Supplementary Material

Gold catalyzed synthesis of tetrahydropyrimidines and octahydroquinazolines under ball milling conditions and evaluation of anticonvulsant potency

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Materials, methods and instruments

All commercially available solvents and reagents were used without further purification. Melting points were determined in capillary tubes and are uncorrected. Mechanochemical reactions were accomplished in a Fritsch ‘‘Pulverisette 7 classic line’’ (Fritsch GmbH, Idar-Oberstein, Germany) planetary ball mill using 45 mL grinding beakers (agate) and milling balls (6 X 15 mm; agate). All reaction vessels were cleaned with aqua regia prior to use to avoid any contamination or memory effects. Infrared (IR) spectra were recorded on a Perkin-Elmer FTIR spectrophotometer as neat samples. ^{1}H and ^{13}C NMR spectra were obtained in CDCl3 on a Bruker spectrometer at 500 and 125 MHz, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in parts per million. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet). Coupling constants (J) are given in hertz. Mass spectra were recorded on a PE-SCIEX API 300 mass spectrometer. HRMS data were collected on a maxis 10138 mass spectrometer. Elemental analyses were recorded using a ThermoFinnigan FLASH EA 1112CHN analyzer. All the compounds gave C, H and N analysis within ±0.5% of the theoretical values. Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany) using analytical grade solvents and visualized with iodine spray (10% (w/w) I_2 in silica gel) or UV light (λ = 254 and 365 nm).

Experimental procedure for the synthesis of 1,3-symmetrically substituted tetrahydropyrimidines **3a-g**:
The grinding beakers (45 mL; agate) were equipped with 6 milling balls of the same material (*d* = 15 mm). Alkyl but-2-ynedioate **1** (1 mmoL), amine **2** (2 mmoL), $NaAuCl_4.2H_2O$ (1 mol%) and formaldehyde (2 mmoL) were added in the given order. Ball-milling was carried out at 400 rpm for 5 min. Then the residue was dissolved in ethyl acetate (20 mL) and extracted with water (3 X 15 mL). The organic layer was dried over anhydrous Na_2SO_4 and removed the solvent under reduced pressure to afford the crude product, which was purified by flash column chromatography using ethyl acetate: petroleum ether (10:90) as elutent to obtain tetrahydropyrimidines **3a-g**.

Diethyl 1,3-diphenyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **(3a)**
Viscous yellowish liquid; IR (neat) ν_{max}: 2984, 1740, 1693, 1597, 1495, 1274, 1167, 1109, 1042. cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 0.98 (t, 3H, *J* = 6.8 Hz), 1.27 (t, 3H, *J* = 6.8 Hz), 4.02 (q, 2H, *J* = 6.8 Hz,), 4.18 (q, 2H, *J* = 6.8 Hz), 4.26 (s, 2H), 4.90 (s, 2H), 6.85-6.93 (m, 3H), 7.01 (d, 2H, *J* = 7.6 Hz), 7.14-7.29 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 13.6, 14.4, 47.6, 60.3, 61.7, 68.7, 100.8, 117.7, 121.1, 125.3, 126.5, 129.3, 129.4, 143.7, 146.5, 148.3, 164.0, 165.7.; MS: *m/z* = 381 $(M+1)^+$. Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36%. Found: C, 69.51; H, 6.28; N,7.43%.

Diethyl 1,3-dibenzyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **(3b)**

Viscous yellow liquid; IR (neat) ν_{max}: 3350, 2979, 1731, 1684, 1585, 1448, 1366, 1279, 1261, 1111, 1036, 1042, 745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.22 (t, 3H, J = 7.6 Hz), 1.30 (t, 3H, J = 6.8 Hz), 3.57 (s, 2H), 3.61 (s, 2H), 3.83 (s, 2H) , 4.12 (q, 2H, J = 6.8 Hz,), 4.17 (s, 2H), 4.35 (q, 2H, J = 7.6 Hz), 7.16-7.31 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 14.5, 48.6, 54.1, 57.1, 59.7, 62.1, 66.1, 92.5, 127.3, 128.0, 128.1, 128.3, 128.4, 128.7, 136.4, 138.1, 148.2, 165.2, 166.4.; MS: *m/z* = 409 $(M^+ +1)^+$. Anal. Calcd for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86%. Found: C, 70.62; H, 6.95; N, 6.78%.

Dimethyl 1,3-di-tert-butyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **(3c)**

Viscous yellowish liquid; IR (neat) ν_{max}: 2982, 1741, 1694, 1631, 1585, 1372, 1284, 1110, 1031, 765 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.09 (s, 9H), 1.28 (s, 9H), 3.32 (s, 2H),3.63 (s, 3H), 3.73 (s, 2H), 3.76 (s, 3H,); ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.0, 29.8, 45.4, 51.2, 52.6, 53.1, 61.6, 67.6, 108.1, 147.8, 166.8, 168.5.; MS: *m/z* = 313 $(M^+ +1)$. Anal. Calcd for $C_{16}H_{28}N_2O_4$: C, 61.51; H, 9.03; N, 8.97%. Found: C, 61.57; H, 9.07; N,8.90%.

Dimethyl 1,3-dibenzyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **(3d)**

Viscous yellow liquid; IR (neat) ν_{max}: 3062, 2983, 1736, 1679, 1587, 1497, 1392, 1287, 1259, 1076, 1042 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.55 (s, 2H), 3.60 (s, 2H), 3.65 (s, 3H), 3.84 (s, 2H), 3.91 (s, 3H), 4.16 (s, 2H), 7.15-7.19 (m, 2H), 7.21-7.34 (m, 8H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ 48.3, 51.2, 53.0, 54.3, 57.0, 66.0, 92.0, 127.4, 128.0, 128.3, 128.4, 128.8(2C), 136.2, 138.0, 148.2, 165.7, 167.; MS: *m/z* = 381 $(M^+ +1)$. Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36%. Found: C, 69.51; H, 6.28; N, 7.43%.

