

ELECTRONIC SUPPORTING INFORMATION

Large scale synthesis of Notum inhibitor 1-(2,4-dichloro-3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (ARUK3001185) employing a modified Sakai reaction as the key step

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Figure S1: Differential Scanning Calorimetry (DSC) of **1**

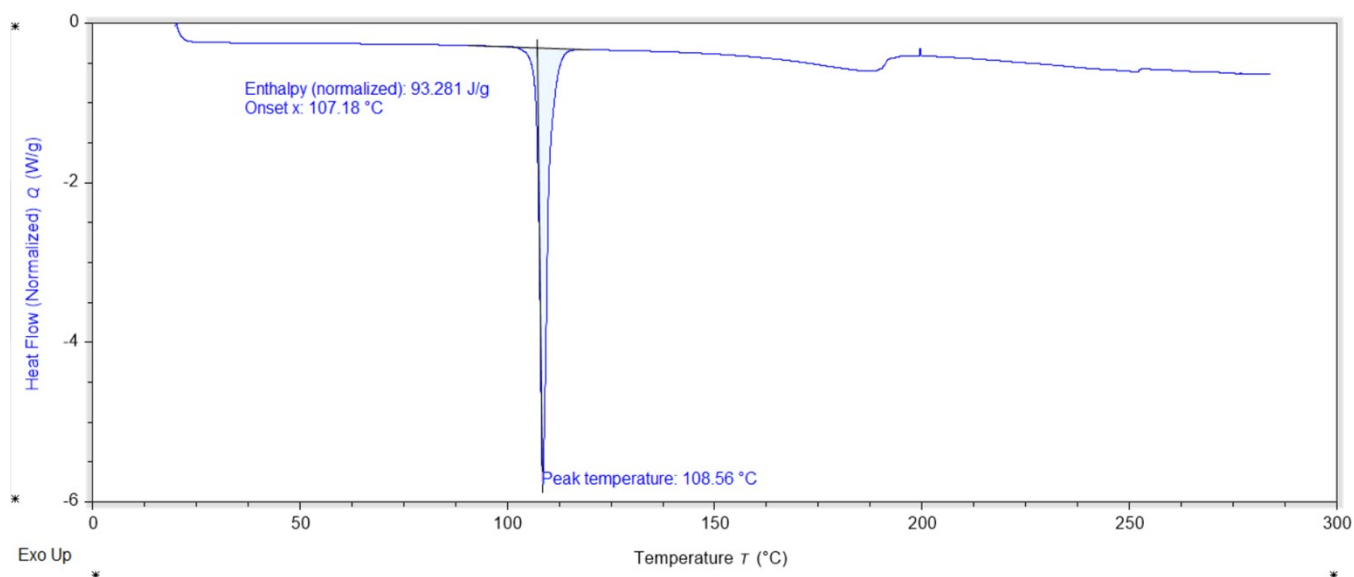


Figure S1. DSC displays an enthalpy of fusion (melt) with an onset at 107.2 °C, a peak at 108.6 °C, and an enthalpy of 93.3 J/g.

Figure S2: ¹H NMR of **1**

¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, *J* = 1.1 Hz, 1H), 7.90 (d, *J* = 1.1 Hz, 1H), 7.70 – 7.61 (m, 2H).

