Design, Synthesis and Preliminary Biological Evaluation of Novel Benzylsulfone Coumarin Derivatives as Anticancer Agents

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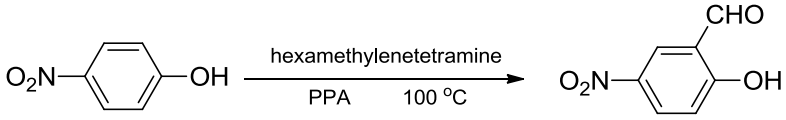
Supplementary Materials

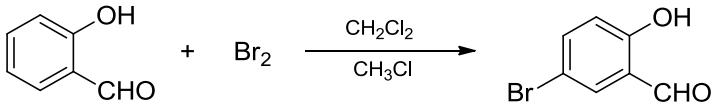
1. Synthesis of Intermediates

1.1. 5-nitrosalicyladehyde (**4b**)



A mixture of 4-nitrophenol (7.5 g, 54 mmol, 1.0 eq.), hexamethylene tetramine (7.5 g, 54 mmol, 1.0 eq.), and 75% PPA (60 mL) was agitated for 5 hours at 100 ℃. Subsequently, the mixture was placed in 100 mL of ethyl acetate and 200 mL of water, and agitated until the mixture became completely dissolved. In addition, as a result of additionally adding 100 ml of ethyl acetate to the foregoing solution, the solution separated into 2 phases. The water phase was removed and the remaining solution was washed with saturated brine (50 mL*2), then the organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated under vacuum to obtain the desired product **4b** as a yellow solid, yield, 33.0%; m.p. 127-129 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.22 (s, 1H, -CHO), 10.30 (s, 1H, -OH), 8.43 (d, 1H, *J* = 2.8 Hz, H-6), 8.35 (d, 1H, *J* = 8.8 Hz, H-4), 7.19 (d, 1H, *J* = 8.8 Hz, H-3).

1.2. 5-Bromosalicylaldehyde (**4c**)



To a solution of salicylaldehyde (3.66 g, 30 mmol, 1.0 eq.) in 20 mL dichloromethane, 5.28 g (33 mmol, 1.1 eq.) bromine in 60 mL chloroform was added dropwisely over a period of 4-5 h. After completion of the reaction (TLC monitoring), the solvent was evaporated to obtain the crude product, which was recrystallized in 90% ethanol to yield the desired product. Yield, 64.2%; white solid, m.p. 105-107 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.94 (s, 1H, -CHO); 9.84 (s, 1H, -OH); 7.68 (d, 1H, *J* = 2.4 Hz, H-6); 7.61 (d, 1H, *J* = 8.8 Hz, H-4); 6.92 (d, 1H, *J* = 8.8 Hz, H-3).

1.3. General Procedure for the Preparation of Benzylthioacetic Acids (2a-2j).

The following benzylthioacetic acids were synthesized according to the procedure described in the literature and identified by comparing their melting points and properties with the literature data.

2-(2-Fluorobenzylthio)acetic Acid (**2a**). Condensation of 2-fluorobenzyl chloride **1a** with mercaptoacetic acid yielded the corresponding 2-(2-fluorobenzylthio)acetic

acid. The yield of this reaction was 98.5%, giving a pale yellow oil. It was identified by comparing its physical data with the literature data [1].

2-(3-Fluorobenzylthio)acetic Acid (**2b**). Condensation of 3-fluorobenzyl chloride **1b** with mercaptoacetic acid yielded the corresponding 2-(3-fluorobenzylthio)acetic acid. The yield of this reaction was 98.1%, giving a pale yellow oil. It was identified by comparing its physical data with the literature data [1].

2-(4-Fluorobenzylthio)acetic Acid (**2c**). Condensation of 4-fluorobenzyl chloride **1c** with mercaptoacetic acid yielded the corresponding 2-(4-fluorobenzylthio)acetic acid. The yield of this reaction was 94.8%, giving a pale yellow oil. It was identified by comparing its physical data with the literature data [2].

2-(2-Chlorobenzylthio)acetic Acid (**2d**). Condensation of 2-chlorobenzyl chloride **1d** with mercaptoacetic acid yielded the corresponding 2-(2-chlorobenzylthio)acetic acid. The yield of this reaction was 89.8%, giving a white solid with a melting point of 52-53 ^{o}C. It was identified by comparing its physical data with the literature data [3].

2-(2-Bromobenzylthio)acetic Acid (**2e**). Condensation of 2-bromobenzyl bromide **1e** with mercaptoacetic acid yielded the corresponding 2-(2-bromobenzylthio)acetic acid. The yield of this reaction was 94.6%, giving a white solid with a melting point of 49-51 ^{o}C. It was identified by comparing its physical data with the literature data [3].

2-(3-Bromobenzylthio)acetic Acid (**2f**). Condensation of 3-bromobenzyl bromide **1f** with mercaptoacetic acid yielded the corresponding 2-(3-bromobenzylthio)acetic acid. The yield of this reaction was 91.7%, giving a pale yellow solid with a melting point of 87-89 ^{o}C. It was identified by comparing its physical data with the literature data [4].

2-(4-Bromobenzylthio)acetic Acid (**2g**). Condensation of 4-bromobenzyl bromide **1g** with mercaptoacetic acid yielded the corresponding 2-(4-bromobenzylthio)acetic acid. The yield of this reaction was 91.2%, giving a pale yellow solid with a melting point of 73-76 ^{o}C. It was identified by comparing its physical data with the literature data [4].

2-(3-Methylbenzylthio)acetic Acid (**2h**). Condensation of 3-methylbenzyl chloride **1h** with mercaptoacetic acid yielded the corresponding 2-(3-methylbenzylthio)acetic acid. The yield of this reaction was 91.5%, giving a pale yellow solid with a melting point of 72-74 ^{o}C. It was identified by comparing its physical data with the literature data [5].

2-(4-Methylbenzylthio)acetic Acid (**2i**). Condensation of 4-methylbenzyl chloride **1i** with mercaptoacetic acid yielded the corresponding 2-(4-methylbenzylthio)acetic acid. The yield of this reaction was 78.7%, giving a pale yellow solid with a melting point of 65-67 ^{o}C. It was identified by comparing its physical data with the literature data [6].

2-[2-(Trifluoromethyl)benzylthio]acetic Acid (**2j**). Condensation of 2-(trifluoro methyl)benzyl bromide **1j** with mercaptoacetic acid yielded the corresponding 2-[2-(trifluoromethyl)benzylthio]acetic acid. The yield of this reaction was 94.5%, giving a pale yellow oil. It was identified by comparing its physical data with the

literature data [5].

1.4. General Procedure for the Preparation of Benzylsulfonylacetic Acids (3a-3j).

The following benzylsulfonylacetic acids were synthesized according to the procedure described in the literature and identified by comparing their melting points and properties with the literature data.

2-[(2-Fluorobenzyl)sulfonyl]acetic Acid (**3a**). Oxidation of 2-(2-fluorobenzylthio)acetic acid **2a** with 30% hydrogen peroxide yielded the corresponding 2-[(2-fluorobenzyl)sulfonyl]acetic acid. The yield of this reaction was 58.9%, giving a white solid with a melting point of 134.5-136 ^{o}C. It was identified by comparing its physical data with the literature data [7].

2-[(3-Fluorobenzyl)sulfonyl]acetic Acid (**3b**). Oxidation of 2-(3-fluorobenzylthio)acetic acid **2b** with 30% hydrogen peroxide yielded the corresponding 2-[(3-fluorobenzyl)sulfonyl]acetic acid. The yield of this reaction was 83.3%, giving a white solid with a melting point of 126-128 ^{o}C. It was identified by comparing its physical data with the literature data [7].

2-[(4-Fluorobenzyl)sulfonyl]acetic Acid (**3c**). Oxidation of 2-(4-fluorobenzylthio)acetic acid **2c** with 30% hydrogen peroxide yielded the corresponding 2-[(4-fluorobenzyl)sulfonyl]acetic acid. The yield of this reaction was 60.5%, giving a white solid with a melting point of 160-164 ^{o}C. It was identified by comparing its physical data with the literature data [2].

2-[(2-Chlorobenzyl)sulfonyl]acetic Acid (**3d**). Oxidation of 2-(2-chlorobenzylthio)acetic acid **2d** with 30% hydrogen peroxide yielded the corresponding 2-[(2-chlorobenzyl)sulfonyl]acetic acid. The yield of this reaction was 70.0%, giving a white solid with a melting point of 162-165^{o}C. It was identified by comparing its physical data with the literature data [8].

2-[(2-Bromobenzyl)sulfonyl]acetic Acid (**3e**). Oxidation of 2-(2-bromobenzylthio)acetic acid **2e** with 30% hydrogen peroxide yielded the corresponding 2-[(2-bromobenzyl)sulfonyl]acetic acid. The yield of this reaction was 78.7%, giving a white solid with a melting point of 175-177 ^{o}C. It was identified by comparing its physical data with the literature data [3].

2-[(3-Bromobenzyl)sulfonyl]acetic Acid (**3f**). Oxidation of 2-(3-bromobenzylthio)acetic acid **2f** with 30% hydrogen peroxide yielded the corresponding 2-[(3-bromobenzyl)sulfonyl]acetic acid. The yield of this reaction was 85.8%, giving a white solid with a melting point of 179-181 ^{o}C. It was identified by comparing its physical data with the literature data [3].

2-[(4-Bromobenzyl)sulfonyl]acetic Acid (**3g**). Oxidation of 2-(4-bromobenzylthio)acetic acid **2g** with 30% hydrogen peroxide yielded the corresponding 2-[(4-bromobenzyl)sulfonyl]acetic acid. The yield of this reaction was 87.7%, giving a white solid with a melting point of 177-179 ^{o}C. It was identified by comparing its physical data with the literature data [9].

2-[(3-Methylbenzyl)sulfonyl]acetic Acid (**3h**). Oxidation of 2-(3-methylbenzylthio)acetic acid **2h** with 30% hydrogen peroxide yielded the corresponding 2-[(3-methylbenzyl)sulfonyl]acetic acid. The yield of this reaction was

82.8%, giving a white solid with a melting point of 134-136 ^{o}C. It was identified by comparing its physical data with the literature data [5].

2-[(4-Methylbenzyl)sulfonyl]acetic Acid (**3i**). Oxidation of 2-(4-methylbenzylthio)acetic acid **2i** with 30% hydrogen peroxide yielded the corresponding 2-[(4-methylbenzyl)sulfonyl]acetic acid. The yield of this reaction was 43.2%, giving a white solid with a melting point of 145-146 ^{o}C. It was identified by comparing its physical data with the literature data [5].

2-{[2-(Trifluoromethyl)benzyl]sulfonyl}acetic Acid (**3j**). Oxidation of 2-[2-(trifluoromethyl)benzylthio]acetic acid **2j** with 30% hydrogen peroxide yielded the corresponding 2-{[2-(trifluoromethyl)benzyl]sulfonyl}acetic acid. The yield of this reaction was 79.0%, giving a white solid with a melting point of 168-169 ^{o}C. It was identified by comparing its physical data with the literature data [8].

