Modified multicomponent Biginelli-Atwal reaction towards a straightforward construction of 5,6-dihydropyrimidin-4-ones

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I-General information

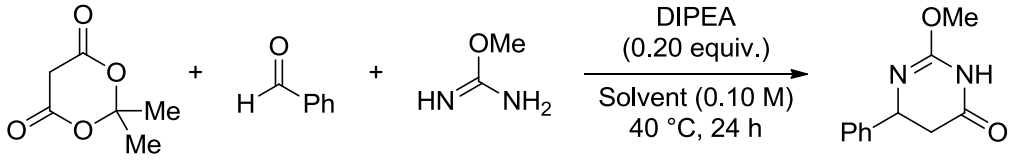
Reactions were performed using oven dried glassware under inert atmosphere of dry argon or nitrogen and monitored by thin-layer chromatography with silica gel 60 F254 pre-coated aluminium plates (0.25 mm). Visualization was performed under UV light and $KMnO_4$ oxidation. Filtrations were performed on Celite® 545. Chromatographic purification of compounds was achieved with 60 silica gel (40-63 μm).[1] Toluene and CH_2Cl_2 were dried by refluxing over CaH_2 and then distilled. Unless otherwise noted, all reagent-grade chemicals and solvents were used as supplied (analytical or HPLC grade) without prior purification. Melting points were measured on a Stuart™ SMP3 melting point apparatus with a precision of +/− 1.5 °C and are uncorrected. Infrared spectra (IR) were recorded on a PerkinElmer Spectrum 100 Series FT-IR spectrometer. Liquids and solids were applied on the Single Reflection Attenuated Total Reflectance (ATR) Accessories. Data are reported in cm^{-1}. Optical rotations were determined with a Perkin-Elmer 341 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg.cm^2.g^{-1} and concentrations in g per 100 mL. ^1H Spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded on a Bruker Advance300 spectrometer. The field was locked by external referencing to the relevant deuteron resonance. Data appear in the following order: chemical shifts in ppm which were referenced to the internal solvent signal, number of protons, multiplicity (*s*, singlet; *d*, doublet; *t*, triplet; *dd*, doublet of doublet, *ddd*, doublet of doublet of doublet, *ddt*, doublet of triplet, *m*, multiplet) and coupling constant *J* in Hertz. The abbreviation *Ar* is used to denote aromatic, *br.* to denote broad and *app.* to denote apparent. Coupling constants, *J*, are measured to the nearest 0.1 Hz and are presented as observed. Accurate Mass measurements (HRMS) were recorded with a Waters LCP 1er XR spectrometer. HPLC analyses were performed with Daicel Chiralpak® columns (4.6 mm × 250 mm) and a mixture of heptane/*i*-PrOH solvents. A spectrosystem UV 1000 thermofisher detector and a chiral detector (polarimeter) JACSCO OR-1590 were used.

[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.*, 1978, **43**, 2923-2925.

II-Optimization of reaction conditions

II-1 Solvent selection

In order to prevent solubility issues, the screening of solvents was carried directly from *O*-methylisourea. Nevertheless, precipitation events did occurred, except in DMF, alcoholic solvents or MeCN/H_2O mixture. Furthermore, we homogeneously employed Hünig's base as acceleration was observed, although this was not general.

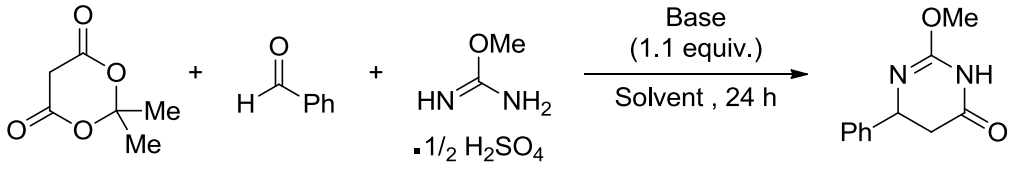


4 **5a** **9** **7aa**

Entry[a]	Solvent	Yield (%)[b,c]
1	Toluene	0
2	CF_3Ph	1
3	THF	7
4	1,4-dioxane	8
5	AcOEt	4
6	CH_2Cl_2	47
7	MeCN	55
8	DMF	51
9	H_2O	37
10	MeOH	85
11	EtOH	98
12	*i*-PrOH	82
13	MeCN/H_2O (9/1)	90
14	MeCN/EtOH (9/1)	91

[a] Reaction conditions: Meldrum's acid **4** (0.10 mmol) at 0.10 M, 24 hours, 40 °C with benzaldehyde **5a** (1.0 equiv.), *O*-methylisourea **9** (1.0 equiv.) and Hünig's base (0.2 equiv.). [b] ^{1}H NMR yield determined by using Bn_2O as an internal standard. [c] Product observable as a mixture of $\Delta^{1,2}$: $\Delta^{2,3}$ tautomers.

II-2 Base screening

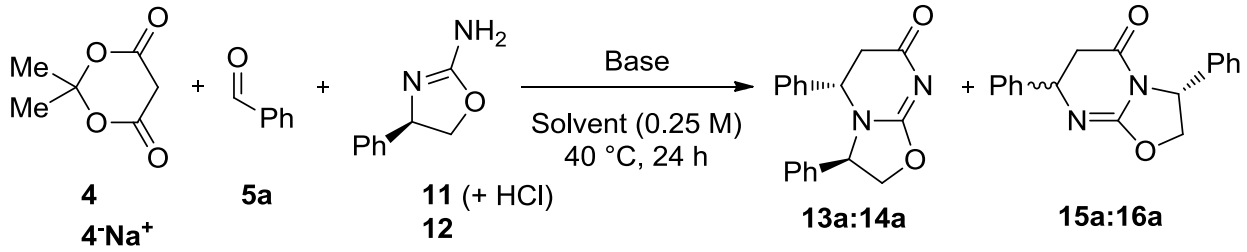


4 **5a** **1a** **7aa**

Entry[a]	Solvent	Conc. (M)	Base	T (°C)	Yield (%)[b,c]
1	EtOH	0.10	Na_2CO_3	40	81
2	MeCN/H_2O (9/1)	0.10	Na_2CO_3	40	87
3	MeCN/H_2O (9/1)	0.10	-	40	2
4	MeCN/H_2O (9/1)	0.10	NaOH	40	79
5	MeCN/H_2O (9/1)	0.10	K_2CO_3	40	79
6	MeCN/H_2O (9/1)	0.10	Cs_2CO_3	40	59
7	MeCN/H_2O (9/1)	0.10	$NaHCO_3$	40	83
8	MeCN/H_2O (9/1)	0.25	Na_2CO_3	20	7
9	MeCN/H_2O (9/1)	0.25	Na_2CO_3	40	92
10	MeCN/H_2O (9/1)	0.25	Na_2CO_3	60	88

[a] Reaction conditions: Meldrum's acid **4** (0.1 mmol), benzaldehyde **5a** (1.0 equiv.), *O*-methylisourea hemisulfate salt **1a** (1.0 equiv.) and base (1.1 equiv.) in solvent during 24 hours. [b] ^1H NMR yield determined by using Bn_2O as an internal standard. [c] Product observable as a mixture of $\Delta^{1,2}$: $\Delta^{2,3}$ tautomers.

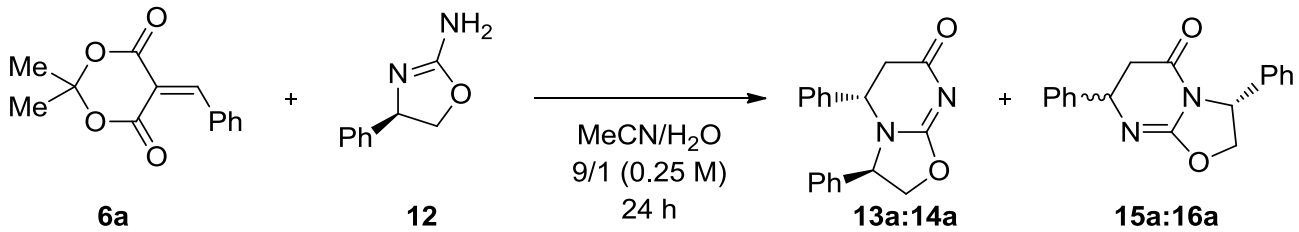
II-3 Diastereoselective reaction



4 / **4⁻Na⁺** **5a** **11** (+ HCl) / **12** **13a:14a** **15a:16a**

Entry[a]	**4** or **4⁻Na⁺**	**11** or **12**	Base	Solvent	**13a/14a/15a/16a**[b]	**13a/14a**[b]	**15a/16a**[b]
1	**4**	**12**	Na_2CO_3 1.1 equiv.	MeCN/H_2O (9/1)	45/5/43/7	90/10	86/14
2	**4⁻Na⁺**	**12**	-	MeCN/H_2O (9/1)	61/5/29/5	92/8	85/15
3	**4**	**11**	-	MeCN/H_2O (9/1)	64/6/25/5	91/9	83/17
4	**4**	**11**	-	EtOH	(68)/25/7	n.d.	78/22

[a] Reaction conditions: Meldrum's acid **4** (0.10 mmol) or Meldrum's acid sodium salt **4⁻Na⁺** (0.10 mmol), benzaldehyde **5a** (1.0 equiv.), (4*R*)-4-phenyloxazolidin-2-ylidene amine **12** (1.0 equiv.) or (4*R*)-4-phenyloxazolidin-2-ylidene amine hydrochloride salt **11** (1.0 equiv.) in solvent (0.25 M) during 24 hours. [b] Ratio determined by NMR.

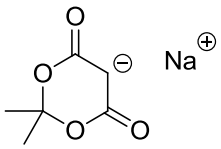


6a **12** **13a:14a** **15a:16a**

Entry[a]	T (°C)	**13a/14a/15a/16a**[b]	**13a/14a**[b]	**15a/16a**[b]
1[c]	40	63/5/27/5	92/8	85/15
2[c]	20	66/6/23/5	92/8	84/16
3	0	traces	-	-

[a] Reaction conditions: benzylidene Meldrum's acid **6a** (0.10 mmol) and (4*R*)-4-phenyloxazolidin-2-ylidene amine **12** (1.0 equiv.) in MeCN/H_2O, 9/1 (0.25 M) for 24 hours. [b] Ratio determined by NMR. [c] 100% conversion by ^1H NMR.

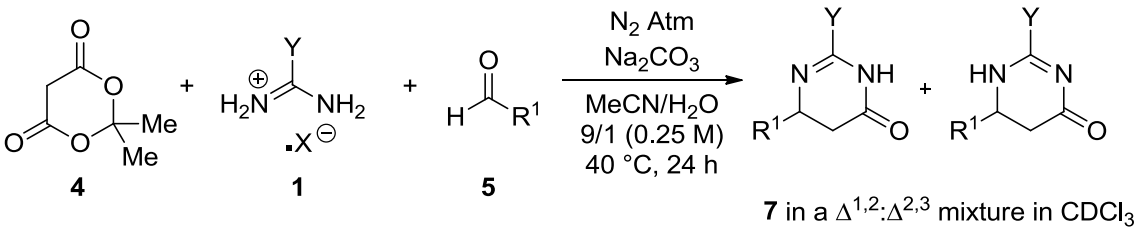
III-Experimental procedures



Meldrum's acid sodium salt ($4^{-}Na^{+}$).[2]

To a solution of Meldrum's acid **4** (360 mg, 2.50 mmol, 1.0 equiv.) in ethanol (10.0 mL) at 0°C under argon atmosphere was added sodium ethoxide (0.52 M) in ethanol (10 mL, 5.2 mmol, 2.1 equiv.). The mixture was allowed to warm to room temperature and stirred for 1 hour. The crude mixture was evaporated under reduced pressure and the residue precipitated in pentane to afford the title product as a white solid, (330.0 mg, 1.98 mmol, 79%). IR (neat) ν_{max} 2993, 1591, 1335, 1243, 1197, 1020, 780 cm^{-1}. ^{1}H NMR (300 MHz; DMSO-d_6) δ_H 3.22 (1H, s), 1.42 (6H, s). ^{13}C NMR (75 MHz; DMSO-d_6) δ_C 162.2 (C=O), 99.9 (C), 62.6 (CH), 26.0 (CH_3). HRMS (ESI^-): calcd for $C_6H_7O_4$ [$(2M+Na)^-$]: 305.0592; Found: 305.0592.

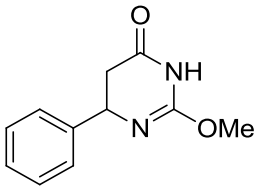
III-1 Racemic synthesis of pyrimidinones



Representative general procedure for the synthesis of pyrimidinones.

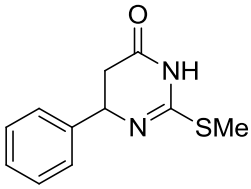
Meldrum's acid **4** (72.1 mg, 0.50 mmol, 1.0 equiv.), sodium carbonate (58.4 mg, 0.55 mmol, 1.1 equiv.) and isourea salt **1** under nitrogen atmosphere were dissolved in acetonitrile (1.8 mL) and water (0.2 mL). The aldehyde **5** was then added and the mixture stirred at 40 °C (oil bath temperature) for 24 hours. The crude reaction mixture was diluted with ethyl acetate and filtrated through celite. The filtrate was evaporated under reduced pressure and the resulting mixture was purified by column chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2/MeOH 98/2 unless otherwise mentioned) to afford product **7**.

[2] Kaumanns, O.; Mayr, H. *J. Org. Chem.* **2008**, *73*, 2738-2745.



2-methoxy-6-phenyl-5,6-dihydropyrimidin-4-one (7aa).

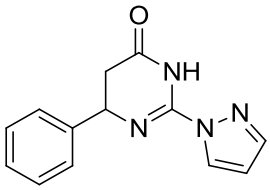
The title compound was prepared according to the above general procedure from benzaldehyde **5a** (51 µl, 0.50 mmol, 1.0 equiv.) and *O*-methylisourea hemisulfate salt **1a** (61.8 mg, 0.50 mmol, 1.0 equiv.). The product was isolated as a white solid (80.9 mg, 0.395 mmol, 79%), displaying a 86/14 mixture of $\Delta^{1,2}$ (*majo*) and $\Delta^{2,3}$ (*mino*) isomers by ^{1}H NMR in $CDCl_3$. R_f = 0.23 (CH_2Cl_2/MeOH 98/2). m.p. 146 °C. IR (neat) ν_{max} 3103, 2943, 1678, 1450, 1246, 757, 693 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.82 (1H *majo*, br s), 7.41-7.28 (5H *majo* and *mino*, m), 5.61 (1H *mino*, br s), 4.78 (1H *majo*, dd, *J* = 11.7, 5.3 Hz), 4.73 (1H *mino*, m), 3.95 (3H *mino*, s), 3.87 (3H *majo*, s), 2.79 (1H *mino*, m), 2.78 (1H *majo*, dd, *J* = 16.7, 5.3 Hz), 2.66 (1H *mino*, dd, *J* = 15.7, 11.4 Hz), 2.45 (1H *majo*, dd, *J* = 16.7, 11.8 Hz). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 178.3 (C=O *mino*), 171.3 (C=O *majo*), 165.2 (C2 *mino*), 151.1 (C2 *majo*), 142.7 (C Ar *majo*), 139.3 (C Ar *mino*), 129.4 (CH *mino*), 129.0 (CH *mino*), 128.8 (CH *majo*), 127.5 (CH *majo*), 126.4 (CH *majo* and *mino*), 56.0 (CH *majo*), 55.3 (CH_3 *mino*), 54.4 (CH_3 *majo*), 54.2 (CH *mino*), 39.1 (CH_2 *mino*), 38.4 (CH_2 *majo*). HRMS (ESI^+): calcd for $C_{11}H_{13}N_2O_2$ [$(M+H)^+$]: 205.0972; Found: 205.0977.



2-methylthio-6-phenyl-5,6-dihydropyrimidin-4(3*H*)-one (7ba).

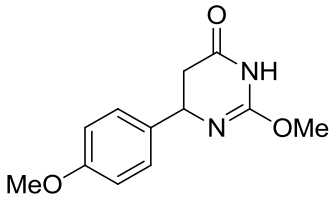
The title compound was prepared according to the above general procedure with benzaldehyde **5a** (51 µl, 0.50 mmol, 1.0 equiv.) and *S*-methyl isothiourea hemisulfate salt **1b** (69.7 mg, 0.50 mmol, 1.0 equiv.). The product was obtained as a white solid (104.7 mg, 0.475 mmol, 95%). The data were in accordance with literature.[3] R_f = 0.37 (CH_2Cl_2/MeOH 98/2). m.p. 165-166 °C. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 8.10 (1H, m), 7.39-7.28 (5H, m), 4.84 (1H, dd, *J* = 12.2, 5.2 Hz), 2.83 (1H, dd, *J* = 16.7, 5.2 Hz), 2.56-2.47 (1H, m), 2.50 (3H, s).

[3] Strekowski, L.; Watson, R. A.; Faunce, M. A. *Synthesis* **1987**, 579-581.



6-phenyl-2-(pyrazol-1-yl)-5,6-dihydropyrimidin-4-one (7ca).

The title compound was prepared according to the above general procedure from benzaldehyde **5a** (51 μl, 0.50 mmol, 1.0 equiv.) and pyrazole-1-carboximidamide hydrochloride salt[4] **1c** (73.5 mg, 0.50 mmol, 1.0 equiv.). The product was isolated as a transparent oil (104.3 mg, 0.434 mmol, 87%), displaying a 82/18 mixture of $\Delta^{1,2}$ (*majo*) and $\Delta^{2,3}$ (*mino*) by ^{1}H NMR. R_f = 0.05-0.15 (CH_2Cl_2/MeOH 98/2). IR (neat) ν_{max} 3400, 3247, 3150, 3063, 3030, 2901, 1721, 1678, 1474, 1391, 1280, 1205, 928, 759, 697 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 9.35 (1H *majo*, br s), 8.54 (1H *mino*, s), 8.39 (1H *majo*, d, *J* = 2.5 Hz), 7.91 (1H *mino*, br s), 7.73 (1H *mino*, s), 7.68 (1H *majo*, s), 7.41-7.29 (5H *majo* and *mino*, m), 6.48 (1H, *majo* and *mino*, s), 4.99 (1H *majo* and *mino*, dd, *J* = 12.2, 5.4 Hz), 2.99-2.77 (2H *mino*, m), 2.90 (1H *majo*, dd, *J* = 16.8, 5.4 Hz), 2.61 (1H *majo*, dd, *J* = 16.8, 12.2 Hz). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 177.6 (C=O *mino*), 169.0 (C=O *majo*), 154.8 (C2 *mino*), 144.4 (CH *mino*, C3"), 142.1 (C2 *majo*, C4), 142.0 (CH *majo*, C3"), 141.9 (C Ar *majo*), 138.6 (C Ar *mino*), 129.7 (CH *mino*), 129.5 (CH *mino*), 129.2 (CH *mino*), 128.9 (CH *majo*), 127.72 (CH *majo*), 127.67 (CH *majo*), 126.4 (CH *majo* and *mino*, C2'), 109.9 (CH *mino*, C4"), 109.5 (CH *majo*, C4"), 57.1 (CH *majo*), 54.4 (CH *mino*), 38.8 (CH_2 *mino*), 38.2 (CH_2 *majo*). HRMS (ESI$^+$): calcd for $C_{13}H_{13}N_4O$ [(M+H)$^+$]: 241.1084; Found: 241.1099.

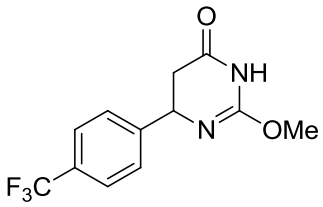


2-methoxy-6-(4-methoxyphenyl)-5,6-dihydropyrimidin-4-one (7ab).

The title compound was prepared according to the above general procedure from *p*-anisaldehyde **5b** (61 μl, 0.50 mmol, 1.0 equiv.) and *O*-methylisourea hemisulfate salt **1a** (61.8 mg, 0.50 mmol, 1.0 equiv.). The product was isolated as a light yellow solid (86.4 mg, 0.37 mmol, 74%), displaying a 83/17 mixture of $\Delta^{1,2}$ (*majo*) and $\Delta^{2,3}$ (*mino*) isomers by ^{1}H NMR in $CDCl_3$. R_f = 0.17 (CH_2Cl_2/MeOH 98/2). m.p. 133 °C. IR (neat) ν_{max} 3196, 3115, 2961, 2914, 2836, 1709, 1673, 1513, 1485, 1239, 1210, 1183, 1029, 906, 828, 708 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.89 (1H *majo*, br s), 7.30-7.26 (2H *majo* and *mino*, d, 8.7 Hz), 6.91-6.88 (2H *majo* and *mino*, d, 8.7 Hz), 5.60 (1H

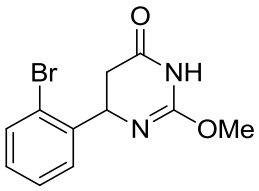
[4] Nilsson, B. L.; Overman, L. E. *J. Org. Chem.* **2006**, *71*, 7706-7714.

mino, br s), 4.74-4.69 (1H *majo* and *mino*, m), 3.86 (3H *majo* and *mino*, br s), 3.80 (3H *majo* and *mino*, s), 2.75 (1H *majo* and *mino*, dd, J = 16.5, 5.3 Hz), 2.48-2.39 (1H, m). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 178.7 (C=O *mino*), 172.0 (C=O *majo*), 165.2 (C4' *mino*), 159.9 (C2 *mino*), 158.8 (C4' *majo*), 151.1 (C2 *majo*), 134.8 (C1' *majo*), 131.3 (C1' *mino*), 127.5 (CH *mino*), 127.3 (CH *majo*), 114.5 (CH *mino*), 114.0 (CH *majo*), 55.33 (OCH_3 *majo*), 55.26 (CH *majo*), 55.1 (OCH_3 *mino*), 54.2 ($ArOCH_3$ *majo* and *mino*), 53.3 (CH *mino*), 38.9 (CH_2 *mino*), 38.3 (CH_2 *majo*). HRMS (ESI^+): calcd for $C_{12}H_{15}N_2O_3$ [$(M+H)^+$]: 235.1077; Found: 235.1080.



2-methoxy-6-(4-(trifluoromethyl)phenyl)-5,6-dihydropyrimidin-4(3*H*)-one (7ac).

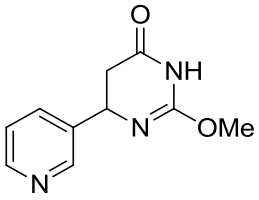
The title compound was prepared according to the above general procedure from 4-trifluoromethylbenzaldehyde **5c** (69 µl, 0.50 mmol, 1.0 equiv.) and *O*-methylisourea hemisulfate salt **1a** (61.8 mg, 0.50 mmol, 1.0 equiv.). The product was isolated as a white solid (107.3 mg, 0.395 mmol, 79%). R_f = 0.37 (CH_2Cl_2/MeOH 98/2). m.p. 139-140 °C. IR (neat) ν_{max} 3202, 3105, 2956, 2914, 1716, 1679, 1485, 1326, 1265, 1160, 1112, 1068, 1056, 1018 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.92 (1H, br s), 7.63 (2H, d, J = 8.2 Hz), 7.52 (2H, d, J = 8.1 Hz), 4.82 (1H, dd, J = 12.2, 5.2 Hz), 3.88 (3H, s), 2.79 (1H, dd, J = 16.7, 5.1 Hz), 2.42 (1H, dd, J = 16.6, 12.4 Hz). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 171.5 (C=O), 151.7 (C2), 146.8 (C1'), 129.7 (C4', q, J = 32 Hz), 126.8 (C2'), 125.7 (CH, C3', d, J = 3.5 Hz), 124.2 (CF_3, q, J = 272 Hz), 55.7 (CH), 54.4 (CH_3), 38.1 (CH_2). HRMS (ESI^+): calcd for $C_{12}H_{12}F_3N_2O_2$ [$(M+H)^+$]: 273.0845; Found: 273.0843.



6-(2-bromophenyl)-2-methoxy-5,6-dihydropyrimidin-4(3*H*)-one (7ad).

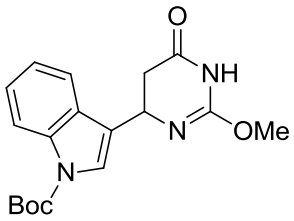
The title compound was prepared according to the above general procedure from 2-bromobenzaldehyde 97% **5d** (60 µl, 0.50 mmol, 1.0 equiv.) and *O*-methylisourea hemisulfate salt **1a** (61.8 mg, 0.50 mmol, 1.0 equiv.). The product was isolated as a white solid (119.8 mg, 0.425 mmol, 85%). R_f = 0.30 (CH_2Cl_2/MeOH 98/2). m.p. 133°C. IR (neat) ν_{max} 3203, 3112, 2957, 2913, 1718, 1681, 1261, 759 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.64 (1H, br s), 7.58-7.54 (2H, m), 7.36 (1H, td, J = 7.6, 1.0 Hz), 7.16 (1H, td, J = 7.6, 1.6 Hz), 5.11 (1H, dd, J = 12.2, 5.1 Hz), 3.89

(3H, s), 2.99 (1H, dd, J = 16.7, 5.2 Hz), 2.29-2.20 (1H, m). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 171.5 (C=O), 151.7 (C2), 142.0 (C1'), 132.9 (CH), 129.0 (CH), 128.4 (CH), 128.1 (CH), 122.5 (C2'), 55.9 (CH), 54.4 (CH_3), 36.5 (CH_2). HRMS (ESI^+): calcd for $C_{11}H_{12}BrN_2O_2$ [$(M+H)^+$]: 283.0077 and 285.0056; Found: 283.0090 and 285.0073.



2-methoxy-6-(pyridin-3-yl)-5,6-dihydropyrimidin-4(3*H*)-one (7ae).

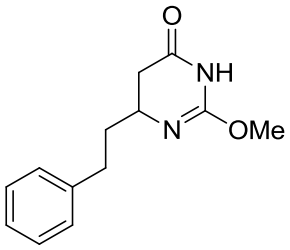
The title compound was prepared according to the above general procedure from 3-pyridine-carboxaldehyde **5e** (47 µl, 0.50 mmol, 1.0 equiv.) and *O*-methylisourea hemisulfate salt **1a** (61.8 mg, 0.50 mmol, 1.0 equiv.). The product was isolated as a white solid (34.7 mg, 0.17 mmol, 34%). R_f = 0.15 (CH_2Cl_2/MeOH 98/2). m.p. 134-136 °C. IR (neat) ν_{max} 3062, 2946, 2841, 2687, 1716, 1669, 1268, 899, 803, 720, 710 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 8.67 (1H, s), 8.55 (1H, s), 8.19 (1H, br s), 7.73 (1H, d, J = 7.9 Hz), 7.31 (1H, dd, J = 7.7, 4.9 Hz), 4.81 (1H, dd, J = 12.1, 5.2 Hz), 3.87 (3H, s), 2.80 (1H, dd, J = 16.6, 5.1 Hz), 2.43 (1H, dd, J = 16.5, 12.2 Hz). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 170.5 (C=O), 151.8 (C2), 148.8 (CH), 148.3 (CH), 138.3 (C Ar), 134.1 (CH), 123.7 (CH), 54.5 (CH_3), 54.0 (CH), 36.5 (CH_2). HRMS (ESI^+): calcd for $C_{10}H_{12}N_3O_2$ [$(M+H)^+$]: 206.0924; Found: 206.0928.



***tert*-butyl 3-(2-methoxy-5,6-dihydropyrimidin-4-one-6-yl)-indole-1-carboxylate (7ag)**

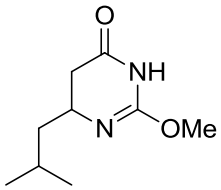
The title compound was prepared according to the above general procedure from *tert*-butyl 3-formyl-indole-1-carboxylate **5g** (122.8 mg, 0.50 mmol, 1.0 equiv.) and *O*-methylisourea hemisulfate salt **1a** (61.8 mg, 0.50 mmol, 1.0 equiv.). The product was purified by column chromatography on silica gel (EtOAc/Petroleum ether 30/70 with 5% NEt_3) and isolated as colorless oil (107.0 mg, 0.310 mmol, 62%), displaying a 88/12 mixture of $\Delta^{1,2}$ (*majo*) and $\Delta^{2,3}$ (*mino*) isomers by ^{1}H NMR in $CDCl_3$. R_f = 0.13 (EtOAc/PE 30/70 with 5% NEt_3). IR (neat) ν_{max} 3200, 2977, 1725, 1678, 1451, 1370, 1254, 1222, 1154, 1081, 745 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 8.13 (1H *majo* and *mino*, d, J = 8.2 Hz), 7.69 (1H *majo*, br s), 7.63 (1H *majo*, d, J = 7.8 Hz), 7.59-7.53 (1H *majo*

and 2H *mino*, m), 7.40-7.22 (2H *majo* and *mino*, m), 5.71 (1H *mino*, br s), 5.04 (1H *majo* an *mino*, dd, *J* = 10.2, 5.6 Hz), 3.96 (3H *mino*, s), 3.85 (3H *majo*, s), 2.96-2.87 (2H *mino*, m), 2.91 (1H, *majo*, dd, *J* = 16.6, 5.4 Hz), 2.68 (1H, *majo*, dd, *J* = 16.7, 10.2 Hz), 1.69 (9H, *mino*, s), 1.67 (9H, *majo*, s). ^{13}C NMR (75 MHz; $CDCl_3$) *majo* isomer only visible δ_C 171.0 (C=O), 151.3 (C C2), 149.9 (N(C=O)O), 136.1 (C C4'), 128.8 (C C9'), 124.7 (CH C6'), 122.7 (CH C2'), 122.5 (CH C7'), 122.1 (Cq C1'), 119.8 (CH C8'), 115.6 (CH C5'), 83.9 ($O\underline{C}(CH_3)_3$), 54.4 (OCH_3), 49.5 (CH C6), 36.2 (CH_2 C5), 28.3 ($OC(\underline{CH_3})_3$). HRMS (ESI^+): calcd for $C_{18}H_{22}N_3O_4$ [$(M+H)^+$]: 344.1605; Found: 344.1616.



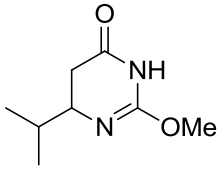
2-methoxy-6-phenethyl-5,6-dihydropyrimidin-4-one (7ah).

