurry was heated to boiling. Hexane (10 ml) was added and the motherliquid was removed leaving **6l** as an orange crystalline solid (74 mg, 78%); $R_f = 0.20$ (hexane/DCM 1:1); mp decompose ~195°C (precipitated from hexane/DCM); ν_{max}/cm^{-1} 3437 (NH), 1709 (CO); δ_H(400 MHz, DMSO-d6) 10.97 (br s, 1H), 8.04 (ddd, *J* = 2.9, 1.3, 0.8 Hz, 1H), 7.74 (ddd, *J* = 5.0, 2.9, 0.5 Hz, 1H), 7.56 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.55 (ddd, *J* = 5.0, 1.3, 0.5 Hz, 1H), 7.53 (ddt, *J* = 7.9, 1.3, 0.7 Hz, 1H), 7.22 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 7.09 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.04 (q, *J* = 0.6 Hz, 1H), 3.54 (s, 2H); δ_C(101 MHz, DMSO-d6) 204.3, 140.4, 139.5, 136.5, 128.3, 127.5, 127.2, 126.9, 123.7, 123.5, 120.3, 120.2, 119.5, 117.2, 113.0, 35.8; HRMS (ESI+ qTOF) calcd for $C_{16}H_{12}NOS$ [M + 1] 266.0640, found 266.0649.

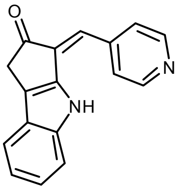


Compound 6n. Ketal **5n** (110 mg, 0.26 mmol), acetone (6.5 ml, 0.04 M) and HCl (0.8 ml, 4.0 mmol) were stirred for 10 min. The crude material still contained unreacted ketal and was treated with HCl (0.8 ml, 4.0 mmol) in acetone (6.5 ml, 0.04 M) for additional 30 min. Crude hydrolysis product, THF (2.0 ml, 0.12 M) and TBAF (0.5 ml, 0.5 mmol) were stirred for 20 min. The workup included extraction of the aqueous phase with EtOAc (10 ml). The crude product was dissolved in acetone and concentrated onto SiO_2 (2 g), purified by column chromatography (ø = 2 cm, 13 g SiO_2, DCM/MeOH 1:0 → 98:2). DCM (5 ml) was added to the product and the resulting slurry was heated to boiling. Hexane (10 ml) was added and the motherliquid was removed to yield **6n** as a red crystalline precipitate (68 mg, 86%); The compound exist as a mixture of E/Z isomers (1:1 in DMSO-d6); $R_f = 0.40$ (minor) and 0.15 (major) (DCM); mp decompose ~235°C (precipitated from hexane/DCM); ν_{max}/cm^{-1} 3244 (NH), 1714 (CO), 1633 (CO); δ_H(400 MHz, DMSO-d6) **E-isomer:** 11.10 (br s, 1H), 8.01 (d, *J* = 4.0 Hz, 1H), 7.69 (dd, *J* = 4.0, 0.9 Hz, 1H), 7.63 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.56 (dq, *J* = 7.9, 0.9 Hz, 1H), 7.28 (ddd, *J* = 8.2 ,7.0, 1.1 Hz, 1H) 7.12 (ddd, *J* = 8.0, 7.0,

1.0 Hz, 1H), 7.08 (d, *J* = 0.8 Hz, 1H), 3.58 (s, 2H), 2.60 (s, 3H). **Z-isomer:** 11.68 (br s, 1H), 7.88 (d, *J* = 4.0 Hz, 1H), 7.64 (dd, *J* = 4.0, 0.8 Hz, 1H), 7.51 (dq, *J* = 7.9, 0.9 Hz, 1H), 7.44 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.26 (d, *J* = 0.8 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.07 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 1H), 3.55 (s, 2H), 2.54 (s, 3H); δ_C(101 MHz, DMSO-d6) **Both E- and Z-isomer:** 203.5, 203.4, 191.2, 190.5, 146.0, 145.1, 144.9, 144.3, 143.1, 140.9, 140.2, 139.0, 135.0, 134.6, 133.5, 131.1, 128.3, 127.5, 124.8, 124.02, 124.00, 123.4, 123.3, 120.6, 120.1, 120.0, 119.8, 118.9, 117.1, 113.8, 113.4, 112.3, 37.1, 35.6, 26.7, 26.6; HRMS (ESI+ qTOF) calcd for $C_{18}H_{14}NO_2S$ [M + 1] 308.0745, found 308.0710.

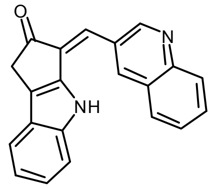


Compound 6q. Ketal **5q** (164 mg, 0.34 mmol), acetone (8.5 ml, 0.04 M) and HCl (1.0 ml, 5.0 mmol) were stirred for 15 min. Crude hydrolysis product, THF (2.8 ml, 0.12 M) and TBAF (0.7 ml, 0.7 mmol) were stirred for 30 min. The crude product was purified by column chromatography (ø = 2 cm, 13 g SiO_2, hexane/DCM 1:1 → 1:3). DCM (4 ml) was added to the product and the resulting slurry was boiled until precipitation appeared. Hexane (5 ml) was added and the mixture was cooled to -20°C for 2 h. The motherliquid was removed leaving **6q** as a yellow crystalline solid (101 mg, 81%); $R_f = 0.30$ (hexane/DCM 1:3); mp 160 – 165°C (precipitated from hexane/DCM); ν_{max}/cm^{-1} 3431 (NH), 1732 (CO); δ_H(400 MHz, Chloroform-d) 8.24 (br s, 1H), 7.55 (dq, *J* = 7.9, 0.9 Hz, 1H), 7.48 – 7.34 (m, 6H), 7.32 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.21 – 7.19 (m, 1H), 7.16 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1H), 7.15 (t, *J* = 0.6 Hz, 1H), 7.05 (dddd, *J* = 8.3, 2.6, 1.0, 0.4 Hz, 1H), 5.13 (s, 2H), 3.56 (s, 2H); δ_C(101 MHz, Chloroform-d) 204.3, 159.4, 139.8, 139.0, 137.8, 136.5, 130.4, 129.2, 128.7, 128.2, 127.4, 124.6, 124.1, 123.9, 121.3, 121.0, 120.2, 120.0, 115.6, 114.5, 112.0, 70.1, 36.4; HRMS (ESI+ qTOF) calcd for $C_{25}H_{20}NO_2$ [M + 1] 366.1494, found 366.1515.

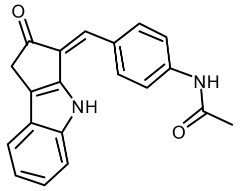


Compound 6r. Ketal **5r** (130 mg, 0.35 mmol), acetone (8.6 ml, 0.04 M) and HCl (1.0 ml, 5.0 mmol) were stirred for 25 min. In addition to water (4 ml) was added $NaHCO_3$ (4 ml, sat. aq.) to neutralize the mixture before workup. Crude hydrolysis product, THF (2.9 ml, 0.12 M) and TBAF (0.7 ml, 0.7 mmol) were stirred for 30 min. The workup included extraction of the aqueous phase with EtOAc (3 × 10 ml). The crude product was dissolved in EtOAc, concentrated onto SiO_2 (1.5 g) and purified by column chromatography (ø = 2 cm, 10 g SiO_2, DCM/MeOH 98:2 → 97:3). DCM (4 ml) was added to the product and the resulting slurry was heated to boiling. Hexane (4 ml) was added and the motherliquid was removed leaving **6r** as a red crystalline solid (59 mg, 66%); The compound exist as a mixture of E/Z isomers (5:1 in DMSO-d6); $R_f = 0.20$ (major)

and 0.15 (minor) (DCM/MeOH 95:5); mp decompose ~255°C (precipitated from hexane/DCM); ν_{max}/cm^{-1} 1728 (CO); δ_H(400 MHz, DMSO-d6) **E-isomer:** 11.03 (br s, 1H), 8.70 (br s, 2H), 7.69 – 7.62 (m, 2H), 7.56 (dq, *J* = 8.0, 1.0 Hz, 1H), 7.52 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.26 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.93 (s, 1H), 3.60 (s, 2H). **Z-isomer:** 11.74 (br s, 1H), 8.62 (s, 2H), 7.86 – 7.79 (m, 2H), 7.54 – 7.51 (m, 1H), 7.46 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.24 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.08 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.94 (s, 1H), 3.56 (s, 2H). δ_C(101 MHz, DMSO-d6) **Both E- and Z-isomer:** 203.6 , 203.0, 150.5, 149.7, 143.2, 142.4, 140.7, 140.1, 138.8, 131.8, 130.7, 124.8, 124.2, 123.9, 123.4, 123.3, 122.52, 122.49 (br s), 120.4, 120.13, 120.07, 120.0, 119.5, 119.2, 113.1, 112.3, 37.5, 35.7. Two peaks cannot be elucidated. One is likely the peak corresponding to the broad singlet at 122.49 of the Z-isomer; HRMS (ESI+ qTOF) calcd for $C_{17}H_{13}N_2O$ [M + 1] 261.1028, found 261.1036.



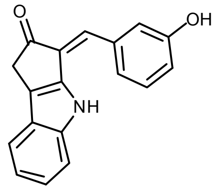
Compound 6s. Ketal **5s** (118 mg, 0.28 mmol), acetone/water (2:1, 21 ml, 0.01 M) and HCl (0.8 ml, 4.0 mmol) were stirred for 30 min. In addition to water (10 ml) was added $NaHCO_3$ (10 ml, sat., aq.) to neutralize the mixture before workup. Crude hydrolysis product, THF (2.3 ml, 0.12 M) and TBAF (0.6 ml, 0.6 mmol) were stirred for 40 min. The workup included extraction of the aqueous phase with EtOAc (3 × 8 ml). The crude product was dissolved in EtOAc, concentrated onto SiO_2 (1.5 g) and purified by column chromatography (ø = 2 cm, 10 g SiO_2, DCM/MeOH 99:1). DCM (4 ml) was added to the product and the resulting slurry was heated to boiling. Hexane (10 ml) was added and the motherliquid was removed leaving **6s** as an orange crystalline solid (46 mg, 54%); R_f = 0.65 (DCM/MeOH 95:5); mp decompose ~225°C (precipitated from hexane/DCM); ν_{max}/cm^{-1} 3280 (NH), 1714 (CO); δ_H(400 MHz, DMSO-d6) 11.25 (br s, 1H), 9.20 (br s, 1H), 8.68 – 8.67 (m, 1H), 8.10 – 8.05 (m, 2H), 7.82 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.67 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.58 – 7.55 (m, 1H), 7.49 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.24 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 7.17 (d, *J* = 1.0 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 3.61 (s, 2H); δ_C(101 MHz, DMSO-d6) 203.8, 150.8, 147.2, 140.6, 139.4, 134.5, 130.1, 129.5, 129.1, 128.7, 128.7, 127.7, 127.1, 124.4, 123.6, 122.4, 120.3, 119.8, 119.3, 113.1, 35.9; HRMS (ESI+ qTOF) calcd for $C_{21}H_{15}N_2O$ [M + 1] 311.1184, found 311.1155.



Compound 6t. Ketal **5t** (175 mg, 0.41 mmol), acetone (10 ml, 0.04 M) and HCl (1.2 ml, 6.0 mmol) were stirred for 20 min. Crude hydrolysis product, THF (3.4 ml, 0.12 M) and TBAF (0.8 ml, 0.8 mmol) were stirred for 30 min. The workup

included extraction of the aqueous phase with EtOAc (3 × 9 ml). The crude product still contained material with an intact TMS-group and was therefore treated with THF (3.4 ml, 0.12 M) and TBAF (0.8 ml, 0.8 mmol) for another 100 min. The second workup also included extraction of the aqueous phase with EtOAc (3 × 9 ml). The crude material was directly concentrated onto SiO_2 (1.5 g) and purified by column chromatography (ø = 2 cm, 12 g SiO_2, DCM/MeOH 97:3). DCM (8 ml) was added to the product and the resulting slurry was heated to boiling. Hexane (8 ml) was added and the mixture was cooled to -20°C for 1 h. The motherliquid was removed with a pipette to yield **6t** as a yellow crystalline solid (60 mg, 47%); R_f = 0.30 (DCM/MeOH 95:5); mp decompose ~265°C (precipitated from hexane/DCM); ν_{max}/cm^{-1} 3406 (NH), 3298 (NH), 1714 (CO), 1658 (CO); δ_H(400 MHz, DMSO-d6) 10.99 (br s, 1H), 10.20 (br s, 1H), 7.77 (AA' part of AA'BB' system, 2H), 7.71 (BB' part of AA'BB' system, 2H), 7.55 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.52 (ddt, *J* = 7.9, 1.3, 0.6 Hz, 1H), 7.21 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H), 7.08 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.98 (s, 1H), 3.53 (s, 2H), 2.10 (s, 3H); δ_C(101 MHz, DMSO-d6) 204.3, 168.6, 140.2, 140.1, 139.5, 129.6, 129.5, 126.7, 123.7, 123.52, 123.48, 120.4, 120.2, 119.4, 119.3, 113.0, 35.8, 24.2; HRMS (ESI+ qTOF) calcd for $C_{20}H_{17}N_2O_2$ [M + 1] 317.1290, found 317.1286.

1.1.8 Preparation of compound 6u



An oven dried round bottom flask containing **6q** (15 mg, 0.04 mmol) was sealed, evacuated of air and refilled with argon (3 cycles). Dry DCM (1.2 ml, 0.035 M) was added and the solution was cooled to -78°C. BBr_3 (82 µl, 1M in DCM) was added dropwise and the solution changed color to dark green from initial yellow. The solution was stirred for 50 min at -78°C, quenched with water (2 ml) and warmed to ambient temperature. EtOAc (10 ml) was added to the now orange mixture and the resulting biphasic system was separated. The organic layer was washed with brine (2 ml), dried over Na_2SO_4, filtered and concentrated to an orange crystalline solid. The crude product was dissolved in acetone, concentrated onto SiO_2 (1 g) and purified by column chromatography (ø = 2 cm, 10 g SiO_2, DCM/MeOH 97:3). DCM (2 ml) was added to the product and heated to boiling. The product was precipitated by the addition of hexane (5 ml) and the motherliquid was removed with a pipette to yield **6u** as an orange crystalline solid (10 mg, 88%); R_f = 0.50 (DCM/MeOH 95:5); mp decompose ~260°C (precipitated from hexane/DCM); ν_{max}/cm^{-1} 3367 and 3340 (NH and OH), 1720 (CO); δ_H(400 MHz, DMSO-d6) 10.87 (br s, 1H), 9.64 (br s, 1H), 7.54 - 7.51 (m, 1H), 7.53 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.34 (dd, *J* = 8.1, 7.6 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.19 (ddt, *J* = 7.5, 1.7, 0.9 Hz, 1H), 7.11 (ddt, *J* = 2.4, 1.8, 0.5 Hz, 1H), 7.08 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H), 6.94 (t, *J* = 0.5 Hz, 1H), 6.85 (ddd, *J* = 8.1, 2.5, 1.1 Hz, 1H), 3.55 (s, 2H); δ_C(101 MHz, DMSO-d6) 204.2, 157.8, 140.2, 139.4, 136.2, 130.4, 127.9, 123.9, 123.6, 123.5, 120.9, 120.1, 119.5, 119.3, 116.3, 115.1, 113.1, 35.8. HRMS (ESI+ qTOF) calcd for $C_{18}H_{14}NO_2$ [M + 1] 276.1025, found 276.1024.

1.2 Procedure for inhibition of peripheral blood mononuclear cell proliferation

Peripheral blood mononuclear cells (PBMC) were isolated from EDTA-blood samples by Ficoll-Hipaque (Amersham Bioscience, Little Chalfont, Buckinghamshire, UK) density gradient centrifugation. PBMC from two healthy donors were incubated for 30 min with 12 different concentrations of compound **6v** (0.003-50 μM). Compound **6v** was dissolved in no more than a final concentration of 0.5% DMSO. After incubation the cells were added to α-CD3 (1μg/mL, eBioscience, San Diego, CA, USA) coated 96-well microplate (100 000 cells/well, TPP, Trasadingen, Switzerland) and lastly α-CD28 (8μg/mL, eBioscience, San Diego, CA, USA) was added. The cells were incubated for 2 days in 5% CO_2 at 37°C. Cellular proliferation was measured *via* the incorporation of ^{3}H-thymidine (20 Ci; 1 Curie/well; Perkin Elmer, Waltham, MA, USA) for 6 h, followed by harvesting. Cell proliferation was quantified as counts per minutes (cpm) using a β-scintillation counter (1450 MicroBeta TriLux; Perkin Elmer). Cell proliferation inhibition ratio was calculated as followed: (cpm of experimental well / cpm of blank control well) × 100. The nonlinear regression fit was employed to determine IC_{50}, using the GraphPad Prism ver. 5.0 software (GraphPad, San Diego, CA, USA). Written informed consent was acquired from all study participants. The study was approved by the Regional Ethical Review Board of Gothenburg, Sweden.

1.3 Apoptosis assays

After 2 days of incubation the cell apoptosis was analyzed by flow cytometry using Annexin V (cat. no 556422, PE, BD Biosciences) and 7AAD (cat. no 559925, BD Biosciences) double staining. Annexin V+/7AAD- cells were defined to be early apoptotic, Annexin V-/7AAD- as non-apoptotic, healthy cells, and Annexin V+/7AAD+ cells as late apoptotic. "Fluorescence Minus One" controls were used to monitor background staining.[4] Samples were acquired using a FACSCanto II^{TM} Flow Cytometer (BD

Biosciences); 10,000 events were acquired and analyzed using the software Flow Jo 7.6.5 (Tree Star Inc., Ashland, OR, USA).

1.4 Image flow cytometry

After PBMC was incubated with **6v** (10 µM) for 2 days; the cells were washed with phosphate buffered saline (PBS) and then stained with DRAQ5 (DNA staining, Abcam, Cambridge, MA, ab108410). "Fluorescence Minus One"-technique was employed.[4] One thousand cells were collected in the image flow cytometer (Image Stream X; Amnis, Seattle, WA, USA) and analyzed with the IDEAS software ver. 6.0

Fig S5. Fluorescent images of PBMC treated with **6v**.See main article for detailed explanation.

1.5 Kinase inhibition

All kinase inhibition experiments were performed by Eurofins KinaseProfiler Service using compound (10 µM) and ATP ≈ Km (Aurora A: 15 µM, Aurora B: 10 µM, BRAF: 120 µM, IRAK4 200 µM).

TABLE S3. Kinase inhibition of scytonemin, nostodione A and monomeric scytonemin **6v**

Kinase	Scytonemin (1) (%)[a]	Nostodione A (2) (%)[a]	6v (%)[a]
Aurora-A(h)	74	92	61
Aurora-B(h)	-	69	36
Aurora-C(h)	-	95	98
B-Raf(V599E)(h)	119	100	56
CDK1/cyclinB(h)	-	103	93
CDK2/cyclinA(h)	92	96	95
CDK6/cyclinD3(h)	93	101	95
CHK1(h)	-	94	100
FGFR4(h)	100	106	122

IKKα(h)	90	94	128
IKKβ(h)	70	86	108
IKKε(h)	107	105	97
IRAK1(h)	99	100	72
IRAK4(h)	128	86	29
JAK2(h)	96	119	105
mTOR(h)	89	101	73
Plk1(h)	95	103	100
Plk3(h)	103	97	100
Ron(h)	101	97	86
TAK1(h)	100	105	99

[a] Percent remaining kinase activity after treatment with 10 μM compound at [ATP]~Km.

1.7 Spectroscopic measurements of 6v

Absorption spectrum was recorded on a Cary 5000 spectrophotometer while excitation- and emission spectra were recorded on a SPEX fluorolog 3 spectrofluorimeter (JY Horiba). Excitation spectrum was recorded from 300nm to 560nm with the emission wavelength 575nm. Emission spectrum was recorded between 390nm and 720nm with the excitation wavelength 375nm. All measurements were performed in acetonitrile.

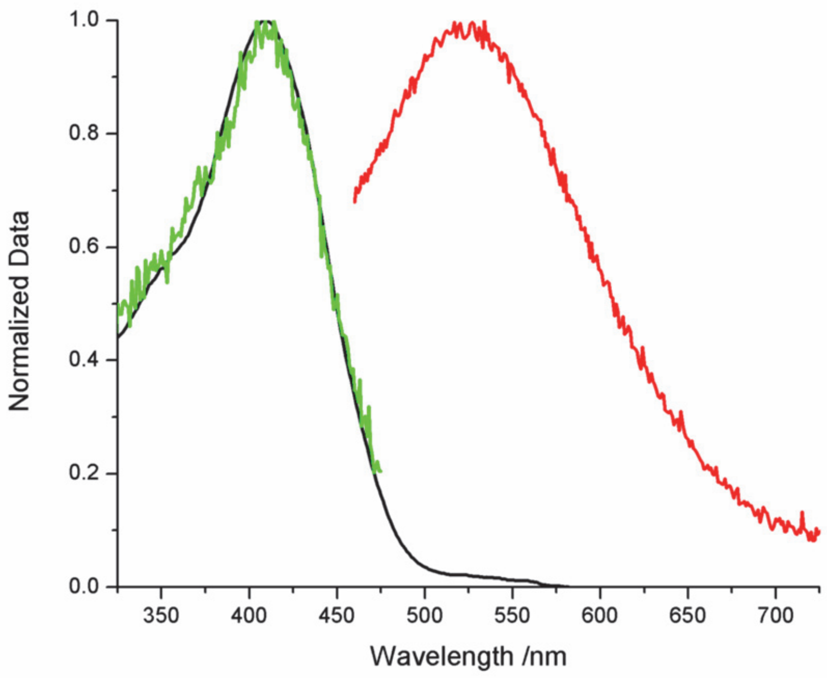


Fig S6. Absorption spectrum (black), emission spectrum (red) and excitation spectrum (green) for **6v** in acetonitrile.

1.8 HPLC calibration curves

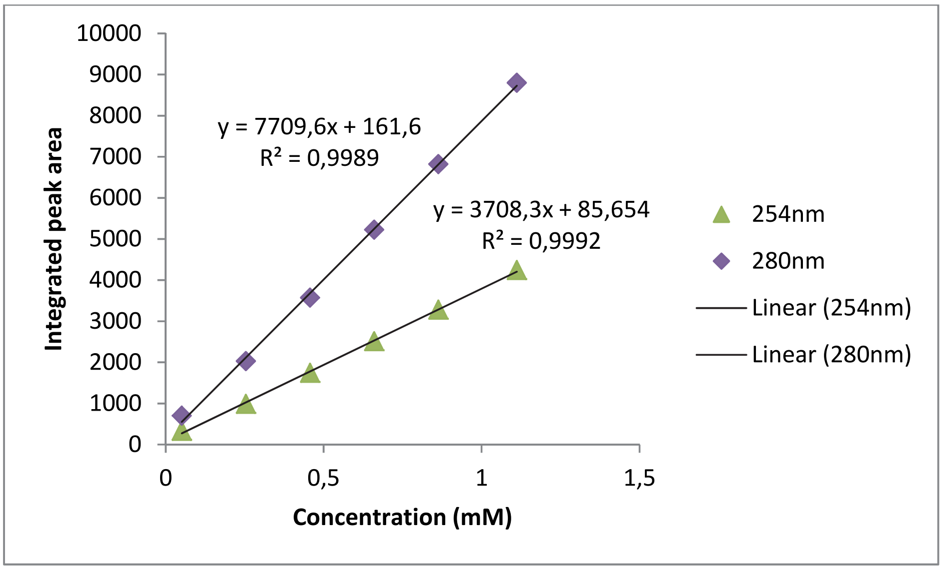


Fig. S7. HPLC calibration curves for substrate **4** analyzed by UV-absorption at 254nm and 280nm.

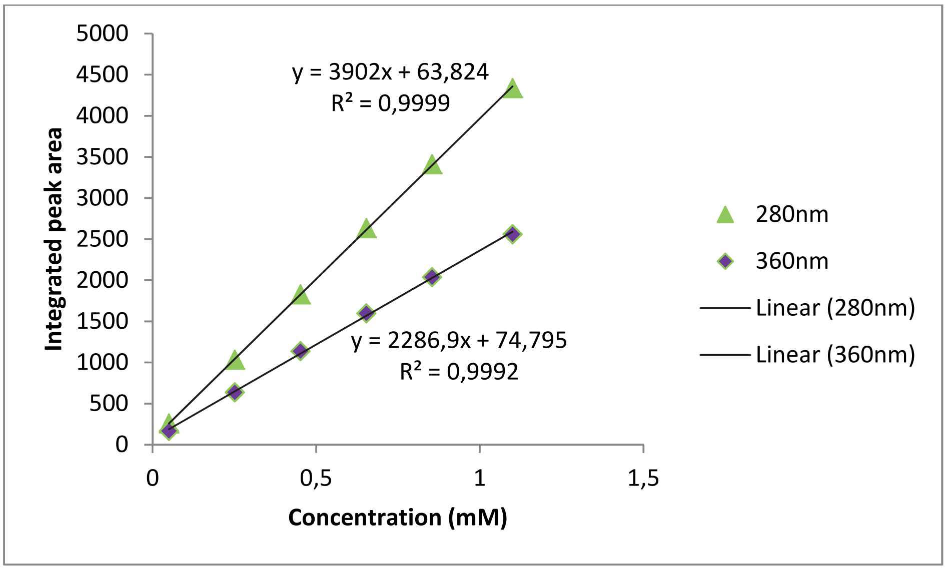


Fig. S8. HPLC calibration curves for product **5a** analyzed by UV-absorption at 280nm and 360nm.

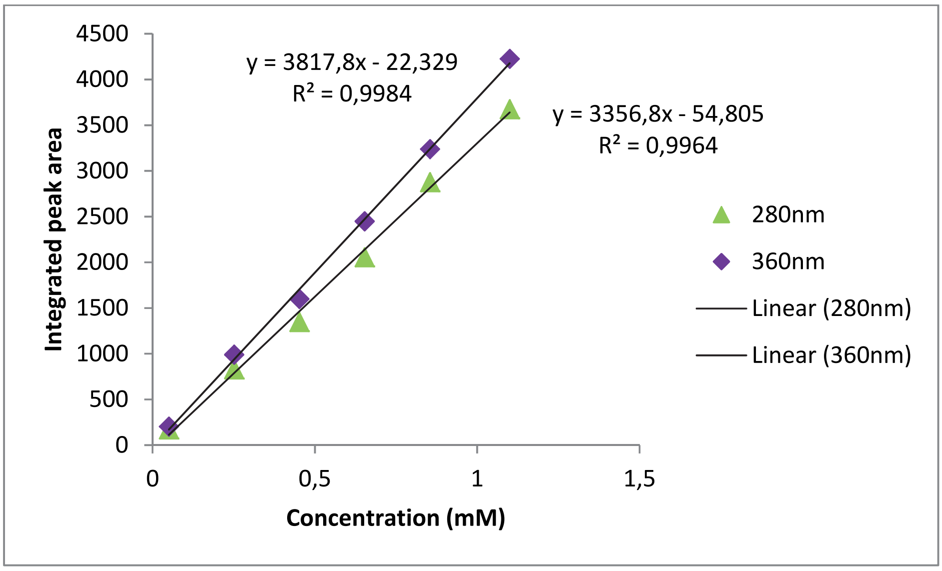


Fig. S9. HPLC calibration curves for product **5b** analyzed by UV-absorption at 280nm and 360nm.

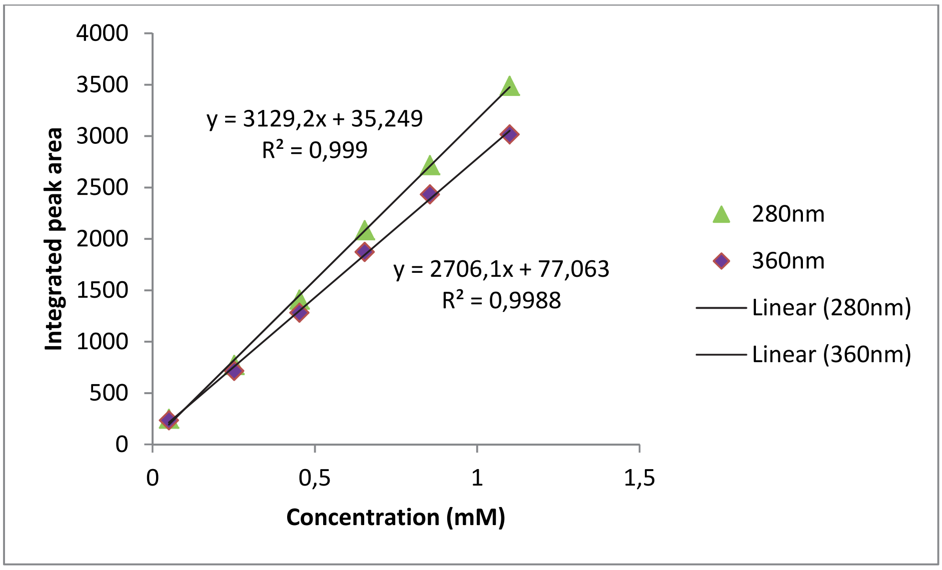


Fig. S10. HPLC calibration curves for product **5c** analyzed by UV-absorption at 280nm and 360nm.

2 References

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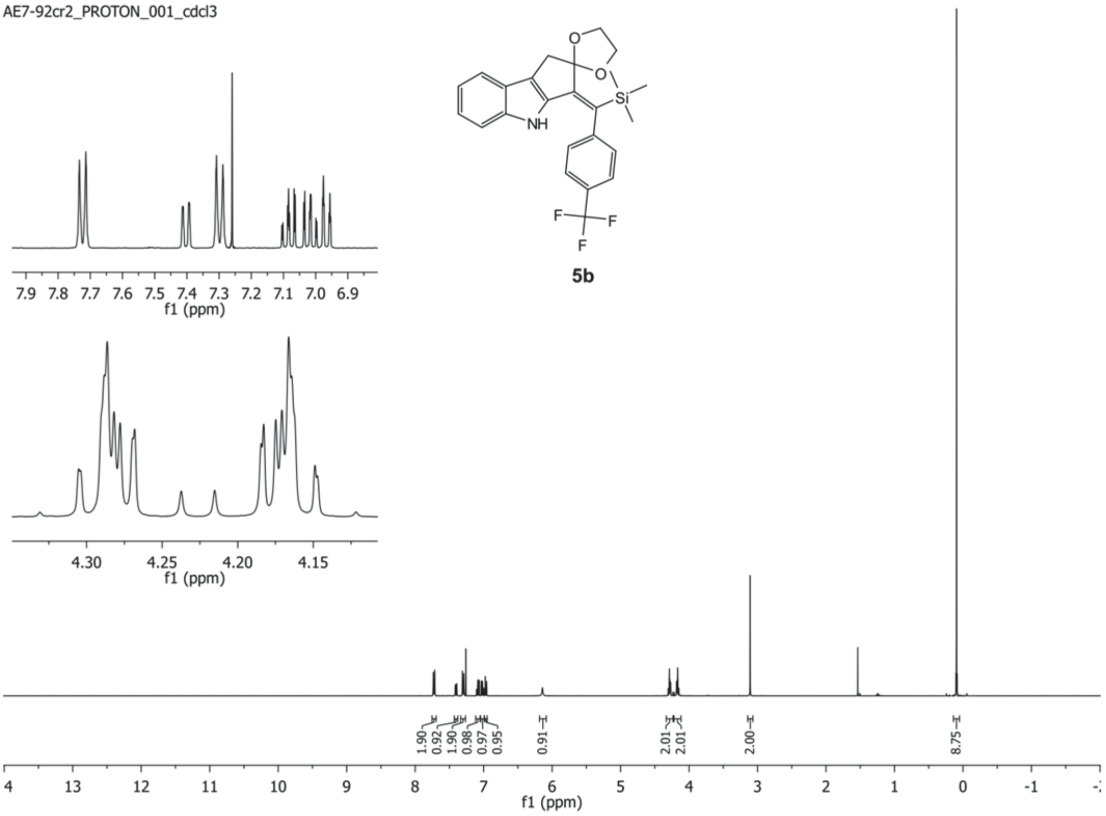
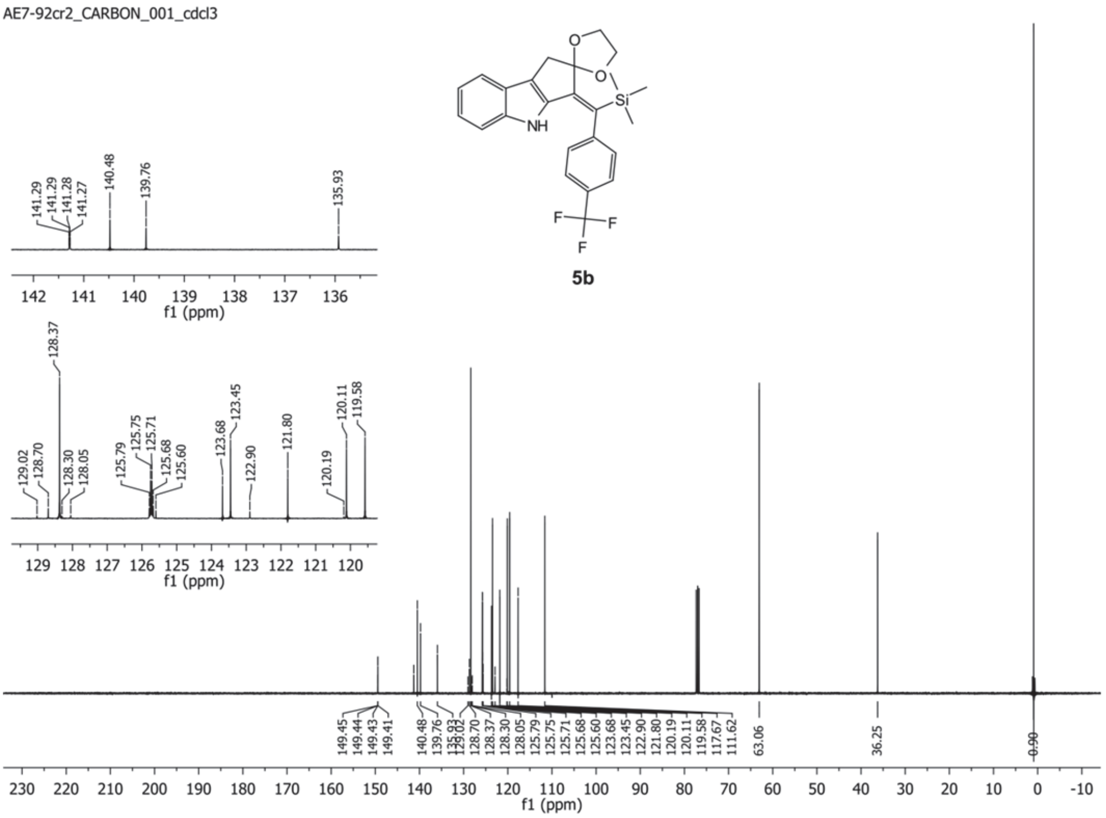
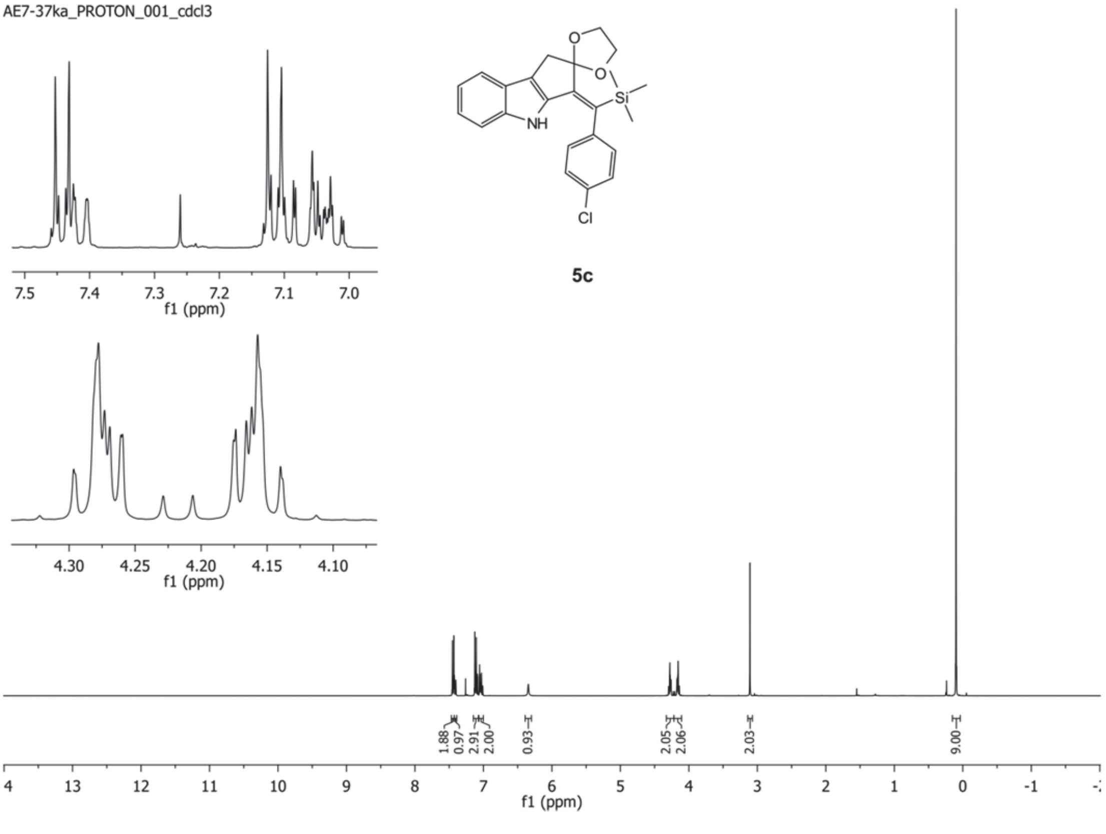
4. M. Roederer, *Curr Protoc Cytom*, 2002, **Chapter 1**, Unit 1 14.