References

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[3] Janczewski, M.; Ksiezopolski, J. Effect of molecular structure on optical properties of sulfoxide systerms, m-Bromobenzylsulfinylacetic acids and some if their derivatives, Part VII. *Pol. J. Chem.* **1984**, *58*, 103-106.

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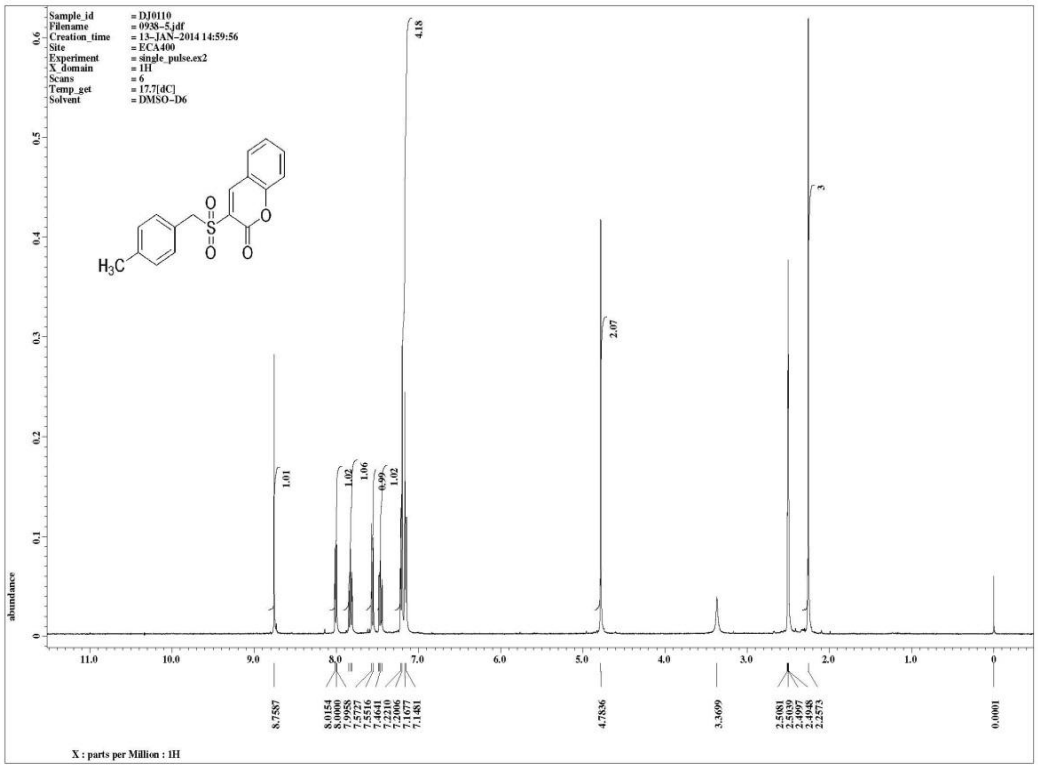
[8] Ning X.L.; Guo Y.; Wang X.W.; Ma X.Y.; Tian C.; Shi X.Q.; Zhu R.Z.; Cheng C.; Du Y.S.; Ma Z.Z.; et al. Design, synthesis, and biological evaluation of (E)-3,4-dihydroxystyryl aralkyl sulfones and sulfoxides as novel multifunctional neuroprotective Agents. *J. Med. Chem*. **2014**, *57*, 4302-4312.

[9] Janczewski, M.; Ksiezopolski, J. Effect of molecular structure on optical properties of sulfoxide systerms, p-Bromobenzylsulfinylacetic acids and some if their derivatives, Part III. *Pol. J. Chem*. **1981**, *55*, 535-546.

2. Copies of ^{1}H-NMR and ^{13} C-NMR for target compounds (5a -5o)

^{1}H-NMR of Compound **5a**:



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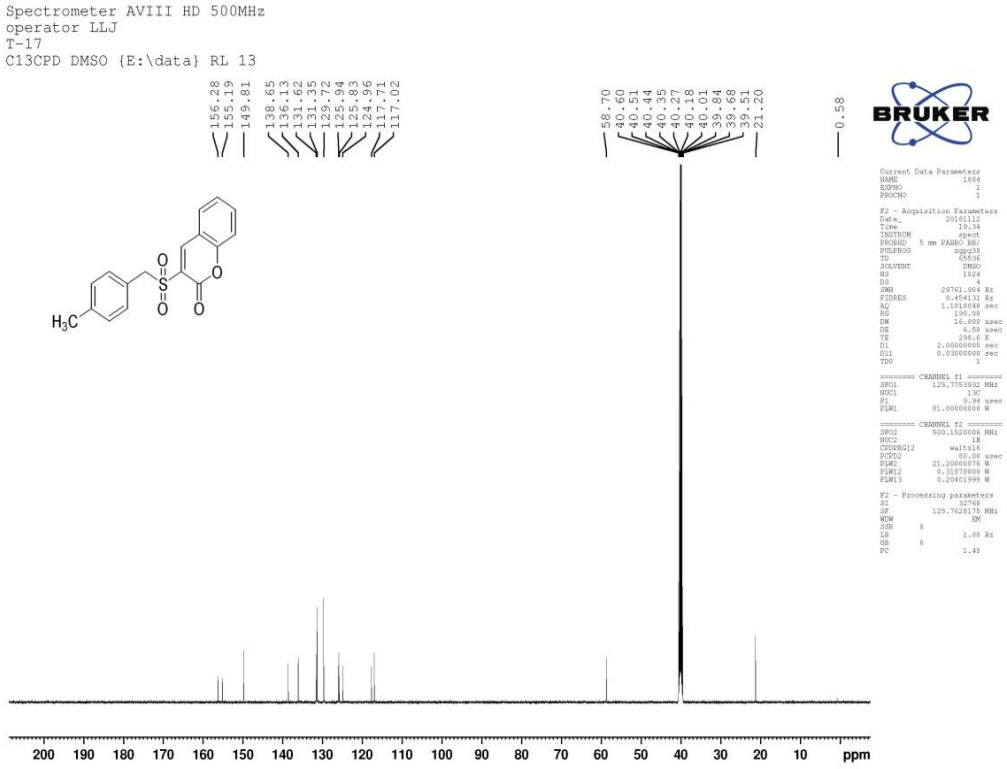

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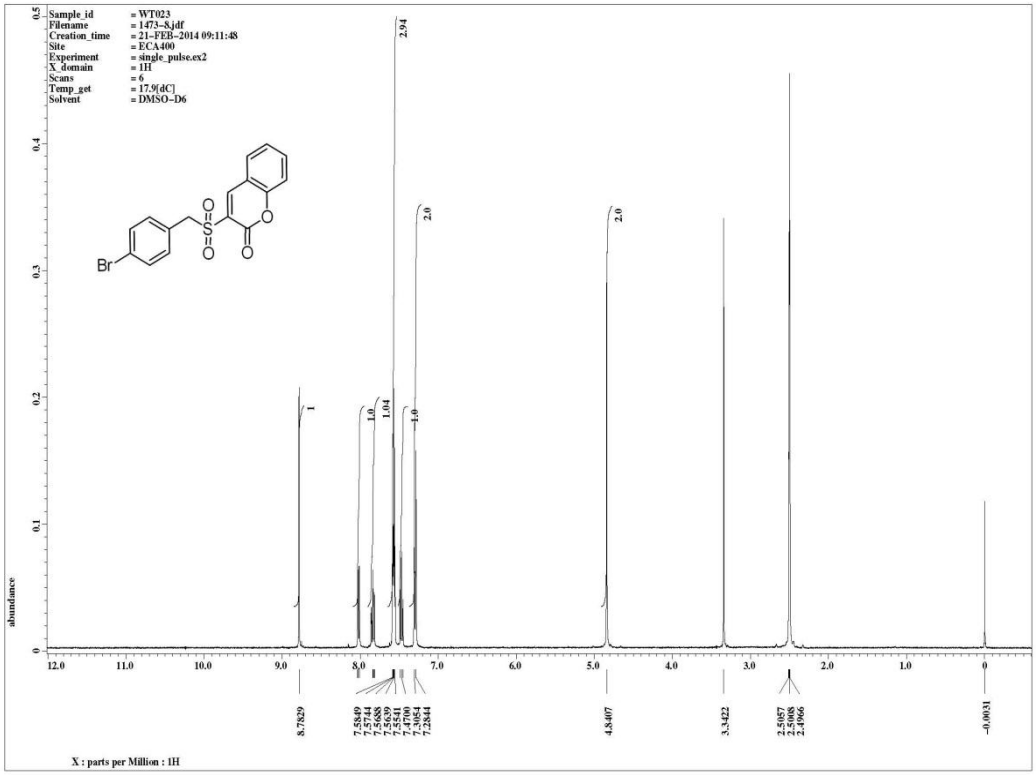

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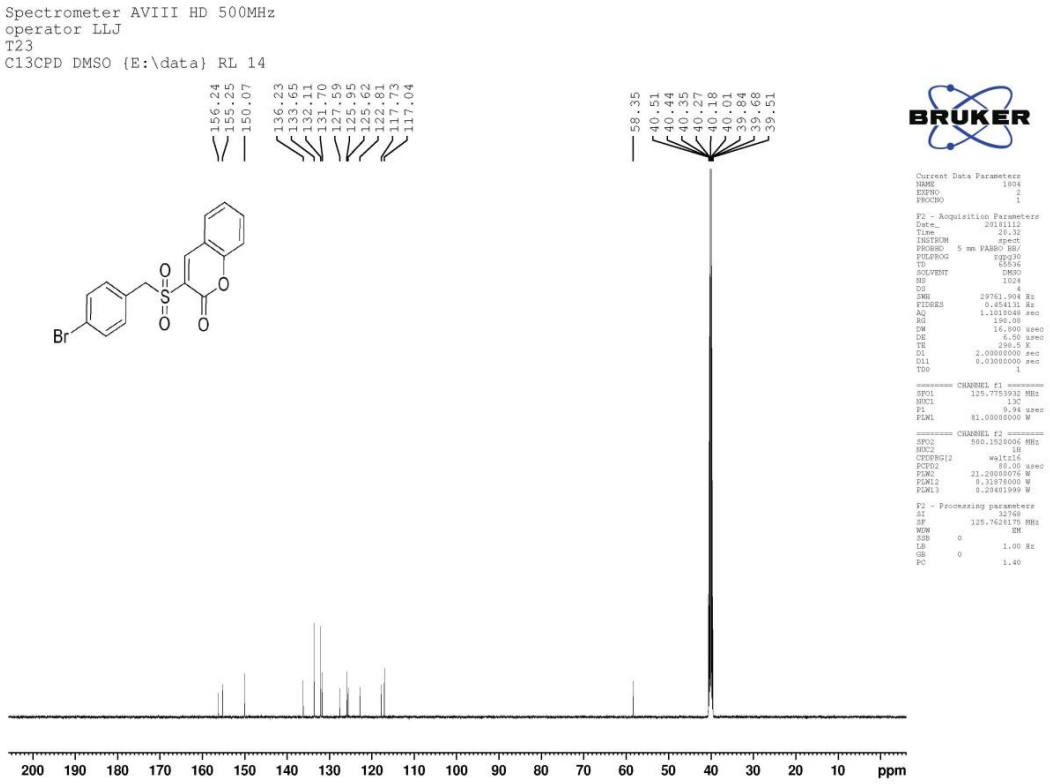

