Supporting Information

AN EFFICIENT TON SCALE PROCESS OF CHLORFLUAZURON

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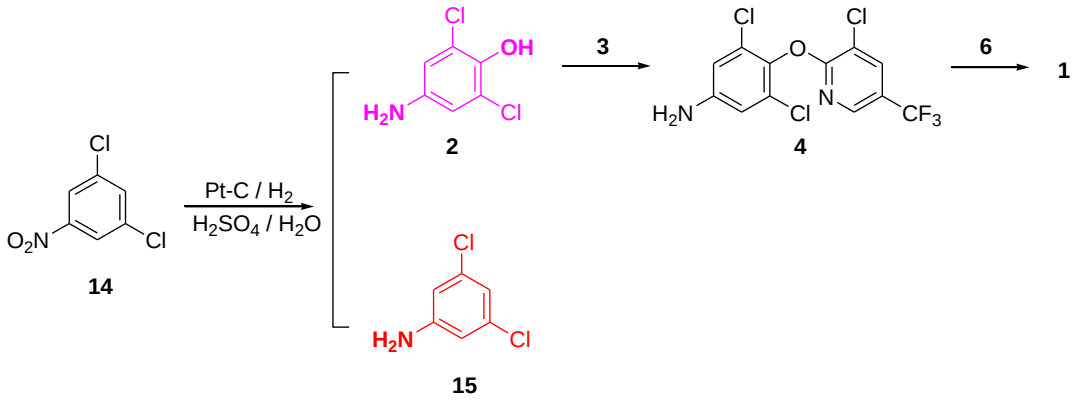
1. General Information

All solvents and reagents were purchased from commerical suppliers and used without further purification. Melting points were recorded on an RY-1 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian INOVA-400 spectrometer using TMS as an internal standard. Mass spectra were obtained from a Finnigan MAT-95/711 spectrometer. HPLC area percent was established on an Agilent 1260 liquid chromatography system with a Zorbax Eclipse Plus C18 column, 250 mm × 4.6 mm (5 μm); λ = 254 nm; mobile phase: A (CH_3OH) and B (H_2O), 80:20 v/v. The HPLC analysis data is reported in area % and is not adjusted to weight %.

2. Synthesis of compounds



4-amino-2,6-dichlorophenol (2) and 3,5-dichloroaniline (15)

Add 3,5-dichloronitrobenzene (**14**) (500 kg, 2.604 kmol), 30% sulfuric acid (150 kg), deionized water (1500 kg), TBAB (2.5 kg), platinum/carbon catalyst with 5% platinum loading (0.5 kg), and 4-aminopyridine (2.5 kg) to the 3000 L autoclave. The autoclave was replaced with N_2 and H_2 three times respectively, and then the reaction was carried out at a temperature of 80℃ and hydrogen pressure of 0.1 MPa for 10 h. Filtering the reaction solution at 60-80℃ to obtain the filtrate and the platinum/carbon catalyst, which is recycled back into the autoclave. The filtrate obtained above was cooled down to 0℃ and kept for 4 h, crystals were precipitated and filtered to obtain the crystalline liquor and the product of 4-amino-2,6-dichlorophenol (**2**) and 3,5-dichloroaniline (**15**). The obtained crystalline liquor was returned to the autoclave for recycling. Water and sodium hydroxide solution was added to the filter cake to adjust pH=9 and stir for 30 minutes, and then filter to obtain 3,5-dichloroaniline (**15**). Finally, add 10% sulfuric acid to the filtrate to adjust pH=4 and filter to obtain 4-amino-2,6-dichlorophenol (**2**). The yields of 4-amino-2,6-dichlorophenol (**2**) and 3,5-dichloroaniline (**15**) were 78.1% and 20.9%, respectively.

4-Amino-2,6-dichlorophenol (**2**): white solid (362.0 kg, 78.1%), HPLC 99.5%, mp 167-170 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.20 (s, 2H, NH_2), 6.58 (s, 2H, C_6H_2), 8.87 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 113.8, 123.5, 139.1, 142.6; LC-MS m/z: 177.92.

3,5-Dichloroaniline (**15**): white solid (88.2 kg, 20.9%), HPLC 99.2%, mp 48-49 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.79 (s, 2H, NH_2), 6.52 (s, 2H, C_6H_3), 6.71 (s, 1H, C_6H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 77.2, 113.3, 118.4, 135.5, 148.3.

3,5-dichloro-4- (3-chloro-5-trifluoromethyl-2-pyridyloxy) aniline (4)

In a 3000 L glass lined reactor, 4-amino-2,6-dichlorophenol (**2**) (362 kg, 2.034 kmol), potassium hydroxide (120 kg, 1.928 kmol), DMF (600 L) and 2,3-dichloro-5-trifluoromethylpyridine (**3**) (440 kg, 2.037 kmol) were reacted at 125 ℃ for 2 h. Samples were taken and tested, and the residue was qualified when 2,3-dichloro-5-trifluoromethylpyridine (**3**) was ≤0.5%. Remove DMF by evaporation under reduced pressure to 120 ℃, lower the temperature to below 20 ℃, remove inorganic salt by filtration, recover DMF by concentration under reduced pressure, add 1500 L of toluene and 1000 L of tap water to the residue in turn, stir for 30 min, and let stand and stratify. The upper layer of toluene solution was partitioned by reflux to obtain 3,5-dichloro-4-(3-chloro-5-trifluoromethyl-2-pyridoxyl)aniline (**4**) in toluene solution, which was directly used in the next reaction with a calibrated yield of 96.7%.

