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Supporting Online Material for

Nanomolar-scale high-throughput chemistry for the synthesis of complex molecules

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Materials and Methods

Supplementary Text

Figs. S1 to S32

Tables S1 to S11

References

Other supplementary material for this manuscript includes the following:

Data files S1 to S5

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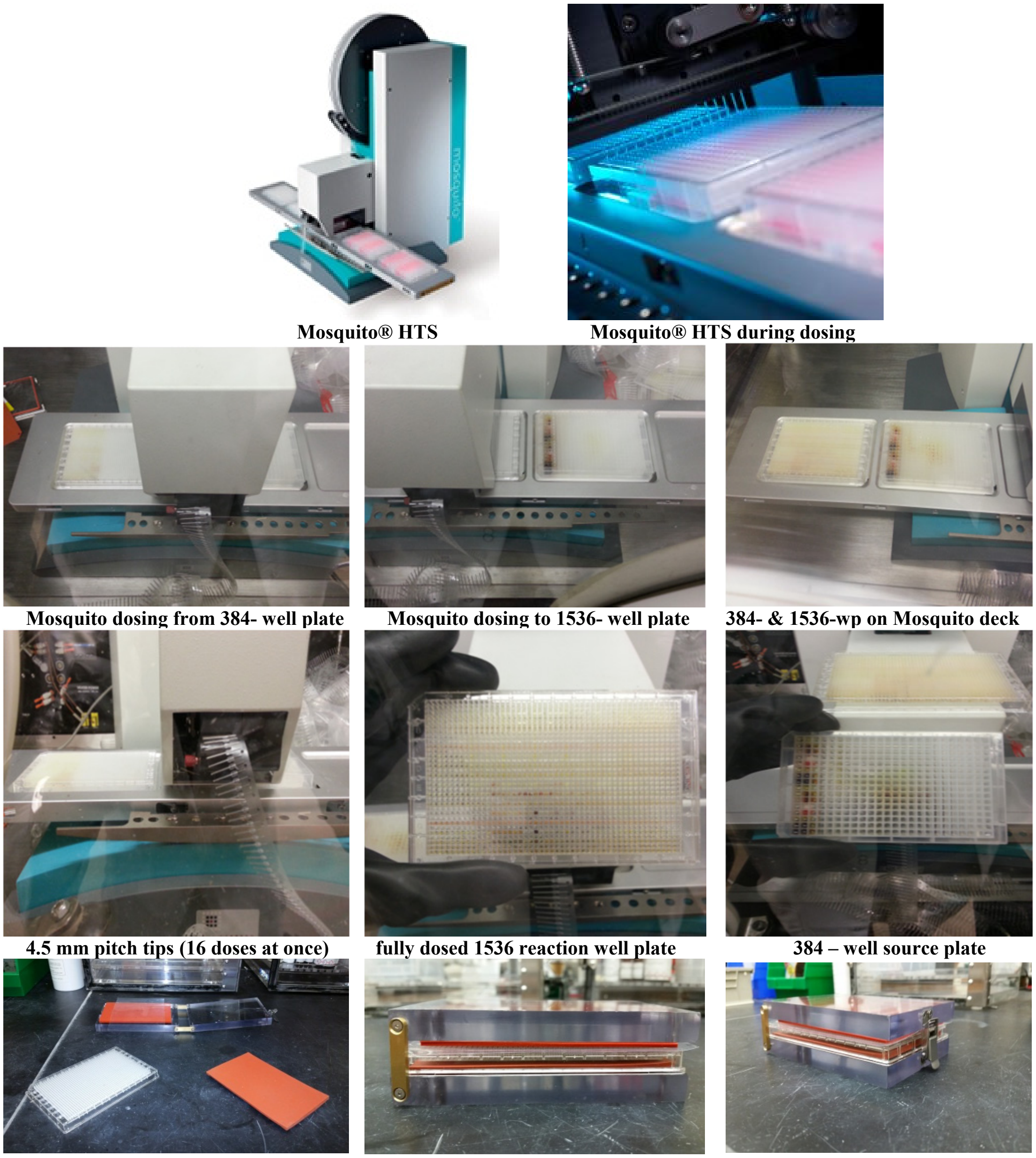
Materials and Methods.

All reagents were used as purchased from commercial suppliers. Solvents were purchased from Sigma Aldrich, anhydrous, sure-seal quality, and used with no further purification. The palladium precratalysts and bases were purchased from commercial sources and stored in the glovebox. All reactions, including parallel synthesis, were performed inside an MBraun glovebox operating with a constant N2-purge (oxygen typically <5 ppm). The experimental design was accomplished using Free-Slate Library Studio.

Nanomolar Scale Chemistry Experiments. Nanoscale reactions (50-100 nmol) were run using Corning® 1536-well plates (Corning Echo™ qualified, Cat. No. 3730, Cyclic Olefin-Copolymer COC, 12.5 µL-wells, flat bottom, clear) as reaction plates, and typically with Advantage™ 384-well plates (Analytical-Sales, Cat. No. 38120, polypropylene, 120 µL-wells, flat bottom, clear) used as solution source plates for stock solutions and for analytical plates on UPLC-MS or HPLC-MS equipment. Dosing of reaction components into the 384- and 1536-well plates was accomplished in the glovebox using a Mosquito® HTS liquid handling robot (**Figure S1**, TTP Labtech, 4.5 mm pitch tip spool) with no special modifications, and using the TTP Labtech native software. Upon dosing, the 1536-well plates were covered by a perfluoroalkoxy alkane (PFA) mat (Analytical-Sales, Cat. No. 96981), followed by a silicon rubber mat (Analytical-Sales, Cat. No. 96982) and then secured with a clamp (Arctic White, Cat. No. AWSC-051001).

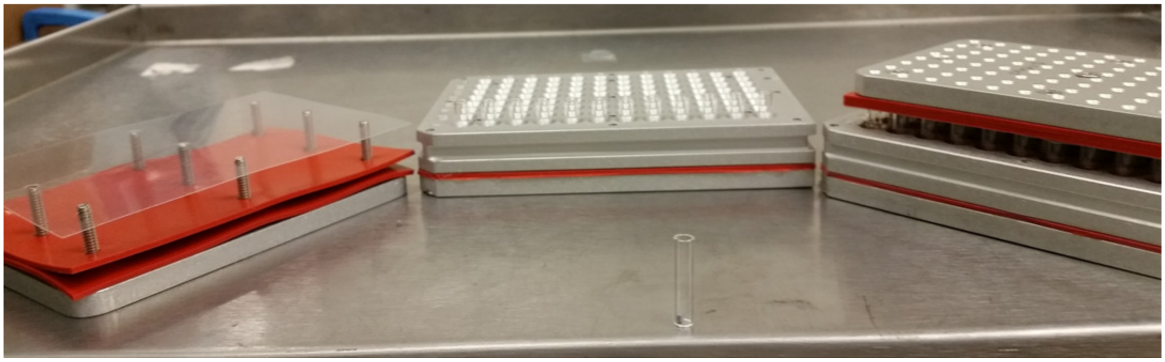
Figure S1. TTP Labtech Mosquito® – Dosing, Tips, and Plates.



Mosquito® HTS
Mosquito® HTS during dosing
Mosquito dosing from 384- well plate
Mosquito dosing to 1536- well plate
384- & 1536-wp on Mosquito deck
4.5 mm pitch tips (16 doses at once)
fully dosed 1536 reaction well plate
384 – well source plate
1536-wp clamping accessories
clamped 1536-wp - lateral view
clamped 1536-wp - perspective view

Micromolar Scale Chemistry Experiments. Micromolar scale reactions (2.5 µmol) were carried out in glass microvials (Analytical-Sales, Cat. No. 10421, 4 x 21 mm, 250 µL, flat bottom) equipped with magnetic tumble stir bars (Analytical-Sales, Cat. No. 13257, 1.32 x 1.57 mm) in anodized aluminum mini 96-well reaction plates (Analytical-Sales, Cat. No. 96970). Liquid handling was done using single and multi-channel Eppendorf pipettors. On completion of solution dosing to the microvials, the plates were covered by a perfluoroalkoxy alkane (PFA) mat (Analytical-Sales, Cat. No. 96981), followed by two silicon rubber mats, and an aluminum cover which was tightly and evenly sealed by 9 screws (**Figure S2**).

Figure S2. Microvials and 96-Well Reaction Plates with Accessories.



Scale-up Chemistry Experiments. Scale-up reactions were run in glass vials, as described in experiments below. Manual liquid handling of solutions or slurries was done using single channel Eppendorf pipettors. Dosing of solids was also done by concentration of their corresponding solutions using a Genevac inside the glovebox or by weighing compounds directly into reaction vials. When heating was required, the reaction vessels were equipped with a heating block and placed on a tumble-stirrer (V&P Scientific) or on an IKA stirring hotplate (Chemglass).

UPLC/ UPLC-MS Reaction Assay. Reactions were monitored using a Waters Acquity UPLC or UPLC-MS. Column: Acquity UPLC BEH C18 1.7um 2.1x50mm (Part # 186002350), pH 3.5 Stock Solution: 12.6g ammonium formate + 7.9ml formic acid to 1L water, Mobile Phase A: 40ml pH 3.5 stock solution + 3960ml Water, Mobile Phase B: 40ml pH 3.5 stock solution + 360ml Water + 3600ml ACN, Strong Wash: 300ml IPA + 693ml ACN + 7ml pH 3.5 stock solution, Weak Wash: 99ml ACN + 891ml Water + 10ml pH 3.5 stock solution. The instrument was equipped with an SQD detector with electrospray ionization (ESI) source in the positive mode. High throughput data analysis to produce Excel spreadsheets was done with Virscidian Analytical Studio^{TM} software.

Compound Purification. Purification of desired products was done via automated CombiFlash Chromatography (Silica gel ISCO column, 0 – 10% MeOH in CH_2Cl_2) or via Mass Spectrometry-directed purification (Reverse phase column C-18, Water/Acetonitrile with 0.1% TFA or NH_4OH modifier; or SFC column, MeOH). Water/Acetonitrile mixtures were lyophilized at -78 ^{o}C and MeOH solutions were evaporated via Genevac at room temperature.

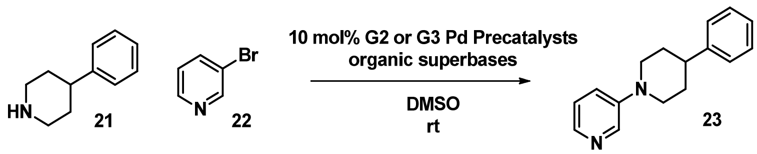
MISER Acquisition. Reversed phase HPLC experiments were performed on an Agilent 1100 system. The Agilent stack was comprised a G1312A binary pump, G1367A WPALS autosampler, G1315B diode array detector and a 6120 Quadrupole LC/MS detector with electrospray ionization in the positive mode. The system was controlled by Chemstation software, with the FIA mode enabled. Separations were carried out on a 3.0 mm i.d. by 20 mm length, 1.8 μm SB-C18 column by isocratic elution at a flow rate of 1.5 mL/ min. The LC eluents were 7 % solvent A (2 mM NH_4HCOO in H_2O, pH 3.5) and 93 % solvent B (2 mM NH_4HCOO in 90/10 ACN/ H_2O, pH 3.5). The column and samples were maintained at a temperature of 35 and 25°C, respectively. The MISERgrams were obtained from continuous sample injections (0.5 μL) every 22s. The positive ion ESI parameters were fragmentor 60 V, skimmer 45 V, desolvation gas (N_2), temperature 350°C and flow rate 12 L/min, the nebulizer was adjusted to 35 psig and the capillary voltage to 3000 V.

MS/MS MISER Approach. Reversed phase parallel HPLC experiments were performed on a Thermo Aria Transcend LX-2 inlet system interfaced with an Applied Biosystems Sciex (AB Sciex) mass spectrometer for detection. The Transcend LX-2 was comprised of a CTC LEAP HTS autosampler, two Flux Rheos 2000 UPLC binary pumps, and a Cohesive Valve Interface Module. This ensemble was controlled by Aria 1.6.3 software. The AB Sciex mass spectrometer was an API 4000 Q-Trap hybrid triple quadrupole/linear ion trap, running Analyst 1.6.2 software. Trap-and-elute chromatography was carried out on a Waters 2.1 mm i.d. by 10 mm length, 3.5 μm XSelect HSS C18 column by step gradient elution at a flow rate of 1 mL/min. Mobile phase A consisted of 0.1% formic acid in water and mobile phase B consisted of 0.1% formic acid in acetonitrile. The gradient was begun at 5% B and held there for 2 seconds, stepped to 100% B and held for 10 seconds, then stepped back to 5% B and held for 20 seconds. The column and samples were maintained at ambient temperature. The Transcend LX-2 was employed in multiplexed mode, allowing for a 22-second injection cycle to be achieved (5ul injected/sample). The mass spectrometer was operated in positive ESI mode and programmed to acquire MRM spectra. The source voltage was set at 3500V and a global collision energy of 5V was used for all MRM experiments.

Compound Characterization. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX400 w/ 5mm 1H/13C/19F/31P Quad probe with Z-Gradient and a Bruker Avance AV-500 w/ 5mm ATM Inverse Broad Band (BBI) probe with XYZ-Gradient with a BACS 120 sample changer. Chemical shifts are reported as parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz). IR Spectra were measured using a Nicolet Nexus 670 FT-IR Spectrometer. HRMS measurements were performed on an Agilent 1290 LC-HRMS Infinity liquid chromatography system equipped with a G4220A binary pump, G4212A diode array detector, G4226 Autosampler, and G1316C thermostated column compartment. The LC system was coupled to an Agilent 6520 Q-TOF mass spectrometer equipped with electrospray ionization (ESI) source in the positive mode. The system was controlled by MassHunter® software, the positive ion ESI parameters were: fragmentor 55 V, skimmer 65 V, desolvation gas (N_2), temperature 350 ˚C and flow rate 13 L/min, nebulizer 60 psig. Full-scan mass spectra were acquired over the range m/z 100–1000 at an acquisition rate of 2 spectra/s. Spectra were recorded in centroid mode. G1969-85001 ES-TOF Reference Mass Solution Kit (Agilent Technologies) was used for continuous autocalibration.

Experimental

Experiment 1. Pd C-N Coupling Reactions of 4-Phenylpiperidine 21 and 3-Bromopyridine 22: A Comparative Experiment between Reactions in 1536-Well and 96-Well Plate Microvials



Procedure for 96 Nanomolar Scale (1 uL volume) Reactions in a 1536-Well Plate (Run in Triplicate). Stock solutions of each of the reaction components were made as follows: 4-phenylpiperidine **21** (0.6 M in DMSO), 3-bromopyridine **22** (17, 0.4 M in DMSO), organic superbases (**24-29**, 0.8 M in DMSO, **Figure S3**), and Pd-precatalyst (**30-45**, 0.04 M in DMSO, **Figure S4**). For the 1536-well plate experiment, each of the solutions was dispensed in 75 uL charges to a 384-well source plate (source plate map is shown in **Figure S5**, components listed in **Table S1**).

Figure S3. Structures of Organic Superbases.

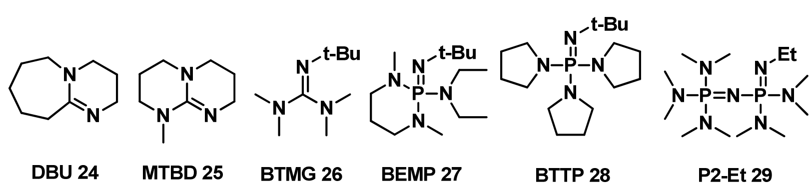


Figure S4. Structures of Phosphine-ligated Pd Pre-catalysts.

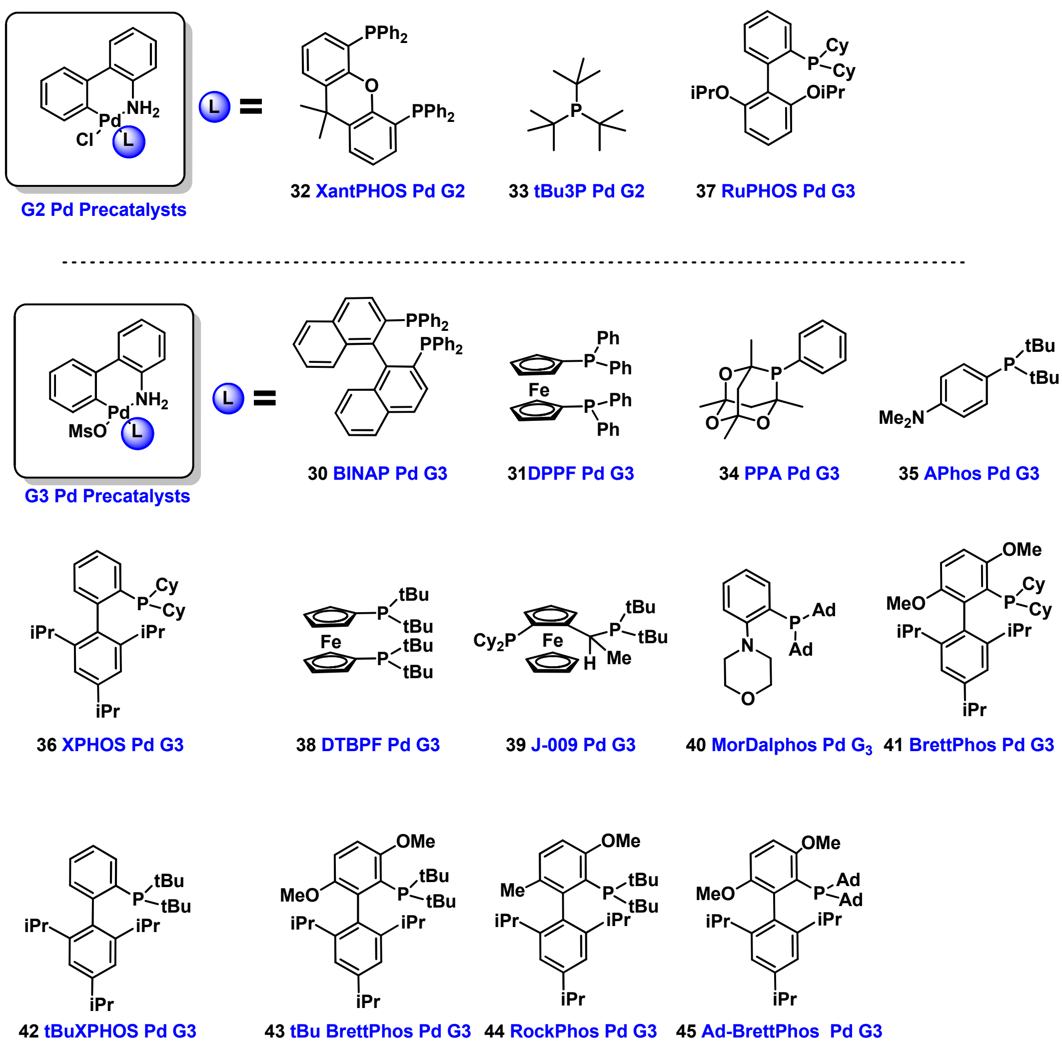


Figure S5– Solution Positions for the 384-Well Source Plate.

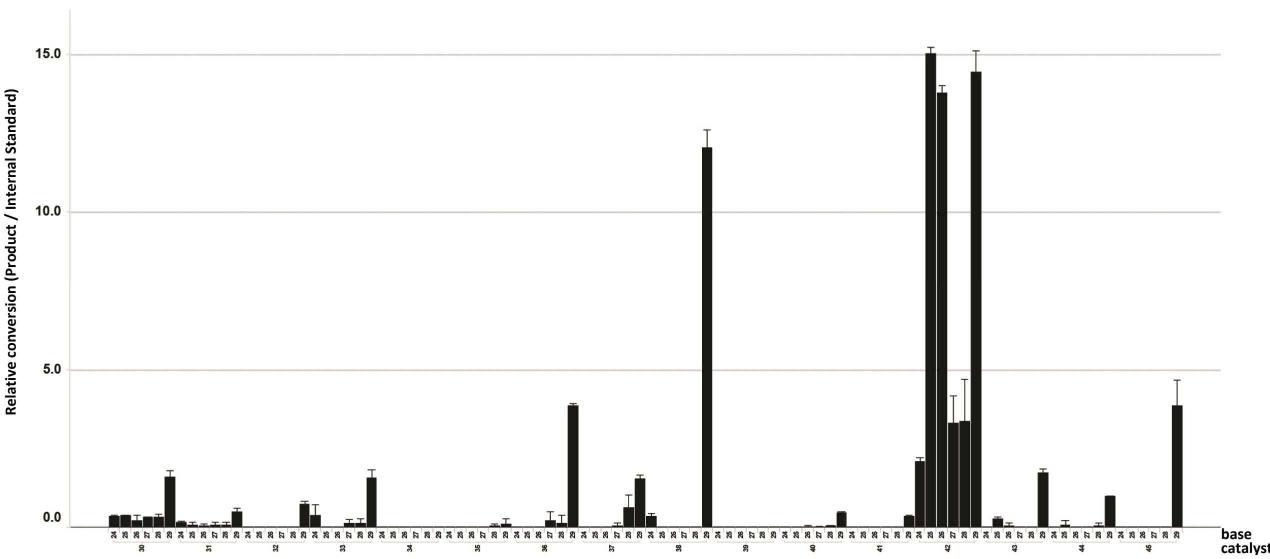
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
A	1	17	18	19	20	21	22	23	24															
B	2	17	18	19	20	21	22	23	24															
C	3	17	18	19	20	21	22	23	24															
D	4	17	18	19	20	21	22	23	24															
E	5	17	18	19	20	21	22	23	24															
F	6	17	18	19	20	21	22	23	24															
G	7	17	18	19	20	21	22	23	24															
H	8	17	18	19	20	21	22	23	24															
I	9	17	18	19	20	21	22	23	24															
J	10	17	18	19	20	21	22	23	24															
K	11	17	18	19	20	21	22	23	24															
L	12	17	18	19	20	21	22	23	24															
M	13	17	18	19	20	21	22	23	24															
N	14	17	18	19	20	21	22	23	24															
O	15	17	18	19	20	21	22	23	24															
P	16	17	18	19	20	21	22	23	24															

Table S1. List of Component Solutions in the 384-Well Source Plate.

1	BINAP Pd G3 **30**	**7**	XPhos Pd G3 **36**	**13**	tBuXPhos Pd G3 **42**	**19**	DBU **24**
2	DPPF Pd G3 **31**	**8**	RuPhos Pd G2 **37**	**14**	tBuBrettPhos Pd G3 **43**	**20**	MTBD **25**
3	XantPhos Pd G2 **32**	**9**	DTBPF Pd G3 **38**	**15**	RockPhos Pd G3 **44**	**21**	BTMG **26**
4	tBu3P Pd G2 **33**	**10**	J-009 Pd G3 **39**	**16**	AdBrettPhos Pd G3 **45**	**22**	BEMP **27**
5	PPA Pd G3 **34**	**11**	MorDalPhos Pd G3 **40**	**17**	3-Bromopyridine **22**	**23**	BTTP **28**
6	APhos Pd G3 **35**	**12**	BrettPhos Pd G3 **41**	**18**	4-Phenylpiperidine **21**	**24**	P2Et **29**

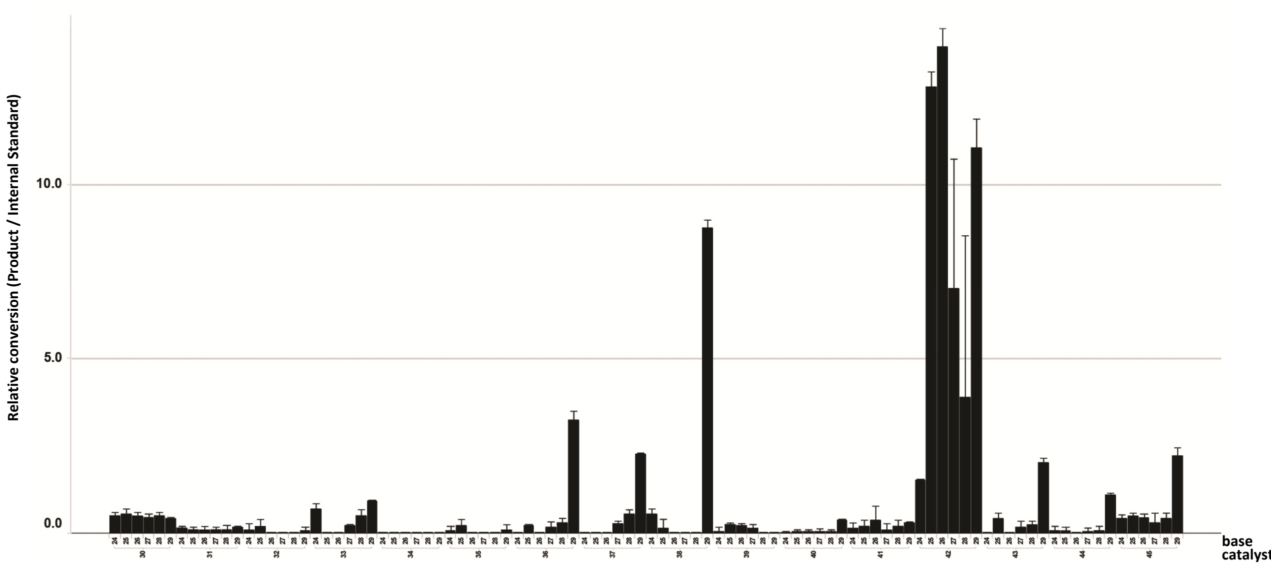
The Mosquito® robotics instrument was used to combine the source plate solutions by multi-aspiration of 250 nL of each of the four reaction components and then to dose the resulting reaction mixture (1 uL) into a 1536-well plate. Once the 1536-well plate was fully dosed, it was covered with a PFA film, clamped to minimize low-level component volatility, and then allowed to sit at room temperature for 22 hours. Using the Mosquito, the plate was then quenched with 3 uL of a DMSO stock solution of acetic acid and biphenyl (resulting in 3 mol% biphenyl relative to **22**), which was transferred from a source 384-well plate. The Mosquito then sampled 1 uL from the quenched reaction plate into a 384-well plate containing 75 uL of DMSO per well. The Mosquito mixing feature was used three times per aspiration and dispense steps in order to ensure homogeneity of the analytical sample. The 384-well plate was then heat-sealed and subjected to chromatographic analysis by a Waters UPLC Instrument. The ratio of the LC area counts of product over internal standard was used to directly compare the relative performance of these reactions. Plate mapping and raw Excel data containing these LC area count ratios for the 1536-well plate **Experiment 1** can be found in **Data S1**. The graphical representation of this data is shown in **Figure S6**.

Figure S6. Relative Performance of the Coupling of **21** and **22** for Each of the 96 Conditions in the 1536-Well Plate Based on Ratio of LC Area Counts of Product to Internal Standard. Statistical Error Bars are Shown for the Triplicate Runs.

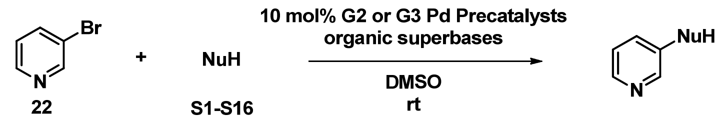


Procedure for 96 Micromolar Scale (25 uL volume) Reactions in Glass Microvials (Run in Triplicate). For the 96-well microvial experiments, freshly generated solutions of starting materials and reagents were used, dispensed via single- or multi-channel pipettors in 4 x 6.25 uL charges into 100 uL microvials equipped with stir bars housed in a metallic 96-well plate. The reaction components were dosed in the following order: precatalyst (**30-45**), 3-bromopyridine **22**, 4-phenylpiperidine **21**, and bases (**24-29)**. The plate was sealed with a PFA film, shaken briefly, then clamped as described in the materials and methods section, and allowed to stir at room temperature for 22 hours. The reactions were then quenched by addition 10 uL of a solution of acetic acid and 3 mol% biphenyl (relative to **22**) in DMSO. The plate was resealed and shaken for thorough mixing. The reaction samples were transferred in charges of 1.82 uL into a 384-well plate containing 90 uL of DMSO per well using multichannel pipettes. The 384-well plate was then heat-sealed and subjected to chromatographic analysis by a Waters UPLC Instrument. The ratio of the LC area counts of product to internal standard was used to directly compare the performance of these reactions in the 1536-well plate and 96-well plate microvials. Plate mapping and raw Excel data containing these LC area count ratios for the 96-well plate **Experiment 1** can be found in **Data S1**. The graphical representation of this data is shown in **Figure S7**.

Figure S7. Relative Performance of the Coupling of **21** and **22** for Each of the 96 Conditions in the 96-Well Plate Based on Ratio of LC Area Counts of Product to Internal Standard. Statistical Error Bars are Shown for the Triplicate Runs.



Experiment 2. 1536-Well Plate Screening of Pd Cross-Coupling Reactions of 3-Bromopyridine 22 with 16 Nucleophiles (16 Precatalysts, 6 Bases)



A 1536-well plate experiment examining the reactivity of 3-bromopyridine **22** with 16 different classes of nucleophiles under 96 Pd cross-coupling reaction conditions was run at 100 nanomolar scale by dosing from a 384-well plate containing stock solutions of the starting materials and reagents into a 1536-Well Plate by Mosquito.

Procedure. Stock solutions of each of the reaction components were prepared as follows: Pd-precatalysts (**30-45**, 0.04 M in DMSO), aryl halide (**22**, 0.4 M in DMSO), nucleophiles (**S1-S16**, 0.6 M in DMSO), and base (**24-29**, 0.8 M in DMSO). Each of the solutions was dispensed in 75 uL charges to a 384-well plate (source plate map is shown in **Figure S8**, components listed in **Table S2**).

Figure S8. Solution Positions for the 384-Well Source Plate.

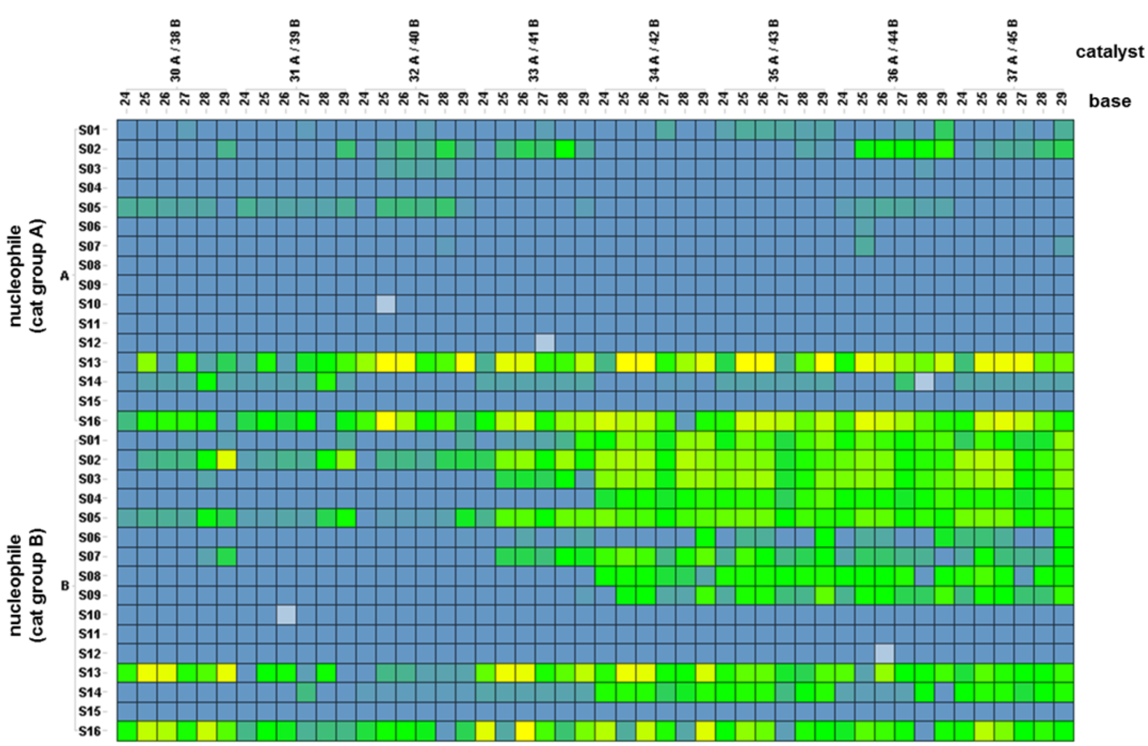
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
A	1	2	17	18	19	20	21	22	23	24	25	34	35	36	37	38	39							
B	3	4	17	18	19	20	21	22	23	24	25	34	35	36	37	38	39							
C	5	6	17	18	19	20	21	22	23	24	25	34	35	36	37	38	39							
D	7	8	17	18	19	20	21	22	23	24	25	34	35	36	37	38	39							
E	9	10	17	18	19	20	21	22	23	24	25	34	35	36	37	38	39							
F	11	12	17	18	19	20	21	22	23	24	25	34	35	36	37	38	39							
G	13	14	17	18	19	20	21	22	23	24	25	34	35	36	37	38	39							
H	15	16	17	18	19	20	21	22	23	24	25	34	35	36	37	38	39							
I	1	2	17	26	27	28	29	30	31	32	33	34	35	36	37	38	39							
J	3	4	17	26	27	28	29	30	31	32	33	34	35	36	37	38	39							
K	5	6	17	26	27	28	29	30	31	32	33	34	35	36	37	38	39							
L	7	8	17	26	27	28	29	30	31	32	33	34	35	36	37	38	39							
M	9	10	17	26	27	28	29	30	31	32	33	34	35	36	37	38	39							
N	11	12	17	26	27	28	29	30	31	32	33	34	35	36	37	38	39							
O	13	14	17	26	27	28	29	30	31	32	33	34	35	36	37	38	39							
P	15	16	17	26	27	28	29	30	31	32	33	34	35	36	37	38	39							

Table S2. List of Component Solutions in the 384-Well Source Plate.

1 BINAP Pd G3 **30**
2 DPPF Pd G3 **31**
3 XantPhos Pd G2 **32**
4 tBu3P Pd G2 **33**
5 PPA Pd G3 **34**
6 APhos Pd G3 **35**
7 XPhos Pd G3 **36**
8 RuPhos Pd G2 **37**
9 DTBPF Pd G3 **38**
10 J-009 Pd G3 **39**
11 MorDalPhos Pd G3 **40**
12 BrettPhos Pd G3 **41**
13 tBuXPhos Pd G3 **42**
14 tBuBrettPhos Pd G3 **43**
15 RockPhos Pd G3 **44**
16 AdBrettPhos Pd G3 **45**
17 3-Bromopyridine **22**
18 4-Phenyl-2-aminobutane **S1**
19 Aniline **S2**
20 5-Phenylaminopyridine **S3**
21 Benzamide **S4**
22 Benzenesulfonamide **S5**
23 Phenylacetamidine **S6**
24 *t*-Butyl carbamate **S7**
25 Indazole **S8**
26 3-Phenyl-1-propanol **S9**
27 Phenol **S10**
28 Thiophenol **S11**
29 Diphenylphosphine **S12**
30 Diethyl malonate **S13**
31 1-Benzylpyrrazole-4-Boronic acid pinacol ester **S14****
****** includes 4 eq. of water
32 (*E*)-Ethyl cinnamate **S15**
33 4-*n*-Butyl-1-ethynylbenzene **S16**
34 DBU **24**
35 MTBD **25**
36 BTMG **26**
37 BEMP **27**
38 BTTP **28**
39 P2Et **29**

The Mosquito was used to combine the source plate solutions by multi-aspiration of 250 nL of each of the four reaction components and then to dose the resulting reaction mixture (1 uL) into a 1536-well plate. Once the 1536-well plate was fully dosed the plate was covered by a PFA film and clamped to minimize low-level component volatility. The plate was then allowed to sit at room temperature for 22 hours. Using the Mosquito, the plate was then quenched with 3 uL of a DMSO stock solution of acetic 5% acid and biphenyl (to give 3 mol% biphenyl relative to **22**), which was transferred from a 384-well source plate. The Mosquito then sampled 1 uL from the quenched reaction plate into 4 x 384-well plates containing 75 uL of DMSO per well. The Mosquito mixing feature was used three times per aspiration and dispense steps in order to ensure homogeneity of the analytical sample. The 384-well plate was then heat-sealed and subjected to chromatographic analysis by a Waters UPLC Instrument. The ratio of the LC area counts of product over internal standard was used to directly compare the relative performance of these reactions. Excel Data containing these ratios and LC area absolutes for starting materials and product for **Experiment 2** can be found in **Data S2**. The graphical representation (generated with TIBCO Spotfire) of this data is shown in **Figure S9**.

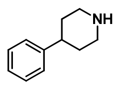
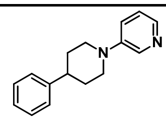
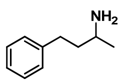
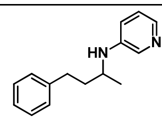
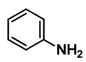
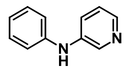
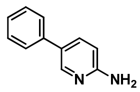
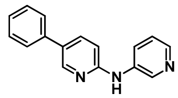
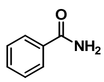
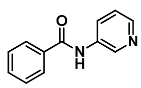
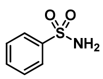
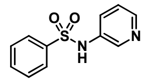
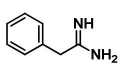
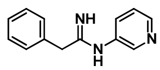
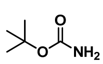
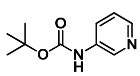
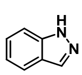
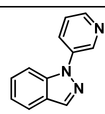
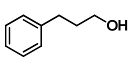
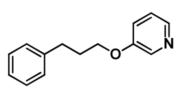
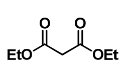
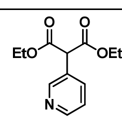
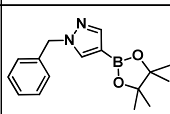
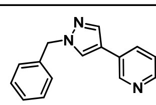
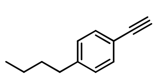
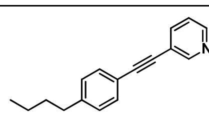
Figure S9. Spotfire Heat Map of the Relative Performance of the Coupling Reactions in Experiment 2 Based on the Ratio of LC Area Counts of Product to Internal Standard.



Experiment 3. Scale-up Experiments for Pd Cross-Coupling Reactions of 3-Bromopyridine 22 and Diverse Nucleophiles - General Procedure

In an oven-dried 4 mL vial equipped with stir bar, the nucleophile (0.480 mmol, 1.5 eq) was dissolved in dry DMSO (to 0.2 M concentration), then 3-bromopyridine **22** (0.320 mmol, 1.0 eq), the corresponding Pd precatalyst (16 µmol, 5 mol%) and organic superbase (0.640 mmol, 2.0 eq) were added sequentially. The reactions were allowed to stir at room temperature for 22 hours. Aliquots of each reaction (10 µL) were taken and treated with a solution of acetic acid in acetonitrile containing the 20 mol% of isopropyl biphenyl and subjected for UPLC-MS analysis to determine the reaction performance. The remaining reaction mixtures were quenched with saturated aqueous NH_4Cl (6.4 mL), followed by dilution and extraction with 2-methyltetrahudrofuran (2-MeTHF, 6.4 mL). The organic layer was separated, and the aqueous layer was extracted with additional 6.4 mL of 2-MeTHF. The combined organic layers were washed with brine (6.4 mL), filtered, and concentrated. The resulting reaction residues were purified via Combiflash Automated Chromatography (Silica gel, gradient 0 – 10% MeOH in CH_2Cl_2) or Mass Spectrometry-directed purification (Reverse phase C-18, Water/Acetonitrile with 0.1% TFA or NH_4OH modifier). For the latter method, the residues were reconstituted in DMSO (1.8 mL) and filtered prior to submission. For those reactions reporting NMR yields, the original reaction mixture was quenched and stirred with a solution of acetic acid in DMSO (1 mL), which contained 20 mol% of 4-isopropylbiphenyl as internal standard. ^{1}H NMR in DMSO-d_6 of the resulting mixture (50 µL, 400 MHz, DS = 10, NS = 32) was taken and representative product peaks were integrated in comparison to those of the internal standard to establish the corresponding yield. **Table S3** below contains conditions and yields for these experiments.

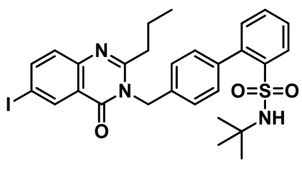
Table S3. Scale-up Conditions and Yields for Successful Coupling Reactions of **22** with Diverse Nucleophiles.

Nucelophile		Product	Pd Precatalyst	Base	% Yield	Conditions
21			tBuXPhos Pd G3 **42**	P2-Et **29**	**93**	
S1			tBuXPhos Pd G3 **42**	P2-Et 29	**91**	
S2			DTBPF Pd G3 **38**	P2-Et 29	**78**	
S3			AdBrettPhos Pd G3 **45**	MTBD 25	**80***	**40^{o}C** ***NMR yield**
S4			AdBrettPhos Pd G3 **45**	BTMG 26	**91**	
S5			tBuBrettPhos Pd G3 **43**	P2-Et 29	**77**	**40^{o}C**
S6			AdBrettPhos Pd G3 **45**	P2-Et 29*	**68****	***3 eq** ****by NMR**
S7			tBuXPhos Pd G3 **42**	MTBD 25	**86**	
S8			AdBrettPhos Pd G3* **45**	MTBD 25	**95****	***10 mol%** **40^{o}C** ****NMR yield**
S9			tBuBrettPhos Pd G3 **43**	P2-Et 29	**84***	***NMR yield**
S13			tBuBrettPhos Pd G3 **43**	MTBD 25	**86**	
S14			XantPhos Pd G2 **32**	MTBD 25	**93**	**w. 2 eq of H_2O**
S16			BrettPhos Pd G3 **41**	BTMG 26	**75**	

Experiment 4. 96-Reactions Scale-up Experiments for Pd-Cross Couplings of 8 Complex Aryl Bromides and 16 Nucleophiles

General Procedure. Stock solutions of the aryl halides[33-40] (**1**, **2**, **3**, **5**, **6**, **7** 0.25 M in DMSO, **4**, **8** 0.25 M in NMP, **Figure S10**), nucleophiles (**9-20**, 0.4 M in DMSO, **Figure S11**) and Pd-precatalysts (0.2 M in DMSO) were prepared in oven-dried 8 mL vials. The aryl halide (200 µL, 50 µmol, 1.0 eq), nucleophile (250 uL, 100 µmol, 2 eq), and precatalyst solutions (25 uL, 5 µmol, 10 mol%) were added via microliter pipettors into oven-dried 8-mL vials equipped with stir bars, followed by the addition of the respective neat base (150 µmol, 3 eq) – See **Table S4** below. The reactions were allowed to stir at room temperature for 24 hours. Aliquots of each reaction (10 µL) were taken and treated with a solution of acetic acid in acetonitrile containing the 20 mol% of isopropyl biphenyl and subjected for UPLC-MS analysis to determine the reaction performance. The remaining reaction mixtures were quenched with saturated aqueous NH_4Cl (2 mL), followed by dilution and extraction with 2-methyltetrahudrofuran (2-Me-THF, 2 mL). The organic layer was separated, and the aqueous layer was extracted with additional 2 mL of 2-Me-THF. The combined organic layers were washed with brine (2 mL), filtered, and concentrated via Genevac. The resulting reaction residues were reconstituted in DMSO (0.6 mL) and filtered in parallel along with a DMSO rinse (0.6 mL) of the original reaction mixture-containing vials into a 96-well recovery plate. The samples were purified by reverse-phase or SFC MS-directed or normal phase silica-gel purification to obtain the desired products.

Figure S10. Structures of Aryl Electrophiles.



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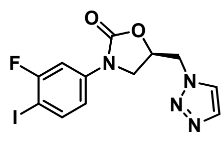

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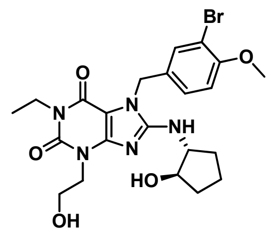

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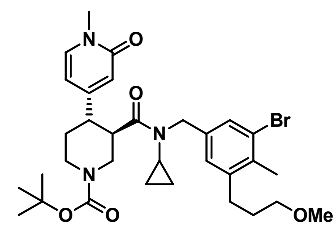

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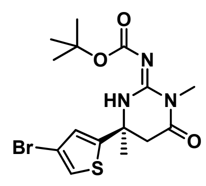

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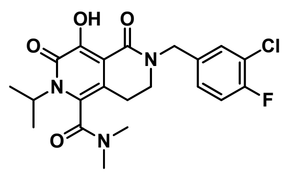

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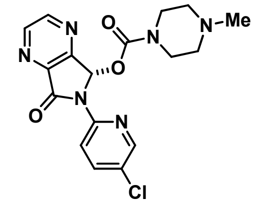

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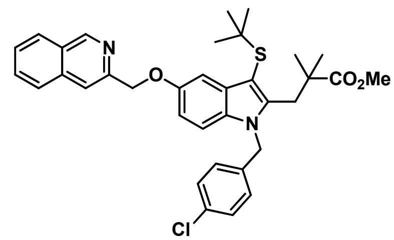
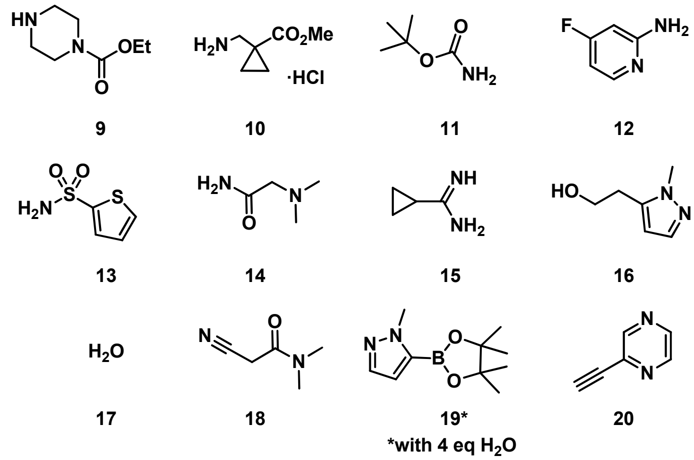


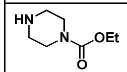
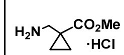
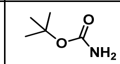
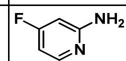
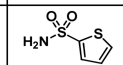
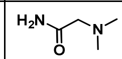
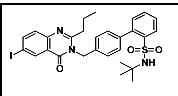
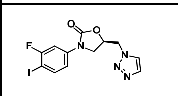
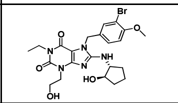
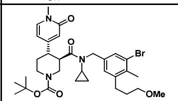
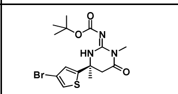
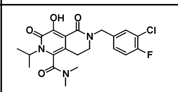
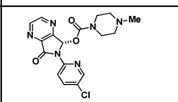
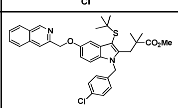
8

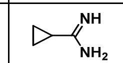
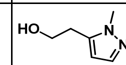
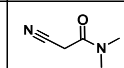
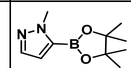
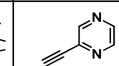
Figure S11. Structures of Nucleophiles.



Graphical positions, conditions and isolated quantities for scale-up reactions can be found in **Table S4**. Compounds from this table are mentioned in subsequent experiments and in characterization tables by their corresponding plate location. For example, the combination of electrophile **1** and nucleophile **9** is **A1** on this graph and is henceforth referred to as **A1**.

Table S4 – Scale Up Reaction Components, Conditions and Isolated Amounts

Aryl Halide / Nucleophile		1	2	3	4	5	6
		 **9**	 **10**	 **11**	 **12**	 **13**	 **14**
A	 **1**	*t*-BuXPHOS Pd G3 **42** P2-Et **29** **6.1 mg**	*t*-BuXPHOS Pd G3 **42** P2-Et **29** **10.5 mg**	*t*-BuXPHOS Pd G3 **42** MTBD **25** **5.0 mg**	*t*-BuXPHOS Pd G3 **42** DBU **24** **14.3 mg**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29** **2.3 mg**	AdBrettPHOS Pd G3 **45** BTMG **26** **3.7 mg**
B	 **2**	*t*-BuXPHOS Pd G3 **42** P2-Et **29**	*t*-BuXPHOS Pd G3 **42** P2-Et **29** **6.1 mg**	*t*-BuXPHOS Pd G3 **42** MTBD **25** **3.1 mg**	*t*-BuXPHOS Pd G3 **42** DBU **24** **7.7 mg**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29**	AdBrettPHOS Pd G3 **45** BTMG **26** **1.3 mg**
C	 **3**	*t*-BuXPHOS Pd G3 **42** P2-Et **29** **13.3 mg**	*t*-BuXPHOS Pd G3 **42** P2-Et **29** **36.4 mg**	*t*-BuXPHOS Pd G3 **42** MTBD **25**	*t*-BuXPHOS Pd G3 **42** DBU **24** **22.6 mg**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29** **24.8 mg**	AdBrettPHOS Pd G3 **45** BTMG **26**
D	 **4**	*t*-BuXPHOS Pd G3 **42** P2-Et **29** **6.0 mg**	*t*-BuXPHOS Pd G3 **42** P2-Et **29** **27.4 mg**	*t*-BuXPHOS Pd G3 **42** MTBD **25** **9.8 mg**	*t*-BuXPHOS Pd G3 **42** DBU **24** **13.8 mg**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29** **7.3 mg**	AdBrettPHOS Pd G3 **45** BTMG **26** **4.2 mg**
E	 **5**	*t*-BuXPHOS Pd G3 **42** P2-Et **29** **4.8 mg**	*t*-BuXPHOS Pd G3 **42** P2-Et **29**	*t*-BuXPHOS Pd G3 **42** MTBD **25**	*t*-BuXPHOS Pd G3 **42** DBU **24**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29**	AdBrettPHOS Pd G3 **45** BTMG **26**
F	 **6**	*t*-BuXPHOS Pd G3 **42** P2-Et **29** **5.9 mg**	*t*-BuXPHOS Pd G3 **42** P2-Et **29**	*t*-BuXPHOS Pd G3 **42** MTBD **25**	*t*-BuXPHOS Pd G3 **42** DBU **24**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29**	AdBrettPHOS Pd G3 **45** BTMG **26** **4.3 mg**
G	 **7**	*t*-BuXPHOS Pd G3 **42** P2-Et **29**	*t*-BuXPHOS Pd G3 **42** P2-Et **29**	*t*-BuXPHOS Pd G3 **42** MTBD **25** **11.9 mg**	*t*-BuXPHOS Pd G3 **42** DBU **24** **5.0 mg**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29**	AdBrettPHOS Pd G3 **45** BTMG **26**
H	 **8**	*t*-BuXPHOS Pd G3 **42** P2-Et **29** **8.3 mg**	*t*-BuXPHOS Pd G3 **42** P2-Et **29** **35.3 mg**	*t*-BuXPHOS Pd G3 **42** MTBD **25** **10.0 mg**	*t*-BuXPHOS Pd G3 **42** DBU **24** **14.7 mg**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29**	AdBrettPHOS Pd G3 **45** BTMG **26** **3.3 mg**

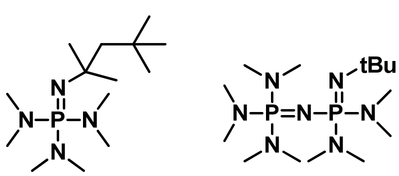
Aryl Halide / Nucleophile	7	8	9	10	11	12
	 **15**	 **16**	H_2O **17**	 **18**	 **19**	 **20**
A	AdBrettPHOS Pd G3 **45** P2Et **29** **23.7 mg**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29** **6.3 mg**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29** **19 mg**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29** **12 mg**	XantPHOS Pd G2 **32** MTBD **25** **11.5 mg**	BrettPHOS Pd G3 **41** BTMG **26** **4.6 mg**
B	AdBrettPHOS Pd G3 **45** P2Et **29**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29**	XantPHOS Pd G2 **32** MTBD **25** **20.0 mg**	BrettPHOS Pd G3 **41** BTMG **26** **12.9 mg**
C	AdBrettPHOS Pd G3 **45** P2Et **29** **2.4 mg**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29** **7.2 mg**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29** **20.8 mg**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29** **32.5 mg**	XantPHOS Pd G2 **32** MTBD **25** **7.6 mg**	BrettPHOS Pd G3 **41** BTMG **26**
D	AdBrettPHOS Pd G3 **45** P2Et **29** **1.7 mg**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29** **2.5 mg**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29** **25.6 mg**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29**	XantPHOS Pd G2 **32** MTBD **25** **29.1 mg**	BrettPHOS Pd G3 **41** BTMG **26** **12.2 mg**
E	AdBrettPHOS Pd G3 **45** P2Et **29**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29**	XantPHOS Pd G2 **32** MTBD **25** **19.4 mg**	BrettPHOS Pd G3 **41** BTMG **26**
F	AdBrettPHOS Pd G3 **45** P2Et **29**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29** **7.1 mg**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29** **3.5 mg**	XantPHOS Pd G2 **32** MTBD **25**	BrettPHOS Pd G3 **41** BTMG **26**
G	AdBrettPHOS Pd G3 **45** P2Et **29**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29**	XantPHOS Pd G2 **32** MTBD **25**	BrettPHOS Pd G3 **41** BTMG **26**
H	AdBrettPHOS Pd G3 **45** P2Et **29** **2.7 mg**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29** **0.7 mg**	*t*-BuBrettPHOS Pd G3 **43** P2Et **29** **2.2 mg**	XantPHOS Pd G2 **32** MTBD **25**	BrettPHOS Pd G3 **41** BTMG **26**

Experiment 5. 1536-Well Plate Screening of 32 Previously Failed Complex Aryl Halide – Nucleophile Combinations against 48 Pd Cross-Coupling Reaction Conditions (Bases vs. Catalysts)

From the previous experiment, those reactions that failed or were suboptimal were subjected to further screening at the nanoscale by dosing from a 384-well plate containing stock solutions of the starting materials and reagents into a 1536-Well Plate via Mosquito.

Procedure. Stock solutions of each of the reaction components were made as follows: aryl halides (**2**, **3**, **5**, **6**, **7** 0.2 M in DMSO, **4**, **8** 0.2 M in NMP), nucleophiles (**9-20**, 0.4 M in DMSO), 6 Pd-precatalysts (**36**, **38**, **42**, **43**, **44**, **45**, 0.04 M in DMSO), and 8 bases (**24-29**, **S17**, **S18**, 0.6 M, **S17** and **S18** shown in **Figure S12**). Each of the solutions was dispensed to a 384-well plate (source plate map is shown in, **Figure S13**, components listed in **Table S5**). Plate mapping and raw Excel data containing the MISER area counts of desired product for **Experiment 5** can be found in **Data S3**.

Figure S12. Additional Super-bases Evaluated.



$P_1{}^t$Octyl **S17** P2-^{t}Bu **S18**

Figure S13. Array of Reaction Components in the 384-Well Source Plate.

	ArX		Nu		Catalysts						Bases													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
A	1	1	7	11	19	20	21	22	23	24	25	26	27	28	29	30	31	32						
B	1	1	14	15	19	20	21	22	23	24	25	26	27	28	29	30	31	32						
C	2	3	16	8	19	20	21	22	23	24	25	26	27	28	29	30	31	32						
D	3	3	9	10	19	20	21	22	23	24	25	26	27	28	29	30	31	32						
E	3	3	11	12	19	20	21	22	23	24	25	26	27	28	29	30	31	32						
F	3	3	13	14	19	20	21	22	23	24	25	26	27	28	29	30	31	32						
G	4	4	8	9	19	20	21	22	23	24	25	26	27	28	29	30	31	32						
H	4	4	10	11	19	20	21	22	23	24	25	26	27	28	29	30	31	32						
I	4	4	13	14	19	20	21	22	23	24	25	26	27	28	29	30	31	32						
J	4	4	18	17	19	20	21	22	23	24	25	26	27	28	29	30	31	32						
K	5	5	7	8	19	20	21	22	23	24	25	26	27	28	29	30	31	32						
L	5	5	11	13	19	20	21	22	23	24	25	26	27	28	29	30	31	32						
M	5	5	14	15	19	20	21	22	23	24	25	26	27	28	29	30	31	32						
N	5	5	18	17	19	20	21	22	23	24	25	26	27	28	29	30	31	32						
O	8	8	11	14	19	20	21	22	23	24	25	26	27	28	29	30	31	32						
P	8	8	18	17	19	20	21	22	23	24	25	26	27	28	29	30	31	32						

Table S5. List of component solutions in the 384-well source plate.

1	Aryl iodide **2**	17	Boronate** **19**
2	Aryl bromide **4**	18	Alkyne **20**
3	Aryl bromide **5**	19	XPhos Pd G3 **36**
4	Aryl chloride **6**	20	tBuXPhos Pd G3 **42**
5	Aryl chloride **7**	21	tBuBrettPhos Pd G3 **43**
6	Aryl chloride **8**	22	RockPhos Pd G3 **44**
7	Amine **9**	23	AdBrettPhos Pd G3 **45**
8	Amine **10**	24	DTBPF Pd G3 **38**
9	Carbamate **11**	25	DBU **24**
10	Aminopyridine **12**	26	MTBD **25**
11	Sulfonamide **13**	27	BTMG **26**
12	Amide **14**	28	BEMP **27**
13	Amidine **15**	29	BTTP **28**
14	Alcohol **16**	30	P1-*t*-Oct **S17**
15	Water **17**	31	P2Et **29**
16	Cyanoester **18**	32	P2-*t*-Bu **S18**
		**	includes 4 eq. of water

The Mosquito® robotics instrument was used to combine the source plate solutions by multi-aspiration of 250 nL of each of the four reaction components and then to dose the resulting reaction mixture (1 uL) into a 1536-well plate. The resulting stoichiometric quantities of the reaction components are: aryl halide (50 nmol, 1 eq), nucleophile (100 nmol, 2 eq), Pd-Precatalyst (10 nmol, 20 mol %), and base (150 nmol, 3 eq). Once the 1536-well plate was fully dosed the plate was covered by a PFA film and clamped to minimize low-level component volatility. This was then allowed to sit at room temperature for 22 hours. Using the Mosquito®, the plate was then quenched with 3 uL of a DMSO stock solution with 5% acetic acid and biphenyl (resulting in 20 mol% of biphenyl relative to aryl halide), which was transferred from a 384-well plate. The Mosquito then sampled 1 uL from the quenched reaction plate into 4 x 384-well plates containing 60 uL of DMSO per well. The Mosquito mixing feature was used three times per aspiration and dispense step in order to ensure homogeneity of the analytical sample. The 384-well plates were then heat-sealed and subjected to analysis by the MISER approaches described below.

MISER Method on Standard Bench-top HPLC-MS

In order to streamline reaction analysis, a simple and fast chromatographic method via MISER analysis was developed. This method consists of continuous sample injections into an HPLC every 22 s from which “MISERgrams” were generated by multiple detection of $[M+H]^+$ ions via ESI-MS(+) by Selected Ion Monitoring (SIM) of the target products. These MISERgrams or serial collection of extracted molecular ion peaks reveal the relative levels of such ion in each sample, allowing determination of the best reaction conditions based on the highest relative size of the molecular ion peaks.

Validation of Mosquito Dosing and MISER Technique.

A stock solution of desloratadine (CAS 100643-71-8) as a standard (17.6 mg/mL in DMSO) was charged into the first column of a 384-well mother plate and dosed across a daughter 384-well plate pre-charged with DMSO (50 µL/well) at different injection volumes via Mosquito®.The resulting daughter plate would now have different concentration gradients of desloratadine throughout. MISER analysis of this plate (see method above, 0.2 µL/22 s injections) generated patterns of the relative amounts of desloratadine per well based on total molecular ion count, qualitatively validating the performance of this technique (**Figure S14**).

Figure S14. Patterns Generated by MISER Analysis of Desloratadine Dosed in Several Concentrations Across a 384-Well Plate

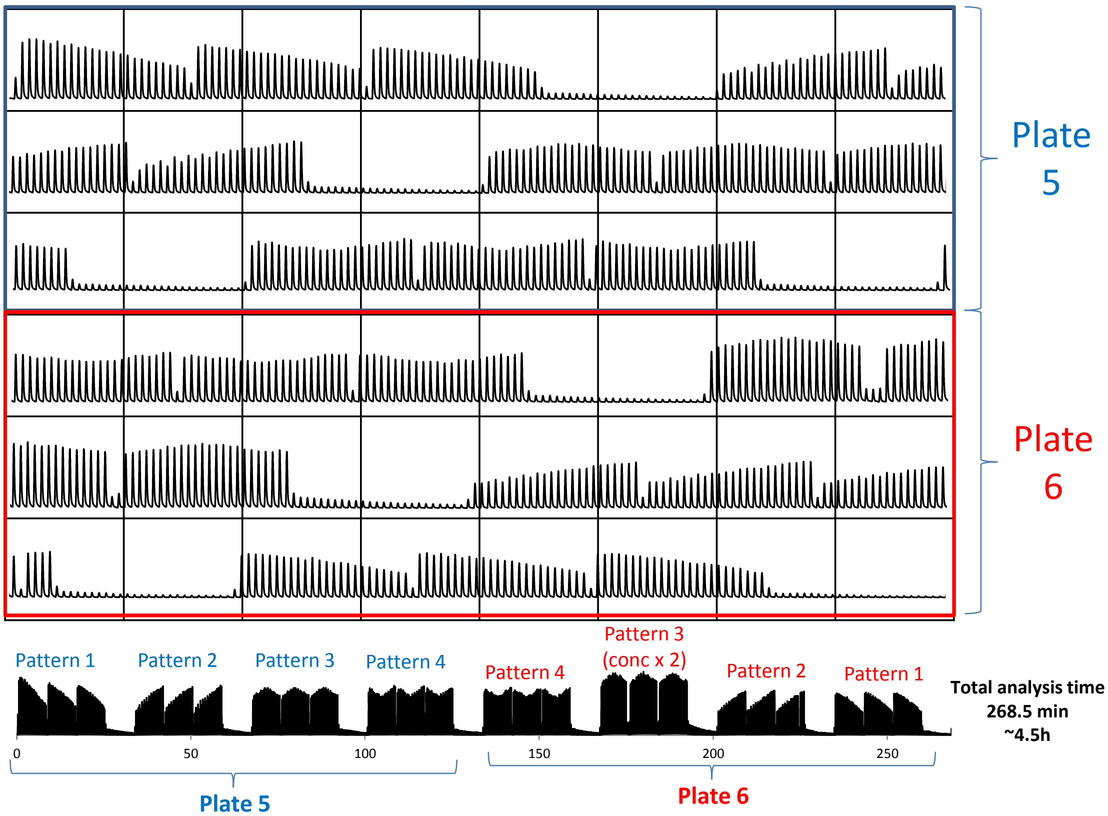


Plate 5

Plate Concentration

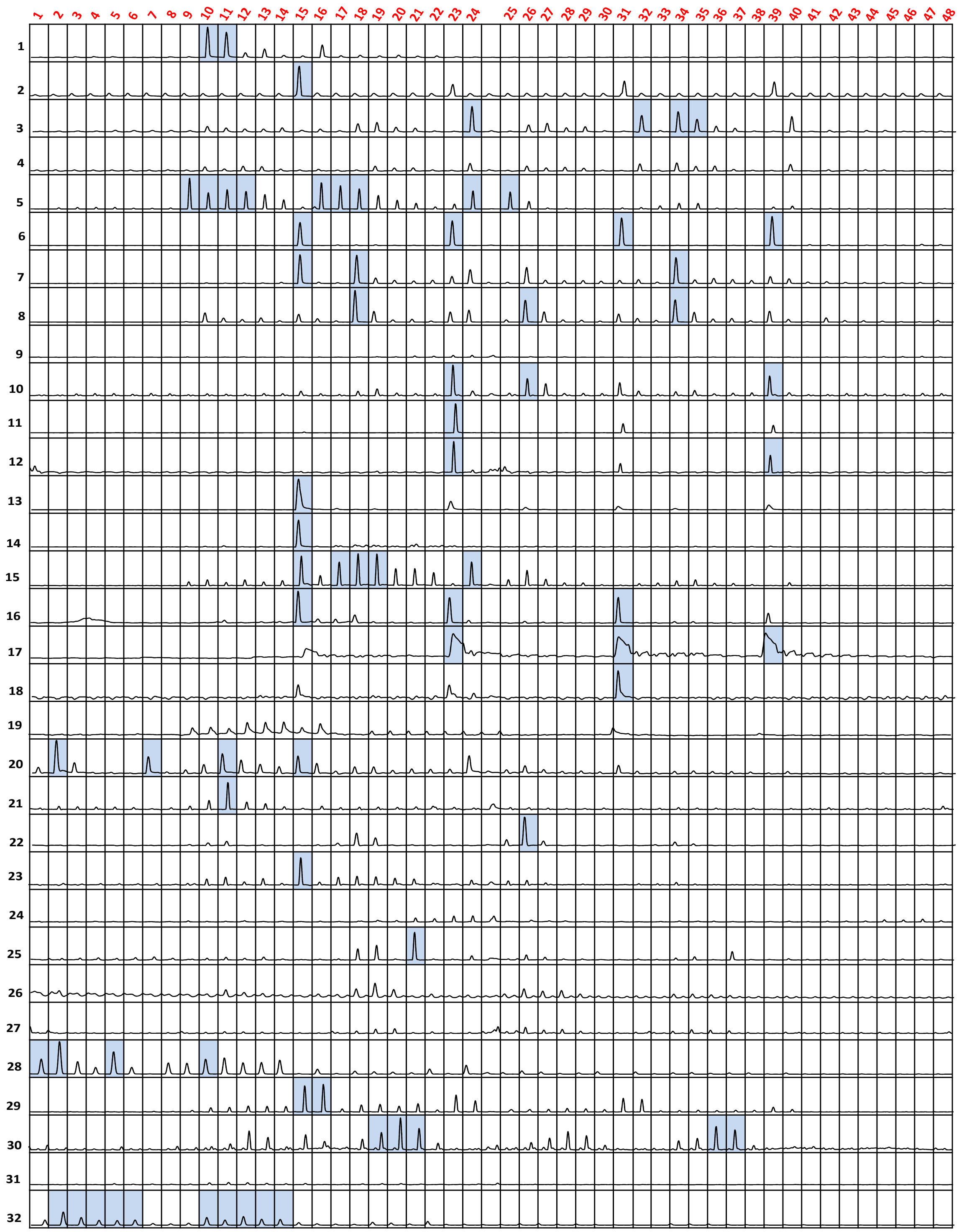
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	
A	0.35	0.34	0.33	0.32	0.31	0.30	0.29	0.27	0.26	0.25	0.24	0.23	0.22	0.21	0.20	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	
B	0.35	0.34	0.33	0.32	0.31	0.30	0.29	0.27	0.26	0.25	0.24	0.23	0.22	0.21	0.20	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	**Pattern 1**
C	0.35	0.34	0.33	0.32	0.31	0.30	0.29	0.27	0.26	0.25	0.24	0.23	0.22	0.21	0.20	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	
D																									
E	0.11	0.12	0.13	0.14	0.15	0.16	0.17	0.18	0.19	0.20	0.21	0.22	0.23	0.24	0.25	0.26	0.27	0.29	0.30	0.31	0.32	0.33	0.34	0.35	
F	0.11	0.12	0.13	0.14	0.15	0.16	0.17	0.18	0.19	0.20	0.21	0.22	0.23	0.24	0.25	0.26	0.27	0.29	0.30	0.31	0.32	0.33	0.34	0.35	**Pattern 2**
G	0.11	0.12	0.13	0.14	0.15	0.16	0.17	0.18	0.19	0.20	0.21	0.22	0.23	0.24	0.25	0.26	0.27	0.29	0.30	0.31	0.32	0.33	0.34	0.35	
H																									
I	0.23	0.24	0.25	0.26	0.27	0.29	0.30	0.31	0.32	0.33	0.34	0.35	0.34	0.33	0.32	0.31	0.30	0.29	0.27	0.26	0.25	0.24	0.23	0.23	
J	0.23	0.24	0.25	0.26	0.27	0.29	0.30	0.31	0.32	0.33	0.34	0.35	0.34	0.33	0.32	0.31	0.30	0.29	0.27	0.26	0.25	0.24	0.23	0.23	**Pattern 3**
K	0.23	0.24	0.25	0.26	0.27	0.29	0.30	0.31	0.32	0.33	0.34	0.35	0.34	0.33	0.32	0.31	0.30	0.29	0.27	0.26	0.25	0.24	0.23	0.23	
L																									
M	0.35	0.34	0.33	0.32	0.31	0.30	0.29	0.27	0.26	0.25	0.24	0.23	0.23	0.24	0.25	0.26	0.27	0.29	0.30	0.31	0.32	0.33	0.34	0.35	
N	0.35	0.34	0.33	0.32	0.31	0.30	0.29	0.27	0.26	0.25	0.24	0.23	0.23	0.24	0.25	0.26	0.27	0.29	0.30	0.31	0.32	0.33	0.34	0.35	**Pattern 4**
O	0.35	0.34	0.33	0.32	0.31	0.30	0.29	0.27	0.26	0.25	0.24	0.23	0.23	0.24	0.25	0.26	0.27	0.29	0.30	0.31	0.32	0.33	0.34	0.35	
P																									

Plate 6

Same concentrations as plate 5, but the opposite patterns with pattern 3 at double concentration of std

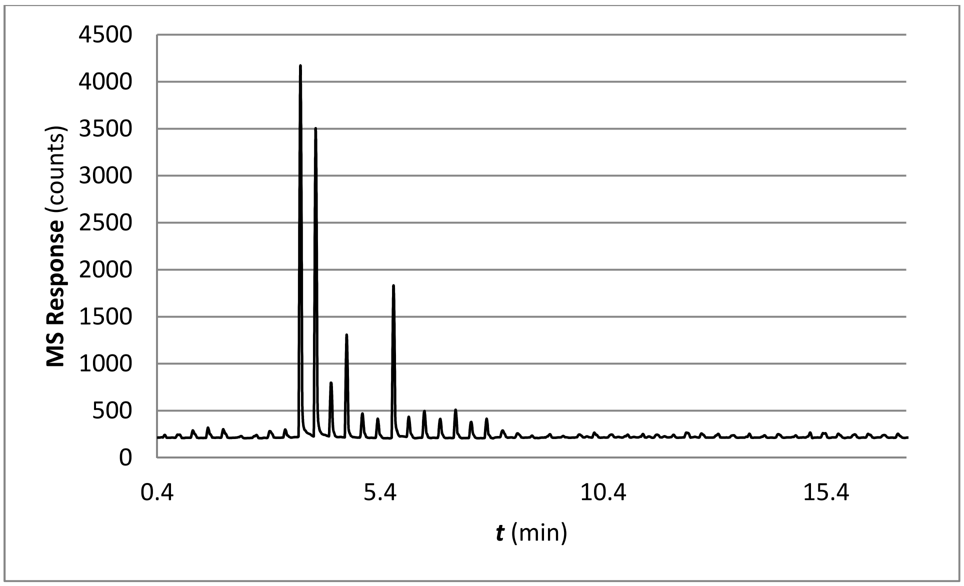
Application of MISER using Bench-top Agilent 1100 HPLC-MS to Catalyst vs. Base Screening. As above, the samples from Experiment 5 were analyzed by MISER HPLC-MS. For 48 reactions, 51 total injections were performed with injections 1, 26 and 51 as a blank injections of solvent. The MISERgrams for the 1536-well plate reactions run above were obtained in about 9 h (**Figure S15**), in which each of the 32 rows of the 1536-well plate represents a series of reactions that would give the same product. In addition, the total analysis time was reduced to 2.5h by pooling four samples containing different molecular ions into a same well plate (1536 reaction samples into a single 384-well plate). The reaction samples corresponding to the best conditions found by MISER HPLC-MS were subsequently run in a UPLC-MS system to assess the overall reaction performance and further scaled up to 1000 fold in aryl halide (50 μmol) as described in the following experiment.