Diethyl 1,3-bis(2-chlorophenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **(3e)**

Viscous yellow liquid; IR (neat) ν_{max}: 2966, 1738, 1695, 1590, 1476, 1271, 1109, 1033, 857, 752 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.92 (t, 3H, J = 6.9Hz), 1.26 (t, 3H, J = 6.9 Hz), 3.92-4.01(m, 2H), 4.19-4.23 (m, 4H), 4.74 (d, 1H, J = 12.2 Hz), 4.88 (d, 1H, J = 12.2 Hz), 6.66-6.76 (m, 2H), 6.80 (d, 1H, J = 9.2 Hz), 6.99 (t, 2H, J = 7.6 Hz), 7.09-7.18 (m, 2H), 7.32-7.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.5, 14.3, 48.7, 60.4, 61.6, 68.8, 112.0, 122.7, 124.9, 127.1, 127.6, 127.9, 128.6, 129.5, 129.9, 130.2, 130.7, 140.3, 145.7, 146.7, 163.4, 165.6.; MS: *m/z* = 449 $(M^+ +1)$ 451 $(M^+ +3)$, 453 $(M^+ +5)$. Anal. Calcd for $C_{22}H_{22}Cl_2N_2O_4$: C, 58.51; H, 4.94; N, 6.23%. Found: C, 58.87; H, 4.86; N, 6.29%.

Dimethyl 1,3-diphenyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **(3f)**

Viscous yellow liquid; IR (neat) ν_{max}: 2982, 1739, 1695, 1583, 1484, 1267, 1158, 1109, 1042 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.57 (s, 3H), 3.73 (s, 3H), 4.26 (s, 2H), 4.91 (s, 2H), 6.86-6.93 (m, 3H), 6.97-7.01 (m, 2H), 7.15-7.29 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 47.5, 51.6, 52.6, 68.8, 100.5, 117.8, 121.2, 124.9, 126.5, 129.3, 143.6, 146.6, 148.2, 164.6, 166.2.; MS: *m/z* = 353 (M^++1). Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95%. Found: C, 68.23; H, 5.66; N, 7.97%.

Diethyl 1,3-di-tert-butyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **(3g)**

Viscous yellow liquid; IR (neat) ν_{max}: 2976, 2918, 1738, 1695, 1628, 1585, 1366, 1280, 1109, 1031, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.09 (s, 9H), 1.21 (t, 3H, *J* = 6.9Hz), 1.28-1.33 (m, 12H), 3.33 (s, 2H), 3.70 (s, 2H), 4.09 (q, 2H, *J* = 6.9 Hz,), 4.21 (q, 2H, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.7, 14.4, 26.6, 29.9, 45.5, 53.5, 59.1, 60.0, 61.6(2C), 108.9, 147.7, 166.5, 168.; MS: *m/z* = 341 (M^++1). Anal. Calcd for $C_{18}H_{32}N_2O_4$: C, 63.50; H, 9.47; N, 8.23%. Found: C, 63.45; H, 9.54; N, 8.28%.

Experimental procedure for the synthesis of 1,3-unsymmetrically substituted tetrahydropyrimidines **5a-e**:

The grinding beakers (45 mL; agate) were equipped with 6 milling balls of the same material (*d* = 15 mm). Alkyl but-2-ynedioate **1** (1 mmoL), amine **2** (1 mmoL), $NaAuCl_4.2H_2O$ (1 mol%) were added in the given order and ball-milled quickly for 1 min at 400 rpm. Then to this mixture was added another amine **2** (1 mmoL) and formaldehyde (2 mmoL) and ball-milled for 5 min at 400 rpm. The residue was dissolved in ethyl acetate (20 mL) and extracted with water (3 X 15 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography using ethyl acetate: petroleum ether (10:90) as elutent to afford tetrahydropyrimidines **5a-e**.

Diethyl 1-benzyl-3-phenyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **(5a)**

Viscous yellow liquid; IR (neat) ν_{max}: 2926, 2851, 1741, 1694, 1586, 1496, 1253, 1107, 1056, 761, 699.cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.02 (t, 3H, *J* = 6.9 Hz), 1.22 (t, 3H, *J* = 7.6 Hz), 3.71(s, 2H), 3.81(s, 2H), 4.05 (q, 2H, *J* = 6.9 Hz,), 4.13 (q, 2H, *J* = 7.6 Hz), 4.33 (s, 2H), 7.12-7.32 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.6, 14.4, 49.1, 56.8, 60.0, 61.6, 69.7, 98.0, 125.2, 126.2, 127.4, 128.4, 129.0, 129.2, 137.9, 143.9, 145.8, 164.2, 166.3.; MS: *m/z* = 395 (M^++H). Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10%. Found: C, 70.08; H, 6.72; N, 7.17%.

Diethyl 3-benzyl-1-phenyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **(5b)**

Viscous yellow liquid; IR (neat) ν_{max}: 2987, 2918, 1728, 1685, 1590, 1447, 1361, 1258, 1157, 1104, 1028, 747, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.25-1.32 (m, 6H), 4.10 (s, 2H), 4.19(q, 2H, *J* = 6.9 Hz,), 4.22 (s, 2H), 4.31 (q, 2H, *J* = 6.8 Hz), 4.40 (s, 2H), 6.79 (d, 2H, *J* = 8.4 Hz), 6.88 (t, 1H, *J* = 6.9 Hz), 7.17-7.31(m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 14.5, 46.5, 54.3, 60.0, 62.1, 65.4, 95.5, 117.7, 121.0, 127.9, 128.0, 128.8,129.3, 136.1, 148.4, 148.8, 165.0, 165.8.; MS: *m/z* = 395 (M^++H). Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10%. Found: C, 70.09; H, 6.69; N,7.06%.

