

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).

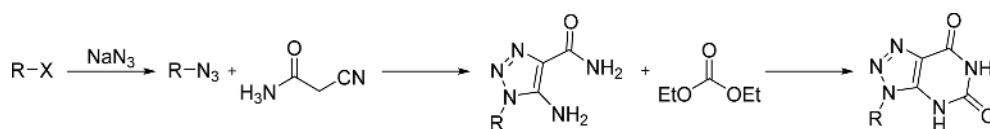
With this in hand, attention was then focused on the subsequent cycloaddition to form the 1,2,3-triazole **3** under flow conditions using benzyl azide **2** as model substrate (Scheme 2). Quantitative conversion was achieved following optimization of the flow conditions (Figure 3a and b), which evaluated 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**.

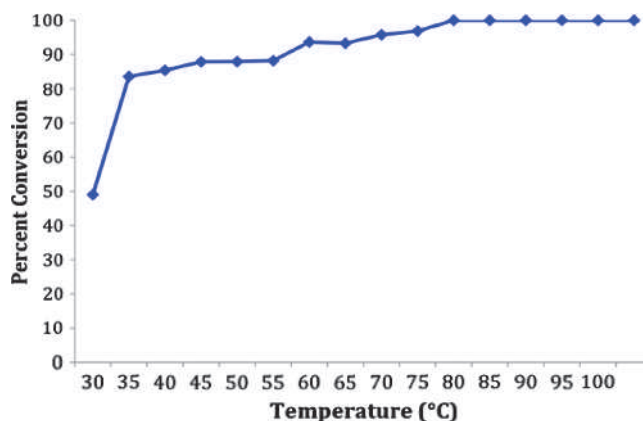


Figure 2. Temperature optimization for the conversion of benzyl bromide **1** to benzyl azide **2** (reactor volume=10 μ L; residence time=750 s (12.5 min))

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

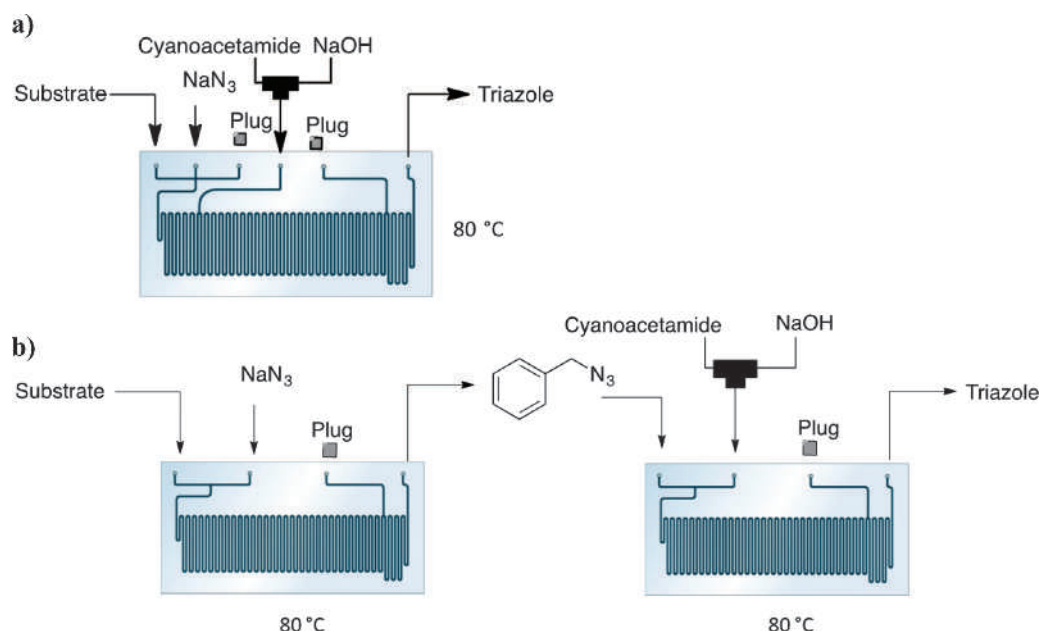
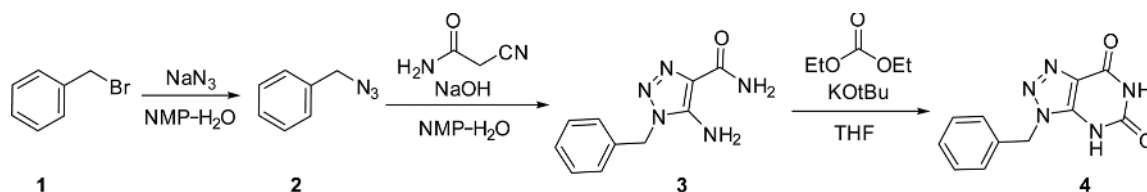


Figure 1. Diagram of continuous-flow reactor for triazole library synthesis: a) two-step, one-pot reaction, b) two-step sequential flow reaction

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 (^1H NMR) spectra were recorded at 400 MHz, and carbon nuclear magnetic

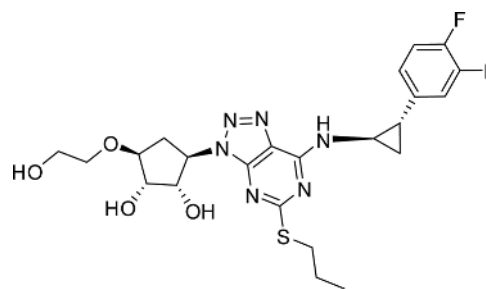


Figure 5. Brilinta[®] (ticagrelor) which contains a triazolopyrimidine core resonance (^{13}C NMR) spectra were recorded at 100 MHz on a Varian NMR instrument; spectra was prepared using ACD/Labs (Toronto, Canada). High-resolution mass spectroscopy was obtained on a Waters 70-VSE (EI) or a Waters Q-ToF Ultima mass spectrometer (electrospray ionization [ESI]) at the UIUC Mass Spectrometry Facility.

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.

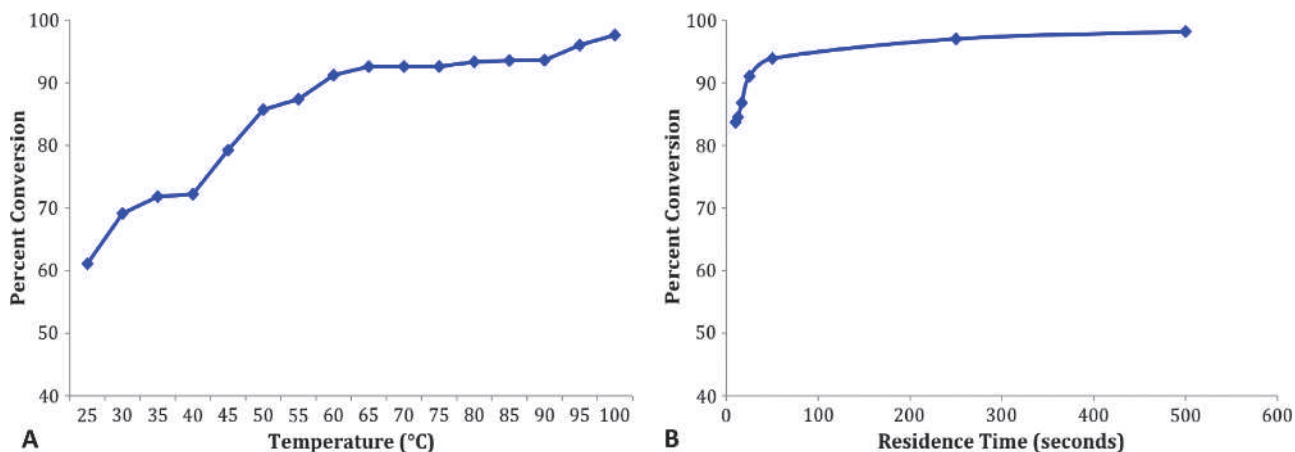


Figure 3. Optimization for the conversion of benzyl azide **2** to 1-benzyl-1,2,3-triazole **3** (A) Temperature optimization performed at a residence time=500 s (8.33 min) and (B) residence time optimization performed at $T=80^\circ\text{C}$

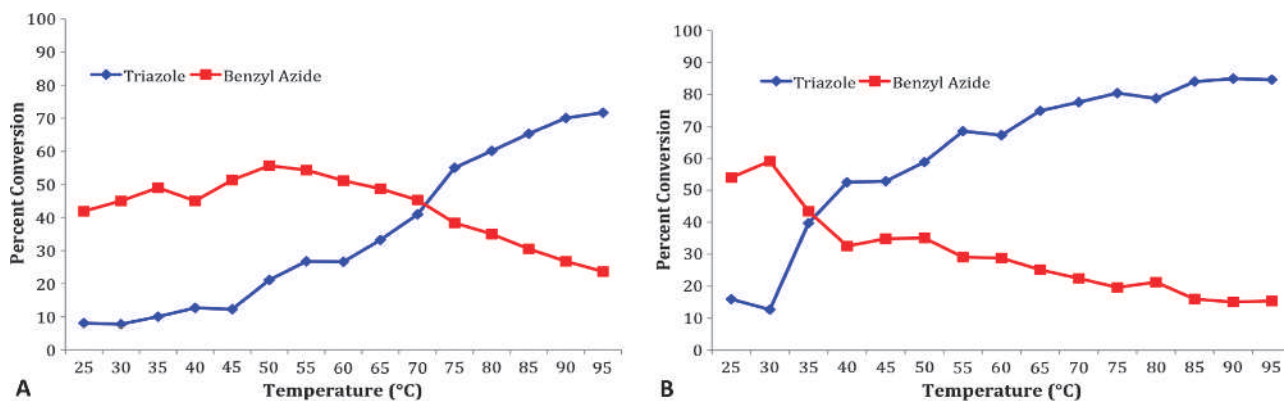
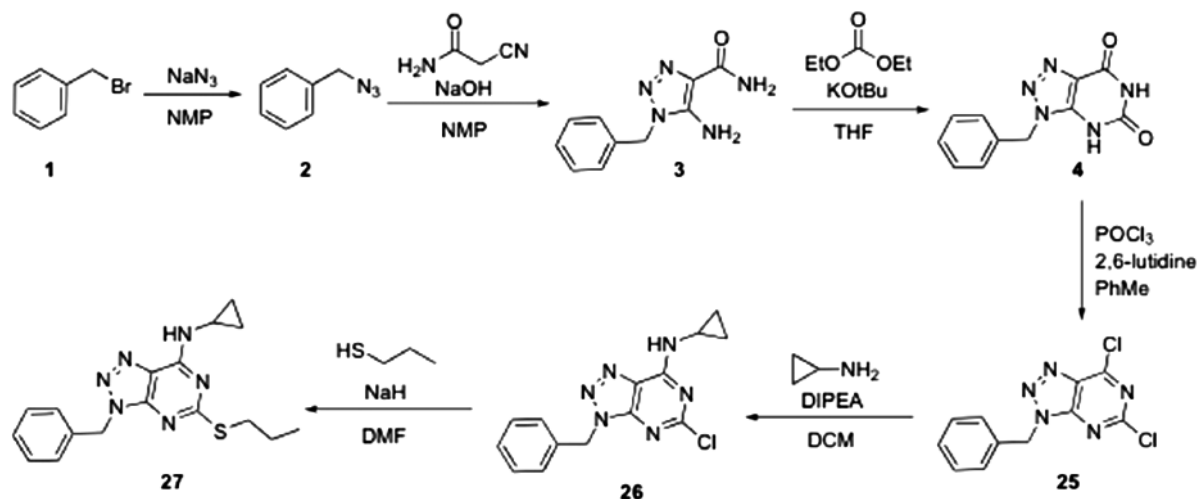


Figure 4. Optimization for the one-pot, two-step triazole formation under flow conditions (A) Residence time=45 s (0.75 min) and (B) residence time=225 s (3.75 min)

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 H₂O (15 mL). The organic layer was isolated and washed with 1 M sodium bicarbonate (10 mL) and H₂O (10 mL), dried over MgSO₄, 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 H₂O (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; ¹H 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); ¹³C 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* C₁₀H₁₁N₅O (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 NaN₃ 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 H₂O (500 μL) prior to analysis by HPLC–UV.

4.4. Continuous-Flow Synthesis of 5-Amino-1-Benzyl-1H-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 NaN₃ 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 H₂O (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 H₂O (450 μL) and dimethylsulfide (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 H₂O (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 H₂O (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

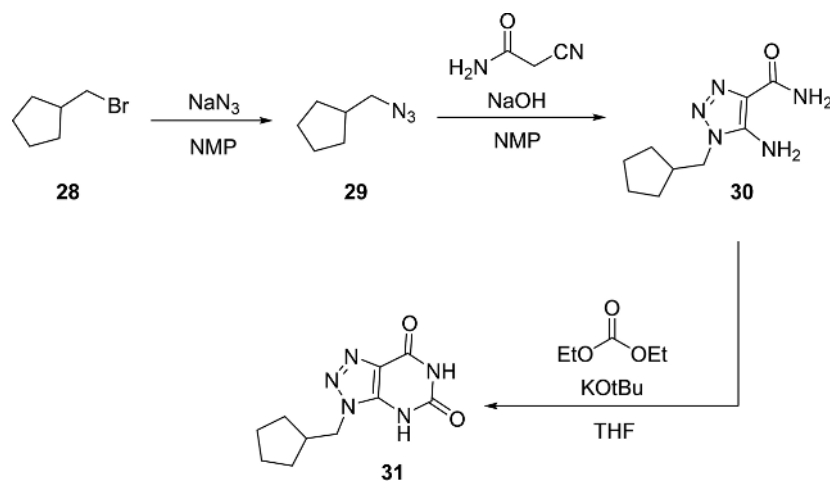


Table 2a. Continuous-flow synthesis of triazole analogs in (a) configuration using 1 eq. of azide and 3 eq. of cyanoacetamide and NaOH

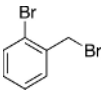
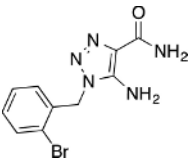
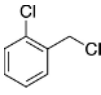
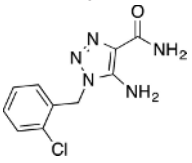
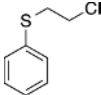
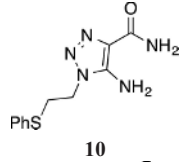
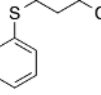
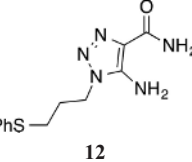
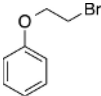
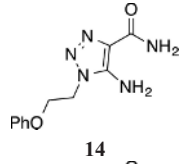
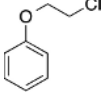
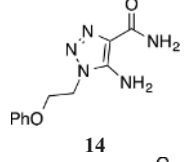
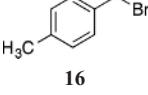
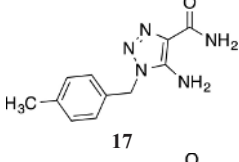
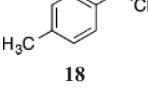
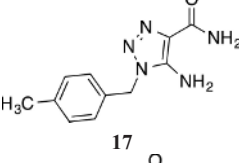
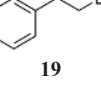
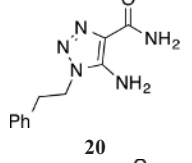
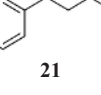
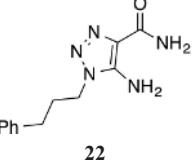
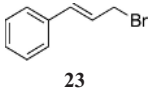
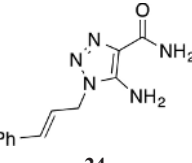


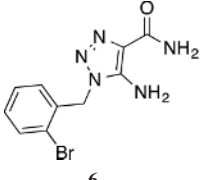

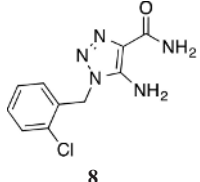

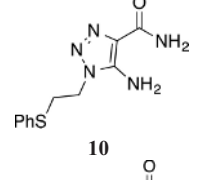

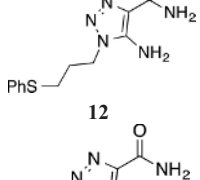

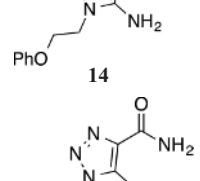

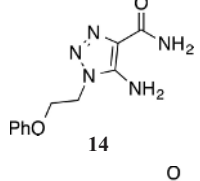
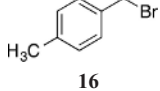
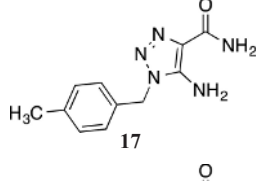
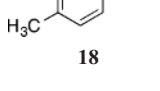
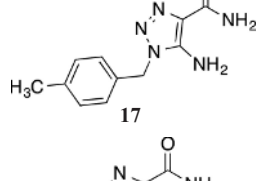
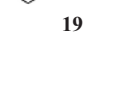
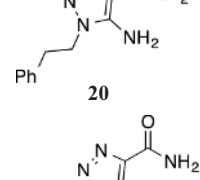
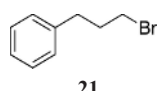
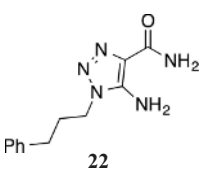
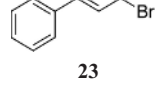
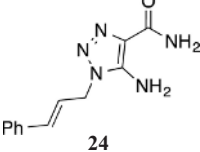
Entry	Substrate	Product	% Conversion to azide (% recovered SM)	% Conversion to Triazole
1	 5	 6	3.58	96.4
2	 7	 8	2.86 (2.4)	94.7
3	 9	 10	5.22 (94.78)	0
4	 11	 12	10.8 (88.2)	0
5	 13	 14	44.5 (32.8)	22.7
6	 15	 14	100	0
7	 16	 17	17.9	82.1
8	 18	 17	19.3 (7.0)	73.7
9	 19	 20	75.7	24.3
10	 21	 20	18.0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

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			100	94.9	98.8
2			0	94.9	97.3
3			16.7	32.9	46.8
4			81.1	66.5	75.4
5			83.9	74.8	72.8
6			100	74.8	72.8
7			100	83.3	85.7
8			0	83.3	85.7
9			100	78.9	83.8
10			100	45.6	70.7
11			100	21.4	30.7

microreactor (#3025), the following solutions were introduced: alkyl halide in *N*-methyl-2-pyrrolidinone (0.5 M), NaN₃ 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 H₂O (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 H₂O (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; ¹H 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); ¹³C 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* C₁₁H₉N₅O₂ (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-5H-[1,2,3]triazolo[4,5-d]pyrimidine-5,7(6H)-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 MgSO₄ 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; ¹H NMR (400 MHz, CDCl₃): δ 7.41–7.28 (m, 5H), 5.83 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 157.8, 155.2, 151.2, 133.6, 133.5, 129.4, 129.3, 128.8, 51.7; HRMS (EI), *m/z* C₁₁H₇Cl₂N₅, 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-3H-[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 CH₂Cl₂ (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 MgSO₄, and then concentrated in vacuo. The residue was purified by flash chromatography (SiO₂; 30 % EtOAc–Hex) to afford the desired compound as a yellow oil (0.102 g, 52 %). ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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* C₁₄H₁₃ClN₆, 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-3H-[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 MgSO₄, and concentrated in vacuo. The residue was purified by flash chromatography (SiO₂; 5 % EtOAc–CH₂Cl₂) to yield a yellow oil (0.091 g, 80 %). ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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* C₁₇H₂₀N₇S, calcd. 340.1470, obsd. 340.1468.

