Electronic Supplementary Information

Synthesis of unsymmetrical urea derivatives *via* one-pot sequential three-component reactions of cyclic 2-diazo-1,3-diketones, carbodiimides, and 1,2-dihaloethanes

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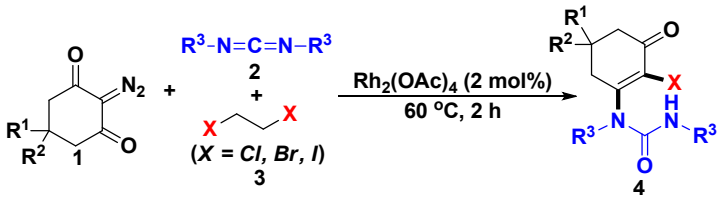
1. General information

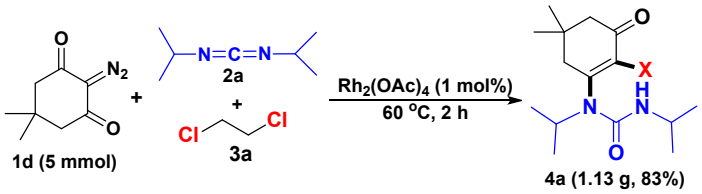
Reactions were monitored by using thin-layer chromatography (TLC) on commercial silica gel plates (GF 254). Visualization of the developed plates was performed under UV lights (GF 254 nm). Flash column chromatography was performed on silica gel (200-300 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts were expressed in parts per million (δ) and the signals were reported as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet), and coupling constants (J) were given in Hz. 13C{1H} NMR spectra were recorded at 100 MHz in $CDCl_3$ solution. Chemical shifts as internal standard was referenced to $CDCl_3$ (δ = 7.26 for 1H and δ = 77.16 for 13C{1H} NMR) as internal standard. HRMS analysis with a quadrupole time-of-flight mass spectrometer yielded ion mass/charge (m/z) ratios in atomic mass units. IR spectra were measured as dry films (KBr), and the peaks are reported in terms of wave number (cm^{-1}). The melting points were measured using SGWX-4 melting point apparatus.

2. General procedure for the synthesis of the urea dirivatives 4



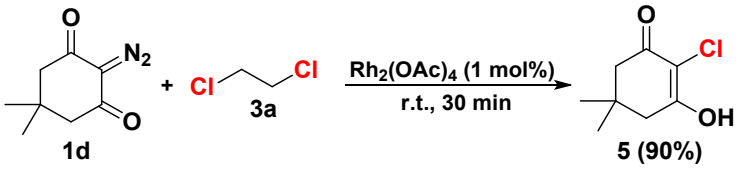
A mixture of cyclic 2-diazo-1,3-diketones **1** (0.5 mmol), carbodiimides **2** (0.5 mmol), and $Rh_2(OAc)_4$ (0.01 mmol) in 1,2-dihaloethane (2 mL) was heated to 60 °C in an oil bath for 2 h. After the reaction completed (as determined using TLC), the reaction mixture was cooled to room temperature, extracted with dichloromethane (3 × 10 mL), and washed with brine. The organic layers were combined, dried over Na_2SO_4, filtered, and then evaporated under vacuum. The residue was purified using flash column chromatography with a silica gel (200-300 mesh), using ethyl acetate and petroleum ether (1:6, v/v) as the elution solvent to give desired product **4**.

3. Procedure for the gram-scale synthesis



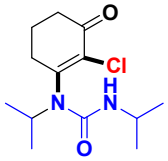
A mixture of 2-diazo-5,5-dimethylcyclohexane-1,3-dione **1d** (5 mmol), *N,N′*-methanediylidenebis(propan-2-amine) **2a** (5 mmol), and $Rh_2(OAc)_4$ (0.1 mmol) in 1,2-dichloroethane (10 mL) was heated to 60 °C in an oil bath for 2 h. After the reaction completed (as determined using TLC), the reaction mixture was cooled to room temperature, extracted with dichloromethane (3 × 20 mL), and washed with brine. The organic layers were combined, dried over Na_2SO_4, filtered, and then evaporated under vacuum. The residue was purified using flash column chromatography with a silica gel (200-300 mesh), using ethyl acetate and petroleum ether (1:6, v/v) as the elution solvent to give desired product **4a**.

4. Procedure for the synthesis of compound **5**

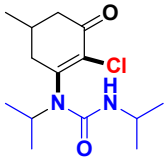


According to the reported literature,[1] the mixture of dry 1,2-dichloroethane (2.0 mL) and dirhodium tetraacetate (1.6 mg, 1 mol %) catalyst stirred in a resealable screw-capped Schlenk tube under N_2 at room temperature. 2-Diazo-5,5-dimethylcyclohexane-1,3-dione (50 mg, 0.30 mmol) was dissolved in the dried dichloroethane (1.0 mL) and added dropwise. After the reaction completed (as determined by TLC), the reaction mixture was extracted with ethyl acetate (3 × 10 mL), and washed with brine. The organic layers were combined, dried over Na_2SO_4, filtered, and then evaporated under vacuum to obtain the desired product **5** in 90% yield (47 mg). Known compound: mp 206-208 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.46 (s, 4H), 1.11 (s, 6H).

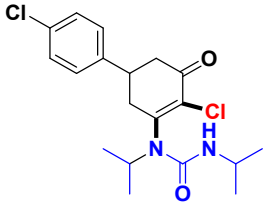
5. Characterization data for all products



1-(2-Chloro-3-oxocyclohex-1-en-1-yl)-1,3-diisopropylurea (**4a**). White solid (85%, 115 mg); R_f = 0.5 (petroleum ether/ethyl acetate 6:1); mp 72-73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29-4.18 (m, 1H), 4.11 (d, J = 6.9 Hz, 1H), 4.02-3.88 (m, 1H), 2.63 (t, J = 6.3 Hz, 4H), 2.09-2.00 (m, 2H), 1.30 (d, J = 6.9 Hz, 6H), 1.11 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.6, 156.6, 153.1, 131.3, 50.2, 42.5, 37.9, 33.2, 23.2, 21.3, 21.1; IR (KBr) ν 3509, 2319, 1731, 1666, 1616, 1484, 1366, 1320 cm^{-1}; HRMS (ESI) calcd for $[C_{13}H_{21}ClN_2O_2 + H]^+$ 273.1325, found 273.1320.

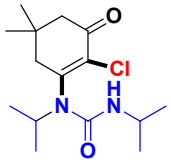


1-(2-Chloro-5-methyl-3-oxocyclohex-1-en-1-yl)-1,3-diisopropylurea (**4b**). White solid (83%, 118 mg); R_f = 0.5 (petroleum ether/ethyl acetate 6:1); mp 77-78 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.29-4.16 (m, 1H), 4.09 (d, J = 6.3 Hz, 1H), 3.99-3.87 (m, 1H), 2.76-2.61 (m, 2H), 2.40-2.27 (m, 2H), 1.30 (dd, J =3.0 Hz, J = 3.0 Hz, 6H), 1.10 (s, 6H), 1.08 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.6, 155.6, 153.1, 131.1, 50.2, 45.8, 42.5, 41.2, 28.8, 23.2, 21.4, 21.2, 20.5; IR (KBr) ν 3516, 2515, 1733, 1661, 1620, 1481, 1366, 1311 cm^{-1}; HRMS (ESI) calcd for $[C_{14}H_{23}ClN_2O_2 + H]^+$ 287.1482, found 287.1480.

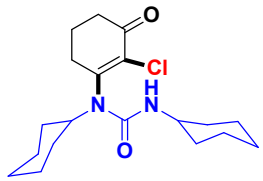


1-(4,4'-Dichloro-5-oxo-1,2,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-1,3-diisopropylurea (**4c**). White solid (77%, 147 mg); R_f = 0.5 (petroleum ether/ethyl acetate 6:1); mp 111-113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 4.29-4.20 (m, 1H), 3.94 (s, 1H),

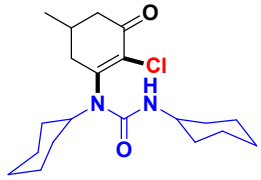
3.92 (s, 1H), 3.47-3.39 (m, 1H), 3.01-2.70 (m, 4H), 1.34 (dd, J = 3.0 Hz, J = 3.0 Hz, 6H), 1.07 (t, J = 85.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.2, 158.1, 154.7, 152.7, 139.7, 133.3, 131.1, 129.0, 127.6, 125.7, 50.4, 43.9, 42.5, 41.5, 40.9, 38.5, 23.1, 21.8, 21.1; IR (KBr) ν 3501, 2346, 1719, 1659, 1612, 1450, 1346, 1320, 1019, 989, 763, 664, 560 cm^{-1}; HRMS (ESI) calcd for $[C_{19}H_{24}Cl_2N_2O_2 + H]^+$ 383.1248, found 383.1249.



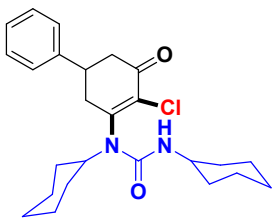
1-(2-Chloro-5,5-dimethyl-3-oxocyclohex-1-en-1-yl)-1,3-diisopropylurea (**4d**). White solid (80%, 120 mg); R_f = 0.5 (petroleum ether/ethyl acetate 6:1); mp 81-82 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.25-4.16 (m, 1H), 3.98-3.91 (m, 2H), 2.52-2.47 (m, 4H), 1.33-1.27 (m, 6H), 1.13-1.06 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.3, 153.7, 152.9, 130.5, 51.1, 50.3, 46.7, 42.4, 32.4, 27.6, 23.0, 21.2; IR (KBr) ν 3510, 2315, 1730, 1660, 1610, 1480, 1365, 1327 cm^{-1}; HRMS (ESI) calcd for $[C_{15}H_{25}ClN_2O_2 + H]^+$ 301.1638, found 301.1630.



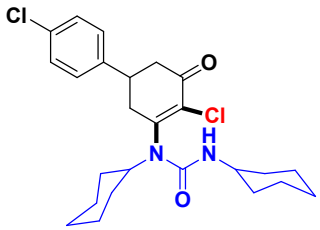
1-(2-Chloro-3-oxocyclohex-1-en-1-yl)-1,3-dicyclohexylurea (**4e**). White solid (80%, 140 mg); R_f = 0.5 (petroleum ether/ethyl acetate 6:1); mp 80-82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (d, J = 7.5 Hz, 1H), 3.91-3.83 (m, 1H), 3.64-3.59 (m, 1H), 2.64 (t, J = 6.3 Hz, 4H), 2.09-2.01 (m, 2H), 1.96-1.88 (m, 4H), 1.80-1.75 (m, 2H), 1.68-1.52 (m, 6H), 1.33-1.25 (m, 4H), 1.13-1.03 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 156.7, 153.1, 131.7, 58.5, 49.4, 37.9, 33.5, 31.6, 26.2, 25.5, 24.9, 21.3; IR (KBr) ν 3523, 2345, 1749, 1663, 1621, 1480, 1376, 1336 cm^{-1}; HRMS (ESI) calcd for $[C_{19}H_{29}ClN_2O_2 + H]^+$ 353.1951, found 353.1955.



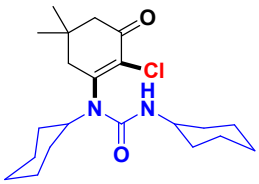
1-(2-Chloro-5-methyl-3-oxocyclohex-1-en-1-yl)-1,3-dicyclohexylurea (**4f**). White solid (75%, 137 mg); R_f = 0.5 (petroleum ether/ethyl acetate 6:1); mp 82-83 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (d, J = 7.5 Hz, 1H), 3.91-3.81 (m, 1H), 3.67-3.55 (m, 1H), 2.76-2.73 (m, 2H), 2.41-2.25 (m, 3H), 1.96-1.89 (m, 4H), 1.80-1.76 (m, 2H), 1.68-1.62 (m, 3H), 1.55-1.44 (m, 2H), 1.42-1.27 (m, 4H), 1.17-.95 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 155.8, 153.3, 131.8, 58.8, 49.6, 46.0, 41.8, 33.9, 32.0, 31.8, 29.2, 26.4, 25.7, 25.1, 20.7; IR (KBr) ν 3511, 2333, 1730, 1660, 1610, 1452, 1376, 1306 cm^{-1}; HRMS (ESI) calcd for $[C_{20}H_{31}ClN_2O_2 + H]^+$ 367.2108, found 367.2110.



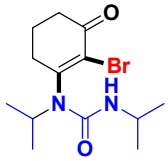
1-(4-Chloro-5-oxo-1,2,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-1,3-dicyclohexylurea (**4g**). White solid (79%, 169 mg); R_f = 0.5 (petroleum ether/ethyl acetate 6:1); mp 100-102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (t, J = 7.2 Hz, 2H), 7.32 (d, J = 6.9 Hz, 1H), 7.24 (d, J = 6.9 Hz, 2H), 4.06 (d, J = 7.8 Hz, 1H), 3.90-3.82 (m, 1H), 3.62-3.53 (m, 1H), 3.51-3.40 (m, 1H), 3.04-2.75 (m, 4H), 2.03-1.94 (m, 2H), 1.89-1.75 (m, 5H), 1.68-1.46 (m, 7H), 1.37-1.25 (m, 5H), 1.15-0.79 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.9, 155.1, 153.0, 141.2, 131.6, 129.1, 127.5, 126.6, 58.7, 49.4, 44.0, 41.3, 39.0, 33.6, 32.0, 31.4, 26.2, 26.1, 25.5, 25.0; IR (KBr) ν 3500, 2316, 1732, 1670, 1613, 1481, 1366, 1325, 1029, 998, 784, 674, 552 cm^{-1}; HRMS (ESI) calcd for $[C_{25}H_{33}ClN_2O_2+ H]^+$ 429.2264, found 429.2260.



1,3-Dicyclohexyl-1-(4,4'-dichloro-5-oxo-1,2,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)urea (**4h**). White solid (84%, 194 mg); R_f = 0.5 (petroleum ether/ethyl acetate 5:1); mp 130-131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 3.97 (d, J = 7.5 Hz, 1H), 3.90-3.80 (m, 1H), 3.61-3.52 (m, 1H), 3.47-3.40 (m, 1H), 2.99-2.73 (m, 4H), 1.93-1.76 (m, 6H), 1.69-1.50 (m, 7H), 1.37-1.25 (m, 6H), 1.69-0.83 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.8, 155.0, 153.2, 139.9, 133.6, 131.9, 129.4, 128.2, 127.7, 58.9, 49.7, 44.0, 41.5, 38.6, 33.8, 32.3, 31.6, 26.4, 263, 25.7, 25.2; IR (KBr) ν 3515, 2315, 1711, 1662, 1620, 1491, 1362, 1313, 1122, 1010, 1000, 995, 782, 655, 551 cm^{-1}; HRMS (ESI) calcd for $[C_{25}H_{32}Cl_2N_2O_2 + H]^+$ 463.1874, found 463.1870.

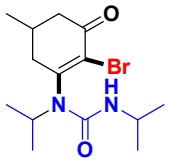


1-(2-Chloro-5,5-dimethyl-3-oxocyclohex-1-en-1-yl)-1,3-dicyclohexylurea (**4i**). White solid (76%, 144 mg); R_f = 0.5 (petroleum ether/ethyl acetate 6:1); mp 109-111 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (d, J = 7.5 Hz, 1H), 3.89-3.79 (m, 1H), 3.66-3.54 (m, 1H), 2.51-2.38 (m, 4H), 1.98-1.87 (m, 4H), 1.80-1.75 (m, 3H), 1.62-1.55 (m, 4H), 1.38-1.16 (m, 6H), 1.12 (s, 6H), 1.08-0.95 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 153.8, 153.0, 131.2, 58.8, 51.3, 49.4, 47.2, 33.7, 32.6, 31.7, 29.6, 27.9, 26.2, 25.5, 24.9; IR (KBr) ν 3520, 2335, 1739, 1662, 1620, 1482, 1366, 1326 cm^{-1}; HRMS (ESI) calcd for $[C_{21}H_{33}ClN_2O_2 + H]^+$ 381.2264, found 381.2265.

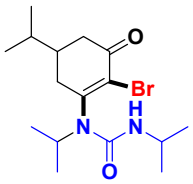


1-(2-Bromo-3-oxocyclohex-1-en-1-yl)-1,3-diisopropylurea (**4j**). White solid (80%, 126 mg); R_f = 0.5 (petroleum ether/ethyl acetate 6:1); mp 108-109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31-4.25 (m, 1H), 4.06-3.91 (m, 2H), 7.70-2.60 (m, 4H), 2.11-2.02 (m, 2H), 1.34 (d, J = 6.6 Hz, 6H), 1.13 (d, J = 6.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 159.5, 152.6, 125.9, 50.0, 42.4, 37.5, 33.7, 30.5, 23.1, 21.2; IR (KBr) ν 3506, 2435, 1749, 1660, 1626, 1480, 1326, 1300 cm^{-1}; HRMS

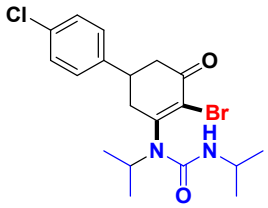
(ESI) calcd for $[C_{13}H_{21}BrN_2O_2+ H]^+$ 317.0820, found 317.0821.



