Supporting Information

for

Continuous flow retro-Diels–Alder reaction: an efficient method for the preparation of pyrimidinone derivatives

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Experimental procedures and analytical data

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1. Experimental procedures

1.1. General information

^{1}H NMR spectra were recorded at 400.13 MHz or 500.20 MHz and the ^{13}C-NMR spectra were recorded at 100.62 MHz or 125.77 MHz in CDCl3 at ambient temperature, with a Bruker AM 400 or Bruker Ascend^{TM} 500 spectrometer. Chemical shifts are given in (ppm) relative to TMS as the internal standard. In the ^{1}H NMR spectra, signal positions (δ) are given in parts per million (ppm) from tetramethylsilane (δ = 0) and were measured relative to residual solvent signal ($CDCl_3$ = 7.26 ppm). ^{13}C NMR spectra were recorded using the same spectrometers. Signal positions (δ) are given in parts per million (ppm) from tetramethylsilane (δ = 0) and were measured relative to the signal of $CDCl_3$ (δ = 77.16 ppm). The multiplicities of signals are given as s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, ArH = aromatic. Coupling constants (*J*) are reported to the nearest 0.1 Hz. HPLC–MS measurements were performed with a Phenomenex 5 µm C18(2) 100 Å column (250 × 4.60 mm). The solvent system consisted of AcOH (0.1%) in water (A), AcOH (0.1%) in MeCN (B); gradient: 5%–100% B over 35 min, at a flow rate of 1 mL min^{-1}. Chromatograms and spectra were recorded in positive ionization mode with electrospray ionization on a Thermo LCQ Fleet mass spectrometer. FTIR spectrum was obtained from KBr pellet on a Perkin-Elmer 100 FTIR spectrometer.

1.2. Procedures for the synthesis of the starting materials 1–8

Starting materials **1-8** were synthesized in our previous work by the cyclization of the di-*exo*- or di-*endo*-norbornene-β-amino acids or esters with ethyl *p*-chlorobenzimidate resulting in tricyclic pyrimidinones **1**, **2a** and **2b** [1-4]. Methanopyrrolo-, methanopyrido- and methanoazepino[2,1-*b*]-quinazolinones **3**-**6** were prepared from di-*exo*-norbornene-fused azetidinone with lactim ethers by ring enlargement [5]. For the preparation of 2-thioxo-pyrimidinones **7**, **8a** and **8b**, the most common method is the reaction of the appropriate amino esters with phenyl isothiocyanate, followed by cyclization of the resulting thiourea with hydrogen chloride under reflux [1,4,6].

1.3. General reactor set-up for continuous-flow reactions

The modular flow system was equipped with a heated 304 stainless steel tubing coil with 14 mL internal volume [Supelco premium grade 304 empty stainless steel tubing; dimensions: length (L) x outer diameter (OD) x inner diameter (ID) = 100 ft x

1/16 in x 0.03 in; product reference number: 20553] and an adjustable back-pressure regulator (ThalesNano, BPR, 0–300 bar). The tube reactor was heated in a Heraeus oven to the desired temperature. Solutions of the starting materials **1–8 (**0.1 mmol) were loaded into the reactor via an HPLC pump. The residence time was measured according to literature methods [7]. The resulting products **9–14** were identified by means of HPLC–MS, ^{1}H NMR and ^{13}C NMR spectroscopic analysis without the need for further purification steps. All physical and spectroscopic data of pyrimidinones **9–14** were identical with their literature data [1-6].

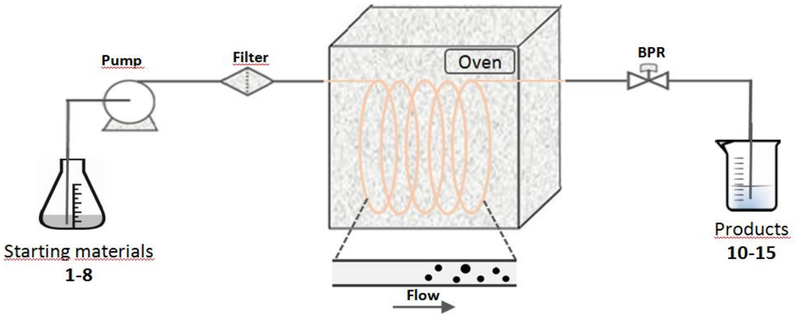


Figure 1: Schematic outline of the continuous flow reactor.

1.4. Additional Table

Table S1: Operating conditions for the rDA reactions in the CF reactor

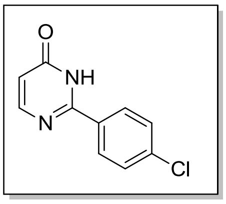
Entry	Product	Continuous flow in the present work				
		Solvent	Temp [°C]	Residence time [min]	Flow rate [mL min^{-1}]	Yield[b] [%]
1	**9**	MeCN	250	15	0.5	92
2a	**9**		250	10		95
2b	**9**	Toluene	230	30		93
3	**10**	MeOH	130	10		95
4	**11**		150	10		97
5	**12**		120	10		95
6	**13**		130	10		94
7	**14**	MeCN	210	15		96
8a	**14**		220	10		96
8b	**14**		250	30		30[a]
8b	**15b**	EtOH/H_2O = 2:1	250	30		90

[a] After column chromatography
[b] Isolated yield

1.5. Syntheses and analytical data of rDA products 9–14

2-(4-Chlorophenyl)-*3H*-pyrimidin-4-one (**9**)

Synthesized from starting materials **1** (Method A), **2a** (Method B) and **2b** (Method C).



Method A

Di-*exo*-2-(4-chlorophenyl)tetrahydro-5,8-methano-4(*3H*)-quinazoline (**1**, 0.1 mmol) was dissolved in 10 mL of acetonitrile (MeCN). The system temperature was set to 250 °C, the pressure to 10 bar and the flow rate to 0.5 mL min^{-1}. When the pressure and the temperature of the flow system were stable, the solution loaded into the reactor passed through the heated reactor coil within a residence time of 15 min and the flow output was collected. The solvent was removed by evaporation and the resulting product **9** was analysed by means of HPLC-MS, ^{1}H NMR and ^{13}C NMR spectroscopy and obtained in a good yield and with high purity. (**9**, m.p. 243-245 °C, yield = 92%).

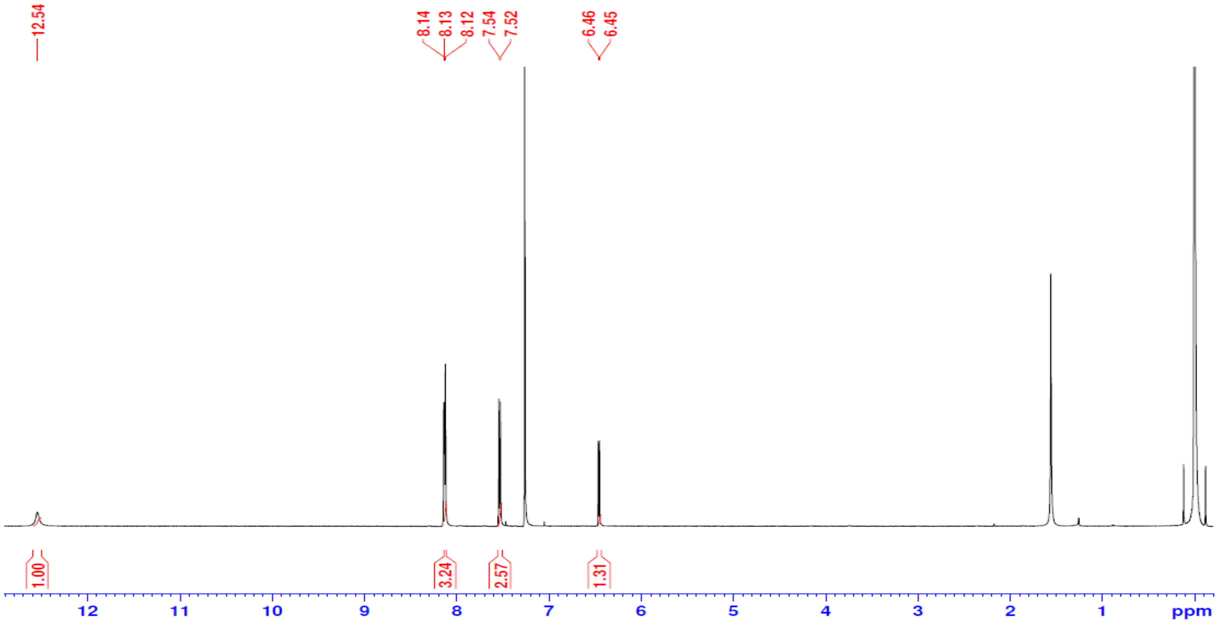
Method B

Di-*endo*-2-(4-chlorophenyl)tetrahydro-5,8-methano-4(*3H*)-quinazoline (**2a**, 0.1mmol) was dissolved in MeCN (6 mL) and reacted at 250 °C with a flow rate of 0.5 mL min^{-1} corresponding to a residence time of 10 min. Product **9** was obtained by applying the same procedure used above, in a good yield and with high purity (**9**, m.p. 243-245 °C, yield = 95%).

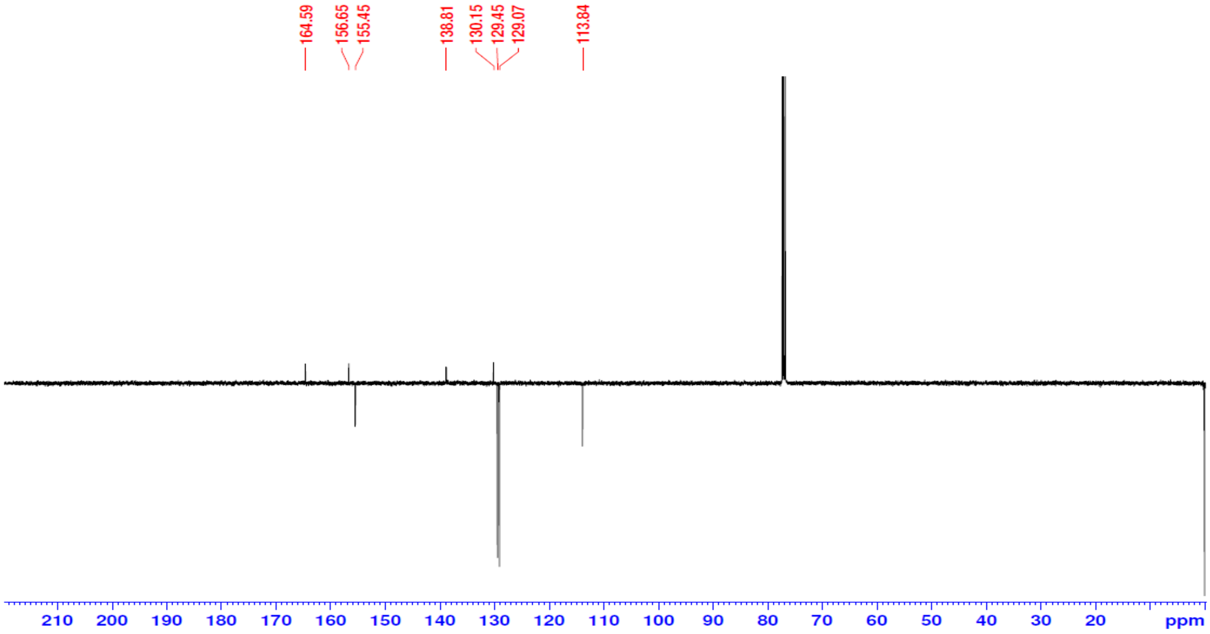
Method C

Di-*endo*-2-(4-chlorophenyl)tetrahydro-5,8-ethano-4(*3H*)-quinazoline (**2b**, 0.01mmol) dissolved in toluene (15 mL) was introduced into the flow reactor at a decreased temperature of 230 °C while using the same flow rate (0.5 mL min^{-1}). The product mixture (brownish-yellow colour) leaving the flow system was collected and analysed by means of HPLC–MS spectroscopy. Based on the result obtained, **2b** showed a moderate conversion to **9**. Therefore, in order to get the complete conversion, we recycled the flow output twice. Product **9** was obtained within an overall residence time of 30 min (**9**, m.p. 243-245 °C, yield = 93%).Spectroscopic data of **9** are in agreement with literature data [2-5].

