Synthesis and antitumor effects of novel benzyl naphthyl sulfoxide/sulfone derivatives modified from Rigosertib

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Supporting Information

1. Synthetic procedures of the intermediates

1.1. 6-bromo-2-naphthol (**2**)

To a solution of 2-naphthol (20.10g, 140mmol) in acetic acid (60mL) was added Br_2 (14mL) in acetic acid (14mL). The reaction mixture was refluxed for 3h, during which three portions of Sn (2×3.56g, 2×0.03mol and 14.56g, 0.12mol) were added. Then, the mixture was cooled to 50℃, and the formed Sn salts were filtered and discarded. The remaining solution was poured into cold water (400mL) where the product precipitated as pink powders. Obtained in 92.9% yield, pink solid, m.p. 125~127℃. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.92 (s, 1H), 7.67 (d, J = 9.6 Hz, 1H), 7.56 (d, J = 8.8Hz, 1H), 7.49 (d, J = 8.9 Hz, 1H), 7.12 (s, 2H), 5.03 (s, 1H, OH).

1.2. 6-O-(2-bromonaphthyl)-dimethylthiocarbamate (**3**)

The previously prepared 6-bromo-2-naphthol (500mg, 2.24mmol) was dissolved in DMF (10mL) and added to a solution of sodium hydride (55% moistened with oil, 193 mg, 6.72mmol) in DMF (8mL) at 0℃. The ice bath was taken away and the mixture was stirred for 30 min. Then dimethyl carbamoyl chloride (830mg, 6.72mmol) was added and it was stirred for 2h at 80℃ and 15h at room temperature. The reaction mixture was then extracted with 1% aqueous NaOH (100mL) and TBME (100mL). The aqueous phase was washed with TBME (2×50mL). The combined organic phases were washed with brine and 5% aqueous HCl (100mL), dried over anhydrous Na_2SO_4 and the solvents was evaporated. The crude was purified by column chromatography to give the product. Obtained in 46.6% yield, colorless

solid, m.p. 129~131℃. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.01 (d, *J* = 1.6 Hz, 1H), 7.76 (d, *J* = 8.9 Hz, 1H), 7.67 (d, J = 8.7 Hz, 1H), 7.55 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.47 (d, *J* = 2.2 Hz, 1H), 7.26 (dd, *J* = 9.0, 2.3 Hz, 1H), 3.49 (s, 3H), 3.40 (s, 3H).

1.3. 6-S-(2-bromonaphthyl)-dimethylthiocarbamate (**4**)

The compound **3** (3.21g, 10.35mmol) prepared in the previous step was melted and kept at 220℃ for 6h and the product was purified by column chromatography, eluting with DCM. After recrystallization in methanol, the product was obtained as yellow crystals. Obtained in 63.9% yield, yellow solid, m.p. 112~114℃. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.03-7.96 (m, 2H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.59–7.53 (m, 2H), 3.12 (s, 3H), 3.05 (s, 3H).

1.4. 6-bromonaphtalene-2-thiol (**5b**)

A solution of the **4** (3.48g, 11.2mmol) in MeOH (250mL) was saturated with Ar. Then solid KOH (5.22 g, 93.0mmol) was added and the mixture was heated to 80℃ for 2.5h. The reaction mixture was then quenched with 1M aqueous HCl (250mL) at 0℃ and it was extracted with DCM (300mL). The aqueous phase was washed with DCM (2×100mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and the solvents was evaporated to give the product. Obtained in 89.2% yield, beige solid, m.p. 160~162℃. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.93 (s, 1H), 7.70 (s, 1H), 7.62 (d, *J* = 8.6 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 3.60 (s, 1H).

1.5. 4-methoxy-3-nitrobenzaldehyde (**7**)

To an ice cold solution of 70% HNO_3 (50mL) was added anisic aldehyde (5.40g, 40.0mmol) dropwise, then the mixture was stirred at room temperature for 2h. The mixture was poured into ice water, the formed white precipitate was filtered, washed with water and dried under vacuum to get the product. Obtained in 90.1% yield, white solid, m.p. 99~101℃. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 9.95 (s, 1H), 8.43 (s, 1H), 8.20 (d, *J*=8.0 Hz, 1H), 7.58 (d, *J*=8.0 Hz, 1H), 4.06 (s, 4H).

1.6. (4-methoxy-3-nitrophenyl)methanol (**8**)

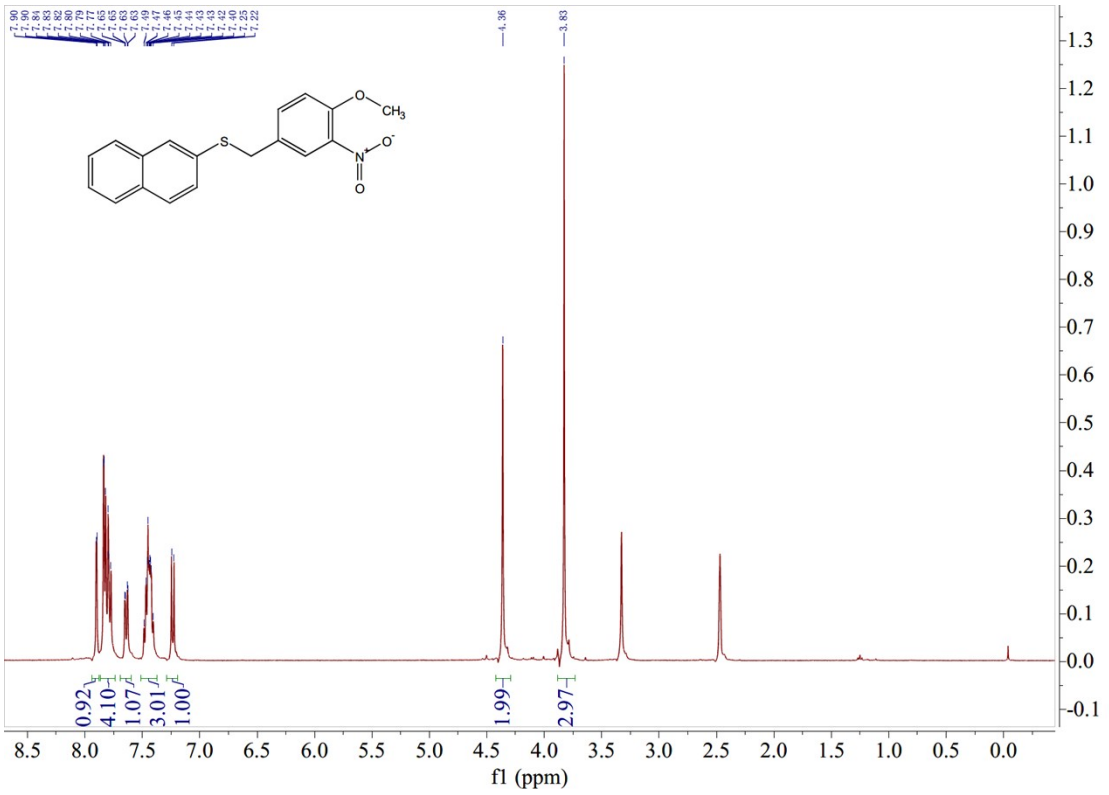
To an ice cold solution of **7** (6.47g, 35.7mmol) in 50mL THF and 10mL EtOH was added sodium borohydride (0.68g, 17.8mmol), then the mixture was stirred at room

temperature for 2h. The mixture was poured into ice water and most of the organic solvents was then evaporated in vacuo. The aqueous phase was extracted with DCM. The organic phase was dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo to give the product. Obtained in 91.3% yield, pale yellow solid, m.p. 69~70℃. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.79 (s, 1H), 7.59 (d, J=8.0Hz, 1H), 7.32 (d, J=8.0Hz, 1H), 5.34 (t, J=6.0Hz, 1H), 4.49 (d, J=5.6Hz, 2H), 3.91 (s, 3H).

1.7. 4-(bromomethyl)-1-methoxy-2-nitrobenzene (**9**)

To an ice cold solution of **8** (5.97g, 35.6mmol) in 50mL DCM was added phosphorus tribromide (9.97g, 35.7mmol) dropwise. The mixture was stirred at room temperature for 2h. 100mL of sodium bicarbonate solution was added in the mixture and the stirring was continued for 30 min. The organic phase was washed with sufficient sodium bicarbonate solution and water, dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo to give the product. Obtained in 98.6% yield, pale green solid, m.p. 110℃. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.00 (s, 1H), 7.75 (d, J=8.0Hz, 1H), 7.39 (d, J=8.0Hz, 1H), 4.81 (s, 2H), 3.94 (s, 3H).

2. Copies of ^{1}H-NMR and ^{13}C-NMR for target compounds（10a, 11a~11d, 12a~12e, 13a~13c, 14b and 15a~15b）



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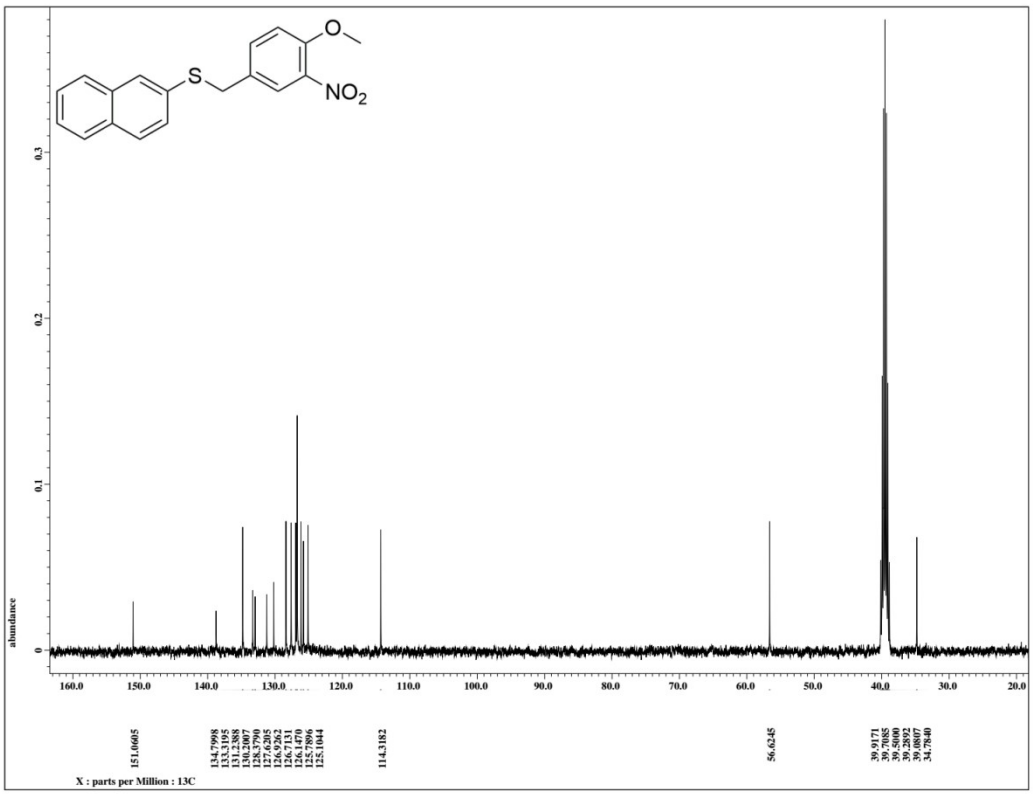