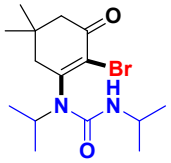
1-(2-Bromo-5-methyl-3-oxocyclohex-1-en-1-yl)-1,3-diisopropylurea (**4k**). White solid (81%, 132 mg); R_f = 0.5 (petroleum ether/ethyl acetate 6:1); mp 101-103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30-4.21 (m, 1H), 4.02-3.90 (m, 2H), 2.79-2.62 (m, 2H), 2.38-2.30 (m, 3H), 1.34 (dd, J = 3.0, J = 3.0 Hz, 6H), 1.14 (s, 3H), 1.13 (d, J = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 158.5, 152.6, 125.7, 50.0, 45.4, 42.4, 41.7, 28.8, 23.0, 21.3, 21.1, 20.2; IR (KBr) ν 3510, 2235, 1729, 1672, 1621, 1483, 1376, 1306 cm^{-1}; HRMS (ESI) calcd for $[C_{14}H_{23}BrN_2O_2 + H]^+$ 331.0976, found 331.0979.



1-(2-Bromo-5-isopropyl-3-oxocyclohex-1-en-1-yl)-1,3-diisopropylurea (**4l**). White solid (73%, 130 mg); R_f = 0.5 (petroleum ether/ethyl acetate 6:1); mp 81-83 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.32-4.20 (m, 1H), 3.99-3.91 (m, 2H), 2.85-2.60 (m, 2H), 2.40-2.28 (m, 2H), 1.95-1.83 (m, 1H), 1.59 (s, 1H), 1.33 (t, J = 6.0 Hz, 6H), 1.13 (d, J = 4.5 Hz, 6H), 0.97 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.2, 159.5, 152.9, 125.6, 50.4, 42.5, 41.6, 40.3, 37.8, 31.4, 30.9, 23.3, 21.7, 21.2, 19.6; IR (KBr) ν 3511, 2345, 1709, 1669, 1622, 1480, 1356, 1316 cm^{-1}; HRMS (ESI) calcd for $[C_{16}H_{27}BrN_2O_2 + H]^+$ 359.1289, found 359.1287.

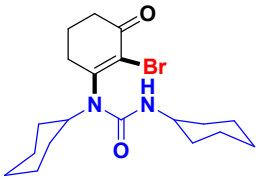


1-(4-Bromo-4'-chloro-5-oxo-1,2,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-1,3-diisopropylurea (**4m**). White solid (78%, 166 mg); R_f = 0.5 (petroleum ether/ethyl acetate 6:1); mp 141-143 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 4.32-4.23 (m, 1H), 3.99-3.88 (m, 2H), 3.50-3.38 (m, 1H), 3.05-2.73 (m, 4H), 1.37-1.34 (m, 6H), 1.28-1.08 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 157.9, 152.7, 139.5, 1334, 129.2, 127.9, 125.8, 50.3, 43.7, 42.5, 41.5, 40.9, 38.5, 23.1, 21.8, 21.1; IR (KBr) ν 3506, 2315, 1719, 1669, 1612, 1490, 1326, 1311, 1114, 1011, 1021, 991, 781, 681, 551 cm^{-1}; HRMS (ESI) calcd for $[C_{19}H_{24}BrClN_2O_2 + H]^+$ 427.0743, found 427.0740.

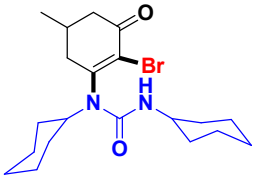


1-(2-Bromo-5,5-dimethyl-3-oxocyclohex-1-en-1-yl)-1,3-diisopropylurea (**4n**). White solid (76%, 130 mg); R_f = 0.5 (petroleum ether/ethyl acetate 6:1); mp 108-109°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.25-4.16 (m, 1H), 3.96-3.87 (m, 2H), 2.50 (s, 2H), 2.47 (s, 2H), 1.32 (d, J = 6.9 Hz, 6H), 1.11 (s,

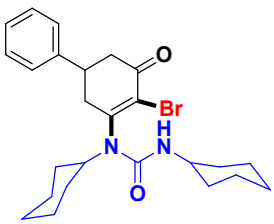
6H), 1.08 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 157.0, 152.8, 125.3, 51.1, 50.4, 47.6, 42.5, 32.7, 27.8, 23.3, 21.4; IR (KBr) ν 3500, 2345, 1719, 1652, 1621, 1480, 1367, 1329 cm^{-1}; HRMS (ESI) calcd for $[C_{15}H_{25}BrN_2O_2+ H]^+$ 345.1133, found 345.1135.



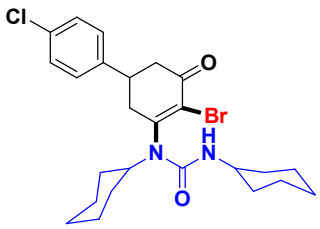
1-(2-Bromo-3-oxocyclohex-1-en-1-yl)-1,3-dicyclohexylurea (**4o**). White solid (81%, 160 mg); R_f = 0.5 (petroleum ether/ethyl acetate 6:1); mp 131-133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (d, J = 7.8 Hz, 1H), 3.91-3.80 (m, 1H), 3.68-3.57 (m, 1H), 2.84-2.60 (m, 2H), 2.40-2.27 (m, 2H), 2.01-1.76 (m, 6H), 1.72-1.50 (m, 9H), 1.40-1.28 (m, 9H), 1.18-1.04 (m, 4H), 0.97 (d, J = 6.6 H, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0, 160.2, 153.5, 126.6, 59.3, 50.1, 42.3, 41.1, 38.8, 34.3, 32.1, 30.3, 26.9, 26.2, 25.6, 20.3; IR (KBr) ν 3510, 2330, 1738, 1663, 1621, 1483, 1355, 1336 cm^{-1}; HRMS (ESI) calcd for $[C_{19}H_{29}BrN_2O_2 + H]^+$ 397.1446, found 397.1449.



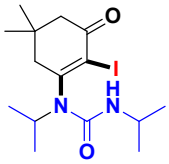
1-(2-Bromo-5-methyl-3-oxocyclohex-1-en-1-yl)-1,3-dicyclohexylurea (**4p**). White solid (81%, 166 mg); R_f = 0.5 (petroleum ether/ethyl acetate 6:1); mp 111-113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (d, J = 7.5 Hz, 1H), 3.90-3.80 (m, 1H), 3.66-3.54 (m, 1H), 2.77-2.61 (m, 2H), 2.36-2.29 (m, 3H), 2.00-1.88(m, 5H), 1.79-1.49 (m, 10H), 1.38-1.24 (m, 6H), 1.13 (d, d, J = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 158.8, 152.8, 126.3, 58.5, 49.4, 45.6, 42.2, 33.7, 31.8, 31.6, 29.1, 26.2, 25.6, 25.0, 20.4; IR (KBr) ν 3505, 2435, 1729, 1665, 1622, 1483, 1367, 1327 cm^{-1}; HRMS (ESI) calcd for $[C_{20}H_{31}BrN_2O_2 + H]^+$ 411.1602, found 411.1605.



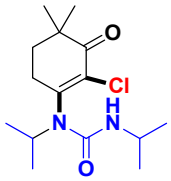
1-(4-Bromo-5-oxo-1,2,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-1,3-dicyclohexylurea (**4q**). White solid (82%, 188 mg); R_f = 0.5 (petroleum ether/ethyl acetate 5:1); mp 111-113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (t, J = 7.2 Hz, 2H), 7.32 (d, J = 6.9 Hz, 1H), 7.27 (d, J = 7.2 Hz, 2H), 4.06 (d, J = 7.5 Hz, 1H), 3.92-3.82 (m, 1H), 3.62-3.52 (m, 1H), 3.49-3.42 (m, 1H), 3.04-2.75 (m, 4H), 2.03-1.95 (m, 2H), 1.89-1.75 (m, 5H), 1.67-1.46 (m, 7H), 1.37-1.25 (m, 5H), 1.15-0.79 (6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0, 158.0, 152.5, 141.0, 128.9, 127.4, 126.4, 126.1, 58.4, 49.3, 43.6, 41.8, 39.0, 33.4, 31.9, 31.2, 26.0, 25.3, 24.8; IR (KBr) ν 3500, 2345, 1729, 1666, 1621, 1480, 1367, 1327, 996, 782, 680, 555 cm^{-1}; HRMS (ESI) calcd for $[C_{25}H_{33}BrN_2O_2 + H]^+$ 473.1759, found 473.1755.



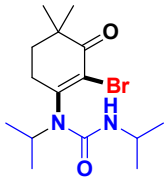
1-(4-Bromo-4'-chloro-5-oxo-1,2,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-1,3-dicyclohexylurea (**4r**). White solid (82%, 207 mg); R_f = 0.5 (petroleum ether/ethyl acetate 5:1); mp 131-132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 4.02 (d, J = 7.8 Hz, 1H), 3.90-3.82 (m, 1H), 3.61-3.52 (m, 1H), 3.49-3.40 (m, 1H), 3.02-2.71 (m, 4H), 2.03-1.95 (m, 2H), 1.89-1.75 (m, 5H), 1.66-1.49(m, 7H), 1.37-1.25 (m, 5H), 1.16-0.87 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 157.7, 152.5, 139.4, 133.2, 129.0, 127.8, 126.1, 58.5, 49.3, 43.4, 41.7, 38.4, 33.5, 32.0, 31.2, 25.9, 25.3, 24.8; IR (KBr) ν 3505, 2335, 1701, 1661, 1621, 1481, 1352, 1313, 1153, 1011, 1021, 991, 781, 681, 551 cm^{-1}; HRMS (ESI) calcd for $[C_{25}H_{32}BrClN_2O_2 + H]^+$ 507.1369, found 507.1367.



1-(2-Iodo-5,5-dimethyl-3-oxocyclohex-1-en-1-yl)-1,3-diisopropylurea (**4s**). White solid (75%, 147 mg); R_f = 0.5 (petroleum ether/ethyl acetate 6:1); mp 128-129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.25-4.16 (m, 1H), 3.99-3.89 (m, 2H), 2.50 (s, 2H), 2.47 (s, 2H) 1.32 (d, J = 6.9 Hz, 6H), 1.11 (s, 6H), 1.08 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.3, 153.7, 152.9, 130.5, 51.1, 50.3, 46.7, 42.4, 32.4, 27.6, 23.0, 21.2; IR (KBr) ν 3560, 2355, 1729, 1653, 1622, 1366, 1320 cm^{-1}; HRMS (ESI) calcd for $[C_{15}H_{25}IN_2O_2 + H]^+$ 393.0994, found 393.0990.



1-(2-Chloro-4,4-dimethyl-3-oxocyclohex-1-en-1-yl)-1,3-diisopropylurea (**4t**). White solid (76%, 130 mg); R_f = 0.5 (petroleum ether/ethyl acetate 6:1); mp 78-79 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36-4.26 (m, 1H), 3.97- 3.91 (m, 2H), 2.62 (t, J = 6.0 Hz, 2H), 1.88 (t, J = 6.0 Hz, 2H), 1.30 (d, J = 6.9 Hz, 6H), 1.20 (s, 6H), 1.11 (d, J = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 159.5, 152.6, 125.9, 50.0, 42.4, 37.5, 30.7, 23.1, 21.2; IR (KBr) ν 3509, 2331, 1741, 1658, 1622, 1480, 1367, 1306 cm^{-1}; HRMS (ESI) calcd for $[C_{15}H_{25}ClN_2O_2 + H]^+$ 301.1683, found 301.1685.



1-(2-Bromo-4,4-dimethyl-3-oxocyclohex-1-en-1-yl)-1,3-diisopropylurea (**4u**). White solid (75%, 137 mg); R_f = 0.5 (petroleum ether/ethyl acetate 6:1); mp 131-133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34-4.25 (m, 1H), 3.98-3.90 (m, 2H), 2.60 (t, J = 6.0 Hz, 2H), 1.88 (t, J = 6.0 Hz, 2H), 1.30 (d,

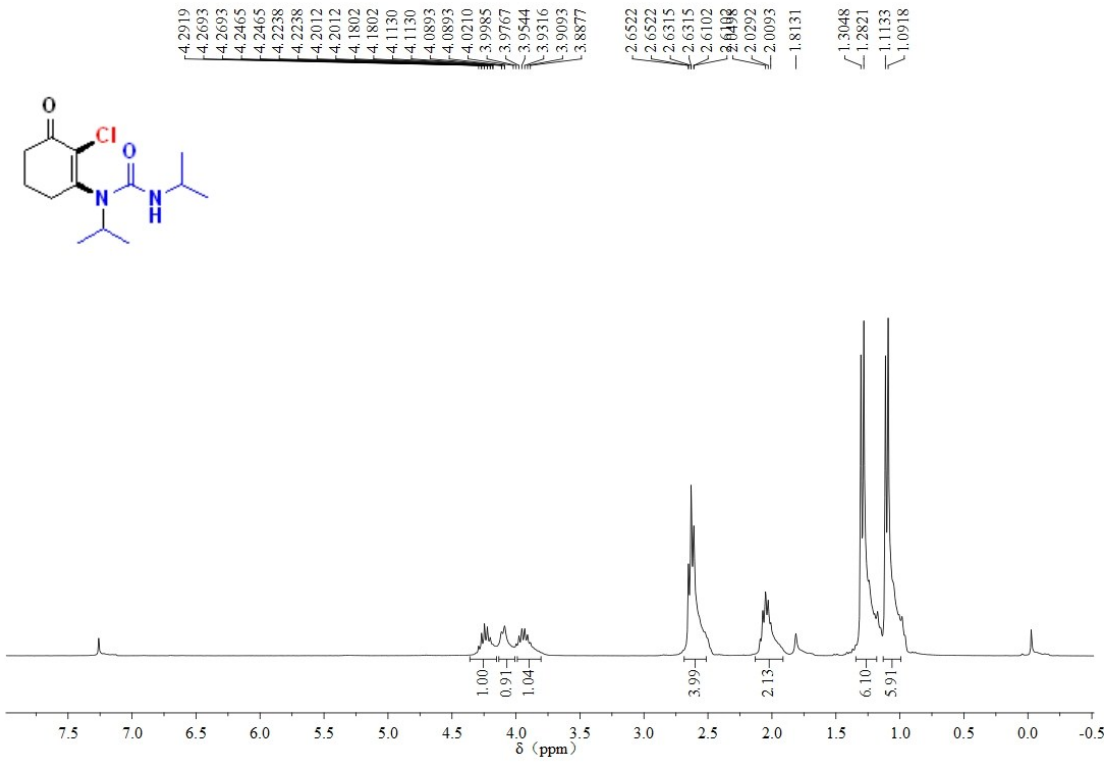
J = 6.9 Hz, 6H), 1.19 (s, 6H), 1.11 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 157.9, 153.3, 126.5, 50.1, 43.0, 42.6, 38.7, 35.0, 31.4, 24.7, 23.8, 22.0; IR (KBr) *v* 3503, 2336, 1733, 1659, 1621, 1480, 1376, 1316 cm^{-1}; HRMS (ESI) calcd for $[C_{15}H_{25}BrN_2O_2+ H]^+$ 345.1133, found 345.1136.

