Supporting Information

for

Potent triazine-based dehydrocondensing reagents substituted by an amido group

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Experimental and characterization data

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General information

Chemical shifts for ^{1}H NMR spectra are reported as δ values relative to tetramethylsilane as an internal standard for chloroform-*d*, DMSO-d_6, and methanol-d_4. Coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. NMR yields were determined by quantitative NMR spectroscopy using coumarin, 6-methylcoumarin, or *p*-nitrotoluene as an internal standard. Chemical shifts for ^{13}C NMR are reported as δ values relative to the center lines of the signals at 77.16 ppm corresponding to chloroform-*d*, 39.52 ppm corresponding to DMSO-d_6, or 49.00 ppm corresponding to methanol-d_4. Flash chromatography separations were performed on KANTO CHEMICAL Silica Gel 60 N (spherical, neutral, 40–100 mesh). All reactions sensitive to oxygen or moisture were conducted under a nitrogen atmosphere. *N*-Methylacetamide, acetamide, and benzamide were purchased from Tokyo Chemical Industry Co., LTD. *N*-Phenylacetamide was prepared from acetyl chloride and aniline. *N*-Methylbenzamide, and *N*-phenylbenzamide were prepared using DMT-MM in methanol from benzamide and methylamine, or benzamide and aniline.

2-Chloro-4-methoxy-6-(N-methylacetamido)-1,3,5-triazine (III)

N-Methylacetamide (1.50 g, 20.5 mmol) in THF (10 mL) was added to a suspension of sodium hydride (1.39 g, 34.9 mmol, 60% dispersion in oil) in THF (10 mL) at 0 °C. After stirring for 2 h at 40 °C, the reaction mixture was cooled to 0 °C. 2,4-Dichloro-6-methoxy-1,3,5-triazine (**6**) (3.69 g, 20.5 mmol) was added to the suspension, and the mixture was stirred at 40 °C for two days. The reaction mixture was quenched with sat. aq. NH_4Cl at 0 °C, extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/AcOEt 9:1) to afford 2-chloro-4-methoxy-6-(*N*-methylacetamido)-1,3,5-triazine (**III**) (1.53 g, 35%) as a white powder. M.p. 35–36 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=2.70 (s, 3H), 3.47 (s, 3H), 4.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=28.31, 32.56, 56.11, 167.94, 171.26, 171.57, 173.16; IR (KBr): 3016, 2952, 1707, 1558, 1362, 1223, 1055, 993 cm^{-1}; HRMS (EI–sector): *m*/*z* [M]$^+$ calcd for $C_7H_9ClN_4O_2$: 216.0414; found: 216.0416; elemental analysis calcd (%) for $C_7H_9ClN_4O_2$: C 38.81, H 4.19, N 25.86; found: C 38.75, H 4.16, N 25.91.

2-Chloro-4-methoxy-6-(N-phenylacetamido)-1,3,5-triazine (IV)

N-Phenylacetamide (2.34 g, 17.3 mmol) was added to a suspension of sodium hydride (692 mg, 17.3 mmol, 60% dispersion in oil) in THF (20 mL) at 0 °C. After stirring for 90 min at 40 °C, the reaction mixture was cooled to 0 °C. The mixture was added dropwise to a THF (20 mL) solution of 2,4-dichloro-6-methoxy-1,3,5-triazine (**6**, 2.83 g, 15.7 mmol), and the mixture was stirred at room temperature for 30 min. The reaction mixture was quenched with sat. aq. NH_4Cl at 0 °C, extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc 6:1) to afford 2-chloro-4-methoxy-6-(*N*-phenylacetamido)-1,3,5-triazine (**IV**) (2.76 g, 63%) as a white powder. M.p. 83–84 °C; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ=2.64 (s, 3H), 3.90 (s, 3H), 7.16 (m, 2H), 7.41 (m, 1H), 7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=27.53, 55.99, 128.62, 128.65, 129.64, 139.24, 168.45, 171.34, 171.84, 172.55; IR (KBr): 3014, 2956, 1712, 1558, 1523, 1427, 1360, 1225, 1198, 1178, 1016, 912 cm^{-1}; HRMS (EI-Sector): *m*/*z* $[M]^+$ calcd for $C_{12}H_{11}ClN_4O_2$: 278.0571; found: 278.0576; elemental analysis calcd (%) for $C_{12}H_{11}ClN_4O_2$: C 51.72, H 3.98, N 20.10; found: C 51.46, H 4.02, N 20.03.

2-Chloro-4-methoxy-6-(N-methylbenzamido)-1,3,5-triazine (V)

N-Methylbenzamide (324 mg, 2.40 mmol) was added to a suspension of sodium hydride (88 mg, 2.2 mmol, 60% dispersion in oil) in THF (4 mL) at 0 °C. After stirring for 30 min at 50 °C, the reaction mixture was cooled to 0 °C. 2,4-Dichloro-6-methoxy-1,3,5-triazine (**6**) (360 mg, 2.00 mmol) was added to the suspension and the mixture was stirred for 43 h at room temperature. The reaction mixture was quenched with sat. aq. NH_4Cl at 0 °C, extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/AcOEt 6:1) to afford 2-chloro-4-methoxy-6-(*N*-methylbenzamido)-1,3,5-triazine (**V**) (467 mg, 84%) as a white powder. M.p. 74–75 °C; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ=3.38 (s, 3H) , 3.61 (s, 3H), 7.37(m, 2H), 7.47 (m, 1H), 7.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=34.00, 55.44, 128.07, 128.52, 131.64, 136.84, 168.60, 170.38, 171.65, 173.42; IR (KBr): 3005, 2949, 1695, 1568, 1508, 1448, 1402, 1375, 1363, 1248, 1030, 1016, 806, 731, 700 cm^{-1}; HRMS (EI-sector): *m*/*z* $[M+H]^+$ calcd for $C_{12}H_{11}ClN_4O_2$: 278.0571; found: 278.0570; elemental analysis calcd (%) for $C_{12}H_{11}ClN_4O_2$: C 51.72, H 3.98, N 20.10; found: C 51.77, H 4.05, N 20.15.

2-Chloro-4-methoxy-6-(N-phenylbenzamido)-1,3,5-triazine (VI)

N-Phenylbenzamide (5.00 g, 25.3 mmol) in THF (25 mL) was added to the suspension of sodium hydride (1.22 g, 30.4 mmol, 60% dispersion in oil) in THF (10 mL) at 0 °C. After stirring for 2.5 h at 50 °C, the reaction mixture was cooled to 0 °C. A THF (7 mL) solution of 2,4-dichloro-6-methoxy-1,3,5-triazine (**6**, 5.48 g, 30.4 mmol) was added dropwise to the suspension and the reaction mixture was stirred for 1 h at 0 °C. AcOEt was added to the mixture, and the mixture was washed with sat. aq. NH_4Cl and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/EtOAc 8:2) to afford 2-chloro-4-methoxy-6-(*N*-phenybenzamido)-1,3,5-triazine (**VI**) (7.07 g, 82%) as a white powder. M.p. 134–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=3.60 (s, 3H), 7.28–7.30 (m, 2H), 7.38–7.54 (m, 6H), 7.74–7.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=55.75, 128.08, 128.43, 128.78, 129.08, 129.71, 132.57, 135.61, 139.15, 169.02, 170.99, 171.94, 172.40; IR (KBr): 3099, 3062, 3037, 2997, 2951, 1693, 1597, 1560, 1522, 1512, 1433, 1375, 1294, 1269, 1255, 1234 cm^{-1}; HRMS (EI-sector): *m*/*z* $[M]^+$ calcd for $C_{17}H_{13}ClN_4O_2$: 340.0727; found: 340.0729; elemental analysis calcd (%) for $C_{17}H_{13}ClN_4O_2$: C 59.92, H 3.85, N 16.44; found: C 59.89, H 3.77, N 16.34.

2-Acetamido-4,6-dichloro-1,3,5-triazine (7a)

Acetamide (710 mg, 12.0 mmol) in THF (10 mL) was added to a suspension of sodium hydride (480 mg, 12.0 mmol, 60% dispersion in oil) in THF (20 mL) at 0 °C. After stirring for 3 h at 50 °C, the reaction mixture was cooled to −78 °C. Cyanuric chloride (1.00 g, 5.42 mmol) in THF (7.5 mL) was added to the suspension, and the mixture was stirred for 15 h at −78 °C. AcOH (0.69 mL, 12 mmol) in THF (5 mL) was added at −78 °C, and the suspension was diluted with AcOEt. The organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc 7:3) and recrystallized from CH_2Cl_2/hexane to afford 2-acetamido-4,6-dichloro-1,3,5-triazine (**7a**, 411 mg, 36%) as a white powder. M.p. 187–188 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ=2.61 (s, 3H), 8.38 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=26.05, 164.07, 170.72, 172.05; IR (KBr): 3217, 3099, 3030, 1709, 1579, 1539, 1475, 1406, 1290, 1234, 845, 804 cm^{-1}; HRMS (DART-TOF): *m*/*z* $[M+H]^+$ calcd for $C_5H_5Cl_2N_4O_1$: 206.9840; found: 206.9865; elemental analysis calcd (%) for $C_5H_4Cl_2N_4O$: C 29.01, H 1.95, N 27.06; found: C 29.18, H 2.20, N 27.22.

2-Benzamido-4,6-dichloro-1,3,5-triazine (7b)

Benzamide (1.45 g, 12.0 mmol) in THF (10 mL) was added to a suspension of sodium hydride (480 mg, 12.0 mmol, 60% dispersion in oil) in THF (20 mL) at 0 °C. After stirring for 50 min at 50 °C, the reaction mixture was cooled to −78 °C. Cyanuric chloride (1.00 g, 5.47 mmol) in THF (5 mL) was added to the suspension, and the mixture was stirred for 5 h at −78 °C. AcOH (0.69 mL, 12 mmol) in THF (5 mL) was added at −78 °C, and the suspension was diluted with AcOEt. The organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc 7:3) to afford 2-benzamido-4,6-dichloro-1,3,5-triazine (**7b**, 955 mg, 65%) as a white powder. M.p. 184–185 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ=7.52–7.56 (m, 2H), 7.63–7.68 (m, 1H), 7.96–7.98 (m, 2H), 9.04 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=128.08, 129.31, 132.44, 133.91, 164.07, 164.73, 172.29; IR (KBr): 3217, 3132, 3103, 1709, 1576, 1535, 1473, 1408, 1298, 1232, 1111, 1099, 843, 804 cm^{-1}; HRMS (DART-TOF): *m*/*z* $[M+H]^+$ calcd (%) for

$C_{10}H_7Cl_2N_4O_1$: 268.9997; found: 269.0019; elemental analysis calcd (%) for $C_{10}H_6Cl_2N_4O$: C 44.64, H 2.25, N 20.82; found: C 44.54, H 2.25, N 20.91.

2-Acetamido-4-chloro-6-methoxy-1,3,5-triazine (I)

2-Acetamido-4,6-dichloro-1,3,5-triazine (**7**a, 50 mg, 0.24 mmol) was added to a solution of 1,10-phenanthroline (87 mg, 0.49 mmol) in MeOH (1.2 mL) at room temperature. After stirring for five days, the solution was concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc 7:3) to afford 2-acetamido-4-chloro-6-methoxy-1,3,5-triazine (**I**, 33 mg, 67%) as a white powder. M.p. 149–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ=2.60 (s, 3H), 4.07 (s, 3H), 8.10 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=26.02, 56.29, 164.89, 171.08, 171.75, 172.34; IR (KBr): 3221, 3126, 1712, 1684, 1577, 1485, 1362, 1290, 1252, 1038, 810 cm^{-1}; HRMS (DART-TOF): *m*/*z* $[M+H]^+$ calcd for $C_6H_8Cl_1N_4O_2$: 203.0336; found: 203.0337.

2-Benzamido-4-chloro-6-methoxy-1,3,5-triazine (II)

N-(4,6-Dichloro-1,3,5-triazin-2-yl)benzamide (**7b**, 50 mg, 0.19 mmol) was added to a solution of 1,10-phenanthroline (68 mg, 0.38 mmol) in MeOH (935 µL, 0.2 M) at 0 °C. After refluxing for 24 h, the solution was concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc 7:3) to afford 2-benzamido-4-chloro-6-methoxy-1,3,5-triazine (**II**, 39 mg, 78%) as a white powder. M.p. 118–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ=4.10 (s, 3H), 7.51–7.55 (m, 2H), 7.61–7.65 (m, 1H), 7.89–7.91 (m, 2H), 8.60 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=56.31, 127.85, 129.18, 133.13, 133.44, 164.39, 165.41, 172.11, 172.44; IR (KBr): 3259, 2951, 1716, 1697, 1581, 1541, 1481, 1406, 1362, 1286, 1259, 1207, 1128, 812, 706 cm^{-1}; HRMS (DART-TOF): *m*/*z* $[M+H]^+$ calcd for $C_{11}H_{10}Cl_1N_4O_2$: 265.0492; found: 265.0468. Crystals suitable for single-crystal X-ray structure analysis were obtained from THF–hexane, 4:1.

4-Methyl-4-(4-methoxy-6-(N-methylacetamido)-1,3,5-triazin-2-yl)morpholinium perchlorate (VII)

NMM (335 µL, 3.05 mmol) was added to a THF (9 mL) solution of 2-chloro-4-methoxy-6-(*N*-methylacetamido)-1,3,5-triazine (**III**, 600 mg, 2.77 mmol) and lithium perchlorate (324 mg, 3.05 mmol) at room temperature. After stirring for 2 h, the mixture was cooled to 0 °C. The resulting precipitate was collected by suction, washed with THF, and dried under reduced pressure to give 4-methyl-4-(4-methoxy-6-(*N*-methylacetamido)-1,3,5-triazin-2-yl)morpholinium perchlorate (**VII**, 1.05 g, 98%) as a white powder. M.p. 182–183 °C; ^{1}H NMR (400 MHz, DMSO-d_6, TMS): δ=2.63 (s, 3H), 3.39 (s, 3H), 3.47 (s, 3H), 3.78 (m, 2H), 3.89 (m, 2H), 4.01 (m, 2H), 4.10 (s, 3H), 4.35 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=27.66, 32.43, 55.18, 56.70, 59.51, 61.39, 168.48, 168.96, 171.80, 172.72; IR (KBr): 3045, 3025, 2992, 2964, 2889, 2875, 1707, 1610, 1541, 1518, 1475, 1444, 1379, 1369, 1288, 1122, 1095, 1011 cm^{-1}; HRMS (FAB-sector): *m*/*z* $[M–ClO_4^-]^+$ calcd for $C_{12}H_{20}N_5O_3$: 282.1561; found: 282.1565.

4-Methyl-4-(4-methoxy-6-(N-phenylacetamido)-1,3,5-triazin-2-yl)morpholinium perchlorate (VIII)

NMM (126 µL, 1.14 mmol) was added to a THF (3.5 mL) solution of 2-chloro-4-methoxy-6-(*N*-phenybenzamido)-1,3,5-triazine (**IV**, 290 mg, 1.04 mmol) and lithium perchlorate (121 mg, 1.14 mmol) at room temperature. After stirring for 45 min, Et_2O was added to the mixture at 0 °C. The resulting precipitate was collected by suction, washed with Et_2O, and dried under reduced pressure to give 4-methyl-4-(4-methoxy-6-(*N*-phenylacetamido)-1,3,5-triazin-2-yl)morpholinium perchlorate (**VIII**, 419 mg, 91%) as a white powder. M.p. 149–150 °C; ^1H NMR (400 MHz, DMSO-*d*$_6$, TMS): δ=2.71 (s, 3H), 3.42 (s, 3H), 3.69 (m, 2H), 3.81–3.94 (m, 4H), 3.97 (s, 3H), 4.13 (m, 2H), 7.27 (m, 2H), 7.42(m, 1H), 7.49 (m, 2H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ=27.50, 54.41, 56.58, 59.48, 61.28, 128.22, 128.53, 129.22, 139.21, 168.66, 168.84, 171.93, 172.66; IR (KBr): 3055, 2960, 2887, 1697, 1626, 1541, 1508, 1435, 1385, 1365, 1261, 1093 cm^{-1}; HRMS (EI-sector): *m*/*z* $[M–ClO_4^-]^+$ calcd for $C_{17}H_{22}N_5O_3$: 344.1717; found: 344.1716. Crystals suitable for single-crystal X-ray structure analysis were obtained from CH_3CN–hexane, 4:1.

4-Methyl-4-(4-methoxy-6-(N-methylbenzamido)-1,3,5-triazin-2-yl)morpholinium chloride (IX)

NMM (495 µL, 4.50 mmol) was added to a solution of 2-chloro-4-methoxy-6-(*N*-methylbenzamido)-1,3,5-triazine (**V**, 500 mg, 1.79 mmol) in Et_2O (9 mL) at 0 °C. After stirring for 3 h, the resulting precipitate was collected by suction, washed with Et_2O, and dried under reduced pressure to give 4-methyl-4-(4-methoxy-6-(*N*-methylbenzamide)-1,3,5-triazine-2-yl)morpholinium chloride monohydrate (**IX**, 642 mg, 90%, water content 4.5% w/w) as a white powder. M.p. 99–100 °C; ^1H NMR (400 MHz, CD_3OD, TMS): δ=3.22 (s, 3H), 3.57 (m, 4H), 3.66 (s, 3H), 3.82 (m, 2H), 3.90 (m, 2H), 3.96 (s, 3H), 7.49 (m, 2H), 7.58 (m, 1H), 7.67 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ=34.54, 56.34, 57.25, 60.94, 63.12, 129.35, 130.05, 133.24, 138.09, 169.83, 170.50, 173.75, 174.38; IR (KBr): 3542, 3379, 3340, 3275, 3028, 2954, 1685, 1658, 1604, 1545, 1522, 1471, 1387, 1313, 1290, 1223, 1111 cm^{-1}; HRMS (FAB-sector): *m*/*z* $[M–Cl^-–H_2O]^+$ calcd for $C_{17}H_{22}ClN_5O_3$: 344.1717; found: 344.1724; elemental analysis calcd (%) for $C_{17}H_{24}ClN_5O_4$ (monohydrate): C 51.32, H 6.08, N 17.60; found: C 50.94, H 6.03, N 17.53.

