

Supporting Information

For

Catalyst-free Synthesis of 3-substituted-3-hydroxy-2-oxindoles by Reaction of Isatin and Cyclic Enaminone in Water

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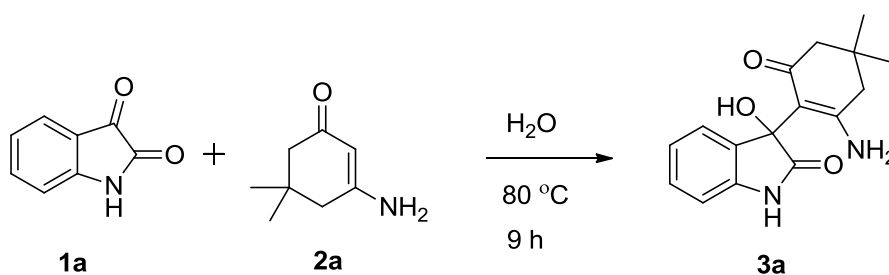
- General remarks
- General experimental procedure
- Characterization data for compounds
- Copies of ^1H and ^{13}C NMR

General remarks

Commercially available isatin, Dimedone and Ammonium acetate from Aldrich, Spectrochem, Himedia were used. The progress of reactions was monitored by thin layer chromatography (TLC). 1D and 2D NMR spectra were recorded in $\text{MeOH-}d_4/\text{DMSO-}d_6$ at 300/400 MHz for ^1H and 75/100 MHz for ^{13}C on Bruker Avance DPX-300MHz/DPX-400MHz. Chemical shifts were reported in δ (ppm) relative to $\text{DMSO-}d_6$ as internal standards. Integrals are in accordance with assignments, coupling constants are given in Hz. The HRMS was recorded on a JOEL-AccuTOF JMS-T100LC Mass spectrometer having a DART source. Yields refer to quantities obtained after column chromatography.

General experimental procedure

3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-3-hydroxyindolin-2-one (3a): A mixture of isatin (**1a**) (0.3 gm, 2.0 mmol) and enaminone^[1] (**2a**) (0.333 gm, 2.4 mmol) in 10 mL of water was heated in an oil bath at 80 °C for 9 hours. Initially reaction mixture appeared to be homogeneous but with the progress of reaction the solid precipitated out. After the TLC indicated the complete consumption of starting materials, the precipitated solid was filtered off. The solid was then dried under vacuum and it was purified by silica gel column chromatography by using EA:hexane (8:2) as an eluent to provide desired product **3a** as a white solid in 72% yield.



All the other experiments were performed in the similar manner and the respective reaction time and yield is mentioned in the results and discussion section of paper.

For the synthesis of enaminone

1. Tiwari, K. N.; Mane, U. R.; Kumari, P.; Vatsa, P.; Prabhakaran, S. M; *Synth. Commun.* **2017**, 47, 1013-1019.

- **Characterization data for compounds**

3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-3-hydroxyindolin-2-one (3a): Isolated as a white solid, 72%, m.p.: 218 - 220 °C ¹H NMR (300 MHz, MeOH-*d*₄) δ ppm 7.24 - 7.21 (m, 1H), 7.20 - 7.17 (m, 1H), 6.99 - 6.94 (m, 1H), 6.87 (d, *J* = 1.00 Hz, 1H), 2.29 (s, 2H), 2.24 (s, 2H), 1.08 (s, 3H), 1.06 (s, 3H), ¹³C NMR (75 MHz, MeOH-*d*₄) δ ppm 198.0, 171.6, 145.7, 134.4, 129.1, 123.3, 122.4, 113.1, 111.1, 102.6, 79.5, 51.6, 44.2, 34.6, 27.5, 27.0, HRMS (ESI) *m/z* for C₁₆H₁₈N₂O₃ [M+H]⁺, calcd., 287.1395, found: 287.1398

3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-chloro-3-hydroxyindolin-2-one (3b): Isolated as a white solid, 68%, m.p.: 174 - 176 °C, ¹H NMR (300 MHz, MeOH-*d*₄) δ ppm 7.18 - 7.17 (m, 1H), 7.15 - 7.14 (m, 1H), 6.82 - 6.80 (m, 1H), 2.54 - 2.48 (m, 1H), 2.38 - 2.28 (m, 1H), 2.18 - 2.12 (m, 1H), 1.99 - 1.92 (m, 1H), 1.09 (s, 3H), 0.99 (s, 3H), ¹³C NMR (75 MHz, MeOH-*d*₄) δ ppm 195.2, 168.2, 142.5, 136.8, 129.9, 128.1, 124.7, 112.1, 106.3, 79.7, 50.9, 45.7, 33.2, 29.0, 27.5, HRMS (ESI) *m/z* for C₁₆H₁₇ClN₂O₃ [M + H]⁺, calcd., 321.1005, found: 321.0993.

3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-bromo-3-hydroxyindolin-2-one (3c): Isolated as a white solid, 67%, m.p.: 196 - 198 °C ¹H NMR (300 MHz, MeOH-*d*₄) δ ppm 7.32 - 7.31 (m, 1H), 7.30 - 7.29 (m, 1H), 6.77 (d, *J* = 8.69 Hz, 1H), 2.54 - 2.38 (m, 1H), 2.33 (dd, *J* = 16.15, 1.42 Hz, 1H), 2.17 - 2.16 (m, 1H), 1.98 - 1.92 (m, 1H), 1.09 (s, 3H), 0.99 (s, 3H), ¹³C NMR (75 MHz, MeOH-*d*₄) δ ppm 195.1, 168.2, 143.0, 137.3, 132.8, 127.6, 115.2, 112.7, 106.3, 79.7, 50.8, 45.7, 33.3, 29.0, 27.5, HRMS (ESI) *m/z* for C₁₆H₁₇BrN₂O₃ [M + H]⁺, calcd., 365.0500, found: 365.0502.

3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-iodo-3-hydroxyindolin-2-one (3d): Isolated as a white solid, 70%, m.p.: 194 - 196 °C, ¹H NMR (300 MHz, MeOH-*d*₄) δ ppm 7.51 - 7.50 (m, 1H), 7.48 (s, 1H), 6.68 - 6.65 (m, 1H), 2.53 - 2.48 (m, 1H), 2.39 - 2.33 (m, 1H), 2.16 - 2.11 (m, 1H), 1.98 - 1.92 (m, 1H), 1.09 (s, 3H), 0.99 (s, 3H), ¹³C NMR (75 MHz, MeOH-*d*₄) δ ppm 198.0, 171.6, 145.7, 134.4, 129.1, 123.3, 113.1, 111.1, 102.6, 81.8, 55.4, 44.2, 33.3, 29.4, 27.5, HRMS (ESI) *m/z* for C₁₆H₁₇IN₂O₃ [M + H]⁺, calcd., 413.0362, found: 413.0326.

3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-methyl-3-hydroxyindolin-2-one (3e): Isolated as a white solid, 69%, m.p.: 192 - 194 °C, ¹H NMR (300 MHz, MeOH-*d*₄) δ ppm 6.91 - 6.88 (dt, *J* = 8.59, 0.80 Hz, 1H), 6.75 - 6.74 (m, 1H), 6.69 - 6.66 (m, 1H), 2.63 (s, 1H), 2.56 - 2.51 (m, 1H), 2.44 - 2.38 (dd, *J* = 17.00 Hz, 1.32 Hz, 1H), 2.18 (s, 3H), 2.06 - 2.00 (m, 1H), 1.09 (s, 3H), 1.01 (s, 3H), ¹³C NMR (75 MHz, MeOH-*d*₄) δ ppm 197.2, 168.0, 152.9, 141.6,

137.7, 132.4, 129.0, 124.6, 112.8, 109.8, 79.0, 52.1, 41.9, 33.3, 29.1, 27.3, 21.2, HRMS (ESI) m/z for $C_{17}H_{20}N_2O_3$ $[M + H]^+$, calcd., 300.1473, found: 300.1570.

3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-nitro-3-hydroxyindolin-2-one (3f):

Isolated as a white solid, 77%, m.p.:188 - 190 °C, 1H NMR (300 MHz, MeOH- d_4) δ ppm 8.18 - 8.15 (dd, J = 8.59, 2.36 Hz, 1H), 8.04 (d, J = 2.27 Hz, 1H), 6.98 (d, J = 8.50 Hz, 1H), 2.55 - 2.50 (m, 1H), 2.43 - 2.38 (m, 1H), 2.18 - 2.17 (m, 1H), 2.01 - 1.98 (m, 1H), 1.10 (s, 3H), 0.99 (s, 3H), ^{13}C NMR (75 MHz, MeOH- d_4) δ ppm 195.3, 168.6, 150.2, 144.3, 136.0, 127.2, 120.0, 110.7, 105.9, 79.2, 50.7, 45.7, 33.3, 28.8, 27.6, HRMS (ESI) m/z for $C_{16}H_{17}N_3O_5$ $[M + H]^+$, calcd., 332.1246, found: 332.1248.

3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-bromo-3-hydroxy-1-methylindolin-2-one (3g):

Isolated as a white solid, 65%, m.p.:178 - 180 °C, 1H NMR (300 MHz, MeOH- d_4) δ ppm 7.42 - 7.41 (m, 1H), 7.39 - 7.38 (m, 1H), 7.35 - 7.34 (m, 1H), 6.85 (d, J = 8.31 Hz, 1H), 3.18 (s, 3H), 2.53 - 2.48 (m, 1H), 2.38 - 2.28 (m, 1H), 2.14 - 2.09 (m, 1H), 1.99 - 1.89 (m, 1H), 1.09 (s, 3H), 0.97 (s, 3H), ^{13}C NMR (75 MHz, MeOH- d_4) δ ppm 195.1, 168.3, 144.7, 135.6, 132.9, 127.2, 115.8, 111.2, 106.3, 79.2, 50.8, 45.7, 33.2, 28.9, 27.5, 26.7, HRMS (ESI) m/z for $C_{17}H_{19}BrN_2O_3$ $[M + H]^+$, calcd., 379.0657, found: 379.0640

3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-iodo-3-hydroxy-1-methylindolin-2-one (3h):

Isolated as a white solid, 68%, m.p.:184 - 186 °C, 1H NMR (300 MHz, MeOH- d_4) δ ppm 7.60 - 7.57 (m, 1H), 7.52 (d, J = 1.70 Hz, 1H), 6.76 (d, J = 8.31 Hz, 1H), 3.17 (s, 3H), 2.53 - 2.48 (m, 1H), 2.39 - 2.33 (m, 1H), 2.14 - 2.09 (m, 1H), 2.01 - 1.95 (m, 1H), 1.09 (s, 3H), 0.97 (s, 3H), ^{13}C NMR (75 MHz, MeOH- d_4) δ ppm 195.1, 168.35, 145.3, 139.1, 136.8, 132.9, 121.2, 111.8, 106.4, 85.3, 79.1, 50.8, 45.7, 33.2, 28.9, 27.5, 26.6, HRMS (ESI) m/z for $C_{17}H_{19}IN_2O_3$ $[M + H]^+$, calcd., 427.0440, found: 427.0505.

3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-methoxy-3-hydroxy-1-ethylindolin-2-one (3i):

Isolated as a white solid, 66%, m.p.:170 - 172 °C, 1H NMR (300 MHz, MeOH- d_4) δ ppm 6.90 - 6.89 (m, 1H), 6.82 - 6.81 (m, 2H), 3.72 (s, 3H), 3.18 (s, 3H), 2.55 - 2.50 (m, 1H), 2.35 - 2.28 (m, 1H), 2.16 - 2.11 (m, 1H), 1.93 - 1.87 (m, 1H), 1.09 (s, 3H), 0.96 (s, 3H), ^{13}C NMR (75 MHz, MeOH- d_4) δ ppm 195.1, 168.1, 157.8, 139.0, 135.6, 125.1, 114.3, 111.8, 109.8, 79.7, 56.3, 51.0, 45.7, 33.3, 29.6, 27.2, 26.7, HRMS (ESI) m/z for $C_{18}H_{22}N_2O_4$ $[M + H]^+$, calcd., 331.1657, found: 331.1665.

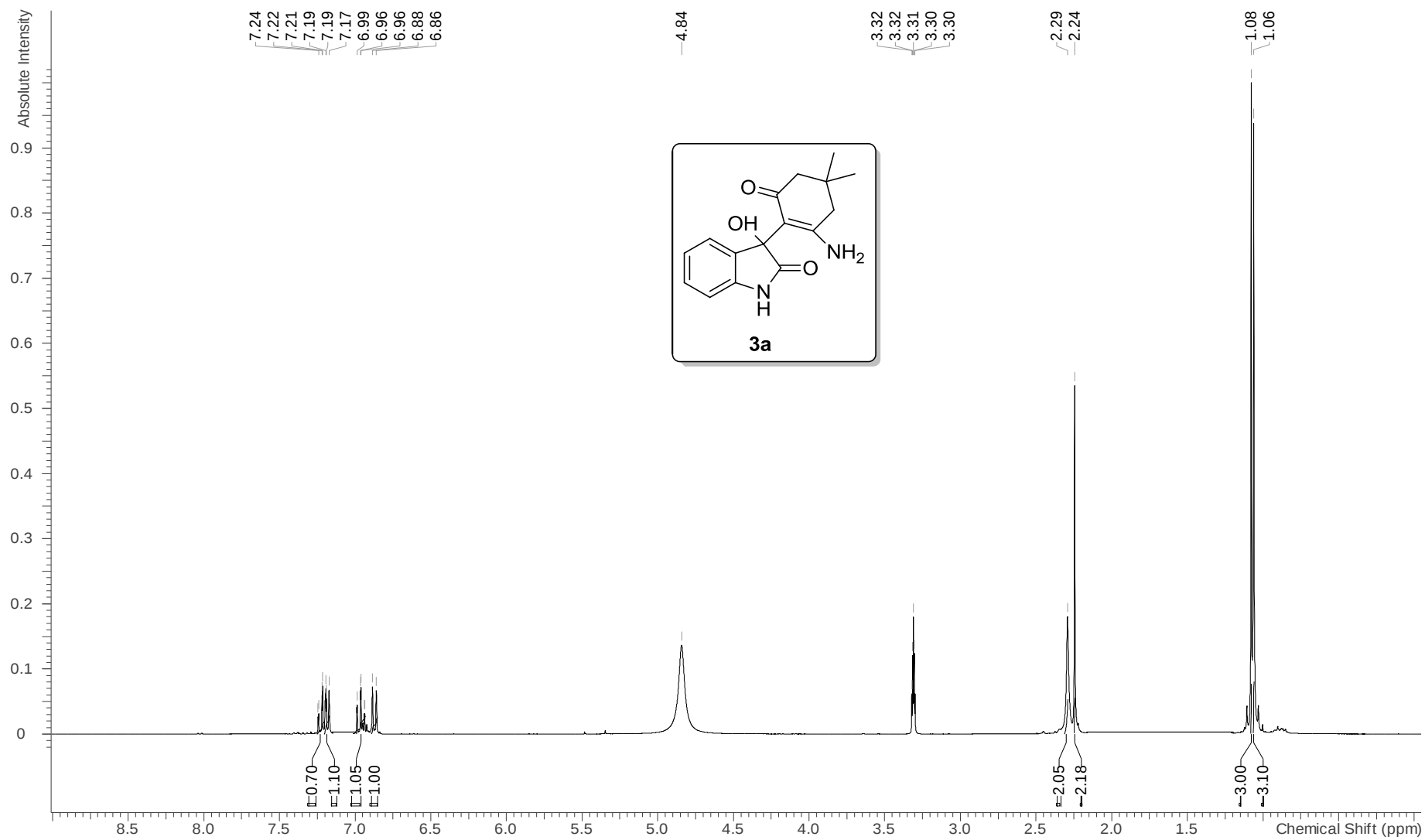
3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-4,7-dichloro-3-hydroxy-1-methyl

indolin-2-one (3j): Isolated as a white solid, 73%, m.p.:172 - 174 °C, ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.53 (s, 1H) 7.19 (d, *J* = 8.78 Hz, 1H), 6.84 (d, *J* = 8.78 Hz, 1H), 6.72 - 6.71 (m, 1H), 2.35 - 2.41 (m, 1H), 2.38 (d, *J* = 16.06 Hz, 1H), 2.18 - 2.11 (m, 1H), 1.96 (d, *J* = 16.06 Hz, 1H), 1.89 - 1.76 (m, 1H), 0.99 (s, 3H), 0.92 (s, 3H), ¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 191.3, 164.3, 153.7, 142.4, 131.9, 129.3, 127.4, 122.3, 112.1, 102.1, 79.4, 49.9, 44.2, 31.5, 28.7, 26.7, HRMS (ESI) *m/z* for C₁₆H₁₆ Cl₂N₂O₃ [M + H]⁺, calcd., 355.0616, found: 355.0615.

