Supporting Information

Radiosynthesis and preliminary PET evaluation of ^{18}F-labeled 2-(1-(3-fluorophenyl)-2-oxo-5-(pyrimidin-2-yl)-1, 2-dihydropyridin-3-yl)benzonitrile for imaging AMPA receptors

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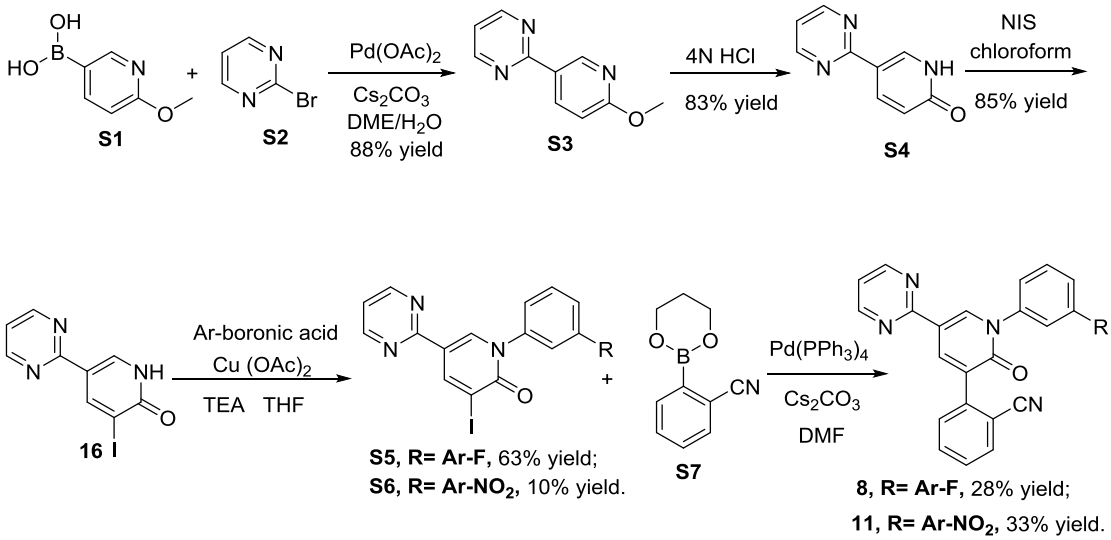
GENERAL INFORMATION

All solvents were of reagent or anhydrous grade quality and purchased from Sigma-Aldrich, Alfa Aesar, or Fisher Scientific. All reagents were purchased from Sigma-Aldrich, Alfa Aesar, Fisher Scientific, or Oakwood Chemical, unless otherwise stated. All deuterated solvents were purchased from Cambridge isotopes. Analytical thin-layer chromatography (TLC) was performed on pre-coated glass-backed plates (EMD TLC Silica gel 60 F_{254}) and visualized using a UV lamp (254 nm), potassium permanganate stain. Automated flash column chromatography was performed using a Biotage Isolera One system and preloaded Biotage Zip silica gel columns. Silica gel for manual flash chromatography was high purity grade 40-63 μm pore size and purchased from Sigma-Aldrich. Yields refer to purified and spectroscopically pure compounds.

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker 300 MHz spectrometer, and resonances are given in parts per million (ppm) relative to the residual solvent. Peak multiplicities are designated by the following abbreviations: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets; br, broad; and *J*, coupling constant in Hz.

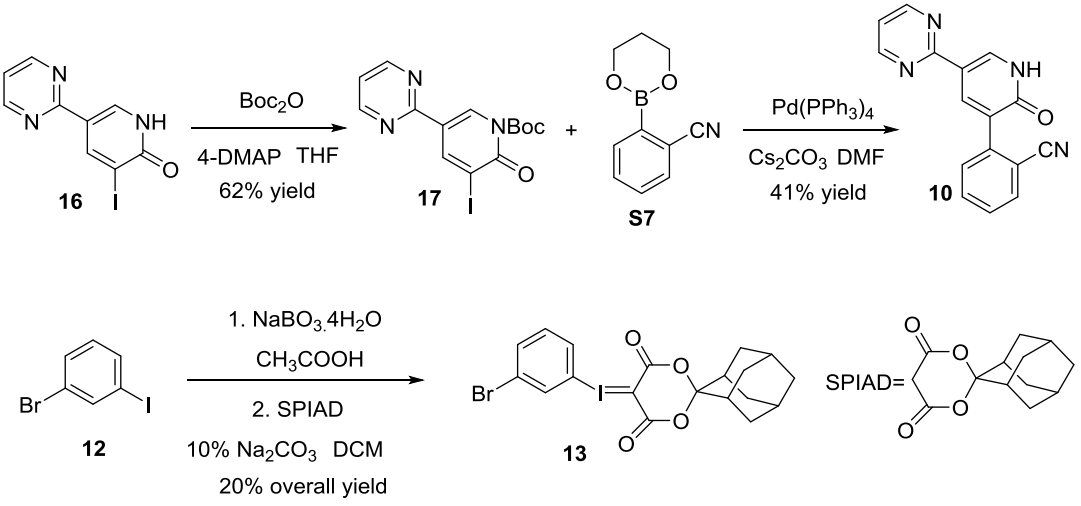
HRMS spectra were recored on a Bruker microTOFII ESI.

ORGANIC CHEMISTRY



Scheme S1: Synthesis of compounds **8** and **11**.

The unlabeled compound **8** and aryl-NO_2 precursor **11** were synthesized according to the literature. [1,2] Namely, iodination of intermediate **S4** followed by sequential couplings under modified Ullmann conditions and Suzuki−Miyaura conditions to give the desired products. The ^{1}H NMR and ^{13}C NMR characterizations match the literature description.



Scheme S2: Synthesis of compounds **10** and **13**.

Synthesis of tert-butyl

3-iodo-2-oxo-5-(pyrimidin-2-yl)pyridine-1(2H)-carboxylate (17):

To an ice cold solution of 3-iodo-5-(pyrimidin-2-yl)pyridin-2(1H)-one **16** (2.0 g, 6.68 mmol) in THF (30 mL) was added 4-dimethylaminopyridine (DMAP) (0.08 g, 0.0668 mmol), followed by dropwise addition of di-tert-butyl dicarbonate (1.6 g, 7.35 mmol). The reaction mixture was allowed to warm to room temperature and stirred for another 1h. After completion of reaction, water was added to quench the reaction, followed by extraction with ethyl acetate (3 x 25 mL). The organic layer was dried with $MgSO_4$, filtered and evaporated in vacuo to give dark brown solid. The residue was purified with flash column chromatography (Hexanes/EtOAc = 3/1, v/v) to afford tert-butyl 3-iodo-2-oxo-5-(pyrimidin-2-yl)pyridine-1(2H)-carboxylate **17** (1.66 g, yield 62.2%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.05 (d, *J* = 2.4 Hz, 1H), 8.80 (d, *J* = 2.3 Hz, 1H), 8.72 (d, *J* = 4.9 Hz, 2H), 7.71 (t, *J* = 4.9 Hz, 1H), 1.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 157.3, 157.2, 150.3, 148.2, 135.8, 119.1, 118.3, 94.0, 87.7, 27.6; Mass-Spectrometry: HRMS-ESI (m/z): Calcd for $C_{14}H_{14}IN_3O_3Na$ $[M+Na]^+$,421.9972. Found, 421.9979.