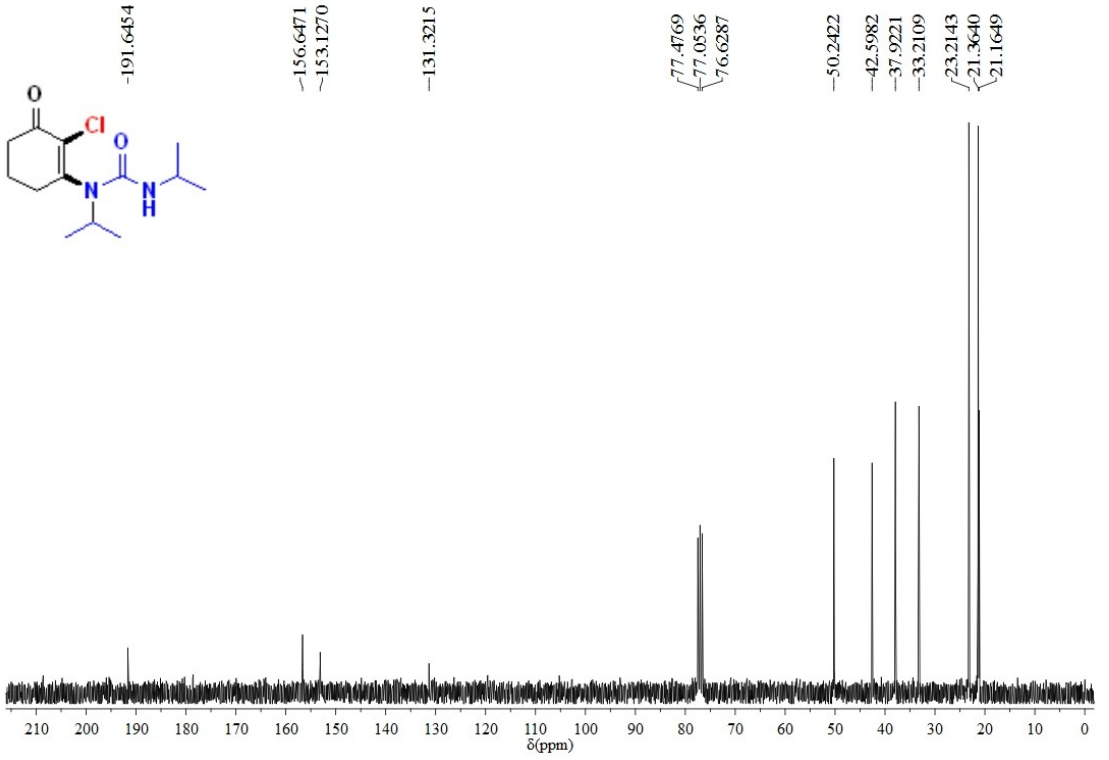
Reference

1. C. P. Michael, J-C. Zhang, L. Karen, D-S. Daniel and B. Frank, *J. Org. Chem.*, 1995, **60**, 2112.

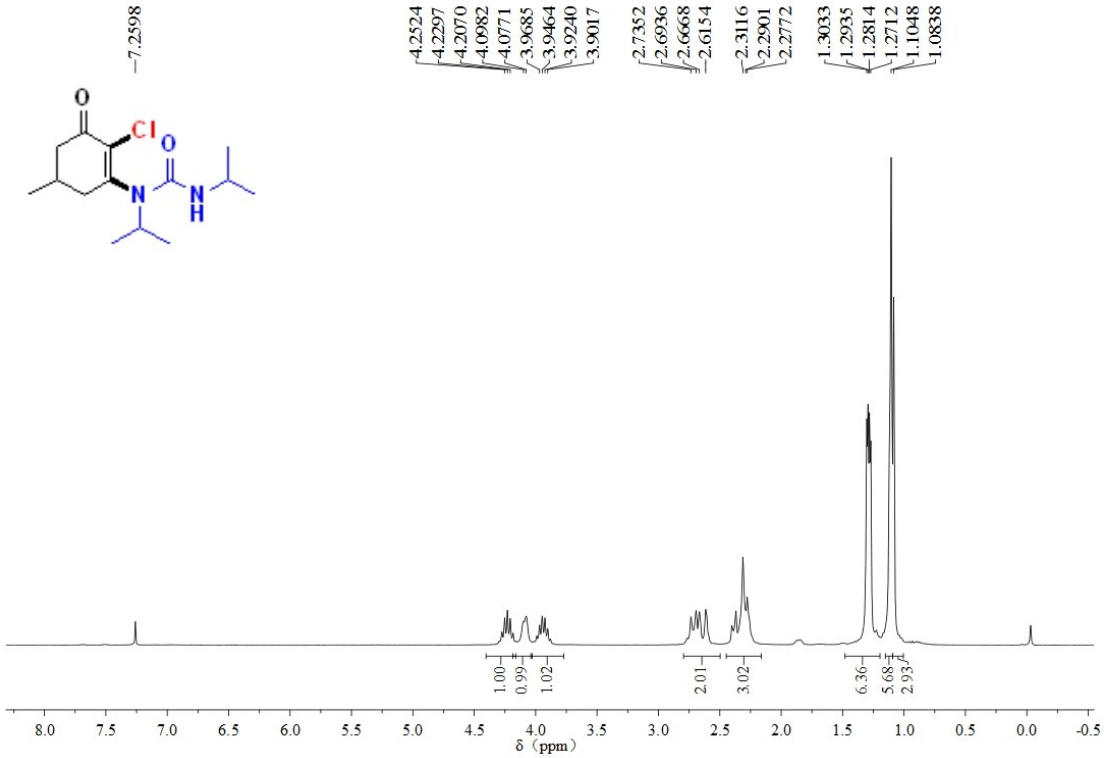
6. NMR spectra for all products

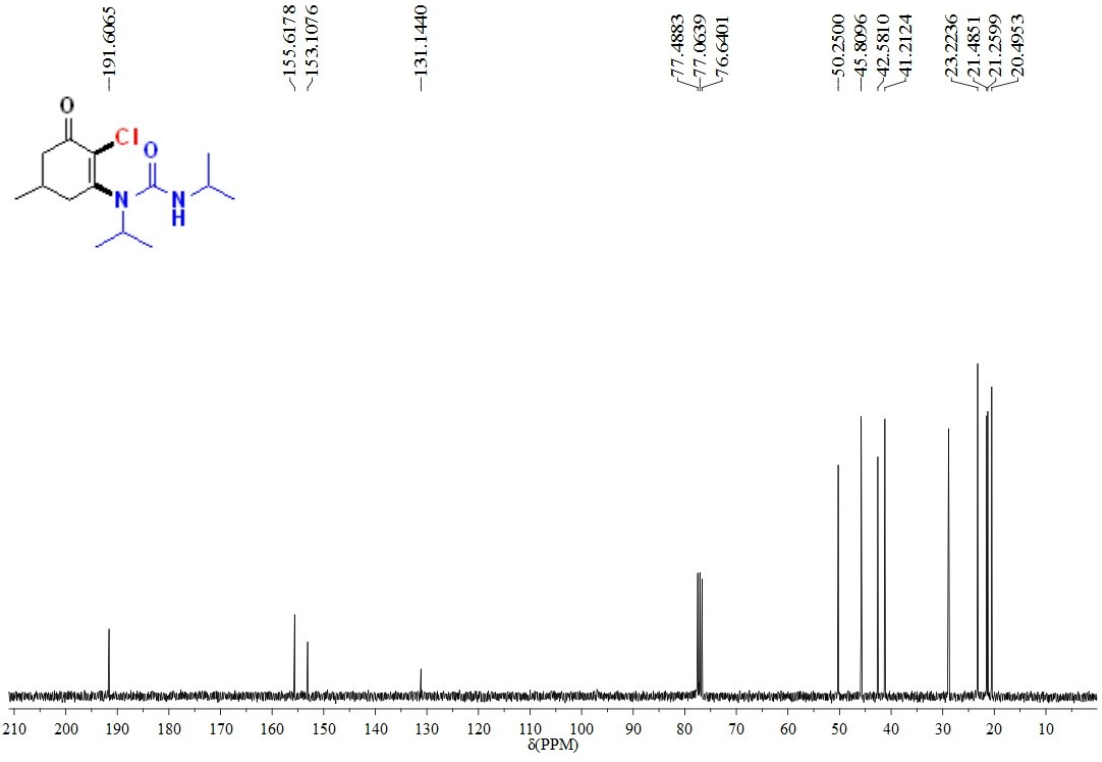
^{1}H and ^{13}C NMR spectra of compound 4a



