

Supplementary information

Design, synthesis and biological evaluation of novel substituted imidazo[2,1-*a*] isoindole derivatives as antibacterial agents

Sirassu Narsimha, Kumara Swamy Battula, Nagavelli Vasudeva Reddy*

Department of Chemistry, Kakatiya University, Warangal-506 009, Telangana State, India.

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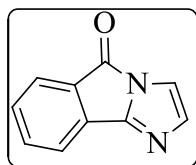
Part 1. Experimental procedures and spectral data of new compounds

Part 2. NMR and Mass Spectra of New Compounds

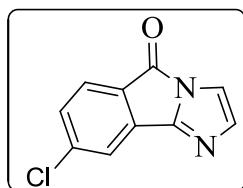
Part 1:

General method for the synthesis of substituted 5H-imidazo[2,1-a]isoindol-5-ones (2a-d):

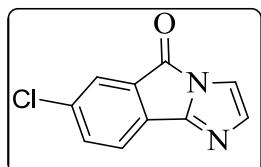
To a argon gas puged mixture of 2-iodo benzoic acids (1) (0.008 mol), Carbonyldiimidazole (0.008 mol) and K_2CO_3 (0.242 mol) in CH_3CN (50 ml) was added $Pd(OAc)_2$ (10 mol %) and stirred at 60 °C temperature for 12h. The reaction was monitored by TLC analysis. After completion of the reaction, the reaction mixture was poured carefully into ice-cold water (50 mL) and the product was extracted with ethyl acetate (2 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 . After filtration, the solvent was evaporated under vacuum and the crude product obtained was purified by column chromatography to afford the pure desired products (**2a-d**).



5H-imidazo[2,1-a]isoindol-5-one (2a): Colorless solid; mp. 132–134 °C; IR (KBr, cm^{-1}) ν_{max} : 1684 (C=O), 1641 (C=N), 1524 (C=C); 1H NMR (400 MHz, $DMSO-d_6$) δ : 8.12 (d, $J= 8.0$, 1H), 7.91 (d, $J= 8.0$ Hz, 1H), 7.65 (t, $J= 4.0$ Hz, 1H), 7.50-7.32 (m, 2H), 7.20 (d, $J= 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ 160.2, 143.1, 136.3, 133.9, 129.9, 129.5, 128.8, 125.4, 120.3, 118.6; LC-MS: m/z : 171 [M+H] $^+$; Anal. Calcd for $C_{10}H_6N_2O$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.62; H, 3.52; N, 16.49.

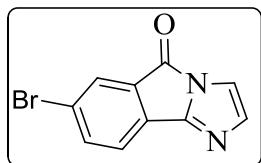


8-chloro-5H-imidazo[2,1-a]isoindol-5-one (2b): Pale yellow solid; mp. 159–161 °C; IR (KBr, cm^{-1}) ν_{max} : 1660 (C=O), 1612 (C=N), 1518 (C=C); 1H NMR (400 MHz, $DMSO-d_6$) δ : 8.16 (d, $J= 8.0$, 1H), 7.97 (d, $J= 6.0$ Hz, 1H), 7.80 (s, 1H), 7.73 (d, $J= 6.0$ Hz, 1H), 7.23 (d, $J= 8.0$ Hz, 1H); ESI-MS: m/z : 205 [M+H] $^+$; Anal. Calcd for $C_{10}H_5ClN_2O$: C, 58.70; H, 2.46; N, 13.69. Found: C, 58.77; H, 2.37; N, 13.58.



7-chloro-5H-imidazo[2,1-a]isoindol-5-one (2c): Pale yellow solid; mp. 143–145 °C; IR (KBr, cm^{-1}) ν_{max} : 1659 (C=O), 1616 (C=N), 1528 (C=C); 1H NMR (400 MHz,

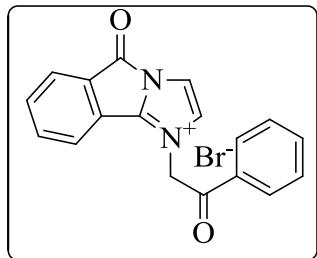
DMSO-*d*₆) δ : 8.18 (d, *J*= 8.0, 1H), 7.94 (s, 1H), 7.79 (d, *J*= 7.8, 1H), 7.70 (d, *J*= 7.8, 1H), 7.25 (d, *J*= 8.0 Hz, 1H); ESI-MS: *m/z*: 205 [M+H]⁺; Anal. Calcd for C₁₀H₅ClN₂O: C, 58.70; H, 2.46; N, 13.69. Found: C, 58.78; H, 2.39; N, 13.60.



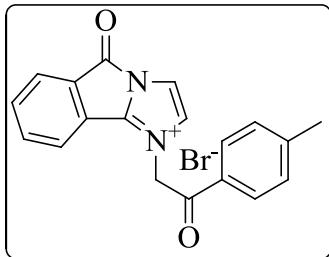
7-bromo-5H-imidazo[2,1-a]isoindol-5-one (2d): Yellow solid; mp. 164–166 °C; IR (KBr, cm⁻¹) ν_{max} : 1671 (C=O), 1620 (C=N), 1521 (C=C); ¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.15 (d, *J*= 6.8, 1H), 7.90 (s, 1H), 7.72–7.62 (m, 2H), 7.19 (d, *J*= 6.8 Hz, 1H); ESI-MS: *m/z*: 249 [M+2H]⁺; Anal. Calcd for C₁₀H₅BrN₂O: C, 48.22; H, 2.02; N, 11.25. Found: C, 48.14; H, 1.96; N, 11.17.

General method for the synthesis of 5H-imidazo[2,1-a]isoindol-1-ium bromide (3a-i):

A mixture of 5H-imidazo[2,1-a]isoindol-5-one **2** (1 mmol) and phenacyl bromides (1.2 mmol) was stirred at 110°C in toluene (10 ml) for 24 h which resulted in the formation of a solid. After completion of the reaction as indicated by TLC, the precipitate was filtered and washed with toluene (2 x 10 ml), then dried to afford compounds (**3a-i**).

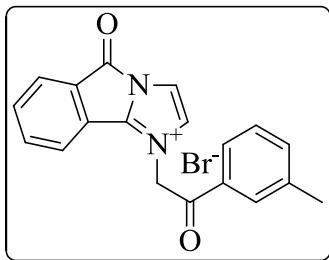


5-oxo-1-(2-oxo-2-phenylethyl)-5H-imidazo[2,1-a]isoindol-1-ium bromide (3a): White solid; mp 196–198 °C; IR (KBr, cm⁻¹) ν_{max} : 1697, 1671 (C=O), 1637 (C=N), 1515 (C=C); ¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.32 (d, *J*=8.0 Hz, 1H), 7.98–7.85 (m, 2H), 7.72–7.63 (m, 2H), 7.50–7.32 (m, 5H), 6.23 (s, 2H, -CH₂); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 189.5, 161.3, 145.6, 137.6, 134.2, 133.8, 130.4, 129.4, 128.6, 127.9, 125.9, 125.1, 124.4, 122.7, 119.5, 61.6; LC-MS: *m/z*: 290 [M+H]⁺; Anal. Calcd for C₁₈H₁₃BrN₂O₂: C, 58.56; H, 3.55; N, 7.59. Found: C, 58.49; H, 3.47; N, 7.55.



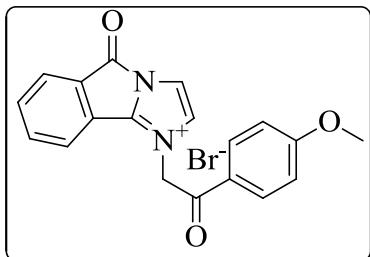
5-oxo-1-(2-oxo-2-(p-tolyl)ethyl)-5H-imidazo[2,1-a]isoindol-1-ium bromide (3b):

Light yellow solid; mp.: 172-174 °C; IR (KBr, cm⁻¹) ν_{max} : 1694, 1668 (C=O), 1625 (C=N), 1542 (C=C); ¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.31 (d, *J*=7.8 Hz, 1H), 7.94- 7.80 (m, 2H), 7.72-7.61 (m, 4H), 7.48 (d, *J*= 8.0 Hz, 2H), 7.32-7.21 (m, 2H), 6.27 (s, 2H, -CH₂), 2.41 (s, 3H, -CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 189.8, 161.2, 145.4, 137.9, 136.6, 136.4, 135.4, 134.1, 132.8, 130.3, 129.6, 128.4, 126.9, 123.8, 119.5, 61.6, 21.2; LC-MS: *m/z*: 304 [M+H]⁺; Anal. Calcd for C₁₉H₁₅BrN₂O₂: C, 59.55; H, 3.95; N, 7.31. Found: C, 59.61; H, 3.87; N, 7.26.



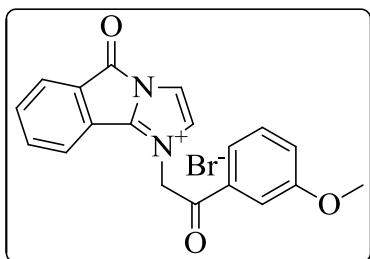
5-oxo-1-(2-oxo-2-(m-tolyl)ethyl)-5H-imidazo[2,1-a]isoindol-1-ium bromide (3c):

Light yellow solid; mp.: 183-185 °C; IR (KBr, cm⁻¹) ν_{max} : 1689, 1664 (C=O), 1620 (C=N), 1532 (C=C); ¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.27 (d, *J*=8.0 Hz, 1H), 7.93- 7.81 (m, 2H), 7.79(d, *J*= 8.0Hz, 1H), 7.55 (t, *J*=4.0Hz, 2H), 7.42 (s, 1H), 7.34-7.20 (m, 3H), 6.32 (s, 2H, -CH₂), 2.44 (s, 3H, -CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 190.3, 161.8, 145.2, 137.9, 137.1, 136.4, 134.9, 134.3, 133.8, 130.8, 129.3, 128.4, 128.0, 126.3, 124.9, 122.5, 120.1, 61.8, 20.1; LC-MS: *m/z*: 304 [M+H]⁺; Anal. Calcd for C₁₉H₁₅BrN₂O₂: C, 59.55; H, 3.95; N, 7.31. Found: C, 59.63; H, 3.88; N, 7.27.



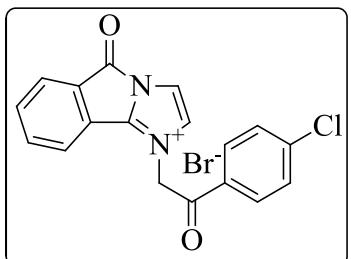
1-(2-(4-methoxyphenyl)-2-oxoethyl)-5-oxo-5H-imidazo[2,1-

a]isoindol-1-ium bromide (3d): White solid; mp.: 211-213 °C; IR (KBr, cm⁻¹) ν_{max} : 1684, 1662 (C=O), 1623(C=N), 1532 (C=C); ¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.28 (d, *J*=7.8 Hz, 1H), 7.95(brs, 1H), 7.85 (t, *J*= 4.0 Hz, 1H), 7.75 (d, *J*= 8.0 Hz, 2H), 7.62(t, *J*= 4.0 Hz, 1H), 7.53-7.48 (m, 2H), 7.30 (d, *J*= 8.0 Hz, 2H), 6.31 (s, 2H, -CH₂), 3.87 (s, 3H, -OCH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 190.2, 161.8, 159.8, 144.6, 137.7, 136.2, 135.8, 135.0, 134.2, 133.4, 131.1, 129.1, 127.3, 125.3, 122.9, 120.5, 119.5, 61.4, 57.6; LC-MS: *m/z*: 320 [M+H]⁺; Anal. Calcd for C₁₉H₁₅BrN₂O₃: C, 57.16; H, 3.79; N, 7.02. Found: C, 57.11; H, 3.82; N, 7.07.



1-(2-(3-methoxyphenyl)-2-oxoethyl)-5-oxo-5H-imidazo[2,1-

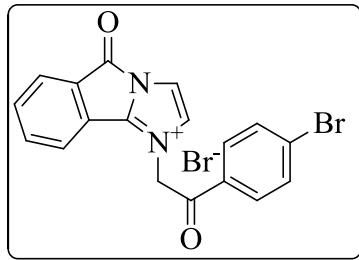
a]isoindol-1-ium bromide(3e): White solid; mp.: 225-227 °C; IR (KBr, cm⁻¹) ν_{max} : 1690, 1661 (C=O), 1627(C=N), 1530 (C=C); ¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.27 (d, *J*= 6.8 Hz, 1H), 7.93-7.81 (m, 2H), 7.74-7.58 (m, 4H), 7.44(t, *J*= 4.0Hz, 2H), 7.33 (s, 1H), 6.33 (s, 2H, -CH₂), 3.82 (s, 3H, -OCH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 190.7, 162.0, 148.7, 144.9, 137.8, 136.7, 135.2, 135.0, 134.1, 133.6, 131.9, 129.6, 127.2, 125.1, 124.4, 123.5, 122.7, 121.6, 120.2, 61.7, 56.8; LC-MS: *m/z*: 320 [M+H]⁺; Anal. Calcd for C₁₉H₁₅BrN₂O₃: C, 57.16; H, 3.79; N, 7.02. Found: C, 57.12; H, 3.76; N, 7.05.



1-(2-(4-chlorophenyl)-2-oxoethyl)-5-oxo-5H-imidazo[2,1-a]

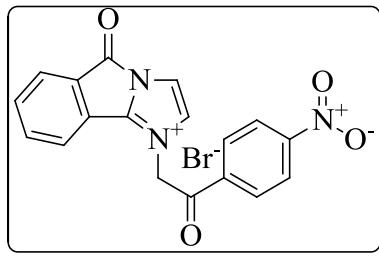
isoindol-1-ium bromide (3f): White solid; mp.: 187-189 °C; IR (KBr, cm⁻¹) ν_{max} : 1687, 1666

(C=O), 1632 (C=N), 1554 (C=C); ^1H NMR (400 MHz, DMSO- d_6) δ : 8.33 (d, $J = 7.2$ Hz, 1H), 7.95-7.80 (m, 2H), 7.78-7.65 (m, 2H), 7.51(t, $J= 4.0$ Hz, 1H), 7.43 (d, $J= 7.2$ Hz, 1H), 7.35-7.20 (m, 2H), 6.35 (s, 2H, -CH₂); ^{13}C NMR (100 MHz, DMSO- d_6) δ 190.1, 161.6, 145.0, 138.1, 137.8, 135.6, 134.5, 133.7, 133.2, 130.1, 129.3, 128.7, 127.3, 125.7, 124.7, 120.6, 61.5; LC-MS: m/z : 324 [M+H]⁺; Anal. Calcd for C₁₈H₁₂BrClN₂O₂: C, 53.56; H, 3.00; N, 6.94. Found: C, 53.50; H, 2.94; N, 6.87.