4.7.5. 5-Amino-1-(Cyclopentylmethyl)-1*H*-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; ¹H 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); ¹³C 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* C₉H₁₅N₅O (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; ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.4 (br s, 1H), 11.2 (s, 1H), 4.27 (d, *J*=7.2 Hz, 2H), 2.36 (m, 1H), 1.63 (m, 4H), 1.50 (m, 2H), 1.23 (m, 2H); ¹³C 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* C₁₀H₁₃N₅O₂ (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

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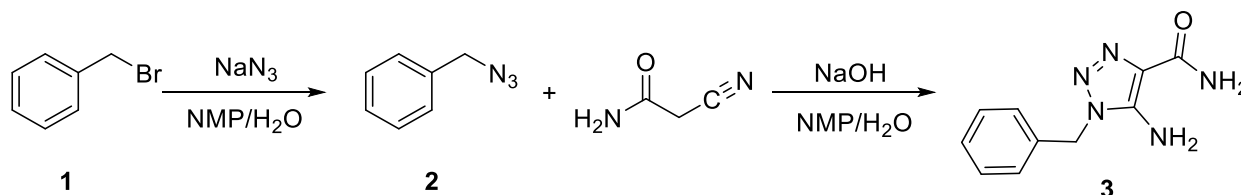
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Materials and Methods

All reagents and solvents were purchased from Fisher Scientific or Sigma Aldrich. THF was distilled from a sodium/benzophenone ketyl for the triazolopyrimidine synthesis. All continuous flow reactions were performed using the Chemtrix Labtrix[®] S1 system (Chemtrix BV, NL) utilizing a T-mixer glass microreactors, which are commercially available through Chemtrix BV. All reagents were dissolved, loaded into 1 mL glass gas-tight syringes (SGE) and dispensed through the microreactor into the autosampler loaded with HPLC vials. The samples were analyzed by HPLC-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. ¹H NMR spectra were recorded at 400 MHz, and ¹³C NMR were recorded at 100 MHz on a Varian NMR instrument, and 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 (ESI) at the UIUC Mass Spectrometry Facility.

Experimental Data

General procedure for batch synthesis of triazole library for spectroscopic analysis



To a solution of benzyl bromide (1.00 g, 5.85 mmol) in *N*-methyl-2-pyrrolidinone (10 mL) was added sodium azide (0.76 g, 11.7 mmol). The reaction was stirred at 80°C for 2 h. The reaction mixture was then cooled to 20°C and quenched with MTBE (10 mL) and H_2O (15 mL). The organic layer was isolated and washed with 1M sodium bicarbonate (10 mL) and H_2O (10 mL), dried over MgSO_4 , and concentrated *in vacuo*. To a solution of the crude azide in *N*-methyl-2-pyrrolidinone (15 mL) was added cyanoacetamide (0.74 g, 8.77 mmol) and sodium hydroxide (0.35 g, 8.77 mmol). The reaction was stirred at 80°C for 3 h. The reaction mixture was then cooled to RT, quenched with H_2O (30 mL) and allowed to stir O/N at RT to allow for complete precipitation. The solid was then filtered and dried *in vacuo* to afford the product.

5-amino-1-benzyl-1*H*-1,2,3-triazole-4-carboxamide (3): light yellow powder (0.314 g, 40%). mp= 236-237°C. ^1H 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 $\text{C}_{10}\text{H}_{11}\text{N}_5\text{O}$ (M)⁺ calcd. 217.10, obsd. 217.09637.

5-amino-1-(2-bromobenzyl)-1*H*-1,2,3-triazole-4-carboxamide (6): white powder (0.58 g, 59%). mp= 215-216°C. ^1H NMR (400 MHz, DMSO-d_6): δ 7.69 (d, $J=8$ Hz, 1H), 7.53 (br s, 1H), 7.36 (t, $J=7.6$ Hz, 1H), 7.28 (t, $J=7.2$ Hz, 1H), 7.16 (br s, 1H), 6.63 (d, $J=7.2$ Hz, 1H), 6.45 (s, 2H), 5.44 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.3, 145.4, 135.0, 132.8, 129.7, 128.1, 128.0, 121.9, 121.6, 48.9. HRMS (EI), m/z $\text{C}_{10}\text{H}_{10}\text{BrN}_5\text{O}$ (M)⁺ calcd. 295.01, obsd. 295.00667.

5-amino-1-(2-chlorobenzyl)-1*H*-1,2,3-triazole-4-carboxamide (8): light yellow powder (0.64 g, 49%). mp= 209-210°C. ^1H NMR (400 MHz, DMSO-d_6): δ 7.53 (m, 2H), 7.34 (m, 2H), 7.17 (br s, 1H), 6.73 (d, $J=7.2$ Hz, 1H), 6.50 (s, 2H), 5.49 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.1, 145.2, 133.2, 131.6, 129.3, 129.2, 128.0, 127.3, 121.4, 48.3 (NMP impurity at 174.5, 49.2, 30.8, 29.7, 17.9). HRMS (EI), m/z $\text{C}_{10}\text{H}_{10}\text{ClN}_5\text{O}$ (M)⁺ calcd. 251.06 obsd. 251.05782.

5-amino-1-(2-phenylthio)ethyl-1*H*-1,2,3-triazole-4-carboxamide (10): white powder (0.21 g, 20%). mp= 161-162°C. ^1H NMR (400 MHz, DMSO-d_6): δ 7.44 (br s, 1H), 7.36 (m, 4H), 7.23 (m, 1H), 7.09 (br s, 1H), 6.35 (br s, 2H), 4.35 (t, $J=7.6$ Hz, 2H), 3.37 (t, $J=7.6$ Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.5, 145.0, 135.1, 129.4, 128.9, 126.4, 122.0, 44.8, 31.3. HRMS (EI), m/z $\text{C}_{11}\text{H}_{13}\text{N}_5\text{OS}$ (M)⁺ calcd. 263.08, obsd. 263.08442.

5-amino-1-(3-(phenylthio)propyl)-1*H*-1,2,3-triazole-4-carboxamide (12): yellow oil (0.469 g, 47%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.47 (br s, 1H), 7.31 (m, 3H), 7.22 (m, 2H), 7.11 (br s, 1H), 6.34 (br s, 2H), 4.30 (t, *J*=6.8 Hz, 2H), 2.97 (t, *J*=7.2 Hz, 2H), 2.00 (t, *J*=7 Hz, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 164.5, 145.0, 135.1, 129.4, 128.9, 126.4, 122.0, 44.8, 28.9, 28.1. HRMS (EI), *m/z* C₁₂H₁₅N₅OS, calcd. 277.10, obsd. 277.0996

5-amino-1-(2-phenoxyethyl)-1*H*-1,2,3-triazole-4-carboxamide (14): white powder (0.32 g, 36%). mp= 188-189°C. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.45 (br s, 1H), 7.28 (m, 3H), 7.10 (br s, 1H), 6.93 (m, 2H), 6.35 (s, 2H), 4.55 (s, 2H), 4.32 (s, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 164.6, 158.2, 145.4, 129.8, 121.9, 121.2, 114.7, 65.5, 45.2. (EI), *m/z* C₁₁H₁₃N₅O₂, calcd. 247.11, obsd. 247.10722.

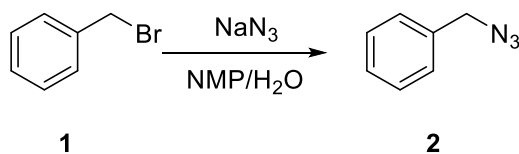
5-amino-1-(4-methylbenzyl)-1*H*-1,2,3-triazole-4-carboxamide (17): white powder (0.59 g, 49%). mp= 222-223°C. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.49 (br s, 1H), 7.14 (m, 5H), 6.40 (s, 2H), 5.37 (s, 2H), 2.27 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 164.8, 145.2, 137.4, 133.4, 129.6, 127.9, 122.1, 48.5, 21.1. HRMS (EI), *m/z* C₁₁H₁₃N₅O (M)⁺ calcd. 231.11, obsd. 231.11174.

5-amino-1-phenethyl-1*H*-1,2,3-triazole-4-carboxamide (20): white powder (0.20 g, 26%). mp= 201-202°C. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.42 (br s, 1H), 7.26 (m, 5H), 7.07 (br s, 1H), 6.33 (s, 2H), 4.35 (t, *J*=7.2 Hz, 2H), 3.04 (t, *J*=7.2 Hz, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 164.6, 144.8, 138.0, 129.1, 128.6, 126.8, 121.9, 46.6, 34.5. HRMS (EI), *m/z* C₁₁H₁₃N₅O (M)⁺ calcd. 231.11, obsd. 231.11182.

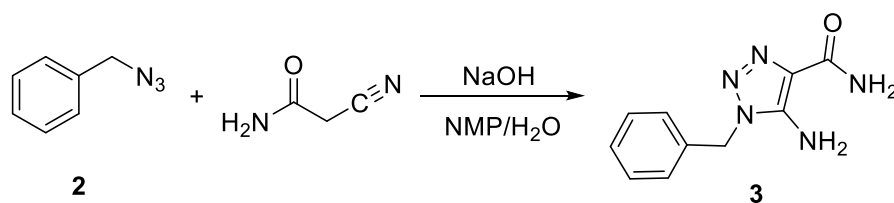
5-amino-1-(3-phenylpropyl)-1*H*-1,2,3-triazole-4-carboxamide (22): white powder (0.69g, 59%). mp= 196-197°C. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.44 (br s, 1H), 7.25 (m, 5H), 7.08 (br s, 1H), 6.31 (s, 2H), 4.14 (t, *J*=7.2Hz, 2H), 2.58 (t, *J*=7.2 Hz, 2H), 2.00 (m, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 164.4, 144.6, 141.0, 128.4, 128.3, 126.0, 121.7, 44.9, 32.0, 30.1. HRMS (EI), *m/z* C₁₂H₁₅N₅O, (M)⁺ calcd. 245.13, obsd. 245.12776.

5-amino-1-cinnamyl-1*H*-1,2,3-triazole-4-carboxamide (24): tan solid (0.69 g, 59%). mp= 235-236°C. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.47 (br s, 1H), 7.24-7.45 (m, 5H), 7.10 (br s, 1H), 6.45 (m, 2H), 6.36 (s, 2H), 4.58 (d, *J*= 6 Hz, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 164.3, 144.6, 135.9, 132.3, 128.7, 128.0, 126.5, 123.5, 121.7, 47.0 (NMP impurity at 174.5, 49.2, 30.8, 29.7, 17.9). HRMS (EI), *m/z* C₁₂H₃N₅O, calcd. 243.11, obsd. 243.11231.

General procedure for the continuous flow synthesis of triazole library compounds



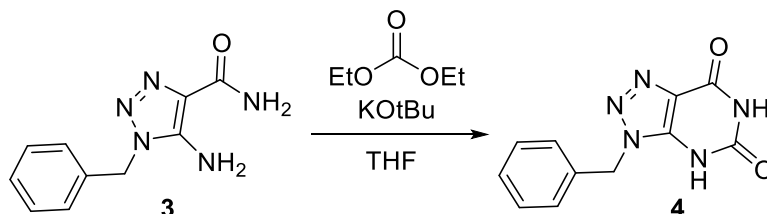
Benzyl azide (2): To a Labtrix[®] T-mixer chip (#3023), the following solutions were introduced: benzyl bromide in *N*-methyl-2-pyrrolidinone (0.5 M) and NaN₃ in aqueous *N*-methyl-2-pyrrolidinone (20% v/v, 0.5 M). The reaction was performed at temperatures ranging from 25–100°C and flow rates of 0.5 – 25 μL/min per syringe. Reaction mixtures were collected in 50 μL aliquots, repeated 3x, and diluted with H₂O (500 μL) prior to analysis by HPLC-UV.



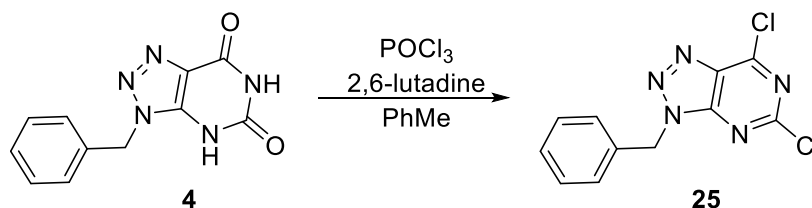
5-amino-1-benzyl-1H-1,2,3-triazole-4-carboxamide (3): Using the setup in Figure 4a, to the Labtrix[®] T-mixer chip (#3025), the following solutions were introduced: benzyl bromide in *N*-methyl-2-pyrrolidinone (0.5 M), NaN₃ in aqueous *N*-methyl-2-pyrrolidinone (20% v/v, 0.5 M), cyanoacetamide in aqueous *N*-methyl-2-pyrrolidinone (20% v/v, 0.75 M), and sodium hydroxide in H₂O (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 3x, and diluted with H₂O (450 μL) and DMSO (300 μL) prior to analysis by HPLC-UV.

5-amino-1-benzyl-1H-1,2,3-triazole-4-carboxamide (3): Using the setup in Figure 4b, to the Labtrix[®] T-mixer chip (#3023), the following solutions were introduced: cyanoacetamide in aqueous NMP (20% v/v, 0.75 M), sodium hydroxide in H₂O (0.75 M), and benzyl azide in aqueous NMP (20% v/v, 0.5 M). The reaction was performed at temperatures ranging from 25–100°C and flow rates of 0.5 – 25 μL/min per syringe. Reaction mixtures were collected in 50 μL aliquots, repeated 3x, and diluted with H₂O (450 μL) and DMSO (300 μL) prior to analysis by HPLC-UV.

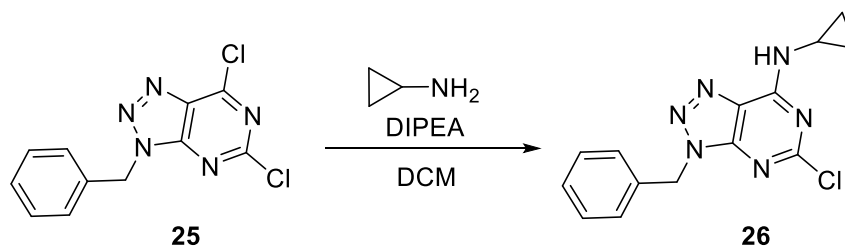
Synthesis of Brilinta[®] analogues



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-(benzyl)-1H-1,2,3-triazole-4-carboxamide (**3**) (0.200g, 0.92 mmol) and diethyl carbonate (0.326g, 2.76 mmol) in dry THF (15 mL) was added potassium tert-butoxide (0.310g, 2.76 mmol). 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 1N HCl to pH=6, and the precipitate was filtered, washed with water, and then air dried to afford the product as a beige solid (0.191g, 85% yield). mp= 281-282°C. ¹H 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). ¹³C 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 C₁₁H₉N₅O₂ (M)⁺ calcd. 245.08, obsd. 245.0834.