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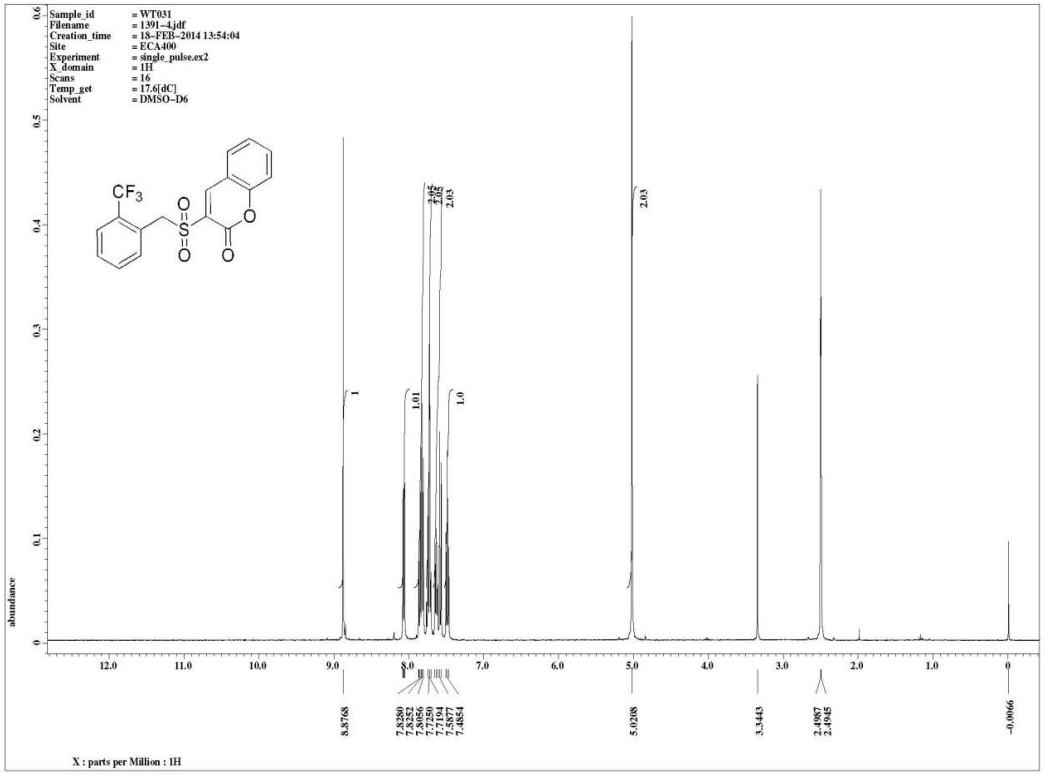

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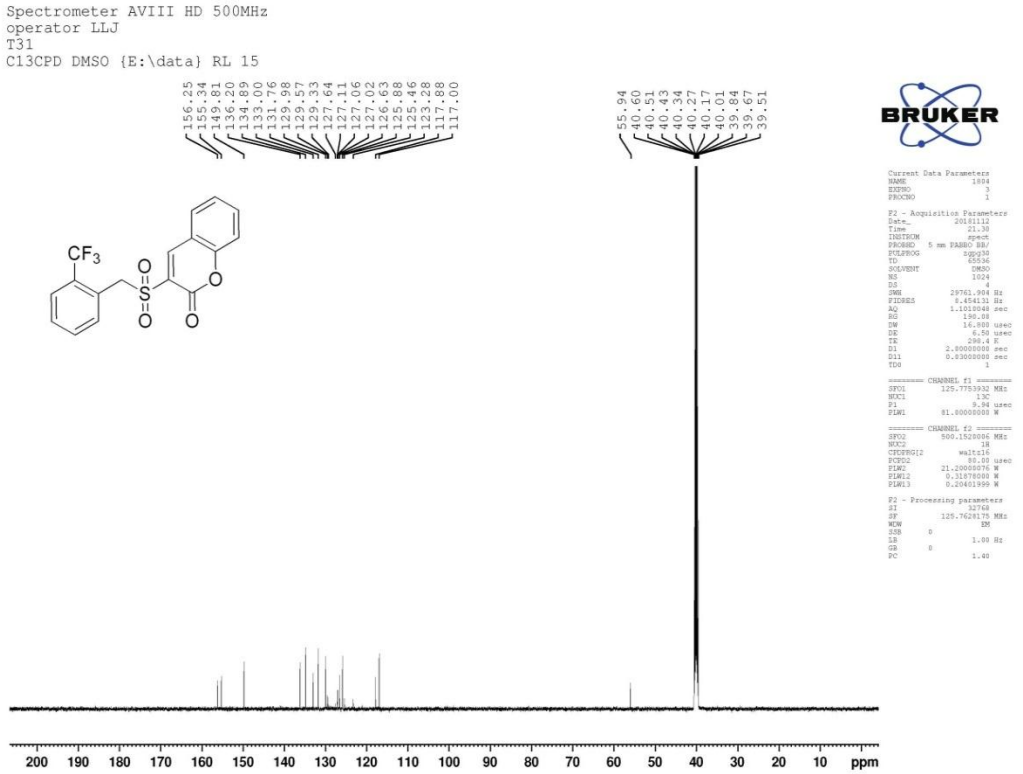

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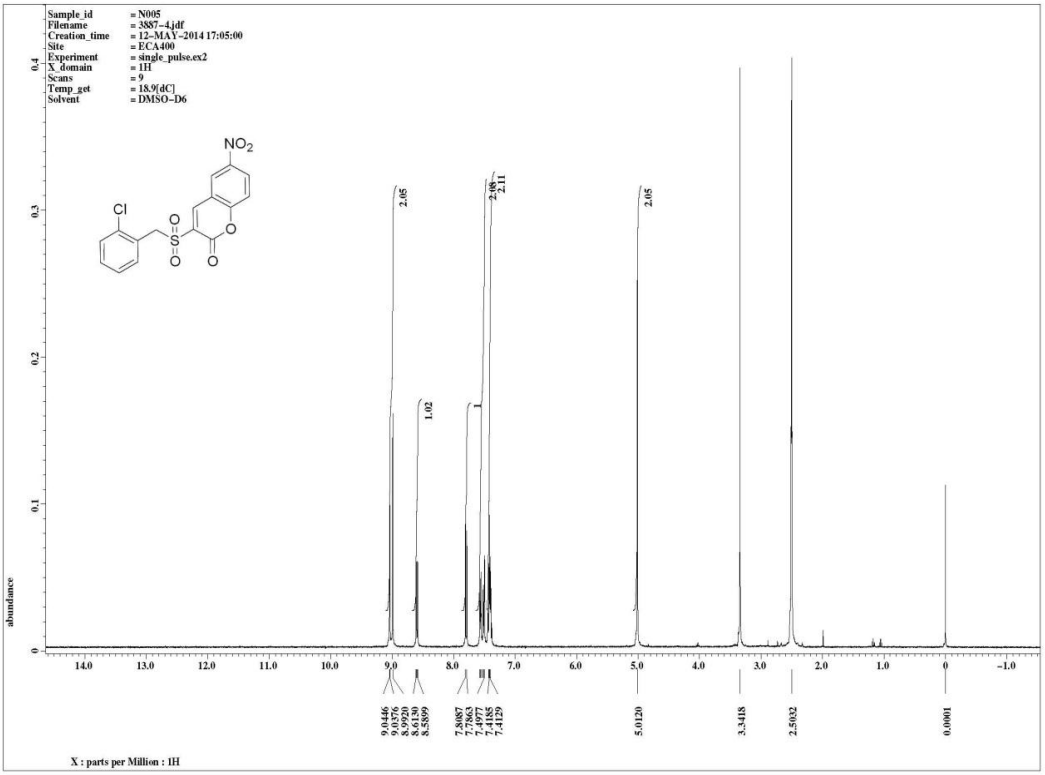

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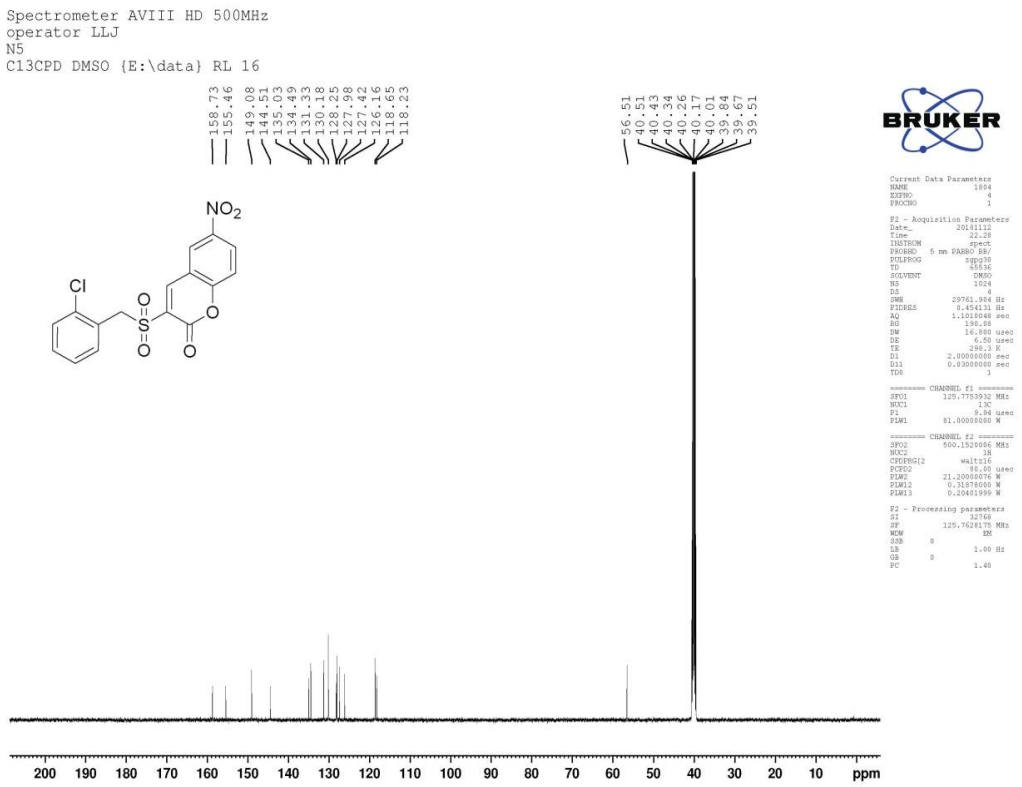