Figure S15. MISER Data Visualization for Catalyst vs. Base Screening: The highest peak in each row represents the best reaction conditions for that particular aryl halide and nucleophile combination.



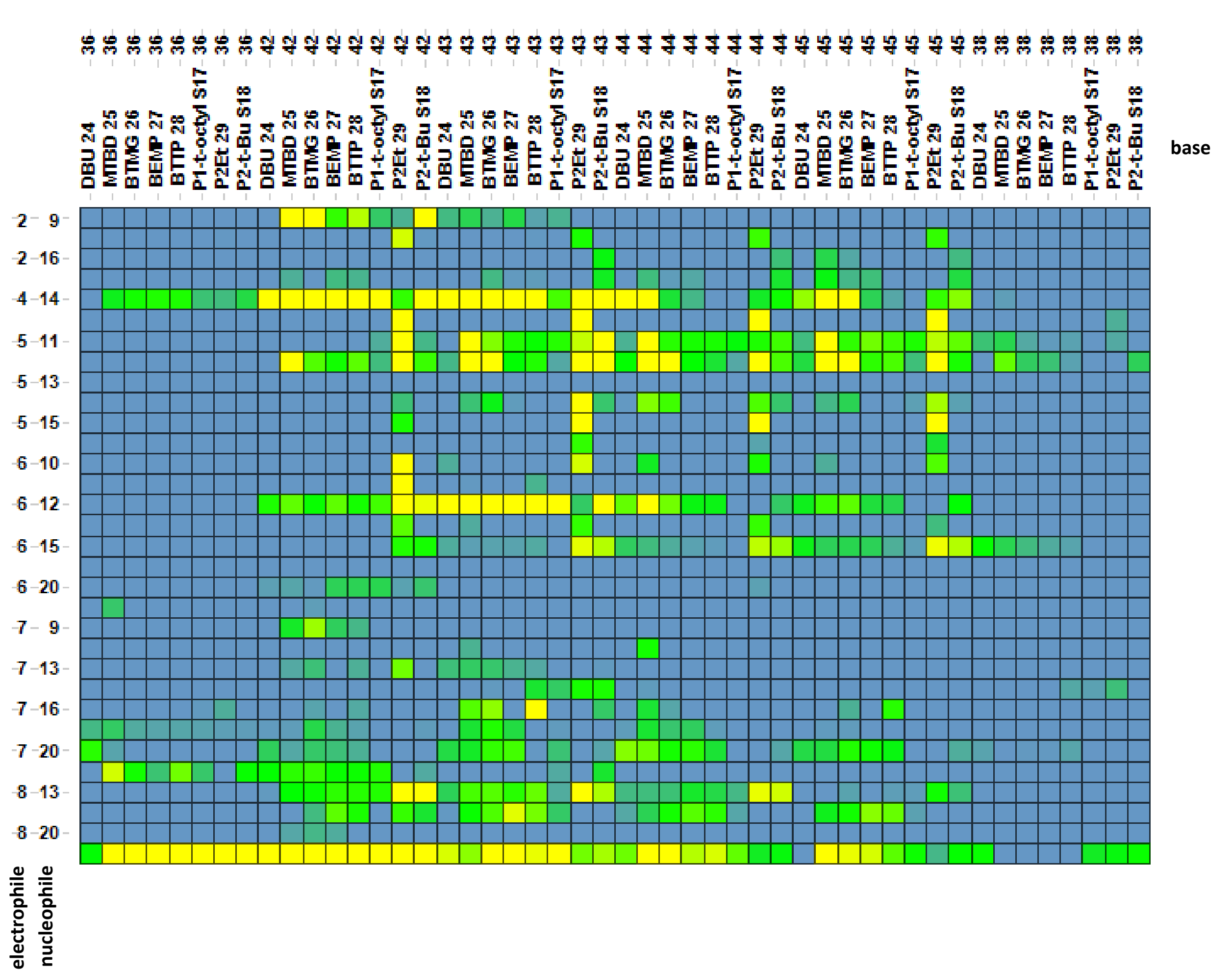
The raw output files from each MISERgram, which show data as an MS area count versus time measured every ~0.01 s with ~1280 data points per MISERgram (see **Figure S16** for an example), were converted to a heat map using the following method.

Figure S16. Agilent 1100 MISERgram for Reaction of **2** with **9** under 48 Different Reaction Conditions.



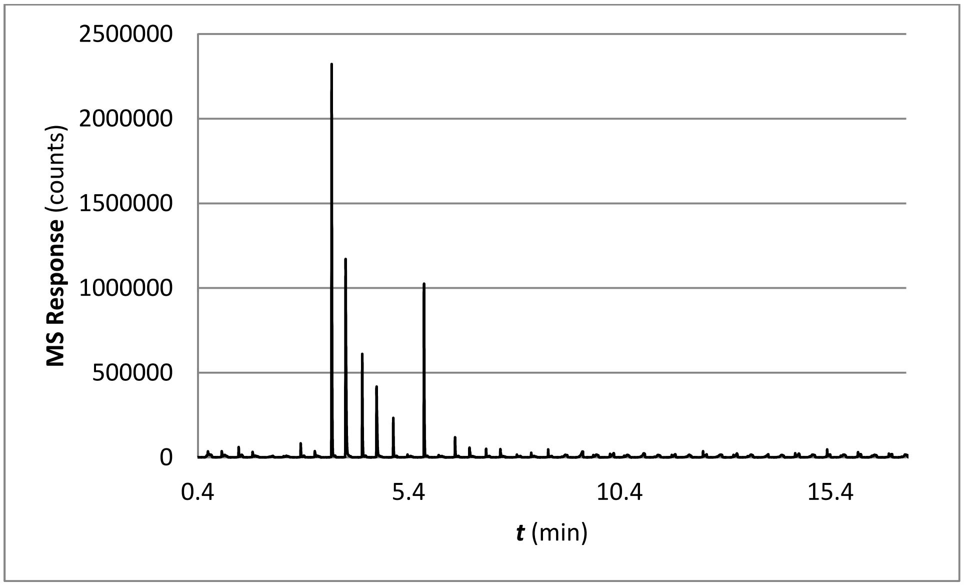
Data was imported into the TIBCO Spotfire program and clustered into 51 evenly spaced bins. The MAX data point from each bin was selected and translated using a pivot function so that data for each MISERgram would read across a row rather than down a column. From the 51 resulting entries, data points 1, 26 and 51, which represent the injection of a blank, were filtered out to give 48 entries for each electrophile/nucleophile pairing. This process was performed for each of the 32 MISERgrams to give 1536 data points which were presented as the heat map in **Figure S17** below.

Figure S17. Spotfire Heat Map Translation of the MISERgram on Figure S15 for the Relative Performance of the Reactions in the Catalyst vs. Base Screening .



MISER tandem HPLC MS/MS approach. As described in the Materials and Methods Section, samples were also analyzed using reversed phase parallel HPLC experiments were performed on a Thermo Aria Transcend LX-2 inlet system interfaced with an Applied Biosystems Sciex (AB Sciex) mass spectrometer for detection. A MISERgram produced using this method for reaction of **2** with **9** under 48 different reaction conditions is presented in **Figure S18**.

Figure S18. Tandem HPLC-MS/MS MISERgram for Reaction of **2** with **9** under 48 Different Reaction Conditions.



Pooled MISER Tandem HPLC MS/MS

The analysis of all 1536 reactions was streamlined by combining 4 reaction samples that could give different product masses, and then examining these pooled samples by monitoring the 4 desired products' *m/z* values simultaneously. By pooling 4 mass-encoded wells, the analysis of all 1536 reactions could be performed in ~2.5 hours. This pooling technique was performed using both MISER techniques and an example of a pooled MISERgram using the tandem HPLC MS/MS is shown in **Figure S19** for electrophile-nucleophile pairs **5/13**, **5/15**, **6/10**, **6/12**, and the deconvolution is shown in **Figure S20**.

Figure S19. Pooled MISERgram (Total Ion Chromatogram) using Tandem HPLC MS/MS Technique for Reaction of **5/13**, **5/15**, **6/10**, **6/12** under 48 Different Reaction Conditions.

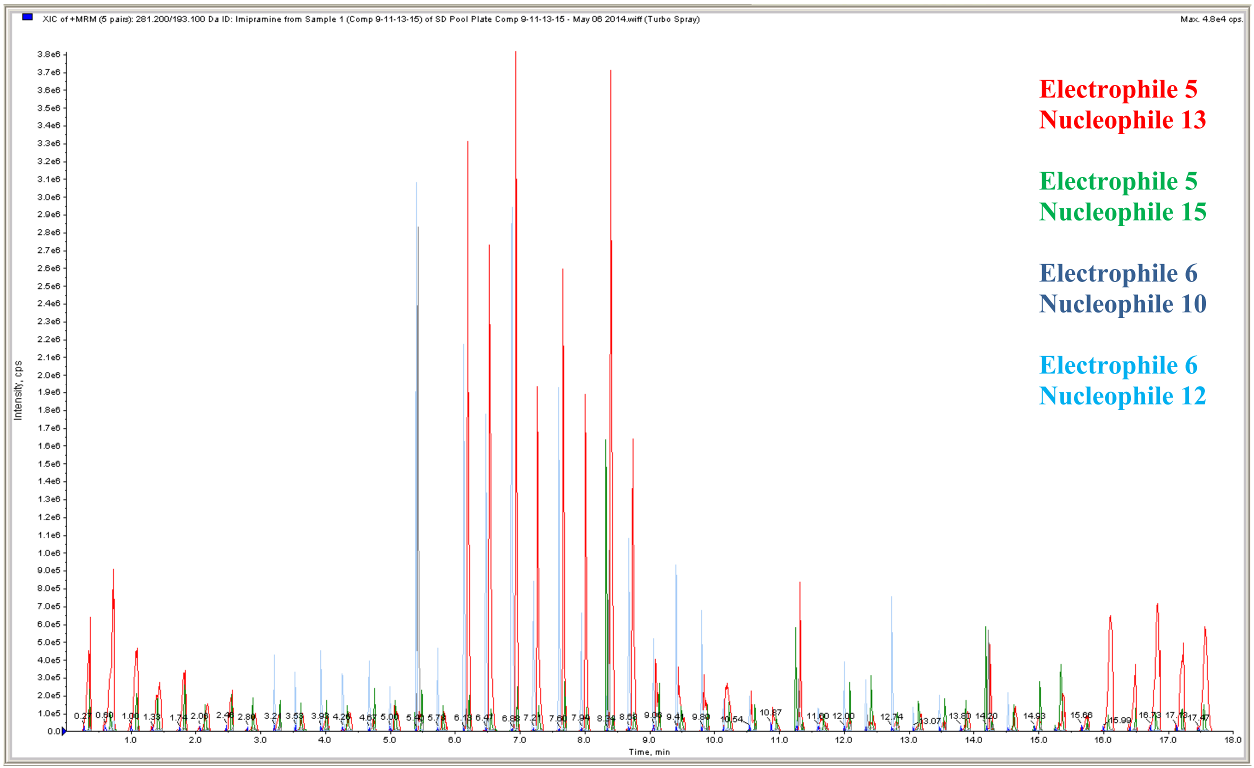
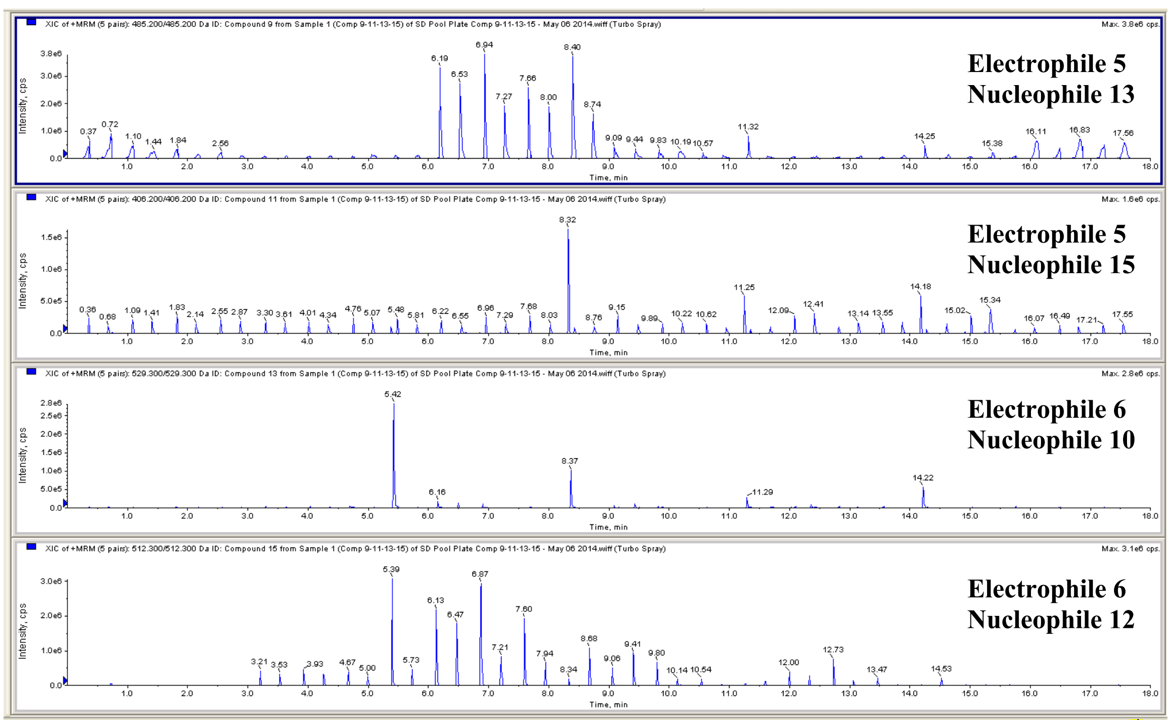


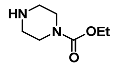
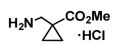
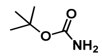
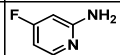
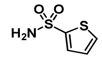
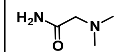
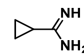
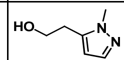
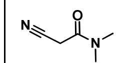
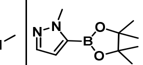
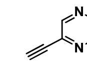
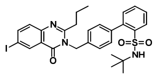
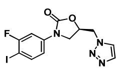
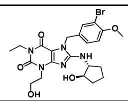
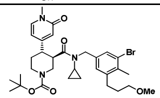
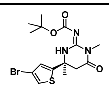
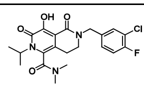
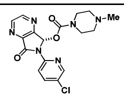
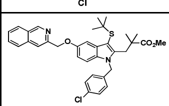
Figure S20. Deconvoluted MISERgrams (Extracted Ion Chromatrograms) from pooled MISER Approach using Tandem HPLC MS/MS Technique for Reaction of **5/13**, **5/15**, **6/10**, **6/12** under 48 Different Reaction Conditions.



Experiment 6. Reactions Scale-up Experiments for New Conditions Found in the Previous 1536-Well Plate Experiment

There were 21 newly found conditions via 1536 well-plate screening and MISER analysis from the previous experiment. These were scaled up 1000 times (50 μmol aryl halide) according to same general procedure described in **Experiment 4**, and 16 of these reactions provided pure product (by ^{1}H-NMR and HRMS analyses). These new products and conditions are highlighted in **Table S6** below.

Table S6. Scale-up Reaction Components, Conditions and Isolated Amounts from Catalyst vs. Base Screening.

	Aryl Halide / Nucleophile	1	2	3	4	5	6	7	8	9	10	11	12
		 9	 10	 11	 12	 13	 14	 15	 16	H_2O 17	 18	 19	 20
A	 1												
B	 2	*t*-BuXPHOS Pd G3 **42** MTBD **25** **18.3 mg**				*t*-BuXPHOS Pd G3 **42** P2-Et **29** **2.6 mg**			improved conditions not observed	improved conditions not observed			
C	 3												
D	 4										improved conditions not observed		
E	 5		AdBrettPHOS Pd G3 **45** P2Et **29** **3.4 mg**	*t*-BuXPHOS Pd G3 **42** P2-Et **29** **7.2 mg**	*t*-BuBrettPHOS Pd G3 **43** MTBD **25** **15.7 mg**	improved conditions not observed		*t*-BuBrettPHOS Pd G3 **43** P2Et **29** **11.2 mg**	improved conditions not observed	improved conditions not observed			
F	 6		*t*-BuXPHOS Pd G3 **42** P2-Et **29** **3.7 mg**	*t*-BuXPHOS Pd G3 **42** P2-Et **29** **9.2 mg**	*t*-BuBrettPHOS Pd G3 **43** BTMG **26** **16.9 mg**	improved conditions not observed		*t*-BuBrettPHOS Pd G3 **43** P2Et **29** **0.6 mg**	improved conditions not observed			improved conditions not observed	improved conditions not observed
G	 7	*t*-BuXPHOS Pd G3 **42** BTMG **26** **4.2 mg**	RockPhos Pd G3 **44** MTBD **25** **0.9 mg**			improved conditions not observed		improved conditions not observed	improved conditions not observed	improved conditions not observed		XPHOS Pd G3 **36** MTBD **25** **4.9 mg**	improved conditions not observed
H	 8					*t*-BuXPHOS Pd G3 **42** P2-tBu **S18** **5.1 mg**			*t*-BuBrettPHOS Pd G3 **43** BTTP **28** **3.5 mg**			XPHOS Pd G3 **36** MTBD **25** **6.6 mg**	improved conditions not observed

Experiment 7. 1536-Well Plate Screening of 6 Previously Failed Complex Aryl Halides – Nucleophile Combinations against 48 Pd Cross-Coupling Reaction Conditions (Reaction Stoichiometries)

From the previous experiments, 6 reactions that failed or were sub-optimal were subjected to further screening of reaction stoichiometries at the nanoscale by dosing from a mother 1536-well plate containing stock solutions of the starting materials and reagents into reaction vials on the same plate via Mosquito.

Procedure:

Stock solutions of each of the reaction components in DMSO were made as follows: aryl halides (**5** and **6**, 0.25 M in DMSO), nucleophiles (**13**, **16**, **19** are 0.4 M in DMSO, **17** is 4.0 M in DMSO), Pd-precatalysts (**36**, **42**, **43**, three concentrations of each, 0.05 M, 0.1M, 0.15M in DMSO), and bases (**24**, **29**, 1.0 M in DMSO). Each of the stock solutions was manually dispensed in 8-10 uL quantities to a 1536-Well Plate, and this same plate was used for the reactions (source and reaction plate map, **Figure S21**, components listed in **Table S7**).

Figure S21. Array of Stock Solutions and Reaction Map on the 1536-well Plate

	Stock Solutions										Reactions																																					
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
A	1		3		12		16		17		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16							
B	2		6		12		16		17		145		146		147		148		149		150		151		152		153		154		155		156		157		158		159		160							
C	1		4		12		16		17		17		18		19		20		21		22		23		24		25		26		27		28		29		30		31		32							
D	2		7		12		16		17		161		162		163		164		165		166		167		168		169		170		171		172		173		174		175		176							
E	1		5		12		16		17		33		34		35		36		37		38		39		40		41		42		43		44		45		46		47		48							
F	2		8		12		16		17		177		178		179		180		181		182		183		184		185		186		187		188		189		190		191		192							
G	1		3		13		16		17		49		50		51		52		53		54		55		56		57		58		59		60		61		62		63		64							
H	2		3		13		16		17		193		194		195		196		197		198		199		200		201		202		203		204		205		206		207		208							
I	1		4		13		16		17		65		66		67		68		69		70		71		72		73		74		75		76		77		78		79		80							
J	2		4		13		16		17		209		210		211		212		213		214		215		216		217		218		219		220		221		222		223		224							
K	1		5		13		16		17		81		82		83		84		85		86		87		88		89		90		91		92		93		94		95		96							
L	2		5		13		16		17		225		226		227		228		229		230		231		232		233		234		235		236		237		238		239		240							
M	1		3		14		16		17		97		98		99		100		101		102		103		104		105		106		107		108		109		110		111		112							
N	2		9		15		16		18		241		242		243		244		245		246		247		248		249		250		251		252		253		254		255		256							
O	1		4		14		16		17		113		114		115		116		117		118		119		120		121		122		123		124		125		126		127		128							
P	2		10		15		16		18		257		258		259		260		261		262		263		264		265		266		267		268		269		270		271		272							
Q	1		5		14		16		17		129		130		131		132		133		134		135		136		137		138		139		140		141		142		143		144							
R	2		11		15		16		18		273		274		275		276		277		278		279		280		281		282		283		284		285		286		287		288							
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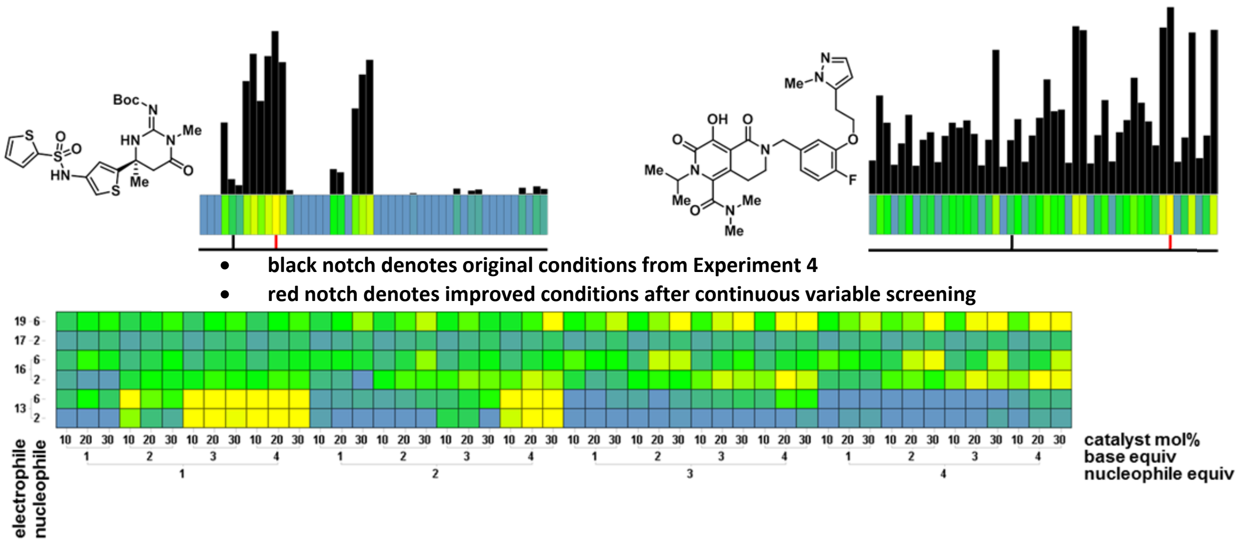
Table S7. List of Component Solutions in the 1536-Well Source Plate.

1	Aryl bromide **5**	**7**	tBuXPhos Pd G3 **42**	**13**	Alcohol **16**
2	Aryl Chloride **6**	**8**	tBuXPhos Pd G3 **42**	**14**	Boronate **19** /Water
3	tBuBrettPhos Pd G3 **43**	**9**	XPhos Pd G3 **36**	**15**	Water **17**
4	tBuBrettPhos Pd G3 **43**	**10**	XPhos Pd G3 **36**	**16**	DMSO
5	tBuBrettPhos Pd G3 **43**	**11**	XPhos Pd G3 **36**	**17**	P2Et **29**
6	tBuXPhos Pd G3 **42**	**12**	Sulfonamide **13**	**18**	MTBD **25**

The Mosquito robotics instrument was used to combine the source plate solutions by multi-aspiration of the appropriate amount (see Excel table in **Data S4** for charges) of each of the five reaction components and then to dose the resulting reaction mixture (1 uL) into a 1536-well plate. Once the 1536-well plate was fully dosed the plate was covered by a PFA film and clamped to minimize low-level component volatility. This was then allowed to sit at room temperature for 22 hours. Using the Mosquito, the plate was then quenched with 3 uL of a DMSO stock solution with 5% acetic acid and biphenyl (resulting in 100 mol% biphenyl relative to aryl electrophile), which was transferred from a 384-well plate. The Mosquito then sampled 1 uL from the quenched reaction plate into a 384-well plate containing 60 uL of DMSO per well. The Mosquito mixing feature was used three times per aspiration and dispense steps in order to ensure homogeneity of the analytical sample. The 384-well plate was then heat-sealed and subjected to chromatographic analysis by a Waters UPLC Instrument. The ratio of the LC area counts of product over internal standard was used to directly compare the relative performance of these reactions. Plate mapping and raw Excel data containing these ratios and LC area absolutes for starting materials and product for **Experiment 7** can be found in **Data S4**. The graphical representation (generated with TIBCO Spotfire) of this data is shown in **Figure S22**.

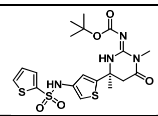
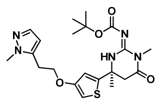
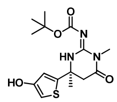
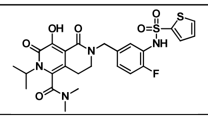
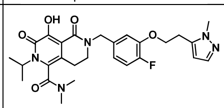
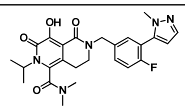
Figure S22. Representative Complex Substrates and Continuous Variables Screening with Corresponding Heat Map of Data from **Experiment 7**, Showing Plate Mapping and Relative Reaction Performance.



Experiment 8. Reactions Scale-up Experiments for New Conditions Found in the Previous 1536-well Plate Experiment

There were 5 newly found conditions via the previous 1536-well plate optimization experiment. These were scaled up 1000 times (50 µmol aryl halide) according to same general procedure described in **Experiment 4**. These new products are highlighted in **Table S8** below.

Table S8. Scale-up of Optimization Conditions Identified in **Experiment 7**.

Product		Aryl electrophile	Nucleophile	Nu equiv	catalyst	catalyst %	Base	Base equiv	Amt Isolated
E5		5	sulfonamide 13	1	tBuBrettPhos Pd G3 **43**	10	P2Et	3	9.2 mg
E8		5	alcohol 16	1	tBuBrettPhos Pd G3 **43**	10	P2Et	3	5.5 mg
E9		5	water 17	1	tBuBrettPhos Pd G3 **43**	30	P2Et	4	improved conditions not observed
F5		6	sulfonamide 13	1	tBuXPhos Pd G3 **42**	20	P2Et	3	7.6 mg
F8		6	alcohol 16	4	tBuXPhos Pd G3 **42**	20	P2Et	2	2.4 mg
F11		6	boronate 19	4	Xphos Pd G3 **36**	20	MTBD	3	1.9 mg

Experiment 9. 1536-Well Plate DOE Experiment

General Experimental Description. A three-factorial four level response surface model was conducted examining catalyst (**42**, 5-20 mol %), nucleophile (**10**, ~1-3 eq.), and base (**29**, 1-4 eq.) in the reaction of **6** with **10**. For clarity, these factors are abbreviated as Cat, Nuc, and Bas. Conditions were randomized and were each repeated twice (**Table S10**). Repeated conditions were averaged and statistical analysis was performed using Design-Expert version 8.0.7.1 published by Stat-Ease, Inc., 2021 E Hennepin Ave, Suite 480, Minneapolis, MN 55413. In order to obtain a better fitting model, all points with 5% catalyst loading were omitted from the model. Data were subjected to square root transform $y' = \sqrt{y + 2.0}$. Model reduction was performed by removing statistically insignificant terms according to analysis of variance (**Table S11**). The best fitting model is presented in Equation S1. Model fit was assessed by normal plot of residuals (**Figure S24**) and predicted vs actual values (**Figure S25**). Examination of Cook's distance indicated no significant outliers (**Figure S26**). Response surface model plots are presented at 10 mol% catalyst (**Figure S27** and **S28**), 15 mol% catalyst (**Figure S29** and **S30**), and 20 mol% catalyst (**Figure S31** and **S32**).

Procedure:

Stock solutions of each of the reaction components in DMSO were made as follows: aryl halide **6** (0.25 M), nucleophile **10** (0.312 M), tBuXPHOS Pd G3 **42** (0.10 M), and P2Et **29** (1.0 M). Each of the stock solutions was manually dispensed in 8-10 uL quantities to a 1536-Well Plate. This same plate was used for the reactions (source and reaction plate map, **Figure S23**, components listed in **Table S9**).

Figure S23. Array of Stock Solutions and Reaction Map on the 1536-Well Plate

	Stock Solutions																Reactions																															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
A	1	1		2	2		3	3		4	4		5	5			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
B	1	1		2	2		3	3		4	4		5	5			33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64
C	1	1		2	2		3	3		4	4		5	5			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
D	1	1		2	2		3	3		4	4		5	5			33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64
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Table S9. List of component solutions in the 1536-well source plate.

1	Aryl Chloride **6**
2	Amine **10**
3	tBuXPhos Pd G3 **42**
4	DMSO
5	P2Et **29**

The Mosquito robotics instrument was used to combine the source plate solutions by multi-aspiration of the appropriate amount (see Excel table in **Data S5** for charges) of each of the five reaction components and then to dose the resulting reaction mixture (1 uL) into a 1536-well plate. Once the 1536-well plate was fully dosed the plate was covered by a PFA film and clamped to minimize low-level component volatility. This was then allowed to sit at room temperature for 22 hours. Using the Mosquito, the plate was then quenched with 3 uL of a DMSO stock solution with 5% acetic acid and biphenyl (resulting in 100 mol% biphenyl relative to aryl electrophile), which was transferred from a 384-well plate. The Mosquito then sampled 1 uL form the quenched reaction plate into a 384-well plate containing 60 uL of DMSO per well. The Mosquito mixing feature was used three times per aspiration and dispense steps in order to ensure homogeneity of the analytical sample. The 384-well plate was then heat-sealed and subjected to chromatographic analysis by a Waters UPLC Instrument. The LC area counts of starting material **6** and product were used to calculate relative conversion given that there was minimal side-product formation. This information can be found on **Table S10**.

Table S10. Conditions and Results for 3-Factorial 4-level Response Surface Modeling Experiment.

Run	Cat mol %	Nuc eq.	Bas eq.	Sub (0.25M) nL	Cat (0.1 M) nL	Nuc (0.312 M) nL	DMSO nL	Bas (1M) nL	Trial 1 conv	Trial 2 conv	Avg conv
1	15	2.34	3	200	75	375	200	150	18.1	12.7	15.4
2	20	0.78	4	200	100	125	375	200	85.6	86.8	86.2
3	5	3.12	4	200	25	500	75	200	30.1	23	26.5
4	5	2.34	4	200	25	375	200	200	38.8	31.9	35.4
5	5	0.78	2	200	25	125	550	100	39.4	39.9	39.6
6	10	3.12	3	200	50	500	100	150	0	5.7	2.8
7	5	1.56	1	200	25	250	475	50	3.7	0	1.9
8	15	3.12	3	200	75	500	75	150	0	0	0
9	10	1.56	3	200	50	250	350	150	71.8	50.1	61
10	10	0.78	2	200	50	125	525	100	36.3	33.3	34.8
11	20	1.56	3	200	100	250	300	150	54.6	30.6	42.6
12	20	3.12	1	200	100	500	150	50	0	0	0
13	5	2.34	1	200	25	375	350	50	4	0	2
14	20	2.34	3	200	100	375	175	150	15.2	13.9	14.6
15	15	1.56	3	200	75	250	325	150	45.5	37.5	41.5
16	5	3.12	1	200	25	500	225	50	0	4.9	2.5
17	5	0.78	1	200	25	125	600	50	4.7	0	2.4
18	20	0.78	1	200	100	125	525	50	0	12.9	6.5
19	15	0.78	4	200	75	125	400	200	74.4	78.7	76.6
20	15	1.56	4	200	75	250	275	200	86.6	87.3	86.9
21	10	2.34	3	200	50	375	225	150	0	7.4	3.7
22	5	1.56	3	200	25	250	375	150	39.4	34.2	36.8
23	10	0.78	1	200	50	125	575	50	0	0	0
24	10	0.78	3	200	50	125	475	150	63.1	61.8	62.5
25	5	3.12	3	200	25	500	125	150	2.1	0	1
26	20	0.78	2	200	100	125	475	100	28.5	13.8	21.1
27	5	0.78	3	200	25	125	500	150	40.9	44.6	42.7
28	5	2.34	3	200	25	375	250	150	8	8.1	8.1
29	5	1.56	4	200	25	250	325	200	54	49.2	51.6
30	20	0.78	3	200	100	125	425	150	85.8	81.6	83.7
31	20	2.34	4	200	100	375	125	200	40.3	53.7	47
32	5	3.12	2	200	25	500	175	100	0	0	0
33	20	3.12	2	200	100	500	100	100	0	0	0
34	15	2.34	4	200	75	375	150	200	60.7	71.6	66.2
35	20	1.56	2	200	100	250	350	100	0	13.3	6.7
36	20	3.12	3	200	100	500	50	150	0	0	0
37	20	1.56	4	200	100	250	250	200	96.2	95.6	95.9
38	15	2.34	2	200	75	375	250	100	0	3.6	1.8
39	15	2.34	1	200	75	375	300	50	0	0	0
40	15	0.78	1	200	75	125	550	50	0	0	0
41	10	2.34	2	200	50	375	275	100	0	0	0
42	5	0.78	4	200	25	125	450	200	38.3	39.2	38.8
43	10	1.56	1	200	50	250	450	50	0	3.1	1.5
44	15	1.56	2	200	75	250	375	100	12.4	11.6	12
45	10	1.56	4	200	50	250	300	200	75.8	78.4	77.1
46	20	2.34	2	200	100	375	225	100	0	0	0
47	10	3.12	1	200	50	500	200	50	0		0
48	20	1.56	1	200	100	250	400	50	0	0	0
49	5	1.56	2	200	25	250	425	100	23.3	7.4	15.3
50	15	0.78	2	200	75	125	500	100	60.7	43.4	52.1
51	10	1.56	2	200	50	250	400	100	10.9	0	5.5
52	10	3.12	2	200	50	500	150	100	3.8	0	1.9
53	15	3.12	4	200	75	500	25	200	9.7	13.2	11.5
54	20	2.34	1	200	100	375	275	50	0	0	0
55	15	3.12	1	200	75	500	175	50	0	0	0
56	15	1.56	1	200	75	250	425	50	5.7	0	2.9
57	5	2.34	2	200	25	375	300	100	0	3.1	1.5
58	15	3.12	2	200	75	500	125	100	0	0	0
59	10	3.12	4	200	50	500	50	200	10	6	8
60	15	0.78	3	200	75	125	450	150	78.8	75.5	77.2
61	10	2.34	4	200	50	375	175	200	61.2	44.8	53
62	10	0.78	4	200	50	125	425	200	63.2	56.1	59.7
63	20	3.12	4	200	100	500	0	200	9.1	9	9
64	10	2.34	1	200	50	375	325	50	0	0	0

Table S11. Analysis of Variance for Response Surface Reduced Cubic Model, Partial Sum of Squares Type III.

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F
Model	405.43	12	33.79	46.93	< 0.0001
Cat	0.21	1	0.21	0.29	0.5934
Nuc	26.48	1	26.48	36.78	< 0.0001
Bas	142.22	1	142.22	197.53	< 0.0001
Cat · Nuc	0.73	1	0.73	1.01	0.3213
Cat · Bas	0.24	1	0.24	0.34	0.5636
Nuc · Bas	24.71	1	24.71	34.33	< 0.0001
Cat^2	0.93	1	0.93	1.29	0.2643
Nuc^2	0.80	1	0.80	1.11	0.3001
Bas^2	0.91	1	0.91	1.26	0.2698
$Nuc^2 \cdot Bas$	12.20	1	12.20	16.94	0.0002
$Nuc \cdot Bas^2$	14.89	1	14.89	20.69	< 0.0001
Nuc^3	0.82	1	0.82	1.14	0.2931
Residual	25.20	35	0.72		
Cor Total	430.63	47			
Std. Dev.	0.85				
Mean	4.32				
C.V. %	19.66				
PRESS	46.36				
R-Squared	0.94				
Adj R-Squared	0.92				
Pred R-Squared	0.89				
Adeq Precision	20.23				

Equation S1. Response Surface Model.

$$
\begin{aligned}
&\sqrt{\text{Conversion} + 2.00} = \\
&- 6.034 \\
&+ 0.398 \cdot \text{Cat} \\
&+ 1.423 \cdot \text{Nuc} \\
&+ 6.388 \cdot \text{Bas} \\
&- 0.035 \cdot \text{Cat} \cdot \text{Nuc} \\
&+ 0.016 \cdot \text{Cat} \cdot \text{Bas} \\
&- 1.040 \cdot \text{Nuc} \cdot \text{Bas} \\
&- 0.012 \cdot \text{Cat}^2 \\
&- 0.762 \cdot \text{Nuc}^2 \\
&- 1.108 \cdot \text{Bas}^2 \\
&- 0.741 \cdot \text{Nuc}^2 \cdot \text{Bas} \\
&+ 0.639 \cdot \text{Nuc} \cdot \text{Bas}^2 \\
&+ 0.411 \cdot \text{Nuc}^3
\end{aligned}
$$

Figure S24. Normal Plot of Residuals for Response Surface Model.

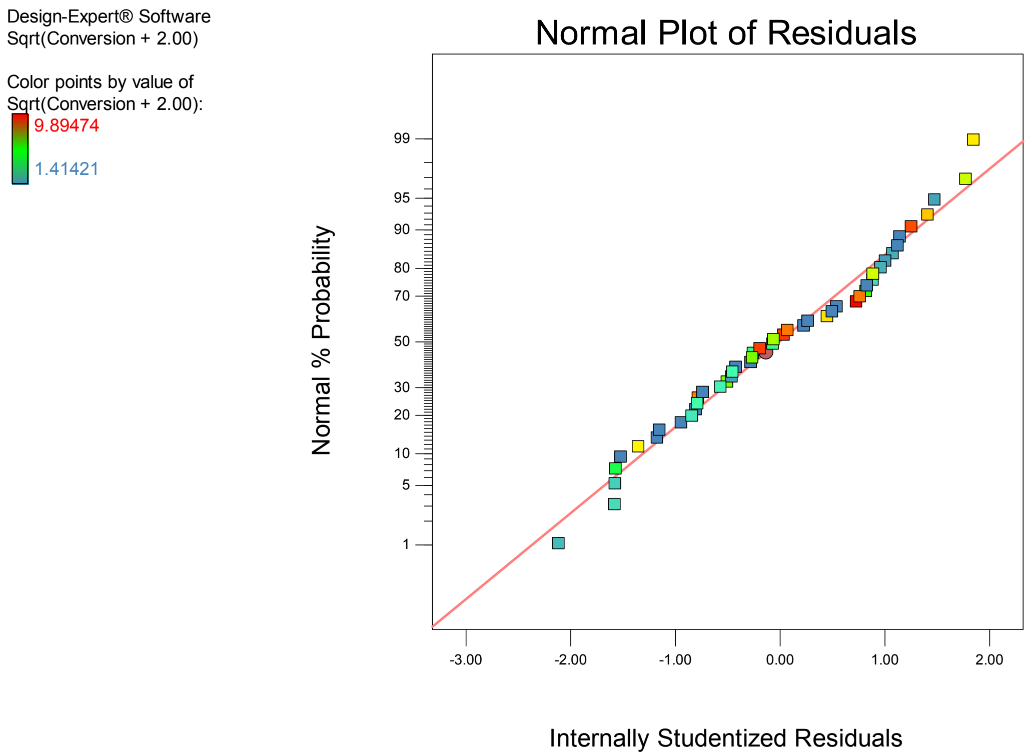


Figure S25. Predicted vs Actual Values for Response Surface Model.

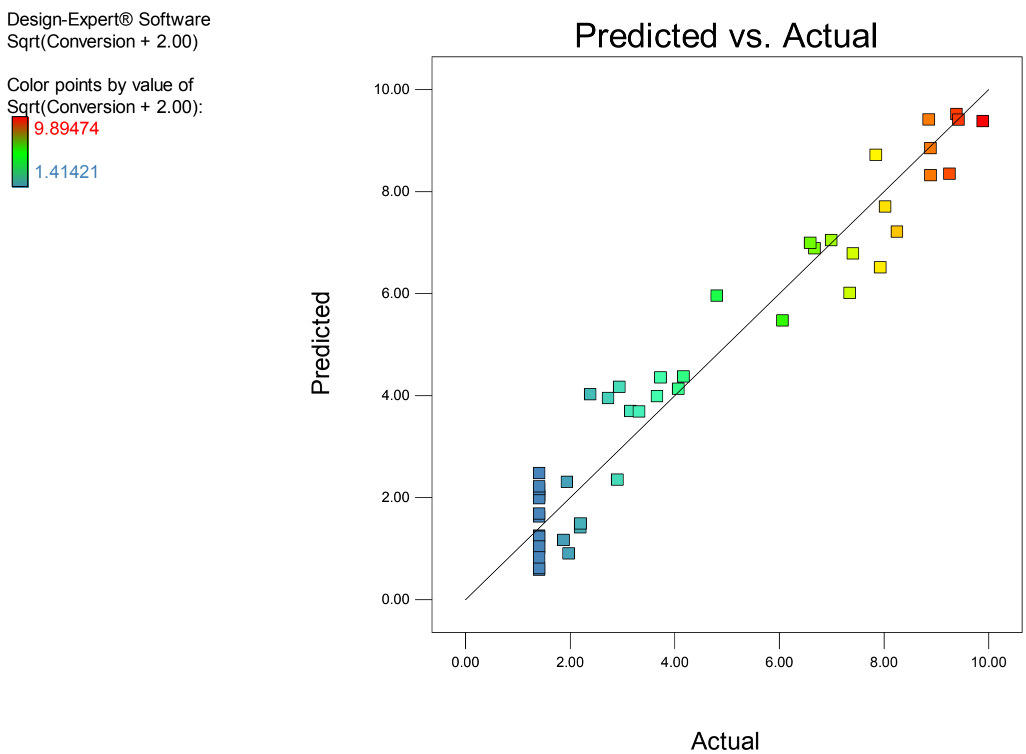


Figure S26. Plot of Cook's Distance for Response Surface Model.

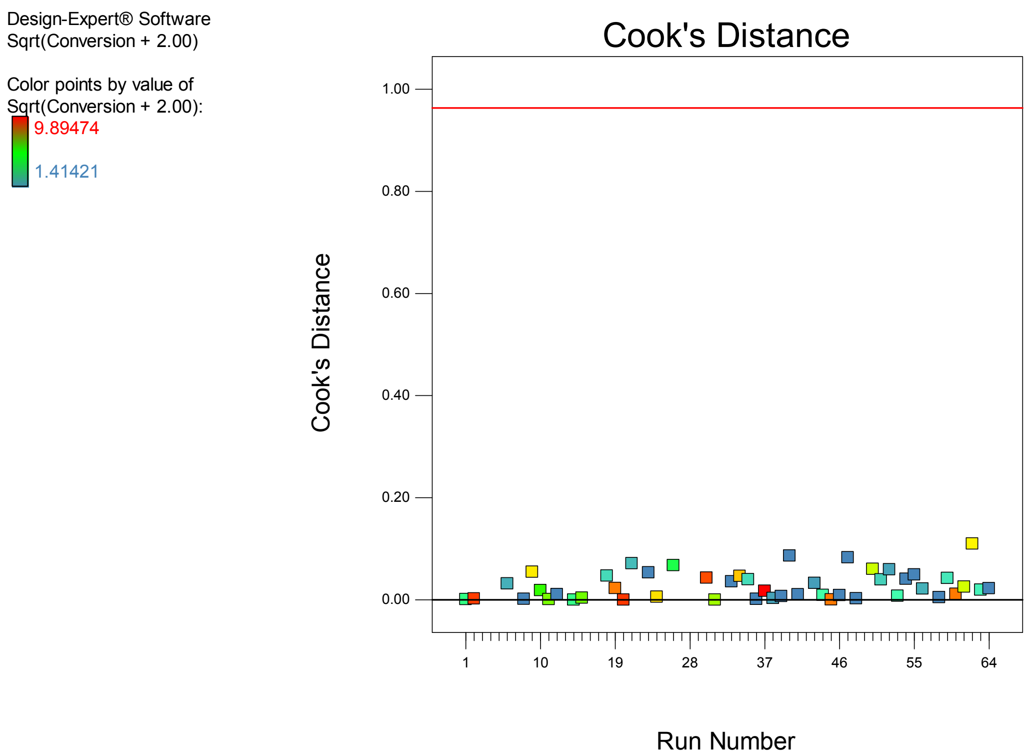


Figure S27. 3D Response Surface Model at 10 mol% Catalyst.

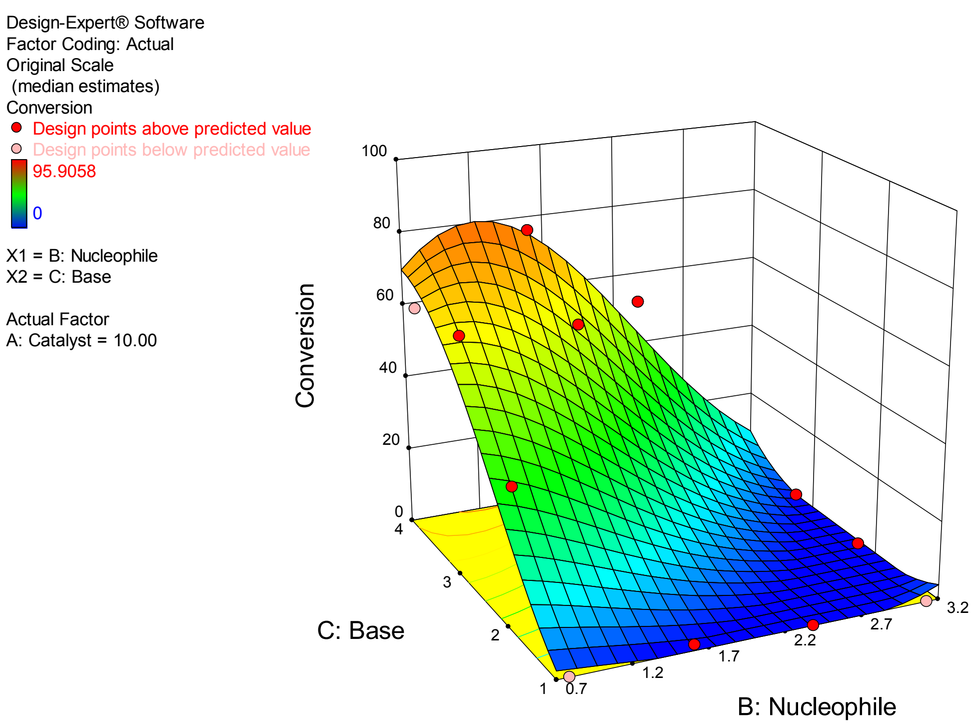


Figure S28. Contour Plot of Response Surface Model at 10 mol% Catalyst.

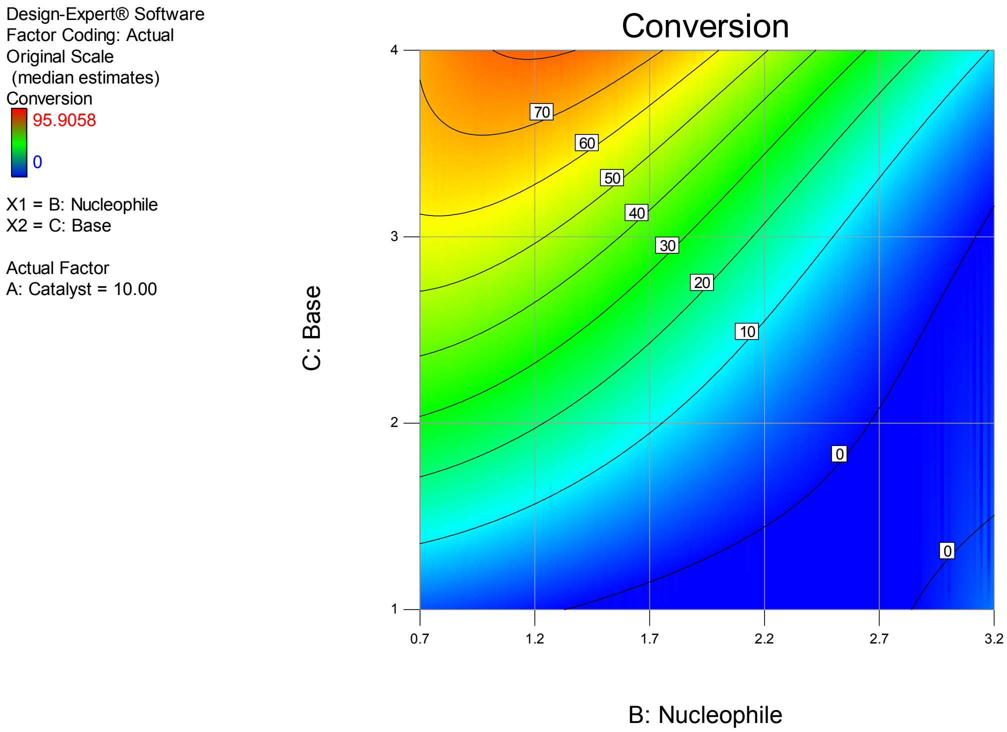


Figure S29. 3D Response Surface Model at 15 mol% Catalyst.

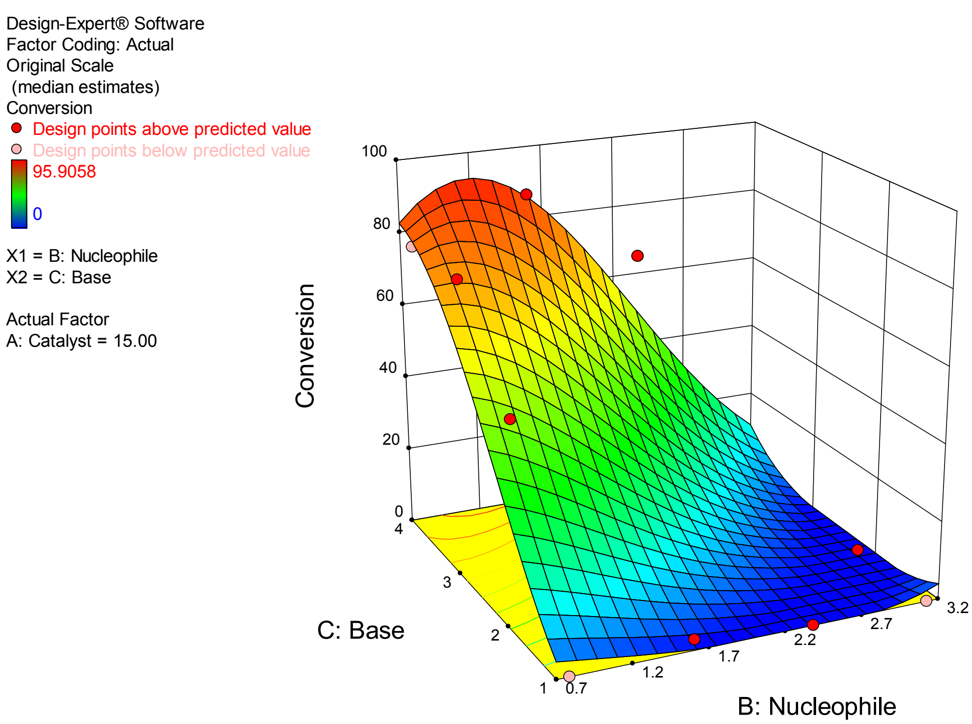


Figure S30. Contour Plot of Response Surface Model at 15 mol% Catalyst.

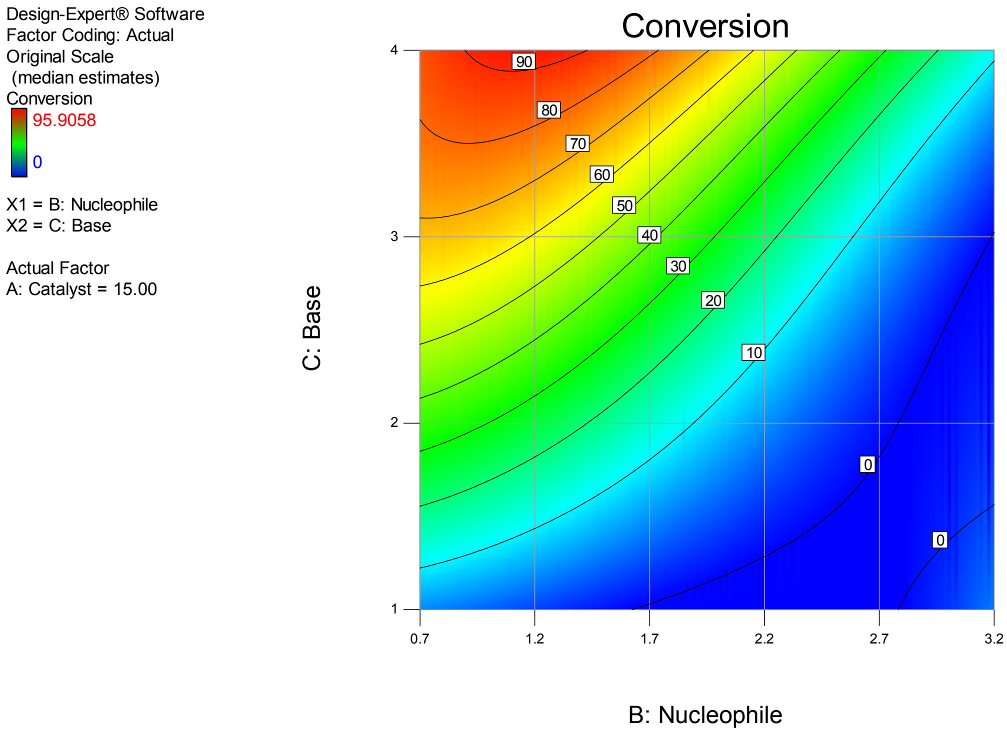


Figure S31. 3D Response Surface Model at 20 mol% Catalyst.

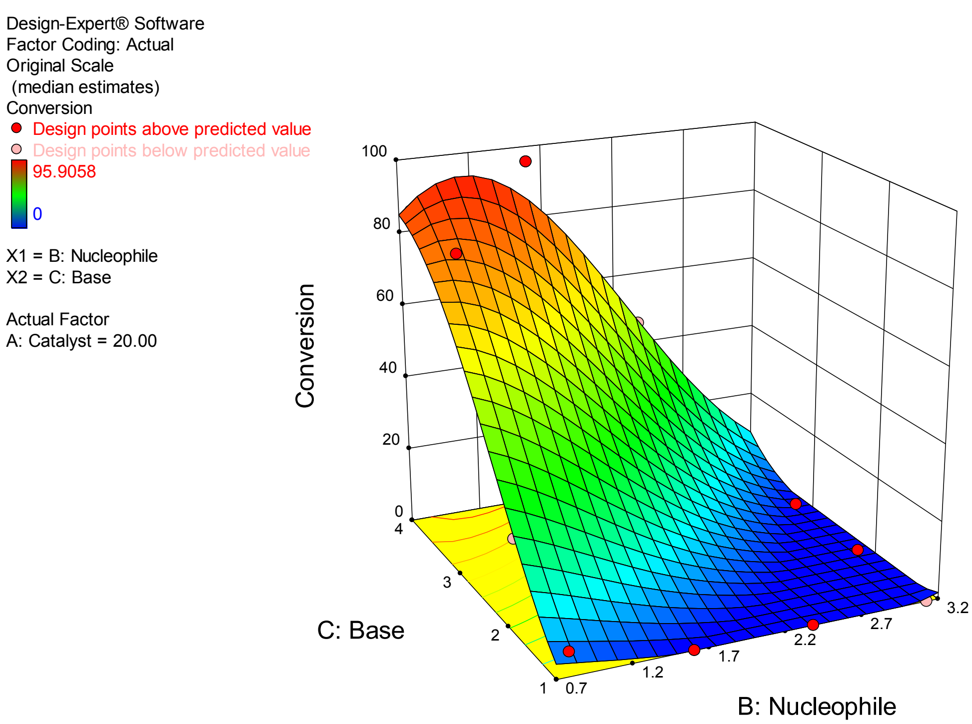
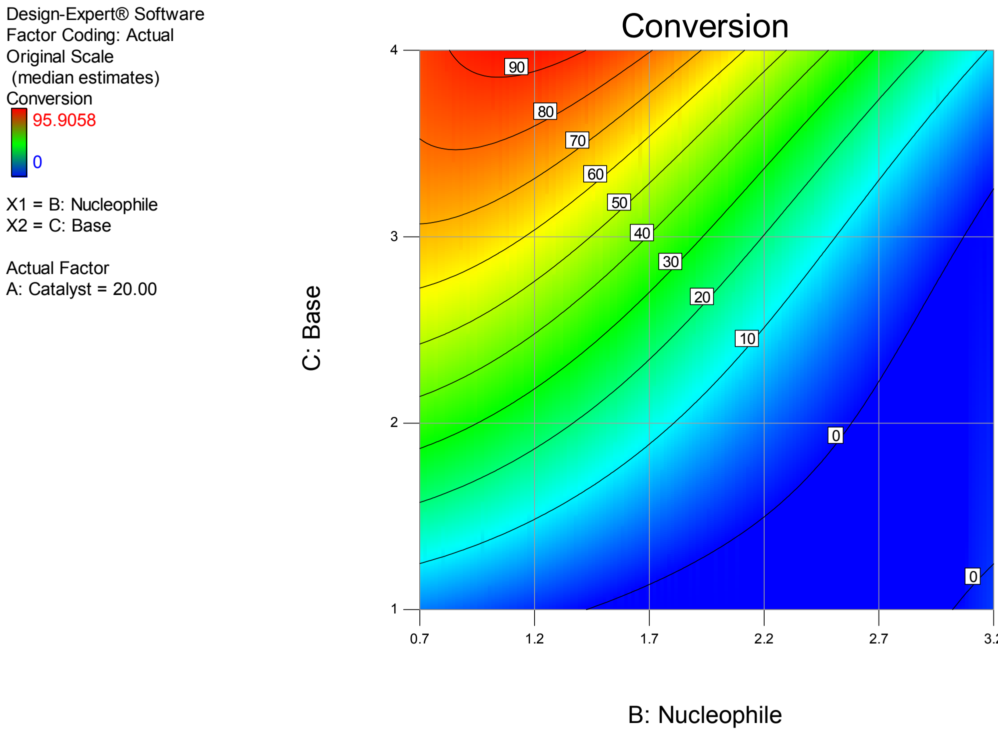
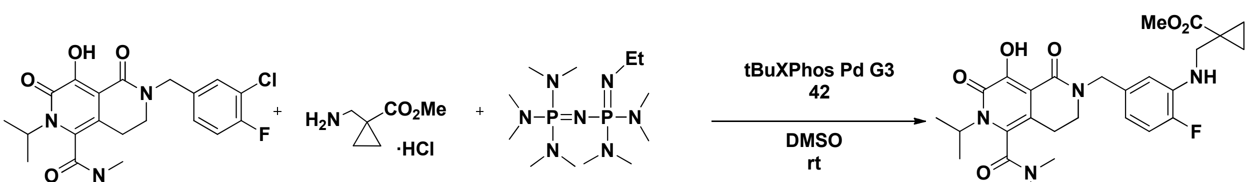


Figure S32. Contour Plot of Response Surface Model at 20 mol% Catalyst.



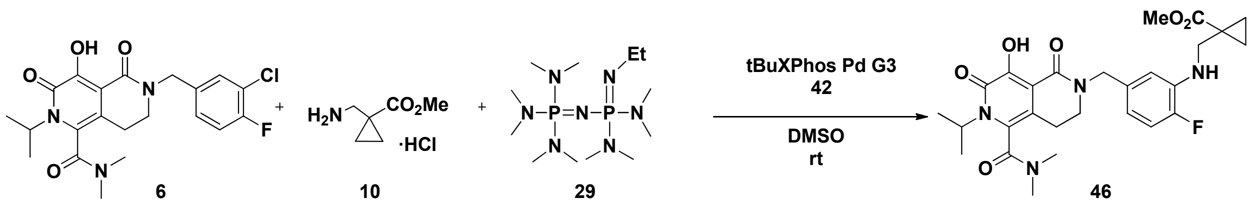
Experiment 10. DOE Confirmation Experiment



Stock solutions of the aryl chloride **6** (0.814 M), the aminoester hydrochloride **10** (0.952 M), and tBuXPhos Pd G3 precatalyst **42** (0.122 M) were prepared in anhydrous DMSO. The solutions were dispensed in the following order inside an oven-dried 4 mL vial equipped with stir bar: DMSO (854 µL), aryl chloride **6** (70 µL, 56.98 µmol), aminoester hydrochloride **10** (70 µL, 66.67 µmol), and tBuXPhos Pd G3 **42** (70 µL, 8.55 µmol, 15 mol %), followed by addition of neat P2Et base **29** (76 µL, 228.40 µmol). The reaction was allowed to stir at room temperature for 24 hours and then diluted with a solution of 4-isopropylbiphenyl as internal standard in

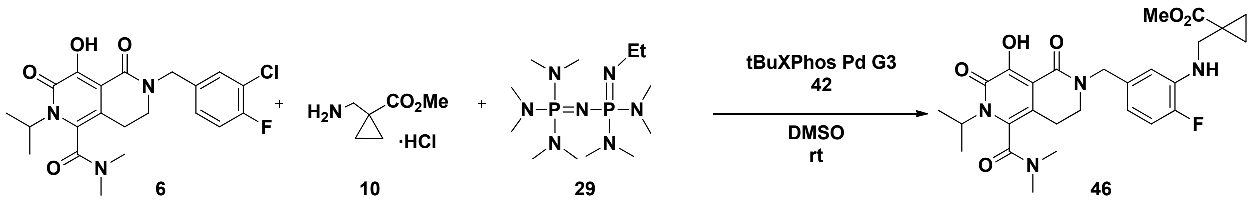
DMSO (1000 µL, 20 mol %). A reaction sample (10 µL, 100X diluted in ACN) was analyzed by UPLC-MS to determine the corresponding conversion based on LC area counts (> 95%, as predicted by **Experiment 9**).

Experiment 11. Post-DOE Optimization Practical Front Run Experiment (25 mg)



Stock solutions of the aryl chloride **6** (0.814 M), the aminoester hydrochloride **10** (0.952 M), and tBuXPhos Pd G3 precatalyst **42** (0.122 M) were prepared in anhydrous DMSO. The solutions were dispensed in the following order inside an oven-dried 4 mL vial equipped with stir bar: aryl chloride **6** (70 µL, 56.98 µmol), aminoester hydrochloride **10** (70 µL, 66.67 µmol), and tBuXPhos Pd G3 **42** (23.33 µL, 2.85 µmol, 5 mol %), followed by addition of neat P2Et base **29** (76 µL, 228.40 µmol). The reaction was allowed to stir at room temperature for 2 hours and then diluted with 2-MeTHF (4 mL) and quenched with saturated NH_4Cl (4 mL). The aqueous layer was extracted with 2-MeTHF (4 mL), and the combined organics were washed with brine (4 mL), dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified using a Combiflash ISCO column (24 g silica gel column, 0 – 100% MeOH in CH_2Cl_2 in 30 min, 79% yield).

