Electronic Supplementary Material (ESI) for Green Chemistry.

Electronic Supplementary Information

An Environmentally Responsible Synthesis of the Antitumor Agent Lapatinib (Tykerb)

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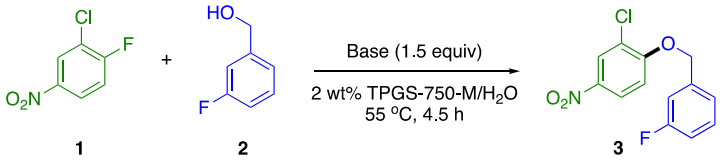
1. General information

Reagents and chemicals were purchased from Sigma-Aldrich, Combi-Blocks, Alfa Aesar, Acros Organics, or TCI Chemicals and used without further purification. Carbonyl iron powder (CIP) used for reductions was 99.9% purity, R10 grade, with average particle size of 2.5-3.5 µm. This material was stored in air with no special precautions. Deuterated solvents were purchased from Cambridge Isotopes Laboratories. TPGS-750-M is either prepared or supplied by PHT International (also available from Sigma-Aldrich catalog #733857). The desired 2 wt % of surfactant solution in HPLC water was prepared by dissolving 2 g of surfactant to 98 g of HPLC water (which was degassed with argon prior to use) and stored under argon. Thin-layer chromatography (TLC) was performed using Silica Gel 60 F254 plates (Merck, 0.25 mm thick). Flash chromatography is performed either manually or in an automated Biotage system using Silica Gel 60 (Silicycle, 40-63 nm). GCMS data were recorded on a 5975C Mass Selective Detector, coupled with a 7890A Gas Chromatograph (Agilent Technologies). ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on either a Bruker Avance III HD 400 MHz (400 MHz for ^{1}H, 100 MHz for ^{13}C), a Bruker Avance NEO 500 MHz (500 MHz for ^{1}H, 125 MHz for ^{13}C, 470 MHz for ^{19}F) or on a Varian Unity Inova 500 MHz (500 MHz for ^{1}H, 125 MHz for ^{13}C); DMSO-d_6, $CDCl_3$, or CD_3OD was used as NMR solvent. Residual peaks for DMSO in DMSO-d_6 (^{1}H = 2.50 ppm, ^{13}C = 39.51 ppm), $CHCl_3$ in $CDCl_3$ (^{1}H = 7.26 ppm, 13C = 77.00 ppm), CH_3OH in CD_3OD (^{1}H = 3.31 ppm, ^{13}C = 49.00 ppm) have been assigned. The chemical shifts are reported in parts per million (ppm), the coupling constants *J* values are given in Hertz (Hz). The peak patterns are indicated as follows: bs, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet. HRMS were recorded on a Waters Micromass LCT TOF ES+ Premier mass spectrometer using ESI ionization.

2. Procedures for the synthesis of lapatinib

A. S_NAr reaction

- **Screening of base**



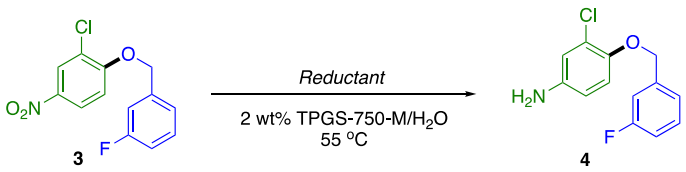
1 2 3

Entry	Base (1.5 equiv)	Conversion to **3** (%)[b]
1	K_3PO_4	97%
2	NaO^tBu	98%
3	KOH	>99%

[a]Reaction conditions: 0.25 mmol **1**, 0.275 mmol of **2**, 0.375 mmol of base, stirred at 55 °C for 4.5 h; [b] conversion was determined by GC-MS.

In a 1 dram vial equipped with a magnetic stir bar, 2-chloro-1-fluoro-4-nitrobenzene **1** (0.25 mmol), (3-fluorophenyl)methanol **2** (0.275 mmol), and base (0.375 mmol) were added. Aqueous 2 wt % TPGS-750-M solution (0.5 mL) was then added. The resulting mixture was stirred at 55 °C until completion (as monitored by TLC or GC-MS). The desired product was isolated by silica plug filtration and dried under vacuum to give a light-yellow powder in 98% yield.

B. Nitro reduction



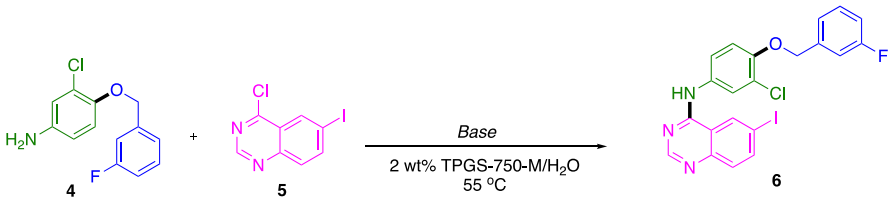
Entry	Conditions	Conversion to **4** (%)[c]
1	1% Pd/C (1 mol %), Et_3SiH (1.5 equiv)	0
2	1% Pd/C (1 mol %), H_2 balloon	~20
3	10% Pd/C (1 mol %), H_2 balloon	~90
4	CIP (5 equiv),[d] NH_4Cl (3 equiv)	100

[c]Conversion was determined by NMR; [d]CIP – Carbonyl Iron Powder.