3 NMR-spectra



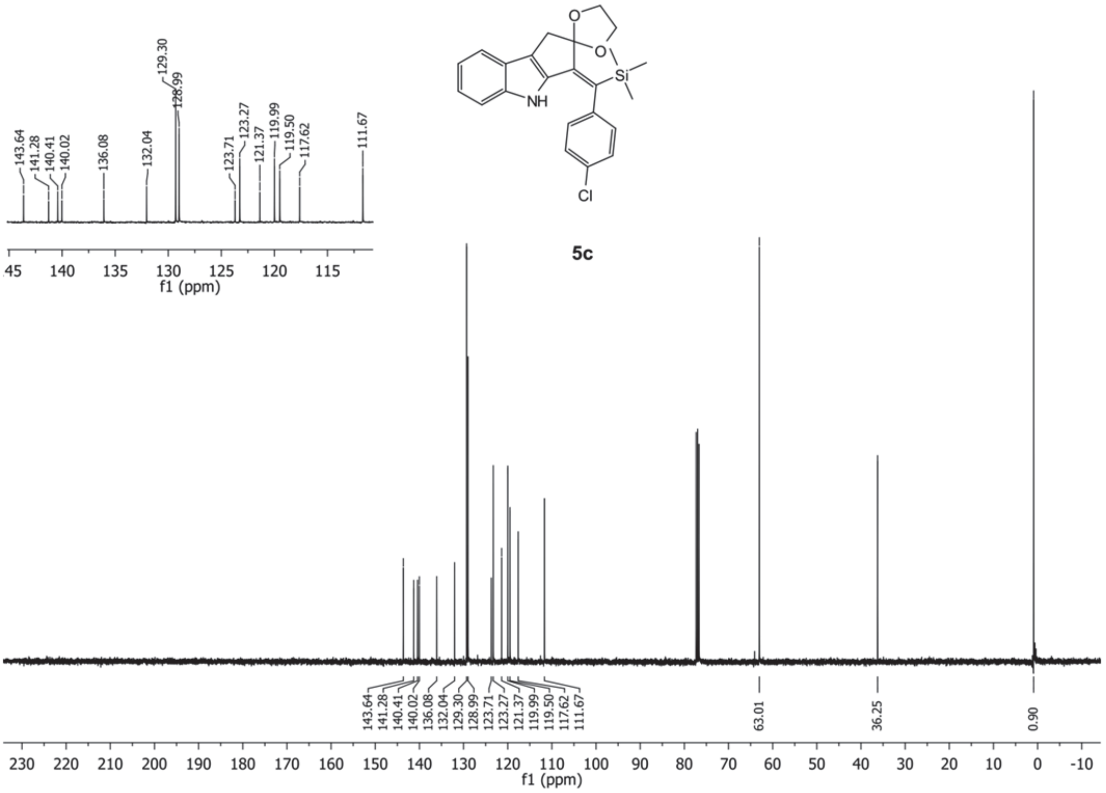

AE7-92cr2_CARBON_001_cdcl3
O
O
Si
NH
F
F
F
141.29
141.29
141.28
141.27
140.48
139.76
135.93
142 141 140 139 138 137 136
f1 (ppm)
129.02
128.70
128.37
128.30
128.05
125.79
125.75
125.71
125.68
125.60
123.68
123.45
122.90
121.80
120.19
120.11
119.58
129 128 127 126 125 124 123 122 121 120
f1 (ppm)
149.45
149.44
149.43
149.41
140.48
139.76
135.93
129.02
128.70
128.37
128.30
128.05
125.79
125.75
125.71
125.68
125.60
123.68
123.45
122.90
121.80
120.19
120.11
119.58
117.67
111.62
63.06
36.25
0.90
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

5b

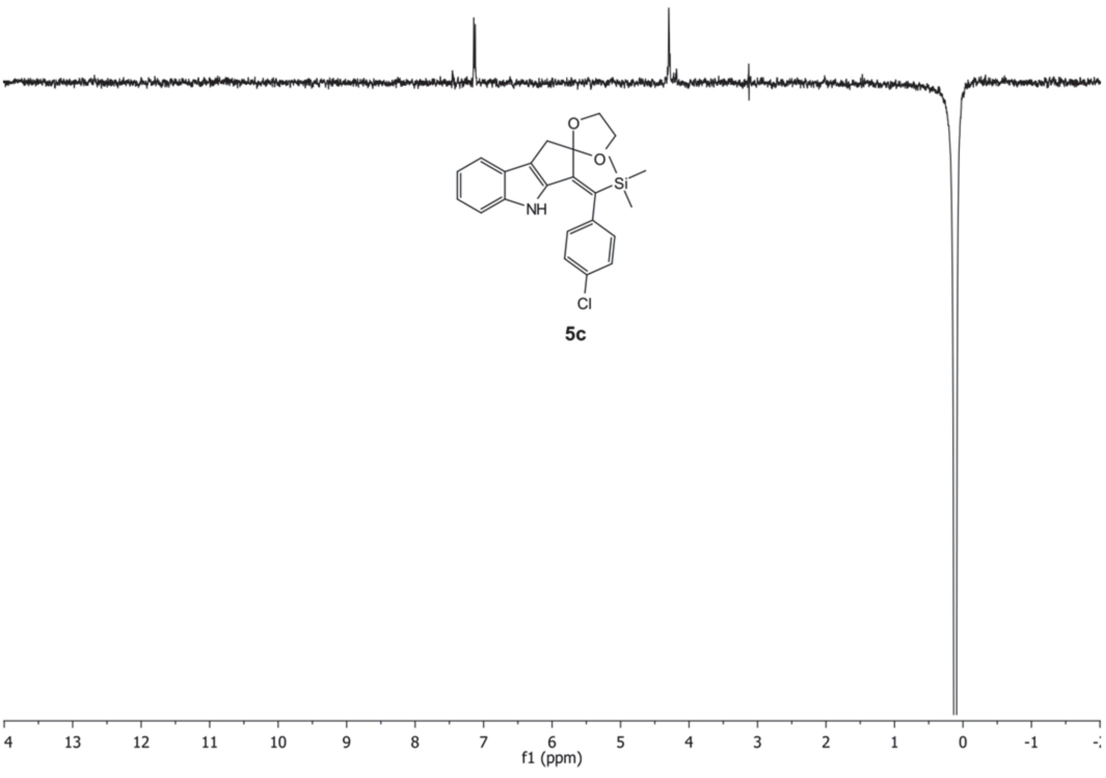

AE7-37ka_PROTON_001_cdcl3
O
O
Si
NH
Cl
7.5 7.4 7.3 7.2 7.1 7.0
f1 (ppm)
4.30 4.25 4.20 4.15 4.10
f1 (ppm)
1.88
0.97
2.91
2.00
0.93
2.05
2.06
2.03
9.00
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)

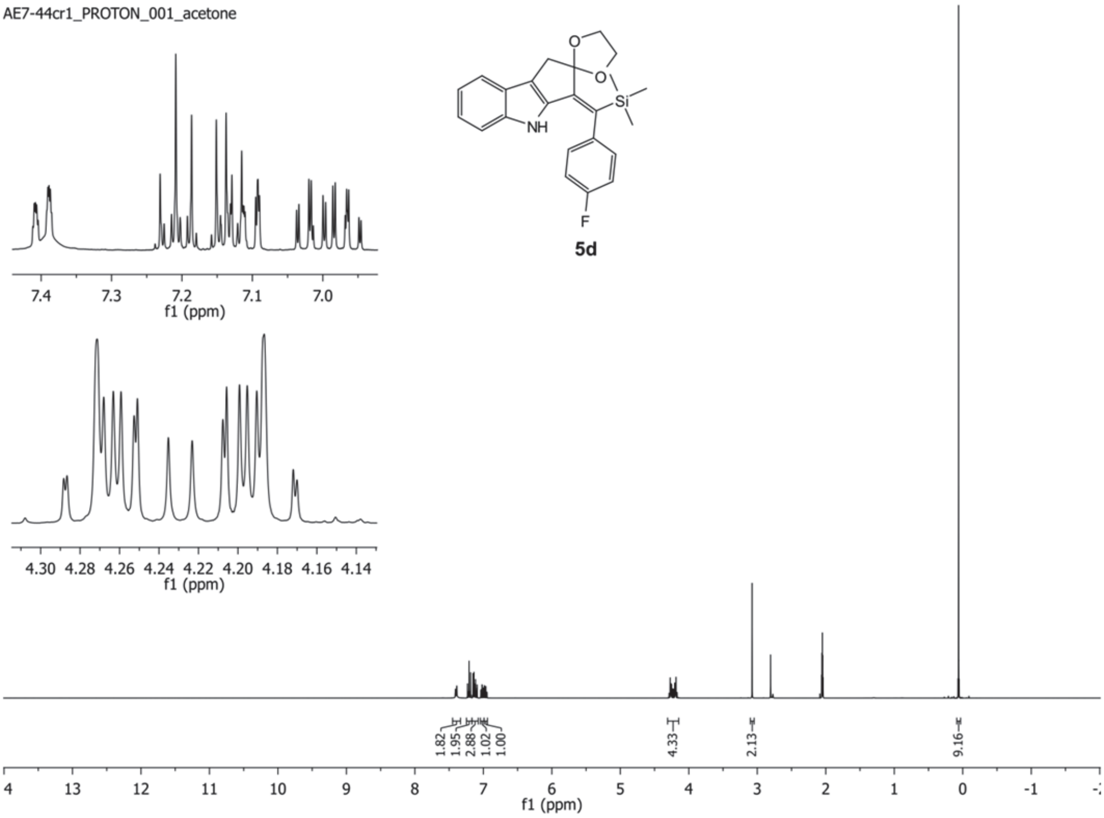
5c

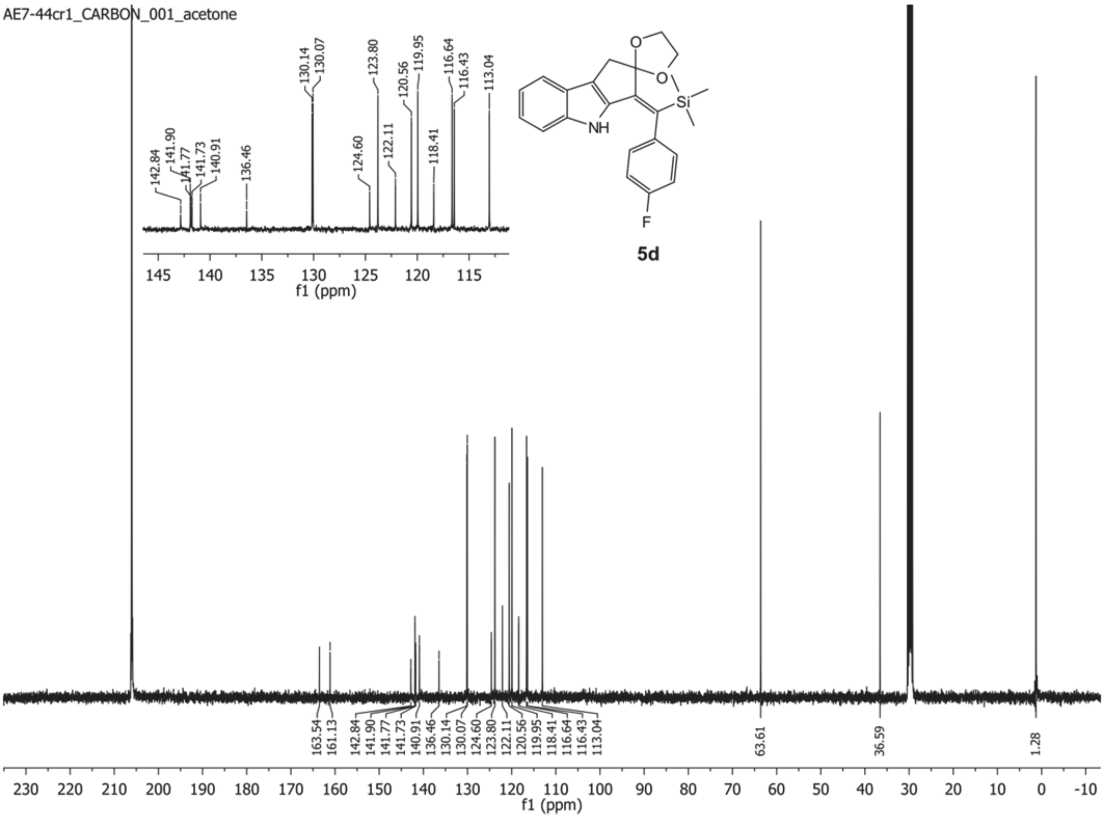
AE7-37ka_CARBON_001_cdcl3



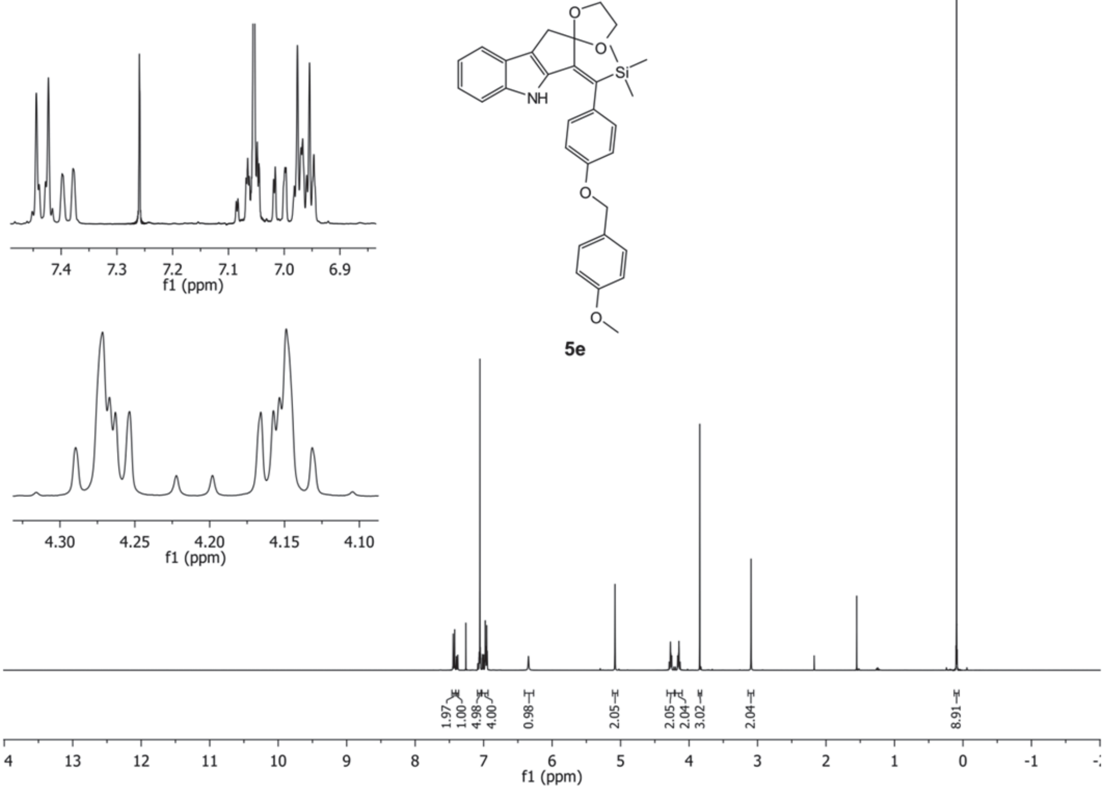
AE7-37ka_NOESY1D_001_cdcl3



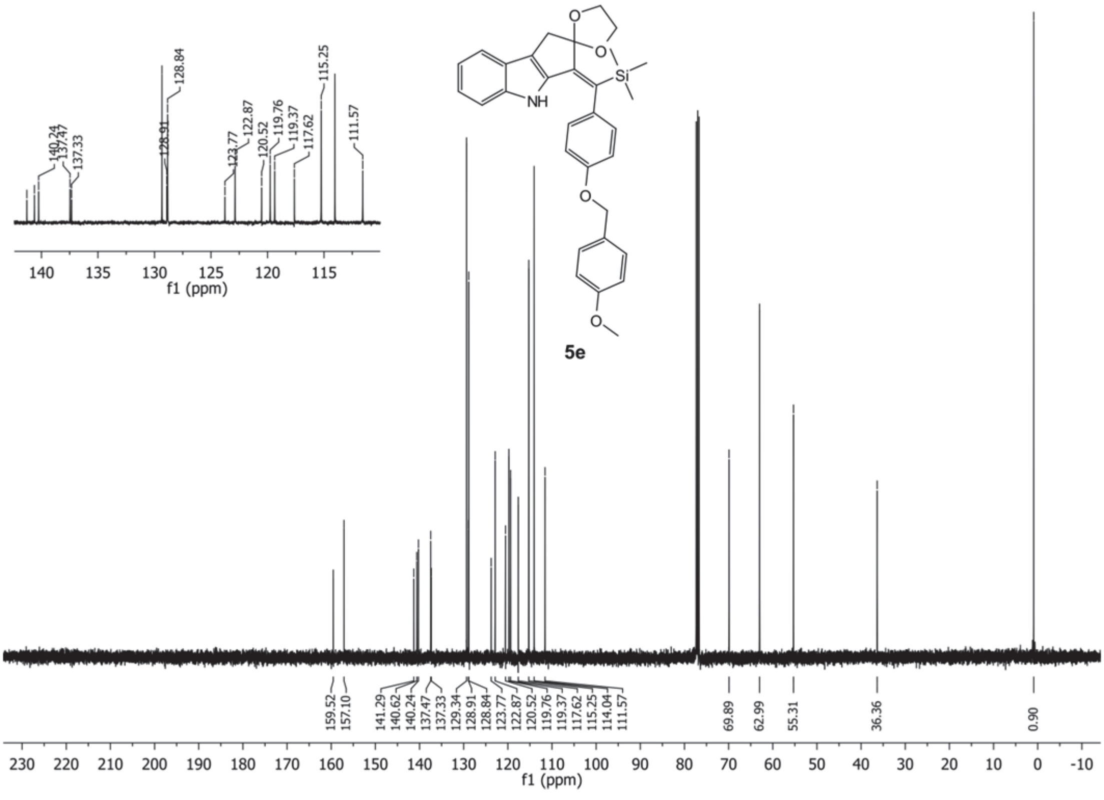

AE7-44cr1_PROTON_001_acetone
5d
NH
O
O
Si
F
7.4
7.3
7.2
7.1
7.0
f1 (ppm)
4.30 4.28 4.26 4.24 4.22 4.20 4.18 4.16 4.14
f1 (ppm)
1.82
1.95
2.88
1.02
1.00
4.33
2.13
9.16
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)


AE7-44cr1_CARBON_001_acetone
5d
NH
O
O
Si
F
142.84
141.90
141.77
141.73
140.91
136.46
130.14
130.07
124.60
123.80
122.11
120.56
119.95
118.41
116.64
116.43
113.04
145 140 135 130 125 120 115
f1 (ppm)
163.54
161.13
142.84
141.90
141.77
141.73
140.91
136.46
130.14
130.07
124.60
123.80
122.11
120.56
119.95
118.41
116.64
116.43
113.04
63.61
36.59
1.28
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