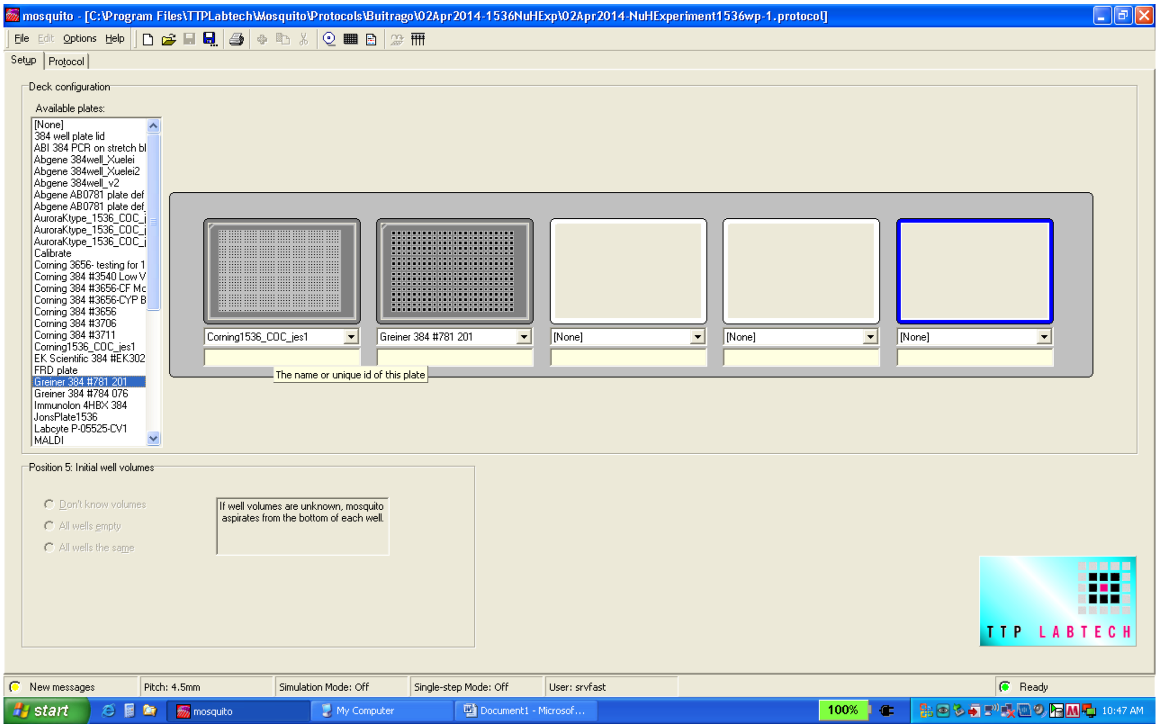
Experiment 12. Gram-scale Demonstration of DOE Experiment Under Practical Conditions

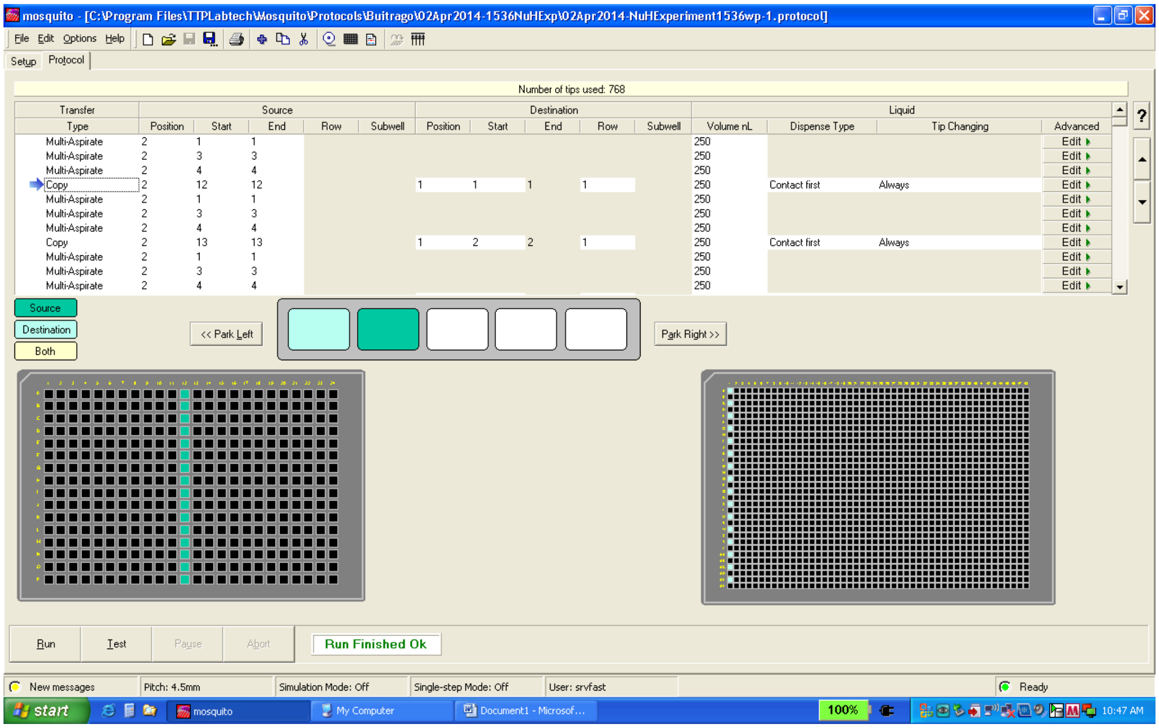


The aryl chloride **6** (1.00 g, 2.294 mmol) was measured inside an oven-dried 40 mL vial equipped with stir bar. A solution of aminoester hydrochloride **10** in anhydrous DMSO was added to the above solid (3.00 mL, 0.895 M, 2.684 mmol), followed by a solution of tBuXPhos Pd G3 **42** in DMSO (2.51 mL, 0.046 M, 0.115 mmol, 5 mol %), and subsequent addition of neat P2Et base **29** (3.05 mL, 9.177 mmol). The reaction was allowed to stir at room temperature for 2 hours. The reaction was diluted with 2-MeTHF (40 mL) and quenched with saturated NH_4Cl (40 mL). The aqueous layer was extracted with 2-MeTHF (40 mL), and the combined organics were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified using a Combiflash ISCO column (80 g silica gel column, 0 – 100% MeOH in CH_2Cl_2 in 30 min, 76% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.97 (s, 1H), 6.92 (dd, *J* = 11.4, 8.1 Hz, 1H), 6.62 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.53 (ddd, *J* = 8.1, 4.5, 2.1 Hz, 1H), 4.61 (dd, *J* = 102.2, 14.5 Hz, 2H), 4.37 (s, 1H), 4.03 (d, *J* = 5.7 Hz, 1H), 3.71 (s, 3H), 3.46 (ddd, *J* = 12.4, 9.1, 4.7 Hz, 1H), 3.40 – 3.18 (m, 3H), 3.11 (s, 3H), 2.97 (s, 3H), 2.62 (ddd, *J* = 15.3, 6.6, 4.7 Hz, 1H), 2.47 (ddd, *J* = 15.3, 9.1, 5.1 Hz, 1H), 1.65 (dd, *J* = 14.6, 6.7 Hz, 6H), 1.61 – 1.49 (m, 3H), 1.34 (q, *J* = 4.0 Hz, 2H), 1.03 – 0.90 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.61, 167.04, 163.93, 157.39, 153.61, 152.47, 150.09, 137.40, 137.28, 132.16, 132.13, 127.97, 116.53, 116.45, 114.62, 114.43, 112.07, 112.04, 110.17, 107.64, 55.97, 52.07, 50.00, 47.28, 45.05, 37.88, 34.44, 23.87, 23.28, 19.69, 19.23, 14.68, 14.59. IR (cm^{-1}): 3380, 2929, 1715, 1624, 1230, 1153, 791,

612. UV/Vis: λ_{max} (nm) 243, 348. HRMS (*m*/*z*): $[M]^+$ calcd. for $C_{27}H_{33}FN_4O_6$, 528.2384; found 529.2432.

Appendix 1 – Mosquito Protocols for Experiment 1





Experiment 1. 1536wp – 96rxns screen for the coupling of 3-Br-Pyridine and 4-Ph-Piperidine

Reaction Dosing from 384wp-Mother Plate into 1536wp-Daughter Plate – Part I

5 position deck
Position:
1: Corning1536_COC_jes1
2: Greiner 384 #781 201
3: [no plate]
4: [no plate]
5: [no plate]

Home tape
Aspirate 250 nL from (P2, C1, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C3, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C4, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C5, R1, S1), well volume 0 µL, no over aspirate
Dispense 1000 nL to (P1, C19, R1, S1), well volume 0 µL
Change pipettes

Aspirate 250 nL from (P2, C1, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C3, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C4, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C6, R1, S1), well volume 0 µL, no over aspirate
Dispense 1000 nL to (P1, C20, R1, S1), well volume 0 µL
Change pipettes

Aspirate 250 nL from (P2, C1, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C3, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C4, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C7, R1, S1), well volume 0 µL, no over aspirate
Dispense 1000 nL to (P1, C21, R1, S1), well volume 0 µL
Change pipettes

Aspirate 250 nL from (P2, C1, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C3, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C4, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C8, R1, S1), well volume 0 µL, no over aspirate
Dispense 1000 nL to (P1, C22, R1, S1), well volume 0 µL
Change pipettes

Aspirate 250 nL from (P2, C1, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C3, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C4, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C9, R1, S1), well volume 0 µL, no over aspirate

Dispense 1000 nL to (P1, C23, R1, S1), well volume 0 µL
Change pipettes

Aspirate 250 nL from (P2, C1, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C3, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C4, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C10, R1, S1), well volume 0 µL, no over aspirate
Dispense 1000 nL to (P1, C24, R1, S1), well volume 0 µL

Reaction Dosing from 384wp-Mother Plate into 1536wp-Daughter Plate – Part II

5 position deck
Position:
1: Corning1536_COC_jes1
2: Greiner 384 #781 201
3: [no plate]
4: [no plate]
5: [no plate]

Home tape
Aspirate 250 nL from (P2, C1, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C3, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C4, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C5, R1, S1), well volume 0 µL, no over aspirate
Dispense 1000 nL to (P1, C7, R1, S1), well volume 0 µL
Change pipettes

Aspirate 250 nL from (P2, C1, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C3, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C4, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C6, R1, S1), well volume 0 µL, no over aspirate
Dispense 1000 nL to (P1, C8, R1, S1), well volume 0 µL
Change pipettes

Aspirate 250 nL from (P2, C1, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C3, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C4, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C7, R1, S1), well volume 0 µL, no over aspirate
Dispense 1000 nL to (P1, C9, R1, S1), well volume 0 µL
Change pipettes

Aspirate 250 nL from (P2, C1, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C3, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C4, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C8, R1, S1), well volume 0 µL, no over aspirate
Dispense 1000 nL to (P1, C10, R1, S1), well volume 0 µL

Change pipettes

Aspirate 250 nL from (P2, C1, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C3, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C4, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C9, R1, S1), well volume 0 µL, no over aspirate
Dispense 1000 nL to (P1, C11, R1, S1), well volume 0 µL
Change pipettes

Aspirate 250 nL from (P2, C1, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C3, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C4, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C10, R1, S1), well volume 0 µL, no over aspirate
Dispense 1000 nL to (P1, C12, R1, S1), well volume 0 µL

Reaction Dosing from 384wp-Mother Plate into 1536wp-Daughter Plate – Part III

5 position deck
Position:
1: Corning1536_COC_jes1
2: Greiner 384 #781 201
3: [no plate]
4: [no plate]
5: [no plate]

Home tape
Aspirate 250 nL from (P2, C1, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C3, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C4, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C5, R1, S1), well volume 0 µL, no over aspirate
Dispense 1000 nL to (P1, C13, R1, S1), well volume 0 µL
Change pipettes

Aspirate 250 nL from (P2, C1, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C3, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C4, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C6, R1, S1), well volume 0 µL, no over aspirate
Dispense 1000 nL to (P1, C14, R1, S1), well volume 0 µL
Change pipettes

Aspirate 250 nL from (P2, C1, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C3, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C4, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C7, R1, S1), well volume 0 µL, no over aspirate
Dispense 1000 nL to (P1, C15, R1, S1), well volume 0 µL
Change pipettes

Aspirate 250 nL from (P2, C1, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C3, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C4, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C8, R1, S1), well volume 0 µL, no over aspirate
Dispense 1000 nL to (P1, C16, R1, S1), well volume 0 µL
Change pipettes

Aspirate 250 nL from (P2, C1, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C3, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C4, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C9, R1, S1), well volume 0 µL, no over aspirate
Dispense 1000 nL to (P1, C17, R1, S1), well volume 0 µL
Change pipettes

Aspirate 250 nL from (P2, C1, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C3, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C4, R1, S1), well volume 0 µL, no over aspirate, no blowback
Multi-aspirate 250 nL from (P2, C10, R1, S1), well volume 0 µL, no over aspirate
Dispense 1000 nL to (P1, C18, R1, S1), well volume 0 µL

Reaction Quench with IS

5 position deck
Position:
1: Corning1536_COC_jes1
2: Greiner 384 #781 201
3: [no plate]
4: [no plate]
5: [no plate]

Home tape
Aspirate 1000 nL from (P2, C15, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C7, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C15, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C9, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C15, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C11, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C15, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C13, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C15, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C15, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C15, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C17, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C15, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C19, R1, S1), well volume 0 µL

Aspirate 1000 nL from (P2, C15, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C21, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C15, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C23, R1, S1), well volume 0 µL
Change pipettes

Aspirate 1000 nL from (P2, C16, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C7, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C16, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C9, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C16, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C11, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C16, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C13, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C16, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C15, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C16, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C17, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C16, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C19, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C16, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C21, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C16, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C23, R1, S1), well volume 0 µL
Change pipettes

Aspirate 1000 nL from (P2, C17, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C7, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C17, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C9, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C17, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C11, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C17, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C13, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C17, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C15, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C17, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C17, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C17, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C19, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C17, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C21, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C17, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C23, R1, S1), well volume 0 µL
Change pipettes

Aspirate 1000 nL from (P2, C15, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C8, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C15, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C10, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C15, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C12, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C15, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C14, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C15, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C16, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C15, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C18, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C15, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C20, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C15, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C22, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C15, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C24, R1, S1), well volume 0 µL
Change pipettes

Aspirate 1000 nL from (P2, C16, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C8, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C16, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C10, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C16, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C12, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C16, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C14, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C16, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C16, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C16, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C18, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C16, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C20, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C16, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C22, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C16, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C24, R1, S1), well volume 0 µL
Change pipettes

Aspirate 1000 nL from (P2, C17, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C8, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C17, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C10, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C17, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C12, R1, S1), well volume 0 µL

Aspirate 1000 nL from (P2, C17, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C14, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C17, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C16, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C17, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C18, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C17, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C20, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C17, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C22, R1, S1), well volume 0 µL
Aspirate 1000 nL from (P2, C17, R1, S1), well volume 0 µL
Dispense 1000 nL to (P1, C24, R1, S1), well volume 0 µL

Transfer from 1536wp into 384wp for UPLC Analysis

5 position deck
Position:
1: Corning1536_COC_jes1
2: Greiner 384 #781 201
3: [no plate]
4: [no plate]
5: [no plate]

Home tape
Aspirate 1000 nL from (P1, C7, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000, no over aspirate
Dispense 1000 nL to (P2, C1, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000
Change pipettes

Aspirate 1000 nL from (P1, C8, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000, no over aspirate
Dispense 1000 nL to (P2, C2, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000
Change pipettes

Aspirate 1000 nL from (P1, C9, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000, no over aspirate
Dispense 1000 nL to (P2, C3, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000
Change pipettes

Aspirate 1000 nL from (P1, C10, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000, no over aspirate
Dispense 1000 nL to (P2, C4, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000
Change pipettes

Aspirate 1000 nL from (P1, C11, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000, no over aspirate

Dispense 1000 nL to (P2, C5, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000
Change pipettes

Aspirate 1000 nL from (P1, C12, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000, no over aspirate
Dispense 1000 nL to (P2, C6, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000
Change pipettes

Aspirate 1000 nL from (P1, C13, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000, no over aspirate
Dispense 1000 nL to (P2, C7, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000
Change pipettes

Aspirate 1000 nL from (P1, C14, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000, no over aspirate
Dispense 1000 nL to (P2, C8, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000
Change pipettes

Aspirate 1000 nL from (P1, C15, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000, no over aspirate
Dispense 1000 nL to (P2, C9, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000
Change pipettes

Aspirate 1000 nL from (P1, C16, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000, no over aspirate
Dispense 1000 nL to (P2, C10, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000
Change pipettes

Aspirate 1000 nL from (P1, C17, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000, no over aspirate
Dispense 1000 nL to (P2, C11, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000
Change pipettes

Aspirate 1000 nL from (P1, C18, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000, no over aspirate
Dispense 1000 nL to (P2, C12, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000
Change pipettes

Aspirate 1000 nL from (P1, C19, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000, no over aspirate
Dispense 1000 nL to (P2, C13, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000
Change pipettes

Aspirate 1000 nL from (P1, C20, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000, no over aspirate
Dispense 1000 nL to (P2, C14, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000

Change pipettes

Aspirate 1000 nL from (P1, C21, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000, no over aspirate
Dispense 1000 nL to (P2, C15, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000
Change pipettes

Aspirate 1000 nL from (P1, C22, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000, no over aspirate
Dispense 1000 nL to (P2, C16, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000
Change pipettes

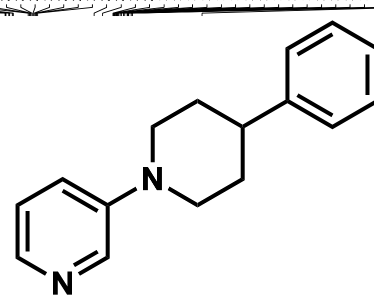
Aspirate 1000 nL from (P1, C23, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000, no over aspirate
Dispense 1000 nL to (P2, C17, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000
Change pipettes

Aspirate 1000 nL from (P1, C24, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000, no over aspirate
Dispense 1000 nL to (P2, C18, R1, S1), well volume 0 µL, mix cycles 3, mix volume 1000

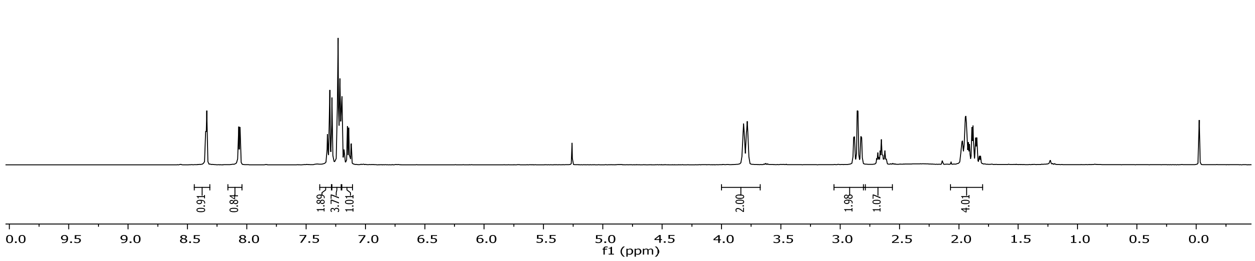
Appendix 2. Characterization for Experiment 3.

Characterization Data for coupling of 3-bromopyridine **22** with Nucleophiles **S1-S16**

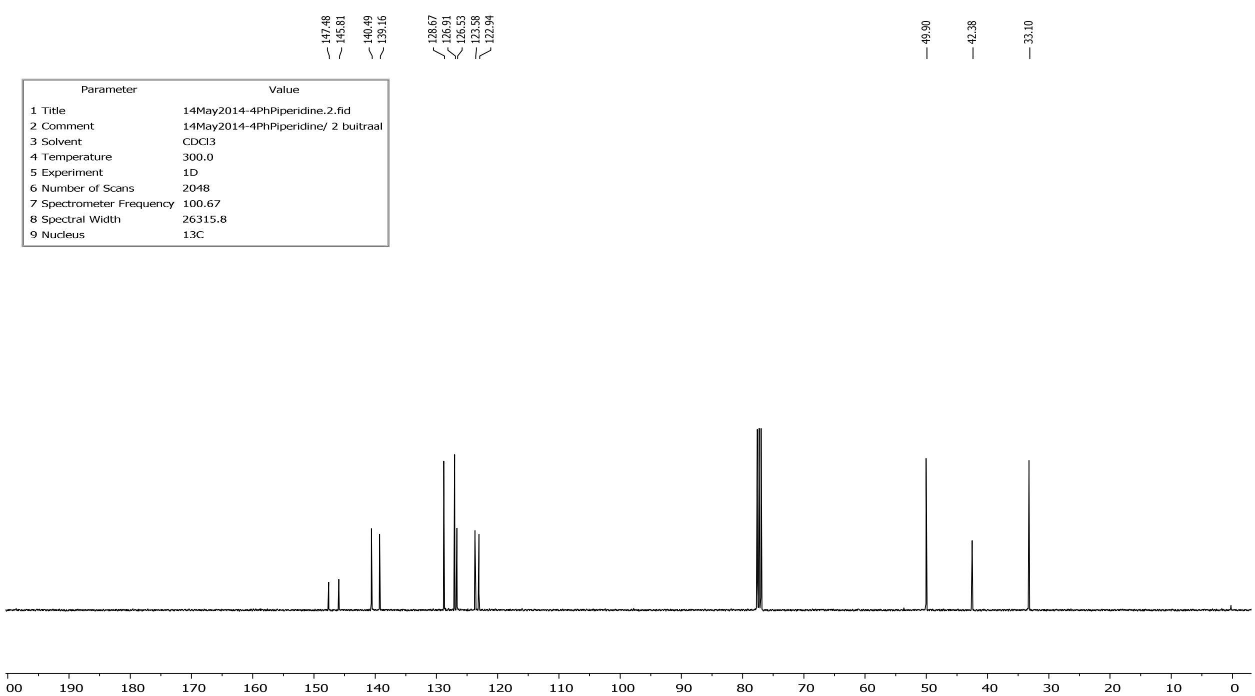
3-(4-phenylpiperidin-1-yl)pyridine:



Parameter	Value
1 Title	14May2014-4PhPiperidine.1.fid
2 Comment	14May2014-4PhPiperidine/ 1 buitraal
3 Solvent	CDCl3
4 Temperature	300.0
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	400.33
8 Spectral Width	6578.9
9 Nucleus	1H

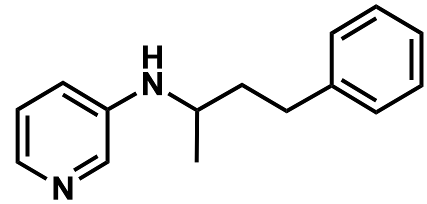


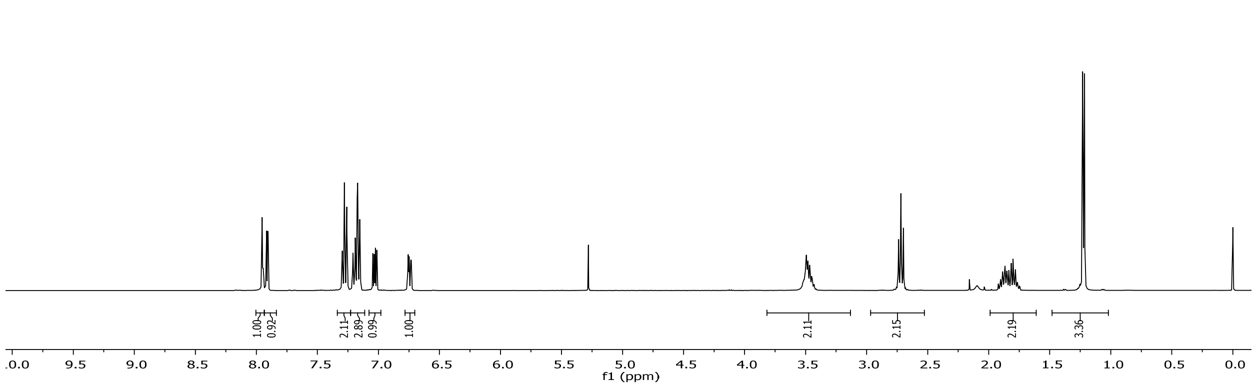
Parameter	Value
1 Title	14May2014-4PhPiperidine.2.fid
2 Comment	14May2014-4PhPiperidine/ 2 buitraal
3 Solvent	CDCl3
4 Temperature	300.0
5 Experiment	1D
6 Number of Scans	2048
7 Spectrometer Frequency	100.67
8 Spectral Width	26315.8
9 Nucleus	13C



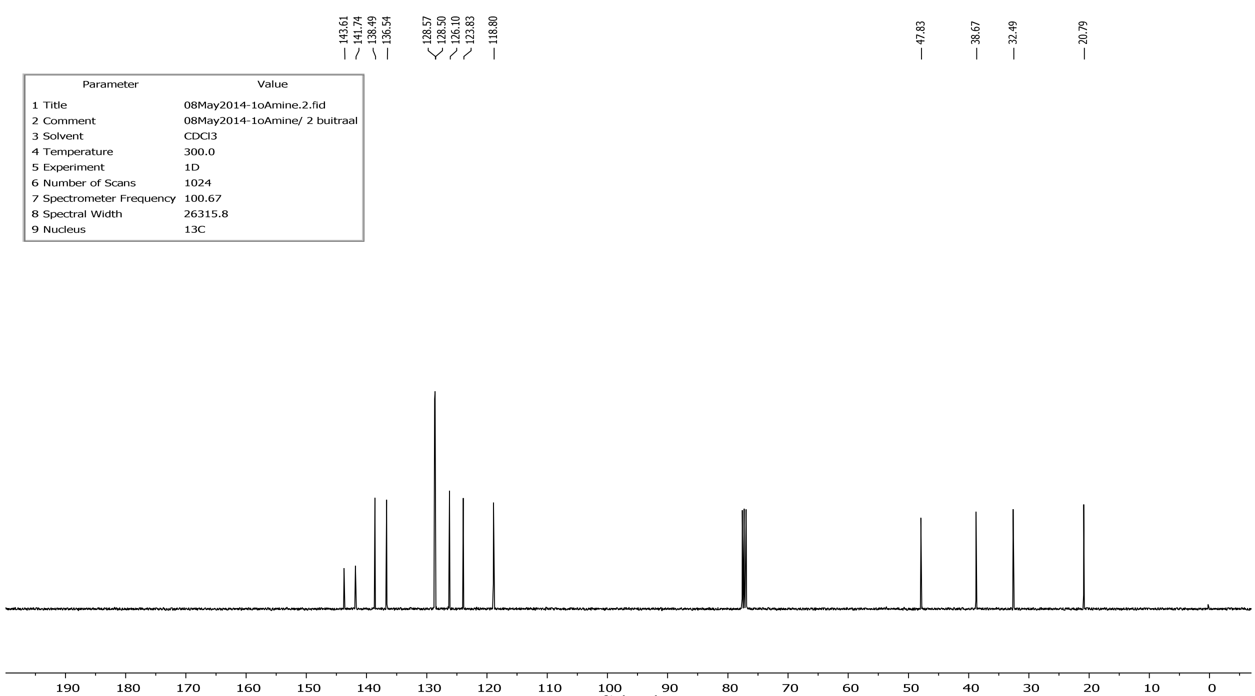
N-(4-phenylbutan-2-yl)pyridin-3-amine:

Parameter	Value
1 Title	08May2014-1oAmine.1.fid
2 Comment	08May2014-1oAmine/ 1 buitraal
3 Solvent	CDCl3
4 Temperature	300.0
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	400.33
8 Spectral Width	6578.9
9 Nucleus	1H

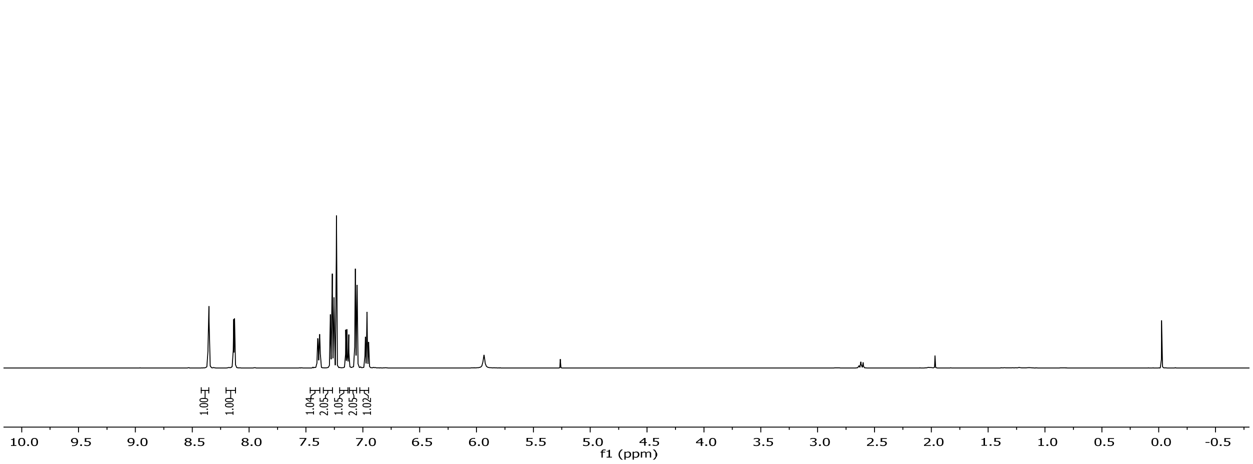




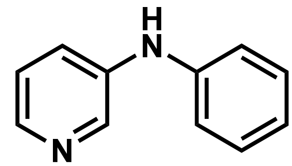
Parameter	Value
1 Title	08May2014-1oAmine.2.fid
2 Comment	08May2014-1oAmine/ 2 buitraal
3 Solvent	CDCl3
4 Temperature	300.0
5 Experiment	1D
6 Number of Scans	1024
7 Spectrometer Frequency	100.67
8 Spectral Width	26315.8
9 Nucleus	13C

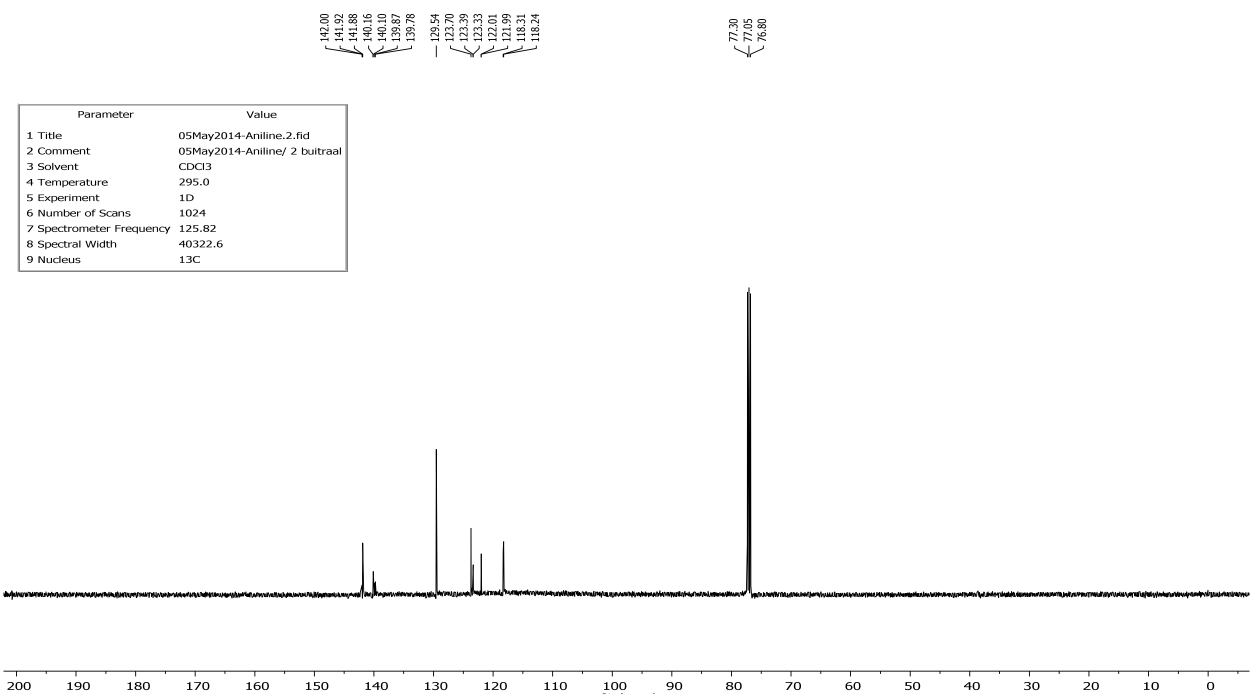


N-phenylpyridin-3-amine:



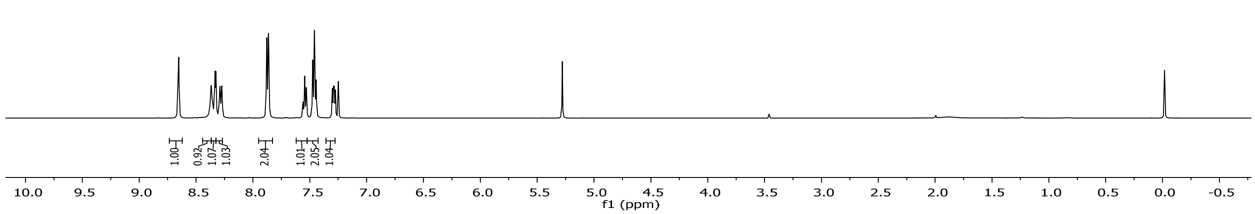
Parameter	Value
1 Title	05May2014-Aniline.1.fid
2 Comment	05May2014-Aniline/ 1 buitraal
3 Solvent	CDCl3
4 Temperature	295.0
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	500.33
8 Spectral Width	13020.8
9 Nucleus	1H



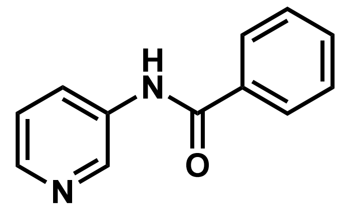


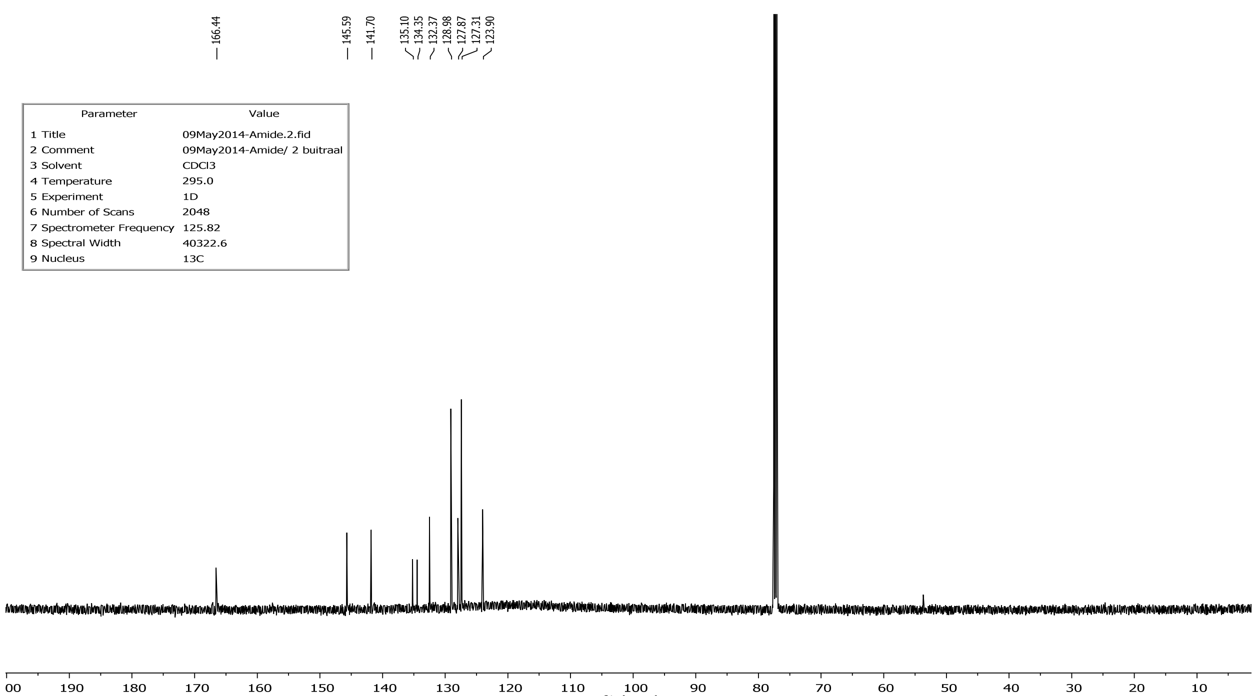
Parameter	Value
1 Title	05May2014-Aniline.2.fid
2 Comment	05May2014-Aniline/ 2 buitraal
3 Solvent	CDCl3
4 Temperature	295.0
5 Experiment	1D
6 Number of Scans	1024
7 Spectrometer Frequency	125.82
8 Spectral Width	40322.6
9 Nucleus	13C

N-(pyridin-3-yl)benzamide:



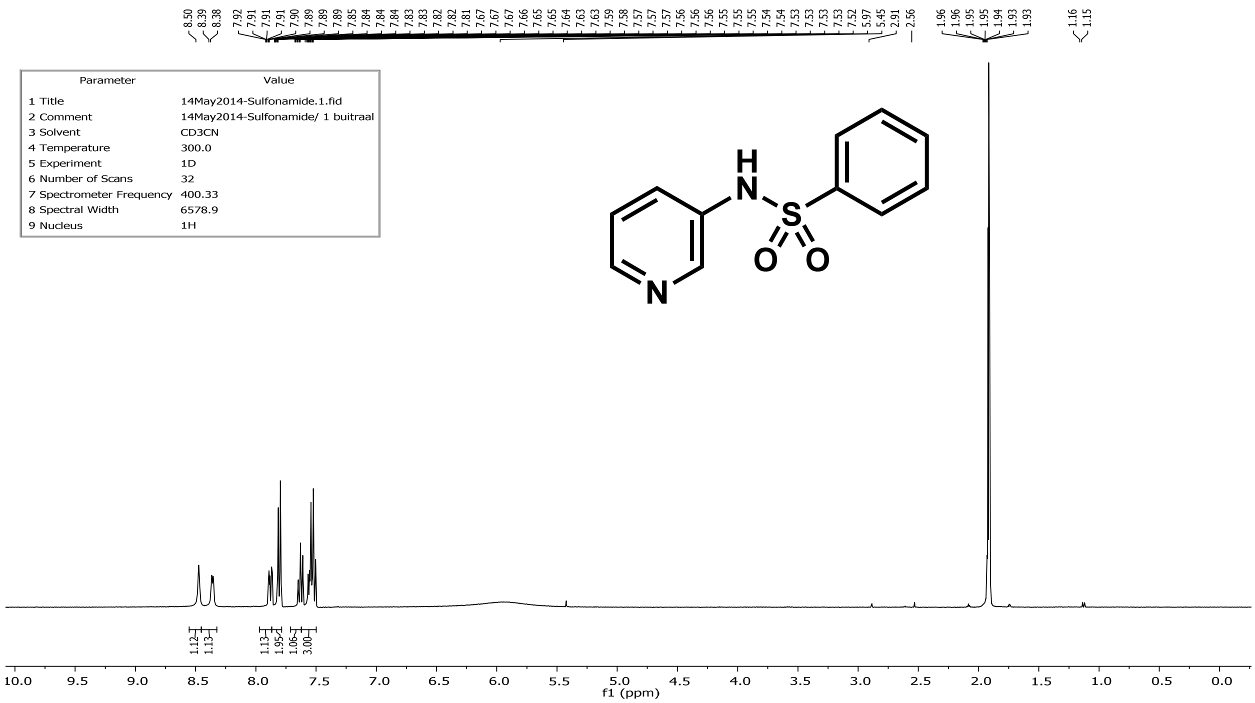
Parameter	Value
1 Title	09May2014-Amide.1.fid
2 Comment	09May2014-Amide/ 1 buitraal
3 Solvent	CDCl3
4 Temperature	295.0
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	500.33
8 Spectral Width	13020.8
9 Nucleus	1H

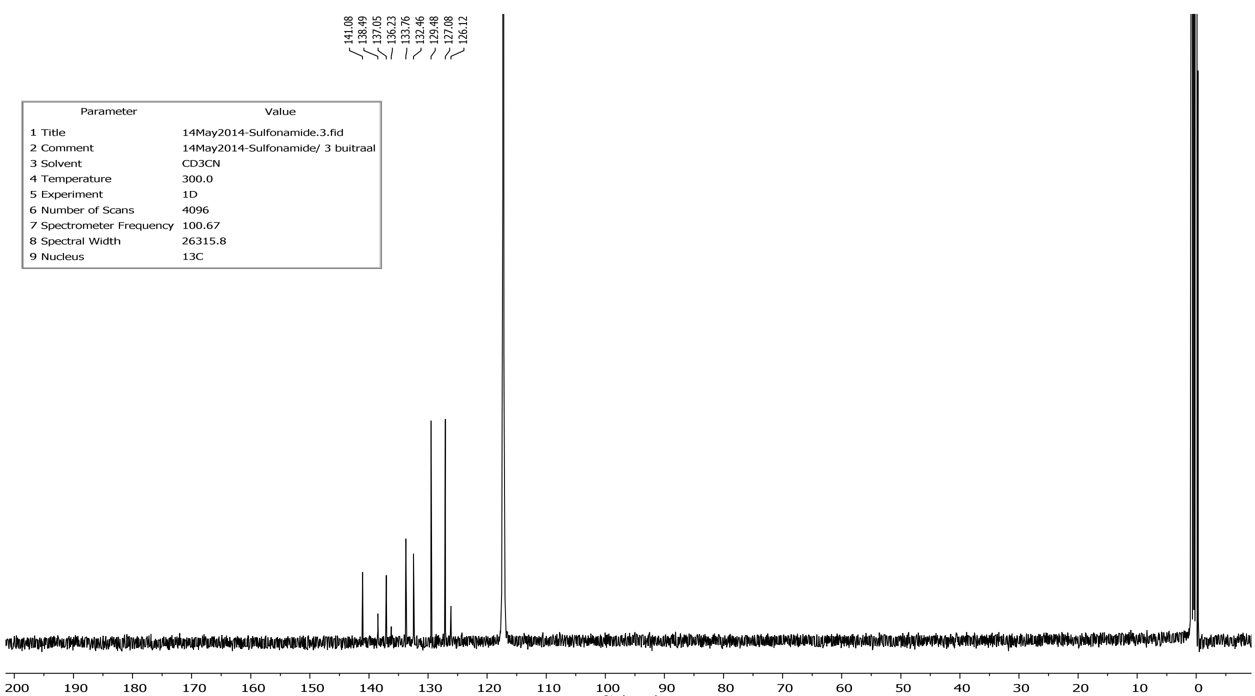




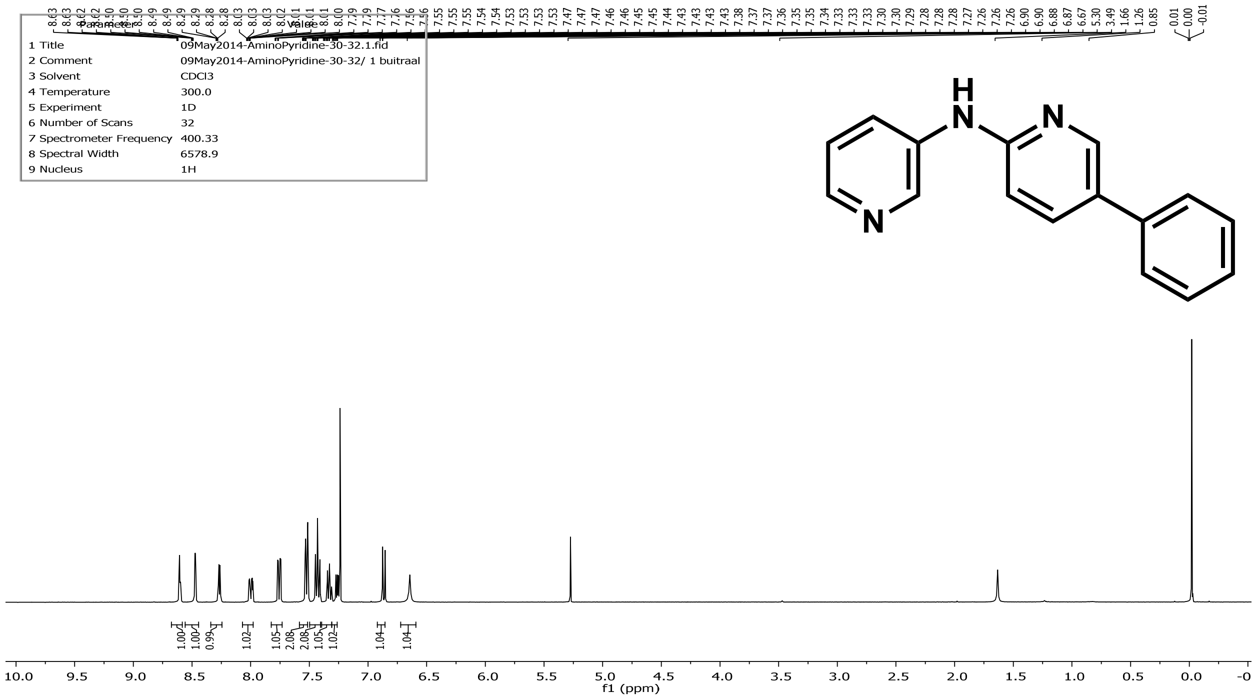
Parameter	Value
1 Title	09May2014-Amide.2.fid
2 Comment	09May2014-Amide/ 2 buitraal
3 Solvent	CDCl3
4 Temperature	295.0
5 Experiment	1D
6 Number of Scans	2048
7 Spectrometer Frequency	125.82
8 Spectral Width	40322.6
9 Nucleus	13C

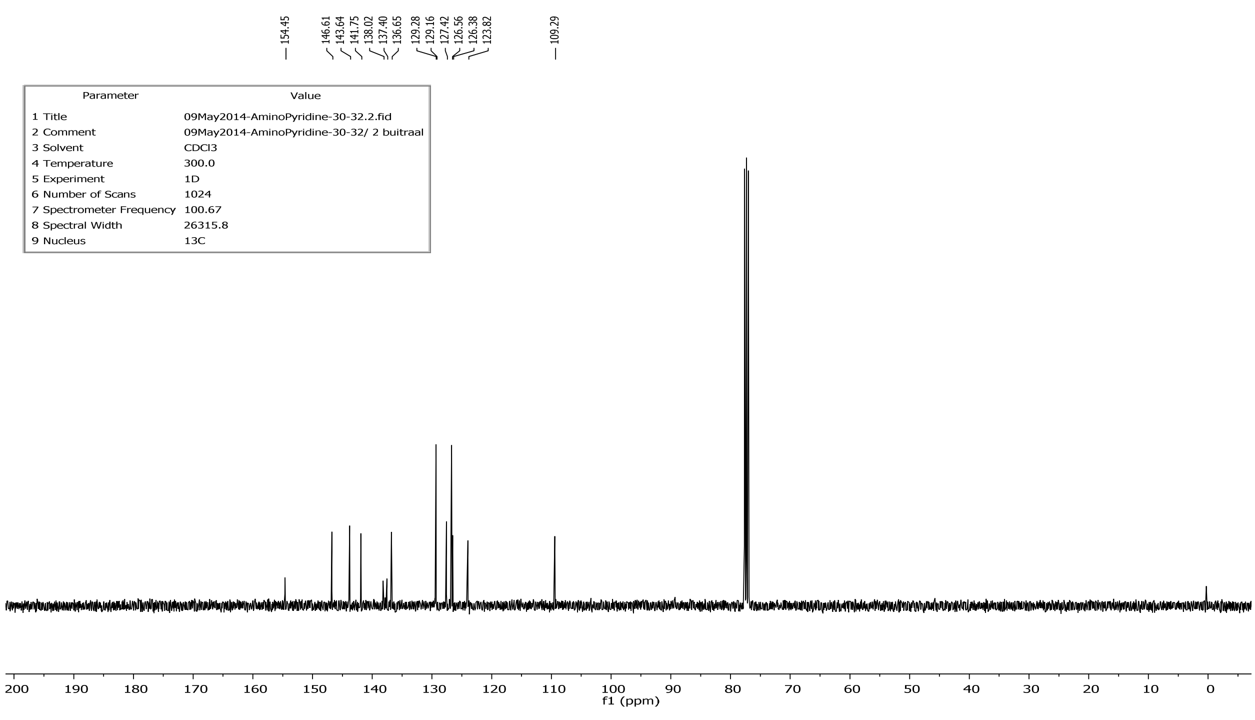
N-(pyridin-3-yl)benzenesulfonamide:



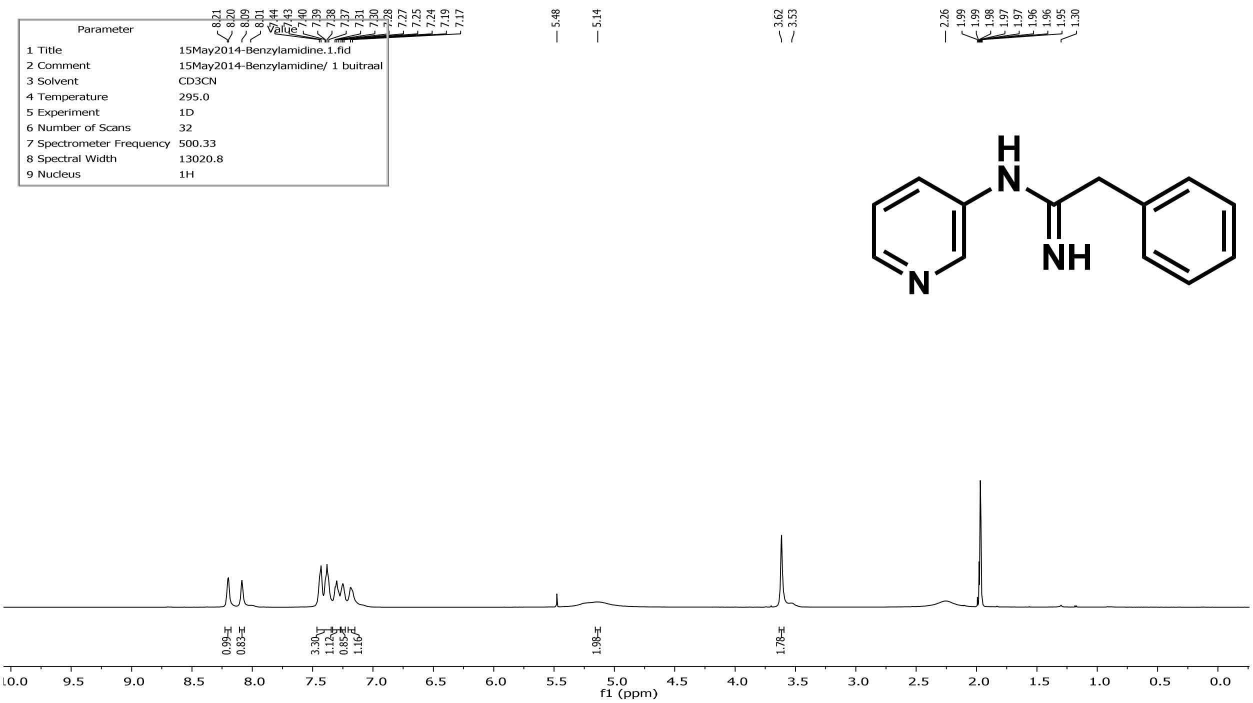


5-phenyl-*N*-(pyridin-3-yl)pyridin-2-amine:

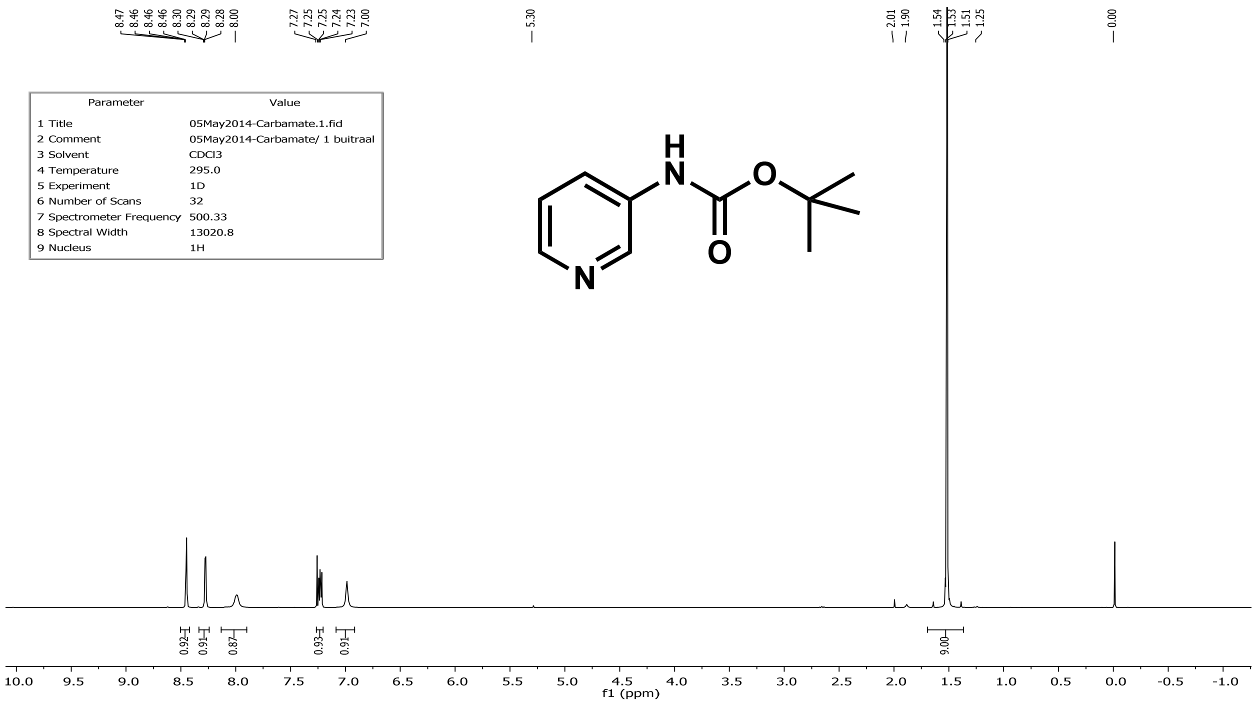


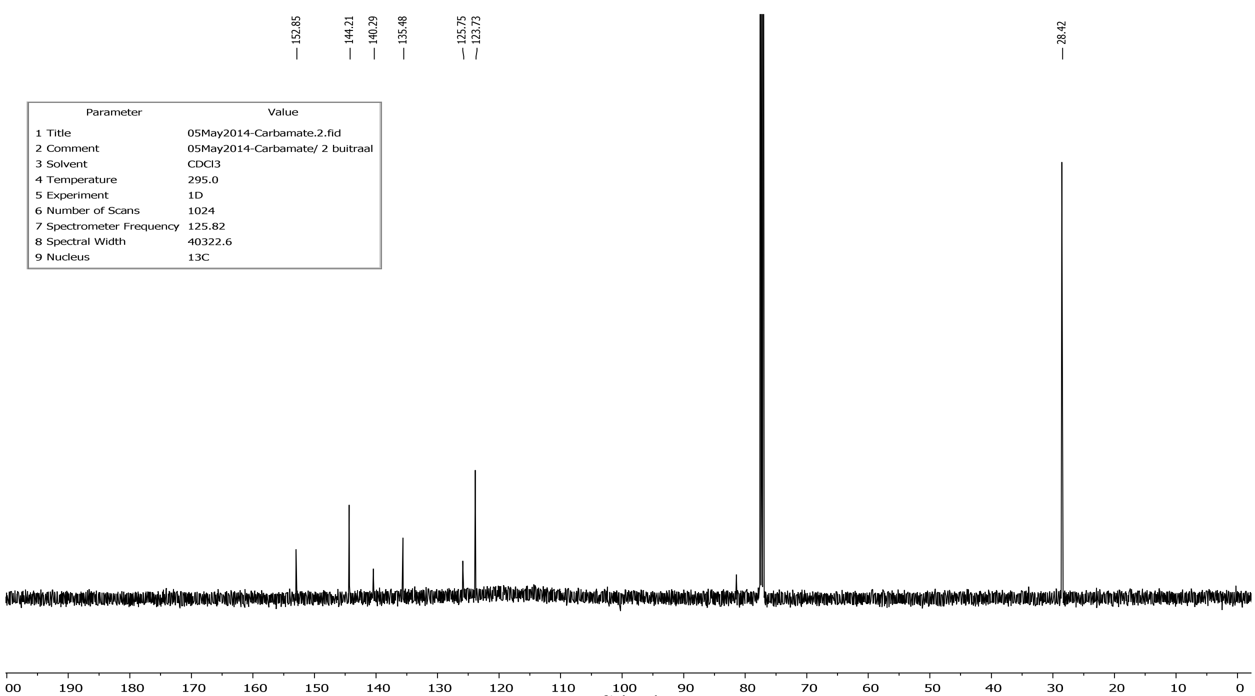


2-phenyl-*N*-(pyridin-3-yl)acetimidamide:



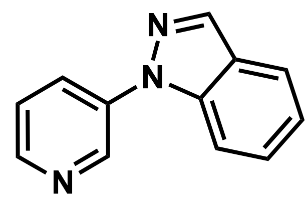
***tert*-butyl pyridin-3-ylcarbamate:**

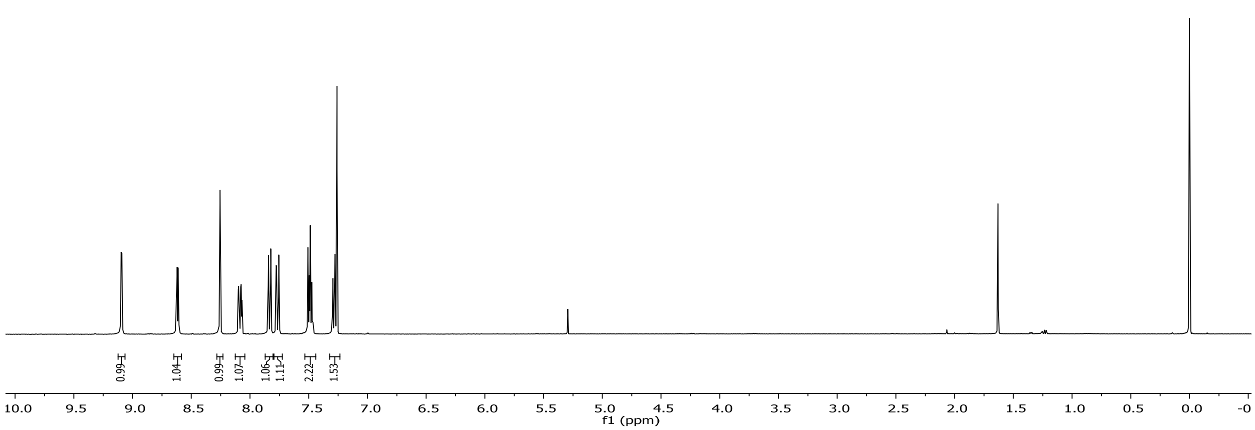




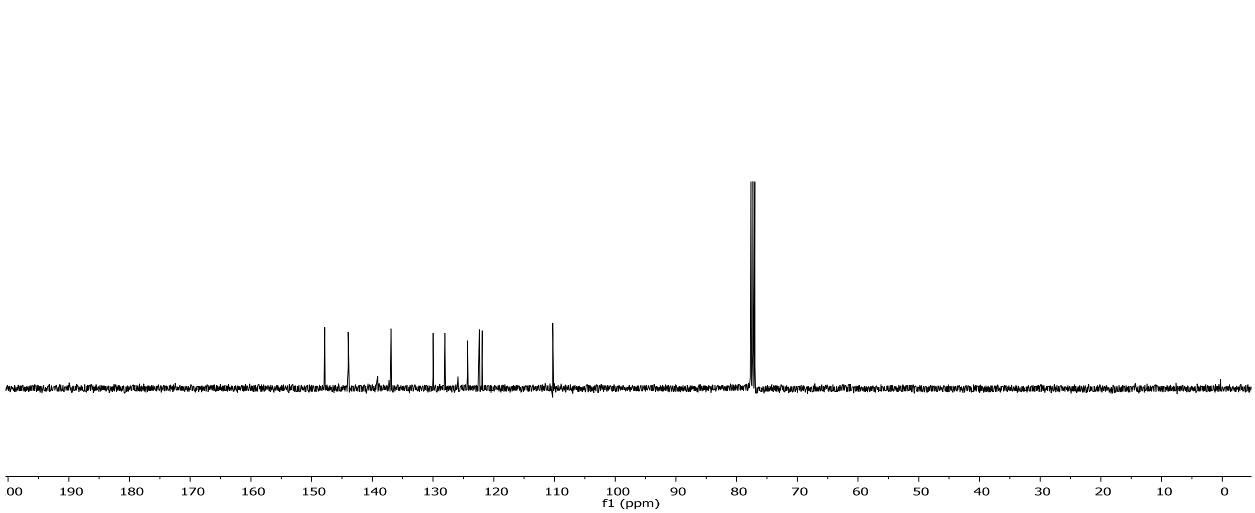
1-(pyridin-3-yl)-1*H*-indazole:

Parameter	Value
1 Title	09May2014-Indazole-1.1.fid
2 Comment	09May2014-Indazole-1/ 1 buitraal
3 Solvent	CDCl3
4 Temperature	300.0
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	400.33
8 Spectral Width	6578.9
9 Nucleus	1H



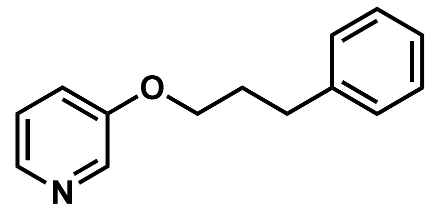


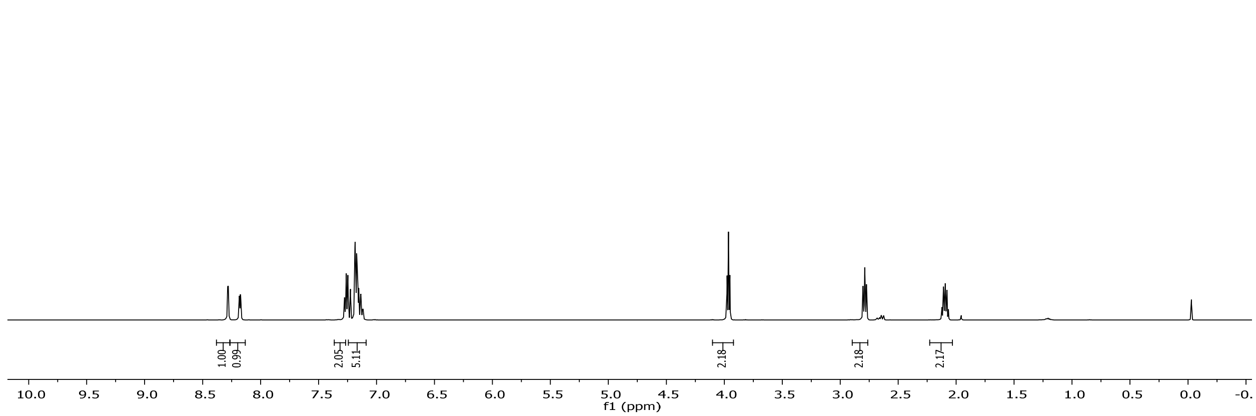
Parameter	Value
1 Title	09May2014-Indazole-1.2.fid
2 Comment	09May2014-Indazole-1/ 2 buitraal
3 Solvent	CDCl3
4 Temperature	300.0
5 Experiment	1D
6 Number of Scans	512
7 Spectrometer Frequency	100.67
8 Spectral Width	26315.8
9 Nucleus	13C



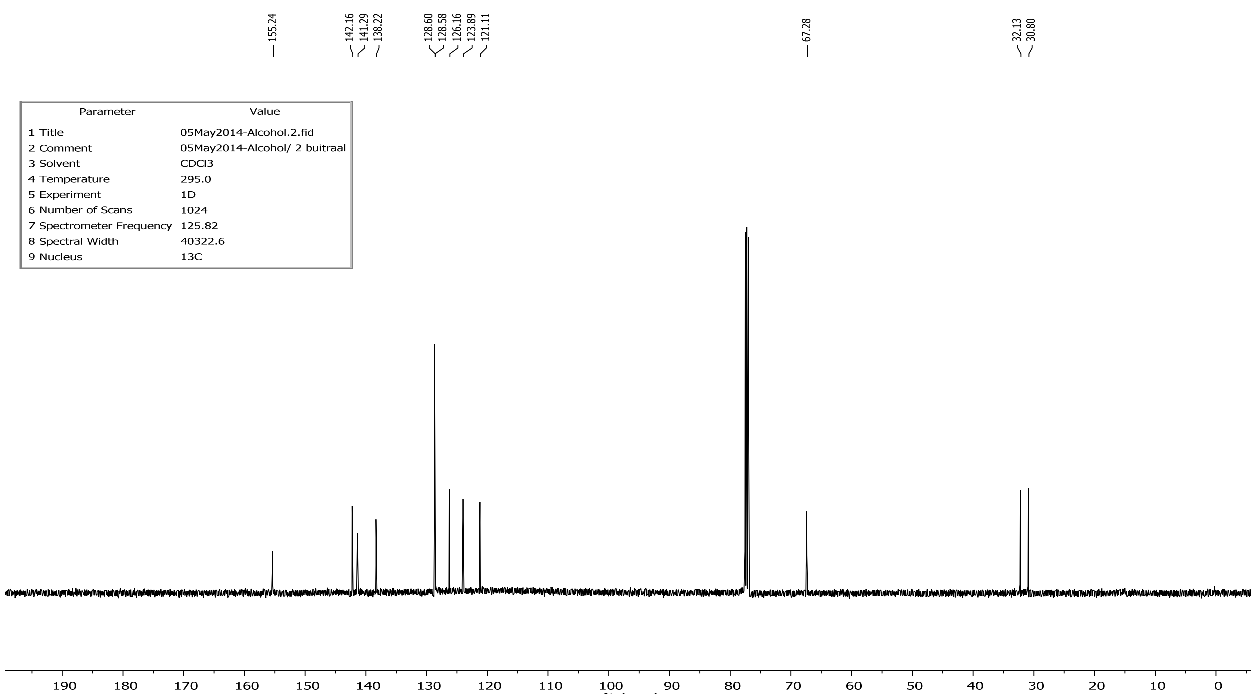
3-(3-phenylpropoxy)pyridine:

Parameter	Value
1 Title	05May2014-Alcohol.1.fid
2 Comment	05May2014-Alcohol/ 1 buitraal
3 Solvent	CDCl3
4 Temperature	295.0
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	500.33
8 Spectral Width	13020.8
9 Nucleus	1H

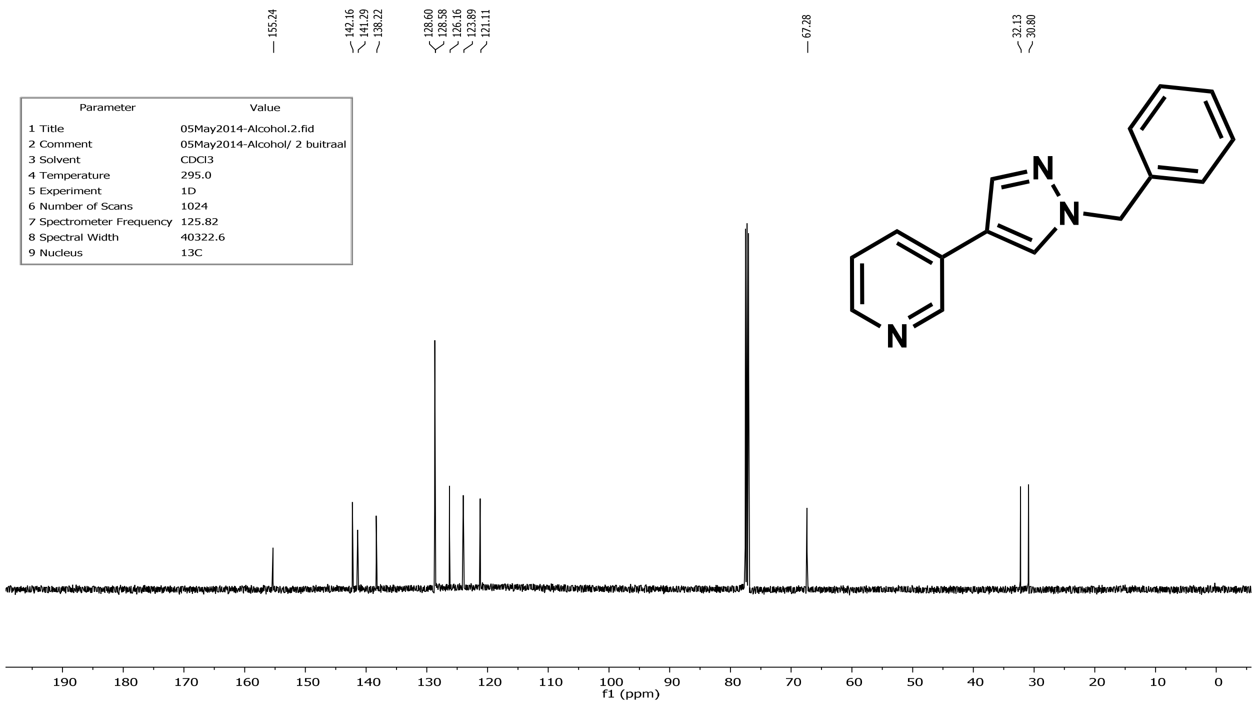


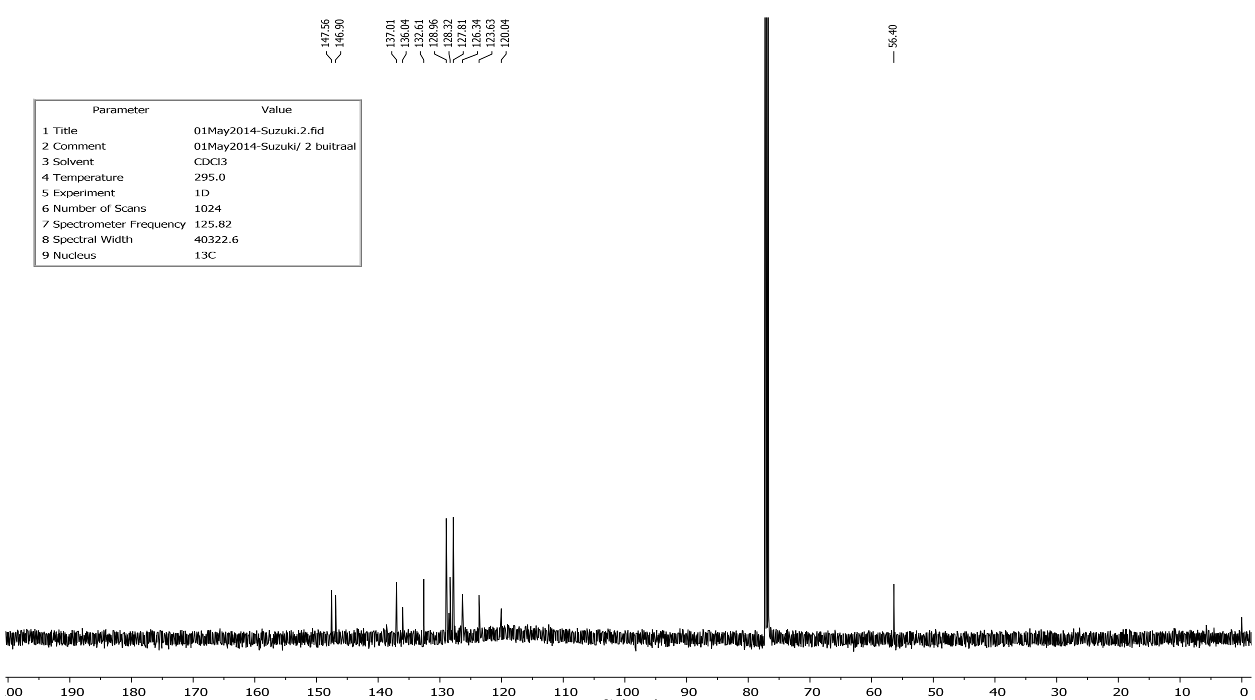


Parameter	Value
1 Title	05May2014-Alcohol.2.fid
2 Comment	05May2014-Alcohol/ 2 buitraal
3 Solvent	CDCl3
4 Temperature	295.0
5 Experiment	1D
6 Number of Scans	1024
7 Spectrometer Frequency	125.82
8 Spectral Width	40322.6
9 Nucleus	13C

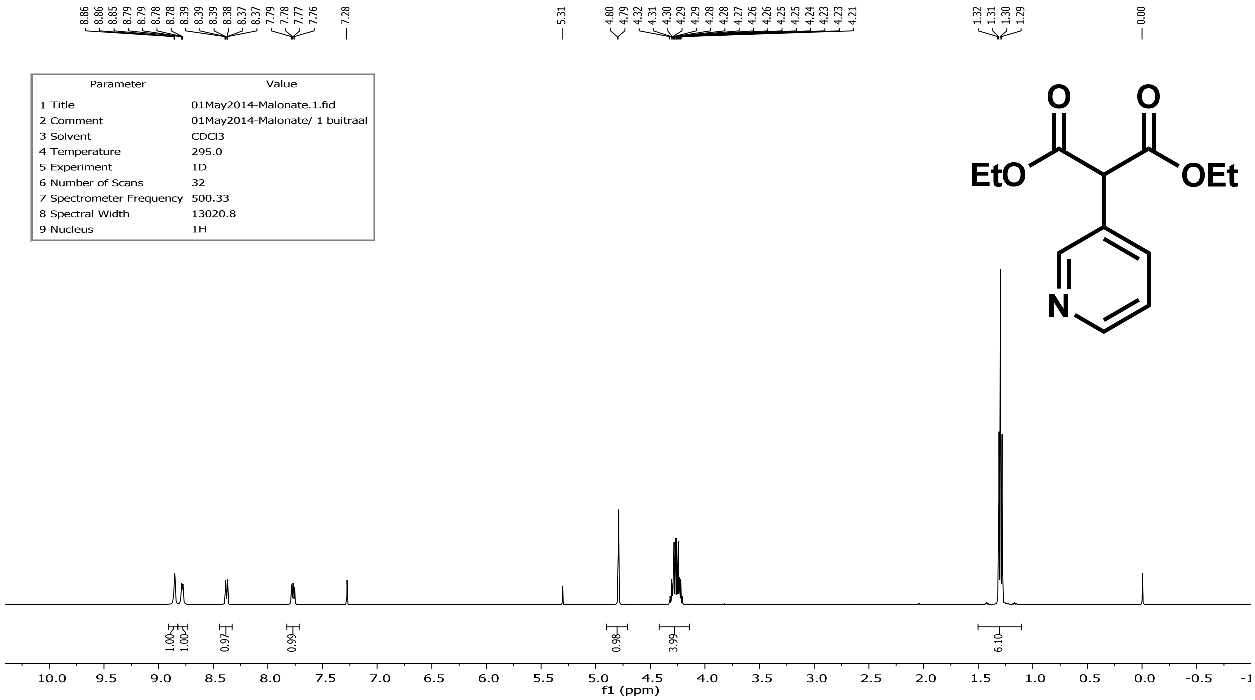


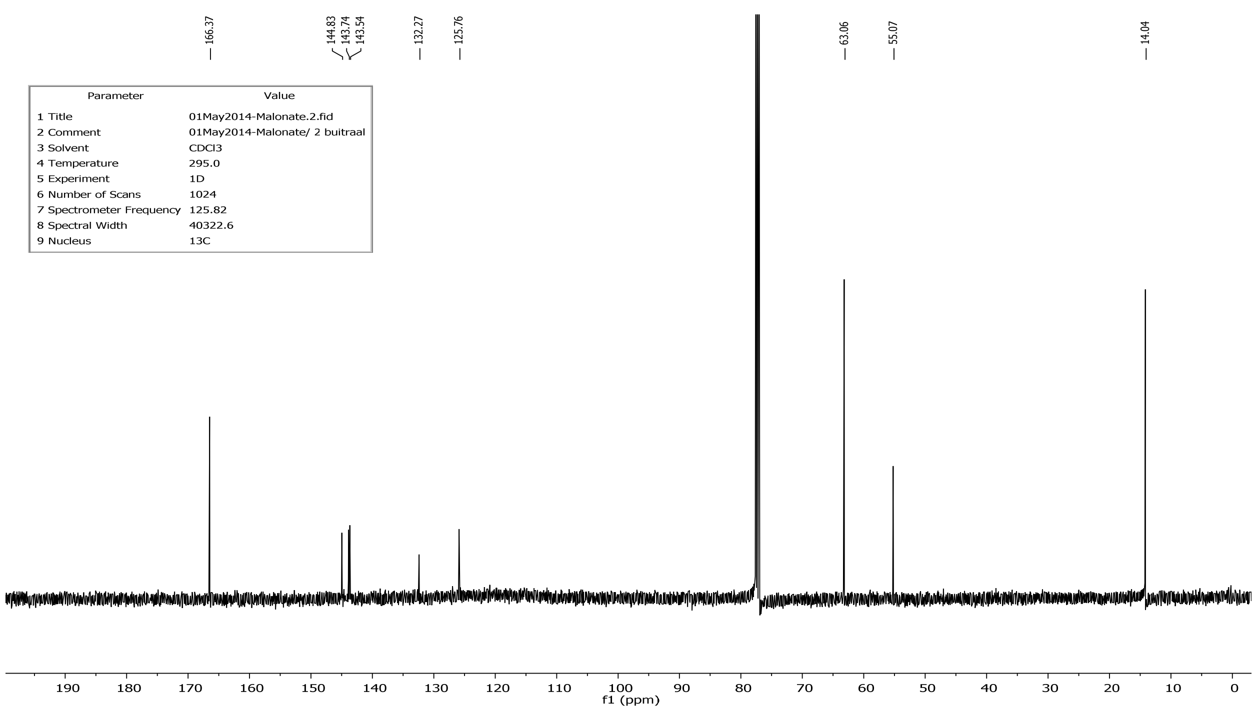
3-(1-benzyl-1*H*-pyrazol-4-yl)pyridine:



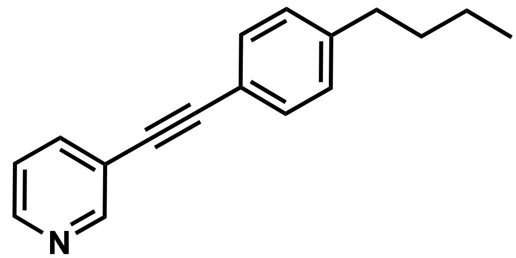


Diethyl 2-(pyridin-3-yl)malonate:

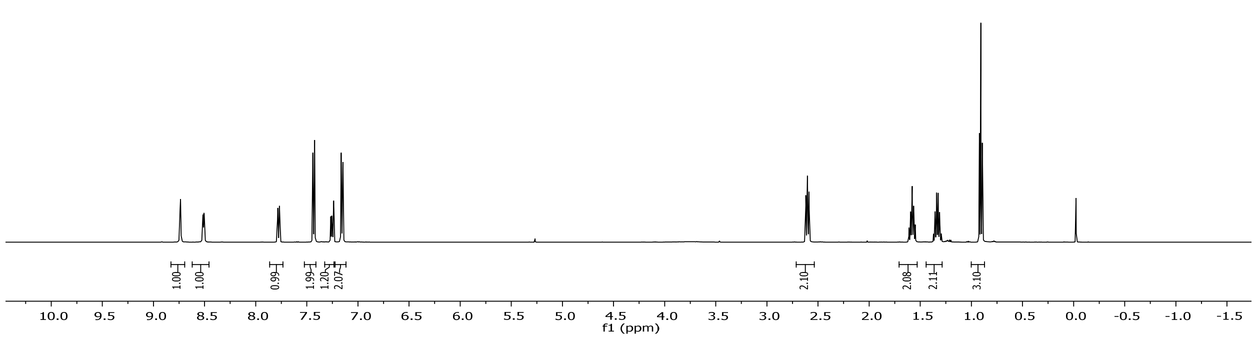




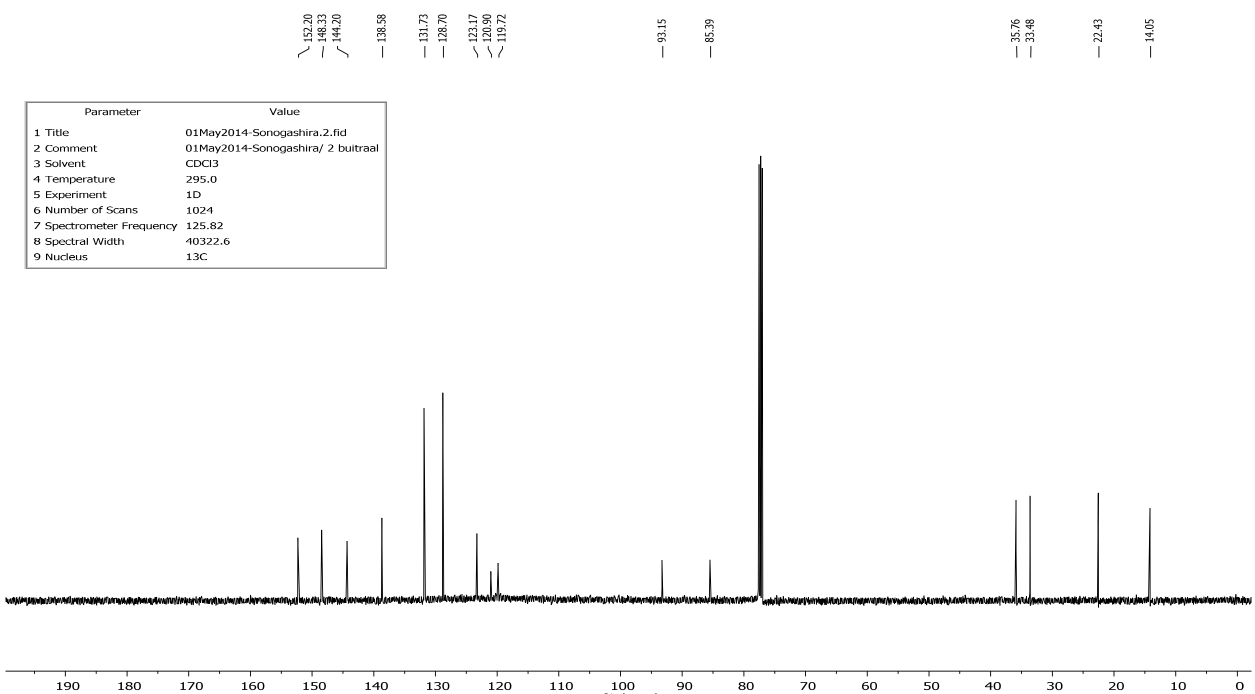
3-((4-butylphenyl)ethynyl)pyridine:



Parameter	Value
1 Title	01May2014-Sonogashira.1.fid
2 Comment	01May2014-Sonogashira/ 1 buitraal
3 Solvent	CDCl3
4 Temperature	295.0
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	500.33
8 Spectral Width	13020.8
9 Nucleus	1H



Parameter	Value
1 Title	01May2014-Sonogashira.2.fid
2 Comment	01May2014-Sonogashira/ 2 buitraal
3 Solvent	CDCl3
4 Temperature	295.0
5 Experiment	1D
6 Number of Scans	1024
7 Spectrometer Frequency	125.82
8 Spectral Width	40322.6
9 Nucleus	13C



3-(4-phenylpiperidin-1-yl)pyridine:

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 2.9 Hz, 1H), 8.09 (dd, *J* = 4.5, 1.4 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.28 – 7.20 (m, 4H), 7.16 (dd, *J* = 8.4, 4.6 Hz, 1H), 3.82 (dp, *J* = 12.3, 1.8 Hz, 2H), 2.88 (td, *J* = 12.2, 2.9 Hz, 2H), 2.68 (tt, *J* = 12.0, 3.9 Hz, 1H), 2.07 – 1.80 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.48, 145.81, 140.49, 139.16, 128.67, 126.91, 126.53, 123.58, 122.94, 49.90, 42.38, 33.10. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{16}H_{18}N_2$, 239.1543; found, 239.1539.