The title compound was prepared according to the above general procedure from hydrocinnamaldehyde **5h** (66 µl, 0.50 mmol, 1.0 equiv.) and *O*-methylisourea hemisulfate salt **1a** (61.8 mg, 0.50 mmol, 1.0 equiv.). The product was isolated as a white solid (94.2 mg, 0.405 mmol, 81%), displaying a 84/16 mixture of $\Delta^{1,2}$ (*majo*) and $\Delta^{2,3}$ (*mino*) isomers by ^{1}H NMR in $CDCl_3$. R_f = 0.17 (CH_2Cl_2/MeOH 98/2). m.p. 101.5 °C. IR (neat) ν_{max} 3175, 3118, 3025, 2945, 1713, 1682, 1484, 1451, 1257, 1246, 694 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 8.73 (1H *majo*, br s), 7.32-7.21 (5H *majo* and *mino*, m), 5.92 (1H *mino*, br s), 3.87 (3H *majo* and *mino*, m), 3.57 (1H *majo* and *mino*, m), 2.85-2.21 (4H *majo* and *mino*, m), 1.94-1.80 (2H *majo* and *mino*, m). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 179.0 (C=O *mino*), 172.7 (C=O *majo*), 164.8 (C2 *mino*), 150.2 (C2 *majo*), 141.7 (C Ar *majo*), 140.3 (C Ar *mino*), 128.6 (CH *mino*), 128.4 (CH *majo*), 128.3 (CH *majo*), 128.0 (CH *mino*), 126.4 (CH *mino*), 125.8 (CH *mino*),54.8 (CH_3 *mino*), 53.8 (CH_3 *majo*), 51.3 (CH *majo*), 48.7 (CH *mino*), 37.8 (CH_2 *majo*), 36.1 (CH_2 *mino*), 36.0 (CH_2 *mino*), 35.4 (CH_2, *majo*), 31.9 (CH_2 *majo*), 31.3 (CH_2 *mino*).HRMS (ESI^+): calcd for $C_{13}H_{17}N_2O_2$ [$(M+H)^+$]: 233.1285; Found: 233.1286.



6-isobutyl-2-methoxy-5,6-dihydropyrimidin-4-one (7ai).

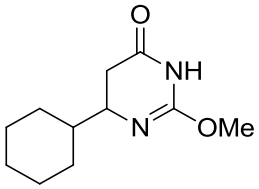
The title compound was prepared according to the above general procedure from isovaleraldehyde 97% **5i** (56 μl, 0.50 mmol, 1.0 equiv.) and *O*-methylisourea hemisulfate salt **1a** (61.8 mg, 0.50 mmol, 1.0 equiv.). The product was isolated as a white solid (68.8 mg, 0.375 mmol, 75%), displaying a 72/28 mixture of $\Delta^{1,2}$ (*majo*) and $\Delta^{2,3}$ (*mino*) isomers by ^{1}H NMR in $CDCl_3$. R_f = 0.18 (CH_2Cl_2/MeOH 98/2). m.p. 50-52 °C. IR (neat) ν_{max} 3195, 3115, 2951, 2920, 2869, 1712, 1680, 1471, 1245, 908 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.76 (1H *majo*, br s), 5.43 (1H *mino*, br s), 3.88 (3H *mino*, s), 3.76 (3H *majo*, s), 3.70-3.59 (1H *majo* and *mino*, m), 2.62 (1H *mino*, dd, *J* = 15.5, 5.4 Hz), 2.50 (1H *majo*, dd, *J* = 16.6, 5.4 Hz), 2.30 (1H *mino*, dd, *J* = 15.5, 9.8 Hz), 2.17 (1H *majo*, dd, *J* = 16.6, 9.5 Hz), 1.86-1.22 (3H *majo* and *mino*, m), 0.94-0.91 (6H *majo* and *mino*, m).^{13}C NMR (75 MHz; $CDCl_3$) δ_C 179.2 (C=O *mino*), 172.6 (C=O *majo*), 164.8 (C2 *mino*), 150.0 (C2 *majo*), 54.9 (CH_3 *mino*), 53.9 (CH_3 *majo*), 50.3 (CH *majo*), 47.5 (CH *mino*), 45.4 (CH_2 *majo*), 43.9 (CH_2 *mino*), 36.7 (CH_2 *mino*), 35.8 (CH_2 *majo*), 24.6 (CH *majo*), 24.3 (CH *mino*), 22.7 (CH_3 *majo*), 22.6 (CH_3 *majo*), 22.5 (CH_3 *mino*), 22.4 (CH_3 *mino*). HRMS (ESI$^+$): calcd for $C_9H_{17}N_2O_2$ [(M+H)$^+$]: 185.1285; Found: 185.1284.



6-isopropyl-2-methoxy-5,6-dihydropyrimidin-4-one (7aj).

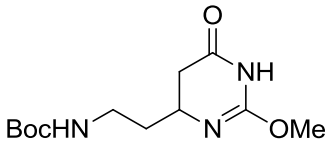
The title compound was prepared according to the above general procedure from isobutyraldehyde 98% **5j** (47 μl, 0.50 mmol, 1.0 equiv.) and *O*-methylisourea hemisulfate salt **1a** (61.8 mg, 0.50 mmol, 1.0 equiv.). The product was isolated as a white solid (76.4 mg, 0.450 mmol, 90%), displaying a 72/28 mixture of $\Delta^{1,2}$ (*majo*) and $\Delta^{2,3}$ (*mino*) isomers by ^{1}H NMR in $CDCl_3$. R_f = 0.13 (CH_2Cl_2/MeOH 98/2). m.p. 55-57 °C. IR (neat) ν_{max} 3196, 3114, 2944, 2912, 2895, 2869, 2851, 1714, 1675, 1484, 1472, 1256, 1044, 904 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.58 (1H *majo*, br s), 5.40 (1H *mino*, br s), 3.89 (3H *mino*, s), 3.77 (3H *majo*, s), 3.44-3.29 (1H *majo* and *mino*, m), 2.58 (1H *mino*, dd, *J* = 15.6, 5.7 Hz), 2.45 (1H *majo*, dd, *J* = 16.6, 5.4 Hz), 2.40 (1H *mino*, dd, *J* = 15.8, 7.8 Hz), 2.22 (1H *majo*, dd, *J* = 16.6, 11.3 Hz), 1.84-1.72 (1H *majo* and *mino*, m), 0.97 (3H, *majo* and *mino*, d, *J* = 6.8 Hz), 0.94 (3H, *majo* and *mino*, d, *J* = 6.7 Hz). ^{13}C NMR (75 MHz; $CDCl_3$)

δ_C 179.5 (C=O *mino*), 173.1 (C=O *majo*), 165.1 (C2 *mino*), 149.9 (C2 *majo*), 57.7 (CH C6 *majo*), 55.0 (OCH_3 *mino*), 54.8 (CH C6 *mino*), 53.8 (OCH_3 *majo*), 33.4 (CH_2 *mino*), 33.3 (CH(CH_3)$_2$ *majo*), 32.6 (CH_2 *majo*), 32.0 (CH(CH_3)$_2$ *mino*), 18.62 (CH_3 *majo*), 18.56 (CH_3 *majo*), 18.1 (CH_3 *mino*), 17.9 (CH_3 *mino*). HRMS (ESI^+): calcd for $C_8H_{15}N_2O_2$ [$(M+H)^+$]: 171.1128; Found: 171.1126.



6-cyclohexyl-2-methoxy-5,6-dihydropyrimidin-4-one (7ak).

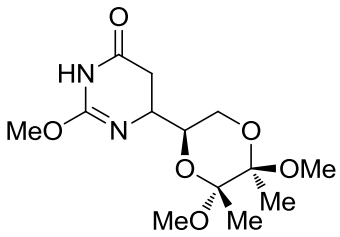
The title compound was prepared according to the above general procedure from cyclohexanecarboxaldehyde **5k** (62 µl, 0.50 mmol, 1.0 equiv.) and *O*-methylisourea hemisulfate salt **1a** (61.8 mg, 0.50 mmol, 1.0 equiv.). The product was isolated as a white solid (92.3mg, 0.440 mmol, 88%), displaying a 75/25 mixture of $\Delta^{1,2}$ (*majo*) and $\Delta^{2,3}$ (*mino*) isomers by ^{1}H NMR in $CDCl_3$. R_f = 0.14 (CH_2Cl_2/MeOH 98/2). m.p. 119 °C. IR (neat) ν_{max} 3202, 3101, 2926, 2850, 1712, 1675, 1480, 1266, 1251, 702 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 8.71 (1H *majo*, br s), 6.05 (1H *mino*, br s), 3.82 (3H *mino*, s), 3.73 (3H *majo*, s), 3.44-3.24 (1H *majo* and *mino*, m), 2.58-2.14 (2H *majo* and *mino*, m), 1.92-1.56 (5H *majo* and *mino*, m), 1.48-1.32 (1H *majo* and *mino*, m),1.30-0.88 (5H *majo* and *mino*, m). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 179.5 (C=O *mino*), 173.2 (C=O *majo*), 165.0 (C2 *mino*), 149.8 (C2 *majo*), 57.0 (CH *majo*, C6), 54.9 (CH_3 *mino*), 54.0 (CH *mino*, C6), 53.8 (CH_3 *majo*), 43.1 (CH *majo*, C1'), 41.7 (CH *mino*, C1'), 33.4 (CH_2 *mino*), 32.7 (CH_2 *majo*), 29.7 (CH_2 *mino*), 29.1 (CH_2 *majo*), 28.9 (CH_2 *majo*), 28.6 (CH_2 *mino*), 28.3 (CH_2 *mino*), 26.5 (CH_2 *majo*), 26.2 (CH_2 *majo*), 25.9 (CH_2 *mino*). HRMS (ESI^+): calcd for $C_{11}H_{19}N_2O_2$ [$(M+H)^+$]: 211.1441; Found: 211.1444.



2-methoxy-6-(2-((*tert*-butoxycarbonyl)amino)ethyl)-5,6-dihydropyrimidin-4-one (7al).

The title compound was prepared according to the above general procedure from 3-((*tert*-butoxycarbonyl)amino)propionaldehyde **5l** (87.0 mg, 0.50 mmol, 1.0 equiv.) and *O*-methylisourea hemisulfate salt **1a** (61.8 mg, 0.50 mmol, 1.0 equiv.). The product was isolated as a colorless oil (61.2 mg, 0.226 mmol, 45%), displaying a 72/28 mixture of $\Delta^{1,2}$ (*majo*) and $\Delta^{2,3}$ (*mino*) isomers by ^{1}H NMR in $CDCl_3$. R_f = 0.10 (CH_2Cl_2/MeOH 98/2). IR (neat) ν_{max} 3318, 2977, 2933, 1677, 1526, 1366, 1247, 1166, 728 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 8.16 (1H *majo*, br s), 7.16

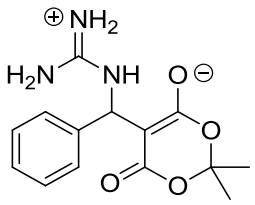
(1H *mino*, br s), 5.69 (1H *majo*, br s), 4.88 (1H *mino*, br s), 3.86 (3H *mino*, s), 3.76 (3H *majo*, s), 3.67-3.57 (1H *majo* and *mino*, m), 3.51-3.00 (2H *majo* and *mino*, m), 2.72 (1H *mino*, dd, J = 15.6, 7.0 Hz), 2.48 (1H *majo*, dd, J = 16.6, 5.0 Hz), 2.32 (1H *mino*, dd, J = 15.6, 4.3 Hz), 2.20 (1H *majo*, dd, J = 16.6, 11.6 Hz), 1.79-1.58 (2H *majo* and *mino*, m), 1.42 (9H *majo* and *mino*, m).^{13}C NMR (75 MHz; $CDCl_3$) δ_C 178.8 (C=O *mino*), 171.8 (C=O *majo*), 164.5 (C2 *mino*), 156.1 (N(C=O)O *majo* and *mino*), 150.5 (C2 *majo*), 80.1 (C6' *mino*), 78.9 (C6' *majo*), 54.8 (OCH_3 *mino*), 54.0 (OCH_3 *mino*), 51.7 (CH *majo*), 50.7 (CH *mino*), 45.8 (NCH_2 *majo* and *mino*), 36.5 (CH_2 C5 *mino*), 35.9 (CH_2 C5 *majo*), 35.7 (CH_2 C1'*majo* and *mino*), 28.5 ((CH_3)$_3$ *majo* and *mino*). HRMS (ESI$^+$): calcd for $C_{12}H_{22}N_3O_4$ [(M+H)$^+$]: 272.1605; Found: 272.1602.



6-((2*S*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-2-methoxy-5,6-dihydropyrimidin-4(3*H*)-one (7am).

Meldrum's acid sodium enolate **4**$^-$**Na**$^+$ (166.1 mg, 1.0 mmol, 1.0 equiv.), *O*-methylisourea hemisulfate salt **1a** (123.0 mg, 1.0 mmol, 1.0 equiv.) and Ley's aldehyde[5] **5m** (204.3 mg, 1.0 mmol, 1.0 equiv.) under nitrogen atmosphere were dissolved in acetonitrile (3.6 mL) and water (0.4 mL) and stirred at 40 °C for 24 hours. The crude reaction mixture was filtrated through fritted glass. The filtrate was evaporated under reduced pressure and the resulting mixture was purified twice by column chromatography on silica gel (EtOAc/Petroleum ether 70/30 and then CH_2Cl_2 to CH_2Cl_2/MeOH 98/2) and isolated as a white foam (153.3 mg, 0.51 mmol, 51%). R_f = 0.30 (EtOAc/Petroleum ether 70/30). R_f = 0.07 (CH_2Cl_2/MeOH 98/2). IR (neat) ν_{max} 3250, 2993, 2950, 2920, 2840, 1681, 1715, 1250, 1118, 1034, 874 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.94 (1H, br s), 3.89-3.53 (4H, m), 3.70 (3H s), 3.27 (3H, s), 3.22 (3H, s), 2.69 (1H, dd, J = 16.9, 5.7 Hz), 2.48 (1H, dd, J = 16.9, 8.2 Hz), 1.282 (3H, m), 1.280 (3H, m).^{13}C NMR (75 MHz; $CDCl_3$) δ_C 171.1 (C=O), 150.9 (C), 99.4 (C), 98.1 (C), 69.6 (CH), 62.5 (CH_2), 54.1 (CH_3), 53.8 (CH), 48.2 (CH_3), 48.1 (CH_3), 31.8 (CH_2), 17.9 (CH_3), 17.7 (CH_3). HRMS (ESI$^+$): calcd for $C_{13}H_{23}N_2O_6$ [(M+H)$^+$]: 303.1551; Found: 303.1554.

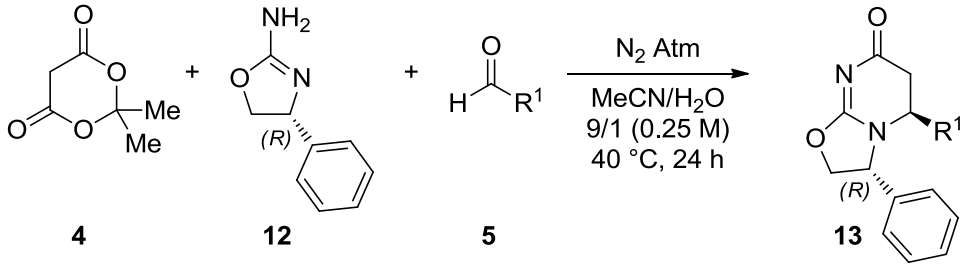
[5] Michel, P.; Ley, S. V. *Synthesis* **2003**, 1598–1602.



5-(((amino(iminio)methyl)amino)(phenyl)methyl)-2,2-dimethyl-4-oxo-1,3-dioxin-6-olate (10).

The title compound was prepared according to the above general procedure from benzaldehyde **5a** (51 μl, 0.50 mmol, 1.0 equiv.) and guanidine hydrochloride **1d** (47.9 mg, 0.50 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2/MeOH 90/10). The product was isolated as a white solid, (105.5 mg, 0.360 mmol, 72%). R_f = 0.36 (CH_2Cl_2/MeOH 90/10). m.p. 170-172 °C. IR (neat) ν_{max} 3339, 3168, 1620, 1538, 1400, 1371, 1259, 1200 cm^{-1}.^{1}H NMR (300 MHz; DMSO-d_6) δ_H 8.07 (1H, dd, J = 8.7 Hz), 7.39-7.13 (7H, m), 6.83 (2H, br s), 5.58 (1H, d, J = 8.7 Hz), 1.48 (6H, s).^{13}C NMR (75 MHz; DMSO-d_6) δ_C 164.9 (C=O), 156.2 (C guanidine), 142.9 (Cq Ar), 127.7 (2 CH), 126.0 (3 CH), 100.1 (<u>C</u>(CH_3)$_2$), 75.9 (C), 51.4 (CH-NH), 25.9 (C(<u>CH_3</u>)$_2$).HRMS (ESI$^+$): calcd for $C_{14}H_{18}N_3O_4$ [(M+H)$^+$]: 292.1292; Found: 292.1301.

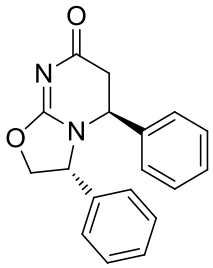
III-2 Diastereoselective synthesis of pyrimidinones



Representative general procedure for the diastereoselective synthesis of pyrimidinones.

Meldrum's acid **4** (72.1 mg, 0.50 mmol, 1.0 equiv.) and (4*R*)-4-phenyl-oxazolidin-2-ylidene amine[6] **12** (81.2 mg, 0.50 mmol, 1.0 equiv.) under nitrogen atmosphere were dissolved in acetonitrile (1.8 mL) and water (0.2 mL). The aldehyde **5** was then added and the mixture stirred at 40 °C for 24 hours. The crude reaction mixture of four compounds was evaporated under reduced pressure and the resulting mixture purified by column chromatography on silica gel to afford product **13**.

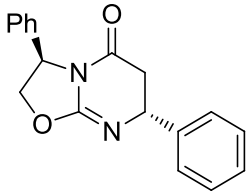
[6] Agami, C.; Cheramy, S.; Dechoux, L.; Melaimi, M. *Tetrahedron* **2001**, *57*, 195-200.



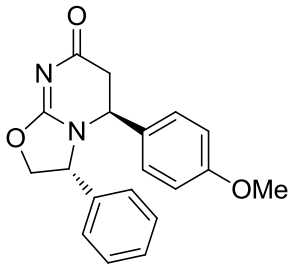
(3*R*,5*S*)-3,5-diphenyl-2,3,5,6-tetrahydro oxazolo [3,2-a] pyrimidin-7-one (13a)

The title compound was prepared according to the above general procedure from benzaldehyde **5a** (51 μL, 0.50 mmol, 1.0 equiv.). The crude mixture (**13a/14a/15a/16a** in a 64/6/25/5 ratio, 100% conversion) was purified by column chromatography on silica gel (AcOEt/MeOH 95/5) and the product was isolated as a white solid (81.5 mg, 0.277 mmol, 55%). The data were in accordance with literature for the opposite enantiomer.[6] R_f = 0.25 (AcOEt/MeOH 95/5). m.p. 90-91 °C. $[\alpha]_D^{20}$ −103 (c 0.50, $CHCl_3$). IR (neat) ν_{max} , 3060, 3033, 2926, 1668, 1563, 1444, 751, 697 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.42-7.36 (6H, m), 7.12-7.07 (4H, m), 4.86 (1H, app.t, *J* = 8.8 Hz), 4.66 (1H, dd, *J* = 8.6, 5.8 Hz), 4.47 (1H, dd, *J* = 9.0, 5.8 Hz), 4.31 (1H, app.t, *J* = 7.2 Hz), 2.92 (1H, dd, *J* = 16.2, 7.1 Hz), 2.74 (1H, dd, *J* = 16.2, 7.4 Hz). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 177.7 (C=O), 167.9 (O(C=N)N), 137.1 (C), 135.5 (C), 129.9 (CH), 129.7 (CH), 129.5 (CH), 129.3 (CH), 127.3 (CH), 126.9 (CH), 73.2 (CH_2), 60.8 (CH), 54.6 (CH), 37.8 (CH_2). HRMS (ESI^+): calcd for $C_{18}H_{17}N_2O_2$ [$(M+H)^+$]: 293.1285; Found: 293.1283.

(3*R*,7*R*)-3,7-diphenyl-2,3,6,7-tetrahydro oxazolo [3,2-a] pyrimidin-5-one (15a)

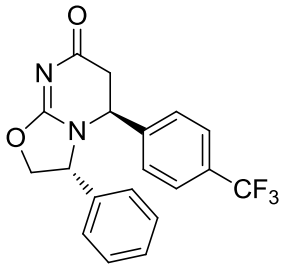


A second careful purification on column chromatography on silica gel of the other fractions (AcOEt/EP 30/70 to AcOEt 100%) allowed the isolation of product **15a** as a white amorphous solid (25.0 mg, 0.085 mmol, 17%). R_f = 0.4 (AcOEt/EP 50/50). ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.43-7.26 (11H, m), 5.44 (1H, dd, *J* = 8.2, 3.5 Hz), 4.86 (1H, dd, *J* = 13.7, 4.8 Hz), 4.73 (1H, app. t., *J* = 8.5 Hz), 4.44 (1H, dd, *J* = 8.8, 3.5 Hz), 2.80 (1H, dd, *J* = 17.1, 4.8 Hz), 2.47 (1H, dd, *J* = 17.1, 13.7 Hz). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 167.9 (C=O), 153.8 (C9), 142.5 (C), 138.5 (C), 129.3 (CH), 128.9 (CH), 128.8 (CH), 127.5 (CH), 126.4 (CH), 126.2 (CH), 72.6 (CH_2), 57.2 (CH), 56.5 (CH), 38.4 (CH_2). HRMS (ESI^+): calcd for $C_{18}H_{17}N_2O_2$ [$(M+H)^+$]: 293.1285; Found: 293.1285.



(3*R*,5*S*)-3-(4-methoxyphenyl)-5-phenyl-2,3,5,6-tetrahydro oxazolo [3,2-a] pyrimidin-7-one (13b).

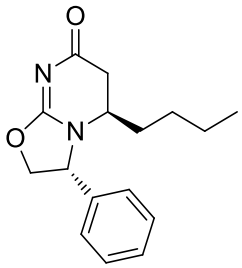
The title compound was prepared according to the above general procedure from *p*-anisaldehyde **5b** (61 μL, 0.50 mmol, 1.0 equiv.). The crude mixture (**13b/14b/15b/16b** in a 61/7/26/6 ratio, 88% conversion) was purified by column chromatography on silica gel (AcOEt/MeOH 95/5) and the product was isolated as a white solid (84.0 mg, 0.26 mmol, 52%). R_f = 0.15 (AcOEt/MeOH 95/5). m.p. 170-172 °C. $[\alpha]_D^{20}$ −106 (c 0.50, $CHCl_3$). IR (neat) ν_{max} 2920, 2840, 1683, 1558, 1513, 1444, 1248, 1021, 701 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.44-7.39 (3H, m), 7.15-7.10 (2H, m), 7.02-6.98 (2H, m), 6.89-6.85 (2H, m), 4.84 (1H, app.t, *J* = 8.8 Hz), 4.64 (1H, dd, *J* = 8.6, 5.9 Hz), 4.45 (1H, dd, *J* = 8.9, 5.9 Hz), 4.27 (1H, app.t, *J* = 7.2 Hz), 3.82 (3H, s), 2.90 (1H, dd, *J* = 16.2, 7.0 Hz), 2.73 (1H, dd, *J* = 16.2, 7.4 Hz). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 178.0 (C=O), 167.8 (O(C=N)N), 160.1 (C), 135.5 (C), 129.8 (CH), 129.7 (CH), 128.9 (C), 128.3 (CH), 127.3 (CH), 114.7 (CH), 73.2 (CH_2), 60.7 (CH), 55.5 (CH_3), 54.0 (CH), 37.8 (CH_2). HRMS (ESI^+): calcd for $C_{19}H_{18}N_2O_3$ [$(M+H)^+$]: 323.1390; Found: 323.1397.



(3*R*,5*S*)-3-phenyl-5-(4-trifluoromethylphenyl)-2,3,5,6-tetrahydro oxazolo [3,2-a] pyrimidin-7-one (13c).

The title compound was prepared according to the above general procedure from 4-trifluoromethylbenzaldehyde **5c** (69 μL, 0.50 mmol, 1.0 equiv.). The crude mixture (**13c/14c/15c/16c** in a 62/8/22/8 ratio, 100% conversion) was evaporated under reduced pressure and purified twice by column chromatography on silica gel (EtOAc/MeOH 95/5 then EtOAc/MeOH 99/1). The product was isolated as a white solid (83.0 mg, 0.23 mmol, 46%). R_f = 0.23 (AcOEt/MeOH 95/5). m.p. 167-169 °C. $[\alpha]_D^{20}$ −103 (c 0.50, $CHCl_3$). IR (neat) ν_{max} 2927, 1678, 1577, 1568, 1460, 1450, 1324, 1164, 1111, 1068, 1017, 700 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$)

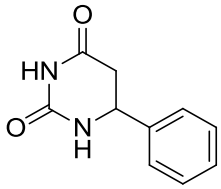
δ_H 7.65-7.62 (2H, m), 7.43-7.41 (3H, m), 7.26-7.23 (2H, m), 7.13-7.10 (2H, m), 4.90 (1H, app.t, *J* = 8.8 Hz), 4.67 (1H, dd, *J* = 8.5, 5.9 Hz), 4.50 (1H, dd, *J* = 9.0, 5.9 Hz), 4.39 (1H, app.t, *J* = 7.1 Hz), 2.94 (1H, dd, *J* = 16.2, 7.2 Hz), 2.70 (1H, dd, *J* = 16.2, 7.2 Hz). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 177.0 (C=O), 167.9 (O(C=N)N), 141.2 (C), 135.1 (C), 131.5 (C, q, *J* = 32.8 Hz), 130.1 (CH), 129.9 (CH), 127.4 (CH), 127.2 (CH), 126.56 (CH, q, *J* = 3.7 Hz), 123.7 (CF_3, q, *J* = 272.5 Hz), 73.3 (CH_2), 60.9 (CH), 54.0 (CH), 37.5 (CH_2). HRMS (ESI^+): calcd for $C_{19}H_{15}F_3N_2O_2$ $[(M+H)^+]$: 361.1158; Found: 361.1155.



(3*R*,5*R*)-5-butyl-3-phenyl-2,3,5,6-tetrahydro oxazolo [3,2-a] pyrimidin-7-one (13n).

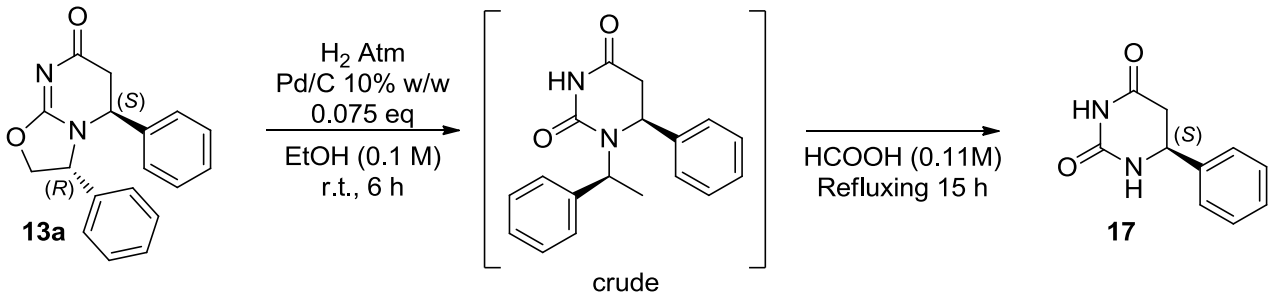
The title compound was prepared according to the above general procedure from valeraldehyde **5n** (54 μL, 0.50 mmol, 1.0 equiv.). The crude mixture (**13n/14n/15n/16n** in a 69/5/17/9 ratio, 100% conversion) was purified by column chromatography on silica gel (AcOEt/MeOH 98/2 to AcOEt/MeOH 95/5). The product was isolated as transparent oil (71.9 mg, 0.264 mmol, 53%). The data were in accordance with literature for the opposite enantiomer.[6] R_f = 0.13 (AcOEt/MeOH 95/5). $[\alpha]_D^{20}$ −119 (c 0.495, $CHCl_3$). IR (neat) ν_{max} , 3031, 2953, 2930, 2861, 2248, 1666, 1583, 1477, 917, 723, 700 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.49-7.43 (3H, m), 7.32-7.29 (2H, m), 5.02 (1H, dd, *J* = 8.7, 6.1 Hz), 4.88 (1H,app. t, *J* = 8.8 Hz), 4.40 (1H, dd, *J* = 8.9, 6.1 Hz), 3.36 (1H, m), 2.65 (1H, dd, *J* = 15.9, 6.8 Hz), 2.48 (1H, dd, *J* = 15.9, 5.5 Hz), 1.67-1.45 (2H, m), 1.32-1.22 (4H, m), 0.84 (3H, t, *J* = 6.9 Hz). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 178.3 (C=O), 167.5 (O(C=N)N), 136.0 (C), 129.90 (CH), 129.88 (CH), 126.9 (CH), 73.4 (CH_2), 60.8 (CH), 49.6 (CH), 34.6 (CH_2), 31.0 (CH_2), 26.7 (CH_2), 22.5 (CH_2), 13.9 (CH_3). HRMS (ESI^+): calcd for $C_{16}H_{21}N_2O_2$ [$(M+H)^+$]: 273.1598; Found: 273.1599.

III-3 Chemical Transformations



6-phenyldihydropyrimidine-2,4-dione. (17).

The title compound was prepared by heating **7aa** (40.8 mg, 0.20 mmol, 1.0 equiv.) in a mixture of methanol (0.05mL) and HCl (2M) (0.6 mL, 0.12 mmol, 0.6 equiv.) at 60°C for 1.5 hours. The crude material was treated with saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The organic phase was dried with Na_2SO_4 and after filtration evaporated under reduced pressure to afford **17** as a white solid (35.0 mg, 0.184 mmol, 92%). m.p. 217 °C (Pentane). The data were in accordance with literature.[7] See below for analysis.

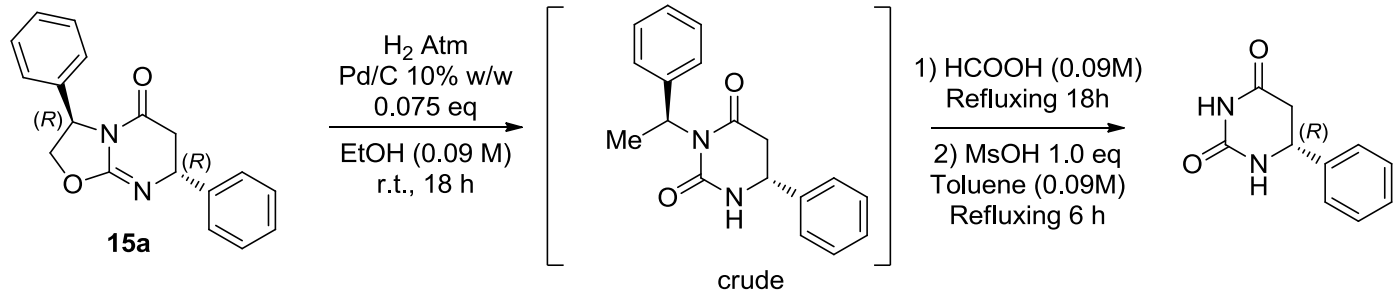


(6*S*)-6-phenyldihydropyrimidine-2,4-dione (17).