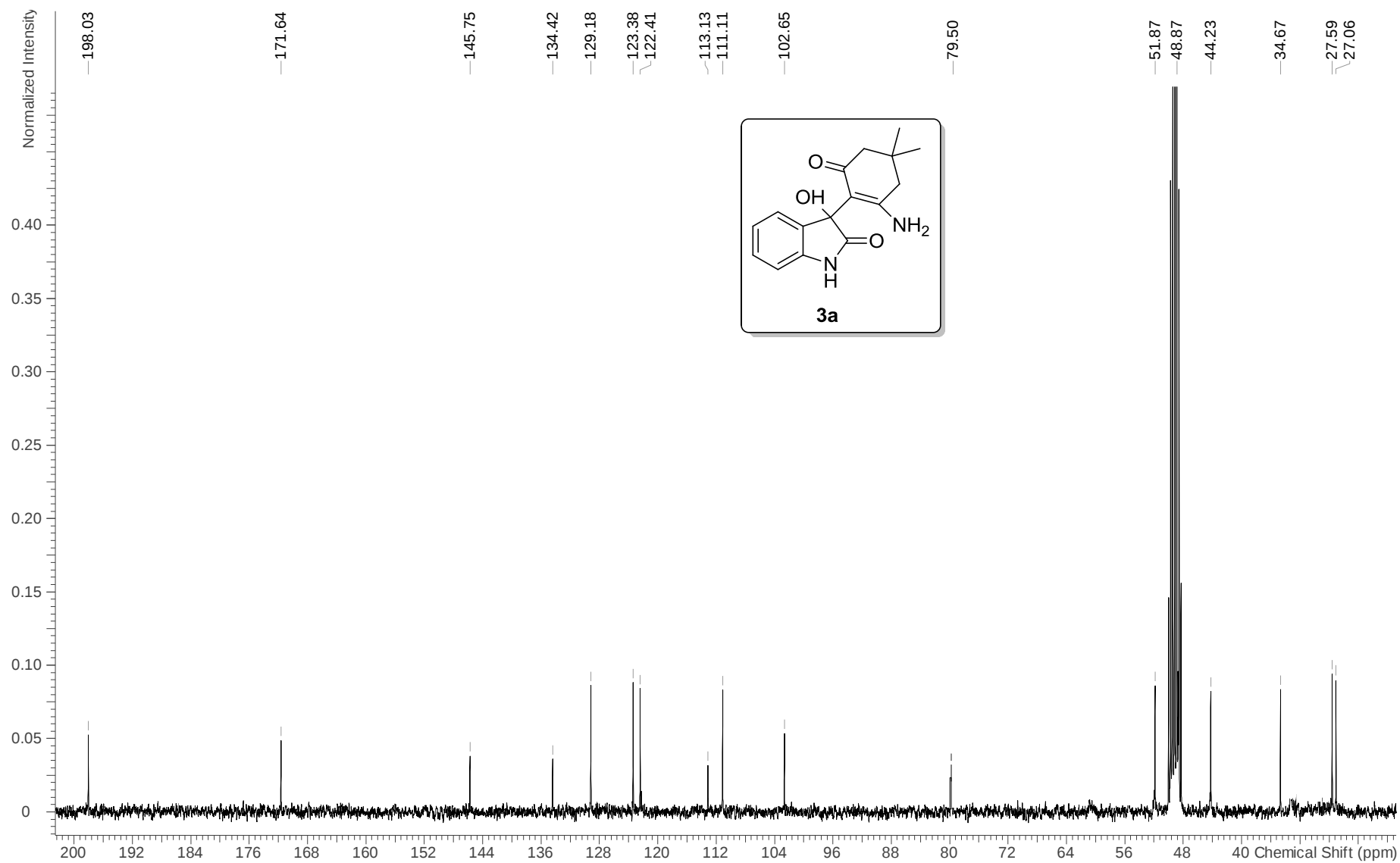
3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5,7-dibromo-3-hydroxy-1-

methyldolin-2-one (3k): Isolated as a white solid, 65%, m.p.:174 - 176 °C, ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.37 (s, 1H) 7.54 - 7.53 (d, *J* = 4 Hz, 1H), 7.11 (d, *J* = 4 Hz, 1H), 6.75 (s, 1H), 2.39 - 2.35 (m, 1H), 2.28 - 2.24 (m, 1H), 1.95 - 1.91 (m, 1H), 1.82 - 1.78 (m, 1H), 0.99 (m, 3H), 0.88 (m, 3H), ¹³C NMR (101 MHz, DMSO-*d*₆) δ ppm 191.3, 163.9, 154.5, 141.7, 137.8, 132.6, 124.6, 112.4, 104.4, 102.3, 78.3, 49.6, 43.9, 31.8, 28.2, 26.8, HRMS (ESI) *m/z* for C₁₆H₁₆ Br₂N₂O₃ [M + H]⁺, calcd., 442.9605, found: 442.9608.

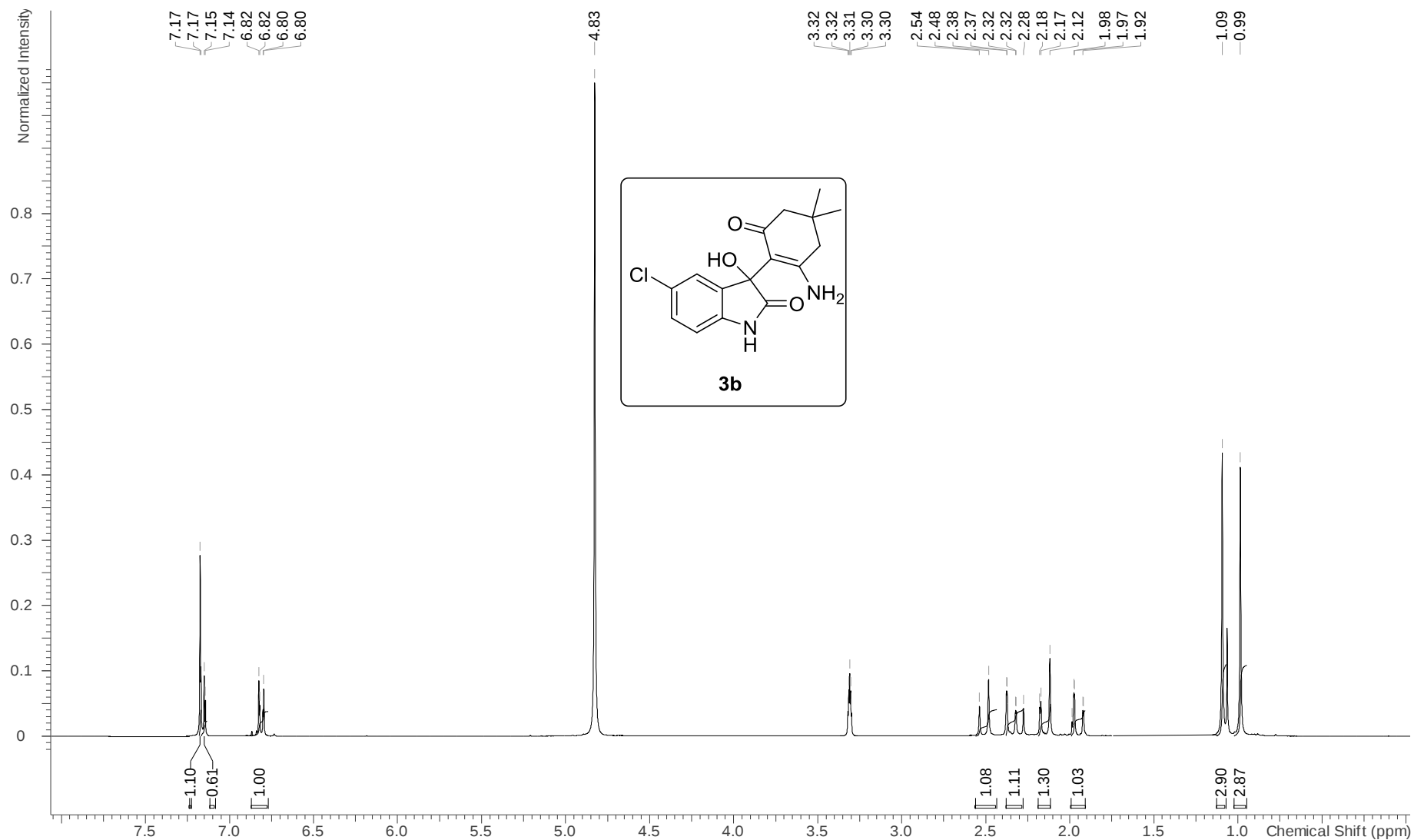
- Copies of ¹H and ¹³C NMR



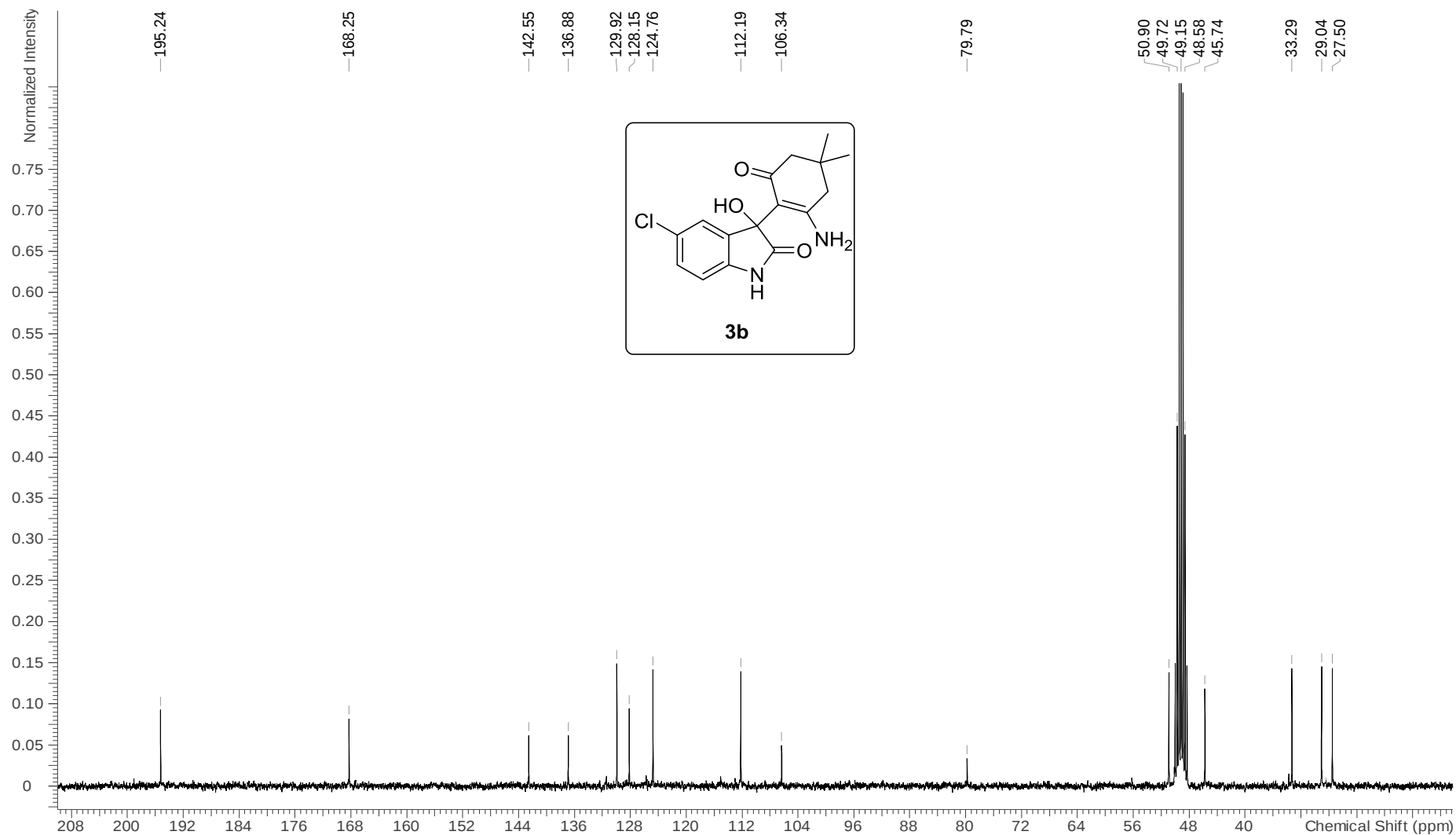
¹H NMR (300 MHz, MeOH-*d*₄) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-3-hydroxyindolin-2-one (**3a**)



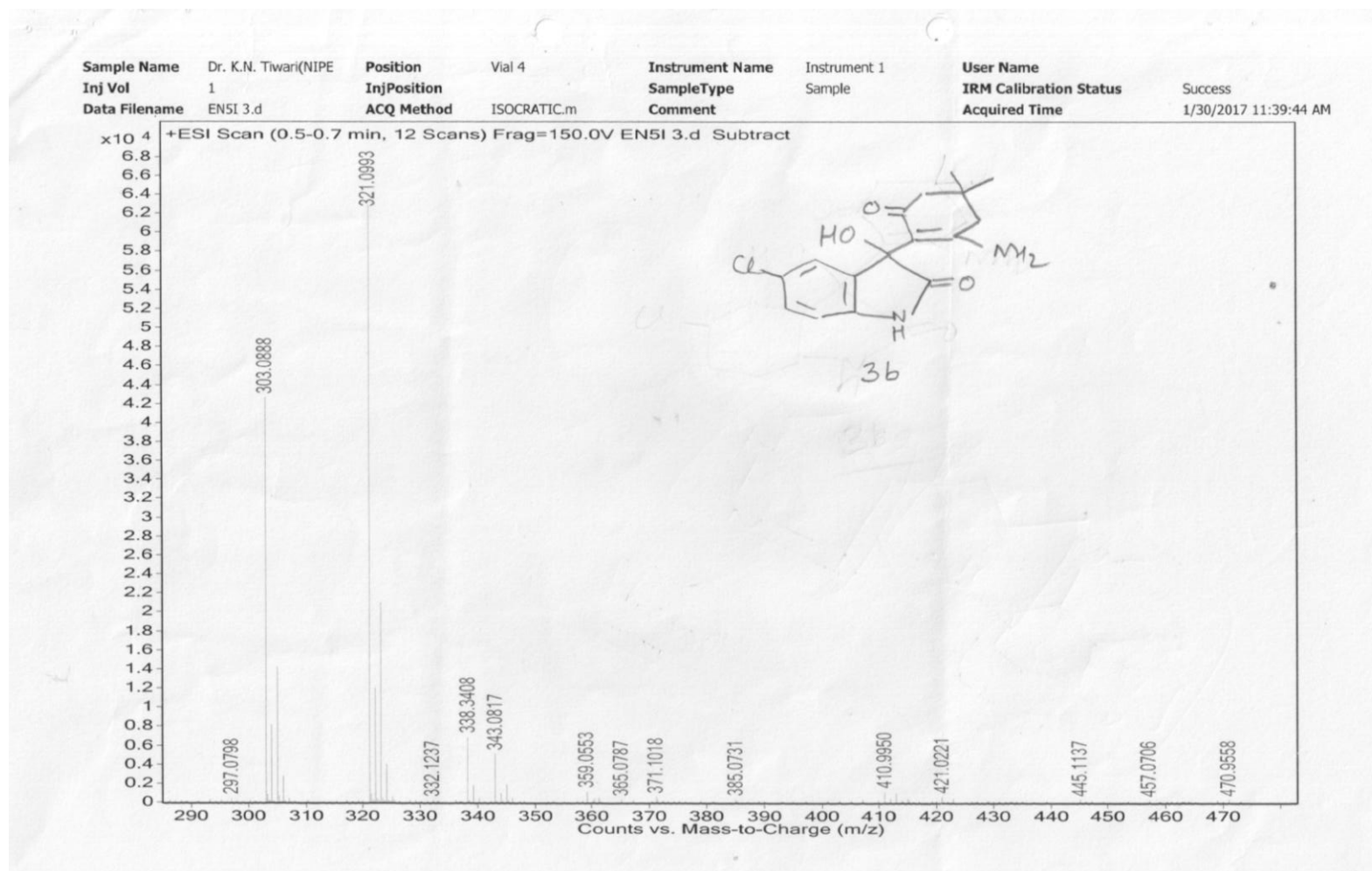
¹³C NMR (75 MHz, MeOH-*d*₄) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-3-hydroxyindolin-2-one (**3a**)