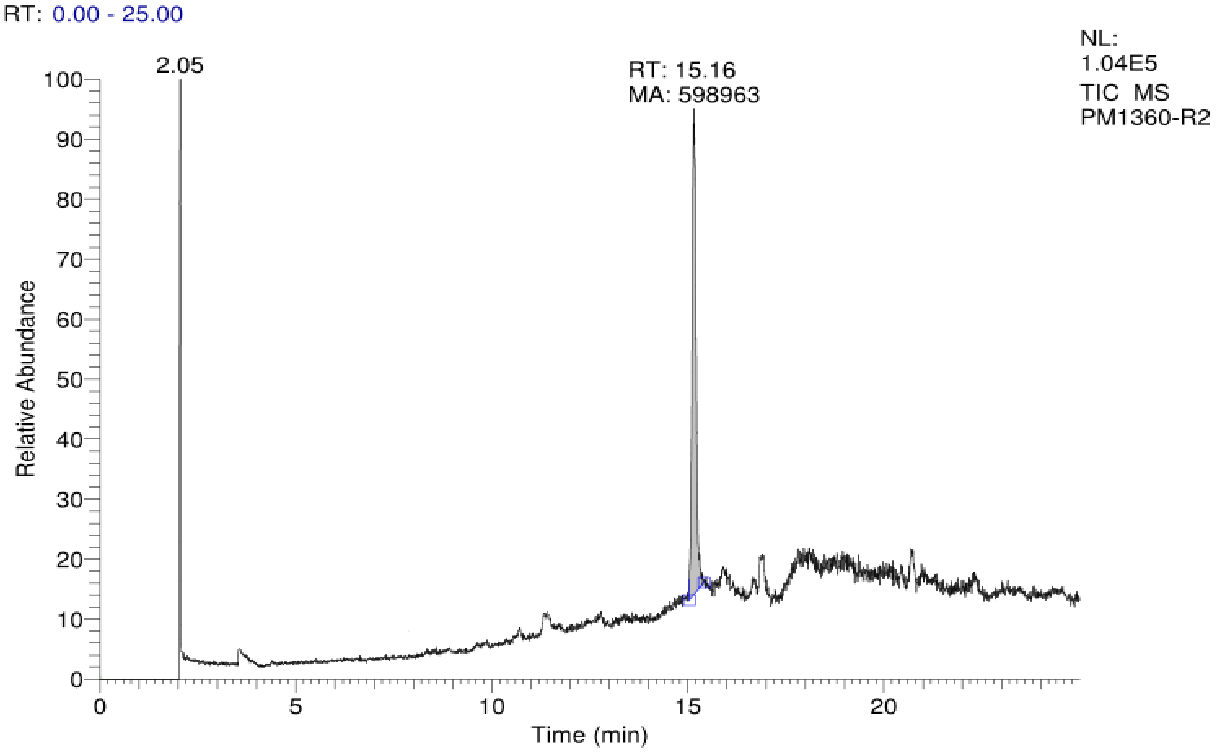
^{1}H NMR (400.1 MHz, $CDCl_3$) δ_H: 6.45 (d, 1H, CH, *J* = 6.5 Hz), 7.53 (d, 2H, ArH, *J* = 8.5 Hz), 8.12–8.14 (m, 3H), 12.54 (s, 1H, NH).

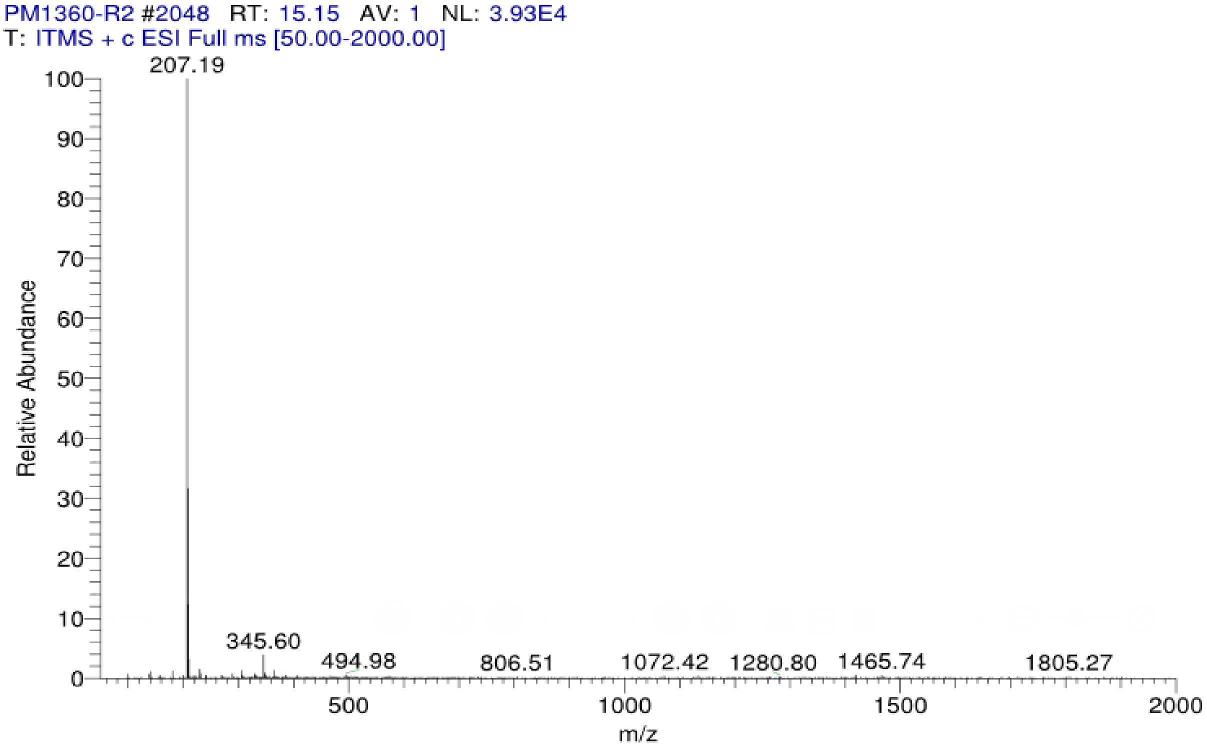


^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 113.84, 129.07, 129.45, 130.15, 138.81, 155.45, 156.65, 164.95.

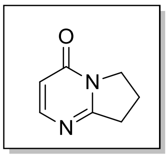


HPLC-MS characterization: The following retention time and molecular weight were determined: **9**: {RT= 15.16, m/z = 207 $[M + H]^+$ }.



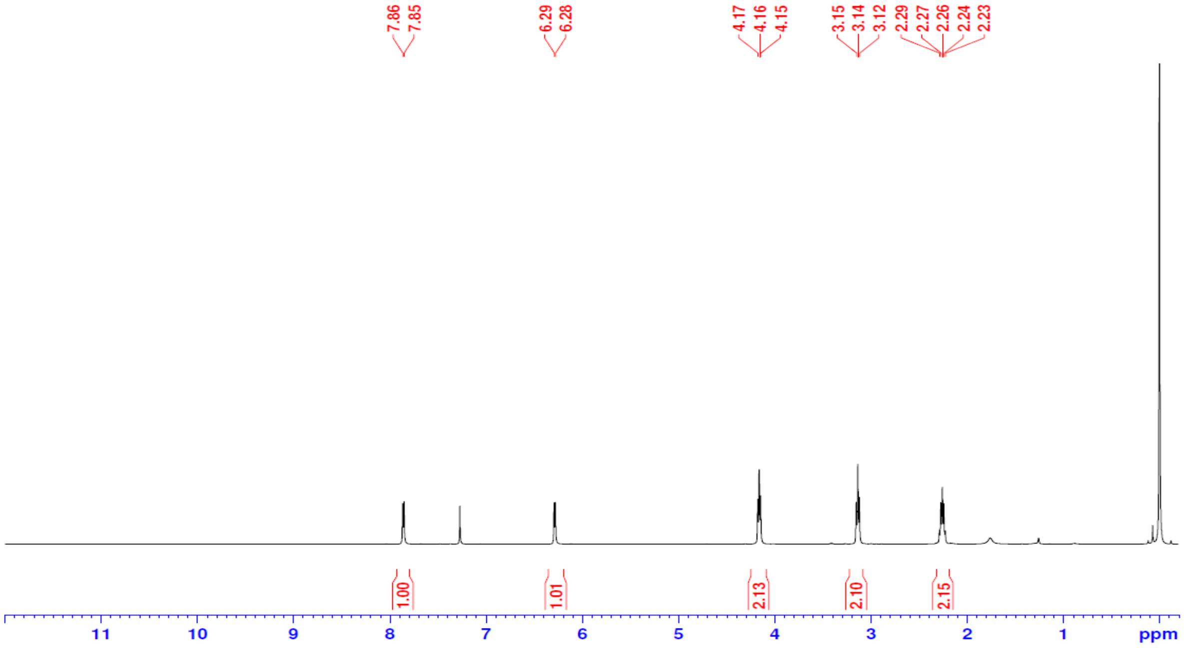


7,8-Dihydropyrrolo[1,2-*a*]pyrimidin-4(*6H*)-one (**10**):

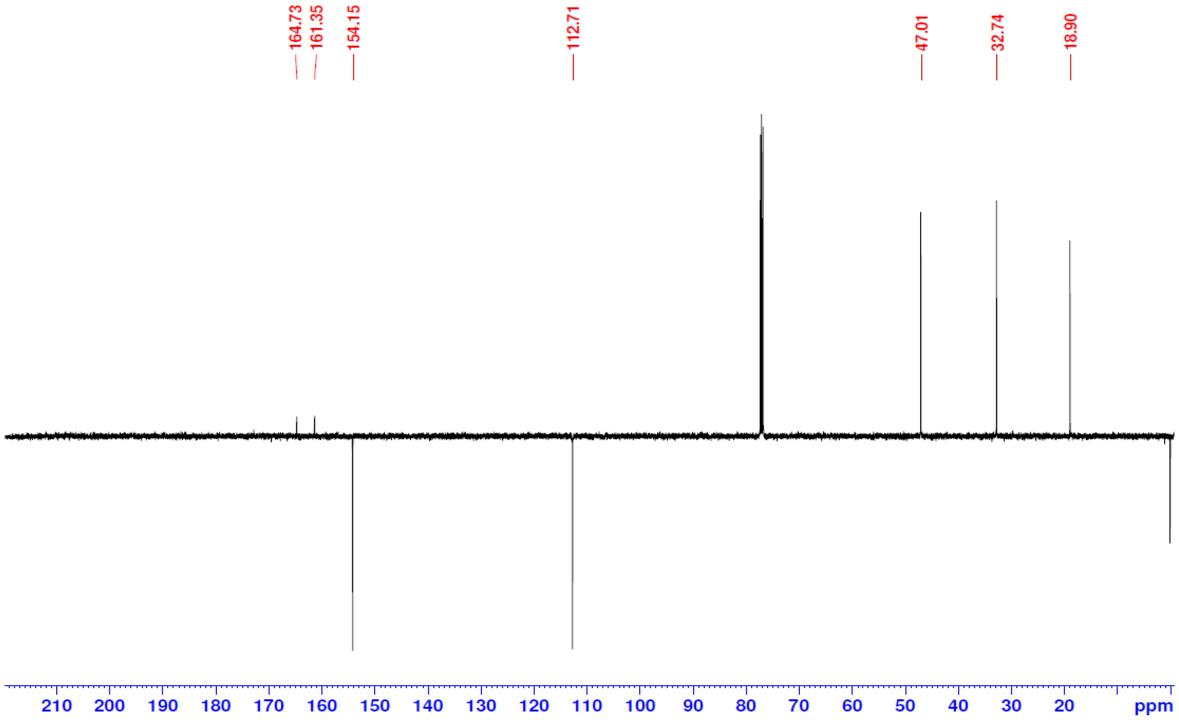


Di-*exo*-hexahydro-5,8-methanopyrrolo[2,1-*b*]quinazolin-9(*1H*)-one (**3**, 0.1 mmol) was dissolved in methanol (MeOH, 6 mL). The system temperature was set to 130 °C otherwise using the same pressure and flow rate as in previous procedures (10 bar, 0.5 mL min^{-1}). The solution fed into the reactor passed through the heated reactor coil within a residence time of 10 min and the flow output was collected. The solvent was removed by evaporation and the resulting product **10** was analysed and obtained in a nearly quantitative yield and with high purity (**10**, yield = 95%). Spectroscopic data are in agreement with the literature data [5].