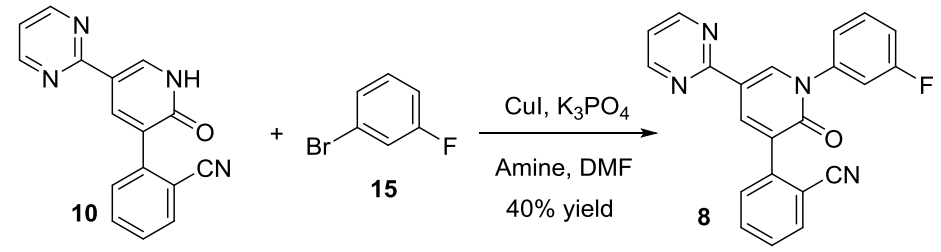
Synthesis of 2-(2-oxo-5-(pyrimidin-2-yl)-1,2-dihydropyridin-3-yl)benzonitrile (10):

A mixture of tert-butyl 3-iodo-2-oxo-5-(pyrimidin-2-yl)pyridine-1(2H)-carboxylate **17** (0.65 g, 1.65 mmol), 2-(1,3,2-dioxaborinan-2-yl)benzonitrile **S7** (0.95 g, 4.95 mmol), cesium carbonate (0.81 g, 2.48 mmol) and tetrakis(triphenylphosphine) palladium (0) (0.19 g, 0.165 mmol) in DMF (35 mL) was stirred at 110 ℃ overnight under nitrogen atmosphere. The reaction mixture was diluted with water, was extracted with ethyl acetate and dried over anhydrous magnesium sulfate. The organic layer was evaporated *in vacuo* and the residue was purified by silica gel column chromatography (Hexanes/EtOAc = 1/1 to 100% EtOAC v/v) to give the title compound 2-(2-oxo-5-(pyrimidin-2-yl)-1,2-dihydropyridin-3-yl)benzonitrile **10** (0.38 g, yield 41%) as a pale yellow powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.22 (brs, 1H), 8.67-8.73 (m, 4H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.67-7.71 (m, 2H), 7.45-7.51 (m,

1H), 7.14 (t, *J* = 4.9 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.4, 161.0, 158.1, 140.6, 139.2, 137.9, 133.44, 133.42, 131.2, 129.0, 128.7, 119.6, 118.6, 116.2, 112.3; Mass-Spectrometry: HRMS-ESI (m/z): Calcd for $C_{16}H_{11}N_4O$ $[M+H]^+$,275.0927. Found, 275.0930.

Synthesis of Spirocyclic hypervalent iodine (III) precursor (13)[3]:

Sodium perborate tetrahydrate (11.55 g, 75 mmol) was added in portions to a 0.15 M solution of 1-bromo-3-iodobenzene **12** (0.96 mL, 7.5 mmol) in glacial acetic acid (50.1 mL) heated to 50 ℃. The reaction mixture was stirred at this temperature overnight, and then it was cooled to room temperature, diluted with water, and extracted three times with dichloromethane. The combined organic layers were dried with anhydrous magnesium sulfate, filtered, and concentrated. The brown yellow crude product was suspended in ethanol (2 mL) and dichloromethane (5 mL) and (1r,3r,5r,7r)-spiro[adamantane-2,2'-[1,3]dioxane]-4',6'-dione (SPIAD) **14** (1.77 g, 7.5 mmol) was added followed by 10% Na_2CO_3 (aq) (w/v). The pH of the reaction mixture was tested and adjusted with Na_2CO_3 until the reaction pH>10. The reaction mixture was stirred overnight, then it was diluted with water and extracted with chloroform. The chloroform extracts were combined and washed with water and brine. The organic layer was dried with anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography (Hexanes/EtOAc = 1/1 to pure EtOAC v/v) to give the title compound **13** (0.77 g, yield 20 %) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.91-7.92 (m, 1H), 7.73-7.76 (m, 2H), 7.41 (t, *J* = 8.0 Hz, 1H), 2.33 (brs, 2H), 1.95 (brs, 2H), 1.91 (brs, 2H), 1.79 (brs, 2H), 1.63-1.67 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.0, 134.4, 134.0, 133.2, 131.4, 123.2, 117.3, 105.7, 58.4, 36.9, 35.3, 33.6, 26.4; Mass-Spectrometry: HRMS-ESI (m/z): Calcd for $C_{19}H_{19}BrIO_4$ $[M+H]^+$,516.9485. Found, 516.9475.



Amine=*trans-N, N'*-dimethylcyclohexane-1,2-diamine

Scheme S3: *De novo* synthesis of standard compound **8.**

***De novo* synthesis of standard compound (8):**

Under nitrogen atmosphere, 1-bromo-3-fluorobenzene **15** (10 μL, 86.4 μmol) was added to a mixture of 2-(2-oxo-5-(pyrimidin-2-yl)-1,2-dihydropyridin-3-yl)benzonitrile **10** (20 mg, 72 μmol), CuI (18 mg, 94.6 μmol), K_3PO_4 (48 mg, 216 μmol) and trans-N, N'-dimethylcyclohexane-1,2-diamine (12 μL, 72 μmol) in DMF (2 mL). The reaction mixture was protected from light by wrapping aluminum foil around the reaction vessel. The reaction was stirred at 110 ℃ for 2 h. The reaction mixture was diluted with water, was extracted with ethyl acetate and dried over anhydrous magnesium sulfate. The organic layer was evaporated *in vacuo* and the residue was purified by silica gel column chromatography (Hexanes/EtOAc = 2: 1 to 1: 1) to give the title compound **8** (11 mg, yield 40%) as greenish yellow powder. The ^{1}H NMR and ^{13}C NMR characterizations match the literature description.[1]

RADIOCHEMISTRY

General methods for radioisotope preparation

A GE PETtrace 16.5 MeV cyclotron was used for [^{18}F]fluoride production by the ^{18}O(p,n)^{18}F nuclear reaction to irradiate ^{18}O-enriched water. [^{18}F]fluoride was delivered to a lead-shielded hot cell in ^{18}O-enriched water by nitrogen gas pressure. [^{18}F]Fluoride was prepared for radiofluorination of aromatics by the following method: a solution of base (tetraethylammonium bicarbonate (TEAB)) or potassium carbonate/2,2,2-crypt (Kryptofix®) in acetonitrile and water (1 mL, v/v 7 : 3) was

added to an aliquot of target water (≤ 1 mL) containing the appropriate amount of [^{18}F]fluoride in a V-shaped vial sealed with a teflon-lined septum. The vial was heated to 110 ℃ (for TEAB) or 95 ℃ (for K_2CO_3/Kryptofix®) while nitrogen gas was passed through a P_2O_5-Drierite™ column followed by the vented vial. When no liquid was visible in the vial, it was removed from heat, anhydrous acetonitrile (1 mL) was added, and the heating was resumed until dryness. This step was repeated an additional three times. The vial was then cooled at room temperature under nitrogen pressure. The contents were resolubilized in the suitable solvents.

General methods for analysis of radiofluorination reactions

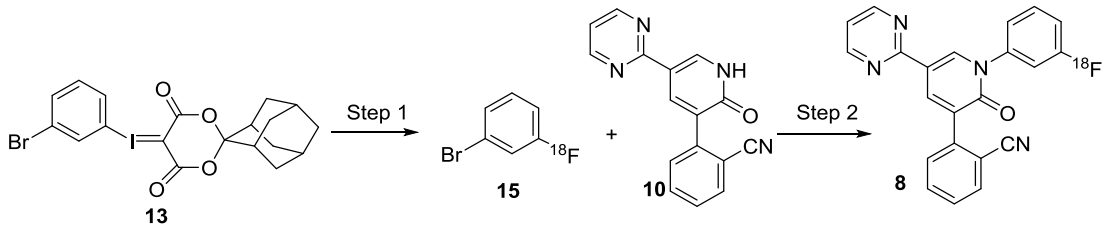
Radiochemical incorporation yields were determined by radioTLC. EMD TLC Silica gel 60 plates (10 x 2 cm) were spotted with an aliquot (1-5 μL) of crude reaction mixture approximately 1.5 cm from the bottom of the plate (baseline). TLC plates were developed in a chamber containing ethyl acetate (EtOAc) until within 2 cm of the top of the plate (front). Analysis was performed using a Bioscan AR-2000 radio-TLC imaging scanner and WinScan software. Radiochemical identity and purity were determined by radioHPLC. A Phenomenex Luna C18, 250 x 4.6 mm, 10 μm HPLC column was used for the analytical analysis with a Waters 1515 Isocratic HPLC Pump equipped with a Waters 2487 Dual λ Absorbance Detector, a Bioscan Flow-Count equipped with a NaI crystal, and Breeze software. The mobile phases for analytical HPLC analysis included: 60% MeCN, 40% 0.1 M NH_4HCO_2 (aq); 40% MeCN, 60% 0.01 M NaOAc(aq). The flow rate was 1mL/min. whereas, the semi-preparative purifications were performed on a Phenomenex Luna C18, 250 x 100 mm, 10 μm HPLC column with 40% MeCN, 60% 0.01 M NaOAc(aq) as mobile phase and the flow rate was 7mL/min. All radiochemical yields are non-decay corrected. Each radiochemical labeling was conducted at least two times ($n \geq 2$).

