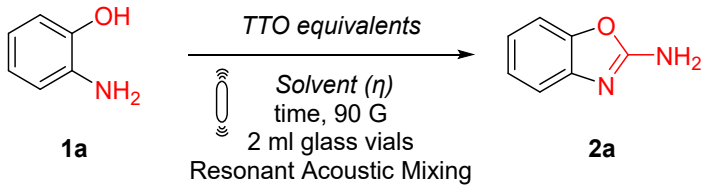
Oxidized Thiourea Derivatives: Uncovering New Frontiers with Resonant Acoustic Mixing (RAM)

1. General Information

Commercially available reagents were purchased from Aldrich, Strem Chemicals, Alfa-Aesar, TCI Europe and used as received. All reactions were monitored by thin-layer chromatography (TLC) with a n-hexane-ethyl acetate mixture 1:1, and compounds were visualized under UV light (254 nm). The eluents were technical grade. Chemical reactions were carried out using a Resodyn Acoustic Mixer LabRAM II. The reagents were mixed using a 2 mL glass vials with plastic stopper. These parameters were applied if not stated otherwise. ^{1}H and ^{13}C liquid NMR spectra were recorded on a Varian 600 MHz and Bruker Avance III HD 600 MHz NMR spectrometer at 298 K and were calibrated using trimethylsylane (TMS). Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referred to the residual hydrogen in the solvent ($CHCl_3$, 7.27 ppm or DMSO 2.54 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, bs = broad singlet, and combination of thereof), coupling constant (J) in Hertz (Hz) and integration. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, δ 77.0 ppm or δ DMSO-d_6 δ 39.5 ppm). Deuterated NMR solvents were obtained from Aldrich. Samples were analysed using an Agilent 5977B MS interfaced to the GC 7890B equipped with a DB-5ms column (J & W), injector temperature at 230 °C, detector temperature at 280 °C, helium carrier gas flow rate of 1 ml/min. The GC oven temperature program was 60 °C initial temperature with 4 min hold time and ramping at 15°C/min to a final temperature of 270°C with 7 min hold time. 1 µL of each sample was injected in split (1:20) mode. After a solvent delay of 3 minutes, mass spectra were acquired in full scan mode using 2.28 scans/s with a mass range of 50–500 Amu. Retention times of different compounds were determined by injecting pure compounds under identical conditions. All the experiments were carried out in duplicate to ensure reproducibility of the experimental data. The temperature for the scale-up approach was evaluated using an infrared thermometer made by Powerfix (measuring range: -50 °C ~ +380 °C). Yields refer to pure, isolated materials.

2. Optimisation of the synthesis of 2-aminobenzoxazole 2a

2.1. Optimisation trials run on a 0.5 mmol scale

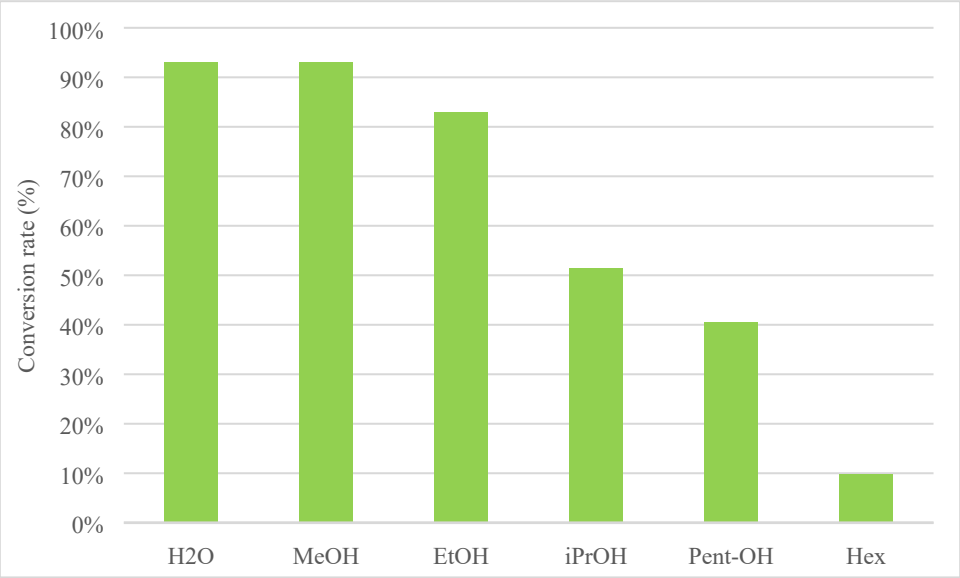


Entry	TTO	Liquid Additive	Time	Conversion rate
1	1 eq	H_2O, 180 µL (η=1)	60 min	80,0%
2	1,5 eq	H_2O, 180 µL (η=1)	60 min	86,0%
3	1,5 eq	H_2O, 180 µL (η=1)	120 min	91,0%
4	2 eq	H_2O, 180 µL (η=1)	30 min	63,0%
5	2 eq	H_2O, 180 µL (η=1)	60 min	73,0%
6	**2 eq**	**H_2O, 180 µL (η=1)**	**75 min**	**93,0%**
7	2 eq	MeOH, 180 µL (η=1)	75 min	93,0%
8	2 eq	EtOH, 180 µL (η=1)	75 min	83,0%
9	2 eq	iPrOH, 180 µL (η=1)	75 min	51,5%
10	2 eq	Pent-OH, 180 µL (η=1)	75 min	40,6%
11	2 eq	Hex, 180 µL (η=1)	75 min	9,7%
12	2 eq	None	75 min	52,0%
13	2 eq	H_2O, 134 µL (η=0,75)	75 min	70,1%
14	2 eq	H_2O, 90 µL (η=0,5)	75 min	49,3%
15	2 eq	H_2O, 46 µL (η=0,25)	75 min	21,0%
16	2 eq	H_2O, 134 µL (η=0,75)	120 min	68,0%

Table 1. Optimisation table for the synthesis of 2-aminobenzoxazole **2a**. All the reactions were run using a 2 mL glass vials equipped with 0.5 mmol of 2-amino phenol (**1a**) and 1.0 mmol of thiourea trioxide (TTO) at an acceleration rate of 90g. The conversions were calculated through ^{1}H-NMR.

To our delight, when we mixed **1a** with thiourea trioxide in a ratio of 1:1, in the presence of water as a liquid additive (ratio of the water volume to the weight of reaction mixture η = 1.00 mL mg^{-1}) and with a g-factor of 90, the yield was 80,0% (Table 1, entry 1). For purification, the crude was simply recovered with ethyl acetate and filtered on filter paper with a pore size of 6 µm. The crude was analysed by ^{1}H-NMR spectroscopy and a spectrum free of impurities was reported. Then, we decided to increase the thiourea trioxide equivalents to 1,5 eq. to see if it was necessary to work with an excess. In this case the yield was increased to 86,0% in 1 hour and even to 91,0% in 2 hours (Table 1, entries 2 and 3). It was then tried to double the equivalents of TTO which resulted in obtaining the target product with a conversion rate of 63% in 30 min (Table 1, entry 4). The same experiment performed for 1 hour led to an increase of the conversion rate to 73,0% (Table 1, entry 5). By further increasing the reaction time, we found that 2 equivalents were the optimum amount to convert the starting material with a percentage of 93% (Table 1, entry 6). The last useful parameter to be modulated to achieve a full optimisation was the solvent, so several experiments were carried out with different organic solvents. At first glance, it can be said that the reaction carried out by using methanol as a liquid additive is better performing (Table 1, entry 7). However, the reaction run in presence of water is better in terms of sustainability of the whole process. By increasing the number of carbon atoms in the alcohol, it was found that the reaction yield decreased significantly. This might be due to the poor solubility of thiourea

trioxide in the solvents in question (Table 1, entries 8-11). The amount of solvent also proved to be critical, as optimal mixing is required to promote the contact among the reaction components and thus have a high-performance process. The trials were therefore carried out by reducing the η factor, i.e. the amount of solvent, to 0.75, 0.5, 0.25 and 0 (Table 1, entries 12-16). Nonetheless, the results showed that the conversion rates were poorer in all cases.



Graph 1. Comparison of the conversion rate of **2a** with respect to the solvent.

2.2. Optimisation trials run on a 10 mmol scale

For completeness, the relevance of the g factor was also evaluated on a gram scale. After completing the reaction and purification steps, the recovered solid was analysed (Figure 1). When the process was conducted at 30 g, a total of 761.9 mg was obtained (56% yield), but ^{1}H-NMR analysis revealed a mixture of 2-aminobenzoxazole and 2-aminophenol, with only 42% of the desired benzoxazole in the final product (Figure 2). In contrast, scaling up the reaction to 90 g significantly improved the outcome, yielding 1046.3 mg (78%) of pure 2-aminobenzoxazole (Figure 3).

Figure 1. Part of the solids recovered from the gram-scale reactions. The powder recovered from the reaction run at 30 *g* appears darker due to the presence of unreacted 2-amino phenol.

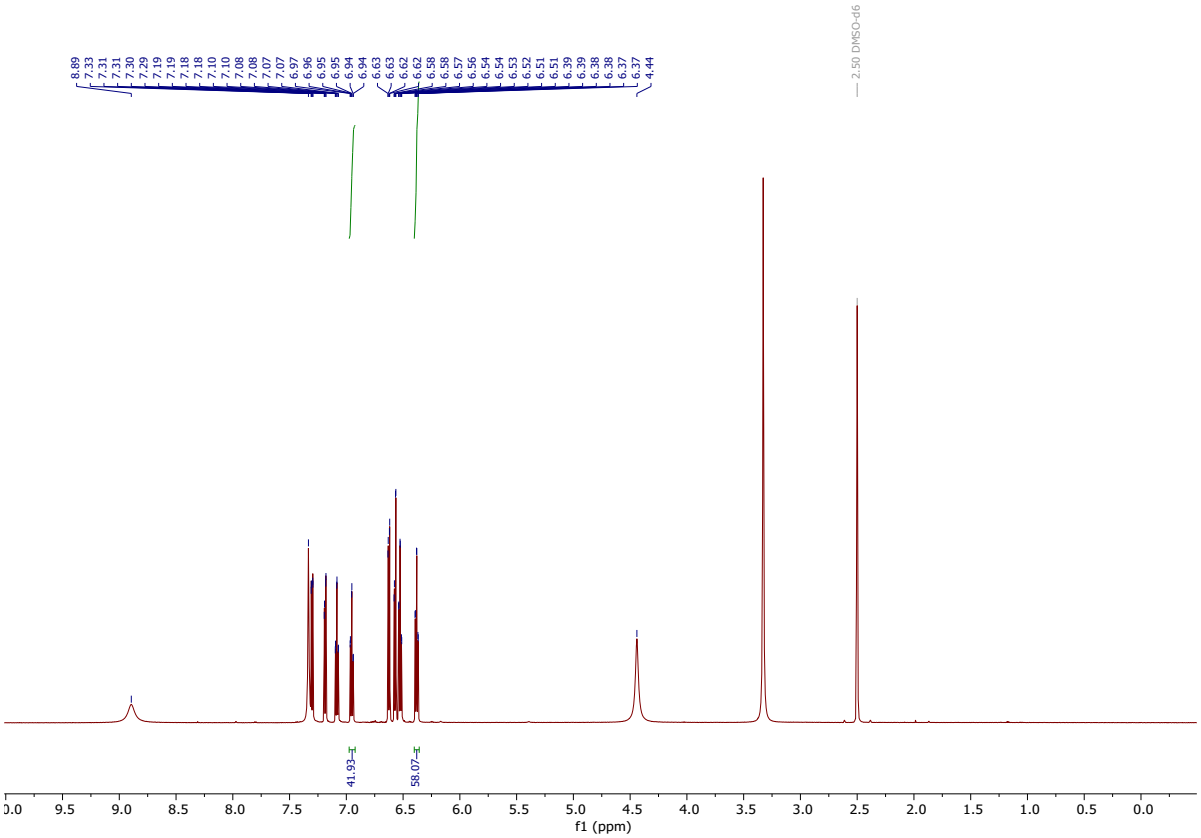


Figure 2. ^{1}H-NMR spectra of the reaction run at 30 *g*.

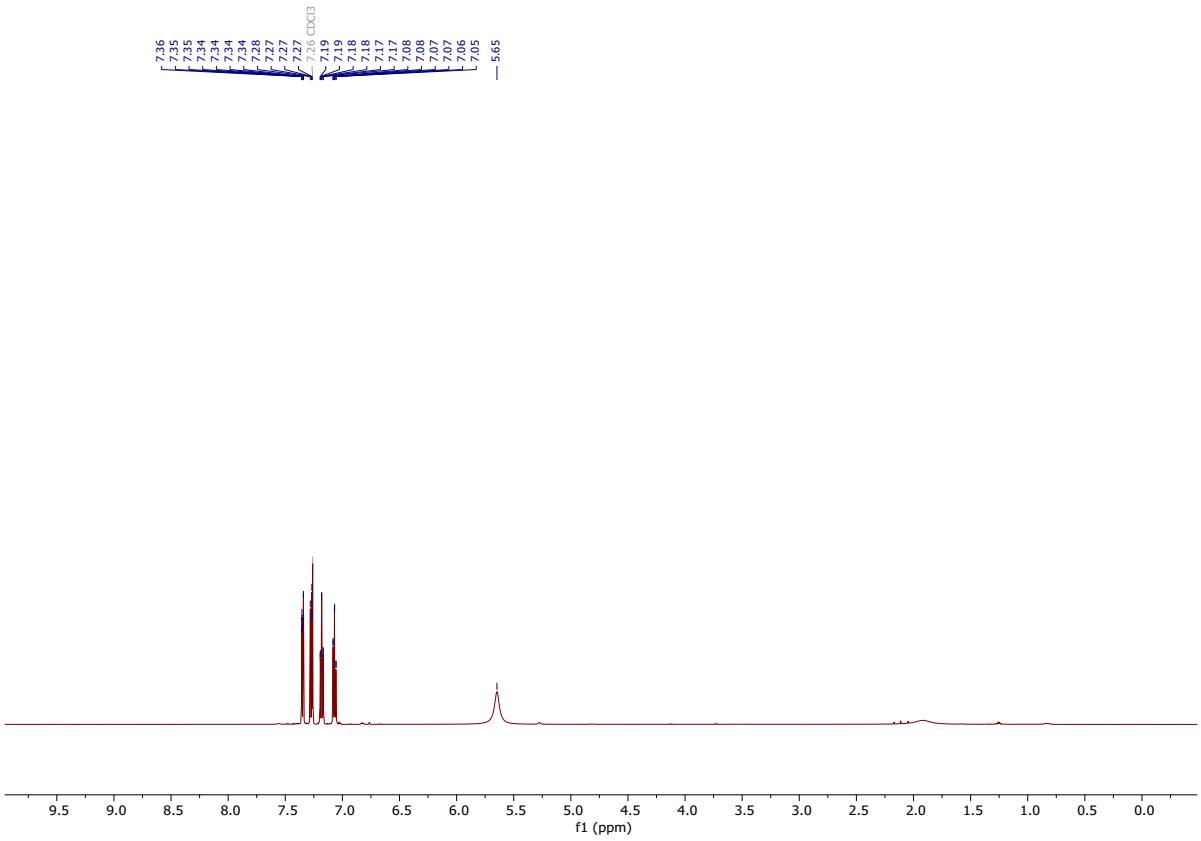


Figure 3. ^{1}H-NMR spectra of the reaction run at 90 *g*.