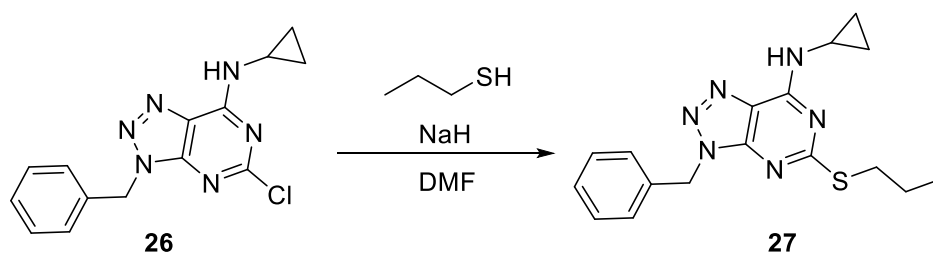


3-benzyl-5,7-dichloro-3H-[1,2,3]triazolo[4,5-d]pyrimidine (25): To a cooled (-20°C) solution of (**4**) (1.00 g, 4.11 mmol) and phosphoryl chloride (2.52 g, 16.4 mmol) in toluene (50 mL) was added dropwise 2,6-lutidine (0.441 g, 4.11 mmol). The reaction was refluxed for 5 h. After concentration *in vacuo*, the residue was dissolved in water (50 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO₂; 5% MeOH/CH₂Cl₂) to afford the desired compound as a yellow solid (0.069 g, 6.40%) mp= 83-84°C. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.41-7.28 (m, 5H), 5.83 (s, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 157.8, 155.2, 151.2, 133.6, 133.5, 129.4, 129.3, 128.8, 51.7. HRMS (EI), m/z C₁₁H₇Cl₂N₅, calcd. 279.01, obsd. 279.00786.

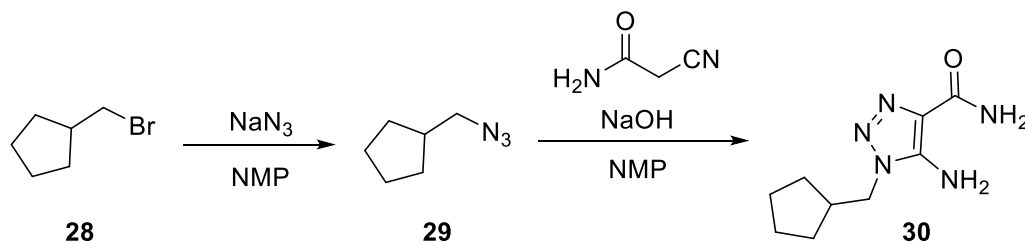


3-benzyl-5-chloro-N-cyclopropyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-amine (26): To a stirring solution of (**25**) (0.185 g, 0.66 mmol) and cyclopropylamine (0.034 g, 0.60 mmol) in dry

CH₂Cl (10 mL) was added N,N-diisopropylethylamine (0.077 g, 0.60 mmol). The reaction was stirred at room temperature for 5 hours, at which time an additional 0.9 eq of the cyclopropylamine and N,N-diisopropylethylamine was added. The reaction was stirred for another 16 hours and the additional 0.9 equivalent addition was repeated. The reaction mixture was stirred for an additional 2 hours (total reaction time = 24 h), and then the reaction mixture was washed with water, dried with MgSO₄, then concentrated *in vacuo*. The residue was purified by flash chromatography (SiO₂; 30% EtOAc:Hex) to afford the desired compound as a yellow oil (0.102 g, 52%). ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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), *m/z* C₁₄H₁₃ClN₆, calcd. 300.0890, obsd. 300.0893.

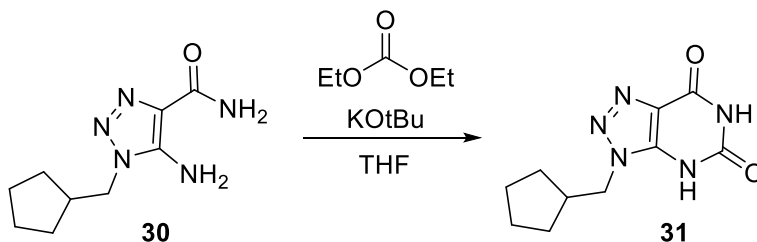


3-benzyl-N-cyclopropyl-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-amine (27): To a cooled (0°C) solution of sodium hydride (0.010 g, 0.40 mmol) in dry DMF (10 mL) was added propane thiol (0.030 g, 0.40 mmol) and allowed to stir until gas evolution ceased. The substrate (**26**) was then added 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 hours of reaction time, the addition of 2 equivalents was repeated. The reaction was stirred for a total of 28 hours, at which time it was poured onto a saturated sodium carbonate solution (20 mL) and extracted with EtOAc (3 x 15 mL). The organic extracts were combined, washed with water (20 mL) and brine (20 mL), dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO₂; 5% EtOAc/CH₂Cl₂) to yield a yellow oil (0.091 g, 80%). ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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* C₁₇H₂₀N₇S, calcd. 340.1470, obsd. 340.1468.

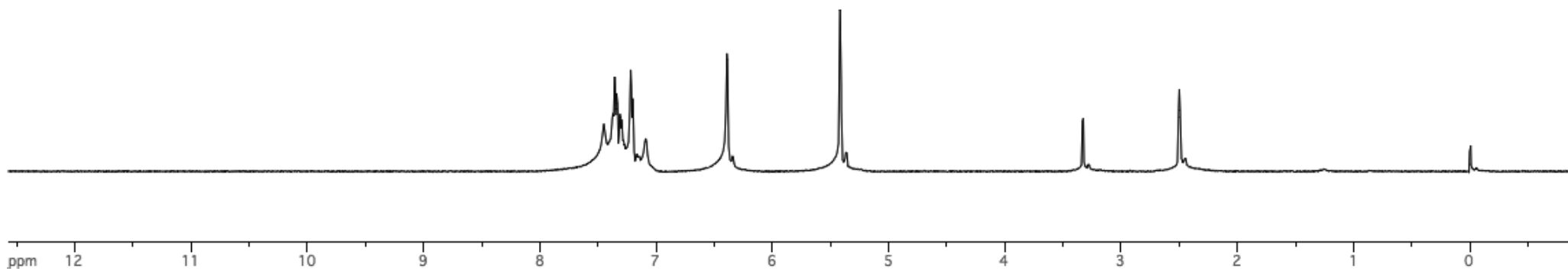
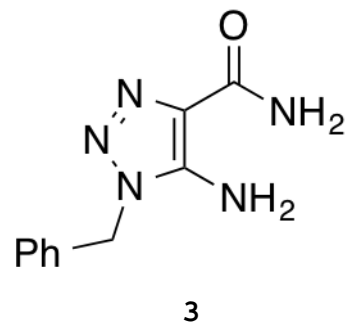


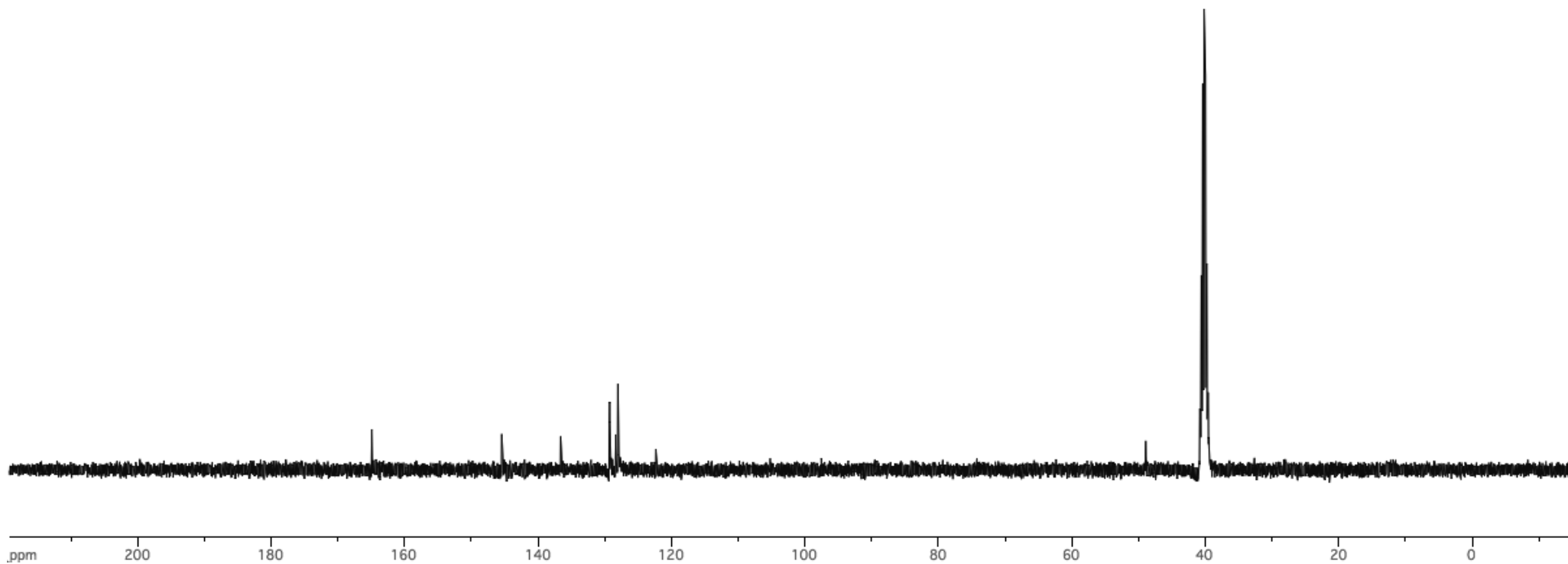
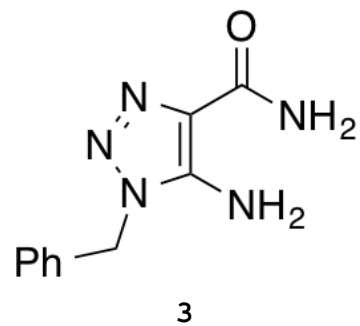
5-amino-1-(cyclopentylmethyl)-1H-1,2,3-triazole-4-carboxamide (30): Following the same procedure for (**3**) produced the desired compound as slender yellow crystals (0.177 g, 52%). mp= 226-227°C. ¹H NMR (400 MHz, DMSO-d₆): δ 7.41 (br s, 1H), 7.06 (br s, 1H) 6.28 (br s,

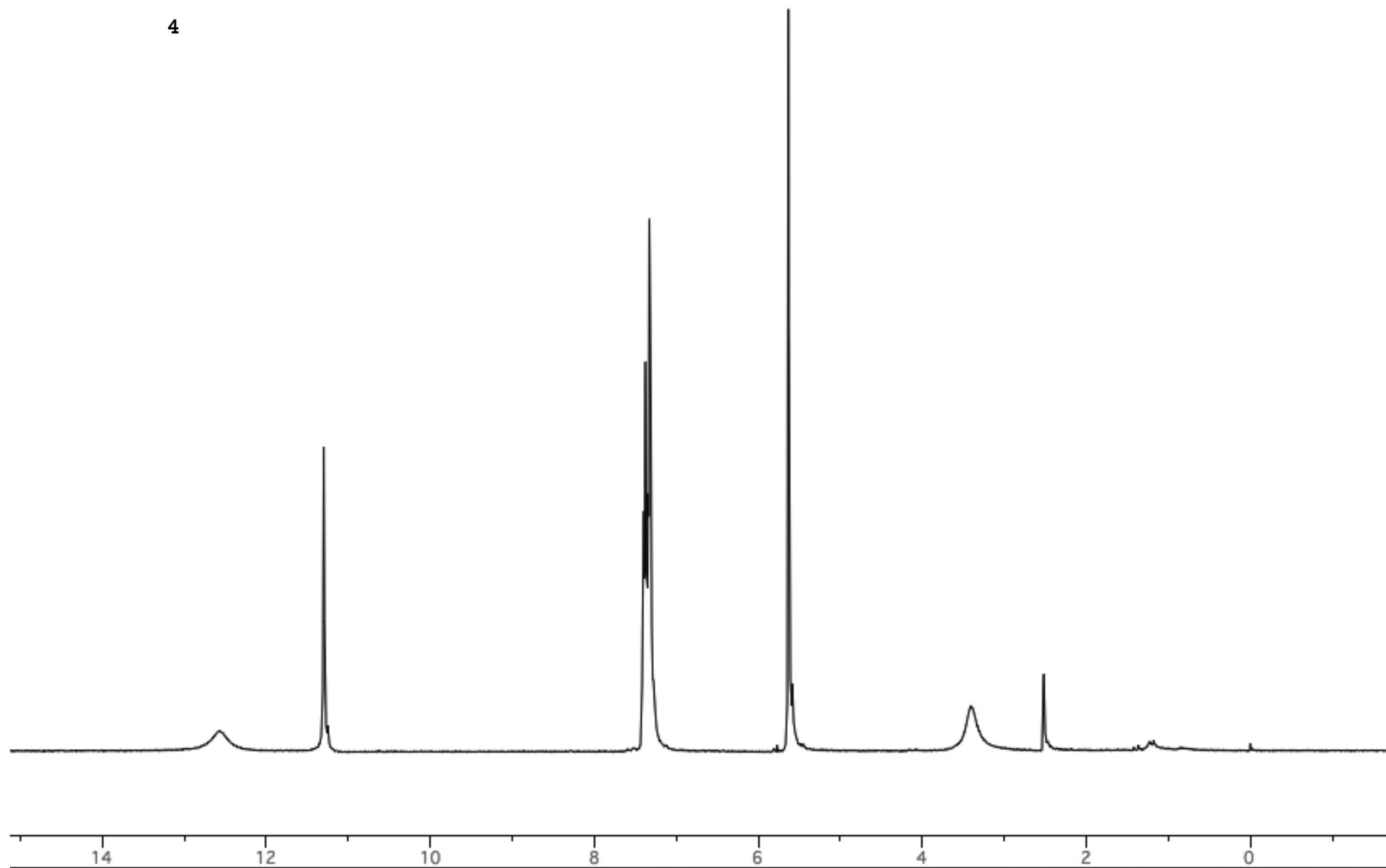
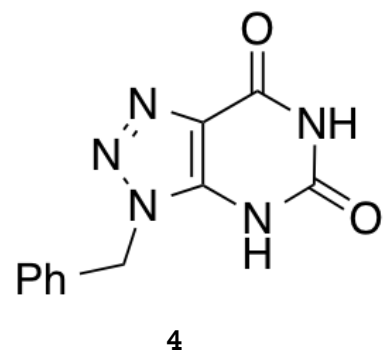
2H), 4.05 (d, $J=8$ Hz, 2H), 2.37 (m, 1H), 1.61 (m, 4H), 1.50 (m, 2H), 1.26 (m, 2H) (NMP impurity at 3.30, 2.70, 2.19, 1.90). ^{13}C NMR (100 MHz, DMSO- d_6): δ 164.4, 144.6, 121.5, 49.5, 38.9, 29.5, 24.5. HRMS (ESI), m/z $\text{C}_9\text{H}_{15}\text{N}_5\text{O}$ ($\text{M}+\text{H}$) $^+$ calcd. 210.13, obsd. 210.1355.

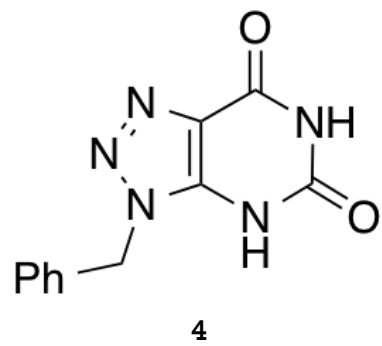


3-(cyclopentylmethyl)-3,4-dihydro-5H-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(6H)-dione (31): Following the same procedure for (4) produced the desired compound as a light yellow solid (0.035 g, 21% yield). mp= 294-295°C. ^1H NMR (400 MHz, DMSO- d_6): δ 12.4 (br s, 1H), 11.2 (s, 1H), 4.27 (d, $J=7.2$ Hz, 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 $\text{C}_{10}\text{H}_{13}\text{N}_5\text{O}_2$ ($\text{M}+\text{H}$) $^+$ calcd. 236.11, obsd. 236.1147.