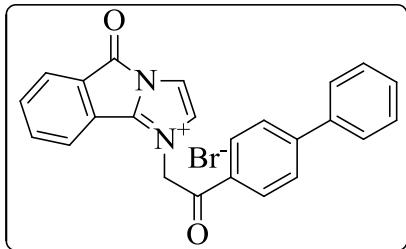
1-(2-(4-bromophenyl)-2-oxoethyl)-5-oxo-5H-imidazo[2,1-a]

isoindol-1-ium bromide (3g): Yellow solid; mp.: 210-212 °C; IR (KBr, cm⁻¹) ν_{\max} : 1690, 1661 (C=O), 1627(C=N), 1530 (C=C); ^1H NMR (400 MHz, DMSO- d_6) δ : 8.27 (d, $J = 8.0$ Hz, 1H), 7.94-7.83 (m, 2H), 7.65(d, $J= 8.0$ Hz, 2H), 7.58 (d, $J= 8.0$ Hz, 2H), 7.48-7.31 (m, 3H), 6.29 (s, 2H, -CH₂); ^{13}C NMR (100 MHz, DMSO- d_6) δ 189.9, 161.8, 144.7, 137.5, 136.8, 134.7, 134.2, 133.2, 130.4, 129.2, 127.6, 125.7, 124.9, 123.8, 120.7, 61.6; LC-MS: m/z : 370 [M+2H]⁺; Anal. Calcd for C₁₈H₁₂Br₂N₂O₂: C, 48.25; H, 2.70; N, 6.25. Found: C, 48.21; H, 2.64; N, 6.17.



1-(2-(4-nitrophenyl)-2-oxoethyl)-5-oxo-5H-imidazo[2,1-a]

isoindol-1-ium bromide (3h): Yellow solid; mp.: 227-229 °C; IR (KBr, cm⁻¹) ν_{\max} : 1687, 1666 (C=O), 1632 (C=N), 1554 (C=C); ^1H NMR (400 MHz, DMSO- d_6) δ : 8.37 (d, $J= 8.0$ Hz, 1H), 8.11 (d, $J= 8.0$ Hz, 2H), 7.93(m, 2H), 7.80 (d, $J= 8.0$ Hz, 2H), 7.65-7.30 (m, 3H), 6.46 (s, 2H, -CH₂); ^{13}C NMR (100 MHz, DMSO- d_6) δ 191.8, 162.2, 149.8, 145.6, 138.8, 136.5, 134.9, 133.7, 132.7, 131.3, 129.8, 127.3, 125.7, 124.9, 121.7, 62.1; LC-MS: m/z : 335 [M+H]⁺; Anal. Calcd for C₁₈H₁₂BrN₃O₄: C, 52.19; H, 2.92; N, 10.14. Found: C, 52.12; H, 2.84; N, 10.10.

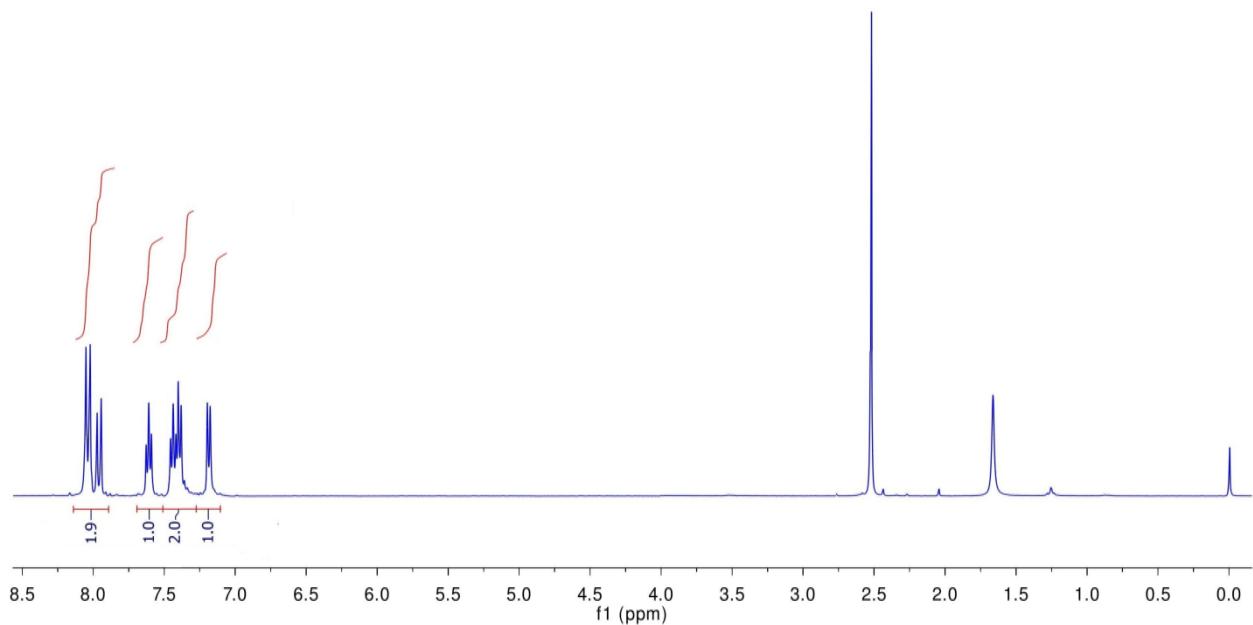


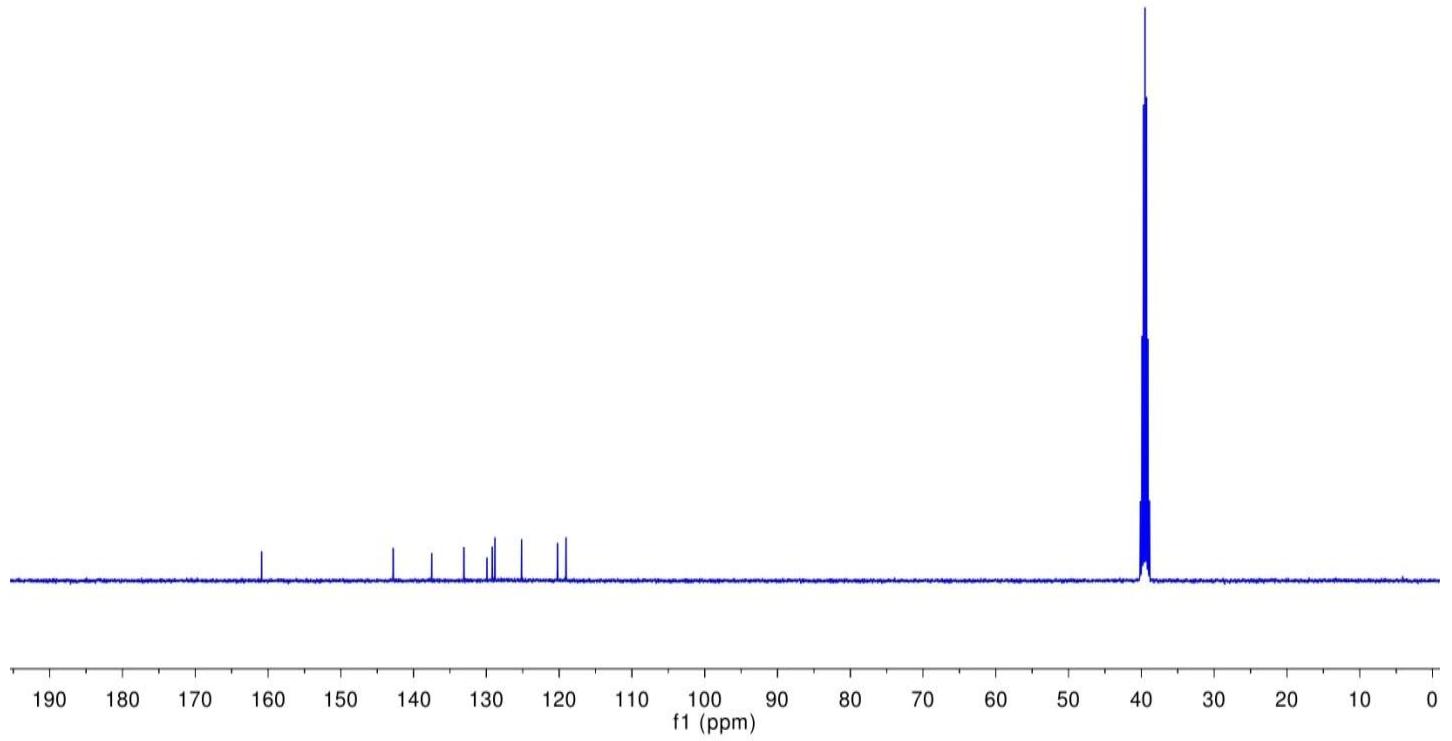
1-(2-((1,1'-biphenyl)-4-yl)-2-oxoethyl)-5-oxo-5H-imidazo

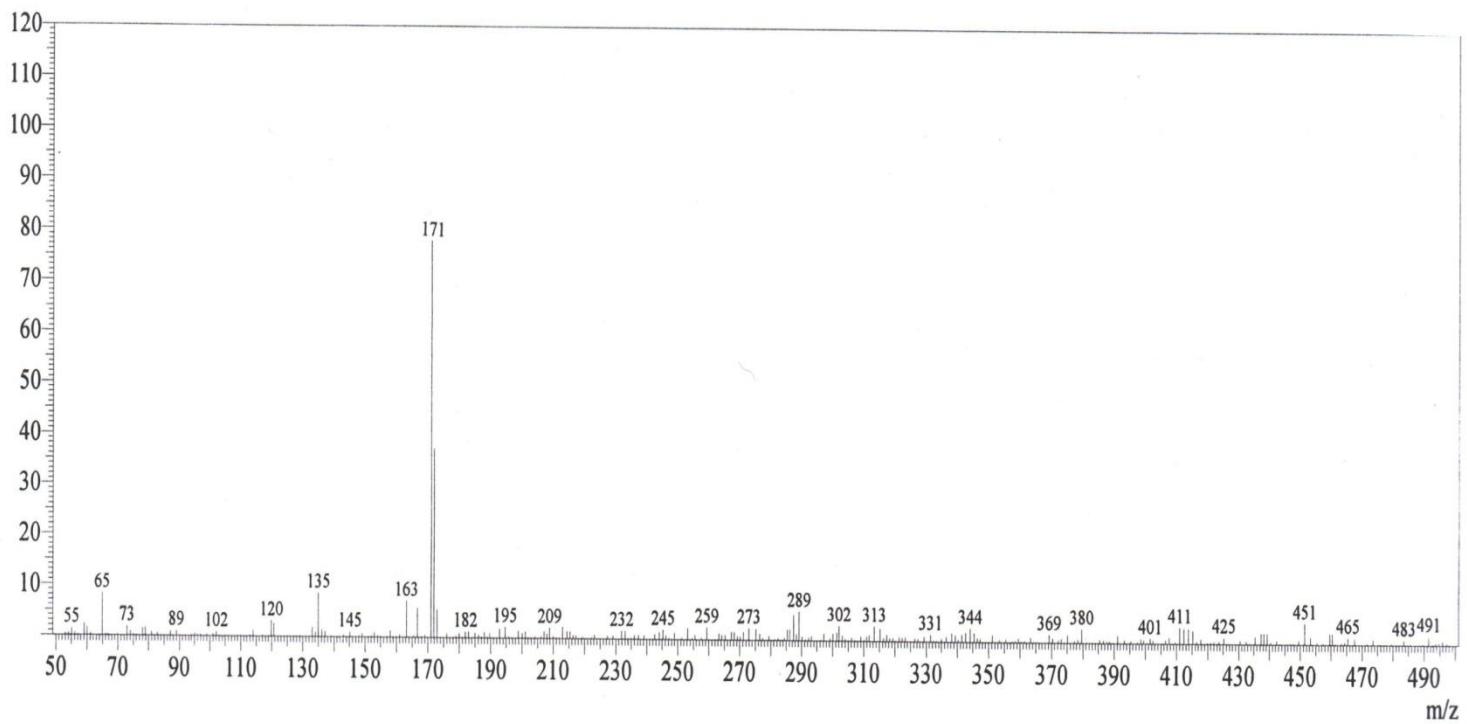
[2,1-a]isoindol-1-ium bromide (3i): Light yellow solid; mp.: 251-253 °C; IR (KBr, cm⁻¹) ν_{max} : 1686, 1661 (C=O), 1623(C=N), 1518 (C=C); ¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.25 (d, *J* = 8.0 Hz, 1H), 7.92-7.65 (m, 4H), 7.70 (d, *J*=6.8 Hz, 2H), 7.53 (m, 1H), 7.50-7.28 (m, 4H), 7.20-7.04 (m, 3H), 6.21 (s, 2H, -CH₂); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 190.7, 161.3, 144.9, 138.2, 137.7, 136.1, 135.9, 135.3, 134.5, 132.6, 129.8, 128.7, 127.3, 126.8, 126.2, 125.4, 124.8, 122.9, 120.2, 61.6; LC-MS: *m/z*: 366 [M+H]⁺; Anal. Calcd for C₂₄H₁₇BrN₂O₂: C, 64.73; H, 3.85; N, 6.29. Found: C, 64.80; H, 3.88; N, 6.22.