3. Synthesis and spectroscopic characterisation of 2-aminobenzoxazoles 2a-q

General procedure for the synthesis of 2-aminobenzoxazoles 2a-q

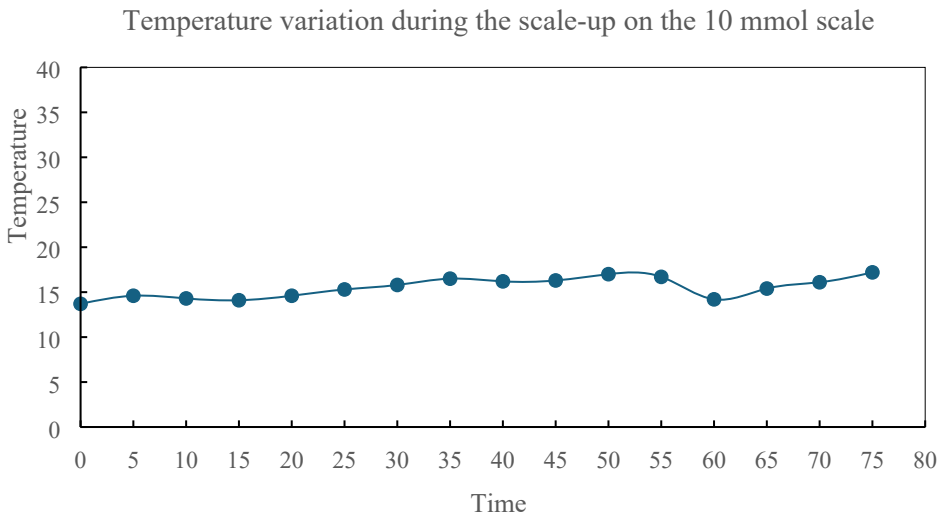
A 2 ml glass vial was filled with 2-aminophenol **1a-q** (0.5 mmol), thiourea trioxide (1.0 mmol), and distilled water (ratio of the water volume to the weight of reaction mixture η = 1.00 mL mg^{-1}). The vial was closed, and the reaction ranged from 75 to 180 minutes at 90 *g*. At the end of the reaction, the mixture was recovered with ethyl acetate and filtered on paper. Lastly, the solvent was removed under reduced pressure to afford the pure product. When the conversion of the starting material was incomplete, additional purification steps were required. For products **2j** and **2k**, a small silica gel pad was employed for purification, using a 1:1 hexane/ethyl acetate mixture as the eluent.

General procedure for the scale-up process in the synthesis of 2a

A 25 ml glass vial was filled with 2-aminophenol **1** (10.0 mmol), thiourea trioxide (20.0 mmol), and distilled water (ratio of the water volume to the weight of reaction mixture *η* = 1.00 mL mg^{-1}, 3.57 mL). The vial was closed with an aluminum stopper, and the reaction for 75 minutes at 90 *g*. At the end of the reaction, the mixture was recovered with ethyl acetate and filtered on paper. Lastly, the solvent was removed under reduced pressure to afford the pure product. The equipment for the scale-up approach was composed of a 25 mL reaction vial, five 25 mL vials filled with distilled water for balancing purposes, and a 6-hole plastic holder (Figure 4 and 5). The temperature was monitored through an Infrared thermometer every 5 minutes with an average temperature of 15.5 °C as shown in Graph 2.

Figure 4. Initial setup for the gram-scale scale-up on the LAB RAM II.

Figure 5. Loading and running of the gram-scale on the LAB RAM II along with the Infrared thermometer used for checking the temperature during the reaction.

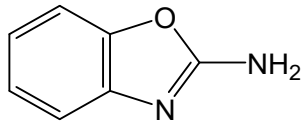


Graph 2. Analysis of the temperature changes throughout the whole process. The reaction has been monitored every 5 minutes with an infrared thermometer showing a stable pattern with temperature increments higher no more than 3.1 °C.

Time	0	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75
Temperature	13.7	14.6	14.3	14.1	14.6	15.3	15.8	16.5	16.2	16.3	17.0	16.7	14.2	15.4	16.1	17.2

Average Temperature	**Room Temperature**
15.5 °C	13.9 °C

2-Amino-Benzoxazole (**2a**)



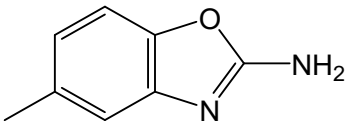
The title compound was synthesized according to the general procedure. 2-aminophenol **1a** (54.6 mg, 0.5 mmol), thiourea trioxide (124.11 mg, 1.0 mmol), and 178 µL of distilled water were mixed for 75 minutes to afford the 2-aminobenzoxazole **2a** as a brownish solid (61.23 mg, 0.456 mmol, 91%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.19 (td, *J* = 7.8, 1.2 Hz, 1H), 7.08 (td, *J* = 7.8, 1.2 Hz, 1H), 4.98 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 161.7, 149.2, 141.2, 124.1, 121.5, 116.9, 109.0.

The spectroscopic data closely match the ones previously reported in the literature.[1]

2-Amino-5-Methyl-Benzoxazole (**2b**)



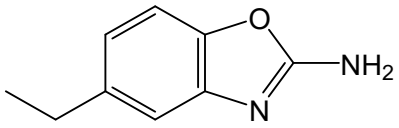
The title compound was synthesized according to the general procedure. 2-amino-4-methylphenol **1b** (74.1 mg, 0.5 mmol), thiourea trioxide (124.11 mg, 1.0 mmol), and 198 µL of distilled water were mixed for 90 minutes to afford the 2-amino-5-methylbenzoxazole **2b** as a white solid (69.8 mg, 0.471 mmol, 94.2%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 – 7.12 (m, 2H), 6.89 – 6.85 (m, 1H), 5.30 (s, 2H), 2.4 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 161.8, 147.0, 142.9, 133.9, 122.2, 117.2, 108.5, 21.6.

The spectroscopic data closely match the ones previously reported in the literature.[2]

2-Amino-5-Ethyl-Benzoxazole (**2c**)



The title compound was synthesized according to the general procedure. 2-amino-4-ethylphenol **1c** (54.9 mg, 0.4 mmol), thiourea trioxide (99.3 mg, 0.8 mmol), and 154 µL of distilled water were mixed for 90 minutes to afford the 2-amino-5-ethylbenzoxazole **2c** as a white solid (36.2 mg, 0.223 mmol, 55.8%).

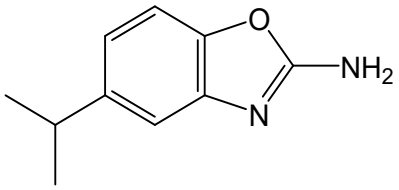
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18 – 7.15 (m, 2H), 6.90 – 6.89 (m, 1H), 5.72 (s, 2H), 2.71 – 2.67 (q, *J* = 7.6 Hz, 2H), 1.26 – 1.24 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 162.2, 146.9, 142.8, 140.6, 121.1, 115.8, 108.6, 29.1, 16.4.

HRMS: calculated for $C_9H_{10}N_2O$: 162.1920 $[M]^+$; found: 162.1918.

IR-ATR (cm^{-1}): 3343.42, 2970.68, 2984.95, 1684.75, 1502.57, 1382.12, 1312.29, 1159.20, 1129.38, 950.47, 829.16.

2-Amino-5-Isopropyl-Benzoxazole (**2d**)



The title compound was synthesized according to the general procedure. 2-amino-4-isopropylphenol **1d** (75.6 mg, 0.5 mmol), thiourea trioxide (124.1 mg, 1.0 mmol), and 200 µL of distilled water were mixed for 90 minutes to afford 2-amino-5-isopropylbenzoxazole **2d** as a white solid (80.9 mg, 0.459 mmol, 91.8%).

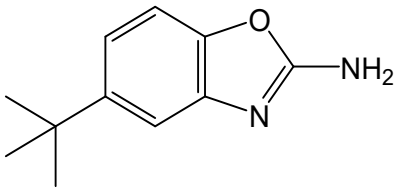
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 – 7.20 (d, *J* = 1.9 Hz, 2H), 7.18 – 7.16 (d, *J* = 8.3 Hz, 1H), 6.94 – 6.92 (dd, *J* = 1.9, 8.3 Hz, 1H), 5.75 (s, 2H), 2.99 – 2.92 (m, *J* = 6.9 Hz, 1H), 1.27 – 1.26 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 162.3, 147.0, 145.3, 142.7, 119.7, 114.3, 108.5, 34.4, 24.6.

HRMS: calculated for $C_{10}H_{13}N_2O$: 177.1028 $[M+H]^+$; found: 177.1046.

IR-ATR (cm^{-1}): 3343.42, 2970.68, 2884.95, 1673.57, 1498.57, 1379.11, 1308.29, 1159.20, 1129.38, 950.47, 816.29.

2-Amino-5-Tert-Butyl-Benzoxazole (**2e**)



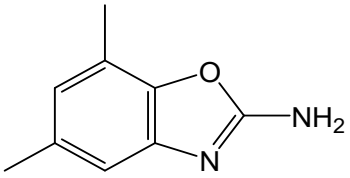
The title compound was synthesized according to the general procedure. 2-amino-4-tert-butylphenol **1e** (82.6 mg, 0.5 mmol), thiourea trioxide (124.1 mg, 1.0 mmol) and 207 µL of distilled water were mixed for 180 minutes, to afford the 2-amino-5-tertbutylbenzoxazole **2e** as a brownish solid (35.2 mg, 0.185 mmol, 37%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.37 (d, *J* = 2.1 Hz, 1H), 7.19 – 7.17 (d, *J* = 8.4 Hz, 1H), 7.12 – 7.11 (dd, *J* = 2.1, 8.4 Hz, 1H), 5.39 (s, 2H), 1.35 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 162.0, 147.7, 146.7, 142.5, 118.7, 113.7, 108.2, 34.9, 31.9.

The spectroscopic data closely match the ones previously reported in the literature.[3]

2-Amino-5,7-Dimethyl-Benzoxazole (**2f**)



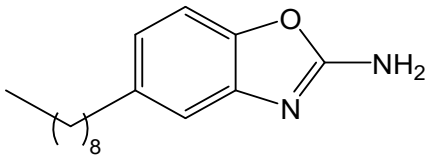
The title compound was synthesized according to the general procedure. 2-amino-4,6-dimethyphenol **1f** (68.6 mg, 0.5 mmol), thiourea trioxide (124.1 mg, 1.0 mmol), and 193 µL of distilled water were mixed for 180 minutes to afford the 2-amino-5,7-dimethylbenzoxazole **2f** as a white solid (68.8 mg, 0.424 mmol, 84.8%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.70 (s, 1H), 4.93 (s, 2H), 2.37 (s, 3H), 2.36 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 161.2, 146.0, 142.3, 133.6, 123.8, 118.8, 114.5, 21.4, 14.8.

The spectroscopic data closely match the ones previously reported in the literature. [4]

2-Amino-5-Nonyl-Benzoxazole (**2g**)



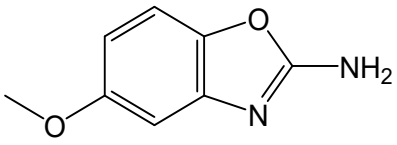
The title compound was synthesized according to the general procedure. 2-amino-4-nonylphenol **1g** (235.37 mg, 1.0 mmol), thiourea trioxide (248.11 mg, 2.0 mmol), and 483 µL of distilled water were mixed for 120 minutes to yield 2-amino-5-nonylbenzoxazole **2g** as a brownish liquid (165.91 mg, 0.637 mmol, 63.7%).
^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.34 – 7.23 (m, 1H), 7.17 (dd, *J* = 8.3, 5.5 Hz, 1H), 7.09 – 6.95 (m, 1H), 5.73 (s, 2H), 1.75 – 0.45 (m, 19H).

^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers) δ 162.0, (**1C**: 147.0, 146.4, 146.1), (**1C**: 144.6, 144.2), (**1C:** 142.4), (**1C:** 120.0, 119.7, 119.4), (**1C:** 115.0, 114.8, 114.4), (**1C:** 108.0, 107.9, 107.8), (**8C:** 53.2, 52.2, 48.6, 47.4, 46.5, 45.2, 44.7, 43.9, 41.4, 41.2, 41.0, 39.7, 38.9, 38.2, 37.8, 37.0, 36.8, 36.2, 35.0, 34.4, 33.9, 33.3, 31.8, 31.3, 30.8, 30.5, 29.8, 29.6, 29.3, 28.7, 27.8, 26.9, 26.4, 25.9), (**1C :**25.3, 24.5, 23.7, 23.2, 22.9, 22.5, 21.8, 21.2, 19.9, 19.2, 18.9, 18.4, 18.1, 17.8, 17.6, 17.3), (**1C:** 14.9, 14.5, 13.5, 13.3, 11.2, 10.6, 9.0, 8.6).

HRMS: calculated for $C_{16}H_{25}N_2O$: 261.1967 $[M+H]^+$; found: 261.1942.

IR-ATR (cm^{-1}): 3343.42, 2970.68, 2929.68, 2877.50, 1666.12, 1572.94, 1464.84, 1379.12, 1304.57, 1159.20, 1129.38, 950.74, 816.29.

