SUPPLEMENTARY MATERIAL

Total Synthesis and Antiproliferative Activity Screening of (±)-Aplicyanins A, B and E and Related Analogs

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General Data: Reagents and solvents were purified according to *Purification of Laboratory Chemicals,* Armarego, W. and Chai C., Elsevier (2003). Melting points (mp) were determined in a Büchi Melting Point B540 in open capillaries and are uncorrected. Automatic flash chromatography was done in an Isco Combiflash medium pressure liquid chromatograph with Redisep silica gel columns (47-60 μm). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer and a Gemini 200 MHz spectrometer. Multiplicity of the carbons was assigned with DEPT and gHSQC experiments, although the usual abbreviations according to off-resonance decoupling are used: (s) singlet, (d) doublet, (t) triplet, and (q) quartet. The same abbreviations were used for the multiplicity of signals in H NMR and also: (m) multiplet, (bs) broad singlet, (bd) broad doublet. Spectra were referenced to appropriate residual solvent peaks (d_6-acetone, d_6-DMSO, d_4-MeOH or $CDCl_3$). IR spectra were obtained on a Thermo Nicolet FT-IR spectrometer. HRMS were performed on a Bruker Autoflex high resolution mass spectometer by Unidad de Espectrometría de Masas (Universidad de Santiago de Compostela) and by Servei d'Espectrometria de Masses (Universitat de Barcelona). Microwave-assisted reactions were carried out in a CEM Discover microwave. The automatic syringe pump was used as specified for controlled addition of some reactants. Reversed phase analytical HPLC was performed on a Waters Alliance separation module 2695 and a Waters 996 PDA detector at 254 nm, using the following columns: a Waters Xterra MS C_{18} column (150 x 4.6 mm, 5 μm) for runs of 15 min, a Waters XBridge C_{18} column (75 x 4.6 mm, 2.5 μm) for runs of 8 min. Purification by semipreparative reversed phase HPLC were performed on a Symmetry C18 (5 μm, 30x100 mm) column, UV detection at 220 nm, with a flow of 10 mL/min, and using H_2O - 0.1% TFA / CH_3CN - 0.05% TFA as solvent system with a gradient specified for each case.

Experimental Procedures and Characterization of 3a-e

(*E*)-3-(1-Methylindol-3-yl)acrylaldehyde (3a).[1] NaOEt (1.35 g, 18.8 mmol) was added to a suspension of 2-(1,3-dioxolan-2-yl)ethyltriphenylphosphonium bromide (**2x**) (4.40 g, 10.1 mmol) in THF-EtOH (99:1, 100 mL). The mixture was stirred at r.t. for 1 h during which time it turned yellow. Then, 3-formyl-1-methylindole **7** (1.0 g, 6.3 mmol) was added, and the mixture was stirred for 72 h at reflux. The solvent was removed and the residue was dissolved in EtOAc, and washed with sat. NH_4Cl then brine. The organic solution was dried over $MgSO_4$ and solvent removed. The residue was digested with hexane. The hexane solution was collected and evaporated. The residue was purified by SiO_2 flash chromatography. Elution with CH_2Cl_2 gave **3a** (1.02 g, 71%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.85 (s, 3H); 6.74 (dd, *J* = 15.7, 7.9 Hz, 1H); 7.26-7.37 (m, 3H); 7.38 (s, 1H); 7.65 (d, *J* = 15.7, 1H); 7.90 (dd, *J* = 7.9 and 2.3 Hz, 1H); 9.60 (d, *J* = 7.9 Hz, 1H). MS (ESI) 186 (M+1, 100).

(*E*)-3-(5,6-Dibromo-1-methoxyindol-3-yl)acrylaldehyde (3b) was obtained as a yellow oil in 19% yield by Wittig reaction of 5,6-dibromo-1-methoxy-*1H*-indole-3-carbaldehyde (**1b**) and 2-(1,3-dioxolan-2-yl)ethyltriphenylphosphonium bromide (**2x**). ^{1}H NMR (400 MHz, $CDCl_3$) 4.15 (s, 3H), 6.63 (dd, *J* = 15.9 and 7.7 Hz, 1H); 7.50 (d, *J* = 15.9 Hz); 7.64 (s, 1H), 7.77 (s, 1H), 8.12 (s, 1H), 9.61 (d, *J* = 7.7 Hz, 1H).

(*E*)-Ethyl 3-(3-indolyl)acrylate (3c).[2] Cs_2CO_3 (6.81 g, 20.7 mmol) was added to a solution of ethyl (diethoxyphosphoryl)acetate (4.81 g, 20.7 mmol) and 3-formylindole (1.06 g, 6.9 mmol) in dioxane-DMSO (99:1, 100 mL). The mixture was stirred at 70 ºC for 43 h. The solvent was removed and the residue was dissolved in EtOAc. The organic solution was washed with sat. NH_4Cl, sat. $NaHCO_3$, and brine. The organic solution was dried over $MgSO_4$ and concentrated

[1] Pla, D.; Mills, K.; Joule, J. A.; Albericio, F.; Álvarez, M. The synthesis of 1,2,3,6,6a,7-hexahydro-7-methyl-5-imino-1*H*-pyrrolo[1,2-*c*]imidazolo[5,4-*b*]indole. *Arkivoc*. **2009**, *6*, 260-269.
[2] Hanley, A. B.; Parsley, K. R.; Lewis, J. A.; Fenwick, G. R. Chemistry of indole glucosinolates: intermediacy of indol-3-ylmethyl isothiocyanates in the enzymic hydrolysis of indole glucosinolates. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2273-2276.

in vacuo. Purification by silica-gel chromatography (hexane-EtOAc; 90:10 to 80:20) afforded **3c** (1.39 g, 93%) as a yellow solid. Characterization data is in accordance with literature. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.2 Hz, 3H, Me); 4.28 (q, *J* = 7.2 Hz, 2H, CH_2); 6.47 (d, *J* = 16.0 Hz, 1H); 7.19-7.30 (m, 2H); 7.38-7.43 (m, 2H); 7.88-7.96 (m, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.5; 60.2; 111.8; 113.1; 113.3; 120.3; 121.4; 123.2; 125.2; 129.0; 137.1; 138.4; 168.4. MS (ESI) 214 (M-1, 100); 215 (M, 7).

(*E*)-Ethyl 3-(1-methoxyindol-3-yl)acrylate (3d). Cs_2CO_3 (3.42 g, 10.5 mmol) was added to a solution of ethyl (diethoxyphosphoryl)acetate (2.39 g, 10.5 mmol) and 1-methoxy-3-formylindole (611 mg, 3.5 mmol) in dioxane-DMSO (99:1, 50 mL). The mixture was stirred at 70 ºC for 43 h. The solvent was removed and the residue was dissolved in EtOAc. The organic solution was washed with sat. NH_4Cl, sat. $NaHCO_3$, and brine. The organic solution was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by silica-gel chromatography (hexane-EtOAc; 95:10 to 90:10) afforded **3d** (608 mg, 71%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.2 Hz, 3H, Me); 4.11 (s, 3H, OMe); 4.27 (q, *J* = 7.2 Hz, 2H, CH_2); 6.41 (d, *J* = 16.0 Hz, 1H); 7.20-7.36 (m, 2H); 7.44-7.55 (m, 2H); 7.79-7.91 (m, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.5; 60.1; 66.4; 108.8; 113.9; 120.5; 121.7; 122.2; 123.5; 125.8; 132.8; 137.2; 167.9. MS (ESI) 246 (M+1, 100); 247 (M+2, 30).

(*E*)-Ethyl 3-(1-methylindol-3-yl)acrylate (3e).[3] Cs_2CO_3 (1.27 g, 3.8 mmol) was added to a solution of ethyl (diethoxyphosphoryl)acetate (880 mg, 3.8 mmol) and 1-methyl-3-formylindole (204 mg, 1.3 mmol) in dioxane-DMSO (99:1, 15 mL). The mixture was stirred at 70 ºC for 43 h. The solvent was removed and the residue was

[3] Compound **3e** has been recently synthesized using a different approach. See Li, X.; Wang, J.-Y.; Yu, W.; Wu, L.-M. $PtCl_2$-catalyzed reactions of o-alkynylanilines with ethyl propiolate and dimethyl acetylenedicarboxylate. *Tetrahedron* **2009**, *65*, 1140-1146.

dissolved in EtOAc. The organic solution was washed with sat. NH_4Cl, sat. $NaHCO_3$, and brine. The organic solution was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by silica gel chromatography with (hexane-EtOAc; 90:10 to 85:15) afforded **3e** (234 mg, 80%) as a yellow solid. Characterization data is in accordance with literature. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.1 Hz, 3H, Me); 3.81 (s, 3H, Me); 4.27 (q, *J* = 7.1 Hz, 2H, CH_2); 6.41 (d, *J* = 16.0 Hz, 1H); 7.21-7.37 (m, 4H); 7.84-7.94 (m, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.5; 33.2; 60.0; 109.9; 112.1; 112.6; 120.6; 121.2; 122.9; 126.0; 133.0; 137.9; 138.0; 168.2. MS (ESI) 230 (M+1, 100); 231 (M+2, 10).

Experimental Procedure and Characterization of 4a

(*E*)-3-(1-Methylindol-3-yl)allylguanidine (4a). *tert*-BuONa (440 mg, 4.4 mmol) was added to a solution of (*E*)-3-(1-methylindol-3-yl)acrylaldehyde (**3a**)[30] (274 mg, 1.5 mmol) and guanidine hydrochloride (708 mg, 7.4 mmol) in *tert*-BuOH (10 mL). The mixture was refluxed for 72 h. The solvent was removed, and the residue was dissolved in MeOH. The solution was then cooled to 0 ºC, and $NaBH_4$ (402 mg, 10.6 mmol) was added in one solid portion. The mixture was stirred for 4 h at r.t. The solvent was removed, and the crude was dissolved in CH_2Cl_2, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by silica gel chromatography (CH_2Cl_2-MeOH; 97:3 to 92:8) afforded **4a** (73 mg, 20%) as a yellow solid. ^{1}H NMR (d_6-DMSO, 400 MHz) δ 3.16 (d, *J* = 5.3 Hz, 1H); 3.81 (s, 3H); 6.50 (bs, 3H); 6.57 (d, *J* = 16.0 Hz, 1H); 7.19 (t, *J* = 7.8 Hz, 1H); 7.26 (t, *J* = 8.0 Hz, 1H); 7.51 (d, *J* = 8.0 Hz, 1H); 7.78 (s, 1H); 7.81 (d, *J* = 7.8 Hz, 1H); 7.98 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR (d_6-DMSO, 100 MHz) δ 42.3; 58.1; 120.1; 121.1; 129.1; 131.1; 131.7; 135.1; 140.9; 142.5; 147.3; 176.6; 180.8. MS (ESI) 229 (M+1, 100); 230 (M+2, 14).

Experimental Procedures and Characterization of 5a-e

5,6-Dibromo-1-methoxy-3-(3-phthalimidopropanoyl)indole (5a). A solution of 3-(3-phthalimidopropanoyl)chloride (139 mg, 0.6 mmol) and 1M Et_2AlCl in hexane (0.6 mL, 0.6 mmol) was stirred in CH_2Cl_2 (10 mL) at 0 ºC under Ar. A solution of 5,6-dibromo-1-methoxyindole (119 mg, 0.4 mmol) in CH_2Cl_2 (5 mL) was then added dropwise after 30 min. The reaction mixture was stirred for 16 h at r.t. and then washed with a sat. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by silica gel chromatography (hexane-EtOAc; 70:30 to 60:40) afforded **5a** (45.4 mg, 23%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.25 (t, J = 7.2 Hz, 2H); 4.14 (s, 3H); 4.15 (t, J = 7.2 Hz, 2H); 7.71-7.73 (m, 2H); 7.74 (s, 1H); 7.84-7.86 (m, 2H); 7.92 (s, 1H); 8.69 (s, 1H).

3-(3-Phthalimidopropanoyl)indole (5b). A solution of 3-(3-phtalimidopropanoyl)chloride (471 mg, 1.98 mmol) and 1M Et_2AlCl in hexane (2.0 mL, 2.0 mmol) was stirred in CH_2Cl_2 (10 mL) at 0 ºC under Ar. After 30 min, a solution of indole (155 mg, 1.3 mmol) in CH_2Cl_2 (7 mL) was added dropwise. The reaction mixture was stirred for 2 h at 0 ºC, and then washed with a sat. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by silica gel chromatography (hexane-EtOAc; 70:30 to 50:50) afforded **5b** (231 mg, 55%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.24 (t, J = 7.3 Hz, 2H); 3.94 (t, J = 7.3 Hz, 2H); 7.16 (t, J = 7.4 Hz, 1H); 7.20 (t, J = 7.6 Hz, 1H); 7.45 (d, J = 7.4 Hz, 1H); 7.80-7.87 (m, 4H); 8.14 (d, J = 7.6 Hz, 1H); 8.27 (s, 1H); 11.95 (bs, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ 34.6; 37.9; 112.8; 116.7; 122.0; 122.5; 123.5; 123.7; 125.9; 132.4; 134.8; 135.1; 137.3; 168.4; 193.2.

3-(3-Bromopropanoyl)-1-methylindole (5c). A solution of 3-bromopropanoyl chloride (1.54 mL, 15.2 mmol) and 1M Et_2AlCl in hexane (11.4 mL, 11.4 mmol) was stirred in CH_2Cl_2 (10 mL) at 0 ºC under Ar. After 30 min, a solution of 1-methylindole (1.0 g, 7.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The mixture was stirred for 4 h at r.t. and then washed with sat. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by silica gel chromatography (hexane-EtOAc; 70:30 to 60:40) afforded **5c** (602 mg, 30%) as a red oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.43 (t, *J* = 7.0 Hz, 2H); 3.80 (t, *J* = 7.0 Hz, 2H); 3.86 (s, 3H); 7.31-7.36 (m, 3H); 7.74 (s, 1H) and 8.36-8.38 (m, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ 27.2; 33.8; 42.7; 109.9; 116.2; 122.8; 123.1; 123.8; 126.4; 135.8; 137.7; 191.7. MS (CI) 267 (MBr^{81}, 100); 265 (MBr^{79}, 92).

3-(3-Formamidopropanoyl)-1-methylindole (5d). To a stirring solution of **5c** (98 mg, 0.37 mmol) in dry DMF (5 mL) was added sodium diformylamide (105 mg, 1.1 mmol) in one portion. The mixture was stirred at 80 ºC overnight, and then concentrated *in vacuo* and the crude mixture was dissolved in MeOH (10 mL) and refluxed for 2 h. The mixture was concentrated, and then dissolved in CH_2Cl_2, washed with water, dried over $MgSO_4$ and concentrated again to give **5d** in quantitative yield as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.14 (t, *J* = 5.5 Hz, 2H); 3.75 (dt, *J* = 5.5, 5.5 Hz, 2H); 3.87 (s, 3H); 6.46 (bs, 1H); 7.35 (m, 3H); 7.76 (s, 1H); 8.14 (s, 1H); 8.33 (m, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ 33.7; 33.9; 38.8; 110.0; 120.1; 122.5; 123.1; 123.8; 135.9; 161.4.

***N*-(2,2,2-Trichloroethoxysulfonyl)-*N'*-(3-(1-methylindol-3-yl)-3-oxopropyl)guanidine (5e).** A solution of **5d** (1.56 g, 6.78 mol) in MeOH (1.25 M HCl) was refluxed with for 2 h. The solvent was evaporated off and the crude was dissolved in CH_2Cl_2, washed with an aqueous solution of 50% NaOH, dried, and concentrated *in vacuo* to give 3-(3-aminopropanoyl)-1-methylindole in quantitative

yield as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.00 (t, *J* = 6.2 Hz, 2H); 3.13 (t, *J* = 6.2 Hz, 2H); 3.84 (s, 3H); 7.32 (m, 3H); 7.74 (s, 1H); 8.38 (m, 1H).

A solution of 3-(3-aminopropanoyl)-1-methylindole (1.37 g, 6.78 mmol) and protected isothiourea **6** (2.25 g, 7.46 mmol) in H_2O (50 mL) was refluxed overnight, and then cooled to r.t.. The crude mixture were diluted with 20 mL of H_2O, extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by silica gel chromatography (hexane-EtOAc; 60:40 to 50:50) afforded **5e** (632 mg, 20%) as a yellow solid; m.p. (MeCN) 172-174 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.22 (bs, 2H); 3.70 (m, 2H)); 3.81 (s, 3H); 4.56 (bs, 2H); 6.39 (bs, 1H); 7.32 (m, 3H); 7.79 (s, 1H) and 8.24 (bs, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ 29.9; 33.8; 37.2; 78.3; 94.4; 116.0; 122.3; 123.3; 123.9; 126.2; 137.0; 137.7; 158.3. MS (CI) 911 (2M, 25); 457 (M+2, 100); 403 (20); 227 (20); 130 (55); 124 (95). HRMS m/z calcd. for $C_{15}H_{17}Cl_3N_4O_4S$ $(M+H)^+$ 455.0109, found 455.0119.

Experimental Procedure and Characterization of 7

2,2,2-Trichloroethyl 6-(1-methylindol-3-yl)-tetrahydropyrimidin-2(1*H*)-ylidenesulfamate (7). A solution of **5e** (251 mg, 0.55 mmol) in diphenylether (8 mL) and two drops of formic acid was stirred at 200 ºC overnight. The reaction mixture was cooled to r.t. and run through a small column of silica gel: firstly, with hexane, to remove all the diphenylether, and then, with EtOAc, to elute the crude product. Purification by semipreparative reverse phase HPLC (H_2O-MeCN; gradient 60:40 to 50:50 in 30 min) afforded **7** (10 mg, 7%) as a yellow solid; m.p. (MeCN) 104-106 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.25 (m, 2H); 3.78 (s, 3H); 4.60 (s, 2H); 5.00 (m, 1H); 6.74 (bs, 1H); 6.99 (bs, 1H); 7.02 (s, 1H); 7.15 (t, *J* = 7.0, 1H); 7.29 (t, *J* = 8.0 Hz, 1H); 7.34 (d, *J* = 7.0 Hz, 1H); 7.54 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ 27.2;

32.9; 37.9; 47.6; 77.9; 94.5; 109.9; 113.7; 118.4; 119.8; 122.5; 124.9; 126.6; 137.5; 154.6.

Experimental Procedures and Characterization of 8a,b,d,f-i

2,2-Dimethyl-5-[(1-methylindol-3-yl)methylene]-1,3-dioxane-4,6-dione (8a). Starting from **1a** (1.05 mg, 6.60 mmol) and following the general procedure, **8a** (81%) was obtained as a yellow solid; m.p. (MeCN) 212-213 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77 (s, 6H); 3.97 (s, 3H); 7.37-7.45 (m, 3H); 7.93-7.99 (m, 1H); 8.9 (s, 1H); 9.39 (s, 1H). MS (CI) 286 (M+1, 100).

2,2-Dimethyl-5-[(5,6-dibromo-1-methoxyindol-3-yl)methylene]-1,3-dioxane-4,6-dione (8b). Starting from **1b**[4] (200 mg, 0.60 mmol) and following the general procedure, **8b** (87%) was obtained as a yellow oil. This compound was used without further purification in the following step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74 (s, 6H); 4.38 (s, 3H); 8.10 (s, 1H); 8.48 (s, 1H); 8.67 (s, 1H); 9.46 (s, 1H). MS (ESI-TOF) 458 ($M(Br^{79})_2$+1, 52); 460 ($MBr^{79}Br^{81}$+1, 100); 462 ($M(Br^{81})_2$+1, 54).

2,2-Dimethyl-5-[(1-methoxyindol-3-yl)methylene]-1,3-dioxane-4,6-dione (8d). Starting from **1d**[2] (627 mg, 3.58 mmol) and following the general procedure, **8d** (quantitative yield) was obtained as a yellow oil. ^{1}H NMR (400 MHz, d_6-acetone) δ 1.78 (s, 6H); 4.26 (s, 3H); 7.37-7.45 (m, 2H); 7.52-7.57 (m, 1H); 7.93-8.00 (m, 1H); 8.88 (s, 1H); 9.55 (s, 1H). MS (ESI-TOF) 625 (2M+Na, 100).