Part 2

5H-imidazo[2,1-a]isoindol-5-one(2a)

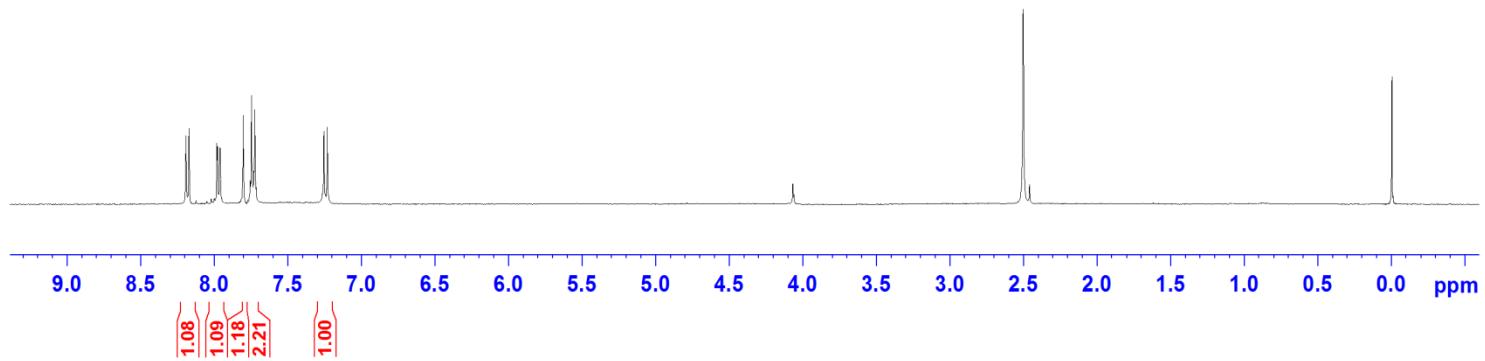


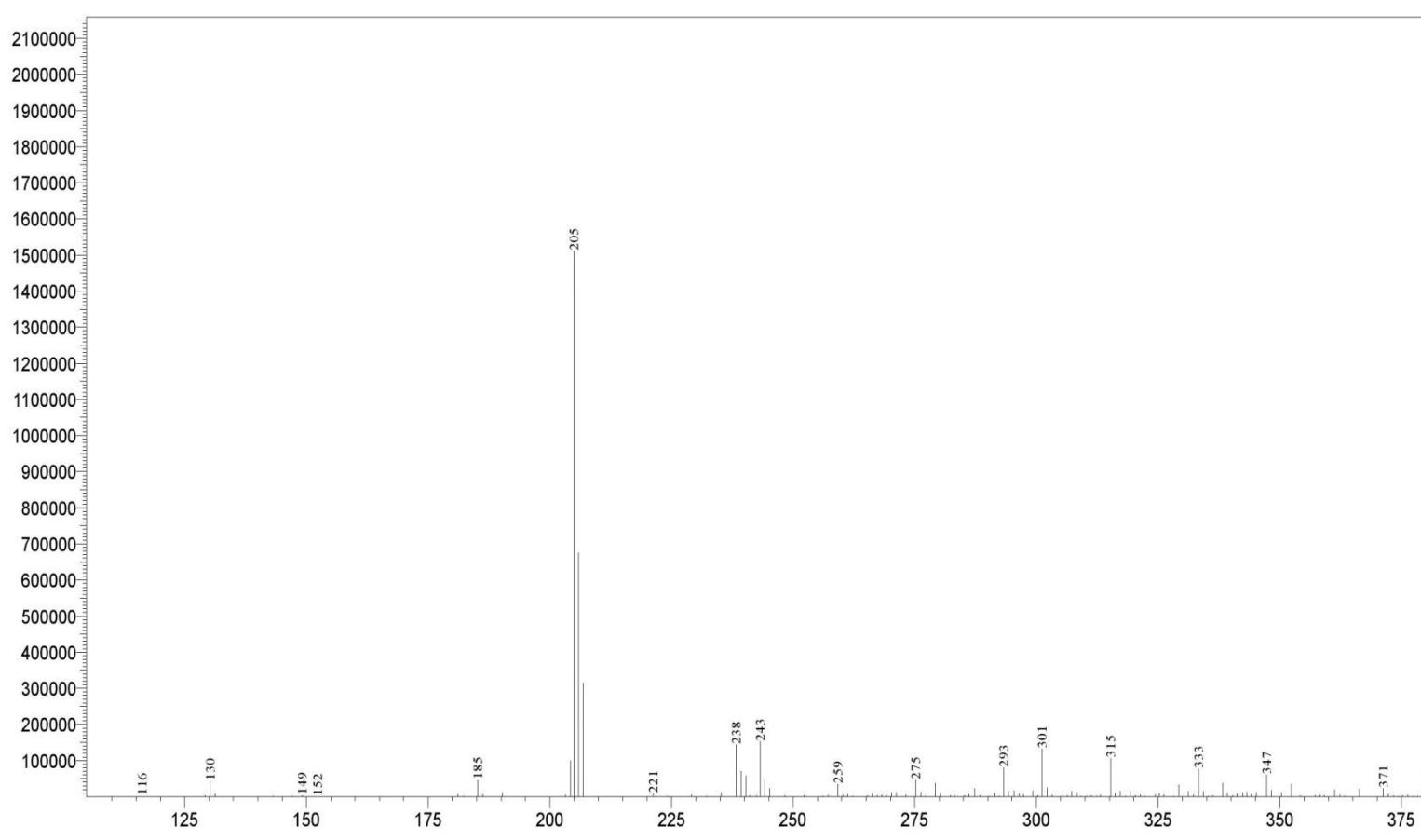




*8-chloro-5H-imidazo[2,1-*a*]isoindol-5-one (2b)*

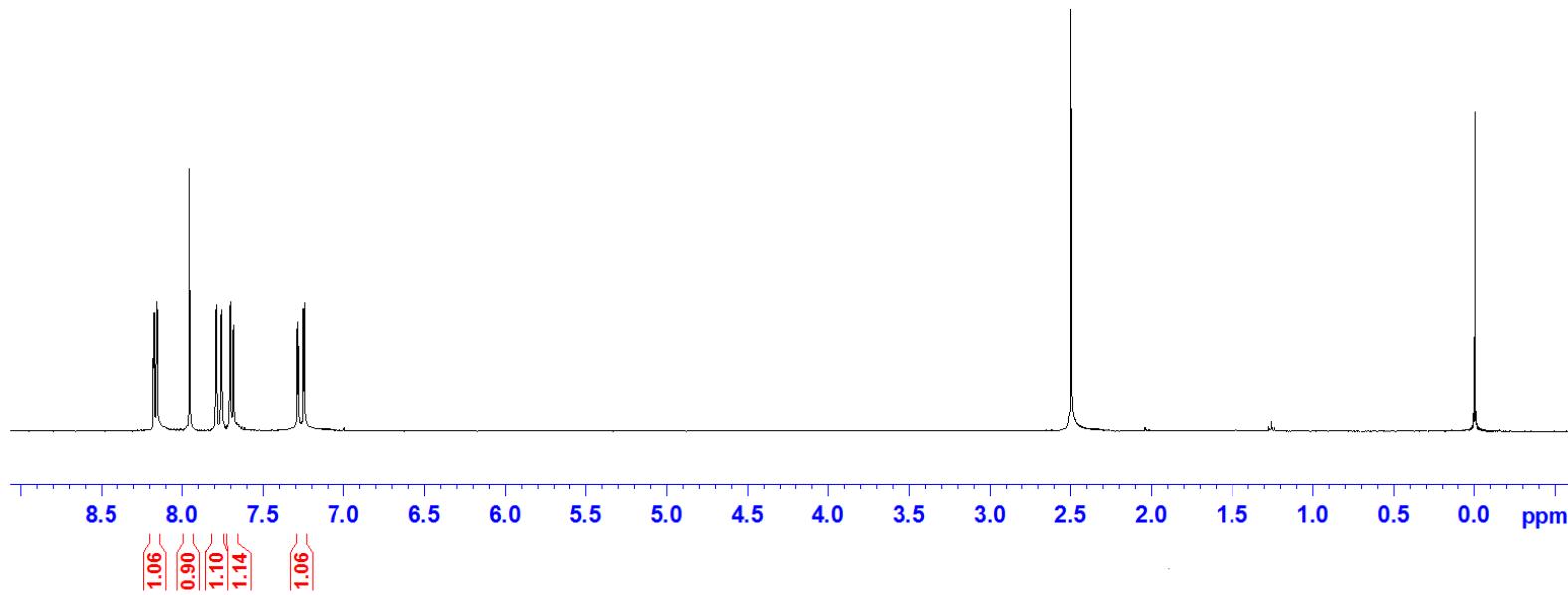
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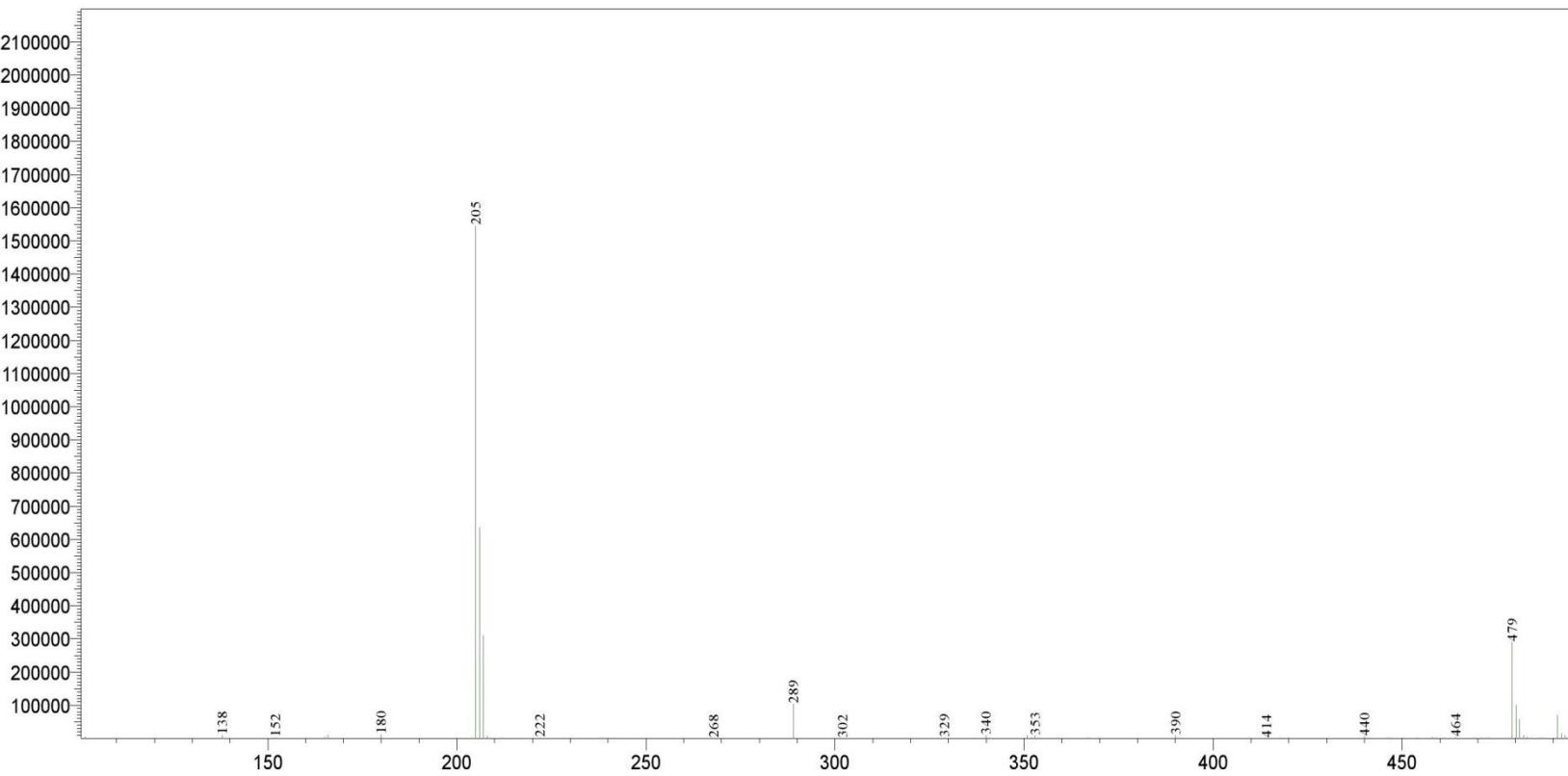




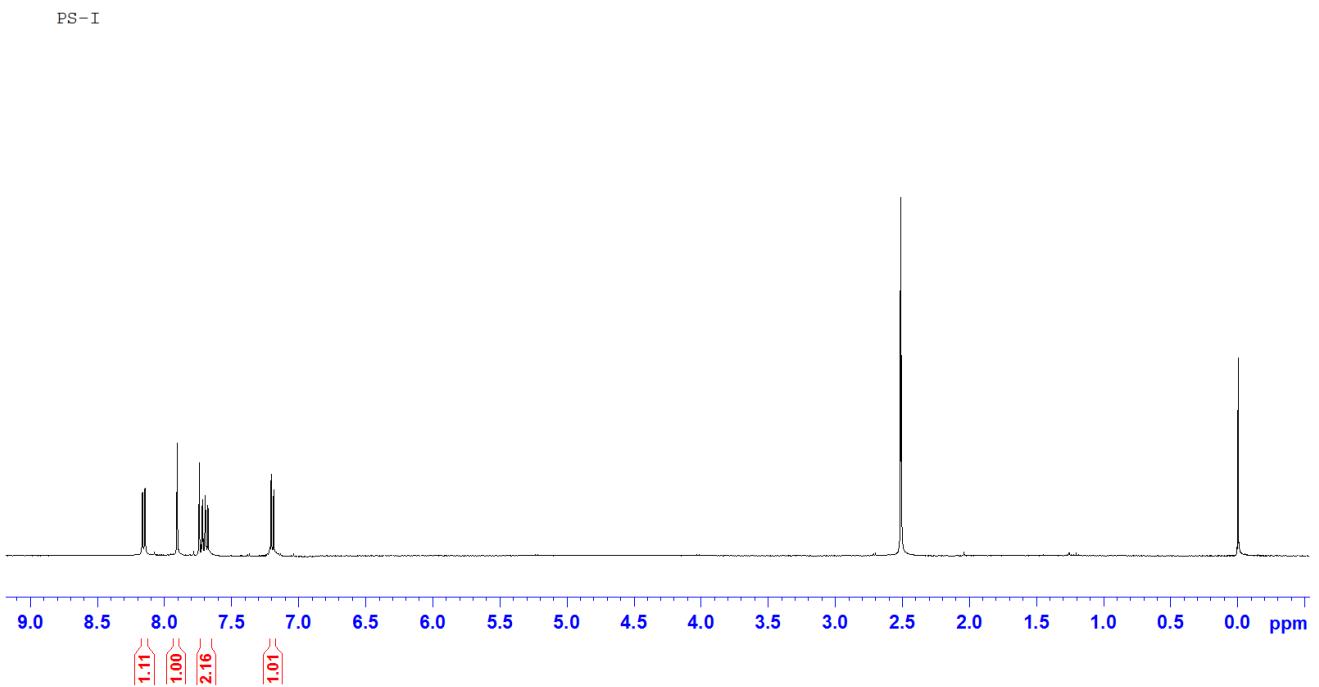
7-chloro-5H-imidazo[2,1-a]isoindol-5-one (2c)