***N*-(4-phenylbutan-2-yl)pyridin-3-amine:**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 2.9, 0.7 Hz, 1H), 7.91 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.34 – 7.23 (m, 2H), 7.23 – 7.11 (m, 3H), 7.03 (ddd, *J* = 8.3, 4.7, 0.7 Hz, 1H), 6.74 (ddd, *J* = 8.3, 2.9, 1.4 Hz, 1H), 3.82 – 3.13 (m, 2H), 2.72 (t, *J* = 7.8 Hz, 2H), 1.99 – 1.61 (m, 2H), 1.22 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.61, 141.74, 138.49, 136.54, 128.57, 128.50, 126.10, 123.83, 118.80, 47.83, 38.67, 32.49, 20.79. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{15}H_{18}N_2$, 227.1543; found, 227.1538.

***N*-phenylpyridin-3-amine:**

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 2.8 Hz, 1H), 8.16 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.41 (ddt, *J* = 8.3, 2.8, 1.4 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.16 (dd, *J* = 8.3, 4.6 Hz, 1H), 7.12 – 7.05 (m, 2H), 7.03 – 6.95 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.00, 141.92, 141.88, 140.16, 140.10, 139.87, 139.78, 129.54, 123.70, 123.39, 123.33, 122.01, 121.99, 118.31, 118.24. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{11}H_{10}N_2$, 171.0917; found, 171.0915.

***N*-(pyridin-3-yl)benzamide:**

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, *J* = 2.8 Hz, 1H), 8.38 (s, 1H), 8.35 (dd, *J* = 4.7, 1.4 Hz, 1H), 8.30 (dt, *J* = 8.4, 2.0 Hz, 1H), 7.95 – 7.83 (m, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.31 (dd, *J* = 8.3, 4.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.44, 145.59, 141.70, 135.10, 134.35, 132.37, 128.98, 127.87, 127.31, 123.90. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{12}H_{10}N_2O$, 199.0866; found, 199.0859.

***N*-(pyridin-3-yl)benzenesulfonamide:**

^{1}H NMR (400 MHz, CD_3CN) δ 8.50 (s, 1H), 8.38 (d, *J* = 5.2 Hz, 1H), 7.90 (ddd, *J* = 8.5, 2.6, 1.3 Hz, 1H), 7.87 – 7.79 (m, 2H), 7.71 – 7.62 (m, 1H), 7.62 – 7.50 (m, 3H). ^{13}C NMR (101 MHz, CD_3CN) δ 141.08, 138.49, 137.05, 136.23, 133.76, 132.46, 129.48, 127.08, 126.12. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{11}H_{10}N_2O_2S$, 235.0536; found, 235.0533.

5-phenyl-*N*-(pyridin-3-yl)pyridin-2-amine:

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (dd, *J* = 2.8, 0.8 Hz, 1H), 8.49 (dd, *J* = 2.5, 0.8 Hz, 1H), 8.29 (dd, *J* = 4.7, 1.4 Hz, 1H), 8.02 (ddd, *J* = 8.3, 2.8, 1.5 Hz, 1H), 7.78 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.59 – 7.51 (m, 2H), 7.50 – 7.40 (m, 2H), 7.39 – 7.31 (m, 1H), 7.31 – 7.26 (m, 1H), 6.89 (dd, *J* = 8.5, 0.8 Hz, 1H), 6.67 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.45, 146.61, 143.64, 141.75, 138.02, 137.40, 136.65, 129.28, 129.16, 127.42, 126.56, 126.38, 123.82, 109.29. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{16}H_{13}N_3$, 248.1182; found, 248.1178.

2-phenyl-*N*-(pyridin-3-yl)acetimidamide:

^{1}H NMR (400 MHz, CD_3CN) δ 8.20 (d, *J* = 4.7 Hz, 1H), 8.11 – 8.06 (m, 1H), 7.41 – 7.18 (m, 7H), 5.14 (s, 2H), 3.61 (s, 2H). HRMS (*m*/*z*): $[M]^+$ calcd for $C_{13}H_{13}N_3$, 212.1182; found, 212.1174.

***tert*-butyl pyridin-3-ylcarbamate:**

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 – 8.42 (m, 1H), 8.29 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.00 (s, 1H), 7.24 (dd, *J* = 8.4, 4.7 Hz, 1H), 7.00 (s, 1H), 1.53 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.85, 144.21, 140.29, 135.48, 125.75, 123.73, 28.42. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{10}H_{14}N_2O_2$, 195.1128; found, 195.1126.

1-(pyridin-3-yl)-1*H*-indazole:

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (s, 1H), 10.92 (ddd, *J* = 8.2, 2.6, 1.5 Hz, 1H), 10.74 – 10.64 (m, 1H), 10.59 (d, *J* = 0.9 Hz, 1H), 10.35 (t, *J* = 0.7 Hz, 2H), 10.12 (d, *J* = 10.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.71, 143.81, 136.77, 129.84, 127.90, 124.18, 122.20, 121.74, 110.13. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{12}H_9N_3$, 196.0869; found, 196.0857.

3-(3-phenylpropoxy)pyridine:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 2.9 Hz, 1H), 8.21 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.24 – 7.09 (m, 5H), 3.99 (t, *J* = 6.2 Hz, 2H), 2.82 (t, *J* = 7.6 Hz, 2H), 2.23 – 2.03 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.24, 142.16, 141.29, 138.22, 128.60, 128.58, 126.16, 123.89, 121.11, 67.28, 32.13, 30.80. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{14}H_{15}NO$, 214.1226; found, 214.1214.

3-(1-benzyl-1*H*-pyrazol-4-yl)pyridine:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 – 8.70 (m, 1H), 8.45 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.85 (d, *J* = 0.8 Hz, 1H), 7.73 (ddd, *J* = 7.9, 2.3, 1.7 Hz, 1H), 7.67 (d, *J* = 0.9 Hz, 1H), 7.42 – 7.31 (m, 3H), 7.31 – 7.23 (m, 4H), 5.36 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.56, 146.90, 137.01, 136.04, 132.61, 128.96, 128.32, 127.81, 126.34, 123.63, 120.04, 56.40. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{15}H_{13}N_3$, 236.1182; found, 236.1175.

Diethyl 2-(pyridin-3-yl)malonate:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 – 8.82 (m, 1H), 8.82 – 8.73 (m, 1H), 8.38 (dt, *J* = 8.2, 1.7 Hz, 1H), 7.77 (dd, *J* = 8.1, 5.3 Hz, 1H), 4.79 (s, 1H), 4.42 – 4.14 (m, 4H), 1.30 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.37, 144.83, 143.74, 143.54, 132.27, 125.76, 63.06, 55.07, 14.04. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{12}H_{15}NO_4$, 238.1074; found, 238.1061.

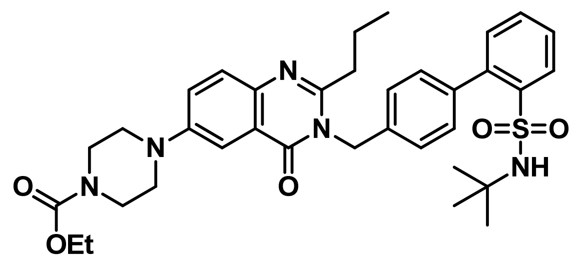
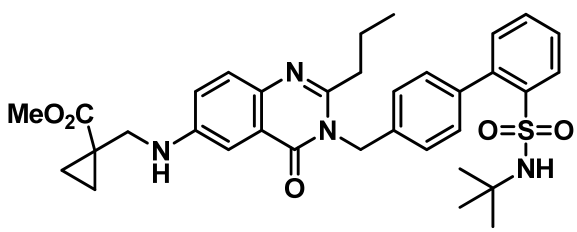
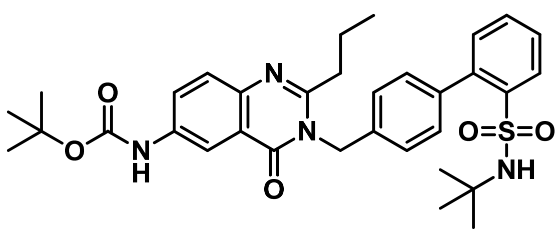
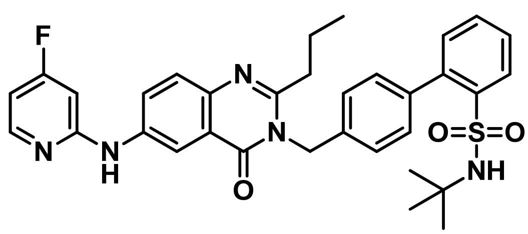
3-((4-butylphenyl)ethynyl)pyridine:

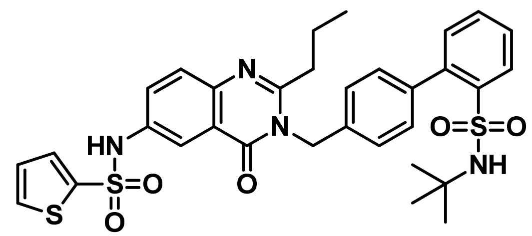
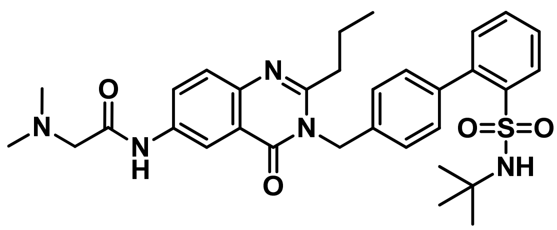
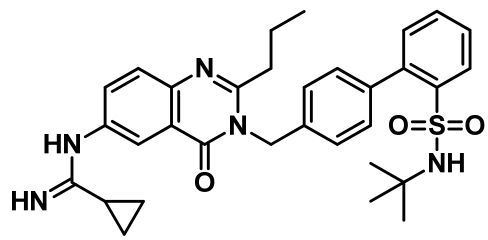
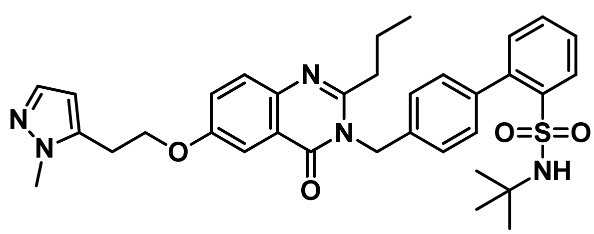
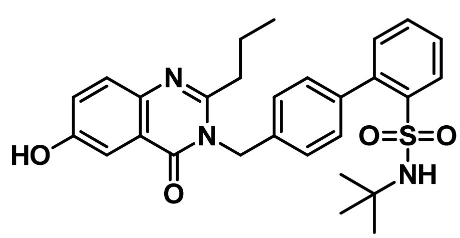
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 – 8.69 (m, 1H), 8.53 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.80 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.52 – 7.41 (m, 2H), 7.28 (ddd, *J* = 7.8, 4.8, 0.9 Hz, 1H), 7.22 – 7.12 (m, 2H), 2.71 – 2.54 (m, 2H), 1.71 – 1.53 (m, 2H), 1.36 (h, *J* = 7.3 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.20, 148.33, 144.20, 138.58, 131.73, 128.70, 123.17, 120.90, 119.72, 93.15, 85.39, 35.76, 33.48, 22.43, 14.05. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{17}H_{17}N$, 235.1361; found, 236.1683.

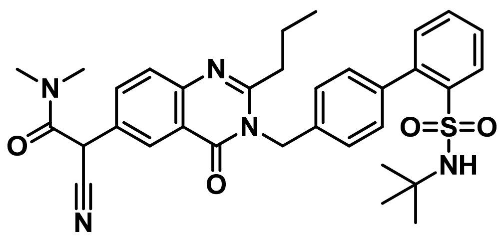
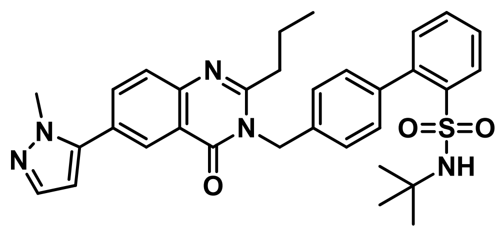
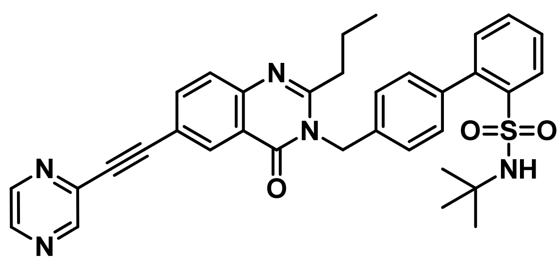
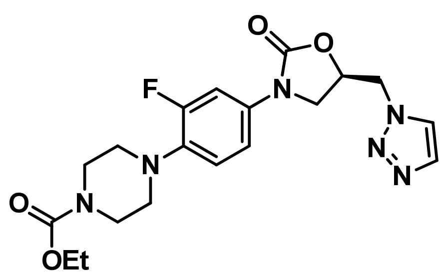
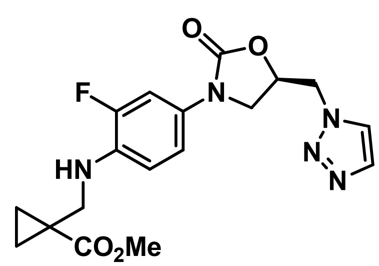
Appendix 3. Characterization for Experiment 4,6,8.

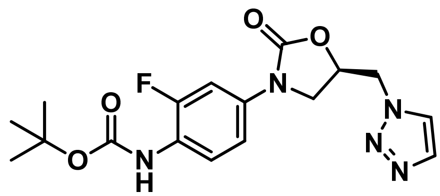
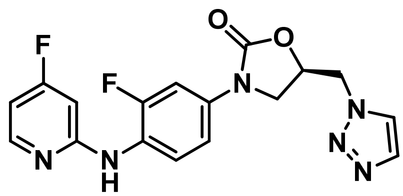
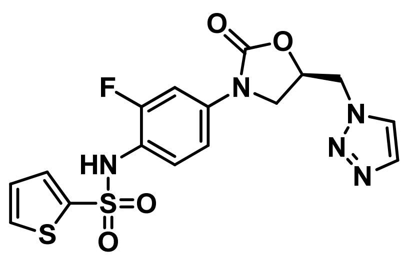
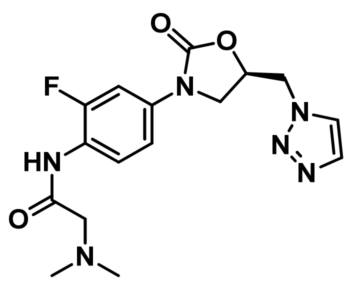
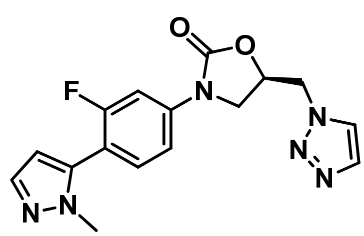
Characterization Data for coupling of aryl halides **1-8** with nucleophiles **9-20**.

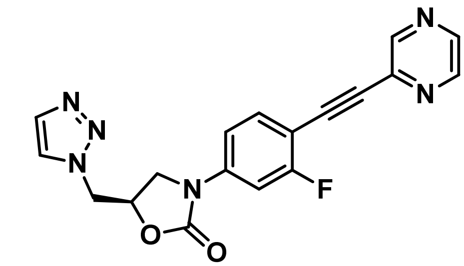
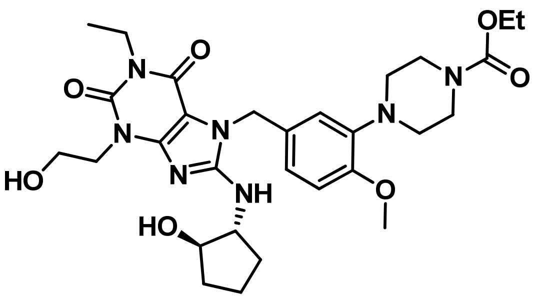
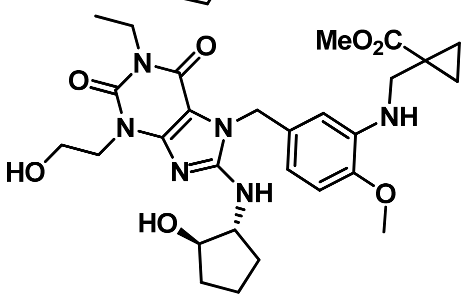
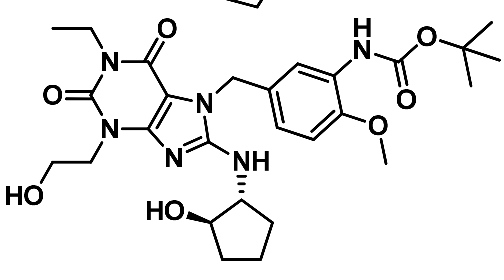
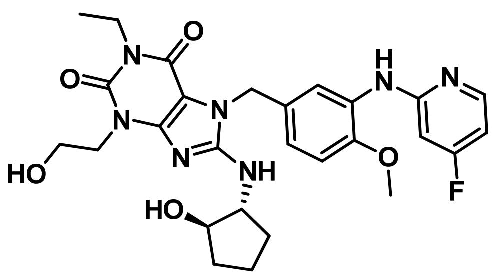
HRMS Data for products of isolated aryl halides **1-8** with nucleophiles **9-20**:

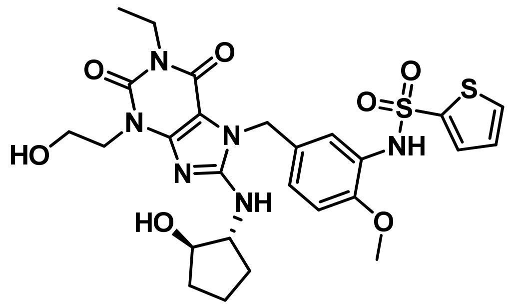
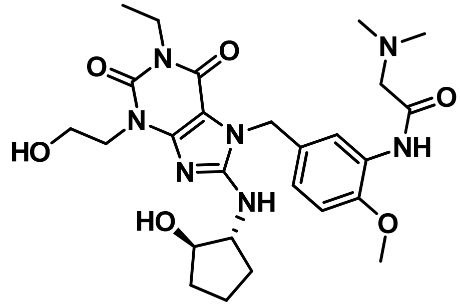
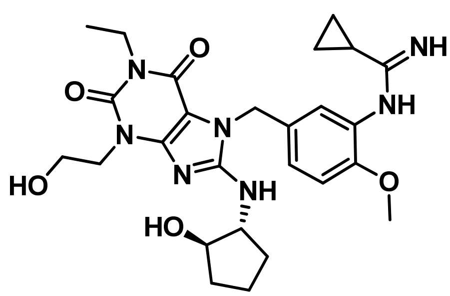
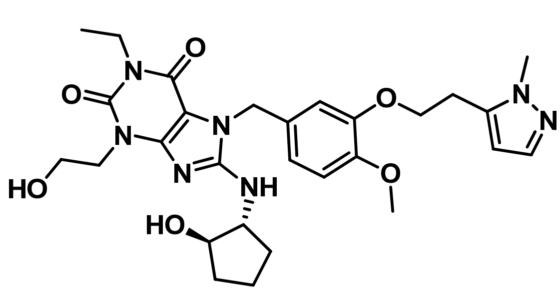
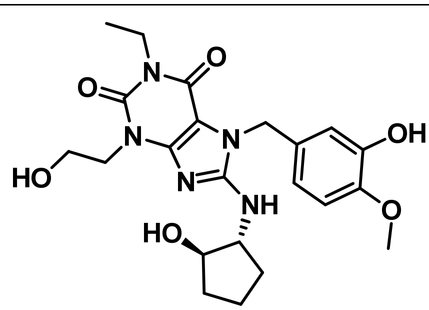
Plate #	Structure	Molecular Formula	*m/z* calcd for $[M]^+$	*m/z found* $[M+1]^+$
A1		$C_{35}H_{43}N_5O_5S$	645.2985	646.3060
A2		$C_{34}H_{40}N_4O_5S$	616.2719	617.2802
A3		$C_{33}H_{40}N_4O_5S$	604.2719	605.2791
A4		$C_{33}H_{34}FN_5O_3S$	599.2366	600.2439

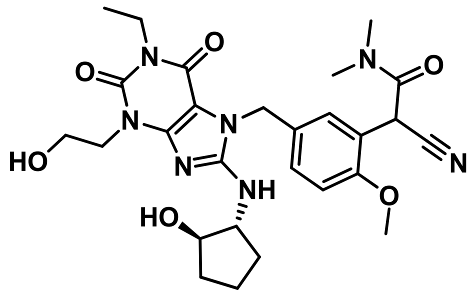
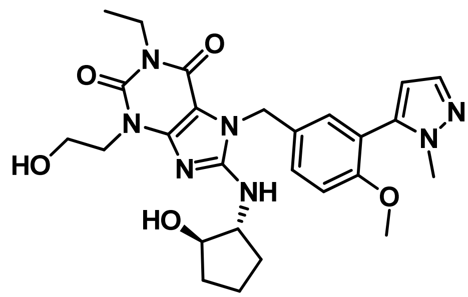
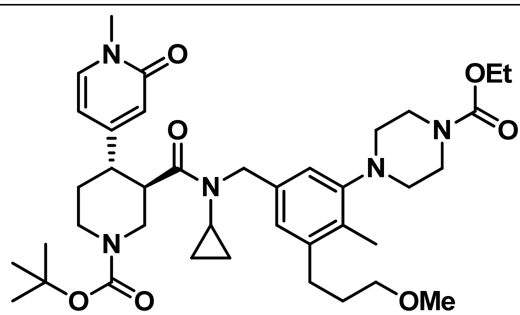
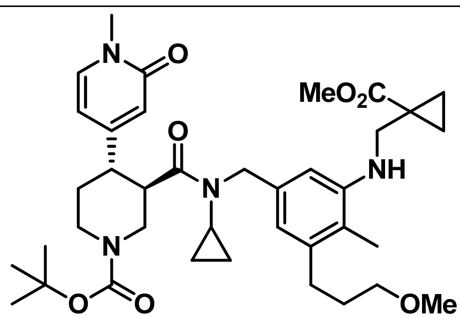
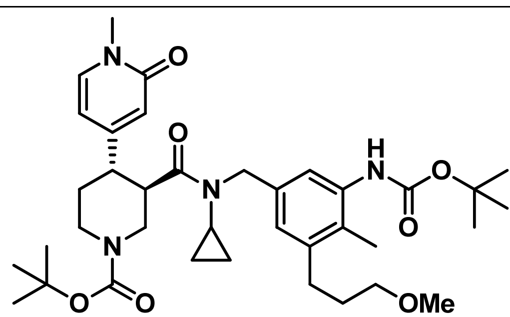
A5		$C_{32}H_{34}N_4O_5S_3$	650.1691	651.1775
A6		$C_{32}H_{39}N_5O_4S$	589.2723	590.2797
A7		$C_{32}H_{37}N_5O_3S$	571.2617	572.2691
A8		$C_{34}H_{39}N_5O_4S$	613.2723	614.2799
A9		$C_{28}H_{31}N_3O_4S$	505.2035	506.2045

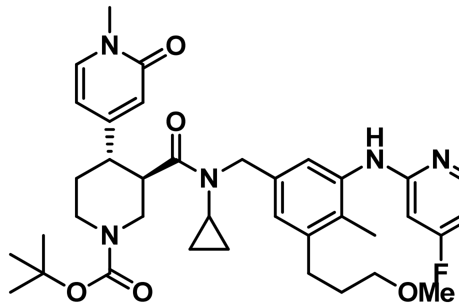
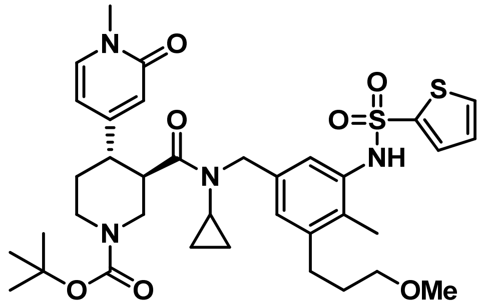
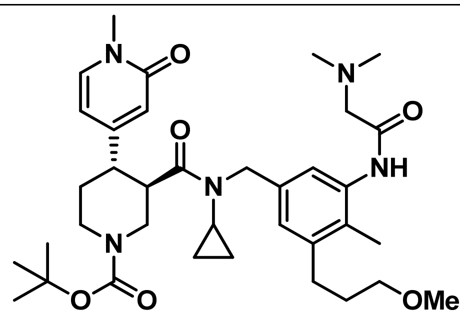
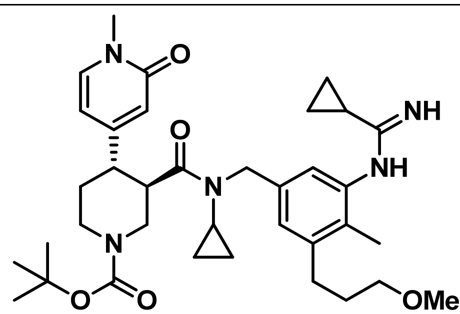
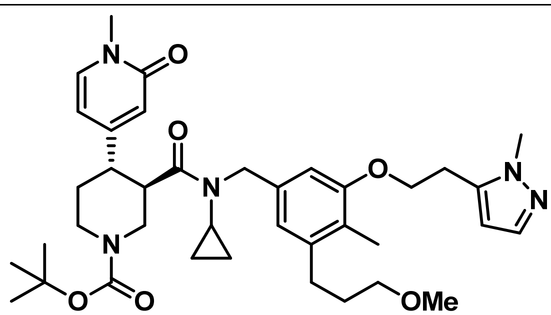
A10		$C_{33}H_{37}N_5O_4S$	599.2566	600.2556
A11		$C_{32}H_{35}N_5O_3S$	569.2461	570.2478
A12		$C_{34}H_{33}N_5O_3S$	591.2304	592.2387
B1		$C_{19}H_{23}FN_6O_4$	418.1765	419.1827
B2		$C_{18}H_{20}FN_5O_4$	389.1499	390.1533

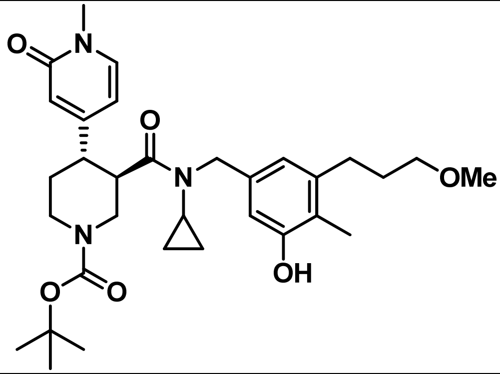
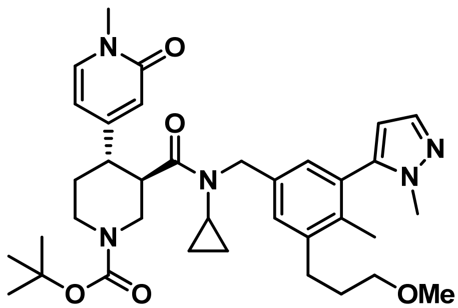
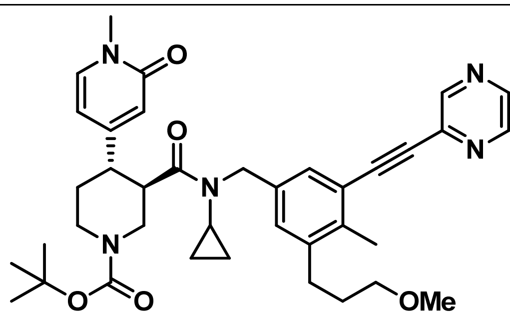
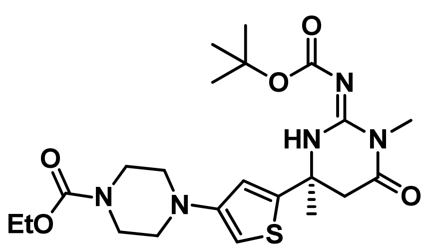
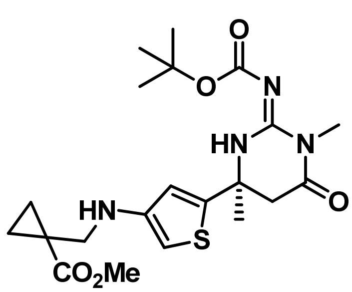
B3		$C_{17}H_{20}FN_5O_4$	377.1499	378.1567
B4		$C_{17}H_{14}F_2N_6O_2$	372.1146	373.1203
B5		$C_{16}H_{14}FN_5O_4S_2$	423.0471	424.0538
B6		$C_{16}H_{19}FN_6O_3$	362.1503	363.1563
B11		$C_{18}H_{13}FN_6O_2$	364.1084	365.1128

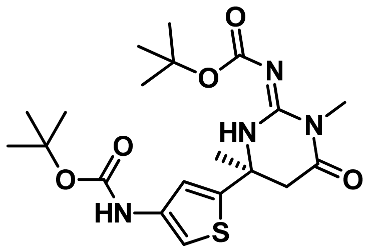
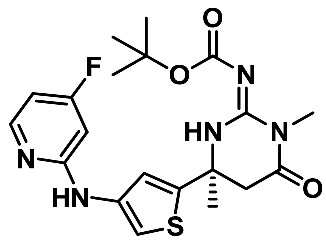
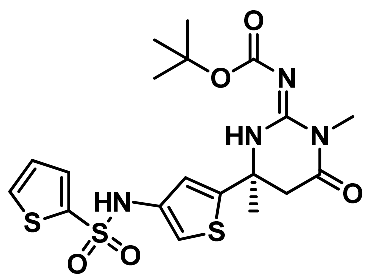
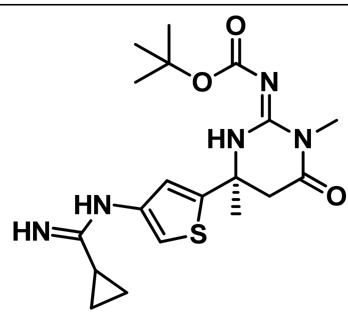
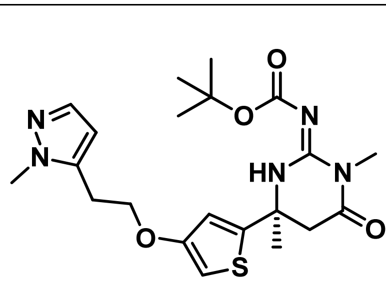
B12		$C_{16}H_{15}FN_6O_2$	342.1241	343.1308
C1		$C_{29}H_{41}N_7O_7$	599.3067	600.3141
C2		$C_{28}H_{38}N_6O_7$	570.2802	571.2890
C3		$C_{27}H_{38}N_6O_7$	558.2802	559.2885
C4		$C_{27}H_{32}FN_7O_5$	553.2449	554.2516

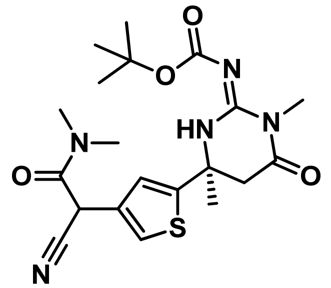
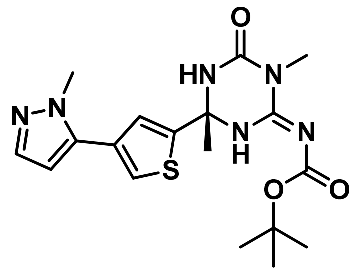
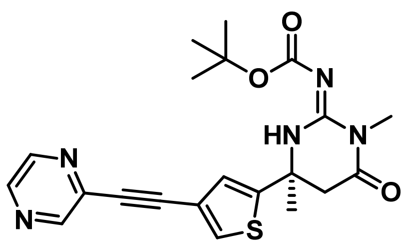
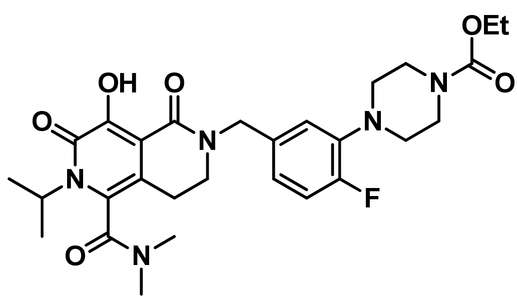
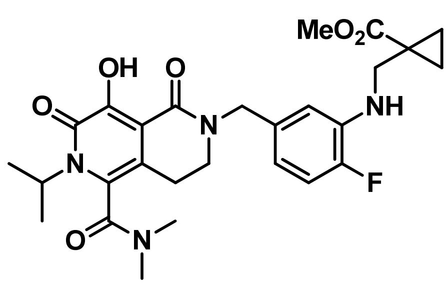
C5		$C_{26}H_{32}N_6O_7S_2$	604.1774	605.1856
C6		$C_{26}H_{37}N_7O_6$	543.2805	544.2883
C7		$C_{26}H_{35}N_7O_5$	525.2700	526.2773
C8		$C_{28}H_{37}N_7O_6$	567.2805	568.2882
C9		$C_{22}H_{29}N_5O_6$	459.2118	460.2182

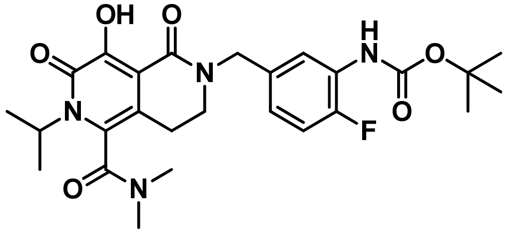
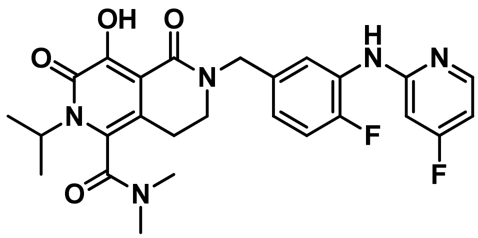
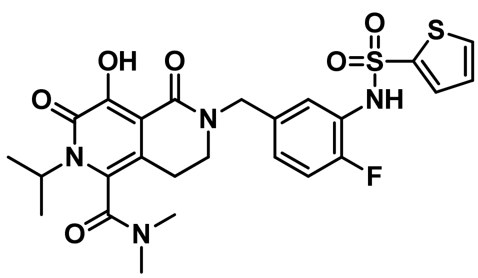
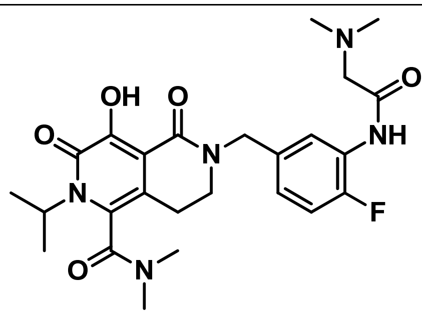
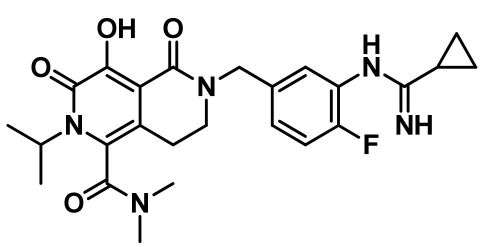
C10		$C_{27}H_{35}N_7O_6$	553.2649	554.2695
C11		$C_{26}H_{33}N_7O_5$	523.2543	524.2620
D1		$C_{39}H_{57}N_5O_7$	707.4258	708.4276
D2		$C_{38}H_{54}N_4O_7$	678.3993	679.4006
D3		$C_{37}H_{54}N_4O_7$	666.3993	667.4061

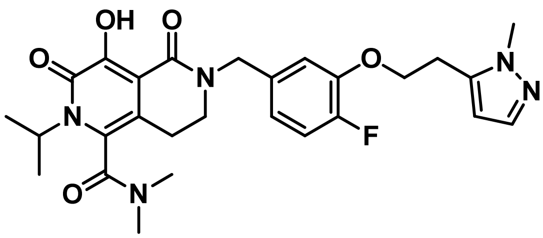
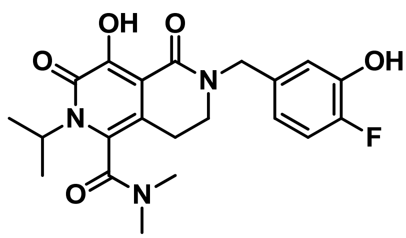
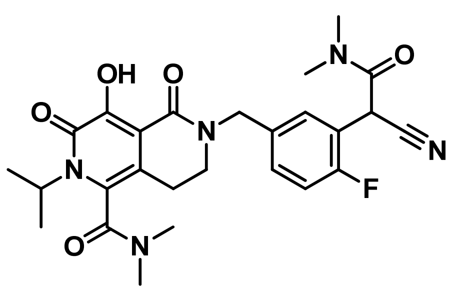
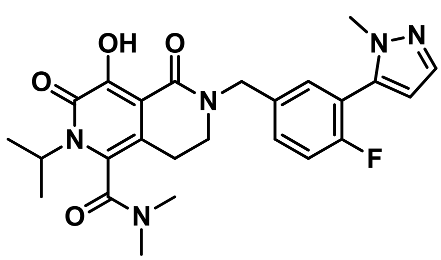
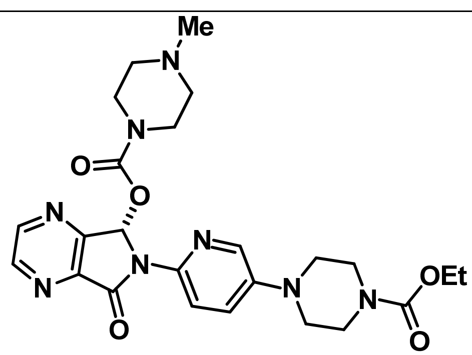
D4		$C_{37}H_{48}FN_5O_5$	661.3639	662.3691
D5		$C_{36}H_{48}N_4O_7S_2$	712.2964	713.2994
D6		$C_{36}H_{53}N_5O_6$	651.3996	652.4026
D7		$C_{36}H_{51}N_5O_5$	633.3890	634.3945
D8		$C_{38}H_{53}N_5O_6$	675.3996	676.4018

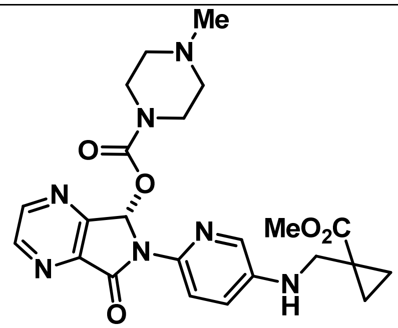
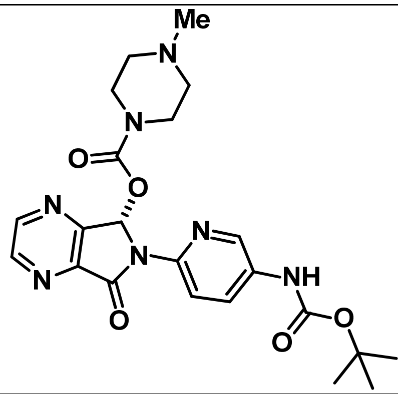
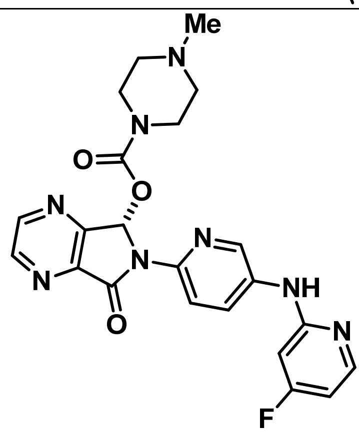
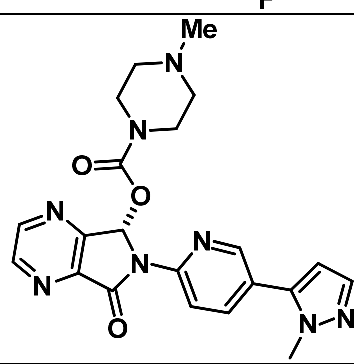
D9		$C_{32}H_{45}N_3O_6$	567.3308	568.3303
D11		$C_{36}H_{49}N_5O_5$	631.3734	632.3659
D12		$C_{38}H_{47}N_5O_5$	653.3577	654.3575
E1		$C_{22}H_{33}N_5O_5S$	479.2202	480.2061
E2		$C_{21}H_{30}N_4O_5S$	450.1937	451.1955

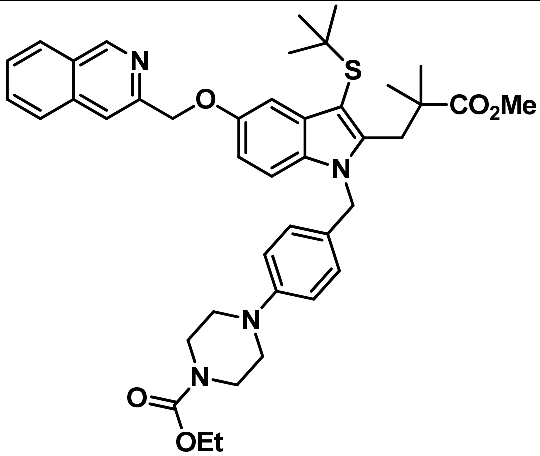
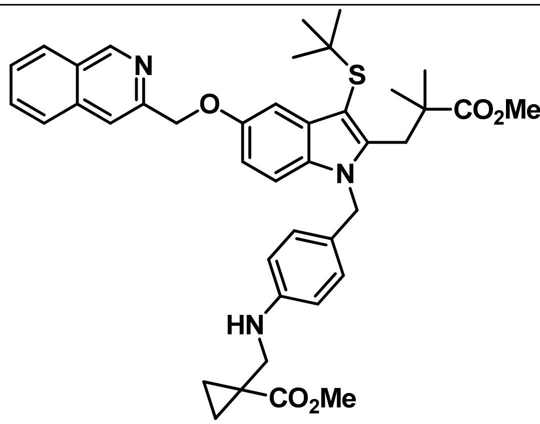
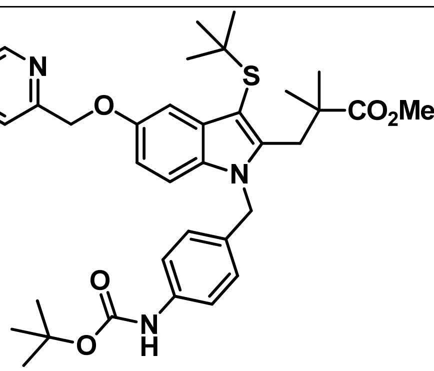
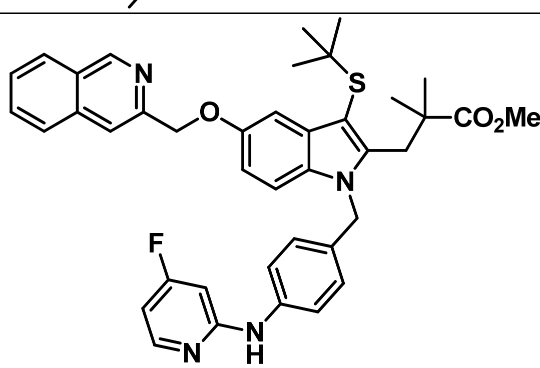
E3		$C_{20}H_{30}N_4O_5S$	438.1937	439.1992
E4		$C_{20}H_{24}FN_5O_3S$	433.1584	434.1650
E5		$C_{19}H_{24}N_4O_5S_3$	484.0909	485.0982
E7		$C_{19}H_{27}N_5O_3S$	405.1835	406.1750
E8		$C_{21}H_{29}N_5O_4S$	447.1940	448.1989

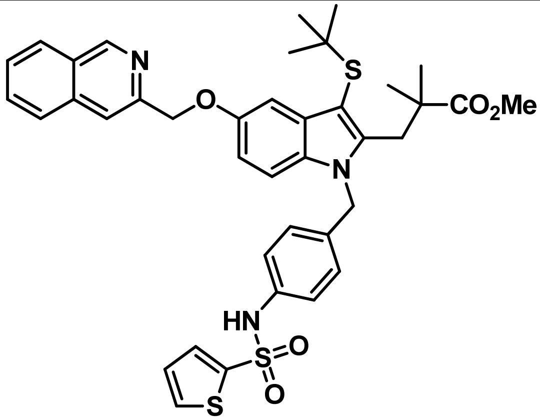
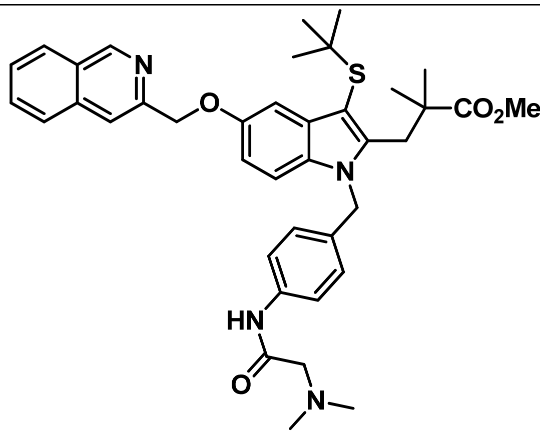
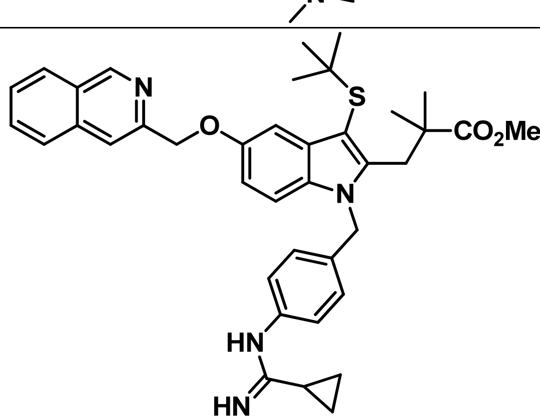
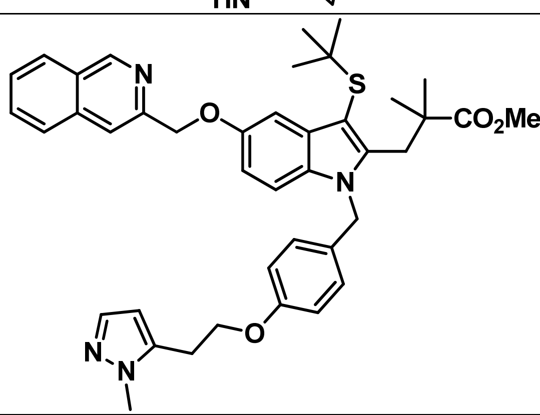
E10		$C_{20}H_{27}N_5O_4S$	433.1784	434.1793
E11		$C_{19}H_{25}N_5O_3S$	403.1678	404.1756
E12		$C_{21}H_{23}N_5O_3S$	425.1522	426.1563
F1		$C_{28}H_{36}FN_5O_6$	557.2650	558.2732
F2		$C_{27}H_{33}FN_4O_6$	528.2384	529.2432

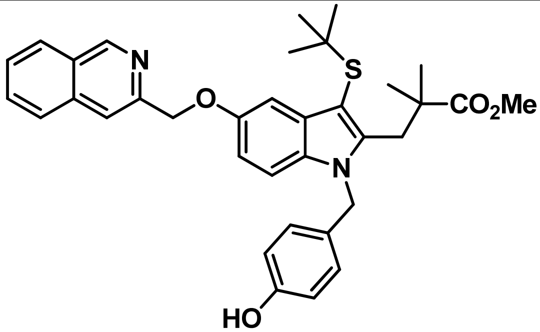
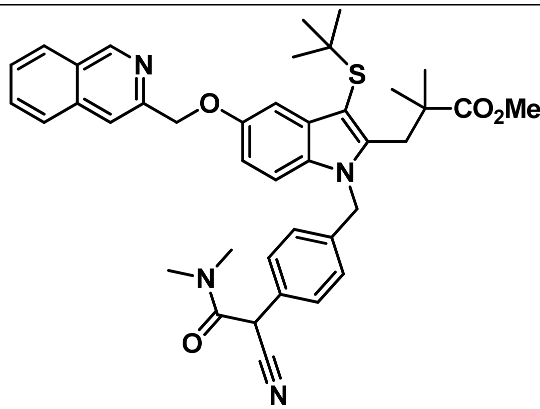
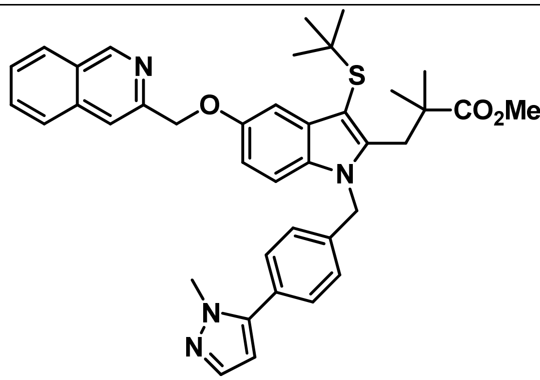
F3		$C_{26}H_{33}FN_4O_6$	516.2384	517.2424
F4		$C_{26}H_{27}F_2N_5O_4$	511.2031	512.1952
F5		$C_{25}H_{27}FN_4O_6S_2$	562.1356	563.1393
F6		$C_{25}H_{32}FN_5O_5$	501.2387	502.2354
F7		$C_{25}H_{30}FN_5O_4$	483.2282	484.2280

F8		$C_{27}H_{32}FN_5O_5$	525.2387	526.2419
F9		$C_{21}H_{24}FN_3O_5$	417.1700	418.1695
F10		$C_{26}H_{30}FN_5O_5$	511.2231	512.2170
F11		$C_{25}H_{28}FN_5O_4$	481.2125	482.2171
G1		$C_{24}H_{30}N_8O_5$	510.2339	511.2427

G2		$C_{23}H_{27}N_7O_5$	481.2074	482.2038
G3		$C_{22}H_{27}N_7O_5$	469.2074	470.2106
G4		$C_{22}H_{21}FN_8O_3$	464.1721	465.1732
G11		$C_{21}H_{22}N_8O_3$	434.1815	435.1817

H1		$C_{42}H_{50}N_4O_5S$	722.3502	723.3577
H2		$C_{41}H_{47}N_3O_5S$	693.3236	694.3322
H3		$C_{40}H_{47}N_3O_5S$	681.3236	682.3309
H4		$C_{40}H_{41}FN_4O_3S$	676.2883	677.2973

H5		$C_{39}H_{41}N_3O_5S_3$	727.2208	728.2231
H6		$C_{39}H_{46}N_4O_4S$	666.3240	667.3319
H7		$C_{39}H_{46}N_4O_3S$	650.3291	651.3213
H8		$C_{41}H_{46}N_4O_4S$	690.3240	691.3240

H9		$C_{35}H_{38}N_2O_4S$	582.2552	583.2243
H10		$C_{40}H_{44}N_4O_4S$	676.3083	677.3151
H11		$C_{39}H_{42}N_4O_3S$	646.2978	647.3006

Tabulated ^{1}H-NMR Data for products of isolated aryl halides **1-8** with nucleophiles **9-20**:

A1

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (dd, J = 7.8, 1.5 Hz, 1H), 7.66 – 7.46 (m, 5H), 7.42 – 7.34 (m, 2H), 7.18 (d, J = 8.2 Hz, 2H), 6.60 (s, 1H), 5.44 (s, 2H), 4.07 (q, J = 7.1 Hz, 2H), 3.55 (s, 4H), 3.25 (t, J = 5.2 Hz, 4H), 2.72 (t, J = 7.4 Hz, 2H), 1.73 (q, J = 7.4 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H), 0.95 (s, 9H), 0.92 (t, J = 7.4 Hz, 3H).

A2

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 1H), 8.03 (dd, J = 7.9, 1.5 Hz, 1H), 7.58 (dtd, J = 26.5, 7.5, 1.5 Hz, 2H), 7.43 – 7.33 (m, 3H), 7.29 (dd, J = 7.5, 1.5 Hz, 1H), 7.20 (d, J = 2.8 Hz, 1H), 7.18 (d, J = 3.1 Hz, 2H), 7.16 (d, J = 1.8 Hz, 1H), 7.10 (d, J = 2.7 Hz, 1H), 6.57 (s, 1H), 6.20 (s, 1H), 5.41 (s, 2H), 3.61 (s, 3H), 2.67 (t, J = 7.5 Hz, 2H), 1.71 (h, J = 7.4 Hz, 2H), 1.14 (q, J = 3.9 Hz, 2H), 0.94 (s, 9H), 1.02 – 0.86 (m, 5H).

A3

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.75 (s, 1H), 8.38 (d, J = 2.5 Hz, 1H), 8.03 (dd, J = 7.9, 1.4 Hz, 1H), 7.81 (dd, J = 8.9, 2.6 Hz, 1H), 7.65 – 7.51 (m, 3H), 7.40 – 7.35 (m, 2H), 7.29 (dd, J = 7.6, 1.5 Hz, 1H), 7.19 (d, J = 8.2 Hz, 2H), 6.55 (s, 1H), 5.43 (s, 2H), 2.73 (t, J = 7.5 Hz, 2H), 1.74 (q, J = 7.4 Hz, 2H), 1.50 (s, 9H), 0.94 (s, 9H), 0.92 (t, J = 7.4 Hz, 3H).

A4

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (s, 1H), 8.60 (d, J = 2.6 Hz, 1H), 8.26 (dd, J = 9.6, 5.9 Hz, 1H), 8.03 (ddd, J = 7.9, 4.7, 2.0 Hz, 2H), 7.66 – 7.50 (m, 3H), 7.38 (d, J = 8.0 Hz, 2H), 7.29 (dd, J = 7.5, 1.5 Hz, 1H), 7.20 (d, J = 8.0 Hz, 2H), 6.75 (ddd, J = 8.4, 5.8, 2.3 Hz, 1H), 6.68 – 6.56 (m, 2H), 5.44 (s, 2H), 2.73 (t, J = 7.5 Hz, 2H), 1.75 (q, J = 7.4 Hz, 2H), 0.94 (s, 9H), 0.92 – 0.95 (m, 3H).

A5

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 8.03 (dd, J = 7.9, 1.5 Hz, 1H), 7.94 – 7.87 (m, 2H), 7.66 – 7.50 (m, 5H), 7.41 – 7.34 (m, 2H), 7.29 (dd, J = 7.5, 1.5 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.12 (dd, J = 5.0, 3.8 Hz, 1H), 6.56 (d, J = 1.6 Hz, 1H), 5.40 (s, 2H), 3.35 (d, J = 0.9 Hz, 5H), 2.72 (t, J = 7.4 Hz, 2H), 1.71 (h, J = 7.4 Hz, 2H), 0.93 (s, 9H), 0.90 (t, J = 7.3 Hz, 3H).

A6

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (dd, J = 7.9, 1.5 Hz, 1H), 7.58 (dtd, J = 26.3, 7.5, 1.5 Hz, 2H), 7.46 – 7.25 (m, 5H), 7.18 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 2.7 Hz, 1H), 6.59 (s, 1H), 5.43 (s, 2H), 4.01 (s, 2H), 3.05 (s, 3H), 2.89 (s, 3H), 2.70 (t, J = 7.5 Hz, 2H), 1.72 (h, J = 7.4 Hz, 2H), 0.95 (s, 9H), 0.92 (t, J = 7.3 Hz, 3H).

A7

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.14 (s, 1H), 9.04 (s, 1H), 8.53 (s, 1H), 8.10 (d, *J* = 2.4 Hz, 1H), 8.03 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 1H), 7.75 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.62 (td, *J* = 7.5, 1.5 Hz, 1H), 7.56 (td, *J* = 7.6, 1.5 Hz, 1H), 7.40 (d, *J* = 1.7 Hz, 1H), 7.39 (d, *J* = 1.9 Hz, 1H), 7.29 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 2H), 6.69 (s, 1H), 5.48 (s, 2H), 2.81 (t, *J* = 7.4 Hz, 2H), 2.00 (s, 1H), 1.76 (h, *J* = 7.4 Hz, 2H), 1.32 (dt, *J* = 5.0, 3.3 Hz, 2H), 1.25 (d, *J* = 8.5 Hz, 2H), 0.97 (s, 8H), 0.94 (t, *J* = 7.4 Hz, 3H).

A8

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 8.03 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.64 – 7.58 (m, 2H), 7.55 (td, *J* = 7.6, 1.5 Hz, 1H), 7.43 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.41 – 7.34 (m, 2H), 7.31 (d, *J* = 1.8 Hz, 1H), 7.29 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.20 (s, 1H), 7.18 (d, *J* = 1.7 Hz, 1H), 6.60 (s, 1H), 6.18 (d, *J* = 1.8 Hz, 1H), 5.45 (s, 2H), 4.35 (t, *J* = 6.5 Hz, 2H), 3.81 (s, 3H), 3.16 (t, *J* = 6.5 Hz, 2H), 2.73 (t, *J* = 7.5 Hz, 2H), 1.74 (q, *J* = 7.4 Hz, 2H), 0.94 (s, 9H), 0.88 – 0.94 (m, 3H).

A9

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.37 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.95 (td, *J* = 7.5, 1.5 Hz, 1H), 7.92 – 7.84 (m, 2H), 7.81 (d, *J* = 2.8 Hz, 1H), 7.75 – 7.68 (m, 2H), 7.68 – 7.59 (m, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 6.93 (s, 1H), 5.77 (s, 2H), 3.08 (t, *J* = 7.6 Hz, 2H), 2.06 (h, *J* = 7.4 Hz, 2H), 1.29 (s, 9H), 1.26 (t, *J* = 7.4 Hz, 3H).

A10

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, *J* = 2.2 Hz, 1H), 8.03 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.85 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.79 – 7.70 (m, 1H), 7.58 (dtd, *J* = 26.5, 7.4, 1.4 Hz, 2H), 7.42 – 7.35 (m, 2H), 7.29 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 2H), 6.58 (s, 1H), 6.07 (s, 1H), 5.46 (s, 2H), 3.01 (s, 3H), 2.88 (s, 3H), 2.78 (t, *J* = 7.4 Hz, 2H), 1.76 (q, *J* = 7.4 Hz, 2H), 0.94 (s, 9H), 0.93 (t, *J* = 7.4 Hz, 3H).

A11

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (d, *J* = 2.1 Hz, 1H), 8.02 (ddd, *J* = 10.3, 8.1, 1.8 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.61 (td, *J* = 7.5, 1.5 Hz, 1H), 7.55 (td, *J* = 7.7, 1.6 Hz, 1H), 7.52 (d, *J* =

1.9 Hz, 1H), 7.43 – 7.37 (m, 2H), 7.29 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.27 – 7.20 (m, 2H), 6.61 (s, 1H), 6.56 (d, *J* = 1.9 Hz, 2H), 5.48 (s, 2H), 3.92 (s, 3H), 2.80 (t, *J* = 7.5 Hz, 2H), 1.87 – 1.71 (m, 2H), 0.95 (s, 9H), 0.95 (t, *J* = 7.4 Hz, 3H).

A12

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (d, *J* = 1.6 Hz, 1H), 8.72 (dd, *J* = 2.6, 1.5 Hz, 1H), 8.67 (d, *J* = 2.5 Hz, 1H), 8.40 (dd, *J* = 2.0, 0.6 Hz, 1H), 8.04 (dd, *J* = 2.9, 1.7 Hz, 1H), 8.02 (t, *J* = 2.0 Hz, 1H), 7.73 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.61 (td, *J* = 7.4, 1.5 Hz, 1H), 7.55 (td, *J* = 7.6, 1.5 Hz, 1H), 7.43 – 7.35 (m, 2H), 7.30 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 2H), 6.59 (s, 1H), 5.47 (s, 2H), 2.79 (t, *J* = 7.5 Hz, 2H), 1.76 (q, *J* = 7.4 Hz, 2H), 0.94 (s, 9H), 0.94 (t, *J* = 7.4 Hz, 3H).

B1

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, *J* = 1.0 Hz, 1H), 7.77 (d, *J* = 1.0 Hz, 1H), 7.42 (dd, *J* = 14.7, 2.5 Hz, 1H), 7.16 – 7.01 (m, 2H), 5.18 – 5.06 (m, 1H), 4.82 (d, *J* = 5.1 Hz, 2H), 4.20 (t, *J* = 9.2 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.86 (dd, *J* = 9.4, 5.7 Hz, 1H), 3.51 (d, *J* = 5.6 Hz, 4H), 2.93 (t, *J* = 5.1 Hz, 4H), 1.20 (t, *J* = 7.1 Hz, 3H).

B2

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, *J* = 1.0 Hz, 1H), 7.77 (d, *J* = 1.0 Hz, 1H), 7.33 – 7.21 (m, 1H), 7.00 – 6.92 (m, 1H), 6.83 – 6.73 (m, 1H), 5.08 (dq, *J* = 9.0, 5.3 Hz, 1H), 4.81 (d, *J* = 5.1 Hz, 2H), 4.15 (t, *J* = 9.1 Hz, 1H), 3.80 (dd, *J* = 9.3, 5.7 Hz, 1H), 3.60 (s, 3H), 3.37 (s, 2H), 1.09 (q, *J* = 3.9 Hz, 2H), 0.92 (q, *J* = 4.0 Hz, 2H).

B3

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.17 (d, *J* = 1.1 Hz, 1H), 7.76 (d, *J* = 1.0 Hz, 1H), 7.57 – 7.47 (m, 1H), 7.44 (dd, *J* = 13.0, 2.5 Hz, 1H), 7.20 – 7.10 (m, 1H), 5.14 (ddt, *J* = 14.3, 9.1, 5.4 Hz, 1H), 4.83 (d, *J* = 5.1 Hz, 3H), 4.22 (td, *J* = 9.2, 4.0 Hz, 1H), 3.88 (dt, *J* = 9.3, 5.9 Hz, 1H), 1.44 (s, 7H).

B4

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 1H), 8.18 (d, J = 1.0 Hz, 1H), 8.12 (dd, J = 9.2, 6.0 Hz, 1H), 7.94 (t, J = 9.1 Hz, 1H), 7.77 (d, J = 1.0 Hz, 1H), 7.51 (dd, J = 13.4, 2.6 Hz, 1H), 7.26 – 7.15 (m, 1H), 6.77 – 6.65 (m, 2H), 5.20 – 5.09 (m, 1H), 4.85 (d, J = 5.1 Hz, 2H), 4.24 (t, J = 9.2 Hz, 1H), 3.90 (dd, J = 9.4, 5.7 Hz, 1H).

B5

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 8.16 (d, J = 1.0 Hz, 1H), 7.94 (dd, J = 5.0, 1.4 Hz, 1H), 7.76 (d, J = 1.0 Hz, 1H), 7.48 – 7.40 (m, 2H), 7.29 – 7.17 (m, 2H), 7.15 (dd, J = 5.0, 3.7 Hz, 1H), 5.13 (dq, J = 9.1, 5.5 Hz, 1H), 4.83 (d, J = 5.2 Hz, 2H), 4.20 (t, J = 9.2 Hz, 1H), 3.95 – 3.82 (m, 1H).

B6

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, J = 1.0 Hz, 1H), 7.77 (d, J = 1.0 Hz, 1H), 7.30 (dd, J = 13.8, 2.5 Hz, 1H), 7.01 – 6.93 (m, 1H), 6.73 (dd, J = 9.9, 8.8 Hz, 1H), 5.22 (s, 1H), 5.08 (dt, J = 9.0, 5.2 Hz, 1H), 4.81 (d, J = 5.1 Hz, 2H), 4.16 (t, J = 9.2 Hz, 1H), 3.93 (s, 2H), 3.81 (dd, J = 9.3, 5.7 Hz, 1H), 3.01 (s, 3H), 2.87 (s, 3H).

B11

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, J = 1.0 Hz, 1H), 7.78 (d, J = 1.0 Hz, 1H), 7.60 (dd, J = 12.7, 2.2 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.41 (dd, J = 8.6, 2.3 Hz, 1H), 6.38 (dd, J = 1.9, 0.7 Hz, 1H), 5.19 (dq, J = 9.2, 5.3 Hz, 1H), 4.87 (d, J = 5.1 Hz, 2H), 4.30 (t, J = 9.3 Hz, 1H), 3.96 (dd, J = 9.5, 5.7 Hz, 1H), 3.73 (d, J = 1.2 Hz, 3H).

B12

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.89 (d, J = 1.5 Hz, 1H), 8.72 (dd, J = 2.5, 1.5 Hz, 1H), 8.67 (d, J = 2.6 Hz, 1H), 8.19 (d, J = 1.0 Hz, 1H), 7.81 – 7.71 (m, 2H), 7.62 (dd, J = 12.3, 2.2 Hz, 1H), 7.43 (dd, J = 8.6, 2.2 Hz, 1H), 5.18 (dt, J = 10.6, 5.3 Hz, 1H), 4.92 – 4.77 (m, 2H), 4.29 (t, J = 9.3 Hz, 1H), 3.96 (dd, J = 9.5, 5.7 Hz, 1H).

C1

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.03 (d, J = 2.0 Hz, 1H), 6.99 (d, J = 6.7 Hz, 1H), 6.96 – 6.83 (m, 2H), 5.21 (s, 2H), 4.91 – 4.71 (m, 2H), 4.06 (q, J = 7.1 Hz, 2H), 3.97 (t, J = 6.1 Hz, 3H), 3.87 (q, J = 7.4, 6.9 Hz, 3H), 3.74 (s, 3H), 3.61 (q, J = 6.3 Hz, 2H), 2.86 (t, J = 5.1 Hz, 4H), 2.05 (dq, J = 13.8, 7.7 Hz, 1H), 1.85 (ddd, J = 14.9, 12.7, 6.4 Hz, 1H), 1.63 (p, J = 7.1 Hz, 2H), 1.47 (s, 2H), 1.19 (t, J = 7.1 Hz, 3H), 1.08 (t, J = 6.9 Hz, 3H).

C2

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.95 (d, J = 6.7 Hz, 1H), 6.82 (d, J = 8.6 Hz, 1H), 6.74 – 6.69 (m, 2H), 5.19 (s, 2H), 4.01 – 3.92 (m, 3H), 3.92 – 3.80 (m, 3H), 3.76 (s, 3H), 3.60 (t, J = 6.5 Hz, 2H), 3.56 (s, 3H), 3.29 (s, 2H), 2.13 – 1.98 (m, 1H), 1.83 (ddd, J = 12.7, 8.4, 6.2 Hz, 1H), 1.63 (h, J = 7.5, 6.9 Hz, 2H), 1.53 – 1.39 (m, 2H), 1.12 – 1.02 (m, 6H), 0.88 (q, J = 3.6 Hz, 2H).

C4

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1H), 8.05 (dd, J = 8.7, 6.1 Hz, 1H), 7.82 (s, 1H), 7.03 (s, 2H), 7.03 – 6.94 (m, 1H), 6.84 – 6.75 (m, 1H), 5.28 (s, 2H), 4.03 – 3.93 (m, 3H), 3.87 (dq, J = 19.6, 6.7 Hz, 3H), 3.79 (s, 3H), 3.62 (t, J = 6.5 Hz, 2H), 2.10 – 1.96 (m, 1H), 1.81 (ddt, J = 12.8, 8.7, 6.4 Hz, 1H), 1.66 – 1.54 (m, 2H), 1.45 (dt, J = 13.4, 6.7 Hz, 2H), 1.05 (t, J = 6.9 Hz, 3H).