Chemist JS
HW-6003-b1

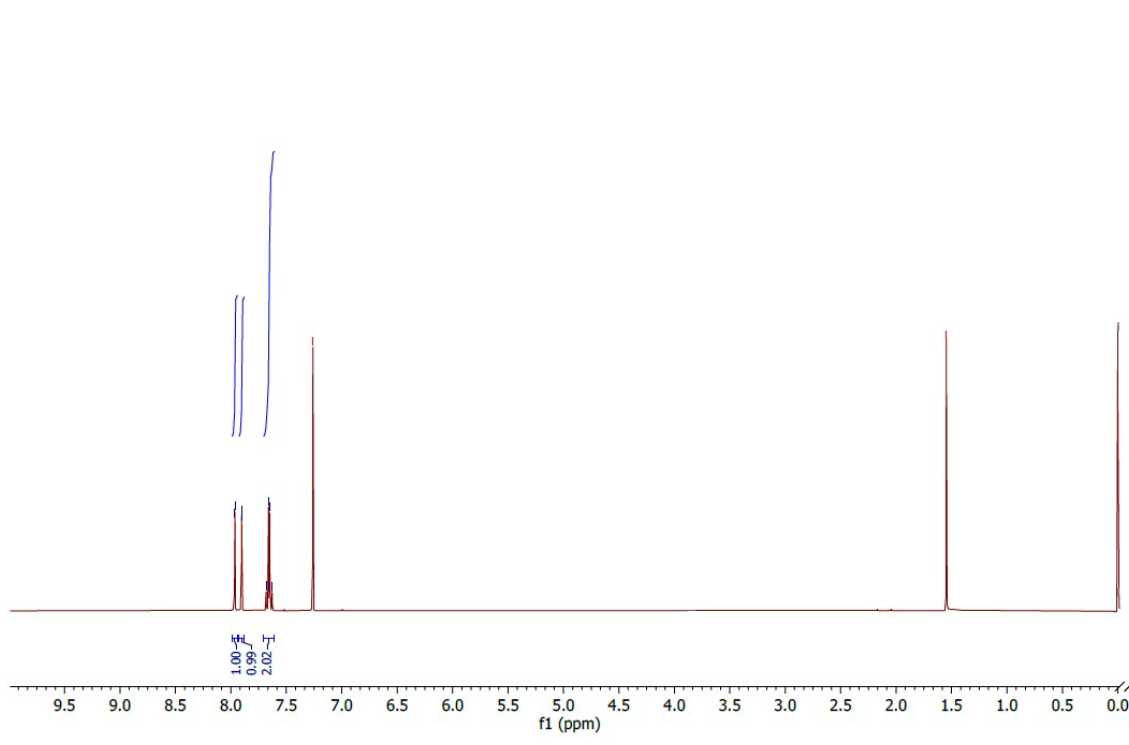


Figure S3: ^{13}C and DEPT NMR of 1

^{13}C NMR (101 MHz, CDCl_3) δ 136.37, 135.76, 133.92, 131.52, 130.98, 130.78, 128.16, 127.84, 126.00, 120.65.

