Supporting Information

Two-step electrochemically driven synthesis of sunitinib

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1. General information

Electrochemical synthesis was performed in undivided cells exposed to air using Electrasyn® reactor. The progress of the reactions was monitored using thin-layer chromatography (TLC) on 0.25 mm silica gel plates (60F-254), analyzed by observing fluorescence under UV lamp at 254 nm. All chemicals were obtained from commercial suppliers and were used without additional purification. The synthesis products were characterized using an NMR spectrometer (DD2, 500 MHz, Agilent, Varian), an HPLC system (Shimadzu LC20AD), and high-resolution mass spectrometry (HRMS) using an ESI-TOF mass spectrometer (LCT Premier XE, Waters).

2. Electrochemical setup

For screening reactions, reaction was performed in undivided cells using IKA ElectraSyn 2.0 with graphite electrode. For scale-up, reaction was conducted using a BIO RAD (Power Pac 1000) potentiostat. The electrodes used measure 24 x 100 x 2 mm.

a. b.

Figure 1. a. Electrochemical setup; b. Electrochemical scale-up experiment.

3. General procedure for the amidation

Compound **1** (0.3 mmol, 50.1 mg, 1 eq), PPh_3 (0.45 mmol, 118.0 mg, 1.5 eq), iodide (0.22 mmol, 1.1 eq), CH_3CN 6 mL, and *N,N*-diethylethylenediamine (**2**) (0.45 mmol, 1.5 eq) were added into a vial. Electrodes C(+)/C(-) were placed in the vial and charged with 2.2 F/mol of PPh_3 at a constant current of 70 mA (j= 15.90 mA/cm^2). Reaction conditions were optimized

using various variables. Afterward, the solution was added to 10 mL of distilled water, adjusted to pH 3 with 5% HCl, and then extracted with DCM (3 x 10 mL). The aqueous phase was adjusted to pH 9-10 with saturated sodium bicarbonate, and then extracted with DCM (3 x 10 mL). The organic phase was evaporated and weighed. The obtained mass was then dissolved in acetonitrile at a concentration of 250 mg/L for HPLC analysis. Compound **3** as a result of purification was used as a standard (10 mg/L - 320 mg/L) to create a calibration curve. With the calibration curve of compound **3**, the percent yield (% HPLC yield) of compound **3** in the crude was calculated.

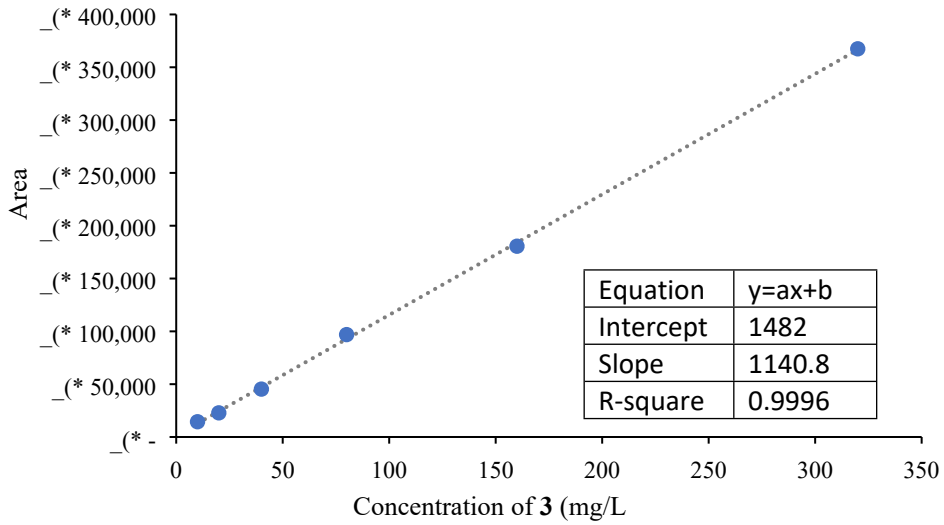


Figure 2. Calibration curve of compound **3**.

3.1. Optimization of electrochemical amidation of compound 3

Table 1. The effect of solvents and electrolytes on the amidation reaction of compound **3**.

No.	Solvent	Electrolyte	Current (mA)	F/mol	Electrode (W/C)	Yield (%)[a]
1	CH_3CN	KI	70	2.2	C/C	25
2	DCE	KI	70	2.2	C/C	4
3	EtOH	KI	70	2.2	C/C	trace
4	DMF/CH_3CN (1:1)	KI	70	2.2	C/C	trace
5	Acetone	KI	70	2.2	C/C	trace
6	THF	KI	70	2.2	C/C	nd
7	CH_3CN	NaI	70	2.2	C/C	23
8	CH_3CN	NaBr	70	2.2	C/C	2
9	CH_3CN	NaCl	70	2.2	C/C	trace
10	CH_3CN	$LiClO_4$	10	2.2	C/C	trace

[a]HPLC Yield; nd: Product not detected

The reaction was performed under the following conditions: compound **1** (0.3 mmol, 50.1 mg, 1 equiv), PPh_3 (0.45 mmol, 118.0 mg, 1.5 equiv), iodide (0.36 mmol, 1.2 equiv), and *N,N*-diethylethylenediamine (**2**) (0.45 mmol, 1.5 equiv). Carbon electrodes (C(+)/C(-)) were placed in a vial, and a charge of 2.2 F/mol relative to PPh_3 was applied at a current of 70 mA (j = 15.90 mA/cm²) at room temperature.

Table 2. The effect of electrodes on the amidation reaction of compound **3**.

No.	Solvent	Electrolyte	Current (mA)	F/mol	Electrode (W/C)	Addive	Yield (%)[a]
1	CH_3CN	KI	70	2.2	C/C	-	25
2	CH_3CN	KI	70	2.2	Pt/C	-	11
3	CH_3CN	KI	70	2.2	C/Pt		28
4	CH_3CN	KI	70	2.2	C/C	TEA	19
5	CH_3CN	KI	70	2.2	Pt/C	TEA	11
6	CH_3CN	KI	70	2.2	C/Pt	TEA	19

[a] HPLC yields

The reaction was performed under the following conditions: compound **1** (0.3 mmol, 50.1 mg, 1 equiv), PPh_3 (0.45 mmol, 118.0 mg, 1.5 equiv), iodide (0.36 mmol, 1.2 equiv), and *N,N*-diethylethylenediamine (**2**) (0.45 mmol, 1.5 equiv). Carbon electrodes were placed in a vial, and a charge of 2.2 F/mol relative to PPh_3 was applied at a current of 70 mA (j = 15.90 mA/cm²) at room temperature.

Table 3. The effect of charge on the amidation reaction of compound **3**.

No.	Solvent	Equiv.		Current (mA)	F/mol	Electrode (W/C)	Yield (%)[a]
		KI	PPh_3				
1	CH_3CN	1.5	1.1	50	2.2	C/C	trace
2	CH_3CN	2	2.0	50	2.2	C/C	5
3	CH_3CN	1.5	1.1	70	2.2	C/C	25
4	CH_3CN	1.5	1.1	80	2.2	C/C	28
5	CH_3CN	1.5	1.1	70	4.4	C/C	8
6	CH_3CN	2	2	70	1.1	C/C	4
7	CH_3CN	1.5	1.1	-	-	C/C	nd

[a] HPLC yields

The reaction was performed under the following conditions: compound **1** (0.3 mmol, 50.1 mg, 1 equiv), PPh_3 (0.45 mmol, 118.0 mg, 1.5 equiv), iodide (0.36 mmol, 1.2 equiv), and *N,N*-diethylethylenediamine (**2**) (0.45 mmol, 1.5 equiv). Carbon electrodes (C(+)/C(-)) were placed in a vial, and a charge of 2.2 F/mol relative to PPh_3 was applied at a current of 70 mA (j = 15.90 mA/cm²) at room temperature.

Table 4. The effect of reagent equivalents on the amidation reaction of compound **3**.

No.	Solvent	Equivalent			Current (mA)	F/mol	Yield (%)[a]
		KI	PPh_3	2			
1	CH_3CN	1.1	0	1.2	70	2.2	nd
2	CH_3CN	2	2	1.2	70	2.2	26
3	CH_3CN	2	2	1.2	70	2.2	33[c]
4	CH_3CN	3	2	1.2	70	2.2	25
5	CH_3CN	4.5	3.0	2.0	70	2.2	67
6	CH_3CN	4.5	3.0	3.0	70	2.2	45
7	CH_3CN	4.5	4.5	2.0	70	2.2	72[b]

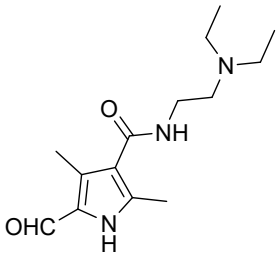
[a] HPLC yields; [b]isolated yield; [c]addition TEA (1 equiv)

The reaction was performed under the following conditions: compound **1** (0.3 mmol, 50.1 mg, 1 equiv), PPh_3 (0.45 mmol, 118.0 mg, 1.5 equiv), iodide (0.36 mmol, 1.2 equiv), and *N,N*-diethylethylenediamine (**2**) (0.45 mmol, 1.5 equiv). Carbon electrodes (C(+)/C(-)) were placed in a vial, and a charge of 2.2 F/mol relative to PPh_3 was applied at a current of 70 mA (j = 15.90 mA/cm²) at room temperature.

