# A Facile Route to Triazolopyrimidines Using a [3+2] Cycloaddition and Continuous-Flow Chemistry

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A facile and benign route to *N*-heterocycles, including triazoles and triazolopyrimidines, has been developed. Using continuous-flow microreactor technology, organic azides are prepared in situ and reacted with cyanoacetamide in a [3+2] cycloaddition to produce a variety of substituted 1,2,3-triazoles, which can be elaborated into useful building blocks. A benzyl-substituted triazole was further functionalized to an analog of the core structure of the antiplatelet agent Brilinta®. The methodology lends itself well to flow chemistry, where reaction volumes are minimized, heating and mixing are consistent, and the need for intermediate azide isolation bypassed. The scope of the process is wide, and the efficiency is high, suggesting this as a practical, green route for the production of triazolo-based heterocycles.

**Keywords:** [3+2] cycloaddition, azide, continuous flow, triazole, triazolopyrimidine, one-pot reaction

## 1. Introduction

Triazoles and their fused heterocyclic derivatives have become important pharmacophores in medicinal chemistry, with several drugs currently in the marketplace and many more in the pipeline [1]. Of interest to this work is Brilinta® (ticagrelor), developed by AstraZeneca and approved by the Food and Drug Administration (FDA) in 2011 as a novel antiplatelet agent [2]. Triazole chemistry has gained resurgent popularity from the work of Sharpless [3], the copper-catalyzed Huisgen-type cyclization of azides with alkynes affording efficient access to substituted 1,2,3-triazole derivatives [4]. Coined, and popularized, as "click chemistry," this reaction has many useful applications in synthetic [5], polymer [6], and biological [7] chemistries. A similar core can be accessed via [3+2] cycloaddition of functionalized azides with cyano-containing amides, such as cyanoacetamide, as shown in Scheme 1.

Given elevated concerns regarding the use of organic azides in macroscale synthesis [8], a number of adaptations have been examined to mitigate risk, including the use of continuous-flow methods [9]. Continuous-flow chemistry is a rapidly developing field with a variety of distinct advantages [10]. The superior mixing capabilities are derived from a high surface-to-volume ratio, which allows for reactions to take place more efficiently, and employing temperatures above the boiling point of the solvent. Reactant heating is highly consistent, often allowing for superb temperature control and reaction reproducibility. Such methodology has obvious potential for the reduction of waste and decrease in the direct handling of potentially hazardous materials. The nature of flow chemistry also allows for reaction conditions to be firstly optimized in a microscale environment and then directly scaled to the macroscale level, of particular importance when considering active pharmaceutical ingredient (API) production [11].

Though continuous-flow chemistry has been shown to be a highly effective method for azide synthesis, an obvious limitation lies in the need to prepare and handle bulk quantities of the organic azide, posing additional hazards in the case of low molecular weight variants [12]. To address this issue, we elected to investigate the in situ production of organic azides in a flow reactor, and then directly utilize this in-line for the production of triazoles, as shown in Figure 1.

## 2. Results and Discussion

**2.1. Proof of Principle with Benzyl Bromide and Benzyl Azide.** Using a Labtrix® S1 flow system (Chemtrix BV, NL) equipped with a T-mixer microreactor, the conversion of benzyl bromide **1** to benzyl azide **2** was verified under flow conditions. Under optimal conditions (Figure 2), essentially quantitative yields could be obtained within a few minutes at reaction temperatures <100 °C (data not shown).

With this in hand, attention was then focused on the subsequent cycloaddition to form the 1,2,3-triazole **3** under flow conditions using benzyl azide **2** as model substrate (Scheme 2). Quantitative conversion was achieved following optimization of the flow conditions (Figure 3a and b), which evaluated the effect of reaction time (0.75–8.33 min) and temperature (25–100 °C) ($n$=3). Following successful optimization, a two-step continuous-flow route, directly from the bromide **1** to the triazole **3**, was investigated and accomplished with ease (Figure 4a and b).

The stoichiometry of cyanoacetamide and sodium hydroxide was also probed with respect to triazole formation (Table 1). Notably, under flow conditions, azide is converted to triazole in good yield with only 1 eq. of cyanoacetamide and NaOH, while batch process required 2 eq. to afford similar yields. In order to confirm utility of pyrimidine derivatives of the product, subsequent conversion to the corresponding triazolopyrimidine **4** was investigated and conditions were optimized, where $T$=80 °C and flow rate=20 μL/min (Scheme 2).

**Table 1.** Effect of stoichiometry for two-step, one-pot triazole synthesis

| Equivalents of cyanoacetamide–NaOH | Percent conversion to triazole |
|---|---|
| 1 | 70.7 |
| 2 | 79.1 |
| 3 | 91.1 |

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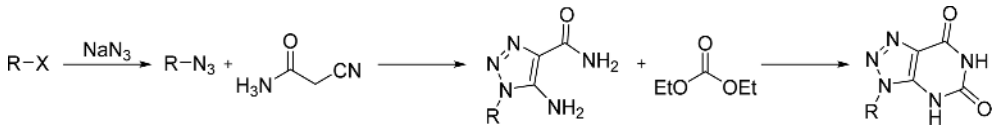
**Scheme 1.** 1,2,3-Triazoles and triazolopyrimidines via [3+2] cycloaddition chemistry




***2.1.1.*** *Synthesis of a Triazole Library under Continuous-Flow Process*. With an effective route secured, reaction scope was explored by forming a library of triazoles (Table 2). Products 6, 8, 17, and 22 were successfully synthesized in a two-step, one-pot flow reaction in good to excellent yields. The azides were produced in situ with a residence time of 2.5 min, and subsequently, the triazole was prepared with a residence time of 1.9 min for a total reaction time of 4.4 min. The remaining products were generated effectively in a two-step sequential flow reaction, where the azide was first prepared (6 min), and then crude azide solution was reinjected into the chip, along with cyanoacetamide and sodium hydroxide, to produce the triazole in 4.2 min, for a total reaction time of 10.2 min. Figure 1 details the flow reactor assembly for the production of the library.

When reactions were carried out sequentially, chlorinated substrates **7** and **18** produced insoluble salts during azide formation, likely due to the decrease in water present in that reaction system. However, when reacted in a one-pot fashion, the amount of water in the system increased, and the reaction proceeded without incident. Sulfur-containing substrates **9** and **11** suffered from low yields, which may be attributable to the formation of intermediate sulfonium ions. Similarly, the allyl group in substrate **23** has the ability to undergo [3+2] side reactions, accounting for diminished yields.

***2.1.2.*** *Synthesis of Brilinta® Core Analogs*. We expect this methodology to be of use in the design of triazole and triazolopyrimidine APIs and drug candidates. Aromatization and substitution on the 6-membered ring is a facile process and can be used to gain access to advanced intermediates related to the cardiovascular agent, Brilinta® (Ticagrelor) depicted in Figure 5 [2c]. To afford such compounds, an efficient three-step synthesis was completed (Scheme 3) involving chlorination of triazolopyrimidine **4**, selective (cyclopropyl) amination to yield **26**, and, finally, thioalkylation to give target **27**.

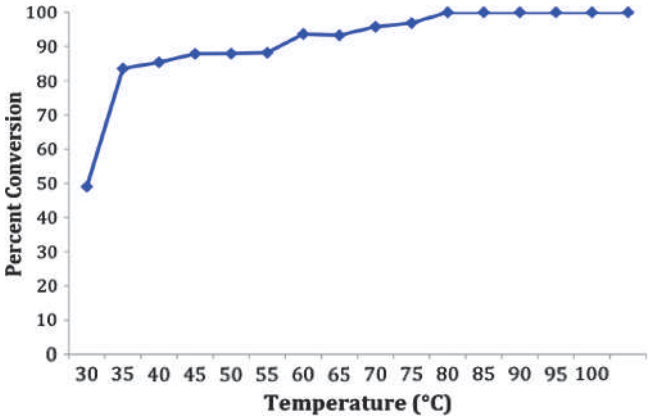



**Figure 2.** Temperature optimization for the conversion of benzyl bromide **1** to benzyl azide **2** (reactor volume=10 μL; residence time=750 s (12.5 min))

In order to show the utility of the methodology with an alkyl cyclopentyl core analog, (bromomethyl)cyclopentane (**28**) was used as a substrate (Scheme 4). Using conditions previously described, this afforded 1,2,3-triazole (**30**), which was elaborated to the triazolopyrimidine (**31**). The ready availability of the starting material (Matrix Scientific) suggests that optimization and application in large scale API synthesis may be viable.

## 3. Conclusion

In conclusion, a flow-based method for the production of 1,2,3-triazoles and triazolopyrimidines has been developed. The process avoids direct isolation of organic azides, enhancing safety considerations in comparison to standard macroscale procedures. The flow process is highly efficient and amenable to a wide range of substrates. The route can be applied to the synthesis of analogs

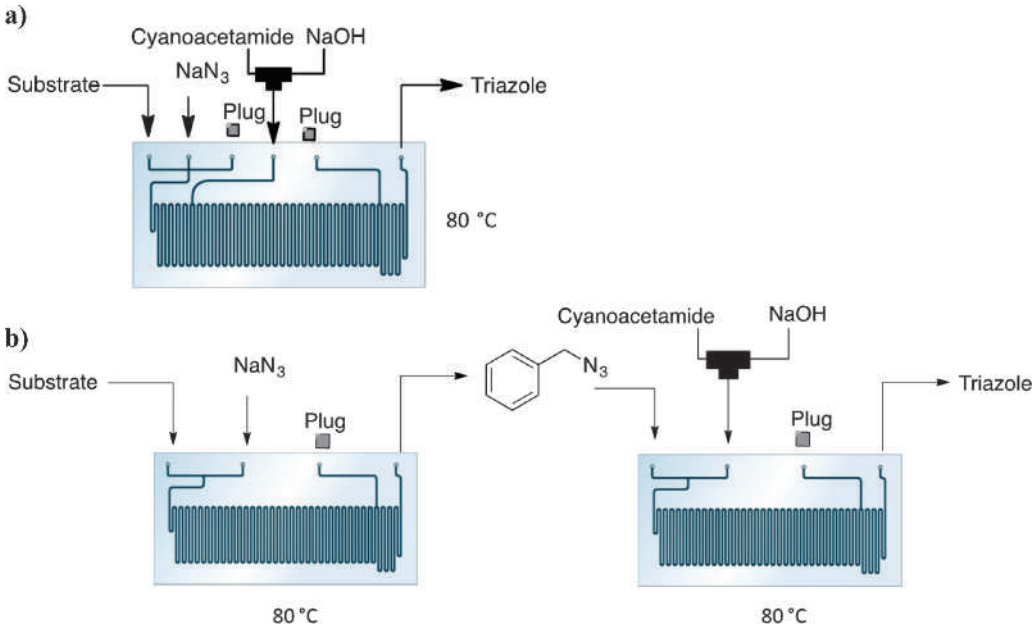
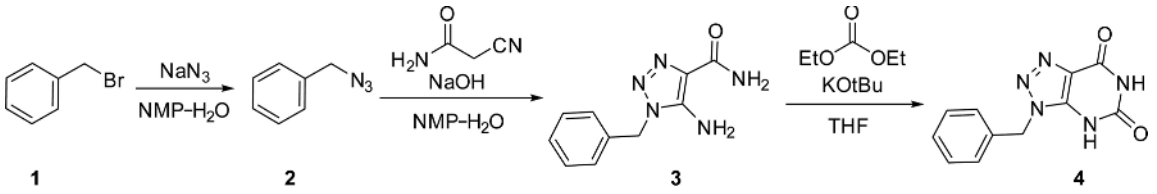



**Figure 1.** Diagram of continuous-flow reactor for triazole library synthesis: a) two-step, one-pot reaction, b) two-step sequential flow reaction

**Scheme 2.** Optimized route to 1-benzyl-1,2,3-triazole (**3**) and its triazolopyrimidine derivative (**4**)




of the core of Brilinta®. As processes such as this become commonplace, the role of flow methodology seems destined to have an increased impact in good manufacturing practice (GMP) production of APIs and end products [13].

## Experimental

**4.1. General Methods.** All continuous-flow reactions were performed using the automated Labtrix® S1 screening system (Chemtrix BV, NL) utilizing T-mixer glass microreactors of the type 3023 (reactor volume=10 μL; A+B+Q type) and 3025 (reactor volume=10 μL; A+B+C+D+Q type). All reagents were dissolved, loaded into 1-mL glass gas-tight syringes (SGE) and dispensed through the microreactor into the auto-sampler loaded with high-performance liquid chromatography (HPLC) vials. The samples were analyzed by HPLC–ultraviolet (UV) (Waters Alliance; Agilent Eclipse Plus C18 Column; 254 nm), and yields for the continuous-flow reactions were determined using a prepared calibration curve of each standard. Tetrahydrofuran (THF) was distilled from a sodium–benzophenone ketyl. Proton nuclear magnetic resonance ($^1$H NMR) spectra were recorded at 400 MHz, and carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded at 100 MHz on a Varian NMR instrument; spectra was prepared using ACD/Labs (Toronto, Canada). High-resolution mass spectroscopy was obtained on a Waters 70-VSE (EI) or a Waters Q-ToF Ultima mass spectrometer (electrospray ionization [ESI]) at the UIUC Mass Spectrometry Facility.

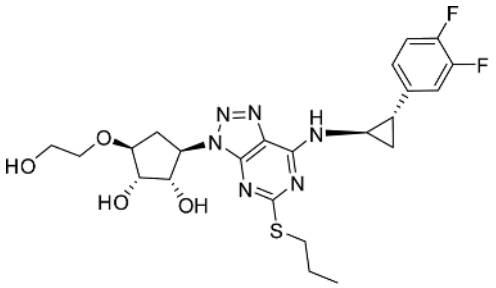



**Figure 5.** Brilinta® (ticagrelor) which contains a triazolopyrimidine core

**4.2. Batch Synthesis of 1,2,3-Triazole Library.** All substrates followed the same protocol; see Supporting Information for detailed procedures and spectral information.

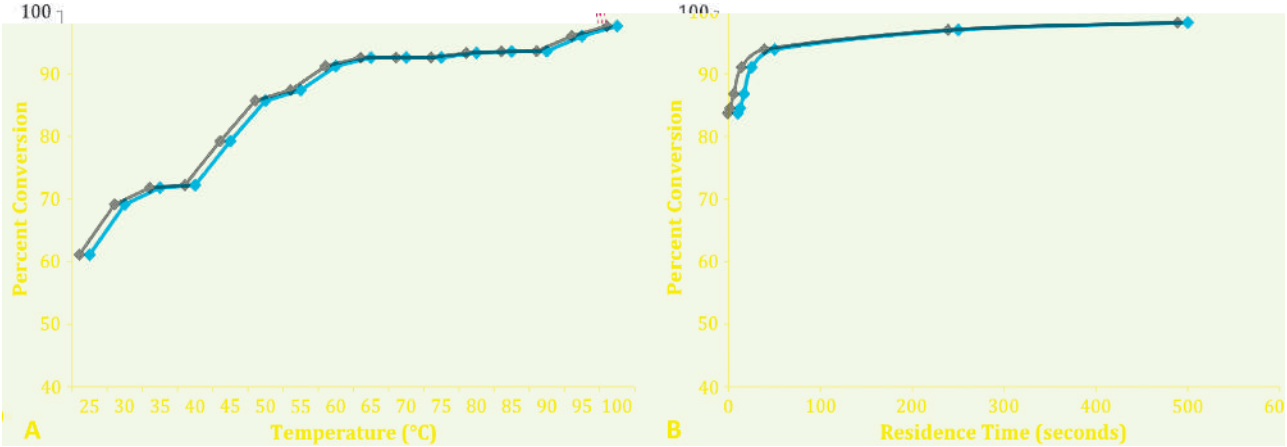



**Figure 3.** Optimization for the conversion of benzyl azide **2** to 1-benzyl-1,2,3-triazole **3** (A) Temperature optimization performed at a residence time=500 s (8.33 min) and B) residence time optimization performed at $T$=80 °C

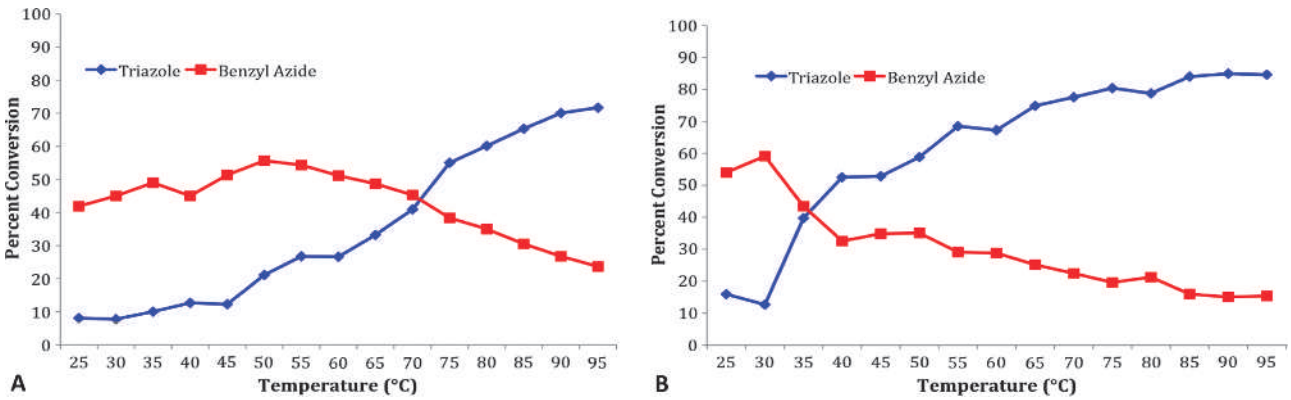
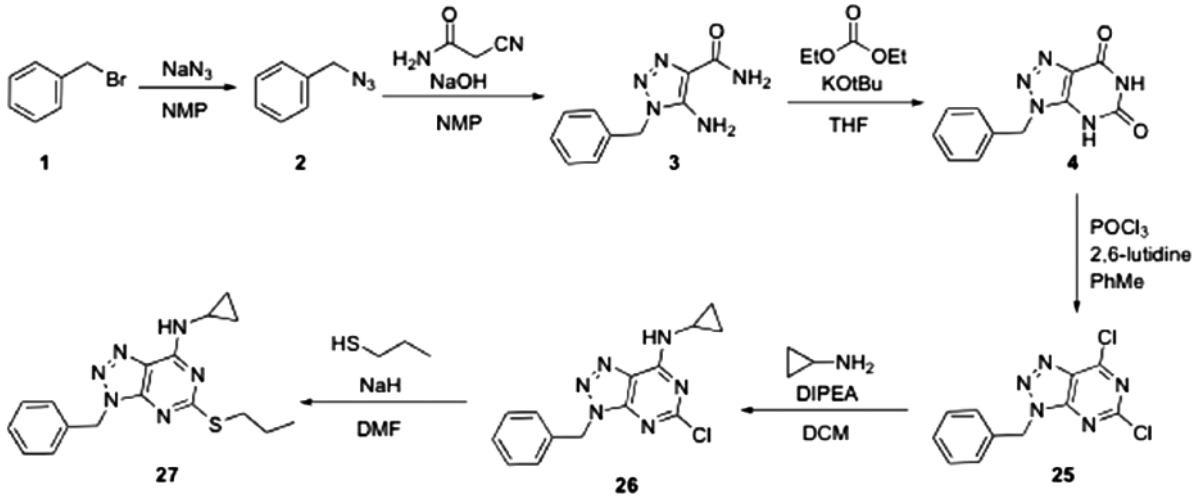



**Figure 4.** Optimization for the one-pot, two-step triazole formation under flow conditions (A) Residence time=45 s (0.75 min) and B) residence time=225 s (3.75 min)

**Scheme 3.** Synthetic route to access Brilinta® analogs




***4.2.1.*** *5-Amino-1-Benzyl-1H-1,2,3-Triazole-4-Carboxamide (3)*. To a solution of benzyl bromide (**1**) (1.00 g, 5.85 mmol) in *N*-methyl-2-pyrrolidinone (10 mL), sodium azide (0.76 g, 11.7 mmol) was added, and the reaction was stirred at 80 °C for 2 h. The reaction mixture was then cooled to 20 °C and quenched with methyl tertiary butyl ether (MTBE) (10 mL) and $H_2O$ (15 mL). The organic layer was isolated and washed with 1 M sodium bicarbonate (10 mL) and $H_2O$ (10 mL), dried over $MgSO_4$, and concentrated in vacuo. To a solution of the crude azide (**2**) in *N*-methyl-2-pyrrolidinone (15 mL), cyanoacetamide (0.74 g, 8.77 mmol) and sodium hydroxide (0.35 g, 8.77 mmol) were added. The reaction was stirred at 80 °C for 3 h. The reaction mixture was then cooled to room temperature (RT), quenched with $H_2O$ (30 mL), and allowed to stir overnight (O/N) at RT to allow for complete precipitation. The solid was then filtered and dried in vacuo to afford the product as a light yellow powder (0.31 g, 40 %). mp=236–237 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 7.45–7.17 (m, 5H), 7.09 (br s, 2H), 6.39 (br s, 2H), 5.41 (s, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 164.5, 145.0, 136.1, 128.9, 127.9, 127.6, 121.9, 48.5; HRMS (EI), m/z $C_{10}H_{11}N_5O$ $(M)^+$ calcd. 217.10, obsd. 217.09637.