Experimental Procedures:

Radiosynthesis of [^{18}F]8. Fluorine-18 labeled fluoride (25-30 mCi) was separated from ^{18}O-enriched water using an ion exchange cartridge (Waters QMA, Part No.

186004540) and subsequently released into V-shaped glass Vial (Wheaton, 5 mL) via a solution of K_2CO_3/K_{222} (K_2CO_3 (3 mg) and K_{222} (15 mg) in a 1 mL solution of MeCN/H_2O, (v/v 7:3)). The solution was azeotropically dried over 3 cycles with addition of anhydrous MeCN (1 mL each cycle) at 95 ℃ and resolubilized in anhydrous DMF (0.6 mL). This [^{18}F]fluoride solution was transferred into a vial containing compound **13** (6 mg). The reaction was heated to 120 ℃ for 10 min, after which K_3PO_4 (14.4 mg) and a solution of compound **10** (12 mg), CuI (36 mg) and *trans-N,N'*-dimethylcyclohexane-1, 2-diamine (21.6 μL) in DMF (0.4 mL) were added at room temperature. The reaction was allowed to react for 20 min at 130 ℃. Then, the reaction mixture was quenched with water (10 mL) and filtered through a syringe filter (MCE, 0.22μm, 30mm) connected in series with a t-C18 plus Sep-Pak® cartridge, (Waters; pre-activated with 10 mL EtOH followed by 10 mL H_2O) to remove the precipitates and trap the [^{18}F]**8**. Subsequently, 1.5 mL MeCN was passed through the cartridge to elute off the [^{18}F]**8**, to which NaOAc (3 mL 0.01 M) aqueous solution was added to reformulate the solution into 4.5 mL of 33% MeCN in 0.01 M NaOAc solution before semi-preparative HPLC purification. Semi-preparative HPLC was carried out with a Phenomenex Luna C18, 250 x 100 mm, 10 μm column, and eluted with 40% MeCN in 0.01 M NaOAc, using a flow rate of 7 mL/min and monitored at a wavelength of 254 nm. The major radioactive product, [^{18}F]**8**, was separated at 24 min and its identity was confirmed by HPLC-coinjections on an analytical HPLC system with a Phenomenex Luna C18, 250 x 4.6 mm, 10 μm column and eluted with 40% MeCN in 0.01 M NaOAc(aq), using a flow rate of 1 mL/min.

Optimization of radiofluorination conditions



Scheme S4: Radiosynthesis of [^{18}F]**8** with compound **13** as the precursor.

Optimizations of the 1st step radiosynthesis of [^{18}F]**15**

(1) Method:

Tetraethyl ammonium bicarbonate (TEAB) as the base: 7 mg TEAB was used to dry [^{18}F] fluoride. DMF (1.4 mL) was used to solubilize the TEA^{18}F; precursor (2 mg) was added into the vial. The resulting activity solution was divided into several aliquots (0.2 mL) into separate vials. Each reaction was tested at indicated reaction conditions, and then quenched with mobile phase (0.4 mL).

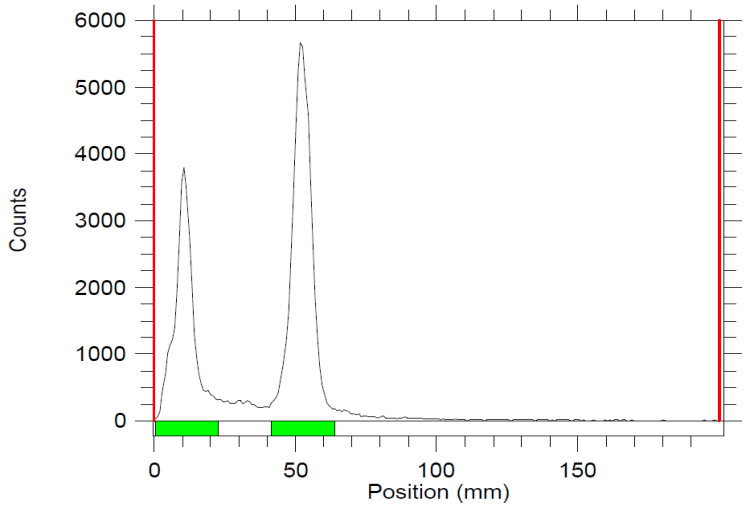
Potassium carbonate as the base: 5mg K_2CO_3 and 15mg Kryptofix® were used to dry [^{18}F]fluoride. DMF (1.0 mL) was used to solubilize the TEA^{18}F; precursor (2 mg) was added into the vial. The resulting activity solution was divided into several aliquots (0.2 mL) into separate vials. Each reaction was tested at indicated reaction conditions, and then quenched with mobile phase (0.4 mL).

*(2) 1st step radiosynthesis of [^{18}F]**15** optimization results*

Entry	**13** (mg)	Base (mg)	K_{222} (mg)	T (°C)	Time (min)	DMF (mL)	RCC (%)
1 (n = 3)	2	TEAB (1.0)	N	80	10	0.2	25 ± 2
2 (n = 3)	2	TEAB (1.0)	N	100	10	0.2	41 ± 3
3 (n = 3)	2	TEAB (1.0)	N	120	10	0.2	69 ± 2
4 (n > 10)	2	K_2CO_3 (1.0)	5.0	120	10	0.2	72 ± 3
5 (n = 3)	2	K_2CO_3 (1.5)	7.5	120	10	0.2	46 ± 2
6 (n = 3)	2	K_2CO_3 (2.0)	10.0	120	10	0.2	15 ± 3
7 (n = 3)	2	K_2CO_3 (1.0)	5.0	120	5	0.2	50 ± 2
8 (n = 3)	2	K_2CO_3 (1.0)	5.0	120	15	0.2	45 ± 2
9 (n = 3)	3	K_2CO_3 (1.0)	5.0	120	10	0.2	60 ± 1
10 (n = 3)	4	K_2CO_3 (1.0)	5.0	120	10	0.2	48 ± 2
11 (n = 3)	3	K_2CO_3 (1.5)	7.5	120	10	0.3	45 ± 3
12 (n = 3)	4	K_2CO_3 (2.0)	10.0	120	10	0.4	55 ± 3
13 (n > 5)	6	K_2CO_3 (3.0)	15.0	120	10	0.6	68 ± 3

Table S1: Optimizations of the first radiosynthetic step [^{18}F]**15.**

(3) RadioTLC chromatogram of 1st step reaction mixture:



	1	2	3	4	5	mean	Standard deviation
RCC (%)	64	68	73	74	63	68	5

(4) RadioHPLC chromatogram:

Column: Luna 10u C18 100 Å 250 × 4.6 mm

Mobile phase: 40% MeCN, 60% 0.01 M NaOAc (aq)

Flow rate: 1 mL/min

Optimizations of the 2nd step radiosynthesis of [^{18}F]**8**

(1) Method:

K_3PO_4 and a solution of compound **10**, copper (I) iodide and *trans*-N, N′-dimethylcyclohexane-1, 2-diamine in DMF were added into the 1st step reaction mixture at room temperature. The reaction was allowed to react for 10 at 130 ℃. Then, the reaction mixture was quenched with water (10 mL) and filtered through a syringe filter in connection with the t-C18 plus Sep-Pak® cartridge, (Waters; pre-activated with 10 mL EtOH followed by 10 mL H_2O) to remove the precipitates and trap the [^{18}F]**8**. Subsequently, 1.5 mL MeCN was pushed through the cartridge to elute off the [^{18}F]**8**, to which 3 mL 0.01 M NaOAc aqueous solution was added to reformulated it into 4.5 mL 33% MeCN in 0.01 M NaOAc solution before semi-preparative HPLC purification with 40% MeCN in 0.01 M NaOAc to get the [^{18}F]**8**.