4-Methyl-4-(4-methoxy-6-(N-phenylbenzamido)-1,3,5-triazin-2-yl)morpholinium chloride (X)

NMM (484 μL, 4.40 mmol) was added to a Et_2O (20 mL), THF (4 mL), and H_2O (146 μL, 8.10 mmol) solution of 2-chloro-4-methoxy-6-(*N*-phenybenzamido)-1,3,5-triazine (**VI**, 1.00 g, 2.93 mmol) at 0 °C. After stirring for 3.5 h at room temperature, Et_2O (20 mL) was added. The resulting precipitate was collected by suction, washed with Et_2O, and dried under reduced pressure to give 4-methyl-4-(4-methoxy-6-(*N*-phenylbenzamido)-1,3,5-triazin-2-yl)morpholinium chloride dihydrate (**X**, 1.12 g, 80%, water content 3.8% w/w) as a white powder. M.p. 91–92 °C; ^{1}H NMR (400 MHz, CD_3OD, TMS) δ=3.30 (s, 3H), 3.53–3.69 (m, 4H), 3.77 (s, 3H), 3.83 (m, 2H), 4.00 (m, 2H), 7.43–7.65 (m, 8H), 7.89–7.90 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ=56.51 57.15, 61.11, 63.06, 129.33, 129.78, 130.25, 130.27, 130.66, 134.19, 136.64, 140.18, 170.29, 170.65, 173.29, 173.84; IR ($CHCl_3$): 3425, 3037, 2916, 2860, 1716, 1610, 1593, 1522, 1437, 1383, 1238, 1144 cm^{-1}; HRMS (FAB-sector): *m*/*z* $[M–Cl^-–2H_2O]^+$ calcd for $C_{22}H_{24}N_5O_3$: 406.1874; found: 406.1871; elemental analysis calcd (%) for $C_{22}H_{28}ClN_5O_5$ (dihydrate): C 55.29, H 5.91, N 14.65; found: C 55.10, H 5.78, N 14.58. Crystals suitable for single-crystal X-ray structure analysis were obtained from CH_3CN–MeOH–Et_2O, 3:1:1.

General procedure for condensation of carboxylic acids and amines

N-Phenethyl-3-phenylpropanamide (3a)[1,2]**:** **X** (194 mg, 0.44 mmol) was added to a mixture of 3-phenylpropinoic acid **1a** (60 mg, 0.40 mmol) and 2-phenylethylamine **2a** (55 μL, 0.44 mmol) in THF (2.0 mL). After stirring for 3 h at room temperature, the reaction mixture was quenched with 1 M $KHSO_4$, and was concentrated under reduced pressure to remove THF. The mixture was diluted with AcOEt, and washed with 0.5 M HCl, sat. aq. $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/AcOEt 7:3) to afford *N*-phenethyl-3-phenylpropanamide (**3a**, 90 mg, 89%) as a white powder. The yield in MeOH was 95%. M.p. 97–98 °C (lit.[2] m.p. 96–97.5 °C) ; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=2.42 (t, *J*=7.8 Hz, 2H), 2.73 (t, *J*=6.9 Hz, 2H), 2.94 (t, *J*=7.8 Hz, 2H), 3.47 (dt, *J*=6.9, 6.9 Hz, 2H), 5.36 (br s, 1H), 7.07–7.30 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=31.81, 35.77, 38.67, 40.67, 126.38, 126.61, 128.50, 128.66, 128.74, 128.87, 138.98, 140.98, 172.12; HRMS (DART–TOF): m/z $[M+H]^+$ calcd for $C_{17}H_{20}N_1O_1$: 254.1545; found: 254.1516.

N-Phenyl-3-phenylpropanamide (3b)[3,4]

Silica gel column chromatography; hexane/AcOEt 85:15. The yields in MeOH and THF were 80% and 75%, respectively. A white powder; m.p. 96–97 °C (lit.[3] m.p. 98 °C); ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ=2.66 (t, *J*=7.6 Hz, 2H), 3.06 (t, *J* = 7.6 Hz, 2H), 7.02 (br s, 1H) 7.09 (m, 1H), 7.22–7.25 (m, 3H), 7.28–7.32 (m, 4H), 7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$):

δ=31.69, 39.59, 120.07, 124.44, 126.52, 128.52, 128.78, 129.09, 137.84, 140.75, 170.54; HRMS (DART–TOF): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{16}N_1O_1$: 226.1232; found: 226.1232.

N,N-Diethyl-3-phenylpropanamide (3c)[1,5]

Silica gel column chromatography; hexane/AcOEt 8:2. The yields in MeOH and THF were 65% and 85%, respectively. A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=1.10 (t, *J*=7.3 Hz, 3H), 1.11 (t, *J*=7.3 Hz, 3H), 2.59 (t, *J*=7.3 Hz, 2H), 2.99 (t, *J*=7.3 Hz, 2H), 3.22 (q, *J*=7.3 Hz, 2H), 3.38 (q, *J*=7.3 Hz, 2H), 7.20–7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.21, 14.39, 31.79, 35.24, 40.34, 42.02, 126.20, 128.59, 128.59, 141.70, 171.43; HRMS (DART–TOF): *m*/*z* $[M+H]^+$ calcd for $C_{13}H_{20}N_1O_1$: 206.1545; found: 206.1565.

N-Phenethyl-2,2-dimethylpropanamide (3d)[1,6]

Silica gel column chromatography; hexane/AcOEt 9:1 to 7:3. The yields in MeOH and THF were 87% and 90%, respectively. A white powder; m.p. 81–82 °C (lit.[1] m.p. 81–82 °C); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=1.14 (s, 9H), 2.81 (t, *J*=6.9 Hz, 2H), 3.50 (dt, *J*=6.9, 7.8 Hz, 2H), 5.64 (br s, 1H), 7.18–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$): δ=27.66, 35.79, 38.77, 40.75, 126.62, 128.73, 128.95, 139.18, 178.49; HRMS (DART–TOF): *m*/*z* $[M+H]^+$ calcd for $C_{13}H_{20}N_1O_1$: 206.1545; found: 206.1564.

N-Phenethylbenzamide (3e)[1,6]

Silica gel column chromatography; hexane/AcOEt 70:30. The yields in MeOH and THF were 97% and 95%, respectively. A white powder; m.p. 111–112 °C (lit.[6] 113–116 °C); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=2.95 (t, *J*=6.8 Hz, 2H), 3.73 (dt, *J*=6.8, 6.8 Hz, 2H), 6.10 (br s, 1H), 7.24–7.26 (m, 3H), 7.32–7.35 (m, 2H), 7.39–7.43 (m, 2H), 7.47–7.51 (m, 1H), 7.67-7.70 (m, 2H); ^{13}C NMR ($CDCl_3$): δ=35.84, 41.26, 126.74, 126.93, 128.69, 128.86, 128.96, 131.54, 134.79, 139.04, 167.60; HRMS (DART–TOF): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{16}N_1O_1$: 226.1232; found: 226.1231.

N-Phenethyl-4-nitrobenzamide (3f)[1,7]

Silica gel column chromatography; hexane/AcOEt 80:20 to 70:30. The yields in MeOH and THF were 91% and 96%, respectively. A white powder; m.p. 149–150 °C (lit.[1] 149.5–150.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ=2.96 (t, *J*=6.9 Hz, 2H), 3.75 (dt, *J*=6.9, 6.9 Hz, 2H), 6.18 (br s, 1H), 7.23–7.29 (m, 3H), 7.32–7.36 (m, 2H), 7.83 (m, 2H), 8.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=35.58, 41.51, 123.94, 126.93, 128.14, 128.88, 128.94, 138.59, 140.31, 149.61, 165.58; HRMS (DART–TOF): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{15}N_2O_3$: 271.1083; found: 271.1112.

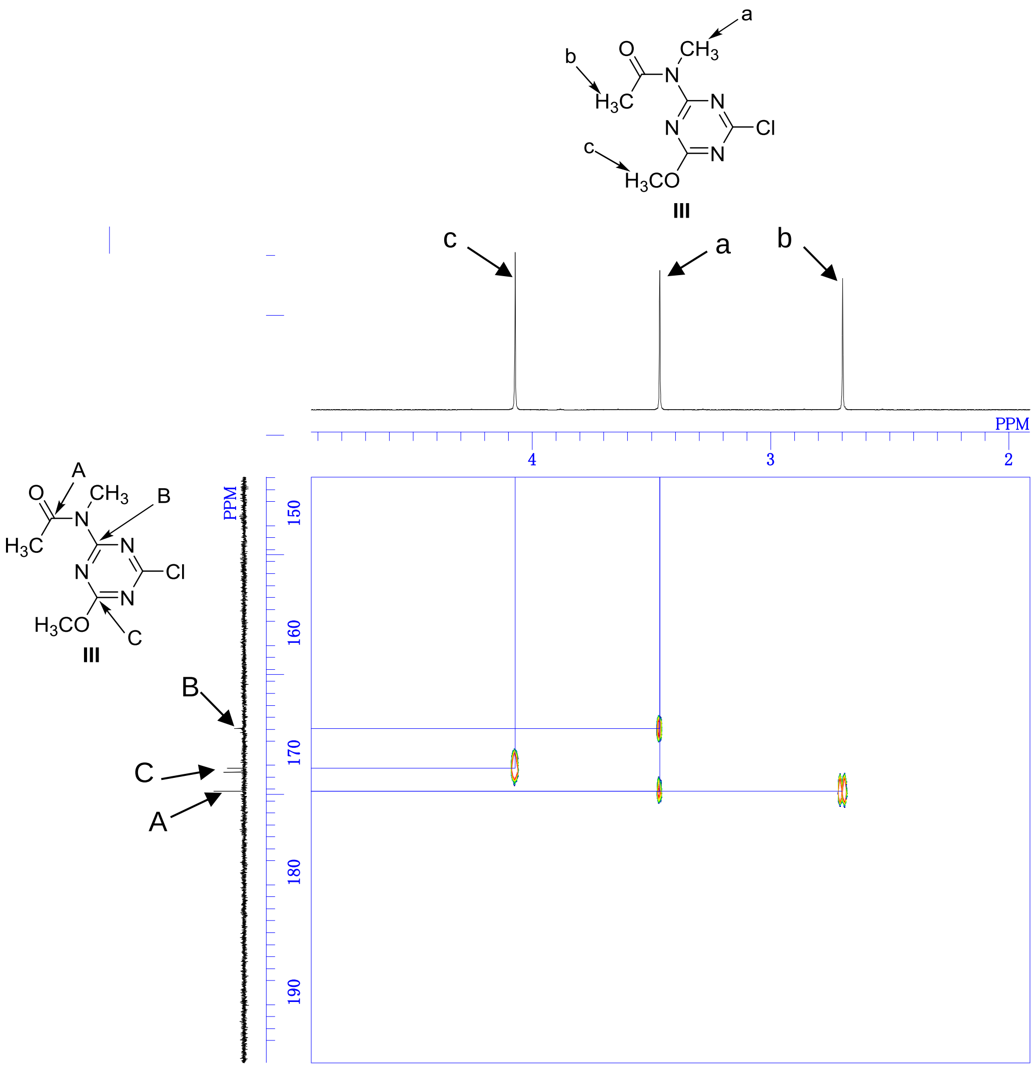


Figure S1: HMBC spectrum of **III**.

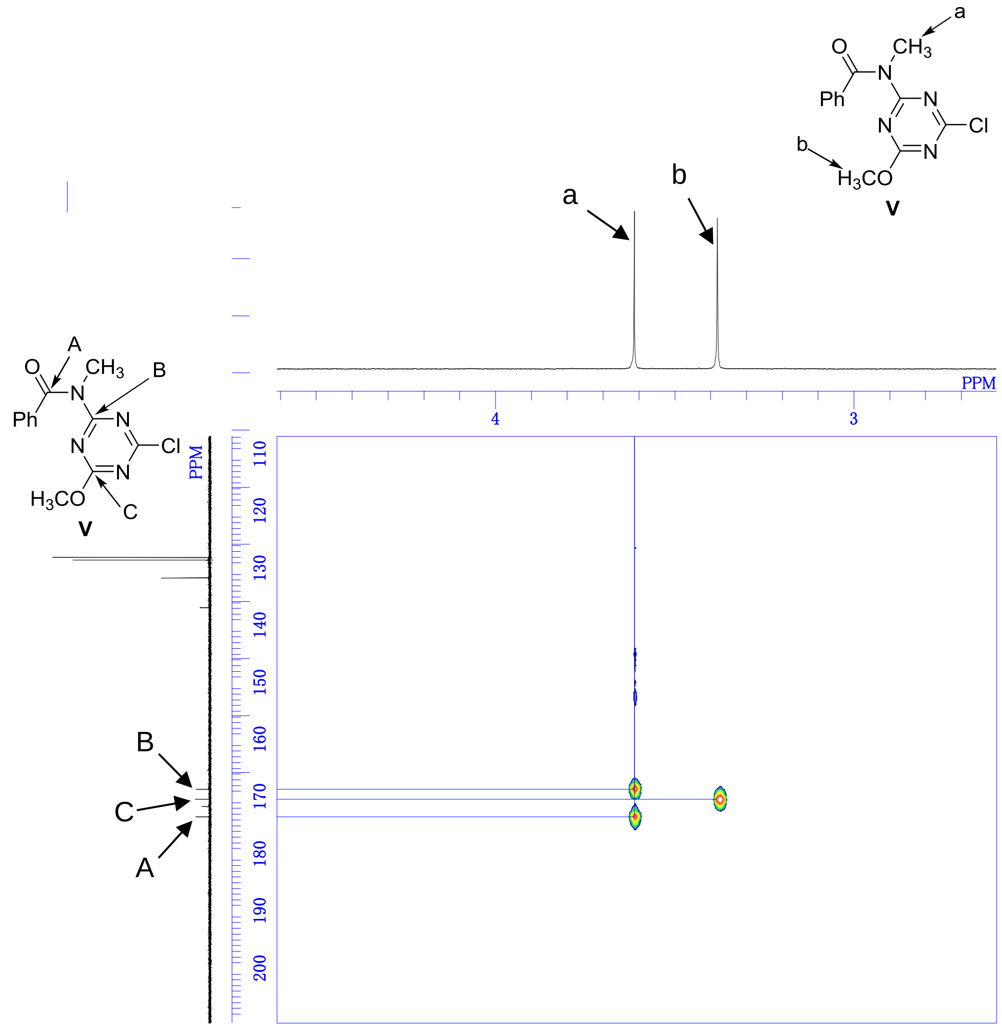
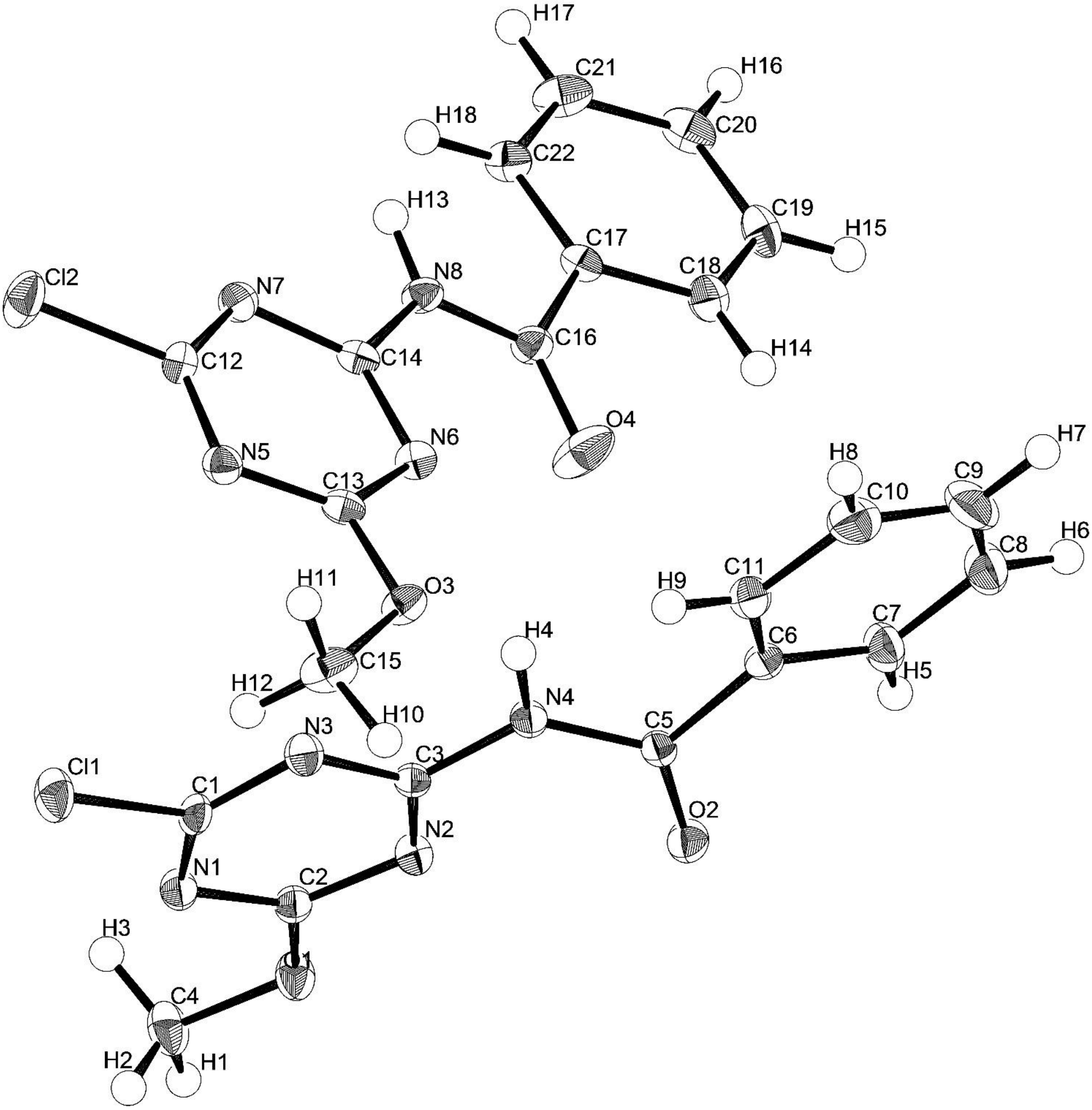
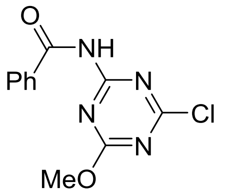


Figure S2: HMBC spectrum of **V**.