C5

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.58 (s, 1H), 7.82 (dd, J = 5.0, 1.4 Hz, 1H), 7.35 (dd, J = 3.7, 1.4 Hz, 1H), 7.24 (d, J = 2.2 Hz, 1H), 7.06 (dd, J = 8.5, 2.2 Hz, 1H), 7.02 (dd, J = 5.0, 3.7 Hz, 1H), 6.95 (d, J = 6.6 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H), 5.24 (s, 2H), 4.84 (t, J = 5.7 Hz, 1H), 4.77 (d, J = 4.0 Hz, 1H), 3.98 (dt, J = 13.1, 5.9 Hz, 3H), 3.87 (dq, J = 14.1, 6.7 Hz, 4H), 3.63 (q, J = 6.3 Hz, 2H), 3.53 (s, 3H), 2.07 (s, 1H), 2.04 (td, J = 13.4, 7.7 Hz, 1H), 1.83 (ddd, J = 12.7, 8.4, 6.3 Hz, 1H), 1.62 (qd, J = 7.8, 5.6 Hz, 2H), 1.47 (dq, J = 12.5, 6.0 Hz, 2H), 1.08 (t, J = 7.0 Hz, 3H).

C7

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.67 (s, 1H), 8.82 (s, 1H), 8.11 (s, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.30 – 7.23 (m, 1H), 7.19 (d, J = 8.7 Hz, 1H), 7.07 – 6.98 (m, 1H), 5.28 (s, 2H), 4.01 – 3.93

(m, 3H), 3.87 (q, J = 6.9 Hz, 3H), 3.79 (s, 3H), 3.61 (t, J = 6.4 Hz, 2H), 2.05 (td, J = 13.3, 7.5 Hz, 1H), 1.94 (s, 1H), 1.85 (ddd, J = 14.9, 12.7, 6.5 Hz, 1H), 1.64 (dt, J = 14.4, 7.2 Hz, 2H), 1.54 – 1.41 (m, 2H), 1.20 (t, J = 7.5 Hz, 4H), 1.08 (t, J = 6.9 Hz, 3H).

C8

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32 (d, J = 1.8 Hz, 1H), 7.09 (d, J = 1.9 Hz, 1H), 7.03 – 6.95 (m, 1H), 6.90 (d, J = 8.3 Hz, 1H), 6.84 (dd, J = 8.3, 1.9 Hz, 1H), 6.12 (d, J = 1.9 Hz, 1H), 5.21 (s, 2H), 4.09 (t, J = 6.7 Hz, 2H), 3.96 (q, J = 5.6, 5.2 Hz, 3H), 3.89 – 3.83 (m, 3H), 3.80 (s, 3H), 3.70 (s, 3H), 3.60 (t, J = 6.5 Hz, 2H), 3.09 (t, J = 6.6 Hz, 2H), 2.03 (td, J = 13.1, 7.7 Hz, 1H), 1.82 (ddd, J = 12.6, 8.4, 6.3 Hz, 1H), 1.74 – 1.53 (m, 2H), 1.45 (tt, J = 14.0, 6.3 Hz, 2H), 1.05 (t, J = 7.0 Hz, 3H).

C9

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (s, 1H), 6.89 (d, J = 6.7 Hz, 1H), 6.84 (d, J = 8.3 Hz, 1H), 6.70 (d, J = 2.1 Hz, 1H), 6.67 (dd, J = 8.2, 2.2 Hz, 1H), 5.18 (s, 2H), 4.04 – 3.92 (m, 3H), 3.87 (dq, J = 14.0, 6.8 Hz, 3H), 3.71 (s, 3H), 3.62 (t, J = 6.5 Hz, 2H), 2.12 – 1.98 (m, 1H), 1.84 (ddt, J = 12.7, 8.7, 6.4 Hz, 1H), 1.63 (q, J = 8.1, 7.7 Hz, 2H), 1.47 (dt, J = 13.3, 7.0 Hz, 2H), 1.08 (t, J = 6.9 Hz, 3H).

C10

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30 (dd, J = 8.4, 2.2 Hz, 1H), 7.24 (dd, J = 17.9, 2.2 Hz, 1H), 7.07 (dd, J = 8.6, 1.2 Hz, 1H), 7.03 (dd, J = 6.6, 3.2 Hz, 1H), 5.67 (d, J = 2.6 Hz, 1H), 5.28 (s, 2H), 4.11 – 3.91 (m, 3H), 3.91 – 3.82 (m, 3H), 3.81 (d, J = 1.3 Hz, 3H), 3.62 (t, J = 6.5 Hz, 2H), 2.82 (d, J = 5.0 Hz, 3H), 2.78 (d, J = 11.5 Hz, 3H), 2.04 (dp, J = 13.0, 7.1 Hz, 1H), 1.93 – 1.73 (m, 1H), 1.63 (q, J = 5.0, 2.7 Hz, 2H), 1.47 (dt, J = 12.9, 6.1 Hz, 2H), 1.08 (td, J = 7.0, 1.5 Hz, 3H).

C11

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43 (d, J = 1.9 Hz, 1H), 7.38 (dd, J = 8.6, 2.3 Hz, 1H), 7.29 (d, J = 2.3 Hz, 1H), 7.12 (d, J = 8.7 Hz, 1H), 7.03 (d, J = 6.5 Hz, 1H), 6.17 (d, J = 1.8 Hz, 1H), 5.31 (s, 2H), 4.79 (s, 2H), 3.97 (dt, J = 10.9, 6.0 Hz, 3H), 3.88 (dq, J = 14.0, 6.7 Hz, 3H), 3.76 (s, 3H), 3.62 (t, J = 6.4 Hz, 2H), 3.59 (s, 3H), 2.26 – 1.91 (m, 1H), 1.81 (ddt, J = 12.6, 8.7, 6.3 Hz, 1H), 1.73 – 1.53 (m, 2H), 1.53 – 1.29 (m, 2H), 1.08 (t, J = 6.9 Hz, 3H).

D1

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 – 8.06 (m, 1H), 7.61 – 7.46 (m, 2H), 7.26 (dddd, J = 90.3, 8.0, 7.1, 1.1 Hz, 1H), 6.53 (d, J = 22.7 Hz, 2H), 6.21 – 6.06 (m, 2H), 4.35 (s, 4H), 4.07 (t, J = 7.1 Hz, 2H), 3.33 (s, 4H), 3.30 (d, J = 6.2 Hz, 1H), 3.24 (s, 3H), 2.95 (s, 1H), 2.82 (s, 2H), 2.67 (s, 4H), 2.46 (d, J = 7.7 Hz, 1H), 2.16 (s, 3H), 1.76 – 1.48 (m, 4H), 1.40 (s, 9H), 1.20 (t, J = 7.1 Hz, 3H), 0.74 (d, J = 73.9 Hz, 4H). (diastereomers)

D2

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 1H), 7.51 (d, J = 6.9 Hz, 1H), 6.21 – 6.10 (m, 3H), 6.05 (s, 1H), 4.40 (s, 5H), 3.61 (s, 3H), 3.33 (s, 3H), 3.28 (dd, J = 7.8, 4.9 Hz, 4H), 3.22 (s, 3H), 2.93 (d, J = 94.7 Hz, 3H), 2.42 (ddd, J = 29.0, 14.3, 7.3 Hz, 2H), 1.93 (s, 3H), 1.73 – 1.47 (m, 4H), 1.40 (s, 9H), 1.08 (d, J = 3.5 Hz, 2H), 1.01 – 0.71 (m, 5H).

D3

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H), 7.51 (d, J = 7.3 Hz, 1H), 6.80 (s, 1H), 6.56 (d, J = 15.8 Hz, 1H), 6.16 (s, 2H), 4.32 (s, 2H), 4.26 – 3.91 (m, 2H), 3.42 (d, J = 14.9 Hz, 1H), 3.29 (t, J = 6.3 Hz, 2H), 3.23 (s, 3H), 3.06 – 2.90 (m, 1H), 2.82 (s, 2H), 2.48 (s, 2H), 2.05 (s, 3H), 1.76 – 1.48 (m, 4H), 1.43 (d, J = 10.9 Hz, 18H), 0.74 (d, J = 60.6 Hz, 4H).

D4

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.14 (s, 1H), 8.04 (dd, J = 9.4, 5.9 Hz, 1H), 7.47 (d, J = 7.5 Hz, 1H), 6.93 (s, 1H), 6.60 (d, J = 10.3 Hz, 2H), 6.28 (d, J = 11.8 Hz, 1H), 6.20 – 6.10 (m, 2H), 4.48 – 3.92 (m, 4H), 3.41 (s, 2H), 3.32 (d, J = 3.0 Hz, 6H), 3.24 (s, 3H), 2.80 (s, 3H), 2.69 – 2.52 (m, 2H), 2.07 (s, 3H), 1.68 (q, J = 6.9, 6.5 Hz, 4H), 1.39 (s, 9H), 1.04 – 0.48 (m, 4H).

D5

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.65 (s, 1H), 7.91 (dd, J = 5.0, 1.4 Hz, 1H), 7.50 (d, J = 7.0 Hz, 1H), 7.31 (d, J = 3.6 Hz, 1H), 7.12 (dd, J = 5.0, 3.7 Hz, 1H), 6.63 (s, 2H), 6.14 (d, J = 6.9

Hz, 2H), 4.54 – 3.80 (m, 5H), 3.33 (s, 3H), 3.22 (d, J = 12.3 Hz, 5H), 2.81 (s, 3H), 2.47 – 2.32 (m, 2H), 1.86 (s, 3H), 1.69 (d, J = 12.9 Hz, 1H), 1.54 (tt, J = 13.2, 5.5 Hz, 3H), 1.41 (s, 8H), 1.07 – 0.44 (m, 5H).

D6

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 1H), 7.52 (dd, J = 15.5, 7.0 Hz, 1H), 6.32 – 5.93 (m, 4H), 4.21 (s, 5H), 3.81 (d, J = 4.4 Hz, 3H), 3.33 (d, J = 4.2 Hz, 3H), 3.28 (t, J = 6.3 Hz, 2H), 3.23 (s, 3H), 3.00 (s, 3H), 2.90 (s, 3H), 2.54 (s, 1H), 1.99 (s, 3H), 1.74 – 1.52 (m, 3H), 1.47 – 1.28 (m, 9H), 0.74 (d, J = 65.9 Hz, 4H).

D7

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (s, 0H), 7.54 (d, J = 7.0 Hz, 1H), 6.71 (s, 2H), 6.15 (d, J = 63.7 Hz, 1H), 4.34 (d, J = 179.2 Hz, 3H), 3.24 (s, 4H), 2.83 (s, 2H), 2.00 (s, 3H), 1.65 (q, J = 8.7, 7.6 Hz, 2H), 1.42 (s, 9H), 1.31 – 0.48 (m, 9H).

D8

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, J = 6.9 Hz, 1H), 7.30 (d, J = 1.8 Hz, 1H), 6.51 (s, 1H), 6.33 (s, 1H), 6.24 – 6.07 (m, 3H), 4.66 – 3.88 (m, 6H), 3.80 (s, 3H), 3.54 – 3.38 (m, 2H), 3.29 (d, J = 9.6 Hz, 5H), 3.22 (s, 3H), 3.11 (t, J = 6.4 Hz, 2H), 2.94 (s, 1H), 2.81 (s, 2H), 2.48 – 2.39 (m, 2H), 1.99 (s, 3H), 1.61 (t, J = 7.0 Hz, 4H), 1.40 (s, 9H), 0.75 (d, J = 60.4 Hz, 4H).

D9

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1H), 8.14 (s, 1H), 7.54 (d, J = 6.8 Hz, 1H), 6.30 (d, J = 1.7 Hz, 1H), 6.21 (s, 3H), 4.66 – 3.86 (m, 5H), 3.40 (s, 2H), 3.29 (t, J = 6.3 Hz, 2H), 3.23 (s, 3H), 3.06 – 2.70 (m, 3H), 2.44 (s, 2H), 2.00 (s, 3H), 1.78 – 1.48 (m, 4H), 1.41 (s, 9H), 0.79 (d, J = 91.6 Hz, 5H).

D11

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 1H), 7.54 – 7.40 (m, 2H), 6.80 (d, J = 16.9 Hz, 2H), 6.22 – 6.12 (m, 2H), 4.77 – 3.78 (m, 5H), 3.51 (s, 4H), 3.33 (d, J = 6.3 Hz, 2H), 3.31 (s, 2H), 3.25 (s, 3H), 2.80 (s, 2H), 2.66 – 2.52 (m, 2H), 1.98 (s, 3H), 1.60 (ddd, J = 74.4, 9.7, 4.9 Hz, 4H), 1.40 (s, 9H), 1.16 – 0.39 (m, 5H).

D12

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 (d, J = 7.0 Hz, 2H), 7.08 – 6.03 (m, 5H), 4.60 (s, 1H), 4.10 (d, J = 21.5 Hz, 4H), 3.34 (s, 3H), 3.28 (s, 2H), 3.24 (s, 3H), 2.94 (td, J = 11.8, 3.6 Hz, 1H), 2.81 (s, 2H), 2.69 – 2.53 (m, 2H), 2.27 (s, 3H), 1.65 (qd, J = 8.9, 6.6 Hz, 5H), 1.42 (s, 9H), 1.09 – 0.50 (m, 5H).

E1

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (s, 1H), 6.71 (d, J = 1.8 Hz, 1H), 6.12 (d, J = 1.7 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.65 – 3.57 (m, 4H), 3.28 (s, 3H), 3.13 (dd, J = 16.2, 1.3 Hz, 1H), 3.01 (t, J = 5.2 Hz, 4H), 2.91 (d, J = 16.2 Hz, 1H), 1.58 (s, 3H), 1.55 (s, 9H), 1.30 (t, J = 7.1 Hz, 3H).

E2

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 6.56 (d, J = 1.7 Hz, 1H), 5.80 (d, J = 1.7 Hz, 1H), 3.60 (s, 4H), 3.21 – 3.01 (m, 7H), 1.64 (s, 3H), 1.48 – 1.38 (s, 9H), 1.08 (q, J = 3.8 Hz, 2H), 0.91 (q, J = 3.9 Hz, 2H).

E3

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 9.60 (s, 1H), 7.05 (s, 1H), 6.91 (d, J = 1.6 Hz, 1H), 3.24 – 3.06 (m, 2H), 3.05 (s, 3H), 1.67 (s, 3H), 1.44 (d, J = 0.9 Hz, 18H).

E4

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 9.57 (s, 1H), 8.17 (dd, J = 9.6, 5.9 Hz, 1H), 7.53 (d, J = 1.6 Hz, 1H), 6.91 (d, J = 1.6 Hz, 1H), 6.65 (ddd, J = 8.7, 5.9, 2.3 Hz, 1H), 6.49 (dd, J = 11.7, 2.3 Hz, 1H), 3.24 – 3.12 (m, 2H), 3.07 (s, 3H), 2.54 (s, 2H), 1.71 (s, 3H), 1.45 (s, 9H).

E5

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (s, 1H), 7.59 (dd, J = 5.0, 1.4 Hz, 1H), 7.52 (dd, J = 3.8, 1.4 Hz, 1H), 7.06 (dd, J = 5.0, 3.7 Hz, 1H), 6.92 (s, 1H), 6.89 (d, J = 1.6 Hz, 1H), 6.72 (d, J = 1.6 Hz, 1H), 3.23 (s, 3H), 3.11 – 2.74 (m, 2H), 1.73 (s, 3H), 1.54 (s, 9H).

E7

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (s, 1H), 7.30 (s, 1H), 6.94 (d, J = 1.6 Hz, 1H), 3.17 (s, 2H), 3.06 (s, 3H), 1.91 (s, 1H), 1.71 (s, 3H), 1.44 (s, 9H), 1.17 (dt, J = 6.2, 3.4 Hz, 2H), 1.09 (d, J = 8.1 Hz, 2H).

E8

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 7.29 (d, J = 1.8 Hz, 1H), 6.79 (d, J = 1.8 Hz, 1H), 6.54 (d, J = 1.8 Hz, 1H), 6.12 (d, J = 1.8 Hz, 1H), 4.11 (dt, J = 10.6, 6.6 Hz, 2H), 3.77 (s, 3H), 3.22 – 3.11 (m, 2H), 3.12 – 2.99 (m, 6H), 1.65 (s, 3H), 1.44 (s, 9H).

E11

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.07 (s, 1H), 7.70 (d, J = 1.5 Hz, 1H), 7.42 (d, J = 1.9 Hz, 1H), 7.37 (d, J = 1.5 Hz, 1H), 6.43 (d, J = 1.9 Hz, 1H), 3.90 (s, 3H), 3.39 – 3.16 (m, 2H), 3.06 (s, 3H), 1.75 (s, 3H), 1.44 (s, 9H).

F1

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.99 (s, 1H), 7.12 (dd, J = 12.6, 8.2 Hz, 1H), 7.00 (dd, J = 8.5, 2.1 Hz, 1H), 6.94 (ddd, J = 8.2, 4.3, 2.0 Hz, 1H), 4.75 – 4.44 (m, 1H), 4.06 (q, J = 7.1 Hz, 2H), 3.94 (s, 1H), 3.52 (s, 4H), 3.45 (td, J = 6.5, 4.3 Hz, 2H), 2.98 (d, J = 4.4 Hz, 8H), 2.91 (s, 3H), 2.51 – 2.42 (m, 2H), 1.52 (d, J = 6.7 Hz, 3H), 1.45 (d, J = 6.7 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H), .

F2

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.97 (s, 1H), 6.92 (dd, J = 11.4, 8.1 Hz, 1H), 6.62 (dd, J = 8.2, 2.1 Hz, 1H), 6.53 (ddd, J = 8.1, 4.5, 2.1 Hz, 1H), 4.61 (dd, J = 102.2, 14.5 Hz, 2H), 4.37 (s, 1H), 4.03 (d, J = 5.7 Hz, 1H), 3.71 (s, 3H), 3.46 (ddd, J = 12.4, 9.1, 4.7 Hz, 1H), 3.40 – 3.18 (m, 3H), 3.11 (s, 3H), 2.97 (s, 3H), 2.62 (ddd, J = 15.3, 6.6, 4.7 Hz, 1H), 2.47 (ddd, J = 15.3, 9.1, 5.1 Hz, 1H), 1.65 (dd, J = 14.6, 6.7 Hz, 6H), 1.61 – 1.49 (m, 3H), 1.34 (q, J = 4.0 Hz, 2H), 1.03 – 0.90 (m, 2H).

F3

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (s, 1H), 8.95 (s, 1H), 7.57 (d, J = 6.8 Hz, 1H), 7.17 (dd, J = 10.7, 8.4 Hz, 1H), 7.06 (ddd, J = 8.3, 4.6, 2.2 Hz, 1H), 4.78 (d, J = 14.9 Hz, 1H), 4.53 (d, J = 14.9 Hz, 1H), 4.07 – 3.86 (m, 1H), 3.45 (q, J = 6.4 Hz, 2H), 2.98 (s, 3H), 2.91 (s, 3H), 2.50 (m, J = 3.8, 1.9 Hz, 2H), 1.53 (d, J = 6.7 Hz, 3H), 1.46 (d, J = 6.7 Hz, 4H), 1.44 (s, 9H).

F4

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 8.34 – 7.83 (m, 2H), 7.23 (dd, J = 11.2, 8.4 Hz, 1H), 7.02 (ddd, J = 8.3, 4.5, 2.2 Hz, 1H), 6.90 – 6.54 (m, 2H), 4.89 – 4.45 (m, 2H), 3.94 (s, 1H), 3.48 (s, 2H), 2.98 (s, 3H), 2.90 (s, 3H), 2.53 (d, J = 4.9 Hz, 2H), 1.52 (d, J = 6.7 Hz, 3H), 1.45 (d, J = 6.7 Hz, 3H).

F5

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (s, 1H), 10.33 (s, 1H), 7.82 (dd, J = 5.0, 1.4 Hz, 1H), 7.43 (dd, J = 3.7, 1.4 Hz, 1H), 7.24 – 7.11 (m, 3H), 7.04 (dd, J = 5.0, 3.7 Hz, 1H), 4.63 (s, 2H), 4.11 – 3.88 (m, 1H), 3.42 – 3.31 (m, 2H), 3.00 (s, 3H), 2.92 (s, 3H), 2.52 – 2.37 (m, 1H), 1.54 (d, J = 6.7 Hz, 3H), 1.48 (d, J = 6.7 Hz, 3H).

F6

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.01 (dd, J = 11.9, 8.2 Hz, 1H), 6.61 (dd, J = 8.5, 2.1 Hz, 1H), 6.52 (ddd, J = 8.2, 4.4, 2.1 Hz, 1H), 4.80 – 4.41 (m, 2H), 3.92 (s, 2H), 3.50 – 3.35 (m, 2H), 2.98 (d, J = 2.4 Hz, 6H), 2.92 (d, J = 9.9 Hz, 3H), 2.84 (d, J = 5.7 Hz, 3H), 2.48 (d, J = 7.7 Hz, 2H), 1.52 (d, J = 6.7 Hz, 3H), 1.45 (d, J = 6.7 Hz, 3H).

F7

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.04 (dd, J = 10.7, 8.3 Hz, 1H), 6.90 – 6.82 (m, 1H), 6.73 (d, J = 7.9 Hz, 1H), 6.07 (s, 2H), 4.69 (d, J = 14.6 Hz, 1H), 4.47 (d, J = 14.6 Hz, 1H), 3.94 (s, 1H), 3.43 (s, 3H), 2.98 (s, 3H), 2.90 (s, 3H), 2.46 (d, J = 5.8 Hz, 2H), 1.52 (d, J = 6.7 Hz, 3H), 1.45 (d, J = 6.7 Hz, 3H), 0.85 (dt, J = 6.0, 3.0 Hz, 2H), 0.70 (d, J = 6.7 Hz, 2H).

F8

1H NMR (400 MHz, DMSO-d6) δ 7.29 (d, J = 1.8 Hz, 1H), 7.25 – 7.11 (m, 2H), 6.90 (ddd, J = 8.3, 4.3, 2.0 Hz, 1H), 6.13 (d, J = 1.8 Hz, 1H), 4.65 (dd, J = 73.6, 14.8 Hz, 2H), 4.27 (t, J = 6.6 Hz, 2H), 3.96 (s, 1H), 3.79 (s, 3H), 3.45 (q, J = 6.2 Hz, 2H), 3.12 (t, J = 6.5 Hz, 2H), 2.98 (s, 3H), 2.90 (s, 3H), 2.48 (dd, J = 6.3, 2.1 Hz, 2H), 1.53 (d, J = 6.7 Hz, 3H), 1.46 (d, J = 6.7 Hz, 3H).

F9

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.09 (dd, J = 11.3, 8.3 Hz, 1H), 6.90 (dd, J = 8.5, 2.2 Hz, 1H), 6.74 (ddd, J = 8.3, 4.2, 2.2 Hz, 1H), 4.59 (dd, J = 84.0, 14.8 Hz, 2H), 3.94 (s, 1H), 3.43 (td, J = 6.7, 2.4 Hz, 2H), 3.35 (s, 9H), 2.98 (s, 3H), 2.90 (s, 3H), 1.52 (d, J = 6.7 Hz, 3H), 1.45 (d, J = 6.6 Hz, 3H),

F10

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (s, 1H), 7.44 (ddd, J = 7.7, 5.0, 2.2 Hz, 1H), 7.37 (dt, J = 6.5, 3.1 Hz, 1H), 7.31 (dd, J = 10.0, 8.5 Hz, 1H), 5.95 (s, 1H), 4.72 (dt, J = 55.2, 15.5 Hz, 2H), 3.95 (s, 1H), 3.48 (s, 2H), 2.99 (s, 3H), 2.97 (d, J = 0.7 Hz, 3H), 2.92 – 2.89 (m, 3H), 2.87 (d, J = 1.9 Hz, 3H), 2.60 – 2.51 (m, 2H), 1.52 (d, J = 6.7 Hz, 3H), 1.45 (d, J = 6.6 Hz, 3H).

F11

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (s, 1H), 7.52 (d, J = 1.9 Hz, 1H), 7.48 (tt, J = 7.0, 3.8 Hz, 2H), 7.37 (dd, J = 9.9, 8.4 Hz, 1H), 6.41 (dd, J = 1.9, 0.8 Hz, 1H), 4.89 – 4.57 (m, 2H), 3.95 (s, 1H), 3.73 (d, J = 1.2 Hz, 3H), 3.52 (td, J = 6.3, 2.3 Hz, 2H), 2.99 (s, 3H), 2.91 (s, 3H), 2.59 – 2.53 (m, 2H), 1.52 (d, J = 6.7 Hz, 3H), 1.45 (d, J = 6.6 Hz, 3H).

G1

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (dd, J = 16.3, 2.7 Hz, 2H), 8.20 – 8.09 (m, 2H), 7.75 (s, 1H), 7.59 (dd, J = 9.2, 3.0 Hz, 1H), 4.08 (q, J = 7.1 Hz, 2H), 3.54 (t, J = 5.2 Hz, 4H), 3.45 (s, 1H), 3.22 (dd, J = 6.2, 4.1 Hz, 6H), 3.11 (s, 2H), 2.29 (s, 1H), 2.20 (s, 1H), 2.09 (s, 3H), 2.03 (s, 1H), 1.79 (s, 1H), 1.21 (t, J = 7.1 Hz, 3H).

G2

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (dd, J = 2.6, 0.4 Hz, 1H), 8.80 (d, J = 2.6 Hz, 1H), 8.22 (dd, J = 8.9, 0.7 Hz, 1H), 7.86 (dd, J = 3.0, 0.7 Hz, 1H), 7.06 (dd, J = 8.9, 3.0 Hz, 1H), 4.25 (s, 1H), 4.06 – 3.83 (m, 1H), 3.73 (s, 3H), 3.57 (s, 2H), 3.43 – 3.15 (m, 4H), 2.26 (s, 3H), 1.40 – 1.33 (m, 2H), 1.25 (d, J = 6.1 Hz, 2H), 0.99 – 0.91 (m, 2H).

G3

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (dd, J = 19.7, 2.5 Hz, 2H), 8.53 – 8.30 (m, 2H), 8.03 (s, 2H), 6.64 (s, 1H), 3.59 (d, J = 30.2 Hz, 2H), 3.25 (s, 2H), 2.42 (s, 2H), 1.84 (s, 2H), 1.55 (s, 9H).

G4

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (dd, J = 2.6, 0.5 Hz, 1H), 8.84 (d, J = 2.6 Hz, 1H), 8.54 (dd, J = 2.8, 0.7 Hz, 1H), 8.50 (dd, J = 8.9, 0.7 Hz, 1H), 8.20 (dd, J = 8.9, 5.7 Hz, 1H), 8.07 (d, J = 0.4 Hz, 1H), 8.03 (dd, J = 8.9, 2.8 Hz, 1H), 6.91 (s, 1H), 6.59 (ddd, J = 8.0, 5.8, 2.2 Hz, 1H), 6.50 (dd, J = 10.7, 2.1 Hz, 1H), 3.62 (d, J = 41.2 Hz, 2H), 3.29 (s, 2H), 2.25 (s, 4H), 2.09 (s, 2H).

G11

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (dd, J = 17.9, 2.5 Hz, 2H), 8.66 (dd, J = 8.6, 0.8 Hz, 1H), 8.55 (dd, J = 2.3, 0.8 Hz, 1H), 8.11 (s, 1H), 7.90 (dd, J = 8.6, 2.4 Hz, 1H), 7.58 (d, J = 1.9 Hz, 1H), 6.41 (d, J = 1.9 Hz, 1H), 3.95 (s, 3H), 3.62 (d, J = 43.4 Hz, 2H), 3.30 (s, 3H), 2.47 – 2.36 (m, 1H), 2.25 (s, 3H), 1.88 (s, 3H).

H1

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 – 8.31 (m, 1H), 8.08 – 8.00 (m, 1H), 7.99 – 7.92 (m, 1H), 7.78 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.67 – 7.55 (m, 2H), 7.28 (d, J = 8.9 Hz, 1H), 7.10 (d, J = 2.5 Hz, 1H), 6.87 (dd, J = 8.9, 2.5 Hz, 1H), 6.84 – 6.77 (m, 2H), 6.72 (d, J = 8.7 Hz, 2H), 5.38 (s, 2H), 5.31 (s, 2H), 4.04 (q, J = 7.1 Hz, 2H), 3.59 (s, 3H), 3.47 – 3.40 (m, 4H), 3.21 (s, 2H), 3.02 (t, J = 5.2 Hz, 4H), 1.18 (t, J = 7.1 Hz, 3H), 1.12 (s, 6H), 0.95 (s, 9H).

H2

[1]H NMR (400 MHz, DMSO-d_6) δ 8.46 (d, J = 8.5 Hz, 1H), 8.09 (dd, J = 8.4, 1.0 Hz, 1H), 8.01 (dd, J = 8.1, 1.4 Hz, 1H), 7.83 (ddd, J = 8.5, 6.9, 1.5 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.65 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.31 (d, J = 8.9 Hz, 1H), 7.10 (d, J = 2.5 Hz, 1H), 6.89 (dd, J = 8.9, 2.5 Hz, 1H), 6.66 (d, J = 8.4 Hz, 2H), 6.57 (d, J = 8.3 Hz, 2H), 5.43 (s, 2H), 5.27 (s, 2H), 3.60 (s, 3H), 3.56 (s, 3H), 3.24 (s, 2H), 3.21 (s, 2H), 1.12 (s, 6H), 1.08 (q, J = 3.9 Hz, 2H), 0.96 (s, 9H), 0.90 (q, J = 4.0 Hz, 2H).

H3

[1]H NMR (400 MHz, DMSO-d_6) δ 9.29 (s, 1H), 8.35 (dd, J = 8.7, 0.8 Hz, 1H), 8.08 – 8.00 (m, 1H), 8.00 – 7.92 (m, 1H), 7.78 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.60 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.28 (dd, J = 8.7, 1.4 Hz, 3H), 7.09 (d, J = 2.5 Hz, 1H), 6.87 (dd, J = 8.9, 2.5 Hz, 1H), 6.72 (d, J = 8.7 Hz, 2H), 5.38 (s, 2H), 5.34 (s, 2H), 3.59 (s, 3H), 3.20 (s, 2H), 1.43 (s, 9H), 1.11 (s, 6H), 0.95 (s, 9H).

H4

[1]H NMR (400 MHz, DMSO-d_6) δ 9.39 (s, 1H), 8.49 (d, J = 8.5 Hz, 1H), 8.16 – 8.06 (m, 2H), 8.02 (dd, J = 8.2, 1.4 Hz, 1H), 7.85 (ddd, J = 8.5, 6.9, 1.5 Hz, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.66 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.33 (d, J = 8.9 Hz, 1H), 7.13 (d, J = 2.5 Hz, 1H), 6.91 (dd, J = 8.8, 2.5 Hz, 1H), 6.79 (d, J = 8.6 Hz, 2H), 6.69 (ddd, J = 8.4, 6.0, 2.3 Hz, 1H), 6.57 (dd, J = 11.6, 2.3 Hz, 1H), 5.45 (s, 2H), 5.38 (s, 2H), 3.60 (s, 3H), 3.23 (s, 2H), 1.13 (s, 6H), 0.98 (s, 9H).

H5

[1]H NMR (400 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.48 (d, J = 8.5 Hz, 1H), 8.06 (ddd, J = 26.1, 8.2, 1.2 Hz, 2H), 7.89 – 7.80 (m, 2H), 7.76 – 7.61 (m, 2H), 7.47 (dd, J = 3.7, 1.4 Hz, 1H), 7.25 (d, J = 8.9 Hz, 1H), 7.14 – 7.03 (m, 2H), 7.02 – 6.95 (m, 2H), 6.88 (dd, J = 8.9, 2.5 Hz, 1H), 6.73 (d, J = 8.6 Hz, 2H), 5.43 (s, 2H), 5.35 (s, 2H), 3.56 (s, 3H), 3.15 (s, 2H), 1.09 (s, 6H), 0.96 (s, 9H).

H6

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, J = 8.5 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.81 (ddd, J = 8.4, 6.8, 1.5 Hz, 1H), 7.68 (dd, J = 8.5, 1.3 Hz, 1H), 7.62 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.43 – 7.20 (m, 1H), 7.15 – 6.96 (m, 1H), 6.87 (dd, J = 8.8, 2.6 Hz, 2H), 6.75 – 6.39 (m, 2H), 5.41 (s, 3H), 5.26 (s, 2H), 3.82 (s, 2H), 3.59 (d, J = 3.8 Hz, 3H), 3.20 (d, J = 12.4 Hz, 2H), 3.09 – 2.76 (m, 6H), 1.12 (s, 6H), 0.96 (d, J = 9.0 Hz, 9H).

H7

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 (s, 1H), 8.89 (s, 1H), 8.38 (d, J = 8.5 Hz, 1H), 8.08 – 8.01 (m, 1H), 7.98 (dd, J = 8.2, 1.4 Hz, 1H), 7.80 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.62 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.30 (d, J = 8.9 Hz, 1H), 7.27 – 7.19 (m, 2H), 7.19 – 7.11 (m, 1H), 6.94 – 6.87 (m, 3H), 5.49 (s, 2H), 5.40 (s, 2H), 3.60 (s, 3H), 3.17 (s, 2H), 1.91 (s, 1H), 1.26 – 1.16 (m, 4H), 1.13 (s, 6H), 0.99 (s, 9H).

H8

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 – 8.31 (m, 1H), 8.08 – 8.00 (m, 1H), 7.96 (dd, J = 8.0, 1.4 Hz, 1H), 7.78 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.67 – 7.55 (m, 2H), 7.32 – 7.24 (m, 2H), 7.10 (d, J = 2.5 Hz, 1H), 6.92 – 6.73 (m, 5H), 6.09 (d, J = 1.8 Hz, 1H), 5.38 (s, 2H), 5.35 (s, 2H), 4.11 (t, J = 6.6 Hz, 2H), 3.75 (s, 3H), 3.59 (s, 3H), 3.20 (s, 2H), 3.03 (t, J = 6.6 Hz, 2H), 1.12 (s, 6H), 0.95 (s, 9H).

H9

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (d, J = 8.6 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.80 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.61 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.31 (dd, J = 8.9, 4.8 Hz, 1H), 7.18 – 7.03 (m, 1H), 6.88 (dd, J = 8.8, 2.5 Hz, 1H), 6.84 – 6.51 (m, 4H), 5.39 (d, J = 6.9 Hz, 4H), 3.66 (s, 3H), 3.18 (s, 2H), 1.09 (d, J = 14.4 Hz, 6H), 0.95 (d, J = 5.9 Hz, 8H).

H10

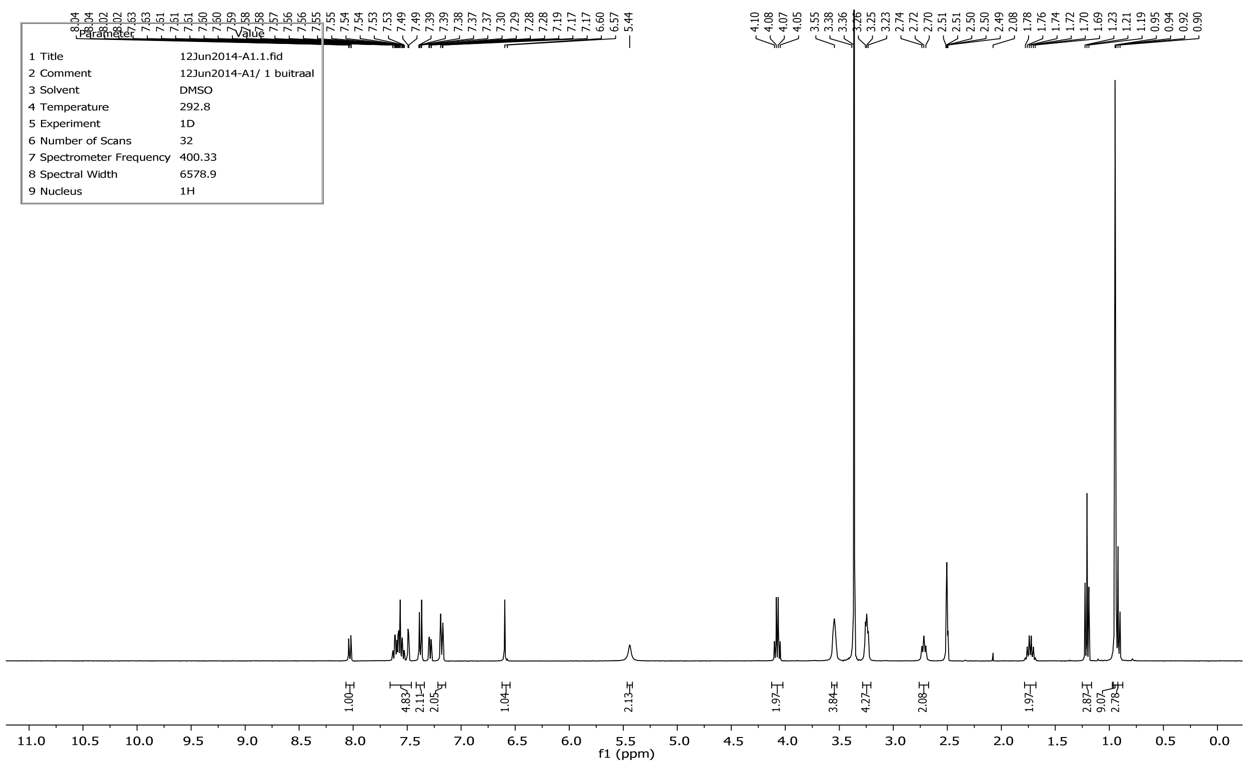
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, J = 8.7 Hz, 1H), 8.04 (dd, J = 8.3, 1.0 Hz, 1H), 8.01 – 7.93 (m, 1H), 7.79 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.69 – 7.56 (m, 2H), 7.28 (t, J = 8.3 Hz, 3H), 7.13 (d, J = 2.5 Hz, 1H), 6.92 – 6.81 (m, 3H), 5.71 (s, 1H), 5.47 (s, 2H), 5.39 (s, 2H), 3.58 (s, 3H), 3.19 (s, 2H), 2.89 (s, 3H), 2.81 (s, 3H), 1.12 (s, 6H), 0.98 (s, 9H).

H11

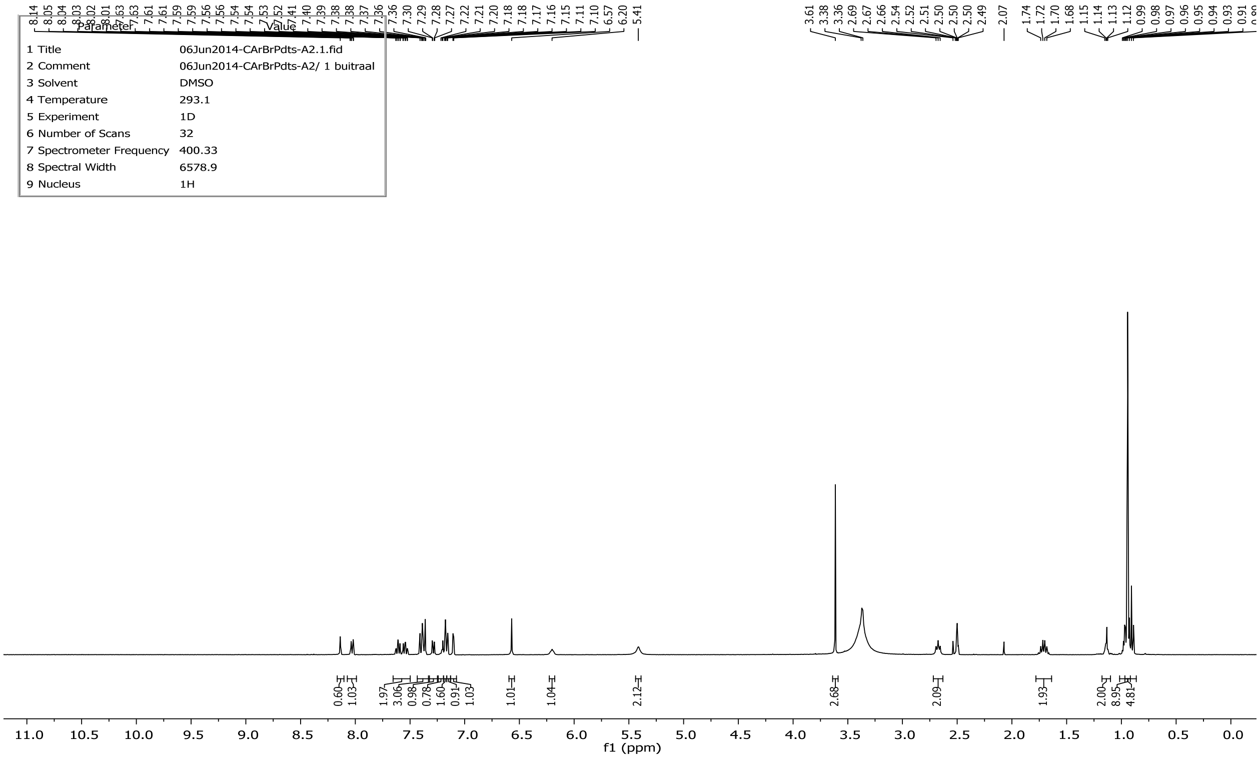
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (dd, J = 8.7, 0.8 Hz, 1H), 8.04 (dq, J = 8.4, 0.8 Hz, 1H), 8.00 – 7.93 (m, 1H), 7.78 (ddd, J = 8.5, 6.9, 1.5 Hz, 1H), 7.69 – 7.56 (m, 2H), 7.46 – 7.38 (m, 3H), 7.33 (d, J = 8.9 Hz, 1H), 7.14 (d, J = 2.5 Hz, 1H), 6.95 – 6.87 (m, 3H), 6.34 (d, J = 1.9 Hz, 1H), 5.51 (s, 2H), 5.39 (s, 2H), 3.78 (s, 3H), 3.60 (s, 3H), 3.22 (s, 2H), 1.14 (s, 6H), 0.98 (s, 9H).

^{1}H NMR Spectra

A1

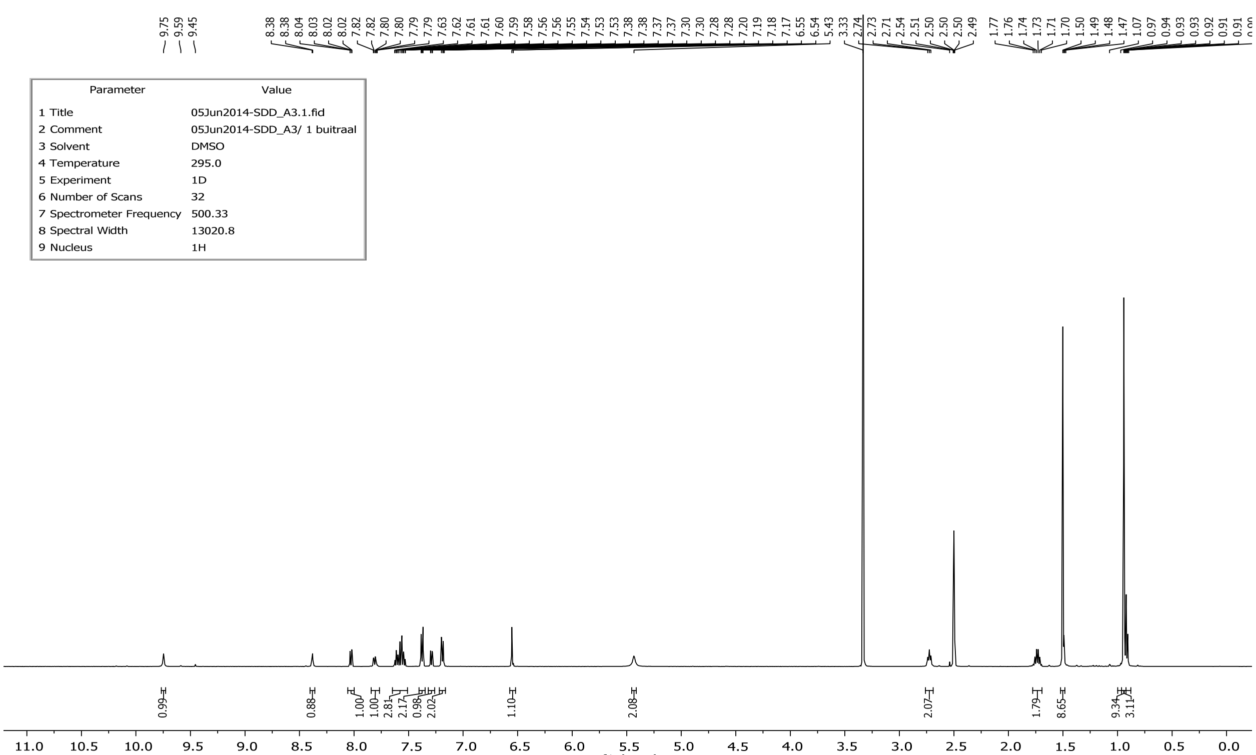


A2



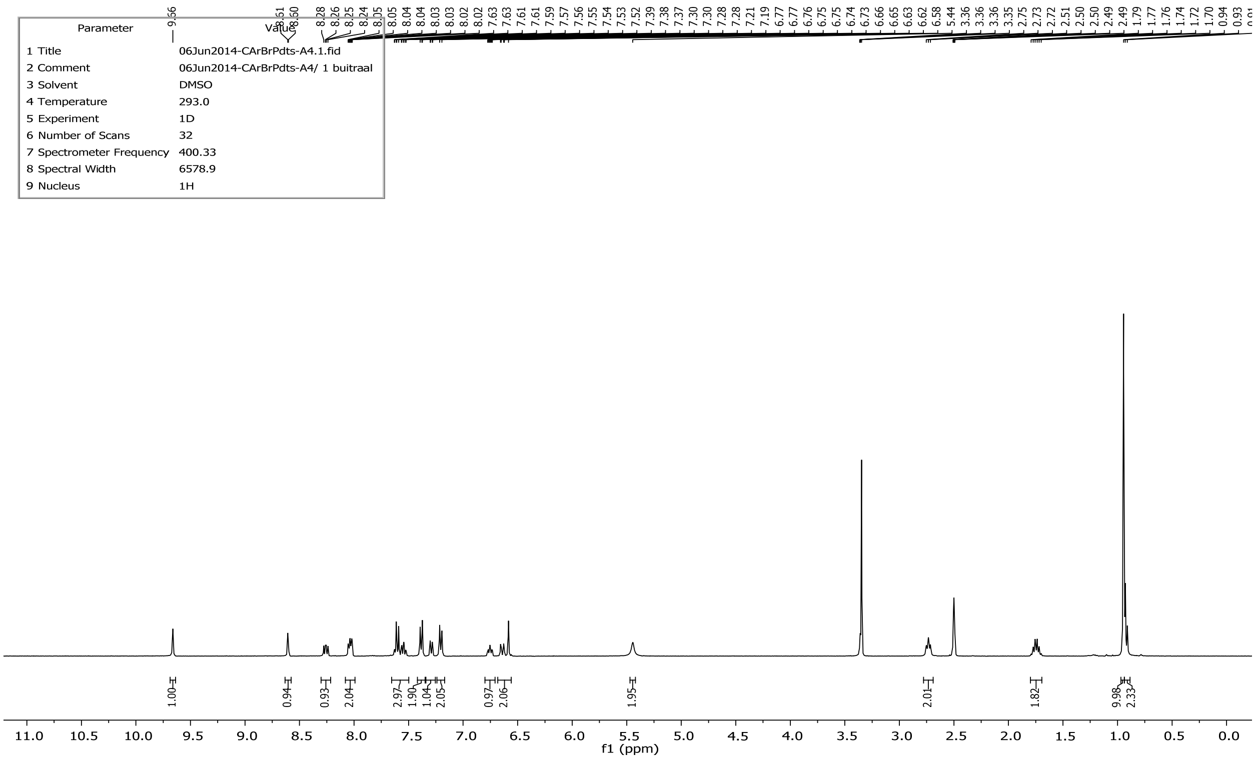
Parameter	Value
1 Title	06Jun2014-CArBrPdts-A2.1.fid
2 Comment	06Jun2014-CArBrPdts-A2/ 1 buitraal
3 Solvent	DMSO
4 Temperature	293.1
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	400.33
8 Spectral Width	6578.9
9 Nucleus	1H

A3

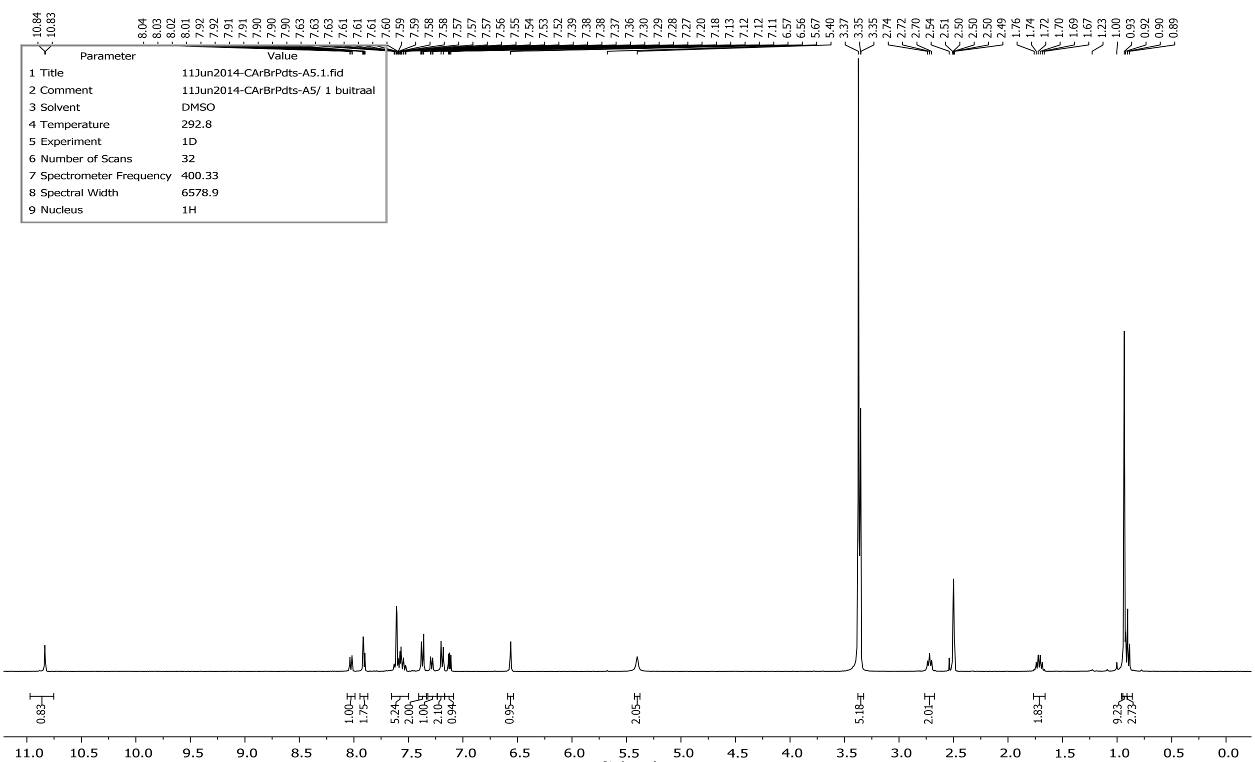


Parameter	Value
1 Title	05Jun2014-SDD_A3.1.fid
2 Comment	05Jun2014-SDD_A3/ 1 buitraal
3 Solvent	DMSO
4 Temperature	295.0
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	500.33
8 Spectral Width	13020.8
9 Nucleus	1H

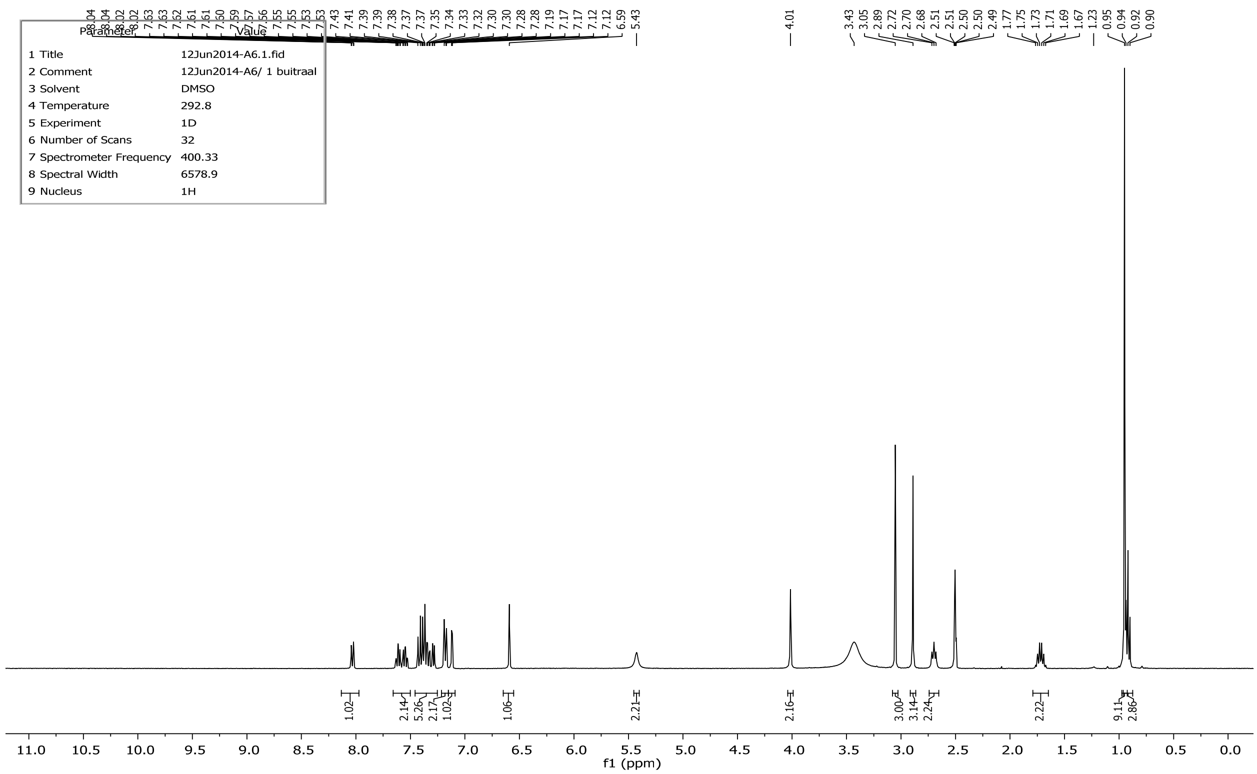
A4


Parameter
Value
1 Title
06Jun2014-CArBrPdts-A4.1.fid
2 Comment
06Jun2014-CArBrPdts-A4/ 1 buitraal
3 Solvent
DMSO
4 Temperature
293.0
5 Experiment
1D
6 Number of Scans
32
7 Spectrometer Frequency
400.33
8 Spectral Width
6578.9
9 Nucleus
1H
f1 (ppm)

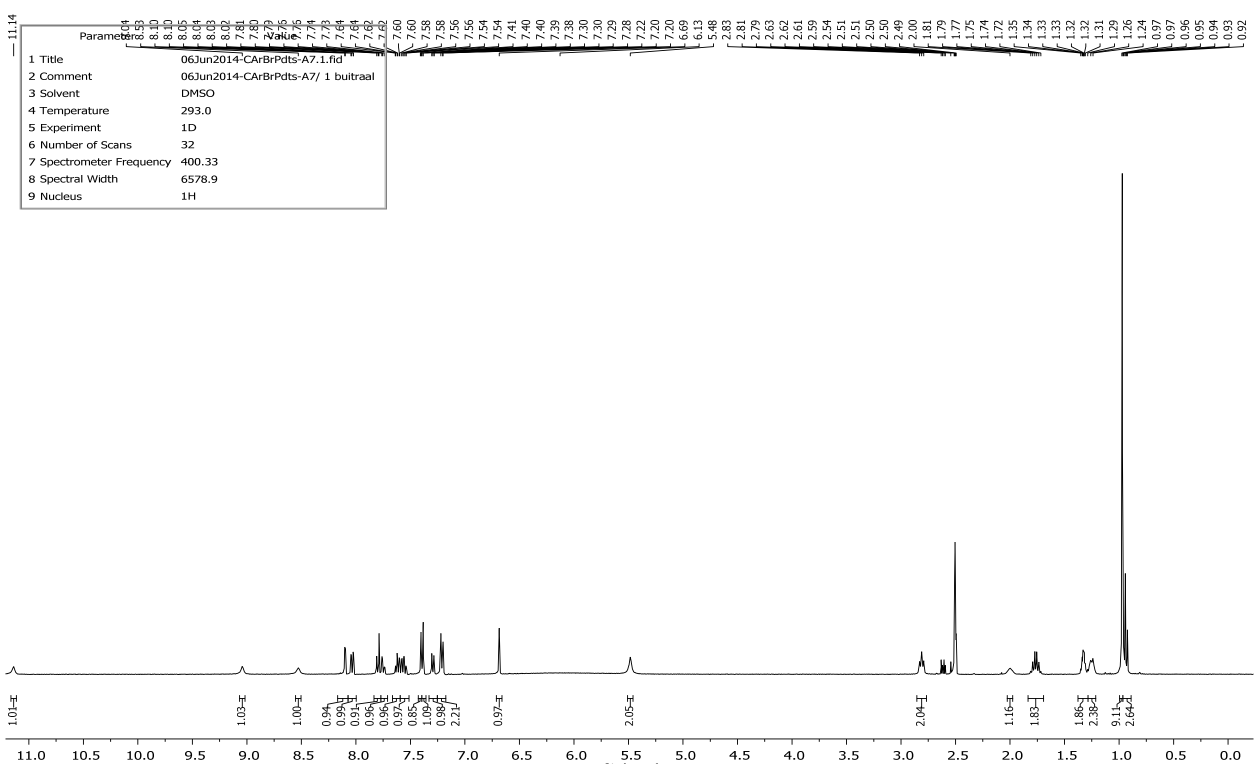
A5


Parameter
Value
1 Title
11Jun2014-CArBrPdts-A5.1.fid
2 Comment
11Jun2014-CArBrPdts-A5/ 1 buitraal
3 Solvent
DMSO
4 Temperature
292.8
5 Experiment
1D
6 Number of Scans
32
7 Spectrometer Frequency
400.33
8 Spectral Width
6578.9
9 Nucleus
1H
f1 (ppm)

A6


Parameter Value
1 Title 12Jun2014-A6.1.fid
2 Comment 12Jun2014-A6/ 1 buitraal
3 Solvent DMSO
4 Temperature 292.8
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

A7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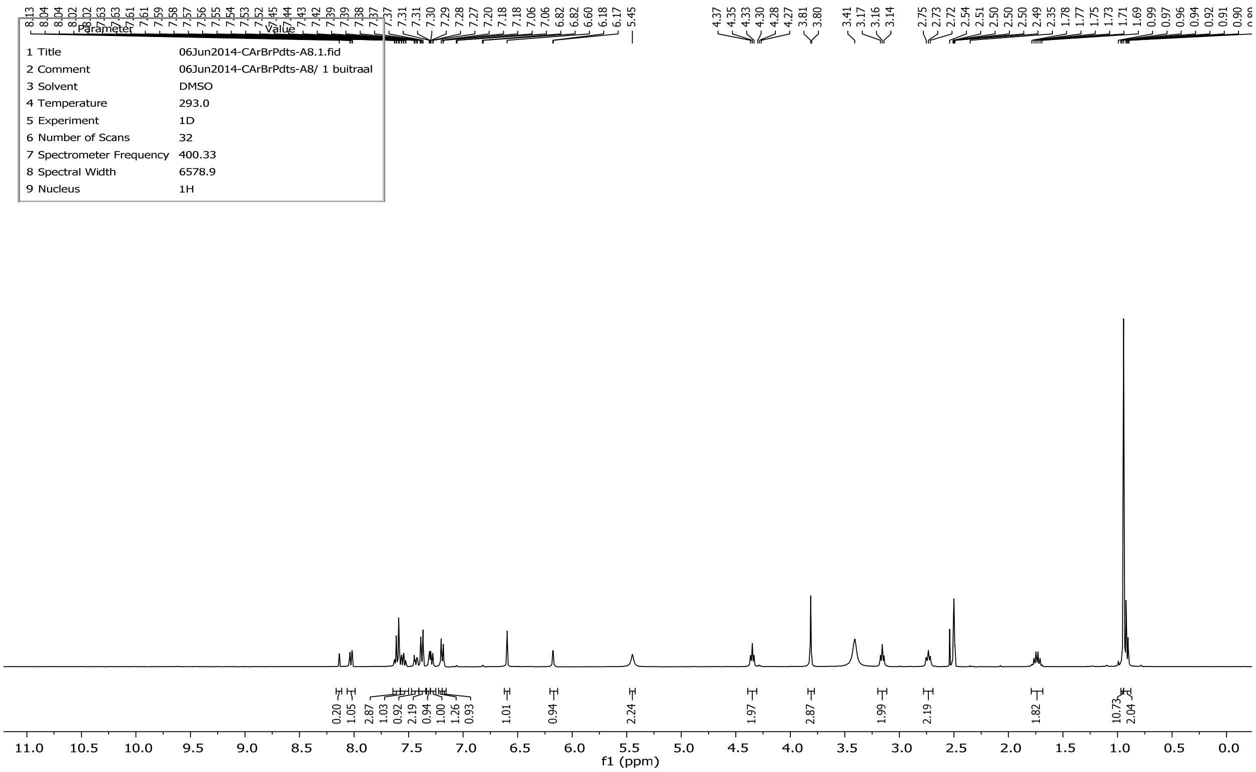
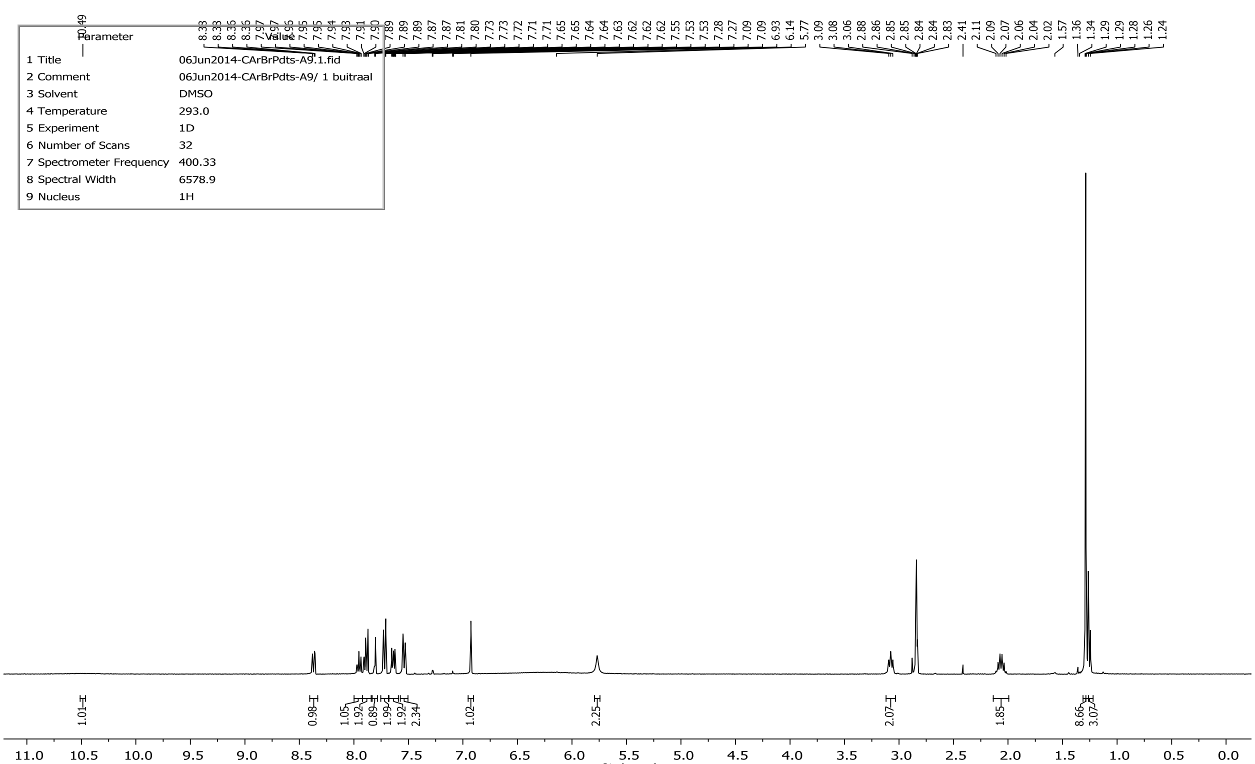
1 Title 06Jun2014-CArBrPdts-A7.1.fid
2 Comment 06Jun2014-CArBrPdts-A7/ 1 buitraal
3 Solvent DMSO
4 Temperature 293.0
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

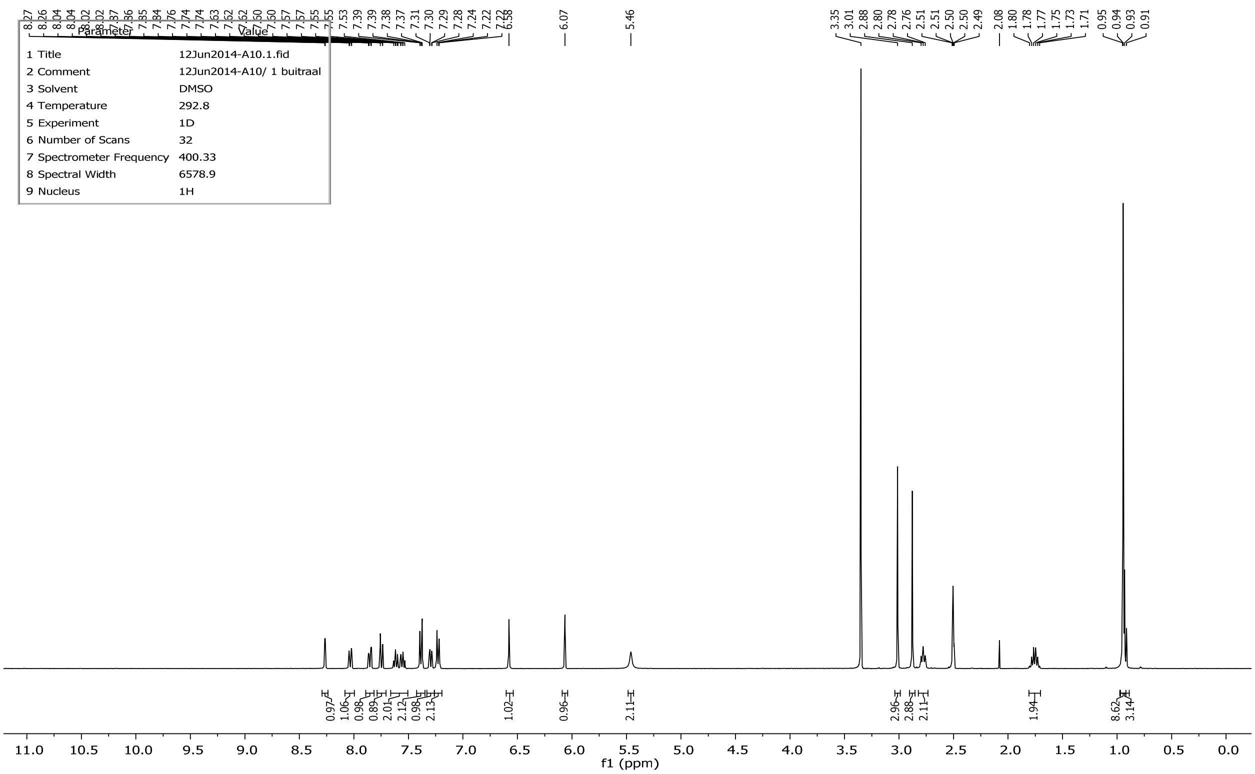
A8



A9



A10



Parameter Value
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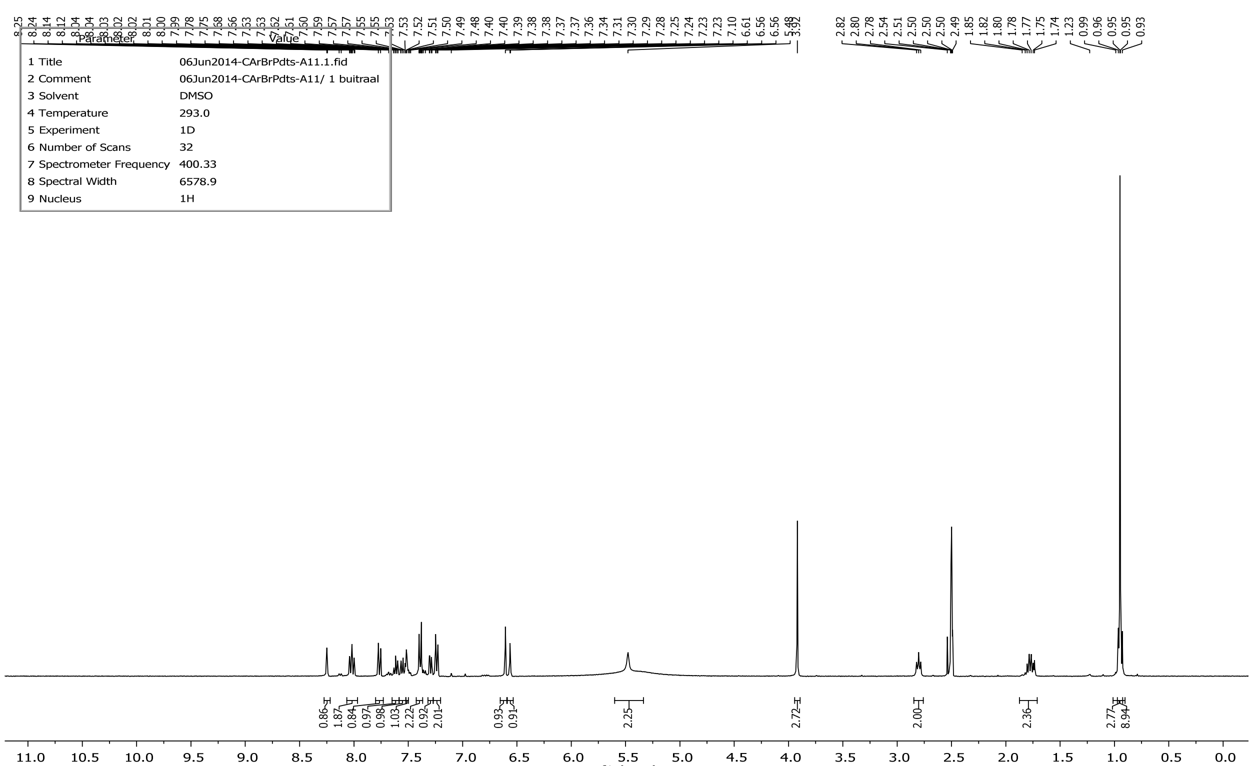
3 Solvent DMSO
4 Temperature 292.8
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