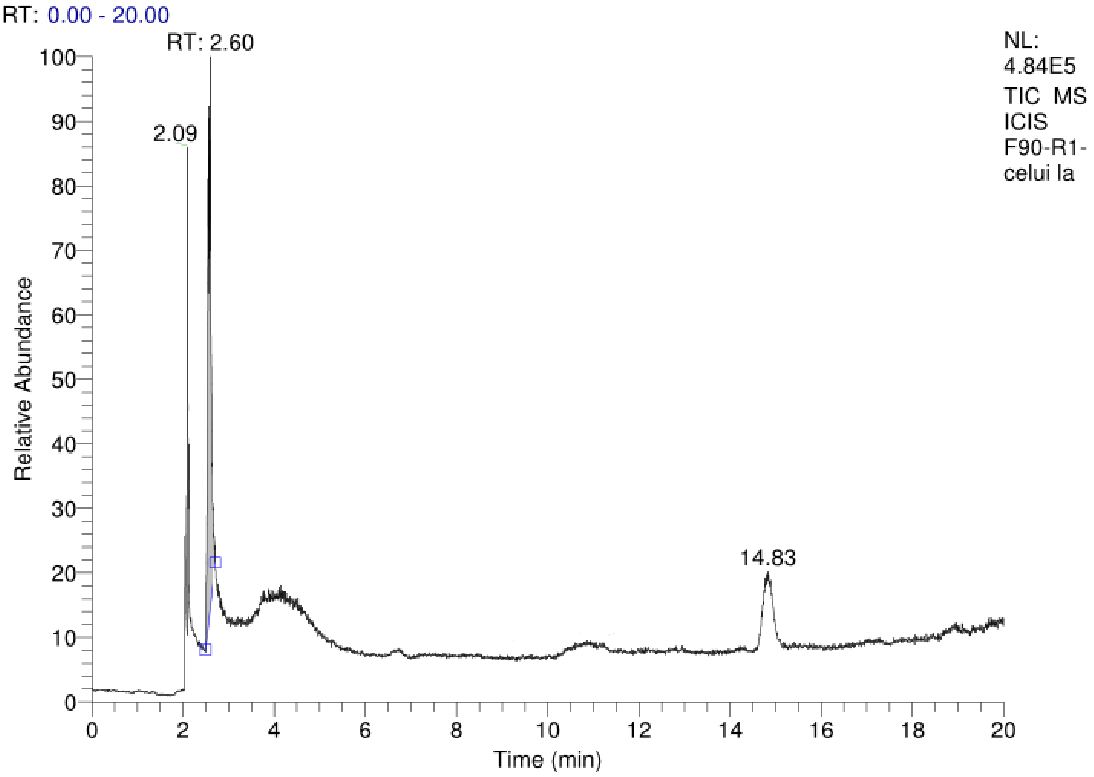
^{1}H NMR (400.1 MHz, CDCl$_3$) δ_H: 2.23–2.29 (m, 2H, CH$_2$), 3.12–3.15 (t, 2H, CH$_2$ J = 7.6 Hz), 4.15–4.17 (t, 2H, CH$_2$ J = 7.6 Hz), 6.28 (d, 1H, CH, J = 7.6 Hz), 7.86 (d, 1H, CH, J = 6.6 Hz).

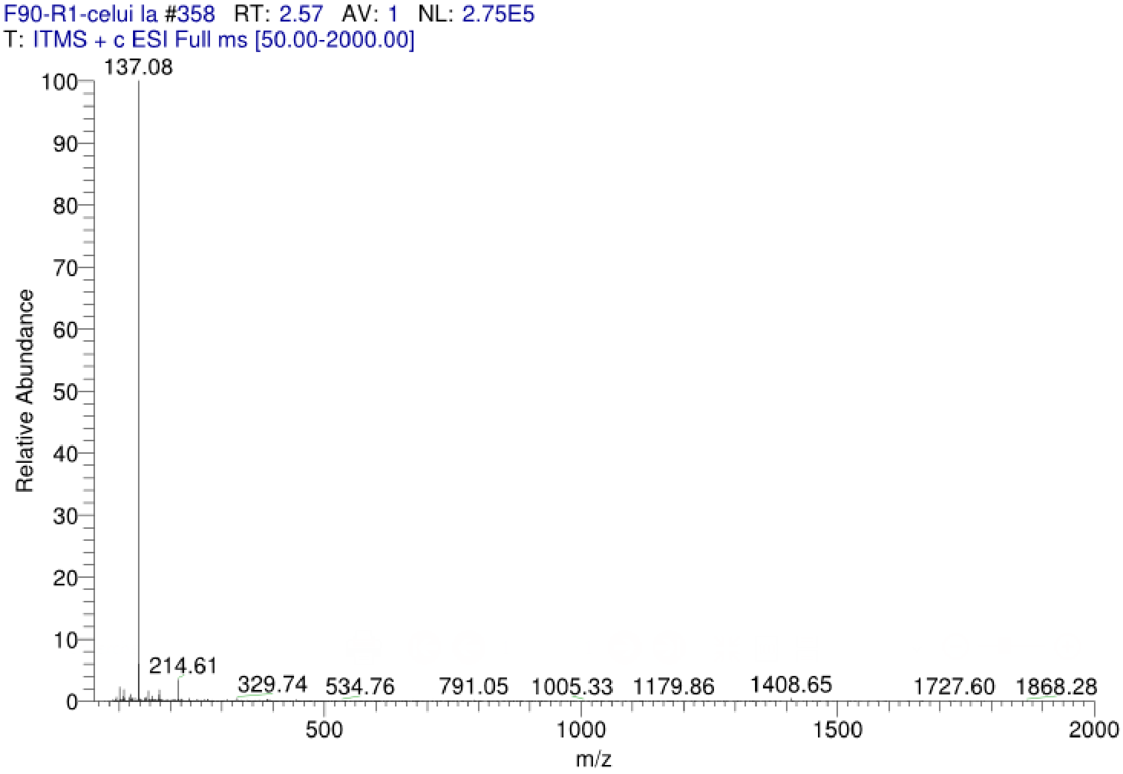


^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 18.90, 32.74, 47.01, 112.71, 154.15, 161.35, 164.73.

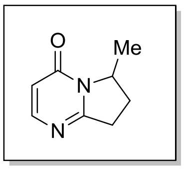


HPLC-MS characterization: The following retention time and molecular weight were determined: **10**: {RT= 2.60, m/z = 137 $[M + H]^+$ }.





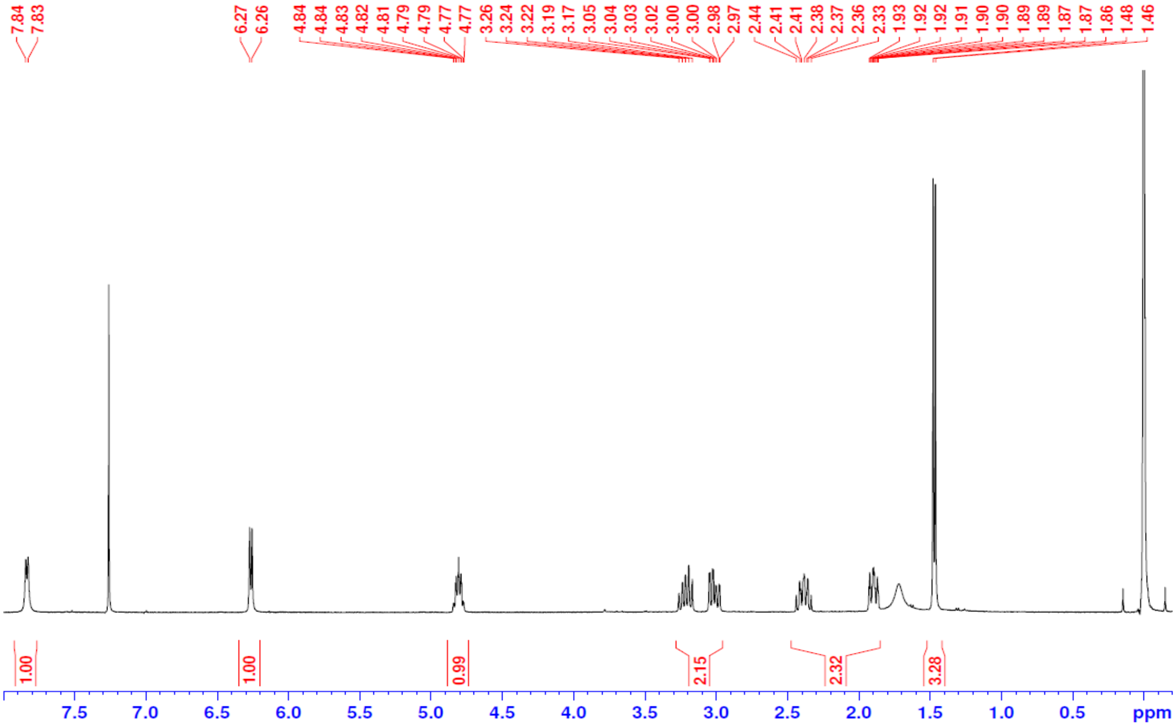
6-Methyl-7,8-dihydropyrrolo[1,2-*a*]pyrimidin-4(*6H*)-one (**11**)



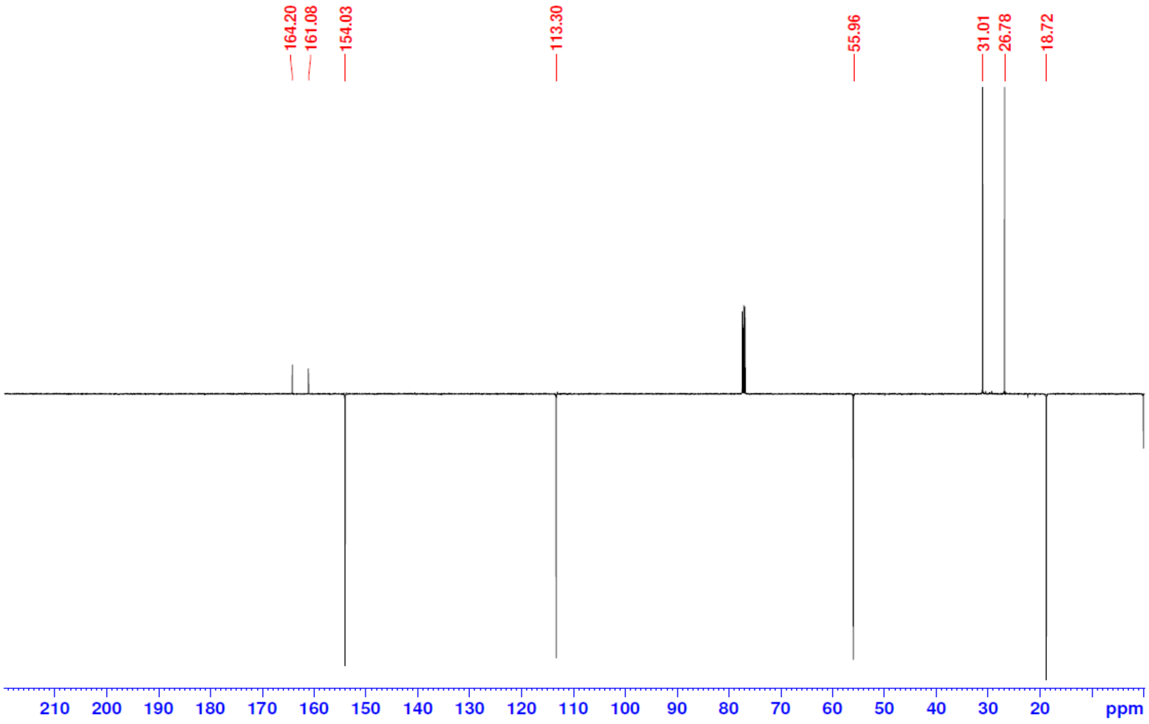
1-Methyl-hexahydro-5,8-methanopyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (**4**, 0.1 mmol) was dissolved in MeOH (6 mL) at 150 °C, pressure = 10 bar, flow rate = 0.5 mL min^{-1}. The solution fed into the reactor passed through the heated reactor coil within a residence time of 10 min and the flow output was collected. The solvent was removed by evaporation and the resulting product **11** was analysed and obtained in a high yield and with high purity (**11**, yield = 97%).

Spectroscopic data are in agreement with the literature data [5].