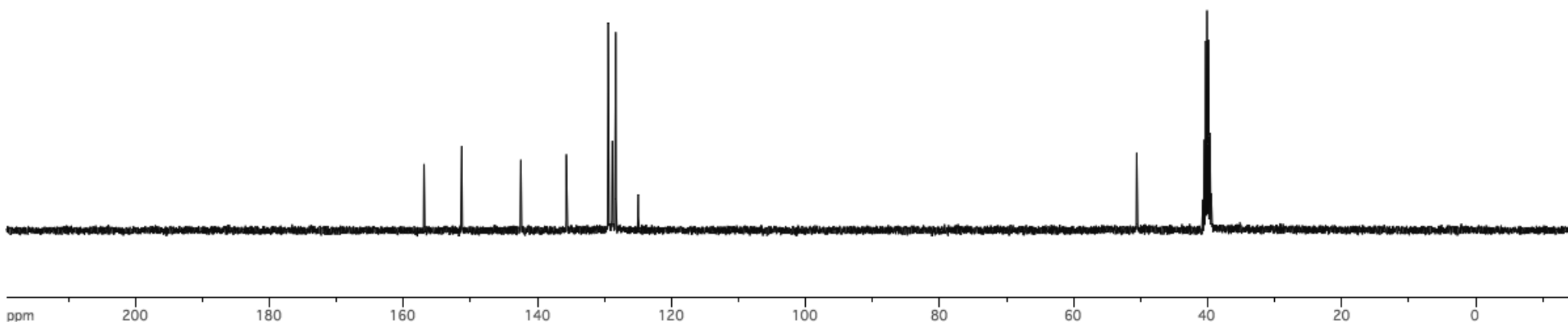


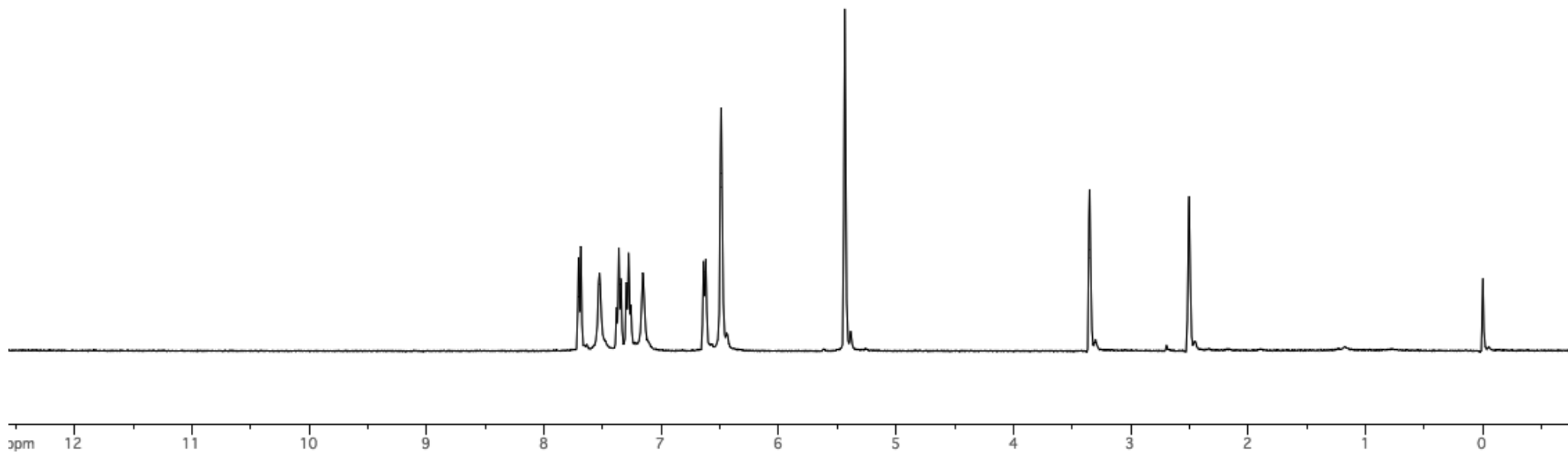
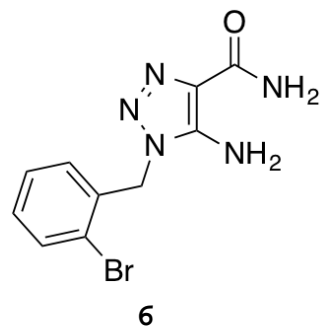


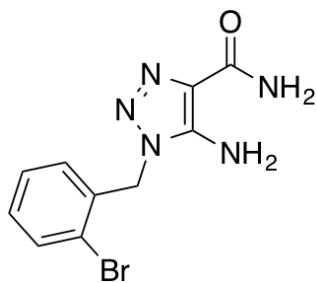




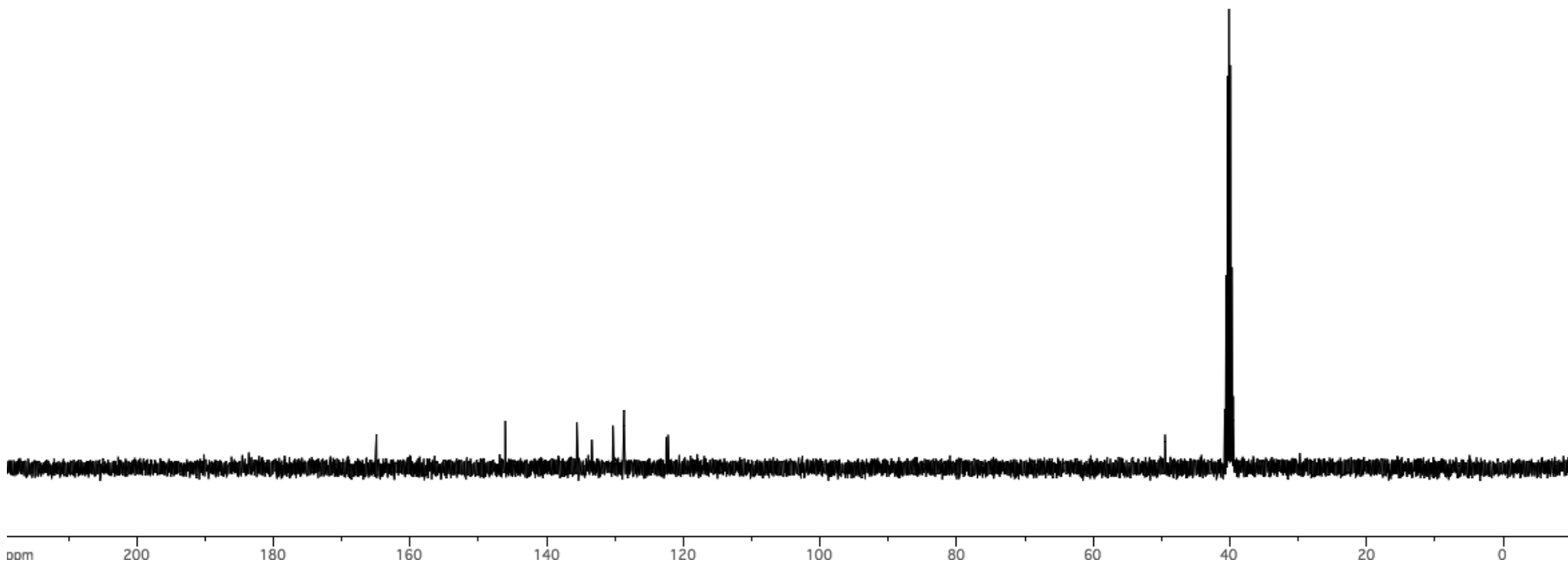
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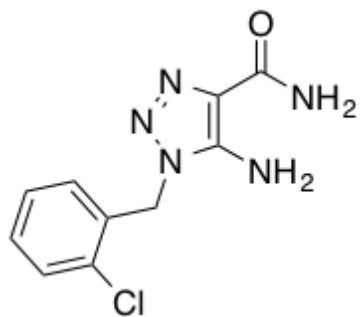




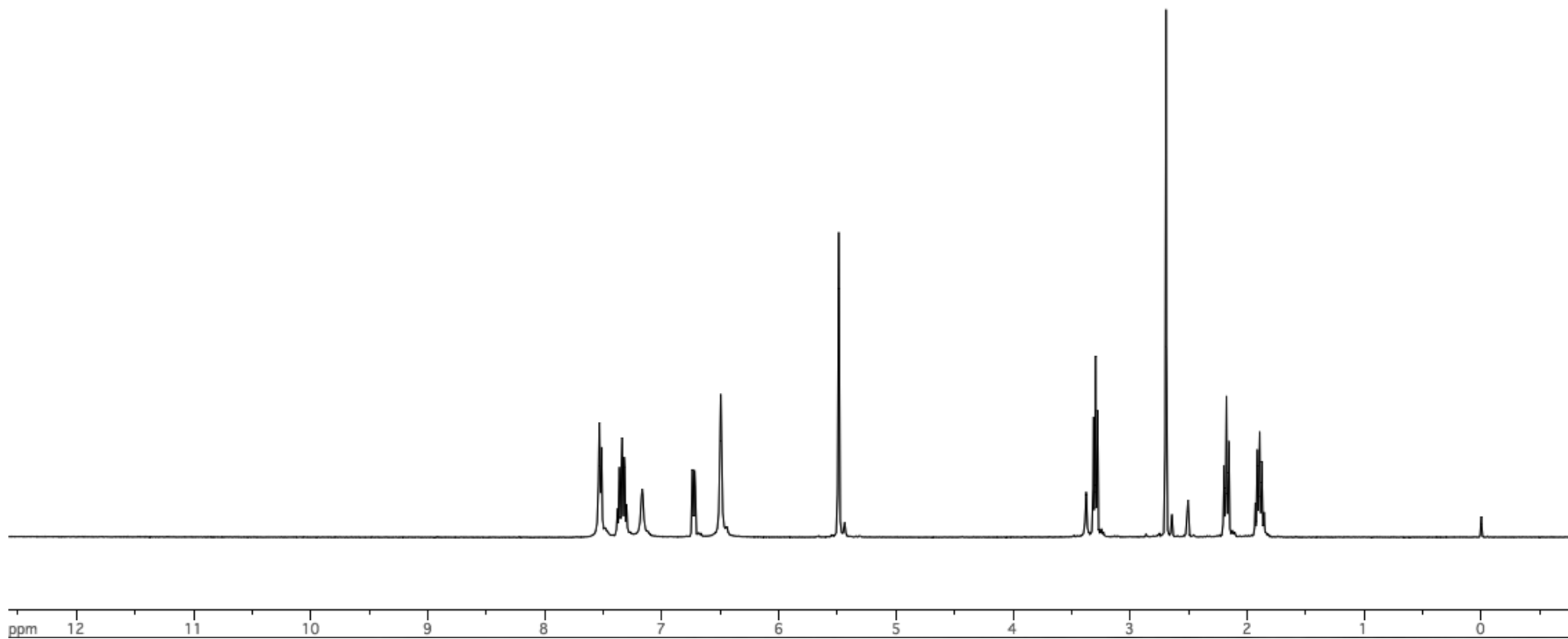


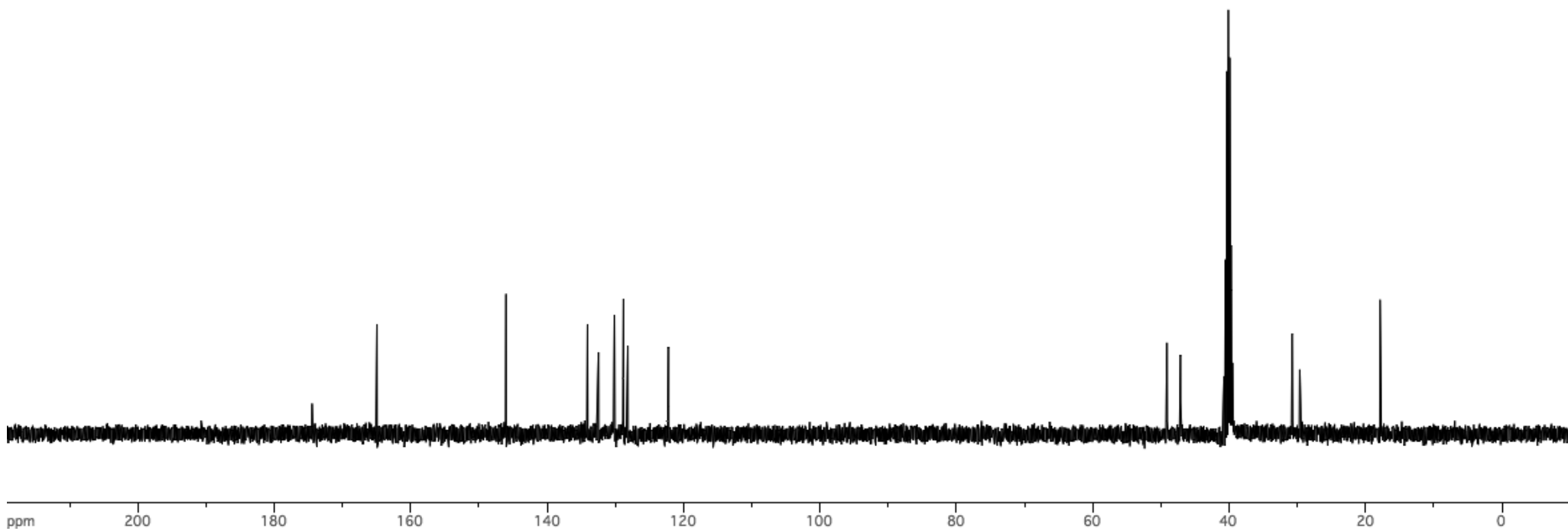
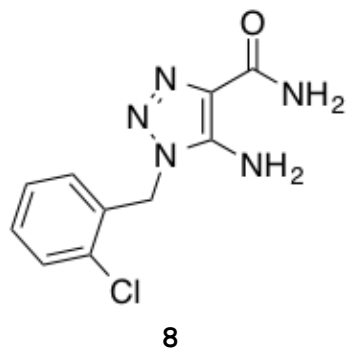
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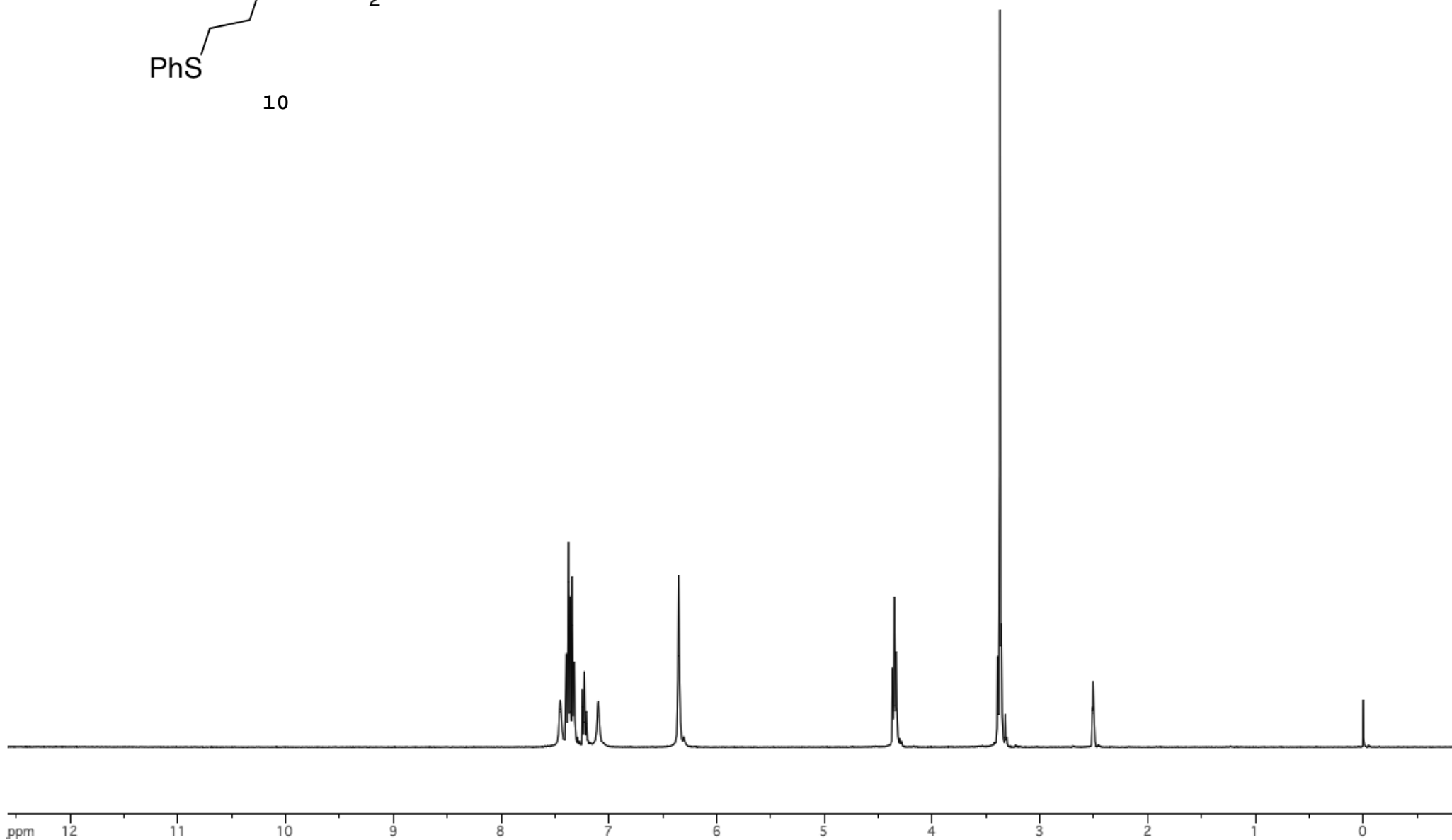
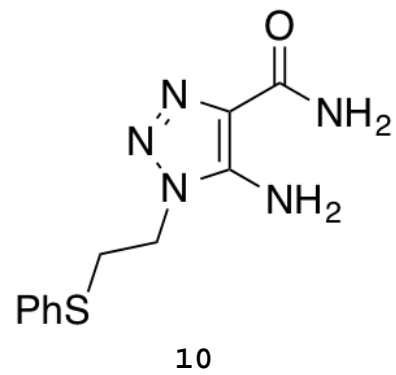