2,2-Dimethyl-5-[(5-bromoindol-3-yl)methylene]-1,3-dioxane-4,6-dione (8f). Starting from **1f** (500 mg, 2.23 mmol) and following the general procedure, **8f** (65%) was obtained as an orange solid; m.p. (MeCN) 333-334 ºC. ^{1}H NMR (400 MHz, d_6-

[4] Mouloungui, Z.; Murengezi, I.; Delmas, M.; Gaset, A. Cesium carbonate in a weakly hydrated solid-liquid heterogeneous medium: a new reagent for anionic activation synthesis. *Synth. Commun.* **1988**, *18*, 1241-1245.

acetone) δ 1.74 (s, 6H); 7.48 (dd, *J* = 8.6 and 2.0 Hz, 1H); 7.62 (d, *J* = 8.6 Hz, 1H); 8.18 (d, *J* = 2.0 Hz, 1H); 8.77 (s, 1H); 9.44 (s, 1H). MS (ESI-TOF) 723 (2M+Na, 100).

2,2-Dimethyl-5-[(6-bromoindol-3-yl)methylene]-1,3-dioxane-4,6-dione (8g). Starting from **1g** (500 mg, 2.23 mmol) and following the general procedure, **8g** (650 mg, 83%) was obtained as a yellow solid; m.p. (MeCN) 342-344 ºC. ^{1}H NMR (400 MHz, d_6-acetone) δ 1.74 (s, 6H); 7.50 (dd, *J* = 8.4 and 2.0 Hz, 1H); 7.85 (d, *J* = 2.0 Hz, 1H); 7.96 (d, *J* = 8.4 Hz, 1H); 8.79 (s, 1H); 9.44 (s, 1H). MS (ESI-TOF) 350 (MBr^{79}+1, 100); 352 (MBr^{81}+1, 93).

2,2-Dimethyl-5-[(5-bromo-1-methylindol-3-yl)methylene]-1,3-dioxane-4,6-dione (8h). Starting from **1h**[5] (1.06 g, 4.46 mmol) and following the general procedure, **8h** (62%) was obtained as a yellow solid; m.p. (MeCN) 221-223 ºC. ^{1}H NMR (400 MHz, d_6-acetone) δ 1.73 (s, 6H); 4.11 (s, 3H); 7.53 (dd, *J* = 8.4 and 1.6 Hz, 1H); 7.63 (d, *J* = 8.4 Hz, 1H); 8.16 (d, *J* = 1.6 Hz, 1H); 8.70 (s, 1H); 9.30 (s, 1H). MS (ESI-TOF) 364 (MBr^{79}+1, 100); 366 (MBr^{81}+1, 90).

2,2-Dimethyl-5-[(6-bromo-1-methylindol-3-yl)methylene]-1,3-dioxane-4,6-dione (8i). Starting from **1i**[5] (1.05 g, 4.41 mmol) and following the general procedure, **8i** (75%) was obtained as a yellow solid; m.p. (MeCN) 198-200 ºC. ^{1}H NMR (400 MHz, d_6-acetone) δ 1.73 (s, 6H); 4.11 (s, 3H); 7.52 (dd, *J* = 8.4 and 1.6 Hz, 1H); 7.87 (d, *J* = 1.6 Hz, 1H); 7.93 (d, *J* = 8.4 Hz, 1H); 8.71 (s, 1H); 9.29 (s, 1H). MS (ESI-TOF) 364 (MBr^{79}+1, 100); 366 (MBr^{81}+1, 95).

Experimental Procedures and Characterization of 9a,b,d,f-i

2-Amino-6-(1-methylindol-3-yl)-1*H*-5,6-dihydropyrimidin-4-one (9a). Compound **8a** (1.05 g, 1.43 mmol) was converted into **9a** (90%) as a white solid;

[5] The *N*-methylindole derivative was obtained in quantitative yield by methylation of indole with methyl iodide and NaH in THF at 0 ºC.

m.p. (MeCN) 274-276 ºC. IR (KBr film): 3418, 2977, 1717, 1657, 1552, 1509, 1477, 1427, 1411, 1385, 1357, 1326, 1304, 1250, 1174, 1156, 1141, 1072, 1013, 795, 746, 714. ^{1}H NMR (400 MHz, d_4-MeOH) δ 2.70-2.90 (m, 2H), 3.78 (s, 3H); 4.94 (dd, *J* = 5.9 and 9.2 Hz, 1H); 7.09 (t, *J* = 7.5 Hz, 1H); 7.16-7.25 (m, 2H); 7.37 (d, *J* = 8.1 Hz, 1H); 7.63 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (400 MHz, d_4-MeOH) δ 29.7, 32.6, 46.5, 47.0, 68.2, 110.4, 119.5, 120.1, 122.8, 126.8, 127.5, 131.1, 138.7. MS (ESI-TOF) 243 (M+1, 100); 265 (M+Na, 82). HRMS *m/z* calcd. for $C_{13}H_{14}N_4NaO$ 265.1060, found 265.1058.

2-Amino-6-(5,6-dibromo-1-methoxyindol-3-yl)- 1*H*-5,6-dihydropyrimidin-4-one (9b). Compound **8b** (240 mg, 0.52 mmol) was converted into **9b** (20%) as a yellow oil. IR (KBr film) 2924, 1665, 1459, 1205, 801, 724. ^{1}H NMR (400 MHz, d_4-MeOH) δ 3.01 (dd, *J* = 16.8 and 5.0 Hz, 1H); 3.21 (dd, *J* = 16.8 and 10.0 Hz, 1H); 4.11 (s, 3H); 5.26 (dd, *J* = 10.0 and 5.0 MHz, 1H); 7.68 (s, 1H); 7.88 (s, 1H); 8.12 (s, 1H). ^{13}C NMR (400 MHz, d_4-MeOH) δ 37.0, 46.4, 66.9, 108.7, 114.4, 116.6, 119.4, 123.3, 124.5, 124.9, 133.2, 168.4, 198.4. MS (ESI-TOF) 415 ($M(Br^{79})_2$+1, 48); 416 ($M(Br^{79})_2$+2, 8); 417 ($MBr^{79}Br^{81}$+1, 100); 419 ($M(Br^{81})_2$+2, 54). HRMS *m/z* calcd. for $C_{13}H_{13}Br_2N_4O_2$ 414.9400, found 414.9401.

2-Amino-6-(1-methoxyindol-3-yl)-1*H*-5,6-dihydropyrimidin-4-one (9d). Compound **8d** (1.08 g, 3.58 mmol) was converted into **9d** (5%) as a yellow oil. IR (KBr film) 3315, 2933, 1611, 1542, 1473, 1373, 1320, 1303, 1232, 1147, 1094, 1030, 945, 750, 738, 703, 575, 548, 508, 425. ^{1}H NMR (400 MHz, d_4-MeOH) δ 2.68-2.82 (m, 2H); 4.47 (s, 1H); 5.01 (dd, *J* = 8.8 and 6.4 Hz, 1H); 7.06-7.11 (m, 1H); 7.19-7.24 (m, 1H); 7.39-7.43 (m, 2H); 7.62 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (400 MHz, d_4-MeOH) δ 38.1, 47.3, 66.5, 83.2, 84.6, 100.4, 109.6, 120.2, 121.3, 122.1, 124.0, 162.5, 188.8. MS (ESI-TOF) 259 (M+1, 90); 260 (M+2, 100). HRMS *m/z* calcd. for $C_{13}H_{15}N_4O_2$ 259.1190, found 259.1190.

2-Amino-6-(5-bromoindol-3-yl)-1*H*-5,6-dihydropyrimidin-4-one (9f). Compound **8f** (1.35 g, 3.84 mmol) was converted into **9f** (47%) as a white solid; m.p. (MeCN) 295-296 ºC. IR (KBr film) 3261, 1631, 1567, 1506, 1434, 1363. ^{1}H NMR (400 MHz, d_4-MeOH) δ 2.71-2.87 (m, 1H); 5.03 (dd, *J* = 8.4 and 6.2 Hz, 1H); 7.22-7.34 (m, 3H); 7.80 (d, *J* = 1.6 Hz, 1H). ^{13}C NMR (400 MHz, d_4-MeOH) δ 46.9, 54.6, 121.0, 123.3, 124.2, 130.7, 133.4, 133.8, 136.7, 144.7, 171.3, 186.5. MS (ESI-TOF) 307 (MBr^{79}+1, 98); 308 (MBr^{79}+2, 17); 309 (MBr^{81}+1, 100); 310 (MBr^{81}+2, 15). HRMS *m/z* calcd. for $C_{12}H_{12}BrN_4O$ 307.0189, found 307.0188.

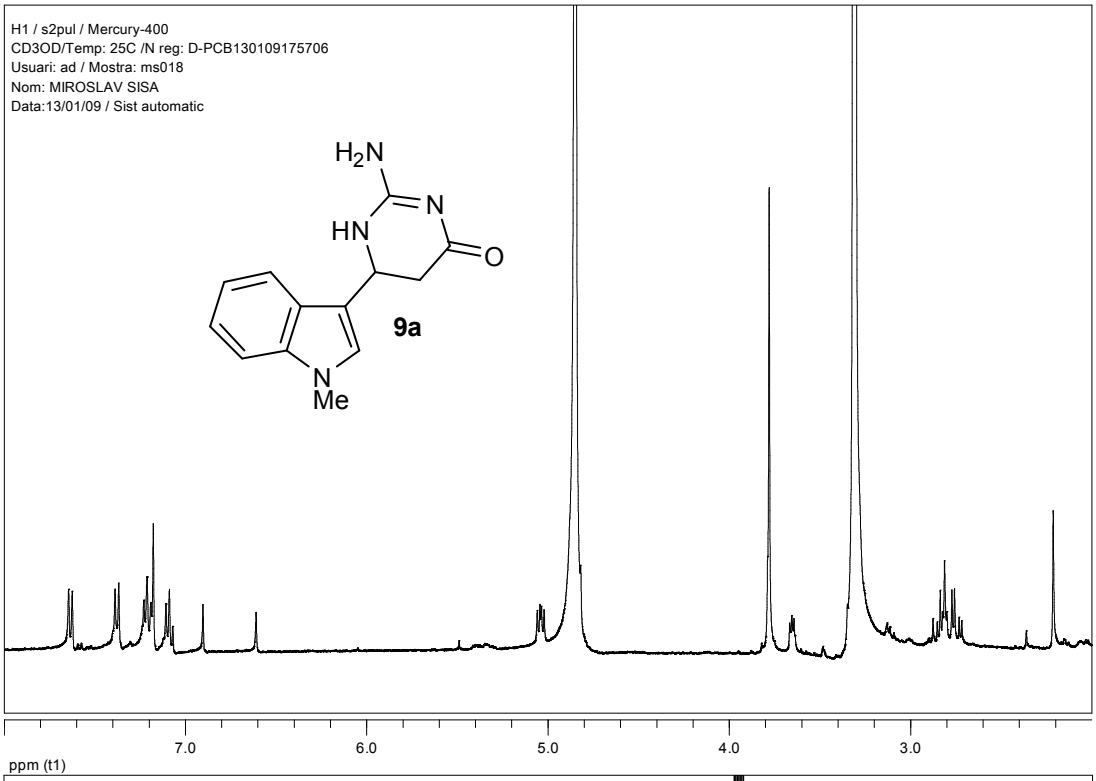
2-Amino-6-(6-bromoindol-3-yl)-1*H*-5,6-dihydropyrimidin-4-one (9g). Compound **8g** (50 mg, 0.14 mmol) was converted into **9g** (49%) as a white solid; m.p. (MeCN) 290-291 ºC. IR (KBr film) 3462, 1721, 1624, 1500, 1452, 1422, 1348, 1231, 1145, 1110, 803, 533. ^{1}H NMR (400 MHz, d_4-MeOH) δ 2.68-2.82 (m, 2H); 4.99 (dd, *J* = 8.6 and 6.0 Hz, 1H); 7.17-7.30 (m, 3H); 7.76 (d, *J* = 1.7 Hz, 1H). ^{13}C NMR (400 MHz, d_4-MeOH) δ 47.1, 54.8, 123.7, 123.8, 124.6, 130.2, 131.1, 133.3, 133.8, 146.9, 171.4, 186.4. MS (ESI-TOF) 307 (MBr^{79}+1, 98); 308 (MBr^{79}+2, 15); 309 (MBr^{81}+1, 100); 310 (MBr^{81}+2, 15). HRMS *m/z* calcd. for $C_{12}H_{12}BrN_4O$ 307.0189, found 307.0188.

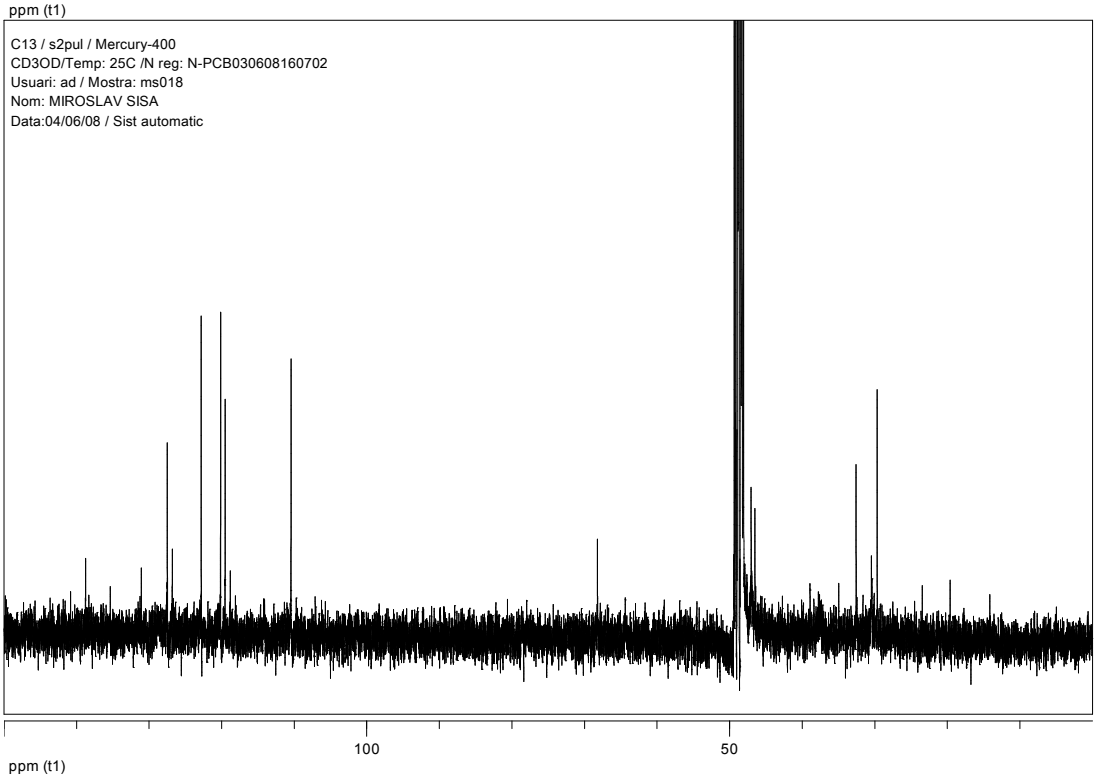
2-Amino-6-(5-bromo-1-methylindol-3-yl)-1*H*-5,6-dihydropyrimidin-4-one (9h). Compound **8h** (994 mg, 2.73 mmol) was converted into **9h** (74%) as a white solid; m.p. (MeCN) 318-320 ºC. IR (KBr film) 3353, 3267, 3031, 2977, 1662, 1632, 1543, 1498, 1428, 1446, 1386, 1324, 1269, 1148, 1060, 797, 677, 516. ^{1}H NMR (400 MHz, d_6-DMSO) δ 3.73 (s, 3H); 4.88 (dd, *J* = 7.2 and 7.2 Hz, 1H); 7.25-7.29 (m, 2H); 7.41 (d, *J* = 8.8, 1H); 7.82 (d, *J* = 2.0, 1H). MS (ESI-TOF) 321 (MBr^{79}+1, 100); 322 (MBr^{79}+2, 18); 323 (MBr^{81}+1, 90); 324 (MBr^{81}+2, 16). HRMS *m/z* calcd. for $C_{13}H_{14}BrN_4O$ 321.0346, found 321.0348.

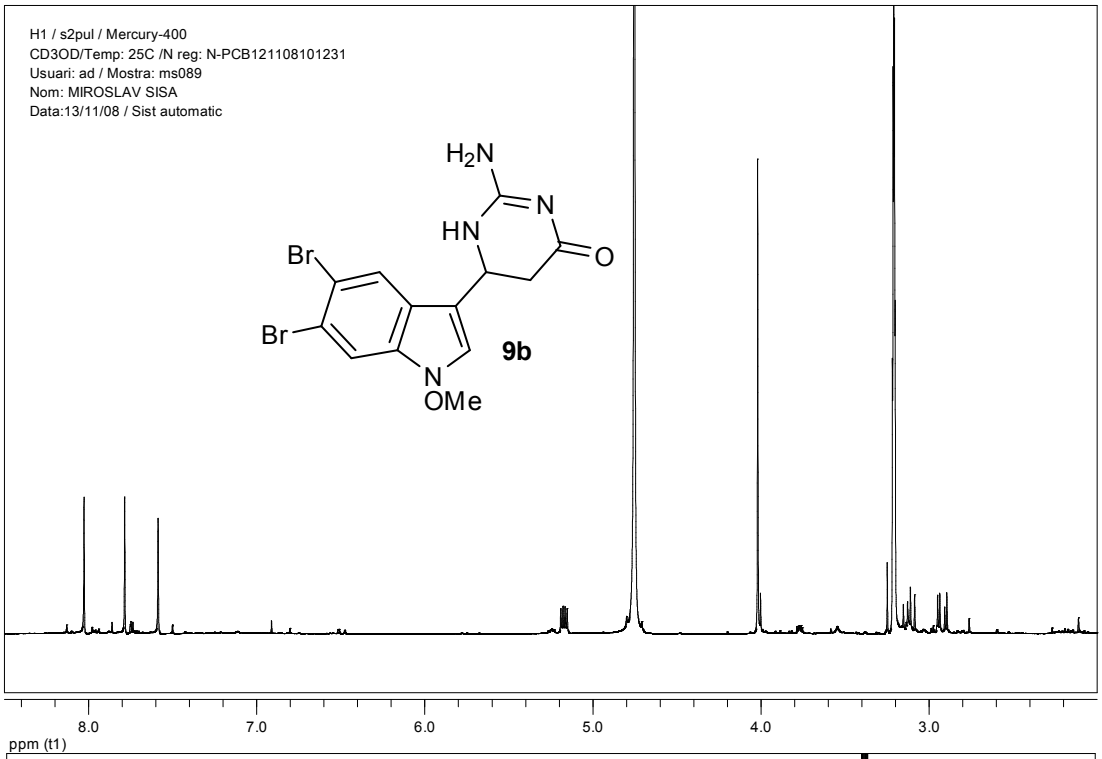
2-Amino-6-(6-bromo-1-methylindol-3-yl)-1*H*-5,6-dihydropyrimidin-4-one (9i).

Compound **8i** (1.14 g, 3.13 mmol) was converted into **9i** (60%) as a white solid; m.p. (MeCN) 272-273 ºC. IR (KBr film) 3322, 3094, 1636, 1609, 1544, 1494, 1407, 1323, 1294, 1255, 1230, 1134, 1134, 836, 804, 675, 590. ^{1}H NMR (400 MHz, d_6-DMSO) δ 3.73 (s, 3H); 4.88 (dd, *J* = 7.6 and 7.6 Hz, 1H); 7.16 (d, *J* = 8.4 Hz, 1H); 7.58 (d, *J* = 8.8, 1H); 7.69 (s, 1H). ^{13}C NMR (400 MHz, d_6-DMSO) δ 41.9, 46.9, 108.1, 122.2, 123.8, 130.1, 131.0, 133.9, 137.1, 147.1, 157.1, 186.3. MS (ESI-TOF) 321 (MBr^{79}+1, 100); 322 (MBr^{79}+2, 15); 323 (MBr^{81}+1, 92); 324 (MBr^{81}+2, 15). HRMS *m/z* calcd. for $C_{13}H_{14}BrN_4O$ 321.0346, found 321.0352.