For determination of relative configuration. **13a** (57.5 mg, 0.20 mmol, 1.0 equiv.) was stirred in ethanol (2.0 mL) with Pd/C 10% w/w (16.0 mg, 0.015 mmol, 0.075equiv.) at room temperature for 6 hours H_2 atmosphere. The crude mixture was filtrated on celite with dichloromethane and evaporated under reduced pressure.[6] The resulting off-white solid was dissolved in formic acid (1.8 mL) and heated to reflux (~ 110°C) for 15 hours.[8] The crude mixture was filtrated on celite and evaporated under reduced pressure (Caution: evaporate under fume hood). The resulting solid was washed with diethyl ether to give the titled compound as a white solid (31.5 mg, 0.165 mmol, 83%, ee > 99%). The data were in accordance with literature.[7] m.p. 217-219 °C (Et_2O). $[\alpha]_D^{20}$ was not measurable due to solubility issues. ^1H NMR (300 MHz; DMSO-d_6) δ_H 10.17 (1H, s), 8.0 (1H, s), 7.40-7.27 (5H, m), 4.67 (1H, m), 2.84 (1H, dd, J = 16.4, 5.8 Hz), 2.61 (1H, dd, J = 16.4, 6.8 Hz). HPLC analysis: chiral

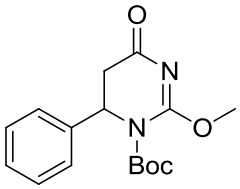
[7] Světlík, J.; Veizerová, L. *Helvetica Chimica Acta* **2011**, *94*, 199-205.
[8] Aitken, D.; Fernandes, C.; Gauzy, C.; Yang, Y.; Roy, O.; Pereira, E.; Faure, S. *Synthesis* **2007**, 2222-2232.

column IC (Heptane/*i*-PrOH: 70/30, flow rate 1 mL/min, UV 210 nm, T ~ 25 °C, t = 18.2 min for minor enantiomer *R*; t = 22.7 min for major enantiomer *S*).[9]



(6*R*)-6-phenyldihydropyrimidine-2,4-dione (17).

15a (19.5 mg, 0.067 mmol, 1.0 equiv.) was stirred in ethanol (0.75 mL) with Pd/C 10% w/w (5.5 mg, 0.005 mmol, 0.075equiv.) at room temperature for 18 hours under H_2 atmosphere. The crude mixture was filtrated on celite with dichloromethane and evaporated under reduced pressure.[6] The resulting off-white solid was dissolved in formic acid (0.75 mL) and heated to reflux (~ 110°C) for 18 hours.[8] The crude mixture was filtrated on celite and evaporated under reduced pressure (Caution: evaporate under fume hood). As the crude mixture showed no changes it was diluted in toluene, methane sulfonic acid (46 µl, 0.067 mmol, 1.0 equiv) was added and the medium was heated to reflux for 6 hours.[10] The crude mixture was evaporated under reduced pressure (Caution: evaporate under fume hood). The resulting solid was washed with diethyl ether to give the titled compound as a white solid (4.7 mg, 0.025 mmol, 37%, ee > 99%). The data were in accordance with literature.[7] See before for analysis. HPLC analysis: chiral column IC (Heptane/*i*-PrOH: 70/30, flow rate 1 mL/min, UV 210 nm, T ~ 20 °C, t = 19.7 min for major enantiomer *R*; t = 23.9 min for minor enantiomer *S*).[9]

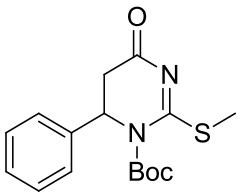


***tert*-butyl 2-methoxy-4-oxo-6-phenyl-5,6-dihydropyrimidine-1-carboxylate (18).**

The title compound was prepared by mixing **7aa** (102.2 mg, 0.50 mmol, 1.0 equiv.), di-*tert*-butyl dicarbonate (132.4 mg, 0.60 mmol, 1.2 equiv.) and DMAP (2.0 mg, 0.02 mmol, 0.04 equiv.) in acetonitrile (2.0 mL) at room temperature for 15 h. The solvent was evaporated under reduced pressure and the crude mixture purified by column chromatography on silica gel (CH_2Cl_2 to

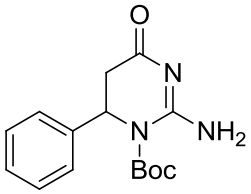
[9] *R* and *S* attributions are made assuming the configuration of the starting material is retained.
[10] Paik, S.; Lee, J. Y. *Tetrahedron Letters* **2006**, *47,* 1813-1815.

CH_2Cl_2/MeOH 99/1) The product was isolated as a yellow solid, (152.6 mg, 0.50 mmol, 99%). R_f = 0.16 (CH_2Cl_2/MeOH 99/1). m.p. 136-137 °C. IR (neat) ν_{max} 2979, 1750, 1700, 1551, 1131, 1098 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.33-7.18 (5H, m), 5.47 (1H, dd, *J* = 7.3, 2.7 Hz), 4.05 (3H, s), 3.04 (1H, dd, *J* = 15.8, 7.3 Hz), 2.86 (1H, dd, *J* = 15.8, 2.8 Hz), 1.38 (9H, s). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 176.0 (C), 161.0 (C), 149.9 (C), 138.7 (C), 128.9 (CH), 128.2 (CH), 125.4 (CH), 84.5 (C), 56.6 (CH), 56.3 (OCH_3), 38.4 (CH_2), 27.6 (CH_3). HRMS (ESI^+): calcd for $C_{16}H_{21}N_2O_4$ [$(M+H)^+$]: 305.1496; Found: 305.1503.



***tert*-butyl 2-methylthio-4-oxo-6-phenyl-5,6-dihydropyrimidine-1-carboxylate (19).**

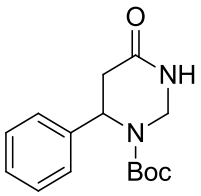
The title compound was prepared by mixing **7ba** (99.0 mg, 0.45 mmol, 1.0 equiv.), di-*tert*-butyl dicarbonate (119 mg, 0.54 mmol, 1.2 equiv.) and DMAP (2.3 mg, 0.016 mmol, 0.04 equiv.) in acetonitrile (2.0 mL) at room temperature for 7 h. The solvent was evaporated under reduced pressure and the crude mixture purified by column chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2/MeOH 99/1) The product was isolated as a yellow oil, (122.7 mg, 0.38 mmol, 85%). R_f = 0.70 (CH_2Cl_2/MeOH 99/1). IR (neat) ν_{max} 2980, 2928, 1732, 1695, 1490, 1302, 1274, 1250, 1133, 1105, 698 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.32-7.29 (3H, m), 7.13-7.10 (2H, m), 5.57 (1H, dd, *J* = 7.7, 2.1 Hz), 3.03 (1H, dd, *J* = 15.0, 7.6 Hz), 2.79 (1H, dd, *J* = 15.0, 2.1 Hz), 2.46 (3H, s), 1.36 (9H, s). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 172.0 (C), 171.9 (C), 151.1 (C), 138.9 (C), 129.1 (CH), 128.3 (CH), 125.1 (CH), 85.8 (C), 57.9 (CH), 37.7 (CH_2), 27.7 (CH_3), 16.7 (SCH_3). HRMS (ESI^+): calcd for $C_{16}H_{21}N_2O_3S$ [$(M+H)^+$]: 321.1267; Found: 321.1269.



***tert*-butyl 2-amino-4-oxo-6-phenyl-5,6-dihydropyrimidine-1-carboxylate (20).**

The title compound was prepared by mixing either **7aa** (61.0 mg, 0.20 mmol, 1.0 equiv.) or **7ba** (64.0 mg, 0.20 mmol, 1.0 equiv.) with ammonium chloride (5.4 mg, 0.10 mmol, 0.5 equiv.) in THF (1.0 mL) at 0 °C in a sealed vessel. Then, gaseous ammonia was bubbled through for 30 min. After that time, the medium was heated at 70 °C for 7 h. Then, the solvent was evaporated under reduced pressure and the crude mixture purified by column chromatography on silica gel (CH_2Cl_2 to

CH_2Cl_2/MeOH 95/5). The product was isolated as a white solid (47.1 mg, 0.16 mmol, 81% from **7aa** and 52.1 mg, 0.18 mmol, 90% from **7ba**). R_f = 0.36 (CH_2Cl_2/MeOH 95/5). m.p. 248-249 °C. IR (neat) ν_{max} 3375, 2981, 2927, 1724, 1672, 1635, 1514, 1369, 1302, 1245, 1146, 1111, 757 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 8.77 (2H, br s), 7.34-7.17 (5H, m), 5.51 (1H, dd, *J* = 7.5, 1.8 Hz), 3.05 (1H, dd, *J* = 15.7, 7.5 Hz), 2.74 (1H, dd, *J* = 15.7, 1.9 Hz), 1.36 (9H, s). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 174.5 (C), 158.4 (C), 152.8 (C), 139.8 (C), 129.1 (CH), 128.1 (CH), 125.3 (CH), 85.7 (C), 56.5 (CH), 38.1 (CH_2), 27.8 (CH_3). HRMS (ESI^+): calcd for $C_{15}H_{20}N_3O_3$ [$(M+H)^+$]: 290.1499; Found: 290.1500.

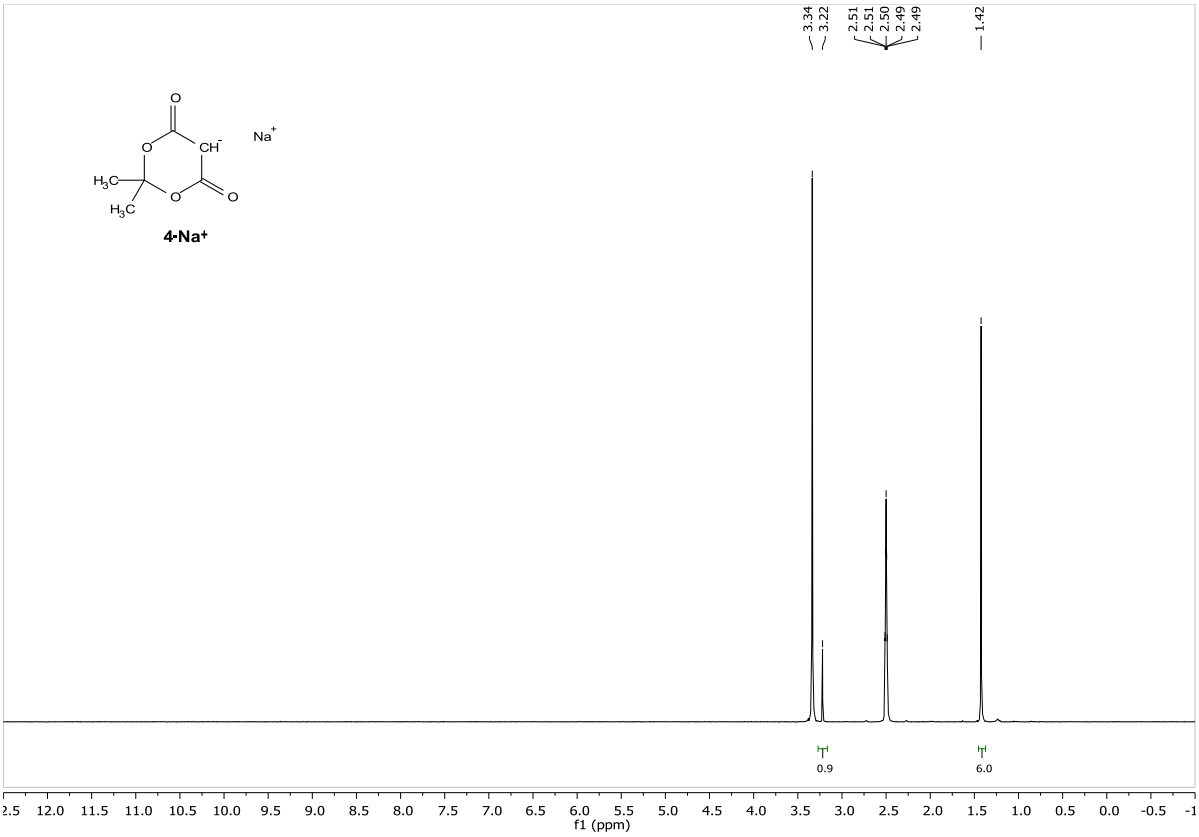


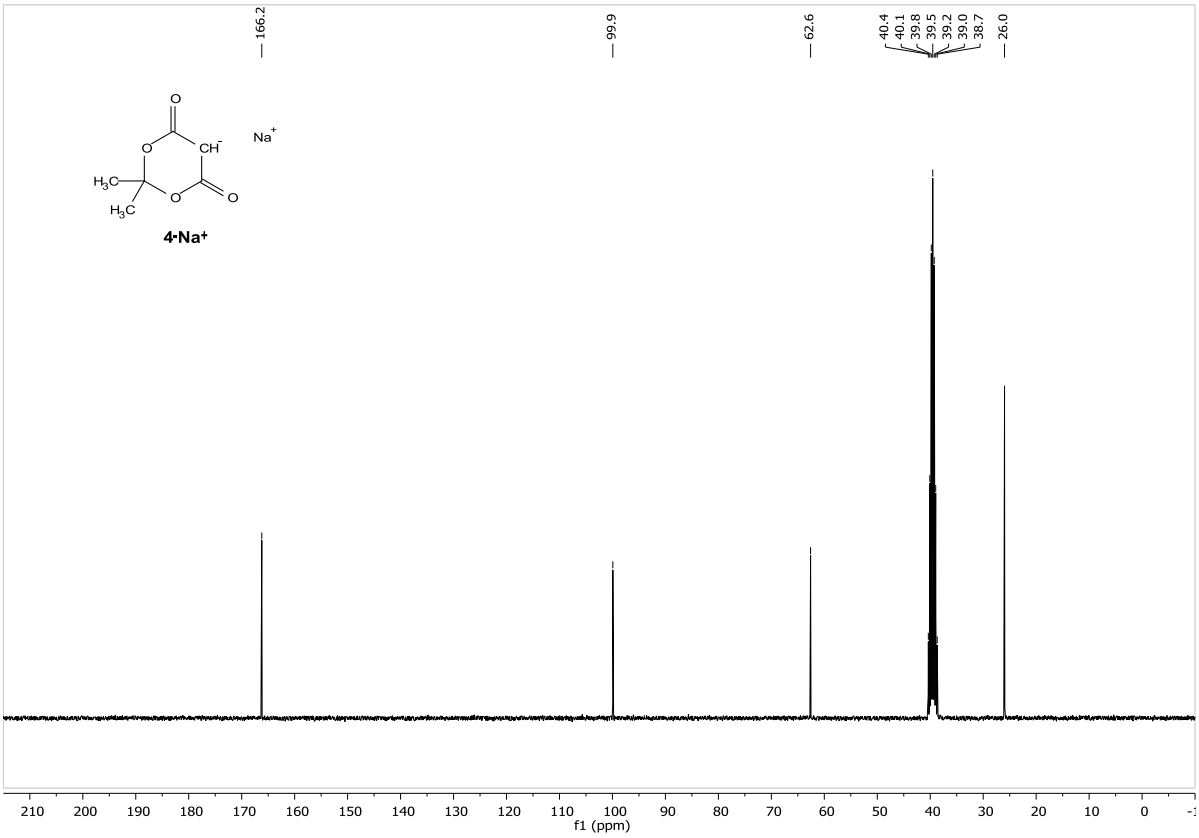
***tert*-butyl 4-oxo-6-phenyltetrahydropyrimidine-1-carboxylate (21).**

To a solution of **18** (60.9 mg, 0.20 mmol, 1.0 equiv.) in ethanol (4.0 mL) at 0°C under argon atmosphere was added sodium borohydride (22.8 mg, 0.60 mmol, 3.0 equiv.). The mixture was then heated at 40 °C for 15 hours. The crude mixture was evaporated under reduced pressure, diluted in CH_2Cl_2. The organic phase was washed with saturated aqueous Na_2CO_3, dried with Na_2SO_4, filtrated and the solvent was removed under reduced pressure. The product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH 98/2) and isolated as a white solid, (47.0 mg, 0.17 mmol, 85%). R_f = 0.10 (CH_2Cl_2/MeOH 98/2). m.p. 139-140 °C. IR (neat) ν_{max} 3267, 2980, 2927, 1684, 1657, 1403, 1365, 1154, 765, 698 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.76 (1H, s), 7.38-7.26 (5H, m), 5.60-4.90 (2H, C*H*H and C*H*CHH, br s), 4.53 (1H, CH*H*, br s), 2.85 (1H, CHC*H*H, dd, *J* = 16.1, 6.5 Hz), 2.70 (1H, CHCH*H*, dd, *J* = 16.1, 6.9 Hz), 1.33 (9H, s). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 171.7 (C=O), 153.9 (N(C=O)O), 142.0 (C, Ar), 128.8 (CH), 127.7 (CH), 125.8 (CH), 81.3 ($\underline{C}(CH_3)_3$), 54.4 (CH), 52.3 (CH_2), 39.1 (CH_2), 28.2 ($C(\underline{CH_3})_3$). HRMS (ESI^+): calcd for $C_{15}H_{20}N_2O_3$ [$(M+H)^+$]: 277.1547; Found: 277.1555.

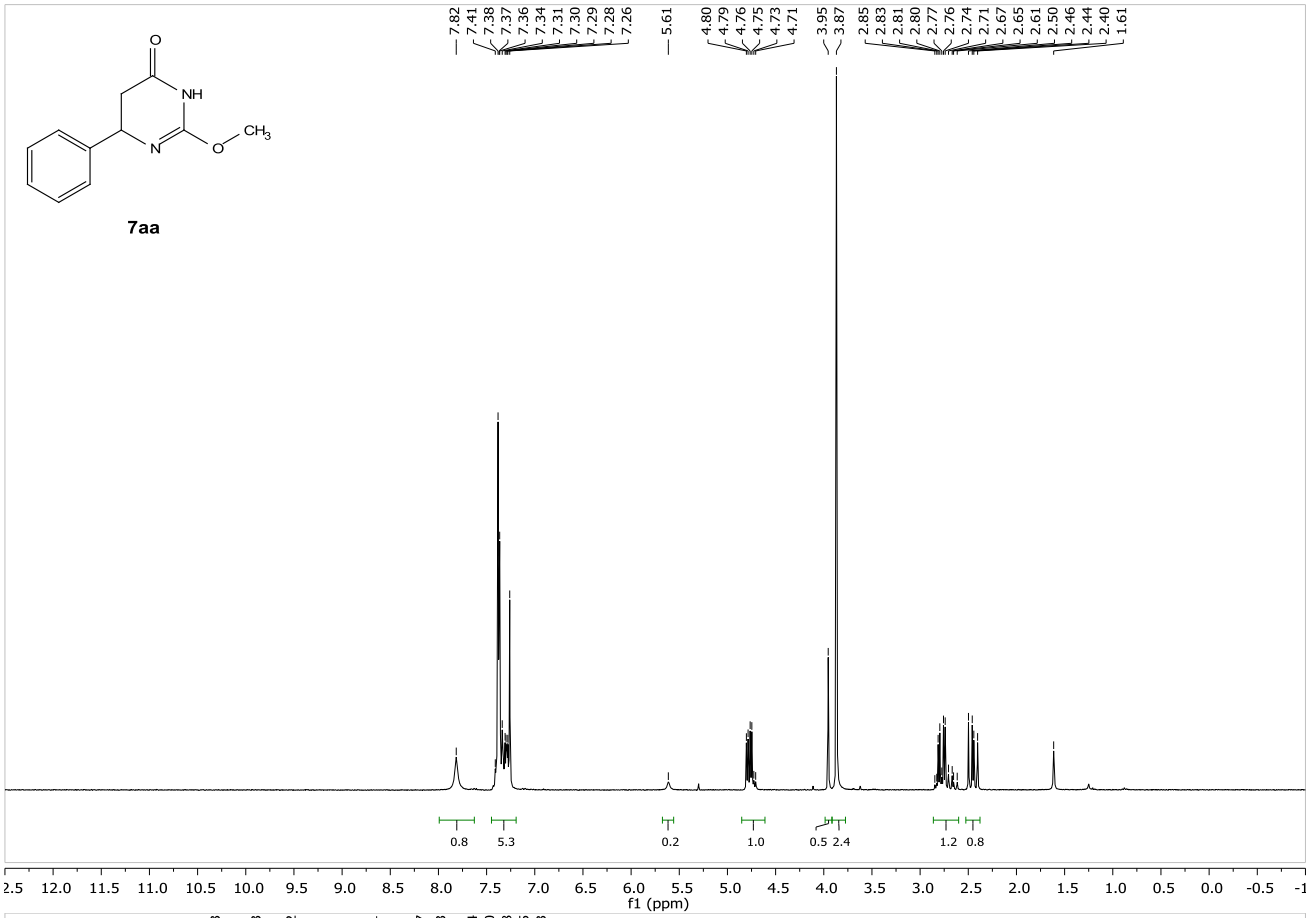
IV-NMR spectra and HPLC chromatograms

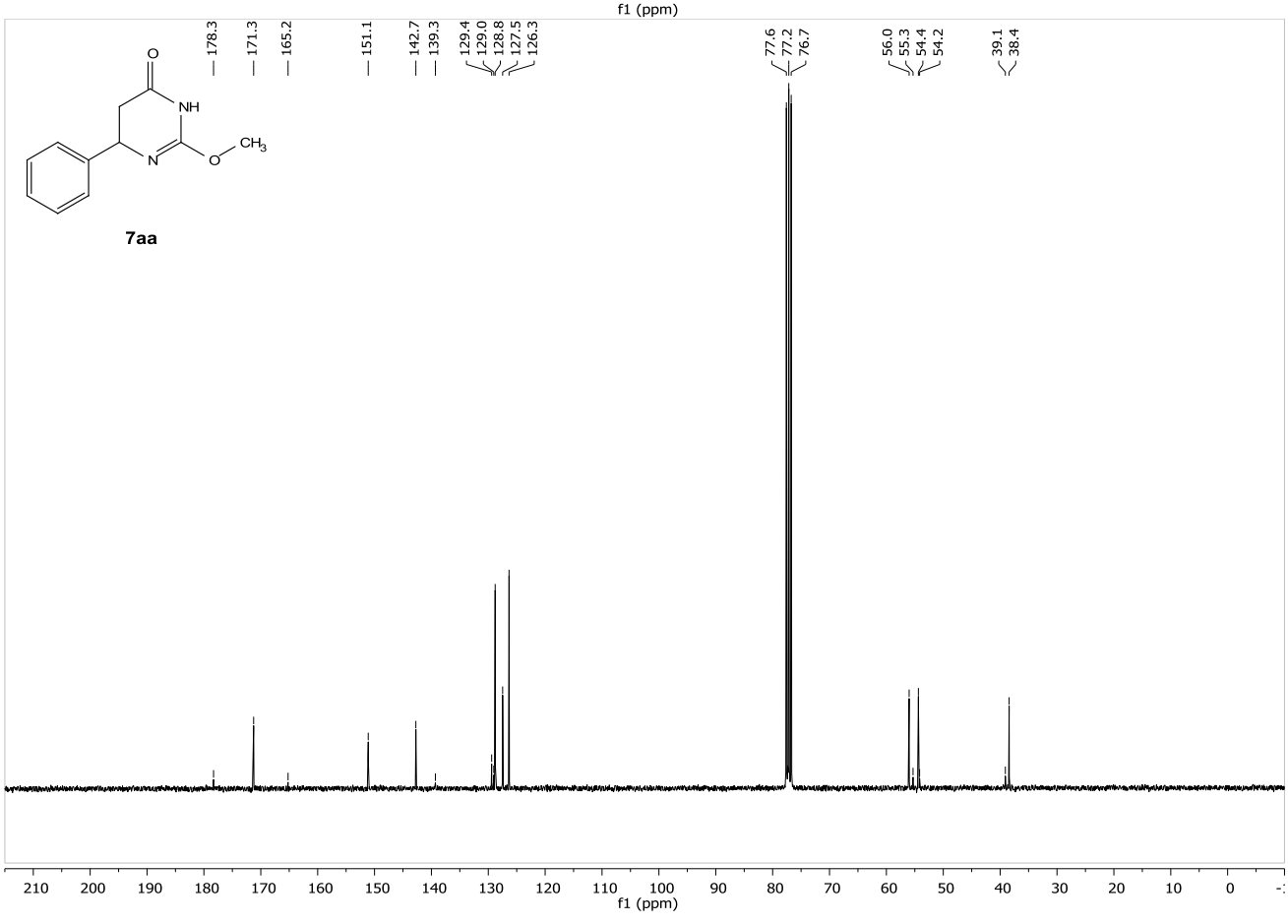
Meldrum's acid sodium salt ($4^{-}Na^{+}$).



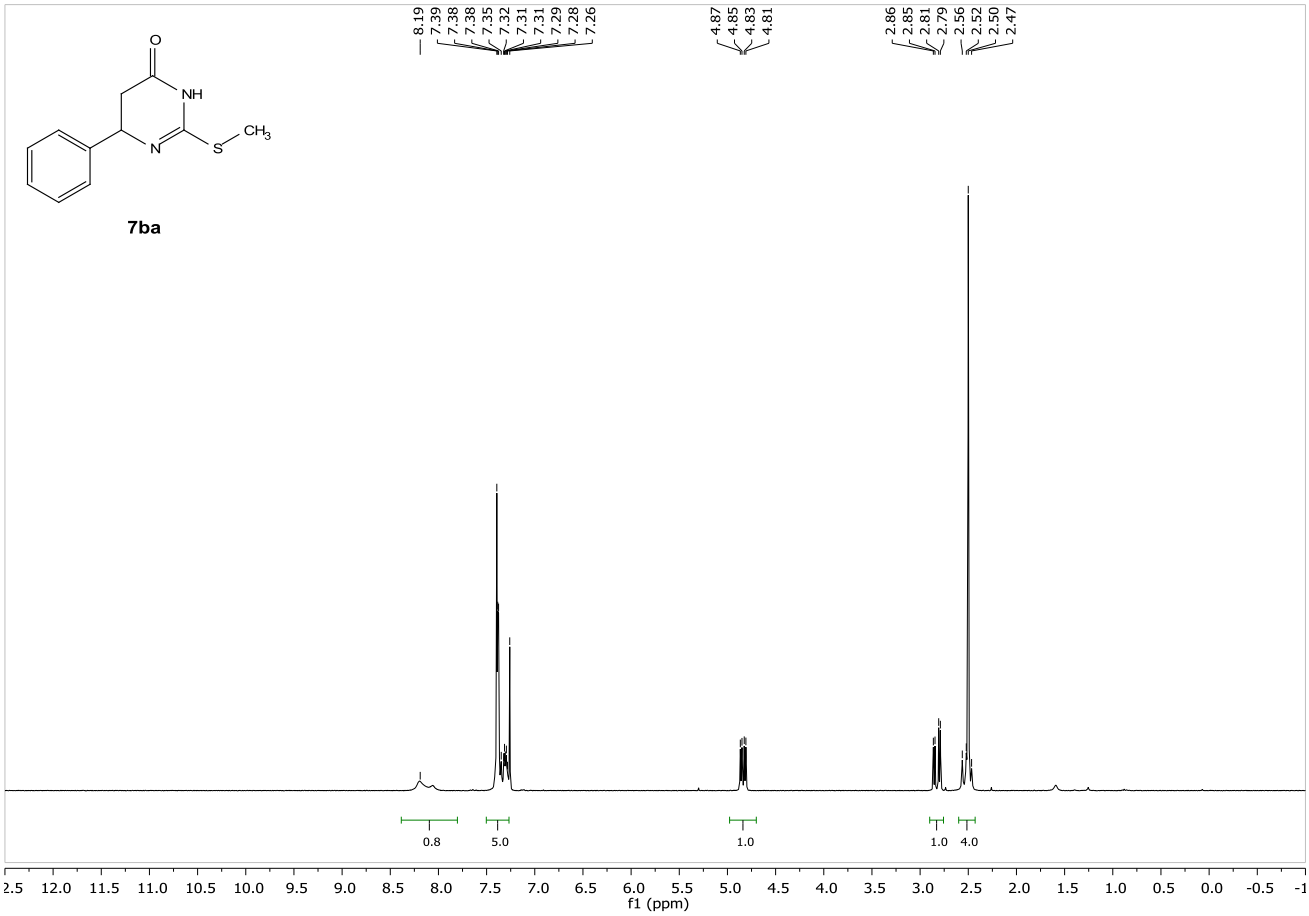


2-methoxy-6-phenyl-5,6-dihydropyrimidin-4-one (7aa).