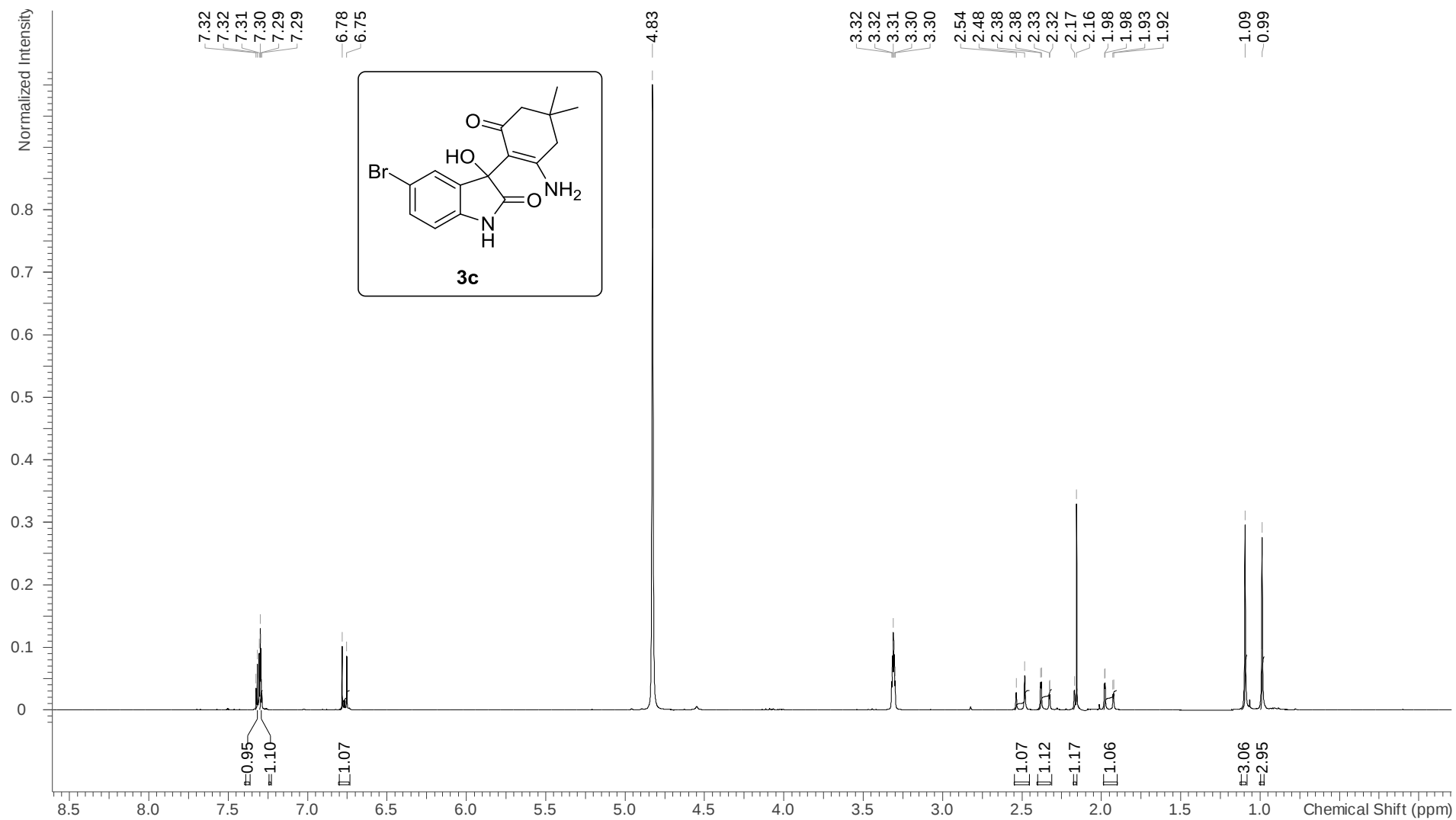
¹H NMR (300 MHz, MeOH-*d*₄) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-chloro-3-hydroxyindolin-2-one (**3b**).



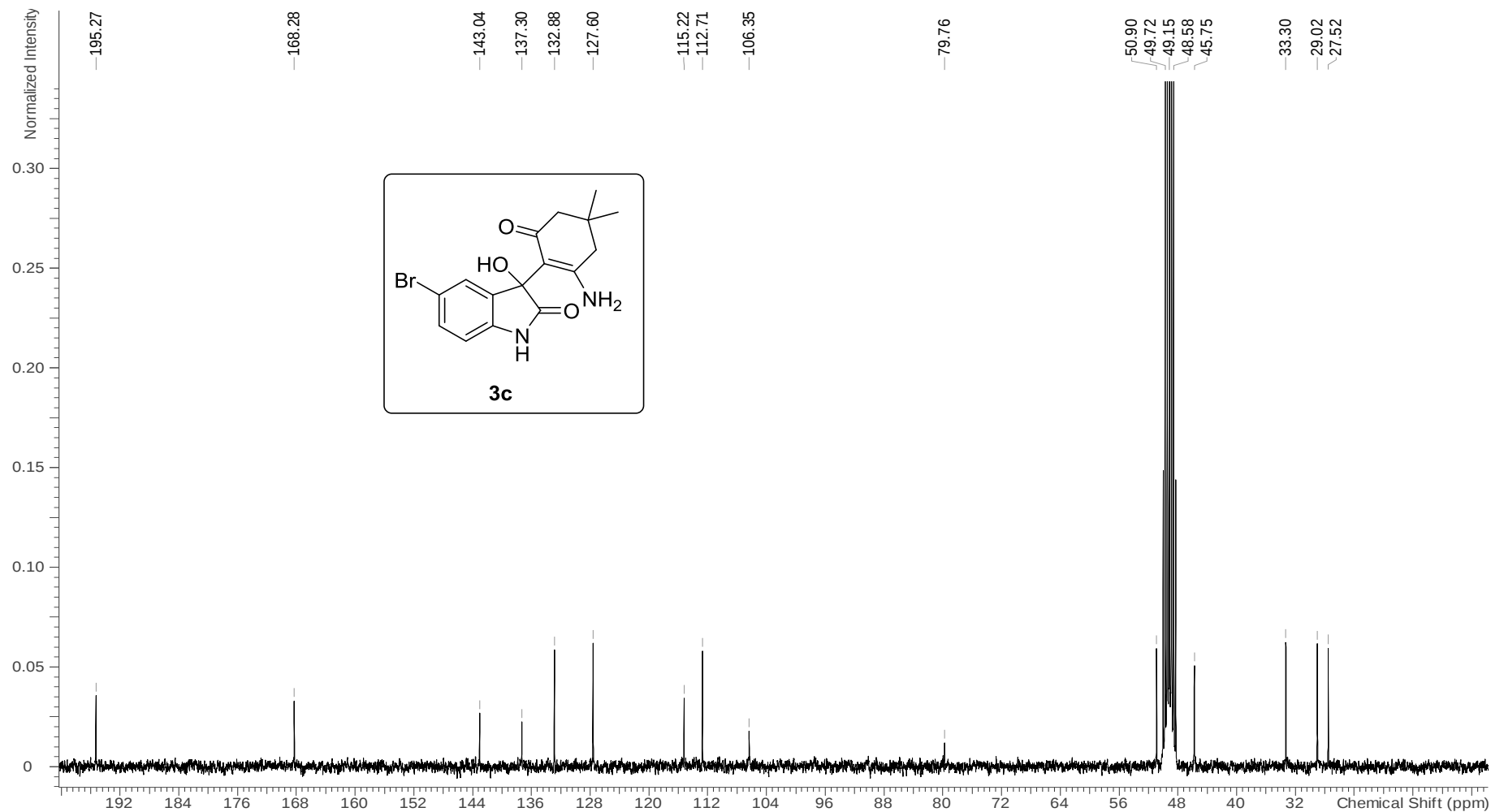
¹³C NMR (75 MHz, MeOH-*d*₄) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-chloro-3-hydroxyindolin-2-one (**3b**).



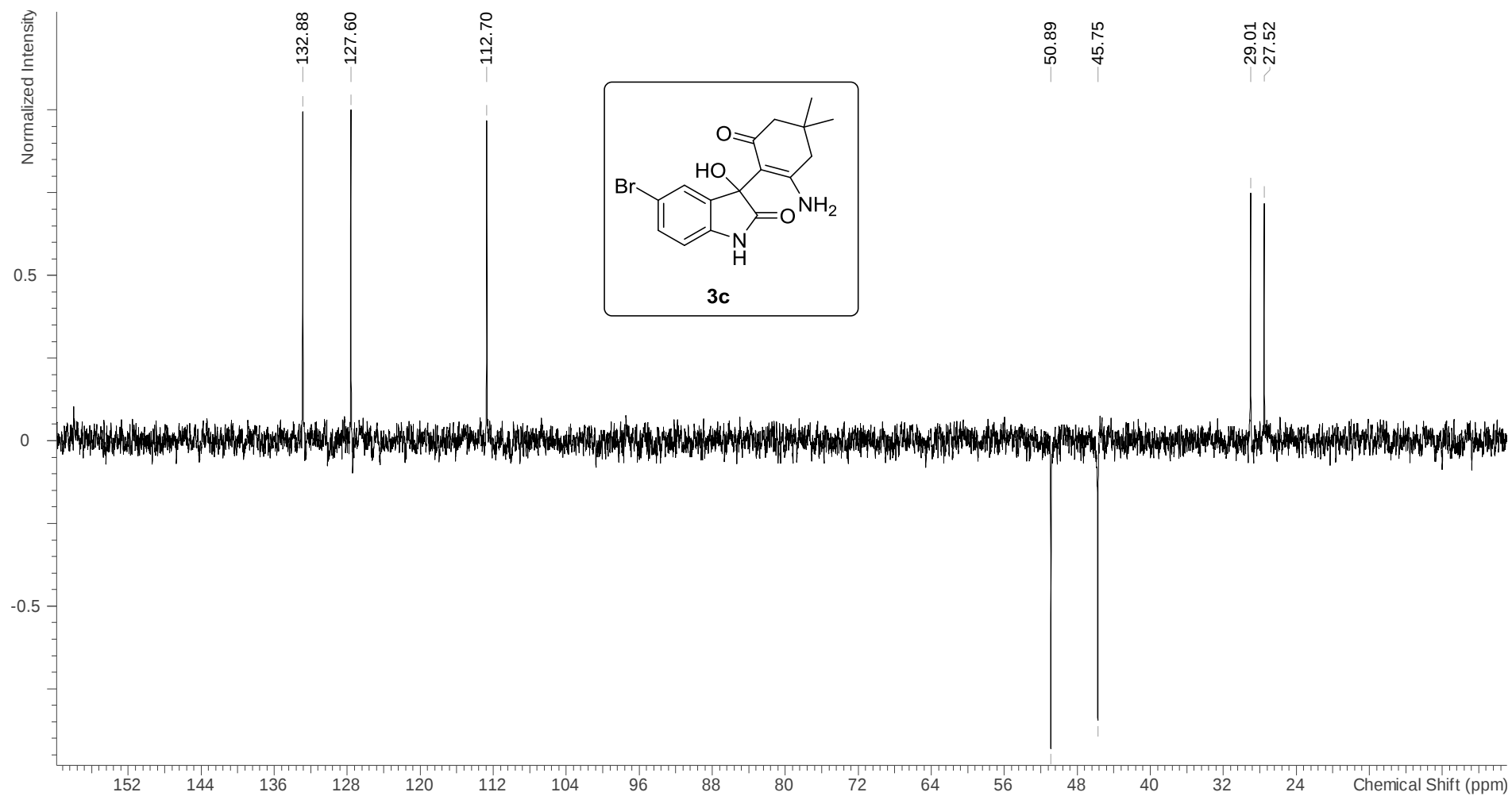
HRMS data of **3b**



¹H NMR (300 MHz, MeOH-*d*₄) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-bromo-3-hydroxyindolin-2-one (**3c**)

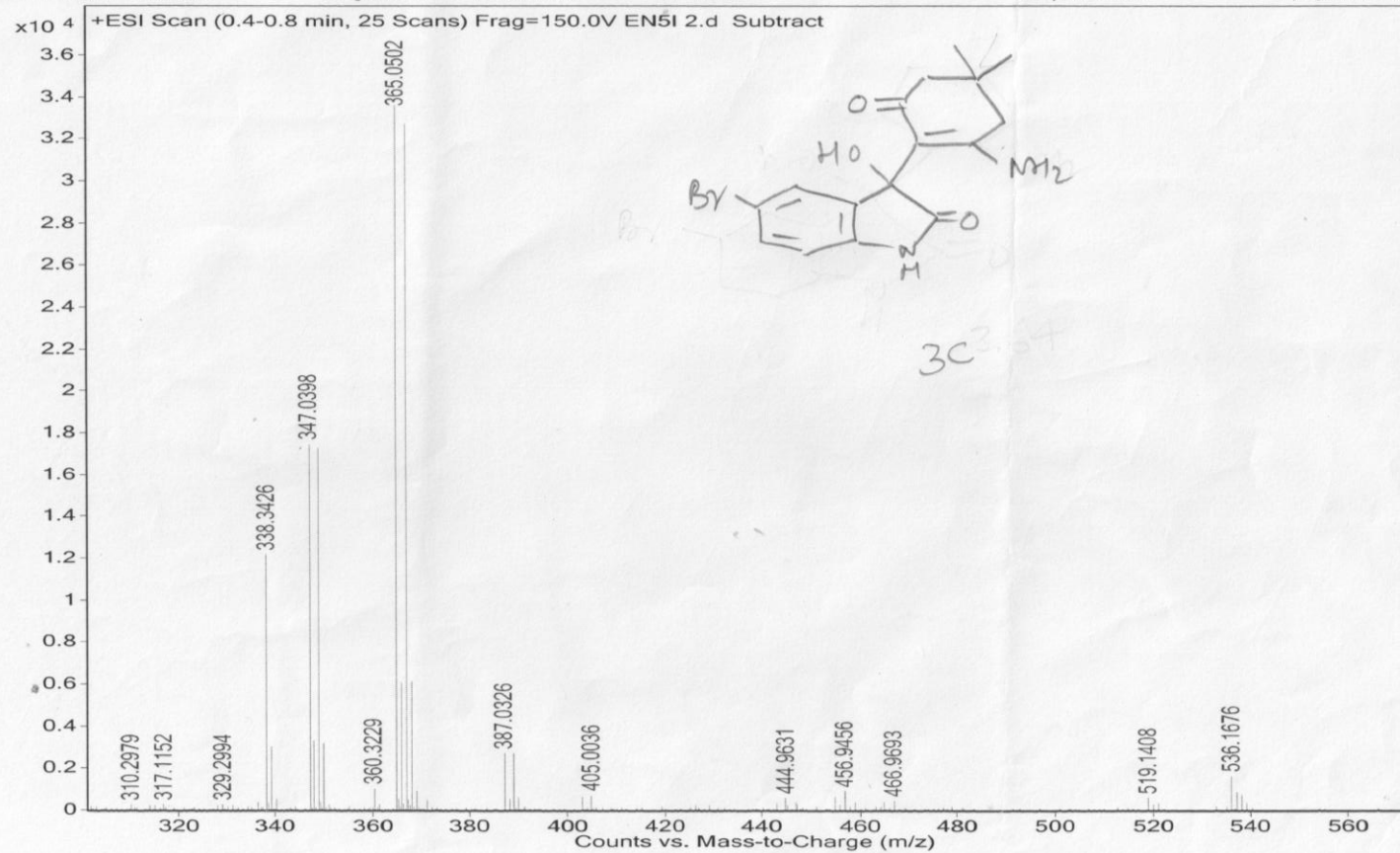


¹³C NMR (75 MHz, MeOH-*d*₄) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-bromo-3-hydroxyindolin-2-one (**3c**)

