Supplementary Information (ESI)

Microwave-assisted synthesis of potent PDE7 inhibitors containing a thienopyrimidin-4-amine scaffold

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Experimental details and characterization data for compounds 1–5 and 7

General information

Reagents of the highest commercial quality were purchased and used without further purification, unless stated otherwise. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60FS-254) using UV light to visualize the components. Column chromatography was performed using silica gel (60 F254, 70–200 mm) as the stationary phase. All NMR spectra were recorded on Varian Unity 200 and 300 spectrometers. Chemical shifts are quoted with reference to external $SiMe_4$. All melting points (mp) are uncorrected. The microwave synthesis was performed in a domestic microwave oven (Panasonic Inverter NN-F359W) using the Teflon disk described in ref. 23a and using 4 mL open glass vials (22 mm diameter). The energy supplied to the sample was calibrated as described in this reference. 25-mL Duran® bottles with polypropylene caps (purchased from Aldrich) inside a Heraeus T5060 oven were used to perform nucleophilic substitutions in parallel after testing that they withstood, without undergoing explosion or any liquid loss, 90 ºC for 24 h when filled with 12 mL of water. For the experiments described they were used at temperatures between 50-75 ºC, without stirring for 12 h, and no problems were observed. The following compounds have been described previously: **2aa**, **2ab**, **2ae–ai**, **2ak–ap**, **2ar**, **2as**, **2au–2bd** and **2bf–bk** from reference 1,[1] **3a**,[2] **3b**,[3] **3c**,[3] **3d**,[3] **4a**,[2] **4b**,[4] **4c**,[4] **4g**,[2] **4h**,[2] **4j**,[5] **4k**,[2] **4n**,[2] **4o**,[2] **4p**,[6] **4q**,[2] **5a–5k**,[1] **7a**,[7] **7b**,[8] **7c**,[9] **7d**,[10] **7e**,[11] **7f**,[12] **8b**,[13] **8c**,[14] **8d**,[15] **8e**,[16] **8f**,[17] **8h**[15] and **8i**.[18]

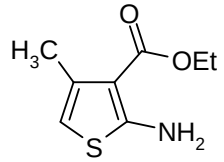
Preparation of starting thiophenes 7

Method B

A suspension of the corresponding ketone (0.1 mol), ethyl cyanoacetate (11.30 g, 10.6 mL, 0.1 mol), sulfur (3.52 g, 0.11 mol) and diethylamine (7.31 g, 10.3 mL, 0.1 mol) in pyridine (30 mL) was stirred at room temperature for 2 days. The black solution was concentrated under reduced pressure and the residue was dissolved in Et_2O and filtered through silica. The solvent was removed under reduced pressure and the residue was

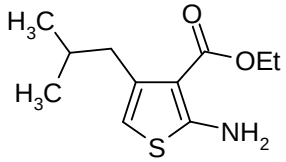
purified by flash chromatography [silica gel, hexane/EtOAc (8:2)] to give the pure product.

Ethyl 2-amino-4-methylthiophene-3-carboxylate 7a (12.02 g, 65%). Yellow solid; mp 76–78 ºC (lit.,[7] 76–78 ºC); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.33 (3 H, t, *J* = 7.2 Hz CH_3CH_2), 2.26 (3 H, s, CH_3), 4.24 (2 H, q, *J* = 7.2 Hz, CH_3CH_2), 5.90 (1 H, s), 6.00 (2 H, br s, NH_2).



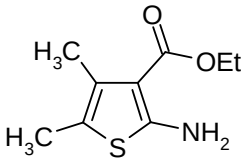
7a

Ethyl 2-amino-4-(2-methylpropyl)thiophene-3-carboxylate 7c (7.95 g, 35%). Yellow solid; mp 62–63 ºC (lit.,[9] 63–64 ºC).



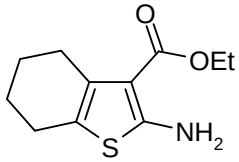
7c

Ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate 7d (16.50 g, 83%). Yellow solid; mp 90–91 ºC (lit.,[10] 91–92 ºC); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.37 (3 H, t, *J* = 7.2 Hz CH_3CH_2), 2.25 (6 H, br s, $2CH_3$), 4.38 (2 H, q, *J* = 7.2 Hz, CH_3CH_2), 8.00 (2 H, br s, NH_2).



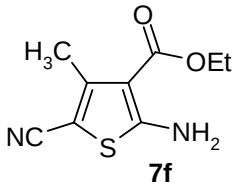
7d

Ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate 7e (18.05 g, 80%). Yellow solid; mp 111–113 ºC (lit.,[11] 111–115 ºC); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.31 (3 H, t, *J* = 7.1 Hz CH_3CH_2), 1.68–1.77 (4 H, m), 2.45–2.49 (2 H, m), 2.66–2.70 (2 H, m), 4.22 (2 H, q, *J* = 7.1 Hz, CH_3CH_2), 5.90 (2 H, br s, NH_2).



7e

Method C: Preparation of ethyl 2-amino-5-cyano-4-methylthiophene-3-carboxylate 7f. To a solution of 3-aminocrotonitrile (8.20 g, 0.1 mol) in ethanol (300 mL) were added sulfur (3.52 g, 0.11 mol), ethyl cyanoacetate (11.30 g, 10.6 mL, 0.1 mol) and a catalytic amount of piperidine. The mixture was carefully heated to 50–60 ºC and, when the exothermic process had finished, under reflux for 24 h. The mixture was cooled to room temperature and water was added. The resulting yellow solid was filtered off, dried under vacuum and recrystallized from ethanol. **7f** (14.70 g, 70%). Yellow solid; mp 192–193 ºC (from EtOH) (lit.,[12] 194 ºC); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.38 (3 H, t, *J* = 7.0 Hz CH_3CH_2), 2.49 (3 H, s, CH_3), 4.35 (2 H, q, *J* = 7.0 Hz, CH_3CH_2), 6.63 (2 H, br s, NH_2).



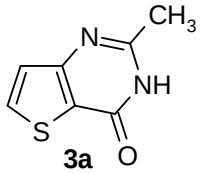
7f

Preparation of substituted thienopyrimidinones 3a–d and 4a–q using a microwave-assisted parallel synthesis approach

General procedure: Twenty 4 mL vials, each containing a homogenized mixture of the appropriate thioamide **8** (3 mmol) and amino-thiophene-carboxylates **6** and **7** as hydrochlorides (1 mmol) without solvent, were inserted into a Teflon disc as described. The samples were irradiated at 550 Watts power for 3.5 minutes (time related to the number of samples) and melting was observed along with the evolution of gas. The samples were allowed to cool to room temperature and each reaction mixture was dissolved in a mixture of hexane/AcOEt (8:2) (2 mL). Reaction mixtures were treated in a parallel manner in a Vac Master Station SPE, using for each vial an additional 1 mL

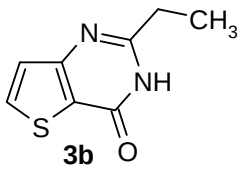
of a mixture of hexane/AcOEt (8:2) as eluent. The resulting solid thienopyrimidones were dried under vacuum and used in the next step without further purification.

2-Methyl-3*H*-thieno[3,2-*d*]pyrimidin-4-one 3a[2] (0.161 g, 97%). Yellow solid; mp > 240 ºC (lit.,[19] 242 ºC); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.57 (3 H, s, CH_3), 7.31 (1 H, d, *J* = 6.4 Hz), 7.81 (1 H, d, *J* = 6.4 Hz), 11.62 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 167.1 $[M + H]^+$.



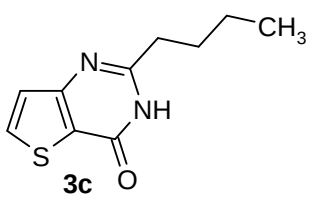
3a

2-Ethyl-3*H*-thieno[3,2-*d*]pyrimidin-4-one 3b[3] (0.137 g, 76%). Yellow solid; mp 230–235 ºC (lit.,[3] 233–237 ºC); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.23 (3 H, t, *J* = 7.5 Hz, $CH_2C\mathit{H_3}$), 2.84 (2 H, q, *J* = 7.5 Hz, $C\mathit{H_2}CH_3$), 7.31 (1 H, d, *J* = 6.4 Hz), 7.81 (1 H, d, *J* = 6.4 Hz), 11.82 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 181.1 $[M + H]^+$.



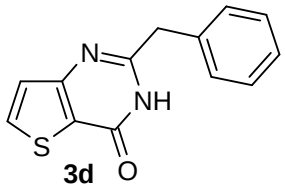
3b

2-Butyl-3*H*-thieno[3,2-*d*]pyrimidin-4-one 3c[3] (0.133 g, 64%). Yellow solid; δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.98 (3 H, t, *J* = 8.0 Hz, $CH_2C\mathit{H_3}$), 1.65–1.82 (4 H, m), 2.85 (2 H, t, *J* = 8.0 Hz), 7.31 (1 H, d, *J* = 6.4 Hz), 7.81 (1 H, d, *J* = 6.4 Hz), 11.75 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 209.1 $[M + H]^+$.



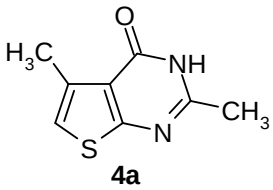
3c

2-Benzyl-3*H*-thieno[3,2-*d*]pyrimidin-4-one 3d[3] (0.186 g, 77%). Yellow solid; δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.08 (2 H, s, CH_2Ph), 7.24–7.80 (6 H, m), 7.81 (1 H, d, *J* = 6.3 Hz), 11.30 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 243.0 $[M + H]^+$.



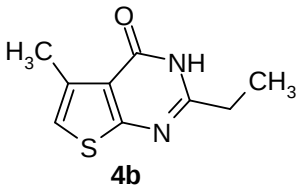
3d

2,5-Dimethyl-3*H*-thieno[2,3-*d*]pyrimidin-4-one 4a[2] (0.087 g, 48%). Yellow solid; mp >250 ºC (lit.,[2] 263 ºC); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.28 (3 H, s, CH_3), 2.46 (3 H, s, CH_3), 6.77 (1 H, s), 11.30 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 181.1 $[M + H]^+$.



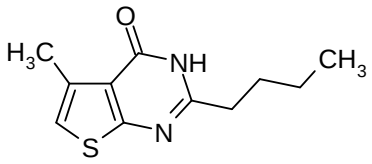
4a

2-Ethyl-5-methyl-3*H*-thieno[3,2-*d*]pyrimidin-4-one 4b[4] (0.109 g, 56%). Yellow solid; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.37 (3 H, t, *J* = 7.6 Hz, CH_2CH_3), 2.55 (3 H, s, CH_3), 2.76 (2 H, q, *J* = 7.6 Hz, CH_2CH_3), 6.67 (1 H, s), 11.34 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 195.5 $[M + H]^+$.



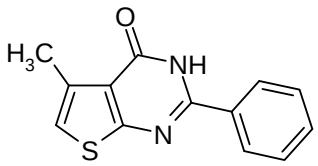
4b

2-Butyl-5-methyl-3*H*-thieno[2,3-*d*]pyrimidin-4-one 4c[4] (0.149 g, 67%). Brown solid; mp 233–235 ºC (lit.,[3] 233–237 ºC); δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.93 (3 H, t, *J* = 7.2 Hz, CH_2CH_3), 1.23–1.43 (2 H, m), 1.75–1.77 (2 H, m), 2.55 (3 H, s), 2.65–2.71 (2 H, m), 6.74 (1 H, s), 11.55 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 223.09 $[M + H]^+$.



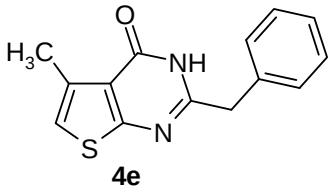
4c

5-Methyl-2-phenyl-3*H*-thieno[3,2-*d*]pyrimidin-4-one 4d (0.153 g, 63%). Brown solid; mp 223–227 ºC; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.63 (3 H, s, CH_3), 6.83 (1 H, s), 7.49–7.51 (3 H, m), 8.22 (2 H, d, *J* = 7.6 Hz), 11.87 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 243.04 $[M + H]^+$.



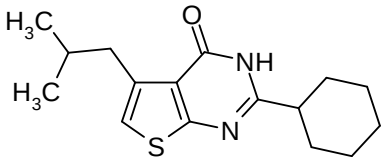
4d

2-Benzyl-5-methyl-3*H*-thieno[2,3-*d*]pyrimidin-4-one 4e (0.240 g, 94%). Yellow solid; mp > 250 ºC; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.56 (3 H, s, CH_3), 4.04 (2 H, s, CH_2Ph), 6.77 (1 H, s), 7.12–7.42 (5 H, m), 10.40 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 257.1 $[M + H]^+$.



4e

2-Cyclohexyl-5-(2-methylpropyl)-3*H*-thieno[2,3-*d*]pyrimidin-4-one 4f (0.234 g, 81%). Brown solid; mp > 250; δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.90 (6 H, d, *J* = 6.2 Hz, $2CH_3$), 0.93–0.98 (1 H, m), 1.21–1.99 (9 H, m), 2.09–2.14 (1 H, m), 2.50–2.53 (1 H, m), 3.01 (2 H, d, *J* = 5.8 Hz, CH_2CH), 6.70 (1H, br s), 12.66 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 291.1 $[M + H]^+$.



4f

5-(2-Methylpropyl)-2-phenyl-3*H*-thieno[2,3-*d*]pyrimidin-4-one 4g[2] (0.278 g, 98%). Yellow solid; δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.95 (6 H, d, *J* = 6.1 Hz, $2CH_3$), 2.01–2.15 (1 H, m), 2.95 (2 H, d, *J* = 5.8 Hz, C*H*$_2$CH), 6.89 (1 H, s), 7.15–8.10 (5 H, m), 11.85 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 285.1 $[M + H]^+$.

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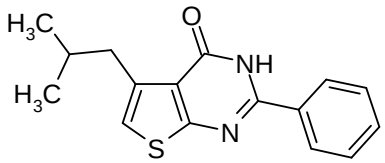
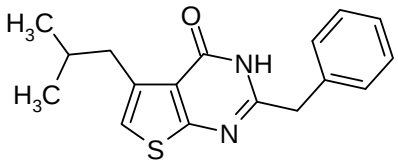


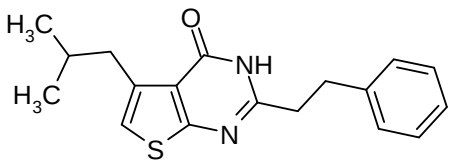
4g

2-Benzyl-5-(2-methylpropyl)-3*H*-thieno[2,3-*d*]pyrimidin-4-one 4h[2] (0.182 g, 61%). Yellow solid; δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.97 (6 H, d, *J* = 6.1 Hz, $2CH_3$), 1.99–2.18 (1 H, m), 2.79 (2 H, d, *J* = 5.8 Hz, C*H*$_2$CH), 4.01 (2 H, s, CH_2Ph), 6.78 (1 H, s), 7.20–7.43 (5 H, m), 10.60 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 299.0 $[M + H]^+$.



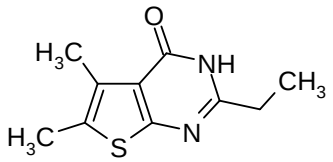
4h

5-(2-Methylpropyl)-2-phenethyl-3*H*-thieno[2,3-*d*]pyrimidin-4-one 4i (0.210 g, 67%). Yellow solid; δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.98 (6 H, d, *J* = 6.1 Hz, $2CH_3$), 1.83–2.20 (1 H, m), 2.65 (2 H, d, *J* = 5.8 Hz, C*H*$_2$CH), 3.30–3.40 (4 H, m), 6.88 (1 H, s), 7.12–7.18 (5 H, m), 12.10 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 313.0 $[M + H]^+$.



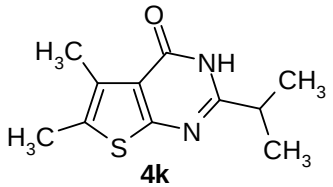
4i

2-Ethyl-5,6-dimethyl-3*H*-thieno[2,3-*d*]pyrimidin-4-one 4j[5] (0.131 g, 63%). Yellow solid; mp > 250 ºC (lit.,[5] 258–261 ºC); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.35 (3 H, t, *J* = 7.5 Hz, CH_2CH_3), 2.34 (3 H, s, CH_3), 2.51 (3 H, s, CH_3), 2.74 (2 H, q, *J* = 7.5 Hz, CH_2CH_3), 12.02 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 209.1 $[M + H]^+$.



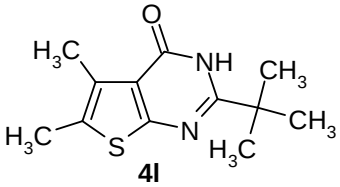
4j

5,6-Dimethyl-2-(1-methylethyl)-3*H*-thieno[2,3-*d*]pyrimidin-4-one 4k[2] (0.082 g, 37%). Yellow solid; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.34 (6 H, d, *J* = 6.1 Hz, $2CH_3$), 2.34 (3 H, s, CH_3), 2.44 (3 H, s, CH_3), 2.92 (1 H, hp, *J* = 6.1 Hz, CH), 10.85 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 223.1 $[M + H]^+$.



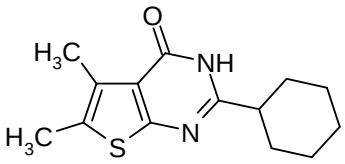
4k

5,6-Dimethyl-2-(1,1-dimethylethyl)-3*H*-thieno[2,3-*d*]pyrimidin-4-one 4l (0.031 g, 13%). Yellow solid; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.23 (9 H, s, $3CH_3$), 2.38 (3 H, s, CH_3), 2.47 (3 H, s, CH_3), 9.95 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 237.1 $[M + H]^+$.



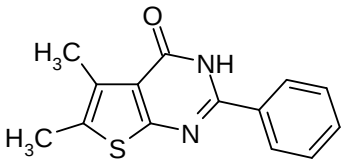
4l

2-Cyclohexyl-5,6-dimethyl-3*H*-thieno[2,3-*d*]pyrimidin-4-one 4m (0.212 mg, 81%). Yellow solid; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.31–1.88 (10 H, m), 2.38 (3 H, s, CH_3), 2.48 (3 H, s, CH_3), 2.81–2.93 (1 H, m), 10.22 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 263.1 $[M + H]^+$.



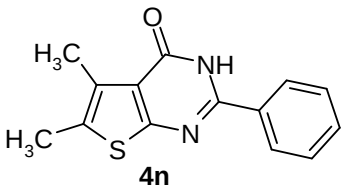
4m

5,6-Dimethyl-2-phenyl-3*H*-thieno[2,3-*d*]pyrimidin-4-one 4n[2] (0.059 g, 23%). Yellow solid; mp > 250 ºC (lit.,[2] 298 ºC); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.37 (3 H, s, CH_3), 2.42 (3 H, s, CH_3), 7.45–7.55 (3 H, m), 8.80–9.00 (2 H, m), 12.50 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 257.1 $[M + H]^+$.



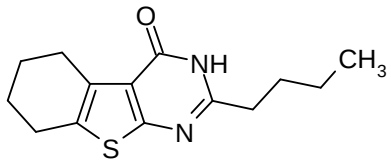
4n

2-Benzyl-5,6-dimethyl-3*H*-thieno[2,3-*d*]pyrimidin-4-one 4o[2] (0.075 g, 28%). Yellow solid; mp > 250 ºC (lit.,[2] 268–270 ºC); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.39 (3 H, s, CH_3), 2.46 (3 H, s, CH_3), 4.04 (2 H, s, CH_2), 7.29–7.35 (5 H, m), 10.50 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 271.1 $[M + H]^+$.



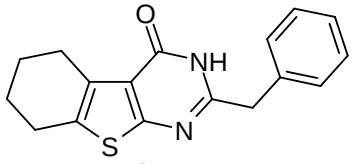
4n

2-Butyl-5,6,7,8-tetrahydro-3*H*-benzo[4,5]thieno[2,3-*d*]pyrimidin-4-one 4p[6] (0.131 g, 50%). Yellow solid; mp 205–208 ºC (lit.,[6] 210 ºC); δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.94 (3 H, t, *J* = 7.2 Hz, CH_3), 1.36–1.47 (2 H, m), 1.64–1.85 (6 H, m), 2.66–2.74 (4 H, m), 2.98–3.06 (2 H, m), 11.39 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 263.1 $[M + H]^+$.



4p

2-Benzyl-5,6,7,8-tetrahydro-3*H*-benzo[4,5]thieno[2,3-*d*]pyrimidin-4-one 4q[2] (0.163 g, 55%). Yellow solid; mp > 250 ºC (lit.,[2] 265–268 ºC); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.75–1.84 (4 H, m), 2.73–2.80 (2 H, m), 2.96–3.10 (2 H, m), 4.01 (2 H, s, CH_2), 7.31–7.50 (5 H, m), 11.20 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 297.0 $[M + H]^+$.

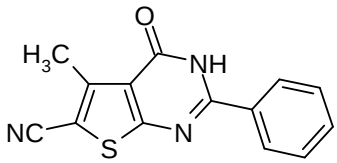


4q

Preparation of 6-cyano-substituted thienopyrimidin-4-ones 5 in the presence of HCl gas

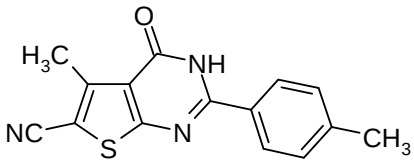
General procedure[20]*:* A solution of the thiophene derivative **7f** (0.210 g, 1 mmol) and the corresponding benzonitrile **9** (1.5 mmol) in dry dioxane (7 mL) was cooled to 0 ºC and dry HCl(g) was bubbled through for 2 h (until saturation) and the reaction was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the residue was triturated with diethyl ether. The resulting solid thienopyrimidones were triturated with diethyl ether, dried under vacuum and used in the next step without further purification.

5-Methyl-4-oxo-2-phenyl-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carbonitrile 5a[1] (0.246 g, 92%). Yellow solid; υ_{max}(KBr) /cm^{-1} 3415, 2219 (conj. CN), 1663, 1539, 700; δ_H (300 MHz; DMSO-d_6; Me_4Si) 2.73 (3 H, s, CH_3), 7.61–7.66 (3 H, m), 8.21 (2 H, d, *J* = 6.6 Hz), 13.02 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 268.1 $[M + H]^+$.



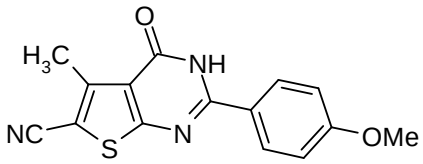
5a

5-Methyl-2-(4-methylphenyl)-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carbonitrile 5b[1] (0.202 g, 72%). Yellow solid; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.45 (3 H, s, CH_3), 2.78 (3 H, s, CH_3), 7.29 (2 H, d, *J* = 7.7 Hz), 7.97 (2 H, d, *J* = 7.7 Hz), 10.30 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 282.1 $[M + H]^+$.



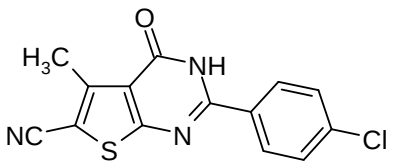
5b

2-(4-Methoxyphenyl)-5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carbonitrile 5c[1] (0.288 g, 97%). Yellow solid; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.56 (3 H, s, CH_3), 3.88 (3 H, s, OCH_3), 6.91 (2 H, d, *J* = 8.4 Hz), 7.84 (2 H, d, *J* = 8.4 Hz), 10.21 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 298.1 $[M + H]^+$.



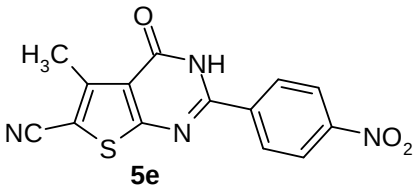
5c

2-(4-Chlorophenyl)-5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carbonitrile 5d[1] (0.253 g, 84%). Yellow solid; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.78 (3 H, s, CH_3), 7.41 (2 H, d, *J* = 8.7 Hz), 7.73 (2 H, d, *J* = 8.7 Hz), 13.16 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 302.1 $[M + H]^+$.



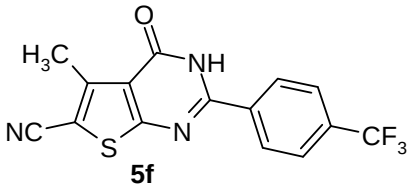
5d

5-Methyl-2-(4-nitrophenyl)-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carbonitrile 5e[1] (0.147 g, 47%). Yellow solid; δ_H (300 MHz; DMSO-d_6; Me_4Si) 2.69 (3 H, s, CH_3), 8.08 (2 H, d, J = 8.6 Hz), 8.29 (2 H, d, J = 8.6 Hz), 13.26 (1 H, br s, NH); MS (ES, pos. mode) m/z = 313.1 $[M + H]^+$.



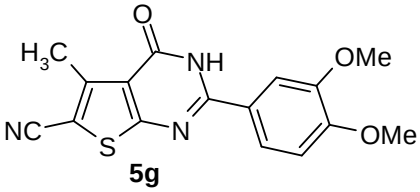
5e

5-Methyl-4-oxo-2-[4-(trifluoromethyl)phenyl)]-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carbonitrile 5f[1] (0.271 g, 81%). Yellow solid; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.56 (3 H, s, CH_3), 7.65 (2 H, d, J = 8.0 Hz), 8.12 (2 H, d, J = 8.0 Hz), 13.00 (1 H, br s, NH); MS (ES, pos. mode) m/z = 313.1 $[M + H]^+$.



