Supplementary Information

New Method of Synthesis of 6,7-dihydro-5*H*-pyrrolo[2,1-*a*][2]benzazepines and 5,6,7,9,10,11-hexahydro-12*H*-indolo[2,1-*a*][2]benzazepines and evaluation of their bioactivity

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Supplementary Information

Experimental section

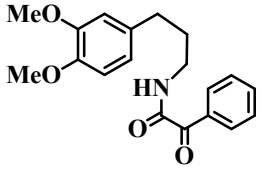
Materials and general procedures

All reagents and solvents were purchased from Merck, J.T. Baker, or Sigma-Aldrich Chemical Co., and were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded in chloroform-*d* ($CDCl_3$) or dimethylsulfoxide-d_6 (DMSO-d_6) solution at 25 °C, with a 600 MHz (^{1}H) or 150MHz (^{13}C) NMR spectrometer; peak positions are given in parts per million (δ) referenced to the appropriate solvent residual peak. Mass spectra (LC-MS) of compounds were acquired on an Agilent 1100/Agilent Technologies LC/MSD VL LC-MS system (electrospray ionization). Melting points were measured with a melting point apparatus Stuart SMP 30 in the open capillary tubes. Microwave syntheses were performed in an Anton Paar monowave 400 microwave reactor. Temperature monitoring during microwave syntheses was achieved via the use of an external surface temperature sensor. Column chromatography was carried out with silica gel grade 60 (0.040−0.063 mm) 230−400 mesh. Elemental analyses were carried out on Euro Vector EA-3000 Elemental Analyzer for C, H, and N; experimental data agreed to within 0.04 % of the theoretical values.

Synthesis of *N*-[3-(3,4-dimethoxyphenyl)propyl]-2-oxo-2-phenylacetamides 1a,b (general procedure):

To a mixture of benzoylformic or 3,4-dimethoxybenzoylformic acid (2.25 mmol) and triethylamine (5.33 mmol) in 10 ml of absolute CH_2Cl_2, thionyl chloride (5.30 mmol) was added at 0°C under an argon atmosphere. The mixture was stirred for 20 minutes. Then, without changing the conditions, a solution of 3-(3,4-dimethoxyphenyl)propan-1-amine (2.06 mmol) in 10 ml of absolute CH_2Cl_2 was added to the reaction mixture. The reaction was stirred for 2 days at 50°C. The reaction progress was monitored by TLC (Sorbfil, ethyl acetate-ethanol, 1:1). The reaction mixture was then poured onto ice, and a saturated sodium bicarbonate solution was added until a basic pH of 10 was reached. The mixture was extracted with dichloromethane (3 × 15 ml). The extract was washed with water and dried over $MgSO_4$. After solvent removal, amides **1a,b** were obtained as a thick, dark oil.

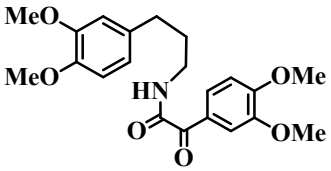
***N*-[3-(3,4-dimethoxyphenyl)propyl]-2-oxo-2-phenylacetamide (1a):**



Yield: 442 mg (60%), dark oil. NMR ^{1}H (600 MHz, $CDCl_3$), δ = 1.90 – 1.95 (m, 2H, CH_2), 2.65 (t, 2H, J = 8.1 Hz, CH_2), 3.40 – 3.43 (m, 2H, CH_2), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.72-6.74 (m, 2H, H-Ar), 6.78 (d, 1H, J = 8.1 Hz, H-Ar), 7.17 (br.s., 1H, NH), 7.46 – 7.48 (m, 2H, H-Ar), 7.61 (t, 1H, J = 8.1 Hz, H-Ar), 8.32 – 8.33 (m, 2H, H-Ar). NMR ^{13}C (150 MHz, $CDCl_3$), δ = 31.1, 32.8, 39.1, 55.9, 56.0, 111.5, 111.8, 120.3, 128.6 (2C), 131.3 (2C), 133.4, 133.7, 134.5,

147.5, 149.1, 161.9, 187.8. MS (LCMS), *m/z*: 328 $[M+H]^+$. Found, $C_{19}H_{21}NO_4$, Exact Mass: 327 (%): C, 69.86; H, 6.32; N, 4.21. Anal. calcd, (%): C, 69.71; H, 6.47; N, 4.28.

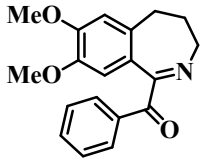
2-(3,4-Dimethoxyphenyl)-*N*-[3-(3,4-dimethoxyphenyl)propyl]-2-oxoacetamide (1b): Yield: 549 mg (63%), dark oil. NMR ^1H (600 MHz, $CDCl_3$), δ = 1.89 – 1.94 (m, 2H, CH_2), 2.64 (t, 2H, J = 8.1 Hz, CH_2), 3.38 – 3.41 (m, 2H, CH_2), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.71 – 7.73 (m, 2H, H-Ar), 6.77 (d, 1H, J = 7.1 Hz, H-Ar), 6.89 (d, 1H, J = 8.1 Hz, H-Ar), 7.17 (br.s., 1H, NH), 7.88 (d, 1H, J = 2.0 Hz, H-Ar), 8.33 (dd, 1H, J = 2.0, 8.1 Hz, H-Ar). NMR ^{13}C (150 MHz, $CDCl_3$), δ = 31.1, 32.8, 39.0, 55.9, 56.0 (2C), 56.2, 110.3, 111.4, 111.8, 112.8, 120.3, 126.5, 127.5, 133.8, 147.5, 148.9, 149.1, 154.8, 162.3, 185.6. MS (LCMS), *m/z*: 388 $[M+H]^+$. Found, $C_{21}H_{25}NO_6$, Exact Mass: 387 (%): C, 65.22; H, 6.57; N, 3.81. Anal. calcd (%): C, 65.10; H, 6.50; N, 3.62.



Synthesis of (7,8-dimethoxy-4,5-dihydro-3H-2-benzazepin-1-yl)(phenyl)methanones 2a,b (general procedure):

To *N*-(3-(3,4-dimethoxyphenyl)propyl)-2-oxo-2-phenylacetamides **1a,b** (0.61 mmol), $POCl_3$ (15.2 mmol) was added at 0°C under an argon atmosphere. The reaction mixture was then heated to 50°C and stirred for 8 hours under argon. The reaction progress was monitored by TLC (Sorbfil, ethyl acetate/hexane, 2.5:4). The reaction mixture was poured onto ice (10 g) and neutralized with a 25% ammonia solution to a basic pH of 10. The mixture was extracted with ethyl acetate (3 × 15 mL), and the organic extract was dried over $MgSO_4$. The solvent was then removed under reduced pressure to afford benzazepines **2a,b** as a yellow oil.

(7,8-Dimethoxy-4,5-dihydro-3H-2-benzazepin-1-yl)(phenyl)methanone (2a): Yield: 96 mg (51%), yellow oil. NMR ^1H (600 MHz, $CDCl_3$), δ = 2.43 – 2.46 (m, 2H, 4-CH_2), 2.65 (t, 2H, J = 7.3 Hz, 5-CH_2), 3.57 (t, 2H, J = 6.8 Hz, 3-CH_2), 3.82 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.78 (s, 1H, H-6), 7.00 (s, 1H, H-9), 7.45 – 7.48 (m, 2H, H-Ar), 7.58 – 7.59 (m, 1H, H-Ar), 8.04 – 8.05 (m, 2H, H-Ar). NMR ^{13}C (150 MHz, $CDCl_3$), δ = 30.7, 35.0, 50.6, 56.0, 56.2, 111.3, 112.0, 127.5, 128.6, 130.6, 131.2, 132.1, 133.6, 134.6, 135.8, 147.4, 150.5, 169.5, 194.0. MS (LCMS), *m/z*: 310 $[M+H]^+$. Found, $C_{19}H_{19}NO_3$, Exact Mass: 309 (%): C, 73.65; H, 6.04; N, 4.43. Anal. calcd (%): C, 73.77; H, 6.19; N, 4.53.



(7,8-Dimethoxy-4,5-dihydro-3*H*-2-benzazepin-1-yl)(3,4-dimethoxyphenyl)methanone (2b): Yield: 106 mg (47%), yellow oil. NMR ^{1}H (600 MHz, $CDCl_3$), δ = 2.43 – 2.46 (m, 2H, 4-CH_2), 2.66 (t, 2H, J = 7.1 Hz, 5-CH_2), 3.56 (t, 2H, J = 7.1 Hz, 3-CH_2), 3.81 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.77 (s, 1H, H-6), 6.89 (d, 1H, J = 8.1 Hz, H-Ar), 7.01 (s, 1H, H-9), 7.62 – 7.63 (m, 1H, H-Ar), 7.69 (dd, 1H, J = 1.5, 8.1 Hz, H-Ar). NMR ^{13}C (150 MHz, $CDCl_3$), δ = 30.8, 35.1, 50.4, 56.0, 56.1, 56.2 (2C), 110.1, 111.2, 111.8, 112.0, 125.7, 126.3, 128.7, 134.4, 147.4, 149.2, 150.4, 154.0, 169.7, 192.8. MS (LCMS), *m/z*: 370 $[M+H]^+$. Found, $C_{21}H_{23}NO_5$, Exact Mass: 369 (%): C, 68.31; H, 6.15; N, 3.64. Anal. calcd (%): C, 68.28; H, 6.28; N, 3.79.

Synthesis of 9,10-dimethoxy-1-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*a*][2]benzazepine-2-carbaldehydes 3a-g and 2,3-dimethoxy-13-phenyl-5,6,7,9,10,11-hexahydro-12*H*-indolo[2,1-*a*][2]benzazepin-12-ones 3h,i (general procedure):

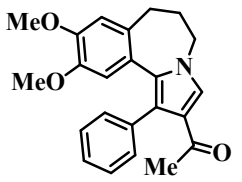
To a solution of (4,5-dihydro-3*H*-benzo[*c*]azepin-1-yl)(phenyl)methanones **2a,b** (0.16 mmol) in 2 ml of trifluoroethanol was added 0.23 mmol of an alkene: acrolein (for **3a,b**), methyl vinyl ketone (for **3c,d**), cinnamaldehyde (for **3f,g**) or cyclohexenone (for **3h,i**). The reaction was carried out at 40 ^{o}C, the reaction progress was monitored by TLC (sorbfil, ethyl acetate-hexane, 2:1). After removing the solvent, the reaction mixture was purified by column chromatography (aluminum oxide, ethyl acetate-petroleum ether, 1:10).

9,10-Dimethoxy-1-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*a*][2]benzazepine-2-carbaldehyde (3a): Yield: 48 mg (86%), white powder, mp 180-182 ^{o}C. NMR ^{1}H (600 MHz, $CDCl_3$), δ = 2.26 – 2.28 (m, 2H, 6-CH_2), 2.73 (t, 2H, J = 7.1 Hz, 7-CH_2), 3.36 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.91 (t, 2H, J = 6.8 Hz, 5-CH_2), 6.31 (s, 1H, H-11), 6.76 (s, 1H, H-8), 7.23 – 7.30 (m, 5H, H-Ar), 7.49 (s, 1H, H-3), 9.78 (s, 1H, CHO). NMR ^{13}C (150 MHz, $CDCl_3$), δ = 30.3, 31.2, 46.5, 55.6, 56.0, 112.3, 113.2, 122.9, 123.3, 126.5, 126.8, 128.3 (2C), 130.8 (2C), 130.9, 132.7, 133.6, 147.2, 148.5, 185.0, 186.7. MS (LCMS), *m/z*: 348 $[M+H]^+$. Found, $C_{22}H_{21}NO_3$, Exact Mass: 347 (%): C, 75.91; H, 6.12; N, 3.94. Anal. calcd (%): C, 76.06; H, 6.09; N, 4.03.

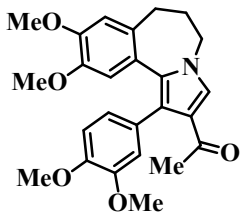
1-(3,4-Dimethoxyphenyl)-9,10-dimethoxy-6,7-dihydro-5*H*-pyrrolo[2,1-*a*][2]benzazepine-2-carbaldehyde (3b): Yield: 52 mg (80%), yellow oil. NMR ^{1}H (600 MHz, $CDCl_3$), δ = 2.25 – 2.27 (m, 2H, 6-CH_2), 2.72 (t, 2H, J = 7.1 Hz, 7-CH_2), 3.43 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.83 – 3.90 (m, 8H, 5-CH_2, 2 OCH_3), 6.40 (s, 1H, H-8), 6.76 (s, 1H, H-Ar), 6.78 – 6.79 (m, 2H, H-Ar),

6.82 (s, 1H, H-11), 7.47 (s, 1H, H-3), 9.80 (s, 1H, CHO). NMR ^{13}C (150 MHz, $CDCl_3$), δ = 24.8, 30.3, 31.2, 36.7, 46.5, 55.8, 56.0, 111.1, 112.3, 113.1, 114.1, 123.0, 123.2 (2C), 123.4, 126.1, 126.6, 130.9, 132.4, 147.3, 148.1, 148.5, 148.6, 186.6. MS (LCMS), *m/z*: 408 $[M+H]^+$. Found, $C_{24}H_{25}NO_5$, Exact Mass: 407 (%): C, 70.70; H, 6.10; N, 3.48. Anal. calcd (%): C, 70.75; H, 6.18; N, 3.44.