Diethyl 1-(tert-butyl)-3-phenyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **(5c)**

Viscous yellow liquid; IR (neat) ν_{max}: 3052, 2980, 2918, 1738, 1685, 1587, 1499, 1386, 1221, 1039, 946, 783 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.99 (t, 3H, *J* = 6.9 Hz), 1.09 (s, 9H), 1.22 (t, 3H, *J* = 6.9 Hz), 3.62 (s, 2H) 4.02 (q, 2H, *J* = 6.9 Hz), 4.14 (q, 2H, *J* = 6.9 Hz), 4.30 (s, 2H), 7.01-7.08 (m, 3H), 7.21-7.26 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.6, 14.3, 27.1, 44.1, 53.7, 60.1, 61.5, 66.5, 103.7, 124.6, 125.8, 129.1, 143.9, 145.9, 164.6, 166.; MS *m/z* = 361 (M^++H). Anal. Calcd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77%. Found: C, 66.70; H, 7.78; N, 7.84%.

Diethyl 1-(2-chlorophenyl)-3-phenyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **(5d)**

Viscous yellow liquid; IR (neat) ν_{max}: 3375, 2980, 1738, 1694, 1588, 1495, 1671, 1258, 1109, 861, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.97 (t, 3H, *J* = 7.6 Hz), 1.25 (t, 3H, *J* = 6.9 Hz), 4.03 (q, 2H, *J* = 7.6 Hz,), 4.18-4.12 (m, 4H), 4.84 (s, 2H), 6.89 (d, 2H, 7.6 Hz), 6.97 (t, 1H, *J* = 7.6 Hz), 7.10 (t, 1H, *J* = 7.6 Hz), 7.15-7.28 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.6,14.3, 48.9, 60.3, 61.7, 69.1, 100.0, 122.6, 124.9, 125.4, 126.4, 127.7, 128.7, 129.1, 130.7, 143.3, 145.9, 146.8, 163.9, 165.7.; MS: *m/z* = 415 (M^++H), 417 (M^{++}+H). Anal. Calcd for $C_{22}H_{23}ClN_2O_4$: C, 63.69; H, 5.59; N, 6.75%. Found: C, 63.56; H, 5.69; N, 6.89%.

Diethyl 3-(2-chlorophenyl)-1-phenyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **(5e)**

Viscous yellow liquid; IR (neat) ν_{max}: 3382, 3052, 2981, 1733, 1694, 1593, 1109, 1038, 861, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.98 (t, 3H, *J* = 7.6 Hz), 1.27 (t, 3H, *J* = 6.8 Hz), 4.02 (q, 2H, *J* = 7.6 Hz,), 4.20 (q, 2H, *J* = 6.8 Hz), 4.26 (s, 2H), 4.90 (s, 2H), 6.85-6.92 (m, 3H), 7.00 (d, 2H, *J* = 7.6 Hz), 7.15-7.29 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.6,14.4, 47.6, 60.3, 61.6, 68.7, 100.8, 117.7, 121.1, 125.3, 125.4, 126.4, 126.5, 129.2, 129.3, 143.7, 146.5, 148.3, 164.0, 165.7.; MS: *m/z* = 415 (M^++1) and 417 (M^{++}+1). Anal. Calcd for $C_{22}H_{23}ClN_2O_4$: C, 63.69; H, 5.59; N, 6.75%. Found: C, 63.75; H, 5.52; N, 6.81%.

Experimental procedure for the synthesis of 5-oxo-octahydroquinazolines **8a-k:**

The grinding beakers (45 mL; agate) were equipped with 6 milling balls of the same material (d = 15 mm). Dimedone **6** (1 mmoL), amine **2a** (1 moL) and $NaAuCl_4.2H_2O$ (1 mol%) was ball-milled for 30 min at 400 rpm. Then to this mixture was added amine **2a** (1 mmoL) and formaldehyde (2 mmoL) and ball-milled for further 30 min at 400 rpm. Afterwards, the residue was dissolved in ethyl acetate (20 mL) and extracted with water (3 X 15 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give crude product, which was purified by flash column chromatography using ethyl acetate/petroleum ether (20:80) as elutent to obtain 5-oxo-octahydroquinazolines **8a**-**k**.

7,7-dimethyl-1,3-diphenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one **(8a)**

Yellow viscous oil; IR (neat) ν_{max}: 3056, 2953, 2873, 1647, 1573, 1495, 1396, 1290, 1154, 757, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.93 (6H, s), 2.00 (2H, s), 2.22 (2H, s), 4.31 (2H, s), 4.94 (2H, s), 6.89 (1H, t, J = 6.9 Hz), 6.97 (4H, t, J = 8.4 Hz), 7.24 (2H, t, J = 8.4 Hz),7.30 (1H, t, J = 7.6 Hz), 7.37 (2H, t, J = 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.4, 32.7, 41.1, 45.6, 50.1, 70.2, 104.9, 117.7, 120.9, 127.3, 127.5, 129.3, 129.8, 142.8, 148.4, 157.4, 194.2; MS: *m/z* = 333 (M^++H^+); Anal.Calcd for $C_{22}H_{24}N_2O$: C, 79.48; H, 7.28; N 8.43%; Found: C, 79.37; H, 7.34; N, 8.49%.