^{1}H, ^{13}C-NMR spectra and HPLC analysis of final compounds



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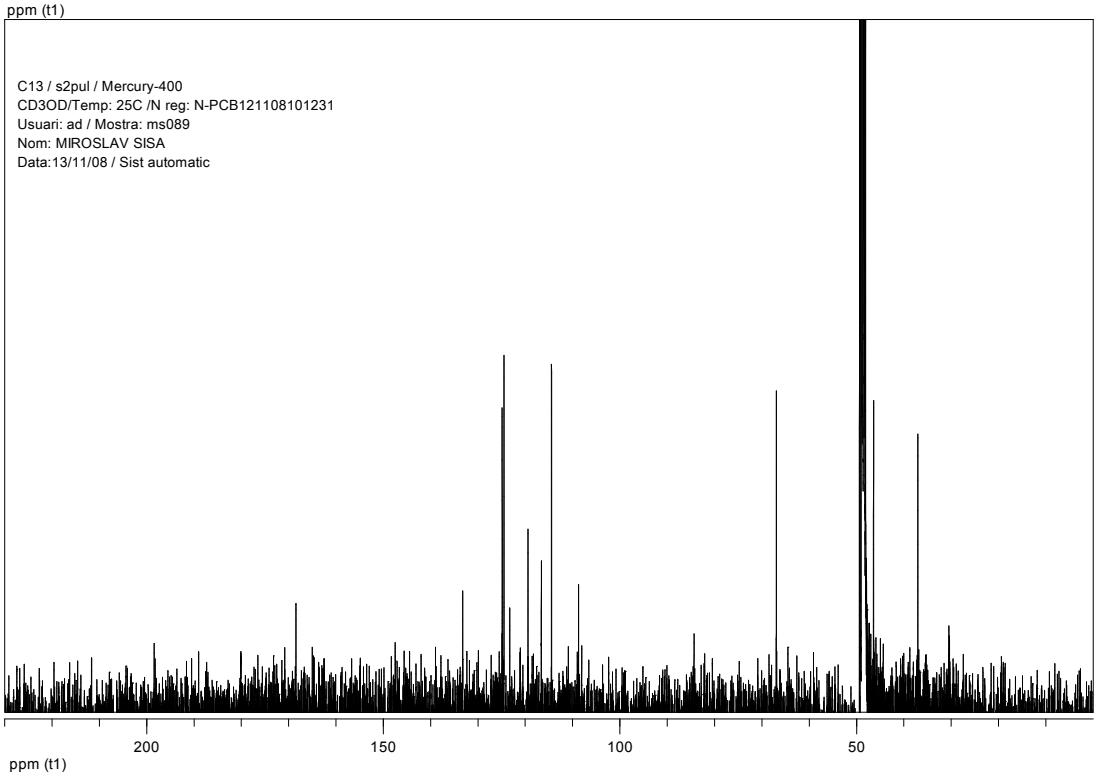
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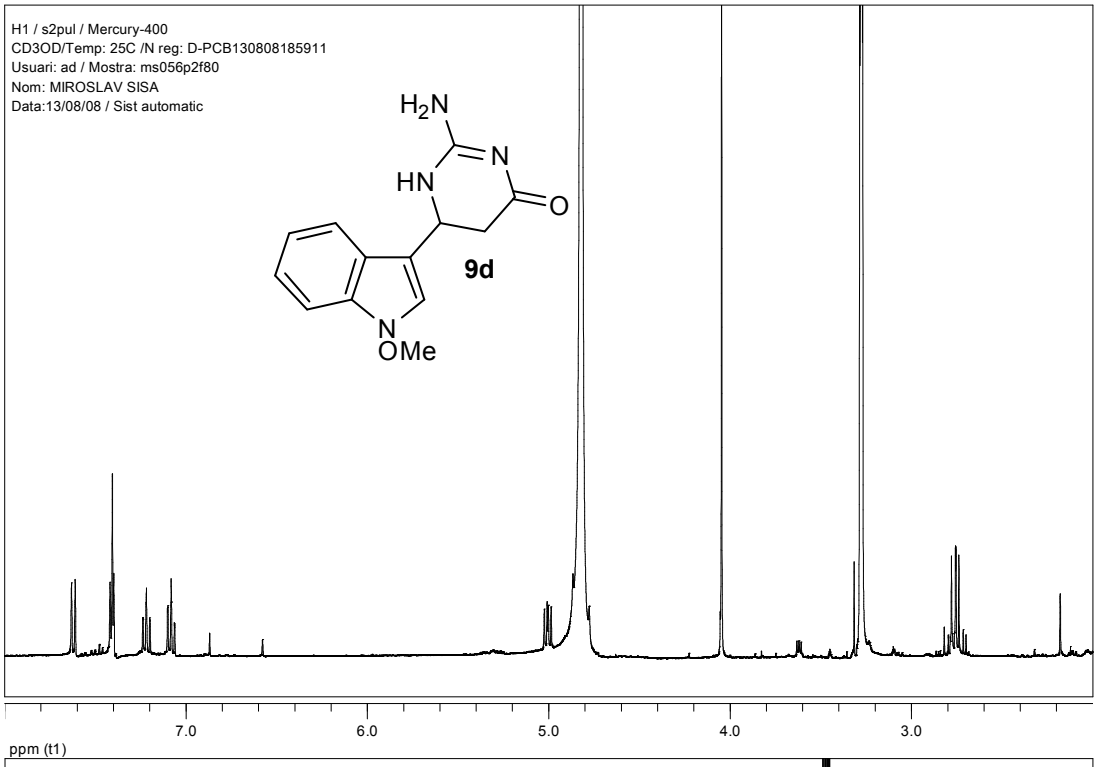
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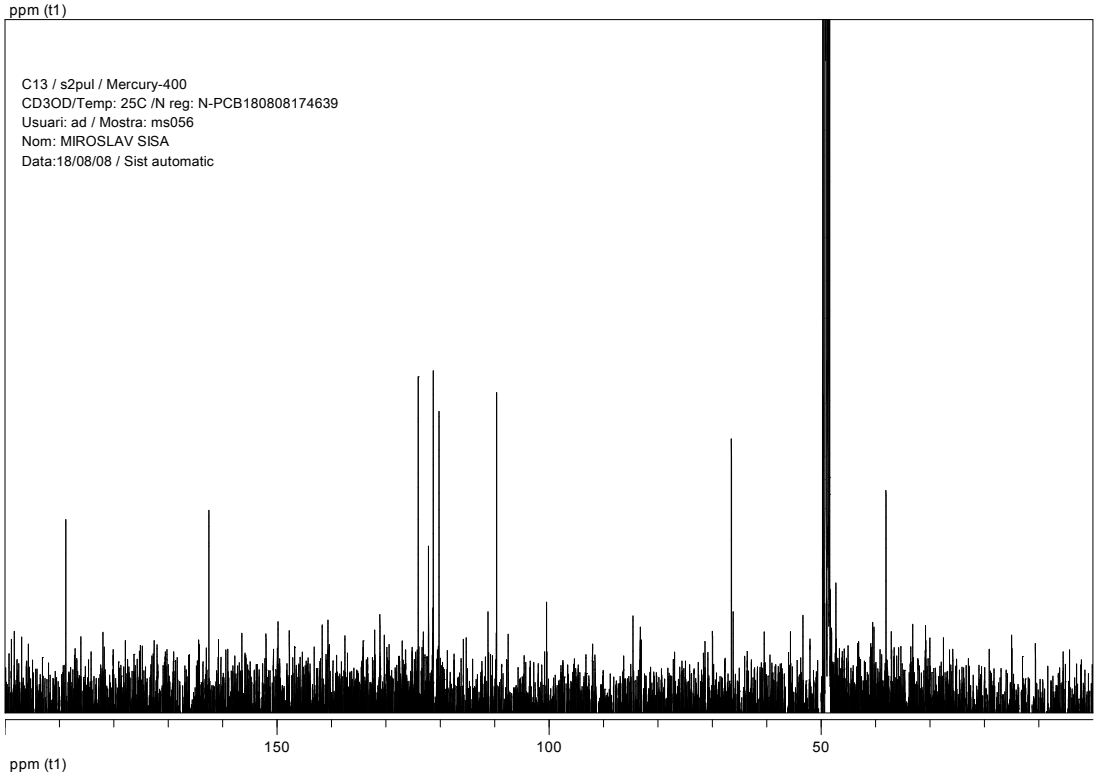
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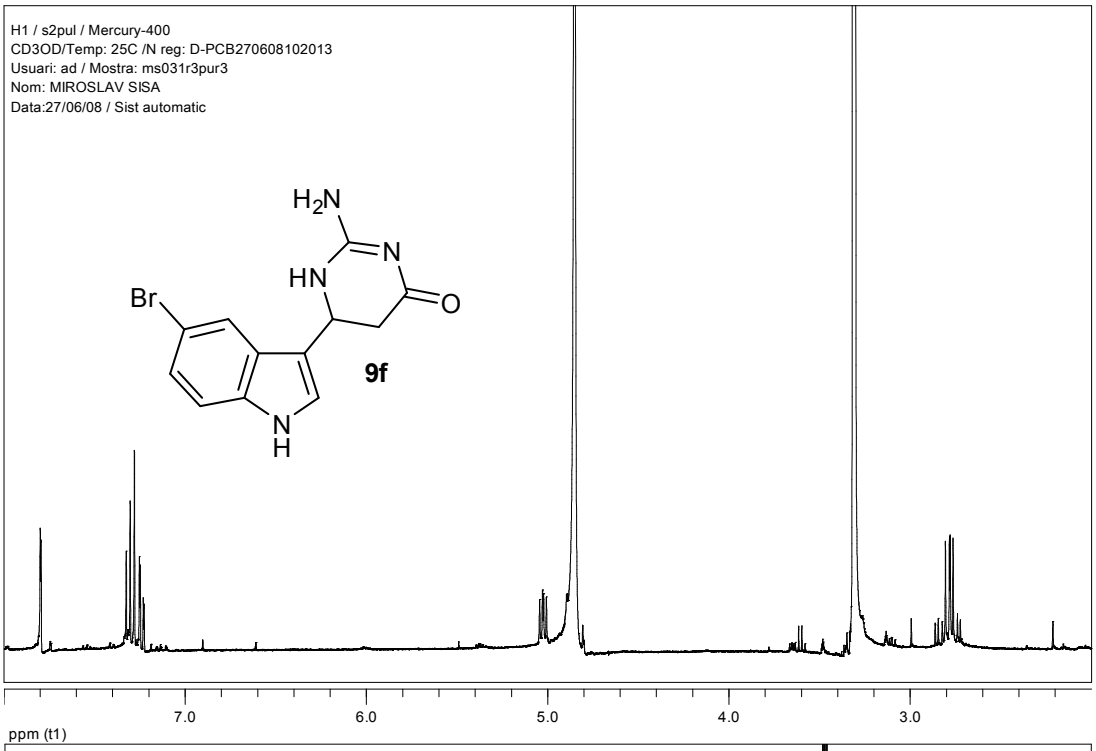
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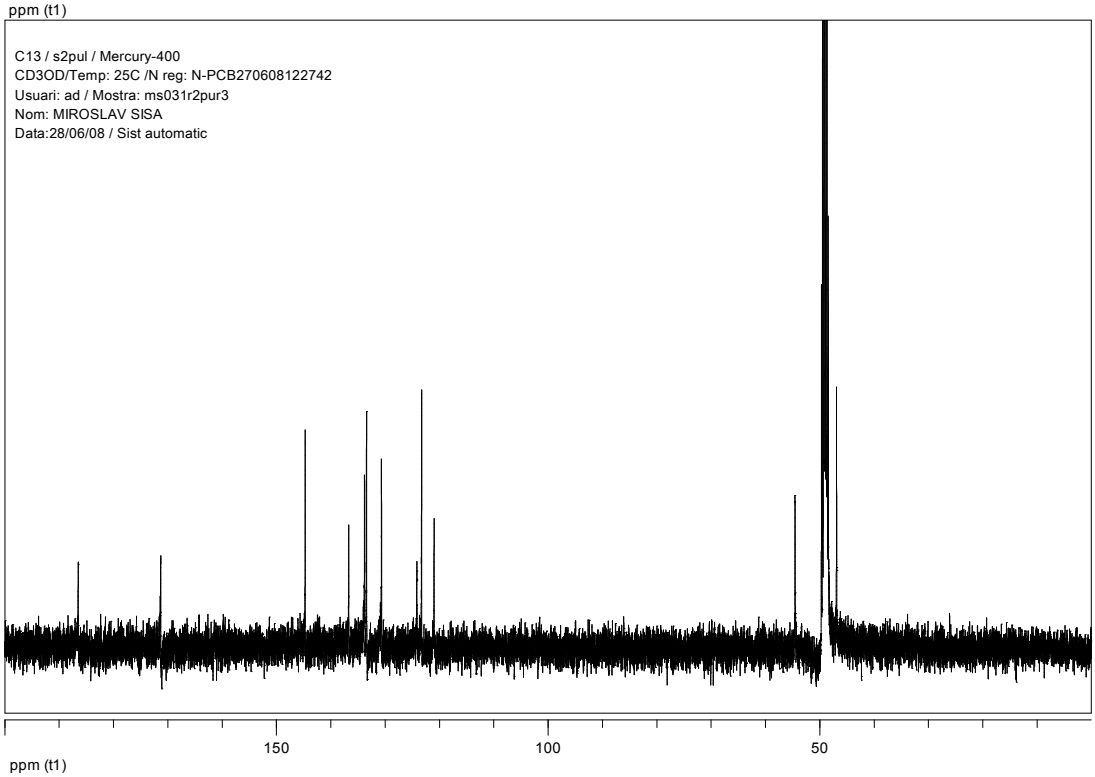
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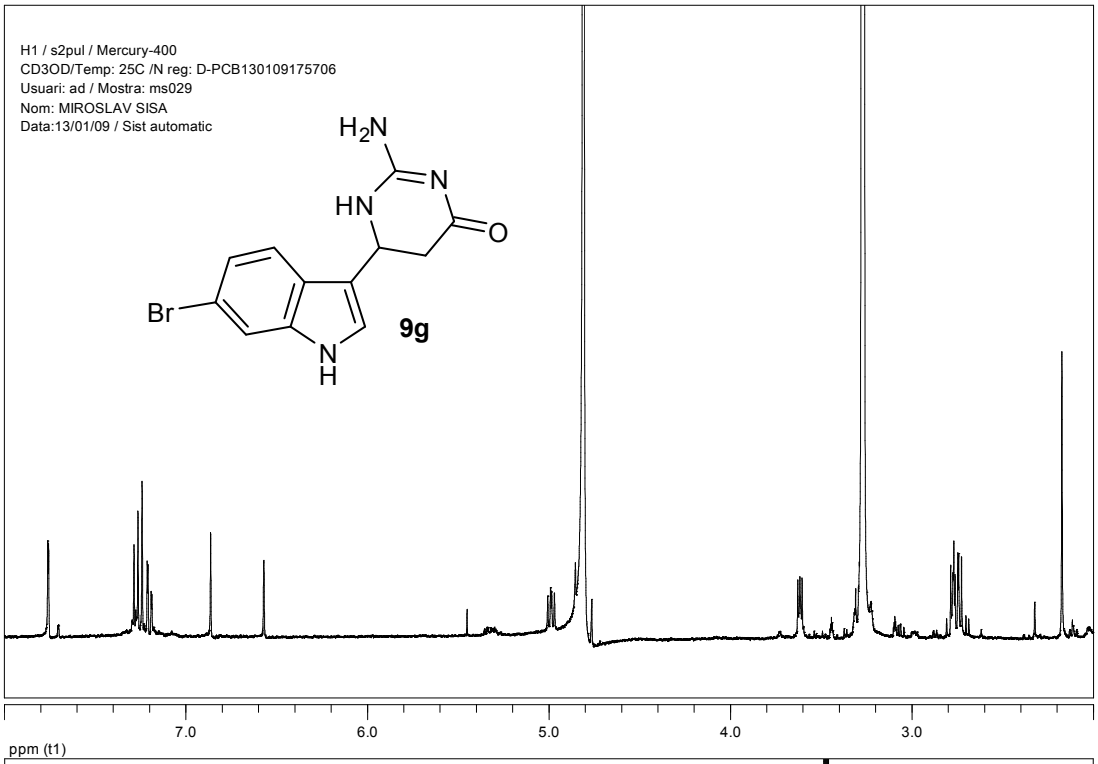
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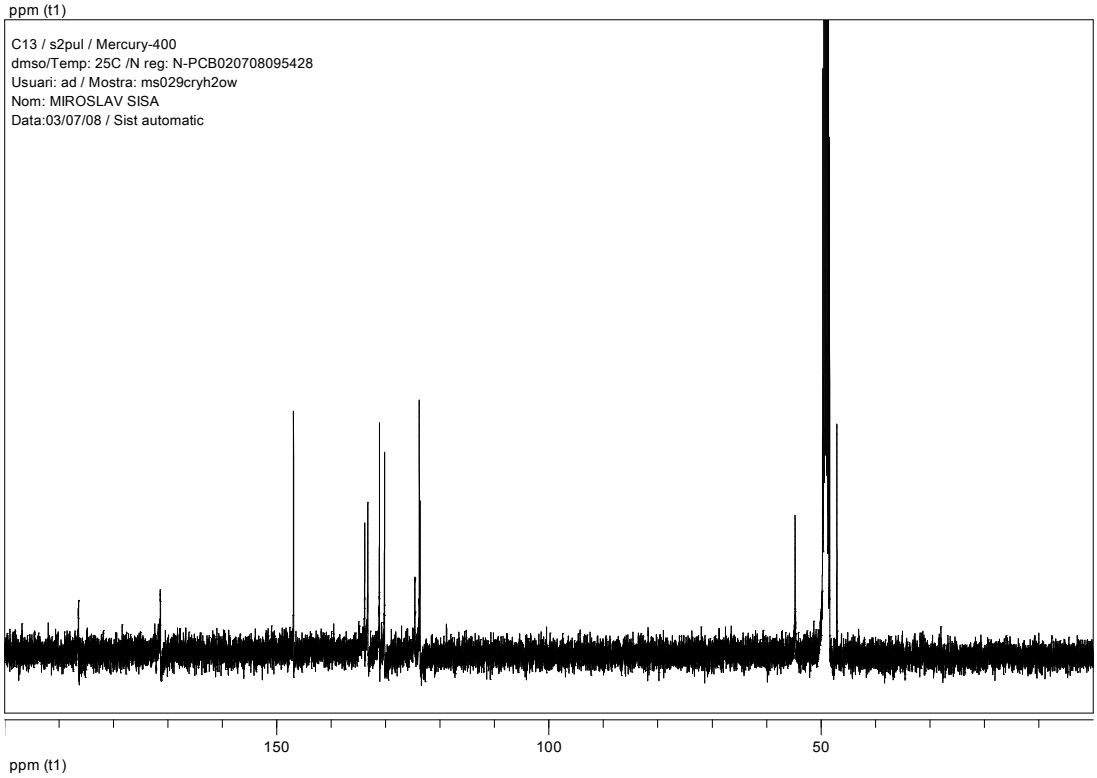