3.2. General procedure for scale-up of electrochemical amidation

Compound **1** (3 mmol, 0.501 g, 1 equiv.), PPh_3 (13.5 mmol, 3.541 g, 4.5 equiv.), KI (13.4 mmol, 2.241 g, 4.5 equiv.), CH_3CN 60 mL, and *N,N*-diethylethylenediamine (**2**) (6 mmol, 2.0 equiv.) were added into a glass. The reaction was carried out at room temperature in an undivided cell equipped with graphite plate electrodes (anode/cathode), and 2.2 F/mol of charge was applied in the presence of PPh_3 at a constant current of 70 mA (j = 2.5 mA/cm²). Upon completion, the solution was acidified to pH 3 using 5% HCl and extracted with DCM. The aqueous layer was then basified to pH 9–10 with saturated sodium bicarbonate and re-extracted with DCM. The combined organic layers were evaporated, and the crude product was purified by column chromatography using DCM:MeOH (9:1) as eluent, affording a light brown solid 0.2805 g (35%).

Figure 3. Scale-up reaction set up for electrochemical amidation.



***N*-(2-(diethylamino)ethyl)-5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxamide (3)**. a brown olid product: 72% yield.

Mealting point: 134 °C

^{1}H NMR (500 MHz, DMSO-d_6) δ_H 11.81 (s, 1H), 9.53 (s, 1H), 7.31 (t, J = 5.5 Hz, 1H), 3.24 (q, J = 6.5 Hz, 2H), 2.54 – 2.45 (m, 4H), 2.36 (s, 3H), 2.31 (s, 3H), 0.95 (t, J = 7.1 Hz, 6H)

^{13}C NMR (125 MHz, DMSO-d_6) δ_C 177.74, 164.83, 138.32, 131.05, 128.18, 119.92, 52.11, 46.96 (2C), 37.39, 12.94, 12.35, 10.09 (2C).

HRMS (ESI-TOF): calculated for $C_{14}H_{23}N_3O_2$ $[M+H]^+$: 266.1863; Found: 266.1858.

The analytical data are consistent with those reported in the literature[1,2].

3.3. Control experiments for the amidation

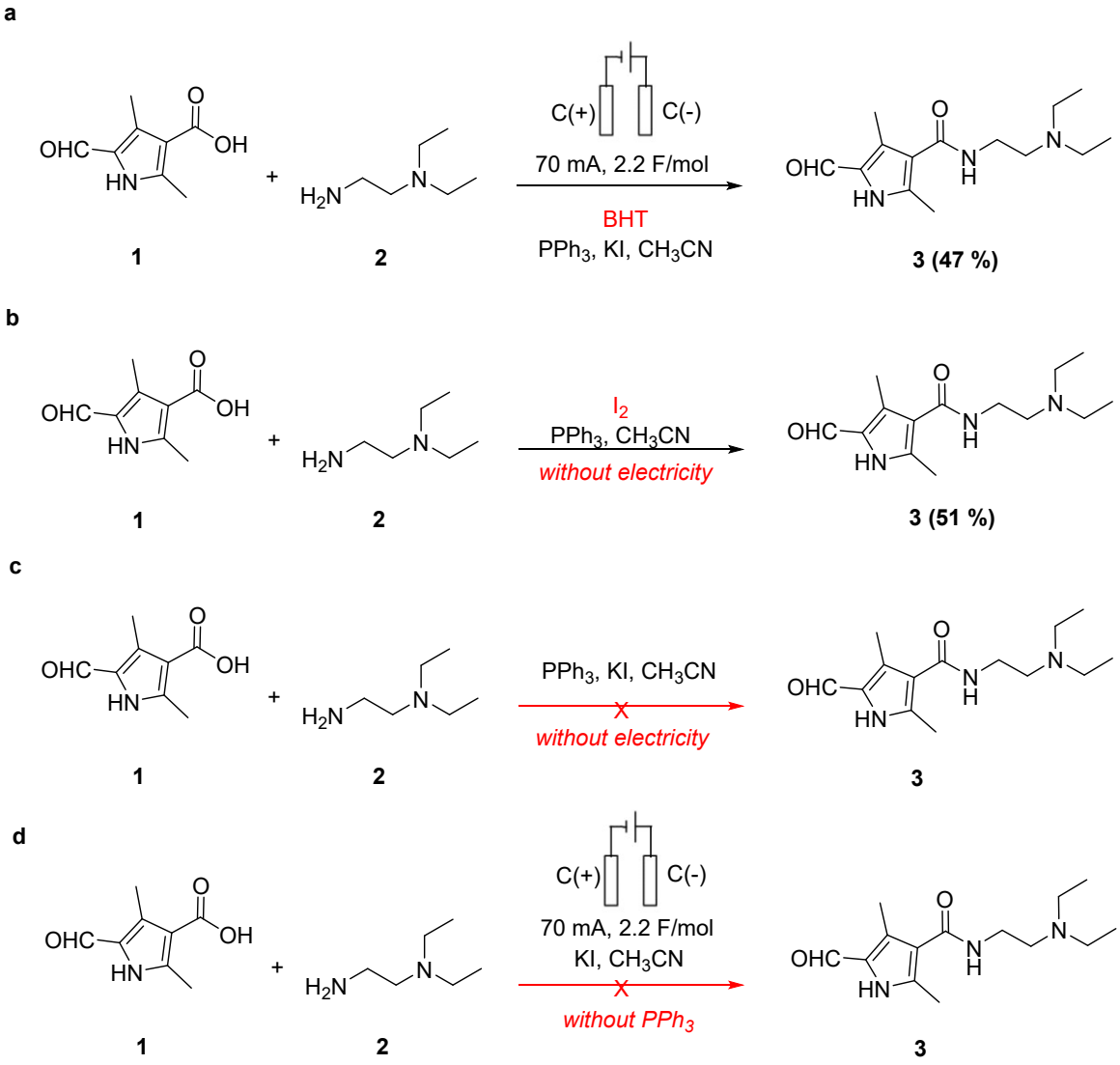


Figure 4. Control experiments for the amidation with **1** (1.0 equiv.), *N,N*-diethylethylenediamine **2** (2 equiv.) under following conditions: a. PPh_3 (4.5 equiv), KI (4.5 equiv.) BHT (2.0 equiv.); b. PPh_3 (4.5 equiv), I_2 (2 equiv.); c. PPh_3 (4.5 equiv), KI (4.5 equiv.); d. KI (4.5 equiv.).

4. General procedure for condensation

Compounds **4** (0.248 mmol, 1.5 equiv) and **3** (0.165 mmol, 1 equiv) were dissolved in 4 mL of solvent. The reaction was conducted at room temperature using C(+) and C(-) electrodes under a constant current. The reaction conditions were optimized by varying the parameters. Upon completion of the reaction, 5 mL of distilled water and a few drops of ethanol were added to the reaction mixture. The resulting precipitate was filtered to obtain pure sunitinib.

4.1. Optimization of electrochemical condensation

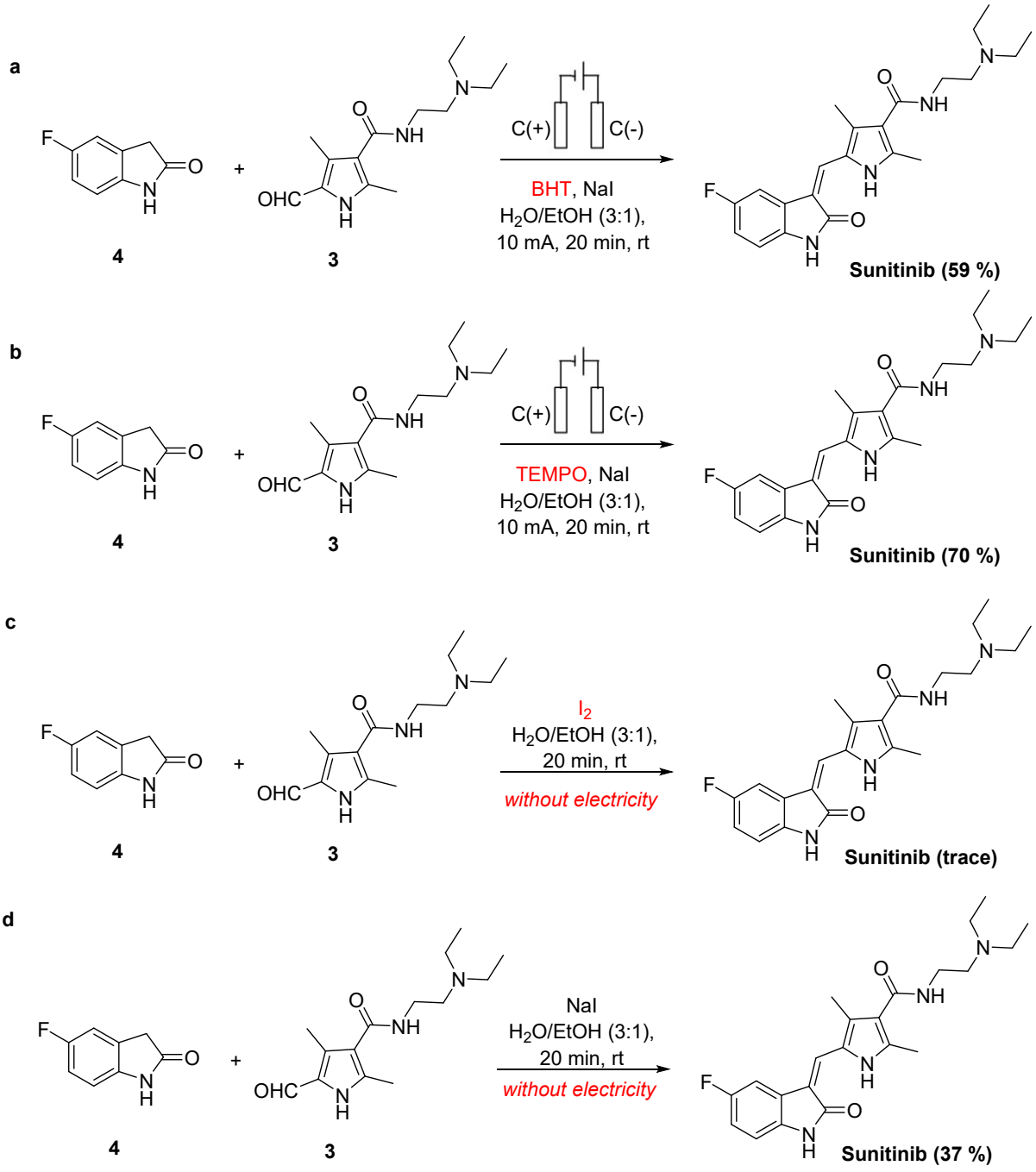
Table 5. Optimization of electrochemical condensation of sunitinib