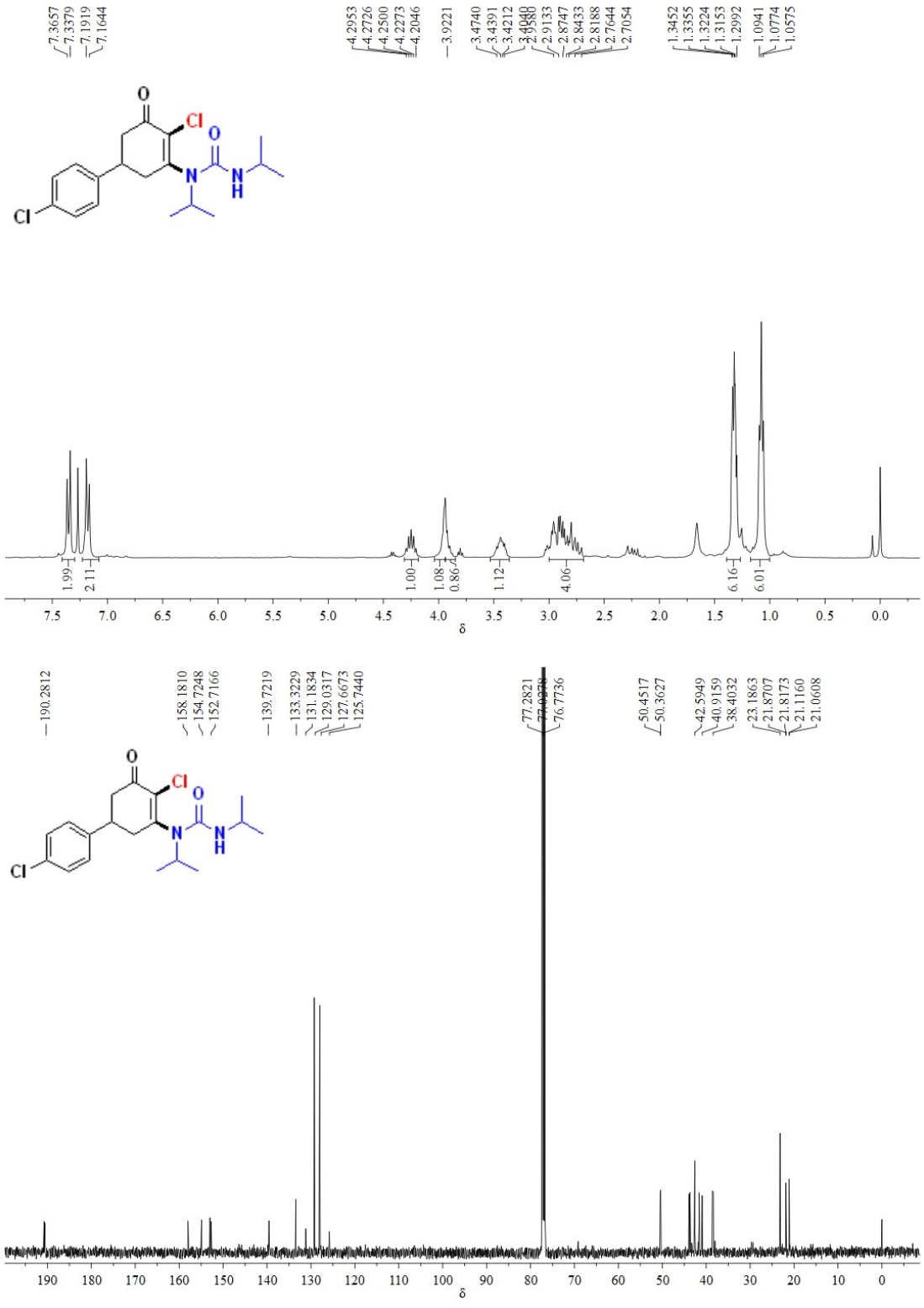


^{1}H and ^{13}C NMR spectra of compound 4b

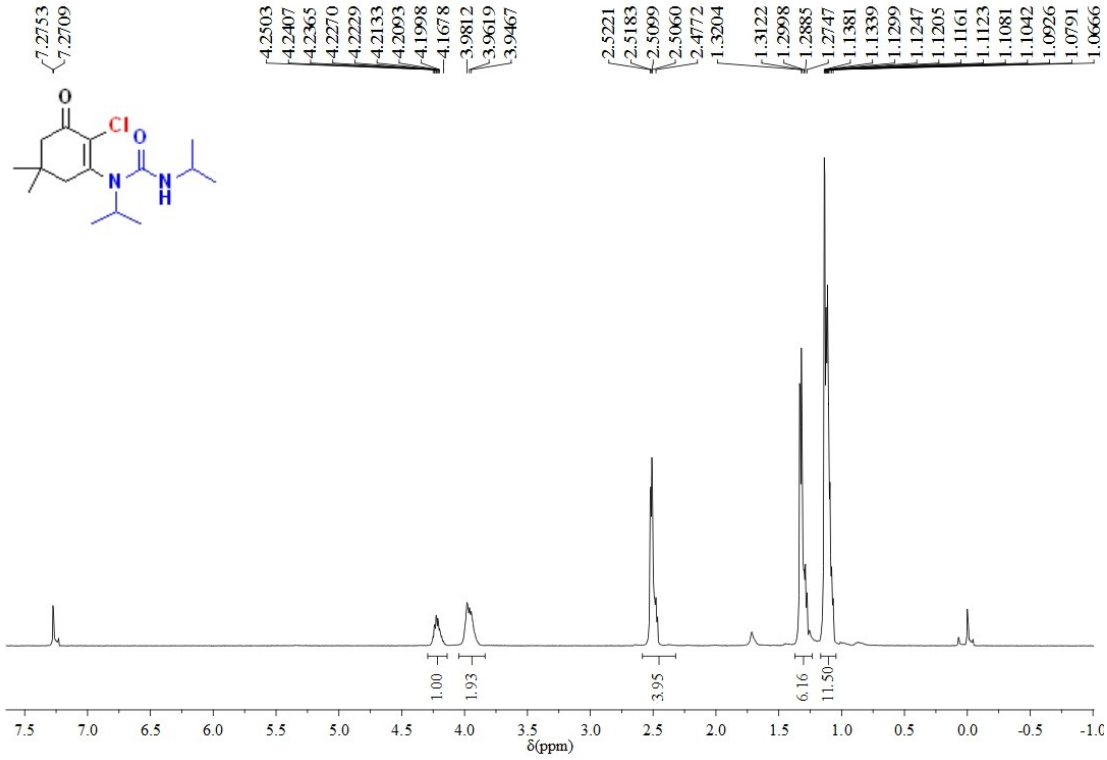


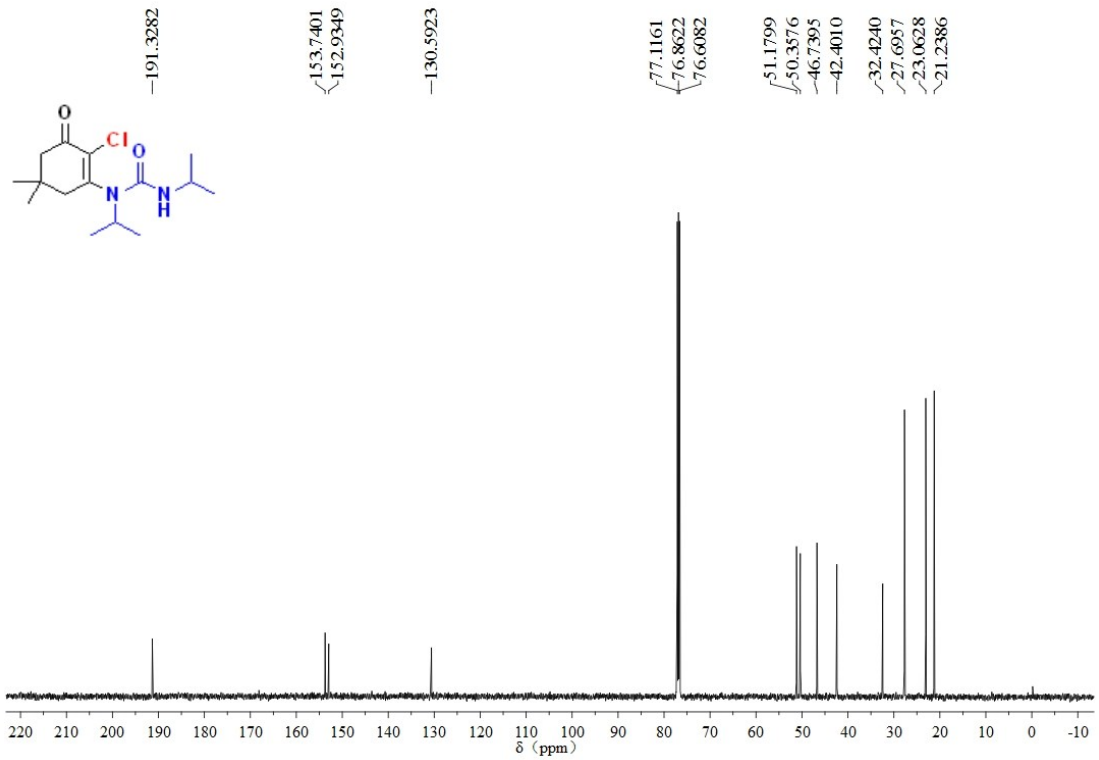


^{1}H and ^{13}C NMR spectra of compound 4c

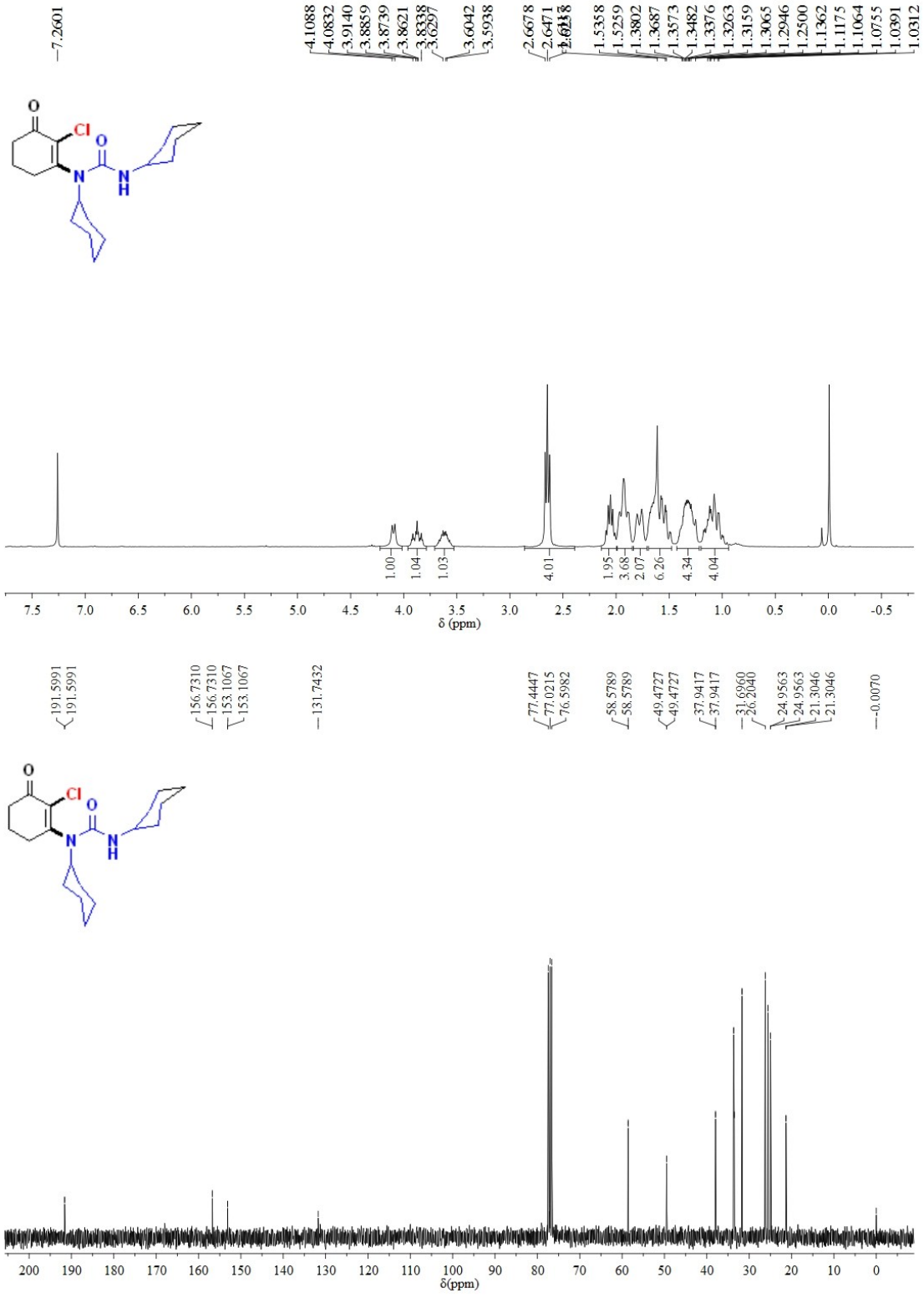


^{1}H and ^{13}C NMR spectra of compound 4d

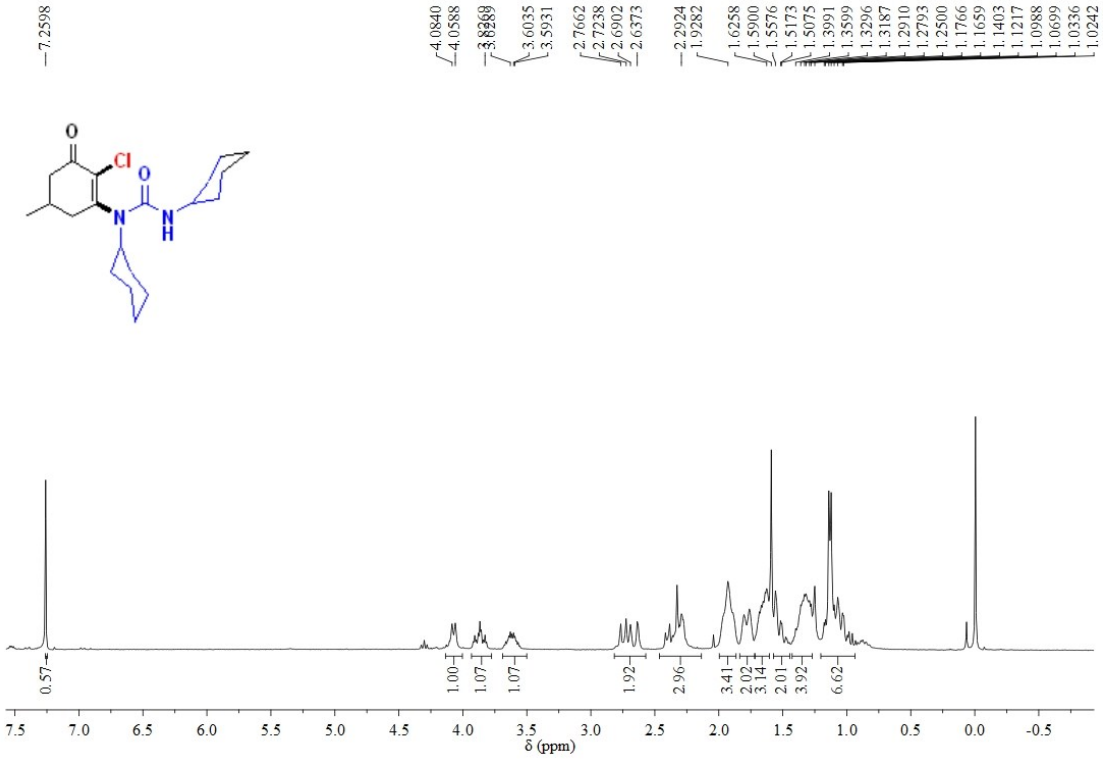


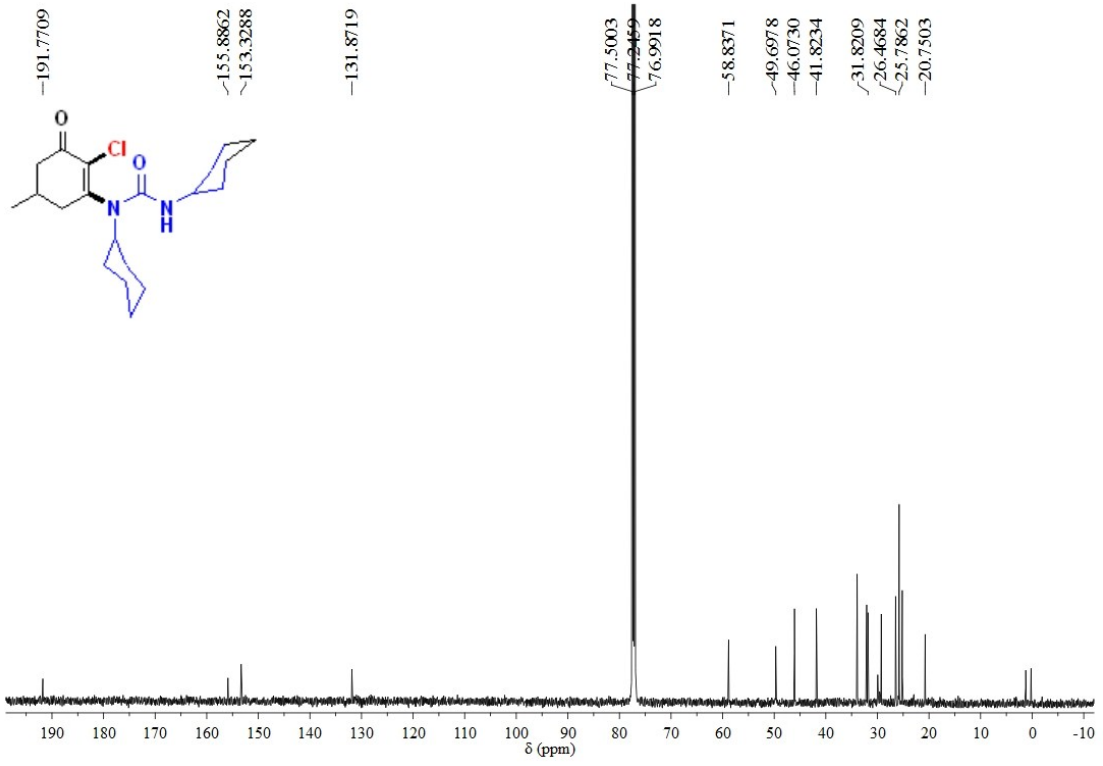


^{1}H and ^{13}C NMR spectra of compound 4e

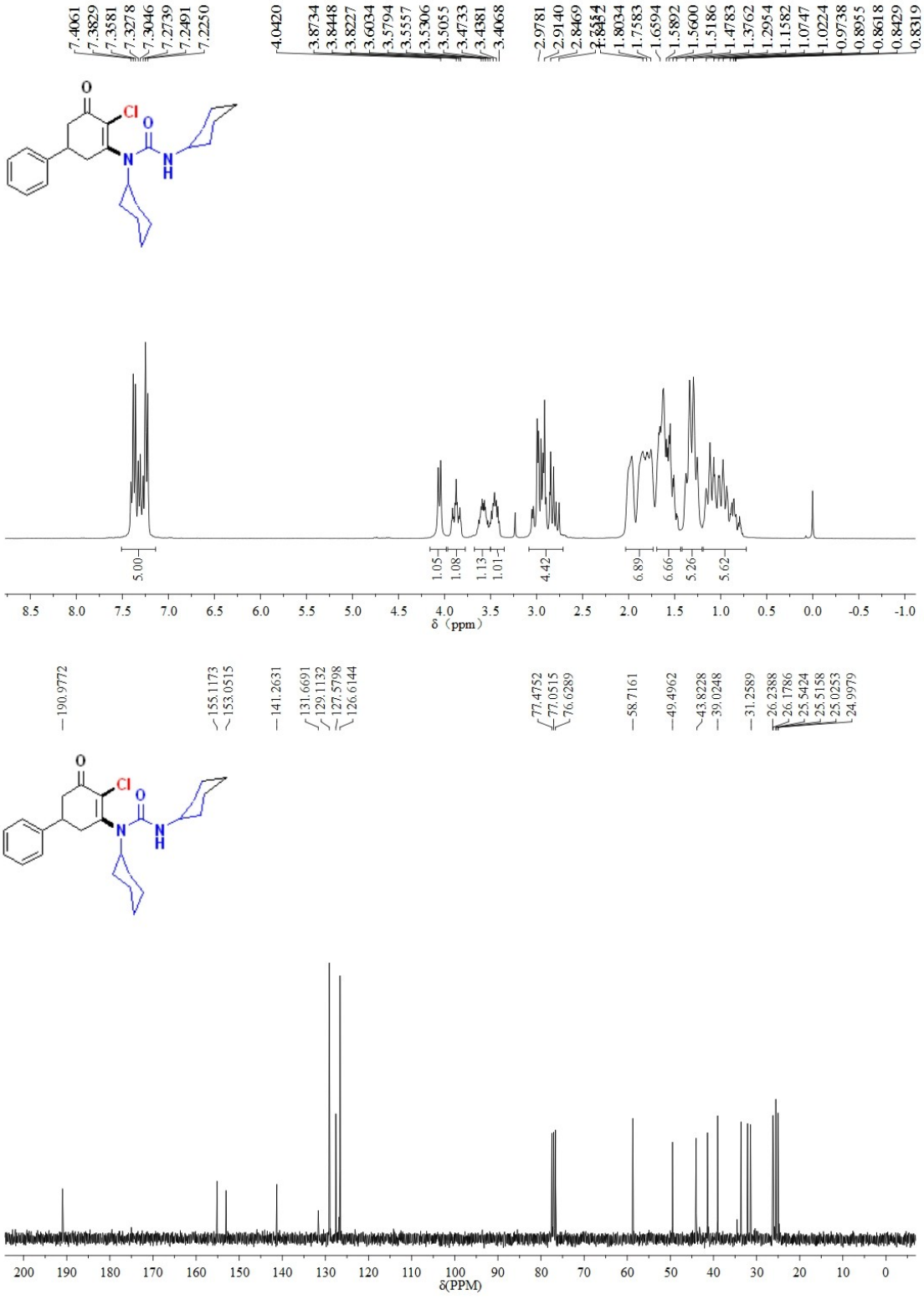


^{1}H and ^{13}C NMR spectra of compound 4f

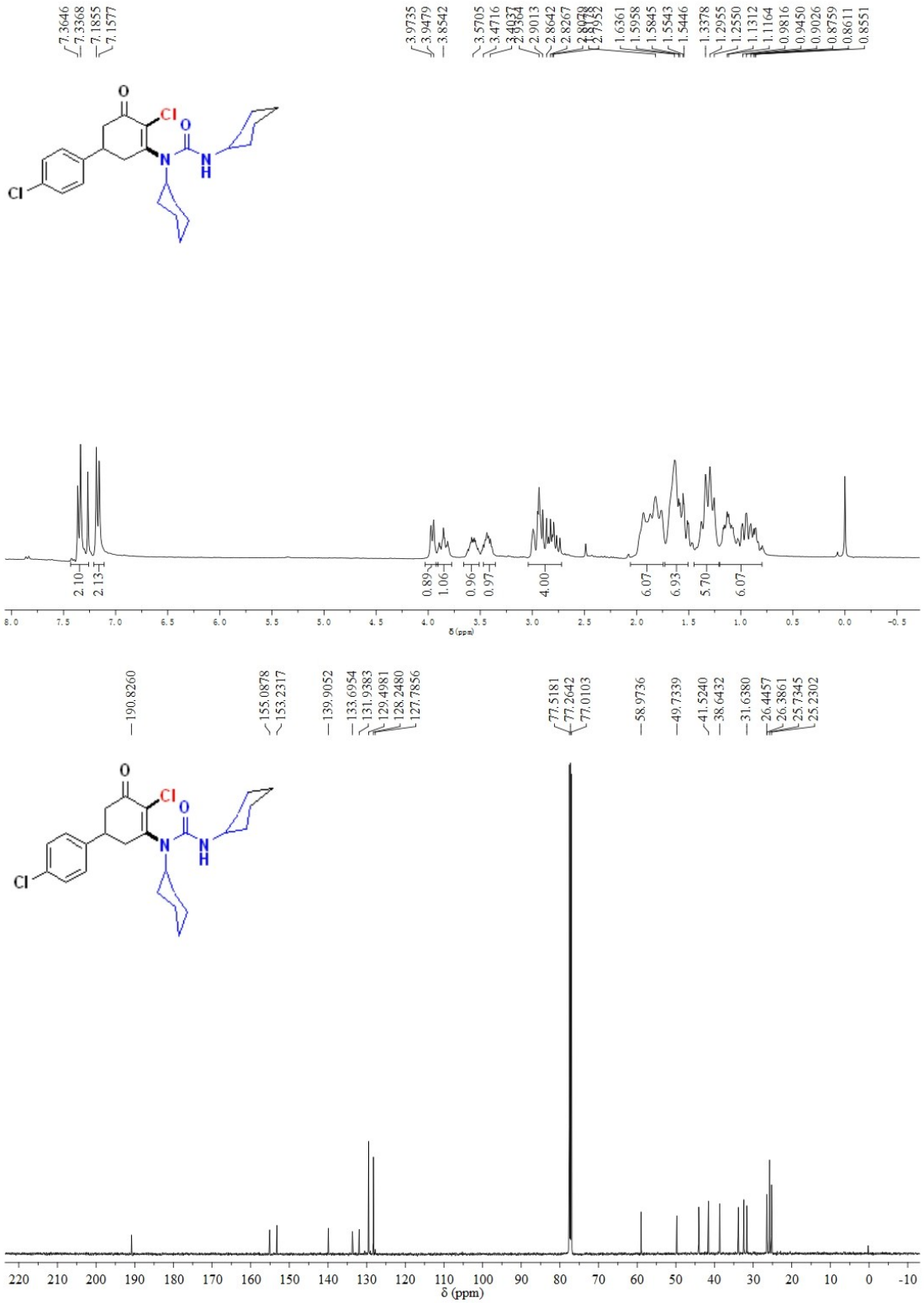




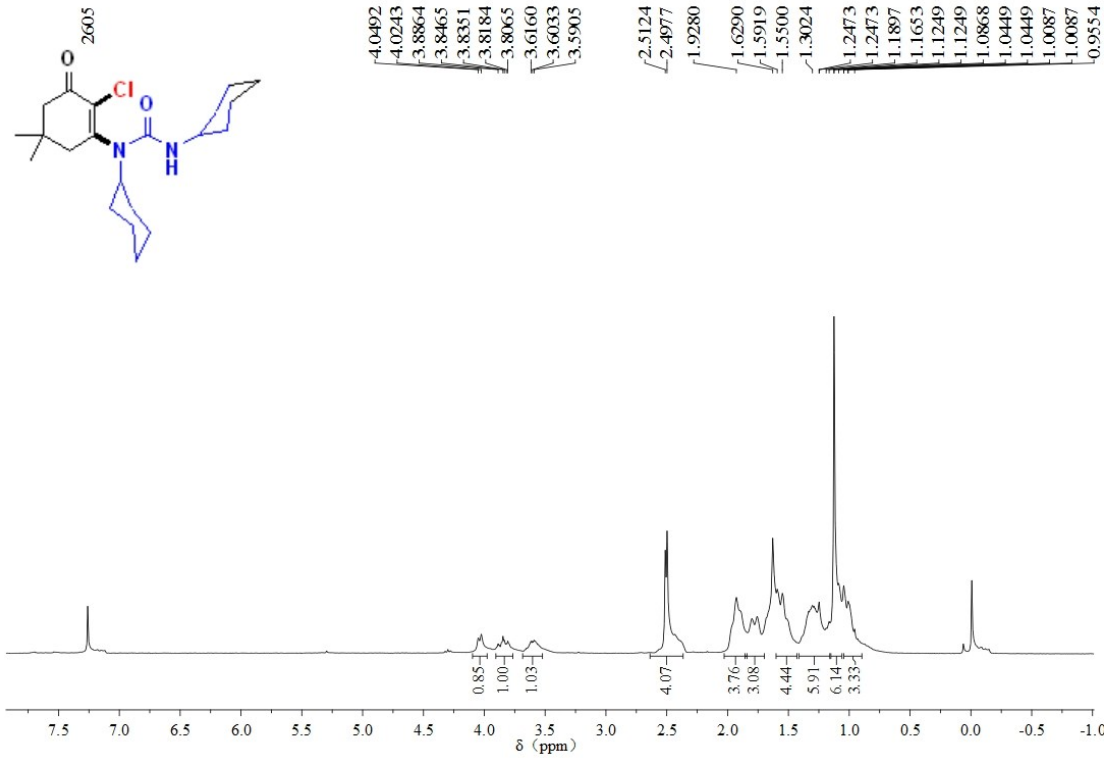
^{1}H and ^{13}C NMR spectra of compound 4g