2-Amino-5-Methoxy-Benzoxazole (**2h**)



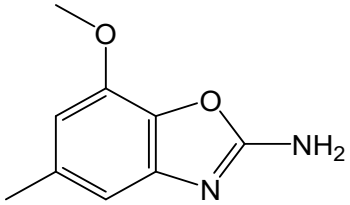
The title compound was synthesized according to the general procedure. 2-amino-4-methoxyphenol **1h** (69.6 mg, 0.5 mmol), thiourea trioxide (124.11 mg, 1.0 mmol), and 194 µL of distilled water were mixed for 75 minutes to afford the 2-amino-5-methoxybenzoxazole **2h** as a brownish solid (68.1 mg, 0.415 mmol, 83.0%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15 – 7.14 (d, *J* = 8.7 Hz, 1H), 6.92 – 6.91 (d, *J* = 2.6 Hz, 1H), 6.65 – 6.63 (dd, *J* = 8.7, 2.6 Hz, 1H), 5.03 (s, 2H), 3.82 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 157.3, 143.8, 143.4, 109.1, 108.9, 108.3, 102.0, 56.1.

The spectroscopic data closely match the ones previously reported in the literature.[5]

2-Amino-5-Methyl-7-Methoxy-Benzoxazole (**2i**)



The title compound was synthetized according to the general procedure. 2-amino-4-methyl-6-methoxyphenol **1i** (76.5 mg, 0.5 mmol), thiourea trioxide (124.1 mg, 1.0 mmol) and 201 µL of distilled water were mixed for 180 minutes, to afford the 2-amino-5-methyl-7-methoxy-benzoxazole **2i** as a pale brown solid (45.2 mg, 0.254 mmol, 50.7%).

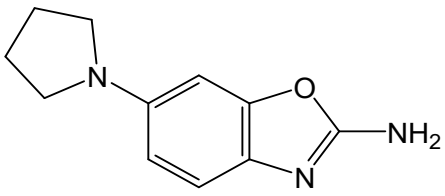
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.80 (s, 1H), 6.48 (s, 1H), 5.23 (s, 2H), 3.95 (s, 3H), 2.38 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 176.8, 146.6, 143.2, 134.8, 129.9, 110.1, 106.8, 56.4, 22.0.

HRMS: calculated for $C_9H_{11}N_2O_2$: 179.0821 $[M+H]^+$; found: 179.0824.

IR-ATR (cm^{-1}): 3429.78, 3127.01, 2919.70, 1658.45, 1664.95, 1453.1, 1330.64, 1167.54, 1069.73, 951.09, 890.69, 748.25.

2-Amino-5-Pyrrolydinyl-Benzoxazole **2j**



The title compound was synthetized according to the general procedure. 2-amino-5-pyrrolydinylphenol **1j** (89.1 mg, 0.5 mmol), thiourea trioxide (124.1 mg, 1.0 mmol) and 213 µL of distilled water were mixed for 180

minutes. The crude mixture was then purified through a silica pad to afford the 2-amino-6-pyrrolydinylbenzoxazole **2j** as a red solid (38.2 mg, 0.188 mmol, 37.6%).

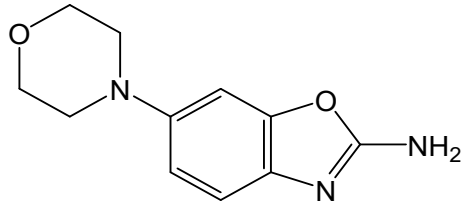
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 – 7.20 (d, *J* = 8.5 Hz, 1H), 6.55 – 6.54 (d, *J* = 2.3 Hz, 1H), 6.45 – 6.43 (dd, *J* = 8.5 Hz, 2.3 Hz, 1H), 4.77 (s, 2H), 3.28 – 3.26 (m, 4H), 2.03 – 2.01 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 159.5, 150.4, 144.9, 132.4, 116.9, 108.4, 93.3, 48.5, 25.6.

HRMS: calculated for $C_{11}H_{13}N_3ONa$: 226.0956 $[M+Na]^+$; found: 226.0967.

IR-ATR (cm^{-1}): 3423.03, 3334.32, 3066.26, 3041.19, 2825.48, 2854.13, 2825.20, 2763.49, 1673.91, 1571.70, 1482.99112.73, 806.09.

2-Amino-6-Morpholinyl-Benzoxazole (**2k**)



The title compound was synthesized according to the general procedure. 2-amino-5-morpholinylphenol **1k** (97.1 mg, 0.5 mmol), thiourea trioxide (124.1 mg, 1.0 mmol), and 221 µL of distilled water were mixed for 180 minutes. The crude mixture was then purified through a silica pad to afford the 2-amino-6-morphonilylbenzoxazole **2k** as a pale purple solid (11.2 mg, 0.051 mmol, 17.2%).

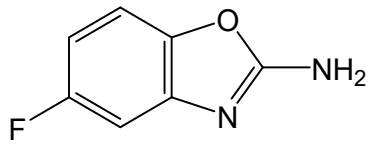
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (s, 1H), 6.91 (s, 1H), 6.83 – 6.82 (m, 1H), 5.02 (s, 2H), 3.90 – 3.85 (m, 4H), 3.11 (s, 4H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 164.3, 151.9, 147.8, 136.3, 116.7, 113.7, 98.6, 67.1, 51.2.

HRMS: calculated for $C_{11}H_{14}N_3O_2$: 220.1086 $[M+H]^+$; found: 220.1079.

IR-ATR (cm^{-1}): 3178.11, 2875.34, 1660.41, 1619.91, 1531.20, 1444.42, 1400.07, 1058.73, 1033.66, 923.74, 609.40

2-Amino-5-Fluoro-Benzoxazole **2l**



The title compound was synthesized according to the general procedure. 2-amino-4-fluorophenol **1l** (45.7 mg, 0.36 mmol), thiourea trioxide (89.4 mg, 0.72 mmol), and 135 µL of distilled water were mixed for 120 minutes to afford the 2-amino-5-fluorobenzoxazole **2l** as a white solid (38.9 mg, 0.256 mmol, 71.03%).

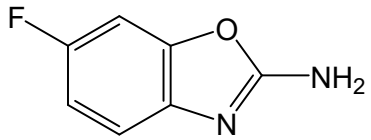
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18 – 7.16 (dd, *J* = 8.8, 4.3 Hz, 1H), 7.07 – 7.03 (dd, *J* = 8.8, 4.3 Hz, 1H), 6.80 – 6.75 (m, 1H), 5.33 – 5.18 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 162.9, 160.3 (d, J = 238.8 Hz), 145.1, 143.9 (d, J = 13.3 Hz), 109.1 (d, J = 10.0 Hz), 108.2 (d, J = 26.0 Hz), 104.0 (d, J = 26.5 Hz).

^{19}F NMR (565 MHz, $CDCl_3$) δ -118.90 (s, 1F).

The spectroscopic data closely match the ones previously reported in the literature. [6]

2-Amino-6-Fluoro-Benzoxazole **2m**



The title compound was synthetized according to the general procedure. 2-amino-5-fluorophenol **1m** (38.1 mg, 0.3 mmol), thiourea trioxide (74.5 mg, 0.6 mmol) and 113 µL of distilled water were mixed for 180 minutes, to afford the 2-amino-6-fluorobenzoxazole **2m** as a pale-yellow solid (31.2 mg, 0.021 mmol, 68.4%).

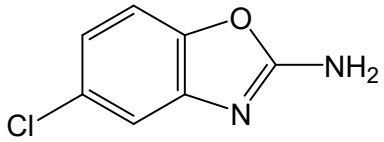
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 – 7.24 (m, 1H), 7.03 – 7.03 (m, 1H), 6.94 – 6.91 (m, 1H), 5.36 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 162.2, 158.7 (d, *J* = 239.4 Hz), 148.6, 139.1, 116.7 (d, *J* = 9.4 Hz), 111.4 (d, *J* = 23.8 Hz), 98.2 (d, *J* = 28.7 Hz).

^{19}F NMR (565 MHz, $CDCl_3$) δ -120.47 (s, 1F).

The spectroscopic data closely match the ones previously reported in the literature. [7]

2-Amino-5-Chloro-Benzoxazole **2n**



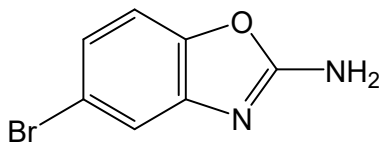
The title compound was synthesized according to the general procedure. 2-amino-4-chlorophenol **1n** (144.57 mg, 1.0 mmol), thiourea trioxide (248.22 mg, 2.0 mmol), and 392 µL of distilled water were mixed for 120 minutes to afford the 2-amino-5-chlorobenzoxazole **2n** as a white solid (0.122 mg, 0.721 mmol, 72.1%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 – 7.33 (d, *J* = 2.1 Hz, 1H), 7.18 – 7.17 (d, *J* = 8.5 Hz, 1H), 7.05 – 7.03 (dd, *J* = 8.5, 2.1 Hz, 1H), 5.37 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 162.7, 147.7, 144.4, 129.8, 121.7, 117.2, 109.9.

The spectroscopic data closely match the ones previously reported in the literature.[8]

2-Amino-5-Bromo-Benzoxazole **2o**



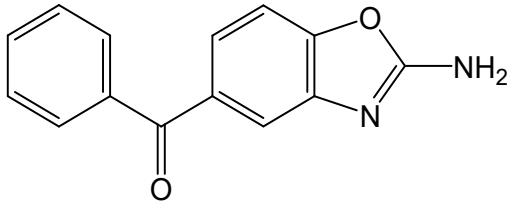
The title compound was synthetized according to the general procedure. 2-amino-4-bromophenol **1o** (94.01 mg, 0.5 mmol), thiourea trioxide (124.11 mg, 1.0 mmol) and 218 µL of distilled water were mixed for 120 minutes, to afford the 2-amino-5-bromobenzoxazole **2o** as a white solid (85.7 mg, 0.402 mmol, 80.5%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 – 7.49 (d, *J* = 2.0 Hz, 1H), 7.20 – 7.18 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.15 – 7.13 (d, *J* = 8.5 Hz, 1H), 5.22 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 162.2, 147.9, 144.6, 124.4, 120.0, 116.9, 110.3.

The spectroscopic data closely match the ones previously reported in the literature.[7]

(2-Amino-Benzoxazol-5-yl)-(Phenyl)-Methanone (**2p)**



The title compound was synthesized according to the general procedure. (3-amino-4-hydroxyphenyl)-(phenyl)-methanone **1p** (106.5 mg, 0.3 mmol), thiourea trioxide (74.5 mg, 0.6 mmol) and 181 µL of distilled water were mixed for 180 minutes to afford the (2-aminobenzo[d]oxazol-5-yl)(phenyl)methanone **2p** as a pale brown solid (46.2 mg, 0.194 mmol, 64.6%).

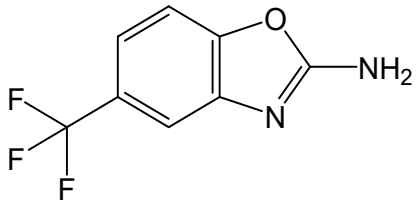
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 – 7.76 (m, 3H), 7.66 – 7.56 (m, 2H), 7.51 – 7.45 (t, *J* = 8.3 Hz, 2H), 7.39 – 7.35 (d, *J* = 8.3 Hz, 1H), 5.20 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 195.9, 163.2, 151.2, 140.8, 138.2, 134.7, 132.4, 130.2, 128.4, 124.9, 119.2, 108.9.

HRMS: calculated for $C_{14}H_{11}N_2O_2$: 239.0821 $[M+H]^+$; found: 239.0833.

IR-ATR (cm^{-1}): 3350.71, 3057.23, 2958.27, 2706.60, 1634.38, 1570.74, 1433.82, 1276.66, 877.45, 709.68.

2-Amino-5-(1,1,1-Trifluoro)-Methyl-Benzoxazole **2q**



The title compound was synthesized according to the general procedure. 2-amino-4-(1,1,1-trifluoro)methylphenol **1q** (88.5 mg, 0.5 mmol), thiourea trioxide (124.1 mg, 1.0 mmol) and 213 µL of distilled water were mixed for 90 minutes, to afford the 2-amino-5-(1,1,1-trifluoro)-methyl benzoxazole **2q** as a white solid (98.1 mg, 0.485 mmol, 97.1%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.36 – 7.33 (m, 2H), 6.18 (s, 2H).

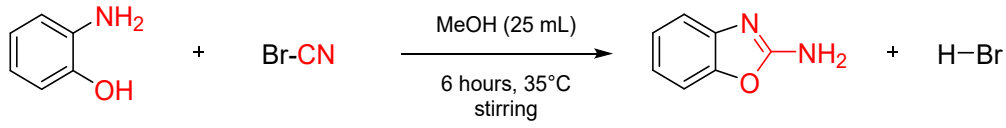
^{13}C NMR (151 MHz, $CDCl_3$) δ 163.3, 150.5, 143.0, 127.5 – 126.4 (m), 124.5 (d, J = 272.0 Hz), 121.8, 118.9 (q, J = 3.9 Hz), 113.7 (q, J = 3.9 Hz), 109.2.

^{19}F NMR (565 MHz, $CDCl_3$) δ -61.12 (s, 3F).

The spectroscopic data closely match the ones previously reported in the literature.[6]

4. Green Metrics

a) Synthesis from the literature[9]



MW: 109,128 g/mol	MW: 105,922 g/mol		MW: 134,138 g/mol	MW: 80,912 g/mol
26,500 mmol	35,900 mmol		23,320 mmol	39,080 mmol
2,892 g	3,803 g		3,128 g	3,162 g

The work-up step involved washing with a saturated sodium bicarbonate solution, so we calculated the amount used based on the solubility of $NaHCO_3$ in water (99,6 g/L).