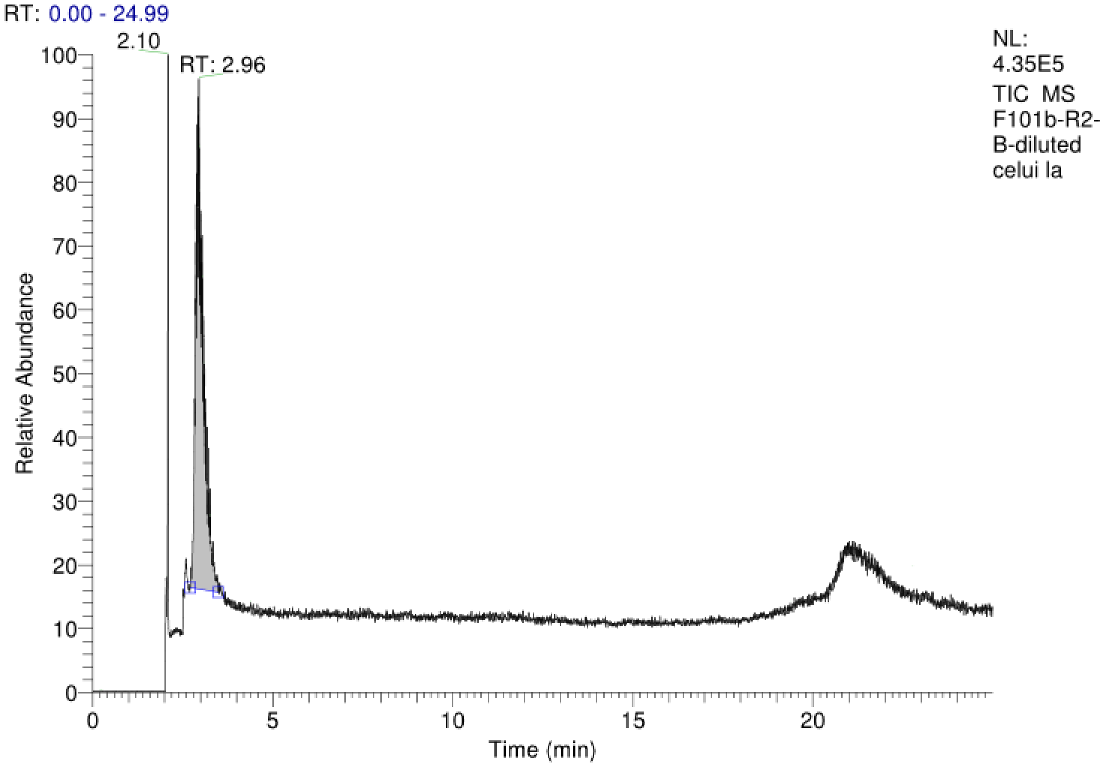
^{1}H NMR (400.1 MHz, $CDCl_3$) δ_H: 1.47 (d, 3H, CH_3, *J* = 6.5 Hz), 1.86–2.44 (m, 2H, CH_2), 2.79–3.26 (m, 2H, CH_2), 4.77–4.84 (m, 1H, CH), 6.26 (d, 1H, CH, *J* = 6.6 Hz), 7.83 (d, 1H, CH, *J* = 6.4 Hz).

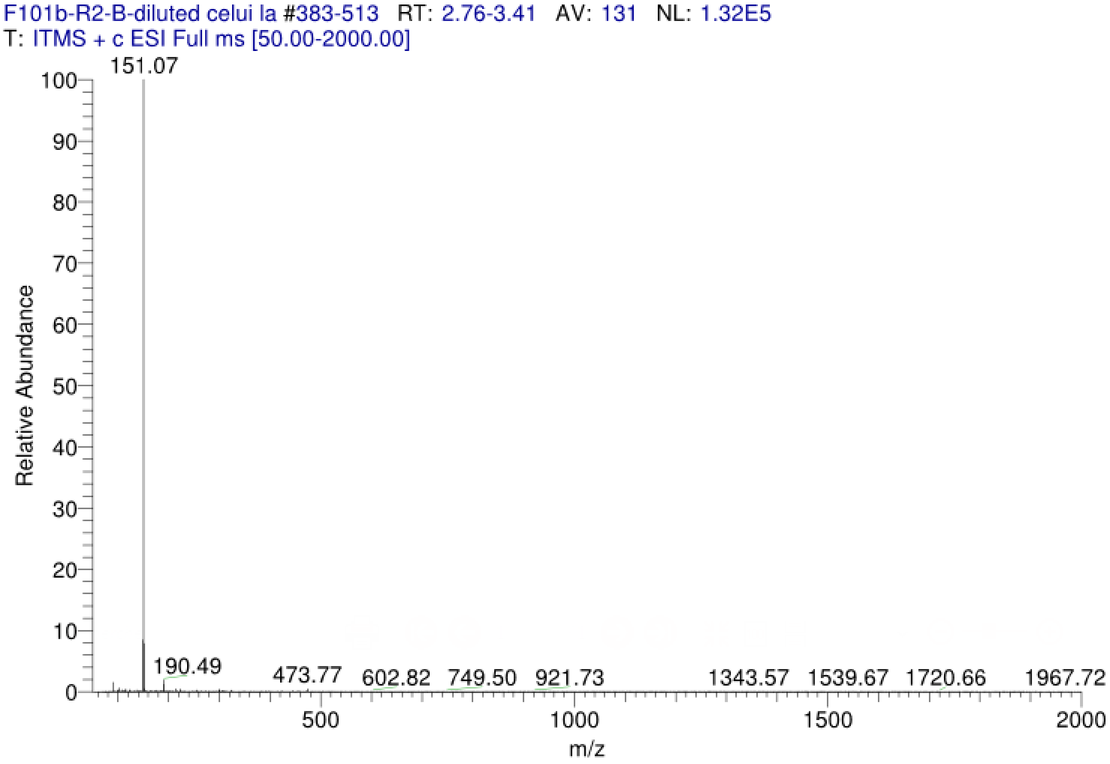


^{13}C NMR (100.6 MHz, CDCl$_3$): δ_C = 18.72, 26.78, 31.01, 55.96, 113.30, 154.03, 161.08, 164.20.

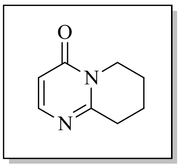


HPLC-MS characterization: The following retention time and molecular weight were determined: **11**: {RT= 2.96, m/z = 151 [M + H]$^+$ }.



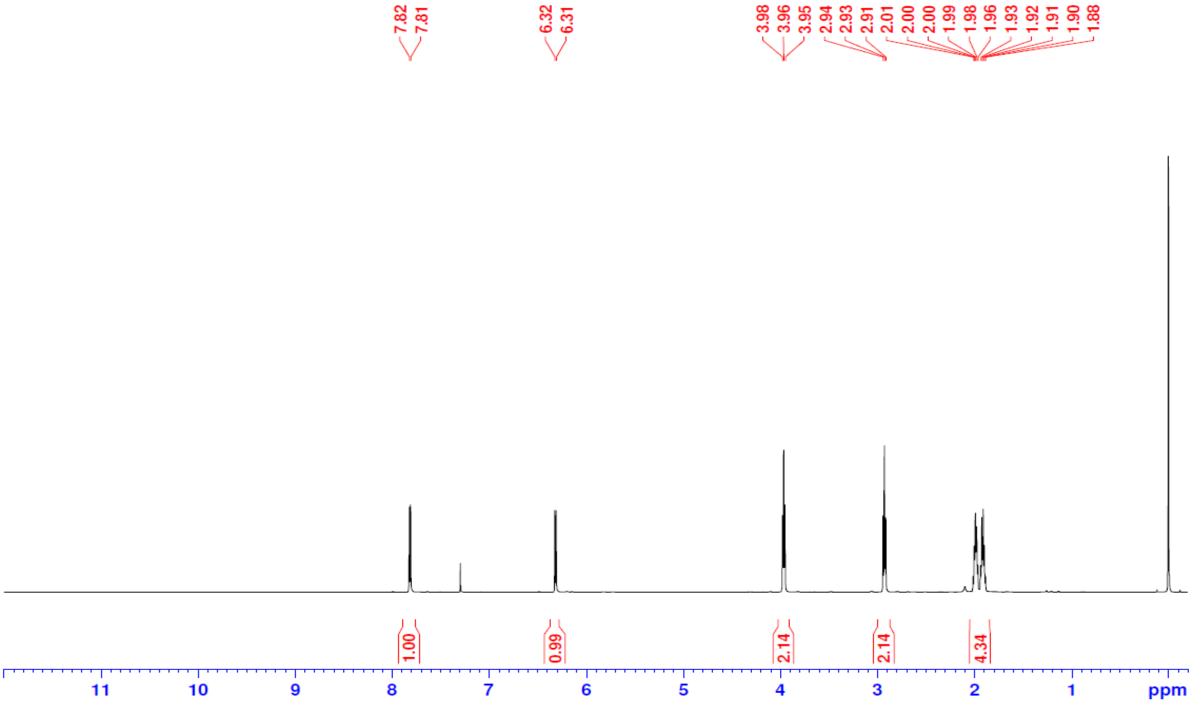


6,7,8,9-Tetrahydropyrido[1,2-*a*]pyrimidin-4(*4H*)-one (**12**):

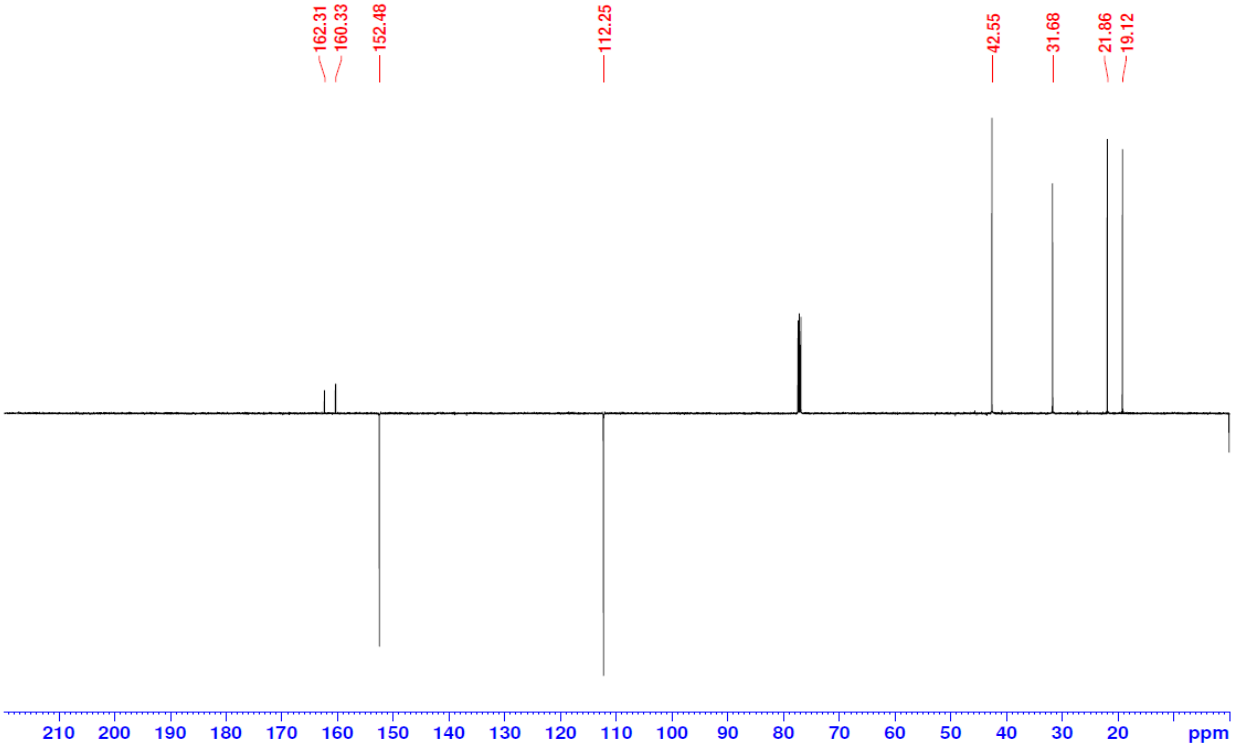


1,4-Hexahydromethanopyrido[2,1-*b*]quinazolin-11(11a*H*)-one (**5**, 0.1 mmol) was dissolved in MeOH (6 mL) at 120 °C, pressure = 10 bar, flow rate = 0.5 mL min^{-1}. The solution fed into the reactor passed through the heated reactor coil within a residence time of 10 min and the flow output was collected. The MeOH was removed by evaporation and the resulting product **12** was analysed and obtained in a high yield and with high purity (**12**, yield = 95%). Spectroscopic data are in agreement with the literature data [5].