3-(4-bromophenyl)-7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one **(8b)**

Yellow viscous oil; IR (neat) ν_{max}: 3055, 2943, 1666, 1562, 1509, 1392, 1274, 1036, 819, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.92 (6H, s), 1.99 (2H, s), 2.21 (2H, s), 4.28 (2H, s), 4.90 (2H, s), 6.81 (2H, d, J = 9.2 Hz), 6.97 (2H, d, J = 9.1 Hz), 7.31 (3H, d, J = 9.2), 7.38 (2H, t, J = 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.4, 32.7, 41.1, 45.5, 50.0, 69.9, 104.5, 113.1, 119.4, 127.3, 127.6, 129.9, 132.1, 142.6, 147.5, 157.4, 194.2; MS: *m/z* = 411 (M^++H^+), 413 (M^{++}+H^+); Anal.Calcd for $C_{22}H_{23}BrN_2O$: C, 64.24; H, 5.64; N 6.81%; Found: C, 64.32; H, 5.61; N, 6.76%.

3-(4-methoxyphenyl)-7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one **(8c)**

Yellow viscous oil; IR (neat) ν_{max}: 3049, 2949, 1672, 1568, 1505, 1399, 1289, 1252, 1036, 829, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.92 (6H, s), 1.98 (2H, s), 2.21 (2H, s), 3.74 (3H, s), 4.23 (2H, s), 4.84 (2H, s), 6.78 (2H, d, J = 9.2 Hz), 6.92 (4H, t, J = 6.1 Hz), 7.27 (1H, t, J = 7.7 Hz), 7.34 (2H, t, J = 7.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.4, 32.7, 41.1, 46.0, 50.1, 55.5, 71.4, 104.5, 114.5, 119.7, 127.4, 127.5, 129.7, 142.3, 142.8, 154.3, 157.5, 194.2; MS *m/z* = 363 (M^++H^+); Anal.Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N 7.73%; Found: C, 76.14; H, 7.28; N, 7.80%.

3-(2,4-dimethylphenyl)-7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one **(8d)**

Yellow viscous oil; IR (neat) ν_{max}: 2938, 2227, 1638, 1564, 1495, 1394, 1289, 1204, 911, 821, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.00 (6H, s), 2.09 (2H, s), 2.21 (3H, s), 2.25 (4H, s),4.09 (2H, s), 4.60 (2H, s), 6.89 (4H, m), 7.00 (1H, d, J = 8.0 Hz), 7.25 (2H, t, J = 7.7 Hz),7.33 (2H, t, J = 7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.2, 20.7, 28.5, 32.7, 41.3, 47.6, 50.2, 71.2, 105.9, 117 120.4, 127.0, 127.2, 127.3, 129.7, 122.0, 133.2, 143.4,146.1, 157.3, 194.0; MS: *m/z* = 361 (M^++H^+); Anal.Calcd for $C_{24}H_{28}N_2O$: C, 79.96; H, 7.83; N, 7.77%; Found: C, 79.87; H, 7.89; N, 7.70%.

3-(2-methoxyphenyl)-7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one **(8e)**

Yellow viscous oil; IR (neat) ν_{max}: 3042, 2947, 1681, 1564, 1505, 1493, 1289, 1242, 1105, 1024, 750, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.93 (6H, s), 2.00 (2H, s), 2.20 (2H, s), 3.70 (3H, s), 4.22 (2H, s), 4.85 (2H, s), 6.77-6.85 (4H, m), 6.94-7.00 (2H, m), 7.20 (1H, t, J = 6.8 Hz), 7.26 (2H, t, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.4, 32.7, 41.1, 46.7, 50.2, 55.5, 70.0, 104.9, 114.4, 120.1, 121.0, 123.7, 127.2, 127.3, 129.6, 137.5, 143.0, 152.0, 157.0, 194.2; MS: *m/z* = 363 (M^++H^+); Anal.Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N 7.73%; Found: C, 76.14; H, 7.28; N, 7.80%.

3-(2-chlorophenyl)-7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one **(8f)**

Yellow viscous oil; IR (neat) ν_{max}: 3071, 2957, 2350, 1659, 1569, 1505, 1484, 1422, 1394, 1289, 1209, 1039, 750, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.98 (6H, s), 2.05 (2H, s), 2.25 (2H, s), 4.23 (2H, s), 4.85 (2H, s), 6.83 (2H, d, J = 7.5 Hz) 6.96 (1H, t, J = 8.1 Hz) 7.12-7.18 (2H, m), 7.23 (1H, d, J = 6.8 Hz), 7.29 (3H, t, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.5, 32.6, 41.1, 47.3, 50.1, 70.2, 104.9, 122.0, 124.5, 127.3, 127.4, 127.6, 128.2, 129.7,130.8, 142.6, 146.0, 157.4, 194.2; MS: *m/z* = 367 (M^++H^+), 369 (M^{++}+H^+); Anal.Calcd for $C_{22}H_{23}ClN_2O$: C, 72.02; H, 6.32; N 7.73%; Found: C, 71.4; H, 6.26; N, 7.72%.

3-(2,4-dichlorophenyl)-7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one **(8g)**

Yellow viscous oil; IR (neat) ν_{max}: 3058, 2956, 1674, 1571, 1482, 1392, 1293, 1209, 1038, 821, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.97 (6H, s), 2.05 (2H, s), 2.24 (2H, s), 4.19 (2H, s), 4.81 (2H, s), 6.82 - 6.86 (2H, m) 7.10 - 7.15 (1H, m) (7.03 - 7.08 (1H, m) 7.22-7.27 (1H, m), 7.28 – 7.34 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.5, 32.6, 41.6, 47.3, 50.1, 70.0, 104.7, 127.2, 127.5, 127.6, 128.9 (2C), 130.5, 142.4, 144.9, 157.4, 194.0; MS: *m/z* = 401 (M^++H^+), 403 (M^{++}+H^+), 405 (M^{++++}+H^+); Anal.Calcd for $C_{22}H_{22}Cl_2N_2O$: C, 65.84; H, 5.53; N 6.98%; Found: C, 65.72; H, 5.59; N, 6.92%.