No.	Solvent	Electrolyte	Current (mA)	Time (min)	Temp. (°C)	Electrode (W/C)	Yield (%)[b]
1	H_2O/EtOH (3:1)	NaBr (0.025 M)	10	20	RT	C/C	68
2	H_2O/EtOH (1:1)	NaBr (0.025 M)	10	20	RT	C/C	47
3	H_2O	NaBr (0.025 M)	10	20	RT	C/C	60
4	H_2O	NaBr (0.05 M)	10	20	RT	C/C	65
5	H_2O	NaBr (0.1 M)	10	20	RT	C/C	66
6	H_2O	NaBr (0.05 M)	10	20	50	C/C	73
7	H_2O	NaBr (0.05 M)	10	20	65	C/C	74
8	H_2O/EtOH (3:1)	NaBr (0.025 M)	20	20	50	C/C	56
9	H_2O/EtOH (3:1)	NaBr (0,025 M)	-	20	50	C/C	37
10	H_2O/EtOH (3:1)	-	10	20	RT	C/C	30
11	H_2O/EtOH (3:1)	NaBr (0.025 M)	10	30	RT	C/C	78
12	H_2O/EtOH (3:1)	NaI (0.025 M)	10	20	RT	C/C	95
13	H_2O/EtOH (3:1)	NaCl (0.025 M)	10	20	RT	C/C	68
14	H_2O/EtOH (3:1)	$LiClO_4$ (0.025 M)	10	20	RT	C/C	34
15	H_2O/EtOH (3:1)	NBu_4PF_6 (0.025 M)	10	20	RT	C/C	56
16	H_2O	NaI (0.025 M)	10	20	RT	C/C	89
17	H_2O/EtOH (3:1)	NaI (0.025 M)	-	20	RT	C/C	36
18	H_2O/EtOH (3:1)	NaI (0.025 M)	10	40	RT	C/C	73
19	H_2O/EtOH (3:1)	NaI (0.025 M)	10	30	RT	C/C	81
20	H_2O/EtOH (3:1)	NaI (0.025 M)	10	10	RT	C/C	74
21	H_2O/EtOH (3:1)	NaI (0.025 M)	10	20	RT	Pt/C	90
22	H_2O/EtOH (3:1)	NaI (0.025 M)	10	20	RT	C/Pt	87

[b]Isolated yield.

Reaction conditions: **4** (0.248 mmol, 1.5 equiv), **3** (0.165 mmol, 1 equiv), 4 mL of solvent.

4.2. Control experiments for the condensation



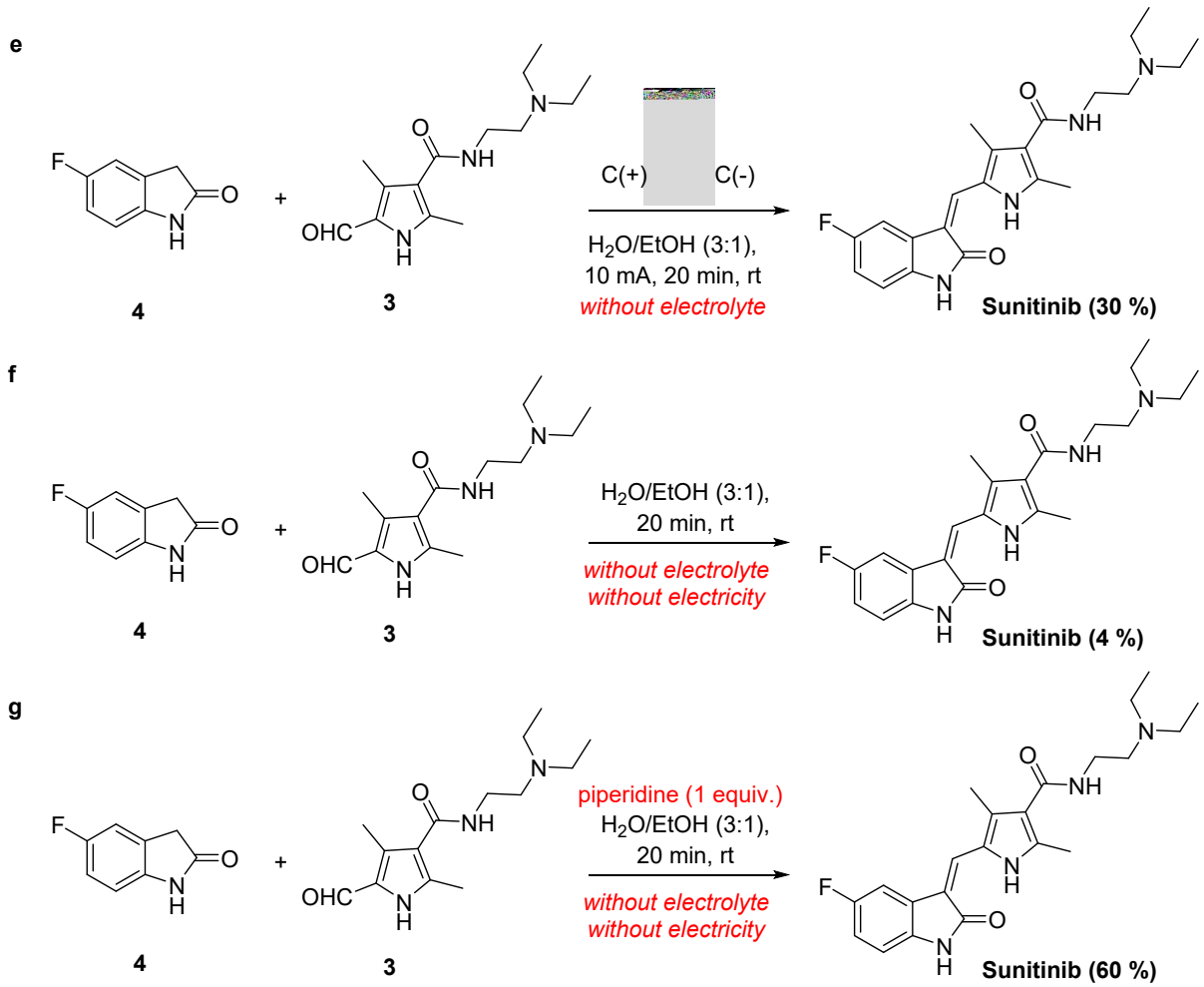


Figure 5. Control experiments for the condensation with **4** (1.5 equiv.), **3** (1.0 equiv.) under following conditions: a. NaI (0.025 M), BHT (2.0 equiv.); b. I_2 (1.0 equiv.); c. NaI (0.025 M), no electricity was used; d. no electrolyte was used; e. no electrolyte and electricity.

4.3. General procedure for scale-up of electrochemical condensation

Compounds **3** (1.9 mmol, 0.5 g, 1.0 equiv), **4** (2.83 mmol, 0.43 g, 1.5 equiv), and NaI (1.1 mmol, 0.17 g, 0.6 equiv) were dissolved in 12 mL of ethanol, followed by the addition of 36 mL of water. The reaction was conducted at room temperature using C(+) and C(-) electrodes under a constant current 10 mA (j = 0.365 mA/cm^2) for 20 min. Upon completion of the reaction, water added to the reaction mixture. The resulting yellow precipitate was filtered and recrystallized with ethanol to afford pure sunitinib (0.643 mg, 86%).