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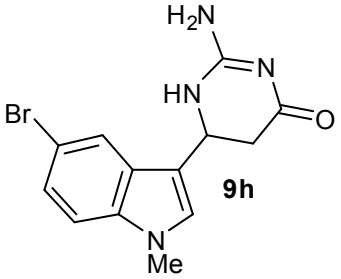
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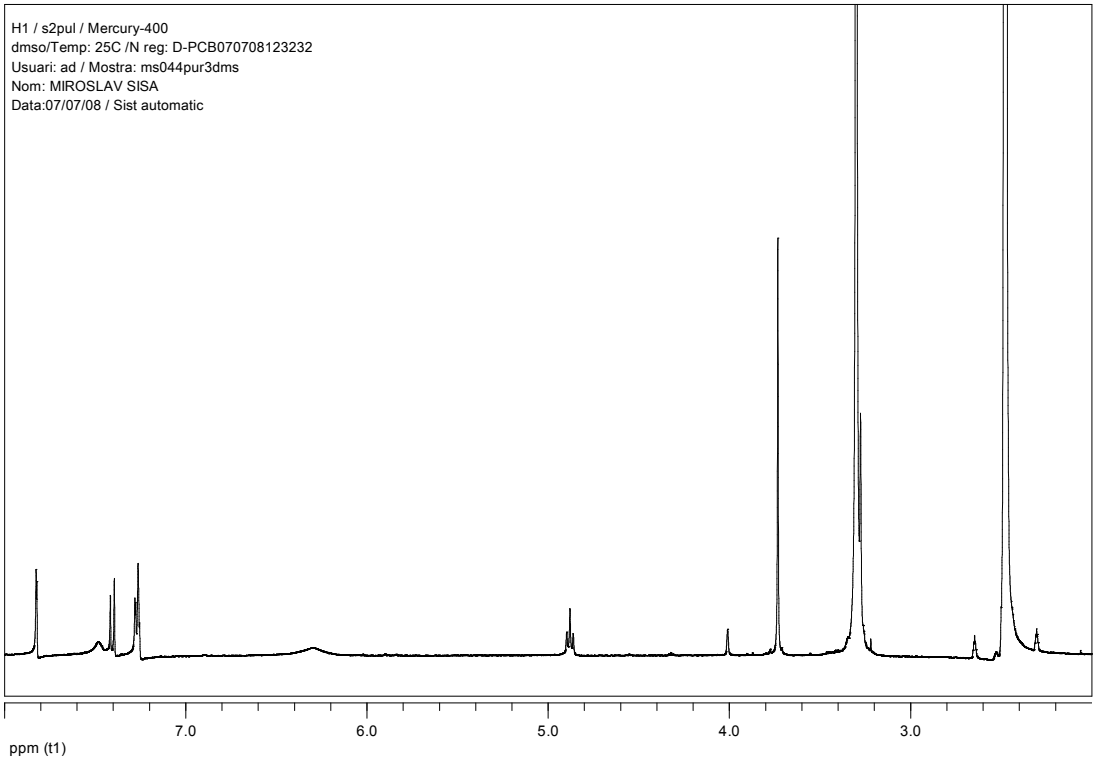
9h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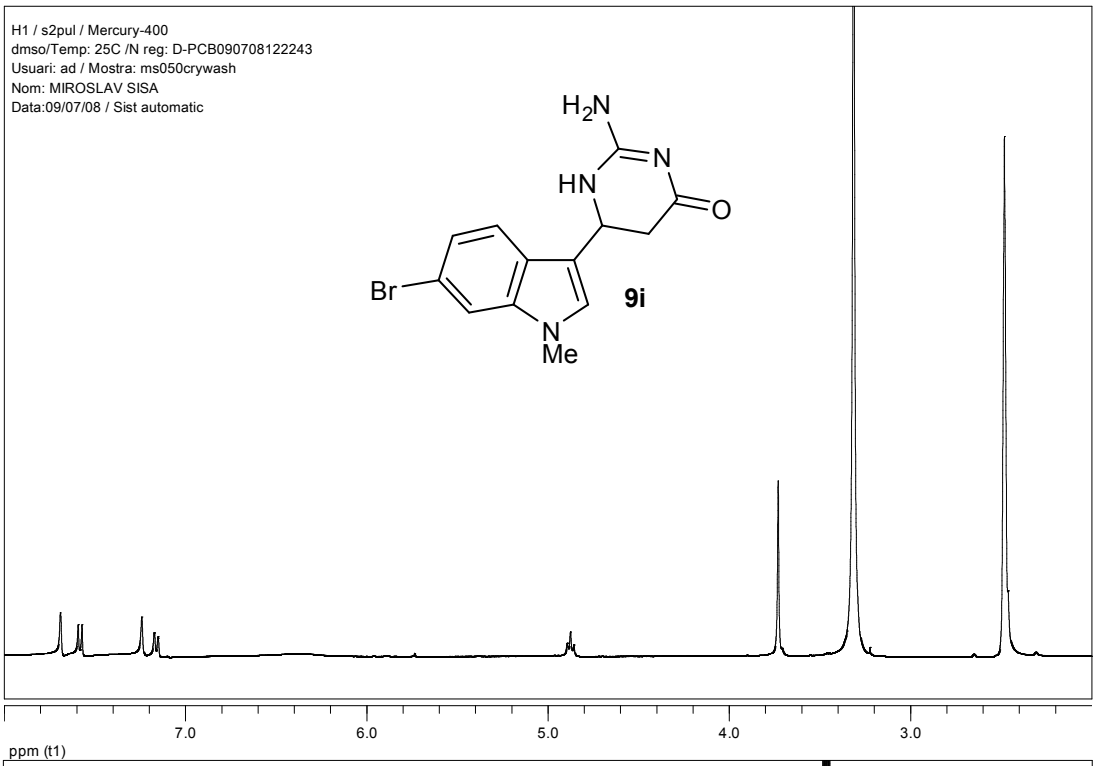
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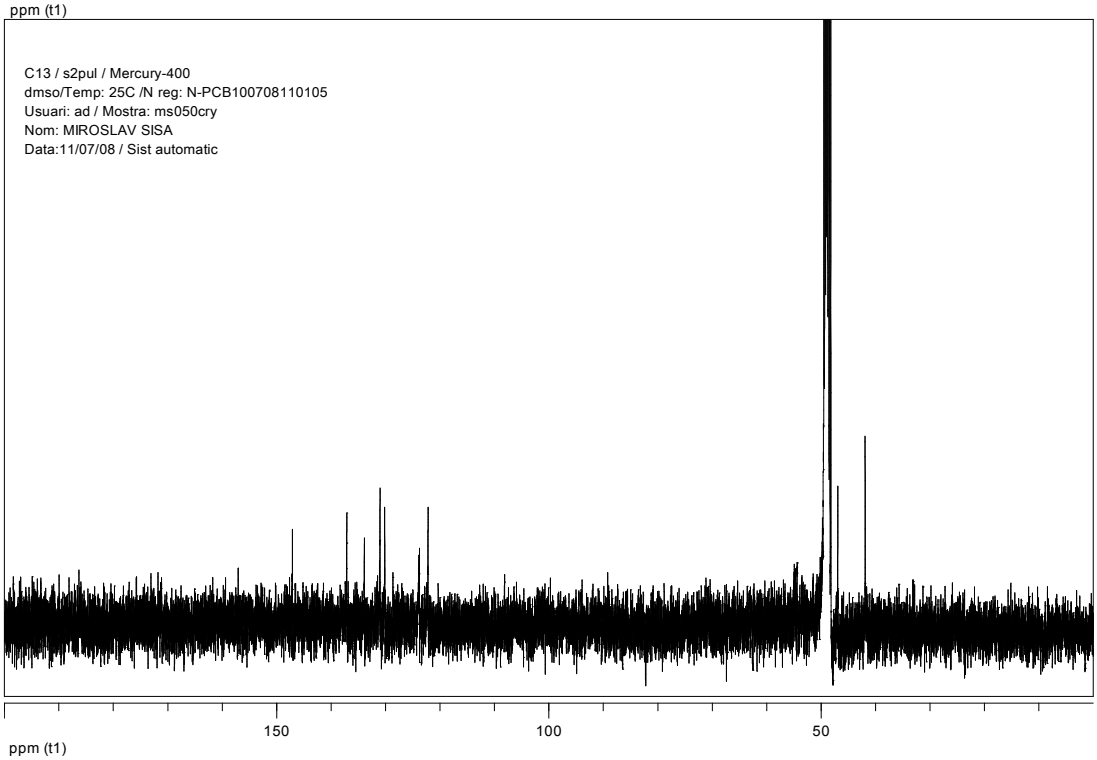
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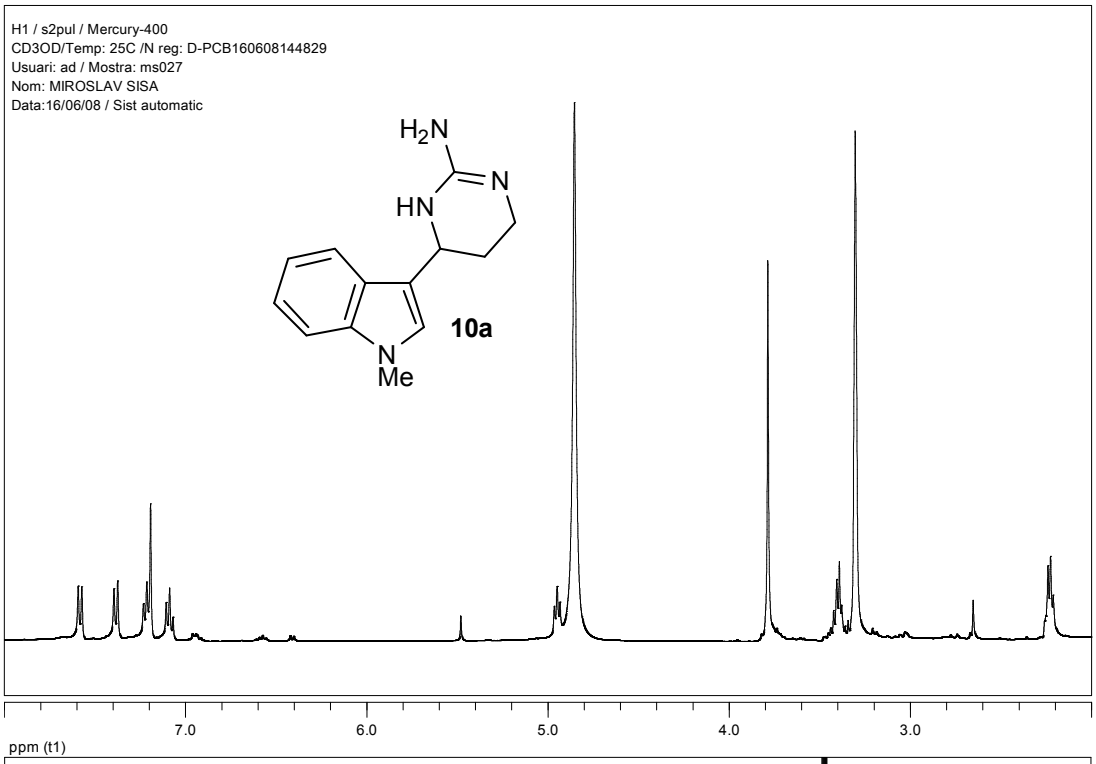
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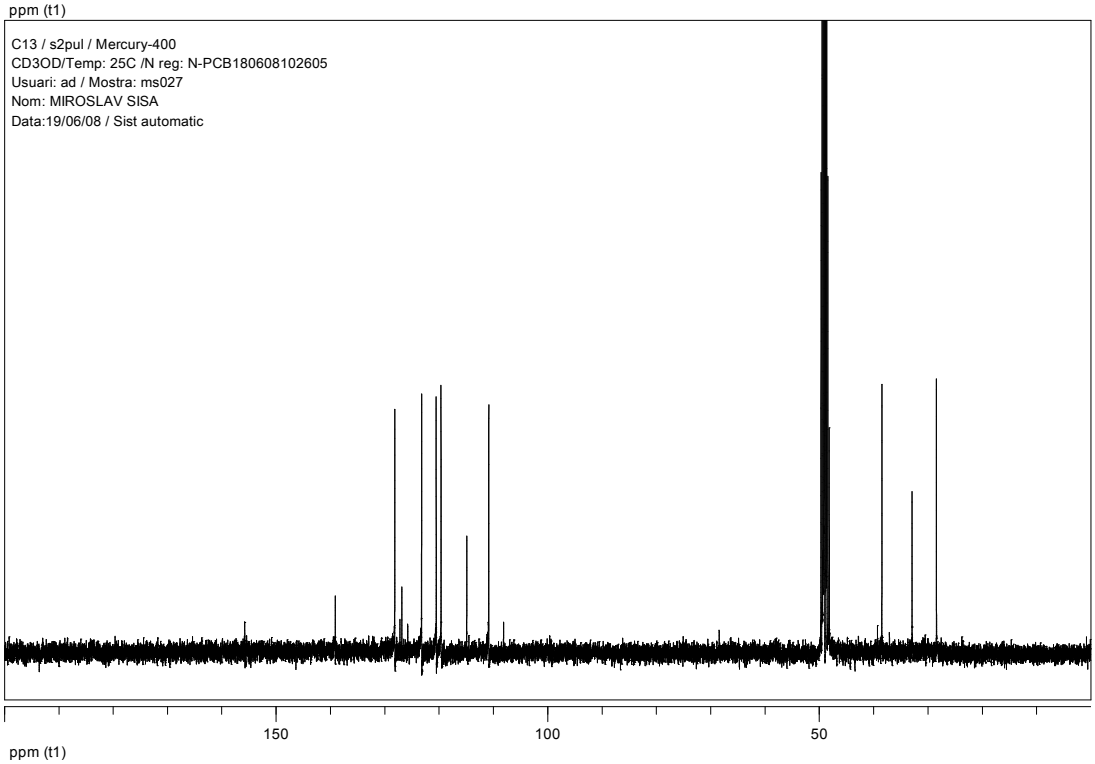
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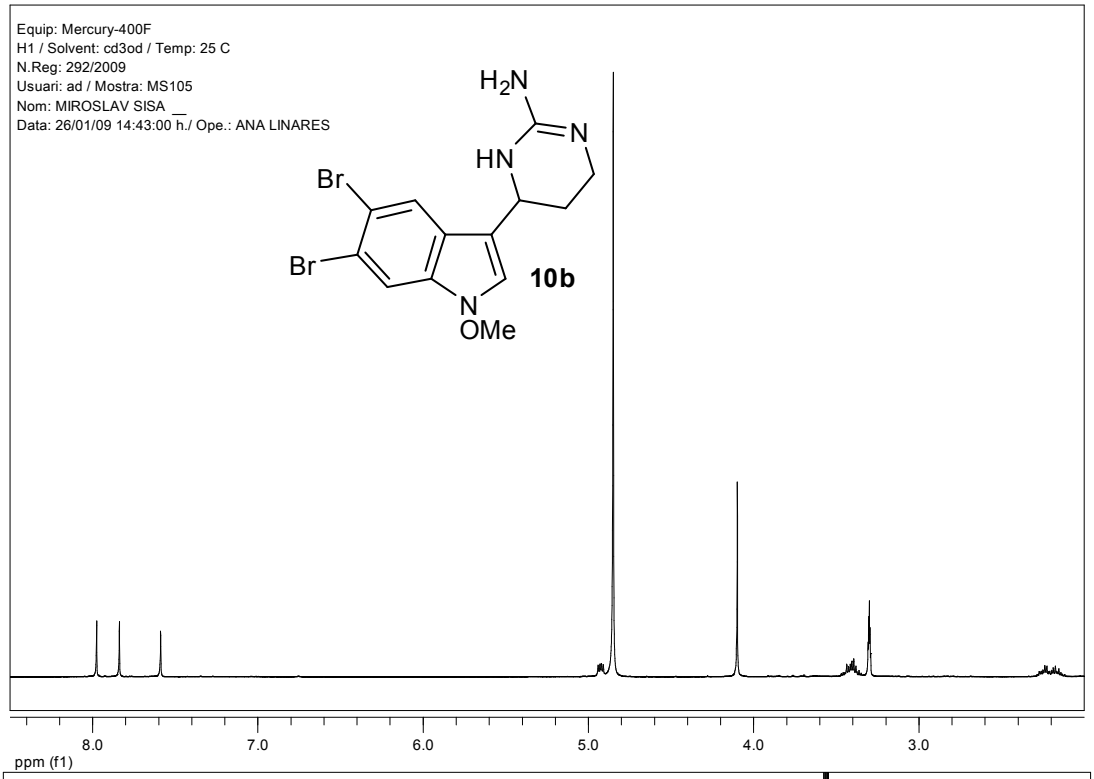
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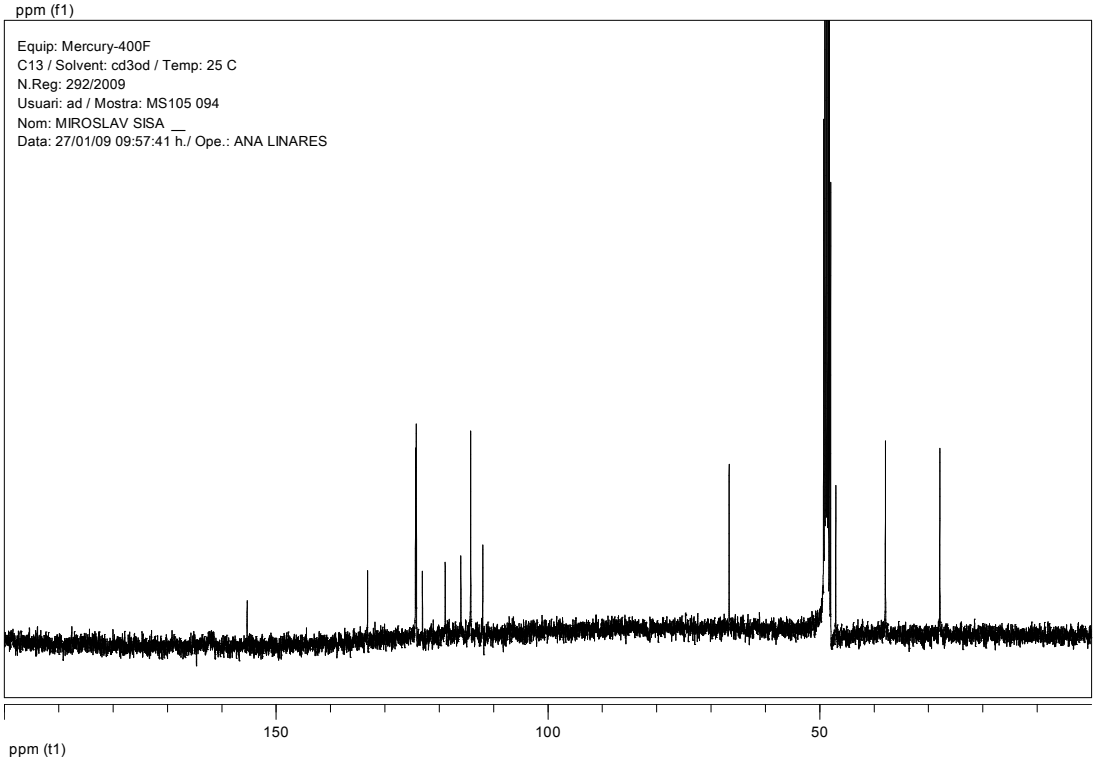