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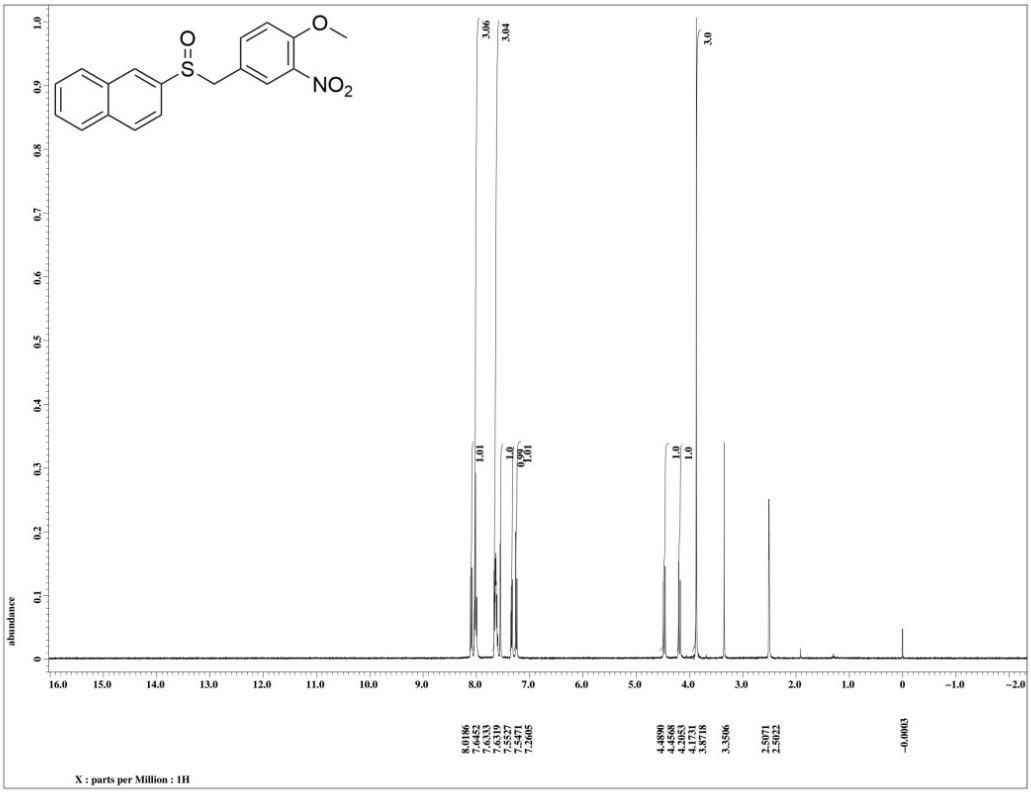

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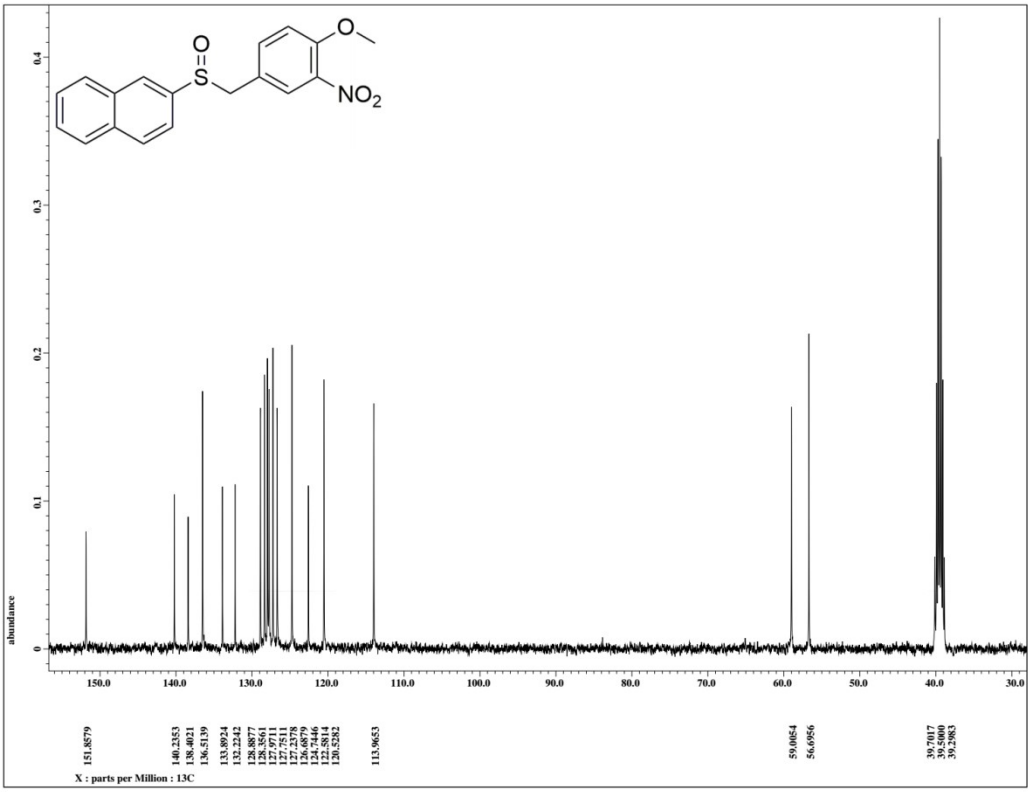

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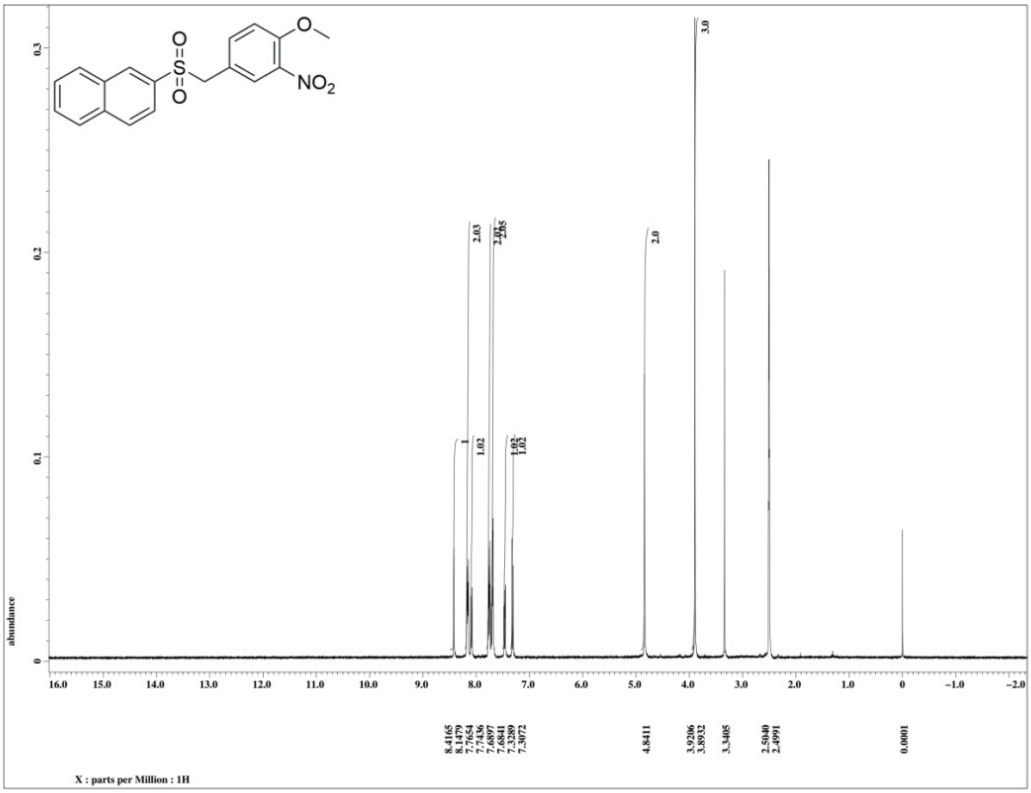

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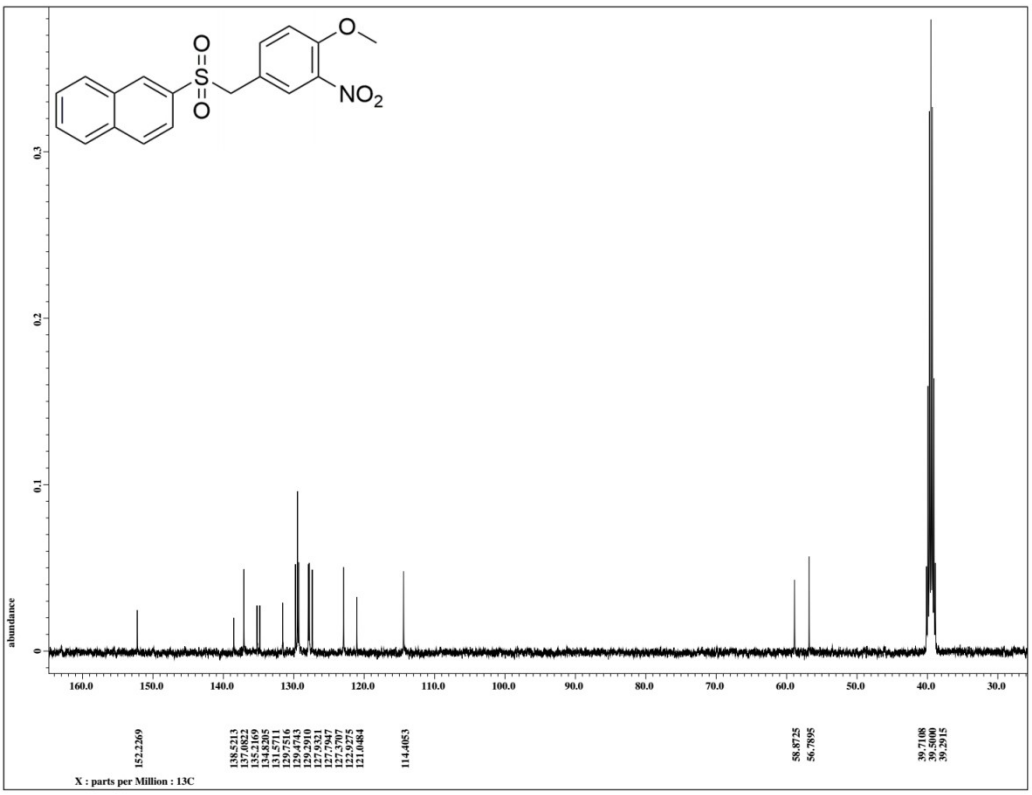