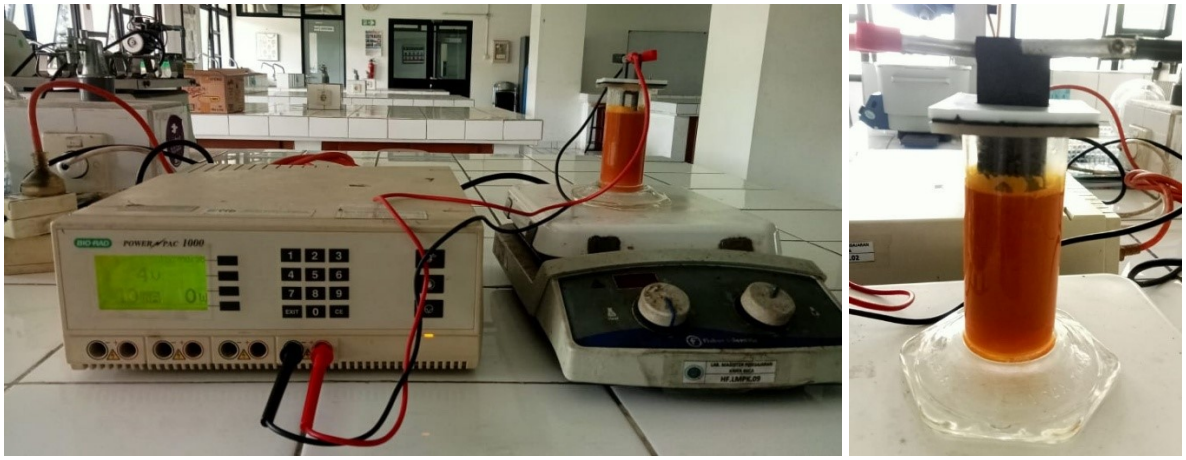
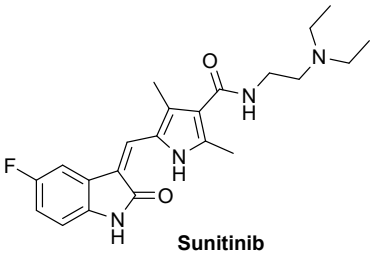


Figure 6. Scale-up reaction set up for electrochemical condensation.



Sunitinib

Sunitinib. a yellow solid product: 86% yield from scale-up reaction after recrystallisation.

Melting point: 223°C

^{1}H NMR (500 MHz, DMSO-d_6) δ 13.70 (s, 1H, pyrrole-NH), 10.92 (s, 1H, oxindole-NH), 7.77 (dd, J = 9.4, 2.6 Hz, 1H), 7.72 (s, 1H, alkene-CH), 7.45 (t, J = 5.6 Hz, 1H), 6.94 (td, J = 9.0, 2.6 Hz, 1H), 6.86 (dd, J = 8.4, 4.5 Hz, 1H), 3,30 (q, J = 6.5 Hz, 2H), 2.57 – 2.54 (m, 2H), 2.52 (d, J = 6.8 Hz, 4H), 2.46 (s, 3H, pyrrole-CH_3), 2.44 (s, 3H, pyrrole-CH_3), 0.99 (t, J = 7.1 Hz, 6H, N(CH_2CH_3)$_2$).

^{13}C NMR (125 MHz, DMSO-d_6) δ 170.02 (C=O), 164.96 (C=O), 158.68 (d, J_{CF} = 234.1 Hz, Ar-C), 137.06, 134.95 (Ar-C), 130.66 (Ar-C), 127.61 (d, J_{CF} = 9.6 Hz, Ar-C), 126.24 (Ar-C), 125.28 (Ar-C), 121.19 (Ar-C), 115.02 (d, J_{CF} = 2.7 Hz, Ar-C), 112.84 (d, J_{CF} = 23.9 Hz, Ar-C), 110.48 (d, J_{CF} = 8.5 Hz, Ar-C), 106.41 (d, J_{CF} = 25.4 Hz, Ar-C), 52.08 (NHCH$_2$CH$_2$), 46.95 (N(CH_2CH$_3$)$_2$), 37.41 (NHCH_2CH$_2$), 13.81 (pyrrole-CH_3), 12.33 (pyrrole-CH_3), 11.06.

^{19}F NMR (470 MHz, DMSO-d_6) δ 122.17.

HRMS (ESI-TOF): calculated for $C_{22}H_{27}FN_4O_2$ $[M-H]^-$: 397,2045; Found: 397,2046.

The analytical data are consistent with those reported in the literature[2,3].

5. Cyclic voltammetry experiments

Cyclic voltammograms were recorded using Metrohm - potentiostats & galvanostats in potentiostatic mode and IKA ElectraSyn 2.0, employing a Pt wire working and counter electrode and an Ag/AgCl (saturated KCl) reference electrode at room temperature °C. The CV curves was initiated at a starting potential of 0 V, with a current range of 1 mA and a scan rate of 0.1 V/s. All measurements were conducted in dry CH_3CN. In some measurements (particularly in Figure 6), we used an additional electrolyte, 0.1 M NBu_4PF_6.

Figure 7. Cyclic voltammetry experiments.

6. References

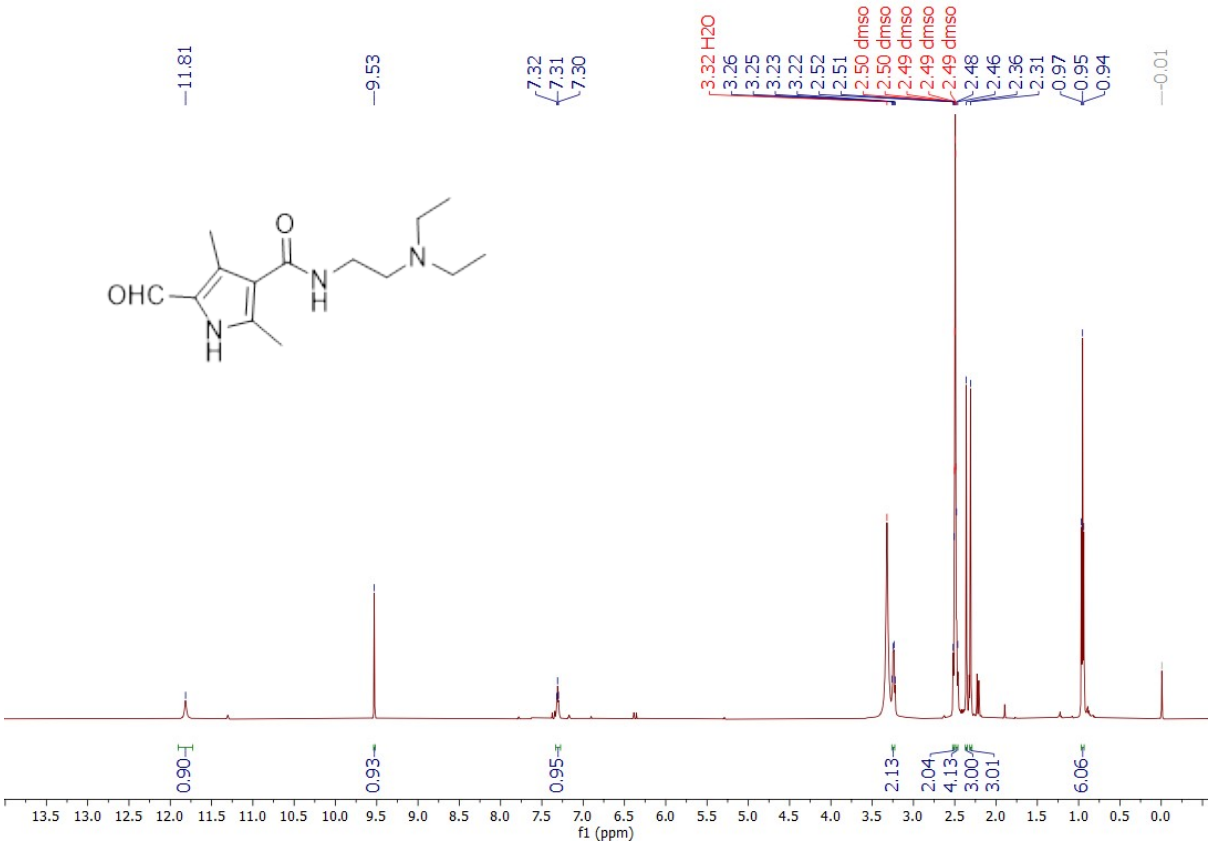
1 K. Lv, L.-L. Wang, M.-L. Liu, X.-B. Zhou, S.-Y. Fan, H.-Y. Liu, Z.-B. Zheng and S. Li, *Bioorganic & Medicinal Chemistry Letters*, 2011, **21**, 3062–3065.

2 C. J. Matheson, K. A. Casalvieri, D. S. Backos, M. Minhajuddin, C. T. Jordan and P. Reigan, *European Journal of Medicinal Chemistry*, 2020, **197**, 112316.