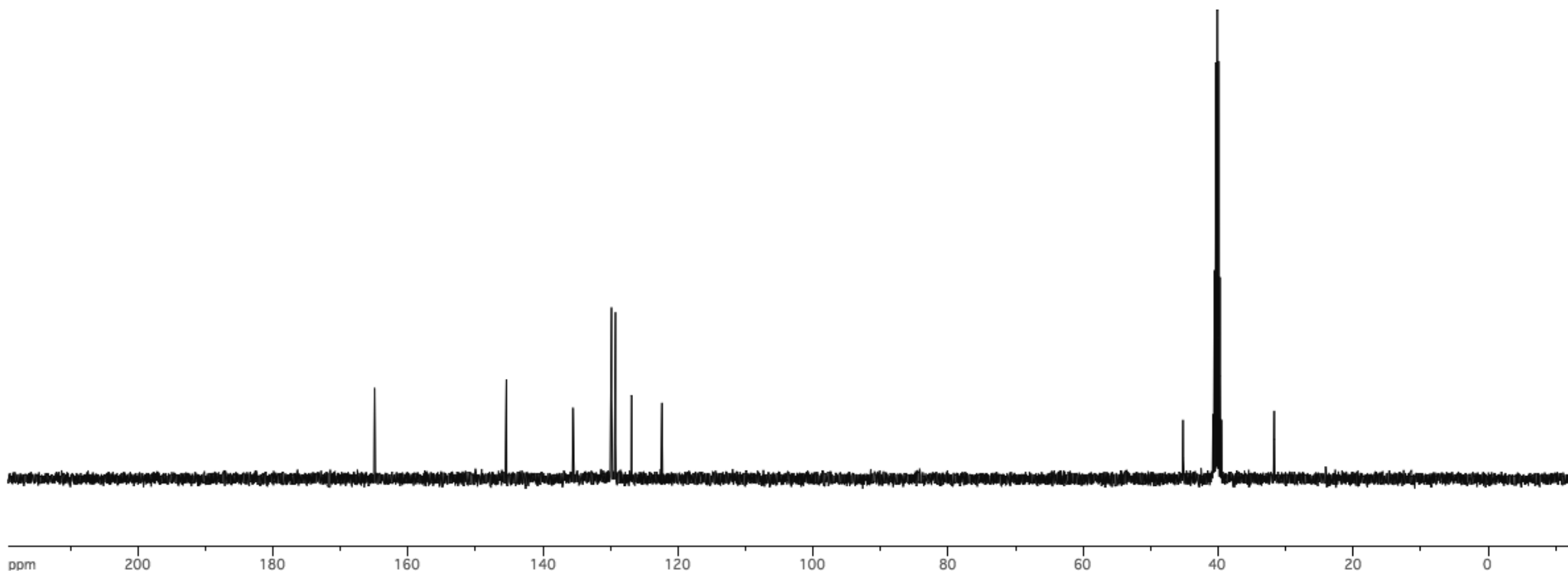
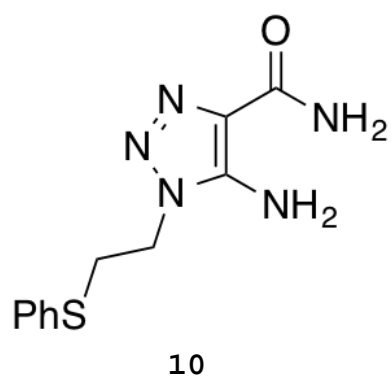


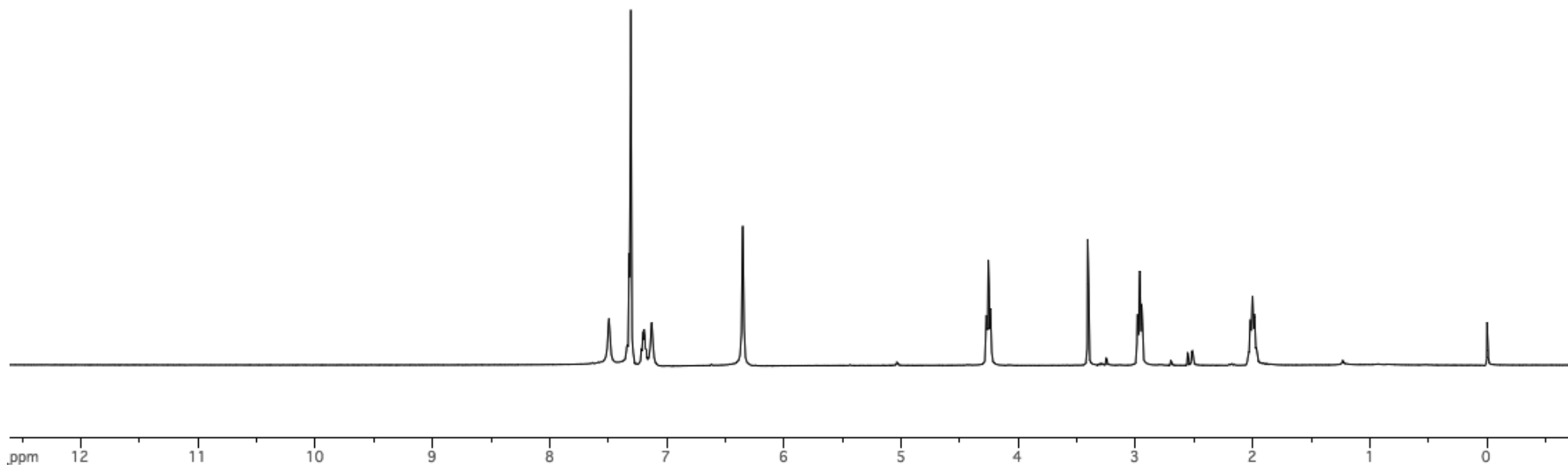
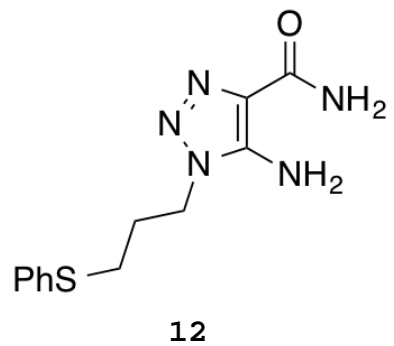
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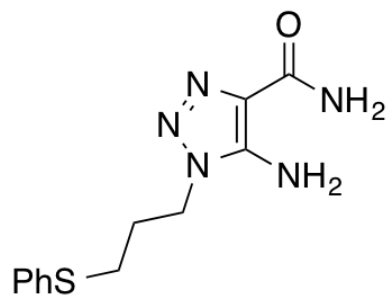




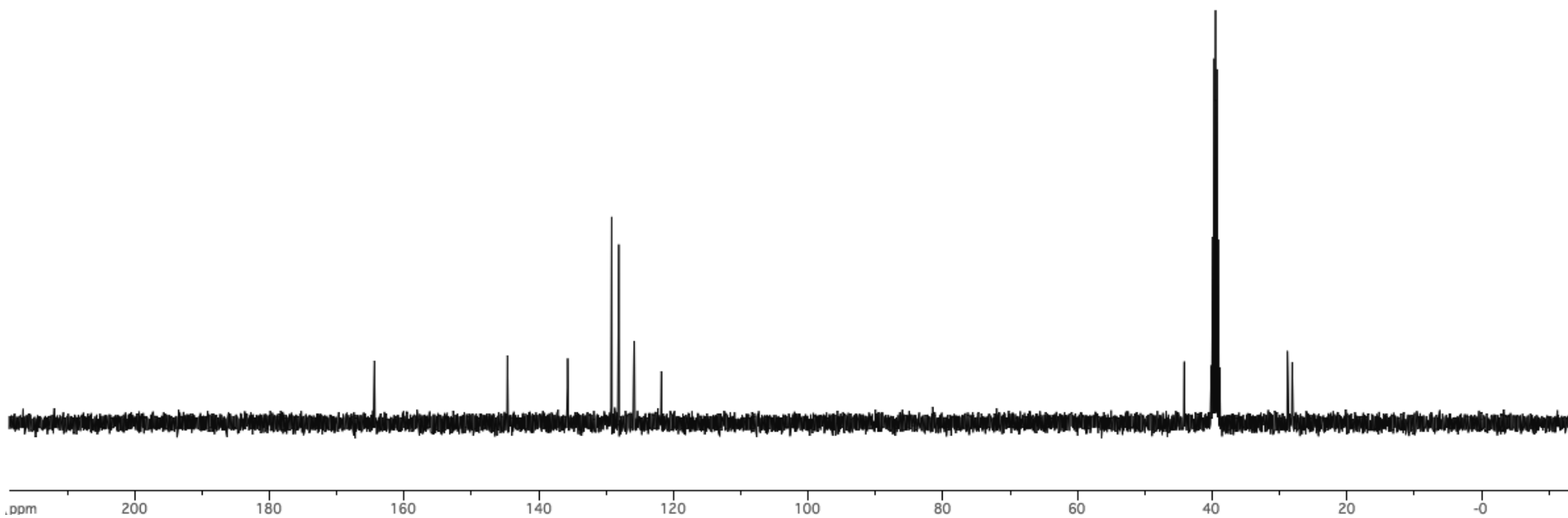


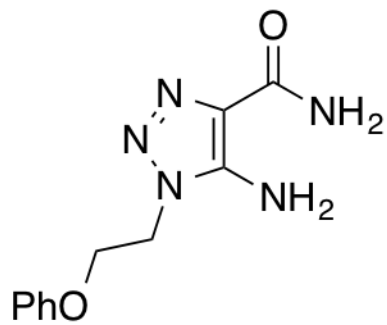




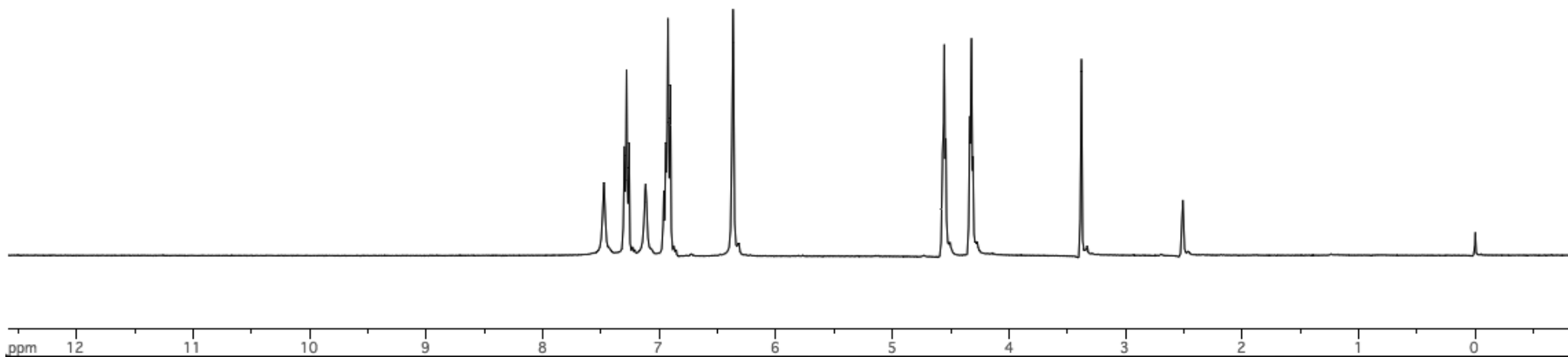


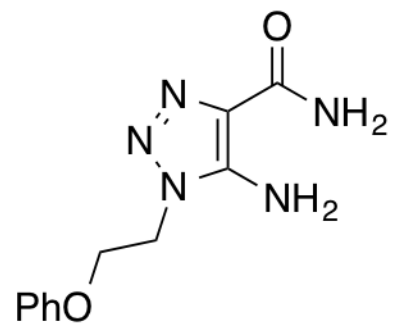
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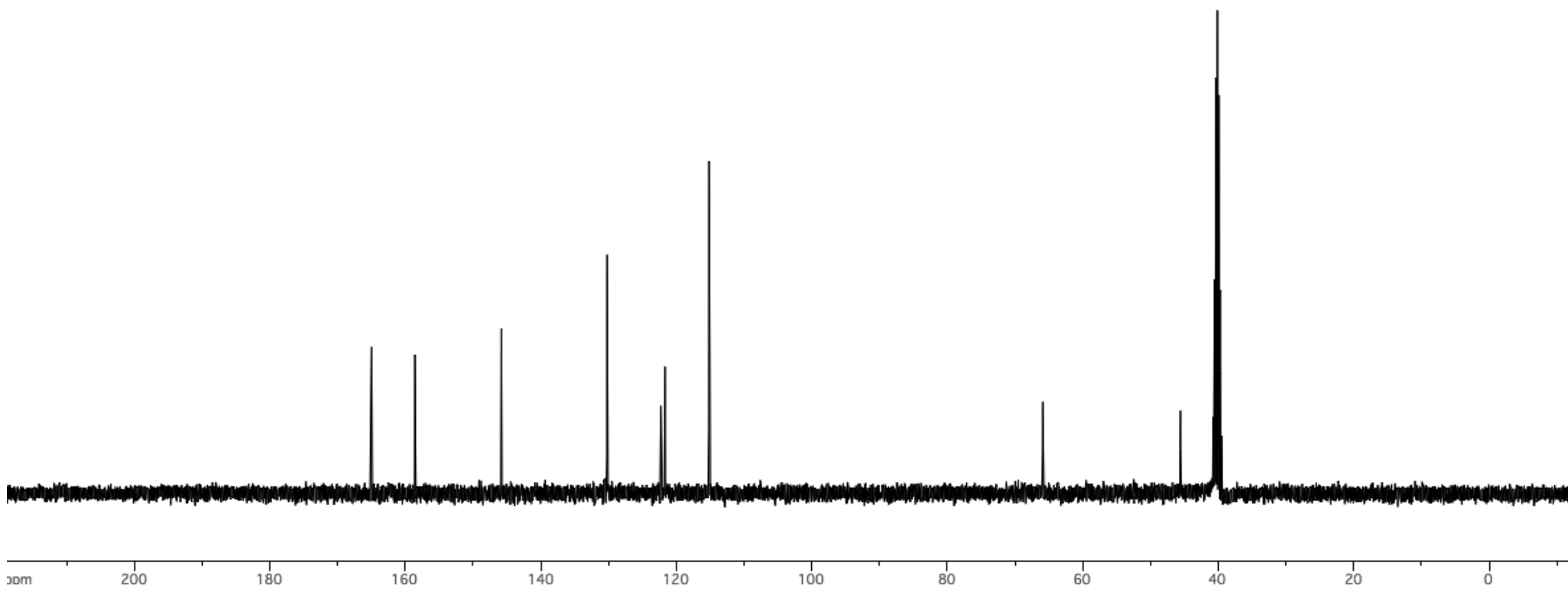


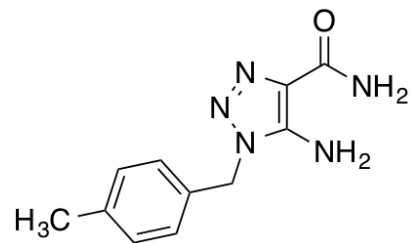
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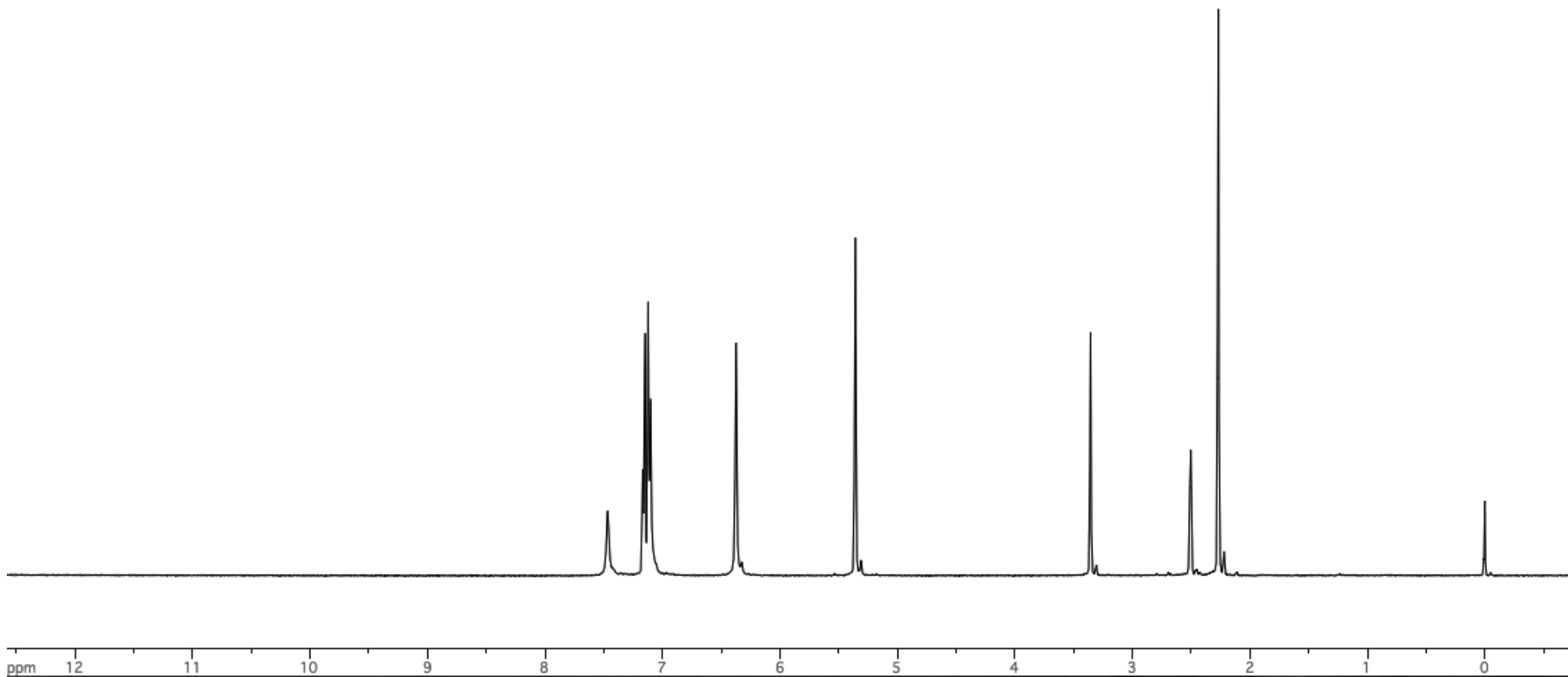