In a 1 dram vial equipped with a magnetic stir bar, 2-chloro-1-((3-fluorobenzyl)oxy)-4-nitrobenzene **3** (0.25 mmol) and the reducing agents were added. Aqueous 2 wt % TPGS-750-M (0.5 mL) solution was added, and the vial was stirred at 55 °C until completion (as monitored by TLC or GC-MS). The reaction mixture was filtered through cotton and then washed with EtOAc or Et_2O (3 x 1 mL). The combined organic layers were evaporated to give the crude product as a brown colored oil, which was analyzed by GC-MS or crude NMR and used subsequently without further purification.

C. S_NAr reaction

- **Screening of base**



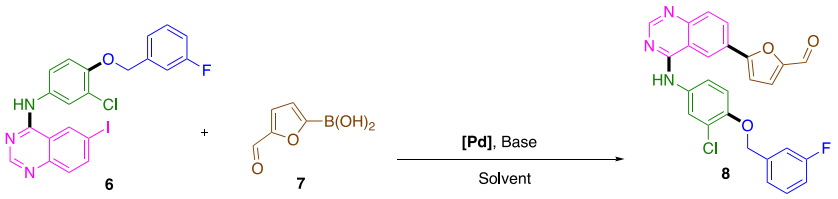
Entry	Base (1 equiv)	Time	Conversion to **6** (%)[e]
1	No base	1.5 h	100
2	K_3PO_4	1.5 h	~95
3	Et_3N	8 h	~75
4	KOH	8 h	~85
5	KO^{t}Bu	3 days	-

Reaction conditions: 0.25 mmol **4**, 0.25 mmol **5** and base stirred at 55 °C; [e]conversion was determined by crude NMR.

In a 1 dram vial with a magnetic stir bar, the crude product from the previous step (**4**; 0.25 mmol) was used along with 0.25 mmol **5**. Aqueous 2 wt % TPGS-750-M (0.5 mL) solution was then added, and the reaction was stirred at 55 °C until completion (as monitored by TLC or GC-MS). The product was then separated by vacuum filtration to give a light-yellow powder, **6**.

D. Suzuki-Miyaura coupling reaction

- **Screening of palladium catalysts**

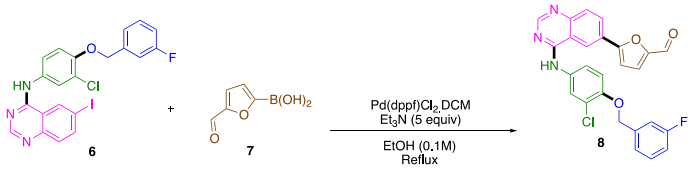


Entry	Catalyst	Base	Solvent	Conversion to **8** (%)[f]
1	$Pd(dtbpf)Cl_2$ (1 mol %)	Et_3N (3 equiv)	2 wt % TPGS-750-M	<3
2	$Pd(dtbpf)Cl_2$ (3 mol %)	Et_3N (3 equiv)	2 wt % TPGS-750-M	<50
3	$Pd(dppf)Cl_2$·DCM (4 mol %)	Et_3N (5 equiv)	2 wt % TPGS-750-M	~50
4[g]	$Pd(dppf)Cl_2$·DCM (4 mol %)	Et_3N (5 equiv)	EtOH (reflux)	100
5	$Pd(dppf)Cl_2$·DCM (4 mol %)	Et_3N (5 equiv)	2 wt % TPGS-750-M, 20 v/v% EtOH	<40
6	$Pd(dppf)Cl_2$·DCM (4 mol %)	Et_3N (5 equiv)	50:50 2 wt % TPGS-750-M: EtOH	<50
7	10 wt% Pd/C (3 mol %)	Et_3N (5 equiv)	EtOH (reflux)	>90

Reaction conditions: 0.25 mmol **6,** 0.5 mmol **7** and base, stirred at 55 ^{0}C (with TPGS-750-M) or under reflux conditions (with EtOH) overnight. [f]Conversion was determined by crude NMR or GC-MS. [g]Reaction time = 2 h.

In a 2 dram vial with a magnetic stir bar, 0.25 mmol **6,** 0.5 mmol **7**, Pd catalyst and base (1.25 mmol) were added. Aqueous 2 wt % TPGS-750-M solution (0.5 mL) or EtOH (2.5 mL) was subsequently added, and the reaction was allowed to stir at 55 ^{o}C (TPGS-750-M) or at 80 ^{o}C (EtOH) until completion (as monitored by TLC or GC-MS). The crude product was used for the subsequent reaction without further purification.

- **Screening of catalyst loading**

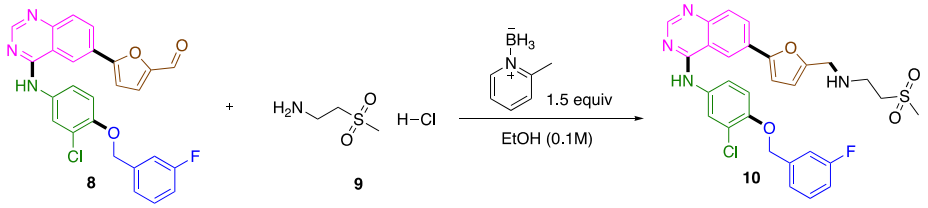


Entry	Catalyst loading	Base	Conversion to **8** (%)[h]
1	2 mol % (20,000 ppm)	Et_3N (3 equiv)	100
2	1 mol % (10,000 ppm)	Et_3N (3 equiv)	100
3	0.5 mol % (5000 ppm)	Et_3N (5 equiv)	100
4[g]	0.1 mol % (1000 ppm)	Et_3N (5 equiv)	100
5	0.05 mol % (500 ppm)	Et_3N (5 equiv)	100

Reaction conditions: 0.25 mmol **6**, 0.5 mmol **7**, 1.25 mmol Et_3N, stirred at 80 ^oC for 2 h; [h]Determined by crude NMR or GC-MS.