Chemist JS
HW-6003-b1

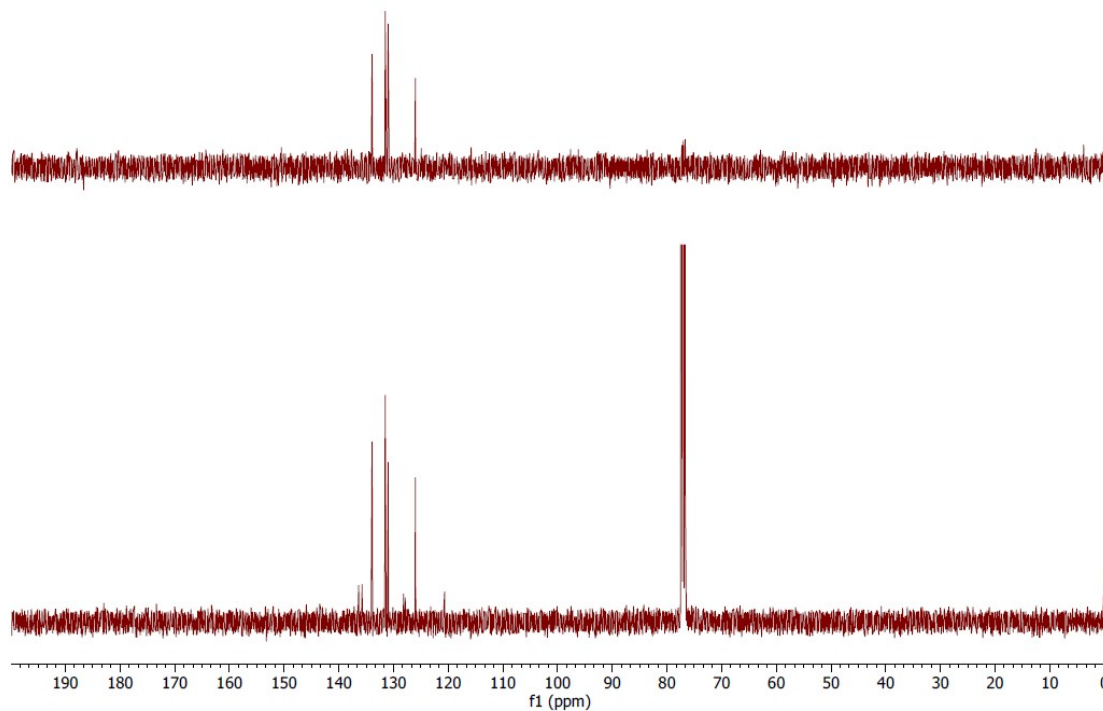


Figure S4: ^{19}F NMR of 1

-55.794

Supervisor: Tao

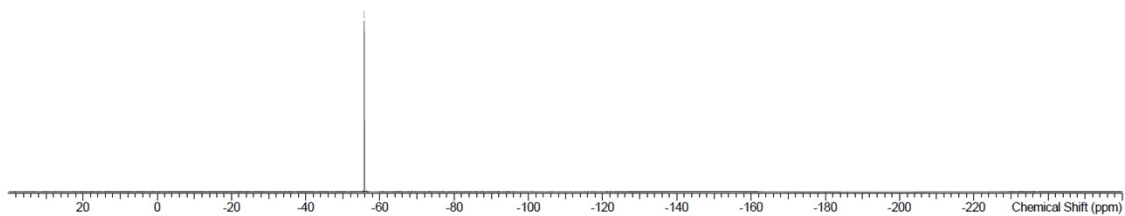
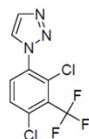
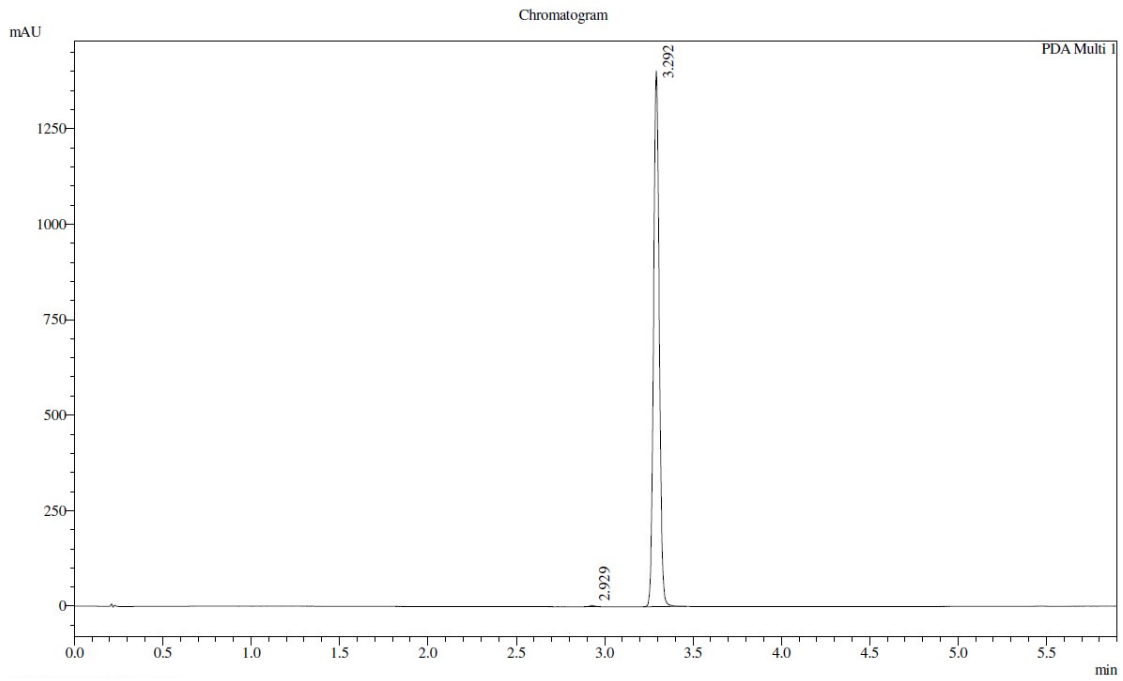


Figure S5: HPLC of 1



PDA Ch1 220nm 4nm

| Peak# | Ret. Time | Height | Height % | USP Width | Area | Area % |
|-------|-----------|---------|----------|-----------|---------|--------|
| 1 | 2.929 | 3030 | 0.215 | 0.057 | 6247 | 0.198 |
| 2 | 3.292 | 1403297 | 99.785 | 0.060 | 3151804 | 99.802 |