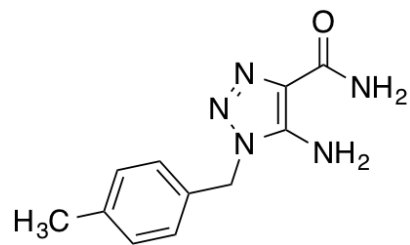
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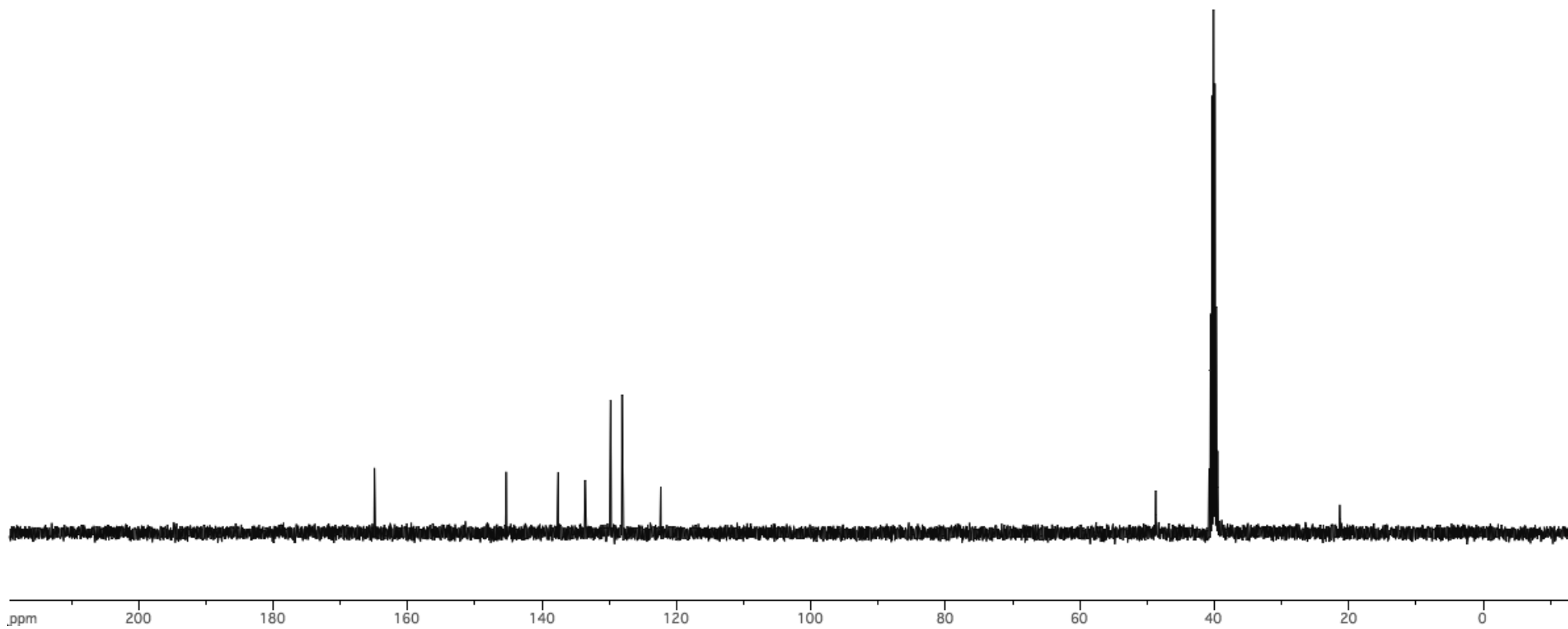


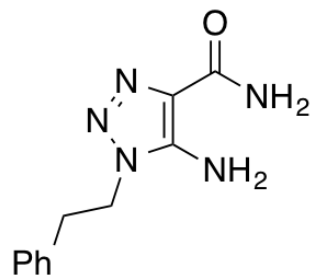
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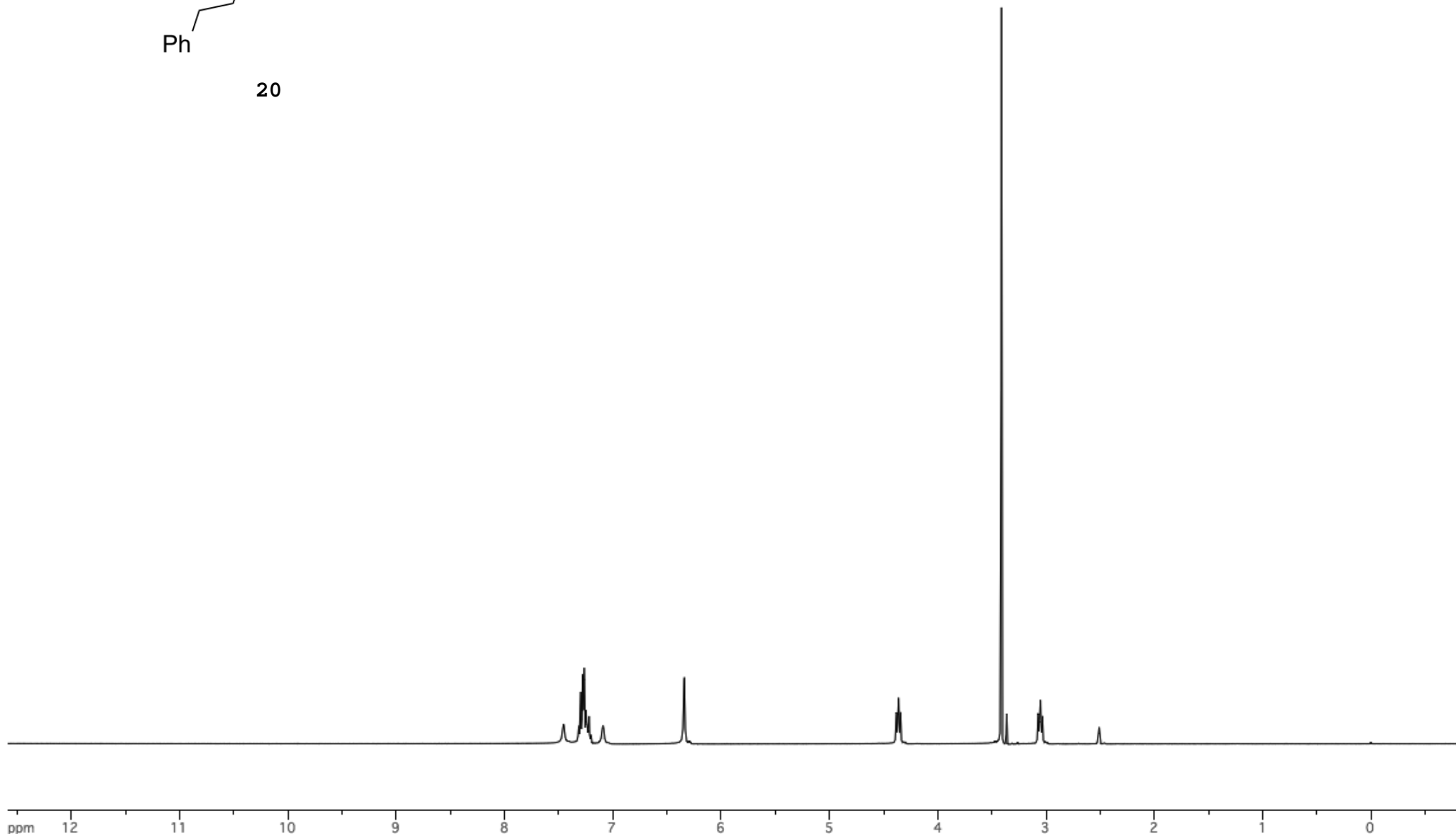


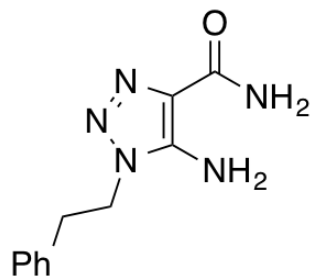
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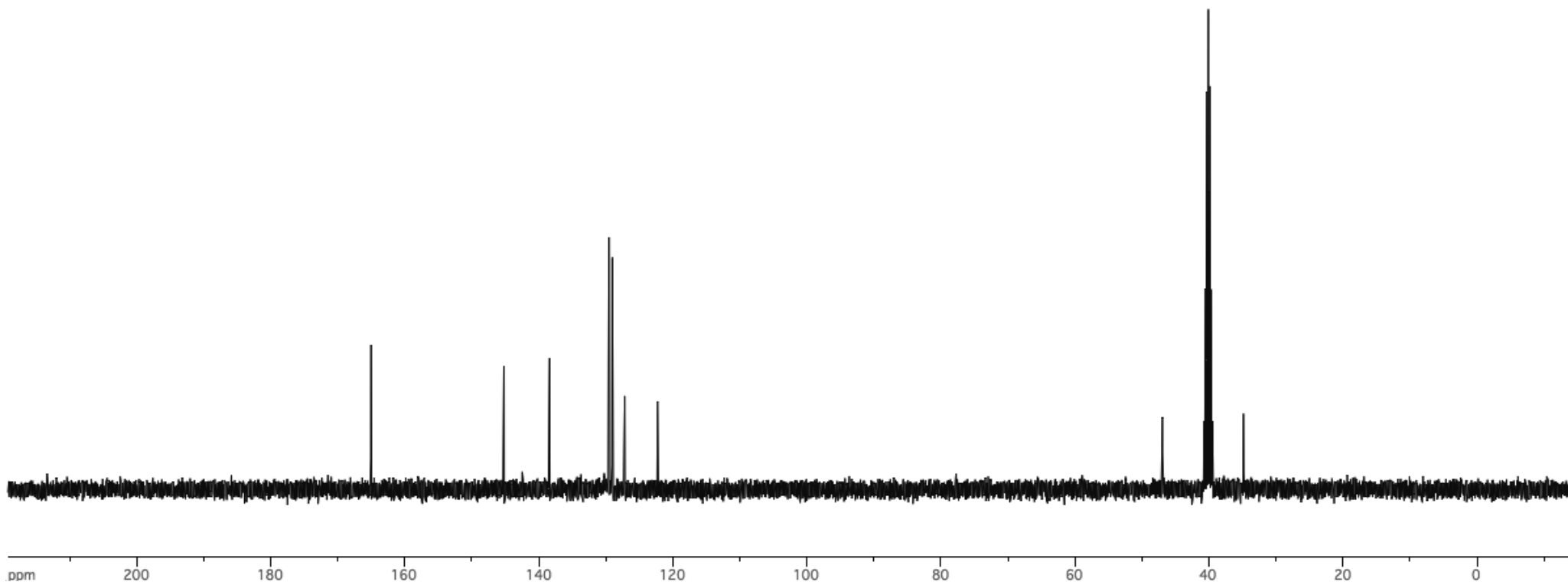


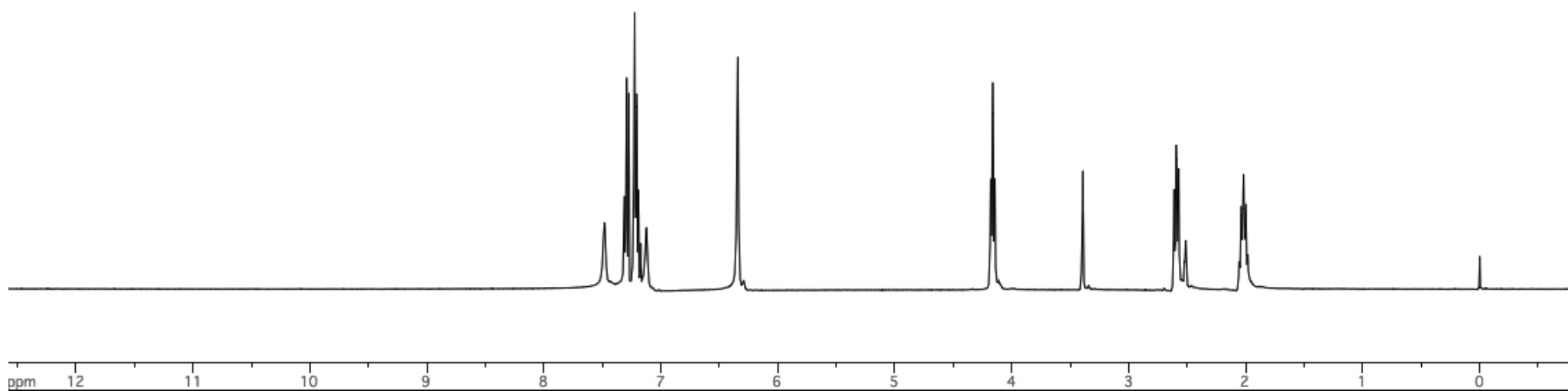
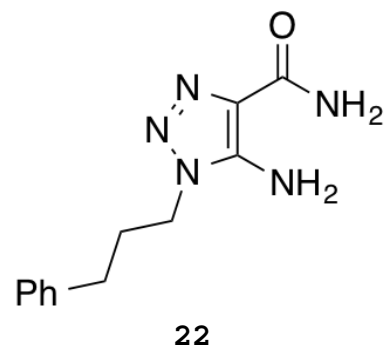
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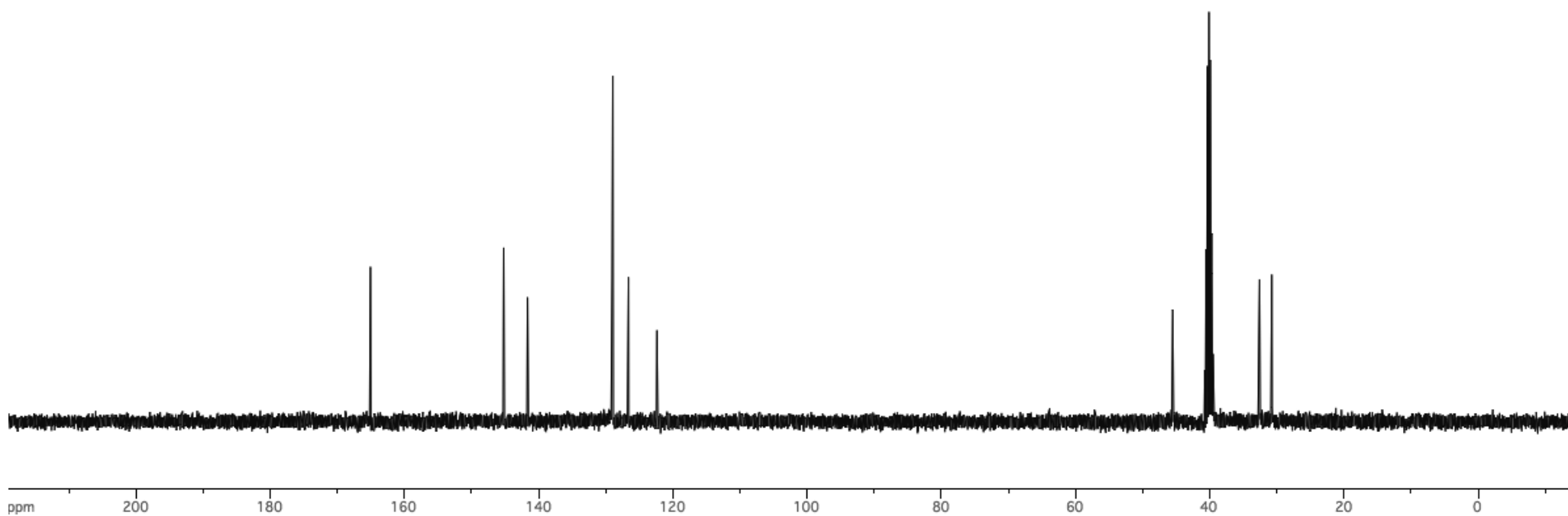
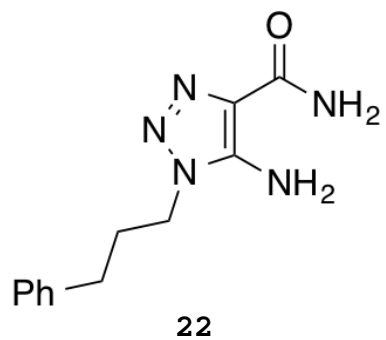