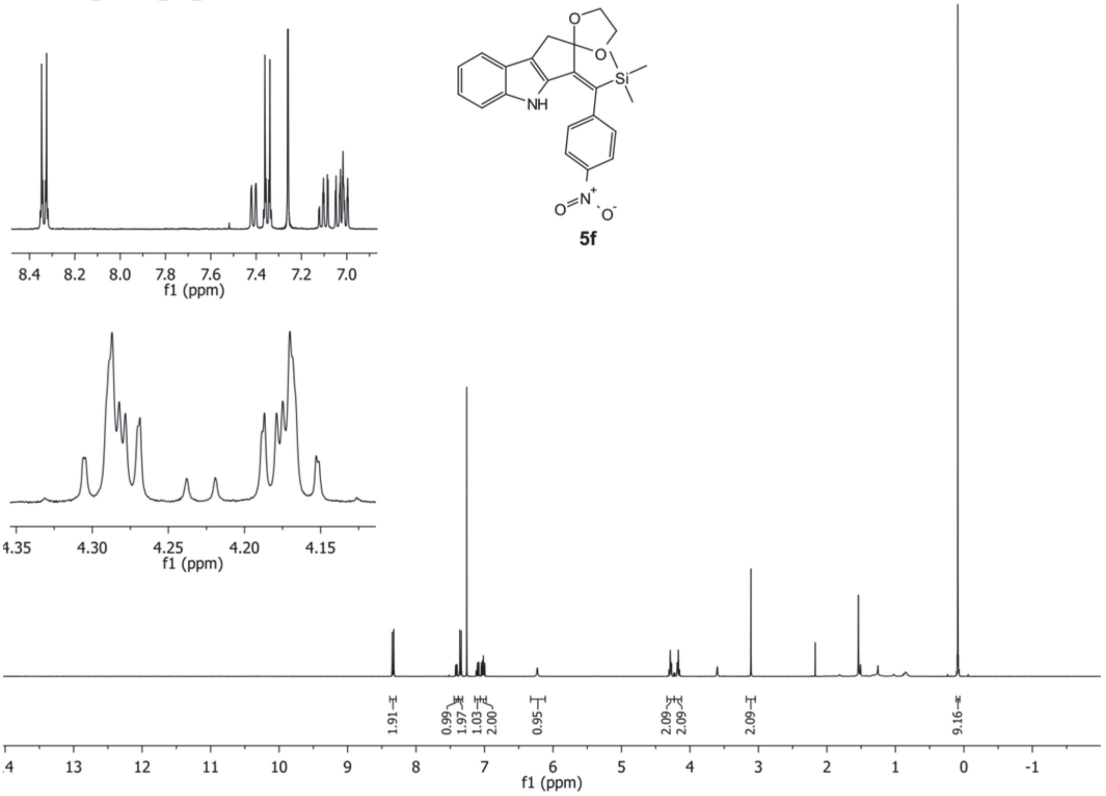
AE7-74cr1_PROTON_001_cdcl3



AE7-74cr1_CARBON_001_cdcl3

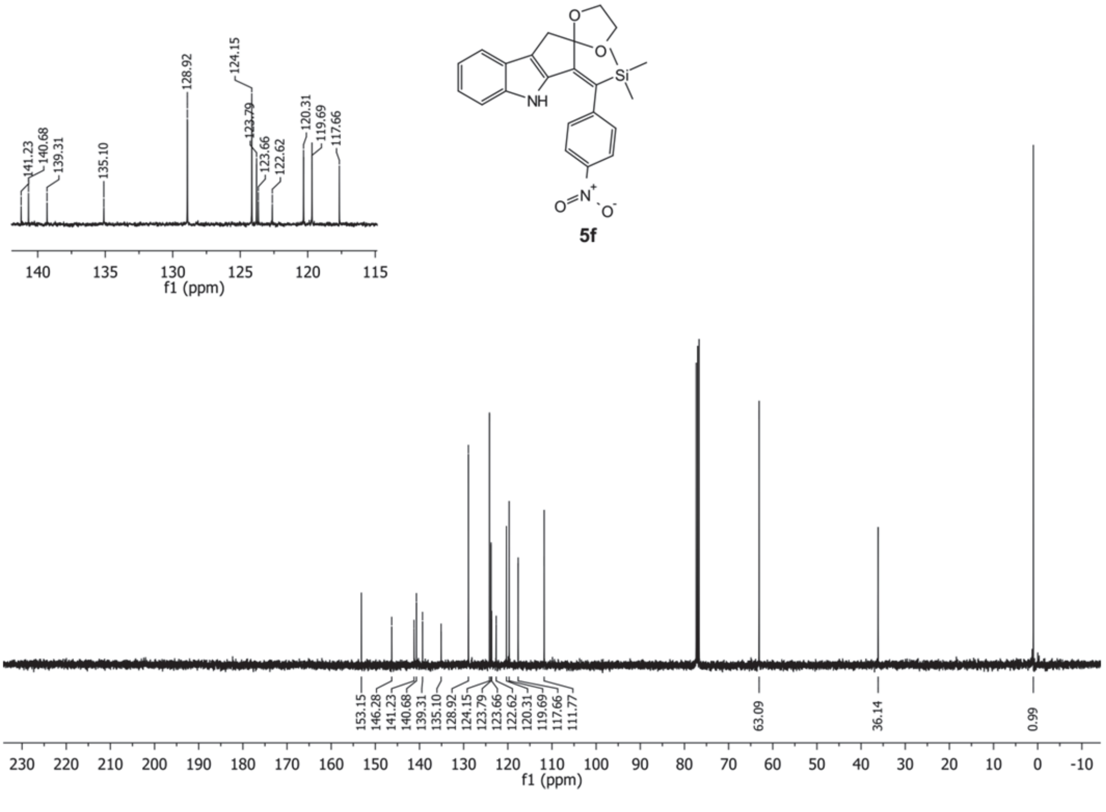


AE7-THSNO2_PROTON_001_cdcl3

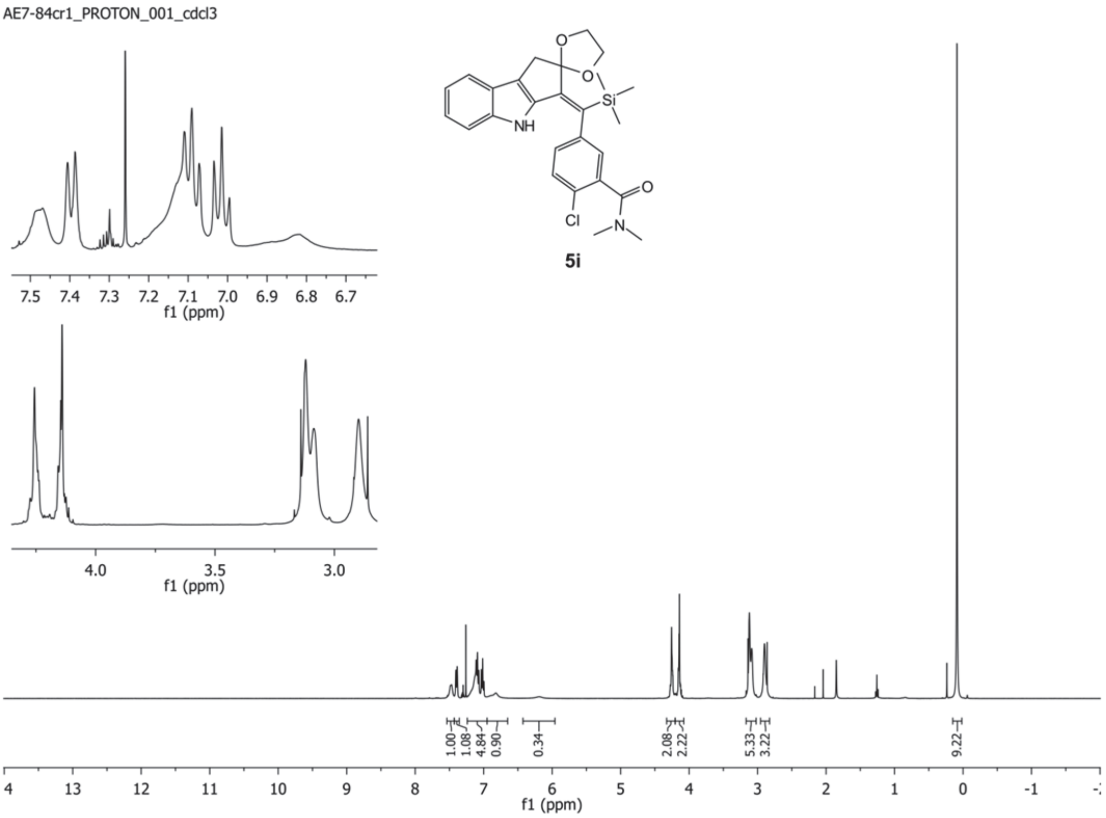


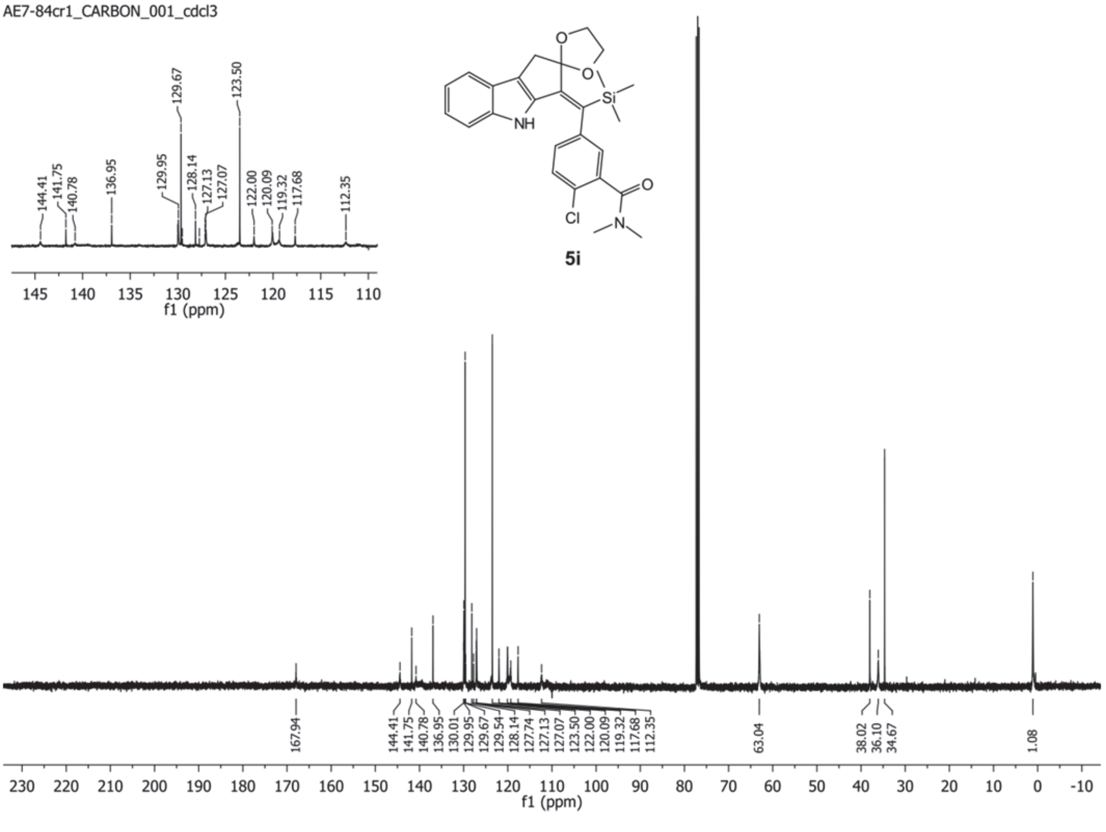
5f

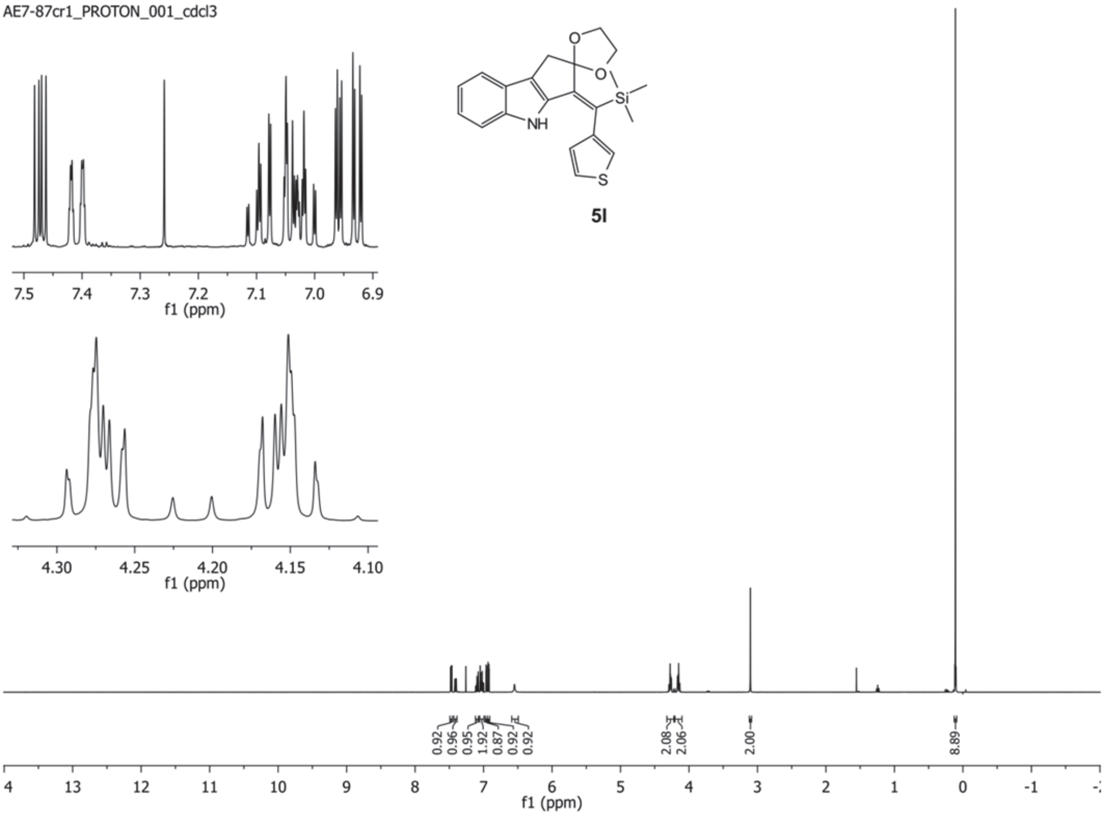
AE7-56cr1_CARBON_001_cdcl3

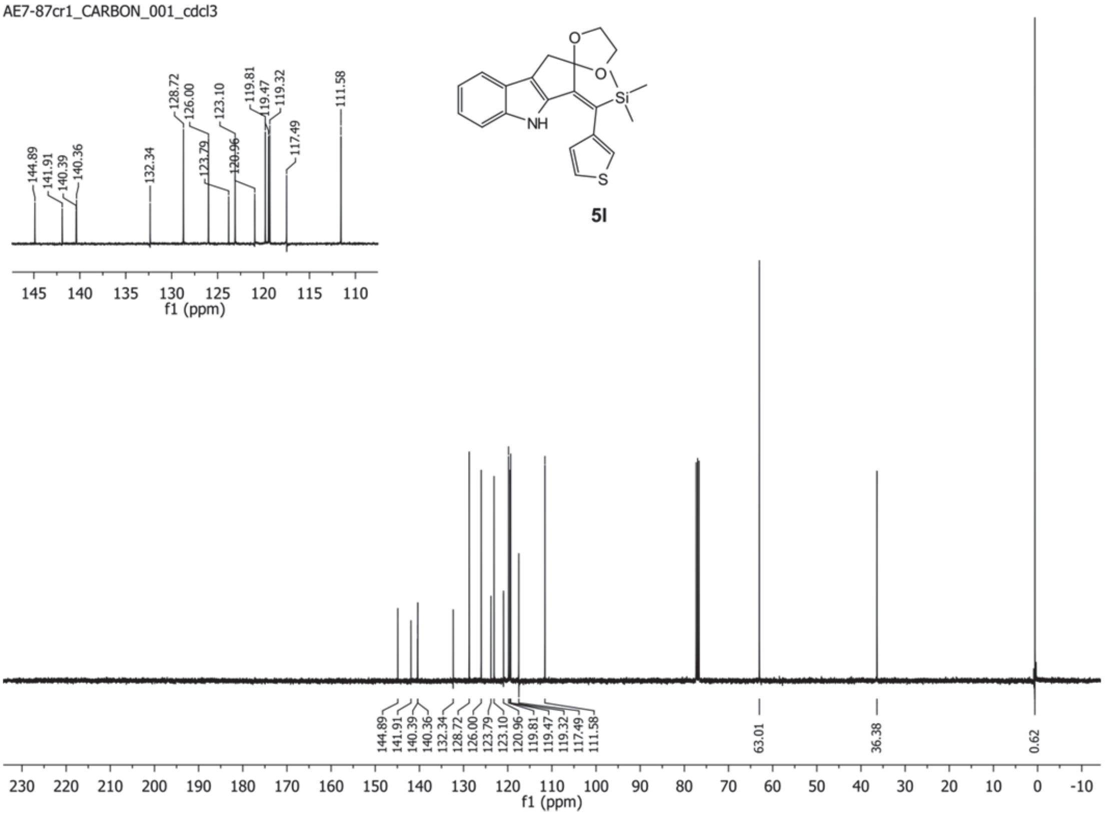


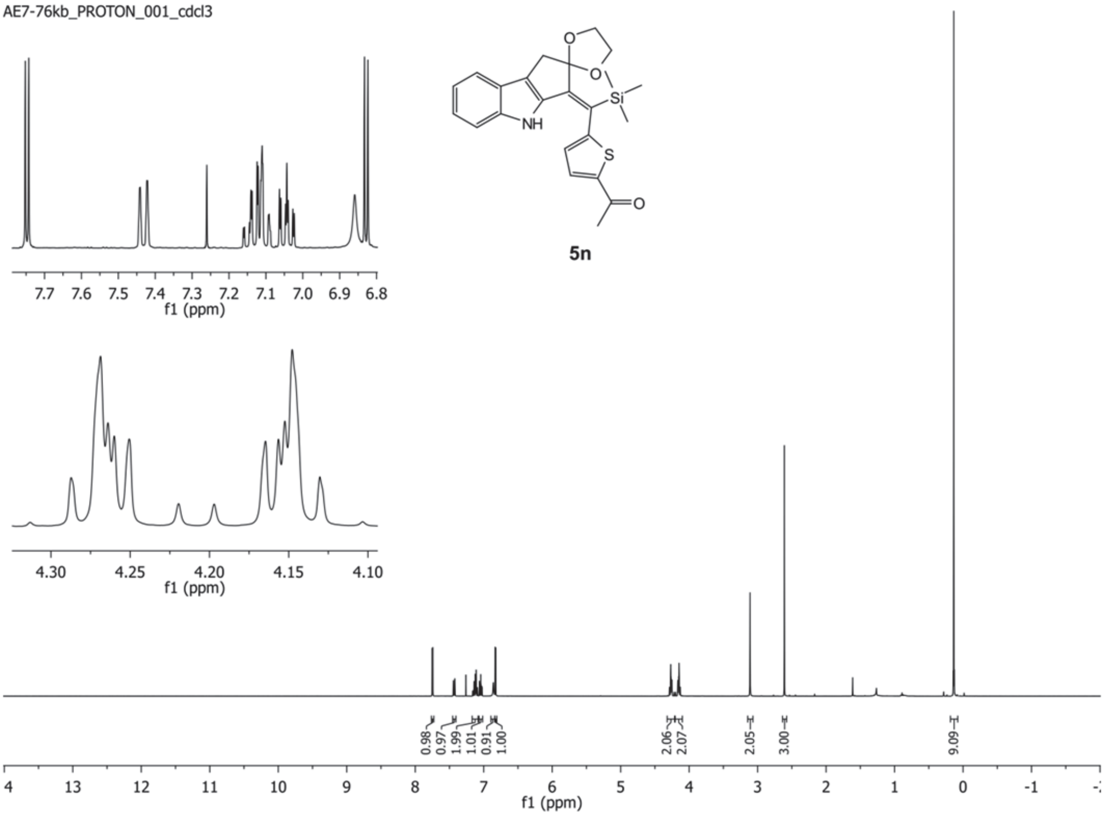
5f

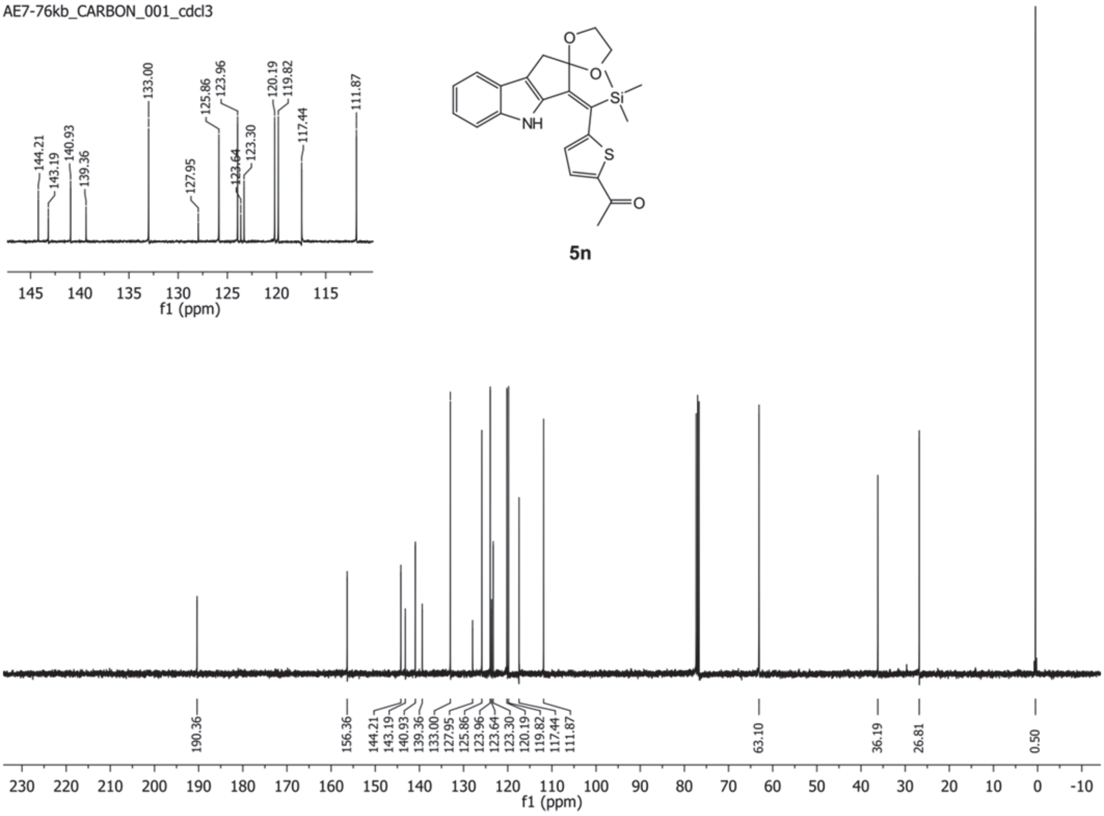

AE7-84cr1_PROTON_001_cdcl3
O
O
Si
NH
O
N
Cl
5i
7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7
f1 (ppm)
4.0 3.5 3.0
f1 (ppm)
1.00
1.08
4.84
0.90
0.34
2.08
2.22
5.33
3.22
9.22
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)

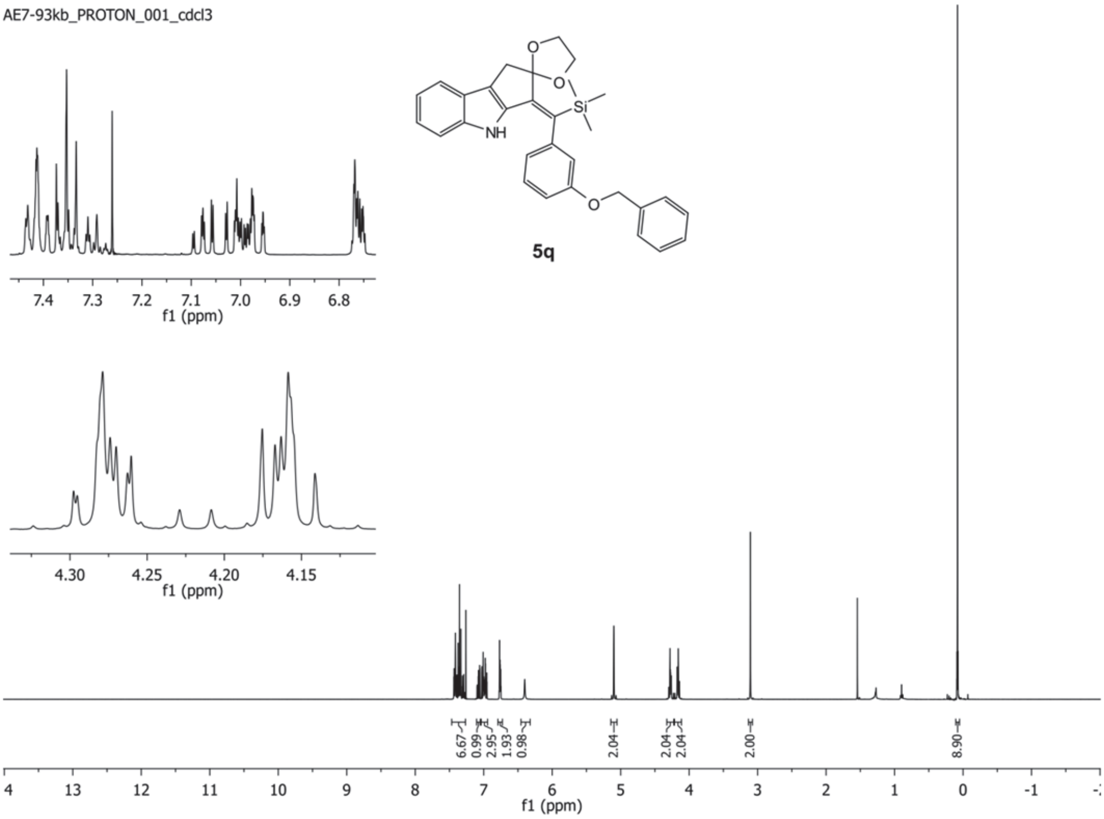

AE7-84cr1_CARBON_001_cdcl3
O
O
Si
NH
O
N
Cl
5i
144.41
141.75
140.78
136.95
129.95
129.67
128.14
127.13
127.07
123.50
122.00
120.09
119.32
117.68
112.35
145 140 135 130 125 120 115 110
f1 (ppm)
167.94
144.41
141.75
140.78
136.95
130.01
129.95
129.67
129.54
128.14
127.74
127.13
127.07
123.50
122.00
120.09
119.32
117.68
112.35
63.04
38.02
36.10
34.67
1.08
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

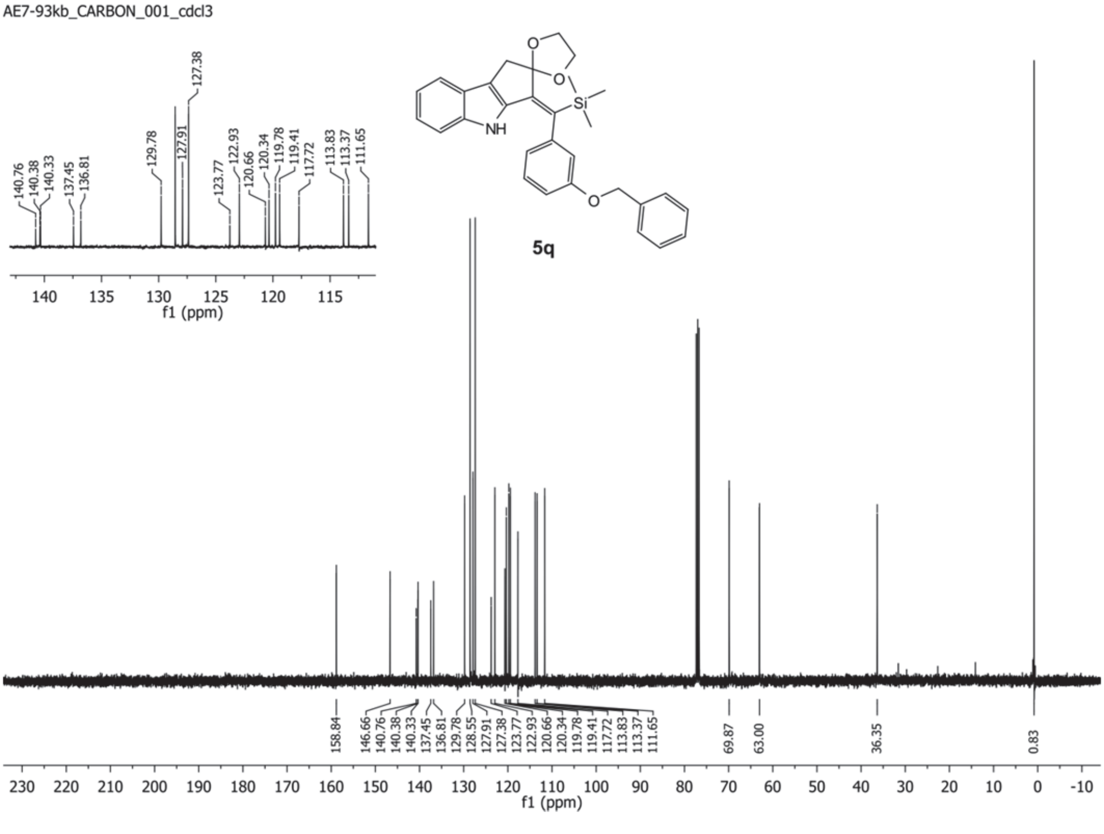

AE7-87cr1_PROTON_001_cdcl3
NH
O
O
Si
S
5l
7.5 7.4 7.3 7.2 7.1 7.0 6.9
f1 (ppm)
4.30 4.25 4.20 4.15 4.10
f1 (ppm)
0.92
0.96
0.95
1.92
0.87
0.92
0.92
2.08
2.06
2.00
8.89
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)


AE7-87cr1_CARBON_001_cdcl3
NH
O
O
Si
S
5l
144.89
141.91
140.39
140.36
132.34
128.72
126.00
123.79
123.10
120.96
119.81
119.47
119.32
117.49
111.58
145 140 135 130 125 120 115 110
f1 (ppm)
63.01
36.38
0.62
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

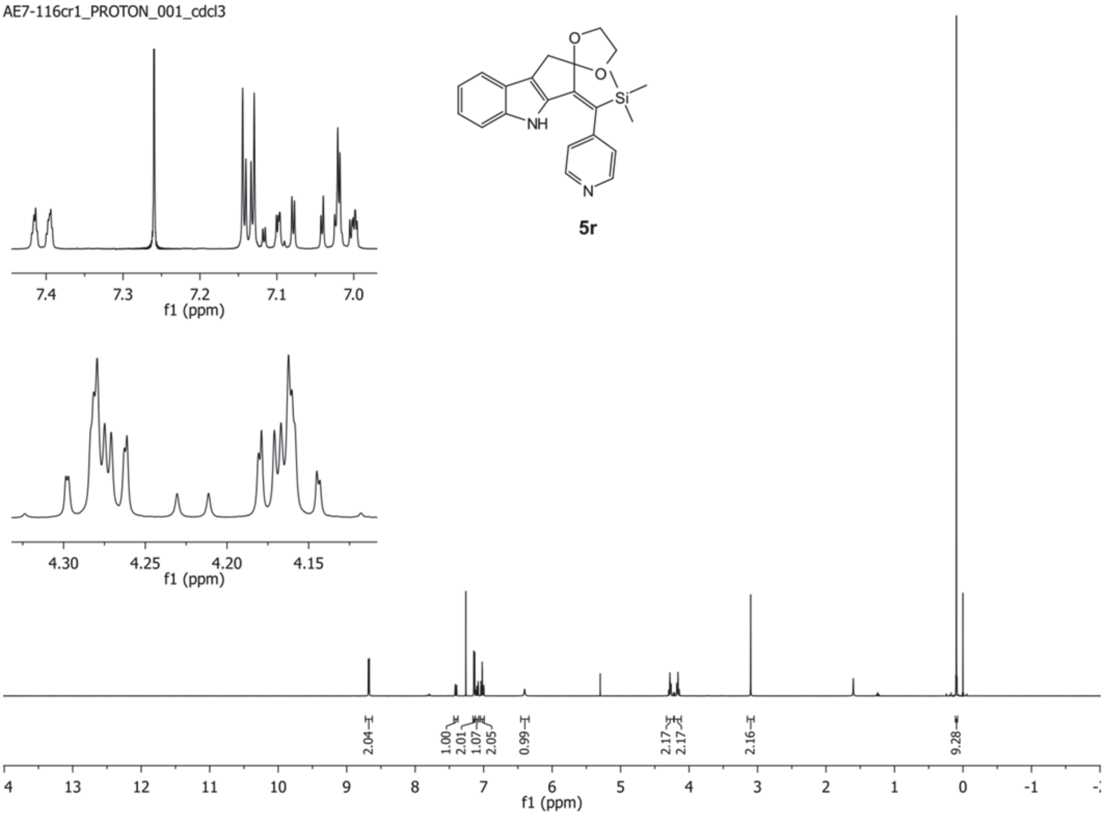

AE7-76kb_PROTON_001_cdcl3
5n
NH
O
O
Si
S
O
7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8
f1 (ppm)
4.30 4.25 4.20 4.15 4.10
f1 (ppm)
0.98 0.97 1.99 1.01 0.91 1.00
2.06 2.07
2.05
3.00
9.09
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)


AE7-76kb_CARBON_001_cdcl3
5n
NH
O
O
Si
S
O
144.21
143.19
140.93
139.36
133.00
127.95
125.86
123.96
123.64
123.30
120.19
119.82
117.44
111.87
145 140 135 130 125 120 115
f1 (ppm)
190.36
156.36
144.21
143.19
140.93
139.36
133.00
127.95
125.86
123.96
123.64
123.30
120.19
119.82
117.44
111.87
63.10
36.19
26.81
0.50
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

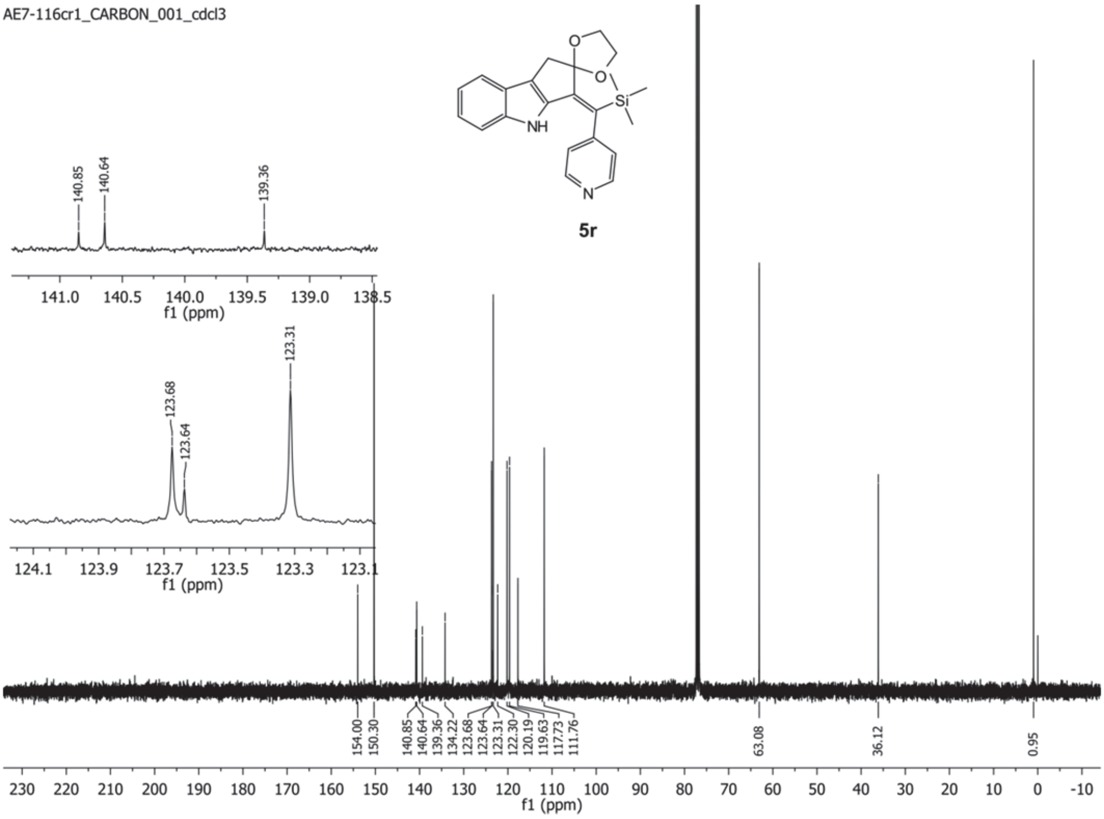

AE7-93kb_PROTON_001_cdcl3
5q
O
O
Si
NH
O
7.4
7.3
7.2
7.1
7.0
6.9
6.8
f1 (ppm)
4.30
4.25
4.20
4.15
f1 (ppm)
6.67
0.99
2.95
1.93
0.98
2.04
2.04
2.04
2.00
8.90
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

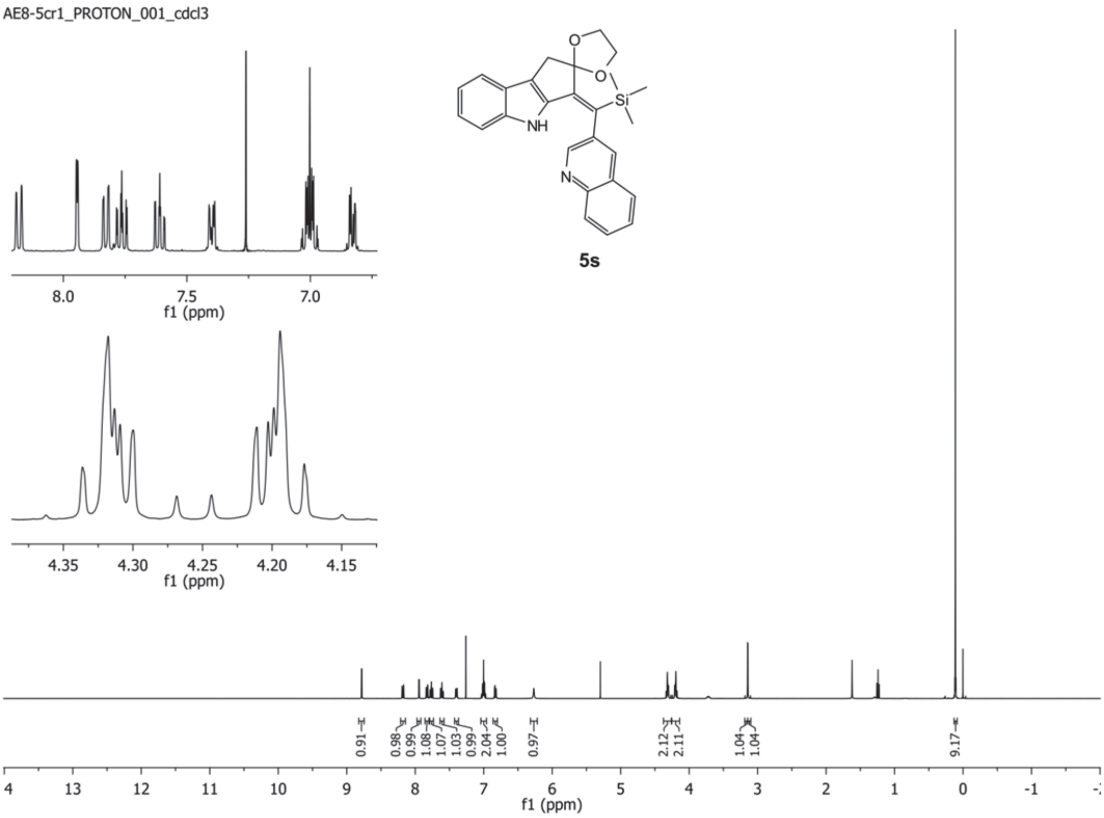

AE7-93kb_CARBON_001_cdcl3
5q
O
O
Si
NH
O
140.76
140.38
140.33
137.45
136.81
129.78
127.91
127.38
123.77
122.93
120.66
120.34
119.78
119.41
117.72
113.83
113.37
111.65
140
135
130
125
120
115
f1 (ppm)
158.84
146.66
140.76
140.38
140.33
137.45
136.81
129.78
128.55
127.91
127.38
123.77
122.93
120.66
120.34
119.78
119.41
117.72
113.83
113.37
111.65
69.87
63.00
36.35
0.83
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

AE7-116cr1_PROTON_001_cdcl3

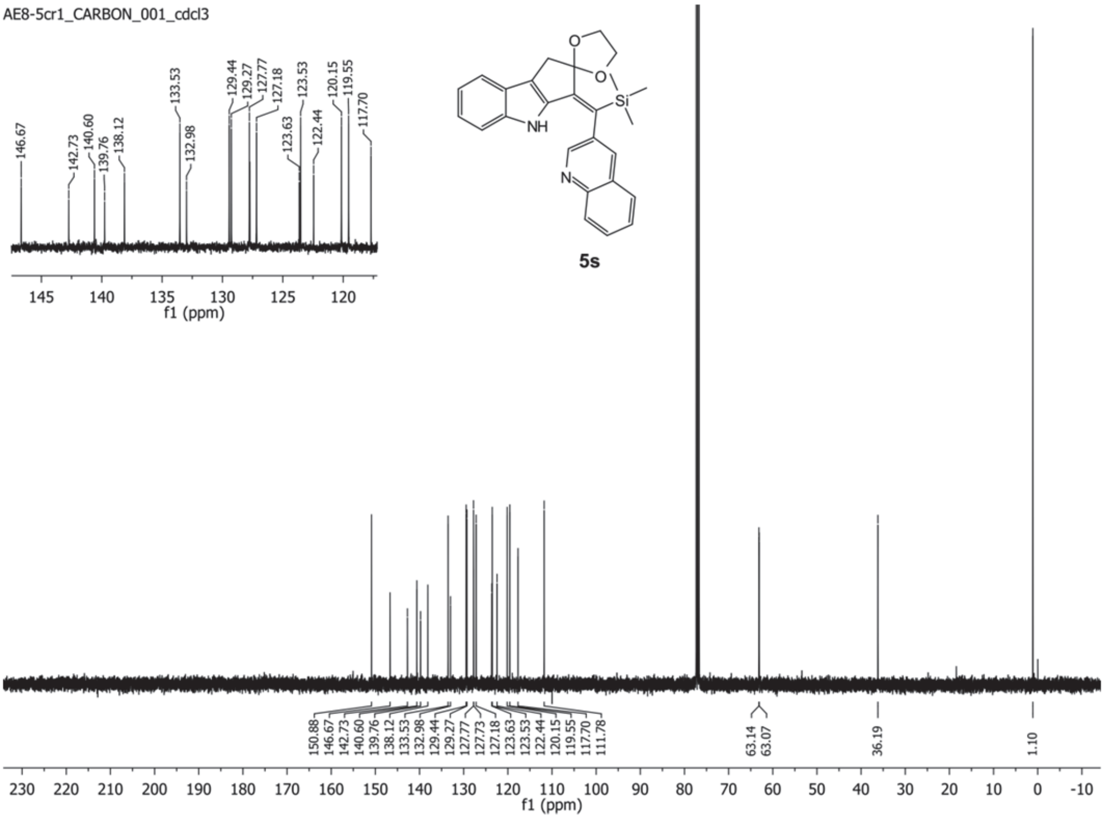


AE7-116cr1_CARBON_001_cdcl3

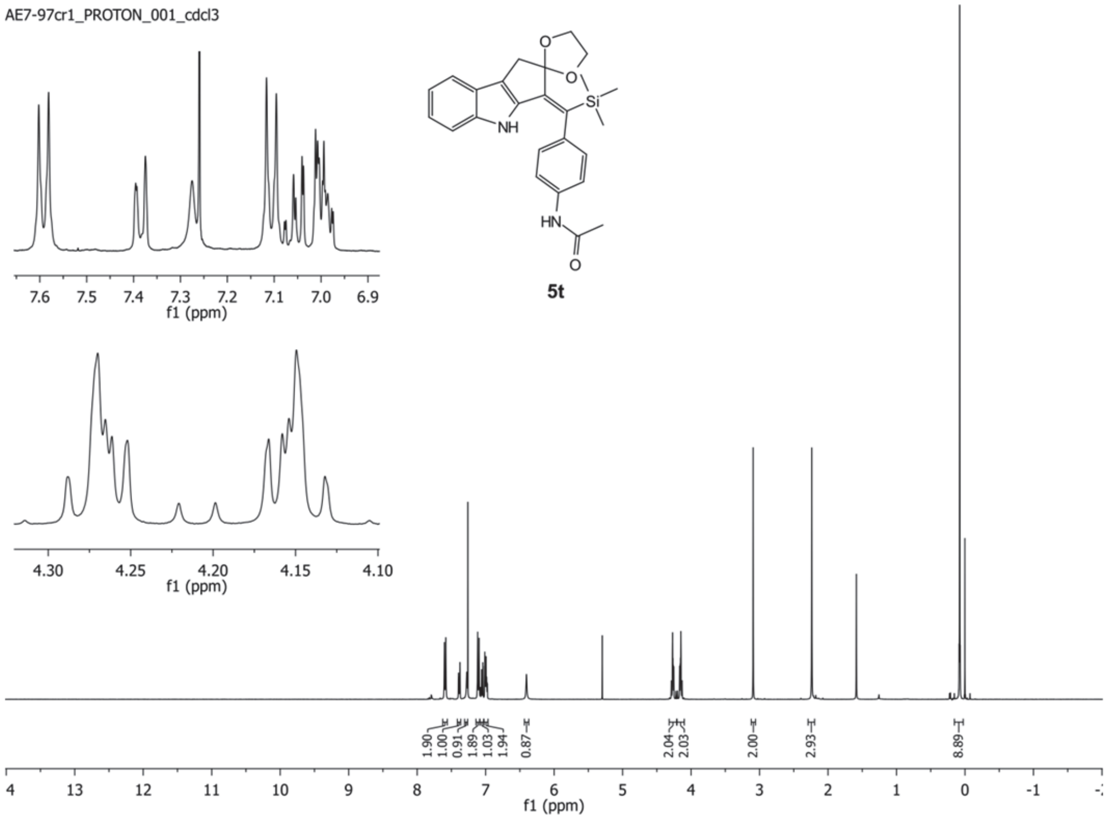


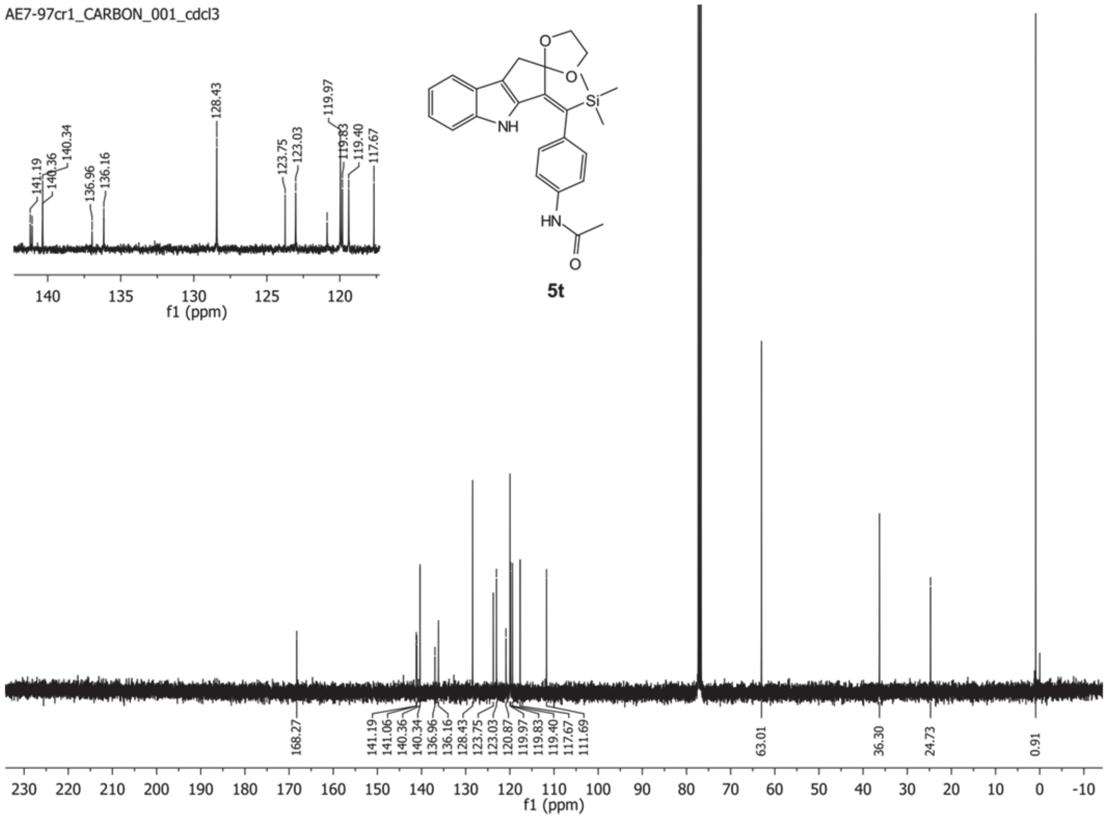

AE8-5cr1_PROTON_001_cdcl3
O
O
Si
NH
N
8.0
7.5
7.0
f1 (ppm)
4.35
4.30
4.25
4.20
4.15
f1 (ppm)
0.91
0.98
0.99
1.08
1.07
1.03
0.99
2.04
1.00
0.97
2.12
2.11
1.04
1.04
9.17
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

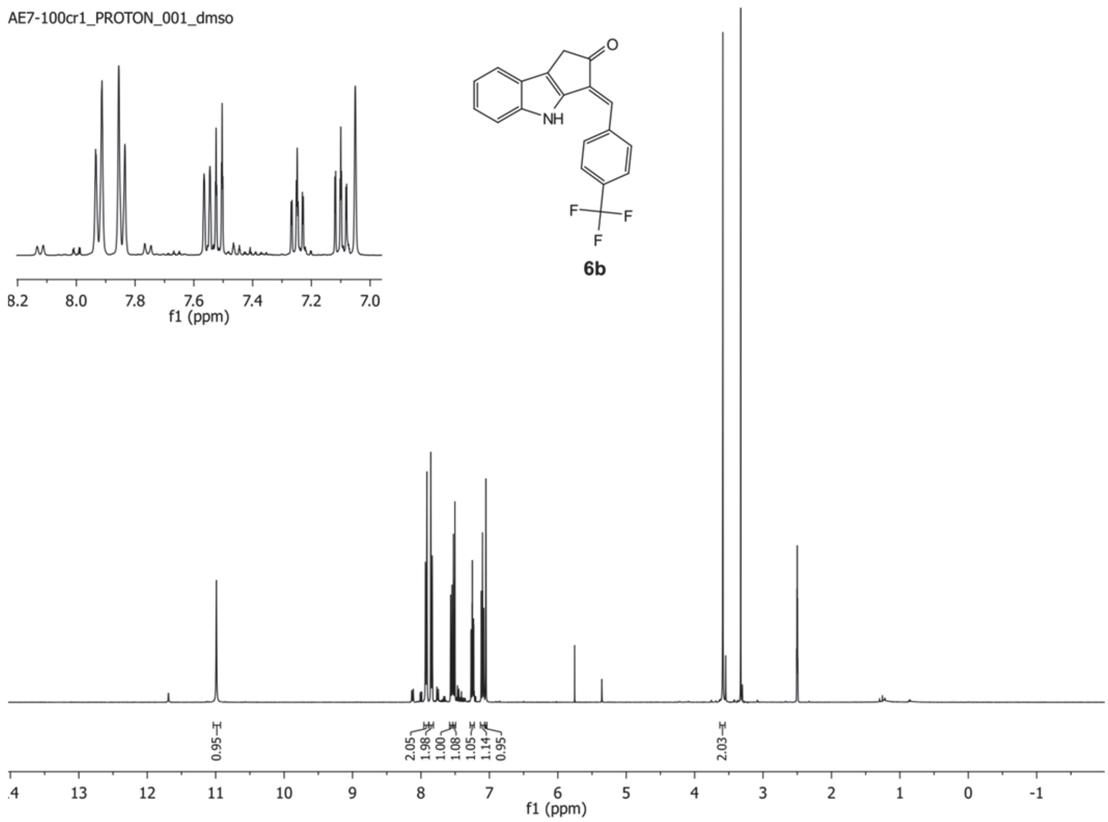
5s


AE8-5cr1_CARBON_001_cdcl3
146.67
142.73
140.60
139.76
138.12
133.53
132.98
129.44
129.27
127.77
127.18
123.63
123.53
122.44
120.15
119.55
117.70
145
140
135
130
125
120
f1 (ppm)
O
O
Si
NH
N
150.88
146.67
142.73
140.60
139.76
138.12
133.53
132.98
129.44
129.27
127.77
127.73
127.18
123.63
123.53
122.44
120.15
119.55
117.70
111.78
63.14
63.07
36.19
1.10
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