2,6-difluorobenzoyl isocyanate (6)

2,6-Difluorobenzamide (**5**) (318 kg, 2.027 kmol) and toluene (800 L) were put into the 2000 L reaction kettle and stirred, oxalyl chloride (270 kg, 2.126 kmol) was slowly added dropwise at room temperature. After dropping, the temperature was slowly raised to reflux for 4 h, and the tail gas was absorbed by water. After refluxing, the temperature is lowered, the excess oxalyl chloride is recovered by rotary evaporation, and the distillation product is a toluene solution of 2,6-difluorobenzoyl isocyanate (**6**), which was directly used in the next reaction with a calibrated yield of 97.2%.

Chlorfluazuron (1)

In a 3000 L glass lined reactor, 3,5-dichloro-4-(3-chloro-5-trifluoromethyl-2-pyridoxyl)aniline (**4**) (1.967 kmol) and toluene (1500 L) were put into and stirred, the toluene solution of 2,6-difluorobenzoyl isocyanate (**6**) (1.970 kmol) was slowly added dropwise at room temperature. After dropping, the temperature was slowly raised to reflux for 2 h, then the mixture was cooled, filtered with suction, and dried to afford a white solid.

Chlorfluazuron **(1)**: white solid, 1010 kg, yield 95.0%, HPLC 99.2%, m.p.231-233°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.04-7.08 (m, 2H, C_6H_2), 7.47-7.57 (m, 3H, C_6H_3), 8.02-8.03 (m, 1H, C_5NH_2),

8.23-8.24 (m, 1H, C_5NH_2), 9.94 (s, 1H, NH), 10.70 (s, 1H, NH); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -61.37～-62.10 (m, 3F), -110.62～-110.66 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 112.2 (t, *J* = 18.3 Hz), 112.9-112.3 (m), 119.0, 120.3, 122.9 (q, *J* = 272.2 Hz), 123.5 (q, *J* = 33.9 Hz), 129.5, 134.2 (t, *J* = 10.4 Hz), 135.7, 136.3 (q, *J* = 3.0 Hz), 142.2, 142.7 (q, *J* = 4.2 Hz), 151.5, 159.5, 160.1 (dd, *J* = 255.6, 5.8 Hz), 162.9; LC-MS m/z: 537.91.

3. The HPLC analysis

The HPLC analysis of 4-amino-2,6-dichlorophenol **(2)**

数据文件: E:\新建文件夹\1\Data\Chlorfluazuron\def_LC 2022-11-05 10-15-42\003-3-Compound 2.D
样品名称: Compound 2

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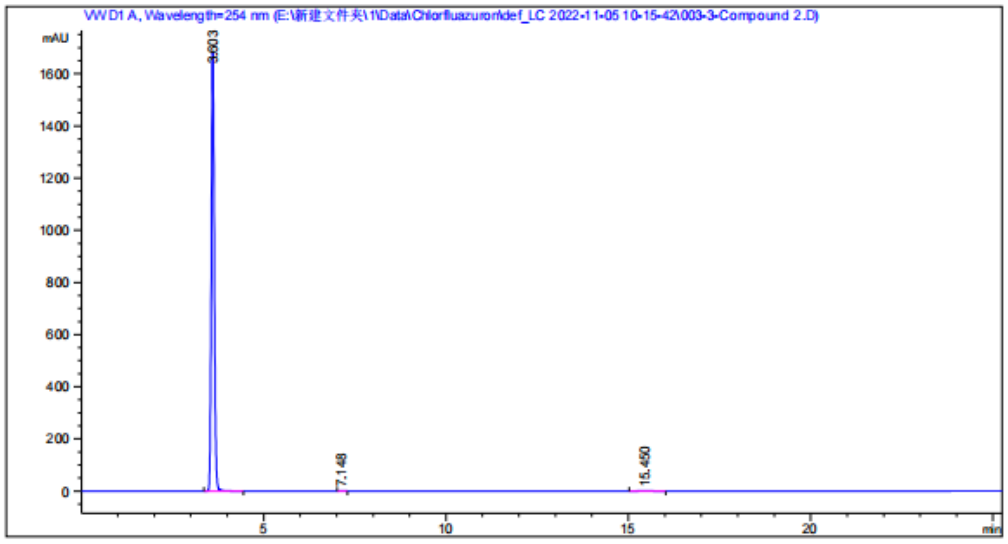

面积百分比报告

排序	:	信号
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稀释因子	:	1.0000

内标使用乘积因子和稀释因子

信号 1: VWD1 A, Wavelength=254 nm

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1	3.603	BB	0.0860	9390.30957	1684.77466	99.5050
2	7.148	MM	0.1409	11.69241	1.38338	0.1239
3	15.450	BB	0.2912	35.02516	1.83877	0.3711
总量 :				9437.02714	1687.99681	

The HPLC analysis of 3,5-dichloroaniline (**15**)

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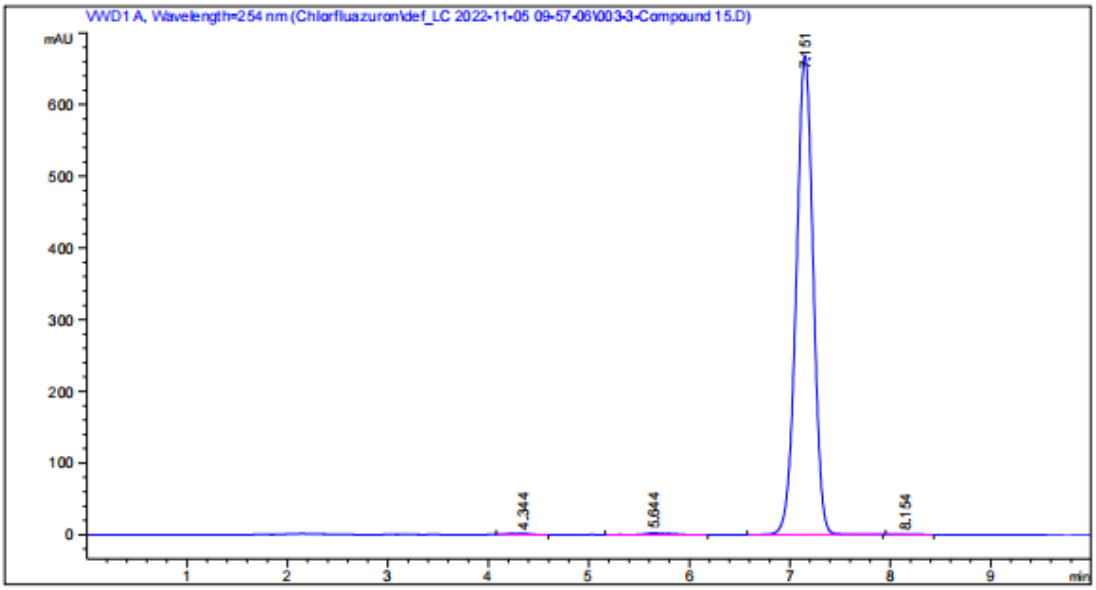