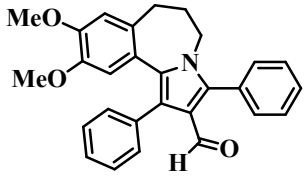
1-(9,10-Dimethoxy-1-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*a*][2]benzazepin-2-yl)ethanone (3c): Yield: 46 mg (80%), yellow oil. NMR ^{1}H (600 MHz, $CDCl_3$), δ = 2.21 (s, 3H, $COCH_3$), 2.24 – 2.26 (m, 2H, 6-CH_2), 2.70 (t, 2H, *J* = 7.1 Hz, 7-CH_2), 3.32 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.89 (t, 2H, *J* = 6.6 Hz, 5-CH_2), 6.22 (s, 1H, H-11), 6.71 (s, 1H, H-8), 7.19 – 7.27 (m, 5H, H-Ar), 7.44 (s, 1H, H-3). NMR ^{13}C (150 MHz, $CDCl_3$), δ = 28.8, 30.4, 31.3, 46.3, 55.5, 55.9, 112.2, 113.1, 122.8, 123.4, 123.7, 126.7, 128.0, 129.0, 130.8, 131.0, 131.3, 133.1, 135.5, 135.7, 147.0, 148.1, 194.3. MS (LCMS), *m/z*: 362 $[M+H]^+$. Found, $C_{23}H_{23}NO_3$, Exact Mass: 361 (%): C, 76.54; H, 6.56; N, 4.01. Anal. calcd (%): C, 76.43; H, 6.41; N, 3.88.



1-[1-(3,4-Dimethoxyphenyl)-9,10-dimethoxy-6,7-dihydro-5*H*-pyrrolo[2,1-*a*][2]benzazepin-2-yl]ethanone (3d): Yield: 53 mg (79%), yellow oil. NMR^{1}H (600 MHz, $CDCl_3$), δ = 2.23 (s, 3H, $COCH_3$), 2.24 – 2.25 (m, 2H, 6-CH_2), 2.70 (t, 2H, 7-CH_2, *J* = 7.1 Hz), 3.40 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.86 – 3.88 (m, 5H, OCH_3, 5-CH_2), 6.33 (s, 1H, H-11), 6.72 – 6.76 (m, 3H, H-Ar), 6.84 (s, 1H, H-8), 7.41 (s, 1H, H-3). NMR ^{13}C (150 MHz, $CDCl_3$), δ = 28.9, 30.4, 31.3, 46.2, 55.6, 55.9 (2C), 56.0, 110.8, 112.2, 113.0, 114.6, 122.3, 123.3, 123.4, 123.9, 126.5, 128.0, 130.8, 133.0, 147.1, 148.0, 148.2, 148.4, 194.0. MS (LCMS), *m/z*: 422 $[M+H]^+$. Found, $C_{25}H_{27}NO_5$, Exact Mass: 421 (%): C, 71.43; H, 6.31; N, 3.14. Anal. calcd (%): C, 71.24; H, 6.46; N, 3.32.

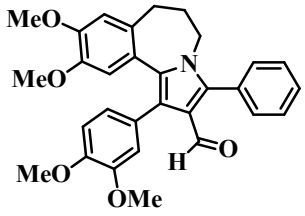


9,10-Dimethoxy-1,3-diphenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*a*][2]benzazepine-2-carbaldehyde (3f): Yield: 48 mg (71 %), yellow powder, mp 180-182 ^{o}C. NMR ^{1}H (600 MHz, $CDCl_3$), δ = 2.17 – 2.20 (m, 2H, 6-CH_2), 2.80-2.81 (m, 2H, 7-CH_2), 3.28 (s, 3H, OCH_3), 3.67-3.68 (m, 2H, 5-CH_2), 3.83 (s, 3H, OCH_3), 6.27 (s, 1H, H-11), 6.70 (s, 1H, H-8), 7.16 (t, 1H, *J* = 7.3 Hz, H-Ar), 7.22 (t, 2H, *J* = 7.3 Hz, H-Ar), 7.27 (d, 2H, *J* = 7.3 Hz, H-Ar), 7.41-7.43 (m, 2H, H-Ar), 7.44-7.45 (m, 3H, H-Ar), 9.62 (s, 1H, CHO). NMR ^{13}C (150 MHz, $CDCl_3$), δ = 30.4, 32.0, 42.9, 55.4, 55.9, 111.4, 112.1, 113.5, 115.7, 115.9, 120.3, 120.7, 122.7, 123.5, 126.7, 127.9, 128.5, 129.1, 130.0, 130.9, 131.0 (2C), 133.2, 134.0, 142.2, 147.1, 148.3, 186.8.



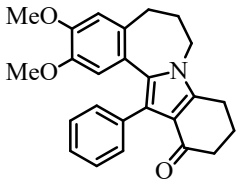
MS (LCMS), *m/z*: 424 $[M+H]^+$. Found, $C_{28}H_{25}NO_3$, Exact Mass: 423 (%): C, 79.84; H, 6.76; N, 3.14. Anal. calcd (%): C, 79.41; H, 5.95; N, 3.31.

1-(3,4-Dimethoxyphenyl)-9,10-dimethoxy-3-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*a*][2]benzazepine-2-carbaldehyde (3g): Yield: 33 mg (42 %), beige powder, mp 187-188 °C.

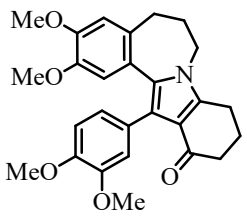


NMR ^1H (600 MHz, $CDCl_3$), δ = 2.17 – 2.20 (m, 2H, 6-CH_2), 2.79-2.81 (m, 2H, 7-CH_2), 3.35 (s, 3H, OCH_3), 3.66-3.68 (m, 2H, 5-CH_2), 3.71 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.37 (s, 1H, H-11), 6.71 (d, 2H, *J* = 8.3 Hz, H-Ar), 6.77 (d, 1H, *J* = 7.4 Hz, H-Ar), 6.91 (s, 1H, H-8), 7.42-7.45 (m, 5H, H-Ar), 9.62 (s, 1H, CHO). NMR ^{13}C (150 MHz, $CDCl_3$), δ = 30.4, 32.0, 42.9, 55.6 (2C), 55.9 (2C), 110.7, 112.1, 113.4, 114.6, 120.3, 122.2, 123.3 (2C), 123.6, 126.4, 128.6 (2C), 129.1, 130.8, 130.9, 133.0, 134.2, 142.5, 147.1, 147.9, 148.3, 148.4, 186.8. MS (LCMS), *m/z*: 484 $[M+H]^+$. Found, $C_{30}H_{29}NO_5$, Exact Mass: 483 (%): C, 74.73; H, 6.42; N, 2.31. Anal. calcd (%): C, 74.52; H, 6.04; N, 2.90.

2,3-Dimethoxy-13-phenyl-5,6,7,9,10,11-hexahydro-12*H*-indolo[2,1-*a*][2]benzazepin-12-one (3h): Yield: 30 mg (48 %), pink powder, mp 201-202 °C. NMR ^1H (600 MHz, $CDCl_3$), δ = 2.18 – 2.23 (m, 4H, CH_2), 2.50 (t, 2H, *J* = 6.4 Hz, CH_2), 2.73 (t, 2H, *J* = 6.4 Hz, CH_2), 2.82 (t, 2H, *J* = 6.4 Hz, CH_2), 3.32 (s, 3H, OCH_3), 3.78 (t, 2H, *J* = 6.4 Hz, CH_2), 3.88 (s, 3H, OCH_3), 6.26 (s, 1H, H-11), 6.74 (s, 2H, H-8), 7.15 (d, 1H, *J* = 7.3 Hz, H-Ar), 7.21 (t, 2H, *J* = 7.3 Hz, H-Ar), 7.26 (d, 2H, *J*=7.3 Hz, H-Ar). NMR ^{13}C (150 MHz, $CDCl_3$), δ = 15.4, 22.2, 23.4, 30.3, 30.8, 39.0, 42.0, 55.5, 55.9, 66.0, 112.1, 113.5, 117.6, 120,3, 123.8, 127.6 (2C), 130.8 (2C), 132.5, 134.5, 142.4, 147.1, 148.2, 193.5. MS (LCMS), *m/z*: 388 $[M+H]^+$. Found, $C_{25}H_{25}NO_3$, Exact Mass: 387 (%): C, 74.73; H, 6.42; N, 2.31. Anal. calcd (%): C, 77.49; H, 6.50; N, 3.61.



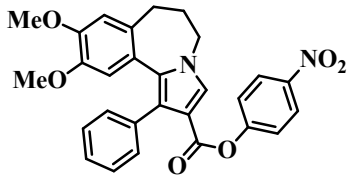
13-(3,4-Dimethoxyphenyl)-2,3-dimethoxy-5,6,7,9,10,11-hexahydro-12*H*-indolo[2,1-*a*][2]benzazepin-12-one (3i): Yield: 35mg (50 %), beige powder, mp 201-202 °C. NMR ^1H (600 MHz, $CDCl_3$), δ = 2.18 – 2.23 (m, 4H, CH_2), 2.52 (t, 2H, *J* = 6.6 Hz, CH_2), 2.72 (t, 2H, *J* = 6.6 Hz, CH_2), 2.82 (t, 2H, *J* = 6.6 Hz, CH_2), 3.39 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.76-3.78 (m, 2H, CH_2), 3.82 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.35 (s, 1H, H-11), 6.70 (d, 1H, *J* = 8.1 Hz, H-Ar), 6.73 (d, 1H, *J* = 1.5 Hz, H-Ar), 6.74 (s, 1H, H-8), 7.00 (d, 1H, *J* = 1.5 Hz, H-Ar). NMR ^{13}C (150 MHz, $CDCl_3$), δ = 22.3, 23.3, 30.2, 30.7, 39.0, 42.0, 55.7, 55.9, 56.0 (2C), 110.6, 112.2, 113.4, 114.7, 117.4, 120.0, 123.2, 123.9, 126.8, 130.8, 132.4, 142.7, 147.2, 147.7, 148.1, 148.3,



193.7. MS (LCMS), *m/z*: 448 $[M+H]^+$. Found, $C_{27}H_{29}NO_5$, Exact Mass: 447 (%): C, 73.73; H, 6.42; N, 2.31. Anal. calcd (%): C, 72.46; H, 6.53; N, 3.13.

4-Nitrophenyl 9,10-dimethoxy-1-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*a*][2]benzazepine-2-carboxylate (3e).

To 0.5 mmol of compound **2a**, 7 mL of toluene and *p*-nitrophenyl acrylate (0.51 mmol) were added. The resulting solution was stirred at 40 °C until the starting material spot had disappeared on TLC (Sorbfil, ethyl acetate/hexane, 1:2). The solvent was removed under reduced pressure to afford compound **3e** as a yellow oil.

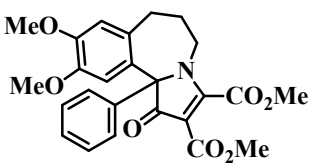


Yield: 179 mg (74%), yellow oil. NMR ^{1}H (600 MHz, DMSO-d6), δ = 2.17 – 2.19 (m, 2H, 6-CH_2), 2.64 (t, 2H, *J* = 6.6 Hz, 7-CH_2), 3.19 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.92 – 3.94 (m, 2H, 5-CH_2), 6.16 (s, 1H, H-11), 6.92 (s, 1H, H-8), 7.18 – 7.22 (m, 5H, H-Ar), 7.38 (d, 2H, *J* = 8.6 Hz, H-Ar), 8.00 (s, 1H, H-3), 8.24 (d, 2H, *J* = 8.6 Hz, H-Ar). NMR ^{13}C (150 MHz, $CDCl_3$), δ = 30.3, 31.3, 46.5, 55.5, 56.0, 111.2, 112.3, 113.3, 115.9, 122.5, 123.4, 124.0, 125.0 (2C), 125.3, 126.8, 127.8 (2C), 128.1, 130.8, 130.9, 133.4, 134.5, 144.8, 147.2, 148.4, 156.2, 161.5. MS (LCMS), *m/z*: 485 $[M+H]^+$. Found, $C_{28}H_{24}N_2O_6$, Exact Mass: 484 (%): C, 69.54; H, 5.11; N, 5.51. Anal. calcd (%): C, 69.41; H, 4.99; N, 5.78.

9,10-Dimethoxy-1-oxo-11b-phenyl-5,6,7,11*b*-tetrahydro-1*H*-pyrrolo[2,1-*a*][2]benzazepine-2-carboxylates (4a-c)

To a solution of 77 mg (0.25 mmol) of compound **2a,b** in 5 mL of acetonitrile, 0.42 mmol of acetylenedicarboxylate (for **4a**) or but-3-yn-2-one (for **4b,c**) was added. The reaction was carried out in a microwave reactor at 150°C for 15-25 minutes. The reaction progress was monitored by TLC (Sorbfil, ethyl acetate/hexane, 2:1). The solvent was then removed under reduced pressure, and the product was purified by column chromatography on aluminum oxide using an ethyl acetate/petroleum ether mixture (1:10) as the eluent.