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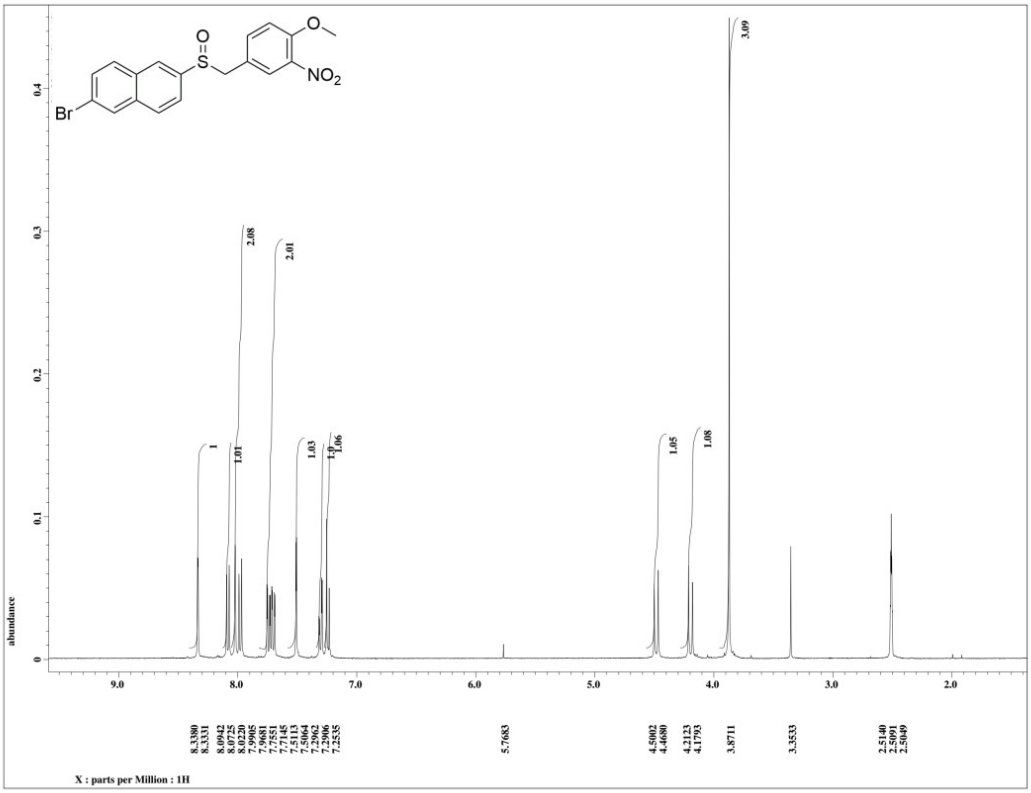

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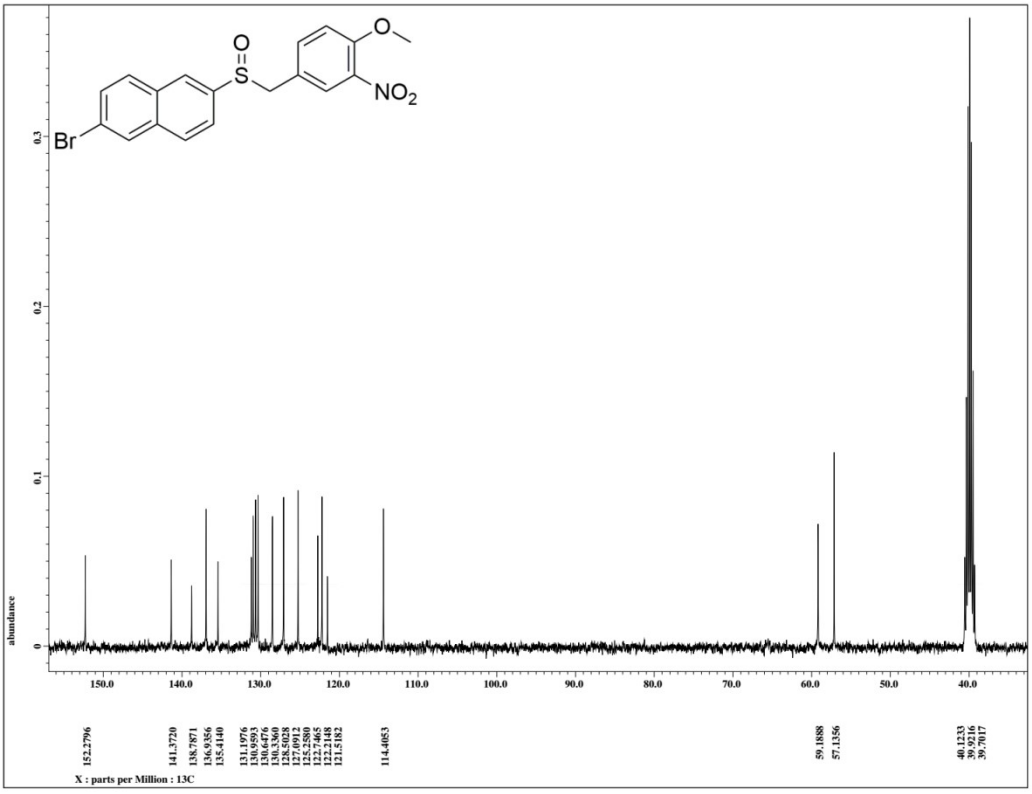

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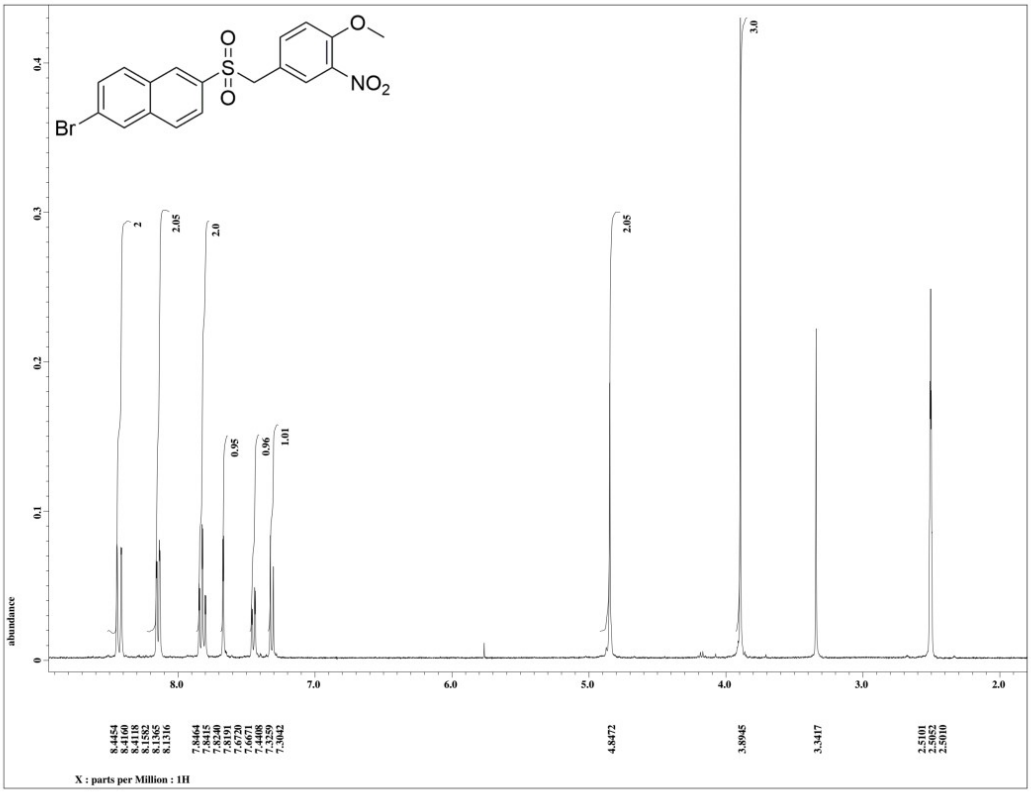

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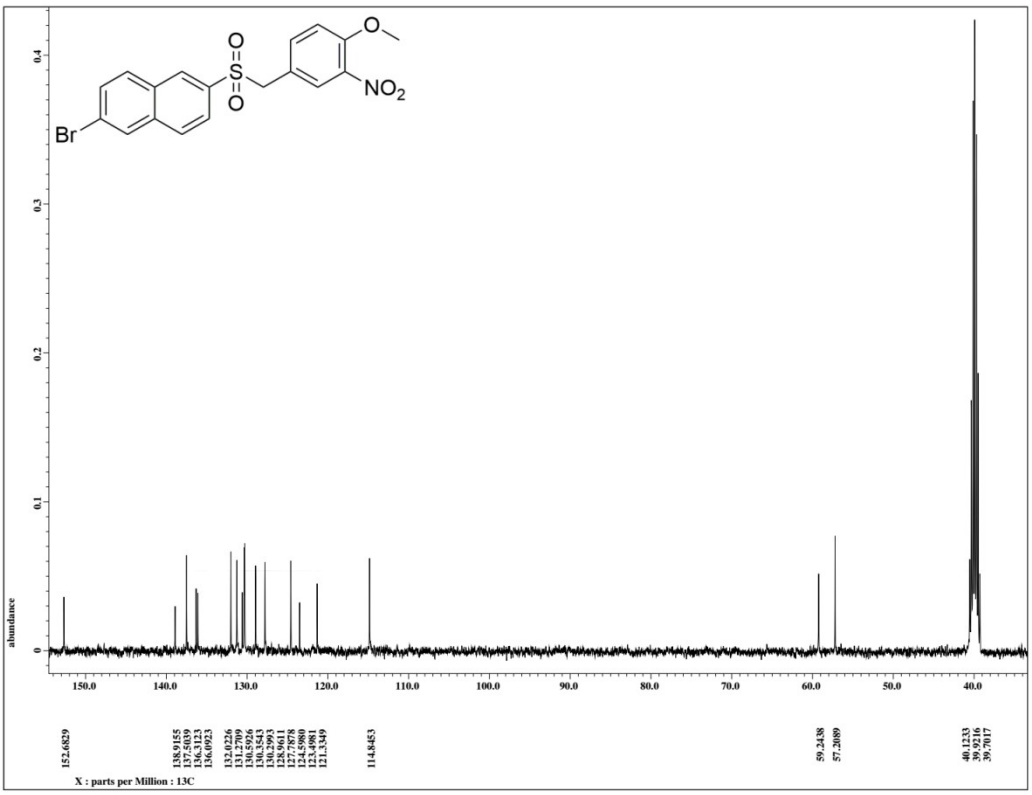

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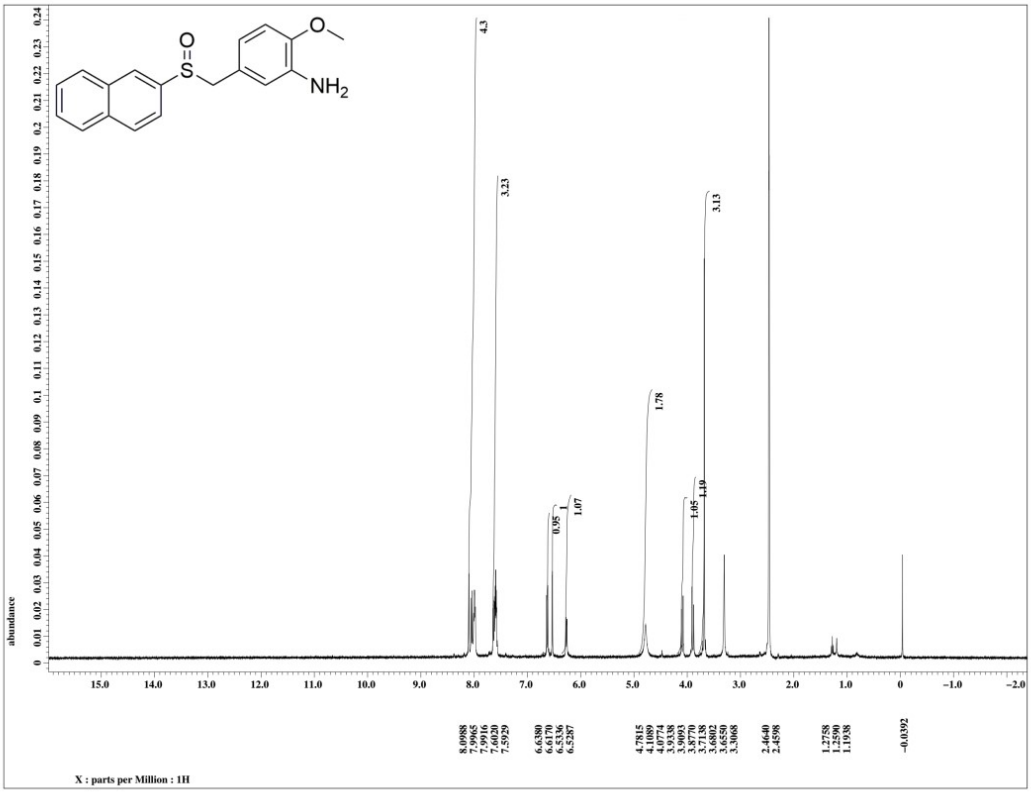