Figure S6: LCMS of 1

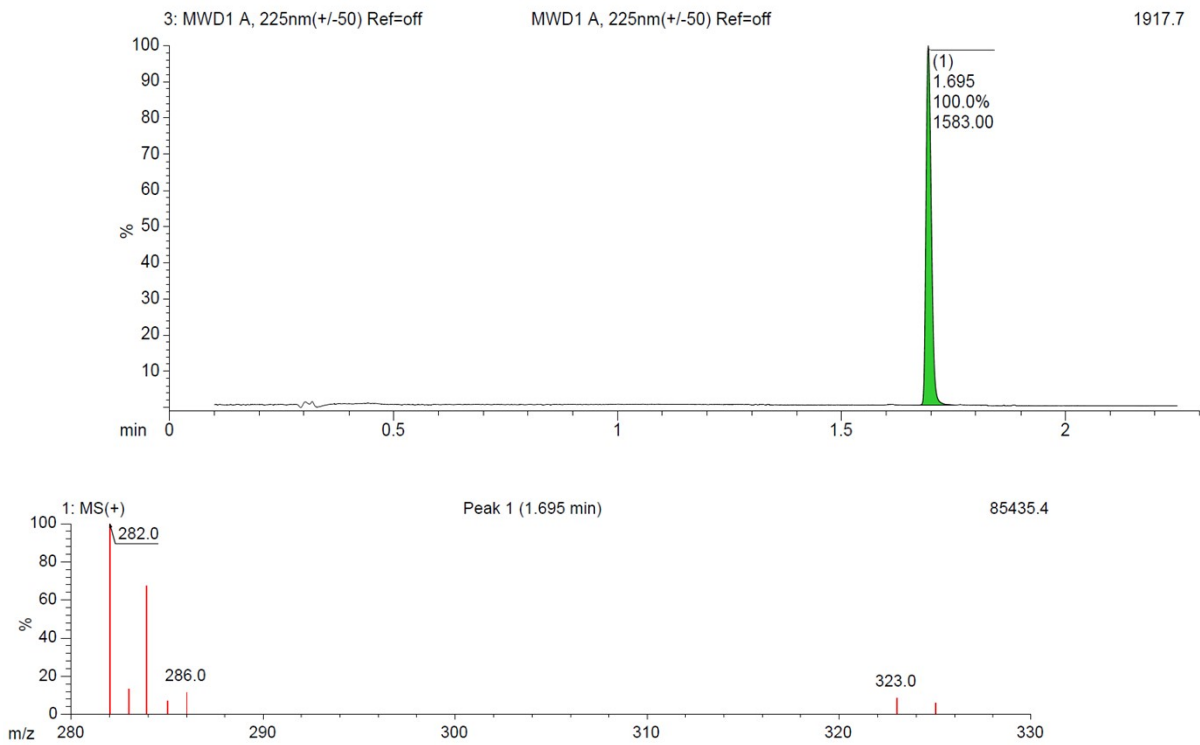
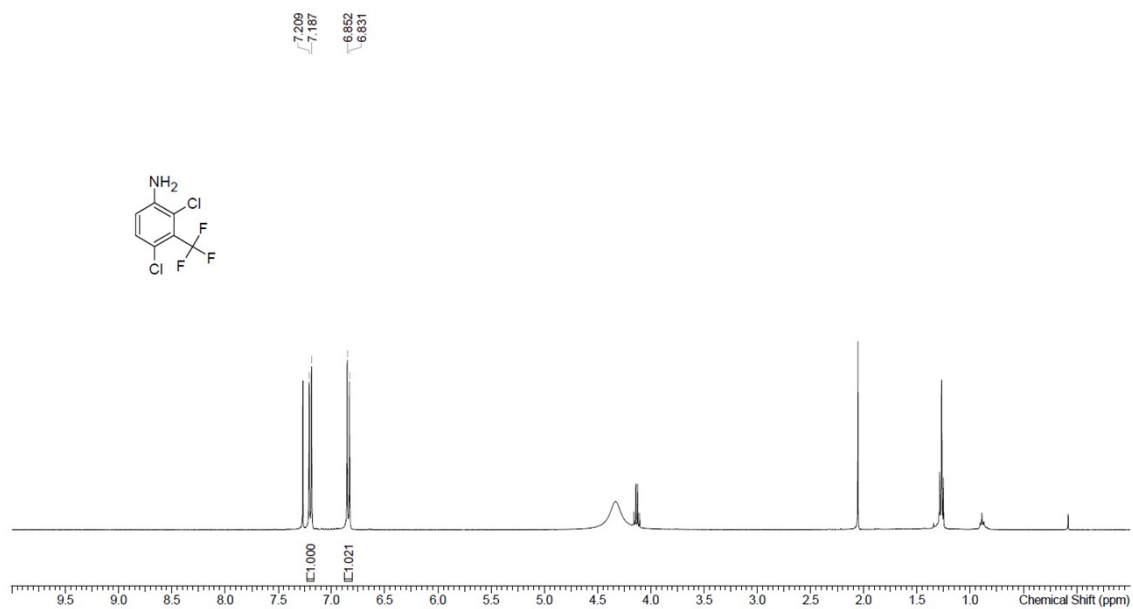
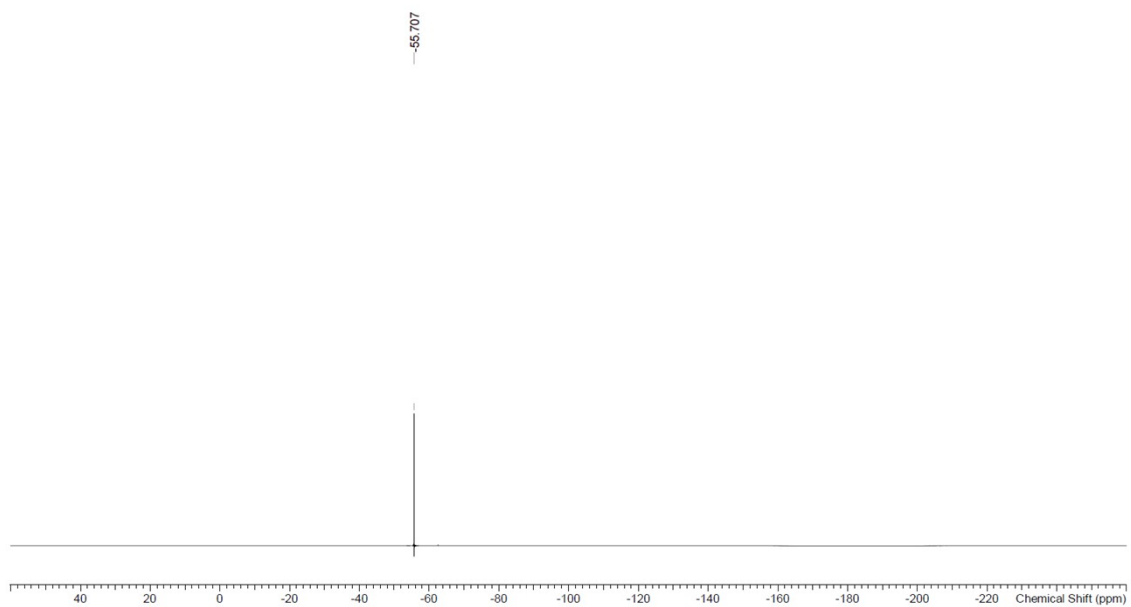