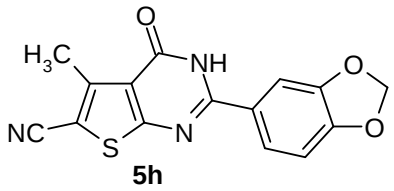
5f

2-(3,4-Dimethoxyphenyl)-5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carbonitrile 5g[1] (0.320 g, 98%). Yellow solid; δ_H (300 MHz; DMSO-d_6; Me_4Si) 2.56 (3 H, s, CH_3), 3.84 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 6.94 (1 H, d, J = 8.4 Hz), 8.04 (1 H, s), 8.09 (1 H, d, J = 8.4 Hz), 12.62 (1 H, br s, NH); MS (ES, pos. mode) m/z = 328.1 $[M + H]^+$.



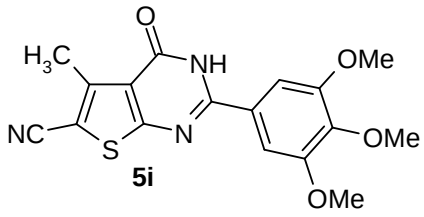
5g

2-(1,3-Benzodioxol-5-yl)-5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carbonitrile 5h[1] (0.068 g, 22%). Yellow solid; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.65 (3 H, s, CH_3), 6.15 (2 H, s, OCH_2O), 7.08 (1 H, d, J = 7.5 Hz), 7.70 (1 H, s), 7.79 (1 H, d, J = 7.5 Hz), 13.00 (1 H, br s, NH); MS (ES, pos. mode) m/z = 312.1 $[M + H]^+$.



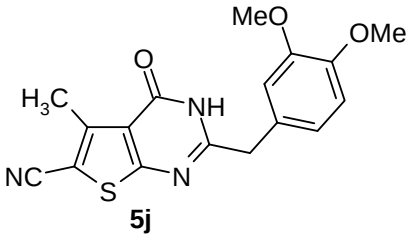
5h

5-Methyl-4-oxo-2-(3,4,5-trimethoxyphenyl)-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carbonitrile 5i[1] (0.225 g, 63%). Yellow solid; mp > 250 ºC; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.76 (3 H, s, CH_3), 3.95 (3 H, s, OCH_3), 3.98 (6 H, s, $2OCH_3$), 7.28 (2 H, s), 12.48 (1 H, br s, NH); MS (ES, pos. mode) m/z = 358.1 $[M + H]^+$.



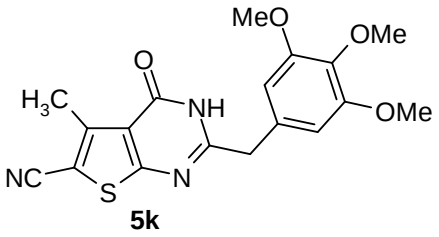
5i

2-(3,4-Dimethoxybenzyl)-5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carbonitrile 5j[1] (0.160 g, 47%). Yellow solid; mp > 250 ºC; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.83 (3 H, s, CH_3), 3.79 (3 H, s, OCH_3), 3.83 (3 H, s, OCH_3), 4.50 (2 H, s, CH_2), 6.73–6.77 (1 H, m), 6.89–6.99 (2 H, m), 12.40 (1 H, br s, NH); MS (ES, pos. mode) m/z = 342.1 $[M + H]^+$.



5j

5-Methyl-4-oxo-2-(3,4,5-trimethoxybenzyl)-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carbonitrile 5k[1] (0.256 g, 69%). Yellow solid; mp > 250 ºC; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.85 (3 H, s, CH_3), 3.82 (3 H, s, OCH_3), 3.83 (6 H, s, $2OCH_3$), 4.23 (2 H, s, CH_2), 6.27 (2 H, s), 9.80 (1 H, br s, NH); MS (ES, pos. mode) *m*/*z* = 372.1 $[M + H]^+$.



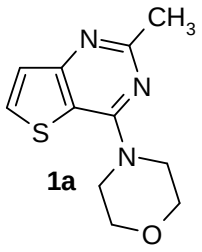
5k

Preparation of libraries of thieno[3,2-*d*]pyrimidin-4-amines 1 and thieno[2,3-*d*]pyrimidin-4-amines 2

General procedure: A solution of the corresponding thienopyrimid-4-one **3**–**5** (0.1 mmol) in phosphorus oxychloride (4 mL) was heated under reflux for 2–12 h. As soon as the starting material had been consumed (TLC analysis), the mixture was allowed to cool down to room temperature and phosphorus oxychloride was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL) and the organic phase was washed successively with saturated aqueous $NaHCO_3$, water and saturated aqueous sodium chloride. The organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under vacuum. The corresponding 4-chloro-derivative **10** or **11** was obtained and was used in the next step without further purification. The chloro-derivative **10** or **11** was dissolved in ethanol (12 mL) in a Duran® bottle and the corresponding amine (0.13 mmol) was added. The bottle was closed with a polypropylene cap and heated in an Heraeus T5060 oven (T = 50–75 ºC) for 2–12 h. The mixture was allowed to cool down to room temperature, the solvent was removed under reduced pressure and the residue was purified by column chromatography [hexane/EtOAc (4:6)] to give the corresponding thienopyrimidin-4-yl-amines **1** and **2**.

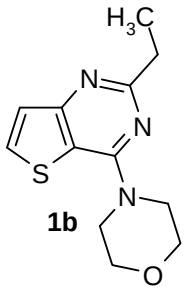
2-Methyl-4-morpholin-4-yl-thieno[3,2-*d*]pyrimidine 1a (20.0 mg, 85%). Yellow solid; mp > 250 ºC; elemental analysis: Found: C, 55.95; H, 5.4; N, 17.94. Calc. for $C_{11}H_{13}N_3OS$: C, 56.15; H, 5.6; N, 17.87%; υ_{max}(KBr) /cm^{-1} 2959, 1665, 1603, 1538,

1493, 1364, 1305, 1262, 930, 846, 751, 699; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.56 (3 H, s, CH_3), 3.43–3.47 (4 H, m), 3.85–3.90 (4 H, m), 7.35 (1 H, d, *J* = 5.4 Hz), 7.65 (1 H, d, *J* = 5.4 Hz); MS (ES, pos. mode) *m*/*z* = 236.1 $[M + H]^+$.



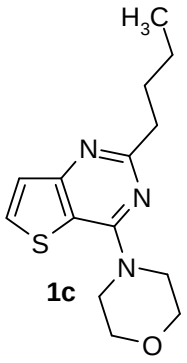
1a

2-Ethyl-4-morpholin-4-yl-thieno[3,2-*d*]pyrimidine 1b (21.0 mg, 84%). Yellow solid; mp > 250 ºC; elemental analysis: Found: C, 58.00; H, 6.4; N, 17.01. Calc. for $C_{12}H_{15}N_3OS$: C, 57.81; H, 6.1; N, 16.85%; υ_{max}(KBr) /cm^{-1} 2957, 2926, 1683, 1538, 1490, 1241, 1276, 1264, 1119, 1017, 798; δ_H (200 MHz; $CDCl_3$; Me_4Si) 1.32 (3 H, t, *J* = 7.6 Hz, $CH_2C\mathit{H}_3$), 2.83 (2 H, q, *J* = 7.6 Hz, CH_2CH_3), 3.79–3.85 (4 H, m), 3.92–3.99 (4 H, m), 7.35 (1 H, d, *J* = 5.5 Hz), 7.66 (1 H, d, *J* = 5.5 Hz); MS (ES, pos. mode) *m*/*z* = 250.1 $[M + H]^+$.



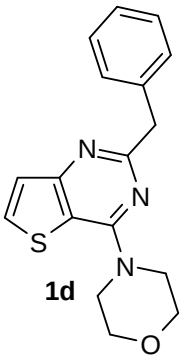
1b

2-Butyl-4-morpholin-4-yl-thieno[3,2-*d*]pyrimidine 1c (23.8 mg, 86%). Yellow solid; mp > 250 ºC; elemental analysis: Found: C, 60.75; H, 7.1; N, 15.01. Calc. for $C_{14}H_{19}N_3OS$: C, 60.62; H, 6.9; N, 15.15%; υ_{max}(KBr) /cm^{-1} 3066, 2971, 2915, 2851, 1682, 1537, 1493, 1448, 1431, 1257, 1217, 1117, 1019, 807, 790, 729, 662; δ_H (200 MHz; $CDCl_3$; Me_4Si) 0.92 (3 H, t, *J* = 7.6 Hz, CH_3), 1.30–1.49 (2 H, m), 1.70–1.86 (2 H, m), 2.82 (2 H, t, *J* = 7.7 Hz, $ArCH_2$), 3.80–3.86 (4 H, m), 3.94–3.99 (4 H, m), 7.36 (1 H, d, *J* = 5.6 Hz), 7.67 (1 H, d, *J* = 5.6 Hz); MS (ES, pos. mode) *m*/*z* = 278.1 $[M + H]^+$.



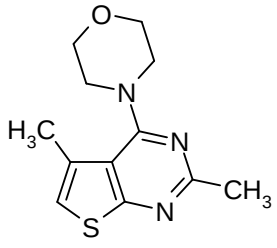
1c

2-Benzyl-4-morpholin-4-yl-thieno[3,2-*d*]pyrimidine 1d (2.8 mg, 9%). Yellow solid; mp > 250 ºC; elemental analysis: Found: C, 65.76; H, 5.2; N, 13.20. Calc. for $C_{17}H_{17}N_3OS$: C, 65.57; H, 5.5; N, 13.49%; δ_H (300 MHz; $CDCl_3$; Me_4Si) 3.78–3.82 (4 H, m), 3.91–3.95 (4 H, m), 4.14 (2 H, s, CH_2), 7.17–7.28 (3 H, m), 7.34–7.44 (3 H, m), 7.67 (1 H, d, J = 5.6 Hz); MS (ES, pos. mode) m/z = 312.1 $[M + H]^+$.



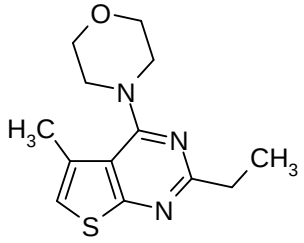
1d

2,5-Dimethyl-4-morpholin-4-yl-thieno[2,3-*d*]pyrimidine 2a (10.7 mg, 43%). Yellow solid; mp > 250 ºC; elemental analysis: Found: C, 58.05; H, 6.0; N, 17.01. Calc. for $C_{12}H_{15}N_3OS$: C, 57.81; H, 6.1; N, 16.85%; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.50 (3 H, s, CH_3), 2.61 (3 H, s, CH_3), 3.30–3.40 (4 H, m), 3.80–3.90 (4 H, m), 6.86 (1 H, s); MS (ES, pos. mode) m/z = 250.1 $[M + H]^+$.



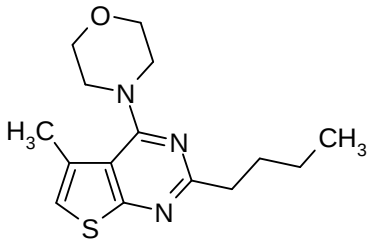
2a

2-Ethyl-5-methyl-4-morpholin-4-yl-thieno[2,3-*d*]pyrimidine 2b (3.7 mg, 14%). Yellow solid; mp > 250 ºC; elemental analysis: Found: C, 59.08; H, 6.2; N, 16.11. Calc. for $C_{13}H_{17}N_3OS$: C, 59.29; H, 6.5; N, 15.96%; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.34 (3 H, t, *J* = 7.5 Hz, CH_2CH_3), 2.52 (3 H, s, CH_3), 2.89 (2 H, q, *J* = 7.5 Hz, CH_2CH_3), 3.40–3.43 (4 H, m), 3.83–3.86 (4 H, m), 6.88 (1 H, s); MS (ES, pos. mode) *m*/*z* = 264.1 $[M + H]^+$.



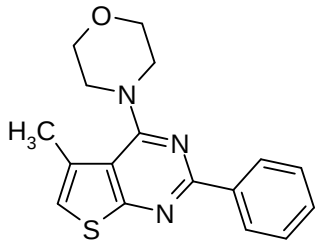
2b

2-Butyl-5-methyl-4-morpholin-4-yl-thieno[2,3-*d*]pyrimidine 2c (13.1 mg, 45%). Yellow solid; mp = 245–247 ºC; elemental analysis: Found: C, 62.09; H, 7.2; N, 14.11. Calc. for $C_{15}H_{21}N_3OS$: C, 61.82; H, 7.3; N, 14.42%; δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.93 (3 H, t, *J* = 7.4 Hz, CH_2CH_3), 1.24–1.42 (2 H, m), 1.75–1.79 (2 H, m), 2.52 (3 H, s, CH_3), 2.86 (2 H, t, *J* = 7.6 Hz, $ArCH_2$), 3.39–3.44 (4 H, m), 3.83–3.87 (4 H, m), 6.87 (1 H, s); δ_C (75 MHz; $CDCl_3$; Me_4Si) 14.1, 16.9, 22.6, 30.7, 38.7, 51.0 (2C), 66.6 (2C), 118.1, 118.8, 129.0, 129.1, 165.1, 165.9; MS (ES, pos. mode) *m*/*z* = 292.1 $[M + H]^+$.



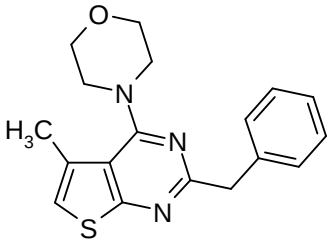
2c

5-Methyl-4-morpholin-4-yl-2-phenylthieno[2,3-*d*]pyrimidine 2d (19.6 mg, 63%). Yellow solid; mp = 213–215 ºC; elemental analysis: Found: C, 65.78; H, 5.2; N, 13.12. Calc. for $C_{17}H_{17}N_3OS$: C, 65.57; H, 5.5; N, 13.49%; δ_H (200 MHz; $CDCl_3$; Me_4Si) 2.56 (3 H, s, CH_3), 3.51–3.54 (4 H, m), 3.89–3.93 (4 H, m), 6.97 (1 H, s), 7.44–7.46 (3 H, m), 8.47–8.49 (2 H, m); MS (CI) *m*/*z* = 312 (100) $[M + H]^+$.



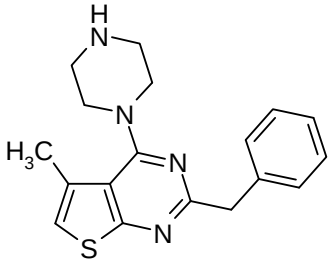
2d

2-Benzyl-5-methyl-4-morpholin-4-yl-thieno[2,3-*d*]pyrimidine 2e (26.6 mg, 82%). Yellow solid; mp > 250 ºC; elemental analysis: Found: C, 66.70; H, 5.8; N, 13.11. Calc. for $C_{18}H_{19}N_3OS$: C, 66.43; H, 5.9; N, 12.91%; υ $_{max}$(KBr) /cm^{-1} 3401, 3060, 3028, 2930, 1724, 1679, 1606, 1515, 1464, 1262, 1115, 1029, 992, 729, 698; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.53 (3 H, s, CH_3), 3.44–3.47 (4 H, m), 3.83–3.87 (4 H, m), 4.22 (2 H, s, CH_2), 6.93 (1 H, s), 7.19–7.46 (5 H, m); MS (CI) *m*/*z* = 326 (100) $[M + H]^+$.



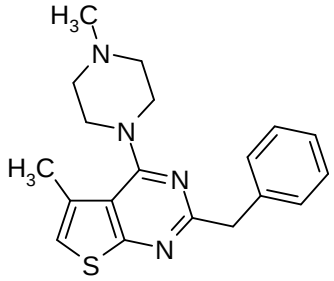
2e

2-Benzyl-5-methyl-4-piperazin-1-yl-thieno[2,3-*d*]pyrimidine 2f (10.4 mg, 32%). Yellow solid; mp = 198–200 ºC; elemental analysis: Found: C, 66.70; H, 5.9; N, 17.11. Calc. for $C_{18}H_{20}N_4S$: C, 66.64; H, 6.2; N, 17.27%; υ $_{max}$(KBr) /cm^{-1} 3417, 2922, 2847, 1538, 1448, 1363, 1261, 992, 764, 695; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.50 (3 H, s, CH_3), 2.98–3.15 (4 H, m), 3.36–3.48 (4 H, m), 4.17 (2 H, s, CH_2), 6.86 (1 H, s), 7.17 (1 H, t, *J* = 7.5 Hz), 7.24–7.29 (2 H, m), 7.40 (2 H, t, *J* = 7.3 Hz); MS (CI) *m*/*z* = 325 (100) $[M + H]^+$.



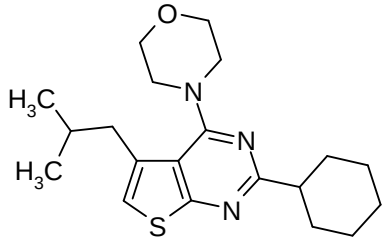
2f

2-Benzyl-5-methyl-4-(4-methylpiperazin-1-yl)-thieno[2,3-*d*]pyrimidine 2g (6.1 mg, 18%). Yellow solid; mp = 187–189 ºC; elemental analysis: Found: C, 67.70; H, 6.2; N, 16.11. Calc. for $C_{19}H_{22}N_4S$: C, 67.42; H, 6.5; N, 16.55%; υ_{max}(KBr) /cm^{-1} 3446, 3028, 2930, 2847, 2796, 1662, 1538, 1493, 1366, 1264, 1140, 1100, 1003, 909, 728; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.34 (3 H, s, CH_3), 2.49 (3 H, s, CH_3), 2.45–2.55 (4 H, m), 3.36–3.48 (4 H, m), 4.18 (2 H, s, CH_2), 6.87 (1 H, s), 7.15–7.43 (5 H, m); MS (CI) *m*/*z* = 339 (100) $[M + H]^+$.



2g

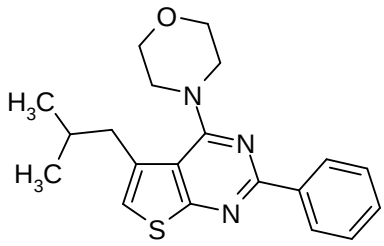
2-Cyclohexyl-5-(2-methylpropyl)-4-morpholin-4-yl-thieno[2,3-*d*]pyrimidine 2h (16.1 mg, 45%). White solid; mp = 176–178 ºC; elemental analysis: Found: C, 66.70; H, 7.9; N, 11.71. Calc. for $C_{20}H_{29}N_3OS$: C, 66.81; H, 8.1; N, 11.69%; δ_H (200 MHz; $CDCl_3$; Me_4Si) 0.86 (6 H, d, *J* = 6.6 Hz, $2CH_3$), 1.23–2.03 (11 H, m), 2.70 (2 H, d, *J* = 7.2 Hz, $ArCH_2$), 2.72–2.78 (1 H, m), 3.35–3.39 (4 H, m), 3.83–3.87 (4 H, m), 6.88 (1 H, s); MS (ES, pos. mode) *m*/*z* = 360.2 $[M + H]^+$.



2h

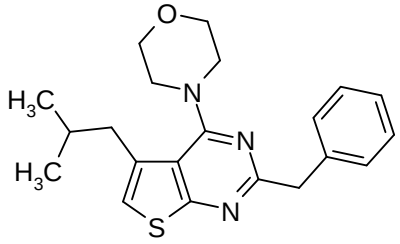
5-(2-Methylpropyl)-4-morpholin-4-yl-2-phenylthieno[2,3-*d*]pyrimidine 2i (4.2 mg, 12%). White solid; mp = 112–114 ºC; elemental analysis: Found: C, 68.07; H, 6.9; N, 11.71. Calc. for $C_{20}H_{23}N_3OS$: C, 67.96; H, 6.6; N, 11.89%; δ_H (200 MHz; $CDCl_3$; Me_4Si) 0.86 (6 H, d, *J* = 6.6 Hz, $2CH_3$), 1.85–2.03 (1 H, m), 2.75 (2 H, d, *J* = 7.1 Hz,

$ArCH_2$), 3.45–3.55 (4 H, m), 3.85–3.95 (4 H, m), 6.98 (1 H, s), 7.42–7.49 (3 H, m), 8.49 (2 H, dd, *J* = 7.9, 3.4 Hz); δ_C (50 MHz; $CDCl_3$; Me_4Si) 22.4 (2C), 29.7, 40.2, 51.1 (2C), 66.6 (2C), 119.8, 120.3, 128.0, 128.1 (2C), 128.3 (2C), 130.1, 134.0, 136.4, 159.3, 162.9; MS (CI) *m*/*z* = 354 (100) $[M + H]^+$.



2i

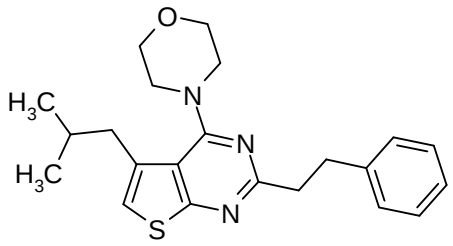
2-Benzyl-5-(2-methylpropyl)-4-morpholin-4-yl-thieno[2,3-*d*]pyrimidine 2j (23.1 mg, 63%). White solid; mp = 129–131 ºC; elemental analysis: Found: C, 68.43; H, 7.1; N, 11.70. Calc. for $C_{21}H_{25}N_3OS$: C, 68.63; H, 6.9; N, 11.43%; δ_H (200 MHz; $CDCl_3$; Me_4Si) 0.77 (6 H, d, *J* = 6.6 Hz, $2CH_3$), 1.80–1.96 (1 H, m), 2.62 (2 H, d, *J* = 7.4 Hz, $ArCH_2$), 3.28–3.30 (4 H, m), 3.72–3.76 (4 H, m), 4.12 (2 H, s, CH_2), 6.83 (1 H, s), 7.10–7.37 (5 H, m); δ_C (50 MHz; $CDCl_3$; Me_4Si) 22.4 (2C), 29.3, 40.1, 45.4, 51.0 (2C), 66.5 (2C), 118.0, 119.5, 126.1, 127.3, 128.1 (2C), 129.2 (2C), 133.5, 138.6, 162.8, 170.5; MS (CI) *m*/*z* = 368 (100) $[M + H]^+$.



2j

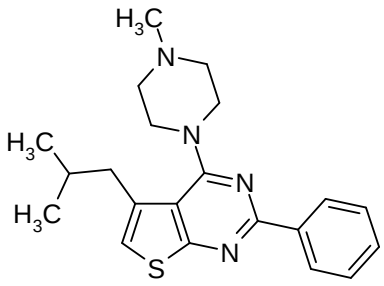
5-(2-Methylpropyl)-4-morpholin-4-yl-2-phenethyl-thieno[2,3-*d*]pyrimidine 2k (16.8 mg, 44%). White solid; mp = 118–120 ºC; elemental analysis: Found: C, 69.45; H, 6.9; N, 11.30. Calc. for $C_{22}H_{27}N_3OS$: C, 69.26; H, 7.1; N, 11.01%; δ_H (200 MHz; $CDCl_3$; Me_4Si) 0.78 (6 H, d, *J* = 6.6 Hz, $2CH_3$), 1.83–1.95 (1 H, m), 2.64 (2 H, d, *J* = 7.2 Hz, $ArCH_2$), 3.09–3.16 (4 H, m), 3.28–3.30 (4 H, m), 3.74–3.78 (4 H, m), 6.83 (1 H, s), 7.06–7.14 (5 H, m); δ_C (50 MHz; $CDCl_3$; Me_4Si) 22.4 (2C), 29.3, 34.5, 40.1, 40.4, 51.0

(2C), 66.5 (2C), 117.7, 119.3, 125.7, 128.1 (2C), 128.3, 128.7 (2C), 133.6, 141.6, 163.1, 163.6; MS (CI) *m*/*z* = 382 (100) $[M + H]^+$.



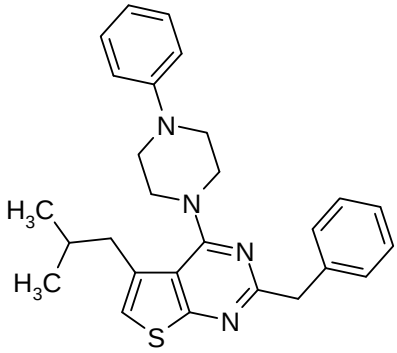
2k

4-(4-Methylpiperazin-1-yl)-5-(2-methylpropyl)-2-phenylthieno[2,3-*d*]pyrimidine 2l (4.4 mg, 12%). White solid; mp = 237–239 ºC; elemental analysis: Found: C, 69.02; H, 7.4; N, 15.62. Calc. for $C_{21}H_{26}N_4S$: C, 68.82; H, 7.1; N, 15.29%; δ_H (200 MHz; $CDCl_3$; Me_4Si) 0.87 (6 H, d, *J* = 6.6 Hz, $2CH_3$), 1.97–2.01 (1 H, m), 2.39 (3 H, s, CH_3), 2.64 (4 H, t, *J* = 4.4 Hz), 2.78 (2 H, d, *J* = 7.1 Hz, $ArCH_2$), 3.55 (4 H, t, *J* = 4.4 Hz), 6.97 (1 H, s), 7.44–7.48 (3 H, m), 8.50 (2 H, dd, *J* = 7.4, 4.1 Hz); MS (ES, pos. mode) *m*/*z* = 367.1 $[M + H]^+$.