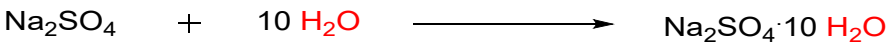
50 mL of water necessary for making the solution = ***50,0 g*** of water
Amount of $NaHCO_3$ necessary for making the solution = ***5,0 g***

This was followed by an extraction with ethyl acetate, using three 50 mL volumes of solvent for a total of 150 mL. We then converted into grams the 150 mL used:

d (EtOAc) = 0,902 g/mL g (EtOAc) = 150 mL x 0,902 g/mL = ***135,3 g***

During the extraction process, 30 mL of brine was also used to allow a better separation between the organic and aqueous phases. From this we calculated that the amount of water and sodium chloride (on the basis of the NaCl solubility in water, 360 g/L) present in such a solution which corresponds to ***30,0 g*** of water and ***10,8 g*** of sodium chloride.

After recovering the organic phase, it was dried on sodium sulphate. Knowing that ethylacetate has a water solubility of 3.3% (https://macro.lsu.edu/HowTo/solvents/ethylacetate.htm), we calculated the moles of water present in the volume of ethyl acetate used for the extraction and compared them to the minimum moles of sodium sulphate required for drying it. Finally, we converted the moles to grams to determine the amount of sodium sulphate required:



g (H_2O in the EtOAc)= 135,3 g x 0.033 = 4,465 g

mol (H_2O in the EtOAc)= 4,465 g/ 18,015 g/mol = 0,248 mol

10 mol H_2O are complexed by 1 mol Na_2SO_4

g Na_2SO_4 = 0,0248 mol x 142,04 g/mol = ***3,522 g***

Estimates of the amount of solvent used to purify the organic mixture can be derived from data reported in the literature. We chose a 50 mm diameter column and a 1:1 Hexane:EtOAc mixture as a model because it allows a $\Delta R_f \geq 0.2$. The theoretical amount of eluent required for the purification step is 1000 mL, so the relative amounts of EtOAc and Hexane are 500 mL and 500 mL, respectively. Using their densities, the amount of waste for this procedure is equal to:

g of EtOAc= 500 mL x 0,902 g/mL = 451,0 g

g of Hexane= 500 mL x 0.655 g/mL = 330,5 g

g of eluent used= g of EtOAc + g of Hex = ***781,5 g***

Green Metrics calculation

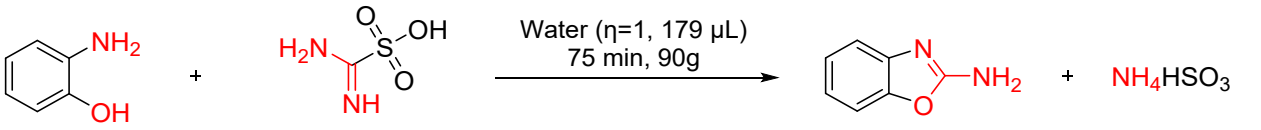
Chemical **Y**ield = (Moles of desired useful product)/ (Moles limiting reagent) = **88,0%**

Atom **E**conomy = [(Mass of desired useful product)/ (Total mass of all reactants)] x100 = [134,1/(109,1+105,9)] x 100= **62,4%**

Environmental **f**actor = (Total mass of waste)/(Mass of desired product) = ((50,0+5,0+135,3+30,0+10,8+3,5+781,5+2,9+3,8+3,2+19,8)-3,1)/3,1 = **336,4**

Reaction **M**ass **E**fficiency = [(Mass of desired product)/ (Total mass of all reactants)] = [3,1/(2,9+3,8)] x 100 = **46,3%**

b) Our work



MW: 109,128 g/mol	MW: 124,114 g/mol		MW: 134,138 g/mol	MW: 99,104 g/mol
0,500 mmol	1,000 mmol		0,456 mmol	0,144 mmol
0,055 g	0,124 g		0,061 g	0.014 g

After the reaction, the product was recovered with 3 mL of ethyl acetate (3 x 0.902 g/ml =***2,706 g***).

Chemical **Y**ield = (Moles of desired useful product)/ (Moles limiting reagent) = 0,456/0,500 = **91,2%**

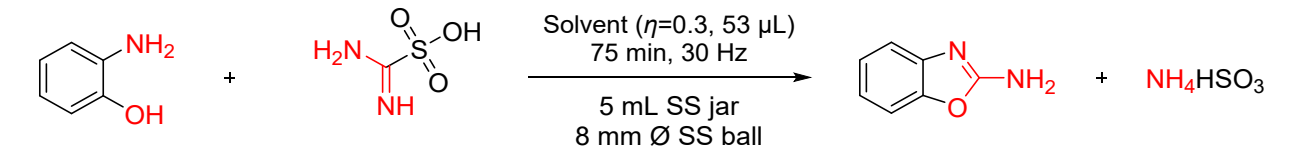
Atom **E**conomy = [(Mass of desired useful product)/ (Total mass of all reactants)] x100 = [134,1/(109,1+124,1)] x 100= **57,5%**

Environmental **F**actor = (Total mass of waste)/(Mass of desired product) = ((0,055+0,124+0,014+0,179+2,706)-0,061)/0,061 = **49,5**

Reaction **M**ass **E**fficiency = [(Mass of desired product)/ (Total mass of waste)] = [0,061/(0,055+0,124)] x 100 = **34,1%**

5. Comparison between Resonant Acoustic Mixing (RAM) and Ball Milling (BM)

The reactivity of TTO was assessed by conducting the synthesis of the 2-amino benzoxazole **2a** using a 5 mL stainless steel jar equipped with an 8 mm (2,0942 g) stainless steel ball. The scale of the reaction and its stoichiometry were maintained equal to the ones reported for the RAM procedure. The mechanochemical trails were run by employing a LAG (η= 0.3) of 4 different solvents (distilled water, methanol, ethanol, and isopropanol).



MW: 109,128 g/mol
0,500 mmol
0,055 g

MW: 124,114 g/mol
1,000 mmol
0,124 g

MW: 134,138 g/mol

MW: 99,104 g/mol

After the reaction, the product was recovered with 3 mL of ethyl acetate (3 x 0.902 g/ml =***2,706 g***)

Chemical **Y**ield = (Moles of desired useful product)/ (Moles limiting reagent)

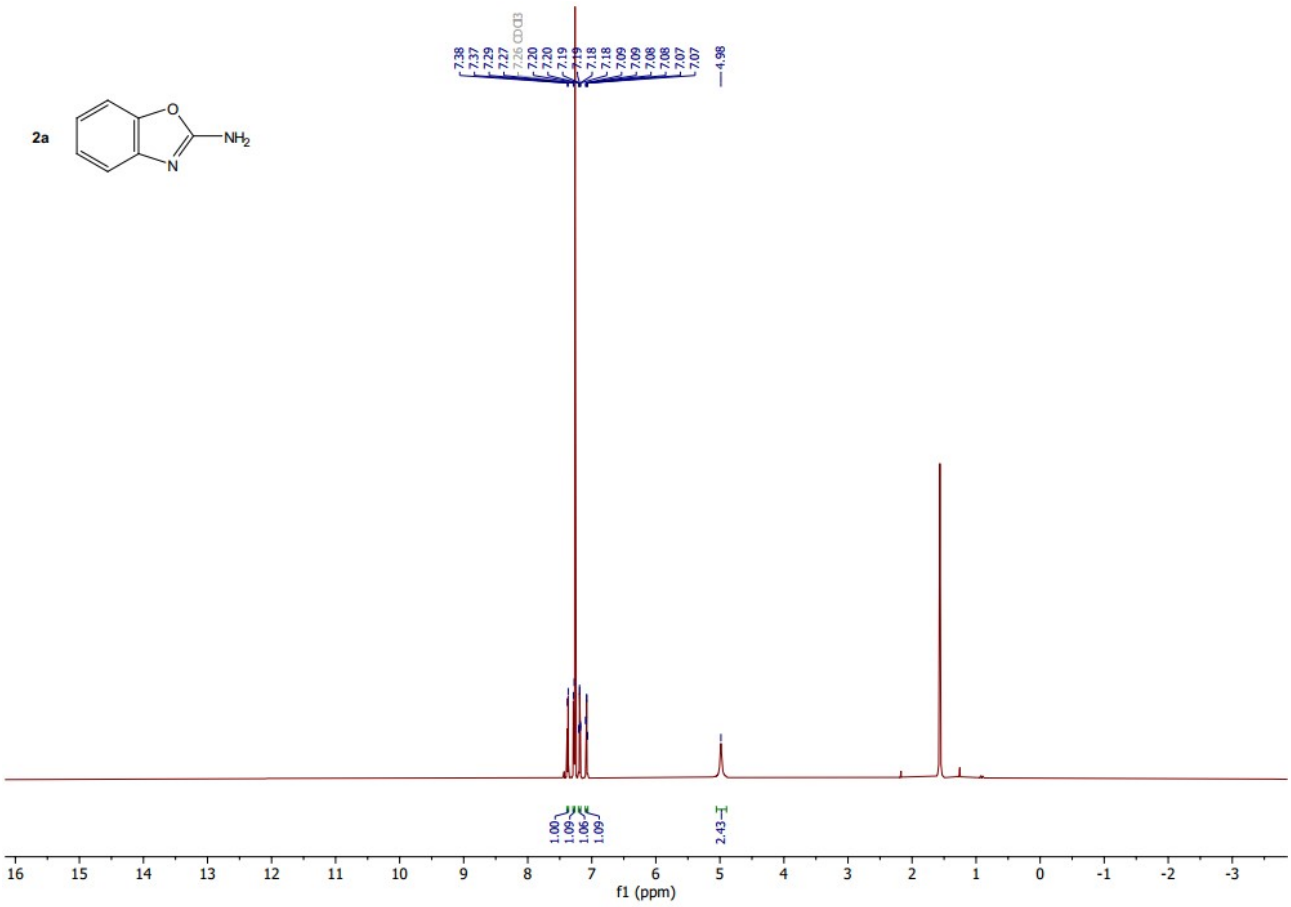
Environmental **F**actor = (Total mass of waste)/(Mass of desired product)

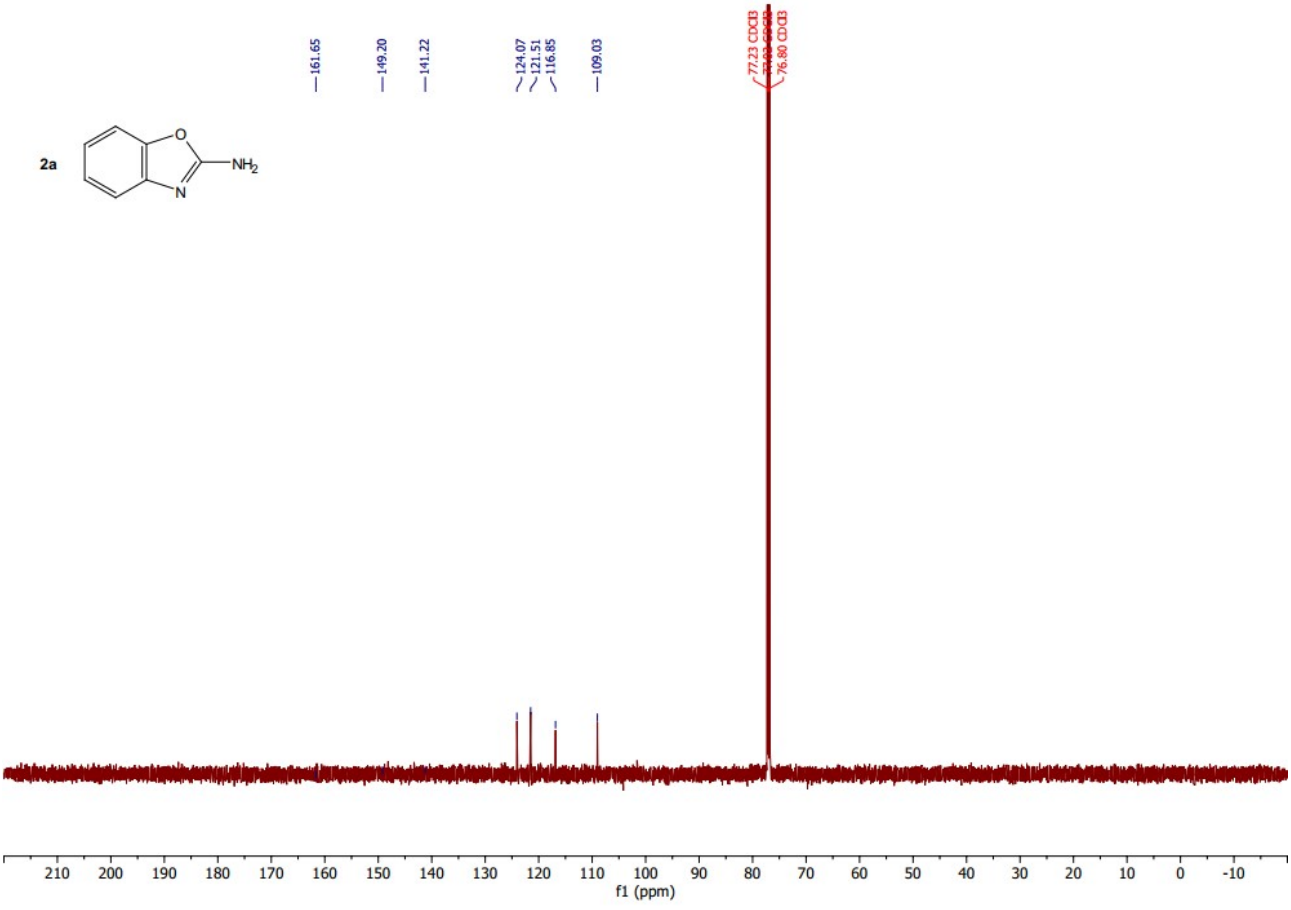
Reaction **M**ass **E**fficiency = [(Mass of desired product)/ (Total mass of waste)]