*(2) 2nd step radiosynthesis of [18F]**8** optimization results*

Entry[a]	**6** (mg)	CuI (mg)	Amine (µL)[c]	K_3PO_4 (mg)	T(°C)	Time (min)	DMF (mL)	[18F]**8** (%)[d]
1 (n = 2)	2	2	1.2	4.8	110	10	0.4	8 ± 4
2 (n = 2)	2	2	TEAB (2.0 mg)	4.8	110	10	0.4	NR
3 (n = 2)	2	2	TMEDA (1.2)	4.8	110	10	0.4	NR
4 (n = 2)	2	2	DMEDA (1.2)	4.8	110	10	0.4	NR
5 (n = 2)	2	2	1.2	4.8	130	10	0.4	16 ± 3
6 (n = 2)	2	2	1.2	4.8	150	10	0.4	NR
7 (n = 2)	4	2	1.2	4.8	130	10	0.4	20 ± 3
8 (n = 2)	8	2	1.2	4.8	130	10	0.4	10 ± 2
9 (n = 2)	16	2	1.2	4.8	130	10	0.4	6 ± 3
10 (n = 2)	4	4	2.4	4.8	130	10	0.4	48 ± 5
11 (n = 2)	4	8	4.8	4.8	130	10	0.4	70 ± 3
12 (n = 5)	4	12	7.2	4.8	130	10	0.4	72 ± 5
13 (n = 2)	4	12	7.2	2	130	10	0.4	60 ± 3
14 (n = 2)	4	12	7.2	10	130	10	0.4	60 ± 3
15 (n = 2)	4	12	7.2	15	130	10	0.4	20 ± 1
16 (n = 2)[b]	4	12	7.2	4.8	130	10	1.0	30 ± 5
17 (n = 2)[b]	12	36	21.6	14.4	130	10	1.0	45 ± 2
18 (n = 5)[b]	12	36	21.6	14.4	130	20	1.0	65 ± 10

Table S2: Optimizations of the 2nd radiosynthetic step [18F]**8.**

(3) Quality Control:

The reformulated [^{18}F]**8** in 10 % EtOH/Saline (v/v) (0.5 mCi; with specific activity of 0.8 Ci/μmol at the time of injection) was analyzed by rHPLC for both its identification and purities. The results shown in **Figure S1** and **Figure S2** separately, indicating the correctness [^{18}F]**8** as well as its high chemical and radiochemical purities > 99%.

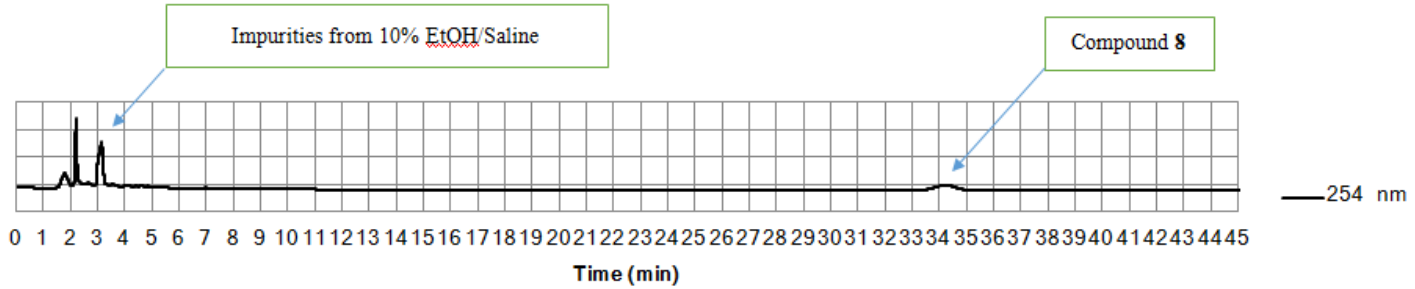


Figure S1, Analysis of reformulated ^{18}F-labeled compound **8** in 10% EtOH/Saline (v/v).

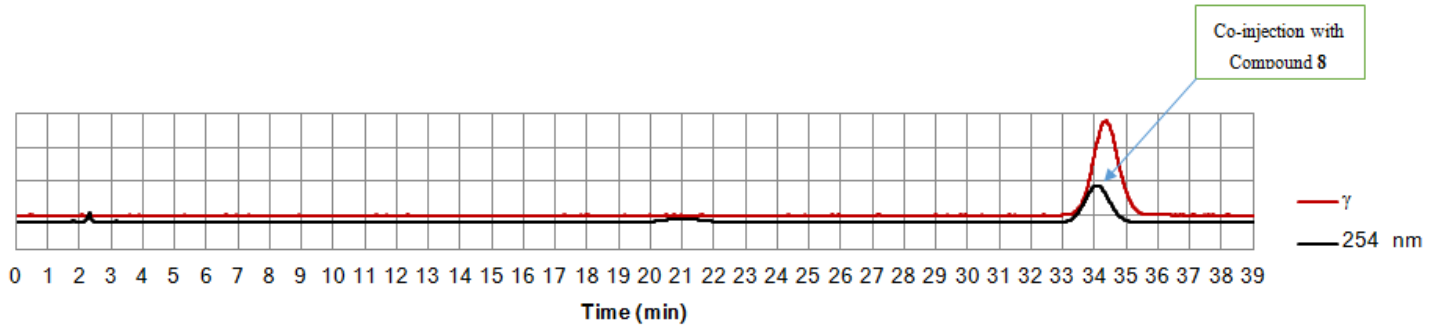


Figure S2, Co-injection of the ^{18}F-labeled compound **8** with its unlabeled analog.

*(4) Specific Activity (SA) determination for [^{18}F]**8**:*

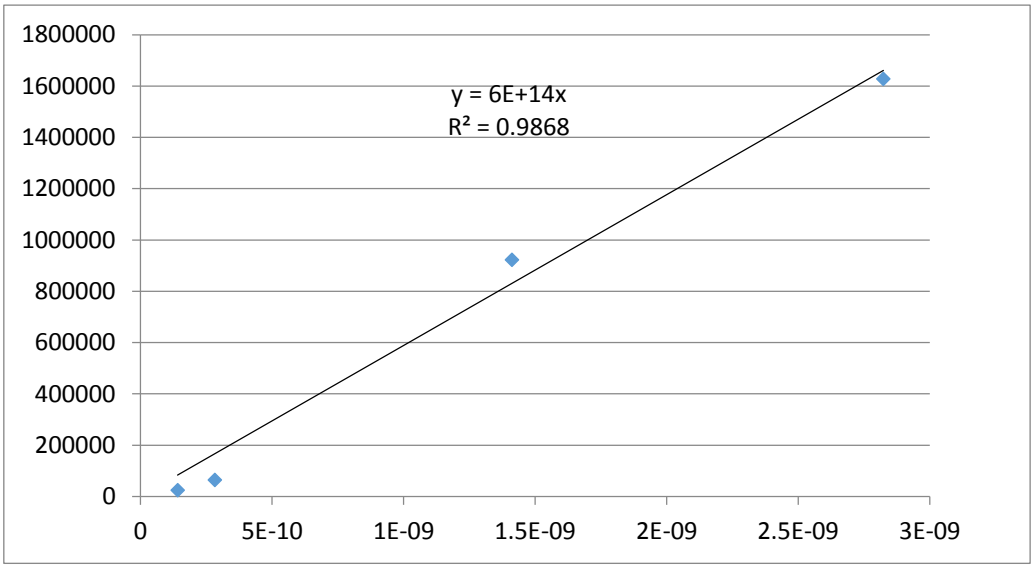


Figure S3. Standard curve for the specific activity determination of [^{18}F]**8**.