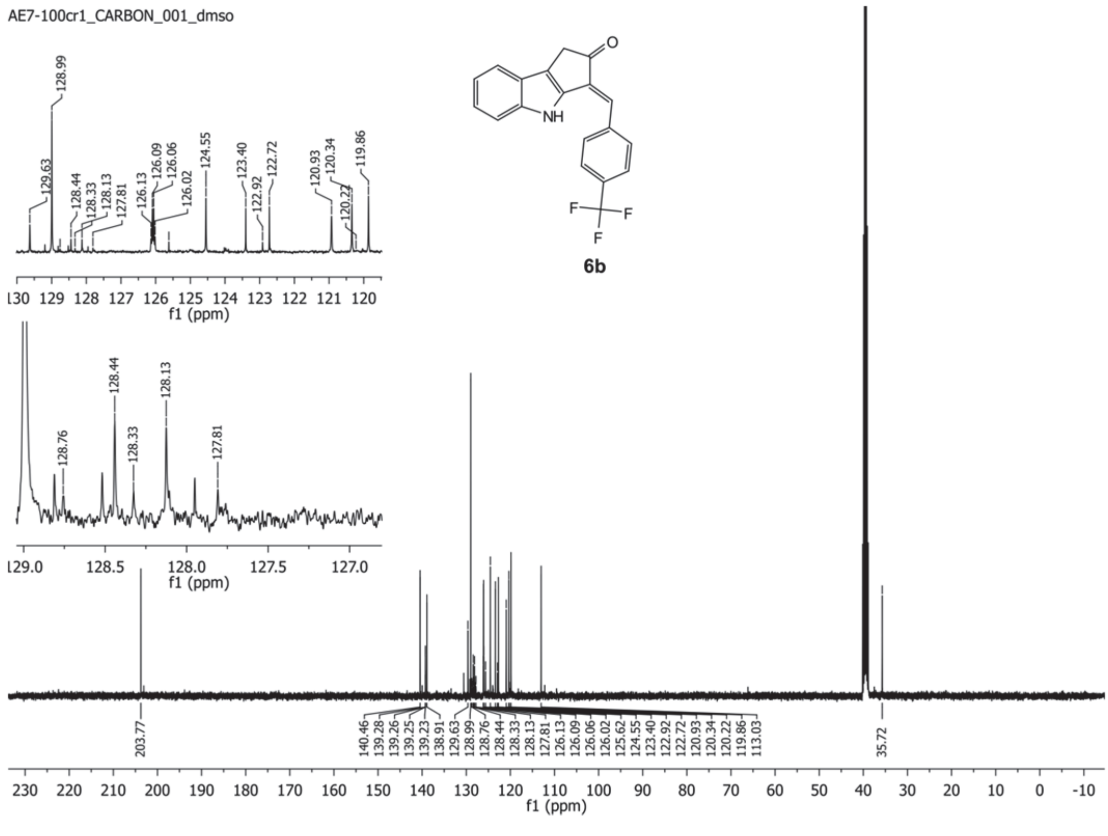
5s


AE7-97cr1_PROTON_001_cdcl3
5t
NH
O
O
Si
HN
O
7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9
f1 (ppm)
4.30 4.25 4.20 4.15 4.10
f1 (ppm)
1.90 1.00 0.91 1.89 1.03 1.94 0.87 2.04 2.03 2.00 2.93 8.89
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)

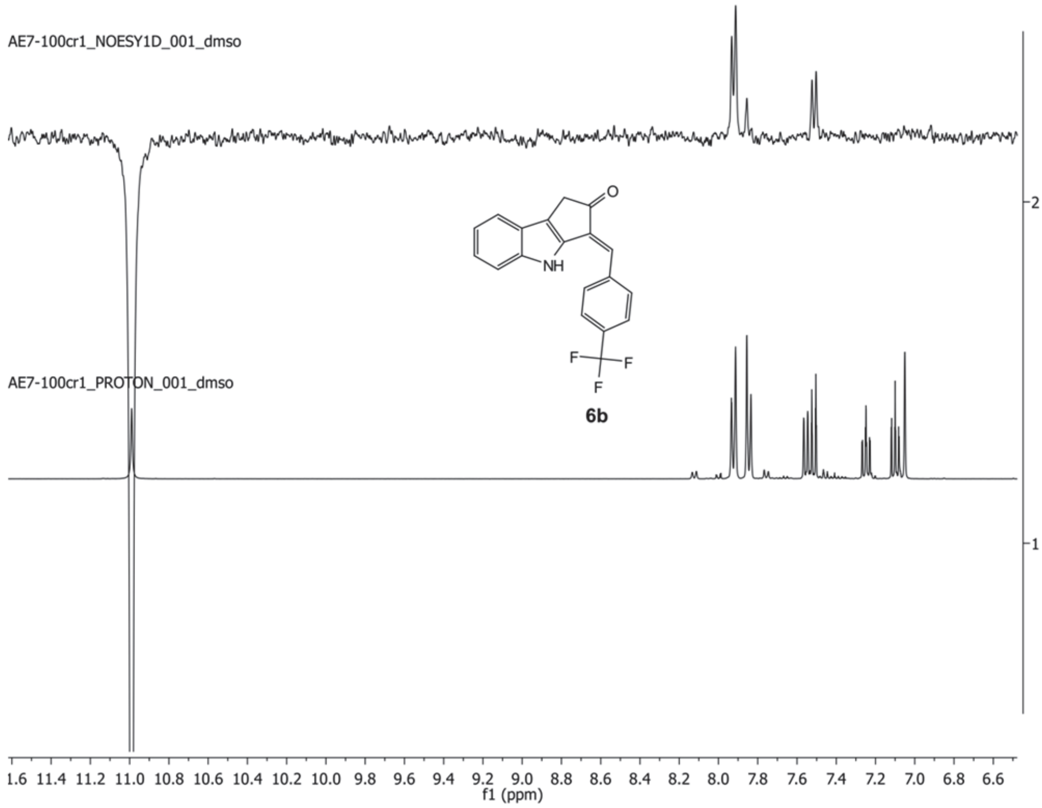

AE7-97cr1_CARBON_001_cdcl3
5t
NH
O
O
Si
HN
O
141.19
140.36
140.34
136.96
136.16
128.43
123.75
123.03
119.97
119.83
119.40
117.67
140 135 130 125 120
f1 (ppm)
168.27
141.19 141.06 140.36 140.34 136.96 136.16 128.43 123.75 123.03 120.87 119.97 119.83 119.40 117.67 111.69
63.01
36.30
24.73
0.91
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

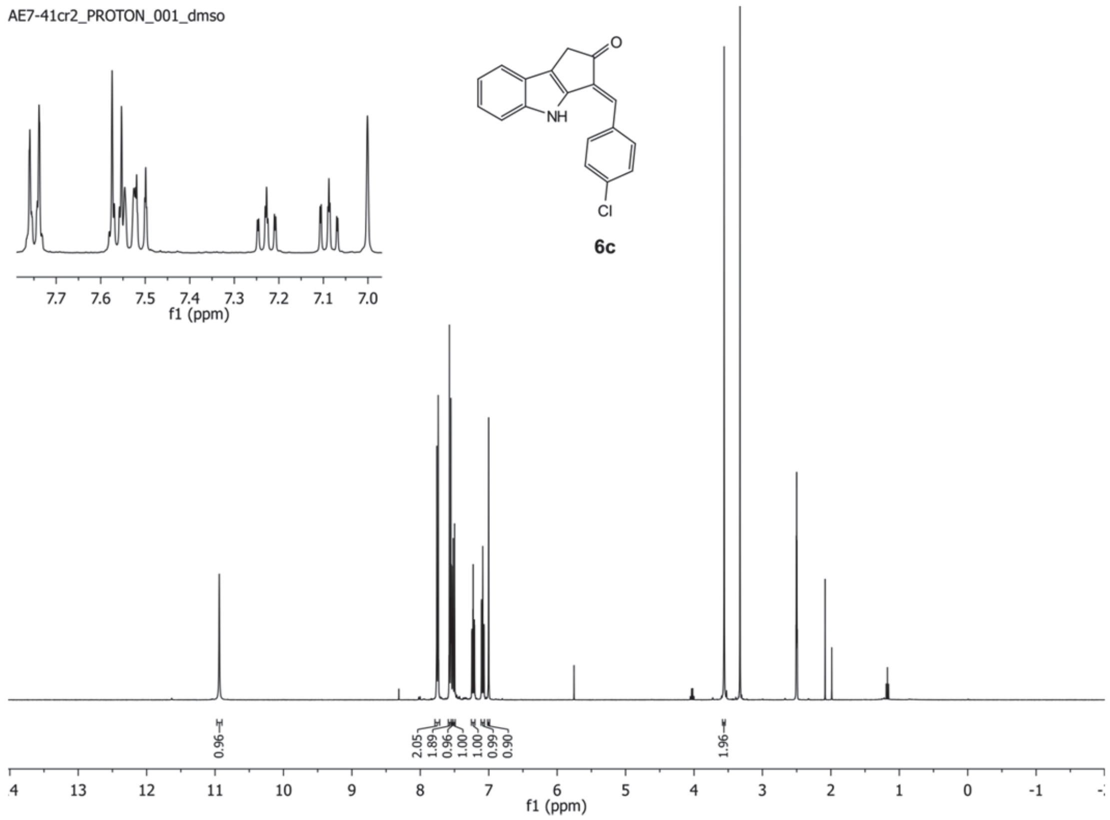

AE7-100cr1_PROTON_001_dmso
NH
O
F
F
F
8.2 8.0 7.8 7.6 7.4 7.2 7.0
f1 (ppm)
0.95
2.05
1.98
1.00
1.08
1.05
1.14
0.95
2.03
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)

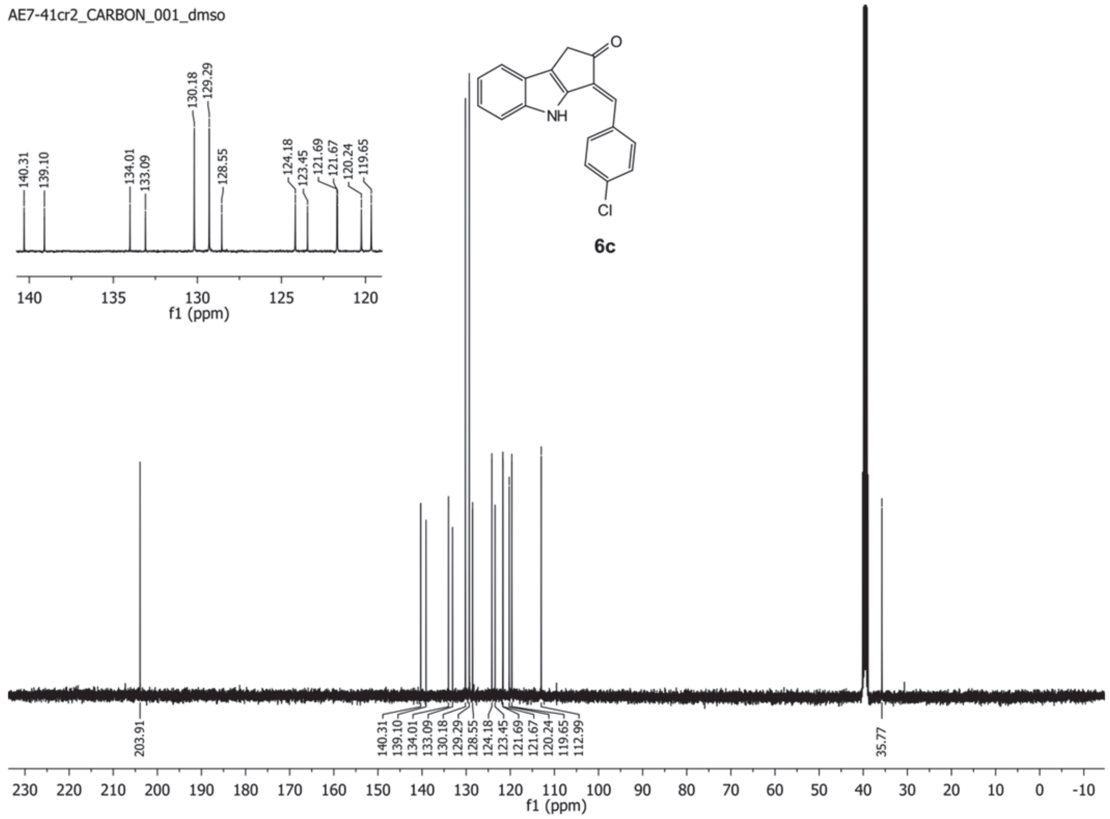
6b

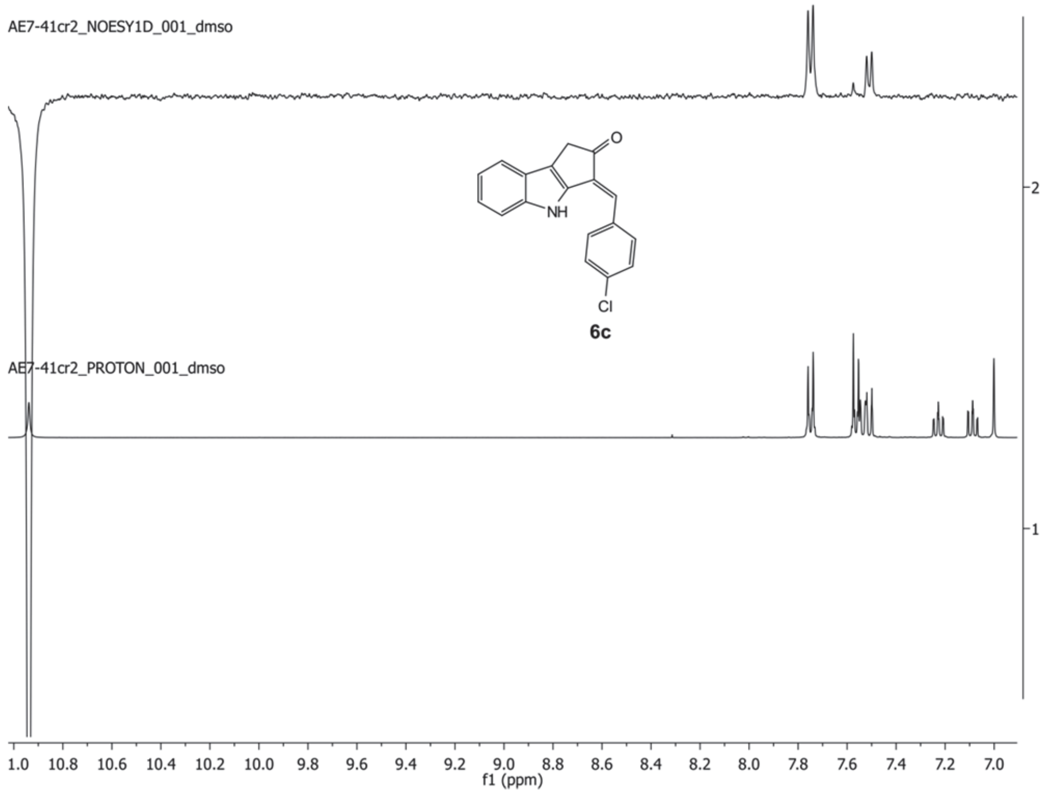

AE7-100cr1_CARBON_001_dmso
NH
O
F
F
F
129.63
128.99
128.44
128.33
128.13
127.81
126.13
126.09
126.06
126.02
124.55
123.40
122.92
122.72
120.93
120.34
120.22
119.86
130 129 128 127 126 125 124 123 122 121 120
f1 (ppm)
128.76
128.44
128.33
128.13
127.81
129.0 128.5 128.0 127.5 127.0
f1 (ppm)
203.77
140.46
139.28
139.26
139.25
139.23
138.91
129.63
128.99
128.76
128.44
128.33
128.13
127.81
126.13
126.09
126.06
126.02
125.62
124.55
123.40
122.92
122.72
120.93
120.34
120.22
119.86
113.03
35.72
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

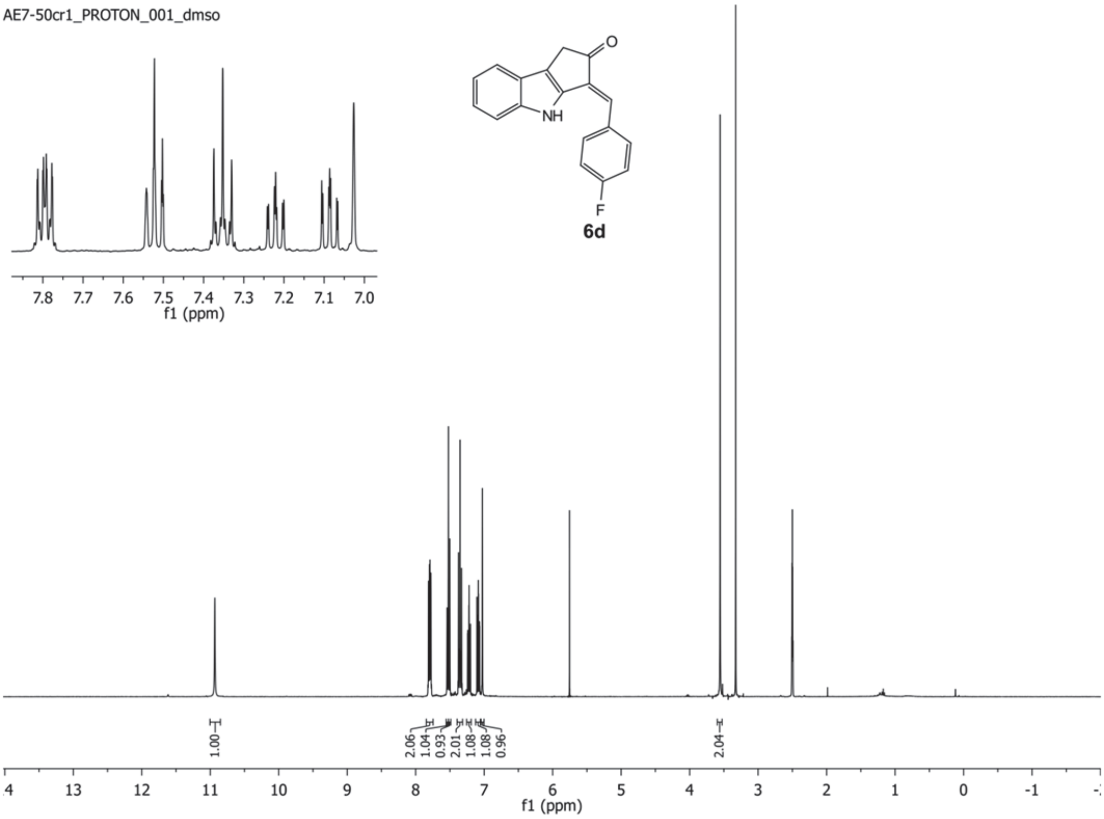
6b

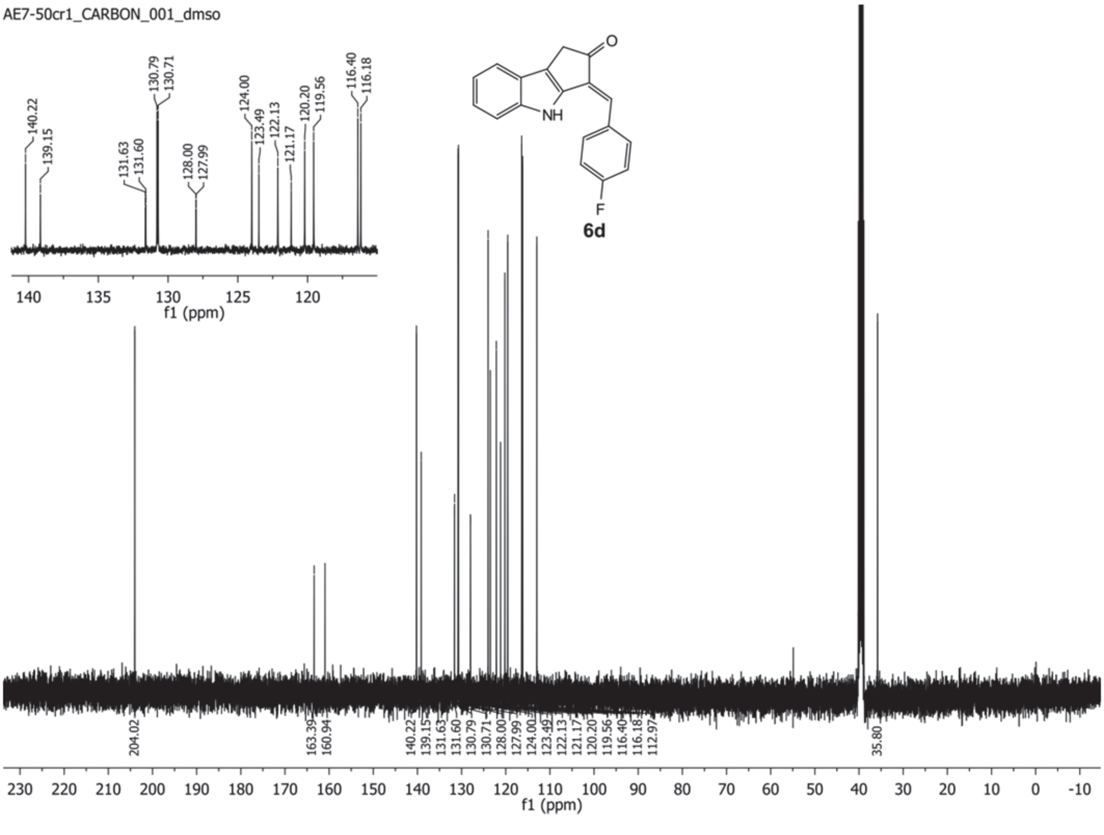

AE7-100cr1_NOESY1D_001_dmso
AE7-100cr1_PROTON_001_dmso
O
NH
F
F
F
6b
2
1
1.6 11.4 11.2 11.0 10.8 10.6 10.4 10.2 10.0 9.8 9.6 9.4 9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6
f1 (ppm)

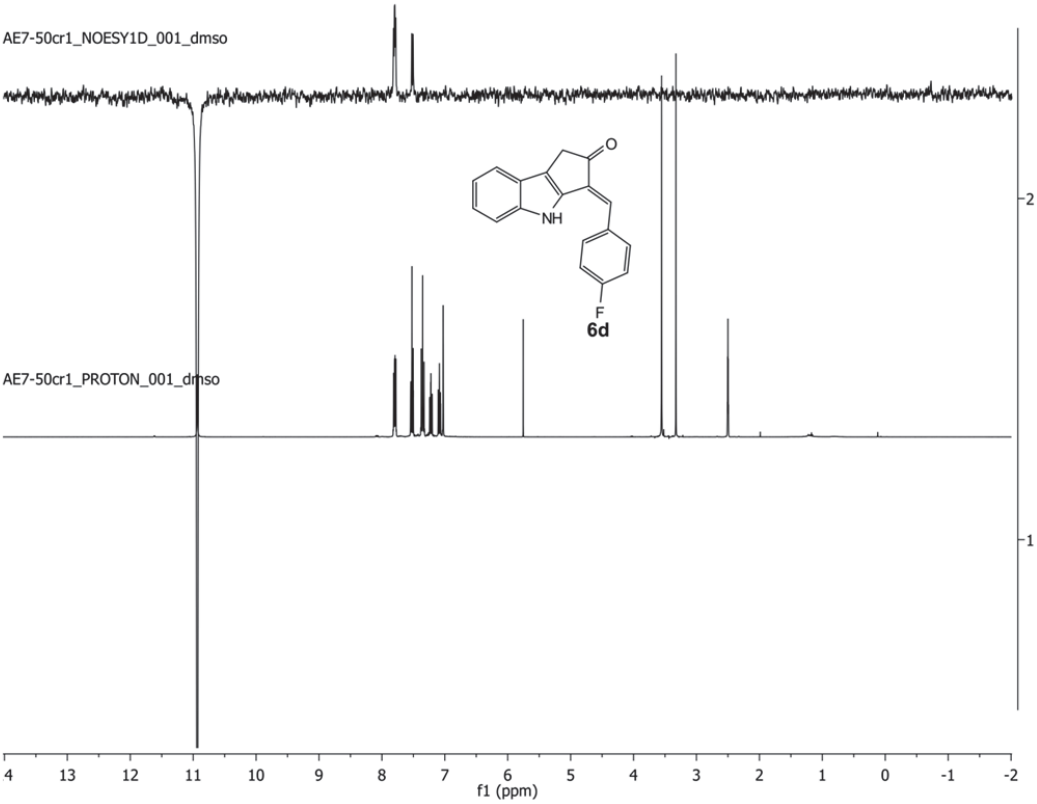

AE7-41cr2_PROTON_001_dmso
7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0
f1 (ppm)
O
NH
Cl
6c
0.96
2.05
1.89
0.96
1.00
1.00
0.99
0.90
1.96
4 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)

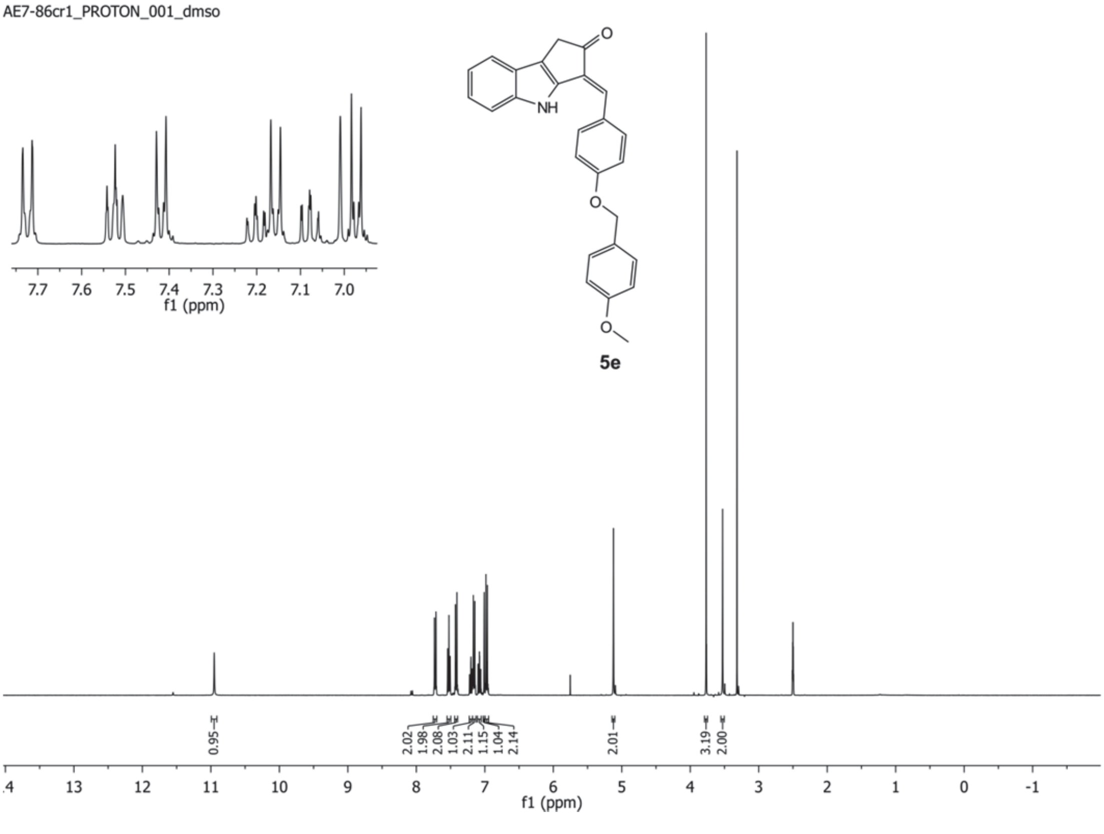

AE7-41cr2_CARBON_001_dmso
140.31
139.10
134.01
133.09
130.18
129.29
128.55
124.18
123.45
121.69
121.67
120.24
119.65
140
135
130
125
120
f1 (ppm)
O
NH
Cl
6c
203.91
140.31
139.10
134.01
133.09
130.18
129.29
128.55
124.18
123.45
121.69
121.67
120.24
119.65
112.99
35.77
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

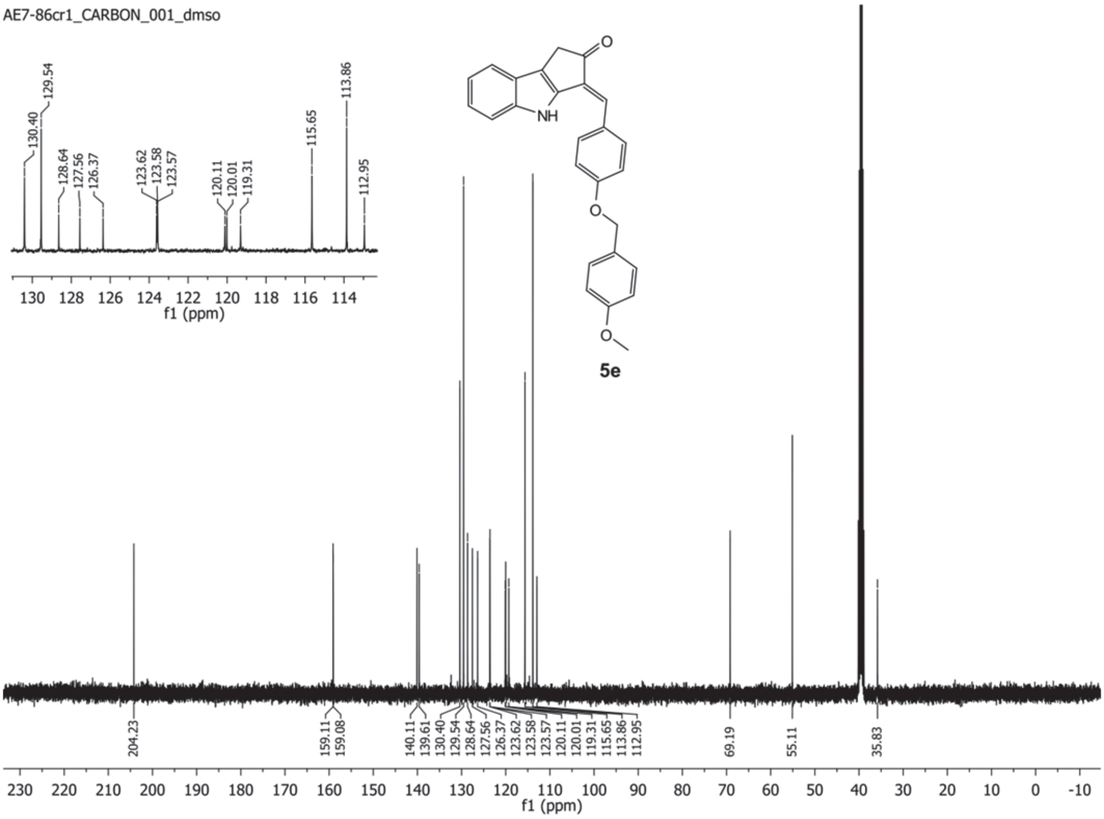

AE7-41cr2_NOESY1D_001_dmso
O
NH
Cl
6c
AE7-41cr2_PROTON_001_dmso
2
1
1.0
10.8
10.6
10.4
10.2
10.0
9.8
9.6
9.4
9.2
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
f1 (ppm)

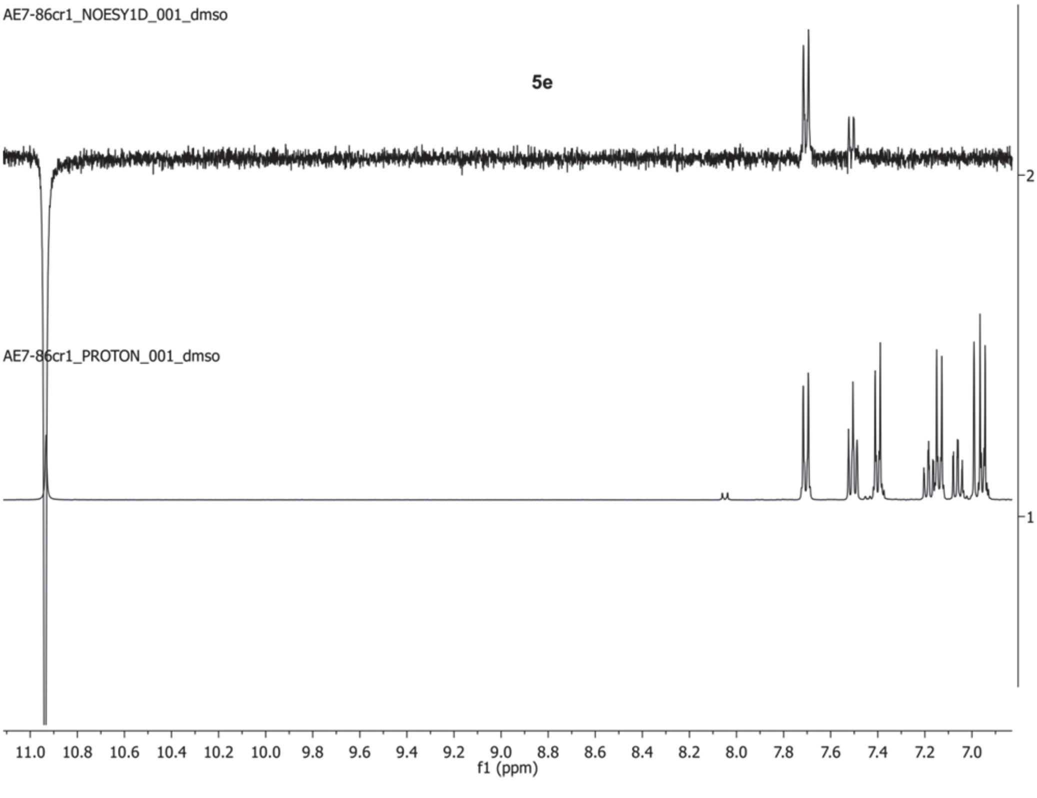

AE7-50cr1_PROTON_001_dmso
O
NH
F
6d
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
f1 (ppm)
1.00
2.06
1.04
0.93
2.01
1.08
1.08
0.96
2.04
4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


AE7-50cr1_CARBON_001_dmso
140.22
139.15
131.63
131.60
130.79
130.71
128.00
127.99
124.00
123.49
122.13
121.17
120.20
119.56
116.40
116.18
140
135
130
125
120
f1 (ppm)
O
NH
F
6d
204.02
163.39
160.94
140.22
139.15
131.63
131.60
130.79
130.71
128.00
127.99
124.00
123.49
122.13
121.17
120.20
119.56
116.40
116.18
112.97
35.80
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

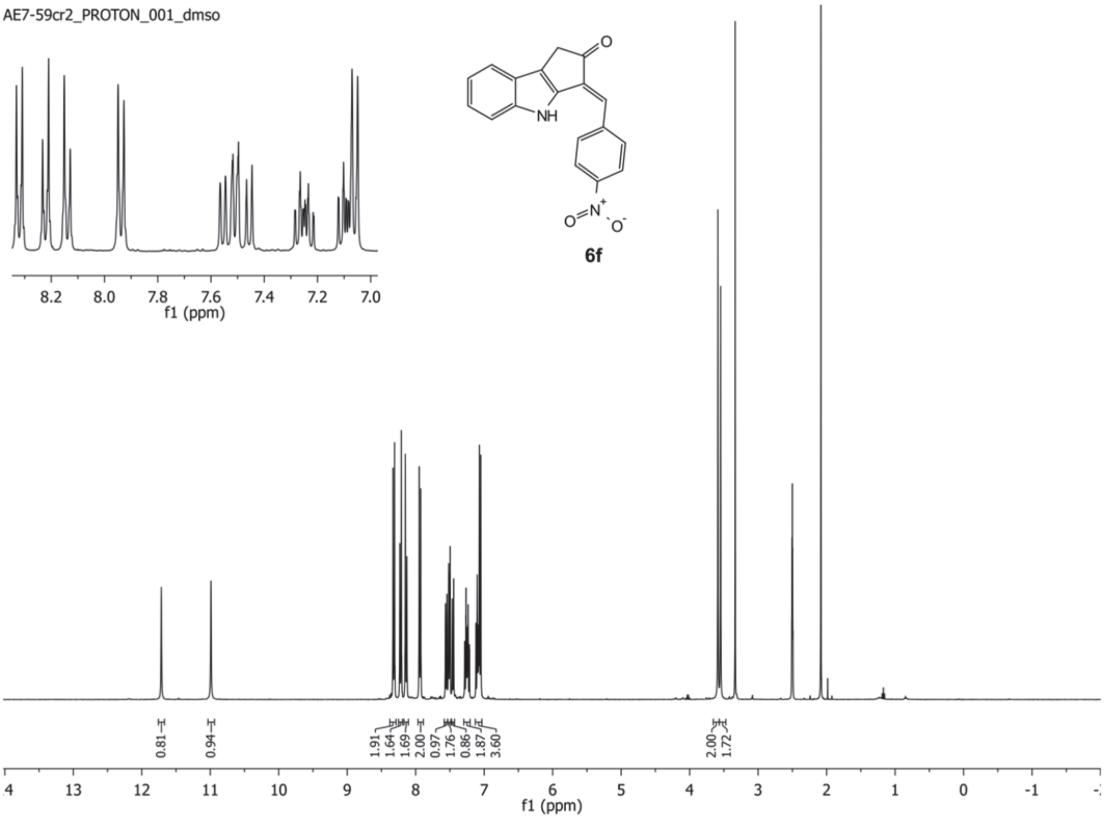

AE7-50cr1_NOESY1D_001_dmso
O
NH
F
6d
AE7-50cr1_PROTON_001_dmso
2
1
4 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)