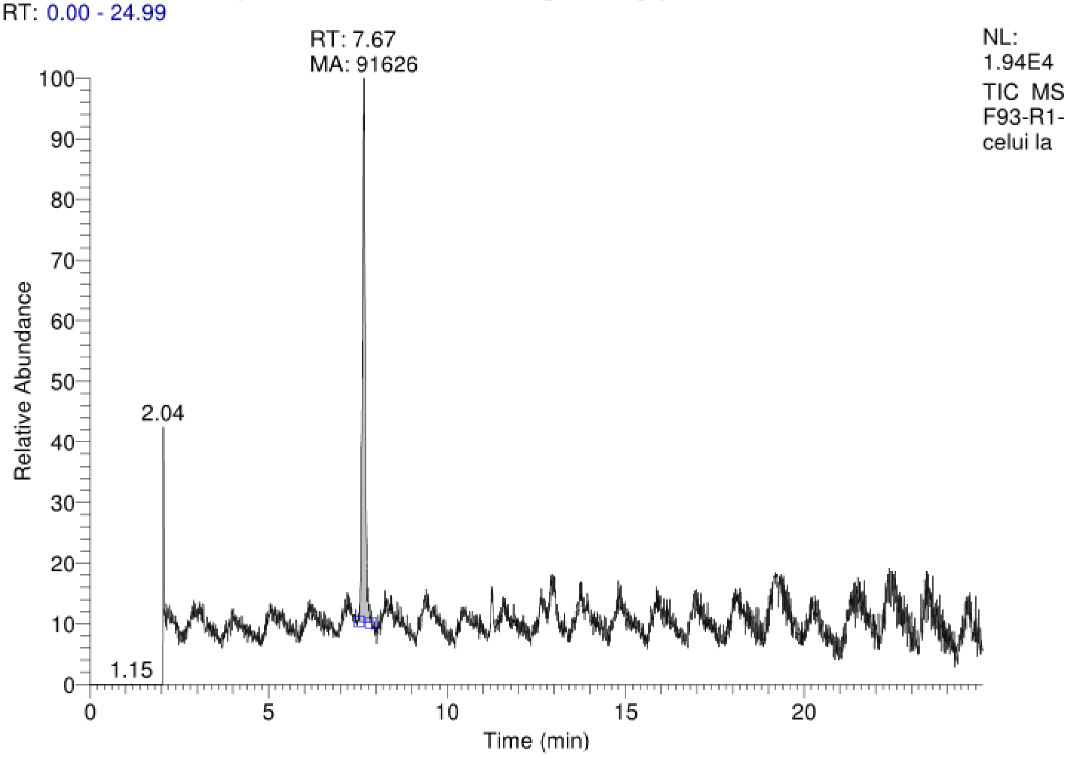
^{1}H NMR (400.1 MHz, CDCl$_3$) δ_H: 1.88–2.01 (m, 4H, CH$_2$), 2.91–2.94 (t, 2H, CH$_2$, J = 6.6 Hz), 3.95–3.98 (t, 2H, CH$_2$ J = 6.6 Hz), 6.31 (d, 1H, CH, J = 6.5 Hz), 7.81 (d, 1H, CH, J = 6.5 Hz).

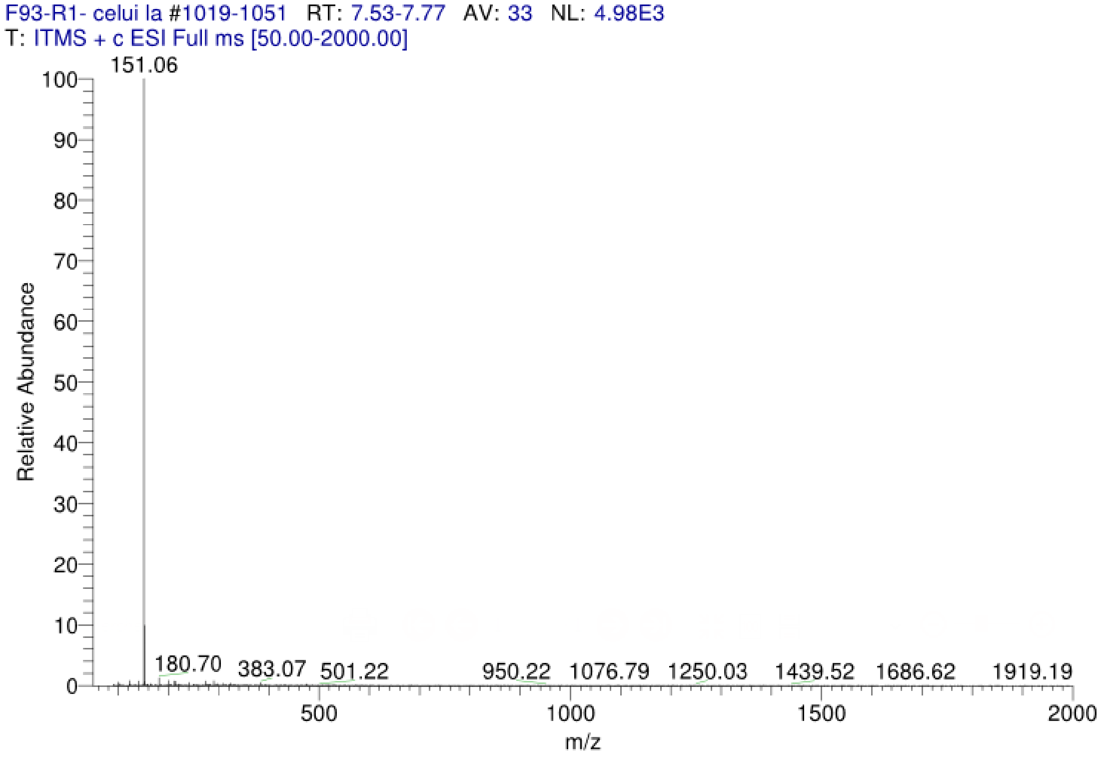


^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 19.12, 21.86, 31.68, 42.55, 112.25, 152.48, 160.33, 162.31.

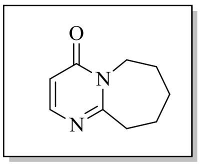


HPLC-MS characterization: The following retention time and molecular weight were determined: **12**: {RT= 7.67, m/z = 151 $[M + H]^+$}.



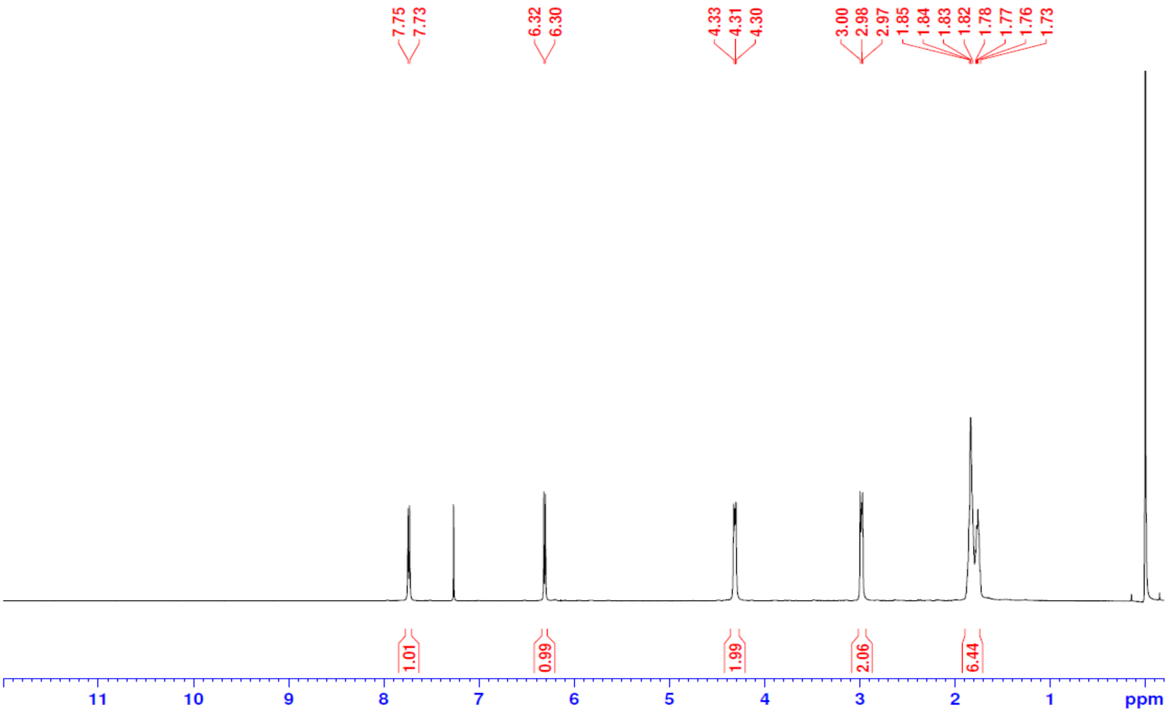


7,8,9,10-Tetrahydropyrimido[1,2-*a*]azepin-4(*6H*)-one (**13**):

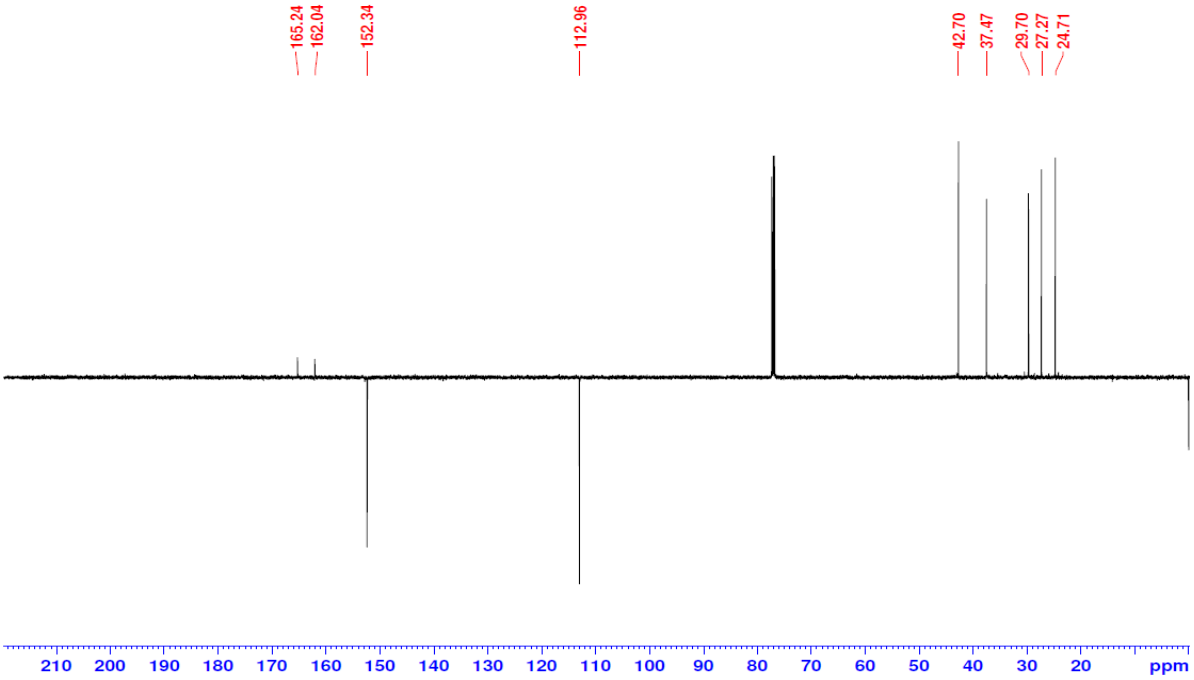


1,4-Octahydromethanoazepino[2,1-*b*]quinazolin-12(*6H*)-one (**6**) (0.1 mmol) was dissolved in MeOH (6 mL) at 130 °C, pressure = 10 bar, flow rate = 0.5 mL min^{-1}. The solution fed into the reactor passed through the heated reactor coil within a residence time of 10 min and the flow output was collected. The MeOH was removed by evaporation and the resulting product **13** was analysed and obtained in a good yield and with high purity (**13**, yield = 94%). Spectroscopic data are in agreement with the literature data [5].