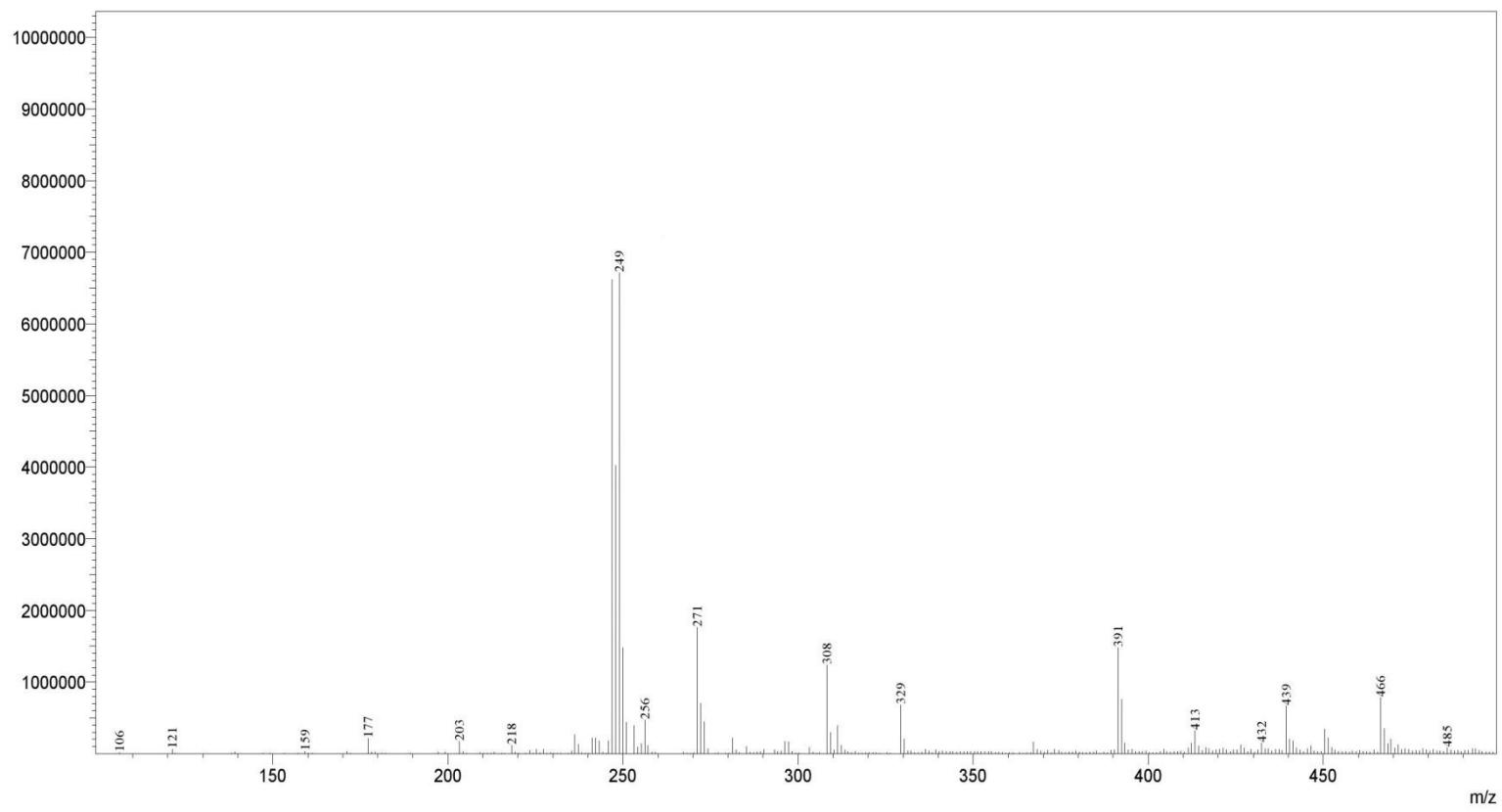
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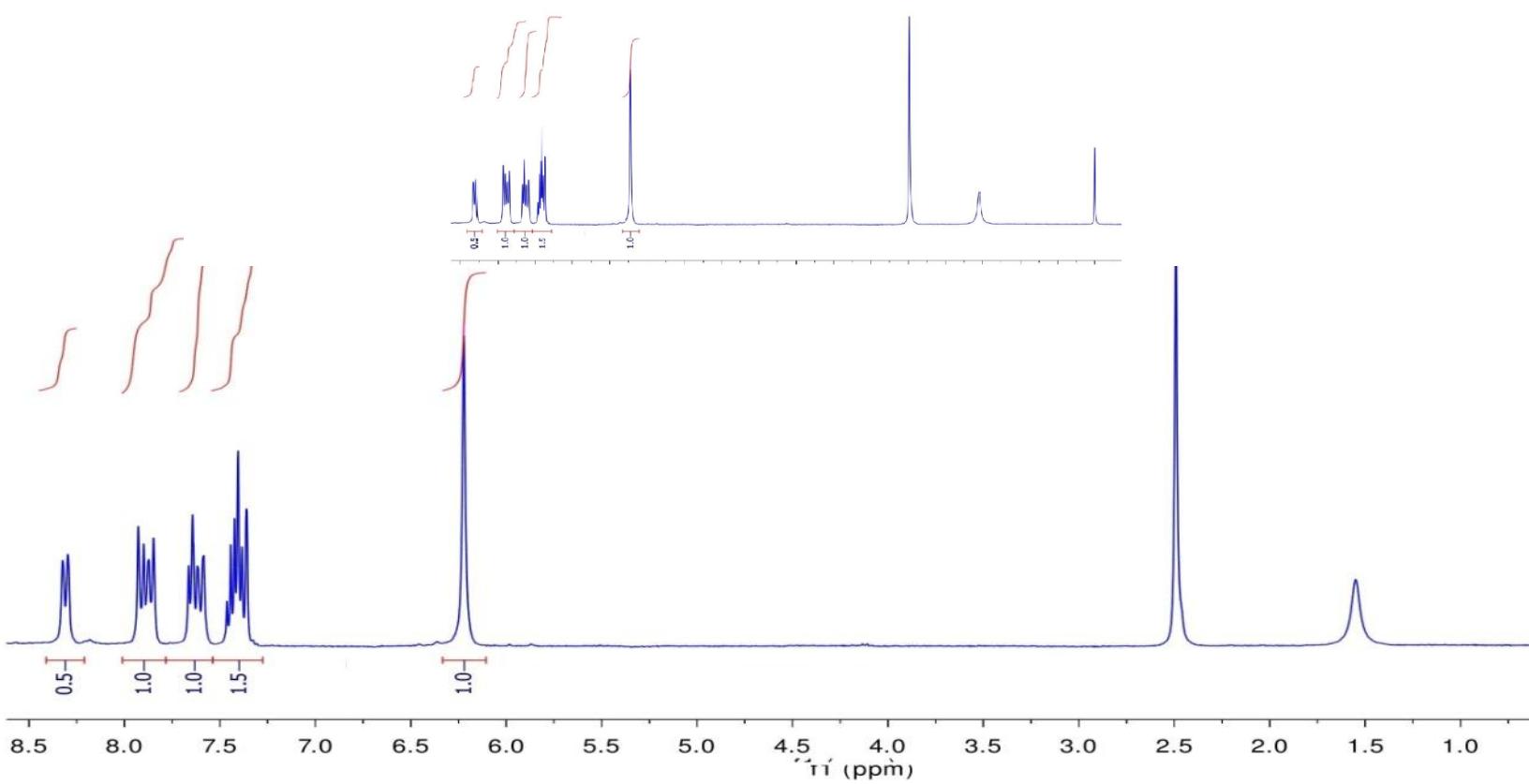


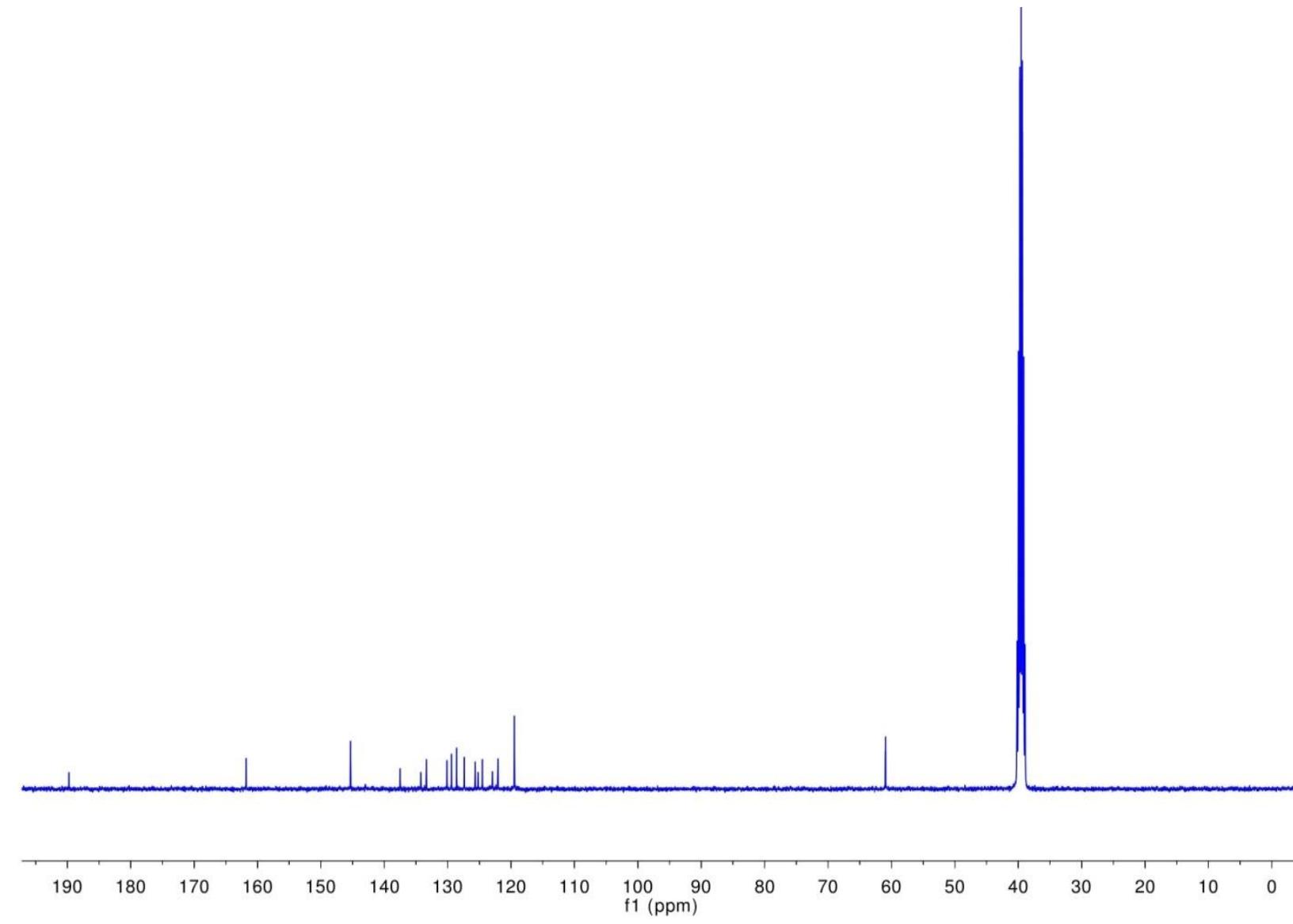
7-bromo-5H-imidazo[2,1-a]isoindol-5-one (2d)

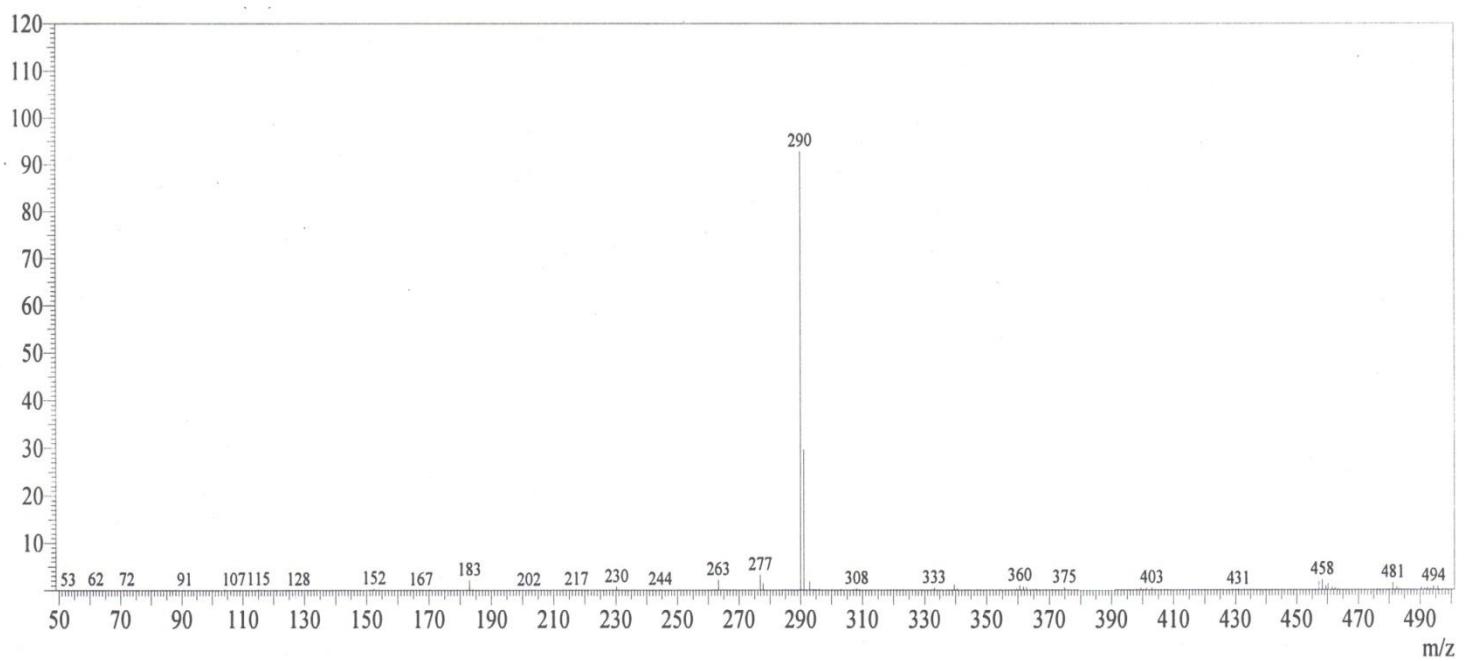




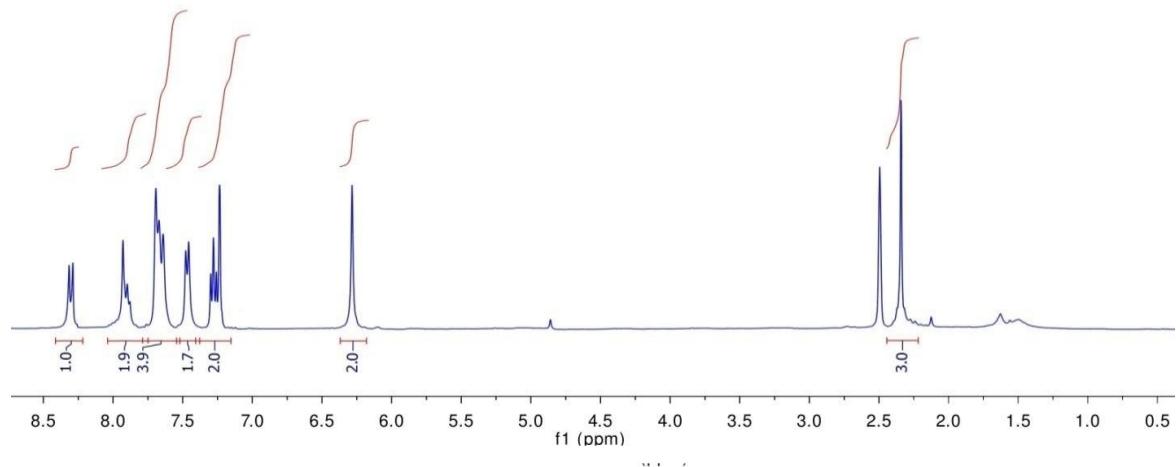
*5-oxo-1-(2-oxo-2-phenylethyl)-5H-imidazo[2,1-*a*]isoindol-1-i um bromide (3*a*)*