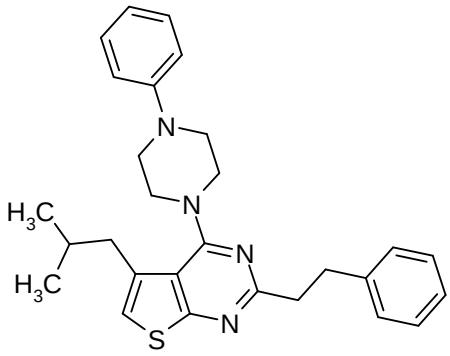
2l

2-Benzyl-5-(2-methylpropyl)-4-(4-phenylpiperazin-1-yl)thieno[2,3-*d*]pyrimidine 2m (26.0 mg, 57%). White solid; mp = 214–216 ºC; elemental analysis: Found: C, 73.56; H, 6.8; N, 12.92. Calc. for $C_{27}H_{30}N_4S$: C, 73.27; H, 6.9; N, 12.66%; δ_H (200 MHz; $CDCl_3$; Me_4Si) 0.75 (6 H, d, *J* = 6.6 Hz, $2CH_3$), 1.86–1.90 (1 H, m), 2.68 (2 H, d, *J* = 7.2 Hz, $ArCH_2$), 3.22–3.27 (4 H, m), 3.42–3.47 (4 H, m), 4.11 (2 H, s, CH_2), 6.79–6.92 (4 H, m), 7.12–7.27 (5 H, m), 7.36–7.40 (2 H, m); MS (CI) *m*/*z* = 443 (100) $[M + H]^+$.



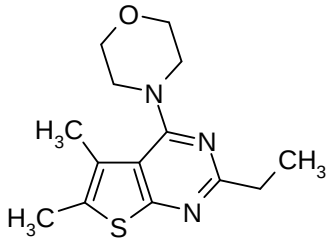
2m

5-(2-Methylpropyl)-2-phenethyl-4-(4-phenylpiperazin-1-yl)thieno[2,3-*d*]pyrimidine 2n (24.7 mg, 54%). White solid; mp = 151–153 ºC; elemental analysis: Found: C, 73.44; H, 7.0; N, 11.95. Calc. for $C_{28}H_{32}N_4S$: C, 73.65; H, 7.1; N, 12.27%; δ_H (200 MHz; $CDCl_3$; Me_4Si) 0.77 (6 H, d, *J* = 6.6 Hz, $2CH_3$), 1.83–1.97 (1 H, m), 2.71 (2 H, d, *J* = 7.2 Hz, $ArCH_2$), 3.12–3.16 (4 H, m), 3.25–3.29 (4 H, m), 3.44–3.47 (4 H, m), 6.79–6.93 (4 H, m), 7.05–7.27 (7 H, m); MS (ES, pos. mode) *m*/*z* = 457.1 $[M + H]^+$.



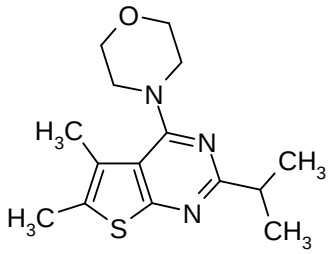
2n

2-Ethyl-5,6-dimethyl-4-morpholin-4-yl-thieno[2,3-*d*]pyrimidine 2o (17.4 mg, 63%). Yellow oil; δ_H (200 MHz; $CDCl_3$; Me_4Si) 1.30 (3 H, t, *J* = 7.4 Hz, CH_3CH_2), 2.37 (6 H, s, $2CH_3$), 2.84 (2 H, q, *J* = 7.4 Hz, CH_3CH_2), 3.35 (4 H, t, *J* = 4.6 Hz), 3.82 (4 H, t, *J* = 4.6 Hz); δ_C (50 MHz; $CDCl_3$; Me_4Si) 12.8, 13.7, 13.8, 32.1, 50.8, 66.5, 119.1, 119.8, 123.7, 130.7, 161.8, 164.7; δ_C (50 MHz; $CDCl_3$; Me_4Si) 12.8, 13.7, 13.8, 32.1, 50.8 (2C), 66.5 (2C), 119.1, 119.8, 123.7, 130.7, 161.8, 164.7; MS (CI) *m*/*z* = 278 (100) $[M + H]^+$.



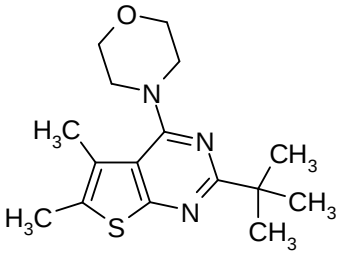
2o

5,6-Dimethyl-2-(1-methylethyl)-4-morpholin-4-yl-thieno[2,3-*d*]pyrimidine 2p (7.0 mg, 24%). Yellow oil; δ_H (200 MHz; $CDCl_3$; Me_4Si) 1.30 (6 H, d, J = 6.6 Hz, $2CH_3$), 2.37 (6 H, br s, $2CH_3$), 3.09 (1 H, hp, J = 6.6 Hz, CH), 3.36–3.40 (4 H, m), 3.81–3.85 (4 H, m); δ_C (50 MHz; $CDCl_3$; Me_4Si) 13.7, 13.9, 21.8 (2C), 37.1, 50.8 (2C), 66.5 (2C), 119.1, 123.6, 128.7, 130.7, 161.8, 168.0; MS (CI) m/z = 292 (100) $[M + H]^+$.



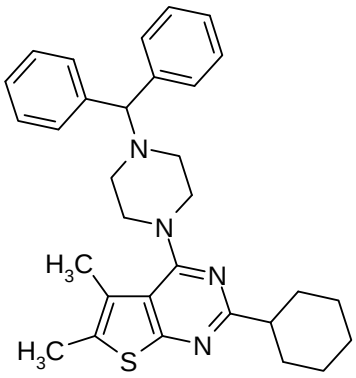
2p

5,6-Dimethyl-2-(1,1-dimethylethyl)-4-morpholin-4-yl-thieno[2,3-*d*]pyrimidine 2q (7.9 mg, 26%). White solid; mp = 70–71 ºC; elemental analysis: Found: C, 70.13; H, 7.6; N, 13.76. Calc. for $C_{16}H_{23}N_3OS$: C, 62.92; H, 7.6; N, 13.76%; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.40 (9 H, s, $3CH_3$), 2.41 (3 H, s, CH_3), 2.42 (3 H, s, CH_3), 3.41 (4 H, t, J = 4.4 Hz), 3.86 (4 H, t, J = 4.4 Hz); MS (ES, pos. mode) m/z = 306.3 $[M + H]^+$.



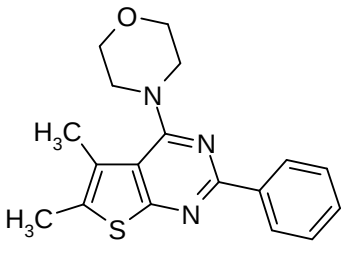
2q

4-(4-Benzhydrylpiperazin-1-yl)-2-cyclohexyl-5,6-dimethylthieno[2,3-*d*]pyrimidine 2r (8.9 mg, 18%). White solid; mp = 243–245 ºC; elemental analysis: Found: C, 75.11; H, 7.5; N, 11.43. Calc. for $C_{31}H_{36}N_4S$: C, 74.96; H, 7.3; N, 11.28%; δ_H (200 MHz; $CDCl_3$; Me_4Si) 1.37–1.86 (8 H, m), 1.95–2.02 (2 H, m), 2.36 (3 H, s, CH_3), 2.39 (3 H, s, CH_3), 2.57 (4 H, t, *J* = 4.3 Hz), 2.70–2.83 (1 H, m), 3.43 (4 H, t, *J* = 4.3 Hz), 4.29 (1 H, s), 7.23–7.33 (6 H, m), 7.47 (4 H, dd, *J* = 7.7, 2.5 Hz); MS (ES, pos. mode) *m*/*z* = 497.1 $[M + H]^+$.



2r

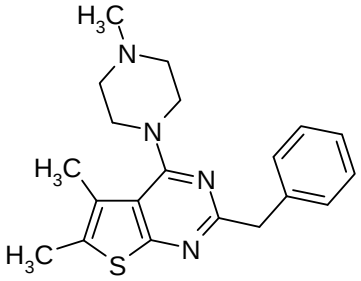
5,6-Dimethyl-4-morpholin-4-yl-2-phenylthieno[2,3-*d*]pyrimidine 2s (5.9 mg, 18%). White solid; mp = 183–185 ºC; elemental analysis: Found: C, 66.72; H, 6.1; N, 13.12. Calc. for $C_{18}H_{19}N_3OS$: C, 66.43; H, 5.9; N, 12.91%; δ_H (200 MHz; $CDCl_3$; Me_4Si) 2.46 (6 H, br s, $2CH_3$), 3.50 (4 H, t, *J* = 4.6 Hz), 3.93 (4 H, t, *J* = 4.6 Hz), 7.44–7.48 (3 H, m), 8.46 (2 H, dd, *J* = 7.7, 4.2 Hz); MS (CI) *m*/*z* = 326 (100) $[M + H]^+$.



2s

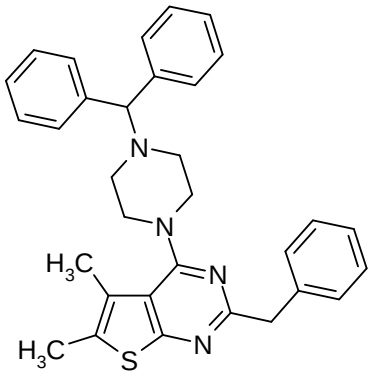
2-Benzyl-5,6-dimethyl-4-(4-methylpiperazin-1-yl)thieno[2,3-*d*]pyrimidine 2t (10.5 mg, 30%). White solid; mp = 164–166 ºC; elemental analysis: Found: C, 68.00; H, 7.0; N, 16.12. Calc. for $C_{20}H_{24}N_4S$: C, 68.15; H, 6.9; N, 15.89%; δ_H (200 MHz; $CDCl_3$; Me_4Si) 2.35 (3 H, s, CH_3), 2.39 (3 H, s, CH_3), 2.41 (3 H, s, CH_3), 2.55 (4 H, t, *J* = 4.4

Hz), 3.43 (4 H, t, *J* = 4.4 Hz), 4.18 (2 H, s, CH_2), 7.26–7.31 (3 H, m), 7.43 (2 H, dd, *J* = 7.0, 3.2 Hz); δ_C (50 MHz; $CDCl_3$; Me_4Si) 13.8, 13.9, 45.5, 46.2, 50.2 (2C), 54.7 (2C), 119.1, 120.0, 123.9, 126.0, 128.0 (2C), 129.1 (2C), 130.7, 138.9, 161.9, 167.6; MS (ES, pos. mode) *m*/*z* = 353.1 $[M + H]^+$.



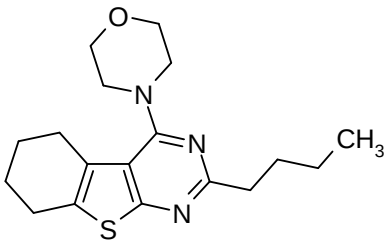
2t

4-(4-Benzhydrylpiperazin-1-yl)-2-benzyl-5,6-dimethyl-4-thieno[2,3-*d*]pyrimidine 2u (5.1 mg, 10%). White solid; mp = 161–163 ºC; elemental analysis: Found: C, 75.97; H, 6.7; N, 10.82. Calc. for $C_{32}H_{32}N_4S$: C, 76.16; H, 6.4; N, 11.10%; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.34 (3 H, s, CH_3), 2.38 (3 H, s, CH_3), 2.54 (4 H, t, *J* = 4.4 Hz), 3.41 (4 H, t, *J* = 4.4 Hz), 4.17 (2 H, s, CH_2), 4.26 (1 H, s), 7.20–7.49 (15 H, m); MS (ES, pos. mode) *m*/*z* = 505.1 $[M + H]^+$.



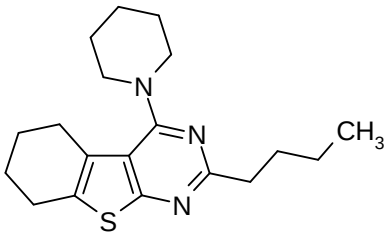
2u

2-Butyl-4-morpholin-4-yl-5,6,7,8-tetrahydrobenzo[4,5]-thieno[2,3-*d*]pyrimidine 2v (22.9 mg, 69%). White solid; mp = 59–61 ºC; elemental analysis: Found: C, 65.51; H, 7.8; N, 12.89. Calc. for $C_{18}H_{25}N_3OS$: C, 65.22; H, 7.6; N, 12.68%; δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.93 (3 H, t, *J* = 7.3 Hz, CH_3), 1.35–1.45 (2 H, m), 1.70–1.98 (6 H, m), 2.81–2.90 (6 H, m), 3.39 (4 H, t, *J* = 4.6 Hz), 3.85 (4 H, t, *J* = 4.6 Hz); MS (ES, pos. mode) *m*/*z* = 332.2 $[M + H]^+$.



2v

2-Butyl-4-piperidin-1-yl-5,6,7,8-tetrahydrobenzo[4,5]-thieno[2,3-*d*]pyrimidine 2w (23.4 mg, 71%). Yellow oil; δ_H (200 MHz; $CDCl_3$; Me_4Si) 0.93 (3 H, t, *J* = 7.2 Hz, CH_3), 1.37–1.44 (2 H, m), 1.67–1.96 (12 H, m), 2.80–2.94 (6 H, m), 3.27–3.34 (4 H, m); MS (EI) *m*/*z* = 329 $[M]^+$, 300, 287, 204.



2w

2-Benzyl-4-(4-methylpiperazin-1-yl)-5,6,7,8-tetrahydrobenzo[4,5]-thieno[2,3-*d*]pyrimidine 2x (6.8 mg, 18%). White solid; mp = 119–121 ºC; elemental analysis: Found: C, 70.00; H, 7.1; N, 14.98. Calc. for $C_{22}H_{26}N_4S$: C, 69.81; H, 6.9; N, 14.80%; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.88–1.96 (4 H, m), 2.32 (3 H, s, CH_3), 2.51–2.59 (4 H, m), 2.81–2.88 (4 H, m), 3.40–3.46 (4 H, m), 4.18 (2 H, s, CH_2), 7.21–7.30 (3 H, m), 7.43 (2 H, d, *J* = 7.7 Hz); MS (ES, pos. mode) *m*/*z* = 379.1 $[M + H]^+$.

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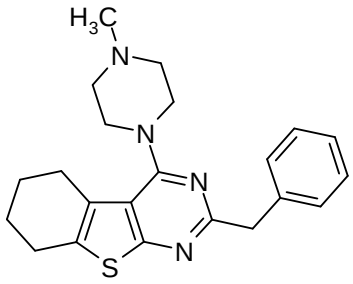
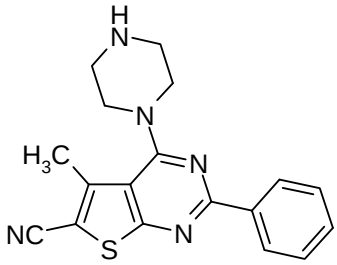


2x

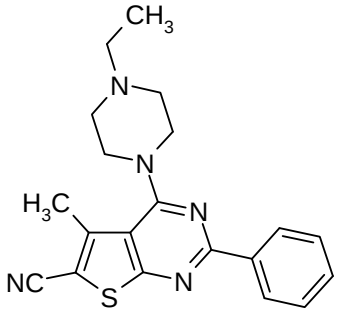
5-Methyl-2-phenyl-4-piperazin-1-yl-thieno[2,3-*d*]pyrimidine-6-carbonitrile 2aa[1] (19.4 mg, 58%). Yellow solid; mp = 189–191 ºC; elemental analysis: Found: C, 64.09;

H, 5.1; N, 21.08. Calc. for $C_{18}H_{17}N_5S$: C, 64.45; H, 5.1; N, 20.88%; υ_{max}(KBr) /cm^{-1} 3432, 2926, 1635, 1490, 1377, 1229; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.73 (3 H, s, CH_3), 3.16–3.20 (4 H, m), 3.66–3.72 (4 H, m), 7.48–7.50 (3 H, m), 8.44–8.46 (2 H, m); MS (CI) *m*/*z* = 336 (100) $[M + H]^+$.



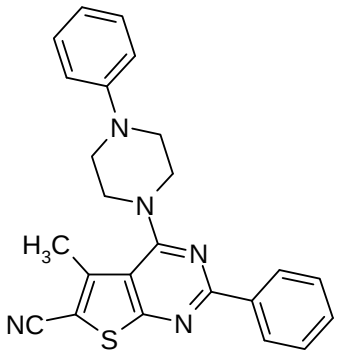
2aa

4-(4-Ethyl-piperazin-1-yl)-5-methyl-2-phenylthieno[2,3-*d*]pyrimidine-6-carbonitrile 2ab[1] (18.9 mg, 52%). Yellow solid; mp = 155–157 ºC; elemental analysis: Found: C, 65.95; H, 5.8; N, 19.65. Calc. for $C_{20}H_{21}N_5S$: C, 66.09; H, 5.8; N, 19.27%; υ_{max} (KBr) /cm^{-1} 2969, 2212, 1533, 1491, 1261; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.14 (3 H, t, *J* = 7.1 Hz, C*H*$_3$CH$_2$), 2.49 (2 H, q, *J* = 7.1 Hz, CH$_3$C*H*$_2$), 2.65 (4 H, t, *J* = 4.4 Hz), 2.73 (3 H, s, CH_3), 3.66 (4 H, t, *J* = 4.4 Hz), 7.47–7.50 (3 H, m), 8.45–8.49 (2 H, m); MS (ES, pos. mode) *m*/*z* = 364.1 $[M + H]^+$.



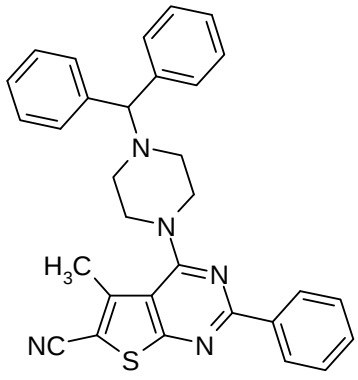
2ab

5-Methyl-2-phenyl-4-(4-phenylpiperazin-1-yl)-thieno[2,3-*d*]pyrimidine-6-carbonitrile 2ac (16.4 mg, 40%). White solid; mp = 180–182 ºC; elemental analysis: Found: C, 69.89; H, 5.3; N, 17.28. Calc. for $C_{24}H_{21}N_5S$: C, 70.05; H, 5.1; N, 17.02%; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.80 (3 H, s, CH_3), 3.41 (4 H, t, *J* = 4.6 Hz), 3.80 (4 H, t, *J* = 4.6 Hz), 6.97–7.02 (3 H, m), 7.28–7.35 (2 H, m), 7.49–7.52 (3 H, m), 8.47–8.51 (2 H, m); MS (ES, pos. mode) *m*/*z* = 412.1 $[M + H]^+$.



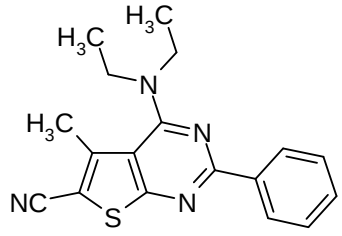
2ac

4-(4-Benzhydrylpiperazin-1-yl)-5-methyl-2-phenylthieno[2,3-*d*]pyrimidine-6-carbonitrile 2ad (16.5 mg, 33%). Orange solid; mp = 212–214 ºC; elemental analysis: Found: C, 74.08; H, 5.7; N, 14.20. Calc. for $C_{31}H_{27}N_5S$: C, 74.22; H, 5.4; N, 13.96%; υ_{max} (KBr) /cm^{-1} 3406, 2914, 2812, 2211, 1639, 1616, 1597, 1534, 983; δ_H (200 MHz; $CDCl_3$; Me_4Si) 2.59 (4 H, br s), 2.67 (3 H, s, CH_3), 3.62 (4 H, br s), 4.56 (1 H, s), 7.18–7.31 (9 H, m), 7.41–7.46 (4 H, m), 8.39–8.46 (2 H, m); MS (ES, pos. mode) *m*/*z* = 502.1 [M + H]$^+$.



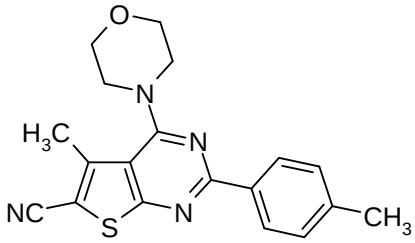
2ad

4-Diethylamino-5-methyl-2-phenylthieno[2,3-*d*]pyrimidine-6-carbonitrile 2ae[1] (16.7 mg, 52%). Yellow solid; mp = 225–227 ºC; elemental analysis: Found: C, 65.24; H, 5.7; N, 17.21. Calc. for $C_{18}H_{18}N_4S$: C, 67.05; H, 5.6; N, 17.38%; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.23 (6 H, t, *J* = 7.1 Hz, 2C*H*$_3$CH$_2$), 2.70 (3 H, s, CH_3), 3.62 (4 H, q, *J* = 7.1 Hz, 2CH$_3$C*H*$_2$), 7.45–7.47 (3 H, m), 8.43–8.46 (2 H, m); MS (ES, pos. mode) *m*/*z* = 323.2 [M + H]$^+$.



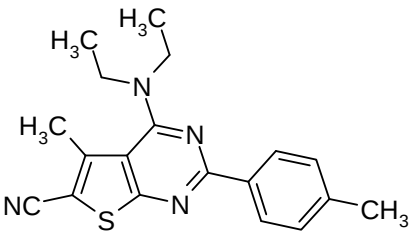
2ae

5-Methyl-2-(4-methylphenyl)-4-morpholin-4-yl-thieno[2,3-*d*]pyrimidine-6-carbonitrile 2af[1] (32.2 mg, 92%). Yellow solid; mp = 186–188 ºC; elemental analysis: Found: C, 65.45; H, 5.5; N, 15.79. Calc. for $C_{19}H_{18}N_4OS$: C, 65.12; H, 5.2; N, 15.99%; υ_{max} (KBr) /cm^{-1} 3447, 2982, 2928, 2210, 1605, 1616, 1524, 987, 868; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.41 (3 H, s, CH_3), 2.72 (3 H, s, CH_3), 3.58–3.61 (4 H, m), 3.88–3.91 (4 H, m), 7.27 (2 H, d, *J* = 8.1 Hz), 8.34 (2 H, d, *J* = 8.1 Hz); MS (ES, pos. mode) *m*/*z* = 351.1 $[M + H]^+$.



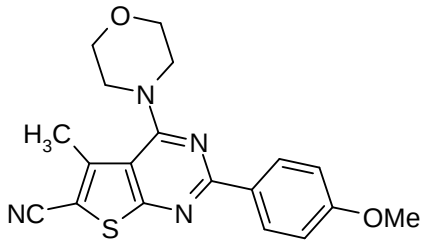
2af

4-Diethylamino-5-methyl-2-(4-methylphenyl)thieno[2,3-*d*]pyrimidine-6-carbonitrile 2ag[1] (10.8 mg, 32%). Yellow solid; mp = 158–159 ºC; elemental analysis: Found: C, 67.74; H, 5.7; N, 16.79. Calc. for $C_{19}H_{20}N_4S$: C, 67.83; H, 6.0; N, 16.65%; υ_{max} (KBr) /cm^{-1} 3440, 2970, 2928, 2209, 1534, 734; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.22 (6 H, t, *J* = 6.9 Hz, 2C*H*$_3$CH$_2$), 2.41 (3 H, s, CH_3), 2.69 (3 H, s, CH_3), 3.58 (4 H, q, *J* = 6.9 Hz, 2 CH$_3$C*H*$_2$), 7.24 (2 H, d, *J* = 8.0 Hz), 8.33 (2 H, d, *J* = 8.0 Hz); MS (ES, pos. mode) *m*/*z* = 337.1 $[M + H]^+$.



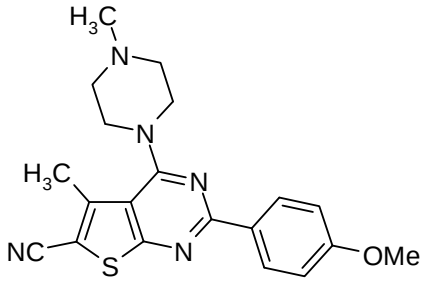
2ag

2-(4-Methoxyphenyl)-5-methyl-4-morpholin-4-yl-thieno[2,3-*d*]pyrimidine-6-carbonitrile 2ah[1] (20.1 mg, 55%). Yellow solid; mp = 204–206 ºC; elemental analysis: Found: C, 62.46; H, 5.2; N, 15.49. Calc. for $C_{19}H_{18}N_4O_2S$: C, 62.28; H, 4.9; N, 15.29%; υ_{max} (KBr) /cm^{-1} 2964, 2210, 1605, 1583, 1464, 1426, 1326, 1252, 1067, 926; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.72 (3 H, s, CH_3), 3.56–3.60 (4 H, m), 3.87 (3 H, s, OCH_3), 3.88–3.92 (4 H, m), 6.97 (2 H, d, *J* = 6.9 Hz), 8.41 (2 H, d, *J* = 6.9 Hz); MS (ES, pos. mode) *m*/*z* = 367.1 $[M + H]^+$.