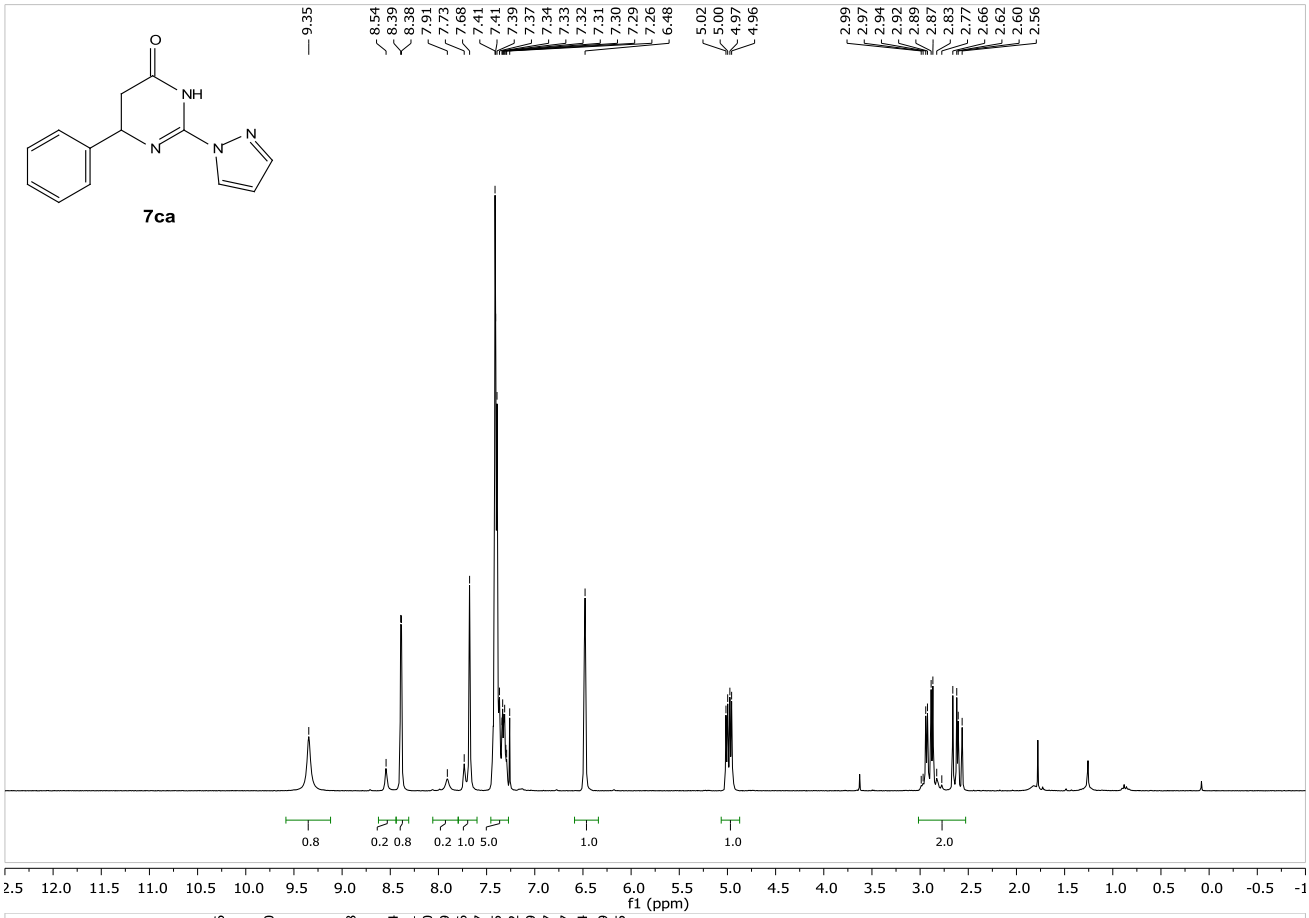


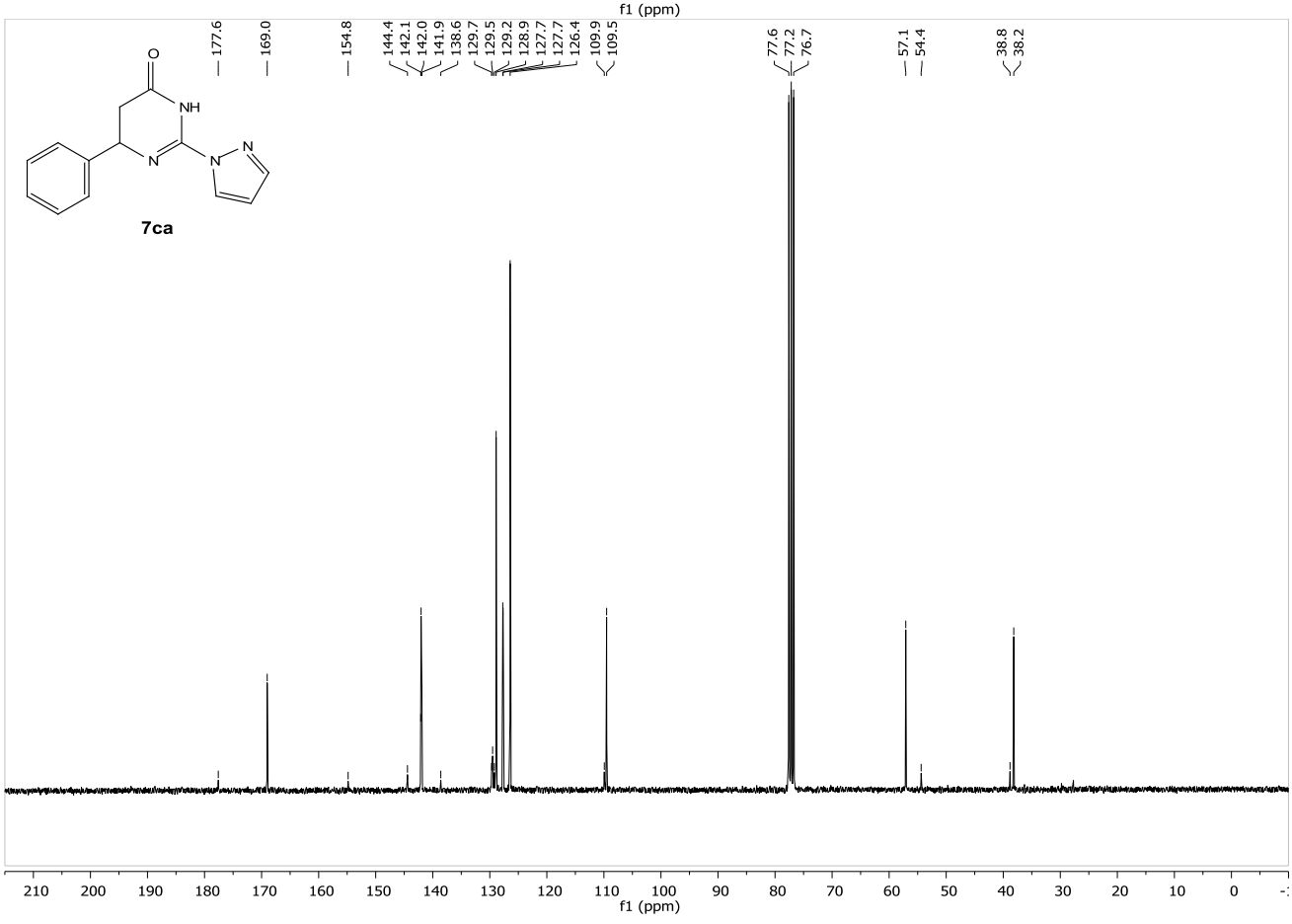


2-methylthio-6-phenyl-5,6-dihydropyrimidin-4(3*H*)-one (7ba).

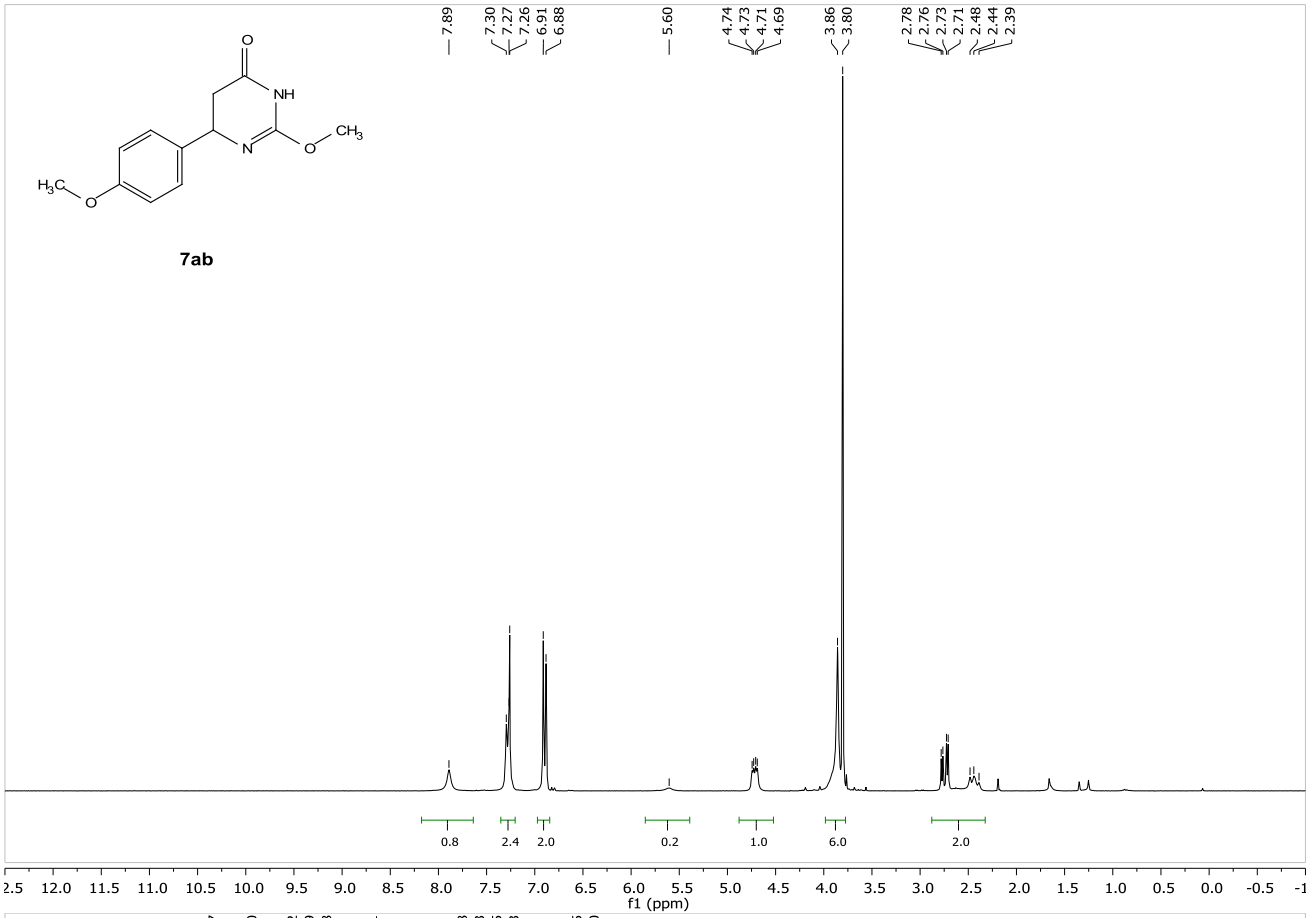


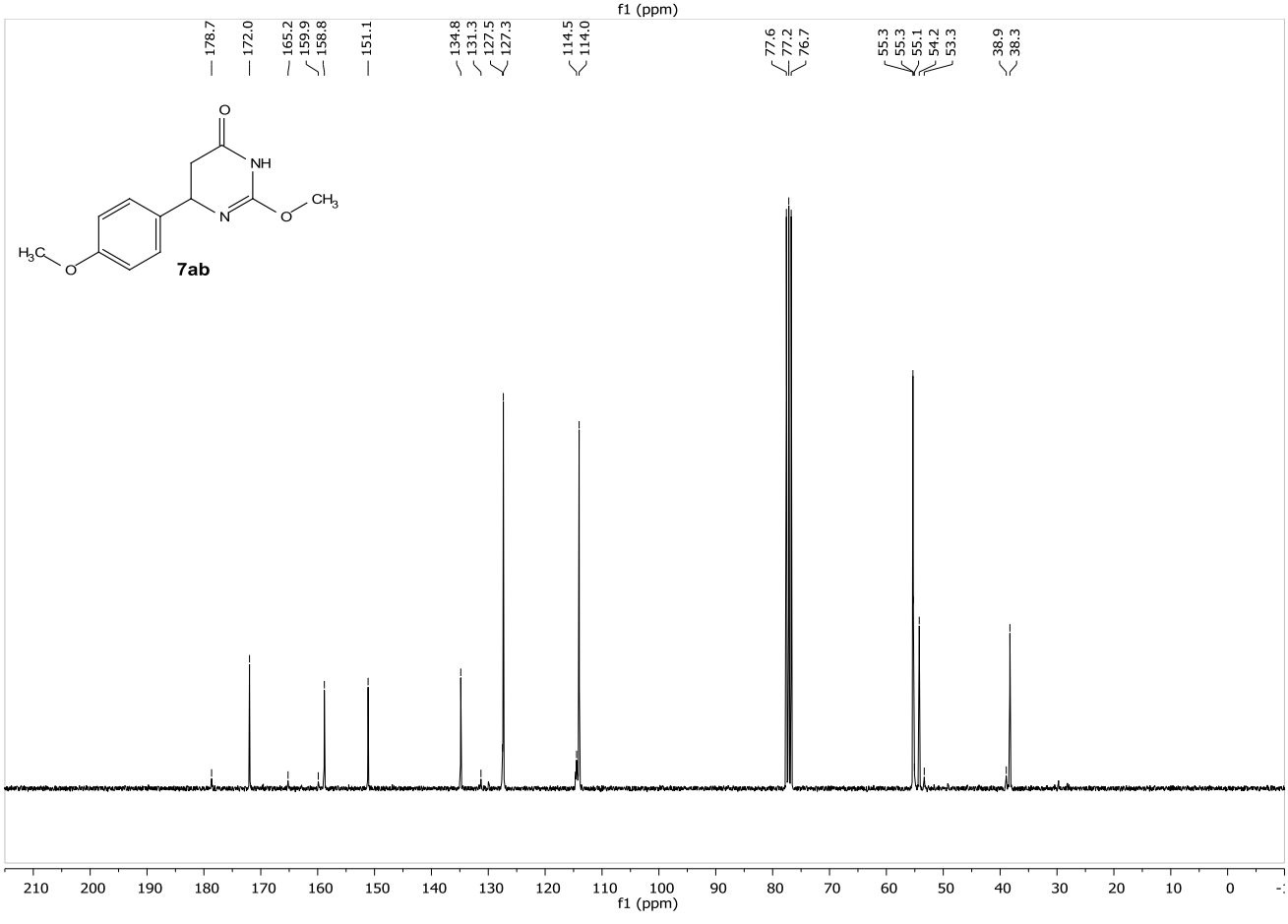
6-phenyl-2-(pyrazol-1-yl)-5,6-dihydropyrimidin-4-one (7ca).



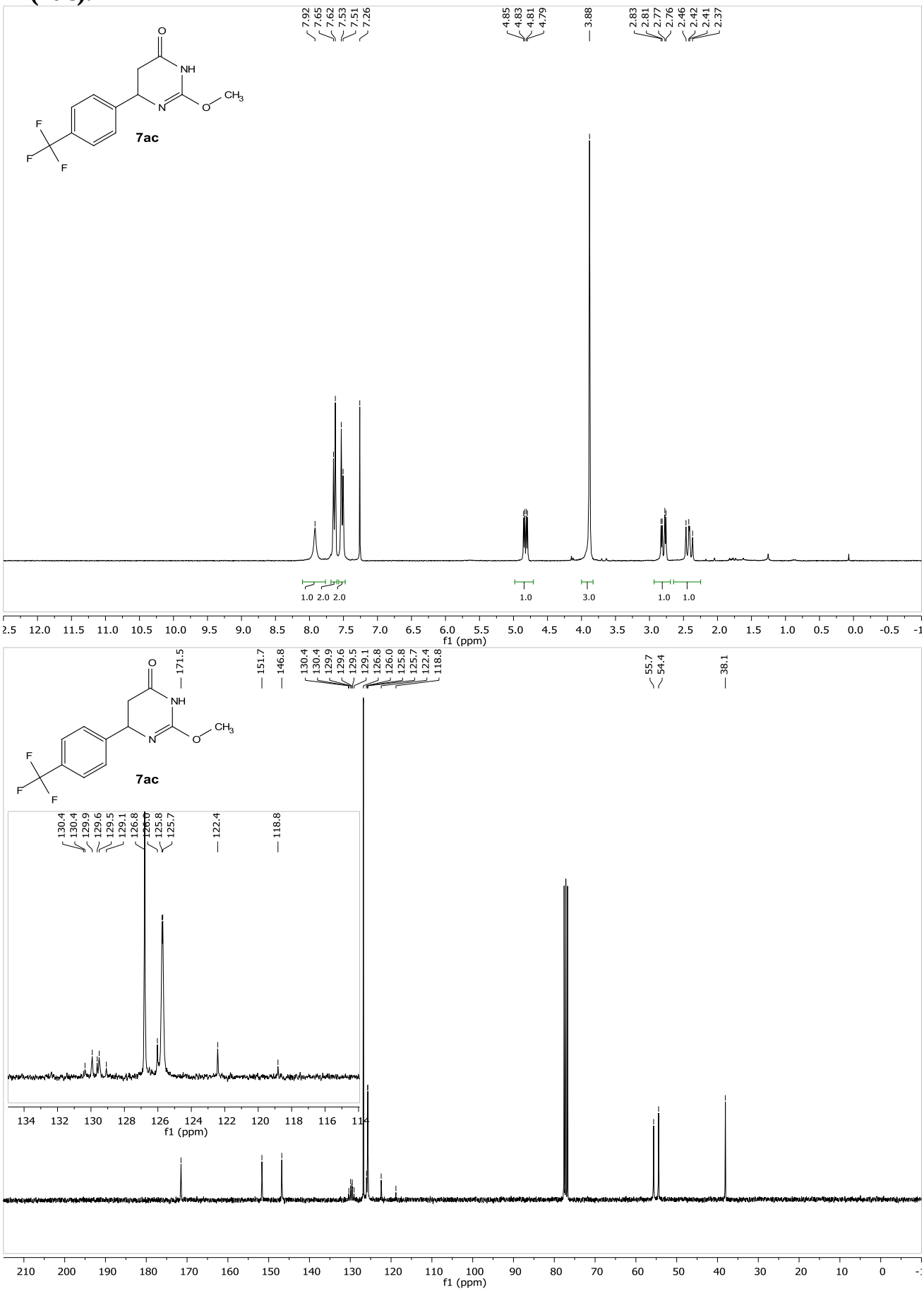


2-methoxy-6-(4-methoxyphenyl)-5,6-dihydropyrimidin-4-one (7ab).

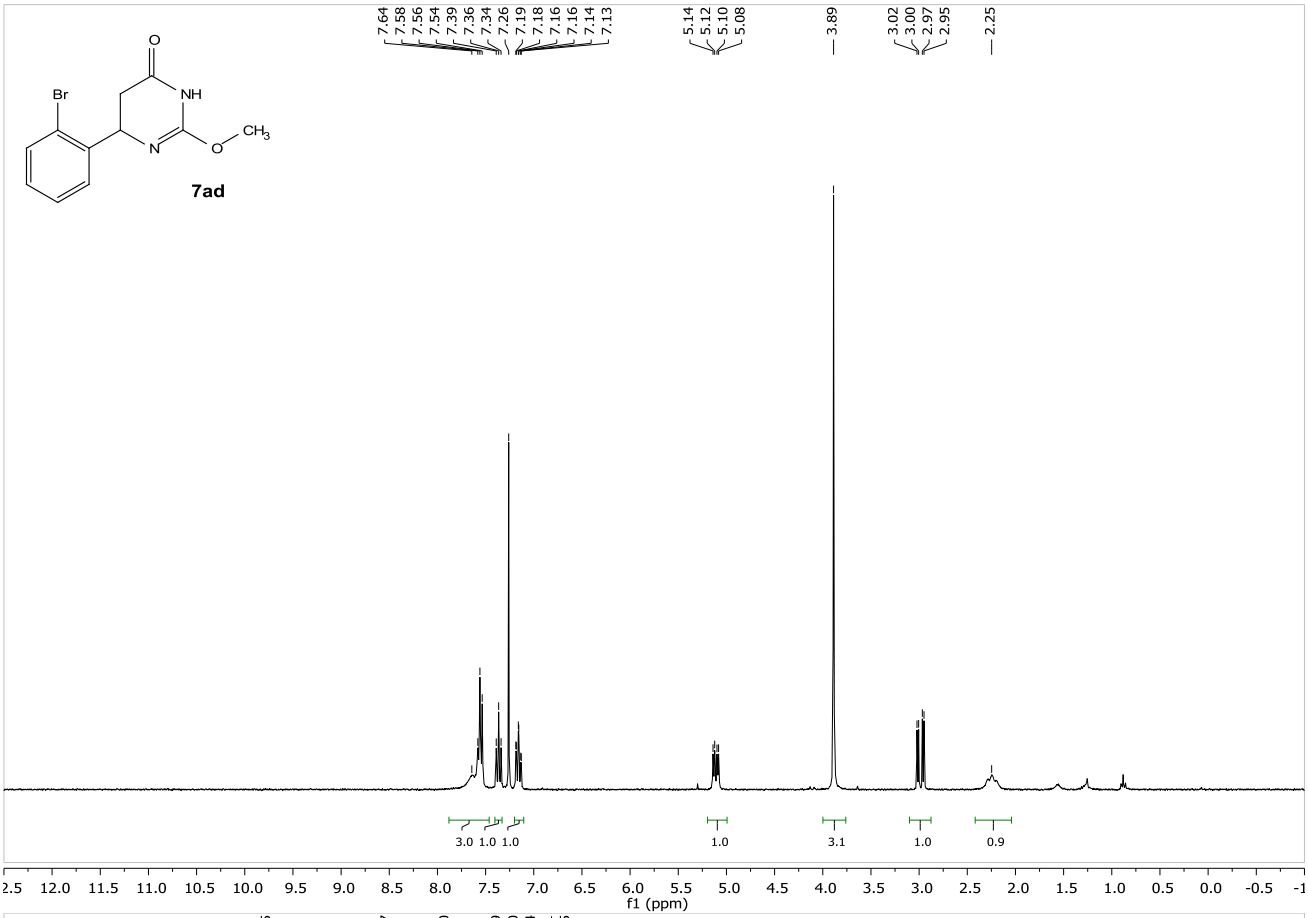


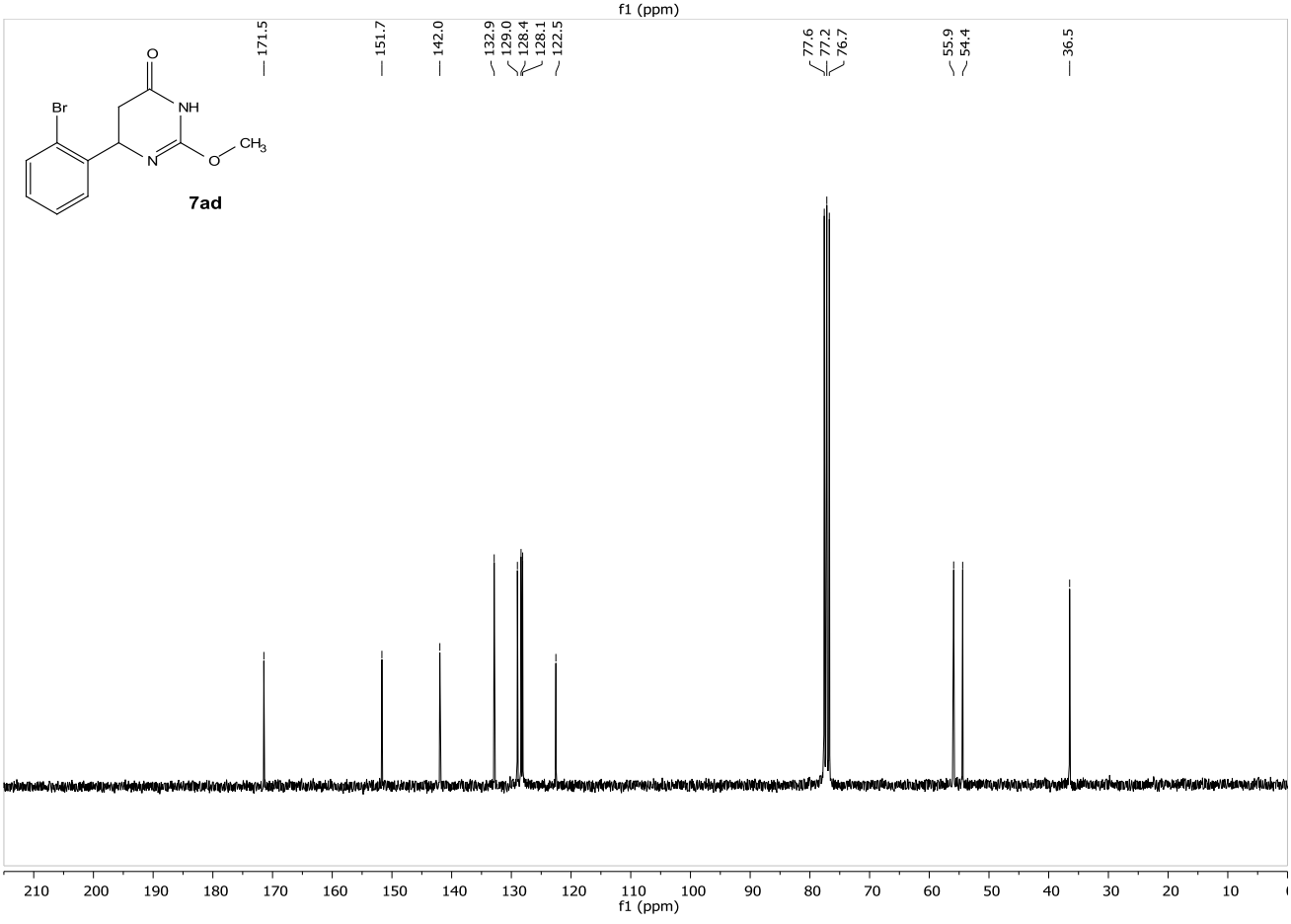


2-methoxy-6-(4-(trifluoromethyl)phenyl)-5,6-dihydropyrimidin-4(3*H*)-one (7ac).

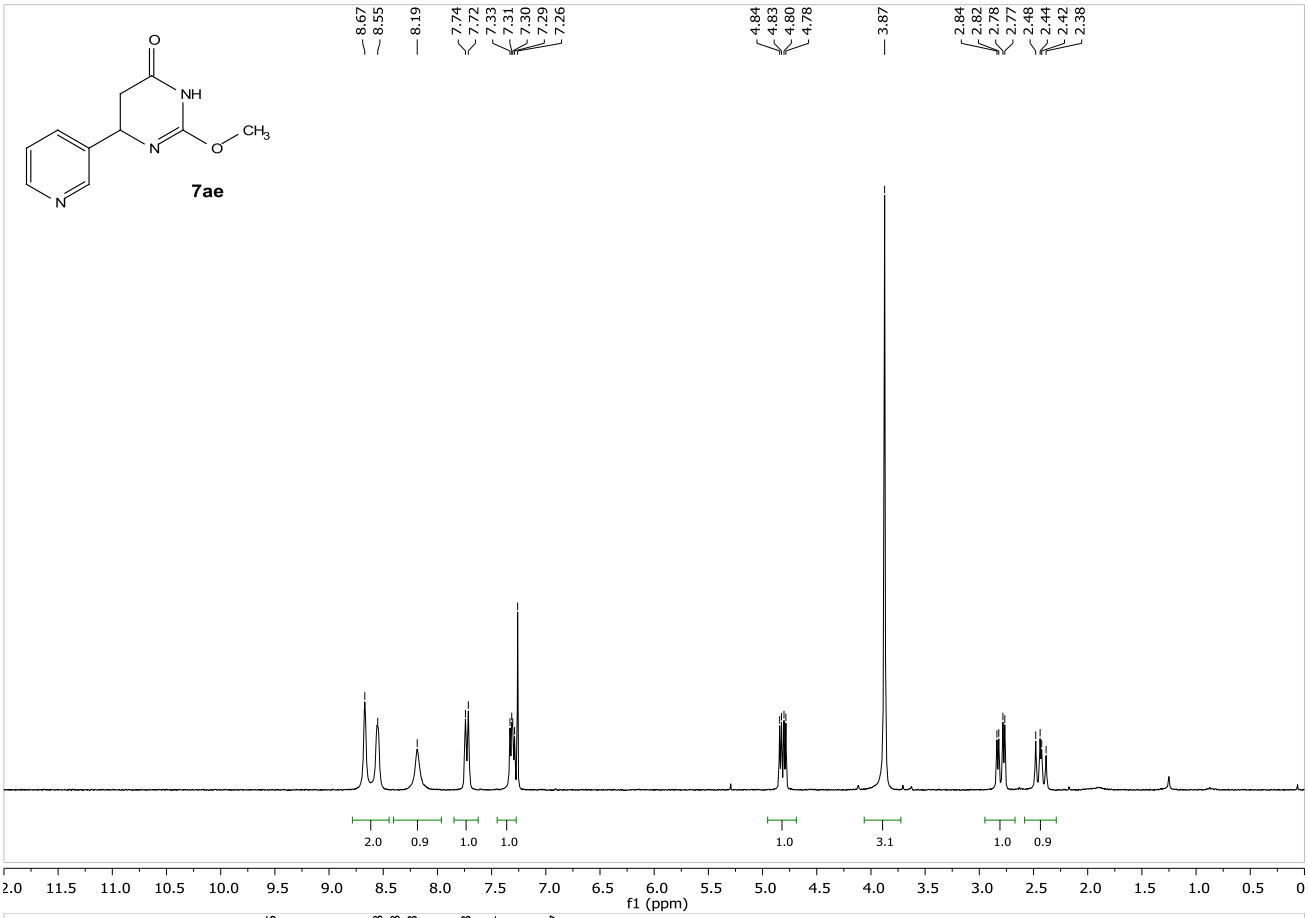


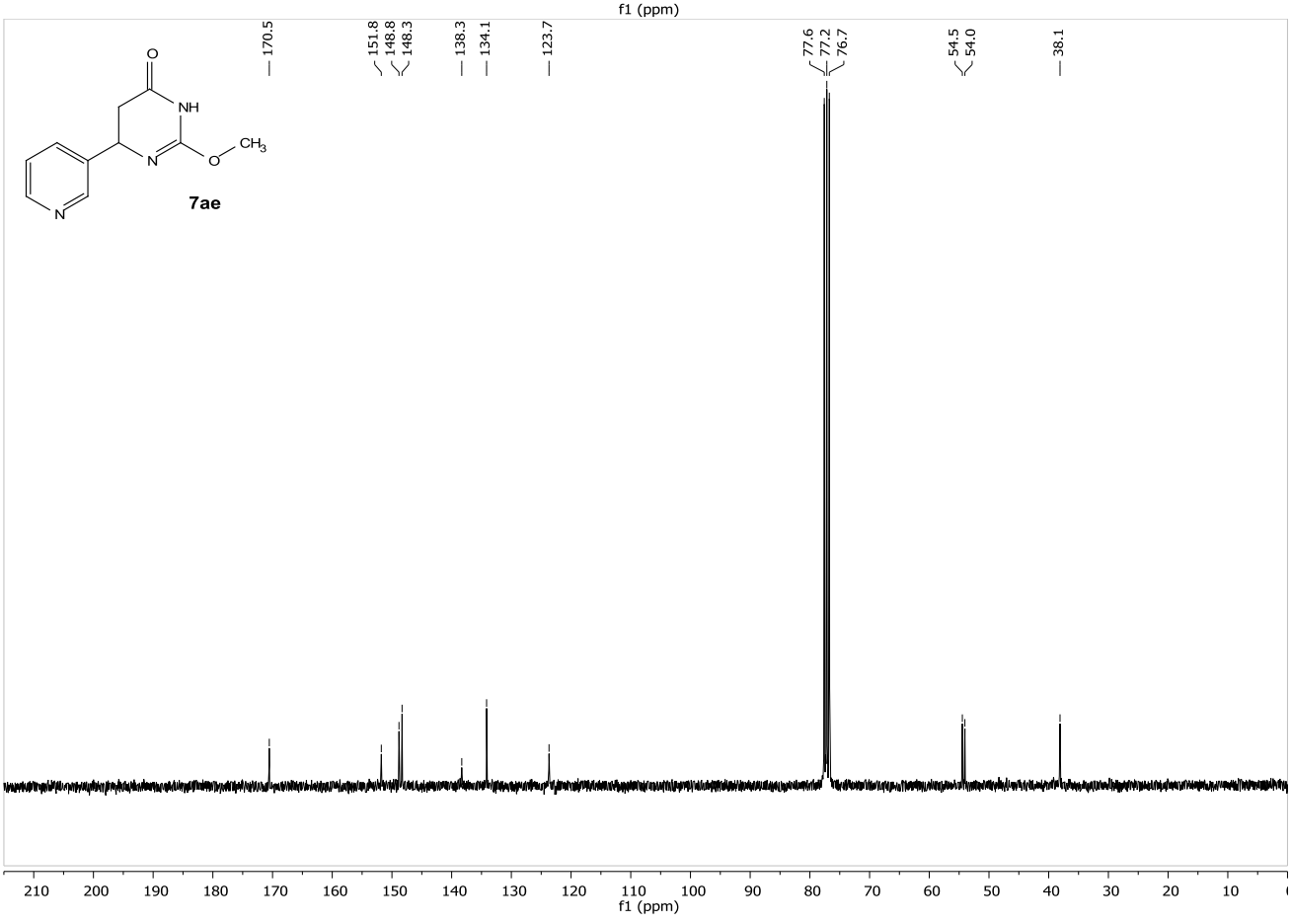
6-(2-bromophenyl)-2-methoxy-5,6-dihydropyrimidin-4(3*H*)-one (7ad).



