# High Yielding, Multigram-Scale Synthesis of TBAJ-876 Fragment, 876A-B

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## Abstract

TBAJ-876 is an anti-tuberculosis drug shown to have high activity against multi-drug resistant tuberculosis (TB). We report a very efficient synthesis of the TBAJ-876 fragment 876A-B using an aldol condensation strategy starting from 6-bromo-3,4-dihydroquinolin-2(H)-one. The synthesis has been accomplished at multigram scale without the need of chromatography purification steps.

## Introduction

The anti-tuberculosis drug TBAJ-876 (**1**) was first described in 2019 as a more potent and less toxic analog to bedaquiline (**2**) (Figure 1).[1] TBAJ-876 is currently in Phase 2 clinical trials and it represents a promising option in the treatment of multi-drug resistant tuberculosis (TB) strains.[2]

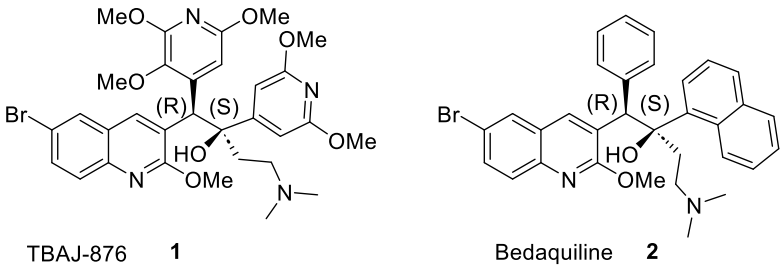
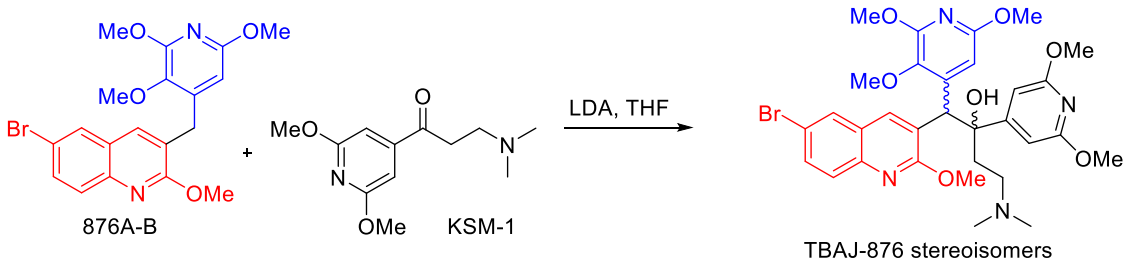


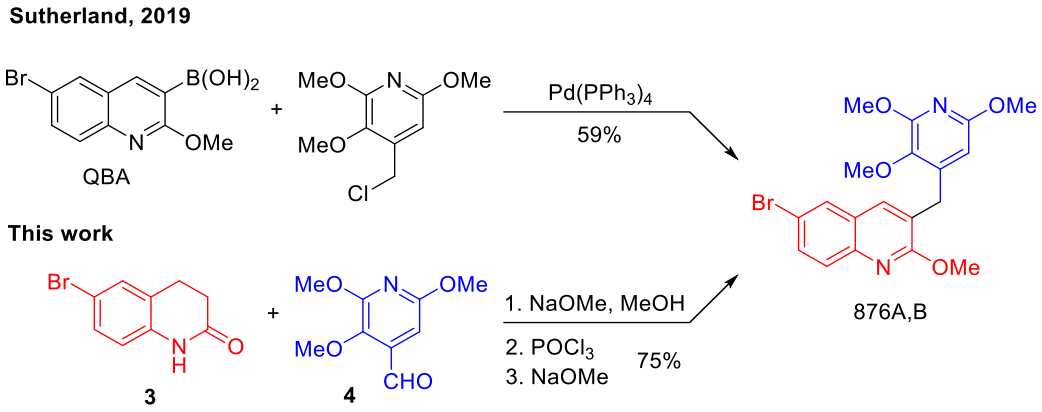

*Figure 1*

Both TBAJ-876 and bedaquiline are prepared by the LDA-promoted coupling of the quinoline fragment and dimethylaminopropanone fragment (Scheme 1). In the non-stereoselective synthesis of TBAJ-876, fragment 876A-B reacts with LDA and the resulting organolithium species is reacted with KSM-1 to provide the mixture of stereoisomers in 90% yield.[3] The desired TBAJ-876 stereoisomer is then isolated by fractional crystallization and chiral SFC column purification. The final API is formulated as the salt with L-tartaric acid.




*Scheme 1*

Previously, fragment 876A-B was prepared in a convergent synthesis starting from 4-bromoaniline and culminating in a Pd-catalyzed Suzuki coupling (Scheme 2)[3]. This route involves six steps to prepare the quinoline boronic acid (QBA) in 20% overall yield from 4-bromoaniline. The Suzuki coupling step can only be accomplished in about 60% - using an expensive Pd catalyst and two costly heterocyclic fragments. Because this route would pose challenges for scale-up of the synthesis, we sought to find a better route to fragment 876A-B. In the following manuscript, we describe an efficient method for coupling the two heterocyclic fragments (Scheme 2). The chemistry involves an aldol condensation of 6-bromo-3,4-dihydroquinolin-2(H)-one (**3**) and aldehyde **4**. The synthetic route does not require Pd catalyst, the three-step sequence is accomplished in 75% overall yield, and no chromatography is used in purification of the intermediates or compound 876A-B.