2ah

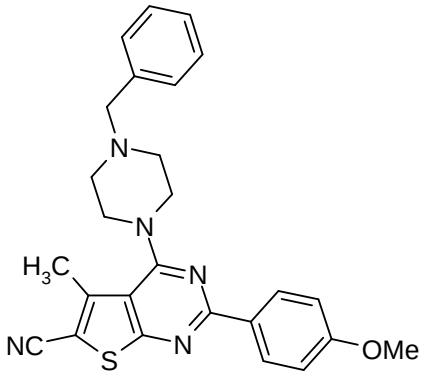
2-(4-Methoxyphenyl)-5-methyl-4-(4-methylpiperazin-1-yl)thieno[2,3-*d*]pyrimidine-6-carbonitrile 2ai[1] (17.1 mg, 46%). Yellow solid; mp > 250 ºC; elemental analysis: Found: C, 62.96; H, 5.7; N, 18.42. Calc. for $C_{20}H_{21}N_5OS$: C, 63.30; H, 5.6; N, 18.45%; υ_{max} (KBr) /cm^{-1} 2963, 1582, 1522, 1495, 1285, 1047, 975; δ_H (200 MHz; $CDCl_3$; Me_4Si) 2.37 (3 H, s, CH_3), 2.63–2.70 (4 H, m), 2.71 (3 H, s, CH_3), 3.63–3.87 (4 H, m), 3.88 (3 H, s, OCH_3), 6,97 (2 H, d, *J* = 8.7 Hz), 8.40 (2 H, d, *J* = 8.7 Hz); MS (ES, pos. mode) *m*/*z* = 380.1 $[M + H]^+$.



2ai

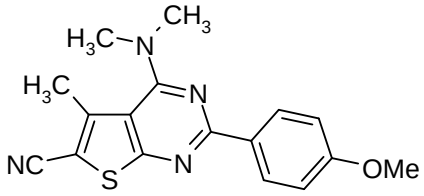
4-(4-Benzylpiperazin-1-yl)-2-(4-methoxyphenyl)-5-methyl-thieno[2,3-*d*]pyrimidine-6-carbonitrile 2aj (18.2 mg, 40%). Yellow solid; mp = 193–195 ºC; elemental analysis: Found: C, 68.49; H, 5.2; N, 15.48. Calc. for $C_{26}H_{25}N_5OS$: C, 68.55; H, 5.5; N, 15.37%; υ_{max} (KBr) /cm^{-1} 3448, 2208, 1606, 1532, 1493; δ_H (200 MHz; $CDCl_3$; Me_4Si) 2.63–2.69

(7 H, m), 3.56–3.60 (7 H, m), 3.87 (2 H, s, CH_2), 6.97 (2 H, d, *J* = 8.9 Hz), 7.27–7.32 (5 H, m), 8.40 (2 H, d, *J* = 8.9 Hz); MS (CI) *m*/*z* = 456 (100) $[M + H]^+$.



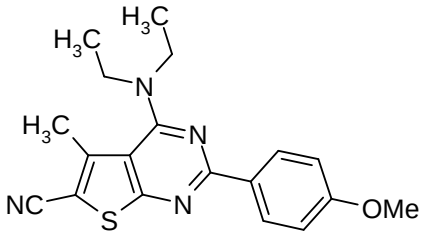
2aj

4-Dimethylamino-2-(4-methoxyphenyl)-5-methylthieno[2,3-*d*]pyrimidine-6-carbonitrile 2ak[1] (7.5 mg, 23%). Yellow solid; mp = 123–125 ºC; elemental analysis: Found: C, 62.75; H, 5.3; N, 17.39. Calc. for $C_{17}H_{16}N_4OS$: C, 62.94; H, 5.0; N, 17.27%; υ_{max} (KBr) /cm^{-1} 3419, 2926, 2206, 2209, 1606, 1512, 839; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.70 (3 H, s, CH_3), 3.36 (6 H, s, $2CH_3$), 3.86 (3 H, s, OCH_3), 6.98 (2 H, d, *J* = 8.7 Hz), 8.42 (2 H, d, *J* = 8.7 Hz); MS (CI) *m*/*z* = 325 (100) $[M + H]^+$.



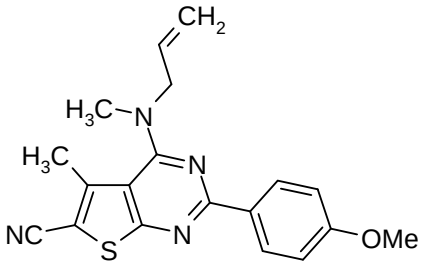
2ak

4-Diethylamino-2-(4-methoxyphenyl)-5-methylthieno[2,3-*d*]pyrimidine-6-carbonitrile 2al[1] (15.5 mg, 44%). Yellow solid; mp = 154–156 ºC; elemental analysis: Found: C, 64.74; H, 5.4; N, 15.59. Calc. for $C_{19}H_{20}N_4OS$: C, 64.75; H, 5.7; N, 15.90%; υ_{max} (KBr) /cm^{-1} 3413, 2212, 2209, 1605, 1538, 1245, 848; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.23 (6 H, t, *J* = 6.8 Hz, $2CH_3CH_3$), 2.69 (3 H, s, CH_3), 3.59 (4 H, q, *J* = 6.8 Hz, 2 CH_3CH_2), 3.87 (3 H, s, OCH_3), 6.97 (2 H, d, *J* = 8.9 Hz), 8.41 (2 H, d, *J* = 8.9 Hz); MS (ES, pos. mode) *m*/*z* = 353.1 $[M + H]^+$.



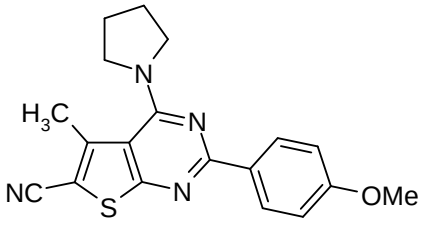
2al

4-(Allylmethylamino)-2-(4-methoxyphenyl)-5-methylthieno[2,3-*d*]pyrimidine-6-carbonitrile 2am[1] (8.0 mg, 23%). Yellow solid; mp = 126–128 ºC; elemental analysis: Found: C, 64.95; H, 5.3; N, 16.19. Calc. for $C_{19}H_{18}N_4OS$: C, 65.12; H, 5.2; N, 15.99%; υ_{max} (KBr) /cm^{-1} 3433, 2962, 2916, 2360, 2206, 1533, 1251, 1168, 847, 790; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.70 (3 H, s, CH_3), 3.09 (3 H, s, CH_3), 3.87 (3 H, s, OCH_3), 4.17 (2 H, d, *J* = 5.4 Hz, CH_2), 5.27–5.37 (2 H, m), 5.92–6.00 (1 H, m), 6.96 (2 H, d, *J* = 8.4 Hz), 8.40 (2 H, d, *J* = 8.4 Hz); MS (CI) *m*/*z* = 351 (100) $[M + H]^+$.



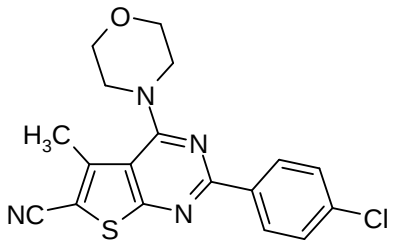
2am

2-(4-Methoxyphenyl)-5-methyl-4-pyrrolidin-1-yl-thieno[2,3-*d*]pyrimidine-6-carbonitrile 2an[1] (15.0 mg, 43%). White solid; mp = 176–178 ºC; elemental analysis: Found: C, 65.26; H, 5.0; N, 15.77. Calc. for $C_{19}H_{18}N_4OS$: C, 65.12; H, 5.2; N, 15.99%; υ_{max} (KBr) /cm^{-1} 2972, 2206, 1607, 1500, 1395, 1248, 1025; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.96–1.99 (4 H, m), 2.69 (3 H, s, CH_3), 3.80–3.86 (4 H, m), 3.87 (3 H, s, OCH_3), 6.97 (2 H, d, *J* = 8.7 Hz), 8.40 (2 H, d, *J* = 8.7 Hz); MS (ES, pos. mode) *m*/*z* = 351.2 $[M + H]^+$.



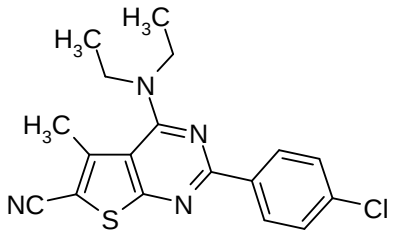
2an

2-(4-Chlorophenyl)-5-methyl-4-morpholin-4-yl-thieno[2,3-*d*]pyrimidine-6-carbonitrile 2ao[1] (25.6 mg, 69%). Yellow solid; mp = 183–185 ºC; elemental analysis: Found: C, 58.26; H, 4.0; N, 15.47. Calc. for $C_{18}H_{15}ClN_4OS$: C, 58.30; H, 4.1; N, 15.11%; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.72 (3 H, s, CH_3), 3.60–3.62 (4 H, m), 3.88–3.91 (4 H, m), 7.43 (2 H, d, *J* = 8.5 Hz), 8.40 (2 H, d, *J* = 8.5 Hz); MS (ES, pos. mode) *m*/*z* = 371.1 $[M + H]^+$.



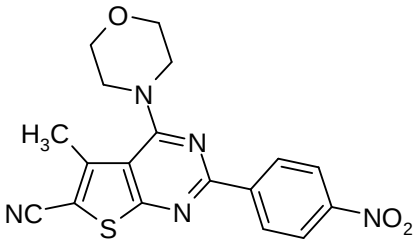
2ao

2-(4-Chlorophenyl)-4-diethylamino-5-methylthieno[2,3-*d*]pyrimidine-6-carbonitrile 2ap[1] (16.1 mg, 45%). Yellow solid; mp = 186–188 ºC; elemental analysis: Found: C, 60.28; H, 5.0; N, 15.97. Calc. for $C_{18}H_{17}ClN_4S$: C, 60.58; H, 4.8; N, 15.70%; δ_H (200 MHz; $CDCl_3$; Me_4Si) 1.23 (6 H, t, *J* = 6.9 Hz, $2CH_3CH_2$), 2.69 (3 H, s, CH_3), 3.58 (4 H, q, *J* = 6.9 Hz, 2 CH_3CH_2), 7.42 (2 H, d, *J* = 8.7 Hz), 8.38 (2 H, d, *J* = 8.7 Hz); MS (ES, pos. mode) *m*/*z* = 357.1 $[M + H]^+$.



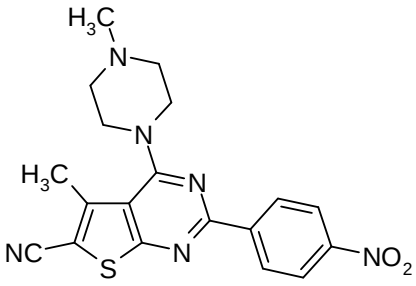
2ap

5-Methyl-4-morpholin-4-yl-2-(4-nitrophenyl)-thieno[2,3-*d*]pyrimidine-6-carbonitrile 2aq (9.1 mg, 24%). Yellow solid; mp > 250 ºC; elemental analysis: Found: C, 56.46; H, 4.3; N, 18.47. Calc. for $C_{18}H_{15}N_5O_3S$: C, 56.68; H, 4.0; N, 18.36%; υ_{max} (KBr) /cm^{-1} 2211, 1528, 1438, 1348, 1116; δ_H (200 MHz; $CDCl_3$; Me_4Si) 2.77 (3 H, s, CH_3), 3.66 (4 H, t, *J* = 4.4 Hz), 3.93 (4 H, t, *J* = 4.4 Hz), 8.32 (2 H, d, *J* = 8.7 Hz), 8.64 (2 H, d, *J* = 8.7 Hz); MS (ES, pos. mode) *m*/*z* = 382.1 $[M + H]^+$.



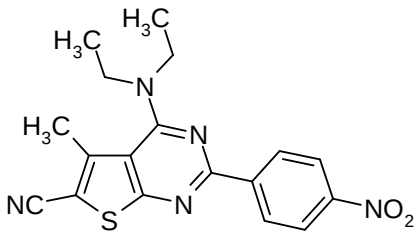
2aq

5-Methyl-2-(4-nitrophenyl)-4-(4-methylpiperazin-1-yl)thieno[2,3-*d*]pyrimidine-6-carbonitrile 2ar[1] (22.4 mg, 57%). Yellow solid; mp = 241–243 ºC; elemental analysis: Found: C, 58.00; H, 4.5; N, 21.27. Calc. for $C_{19}H_{18}N_6O_2S$: C, 57.85; H, 4.6; N, 21.31%; υ_{max} (KBr) /cm^{-1} 3392, 2969, 2215, 1532, 1292, 994; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.36 (3 H, s, CH_3), 2.60–2.63 (4 H, m), 2.73 (3 H, s, CH_3), 3.65–3.68 (4 H, m), 8.30 (2 H, d, *J* = 8.8 Hz), 8.60 (2 H, d, *J* = 8.8 Hz); MS (ES, pos. mode) *m*/*z* = 395.1 $[M + H]^+$.



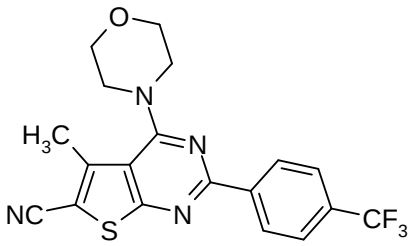
2ar

4-Diethylamino-5-methyl-2-(4-nitrophenyl)thieno[2,3-*d*]pyrimidine-6-carbonitrile 2as[1] (16.1 mg, 44%). Yellow solid; mp = 188–190 ºC; elemental analysis: Found: C, 58.56; H, 4.5; N, 18.88. Calc. for $C_{18}H_{17}N_5O_2S$: C, 58.84; H, 4.7; N, 19.06%; υ_{max} (KBr) /cm^{-1} 3429, 2208, 1730, 1596, 1535, 714; δ_H (200 MHz; $CDCl_3$; Me_4Si) 1.26 (6 H, t, *J* = 6.9 Hz, 2C*H*$_3$CH$_2$), 2.71 (3 H, s, CH_3), 3.64 (4 H, q, *J* = 6.9 Hz, 2 CH$_3$C*H*$_2$), 8.30 (2 H, d, *J* = 9.0 Hz), 8.61 (2 H, d, *J* = 9.0 Hz); MS (ES, pos. mode) *m*/*z* = 368.1 $[M + H]^+$.



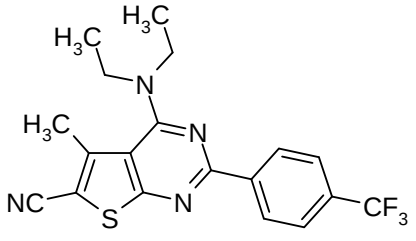
2as

5-Methyl-4-morpholin-4-yl-2-(4-trifluoromethylphenyl)thieno[2,3-*d*]pyrimidine-6-carbonitrile 2at (14.1 mg, 35%). Yellow solid; mp > 250 ºC; elemental analysis: Found: C, 56.56; H, 3.5; N, 13.88. Calc. for $C_{19}H_{15}F_3N_4OS$: C, 56.43; H, 3.7; N, 13.85%; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.69 (3 H, s, CH_3), 3.64–3.68 (4 H, m), 3.76–3.80 (4 H, m), 7.90 (2 H, d, *J* = 8.5 Hz), 8.60 (2 H, d, *J* = 8.5 Hz); MS (CI) *m*/*z* = 405 (100) $[M + H]^+$.



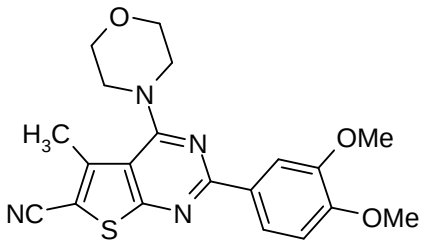
2at

4-Diethylamino-5-methyl-2-(4-trifluoromethylphenyl)thieno[2,3-*d*]pyrimidine-6-carbonitrile 2au[1] (12.9 mg, 33%). Yellow solid; mp = 142–144 ºC; elemental analysis: Found: C, 58.56; H, 4.5; N, 13.98. Calc. for $C_{19}H_{17}F_3N_4S$: C, 58.45; H, 4.4; N, 14.35%; δ_H (200 MHz; $CDCl_3$; Me_4Si) 1.25 (6 H, t, *J* = 6.9 Hz, $2CH_3CH_2$), 2.71 (3 H, s, CH_3), 3.63 (4 H, q, *J* = 6.9 Hz, $2CH_3CH_2$), 7.71 (2 H, d, *J* = 8.2 Hz), 8.55 (2 H, d, *J* = 8.2 Hz); MS (ES, pos. mode) *m*/*z* = 391.1 $[M + H]^+$.



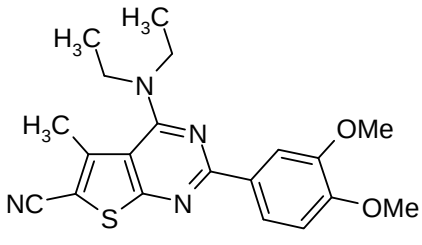
2au

2-(3,4-Dimethoxyphenyl)-5-methyl-4-morpholin-4-yl-thieno[2,3-*d*]pyrimidine-6-carbonitrile 2av[1] (18.6 mg, 47%). Yellow solid; mp = 194–196 ºC; elemental analysis: Found: C, 60.56; H, 5.4; N, 13.89. Calc. for $C_{20}H_{20}N_4O_3S$: C, 60.59; H, 5.1; N, 14.13%; υ_{max} (KBr) /cm^{-1} 3448, 2838, 1535, 1492, 1252, 1230, 1113, 790; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.72 (3 H, s, CH_3), 3.56–3.60 (4 H, m), 3.88–3.92 (4 H, m), 3.95 (3 H, s, OCH_3), 4.00 (3 H, s, OCH_3), 6.95 (1 H, d, *J* = 8.4 Hz), 8.02–8.11 (2 H, m); MS (ES, pos. mode) *m*/*z* = 397.1 $[M + H]^+$.



2av

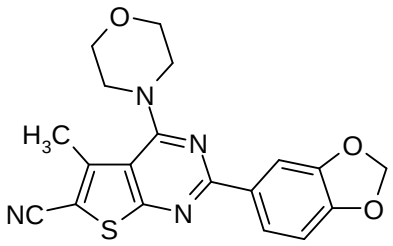
4-Diethylamino-2-(3,4-dimethoxyphenyl)-5-methylthieno[2,3-*d*]pyrimidine-6-carbonitrile 2aw[1] (8.4 mg, 22%). Yellow solid; mp = 159–161 ºC; elemental analysis: Found: C, 63.01; H, 6.0; N, 14.43. Calc. for $C_{20}H_{22}N_4O_2S$: C, 62.81; H, 5.8; N, 14.65%; υ_{max} (KBr) /cm^{-1} 3448, 2987, 2213, 1516, 1018, 796; δ_H (200 MHz; $CDCl_3$; Me_4Si) 1.23 (6 H, t, *J* = 6.9 Hz, 2C*H*$_3$CH$_2$), 2.68 (3 H, s, CH_3), 3.58 (4 H, q, *J* = 6.9 Hz, 2CH$_3$C*H*$_2$), 3.94 (3 H, s, OCH_3), 3.99 (3 H, s, OCH_3), 6.94 (1 H, d, *J* = 8.4 Hz), 8.02–8.11 (2 H, m); MS (ES, pos. mode) *m*/*z* = 383.1 $[M + H]^+$.



2aw

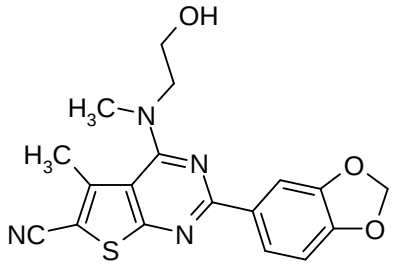
2-Benzo[1,3]dioxol-5-yl-5-methyl-4-morpholin-4-yl-thieno[2,3-*d*]pyrimidine-6-carbonitrile 2ax[1] (21.6 mg, 57%). Yellow solid; mp = 197–198 ºC; elemental analysis: Found: C, 60.18; H, 4.4; N, 14.89. Calc. for $C_{19}H_{16}N_4O_3S$: C, 59.99; H, 4.2; N, 14.73%; υ_{max} (KBr) /cm^{-1} 2960, 2901, 2858, 2207, 1257, 1066, 811, 799; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.71 (3 H, s, CH_3), 3.50–3.59 (4 H, m), 3.87–3.90 (4 H, m), 6.03 (2 H, s,

OCH_2O), 6.89 (1 H, d, *J* = 8.2 Hz), 7.92 (1 H, d, *J* = 1.6 Hz), 8.07 (1 H, dd, *J* = 8.2, 1.6 Hz); MS (ES, pos. mode) *m*/*z* = 381.1 $[M + H]^+$.



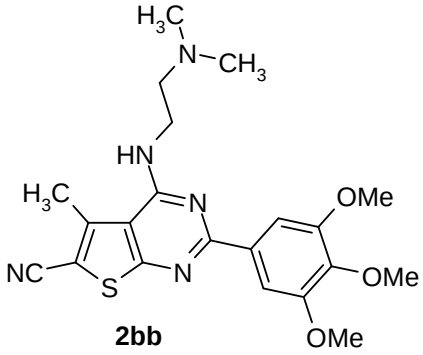
2ax

2-Benzo[1,3]dioxol-5-yl-4-[(2-hydroxyethyl)methylamino]-5-methylthieno[2,3-*d*]pyrimidine-6-carbonitrile 2ay[1] (14.3 mg, 39%). Yellow solid; mp = 195–197 ºC; elemental analysis: Found: C, 58.99.18; H, 4.7; N, 14.99. Calc. for $C_{18}H_{16}N_4O_3S$: C, 58.68; H, 4.4; N, 15.21%; υ_{max} (KBr) /cm^{-1} 3548, 3426, 2906, 1735, 1635, 1539, 1377, 1249, 1066, 914; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.71 (3 H, s, CH_3), 3.22 (3 H, s, CH_3), 3.87–3.91 (2 H, m), 3.97–4.01 (2 H, m), 6.02 (2 H, s, OCH_2O), 6.89 (1 H, d, *J* = 8.2 Hz), 7.86 (1 H, d, *J* = 1.6 Hz), 7.99 (1 H, dd, *J* = 8.2, 1.6 Hz); MS (ES, pos. mode) *m*/*z* = 369.1 $[M + H]^+$.



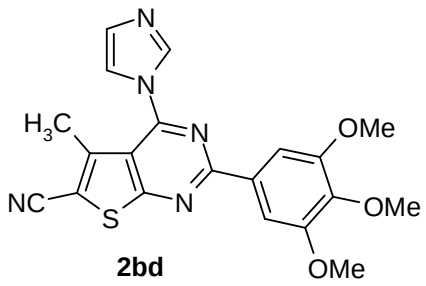
2ay

4-(2-Dimethylaminoethylamino)-5-methyl-2-(3,4,5-trimethoxyphenyl)thieno[2,3-*d*]pyrimidine-6-carbonitrile 2bb[1] (15.4 mg, 36%). Yellow solid; mp = 134–136 ºC; elemental analysis: Found: C, 58.91; H, 6.2; N, 16.43. Calc. for $C_{21}H_{25}N_5O_3S$: C, 59.00; H, 5.9; N, 16.38%; υ_{max} (KBr) /cm^{-1} 3429, 2943, 2825, 2773, 2209, 1570, 1508, 1448, 1223, 1127, 732; δ_H (200 MHz; $CDCl_3$; Me_4Si) 2.34 (6 H, s, $2CH_3$), 2.65 (2 H, br s), 2.75 (3 H, s, CH_3), 3.72 (2 H, br s), 3.94 (3 H, s, OCH_3), 3.98 (6 H, s, $2OCH_3$), 6.72 (1 H, br s, NH), 7.73 (2 H, s); MS (ES, pos. mode) *m*/*z* = 428.1 $[M + H]^+$.



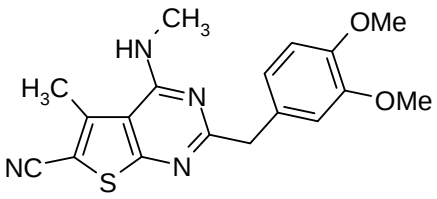
2bb

4-Imidazol-1-yl-5-methyl-2-(3,4,5-trimethoxyphenyl)thieno[2,3-*d*]pyrimidine-6-carbonitrile 2bd[1] (13.4 mg, 33%). Yellow solid; mp = 238–240 ºC; elemental analysis: Found: C, 59.31; H, 4.2; N, 17.43. Calc. for $C_{20}H_{17}N_5O_3S$: C, 58.96; H, 4.2; N, 17.19%; υ_{max} (KBr) /cm^{-1} 3425, 3123, 2933, 2218, 1556, 1408, 1128, 1004, 711; δ_H (200 MHz; $CDCl_3$; Me_4Si) 2.39 (3 H, s, CH_3), 3.94 (3 H, s, OCH_3), 3.98 (6 H, s, $2OCH_3$), 7.34 (1 H, br s), 7.44 (1 H, br s), 7.80 (2 H, s), 8.04 (1 H, br s); MS (ES, pos. mode) *m*/*z* = 408.1 [M + H]$^+$.