Figure S7: Spectral and analytical data for 2,4-dichloro-3-(trifluoromethyl)aniline (4):

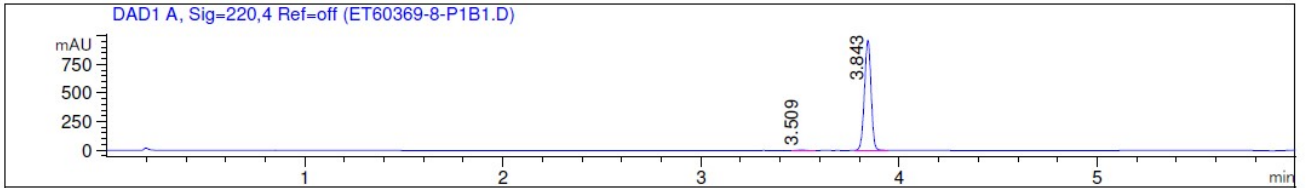
A. ^1H NMR



B. ^{19}F NMR



C. HPLC



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Integration Result
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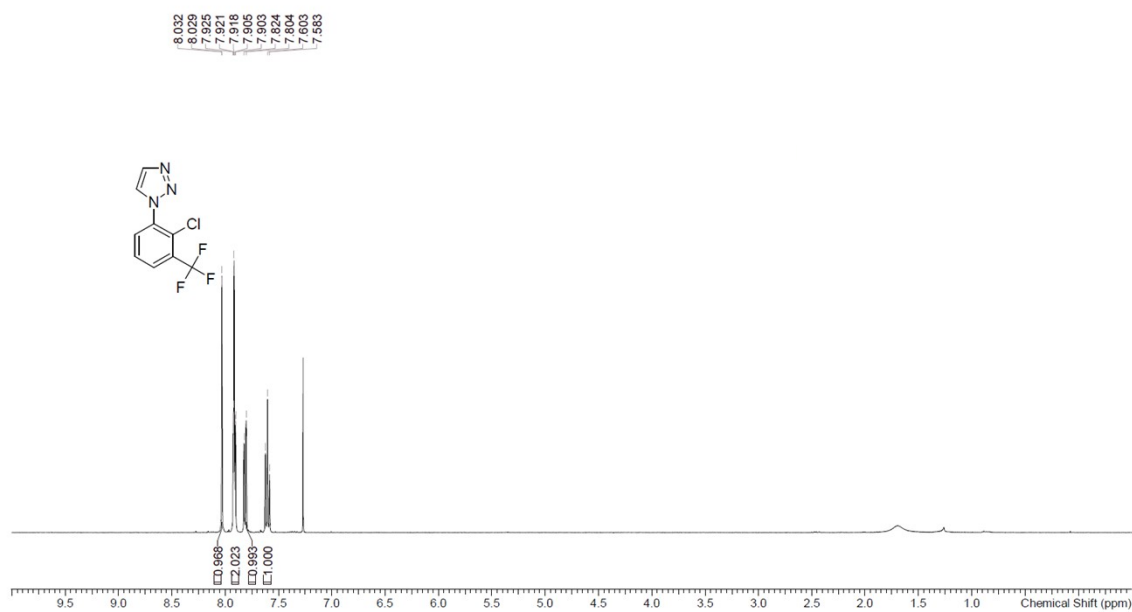
Singal 1 : DAD1 A, Sig=220,4 Ref=off

| # | Meas. R | Area | Height | Height | Width | Area % |
|---|---------|---------|---------|--------|-------|--------|
| 1 | 3.509 | 9.338 | 4.095 | 0.424 | 0.036 | 0.417 |
| 2 | 3.843 | 2.231e3 | 962.743 | 99.576 | 0.036 | 99.583 |