**4.3. Continuous-Flow Synthesis of Benzyl Azide.** To a Labtrix® T-mixer microreactor (#3023), the following separate solutions were introduced: benzyl bromide **1** in *N*-methyl-2-pyrrolidinone (0.5 M) and $NaN_3$ in aqueous *N*-methyl-2-pyrrolidinone (20 % v/v, 0.5 M). The reaction was performed at temperatures ranging from 25 to 100 °C and flow rates of 0.5–25 μL/min per syringe. Reaction mixtures were collected in 50 μL aliquots, repeated 3×, and diluted with $H_2O$ (500 μL) prior to analysis by HPLC–UV.

**4.4. Continuous-Flow Synthesis of 5-Amino-1-Benzyl-1*H*-1,2,3-Triazole-4-Carboxamide.** To the Labtrix® T-mixer microreactor (#3025), the following individual solutions were introduced: benzyl bromide **1** in *N*-methyl-2-pyrrolidinone (0.5 M) and $NaN_3$ in aqueous *N*-methyl-2-pyrrolidinone (20 % v/v, 0.5 M), cyanoacetamide in aqueous *N*-methyl pyrrolidone (NMP) (20 % v/v, 0.25 M), and sodium hydroxide in $H_2O$ (0.25 M). The reaction was performed at temperatures ranging from 25 to 100 °C and flow rates of 0.5–20 μL/min per syringe. Reaction mixtures were collected in 50 μL aliquots, repeated 3×, and diluted with $H_2O$ (450 μL) and dimethylsulfoxide (DMSO) (300 μL) prior to analysis by HPLC–UV.

**4.5. One-Pot Continuous-Flow Synthesis of 5-Amino-1-Benzyl-1H-1,2,3-Triazole-4-Carboxamide (3).** To the Labtrix® T-mixer microreactor (#3023), the following solutions were introduced: cyanoacetamide in aqueous NMP (20 % v/v, 0.75 M), sodium hydroxide in $H_2O$ (0.75 M), and benzyl azide in aqueous NMP (20 % v/v, 0.5 M). The reaction was performed at temperatures ranging from 25 to 100 °C and flow rates of 0.5–25 μL/min per syringe. Reaction mixtures were collected in 50 μL aliquots, repeated 3×, and diluted with $H_2O$ (450 μL) and DMSO (300 μL) prior to analysis by HPLC–UV.

**4.6. General Continuous-Flow Synthesis of the 1-Substituted-1,2,3-Triazole Library.** To the Labtrix® T-mixer

**Scheme 4.** Cyclopentyl methyl analogs of the ticagrelor core

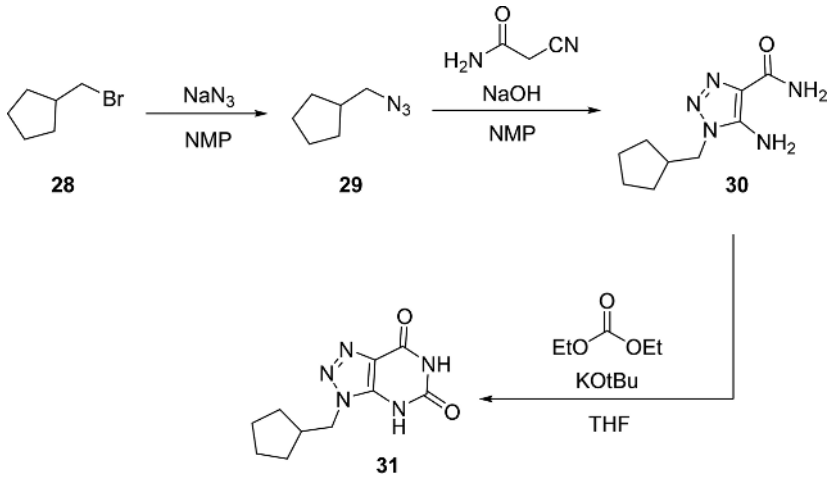


**Table 2a.** Continuous-flow synthesis of triazole analogs in (a) configuration using 1 eq. of azide and 3 eq. of cyanoacetamide and NaOH

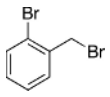
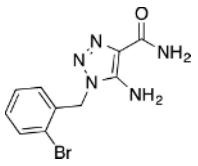
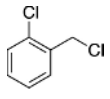
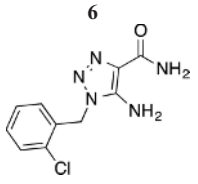
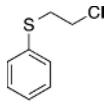
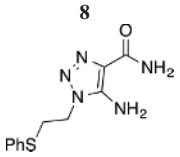
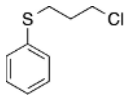
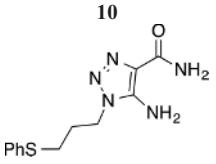
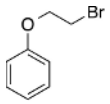
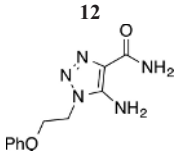
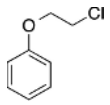
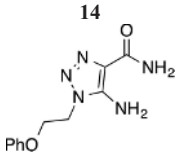
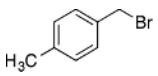
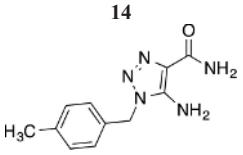
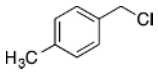
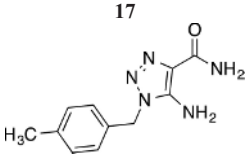
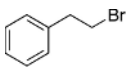
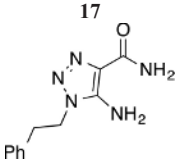
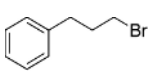
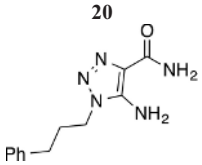
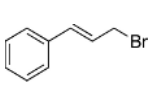
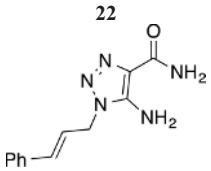
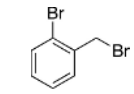
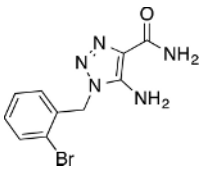
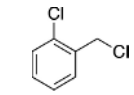
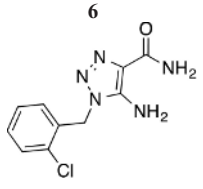
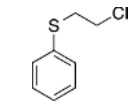
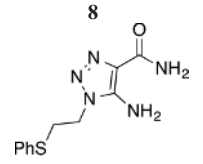
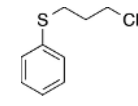
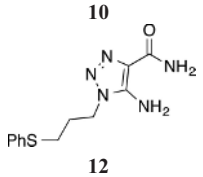
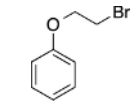
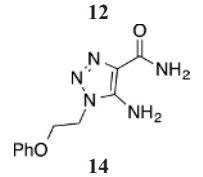
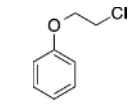
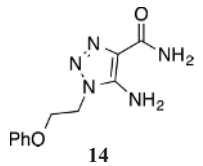
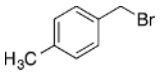
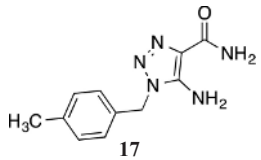
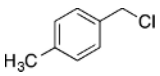
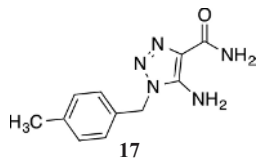
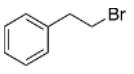
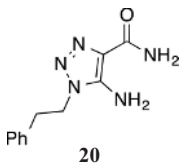
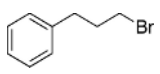
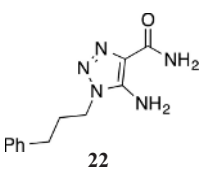
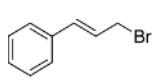
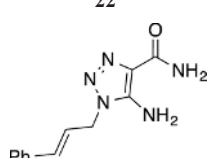
| Entry | Substrate | Product | % Conversion to azide (% recovered SM) | % Conversion to Triazole |
|---|---|---|---|---|
| 1 |  **5** |  **6** | 3.58 | 96.4 |
| 2 |  **7** |  **8** | 2.86 (2.4) | 94.7 |
| 3 |  **9** |  **10** | 5.22 (94.78) | 0 |
| 4 |  **11** |  **12** | 10.8 (88.2) | 0 |
| 5 |  **13** |  **14** | 44.5 (32.8) | 22.7 |
| 6 |  **15** |  **14** | 100 | 0 |
| 7 |  **16** |  **17** | 17.9 | 82.1 |
| 8 |  **18** |  **17** | 19.3 (7.0) | 73.7 |
| 9 |  **19** |  **20** | 75.7 | 24.3 |
| 10 |  **21** |  **22** | 18.0 | 82.0 |
| 11 |  **23** |  **24** | 77.0 | 23.0 |

**Table 2b.** Continuous-flow synthesis of triazole analogs in (b) configuration using 1 eq. of azide and 2 or 3 eq. of cyanoacetamide and NaOH

| Entry | Substrate | Product | % Conversion to azide | % Conversion to triazole (2 eq.) | % Conversion to triazole (3 eq.) |
|---|---|---|---|---|---|
| 1 |  **5** |  **6** | 100 | 94.9 | 98.8 |
| 2 |  **7** |  **8** | 0 | 94.9 | 97.3 |
| 3 |  **9** |  **10** | 16.7 | 32.9 | 46.8 |
| 4 |  **11** |  **12** | 81.1 | 66.5 | 75.4 |
| 5 |  **13** |  **14** | 83.9 | 74.8 | 72.8 |
| 6 |  **15** |  **14** | 100 | 74.8 | 72.8 |
| 7 |  **16** |  **17** | 100 | 83.3 | 85.7 |
| 8 |  **18** |  **17** | 0 | 83.3 | 85.7 |
| 9 |  **19** |  **20** | 100 | 78.9 | 83.8 |
| 10 |  **21** |  **22** | 100 | 45.6 | 70.7 |
| 11 |  **23** |  **24** | 100 | 21.4 | 30.7 |

microreactor (#3025), the following solutions were introduced: alkyl halide in *N*-methyl-2-pyrrolidinone (0.5 M), $NaN_3$ in aqueous *N*-methyl-2-pyrrolidinone (20 % v/v, 0.5 M), cyanoacetamide in aqueous *N*-methyl-2-pyrrolidinone (20 % v/v, 0.75 M), and sodium hydroxide in $H_2O$ (0.75 M). The reaction was performed at 80 °C and a flow rate of 1 μL/min. Reactions were collected in 50 μL aliquots, repeated 3×, and diluted with $H_2O$ (450 μL) and DMSO (300 μL) prior to analysis by HPLC–UV.

**4.7. Batch Synthesis of Brilinta® Analogs**

***4.7.1.*** *3-Benzyl-3,4-Dihydro-5H-[1,2,3]Triazolo[4,5-d]Pyrimidine-5,7(6H)-Dione (4)*. To a solution of 5-amino-1-(phenylmethyl)-1*H*-1,2,3-triazole-4-carboxamide **3** (0.200 g, 0.92 mmol) and diethyl carbonate (0.326 g, 2.76 mmol) in dry THF (15 mL), potassium tert-butoxide (0.310 g, 2.76 mmol) was added. The mixture was refluxed for 5 h. It was then cooled to room temperature, quenched with water (20 mL), and concentrated to ~20 mL in vacuo. The remaining aqueous solution was neutralized with 1 N HCl to pH=6, and the precipitate was filtered, washed with water, and then air-dried to yield a beige solid (0.191 g, 85 % yield). mp=281–282 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 12.57 (br s, 1H), 11.30 (s, 1H), 7.41–7.28 (m, 5H), 5.63 (s, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 156.9, 151.3, 142.5, 135.7, 129.5, 128.8, 128.3, 125.0, 50.6; HRMS (EI), m/z $C_{11}H_9N_5O_2$ $(M)^+$ calcd. 245.08, obsd. 245.0834.

***4.7.2.*** *3-Benzyl-5,7-Dichloro-3H-[1,2,3]Triazolo[4,5-d]Pyrimidine (25)*. To a cooled (−20 °C) solution of 3-benzyl-3,4-dihydro-5*H*-[1,2,3]triazolo[4,5-d]pyrimidine-5,7(6*H*)-dione **4** (2.0 g, 8.20 mmol) and phosphoryl chloride (5.0 g, 32.8 mmol) in toluene (100 mL), 2,6-lutidine (0.88 g, 8.2 mmol) was added dropwise. The reaction was refluxed for 5 h. After concentration in vacuo, the residue was dissolved in water (50 mL) and extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was recrystallized from diethyl ether to afford the desired compound as a yellow solid (0.5213 g, 21.8 %). mp= 83–84 °C; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.41–7.28 (m, 5H), 5.83 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 157.8, 155.2, 151.2, 133.6, 133.5, 129.4, 129.3, 128.8, 51.7; HRMS (EI), m/z $C_{11}H_7Cl_2N_5$, calcd. 279.01, obsd. 279.00786.

***4.7.3.*** *3-Benzyl-5-Chloro-N-Cyclopropyl-3H-[1,2,3]Triazolo [4,5-d]Pyrimidin-7-Amine (26)*. To a stirring solution of 3-benzyl-5,7-dichloro-3*H*-[1,2,3]triazolo[4,5-d]pyrimidine **25** (0.185 g, 0.66 mmol) and cyclopropylamine ( 0.034 g, 0.60 mmol) in dry $CH_2Cl$ (10 mL), *N*,*N*-diisopropylethylamine (0.077 g, 0.60 mmol) was added. The reaction was stirred at room temperature for 5 h, at which time an additional 0.9 eq. of the cyclopropylamine and *N*,*N*-diisopropylethylamine was added. The reaction was stirred for another 16 h, and the additional 0.9 equivalent addition was repeated. The reaction mixture was stirred for an additional 2 h (total reaction time=24 h), and then the reaction mixture was washed with water, dried with $MgSO_4$, and then concentrated in vacuo. The residue was purified by flash chromatography ($SiO_2$; 30 % EtOAc–Hex) to afford the desired compound as a yellow oil (0.102 g, 52 %). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.45–7.27 (m, 5H), 5.71 (s, 2H), 2.32 (br s, 1H) 1.08 (d, *J*=6 Hz, 1 H), 0.95 (m, 2H), 0.73 (br s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.5, 157.6, 156.1, 134.6, 129.0, 128.7, 128.5, 124.2, 50.6, 24.2, 9.1, 7.3; HRMS (EI), m/z $C_{14}H_{13}ClN_6$, calcd. 300.0890, obsd. 300.0893.

***4.7.4.*** *3-Benzyl-N-Cyclopropyl-5-(Propylthio)-3H-[1,2,3]Triazolo[4,5-d]Pyrimidin-7-Amine (27)*. To a cooled (0 °C) solution of sodium hydride (0.010 g, 0.40 mmol) in dry dimethylformamide (DMF) (10 mL), propane thiol (0.030 g, 0.40 mmol) was added and allowed to stir until gas evolution ceased. Then, 3-benzyl-5-chloro-*N*-cyclopropyl-3*H*-[1,2,3]triazolo[4,5-d]pyrimidin-7-amine **26** was then added in one portion, and the reaction mixture was allowed to warm to RT. After stirring overnight, the consumption of starting material was not complete; thus, an additional 2 equivalents of propane thiol and sodium hydride was added. Upon an additional 3 h of reaction time, the addition of 2 eq. was repeated. The reaction was stirred for a total of 28 h, at which time it was poured onto a saturated sodium carbonate solution (20 mL) and extracted with EtOAc (3×15 mL). The organic extracts were combined, washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography ($SiO_2$; 5 % EtOAc–$CH_2Cl_2$) to yield a yellow oil (0.091 g, 80 %). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.45–7.27 (m, 5H), 5.66 (s, 2H), 3.16 (br s, 2H), 1.79 (br s, 2H), 1.23 (s, 1H), 1.05 (m, 4H), 0.95 (m, 1H), 0.73 (br s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 171.3, 168.4, 154.6, 135.19, 128.8, 128.5, 128.4, 123.4, 50.3, 33.5, 23.8, 23.1, 13.7, 9.03, 7.2; HRMS (EI), m/z $C_{17}H_{20}N_7S$, calcd. 340.1470, obsd. 340.1468.

