Synthesis of Quinazolinones from 2-Iodobenzamides and Enaminones via Copper-Catalyzed Domino Reaction

Teerawat Songsichan, Jaturong Promsuk, Vatcharin Rukachaisirikul and Juthanat Kaeobamrung*

Department of Chemistry, Faculty of Science, Prince of Songkla University, Hat Yai, Songkhla 90112, Thailand

E-mail: *juthanat.k@psu.ac.th*

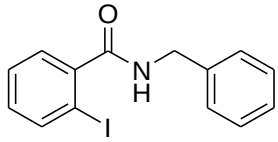
Supporting Information

General Information

CH_3CN was dried over 4 Å molecular sieves. Solvents for extraction and column chromatography were distilled at their boiling point ranges prior to use. Thin-layer chromatography (TLC) was performed on silica gel 60 GF_{254} (Merck) and were visualized by fluorescence quenching under UV light. Column chromatography was performed on SiliaFlash® G60 (70-230 Mesh). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a 300 MHz Bruker FTNMR Ultra Shield spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in parts per million (ppm) downfield from TMS (δ 0.00) and coupling constants are reported as Hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; m, multiplet. Infrared spectra (IR) were measured on a Perkin Elmer Spectrum GX FT-IR system and recorded on wavenumber (cm^{-1}).

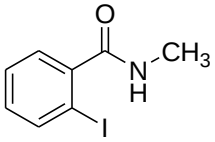
Preparation of Starting Materials

Synthesis of 2-Iodobenzamides

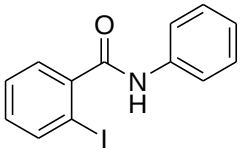


***N*-Benzyl-2-iodobenzamide (1a).**

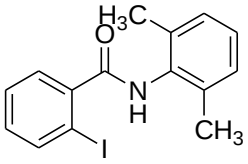
Prepared according to literature procedure.[1] A flame-dried round bottom flask was charged with 1.0 equiv of 2-iodobenzoic acid in CH_2Cl_2 (0.3 M) and DMF (2 drops), followed by the addition of 1.25 equiv of oxalyl chloride at 0 ºC. The reaction mixture was allowed to stir at room temperature for 4 h. After that, the mixture was evaporated to dryness. The prepared acid chloride was dissolved in CH_2Cl_2 (0.3 M). The solution of benzylamine (1.5 equiv) and triethylamine (3.0 equiv) was added at 0 ºC. The reaction mixture was allowed to stir at room temperature for 15 h. The reaction mixture was quenched with sat. NH_4Cl and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (4:1 hexanes:EtOAc) to afford **1a** as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.8 Hz, 1H), 7.40-7.25 (m, 7H), 7.10-7.04 (m, 1H), 6.15 (brs, 1H), 4.61 (d, *J* = 5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 141.9, 139.7, 137.4, 131.0, 128.6, 128.1, 128.0, 127.6, 92.3, 44.1; IR (thin film) ν 3256, 3030, 1646, 1522, 771, 744, 697 cm^{-1}. Other data was identical to the literature values.[1]



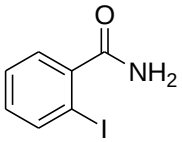
2-Iodo-*N*-methylbenzamide (1b). Prepared according to the procedure described for **1a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.1 Hz, 1H), 7.40-7.33 (m, 2H), 7.14-7.06 (m, 1H), 5.81 (brs, 1H), 3.02 (d, *J* = 4.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 142.4, 139.8, 131.1, 128.3, 128.2, 92.6, 26.8; IR (thin film) ν 3288, 1629, 1542, 1312, 764 cm^{-1}. Other data was identical to the literature values.[2]



2-Iodo-*N*-phenylbenzamide (1c). Prepared according to the procedure described for **1a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.1 Hz, 1H), 7.73 (brs, 1H), 7.62 (d, *J* = 7.8 Hz, 2H), 7.46 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.40-7.33 (m, 2H), 7.19-7.08 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 142.1, 140.1, 137.7, 131.5, 129.2, 128.6, 128.4, 125.0, 120.3, 92.5; IR (thin film) ν 3256, 3056, 1654, 1600, 1542, 1440, 1324, 755, 692 cm^{-1}. Other data was identical to the literature values.[3]



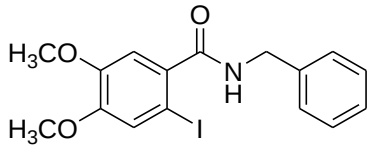
2-Iodo-*N*-(2,6-dimethylphenyl)benzamide (1d). Prepared according to the procedure described for **1a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.1 Hz, 1H), 7.52 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.18-7.07 (m, 4H), 2.35 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 142.2, 140.3, 135.7, 133.1, 131.4, 128.4, 128.2, 127.7, 92.4, 19.0; IR (thin film) ν 3235, 2918, 1653, 1522, 772, 749 cm^{-1}. Other data was identical to the literature values.[4]



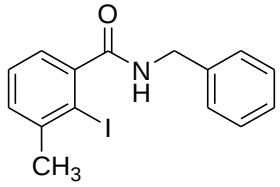
2-Iodobenzamide (1e).

A flame-dried round bottom flask was charged with 1.0 equiv of 2-iodobenzoic acid in CH_2Cl_2 (0.3 M) and DMF (2 drops), followed by the addition of 1.25 equiv of oxalyl chloride at 0 ºC. The reaction mixture was allowed to stir at room temperature for 4 h. After that, the mixture was evaporated to dryness. The prepared acid chloride was dissolved in CH_2Cl_2 (0.3 M). NH_4OH (28-30%, 1.5 equiv) was added dropwise at 0 ºC. The reaction mixture was allowed to stir at room temperature for 2 h. The precipitate was filtered and washed with water to give **1e** as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.14 (td, *J* = 7.8, 1.5 Hz, 1H), 5.88 (brs, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.8,

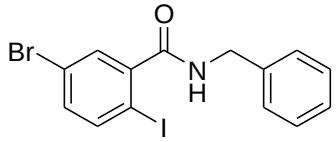
142.9, 139.2, 129.0, 128.0, 127.8, 93.0; IR (thin film) ν 3349, 3174, 1651, 1622, 1399, 1127, 770, 739 cm^{-1}. Other data was identical to the literature values.[3]



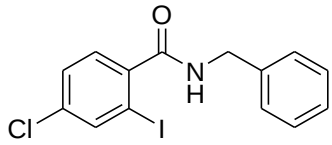
***N*-Benzyl-2-iodo-4,5-dimethoxybenzamide (1f).** Prepared according to the procedure described for **1a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.24 (m, 5H), 7.19 (s, 1H), 7.01 (s, 1H), 6.26 (brs, 1H), 4.62 (d, *J* = 5.7 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 150.5, 149.2, 137.6, 134.1, 128.7, 128.2, 127.7, 122.0, 112.0, 80.9, 56.2, 56.1, 44.4; IR (thin film) ν 3285, 3028, 2932, 1638, 1593, 1498, 1255, 1210, 1027, 862, 772, 699 cm^{-1}. Other data was identical to the literature values.[5]



***N*-Benzyl-2-iodo-3-methylbenzamide (1g).** Prepared according to the procedure described for **1a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.12 (m, 7H), 7.03-6.99 (m, 1H), 6.38 (brs, 1H), 4.51 (d, *J* = 6.0 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 143.7, 142.8, 137.8, 130.4, 128.7, 128.1, 128.0, 127.6, 125.1, 99.4, 44.0, 29.2; IR (thin film) ν 3273, 3031, 1646, 1523, 1313, 1012, 776, 720, 698 cm^{-1}. Other data was identical to the literature values.[6]

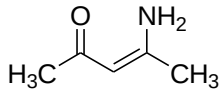


***N*-Benzyl-5-bromo-2-iodobenzamide (1h).** Prepared according to the procedure described for **1a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.37-7.29 (m, 5H), 7.20 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.21 (brs, 1H), 4.59 (d, *J* = 5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 143.5, 141.1, 137.1, 134.1, 131.1, 128.7, 128.0, 127.7, 122.4, 90.3, 44.2; IR (thin film) ν 3276, 3011, 1646, 1541, 1086, 1016, 977, 772, 700 cm^{-1}; HRMS (ESI) $[M+Na]^{+}$ calcd. for $C_{14}H_{11}BrINO$ 437.8966, found 437.8966.



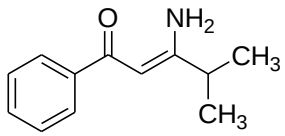
***N*-Benzyl-4-chloro-2-iodobenzamide (1i).** Prepared according to the procedure described for **1a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 1.5 Hz, 1H), 7.43-7.29 (m, 7H), 6.24 (brs, 1H), 4.63 (d, *J* = 5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 140.2, 139.2, 137.2, 136.0, 128.8, 128.6, 128.3, 128.0, 127.6, 92.5, 44.1; IR (thin film) ν 3266, 3030, 1637, 1541, 827, 773, 742 cm^{-1}. Other data was identical to the literature values.[6]

Synthesis of Enaminones



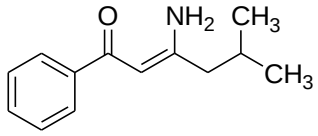
(*Z*)-4-Aminopent-3-en-2-one (2a).

To a round bottom flask with a suspension of acetylacetone (10.0 mmol) and SiO_2 (20 mg) in H_2O (10 ml) was added NH_4OH (28-30%, 1.32 mL) dropwise. After stirring overnight at room temperature, the mixture was extracted with CH_2Cl_2. The organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give the title compound as yellow oil which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (brs, 1H), 5.73 (brs, 1H), 4.92 (s, 1H), 1.92 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1, 162.4, 95.2, 28.9, 21.8; IR (thin film) ν 3348, 3184, 1615, 1538, 1416, 1294 cm^{-1}. Other data was identical to the literature values.[7]

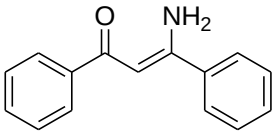


(*Z*)-3-Amino-4-methyl-1-phenylpent-2-en-1-one (2b).

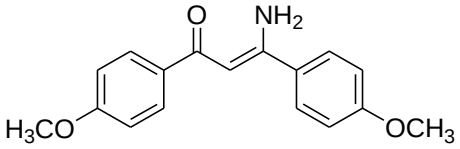
To an oven-dried round bottom flask was added 1.0 equiv of 4-methyl-1-phenylpentane-1,3-dione[8,9], 5.0 equiv of NH_4OAc and EtOH (0.5 M). The reaction mixture was heated to reflux for overnight. After cooling to room temperature, EtOH was removed. H_2O was added and the mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (5:1 hexanes:EtOAc) to afford the title compound as yellow crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.37 (brs, 1H), 7.87 (dd, *J* = 7.2, 1.5 Hz, 2H), 7.46-7.36 (m, 3H), 5.76 (s, 1H), 5.50 (brs, 1H), 2.44 (septet, *J* = 6.9 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 172.8, 140.6, 130.7, 128.2, 127.1, 89.4, 35.3, 21.2; IR (thin film) ν 3350, 3170, 2968, 1603, 1528, 1280, 755, 695 cm^{-1}. Other data was identical to the literature values.[10]



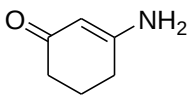
(*Z*)-3-Amino-5-methyl-1-phenylhex-2-en-1-one (2c). Prepared according to the procedure described for **2b**. Purification by column chromatography (6:1 hexanes:EtOAc) to afford the title compound as yellow crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.31 (brs, 1H), 7.91 (dd, *J* = 7.8, 2.4 Hz, 2H), 7.48-7.39 (m, 3H), 5.84 (brs, 1H), 5.72 (s, 1H), 2.11 (d, *J* = 7.2 Hz, 2H), 2.00-1.93 (m, 1H), 0.97 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.3, 167.0, 140.4, 130.8, 128.2, 127.1, 92.2, 46.2, 28.0, 22.4; IR (thin film) ν 3337, 3168, 2958, 1599, 1526, 1292, 744, 693 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd. for $C_{13}H_{17}NO$ 204.1388, found 204.1380.



(*Z*)-3-Amino-1,3-diphenylprop-2-en-1-one (2d). Prepared according to the procedure described for **2b**. Purification by column chromatography (5:1 hexanes:EtOAc) to afford the title compound as pale yellow crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.43 (brs, 1H), 7.98-7.93 (m, 2H), 7.70-7.53 (m, 2H), 7.52-7.39 (m, 6H), 6.15 (s, 1H), 5.46 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.8, 162.8, 140.1, 137.2, 130.8, 130.4, 128.8, 128.0, 127.0, 126.2, 91.5; IR (thin film) ν 3356, 3164, 3060, 1600, 1567, 1526, 1484, 1326, 1225, 772, 740, 694 cm^{-1}. Other data was identical to the literature values.[10]



(*Z*)-3-Amino-1,3-bis(4-methoxyphenyl)prop-2-en-1-one (2e). Prepared according to the procedure described for **2b**. Purification by column chromatography (3:1 hexanes:EtOAc) to afford the title compound as pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.39 (brs, 1H), 7.94 (d, *J* = 9.0 Hz, 2H), 7.59 (d, *J* = 9.0 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 6.09 (s, 1H), 5.38 (brs, 1H), 3.86 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.8, 162.0, 161.8, 161.5, 133.1, 129.8, 129.0, 127.6, 114.2, 113.3, 90.7, 55.3, 55.2; IR (thin film) ν 3362, 1595, 1490, 1255, 1227, 1172, 1028, 840, 777 cm^{-1}. Other data was identical to the literature values.[11]

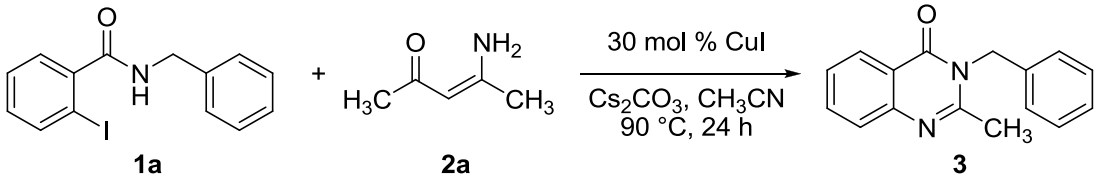


3-Aminocyclohex-2-enone (23). To an oven-dried round bottom flask was added 1.0 equiv of 1,3-cyclohexanedione, 1.0 equiv of NH_4OAc and EtOH (0.5 M). The reaction mixture was heated to reflux for overnight. After cooling to room temperature, EtOH was removed. The crude product was purified by column chromatography (6:1 EtOAc:MeOH) to give the title compound as a pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.76 (brs, 2H), 4.93 (s, 1H), 2.27-2.22 (m, 2H), 2.04-1.99 (m, 2H), 1.81-1.72 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 195.3, 168.0, 97.9, 36.3, 28.4, 22.0; IR (thin film) ν 3336, 3143, 2940, 1671, 1542, 1259, 1190, 1145 cm^{-1}. Other data was identical to the literature values.[12]

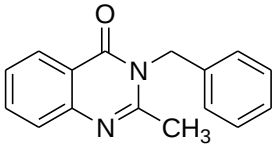
Synthesis of Quinazolinone Derivatives

General Procedure for Copper-Catalyzed Domino Reaction for Synthesis of Quinazolinone Derivatives.

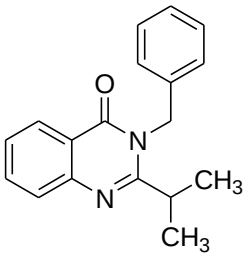
General Procedure A: For the Reaction of *Z*-Enaminone



The reaction of *N*-benzyl-2-iodobenzamide (**1a**) and (*Z*)-4-aminopent-3-en-2-one (**2a**) is representative: A 10 mL round bottom flask equipped with a magnetic stirring bar was charged with *N*-benzyl-2-iodobenzamide (**1a**) (0.5 mmol), (*Z*)-4-aminopent-3-en-2-one (**2a**) (1.0 mmol), CuI (0.15 mmol) and Cs_2CO_3 (1.25 mmol) in CH_3CN (5.0 mL). The reaction mixture was allowed to stir at 90 ºC for 24 h. After completion of the reaction, the reaction mixture was cooled to room temperature, quenched with 1M HCl and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (12:1 CH_2Cl_2:EtOAc) to provide **3** in 97.62 mg (78% yield) as a yellow oil.