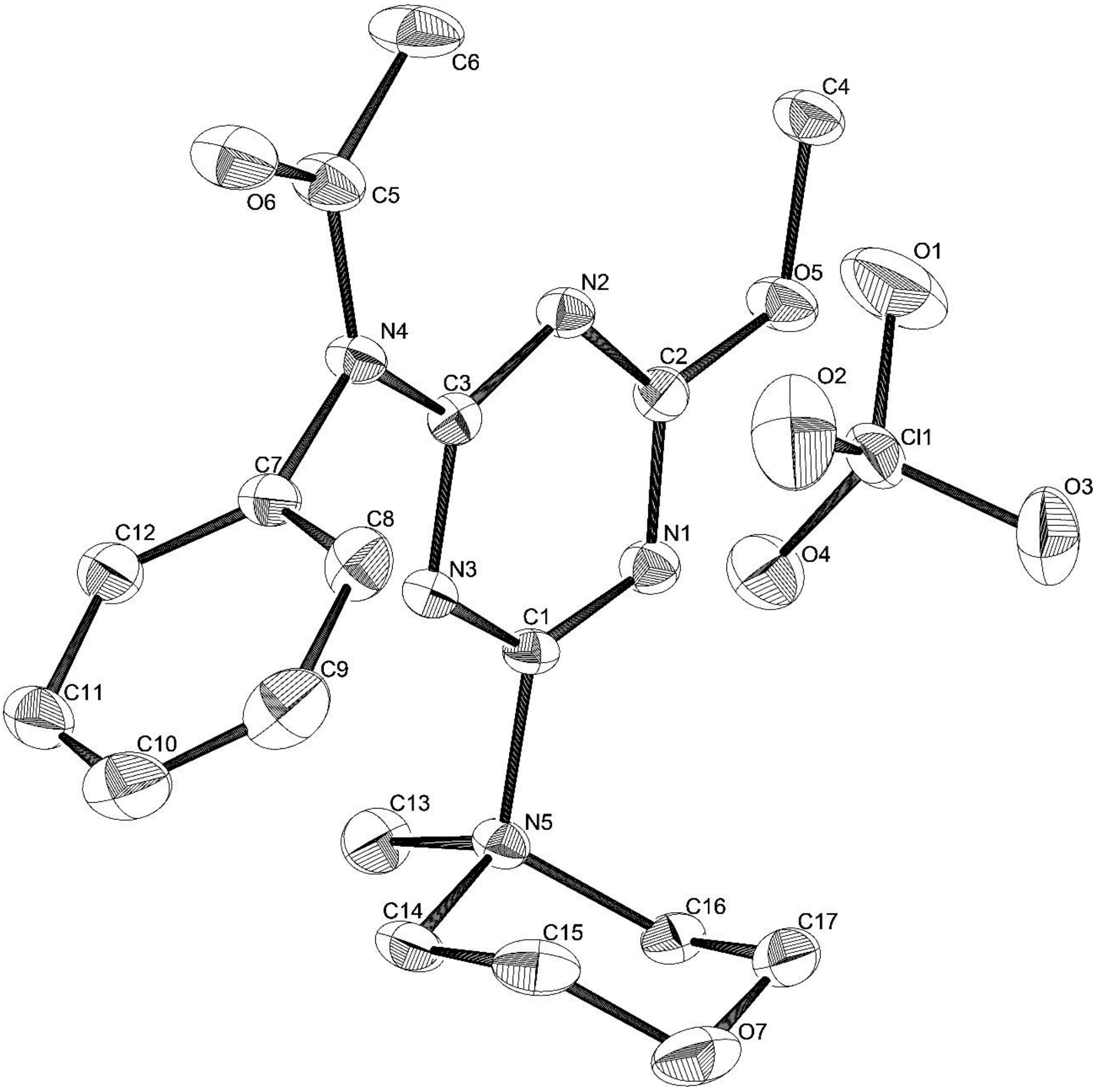


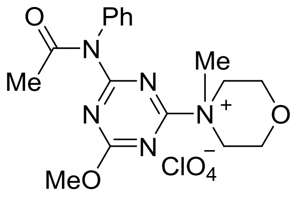


II

Figure S3. Single-crystal X-ray structure analysis of **II** (50% probability ellipsoids).

Crystallographic data of **II** have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1478426.

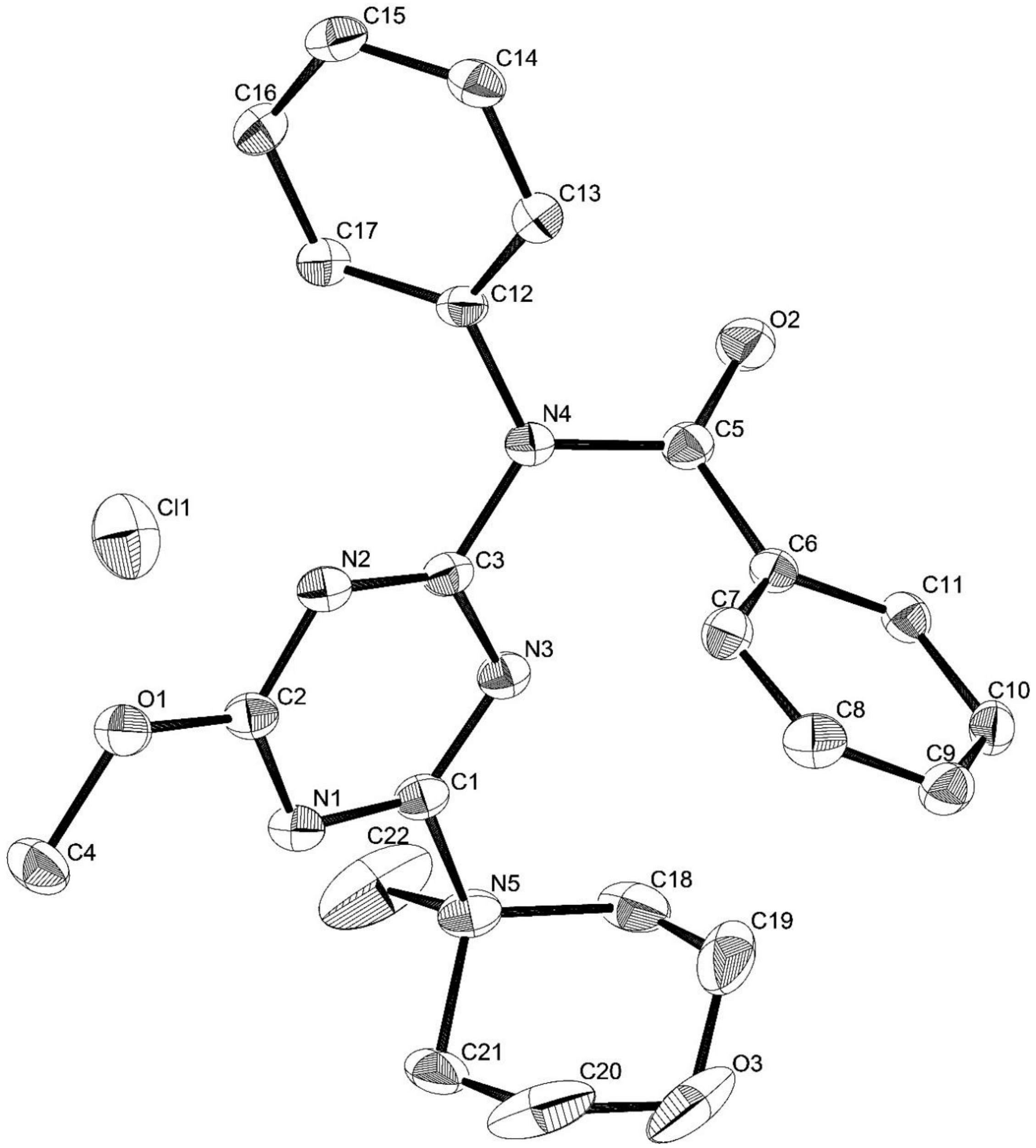


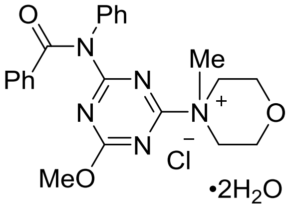


VIII

Figure S4. Single-crystal X-ray structure analysis of **VIII** (50% probability ellipsoids). Hydrogens are omitted for clarity.

Crystallographic data of **VIII** have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1478427.



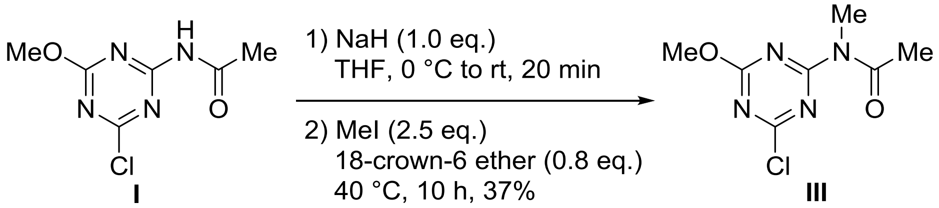


X

Figure S5. Single-crystal X-ray structure analysis of **X** (50% probability ellipsoids). Hydrogens and waters are omitted for clarity.

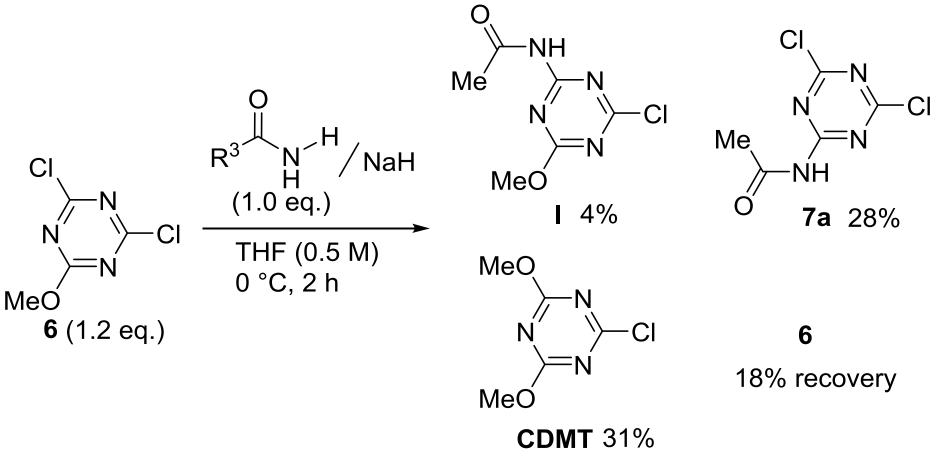
Crystallographic data of **X** have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1478428.

Structure determination of 2-acetamido-4-chloro-6-methoxy-1,3,5-triazine (I) by methylation



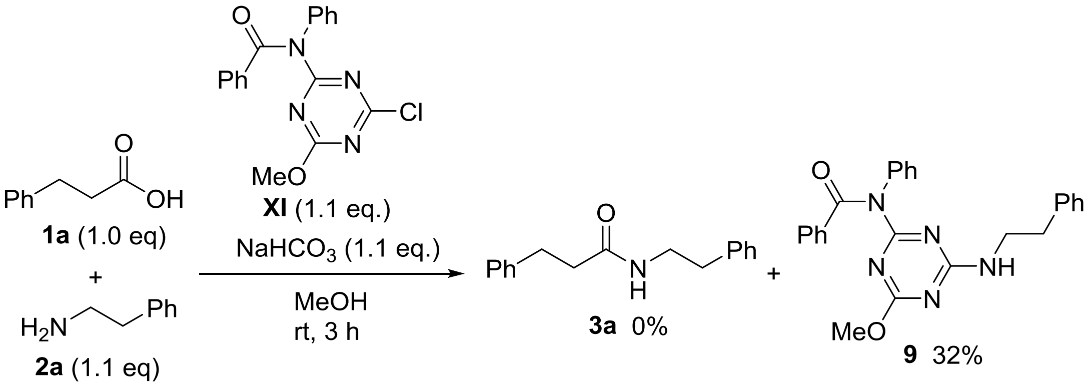
2-Acetamido-4-chloro-6-methoxy-1,3,5-triazine (**I**, 30 mg, 0.15 mmol) in THF (360 μL) was added to a suspension of sodium hydride (3.0 mg, 0.14 mmol) in THF (200 μL) at 0 °C. After stirring for 20 min at rt, the reaction mixture was cooled to 0 °C. 18-crown-6 ether (30 mg, 0.11 mmol) and MeI (21 μL, 0.340 mmol) were added to the mixture, and the mixture was stirred for 10 h at 40 °C. To the mixture was added CH_2Cl_2 and 1 M $KHSO_4$. The organic layer was separated, washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc 8:2) to afford a white solid (11 mg, 37%) whose ^{1}H NMR, ^{13}C NMR, and HMBC spectra were consistent with 2-chloro-4-methoxy-6-(*N*-methylacetamido)-1,3,5-triazine (**III**). Therefore, structure of **I** is confirmed as indicated in the Scheme.

Attempted synthtsis of I from 2,4-dichloro-6-methoxy-1,3,5-triazine (6)



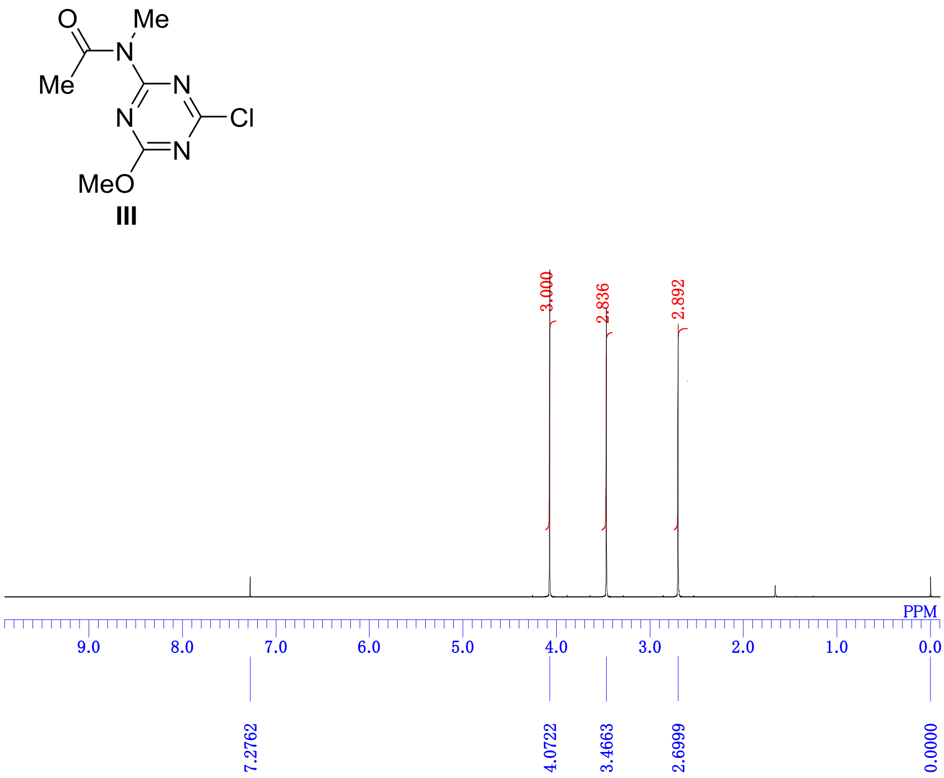
Acetamide (27 mg, 0.46 mmol) in THF (600 µL) was added to a suspension of sodium hydride (20 mg, 0.51 mmol) in THF (300 µL) at 0 °C. After stirring for 45 min at 50 °C, the reaction mixture was cooled to 0 °C. A THF (200 µL) solution of 2,4-dichloro-6-methoxy-1,3,5-triazine (**6**, 100 mg, 0.56 mmol) was added dropwise to the resulting suspension, and the mixture was stirred for 2 h at 0 °C. To the mixture was added CH_2Cl_2 and 1 M $KHSO_4$ at 0 °C. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc 9:1 to 1:1) to afford **I** (4 mg, 4%), 2-acetamido-4,6-dichloro-1,3,5-triazine (**7a**) (27 mg, 28%), CDMT (25 mg, 31%), and **6** (18 mg, 18% recovery).

Amide-forming reaction with XI in the absence of NMM



XI (150 mg, 0.44 mmol) was added to a MeOH solution (2.0 mL) of 3-phenylpropinoic acid (60 mg, 0.40 mmol), 2-phenylethylamine (55 μL 0.44 mmol), and NaHCO$_3$ (37 mg, 0.44 mmol) at rt. After stirring for 3 h, 1 M KHSO$_4$ was added and concentrated under reduced pressure to remove MeOH. The suspension was diluted with AcOEt, and the mixture was washed with 0.5 M HCl, sat. aq. NaHCO$_3$ solution, and brine. The organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/AcOEt 7:3) to afford 2-methoxy-4-(*N*-phenethylamino)-6-(*N*-phenybenzamido)-1,3,5-triazine (**9**, 59 mg, 32%) as a white powder. The amide was not observed by ^{1}H NMR.

9: a white powder; m.p. 174–175 °C; ^{1}H NMR (400 MHz, CDCl$_3$, TMS): δ=2.47 (t, *J*=7.0 Hz, 2H major), 2.82 (t, *J*=7.0 Hz, 2H minor), 3.13 (dt, *J*=6.0, 7.0 Hz, 2H major), 3.50 (s, 3H minor), 3.52 (s, 3H major), 3.62 (dt, *J*=6.0, 7.0 Hz, 2H minor), 5.20 (t, *J*=6.0 Hz, 1H minor), 5.36 (t, *J*=6.0 Hz, 1H major), 6.96 (m, 2H major), 7.13 (m, 2H minor), 7.21–7.47 (m, 11H major and 11H minor), 7.67 (m, 2H minor), 7.71 (m, 2H major); ^{13}C NMR (100 MHz, CDCl$_3$): δ 35.54, 35.59, 42.20, 42.23, 54.40, 54.52, 126.55, 126.69, 127.59, 127.66, 128.23, 128.31, 128.38, 128.46, 128.49, 128.62, 128.74, 128.87, 128.89, 129.30, 129.37, 131.31, 137.29, 137.66, 138.63, 138.73, 140.67, 140.73, 166.97, 167.41, 169.01, 169.25, 170.95, 171.28, 173.00, 173.30; IR (KBr): 3370, 3060, 3005, 2949 1695, 1568, 1473, 1448, 1402, 1375, 1363, 1248 cm^{-1}; HRMS (DART–TOF): *m*/*z* [M+H]$^+$ calcd for $C_{25}H_{24}N_5O_2$: 426.1930; found: 426.1918.