AE7-86cr1_PROTON_001_dmso
7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0
f1 (ppm)
O
NH
O
O
5e
0.95
2.02
1.98
2.08
1.03
2.11
1.15
1.04
2.14
2.01
3.19
2.00
4 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)

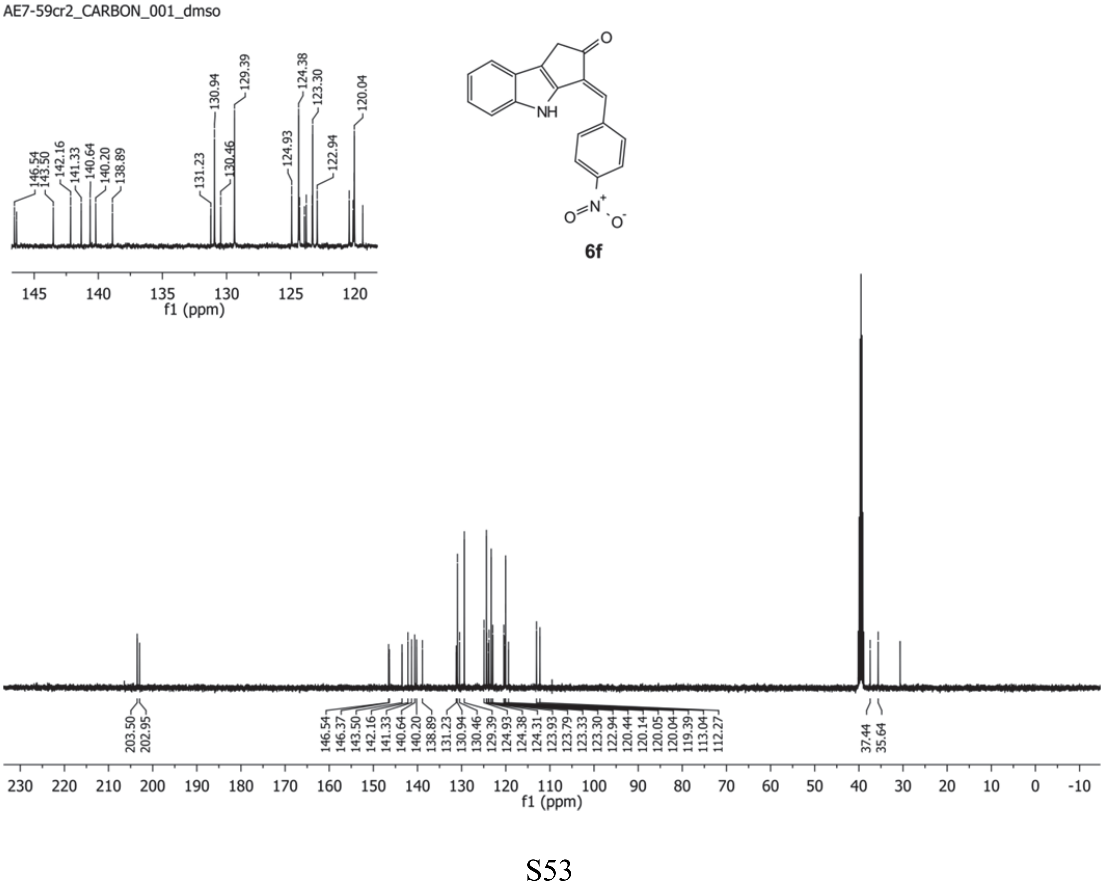

AE7-86cr1_CARBON_001_dmso
130.40
129.54
128.64
127.56
126.37
123.62
123.58
123.57
120.11
120.01
119.31
115.65
113.86
112.95
130 128 126 124 122 120 118 116 114
f1 (ppm)
O
NH
O
O
5e
204.23
159.11
159.08
140.11
139.61
130.40
129.54
128.64
127.56
126.37
123.62
123.58
123.57
120.11
120.01
119.31
115.65
113.86
112.95
69.19
55.11
35.83
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

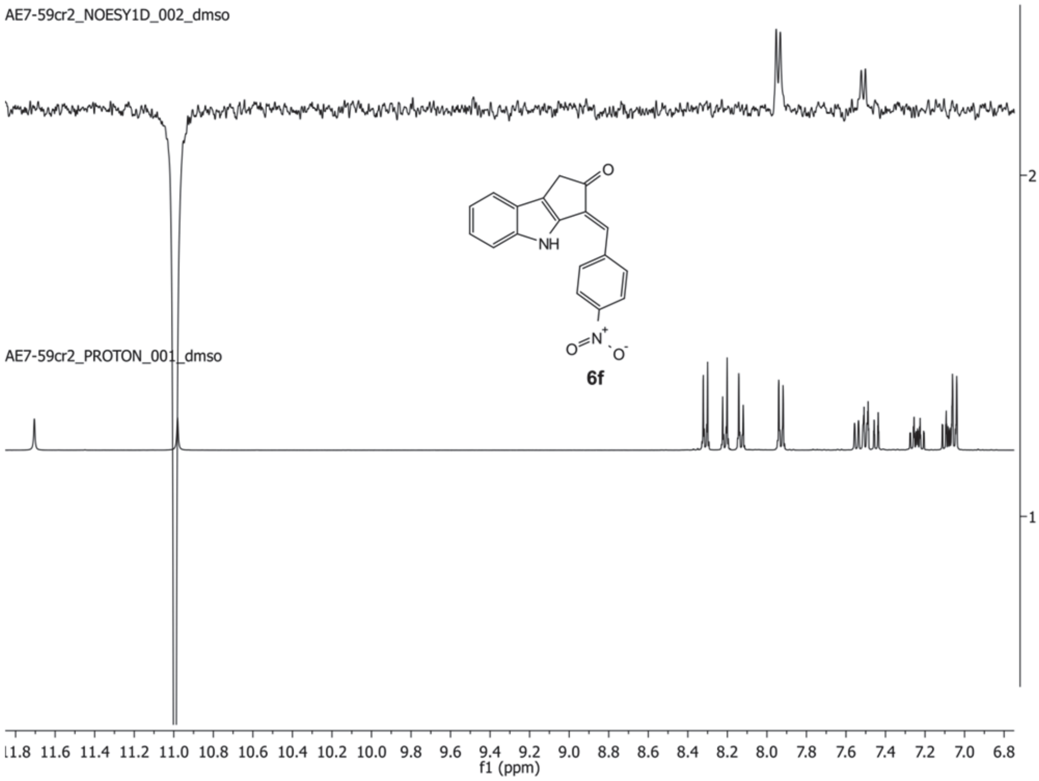

AE7-86cr1_NOESY1D_001_dmso
5e
AE7-86cr1_PROTON_001_dmso
2
1
11.0 10.8 10.6 10.4 10.2 10.0 9.8 9.6 9.4 9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0
f1 (ppm)

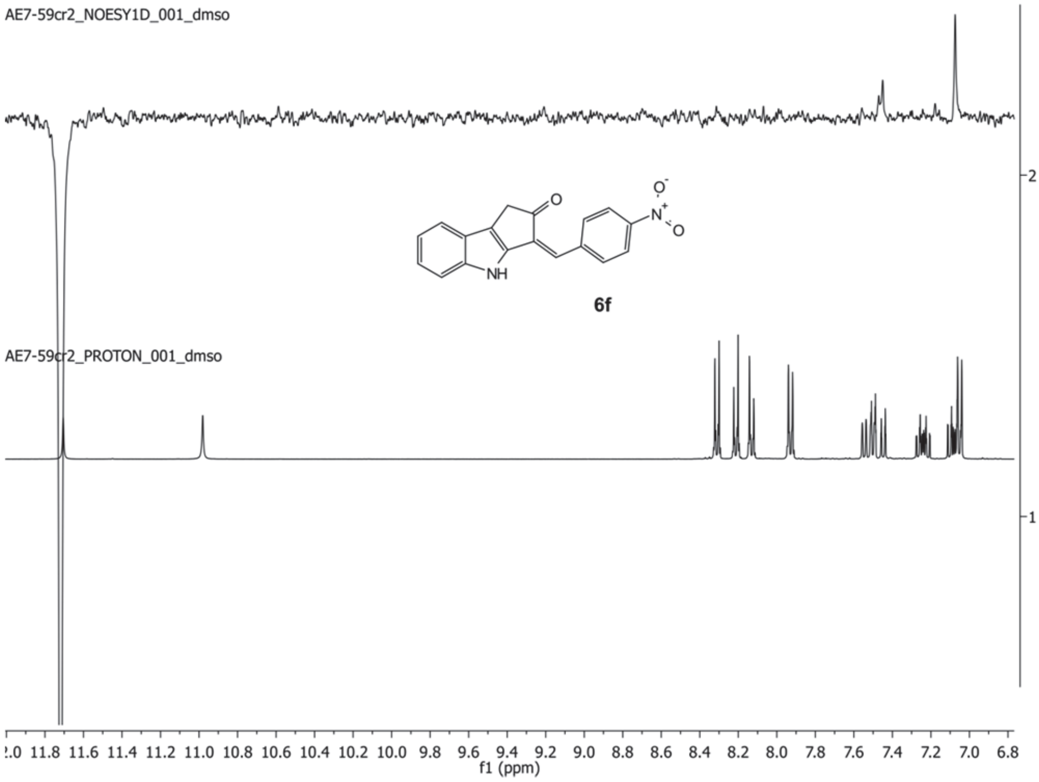
AE7-59cr2_PROTON_001_dmso



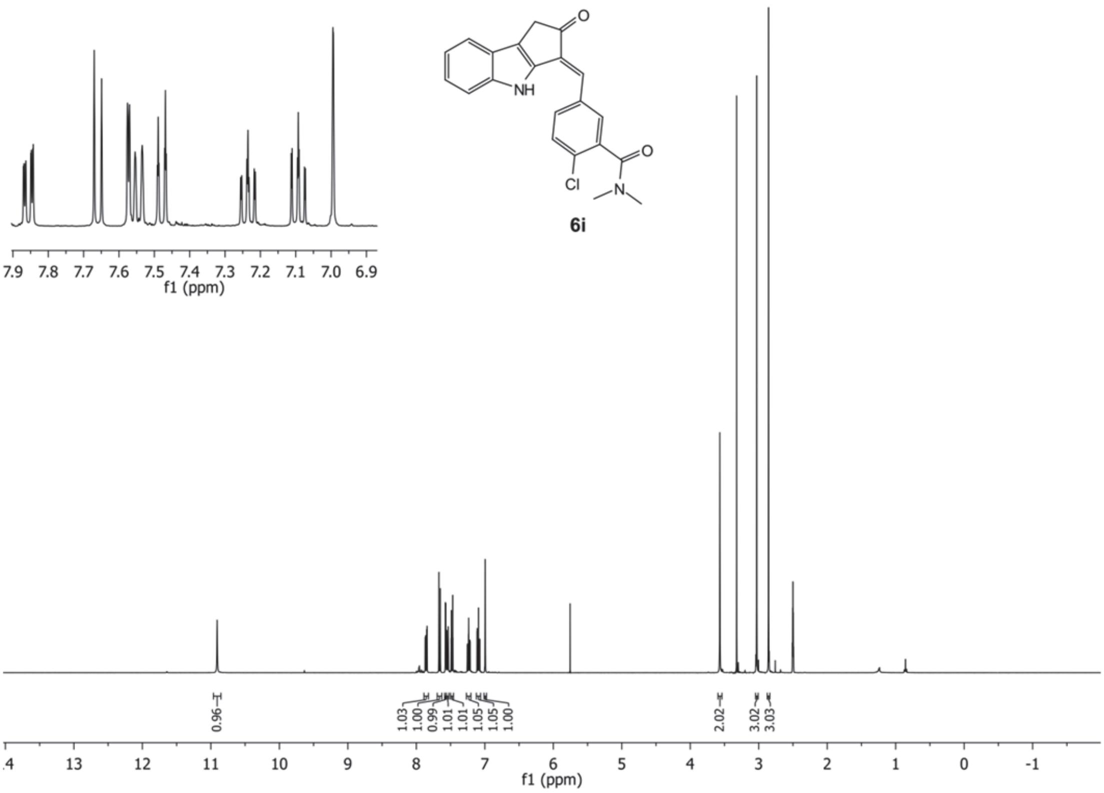
AE7-59cr2_CARBON_001_dmso



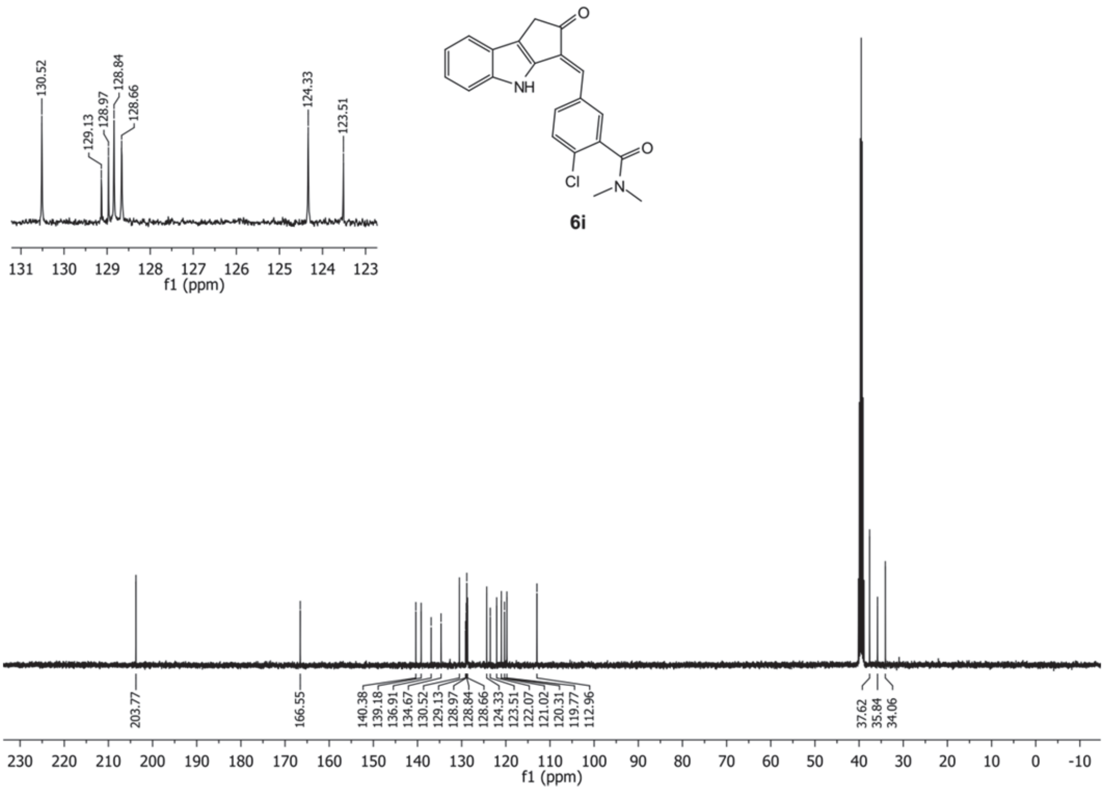

AE7-59cr2_NOESY1D_002_dmso
AE7-59cr2_PROTON_001_dmso
NH
O
N+
O
O-
6f
2
1
11.8 11.6 11.4 11.2 11.0 10.8 10.6 10.4 10.2 10.0 9.8 9.6 9.4 9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8
f1 (ppm)

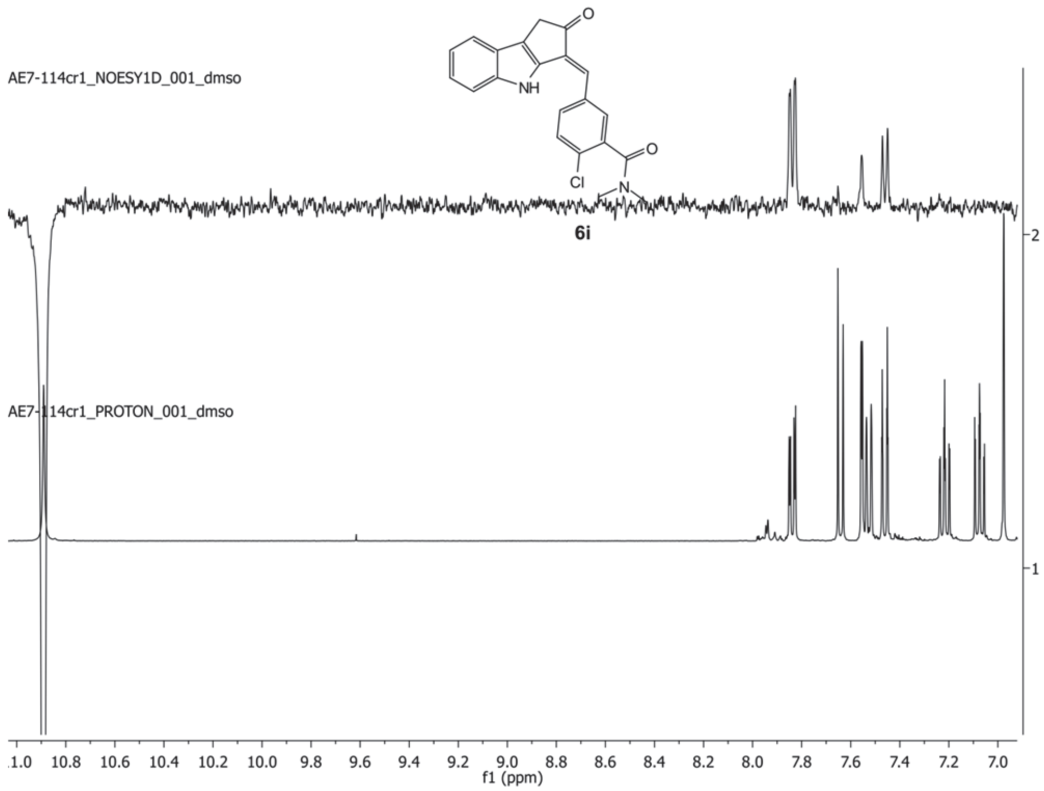

AE7-59cr2_NOESY1D_001_dmso
AE7-59cr2_PROTON_001_dmso
NH
O
O-
N+
O
6f
2
1
12.0 11.8 11.6 11.4 11.2 11.0 10.8 10.6 10.4 10.2 10.0 9.8 9.6 9.4 9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8
f1 (ppm)

AE7-114cr1_PROTON_001_dmso

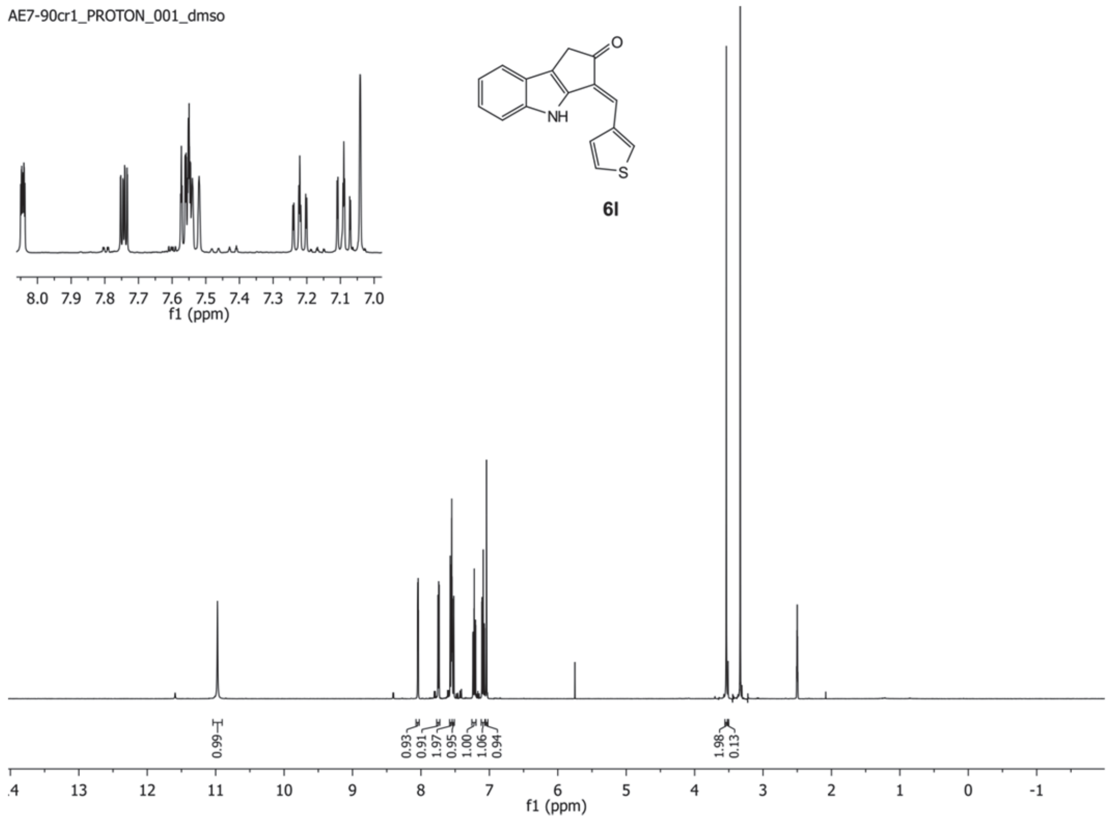


AE7-114cr1_CARBON_001_dmso

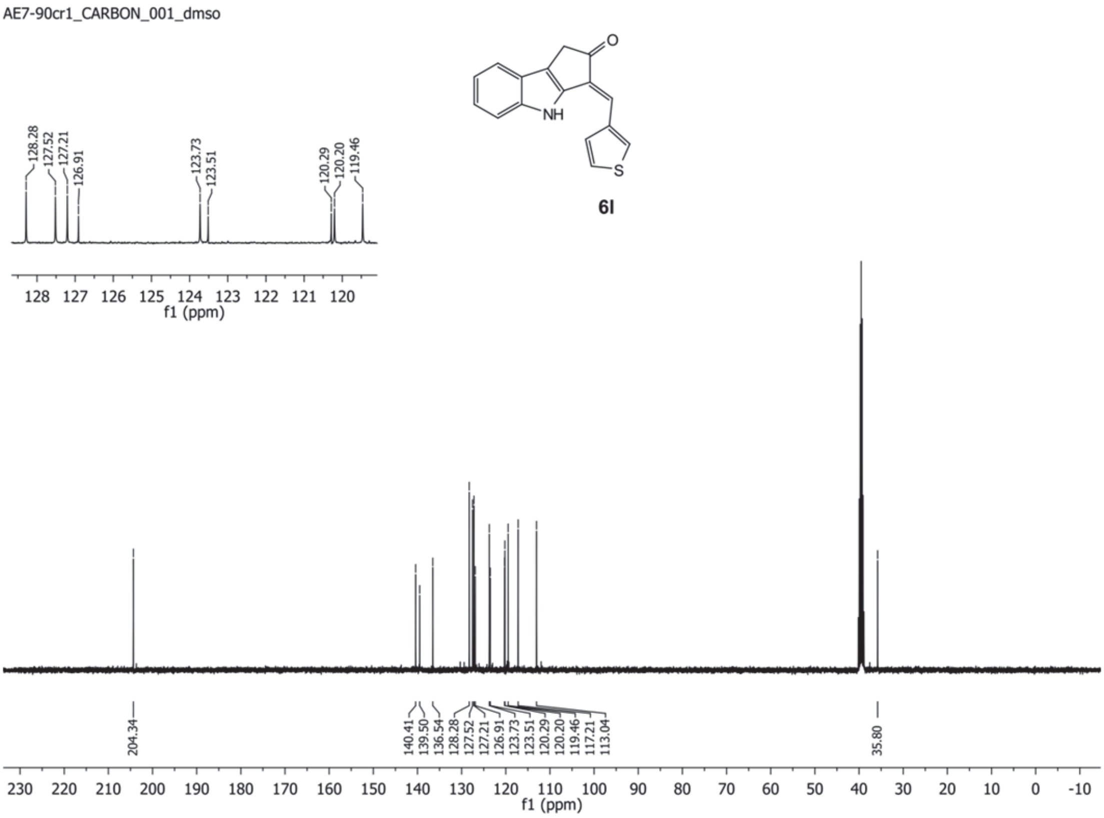


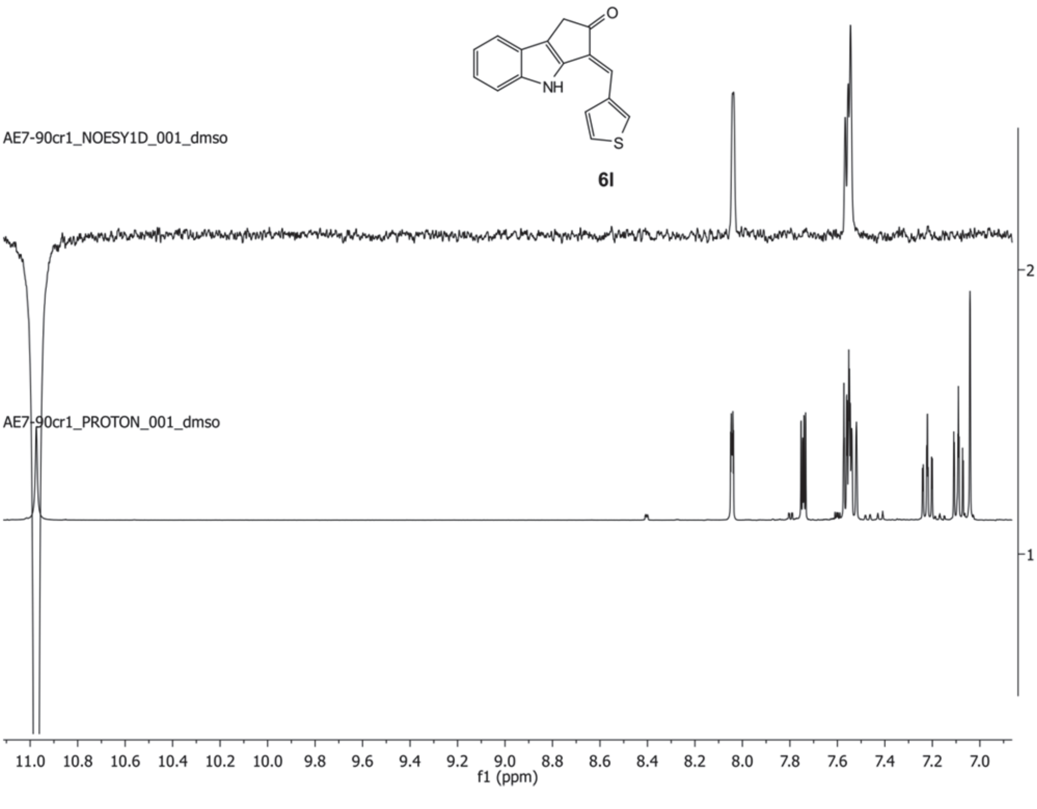

AE7-114cr1_NOESY1D_001_dmso
AE7-114cr1_PROTON_001_dmso
O
NH
O
Cl
N
2
1
11.0 10.8 10.6 10.4 10.2 10.0 9.8 9.6 9.4 9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0
f1 (ppm)

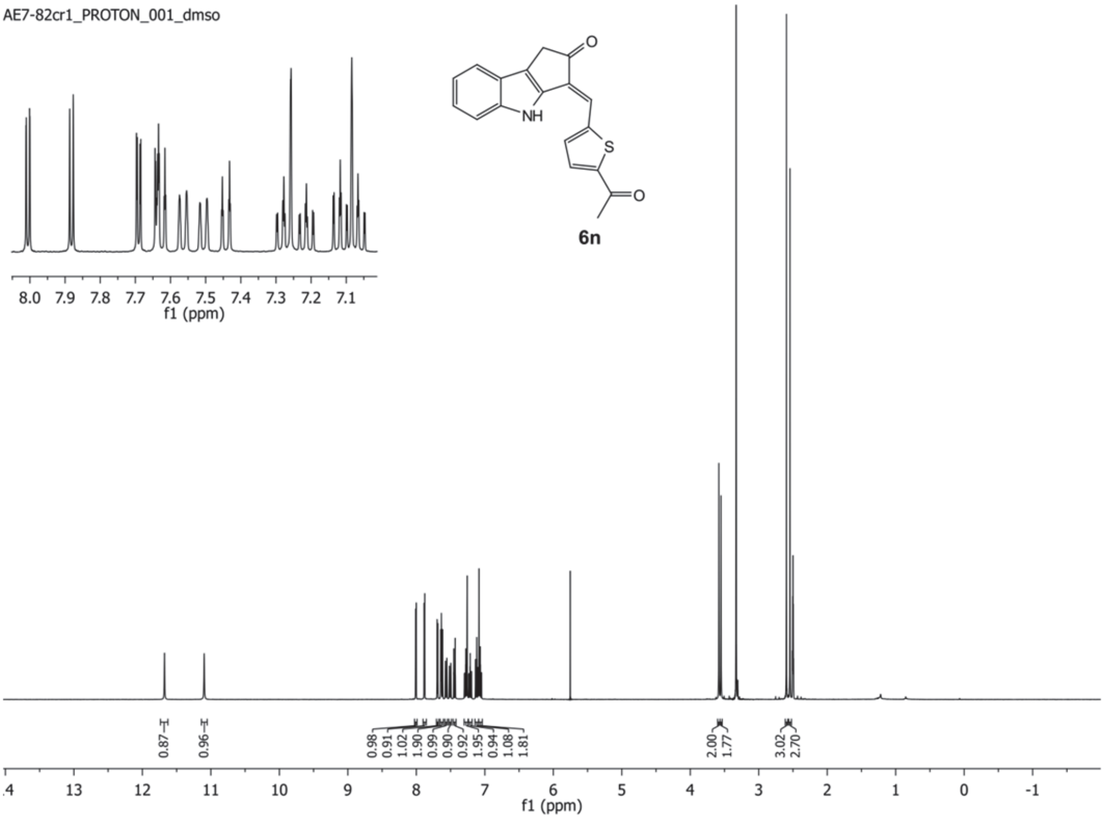
6i

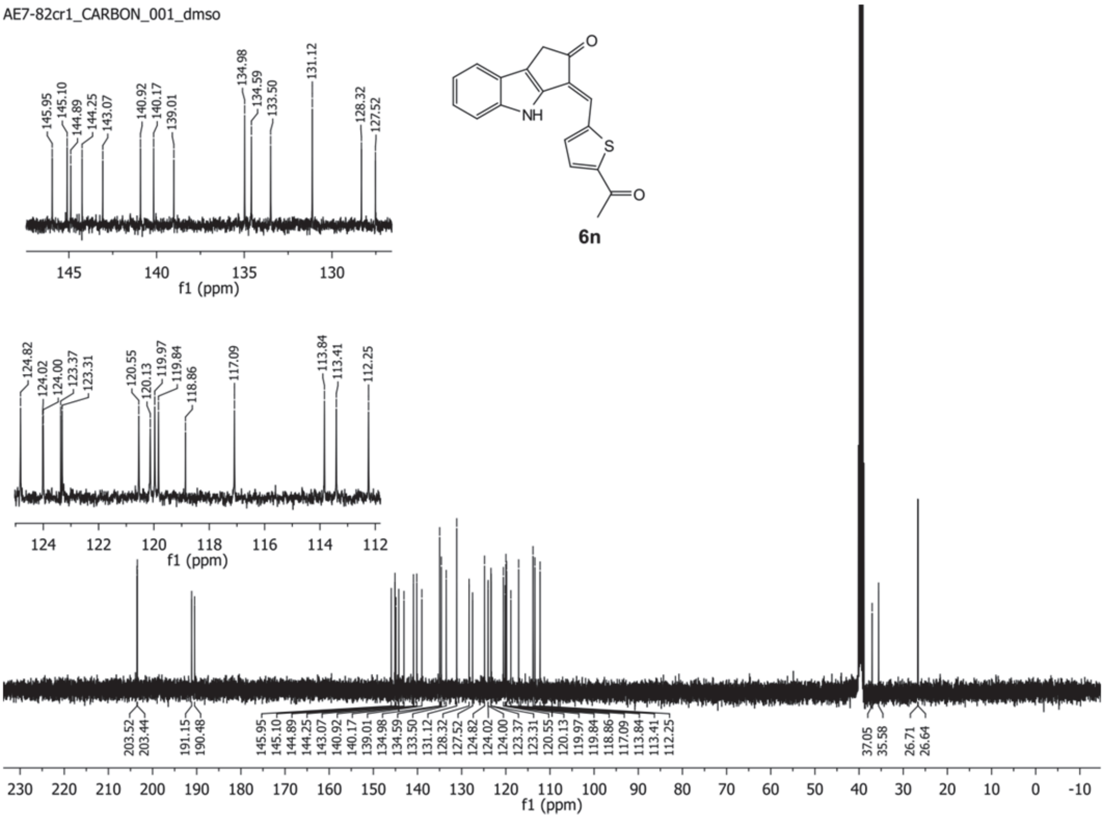

AE7-90cr1_PROTON_001_dmso
O
NH
S
8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0
f1 (ppm)
0.99
0.93
0.91
1.97
0.95
1.00
1.06
0.94
1.98
0.13
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)

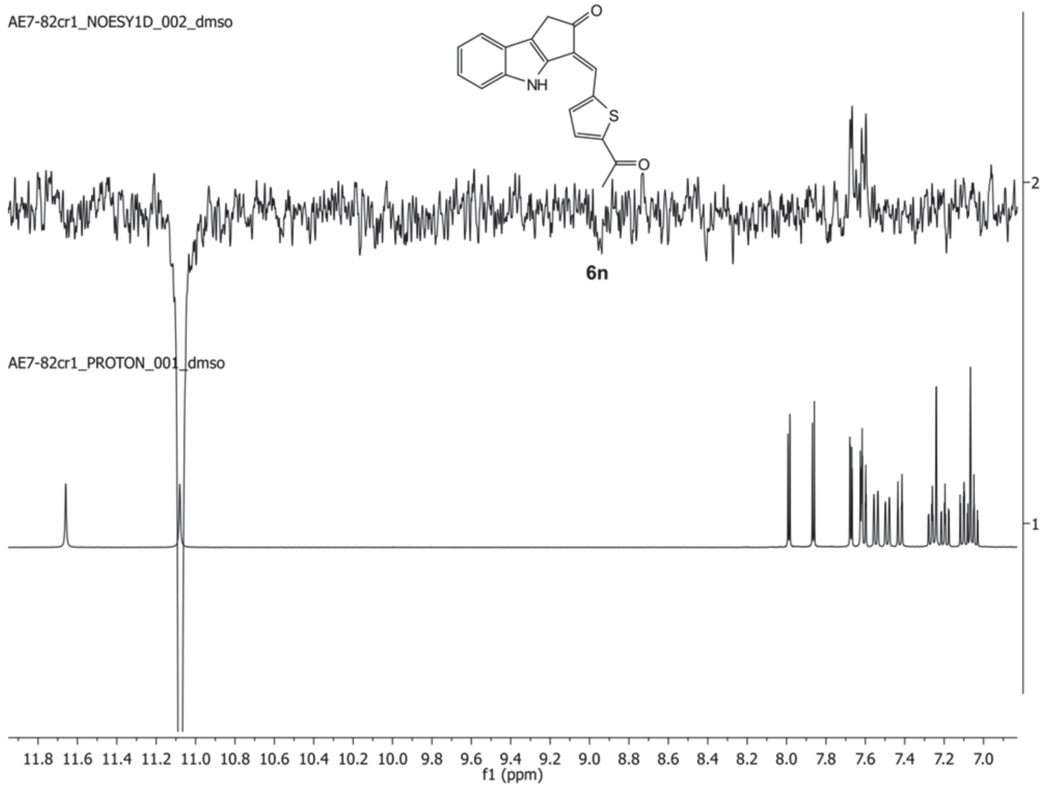
6l


AE7-90cr1_CARBON_001_dmso
O
NH
S
6l
128.28
127.52
127.21
126.91
123.73
123.51
120.29
120.20
119.46
128 127 126 125 124 123 122 121 120
f1 (ppm)
204.34
140.41
139.50
136.54
128.28
127.52
127.21
126.91
123.73
123.51
120.29
120.20
119.46
117.21
113.04
35.80
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