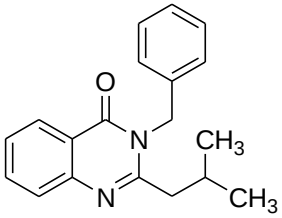


3-Benzyl-2-methylquinazolin-4(3*H*)-one (3). Yield 97.62 mg (78%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.73 (td, *J* = 8.1, 1.5 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.45 (td, *J* = 8.1, 1.5 Hz, 1H), 7.35-7.27 (m, 3H), 7.20-7.17 (m, 2H), 5.38 (s, 2H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 154.7, 147.3, 135.9, 134.4, 129.0, 127.7, 127.1, 126.7, 126.6, 126.5, 120.4, 47.1, 23.4; IR (thin film) ν 3064, 3032, 2960, 1668, 1598, 1389, 1341, 774, 717, 697 cm^{-1}. Other data was identical to the literature values.[13]

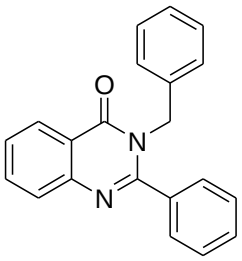


3-Benzyl-2-isopropylquinazolin-4(3*H*)-one (4). Prepared according to general procedure A from *N*-benzyl-2-iodobenzamide (**1a**) and (*Z*)-3-amino-4-methyl-1-phenylpent-2-en-1-one (**2b**). Yield 41.75 mg (30%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.8 Hz, 1H), 7.75-7.66 (m, 2H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.33-7.24 (m, 3H), 7.14 (d, *J* = 7.2 Hz, 2H), 5.46 (s, 2H), 3.09 (septet, *J* = 6.6 Hz, 1H), 1.26 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 161.6, 147.4, 136.4, 134.0, 128.7, 127.3, 127.0, 126.8, 126.1, 125.9,

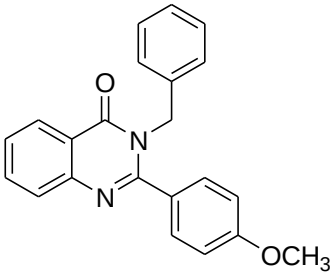
120.2, 45.7, 31.9, 21.2; IR (thin film) ν 2969, 1673, 1593, 774, 697 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd. for $C_{18}H_{18}N_2O$ 279.1497, found 279.1498.



3-Benzyl-2-isobutylquinazolin-4(3*H*)-one (5). Prepared according to general procedure A from *N*-benzyl-2-iodobenzamide (**1a**) and (*Z*)-3-amino-5-methyl-1-phenylhex-2-en-1-one (**2c**). Yield 51.16 mg (35%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 7.5 Hz, 1H), 7.77-7.66 (m, 2H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.34-7.23 (m, 3H), 7.16 (d, *J* = 6.9, 2H), 5.42 (s, 2H), 2.63 (d, *J* = 6.9 Hz, 2H), 2.37-2.23 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 156.2, 146.9, 135.9, 134.0, 128.5, 127.2, 126.7, 126.1, 126.0, 119.9, 46.1, 43.3, 26.8, 22.1; IR (thin film) ν 2957, 1671, 1595, 1168, 773, 697 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd. for $C_{19}H_{20}N_2O$ 293.1654, found 293.1655.

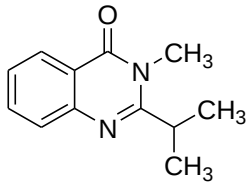


3-Benzyl-2-phenylquinazolin-4(3*H*)-one (6). Prepared according to general procedure A from *N*-benzyl-2-iodobenzamide (**1a**) and (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one (**2d**). Yield 110.89 mg (71%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, *J* = 7.5 Hz, 1H), 7.79-7.77 (m, 2H), 7.56-7.33 (m, 6H), 7.22-7.20 (m, 3H), 6.93-6.92 (m, 2H), 5.28 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 156.4, 147.3, 136.6, 135.3, 134.6, 129.9, 128.6, 128.5, 128.0, 127.6, 127.4, 127.2, 127.1, 127.0, 120.9, 48.8; IR (thin film) ν 3063, 1675, 1568, 1375, 1245, 1148, 970, 771, 697 cm^{-1}. Other data was identical to the literature values.[14]

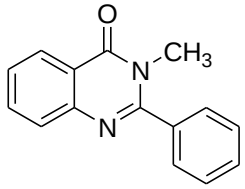


3-Benzyl-2-(4-methoxyphenyl)quinazolin-4(3*H*)-one (7). Prepared according to general procedure A from *N*-benzyl-2-iodobenzamide (**1a**) and (*Z*)-3-amino-1,3-bis(4-methoxyphenyl)prop-2-en-1-one (**2e**). Yield 85.60 mg (50%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, *J* = 7.8 Hz, 1H), 7.85-7.65 (m, 2H), 7.55-7.40 (m, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.25-7.15 (m, 3H), 6.97-6.94 (m, 2H), 6.88 (d, *J* = 8.1 Hz, 2H), 5.28 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 160.6, 156.1, 147.0, 136.5, 134.3, 129.4, 128.3, 127.3, 127.2,

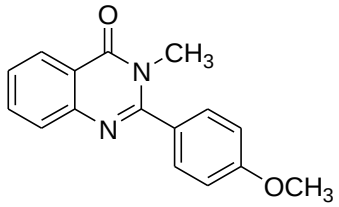
126.8, 126.6, 120.4, 113.7, 55.2, 48.8; IR (thin film) ν 3031, 2959, 1675, 1607, 1250, 1177, 1028, 833, 774 cm^{-1}. Other data was identical to the literature values.[15]



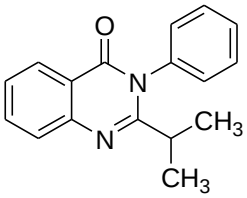
2-Isopropyl-3-methylquinazolin-4(3*H*)-one (8). Prepared according to general procedure A from 2-iodo-*N*-methylbenzamide (**1b**) and (*Z*)-3-amino-4-methyl-1-phenylpent-2-en-1-one (**2b**). Yield 25.28 mg (25%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, *J* = 7.8 Hz, 1H), 7.73-7.64 (m, 2H), 7.42 (t, *J* = 7.8 Hz, 1H), 3.67 (s, 3H), 3.21 (septet, *J* = 6.6 Hz, 1H), 1.39 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 161.1, 147.3, 134.0, 127.0, 126.6, 126.2, 120.2, 32.2, 30.1, 20.8; IR (thin film) ν 2970, 1674, 1591, 775, 697 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd. for $C_{12}H_{14}N_2O$ 203.1184, found 203.1184.



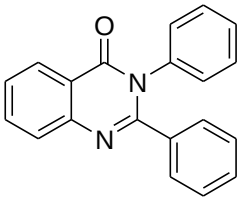
3-Methyl-2-phenylquinazolin-4(3*H*)-one (9). Prepared according to general procedure A from 2-iodo-*N*-methylbenzamide (**1b**) and (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one (**2d**). Yield 82.69 mg (70%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, *J* = 7.5 Hz, 1H), 7.76-7.74 (m, 2H), 7.56-7.47 (m, 6H), 3.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 156.1, 147.3, 135.4, 134.3, 130.1, 128.9, 128.0, 127.5, 127.0, 126.7, 120.6, 34.2; IR (thin film) ν 3064, 1671, 1564, 1354, 1050, 771, 698 cm^{-1}. Other data was identical to the literature values.[16]



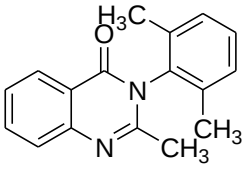
2-(4-Methoxyphenyl)-3-methylquinazolin-4(3*H*)-one (10). Prepared according to general procedure A from 2-iodo-*N*-methylbenzamide (**1b**) and (*Z*)-3-amino-1,3-bis(4-methoxyphenyl)prop-2-en-1-one (**2e**). Yield 86.54 mg (65%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.1 Hz, 1H), 7.67-7.65 (m, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.44-7.39 (m, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 3.82 (s, 3H), 3.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 160.6, 155.7, 147.0, 133.9, 129.5, 127.4, 127.0, 126.4, 126.3, 120.0, 113.9, 55.2, 34.1; IR (thin film) ν 3004, 2958, 1671, 1607, 1589, 1253, 1176, 1025, 834, 774, 698 cm^{-1}. Other data was identical to the literature values.[17]



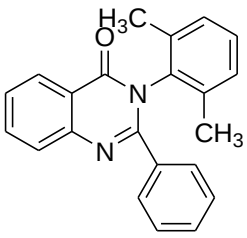
2-Isopropyl-3-methylquinazolin-4(3*H*)-one (11). Prepared according to general procedure A from 2-iodo-*N*-phenylbenzamide (**1c**) and (*Z*)-3-amino-4-methyl-1-phenylpent-2-en-1-one (**2b**). Yield 44.93 mg (34%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, *J* = 7.5 Hz, 1H), 7.78-7.70 (m, 2H), 7.59-7.41 (m, 4H), 7.26 (d, *J* = 6.6 Hz, 2H), 2.69 (septet, *J* = 6.6 Hz, 1H), 1.22 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 161.6, 147.8, 137.5, 134.4, 129.8, 129.1, 128.4, 127.2, 127.0, 126.4, 120.8, 32.4, 21.3; IR (thin film) ν 3064, 2972, 1683, 1588, 773, 697 cm^{-1}. Other data was identical to the literature values.[18]



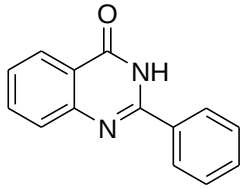
2,3-Diphenylquinazolin-4(3*H*)-one (12). Prepared according to general procedure A from 2-iodo-*N*-phenylbenzamide (**1c**) and (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one (**2d**). Yield 44.75 mg (30%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.1 Hz, 1H), 7.84-7.77 (m, 2H), 7.55-7.49 (m, 1H), 7.35-7.14 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 155.3, 147.6, 137.8, 135.5, 134.8, 129.4, 129.2, 129.0, 128.5, 128.0, 127.8, 127.4, 127.3, 121.0; IR (thin film) ν 3064, 1683, 1559, 1340, 1271, 770, 697 cm^{-1}. Other data was identical to the literature values.[14]



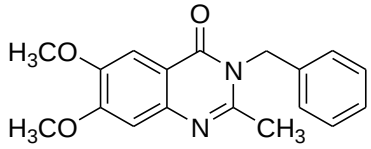
2-Methyl-3-(2,6-dimethylphenyl)quinazolin-4(3*H*)-one (13). Prepared according to general procedure A from 2-iodo-*N*-(2,6-dimethylphenyl)benzamide (**1d**) and (*Z*)-4-aminopent-3-en-2-one (**2b**). Yield 70.04 mg (53%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 7.8 Hz, 1H), 7.79 (t, *J* = 8.1 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.33-7.21 (m, 3H), 2.15 (s, 3H), 2.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 154.4, 147.8, 136.0, 135.0, 134.6, 129.3, 129.1, 127.2, 126.8, 126.6, 120.7, 23.1, 17.7; IR (thin film) ν 2923, 1683, 1603, 1339, 773, 700 cm^{-1}. Other data was identical to the literature values.[19]



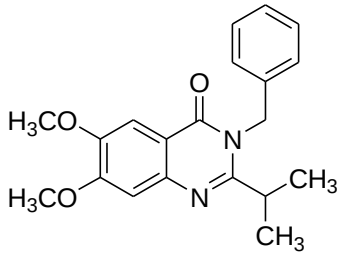
3-(2,6-Dimethylphenyl)-2-phenylquinazolin-4(3*H*)-one (14). Prepared according to general procedure A from 2-iodo-*N*-(2,6-dimethylphenyl)benzamide (**1d**) and (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one (**2d**). Yield 57.12 mg (35%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, *J* = 7.8 Hz, 1H), 7.88-7.82 (m, 2H), 7.55 (td, *J* = 8.1, 1.8 Hz, 1H), 7.35 (d, *J* = 7.5 Hz, 2H), 7.31-7.11 (m, 4H), 7.03 (d, *J* = 7.5 Hz, 2H), 2.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 155.3, 148.0, 136.3, 135.5, 134.8, 129.8, 129.1, 128.6, 128.4, 127.8, 127.7, 127.5, 127.3, 127.2, 120.8, 18.3; IR (thin film) ν 2923, 1685, 1560, 1471, 1330, 1271, 771, 697 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd. for $C_{22}H_{18}N_2O$ 327.1497, found 327.1486.



2-Phenylquinazolin-4(3*H*)-one (15). Prepared according to general procedure A from 2-iodobenzamide (**1e**) and (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one (**2d**). Yield 53.34 mg (48%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.62 (brs, 1H), 8.35-8.31 (m, 1H), 8.28-8.24 (m, 2H), 7.87-7.77 (m, 2H), 7.60-7.58 (m, 3H), 7.54-7.48 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 151.9, 149.6, 134.9, 132.8, 131.6, 129.0, 128.0, 127.5, 126.8, 126.4, 120.8; IR (thin film) ν 3080, 1668, 1297, 768, 694 cm^{-1}. Other data was identical to the literature values.[15]

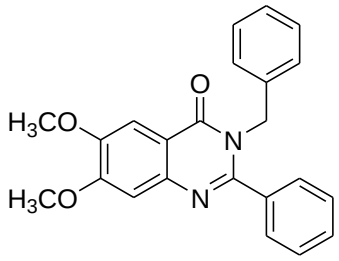


3-Benzyl-6,7-dimethoxy-2-methylquinazolin-4(3*H*)-one (16). Prepared according to general procedure A from *N*-benzyl-2-iodo-4,5-dimethoxybenzamide (**1f**) and (*Z*)-4-aminopent-3-en-2-one (**2a**). Yield 58.97 mg (38%) as yellow crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.38-7.21 (m, 5H), 7.10 (s, 1H), 5.44 (s, 2H), 4.03 (s, 6H), 2.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 155.1, 153.5, 148.9, 143.3, 135.9, 128.9, 127.7, 126.5, 113.6, 107.0, 106.0, 56.3, 56.2, 47.2, 23.2; IR (thin film) ν 2962, 1662, 1498, 1398, 1245, 1026, 774, 703 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd. for $C_{18}H_{18}N_2O_3$ 311.1395, found 311.1382.

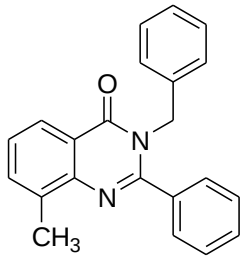


3-Benzyl-2-isopropyl-6,7-dimethoxyquinazolin-4(3*H*)-one (17). Prepared according to general procedure A from *N*-benzyl-2-iodo-4,5-dimethoxybenzamide (**1f**) and (*Z*)-3-amino-4-methyl-1-phenylpent-2-en-1-one (**2b**). Yield 59.22 mg (35%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.33-7.21 (m, 3H), 7.13 (d, *J* = 7.2 Hz, 2H), 7.08 (s, 1H), 5.45 (s, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 3.07 (septet, *J* = 6.6 Hz, 1H), 1.24

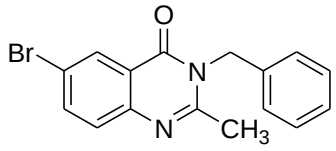
(d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 160.6, 155.0, 148.8, 143.8, 136.7, 128.9, 127.5, 126.1, 113.6, 107.5, 106.0, 56.3, 56.2, 45.9, 32.0, 21.4; IR (thin film) ν 2966, 1664, 1498, 1405, 1235, 1007, 866, 735 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd. for $C_{20}H_{22}N_2O_3$ 339.1708, found 339.1693.



3-Benzyl-6,7-dimethoxy-2-phenylquinazolin-4(3*H*)-one (18). Prepared according to general procedure A from *N*-benzyl-2-iodo-4,5-dimethoxybenzamide (**1f**) and (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one (**2d**). Yield 135.93 mg (73%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.49-7.30 (m, 5H), 7.22-7.18 (m, 4H), 6.95-6.91 (m, 2H), 5.28 (s, 2H), 4.02 (s, 3H), 3.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 155.3, 155.2, 149.4, 143.6, 136.8, 135.4, 129.8, 128.6, 128.5, 128.1, 127.7, 127.0, 114.3, 108.0, 106.0, 56.4, 48.8; IR (thin film) ν 3006, 2962, 1663, 1496, 1246, 1017, 869, 756, 702 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd. for $C_{23}H_{20}N_2O_3$ 373.1552, found 373.1555.

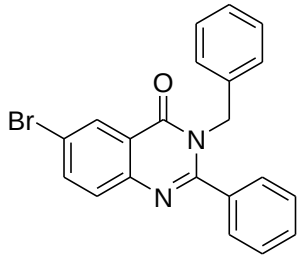


3-Benzyl-8-methyl-2-phenylquinazolin-4(3*H*)-one (19). Prepared according to general procedure A from *N*-benzyl-2-iodo-3-methylbenzamide (**1g**) and (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one (**2d**). Yield 55.49 mg (34%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 6.9 Hz, 1H), 7.48-7.38 (m, 6H), 7.21-7.19 (m, 3H), 7.00-6.92 (m, 2H), 5.29 (s, 2H), 2.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 154.8, 146.0, 136.8, 136.3, 135.8, 135.1, 129.8, 128.5, 128.4, 127.3, 127.0, 126.7, 124.7, 120.8, 48.8, 17.4; IR (thin film) ν 3031, 2924, 1671, 1591, 1455, 1357, 1254, 770, 700 cm^{-1}. Other data was identical to the literature values.[15]

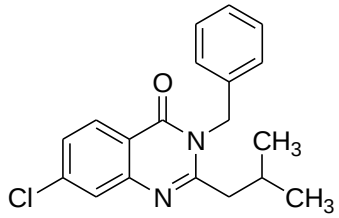


3-Benzyl-6-bromo-2-methylquinazolin-4(3*H*)-one (20). Prepared according to general procedure A from *N*-benzyl-5-bromo-2-iodobenzamide (**1h**) and (*Z*)-4-aminopent-3-en-2-one (**2a**). Yield 32.92 mg (20%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, J = 2.1 Hz, 1H), 7.81 (dd, J = 8.7, 2.4 Hz, 1H), 7.51 (d, J = 8.7 Hz, 1H), 7.37-7.27 (m, 3H), 7.18 (d, J = 8.1 Hz, 2H), 5.38 (s, 2H), 2.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 155.2, 146.1, 137.6, 135.5, 129.6, 129.0, 128.6, 127.9, 126.5, 121.8, 120.0, 47.3, 23.4; IR (thin film) ν

3064, 2926, 1676, 1595, 1467, 1382, 1335, 833, 724 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd. for $C_{16}H_{13}BrN_2O$ 329.0289, found 329.0297.