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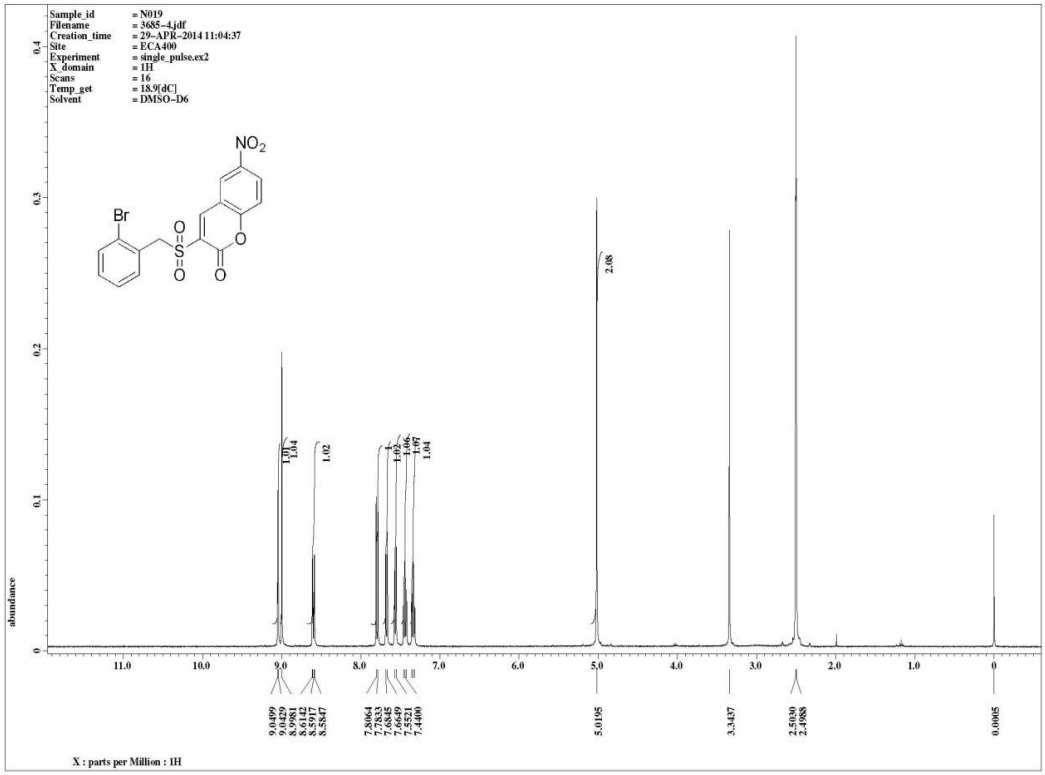

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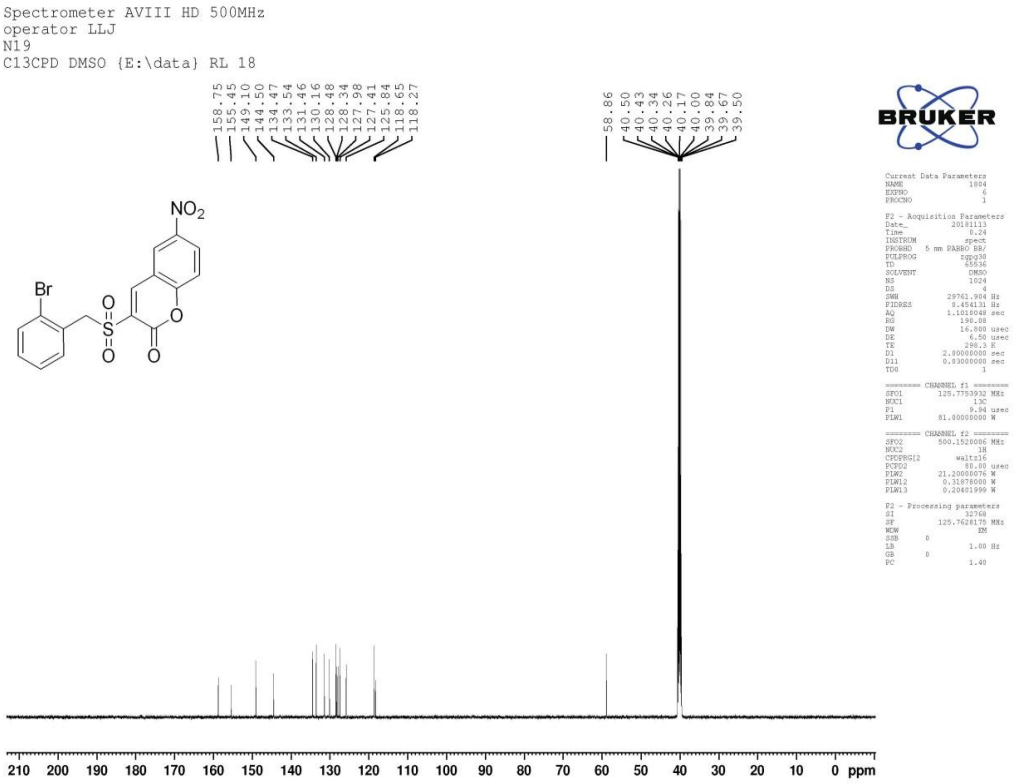

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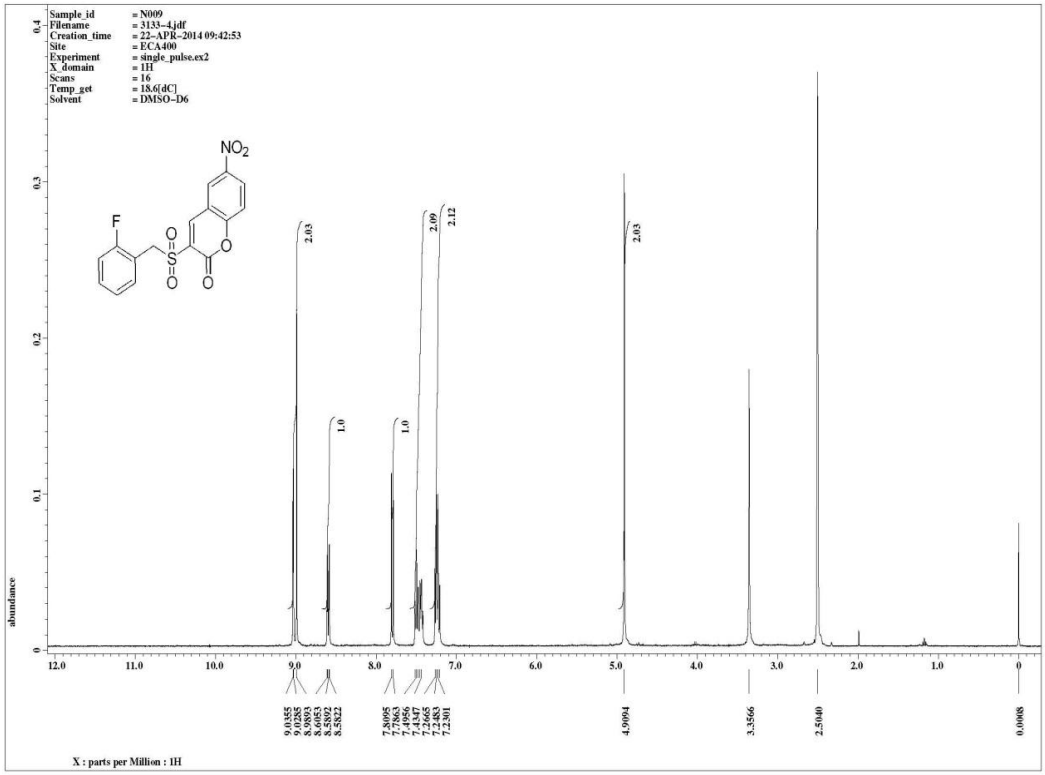

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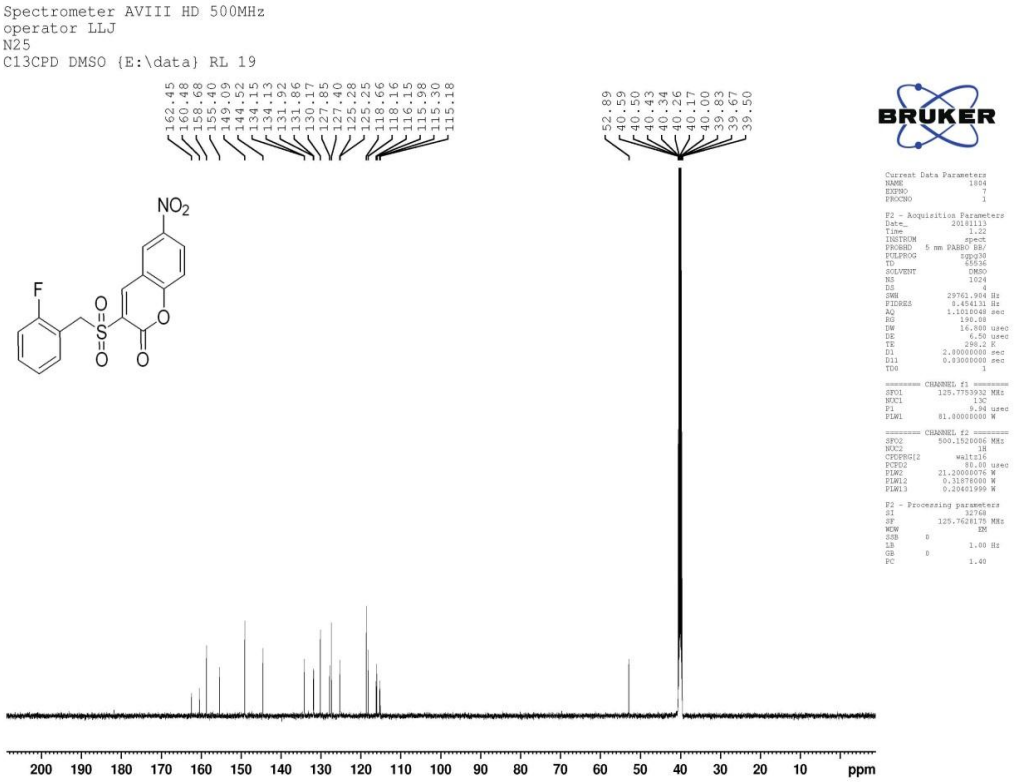