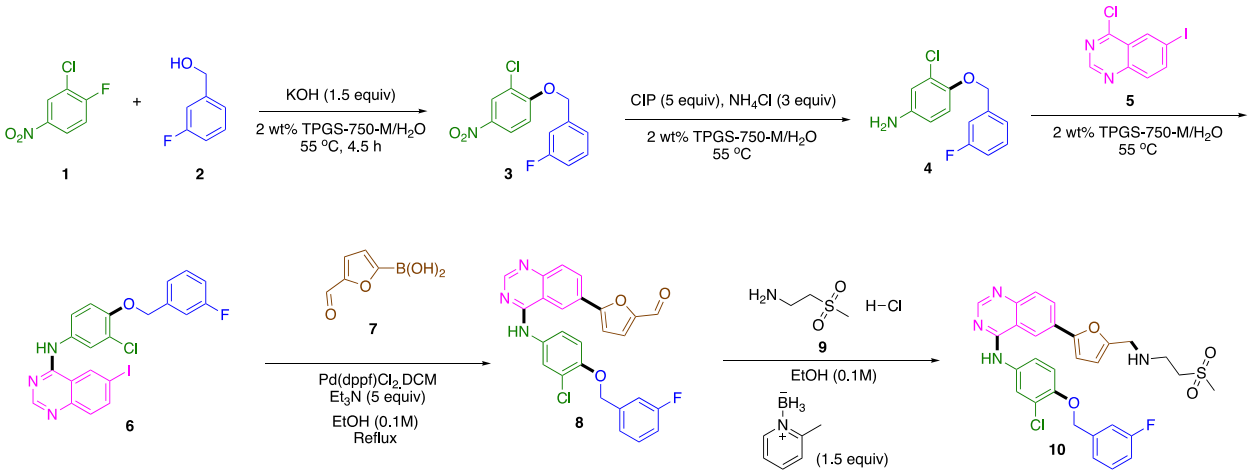
In a 2 dram vial with a magnetic stir bar, 0.25 mmol **6,** 0.5 mmol **7**, Pd(dppf)Cl_2.DCM and base (1.25 mmol) were added. Aqueous 2 wt % TPGS-750-M solution (0.5 mL) or EtOH (2.5 mL) was subsequently added, and the reaction was allowed to stir at 55 ^0C (in aqueous TPGS-750-M) or at 80 ^oC (EtOH) until completion (as monitored by TLC or GC-MS).

- **Reductive amination**



In the same 2 dram vial from the previous reaction was added 2-(methylsulfonyl)ethan-1-amine hydrochloride **9** (1.2 equiv) and 2-picolineborane (1.5 equiv) and the reaction mixture was allowed to stir at 55 °C until completion (as monitored by crude NMR or GC-MS). The resulting product was purified by column chromatography using DCM : EtOAc (3:1) + 2% MeOH + 1% Et_3N as the mobile phase to yield lapatinib free base **10** as a light brown oil.

- **Procedures for the 5-step, 3-pot synthesis of lapatinib**



Step 1: S_NAr reaction

In a 1 dram vial with a magnetic stir bar, 2-chloro-1-fluoro-4-nitrobenzene **1** (0.15 mmol, 1 equiv), (3-fluorophenyl)methanol **2** (1.1 equiv) and KOH (1.5 equiv) were added. Aqueous 2 wt % TPGS-750-M solution (0.5 M global concentration) was then added. The reaction was stirred at 55 °C until completion (as monitored by TLC or GC-MS).

Step 2: Reduction of nitro group

Once step 1 (S_NAr) was completed, CIP (carbonyl iron powder; 5 equiv) and NH_4Cl (3 equiv) were added. 20 v/v% EtOAc (0.1 mL) was added to enhance solubility and stirring. The pH of the system

was adjusted to neutral or slightly acidic (pH 6 – 7) by adding a few drops of concentrated HCl if needed. Subsequently, the resulting mixture was allowed to stir at 55 ^{o}C until completion (as monitored by TLC or GC-MS). The reaction mixture was filtered through a silica plug and washed with EtOAc (~3 mL). The solvents were evaporated to give the crude product as a brown colored oil, which was analyzed by GC-MS or crude NMR and used subsequently without further purification.

Step 3: S_NAr reaction

In a 1 dram vial with a magnetic stir bar, the crude product from step 2 was used along with 4-chloro-6-iodoquinazoline **5** (1 equiv). Aqueous 2 wt % TPGS-750-M (0.5 M global concentration) solution was then added, and the reaction was stirred at 55 ^{o}C until completion (as monitored by TLC or GC-MS). The product was then separated by vacuum filtration to give a light-yellow powder **6.**

Note: The presence of water is detrimental for the subsequent Suzuki-Miyaura coupling. Water can be removed by vacuum filtration. Alternatively, the Suzuki-Miyaura coupling can also be carried out in the same pot if the water is dried by placing the resulting reaction vial from step 3 in an oven at 120 ^{o}C for 2 h, or by placing it in a hot plate at 60 ^{o}C and attaching a high vacuum line overnight.