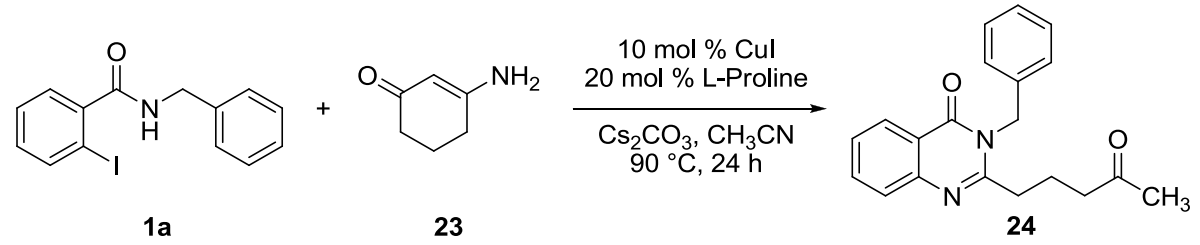


3-Benzyl-8-methyl-2-phenylquinazolin-4(3*H*)-one (21). Prepared according to general procedure A from *N*-benzyl-5-bromo-2-iodobenzamide (**1h**) and (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one (**2d**). Yield 88.03 mg (45%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, *J* = 2.1 Hz, 1H), 7.82 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.48-7.32 (m, 5H), 7.21-7.18 (m, 3H), 6.92-6.90 (m, 2H), 5.26 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 156.8, 146.1, 137.7, 136.3, 135.0, 130.1, 129.6, 129.4, 128.7, 128.6, 128.0, 127.6, 127.0, 122.2, 120.7, 49.0; IR (thin film) ν 3064, 1681, 1559, 1467, 1232, 833, 772, 700 cm^{-1}. Other data was identical to the literature values.[20]



3-Benzyl-7-chloro-2-isobutylquinazolin-4(3*H*)-one (22). Prepared according to general procedure A from *N*-benzyl-4-chloro-2-iodobenzamide (**1i**) and (*Z*)-3-amino-5-methyl-1-phenylhex-2-en-1-one (**2c**)**.** Yield 88.24 mg (54%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.7 Hz, 1H), 7.68 (d, *J* = 1.8 Hz, 1H), 7.40 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.35-7.26 (m, 3H), 7.15 (d, *J* = 6.6 Hz, 2H), 5.39 (s, 2H), 2.61 (d, *J* = 6.6 Hz, 2H), 2.37-2.23 (m, 1H), 0.97 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 157.8, 148.1, 140.4, 135.8, 128.8, 128.4, 127.6, 127.0, 126.5, 126.2, 118.6, 46.4, 43.5, 26.9, 22.3; IR (thin film) ν 2958, 1678, 1593, 1456, 1394, 1332, 1166, 879, 731, 696 cm^{-1}. Other data was identical to the literature values.[14]

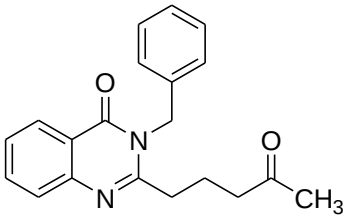
General Procedure B: For the Reaction of 3-Aminocyclohex-2-enone



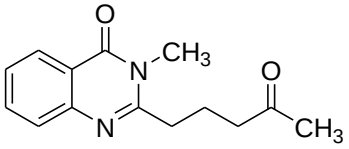
1a **23** **24**

The reaction of *N*-benzyl-2-iodobenzamide (**1a**) and 3-aminocyclohex-2-enone (**23**) is representative: A 10 mL round bottom flask equipped with a magnetic stirring bar was charged with *N*-benzyl-2-iodobenzamide (**1a**) (0.5 mmol), 3-aminocyclohex-2-enone (**23**) (0.75 mmol), CuI (0.05 mmol), L-Proline (0.1 mmol) and Cs_2CO_3 (1.25

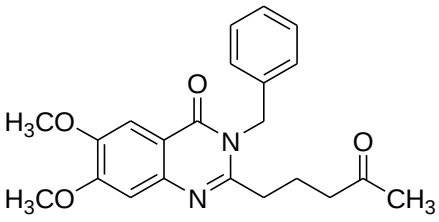
mmol) in CH_3CN (5.0 mL). The reaction mixture was allowed to stir at 90 ºC for 24 h. After completion of the reaction, the reaction mixture was cooled to room temperature, quenched with sat. NH_4Cl and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (5:1 hexanes:EtOAc) to provide **24** in 95.12 mg (81% yield) as a white solid.



3-Benzyl-2-(4-oxopentyl)quinazoline-4(3*H*)-one (24). Yield 95.12 mg (81%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.75 (td, *J* = 8.1, 1.5 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.47 (td, *J* = 8.1, 1.5 Hz, 1H), 7.34-7.25 (m, 3H), 7.20 (d, *J* = 8.1 Hz, 2H), 5.48 (s, 2H), 2.76 (t, *J* = 7.5 Hz, 2H), 2.57 (t, *J* = 6.6 Hz, 2H), 2.11-2.02 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 162.5, 156.6, 147.2, 136.3, 134.3, 128.9, 127.6, 127.5, 127.2, 127.1, 126.9, 126.6, 126.4, 120.4, 46.2, 42.3, 34.0, 30.0, 20.9; IR (thin film) ν 2952, 1673, 1595, 1454, 1170, 976, 879, 775, 697 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd. for $C_{20}H_{20}N_2O_2$ 321.1603, found 321.1603.

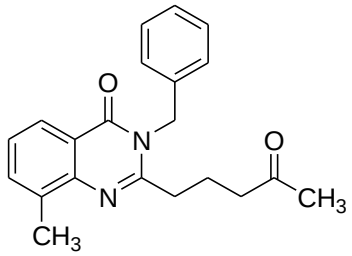


3-Methyl-2-(4-oxopentyl)quinazolin-4(3*H*)-one (25). Prepared according to general procedure B from 2-iodo-*N*-methylbenzamide (**1b**) and 3-aminocyclohex-2-enone (**23**). Yield 94.05 mg (77%) as a brown viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.1 Hz, 1H), 7.62 (t, *J* = 8.1 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 8.1 Hz, 1H), 3.56 (s, 3H), 2.75 (t, *J* = 7.5 Hz, 2H), 2.60 (t, *J* = 6.6 Hz, 2H), 2.09-2.01 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.0, 162.1, 156.1, 146.8, 133.7, 126.5, 126.4, 126.1, 119.9, 42.0, 34.1, 30.1, 29.7, 20.0; IR (thin film) ν 2951, 1674, 1446, 1133, 1013, 964, 887, 777, 698 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd. for $C_{14}H_{16}N_2O_2$ 245.1290, found 245.1290.

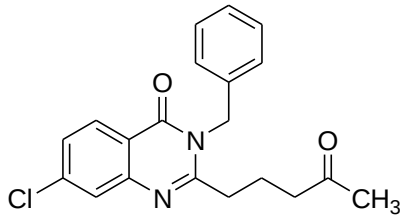


3-Benzyl-6,7-dimethoxy-2-(4-oxopentyl)quinazolin-4(3*H*)-one (26). Prepared according to general procedure B from *N*-benzyl-2-iodo-4,5-dimethoxybenzamide (**1f**) and 3-aminocyclohex-2-enone (**23**). Yield 116.03 mg (61%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.34-7.23 (m, 3H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.06 (s, 1H), 5.47 (s, 2H), 4.00 (s, 3H), 3.99 (s, 3H), 2.72 (t, *J* = 7.2 Hz, 2H), 2.55 (t, *J* = 6.9 Hz, 2H), 2.11-

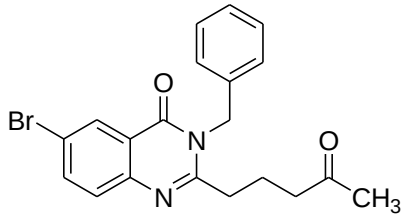
2.02 (m, 5H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 207.8, 161.6, 155.0, 154.8, 148.6, 143.3, 136.2, 128.6, 127.2, 126.1, 113.4, 107.1, 105.7, 56.0, 55.9, 45.9, 42.0, 33.7, 29.7, 20.7; IR (thin film) ν 2932, 1646, 1269, 1180, 1131, 871, 770, 698 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd. for $C_{22}H_{24}N_2O_4$ 381.1814, found 381.1814.



3-Benzyl-8-methyl-2-(4-oxopentyl)quinazolin-4(3*H*)-one (27). Prepared according to general procedure B from *N*-benzyl-2-iodo-3-methylbenzamide (**1g**) and 3-aminocyclohex-2-enone (**23**). Yield 102.00 mg (61%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.1 Hz, 1H), 7.58 (d, *J* = 6.9 Hz, 1H), 7.36-7.23 (m, 4H), 7.17 (d, *J* = 7.5 Hz, 2H), 5.42 (s, 2H), 2.75 (t, *J* = 6.9 Hz, 2H), 2.61-2.55 (m, 5H), 2.15-2.05 (m, 5H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 208.5, 162.9, 154.8, 145.6, 136.2, 135.5, 134.9, 128.9, 127.6, 126.4, 126.2, 124.8, 120.3, 46.1, 42.3, 33.5, 30.0, 20.3, 17.2; IR (thin film) ν 2953, 1670, 1599, 1436, 1338, 1190, 1078, 773, 725 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd. for $C_{21}H_{22}N_2O_2$ 335.1760, found 335.1760.

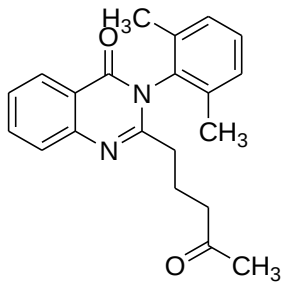


3-Benzyl-7-chloro-2-(4-oxopentyl)quinazolin-4(3*H*)-one (28). Prepared according to general procedure B from *N*-benzyl-4-chloro-2-iodobenzamide (**1i**) and 3-aminocyclohex-2-enone (**23**). Yield 104.67 mg (59%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.4 Hz, 1H), 7.58 (s, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.28-7.19 (m, 3H), 7.10 (d, *J* = 6.9 Hz, 2H) 5.37 (s, 2H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.49 (t, *J* = 6.6 Hz, 2H), 2.04-1.95 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1, 161.9, 158.0, 148.1, 140.5, 136.0, 129.0, 128.6, 127.7, 127.2, 126.5, 126.4, 118.9, 46.3, 42.2, 34.0, 30.0, 20.6; IR (thin film) ν 2919, 1674, 1592, 1163, 1015, 878, 776, 729, 696 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd. for $C_{20}H_{19}ClN_2O_2$ 355.1213, found 355.1213.



3-Benzyl-6-bromo-2-(4-oxopentyl)quinazolin-4(3*H*)-one (29). Prepared according to general procedure B from *N*-benzyl-5-bromo-2-iodobenzamide (**1h**) and 3-aminocyclohex-2-enone (**23**). Yield 125.77 mg (63%) as a yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.80 (d, *J* = 8.7 Hz, 1H), 7.52 (dd, *J* = 8.7, 1.2 Hz, 1H), 7.34-7.23 (m, 3H), 7.17 (d, *J* = 7.5 Hz, 2H), 5.45 (s, 2H), 2.73 (t, *J* = 7.5 Hz, 2H), 2.55 (t, *J* = 6.6 Hz,

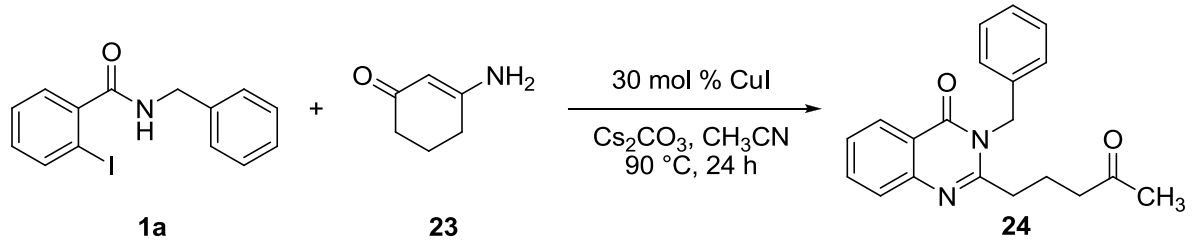
2H), 2.11-2.00 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 161.4, 157.1, 146.0, 137.5, 135.9, 129.6, 129.0, 128.8, 127.7, 126.4, 121.8, 120.0, 46.4, 42.2, 34.0, 30.0, 20.7; IR (thin film) ν 2954, 1678, 1592, 1467, 1160, 877, 834, 726 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd. for $C_{20}H_{19}BrN_2O_2$ 399.0708, found 399.0706.



3-(2,6-Dimethylphenyl)-2-(4-oxopentyl)quinazolin-4(3*H*)-one (30). Prepared according to general procedure B from 2-iodo-*N*-(2,6-dimethylphenyl)benzamide (**1d**) and 3-aminocyclohex-2-enone (**23**). Yield 23.4 mg (14%) as a brown viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.1 Hz, 1H), 7.85-7.80 (m, 2H), 7.52 (t, *J* = 8.1 Hz, 1H), 7.36-7.23 (m, 3H), 2.56 (t, *J* = 6.9 Hz, 2H), 2.33 (t, *J* = 6.9 Hz, 2H), 2.13-2.02 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 161.2, 155.8, 147.7, 135.4, 135.2, 134.5, 129.3, 129.1, 127.2, 127.1, 126.6, 120.8, 42.6, 33.4, 29.9, 19.9, 17.8; IR (thin film) ν 2923, 1682, 1472, 1161, 1117, 964, 892, 775, 701 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd. for $C_{21}H_{22}N_2O_2$ 335.1760, found 335.1760.

Experiments to Investigate the Effect of the Geometry of Enaminones

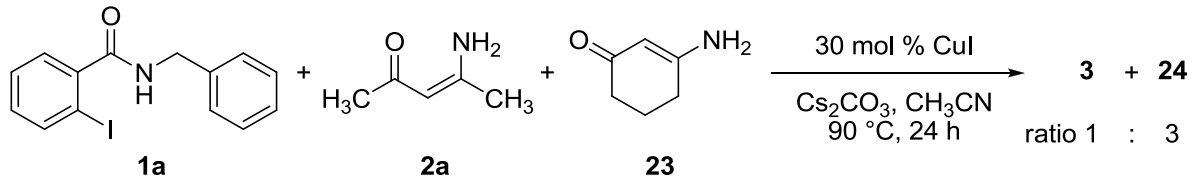
Scheme 1, A:



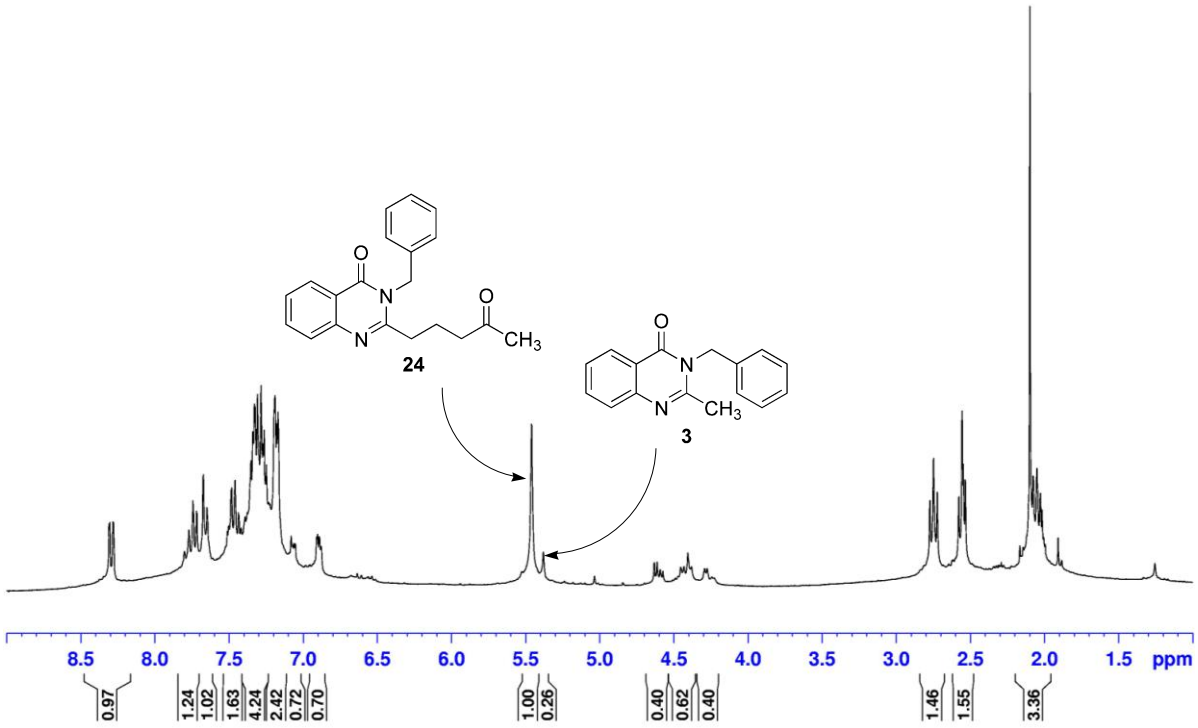
1a **23** **24**

A 10 mL round bottom flask equipped with a magnetic stirring bar was charged with *N*-benzyl-2-iodobenzamide (**1a**) (0.5 mmol), 3-aminocyclohex-2-enone (**23**) (1.0 mmol), CuI (0.15 mmol) and Cs_2CO_3 (1.25 mmol) in CH_3CN (5.0 mL). The reaction mixture was allowed to stir at 90 ºC for 24 h. After completion of the reaction, the reaction mixture was cooled to room temperature, quenched with 1M HCl and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (2% MeOH/CH_2Cl_2) to provide **24** in 14% yield as a white solid.