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内标使用乘积因子和稀释因子

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1	4.344	MM	0.2098	22.08005	1.75401	0.2800
2	5.644	MM	0.2578	35.75779	2.31195	0.4534
3	7.151	BB	0.1817	7823.86475	667.80701	99.2139
4	8.154	MM	0.2042	4.14950	3.38717e-1	0.0526
总量 :				7885.85208	672.21169	

The HPLC analysis of 3,5-dichloro-4-(3-chloro-5-trifluoromethyl-2-pyridoxyl)aniline (**4**)

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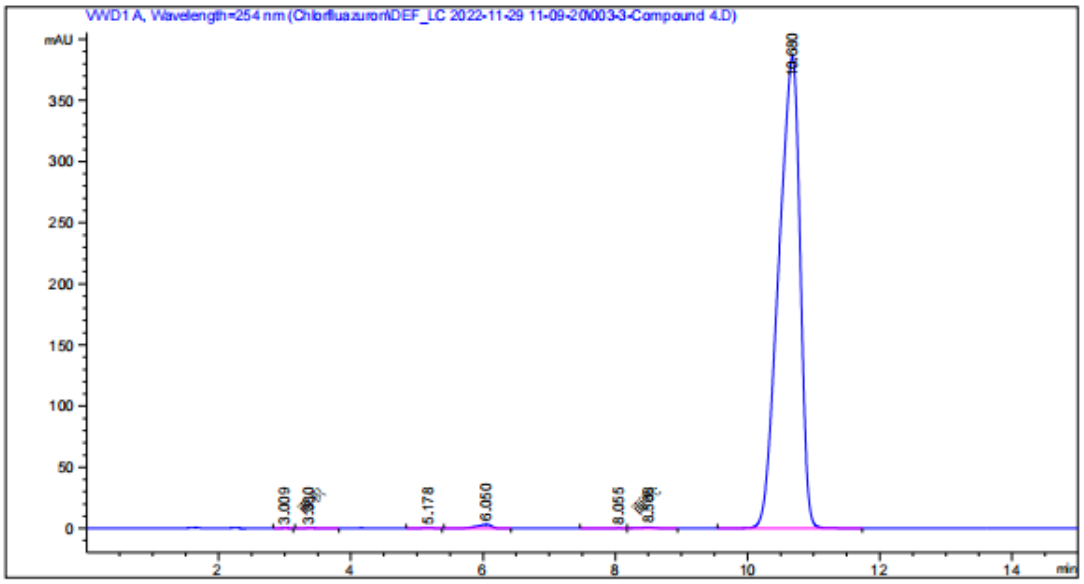

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内标使用乘积因子和稀释因子

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1	3.009	MM	0.1213	2.32015	3.18792e-1	0.0266
2	3.380	MM	0.2778	4.22219	2.53296e-1	0.0485
3	5.178	MM	0.1819	5.55937	5.09494e-1	0.0638
4	6.050	BB	0.2148	47.41135	3.14640	0.5444
5	8.055	MF	0.2808	3.12469	1.85436e-1	0.0359
6	8.508	FM	0.3131	12.03695	6.40687e-1	0.1382
7	10.680	BB	0.3738	8633.92676	386.24313	99.1425

The HPLC analysis of 2,6-difluorobenzoyl isocyanate (**6**)

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样品名称: Compound 6

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		进样量 :	5.000 µl
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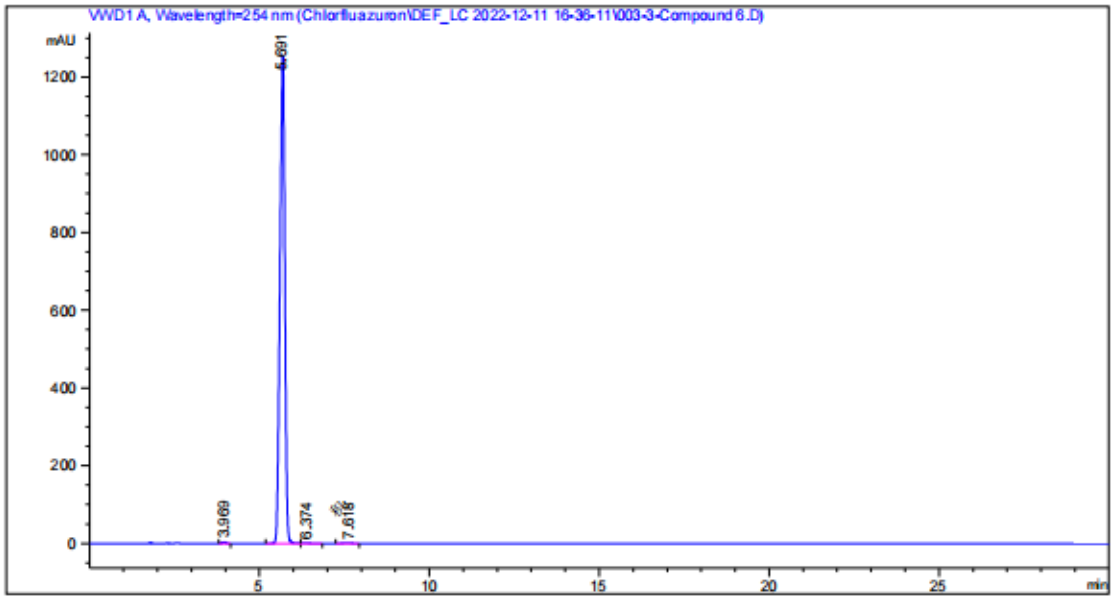