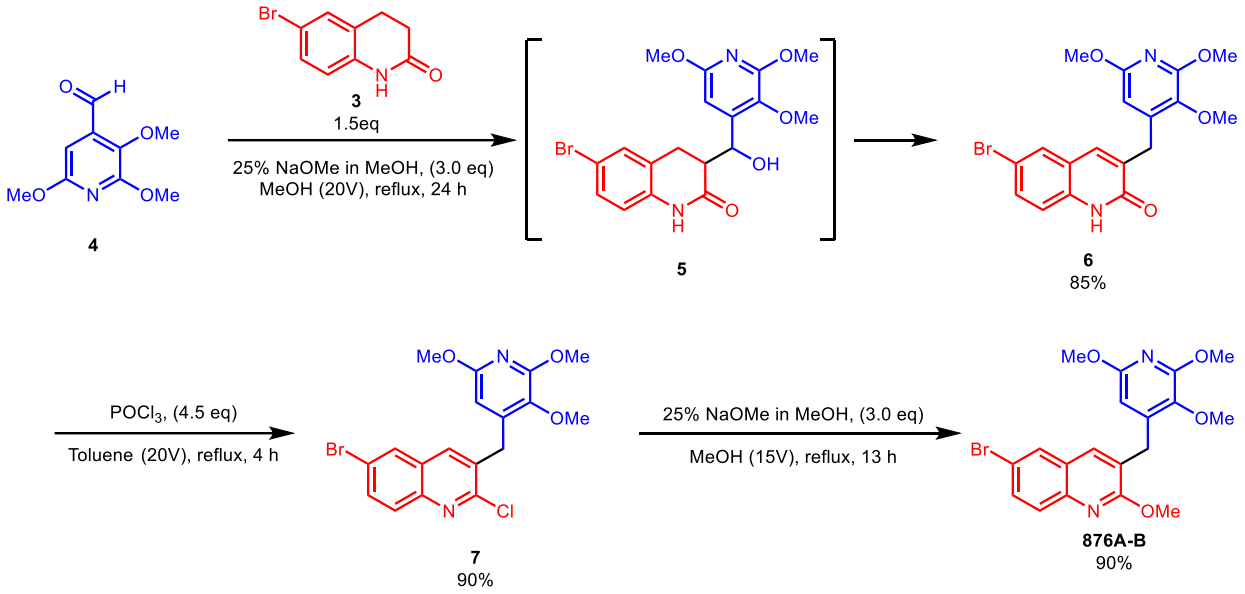

*Scheme 2*

## Discussion

The 3-step synthesis begins with the aldol reaction of aldehyde **4** and an excess of the dihydroquinolone **3** in the presence of sodium methoxide in refluxing methanol (Scheme 3). It was found with less dihydroquinolone that reaction time became extended and that the aldehyde would remain unconsumed. Since the aldehyde is a cost driver in this process, ensuring its consumption ultimately improves cost of the overall process.[i] In-process HPLC shows diastereomeric alcohols **5** which convert to desired quinolone **6** over the course of the reaction. After 24 hours of reflux much of the product precipitates out and is collected by filtration to give

[i] Based on analysis of the overall synthesis of 876A-B and its starting materials, publicly available costs of the known, commercially available starting materials (i.e. from Zauba and Datamyne), and published costs of required reagents to manufacture 876A-B.

70% yield, 99area%. A second crop of less purity can be obtained by concentrating the mother liquor. Total yield for the reaction was 85%.




*Scheme 3*

Chloroquinoline **7** was then obtained by treatment of quinolone **6** with excess phosphorous oxychloride in refluxing toluene. The reaction stalled after starting with 2.5 equivalents of $POCl_3$ and again after 1 additional equivalent was added after 2 and 3 hours of reaction. After 3.5 hours and a total of 4.5 equivalents of $POCl_3$, the reaction was worked up by quenching with cold water and neutralizing to a basic pH followed by extraction with ethyl acetate. This provided 90% yield with 91area% purity.

Finally, the installation the methoxide moiety was accomplished by exposure of the chloroquinoline **7** to sodium methoxide in refluxing methanol. After 13 hours of refluxing the solvent was removed in vacuo and the residue was taken up in ethyl acetate and water. The product was isolated by further extraction with ethyl acetate to give 876A-B in 90% yield with 97area% purity.

## Conclusion

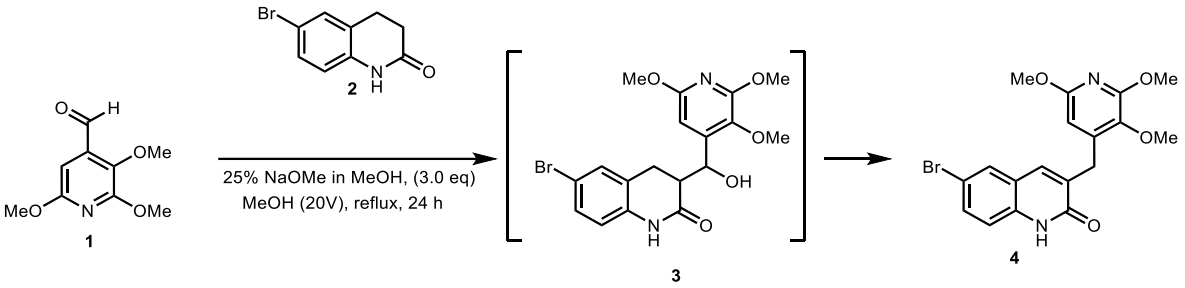
Starting from 6-bromo-3,4-dihydroquinolin-2(1H)-one (**3**) and 2,3,6-trimethoxyisonicotinaldehyde (**4**) an efficient 3-step synthesis of TBAJ-876 fragment 876A-B has been demonstrated on multigram scale. This shorter and more cost-effective route allows for higher overall yields of the eventual API and will increase patient access by reducing production costs.