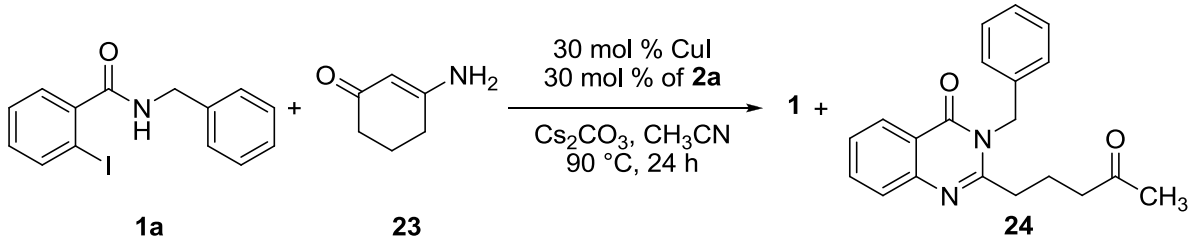
Scheme 1, B:



A sealed tube equipped with a magnetic stirring bar was charged with *N*-benzyl-2-iodobenzamide (**1**) (0.1 mmol), (*Z*)-4-aminopent-3-en-2-one (**2**) (0.2 mmol), 3-aminocyclohex-2-enone (**23**) (0.2 mmol), CuI (0.03 mmol) and Cs_2CO_3 (0.25 mmol) in CH_3CN (1.0 mL). The reaction mixture was allowed to stir at 90 ºC for 24 h. After cooling down to room temperature, the reaction mixture was quenched with sat. NH_4Cl and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The ^1H NMR spectrum of crude mixture showed 1:3 ratio of **3** and **24**. The isolated yield was 15% and 63% respectively.



Scheme 1, C:

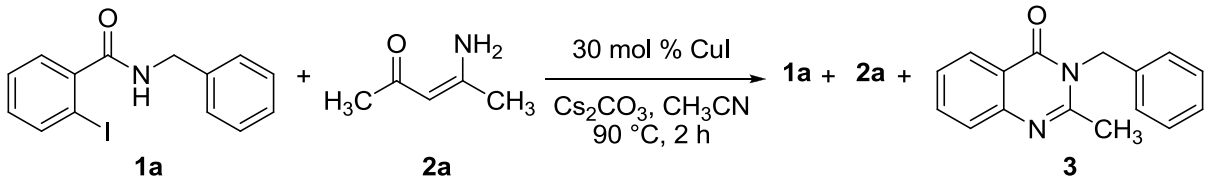


A sealed tube equipped with a magnetic stirring bar was charged with *N*-benzyl-2-iodobenzamide (**1**) (0.1 mmol), (*Z*)-4-aminopent-3-en-2-one (**2**) (0.03 mmol), 3-aminocyclohex-2-enone (**23**) (0.2 mmol), CuI (0.03 mmol) and Cs_2CO_3 (0.25 mmol) in CH_3CN (1.0 mL). The reaction mixture was allowed to stir at 90 ºC for 24 h. After cooling down to room temperature, the reaction mixture was quenched with sat. NH_4Cl and extracted with

EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The ^1H NMR spectrum of residue showed 1:6 ratio of **1** and **24**.

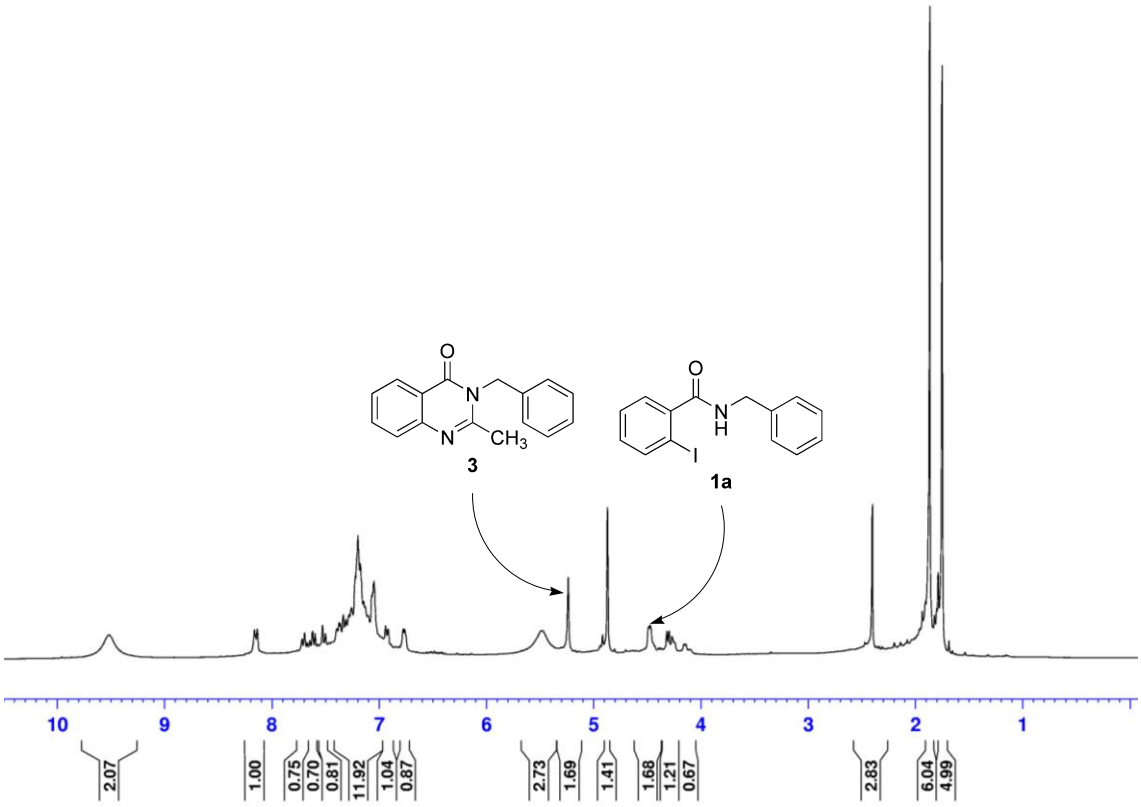
Mechanism Investigation Experiments

Scheme 3, A:

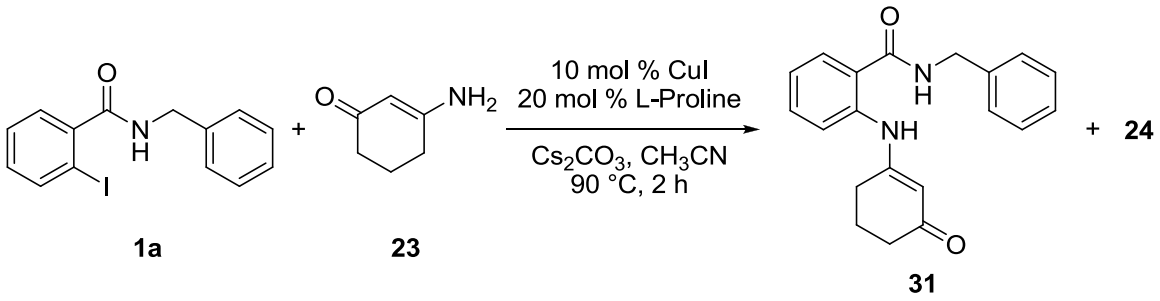


1a **2a** **3**

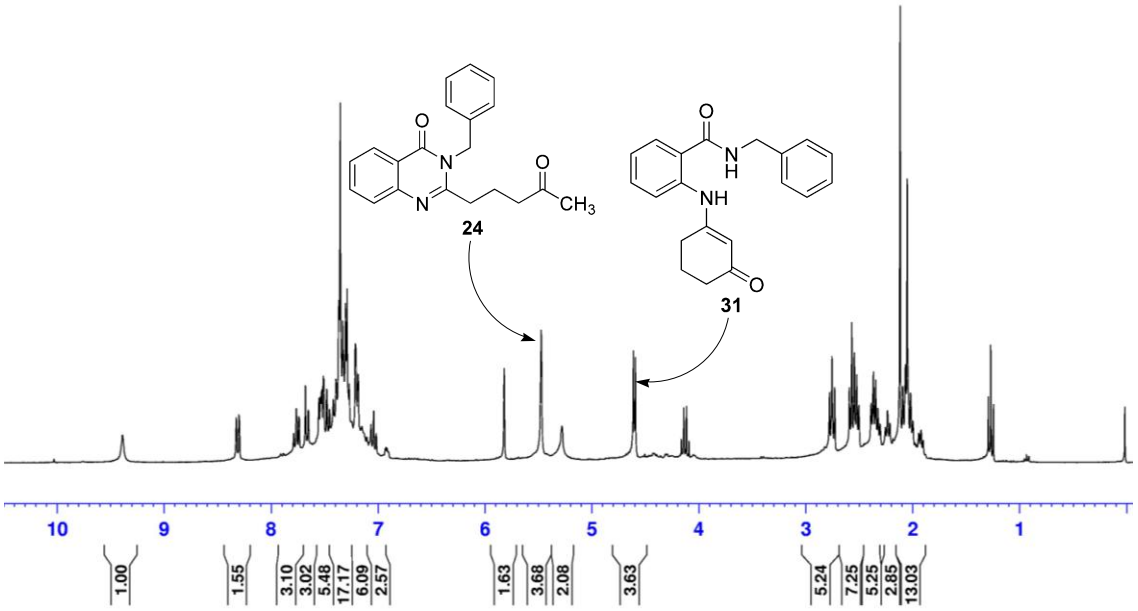
The reaction was performed according to general procedure A from *N*-benzyl-2-iodobenzamide (**1a**) and (*Z*)-4-aminopent-3-en-2-one (**2a**). The reaction time was reduced to 2 h and the reaction mixture was quenched with sat. NH_4Cl. The ^1H NMR spectrum of crude mixture showed 1:1 ratio of **1a** and **3** along with the remaining **2a**.



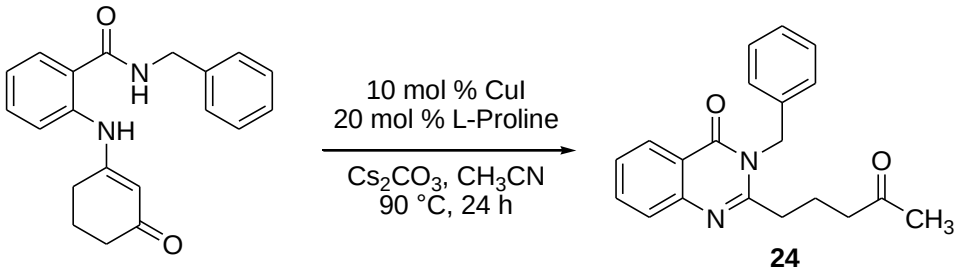
Scheme 3, B:



The reaction was performed according to general procedure B from *N*-benzyl-2-iodobenzamide (**1a**) and 3-aminocyclohex-2-enone (**23**). The reaction time was reduced to 2 h. The ^{1}H NMR spectrum of crude mixture showed 1:1 ratio of *N*-benzyl-2-(3-oxocyclohex-1-enylamino)benzamide (**31**) and **24**. The crude mixture was purified by column chromatography (3:1 hexanes:EtOAc) to provide **31** in 56.07 mg (35% yield) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (brs, 1H), 7.51 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.36-7.26 (m, 6H), 7.00 (td, *J* = 7.8, 1.2 Hz, 1H), 5.72 (s, 1H), 4.56 (d, *J* = 5.7 Hz, 2H), 2.46 (t, *J* = 6.0 Hz, 2H), 2.30 (t, *J* = 6.0 Hz, 2H), 1.99-1.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2, 168.6, 160.8, 139.3, 137.8, 131.8, 128.8, 127.9, 127.8, 127.7, 124.0, 123.2, 122.8, 101.0, 43.9, 36.4, 30.4, 21.6; IR (thin film) ν 2925, 1670, 1594, 1302, 1168, 976, 773, 697 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd. for $C_{20}H_{20}N_2O_2$ 321.1603, found 321.1603.



Scheme 3, C:



31 **24**

A 10 mL round bottom flask equipped with a magnetic stirring bar was charged with *N*-benzyl-2-(3-oxocyclohex-1-enylamino)benzamide (**31**) (0.18 mmol), CuI (0.018 mmol), L-Proline (0.036 mmol) and Cs_2CO_3 (0.45 mmol) in CH_3CN (2.0 mL). The reaction mixture was allowed to stir at 90 ºC for 24 h. After completion of the reaction, the reaction mixture was cooled to room temperature, quenched with sat. NH_4Cl and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The ^1H NMR spectrum of residue showed only signals of **24**.

