Chemo- and Regioselective Functionalization of Uracil Derivatives. Applications to the Synthesis of Oxypurinol and Emivirine

Nadège Boudet and Paul Knochel*

Department Chemie und Biochemie, Ludwig-Maximilians-Universität,
Butenandtstrasse 5-13, 81377, München (Germany).

Paul.Knochel@cup.uni-muenchen.de

Supporting information

Experimental procedures, analytical and spectroscopy data for starting materials and final products (45 pages).

General considerations

Unless otherwise indicated, all reactions were carried out with magnetic stirring and, if air or moisture sensitive, in flame-dried glassware under argon. Syringes used to transfer reagents and solvent were purged with argon prior to use. Reactions were monitored by gas chromatography (GC and GC-MS) or thin layer chromatography (TLC).

Preparation of the reagent *i*-PrMgCl·LiCl:

Magnesium turnings (110 mmol) and anhydrous LiCl (100 mmol) were placed in an Ar-flushed flask and THF (25 mL) was added. A solution of *i*-PrCl (100 mmol) in THF (25 mL) was slowly added at rt. The reaction starts within a few minutes. After addition, the reaction mixture was stirred for 12 h at rt. The grey solution of *i*-PrMgCl·LiCl was cannulated to an other flask under Ar and removed in this way from excess of magnesium. A yield of ca. 95-98% of *i*-PrMgCl·LiCl is obtained.

Preparation of the reagent CuCN·2LiCl in THF [1]: according to the known procedure**.**

General procedure for the Br/Mg exchange reaction:

A dry and argon flushed 10 mL flask, equipped with a magnetic stirring bar and a septum, was charged with the neat 5-bromo-4-halogeno-2,6-dimethoxypyrimidine (1 mmol) dissolved in dry THF (1.0 mL). *i*-PrMgCl·LiCl (1 mL, 1.05 M in THF, 1.05 mmol) was added slowly, dropwise, at appropriate temperature (as stated in the experiment). The reaction mixture was stirred at the same or plus 5°C temperature, and the completion of the Br/Mg exchange was checked by GC-analysis using tetradecane as internal standard or by TLC.

General procedure for the reaction with electrophiles:

The freshly prepared magnesium reagent was cooled to the corresponding temperature or used at room temperature and the corresponding electrophile (1.1 mmol, 1.1 equiv.) was added. The mixture was stirred for time depending of the reactivity of the electrophile. The consumption of the magnesium reagent was checked by GC-analysis, using tetradecane as internal standard. After the reaction was completed, sat. NH_4Cl solution was added and the mixture was extracted three times with Et_2O or AcOEt. The solvent was evaporated and the product was purified by flash chromatography (SiO_2).

---

[1] Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

Starting materials:

5-bromo-4-chloro-2,6-dimethoxypyrimidine (4).

This compound was prepared starting from 4-chloro-2,6-dimethoxypyrimidine according to the literature procedure.[2] The analytic data correspond to the analytic data from the literature.

The product **4** was obtained as a white solid (mp: 98,7-99,7 °C).

^{1}H-NMR (CDCl$_3$, 300 MHz): δ = 4.05 (s, 3H), 3.99 (s, 3H).

^{13}C-NMR (CDCl$_3$, 75 MHz): δ = 168.3, 162.8, 160.4, 97.1, 55.8.

MS (EI, 70 ev), *m/z* (%): 253.9 (100), 252.9 (77), 251.9 (75), 250.9 (58), 238.9 (27), 223.9 (92), 221.0 (70), 208.9 (37), 143.0 (42).

HRMS (EI): calcd. for $C_6H_6BrClN_2O_2$ [M$^+$]: 251.9301, found: 251.9284.

Starting material of 4,5-bromo-2,6-dimethoxypyrimidine (5): 4-bromo-2,6-dimethoxypyrimidine.

4-bromo-2,6-dimethoxypyrimidine was prepared starting from barbituric acid in two steps, according to the literature procedure[3]. The analytic data correspond to the analytic data from the literature.

The product was obtained as a white solid (mp: 90,9-92,0 °C).

^{1}H-NMR (CDCl$_3$, 300 MHz): δ = 6.52 (s, 1H), 3.93 (s, 3H), 3.89 (s, 3H).

^{13}C-NMR (CDCl$_3$, 75 MHz): δ = 172.1, 164.9, 152.4, 105.4, 55.8, 54.8.

MS (EI, 70 ev), *m/z* (%): 219.9 (79), 218.9 (67), 217.9 (78), 216.9 (75), 189.9 (90), 187.9 (100), 174.9 (37), 109.0 (51), 82.0 (65).

IR (KBr): 1589 (m), 1550 (s), 1463 (s), 1363 (m), 1199 (m), 819 (s).

HRMS (EI): calcd. for $C_6H_7BrN_2O_2$ [M$^+$]: 217.9691, found: 217.9692.

5,4-dibromo -2,6-dimethoxypyrimidine (5).

This compound **(5)** was prepared with the same procedure for the synthesis of 5-bromo-4-chloro-2,6-dimethoxypyrimidine **(4)**, starting from 4-bromo-2,6-dimethoxypyrimidine. 5,4-dibromo-2,6-dimethoxypyrimidine (**5**) was isolated as a white solid in 96% yield (mp: 117.6-118.0 °C).

^{1}H-NMR (CDCl$_3$, 400 MHz): δ = 4.05 (s, 3H), 3.99 (s, 3H).

^{13}C-NMR (CDCl$_3$, 100 MHz): δ = 167.7, 162.54, 153.74, 100.80, 55.78.

---

[2] Okafor, C. *J. Org. Chem*. **1973**, *38*, 4386

[3] White, J. D.; Hansen, J. D. *J. Org. Chem*. **2005**, *70*, 1963-1977.

MS (EI, 70 ev), *m/z* (%): 299.8 (46), 298.8 (47), 297.8 (100), 296.8 (71), 295.8 (48), 294.8 (31), 282.8 (20), 269.8 (31), 267.8 (64), 265.8 (30), 188.9 (19), 186.9 (21).

IR (KBr): 2957 (w), 1526 (s), 1455 (m), 1343 (s), 1311 (m), 1008 (s).

HRMS (EI): calcd. for $C_6H_6Br_2N_2O_2$ $[M^+]$: 295.8796, found: 295.8799.

Products 8a-9e:

(4-chloro-2,6-dimethoxypyrimidin-5-yl)(phenyl)methanol (8a).

A dry and argon flushed 10mL flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**4**) (254 mg, 1 mmol) in dry THF (1 mL). *i*-PrMgCl·LiCl (1.0 M/THF, 1.05 mmol, 1.05 equiv) was added slowly at room temperature and the resulting mixture was stirred for 15 min to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots). Benzaldehyde (117 mg, 1.1 mmol, 1.1 equiv) was added dropwise. The mixture was stirred for 5 h and was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ether (3 × 5 mL). The organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 3:2) yielded 255 mg (91% yield) of **3a** as a white solid (mp.: 90,1- 91,4 °C).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.33-7.24 (m, 5H), 6.21 (d, *J* = 11 Hz, 1H), 4.01 (s, 3H), 3.96 (s, 3H), 3.41 (d, *J* = 11 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 100 MHz): 169.67, 163.17, 159.42, 141.68, 128.31, 127.45, 125.26, 113.96, 69.98, 55.44, 55.00.

MS (EI, 70 ev), *m/z* (%): 282.0 (15), 280.0 (44), 262.0 (20), 205.0 (29), 203.0 (100), 105.0 (10), 77.0 (12).

IR (KBr): 3412 (s), 2955 (w), 1583 (s), 1553 (s), 1464 (m), 1375(s), 1242 (m), 1032 (s).

HRMS (EI): calcd. for $C_{13}H_{13}ClN_2O_3$ $[M^+]$: 280.0615, found: 280.0612.

(4-chloro-2,6-dimethoxypyrimidin-5-yl)(2-methoxyphenyl)methanol (8b).

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**4**) (254 mg, 1 mmol) in dry THF (1 mL). *i*-PrMgCl·LiCl (1.0 M/THF, 1.05 mmol, 1.05 equiv) was added slowly at room temperature and the resulting mixture was stirred for 15 min to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots). 2-methoxybenzaldehyde (150 mg, 1.1 mmol, 1.1 equiv) was added in one portion. The mixture was stirred for 10 h and was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ether (3 × 5 mL). The organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 3:2) yielded 258 mg (83% yield) of **8b** as a white solid (mp.: 106.0-107.3 °C) .

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.34 (d, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 8.8 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.38 (d, *J* = 8.4 Hz, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 3.79 (s, 3H), 3.33 (d, *J* = 8.8 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 100 MHz): 170.13, 163.11, 156.76, 129.36, 128.90, 127.07, 120.22, 113.53, 110.60, 66.75, 55.55, 55.51, 55.00.

MS (EI, 70 ev), *m/z* (%): 312.2 (22), 311.2 (15), 310.2 (58), 294.1 (38), 293.1 (23), 292.1 (100), 257.12 (57), 242.1 (12), 205.1 (13), 203.1 (51), 201.1 (53), 175.1 (29), 135.1 (16), 109.1 (17), 108.1 (19), 77.1 (10).

IR (KBr): 3472 (s), 3003 (m), 2963 (w), 1553 (s), 1455 (m), 1375 (s), 1241 (m), 1206 (m), 1021 (s).

HRMS (EI): calcd. for $C_{14}H_{15}ClN_2O_4$ [M^+]: 310.0720, found: 310.0733.

4-chloro-2,6-dimethoxypyrimidin-5-yl)(phenyl)methanone (8c).

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**4**) (254 mg, 1 mmol) in dry THF (1 mL). *i*-PrMgCl·LiCl (1.0 M/THF, 1.05 mmol, 1.05 equiv) was added slowly at room temperature and the resulting mixture was stirred for 15 min to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots) and cooled down to -20 °C. Benzoyl chloride (154 mg, 1.1mmol, 1.1 equiv) was added dropwise. The mixture was warmed up at room temperature for 3 h and was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ether (3 × 5 mL). The organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether= 3:2) yielded 231 mg (86% yield) of **8c** as a white solid (mp.: 116.0-117.3 °C) .

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.83 (d, *J* = 8.5 Hz, 2H), 7.62 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 4.07 (s, 3H), 3.94 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): 190.69, 169.47, 164.27, 158.11, 136.17, 134.19, 129.45, 128.85, 112.81, 55.68, 55.11.

MS (EI, 70 ev), *m/z* (%): 280.2 (17), 278.2 (47), 203.1 (34), 201.1 (100), 105.1 (30), 77.1 (17), 76.1 (11).

IR (KBr): 3436 (m), 3000 (w), 2952 (w), 1676 (s), 1589 (s), 1485 (s), 1485 (m), 1389 (s), 1200 (s), 1027 (m), 921 (m).

HRMS (EI): calcd. for $C_{13}H_{11}ClN_2O_3$ [M^+]: 278.0458, found: 278.0441.

(4-chloro-2,6-dimethoxypyrimidin-5-yl)(morpholino)methanone(8d).

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**4**) (254 mg, 1 mmol) in dry THF (1 mL). *i*-PrMgCl·LiCl (1.0 M/THF, 1.05 mmol, 1.05 equiv) was added slowly at room temperature and the resulting mixture was stirred for 15 min to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots) and cooled down to -20 °C. 4-morpholinecarbonyl chloride (165 mg, 1.1 mmol, 1.1 equiv) was added dropwise. The mixture was warmed up to room temperature for 15 h and was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ether (3 × 5 mL). The organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 2:3) yielded 244 mg (85% yield) of **8d** as a white solid (mp.: 109.9-111.3 °C).

^{1}H-NMR (DMSO, 400 MHz): δ = 4.01 (2 singulets, 6H), 3.86-3.61 (3 multiplets, 6H), 3.28 (m, 2H).

^{13}C-NMR (DMSO, 100 MHz): 168.55, 164.12, 162.02, 157.89, 109.39, 66.75, 66.56, 55.63, 55.21, 46.92, 42.20.

MS (EI, 70 ev), *m/z* (%): 287.0 (9), 252.1 (11), 203.0 (28), 201.0 (100), 75.9 (11).

IR (KBr): 2960 (w), 2862 (w), 1634 (m), 1580 (s), 1534 (s), 1494 (m), 1370 (s), 1357 (m), 1275 (m), 1235 (s), 1111 (s), 1009 (s).

HRMS (EI): calcd. for $C_{11}H_{14}ClN_3O_4$ [M^+]: 287.0673, found: 287.0664.

4-chloro-2,6-dimethoxypyrimidine-5-carbonitrile (8e).

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**4**) (254 mg, 1 mmol) in dry THF (1 mL). i-PrMgCl·LiCl (1.0 M/THF, 1.05 mmol, 1.05 equiv) was added slowly at room temperature and the resulting mixture was stirred for 15 min to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots). *p*-toluenesulfonyl cyanide (200 mg, 1.1 mmol, 1.1 equiv) was added in one portion. The mixture was stirred overnight (12 h) at rt and was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ethyl acetate (2 × 5 mL) and dichloromethane (1 × 5 mL) . The organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 1:4) yielded 178 mg (89% yield) of **8e** as a white solid (mp.: 123.3-124.8 °C) .

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 4.11 (s, 3H), 4.07 (s, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): 169.24, 163.98, 163.41, 158.85, 108.67, 62.14, 55.67, 55.23, 14.01.

MS (EI, 70 ev), *m/z* (%): 201.1 (25), 199.1 (71), 198.1 (32), 171.1 (33), 169.1 (100), 154.1 (32), 106.1 (19), 70.1 (11).

IR (KBr): 3021 (w), 2947 (w), 2233 (m), 1586 (m), 1529 (s), 1474 (m), 1378 (m), 1218 (m), 1071 (m), 1018 (s).

HRMS (EI): calcd. for $C_7H_6ClN_3O_2$ [M^+]: 199.0149, found: 199.0131.

Ethyl 4-chloro-2,6-dimethoxypyrimidine-5-carboxylate (8f).

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**4**) (381 mg, 1.5 mmol) in dry THF (2 mL). *i*-PrMgCl·LiCl (1.0 M/THF, 1.58 mmol, 1.05 equiv) was added slowly at room temperature and the resulting mixture was stirred for 15 min to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots). The mixture was cooled down to -20°C and ethyl cyanoformate (164 mg, 1.1 equiv) was added dropwise. The mixture was stirred at -20 °C for 10 min, warmed up to room temperature for 8 h and was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 4:1) yielded 322 mg (87% yield) of **8f** as a yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 4.40 (q, *J* = 7.1 Hz, 2H), 4.02 (s, 6H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): 172.22, 165.12, 164.89, 111.75, 89.77, 56.39, 55.96.

MS (EI, 70 ev), *m/z* (%): 246.2 (15), 218.1 (13), 203.1 (30), 201.1 (100), 174.1 (13), 76.1 (14).

IR (film): 2957 (w), 1731 (s), 1585 (s), 1540 (s), 1488 (m), 1376 (m), 1218 (m), 1071 (m), 1018 (s).

HRMS (EI): calcd. for $C_7H_6ClN_3O_2$ [M^+]: 246.0407, found: 246.0388.

5-benzyl-4-chloro-2,6-dimethoxypyrimidine (8g).

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**4**) (381 mg, 1.5 mmol) in dry THF (2 mL). *i*-PrMgCl·LiCl (1.0 M/THF, 1.58 mmol, 1.05 equiv) was added slowly at room temperature and the resulting mixture was stirred for 15 min to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots). Benzylbromide (360 mg, 2.1 mmol, 1.4 equiv) was added dropwise. The mixture was stirred at rt for 4 h and was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ethyl acetate (3 × 5 mL). The organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (n-pentane/diethyl ether = 1:4) yielded 300 mg (75% yield) of **8g** as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.14 (m, 5H), 3.90-3.91 (m, 8H).

^{13}C-NMR ($CDCl_3$, 100 MHz): 170.26, 162.65, 160.23, 138.57, 128.30, 126.29, 112.04, 55.13, 54.82, 31.16.

MS (EI, 70 ev), *m/z* (%): 266.2 (31), 264.2 (100), 249.1 (33), 234.2 (19), 173.1 (17), 156.1 (10), 91.1 (18), 77.1 (8).

IR (film): 3028 (w), 2950 (w), 1586 (m), 1541 (s), 1453 (m), 1369 (s), 1213 (m), 1078 (m), 1026 (s).

HRMS (EI): calcd. for $C_{13}H_{13}ClN_2O_2$ [M^+]: 264.0666, found: 264.0639.

4-bromo-2,6-dimethoxy-5-(trimethylsilyl)pyrimidine (9a).

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4,5-dibromo-2,6-dimethoxypyrimidine (**5**) (596 mg, 2 mmol) in dry THF (3 mL). *i*-PrMgCl·LiCl (1.0 M/THF, 2.1 mmol, 1.05 equiv) was added very slowly at room temperature and the resulting mixture was stirred for 15 min to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots). Trimethylsilyl chloride (240 mg, 2.2 mmol, 1.1 equiv) was added dropwise. The mixture was stirred at rt for 24 h and was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ethyl acetate (2 × 10 mL). The organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (n-pentane/diethyl ether = 4:1) yielded 529 mg (91% yield) of **9a** as a white solid (mp.: 71.1-72.2 °C).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 3.98 (s, 3H), 3.92 (s, 3H), 0.37 (s, 9H).

^{13}C-NMR ($CDCl_3$, 100 MHz): 175. 51, 164.45, 159.89, 111.76, 55.05, 54.13, 1.24.

MS (EI, 70 ev), *m/z* (%): 292.1 (10), 290.1 (10), 277.1 (100), 275.1 (99), 247.1 (81), 220.1 (30), 194.1 (13), 137.0 (33), 72.1 (38).

IR (KBr): 2955 (w), 2899 (w), 1556 (m), 1524 (s), 1450 (m), 1344 (s), 1278 (m), 1114 (m), 1015 (m), 839 (s).

HRMS (EI): calcd. for $C_9H_{15}BrN_2O_2Si$ [M^+]: 290.0086, found: 290.0062.

5-allyl-4-bromo-2,6-dimethoxypyrimidine (9b).

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4,5-dibromo-2,6-dimethoxypyrimidine (**5**) (596 mg, 2 mmol) in dry THF (3 mL). *i*-PrMgCl·LiCl (1.0 M/THF, 2.1 mmol, 1.05 equiv) was added very slowly (within 5 min) at room temperature and the resulting mixture was stirred for 15 min to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots). Allyl bromide (266 mg, 2.2 mmol, 1.1 equiv) was added dropwise. The mixture was stirred at rt for 2 h and was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ethyl acetate (2 × 5 mL). The organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (n-pentane/diethyl ether = 9:1) yielded 528 mg (91% yield) of **9b** as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 5.82 (m, 1H), 5.02 (2 dd, $^3J_{trans}$ = 13.2 Hz, J_{gem} and $^3J_{ci\ s}$= 1.7 Hz, 2H), 3.98 (s, 3H), 3.97 (s, 3H), 3.35 (dt, ^3J = 6.1 Hz, ^4J = 1.5 Hz).

^{13}C-NMR ($CDCl_3$, 100 MHz): 170.08, 162.61, 159.98, 133.39, 115.93, 110.71, 55.14, 54.82, 29.57.

MS (EI, 70 ev), *m/z* (%): 260.0 (98), 258.0 (100), 245.0 (23), 243.0 (22), 231.0 (41), 179.0 (25), 163.0 (14).

IR (film): 3081 (w), 2957 (w), 1639 (w), 1586 (m), 1542 (s), 1459 (m), 1370 (s), 1223 (m), 1079 (m), 1026 (s).

HRMS (EI): calcd. for $C_9H_{11}BrN_2O_2$ [M^+]: 258.0004, found: 258.0023.

Ethyl 4-bromo-2,6-dimethoxypyrimidine-5-carboxylate (9c).

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**5**) (298 mg, 1.0 mmol) in dry THF (2 mL). *i*-PrMgCl·LiCl (1.0 M/THF, 1.05 mmol, 1.05 equiv) was added very slowly (within 5 min) at room temperature and the resulting mixture was stirred for 15 min to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots) and cooled down to -20 °C. Ethyl cyanoformate (164 mg, 1.1 equiv) was added dropwise. The mixture was stirred at -20 °C for 1 h, warmed up to room temperature for 12 h and was quenched with saturated aqueous NH_4Cl solution . The aqueous phase was extracted with ethyl acetate (3 × 5 mL). The organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 4:1) yielded 236 mg (81% yield) of **9c** as a white solid (mp.: 42.5-43.8 °C).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 4.38 (q, *J* = 7.1 Hz, 2H), 4.01 (s, 6H), 1.37 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): 166.52, 164.00, 163.61, 149.96, 112.0, 62.21, 55.69, 55.15, 13.98.

MS (EI, 70 ev), *m/z* (%): 292.1 (18), 290.1 (19), 247.1 (96), 245.1 (100), 218.1 (18), 151.1 (8), 122.0 (19), 70.1 (11).

IR (KBr): 2983 (w), 2960 (w), 1725 (s), 1570 (s), 1529 (s), 1491 (m), 1358 (m), 1265 (s), 1229 (s), 1048 (m), 1013 (s).

HRMS (EI): calcd. for $C_9H_{11}BrN_2O_4$ [M^+]: 289.9902, found: 289.9902.

(4-bromo-2,6-dimethoxypyrimidin-5-yl)(phenyl)methanol (9d).

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4,5-dibromo-2,6-dimethoxypyrimidine (**5**) (298 mg, 1.0 mmol) in dry THF (2 mL). *i*-PrMgCl·LiCl (1.0 M/THF, 1.05 mmol, 1.05 equiv) was added very slowly (within 5min) at room temperature and the resulting mixture was stirred for 15 min to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots). Benzaldehyde (117 mg, 1.1 mmol, 1.1 equiv) was added dropwise. The mixture was stirred at rt for 4 h and was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ethyl acetate (3 × 5 mL). The organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (n-pentane/diethyl ether = 3:2) yielded 308 mg (95% yield) of **9d** as a white solid (mp.: 108.9-111.2°C).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.3 (m, 5H), 6.19 (d, *J* = 11.1 Hz, 1H), 4.01 (s, 3H), 3.93 (s, 3H), 3.41 (d, *J* = 11.1 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 100 MHz): 168.95, 162.95, 152.53, 141.65, 128.32, 127.47, 125.29, 116.65, 55.42, 54.96.

MS (EI, 70 ev), *m/z* (%): 326.1 (41), 324.1 (33), 308.1 (18), 306.1 (18), 249.1 (67), 247.1 (100), 227.1 (32), 105.1 (17), 77.1 (22).

IR (KBr): 3337 (s), 2953 (w), 2923 (w), 1572 (w), 1543 (s), 1488 (m), 1448 (m), 1368 (s), 1212 (m), 1016 (s).

HRMS (EI): calcd. for $C_{13}H_{13}BrN_2O_3$ [M^+]: 324.0110, found: 324.0092.

(4-bromo-2,6-dimethoxypyrimidin-5-yl)(morpholino)methanone (9e).

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**5**) (298 mg, 1 mmol) in dry THF (2 mL). *i*-PrMgCl·LiCl (1.0 M/THF, 1.05 mmol, 1.05 equiv) was added slowly at room temperature and the resulting mixture was stirred for 15 min to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots. 4-morpholinecarbonyl chloride (165 mg, 1.1 mmol, 1.1 equiv) was added dropwise. The mixture was stirred at room temperature for 12 h and was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ethyl acetate (3 × 5 mL). The organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 2:3) yielded 210 mg (70% yield) of **9e** as a white solid (mp.: 112.0-113.6 °C) .

^{1}H-NMR (DMSO, 400 MHz): δ = 3.95 (s, 3H), 3.94 (s, 3H), 3.57 (m, 6H), 3.27 (m, 2H).

^{13}C-NMR (DMSO, 100 MHz): 167.20, 163.11, 161.58, 148.66, 112.54, 66.25, 55.27, 54.95, 46.27, 41.63.

MS (EI, 70 ev), *m/z* (%): 333.0 (8), 331.0 (9), 252.1 (30), 247.1 (98), 245.1 (100), 167.2 (12), 122.1 (11), 120.1 (11), 70.1 (6).

IR (KBr): 2960 (w), 2862 (w), 1634 (m), 1580 (s), 1534 (s), 1494 (m), 1370 (s), 1357 (m), 1275 (m), 1235 (s), 1111 (s), 1009 (s).

HRMS (EI): calcd. for $C_{11}H_{14}BrN_3O_4$ [M^+]: 331.0168, found: 331.0177.

Synthesis of annelated heterocycles 10 and 11:

4,6-dimethoxy-3-phenylisoxazolo[5,4-d]pyrimidine (10).

To a stirring solution of 4-chloro-2,6-dimethoxypyrimidin-5-yl)(phenyl)methanone (**8c**) (1.39 mg, 5 mmol) in EtOH 50% (100 mL) at rt was added hydroxylamine hydrochloride (1.04 g, 15 mmol) and sodium acetate (1.25 g, 15 mmol). The mixture was refluxing during 4 h. The product was collected by filtration and washed two times with H_2O (10 mL). Purification by flash chromatography (*n*-pentane/diethyl ether = 3:2) yielded 1.88 g (83% yield) of **10** as a white solid (mp.: 210,1-211.9 °C) .

^{1}H-NMR (DMSO, 400 MHz): δ = 8.20 (m, 2H), 7.60 (m, 3H), 4.14 (s, 3H), 4.00 (s, 3H).

^{13}C-NMR (DMSO, 100 MHz): 166.79, 167.63, 166.76, 132.25, 132.22, 129.16, 128.30, 125.98, 96.27, 55.37, 55.06.

MS (EI, 70 ev), *m/z* (%): 257.1 (100), 227.1 (57), 212.1 (36), 105.0 (65), 91.0 (8), 77.0 (41), 70.0 (12), 51.0 (11).

IR (KBr): 3017 (w), 2951 (w), 1615 (s), 1539 (s), 1441 (s), 1385 (m), 1318 (s), 1138 (m).

HRMS (EI): calcd. for $C_{13}H_{11}N_3O_3$ [M^+]: 257.0800, found: 257.0807.

methyl 2,4-dimethoxy-5-phenylthieno[2,3-d]pyrimidine-6-carboxylate (11).

Triethylamine (0.4 g, 4 mmol) was added dropwise to a mixture of 4-chloro-2,6-dimethoxypyrimidin-5-yl)(phenyl)methanone (**8c**) (0.55 g, 2 mmol) and methyl mercapto-acetate (0,31 g, 2.6 mmol) in EtOH (10 mL). The reaction mixture was heated at reflux until the starting ketone **8c** disappeared according to gas chromatography (12 h). After cooling to room temperature, the precipitate was filtered off and recrystallized in EtOH 95% to give a white powder **11** (mp: 193.3-194.3 ° C) in 69% yield.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.40 (m, 3H), 7.38 (m, 2H), 4.08 (s, 3H), 3.79 (s, 3H), 3.72 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): 170.19, 167.23, 163.85, 162.25, 142.15, 134.89, 129.05, 127.84, 127.20, 122.47, 114.90, 55.33, 54.10, 52.16.

MS (EI, 70 ev), *m/z* (%): 331.1 (16), 330.1 (100), 329.1 (15), 300.1 (11), 299.1 (26), 284.0 (11), 251.9 (7), 227.0 (8), 199.0 (7), 171.0 (6), 127.0 (8).