Step 4: Suzuki-Miyaura reaction

The product from step 3, **6** (1 equiv), was transferred to a 2 dram vial equipped with a magnetic stir bar. To the vial, 5-formyl furan-2-boronic acid **7** (2 equiv), Pd(dppf)Cl_2•DCM (500 ppm) and Et_3N (5 equiv) were added, followed by 95% ethanol (1.5 mL or 0.1 M global concentration). The reaction was allowed to stir at 80 ^{o}C until completion (as monitored by taking a crude NMR, TLC, or GC-MS). The crude product was analyzed by NMR (in DMSO-d_6) and was used in the subsequent step without further purification.

*Note: Pd(dppf)Cl_2•DCM (500 ppm) was added by preparing a stock solution of Pd(dppf)Cl_2•DCM in ethanol.

*$Pd(dppf)Cl_2$ (with no DCM complex) failed to give the product under the same reaction conditions.

Step 5: Reductive amination

To the same 2 dram vial from the previous step was added 2-(methylsulfonyl)ethan-1-amine hydrochloride **9** (1.2 equiv) and 2-picolineborane (1.5 equiv). The reaction mixture was allowed to stir until completion (as monitored by NMR, TLC, or GC-MS). The resulting mixture was purified by recrystallization in EtOAc to yield lapatinib free base **10** as light-yellow solid, (49.7 mg, 0.086 mmol, 57% yield).

Alternatively, the resulting product was purified by column chromatography using DCM : EtOAc (3:1) + 2% MeOH + 1% Et_3N as the mobile phase to yield lapatinib free base **10** as a light brown oil (48.8 mg, 0.084 mmol, 56% yield).

3. E Factor calculations

$$E\ Factor = \frac{grams\ of\ wastes}{grams\ of\ product}$$

- ***This work:***

waste:

0.5 ml TPGS-750-M (aq) + 0.1 ml EtOAc + 3.0 ml EtOAc + 0.5 ml TPGS-750-M (aq) + 2.5 ml EtOH

= 0.5 g TPGS-750-M (aq) + 0.1 g EtOAc + 3.3 ml EtOAc + 0.5 ml TPGS-750-M (aq) + 2.8 ml EtOH

= 7.2 g wastes

(density of EtOAc = 0.902 kg/m^3; density of EtOH = 0.789 kg/m^3)

$$E\ Factor = \frac{7.2\ grams\ of\ wastes}{0.808\ grams\ of\ product} = \underline{\mathbf{8.9}}$$

- ***Literature:*** *(US 8444988 B2) GSK, 2013*

waste:

90.0 mL CH_3CN (aq) + 180.0 mL EtOH + 250.0 mL *i*-PrOH + 740.5 mL THF + x mL (unstated volume) dioxane and THF

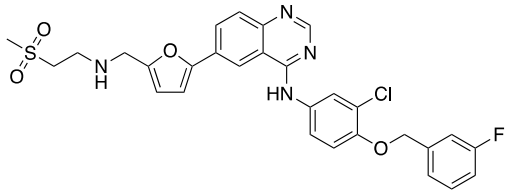
= 114.5 g CH_3CN (aq) + 228.1 g EtOH + 318.1 g *i*-PrOH + 833.9 ml THF + x g dioxane and THF

= 1494.6 g + x waste

(density of CH_3CN = 0.786 kg/m^3; density of EtOH = 0.789 kg/m^3; density of *i*-PrOH = 0.786 kg/m^3; density of THF = 0.888 kg/m^3)

$$E\ Factor = \frac{1494.6\ grams\ of\ wastes}{10.0\ grams\ of\ product} > \underline{\mathbf{149.5}}$$

4. Compound characterization data



lapatinib

^{1}H NMR (600 MHz, CD_3OD) δ 8.75 (s, 1H), 8.51 (s, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 7.91 (dd, *J* = 2.7, 1.2 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 1H), 7.66 – 7.61 (m, 1H), 7.42 – 7.36 (m, 1H), 7.30 (d, *J* = 7.7 Hz, 1H), 7.24 (dd, *J* = 9.9, 2.4 Hz, 1H), 7.17 (dd, *J* = 8.9, 1.1 Hz, 1H), 7.07 – 7.00 (m, 2H), 6.68 (s, 1H), 5.22 (s, 2H), 4.23 (s, 2H), 3.49 (d, *J* = 7.0 Hz, 2H), 3.43 (d, *J* = 8.2 Hz, 2H), 3.06 (s, 3H).