A11



Parameter Value
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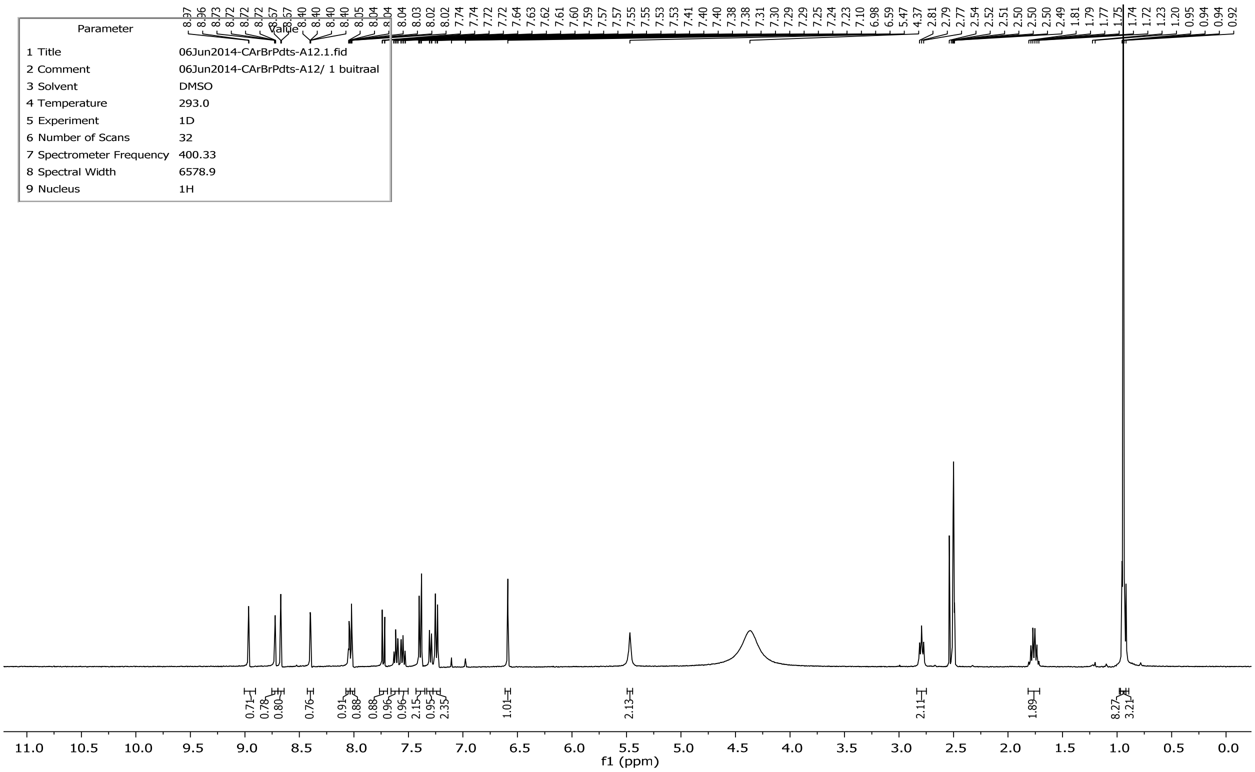
2 Comment 06Jun2014-CArBrPdts-A11/ 1 buitraal
3 Solvent DMSO
4 Temperature 293.0
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

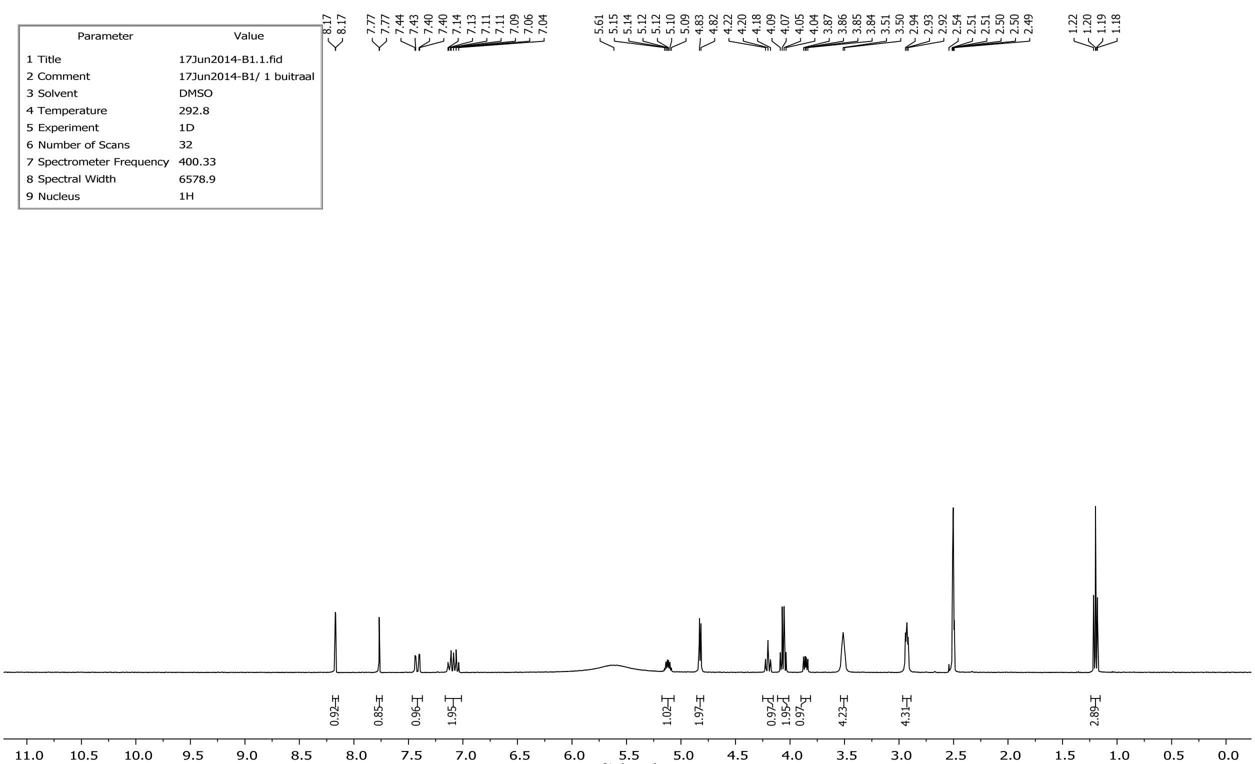
A12

Parameter	Value
1 Title	06Jun2014-CArBrPdts-A12.1.fid
2 Comment	06Jun2014-CArBrPdts-A12/ 1 buitraal
3 Solvent	DMSO
4 Temperature	293.0
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	400.33
8 Spectral Width	6578.9
9 Nucleus	1H

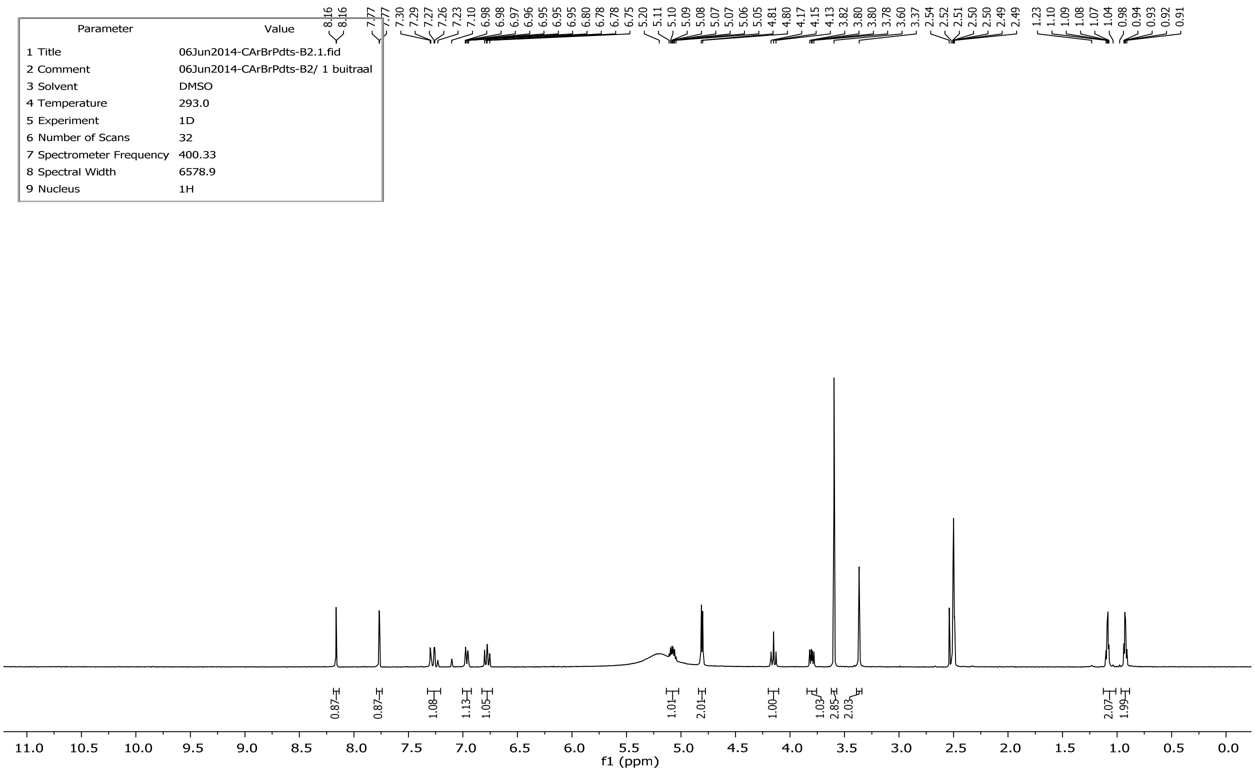


B1

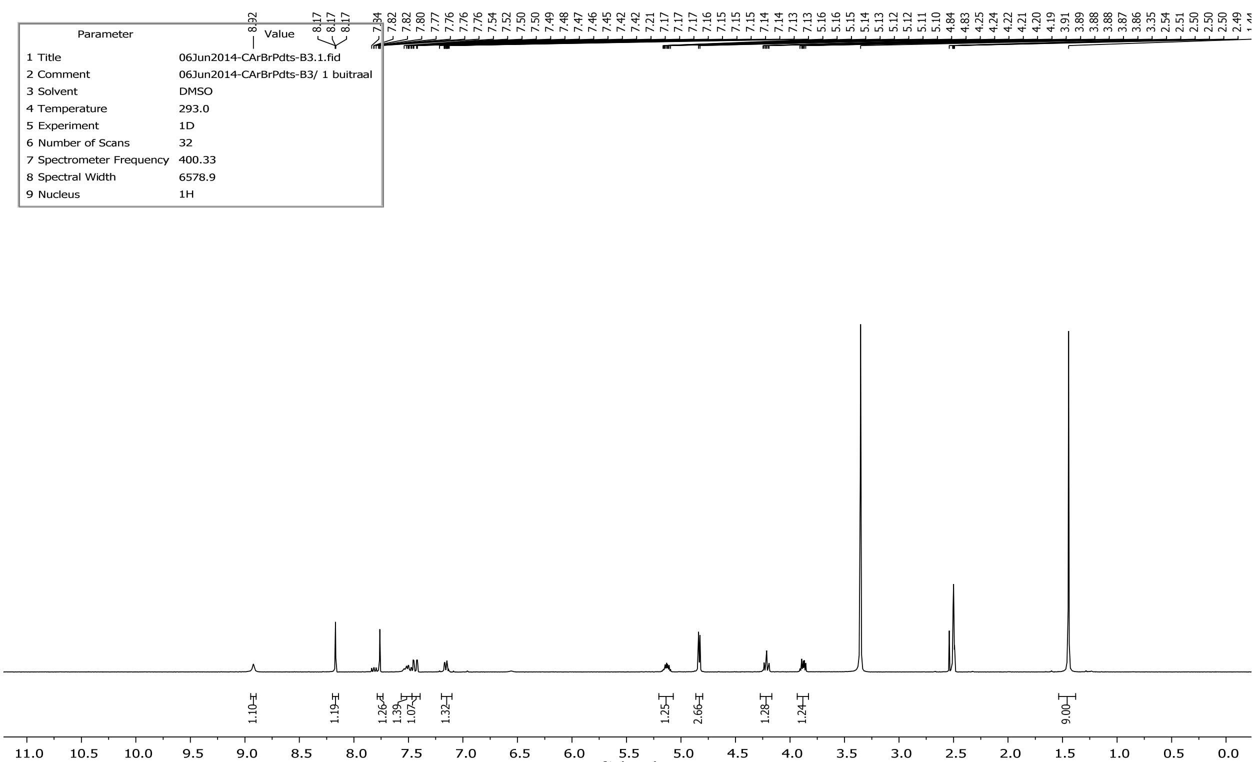
Parameter	Value
1 Title	17Jun2014-B1.1.fid
2 Comment	17Jun2014-B1/ 1 buitraal
3 Solvent	DMSO
4 Temperature	292.8
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	400.33
8 Spectral Width	6578.9
9 Nucleus	1H



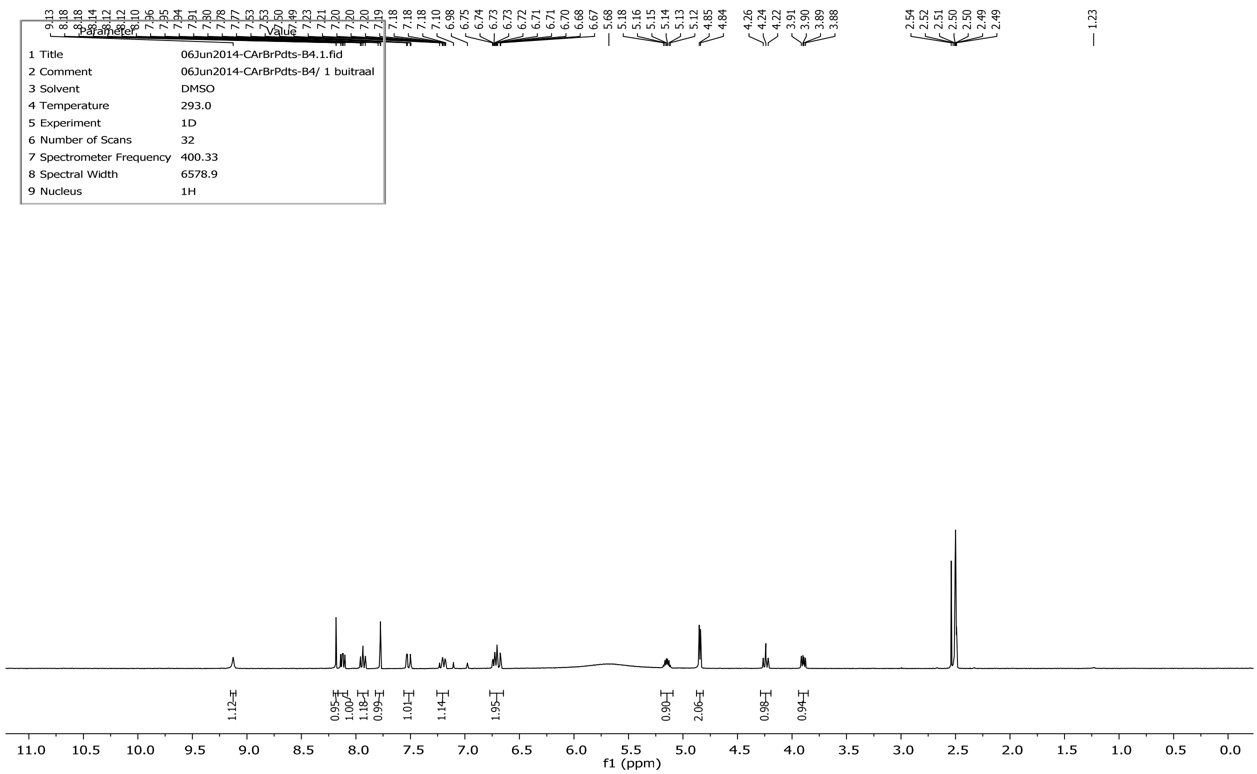
B2


Parameter Value
1 Title 06Jun2014-CArBrPdts-B2.1.fid
2 Comment 06Jun2014-CArBrPdts-B2/ 1 buitraal
3 Solvent DMSO
4 Temperature 293.0
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

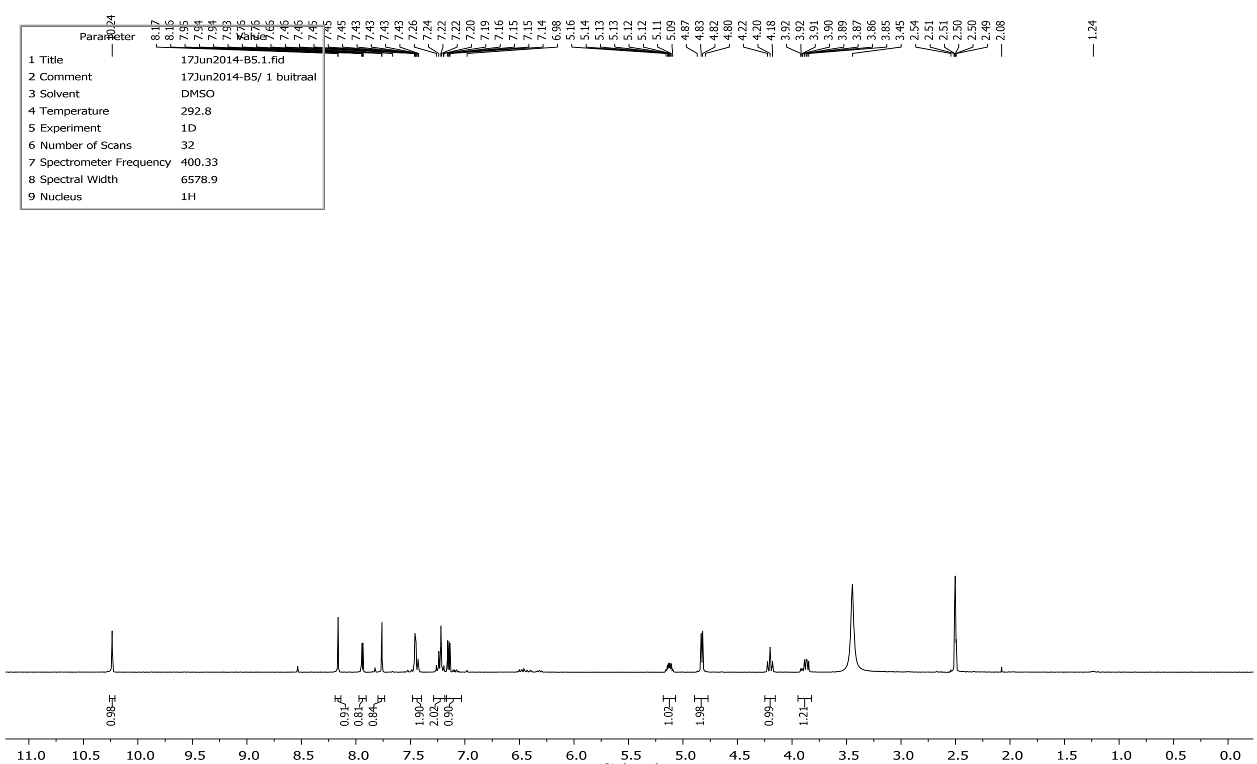
B3


Parameter Value
1 Title 06Jun2014-CArBrPdts-B3.1.fid
2 Comment 06Jun2014-CArBrPdts-B3/ 1 buitraal
3 Solvent DMSO
4 Temperature 293.0
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

B4

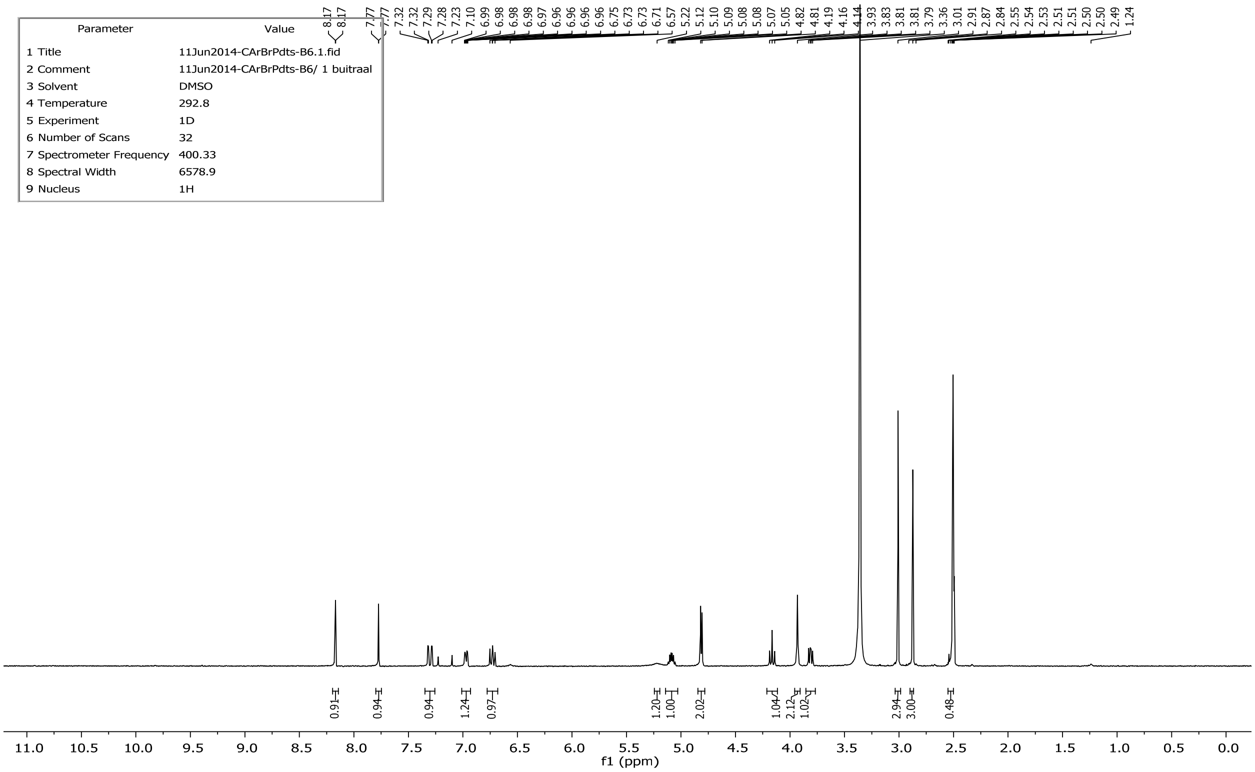

Parameter Value
1 Title 06Jun2014-CArBrPdts-B4.1.fid
2 Comment 06Jun2014-CArBrPdts-B4/ 1 buitraal
3 Solvent DMSO
4 Temperature 293.0
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

B5


Parameter Value
1 Title 17Jun2014-B5.1.fid
2 Comment 17Jun2014-B5/ 1 buitraal
3 Solvent DMSO
4 Temperature 292.8
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

B6

Parameter	Value
1 Title	11Jun2014-CArBrPdts-B6.1.fid
2 Comment	11Jun2014-CArBrPdts-B6/ 1 buitraal
3 Solvent	DMSO
4 Temperature	292.8
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	400.33
8 Spectral Width	6578.9
9 Nucleus	1H



B11

Parameter	Value
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2 Comment	06Jun2014-CArBrPdts-B11/ 1 buitraal
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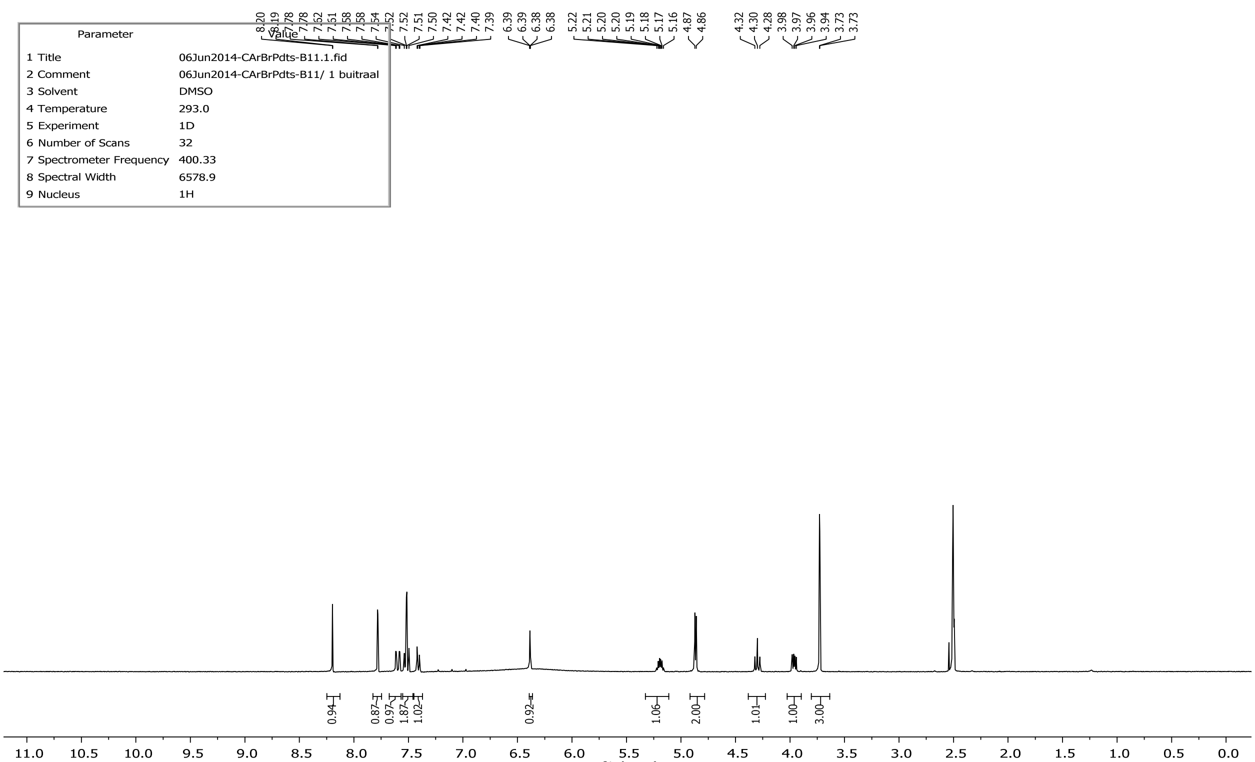
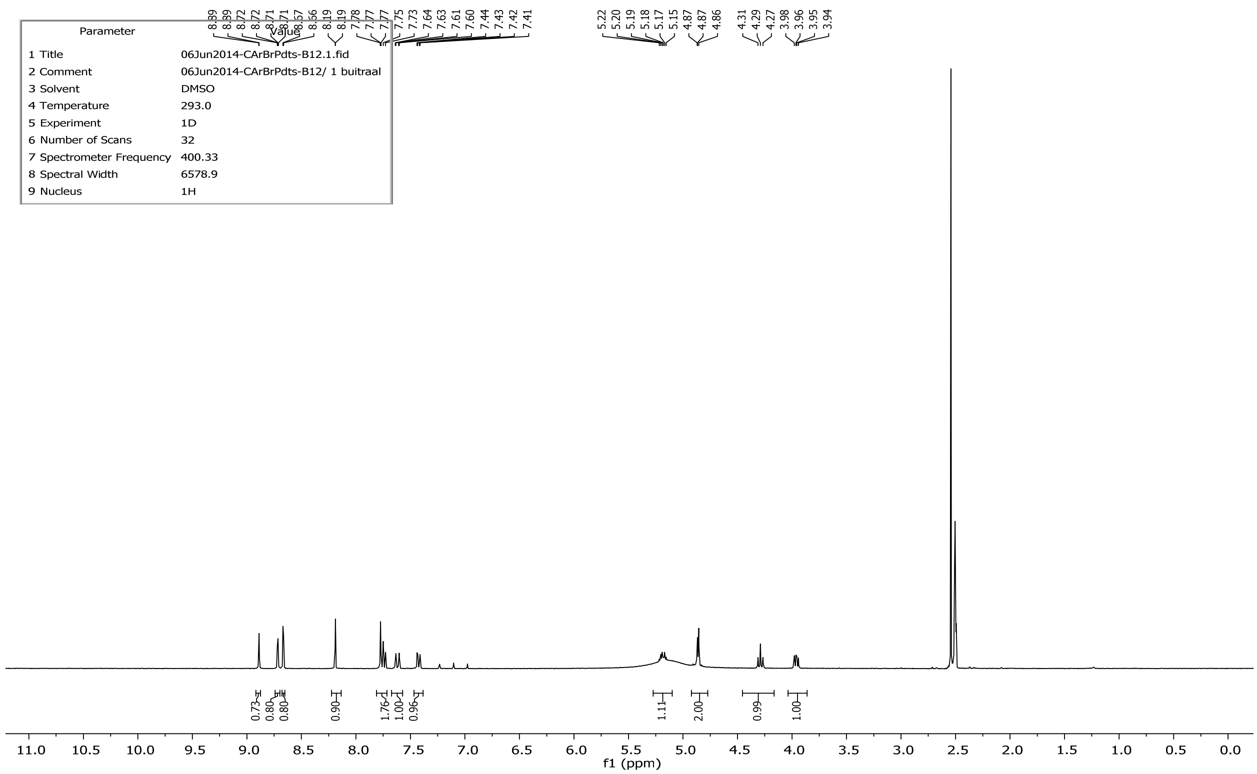
4 Temperature	293.0
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	400.33
8 Spectral Width	6578.9
9 Nucleus	1H



B12



Parameter
Value
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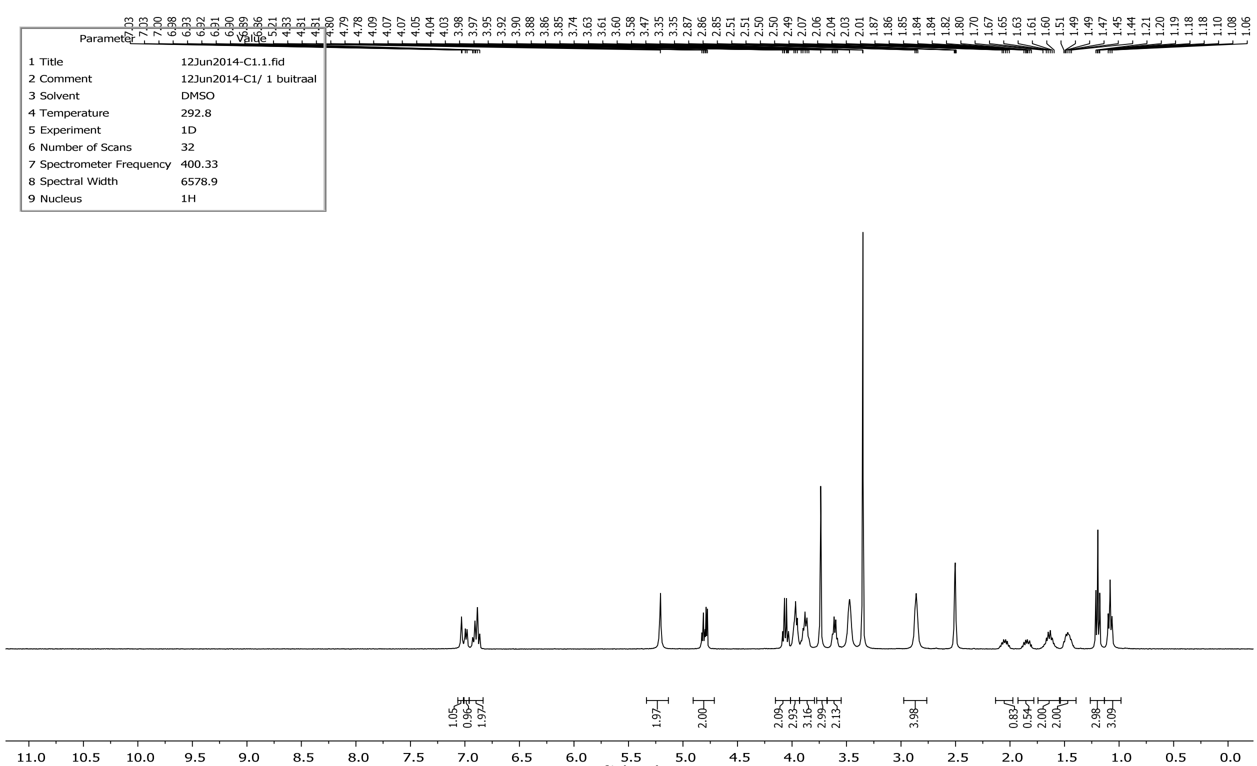
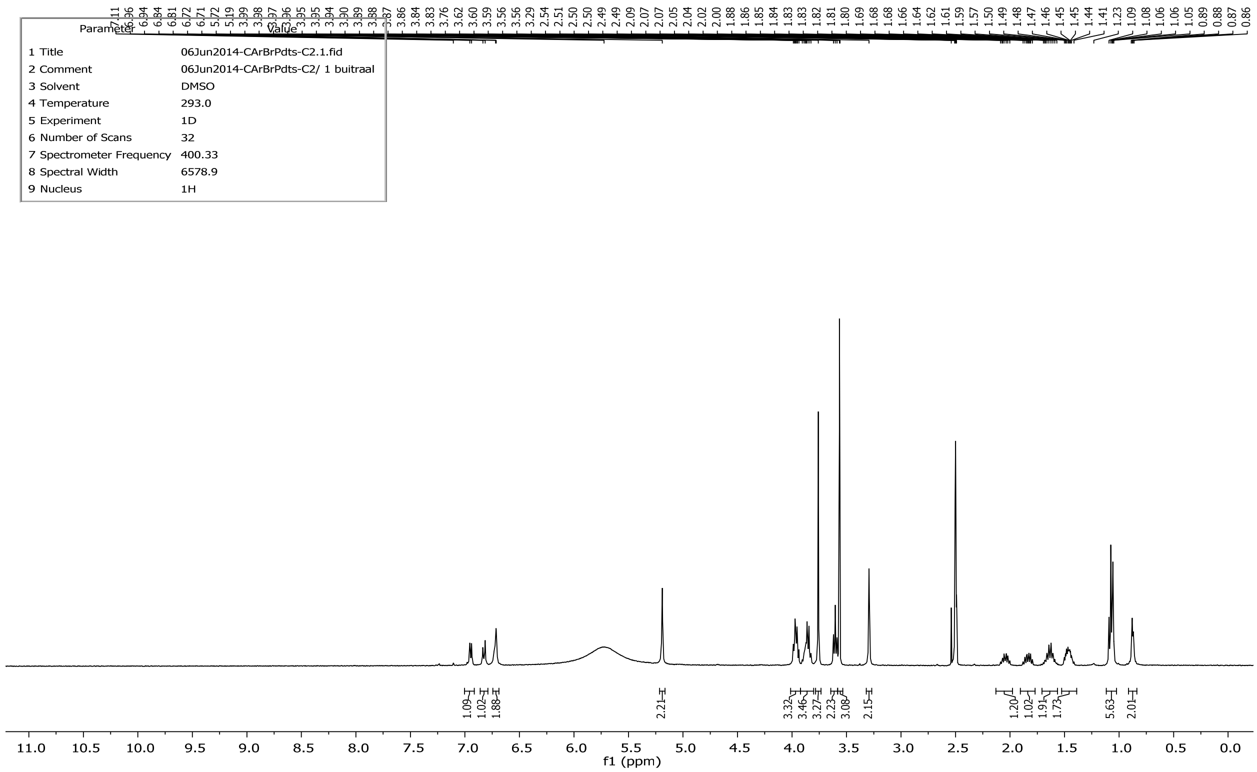
06Jun2014-CArBrPdts-B12.1.fid
2 Comment
06Jun2014-CArBrPdts-B12/ 1 buitraal
3 Solvent
DMSO
4 Temperature
293.0
5 Experiment
1D
6 Number of Scans
32
7 Spectrometer Frequency
400.33
8 Spectral Width
6578.9
9 Nucleus
1H
f1 (ppm)

C1



Parameter
Value
1 Title
12Jun2014-C1.1.fid
2 Comment
12Jun2014-C1/ 1 buitraal
3 Solvent
DMSO
4 Temperature
292.8
5 Experiment
1D
6 Number of Scans
32
7 Spectrometer Frequency
400.33
8 Spectral Width
6578.9
9 Nucleus
1H
f1 (ppm)

C2


Parameter Value
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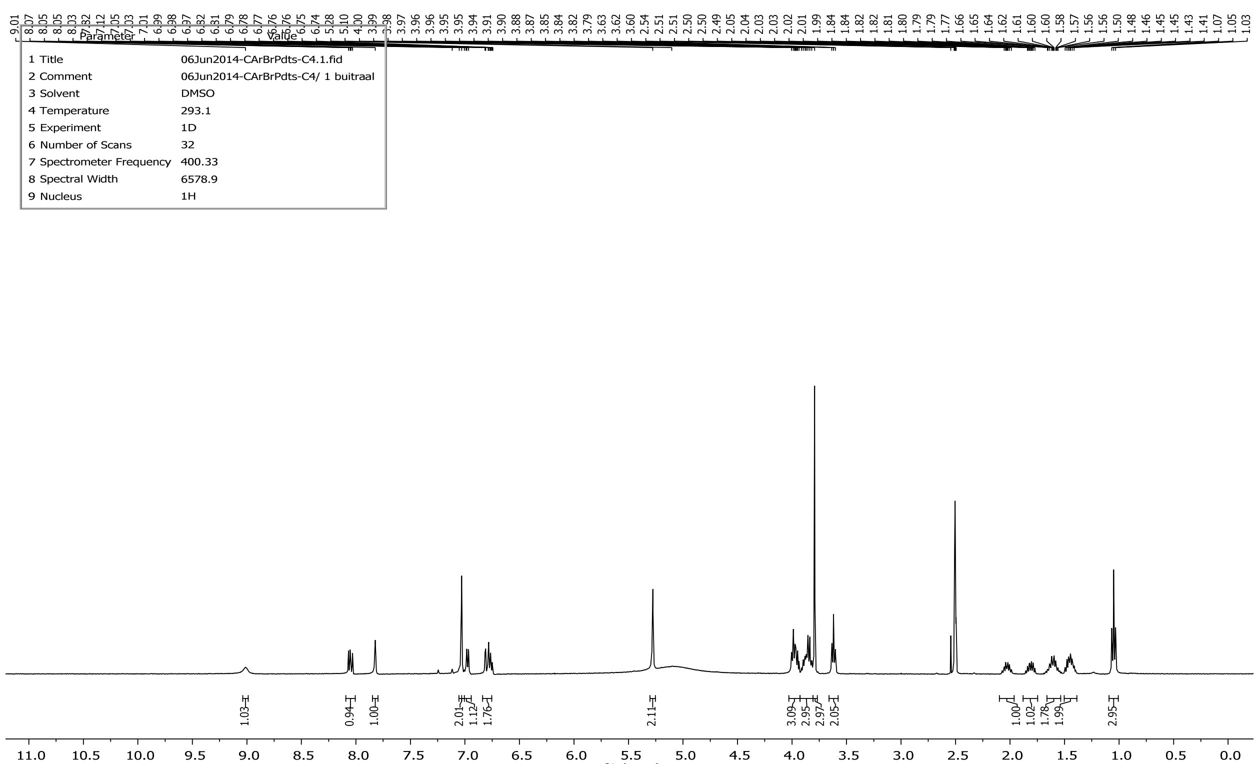
2 Comment 06Jun2014-CArBrPdts-C2/ 1 buitraal
3 Solvent DMSO
4 Temperature 293.0
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

C4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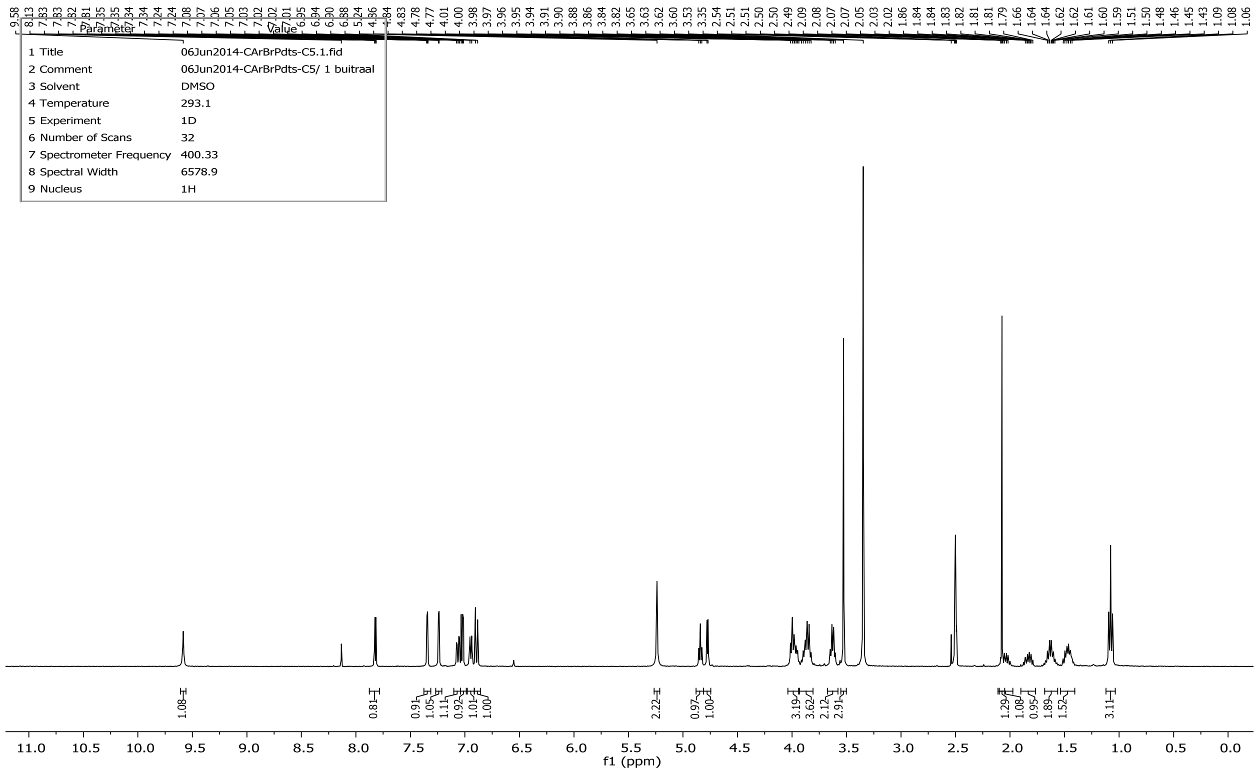
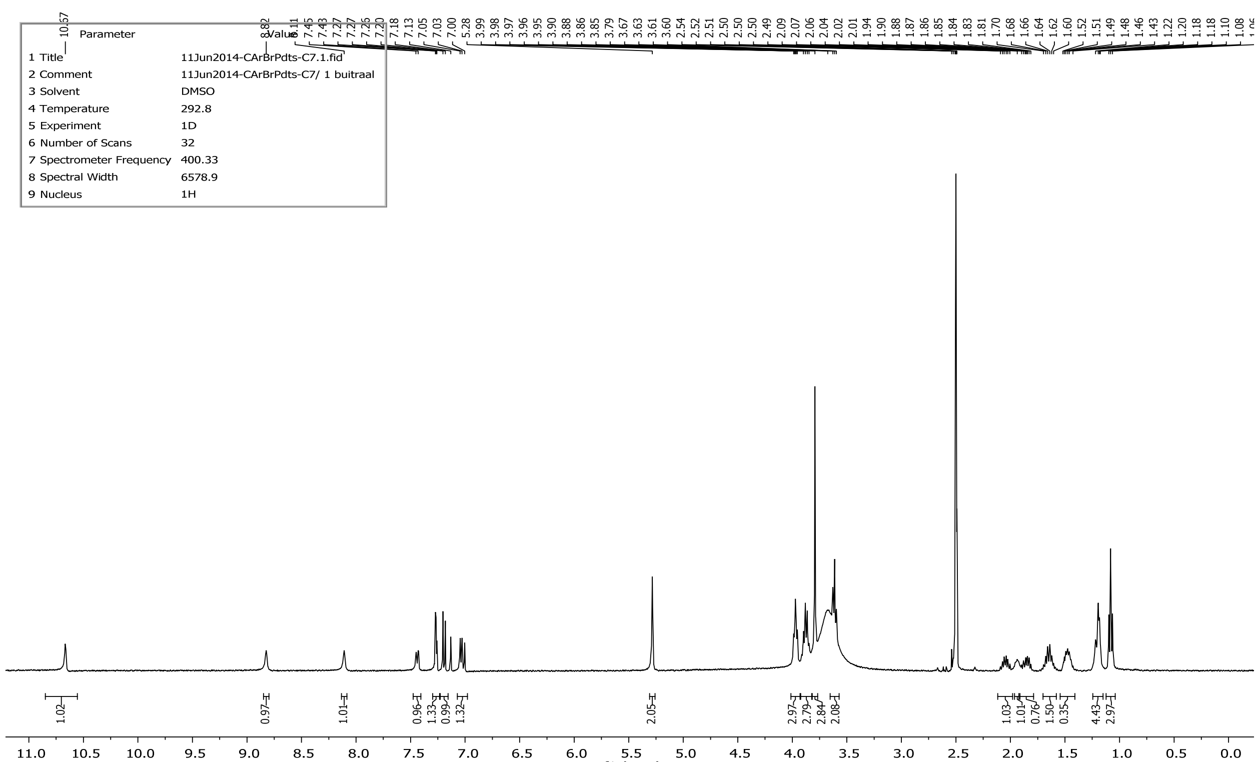
3 Solvent DMSO
4 Temperature 293.1
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

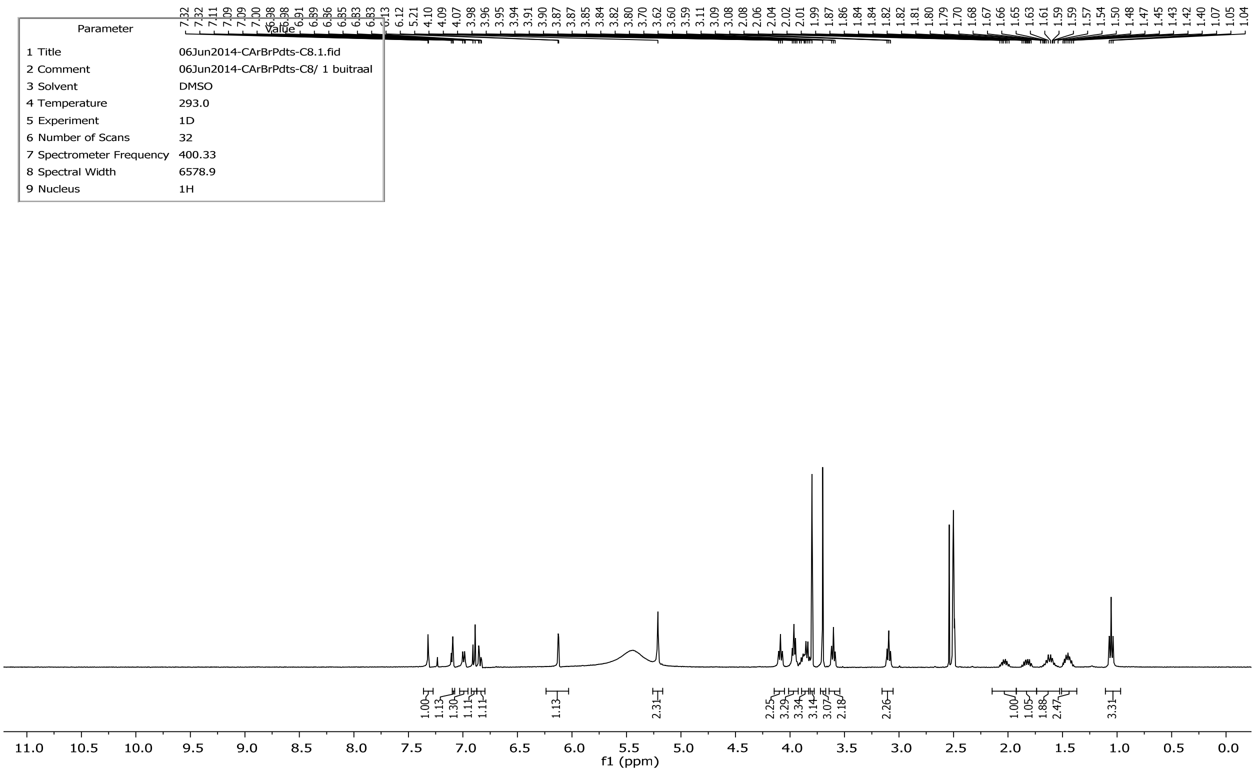
C5



C7

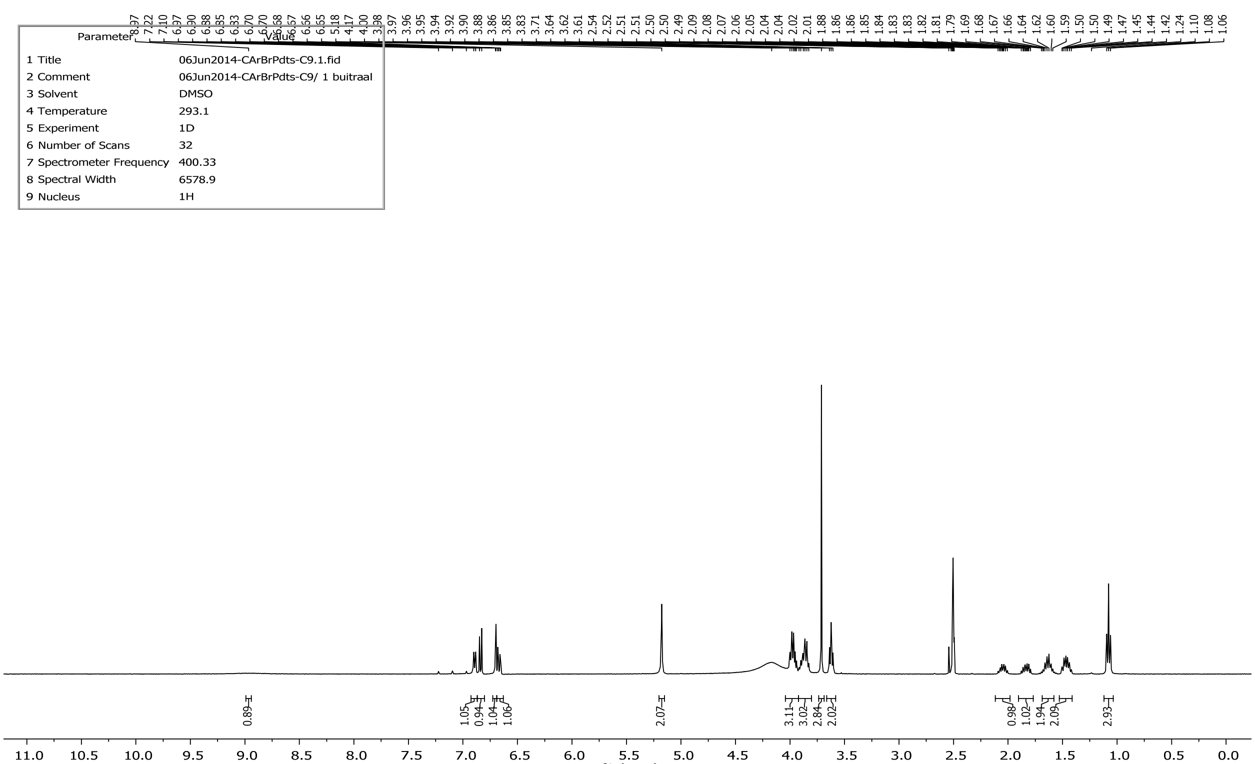


C8



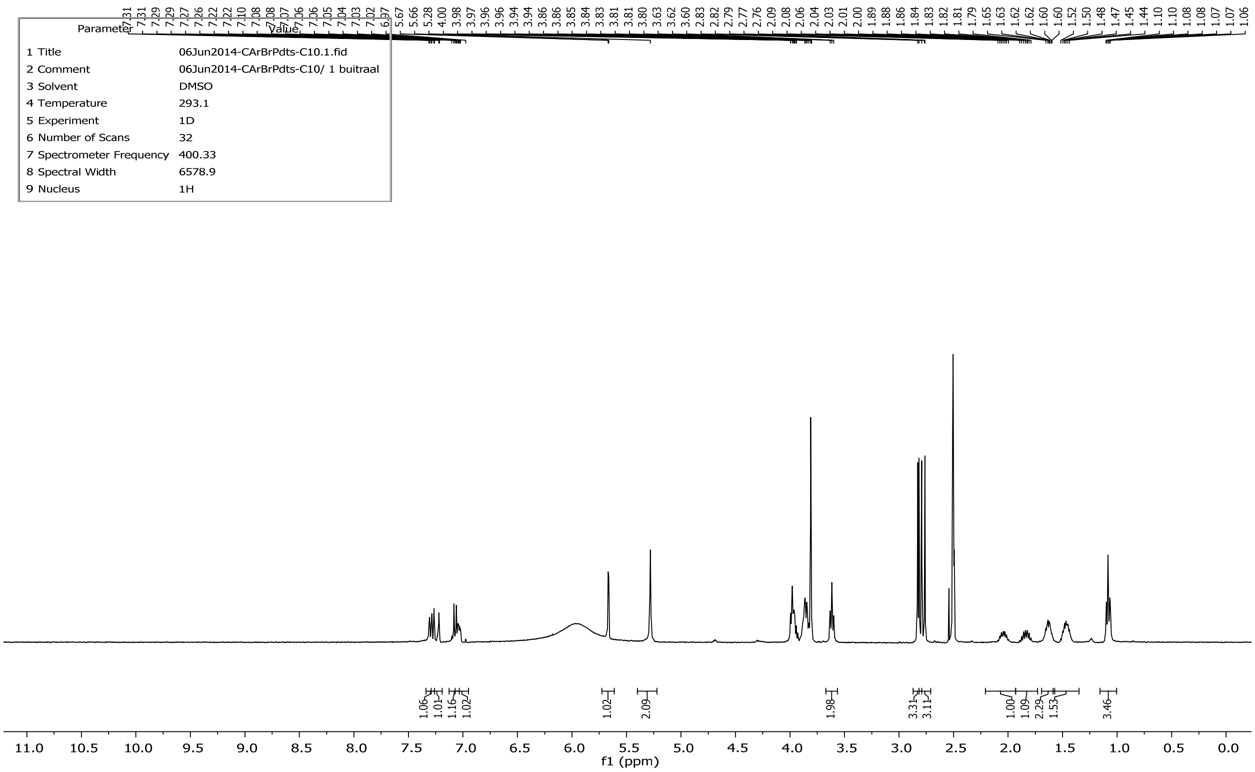
Parameter	Value
1 Title	06Jun2014-CArBrPdts-C8.1.fid
2 Comment	06Jun2014-CArBrPdts-C8/ 1 buitraal
3 Solvent	DMSO
4 Temperature	293.0
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	400.33
8 Spectral Width	6578.9
9 Nucleus	1H

C9



Parameter	Value
1 Title	06Jun2014-CArBrPdts-C9.1.fid
2 Comment	06Jun2014-CArBrPdts-C9/ 1 buitraal
3 Solvent	DMSO
4 Temperature	293.1
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	400.33
8 Spectral Width	6578.9
9 Nucleus	1H

C10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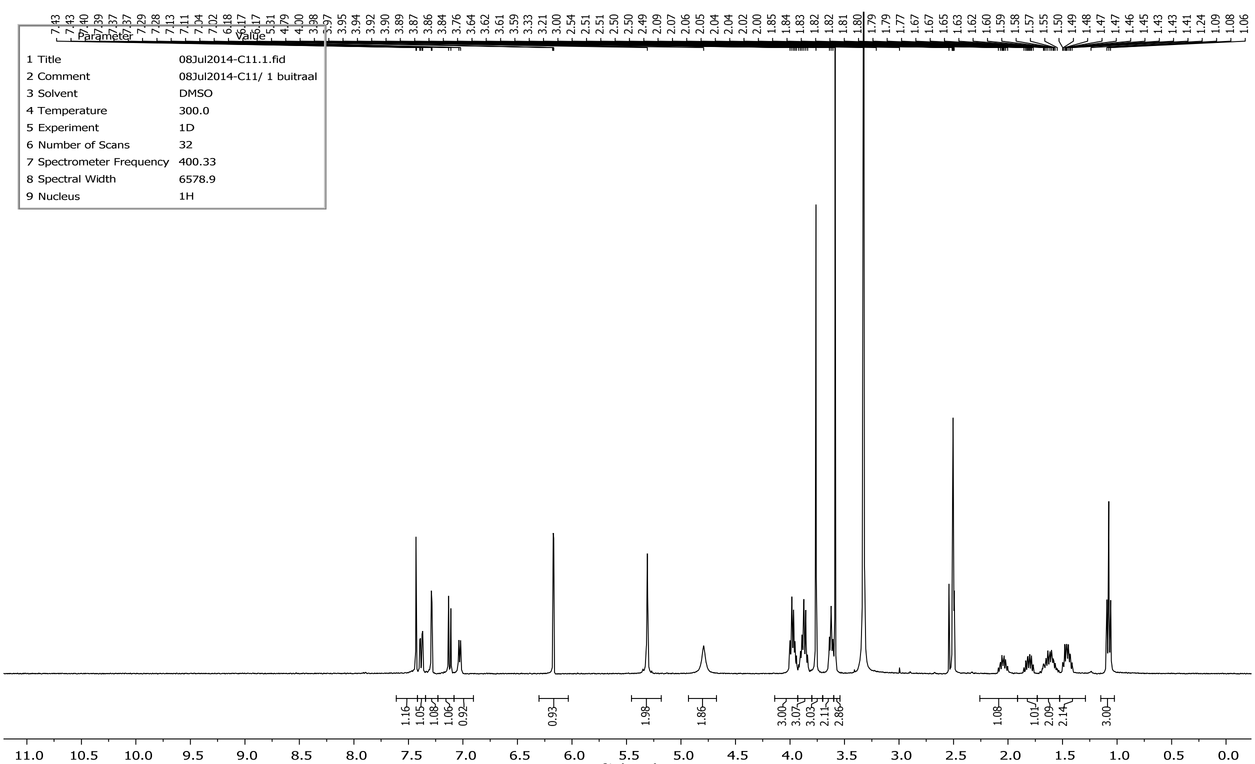
2 Comment 06Jun2014-CArBrPdts-C10/ 1 buitraal
3 Solvent DMSO
4 Temperature 293.1
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

C11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2 Comment 08Jul2014-C11/ 1 buitraal
3 Solvent DMSO
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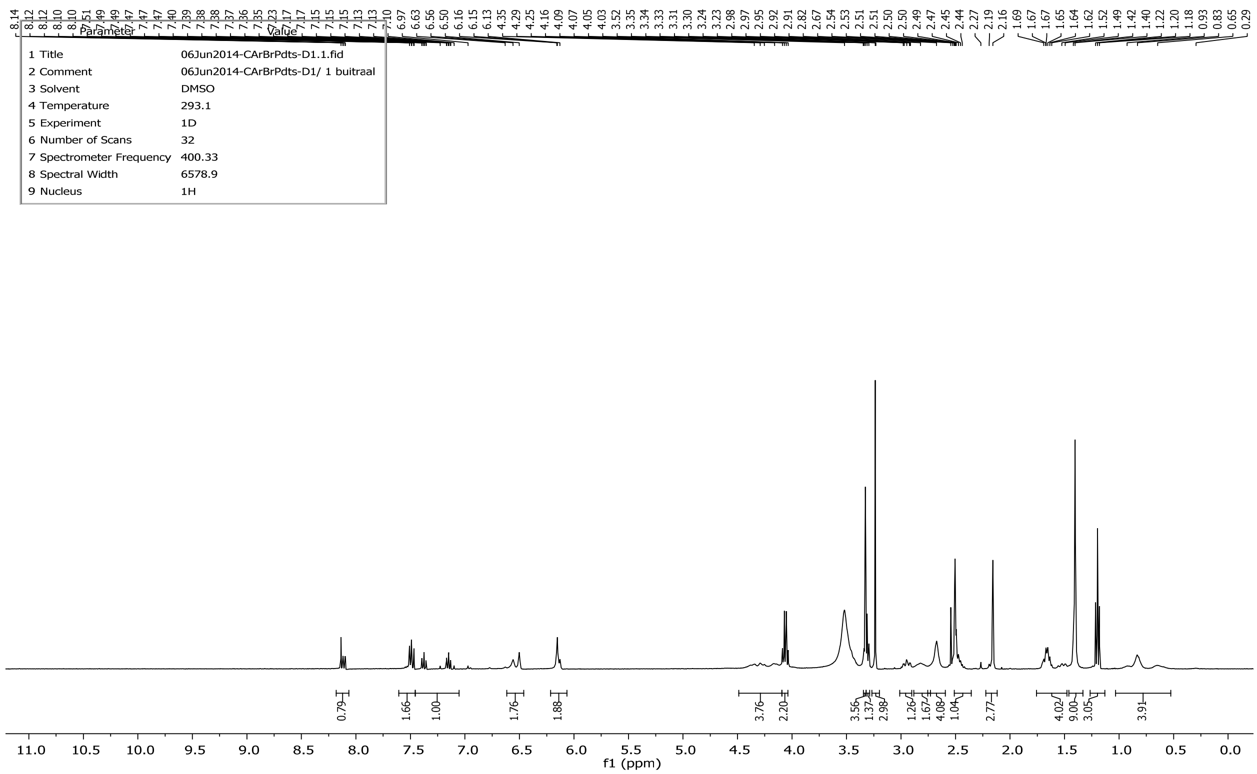
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

D1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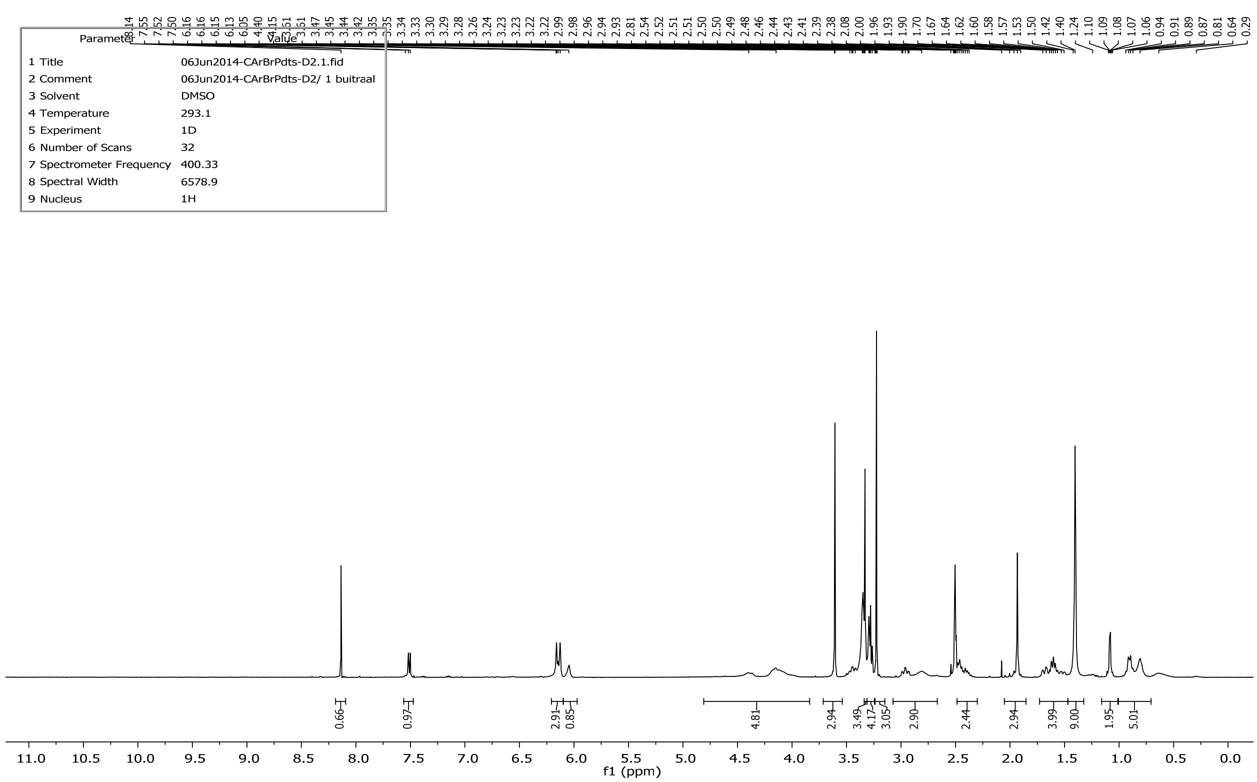
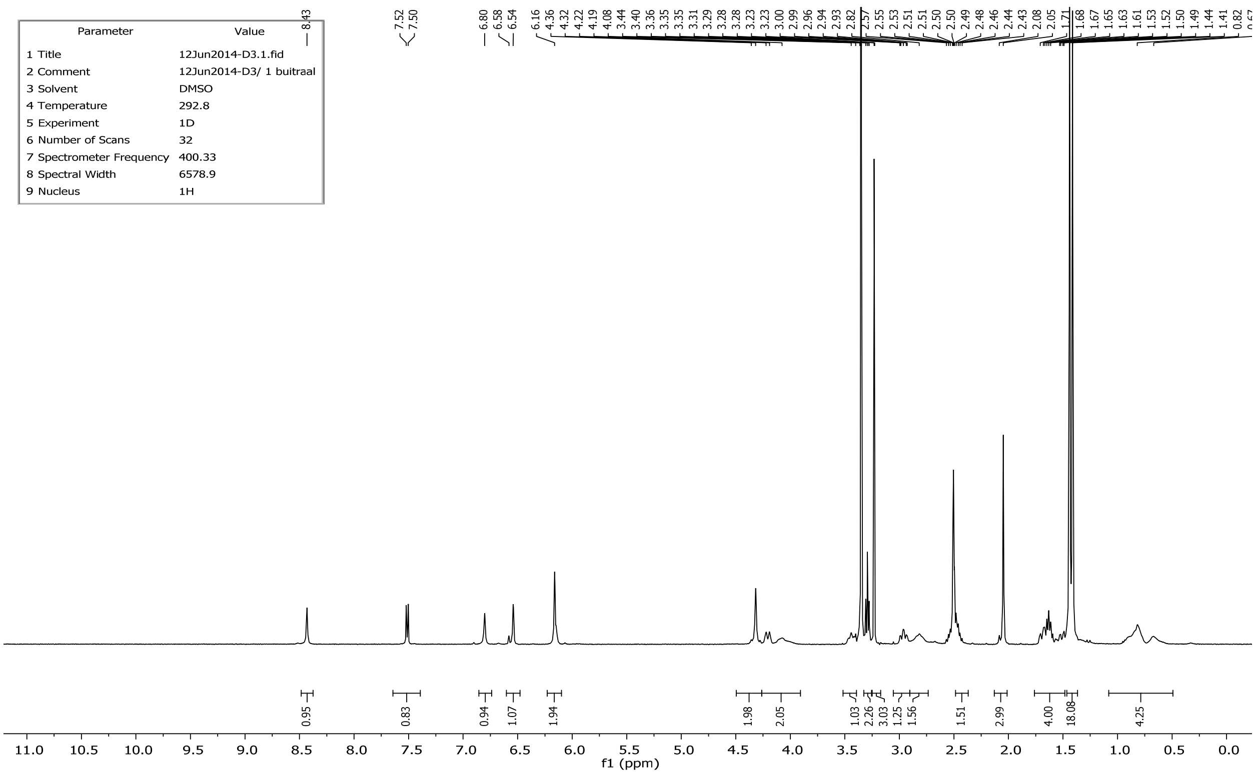
2 Comment 06Jun2014-CArBrPdts-D1/ 1 buitraal
3 Solvent DMSO
4 Temperature 293.1
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

D2


Parameter Value
1 Title 06Jun2014-CArBrPdts-D2.1.fid
2 Comment 06Jun2014-CArBrPdts-D2/ 1 buitraal
3 Solvent DMSO
4 Temperature 293.1
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

D3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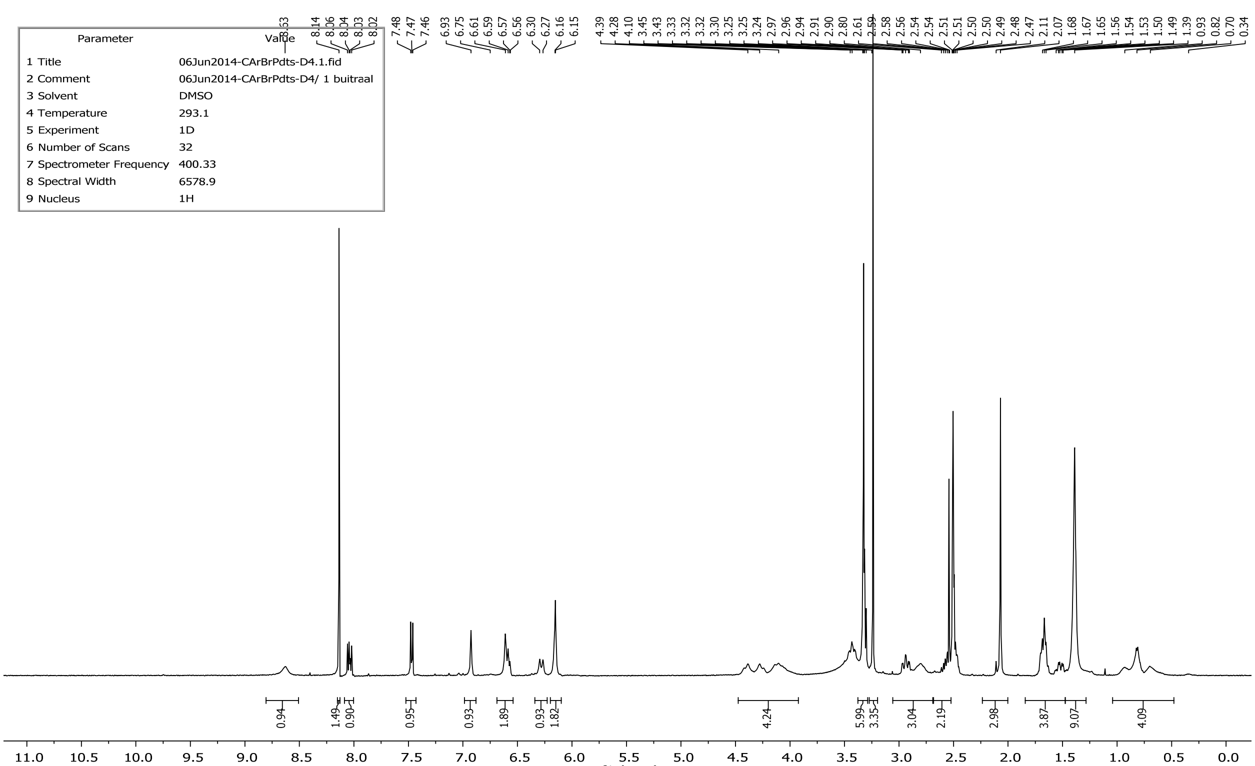
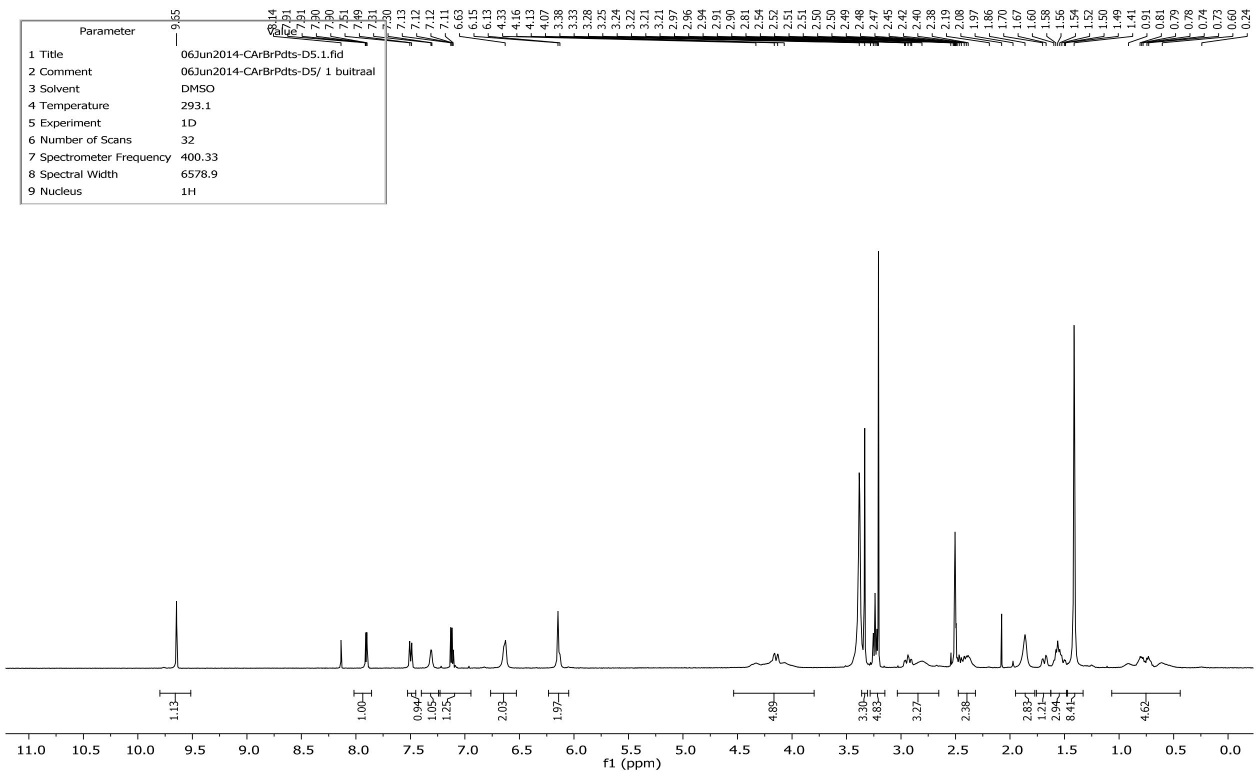
1 Title 12Jun2014-D3.1.fid
2 Comment 12Jun2014-D3/ 1 buitraal
3 Solvent DMSO
4 Temperature 292.8
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