IR (KBr): 3012 (w), 2951 (w), 1716 (s), 1577 (m), 1541 (s), 1473 (m), 1249 (s), 1168 (m), 1027 (m).

HRMS (EI): calcd. for $C_{16}H_{14}N_2O_4S$ [M^+]: 330.0674, found: 330.0660.

Synthesis of oxypurinol (2):

4-chloro-2,6-dimethoxypyrimidine-5-carbaldehyde (12).

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**4**) (1.27 g, 5 mmol) in dry THF (5 mL). *i*-PrMgCl·LiCl (1.0 M/THF, 5.25 mmol, 1.05 equiv) was added slowly at room temperature and the resulting mixture was stirred for 15 min to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots). The mixture was cooled down to -35°C and 4-formylmorpholine (0.635 g, 1.1 equiv) was added dropwise. The mixture was stirred at -35 °C for 4 h and was quenched with a mixture of a solution of acetic acid in water (≈ 1M; 3 mL) and saturated aqueous NH_4Cl solution (15 mL). The aqueous phase was extracted with ether (3 × 20 mL). The organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 3:2) yielded 840 mg (83% yield) of **12** as a white solid (mp.: 97.8-99.1°C).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 10.30 (s, 1H), 4.12 (s, 3H), 4.08 (s, 3H).

^{13}C-NMR ($CDCl_3$, 150 MHz): 165.44, 162.87, 157.71, 97.83, 87.19, 54.54, 53.98.

MS (EI, 70 ev), *m/z* (%): 203.0 (40), 202.0 (76), 201.0 (100), 185.0 (22), 174.0 (17), 172.0 (43), 154.9 (17), 128.9 (10), 75.9 (23), 69.9 (10).

IR: 3008 (w), 2956 (w), 2882 (w), 2797 (w), 1686 (s), 1528 (s), 1449 (s), 1356 (s), 1324 (s), 1205 (m), 1014 (m), 789 (s).

HRMS (EI): calcd. for $C_7H_7ClN_2O_3$ [M^+]: 202.0145, found: 202. 0126.

4,6-dimethoxy-1H-pyrazolo[3,4-d]pyrimidine (13).

To a stirring solution of 4-chloro-2,6-dimethoxypyrimidine-5-carbaldehyde (**12**) (1.01 mg, 5 mmol) in EtOH (80 mL) at rt was added hydrazine monohydrate (0.9 g, 15 mmol). The mixture was refluxing during 30 min. After cooling to room temperature, the precipitate was filtered off and recrystallized in EtOH 95% to give a white powder **13** (mp: > 300 °C) in 91% yield.

^{1}H-NMR (DMSO, 300 MHz): δ = 8.05 (s, 1H), 4.04 (s, 3H), 3.93 (s, 3H).

^{13}C-NMR (DMSO, 75 MHz): 164.44, 163.87, 157.77, 97.83, 88.19, 54.52, 53.93.

MS (EI, 70 ev), *m/z* (%): 180.1 (100), 179.1 (66), 165 0 (12), 150.1 (36), 135.0 (67), 109.0 (13), 69.9 (11).

IR (KBr): 3252 (w), 2955 (w), 1608 (s), 1583 (m), 1503 (m), 1386 (m), 1320 (w), 1153 (m), 1081 (w), 942 (s), 788 (s).

HRMS (EI): calcd. for $C_7H_8N_4O_4$ [M^+]: 180.0647, found: 180.0643.

1*H*-pyrazolo[3,4-d]pyrimidine-4,6(5*H*,7*H*)-dione, oxypurinol (2).

A mixture of 4,6-dimethoxy-1*H*-pyrazolo[3,4-d]pyrimidine (**13**) (0.54 g, 3mmol) with concentrated hydrochloric acid (30 mL) was heated under reflux for 1 h. After the reaction was complete, the solution was treated with activated charcoal and evaporated under reduced pressure. The residue was recrystallized from water to afford 1.60 g of oxypurinol (**2**) (81% yield) as a white solid (mp: > 300 °C).

^{1}H-NMR (DMSO, 300 MHz): δ = 13.27 (s, 1H), 11.30 (s, 1H), 10.63 (s, 1H), 8.33 (s, 1H).

^{13}C-NMR (DMSO, 75 MHz): 159.60, 151.62, 150.78, 128.93, 100.20.

MS (EI, 70 ev), *m/z* (%): 152.0 (100), 109.0 (92), 52.0 (31), 44.0 (14).

IR (KBr): 3268 (m), 3124 (w), 3028 (m), 2804 (w), 1709(s), 1677 (s), 1616 (m), 1419 (m), 1244 (m), 1169 (s), 1025 (m), 810 (m), 748 (s), 700 (s).

HRMS (EI): calcd. for $C_5H_4N_4O_2$ [M^+]: 152.0334, found: 152.0324.

Products 14-16.

4-allyl-2,6-dimethoxy-5-(trimethylsilyl)pyrimidine (14).

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4-bromo-2,6-dimethoxy-5-(trimethylsilyl)pyrimidine (**9a**) (291 mg, 1.0 mmol) in dry THF (2 mL). *i*-PrMgCl·LiCl (1.0 M/THF, 1.05 mmol, 1.05 equiv) was added very slowly (within 5 min) at -15 °C and the resulting mixture was stirred for 12 h at -15 °C to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots). Then, allyl bromide (145 mg, 1.2 mmol, 1.2 equiv) was added dropwise. After 30 min, 3 drops of CuCN·2LiCl (cat., 1M in THF) were added. The mixture was warmed up to rt for 6 h and was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ethyl acetate (3 × 5 mL). The organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (n-pentane/diethyl ether = 3:2) yielded 204mg (81% yield) of **14** as colorless oil.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 6.03 (m, 0.8H), 5.08 (dd, *J* = 9.5 Hz, 0.8H), 5.02 (dd, *J* = 17.1 Hz, 0.8H), 3.96–3.93 (2s, 6H), 3.47 (d, *J* = 6.2 Hz, 2H), 0.31 (s, 9H).

^{13}C-NMR ($CDCl_3$, 150 MHz): 176.02, 175.29, 135.79, 116.2, 107.05, 54.27, 53.40, 42.07, 29.69, 1.41.

MS (EI, 70 ev), *m/z* (%): 253.1 (11), 252.1 (56), 251.1 (100), 237.1 (19), 207.1 (23), 89.0 (25).

IR (film): 3081 (w), 2980 (w), 2960 (w), 2870 (w), 1638 (w), 1571 (s),1457 (m), 1370 (s), 1362 (s), 1210 (m), 1084 (w).

HRMS (EI): calcd. for $C_{12}H_{20}N_2O_2Si$ [M^+]: 252.1294, found: 252.1266.

(5-(cyclohexyl(hydroxy)methyl)-2,6-dimethoxypyrimidin-4-yl)(morpholino)methanone (15).

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4,5-dibromo-2,6-dimethoxypyrimidine (**5**) (596 mg, 2 mmol) in dry THF (3 mL). *i*-PrMgCl·LiCl (1.0 M/THF, 2.1 mmol, 1.05 equiv) was added very slowly (within 5 min) at room temperature and the resulting mixture was stirred for 15 min to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots). Cyclohexanecarboxaldehyde (266 mg, 2.2 mmol, 1.2 equiv) was added at rt and the mixture was stirred at rt for12 h. *i*-PrMgCl·LiCl (1.0 M/THF, 2.0 mmol, 1.5 equiv) was added at rt to the mixture which was stirred for 24 h to complete the second bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots). 4-morpholinecarbonyl chloride (597 mg, 2 equiv) was added and the resulting mixture was stirred at rt for 12 h. Then, the mixture was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (diethyl ether) yielded 503 mg (69% yield) of **15** as a colorless oil.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 8.09 (s, 1H), 5.64 (d, *J* = 6.7 Hz), 3.99 (s, 3H), 3.97 (s, 3H), 1.88-0.88 (m, 11H).

^{13}C-NMR ($CDCl_3$, 75 MHz): 168.34, 164.63, 156.24, 154.62, 114.15, 74.04, 66.57, 54.05, 44.14, 42.13, 28.84, 28.40.

MS (EI, 70 ev), *m/z* (%): 365.3 (1), 282.2 (2), 235.2 (24), 153.1 (100), 114.1 (12), 70.1 (6).

IR (film): 2924 (m), 2852 (m), 1700 (s), 1599 (m), 1567 (m), 1399 (m),1218 (s), 1069 (m).

HRMS (EI): calcd. for $C_{18}H_{27}N_3O_5$ [M^+]: 365.1951, found: 365.1935.

5-allyl-2,4-dimethoxy-6-methylpyrimidine (16).

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4,5-dibromo-2,6-dimethoxypyrimidine (**5**) (596 mg, 2 mmol) in dry THF (3 mL). *i*-PrMgCl·LiCl (1.0 M/THF, 2.1 mmol, 1.05 equiv) was added very slowly (within 5 min) at room temperature and the resulting mixture was stirred for 15 min to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots). Allyl bromide (266 mg, 2.2 mmol, 1.1 equiv) was added dropwise. The mixture was stirred at rt for 2 h. Then, the mixture was cooled down to -5 °C and *i*-PrMgCl·LiCl (1.0 M/THF, 3.0 mmol, 1.5 equiv) was added slowly. After 8 h, the Br/Mg-exchange was complete (checked by GC-MS analysis of reaction aliquots) and methylene iodide (850 mg, 3 equiv) was added to the mixture at -5 °C following by the addition of 3 drops of CuCN·2LiCl (cat., 1M in THF). The mixture was warmed up to room temperature for 4 h and quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*.

Purification by flash chromatography (n-pentane/diethyl ether = 4:1) yielded 408 mg (81% yield) of **16** as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 5.8 (m, 1H), 4.97 (dq, *J* = 10.2 Hz, 1H), 4.90 (dq, *J* = 17.1 Hz, 1H), 3.94 (s, 6H), 3.25 (dt, *J* = 5.9 Hz, 2H), 2.33 (s, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): 169.27, 166.60, 163.0, 134.75, 114.92, 109.71, 54.33, 53.89, 28.67, 21.23.

MS (EI, 70 ev), *m/z* (%): 196.1 (45), 194.1 (100), 193.1 (49), 179.1 (28), 164.1 (29), 138.0 (11), 122.1 (5), 94.1 (6), 56.0 (21).

IR (film): 2980 (w), 2955 (w), 2871 (w), 1638 (w), 1571 (s), 1457 (m), 1369 (s), 1358 (s), 1203 (m), 1090 (w).

HRMS (EI): calcd. for $C_{10}H_{14}N_2O_2$ [M^+]: 194.1055, found: 194.1036.

Synthesis of emivirine (3).

2-(4-bromo-2,6-dimethoxypyrimidin-5-yl)propan-2-ol (17).

In a flame dried, argon-flushed 50 mL Schlenk-flask equipped with a septum and a magnetic stirring bar was placed $LaCl_3{\cdot}2LiCl$ in THF (0.33 M; 30 mL, 10.00 mmol, 1.00 equiv). Acetone (580 mg, 10.0 mmol) was added and the resulting mixture was stirred for 2 h at rt. A second dry and argon flushed 25 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4,5-dibromo-2,6-dimethoxypyrimidine (**5**) (2.98 g, 10 mmol) in dry THF (10 mL). *i*-PrMgCl·LiCl (1.0 M/THF, 10.5 mmol, 1.05 equiv) was added very slowly (within 5 min) at room temperature and the resulting mixture was stirred for 15 min to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots) and obtain the Grignard reagent **7**. The mixture of acetone with $LaCl_3{\cdot}2LiCl$ in THF was cooled to 0 °C and the solution of the Grignard reagent **7** was added dropwise. The resulting mixture was allowed to stir at the same temperature for 4 h and was quenched with sat. aq. NH_4Cl (20 mL) and water (20 mL) was added. The aqueous layer was extracted with ethyl acetate (4 × 30 mL), the combined extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The crude residue was purified by flash column chromatography (n-pentane/diethyl ether = 4:1) yielded 2.40 g (81% yield) of **17** as a white oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 4.03 (s, 3H), 3.97 (s, 3H), 3.95 (s, 3H), 1.70 (s, 6H).

^{13}C-NMR ($CDCl_3$, 150 MHz): 168.97, 161.17, 149.00, 120.74, 72.44, 55.24, 54.99, 30.17.

MS (EI, 70 ev), *m/z* (%): 279.0 (3), 277.0 (3), 262.9 (100), 260.9 (97), 244.9 (29), 220.9 (5), 167.0 (7).

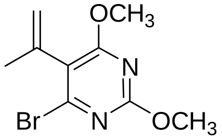
IR (film): 3563 (m), 2950 (w), 1562 (m), 1527 (s), 1481 (m), 1383 (m), 1352 (m), 1215 (m), 1013 (s).

HRMS (EI): calcd. for $C_9H_{13}BrN_2O_3$ $[M+H]^+$: 277.0110, found$[M+H]^+$: 277.0200.

4-bromo-5-isopropyl-2,6-dimethoxypyrimidine (18).

To an ice-cooled, rapidly stirred slurry of **17** (1.38 g, 5mmol) dissolved in dry dichloromethane (20 mL) in triethylsilane (1.74 g, 3 equiv) was slowly added trifluoroacetic acid (1.99 g, 3.5 equiv). When the addition was complete, the mixture was warmed to room temperature and stirred overnight (12 h). At the end of this period, the mixture was poured into 30 mL of saturated $NaHCO_3$ and extracted with dichloromethane (3 × 20 mL). Extracts were combinated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure at 40 °C (oil bath) to give 1.28 g (95 %) of a colorless oil. The product was identified as a mixture of 4-bromo-5-isopropyl-2,6-dimethoxypyrimidine **18** (17%) and the corresponding dehydrated product **18a** (83 %) (4-bromo-2,6-dimethoxy-5-(prop-1-en-2-yl)pyrimidine). The mixture of **18** and **18a** was used for the next step without purification.

^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 5.34 (s, 1.0H), 4.95 (t, 1.0H), 3.95 (m, 7.1H), 3.40 (q, 0.37H), 1.96 (m, 3.03H) *, 1.26-1.23 (d, 1.17H) *.



18a: dehydrated product from **18**

*These integrations give respectively the yield of **18a** (83%) and **18** (17%).

The mixture of **18** and **18a** (1.27 g) is directly used and solved in dry ethanol (10 mL). Platinium oxide (87 mg) is added to the solution and the resulting mixture is stirred at atmospheric pressure in a hydrogen atmosphere for 30 min. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (n-pentane/diethyl ether = 4:1) yielded 1.17 g (91%) of **18** as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 3.98 (s, 3H), 3.95 (s, 3H), 3.39 (septuplet, ^3J = 7.1 Hz), 1.24 (d, ^3J = 7.0 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 150 MHz): 169.49, 161.74, 152.23, 120.21, 55.07, 54.27, 30.47, 19.68.

MS (EI, 70 ev), *m/z* (%): 262.0 (13), 260.0 (13), 246.9 (95), 244.9 (100), 165.0 (8), 151.0 (6).

IR (film): 2986 (w), 2959 (w), 2874 (w), 1575 (m), 1534 (s), 1451 (m), 1362 (s), 1215 (m), 1017 (s).

HRMS (EI): calcd. for $C_9H_{13}BrN_2O_2$ [M+]: 260.0160, found[M+]: 260.0171.

4-benzyl-5-isopropyl-2,6-dimethoxypyrimidine (19).

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4-bromo-5-isopropyl-2,6-dimethoxypyrimidine (**18**) (783 mg, 3.0 mmol) in dry THF (2 mL). *i*-PrMgCl·LiCl (1.0 M/THF, 3.15 mmol, 1.05 equiv) was added at rt and the resulting mixture was stirred for 5 h at this temperature to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots). Then, benzyl bromide (1.03 g, 6 mmol, 2 equiv) was added dropwise. The mixture was stirred for 20 h and was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (n-pentane/diethyl ether = 1:1) yielded 709 mg (87% yield) of **19** as a pale yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.22 (m, 5H), 4.06 (s, 2H), 3.95 (2 singulets, 6H), 3.16 (septuplet, ^3J = 7.0 Hz, 1H), 1.11 (d, ^3J = 7.0 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 150 MHz): 170.25, 166.28, 162.46, 138.77, 126.53, 128.32, 126.17, 117.82, 54.36, 53.42, 41.43, 26.73, 20.10.

MS (EI, 70 ev), *m/z* (%): 272.1 (80), 271.1 (100), 257.1 (93), 244.1 (29), 243.1 (23), 241.1 (16), 227.0 (10), 167.1 (14), 91.1 (14).

IR (film): 2956 (w), 2872 (w), 1562 (s), 1475 (w), 1451 (m), 1366 (s), 1217 (m), 1035 (w).

HRMS (EI): calcd. for $C_{16}H_{20}N_2O_2$ [M+]: 272.1525, found[M+]: 272.1534.

6-benzyl-5-isopropylpyrimidine-2,4(1*H*,3*H*)-dione (20).

A solution of 4-benzyl-5-isopropyl-2,6-dimethoxypyrimidine (**19**) (0.544 g, 2mmol) in MeOH (10 mL) with concentrated hydrochloric acid (30 mL) was heated under reflux for 4 h. After the reaction was complete, the solution was treated with activated charcoal and evaporated under reduced pressure. The residue was recrystallized from MeOH/ H_2O (4/1) to afford 450 mg (**20**) (92% yield) as a white solid (mp: 103.1.-104.2).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 8.18 (s, 1H), 7.94 (s, 1H), 7.38-7.29 (m, 3H), 7.19 (dd, 2H), 3.82 (s, 2H), 3.03 (septuplet, ^3J = 7.0 Hz, 1H), 1.30 (d, ^3J = 7.0 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 150 MHz): 163.73, 150.81, 148.28, 136.95, 128.50, 127.87, 126.51, 113.81, 35.15, 26.28, 20.00.

MS (EI, 70 ev), *m/z* (%): 244.1 (72), 230.1 (17), 215.0 (5), 229.1 (100), 186.0 (14), 153.0 (7), 91.0 (17), 69.0 (7).

IR (KBr): 2957 (w), 2869 (w), 1724 (s), 1640 (S), 1461 (m), 1411 (w), 1358 (w), 1193 (w).

HRMS (EI): calcd. for $C_{14}H_{16}N_2O_2$ [M+]: 244.1212, found[M+]: 244.1225.

6-benzyl-1-(ethoxymethyl)-5-isopropylpyrimidine-2,4(1H,3H)-dione, emivirine (3).

6-benzyl-5-isopropylpyrimidine-2,4(1H,3H)-dione (**20**) (366 mg, 1.5 mmol) was suspended in dry acetonitrile (10 mL) under nitrogen and BSA (1.33 ml, 5.2 mmol) was added. The reaction mixture was stirred for 10 min at rt and then cooled to -45 °C. Diethoxymethane (218 mg, 3 mmol) in dry acetonitrile (1 mL) and TMS-triflate (350 mg, 1.6 mmol) in dry acetonitrile (1 mL) were added to the reaction mixture, which was slowly warmed to rt for 3.5 h. The reaction mixture was quenched with saturated aqueous NaHCO3 (10 mL) followed by evaporation under reduced pressure. Water (20 mL) was added followed by the extraction with diethyl acetate (3 × 20 mL). The combinated organic phases were dried and evaporated under reduce pressure. Purification by recristallization from EtOH/ H_2O (4/1) to afford 407 mg (**3**) (90% yield) as a white solid (mp: 109.1-110.7).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 9.2 (s, 1H), 7.34-7.27 (m, 3H), 7.11-7.12 (m, 2H), 5.12 (s, 2H), 4.18 (s, 2H), 3.62 (q, ^3J = 6.9 Hz, 2H), 2.86 (septuplet, ^3J = 6.9 Hz, 1H), 1.28 (d, ^3J = 6.9 Hz, 6H), 1.18 (t, J = 6.9 Hz, 3H).

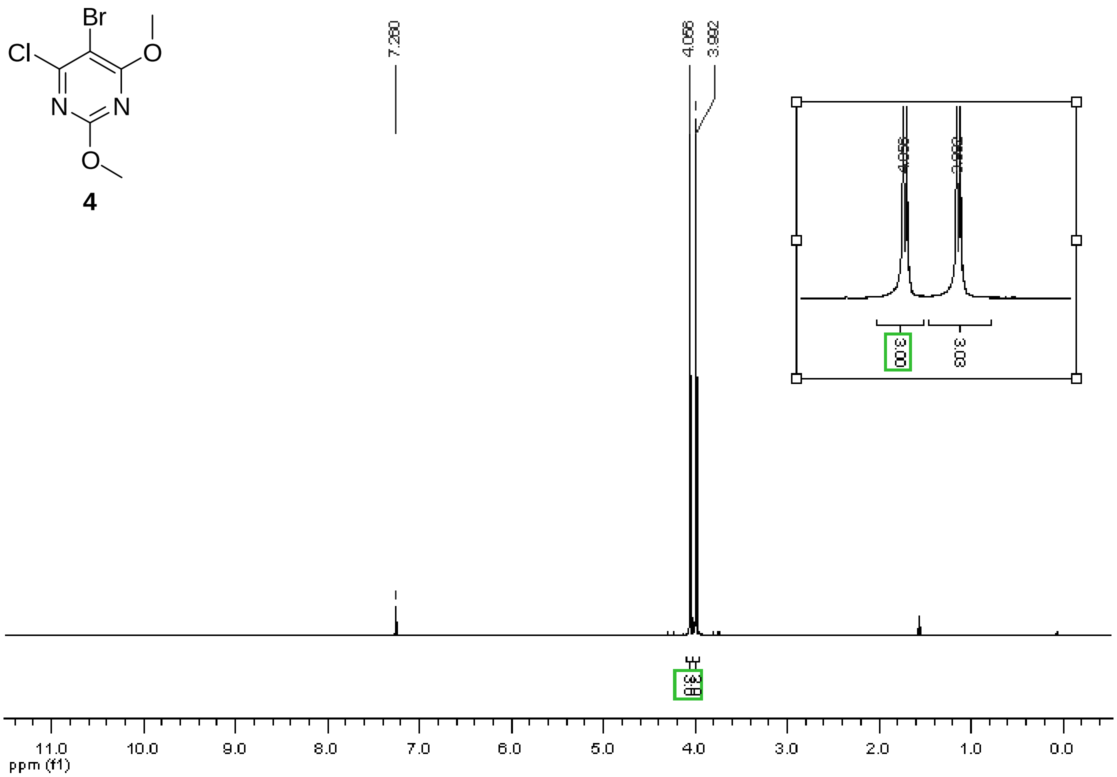
^{13}C-NMR ($CDCl_3$, 150 MHz): 162.33, 151.87, 148.56, 135.35, 129.17, 127.23, 127.20, 119.69, 72.88, 65.00, 33.46, 28.33, 20.37, 15.03.

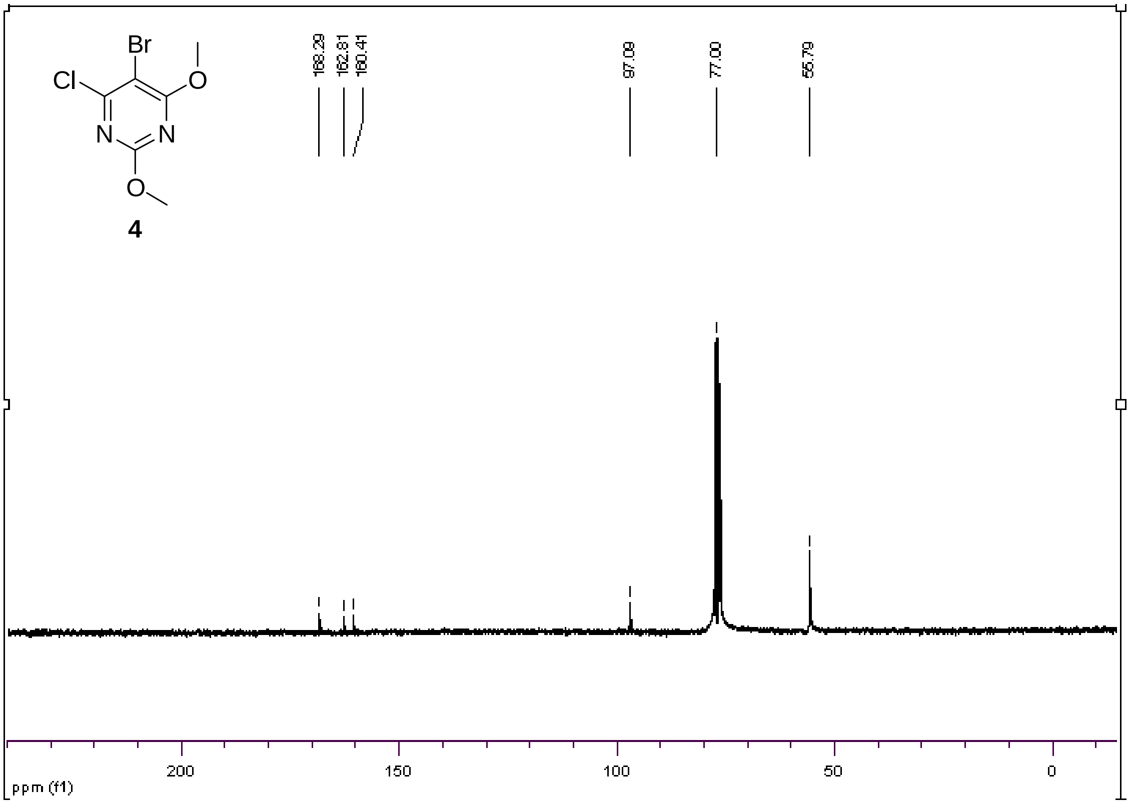
MS (EI, 70 ev), *m/z* (%): 303.1 (19), 302.1 (60), 287.1 (16), 273.1 (39), 257.1 (100), 241.1 (80), 229.1 (64), 135.1 (34), 91.0 (21), 59.0 (29).

IR (KBr): 3188 (w), 2968 (w), 1710 (s), 1673 (s), 1445 (m), 1100 (m), 1025 (m), 719 (m).