## Acknowledgements

This work was supported by funding from the Bill & Melinda Gates Foundation (BMGF). The Medicines For All Institute would like to express our gratitude to Drs. Trevor Laird, John Dillon and Ryan Nelson (BMGF) for their helpful technical guidance throughout this project as well as Silpa Sundaram (BMGF) for her ongoing collaboration and support of the M4ALL mission. The authors would like to thank Janie Wierzbicki for her support of this project.

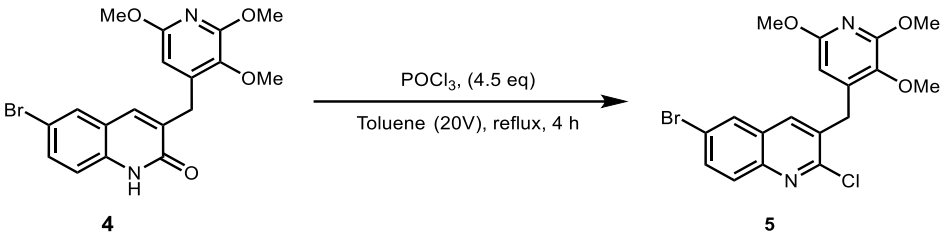
## Experimental

**PVK107-X108 Synthesis of 6-bromo-3-((2,3,6-trimethoxypyridin-4-yl)methyl)quinolin-2(1H)-one:**




To a 4-neck 500 mL round bottom flask equipped with an overhead stirrer, condenser with nitrogen bubbler, internal temperature probe and septum was added **6-bromo-3,4-dihydroquinolin-2(1H)-one** (17.2 g, 76.1 mmol, 1.5 eq.), **2,3,6-trimethoxyisonicotinaldehyde** (10.0 g, 50.7 mmol, 1.0 eq.) and dry MeOH (200 mL, 20V). The mixture was stirred (300 rpm) at rt for 5 mins then **sodium methoxide in MeOH** (32.9 g, 34.8 mL, 25% Wt, 3.0 Eq, 152 mmol) was added in one portion. The turbid reaction mixture was then heated to reflux and turned clear. The reaction was refluxed for 24 h resulting in copious amounts of precipitated product. The HPLC at 24 hours showed the aldehyde was completely consumed. Heating was stopped, the reaction was allowed to cool to room temperature, and the precipitated product was isolated by vacuum filtration. The solid was washed with MeOH (50 mL, 5V) to give the product as a white solid (14.56 g, 70%, 99area%). HPLC of mother liquor showed that it contained a considerable amount of product. The mother liquor was concentrated until formation of solid was observed. The resulting solid was then collected by vacuum filtration and washed with MeOH (20 mL, 2V) to obtain a second crop (4.68 g, 23%, 66area%, 15% purity adjusted yield). The overall isolated yield of the both crops was (19.2 g, %, 85% adjusted yield). The material was carried to the next step without purification. **$^{1}$H NMR** (600 MHz, TFA-D) δ/ppm: 8.28 (s, 1H), 7.95 (s, 1H), 7.83 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.50 (d, *J* = 8.7 Hz, 1H), 6.72 (s, 1H), 4.30 (s, 3H), 4.25 (s, 2H), 3.98 (s, 3H), 3.90 (s, 3H). **$^{13}$C NMR** (150 MHz, $CDCl_3$) δ/ppm: 158.1, 158.0, 156.7, 155.7, 146.9, 140.2, 138.8, 136.5, 132.7, 127.6, 125.4, 122.6, 120.7, 102.2, 63.2, 61.3, 59.9, 33.4.

**PVK107-X109 Synthesis of 6-bromo-2-chloro-3-((2,3,6-trimethoxypyridin-4-yl)methyl)quinoline:**

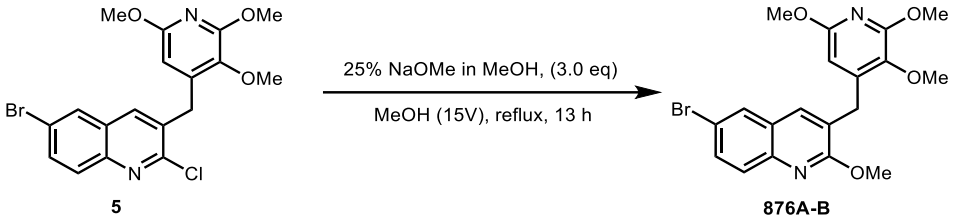



To a 4-neck 500 mL round bottom flask equipped with an overhead stirrer, condenser with nitrogen bubbler, internal temperature probe and septum, was added **6-bromo-3-((2,3,6-trimethoxypyridin-4-yl)methyl)quinolin-2(1H)-one** (15.0 g, 37.014 mmol, 1.0 eq) and toluene (300 mL, 20V) at room temperature. Stirring (300 rpm) was begun. To this heterogeneous mixture, $POCl_3$ (14.188 g, 8.625 mL, 92.535 mmol, 2.5 eq.) was added in one portion at room temperature, and the resulting mixture was heated to reflux and monitored by HPLC. At 2 and at 3 hours of reaction time additional $POCl_3$ (5.675 g, 3.45 mL, 1.0 Eq, 37.014 mmol) was added to the reaction, see table.