D4


Parameter Value
1 Title 06Jun2014-CArBrPdts-D4.1.fid
2 Comment 06Jun2014-CArBrPdts-D4/ 1 buitraal
3 Solvent DMSO
4 Temperature 293.1
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

D5



Parameter	Value
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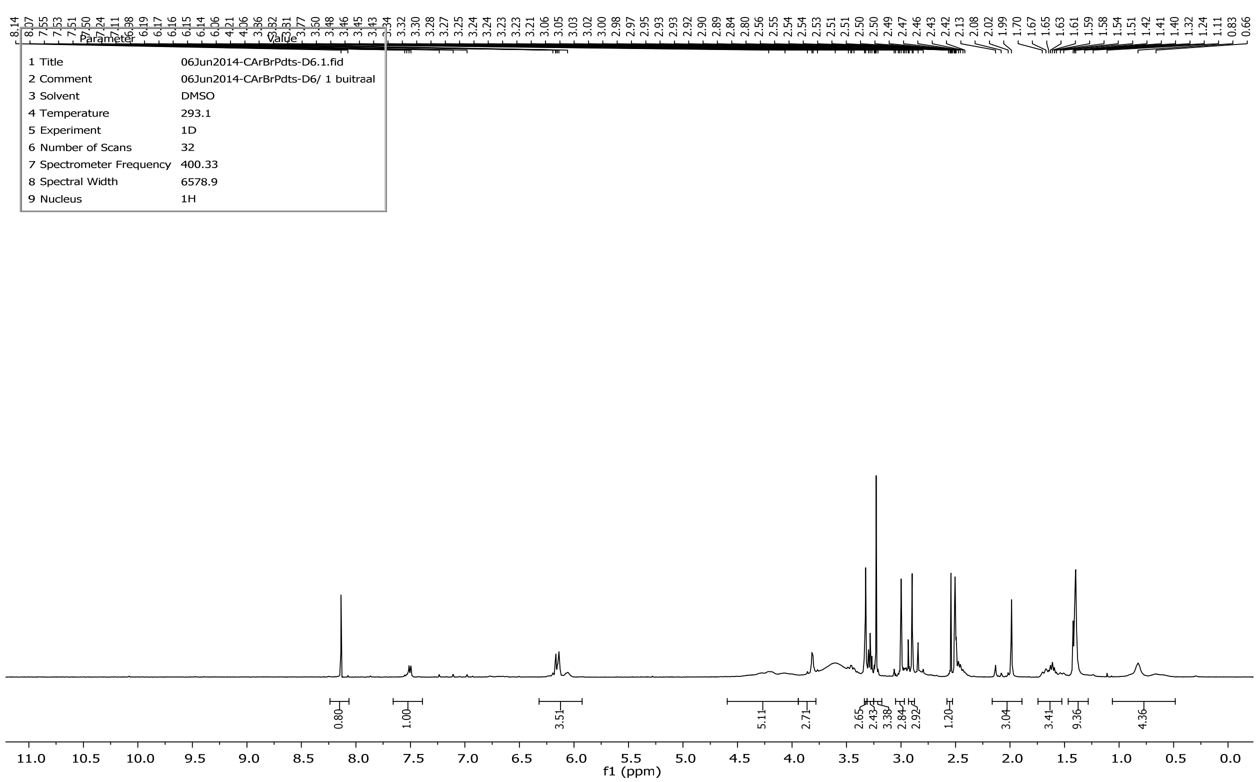
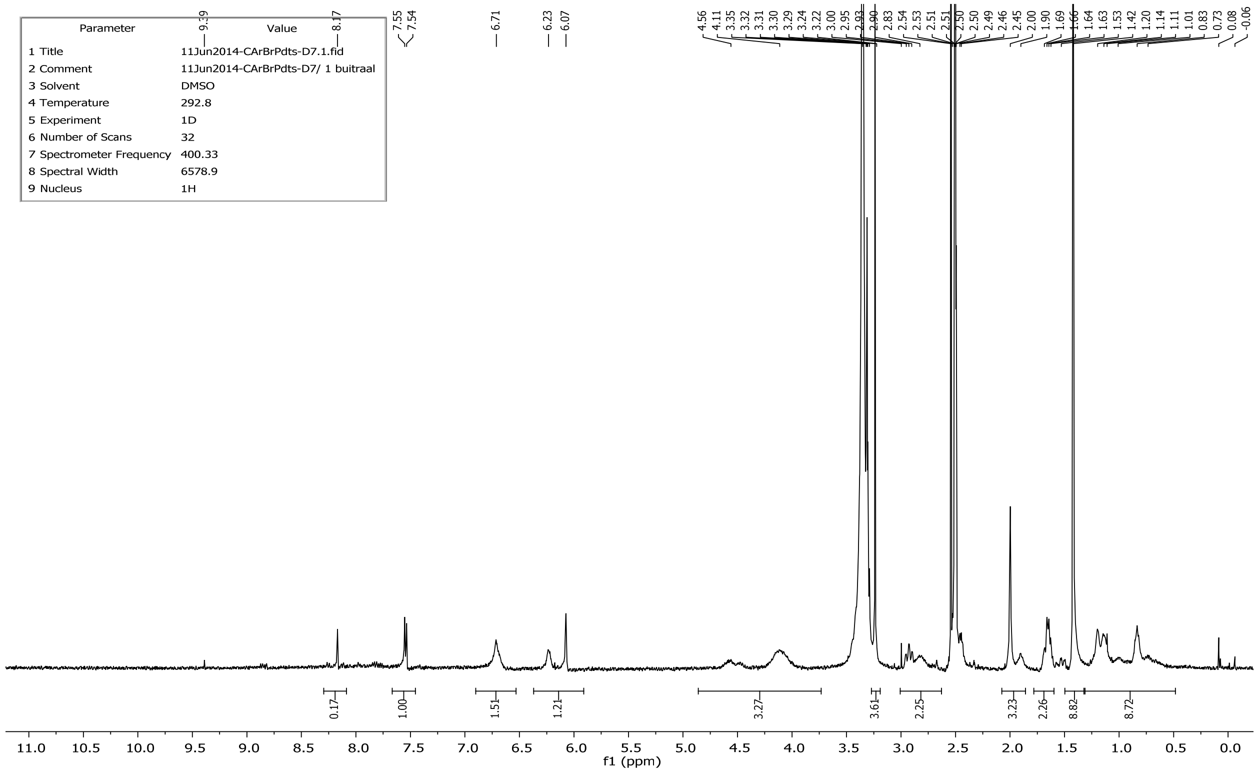
2 Comment	06Jun2014-CArBrPdts-D5/ 1 buitraal
3 Solvent	DMSO
4 Temperature	293.1
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	400.33
8 Spectral Width	6578.9
9 Nucleus	1H

D6



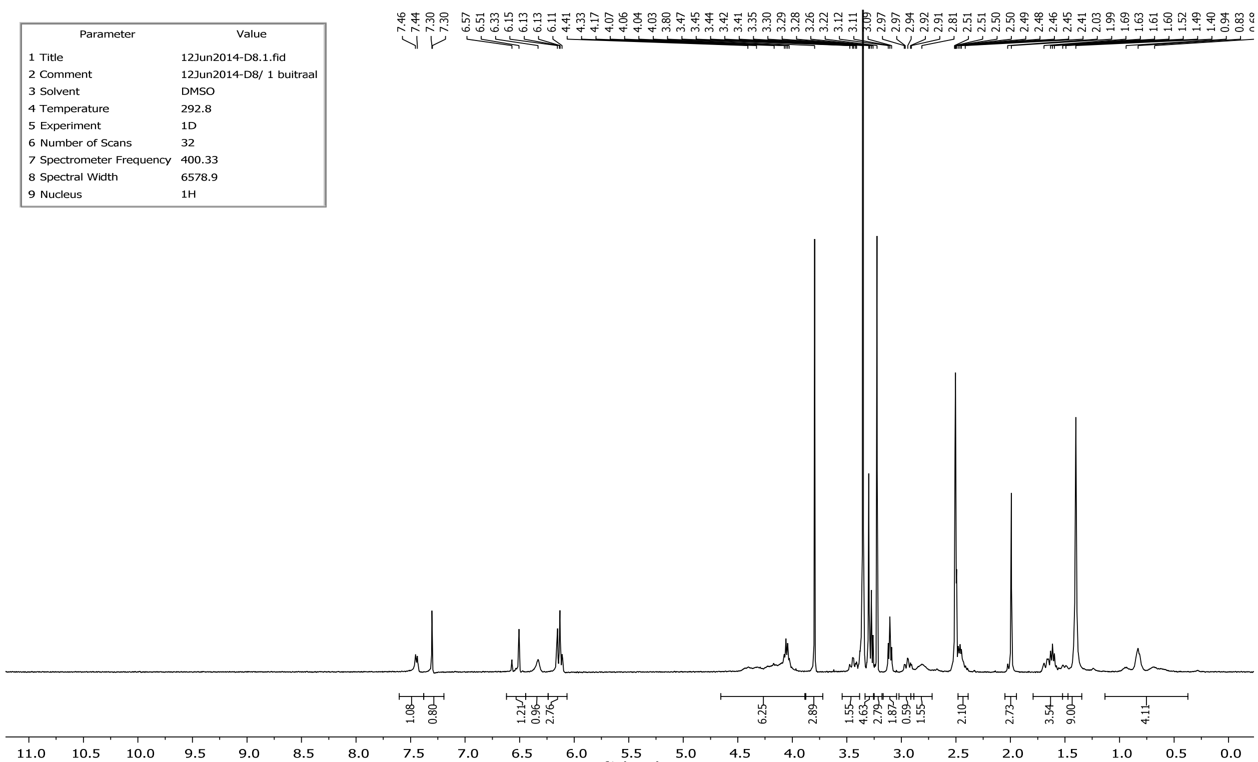
Parameter	Value
1 Title	06Jun2014-CArBrPdts-D6.1.fid
2 Comment	06Jun2014-CArBrPdts-D6/ 1 buitraal
3 Solvent	DMSO
4 Temperature	293.1
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	400.33
8 Spectral Width	6578.9
9 Nucleus	1H

D7



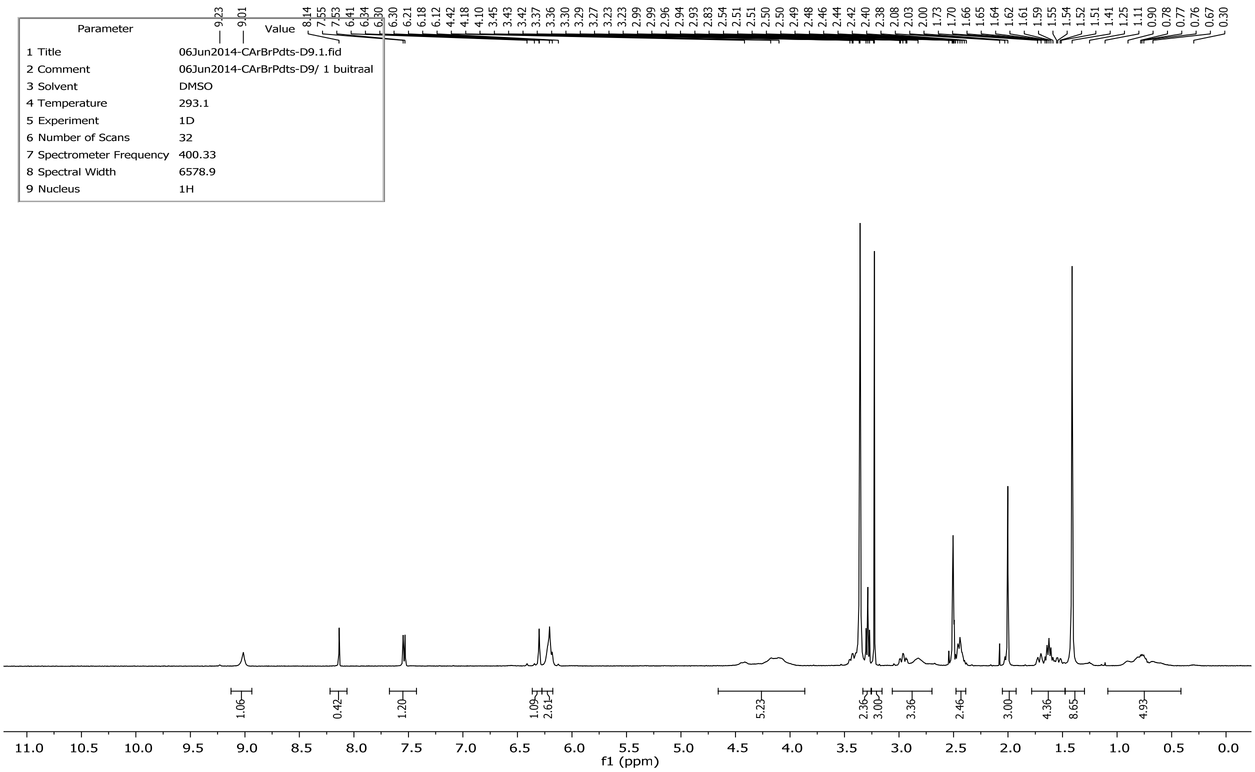
Parameter	Value
1 Title	11Jun2014-CArBrPdts-D7.1.fid
2 Comment	11Jun2014-CArBrPdts-D7/ 1 buitraal
3 Solvent	DMSO
4 Temperature	292.8
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	400.33
8 Spectral Width	6578.9
9 Nucleus	1H

D8

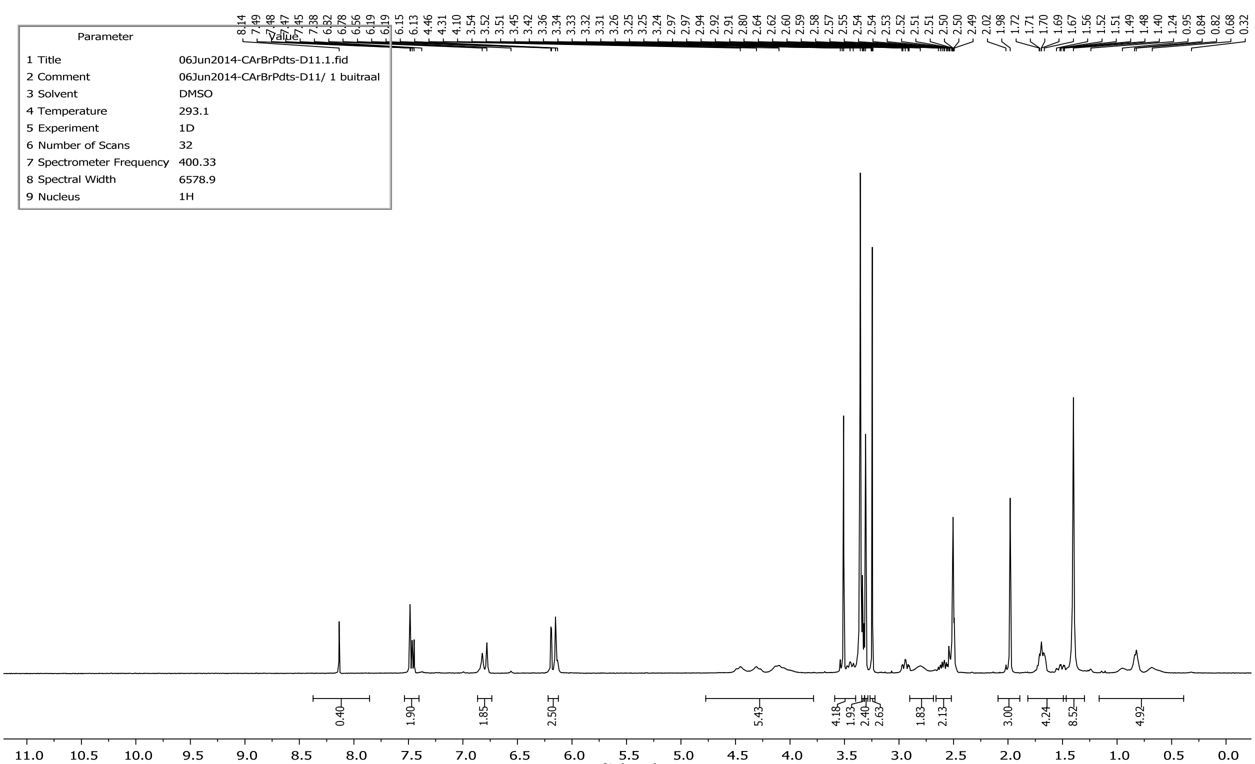


Parameter	Value
1 Title	12Jun2014-D8.1.fid
2 Comment	12Jun2014-D8/ 1 buitraal
3 Solvent	DMSO
4 Temperature	292.8
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	400.33
8 Spectral Width	6578.9
9 Nucleus	1H

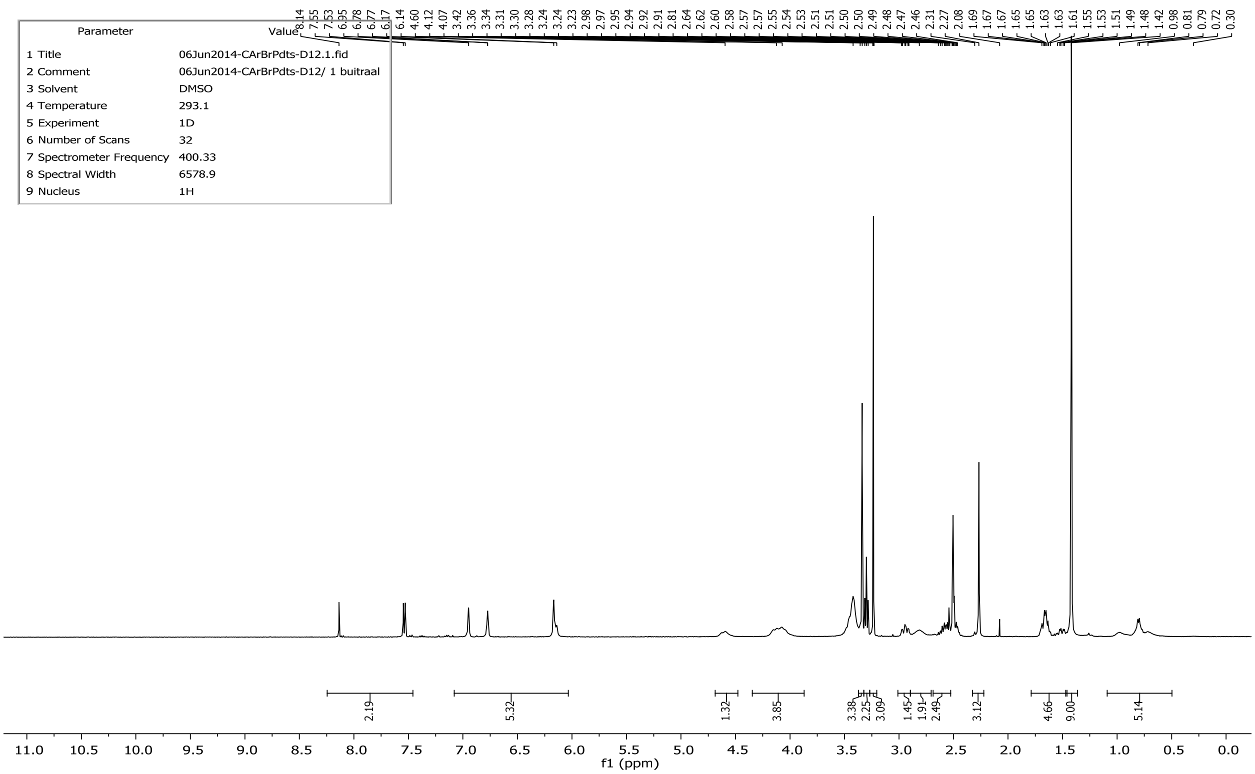
D9


Parameter Value
1 Title 06Jun2014-CArBrPdts-D9.1.fid
2 Comment 06Jun2014-CArBrPdts-D9/ 1 buitraal
3 Solvent DMSO
4 Temperature 293.1
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

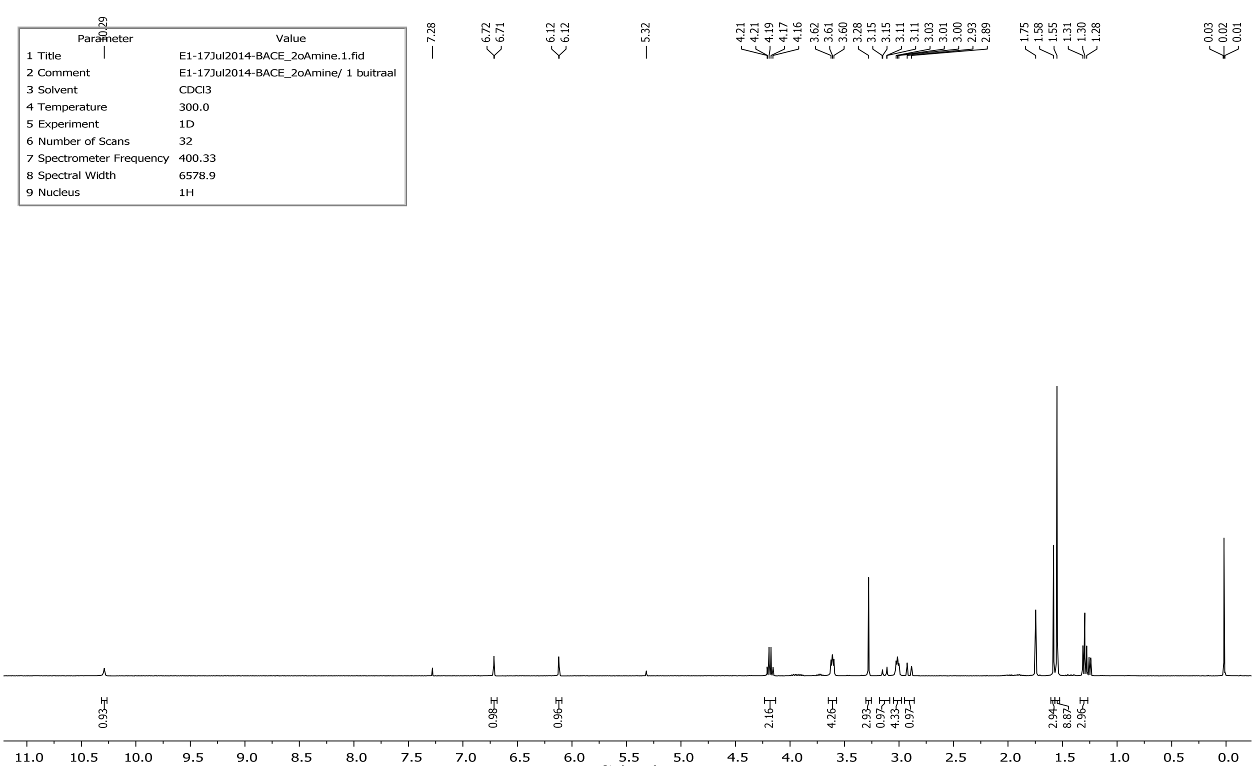
D11


Parameter Value
1 Title 06Jun2014-CArBrPdts-D11.1.fid
2 Comment 06Jun2014-CArBrPdts-D11/ 1 buitraal
3 Solvent DMSO
4 Temperature 293.1
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

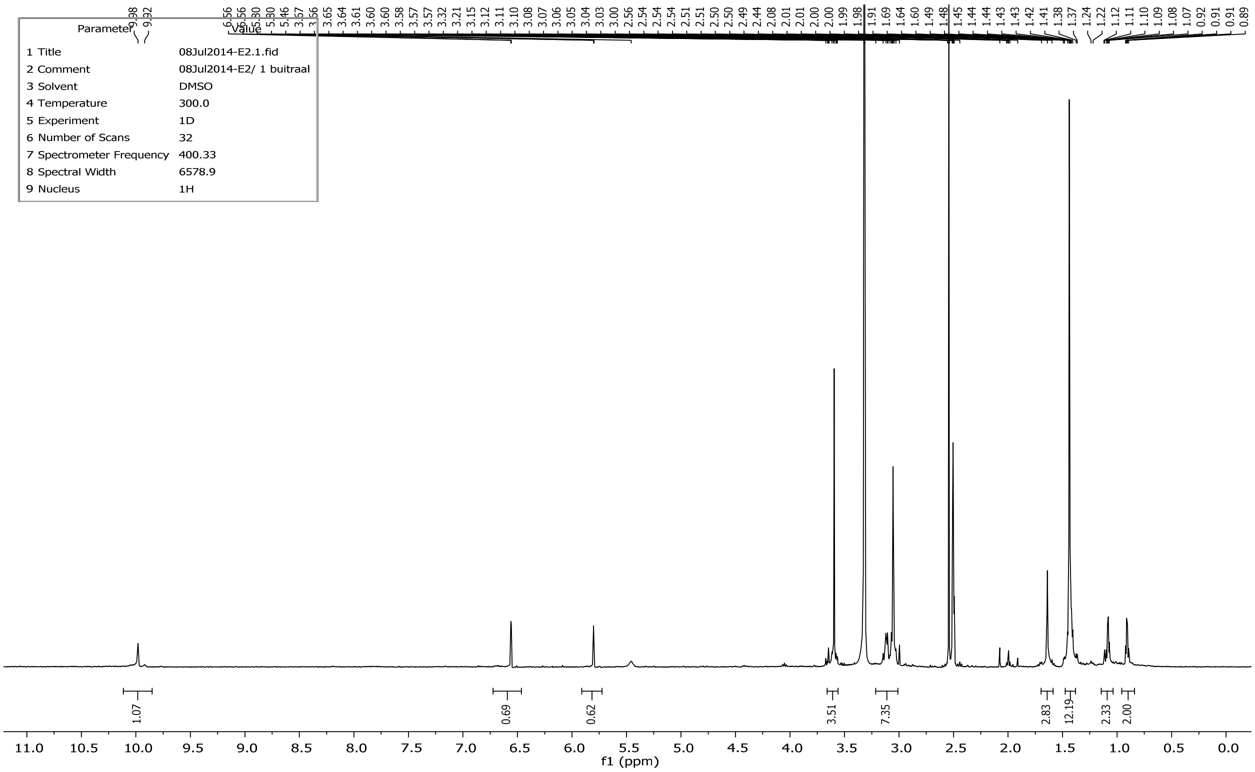
D12


Parameter
Value
1 Title
06Jun2014-CArBrPdts-D12.1.fid
2 Comment
06Jun2014-CArBrPdts-D12/ 1 buitraal
3 Solvent
DMSO
4 Temperature
293.1
5 Experiment
1D
6 Number of Scans
32
7 Spectrometer Frequency
400.33
8 Spectral Width
6578.9
9 Nucleus
1H
f1 (ppm)

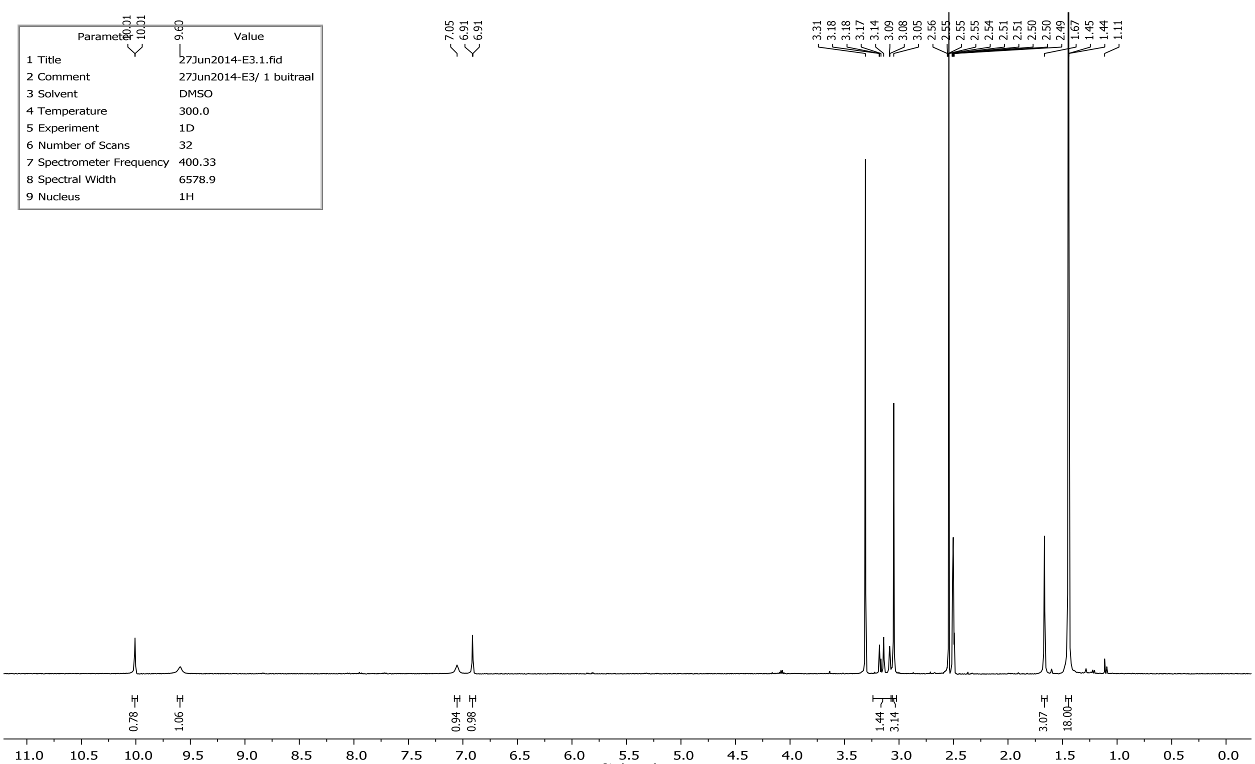
E1


Parameter
Value
1 Title
E1-17Jul2014-BACE_2oAmine.1.fid
2 Comment
E1-17Jul2014-BACE_2oAmine/ 1 buitraal
3 Solvent
CDCl3
4 Temperature
300.0
5 Experiment
1D
6 Number of Scans
32
7 Spectrometer Frequency
400.33
8 Spectral Width
6578.9
9 Nucleus
1H
f1 (ppm)

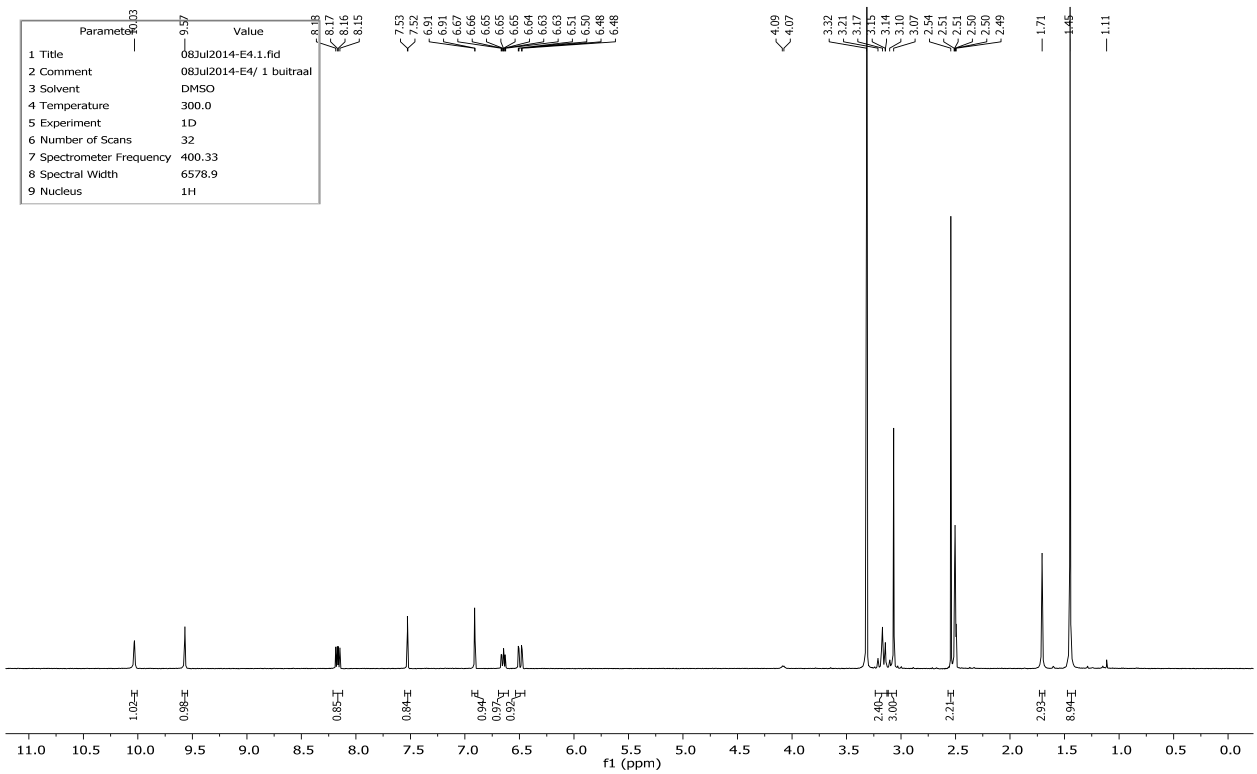
E2


Parameter
Value
1 Title 08Jul2014-E2.1.fid
2 Comment 08Jul2014-E2/ 1 buitraal
3 Solvent DMSO
4 Temperature 300.0
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
1.07
0.69
0.62
3.51
7.35
2.83
12.19
2.33
2.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

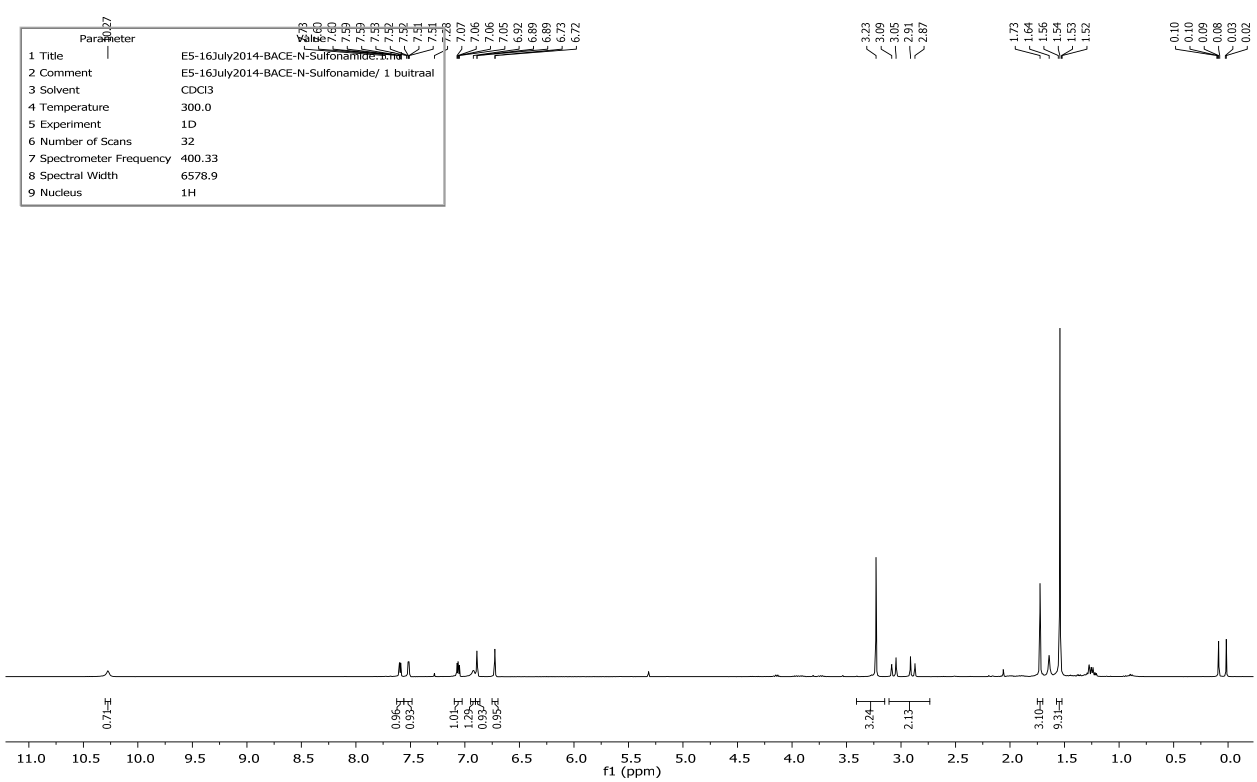
E3


Parameter
Value
1 Title 27Jun2014-E3.1.fid
2 Comment 27Jun2014-E3/ 1 buitraal
3 Solvent DMSO
4 Temperature 300.0
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
0.78
1.06
0.94
0.98
1.44
3.14
3.07
18.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

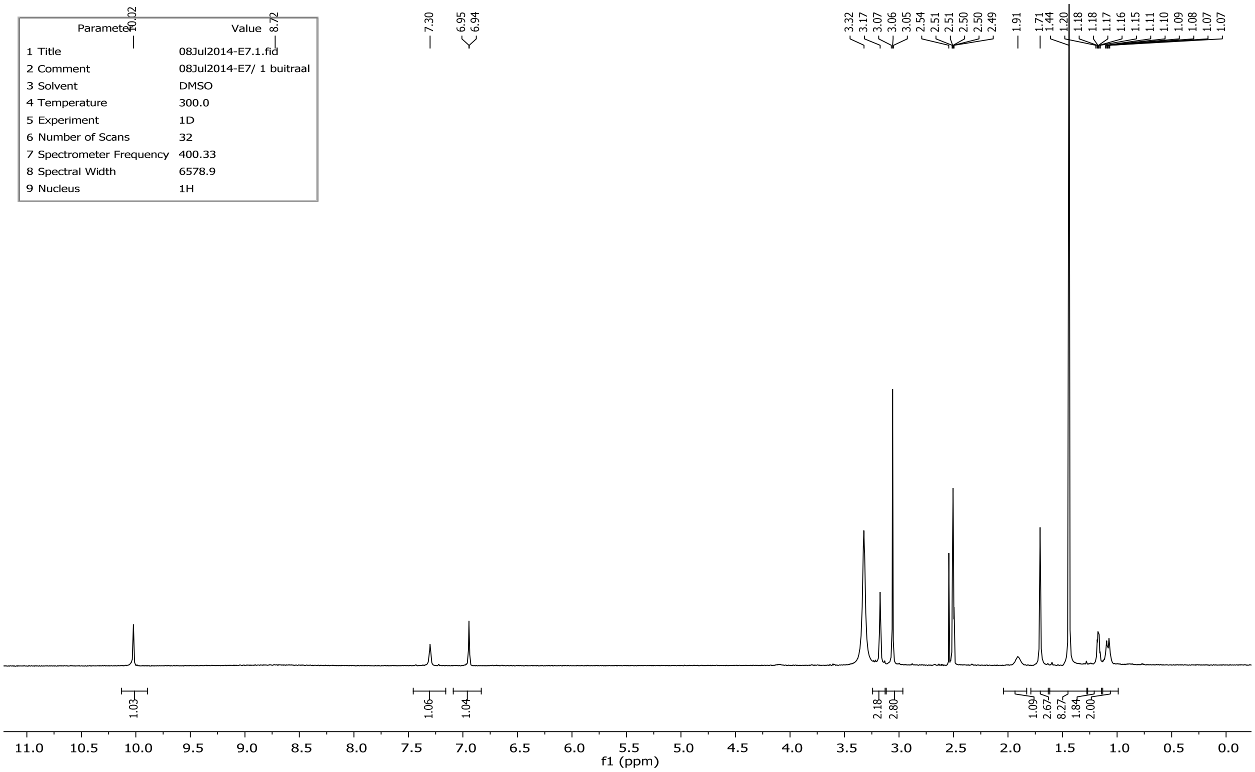
E4


Parameter Value
1 Title 08Jul2014-E4.1.fid
2 Comment 08Jul2014-E4/ 1 buitraal
3 Solvent DMSO
4 Temperature 300.0
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

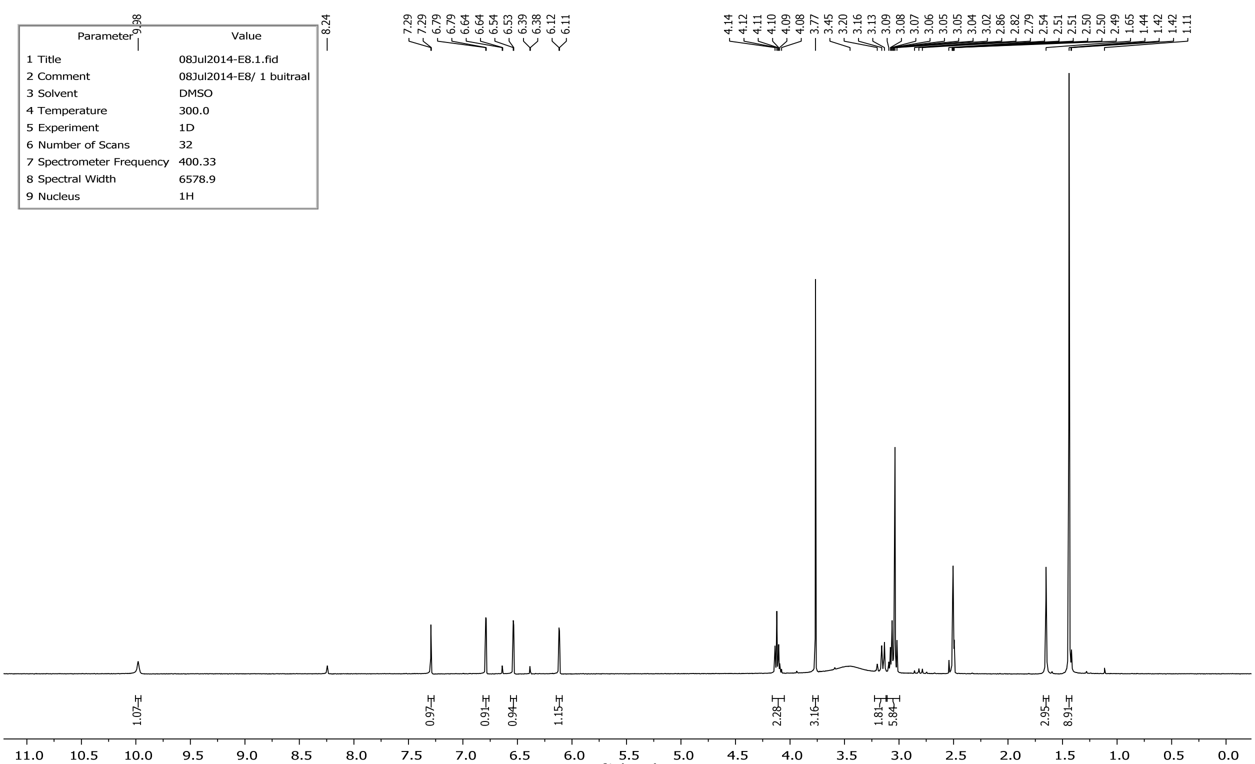
E5


Parameter Value
1 Title E5-16July2014-BACE-N-Sulfonamide.1.fid
2 Comment E5-16July2014-BACE-N-Sulfonamide/ 1 buitraal
3 Solvent CDCl3
4 Temperature 300.0
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

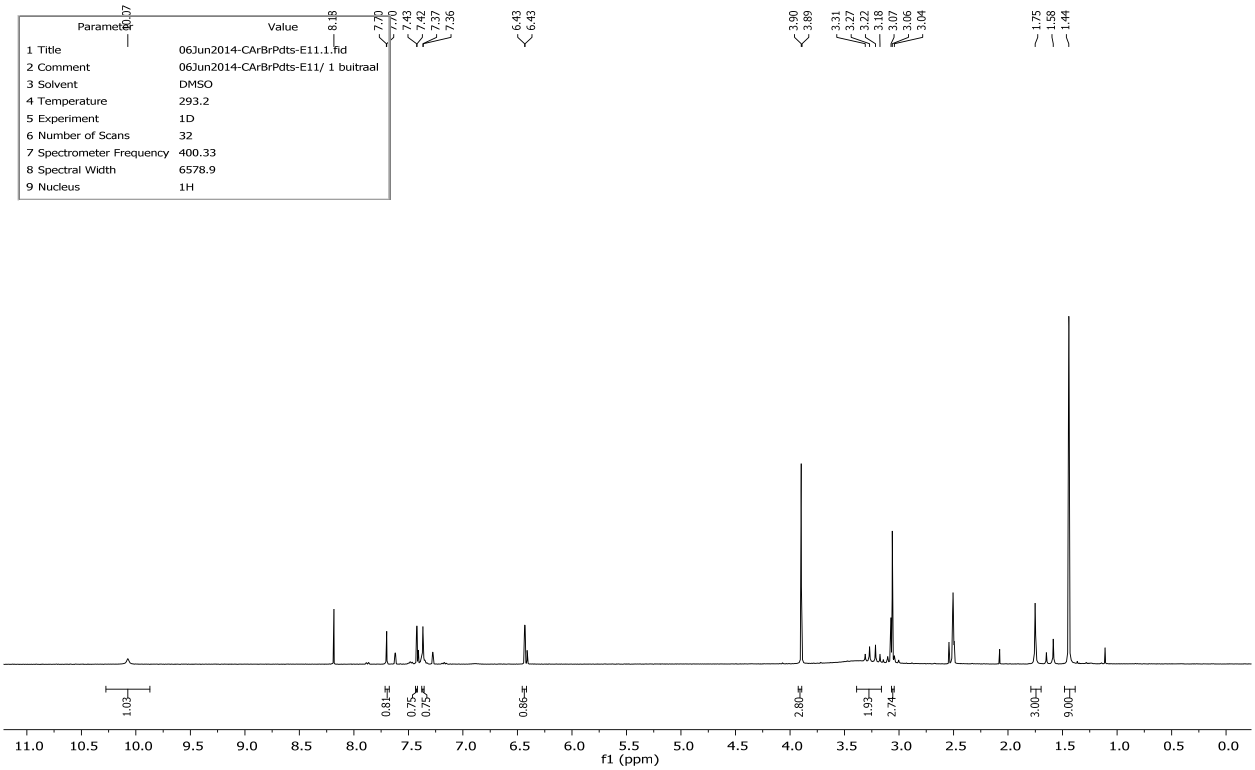
E7


Parameter Value
1 Title 08Jul2014-E7.1.fid
2 Comment 08Jul2014-E7/ 1 buitraal
3 Solvent DMSO
4 Temperature 300.0
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

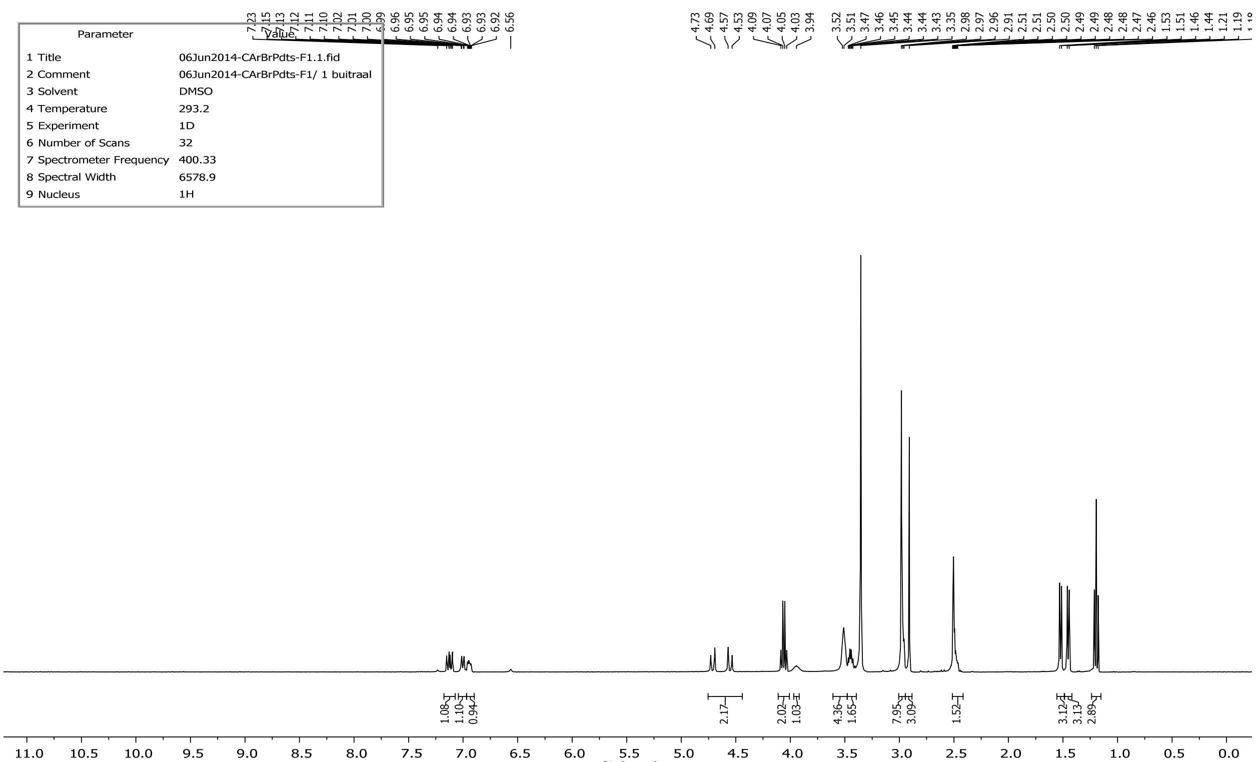
E8


Parameter Value
1 Title 08Jul2014-E8.1.fid
2 Comment 08Jul2014-E8/ 1 buitraal
3 Solvent DMSO
4 Temperature 300.0
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

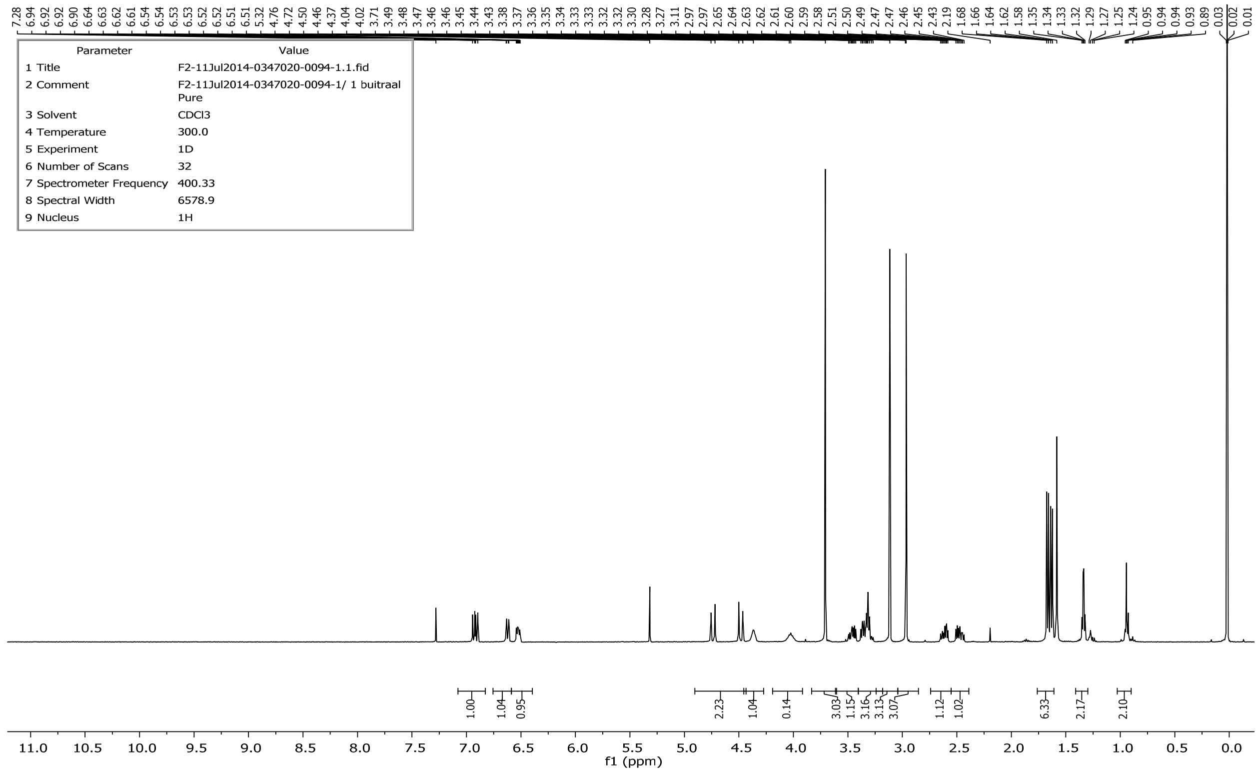
E11

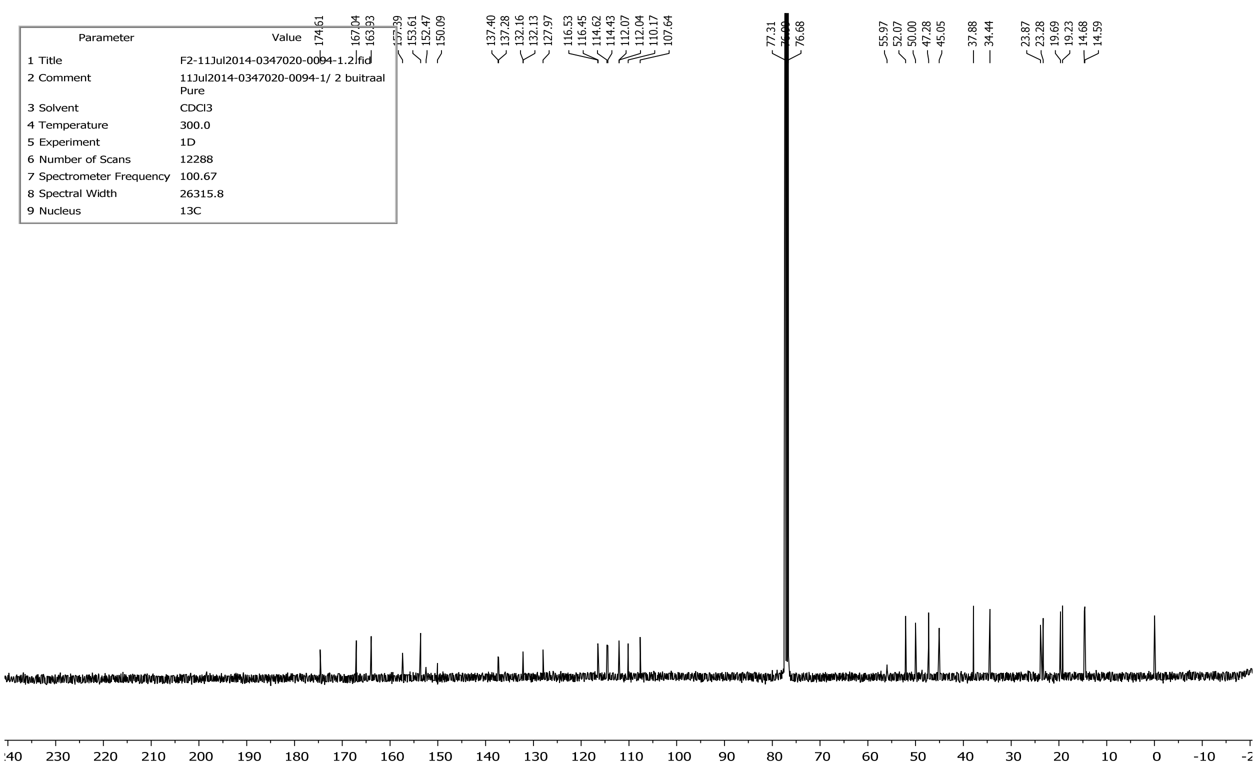

Parameter Value
1 Title 06Jun2014-CArBrPdts-E11.1.fid
2 Comment 06Jun2014-CArBrPdts-E11/ 1 buitraal
3 Solvent DMSO
4 Temperature 293.2
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

F1

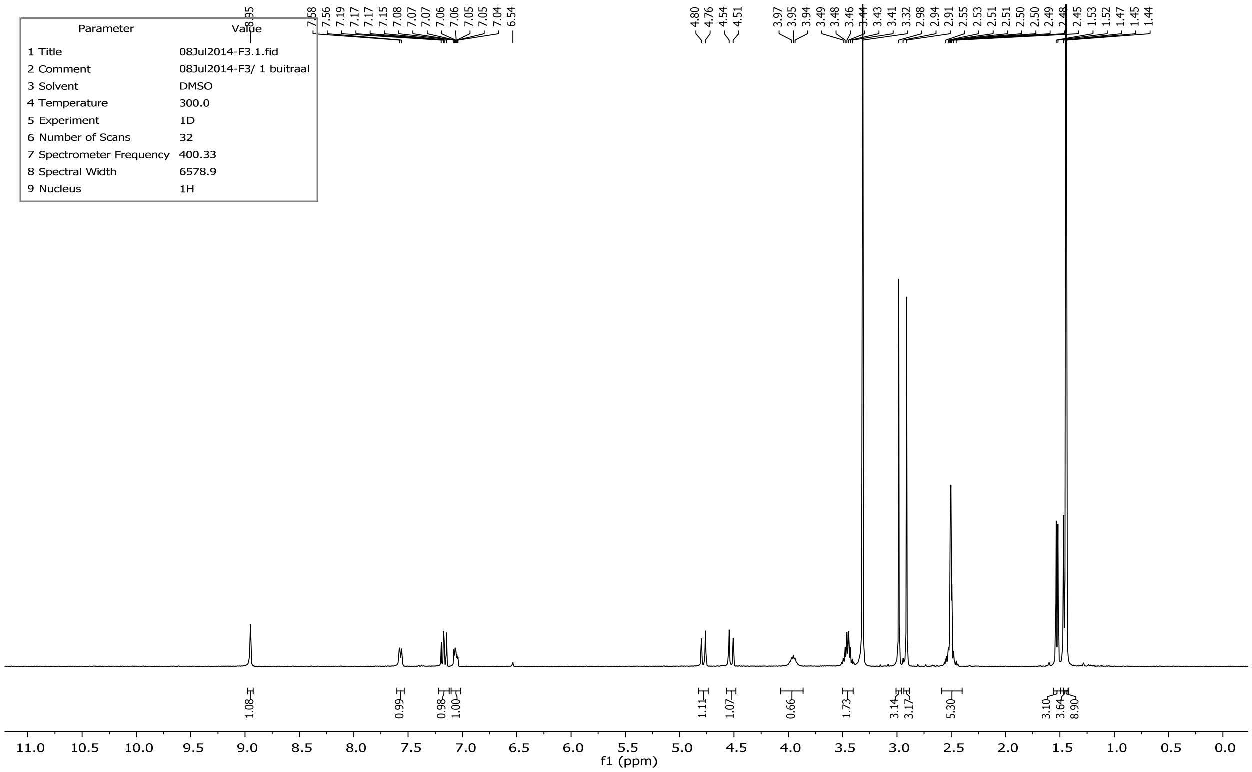

Parameter Value
1 Title 06Jun2014-CArBrPdts-F1.1.fid
2 Comment 06Jun2014-CArBrPdts-F1/ 1 buitraal
3 Solvent DMSO
4 Temperature 293.2
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

F2

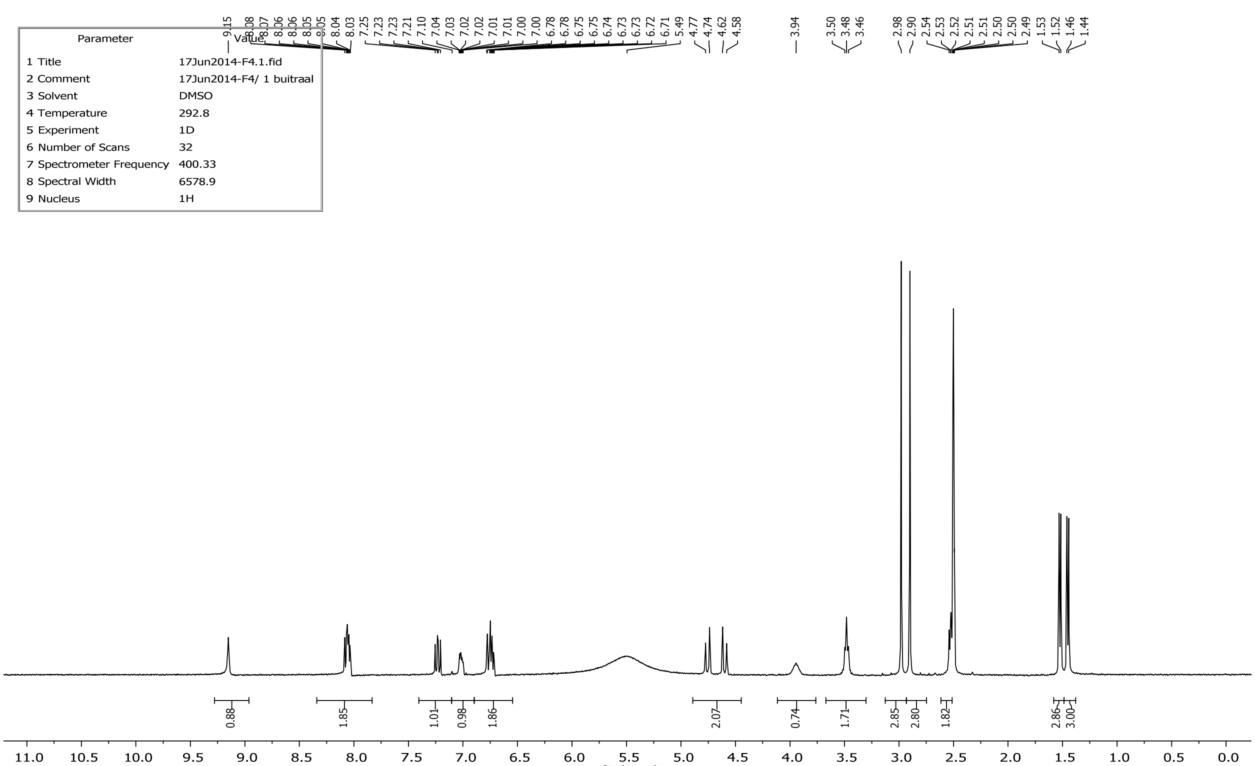

7.28 6.94 6.92 6.92 6.90 6.64 6.63 6.62 6.61 6.54 6.54 6.53 6.53 6.52 6.52 6.51 6.51 5.32 4.76 4.72 4.50 4.46 4.37 4.04 4.02 3.71 3.49 3.48 3.47 3.46 3.46 3.45 3.44 3.43 3.38 3.37 3.36 3.35 3.34 3.33 3.33 3.32 3.32 3.30 3.28 3.27 3.11 2.97 2.65 2.64 2.63 2.62 2.61 2.60 2.59 2.58 2.51 2.50 2.49 2.47 2.47 2.46 2.45 2.43 2.19 1.68 1.66 1.64 1.62 1.58 1.35 1.34 1.33 1.32 1.29 1.27 1.25 1.24 0.95 0.94 0.94 0.93 0.89 0.03 0.02 0.01
Parameter | Value
1 Title | F2-11Jul2014-0347020-0094-1.1.fid
2 Comment | F2-11Jul2014-0347020-0094-1/ 1 buitraal Pure
3 Solvent | CDCl3
4 Temperature | 300.0
5 Experiment | 1D
6 Number of Scans | 32
7 Spectrometer Frequency | 400.33
8 Spectral Width | 6578.9
9 Nucleus | 1H
1.00 1.04 0.95 2.23 1.04 0.14 3.03 1.15 3.16 3.13 3.07 1.12 1.02 6.33 2.17 2.10
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


Parameter | Value
1 Title | F2-11Jul2014-0347020-0094-1.2.fid
2 Comment | 11Jul2014-0347020-0094-1/ 2 buitraal Pure
3 Solvent | CDCl3
4 Temperature | 300.0
5 Experiment | 1D
6 Number of Scans | 12288
7 Spectrometer Frequency | 100.67
8 Spectral Width | 26315.8
9 Nucleus | 13C
174.61 167.04 163.93 157.39 153.61 152.47 150.09 137.40 137.28 132.16 132.13 127.97 116.53 116.45 114.62 114.43 112.07 112.04 110.17 107.64 77.31 76.99 76.68 55.97 52.07 50.00 47.28 45.05 37.88 34.44 23.87 23.28 19.69 19.23 14.68 14.59
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

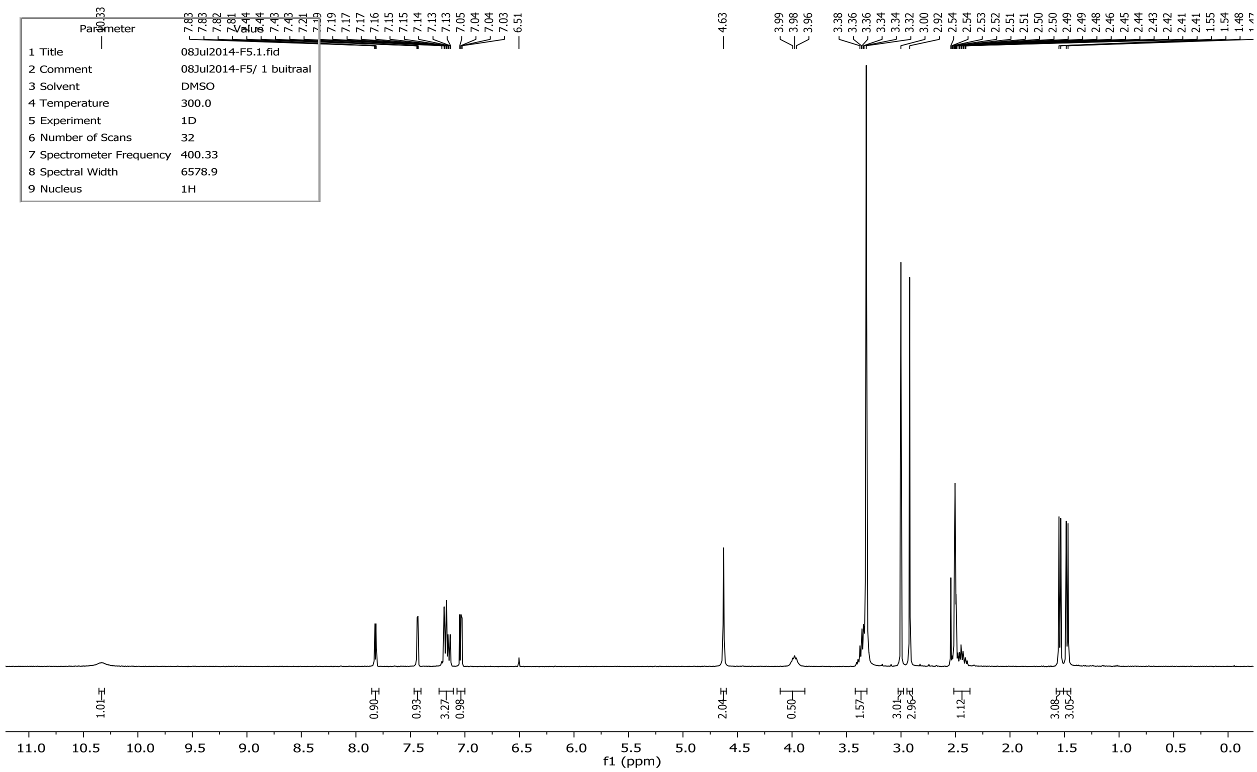
F3


Parameter
Value
1 Title
08Jul2014-F3.1.fid
2 Comment
08Jul2014-F3/ 1 buitraal
3 Solvent
DMSO
4 Temperature
300.0
5 Experiment
1D
6 Number of Scans
32
7 Spectrometer Frequency
400.33
8 Spectral Width
6578.9
9 Nucleus
1H
f1 (ppm)