面积百分比报告

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乘积因子	:	1.0000
稀释因子	:	1.0000

内标使用乘积因子和稀释因子

信号 1: VWD1 A, Wavelength=254 nm

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1	3.969	BB	0.1068	22.19155	3.32758	0.1762
2	5.691	MF	0.1672	1.25561e4	1251.71777	99.7191
3	6.374	FM	0.2416	5.77308	3.98301e-1	0.0458
4	7.618	MM	0.2198	7.40911	5.61782e-1	0.0588
总量 :				1.25915e4	1256.00543	

The HPLCanalysis of Chlorfluazuron **(1)**

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样品名称: Compound 1

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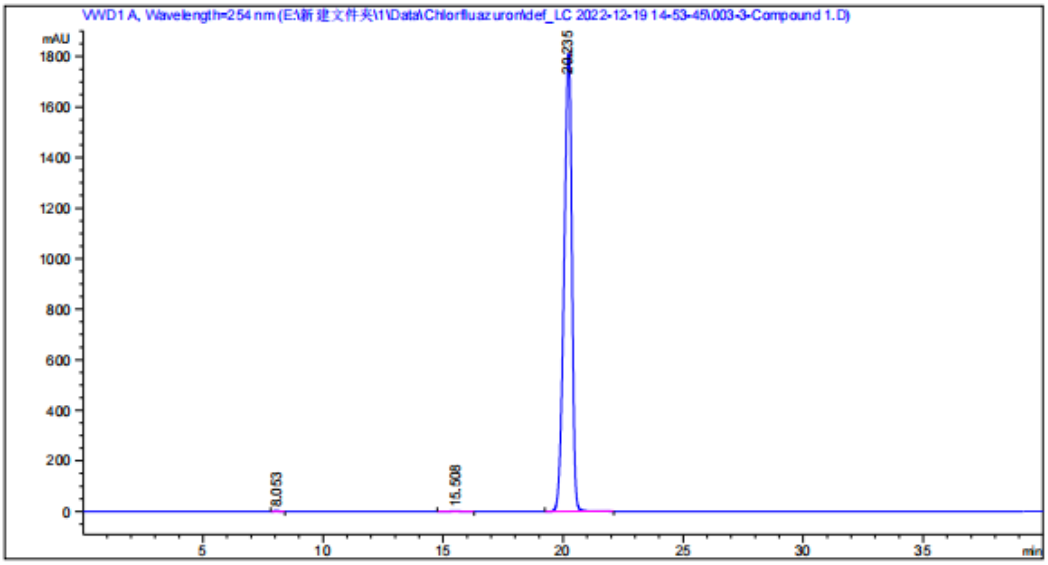