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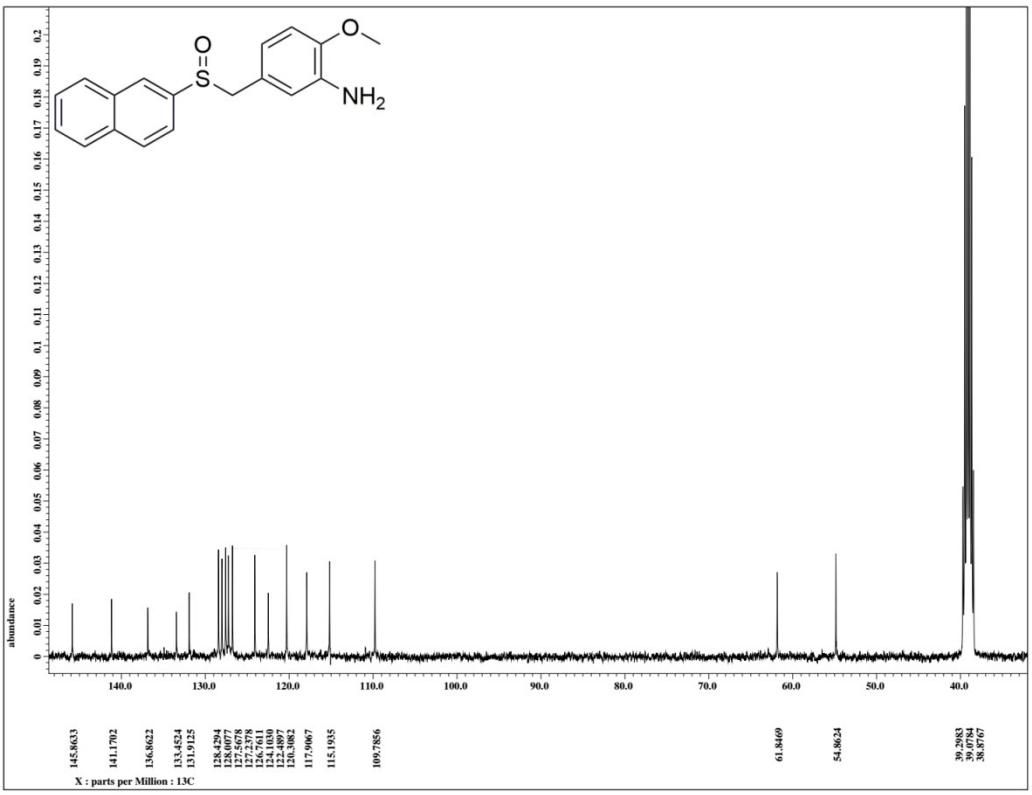

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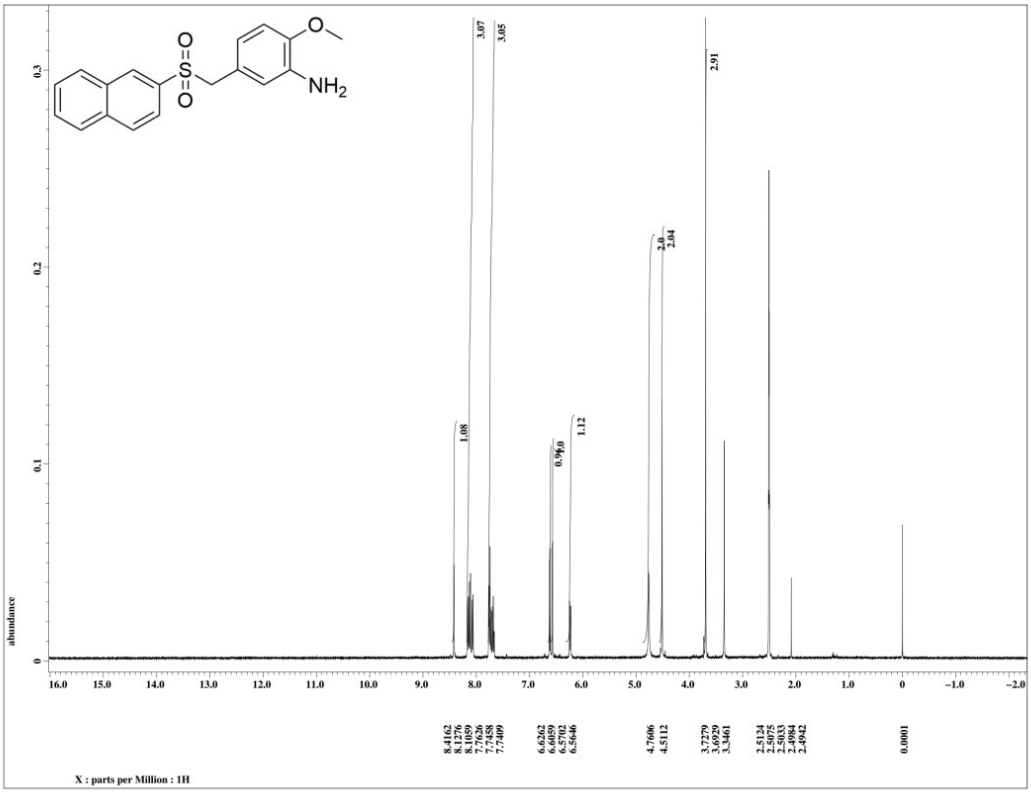

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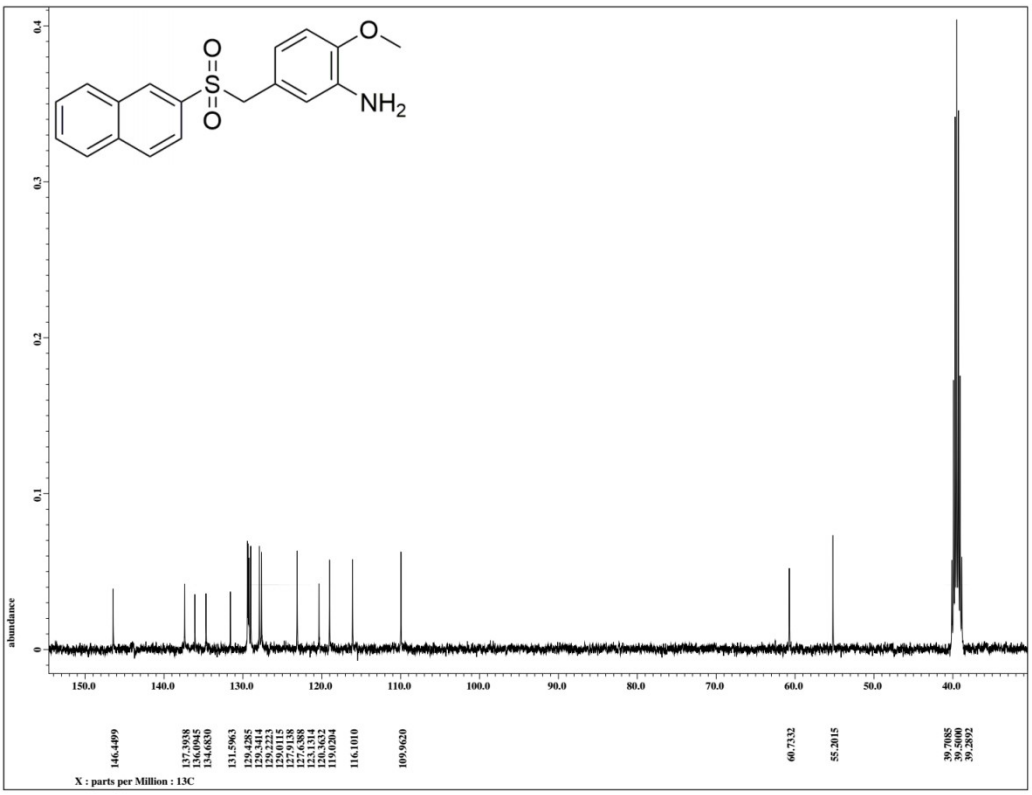

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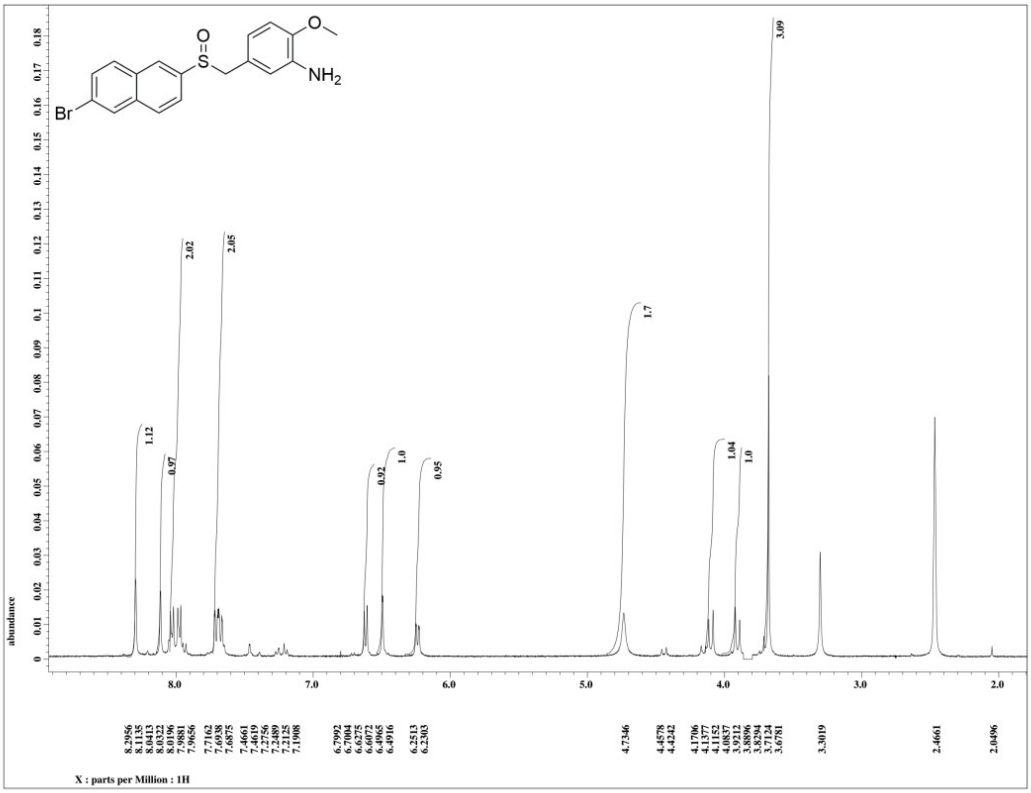