Dimethyl 9,10-dimethoxy-1-oxo-11b-phenyl-5,6,7,11*b*-tetrahydro-1*H*-pyrrolo[2,1-*a*][2]benzazepine-2,3-dicarboxylate (4a): Yield: 93 mg (83%), yellow oil. NMR ^{1}H (600 MHz, $CDCl_3$), δ = 1.80 – 1.92 (m, 2H, 6-CH_2), 2.60 – 2.64 (m, 1H, 7-CH_2), 2.84 – 2.88 (m, 1H, 7-CH_2), 3.57 (t, 2H, 5-CH_2, *J* = 6.6 Hz), 3.77 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.88 (s, 3H, CO_2CH_3), 4.05 (s, 3H, CO_2CH_3), 6.63 (s, 1H, H-11), 6.98 (dd, 2H, *J* = 2.5, 8.1 Hz, H-Ar), 7.31 – 7.34 (m, 3H, H-Ar), 7.43 (s, 1H, H-8). NMR ^{13}C (150 MHz, $CDCl_3$), δ = 26.7, 33.0, 47.5, 51.6, 53.9, 56.0, 56.2, 81.9, 100.0, 113.3, 114.3, 124.4, 127.8 (2C), 128.8, 129.2 (2C), 134.1,

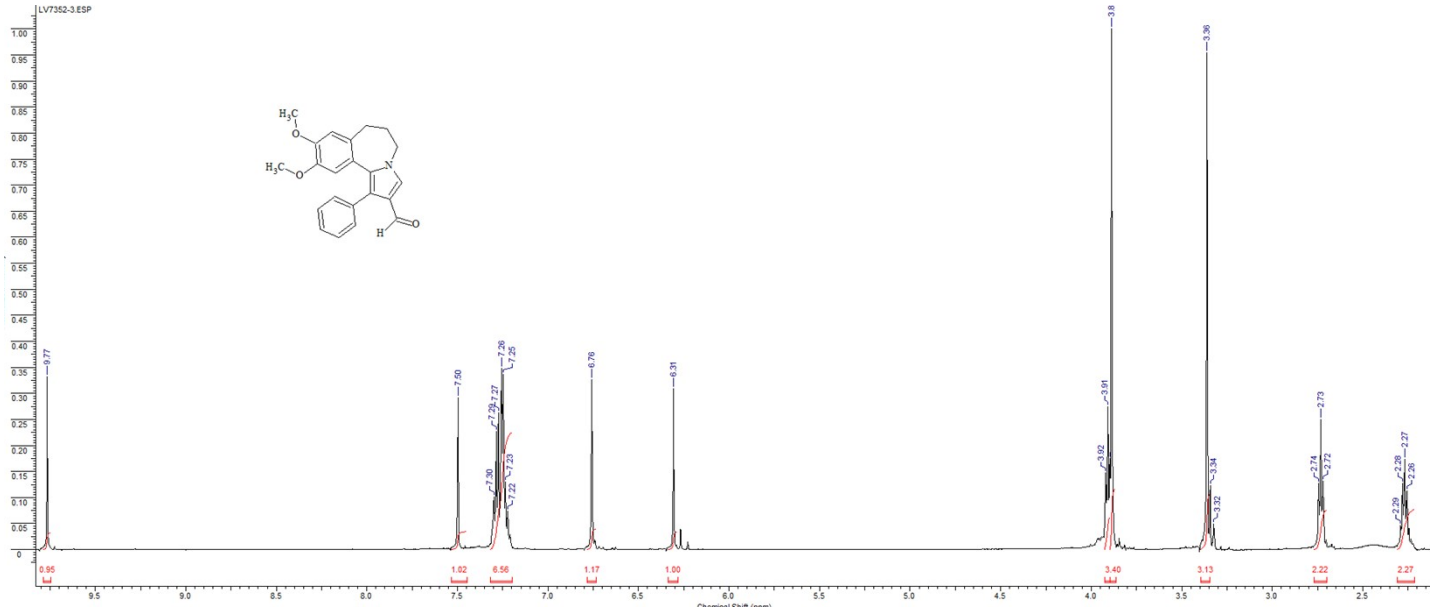


137.2, 147.1, 148.5, 162.2, 163.5, 170.5, 194.6. MS (LCMS), *m/z*: 452 $[M+H]^+$. Found, $C_{25}H_{25}NO_7$, Exact Mass: 451 (%): C, 66.65; H, 5.67; N, 3.15. Anal. calcd (%): C, 66.51; H, 5.58; N, 3.10.

Methyl 9,10-dimethoxy-1-oxo-11b-phenyl-5,6,7,11b-tetrahydro-1*H*-pyrrolo[2,1-*a*][2]benzazepine-2-carboxylate (4b): Yield: 68 mg (72%), yellow oil. NMR^{1}H (600 MHz, $CDCl_3$), δ = 1.59 – 1.61 (m, 2H, 6-CH_2), 2.62 – 2.64 (m, 2H, 7-CH_2), 2.43 (s, 3H, $COCH_3$), 3.85 (s, 3H, OCH_3), 3.86 – 3.87 (m, 2H, 5-CH_2), 3.89 (s, 3H, OCH_3), 6.66 (s, 1H, H-11), 6.90 (d, 2H, *J* = 6.9 Hz, H-Ar), 7.31 – 7.32 (m, 3H, H-Ar), 7.49 (s, 1H, H-8), 8.71 (s, 1H, H-3). NMR ^{13}C (150 MHz, $CDCl_3$), δ = 27.4, 28.6, 33.6, 52.2, 56.0, 56.1, 82.6, 111.4, 113.2, 114.4, 125.1, 127.4, 128.6, 129.0, 129.3, 129.6, 134.5, 136.6, 147.0, 148.5, 168.7, 193.2, 196.6. MS (LCMS), *m/z*: 378 $[M+H]^+$. Found, $C_{23}H_{23}NO_4$, Exact Mass: 377 (%): C, 73.46; H, 6.03; N, 3.56. Anal. calcd (%): C, 73.19; H, 6.14; N, 3.71.

2-Acetyl-11b-(3,4-dimethoxyphenyl)-9,10-dimethoxy-5,6,7,11b-tetrahydro-1*H*-pyrrolo[2,1-*a*][2]benzazepin-1-one (4c): Yield: 79 mg (72%), yellow oil. NMR^{1}H (600 MHz, $CDCl_3$), δ = 1.65-1.67 (m, 2H, 6-CH_2), 1.82 (s, 3H, $COCH_3$), 2.22 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 3.55-3.59 (m, 2H, 7-CH_2), 3.64 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.88-3.91 (m, 2H, 5-CH_2), 6.14 (d, 1H, *J* = 1.9 Hz, H-Ar), 6.26 (dd, 1H, *J* = 1.9, 8.5 Hz, H-Ar), 6.45 (s, 1H, H-11), 6.58 (d, 1H, *J* = 8.5 Hz, H-Ar), 7.05 (s, 1H, H-8), 8.71 (s, 1H, H-3). NMR ^{13}C (150 MHz, $CDCl_3$), δ = 14.2, 21.1, 27.3, 28.5, 33.5, 52.0, 56.0, 60.4, 110.2, 113.0, 114.3, 122.6, 125.1, 128.3, 128.7, 134.4, 138.5, 142.3, 146.8, 148.3, 149.5, 150.2, 168.4, 193.2, 196.9. MS (LCMS), *m/z*: 438 $[M+H]^+$. Found, $C_{25}H_{27}NO_6$, Exact Mass: 437 (%): C, 68.72; H, 6.13, N, 3.11. Anal. calcd (%): C, 68.63; H, 6.22; N, 3.20.

3a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7.27
7.26
7.25
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7.23
7.22
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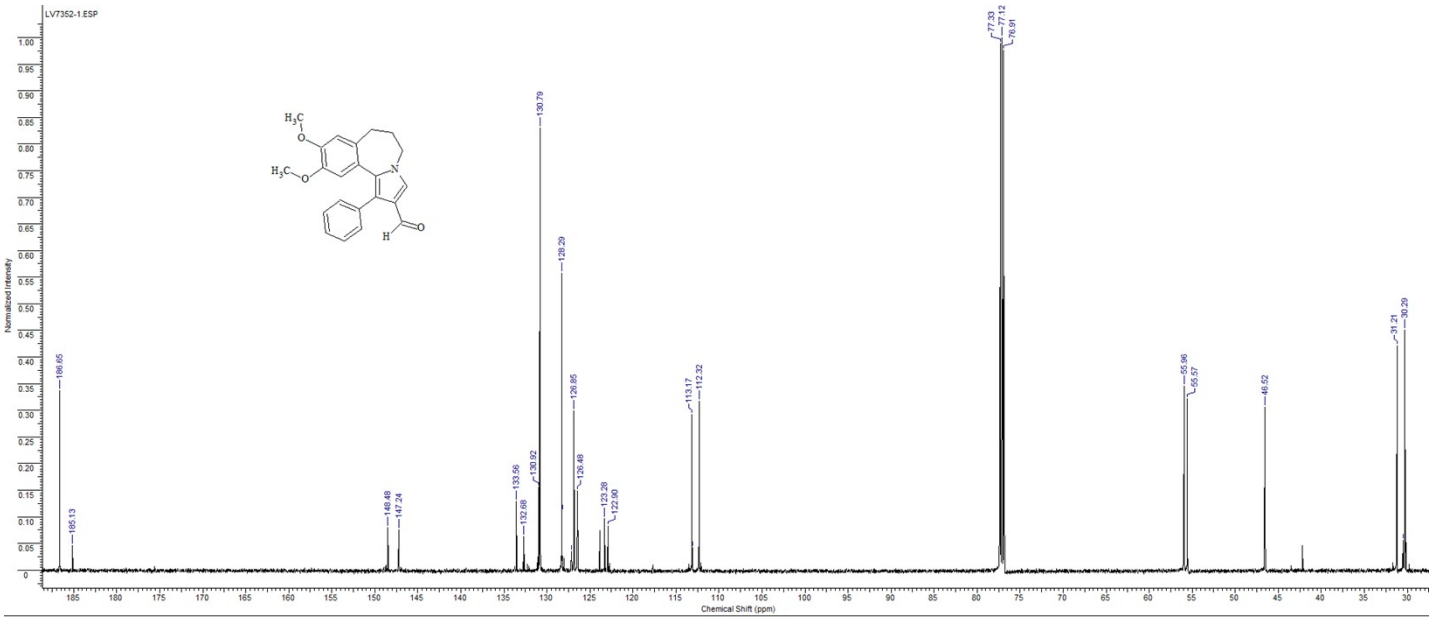
3.92
3.91
3.8
3.36
3.34
3.32
2.74
2.73
2.72
2.29
2.28
2.27
2.26
0.95
1.02
6.56
1.17
1.00
3.40
3.13
2.22
2.27


LV7352-1.ESP
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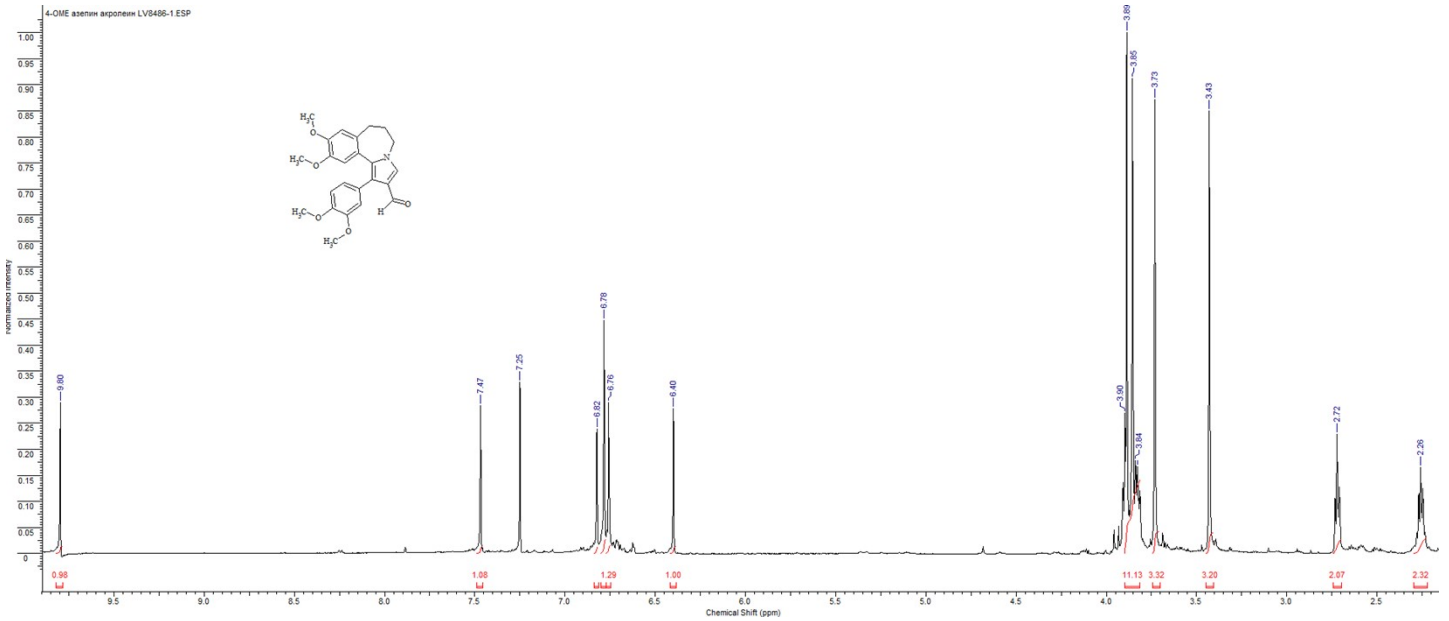
185.13
149.48
147.24
133.56
132.68
130.92
130.79
126.29
126.85
126.48
123.28
122.90
113.17
112.32
77.33
77.12
76.91
55.96
55.57
46.52
31.21
30.29
Chemical Shift (ppm)