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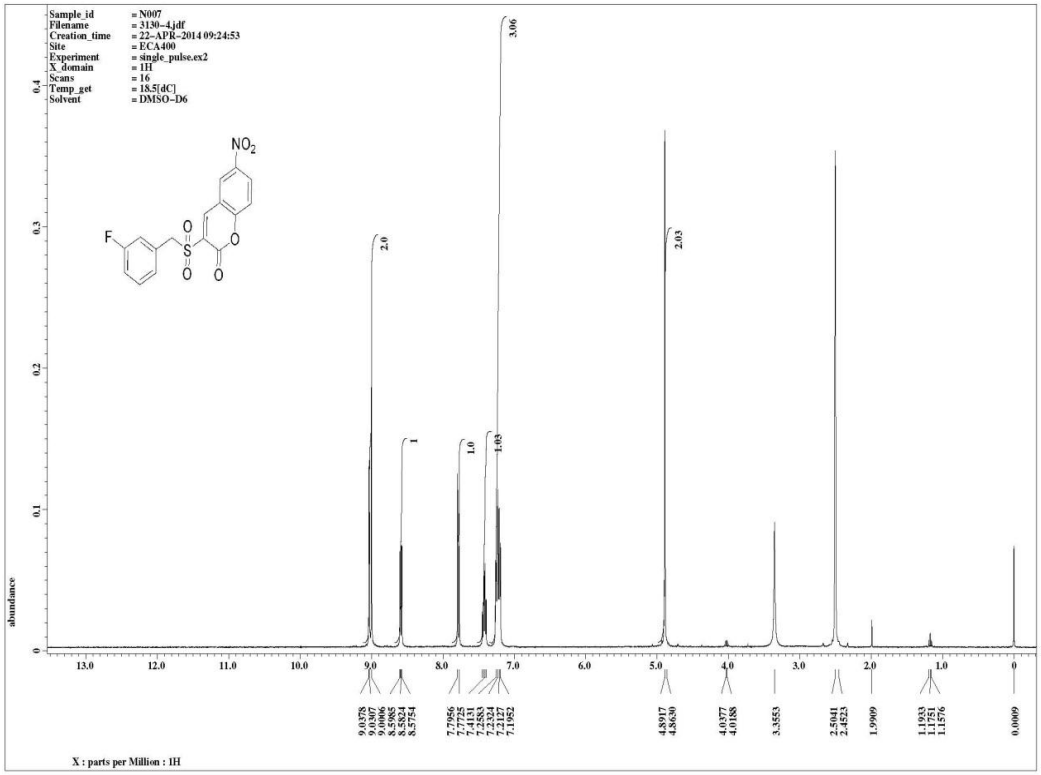

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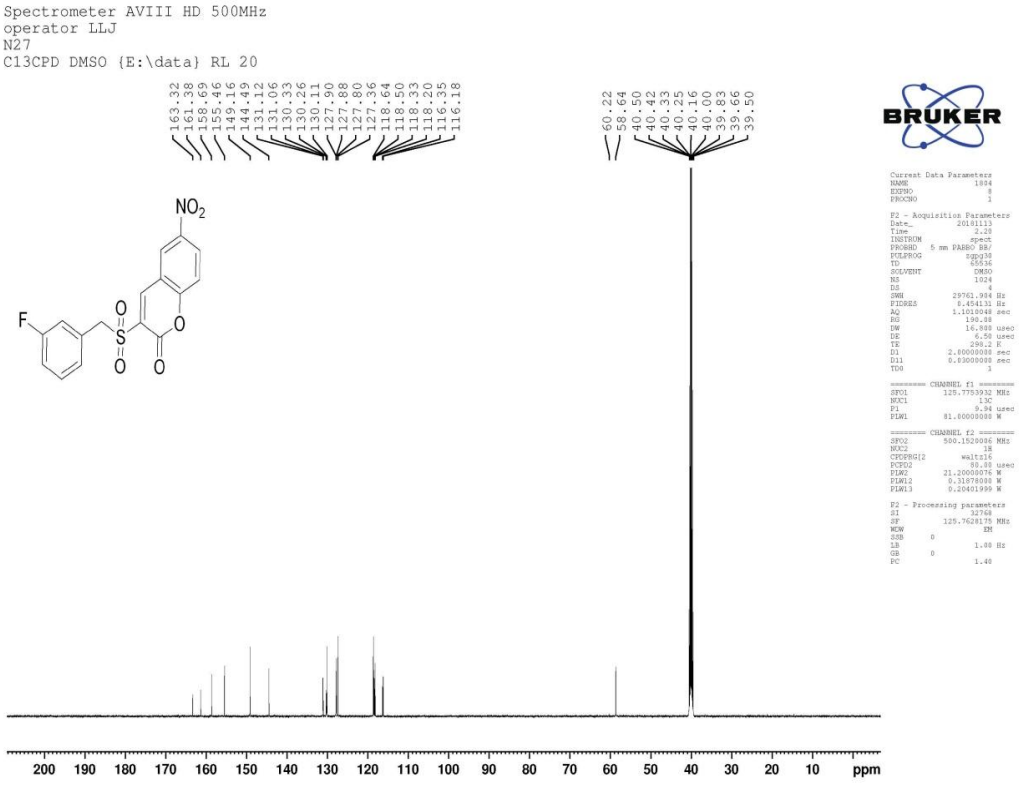

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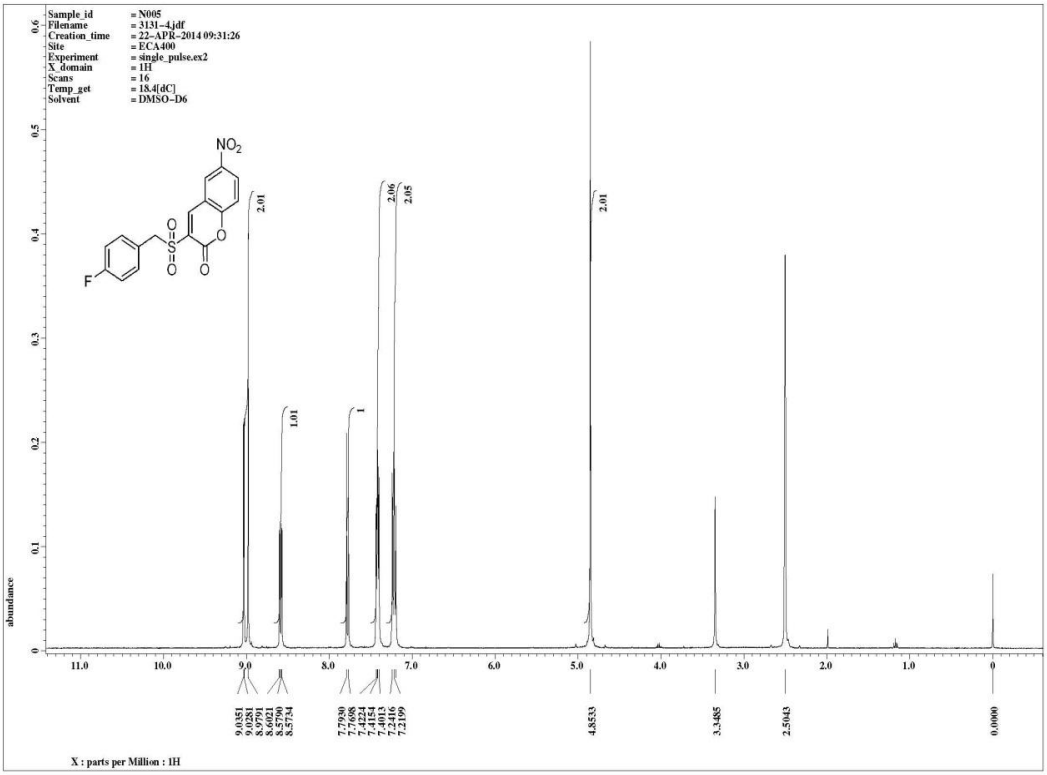

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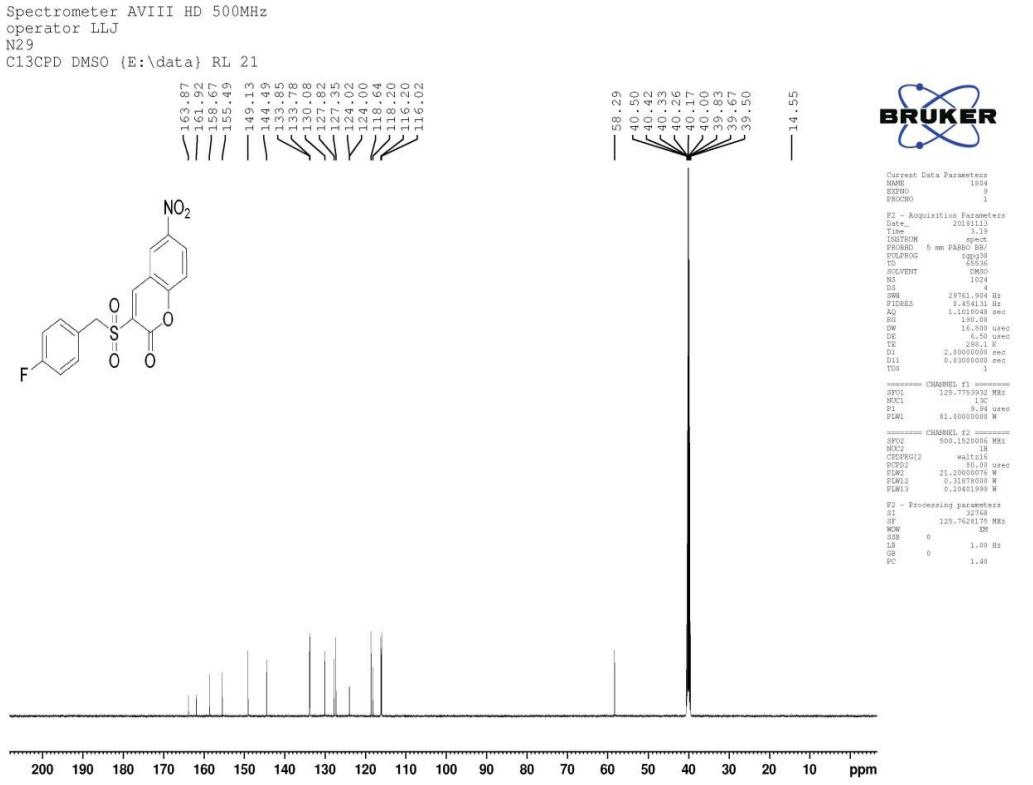