***4.7.5.*** *5-Amino-1-(Cyclopentylmethyl)-1H-1,2,3-Triazole-4-Carboxamide (30)*. Using the same procedure as for (**3**), a yellow solid was obtained (0.177 g, 52 %). mp=226–227 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 7.41 (br s, 1H), 7.06 (br s, 1H) 6.28 (br s, 2H), 4.05 (d, *J*=8 Hz, 2H), 2.37 (m, 1H), 1.61 (m, 4H), 1.50 (m, 2H), 1.26 (m, 2H) (NMP impurity at 3.30, 2.70, 2.19, 1.90); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 164.4, 144.6, 121.5, 49.5, 38.9, 29.5, 24.5; HRMS (ESI), m/z $C_9H_{15}N_5O$ $(M+H)^+$ calcd. 210.13, obsd. 210.1355.

***4.7.6.*** *3-(Cyclopentylmethyl)-3,4-Dihydro-5H-[1,2,3]Triazolo[4,5-d]Pyrimidine-5,7(6H)-Dione (31)*. Same procedure as (**4**) light yellow solid (0.035 g, 21 % yield). mp=294–295 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 12.4 (br s, 1H), 11.2 (s, 1H), 4.27 (d, *J*=7.2Hz, 2H), 2.36 (m, 1H), 1.63 (m, 4H), 1.50 (m, 2H), 1.23 (m, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 156.3, 150.7, 141.6, 124.1, 51.2, 39.0, 29.4, 24.5; HRMS ($ESI^+$), m/z $C_{10}H_{13}N_5O_2$ $(M+H)^+$ calcd. 236.11, obsd. 236.1147.

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## Supporting Information

Electronic Supplementary Material (ESM) (Experimental protocols, NMR spectra) associated with this article is available in the online version at doi: 10.1556/JFC-D-14-00019.

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# A Facile Route to Triazolopyrimidines Using Continuous Flow Chemistry

S S , M M. S , N L. K , D E. B , C A. L ,
D J. , A R. M , B C. N , P N. K ,
C , R J. G B. J [,1]

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## C



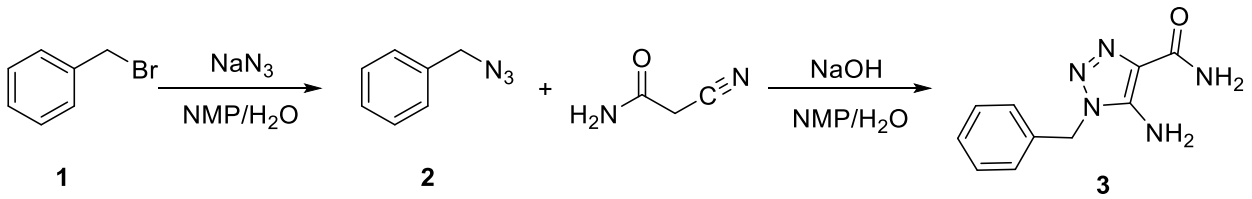
*Email address* _____

## Materials and Methods

A F S S A . HF / . A C L S1 (C B , NL) - , C B . A , 1 L - (SGE) HPLC . HPLC- ( A ; A E P C18 C ; 254 ), . $^{1}$H NMR 400 MH , $^{13}$C NMR 100 MH NMR , ACD/L ( , C ). H - 70- SE (EI) Q- F (ESI) I C M S F .

## Experimental Data

### General procedure for batch synthesis of triazole library for spectroscopic analysis




1 2 3

(1.00 , 5.85 ) *N*- -2- (10 L) (0.76 , 11.7 ). 80 C 2 . 20 C M BE (10 L) $H_2O$ (15 L). 1M (10 L) $H_2O$ (10 L), M $SO_4$, *in vacuo*. *N*- -2- (15 L) (0.74 , 8.77 ) (0.35 , 8.77 ). 80 C 3 . R , $H_2O$ (30 L) O/N R . *in vacuo* .

**5-amino-1-benzyl-1*H*-1,2,3-triazole-4-carboxamide (3):** (0.314 , 40%). = 236-237 C. $^1$H NMR (400 MH , DMSO- $_6$): δ 7.45-7.17 ( , 5H), 7.09 ( , 2H), 6.39 ( , 2H), 5.41 ( , 2H). $^{13}$C NMR (100 MH , DMSO- $_6$): δ 164.5, 145.0, 136.1, 128.9, 127.9, 127.6, 121.9, 48.5. HRMS (EI), / $C_{10}H_{11}N_5O$ $(M)^+$ . 217.10, . 217.09637.

**5-amino-1-(2-bromobenzyl)-1*H*-1,2,3-triazole-4-carboxamide (6):** (0.58 , 59%). = 215-216 C. $^1$H NMR (400 MH , DMSO- $_6$): δ 7.69 ( , *J*=8 H , 1H), 7.53 ( , 1H), 7.36 ( , *J*=7.6 H , 1H), 7.28 ( , *J*=7.2 H , 1H), 7.16 ( , 1H), 6.63 ( , *J*=7.2 H , 1H), 6.45 ( , 2H), 5.44 ( , 2H). $^{13}$C NMR (100 MH , DMSO- $_6$): δ 164.3, 145.4, 135.0, 132.8, 129.7, 128.1, 128.0, 121.9, 121.6, 48.9. HRMS (EI), / $C_{10}H_{10}B\,N_5O$ $(M)^+$ . 295.01, . 295.00667.

**5-amino-1-(2-chlorobenzyl)-1*H*-1,2,3-triazole-4-carboxamide (8):** (0.64 , 49%). = 209-210 C. $^1$H NMR (400 MH , DMSO- $_6$): δ 7.53 ( , 2H), 7.34 ( , 2H), 7.17 ( , 1H), 6.73 ( , *J*=7.2 H , 1H), 6.50 ( , 2H), 5.49 ( , 2H). $^{13}$C NMR (100 MH , DMSO- $_6$): δ 164.1, 145.2, 133.2, 131.6, 129.3, 129.2, 128.0, 127.3, 121.4, 48.3 (NMP 174.5, 49.2, 30.8, 29.7, 17.9). HRMS (EI), / $C_{10}H_{10}C\,N_5O$ $(M)^+$ . 251.06 . 251.05782.

**5-amino-1-(2-phenylthio)ethyl-1*H*-1,2,3-triazole-4-carboxamide (10):** (0.21 , 20%). = 161-162 C. $^1$H NMR (400 MH , DMSO- $_6$): δ 7.44 ( , 1H), 7.36 ( , 4H), 7.23 ( , 1H), 7.09 ( , 1H), 6.35 ( , 2H), 4.35 ( , *J*=7.6 H , 2H), 3.37 ( , *J*=7.6 H , 2H). $^{13}$C NMR (100 MH , DMSO- $_6$): δ 164.5, 145.0, 135.1, 129.4, 128.9, 126.4, 122.0, 44.8, 31.3. HRMS (EI), / $C_{11}H_{13}N_5OS$ $(M)^+$ . 263.08, . 263.08442.

**5-amino-1-(3-(phenylthio)propyl)-1*H*-1,2,3-triazole-4-carboxamide (12):** (0.469 , 47%). $^{1}$H NMR (400 MH , DMSO- $_{6}$): δ 7.47 ( , 1H), 7.31 ( , 3H), 7.22 ( , 2H), 7.11 ( , 1H), 6.34 ( , 2H), 4.30 ( , *J*=6.8 H , 2H), 2.97 ( , *J*=7.2 H , 2H), 2.00 ( , *J*=7 H , 2H). $^{13}$C NMR (100 MH , DMSO- $_{6}$): δ 164.5, 145.0, 135.1, 129.4, 128.9, 126.4, 122.0, 44.8, 28.9, 28.1. HRMS (EI), / $C_{12}H_{15}N_5OS$, . 277.10, . 277.0996

**5-amino-1-(2-phenoxyethyl)-1*H*-1,2,3-triazole-4-carboxamide (14):** (0.32 , 36%). = 188-189 C. $^{1}$H NMR (400 MH , DMSO- $_{6}$): δ 7.45 ( , 1H), 7.28 ( , 3H), 7.10 ( , 1H), 6.93 ( , 2H), 6.35 ( , 2H), 4.55 ( , 2H), 4.32 ( , 2H). $^{13}$C NMR (100 MH , DMSO- $_{6}$): δ 164.6, 158.2, 145.4, 129.8, 121.9, 121.2, 114.7, 65.5, 45.2. (EI), / $C_{11}H_{13}N_5O_2$, . 247.11, . 247.10722.

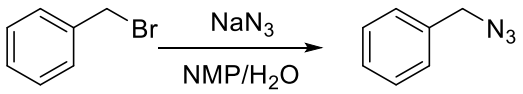
**5-amino-1-(4-methylbenzyl)-1*H*-1,2,3-triazole-4-carboxamide (17):** (0.59 , 49%). = 222-223 C. $^{1}$H NMR (400 MH , DMSO- $_{6}$): δ 7.49 ( , 1H), 7.14 ( , 5H), 6.40 ( , 2H), 5.37 ( , 2H), 2.27 ( , 3H). $^{13}$C NMR (100 MH , DMSO- $_{6}$): δ 164.8, 145.2, 137.4, 133.4, 129.6, 127.9, 122.1, 48.5, 21.1. HRMS (EI), / $C_{11}H_{13}N_5O$ $(M)^+$ . 231.11, . 231.11174.

**5-amino-1-phenethyl-1*H*-1,2,3-triazole-4-carboxamide (20):** (0.20 , 26%). = 201-202 C. $^{1}$H NMR (400 MH , DMSO- $_{6}$): δ 7.42 ( , 1H), 7.26 ( , 5H), 7.07 ( , 1H), 6.33 ( , 2H), 4.35 ( , J=7.2 H , 2H), 3.04 ( , J=7.2 H , 2H). $^{13}$C NMR (100 MH , DMSO- $_{6}$): δ 164.6, 144.8, 138.0, 129.1, 128.6, 126.8, 121.9, 46.6, 34.5. HRMS (EI), / $C_{11}H_{13}N_5O$ $(M)^+$ . 231.11, . 231.11182.

**5-amino-1-(3-phenylpropyl)-1*H*-1,2,3-triazole-4-carboxamide (22):** (0.69 , 59%). = 196-197 C. $^{1}$H NMR (400 MH , DMSO- $_{6}$): δ 7.44 ( , 1H), 7.25 ( , 5H), 7.08 ( , 1H), 6.31 ( , 2H), 4.14 ( , *J*=7.2H , 2H), 2.58 ( , *J*=7.2 H , 2H), 2.00 ( , 2H). $^{13}$C NMR (100 MH , DMSO- $_{6}$): δ 164.4, 144.6, 141.0, 128.4, 128.3, 126.0, 121.7, 44.9, 32.0, 30.1. HRMS (EI), / $C_{12}H_{15}N_5O$, $(M)^+$ . 245.13, . 245.12776.

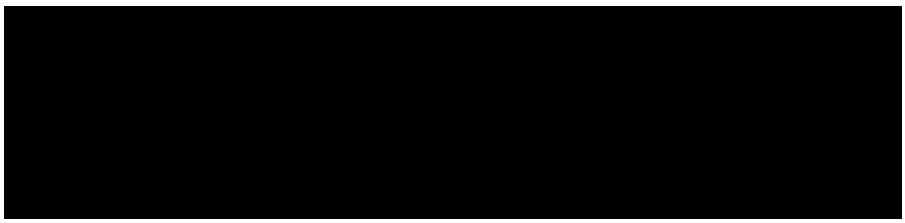
**5-amino-1-cinnamyl-1*H*-1,2,3-triazole-4-carboxamide (24):** (0.69 , 59%). = 235-236 C. $^{1}$H NMR (400 MH , DMSO- $_{6}$): δ 7.47 ( , 1H), 7.24-7.45 ( , 5H), 7.10 ( , 1H), 6.45 ( , 2H), 6.36 ( , 2H), 4.58 ( , *J*= 6 H , 2H). $^{13}$C NMR (100 MH , DMSO- $_{6}$): δ 164.3, 144.6, 135.9, 132.3, 128.7, 128.0, 126.5, 123.5, 121.7, 47.0 (NMP 174.5, 49.2, 30.8, 29.7, 17.9). HRMS (EI), / $C_{12}H_3N_5O$, . 243.11, . 243.11231.

## General procedure for the continuous flow synthesis of triazole library compounds

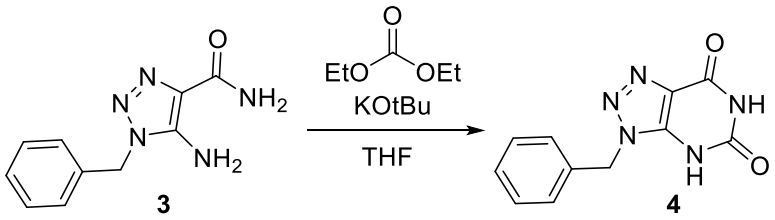



**1** **2**

**Benzyl azide (2):** L - (#3023), :
*N*- -2- (0.5 M) N $N_3$ *N*- -2-
(20% / , 0.5 M). 25-
100 C 0.5 25 L/ . R 50 L
, 3 , $H_2O$ (500 L) HPLC- .

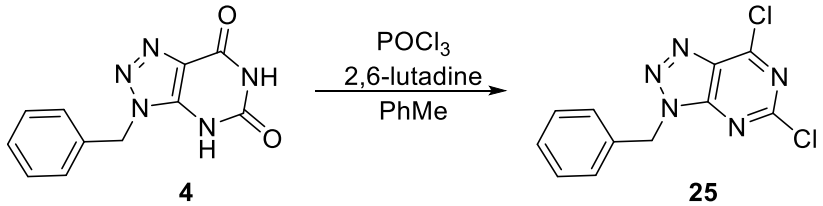


# Synthesis of Brilinta® analogues



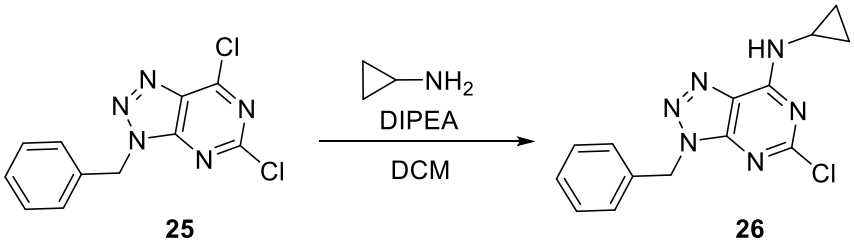

3 4

**3-benzyl-3,4-dihydro-5*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(6*H*)dione (4):** 5- -1-( )-1*H*-1,2,3- -4- (**3**) (0.200 , 0.92 ) (0.326 , 2.76 ) HF (15 L) - (0.310 , 2.76 ). 5 . I , (20 L), 20 L *in vacuo*. 1N HC H=6, , , (0.191 , 85% ). = 281-282 C. $^{1}$H NMR (400 MH , DMSO- $_6$): δ 12.57 ( , 1H), 11.30 ( , 1H), 7.41-7.28 ( , 5H), 5.63 ( , 2H). $^{13}$C NMR (100 MH , DMSO- $_6$): δ 156.9, 151.3, 142.5, 135.7, 129.5, 128.8, 128.3, 125.0, 50.6. HRMS (EI), / $C_{11}H_9N_5O_2$ (M)$^+$ . 245.08, . 245.0834.




4 25

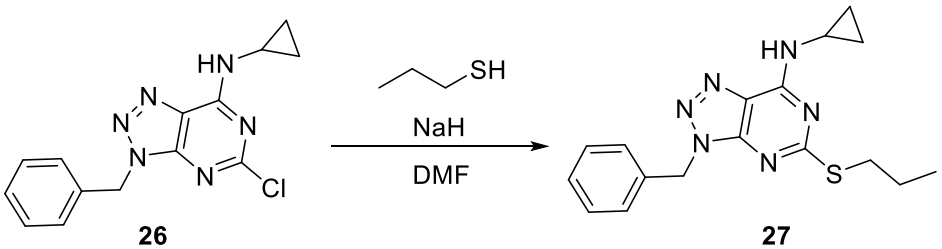
**3-benzyl-5,7-dichloro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine (25):** (-20 C) **(4)** (1.00 , 4.11 ) (2.52 , 16.4 ) (50 L) 2,6- (0.441 , 4.11 ). 5 . A *in vacuo*, (50 L) (3 30 L). M $SO_4$ *in vacuo*. (S $O_2$; 5% M OH/$CH_2C_2$) (0.069 , 6.40%) = 83-84 C. $^{1}$H NMR (400 MH , DMSO- $_6$): δ 7.41-7.28 ( , 5H), 5.83 ( , 2H). $^{13}$C NMR (100 MH , DMSO- $_6$): δ 157.8, 155.2, 151.2, 133.6, 133.5, 129.4, 129.3, 128.8, 51.7. HRMS (EI), / $C_{11}H_7C_2N_5$, . 279.01, . 279.00786.




25 26

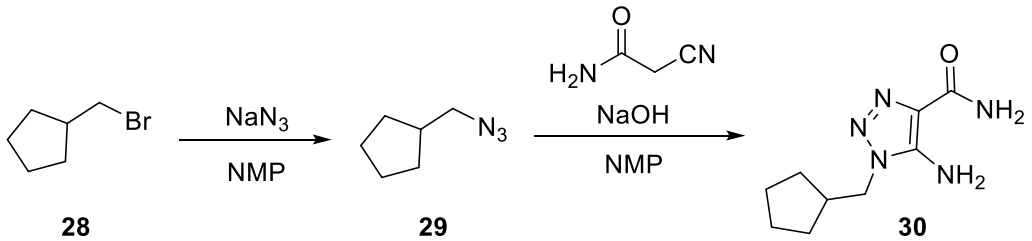
**3-benzyl-5-chloro-*N*-cyclopropyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-amine (26)**: **(25)** (0.185 , 0.66 ) ( 0.034 , 0.60 )

$CH_2C$ (10 L) N,N- (0.077 , 0.60 ).
5 , 0.9
N,N- .
16 0.9 .
2 ( = 24 ),
, M $SO_4$, *in vacuo*.
($S O_2$; 30% E OA :H )
(0.102 , 52%). $^1$H NMR (400 MH , $CDC_3$): δ 7.45-7.27 ( , 5H), 5.71 ( , 2H), 2.32 ( , 1H) 1.08 ( , *J* = 6 H , 1 H), 0.95 ( , 2H), 0.73 ( , 2H). $^{13}$C NMR (100 MH , $CDC_3$): δ 159.5, 157.6, 156.1, 149.8, 134.6, 129.0, 128.7, 128.5, 128.4, 124.1, 50.5. HRMS (EI), / $C_{14}H_{13}C N_6$, . 300.0890, . 300.0893.