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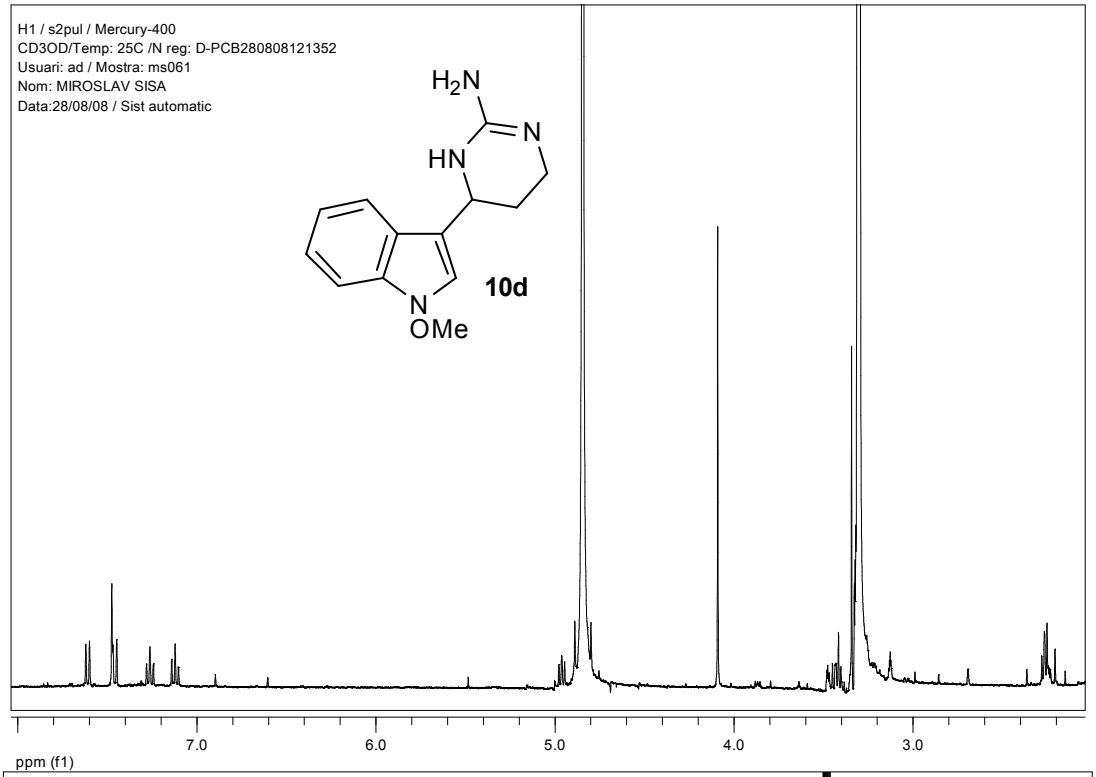
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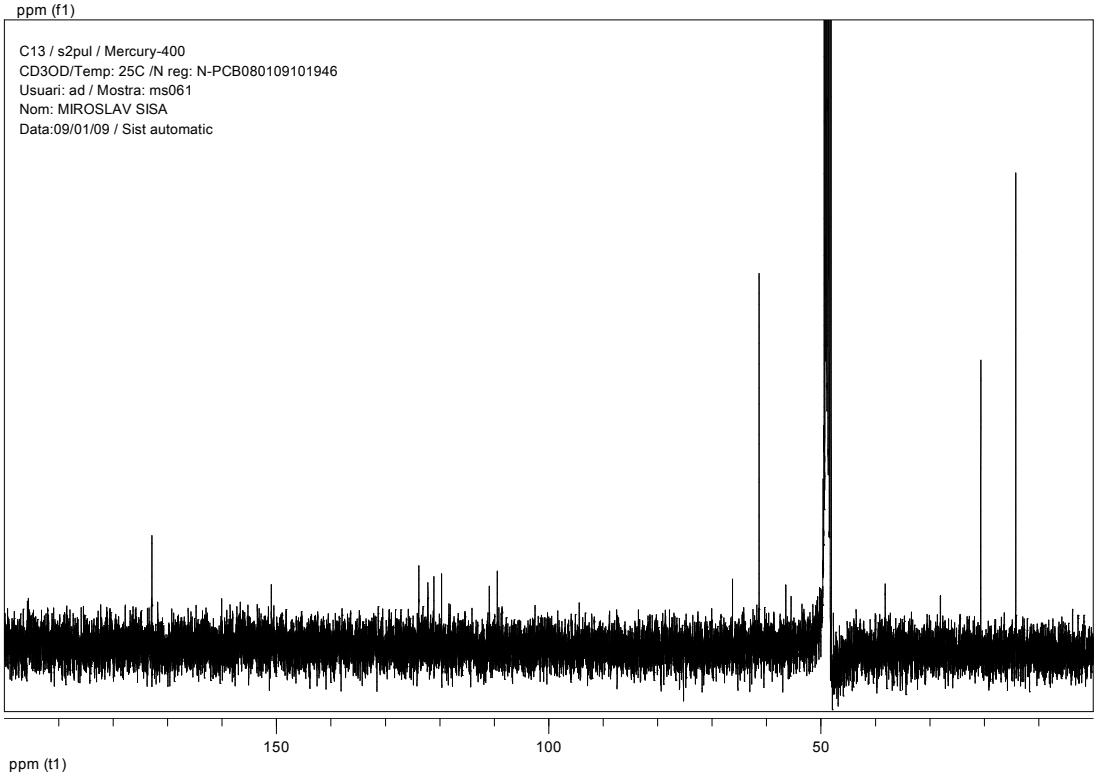
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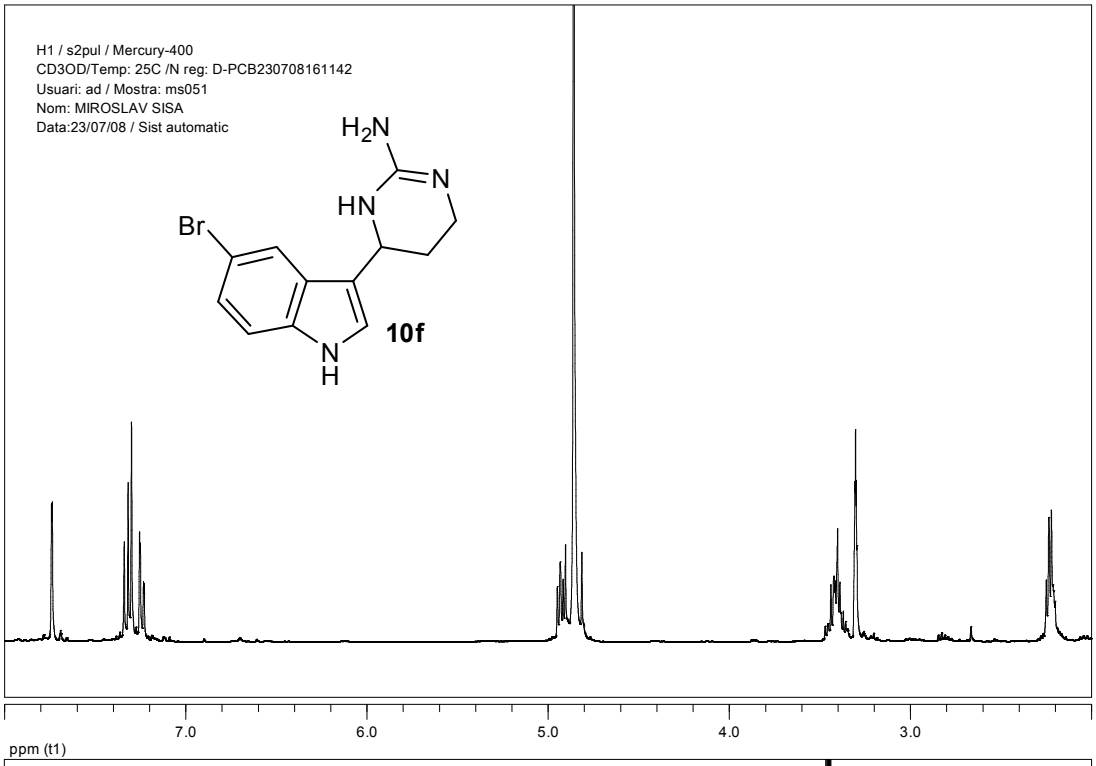
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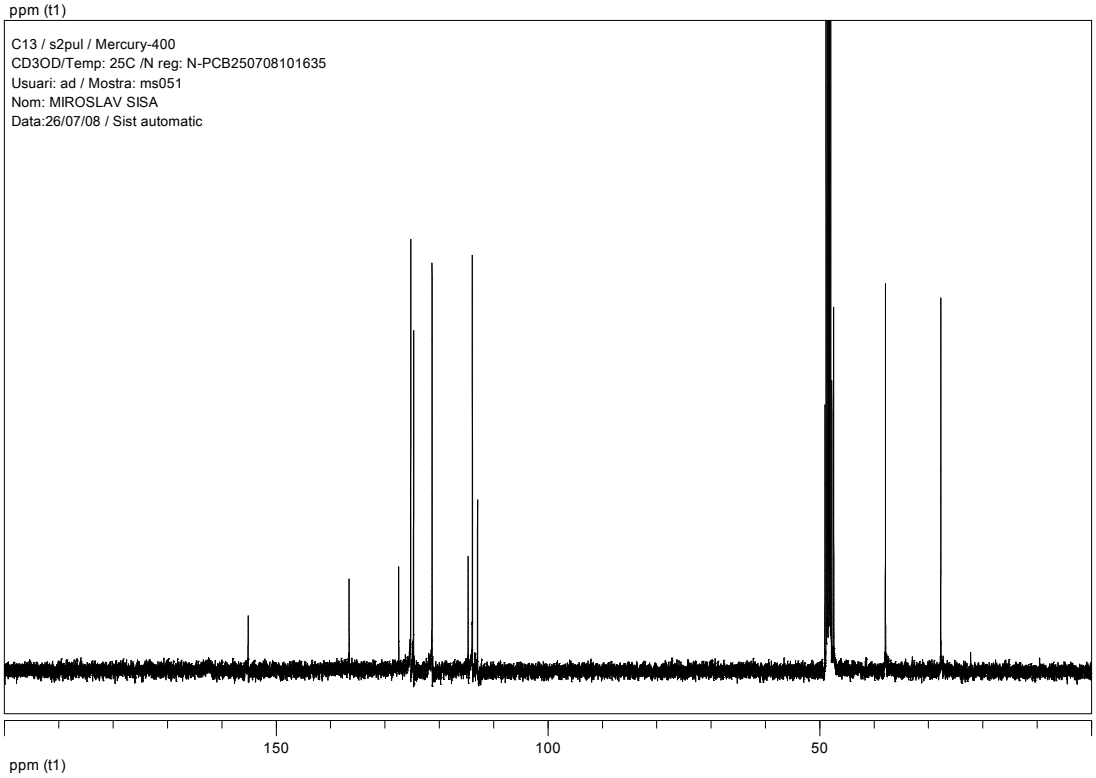
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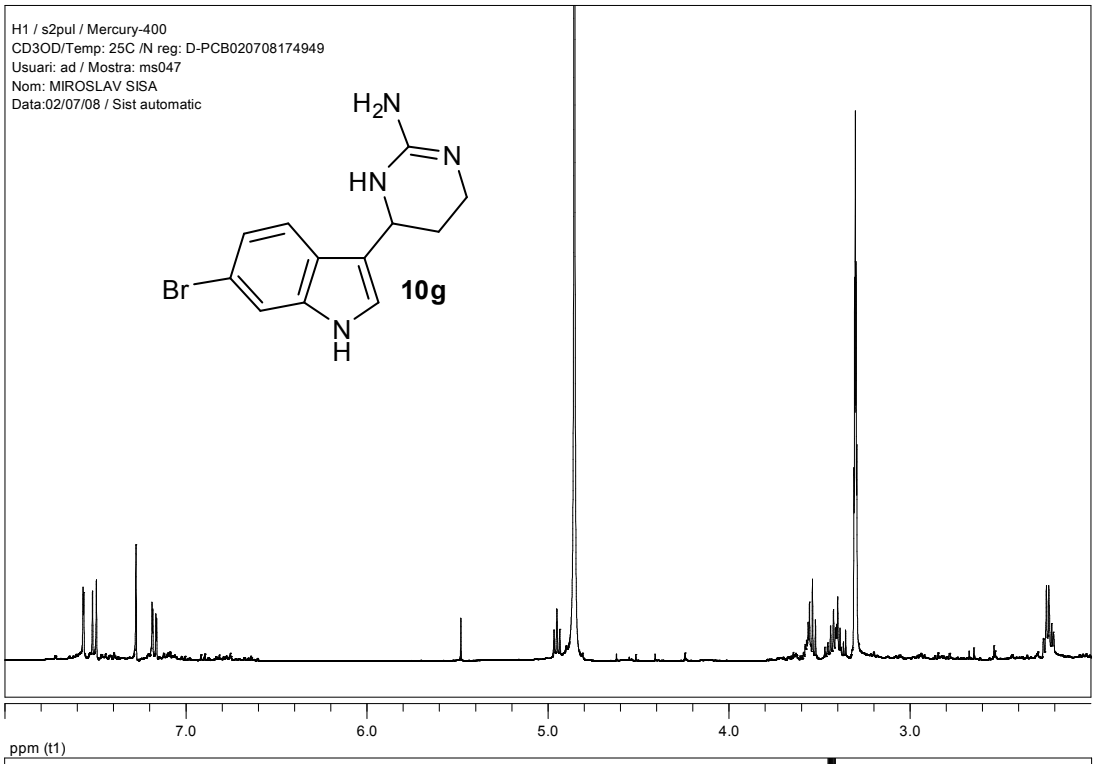
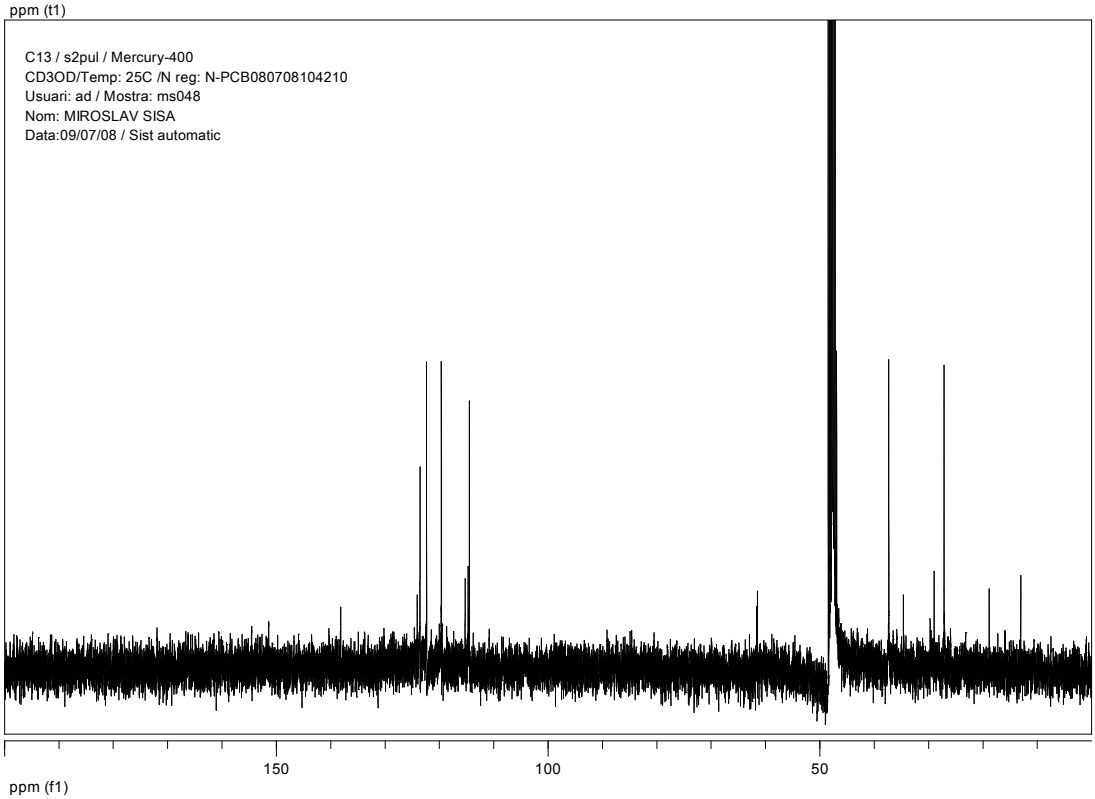
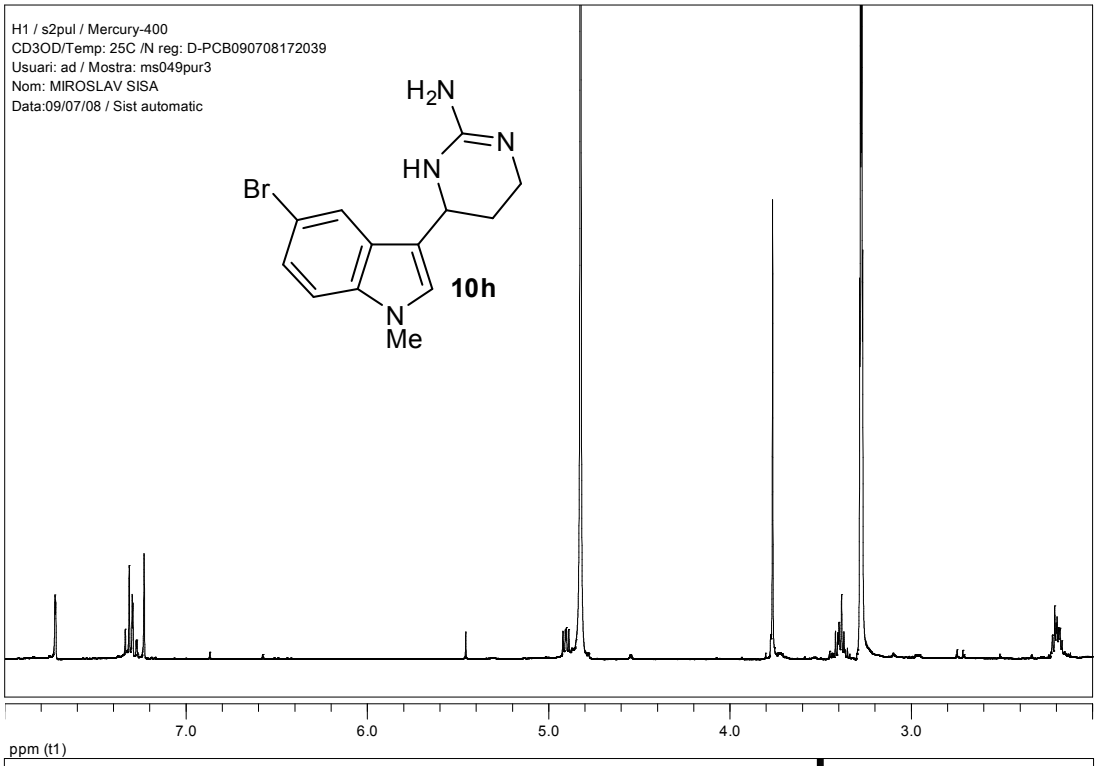
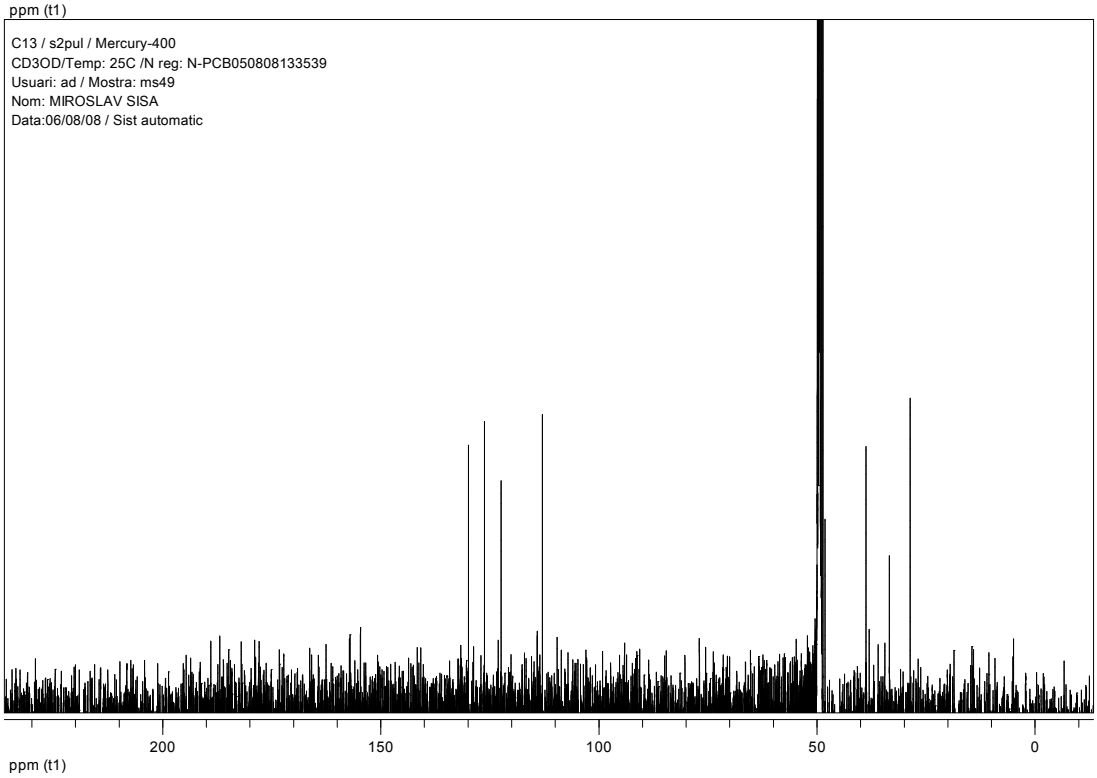
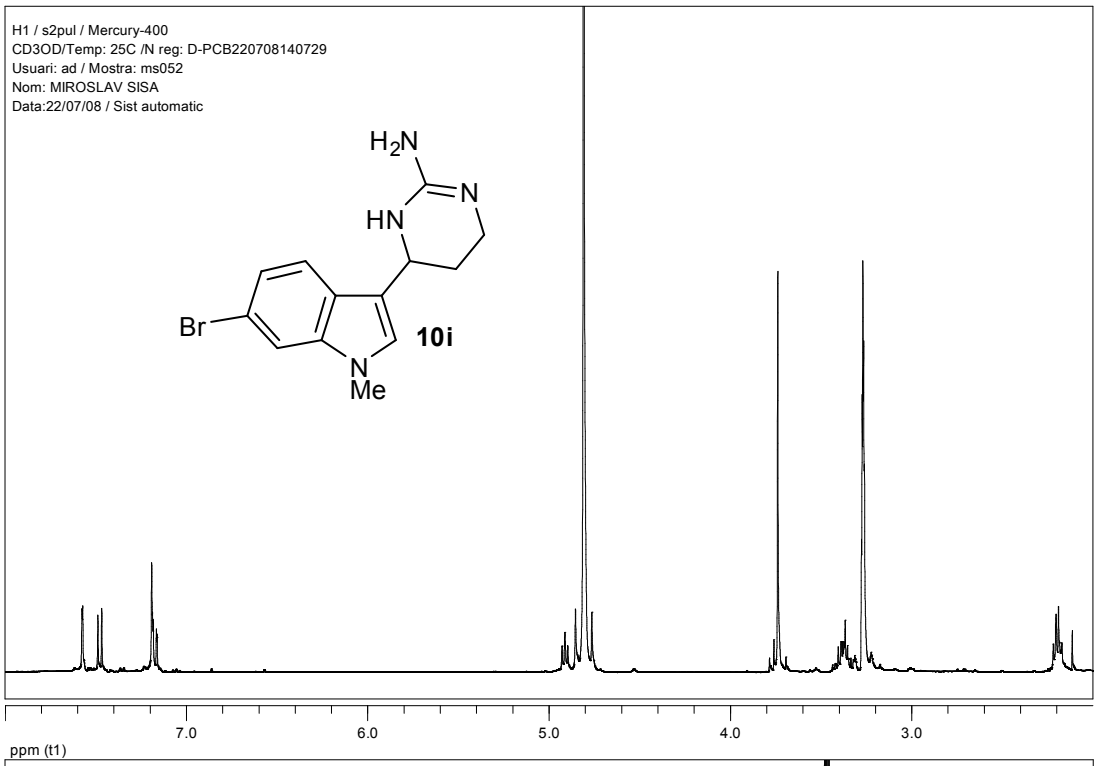
CD3OD/Temp: 25C /N reg: N-PCB250708101635
Usuari: ad / Mostra: ms051
Nom: MIROSLAV SISA
Data:26/07/08 / Sist automatic
150
100
50
ppm (t1)