2bd

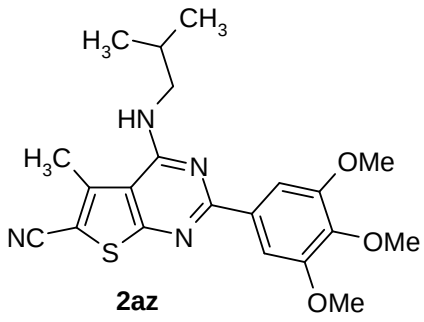
2-(3,4-Dimethoxybenzyl)-5-methyl-4-methylaminothieno[2,3-*d*]pyrimidine-6-carbonitrile 2bf[1] (21.2 mg, 60%). Orange solid; mp = 161–163 ºC; elemental analysis: Found: C, 60.67; H, 5.2; N, 15.66. Calc. for $C_{18}H_{18}N_4O_2S$: C, 61.00; H, 5.1; N, 15.81%; υ_{max} (KBr) /cm^{-1} 3416, 1926, 2212, 1676, 1578, 1512, 1230, 1026, 753; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.70 (3 H, s, CH_3), 3.14 (3 H, d, *J* = 4.9 Hz, NHC*H*$_3$), 3.82 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 4.04 (2 H, s, CH_2), 5.45 (1 H, br s, NH), 6.77 (1 H, d, *J* = 8.2 Hz), 6.94 (1 H, d, *J* = 8.2 Hz), 7.00 (1 H, s); MS (ES, pos. mode) *m*/*z* = 355.1 [M + H]$^+$.



2bf

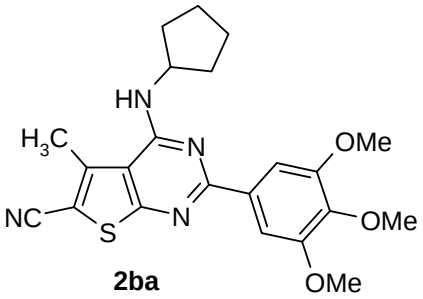
Experimental details and characterization data for final compounds 2az, 2ba, 2bc, 2be and 2bg–2bk.

5-Methyl-4-(2-methylpropylamino)-2-(3,4,5-trimethoxyphenyl)thieno[2,3-*d*]pyrimidine-6-carbonitrile 2az[1] (39.1 mg, 95%). Yellow solid; mp = 182–184 ºC; elemental analysis: Found: C, 61.01; H, 6.2; N, 13.43. Calc. for $C_{21}H_{24}N_4O_3S$: C, 61.15; H, 5.9; N, 13.58%; υ_{max} (KBr) /cm^{-1} 3447, 2952, 2210, 1551, 1507, 1084, 789, 731; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.03 (6 H, d, *J* = 6.9 Hz, $2CH_3$), 2.10–2.14 (1 H, m), 2.76 (3 H, s, CH_3), 3.55 (2 H, t, *J* = 6.2 Hz, CH_2), 3.90 (3 H, s, OCH_3), 3.97 (6 H, s, $2OCH_3$), 5.67 (1 H, t, *J* = 5.4 Hz, NH), 7.76 (2 H, s); δ_C (75 MHz; $CDCl_3$; Me_4Si) 17.3, 20.3 (2C), 28.1, 48.1, 56.1 (2C), 61.0, 101.1, 105.8 (2C), 105.7 (2C), 114.3, 115.5, 129.4, 140.8, 153.0, 154.7, 158,4, 161.0; MS (ES, pos. mode) *m*/*z* = 413.1 $[M + H]^+$.



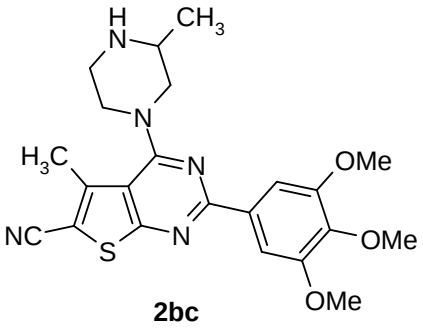
2az

4-Cyclopentylamino-5-methyl-2-(3,4,5-trimethoxyphenyl)thieno[2,3-*d*]pyrimidine-6-carbonitrile 2ba[1] (26.7 mg, 63%). Yellow solid; mp = 218–220 ºC; elemental analysis: Found: C, 62.21; H, 5.5; N, 13.03. Calc. for $C_{22}H_{24}N_4O_3S$: C, 62.24; H, 5.7; N, 13.20%; υ_{max} (KBr) /cm^{-1} 3477, 2962, 2210, 1533, 1372, 1125, 790; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.49–1.77 (6 H, m), 2.22–2.40 (2 H, m), 2.74 (3 H, s, CH_3), 3.90 (3 H, s, OCH_3), 3.96 (6 H, s, $2OCH_3$), 4.60–4.67 (1 H, m), 5.50 (1 H, d, *J* = 6.0 Hz, NH), 7.78 (2 H, s); δ_C (75 MHz; $CDCl_3$; Me_4Si) 17.1, 23.9 (2C), 33.4 (2C), 53.2, 56.1 (2C), 60.9, 100.3, 105.7 (2C), 112.9, 114.4, 119.6, 132.6, 140.6, 141.3, 153,6, 157.8, 161.8; MS (ES, pos. mode) *m*/*z* = 425.1 $[M + H]^+$.



2ba

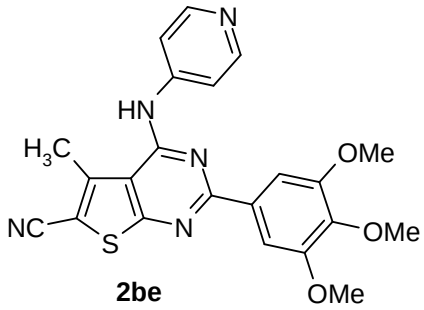
5-Methyl-4-(3-methylpiperazin-1-yl)-2-(3,4,5-trimethoxyphenyl)thieno[2,3-*d*]pyrimidine-6-carbonitrile 2bc[1] (19.3 mg, 44%). Yellow solid; mp = 213–215 ºC; elemental analysis: Found: C, 59.91; H, 6.0; N, 16.13. Calc. for $C_{22}H_{25}N_5O_3S$: C, 60.12; H, 5.7; N, 15.93%; υ_{max} (KBr) /cm^{-1} 2209, 1533, 1498, 1394, 1223, 1126, 1005, 733; δ_H (200 MHz; $CDCl_3$; Me_4Si) 1.11 (3 H, d, *J* = 6.2 Hz, CH_3), 2.70 (3 H, s, CH_3), 2.82 (1 H, dd, *J* = 12.6, 10.6 Hz), 3.08–3.40 (4 H, m), 3.75–3.99 (2 H, m), 3.90 (3 H, s, OCH_3), 3.96 (6 H, s, $2OCH_3$), 7.75 (2 H, s); δ_C (75 MHz; $CDCl_3$; Me_4Si) 16.9, 19.6, 30.0, 45.1, 49.7, 50.4, 55.7, 57.3, 60.9, 101.7, 105.2, 113.9, 116.0, 131.7, 140.0, 142.4, 152.6, 159.8, 162,6, 170.7; MS (ES, pos. mode) *m*/*z* = 440.2 $[M + H]^+$.



2bc

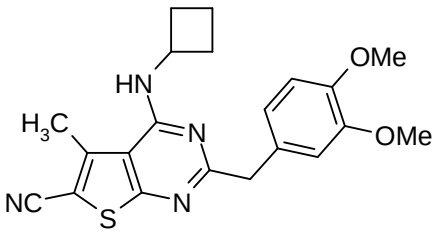
5-Methyl-4-(pyridin-4-yl-amino)-2-(3,4,5-trimethoxyphenyl)thieno[2,3-*d*]pyrimidine-6-carbonitrile 2be[1] (11.2 mg, 26%). Alternatively, to a solution of 4-aminopyridine (0.1 mmol) in dry DMF (15 mL) was added NaH (0.13 mmol) and the reaction was stirred at room temperature for 15 minutes. Then, the chloro-derivative **11** (0.1 mmol) in dry DMF (5 mL) was added and the reaction mixture was stirred at room temperature for 3 h. The reaction was treated with water (10 mL) and extracted with EtOAc. The combined organic phases were dried over anhydrous $MgSO_4$, filtered and the solvent was removed under vacuum. The residue as purified as usual (17.3, 40%). Yellow solid; mp = 175–180 ºC; elemental analysis: Found: C, 61.21; H, 4.2; N, 16.43. Calc. for $C_{22}H_{19}N_5O_3S$: C, 60.96; H, 4.4; N, 16.16%; υ_{max} (KBr) /cm^{-1} 3439, 2929, 2210, 1598, 1503, 1223, 1127; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.94 (3 H, s, CH_3), 3.93 (3 H, s, OCH_3), 3.97 (6 H, s, $2OCH_3$), 7.62 (1 H, br s, NH), 7.73 (2 H, s), 7.82 (2 H, d, *J* = 5.4 Hz), 8.56–8.58 (2 H, m); δ_C (75 MHz; $CDCl_3$; Me_4Si) 17.3, 56.1 (2C), 61.0, 103.8,

104.9, 105.7 (2C), 113.7, 115.1 (2C), 131.7, 140.0, 141.1, 145.0, 150.5 (2C), 153.2, 155.3, 161.7, 170.4; MS (ES, pos. mode) *m*/*z* = 434.2 $[M + H]^+$.



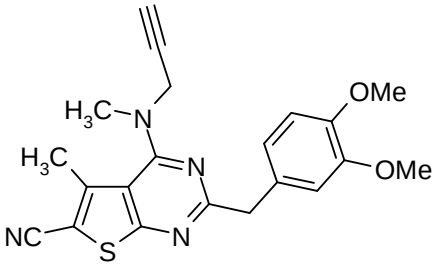
2be

4-Cyclobutylamino-2-(3,4-dimethoxybenzyl)-5-methylthieno[2,3-*d*]pyrimidine-6-carbonitrile 2bg[1] (31.5 mg, 80%). Yellow solid; mp = 193–195 ºC; elemental analysis: Found: C, 64.12; H, 5.3; N, 14.56. Calc. for $C_{21}H_{22}N_4O_2S$: C, 63.94; H, 5.6; N, 14.20%; υ_{max} (KBr) /cm^{-1} 3428, 2939, 2211, 1568, 1547, 1512, 1260, 1234, 731; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.82–2.02 (4 H, m), 2.43–2.45 (2 H, m), 2.70 (3 H, s, CH_3), 3.82 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 4.00 (2 H, s, CH_2), 4.66–4.69 (1 H, m), 5.55 (1 H, d, *J* = 6.2 Hz NH), 6.76 (1 H, d, *J* = 8.0 Hz), 6.91 (1 H, d, *J* = 8.0 Hz), 6.95 (1 H, s); δ_C (75 MHz; $CDCl_3$; Me_4Si) 15.3, 16.6, 17.1, 31.2 (2C), 45.5, 46.4, 55.7, 101.7, 110.9, 112.5, 114.1, 121.2, 130.1, 130.7, 141.2, 147.6, 148.6, 157.5, 168,2, 169.0; MS (ES, pos. mode) *m*/*z* = 395.1 $[M + H]^+$.



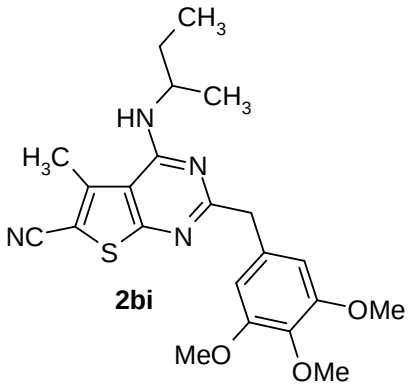
2bg

2-(3,4-Dimethoxybenzyl)-5-methyl-4-(methylprop-2-ynyl-amino)thieno[2,3-*d*]pyrimidine-6-carbonitrile 2bh[1] (15.3 mg, 39%). Yellow oil; υ_{max} (NaCl) /cm^{-1} 3412, 3280, 2931, 2212, 1536, 1547, 1463, 1261, 1028, 730; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.30 (1 H, t, *J* = 2.0 Hz, CH), 2.69 (3 H, s, CH_3), 3.14 (3 H, s, CH_3), 3.83 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 4.09 (2 H, s, CH_2), 4.20 (2 H, d, *J* = 2.0 Hz, CH_2), 6.77 (1 H, d, *J* = 7.9 Hz), 6.93–6.98 (2 H, m); δ_C (75 MHz; $CDCl_3$; Me_4Si) 17.2, 40.3, 42.1, 45.0, 55.7, 55.8, 73.3, 78.4, 102.2, 110.9, 112.6, 114.1, 115.5, 121.3, 138.2, 142.8, 147.7, 148.6, 162.6, 165.9, 170.5; MS (ES, pos. mode) *m*/*z* = 393.1 $[M + H]^+$.



2bh

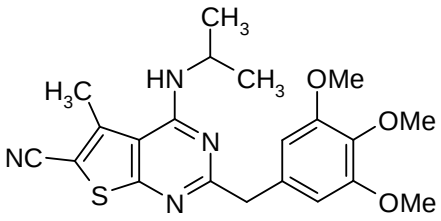
5-Methyl-4-(1-methylpropylamino)-2-(3,4,5-trimethoxybenzyl)thieno[2,3-*d*]pyrimidine-6-carbonitrile 2bi[1] (35.0 mg, 82%). White solid; mp = 134–137 ºC; elemental analysis: Found: C, 62.12; H, 6.3; N, 13.46. Calc. for $C_{22}H_{26}N_4O_3S$: C, 61.95; H, 6.1; N, 13.14%; υ_{max} (KBr) /cm^{-1} 3460, 2965, 2210, 1127, 1006, 732; δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.94 (3 H, t, *J* = 7.3 Hz, C*H*$_3$CH$_2$), 1.24 (3 H, d, *J* = 6.4 Hz, C*H*$_3$CH), 1.56–1.62 (2 H, m), 2.69 (3 H, s, CH_3), 3.78 (3 H, s, OCH_3), 3.82 (6 H, s, 2OCH_3), 3.99 (2 H, s, CH_2), 4.35–4.40 (1 H, m, CH), 5.27 (1 H, br s, NH), 6.63 (2 H, s); δ_C (75 MHz; $CDCl_3$; Me_4Si) 10.2, 17.2, 20.0, 29.3, 46.2, 48.1, 56.0 (2C), 60.8, 100.9, 106.2 (2C), 112.6, 114.1, 128.7, 133.8, 136.1, 141.2, 152.4, 158.1, 167.9; MS (ES, pos. mode) *m*/*z* = 427.2 $[M + H]^+$.



2bi

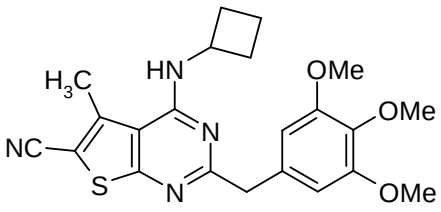
5-Methyl-4-(1-methylethylamino)-2-(3,4,5-trimethoxybenzyl)thieno[2,3-*d*]pyrimidine-6-carbonitrile 2bj[1] (33.0 mg, 80%). White solid; mp = 143–147 ºC; elemental analysis: Found: C, 61.12; H, 6.2; N, 13.46. Calc. for $C_{21}H_{24}N_4O_3S$: C, 61.15; H, 5.9; N, 13.58%; υ_{max} (KBr) /cm^{-1} 3440, 2970, 2832, 2210, 1568, 1548, 1504, 1450, 1006, 973, 732; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.28 (6 H, d, *J* = 6.3 Hz, 2CH_3), 2.69 (3 H, s, CH_3), 3.82 (3 H, s, OCH_3), 3.85 (6 H, s, 2OCH_3), 3.99 (2 H, s, CH_2), 4.46–4.50 (1 H, m), 5.27 (1 H, br s, NH), 6.63 (2 H, s); δ_C (50 MHz; $CDCl_3$; Me_4Si) 16.4, 17.2, 18.0,

23.8, 42.2, 46.3 (2C), 56.6, 100.8, 105.8, 110.4, 112.5, 114.1, 133.8, 136.5, 141.2, 152.9, 157.8, 167.9; MS (ES, pos. mode) m/z = 413.0 $[M + H]^+$.



2bj

4-Cyclobutylamino-5-methyl-2-(3,4,5-trimethoxybenzyl)thieno[2,3-*d*]pyrimidine-6-carbonitrile 2bk[1] (34.8 mg, 82%). White solid; mp = 121–122 ºC; elemental analysis: Found: C, 62.12; H, 5.5; N, 13.46. Calc. for $C_{22}H_{24}N_4O_3S$: C, 62.24; H, 5.7; N, 13.20%; υ_{max} (KBr) /cm^{-1} 3433, 2939, 2250, 2211, 1574, 1322, 1241, 1125, 1006, 908, 729; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.80–1.96 (4 H, m), 2.40–2.50 (2 H, m), 2.72 (3 H, s, CH_3), 3.79 (3 H, s, OCH_3), 3.84 (6 H, s, $2OCH_3$), 4.00 (2 H, s, CH_2), 4.65–4.75 (1 H, m), 5.58 (1 H, d, J = 6.2 Hz, NH), 6.64 (2 H, s); δ_C (75 MHz; $CDCl_3$; Me_4Si) 15.4, 17.1, 31.2 (2C), 46.2, 46.4, 56.0 (2C), 60.7, 101.0, 104.9, 106.2 (2C), 112.4, 114.1, 133.8, 136.5, 141.2, 152.4, 157.5, 167.9; MS (ES, pos. mode) m/z = 425.0 $[M + H]^+$.



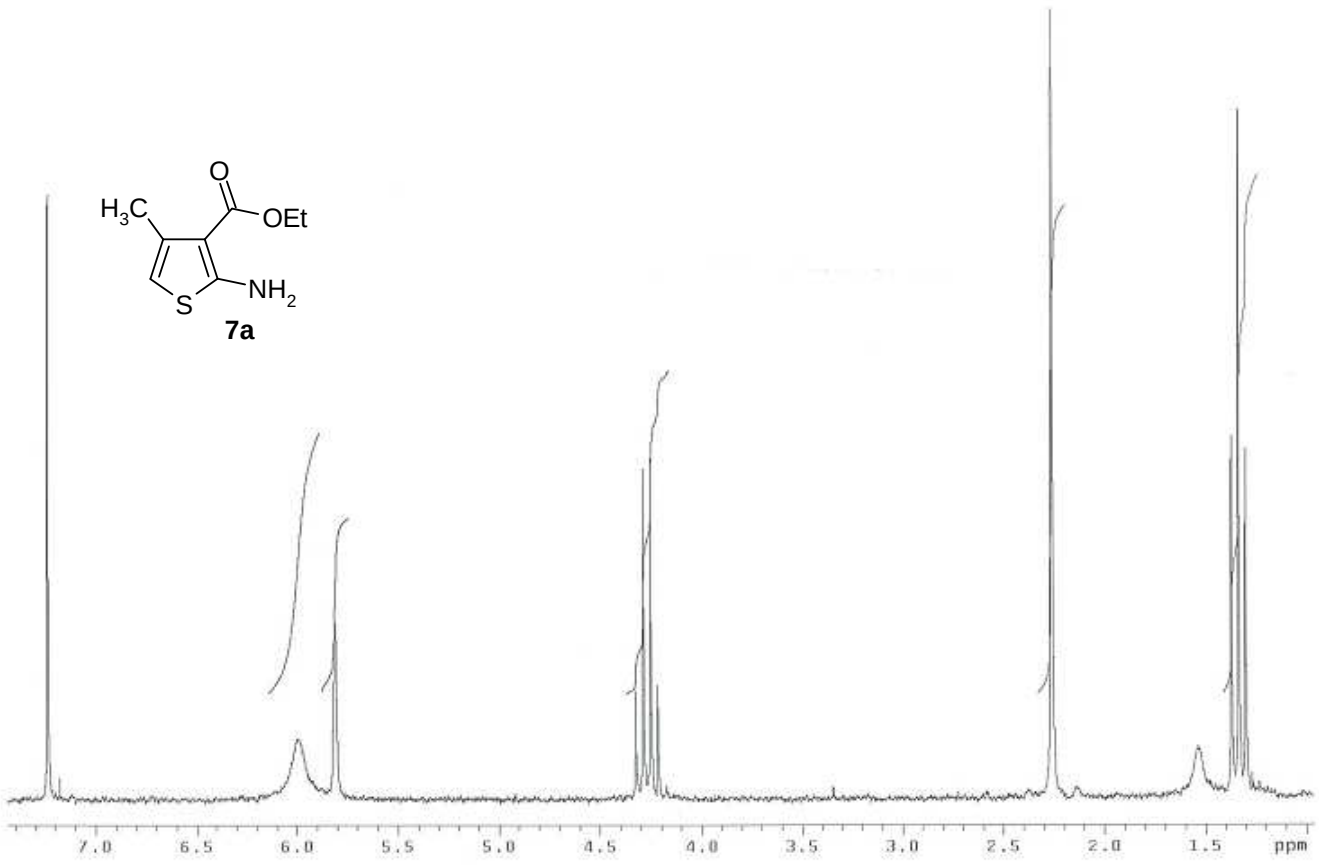
2bk

Phosphodiesterase inhibition assay

Compounds **1a**–**d**, **2a**–**x** and **2aa**–**bk** were resuspended in DMSO at a stock concentration of 10 mM. The compounds were tested at concentrations ranging from 1 mM to 1 nM in order to calculate IC_{50} values. All dilutions were performed in 96 well plates.

For each reaction, 10 µL of the diluted compounds were poured into ‘low binding’ assay plates. 80 µL of a reaction mixture containing 50 mM Tris pH 7.5, 8.3 mM $MgCl_2$, 1.7 mM EGTA, and 15 nM 3',5'[3H]-cAMP (around 150000 dpm) were added to each well. The reaction was initiated by adding 10 µL of a solution containing PDE7, PDE3 or PDE4 to the reaction mixture. The plate was then incubated with stirring for 1 h at room temperature. After incubation the reaction was stopped with 50 µL (0.89 mg) of PDE SPA beads (Amersham Pharmacia Biotech RPNQ0150), and the resulting mixture was allowed to settle for 20 min before counting in a microliter plate counter.