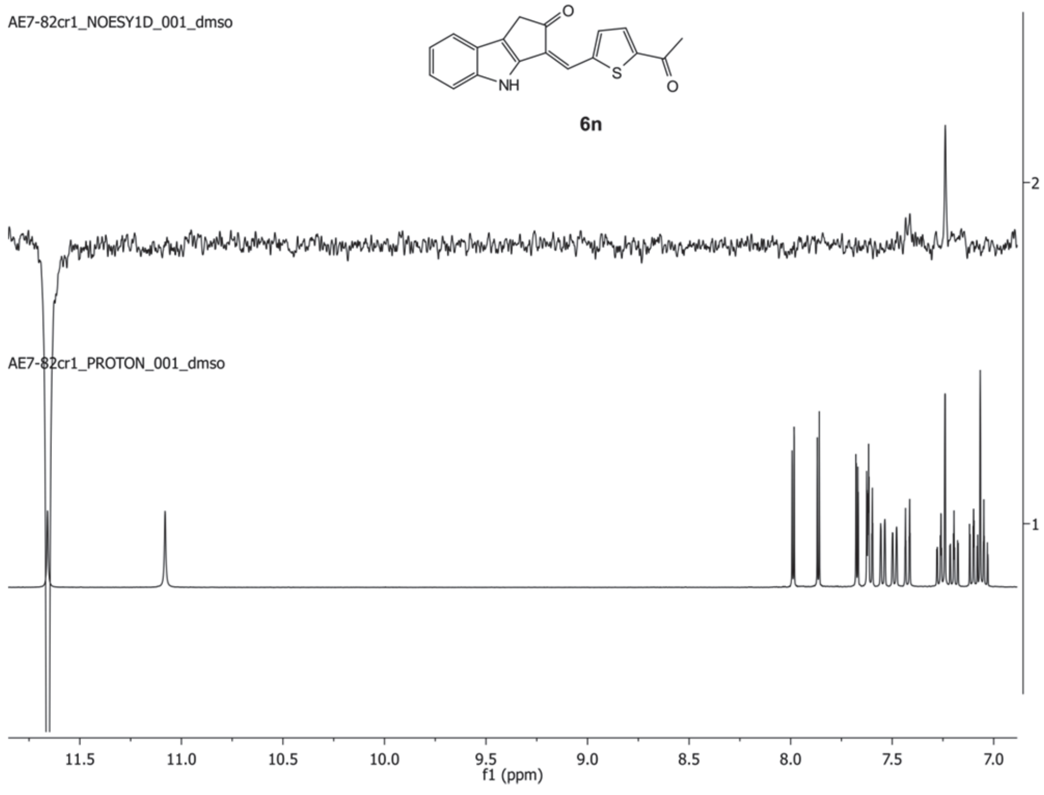

O
NH
S
6l
AE7-90cr1_NOESY1D_001_dmso
AE7-90cr1_PROTON_001_dmso
2
1
11.0 10.8 10.6 10.4 10.2 10.0 9.8 9.6 9.4 9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0
f1 (ppm)


AE7-82cr1_PROTON_001_dmso
6n
NH
S
O
8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1
f1 (ppm)
0.87
0.96
0.98
0.91
1.02
1.90
0.99
0.90
0.92
1.95
0.94
1.08
1.81
2.00
1.77
3.02
2.70
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


AE7-82cr1_CARBON_001_dmso
6n
NH
S
O
145.95
145.10
144.89
144.25
143.07
140.92
140.17
139.01
134.98
134.59
133.50
131.12
128.32
127.52
145 140 135 130
f1 (ppm)
124.82
124.02
124.00
123.37
123.31
120.55
120.13
119.97
119.84
118.86
117.09
113.84
113.41
112.25
124 122 120 118 116 114 112
f1 (ppm)
203.52
203.44
191.15
190.48
145.95
145.10
144.89
144.25
143.07
140.92
140.17
139.01
134.98
134.59
133.50
131.12
128.32
127.52
124.82
124.02
124.00
123.37
123.31
120.55
120.13
119.97
119.84
118.86
117.09
113.84
113.41
112.25
37.05
35.58
26.71
26.64
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

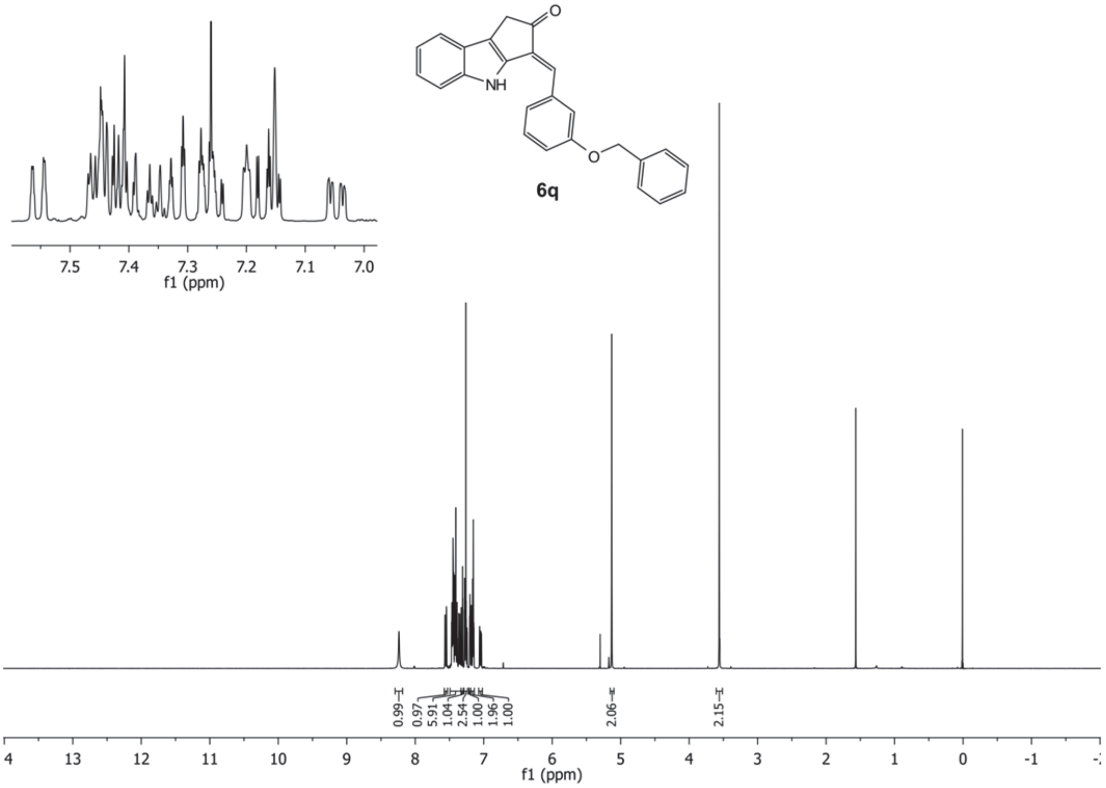

AE7-82cr1_NOESY1D_002_dmso
O
NH
S
O
AE7-82cr1_PROTON_001_dmso
2
1
11.8 11.6 11.4 11.2 11.0 10.8 10.6 10.4 10.2 10.0 9.8 9.6 9.4 9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0
f1 (ppm)

6n

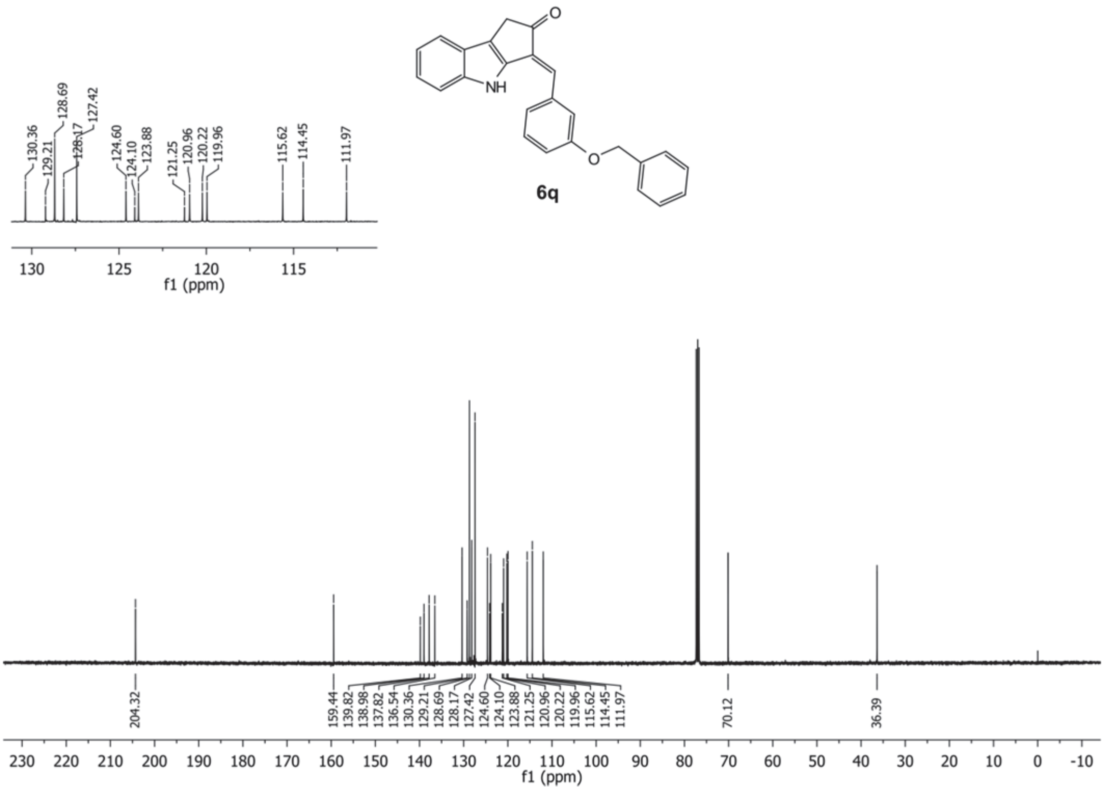

AE7-82cr1_NOESY1D_001_dmso
O
NH
S
O
AE7-82cr1_PROTON_001_dmso
2
1
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0
f1 (ppm)

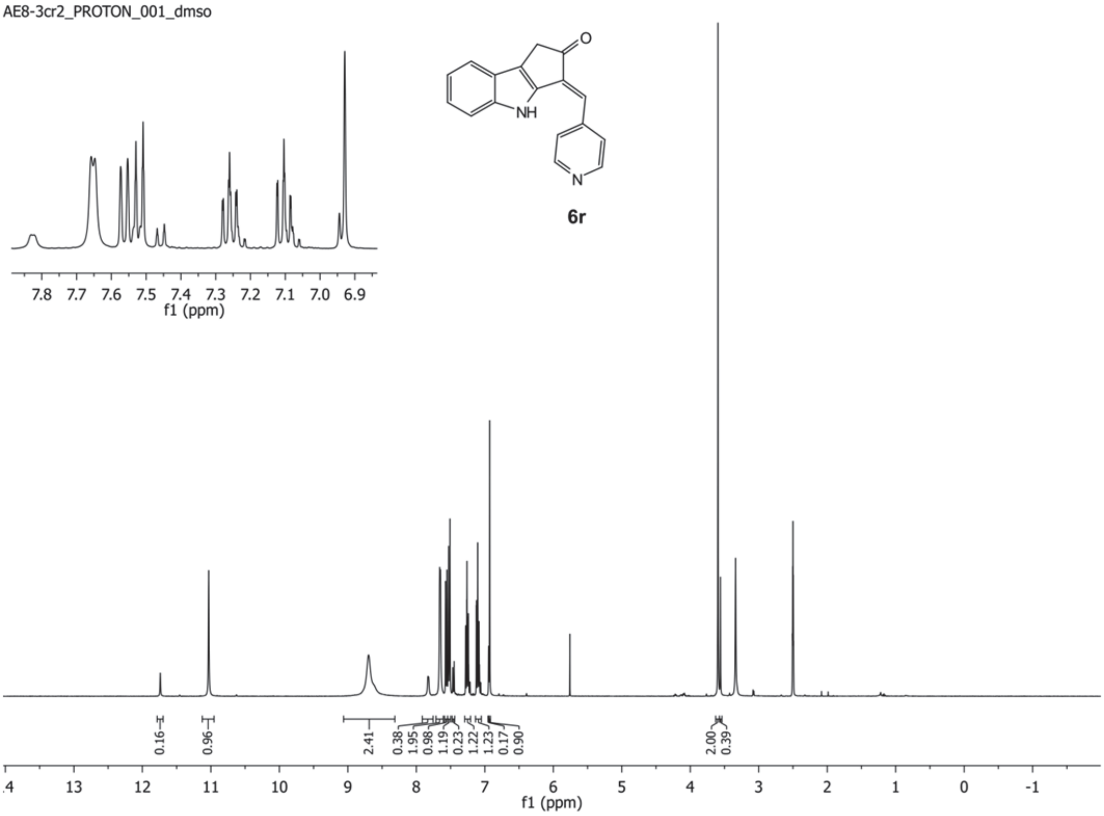
6n

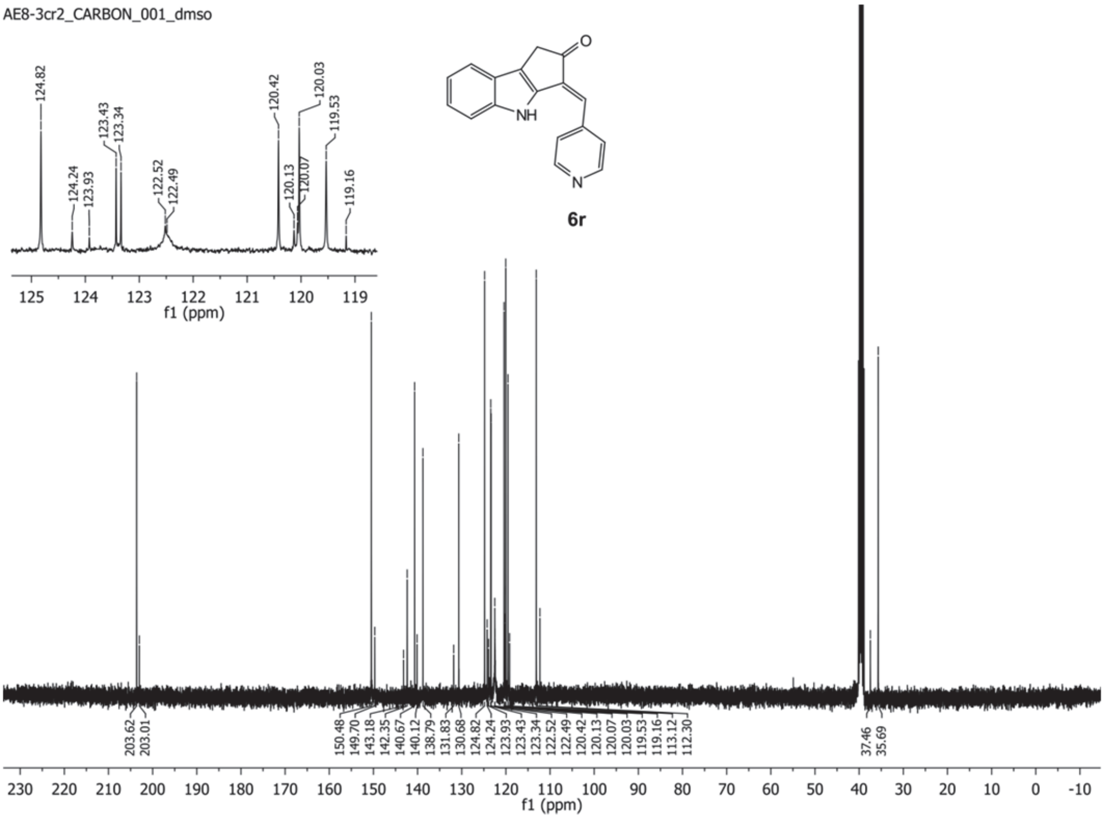
AE7-103cr1_PROTON_001_cdcl3

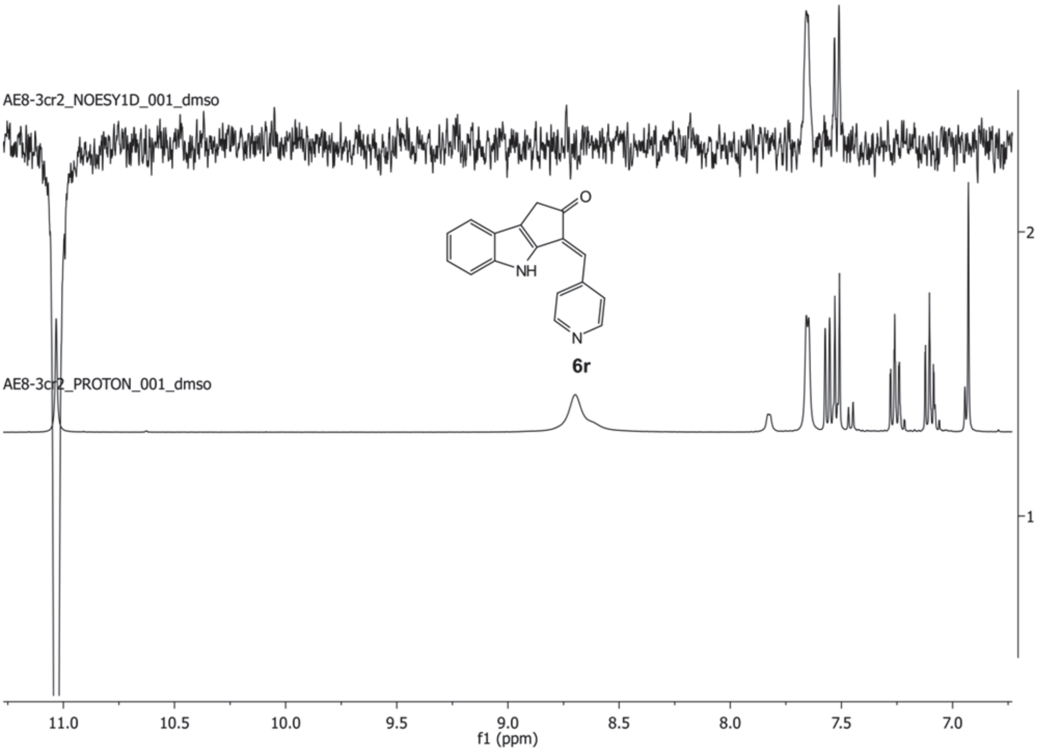


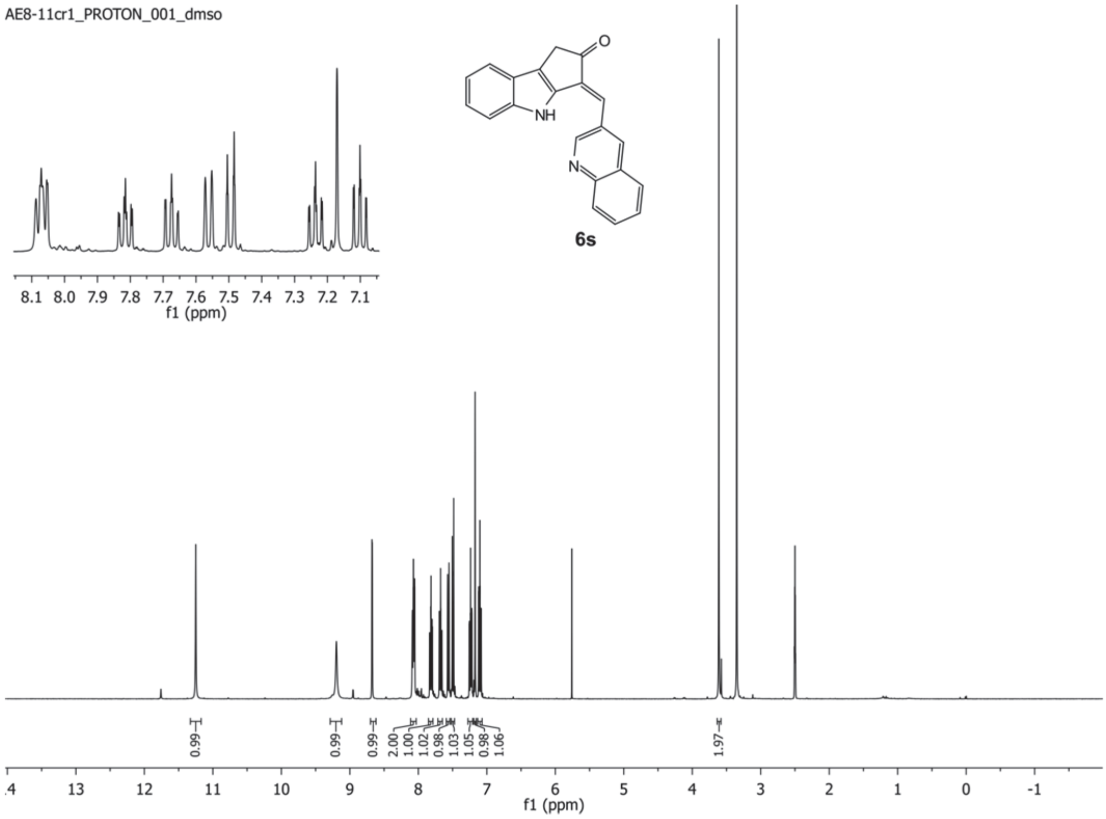
AE7-103cr1_CARBON_001_cdcl3

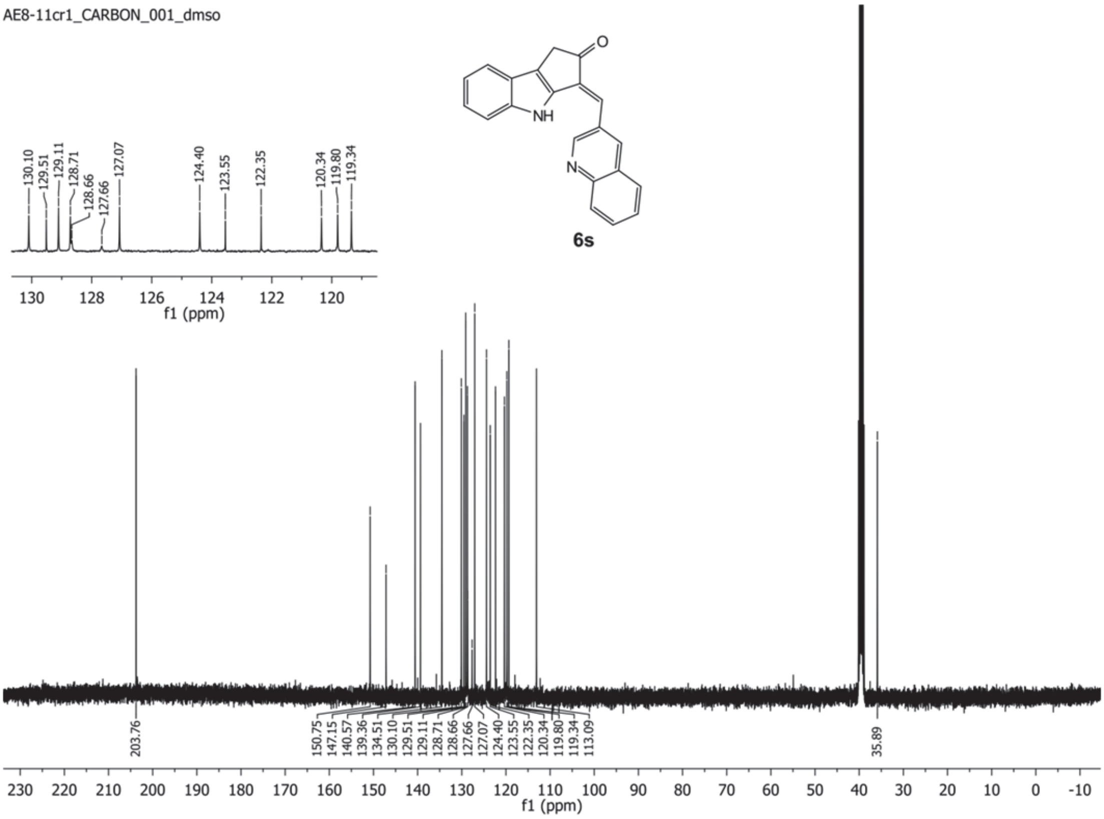


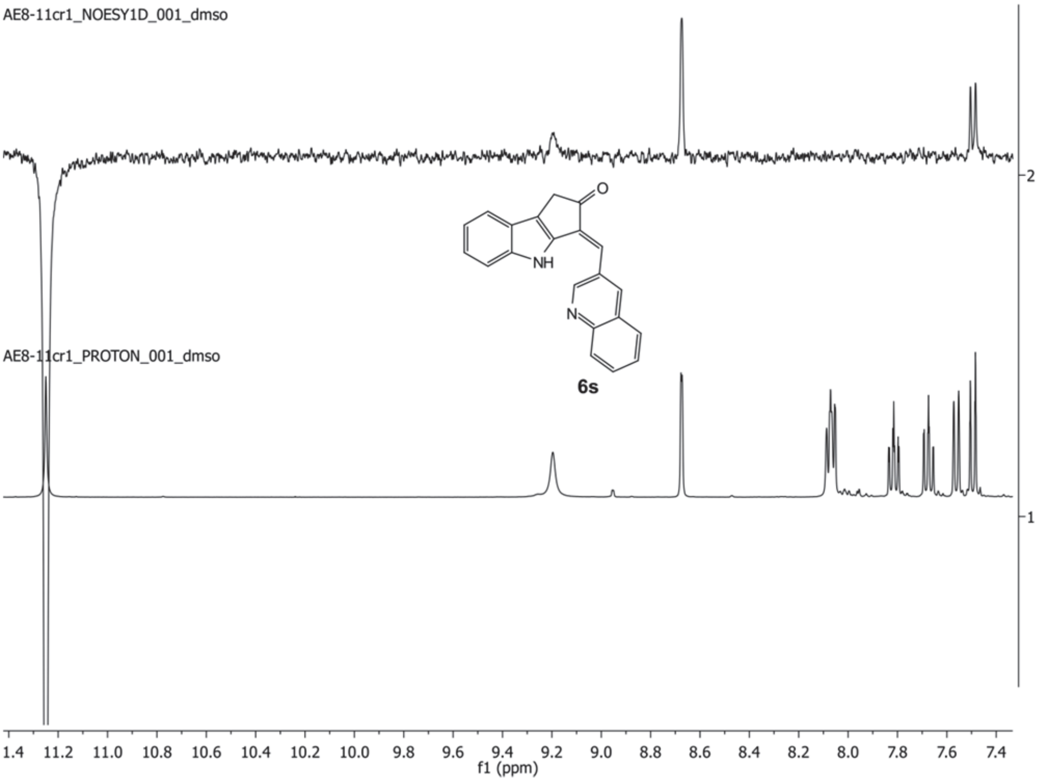

AE8-3cr2_PROTON_001_dmso
O
NH
N
6r
7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9
f1 (ppm)
0.16
0.96
2.41
0.38
1.95
0.98
1.19
0.23
1.22
1.23
0.17
0.90
2.00
0.39
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)

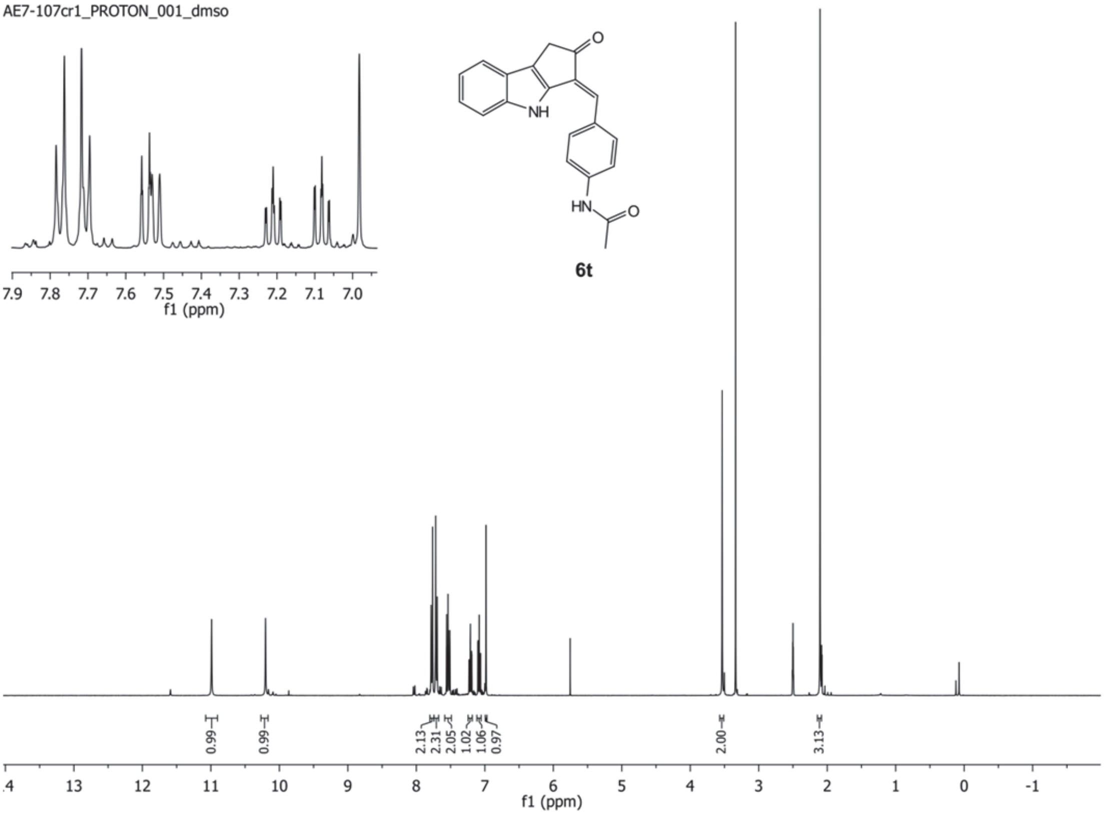

AE8-3cr2_CARBON_001_dmso
O
NH
N
6r
124.82
124.24
123.93
123.43
123.34
122.52
122.49
120.42
120.13
120.07
120.03
119.53
119.16
125 124 123 122 121 120 119
f1 (ppm)
203.62
203.01
150.48
149.70
143.18
142.35
140.67
140.12
138.79
131.83
130.68
124.82
124.24
123.93
123.43
123.34
122.52
122.49
120.42
120.13
120.07
120.03
119.53
119.16
113.12
112.30
37.46
35.69
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

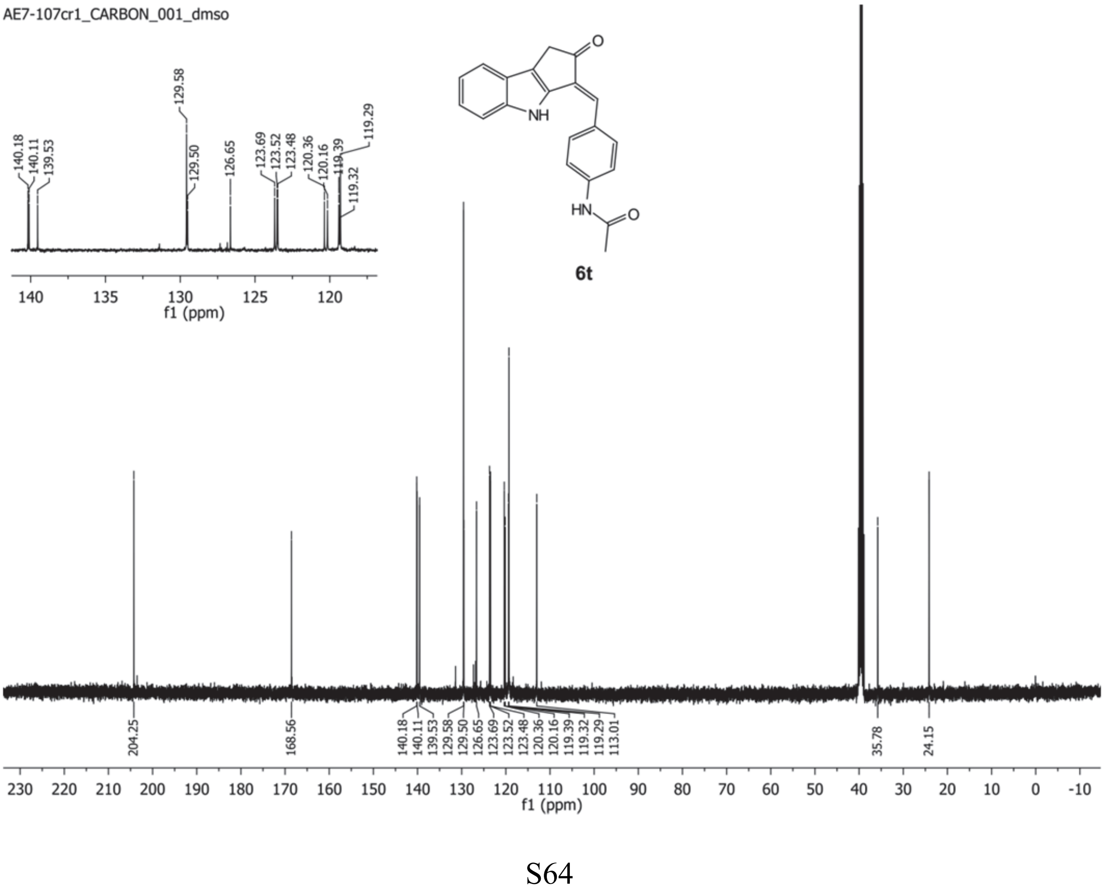

AE8-3cr2_NOESY1D_001_dmso
AE8-3cr2_PROTON_001_dmso
O
NH
N
6r
2
1
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
f1 (ppm)

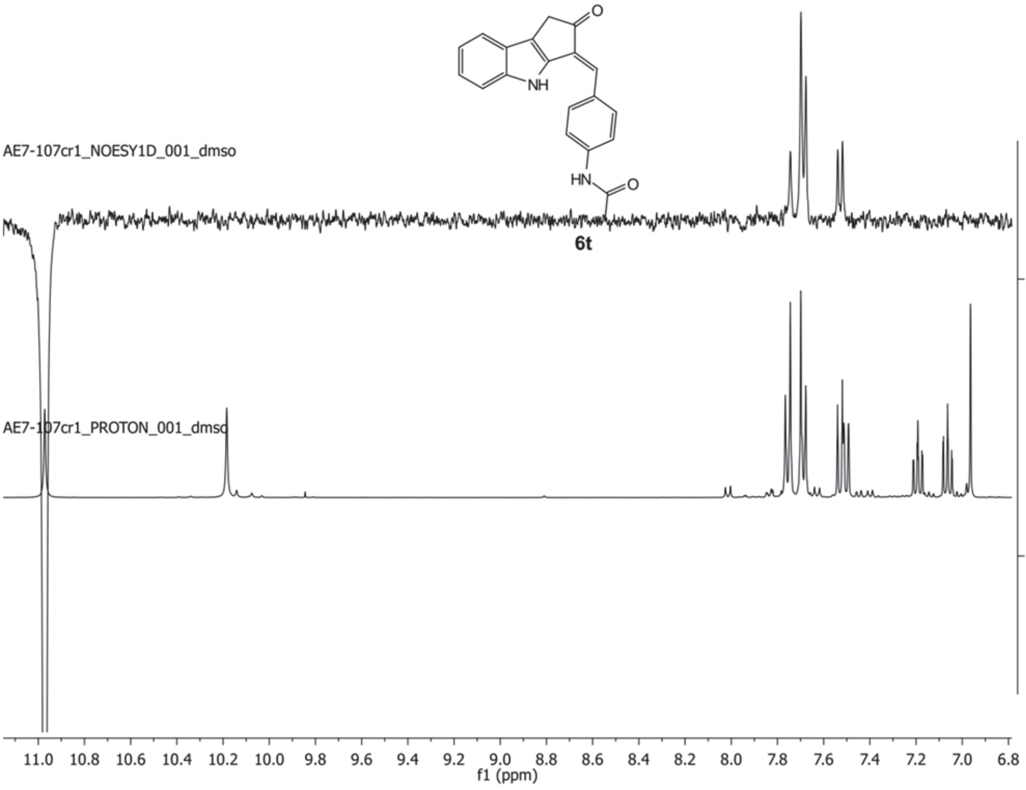

AE8-11cr1_PROTON_001_dmso
O
NH
N
6s
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
f1 (ppm)
0.99
0.99
0.99
2.00
1.00
1.02
0.98
1.03
1.05
0.98
1.06
1.97
.4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