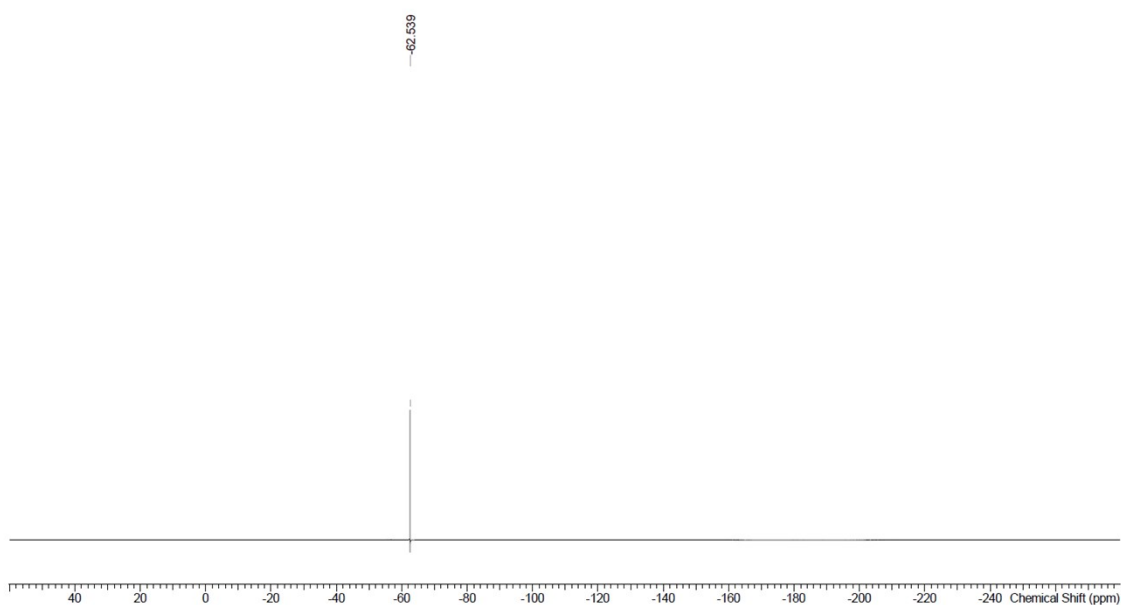
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Figure S8: Spectral and analytical data for minor impurity 1-(2-chloro-3-(trifluoromethyl)phenyl)-1H-1,2,3-triazole (9):