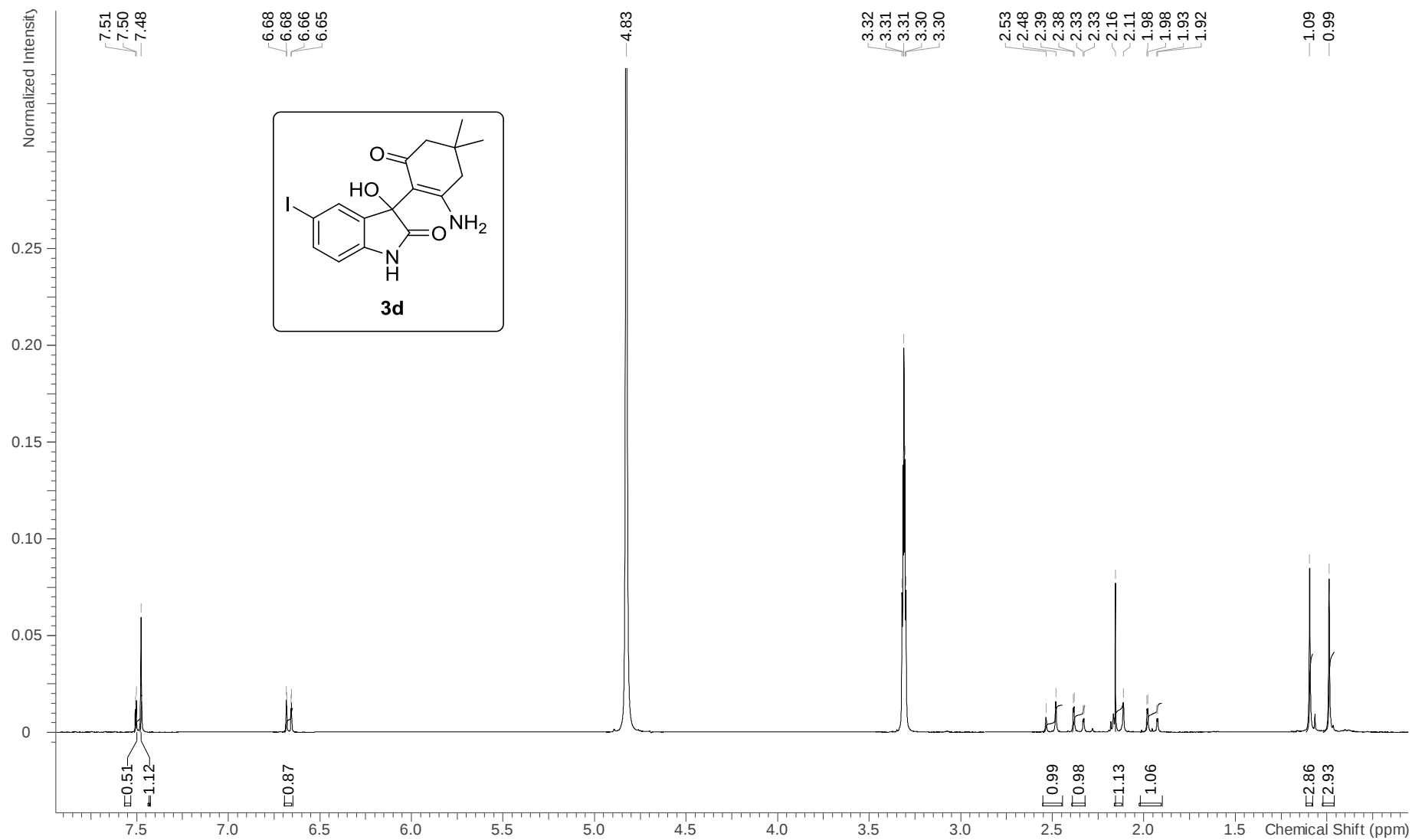


DEPT NMR of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-bromo-3-hydroxyindolin-2-one (**3c**)

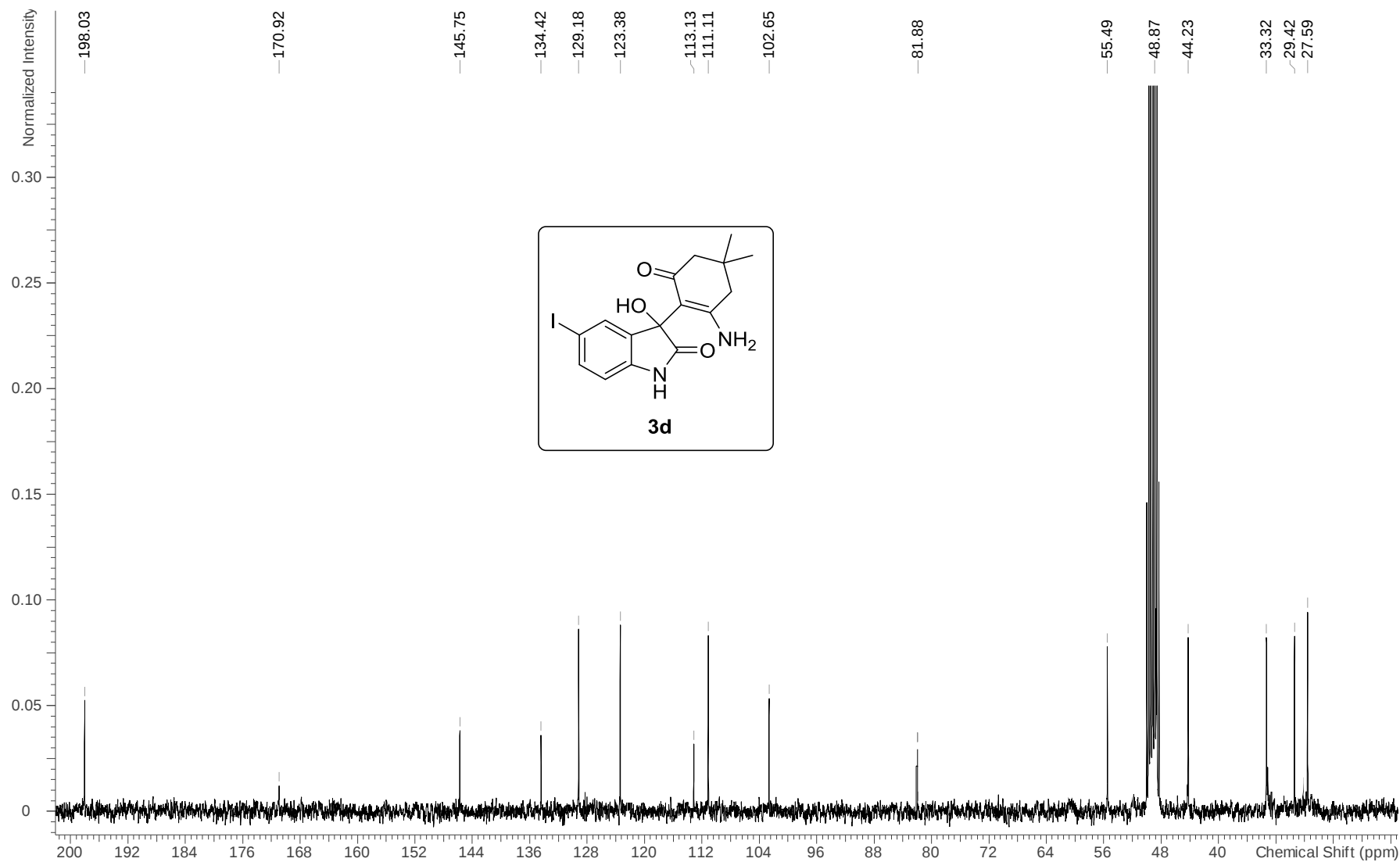
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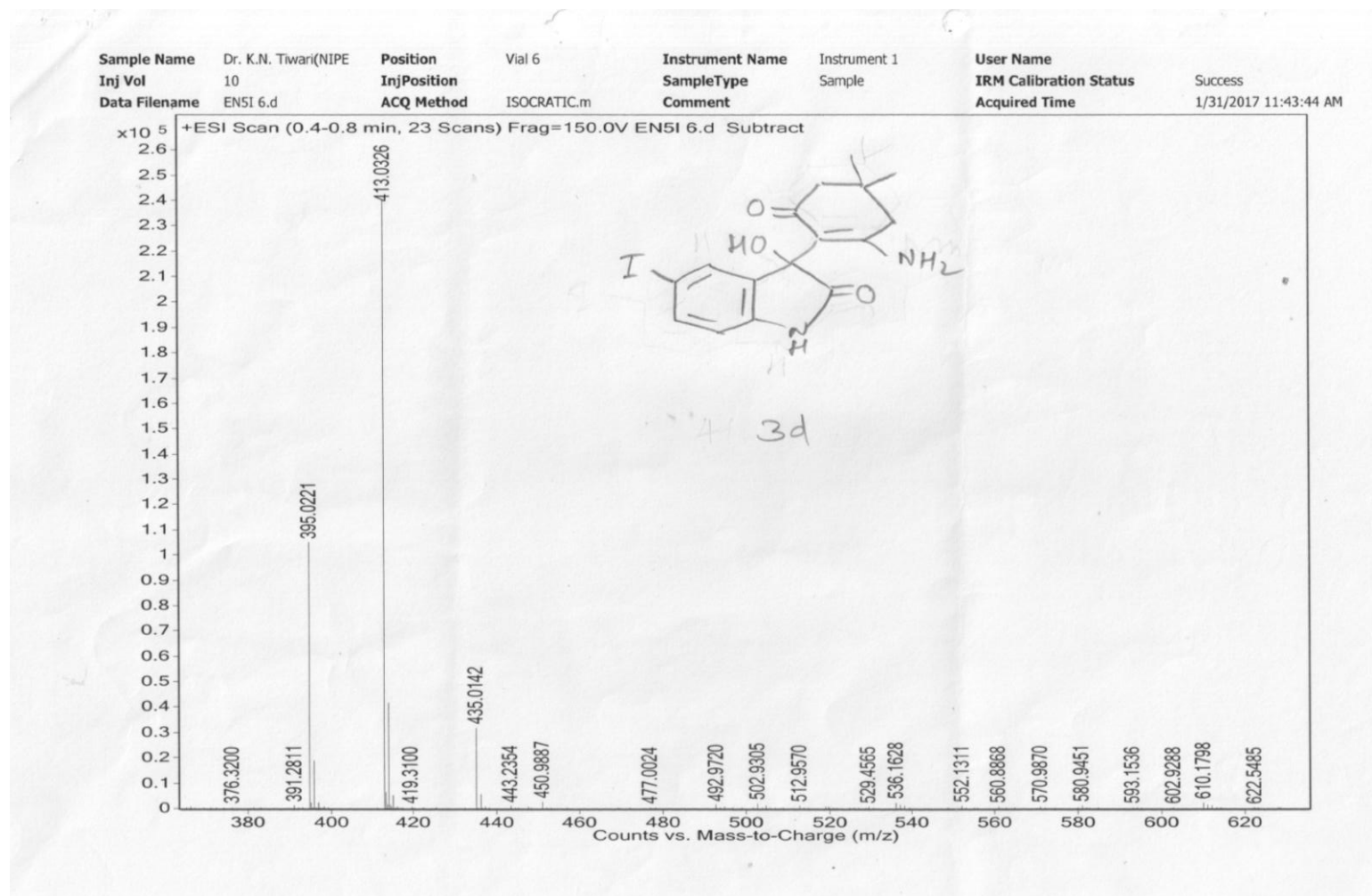
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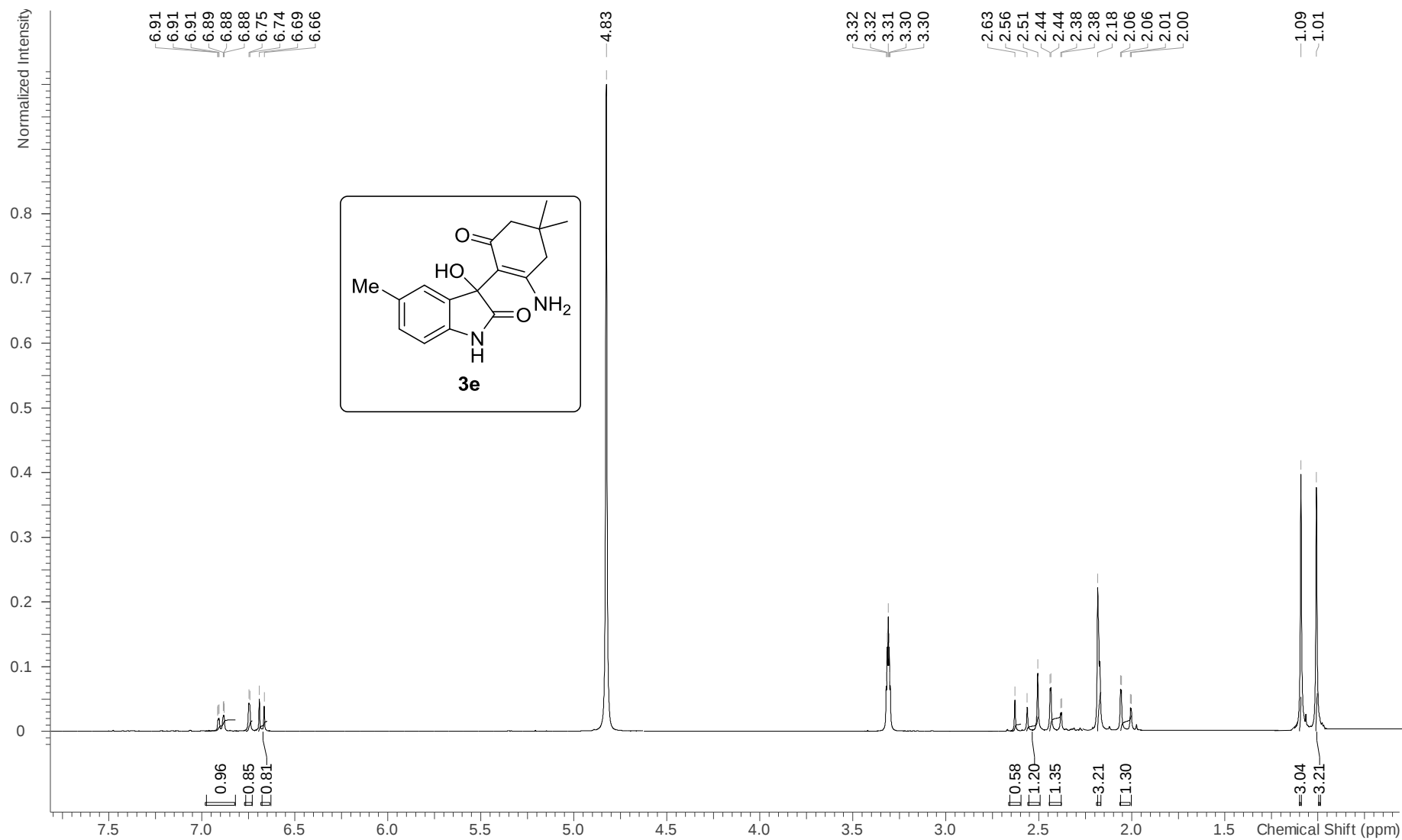
¹H NMR (300 MHz, MeOH-*d*₄) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-iodo-3-hydroxyindolin-2-one (**3d**).