Some selected ^{1}H-NMR spectra for starting materials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H3C
OEt
NH2
S
7a
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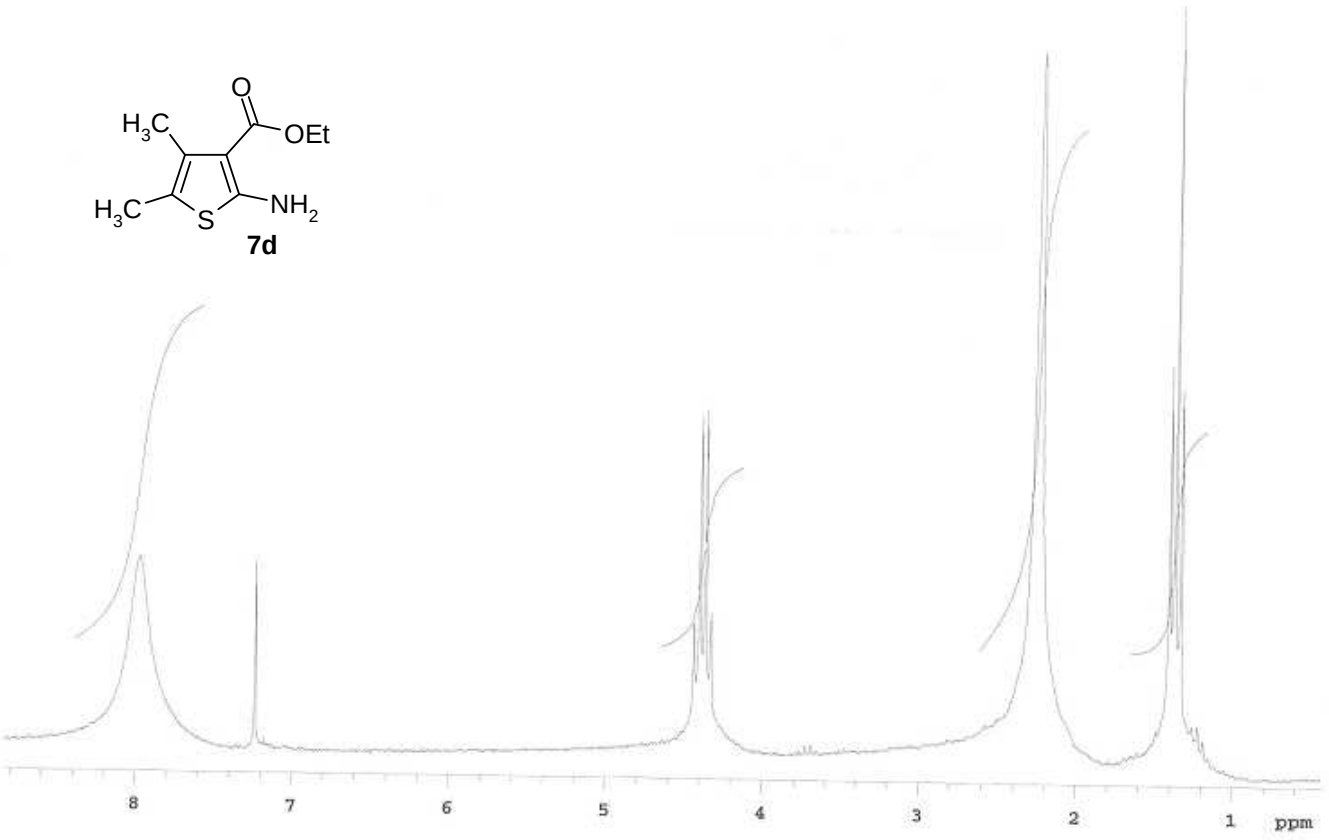
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm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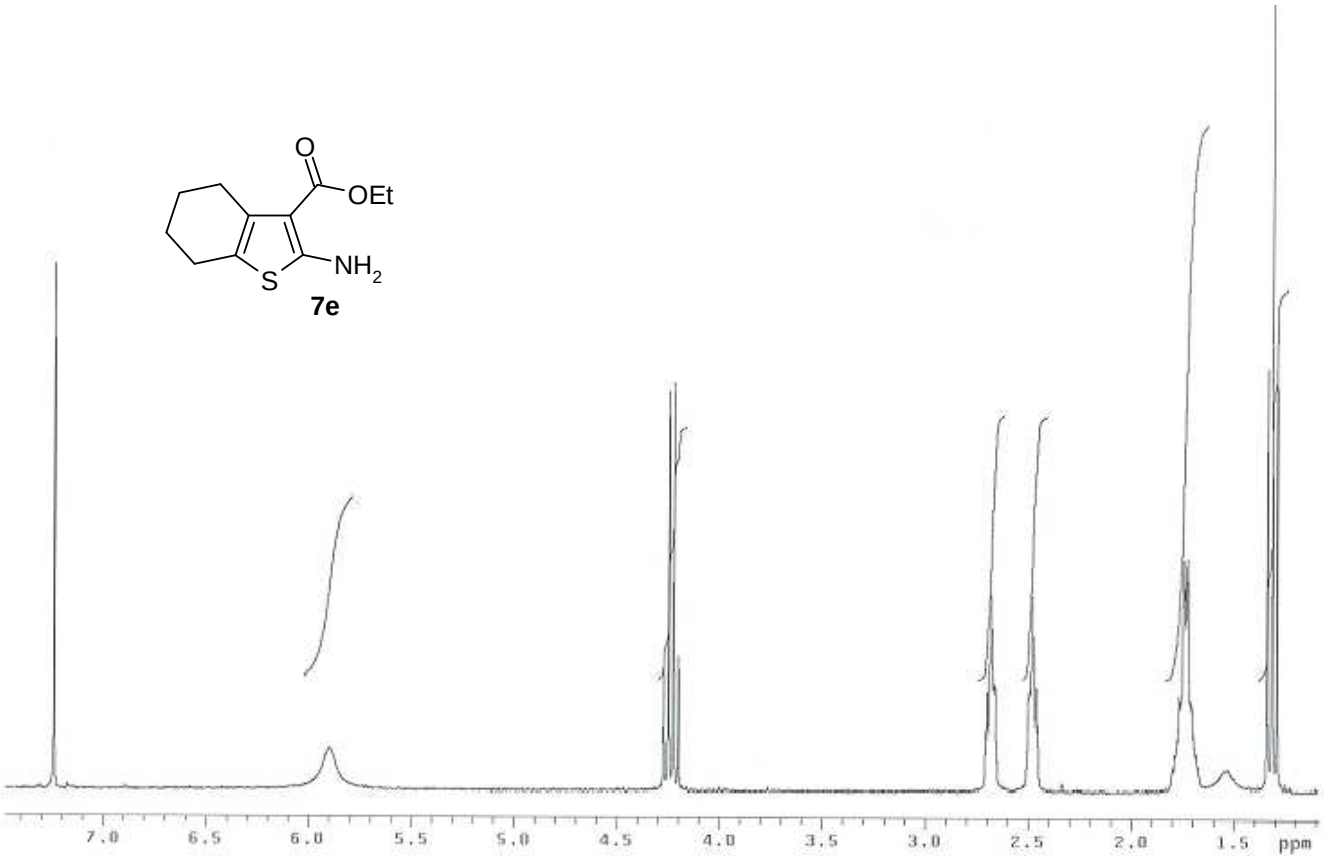
OEt
H3C
NH2
S
7d
8
7
6
5
4
3
2
1
ppm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NH2
S
7e
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5.5
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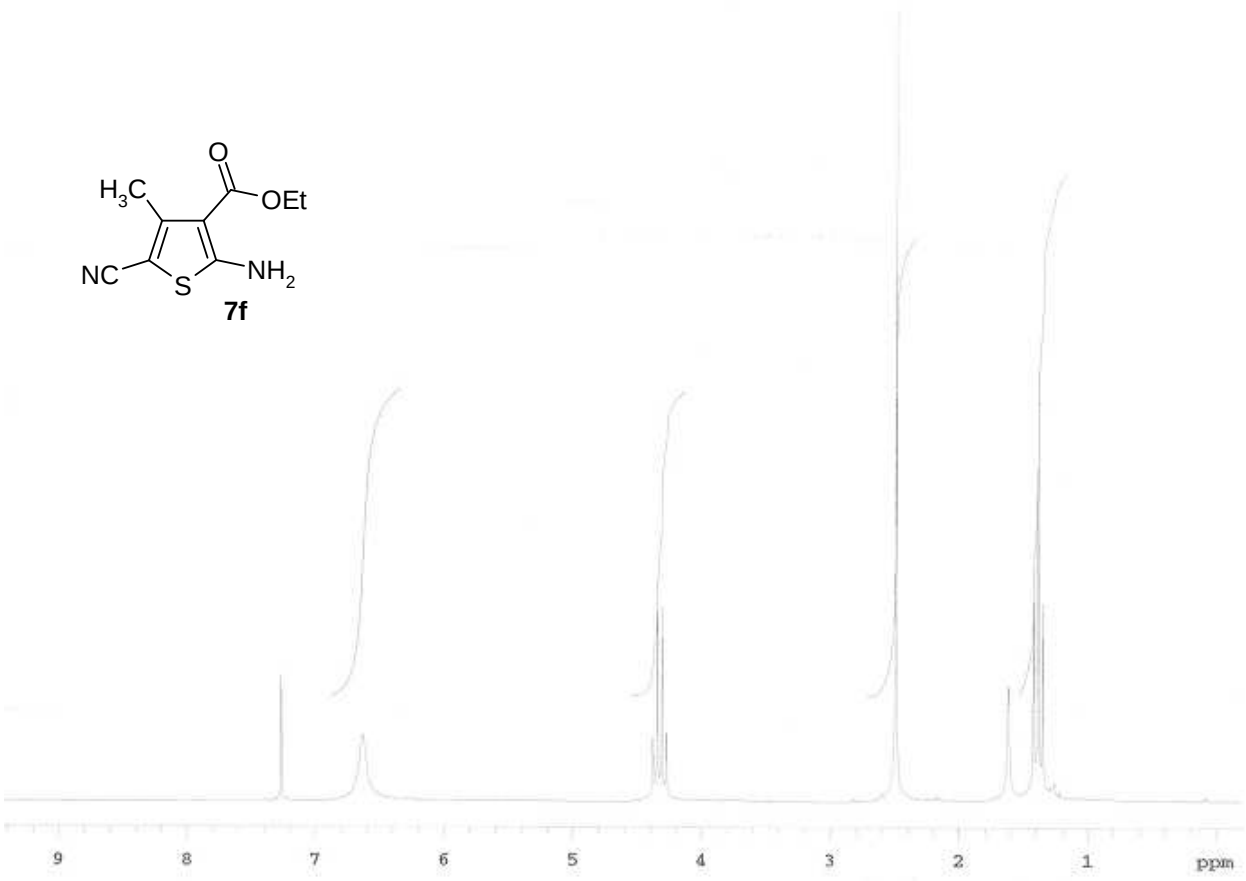
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm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OEt
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NH2
S
7f
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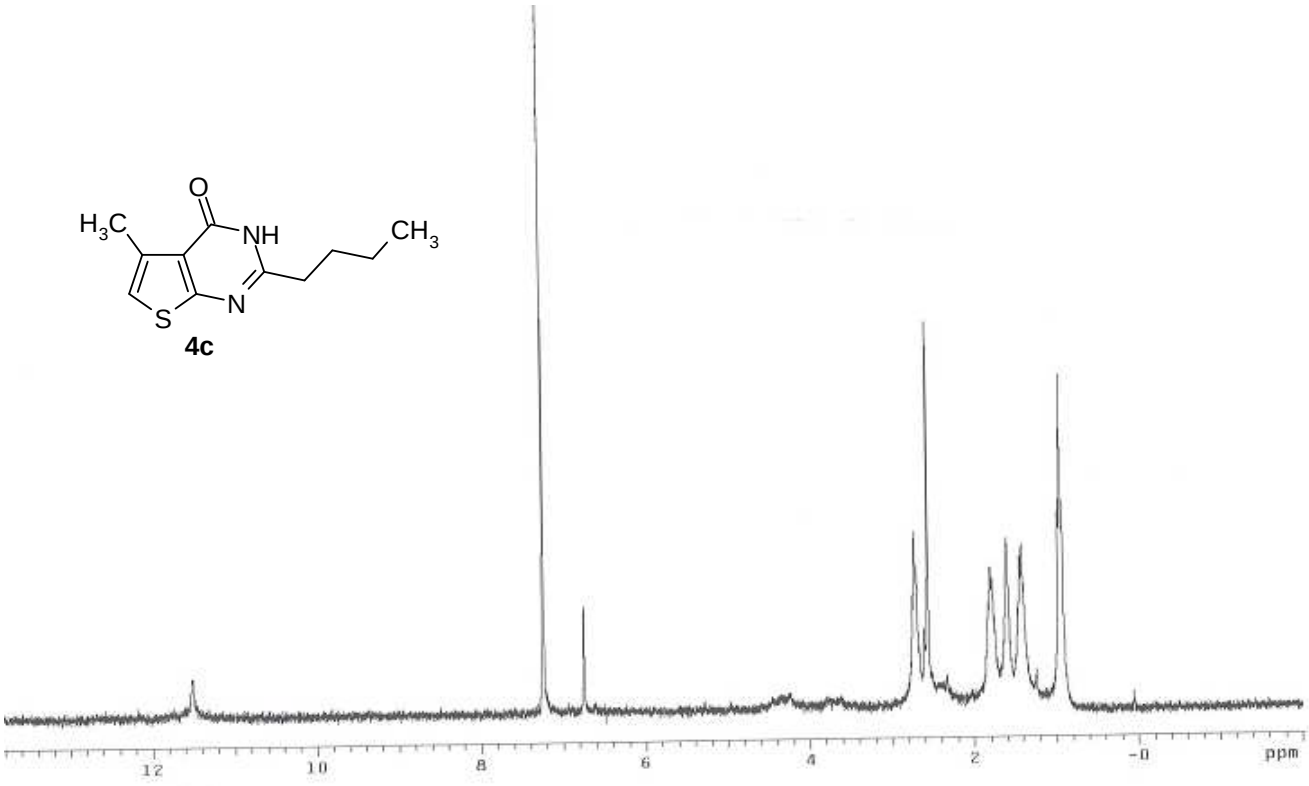
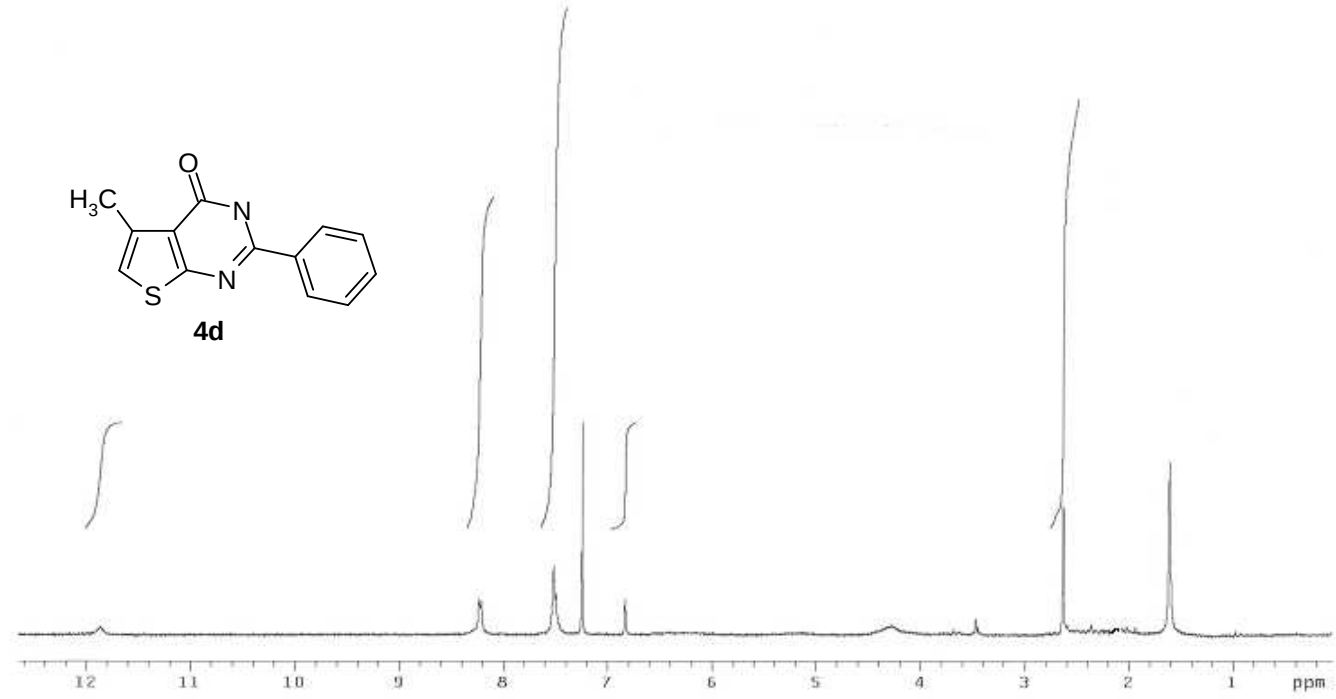
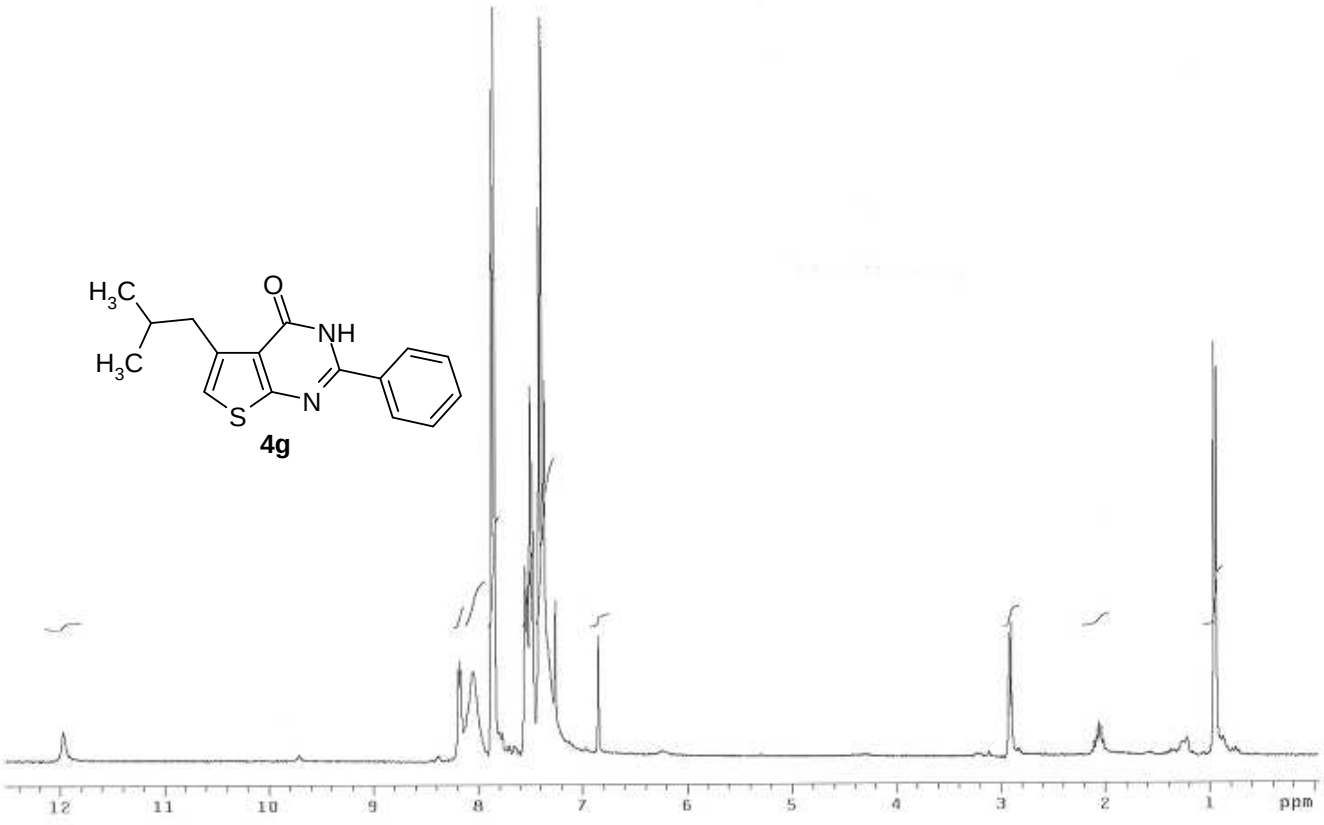
8
7
6
5
4
3
2
1
ppm



4c



4d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H3C
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NH
S
N
4g
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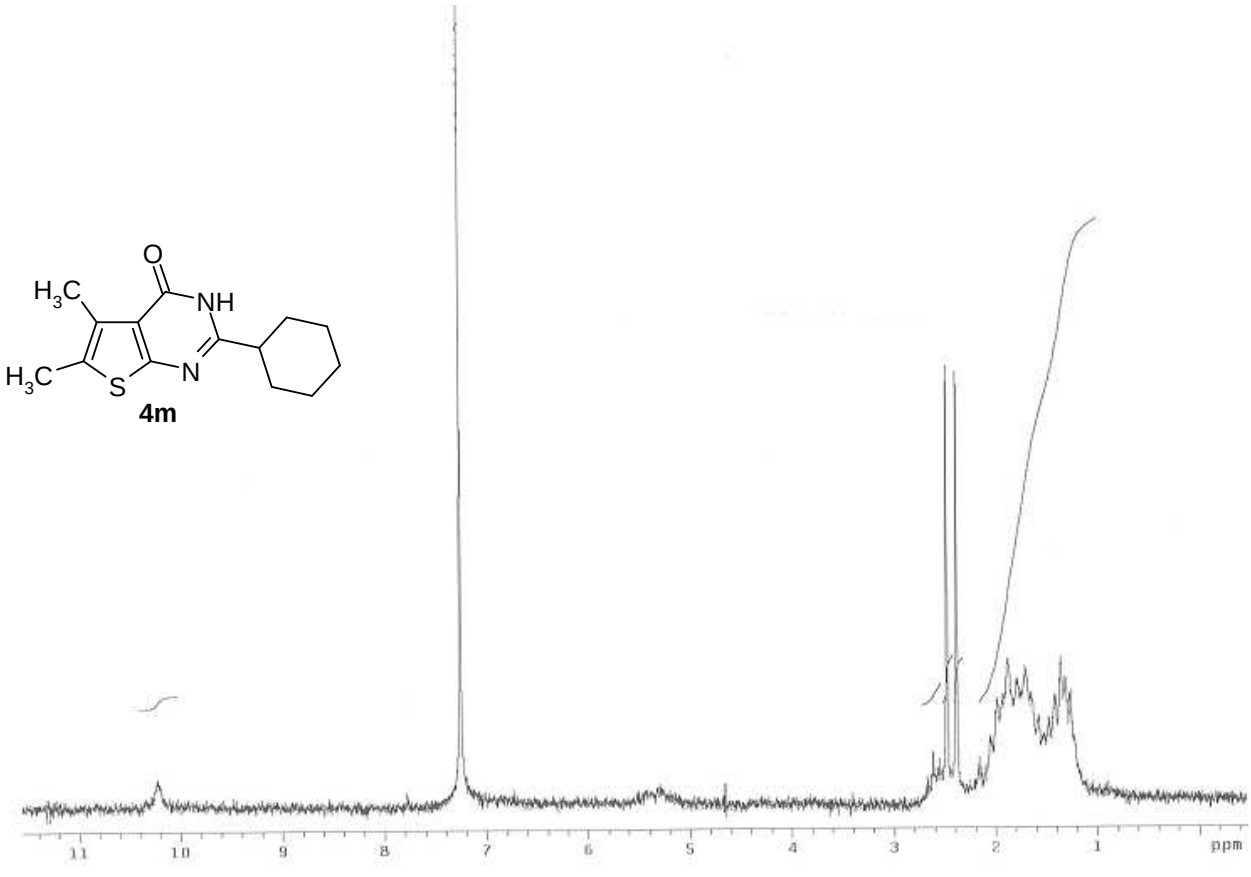
11
10
9
8
7
6
5
4
3
2
1
ppm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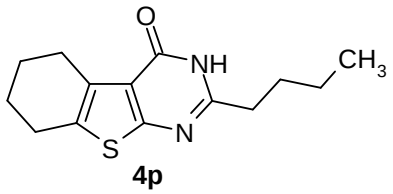
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CH3
S
N

4p

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8
7
6
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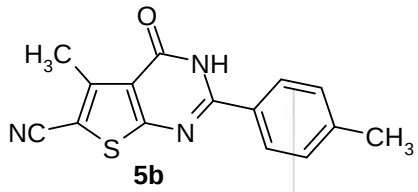
4
3
2
1
ppm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S
N
CH3

5b

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8
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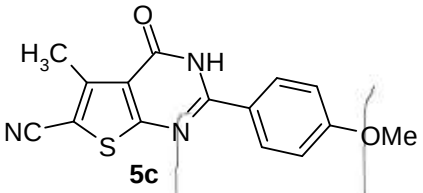
6
5
4
3
2
1
ppm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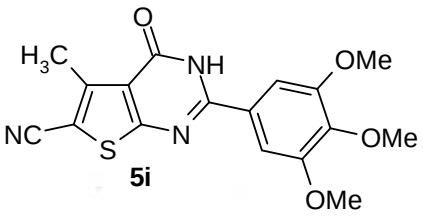
S
N
OMe

5c

9
8
7
6
5
4
3
2
1
ppm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NH
OMe
NC
S
N
OMe
OMe

5i

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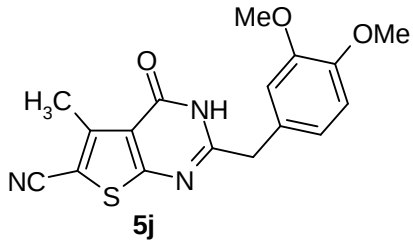
4
3
2
1
ppm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OMe
O
H_3C
NH
NC
S
N

5j

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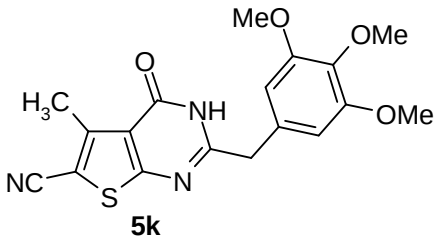
3
2
1
ppm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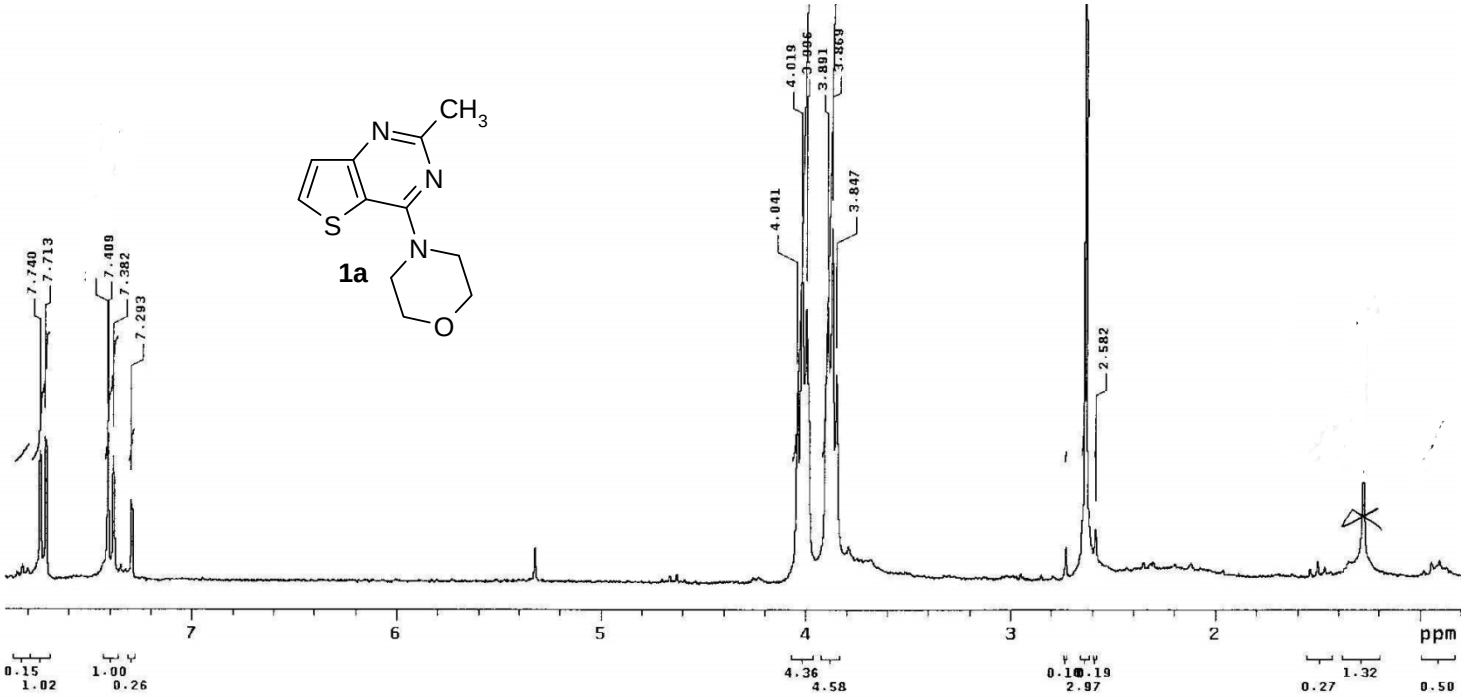
OMe
OMe
O
H_3C
NH
NC
S
N