3-benzyl-7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one **(8h)**

Yellow viscous oil; IR (neat) ν_{max}: 2953, 2848, 1680, 1568, 1495, 1426, 1395, 1285, 1113, 742, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.01 (6H, s), 2.10 (2H, s), 2.23 (2H, s), 3.74 (2H, s), 3.80 (2H, s), 4.30 (2H, s), 7.08 (2H, d, J = 7.6 Hz), 7.32 (1H, t, J = 6.9 Hz), 7.26 – 7.33 (5H, m),7.37 (2H, t, J = 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.5, 32.8, 41.2, 47.5, 50.2, 57.2, 71.2, 103.5, 127.2, 127.3, 127.4, 128.5, 129.0, 129.7, 137.9, 142.9, 156.4, 194.5; MS: *m/z* = 347 (M^++H^+); Anal.Calcd for $C_{23}H_{26}N_2O$: C, 79.73; H, 7.56; N 8.09%; Found: C, 79.63; H, 7.51; N, 8.15%.

3-(tert-butyl)-7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one **(8i)**

Yellow viscous oil; IR (neat) ν_{max}: 2957, 1666, 1573, 1493, 1394, 1285,1204, 1119, 764, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.93 (6H, s), 1.11 (9H, s), 2.03 (2H, s), 2.17 (2H, s), 3.62 (2H, s), 4.23 (2H, s), 7.11 (2H, d, J = 7.6 Hz), 7.26 (1H, t, J = 6.6 Hz), 7.36 (2H, t, J = 7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.8, 28.5, 32.6, 41.0, 42.4, 50.1, 53.9, 67.4, 107.4, 126.9, 127.1, 129.6, 143.2, 157.0, 194.1; MS: *m/z* = 313 (M^++H^+); Anal.Calcd for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03; N 8.97%; Found: C, 76.98; H, 9.08; N, 8.91%.

1,3-bis(4-bromophenyl)-7,7-dimethyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one **(8j)**

Yellow viscous oil; IR(neat) ν_{max}: 3055, 2949, 2882, 2238, 1655, 1573, 1403, 1287, 1209, 1080, 918, 825, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.91 (6H, s), 1.96 (2H, s), 2.19 (2H, s), 4.22 (2H, s), 4.84 (2H, s), 6.76 (2H, d, J = 9.2 Hz), 6.83 (2H, d, J = 8.4 Hz), 7.28 (2H, d, J = 9.2 Hz), 7.87 (2H, d, J = 8.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.3, 32.8, 41.1, 45.5, 50.0, 69.9, 105.4, 113.2, 119.3, 121.2, 128.8, 132.2, 133.0, 141.7, 147.4, 156.9, 194.4; MS: *m/z* = 489 (M^++H^+), 491 (M^++H^+), 493 (M^++H^+); Anal.Calcd for $C_{22}H_{22}Br_2N_2O$: C, 53.90; H, 4.52. N 5.71%; Found: C, 53.76; H, 4.59; N, 5.87%.

1,3-bis(4-methoxyphenyl)-7,7-dimethyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one **(8k)**

Yellow viscous oil; IR (neat) ν_{max}: 3049, 2953, 1647, 1566, 1510, 1397, 1282, 1257, 1035, 833, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.86 (6H, s), 1.89 (2H, s), 2.14 (2H, s), 3.67 (3H, s), 3.72 (3H, s), 4.17 (2H, s), 4.75 (2H, s), 6.73 (2H, d, J = 9.1 Hz), 6.77-6.81 (4H, m), 6.86 (2H, d, J = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.4, 32.5, 41.0, 45.8, 49.9, 55.5(2C), 71.6, 103.7, 114.4, 114.8, 119.6, 128.6, 135.3, 142.3, 154.3, 158.2, 158.9, 193.8; MS: *m/z* = 393 (M^++H^+); Anal.Calcd for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19. N 7.14%; Found: C, 73.32; H, 7.28; N, 7.02%.

Table S1 The effect of compounds **3a-i**, **5a-e** and **8a-k** on seizures induced by MES in mice[a]