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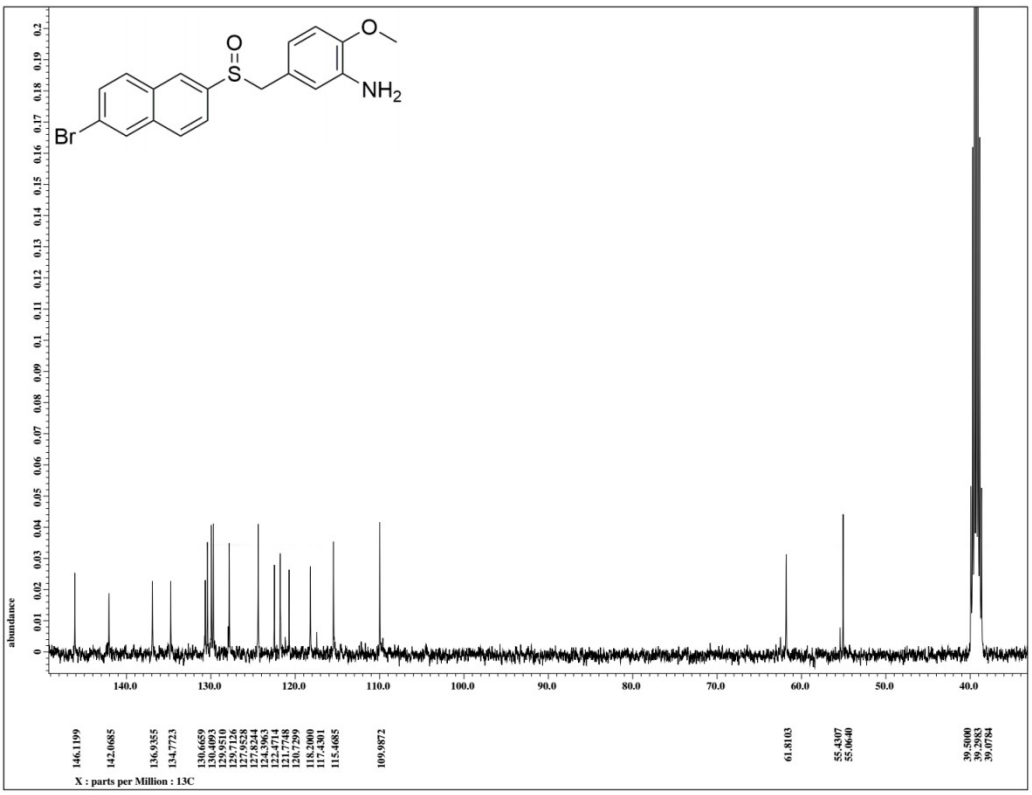

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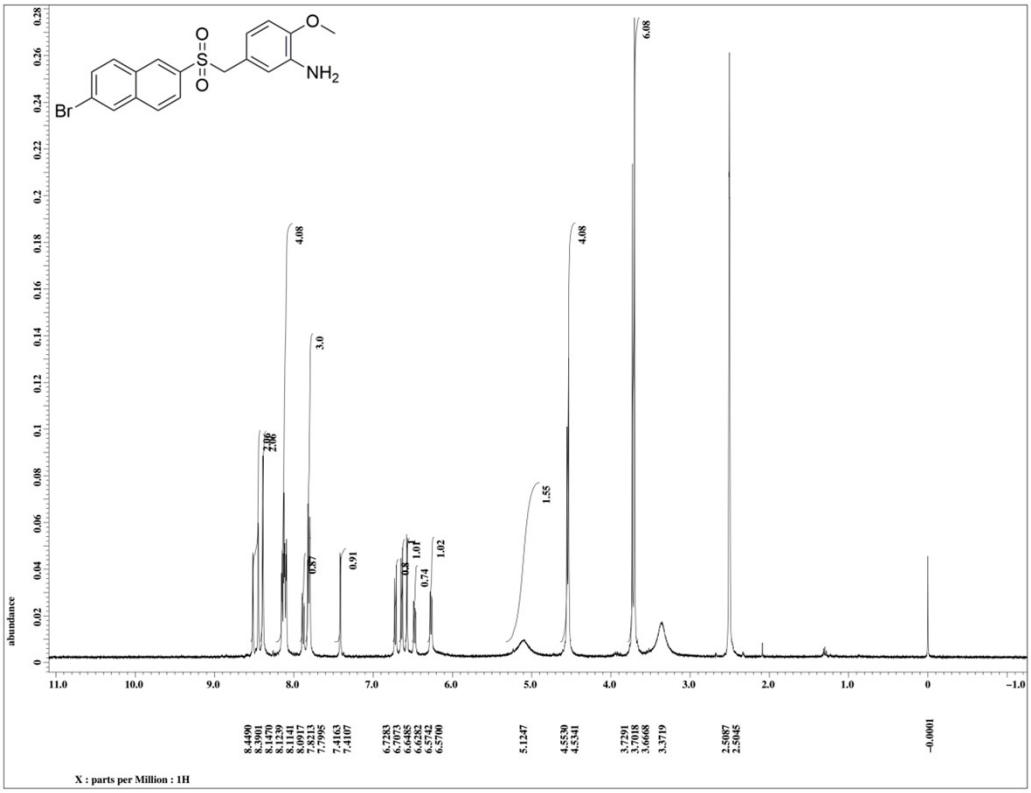

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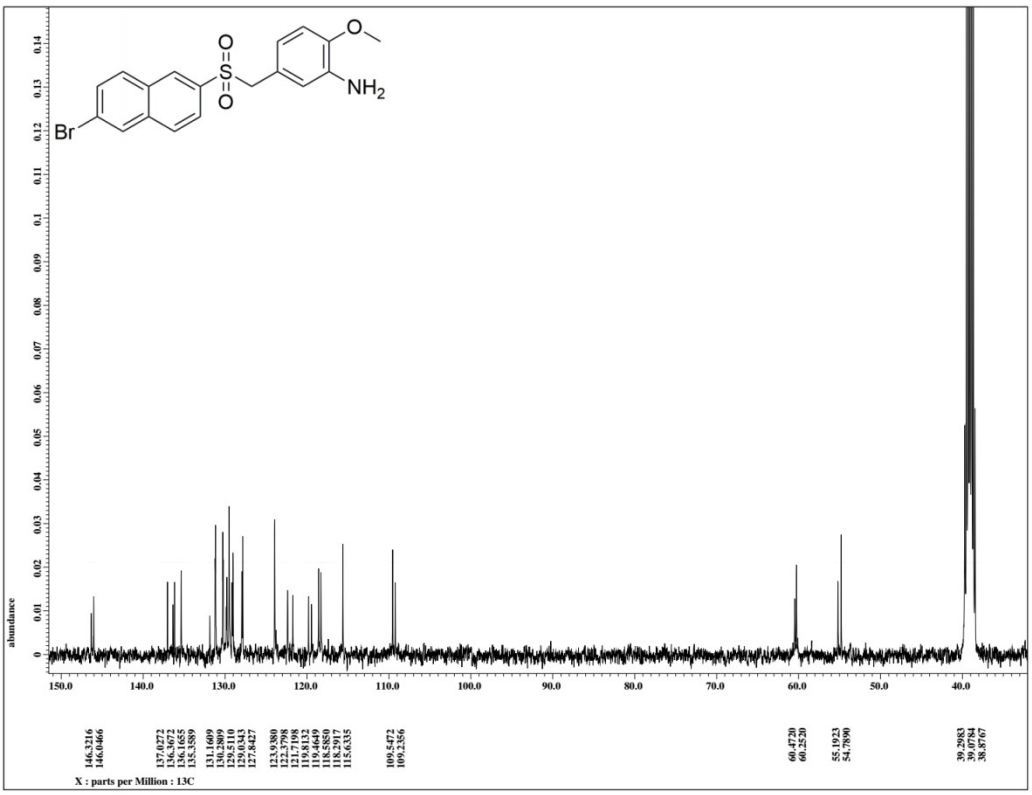

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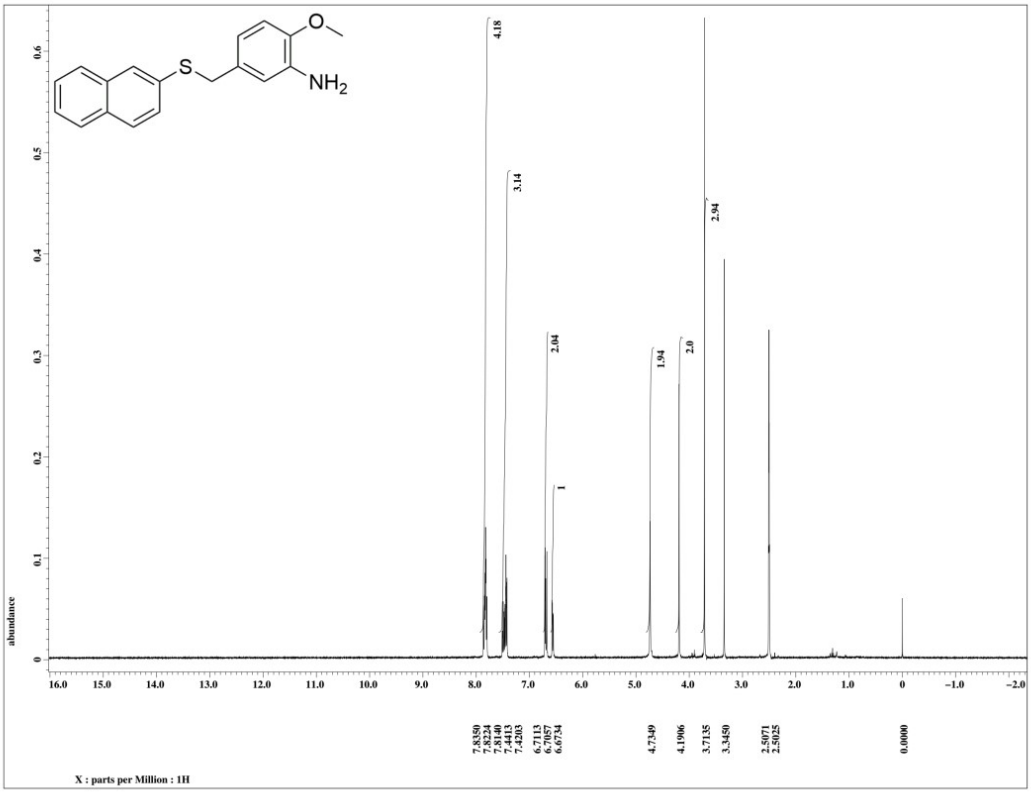