**26** **27**

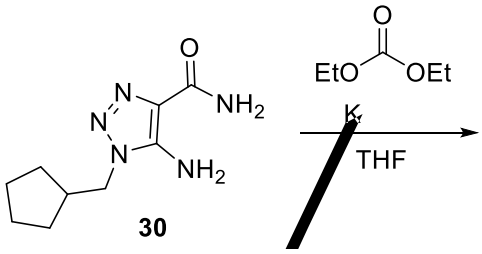
**3-benzyl-*N*-cyclopropyl-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-amine (27):**
(0 C) (0.010 , 0.40 ) DMF (10 L)
(0.030 , 0.40 ) .
(**26**) , R . A
, , 2
. 3
, 2 .
28 , (20 L)
E OA (3 15 L). , (20
L) (20 L), M $SO_4$, *in vacuo*.
($S O_2$; 5% E OA /$CH_2C_2$) (0.091 , 80%). $^1$H NMR (400 MH , $CDC_3$): δ 7.45-7.27 ( , 5H), 5.66 ( , 2H), 3.16 ( , 2H), 1.79 ( , 2H), 1.23 ( , 1H), 1.05 ( , 4H), 0.95 ( , 1H), 0.73 ( , 2H). $^{13}$C NMR (100 MH , $CDC_3$): δ171.3, 168.4, 154.6, 135.19, 128.8, 128.5, 128.4, 123.4, 50.3, 33.5, 23.8, 23.1, 13.7, 9.03, 7.2. HRMS (EI), / $C_{17}H_{20}N_7S$, . 340.1470, . 340.1468.



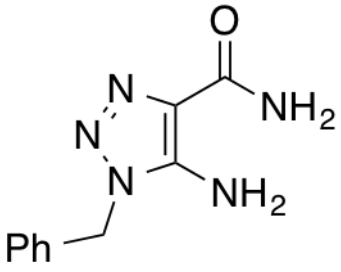

**28** **29** **30**

**5-amino-1-(cyclopentylmethyl)-1*H*-1,2,3-triazole-4-carboxamide (30):** F
**(3)** (0.177 , 52%).
= 226-227 C. $^1$H NMR (400 MH , DMSO- $_6$): δ 7.41 ( , 1H), 7.06 ( , 1H) 6.28 ( ,

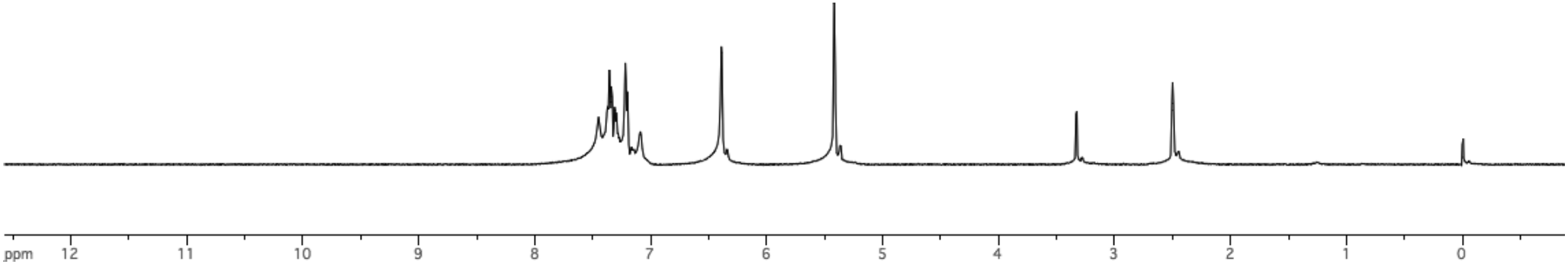
2H), 4.05 ( , *J*=8 H , 2H), 2.37 ( , 1H), 1.61 ( , 4H), 1.50 ( , 2H), 1.26 ( , 2H) (NMP 3.30, 2.70, 2.19, 1.90). $^{13}$C NMR (100 MH , DMSO- $_6$): δ 164.4, 144.6, 121.5, 49.5, 38.9, 29.5, 24.5. HRMS (ESI), / $C_9H_{15}N_5O$ $(M+H)^+$ . 210.13, . 210.1355.

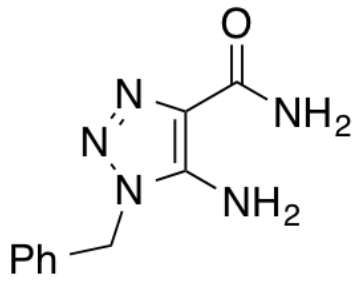



**30**

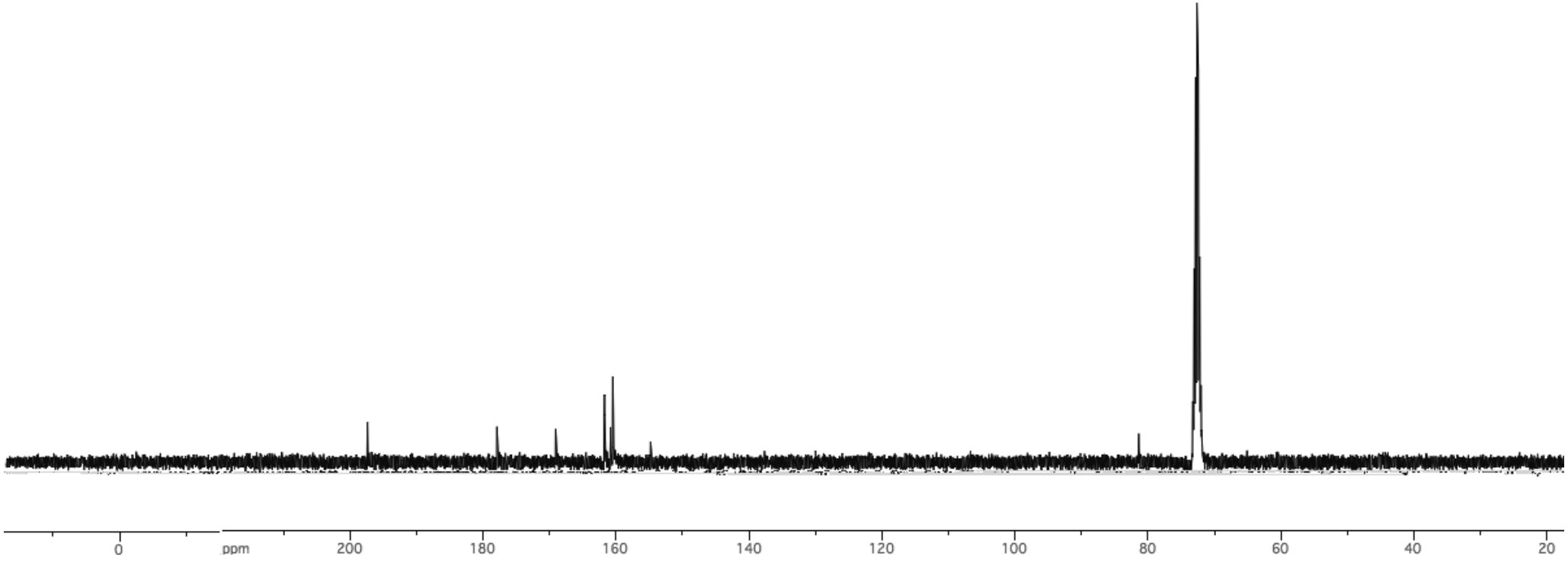


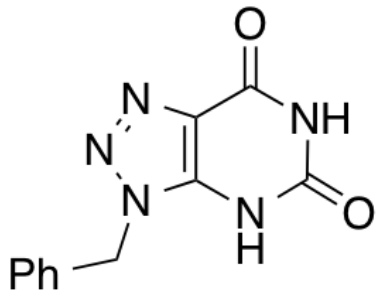

**3**



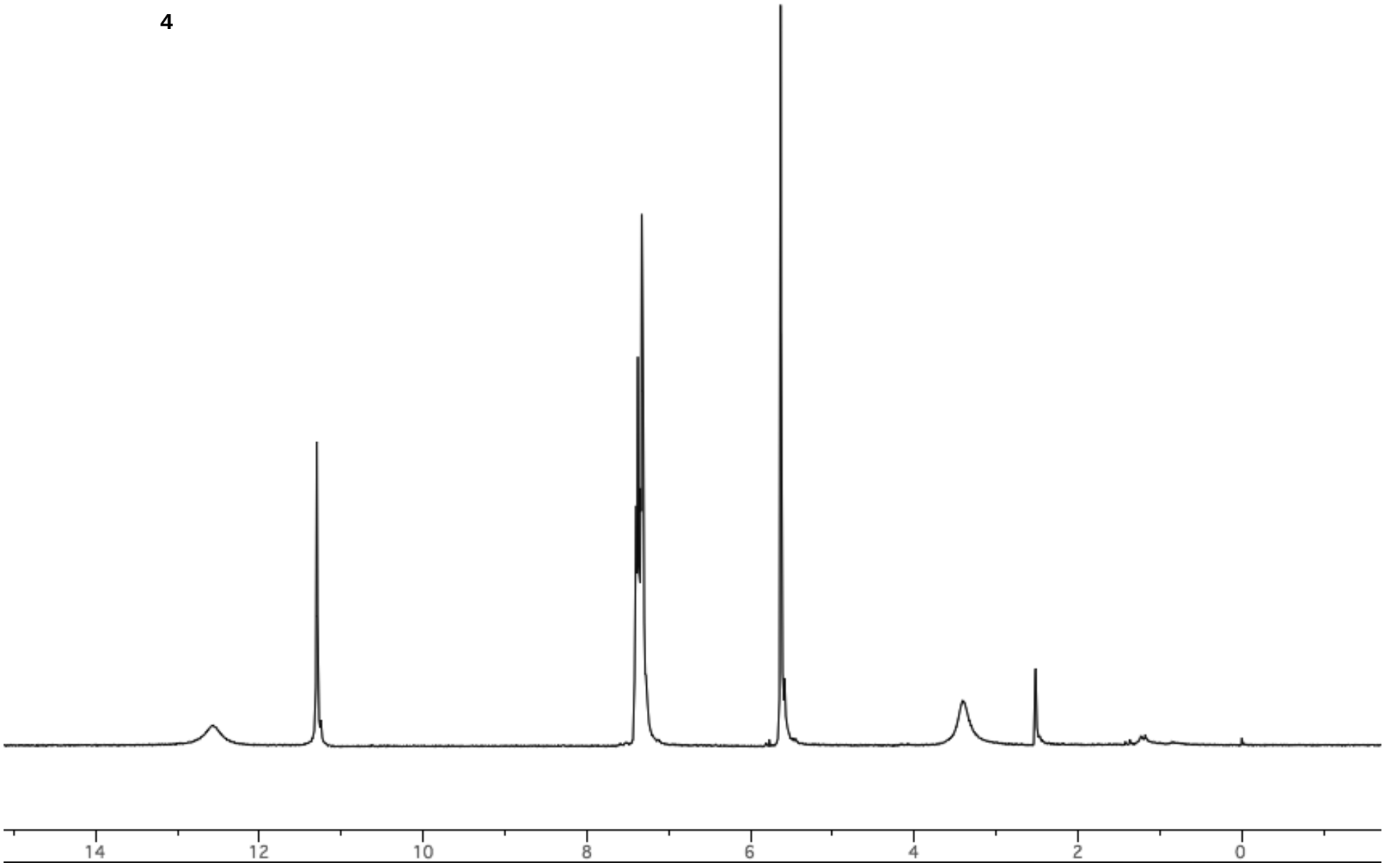


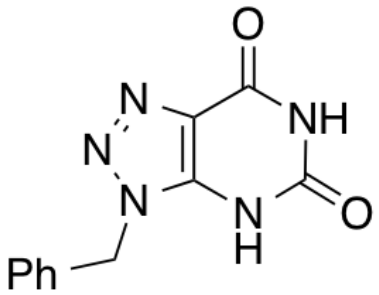

**3**






**4**



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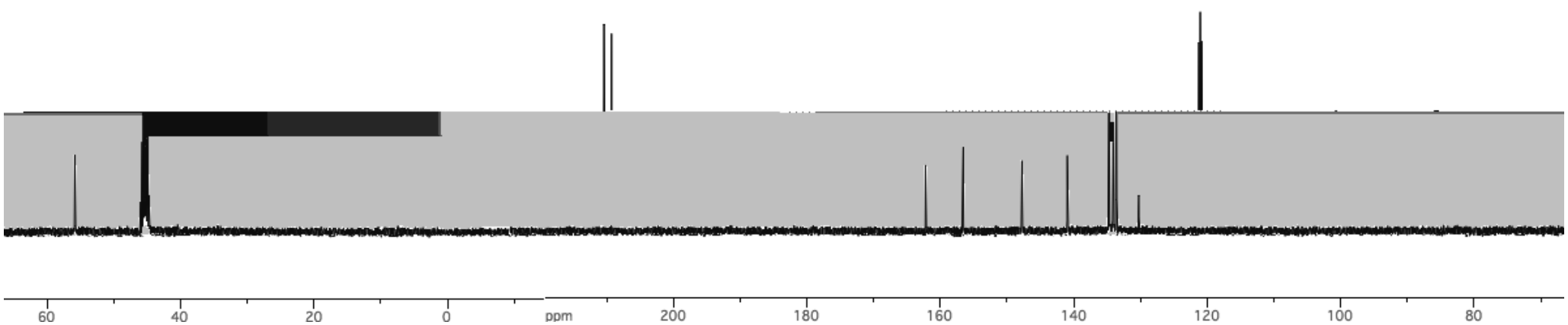

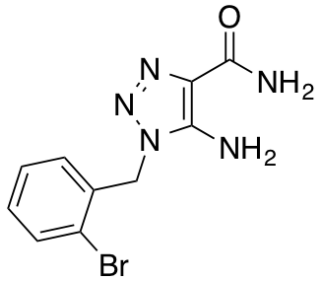


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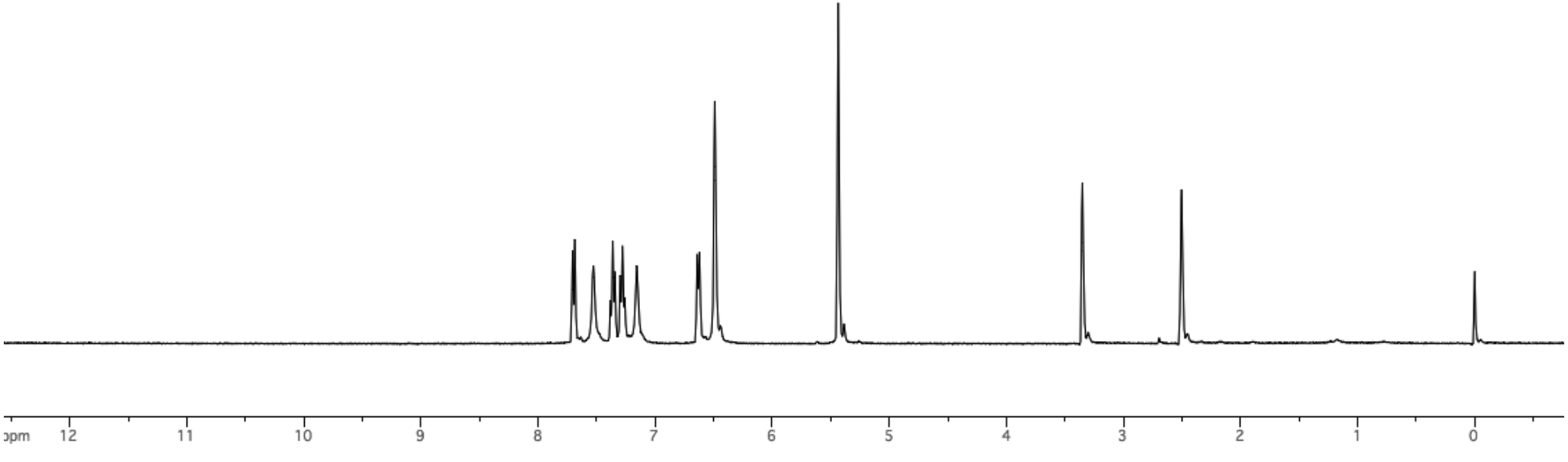

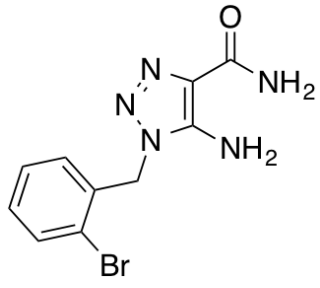


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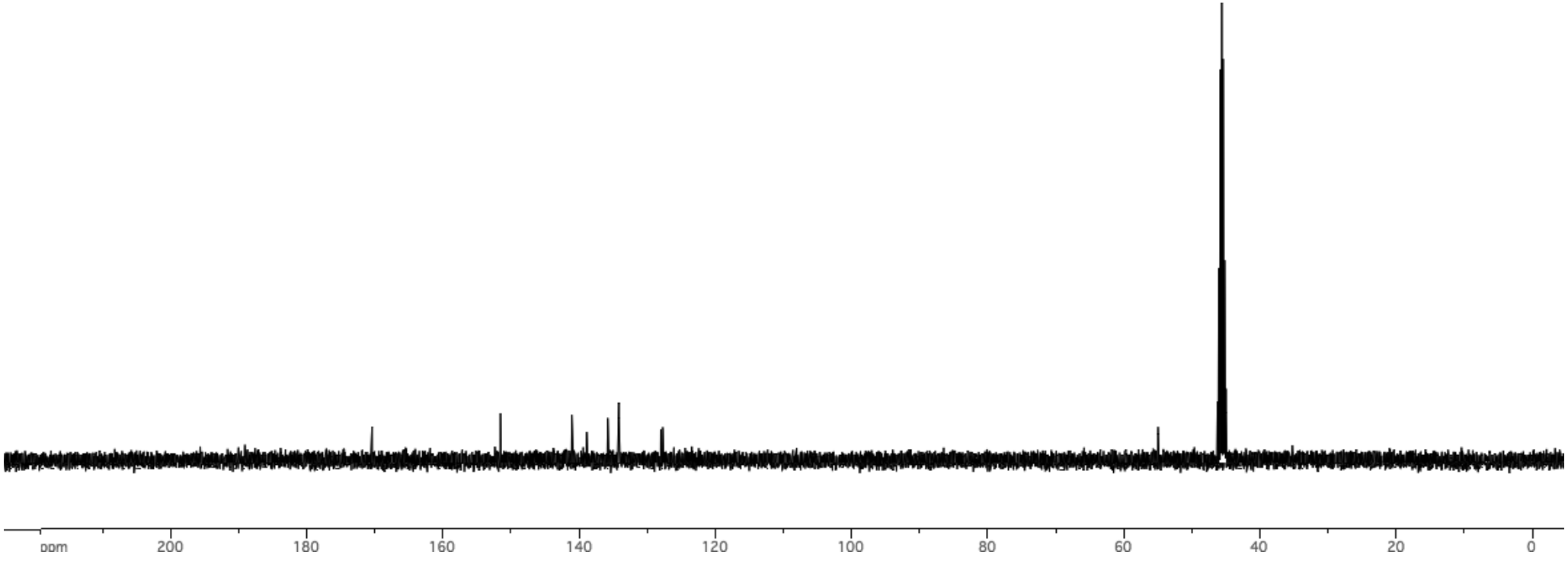