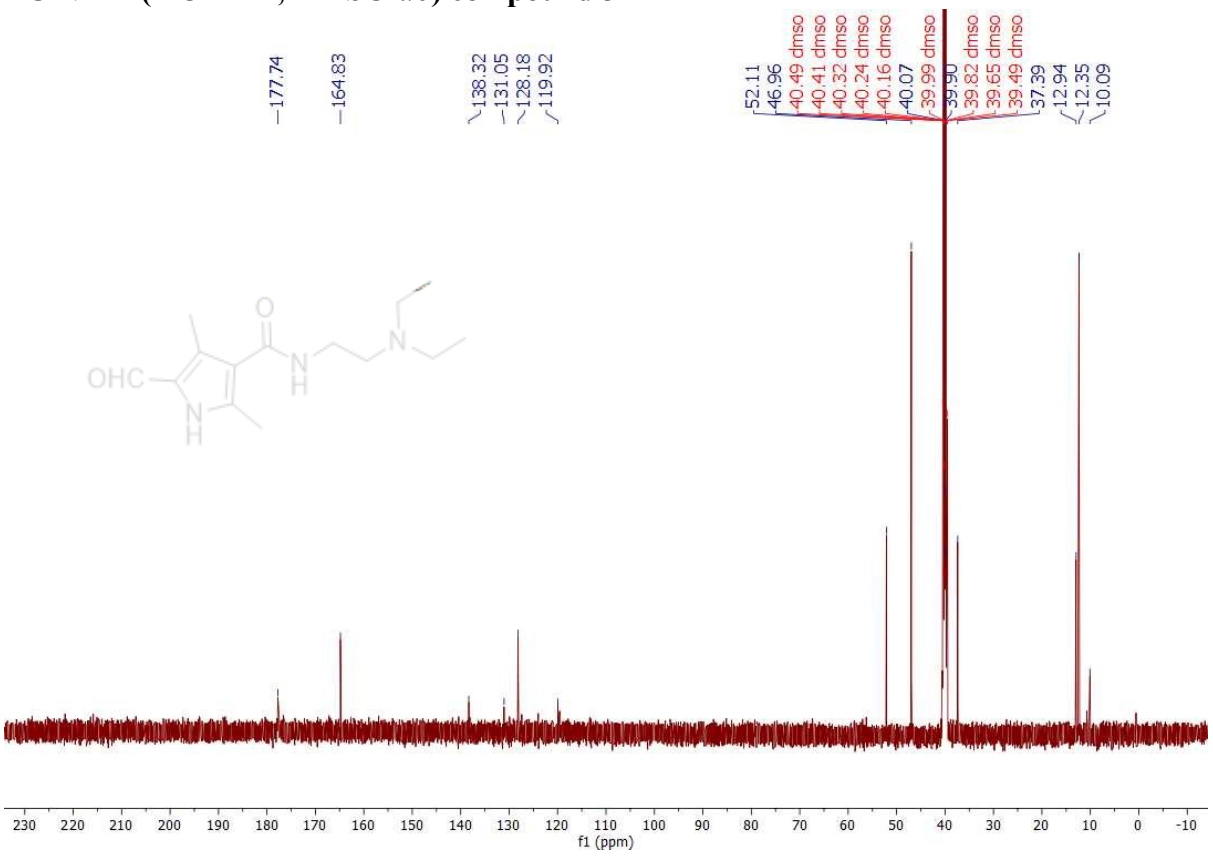
3 G. Meng, C. Liu, S. Qin, M. Dong, X. Wei, M. Zheng, L. Qin, H. Wang, X. He and Z. Zhang, *Res Chem Intermed*, 2015, **41**, 8941–8954.

7. Attachments: NMR & HRMS spectra

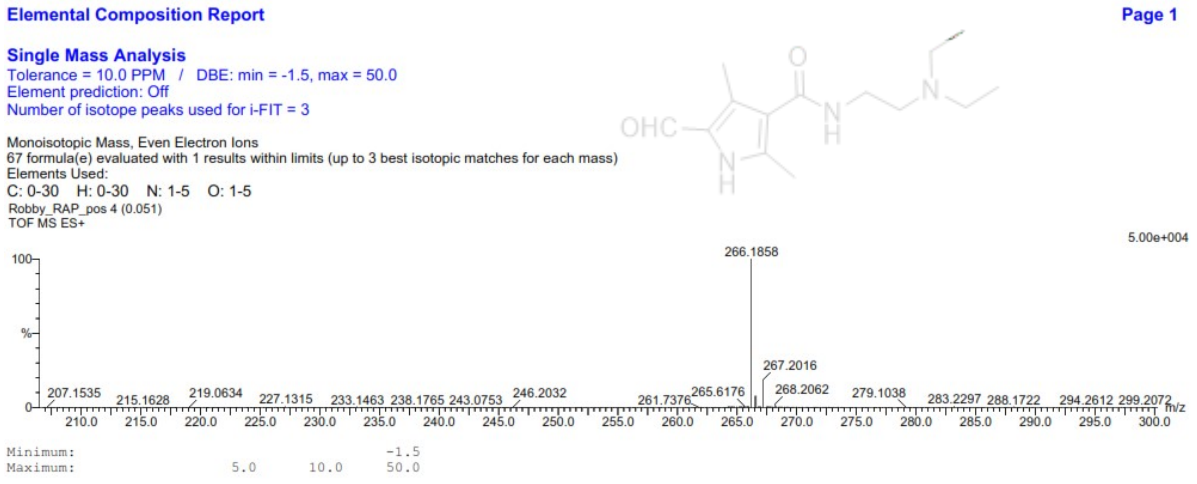
^{1}H NMR (500 MHz, DMSO-*d6*) compound 3



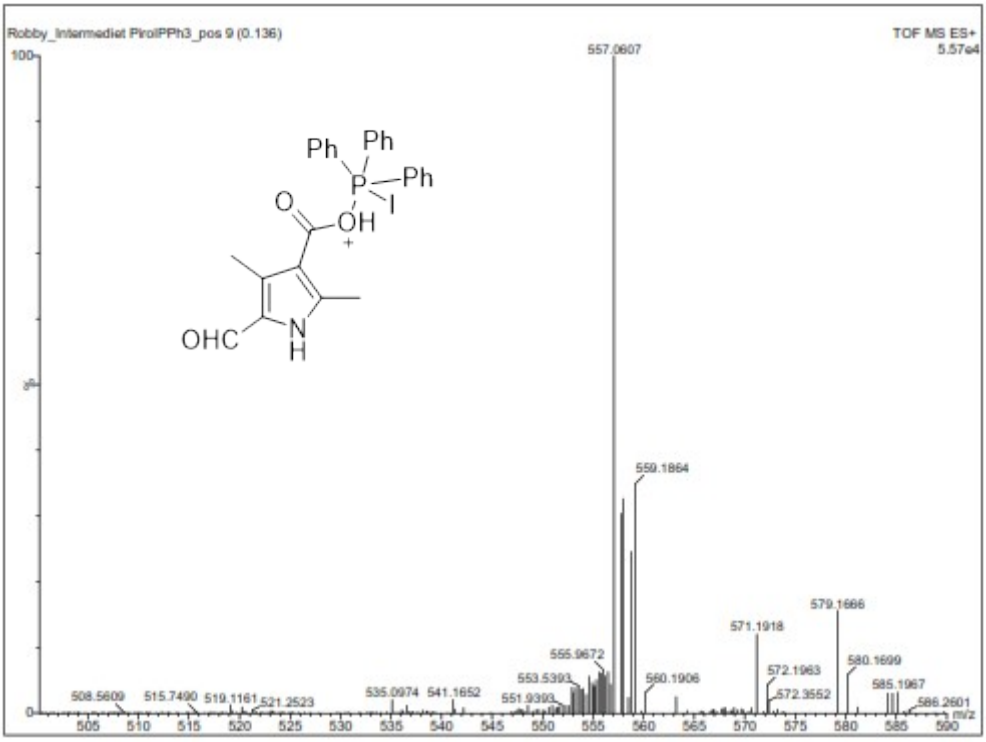
^{13}C NMR (125 MHz, DMSO-*d6*) compound 3