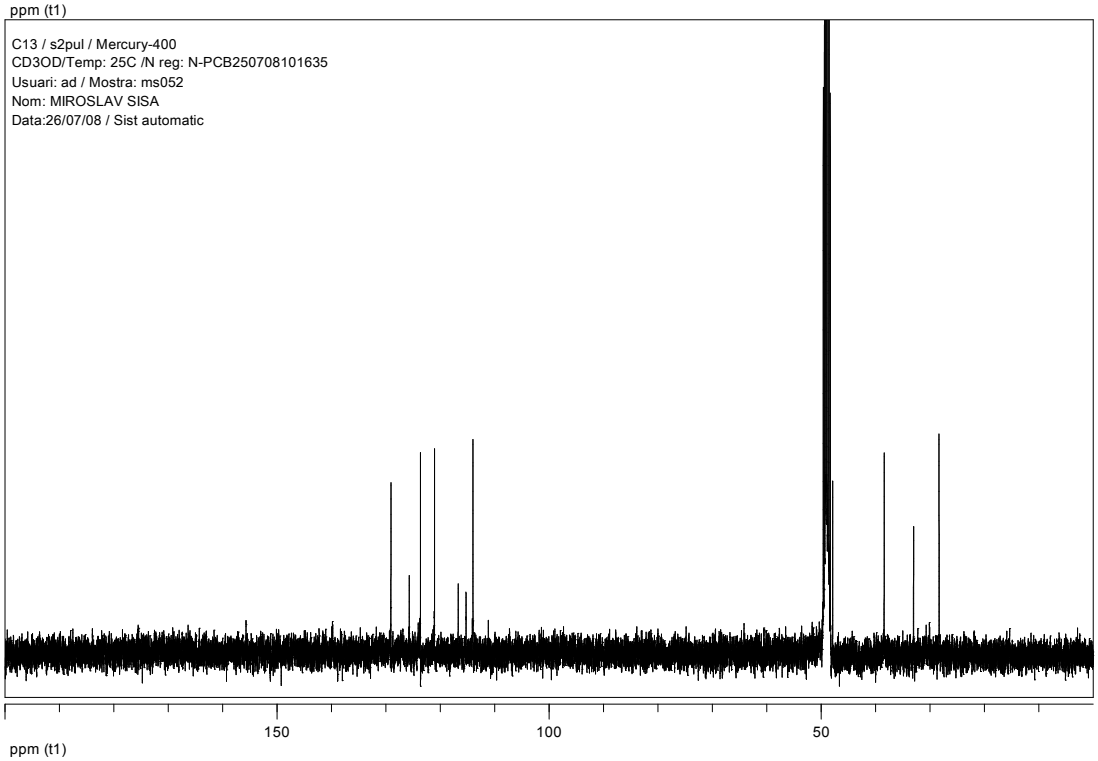

H1 / s2pul / Mercury-400
CD3OD/Temp: 25C /N reg: D-PCB020708174949
Usuari: ad / Mostra: ms047
Nom: MIROSLAV SISA
Data:02/07/08 / Sist automatic
H2N
N
HN
Br
N
H
10g
7.0
6.0
5.0
4.0
3.0
ppm (t1)

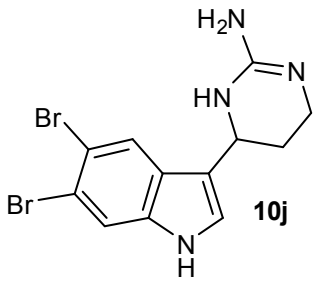

C13 / s2pul / Mercury-400
CD3OD/Temp: 25C /N reg: N-PCB080708104210
Usuari: ad / Mostra: ms048
Nom: MIROSLAV SISA
Data:09/07/08 / Sist automatic
150
100
50
ppm (f1)


H1 / s2pul / Mercury-400
CD3OD/Temp: 25C /N reg: D-PCB090708172039
Usuari: ad / Mostra: ms049pur3
Nom: MIROSLAV SISA
Data:09/07/08 / Sist automatic
H2N
N
HN
Br
10h
N
Me
7.0
6.0
5.0
4.0
3.0
ppm (t1)

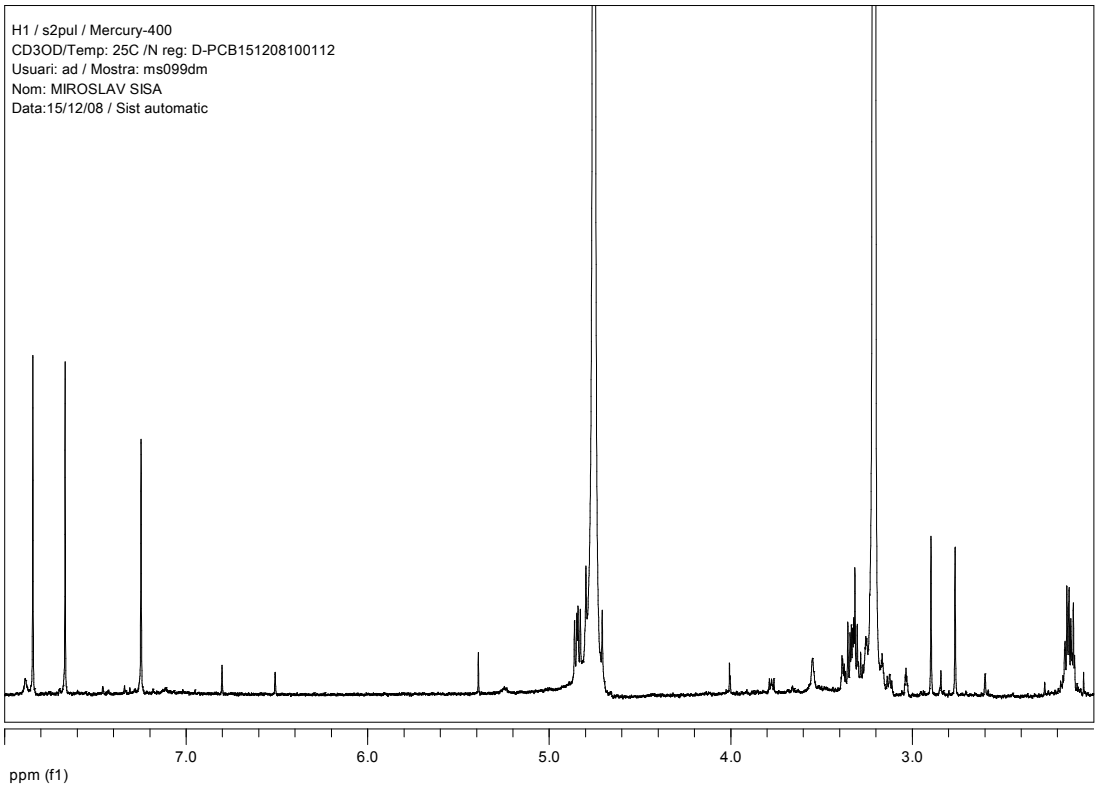

C13 / s2pul / Mercury-400
CD3OD/Temp: 25C /N reg: N-PCB050808133539
Usuari: ad / Mostra: ms49
Nom: MIROSLAV SISA
Data:06/08/08 / Sist automatic
200
150
100
50
0
ppm (t1)

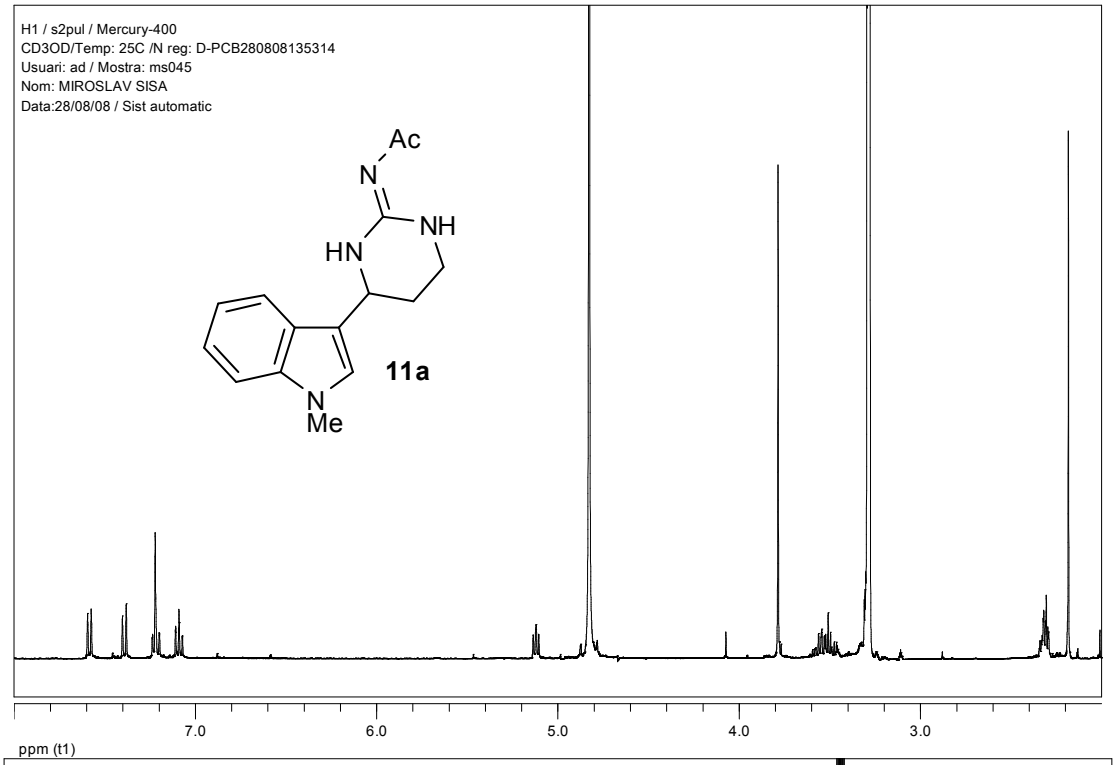

H1 / s2pul / Mercury-400
CD3OD/Temp: 25C /N reg: D-PCB220708140729
Usuari: ad / Mostra: ms052
Nom: MIROSLAV SISA
Data:22/07/08 / Sist automatic
H2N
N
HN
Br
N
Me
10i
7.0
6.0
5.0
4.0
3.0
ppm (t1)

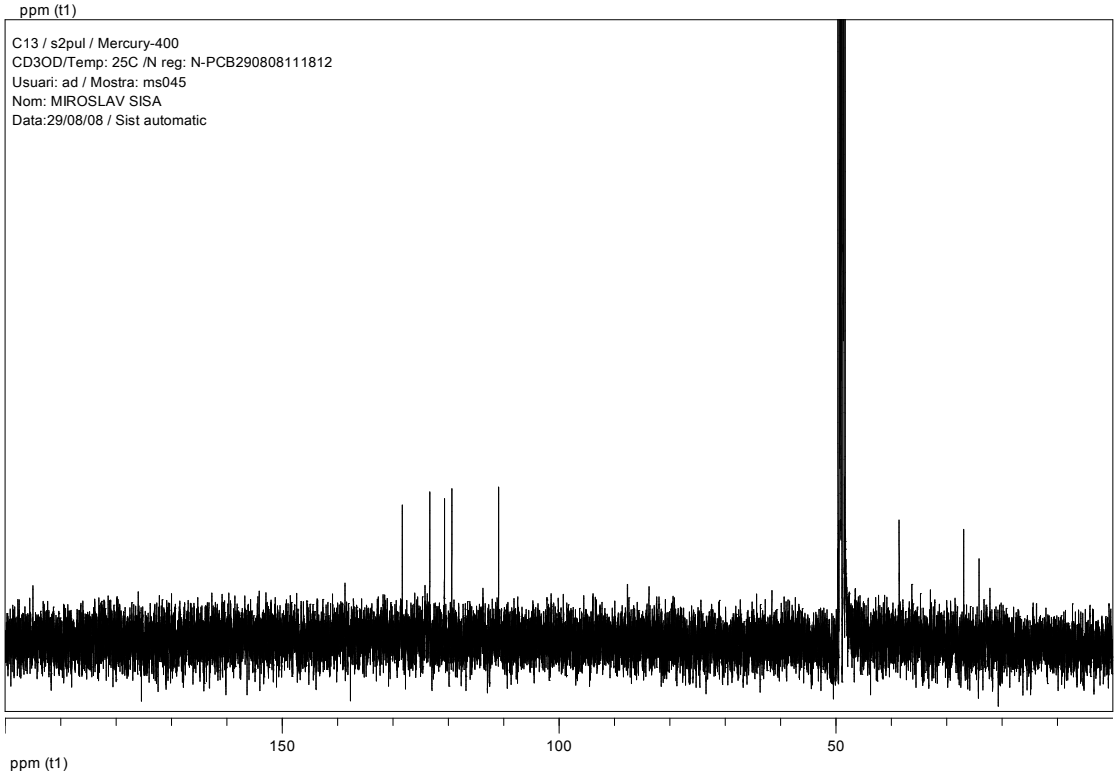

C13 / s2pul / Mercury-400
CD3OD/Temp: 25C /N reg: N-PCB250708101635
Usuari: ad / Mostra: ms052
Nom: MIROSLAV SISA
Data:26/07/08 / Sist automatic
150
100
50
ppm (t1)