面积百分比报告

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稀释因子 : 1.0000
内标使用乘积因子和稀释因子

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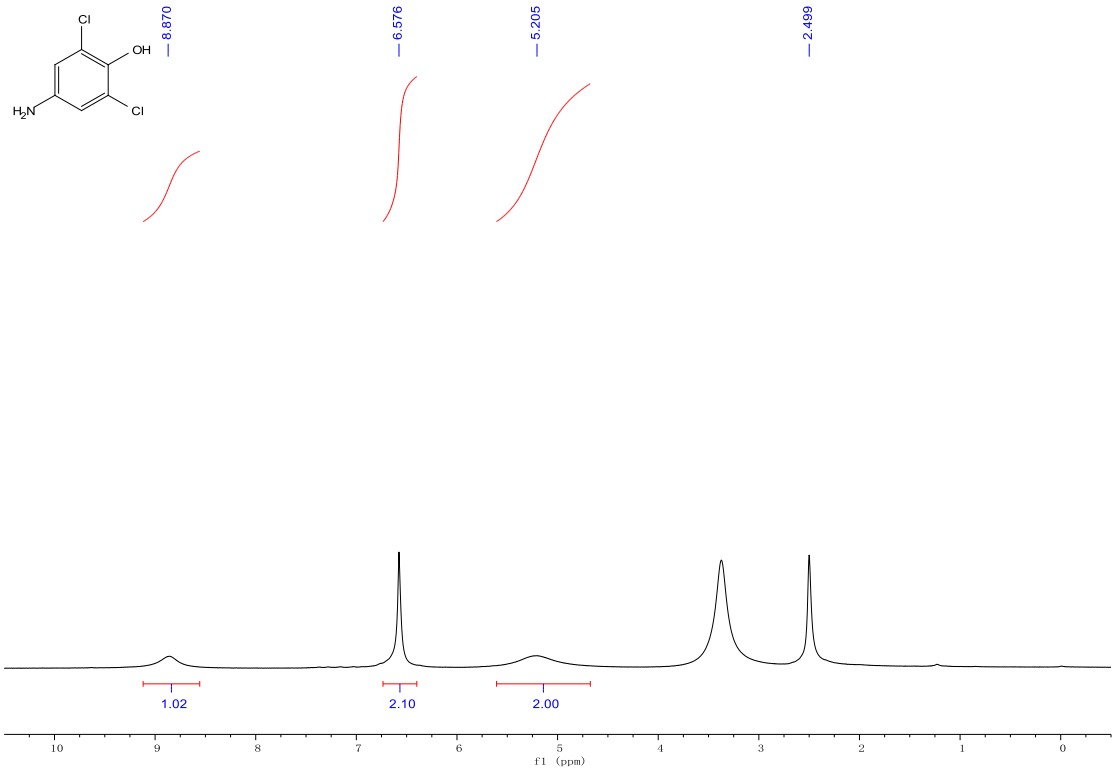
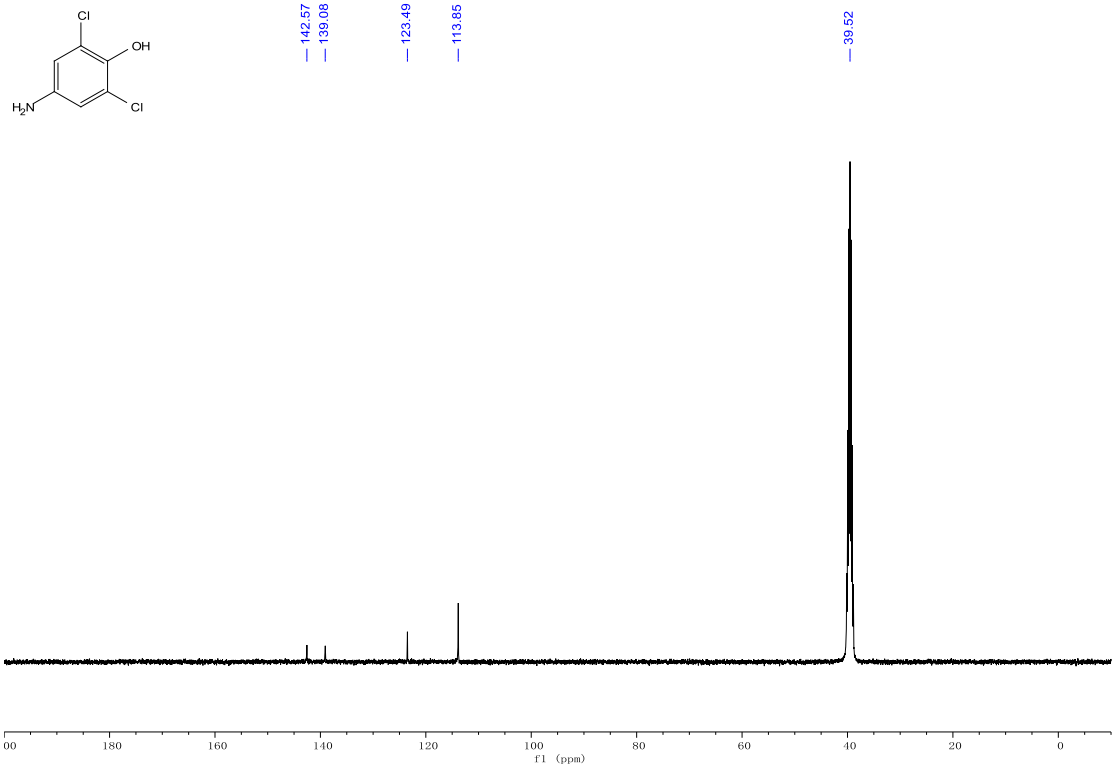
1	8.053	BB	0.1478	154.92815	3.32961	0.3770
2	15.508	MM	0.2830	151.31179	1.64962	0.3682
3	20.235	MM	0.3774	4.07888e4	1812.34949	99.2549
总量 :				4.10950e4	1817.32872	

4. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra

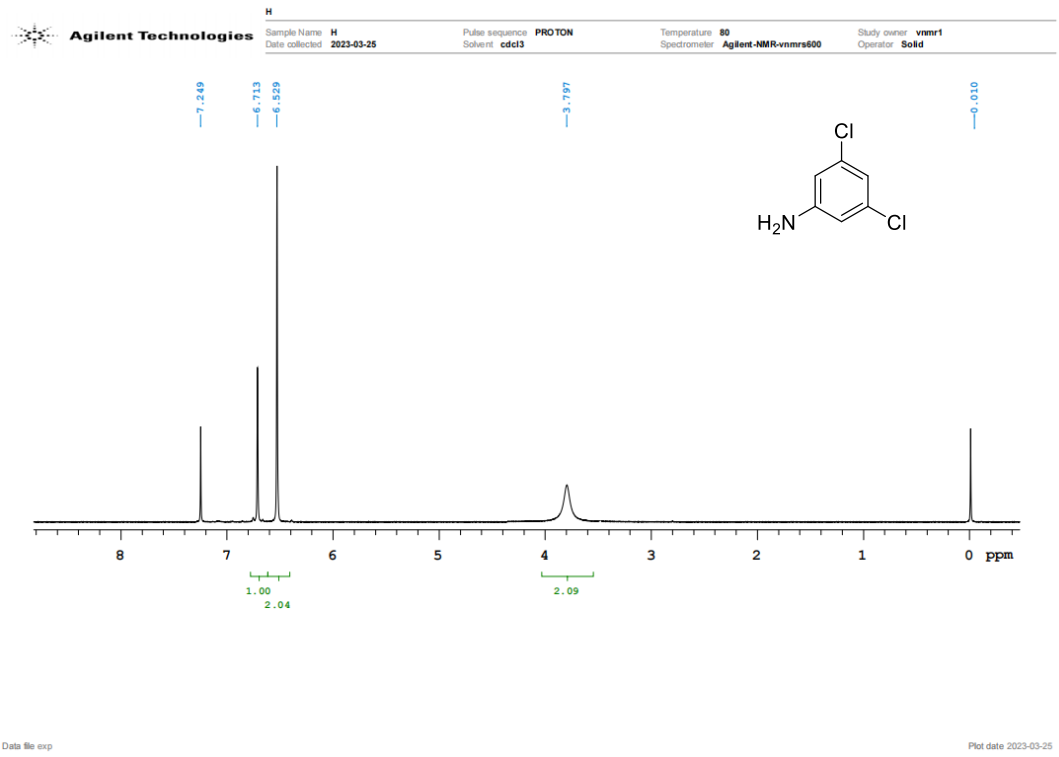
^{1}H NMR spectra of 4-amino-2,6-dichlorophenol **(2)**