| Time (hr) | SM (LCAP) | Product (LCAP) | Note |
|---|---|---|---|
| 0.5 | 50 | 50 | |
| 1 | 28 | 71 | |
| 1.5 | 22 | 74 | |
| 2 | 20 | 71 | Add 1.0 eq $POCl_3$ |
| 2.5 | 11 | 79 | |
| 3 | 11 | 79 | Add 1.0 eq $POCl_3$ |
| 3.5 | 12 | 79 | |

After 4 hours the reaction was not showing any progress, heating was stopped and it was allowed to cool to room temperature. The reaction mixture was poured into ice-cold water (300 mL, 20V), basified with saturated aqueous $NaHCO_3$ to pH 8–8.5 and extracted with ethyl acetate (3 x 100 mL). These combined organic fractions were washed with brine (100 mL), dried over ($Na_2SO_4$), and evaporated in vacuo to yield the crude product as yellow solid (14.1 g, 90%, 91area%). HPLC also showed ~9area% of unreacted starting material 4. This solid product was used as such for the next step. **$^1$H NMR** (600 MHz, $CDCl_3$) δ/ppm: 7.87 (d, *J* = 2.2 Hz, 1H), 7.85 (d, *J* = 8.9 Hz, 1H), 7.74 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.71 (s, 1H), 6.01 (s, 1H), 4.16 (s, 2H), 4.01 (s, 3H), 3.85 (s, 3H), 3.73 (s, 3H). **$^{13}$C NMR** (150 MHz, $CDCl_3$) δ/ppm: 157.8, 155.5, 151.7, 145.1, 143.2, 137.0, 135.4, 133.4, 132.6, 129.8, 129.3, 128.4, 120.9, 101.1, 60.4, 53.6, 53.5, 33.1.

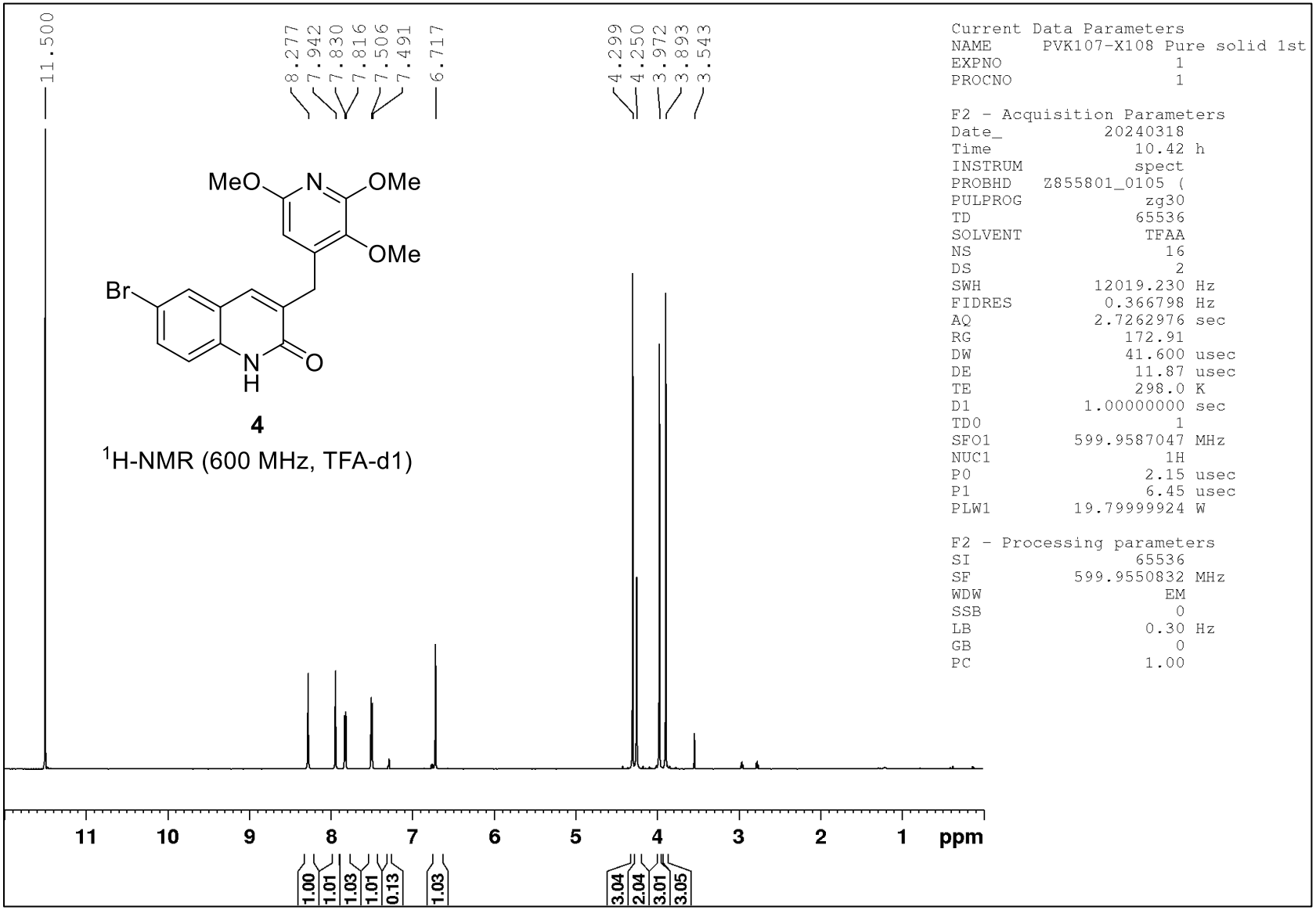
**PVK107-X110 Synthesis of 6-bromo-2-methoxy-3-((2,3,6-trimethoxypyridin-4-yl)methyl)quinoline:**