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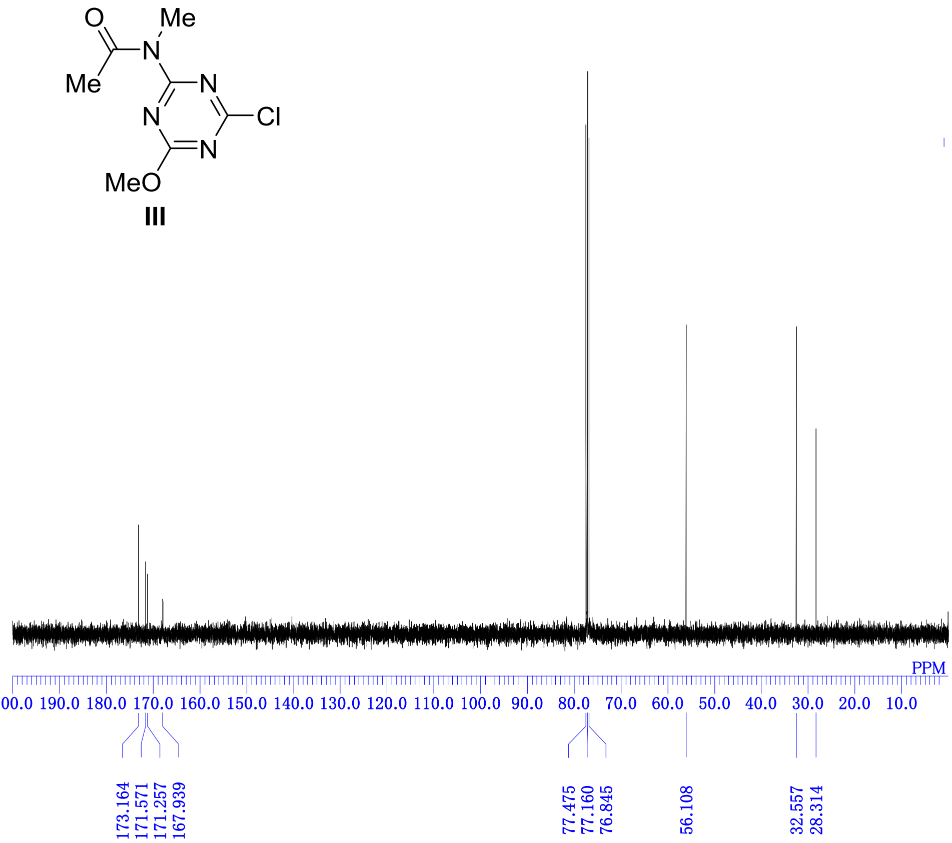

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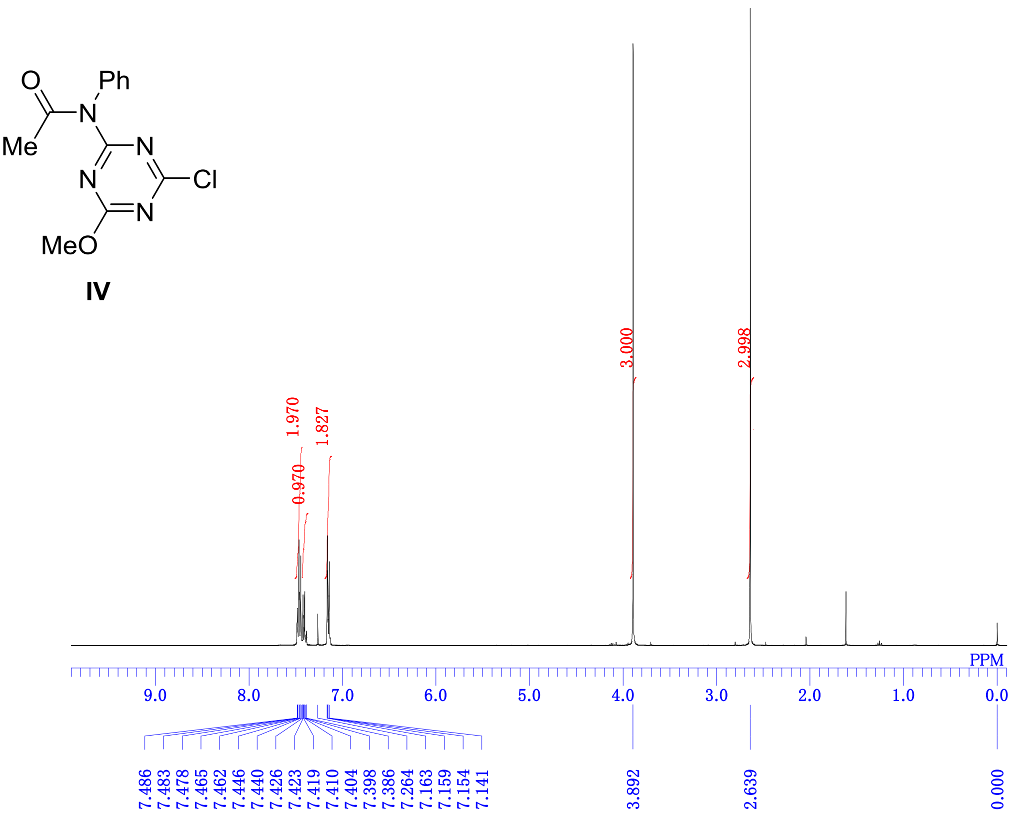
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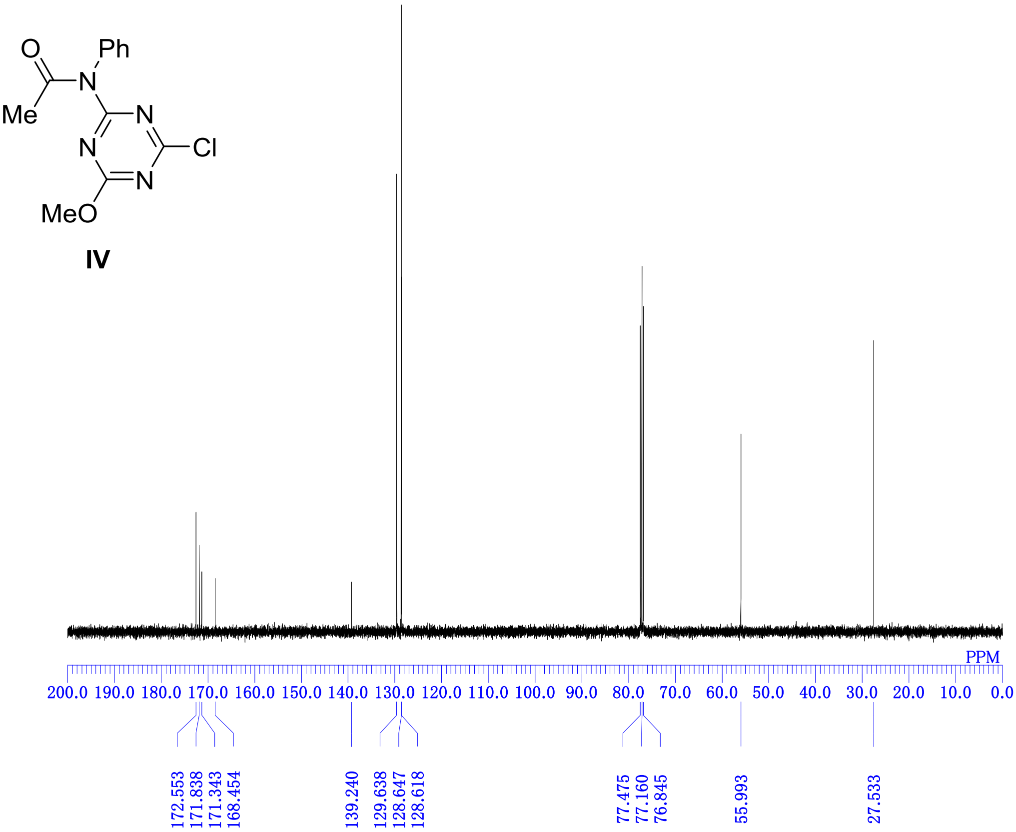
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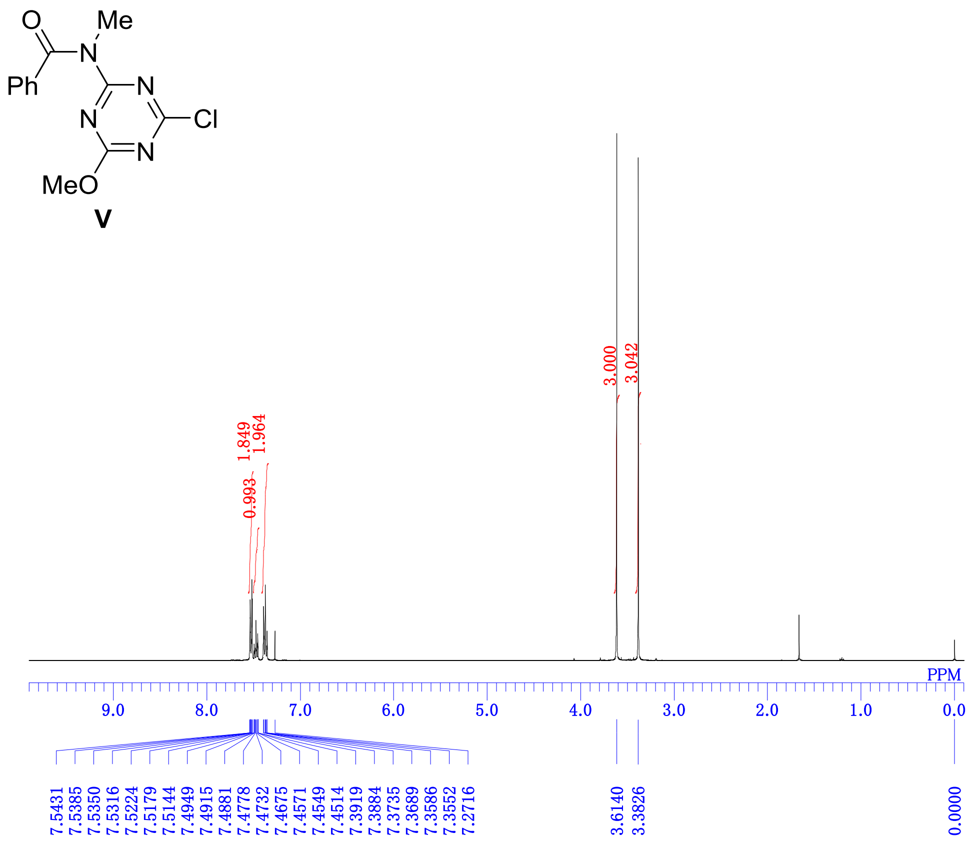

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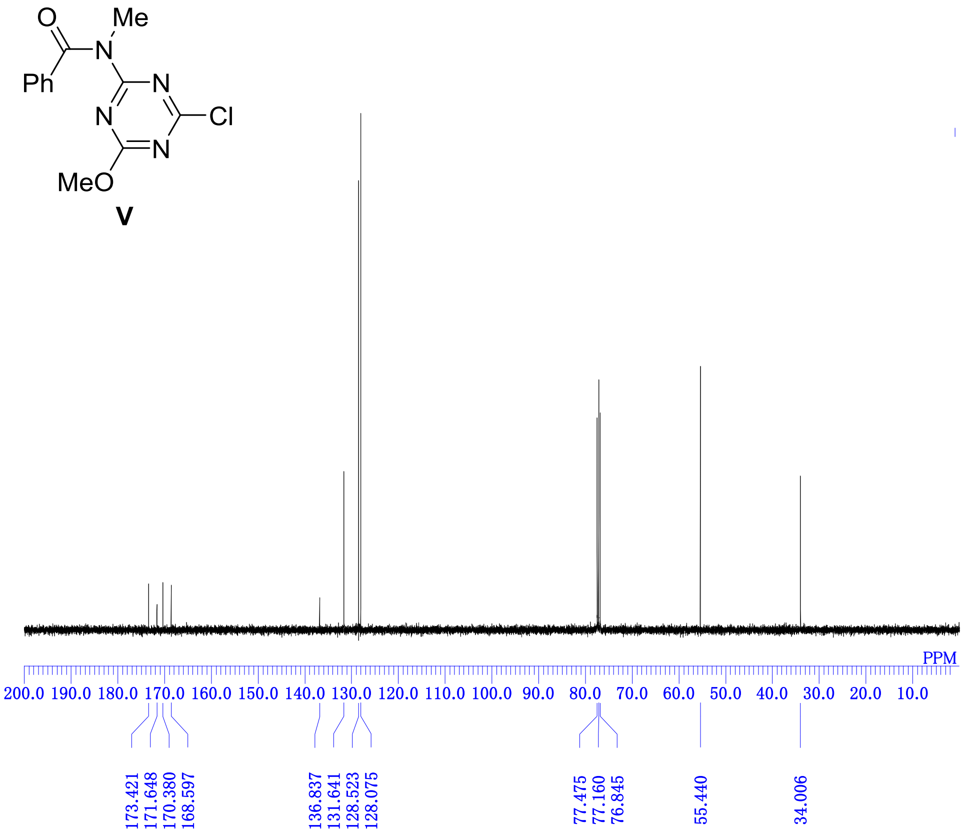

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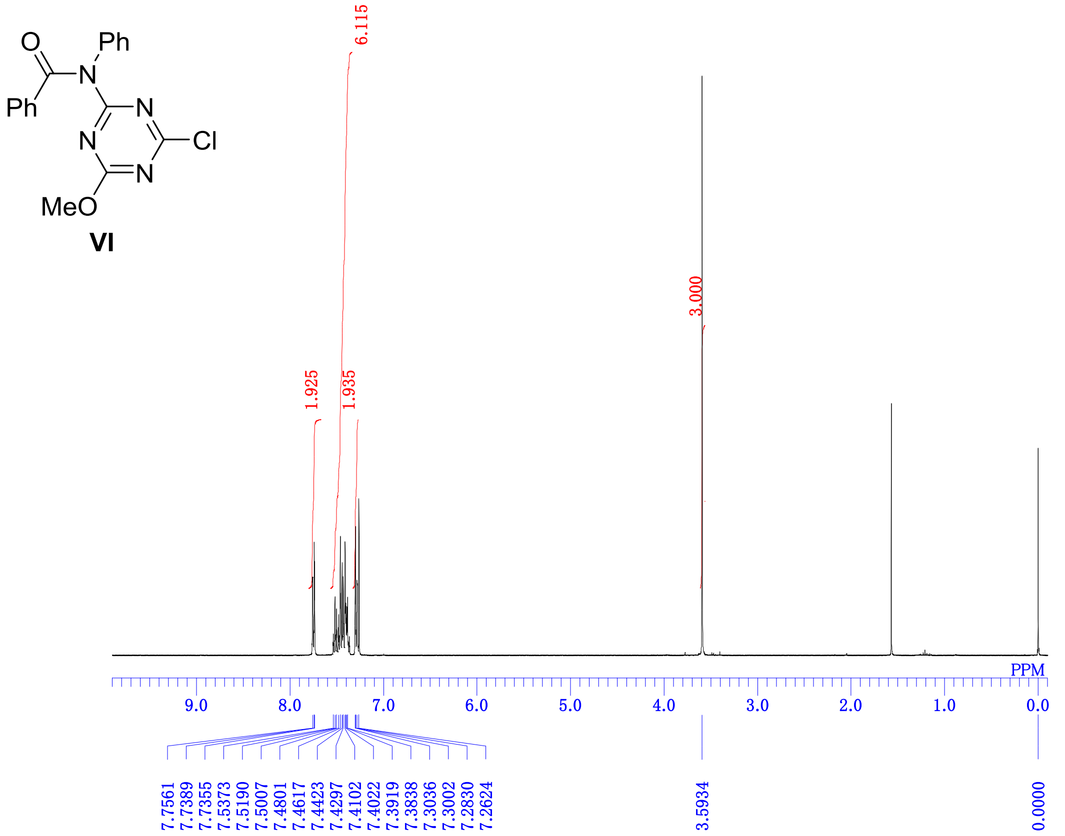

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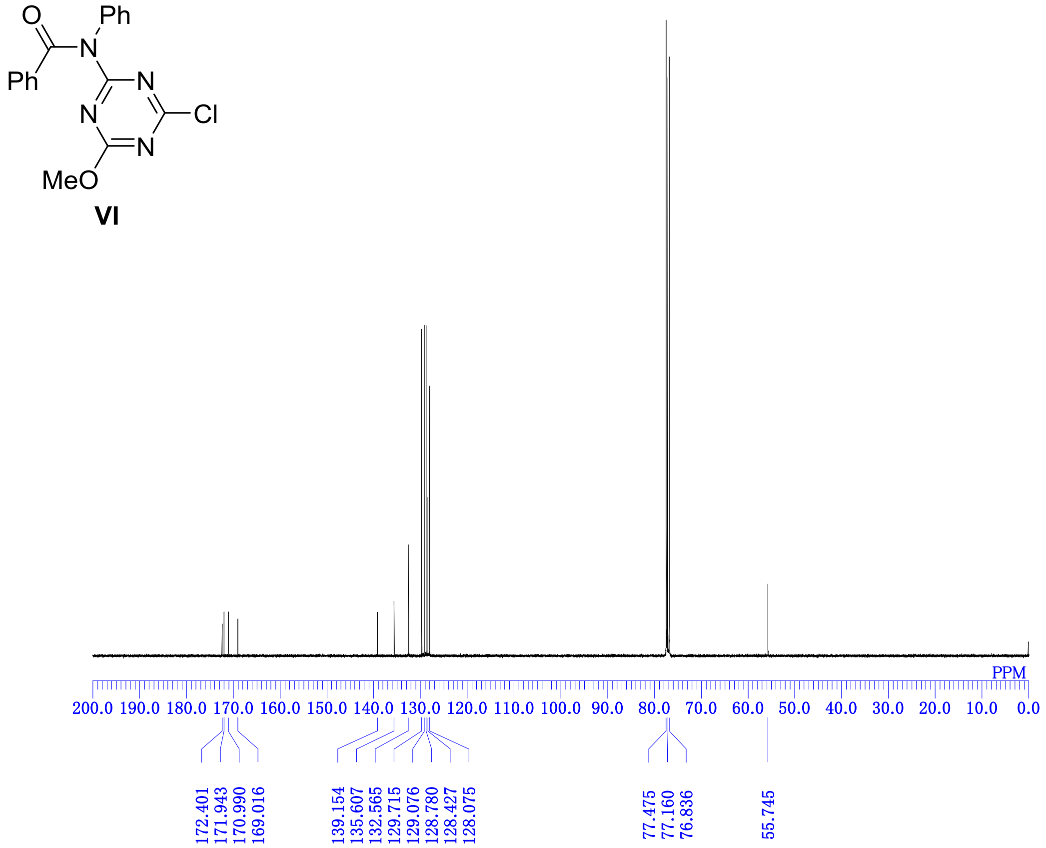