The specific activity of [^{18}F]**8** was determined to be 0.8 ± 0.2 Ci/μmol before injections to the mice.

LogP Measurement

Based on an established method in literature, the LogP of compound **8** was measured via HPLC.[4] A standard curve value was plotted with the reference compounds for their log-corrected retention time (r.t., relative to Catechol according to the literature) against their actual LogP data, as shown in **Table S$_1$** and **Figure S$_1$**. The HPLC analysis were carried out by using a Phenomenex Luna C18, 250 x 4.6 mm, 10 μm HPLC column and MeOH/10 mM aqueous phosphate buffer (pH = 7.4) = 85/15 v/v as the mobile phase with a flow rate of 1mL/min.

Compound Name	r.t.	Corrected r.t.	Log (r.t.)	LogP
Catechol	3.34	0.00	0.00	0.95
Benzene	5.00	1.66	0.22	2.13
Bromobenzene	5.97	2.63	0.42	2.99
Ethylbenzene	6.85	3.51	0.55	3.13
Hexachlorobenzene	33.82	30.48	1.48	6.53
Compound **8**	4.58	1.24	0.09	1.50

Table S3. HPLC chromatograms of the studied compounds.

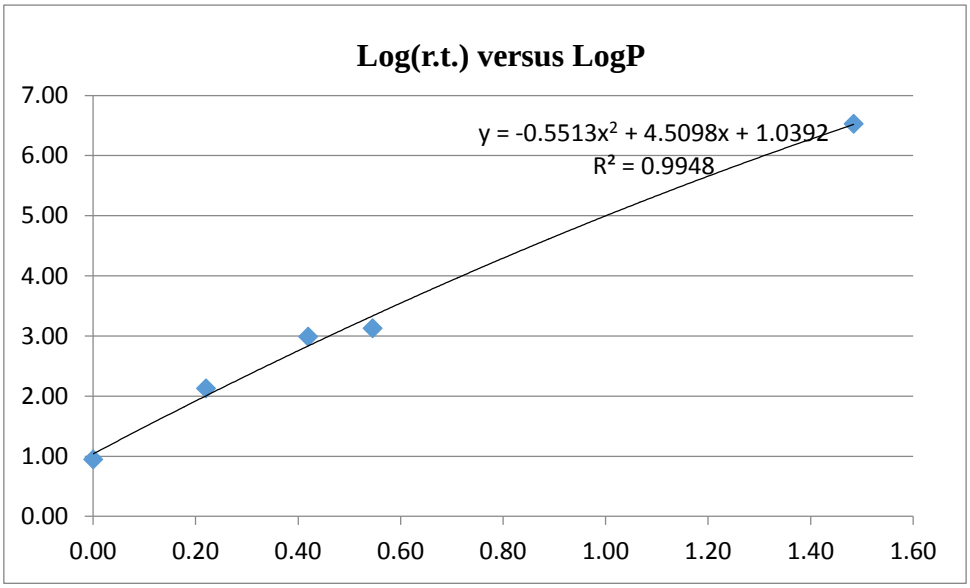


Figure S4. Standard curve of Log (r.t.) versus the corresponding LogP values.

The retention time of compound obtained under the above mentioned HPLC condition was 4.58min, therefore, the resulting LogP was 1.5, in consistent with the reported value (1.7). It demonstrates the feasibility of this HPLC method in the predictions of LogP values for the studied compounds.

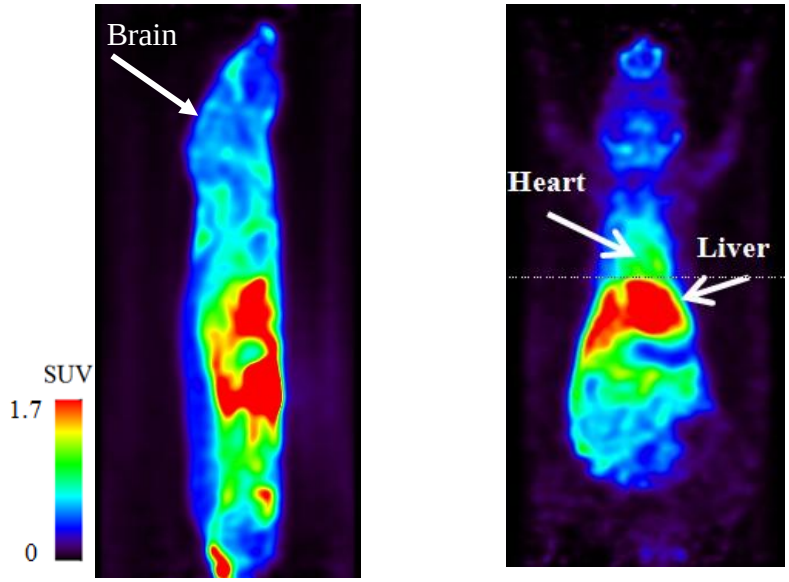
POSITRON EMISSION TOMOGRAPHY IMAGING

All animal procedures were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Massachusetts General Hospital Institutional Animal Care and Use Facility. The mice were serially imaged using a microPET. For all imaging experiments, mice were anesthetized using 2% isoflurane in O_2 at a flow rate of 1.5 L/min, positioned in a prone position along the long axis of the SOFIE Biosciences G_4 Genisys PET/X-Ray (Culver City, CA, USA) and imaged. A 60 min-dynamic PET image acquisition was initiated followed by administration of 0.1 mL of the radiotracer in a homogenous solution of 10% ethanol and 90% isotonic saline (tail iv), and 0.1 mL saline to flush the radiotracer left in the syringe into the mice. Mouse 1 and 2 were injected with 44 μCi and 40 μCi activity separately. Images were dynamically acquired for 10 frames as: 2 x 30 s, 5 x 60 s, 2 x 720 s and 1 x 1800s, and then reconstructed using a filtered back projection reconstruction algorithm. For image analysis, cylindrical regions of interest (ROIs) were manually drawn from three dimensional filtered back projection (FBP) reconstructed PET images using AMIDE software. Regional radioactivity was expressed as the standardized uptake value (SUV). Two- and three-dimensional visualizations were produced using the DICOM viewer OsiriX (© Pixmeo SARL, 2003-2014).

ROI Placement

ROIs were drawn on summed PET data manually as shown below.

(A)



(B)

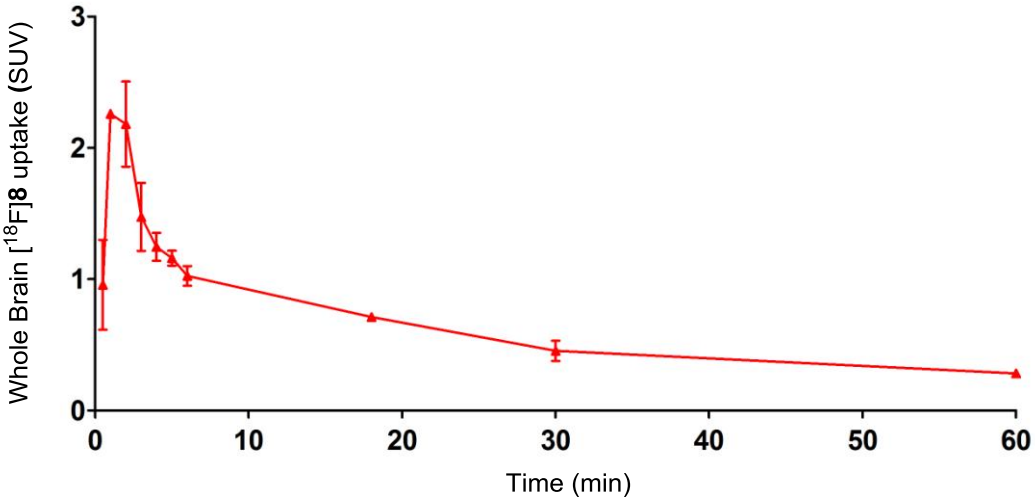


Figure S5. PET imaging studies in rodents with [^{18}F]**8**: (A) Demonstrations of ROI selections, based on summed image 0-60 min post tracer injection. (B)Time-activity curve (TAC) of the radioactivity in brain.