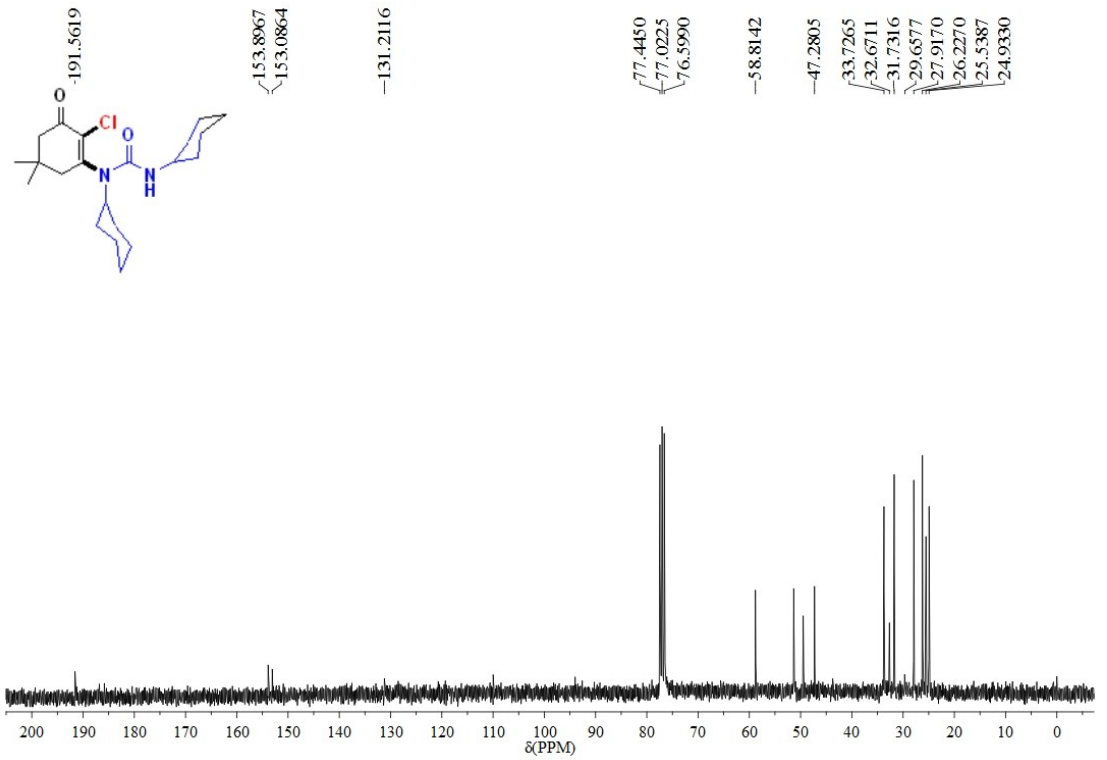


^{1}H and ^{13}C NMR spectra of compound 4h

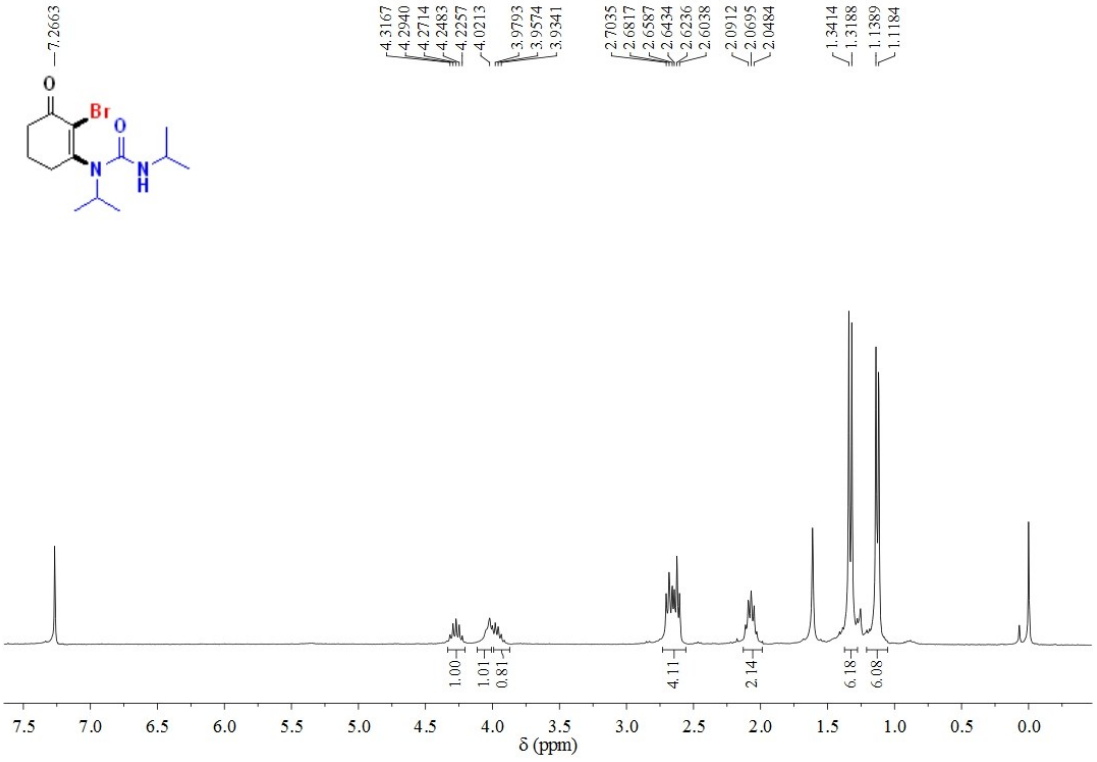


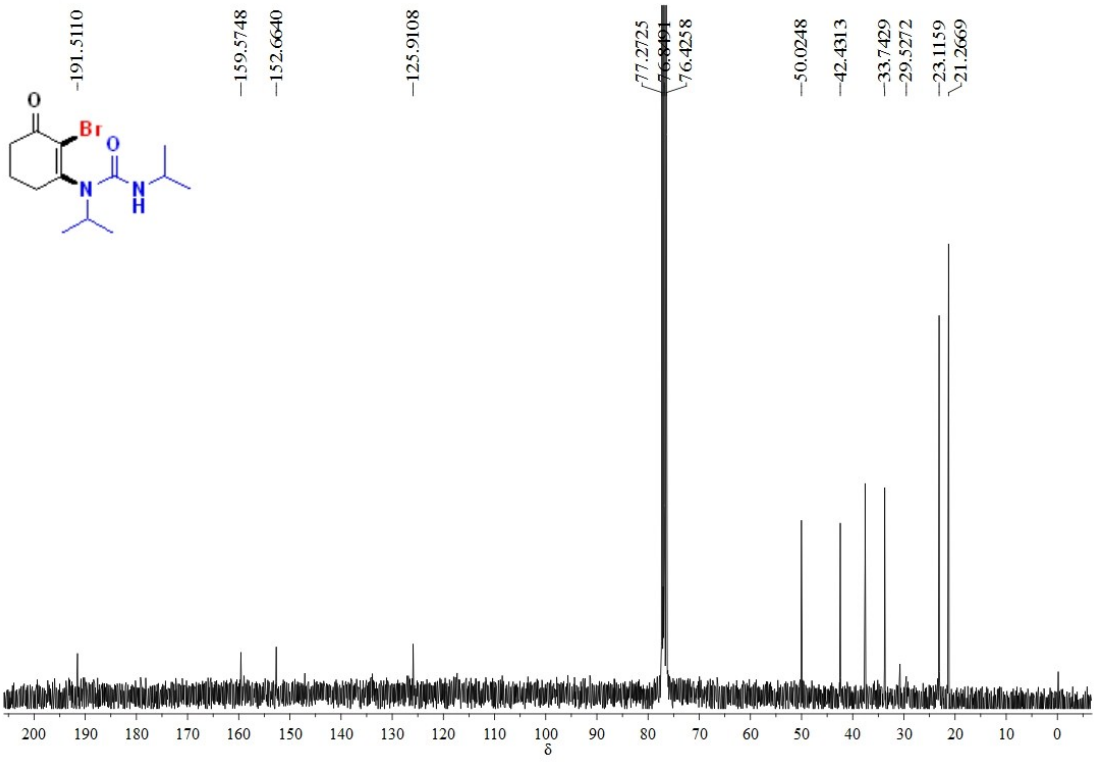
^{1}H and ^{13}C NMR spectra of compound 4i



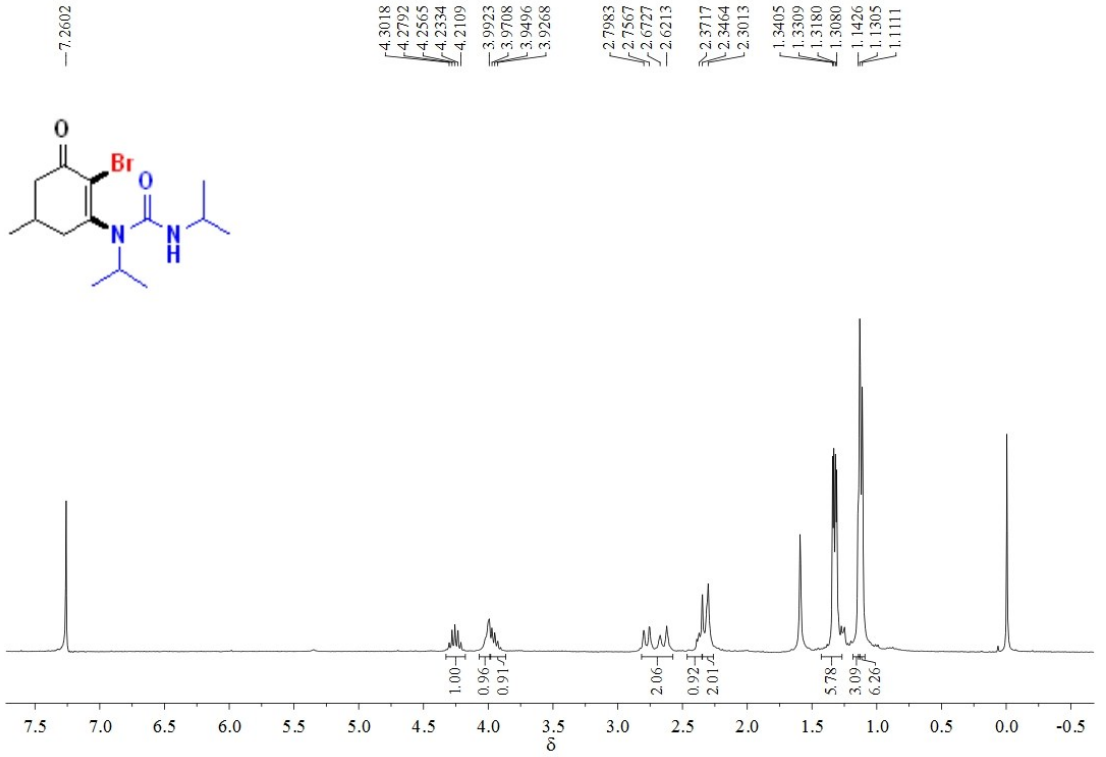


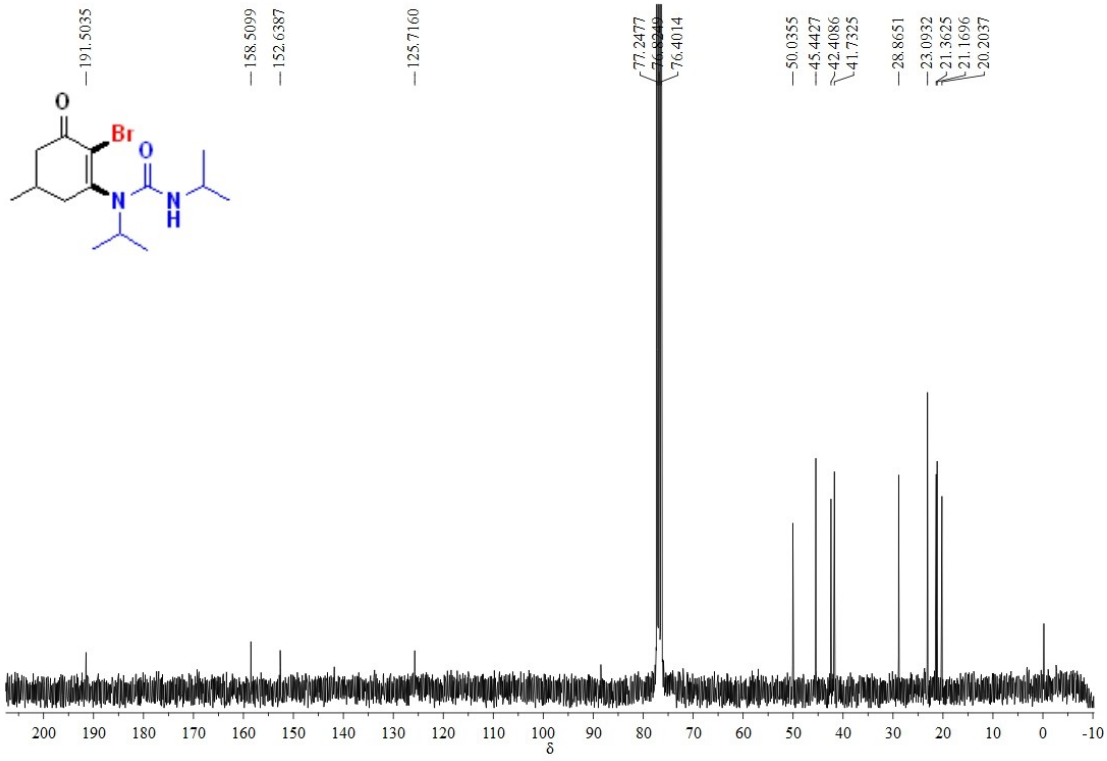
^{1}H and ^{13}C NMR spectra of compound 4j



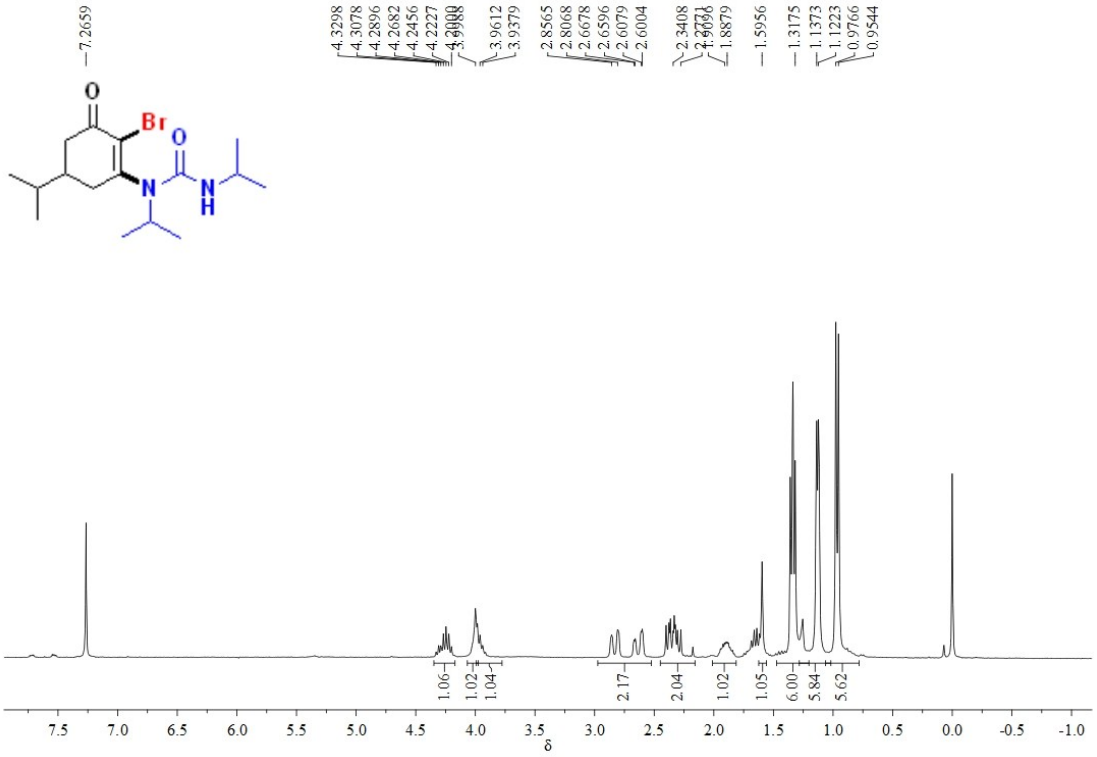


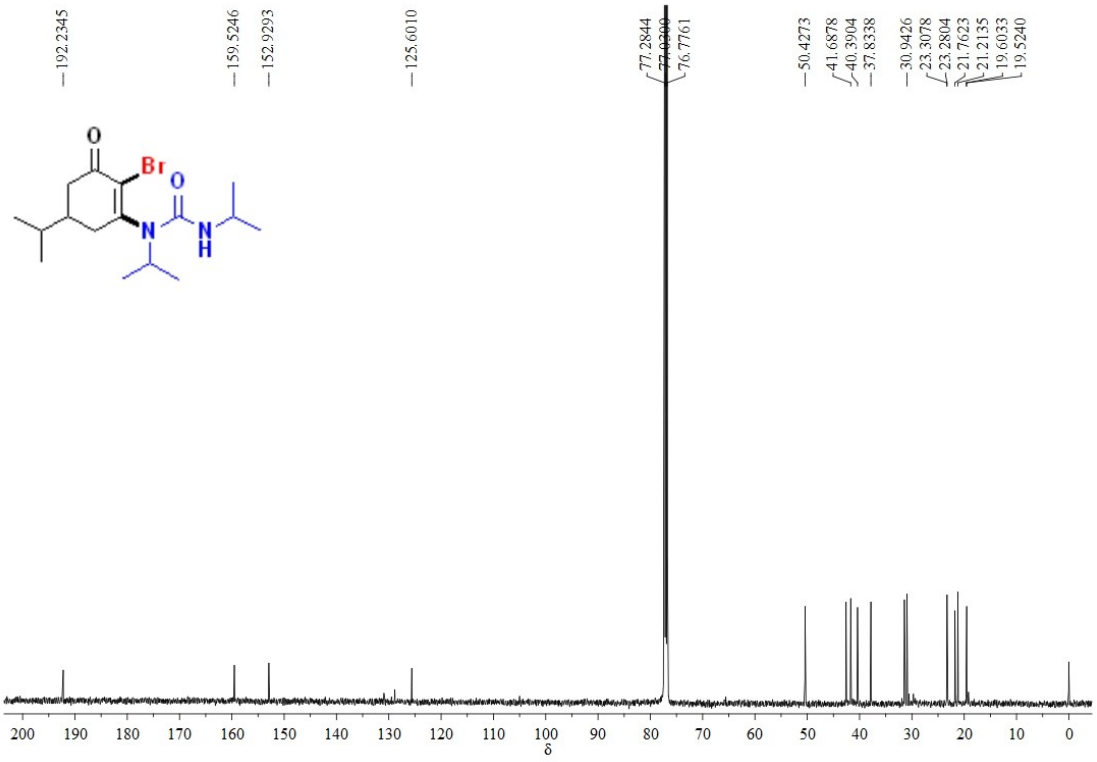
^{1}H and ^{13}C NMR spectra of compound 4k