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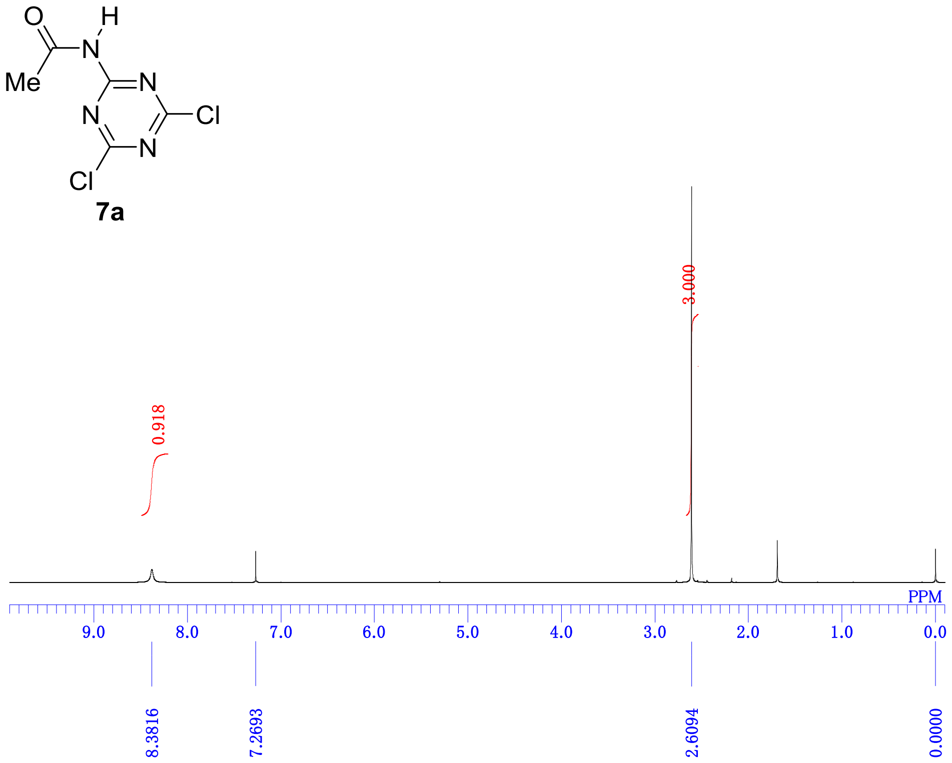
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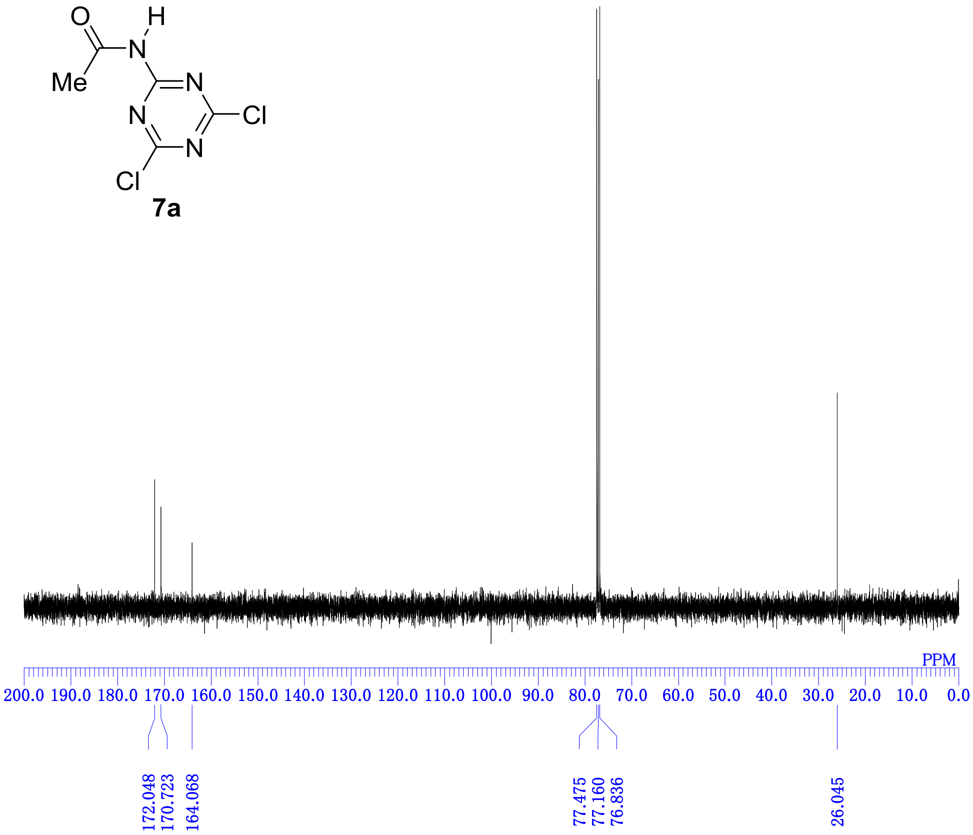
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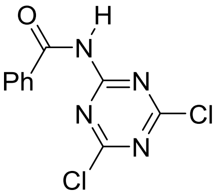

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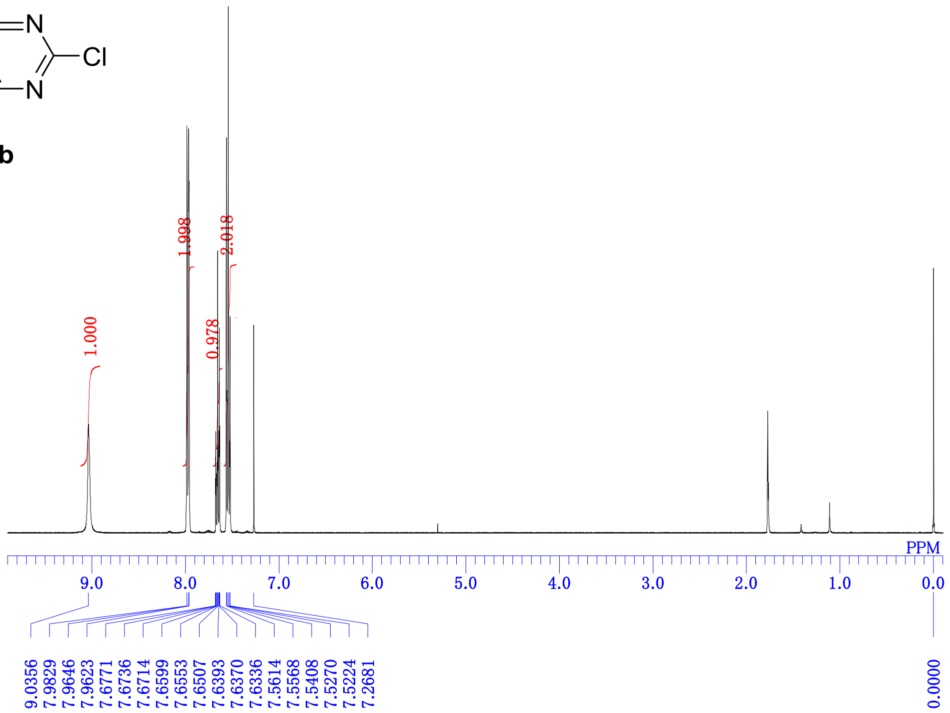

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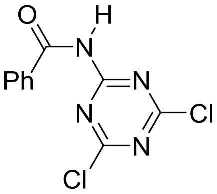

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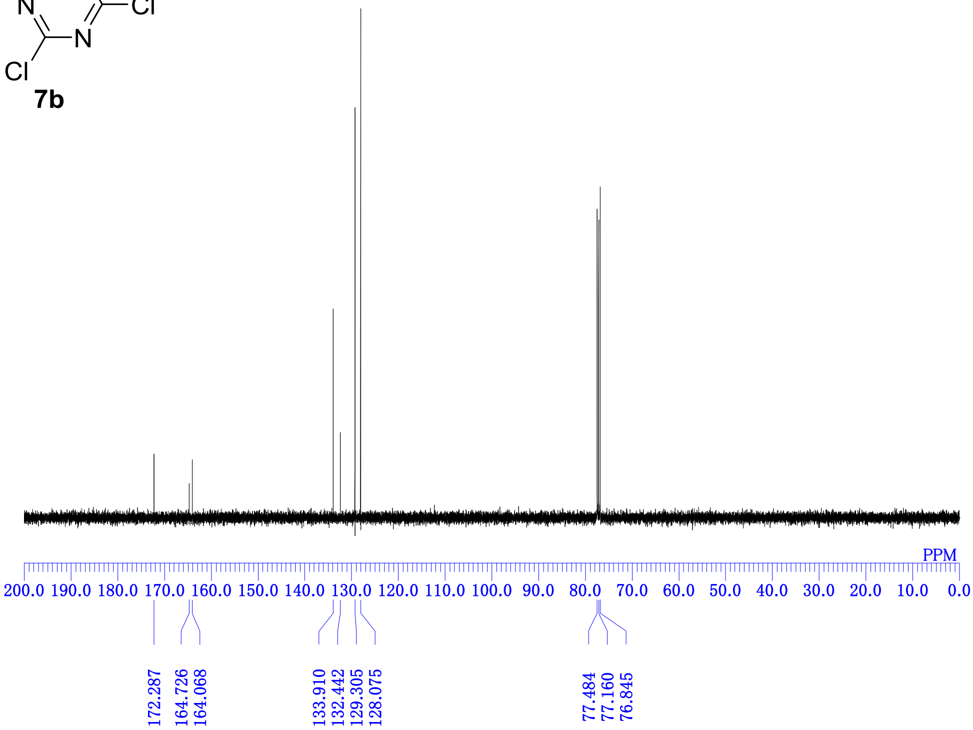

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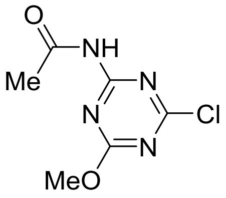
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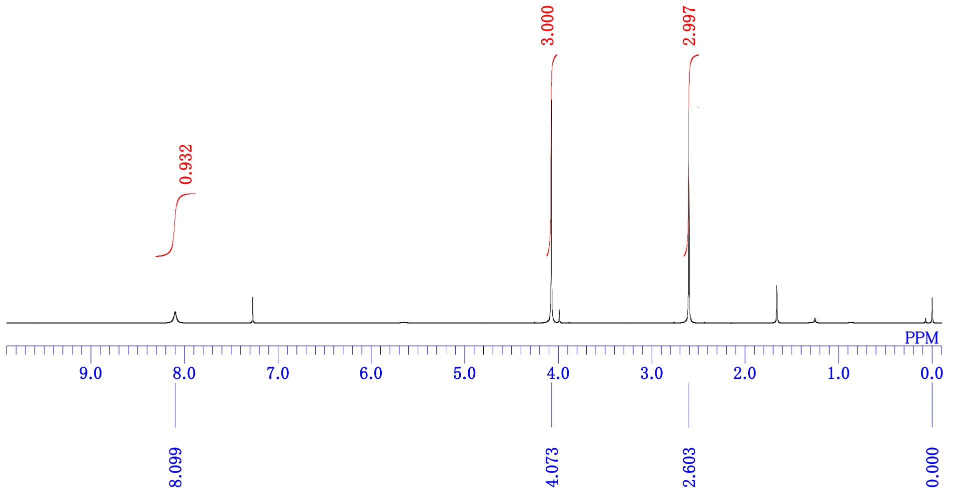
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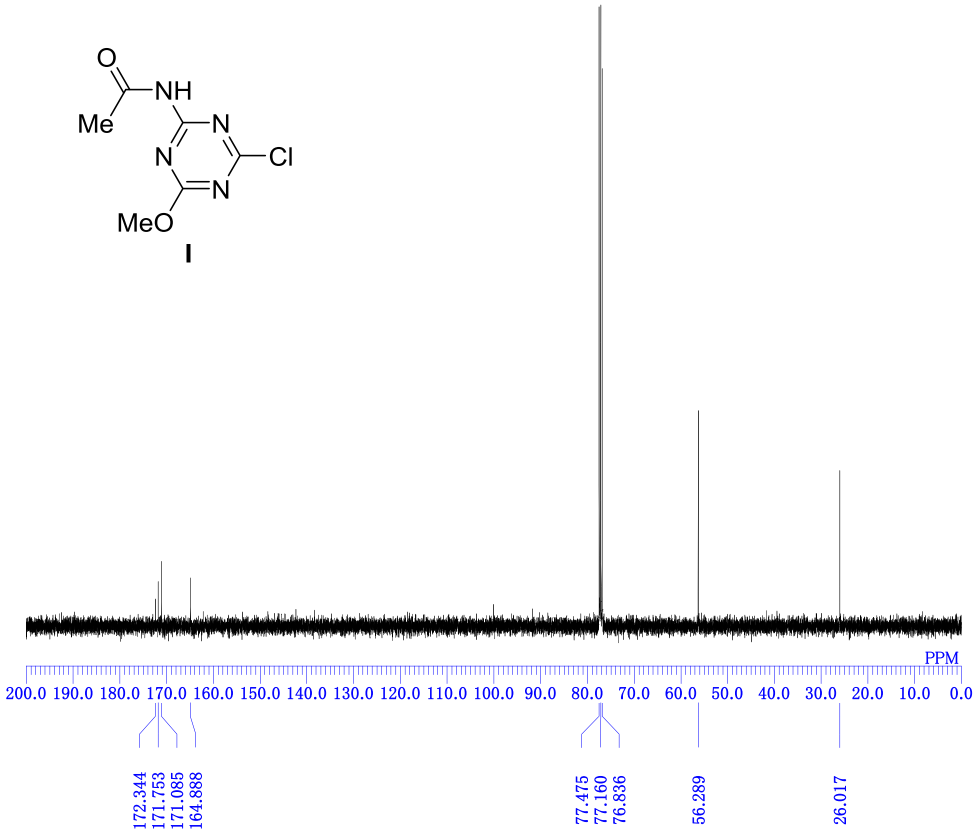
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76.836
56.289
26.017

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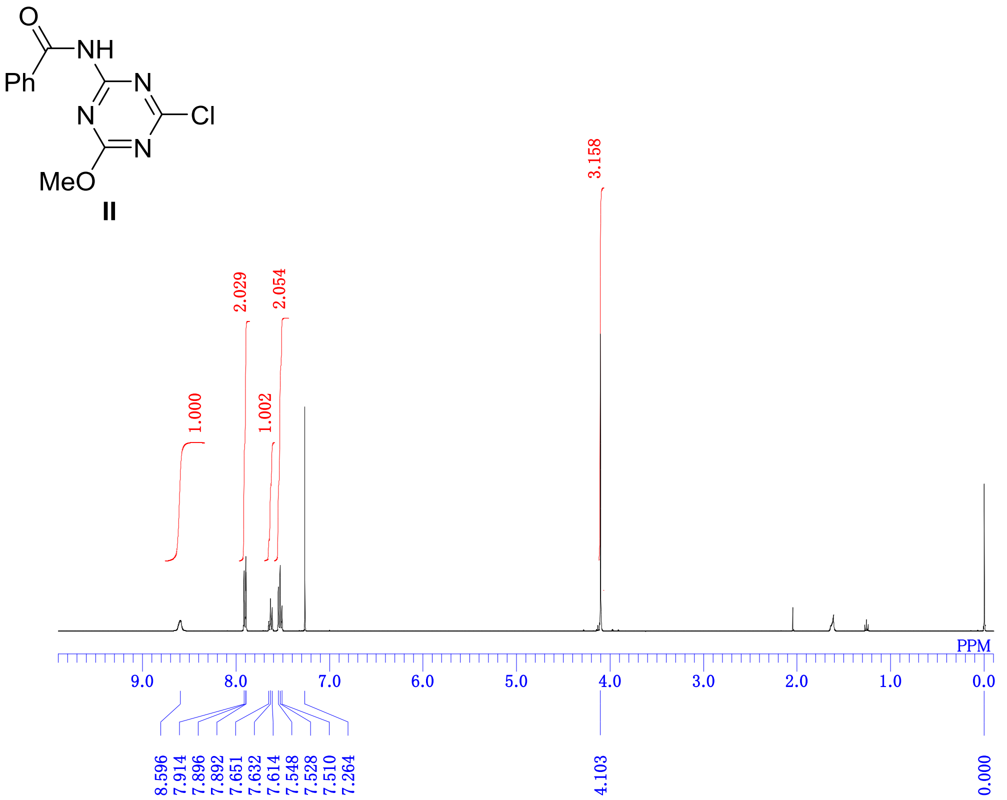
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N
Cl
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MeO
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1.000
1.002
PPM
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7.0
6.0
5.0
4.0
3.0
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1.0
0.0
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7.528
7.510
7.264
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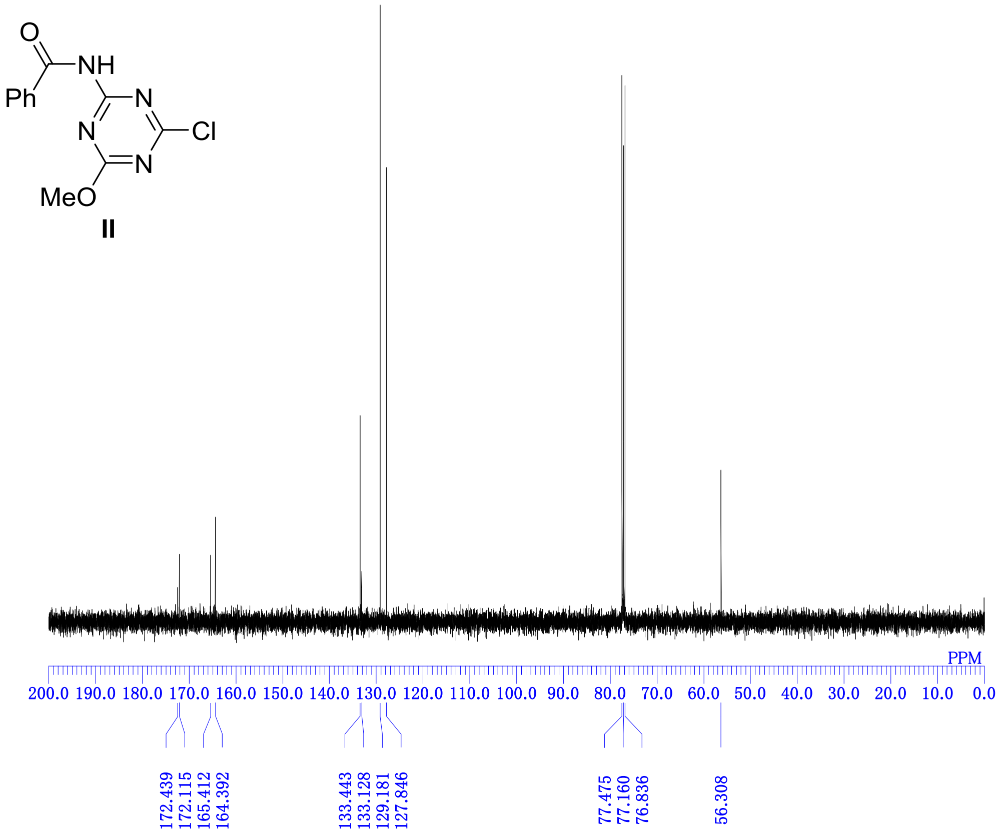
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NH
Ph
N
N
Cl
N
MeO
II
PPM
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140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
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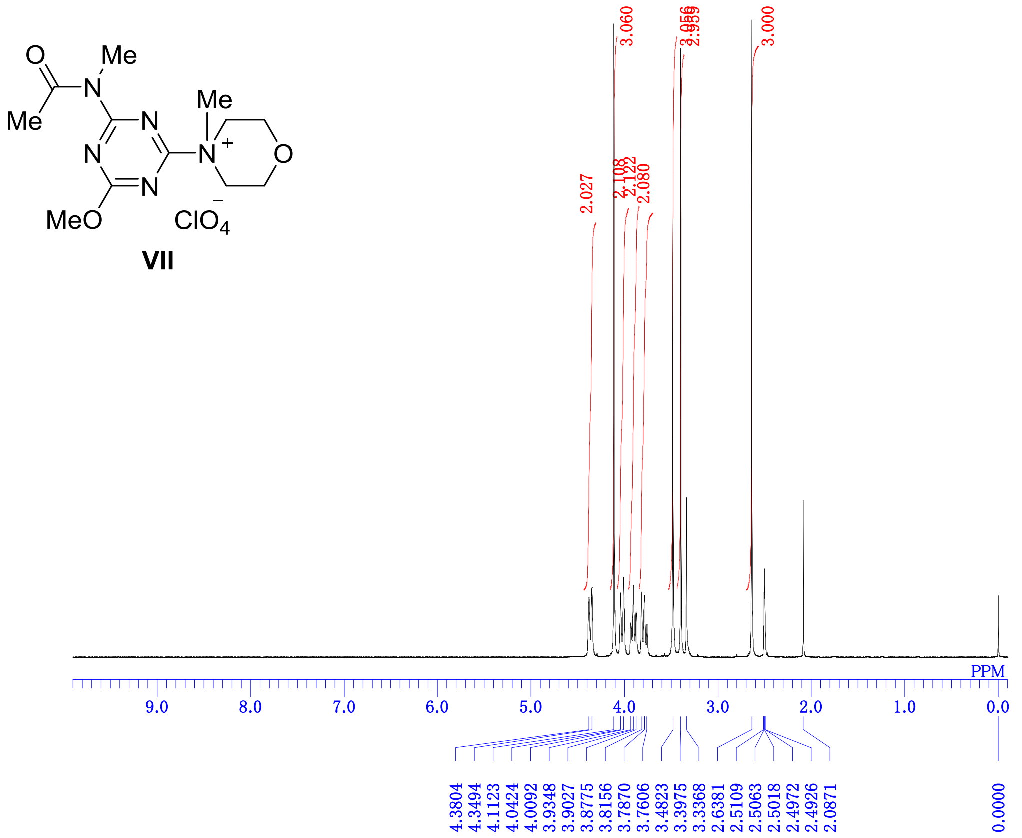
77.160
76.836
56.308