3b


4-OME азепин акролеин LV8486-1.ESP
Normalized Intensity
Chemical Shift (ppm)
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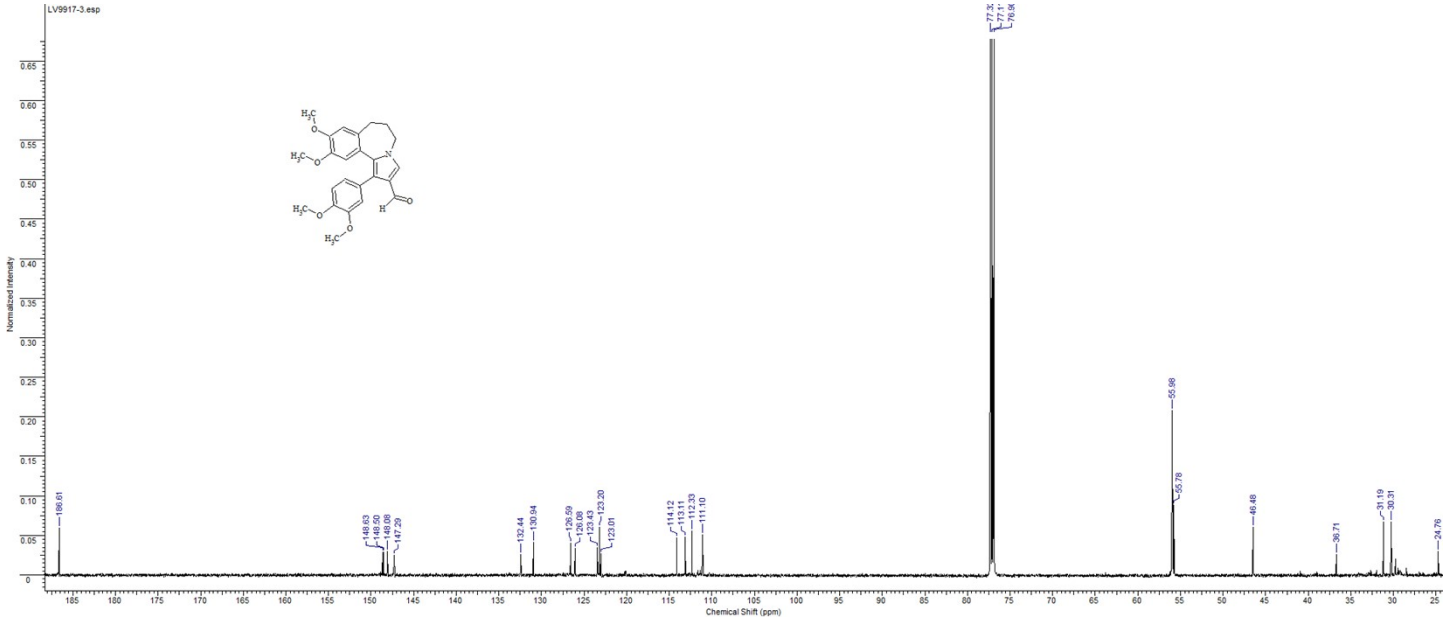
7.25
6.78
6.76
6.82
6.40
3.89
3.85
3.73
3.43
3.90
3.84
2.72
2.26
0.98
1.08
1.29
1.00
11.13
3.32
3.20
2.07
2.32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Normalized Intensity
Chemical Shift (ppm)
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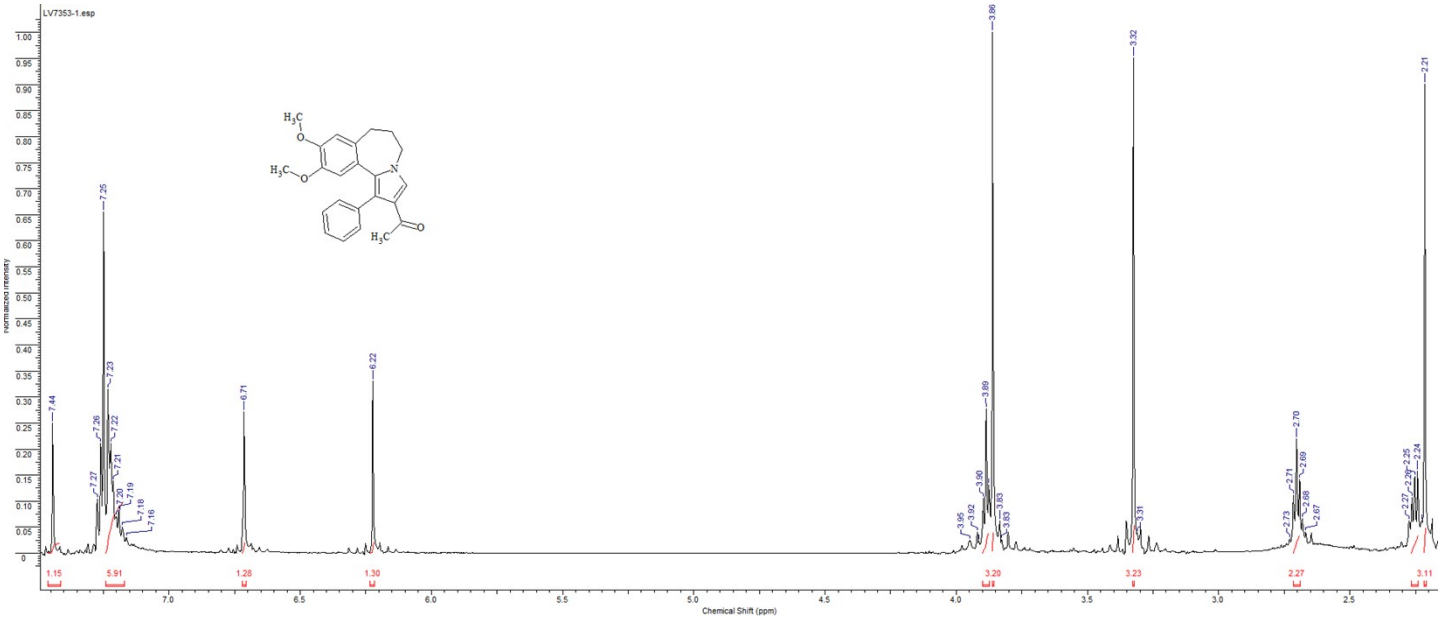
77.11
76.84
186.61
148.63
148.50
148.08
147.29
132.44
130.94
126.59
126.08
125.43
123.20
123.01
114.12
113.11
112.33
111.10
55.86
55.78
46.48
39.71
31.19
30.31
24.76

3c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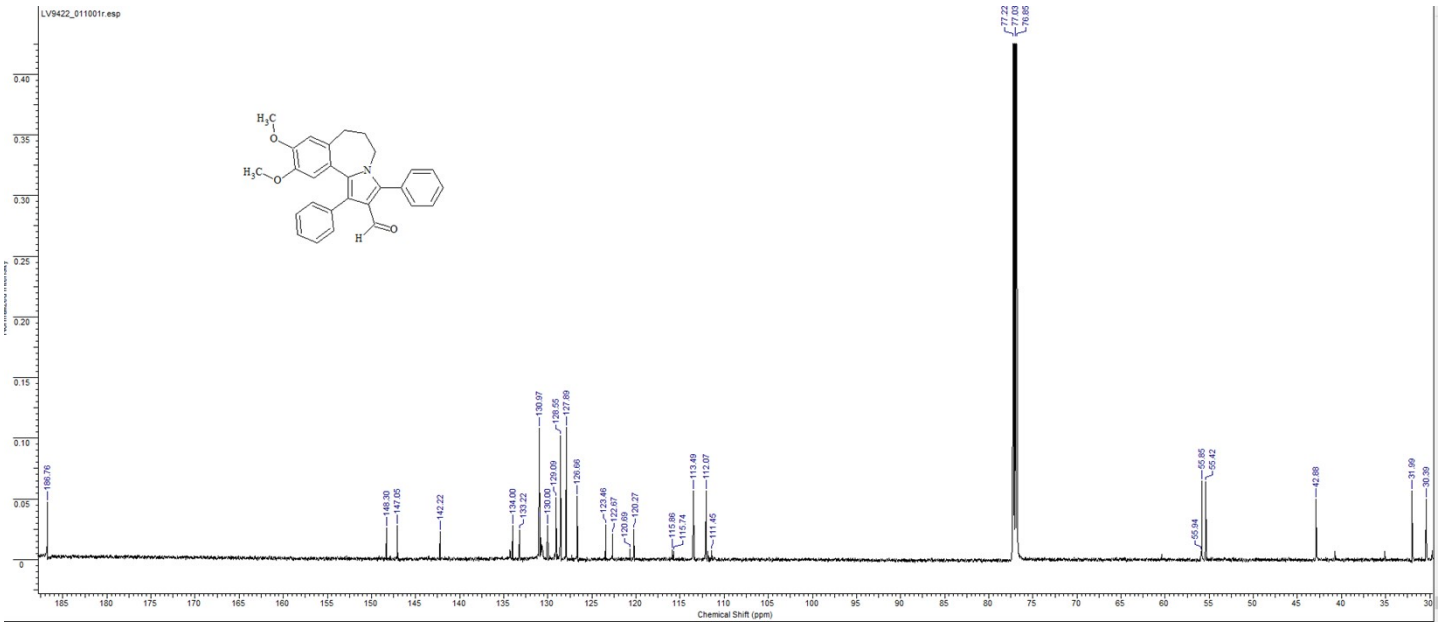
Chemical Shift (ppm)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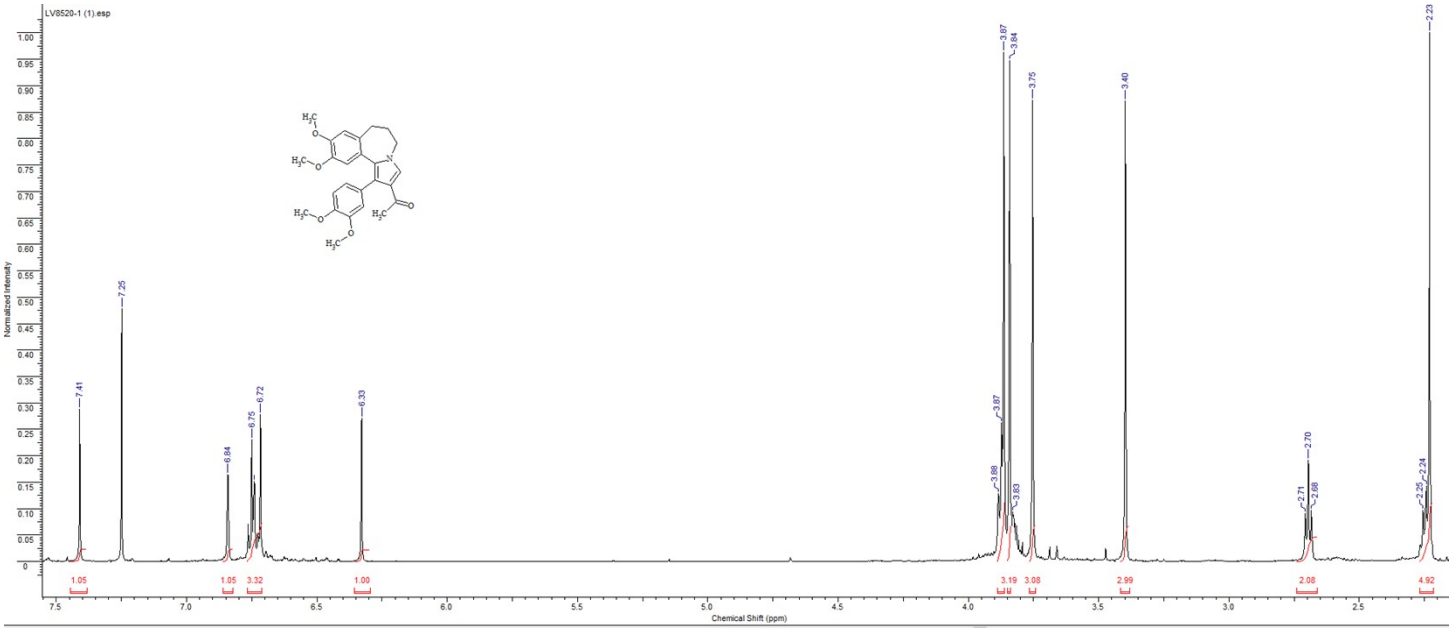
Chemical Shift (ppm)