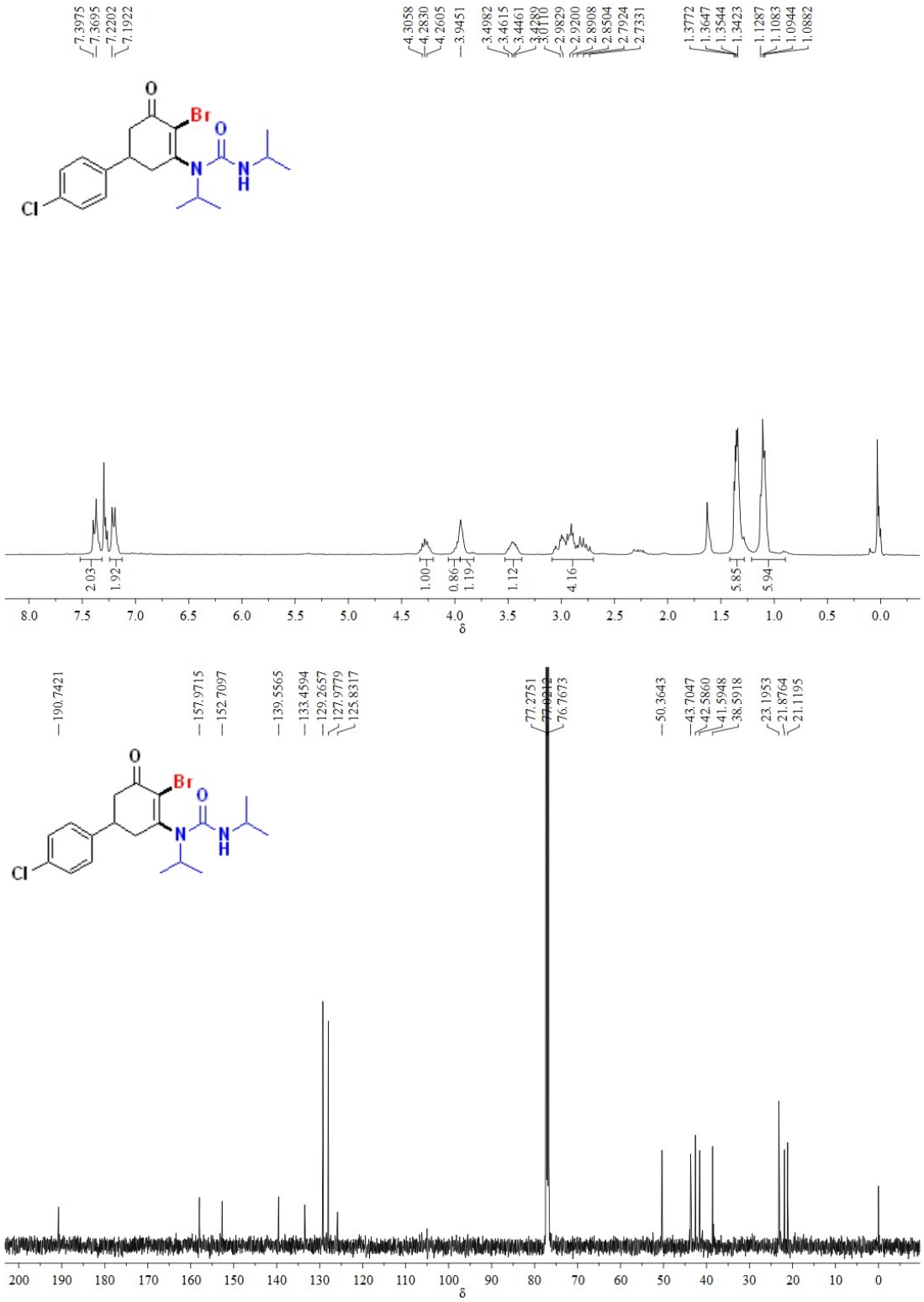


^{1}H and ^{13}C NMR spectra of compound 4l

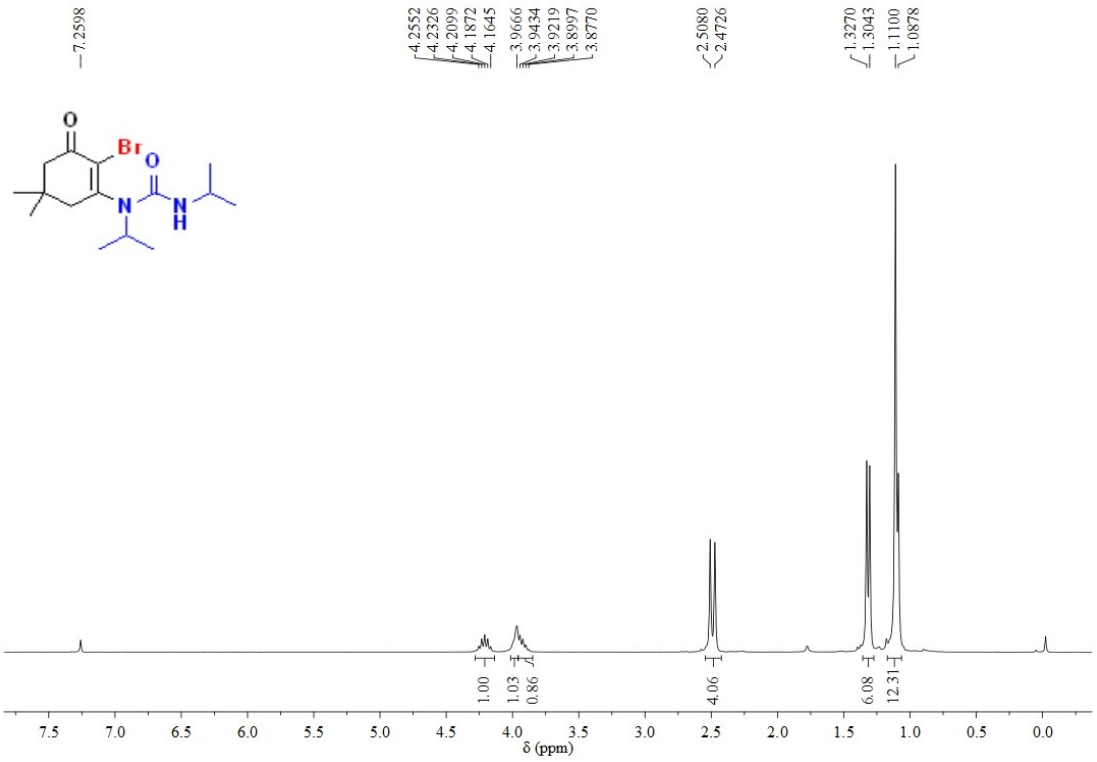


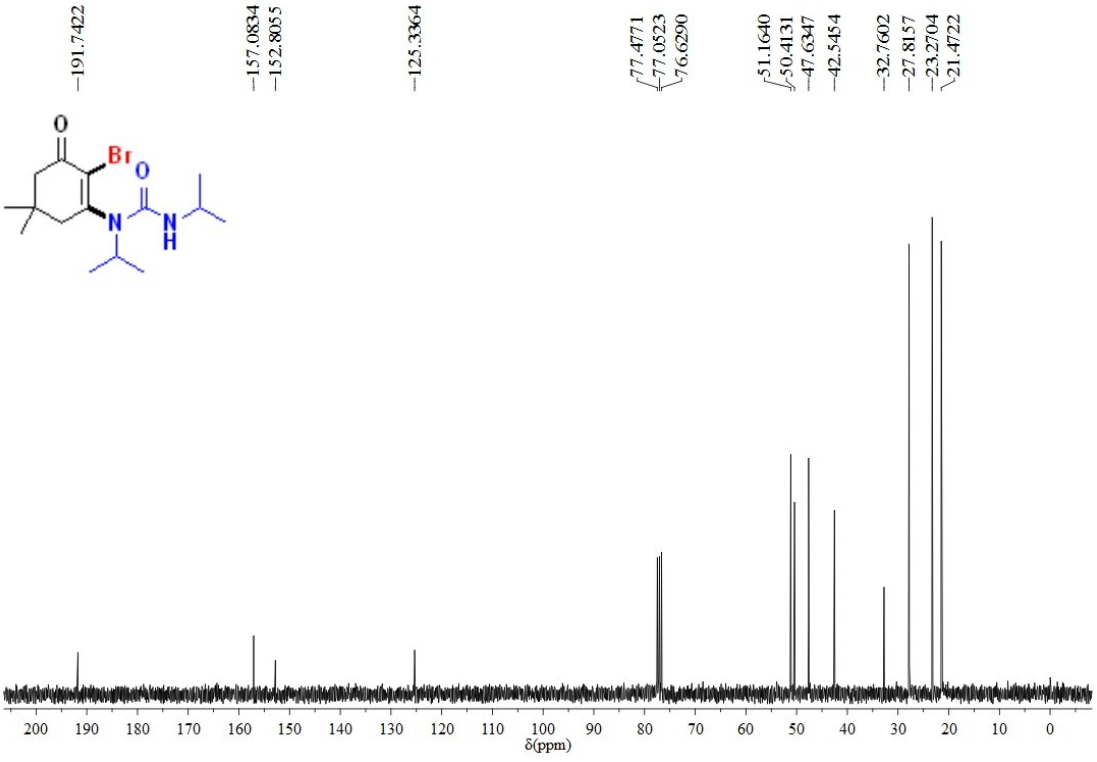


^{1}H and ^{13}C NMR spectra of compound 4m

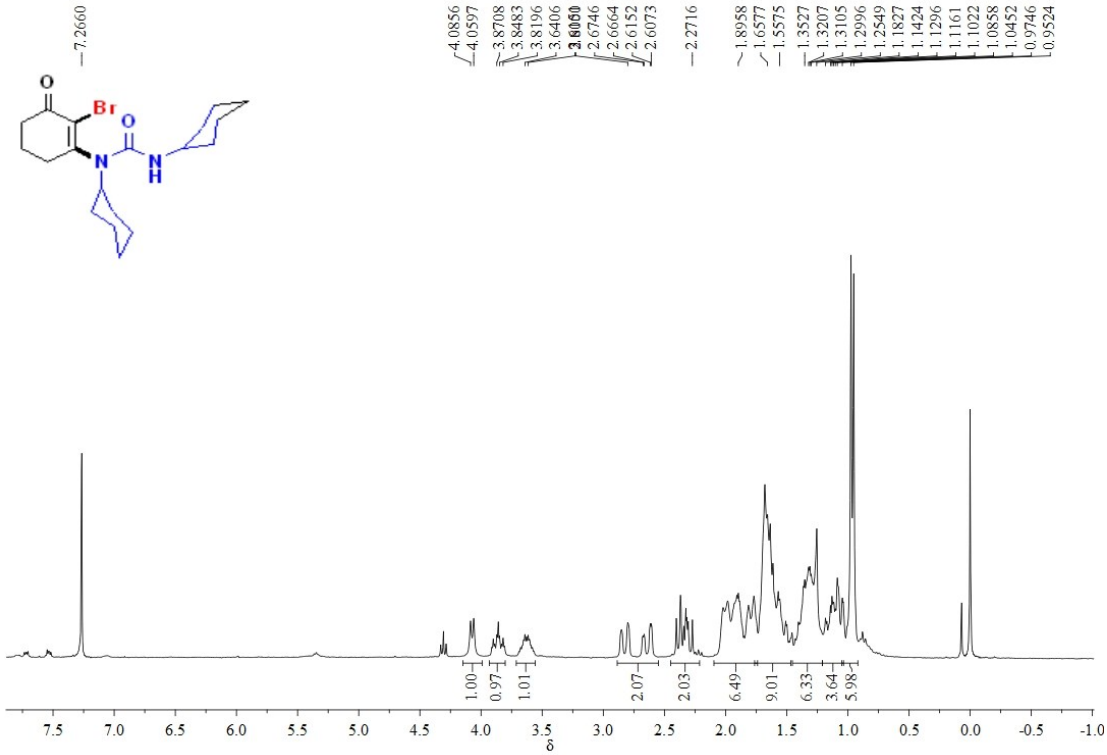


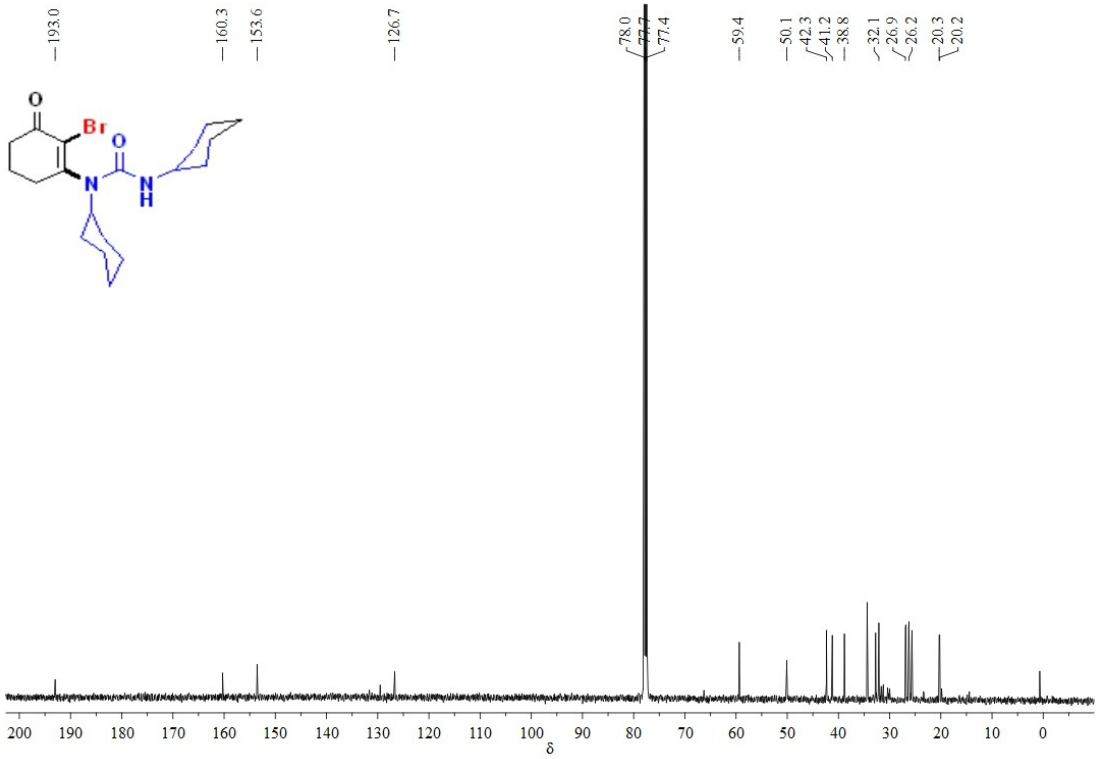
^{1}H and ^{13}C NMR spectra of compound 4n