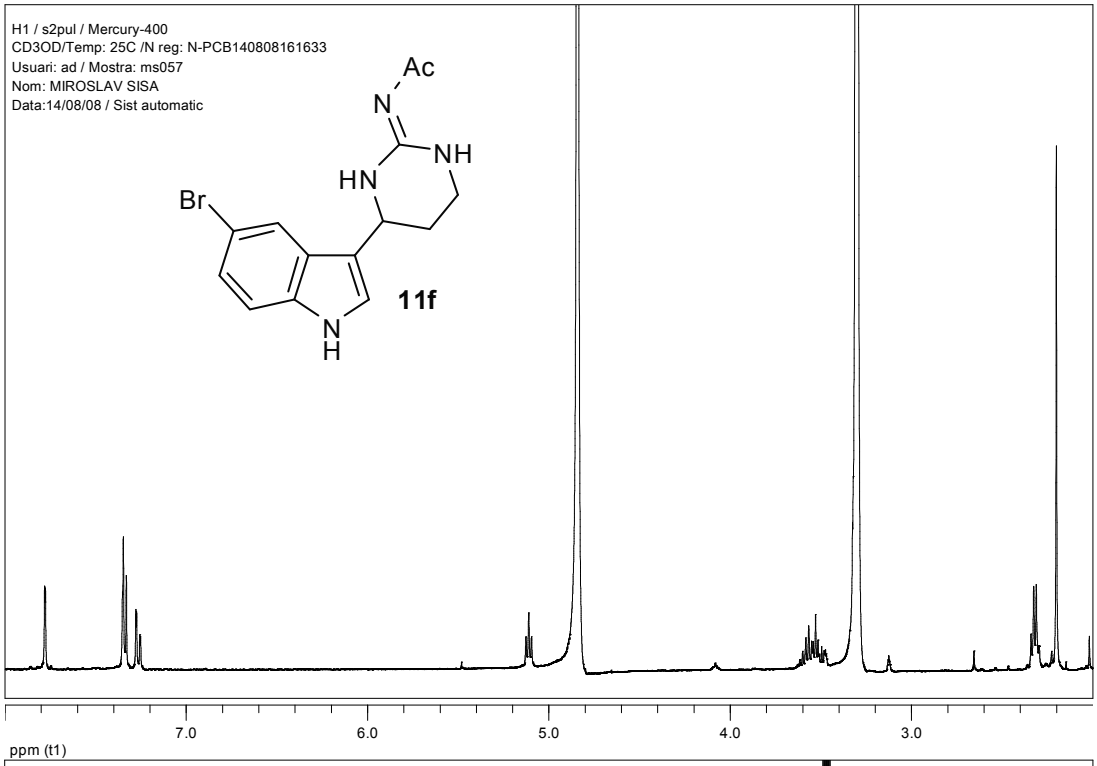

H2N
N
HN
Br
Br
N
H

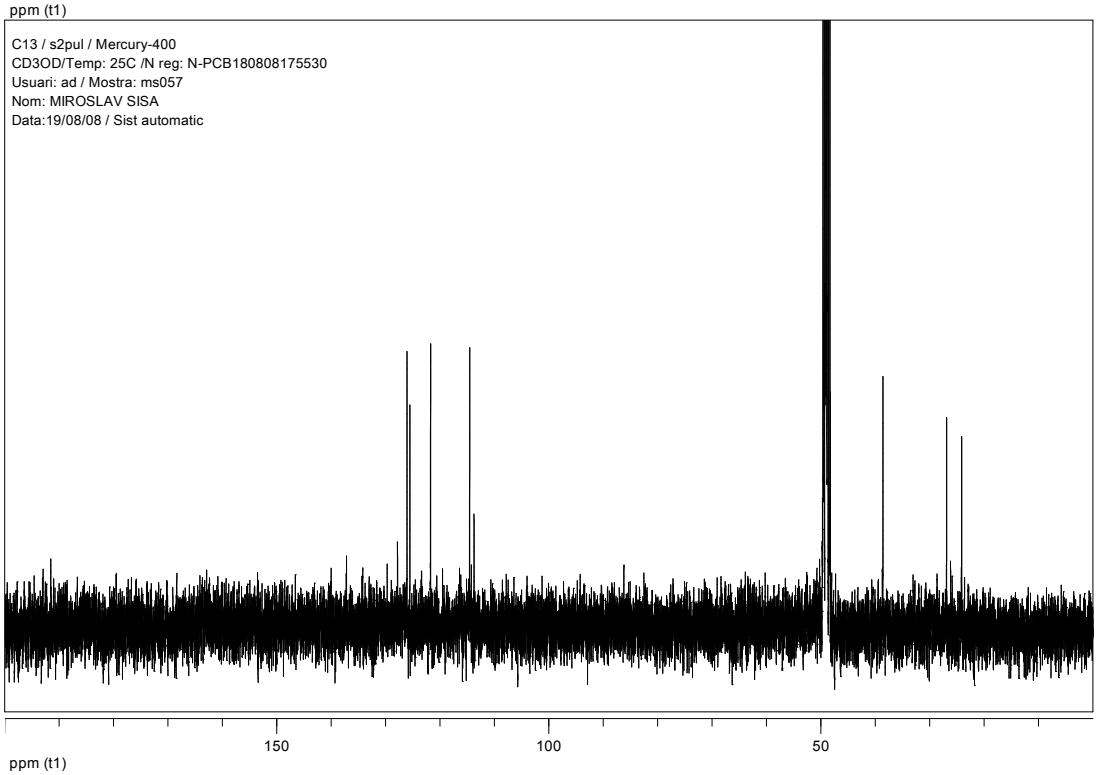
10j

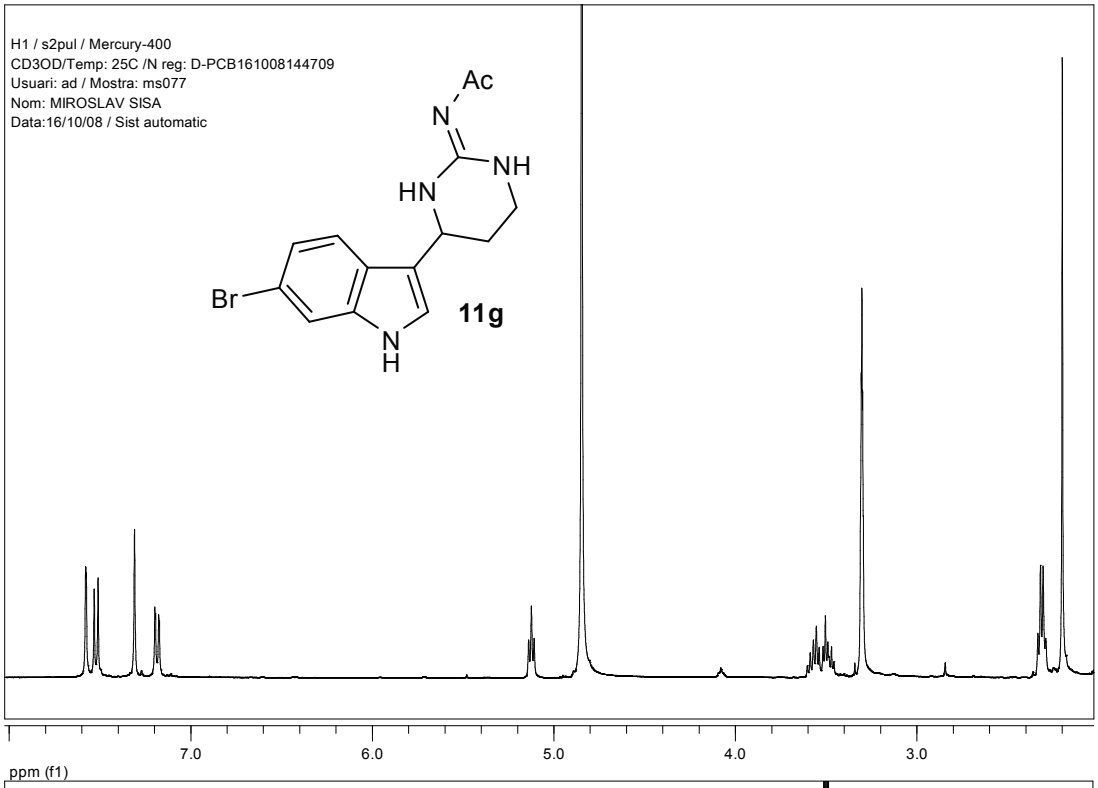

H1 / s2pul / Mercury-400
CD3OD/Temp: 25C /N reg: D-PCB151208100112
Usuari: ad / Mostra: ms099dm
Nom: MIROSLAV SISA
Data:15/12/08 / Sist automatic
7.0
6.0
5.0
4.0
3.0
ppm (f1)

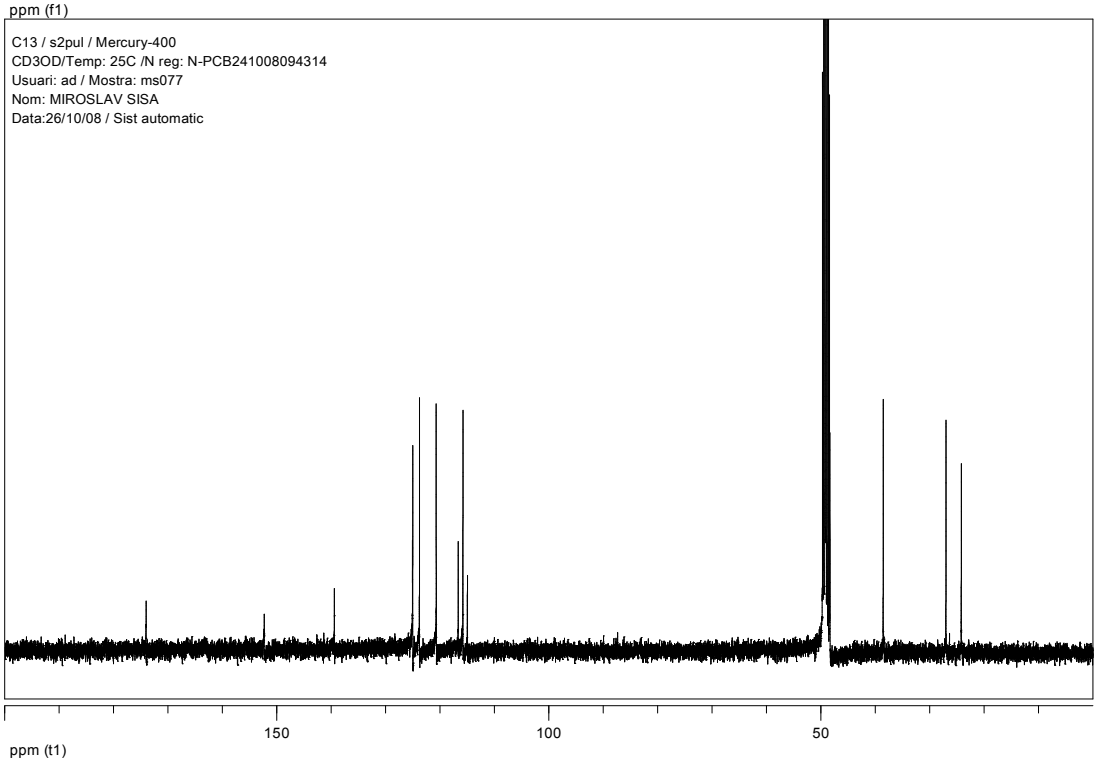

H1 / s2pul / Mercury-400
CD3OD/Temp: 25C /N reg: D-PCB280808135314
Usuari: ad / Mostra: ms045
Nom: MIROSLAV SISA
Data:28/08/08 / Sist automatic
Ac
N
NH
HN
N
Me
11a
7.0
6.0
5.0
4.0
3.0
ppm (t1)

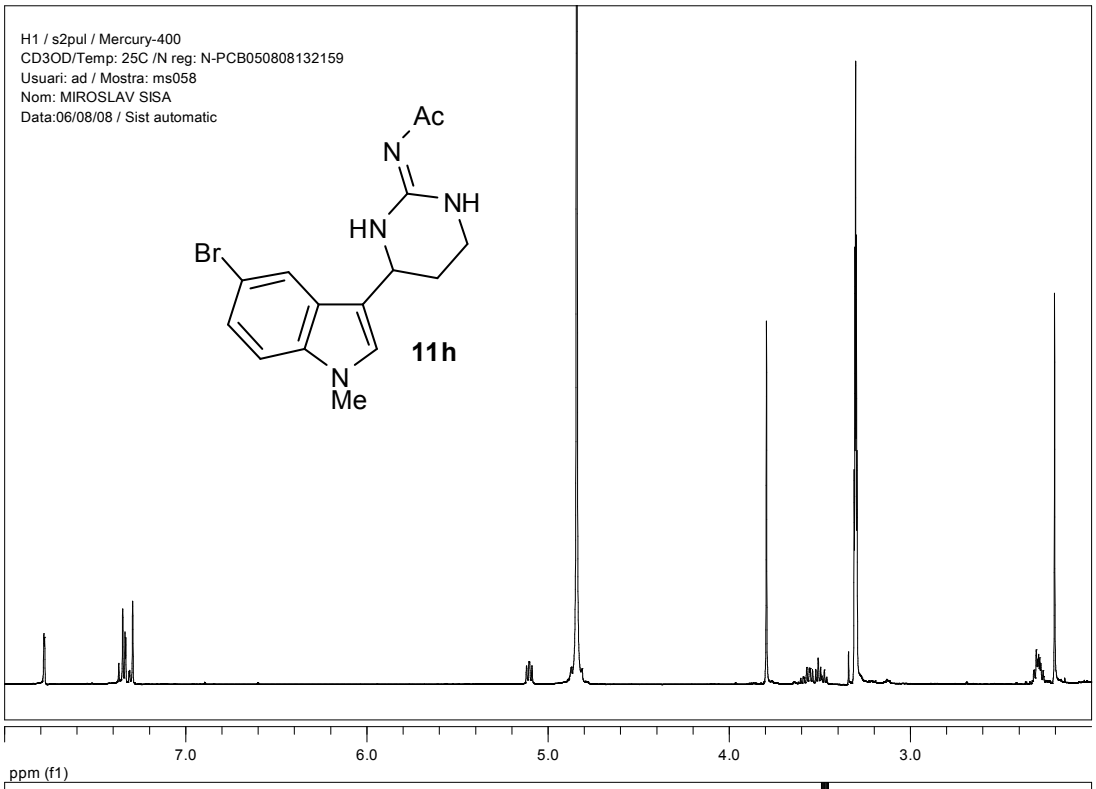

C13 / s2pul / Mercury-400
CD3OD/Temp: 25C /N reg: N-PCB290808111812
Usuari: ad / Mostra: ms045
Nom: MIROSLAV SISA
Data:29/08/08 / Sist automatic
150
100
50
ppm (t1)

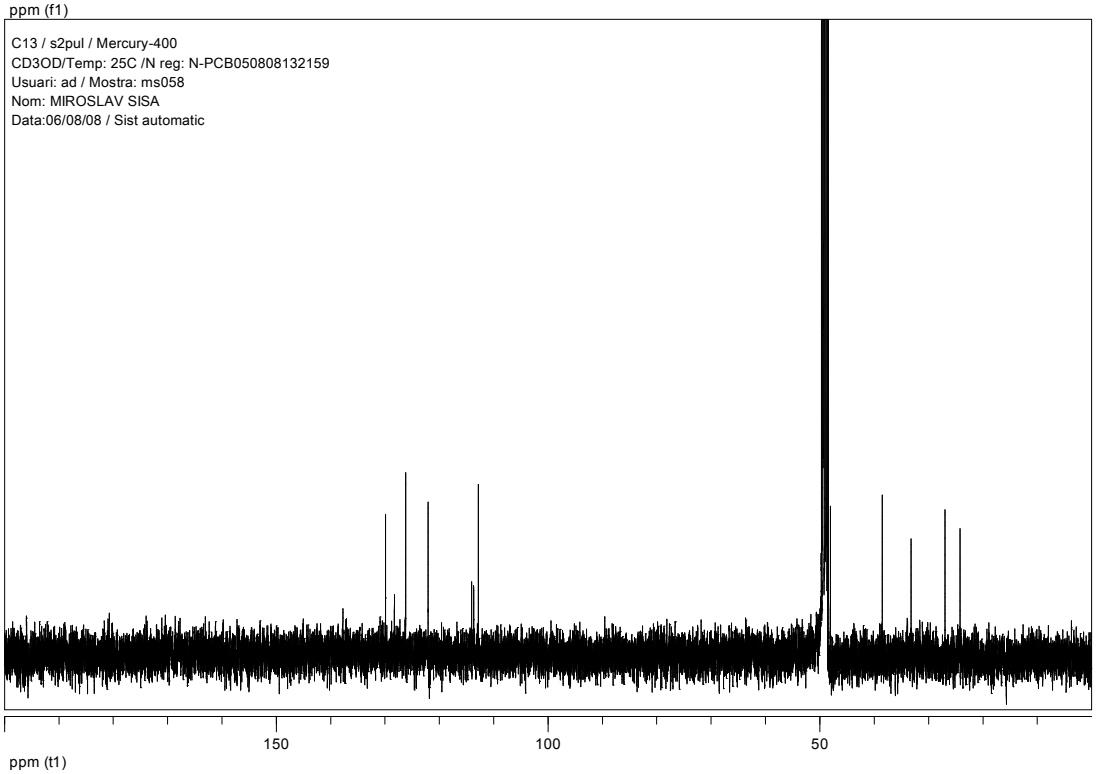

H1 / s2pul / Mercury-400
CD3OD/Temp: 25C /N reg: N-PCB140808161633
Usuari: ad / Mostra: ms057
Nom: MIROSLAV SISA
Data:14/08/08 / Sist automatic
Ac
N
NH
HN
Br
N
H
11f
7.0
6.0
5.0
4.0
3.0
ppm (t1)


C13 / s2pul / Mercury-400
CD3OD/Temp: 25C /N reg: N-PCB180808175530
Usuari: ad / Mostra: ms057
Nom: MIROSLAV SISA
Data:19/08/08 / Sist automatic
150
100
50
ppm (t1)


H1 / s2pul / Mercury-400
CD3OD/Temp: 25C /N reg: D-PCB161008144709
Usuari: ad / Mostra: ms077
Nom: MIROSLAV SISA
Data:16/10/08 / Sist automatic
Ac
N
NH
HN
Br
N
H
11g
7.0
6.0
5.0
4.0
3.0
ppm (f1)


C13 / s2pul / Mercury-400
CD3OD/Temp: 25C /N reg: N-PCB241008094314
Usuari: ad / Mostra: ms077
Nom: MIROSLAV SISA
Data:26/10/08 / Sist automatic
150
100
50
ppm (t1)


H1 / s2pul / Mercury-400
CD3OD/Temp: 25C /N reg: N-PCB050808132159
Usuari: ad / Mostra: ms058
Nom: MIROSLAV SISA
Data:06/08/08 / Sist automatic
Ac
N
NH
HN
Br
N
Me
11h
7.0
6.0
5.0
4.0
3.0
ppm (f1)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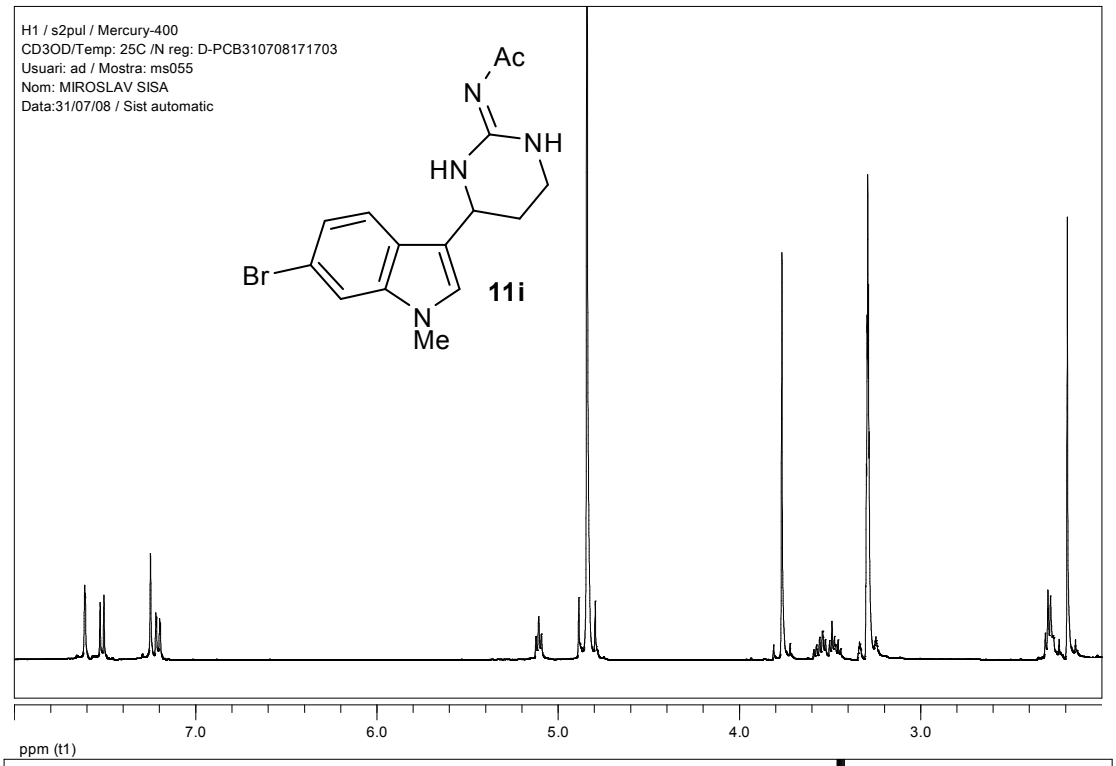
CD3OD/Temp: 25C /N reg: N-PCB050808132159
Usuari: ad / Mostra: ms058
Nom: MIROSLAV SISA
Data:06/08/08 / Sist automatic
150
100
50
ppm (t1)


H1 / s2pul / Mercury-400
CD3OD/Temp: 25C /N reg: D-PCB310708171703
Usuari: ad / Mostra: ms055
Nom: MIROSLAV SISA
Data:31/07/08 / Sist automatic
Ac
N
NH
HN
Br
N
Me
11i
7.0
6.0
5.0
4.0
3.0
ppm (t1)

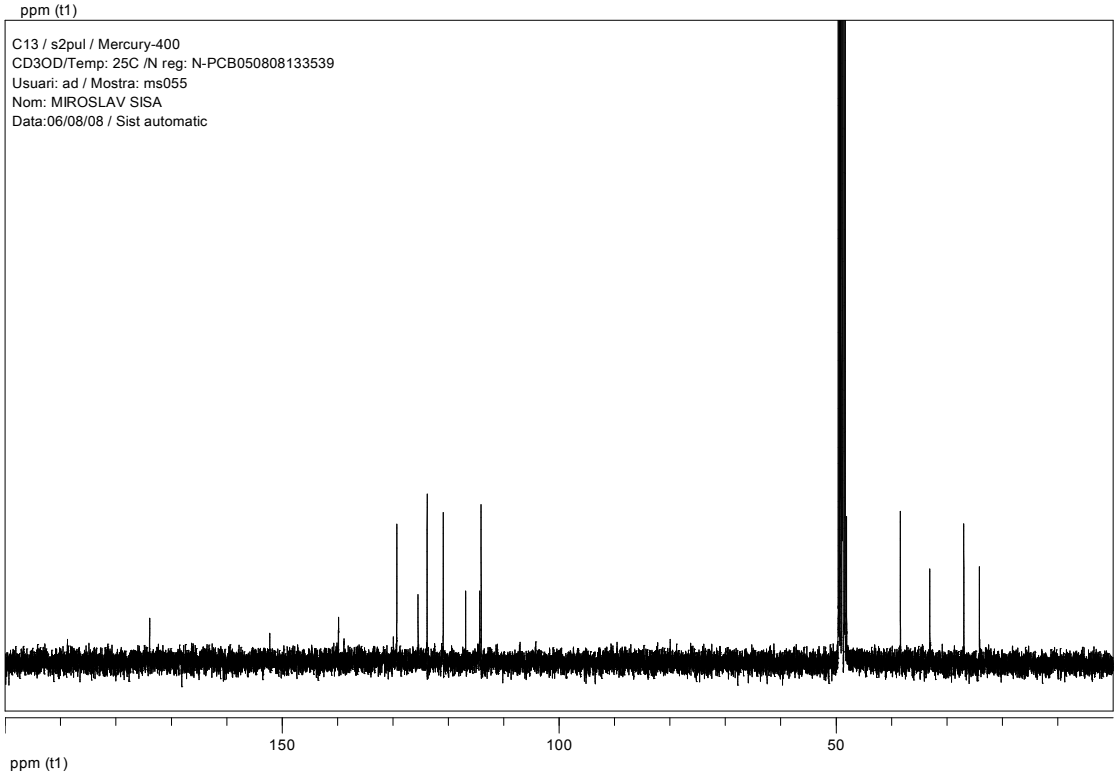

C13 / s2pul / Mercury-400
CD3OD/Temp: 25C /N reg: N-PCB050808133539
Usuari: ad / Mostra: ms055
Nom: MIROSLAV SISA
Data:06/08/08 / Sist automatic
150
100
50
ppm (t1)

Table 1. HPLC analytical results to support final compound purity.