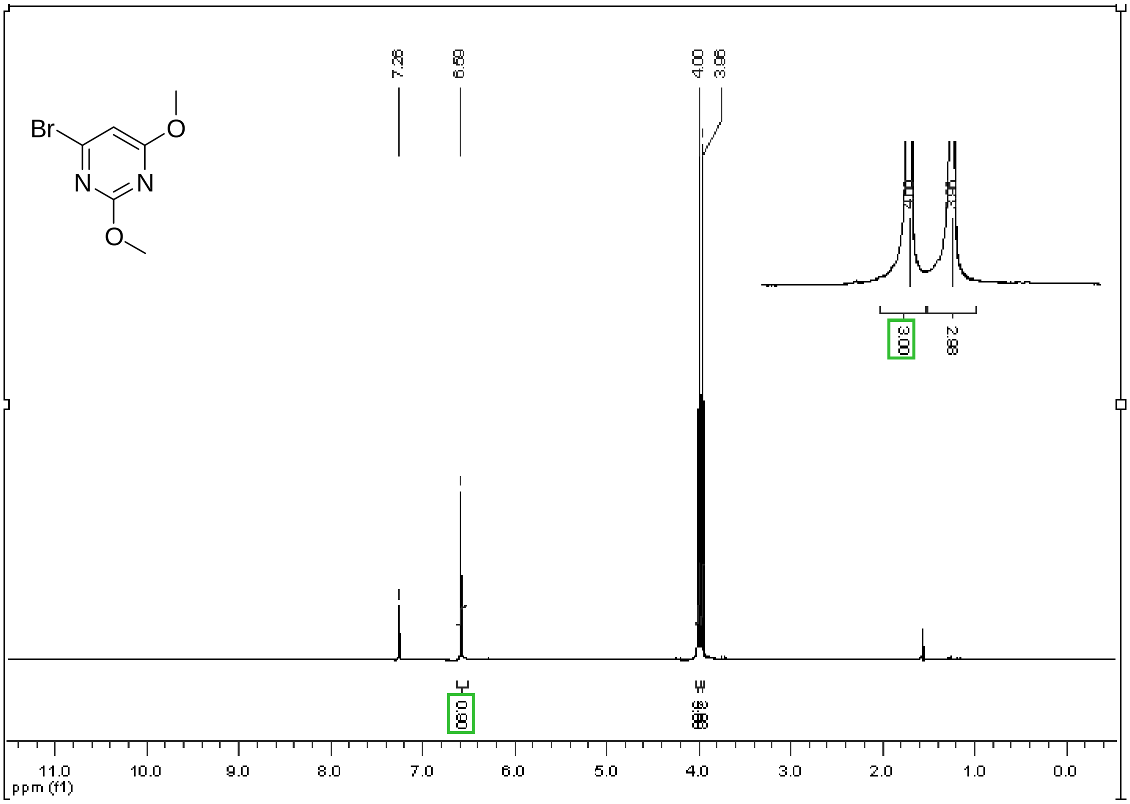
HRMS (EI): calcd. for $C_{17}H_{22}N_2O_3$ [M+]: 302.1630, found[M+]: 302.1641.

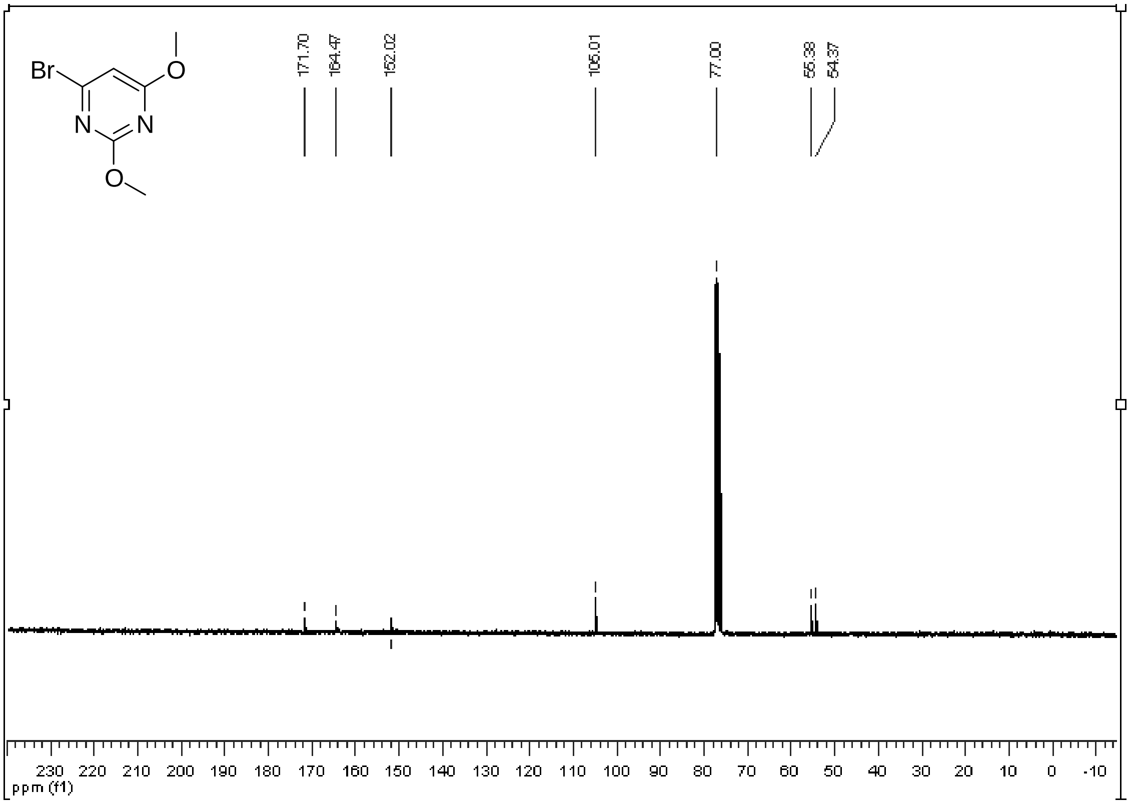
Spectrum:

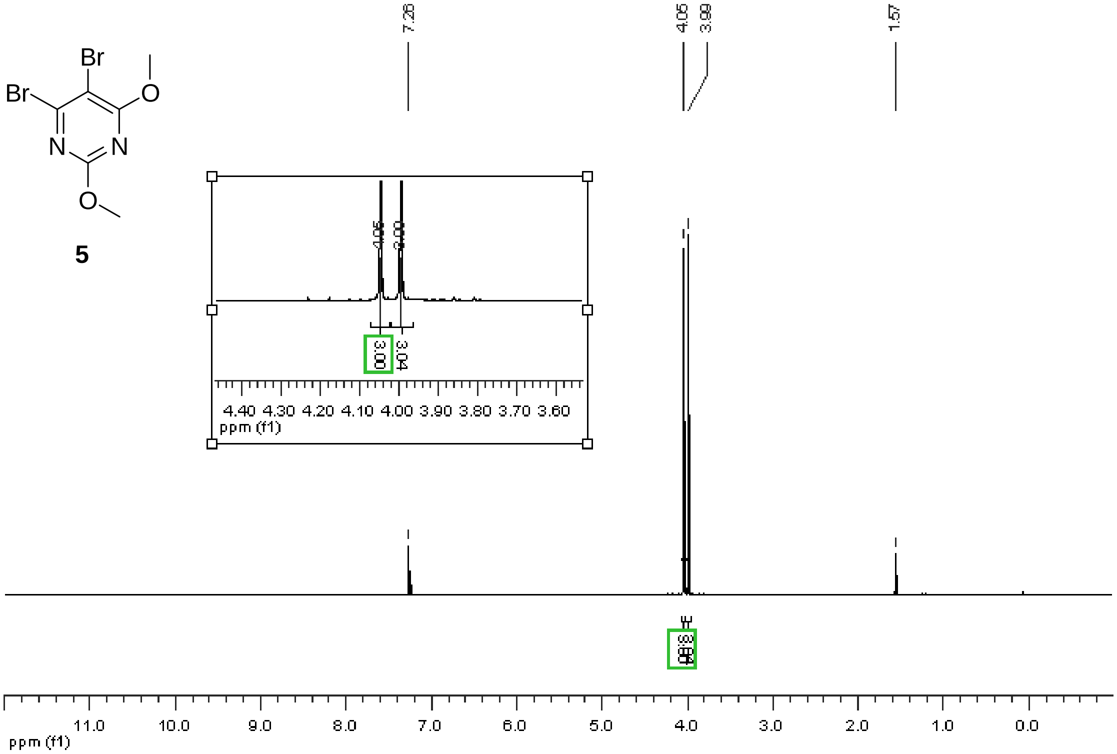

Br
Cl
O
N
N
O
4
7.260
4.056
3.992
4.056
3.992
3.00
3.03
3.00
3.03
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


Br
Cl
O
N
N
O
4
168.29
162.81
160.41
97.09
77.00
55.79
200
150
100
50
0
ppm (f1)

4-bromo -2,6-dimethoxypyrimidine.

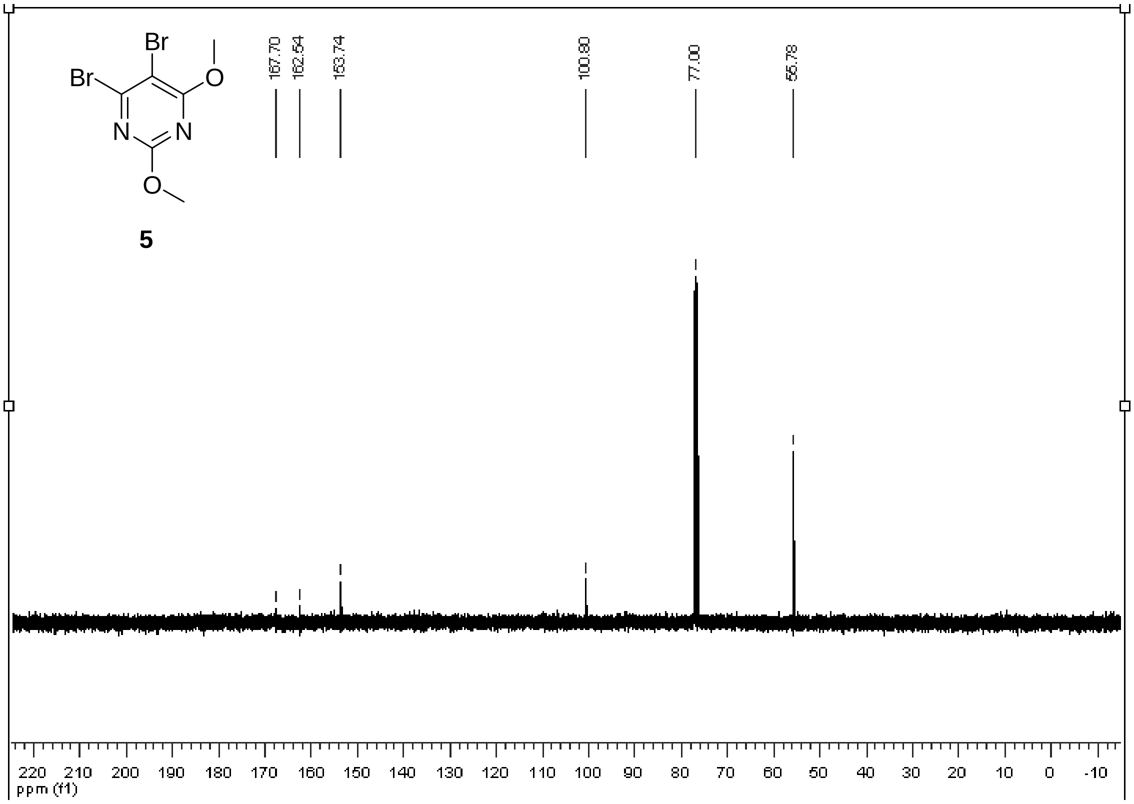






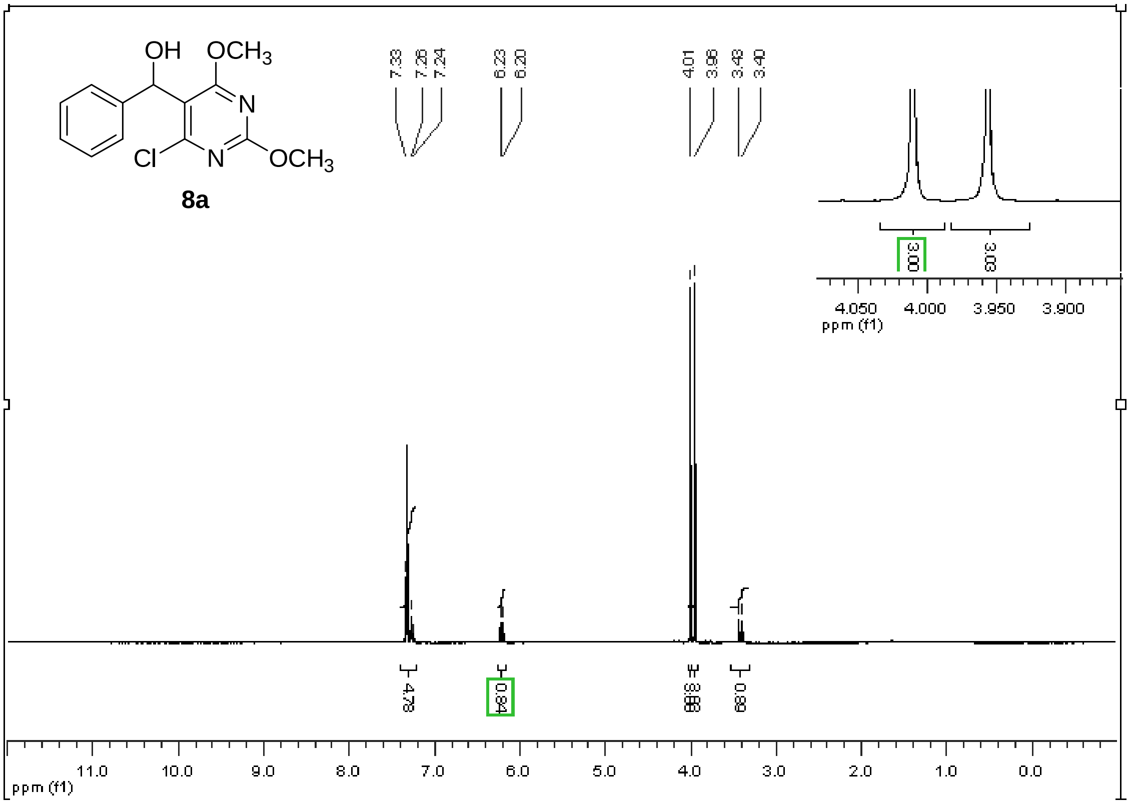
Br
Br
O
N
N
O
7.26
4.05
3.99
1.57
4.05
3.99
3.00
3.04
4.40 4.30 4.20 4.10 4.00 3.90 3.80 3.70 3.60
ppm (f1)
11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
ppm (f1)

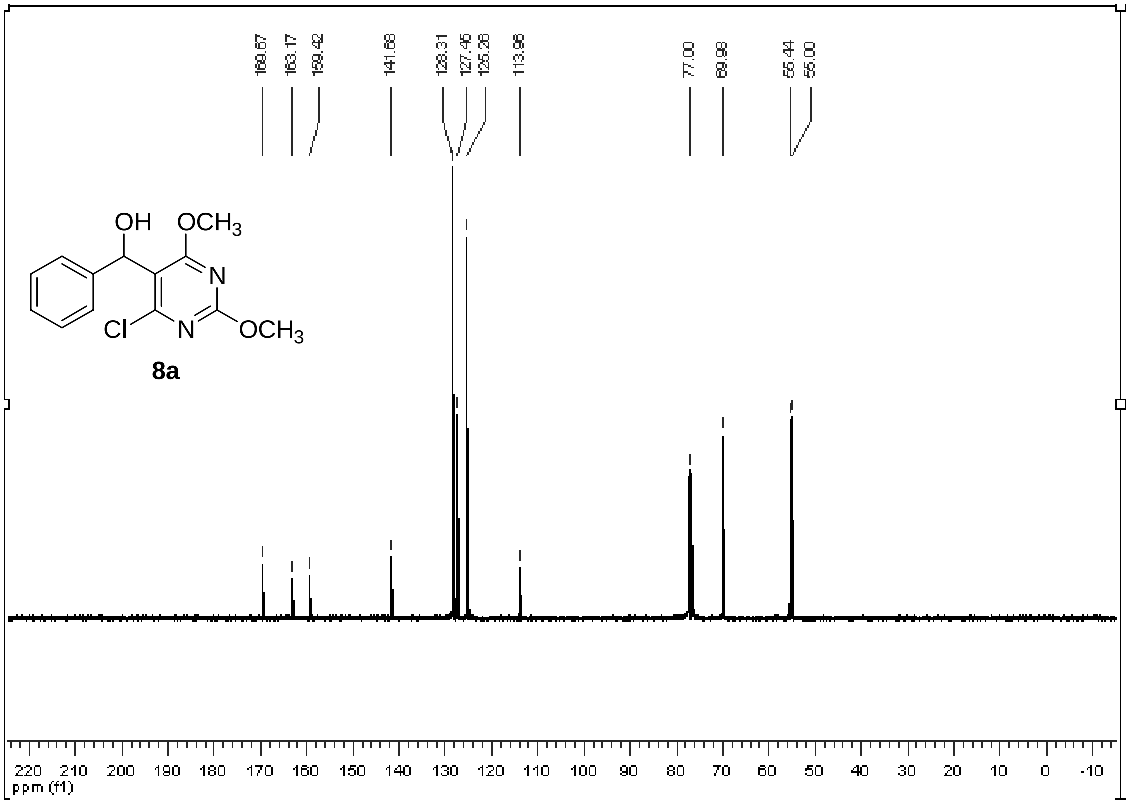
5

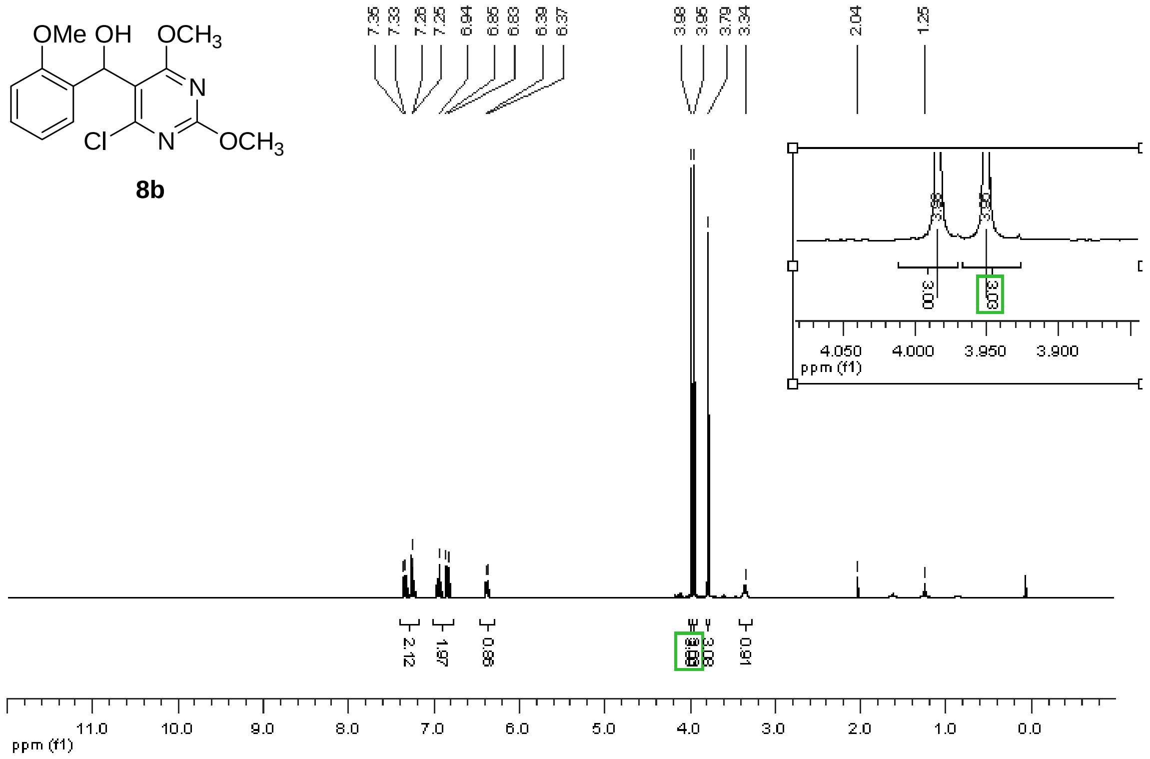


Br
Br
O
N
N
O
167.70
162.54
153.74
100.80
77.00
55.78
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm (f1)

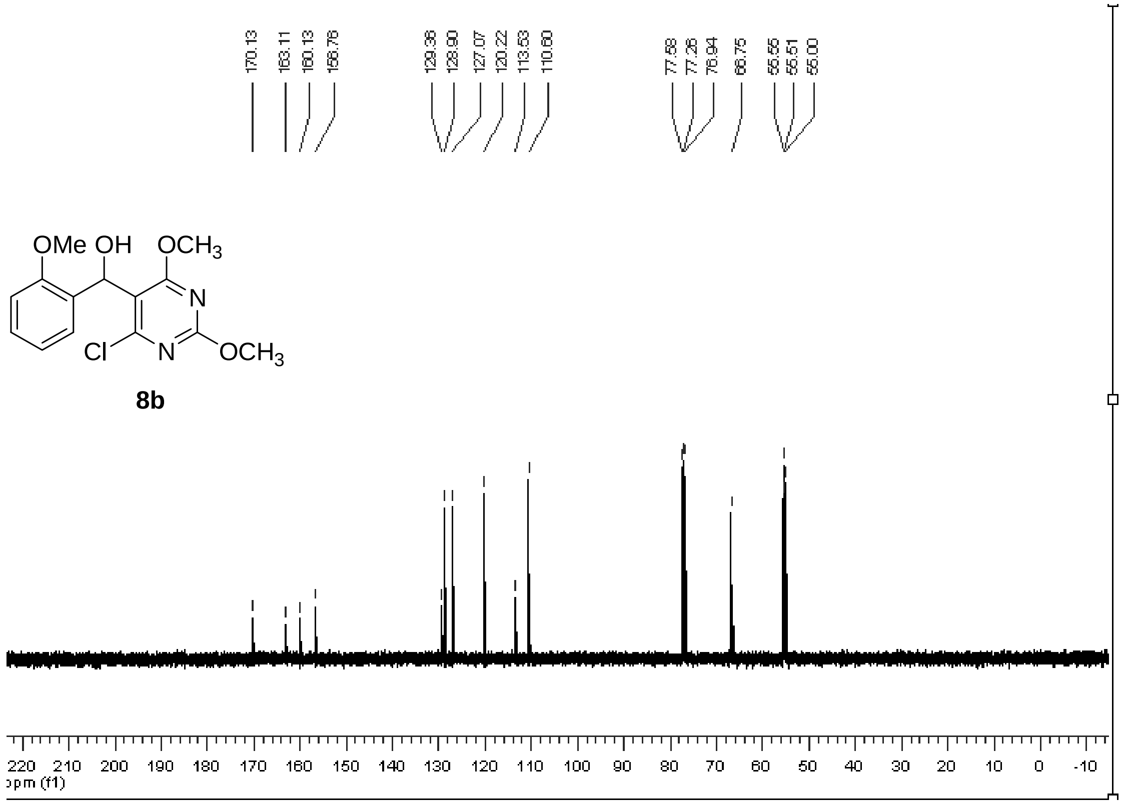
5


OH
OCH3
N
Cl
N
OCH3
8a
7.33
7.26
7.24
6.23
6.20
4.01
3.96
3.43
3.40
4.78
0.84
3.00
3.03
0.89
3.00
3.03
4.050
4.000
3.950
3.900
ppm (f1)
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

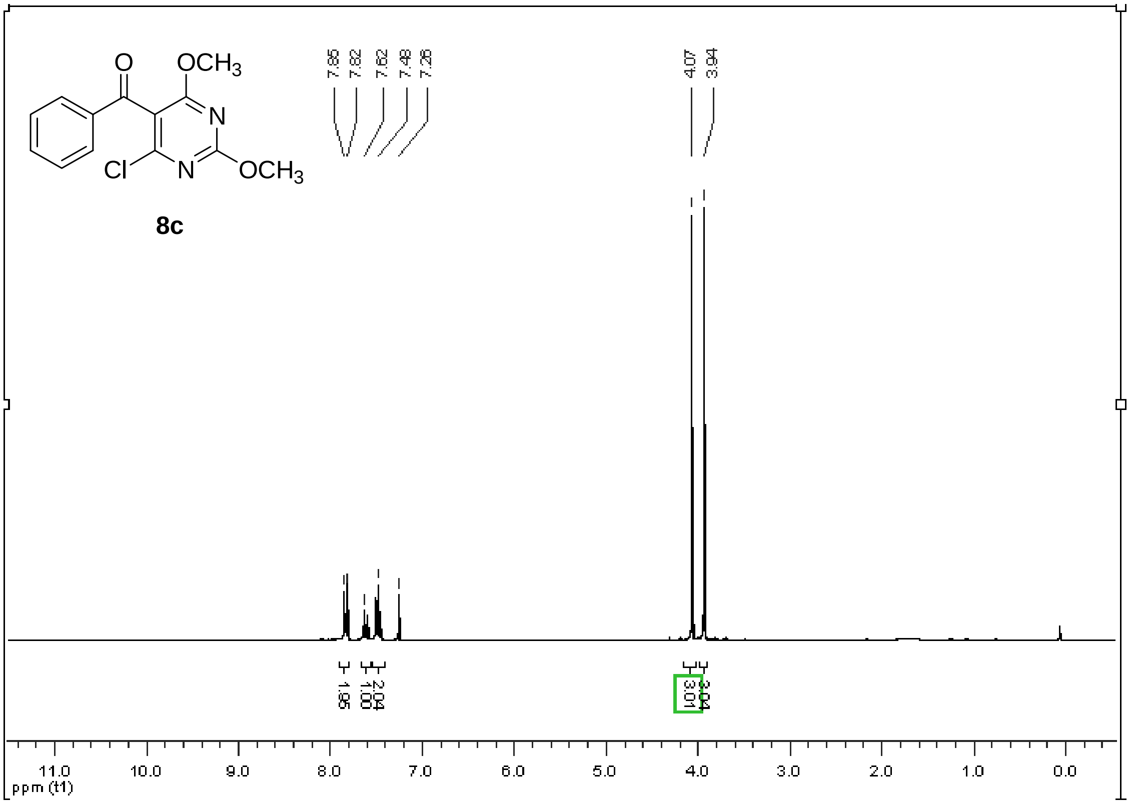

169.67
163.17
159.42
141.68
128.31
127.45
125.26
113.96
77.00
69.98
55.44
55.00
OH
OCH3
N
Cl
N
OCH3
8a
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (f1)