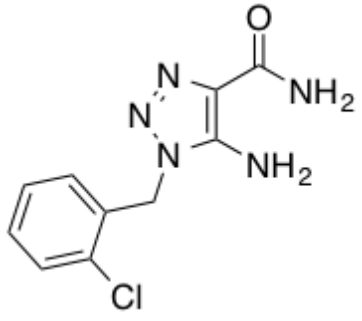


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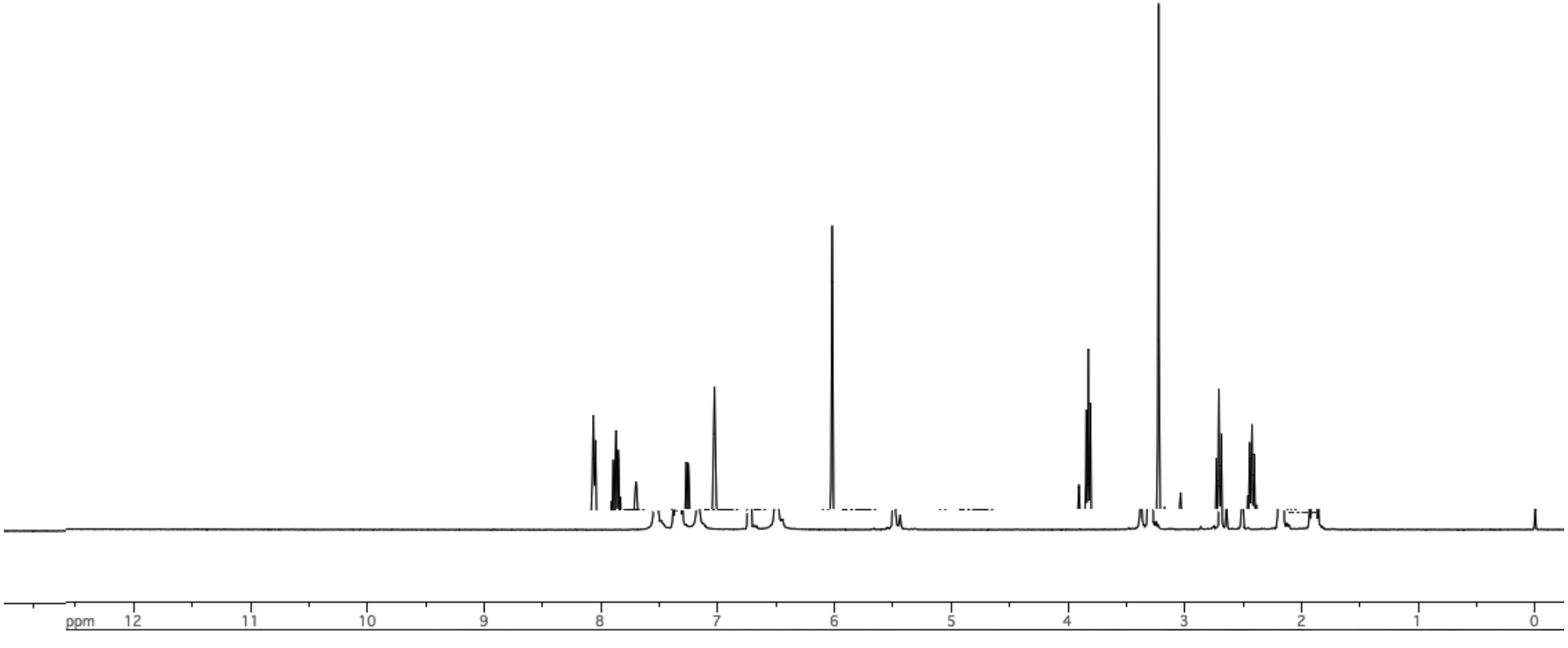

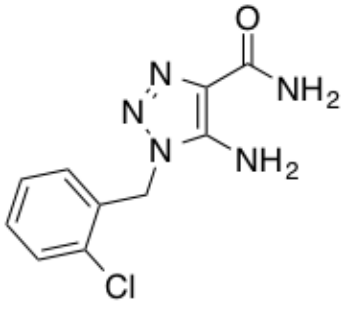


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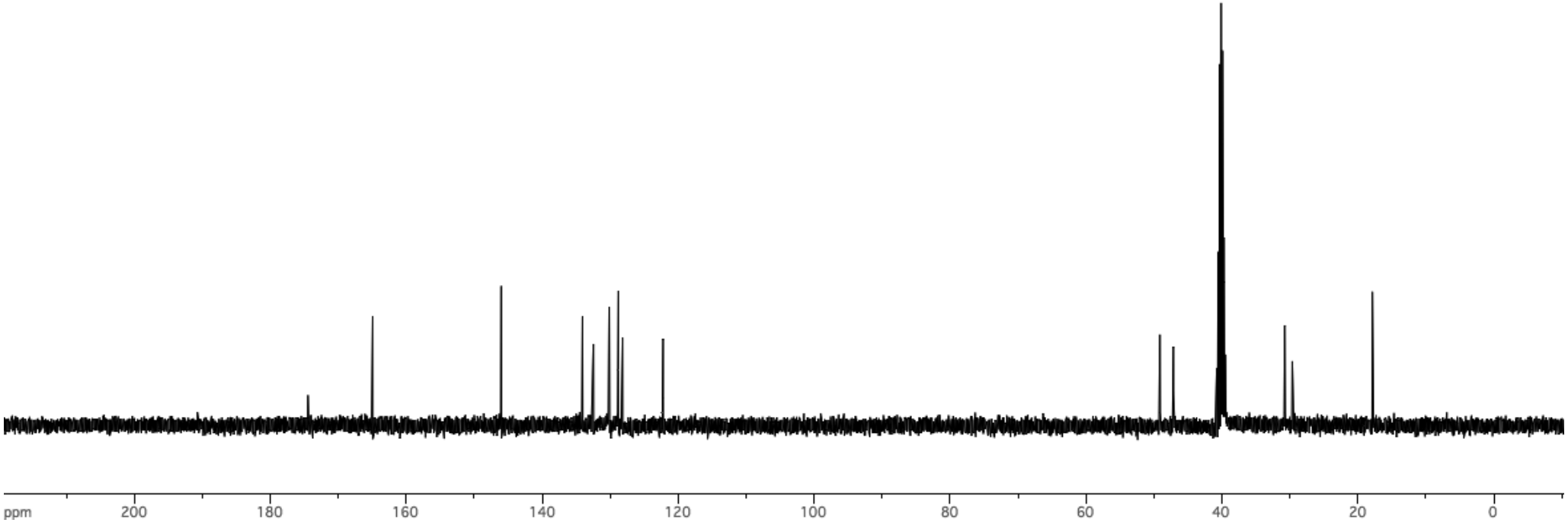

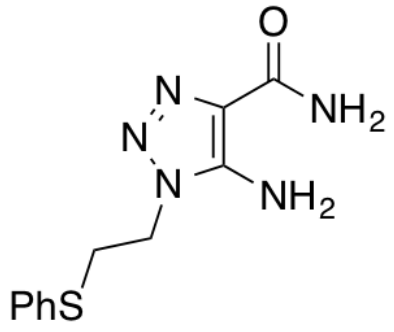


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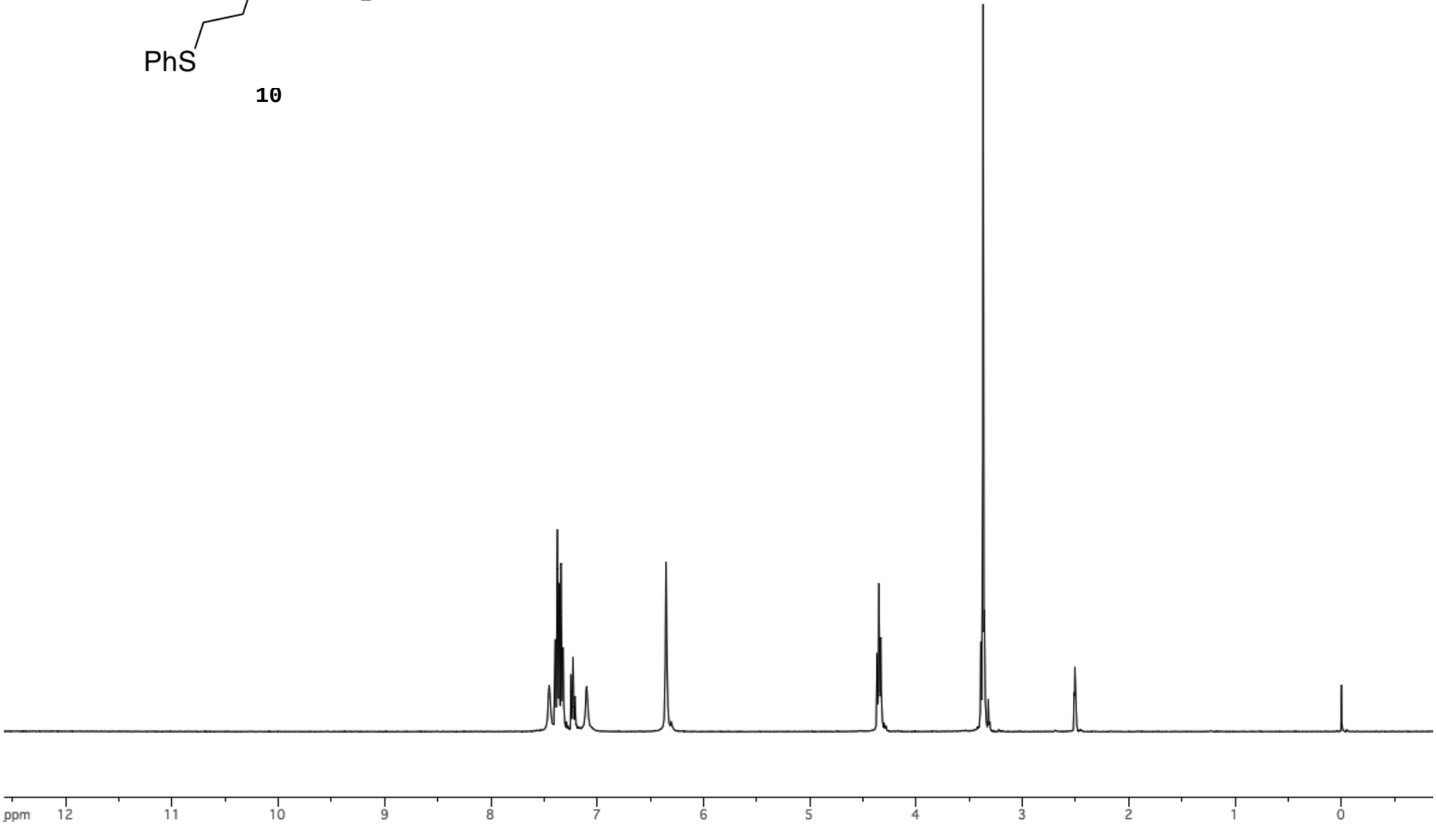

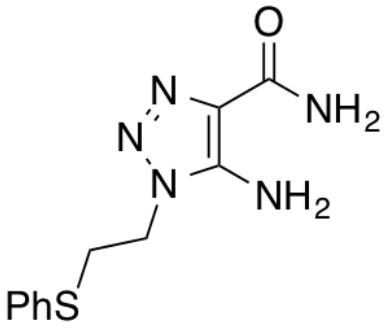


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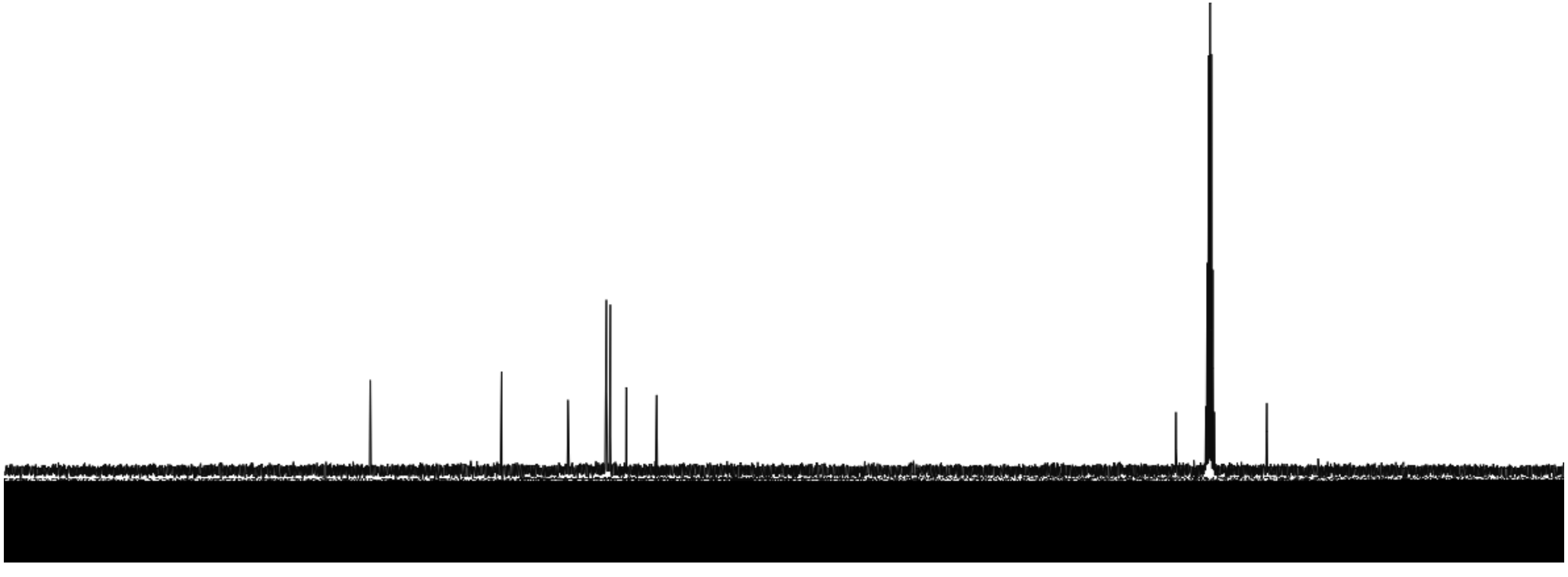

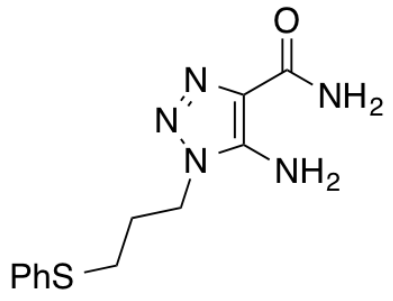


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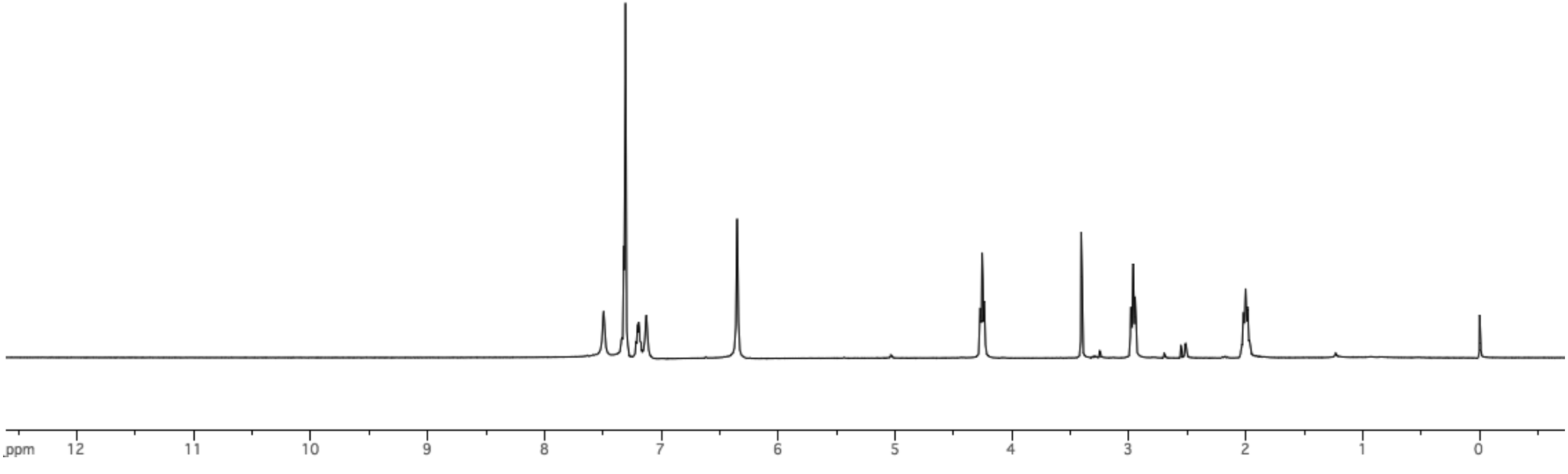