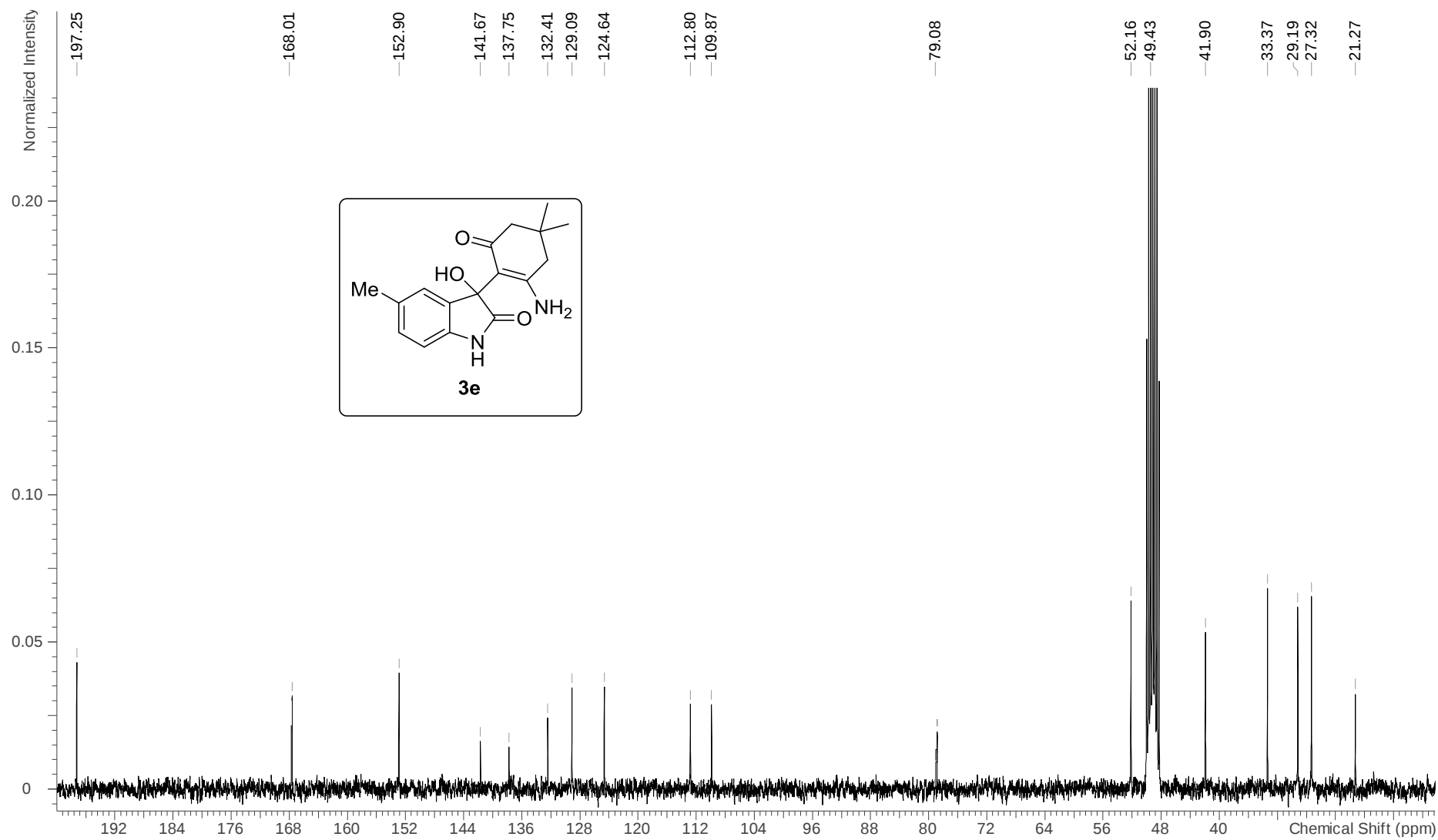
^{13}C NMR (75 MHz, $\text{MeOH-}d_4$) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-iodo-3-hydroxyindolin-2-one (**3d**).



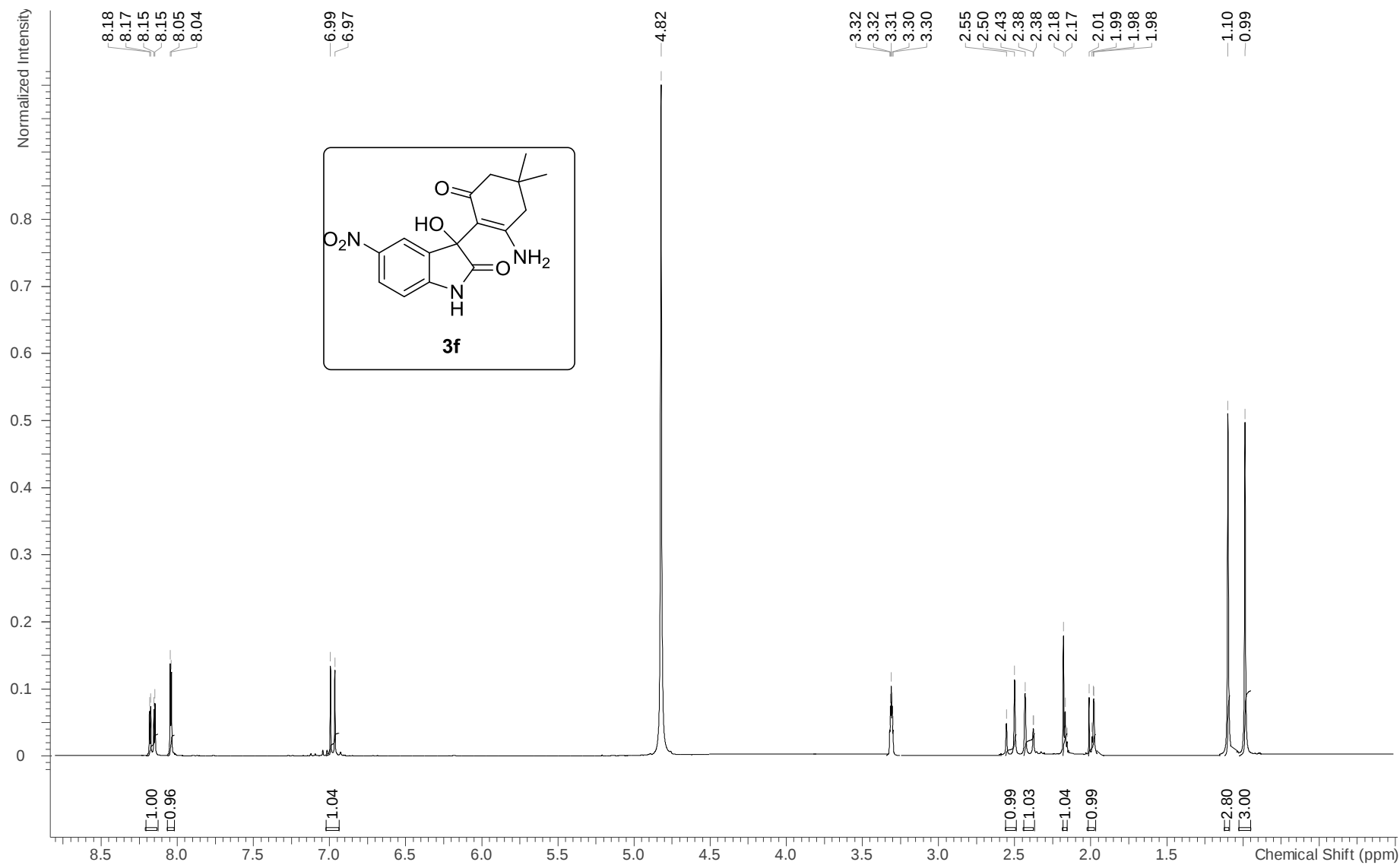
HRMS data of **3d**



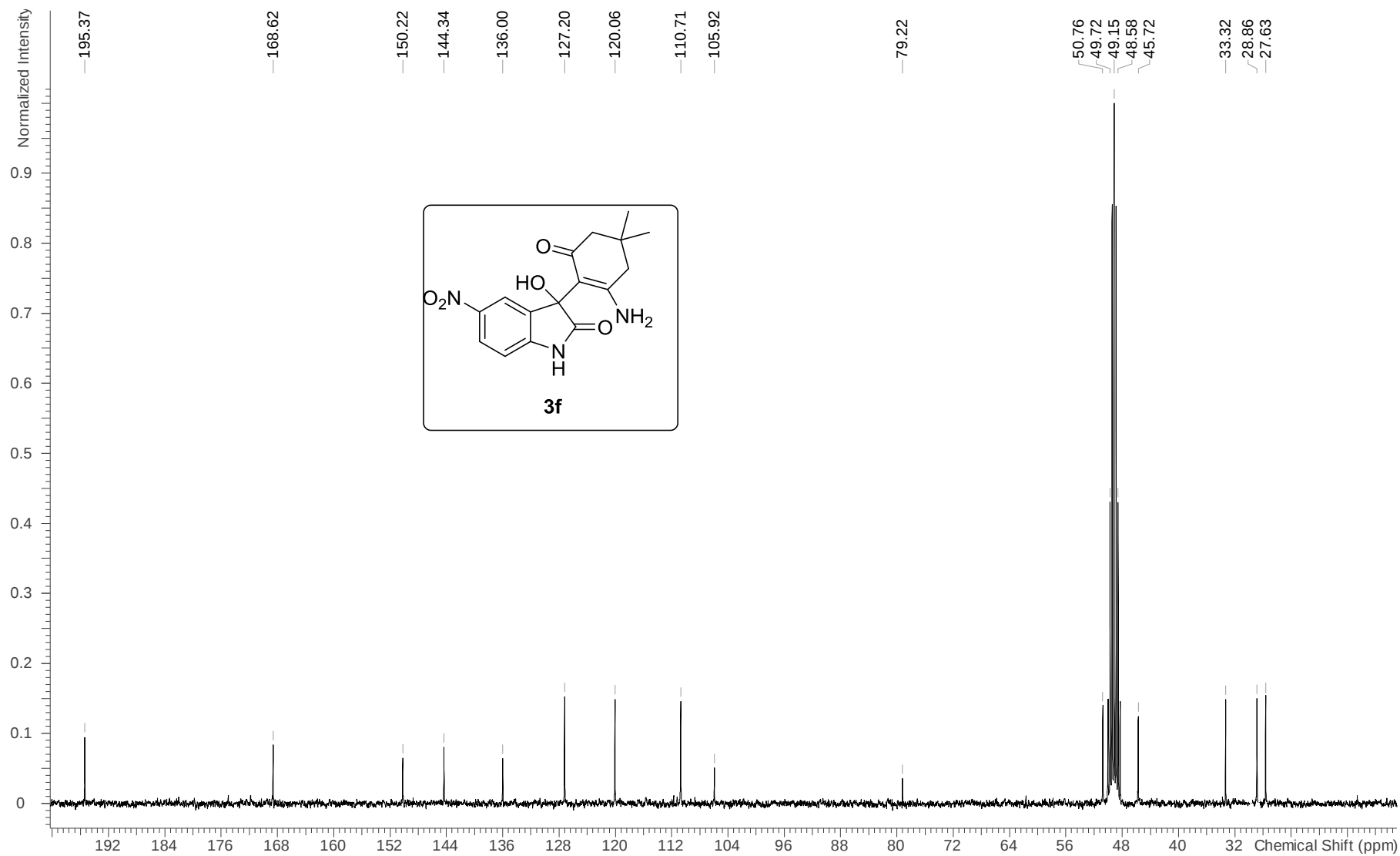
¹H NMR (300 MHz, MeOH-*d*₄) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-methyl-3-hydroxyindolin-2-one (**3e**).



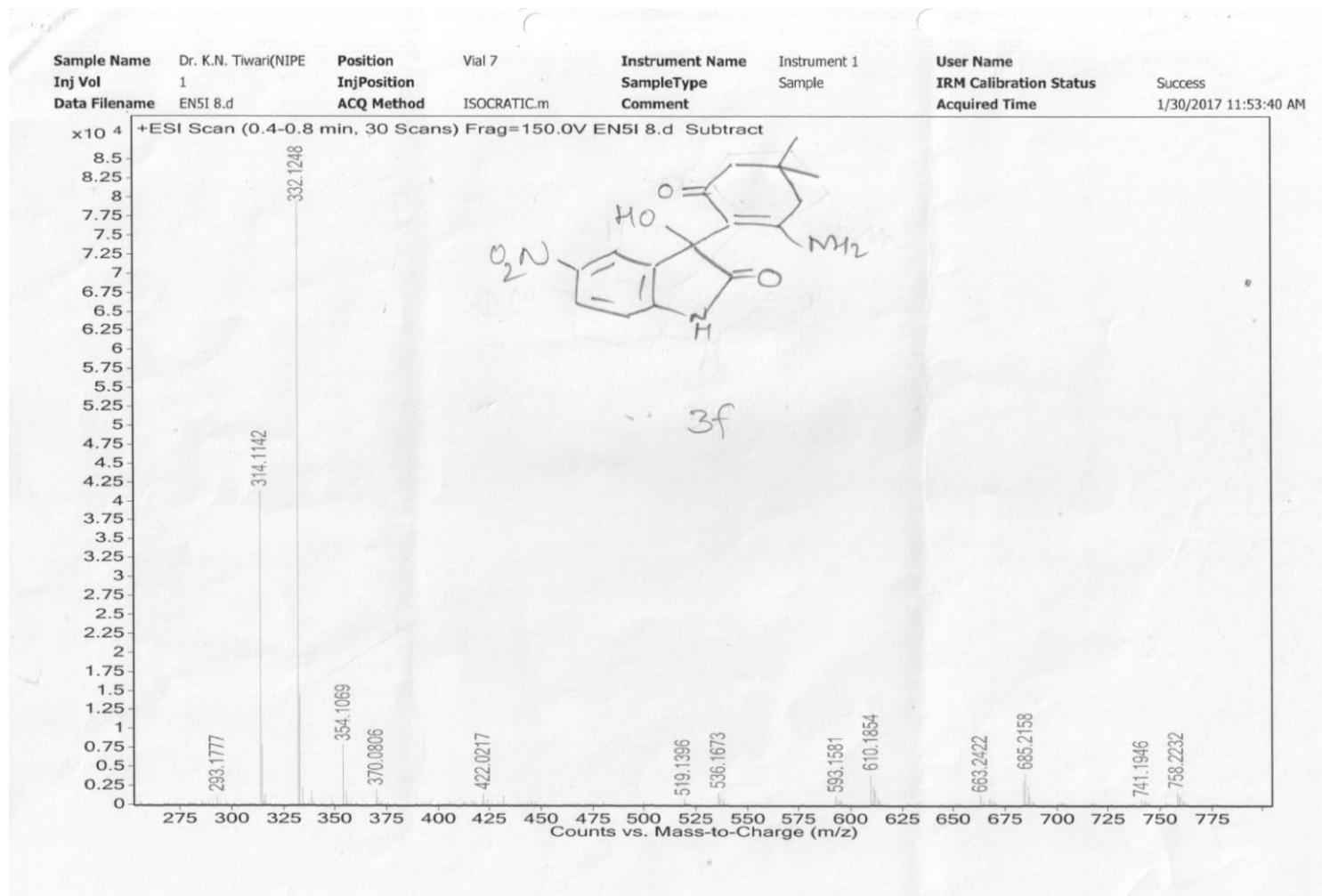
^{13}C NMR (75 MHz, $\text{MeOH-}d_4$) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-methyl-3-hydroxyindolin-2-one (**3e**).