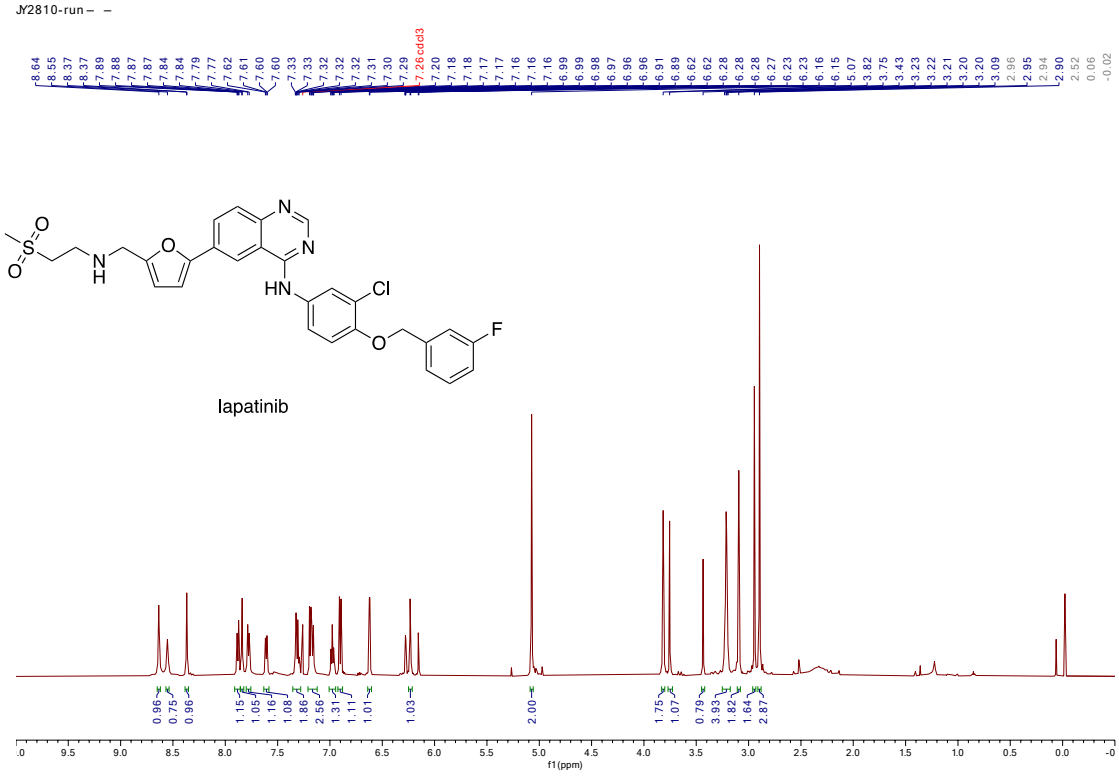
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.95 (d, $J_{C\text{-}F}$ = 246.4), 157.82, 154.69, 153.26, 152.41, 150.75, 149.21, 139.14 (d, $J_{C\text{-}F}$ = 7.1) 132.71, 130.1 (d, $J_{C\text{-}F}$ = 8.1) 128.87, 128.69, 128.64, 124.85, 123.14, 122.44 (d, $J_{C\text{-}F}$ = 3.0), 122.13, 115.59, 114.83 (d, $J_{C\text{-}F}$ = 21.2), 114.26, 113.94 (d, $J_{C\text{-}F}$ = 22.2), 109.63, 107.10, 70.36, 54.45, 45.40, 42.00, 41.83.

^{19}F NMR (376 MHz, $CDCl_3$) δ -112.66 (td, $J_{F\text{-}H}$ = 9.1, 5.6 Hz).

HRMS TOF MS EI+ *m/z* calcd $C_{29}H_{26}ClFN_4O_4SH$ $[M+H]^+$: 581.1426; found 581.1405.

5. NMR spectra

^{1}H, ^{13}C, and ^{19}F NMR of lapatinib



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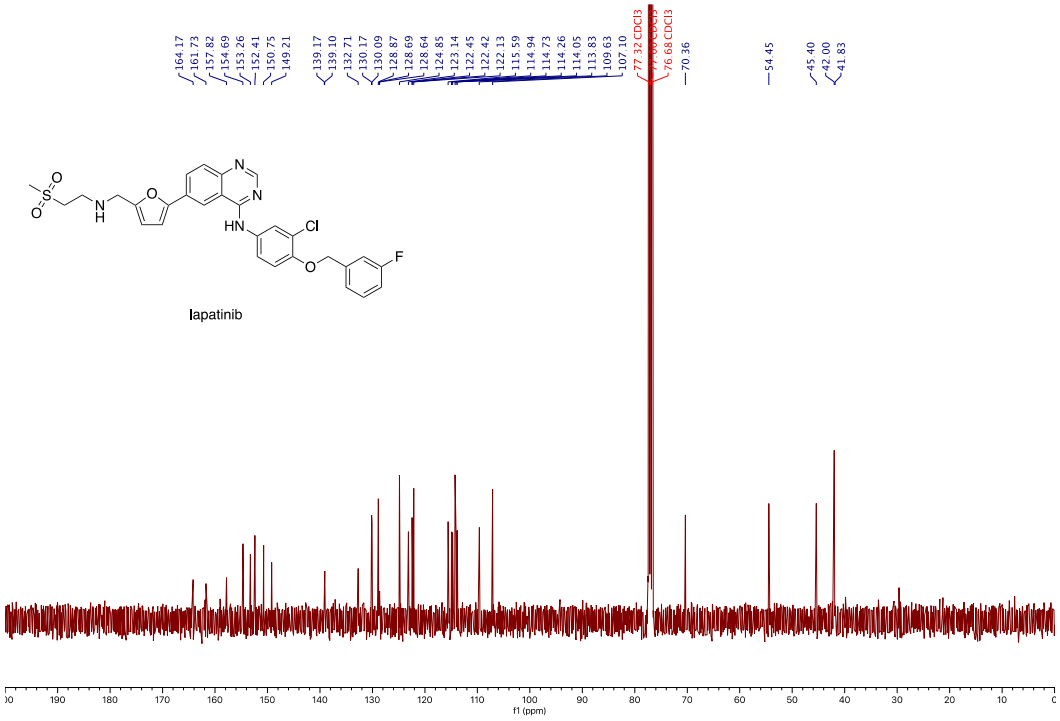