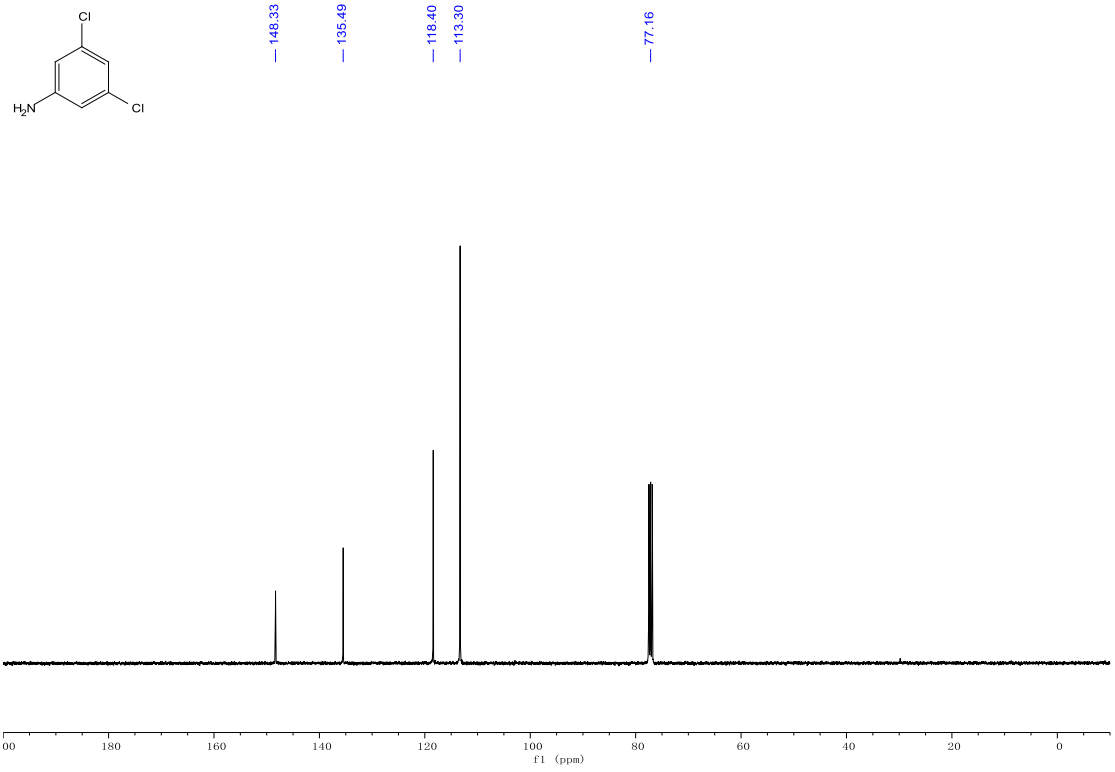
^{13}C NMR spectra of 4-amino-2,6-dichlorophenol **(2)**



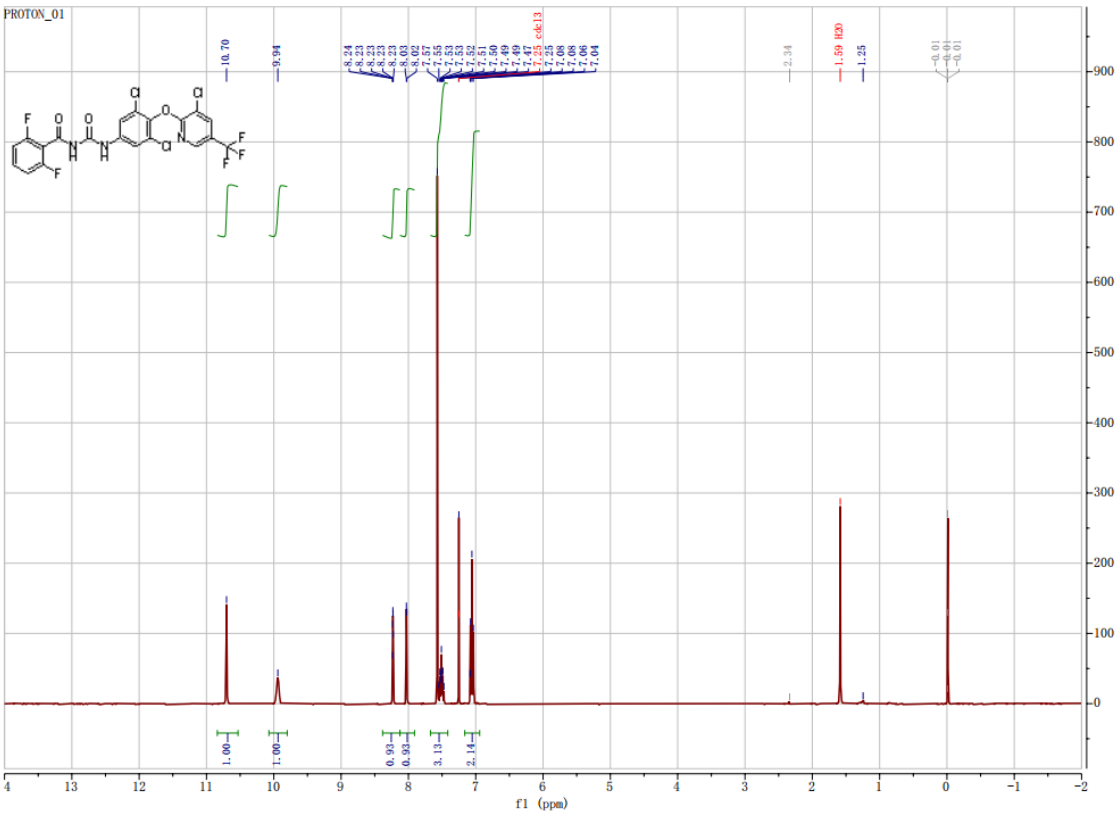
^{1}H NMR spectra of 3,5-dichloroaniline (**15**)