References

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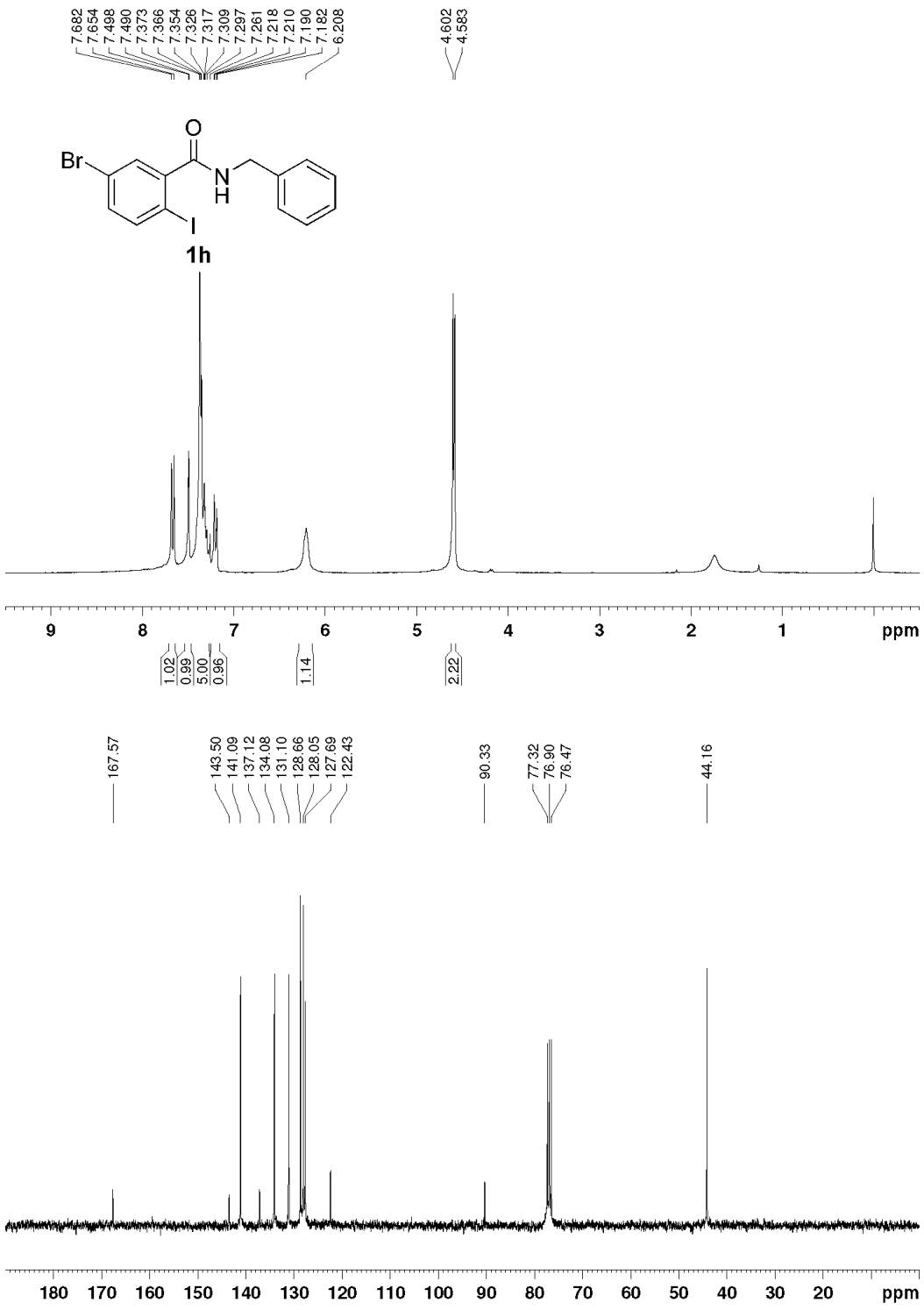
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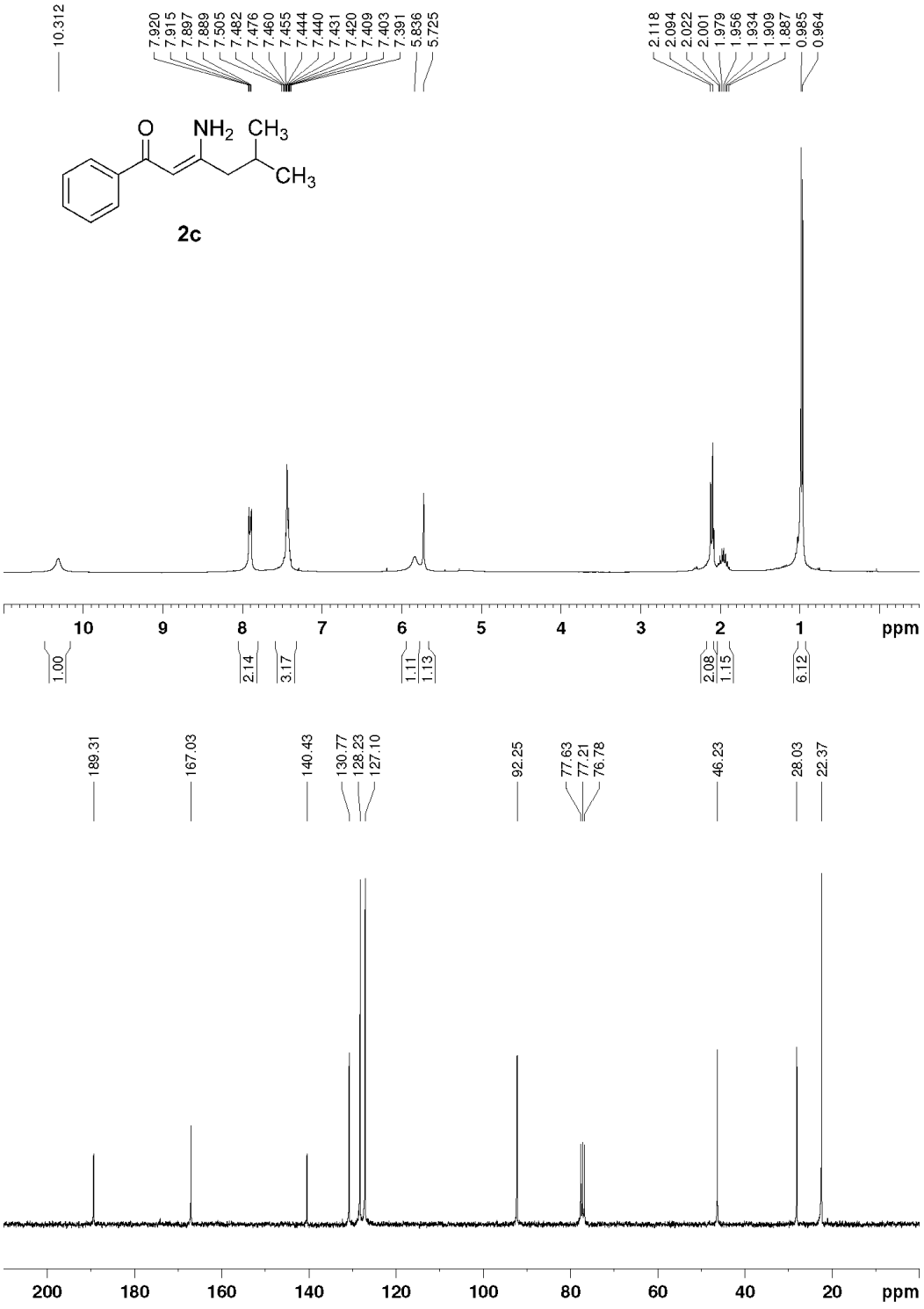
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CH3
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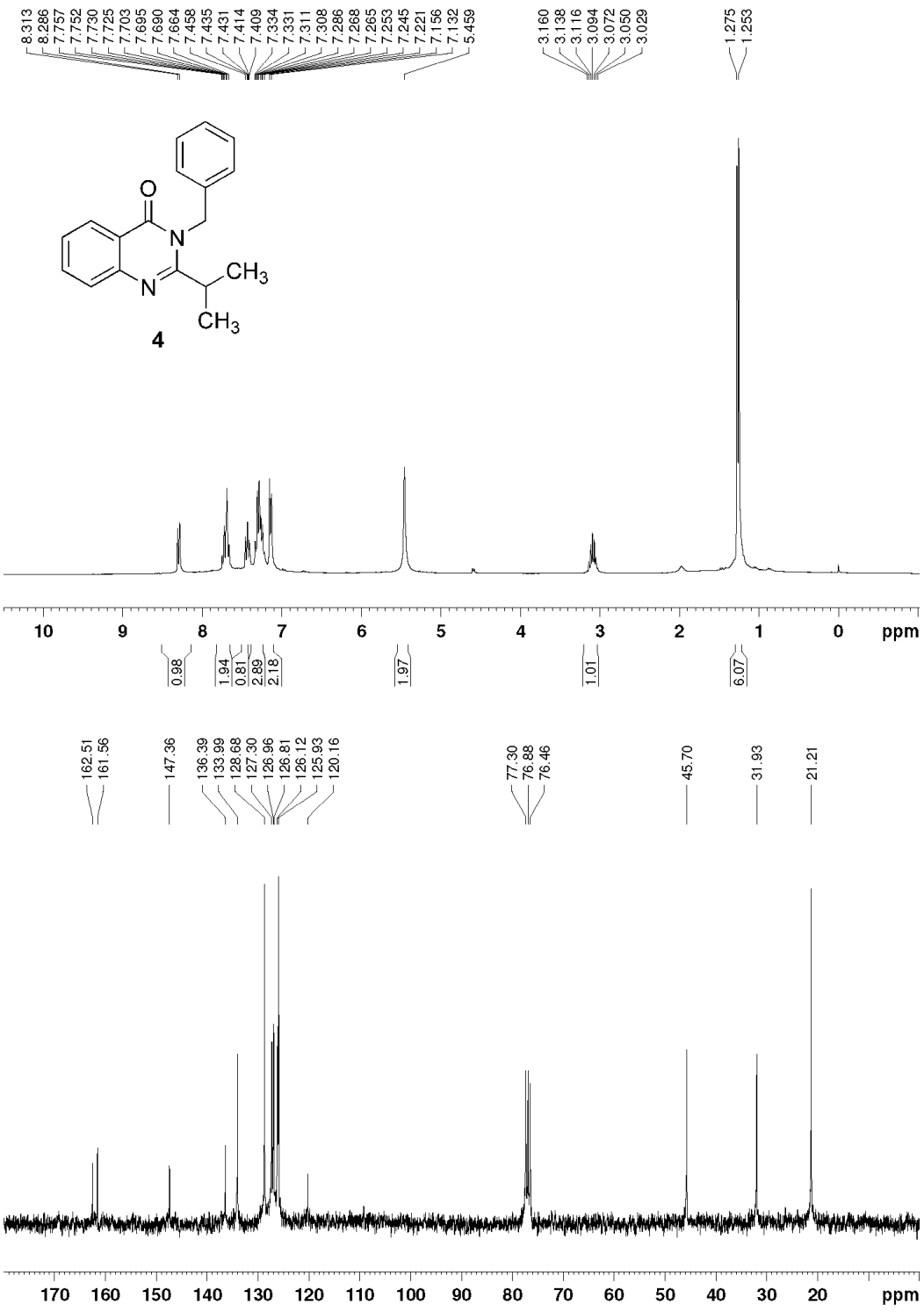
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CH3
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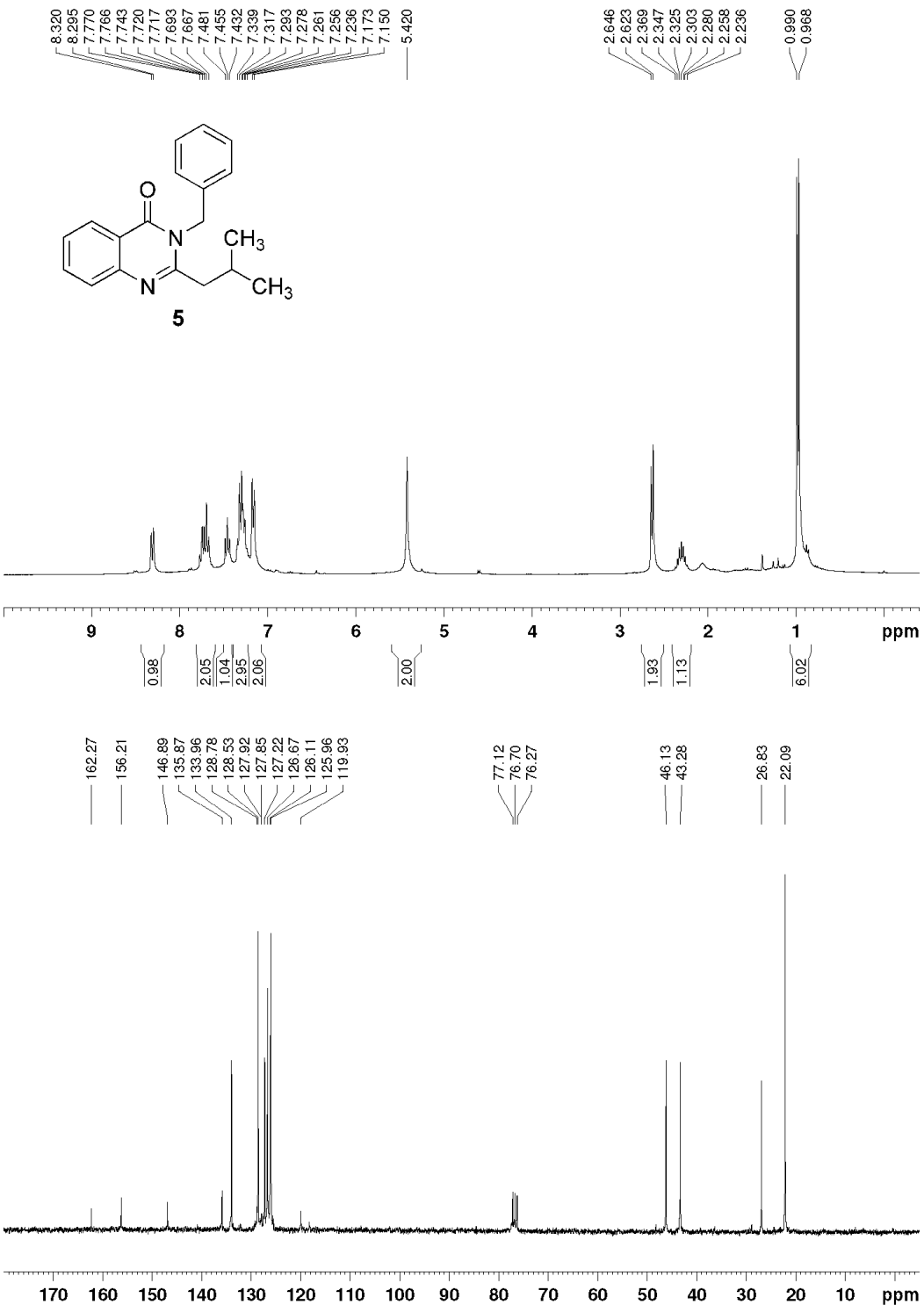
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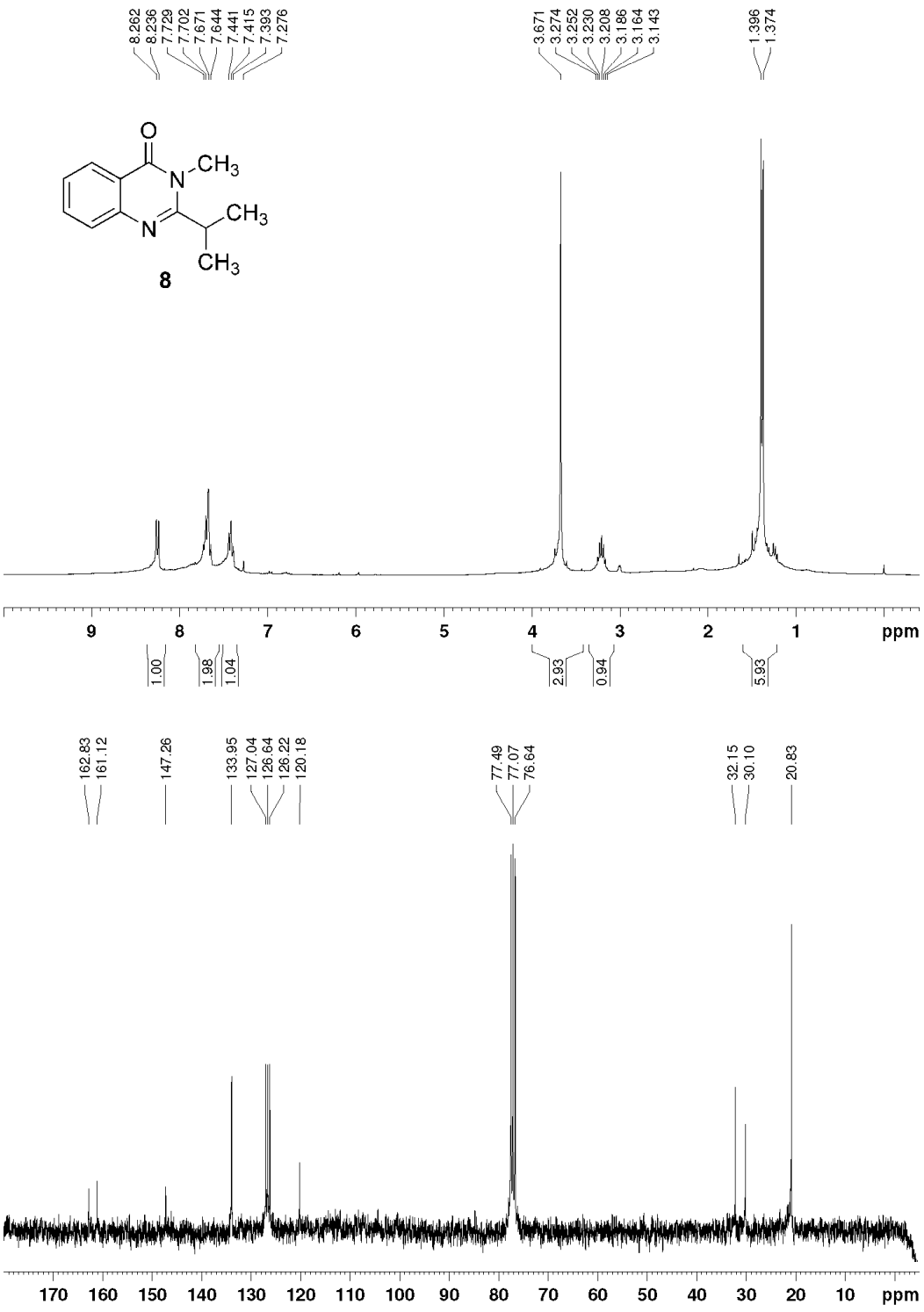