Entry	Treatment group	Dose level	Time (s) in various phases of convulsion (mean ± SEM)[b]		
			Flexion	Extensor	Clonus
1	**3a**[ns]	15 mg.kg^{-1}	4.80 ± 0.30	49.00 ± 0.20	3.20 ± 0.30
2	**3b**[ns]	15 mg.kg^{-1}	5.00 ± 0.20	50.00 ± 0.40	3.60 ± 0.10
3	**3c**[ns]	15 mg.kg^{-1}	5.60 ± 0.20	49.20 ± 0.30	3.10 ± 0.40
4	**3d**[ns]	15 mg.kg^{-1}	5.10 ± 0.10	48.50 ± 0.40	3.30 ± 0.50
5	**3e**[ns]	15 mg.kg^{-1}	5.20 ± 0.40	51.50 ± 0.10	3.60 ± 0.50
6	**3f**[ns]	15 mg.kg^{-1}	4.90 ± 0.60	49.10 ± 0.40	2.90 ± 0.60
7	**3g**[ns]	15 mg.kg^{-1}	5.10 ± 0.50	48.50 ± 0.10	3.40 ± 0.10
8	**3h**[ns]	15 mg.kg^{-1}	5.40 ± 0.50	44.10 ± 0.50	3.00 ± 0.40
9	**3i**[ns]	15 mg.kg^{-1}	5.50 ± 0.40	44.30 ± 0.20	3.30 ± 0.20
10	**5a**[*]	15 mg.kg^{-1}	5.20 ± 0.30	43.30 ± 0.20	3.10 ± 0.30
11	**5b**[*]	15 mg.kg^{-1}	5.00 ± 0.20	42.10 ± 0.30	2.90 ± 0.50
12	**5c**[*]	15 mg.kg^{-1}	5.10 ± 0.30	41.50 ± 0.10	3.60 ± 0.10
13	**5d**[*]	15 mg.kg^{-1}	5.00 ± 0.60	40.20 ± 0.50	3.50 ± 0.50
14	**5e**[*]	15 mg.kg^{-1}	4.90 ± 0.60	40.50 ± 0.30	3.10 ± 0.60
15	**8a**[**]	15 mg.kg^{-1}	4.80 ± 0.50	**36.20 ± 0.10**	3.40 ± 0.40
16	**8b**[**]	15 mg.kg^{-1}	5.60 ± 0.50	**37.40 ± 0.10**	3.30 ± 0.40
17	**8c**[**]	15 mg.kg^{-1}	5.50 ± 0.40	**34.50 ± 0.10**	3.10 ± 0.50
18	**8d**[**]	15 mg.kg^{-1}	5.40 ± 0.30	**35.40 ± 0.10**	3.00 ± 0.10
19	**8e**[**]	15 mg.kg^{-1}	5.10 ± 0.20	**38.10 ± 0.10**	3.60 ± 0.30
20	**8f**[**]	15 mg.kg^{-1}	5.20 ± 0.10	**36.10 ± 0.10**	3.40 ± 0.20
21	**8g**[**]	15 mg.kg^{-1}	5.30 ± 0.10	**38.30 ± 0.10**	3.20 ± 0.20
22	**8h**[**]	15 mg.kg^{-1}	5.00 ± 0.40	**35.40 ± 0.10**	3.10 ± 0.40
23	**8i**[**]	15 mg.kg^{-1}	5.50 ± 0.40	**34.50 ± 0.10**	3.30 ± 0.60
24	**8j**[**]	15 mg.kg^{-1}	5.50 ± 0.50	**39.21 ± 0.10**	3.40 ± 0.50
25	**8k**[**]	15 mg.kg^{-1}	5.10 ± 0.10	**35.20 ± 0.10**	3.30 ± 0.50
26	Phenytoin[c]	15 mg.kg^{-1}	5.70 ± 0.30	45.00 ± 0.20	3.50 ± 0.30
27	Tween 80[d]	0.5% W/V	11.10 ± 0.50	54.90 ± 0.50	7.50 ± 0.20

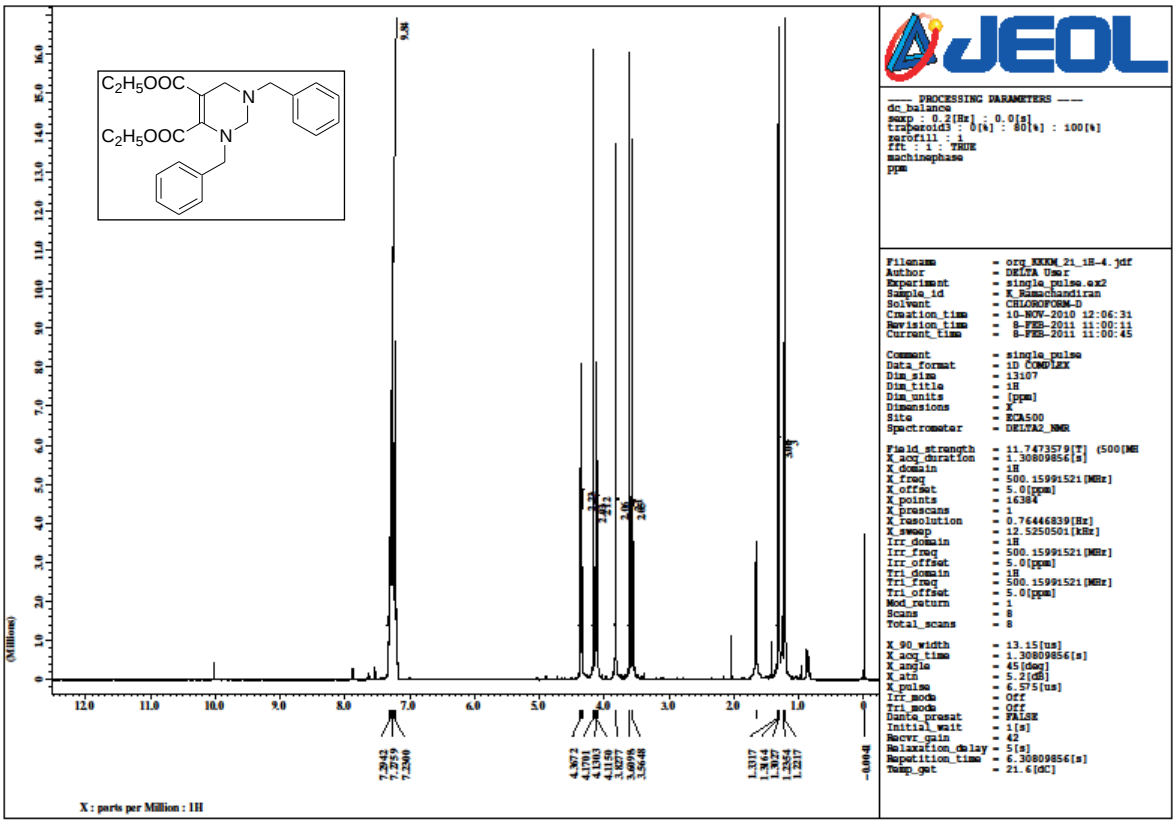
[a]Mortality = recovery

[b]Data were analyzed by one way ANNOVA followed by Dunnet;s test; ns: not significant, P value >0.05; *significant, P value <0.05; **highly significant, P value <0.001; SEM: Standard error of means