**5** **876A-B**

To a 4-neck 500 mL round bottom flask equipped with an overhead stirrer, condenser with nitrogen bubbler, internal temperature probe and septum was added **6-bromo-2-chloro-3-((2,3,6-trimethoxypyridin-4-yl)methyl)quinoline** (10.0 g, 23.6 mmol, 1.0 eq.) and dry MeOH (150mL, 15V). Stirring (300 rpm) was begun. To this was added sodium methoxide in MeOH (15.3 g, 16.2 mL, 25% Wt, 70.8 mmol, 3.0 eq.), and the resulting mixture was heated to reflux and monitored by HPLC. After 13 hours of reflux, HPLC showed the starting material was consumed. The reaction was allowed to cooled to room temperature and the solvent was evaporated to dryness on a rotary evaporator. The residue was dissolved in EtOAc (50 mL) and washed with water (50 mL). The aqueous layer was then extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$, and evaporated to give the crude product (9.2 g, 90%) with 97% purity by HPLC area%. Unreacted aldol product intermediate **4** was observed at 3area%. **$^1$H NMR** (600 MHz, $CDCl_3$) δ/ppm: 7.75 (d, *J* = 2.1 Hz, 1H), 7.68 (d, *J* = 8.9 Hz, 1H), 7.61 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.54 (s, 1H), 6.03 (s, 1H), 4.07 (s, 3H), 4.0 (s, 3H), 3.98 (s, 2H), 3.84 (s, 3H), 3.27 (s, 3H). **$^{13}$C NMR** (150 MHz, $CDCl_3$) δ/ppm: 160.9, 157.7, 155.4, 144.4, 144.2, 136.0, 135.6, 131.9, 129.0, 128.5, 126.6, 125.1, 117.1, 101.1, 60.4, 53.7, 53.6, 53.4, 29.8.

## II. $^{1}H$, and $^{13}C$ NMR Spectra:

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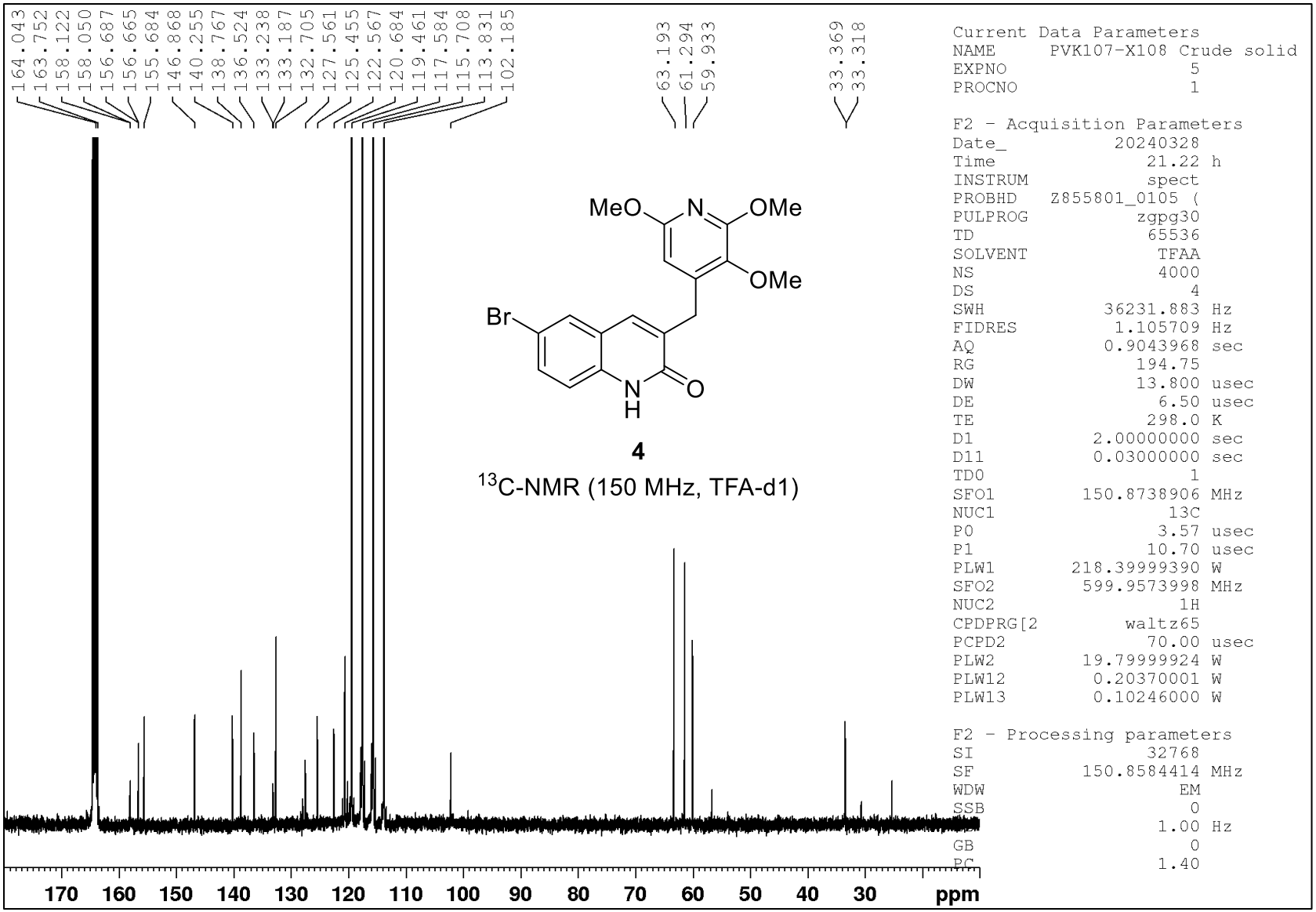