^{13}C NMR spectra of 3,5-dichloroaniline (**15**)



^{1}H NMR spectra of Chlorfluazuron **(1)**



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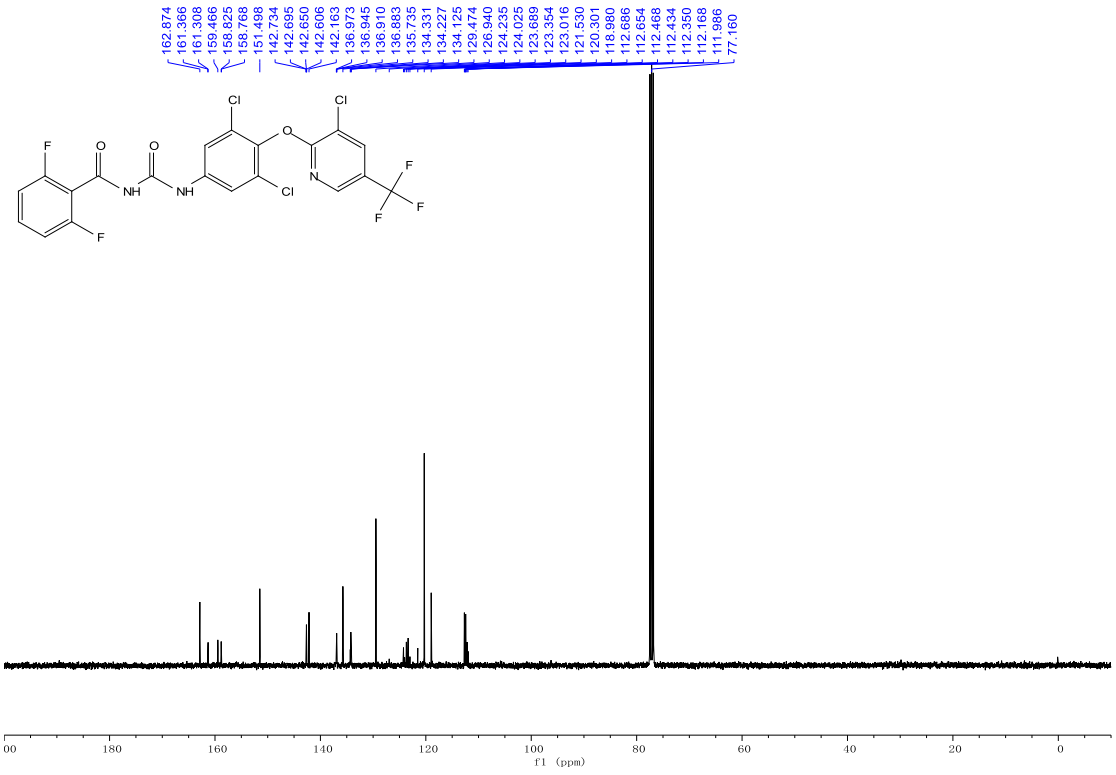
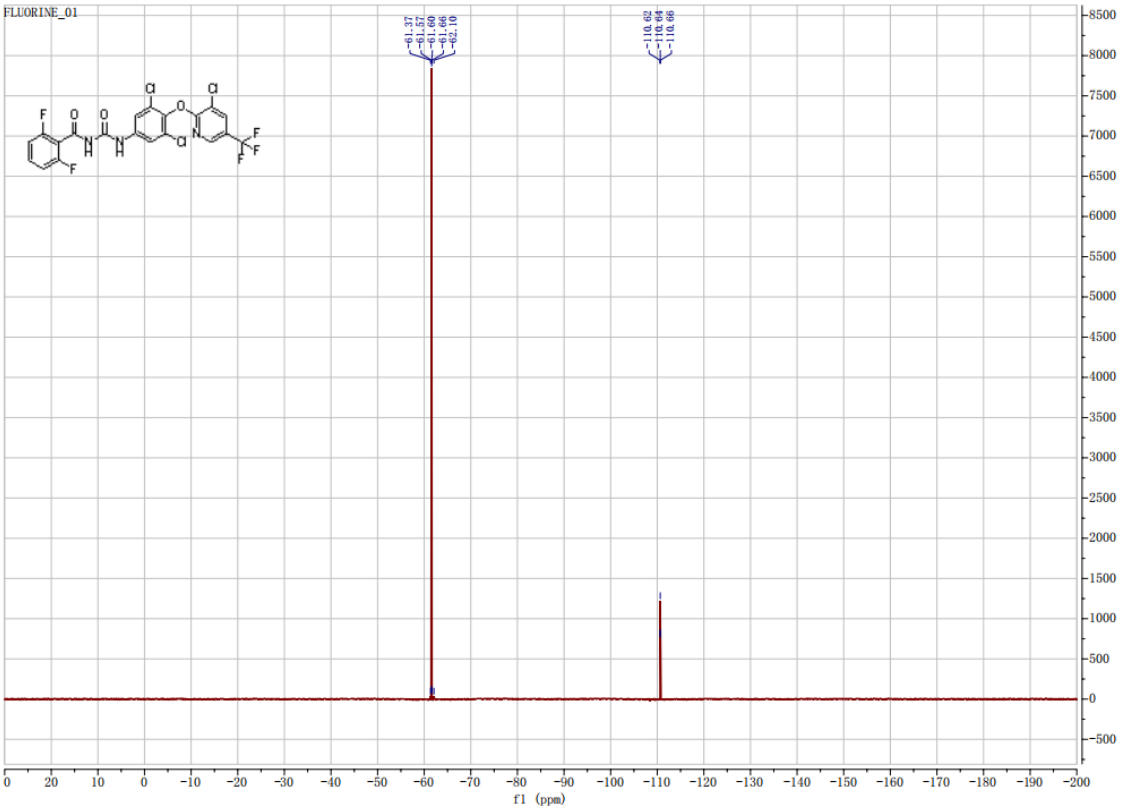
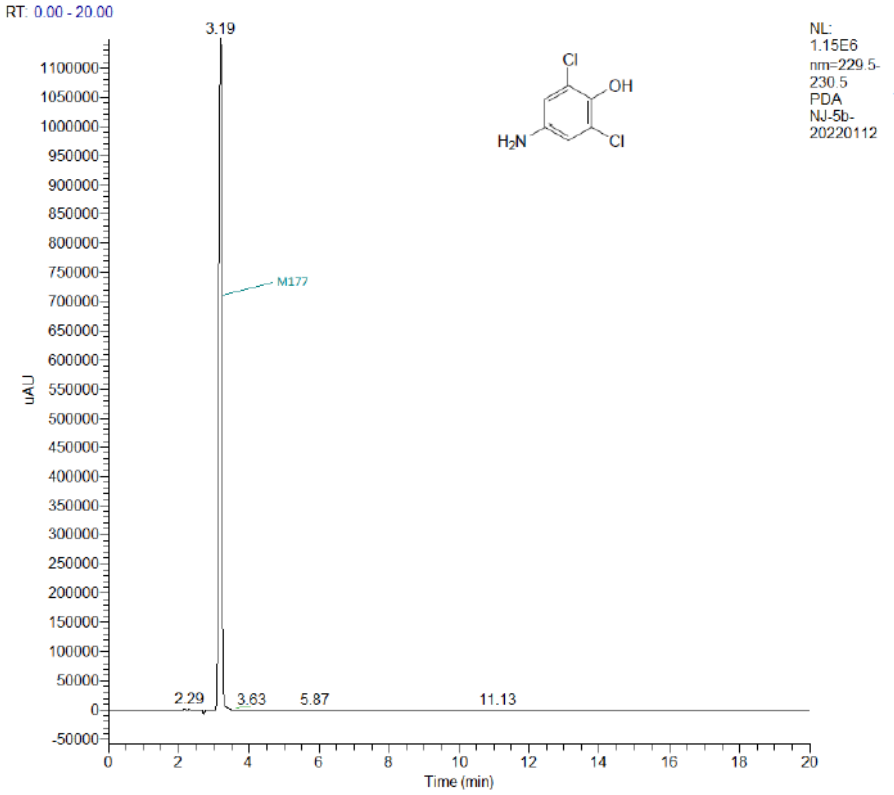