AE8-11cr1_CARBON_001_dmso
O
NH
N
6s
130.10
129.51
129.11
128.71
128.66
127.66
127.07
124.40
123.55
122.35
120.34
119.80
119.34
130
128
126
124
122
120
f1 (ppm)
203.76
150.75
147.15
140.57
139.36
134.51
130.10
129.51
129.11
128.71
128.66
127.66
127.07
124.40
123.55
122.35
120.34
119.80
119.34
113.09
35.89
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


AE8-11cr1_NOESY1D_001_dmso
O
NH
N
6s
AE8-11cr1_PROTON_001_dmso
2
1
1.4
11.2
11.0
10.8
10.6
10.4
10.2
10.0
9.8
9.6
9.4
9.2
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
f1 (ppm)

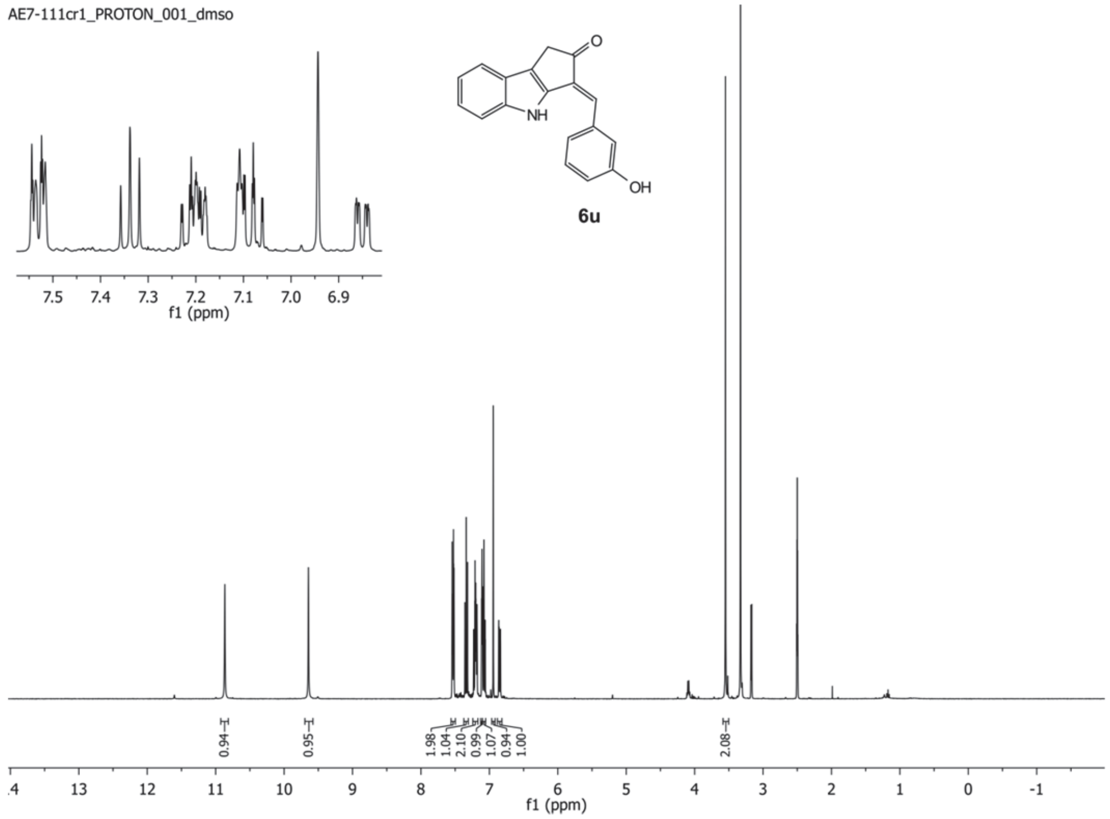

AE7-107cr1_PROTON_001_dmso
6t
NH
HN
O
7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0
f1 (ppm)
0.99
0.99
2.13
2.31
2.05
1.02
1.06
0.97
2.00
3.13
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


AE7-107cr1_CARBON_001_dmso
6t
NH
HN
O
140.18
140.11
139.53
129.58
129.50
126.65
123.69
123.52
123.48
120.36
120.16
119.39
119.32
119.29
140 135 130 125 120
f1 (ppm)
204.25
168.56
140.18
140.11
139.53
129.58
129.50
126.65
123.69
123.52
123.48
120.36
120.16
119.39
119.32
119.29
113.01
35.78
24.15
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



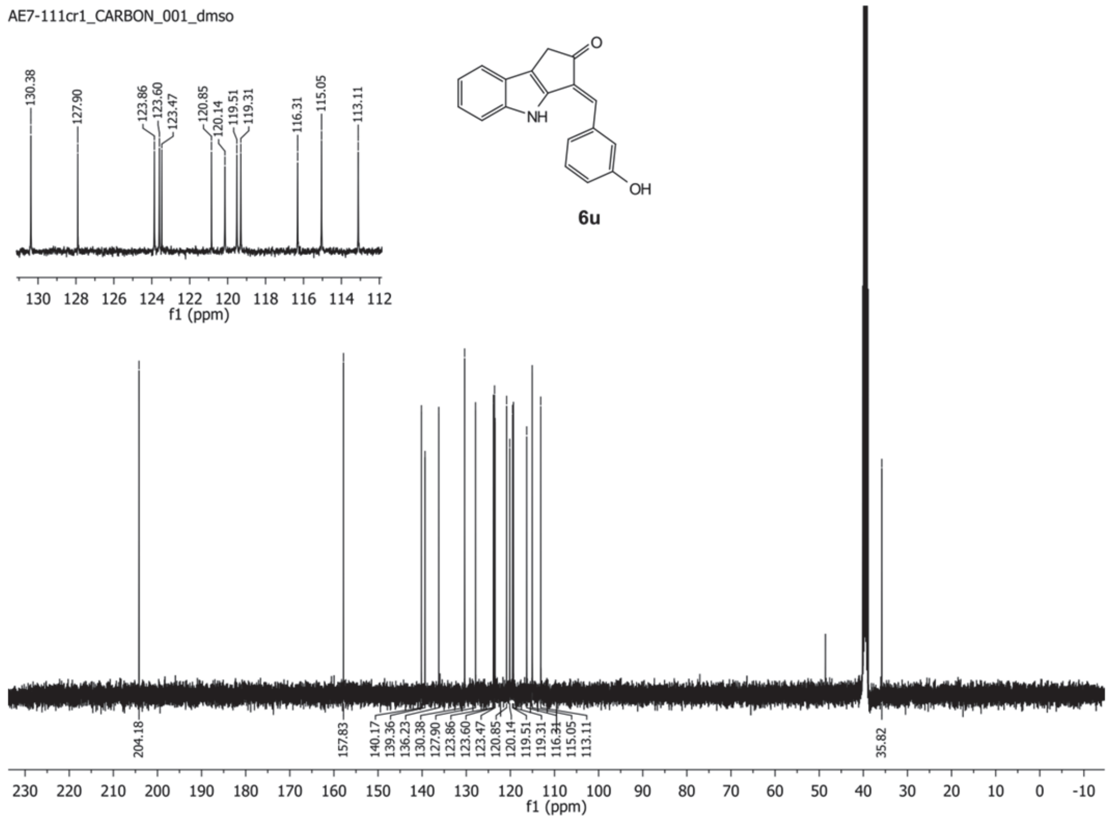
AE7-107cr1_NOESY1D_001_dmso
AE7-107cr1_PROTON_001_dmso
O
NH
HN
O
2
1
11.0
10.8
10.6
10.4
10.2
10.0
9.8
9.6
9.4
9.2
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
f1 (ppm)

6t

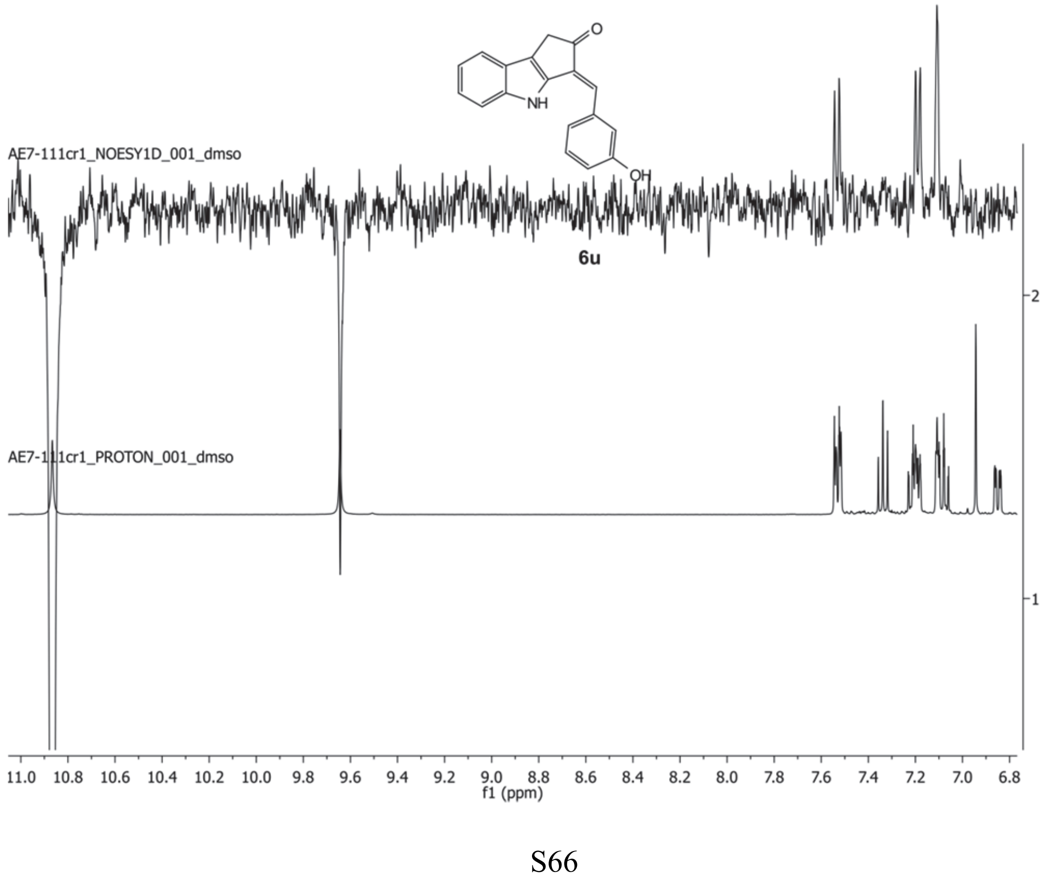


AE7-111cr1_PROTON_001_dmso
O
NH
OH
7.5
7.4
7.3
7.2
7.1
7.0
6.9
f1 (ppm)
0.94
0.95
1.98
1.04
2.10
0.99
1.07
0.94
1.00
2.08
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

6u

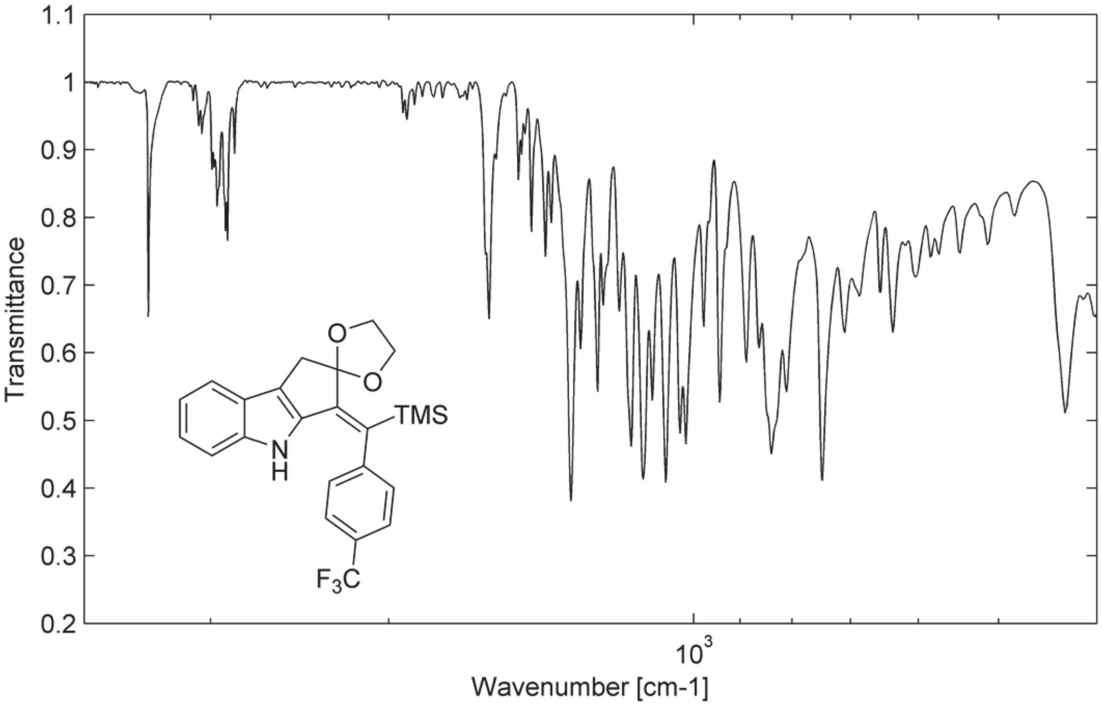

AE7-111cr1_CARBON_001_dmso
130.38
127.90
123.86
123.60
123.47
120.85
120.14
119.51
119.31
116.31
115.05
113.11
130 128 126 124 122 120 118 116 114 112
f1 (ppm)
O
NH
OH
204.18
157.83
140.17
139.36
136.23
130.38
127.90
123.86
123.60
123.47
120.85
120.14
119.51
119.31
116.31
115.05
113.11
35.82
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

6u


O
NH
OH
AE7-111cr1_NOESY1D_001_dmso
AE7-111cr1_PROTON_001_dmso
2
1
11.0 10.8 10.6 10.4 10.2 10.0 9.8 9.6 9.4 9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8
f1 (ppm)

6u

4 IR-spectra



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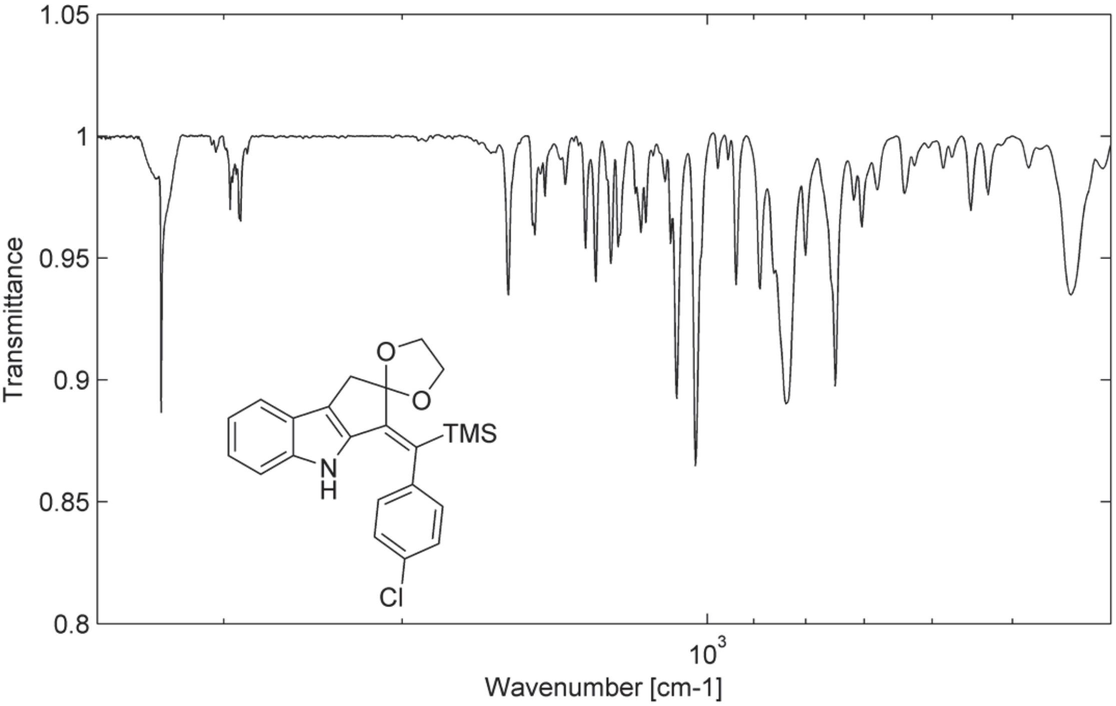

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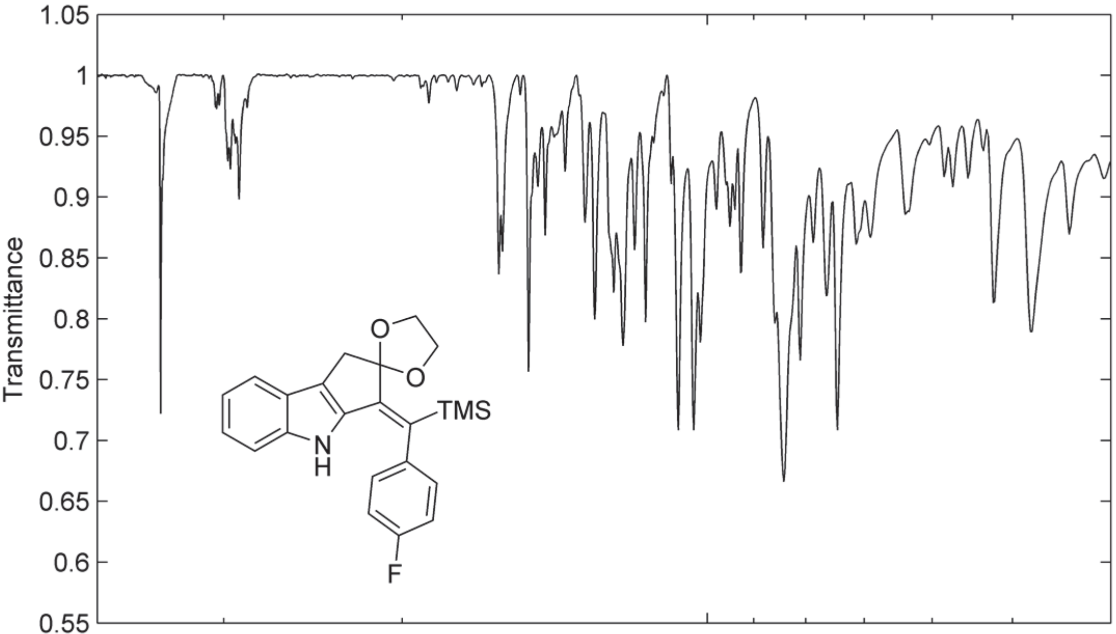

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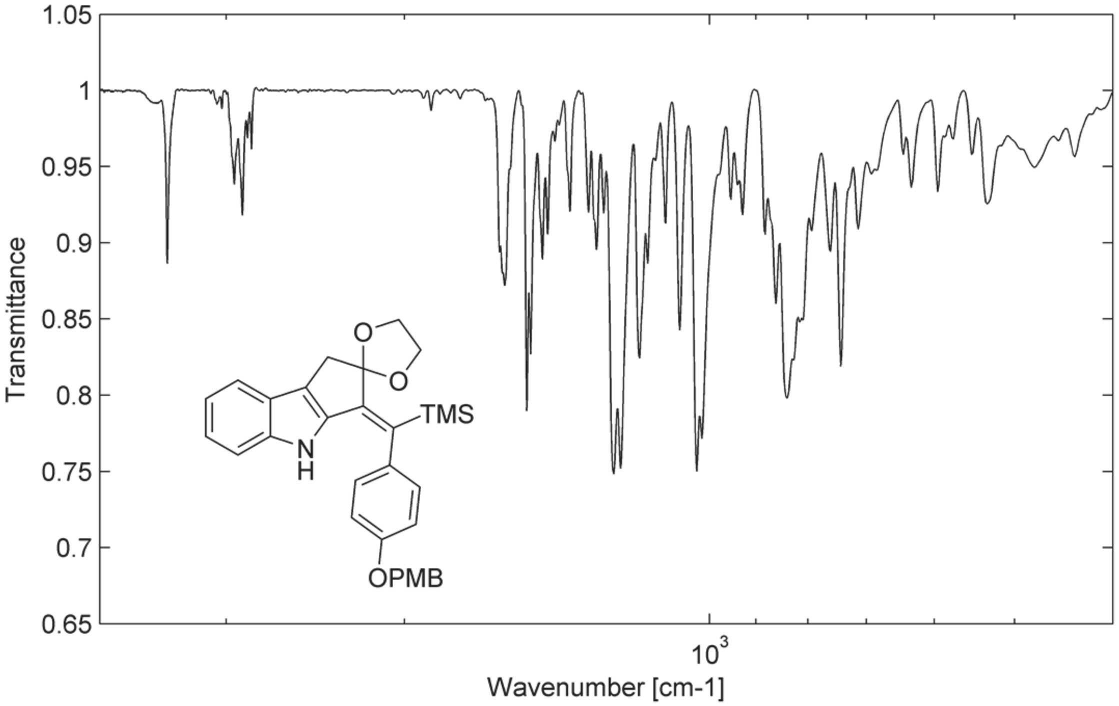

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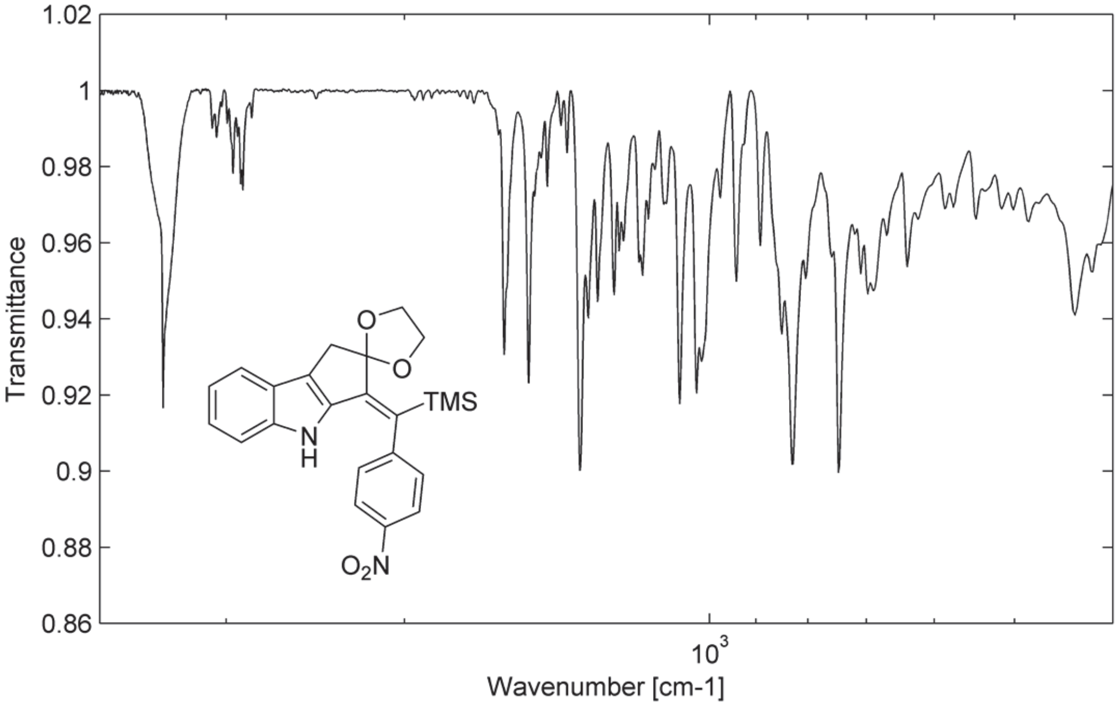

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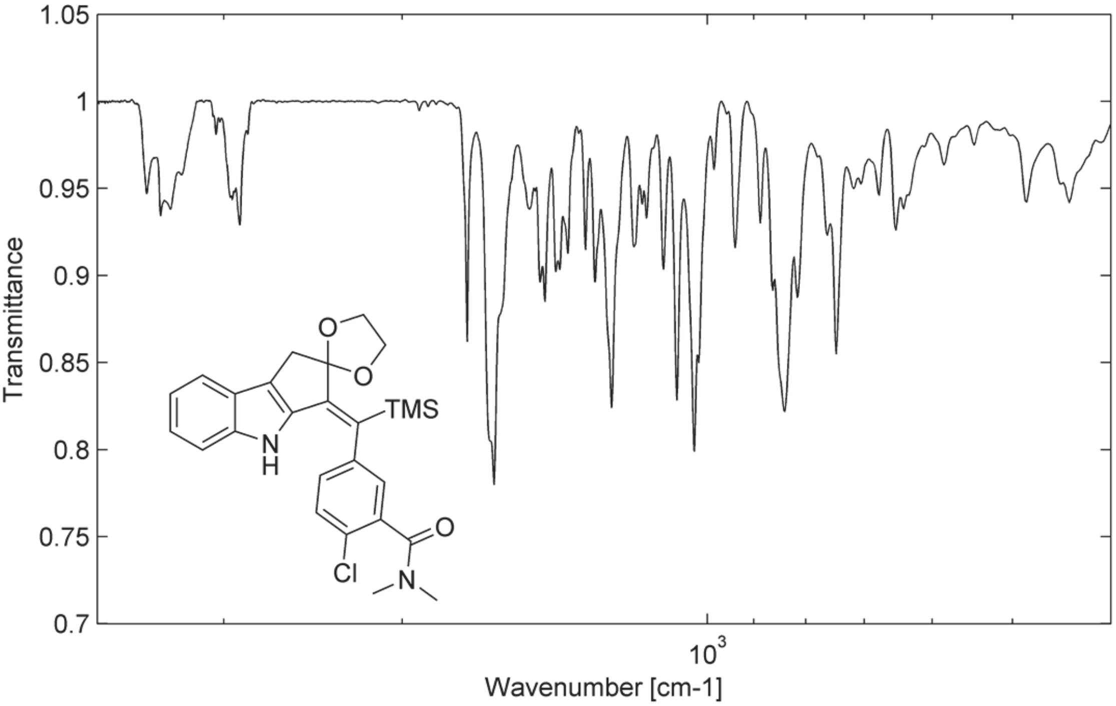

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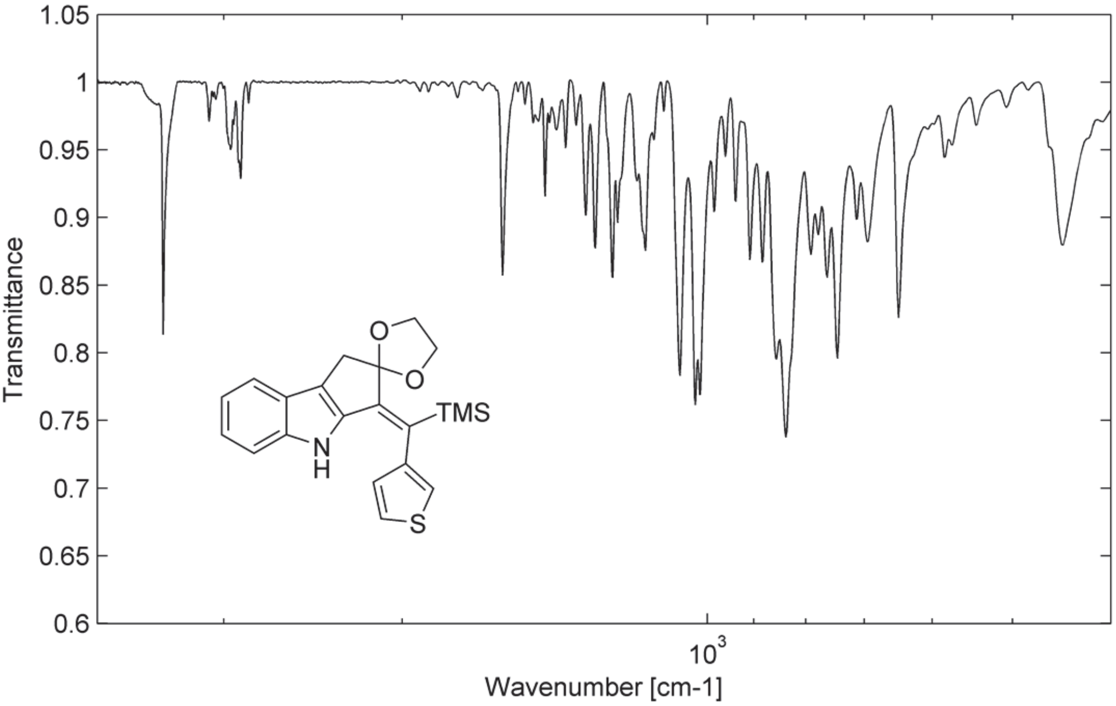

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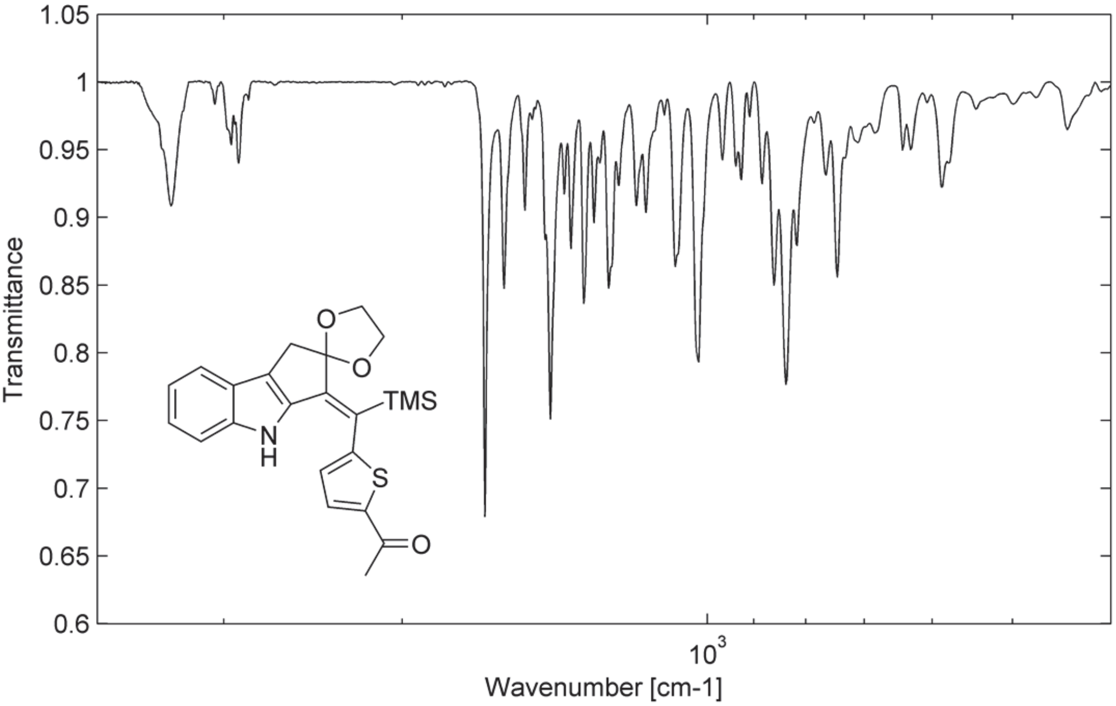

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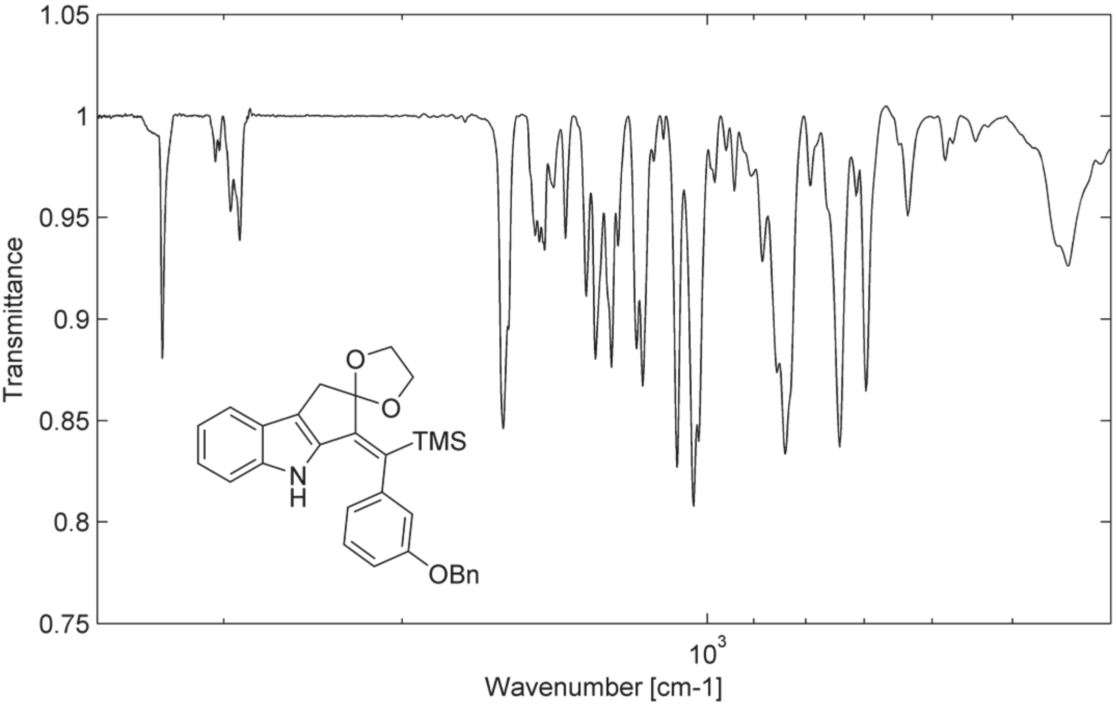

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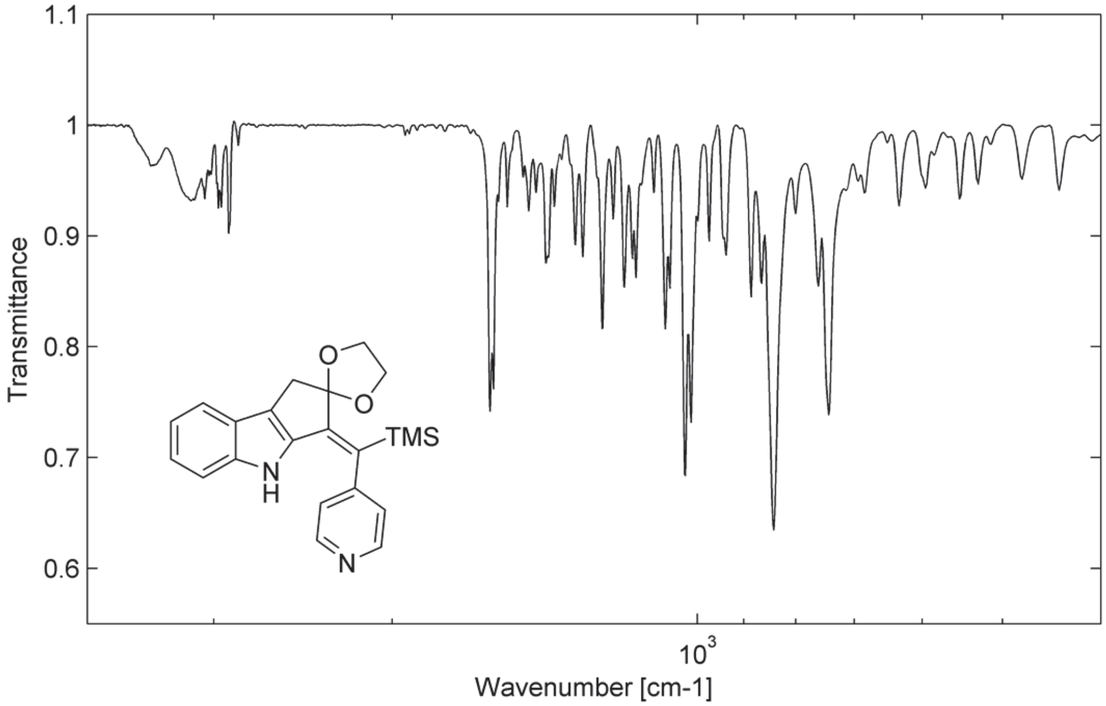