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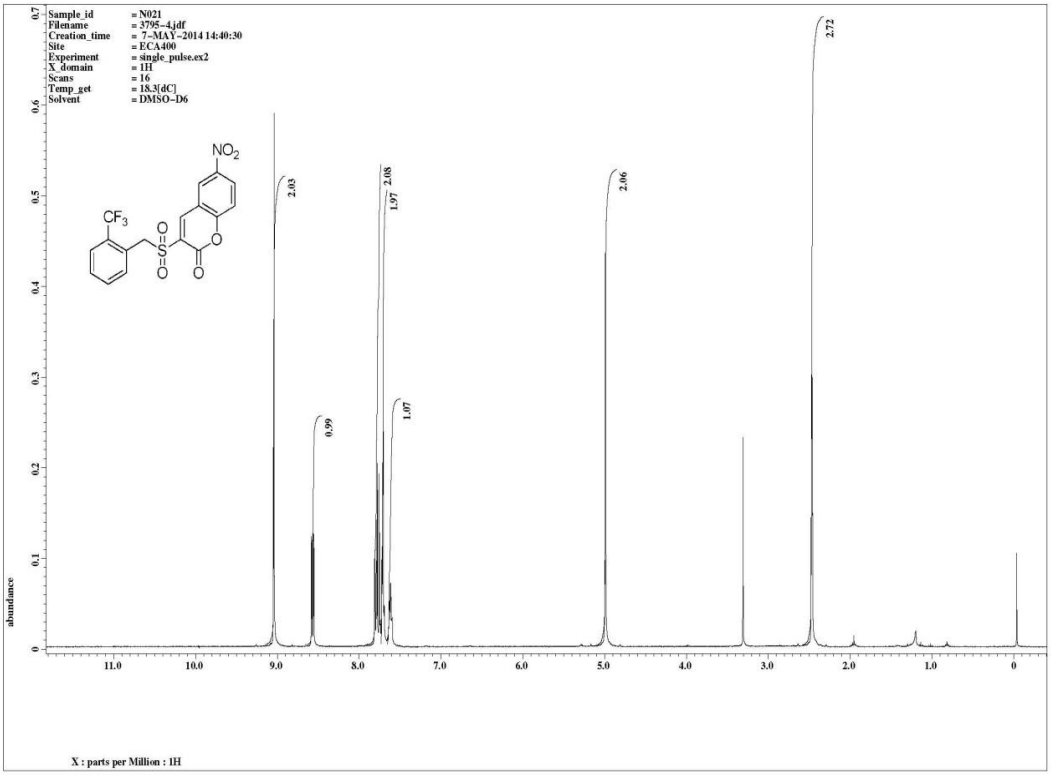

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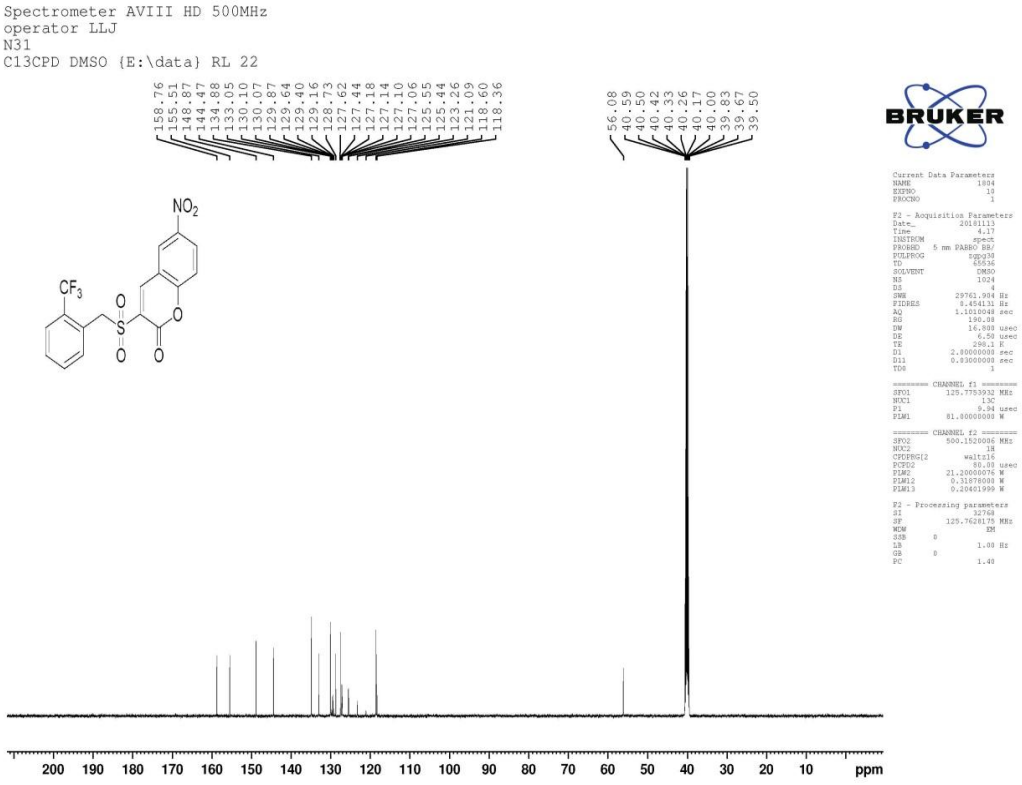

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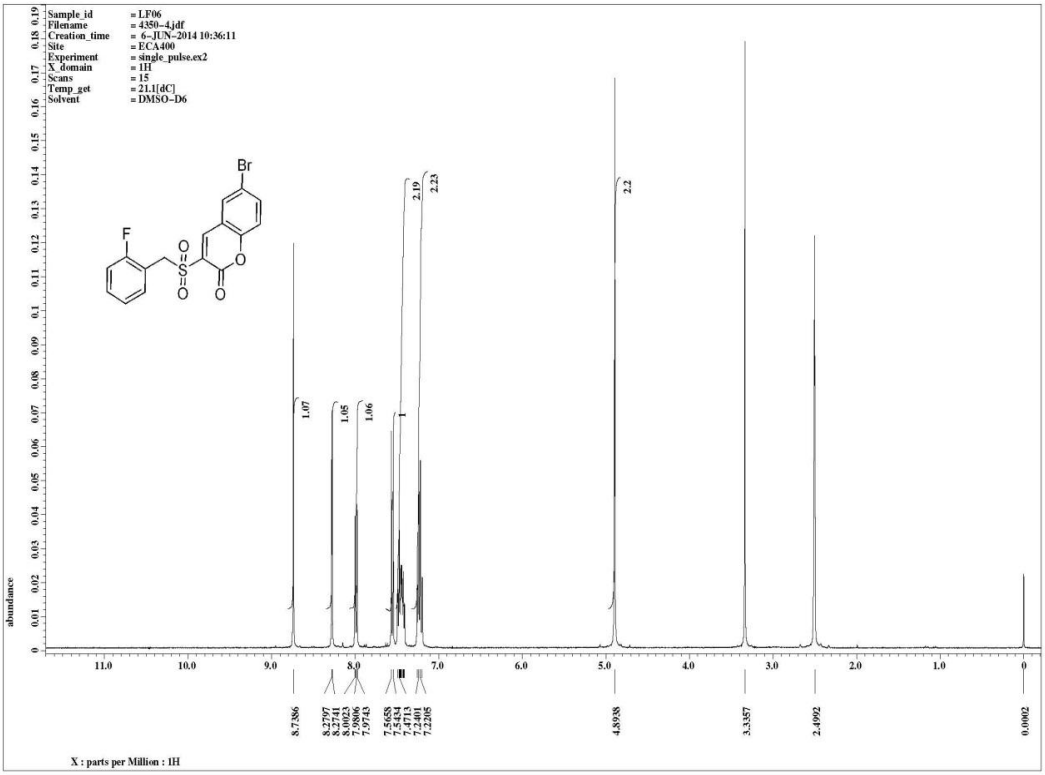

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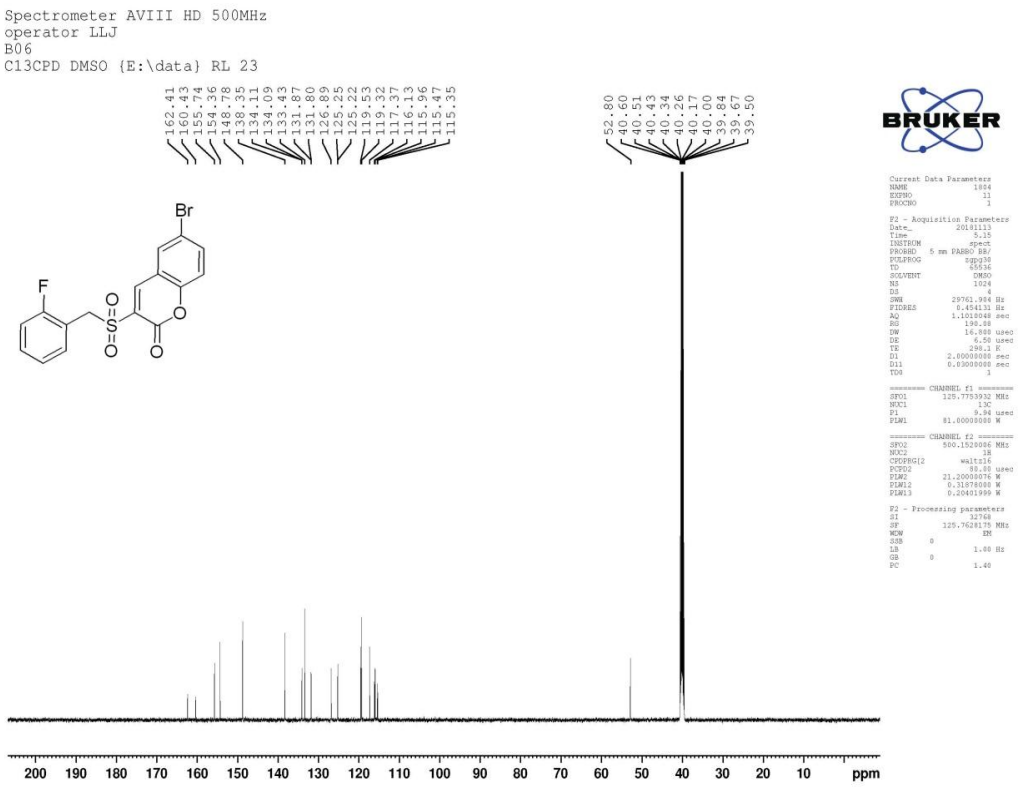

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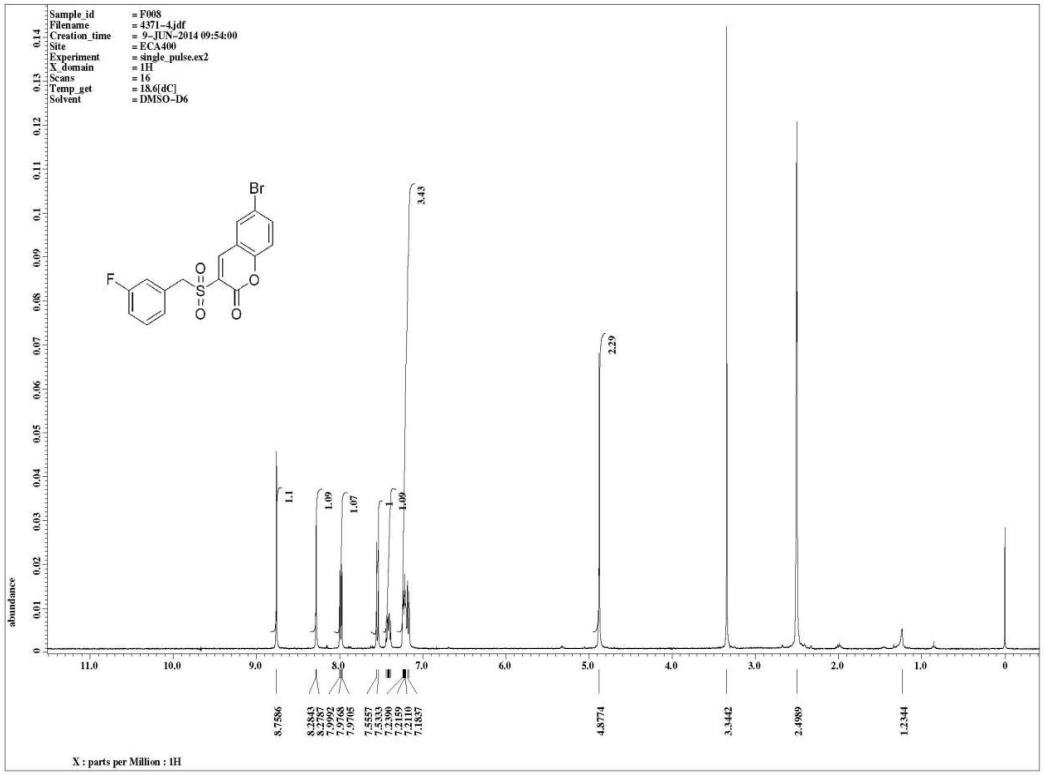