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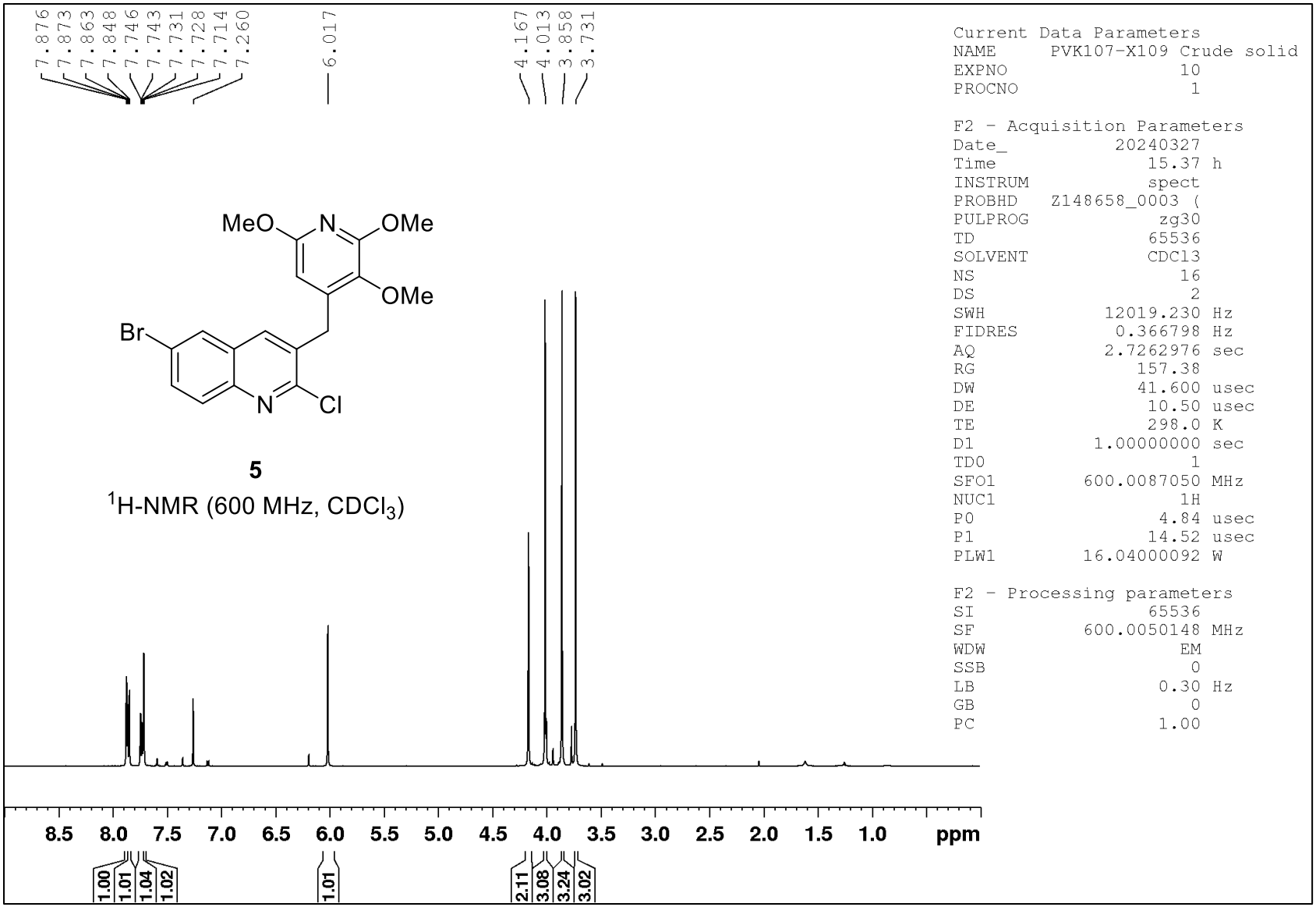