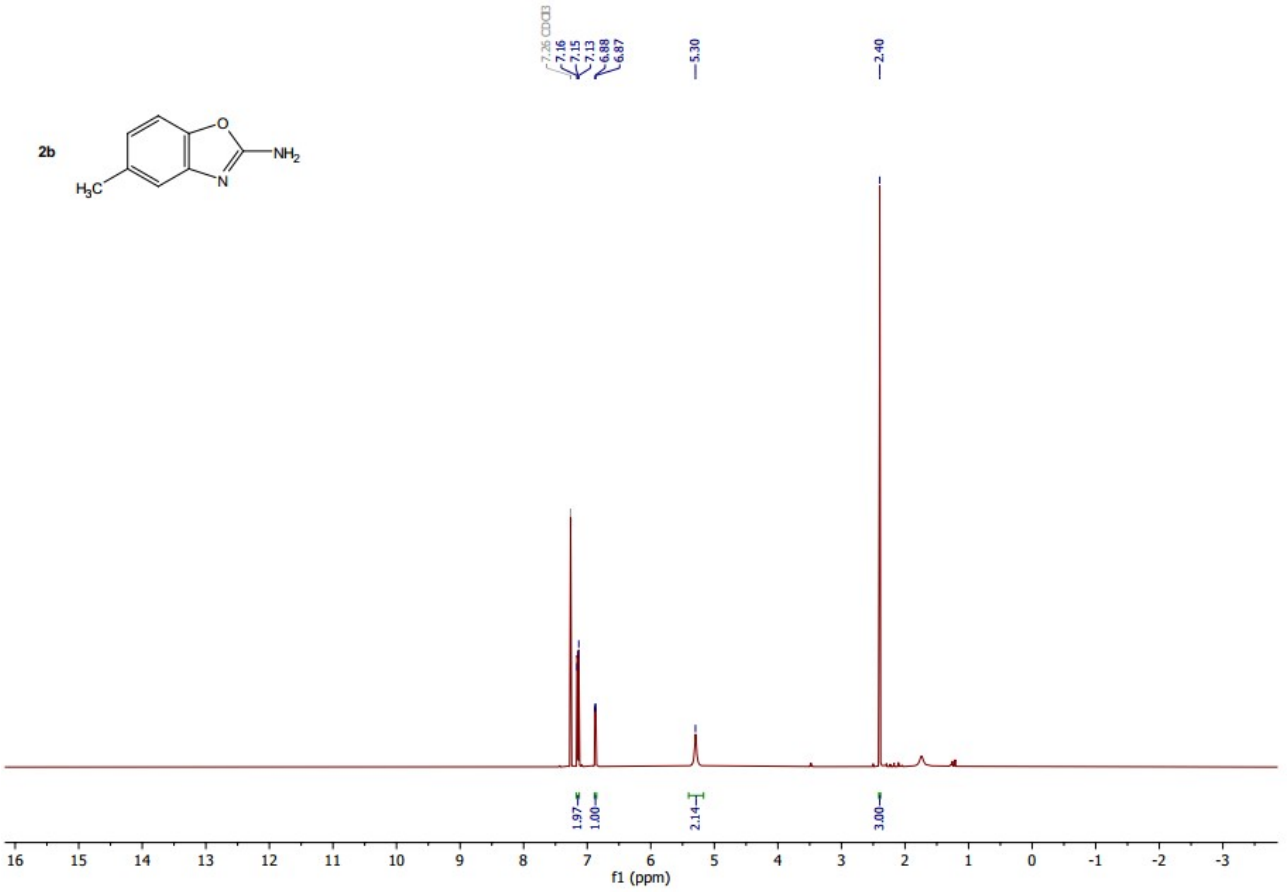
	H_2O BM	MeOH BM	EtOH BM	IprOH BM	H_2O RAM
CY	2,6%	12,0%	10,1%	5,6%	91,2%
EF	1666,8	408,6	431,5	772,9	49,5
RMS	1,0%	4,5%	3,8%	2,1%	34,1

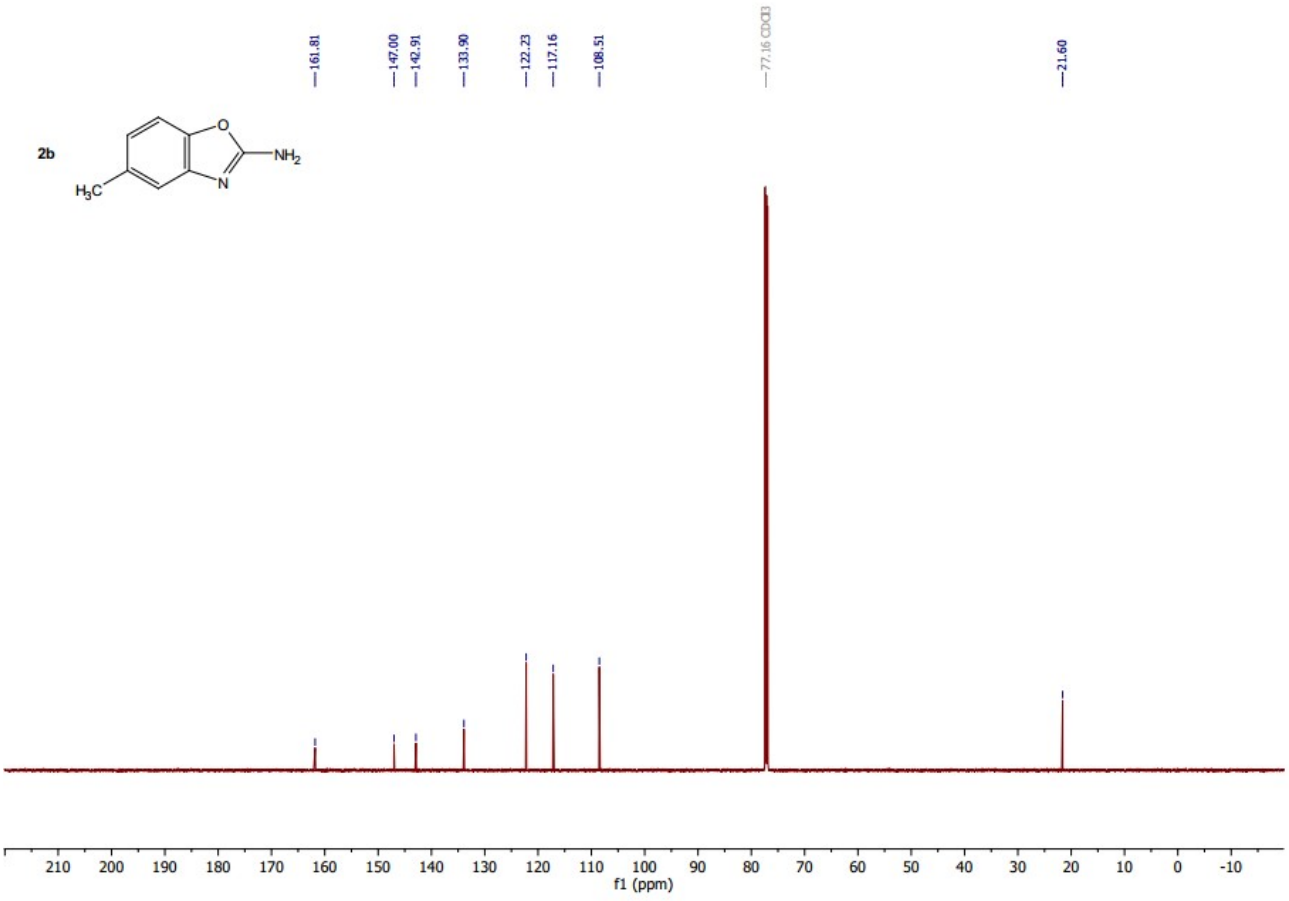
Table 2. Green metrics calculated for the mechanochemical approach compared with the one reported for the RAM methodology.

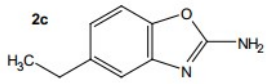
6. Spectra


2a
NH2
7.38
7.37
7.29
7.27
7.26 CDCl3
7.20
7.20
7.19
7.19
7.18
7.18
7.09
7.09
7.08
7.08
7.07
7.07
4.98
1.00
1.09
1.06
1.09
2.43
f1 (ppm)

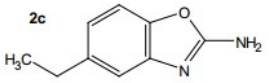

2a
NH2
161.65
149.20
141.22
124.07
121.51
116.85
109.03
77.23 CDCl3
76.80 CDCl3
f1 (ppm)


2b
7.26 CDCl3
7.16
7.15
7.13
6.88
6.87
5.30
2.40
1.97
1.00
2.14
3.00
f1 (ppm)

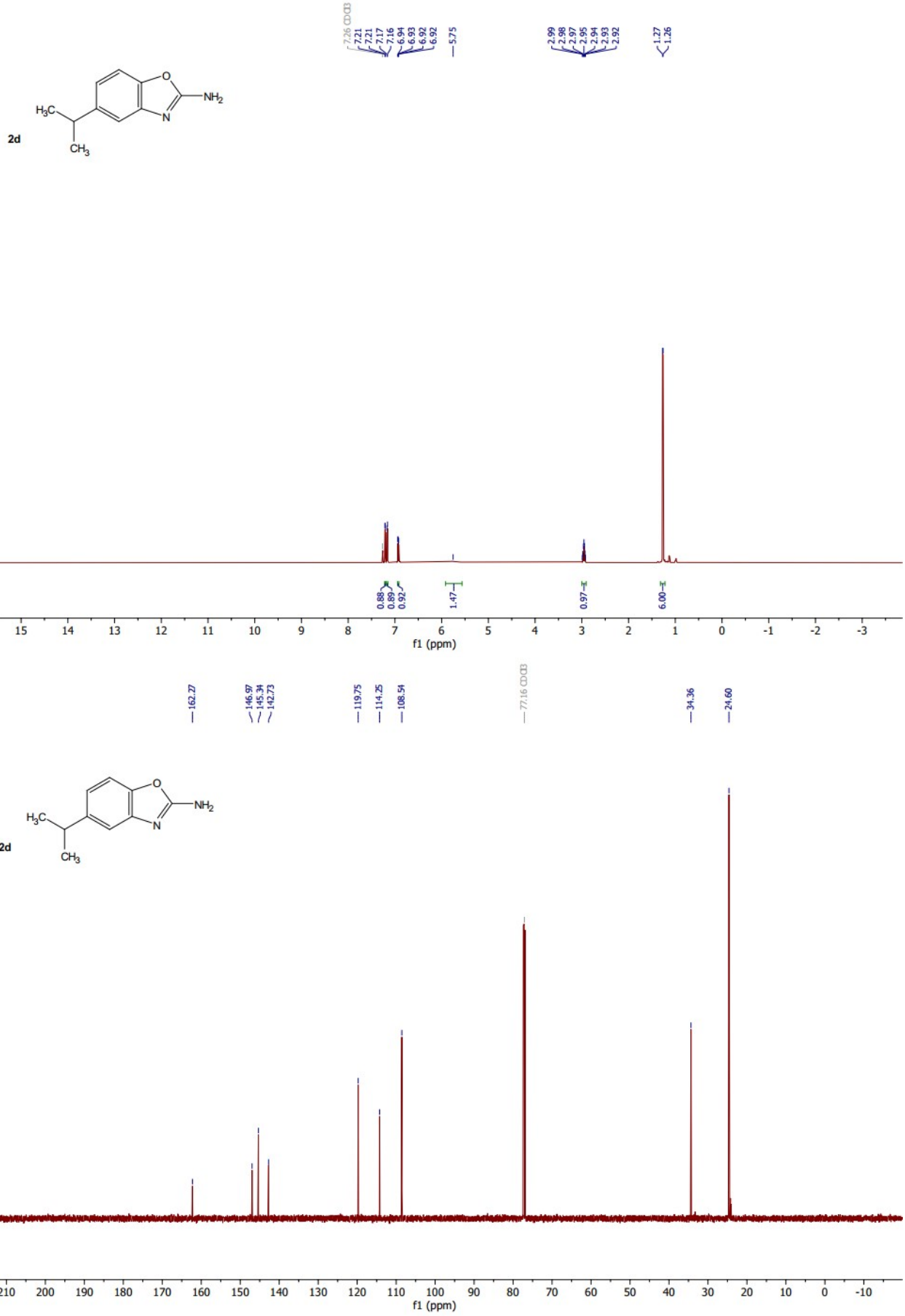

2b
161.81
147.00
142.91
133.90
122.23
117.16
108.51
77.16 CDCl3
21.60
f1 (ppm)

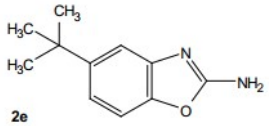

2c
O
NH2
H3C
N

7.26 CDCl3
7.18
7.17
7.15
6.90
6.89
5.72
2.71
2.70
2.68
2.67
1.26
1.25
1.24
1.82
1.05
1.78
1.94
3.00
f1 (ppm)


2c
O
NH2
H3C
N

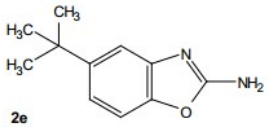
162.20
146.99
142.81
140.57
121.08
115.78
108.57
77.16 CDCl3
29.09
16.37
f1 (ppm)


7.26 CDCl3
7.21
7.21
7.17
7.16
6.94
6.93
6.92
6.92
5.75
2.99
2.98
2.97
2.95
2.94
2.93
2.92
1.27
1.26
O
NH2
H3C
N
CH3
2d
0.88
0.89
0.92
1.47
0.97
6.00
f1 (ppm)
162.27
146.97
145.34
142.73
119.75
114.25
108.54
77.16 CDCl3
34.36
24.60
f1 (ppm)


CH3
H3C
H3C
N
NH2
O

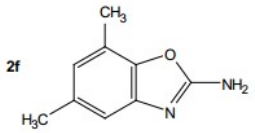
2e

7.39
7.39
7.26 CDCl3
7.19
7.17
7.12
7.12
7.11
7.11
5.39
1.35
1.14
1.00
1.03
1.95
9.00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)