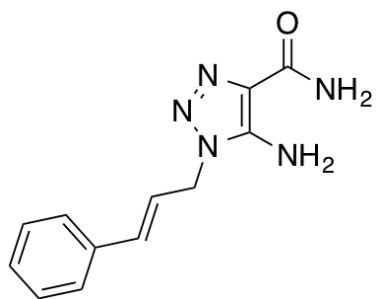
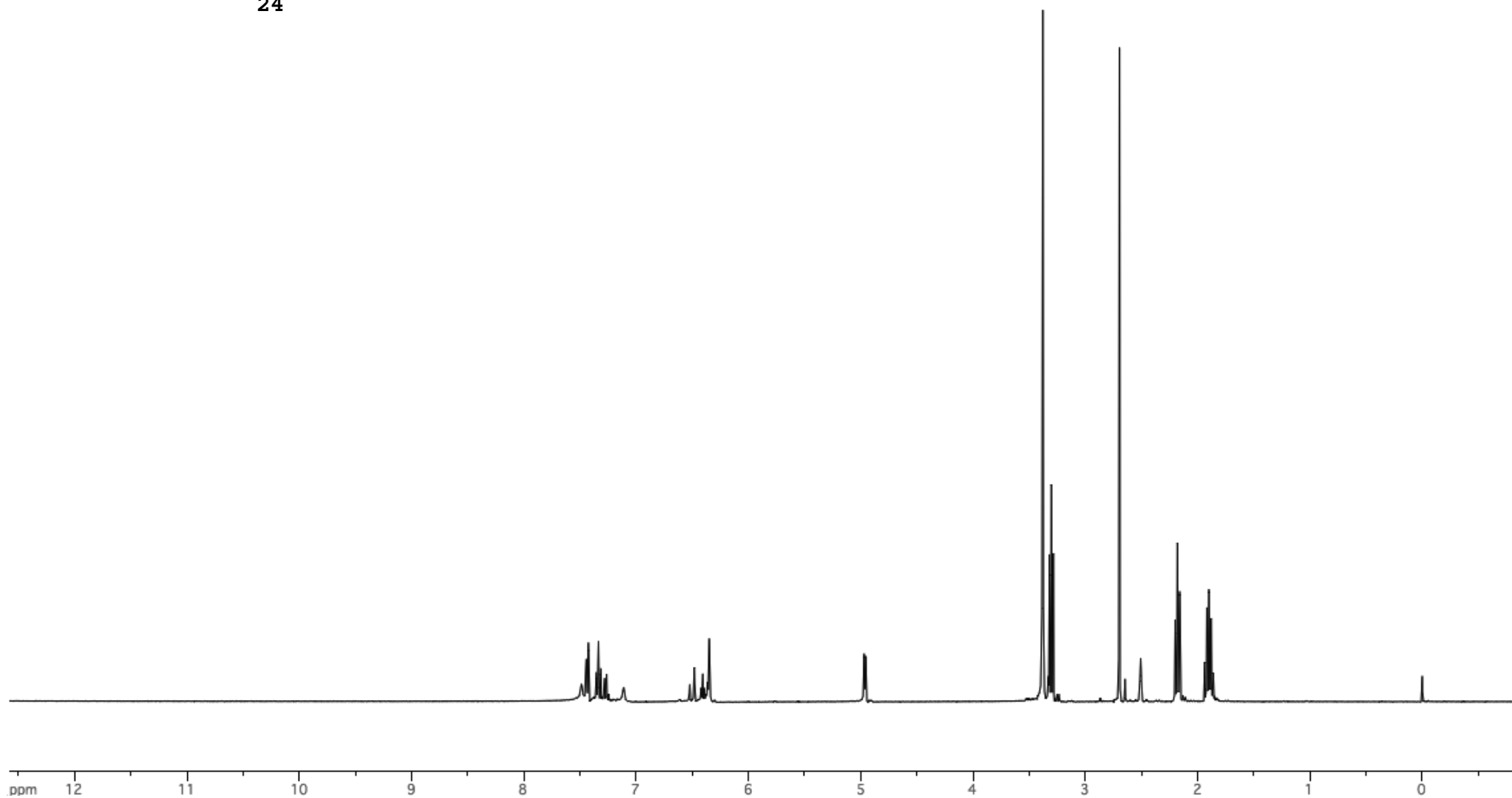


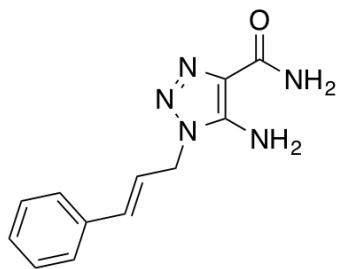
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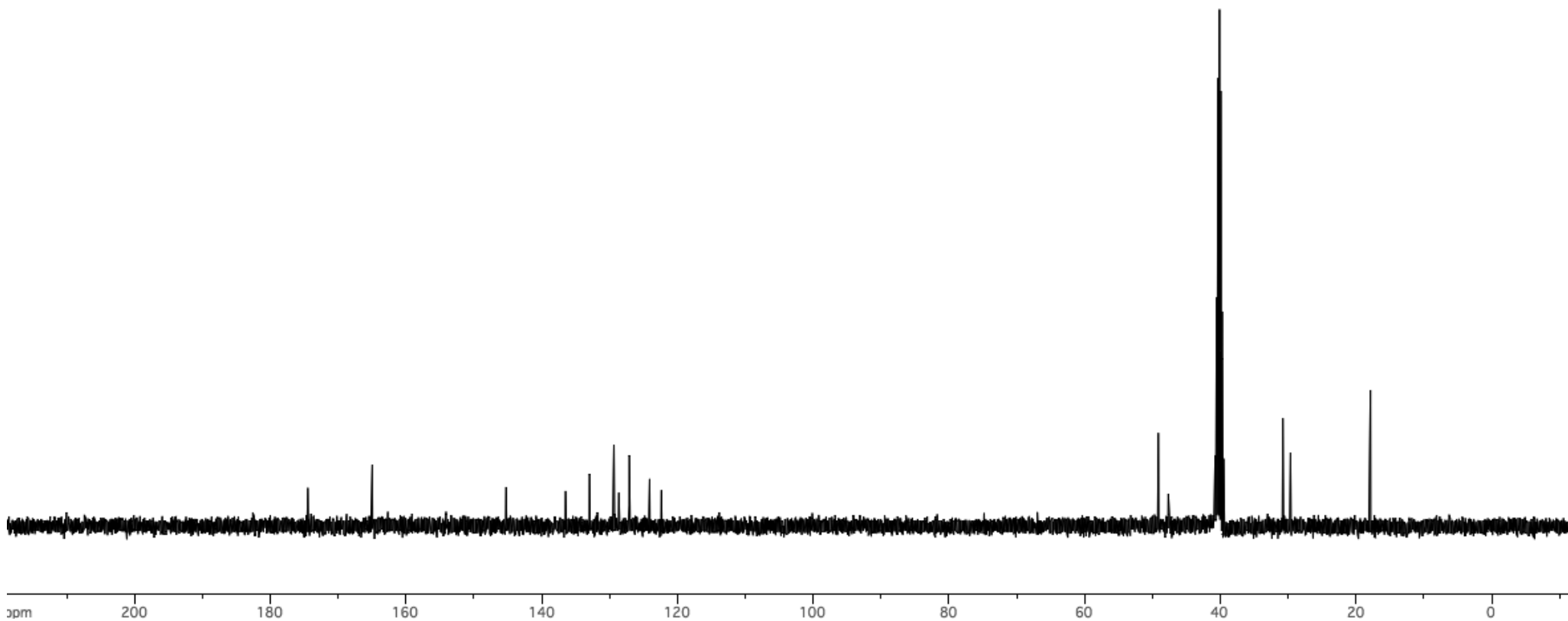


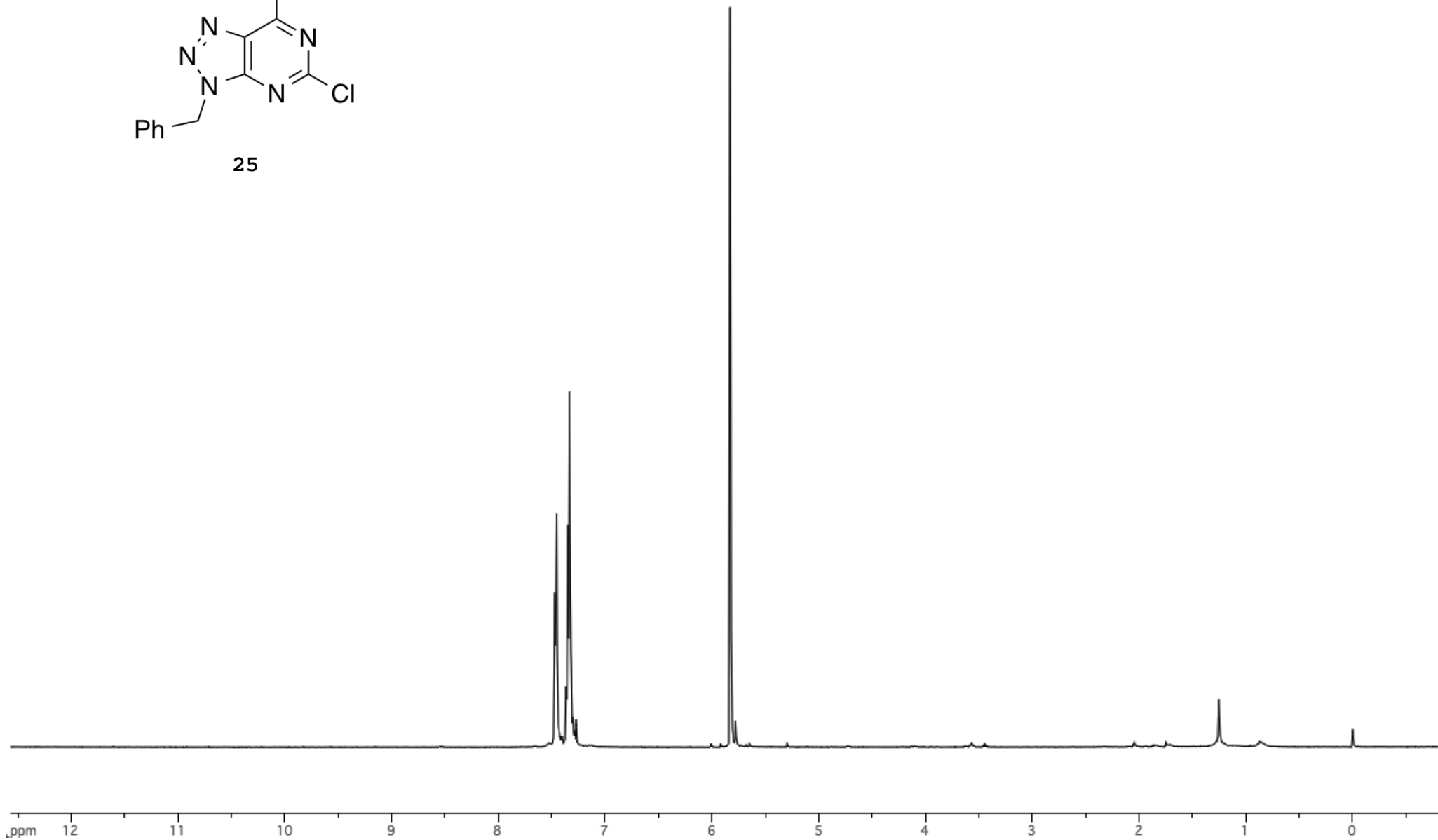
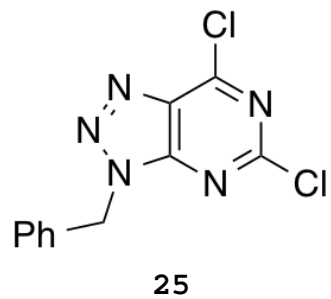


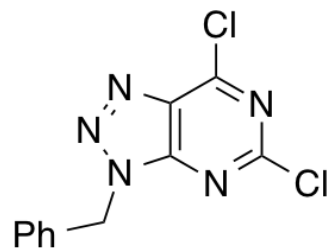
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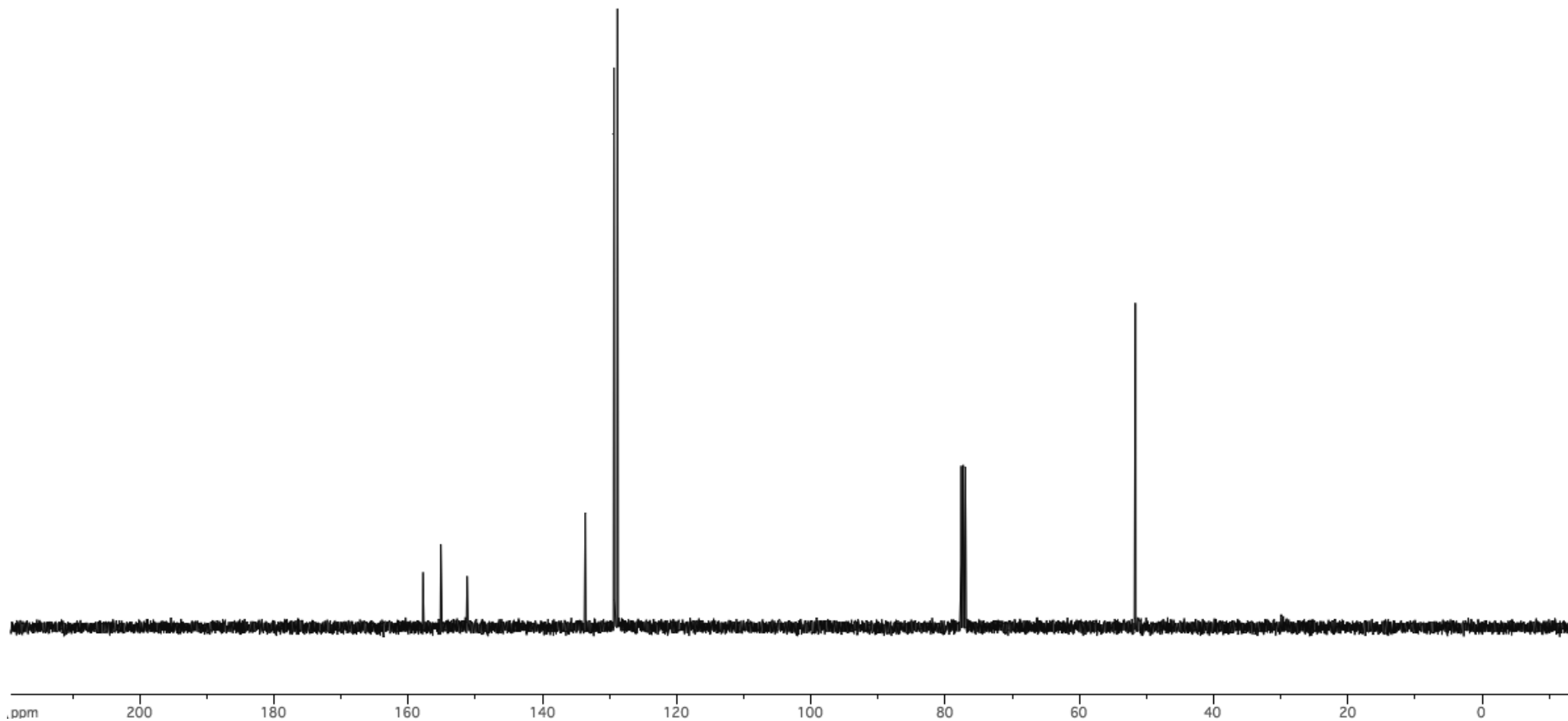
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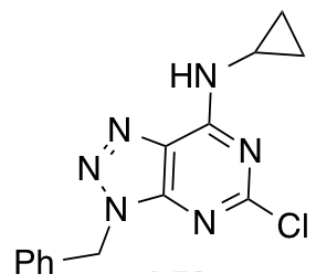