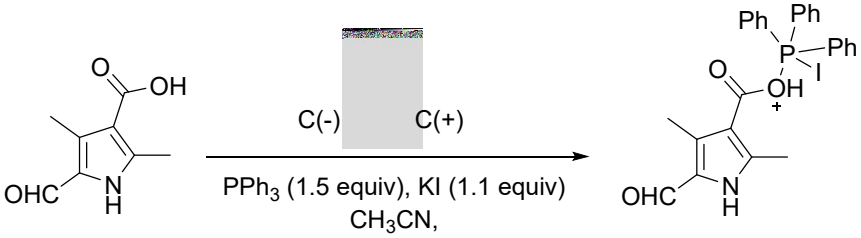


HRMS (ESI-TOF) spectrum of compound 3



HRMS spectrum of intermediate II compound 3



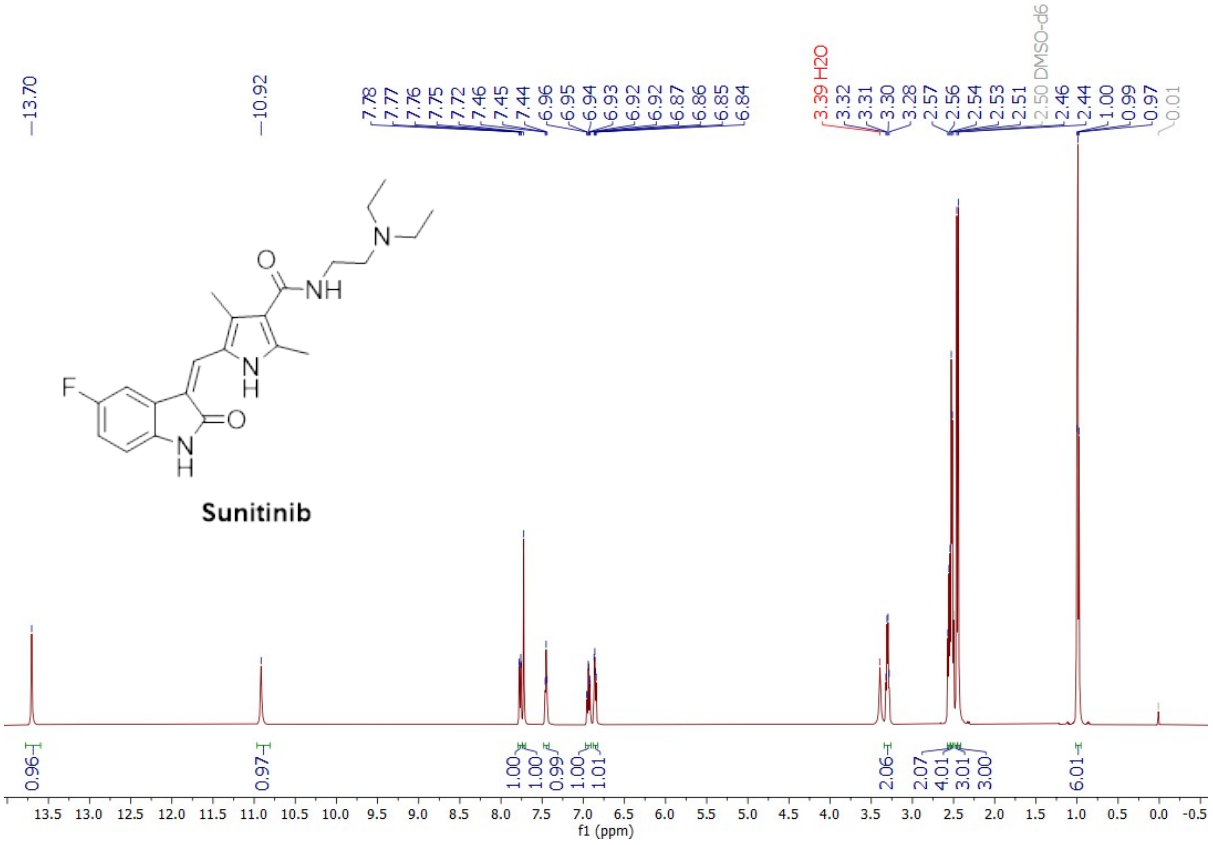


1

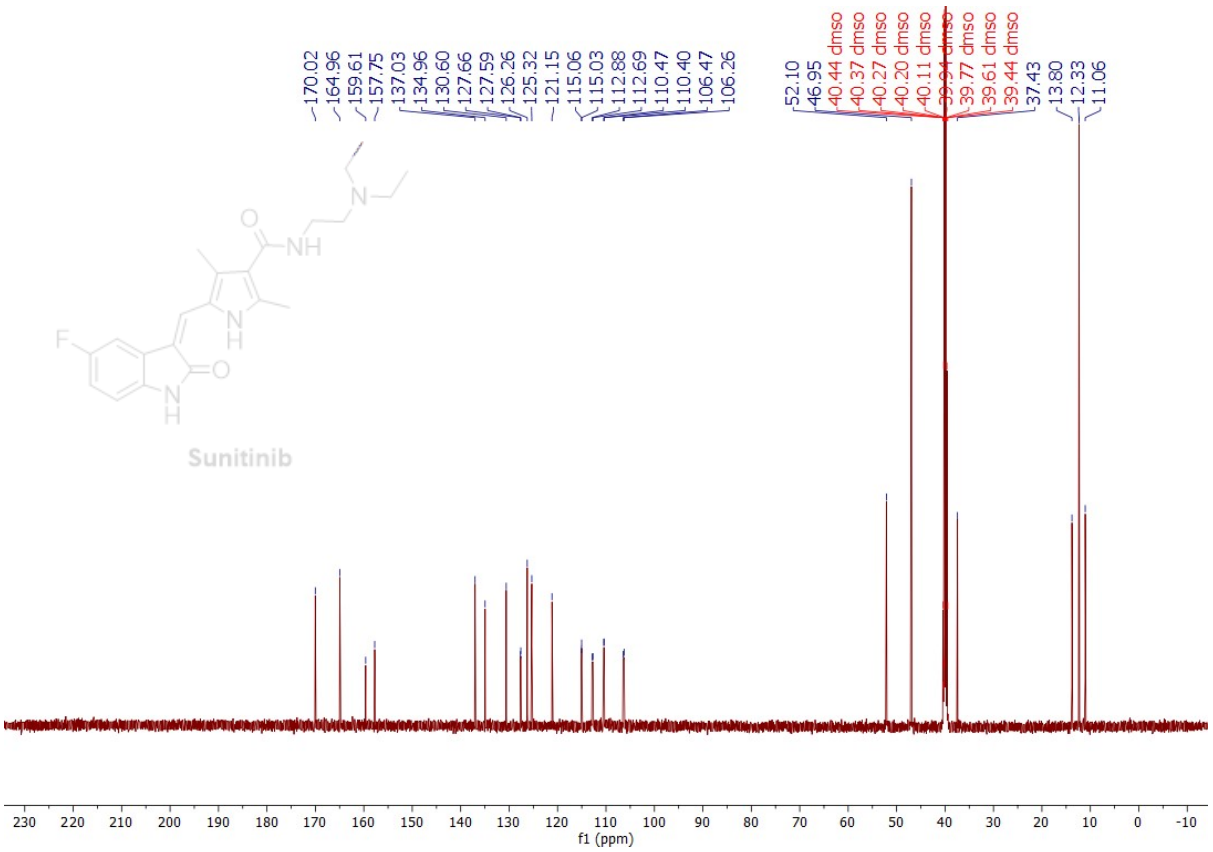
PPh_3 (1.5 equiv), KI (1.1 equiv)
CH_3CN,
2.2 F/mol (27 min), 70 mA

Intermediate II
m/z = 557.0607 $[M+H]^+$
detected by HRMS

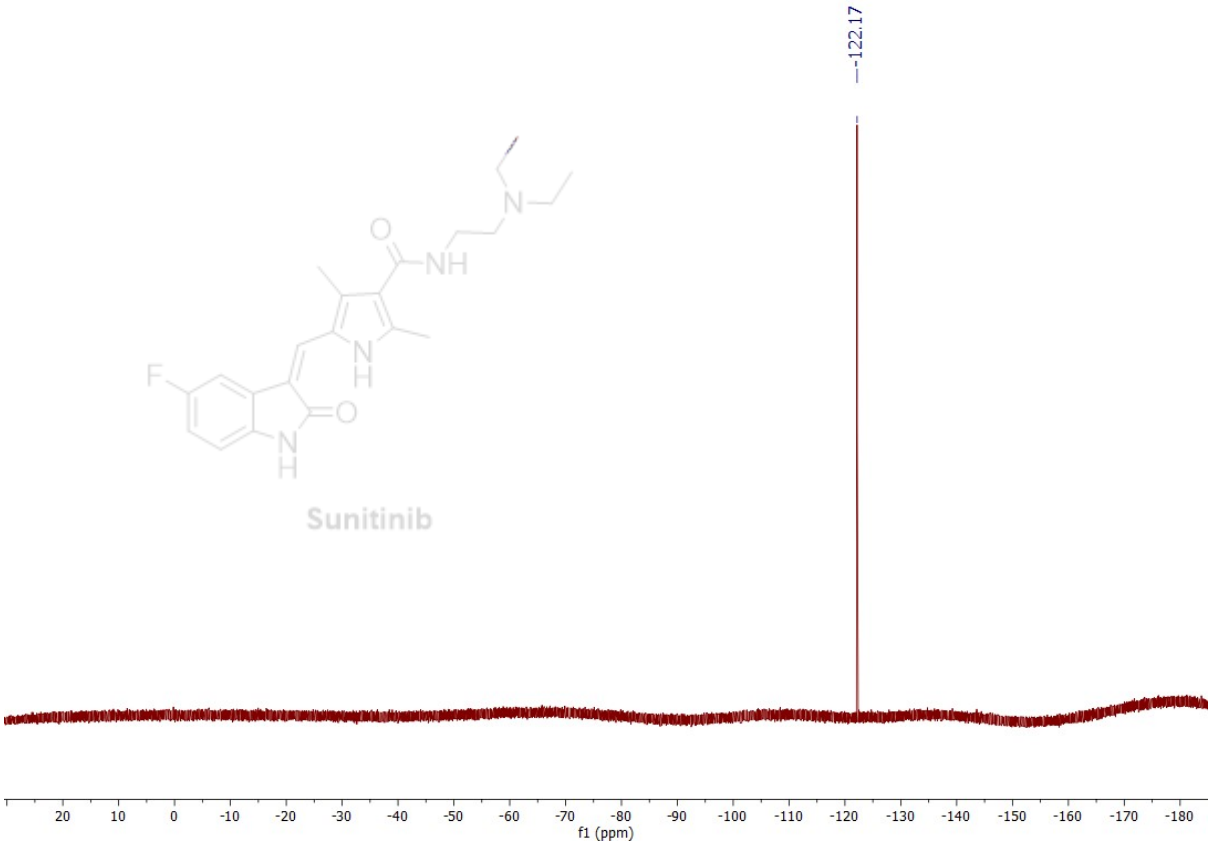
[1]H NMR (500 MHz, DMSO-*d6*) compound sunitinib