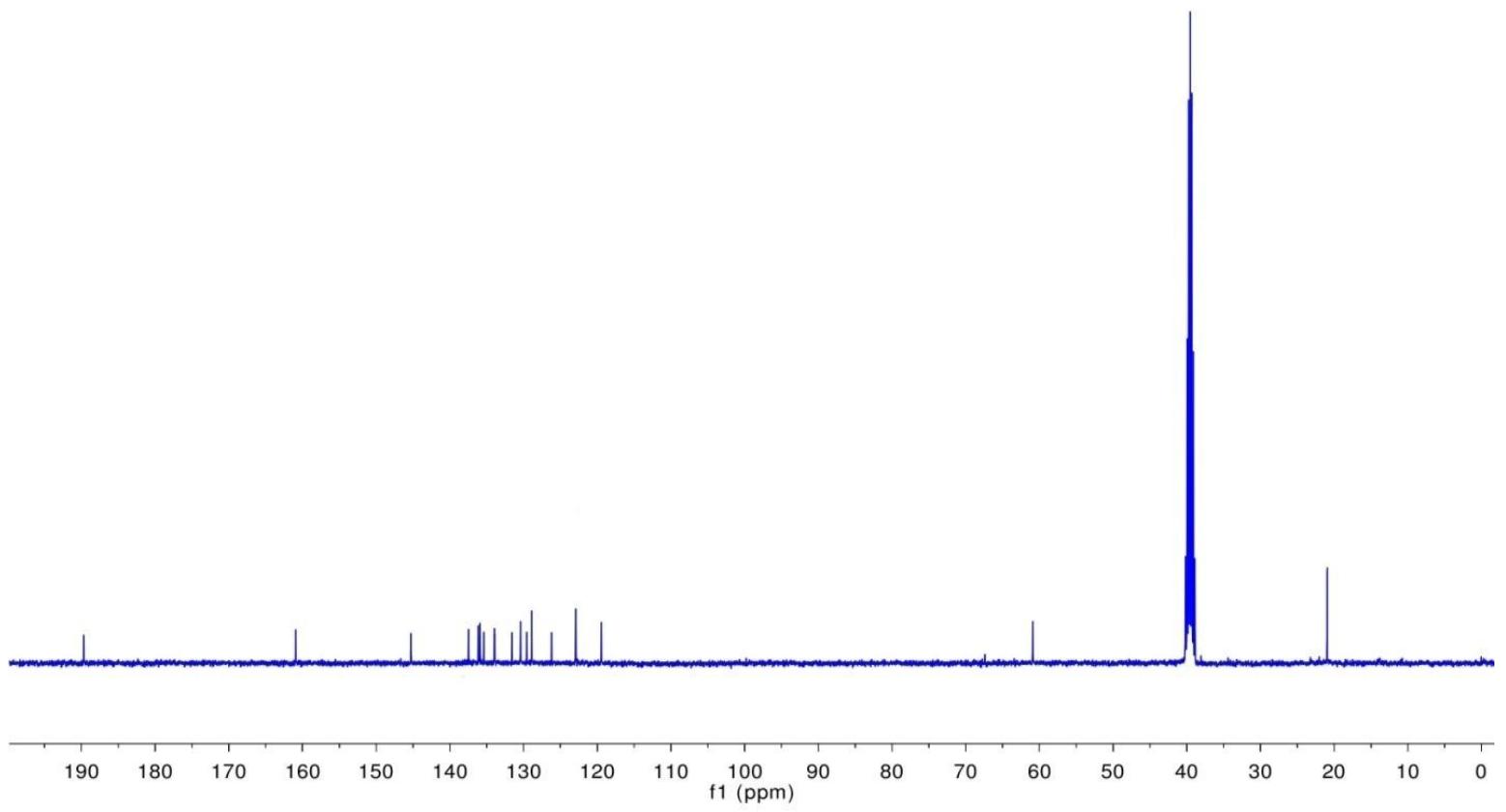


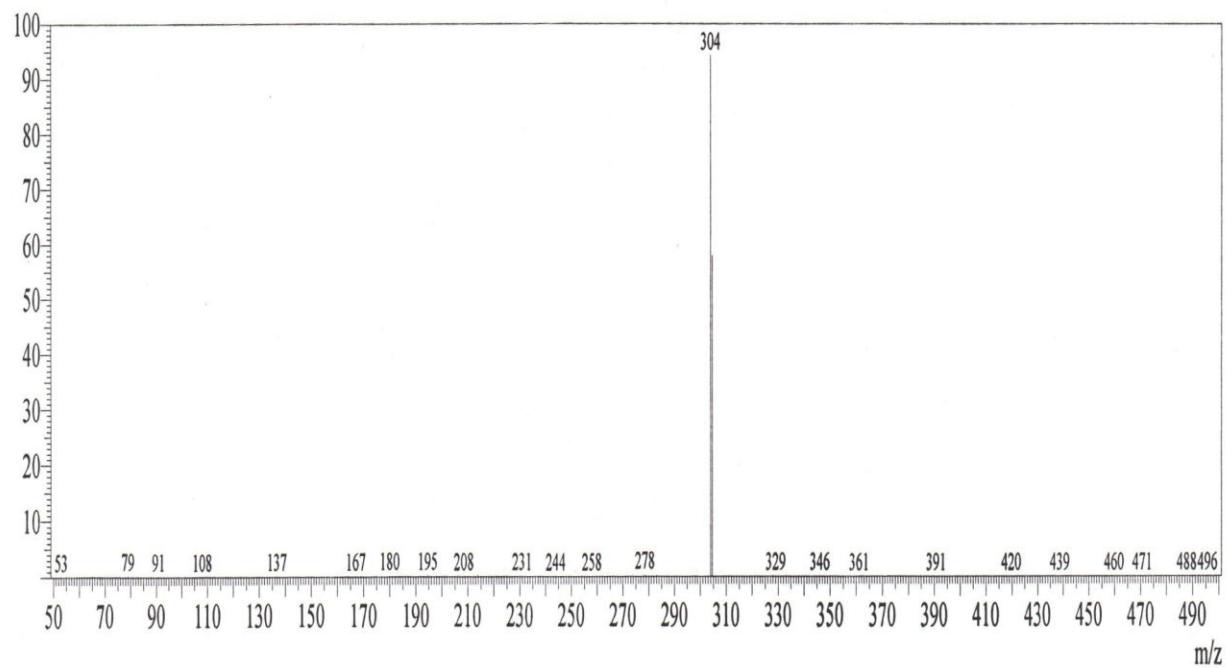




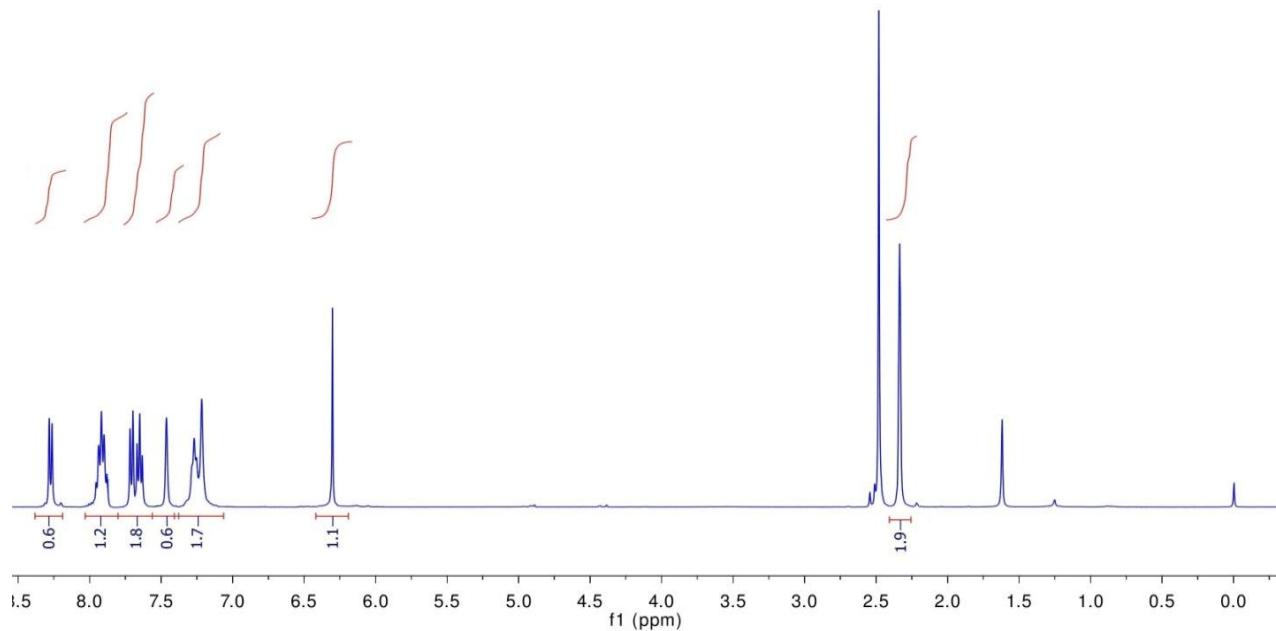
*5-oxo-1-(2-oxo-2-(*p*-tolyl)ethyl)-5*H*-imidazo[2,1-*a*]isoindol-1-ium bromide (3b)*