VII

O
Me
N
Me
N
N
Me
N
+
O
N
N
MeO
ClO4
−
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2.108
2.122
2.080
3.056
2.959
3.000
PPM
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7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
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4.3494
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4.0424
4.0092
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3.9027
3.8775
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3.7870
3.7606
3.4823
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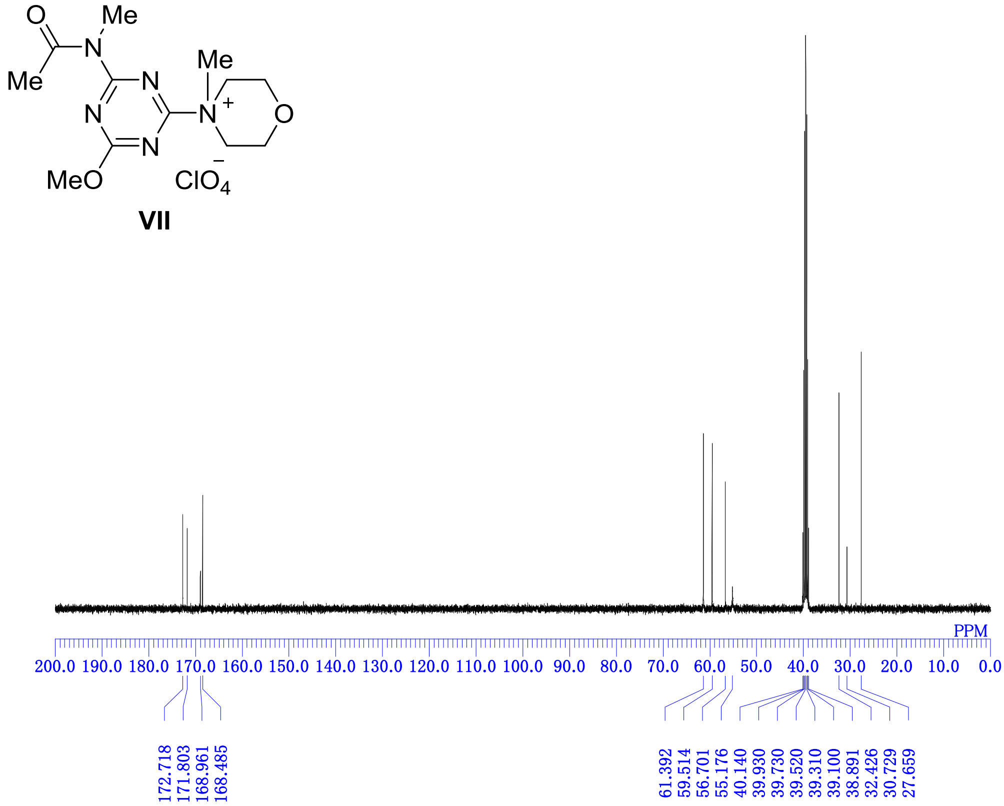

VII

O
Me
N
Me
N
N
Me
N
+
O
N
N
MeO
ClO4
−
PPM
200.0
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180.0
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150.0
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120.0
110.0
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80.0
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60.0
50.0
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30.0
20.0
10.0
0.0
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61.392
59.514
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39.310
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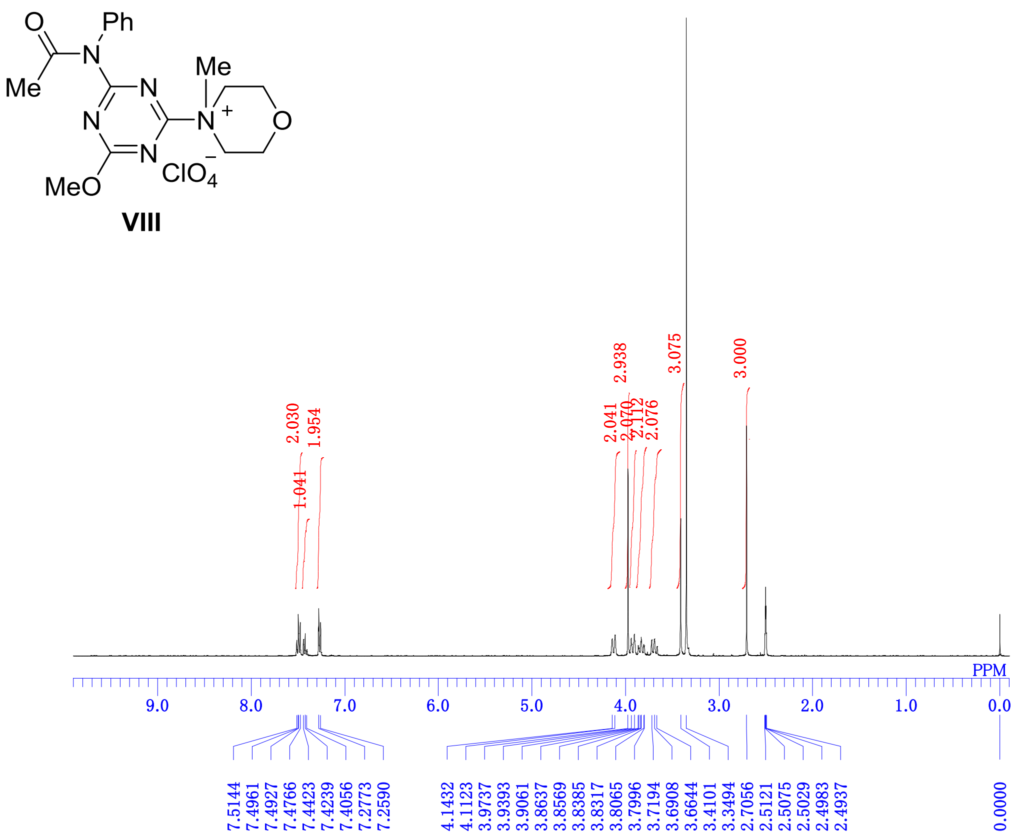
VIII

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2.070
2.112
2.076
3.075
3.000
PPM
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4.0
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7.4423
7.4239
7.4056
7.2773
7.2590
4.1432
4.1123
3.9737
3.9393
3.9061
3.8637
3.8569
3.8385
3.8317
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3.7996
3.7194
3.6908
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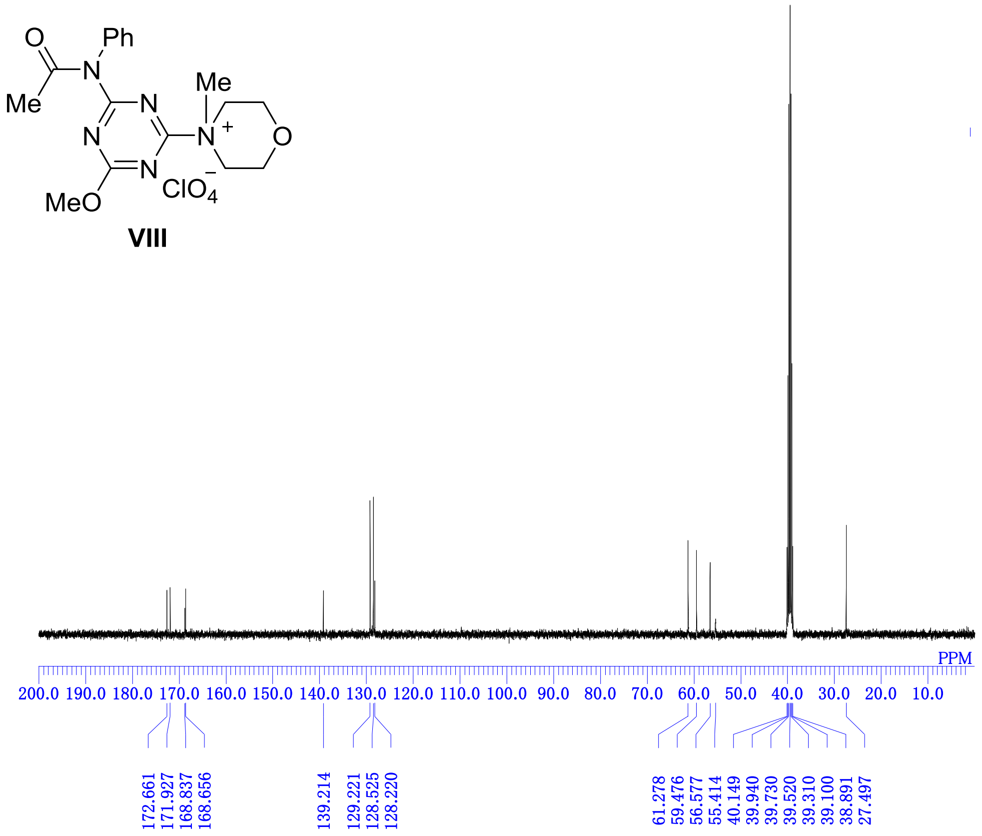
VIII

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Me
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N
N
ClO4−
MeO
PPM
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160.0
150.0
140.0
130.0
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60.0
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128.525
128.220
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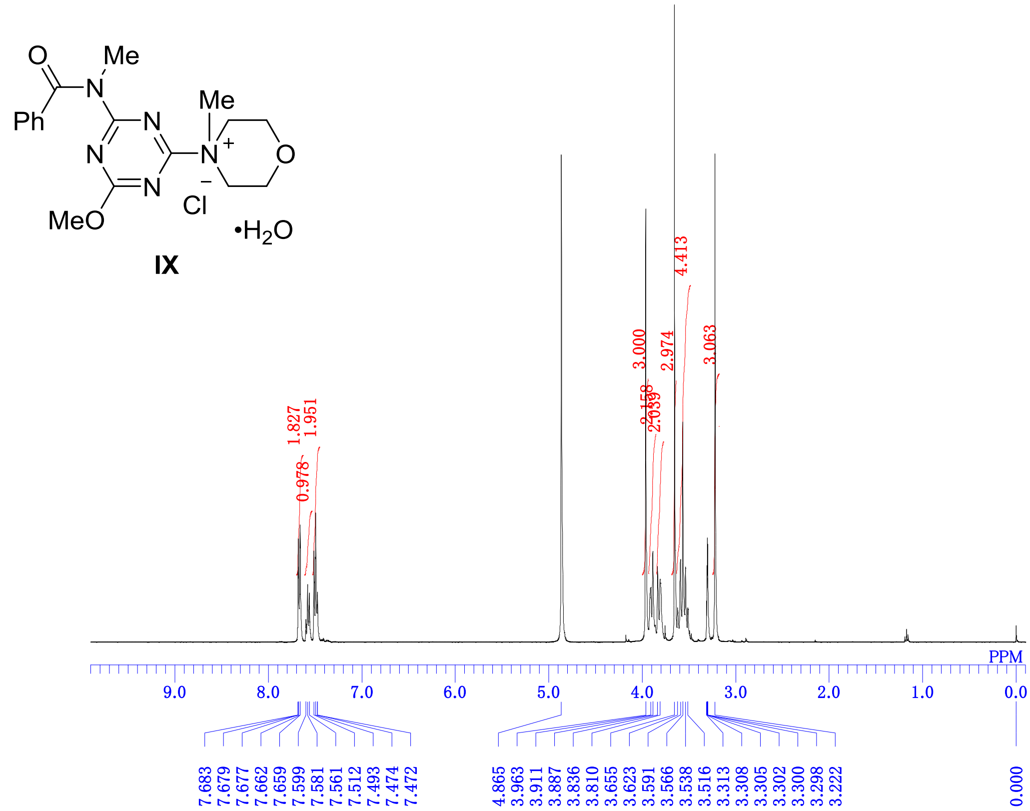
39.520
39.310
39.100
38.891
27.497


O
Me
N
Ph
N
Me
N
N
N+
O
N
–
MeO
Cl
•H2O
IX
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0.978
3.000
2.158
2.039
2.974
4.413
3.063
PPM
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7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
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7.679
7.677
7.662
7.659
7.599
7.581
7.561
7.512
7.493
7.474
7.472
4.865
3.963
3.911
3.887
3.836
3.810
3.655
3.623
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3.538
3.516
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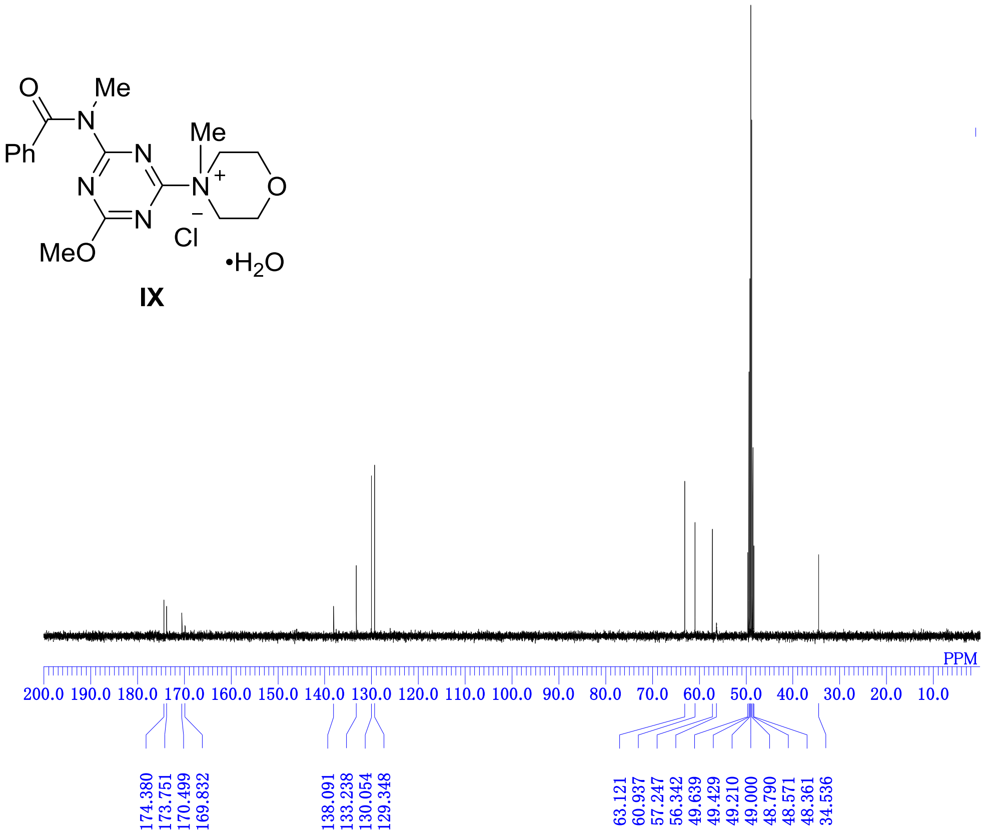
3.305
3.302
3.300
3.298
3.222
0.000


O
Me
N
Ph
N
Me
N
N
N+
O
N
–
MeO
Cl
•H2O
IX
PPM
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190.0
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60.0
50.0
40.0
30.0
20.0
10.0
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170.499
169.832
138.091
133.238
130.054
129.348
63.121
60.937
57.247
56.342
49.639
49.429
49.210
49.000
48.790
48.571
48.361
34.536

O
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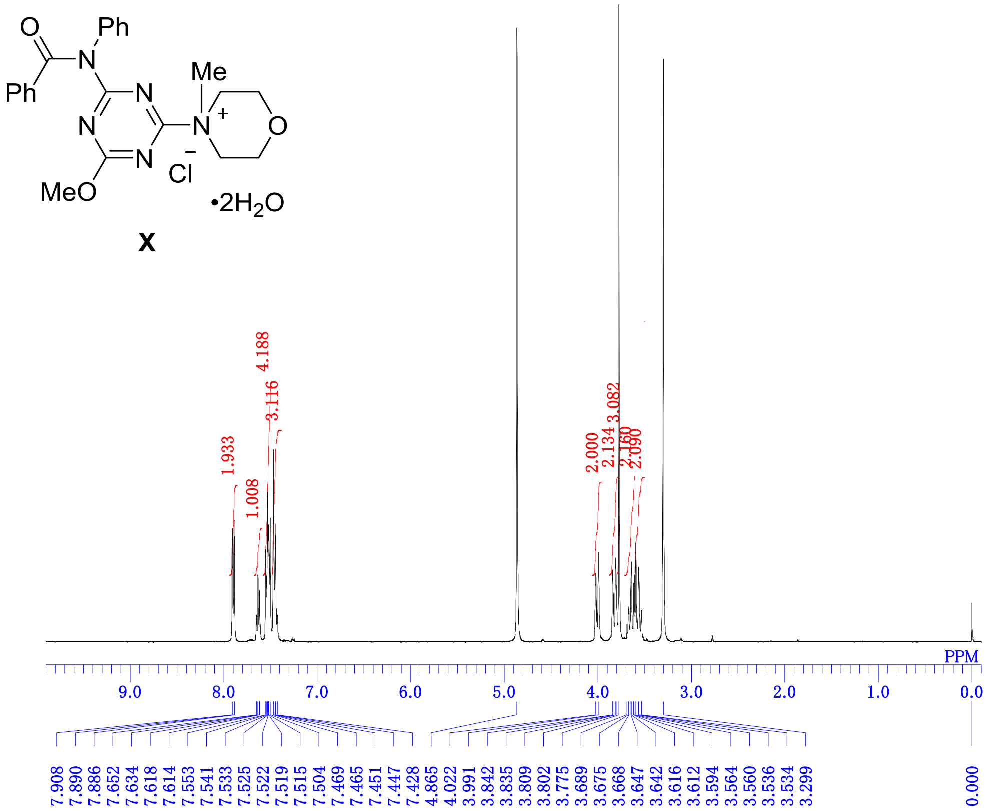
Ph
Me
N
N
N
+
O
N
N
−
Cl
MeO
•2H2O