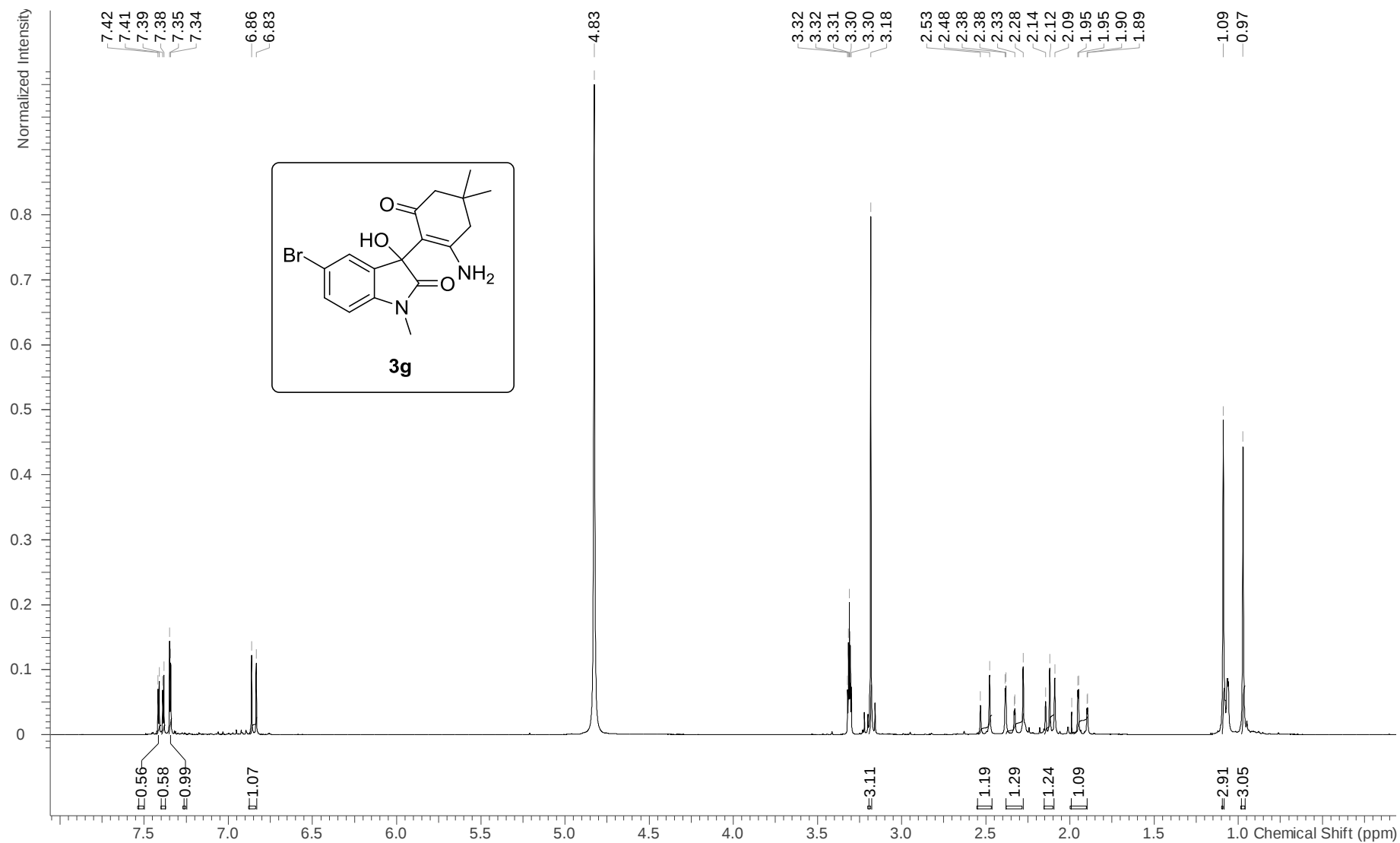
¹H NMR (300 MHz, MeOH-*d*₄) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-nitro-3-hydroxyindolin-2-one (**3f**)



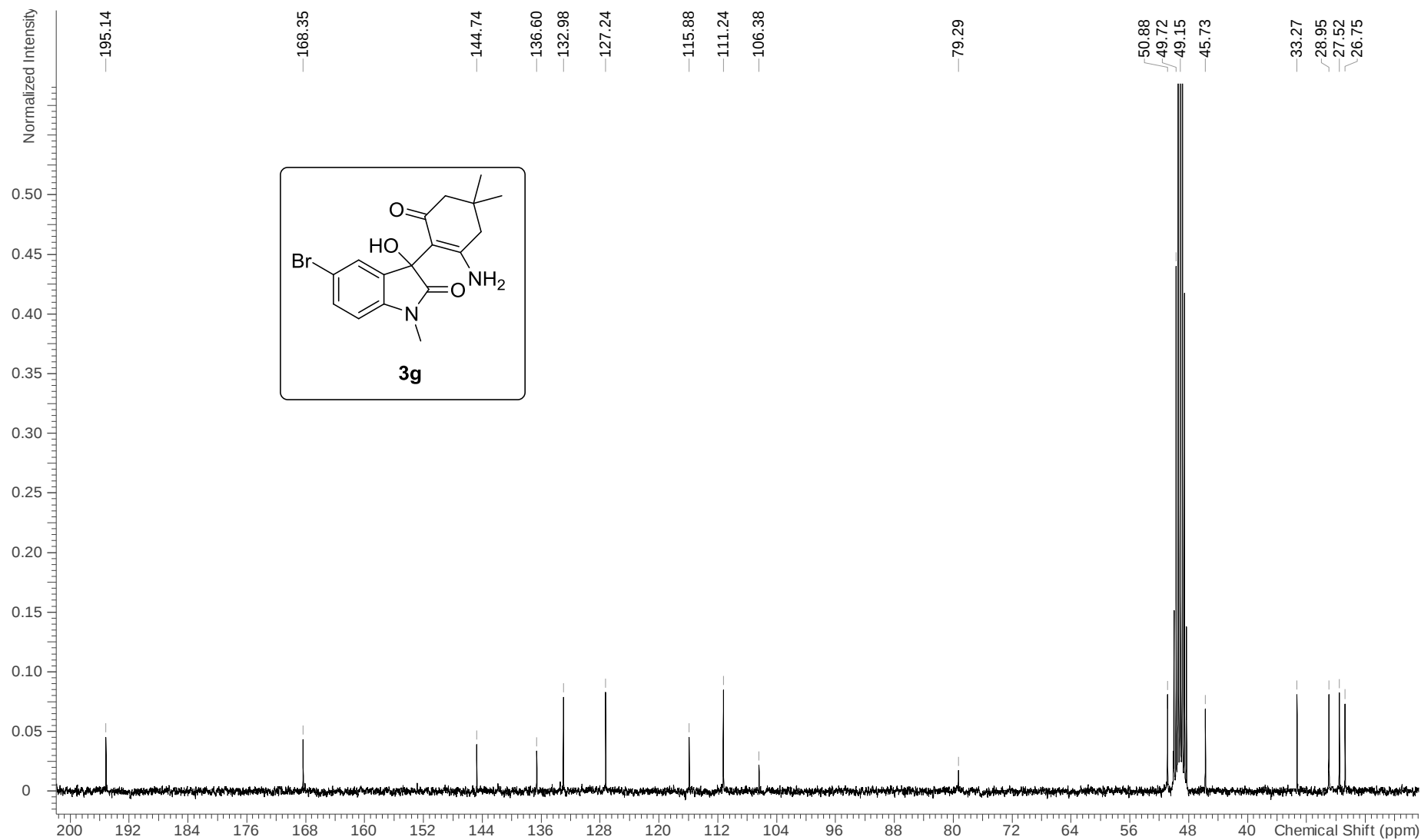
¹³C NMR (75 MHz, MeOH-*d*₄) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-nitro-3-hydroxyindolin-2-one (**3f**).



HRMS data of **3f**

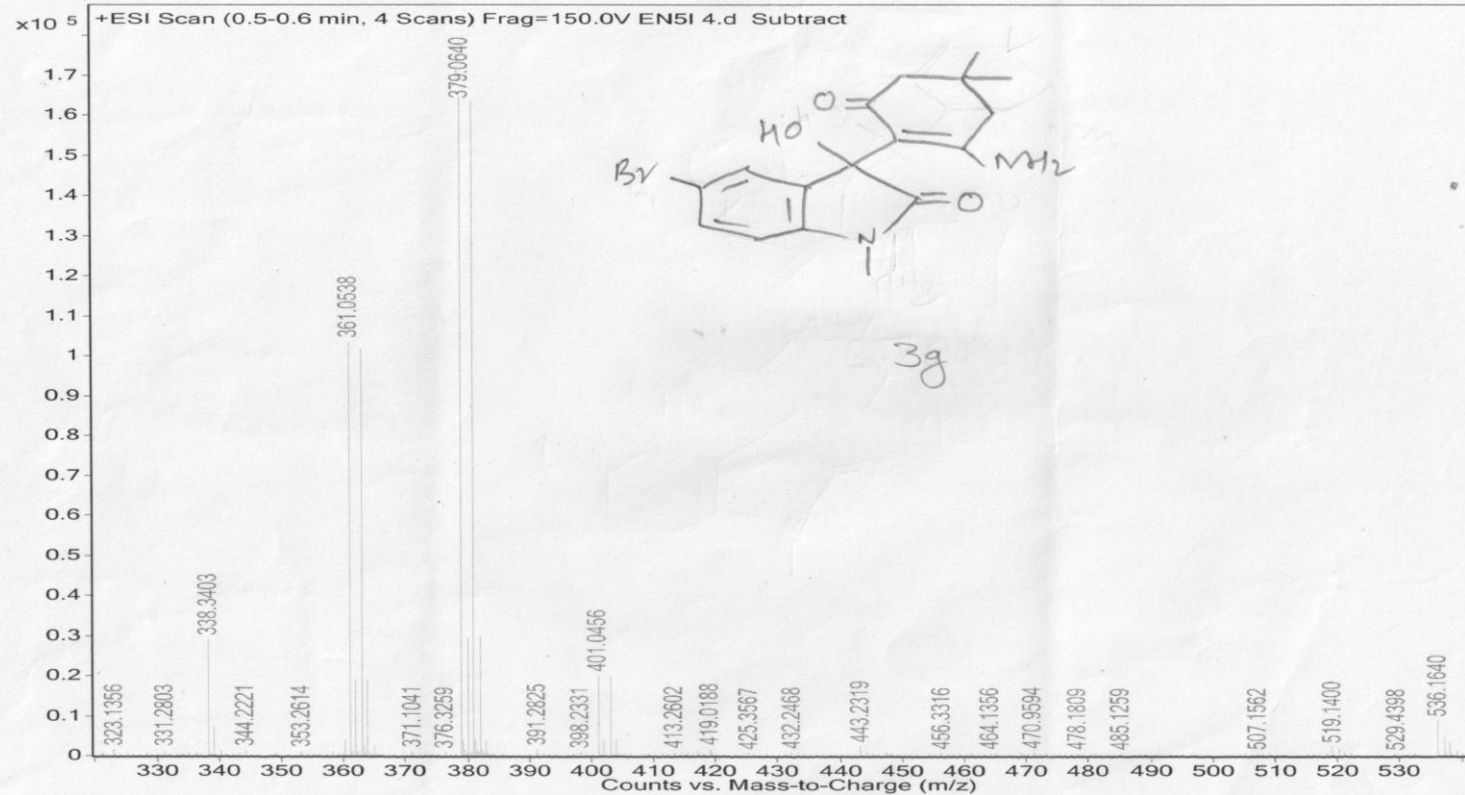


¹H NMR (300 MHz, MeOH-*d*₄) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-bromo-3-hydroxy-1-methylindolin-2-one (**3g**).

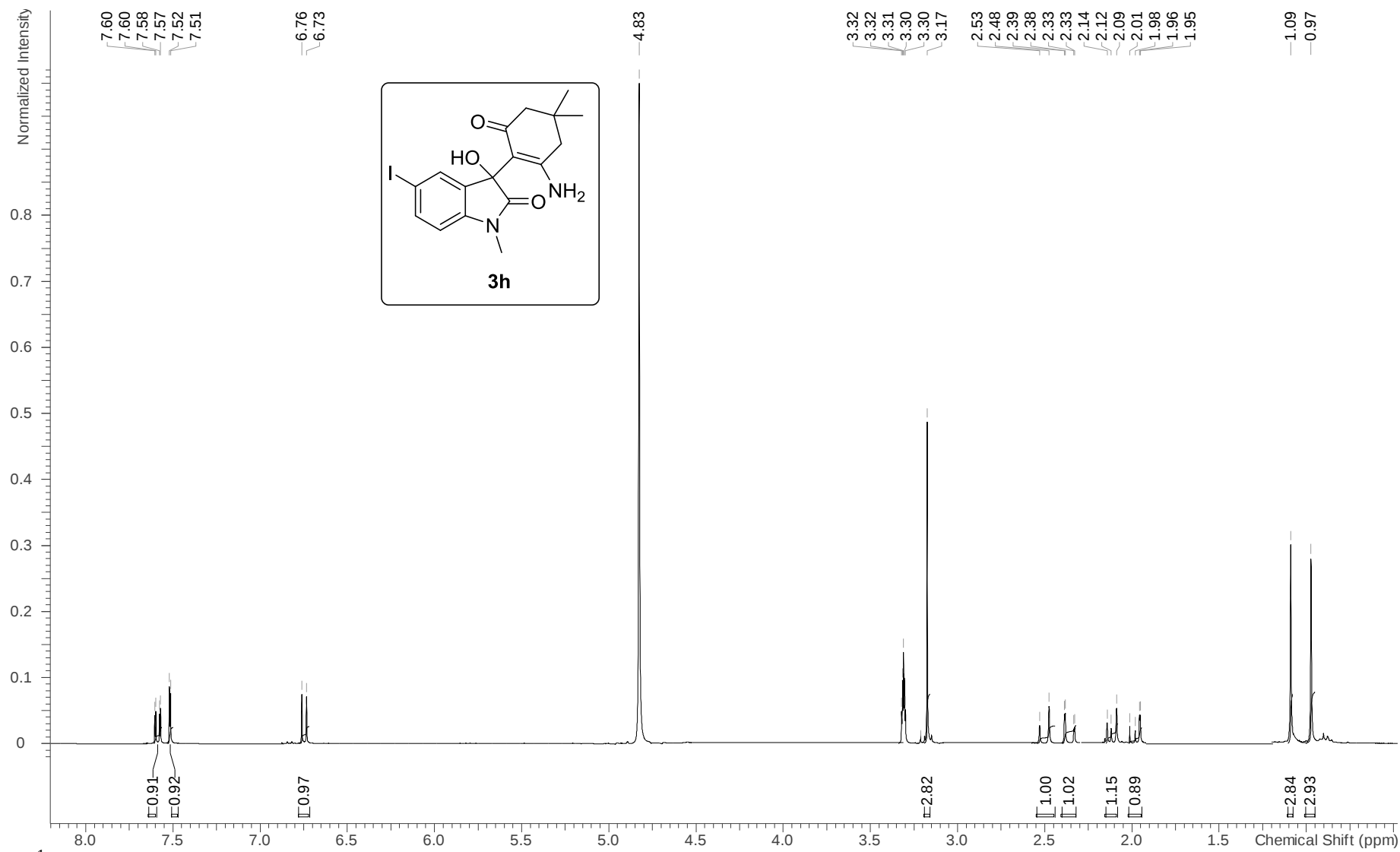


¹³C NMR (75 MHz, MeOH-*d*₄) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-bromo-3-hydroxy-1-methylindolin-2-one (**3g**).