5k

14
12
10
8
6
4
2
0

^{1}H-NMR for compound 1a–d, 2a–x, 2aa–aw, 2bd and 2bf and selected ^{13}C-NMR spectra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3.996
3.891
3.869
3.847
2.582
7
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5
4
3
2
ppm
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0.19
2.97
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1.32
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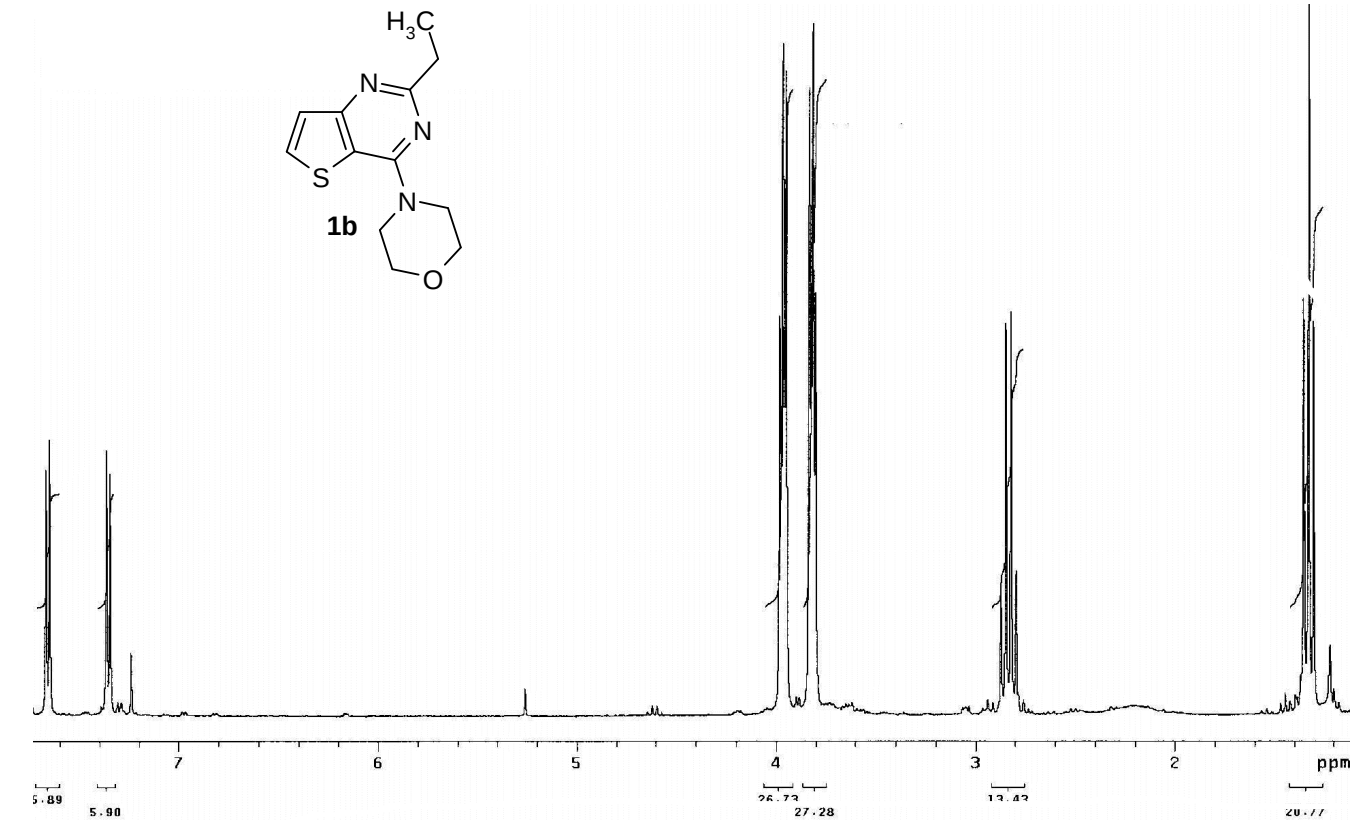
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S
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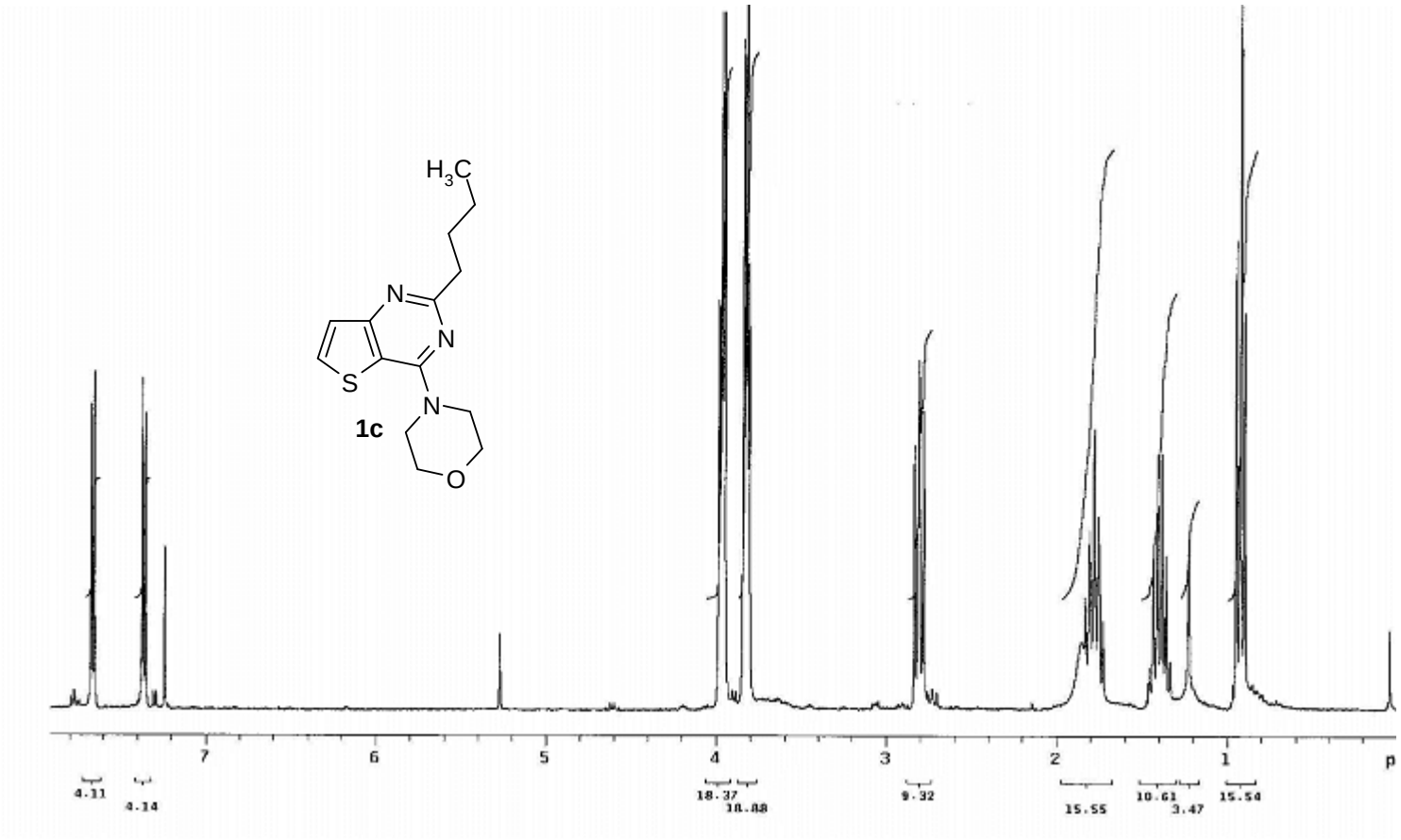
27.28
13.43
20.77


H3C
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S
N
O
1c
7
6
5
4
3
2
1
p
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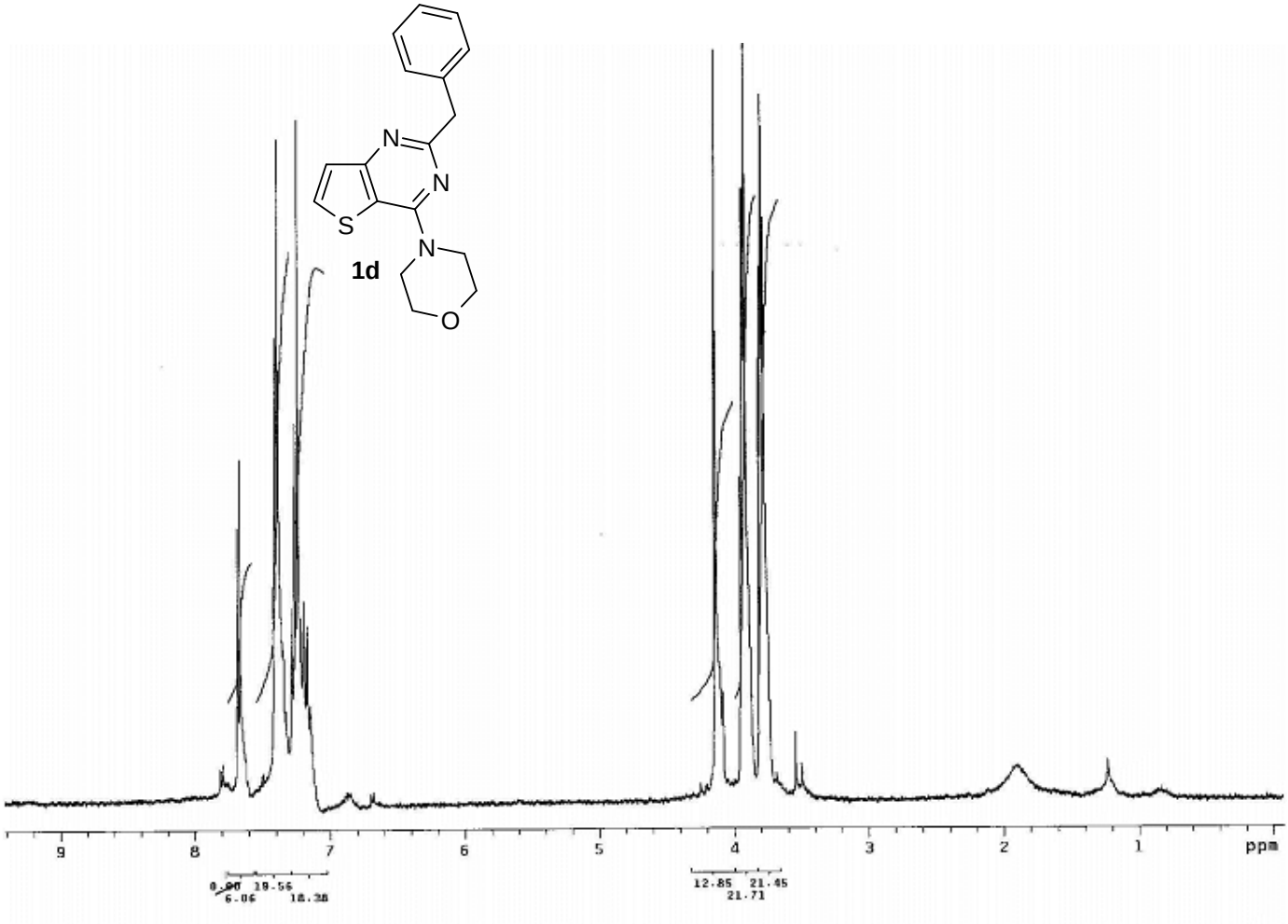
18.88
9.32
15.55
10.61
3.47
15.54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3
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1
ppm
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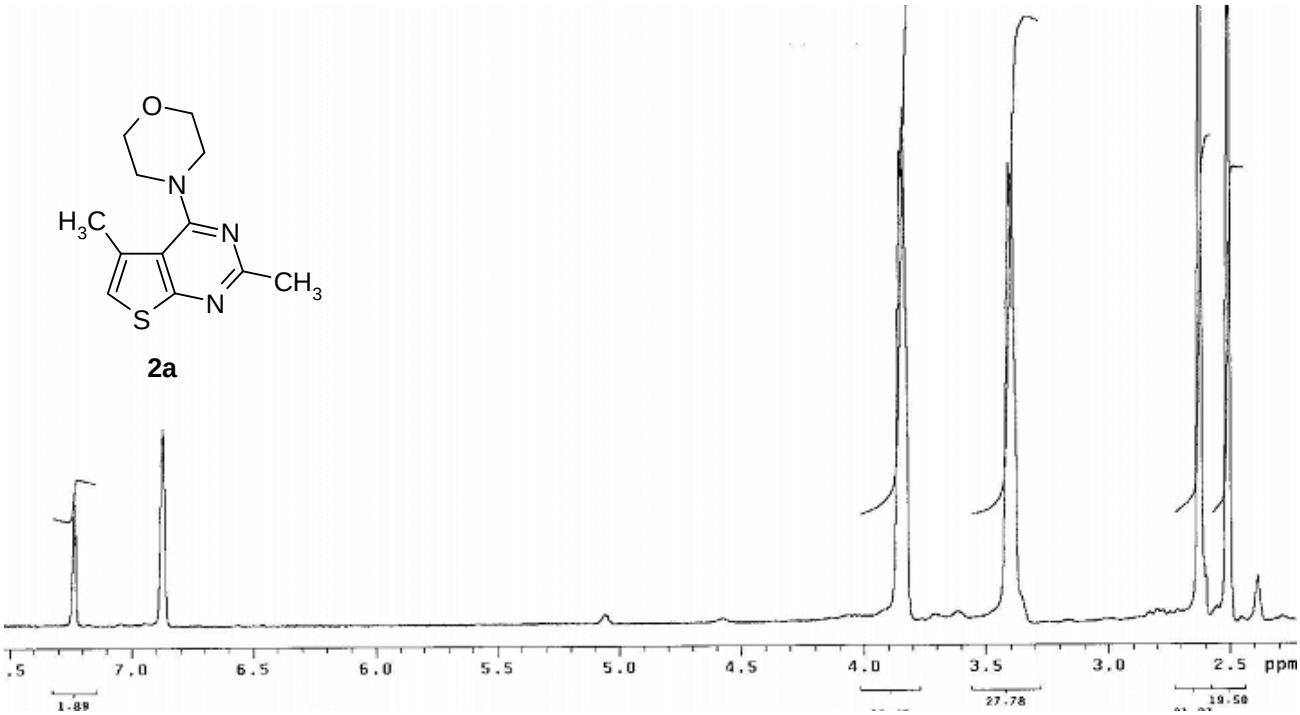
12.85
21.45
21.71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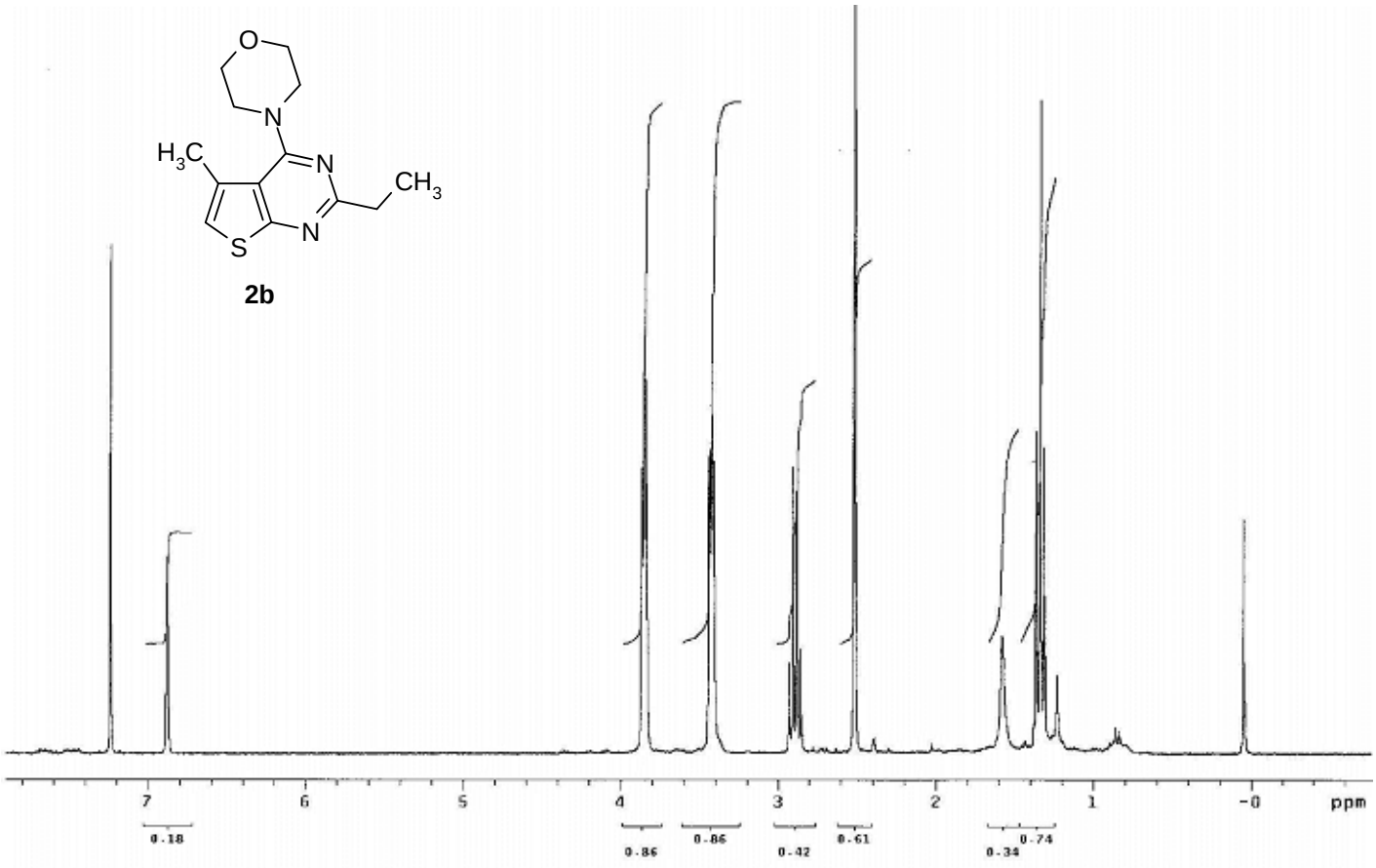
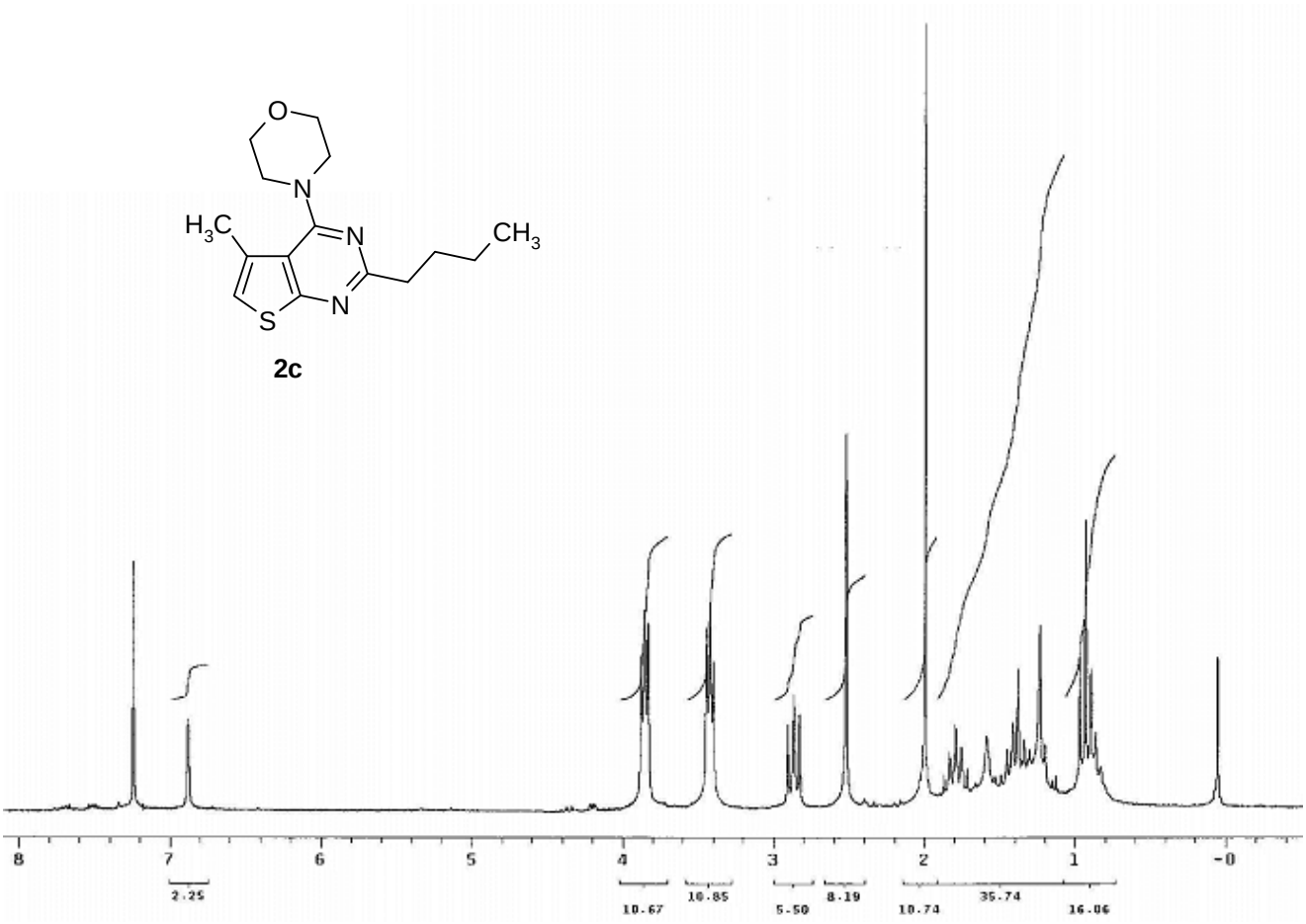
N
H3C
N
CH3
N
S
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm
1.89
27.78
19.50