X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2.160
2.090
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7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
7.908
7.890
7.886
7.652
7.634
7.618
7.614
7.553
7.541
7.533
7.525
7.522
7.519
7.515
7.504
7.469
7.465
7.451
7.447
7.428
4.865
4.022
3.991
3.842
3.835
3.809
3.802
3.775
3.689
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3.668
3.647
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3.616
3.612
3.594
3.564
3.560
3.536
3.534
3.299
0.000

O
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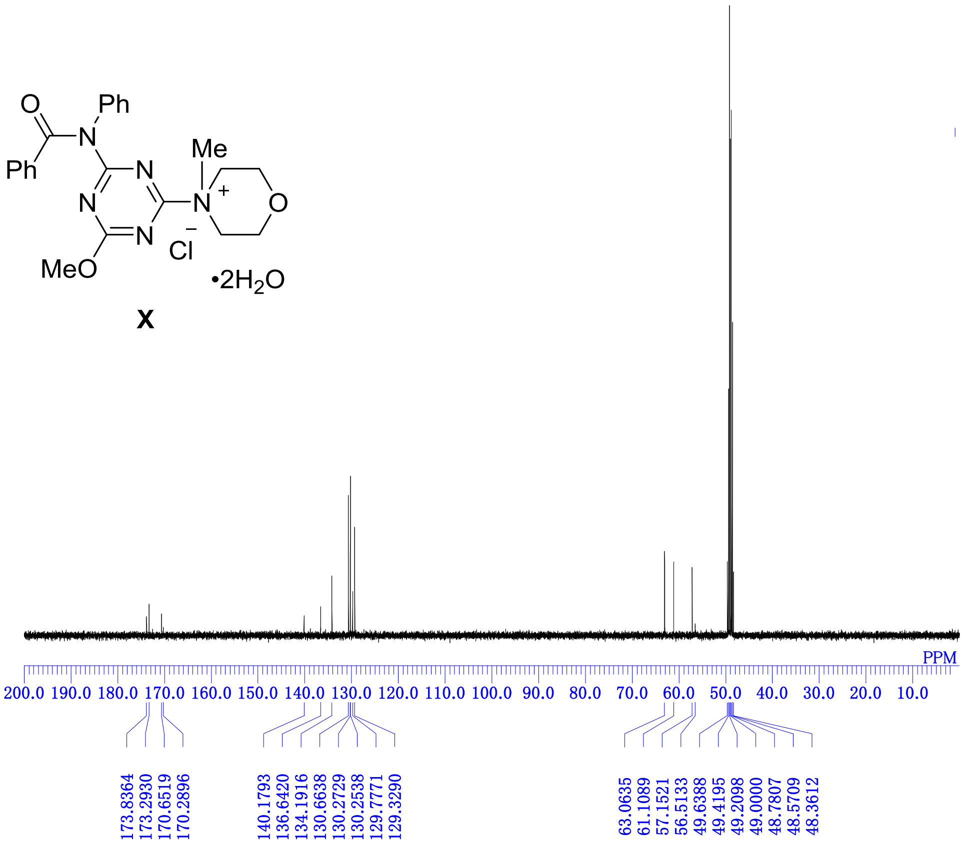
N
Ph
Me
N
N
N
+
O
N
N
−
Cl
MeO
•2H2O

X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160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
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173.2930
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130.2729
130.2538
129.7771
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49.0000
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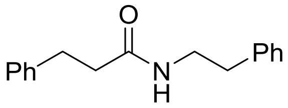
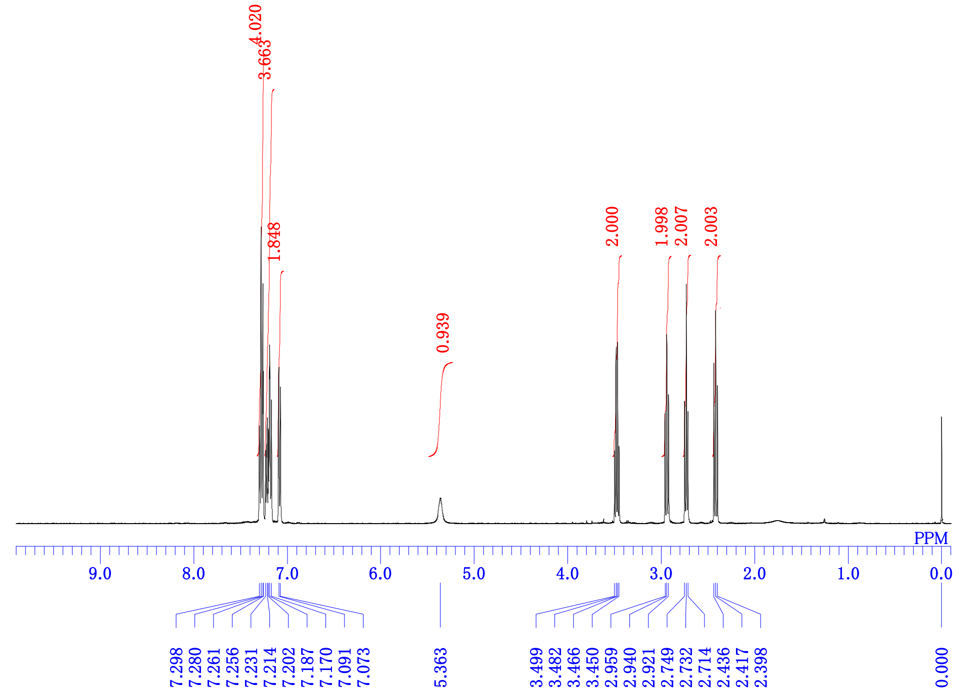
48.3612


O
Ph
N
H
Ph

3a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2.003
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7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
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7.261
7.256
7.231
7.214
7.202
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7.170
7.091
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3.482
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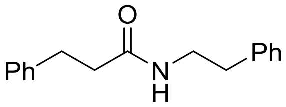
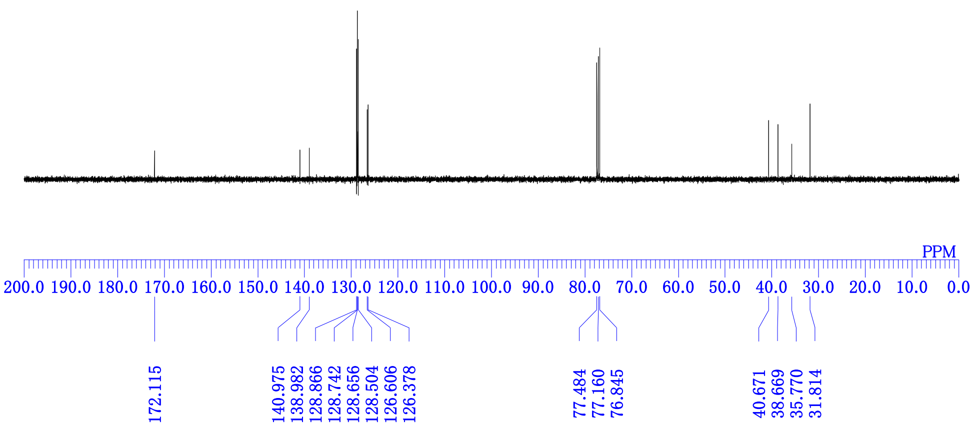

O
Ph
N
H
Ph

3a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180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
172.115
140.975
138.982
128.866
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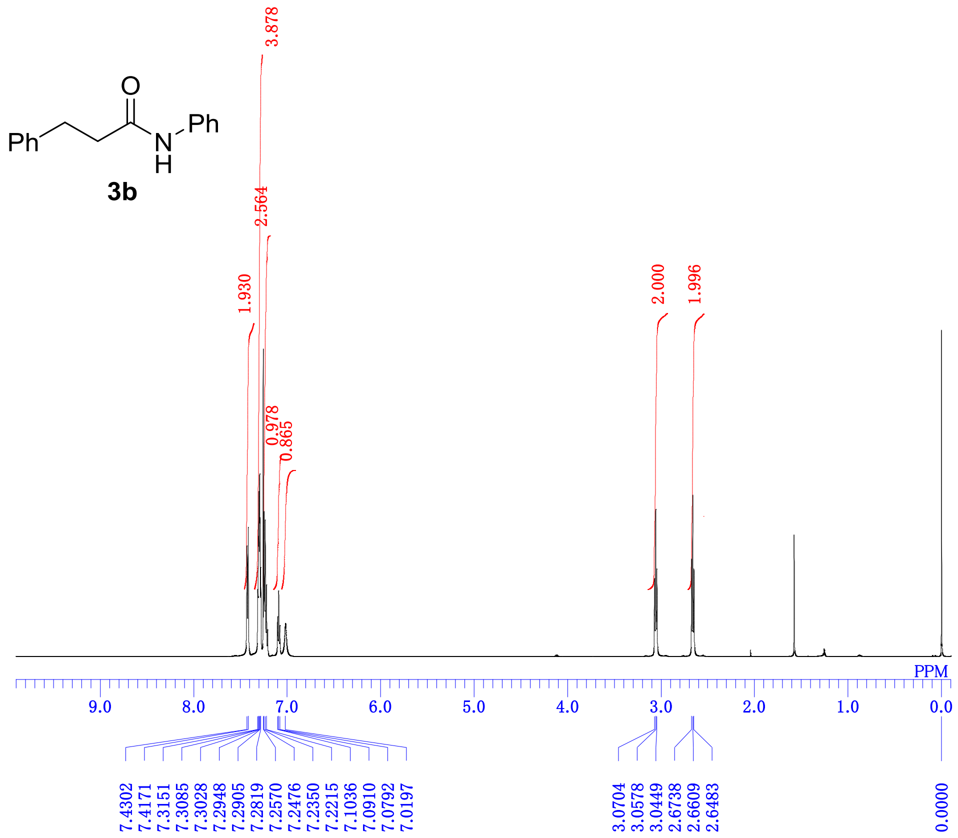
31.814


Ph
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N
H
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1.996
PPM
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7.0
6.0
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4.0
3.0
2.0
1.0
0.0
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7.4171
7.3151
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7.3028
7.2948
7.2905
7.2819
7.2570
7.2476
7.2350
7.2215
7.1036
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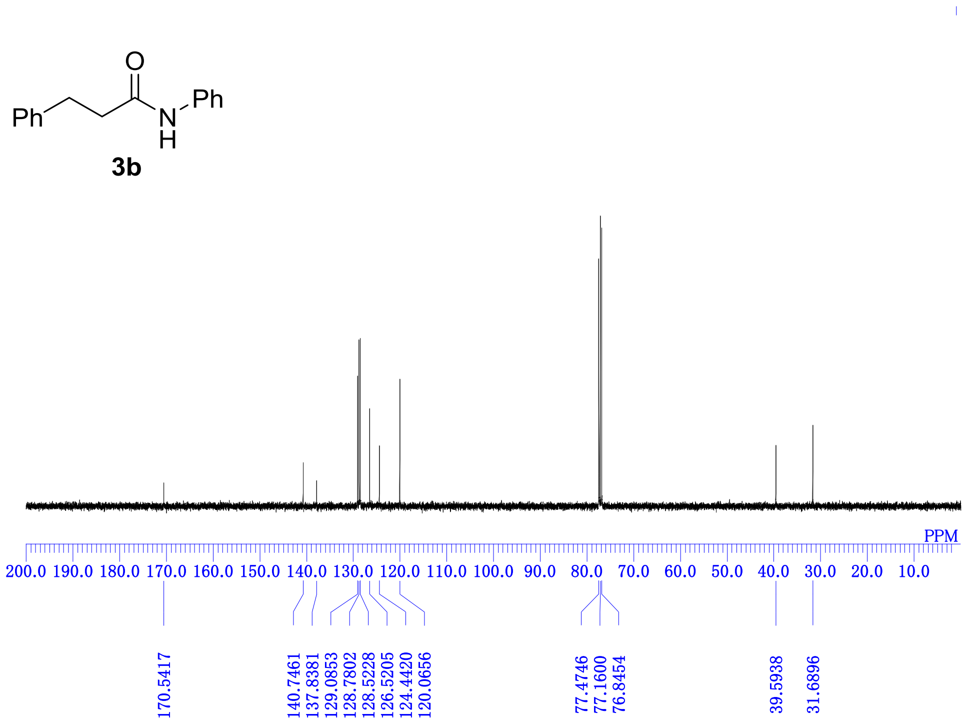
Ph
O
N
H
Ph
3b
PPM
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170.0
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150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
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50.0
40.0
30.0
20.0
10.0
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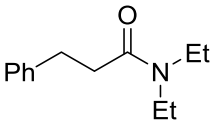
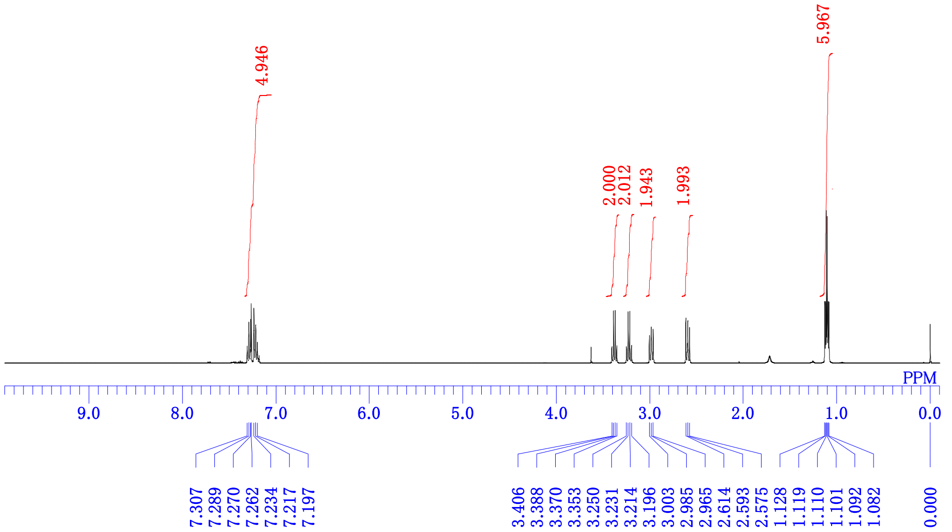


3c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4.0
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0.0
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7.262
7.234
7.217
7.197
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3.370
3.353
3.250
3.231
3.214
3.196
3.003
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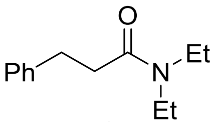
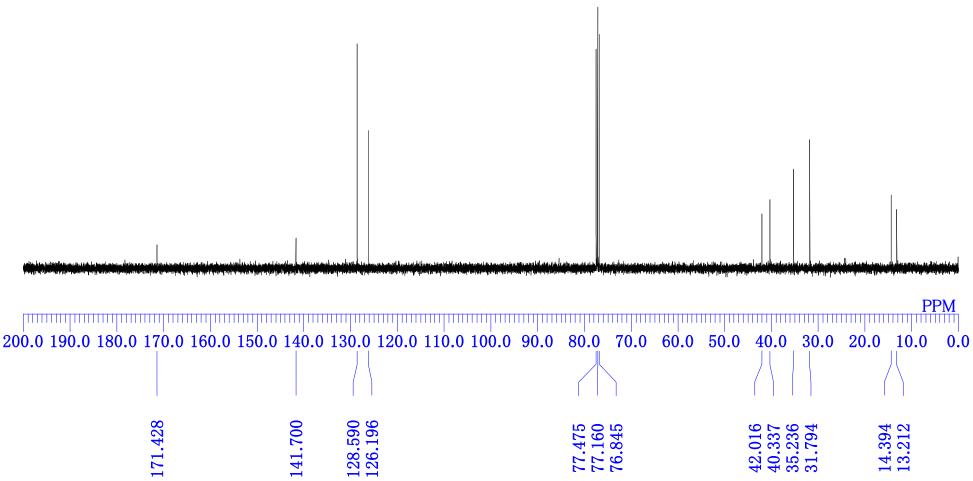
1.119
1.110
1.101
1.092
1.082
0.000



3c


PPM
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130.0
120.0
110.0
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90.0
80.0
70.0
60.0
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10.0
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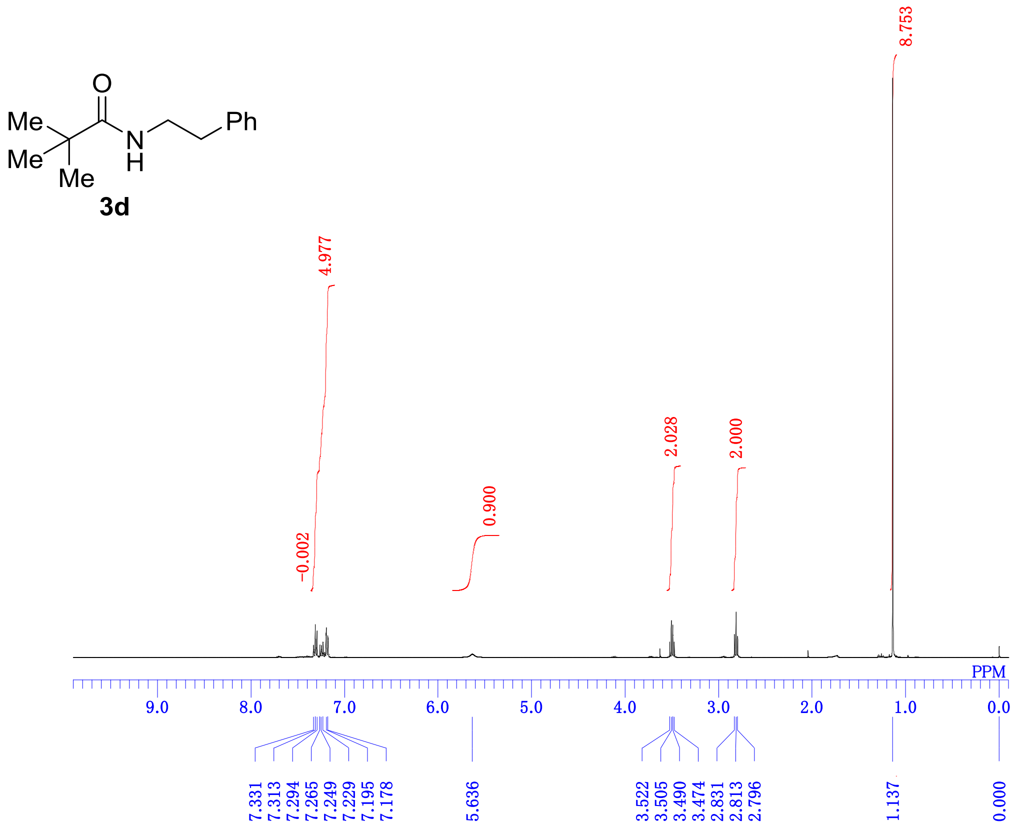
13.212