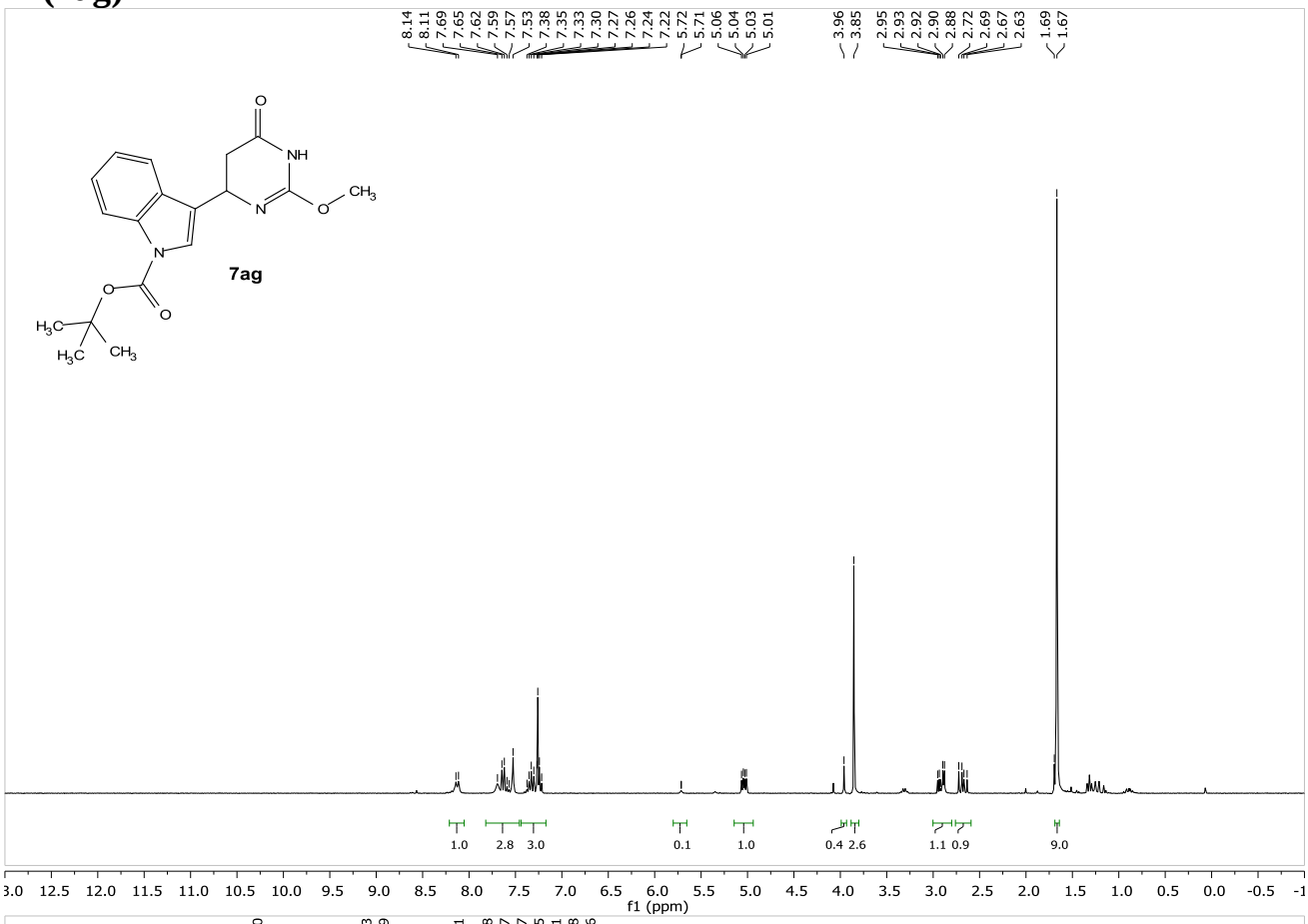


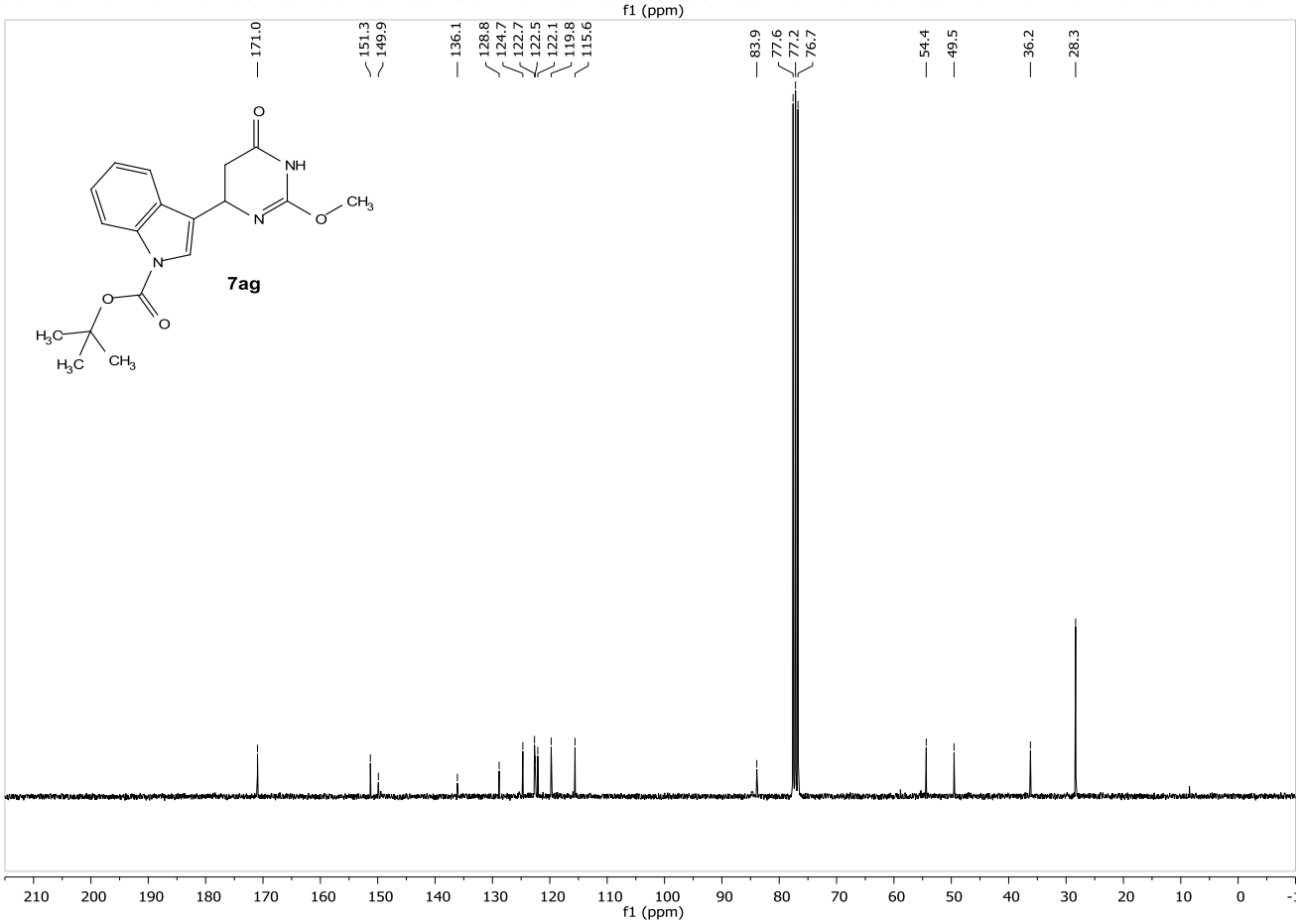
2-methoxy-6-(pyridin-3-yl)-5,6-dihydropyrimidin-4(3*H*)-one (7ae).



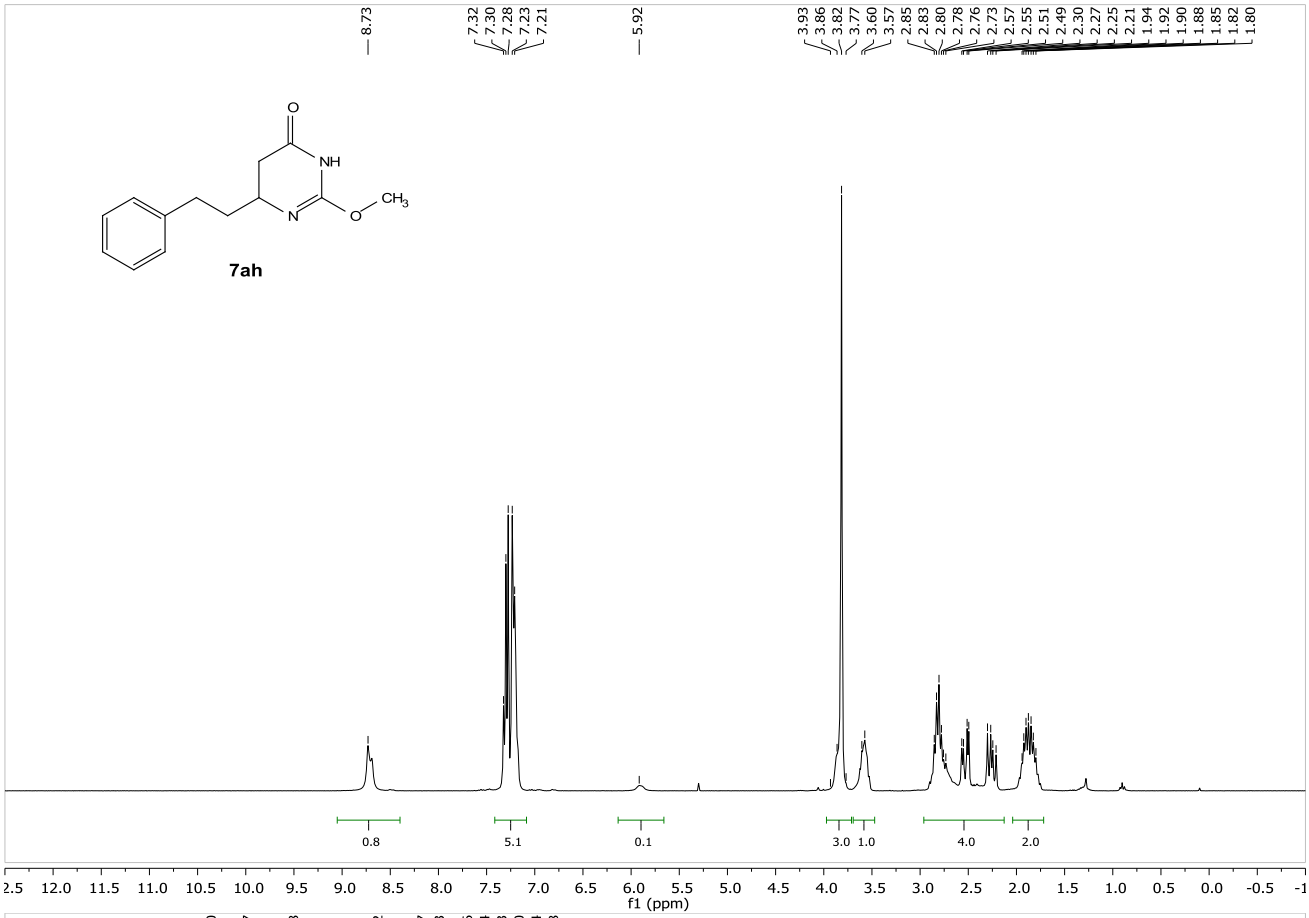


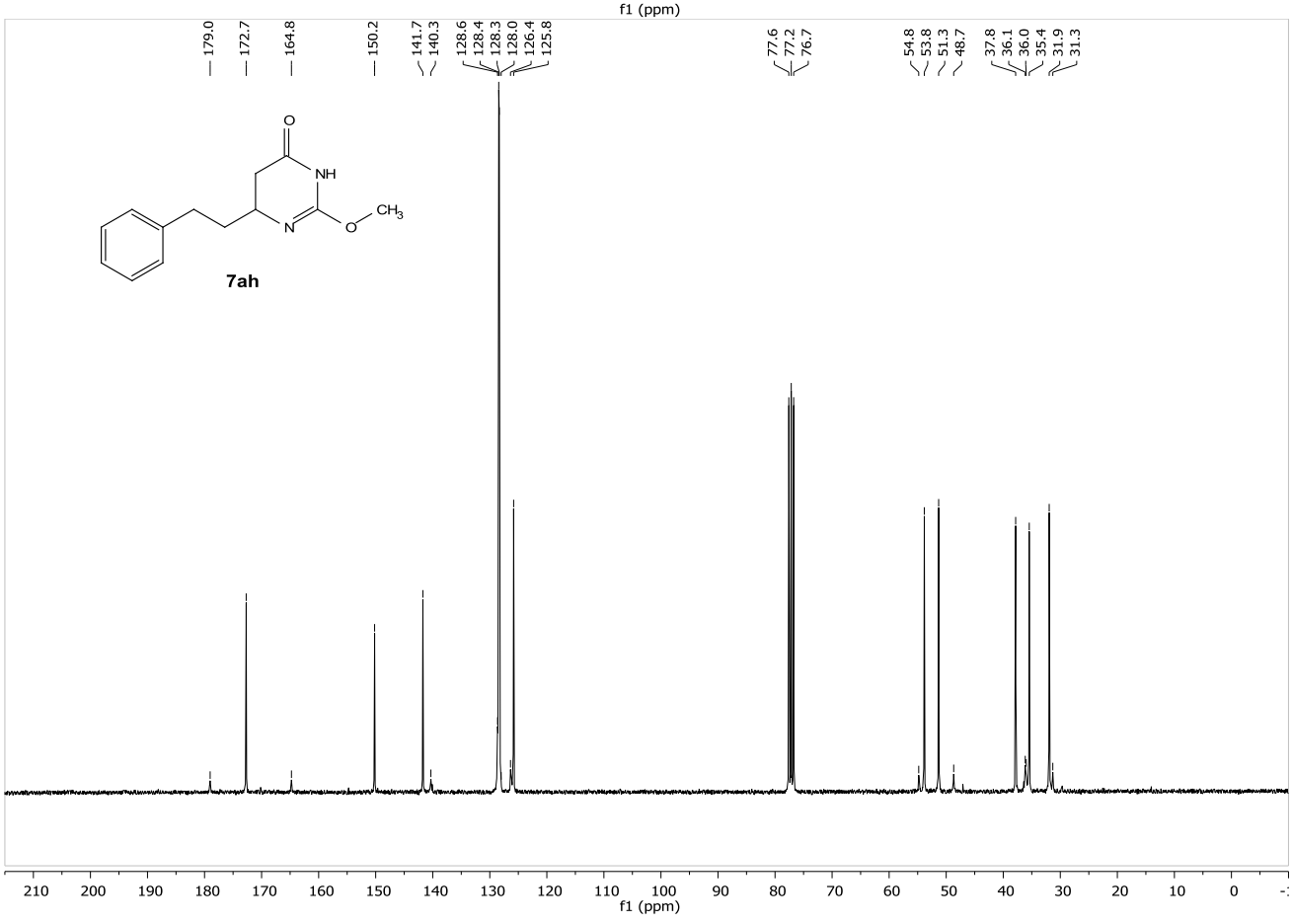
tert-butyl 3-(2-methoxy-5,6-dihydropyrimidin-4-one-6-yl)-indole-1-carboxylate (7ag)



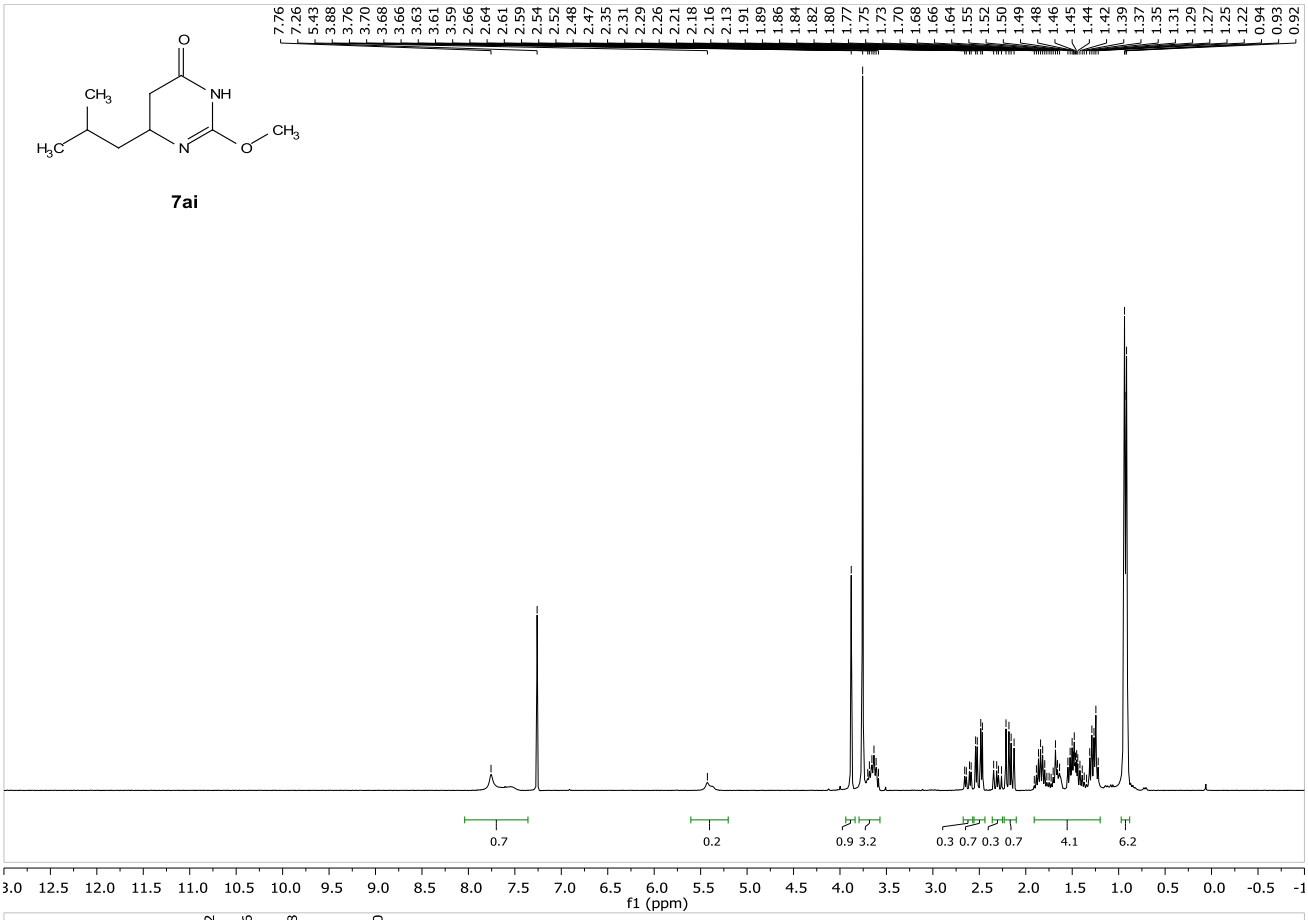


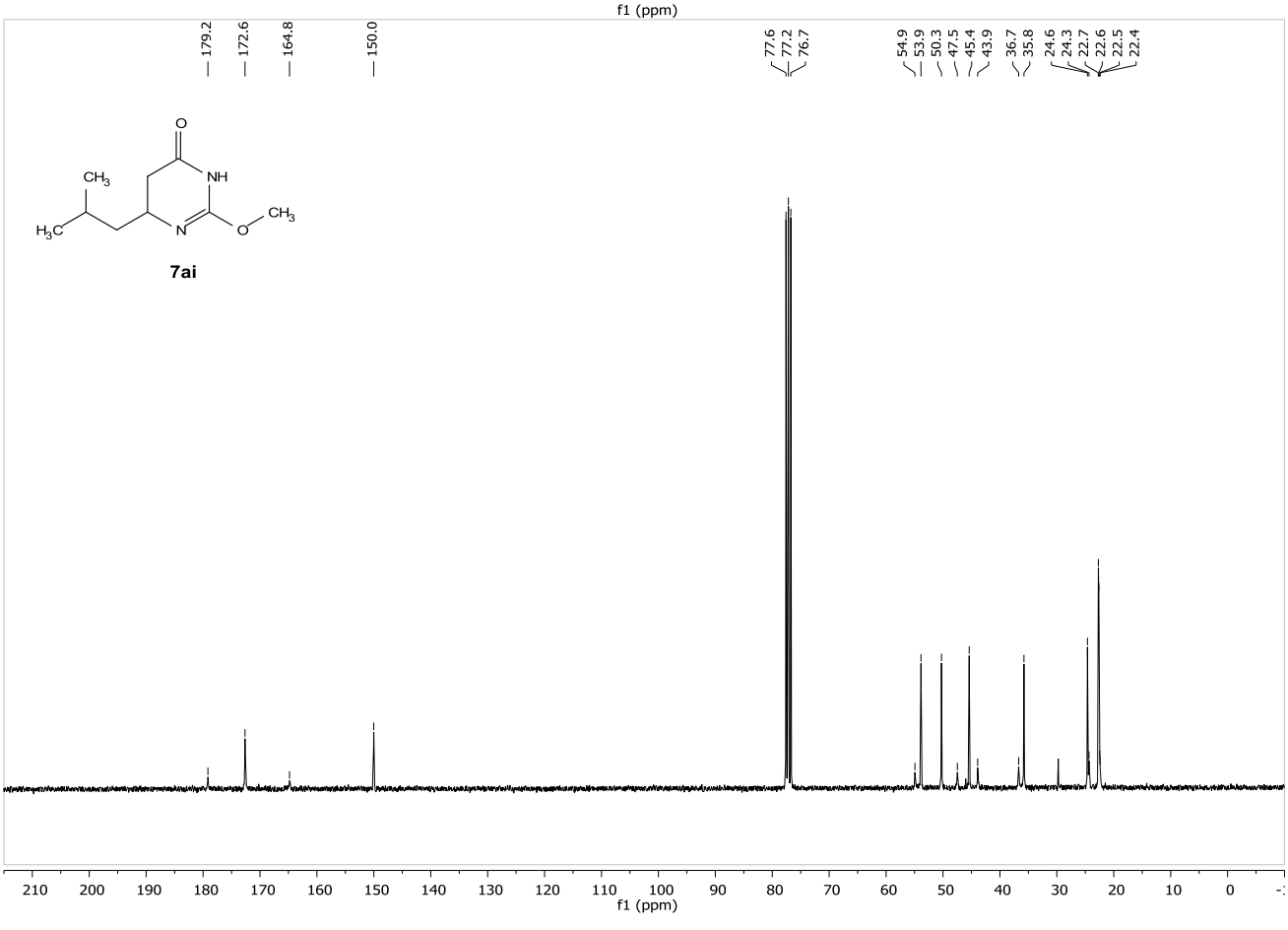
2-methoxy-6-phenethyl-5,6-dihydropyrimidin-4-one (7ah).



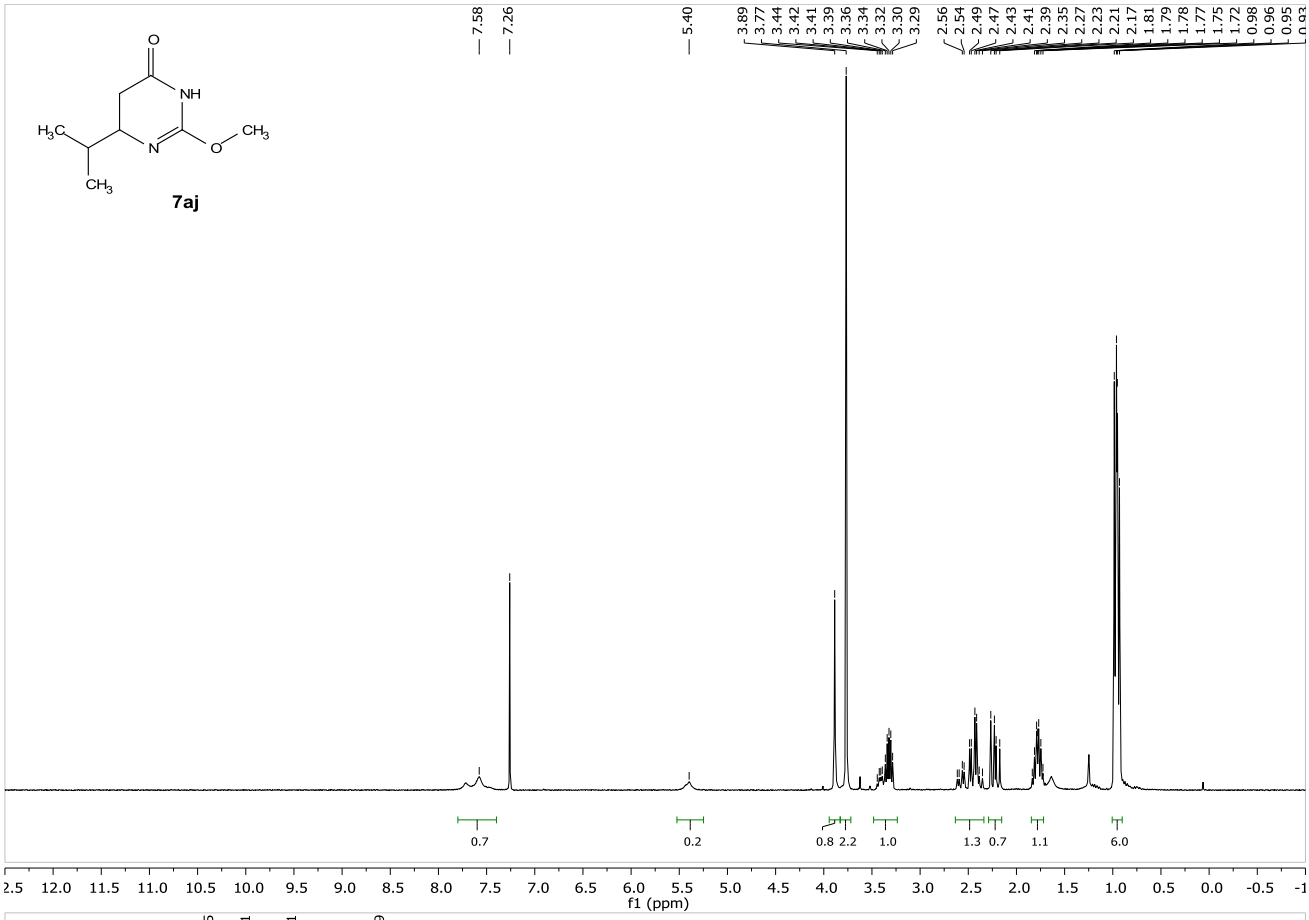


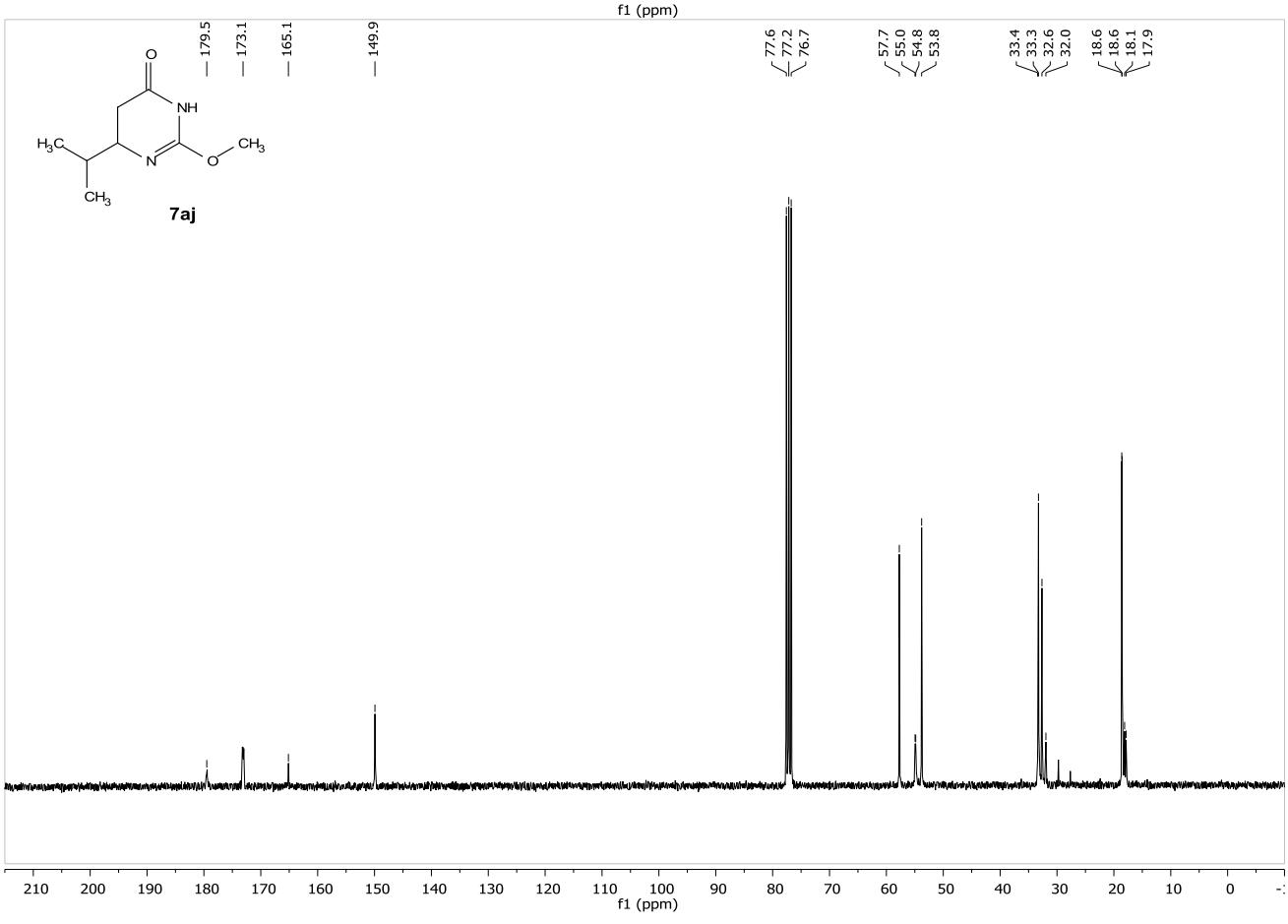
6-isobutyl-2-methoxy-5,6-dihydropyrimidin-4-one (7ai).