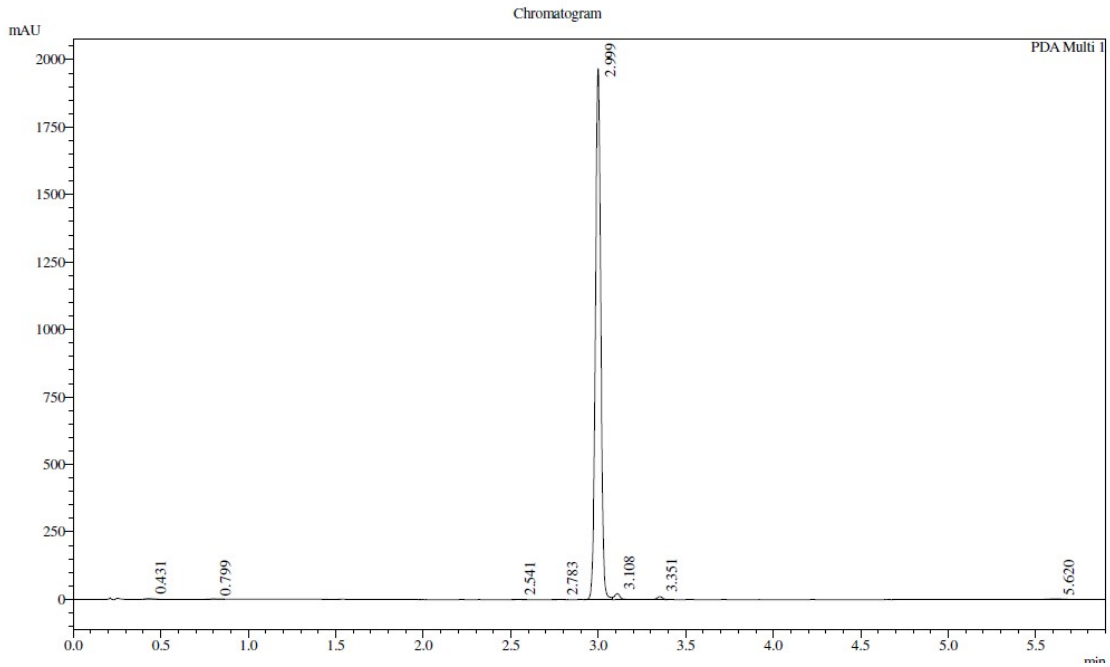
A. ^1H NMR



B. ^{19}F NMR



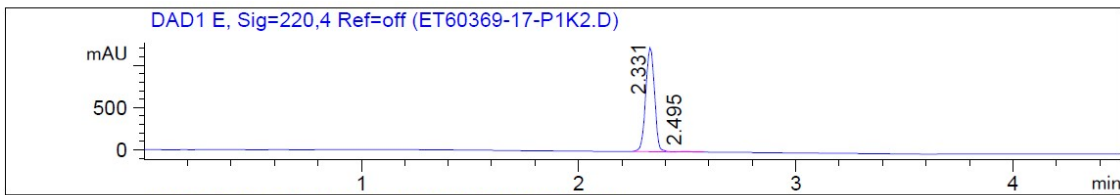
C. HPLC



PDA Ch1 220nm 4nm

| Peak# | Ret. Time | Height | Height % | USP Width | Area | Area % |
|-------|-----------|---------|----------|-----------|---------|--------|
| 1 | 0.431 | 2098 | 0.105 | 0.067 | 5287 | 0.123 |
| 2 | 0.799 | 1085 | 0.054 | 0.073 | 3086 | 0.072 |
| 3 | 2.541 | 1206 | 0.060 | 0.045 | 2236 | 0.052 |
| 4 | 2.783 | 1048 | 0.052 | 0.066 | 2280 | 0.053 |
| 5 | 2.999 | 1967179 | 97.988 | 0.057 | 4200272 | 97.792 |
| 6 | 3.108 | 22056 | 1.099 | 0.061 | 50391 | 1.173 |
| 7 | 3.351 | 11062 | 0.551 | 0.055 | 22810 | 0.531 |

D. LCMS



Signal 1 : DAD1 E, Sig=220,4 Ref=off

| Peak # | RT [min] | Height | Height % | Width [min] | Area | Area % |
|--------|----------|----------|----------|-------------|----------|--------|
| 1 | 2.331 | 1230.021 | 99.364 | 0.045 | 3483.319 | 99.301 |
| 2 | 2.495 | 7.873 | 0.636 | 0.048 | 24.537 | 0.699 |

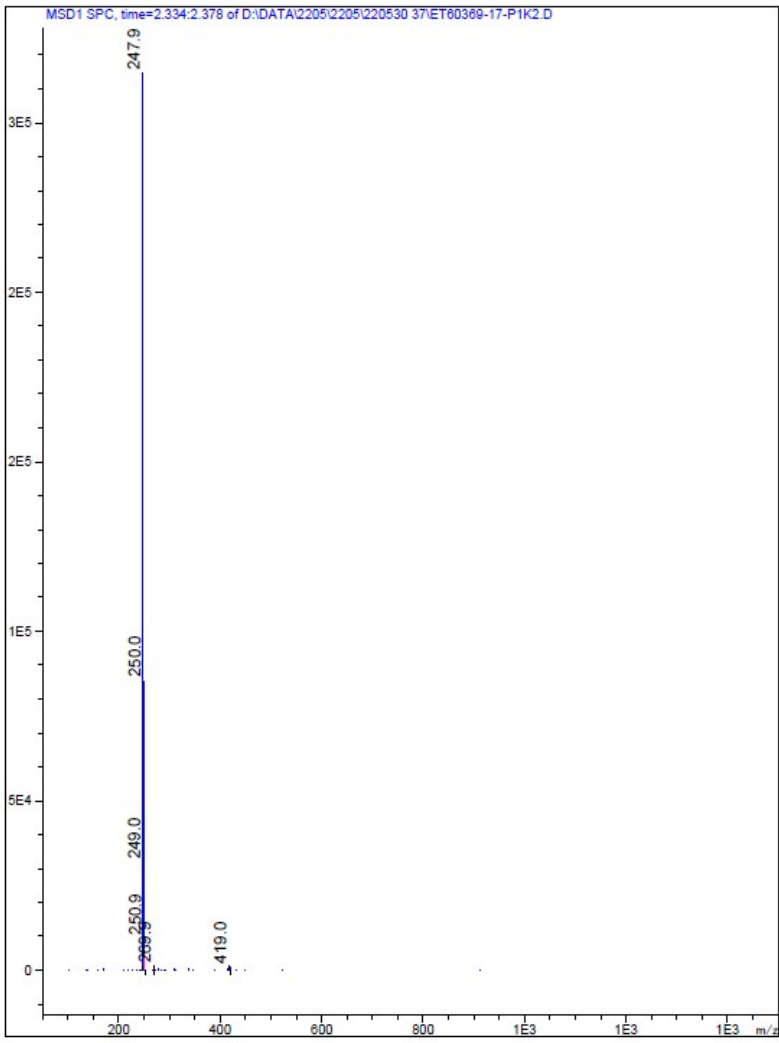
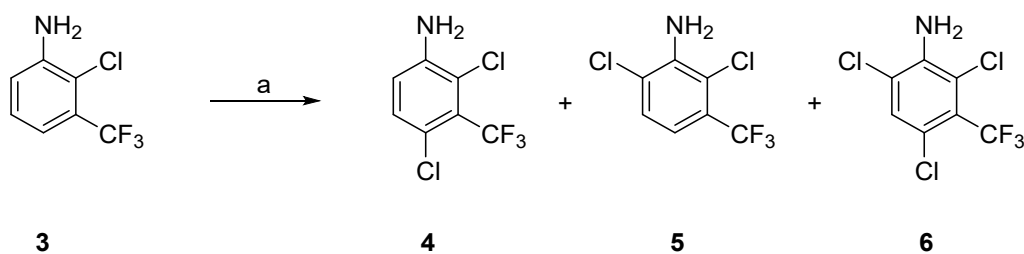