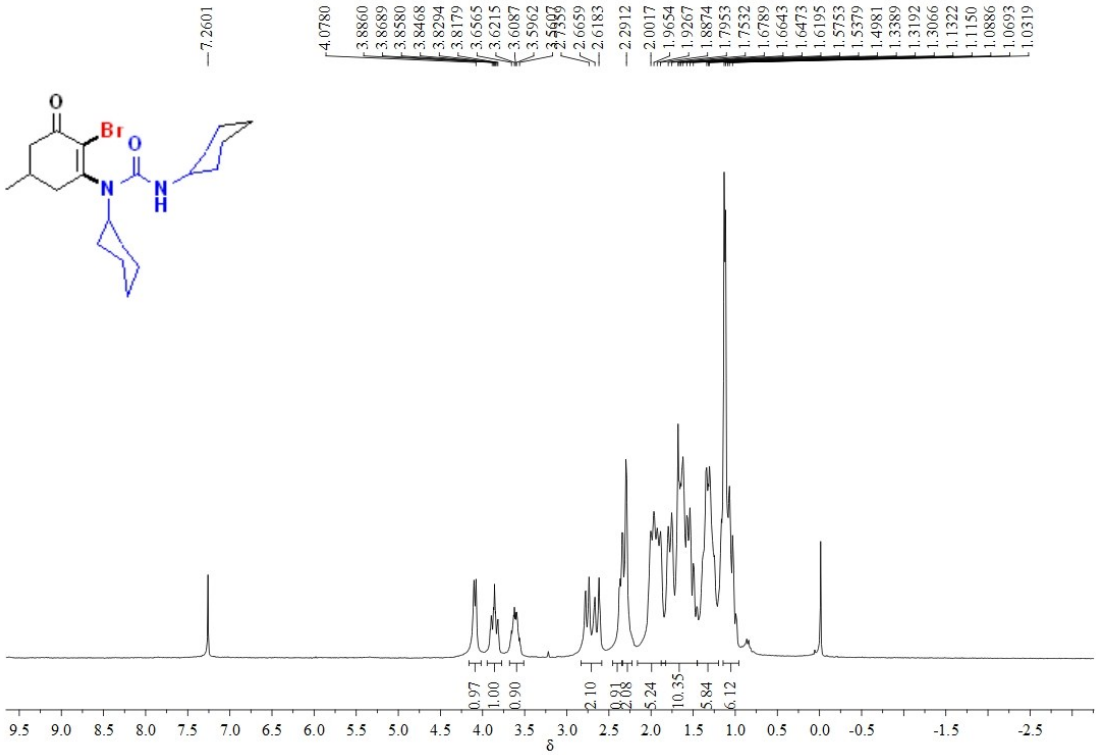


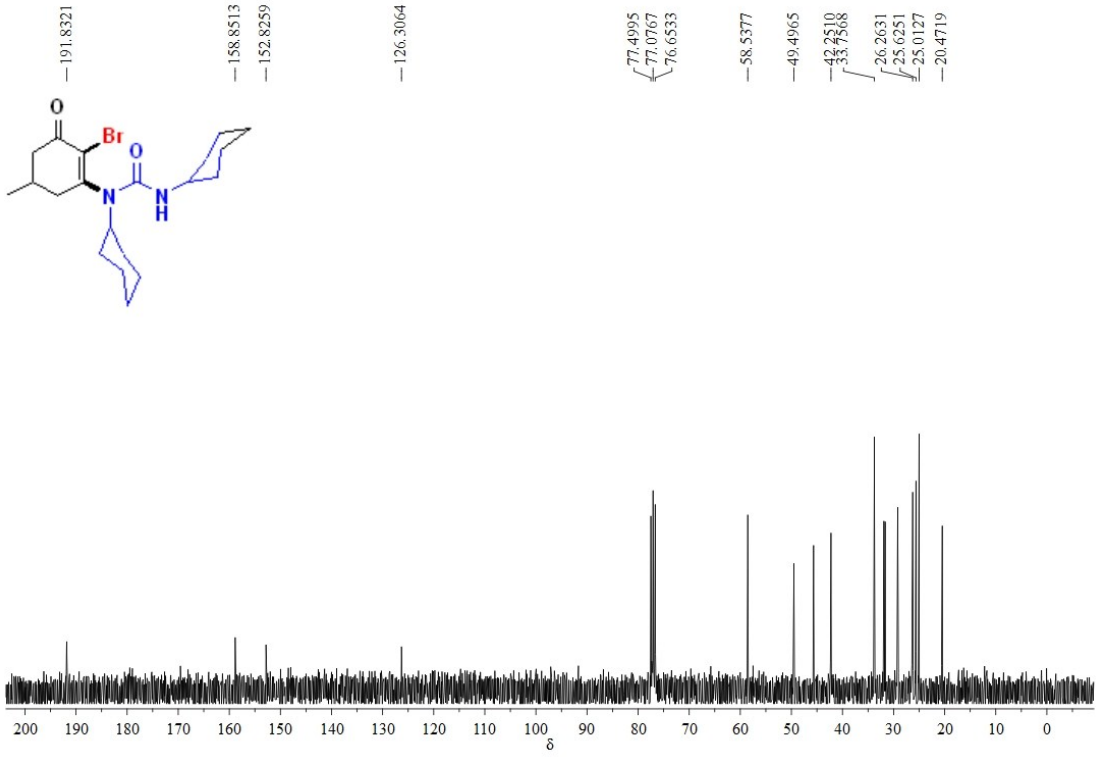
^{1}H and ^{13}C NMR spectra of compound 4o



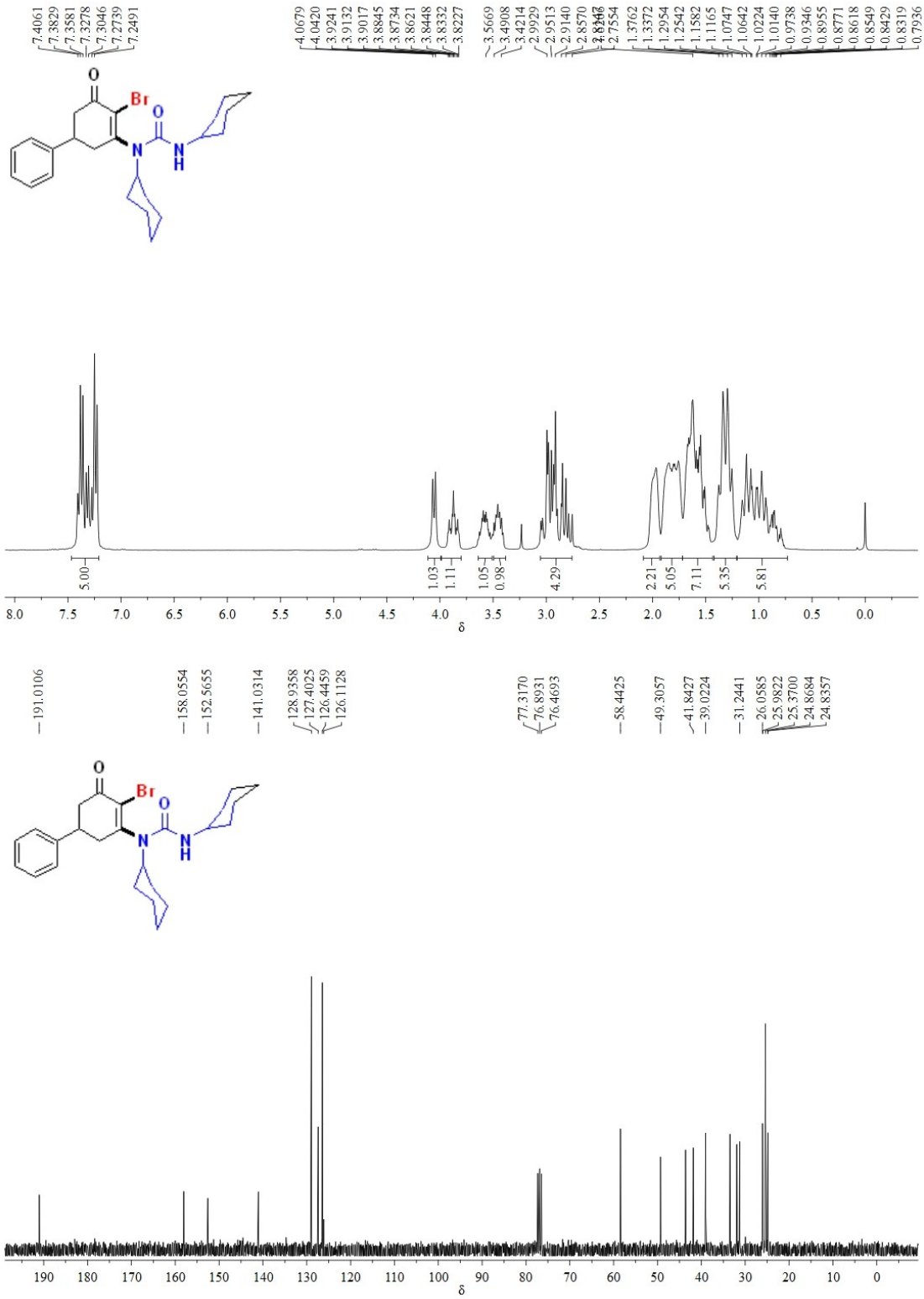


^{1}H and ^{13}C NMR spectra of compound 4p

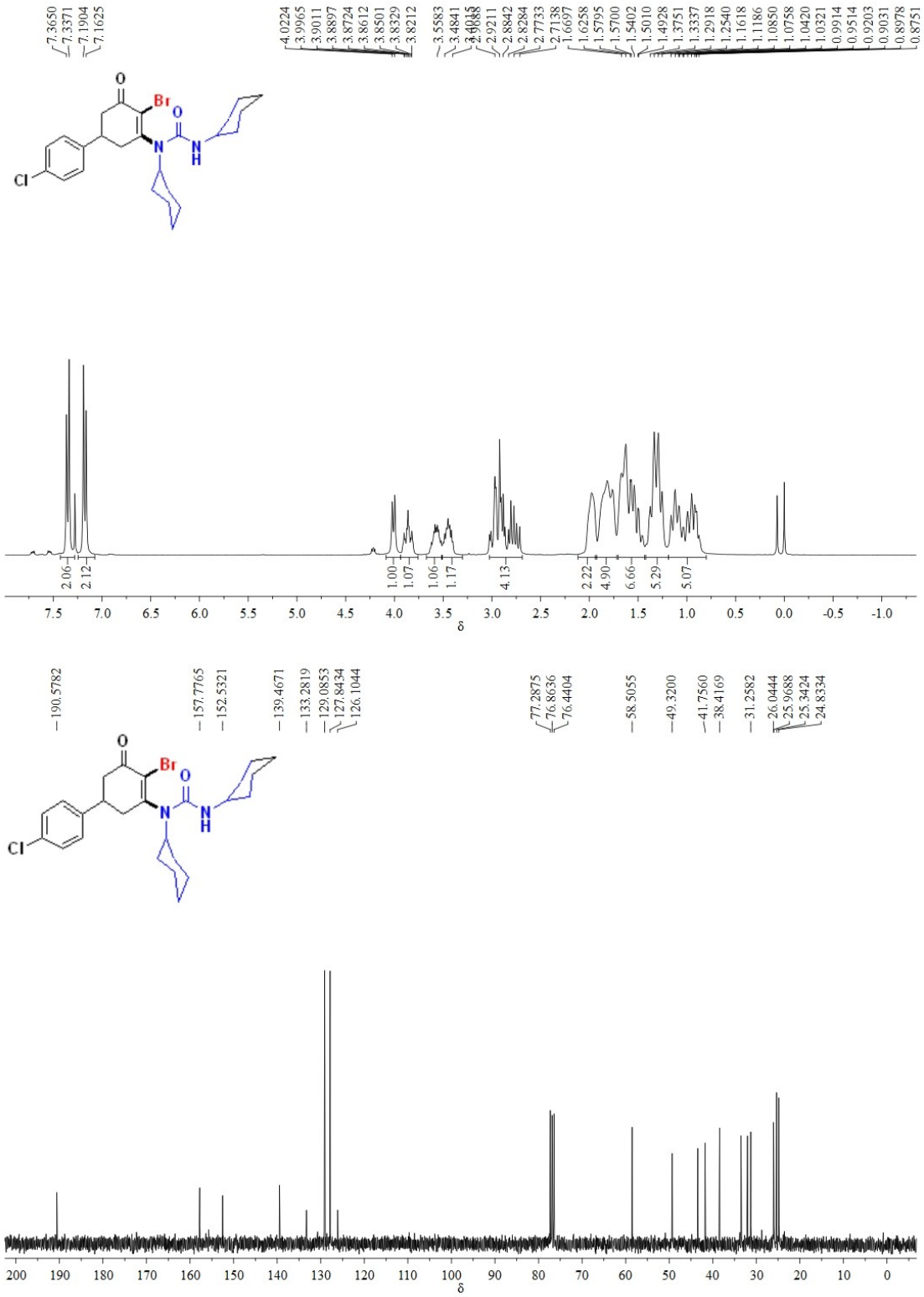




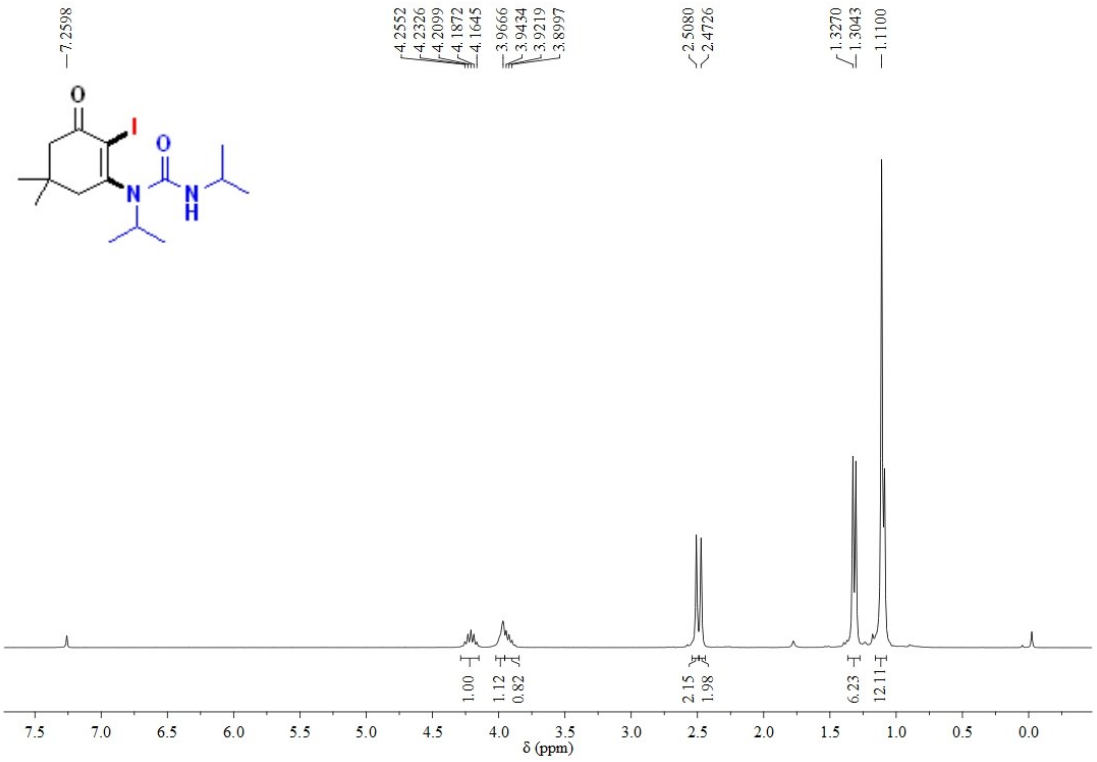
^{1}H and ^{13}C NMR spectra of compound 4q