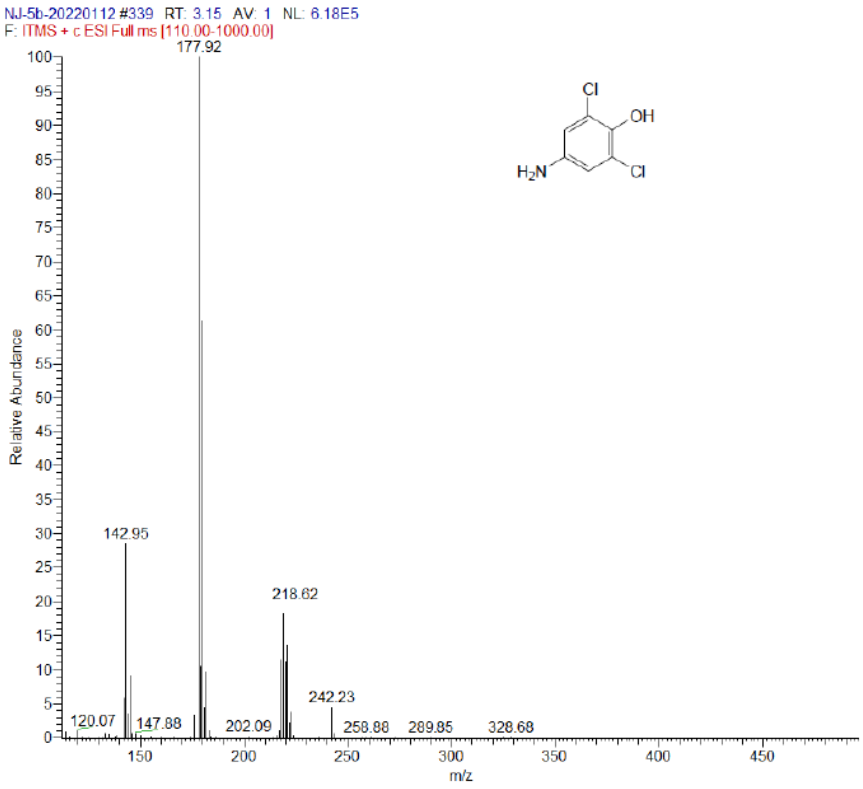
^{19}F NMR spectra of Chlorfluazuron **(1)**



5. LC-MS spectrum

LC-MS spectrum of 4-amino-2,6-dichlorophenol **(2)**





LC-MS spectrum of Chlorfluazuron **(1)**