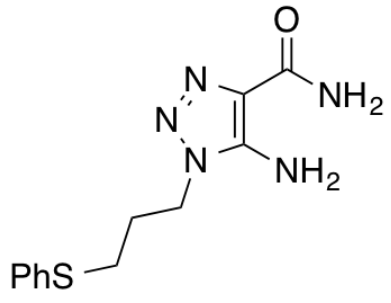


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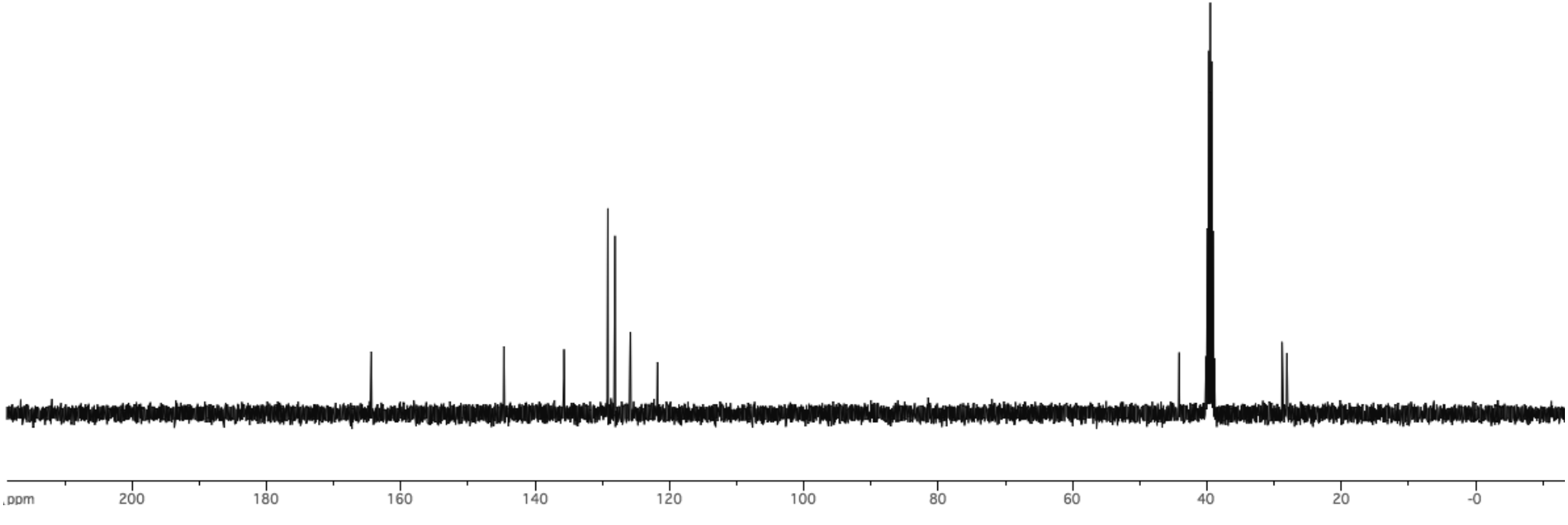

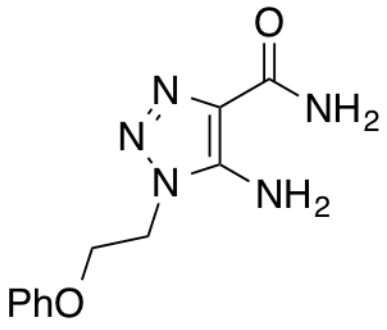


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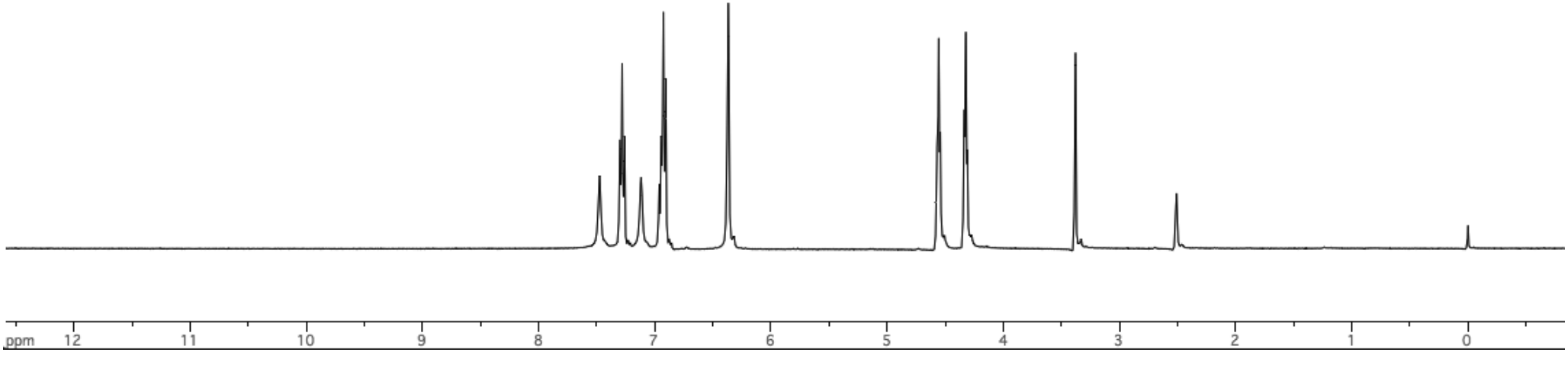

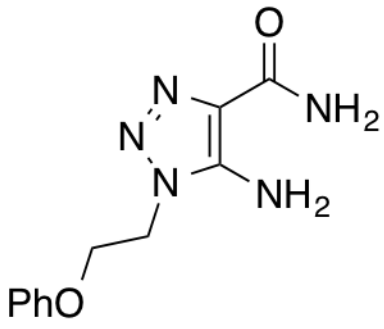


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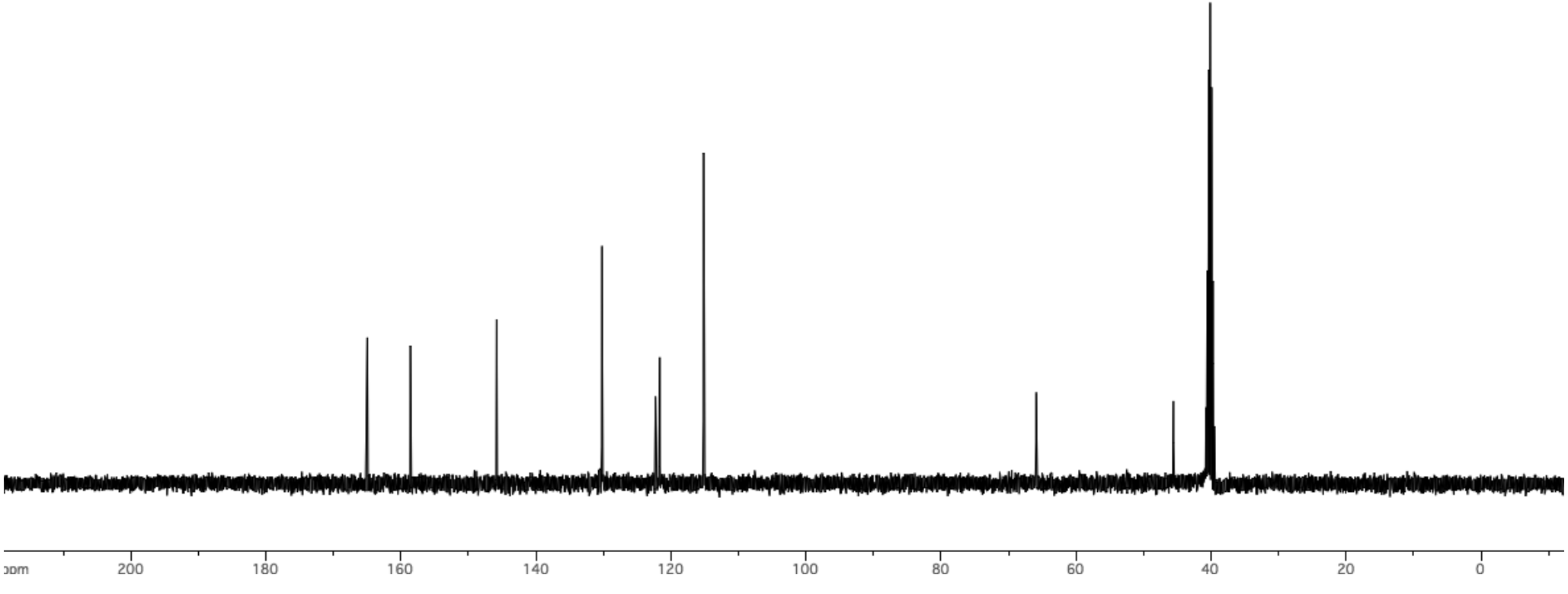

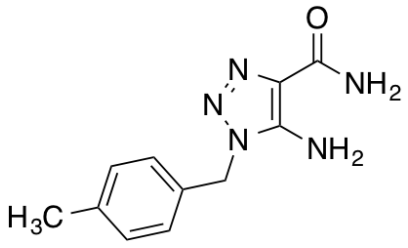


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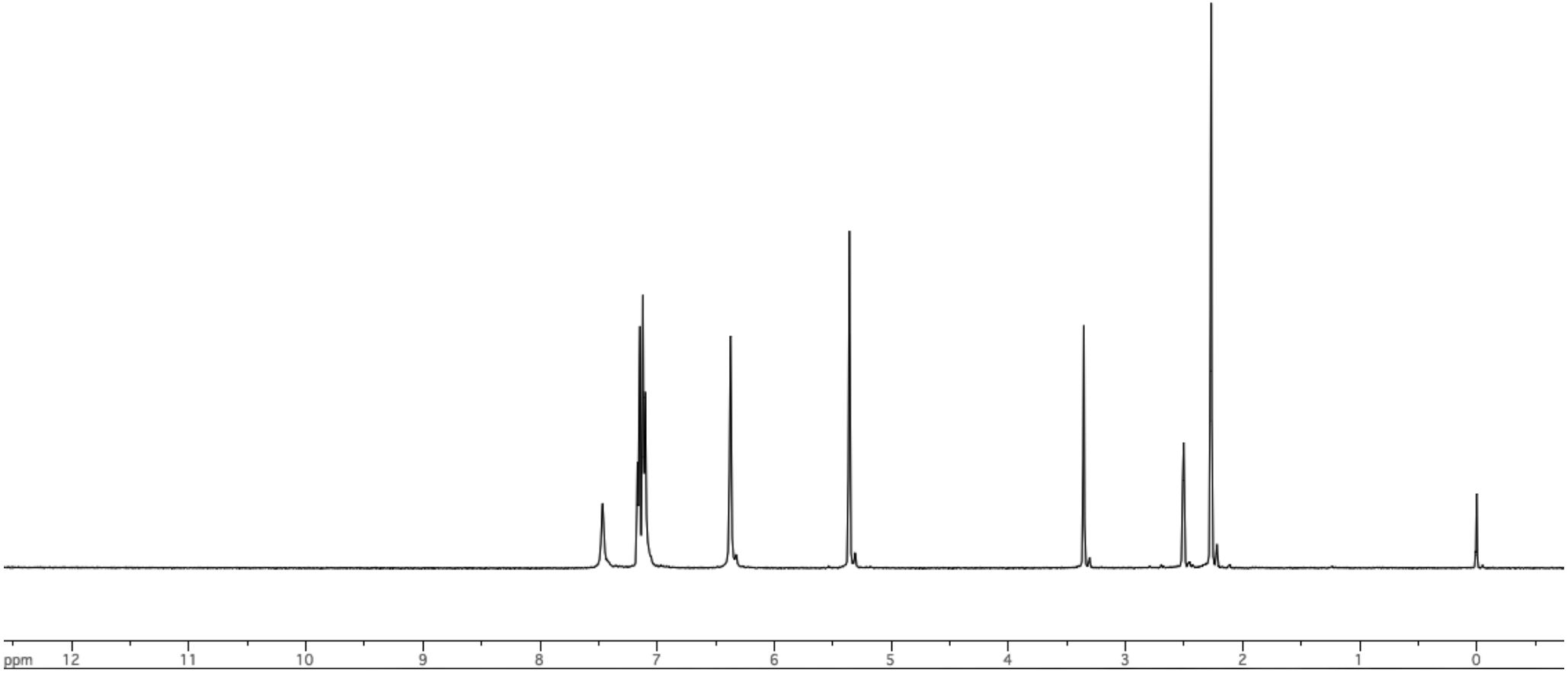

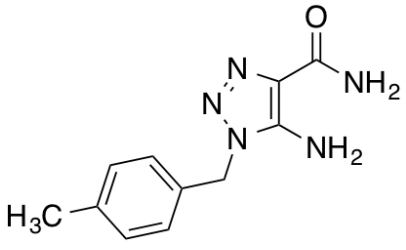


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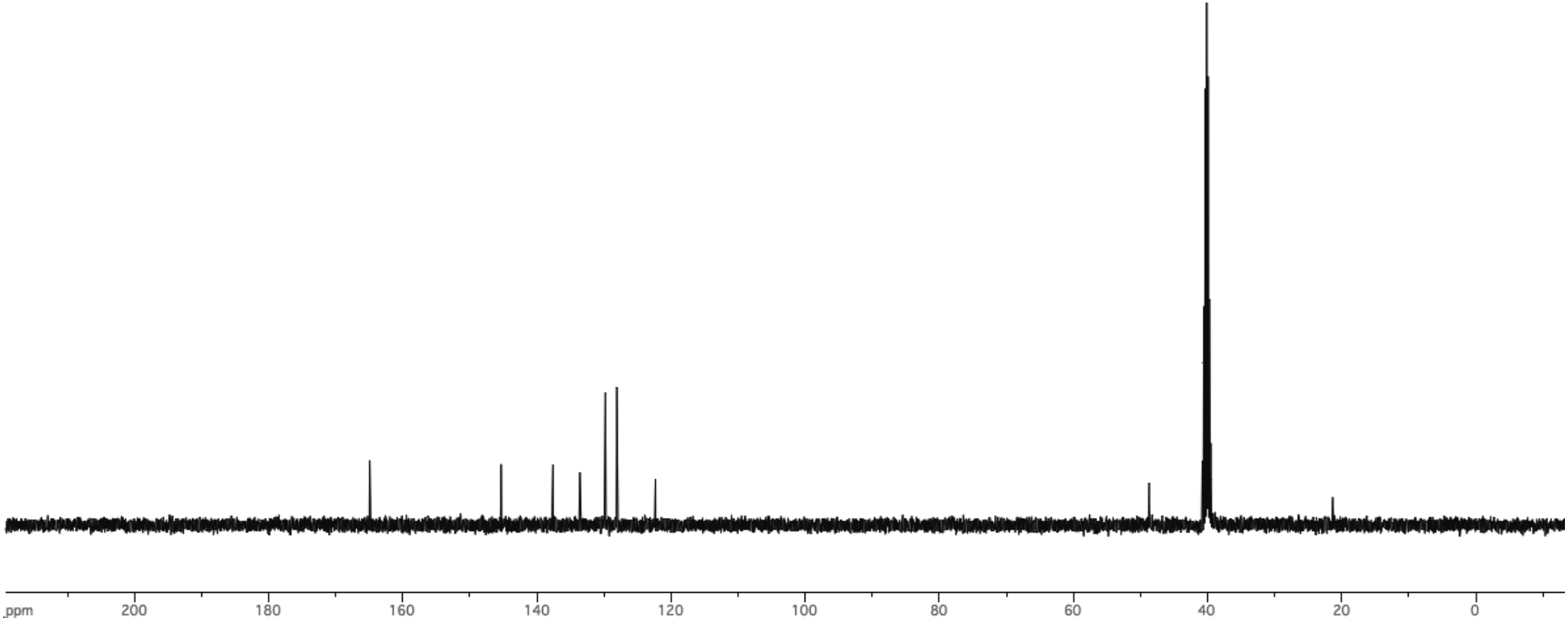

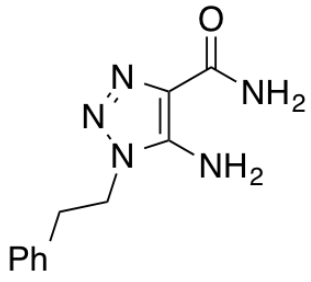


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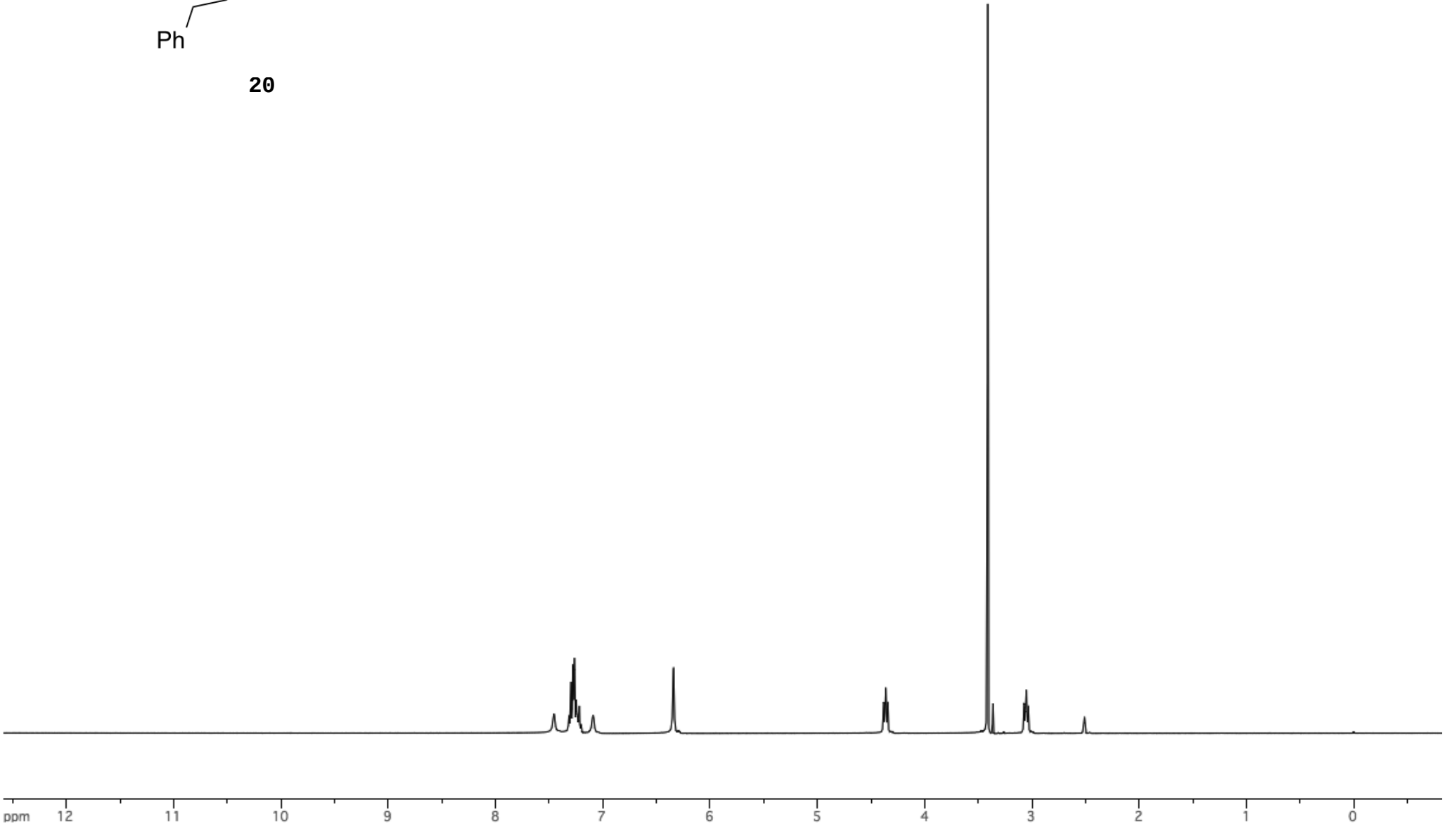