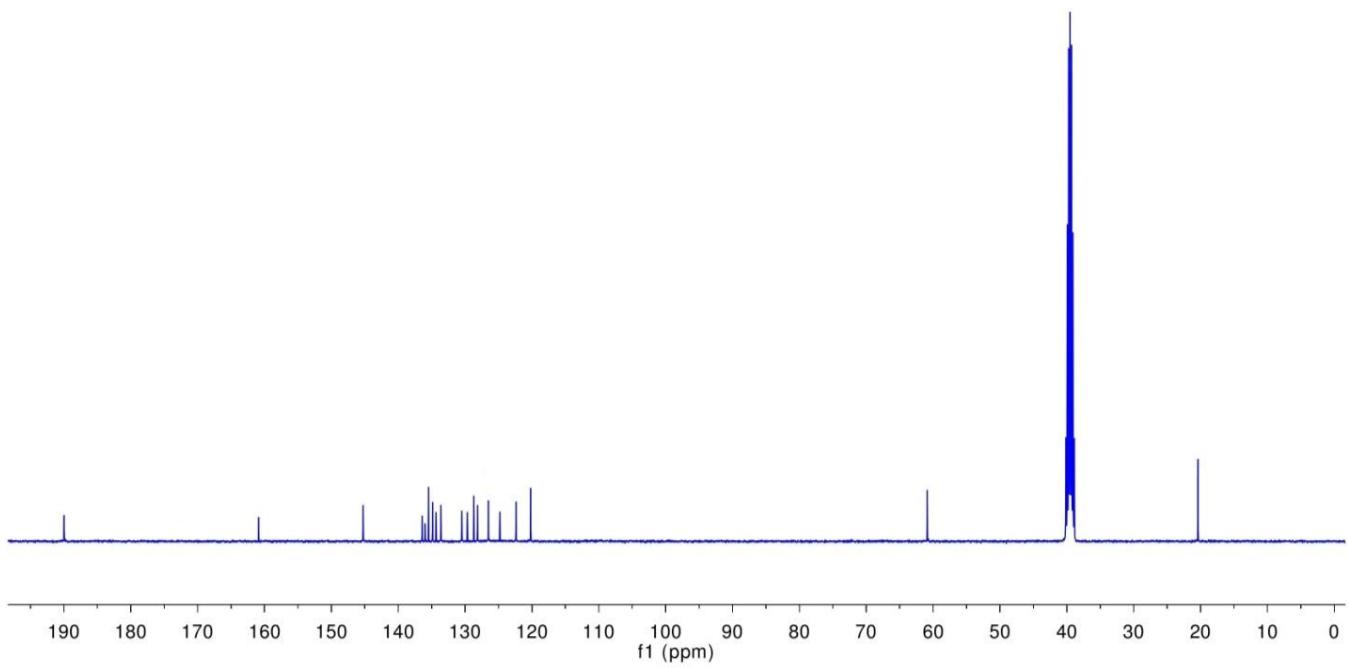


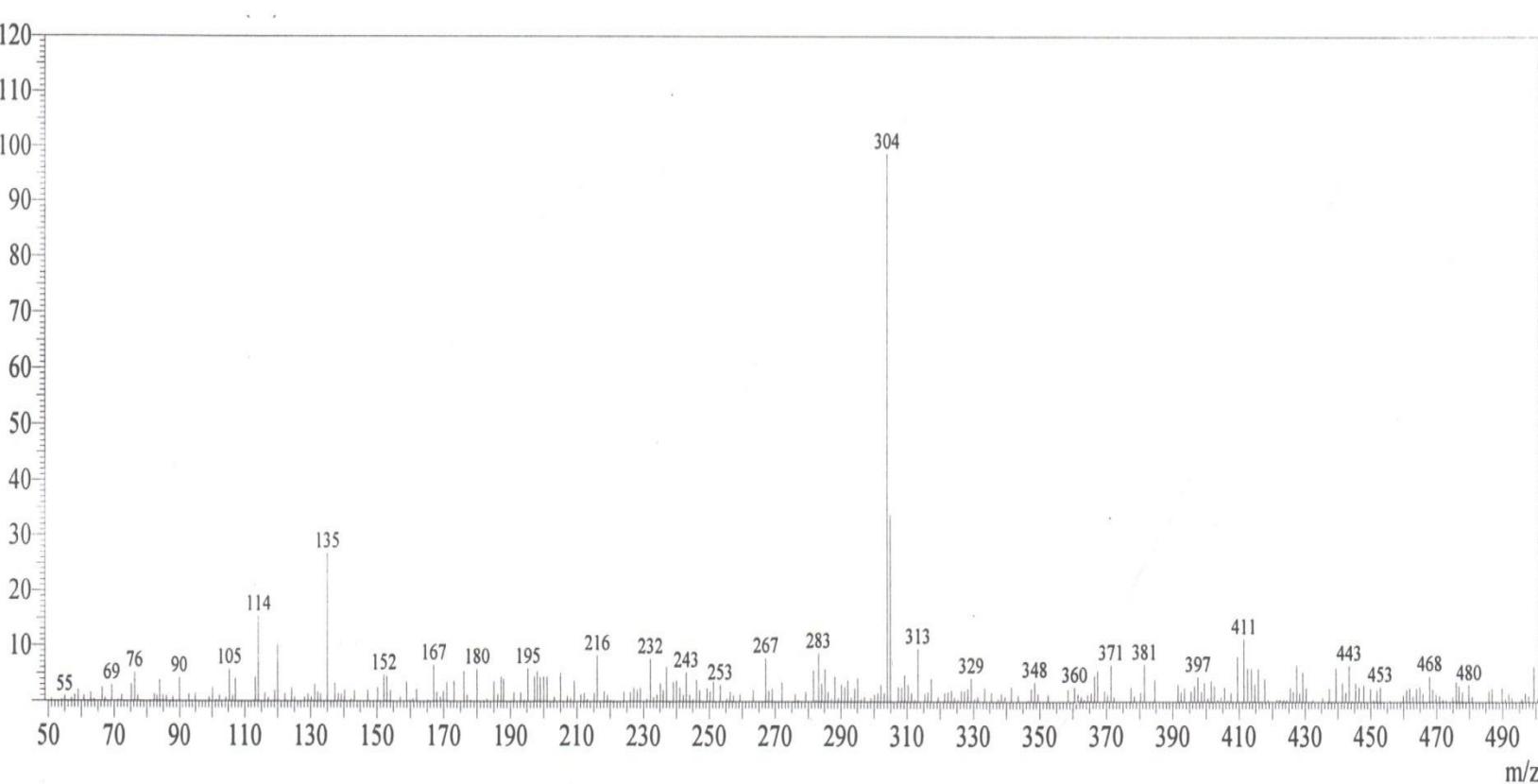




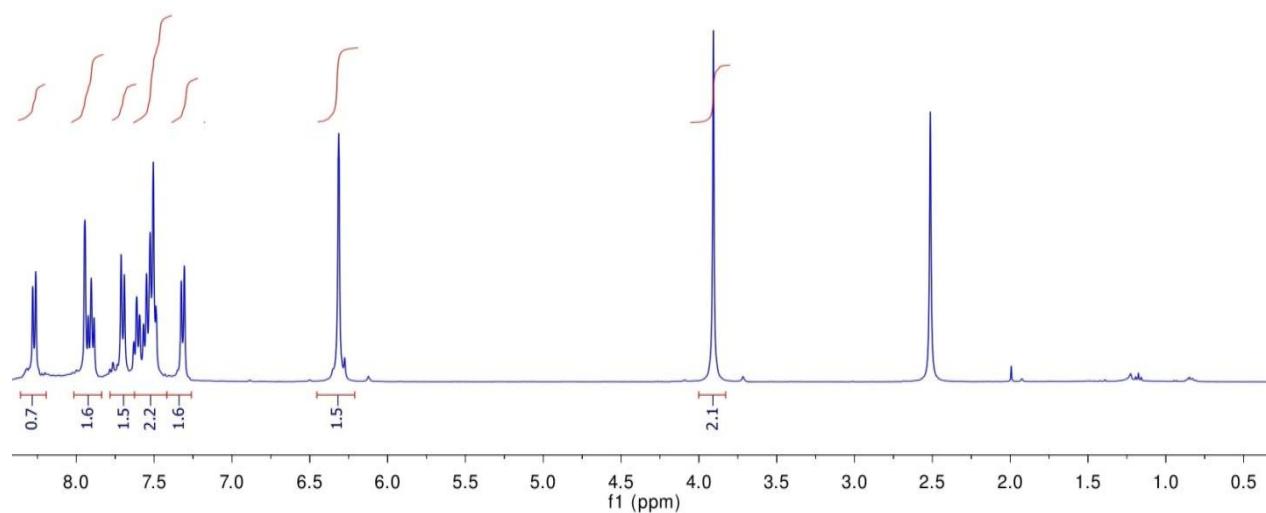
5-oxo-1-(2-oxo-2-(*m*-tolyl)ethyl)-5*H*-imidazo[2,1-*a*]isoindol-1-ium bromide (3c)

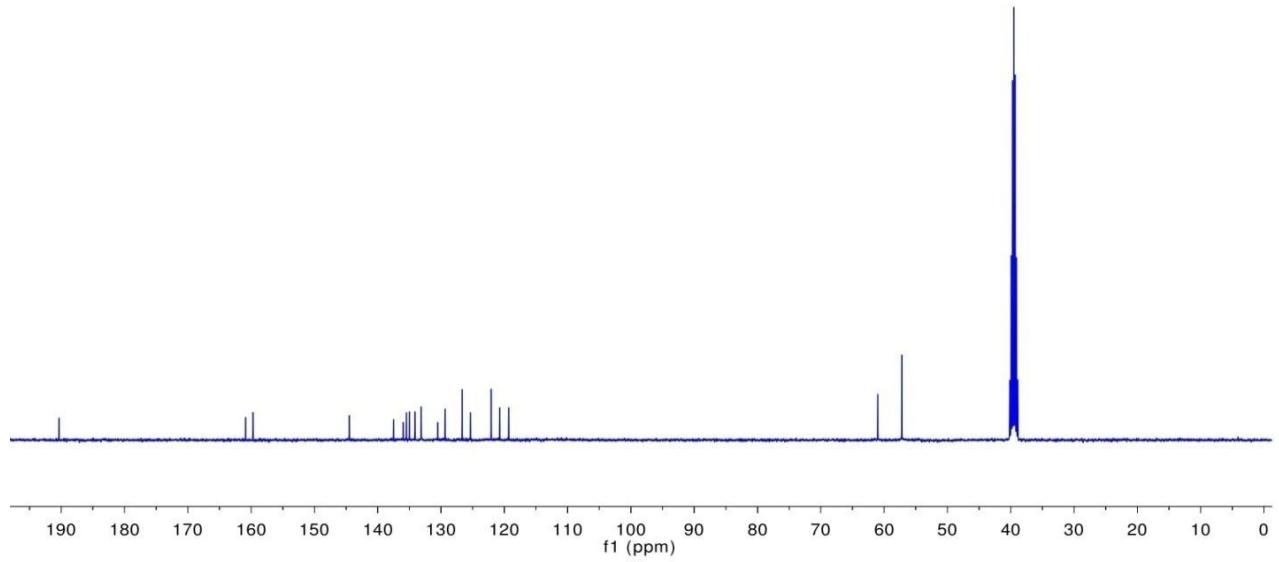


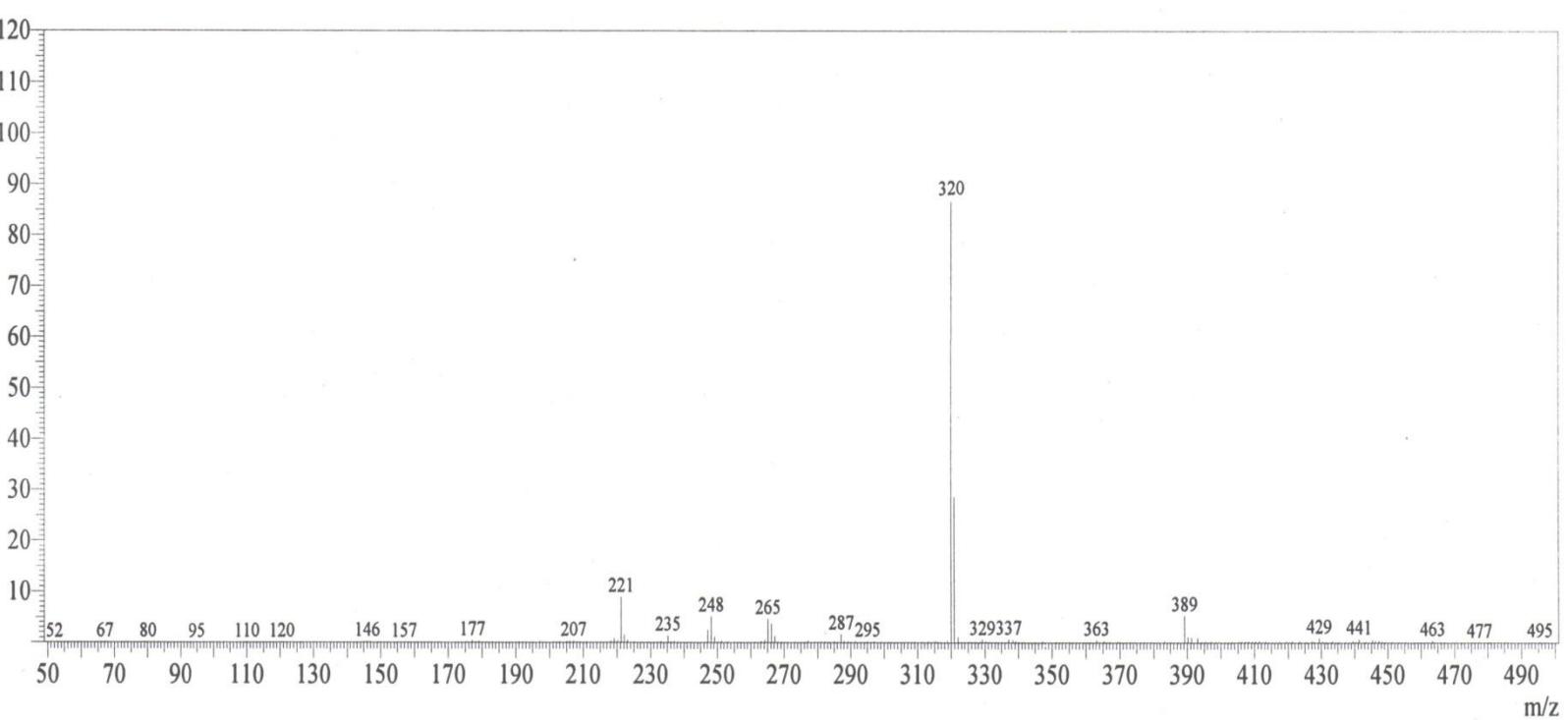




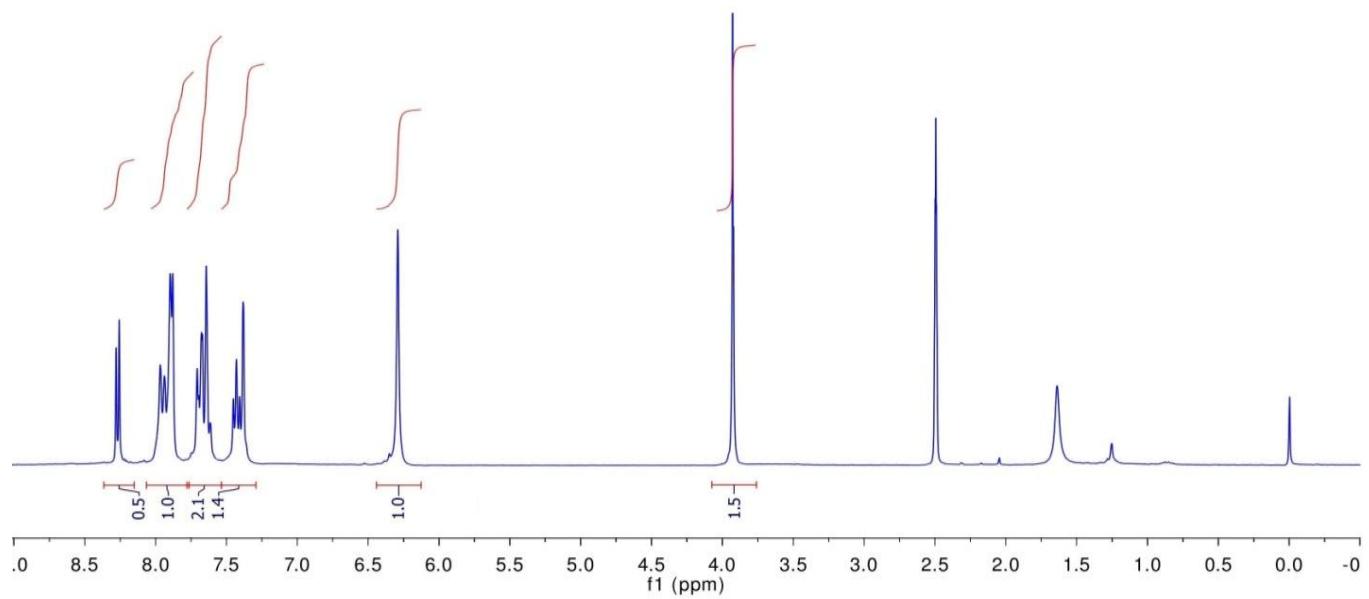
1-(2-(4-methoxyphenyl)-2-oxoethyl)-5-oxo-5H-imidazo[2,1-a]isoindol-1-i um bromide (3d)