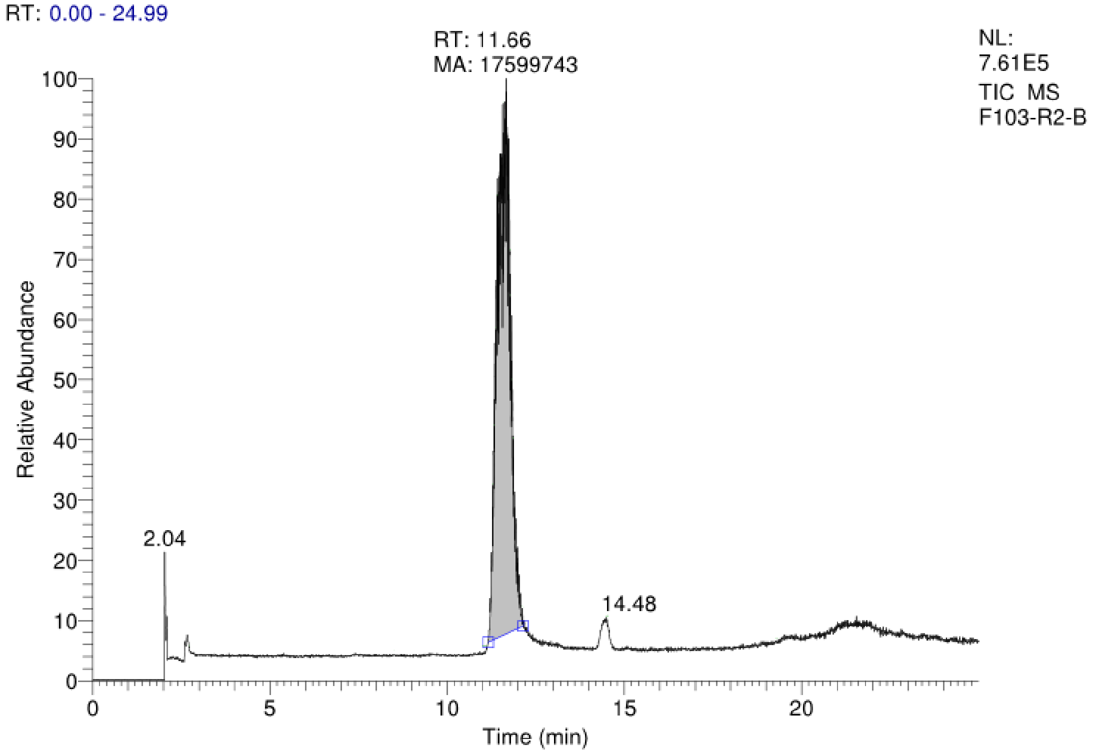
^{1}H NMR (400.1 MHz, $CDCl_3$) δ_H: 1.73–1.85 (m, 6H), 2.97–3.00 (m, 2H, CH_2), 4.30–4.33 (t, 2H, CH_2 *J* = 6.5 Hz), 6.31 (d, 1H, CH, *J* = 6.5 Hz), 7.74 (d, 1H, CH, *J* = 6.5 Hz).

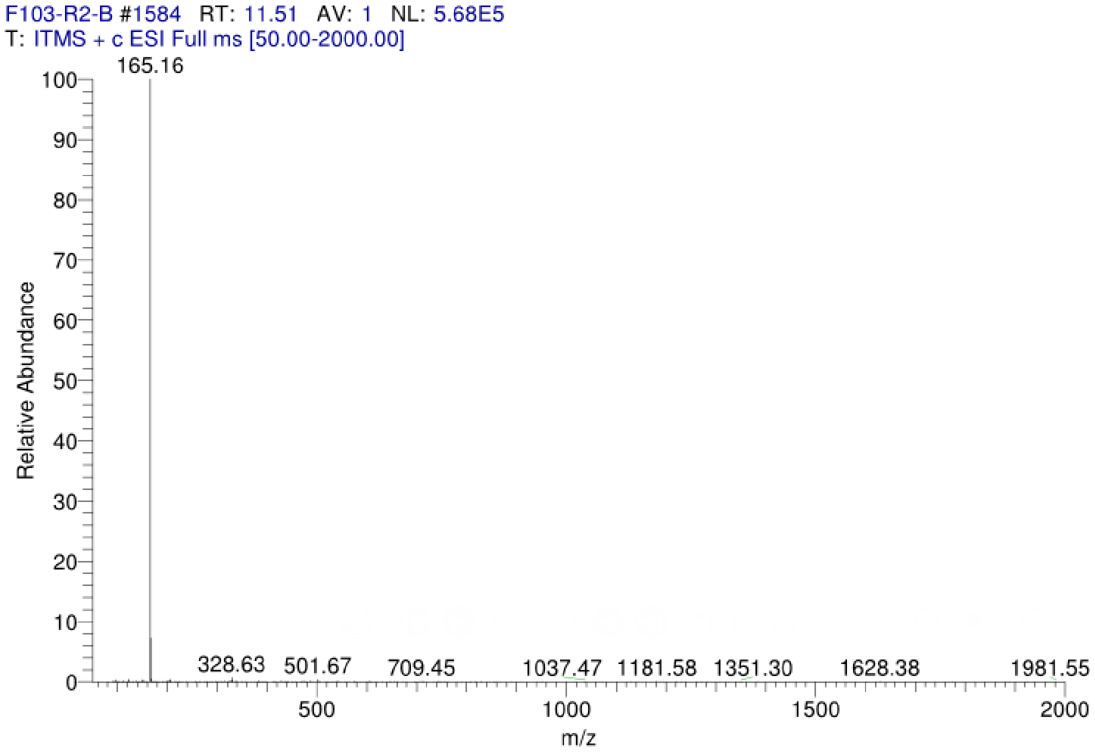


^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 24.71, 27.27, 29.70, 37.47, 42.70, 112.96, 152.34, 162.04, 165.24.



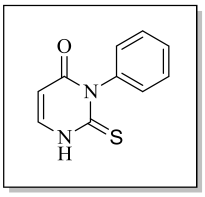
HPLC-MS characterization: The following retention time and molecular weight were determined: **13**: {RT= 11.66, m/z = 165 [M + H]$^+$}.





2,3-Dihydro-3- phenyl-2-thioxopyrimidin-4(*1H*)-one (14)

Synthesized from the following starting materials **7** (Method A), **8a** (Method B) and **8b** (Method C):



Method A

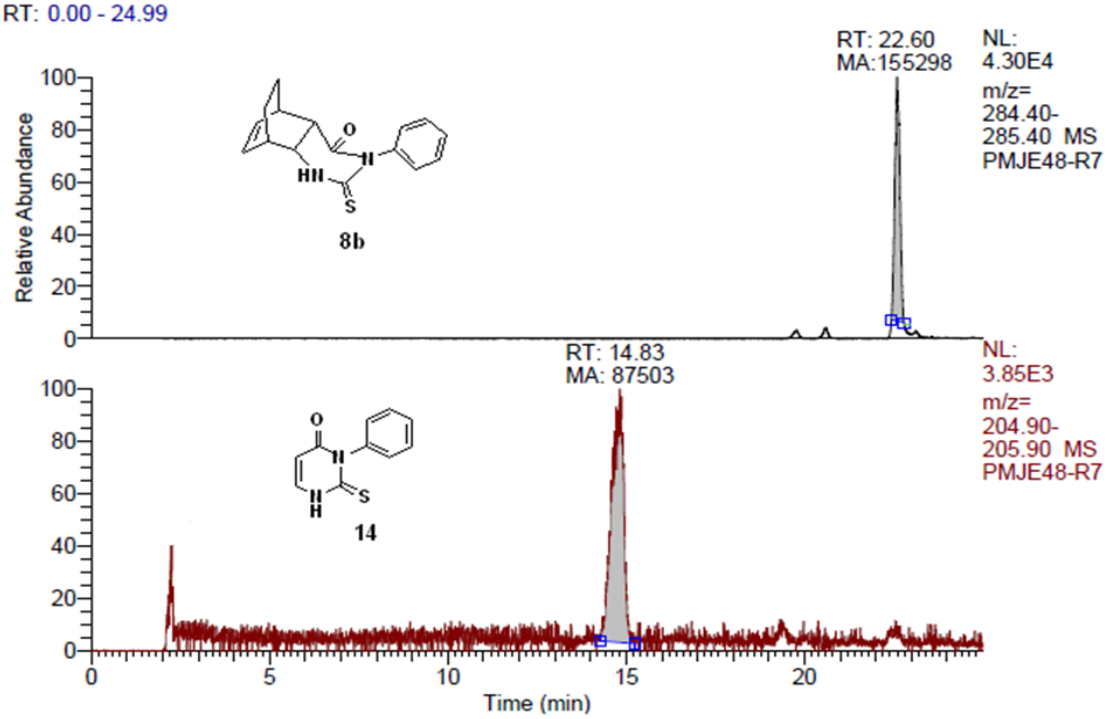
diexo-3-Phenyl-2-thioxohexahydro-5,8-methanoquinazolin-4(1*H*)-one (**7**, 0.1 mmol) was dissolved in MeCN (10 mL). The system temperature was set to 210 °C, the pressure to 10 bar and the flow rate to 0.5 mL min^{-1}. The solution loaded into the reactor passed through the heated reactor coil within a residence time of 15 min and the flow output was collected. The solvent was removed by evaporation and the resulting product **14** was analysed by means of HPLC-MS and ^{1}H NMR and obtained in a high yield and with high purity (**14**, m.p. 247-249 °C, yield = 96%).

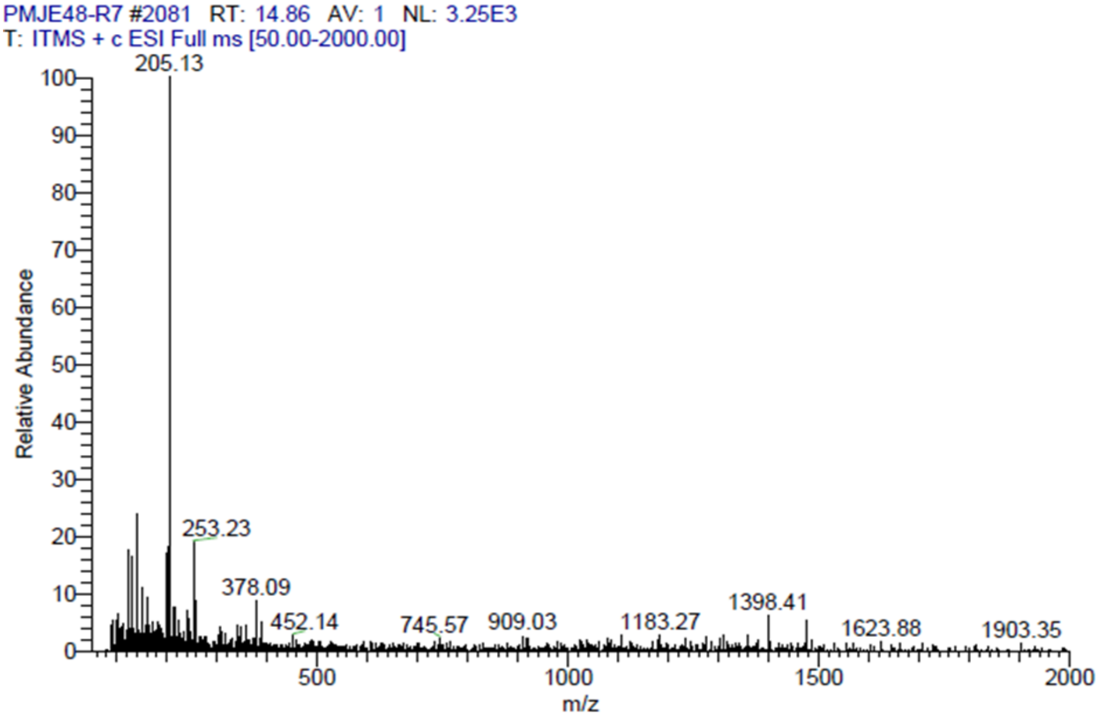
Method B

The synthesis was performed at 220 °C with a flow rate of 0.5 mL min^{-1} corresponding to a residence time of 10 min. Di-*endo*-3-phenyl-2-thioxohexahydro-5,8-methanoquinazolin-4(1*H*)-one (**8a**, 0.1mmol) was dissolved in MeCN (10 mL). Product **14** was isolated by applying the same procedure used above (**14**, m.p. 247–249 °C, yield = 96%).