lapatinib

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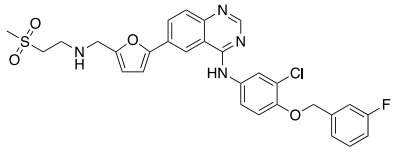
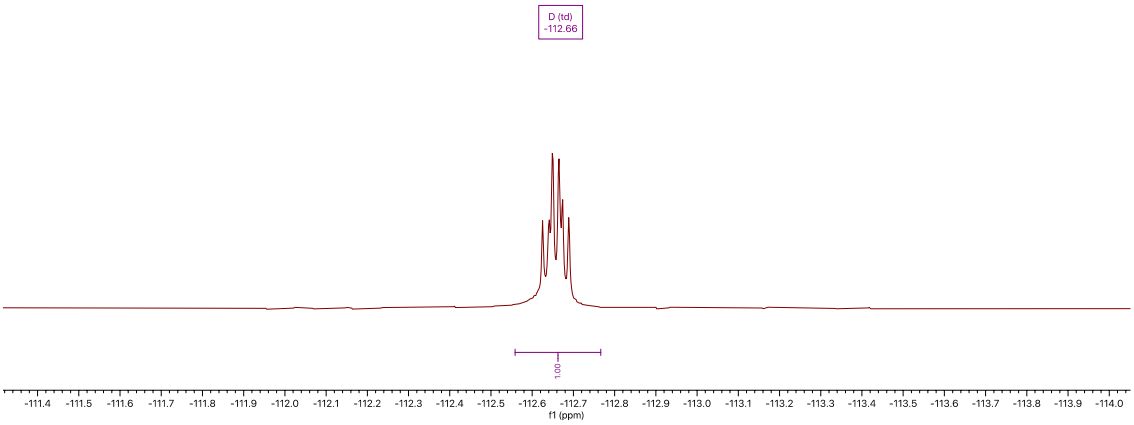
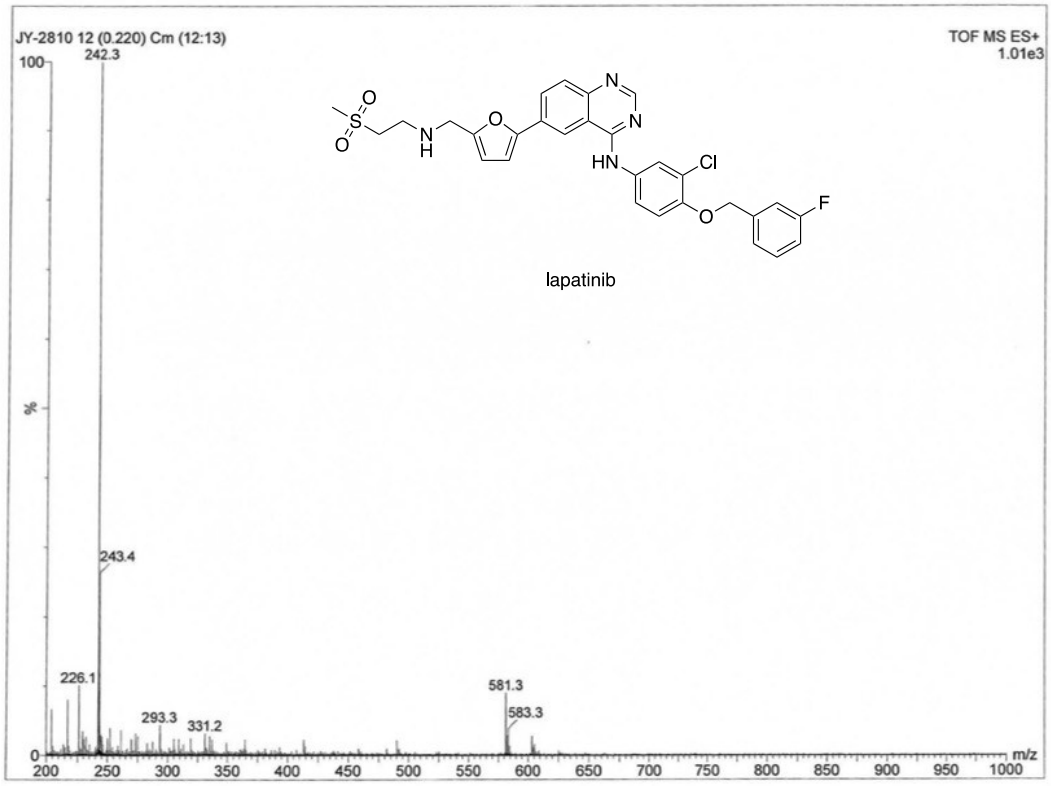
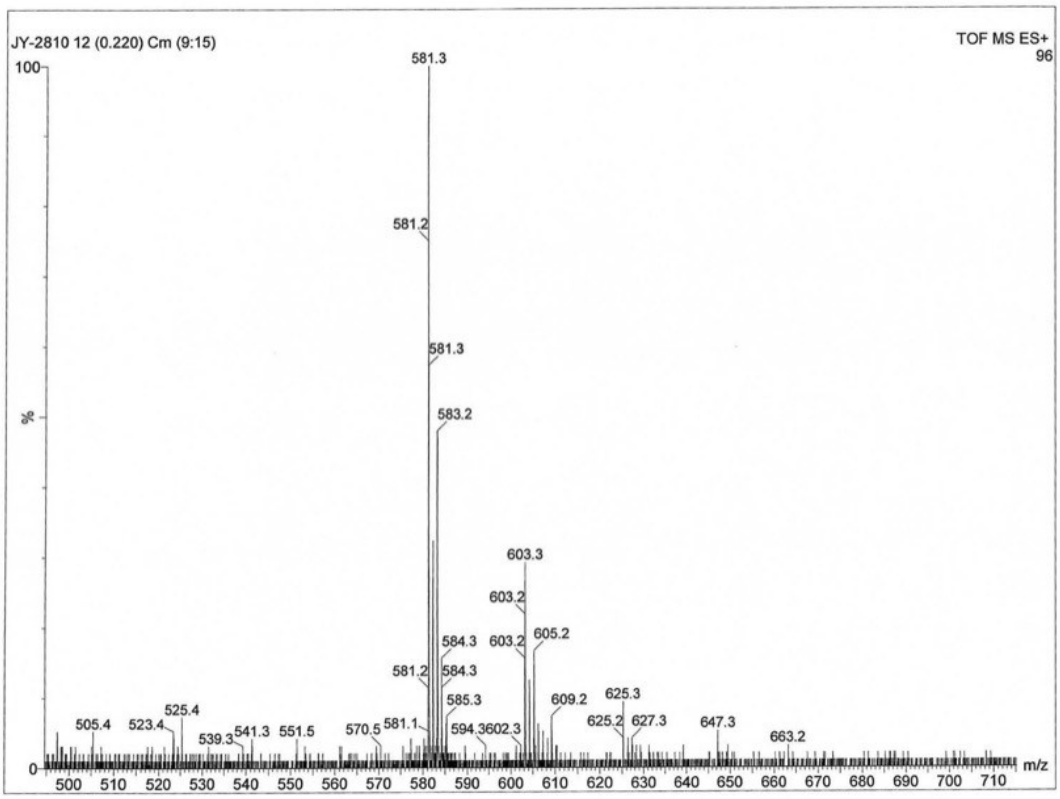