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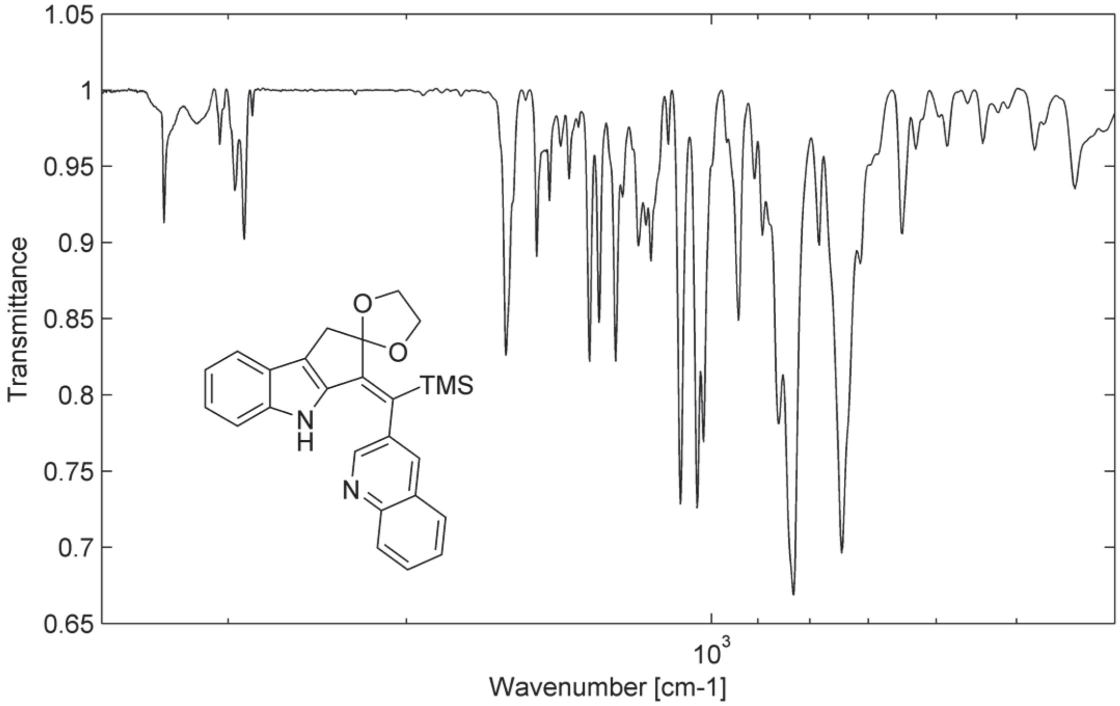

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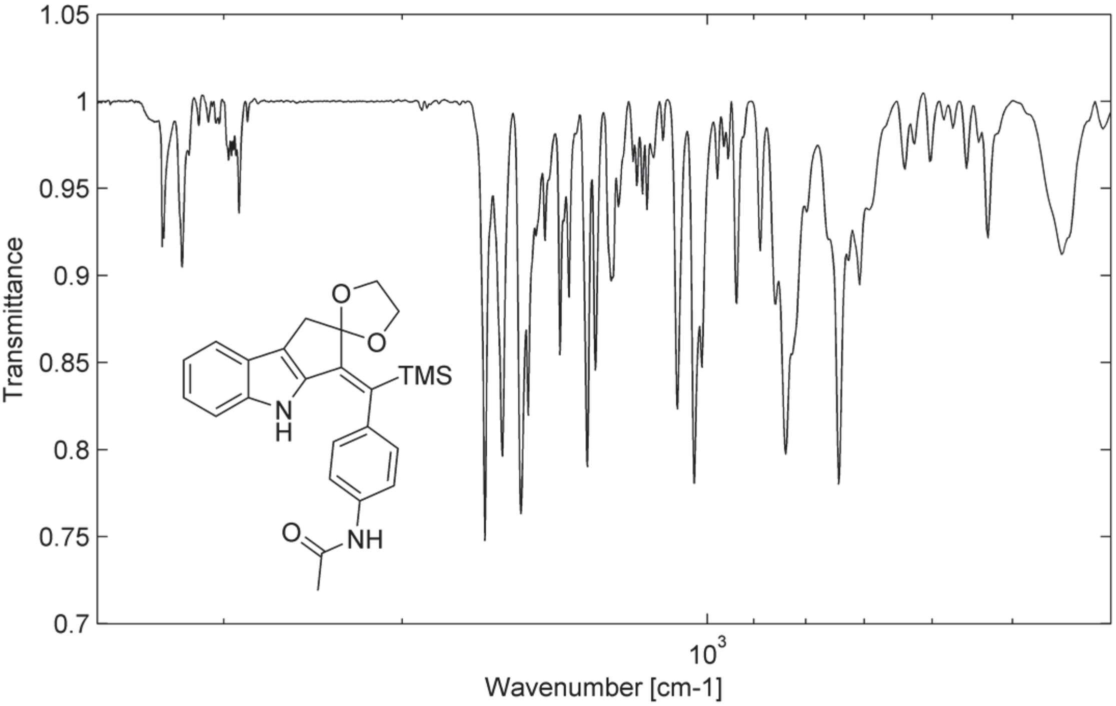

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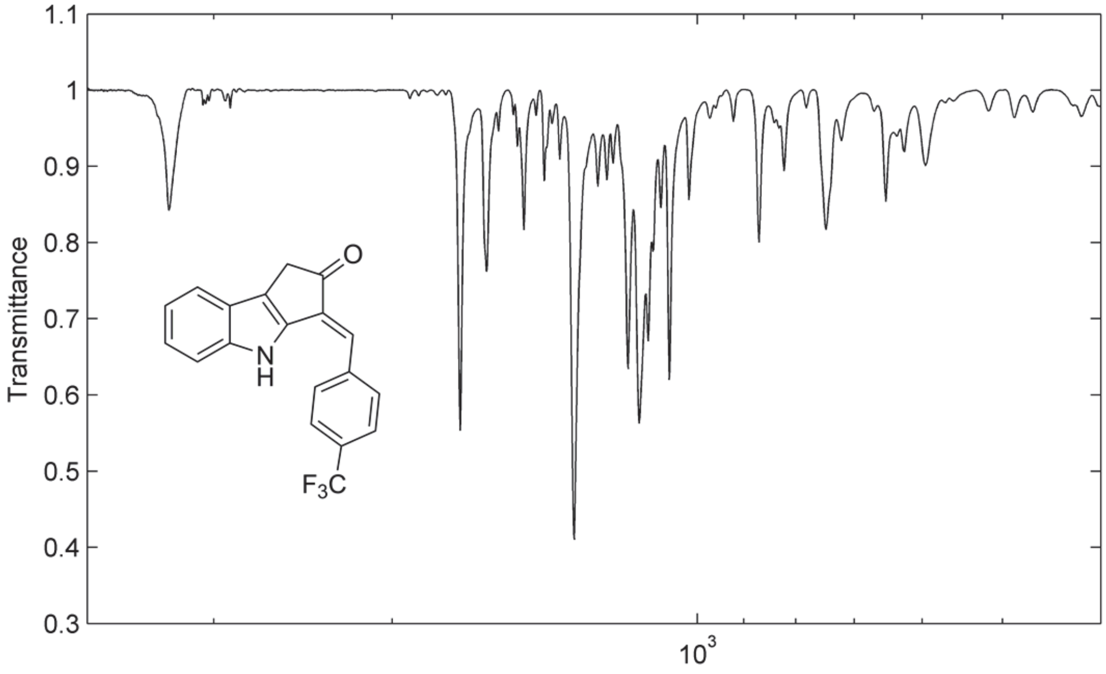

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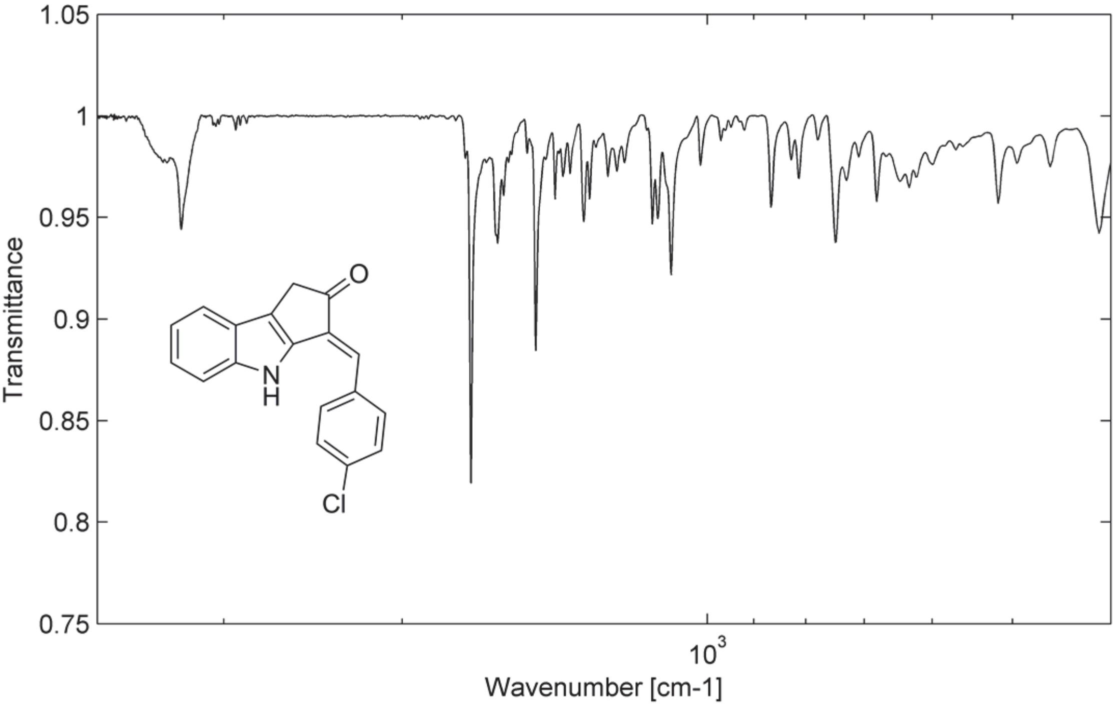

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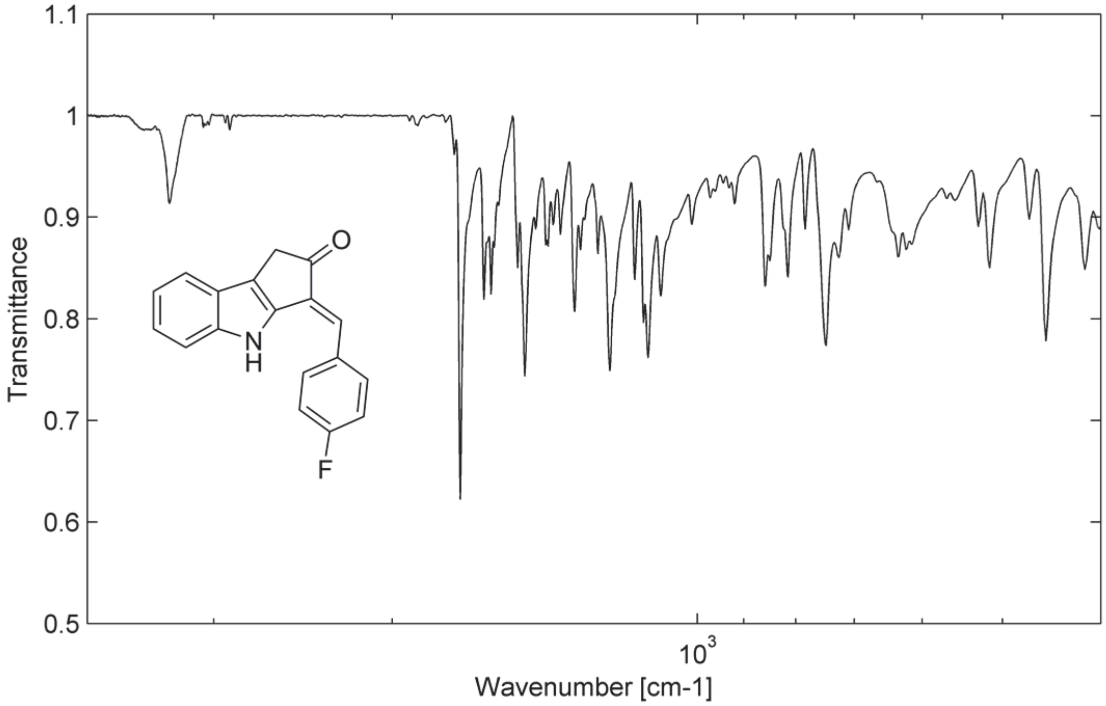

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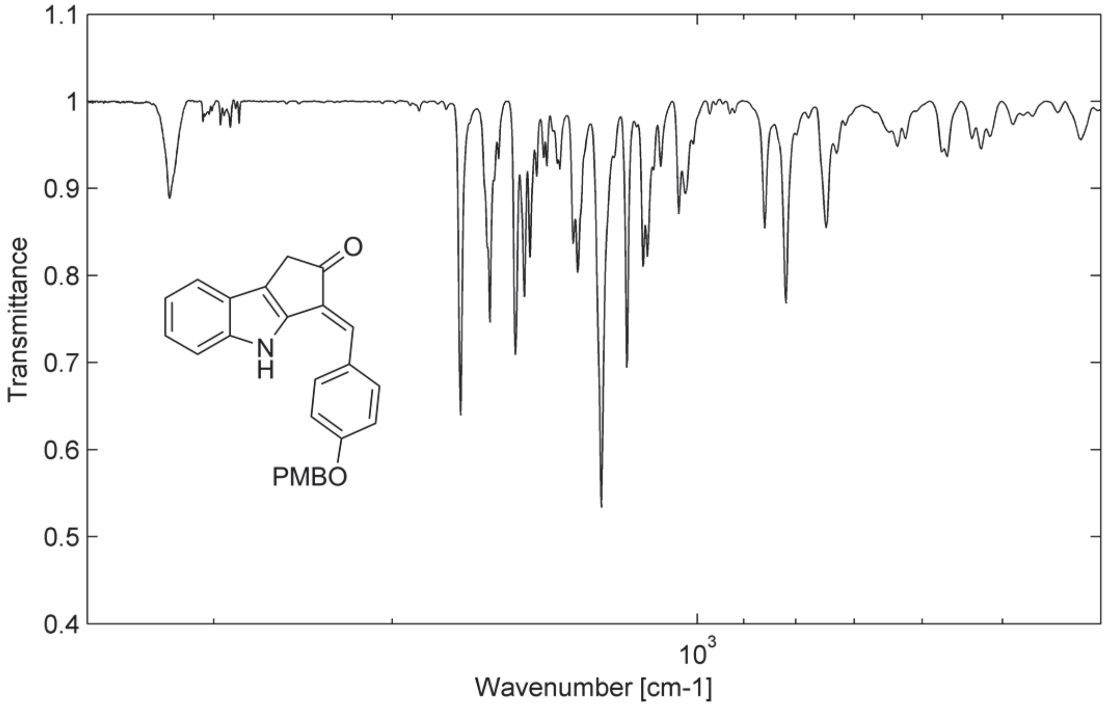

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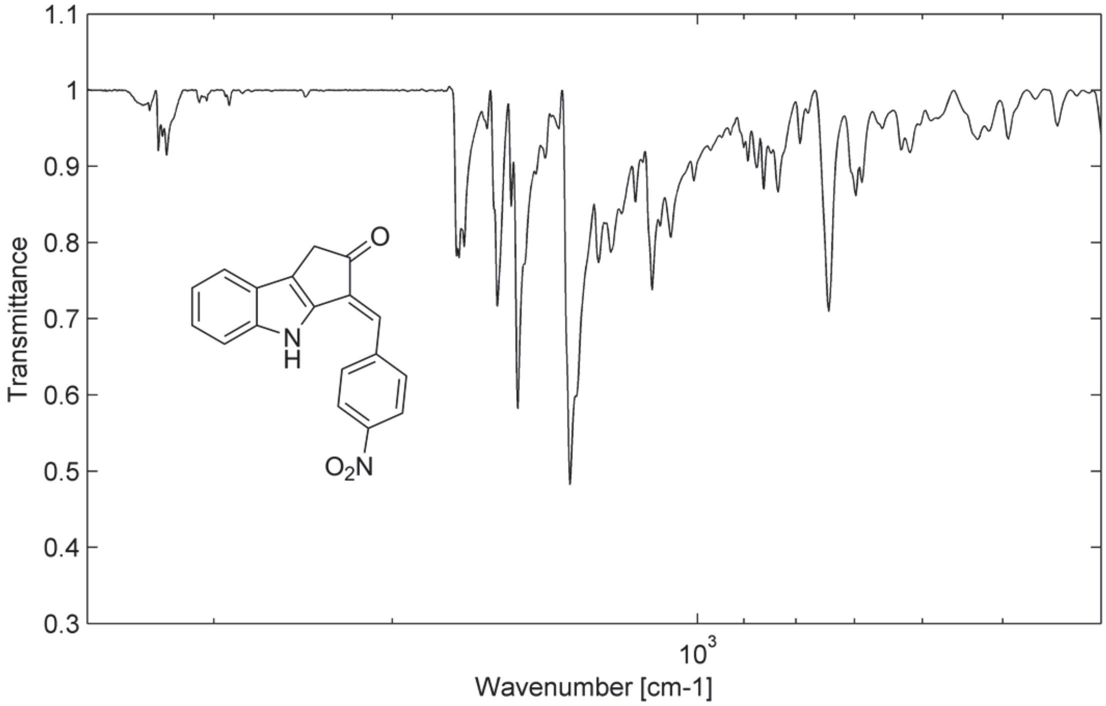

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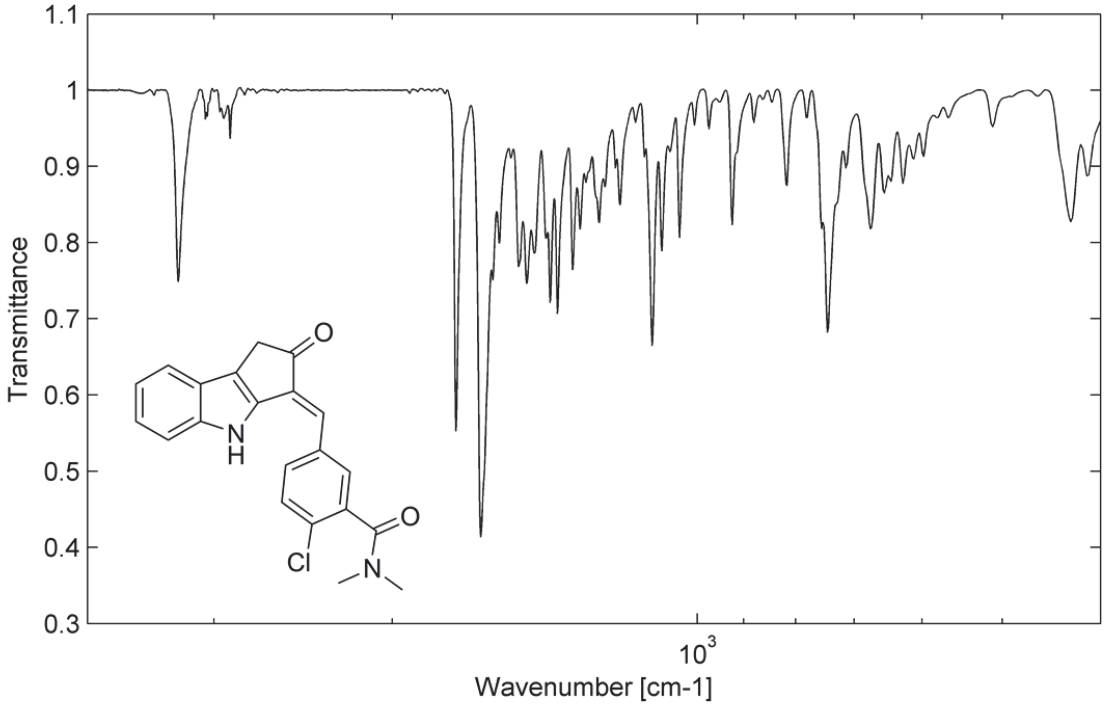

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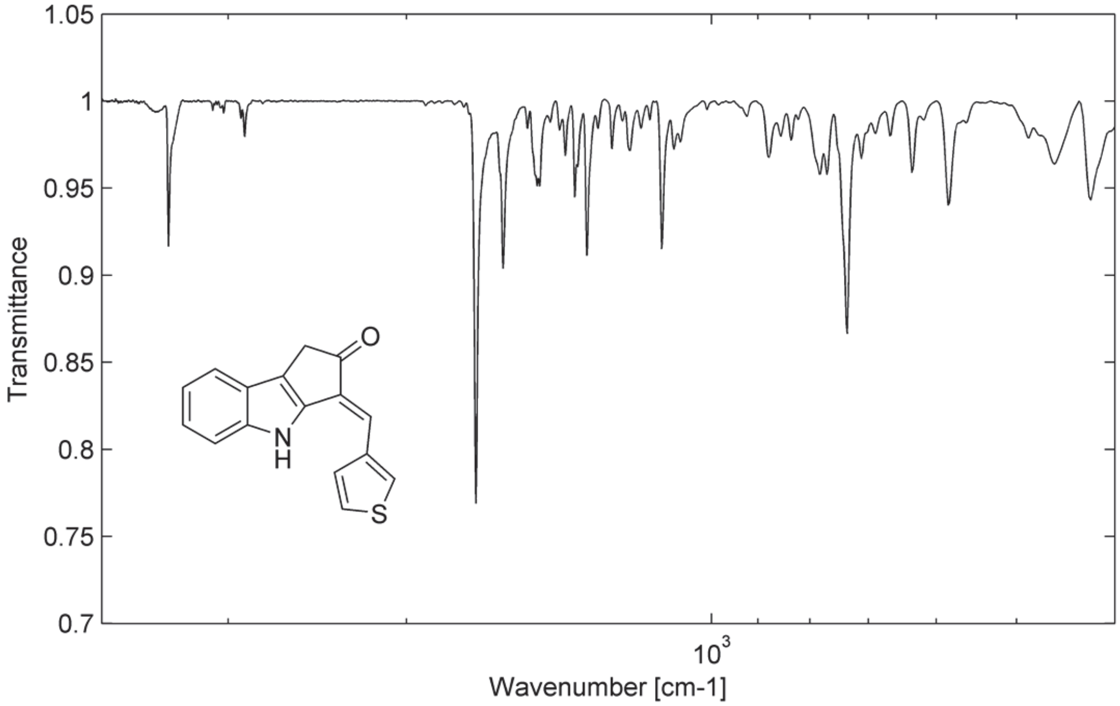

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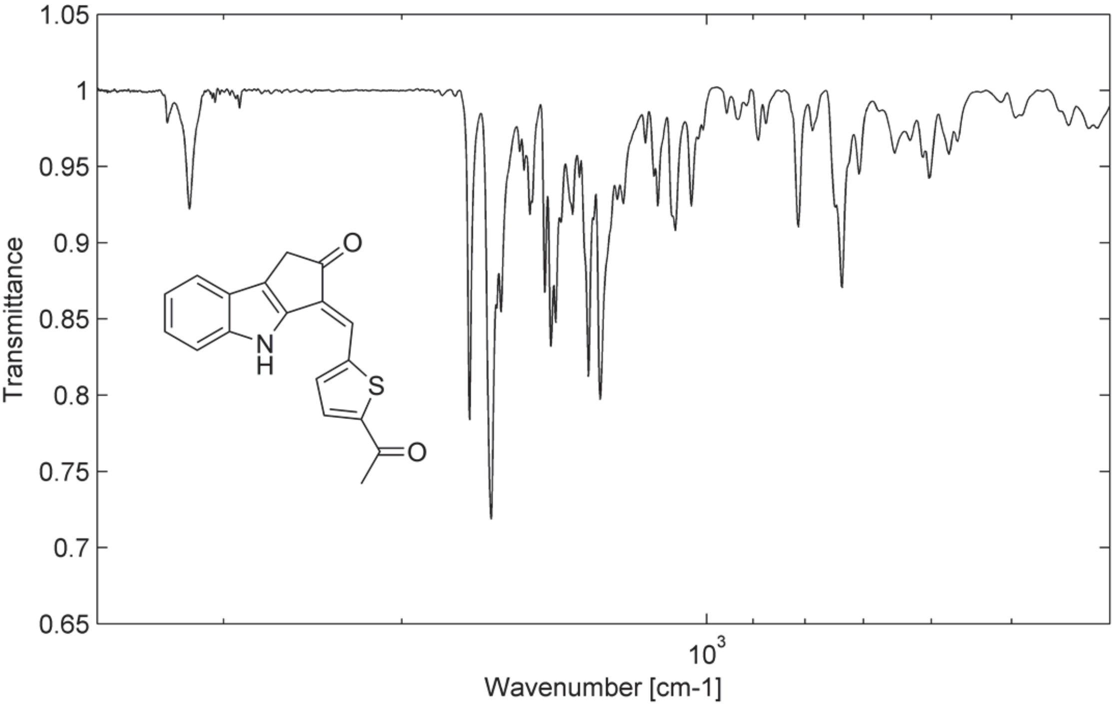

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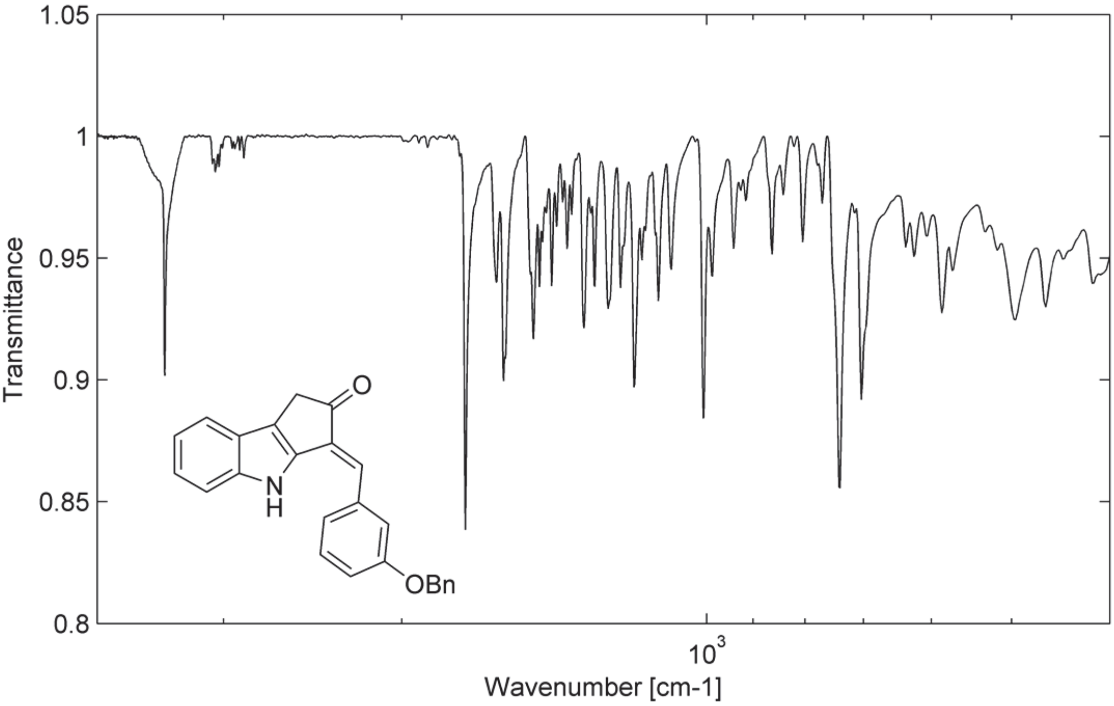

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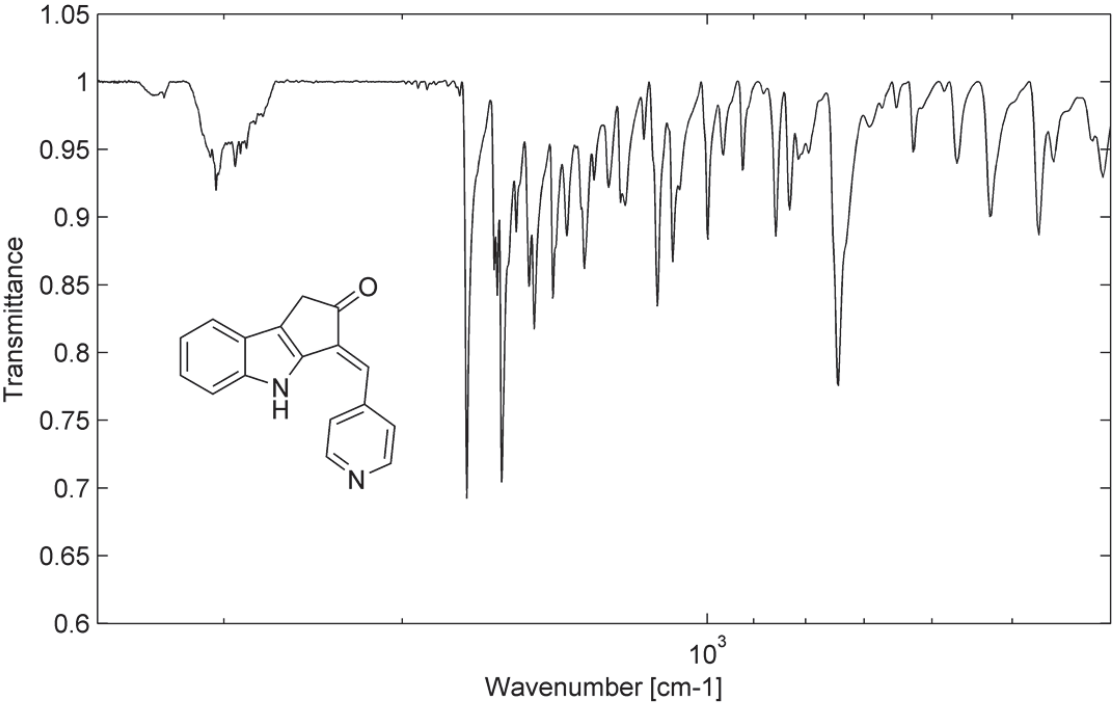

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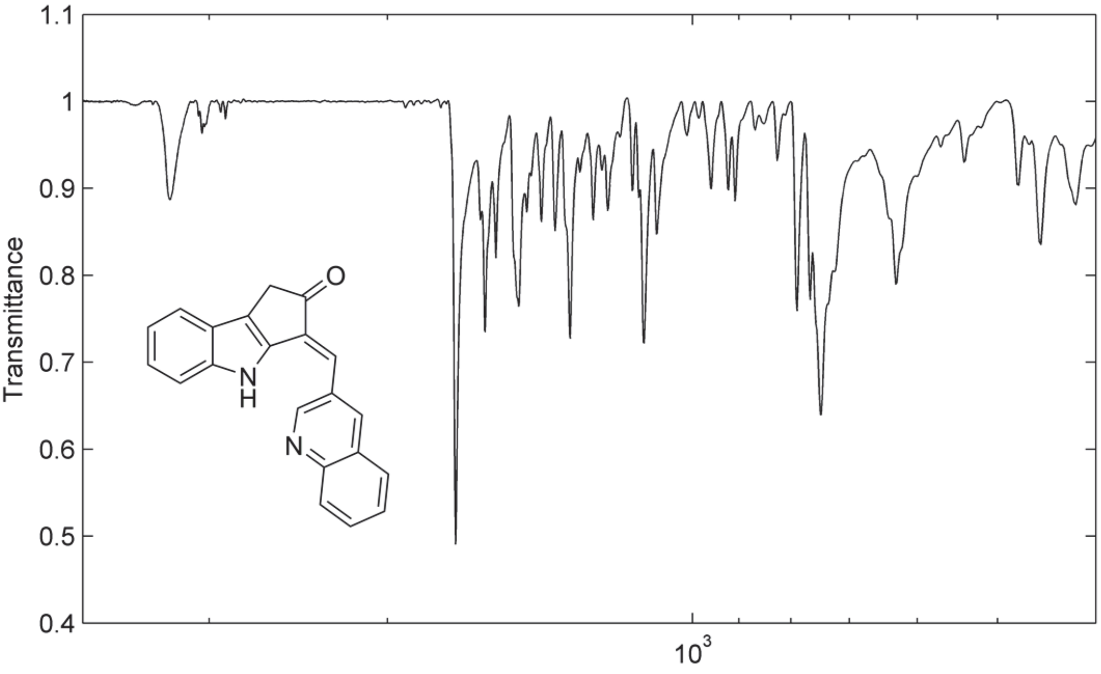

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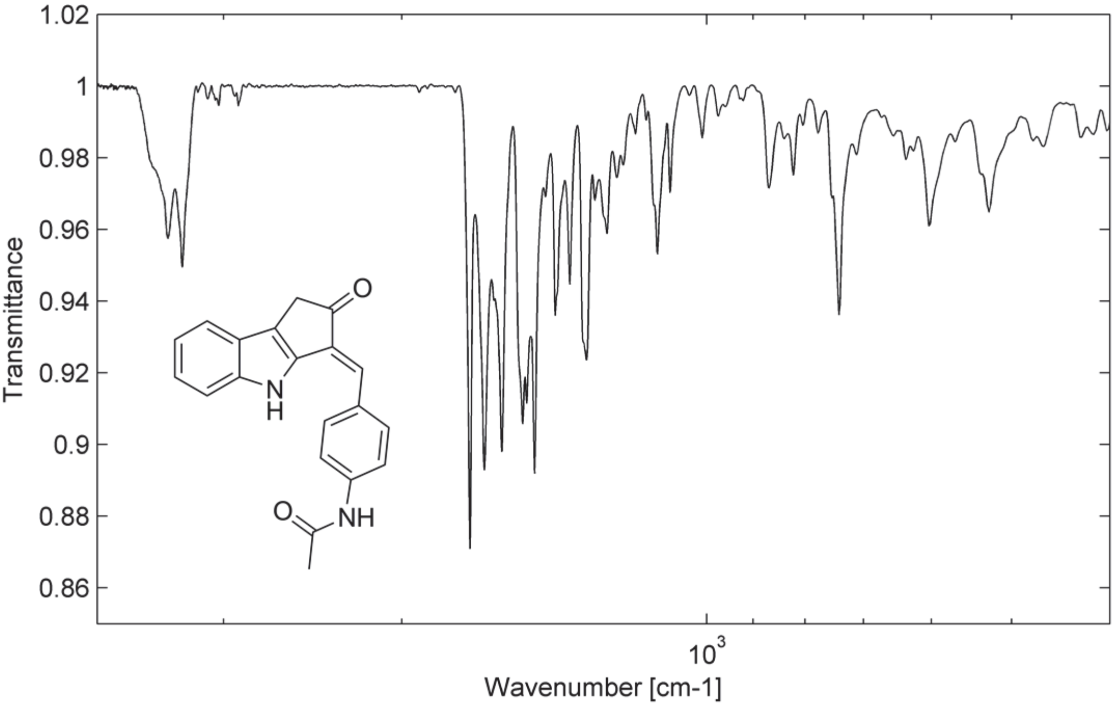

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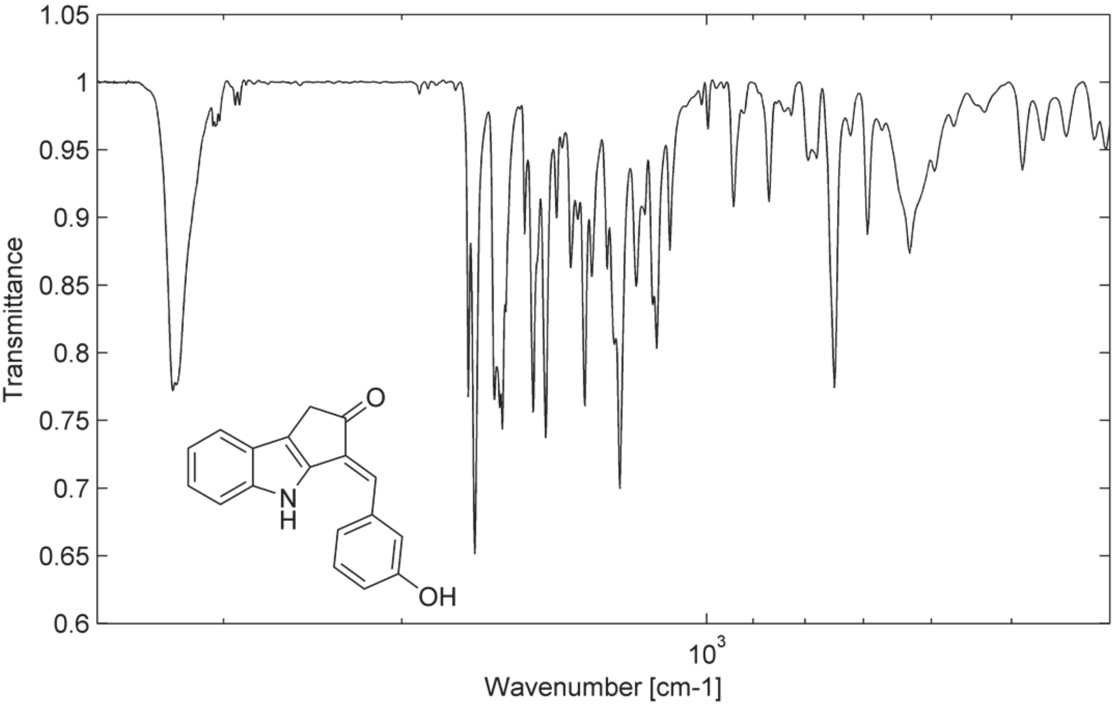

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