3d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Normalized Intensity
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6.72
6.33
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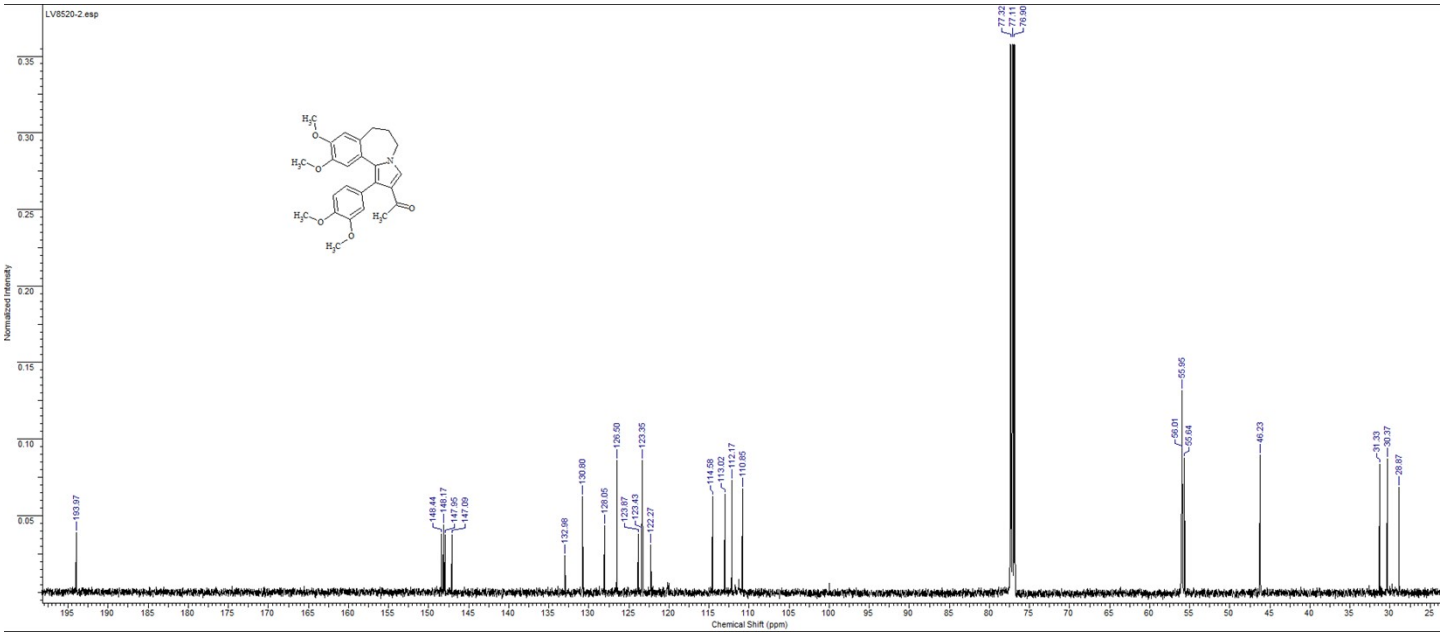
3.84
3.75
3.40
3.88
3.87
3.83
2.71
2.68
2.70
2.25
2.24
2.23
1.05
1.05
3.32
1.00
3.19
3.08
2.99
2.08
4.92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Normalized Intensity
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148.17
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147.09
132.98
130.80
128.05
126.50
123.87
123.43
123.35
122.27
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56.01
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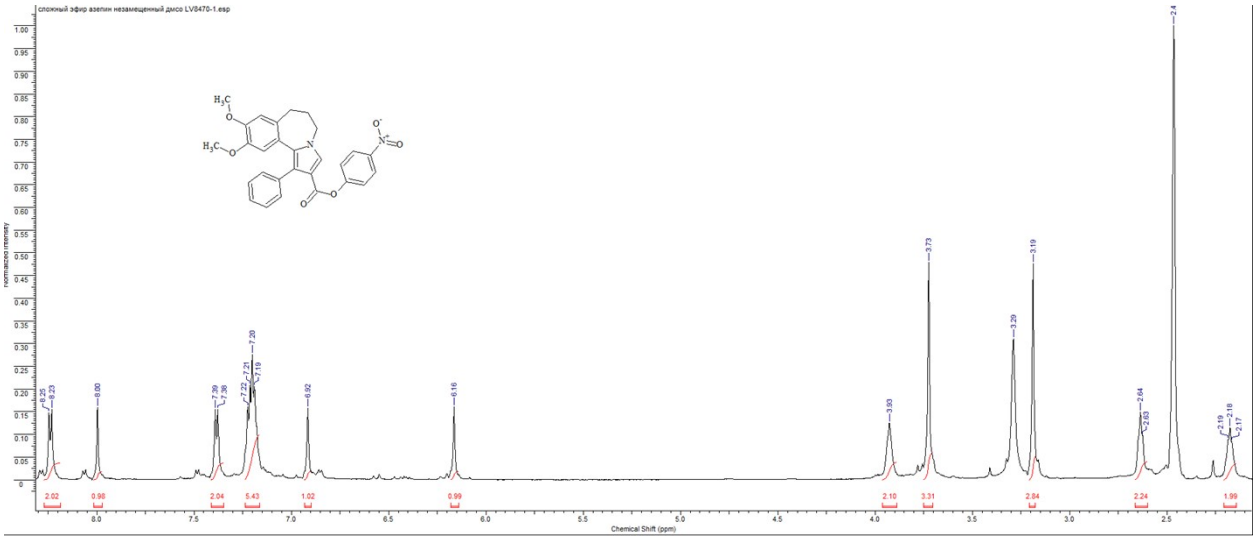
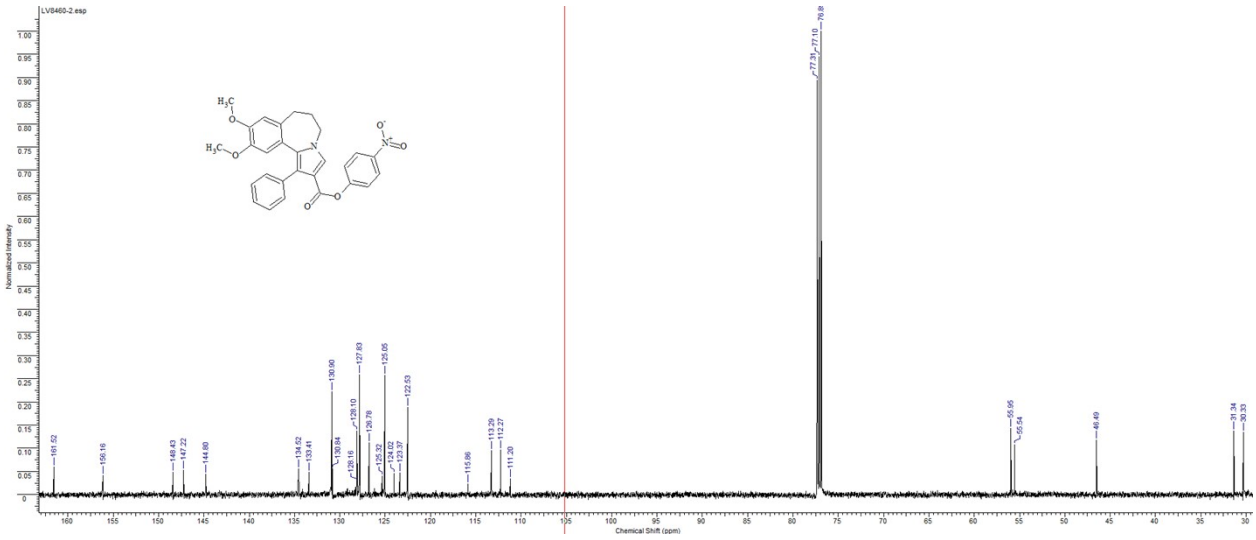
55.95
46.23
31.33
30.37
29.87

3e


сложный эфир азепин незамещенный дихл LV8470-1.esp
Normalized Intensity
Chemical Shift (ppm)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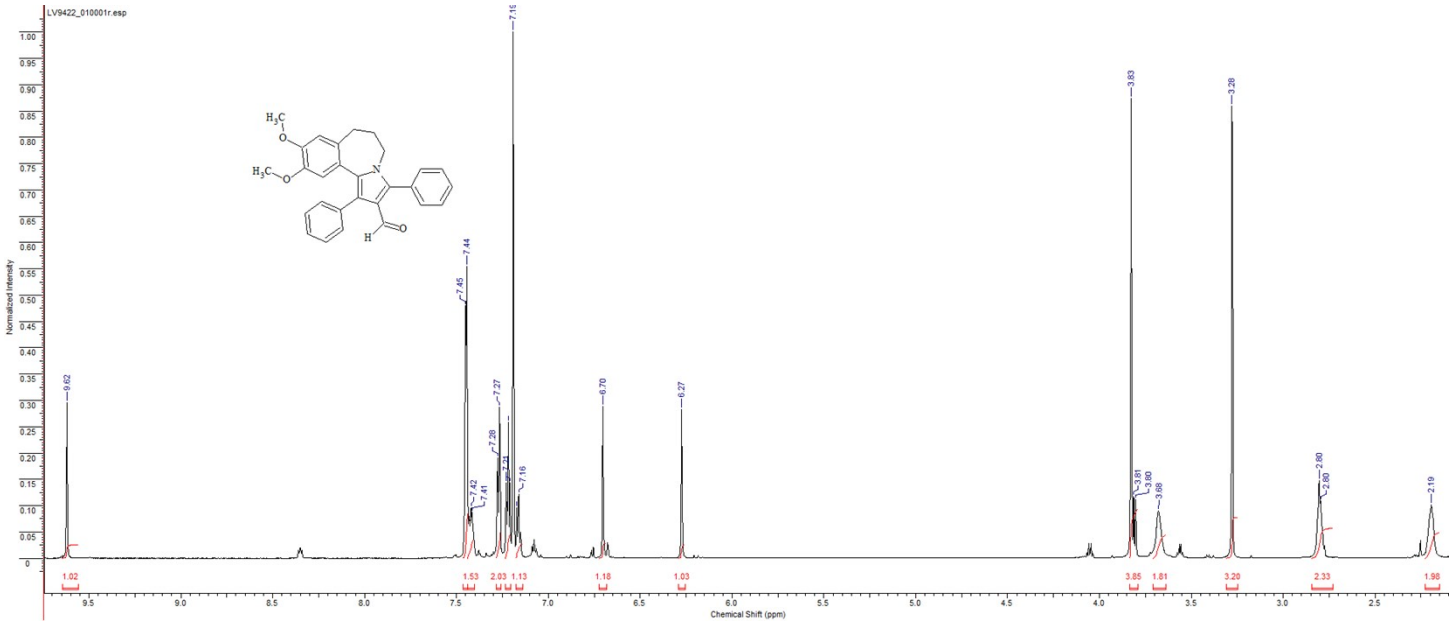
Normalized Intensity
Chemical Shift (ppm)

3f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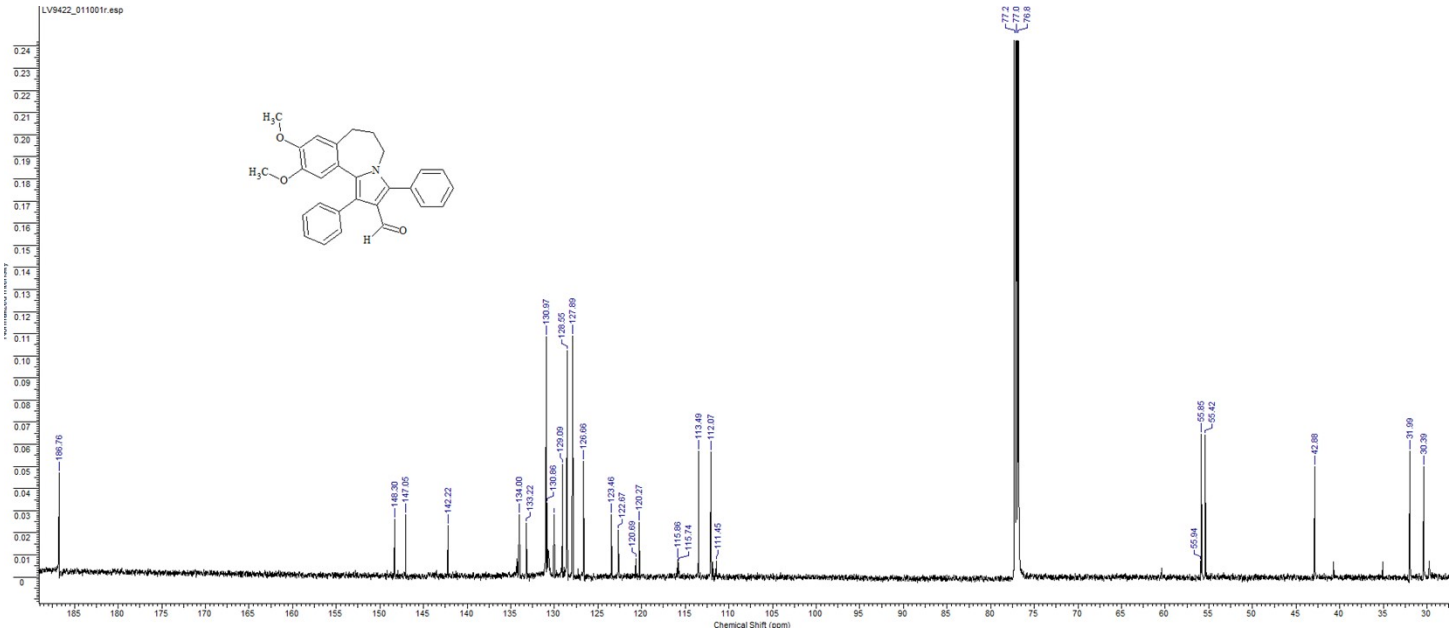
Normalized Intensity
Chemical Shift (ppm)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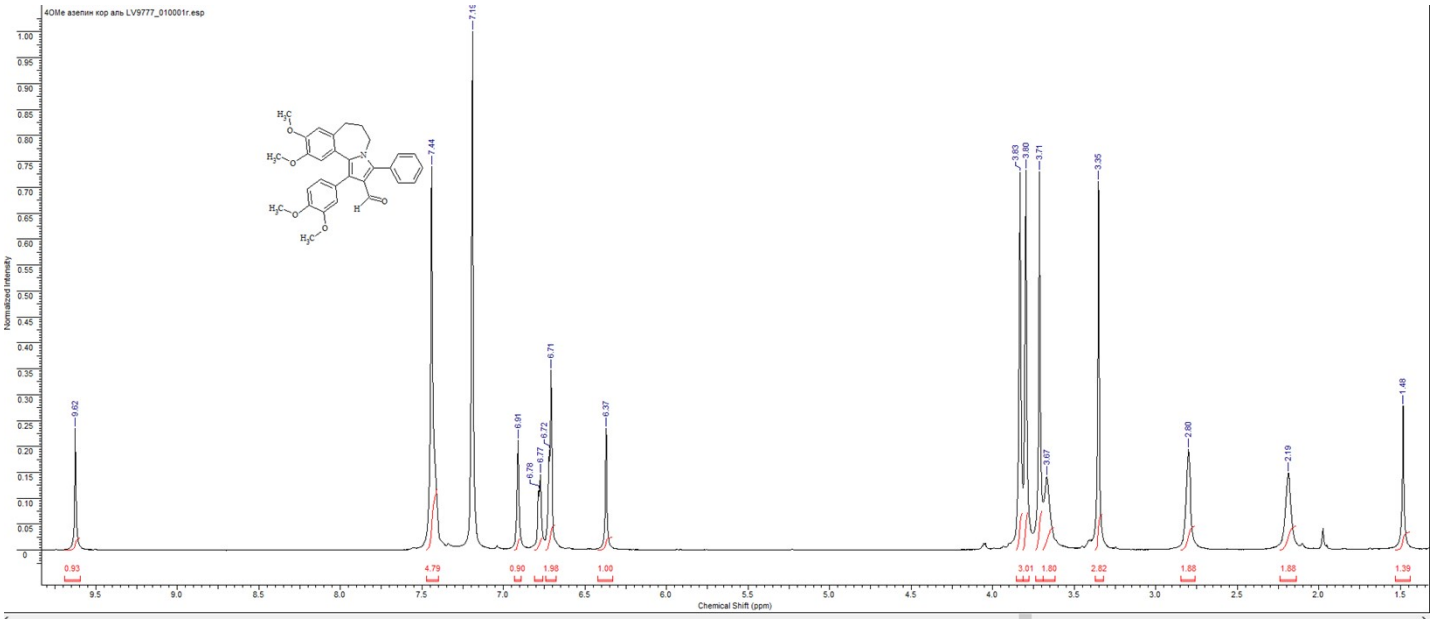
Chemical Shift (ppm)