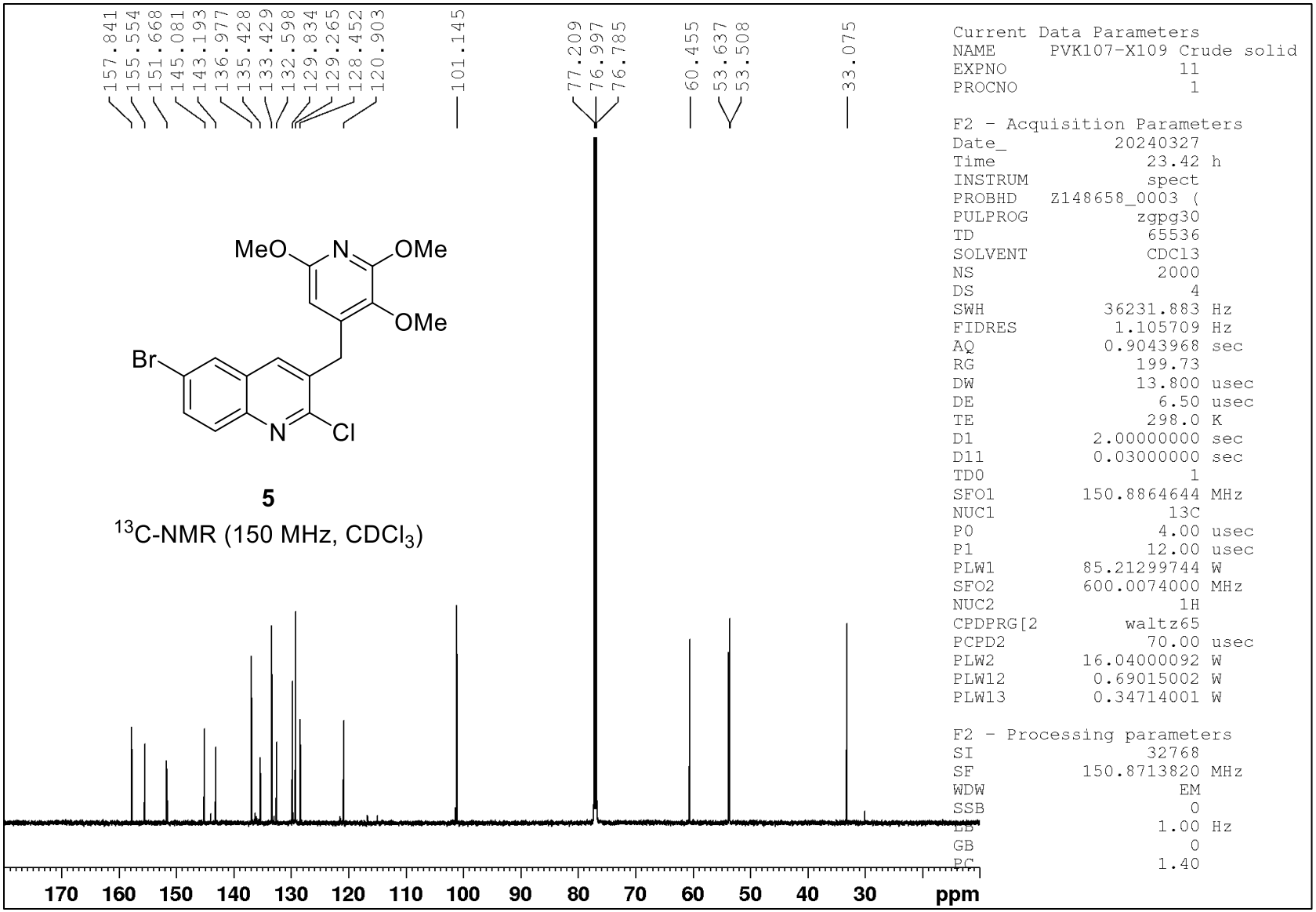

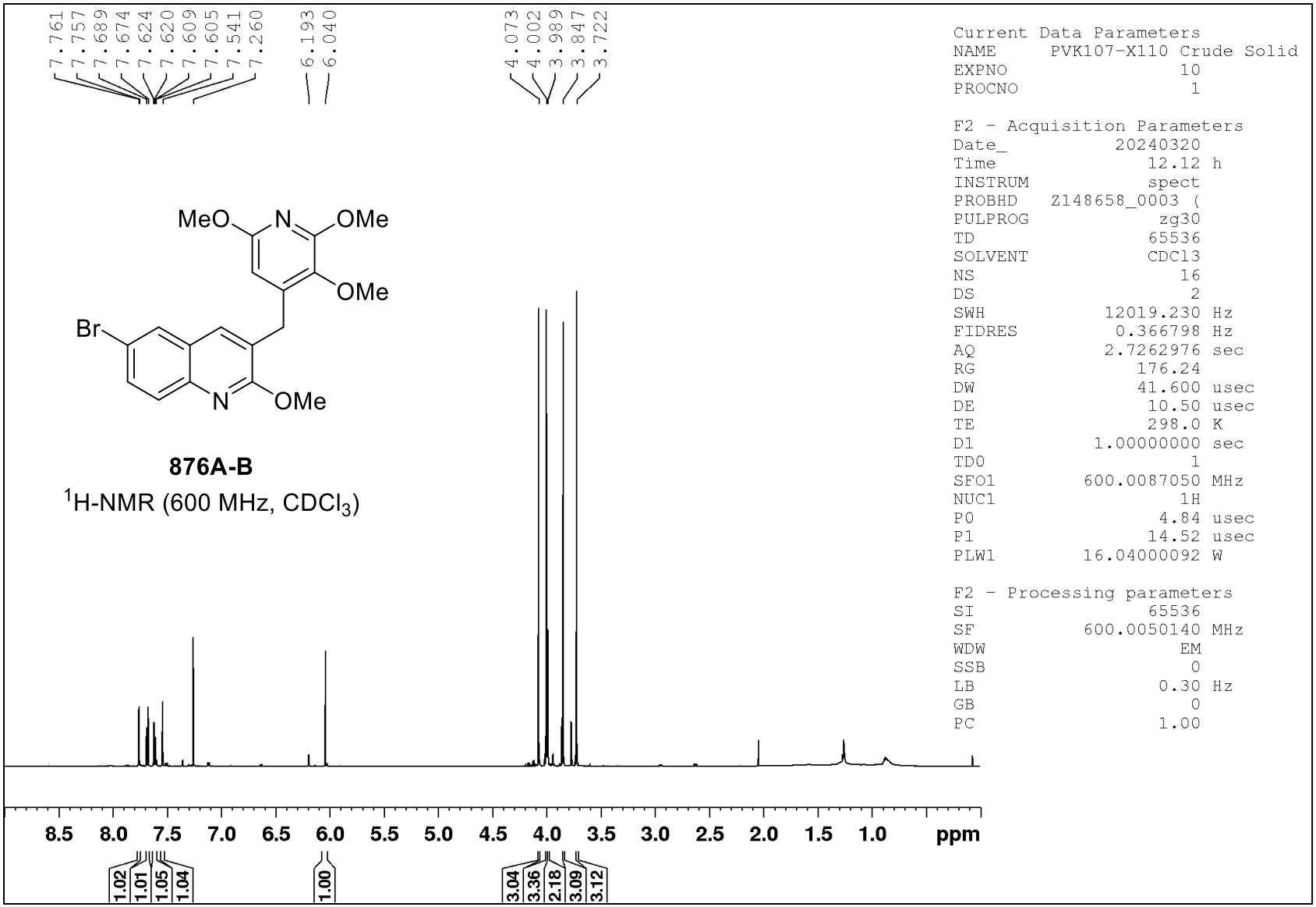


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