References

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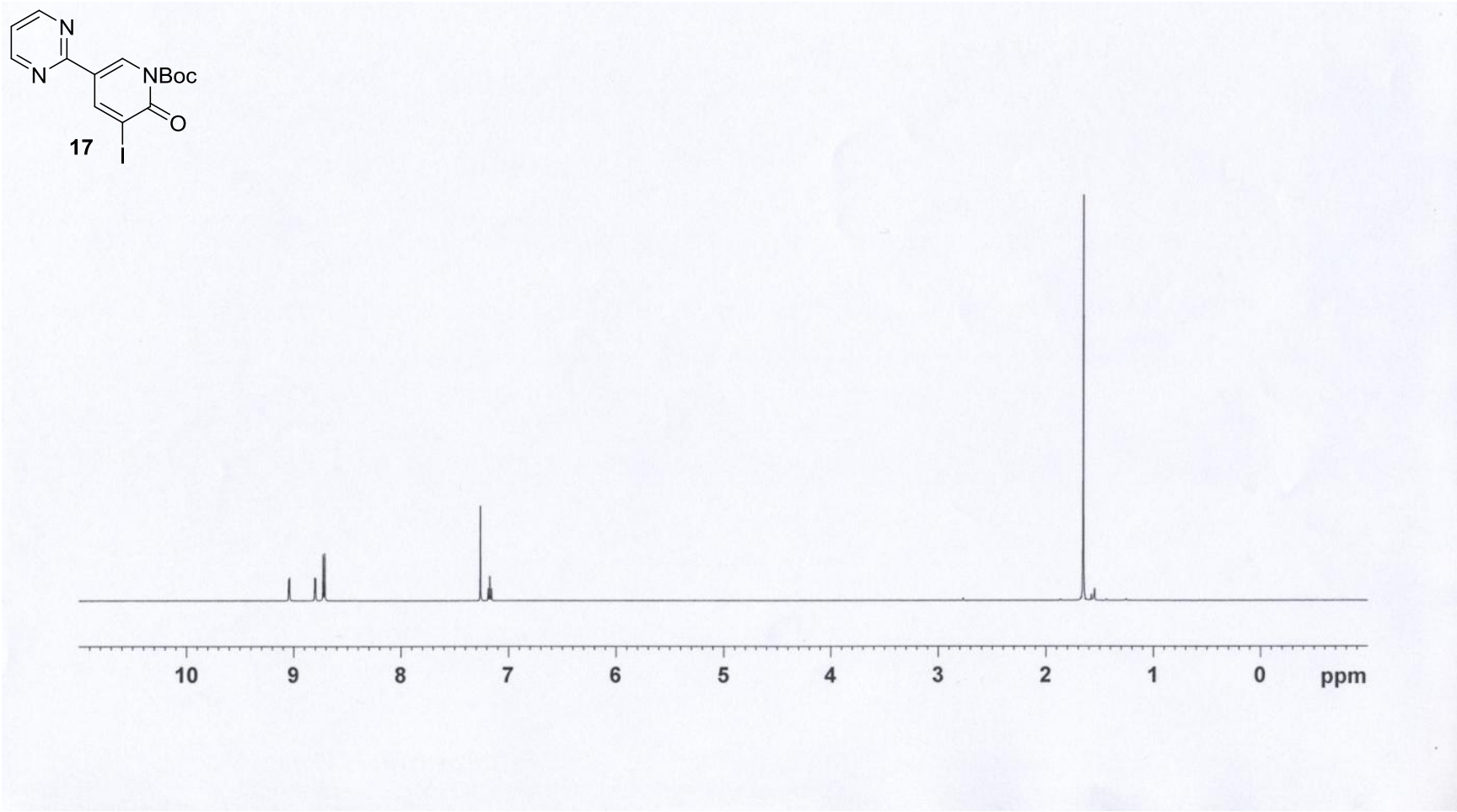
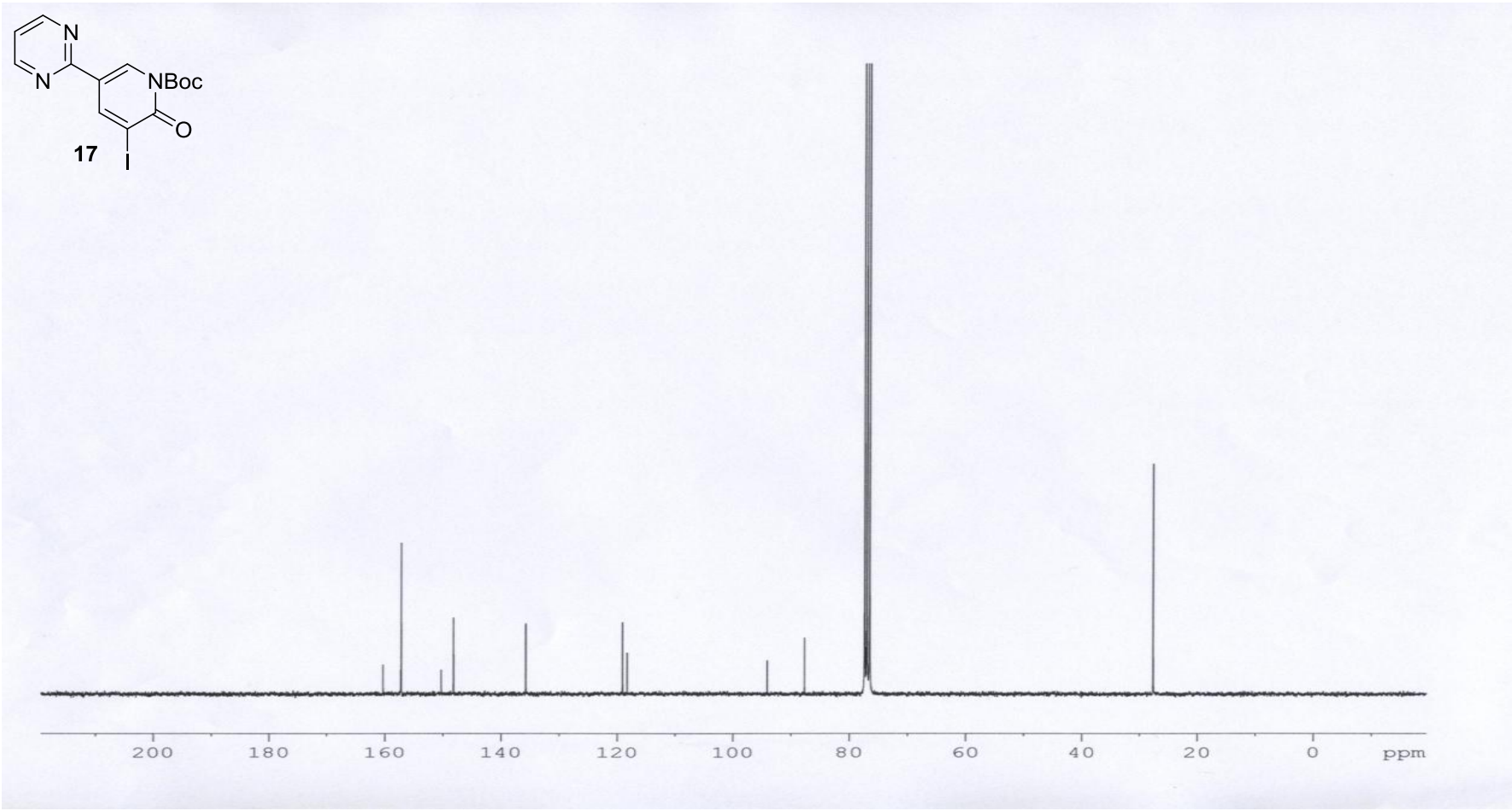
1H NMR and 13C NMR spectra:

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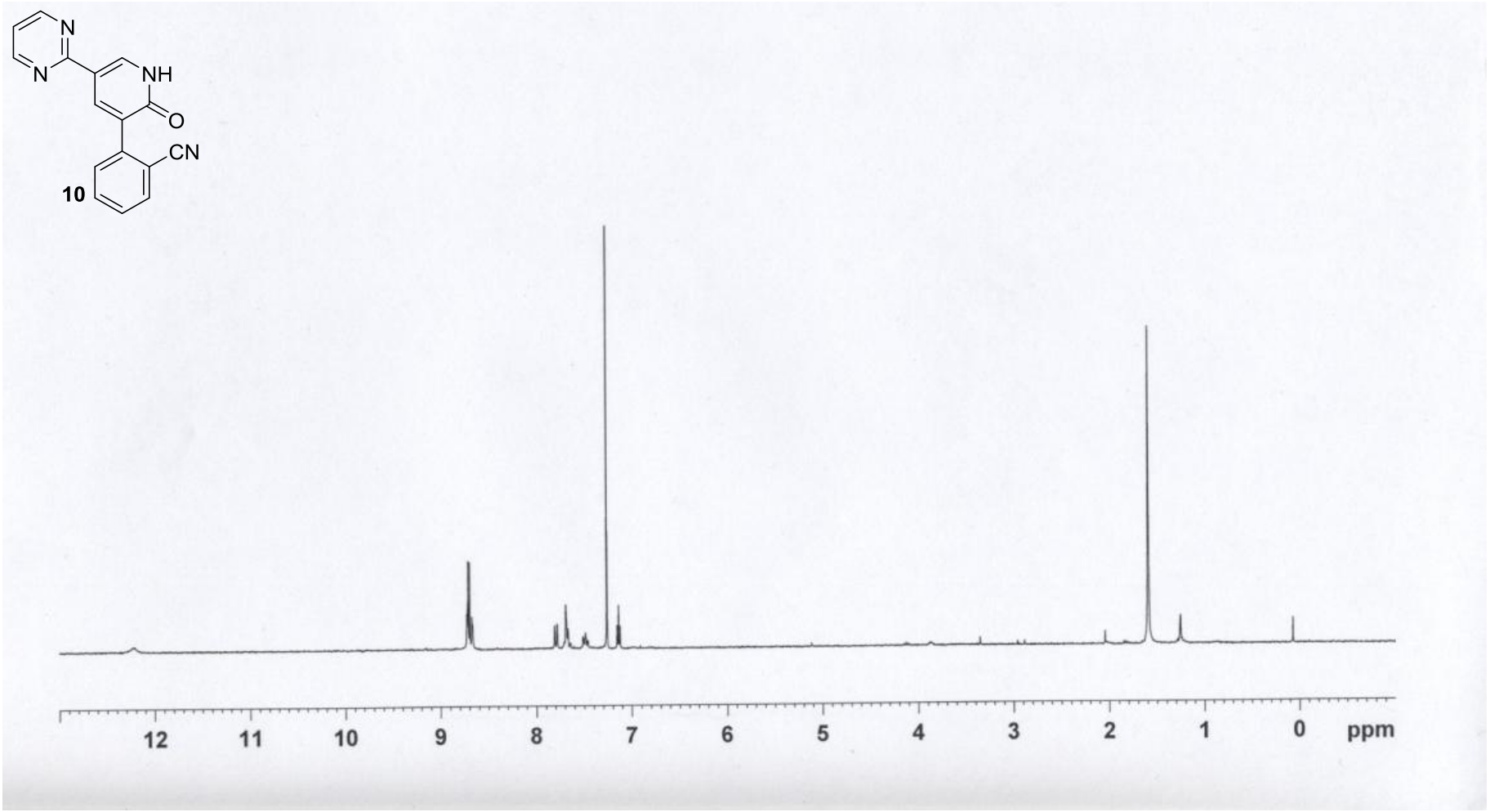
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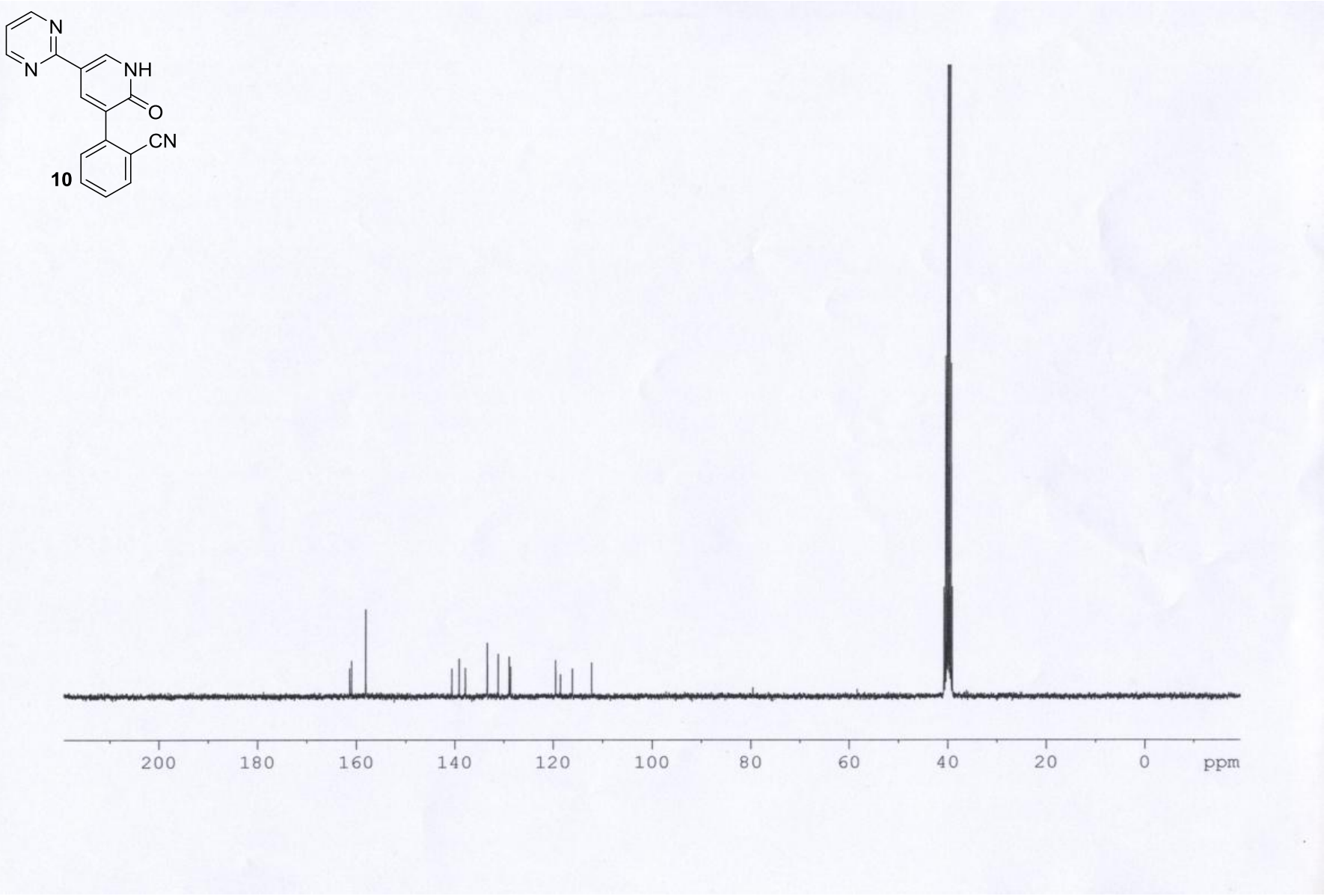