Method C

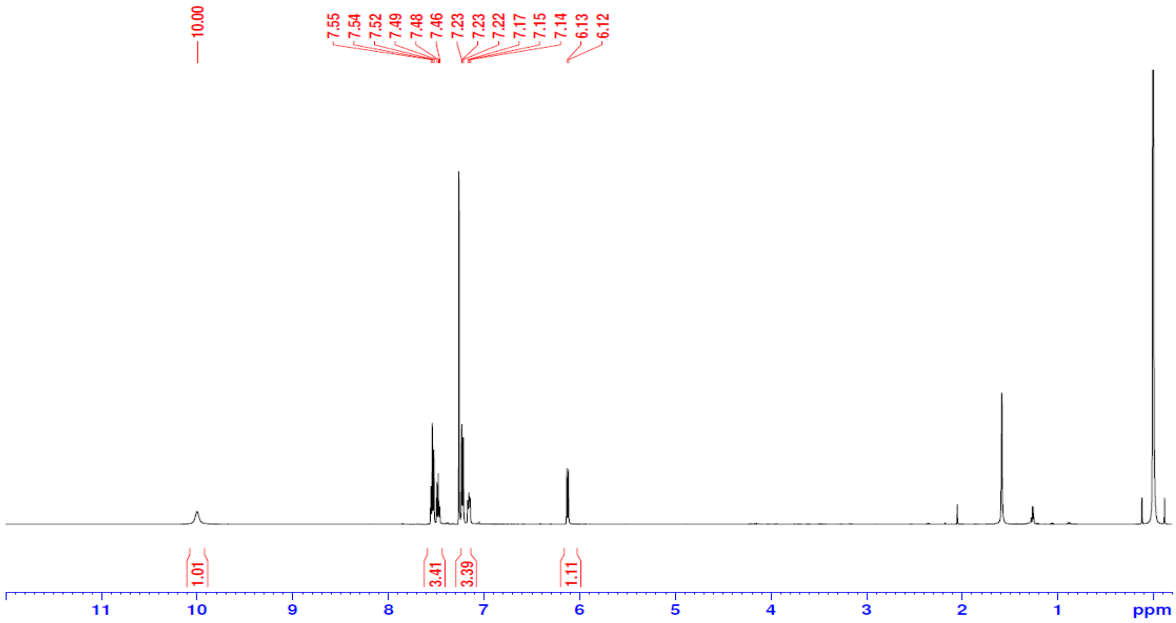
The system temperature was increased to 250 °C, while using the same flow rate (0.5 mL min^{-1}). Di-*endo*-3-Phenyl-2-thioxohexahydro-5,8-ethanoquinazolin-4(1*H*)-one (**8b**) (0.01 mmol) was introduced into the flow reactor in a solution of MeCN (15 mL). The solution fed into the reactor passed through the heated reactor coil within a residence time of 30 min and the flow output was collected and analysed. The solvent was removed by evaporation. The HPLC-MS chromatogram indicates that compound **8b** underwent thermal decomposition with only a moderate conversion of 36% to product **14**. The following retention times and molecular weights were determined: **8b**: {RT= 22.60, m/z = 285 $[M + H]^+$} **14**: {RT= 14.83, m/z = 205 $[M + H]^+$} Conversion: 36%.



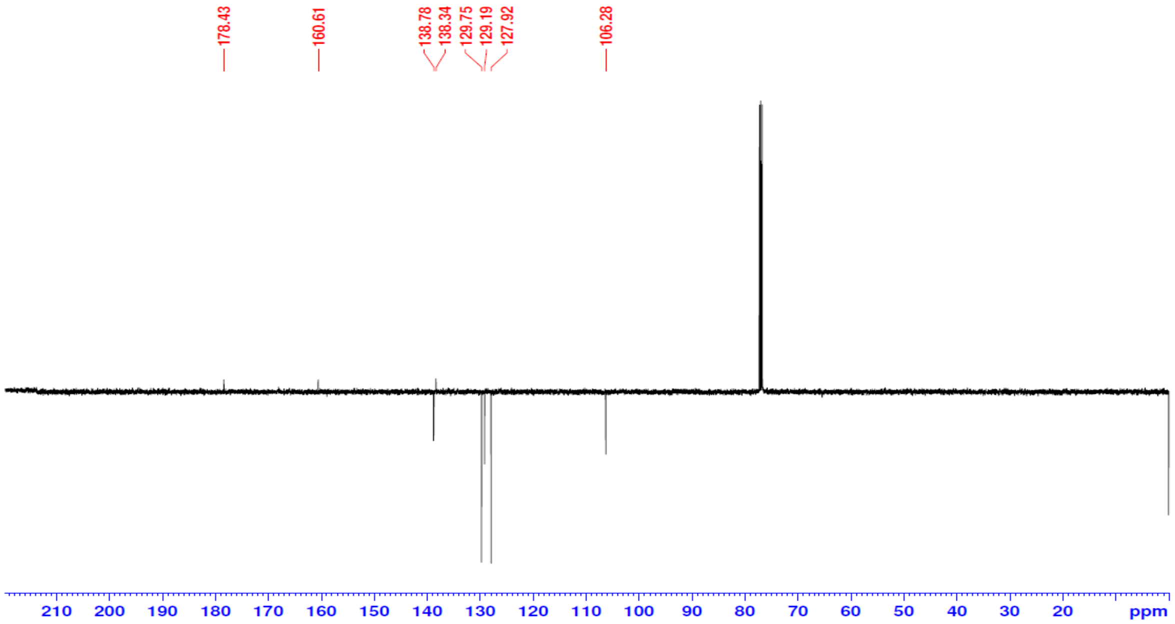


The processed product mixture leaving the flow system was subsequently loaded into a short silica chromatography column and eluted with a mixture of MeOH/toluene (1:1). The title compound was isolated as off-white crystalline material (**14**, m.p. 247-249 °C, yield = 30%). Spectroscopic data are in agreement with literature data [4,6].

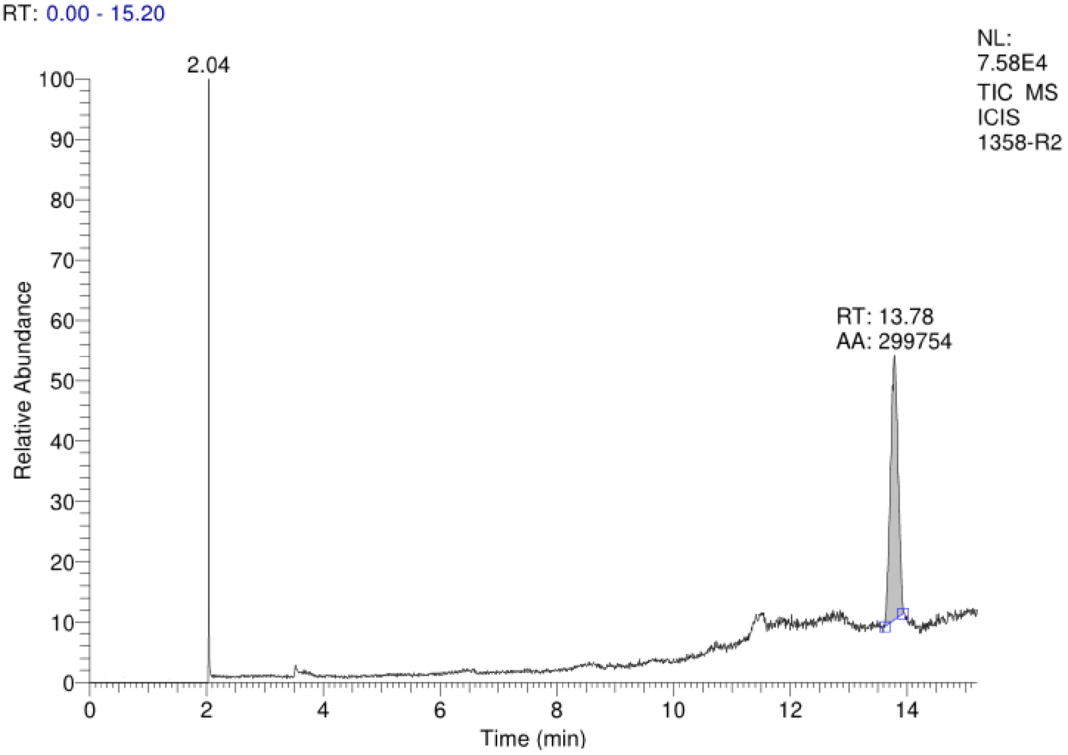
^{1}H NMR (400.1 MHz, CDCl$_3$) δ_H: 6.12 (d, 1H, CH, *J* = 7.6 Hz), 7.14-7.23 (m, 3H), 7.46–7.55 (m, 3H), 10.00 (s, 1H, NH).

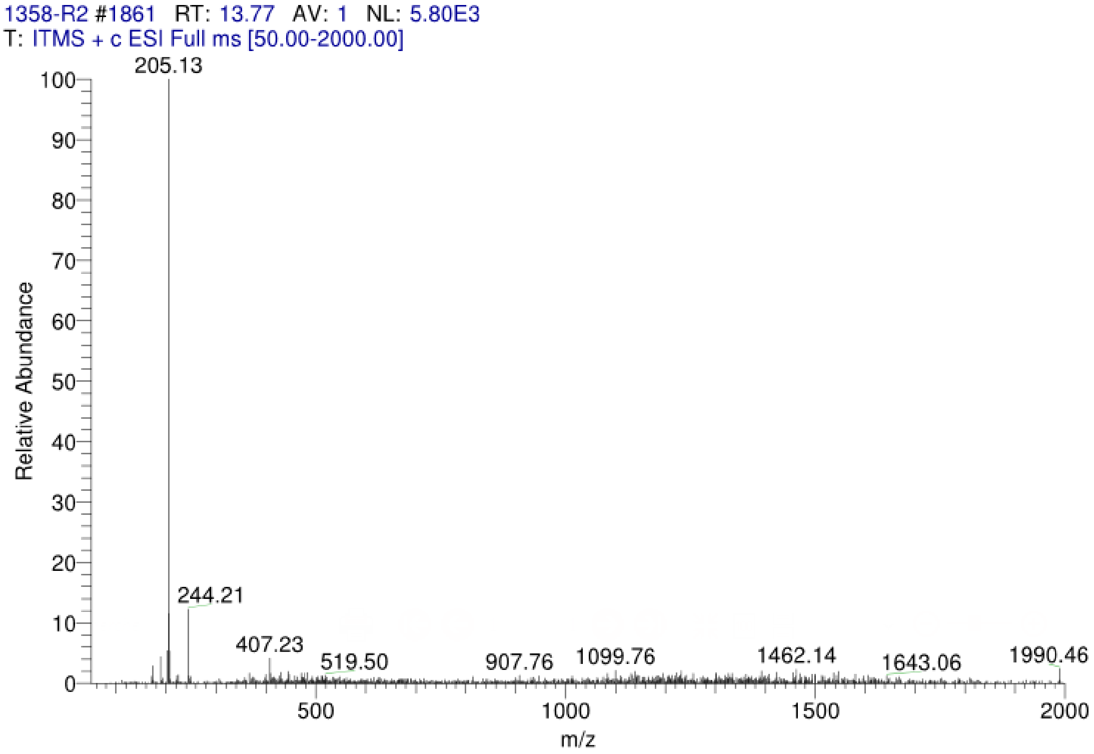


^{13}C NMR (100.6 MHz, CDCl$_3$): δ_C = 106.28, 127.92, 129.19, 129.75, 138.34, 138.78, 160.61, 178.43.



HPLC-MS characterization: The following retention time and molecular weight were determined: **14**: {RT= 13.78, m/z = 205 $[M + H]^+$}.