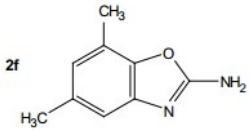

CH3
H3C
H3C
N
NH2
O

2e

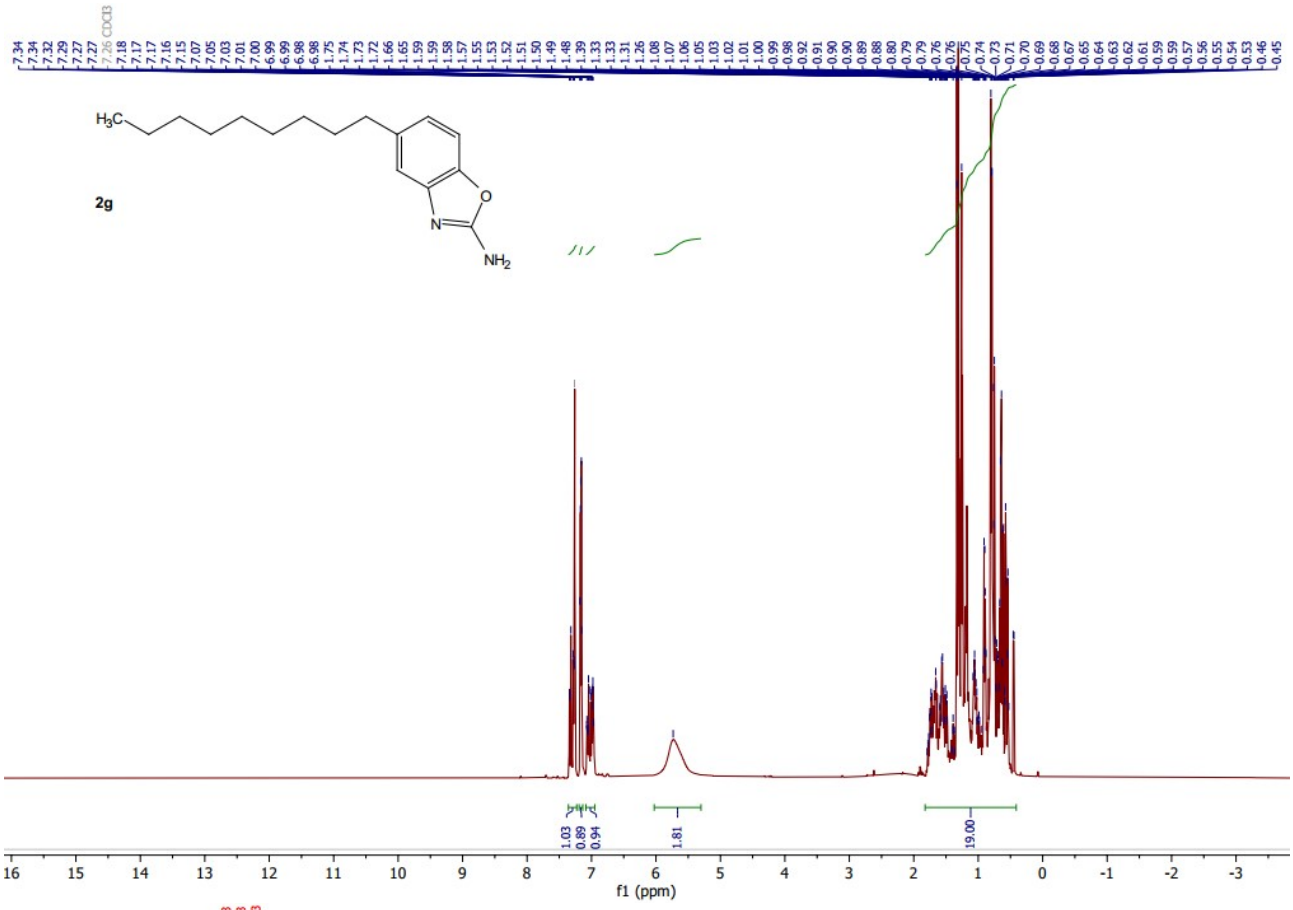
161.96
147.68
146.73
142.53
118.75
113.75
108.22
77.16 CDCl3
34.95
31.95
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

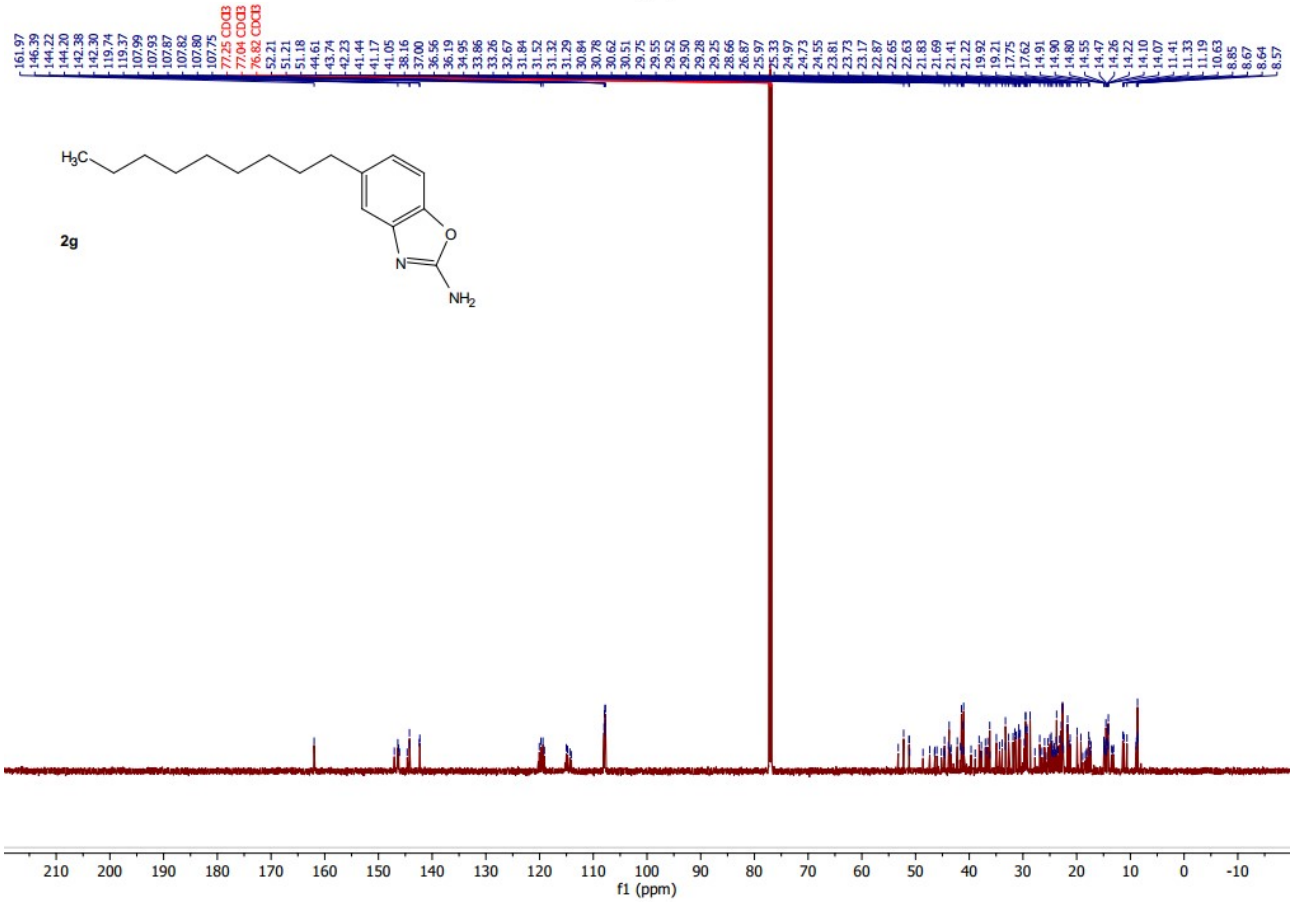

2f
CH3
O
NH2
N
H3C

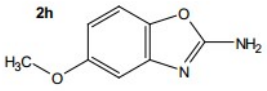
7.26 CDCl3
6.99
6.70
4.93
2.37
2.36
1.08
1.15
2.23
6.00
f1 (ppm)


2f
CH3
O
NH2
N
H3C

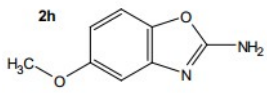
161.20
145.97
142.29
133.61
123.83
118.77
114.54
21.40
14.84
f1 (ppm)


H3C
O
N
NH2
2g
1.03
0.89
0.94
1.81
19.00
f1 (ppm)

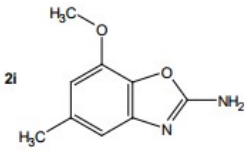

H3C
O
N
NH2
2g
f1 (ppm)


2h
O
NH2
H3C
O
N

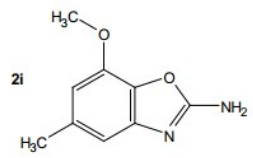
7.26 CDCl3
7.15
7.14
6.92
6.92
6.65
6.64
6.63
6.63
5.03
3.82
1.11
1.15
1.23
2.02
3.00
f1 (ppm)


2h
O
NH2
H3C
O
N

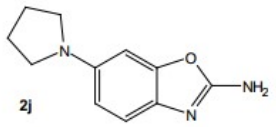
157.26
143.77
143.42
109.06
108.93
108.31
101.96
77.16 CDCl3
56.10
f1 (ppm)


2i
H3C
O
O
NH2
N
H3C

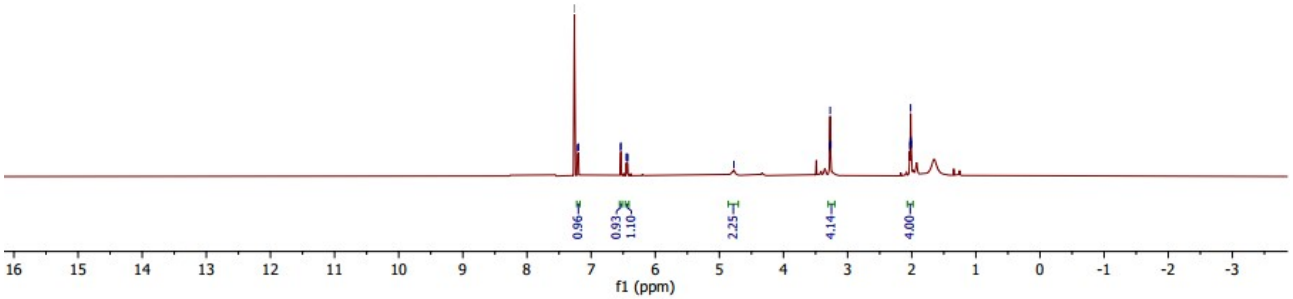
7.26 CDCl3
6.80
6.48
5.23
3.95
2.38
0.92
1.00
1.90
2.99
2.99
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)

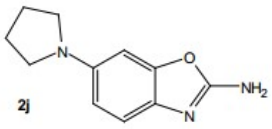

2i
H3C
O
O
NH2
N
H3C

176.84
146.58
143.16
134.76
129.89
110.12
106.78
77.16
56.39
22.01
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

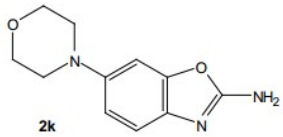

2j


7.26 CDCl3
7.21
7.20
6.54
6.45
6.44
6.43
6.43
4.77
3.28
3.27
3.26
2.03
2.02
2.02
2.01
2.01


0.96
0.93
1.10
2.25
4.14
4.00
f1 (ppm)

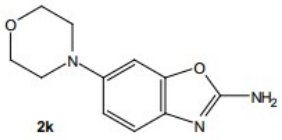

2j

159.49
150.40
144.94
132.36
116.90
108.40
93.27
48.51
25.58
f1 (ppm)


O
N
O
NH2
N

2k

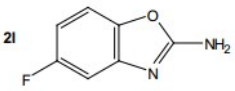
7.26 CDCl3
7.25
6.91
6.83
6.82
5.02
3.89
3.88
3.87
3.11
0.92
1.00
0.93
2.19
3.95
3.97
f1 (ppm)


O
N
O
NH2
N

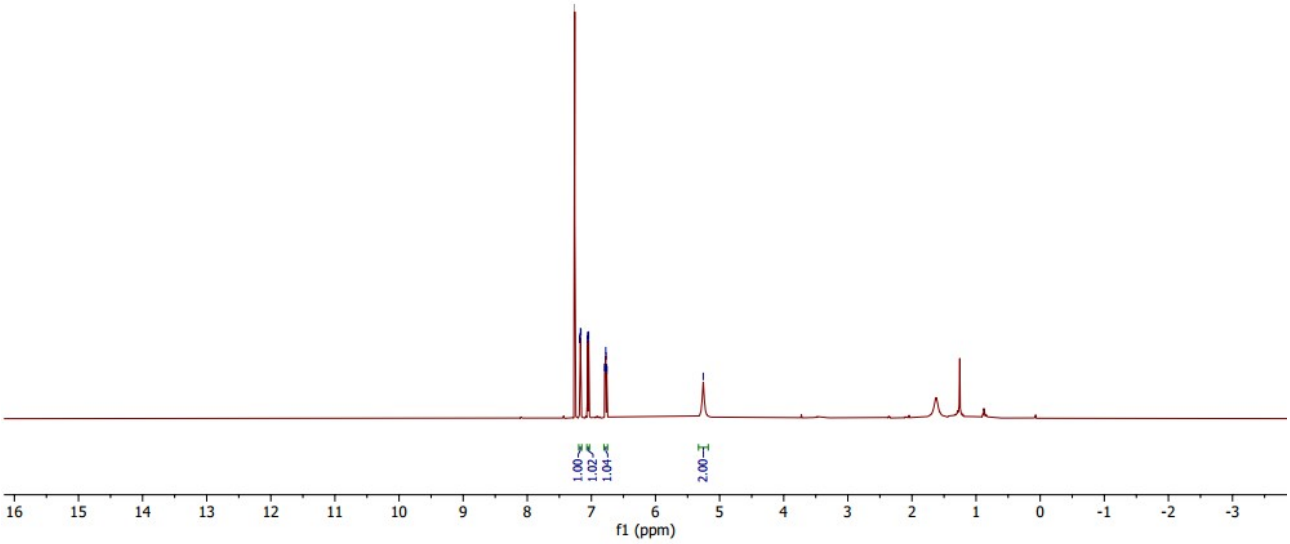
2k

164.35
151.91
147.75
136.29
116.72
113.66
98.58
67.14
51.23
f1 (ppm)

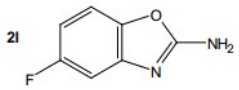
2l


O
NH2
F
N


7.26 CDCl3
7.18
7.18
7.17
7.16
7.06
7.06
7.05
7.04
6.79
6.79
6.78
6.77
6.76
6.76
5.26


1.00
1.02
1.04
2.00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)

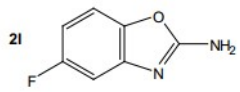
2l


O
NH2
F
N


162.85
161.06
159.48
145.08
143.93
143.84
109.13
109.06
108.31
108.14
104.13
103.96

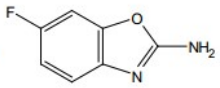
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