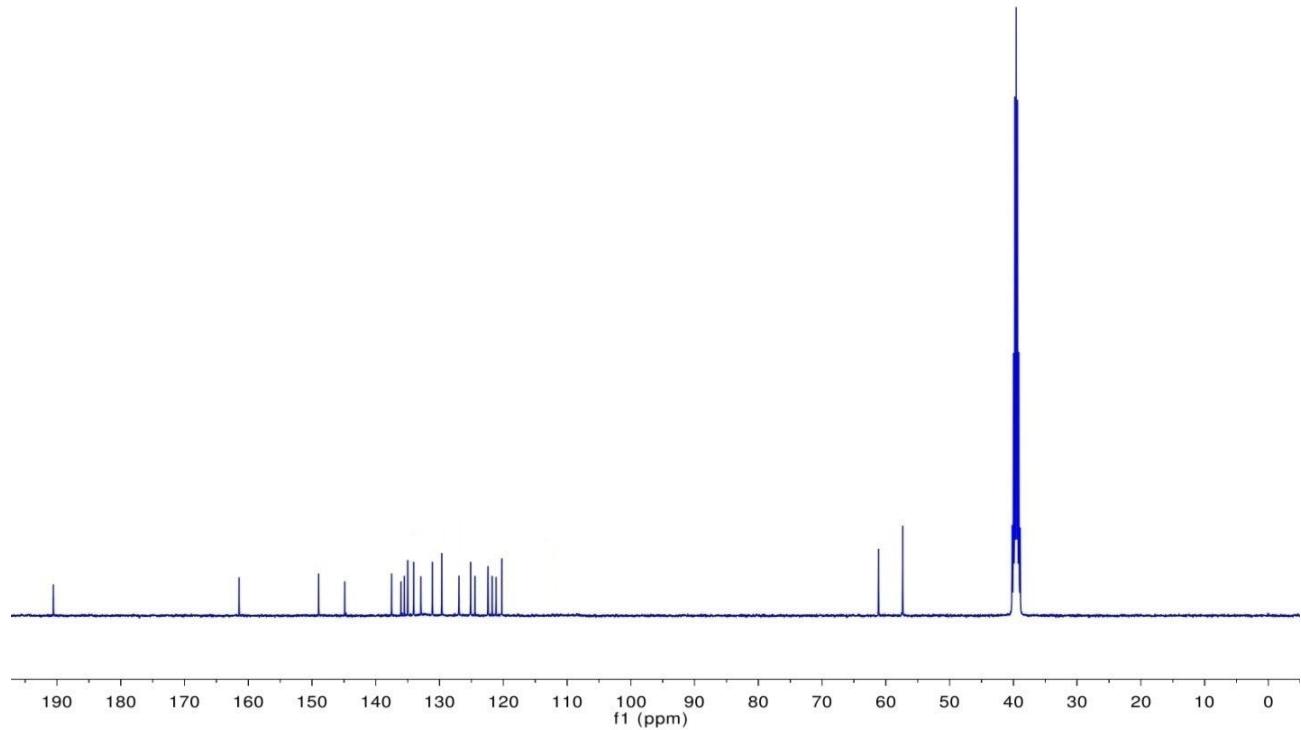


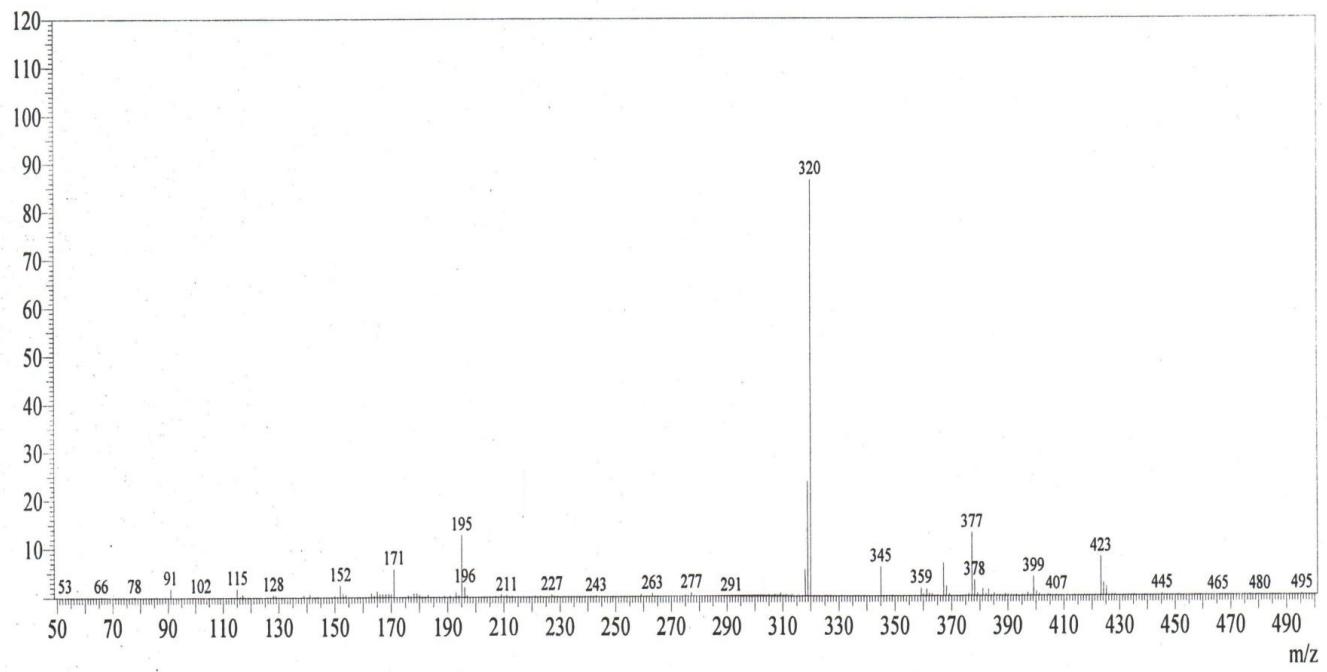




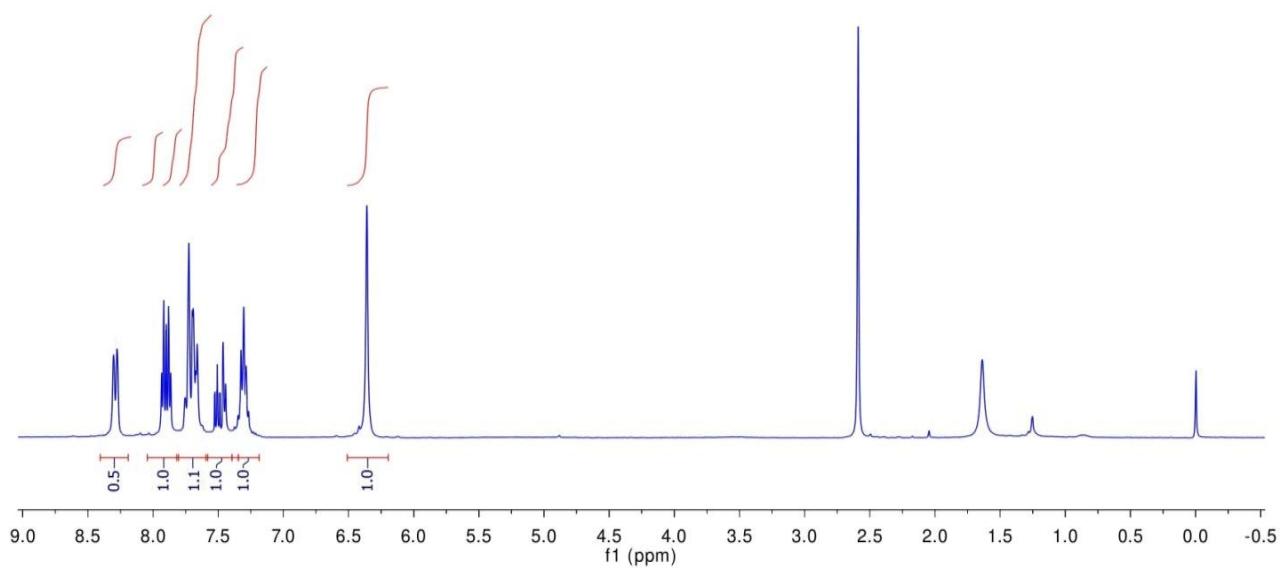
*1-(2-(3-methoxyphenyl)-2-oxoethyl)-5-oxo-5H-imidazo[2,1-*a*]isoindol-1-i^{um} bromide(3e)*

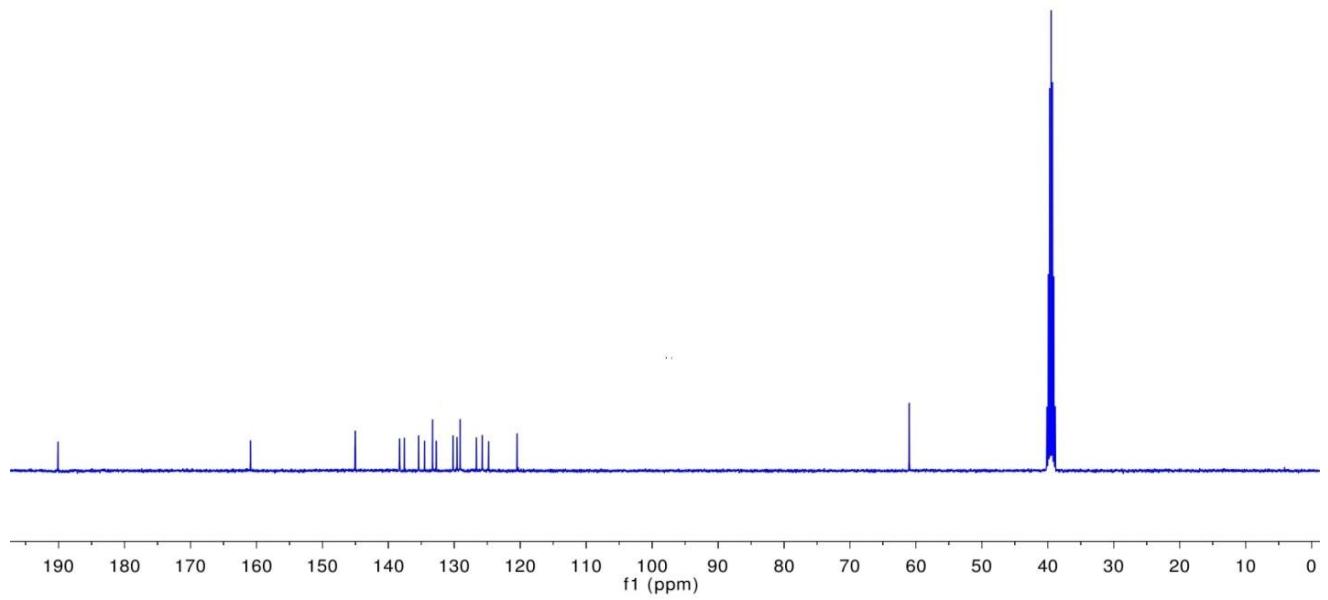


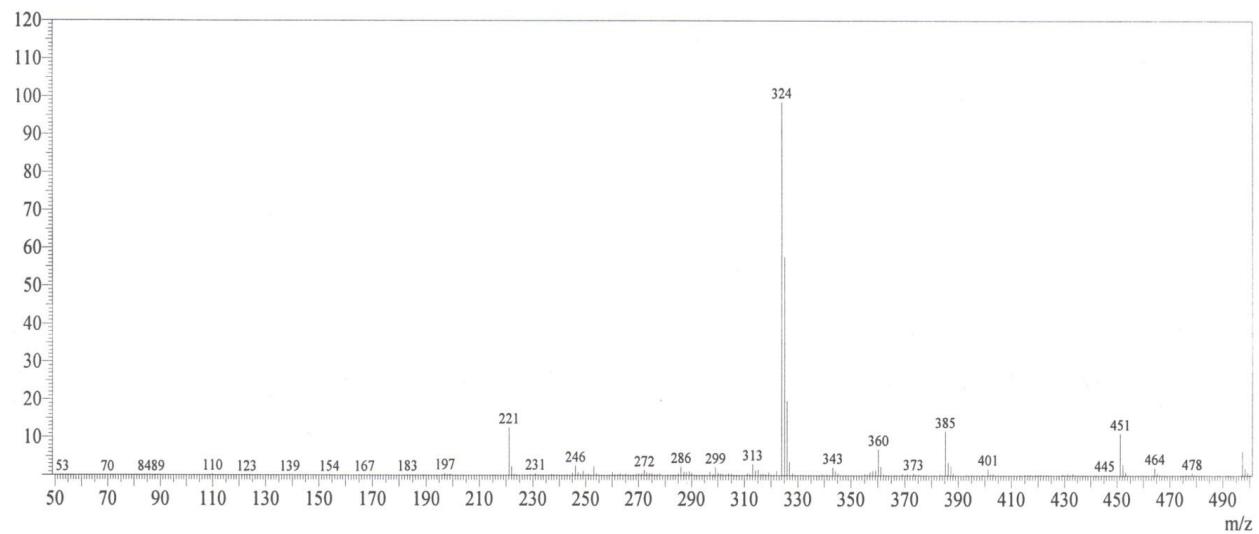




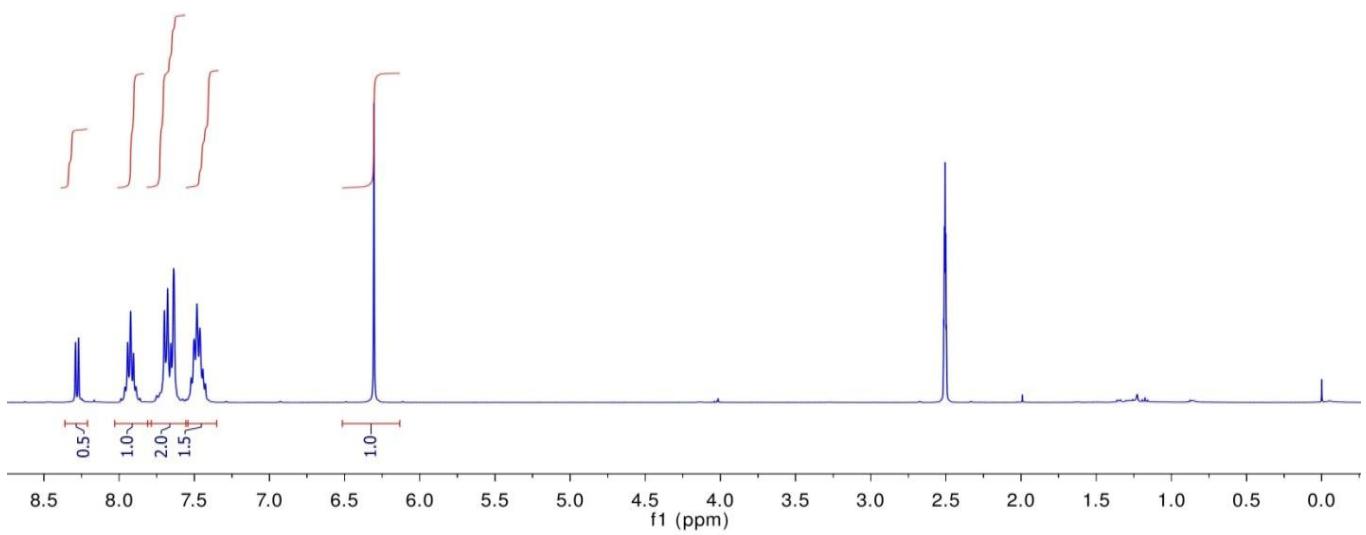
1-(2-(4-chlorophenyl)-2-oxoethyl)-5-oxo-5H-imidazo[2,1-a]isoindol-1-i um bromide (3f)