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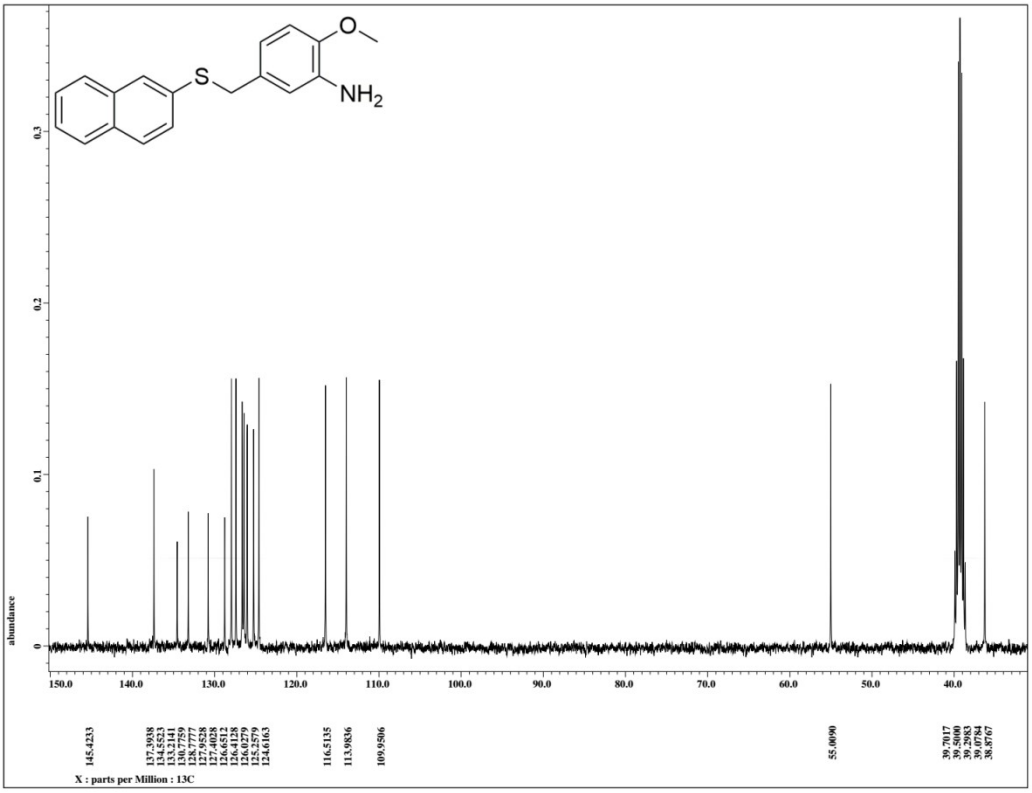

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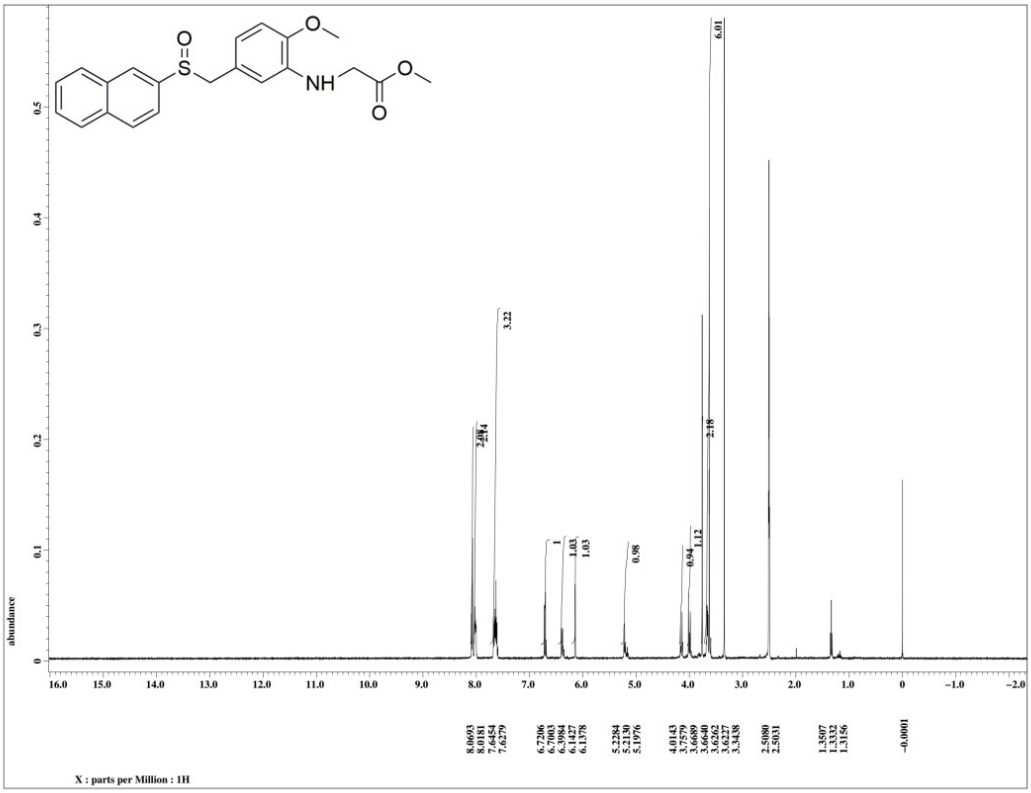

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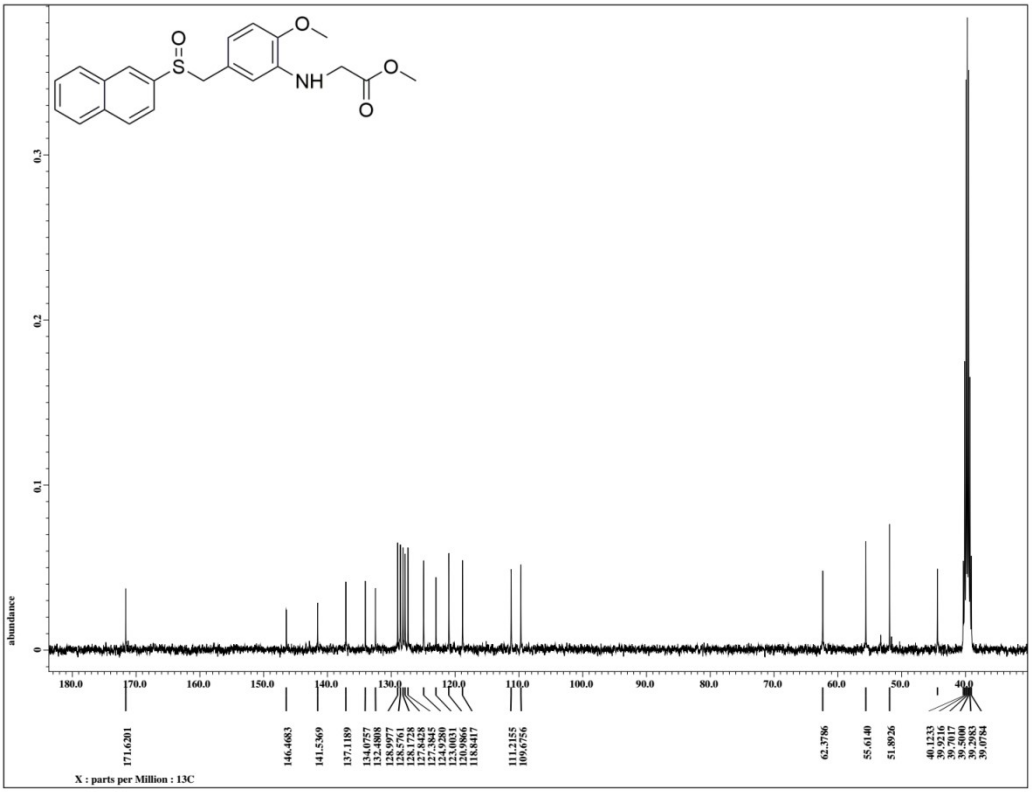

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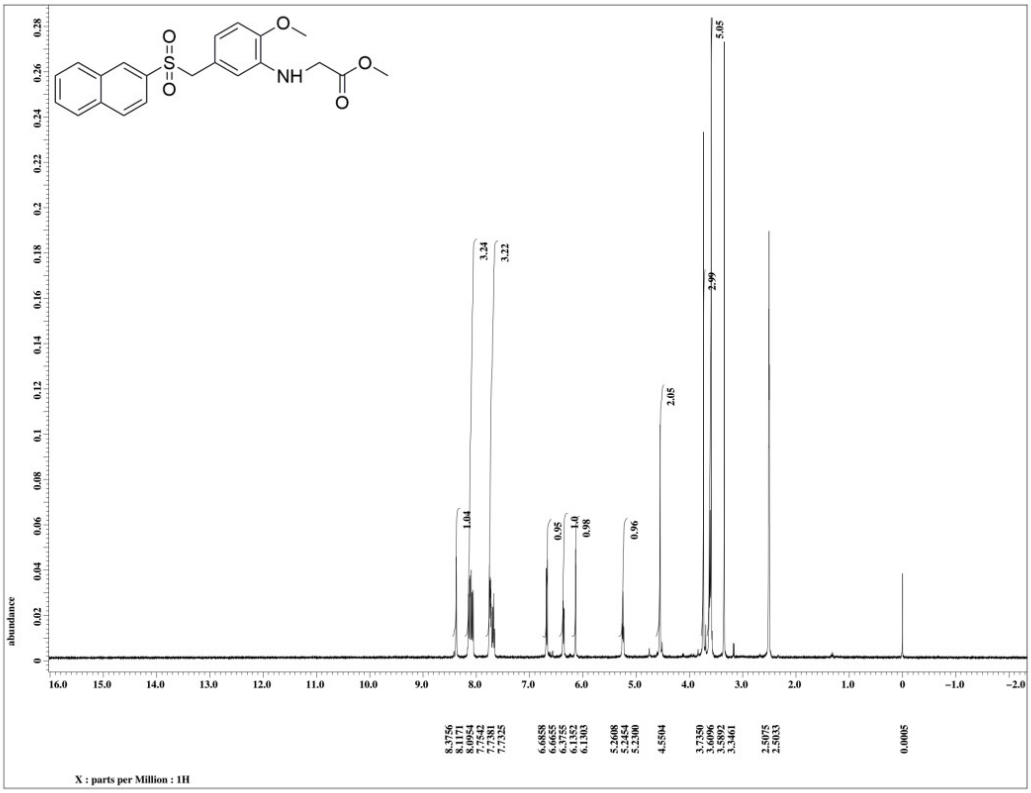