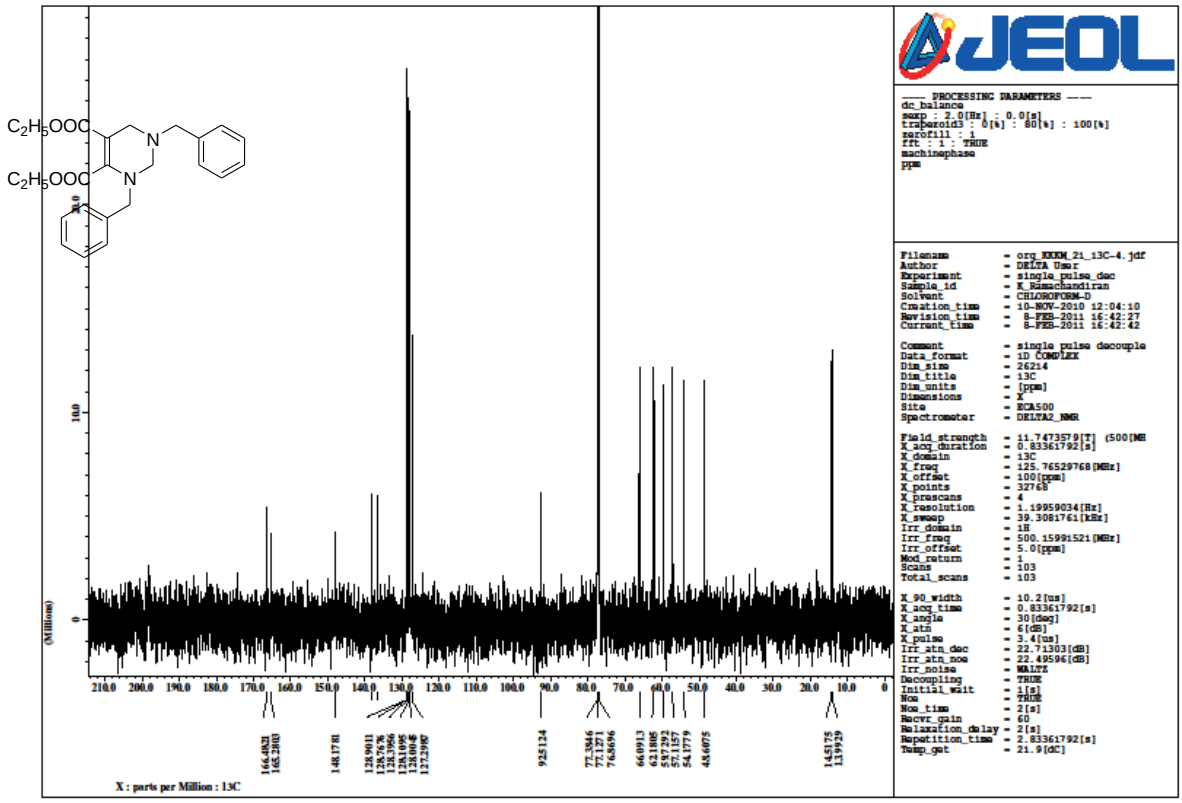
Bold values indicate the superior activity compared to the standard and other compounds

[c]Standard; [d]Control

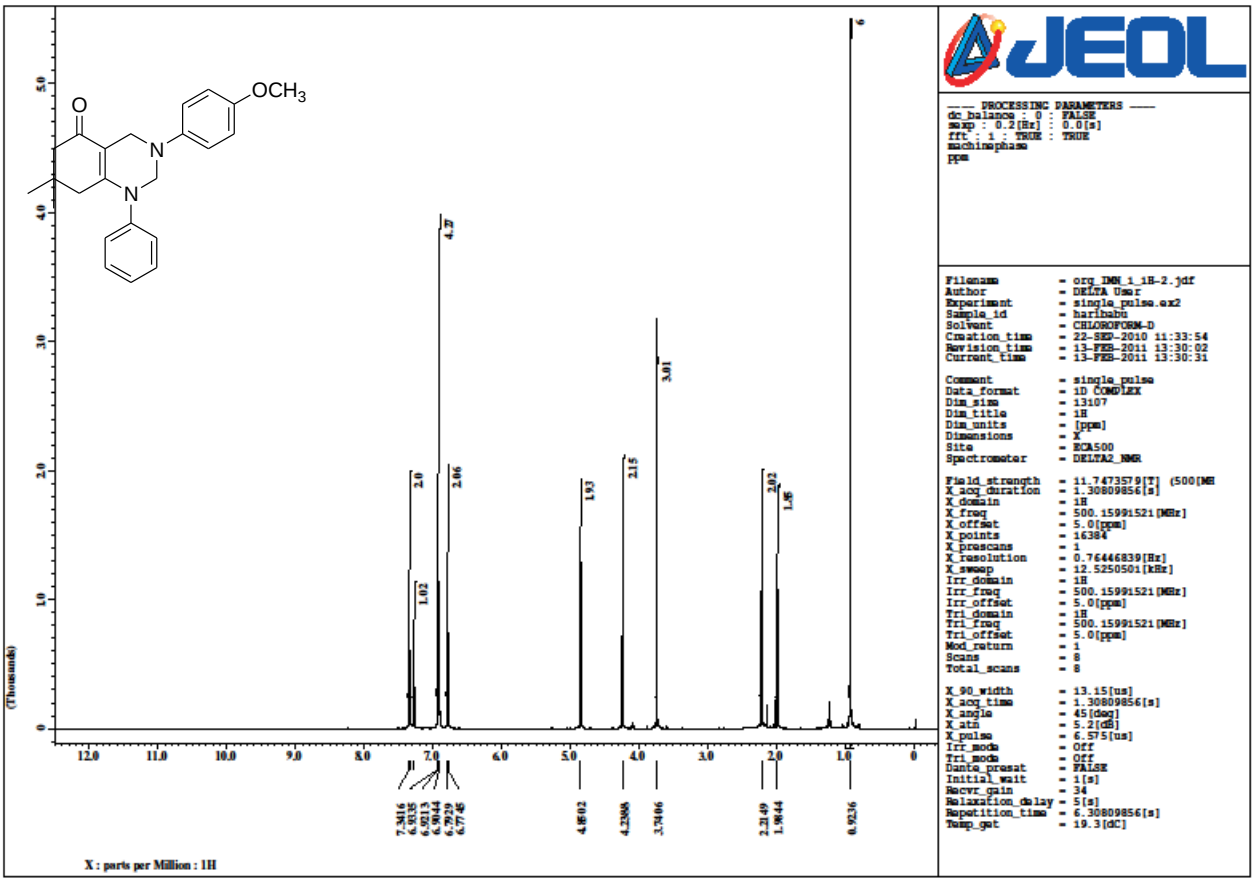
^{1}H NMR and ^{13}C NMR of selected compounds