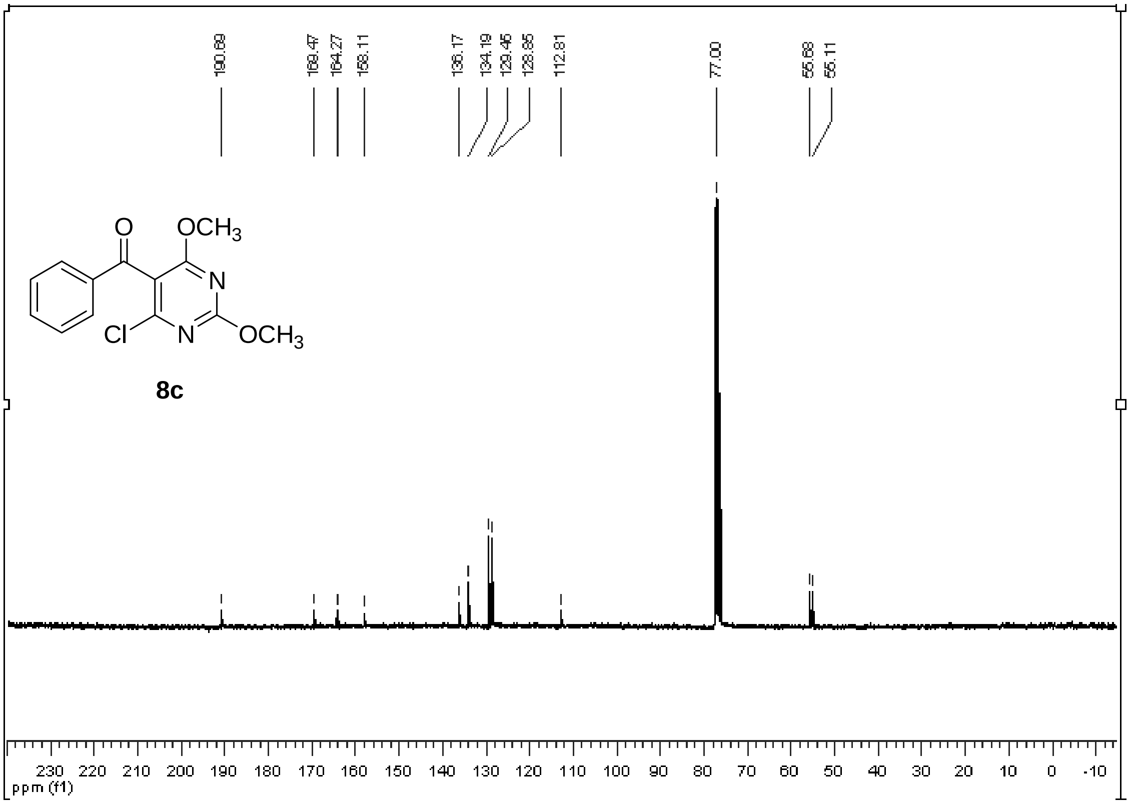

OMe OH OCH3
N
Cl N OCH3
7.35
7.33
7.26
7.25
6.94
6.85
6.83
6.39
6.37
3.98
3.95
3.79
3.34
2.04
1.25
3.98
3.95
3.00
3.03
4.050
4.000
3.950
3.900
ppm (f1)
2.12
1.97
0.86
3.00
3.03
3.08
0.91
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

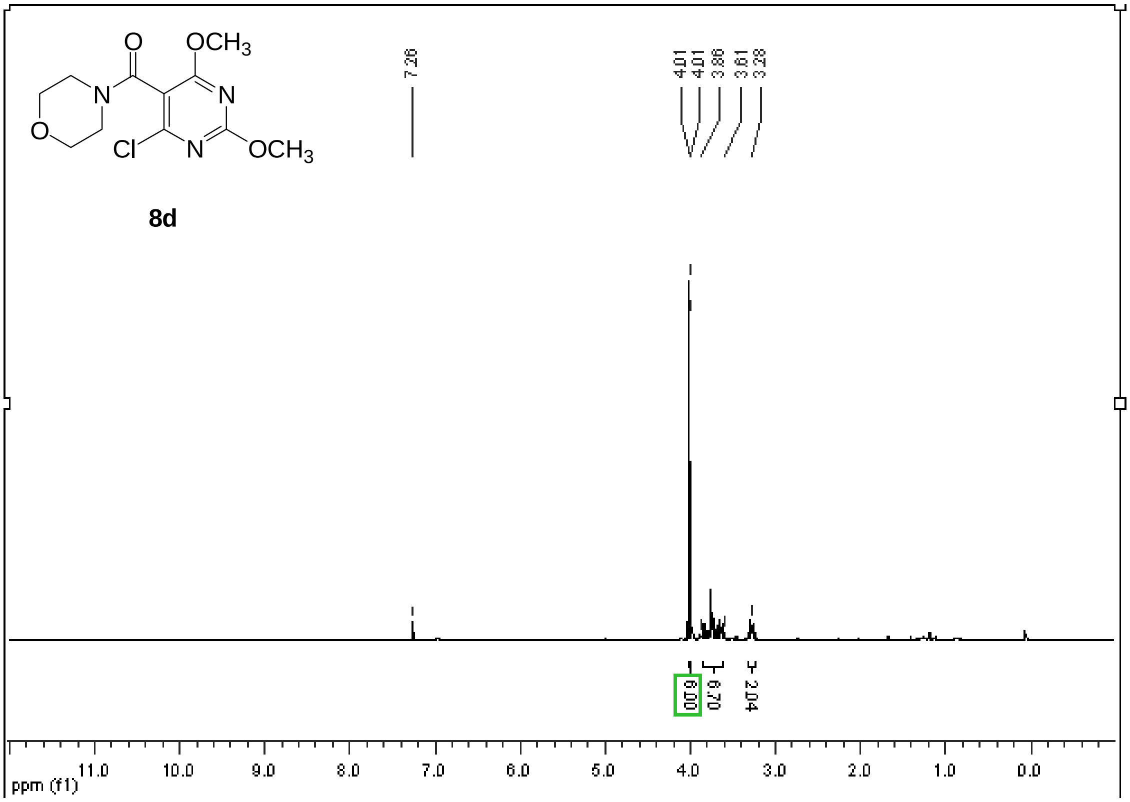
8b

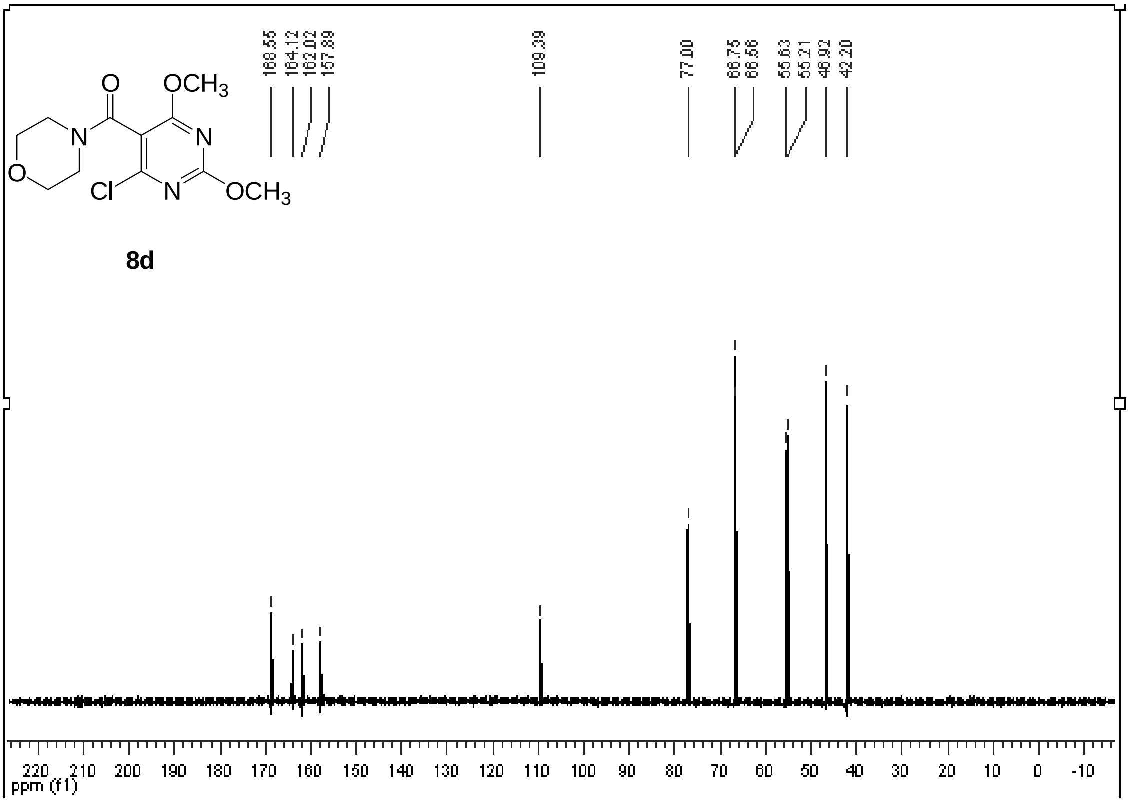

170.13
163.11
160.13
156.76
129.38
128.90
127.07
120.22
113.53
110.60
77.58
77.26
76.94
66.75
55.55
55.51
55.00
OMe OH OCH3
N
Cl N OCH3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (f1)

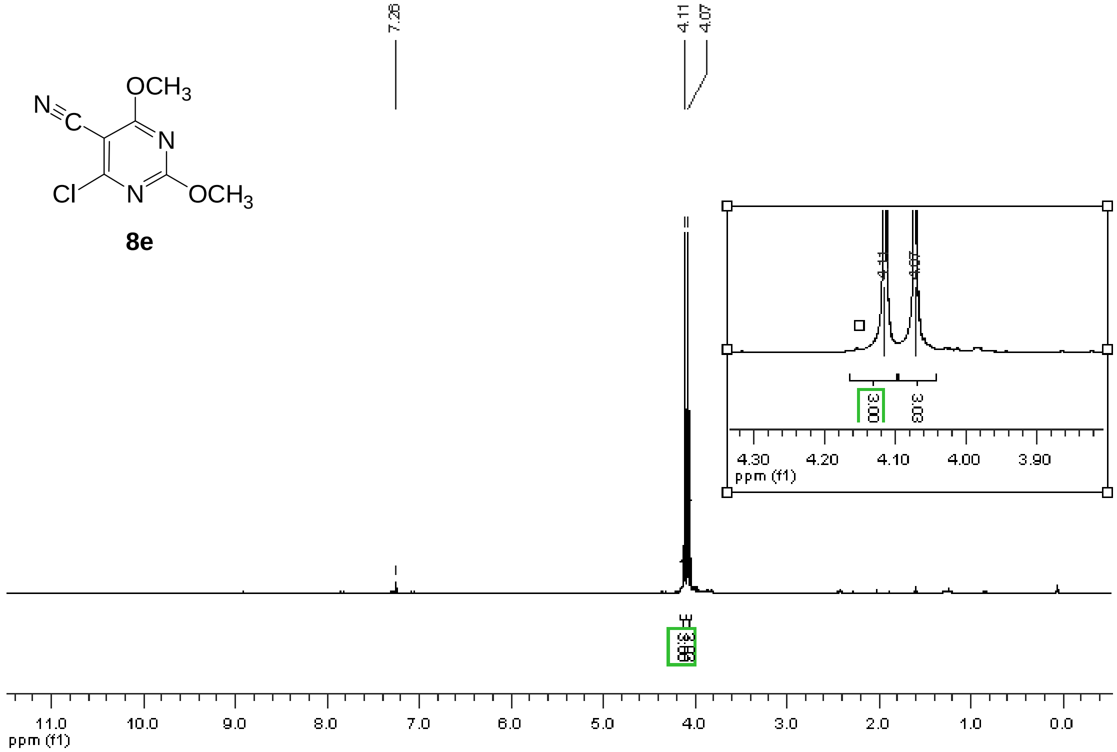
8b


O
OCH3
N
Cl
N
OCH3
8c
7.85
7.82
7.62
7.48
7.26
4.07
3.94
1.96
1.00
2.04
3.01
3.04
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

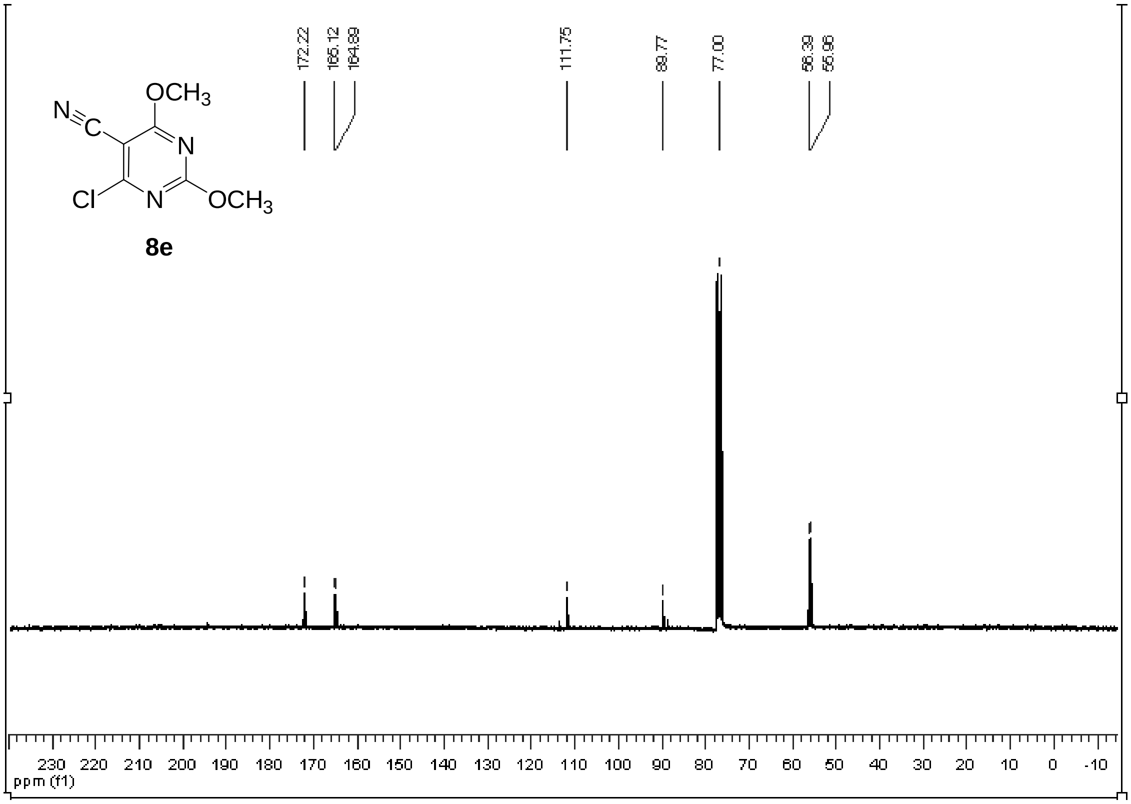

190.69
169.47
164.27
158.11
136.17
134.19
129.45
128.85
112.81
77.00
55.68
55.11
O
OCH3
N
Cl
N
OCH3
8c
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (f1)


O
OCH3
N
O
N
Cl
N
OCH3
8d
7.26
4.01
4.01
3.86
3.61
3.28
6.00
6.70
2.04
ppm (f1)
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

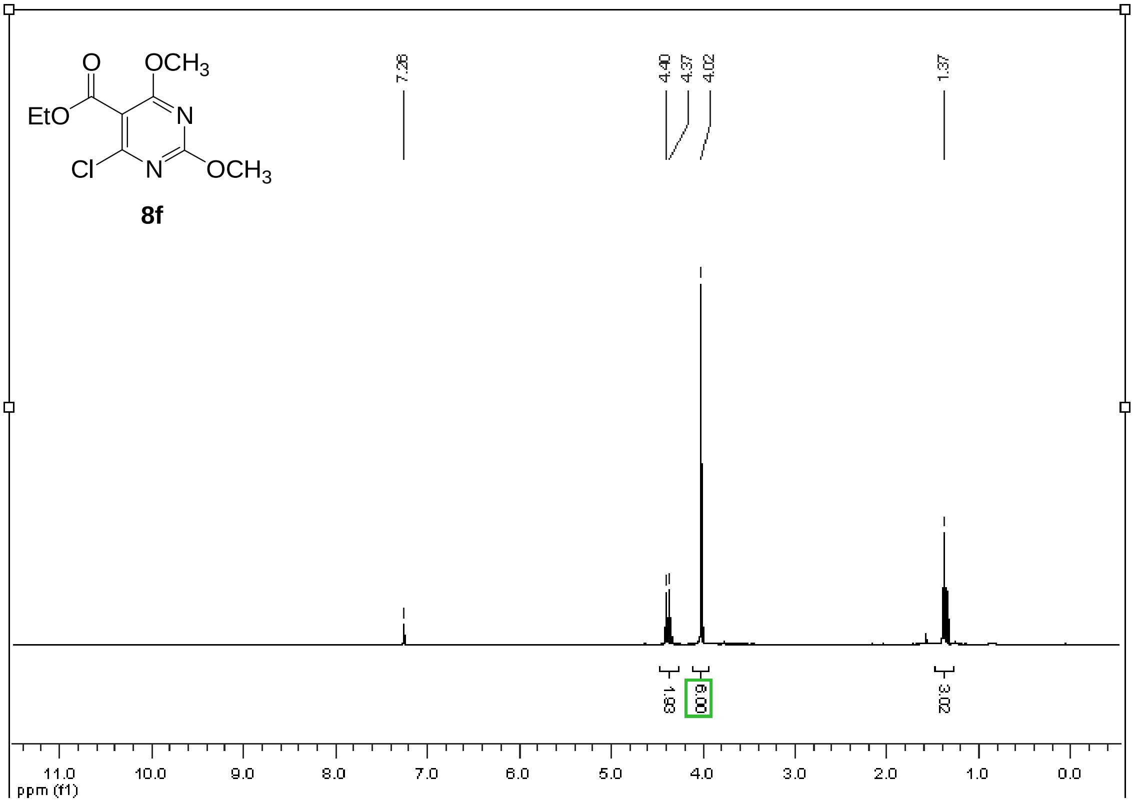

O
OCH3
N
O
N
Cl
N
OCH3
8d
168.55
164.12
162.02
157.89
109.39
77.00
66.75
66.56
55.63
55.21
46.92
42.20
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (f1)

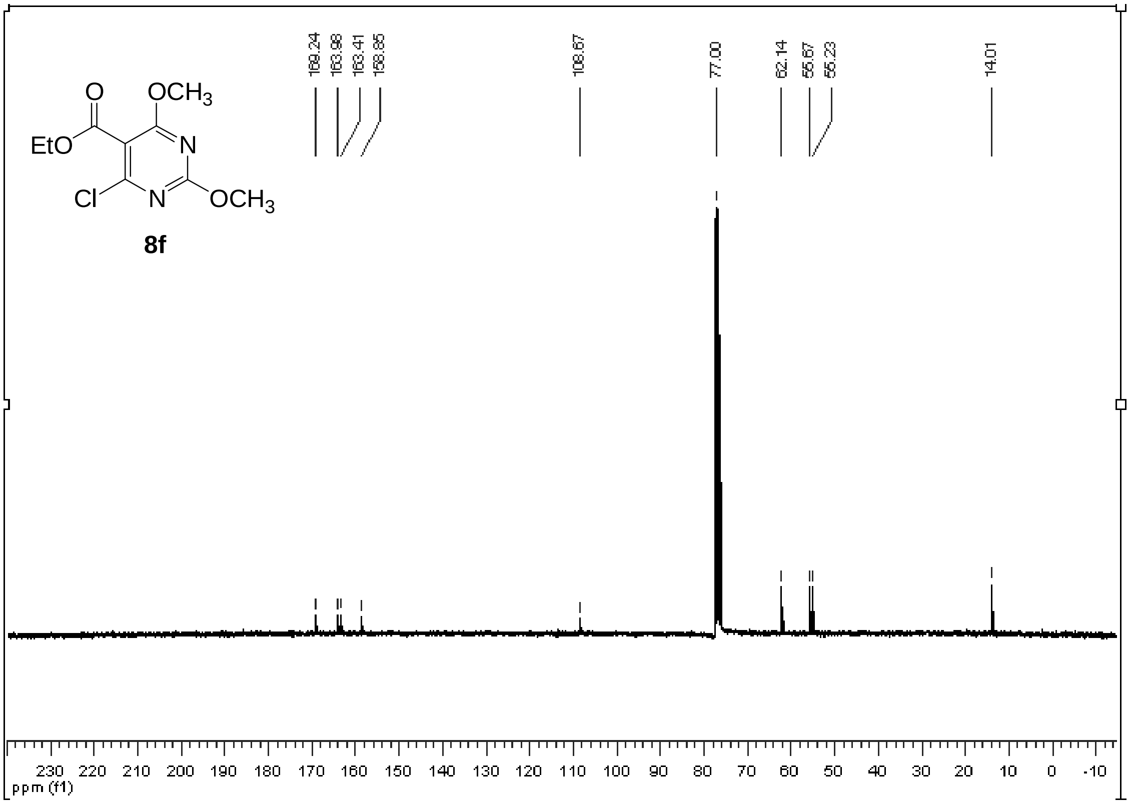


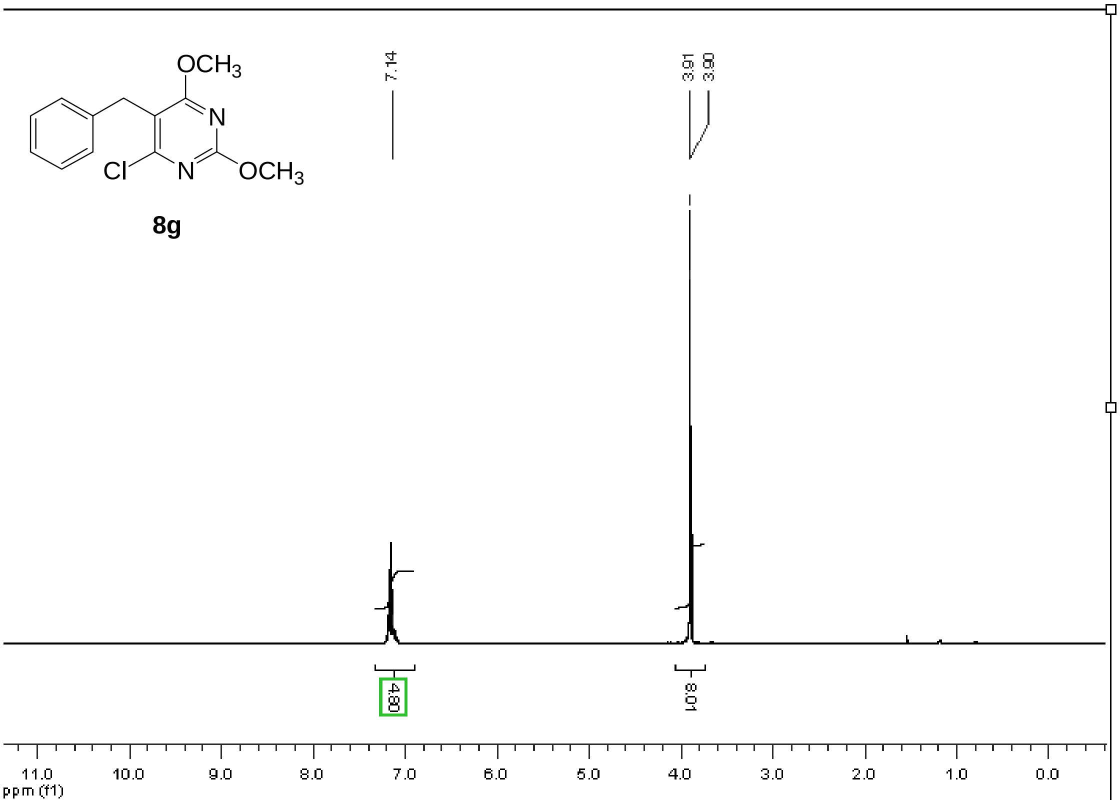
7.26
4.11
4.07
8e
4.11
4.07
3.00
3.03
4.30 4.20 4.10 4.00 3.90
ppm (f1)
3.00
3.03
11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
ppm (f1)

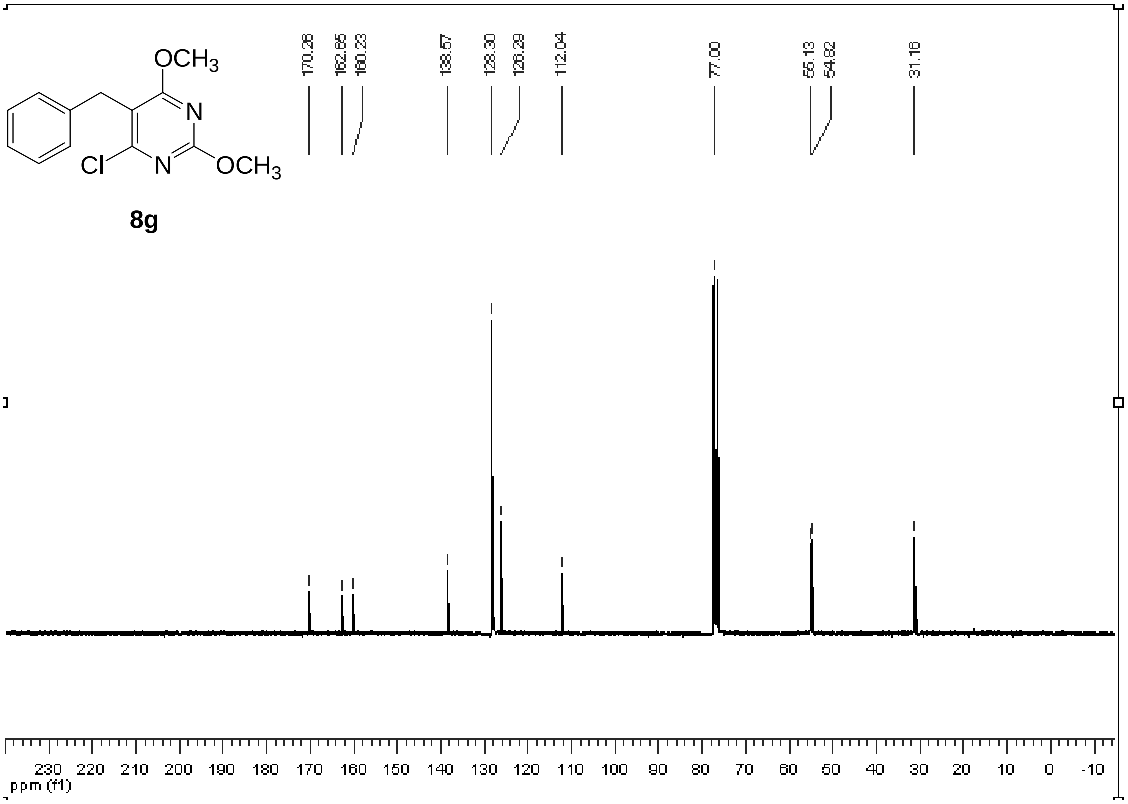


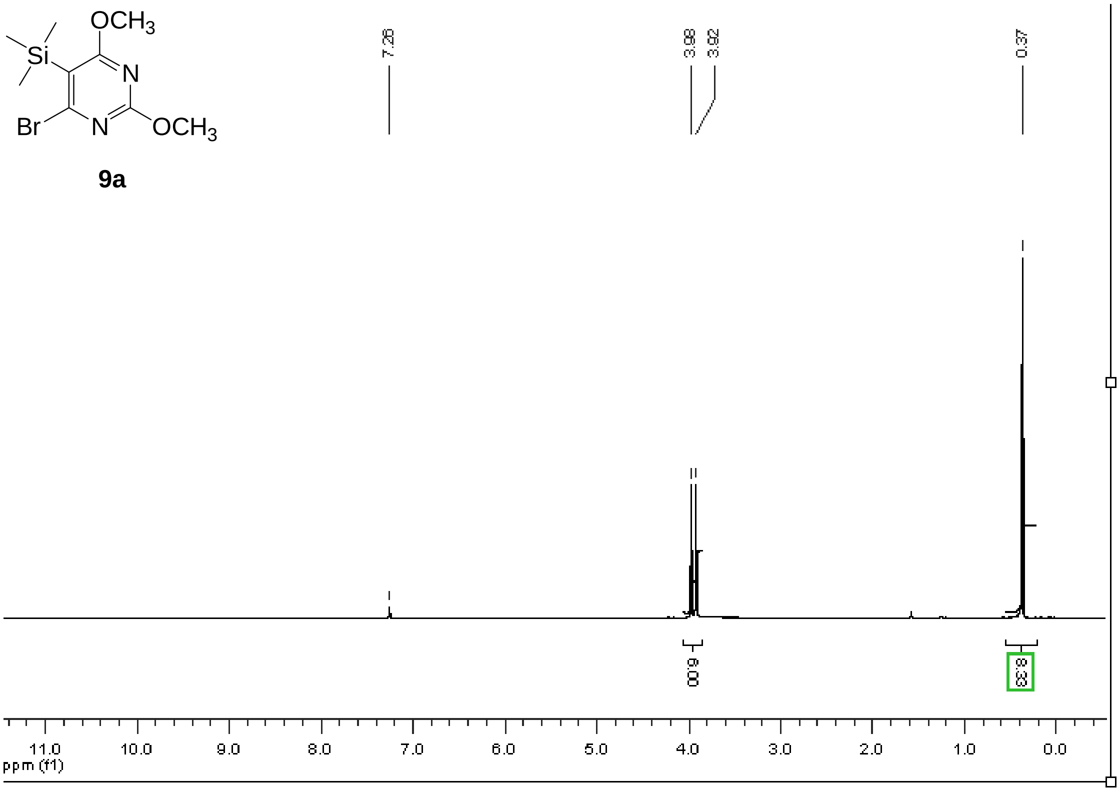
172.22
165.12
164.89
111.75
89.77
77.00
56.39
55.96
8e
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm (f1)