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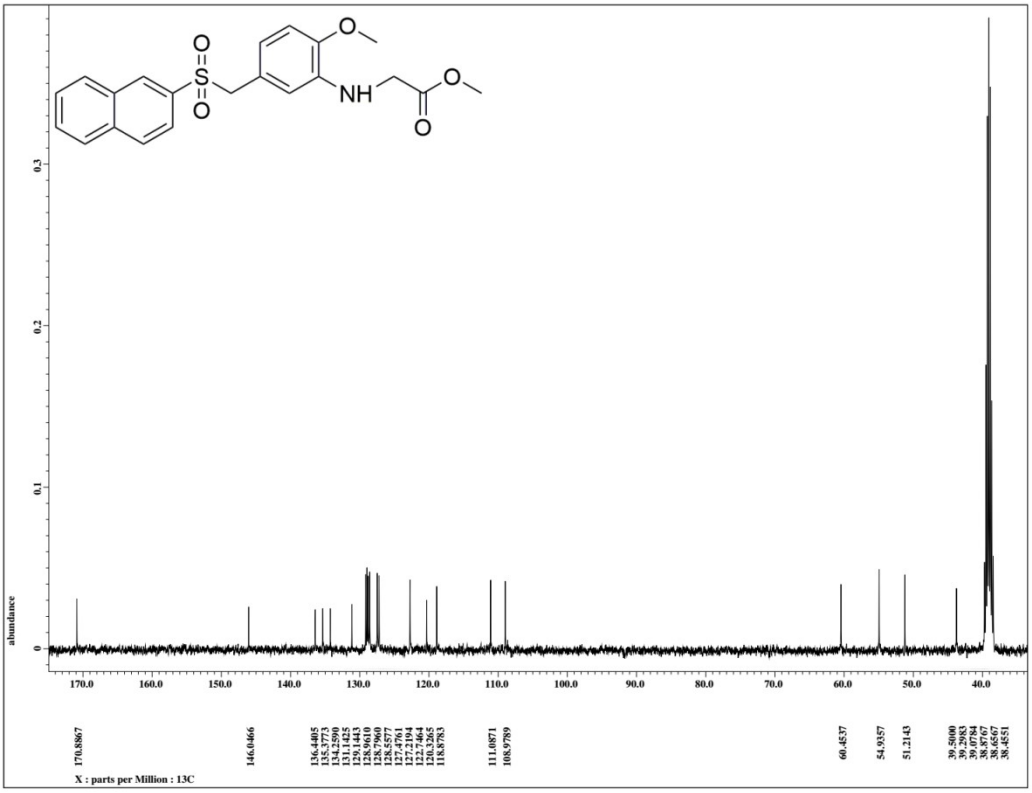

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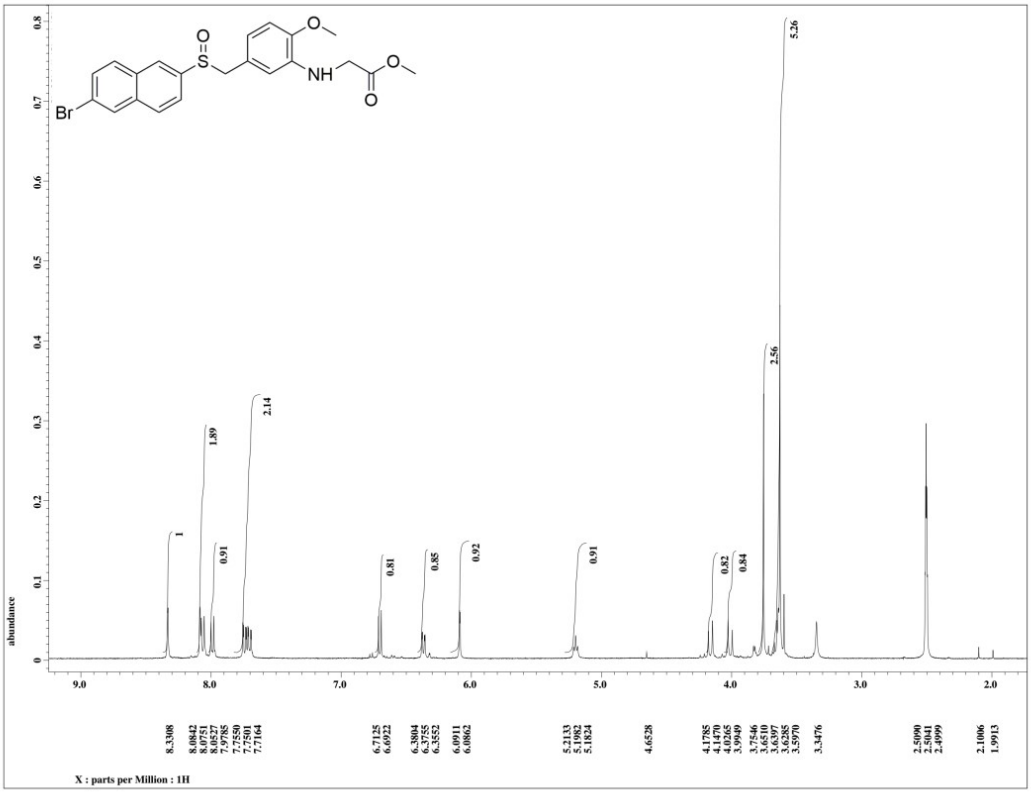

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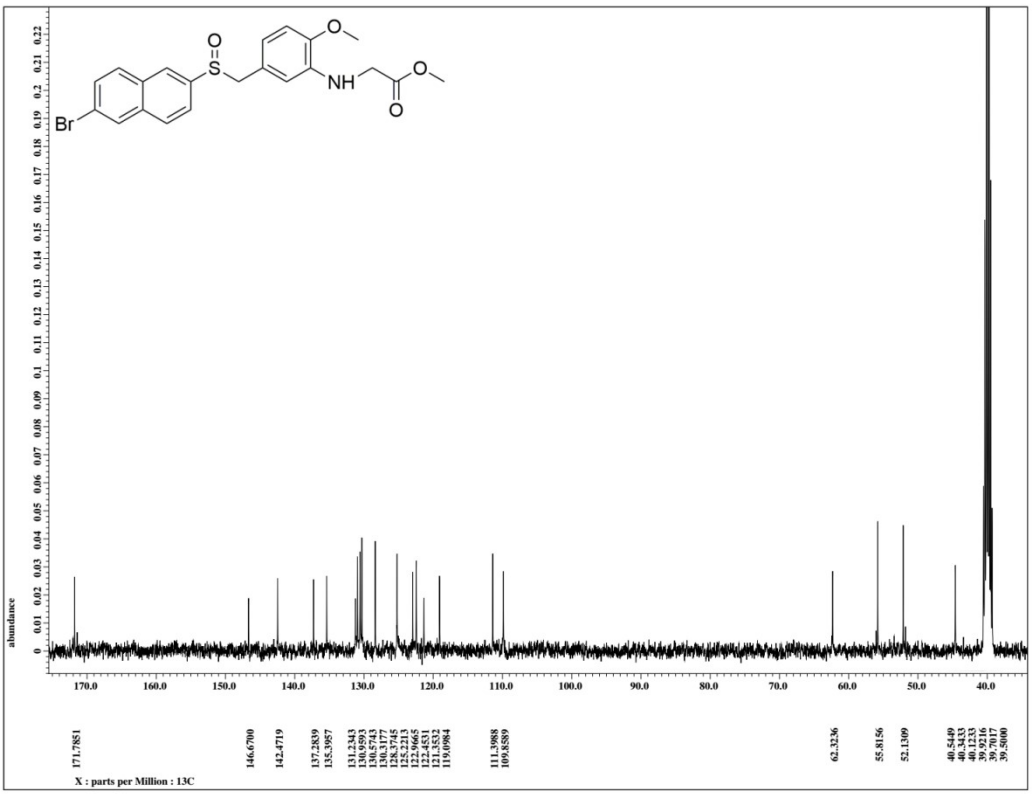

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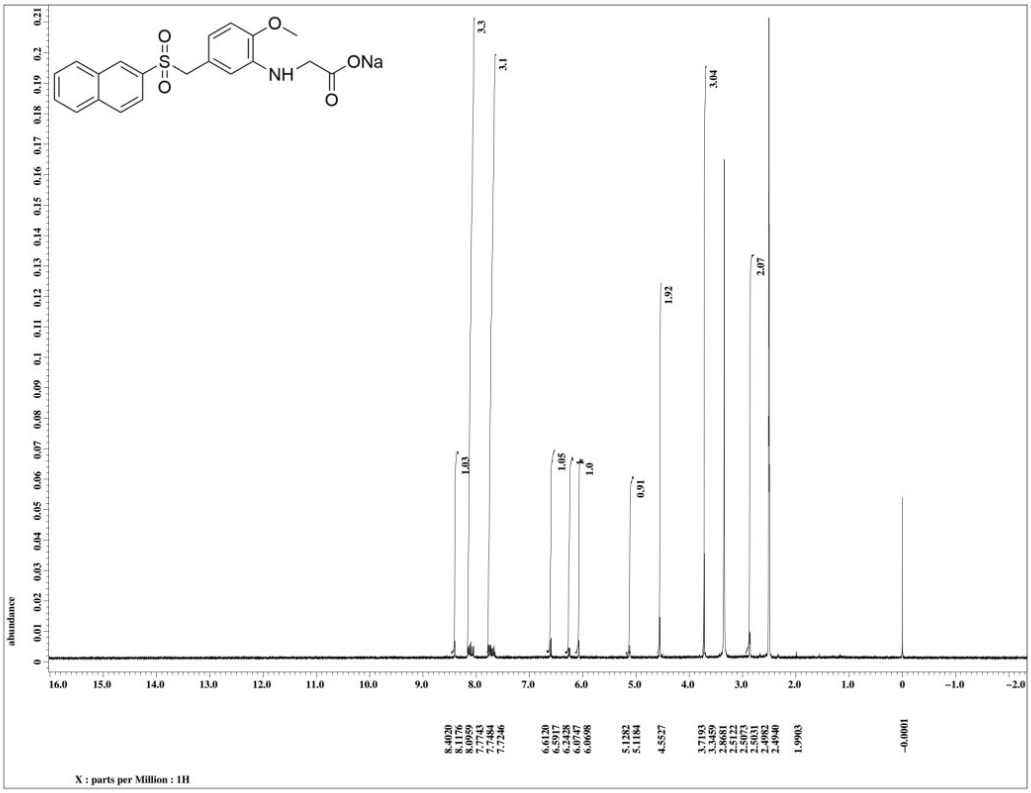

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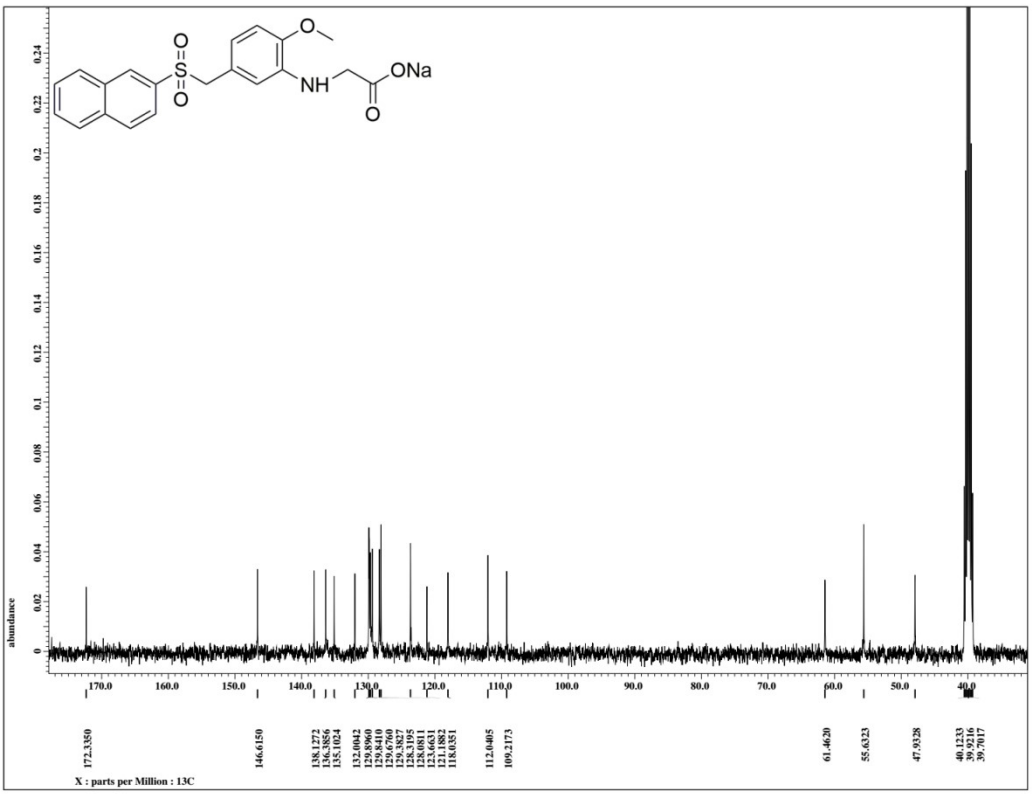