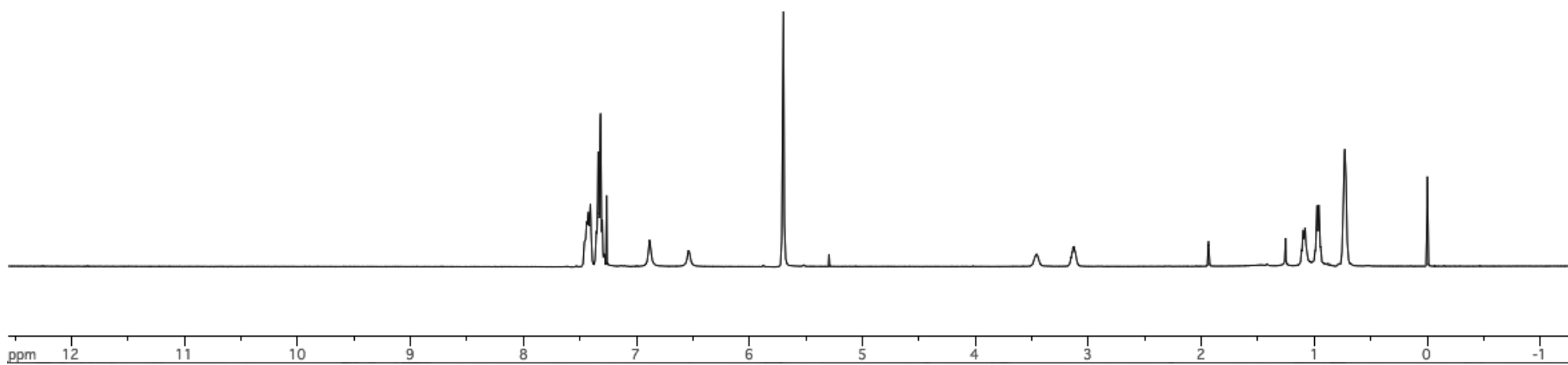


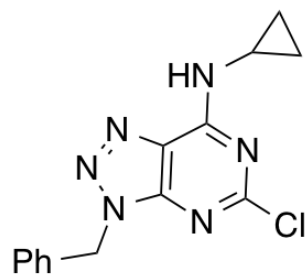
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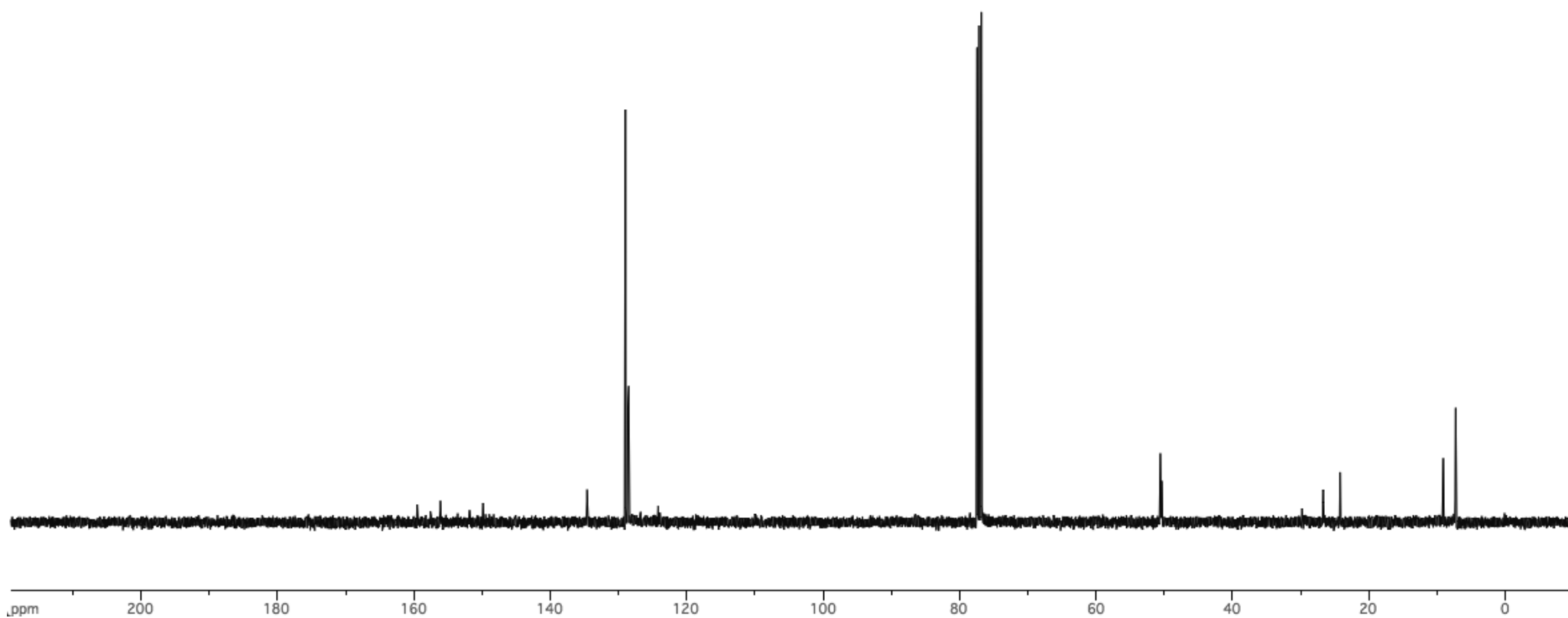


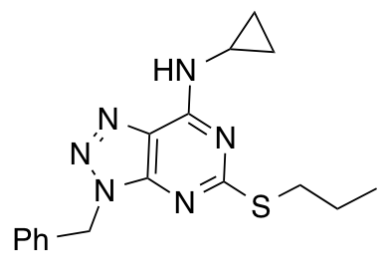
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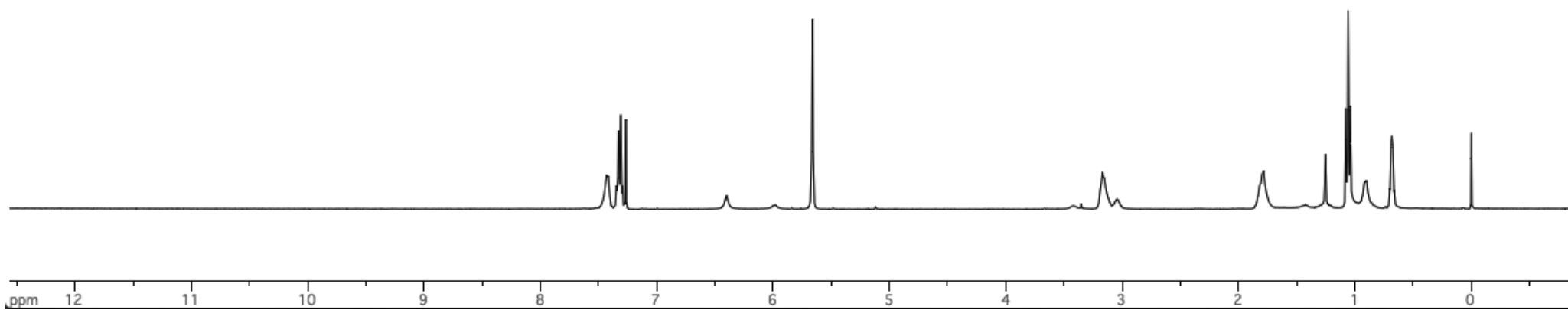


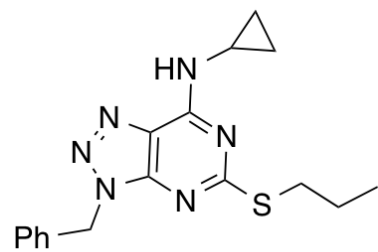
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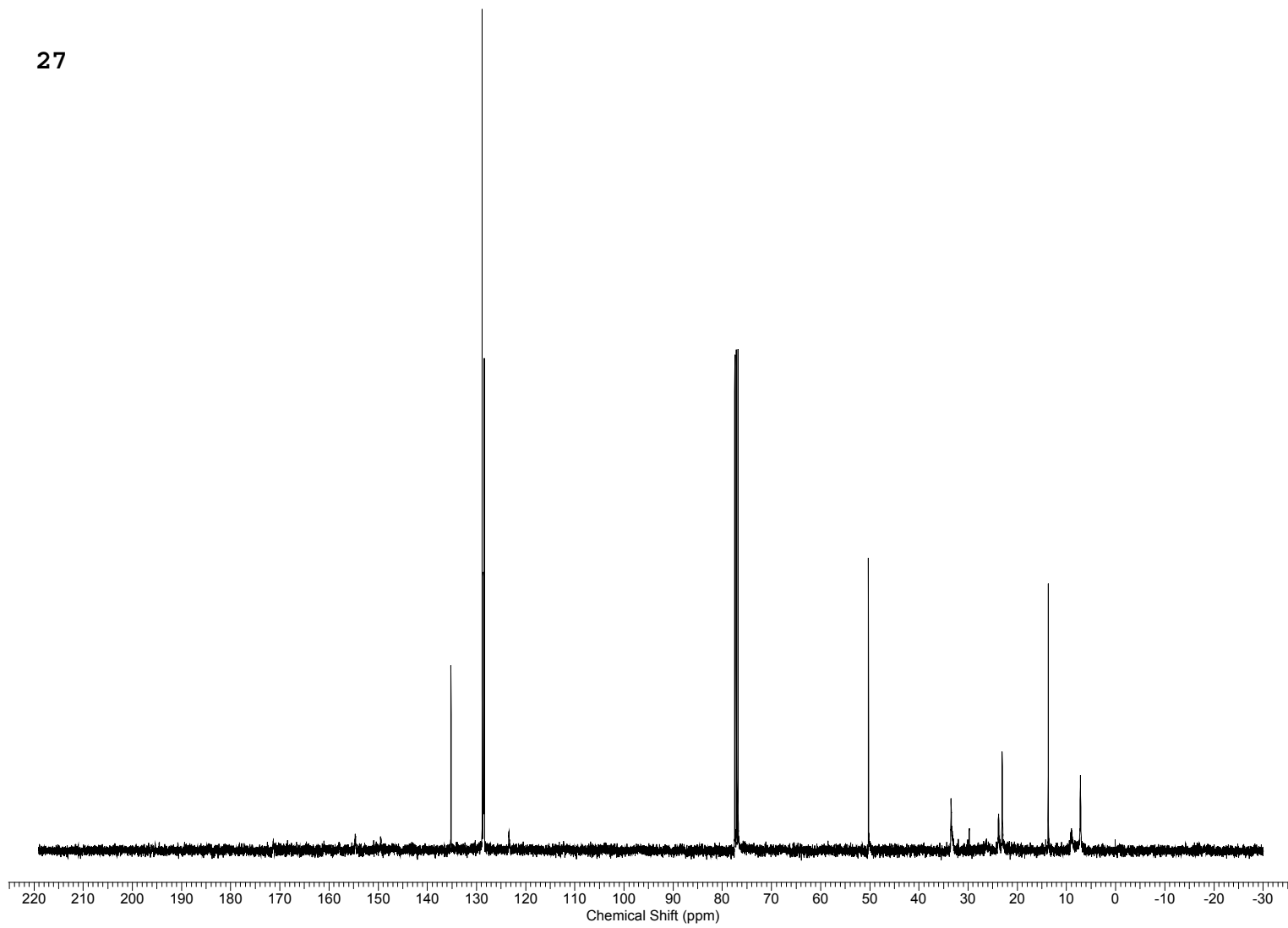


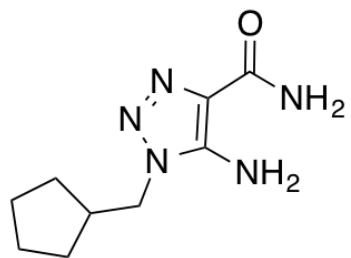
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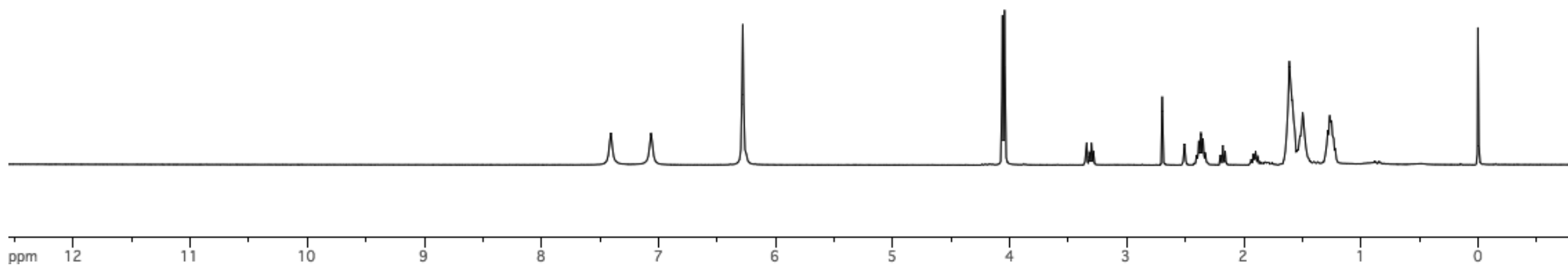


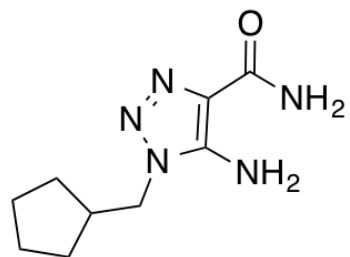
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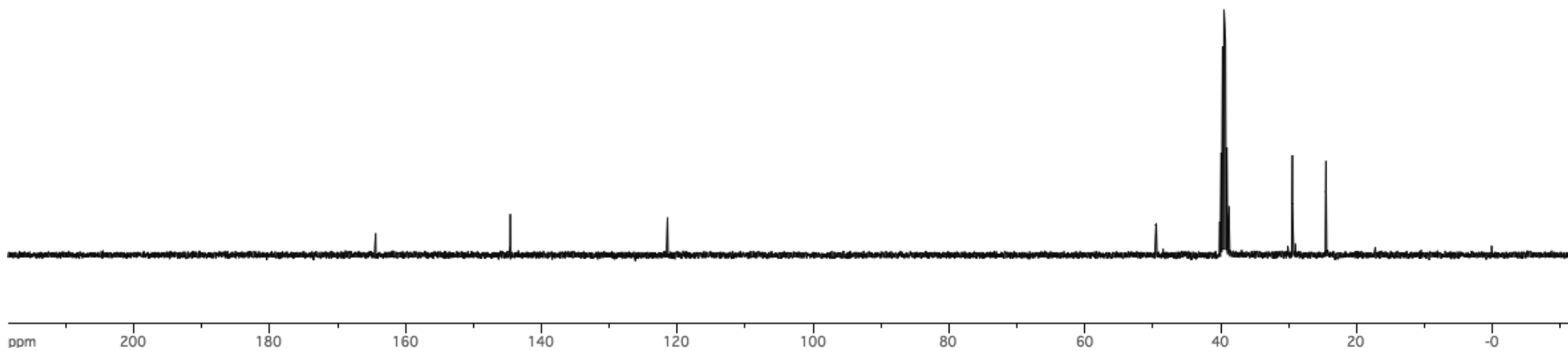


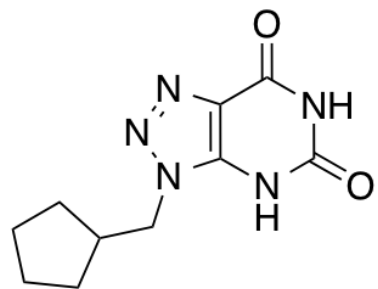
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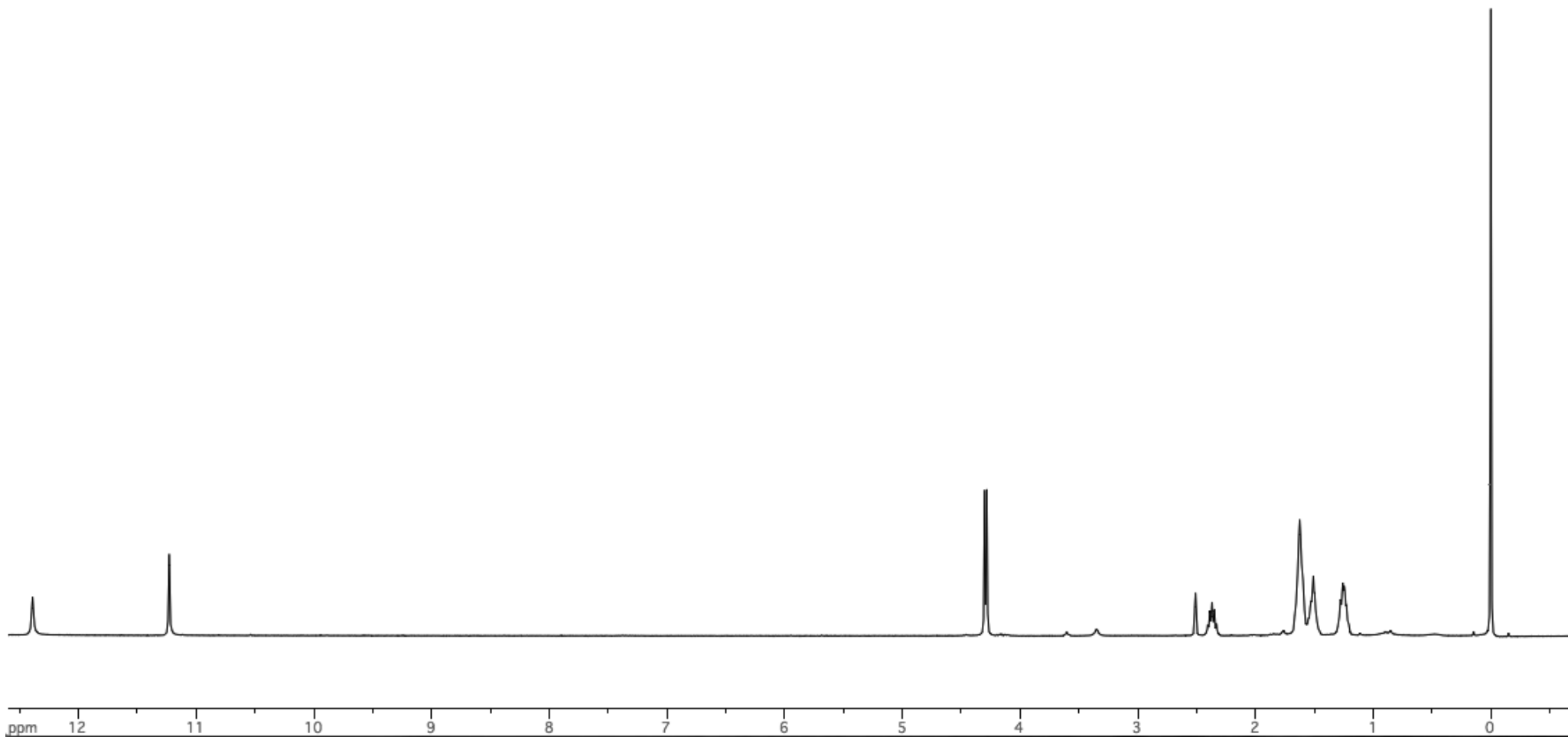


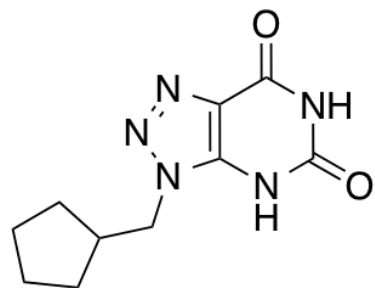
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