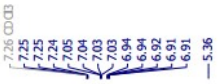
2l

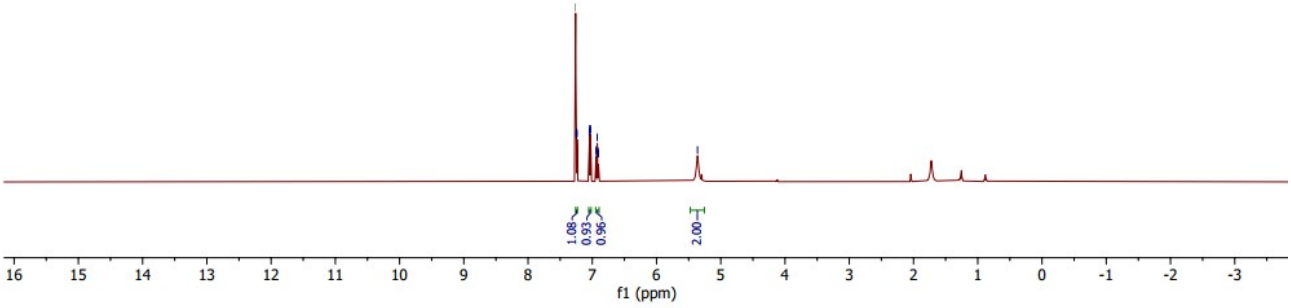

O
NH2
N
F

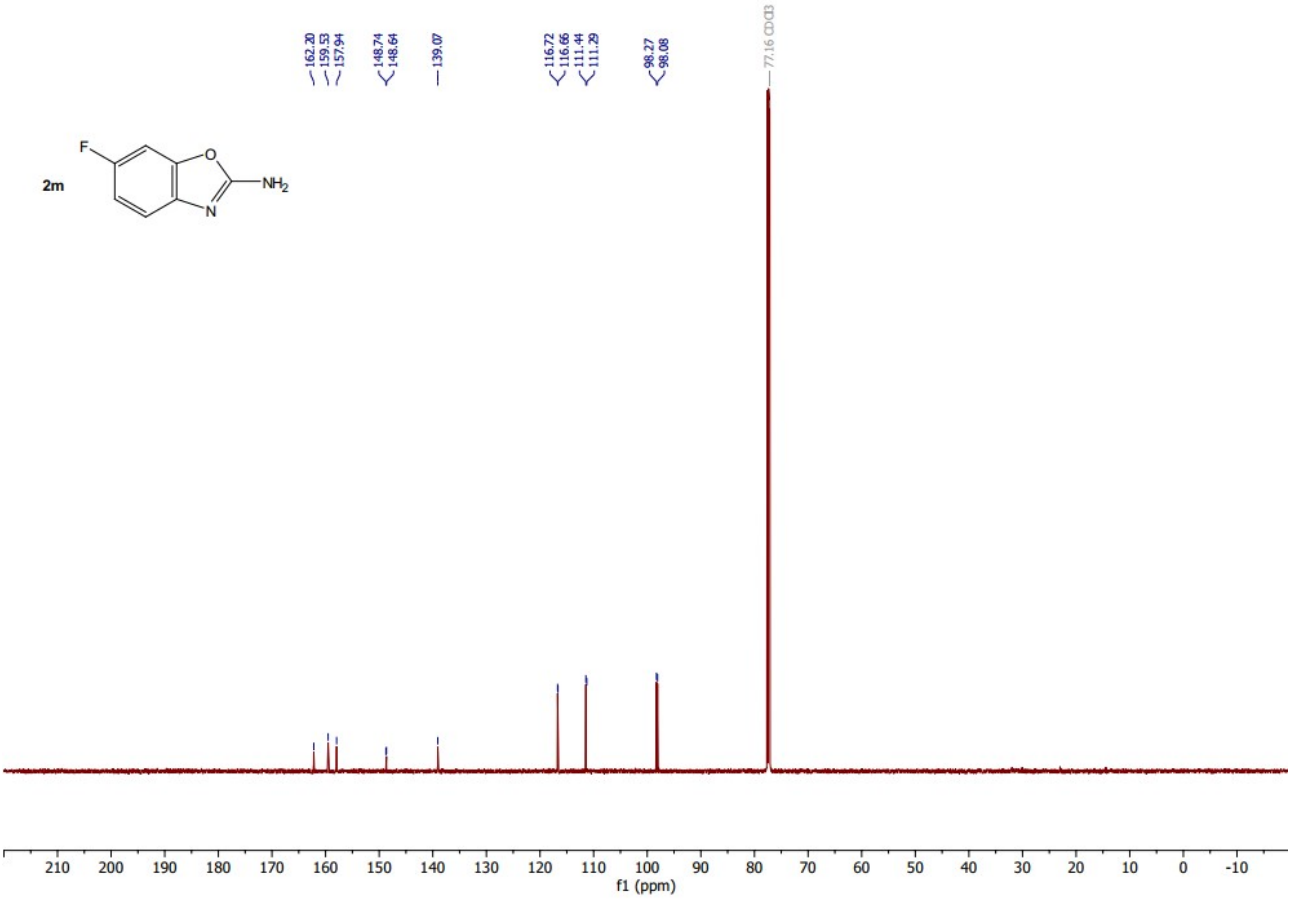
-118.90
-112.5
-113.5
-114.5
-115.5
-116.5
-117.5
-118.5
-119.5
-120.5
-121.5
-122.5
-123.5
-124.5
-125.5
f1 (ppm)

2m


F
O
NH2
N


7.26 CDCl3
7.25
7.25
7.24
7.05
7.04
7.03
7.03
6.94
6.94
6.92
6.91
6.91
5.36

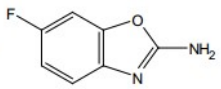

1.08
0.93
0.96
2.00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


162.20
159.53
157.94
148.74
148.64
139.07
116.72
116.66
111.44
111.29
98.27
98.08
77.16 CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

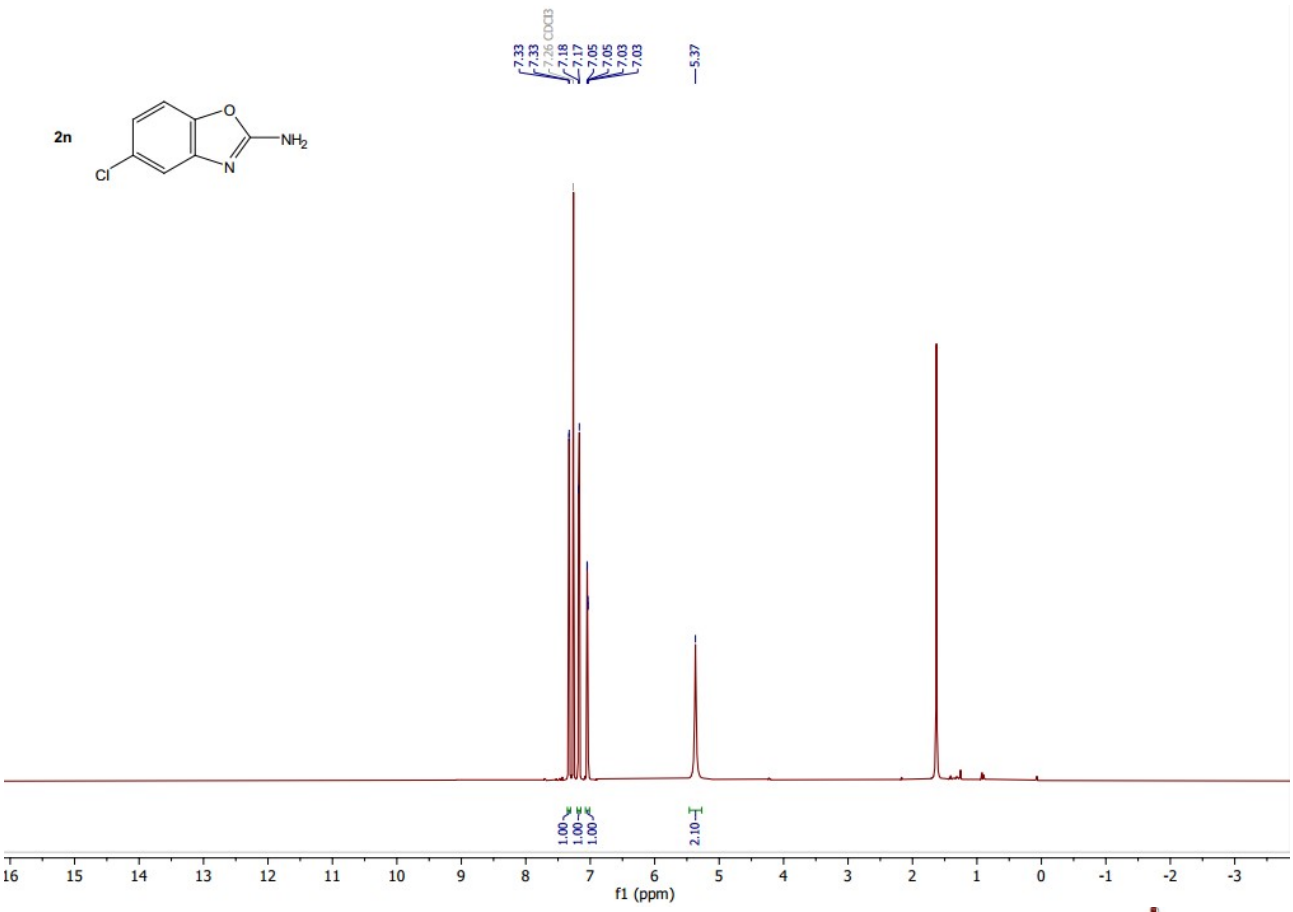
2m

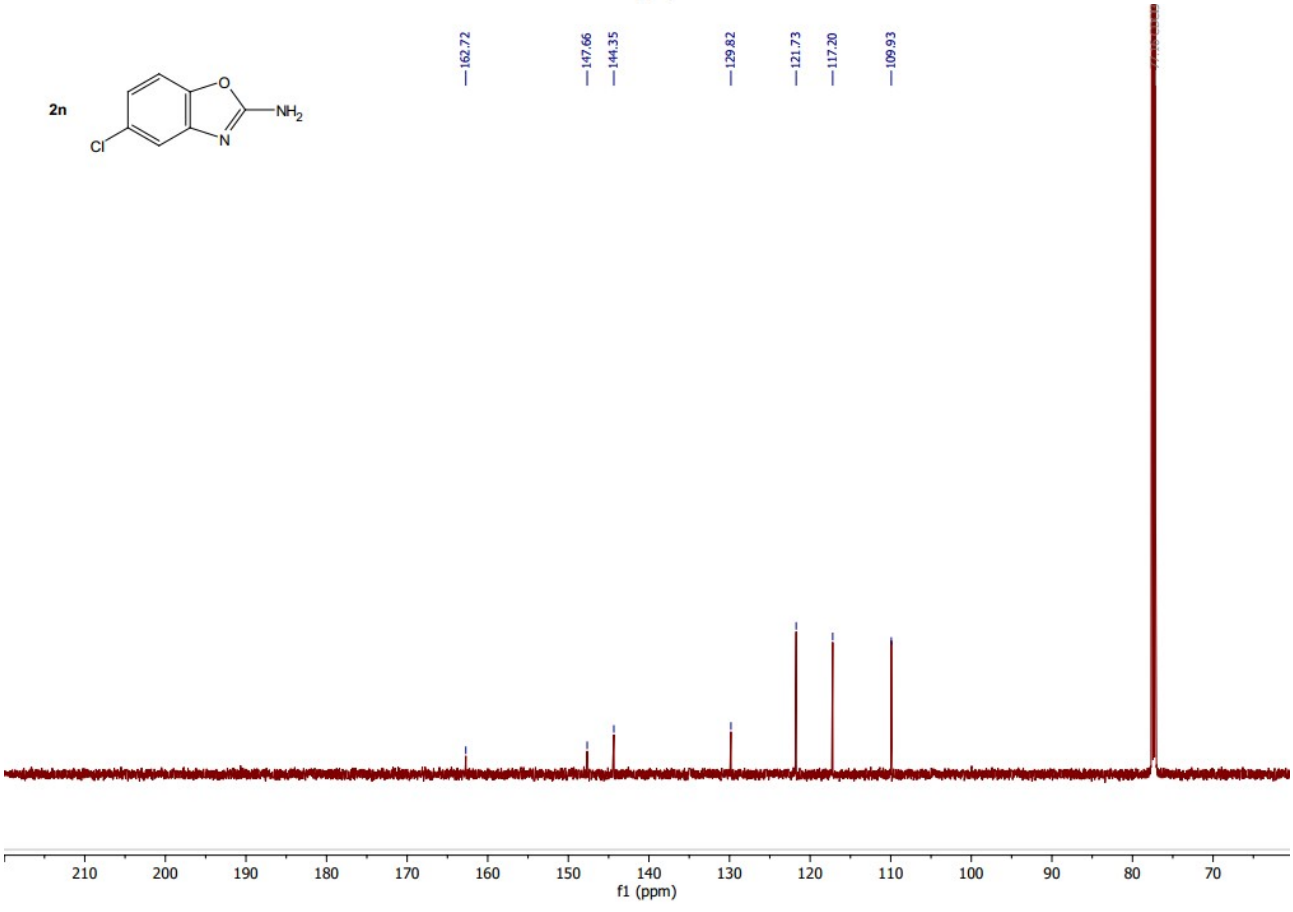
F
O
NH2
N

2m

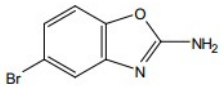

F
O
NH2
N

-120.47
-118.7
-118.9
-119.1
-119.3
-119.5
-119.7
-119.9
-120.1
-120.3
-120.5
-120.7
-120.9
-121.1
-121.3
-121.5
-121.7
f1 (ppm)


2n
O
NH2
N
Cl
7.33
7.33
7.26 CDCl3
7.18
7.17
7.05
7.05
7.03
7.03
5.37
1.00
1.00
1.00
2.10
f1 (ppm)

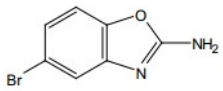

2n
O
NH2
N
Cl
162.72
147.66
144.35
129.82
121.73
117.20
109.93
f1 (ppm)