Table S1: Pilot reactions for the chlorination of 2-chloro-3-(trifluoromethyl)aniline (3**) with *N*-chlorosuccinimide (NCS).**



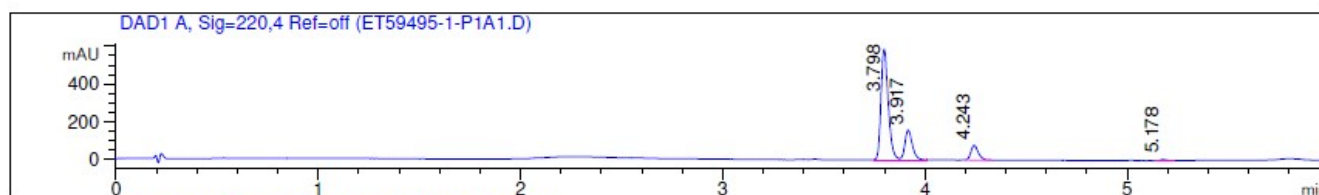
^a Reagents and conditions: (a) **3** (200 mg), NCS (1.1 equiv.), solvent, temperature, time; ratio of products **3:4:5:6** determined by LCMS

| entry | Conditions | Ratio of Products |
|-----------|---|--------------------------|
| | solvent, temperature, time | 3 : 4 : 5 : 6 |
| 1 | CH ₂ Cl ₂ , 30 °C, 16 h | 48.9 : 36.2 : 13.9 : 0 |
| 2 | CH ₂ ClCH ₂ Cl, 20 °C, 16 h | 63.9 : 29.3 : 6.6 : 0 |
| 3 | CH ₂ ClCH ₂ Cl, 60 °C, 16 h | 0 : 61.6 : 26.0 : 9 |
| 4 | <i>i</i> -PrOH, 60 °C, 16 h | 3.8 : 61.8 : 26.9 : 4.7 |
| 5 | AcOH, 60 °C, 16 h | 0 : 50.5 : 32.9 : 11.2 |
| 6 | DMF, 20 °C, 16 h | 6.4 : 67.4 : 20.4 : 1.8 |
| 7 | THF, 60 °C, 16 h | 7.7 : 66.3 : 21.8 : 11.2 |
| 8 | 2-MeTHF, 60 °C, 16 h | 36.0 : 40.5 : 18.6 : 0 |
| 9 | MeCN, 60 °C, 16 h | 0 : 70.2 : 19.5 : 9.6 |
| 10 | NCS (1.0 equiv.), MeCN, 60 °C, 16 h | 4.0 : 69.5 : 21.4 : 4.0 |

LCMS of entry 9:

Compound

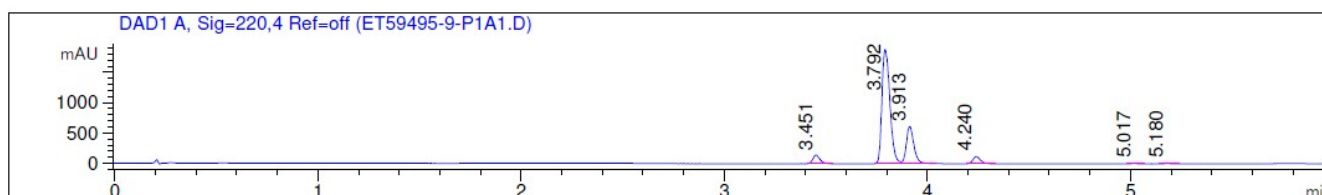
4 5 6



LCMS of entry 10:

Compound

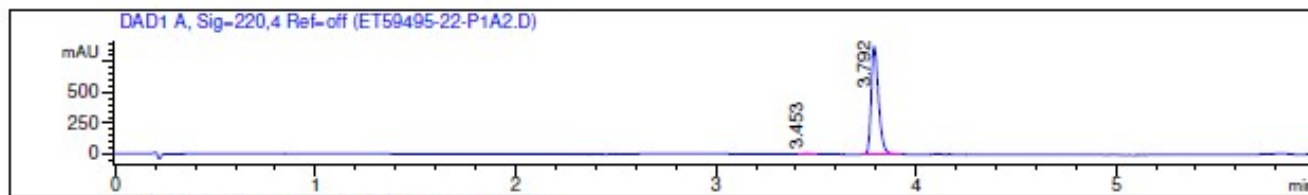
3 4 5 6



LCMS of purified 4:

Compound

3 4



Integration Result

Singal 1 : DAD1 A, Sig=220,4 Ref-off

| # | Meas. R | Area | Height | Height | Width | Area % |
|---|---------|---------|--------|--------|-------|--------|
| 1 | 3.45 | 7.74 | 3.66 | 0.42 | 0.03 | 0.34 |
| 2 | 3.79 | 2246.45 | 873.62 | 99.58 | 0.04 | 99.66 |