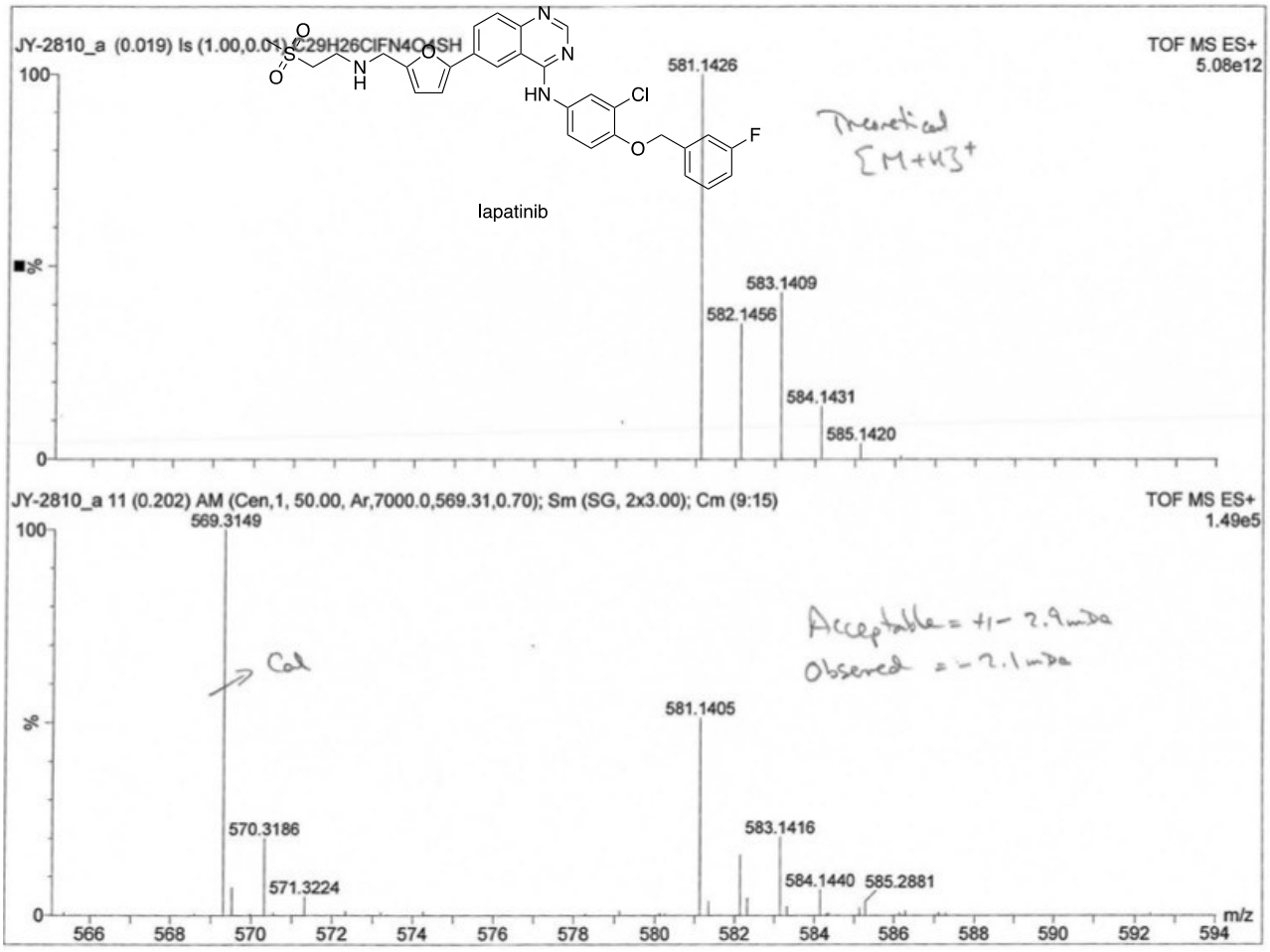
lapatinib



6. HRMS


JY-2810 12 (0.220) Cm (12:13)
TOF MS ES+
1.01e3
100
%
0
242.3
243.4
226.1
293.3
331.2
581.3
583.3
200
250
300
350
400
450
500
550
600
650
700
750
800
850
900
950
1000
m/z
lapatinib


JY-2810 12 (0.220) Cm (9:15)
TOF MS ES+
96
100
%
0
581.3
581.2
581.3
583.2
603.3
603.2
584.3
603.2
605.2
581.2
584.3
585.3
609.2
625.3
625.2
627.3
647.3
505.4
523.4
525.4
539.3
541.3
551.5
570.5
581.1
594.3
602.3
663.2
m/z
500 510 520 530 540 550 560 570 580 590 600 610 620 630 640 650 660 670 680 690 700 710


JY-2810_a (0.019) Is (1.00,0.01) C29H26ClFN4O4SH
TOF MS ES+
5.08e12
100
%
0
581.1426
583.1409
582.1456
584.1431
585.1420
Theoretical
[M+H]+
lapatinib
JY-2810_a 11 (0.202) AM (Cen,1, 50.00, Ar,7000.0,569.31,0.70); Sm (SG, 2x3.00); Cm (9:15)
TOF MS ES+
1.49e5
569.3149
Cal
Acceptable = +/- 7.9mDa
Observed = -2.1mDa
581.1405
570.3186
583.1416
571.3224
584.1440
585.2881
m/z
566
568
570
572
574
576