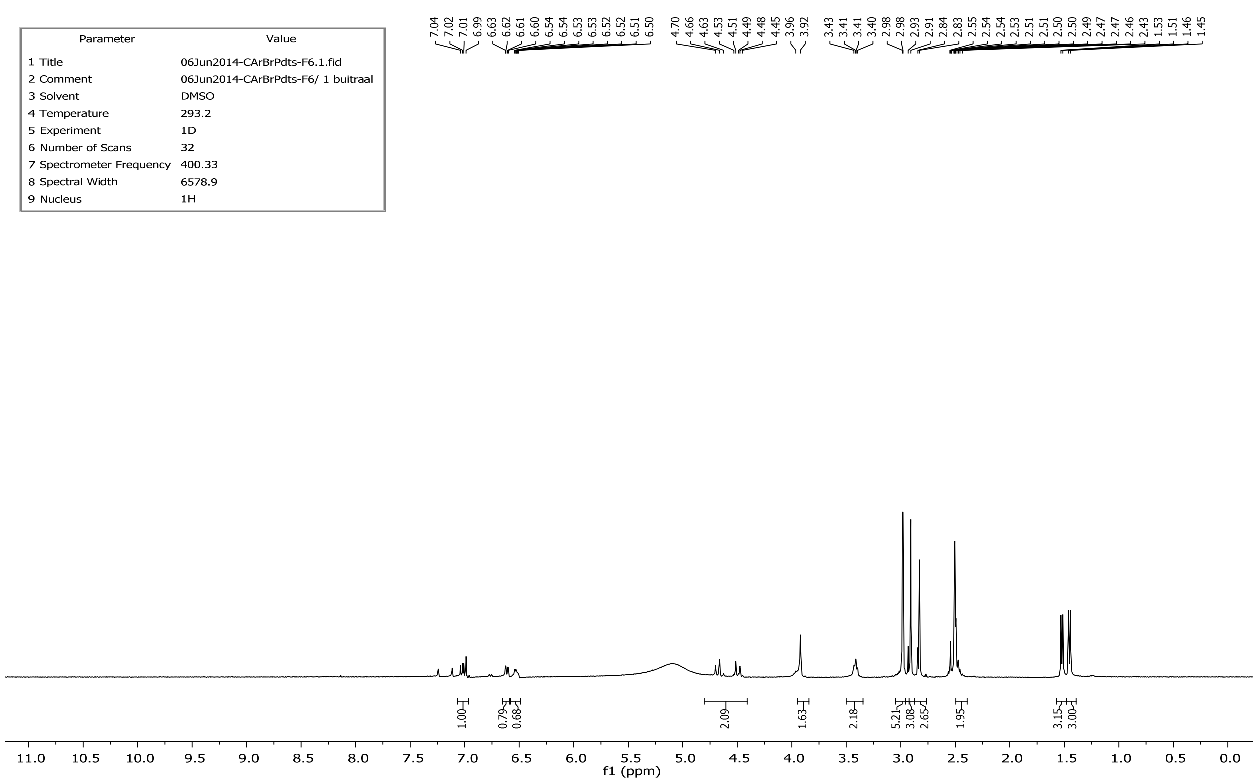
F4


Parameter
Value
1 Title
17Jun2014-F4.1.fid
2 Comment
17Jun2014-F4/ 1 buitraal
3 Solvent
DMSO
4 Temperature
292.8
5 Experiment
1D
6 Number of Scans
32
7 Spectrometer Frequency
400.33
8 Spectral Width
6578.9
9 Nucleus
1H
f1 (ppm)

F5

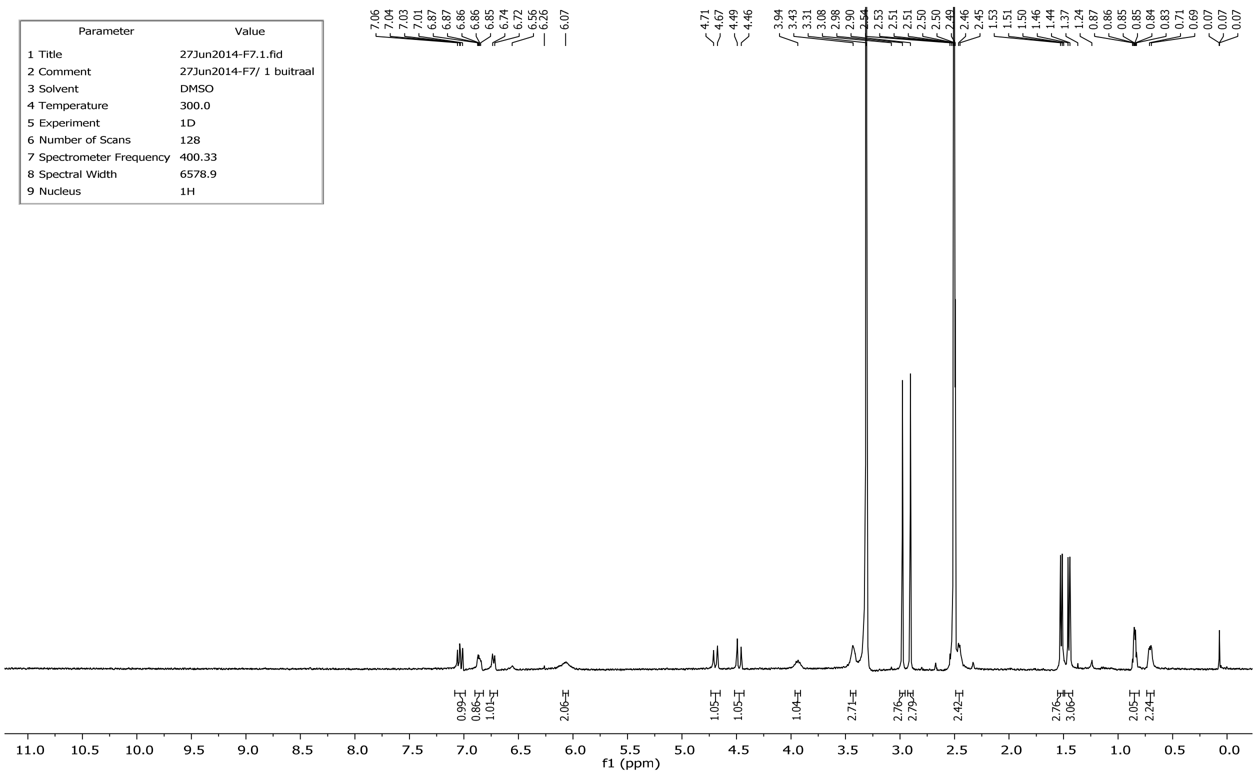

Parameter Value
1 Title 08Jul2014-F5.1.fid
2 Comment 08Jul2014-F5/ 1 buitraal
3 Solvent DMSO
4 Temperature 300.0
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

F6


Parameter Value
1 Title 06Jun2014-CArBrPdts-F6.1.fid
2 Comment 06Jun2014-CArBrPdts-F6/ 1 buitraal
3 Solvent DMSO
4 Temperature 293.2
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

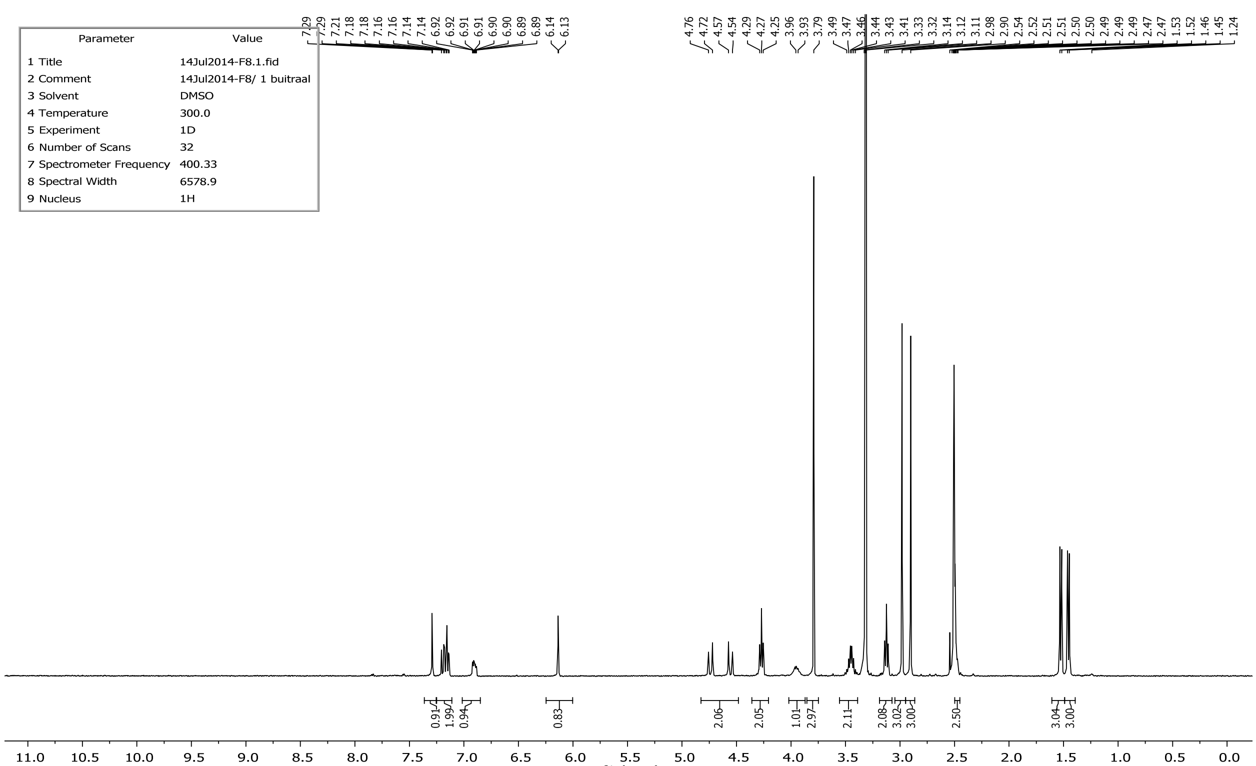
F7

Parameter	Value
1 Title	27Jun2014-F7.1.fid
2 Comment	27Jun2014-F7/ 1 buitraal
3 Solvent	DMSO
4 Temperature	300.0
5 Experiment	1D
6 Number of Scans	128
7 Spectrometer Frequency	400.33
8 Spectral Width	6578.9
9 Nucleus	1H

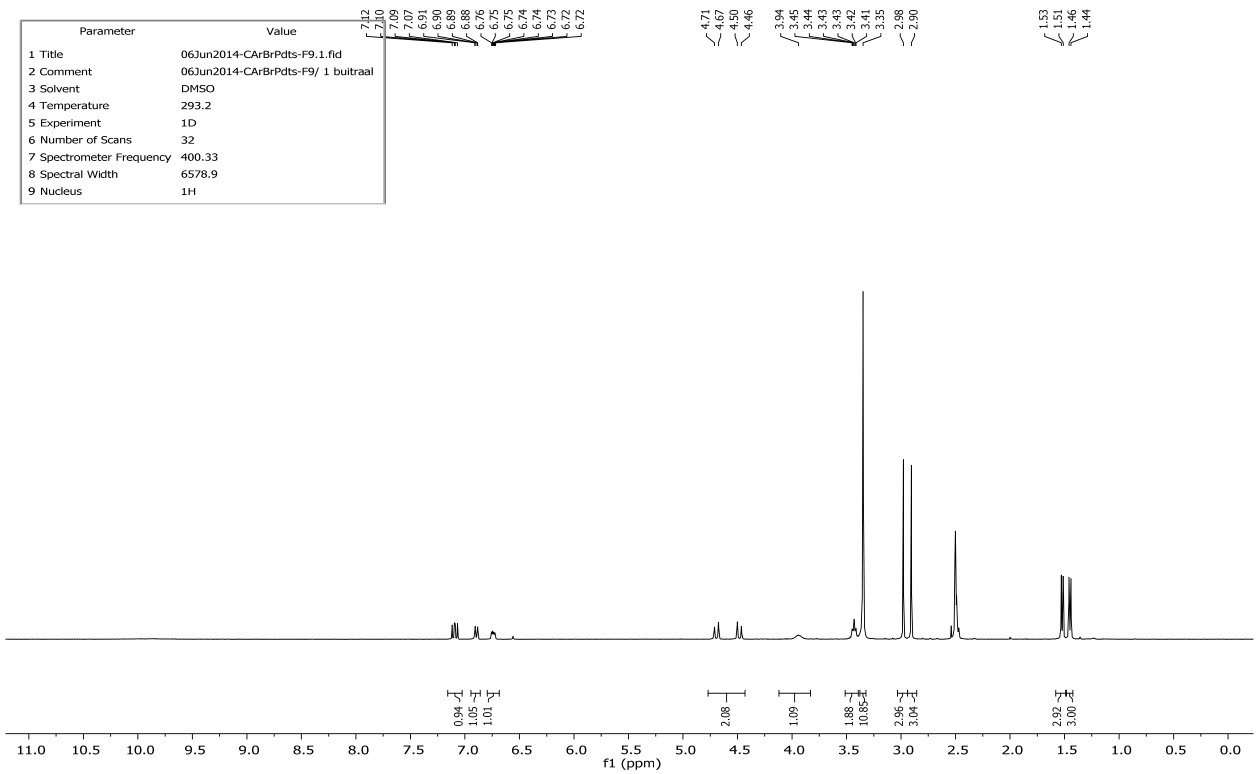


F8

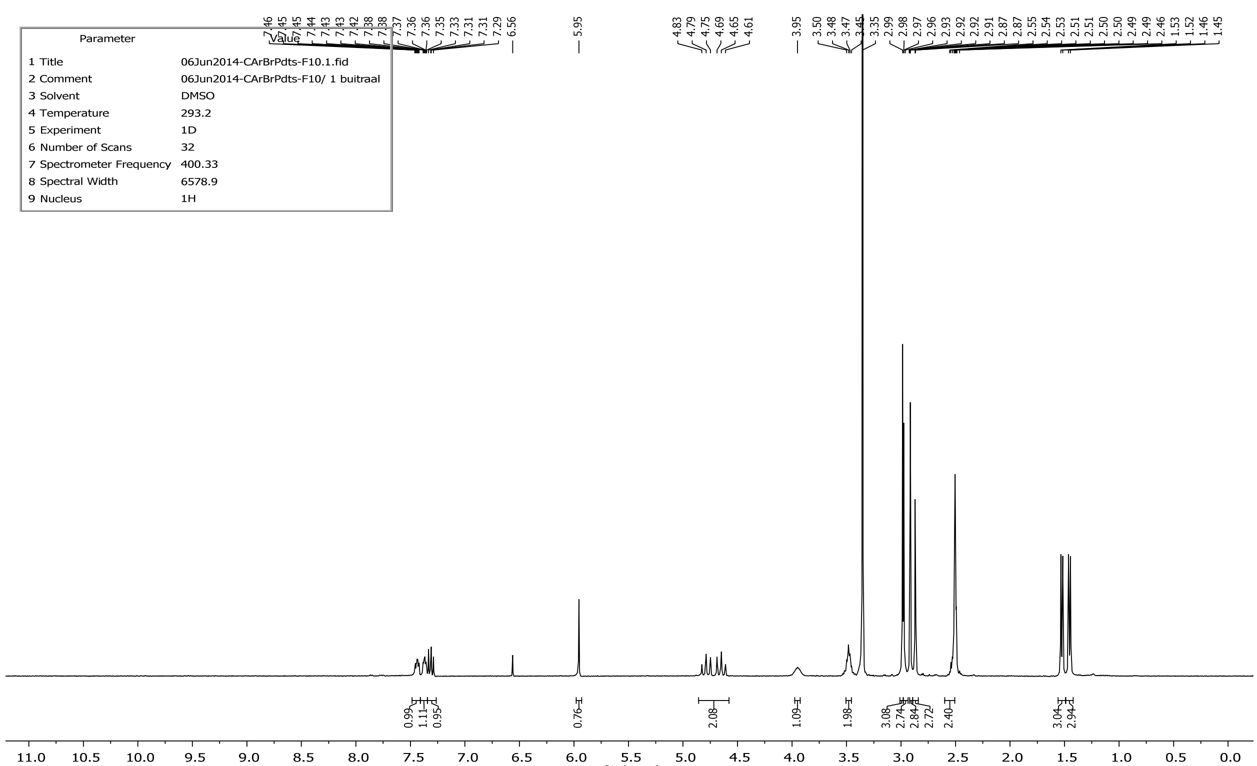
Parameter	Value
1 Title	14Jul2014-F8.1.fid
2 Comment	14Jul2014-F8/ 1 buitraal
3 Solvent	DMSO
4 Temperature	300.0
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	400.33
8 Spectral Width	6578.9
9 Nucleus	1H



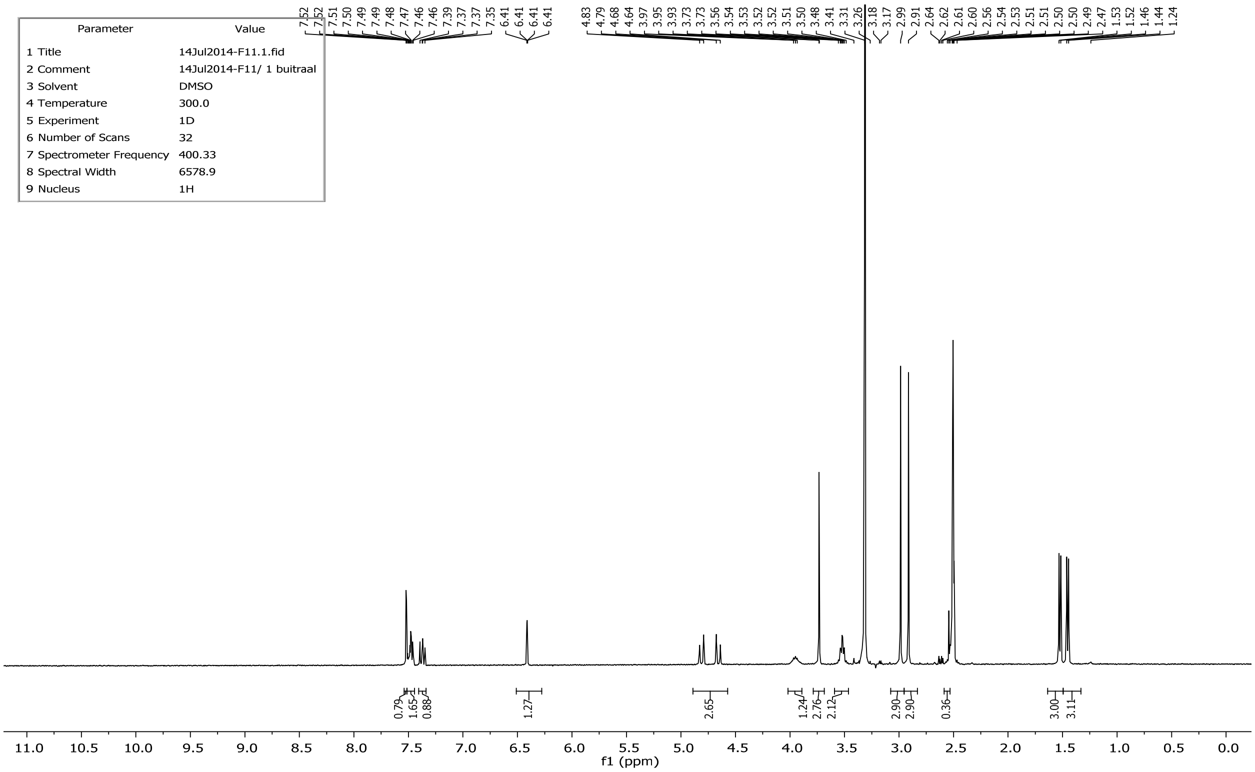
F9


Parameter Value
1 Title 06Jun2014-CArBrPdts-F9.1.fid
2 Comment 06Jun2014-CArBrPdts-F9/ 1 buitraal
3 Solvent DMSO
4 Temperature 293.2
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

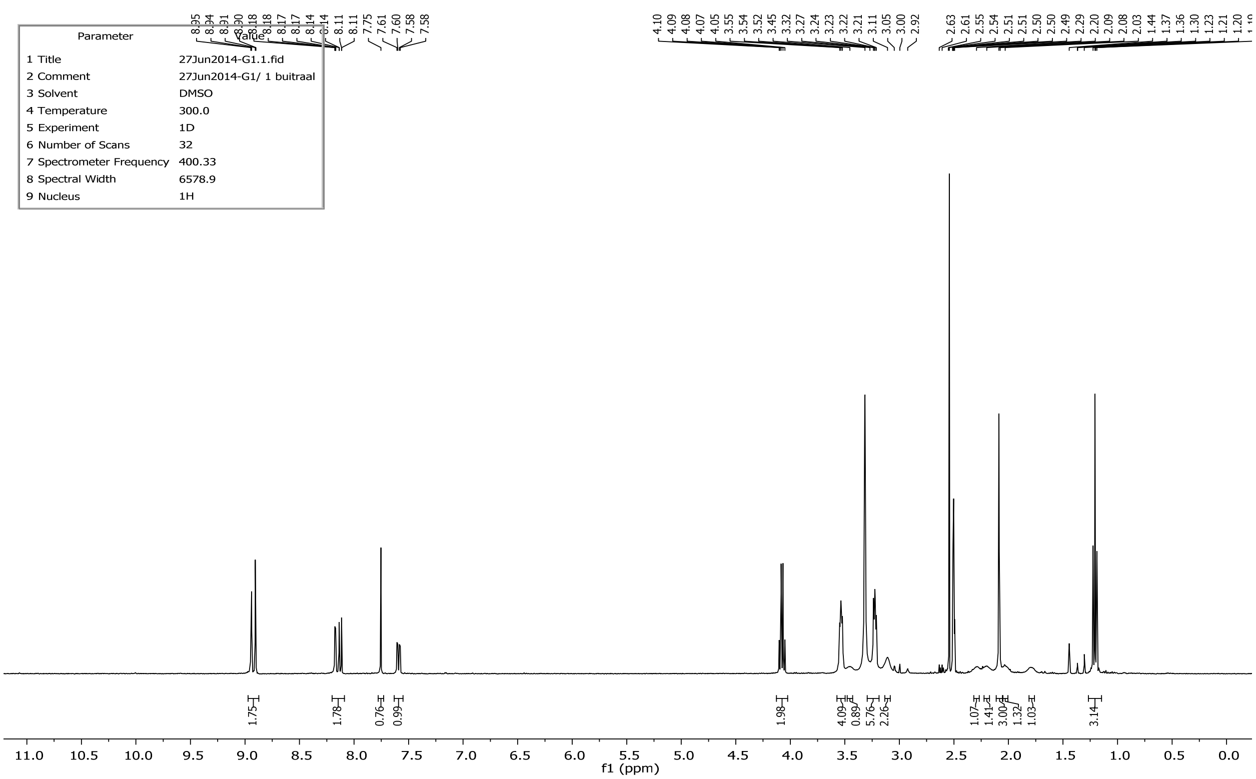
F10


Parameter Value
1 Title 06Jun2014-CArBrPdts-F10.1.fid
2 Comment 06Jun2014-CArBrPdts-F10/ 1 buitraal
3 Solvent DMSO
4 Temperature 293.2
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

F11

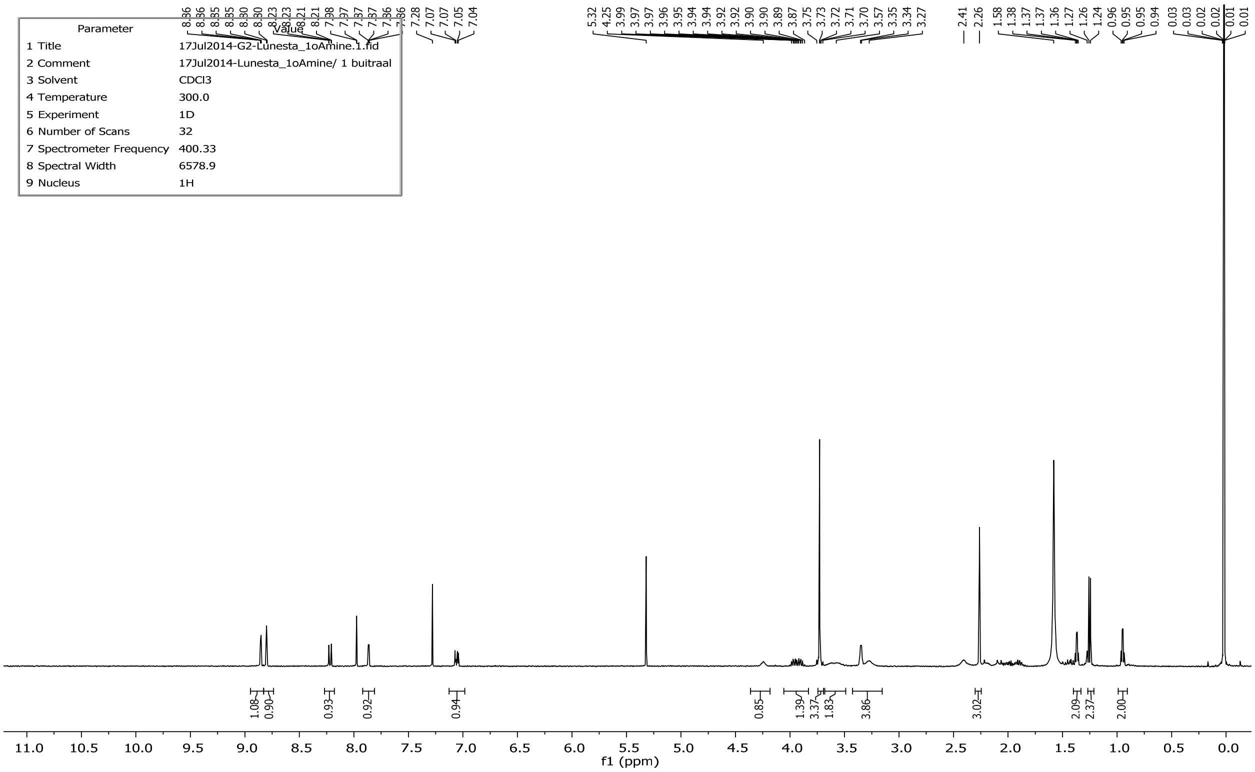

Parameter | Value
1 Title | 14Jul2014-F11.1.fid
2 Comment | 14Jul2014-F11/ 1 buitraal
3 Solvent | DMSO
4 Temperature | 300.0
5 Experiment | 1D
6 Number of Scans | 32
7 Spectrometer Frequency | 400.33
8 Spectral Width | 6578.9
9 Nucleus | 1H
f1 (ppm)

G1


Parameter | Value
1 Title | 27Jun2014-G1.1.fid
2 Comment | 27Jun2014-G1/ 1 buitraal
3 Solvent | DMSO
4 Temperature | 300.0
5 Experiment | 1D
6 Number of Scans | 32
7 Spectrometer Frequency | 400.33
8 Spectral Width | 6578.9
9 Nucleus | 1H
f1 (ppm)

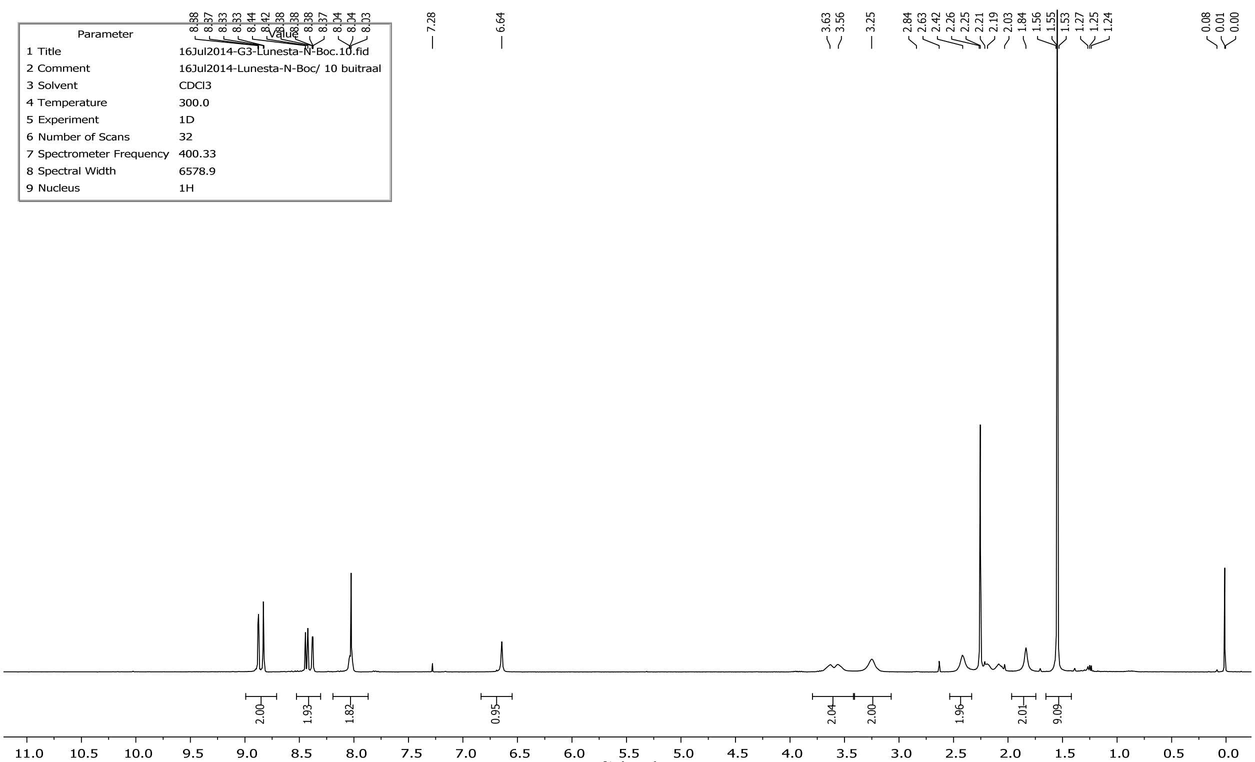
G2

Parameter	Value
1 Title	17Jul2014-G2-Lunesta_1oAmine.1.fid
2 Comment	17Jul2014-Lunesta_1oAmine/ 1 buitraal
3 Solvent	CDCl3
4 Temperature	300.0
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	400.33
8 Spectral Width	6578.9
9 Nucleus	1H

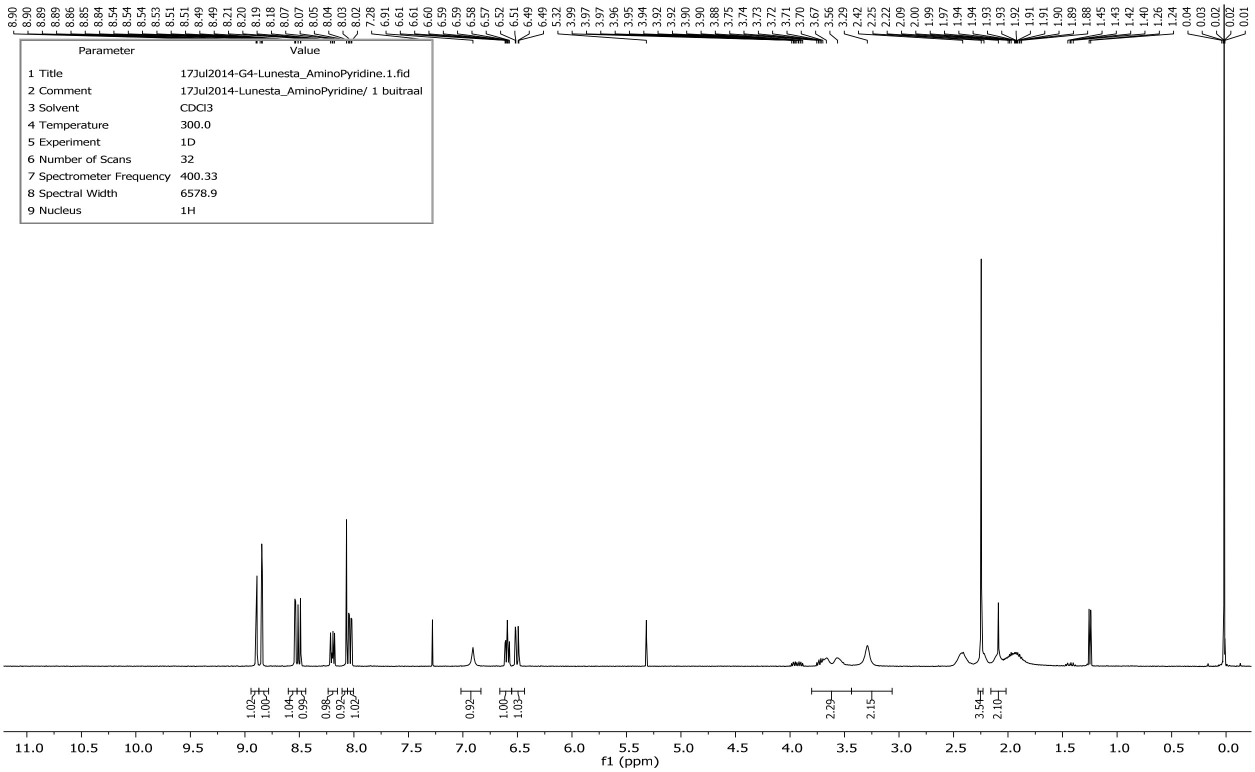


G3

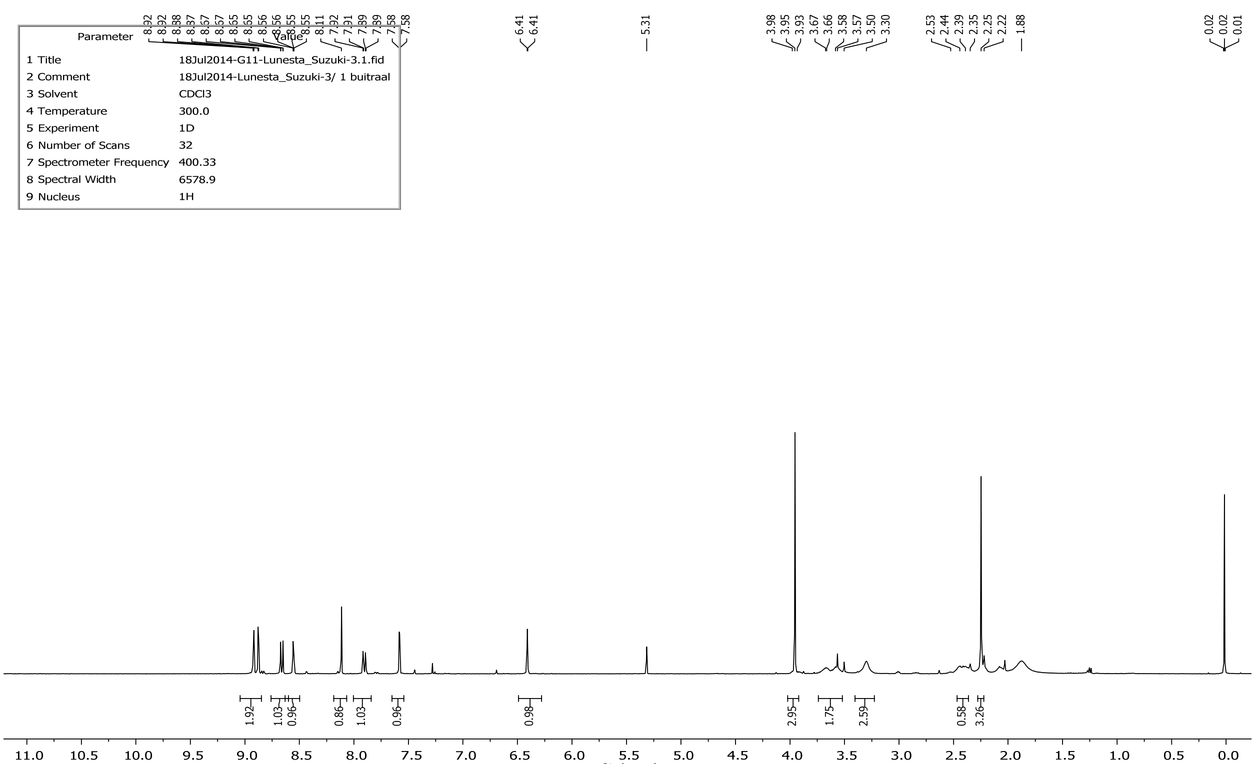
Parameter	Value
1 Title	16Jul2014-G3-Lunesta-N-Boc.10.fid
2 Comment	16Jul2014-Lunesta-N-Boc/ 10 buitraal
3 Solvent	CDCl3
4 Temperature	300.0
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	400.33
8 Spectral Width	6578.9
9 Nucleus	1H



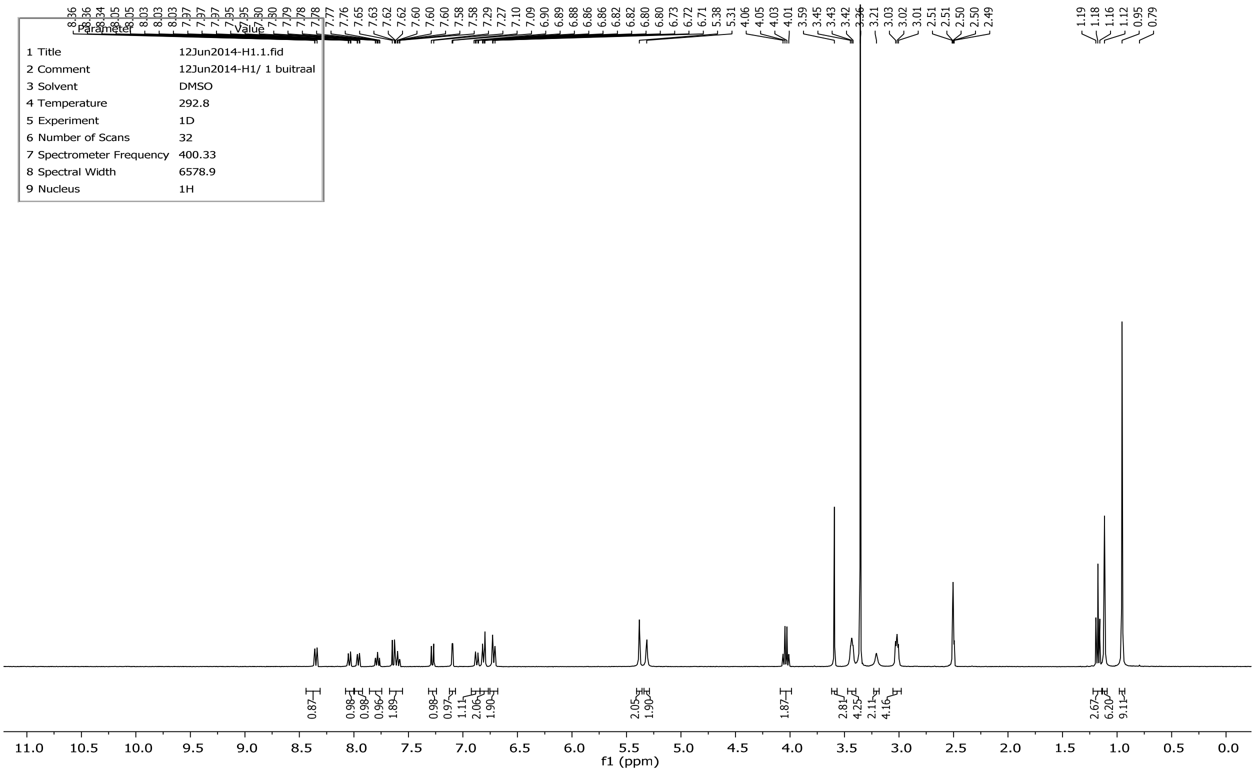
G4


Parameter Value
1 Title 17Jul2014-G4-Lunesta_AminoPyridine.1.fid
2 Comment 17Jul2014-Lunesta_AminoPyridine/ 1 buitraal
3 Solvent CDCl3
4 Temperature 300.0
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

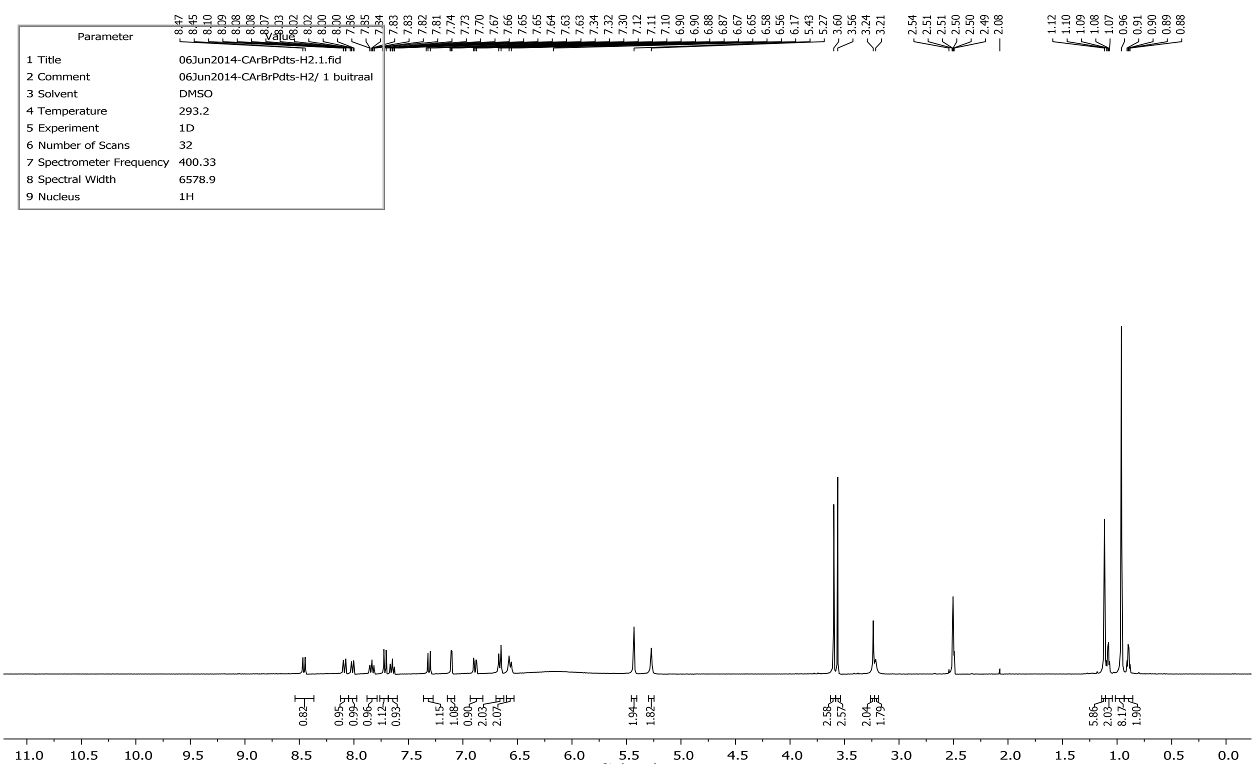
G11


Parameter Value
1 Title 18Jul2014-G11-Lunesta_Suzuki-3.1.fid
2 Comment 18Jul2014-Lunesta_Suzuki-3/ 1 buitraal
3 Solvent CDCl3
4 Temperature 300.0
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

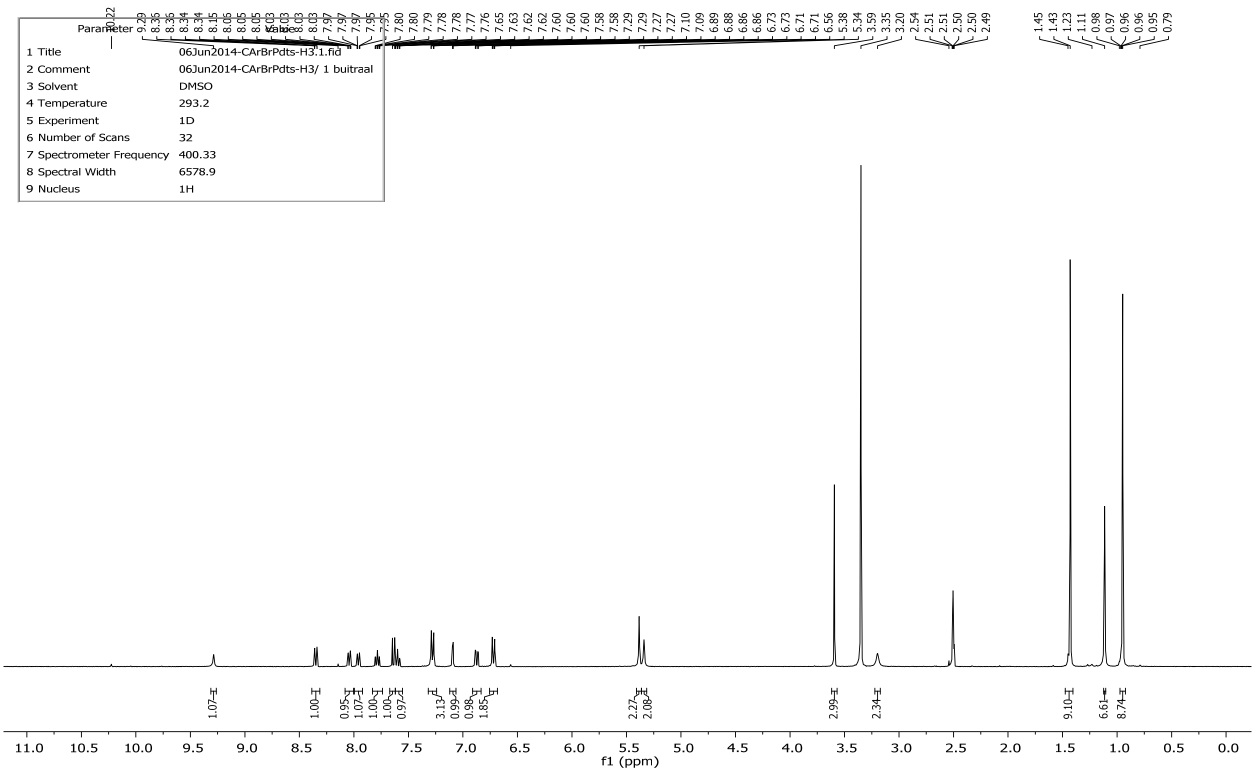
H1


Parameter Value
1 Title 12Jun2014-H1.1.fid
2 Comment 12Jun2014-H1/ 1 buitraal
3 Solvent DMSO
4 Temperature 292.8
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

H2

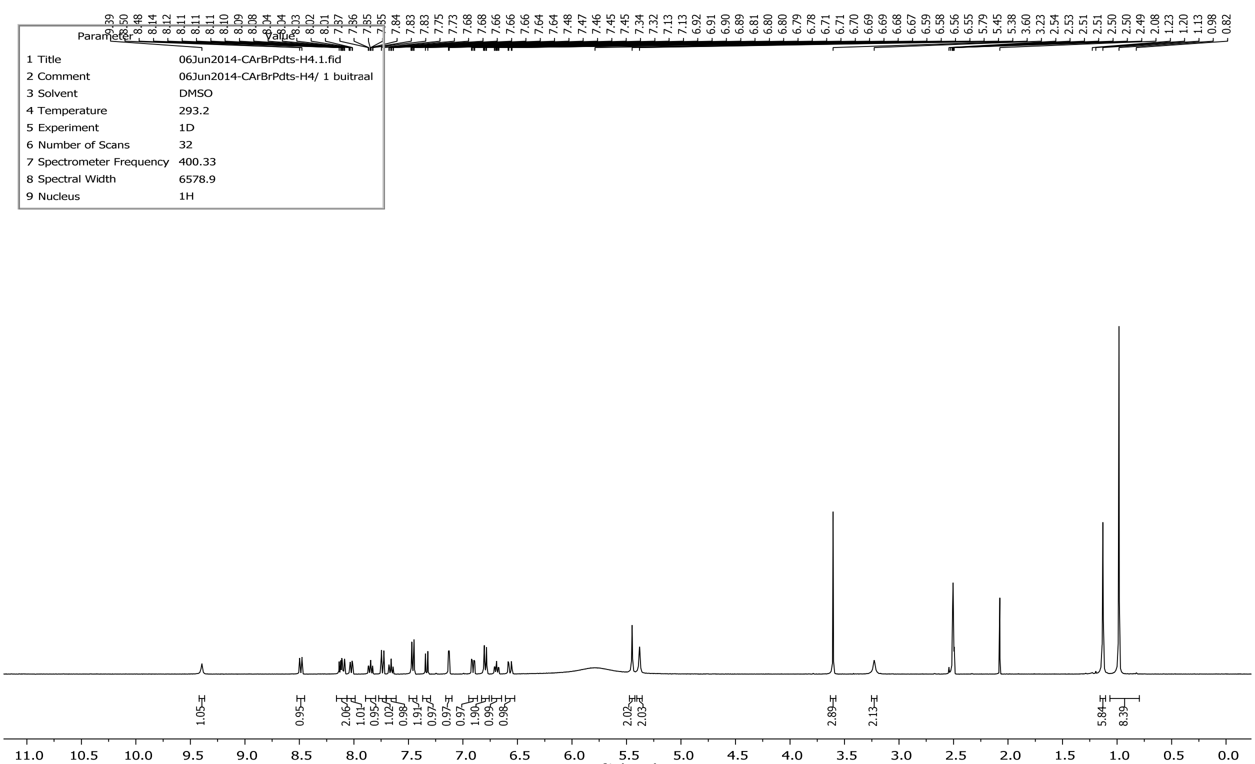

Parameter Value
1 Title 06Jun2014-CArBrPdts-H2.1.fid
2 Comment 06Jun2014-CArBrPdts-H2/ 1 buitraal
3 Solvent DMSO
4 Temperature 293.2
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

H3



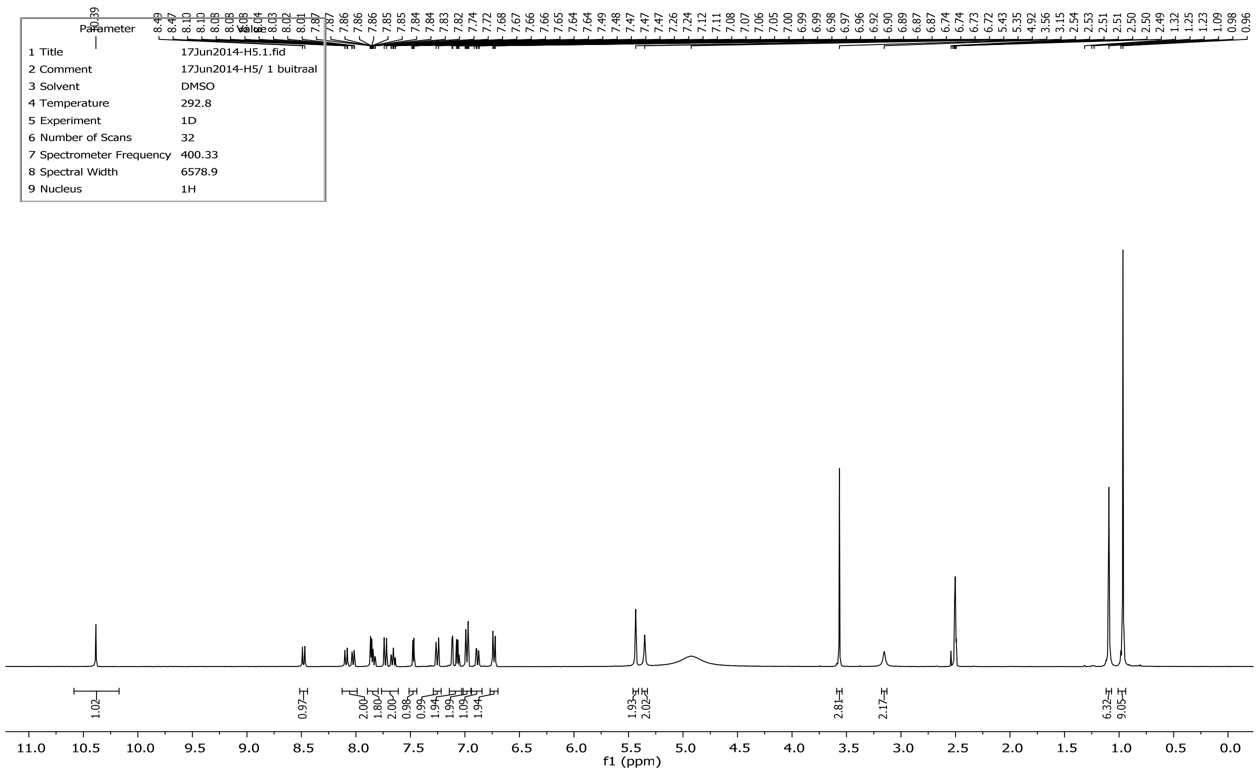
Parameter Value
1 Title 06Jun2014-CArBrPdts-H3.1.fid
2 Comment 06Jun2014-CArBrPdts-H3/ 1 buitraal
3 Solvent DMSO
4 Temperature 293.2
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

H4



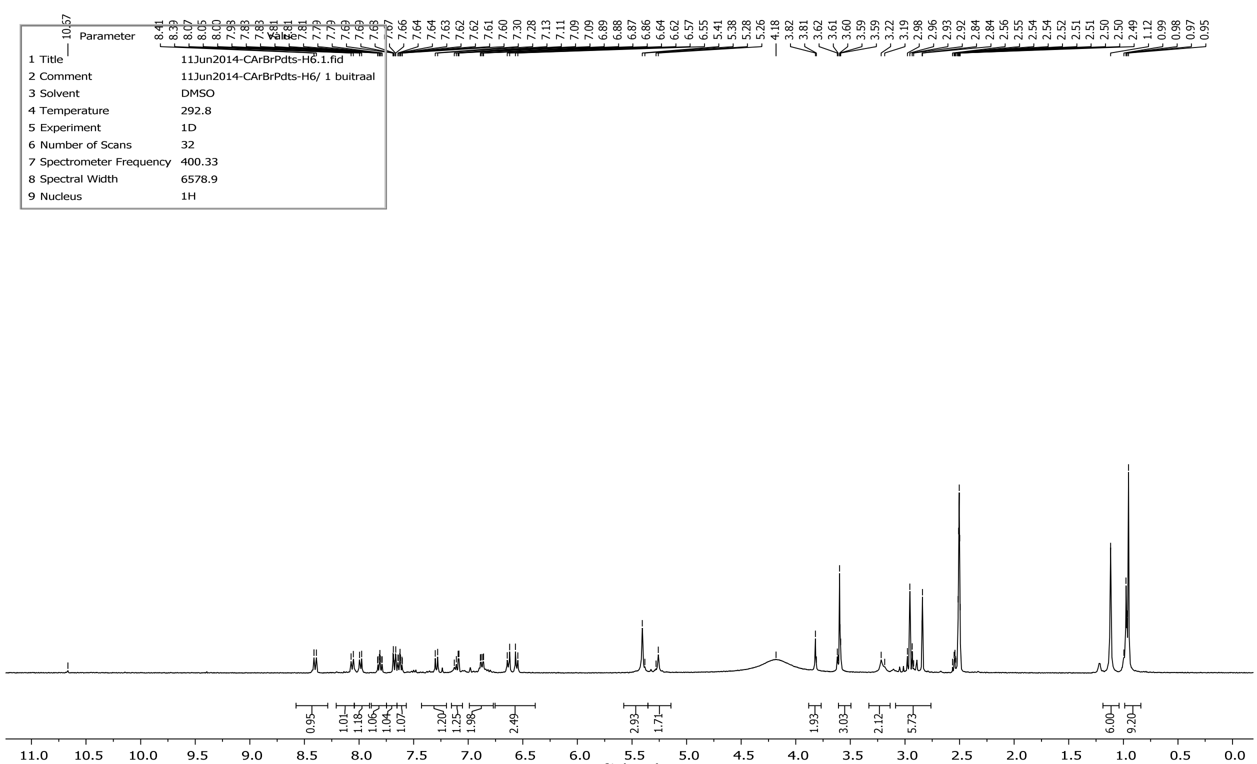
Parameter Value
1 Title 06Jun2014-CArBrPdts-H4.1.fid
2 Comment 06Jun2014-CArBrPdts-H4/ 1 buitraal
3 Solvent DMSO
4 Temperature 293.2
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

H5



Parameter Value
1 Title 17Jun2014-H5.1.fid
2 Comment 17Jun2014-H5/ 1 buitraal
3 Solvent DMSO
4 Temperature 292.8
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

H6



Parameter Value
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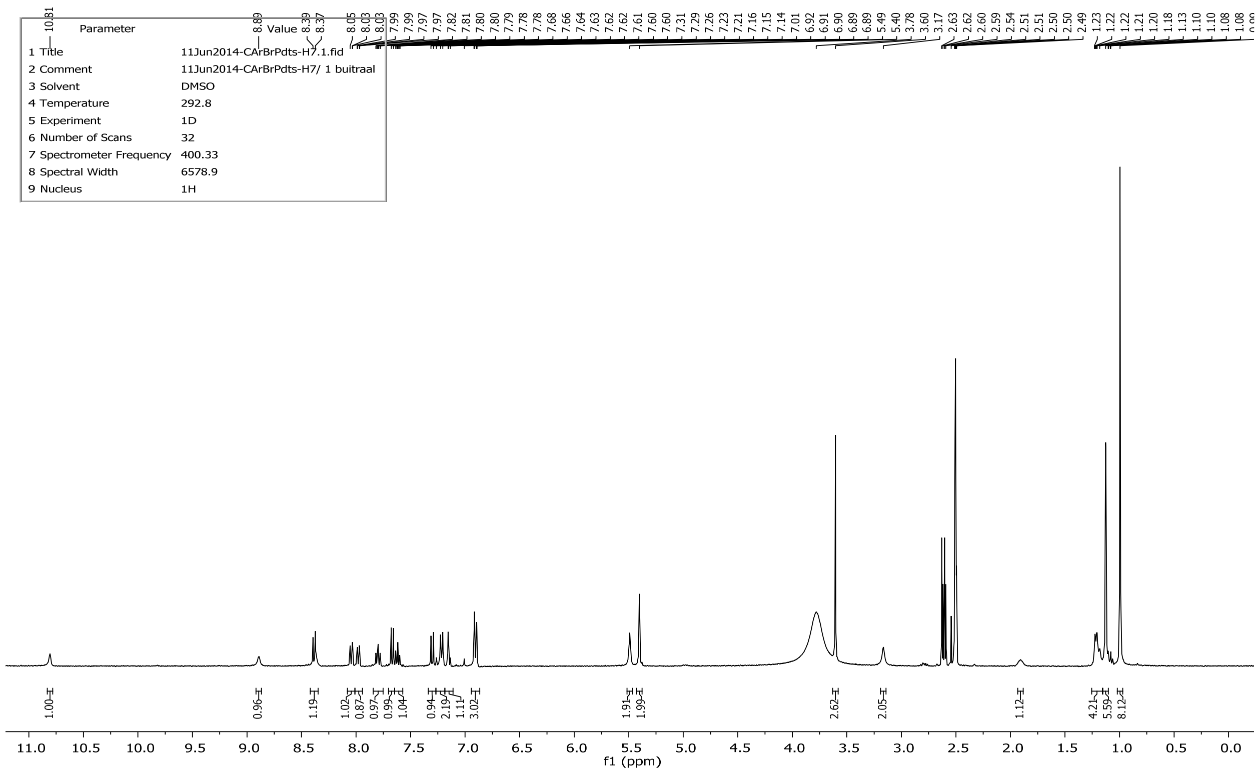
2 Comment 11Jun2014-CArBrPdts-H6/ 1 buitraal
3 Solvent DMSO
4 Temperature 292.8
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

H7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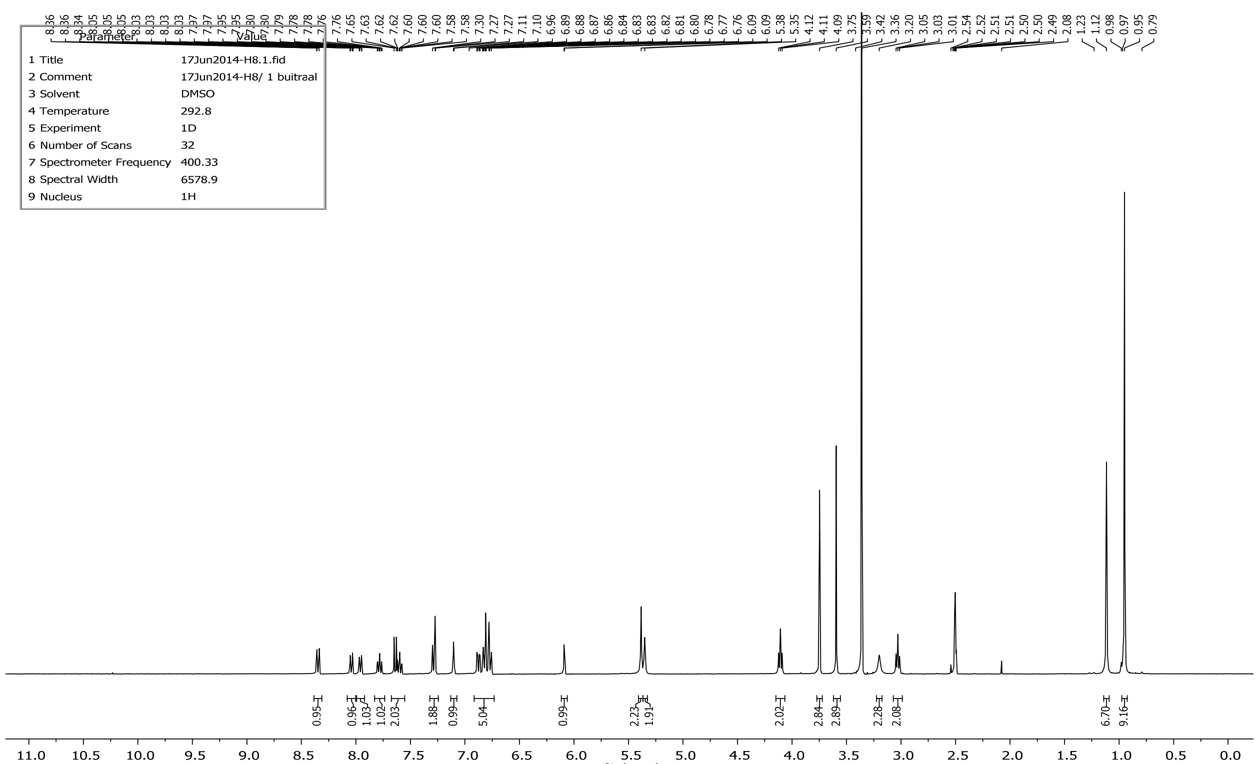
2 Comment 11Jun2014-CArBrPdts-H7/ 1 buitraal
3 Solvent DMSO
4 Temperature 292.8
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

H8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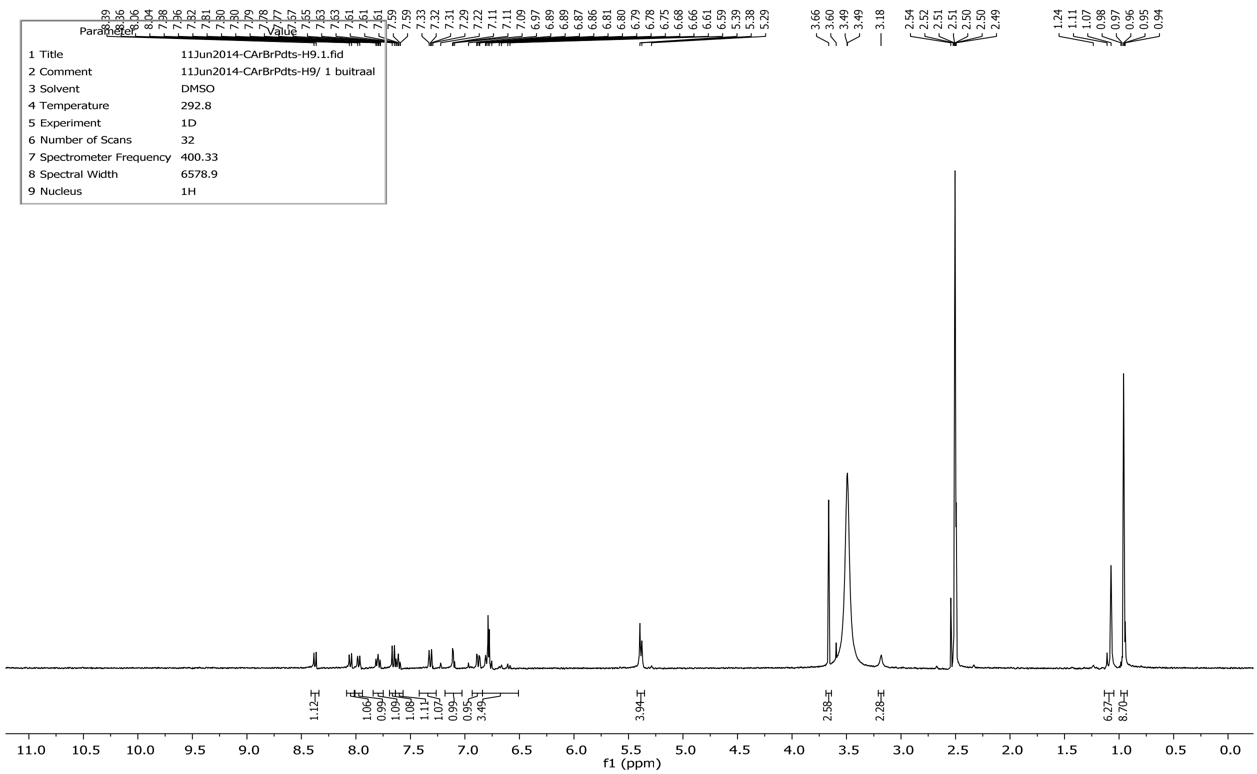
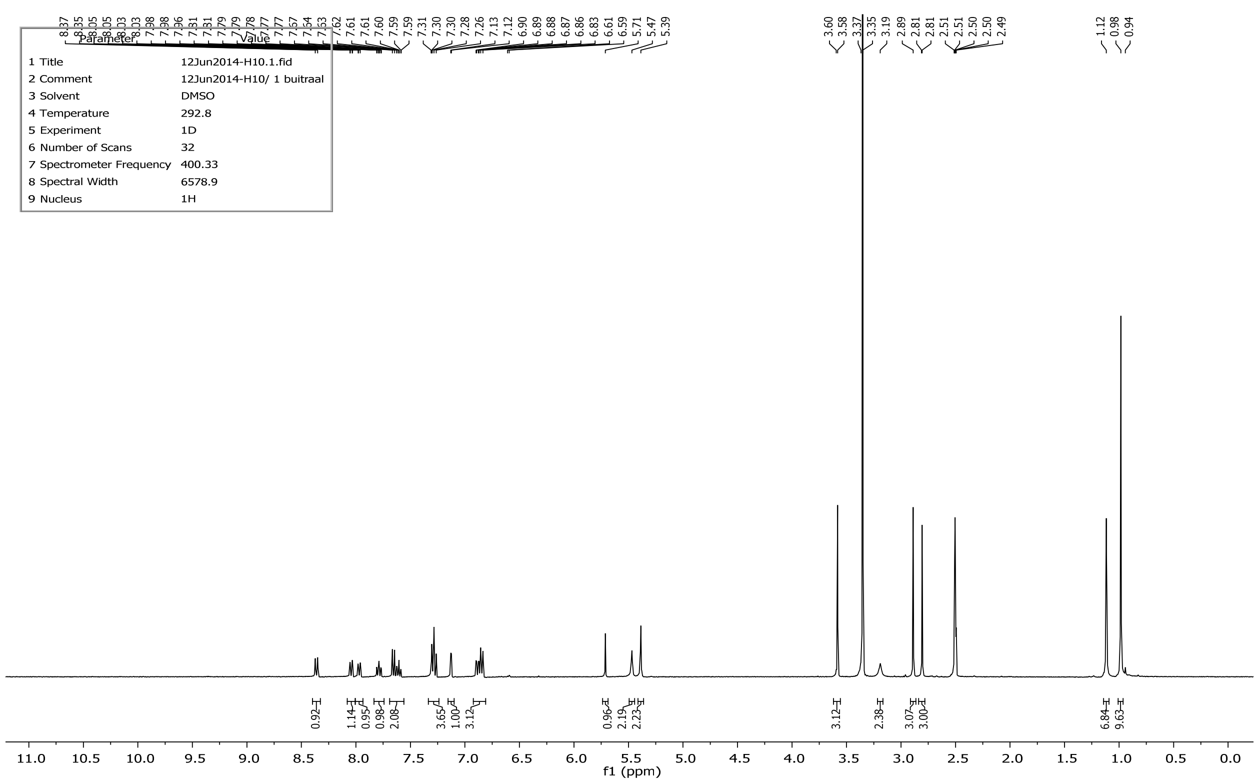
2 Comment 17Jun2014-H8/ 1 buitraal
3 Solvent DMSO
4 Temperature 292.8
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

H9



Parameter	Value
1 Title	11Jun2014-CArBrPdts-H9.1.fid
2 Comment	11Jun2014-CArBrPdts-H9/ 1 buitraal
3 Solvent	DMSO
4 Temperature	292.8
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	400.33
8 Spectral Width	6578.9
9 Nucleus	1H

H10



Parameter	Value
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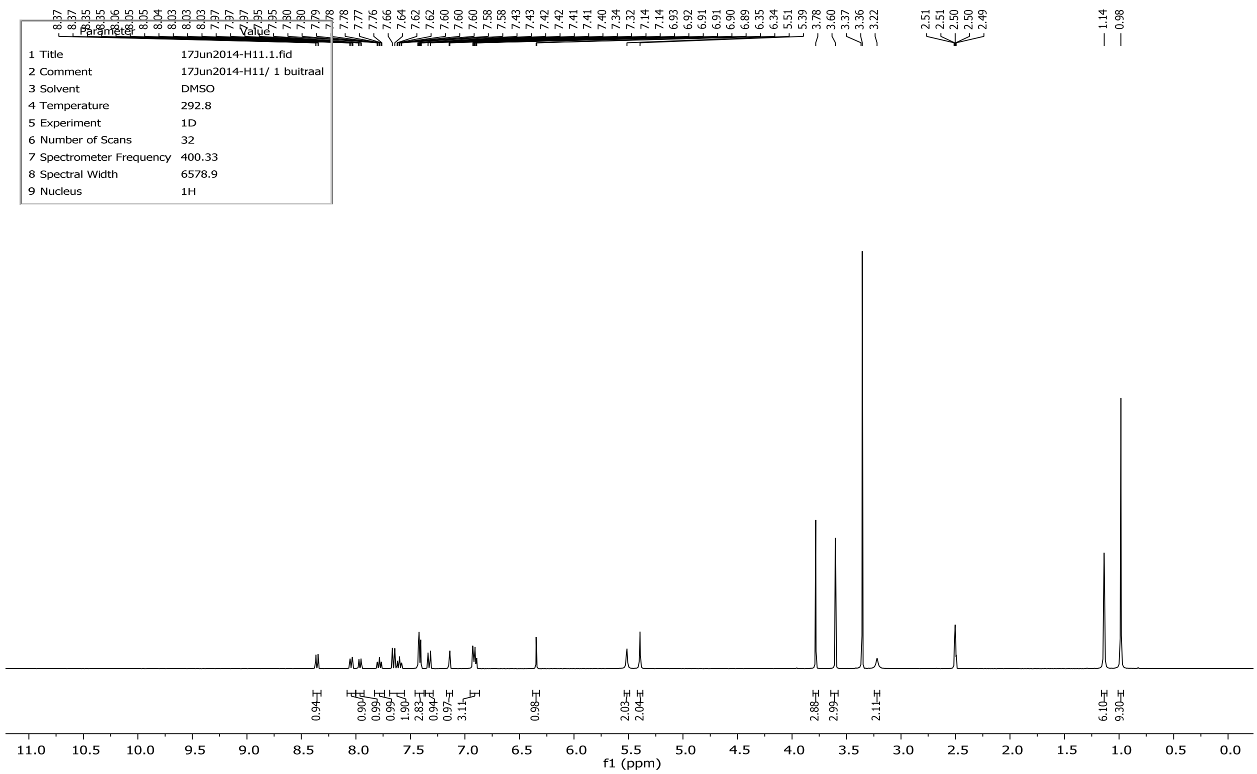
2 Comment	12Jun2014-H10/ 1 buitraal
3 Solvent	DMSO
4 Temperature	292.8
5 Experiment	1D
6 Number of Scans	32
7 Spectrometer Frequency	400.33
8 Spectral Width	6578.9
9 Nucleus	1H

H11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2 Comment 17Jun2014-H11/ 1 buitraal
3 Solvent DMSO
4 Temperature 292.8
5 Experiment 1D
6 Number of Scans 32
7 Spectrometer Frequency 400.33
8 Spectral Width 6578.9
9 Nucleus 1H
f1 (ppm)

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39. (**7**) eszopiclone hydrochloride was purchased from Enamine™.

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