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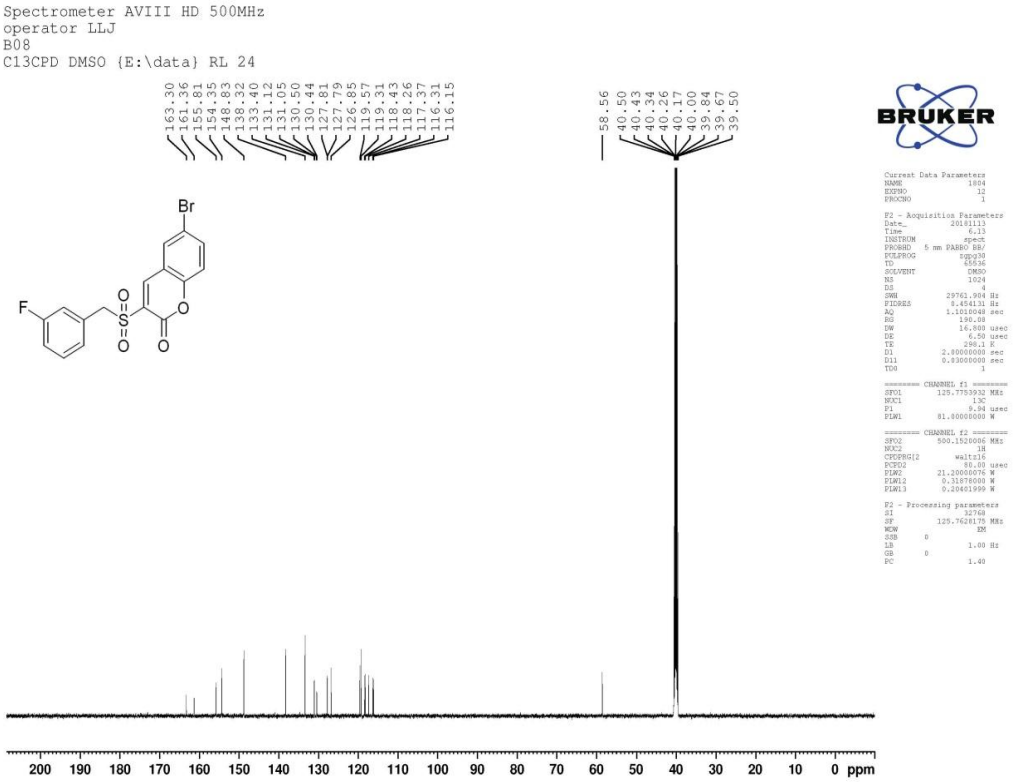

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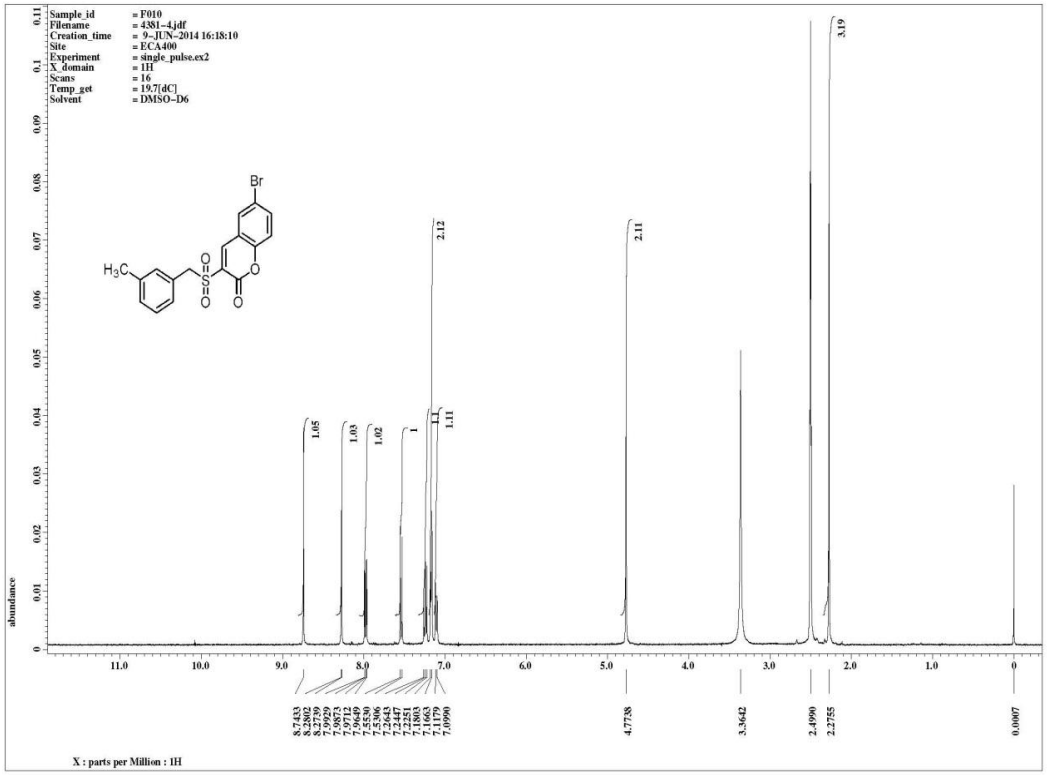

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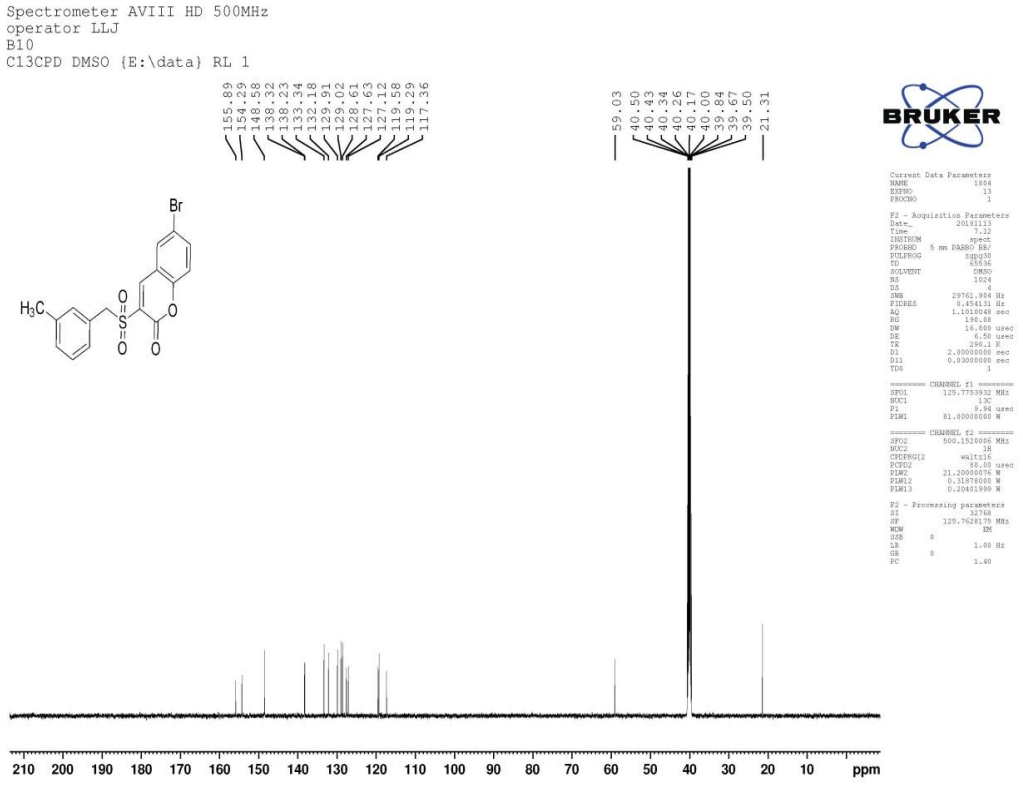

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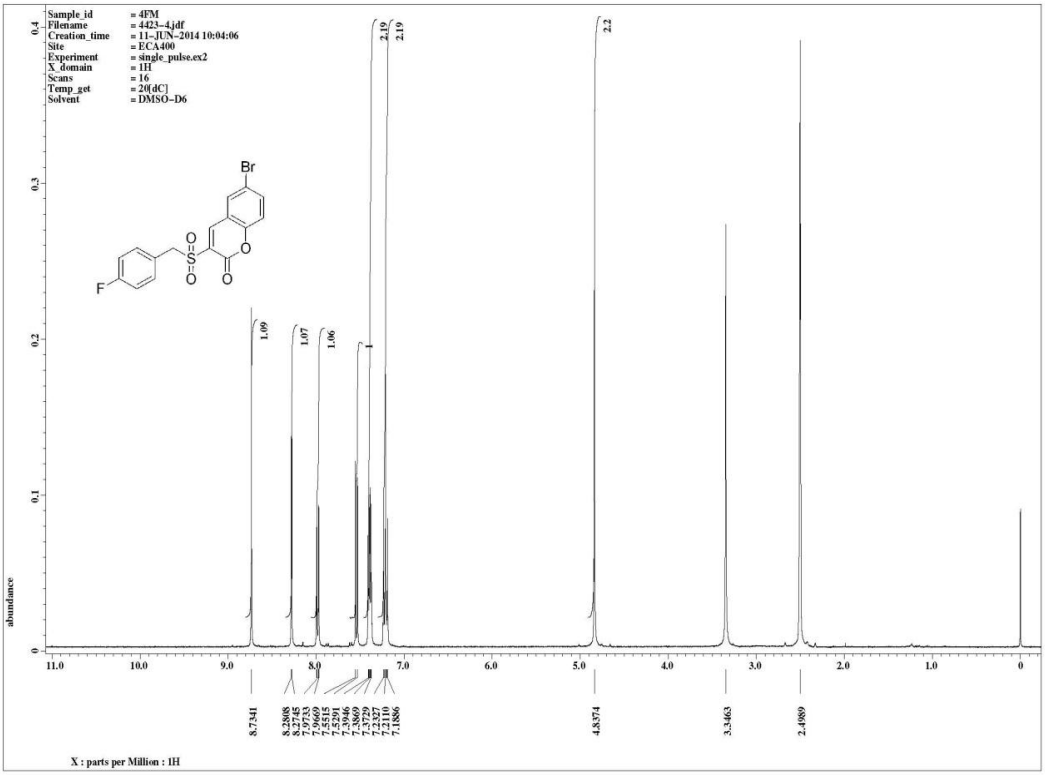