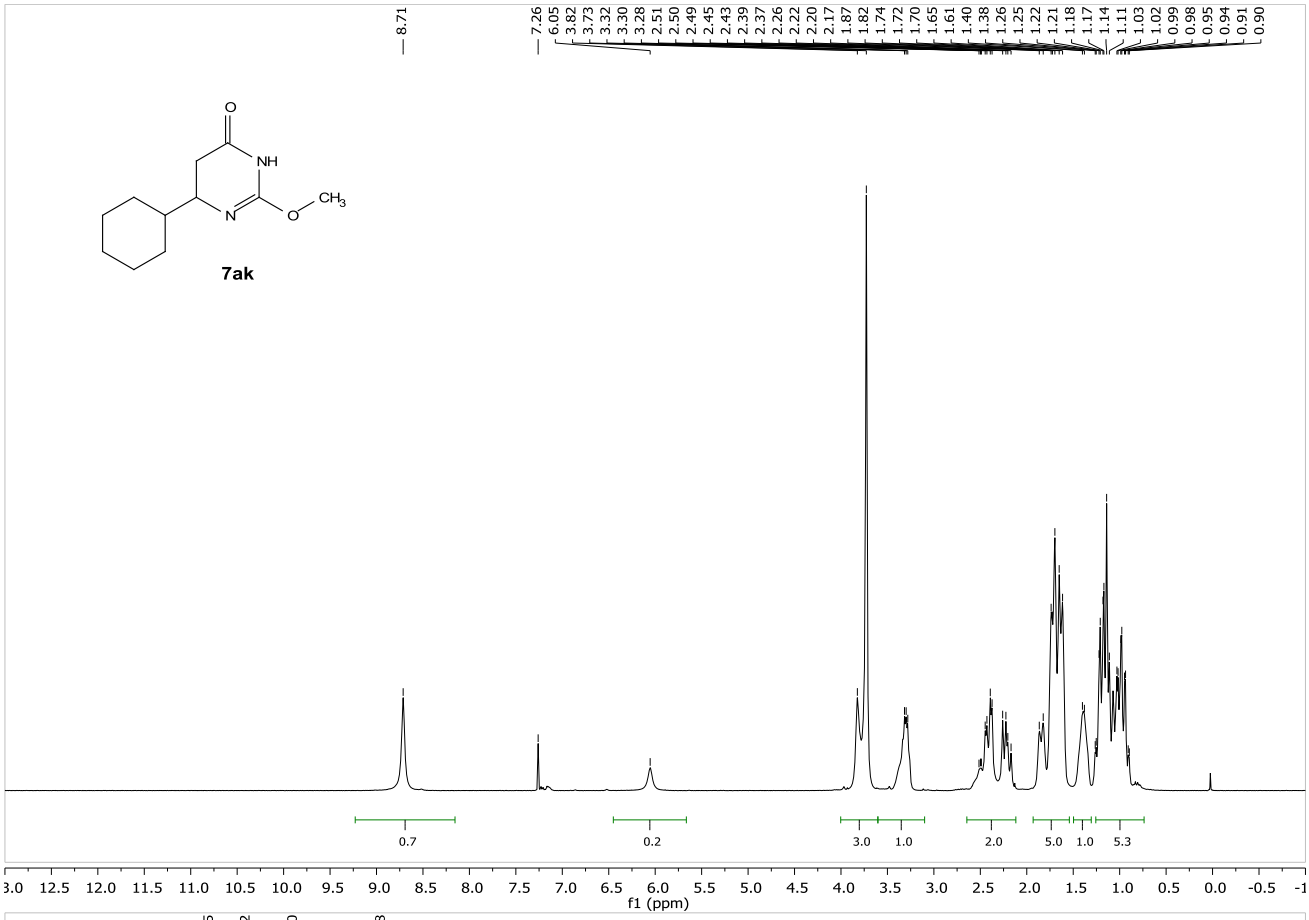


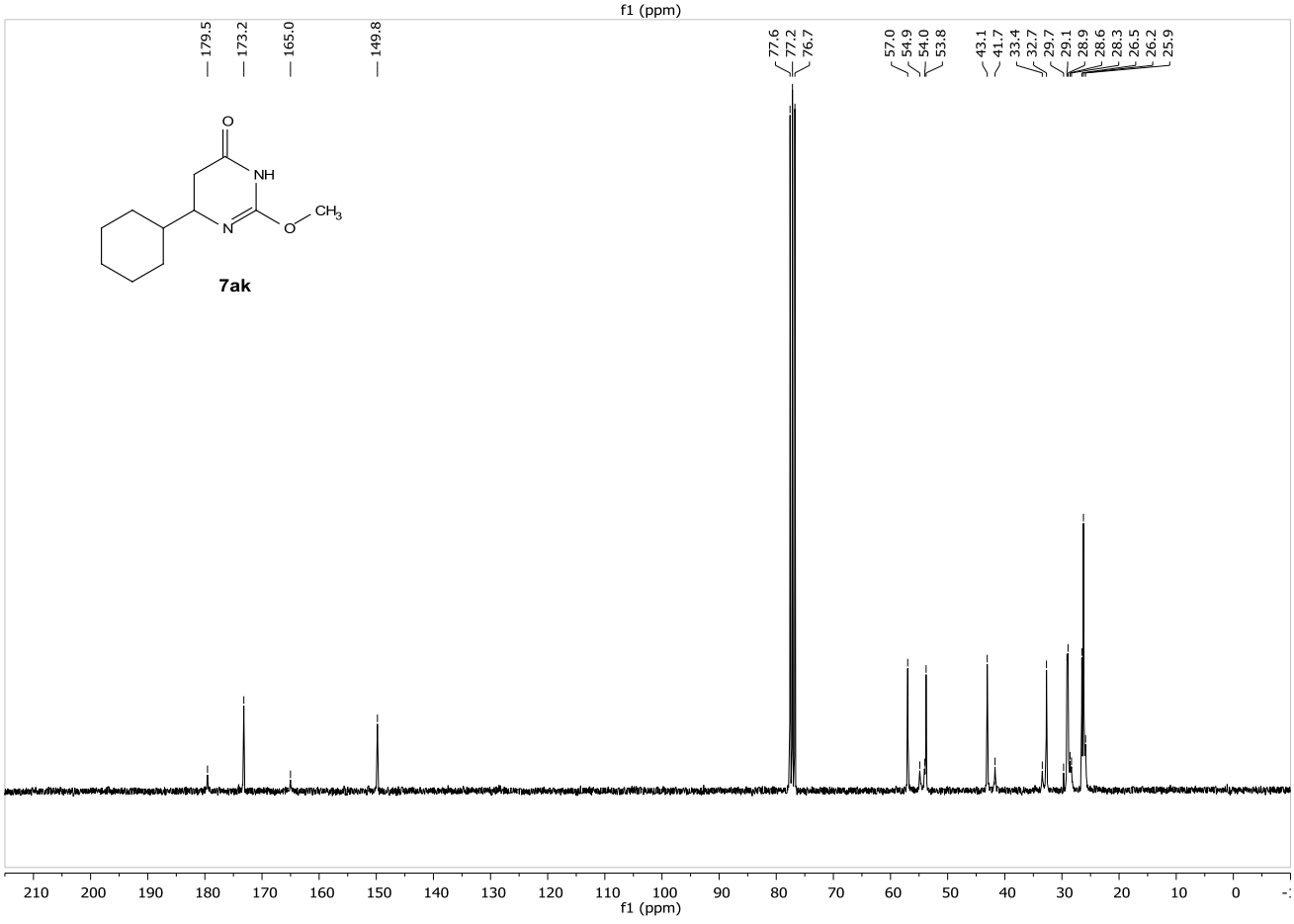
6-isopropyl-2-methoxy-5,6-dihydropyrimidin-4-one (7aj).



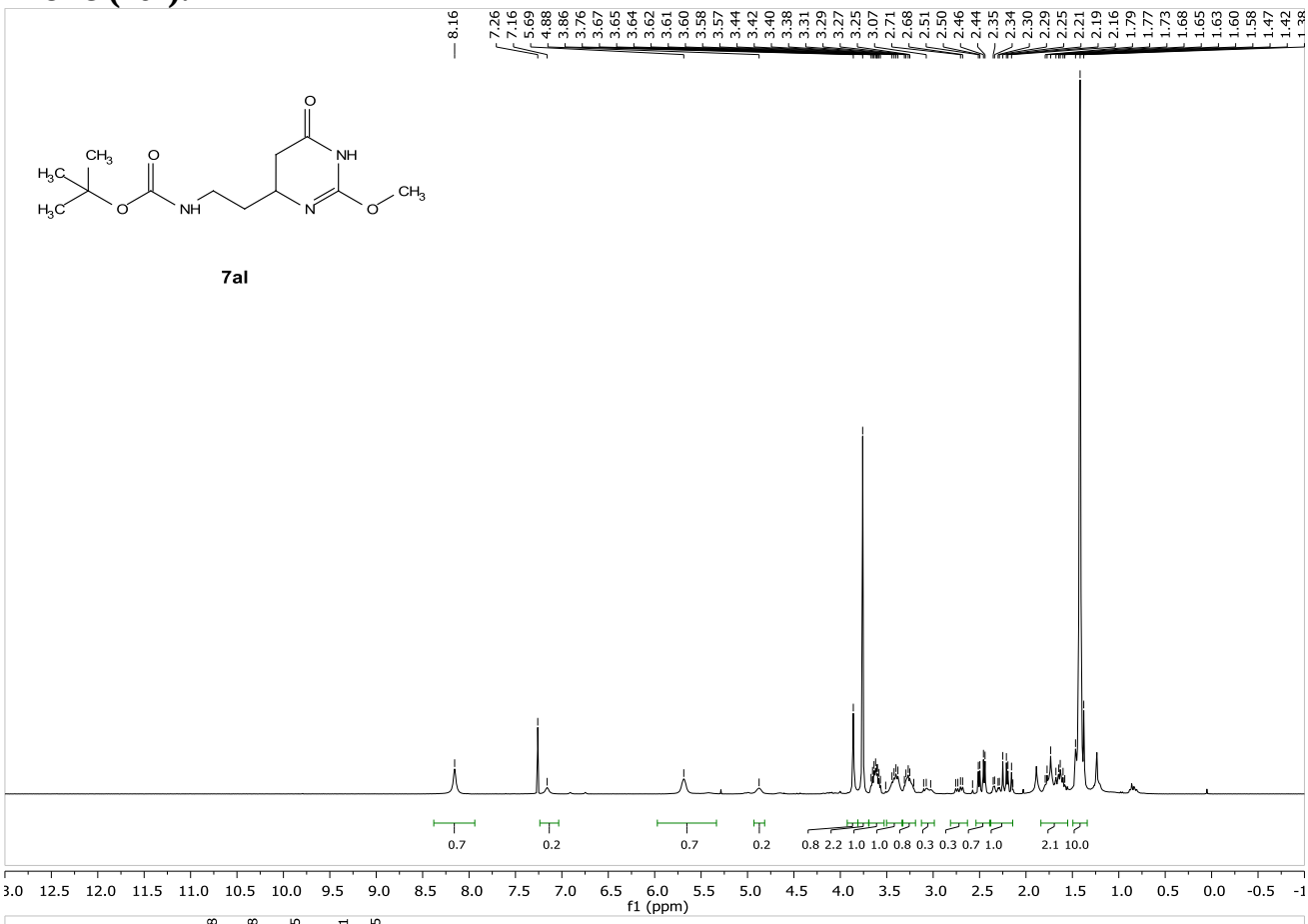


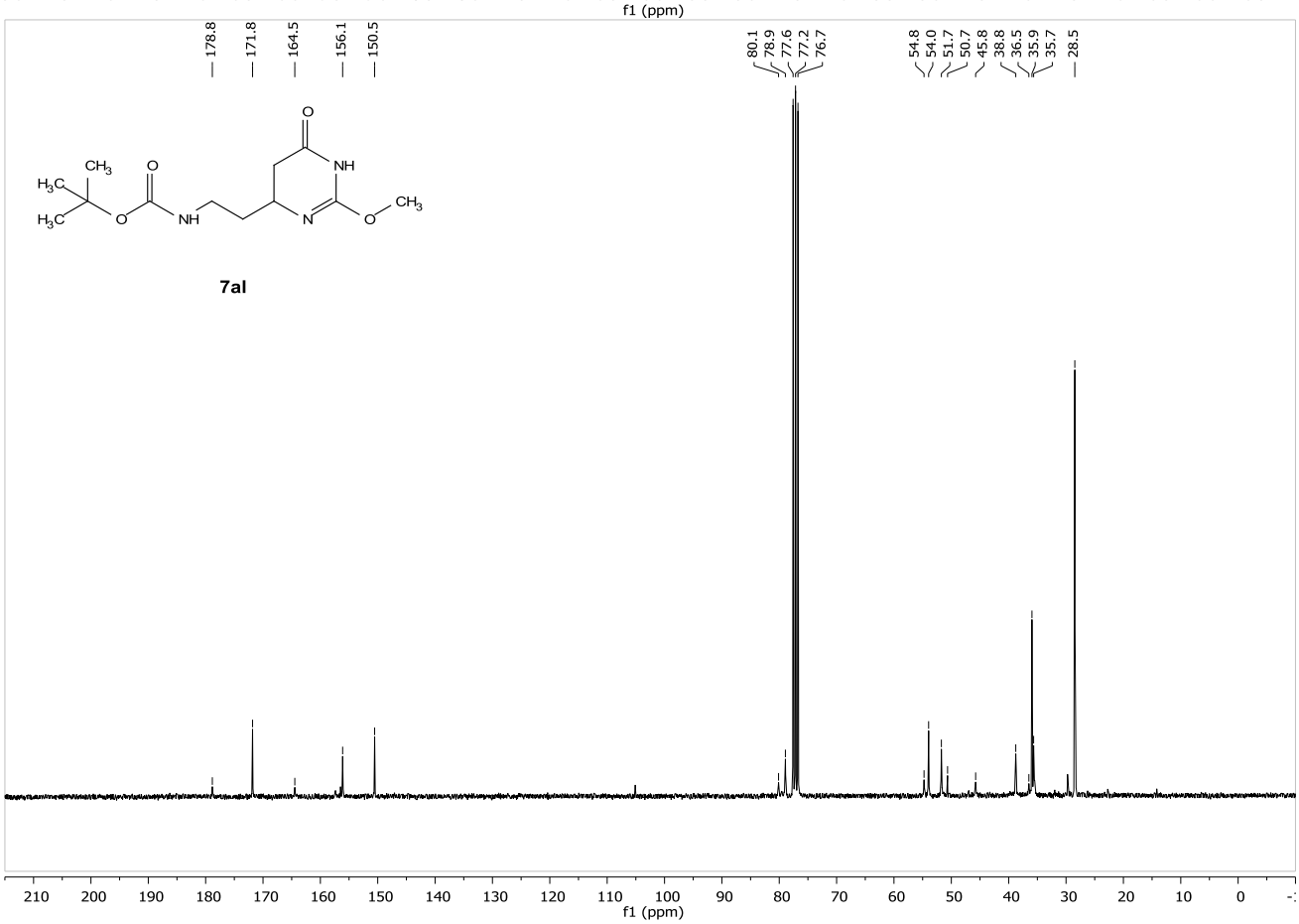
6-cyclohexyl-2-methoxy-5,6-dihydropyrimidin-4-one (7ak).



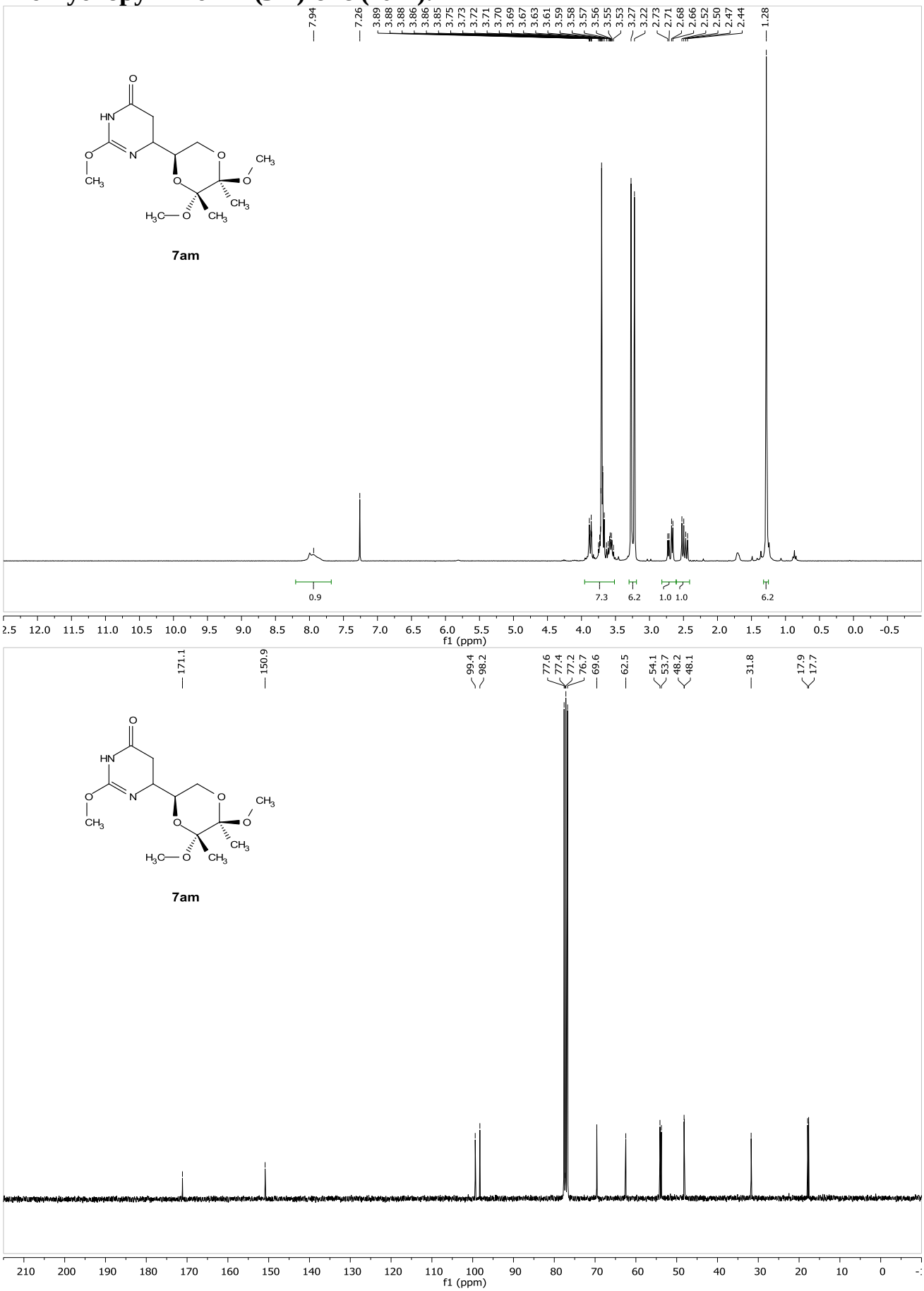


2-methoxy-6-(2-((*tert*-butoxycarbonyl)amino)ethyl)-5,6-dihydropyrimidin-4-one (7al).

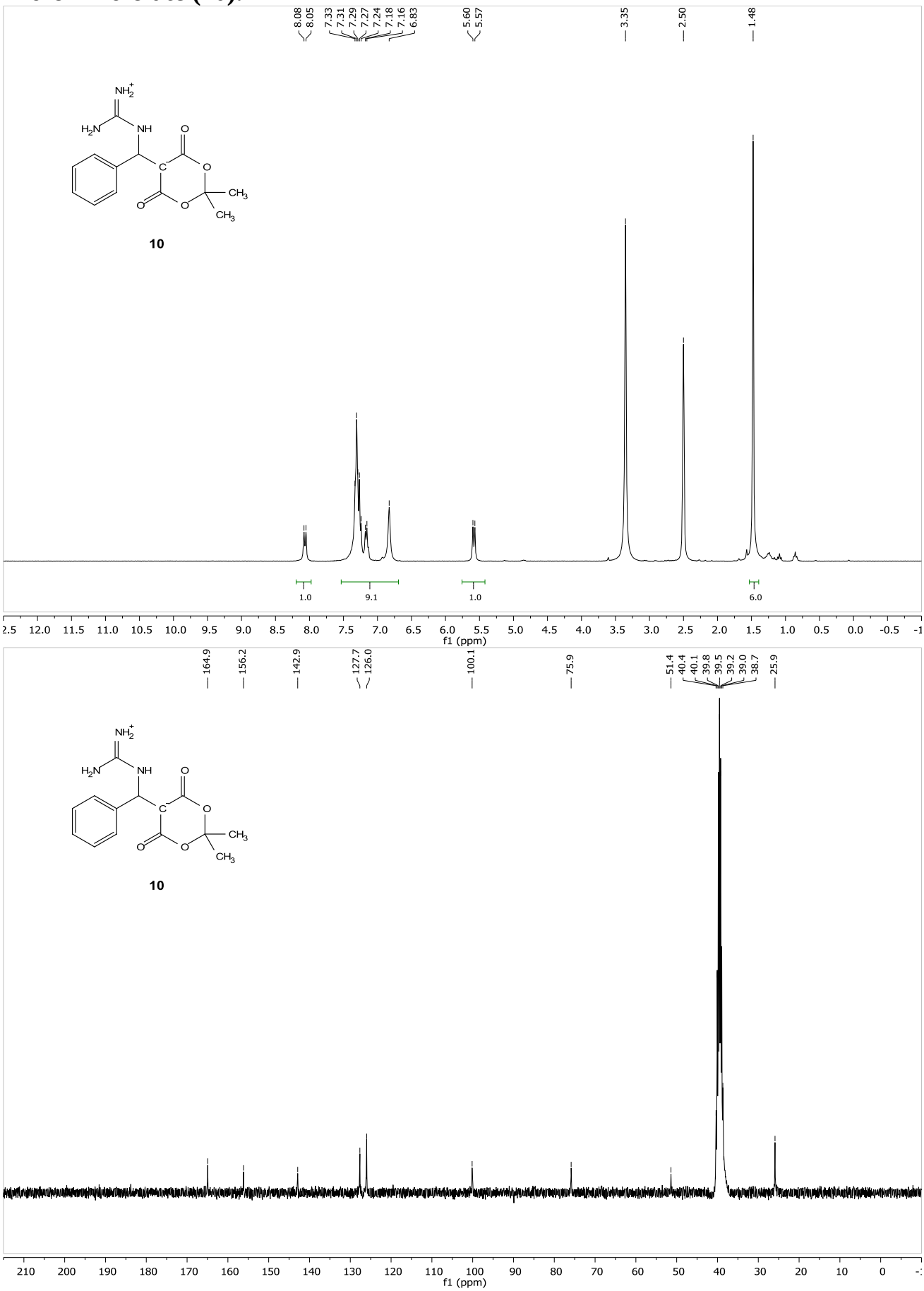




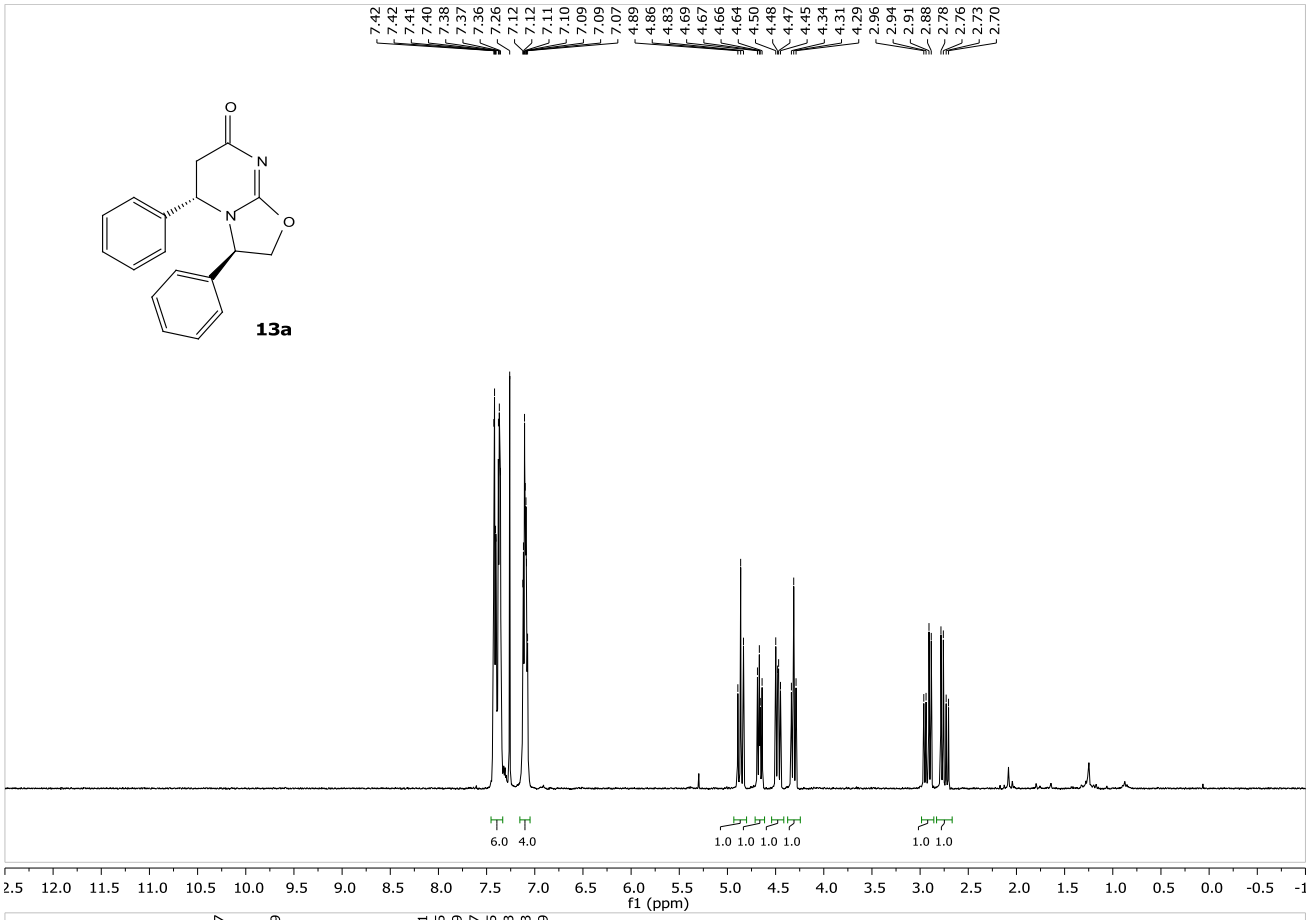
6-((2*S*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-2-methoxy-5,6-dihydropyrimidin-4(*3H*)-one (7am).