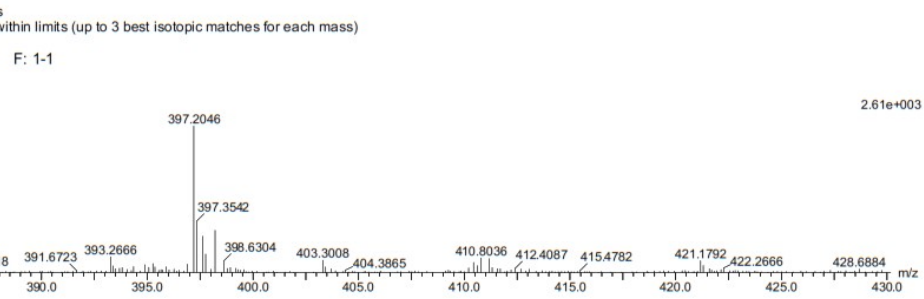
[13]C NMR (125 MHz, DMSO-d6) compound sunitinib



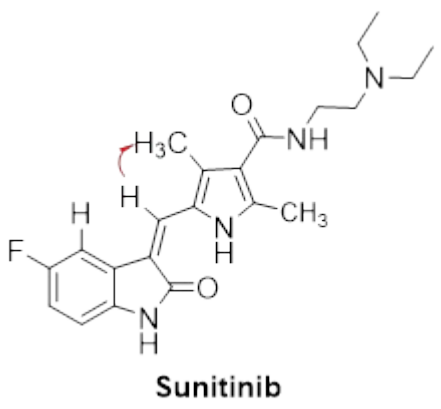
^{19}F NMR (470 MHz, DMSO-d_6) **compound sunitinib**

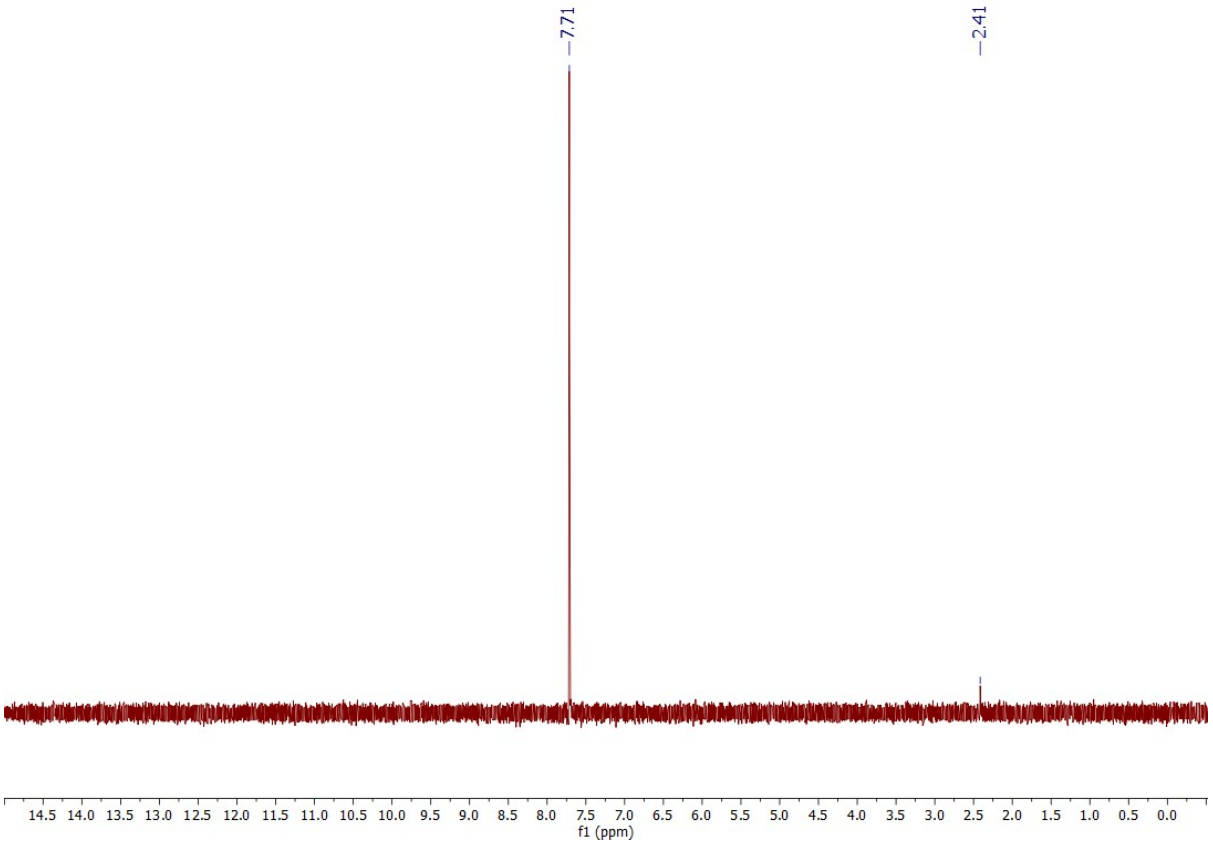


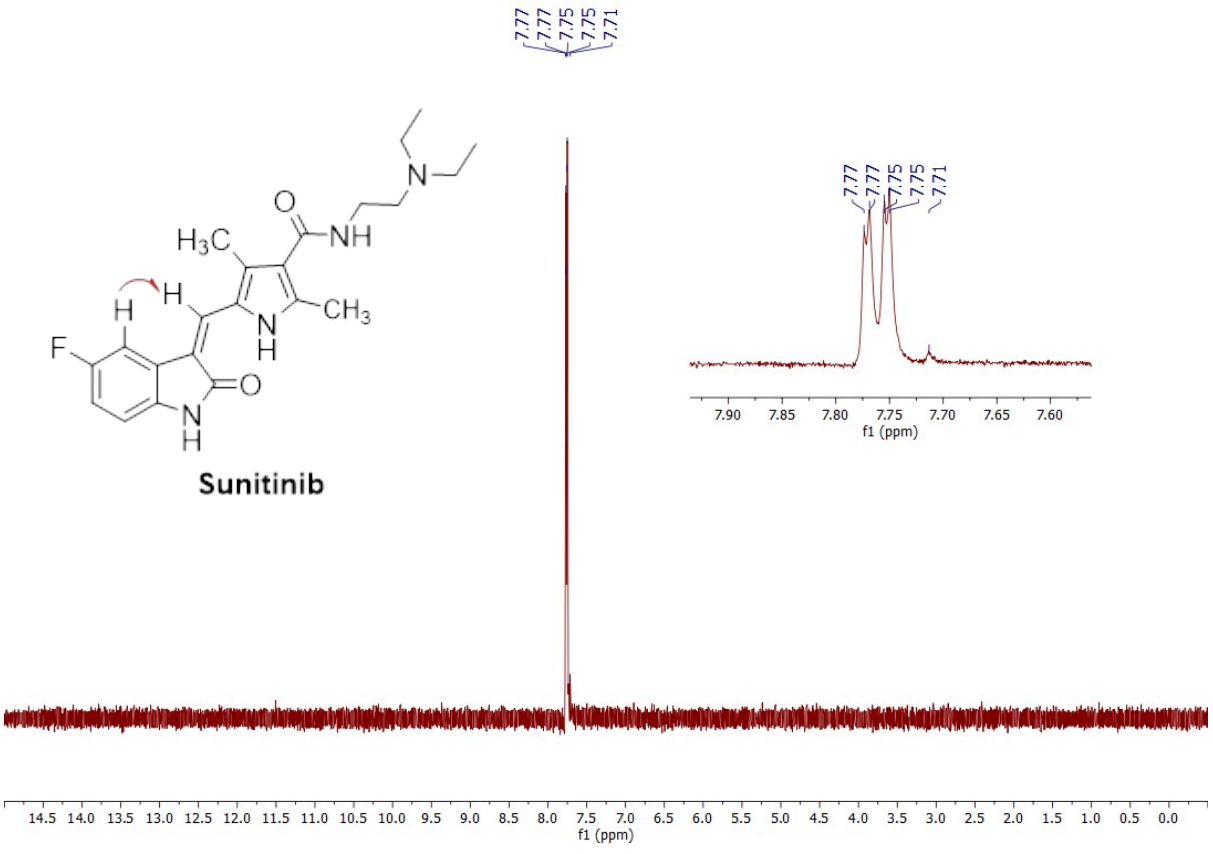
HRMS (ESI-TOF) spectrum of compound sunitinib