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CH3
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CH3
CH3
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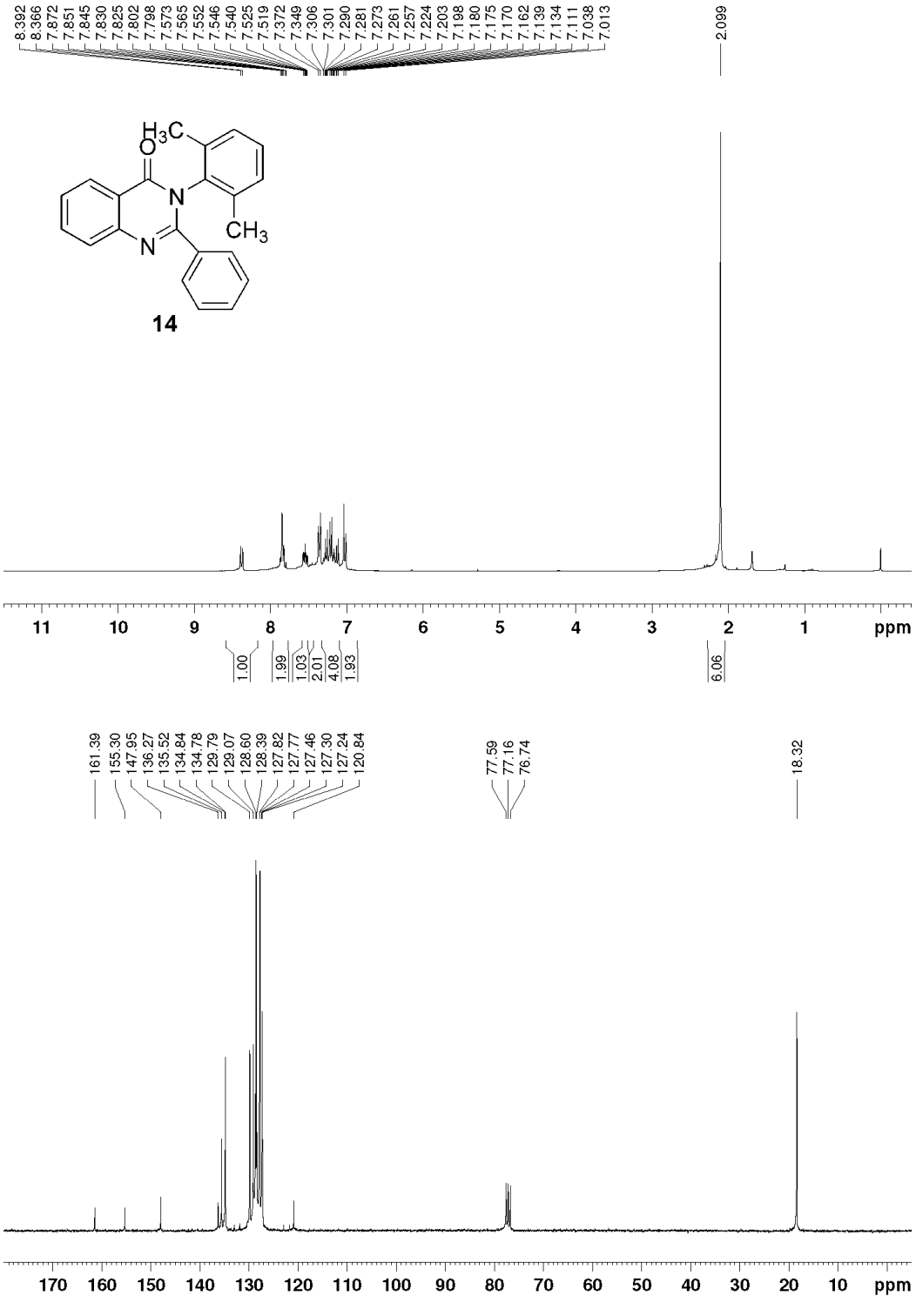
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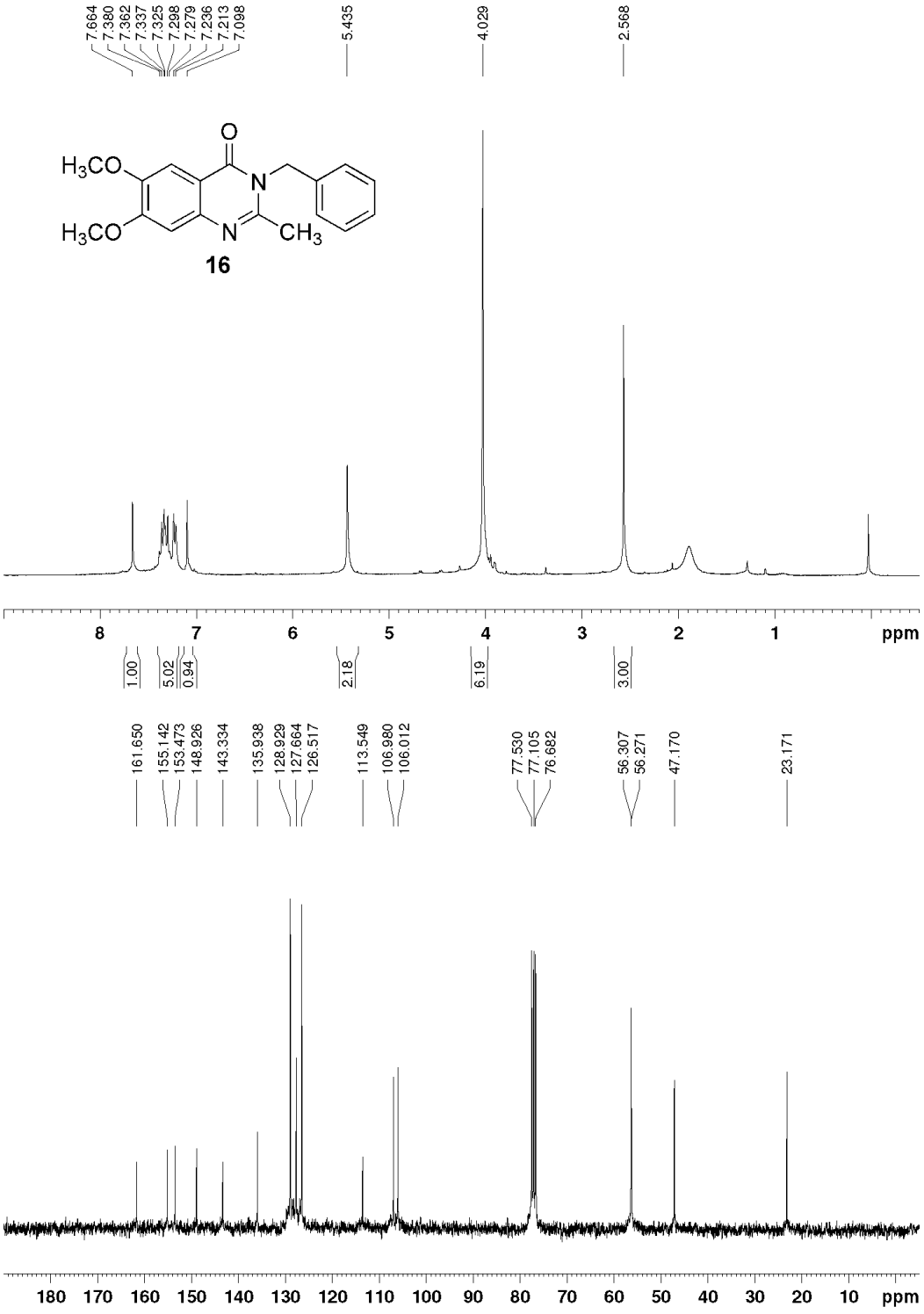
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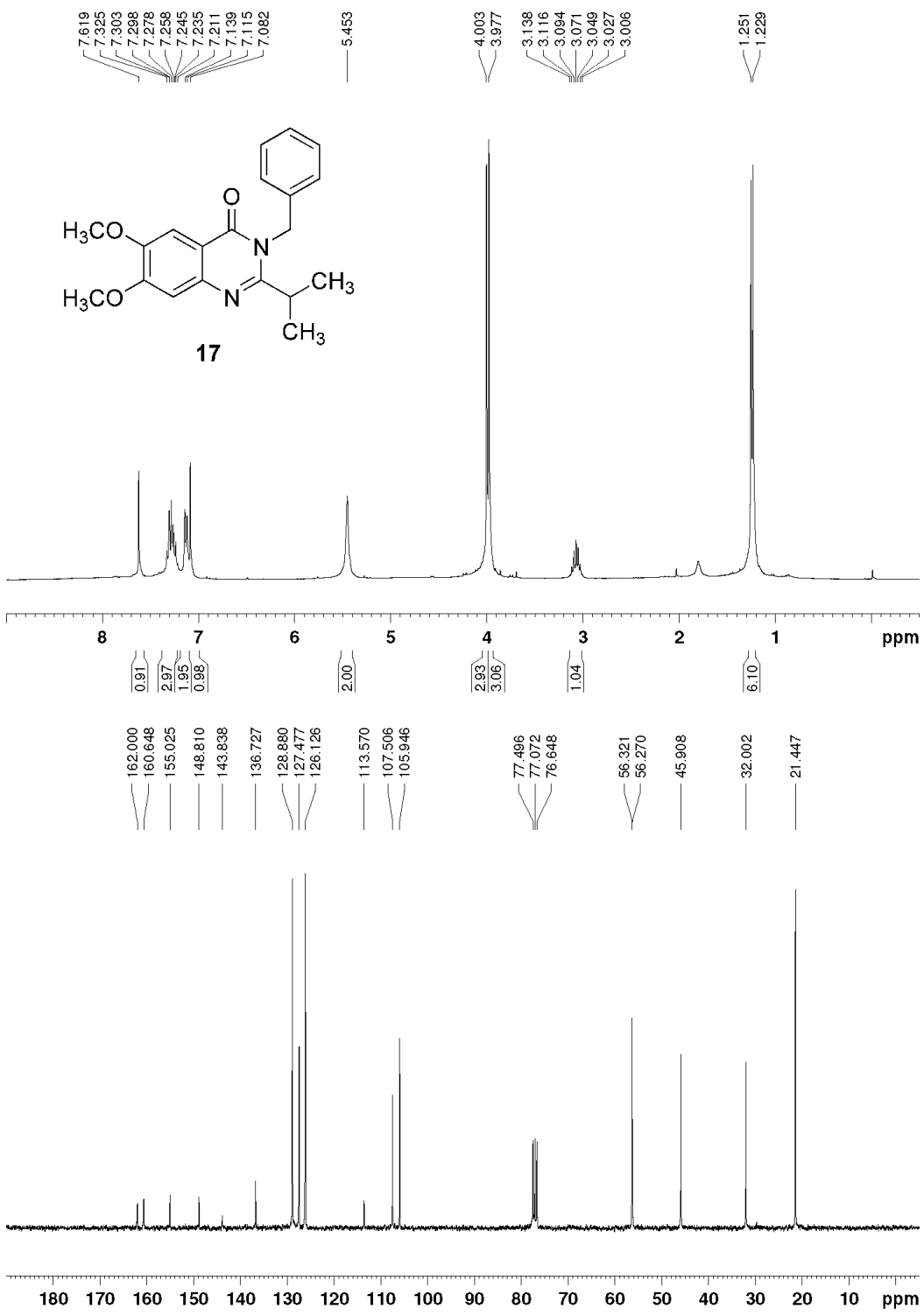
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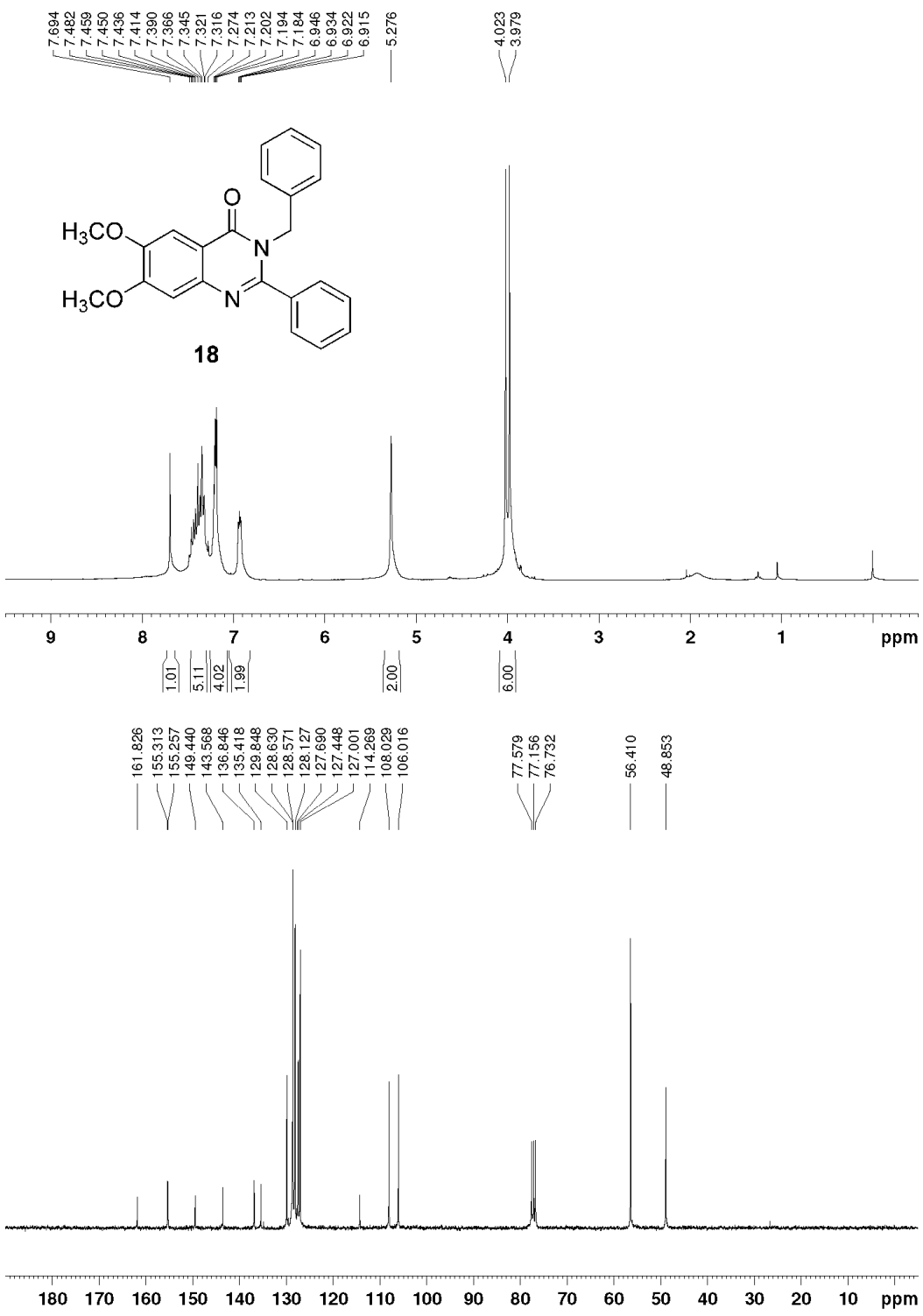