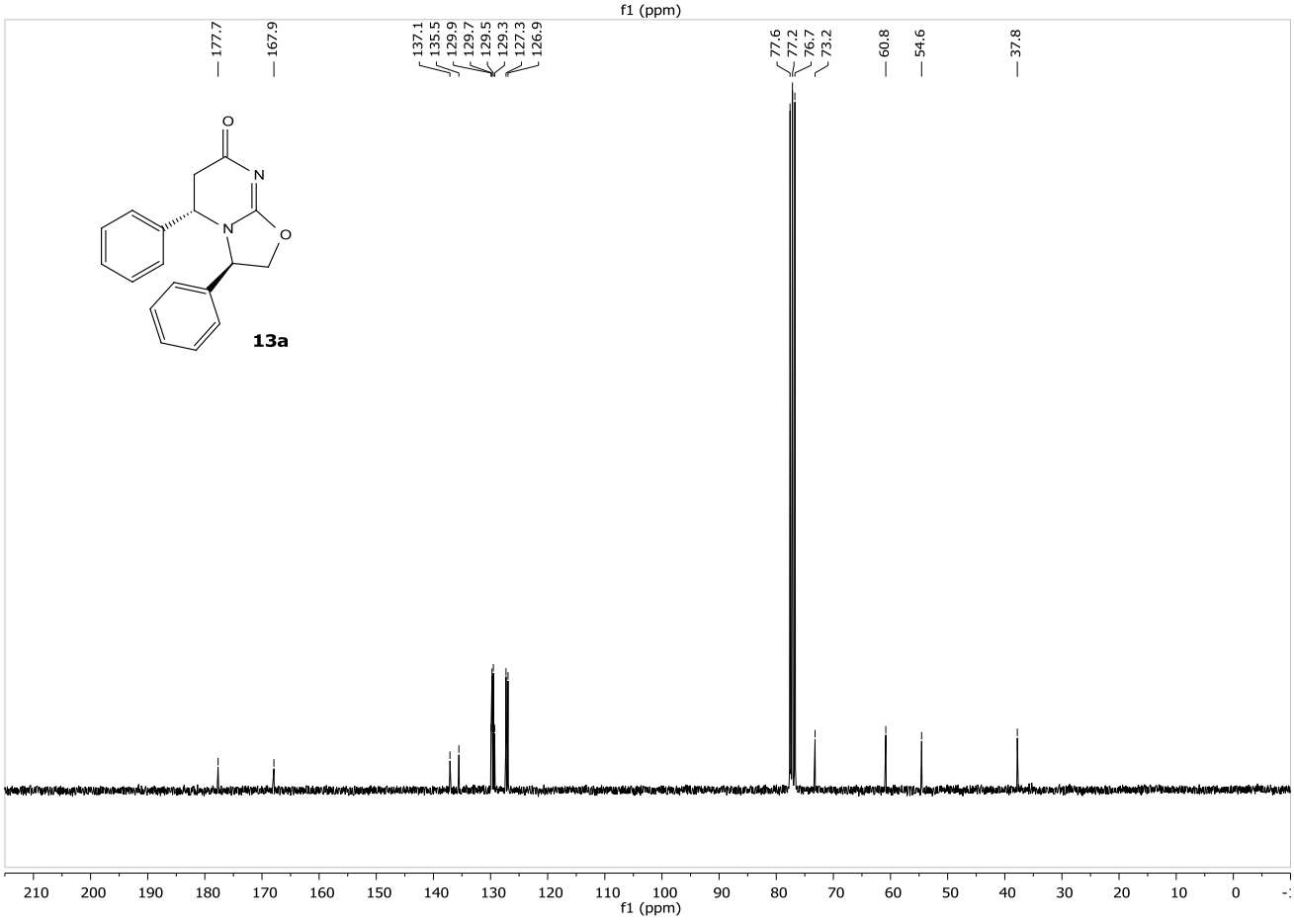


5-(((amino(iminio)methyl)amino)(phenyl)methyl)-2,2-dimethyl-4-oxo-1,3-dioxin-6-olate (10).

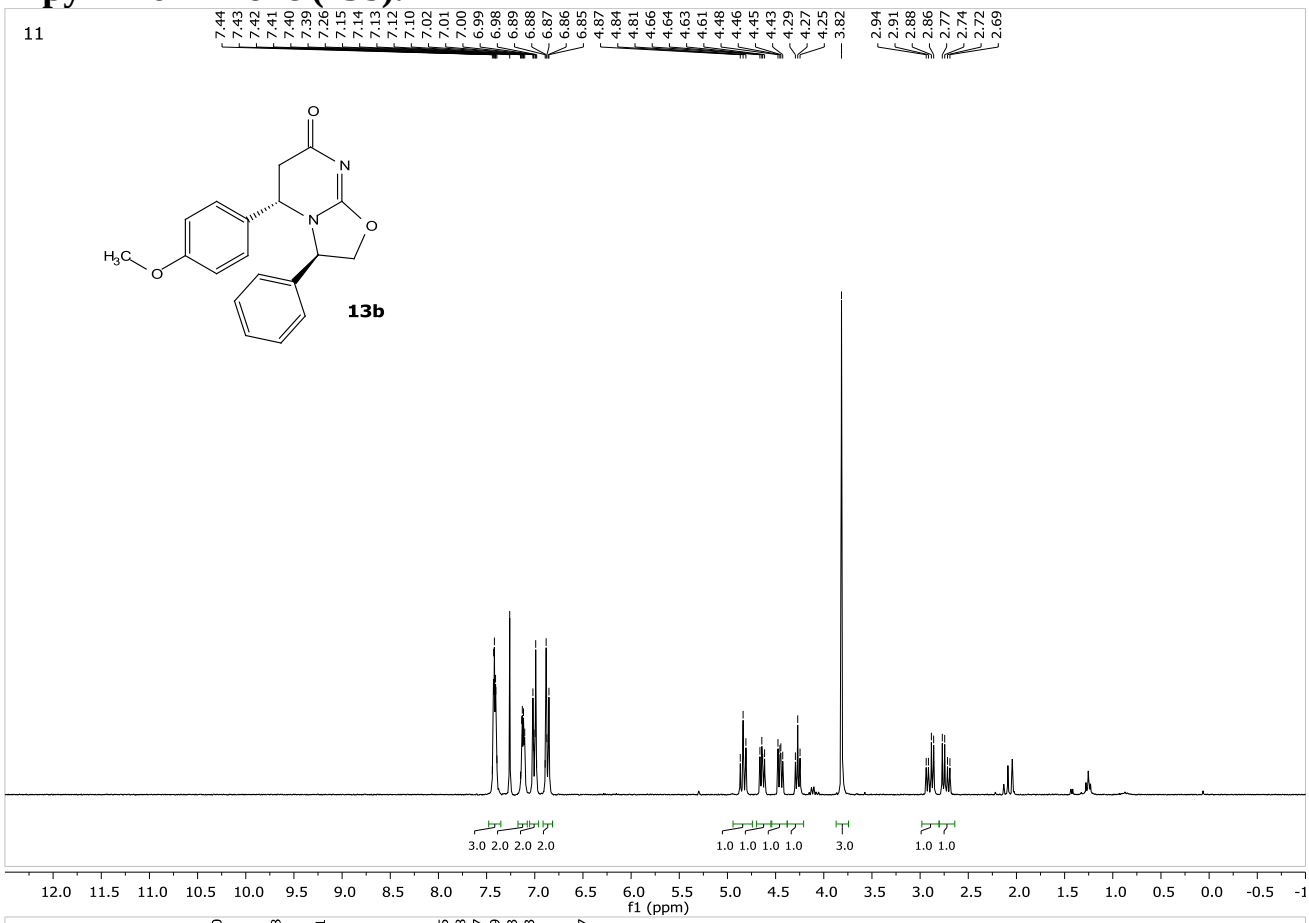


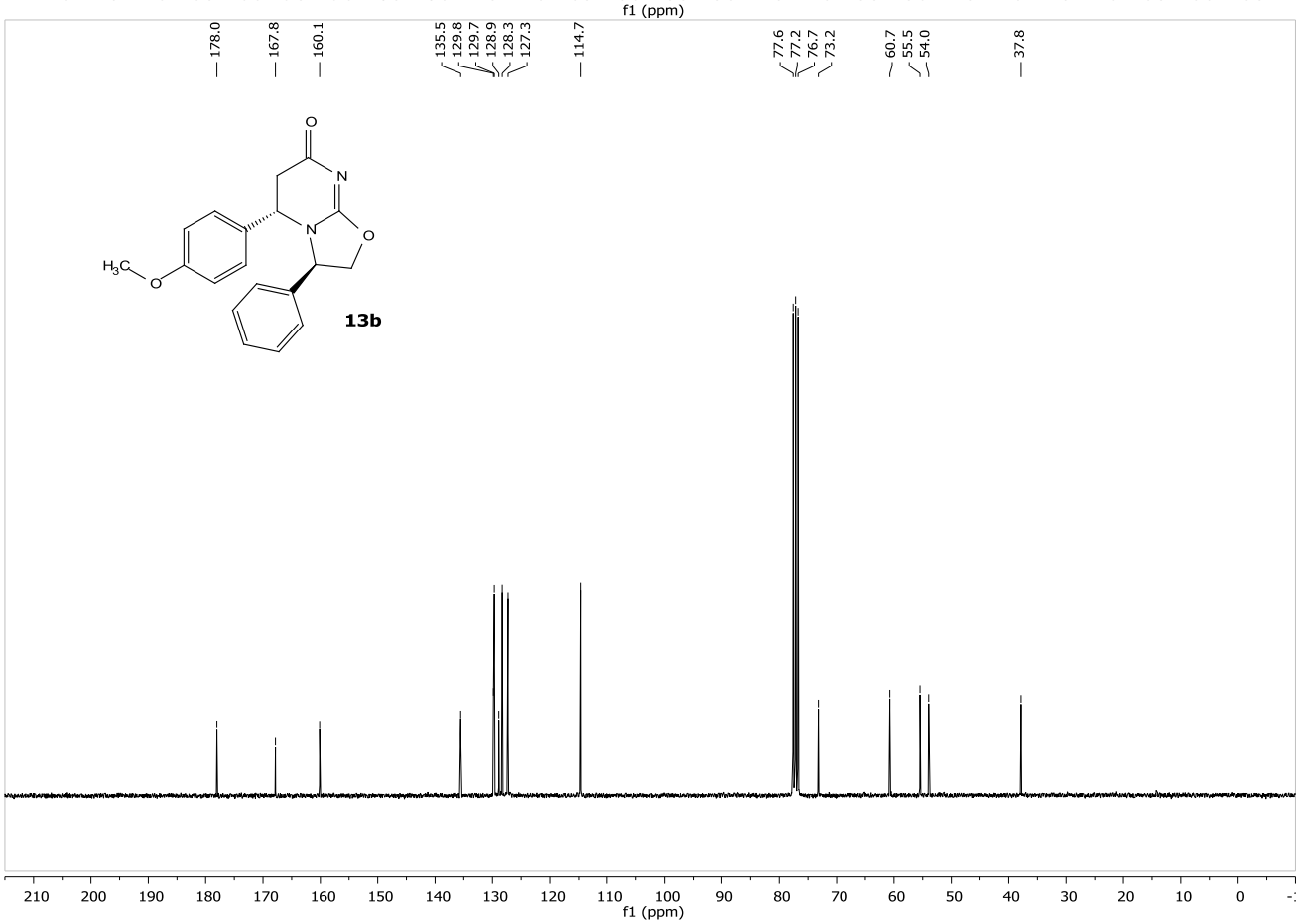
(3*R*,5*S*)-3,5-diphenyl-2,3,5,6-tetrahydro oxazolo [3,2-a] pyrimidin-7-one (13a)



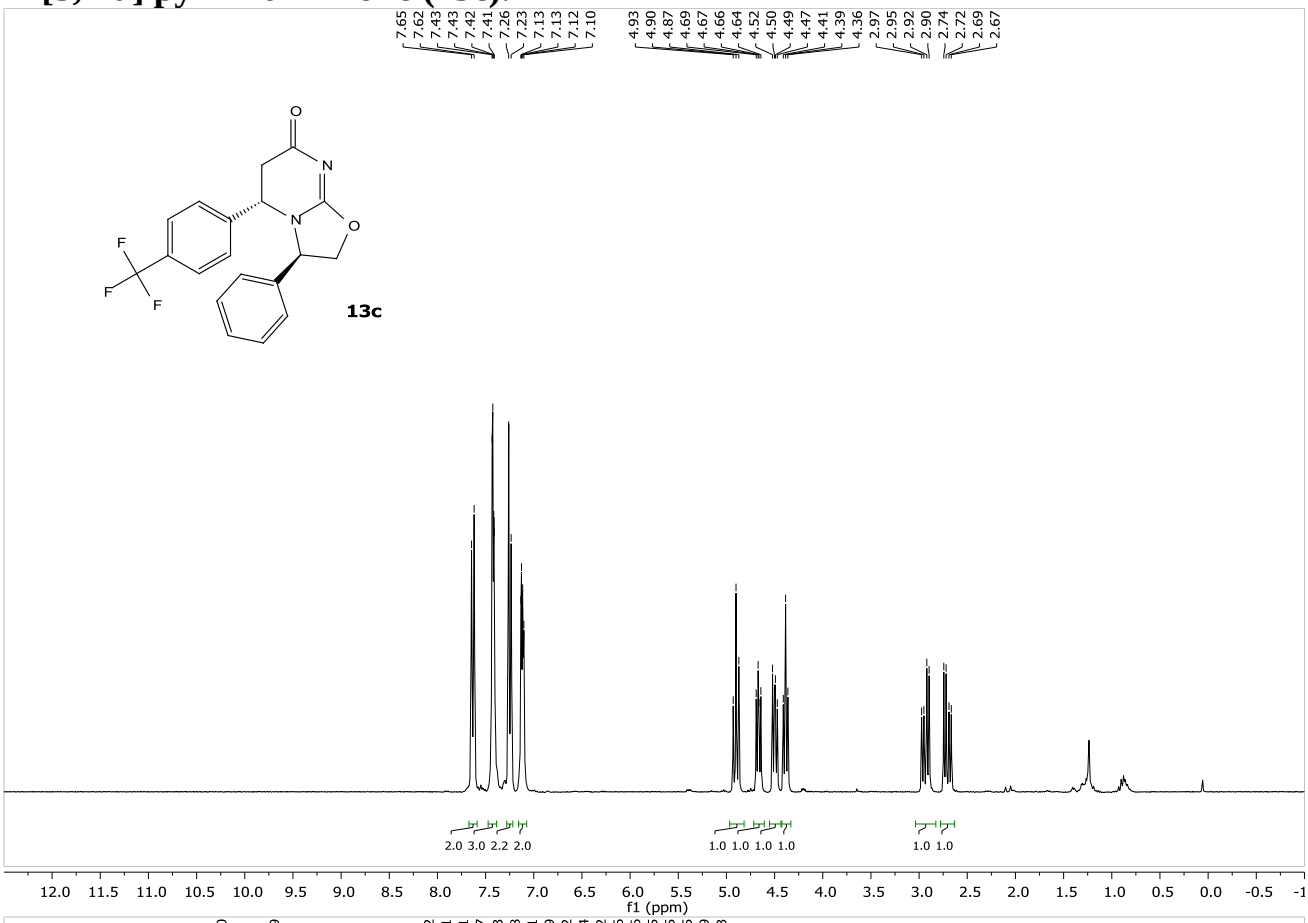


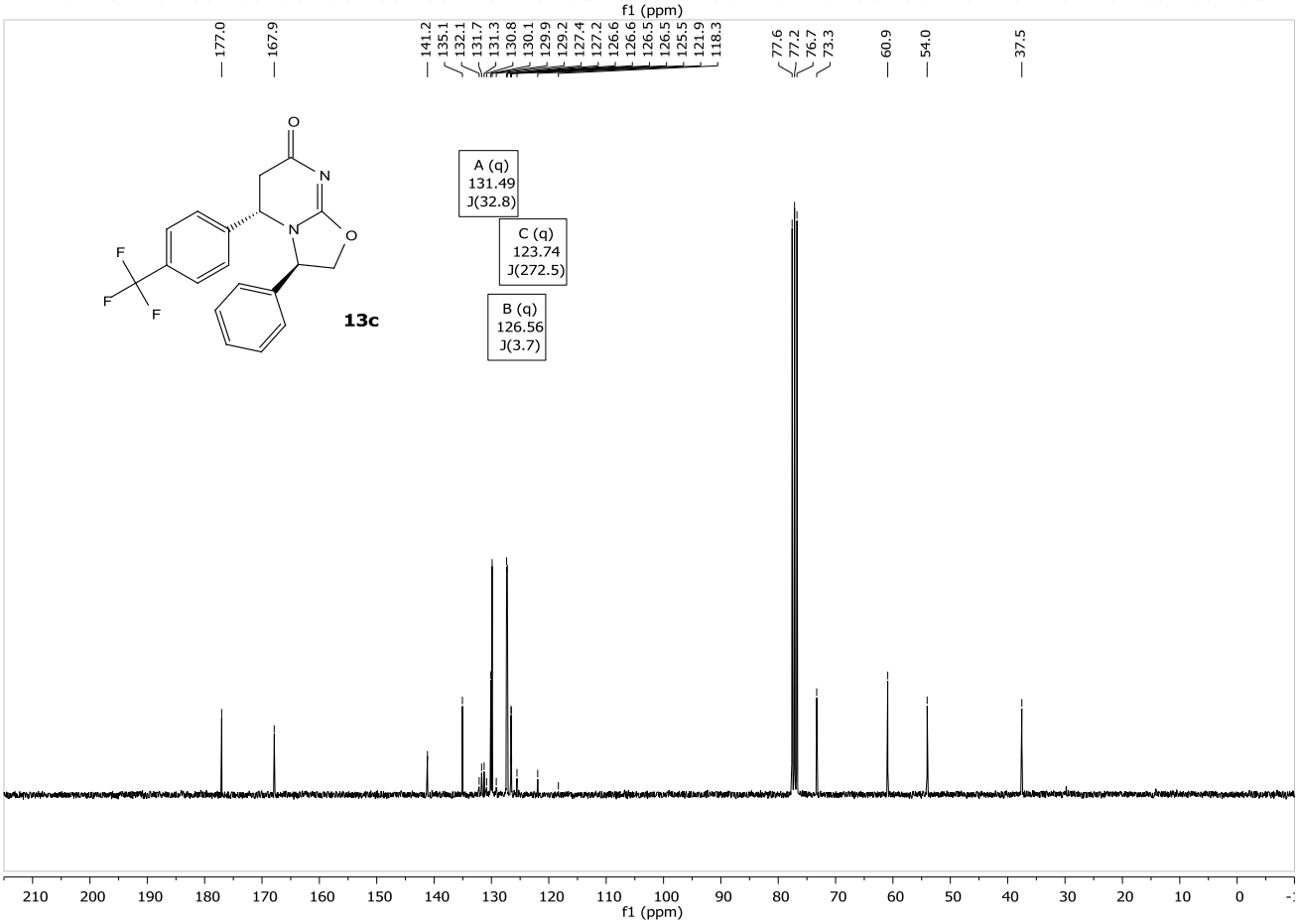
(3*R*,5*S*)-3-(4-methoxyphenyl)-5-phenyl-2,3,5,6-tetrahydro oxazolo [3,2-a] pyrimidin-7-one (13b).



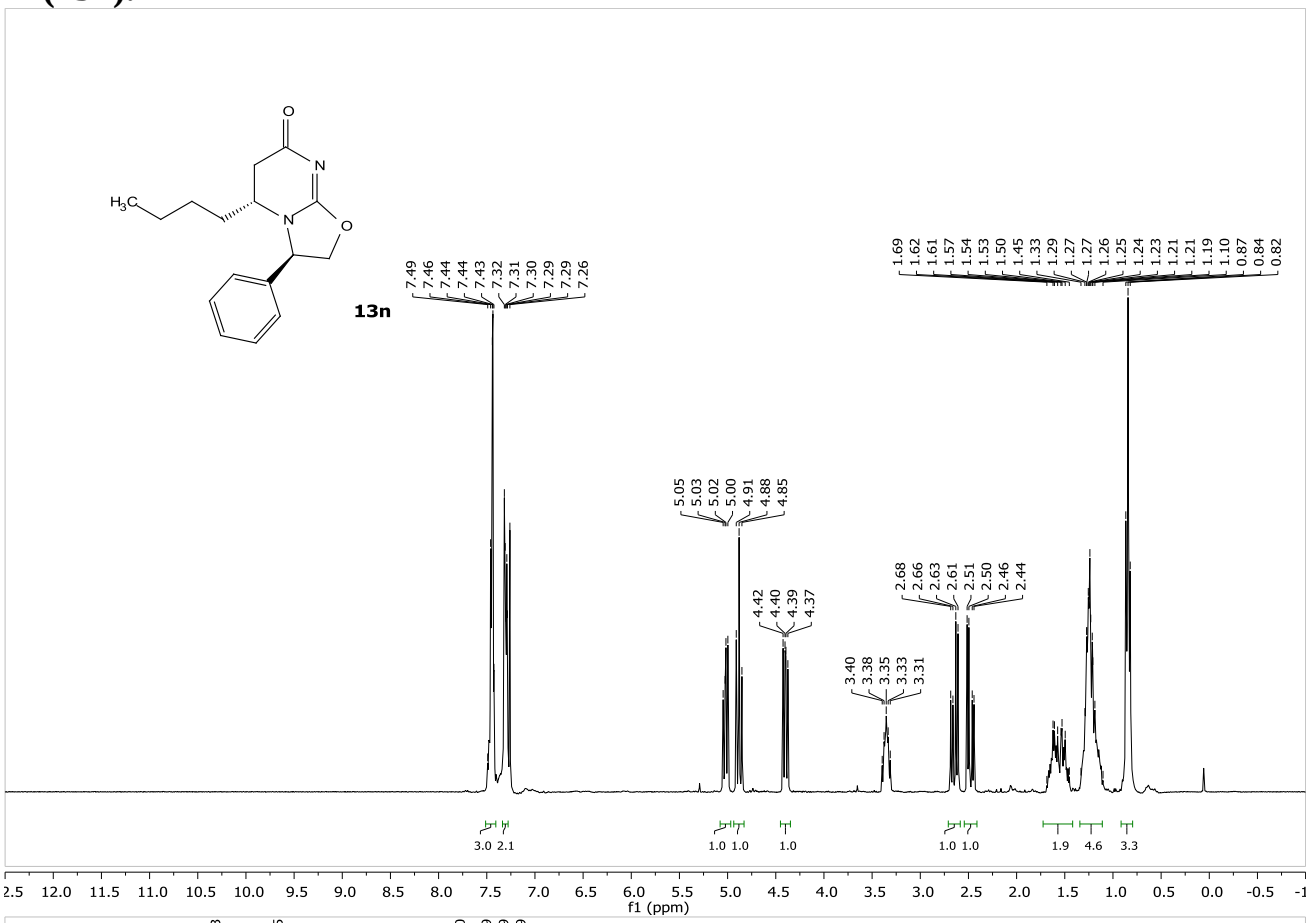


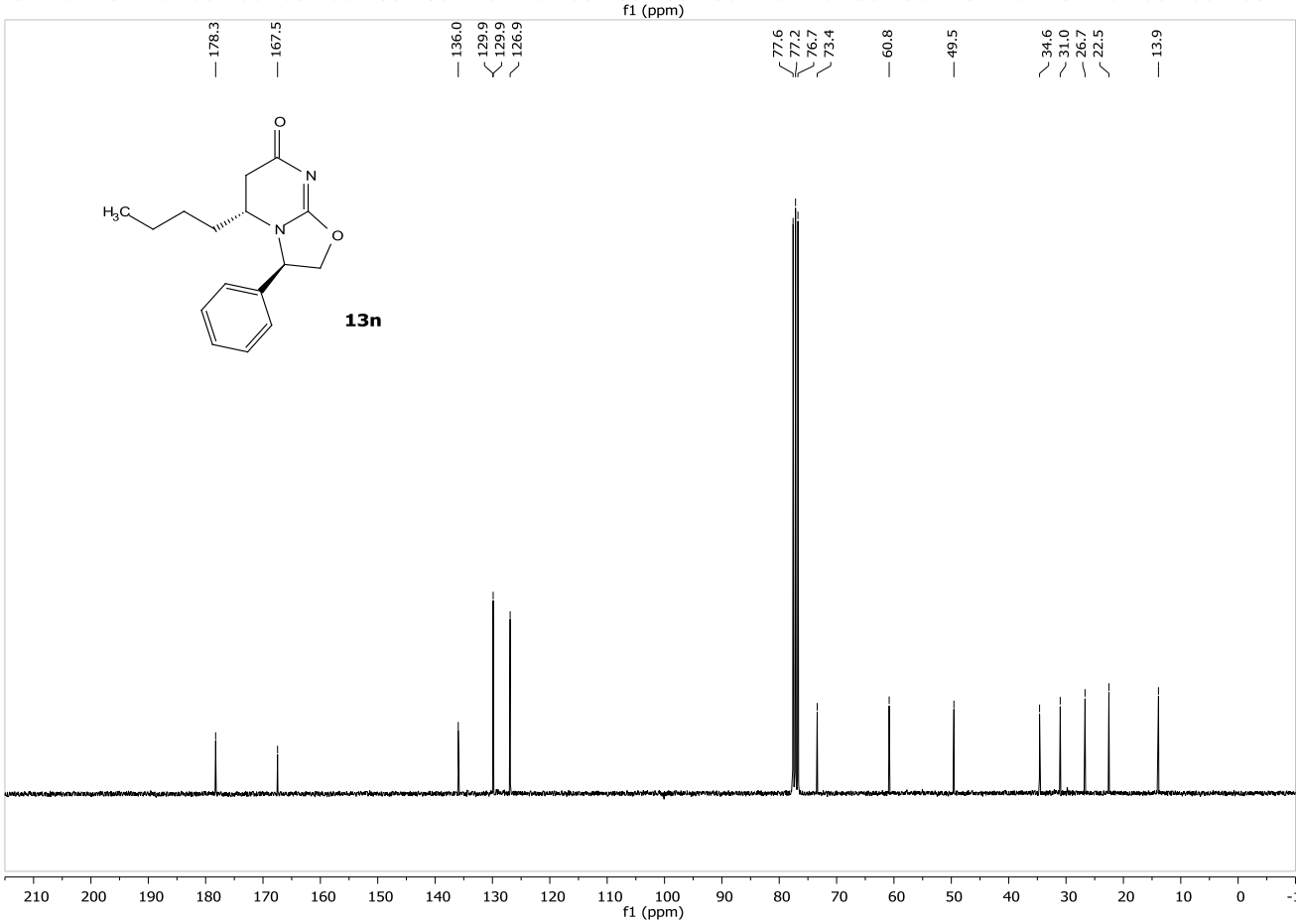
(3*R*,5*S*)-3-phenyl-5-(4-trifluoromethylphenyl)-2,3,5,6-tetrahydro oxazolo [3,2-a] pyrimidin-7-one (13c).



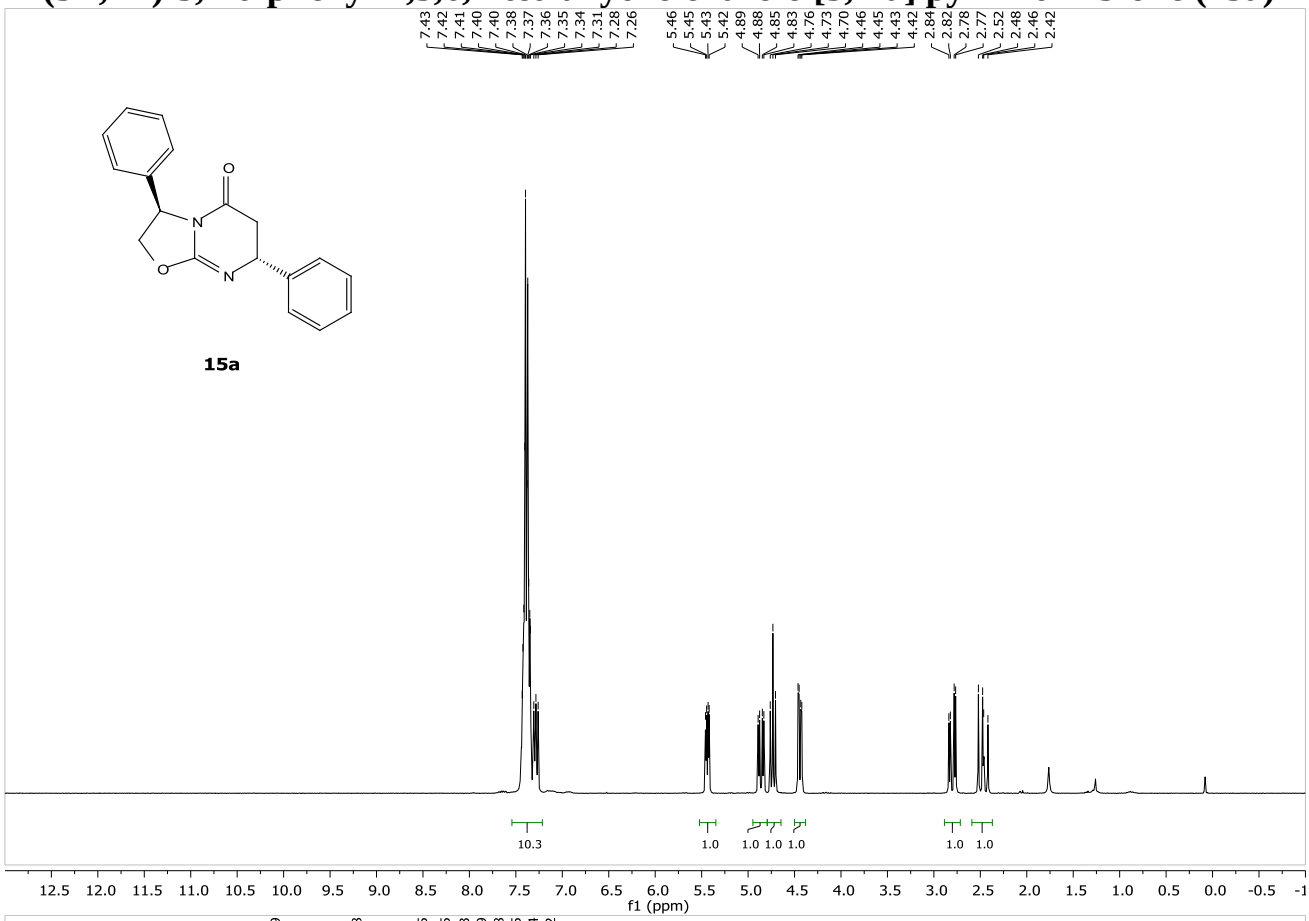


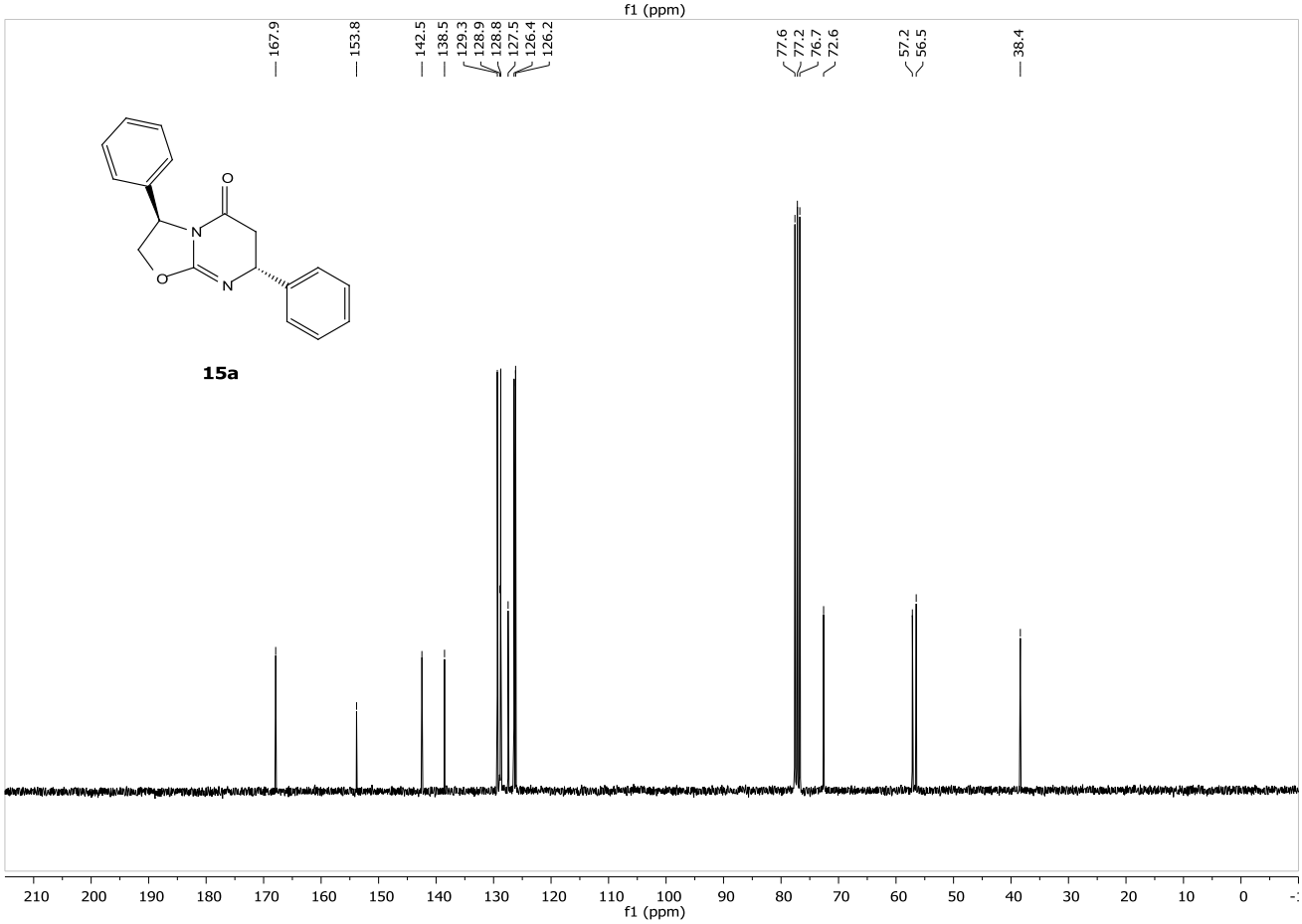
(3*R*,5*R*)-5-butyl-3-phenyl-2,3,5,6-tetrahydro oxazolo [3,2-a] pyrimidin-7-one (13n).