2o

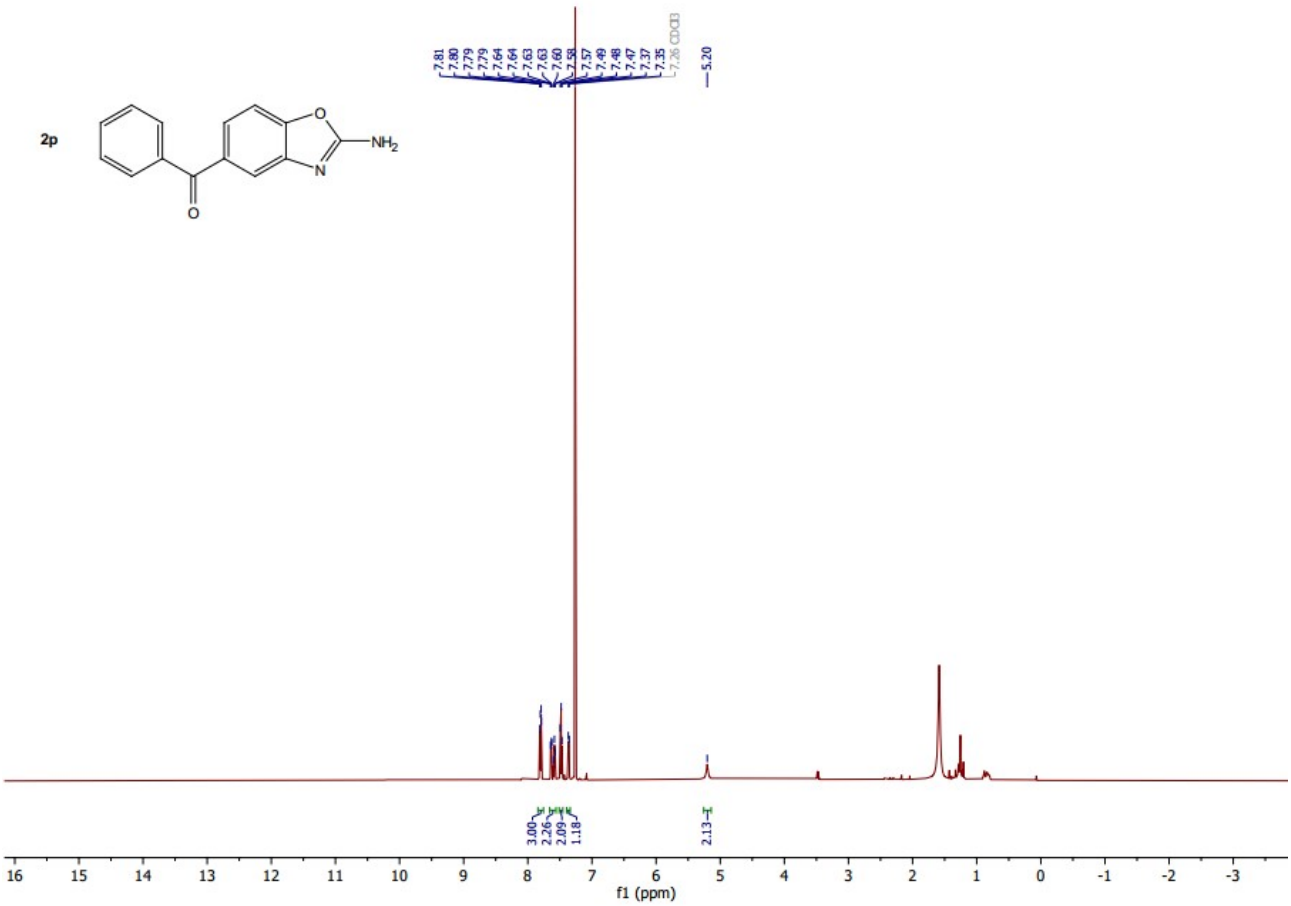

O
NH2
N
Br

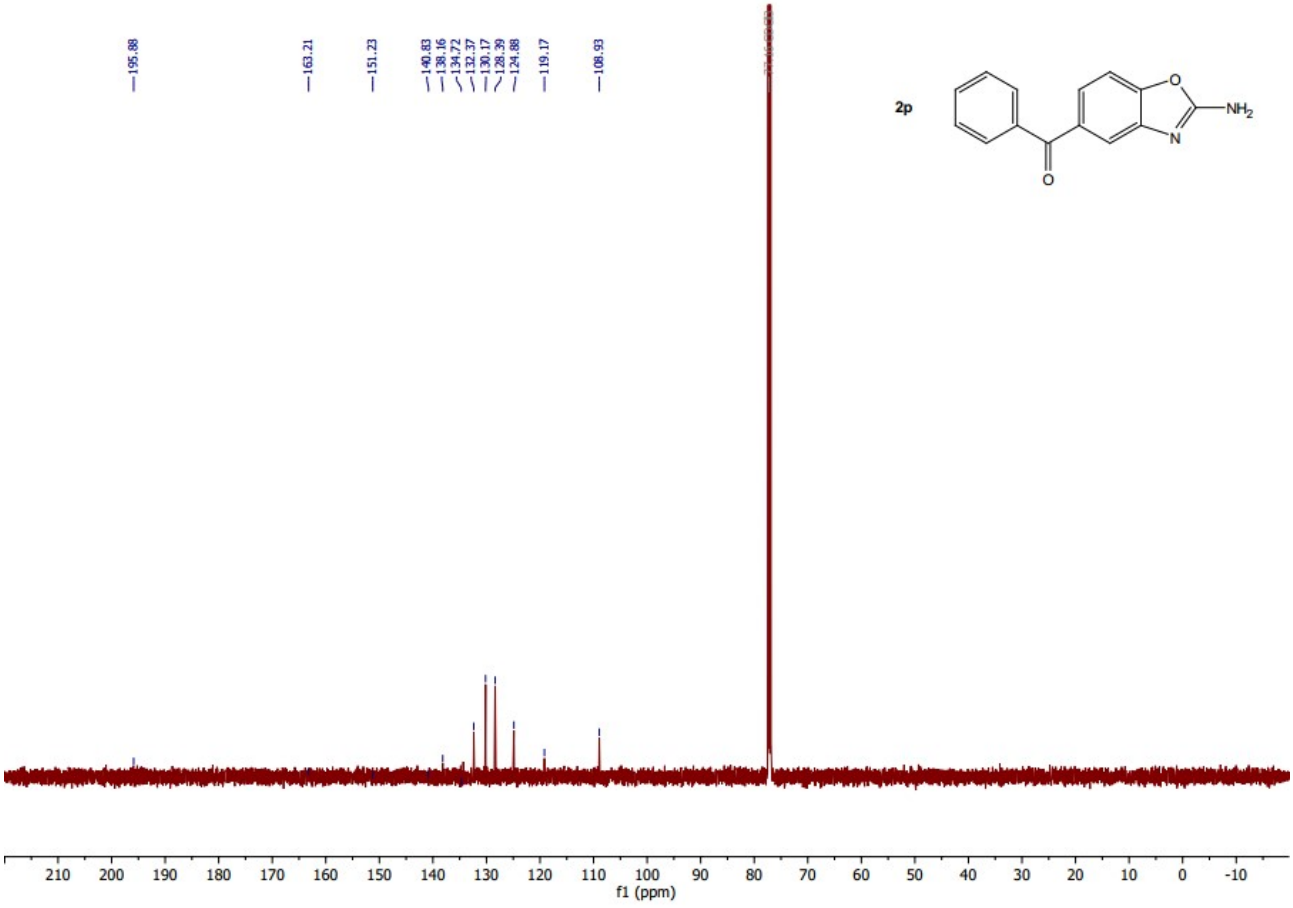
7.49
7.49
7.26 CDCl3
7.20
7.20
7.19
7.18
7.15
7.13
5.22
1.00
1.02
1.01
2.03
f1 (ppm)

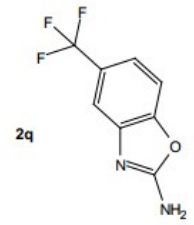
2o


O
NH2
N
Br

162.22
147.92
144.57
124.38
119.96
116.94
110.29
77.16 CDCl3
f1 (ppm)

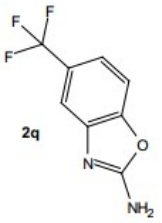

2p
O
NH2
N
O
7.81
7.80
7.79
7.79
7.64
7.64
7.63
7.63
7.60
7.58
7.57
7.49
7.48
7.47
7.37
7.35
7.26 CDCl3
5.20
3.00
2.26
2.09
1.18
2.13
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


195.88
163.21
151.23
140.83
138.16
134.72
132.37
130.17
128.39
124.88
119.17
100.93
2p
O
NH2
N
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


F
F
F
O
N
NH2

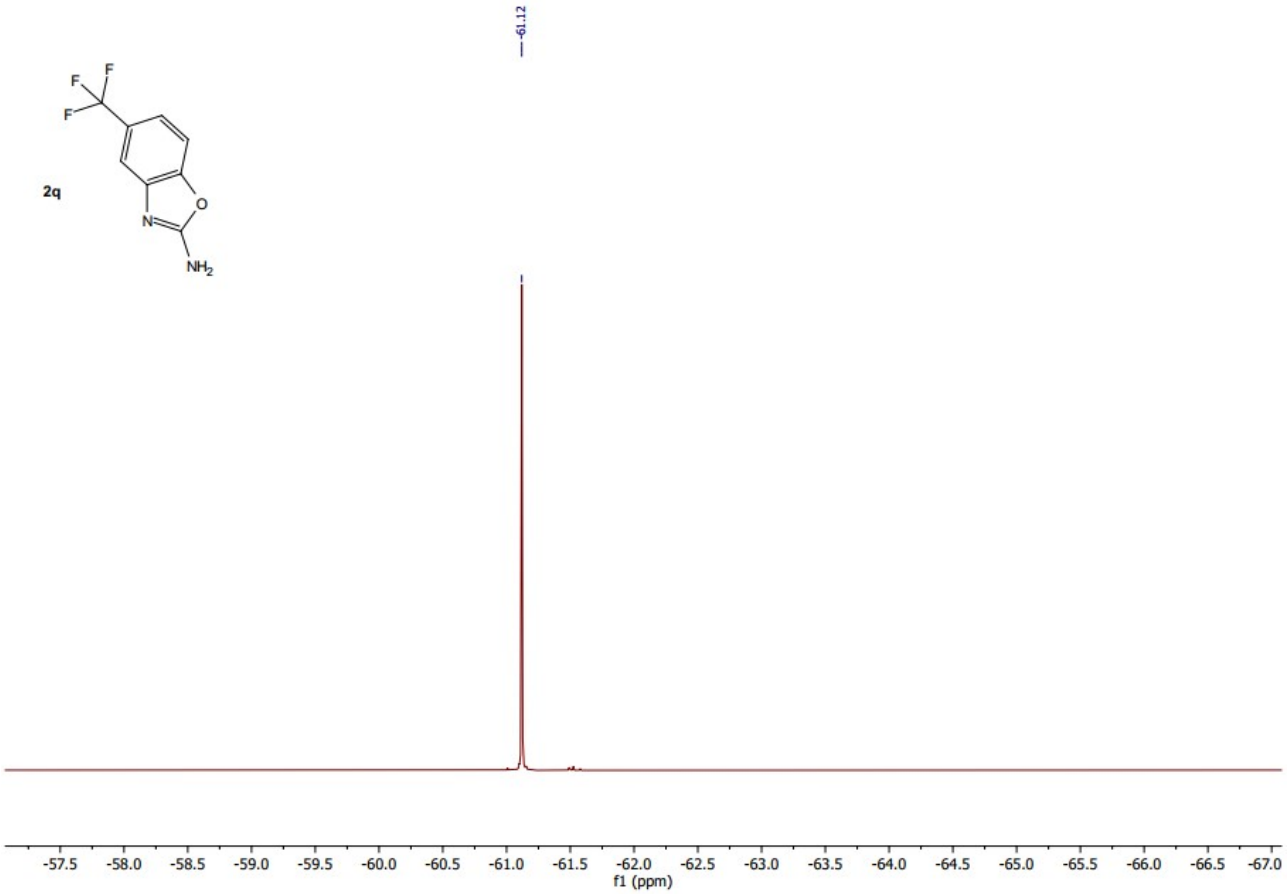
2q

7.57
7.36
7.35
7.34
7.33
7.26 CDCl3
6.18
1.03
2.01
2.00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


F
F
F
O
N
NH2

2q

163.31
150.51
143.05
127.28
127.24
127.06
126.85
126.63
125.44
123.63
121.83
118.92
118.89
118.86
118.84
113.72
113.69
113.66
113.64
109.22
77.16 CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


-61.12
F
F
F
2q
O
N
NH2
-57.5
-58.0
-58.5
-59.0
-59.5
-60.0
-60.5
-61.0
-61.5
-62.0
-62.5
-63.0
-63.5
-64.0
-64.5
-65.0
-65.5
-66.0
-66.5
-67.0
f1 (ppm)

7. References

1. C. L. Cioffi; J. J. Lansing; H. Yüksel *J. Org. Chem.* **2010**, *75*, 7942-7945.
2. J. Y. Kim; S. H. Cho; J. Joseph; S. Chang *Angew. Chem. Int. Ed.* **2010**, *49*, 9899-9903.
3. O. Grytsai; T. Druzhenko; L. Demange; C. Ronco; R. Benhida *Tetrahedron Lett.* **2018**, *59*, 1642-1645.
4. E. (https://scifinder-n.cas.org/searchDetail/substance/66d184887ae4e75126a1144d/substanceDetails).
5. Y. An; E. Lee; Y. Yu; J. Yun; M. Y. Lee; J. S. Kang; W.-Y. Kim; R. Jeon *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3067-3072.
6. T. Morofuji; A. Shimizu; J.-i. Yoshida *Chem. – Eur. J.* **2015**, *21*, 3211-3214.
7. Enamine, https://scifinder-n.cas.org/searchDetail/substance/66d184887ae4e75126a1144d/substanceDetails, (accessed 20/10/2024).
8. V. Šlachtová; J. Chasák; L. Brulíková *ACS Omega* **2019**, *4*, 19314-19323.
9. L. Fan; Z. Luo; C. Yang; B. Guo; J. Miao; Y. Chen; L. Tang; Y. Li *Mol. Div.* **2022**, *26*, 981-992.