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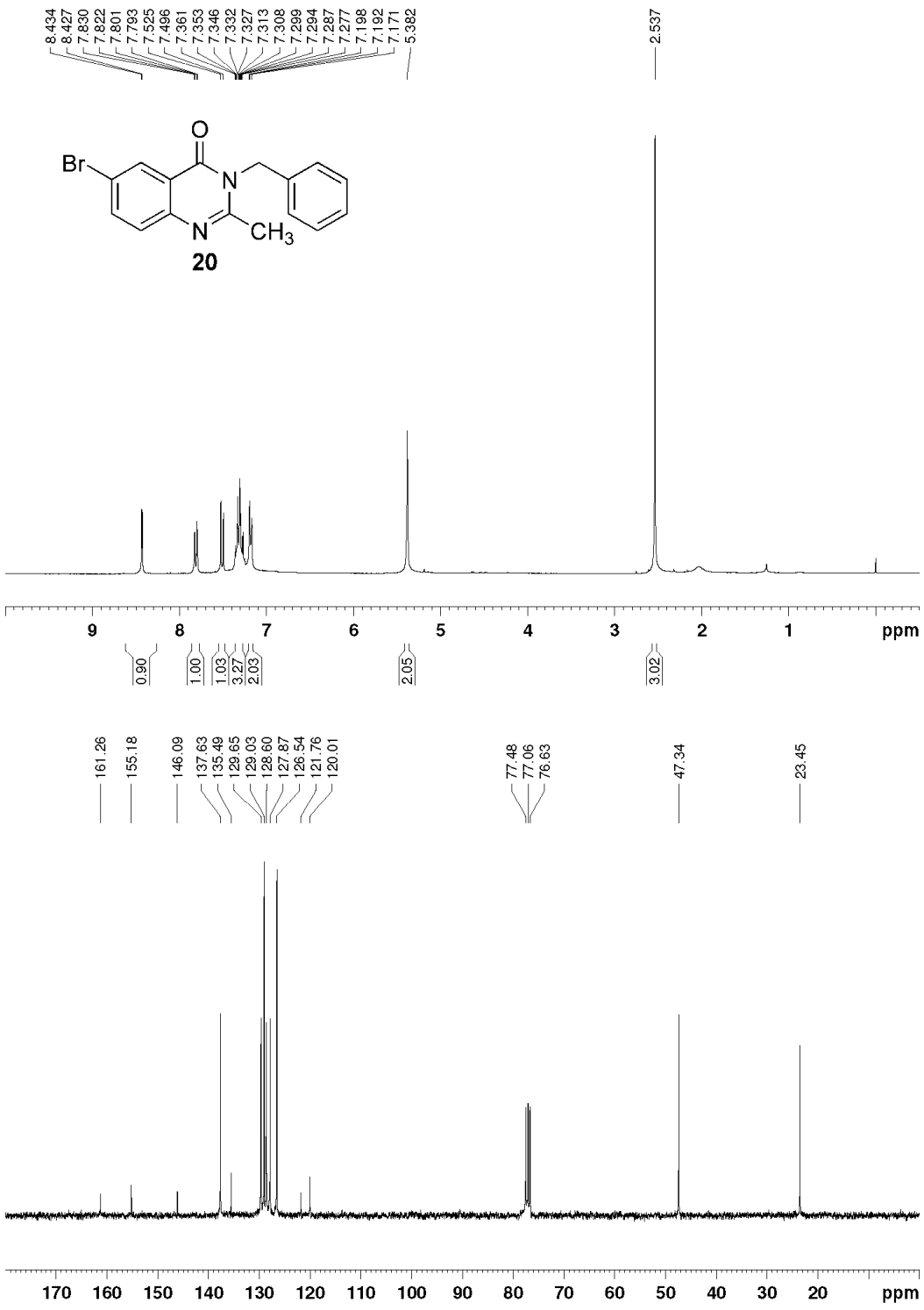
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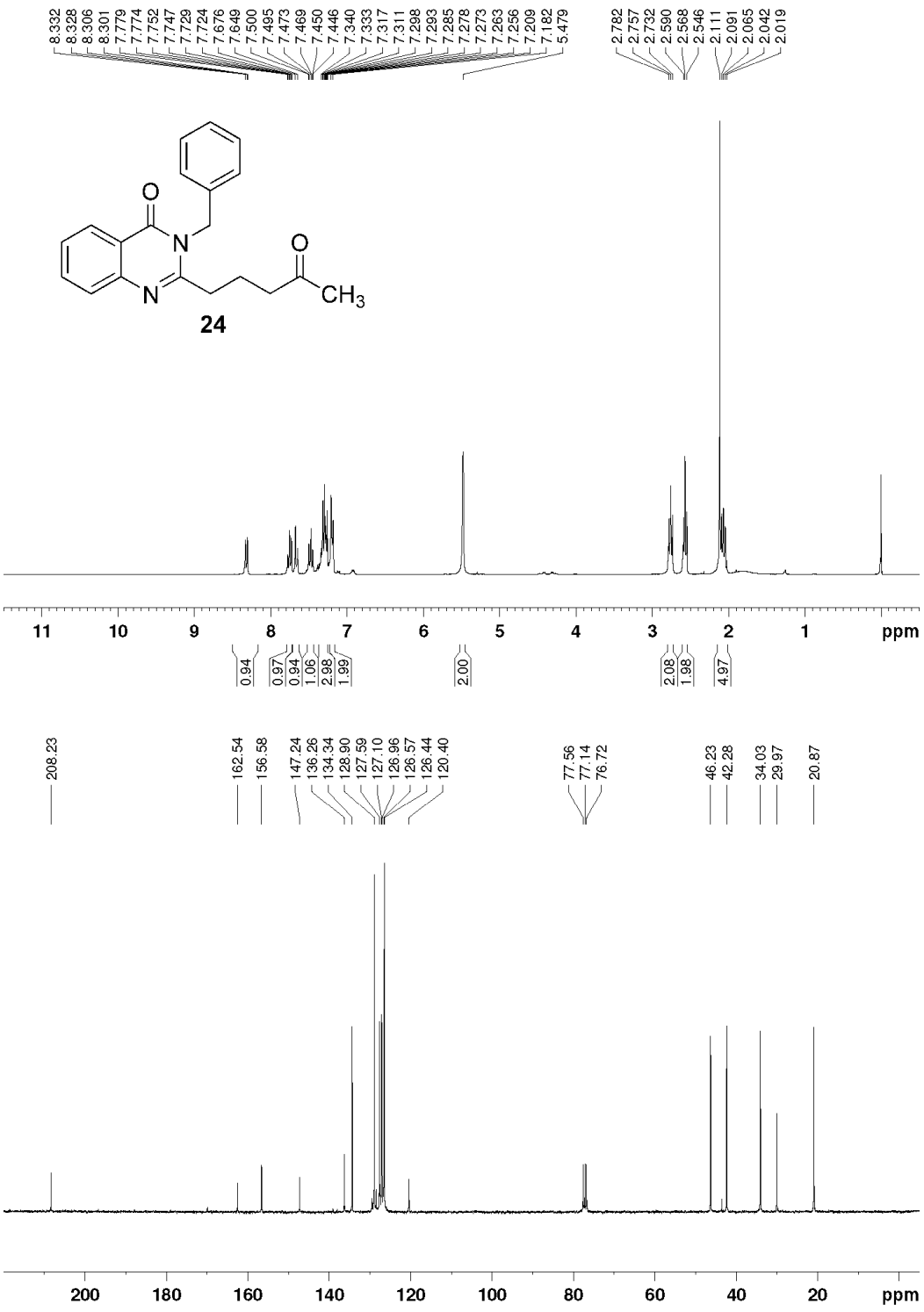
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0.94
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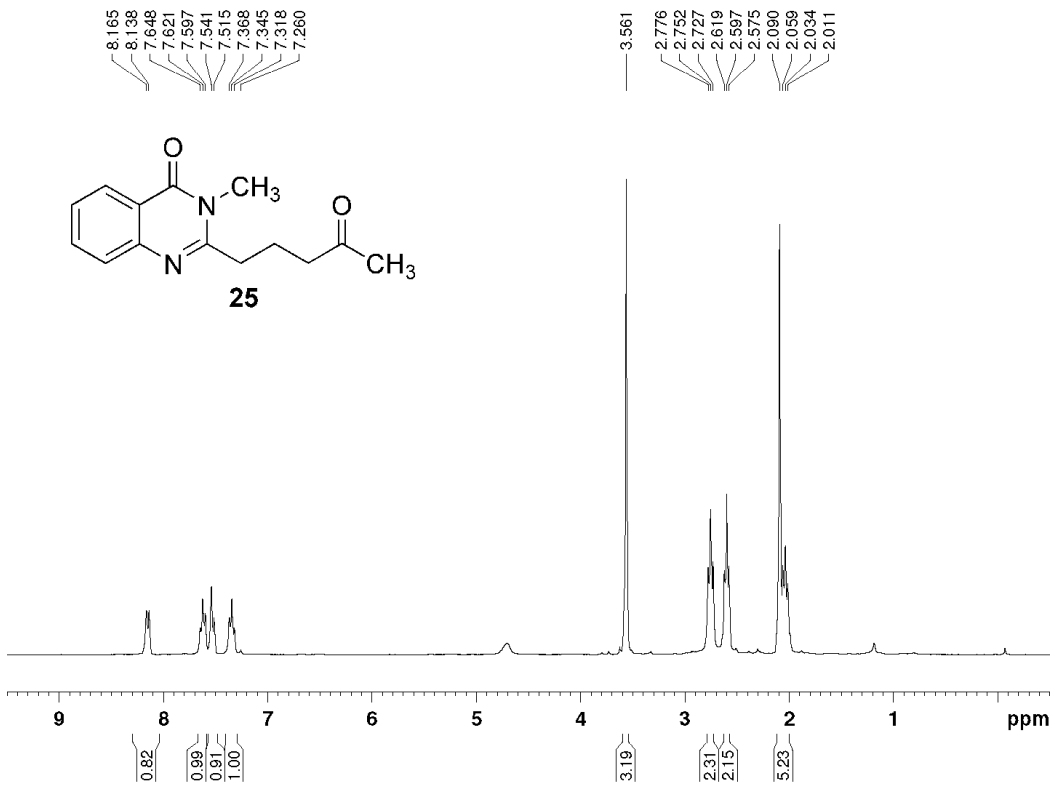
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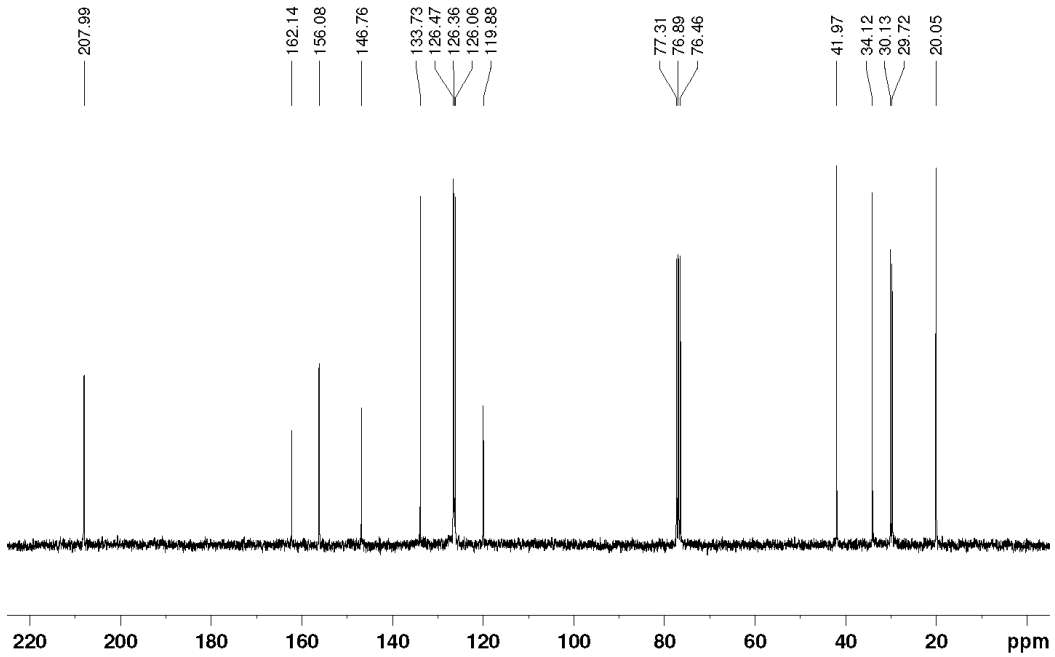
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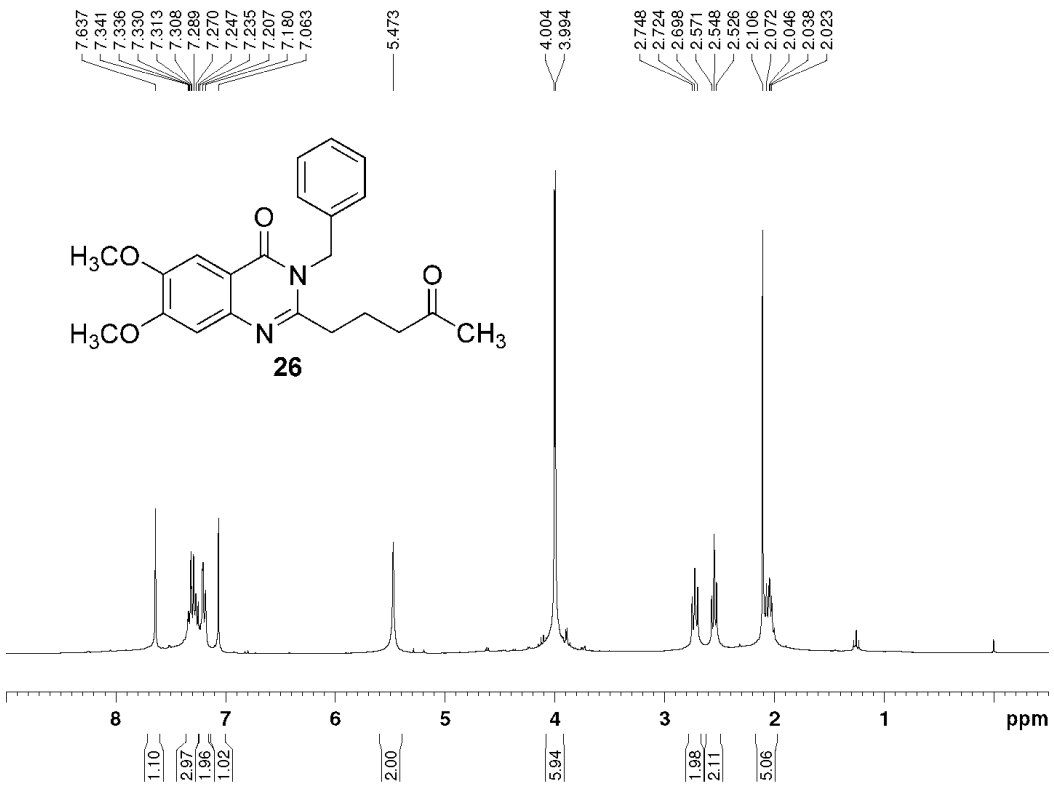
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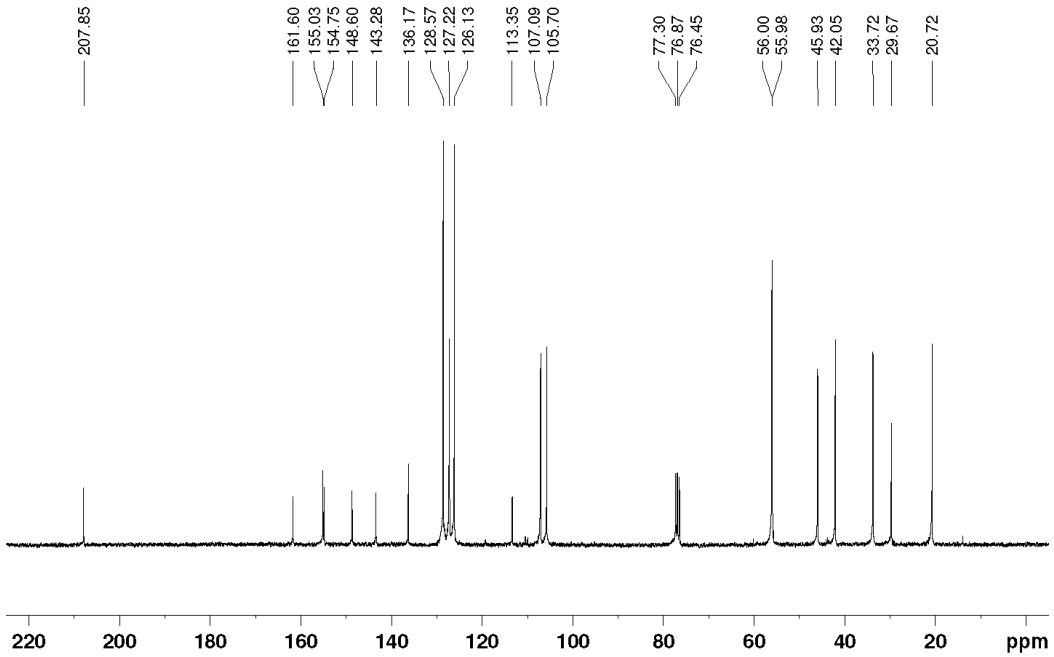