578
580
582
584
586
588
590
592
594

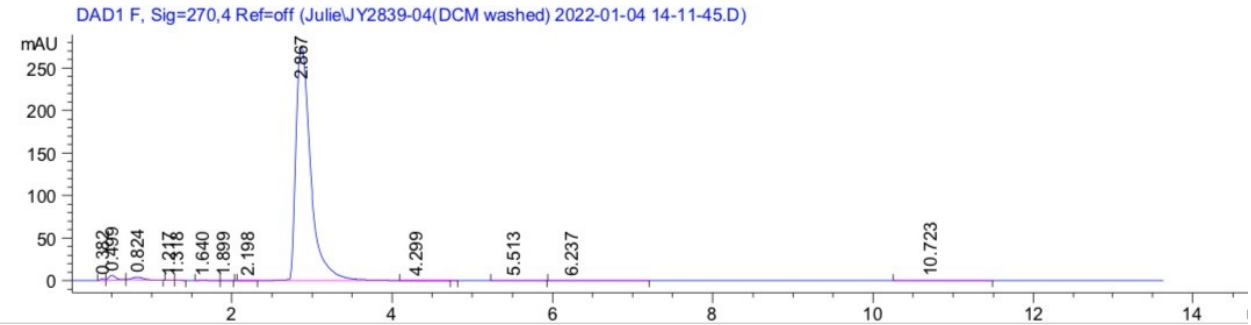
7. Purity analysis by HPLC

Column: InfinityLab Poroshell HPH-C18, 2.7 micron, 4.6 x 50 mm

Eluent: hexane/ *i*-PrOH = 90/10

Flow rate: 1 mL/min

Column temperature: 20 °C



Signal 6: DAD1 F, Sig=270, 4 Ref=off

Peak #	Ret Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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3	0.824	BB	0.1479	30.27498	3.15671	0.8477
4	1.217	BV	0.0648	3.24298e-1	8.08731e-2	9.080e-3
5	1.318	VB	0.0856	2.81078e-1	5.32584e-2	7.870e-3
6	1.640	BV	0.1532	1.94257	1.83929e-1	0.0544
7	1.899	VB	0.0874	3.13159e-1	5.58503e-2	8.769e-3
8	2.198	BV E	0.1127	7.74780e-1	1.09258e-1	0.0217
9	2.867	VV R	0.1953	3483.06519	275.81552	97.5268
10	4.299	VB E	0.2295	2.02840	1.18630e-1	0.0568
11	5.513	BB	0.2504	4.36215	2.61799e-1	0.1221
12	6.237	BB	0.3664	4.30216	1.47452e-1	0.1205
13	10.723	BB	0.3784	3.65734	1.16457e-1	0.1024
Totals :				3571.39438	287.25012	