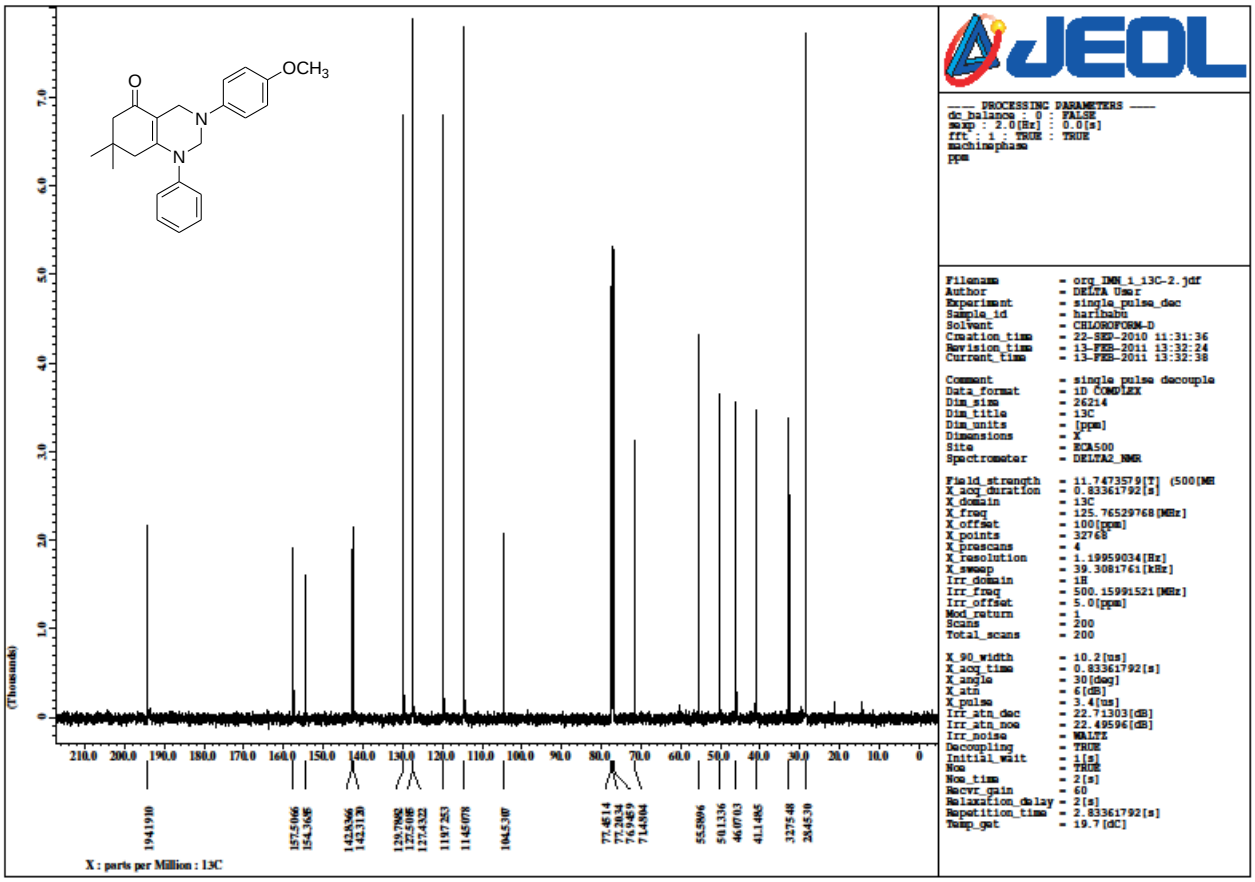
^{1}H NMR spectrum of tetrahydropyrimidine **3b**



^{13}C NMR spectrum of tetrahydropyrimidine **3b**



^{1}H NMR spectrum of tetrahydropyrimidine **8c**



^{13}C NMR spectrum of tetrahydropyrimidine **8c**