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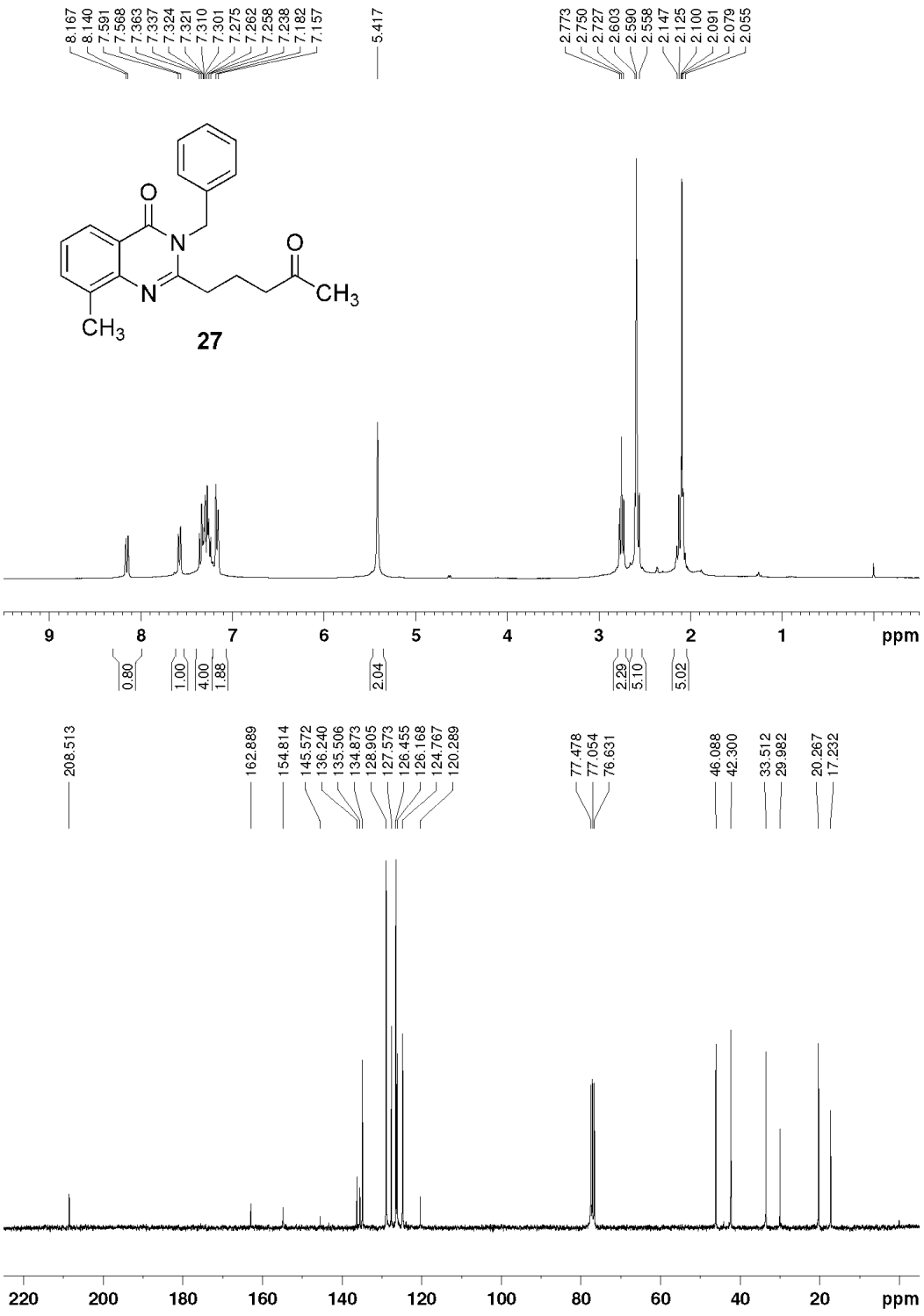
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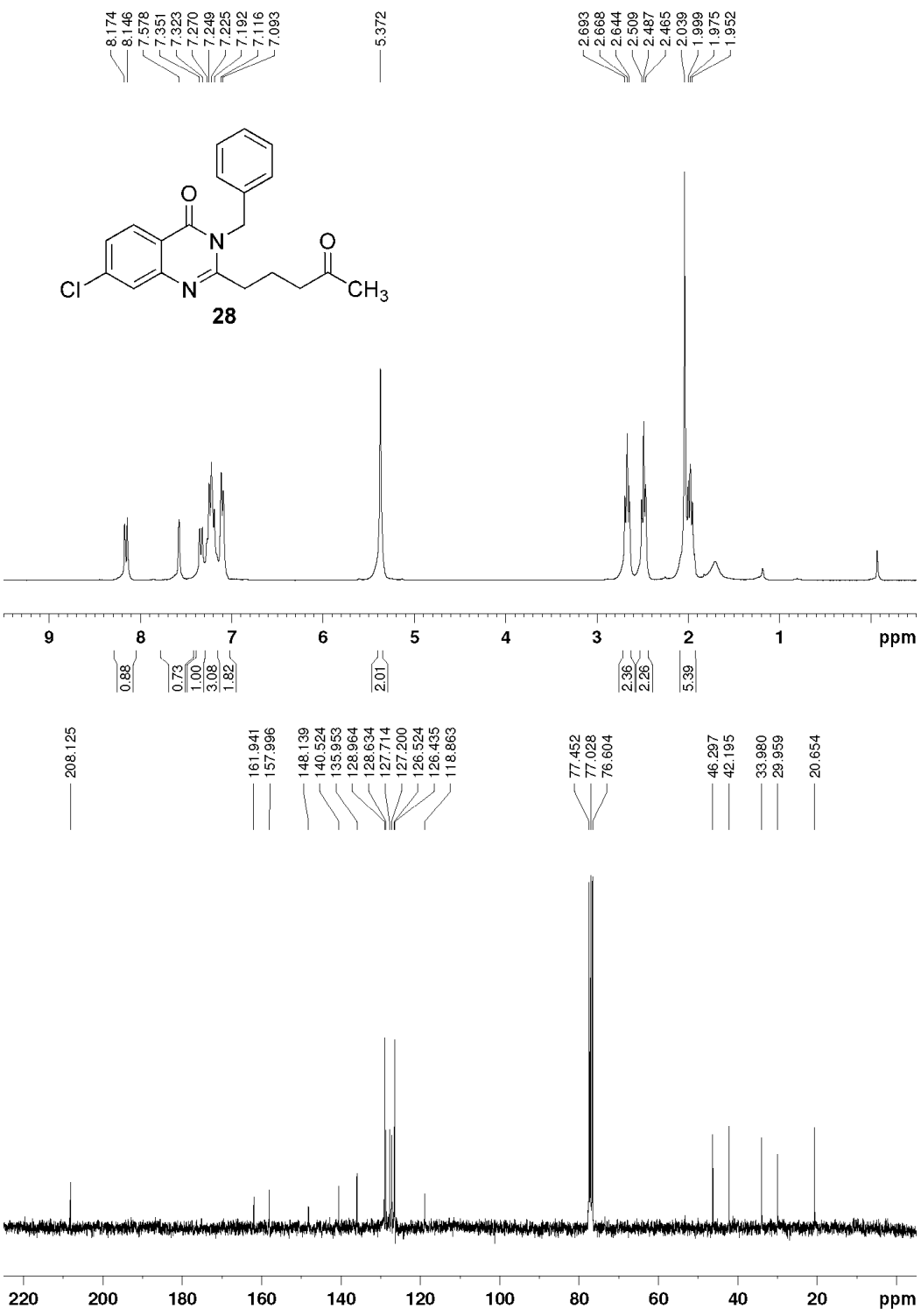
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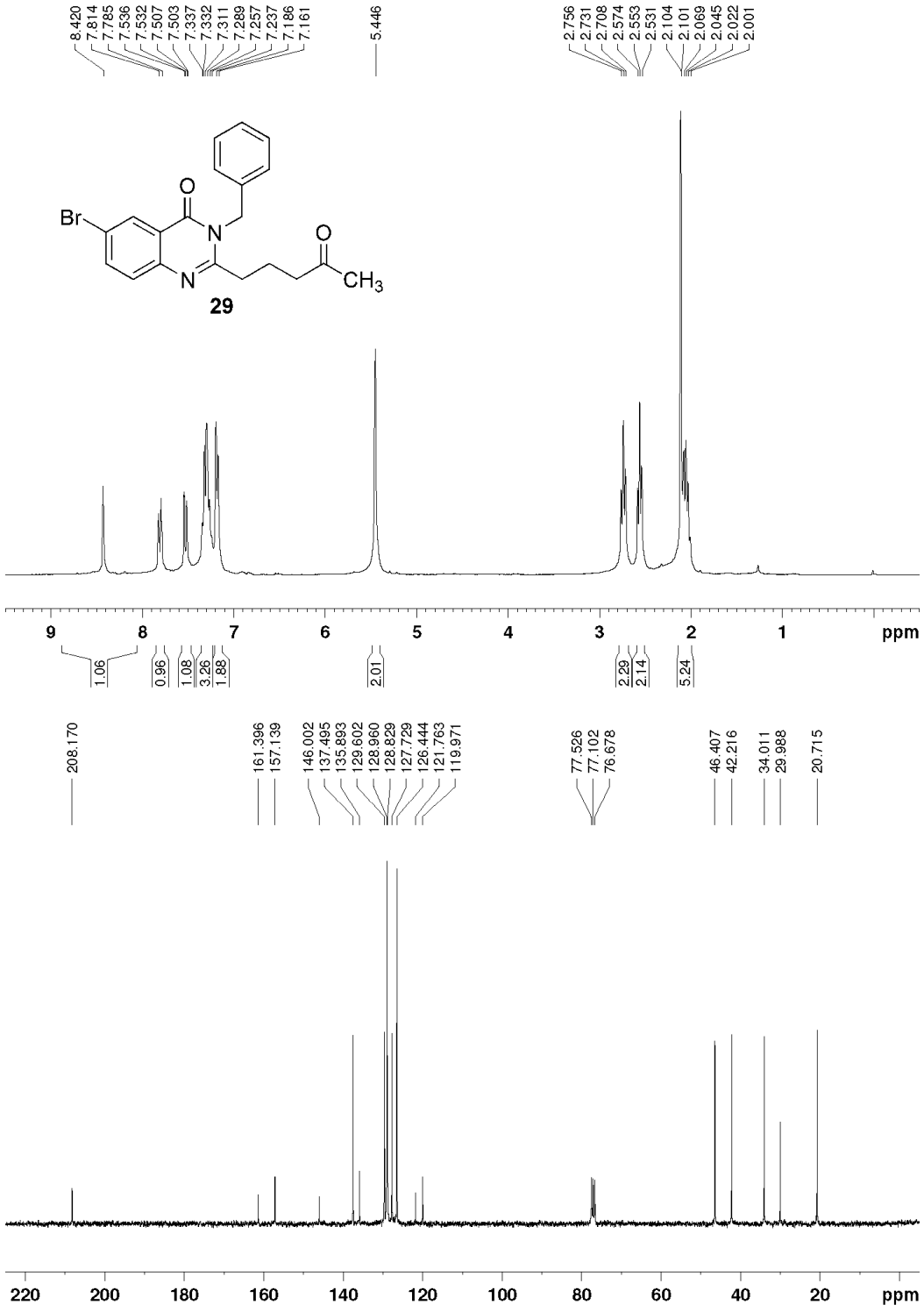
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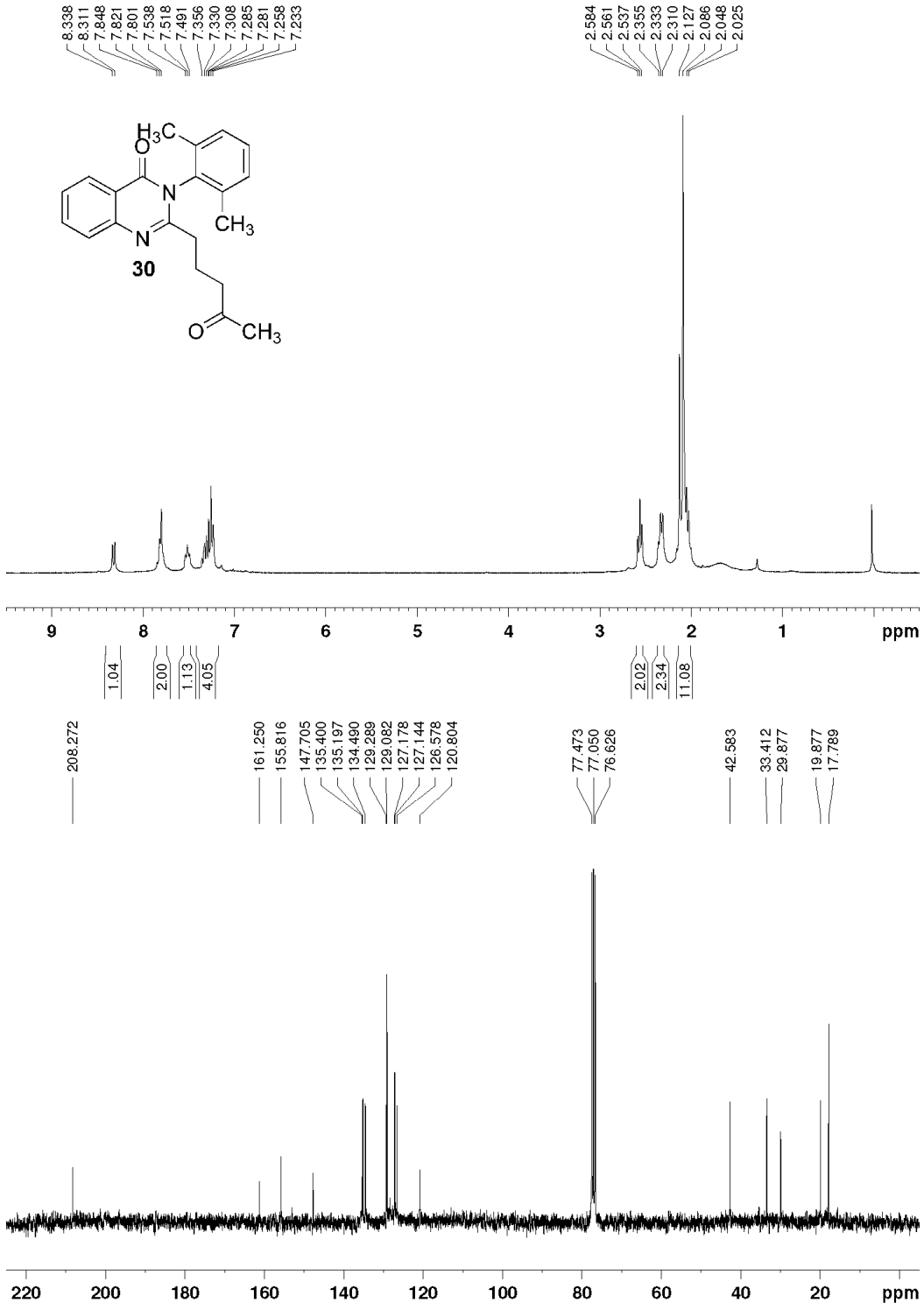
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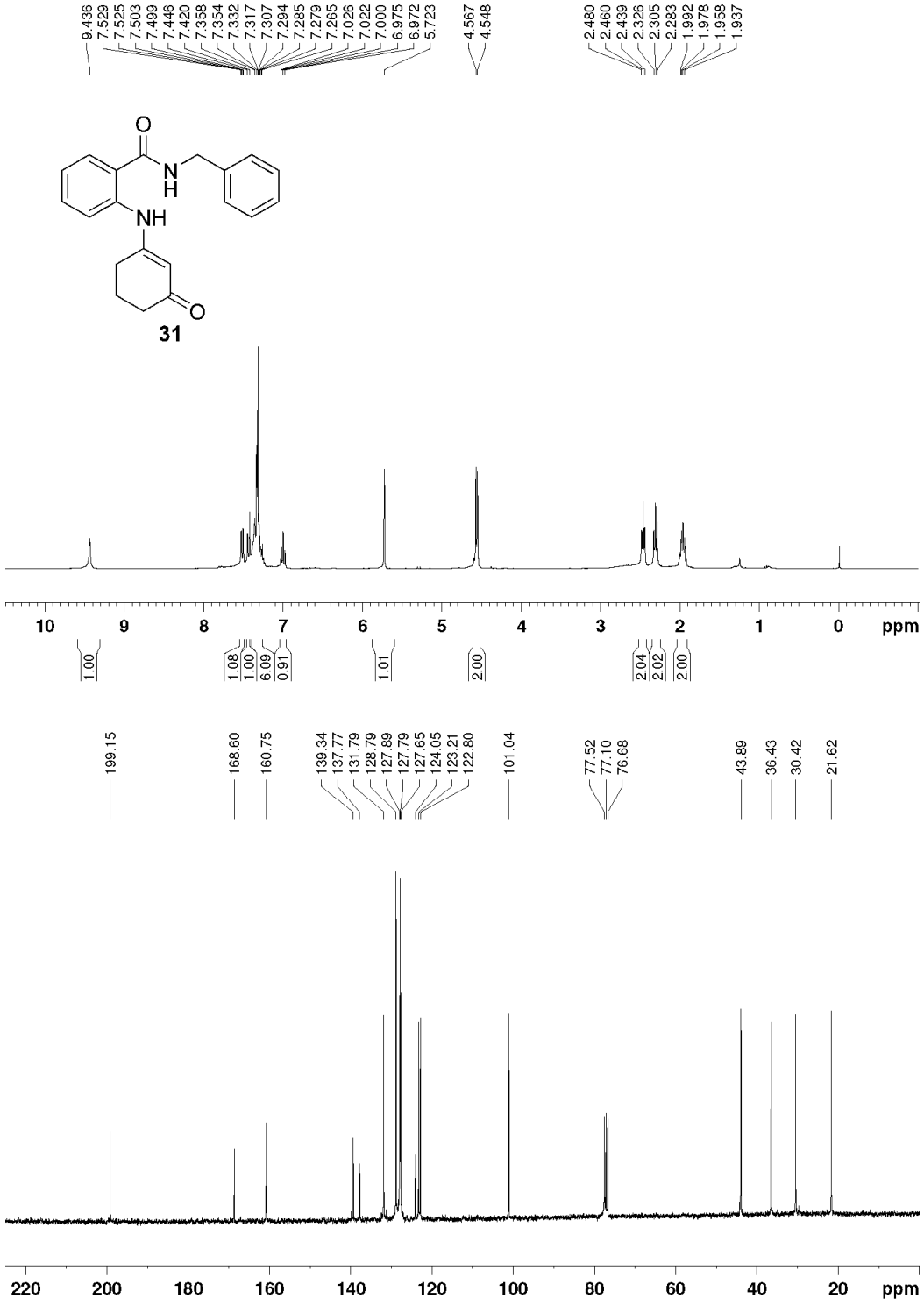
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