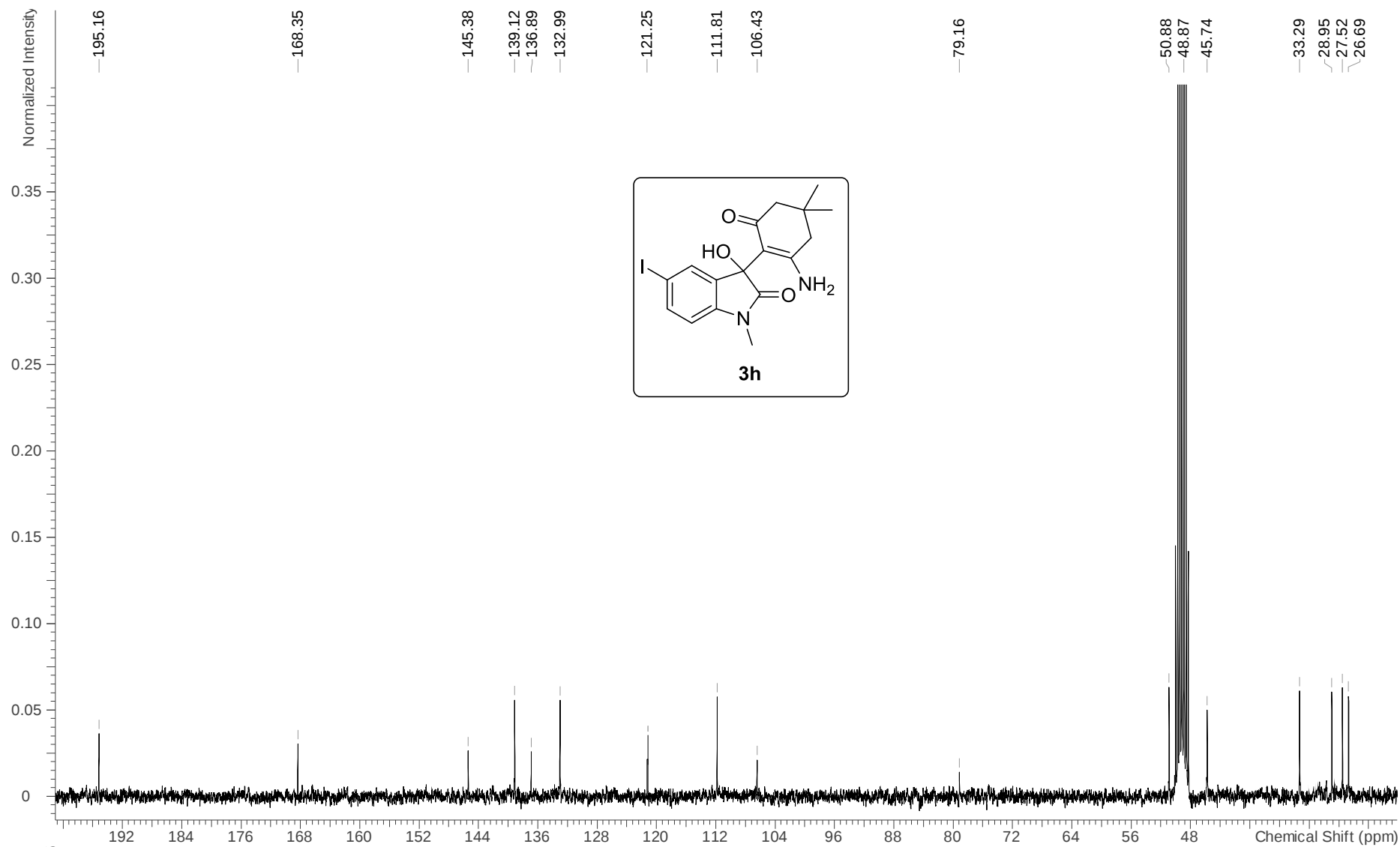
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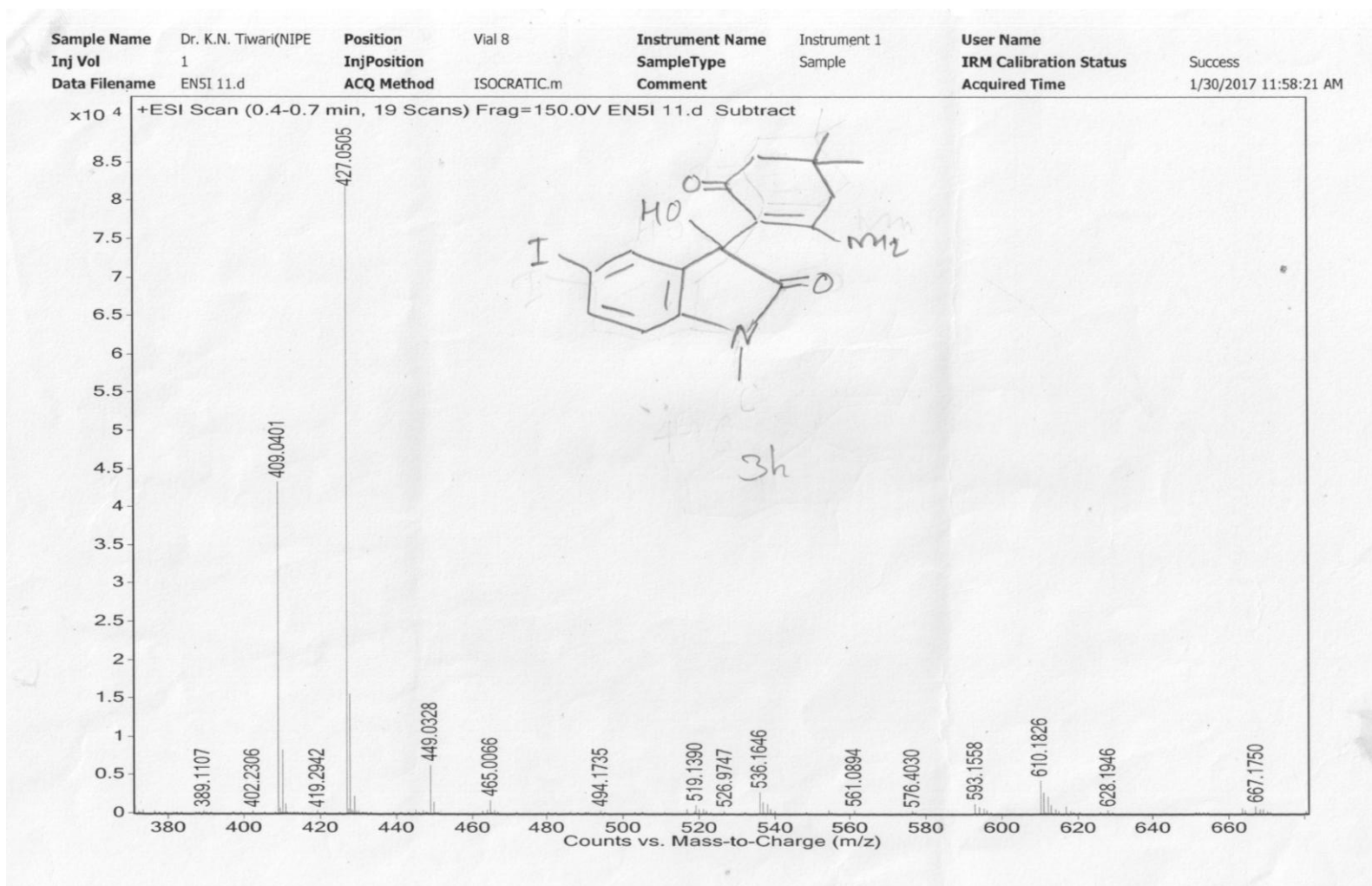
HRMS data of **3g**



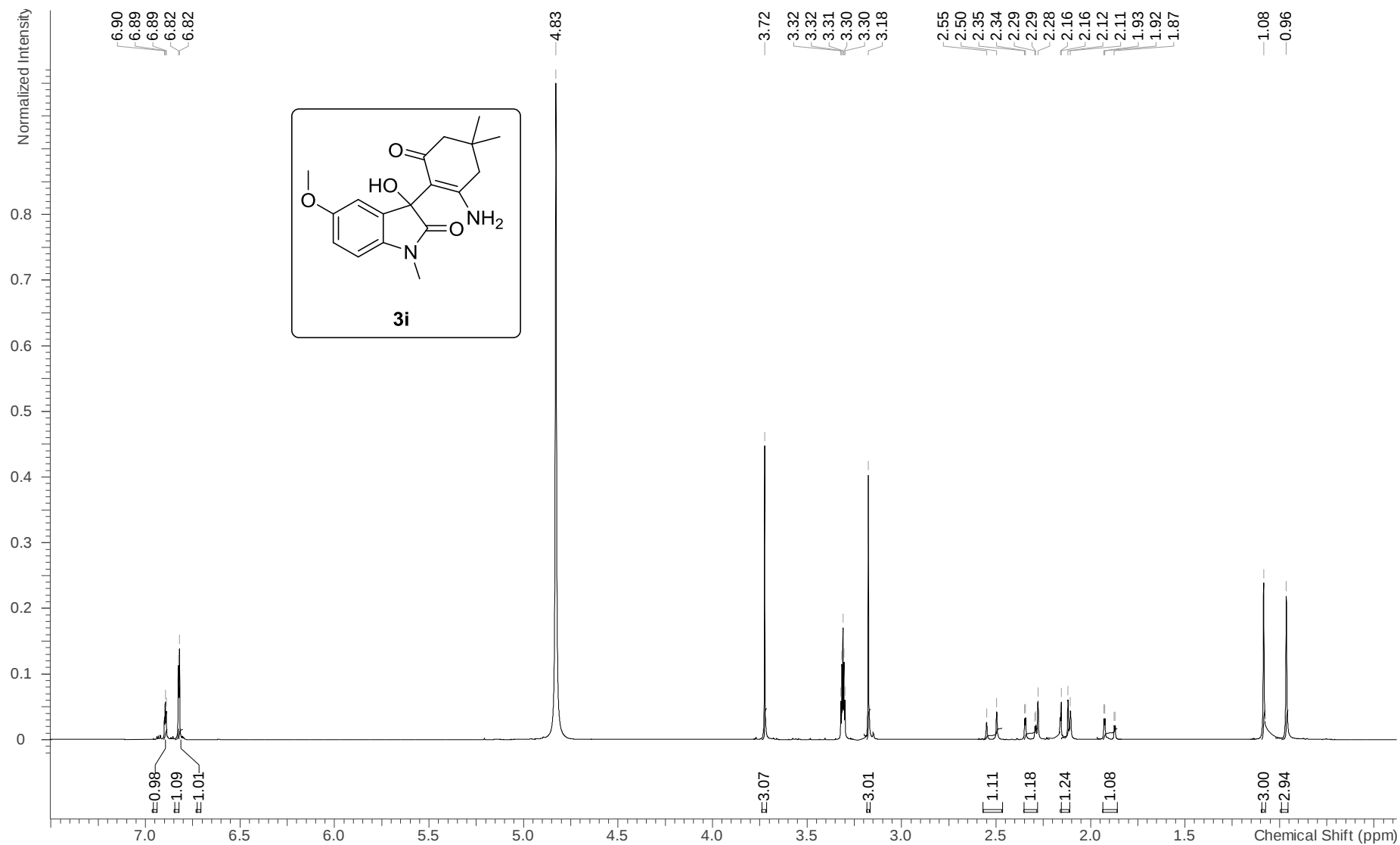
¹H NMR (300 MHz, MeOH-*d*₄) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-iodo-3-hydroxy-1-methylindolin-2-one (**3h**).



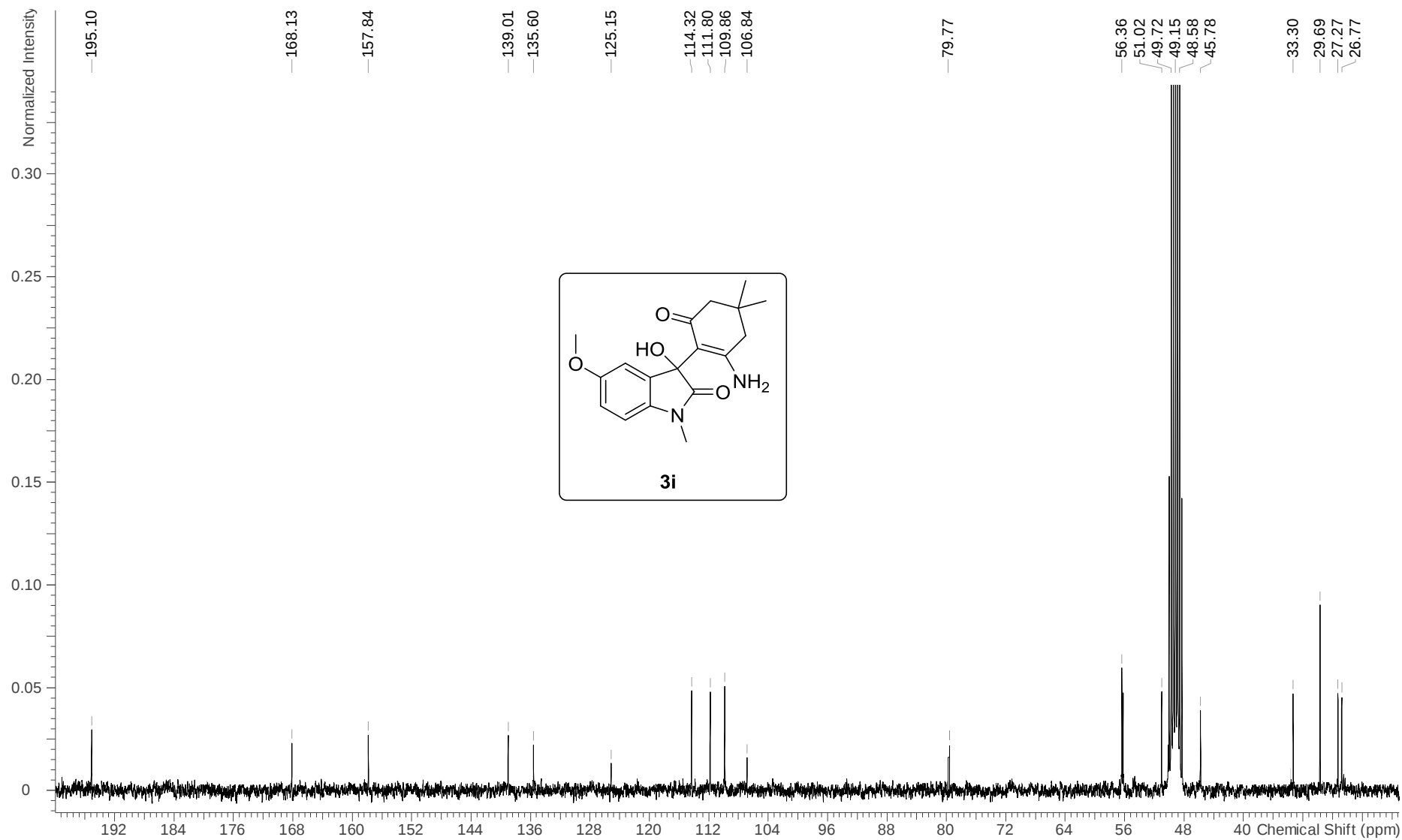
^{13}C NMR (75 MHz, $\text{MeOH-}d_4$) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-iodo-3-hydroxy-1-methylindolin-2-one (**3h**).



HRMS data of **3h**

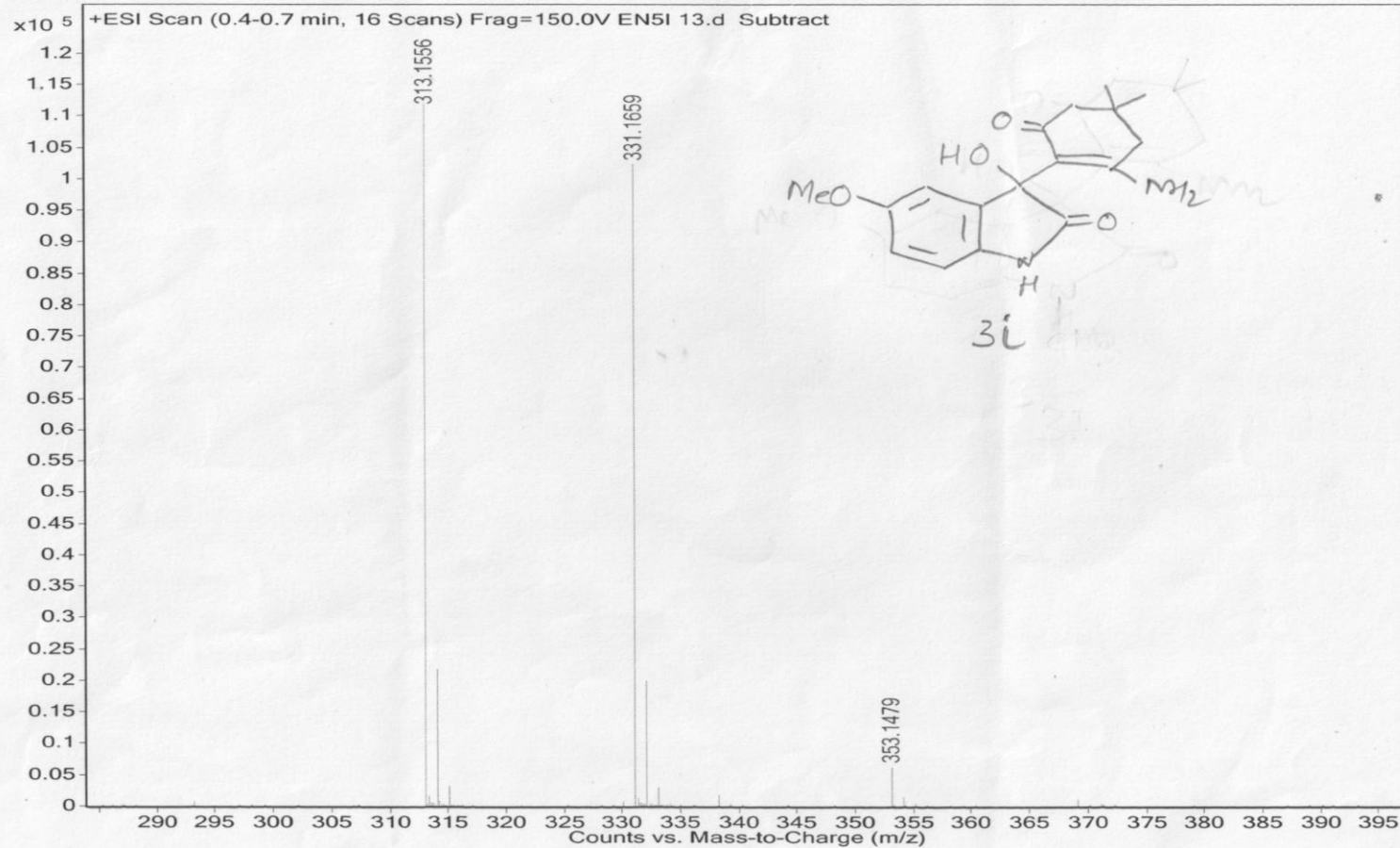


¹H NMR (300 MHz, MeOH-*d*₄) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-methoxy-3-hydroxy-1-methylindolin-2-one (**3i**).