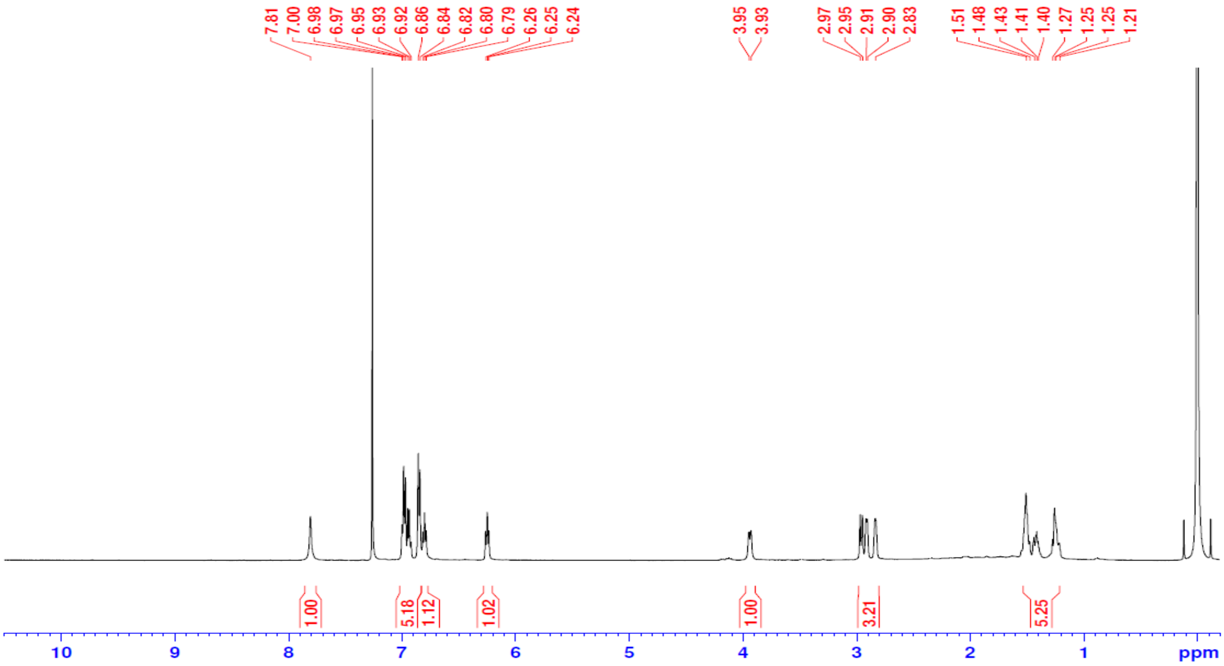




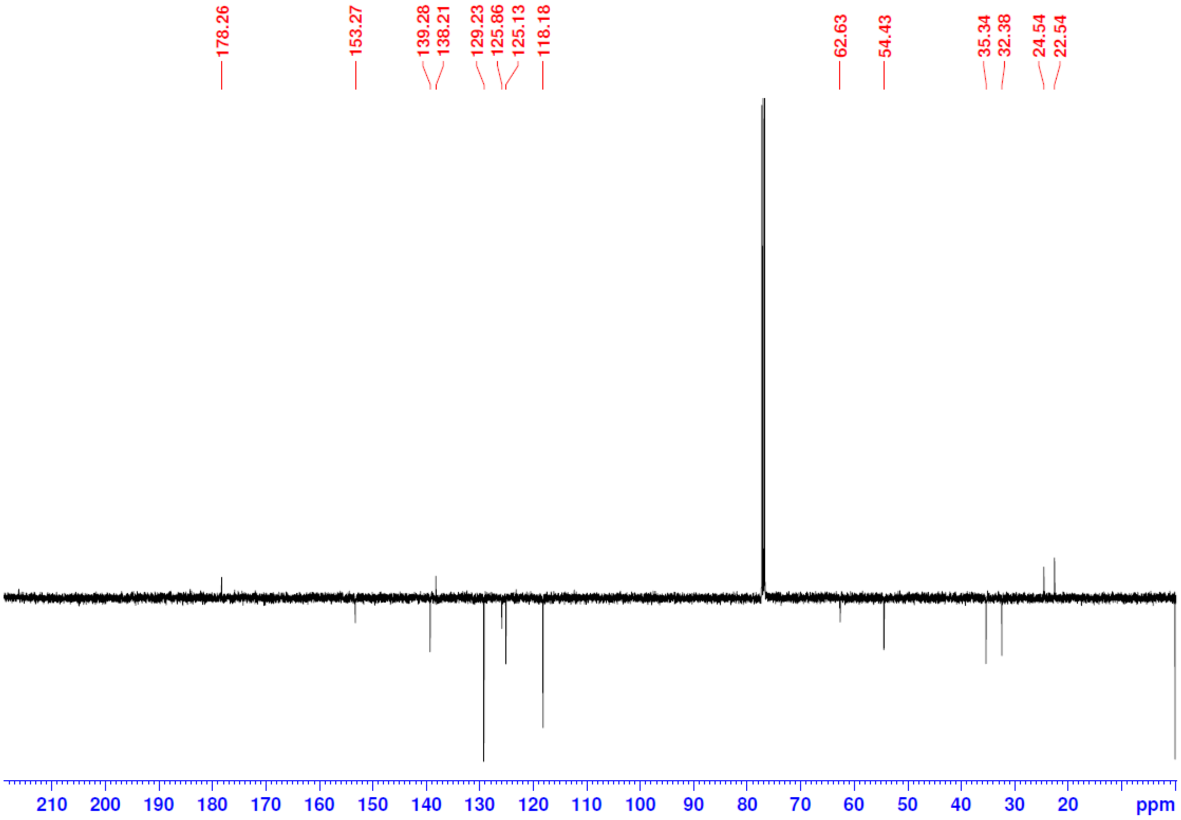
1.6. Desulfurisation reaction of 8b, synthesis of *diendo*-3-phenyl-4a,5,8,8a-tetrahydro-5,8-ethanoquinazolin-4(3*H*)-one (15b)

diendo-3-Phenyl-2-thioxohexahydro-5,8-ethanoquinazolin-4(*1H*)-one (**8b**, 0.01 mmol) was dissolved in a mixture of EtOH/water (2:1) (15 mL) at 250 °C, pressure = 10 bar, flow rate = 0.5 mL min^{-1}. The solution fed into the reactor passed through the heated reactor coil within a residence time of 30 min and the flow output was collected. Solvents were removed by evaporation, and the product residue was analysed. Product **15b** was obtained in a good yield (**15b**, m.p. 247-249, yield = 90%).

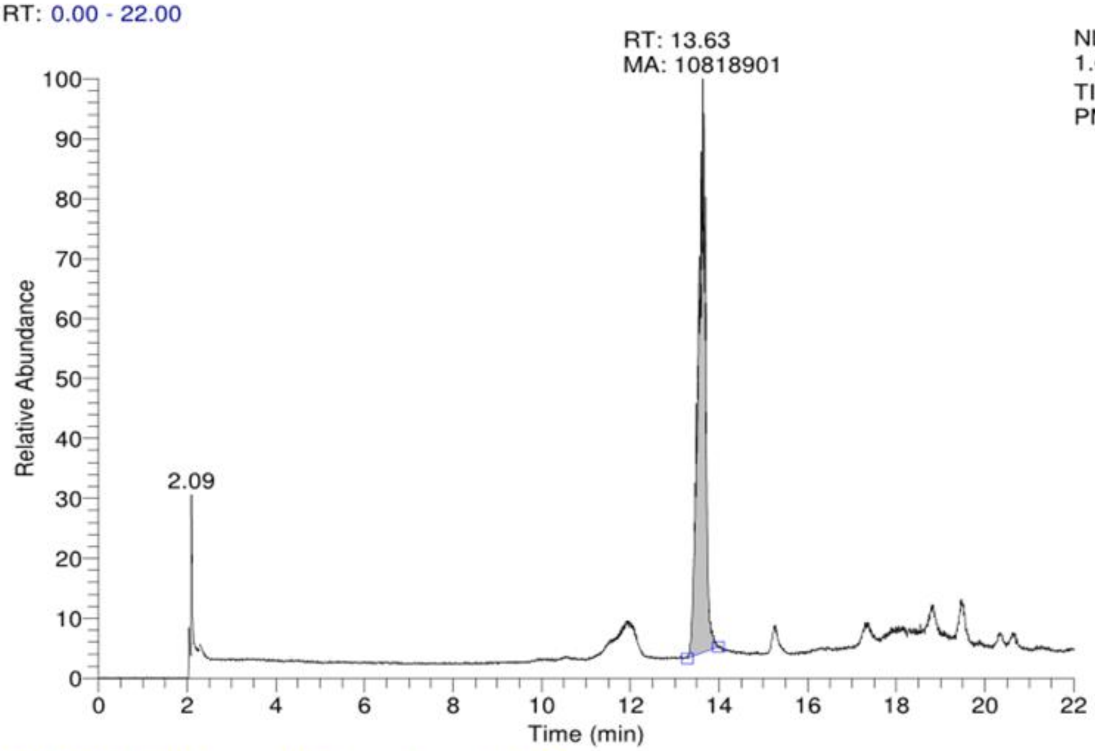
^{1}H NMR (400.1 MHz, CDCl$_3$) δ_H: 1.21-1.51(m, 4H, CH$_2$CH$_2$), 2.83-2.97 (m, 3H, H-4a, H-5, H-8), 3.93 (d, 1H, H-8a, *J* = 8.5 Hz), 6.24-6.26 (t, *J* = 7.17, 1H, H-6), 6.79-7.00 (m, 6H, Ar, H-5), 7.81 (s, 1H, H-2).

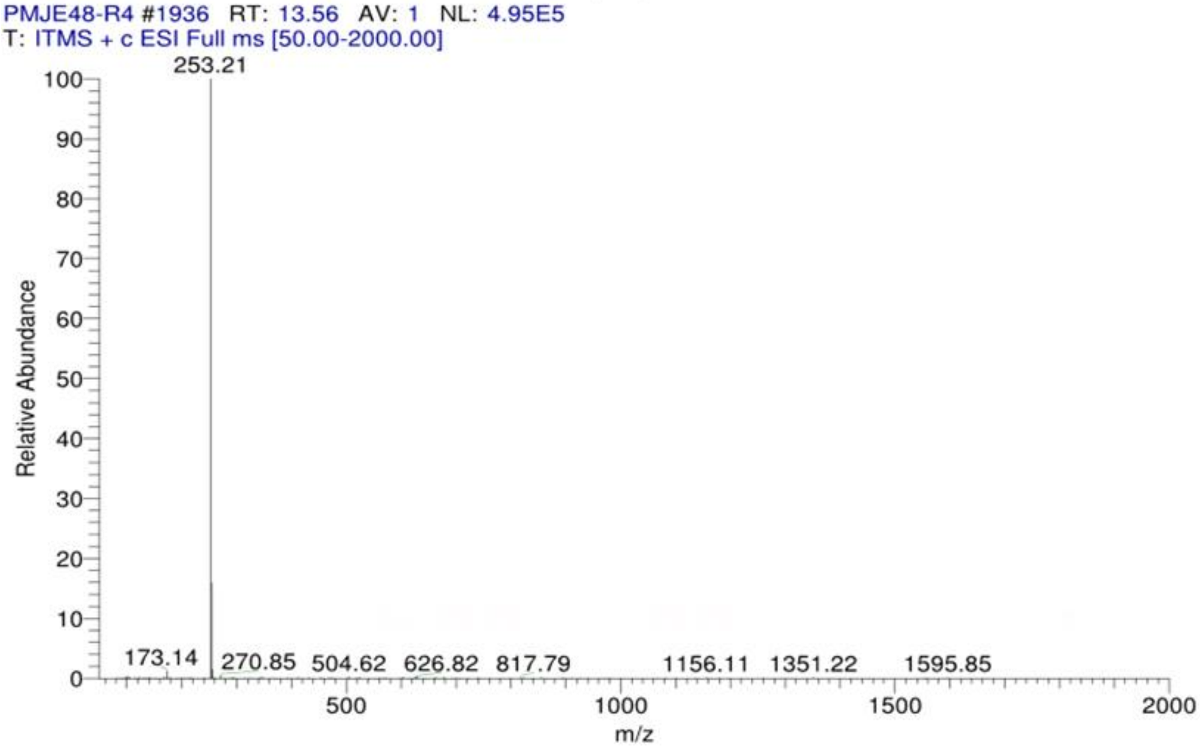


^{13}C NMR (100.6 MHz, CDCl$_3$): δ_C = 22.54, 24.54, 32.38, 35.34, 54.43, 62.63, 118.18, 125.13, 125.86, 129.23, 138.21, 139.28, 153.27, 178.26.



HPLC-MS characterization: The following retention time and molecular weight were determined: **15b**: {RT= 13.63, m/z = 253 [M + H]$^+$}.





1.6.1 Alternative batch synthesis of di-*endo*-3-phenyl-4a,5,8,8a-tetrahydro-5,8-ethanoquinazolin-4(3*H*)-one (15b)

The mixture of 3-aminobicyclo[2.2.2]oct-5-ene-carboxylic acid (1 mmol, 167 mg), triethylorthoformate (1.5 mmol, 222 mg), aniline (1.1 mmol, 108 mg) and acetic acid (0.2 mL) was subjected to microwave irradiation at 120 W at 80 °C for 20 min. After completion of the reaction, as monitored by TLC, 20% methanolic solution in water (10 mL) was added to get precipitation. Solid was filtered off and washed with water to get **15b**. The product was purified by column chromatography on silica gel eluted with toluene/methanol (4:1). Yield: (163 mg, 65%); light pink crystals; m.p. 247–249 °C; IR: νC=O 1703, νC=N 1599 cm^{-1} in KBr; ^{1}H NMR: 1.12-1.55(m, 4H, CH_2CH_2), 2.80-3.05 (m, 3H, H-4a, H-5, H-8), 3.93 (m, 1H, H-8a), 6.24 (t, *J* = 7.17, 1H, H-6), 6.86-6.97 (m, 6H, Ar, H-5), 7.82 (s, 1H, H-2); ^{13}C NMR: 22.92, 24.95, 32.78, 35.76, 54.76, 62.90, 118.58, 125.59, 126.32, 129.66, 138.53, 139.65, 153.74, 178.68.

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