O
OCH3
EtO
N
Cl
N
OCH3
8f
7.26
4.40
4.37
4.02
1.37
1.93
6.00
3.02
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


O
OCH3
EtO
N
Cl
N
OCH3
8f
169.24
163.98
163.41
158.85
108.67
77.00
62.14
55.67
55.23
14.01
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (f1)

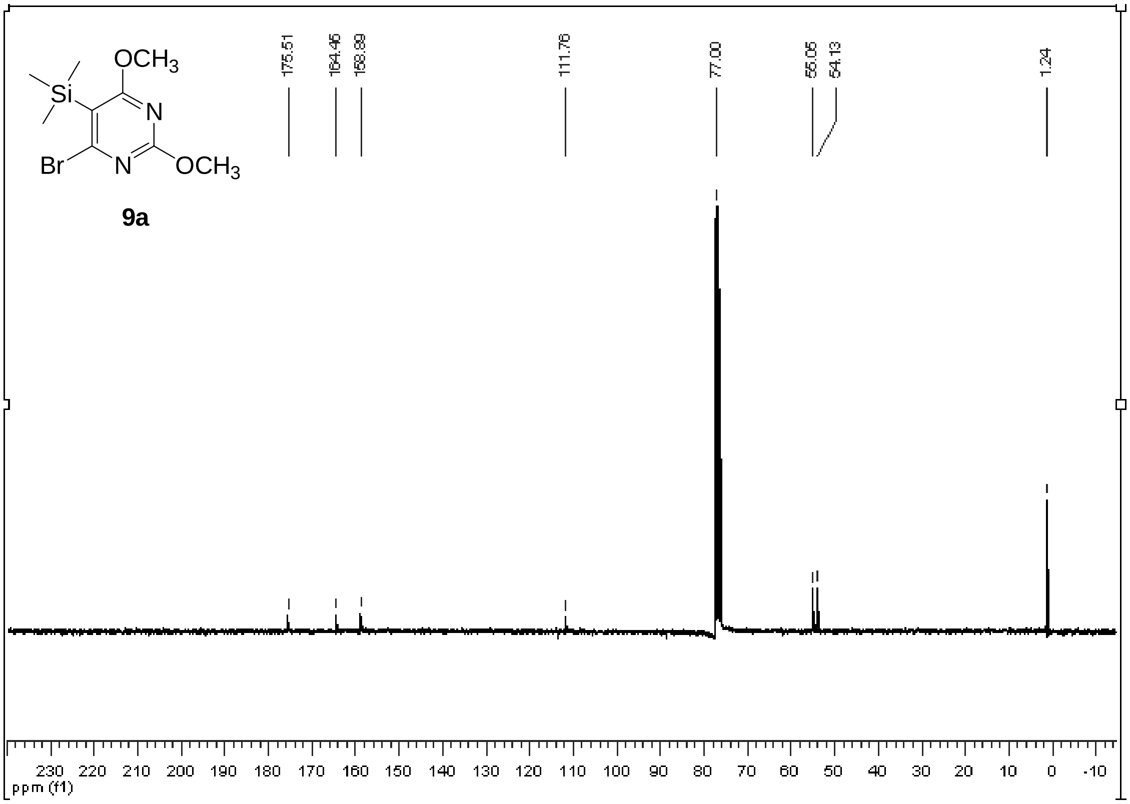

OCH3
N
Cl
N
OCH3
8g
7.14
3.91
3.90
4.80
8.01
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


OCH3
N
Cl
N
OCH3
8g
170.26
162.65
160.23
138.57
128.30
126.29
112.04
77.00
55.13
54.82
31.16
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (f1)



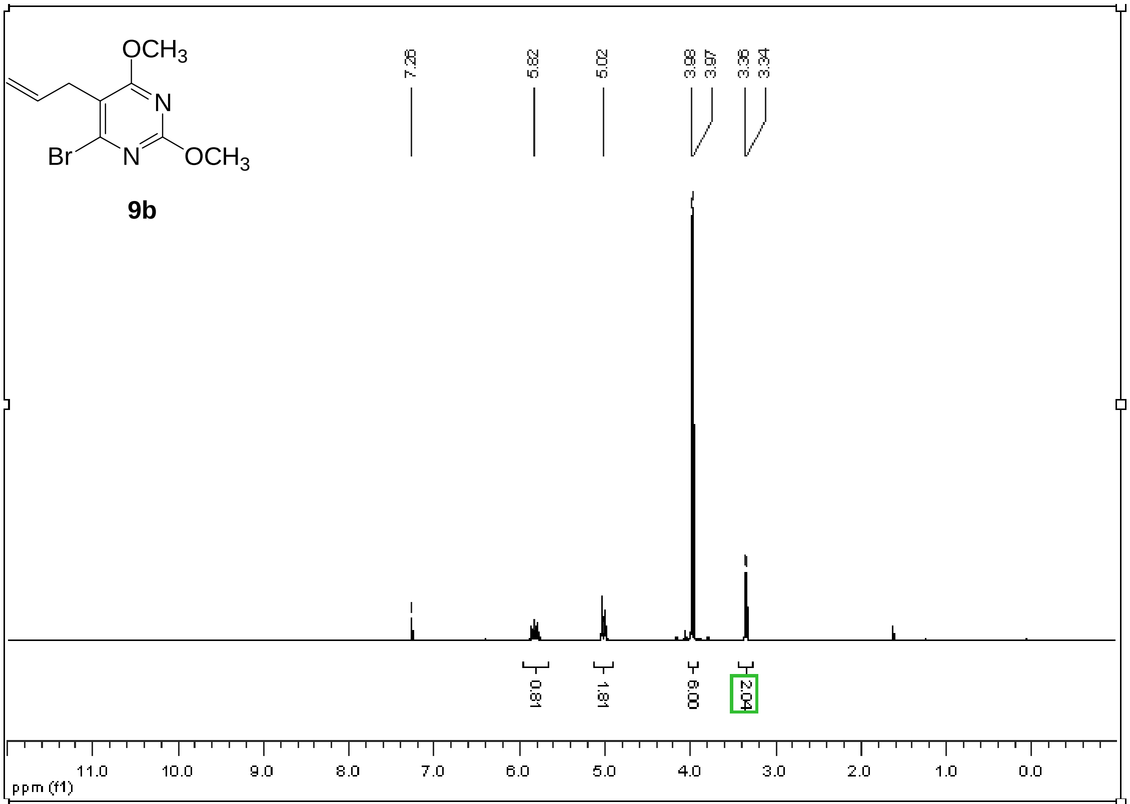
9a

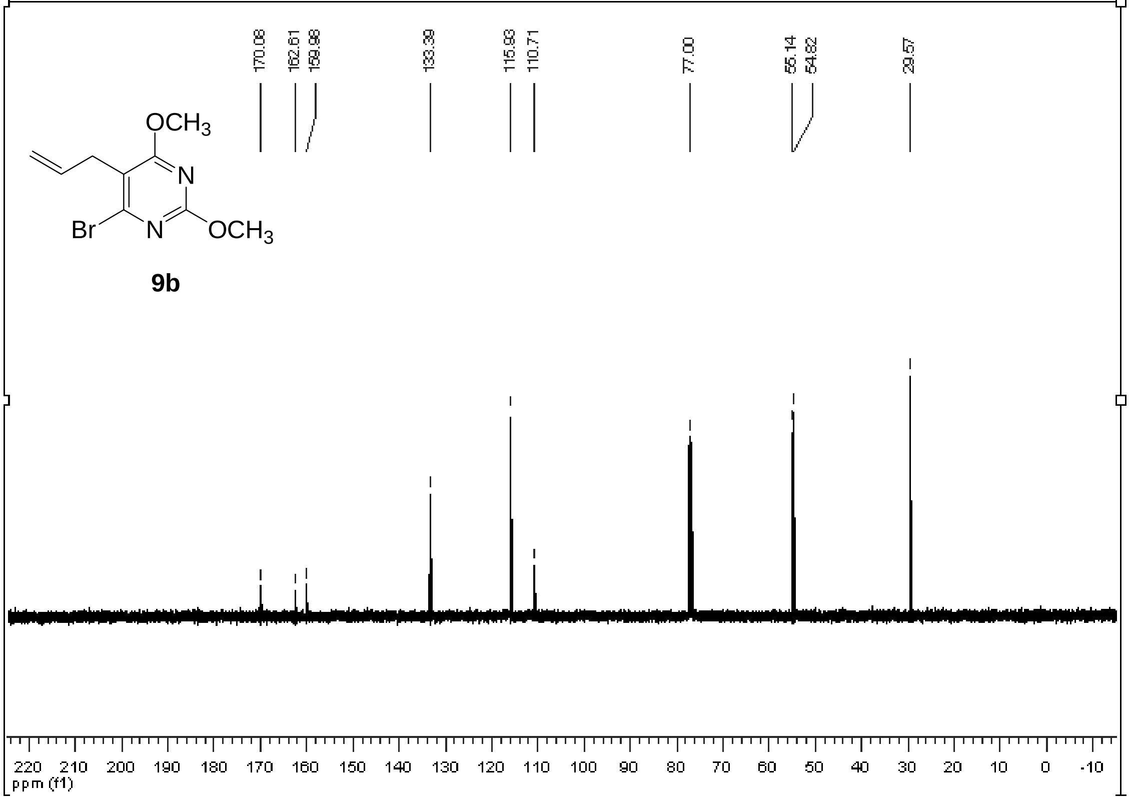
OCH3
Si
N
Br
N
OCH3
7.26
3.98
3.92
0.37
6.00
8.33
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

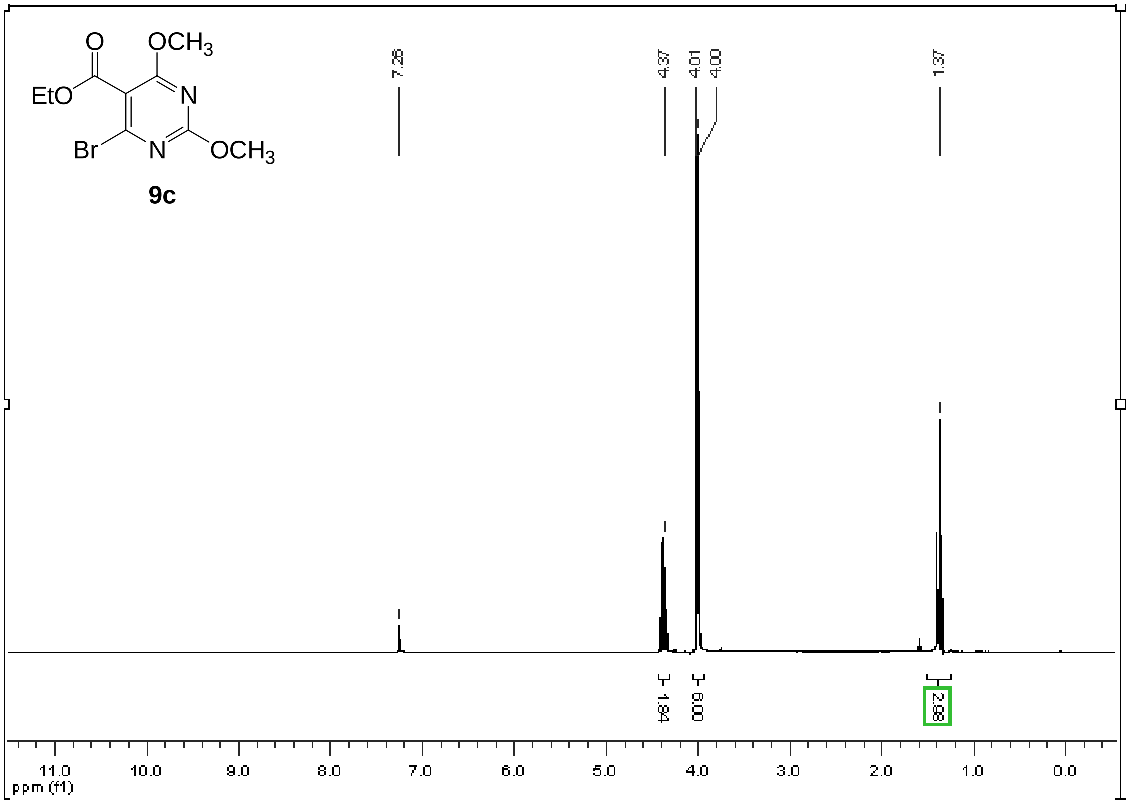


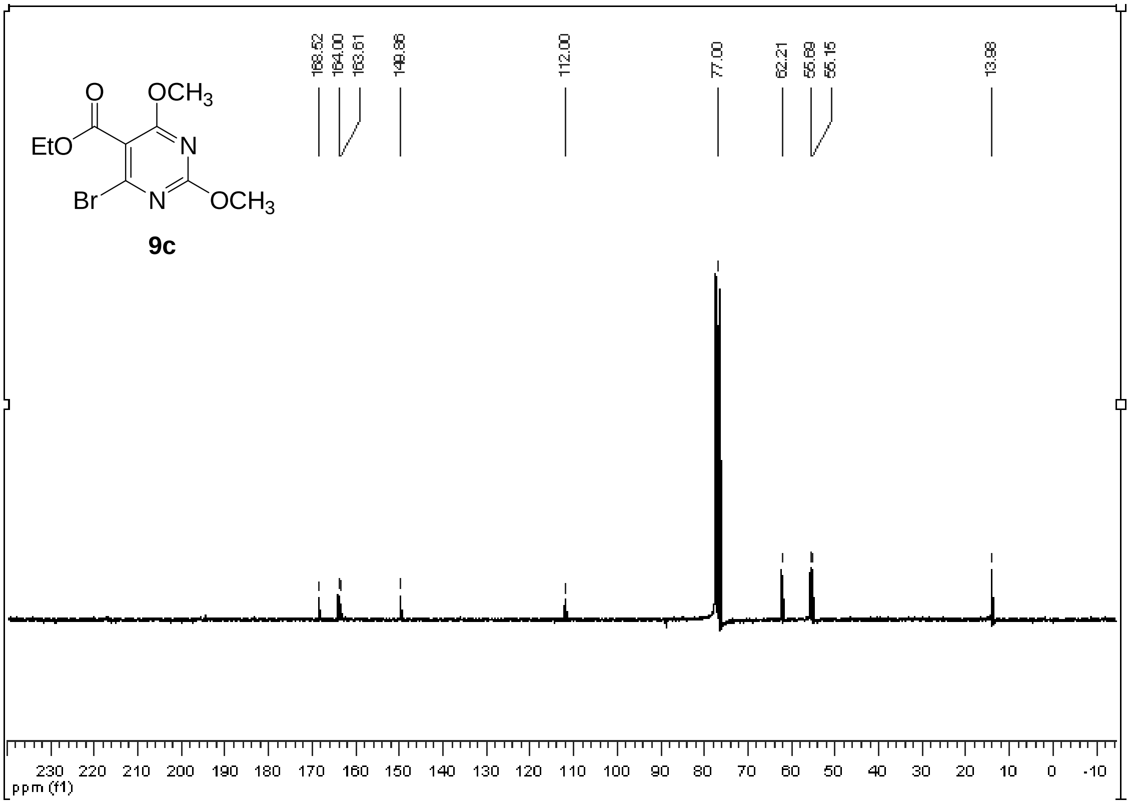
9a

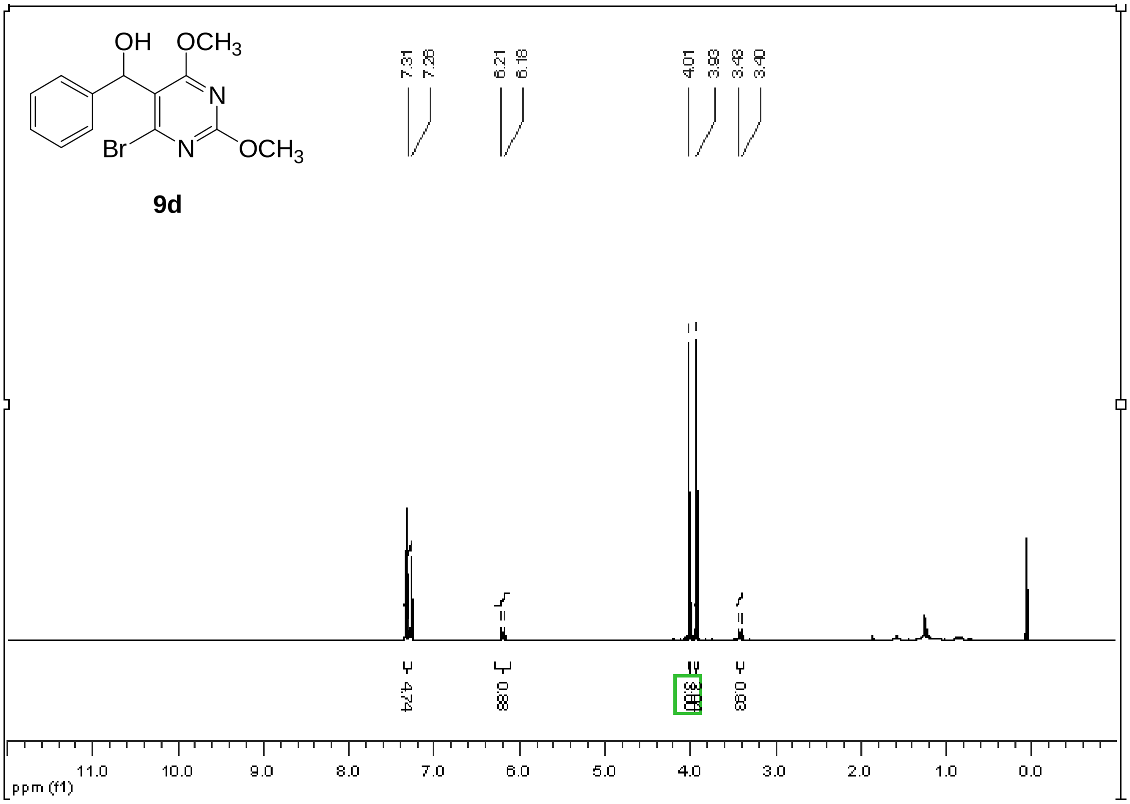
OCH3
Si
N
Br
N
OCH3
175.51
164.45
158.89
111.76
77.00
55.05
54.13
1.24
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (f1)

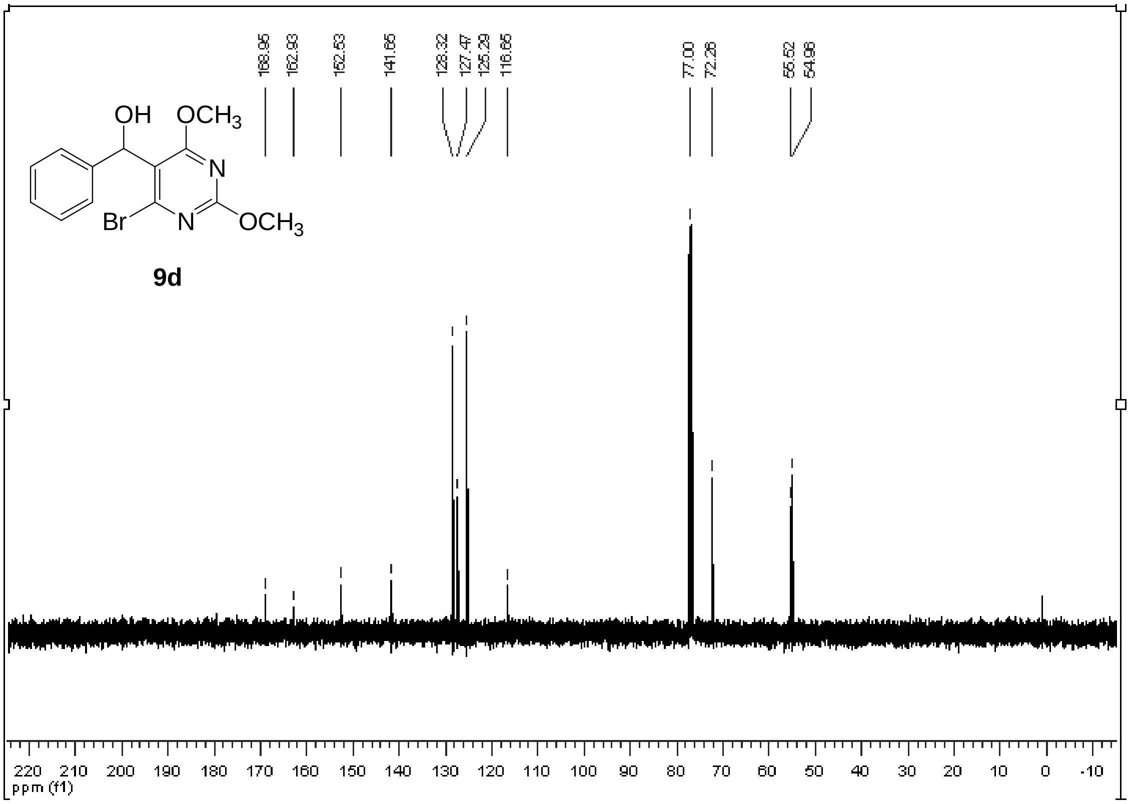

OCH3
N
Br
N
OCH3
9b
7.26
5.82
5.02
3.98
3.97
3.36
3.34
0.81
1.81
6.00
2.04
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

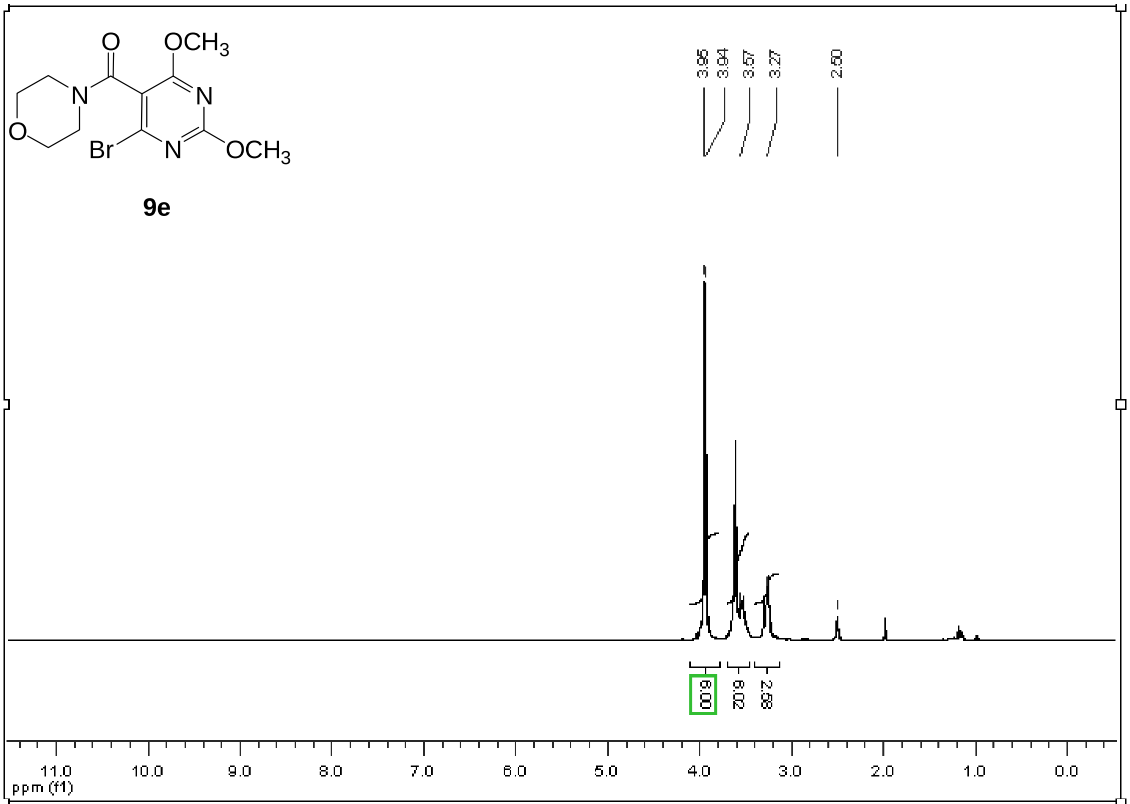

OCH3
N
Br
N
OCH3
9b
170.08
162.61
159.98
133.39
115.93
110.71
77.00
55.14
54.82
29.57
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (f1)