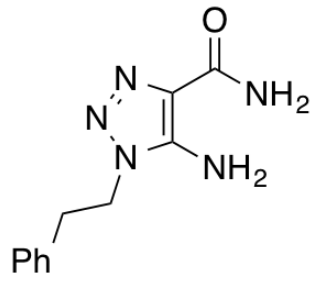


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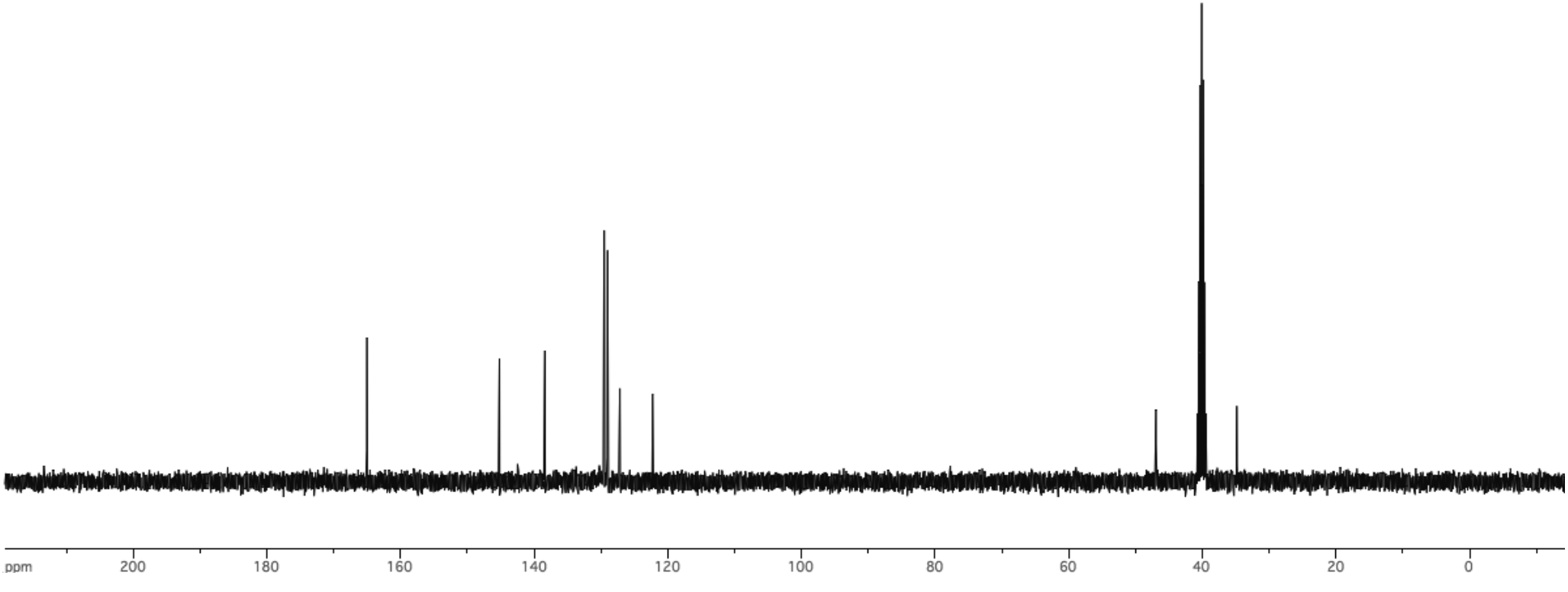

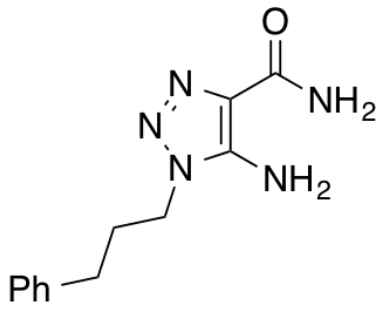


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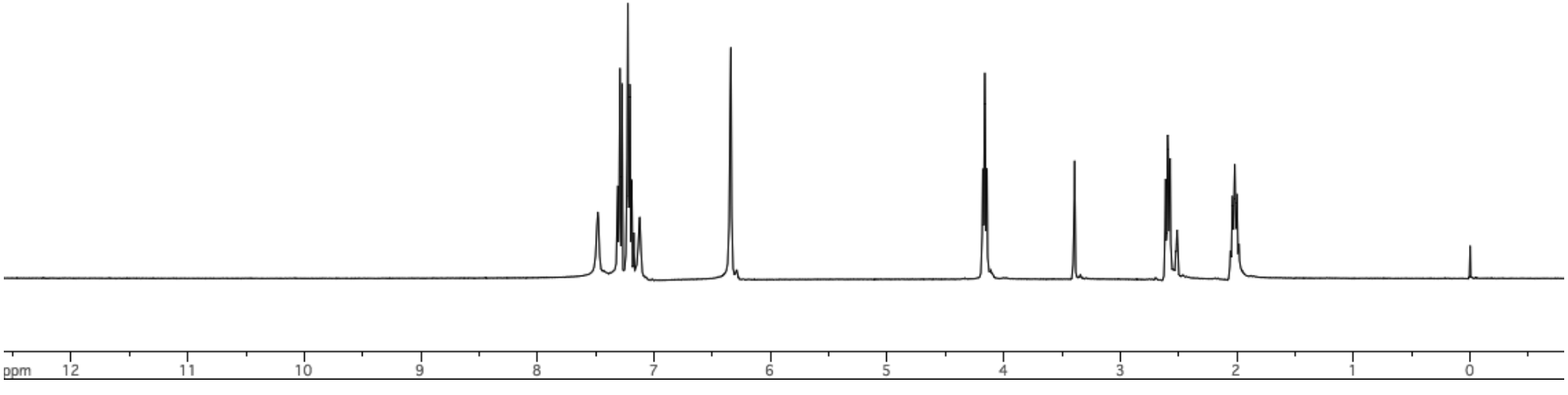

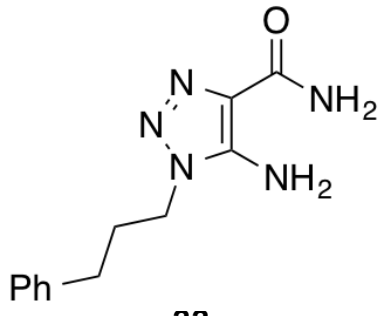


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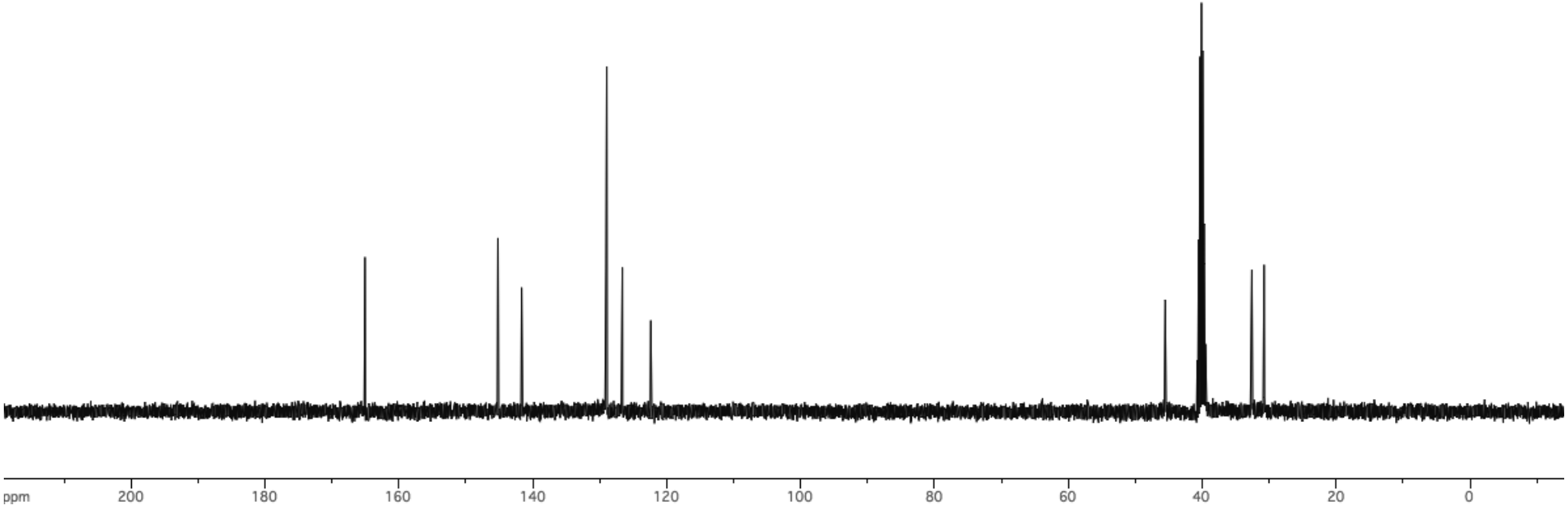

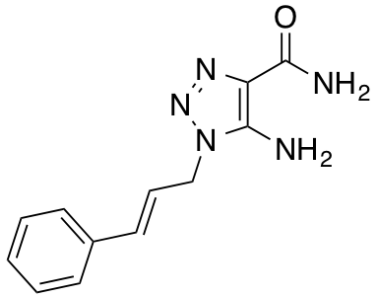


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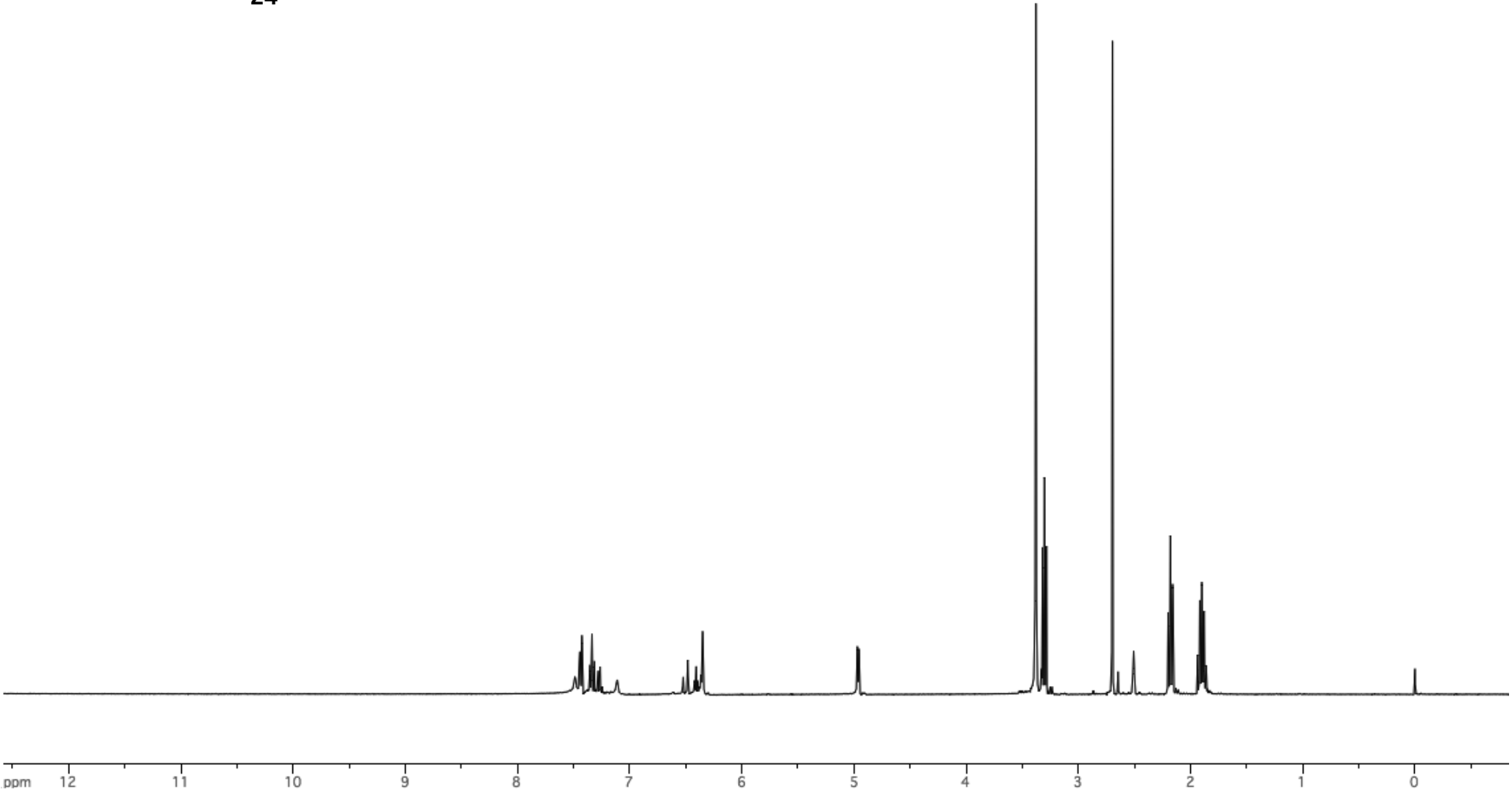

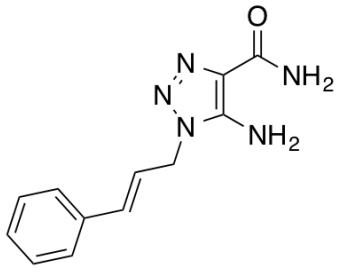


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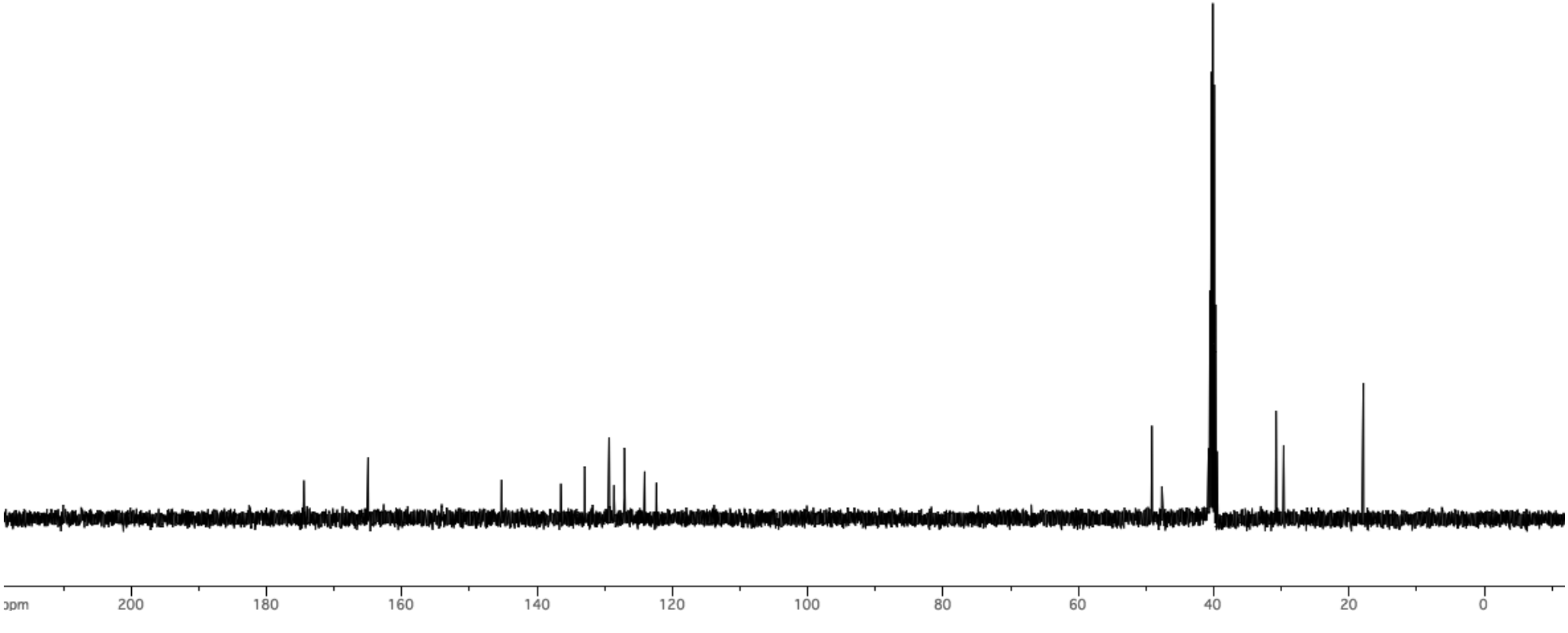

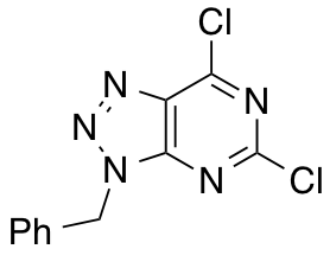


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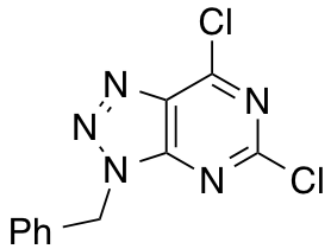