3g


4OMe азелин кор аль LV9777_010001r.esp
Normalized Intensity
Chemical Shift (ppm)
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7.15
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6.77
6.72
6.71
6.37
3.83
3.80
3.71
3.67
3.35
2.80
2.19
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3.01
1.80
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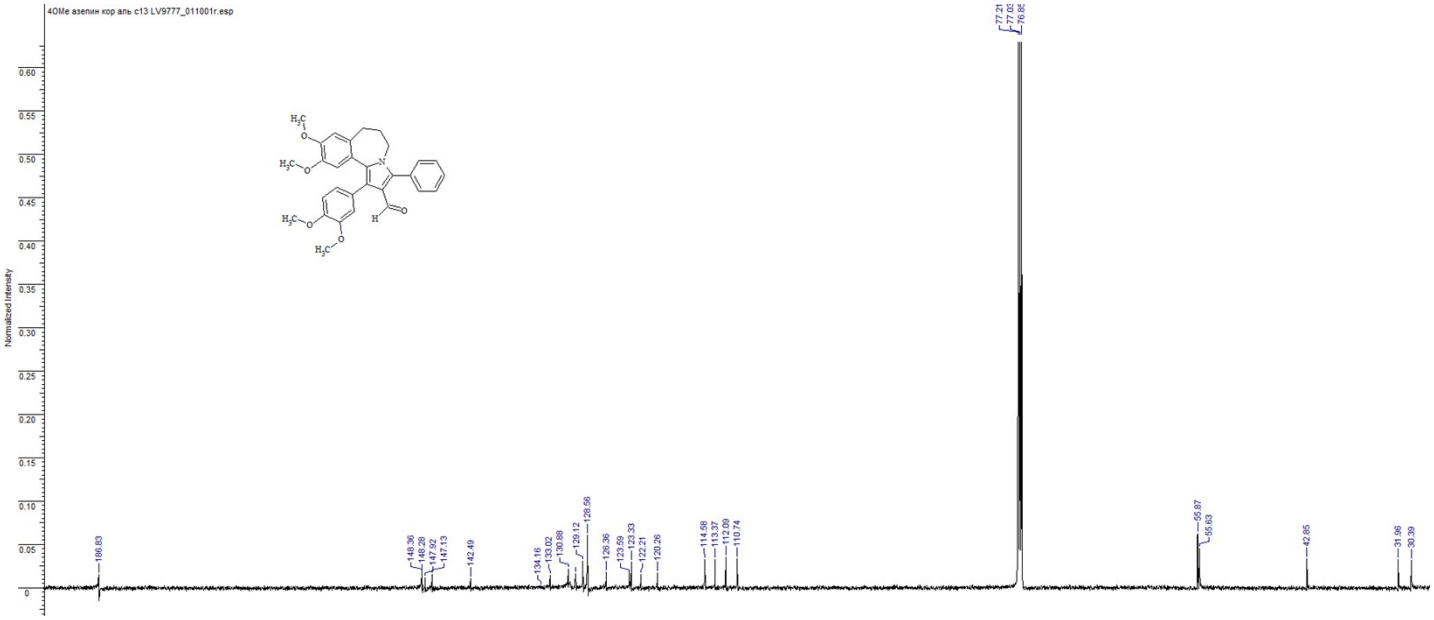
1.88
1.88
1.39


4OMe азелин кор аль c13 LV9777_011001r.esp
Normalized Intensity
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147.13
142.49
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133.02
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129.12
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126.36
123.59
123.33
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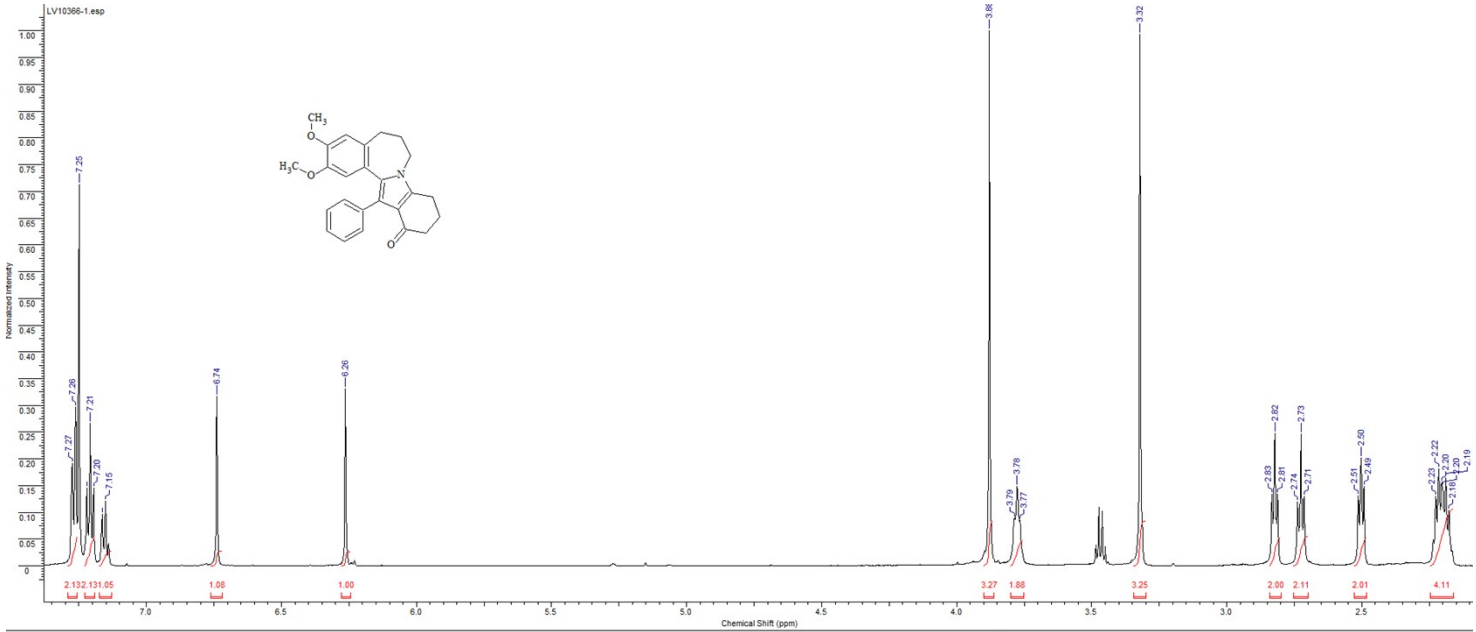
55.63
42.85
31.96
30.39

3h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3.77
2.82
2.83
2.81
2.73
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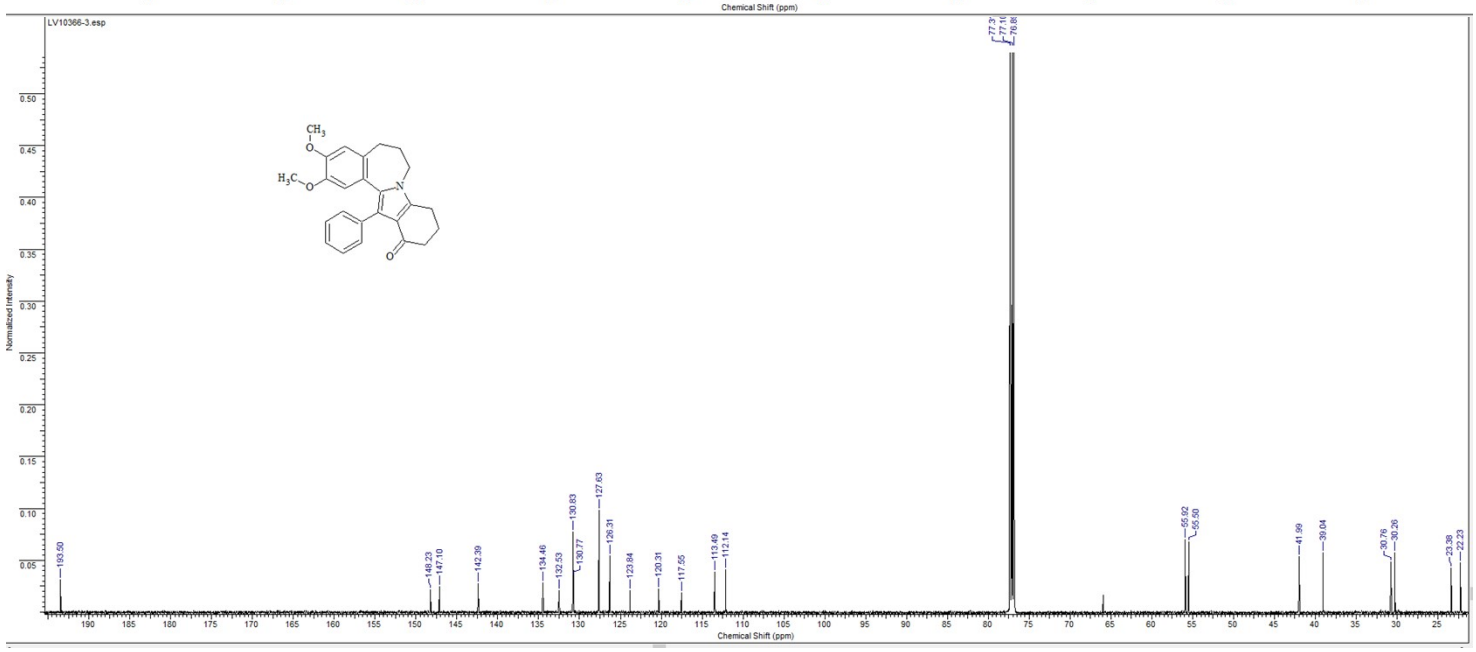
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Normalized Intensity
Chemical Shift (ppm)
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132.53
130.83
130.77
127.63
126.31
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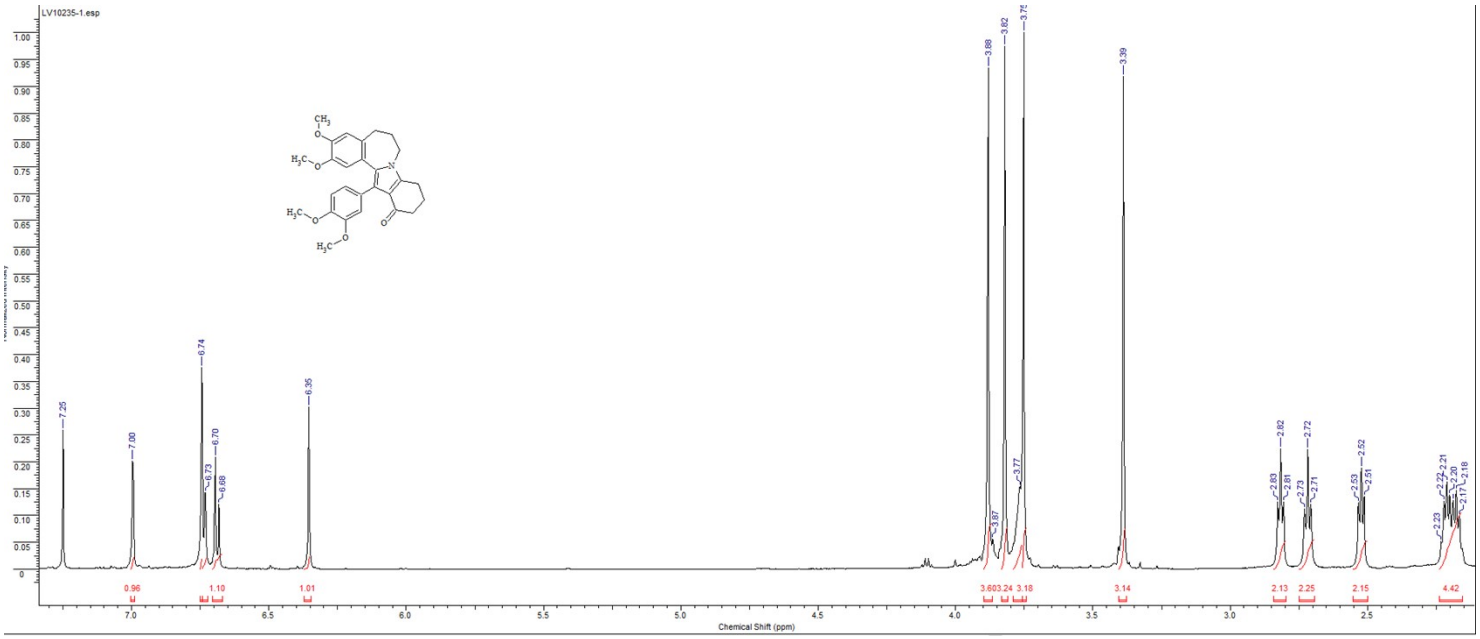
23.38
22.23