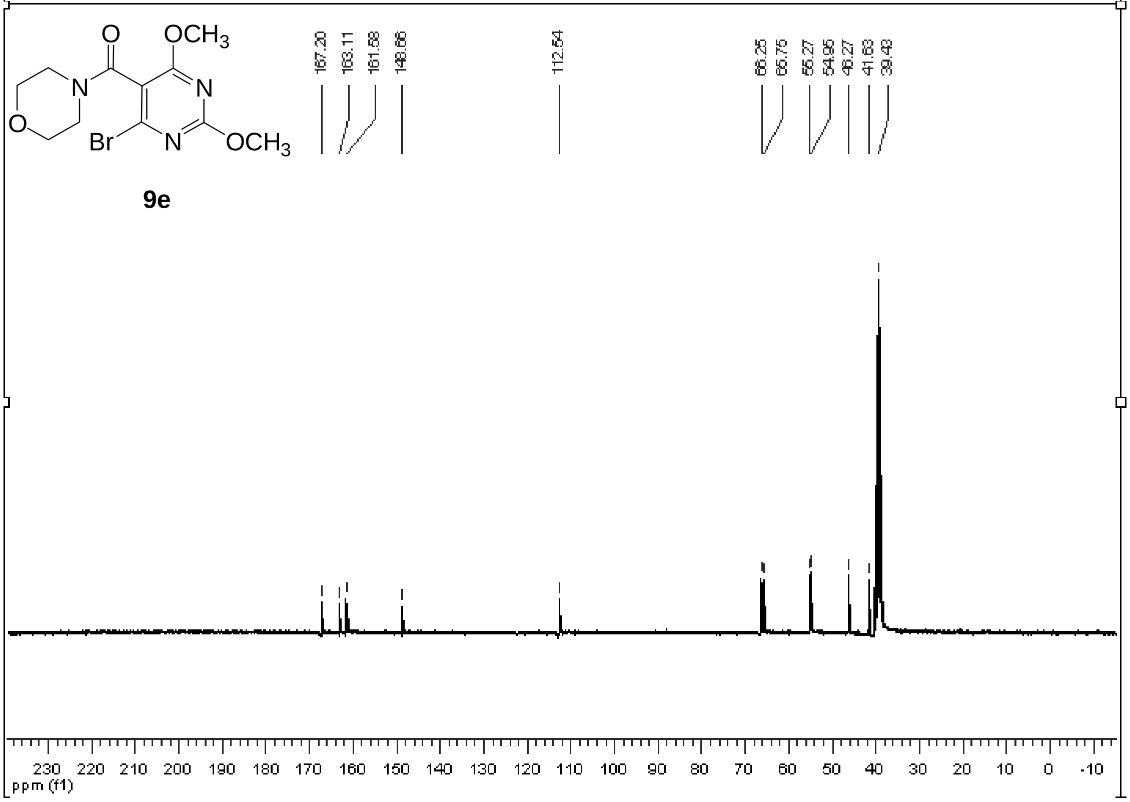

O
OCH3
EtO
N
Br
N
OCH3
9c
7.26
4.37
4.01
4.00
1.37
1.84
6.00
2.98
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

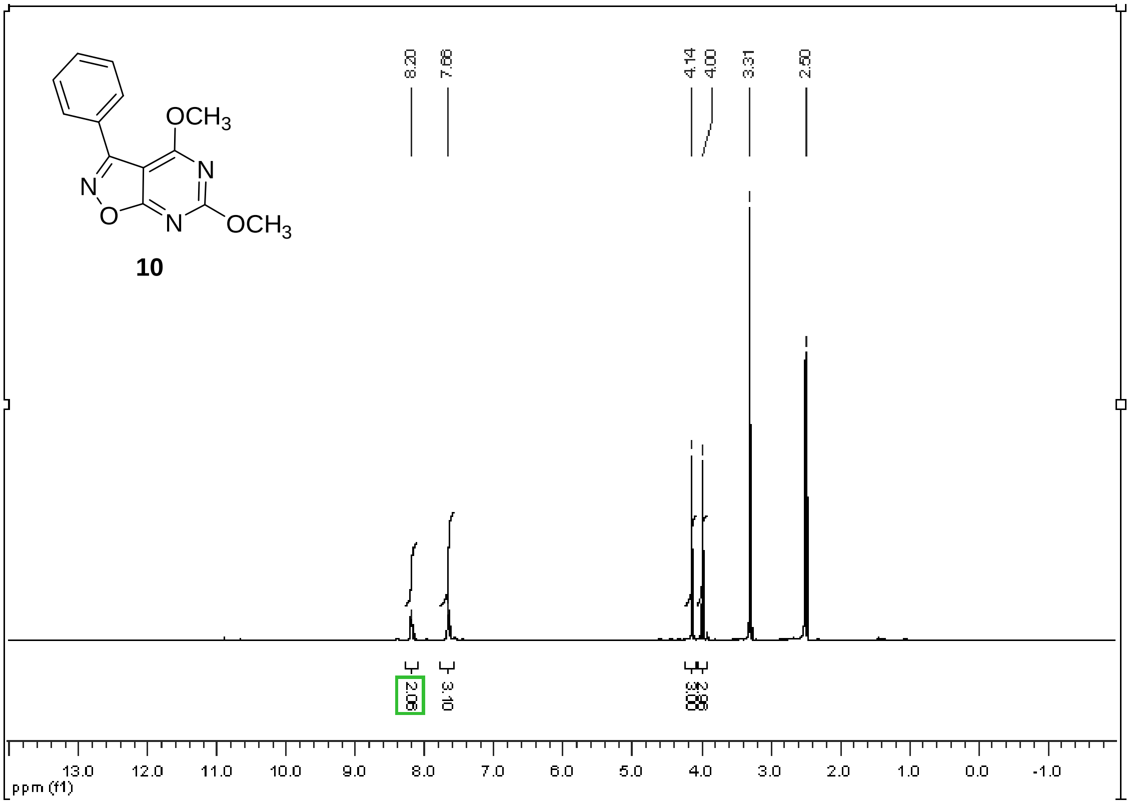

O
OCH3
EtO
N
Br
N
OCH3
9c
168.52
164.00
163.61
149.86
112.00
77.00
62.21
55.69
55.15
13.98
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (f1)


OH
OCH3
N
Br
N
OCH3
9d
7.31
7.26
6.21
6.18
4.01
3.93
3.43
3.40
4.74
0.88
3.00
0.83
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

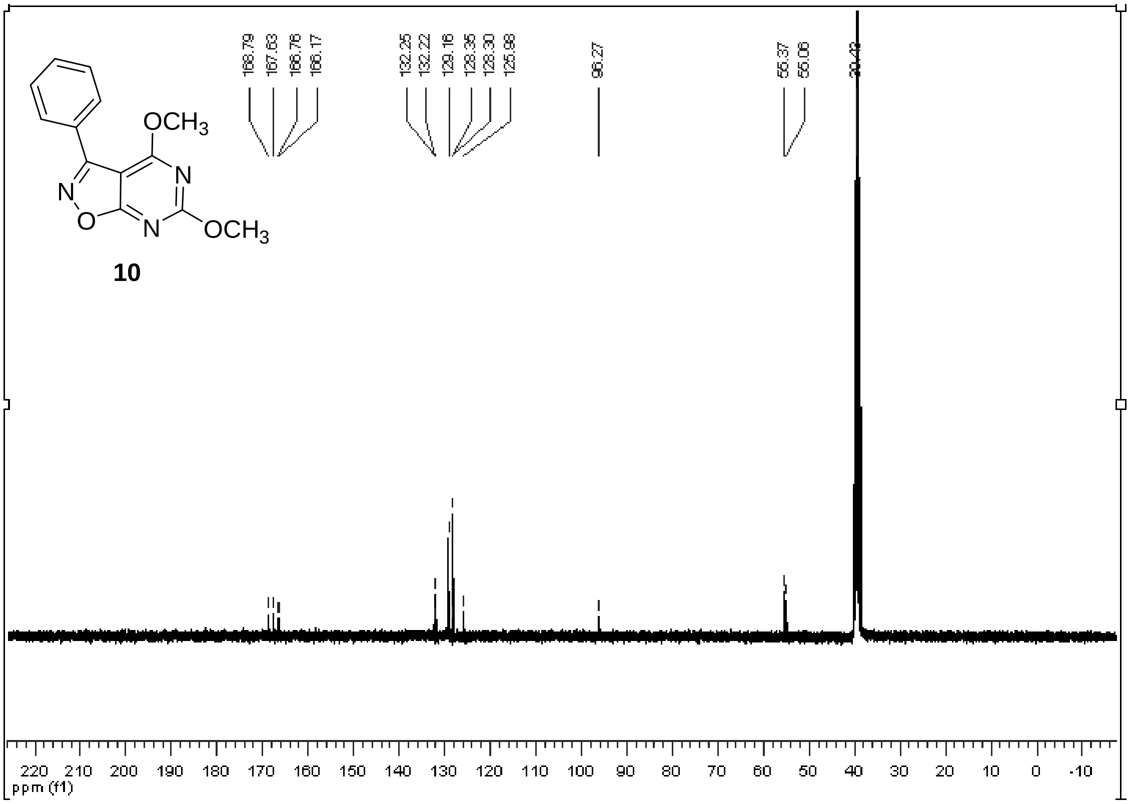

OH
OCH3
N
Br
N
OCH3
9d
168.95
162.93
152.53
141.65
128.32
127.47
125.29
116.65
77.00
72.26
55.52
54.96
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (f1)


9e
O
OCH3
N
N
N
O
Br
OCH3
3.95
3.94
3.57
3.27
2.50
6.00
8.02
2.68
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

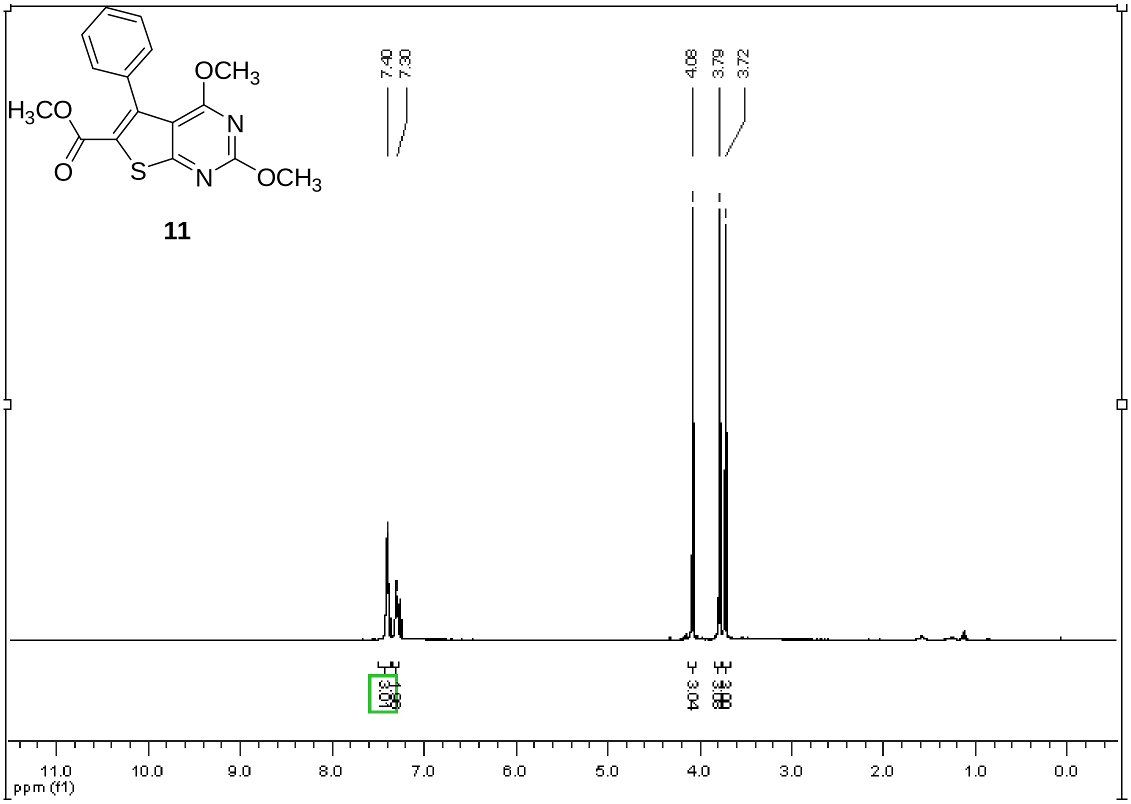

9e
O
OCH3
N
N
N
O
Br
OCH3
167.20
163.11
161.58
148.66
112.54
66.25
65.75
55.27
54.95
46.27
41.63
39.43
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (f1)



OCH3
N
N
O
N
OCH3
10
8.20
7.66
4.14
4.00
3.31
2.50
2.06
3.10
3.08
2.96
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
ppm (f1)

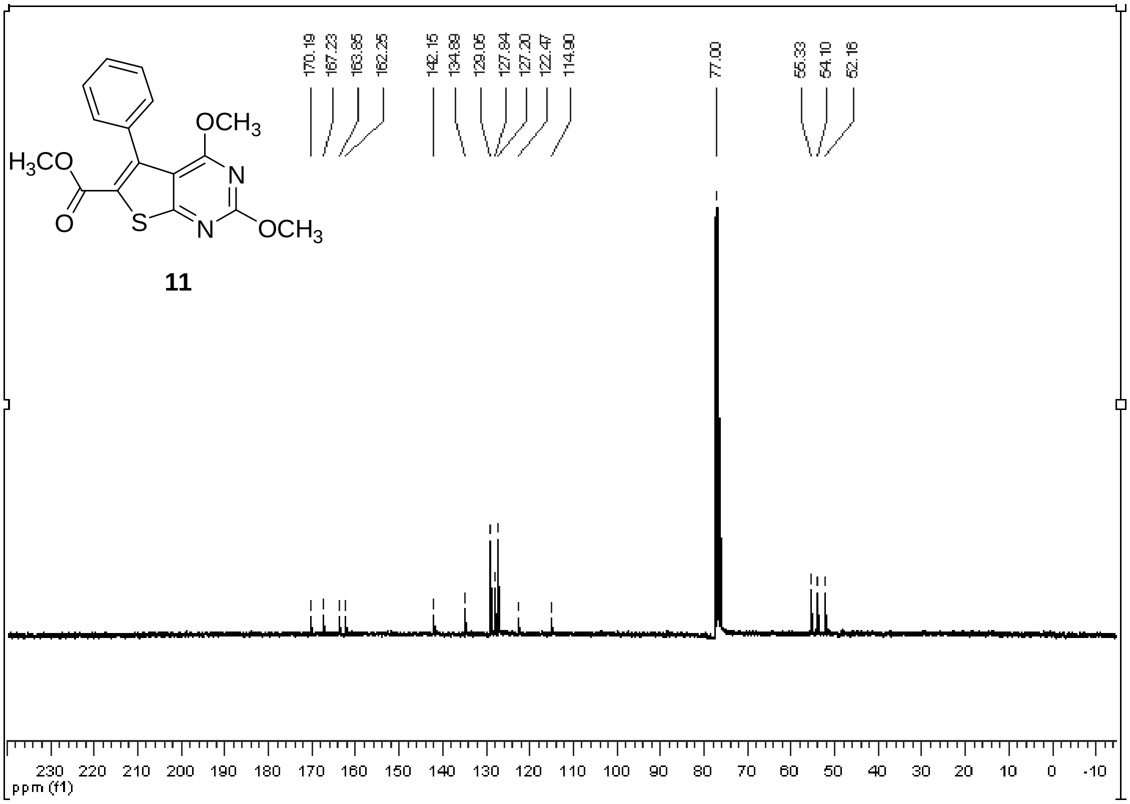


OCH3
N
N
O
N
OCH3
10
168.79
167.63
166.76
166.17
132.25
132.22
129.16
128.35
128.30
125.98
96.27
55.37
55.06
39.43
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (f1)



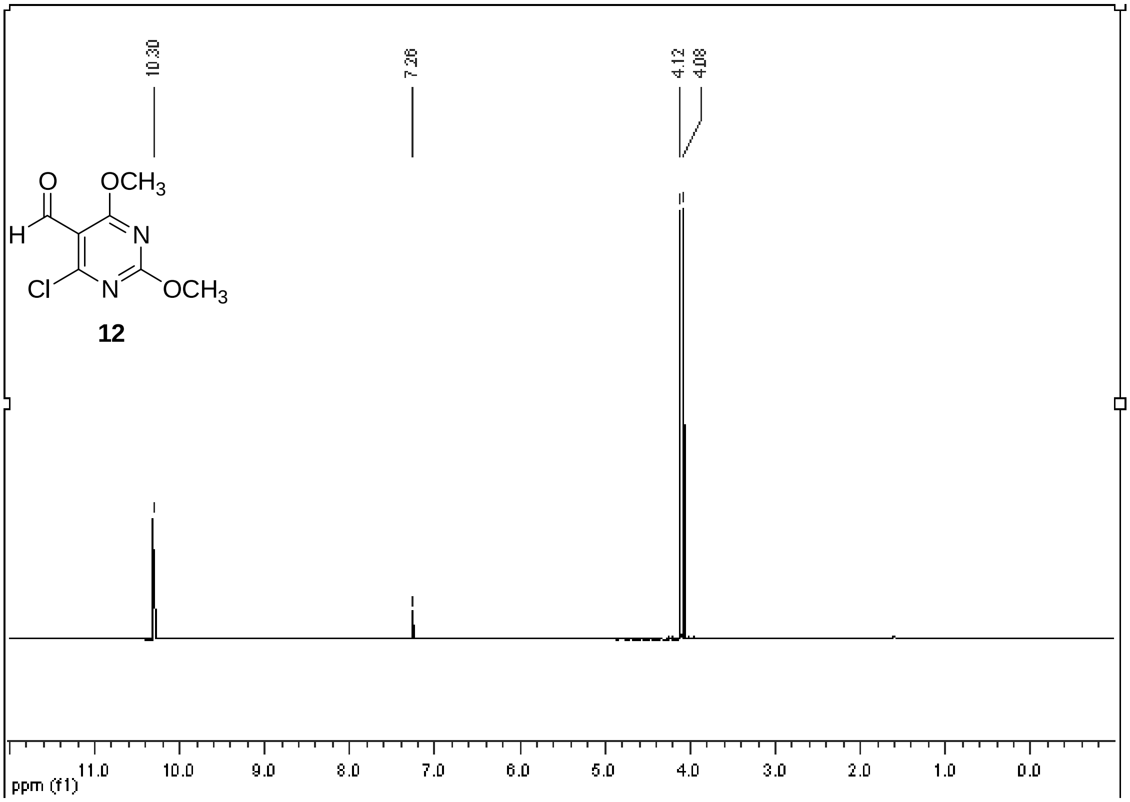
11

7.40
7.30
4.08
3.79
3.72
3.04
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)
H3CO
OCH3
OCH3
O
S
N
N

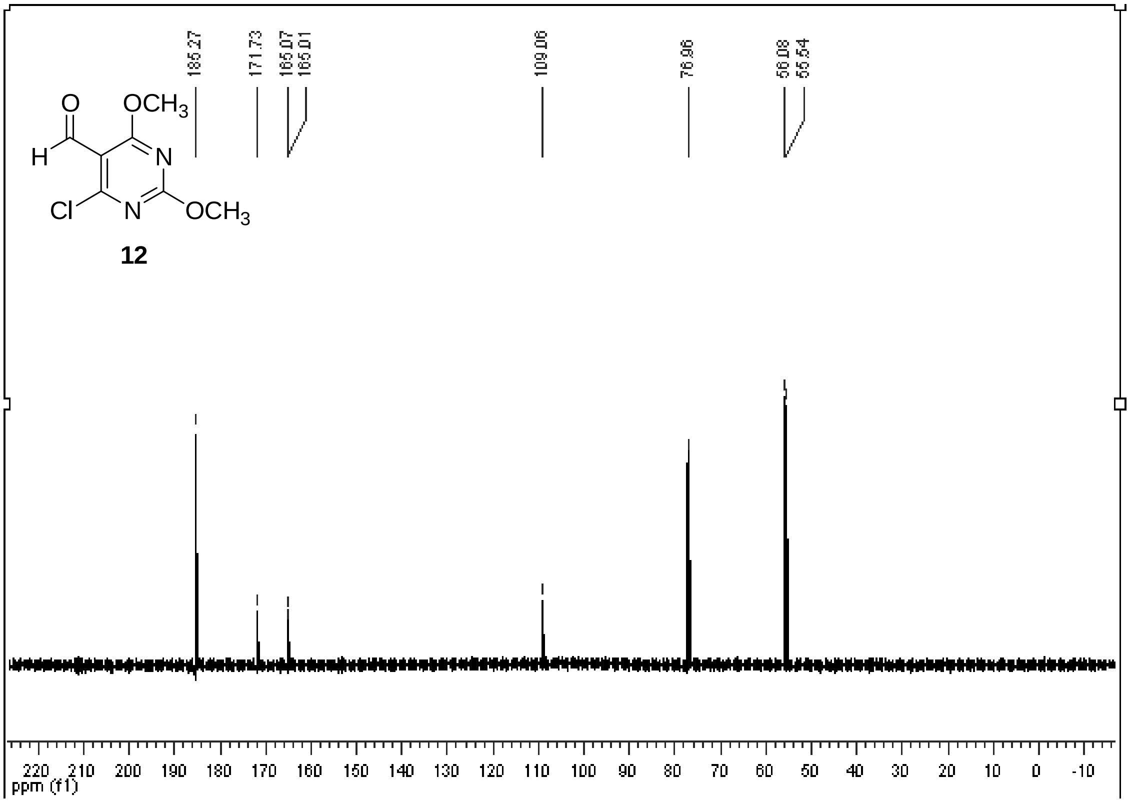


11

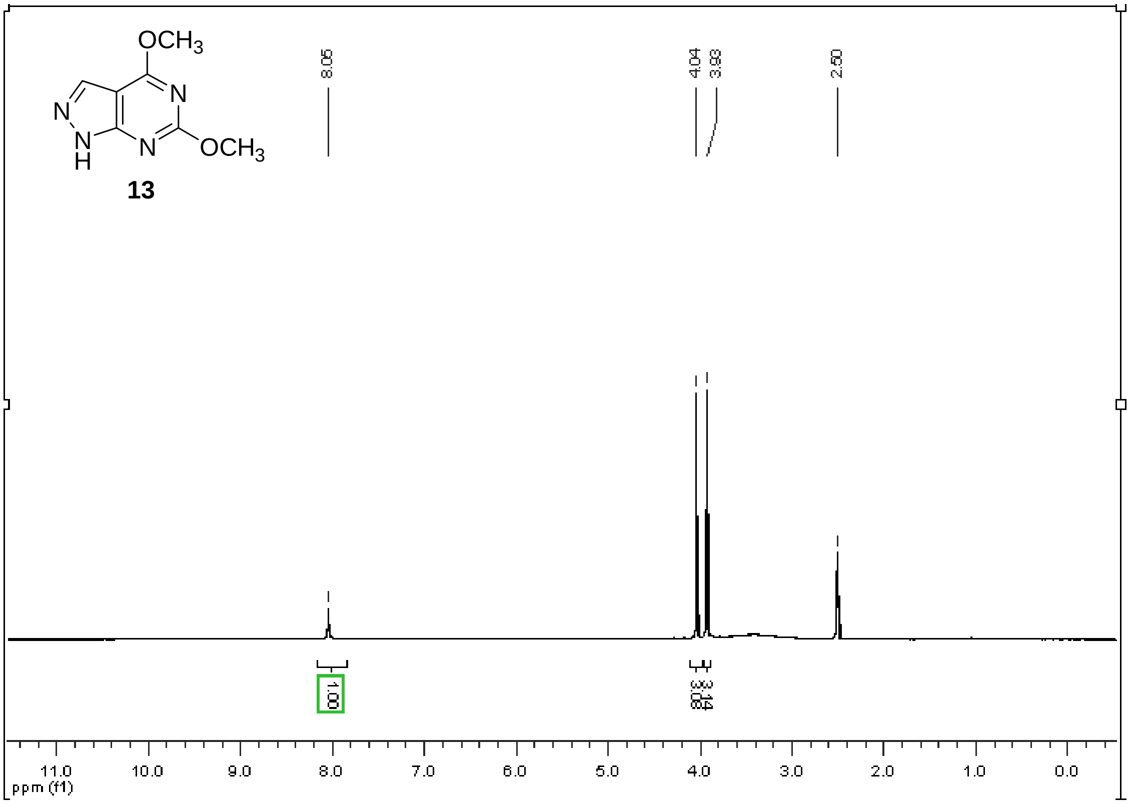
170.19
167.23
163.85
162.25
142.15
134.89
129.05
127.84
127.20
122.47
114.90
77.00
55.33
54.10
52.16
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (f1)
H3CO
OCH3
OCH3
O
S
N
N

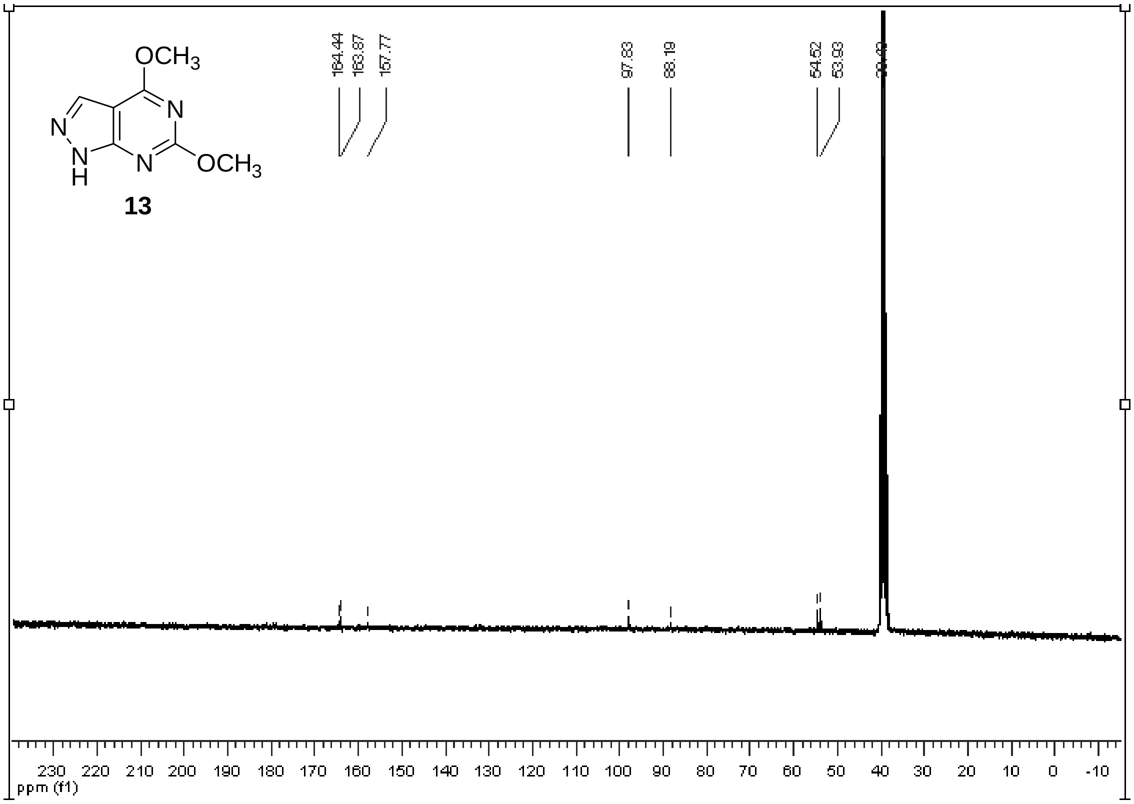

10.30
7.26
4.12
4.08
O
OCH3
H
N
Cl
N
OCH3
ppm (f1)
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