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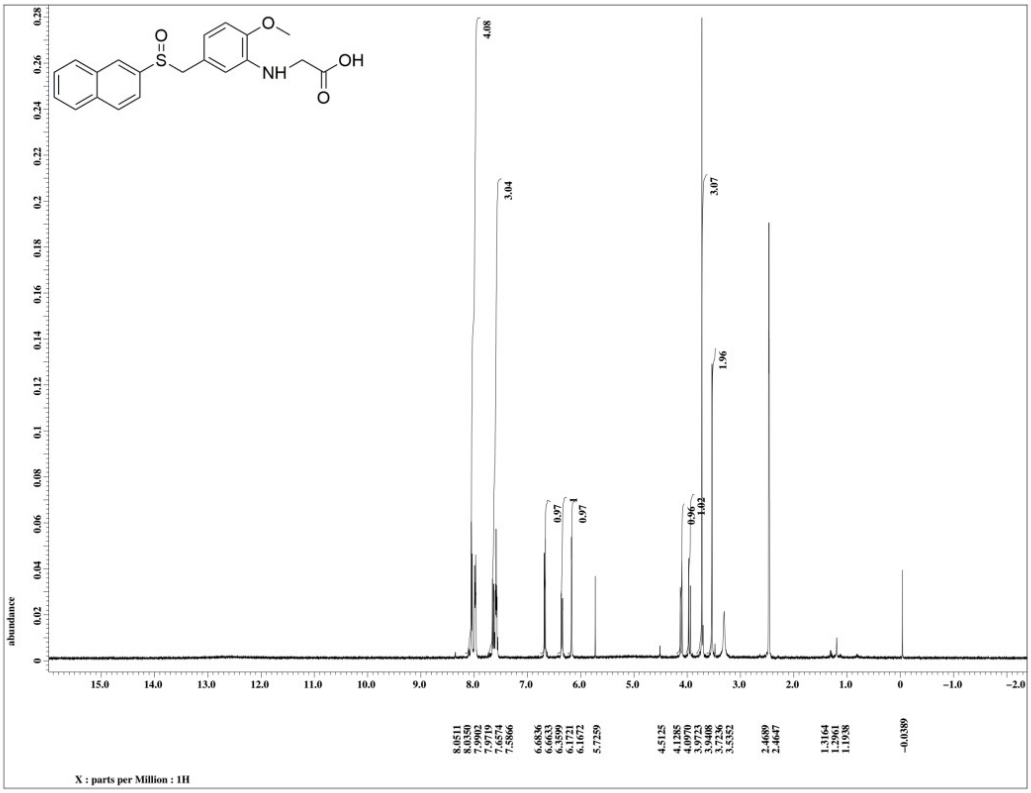

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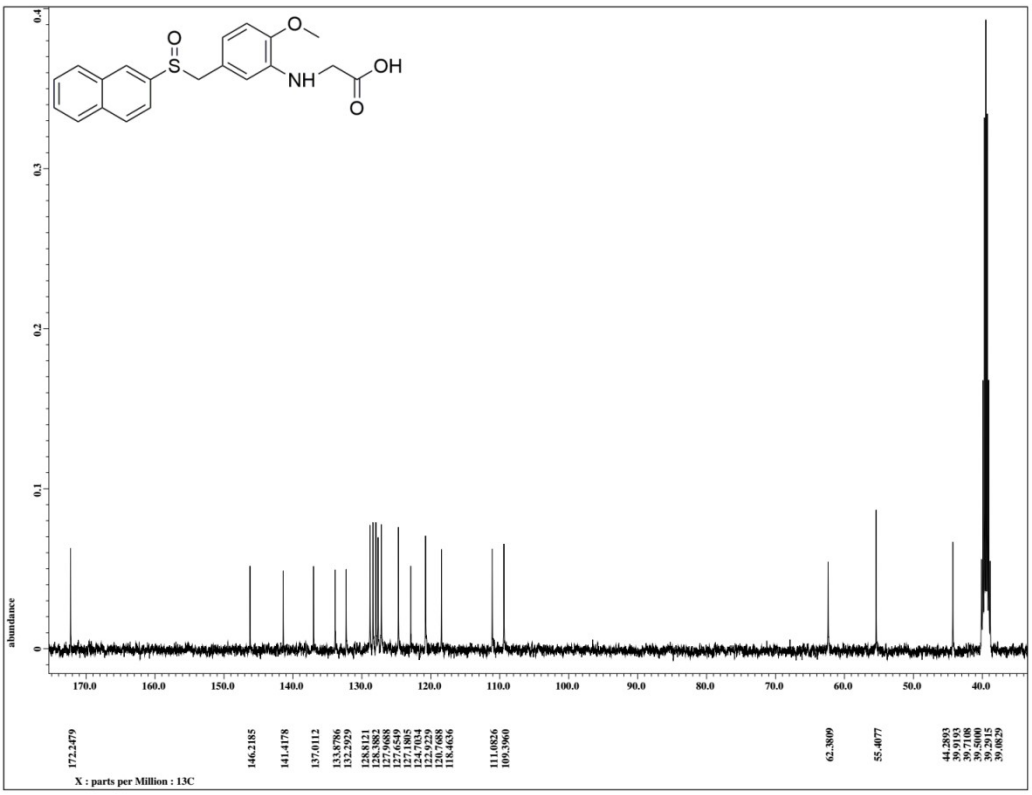

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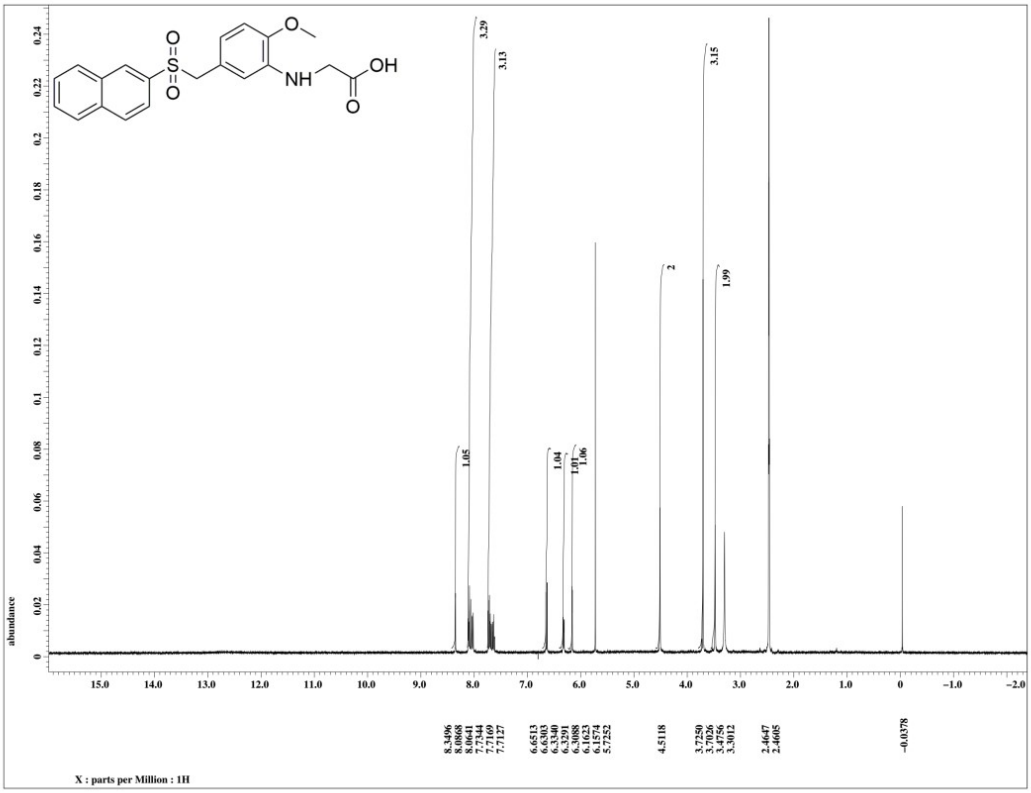

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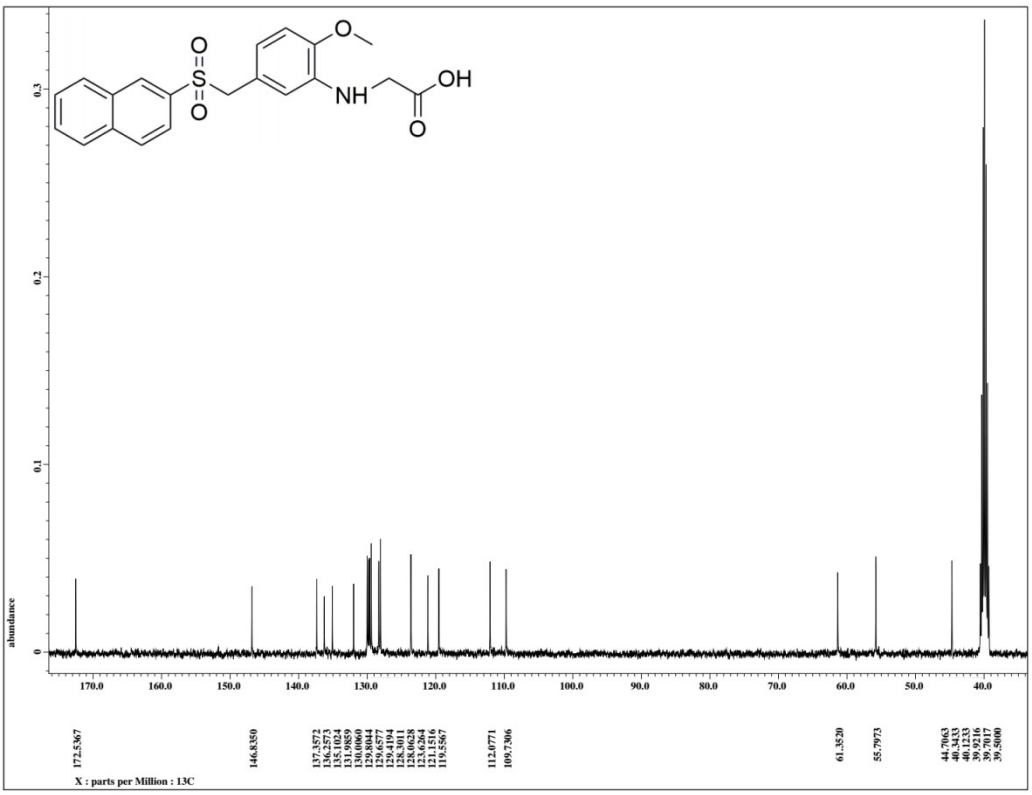

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