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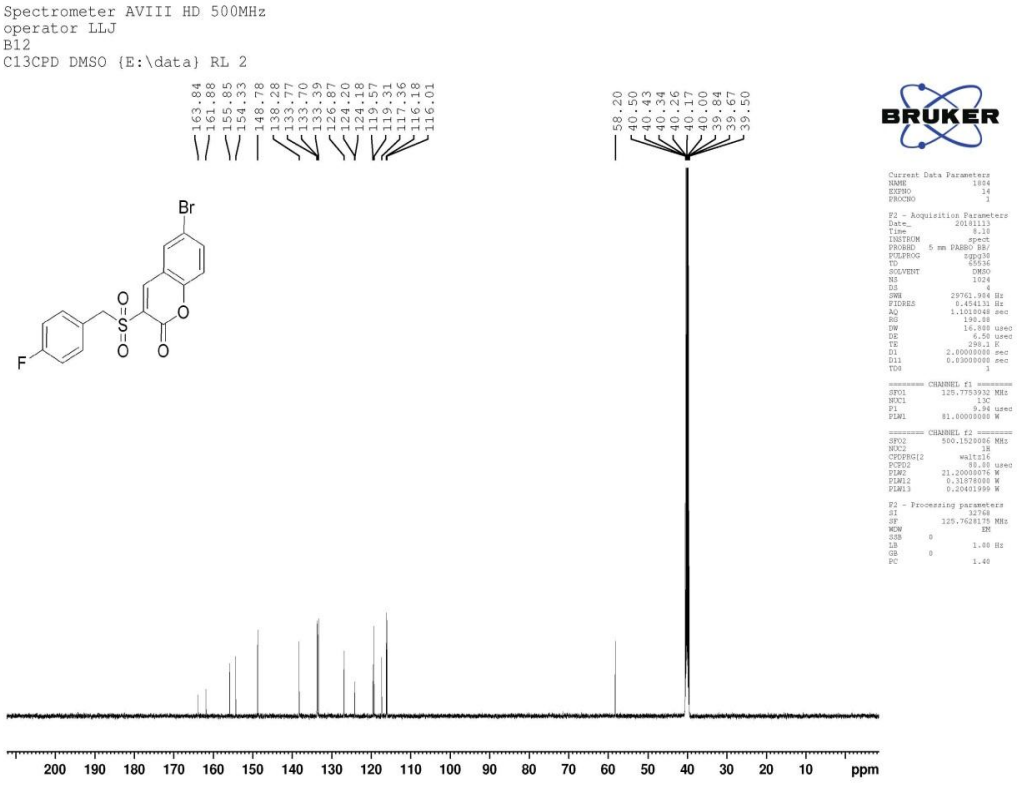

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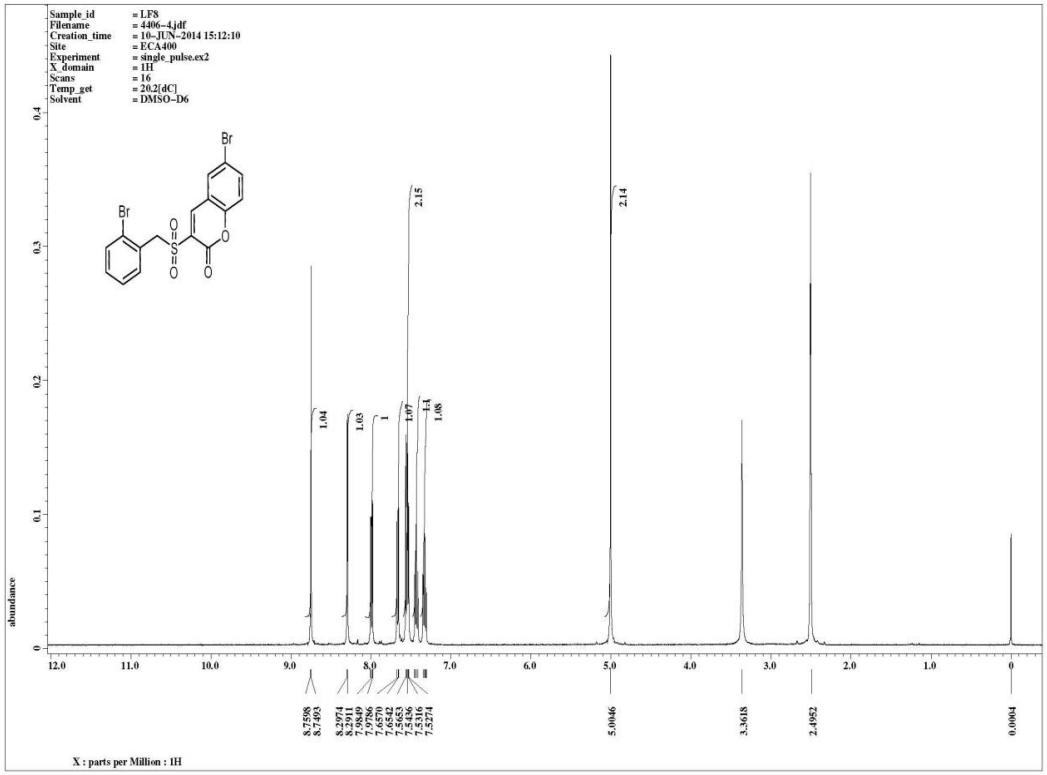

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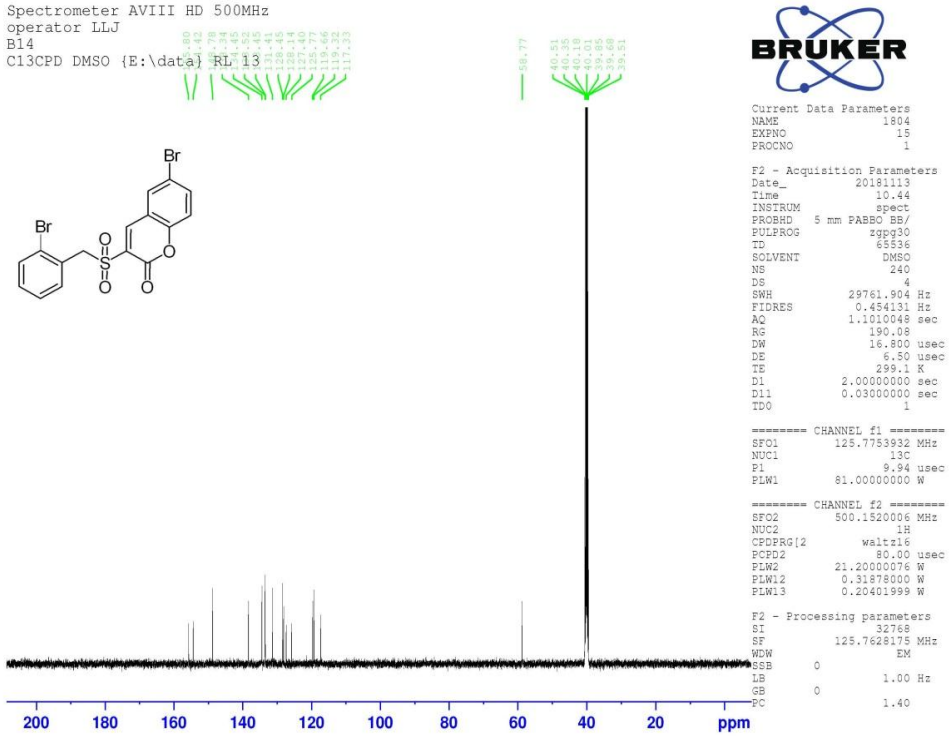

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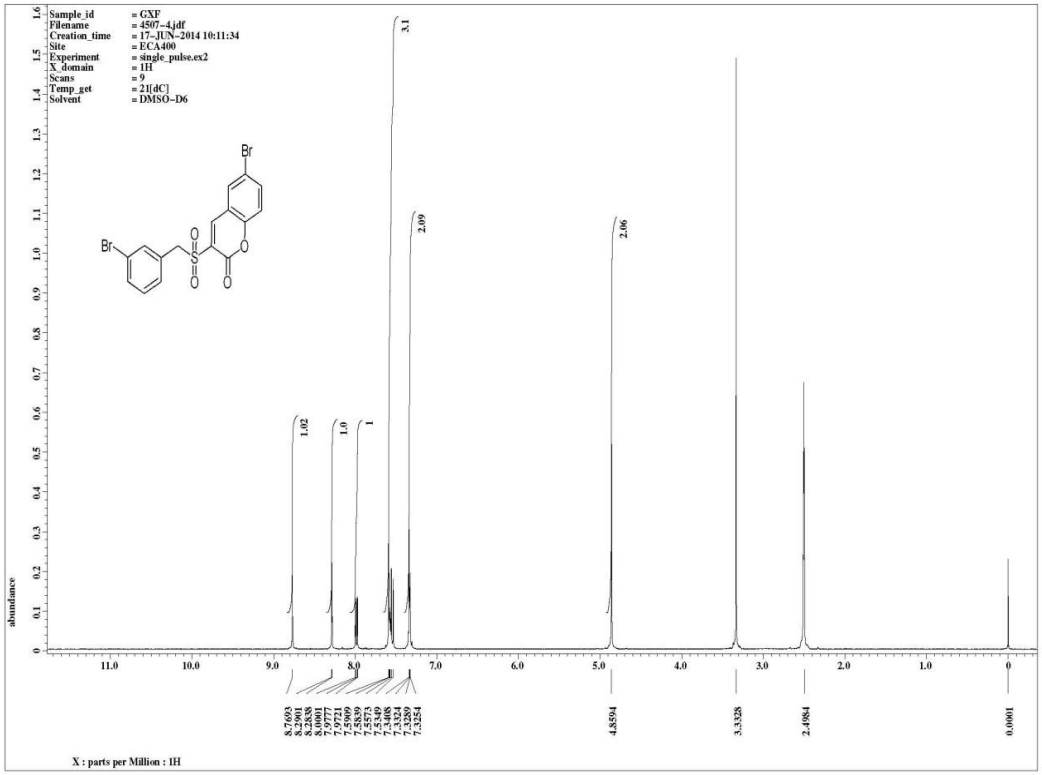

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