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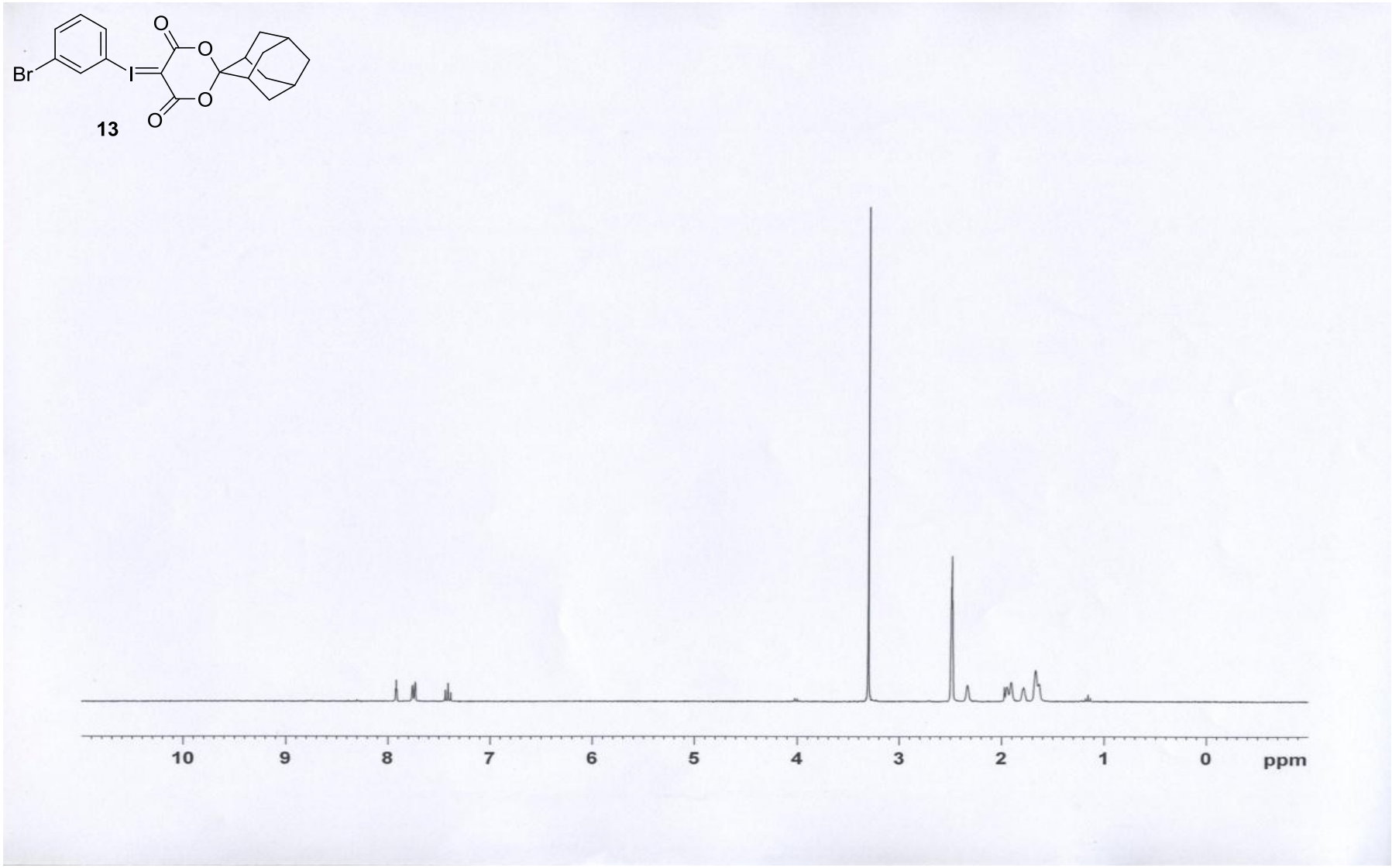
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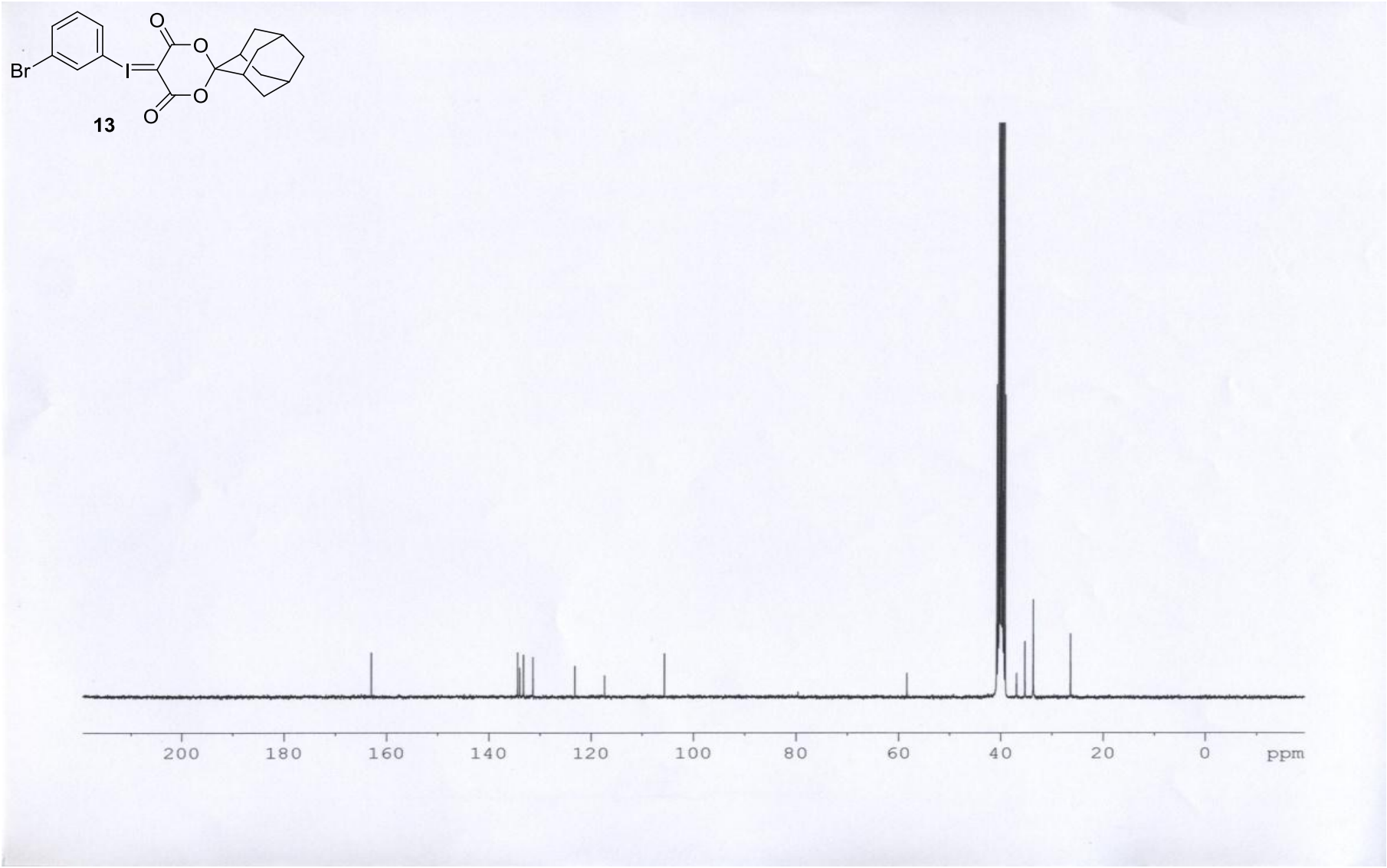
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