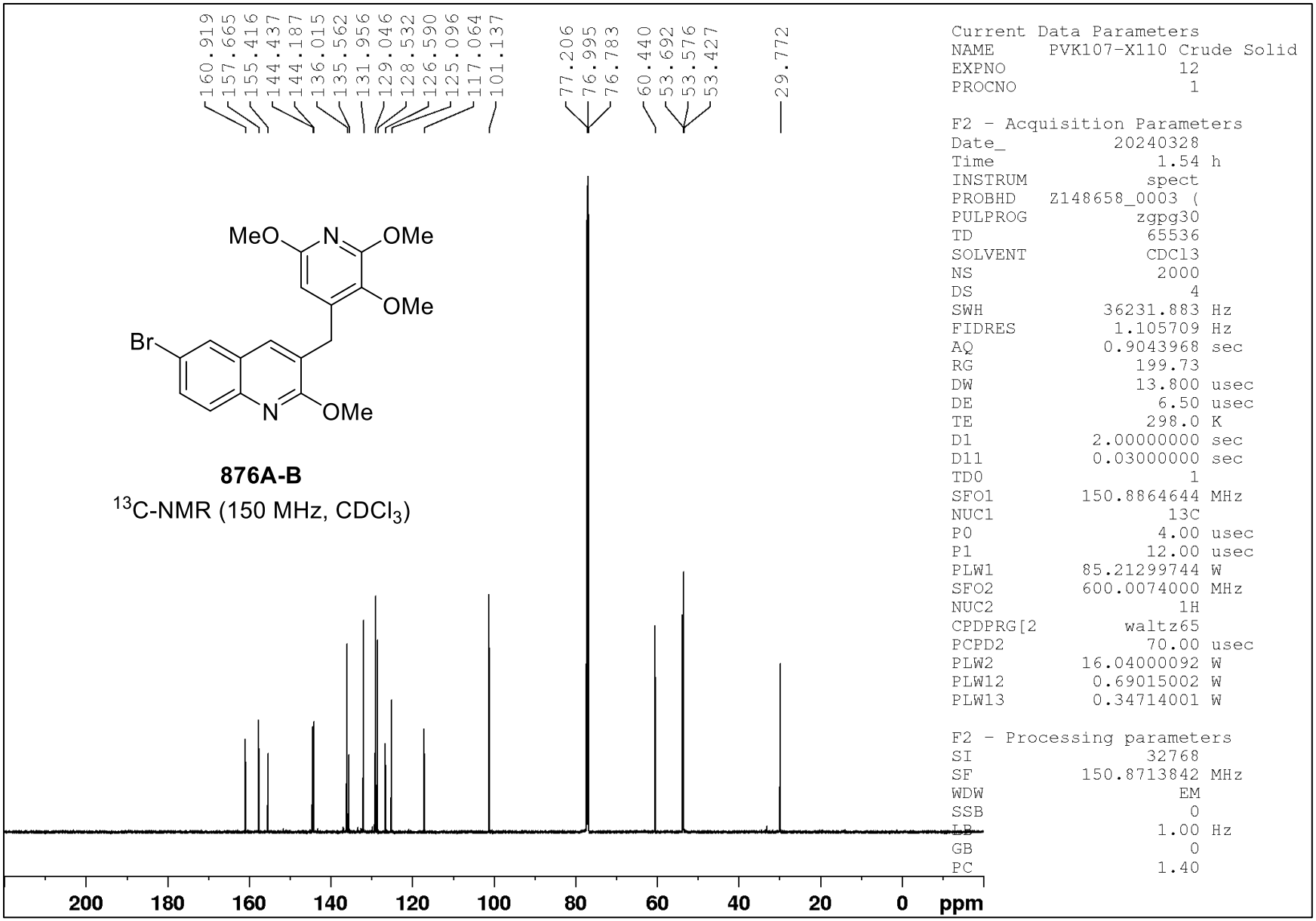


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