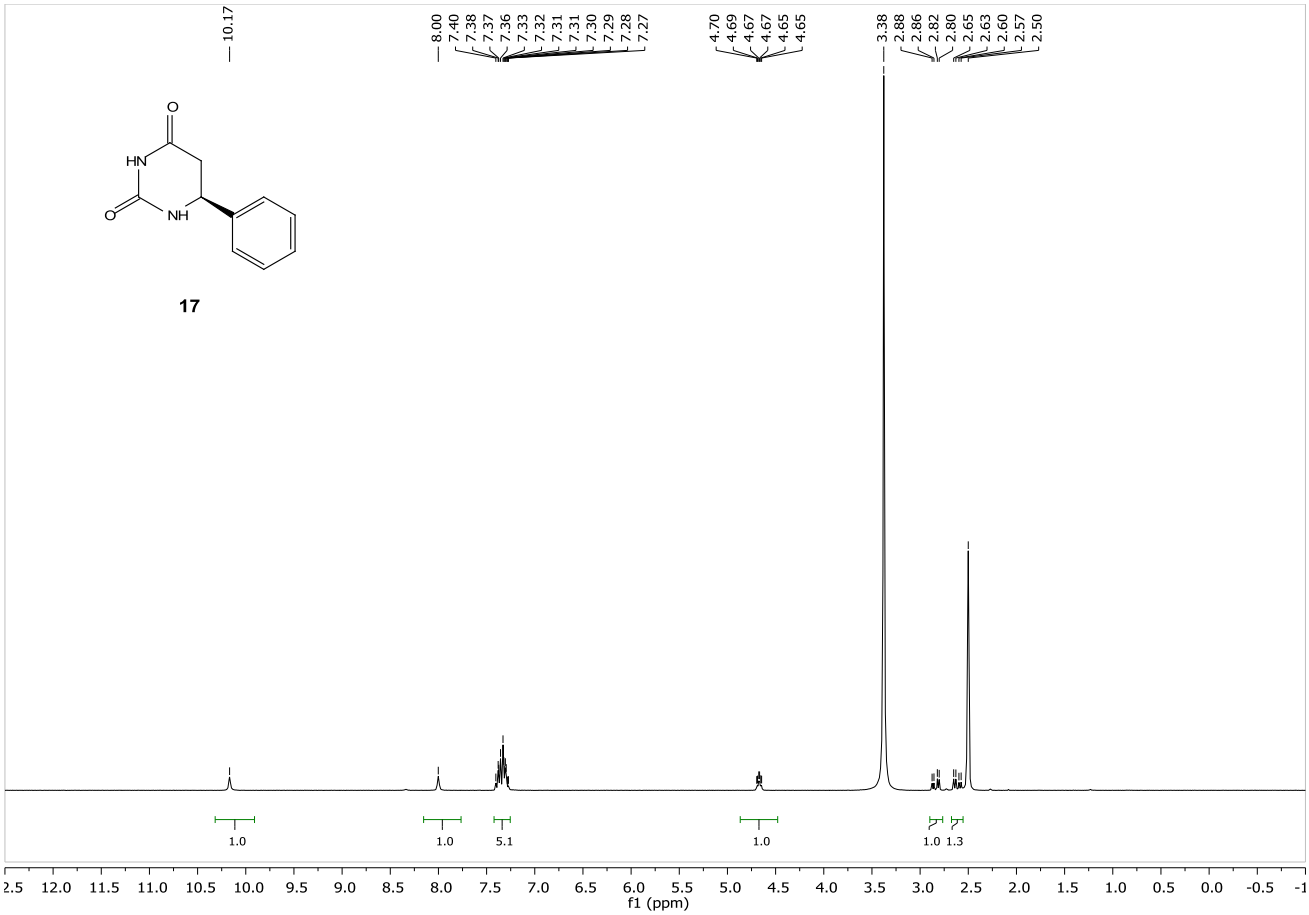
(3*R*,7*R*)-3,7-diphenyl-2,3,6,7-tetrahydro oxazolo [3,2-a] pyrimidin-5-one (15a)





6-phenyldihydropyrimidine-2,4-dione. (17).

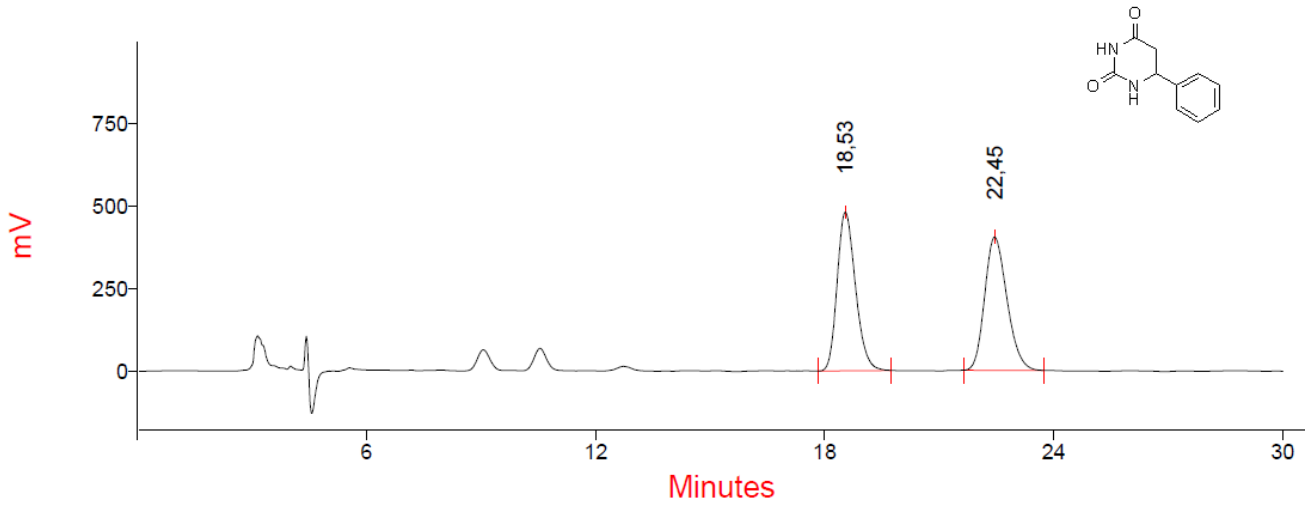
^{1}H NMR



HPLC for (S) enantiomer

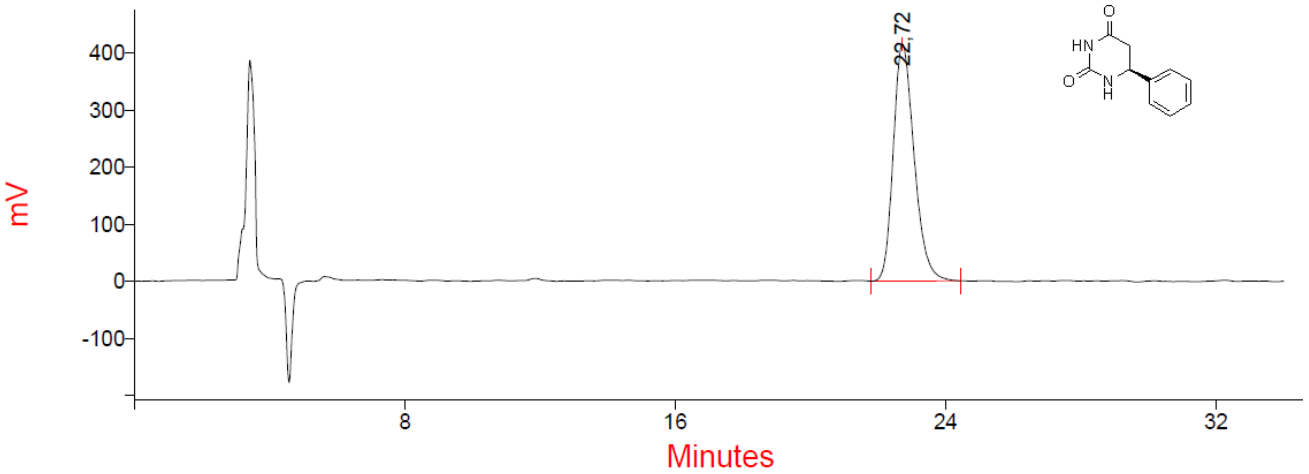
Résultats d'intégration

#	Nom du pic	Tr.	Aire	% Aire	Résultats	% Résultats
1		18,53	16112,73	49,52	0,00	0,00
2		22,45	16425,80	50,48	0,00	0,00
SOMME			**32538,53**	**100,00**	**0,00**	**0,00**



Résultats d'intégration

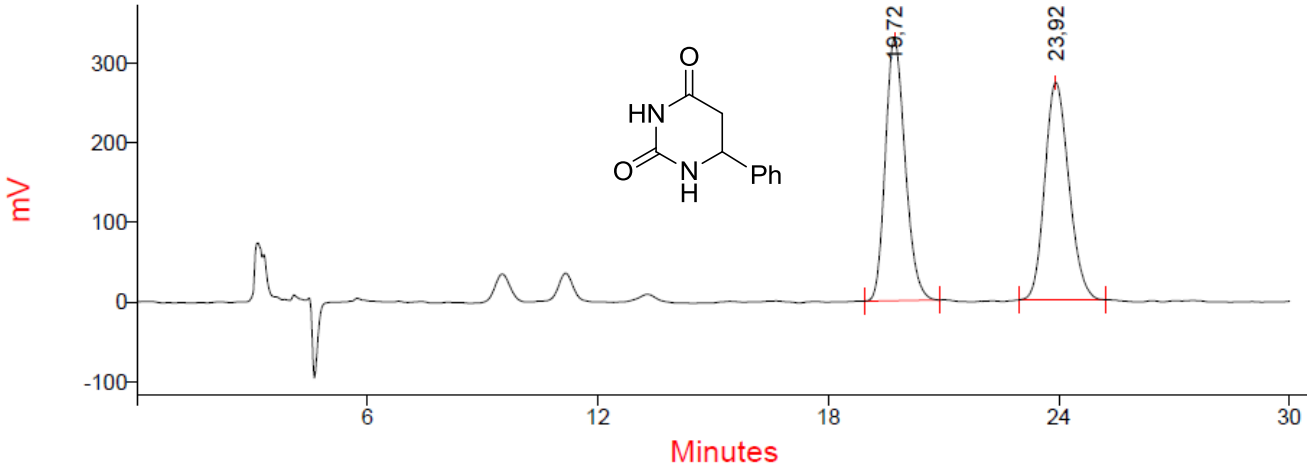
#	Nom du pic	Tr.	Aire	% Aire	Résultats	% Résultats
1		22,72	17840,40	100,00	0,00	0,00
SOMME			**17840,40**	**100,00**	**0,00**	**0,00**



HPLC for (R) enantiomer

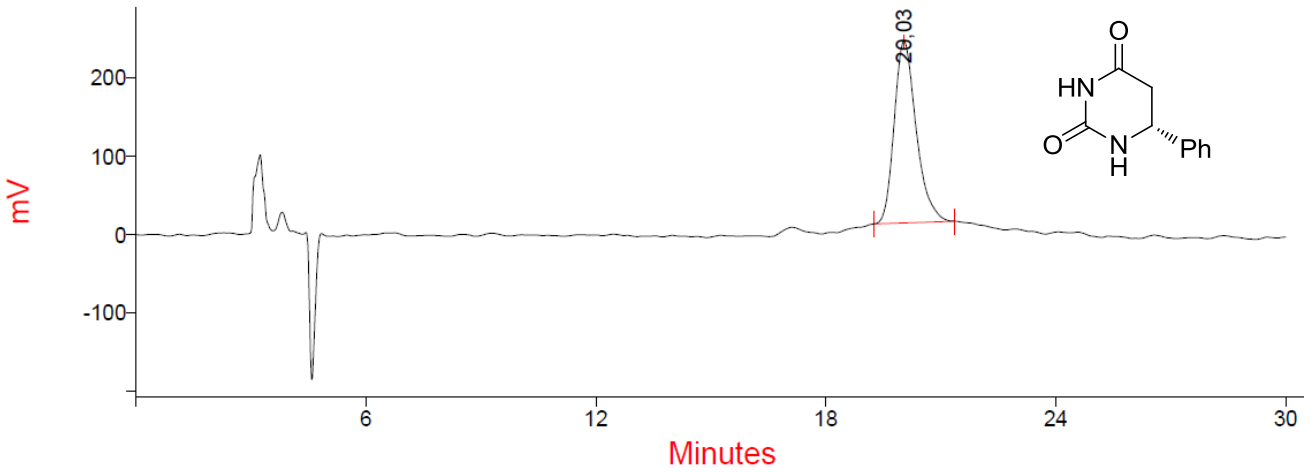
Résultats d'intégration

#	Nom du pic	Tr.	Aire	% Aire	Résultats	% Résultats
1		19,72	11756,44	49,77	0,00	0,00
2		23,92	11867,40	50,23	0,00	0,00
SOMME			**23623,85**	**100,00**	**0,00**	**0,00**

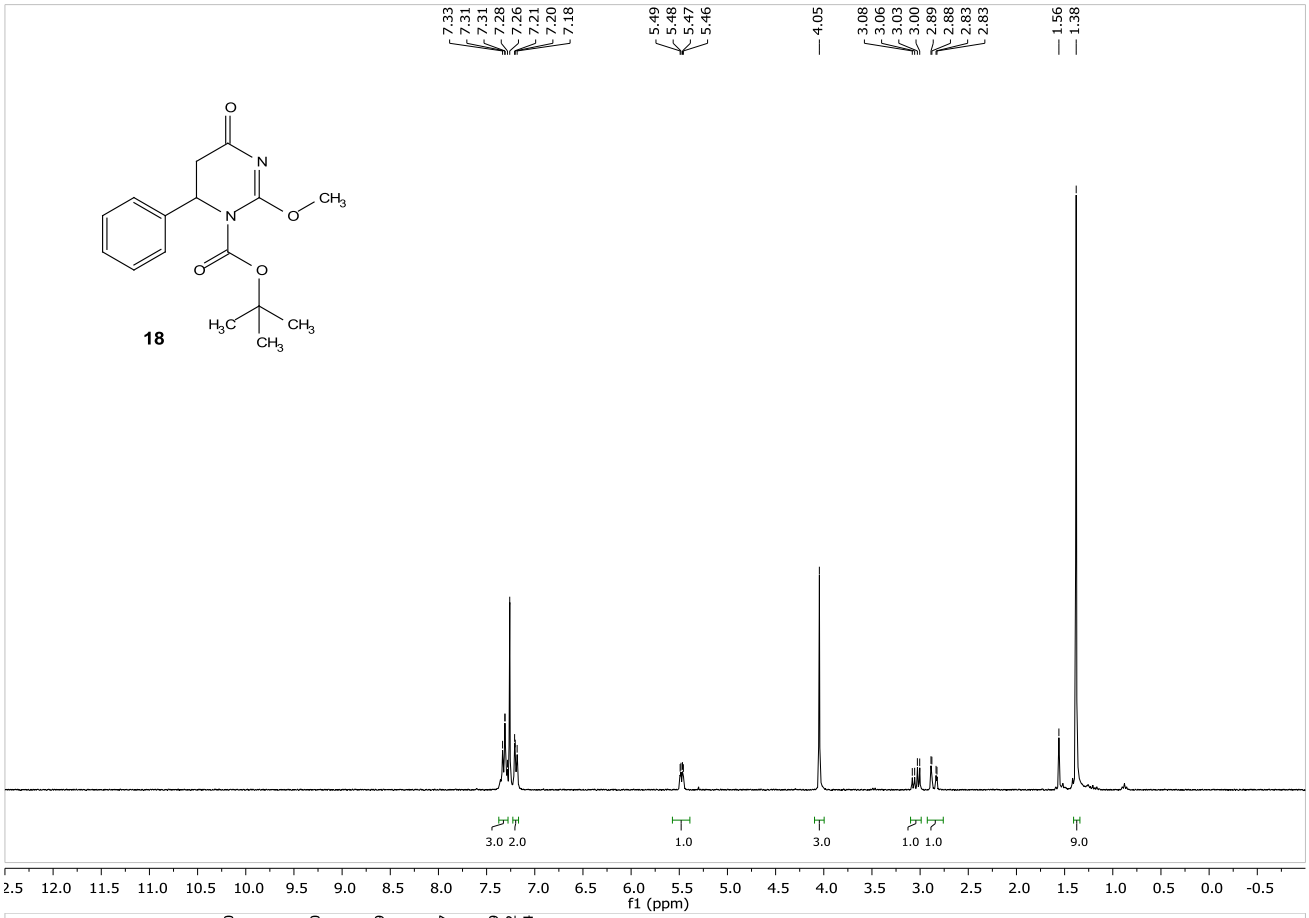


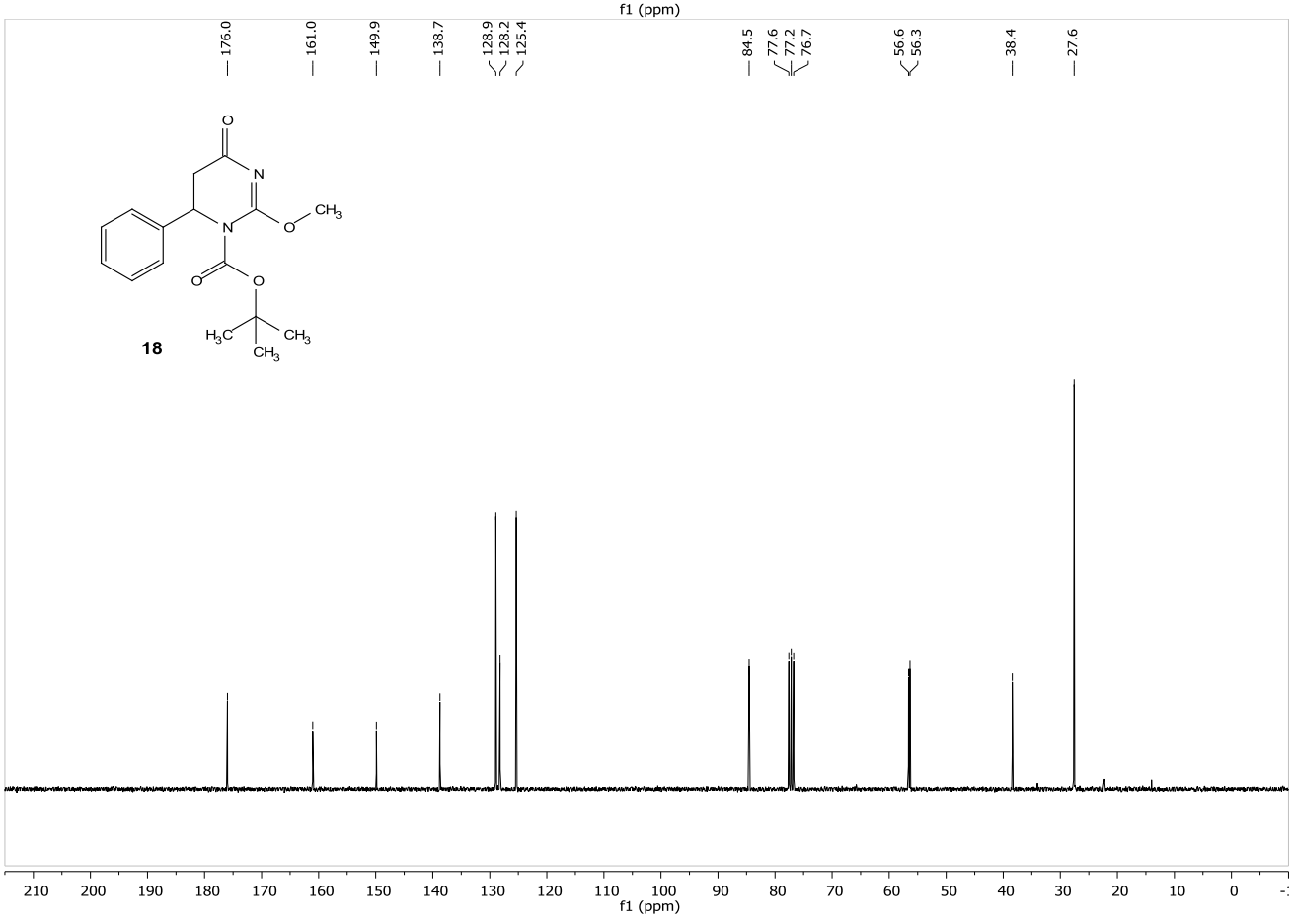
Résultats d'intégration

#	Nom du pic	Tr.	Aire	% Aire	Résultats	% Résultats
1		20,03	9274,74	100,00	0,00	0,00
SOMME			**9274,74**	**100,00**	**0,00**	**0,00**

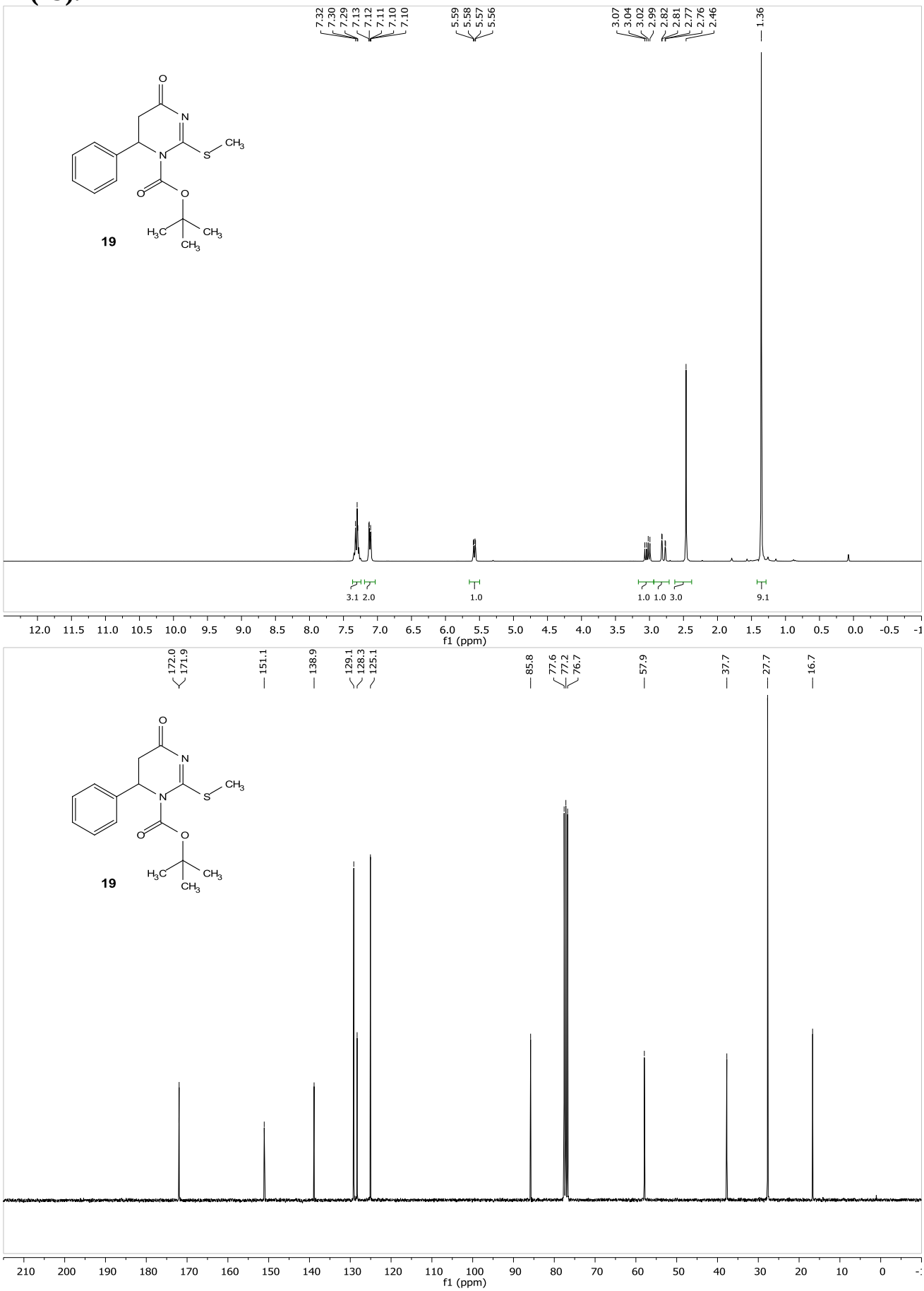


tert-butyl 2-methoxy-4-oxo-6-phenyl-5,6-dihydropyrimidine-1-carboxylate (18).

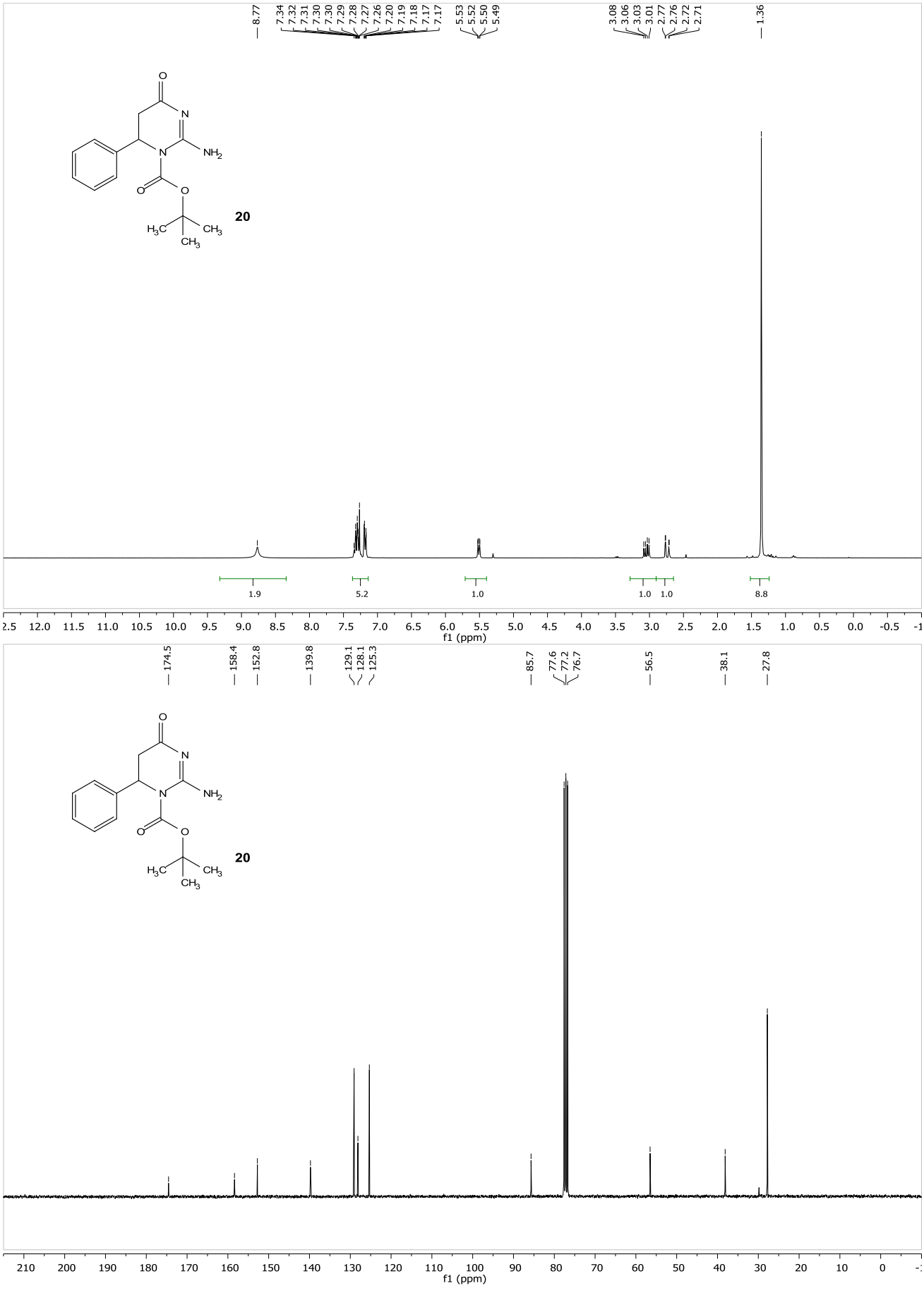




***tert*-butyl 2-methylthio-4-oxo-6-phenyl-5,6-dihydropyrimidine-1-carboxylate (19).**



tert-butyl 2-amino-4-oxo-6-phenyl-5,6-dihydropyrimidine-1-carboxylate (20).



tert-butyl 4-oxo-6-phenyltetrahydropyrimidine-1-carboxylate (21).