Compound	Solvent System[a]				
	SS1[b]			**SS2**[c]	
	Gradient[d]	retention time (min)	% purity	retention time (min)	% purity
9a	A	6.5	95.5	3.9	96.9
9b	B	5.7	96.9	5.6	95.2
9d	A	6.9	96.5	4.5	94.7
9f	A	7.2	96.6	4.2	98.2
9g	A	7.3	96.2	4.2	95.6
9h	A	8.0	95.2	4.6	98.5
9i	A	8.1	95.2	4.7	98.5
10a	A	7.3	95.7	4.5	95.7
10b	B	6.3	96.3	5.0	95.0
10d	A	7.7	95.3	5.0	96.0
10f	A	8.0	96.2	4.7	95.3
10g	A	8.2	94.8	4.7	95.4
10h	A	8.9	96.0	5.2	96.6
10i	A	9.0	95.6	5.2	95.2
10j	B	5.6	96.2	5.3	98.1
11a	A	7.6	96.5	4.9	95.9
11f	A	8.2	95.0	5.1	95.1
11g	A	8.4	96.1	5.2	95.1
11h	A	9.1	95.6	5.7	98.2
11i	A	9.1	96.4	5.8	95.9

a: Analysis were done in two solvent systems (SS), with a flow rate of 1 mL/min.

b: **SS1**: H_2O/0.045% TFA (**V**) and MeCN/0.036% TFA (**X**)

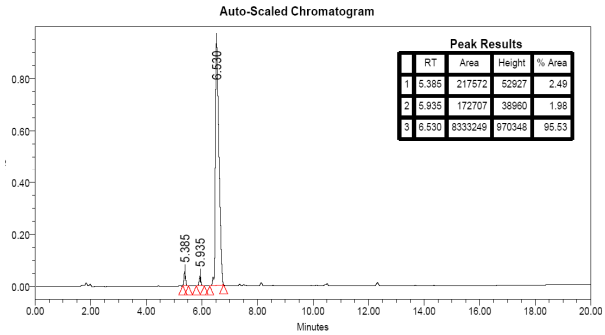
c: **SS2**: 20 mM NH_4AcO (pH = 5) (**Y**) and MeCN (**Z**). All the analysis were performed in a gradient starting from 10 to 100% of eluent **Z** in 8 min.

d: A: 10 to 80% of eluent **X** in 15 min; B: 10 to 80% of eluent **X** in 8 min.

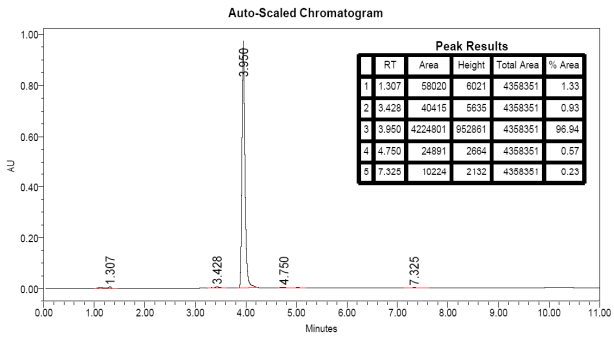
HPLC Chromatograms of Compounds **9**

2-Amino-6-(1-methylindol-3-yl)-1*H*-5,6-dihydropyrimidin-4-one (9a)

SS1

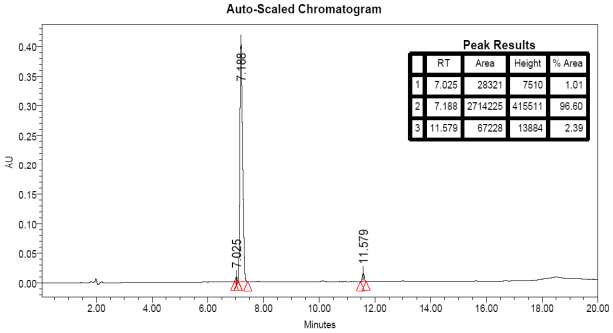


SS2

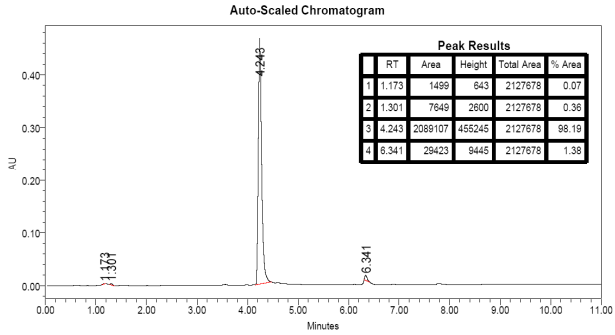


2-Amino-6-(5-bromoindol-3-yl)-1*H*-5,6-dihydropyrimidin-4-one (9f)

SS1

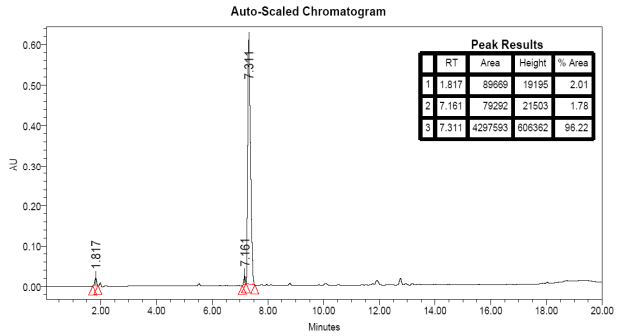


SS2

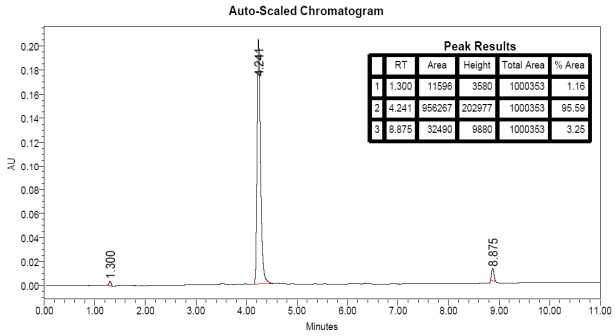


2-Amino-6-(6-bromoindol-3-yl)-1*H*-5,6-dihydropyrimidin-4-one (9g)

SS1

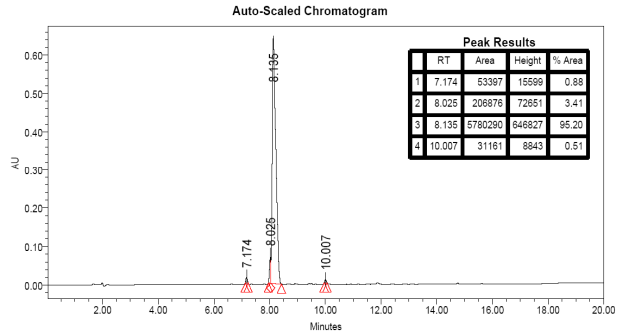


SS2

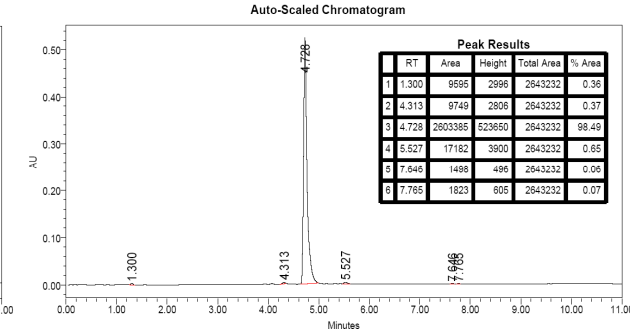


2-Amino-6-(6-bromo-1-methylindol-3-yl)-1*H*-5,6-dihydropyrimidin-4-one (9i)

SS1



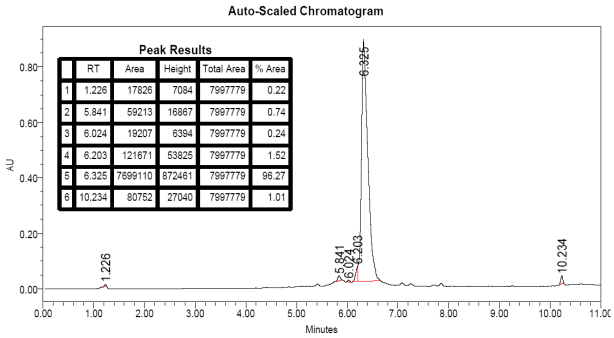
SS2



HPLC Chromatograms of Compounds **10**

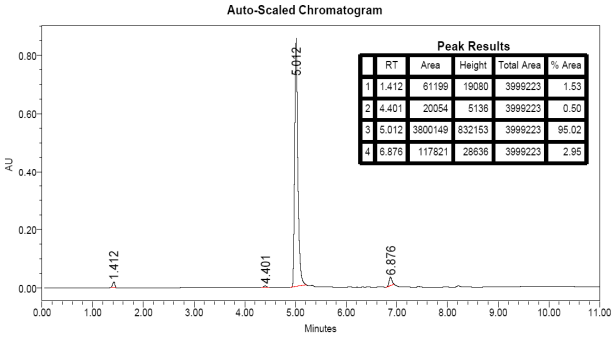
2-Amino-4-(5,6-dibromo-1-methoxyindol-3-yl)-1,4,5,6-tetrahydropyrimidine (10b)

SS1



	RT	Area	Height	Total Area	% Area
1	1.226	17826	7084	7997779	0.22
2	5.841	59213	16867	7997779	0.74
3	6.024	19207	6394	7997779	0.24
4	6.203	121671	53825	7997779	1.52
5	6.325	7699110	872461	7997779	96.27
6	10.234	80752	27040	7997779	1.01

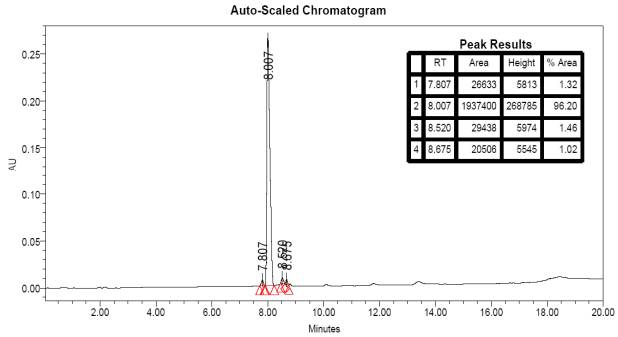
SS2



	RT	Area	Height	Total Area	% Area
1	1.412	61199	19080	3999223	1.53
2	4.401	20054	5136	3999223	0.50
3	5.012	3800149	832153	3999223	95.02
4	6.876	117821	28636	3999223	2.95

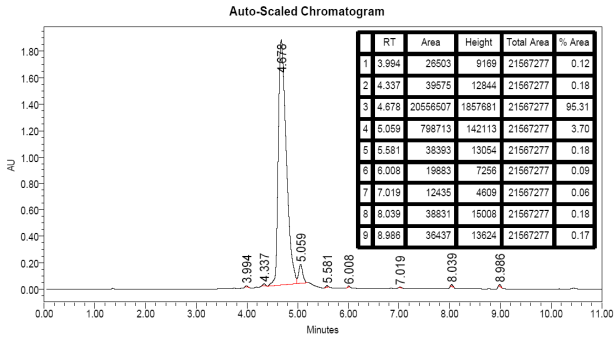
2-Amino-4-(5-bromoindol-3-yl)-1,4,5,6-tetrahydropyrimidine (10f)

SS1



	RT	Area	Height	% Area
1	7.807	26633	5813	1.32
2	8.007	1937400	268785	96.20
3	8.520	29438	5974	1.46
4	8.675	20506	5545	1.02

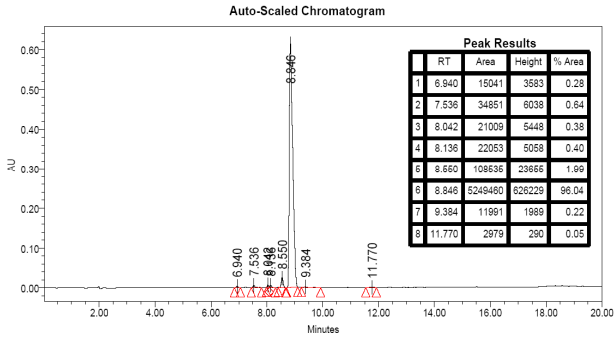
SS2



	RT	Area	Height	Total Area	% Area
1	3.994	26503	9169	21567277	0.12
2	4.337	39575	12844	21567277	0.18
3	4.678	20556507	1857681	21567277	95.31
4	5.059	798713	142113	21567277	3.70
5	5.581	38393	13054	21567277	0.18
6	6.008	19883	7256	21567277	0.09
7	7.019	12435	4609	21567277	0.06
8	8.039	38831	15008	21567277	0.18
9	8.986	36437	13624	21567277	0.17

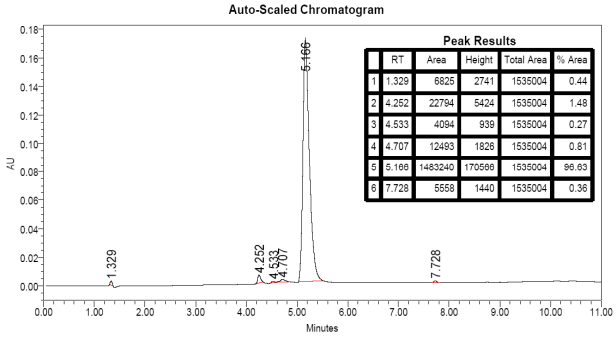
2-Amino-4-(5-bromo-1-methylindol-3-yl)-1,4,5,6-tetrahydropyrimidine (10h)

SS1



	RT	Area	Height	% Area
1	6.940	15041	3583	0.28
2	7.536	34851	6038	0.64
3	8.042	21009	5448	0.38
4	8.136	22053	5058	0.40
5	8.550	108536	23666	1.99
6	8.846	5249460	626229	96.04
7	9.384	11991	1989	0.22
8	11.770	2979	290	0.05

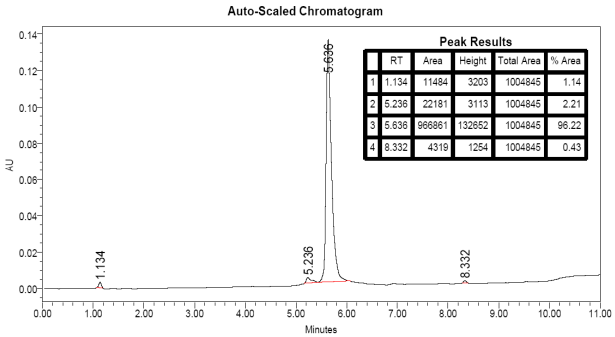
SS2



	RT	Area	Height	Total Area	% Area
1	1.329	6825	2741	1535004	0.44
2	4.252	22794	5424	1535004	1.48
3	4.533	4094	939	1535004	0.27
4	4.707	12493	1826	1535004	0.81
5	5.166	1483240	170566	1535004	96.63
6	7.728	5558	1440	1535004	0.36

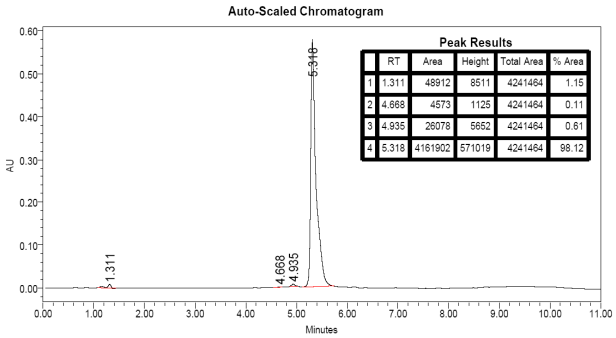
2-Amino-4-(5,6-dibromoindol-3-yl)-1,4,5,6-tetrahydropyrimidin-4-one (10j)

SS1



	RT	Area	Height	Total Area	% Area
1	1.134	11484	3203	1004845	1.14
2	5.236	22181	3113	1004845	2.21
3	5.636	966861	132652	1004845	96.22
4	8.332	4319	1254	1004845	0.43

SS2

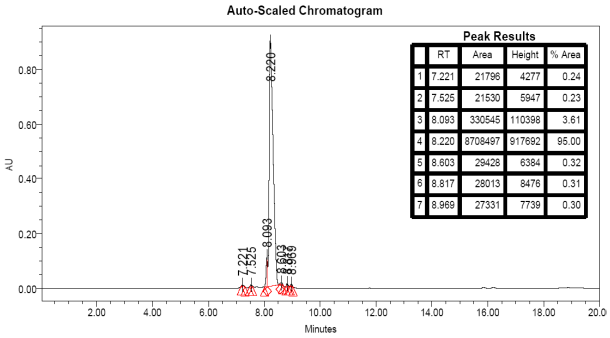


	RT	Area	Height	Total Area	% Area
1	1.311	48912	8511	4241464	1.15
2	4.668	4573	1125	4241464	0.11
3	4.935	26078	5652	4241464	0.61
4	5.318	4161902	571019	4241464	98.12

HPLC Chromatograms of Compounds **11**

2-(Acetylamino)-4-(5-bromoindol-3-yl)-1*H*-3,4,5,6-tetrahydropyrimidine (11f)

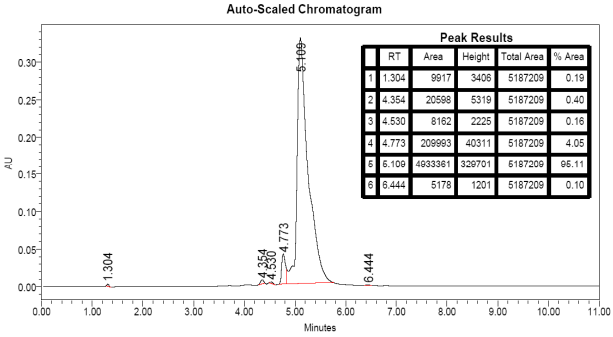
SS1



Peak Results

	RT	Area	Height	% Area
1	7.221	21796	4277	0.24
2	7.525	21530	5947	0.23
3	8.093	330545	110398	3.61
4	8.220	8708497	917692	95.00
5	8.603	29428	6384	0.32
6	8.817	28013	8476	0.31
7	8.969	27331	7739	0.30

SS2

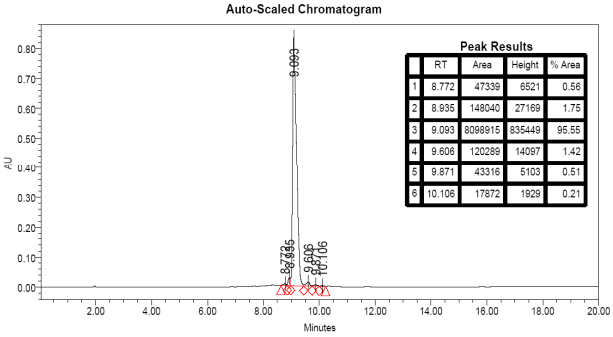


Peak Results

	RT	Area	Height	Total Area	% Area
1	1.304	9917	3406	5187209	0.19
2	4.354	20598	5319	5187209	0.40
3	4.530	8162	2225	5187209	0.16
4	4.773	209993	40311	5187209	4.05
5	5.109	4933361	329701	5187209	95.11
6	6.444	5178	1201	5187209	0.10

2-(Acetylamino)-4-(5-bromo-1-methylindol-3-yl)-1,2,3,4-tetrahydropyrimidine (11h)

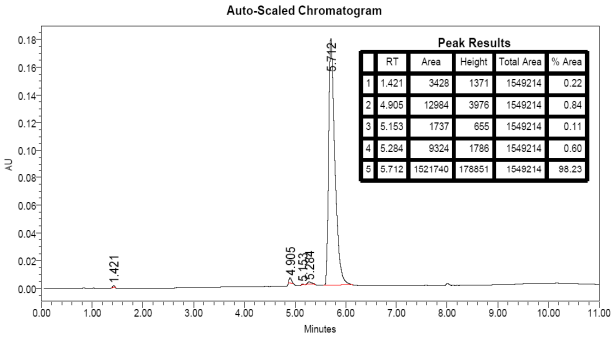
SS1



Peak Results

	RT	Area	Height	% Area
1	8.772	47339	6521	0.56
2	8.935	148040	27169	1.75
3	9.093	8098915	835449	95.55
4	9.606	120289	14097	1.42
5	9.871	43316	5103	0.51
6	10.106	17872	1929	0.21

SS2



Peak Results

	RT	Area	Height	Total Area	% Area
1	1.421	3428	1371	1549214	0.22
2	4.905	12984	3976	1549214	0.84
3	5.153	1737	655	1549214	0.11
4	5.284	9324	1786	1549214	0.60
5	5.712	1521740	178851	1549214	98.23