3d

O
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Me
Me
N
H
Ph
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-0.002
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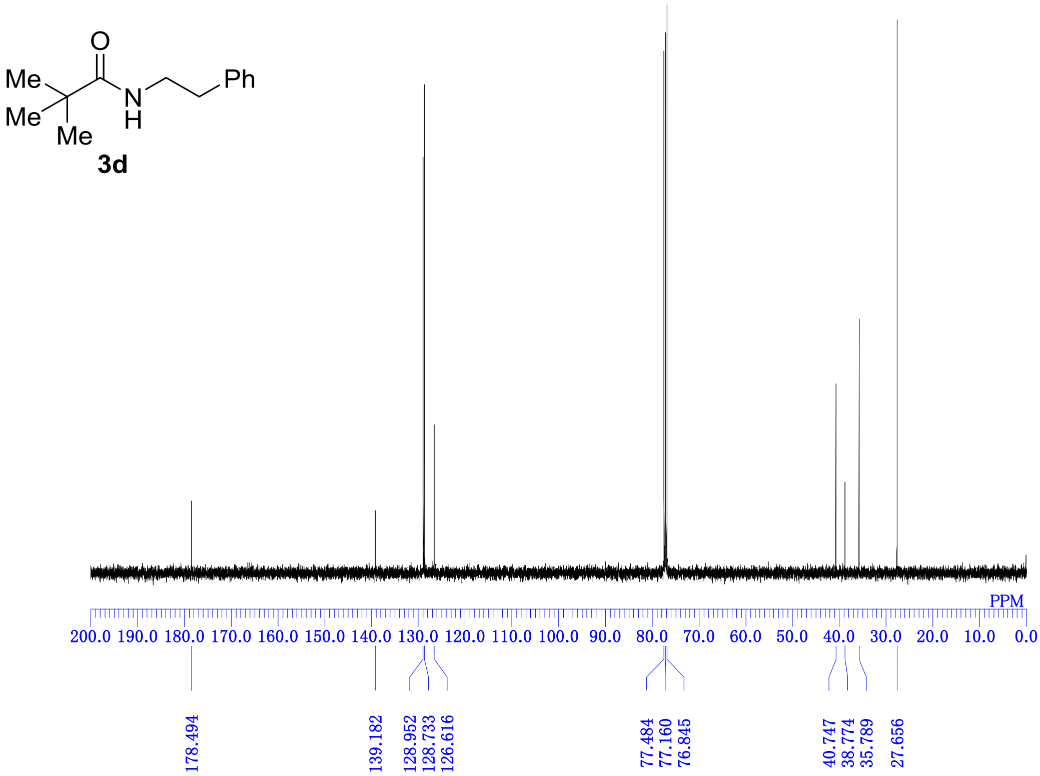
3d

O
Me
Me
Me
N
H
Ph
PPM
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180.0
170.0
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150.0
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120.0
110.0
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90.0
80.0
70.0
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20.0
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0.0
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77.160
76.845
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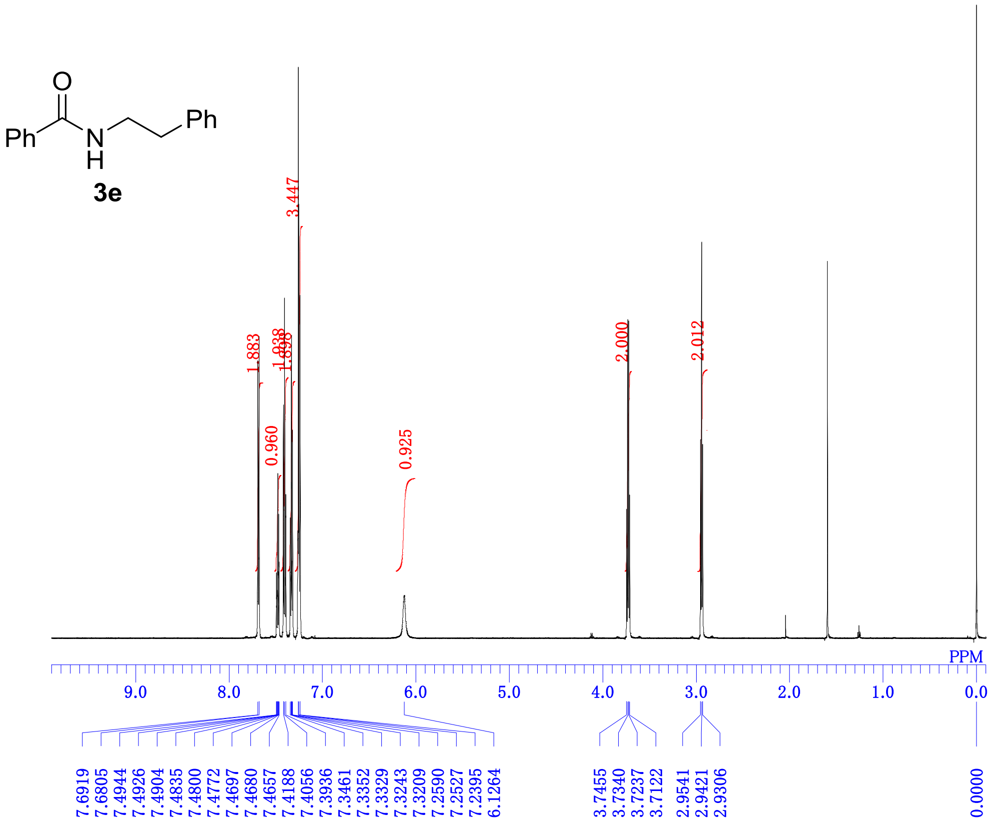
38.774
35.789
27.656



3e

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1.098
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2.012
PPM
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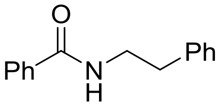
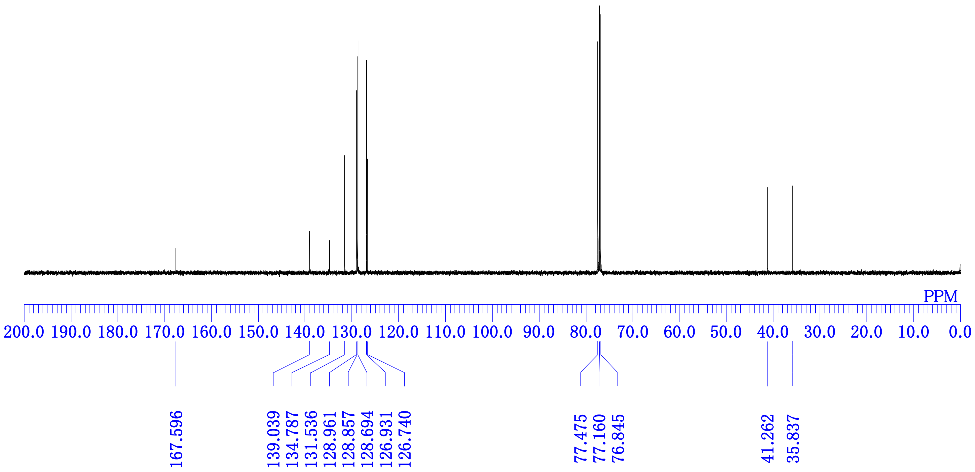


3e



PPM
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150.0
140.0
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120.0
110.0
100.0
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80.0
70.0
60.0
50.0
40.0
30.0
20.0
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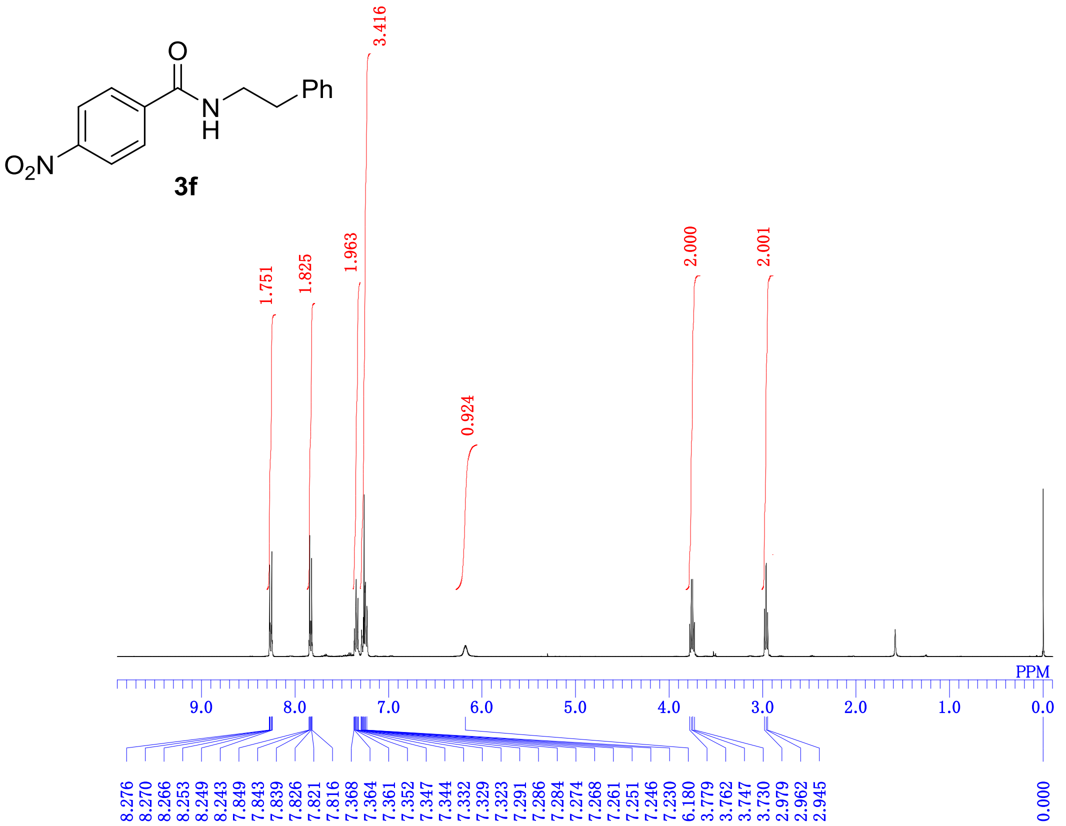
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H
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7.347
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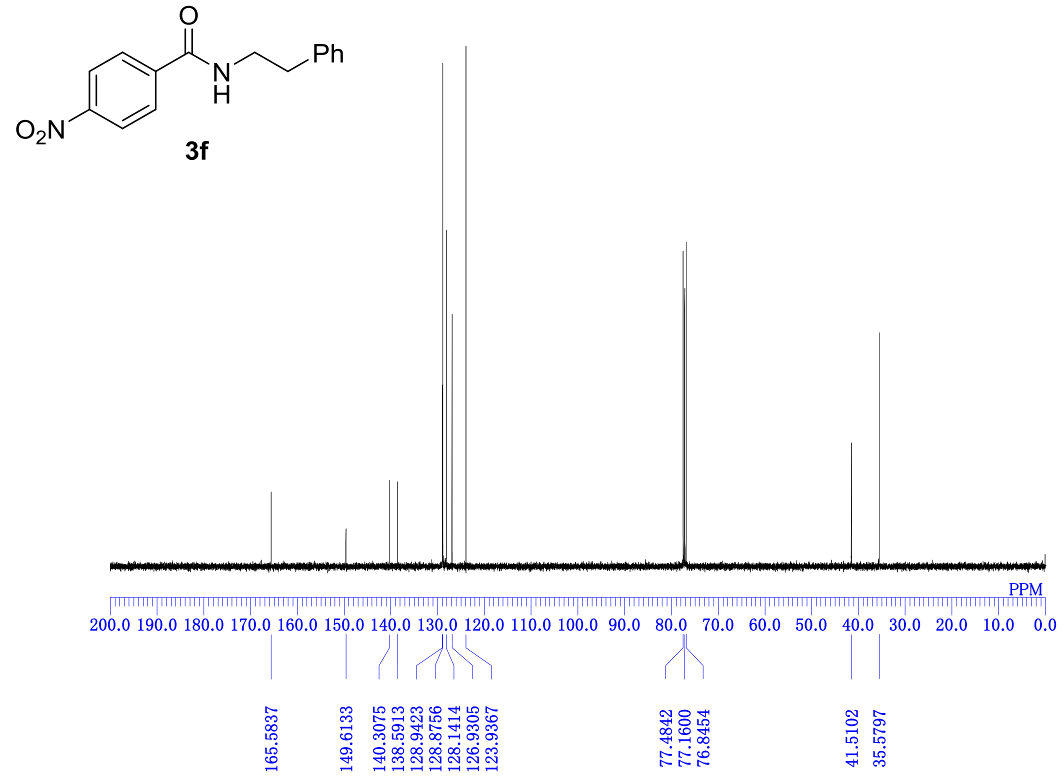
O
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O2N
3f
PPM
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180.0
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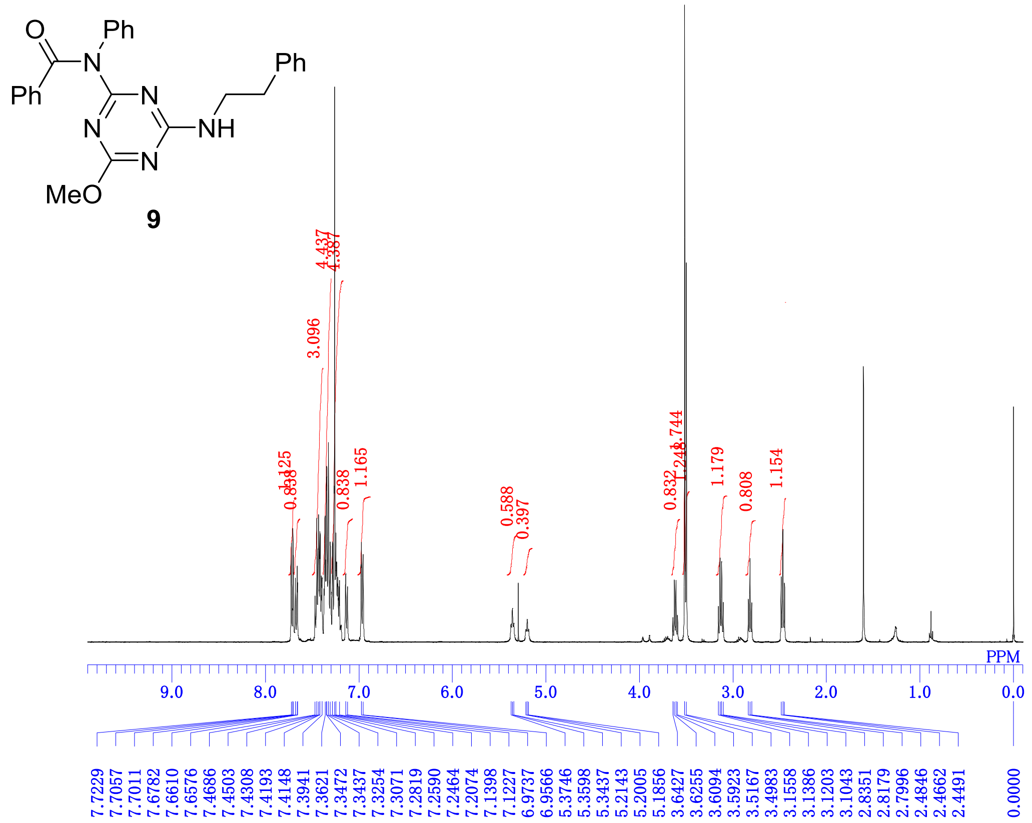
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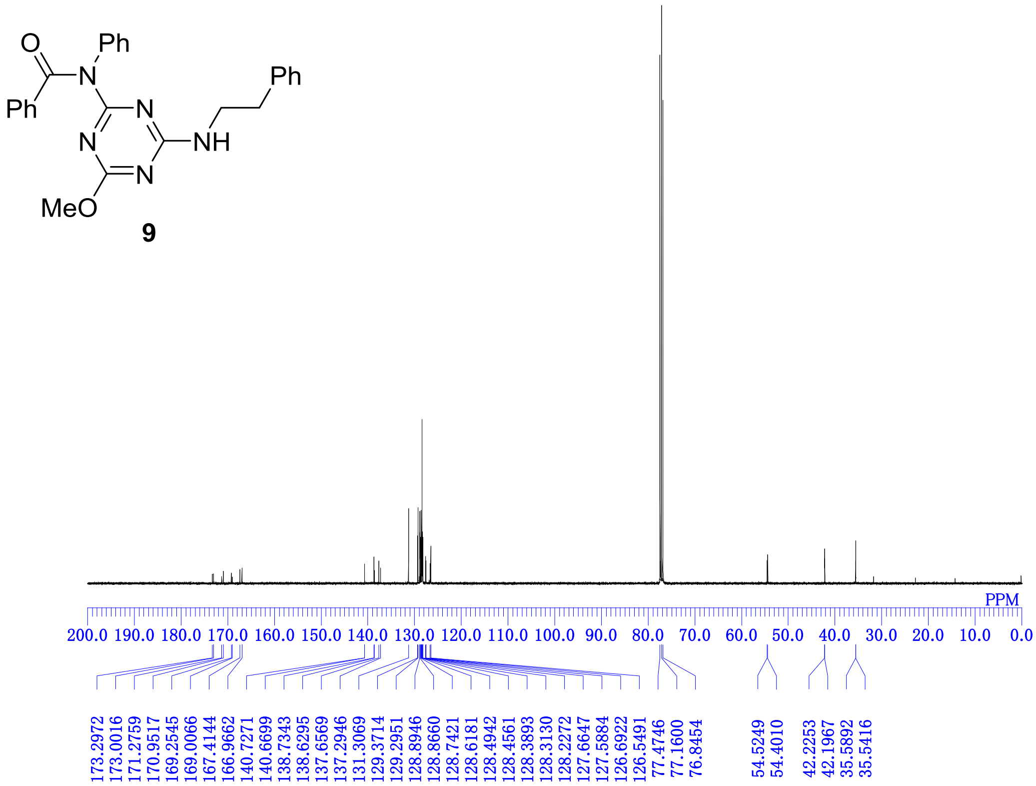
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