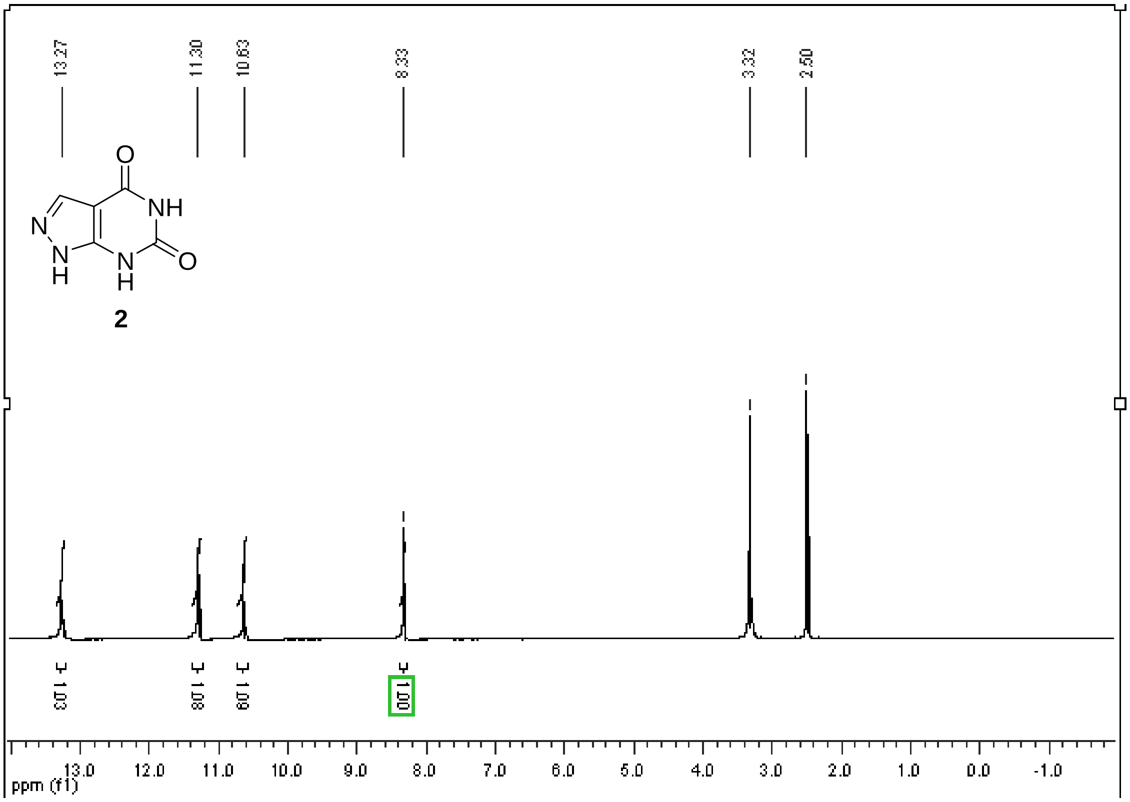
12

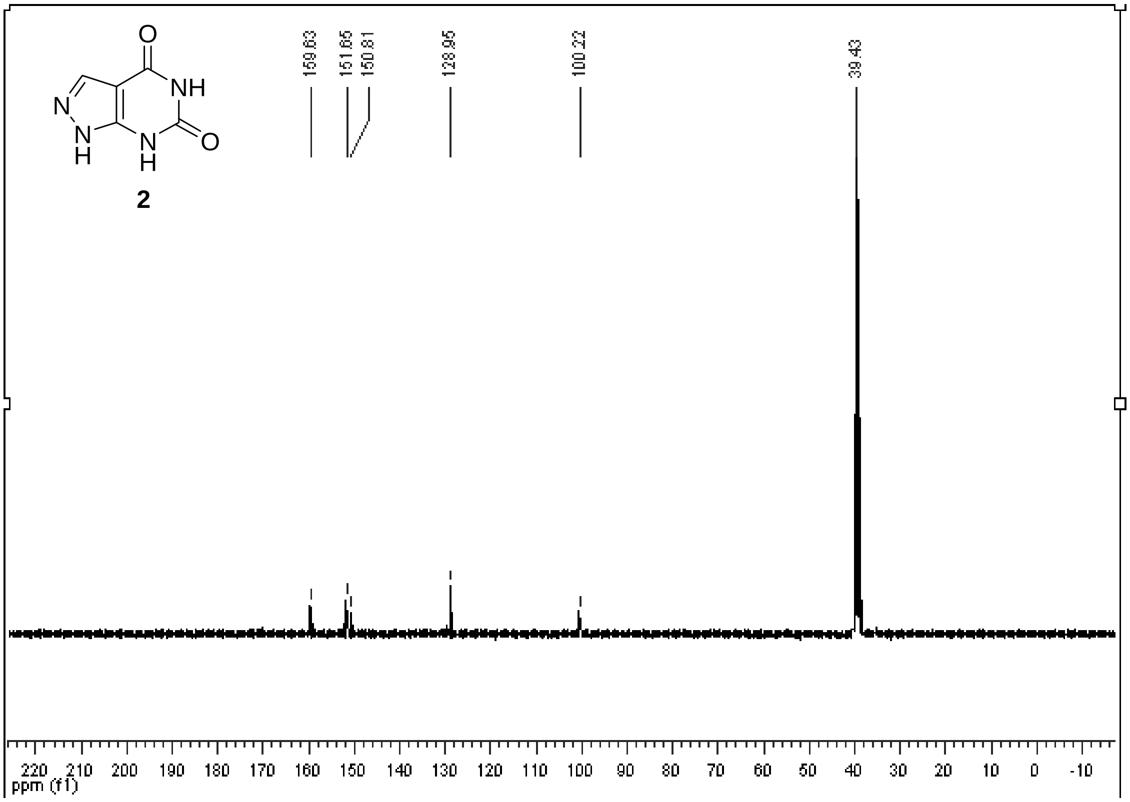

185.27
171.73
165.07
165.01
109.06
76.96
56.08
55.54
O
OCH3
H
N
Cl
N
OCH3
ppm (f1)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

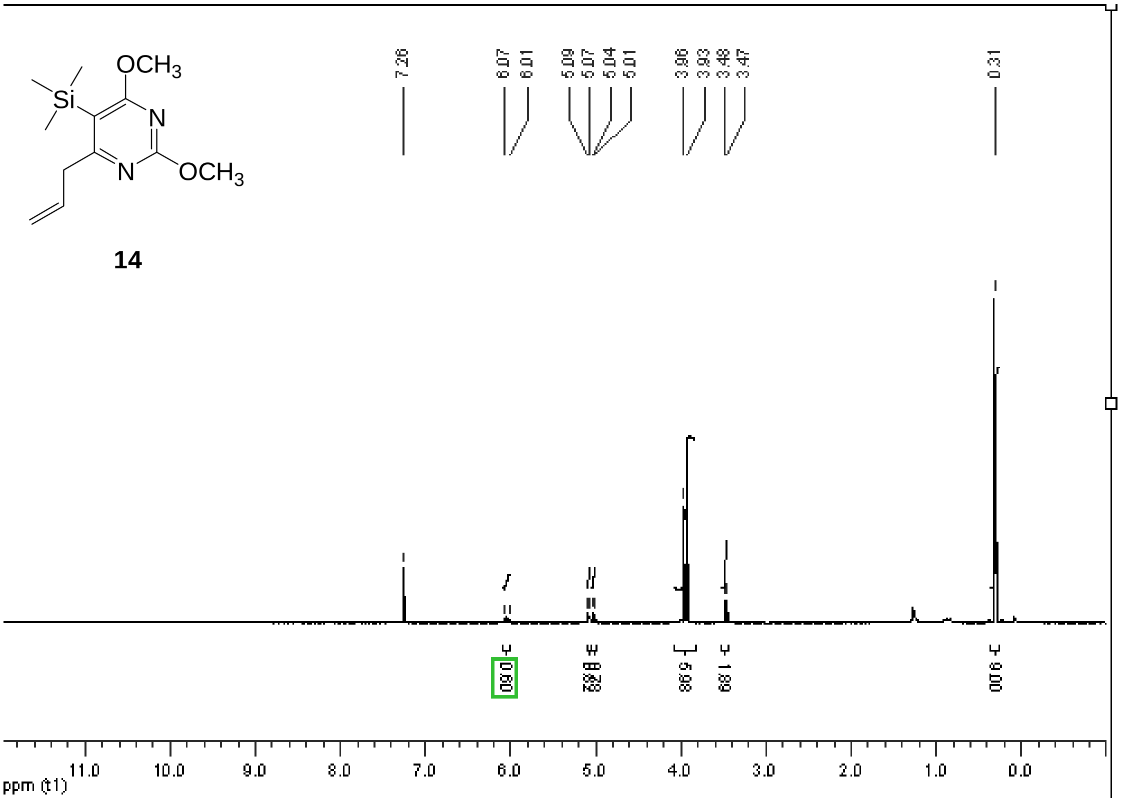
12

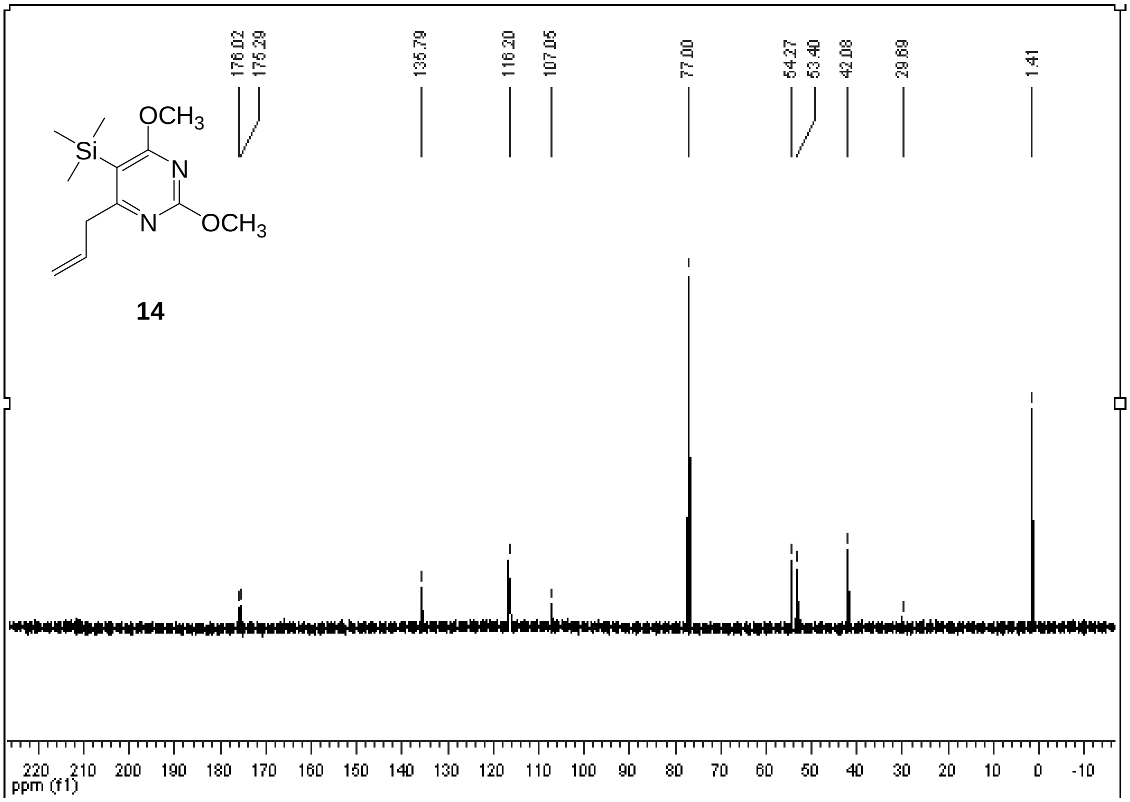

OCH3
N
N
H
N
N
OCH3
13
8.05
4.04
3.93
2.50
1.00
3.14
3.08
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

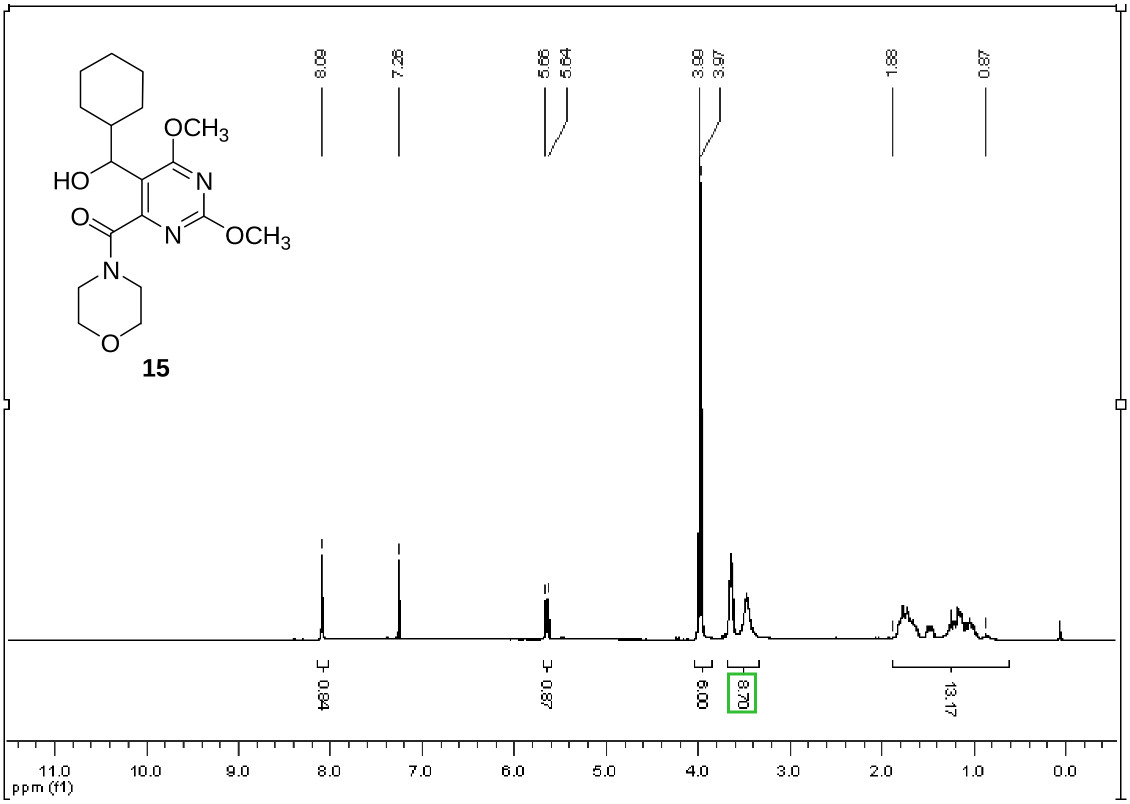

OCH3
N
N
H
N
N
OCH3
13
164.44
163.87
157.77
97.83
88.19
54.52
53.93
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (f1)

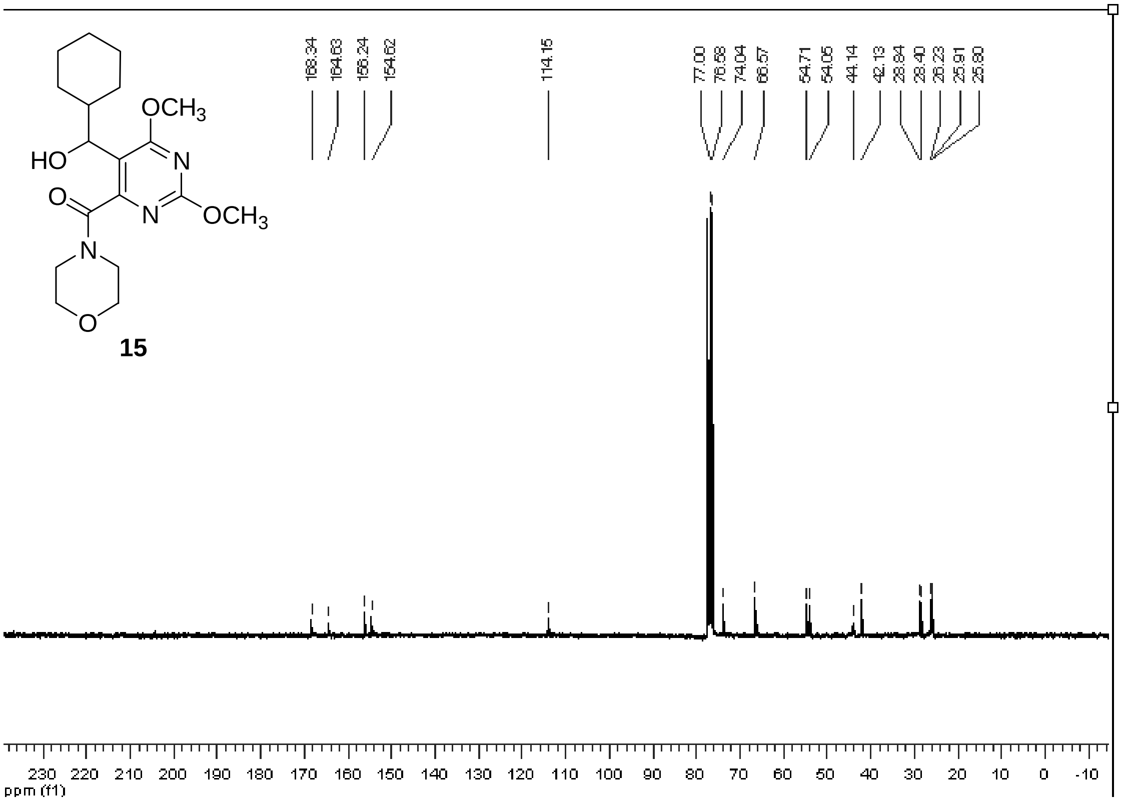

13.27
11.30
10.63
8.33
3.32
2.50
O
NH
N
N
H
N
H
O
2
1.03
1.08
1.09
1.00
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
ppm (f1)

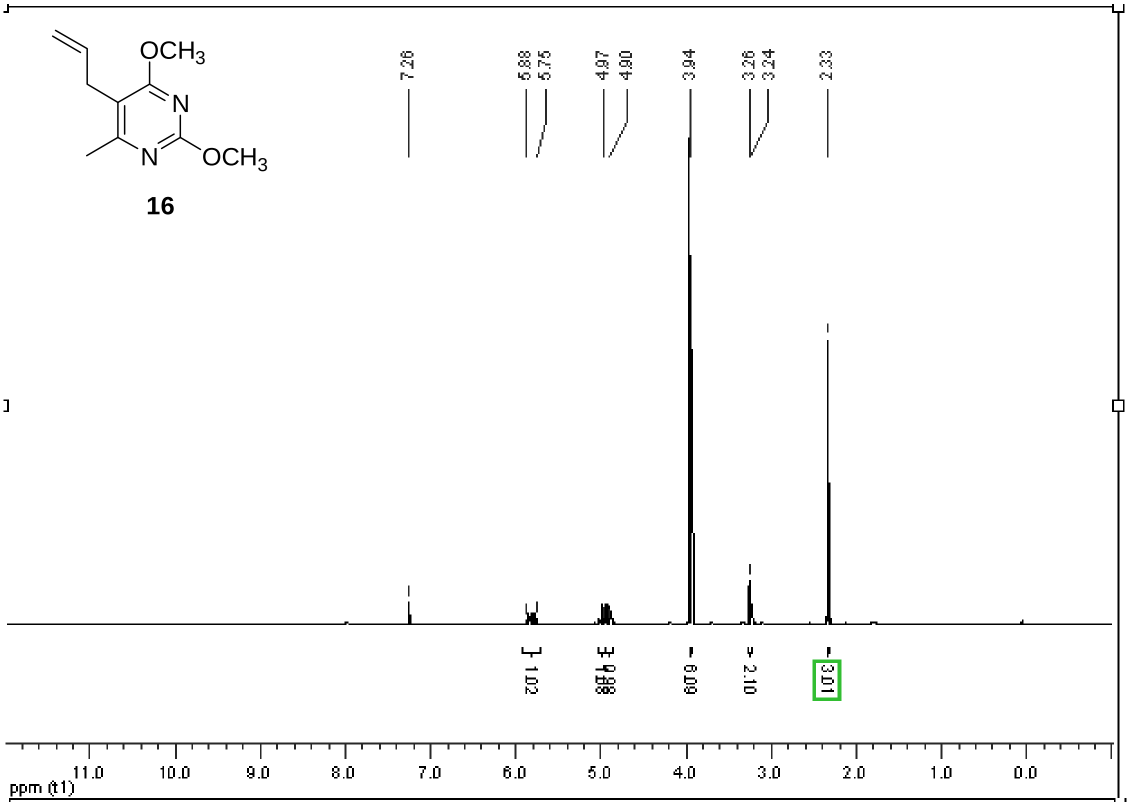

O
NH
N
N
H
N
H
O
2
159.63
151.65
150.81
128.95
100.22
39.43
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (f1)

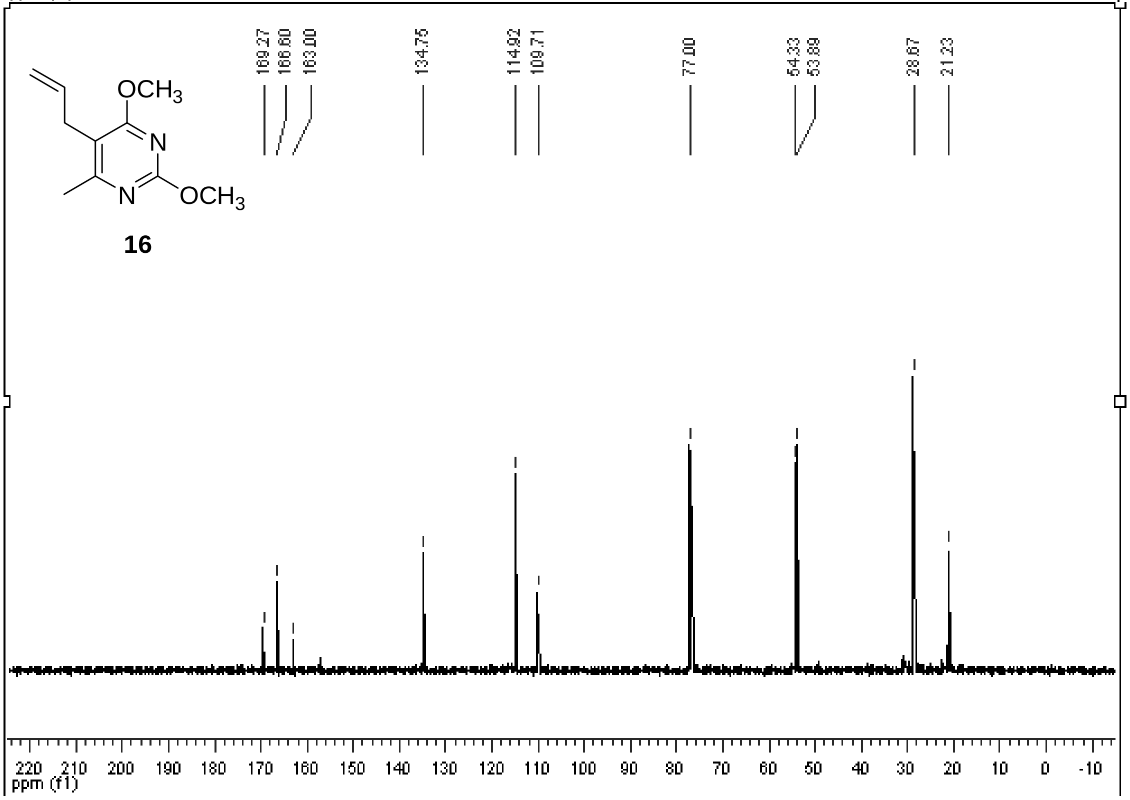

OCH3
Si
N
N
OCH3
14
7.26
6.07
6.01
5.09
5.07
5.04
5.01
3.96
3.93
3.48
3.47
0.31
0.60
0.82
6.98
1.89
9.00
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

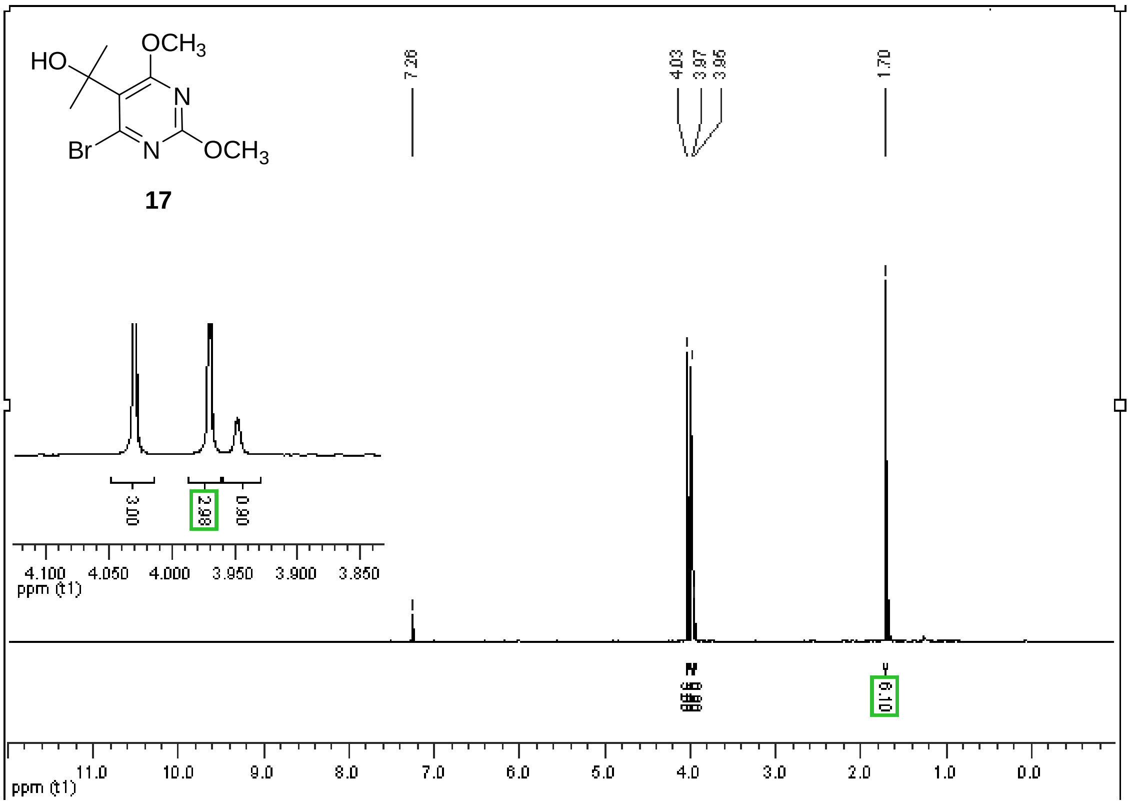

OCH3
Si
N
N
OCH3
14
176.02
175.29
135.79
116.20
107.05
77.00
54.27
53.40
42.08
29.69
1.41
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (f1)