3i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2.82
2.81
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2.71
2.63
2.53
2.52
2.51
2.23
2.22
2.21
2.20
2.18
2.17
0.96
1.10
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3.60
3.24
3.18
3.14
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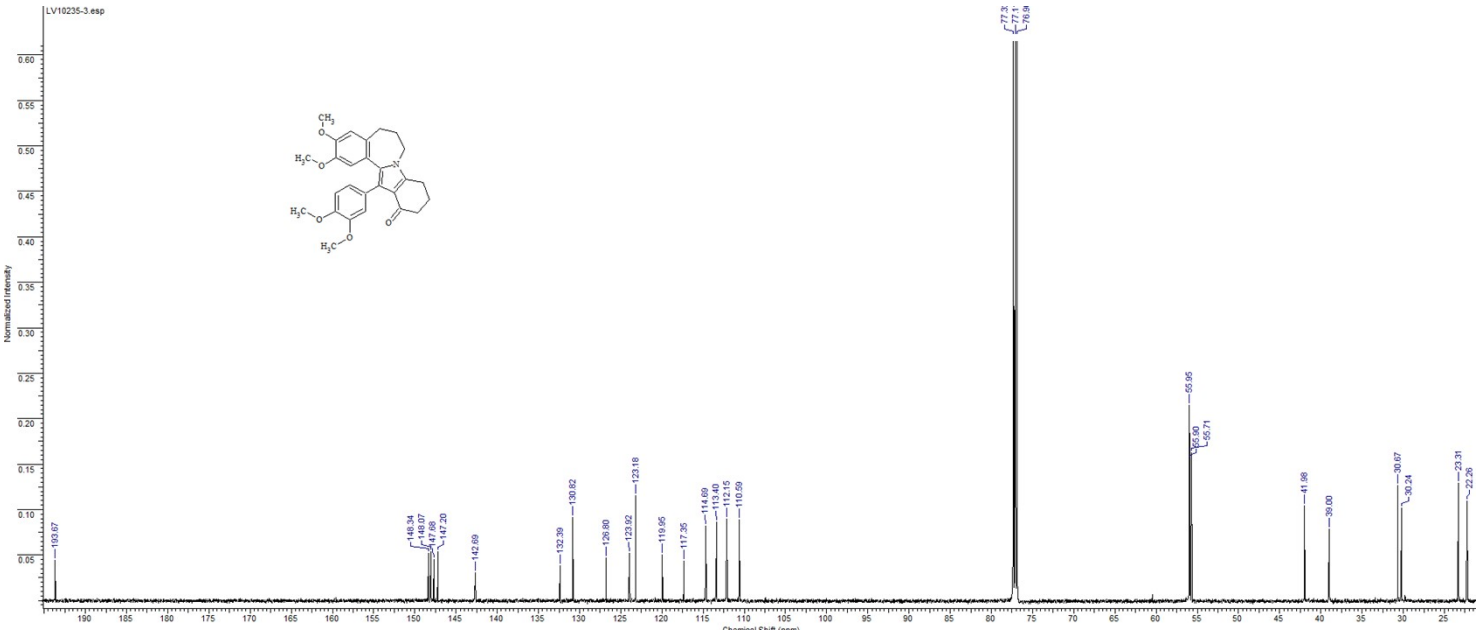
2.25
2.15
4.42
Chemical Shift (ppm)


LV10235-3.esp
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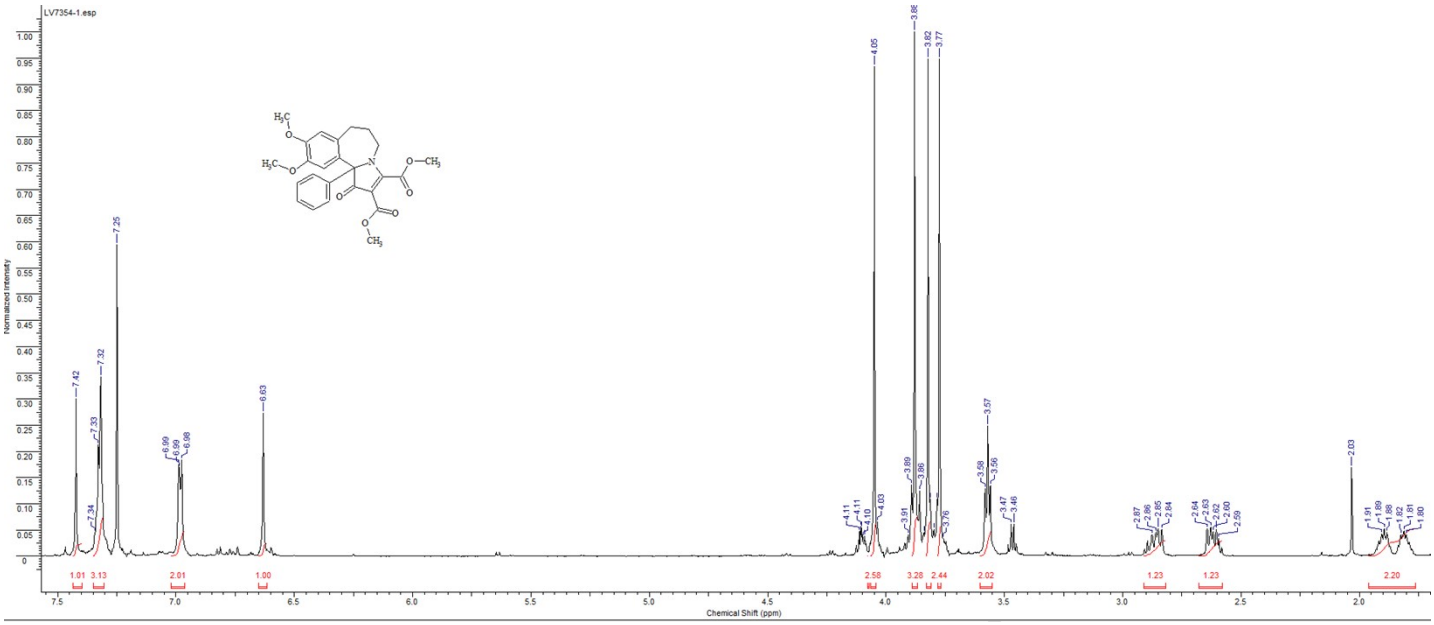
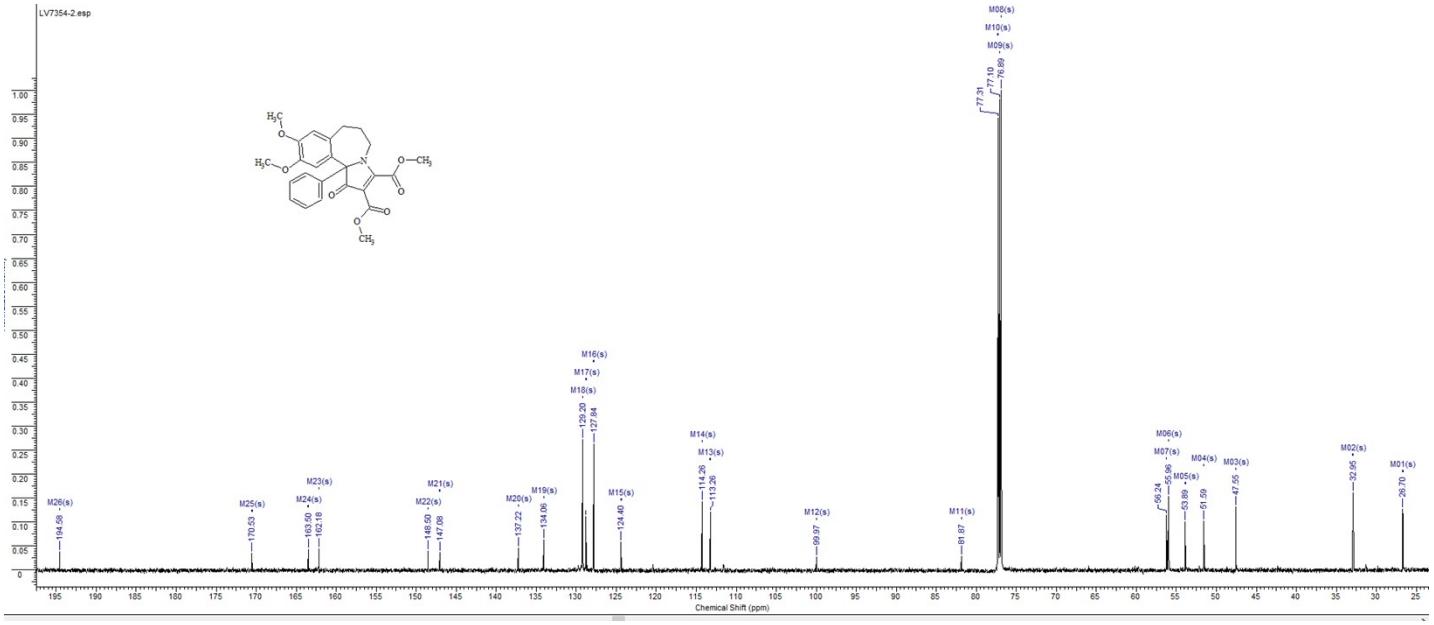
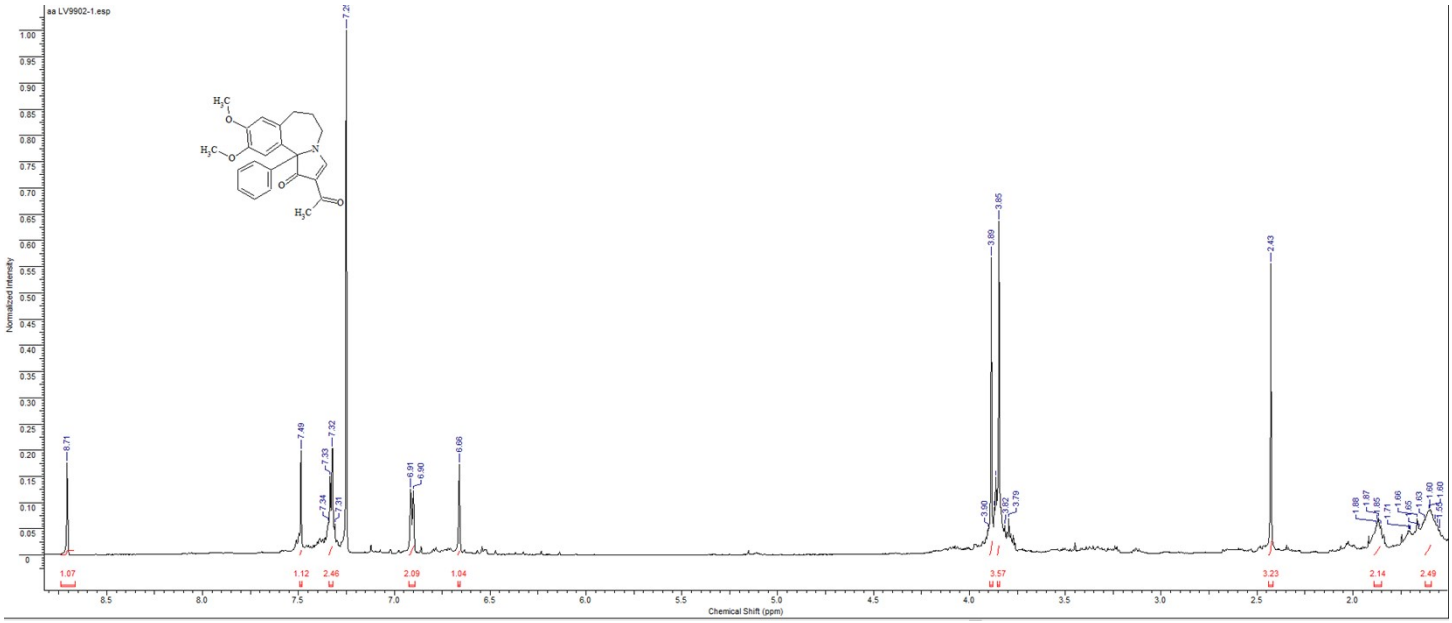
147.20
142.69
132.39
130.82
129.80
123.92
123.18
119.95
117.35
114.69
113.40
112.45
110.69
55.95
55.90
55.71
41.98
39.00
30.67
30.24
23.31
22.26
Chemical Shift (ppm)