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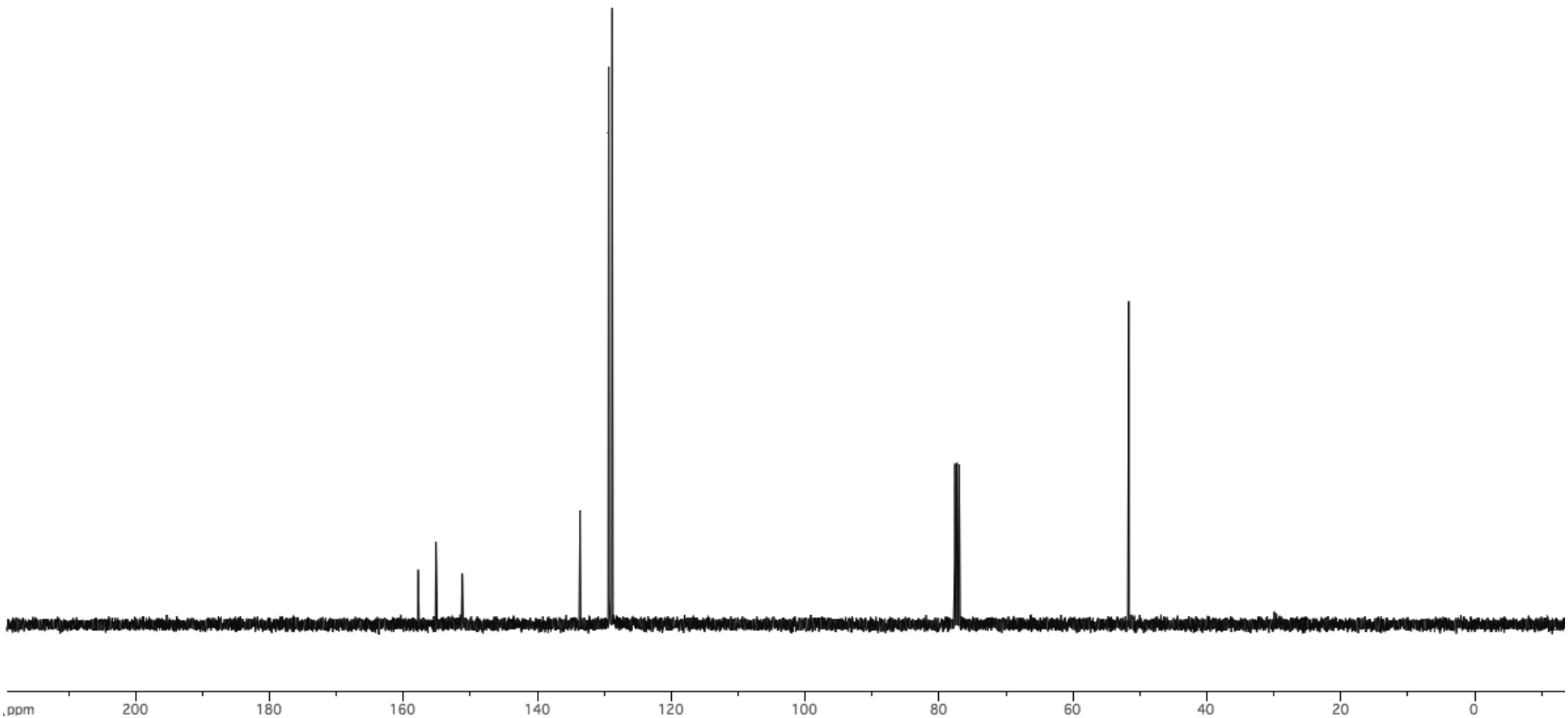

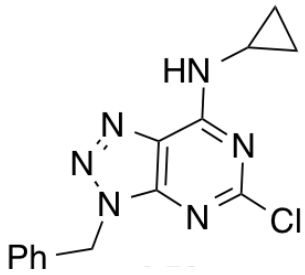


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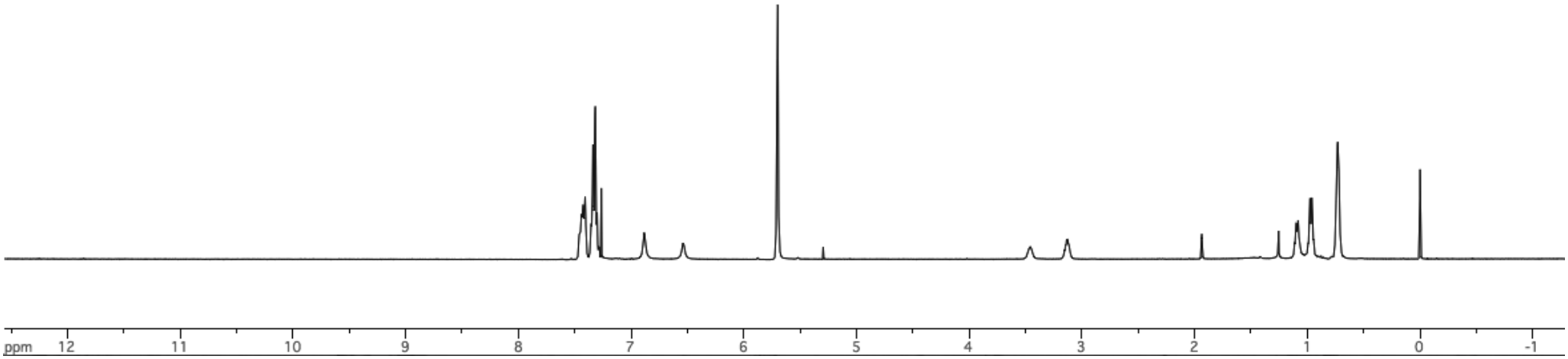

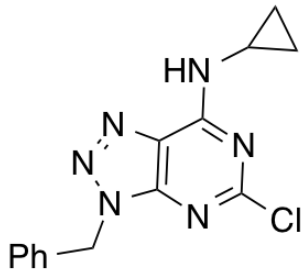


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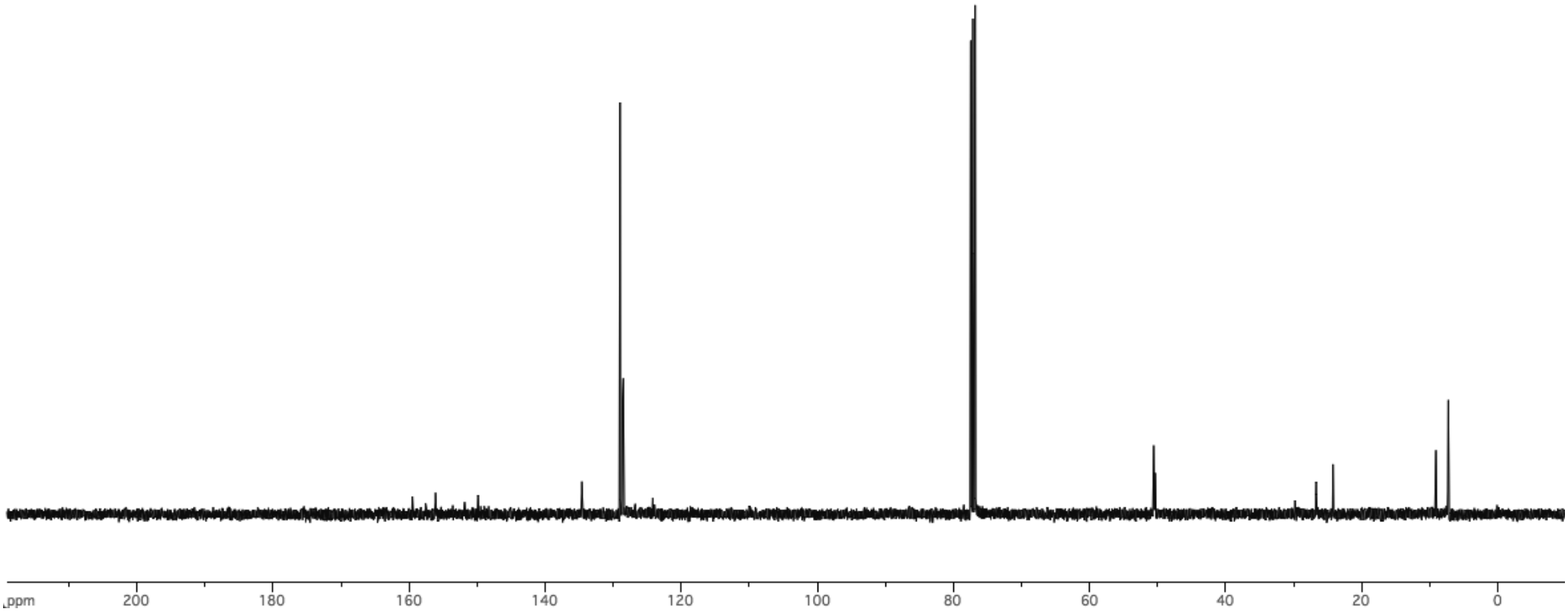

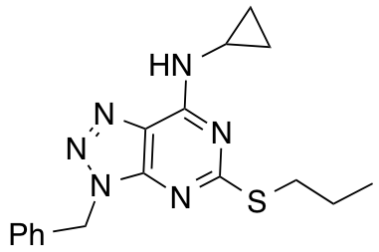


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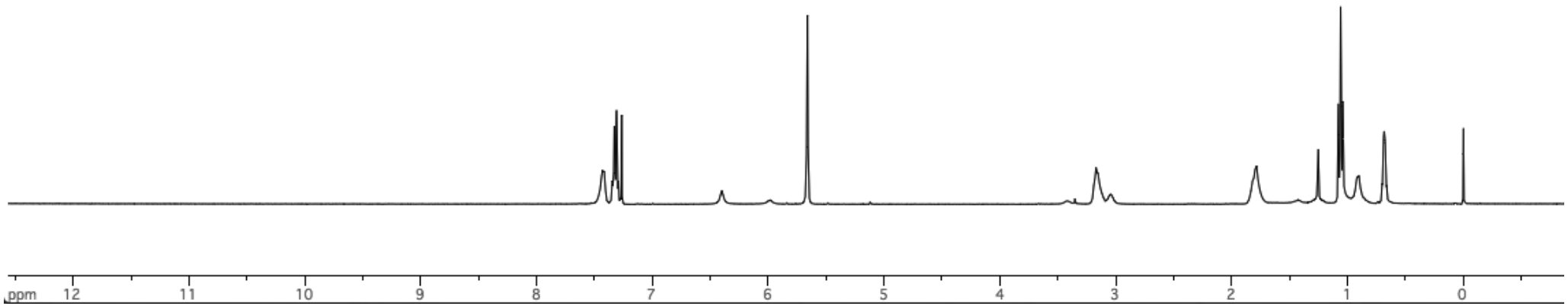

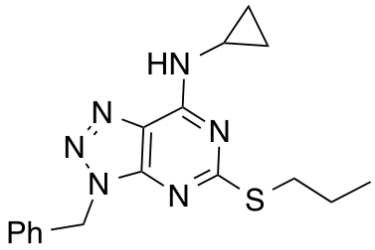
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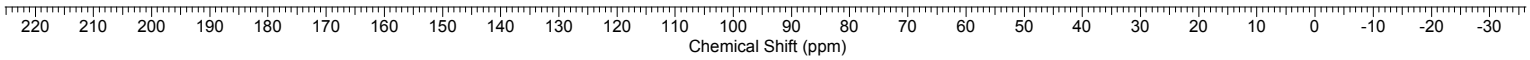
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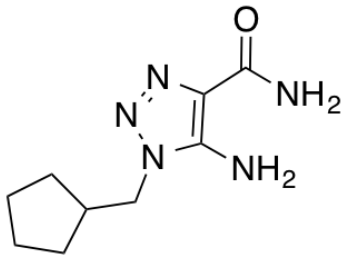


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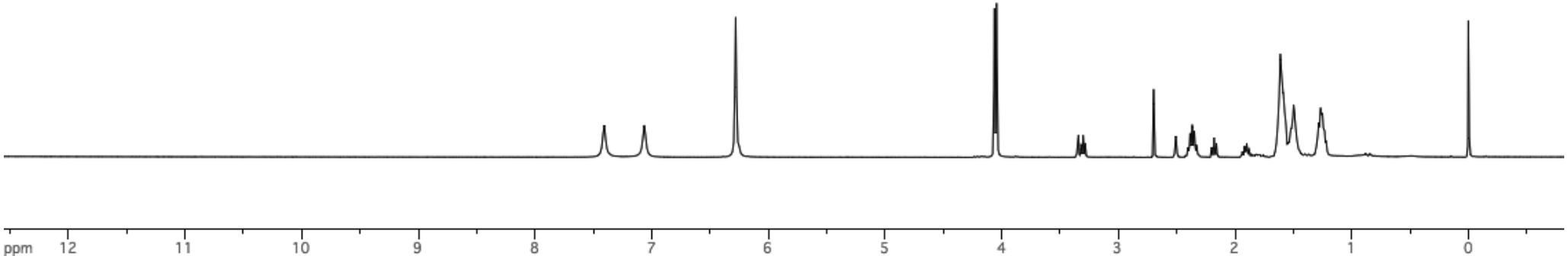

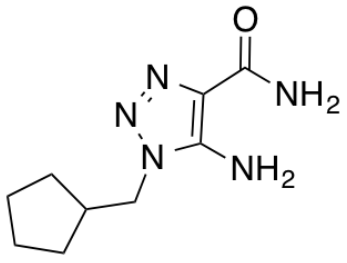


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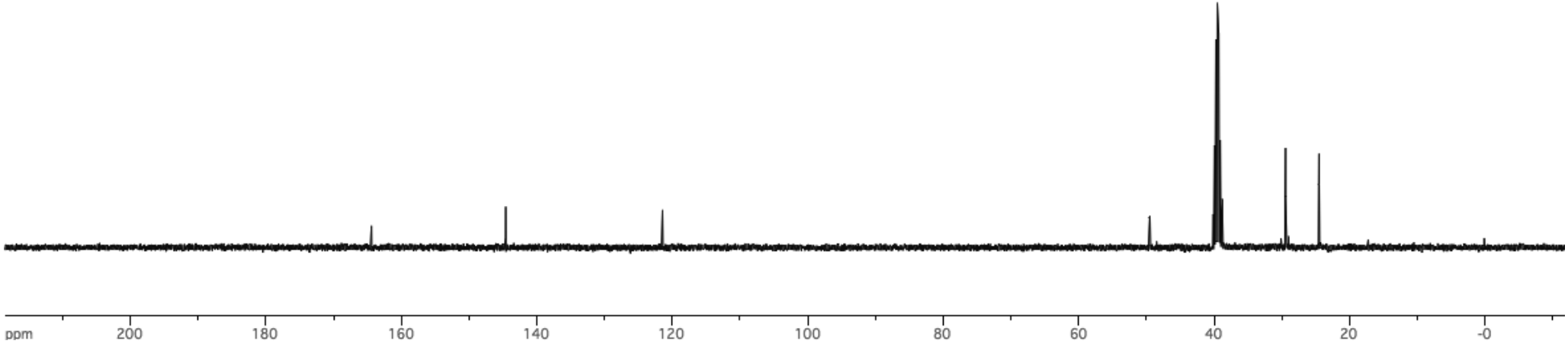

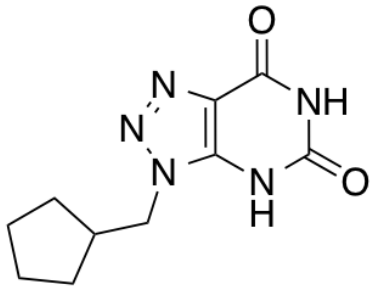


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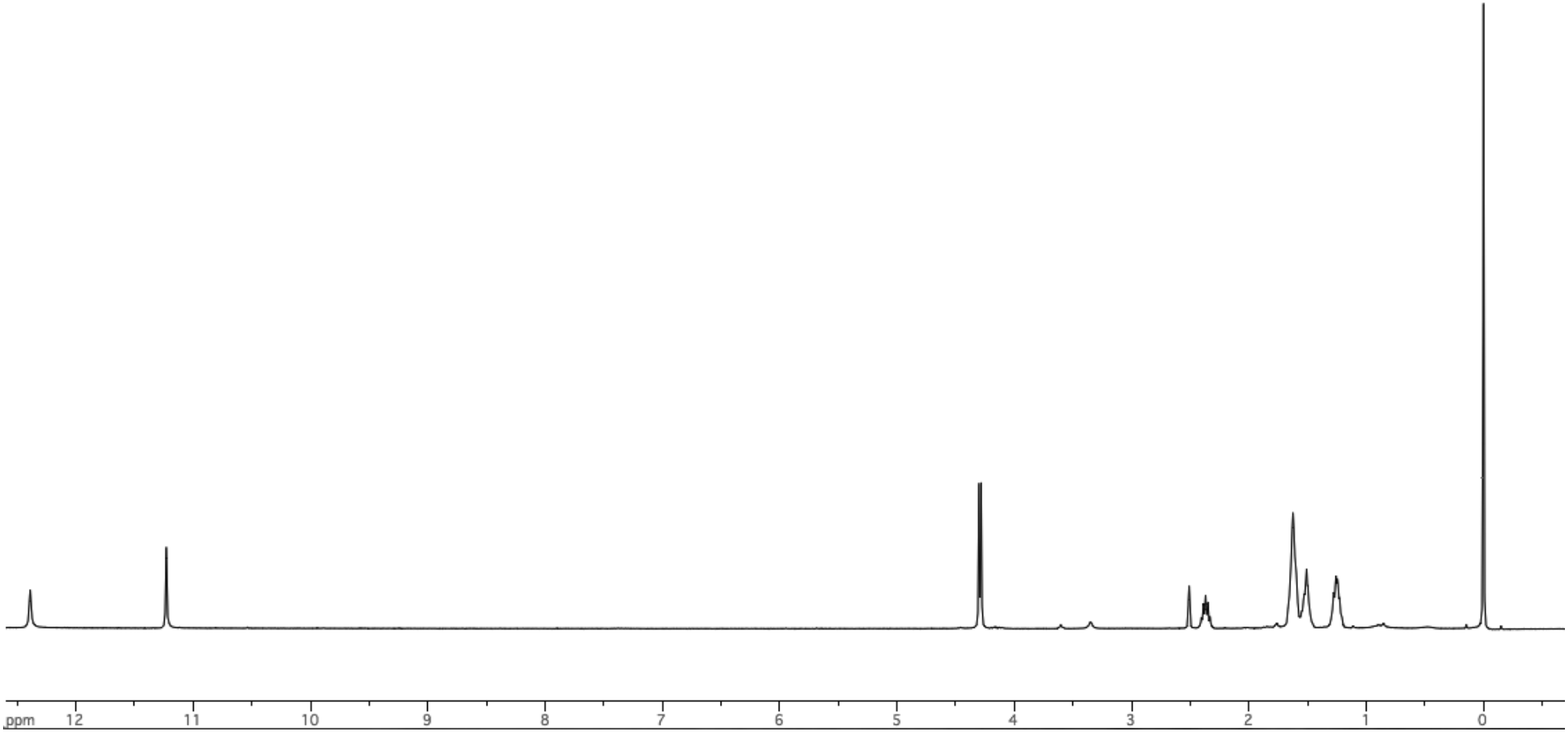

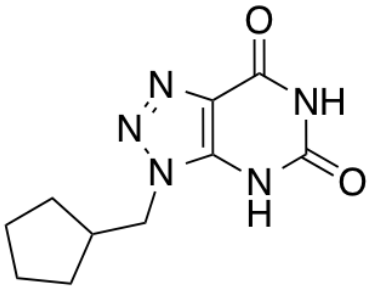
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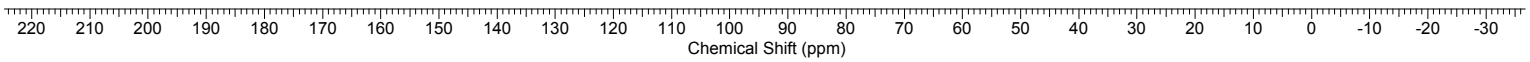
N
NH
N
H
O

**31**


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
Chemical Shift (ppm)