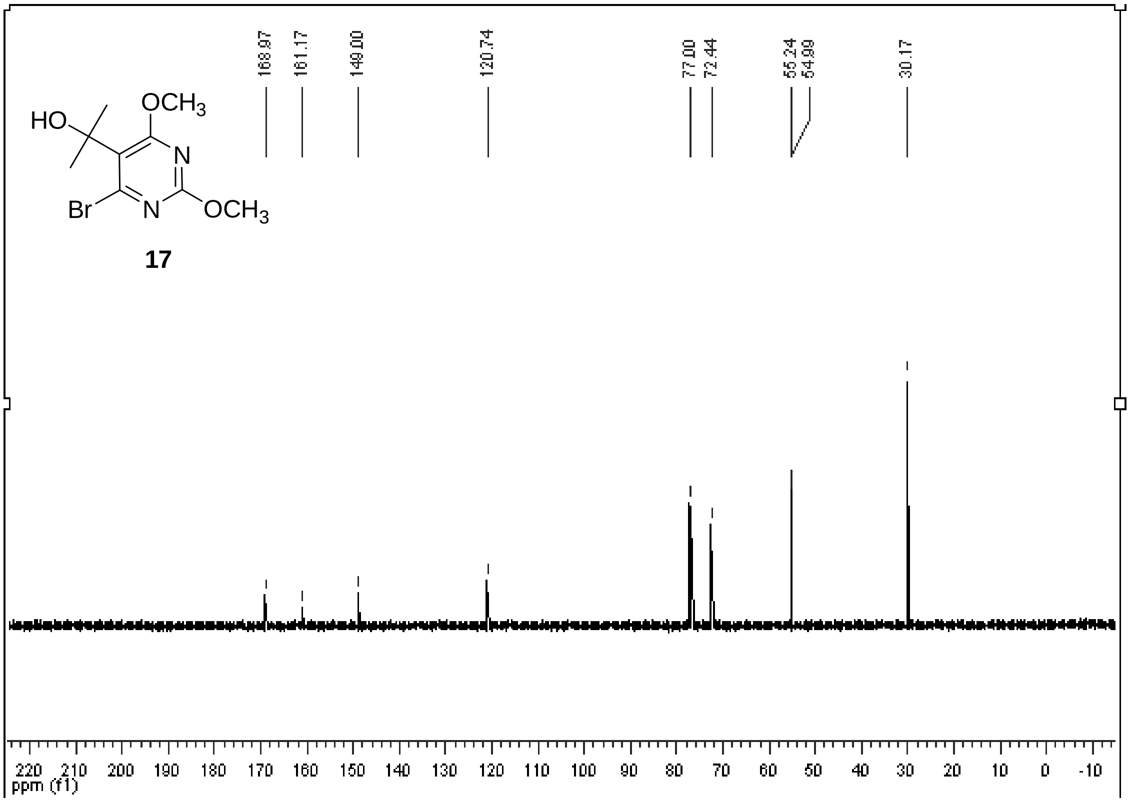

OCH3
HO
N
O
N
OCH3
N
O
15
8.09
7.26
5.66
5.64
3.99
3.97
1.88
0.87
0.84
0.87
6.00
8.70
13.17
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

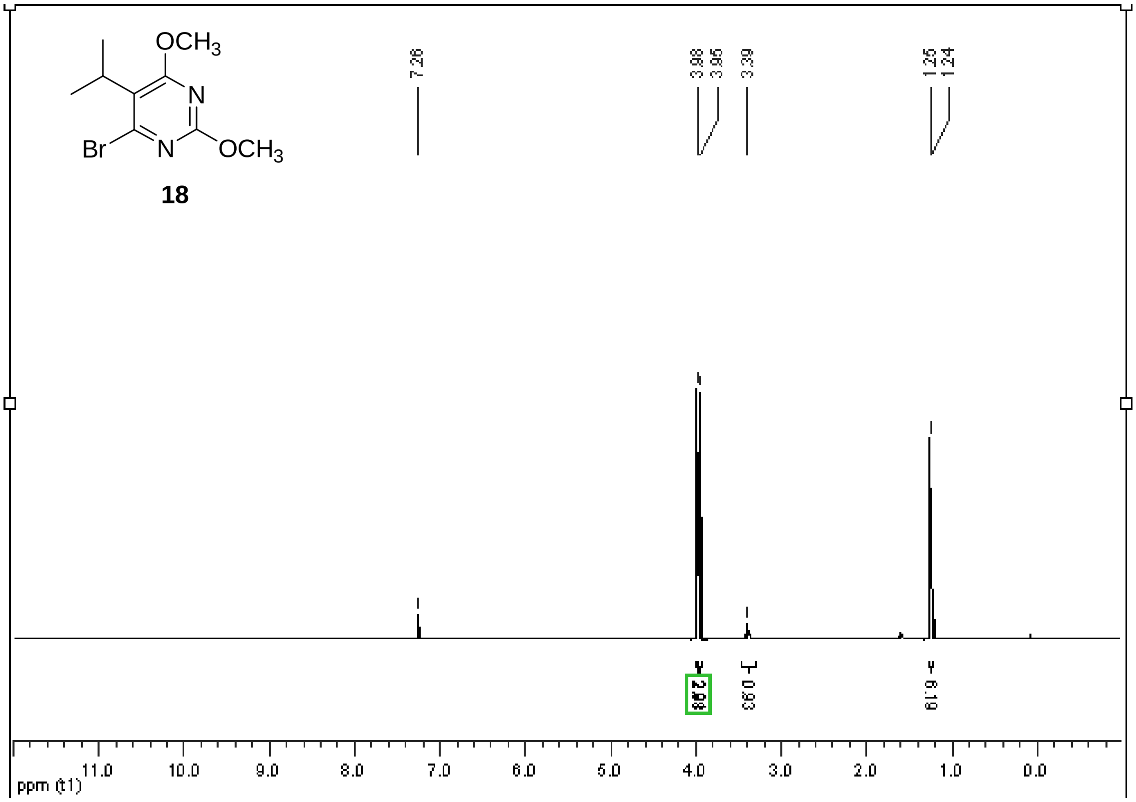

OCH3
HO
N
O
N
OCH3
N
O
15
168.34
164.63
156.24
154.62
114.15
77.00
76.58
74.04
66.57
54.71
54.05
44.14
42.13
28.84
28.40
26.23
25.91
25.80
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (f1)

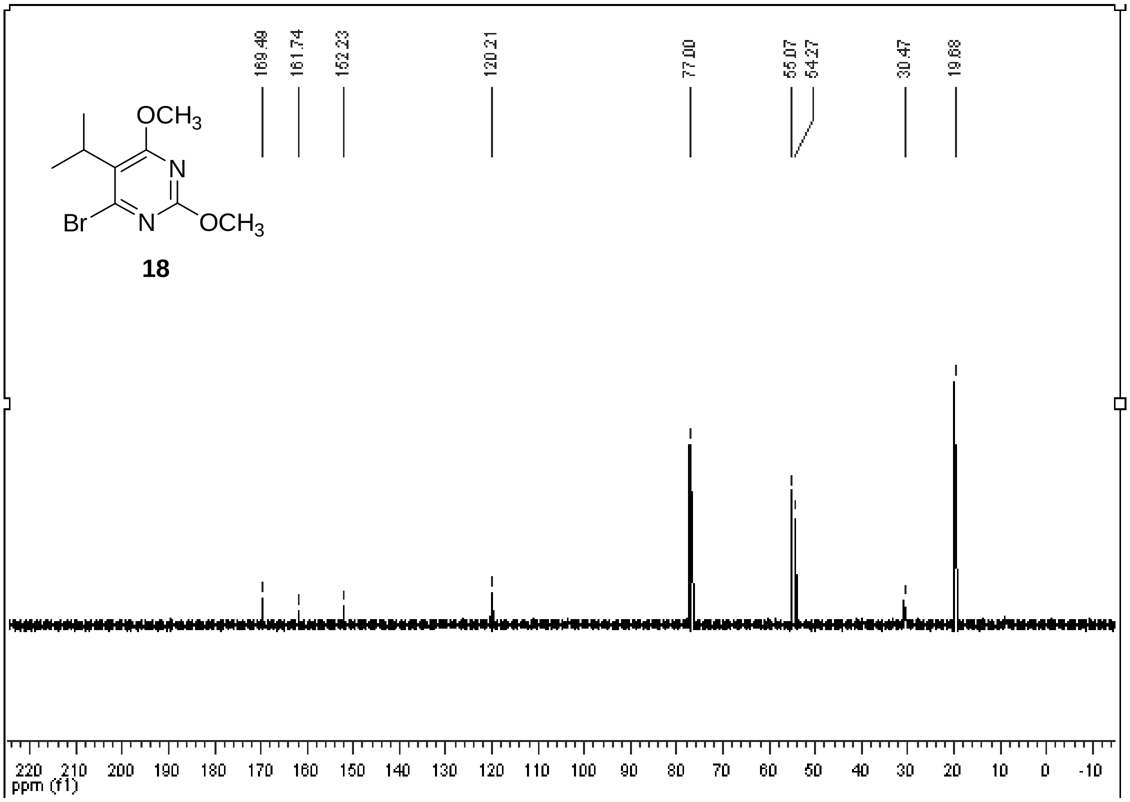

OCH3
N
N
OCH3
16
7.26
5.88
5.75
4.97
4.90
3.94
3.26
3.24
2.33
1.02
1.98
6.09
2.10
3.01
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

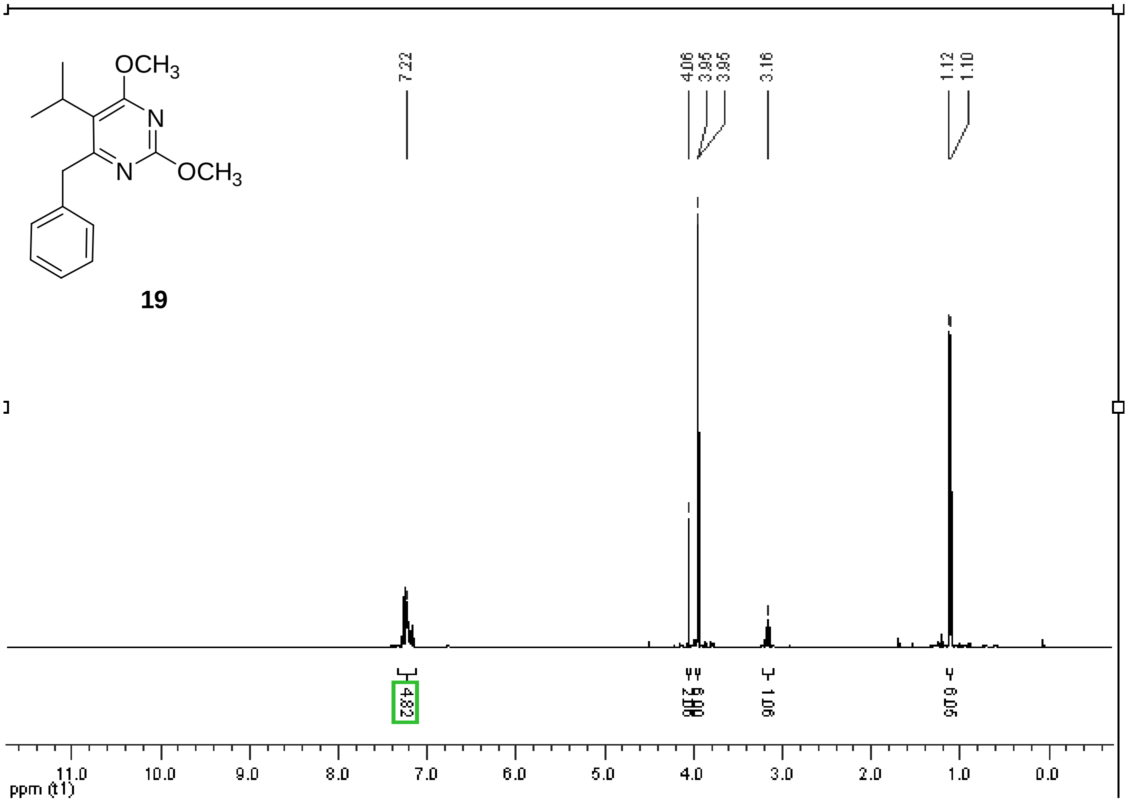

OCH3
N
N
OCH3
16
169.27
166.60
163.00
134.75
114.92
109.71
77.00
54.33
53.89
28.67
21.23
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (f1)

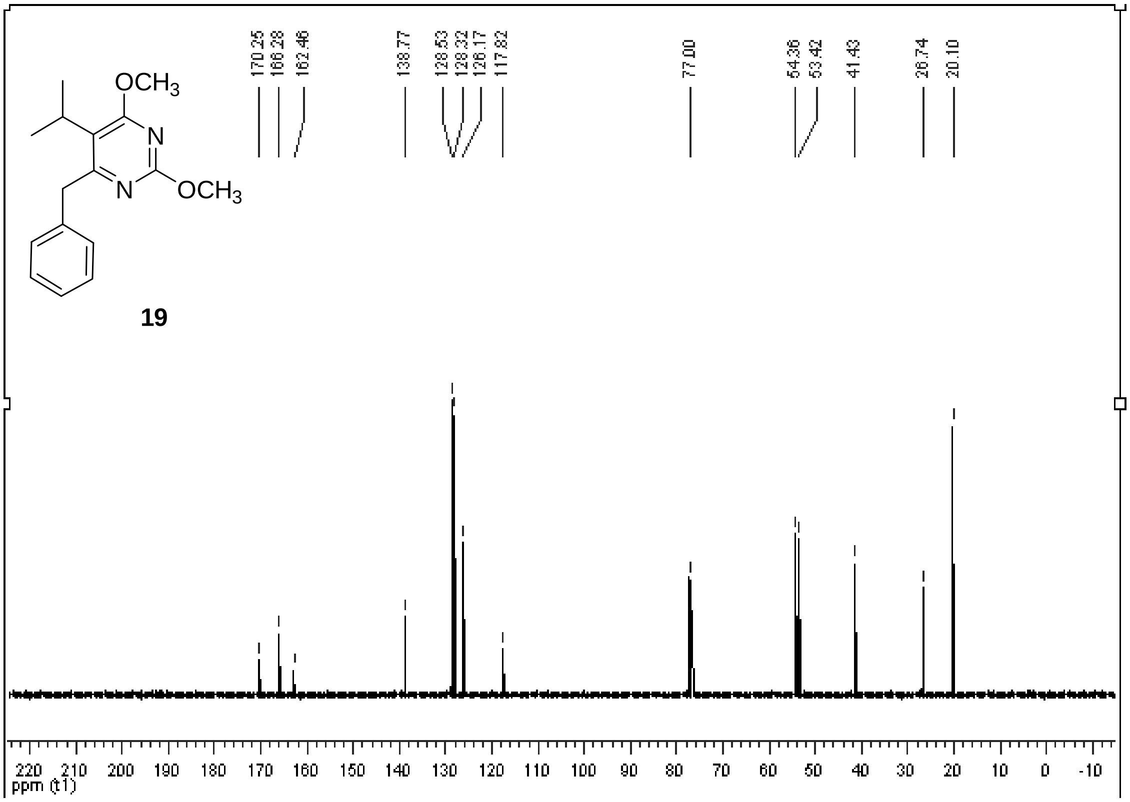

HO
OCH3
N
Br
N
OCH3
17
7.26
4.03
3.97
3.95
1.70
3.00
2.98
0.90
4.100
4.050
4.000
3.950
3.900
3.850
ppm (t1)
6.10
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

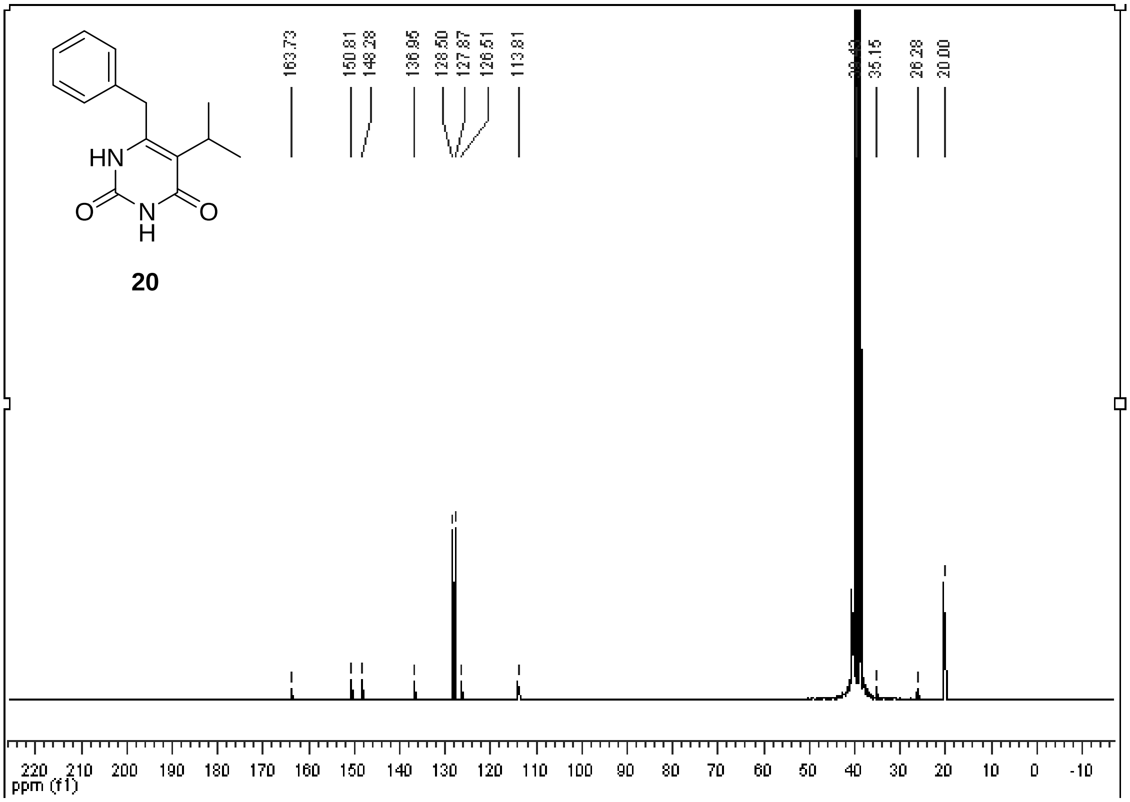

HO
OCH3
N
Br
N
OCH3
17
168.97
161.17
149.00
120.74
77.00
72.44
55.24
54.99
30.17
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (f1)


OCH3
N
Br
N
OCH3
18
7.26
3.98
3.95
3.39
1.25
1.24
2.98
0.93
6.19
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

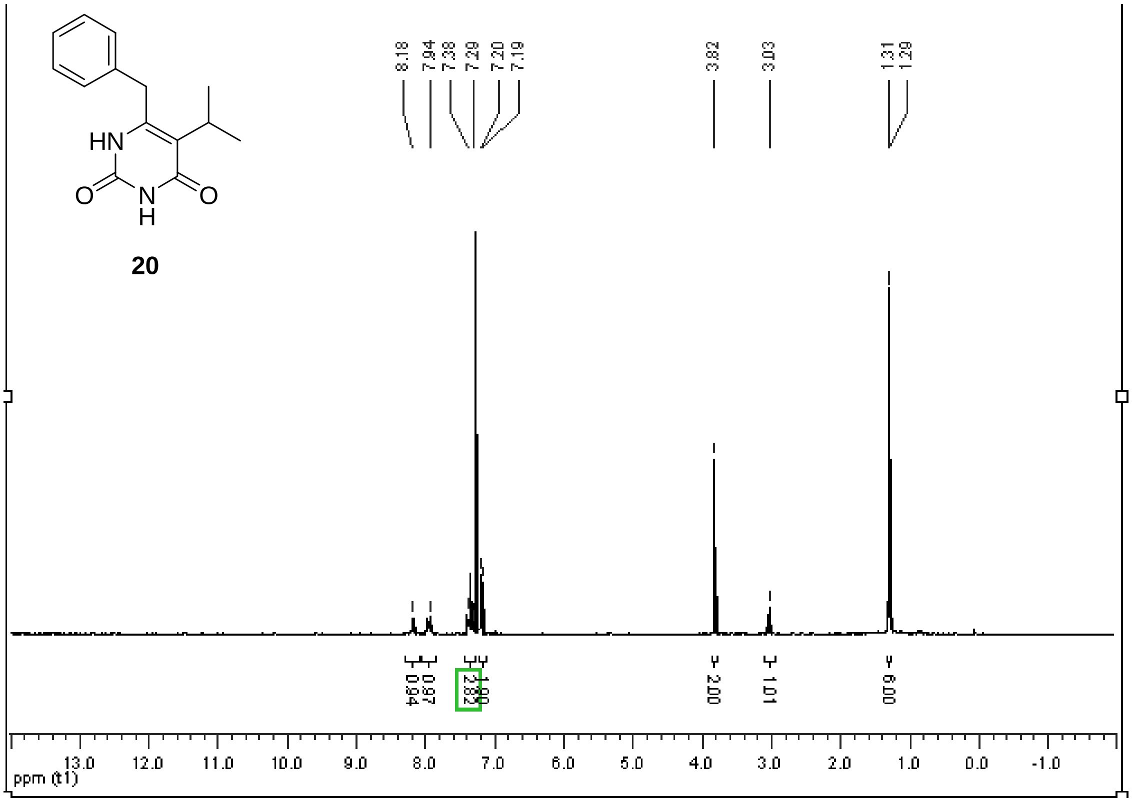

169.49
161.74
152.23
120.21
77.00
55.07
54.27
30.47
19.68
OCH3
N
Br
N
OCH3
18
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (f1)


OCH3
N
N
OCH3
19
7.22
4.06
3.95
3.95
3.16
1.12
1.10
4.82
2.00
6.00
1.06
6.05
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

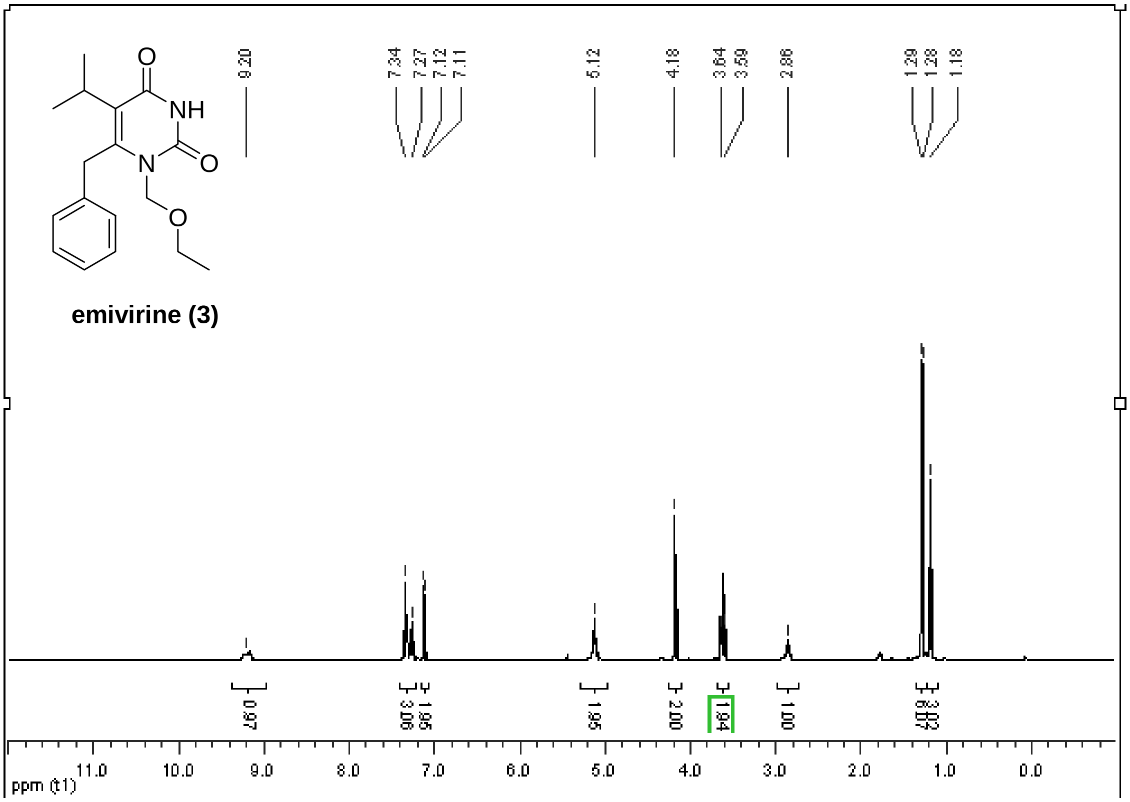

OCH3
N
N
OCH3
19
170.25
166.28
162.46
138.77
128.53
128.32
126.17
117.82
77.00
54.36
53.42
41.43
26.74
20.10
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (t1)


HN
O
N
H
O
163.73
150.81
148.28
136.95
128.50
127.87
126.51
113.81
35.15
26.28
20.00
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm (f1)

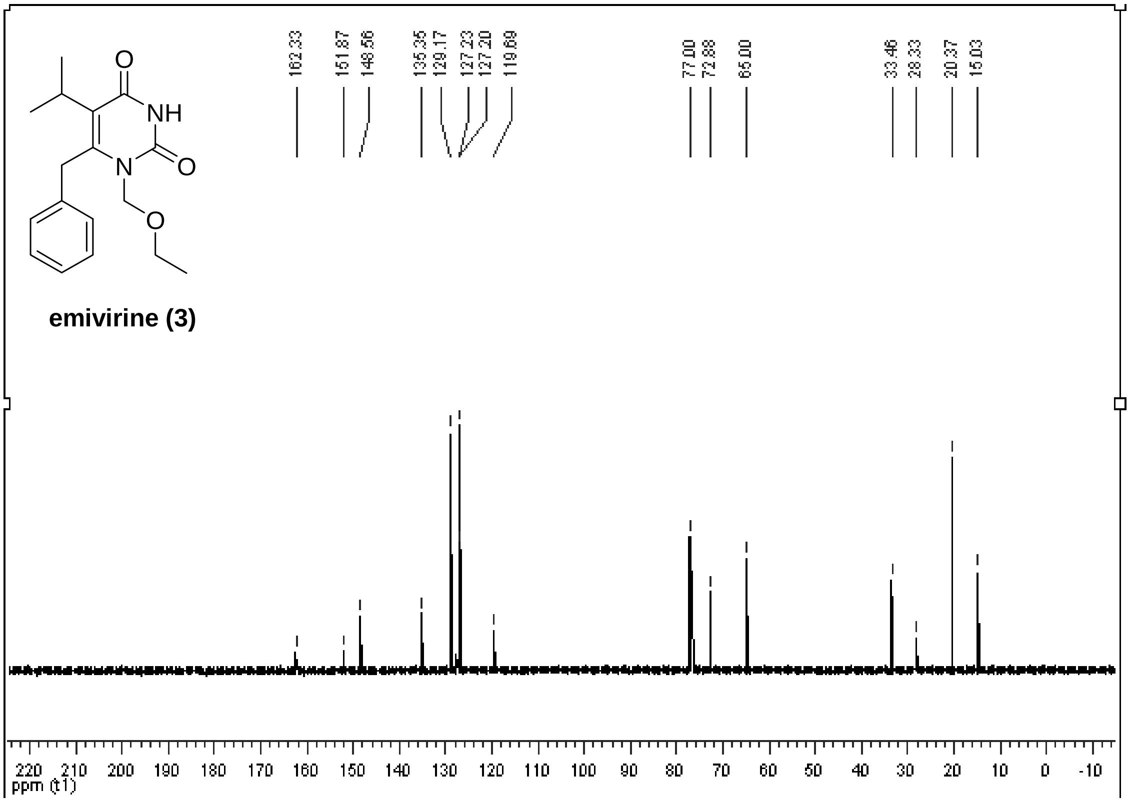
20


HN
O
N
H
O
8.18
7.94
7.38
7.29
7.20
7.19
3.82
3.03
1.31
1.29
0.94
0.97
2.82
1.00
2.00
1.01
6.00
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
ppm (t1)

20



emivirine (3)



emivirine (3)