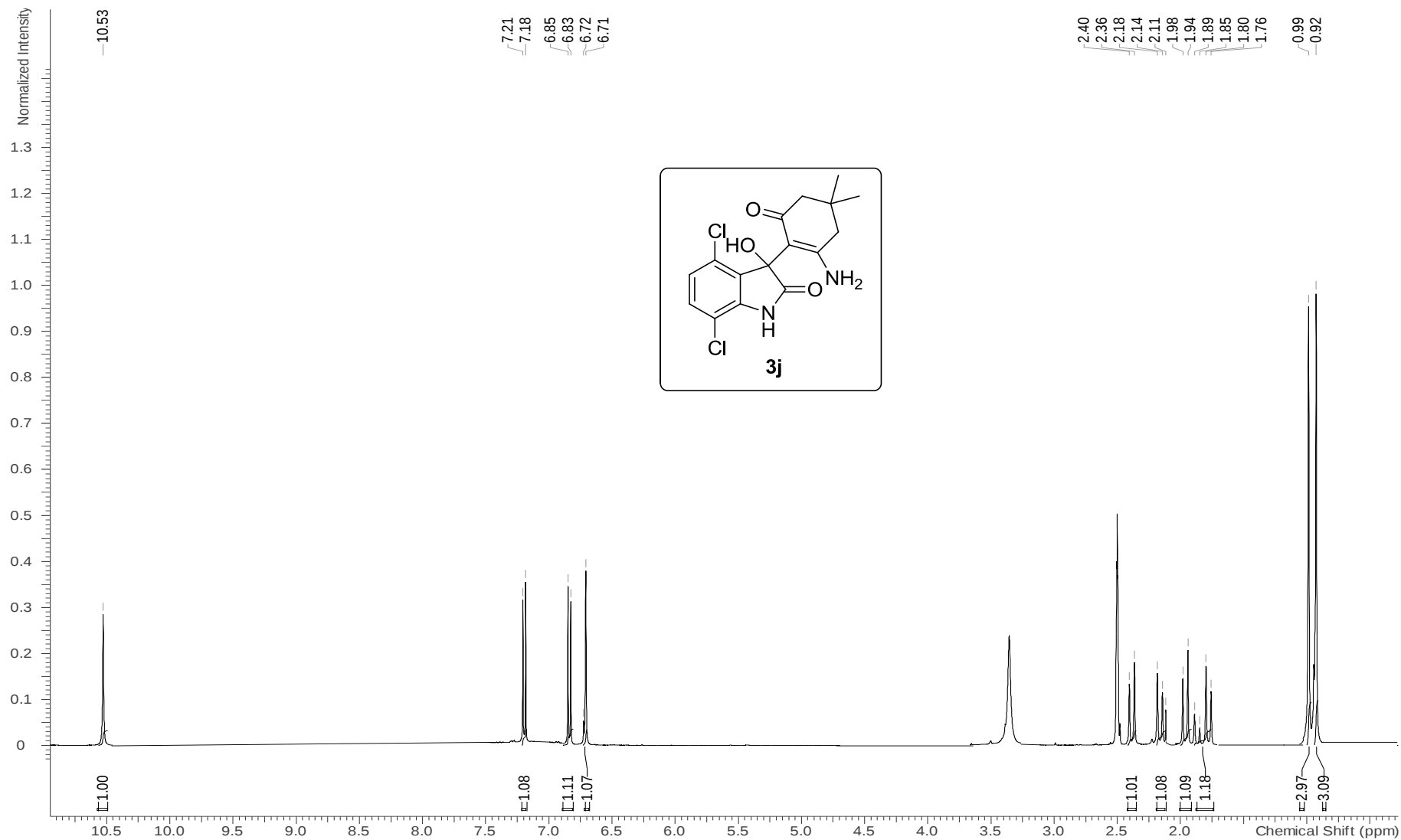


^{13}C NMR (75 MHz, $\text{MeOH-}d_4$) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-methoxy-3-hydroxy-1-methylindolin-2-one (**3i**).

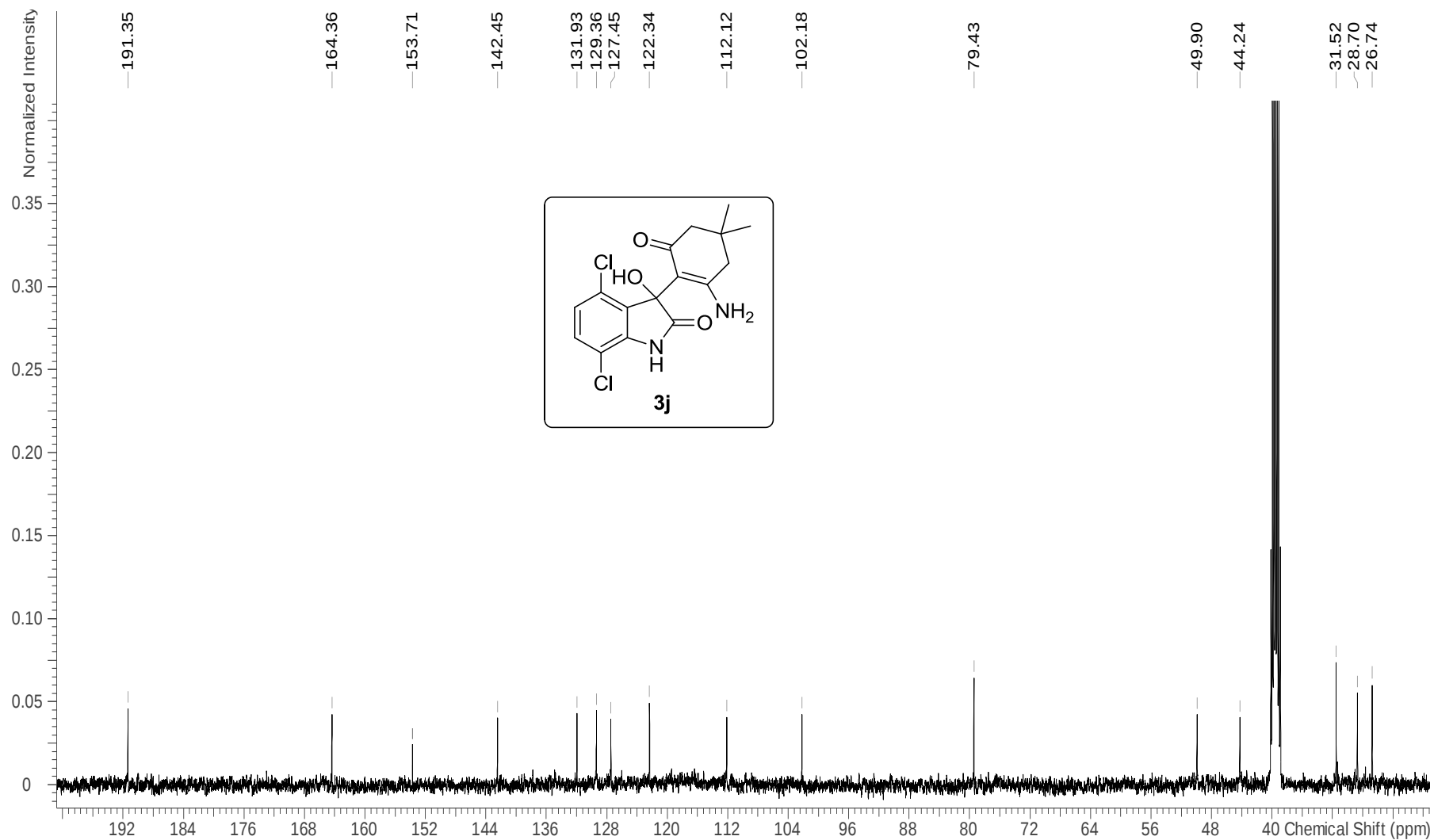
Sample Name	Dr. K.N. Tiwari(NIPE	Position	Vial 9	Instrument Name	Instrument 1	User Name	
Inj Vol	1	InjPosition		SampleType	Sample	IRM Calibration Status	Success
Data Filename	EN5I 13.d	ACQ Method	ISOCRATIC.m	Comment		Acquired Time	1/30/2017 12:03:01 PM



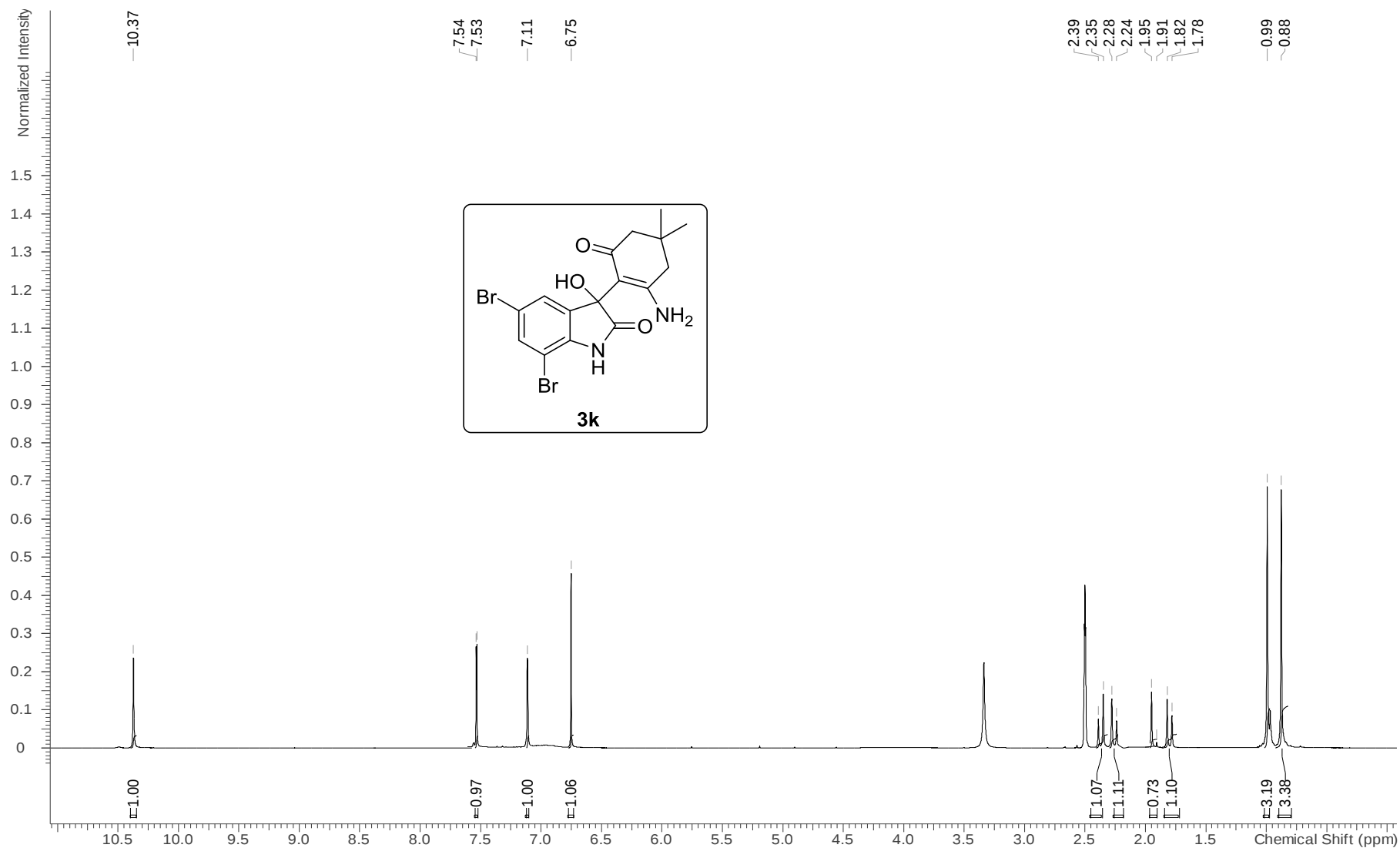
HRMS data of **3i**



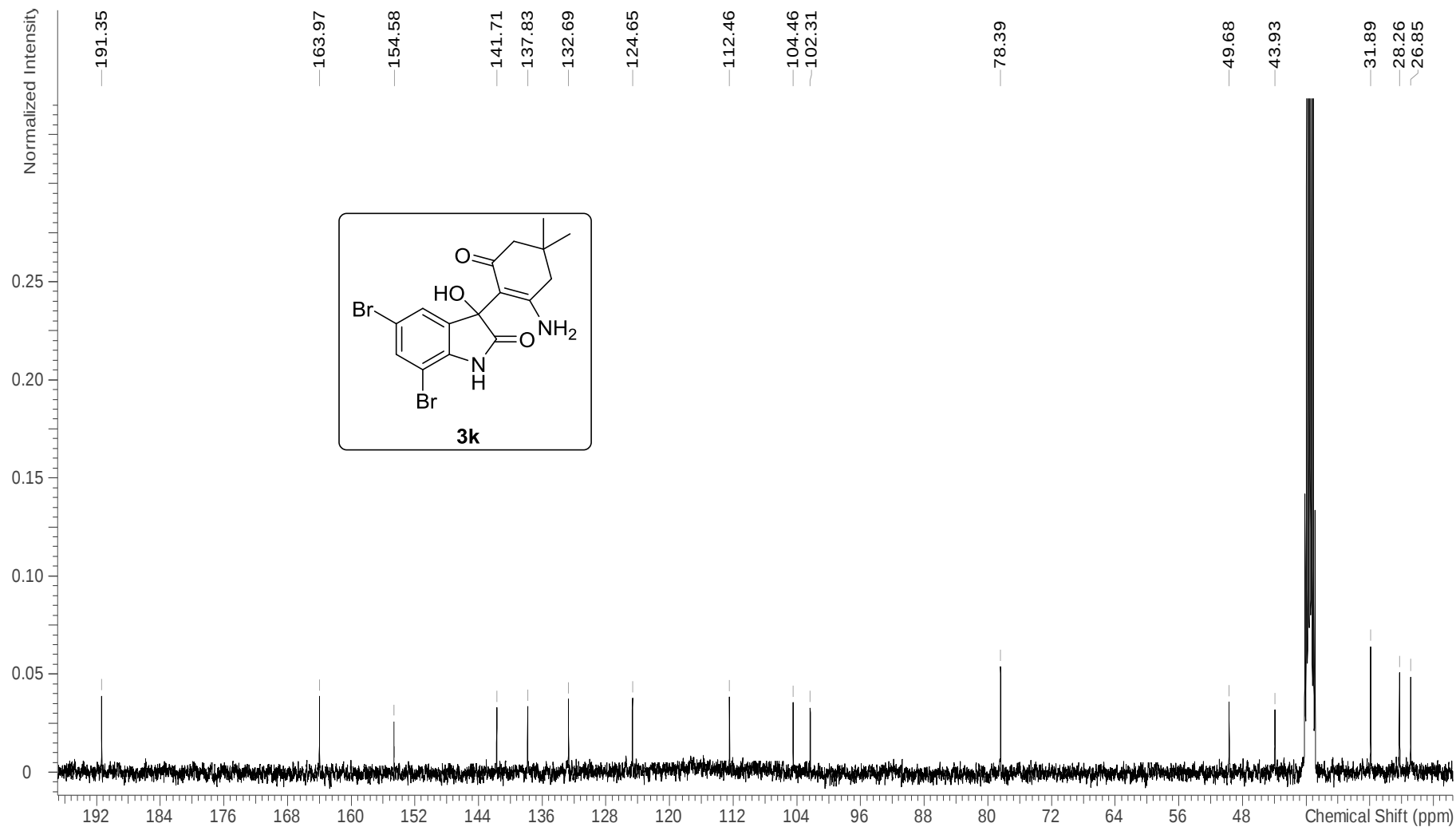
¹H NMR (400 MHz, DMSO-*d*₆) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5,7-dichloro-3-hydroxy-1-methylindolin-2-one (**3j**)



^{13}C NMR(100 MHz, $\text{DMSO}-d_6$) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-4,7-dichloro-3-hydroxy-1-methylindolin-2-one (**3j**)



¹H NMR(400 MHz, DMSO-*d*₆) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5,7-dibromo-3-hydroxy-1-methylindolin-2-one (**3k**).



¹³C NMR(100 MHz, DMSO-*d*₆) of 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5,7-dibromo-3-hydroxy-1-methylindolin-2-one (**3k**).