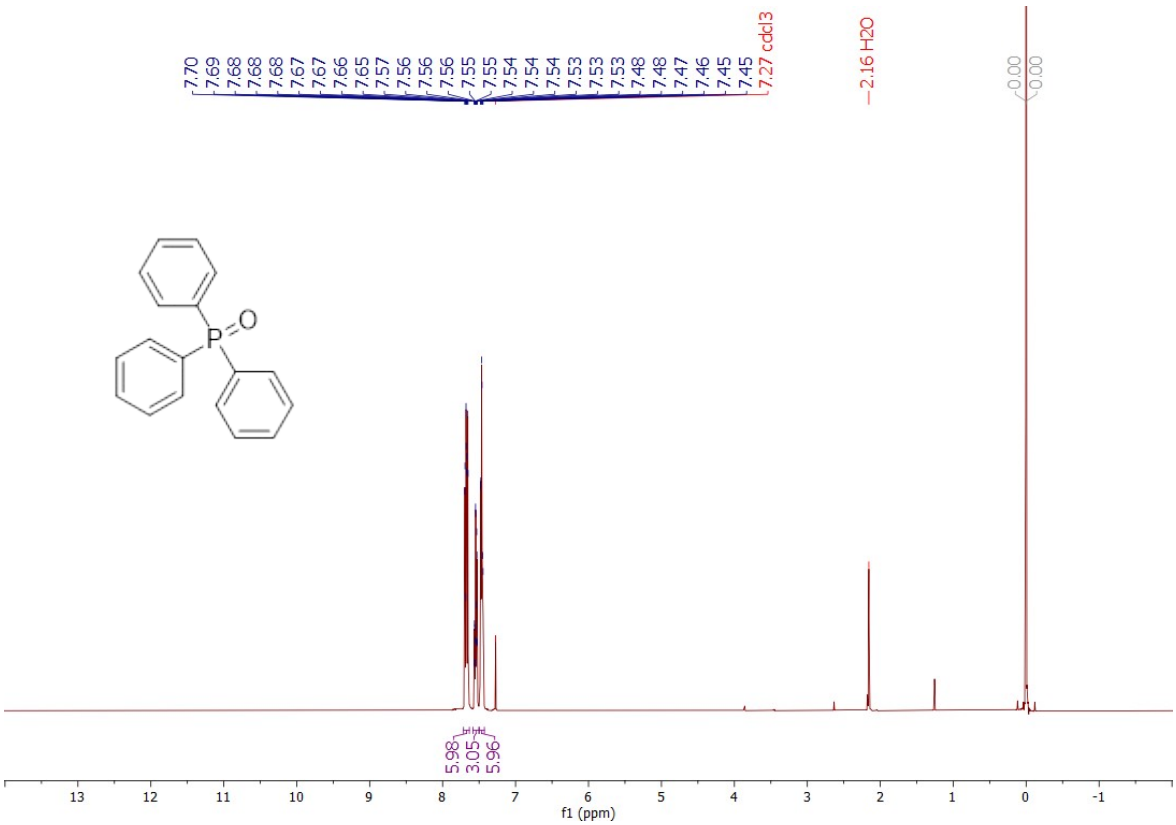
1D-NOESY NMR (500 MHz, DMSO-*d6*) to confirm the *Z*-configuration of electrochemically synthesized sunitinib



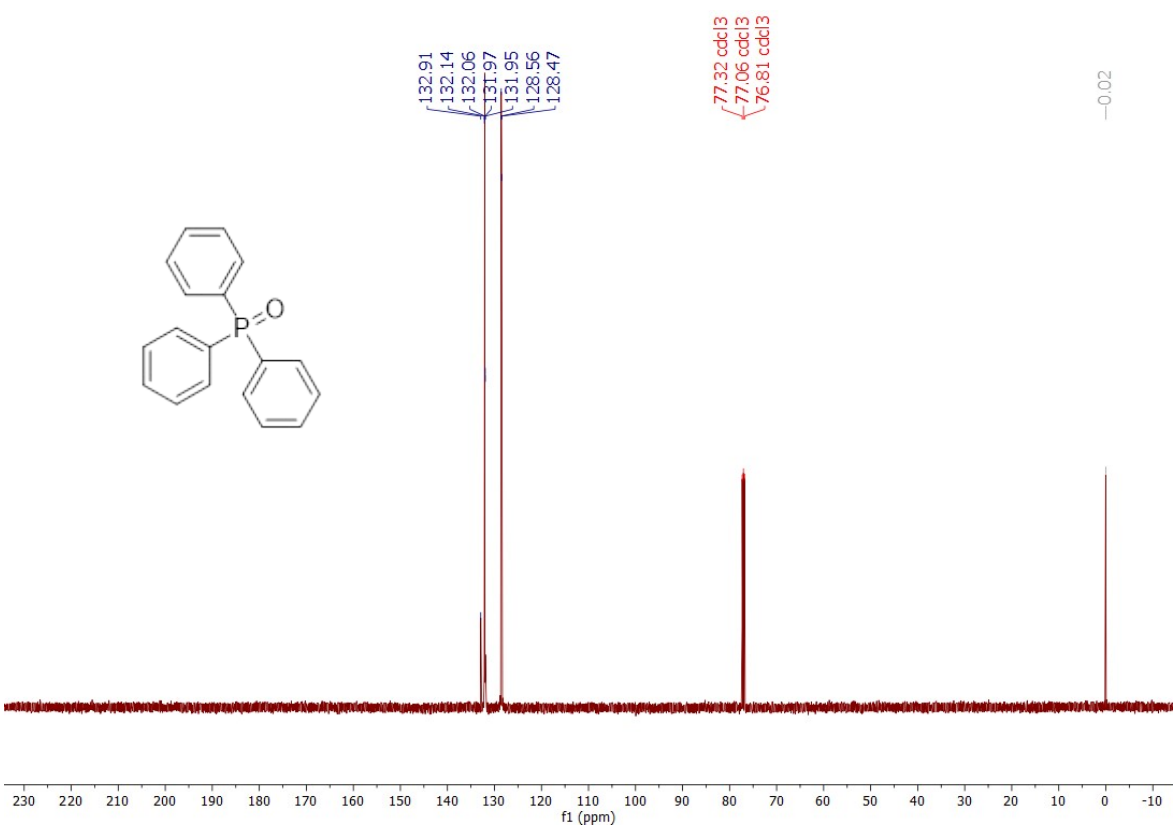




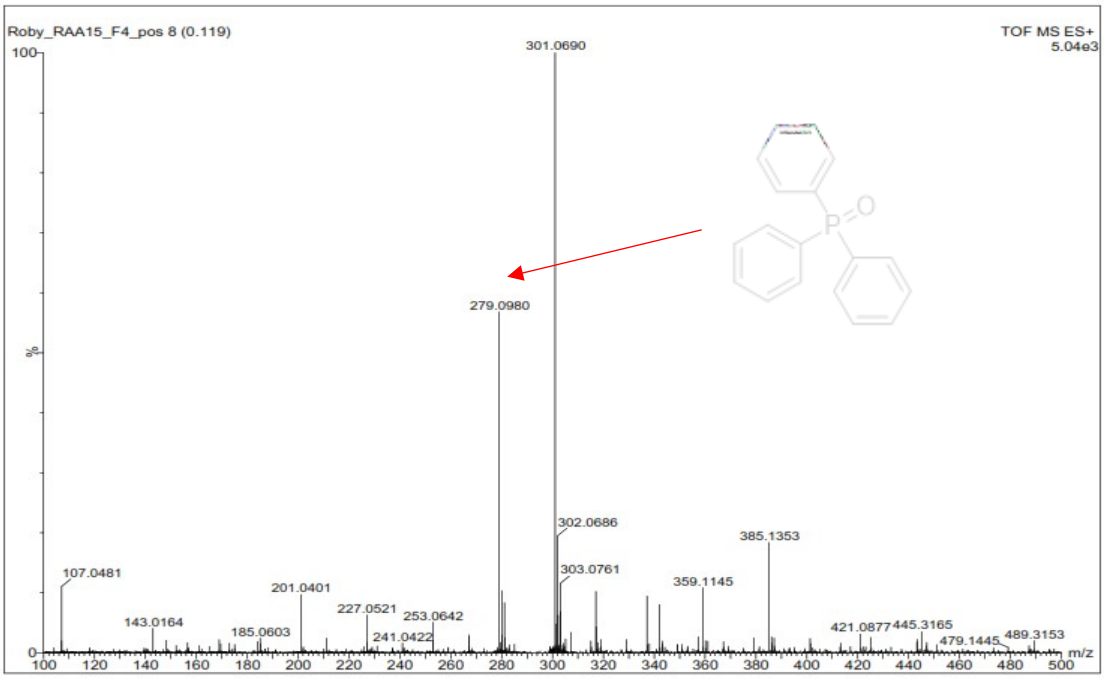
^{1}H NMR (500 MHz, $CDCl_3$) compound $Ph_3P=O$



^{13}C NMR (125 MHz, $CDCl_3$) compound $Ph_3P{=}O$



HRMS (ESI-TOF) spectrum of compound Ph_3PO


Roby_RAA15_F4_pos 8 (0.119)
TOF MS ES+
5.04e3
100
%
0
301.0690
279.0980
302.0686
303.0761
385.1353
359.1145
107.0481
201.0401
227.0521
253.0642
241.0422
143.0164
185.0603
421.0877
445.3165
479.1445
489.3153
m/z
100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500