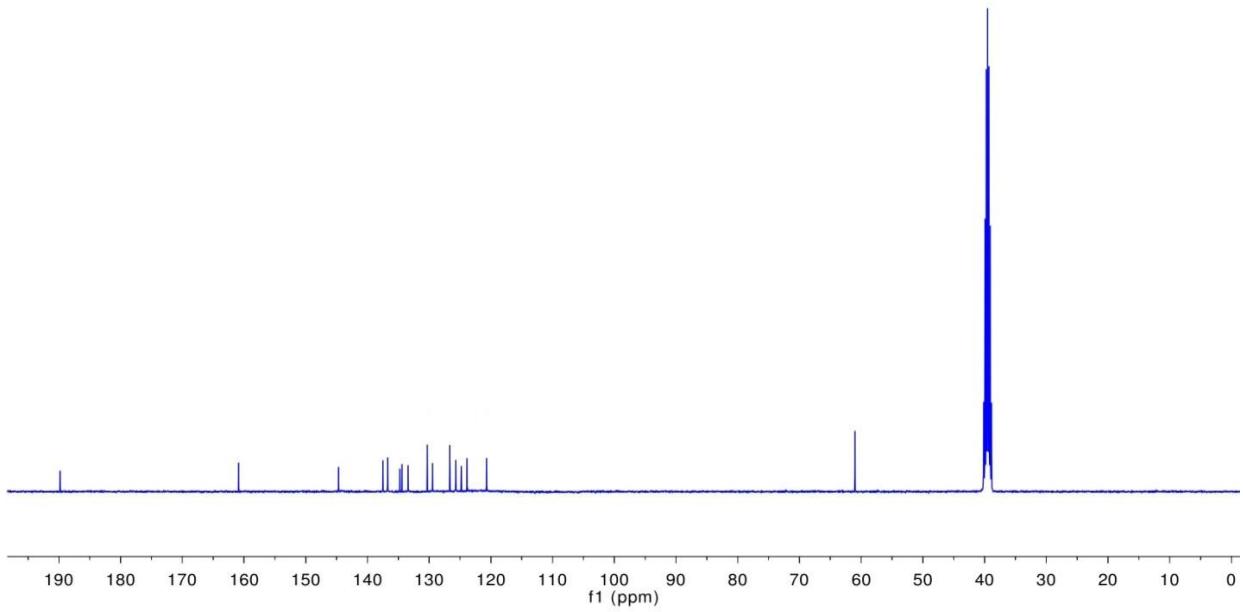


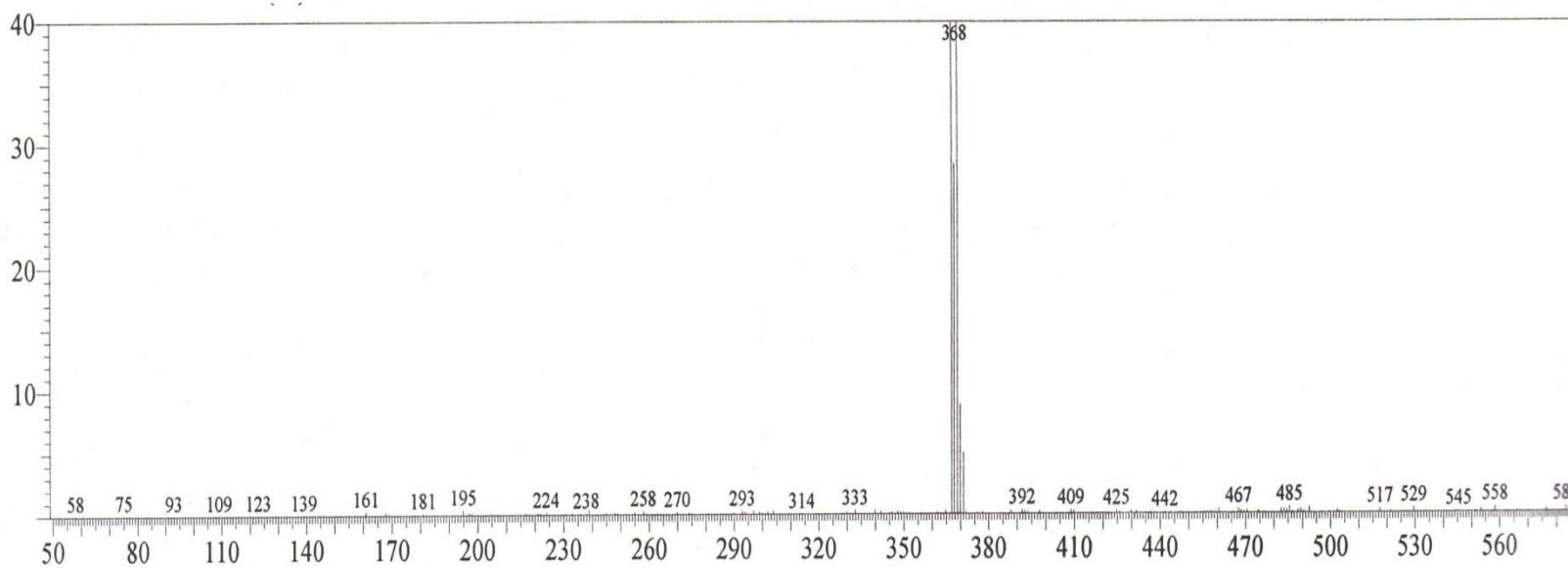




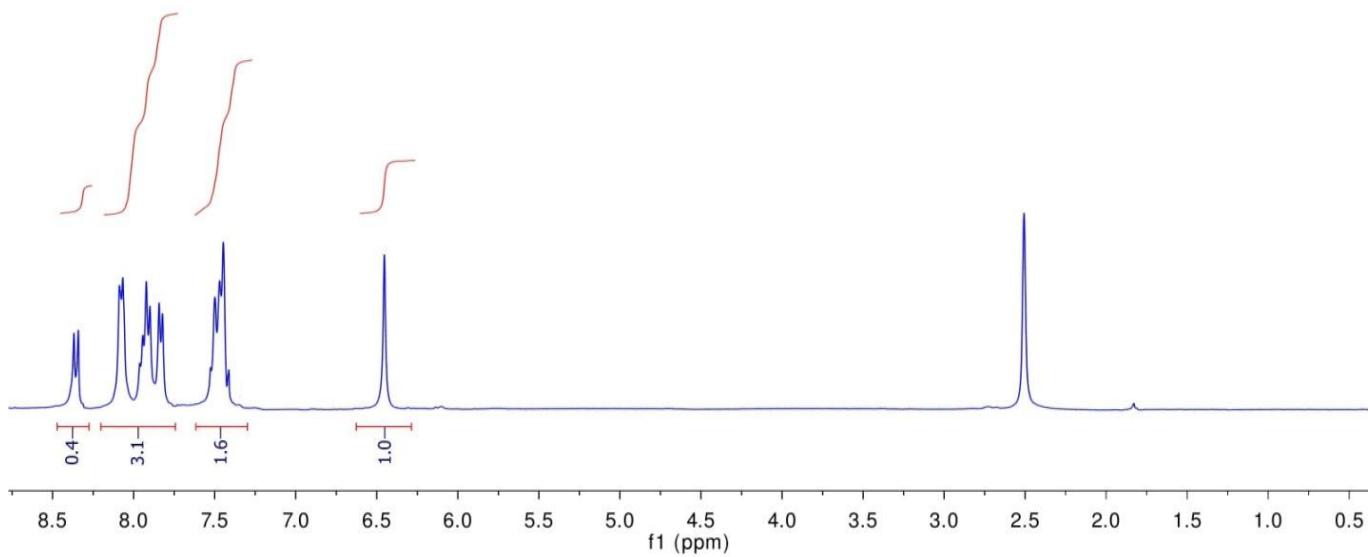
1-(2-(4-bromophenyl)-2-oxoethyl)-5-oxo-5H-imidazo[2,1-a]isoindol-1-i um bromide (3g)

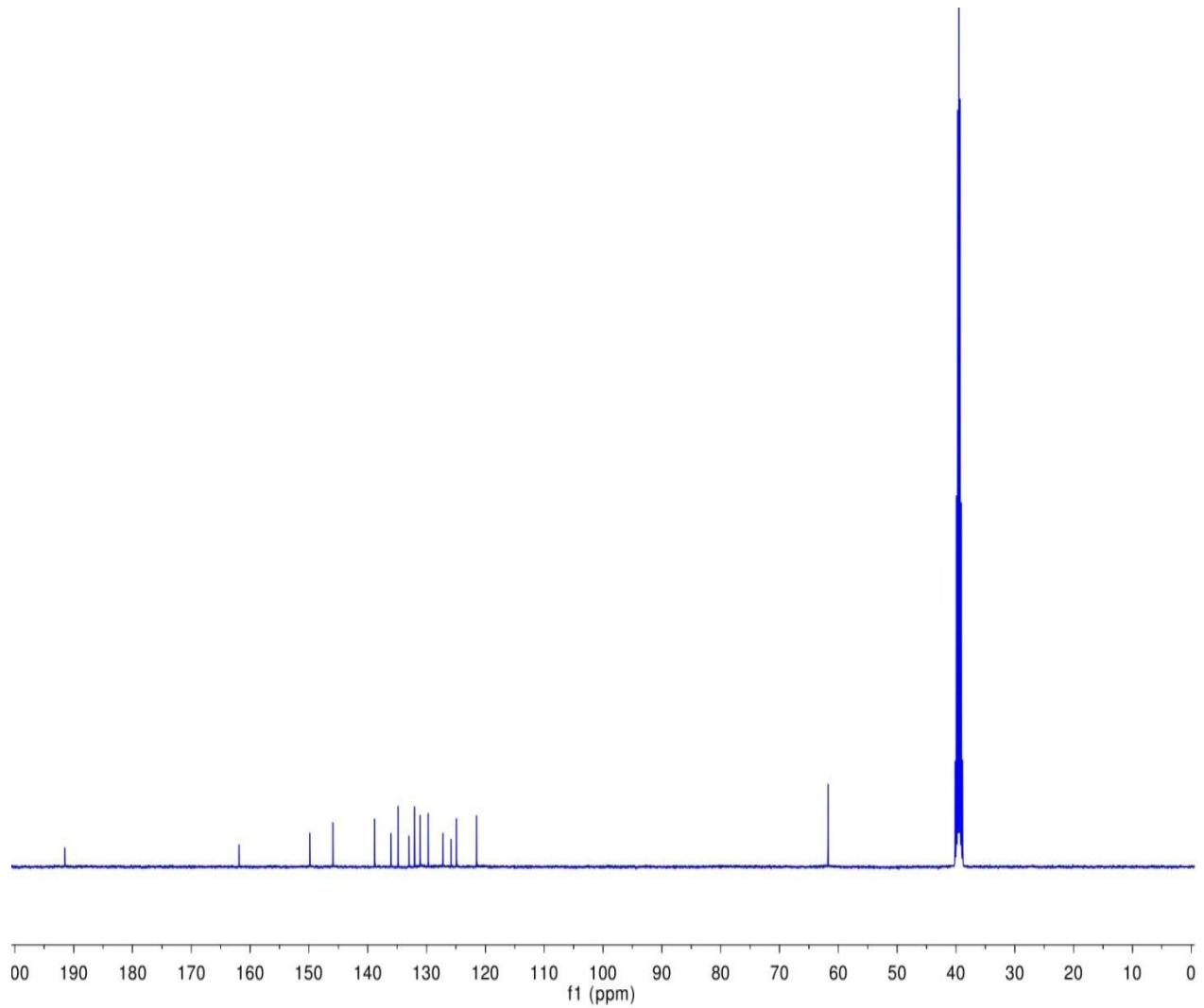


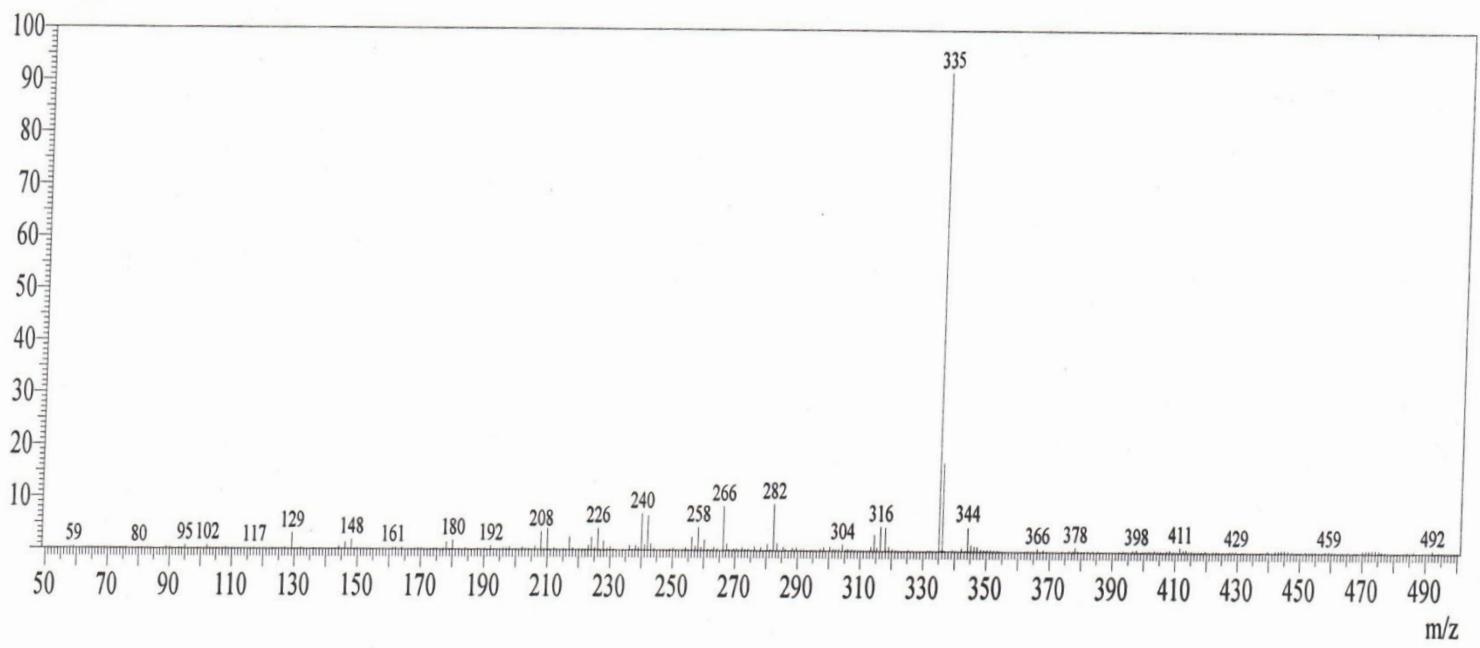




1-(2-(4-nitrophenyl)-2-oxoethyl)-5-oxo-5H-imidazo[2,1-a]isoindol-1-i um bromide (3h)







1-(2-([1,1'-biphenyl]-4-yl)-2-oxoethyl)-5-oxo-5H-imidazo[2,1-a]isoindol-1-i um bromide (3i)