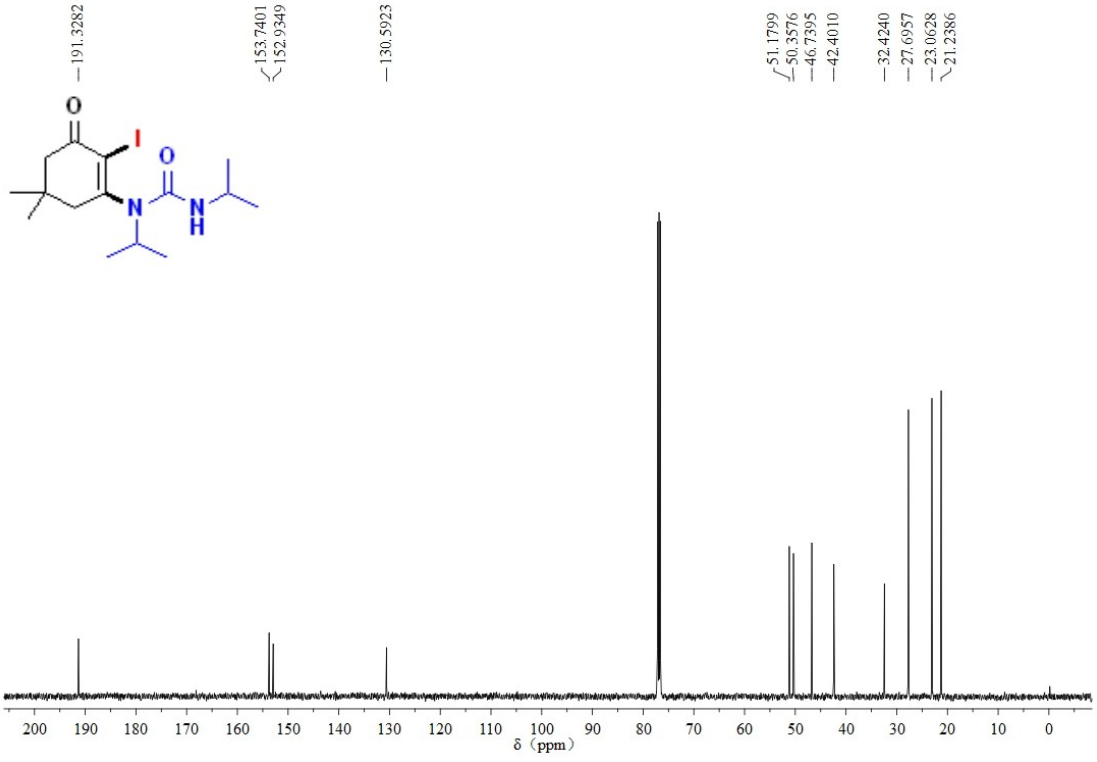


^{1}H and ^{13}C NMR spectra of compound 4r

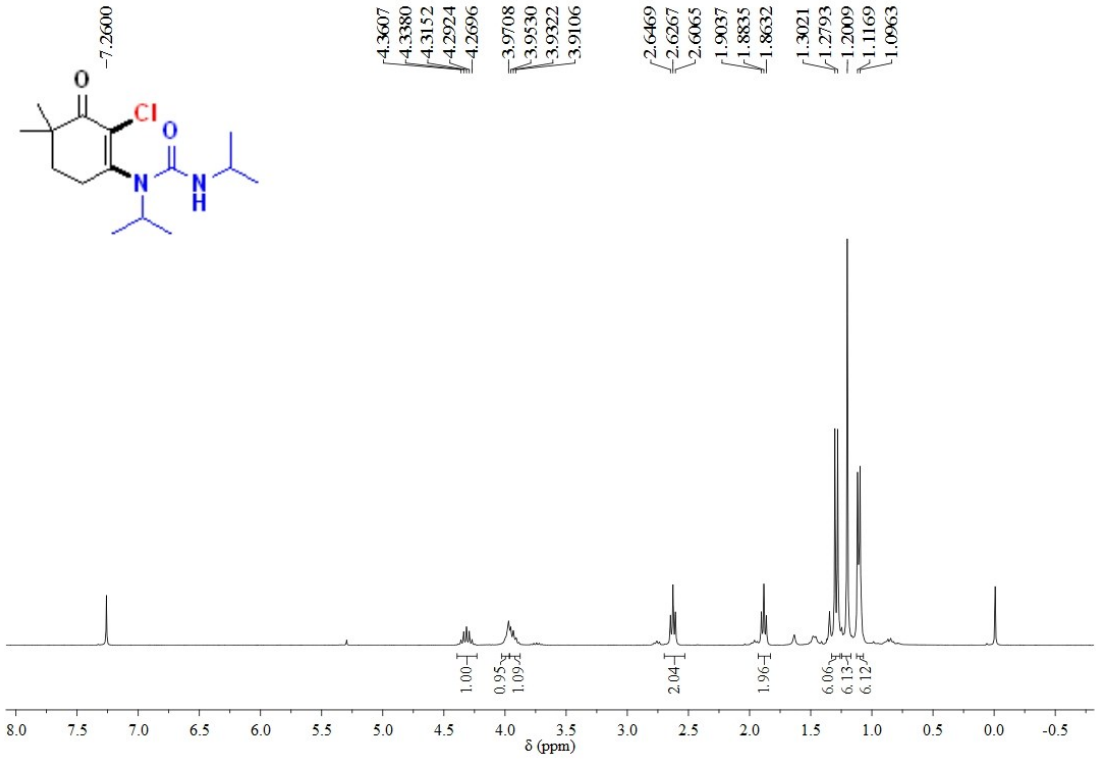


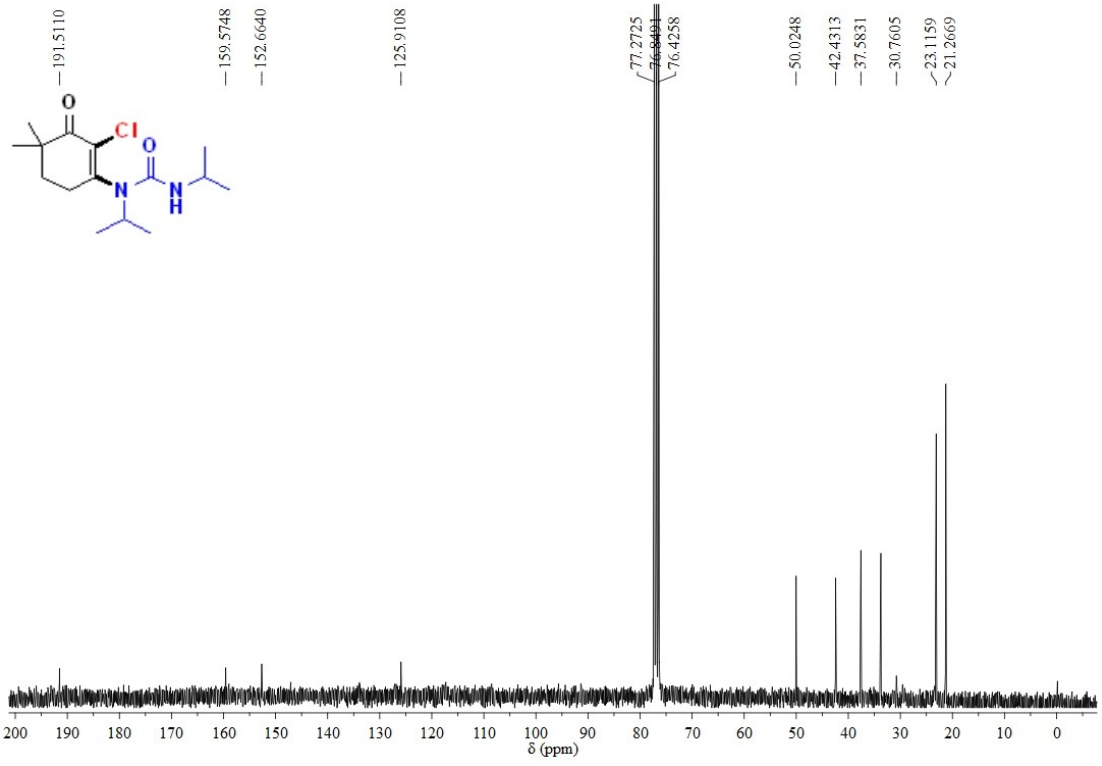
^{1}H and ^{13}C NMR spectra of compound 4s



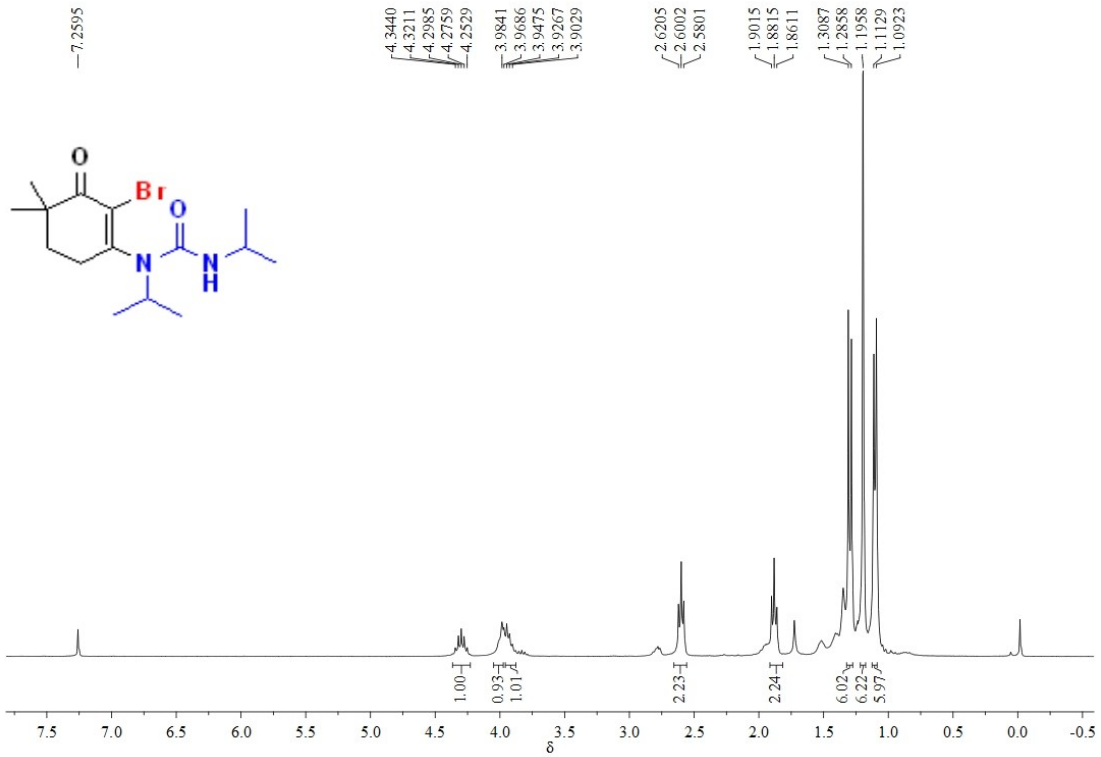


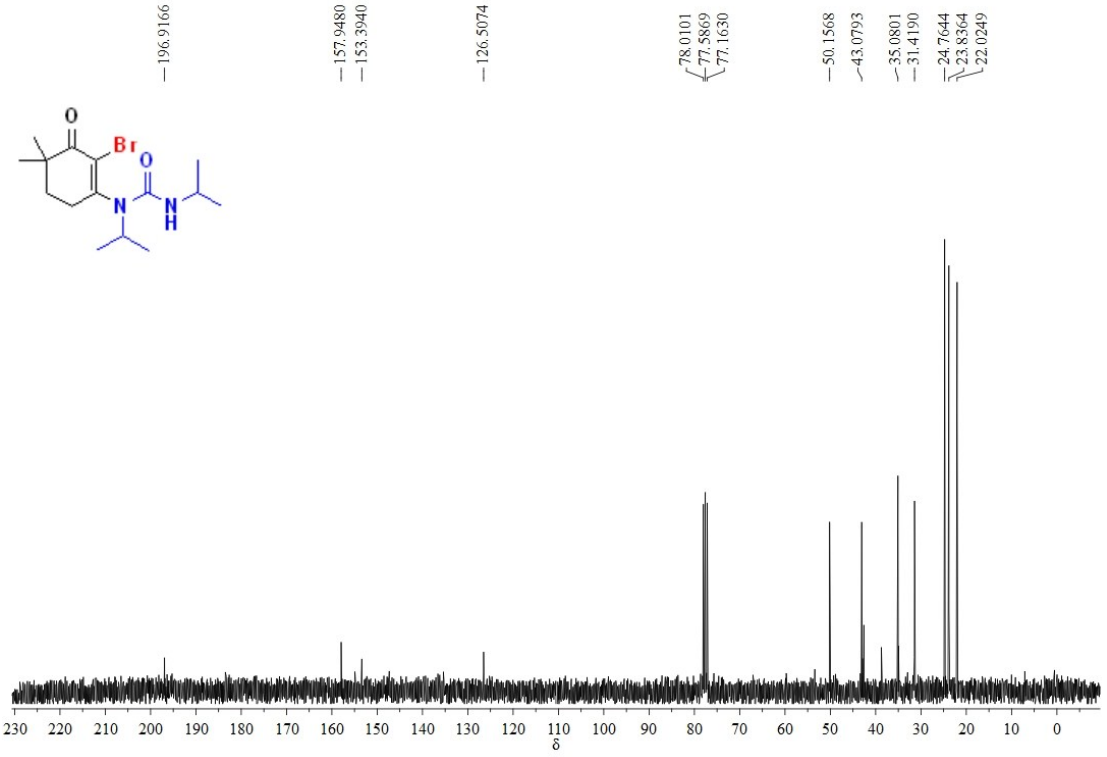
^{1}H and ^{13}C NMR spectra of compound 4t



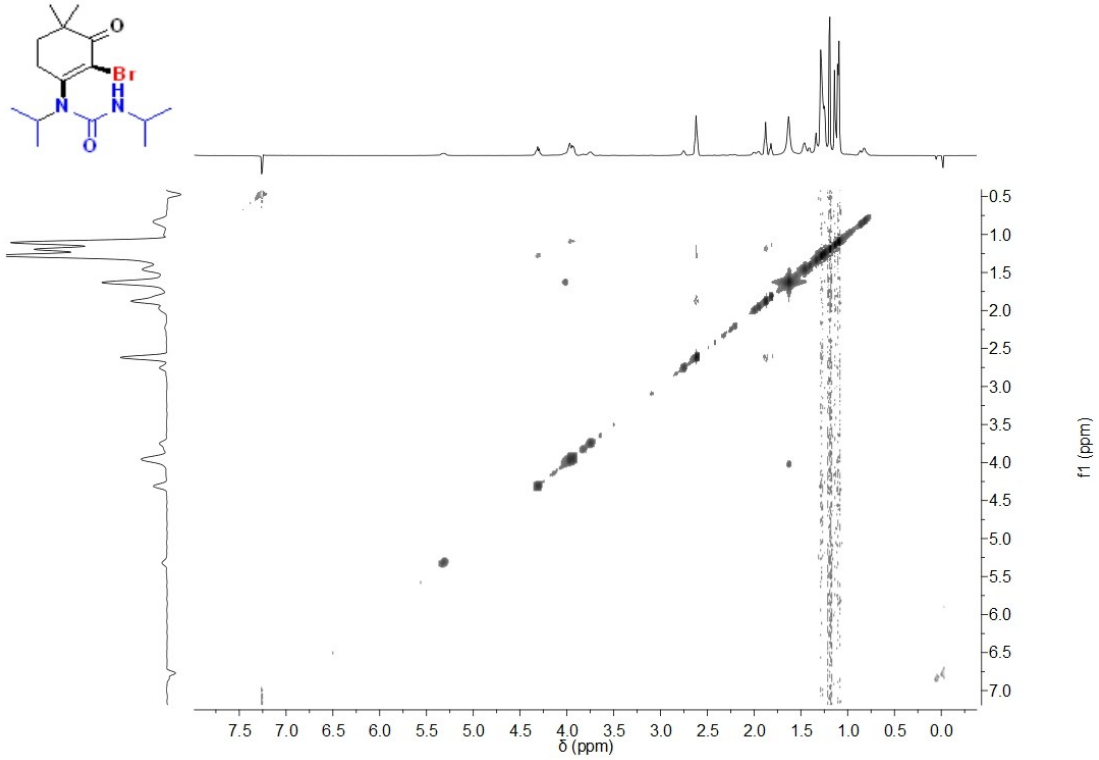


^{1}H and ^{13}C NMR spectra of compound 4u





7. The NOESY spectra of compound 4u



8. X-ray crystallography structure of compound 4b

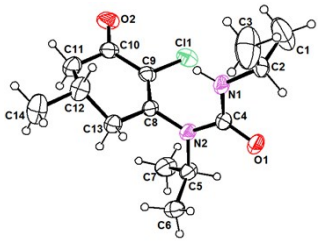


Figure S1. X-ray crystal structure of **4b**

Crystal data for **4b**: $C_{14}H_{23}ClN_2O_2$, monoclinic, Mr = 286.79, a = 13.9531(13) Å, b = 18.3735(17) Å, c = 12.4880(12) Å, α = 90 °, β = 90.003(3) °, γ = 90°, V = 3201.5(5) Å^3, T = 293 (2) K, space group $P2_1/c$, Z = 8, 27226 reflections collected, 7192 unique (Rint = 0.1008) which were used in all calculation. The ellipsoid contour probability level in the caption of 30 %. Crystallographic data for compound **4b** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. **CCDC-1993682**.

Table S1. Crystal data and structure refinement for 151209a.

Identification code	151209a	
Empirical formula	$C_{14}H_{23}ClN_2O_2$	
Formula weight	286.79	
Temperature/K	293.15	
Crystal system	monoclinic	
Space group	$P2_1/c$	
	a = 13.9531(13) Å	α = 90°
	b = 18.3735(17) Å	β = 90.003(3)°
	c = 12.4880(12) Å	γ = 90°
Volume/Å^3	3201.5(5)	
Z	8	
ρ_{calc}g/cm^3	1.190	
μ/mm^{-1}	0.239	
F(000)	1232.0	
Crystal size/mm^3	0.23 × 0.22 × 0.21	
Radiation	MoKα (λ = 0.71073)	
2Θ range for data collection/°	2.918 to 54.948	
Index ranges	-16 ≤ h ≤ 18, -23 ≤ k ≤ 23, -16 ≤ l ≤ 16	
Reflections collected	27226	
Independent reflections	7192 [R_{int} = 0.1008, R_{sigma} = 0.0660]	
Data/restraints/parameters	7192/55/392	
Goodness-of-fit on F^2	1.018	
Final R indexes [I>=2σ (I)]	R_1 = 0.0580, wR_2 = 0.1420	
Final R indexes [all data]	R_1 = 0.1040, wR_2 = 0.1678	
Largest diff. peak/hole / e Å^{-3}	0.31/-0.29	