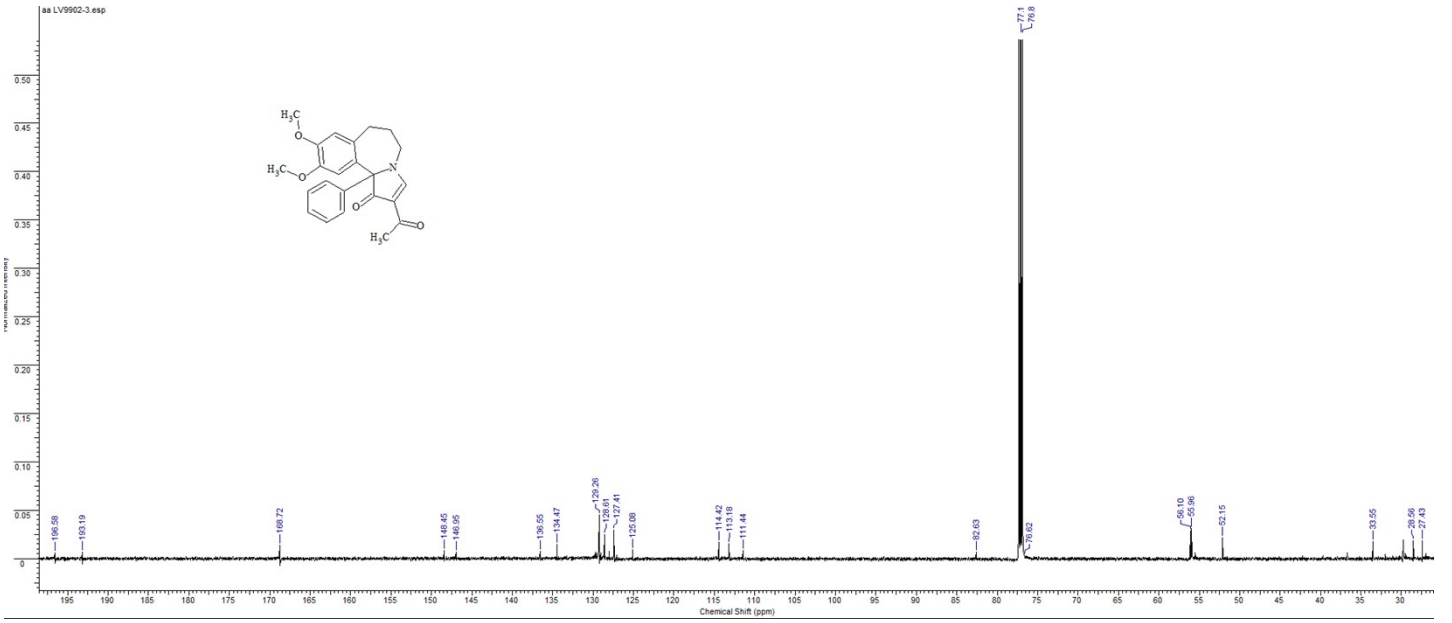
4a


LV7354-1.esp
Normalized Intensity
Chemical Shift (ppm)

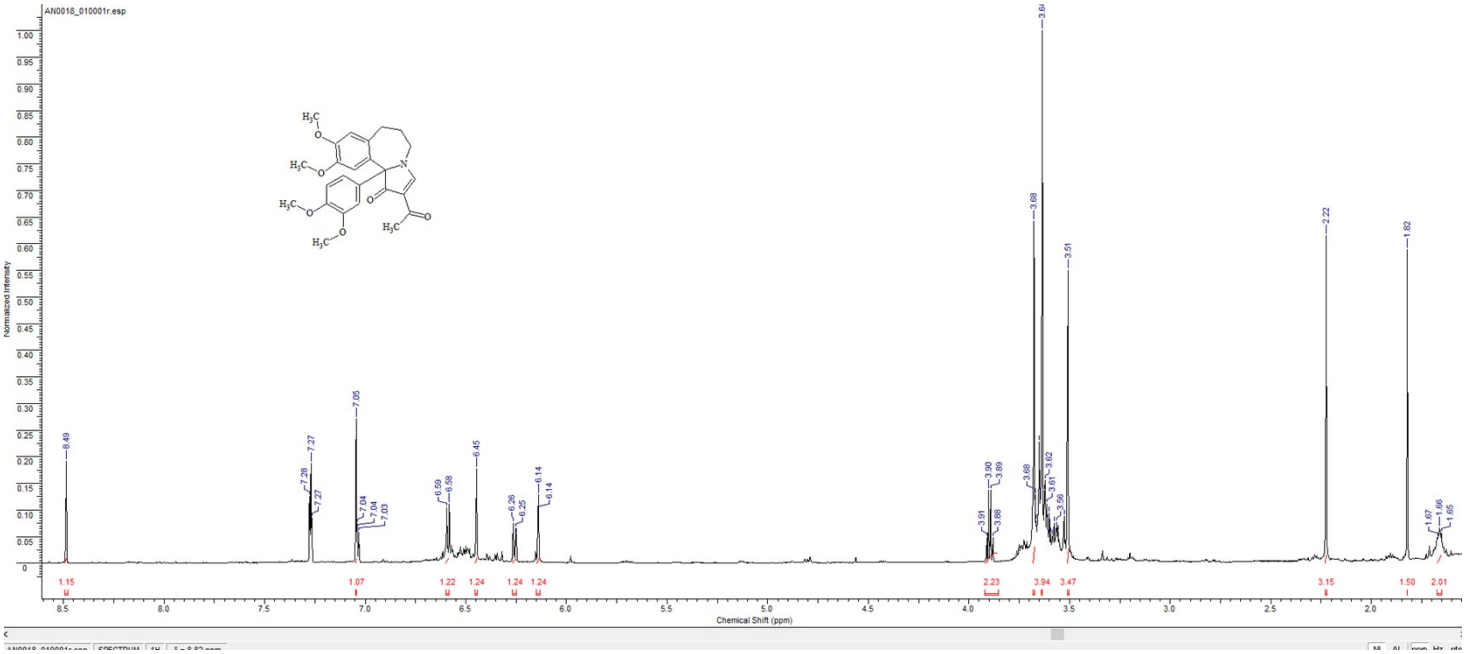

LV7354-2.esp
Chemical Shift (ppm)

4b


aa LV9902-1.esp
Normalized Intensity
Chemical Shift (ppm)
8.71
7.49
7.34
7.33
7.32
7.31
7.24
6.91
6.90
6.66
3.90
3.89
3.85
3.79
2.43
1.89
1.87
1.85
1.71
1.66
1.65
1.63
1.60
1.58
1.07
1.12
2.46
2.09
1.04
3.57
3.23
2.14
2.49


aa LV9902-3.esp
Chemical Shift (ppm)
196.58
193.19
168.72
148.45
146.95
136.55
134.47
129.26
128.61
127.41
125.08
114.42
113.18
111.44
82.63
77.1
76.8
76.62
56.10
55.96
52.15
33.55
28.56
27.43

4c


AN0018_010001r.esp
Normalized Intensity
Chemical Shift (ppm)

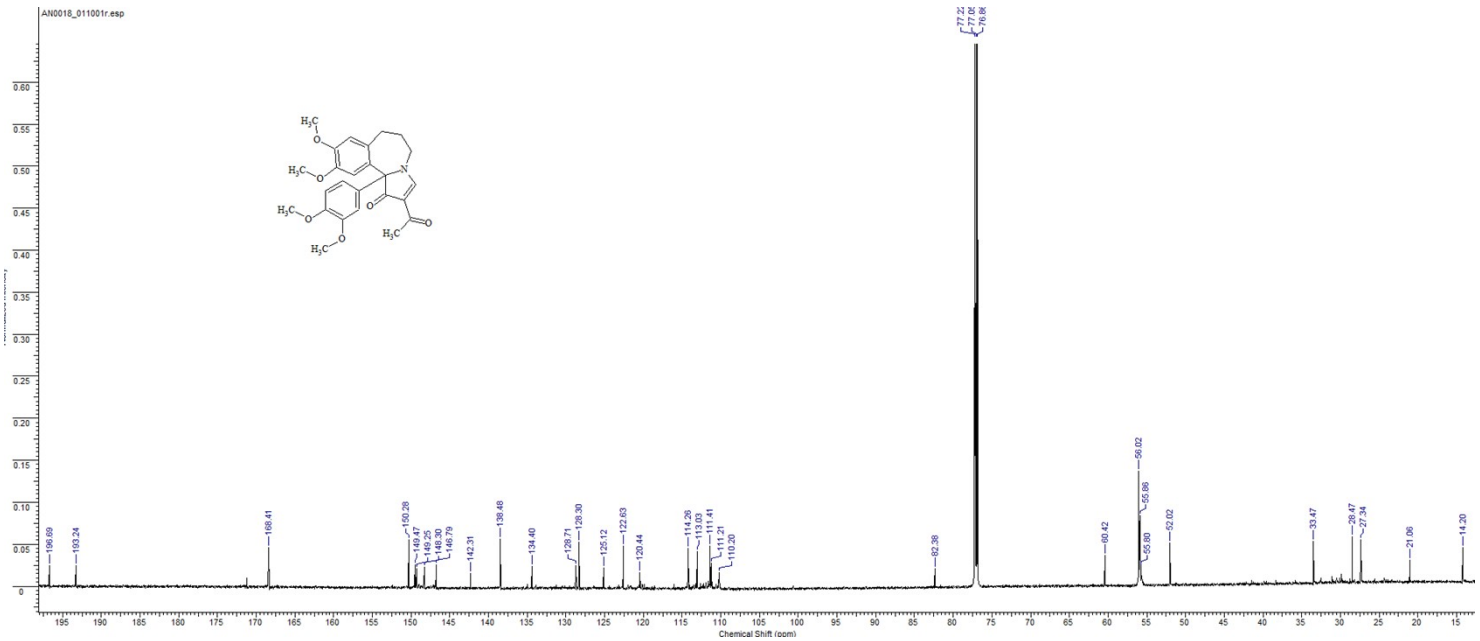
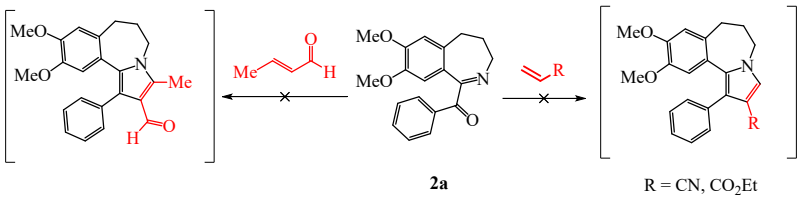
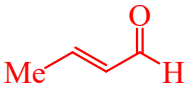
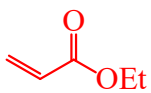

AN0018_011001r.esp
Chemical Shift (ppm)

Table S1. Optimization of the reaction conditions of benzazepine **2a** with crotonic aldehyde, acrylonitrile and ethyl acrylate



2a R = CN, CO_2Et

Reagent	T, °C	eq of reagent	Conditions	Result
	25	1.5	CF_3CH_2OH	No reaction
	70	1.5	CF_3CH_2OH	No reaction
	150	1.5	CF_3CH_2OH, MW	No reaction
	150	1.5	CF_3CH_2OH, MW, AcOH	No reaction
	150	1.5	CF_3CH_2OH, MW, CuOAc 10%	No reaction
	25	1.2	CF_3CH_2OH	No reaction
	40	4	CH_3CN	No reaction
	reflux	1.2	CF_3CH_2OH	No reaction
	reflux	1.2	CF_3CH_2OH, Ag_2OAc	No reaction
	reflux	7	CF_3CH_2OH, Ag_2OAc	Decomposition
	100	7	CF_3CH_2OH, MW	No reaction
	120	1.2	CF_3CH_2OH, MW	No reaction
	150	1.2	CF_3CH_2OH, MW	No reaction
	170	1.2	CF_3CH_2OH, MW	Decomposition
	25	95	No solvent	No reaction
	40	95	No solvent	No reaction
	40	95	No solvent, ZnO 10%	No reaction
	60	95	No solvent, ZnO 10%	No reaction
	60	95	CH_3CN, ZnO 10%	No reaction
	25	59	No solvent	No reaction
	40	59	No solvent	No reaction
	40	59	No solvent, ZnO 10%	No reaction
	60	59	No solvent, ZnO 10%	No reaction
	60	59	CH_3CN, ZnO 10%	No reaction
	120	59	CH_3CN, ZnO 10%, MW	Decomposition