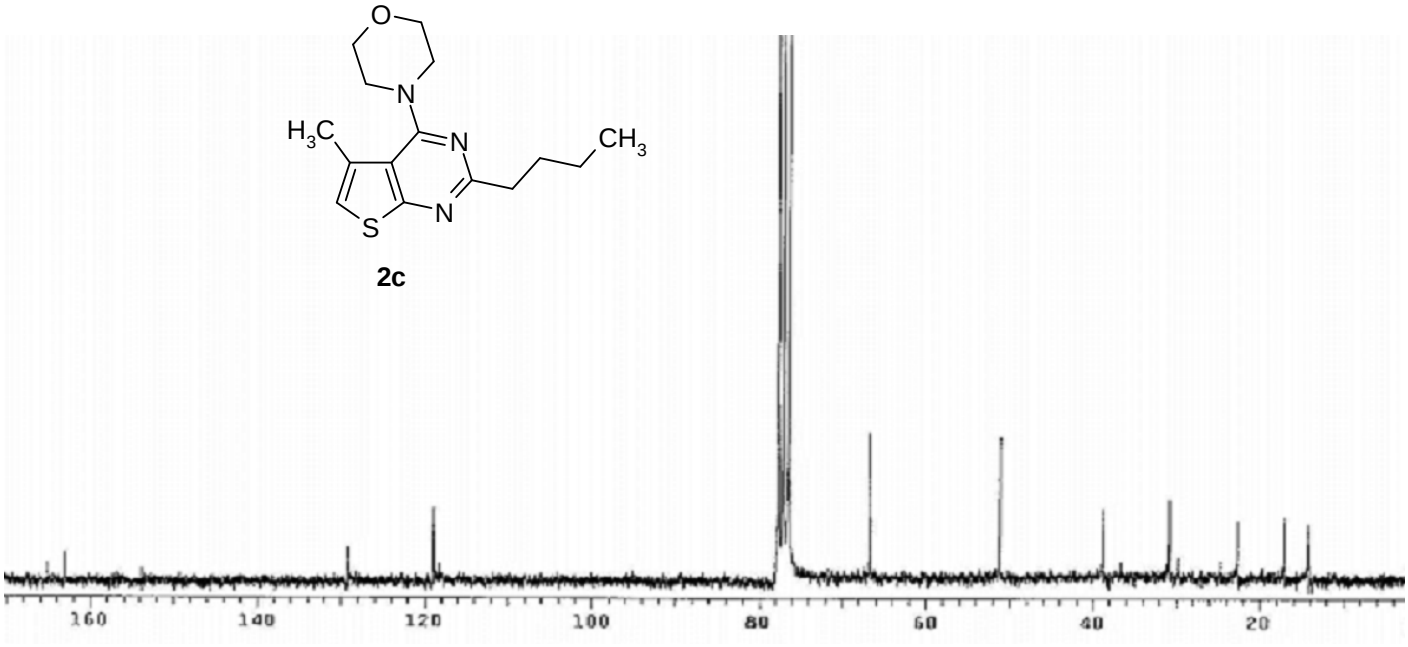
2a


O
N
H3C
N
CH3
N
S
7
6
5
4
3
2
1
-0
ppm
0.18
0.86
0.86
0.42
0.61
0.34
0.74

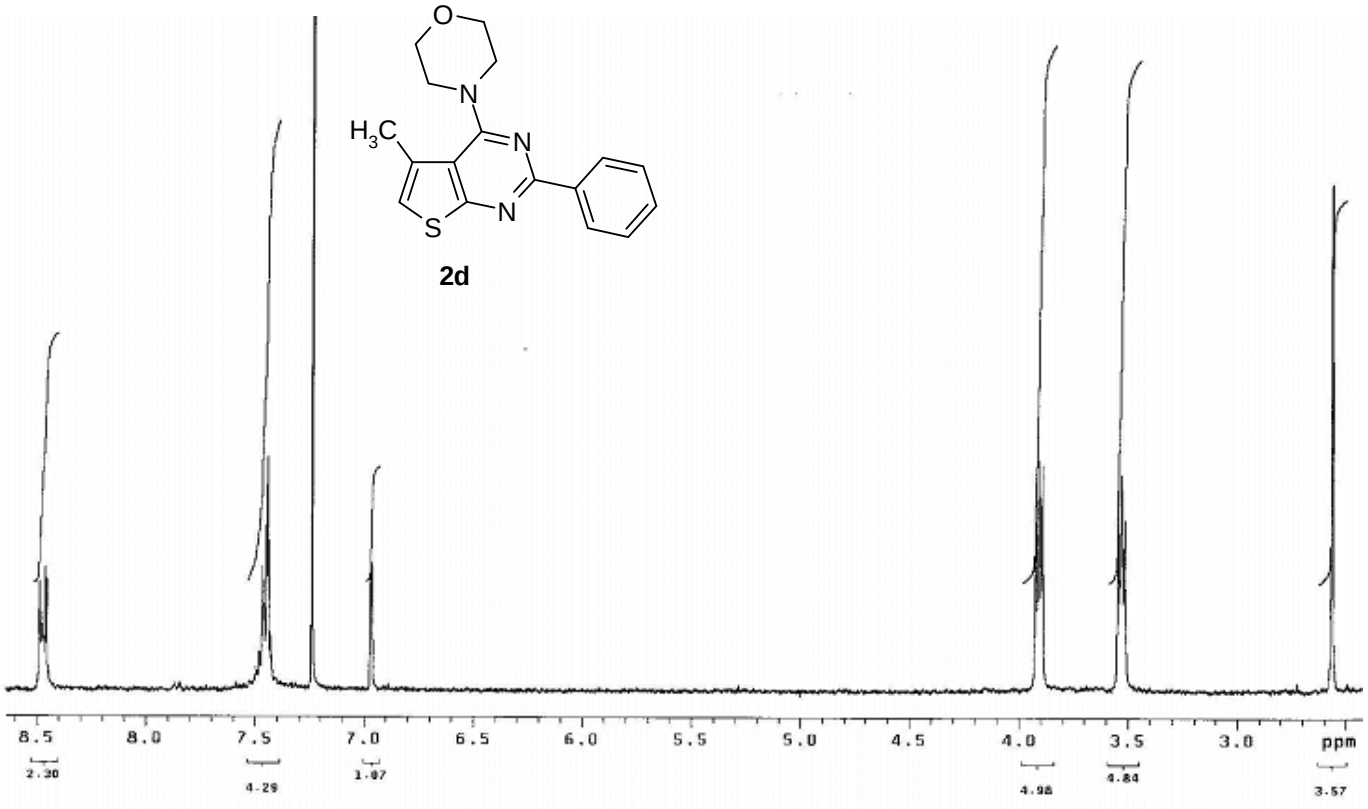
2b


O
N
H3C
N
CH3
S
N
8
7
6
5
4
3
2
1
-0
2.25
10.67
10.85
5.50
8.19
10.74
35.74
16.06

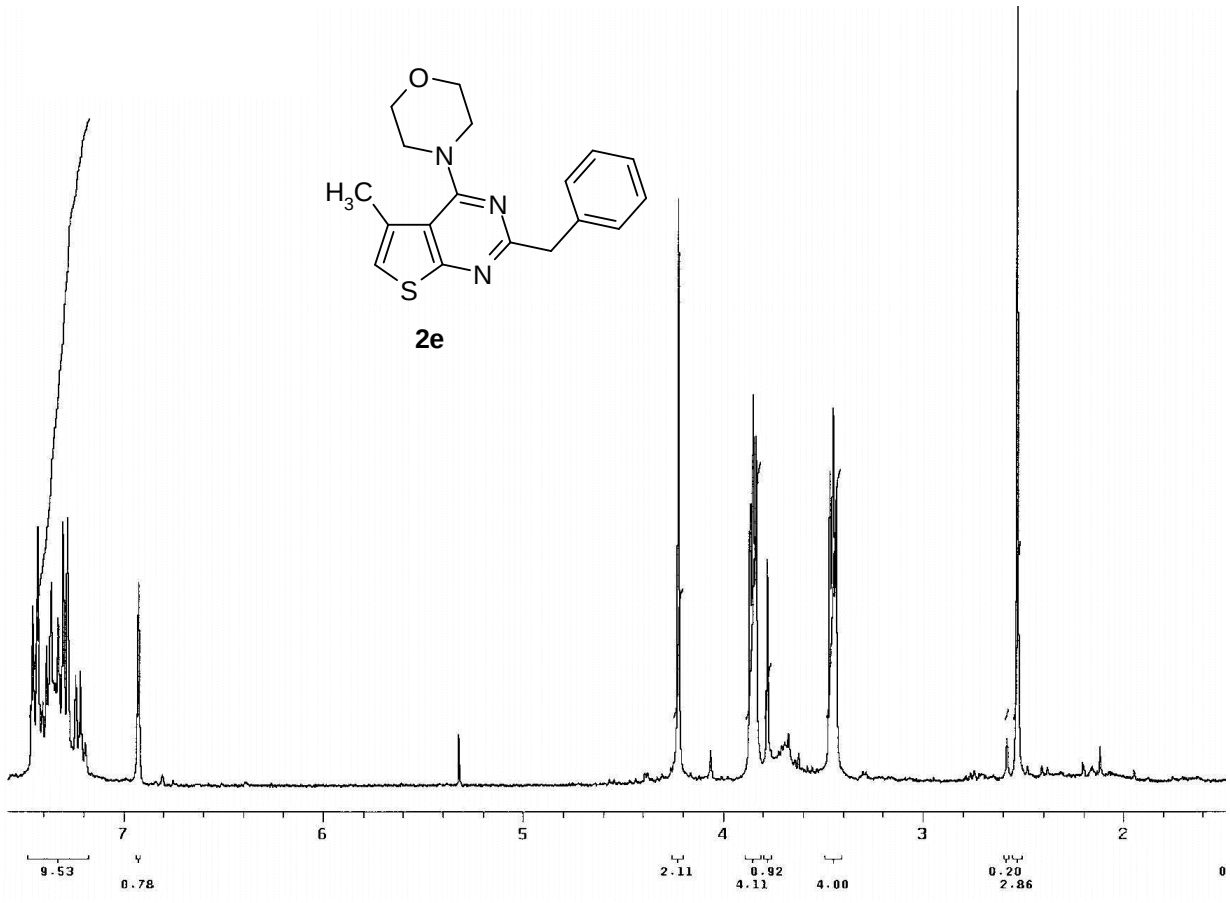
2c


O
N
H3C
N
CH3
S
N
160
140
120
100
80
60
40
20

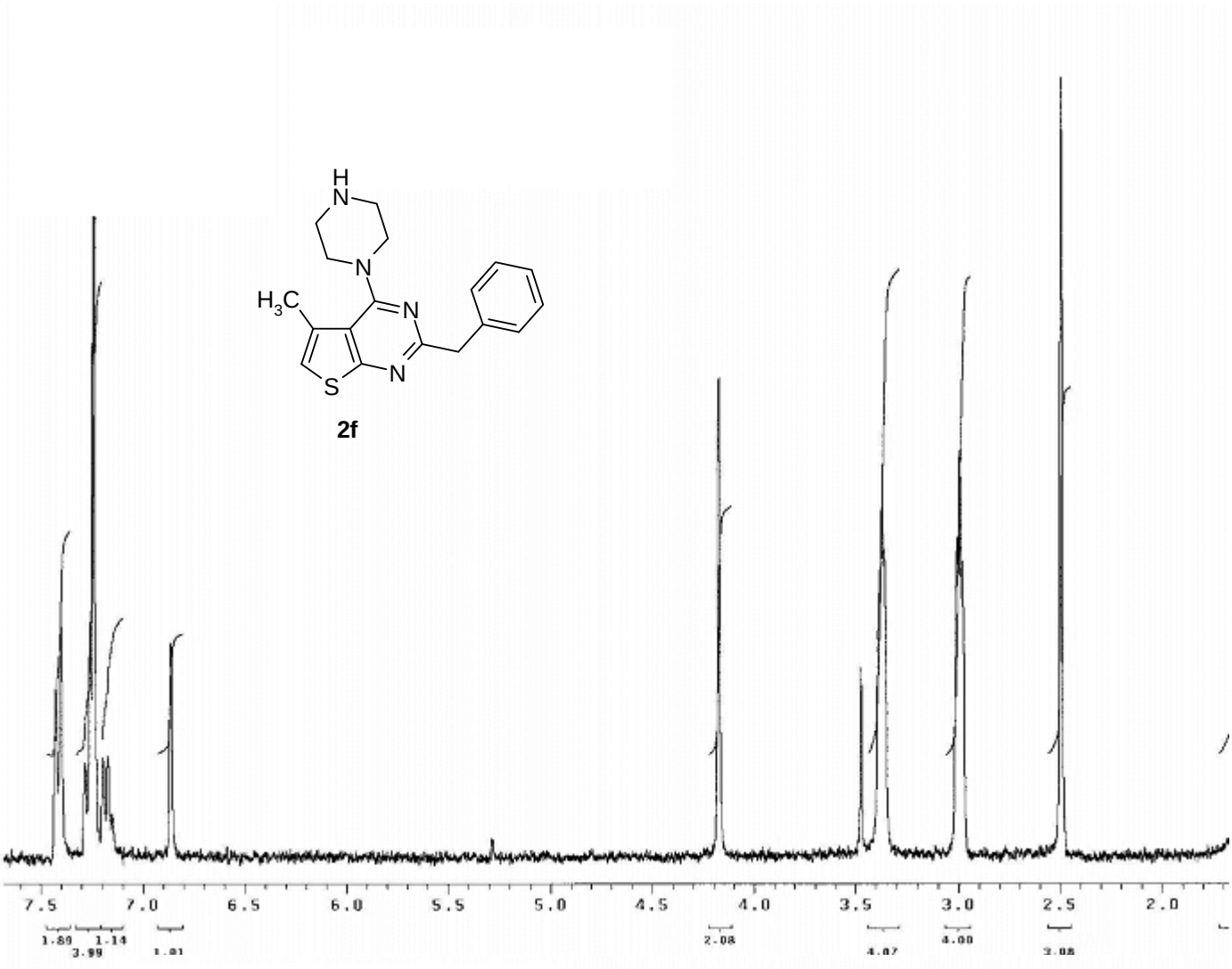
2c


O
N
H3C
N
S
N
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm
2.30
4.29
1.07
4.98
4.84
3.57

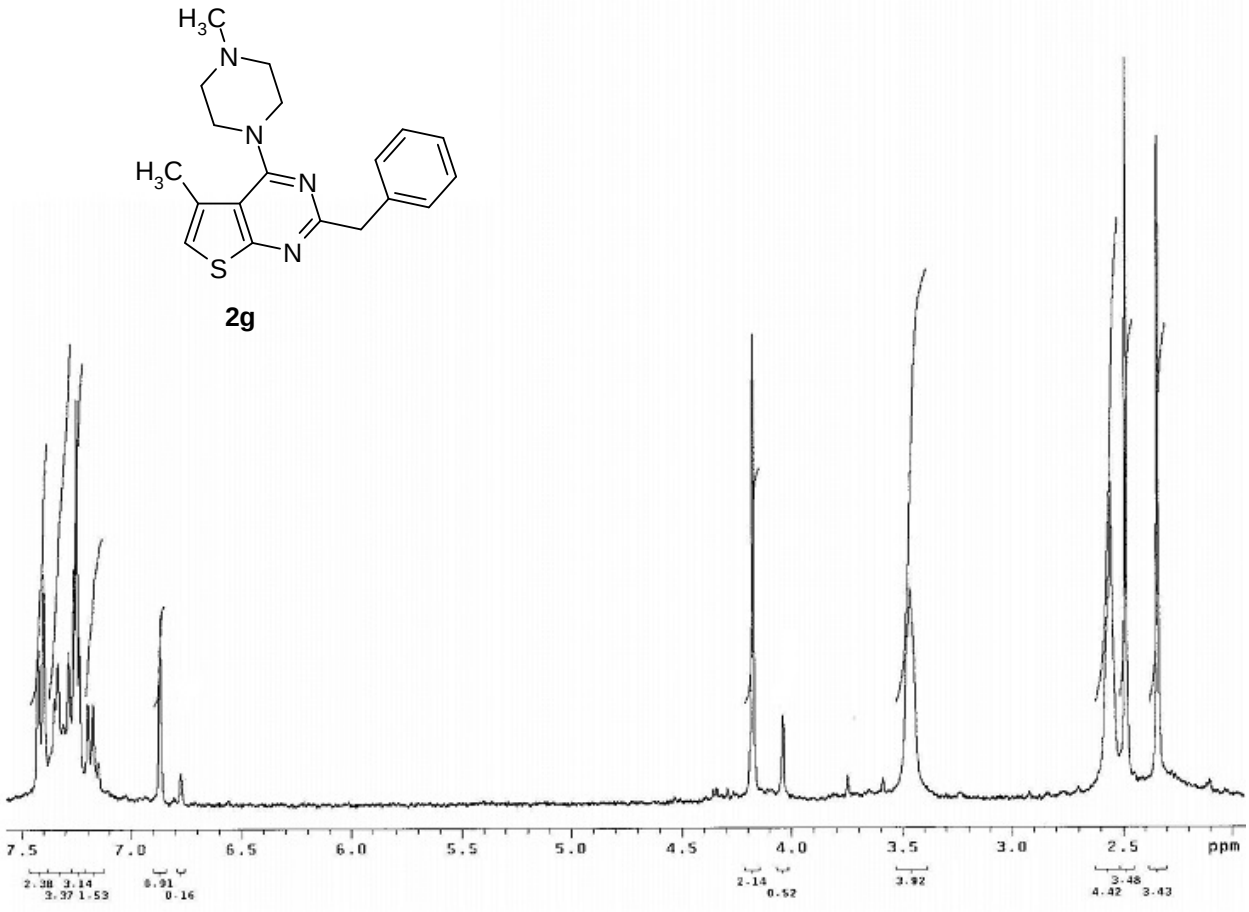
2d


O
N
H3C
N
S
N
7
6
5
4
3
2
9.53
0.78
2.11
0.92
4.11
4.00
0.20
2.86
0

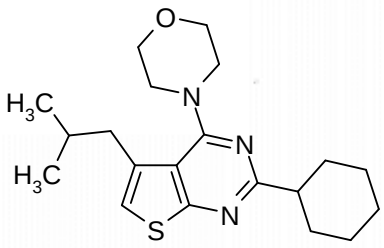
2e


H
N
N
H3C
N
S
N
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.89
1.14
3.99
2.08
4.00

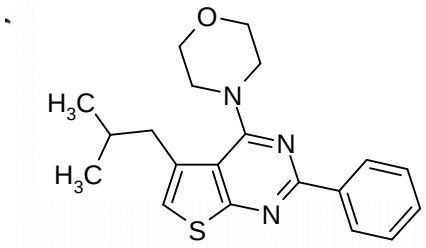
2f


H3C
N
N
H3C
N
S
N
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm
2.38
3.14
3.37
1.53
0.91
0.16
2.14
0.52
3.92
3.48
4.42
3.43

2g

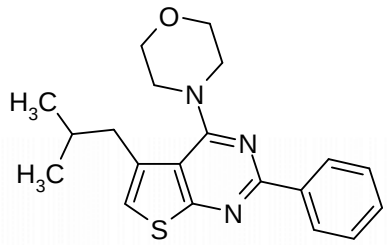


2h

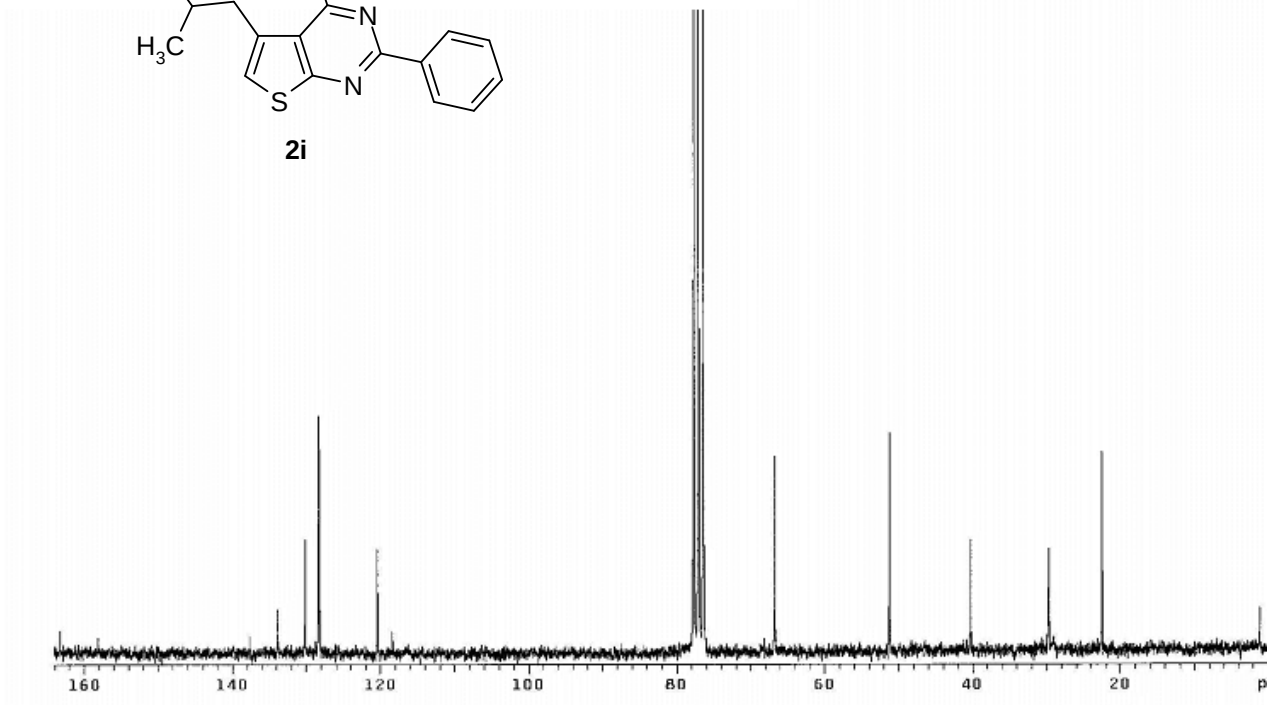

O
N
H_3C
H_3C
N
N
S

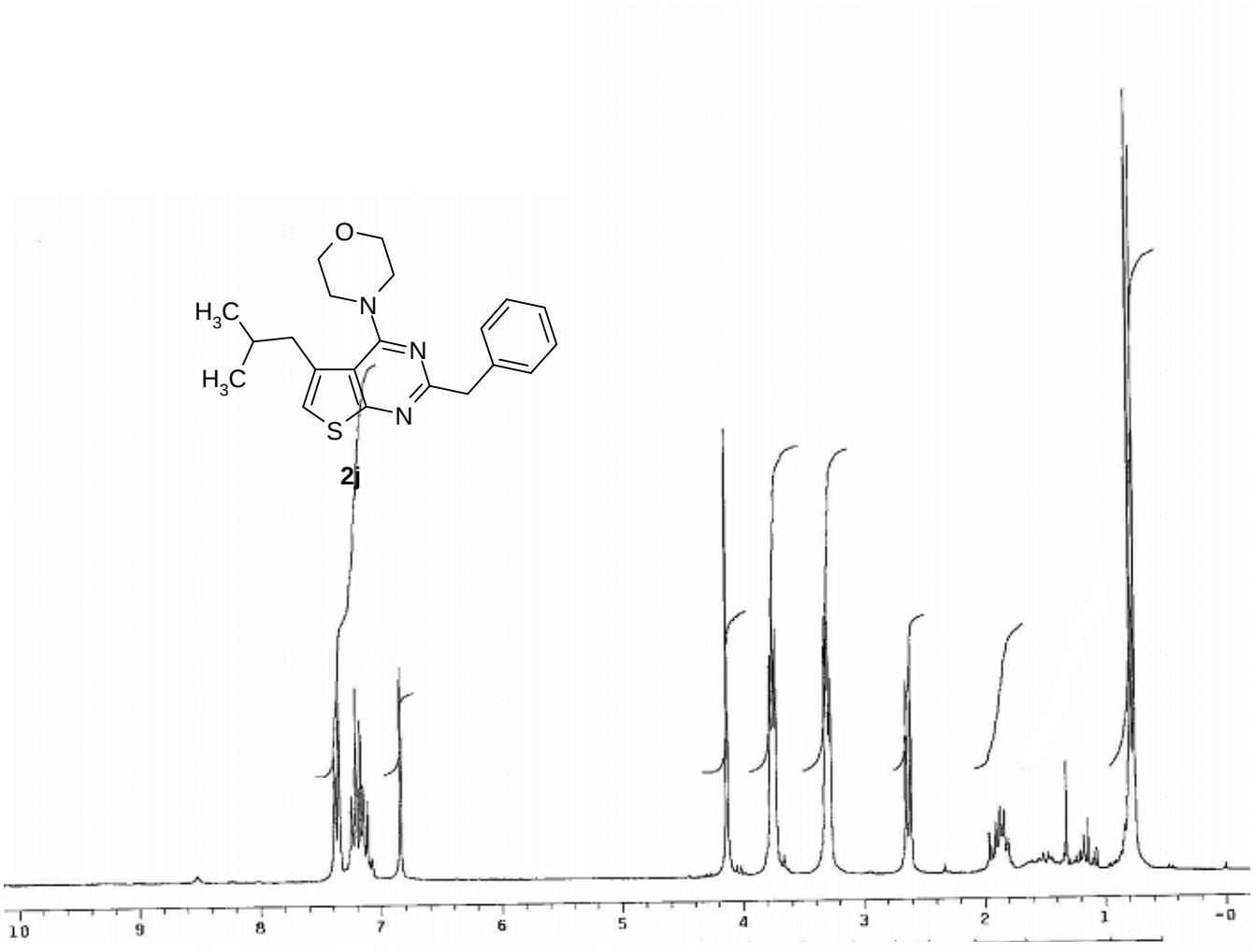
2i

8
7
6
5
4
3
2
1
ppm
7.76
12.51
3.88
16.63
16.51
8.22
4.37
30.12

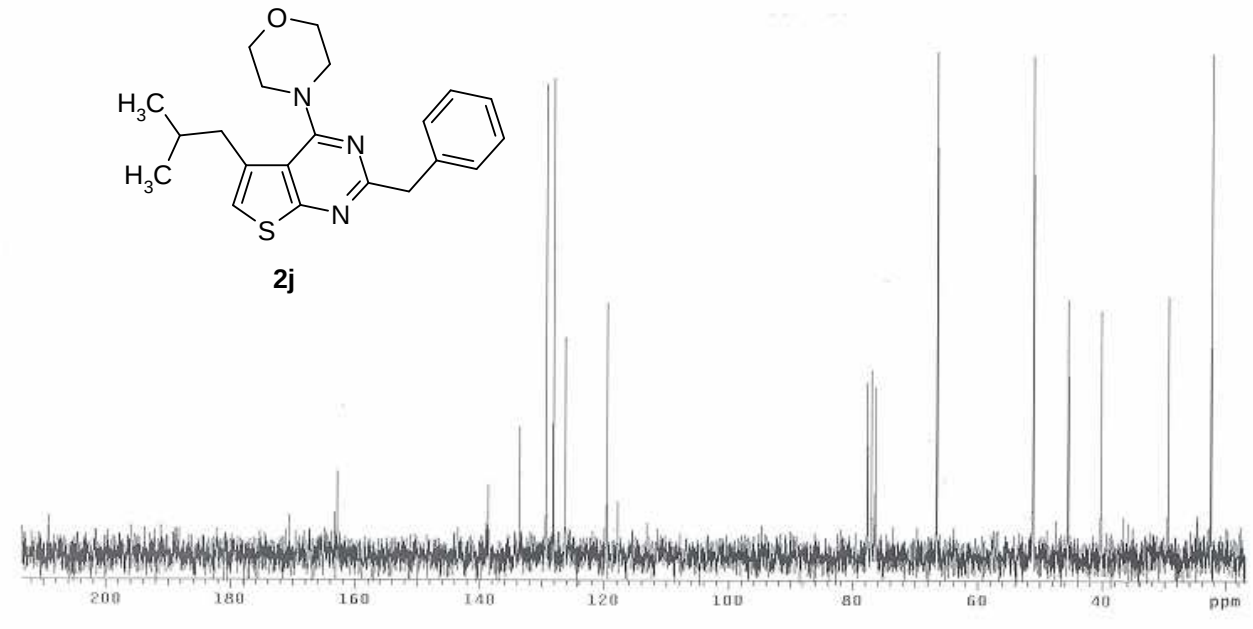

O
N
H_3C
H_3C
N
N
S

2i

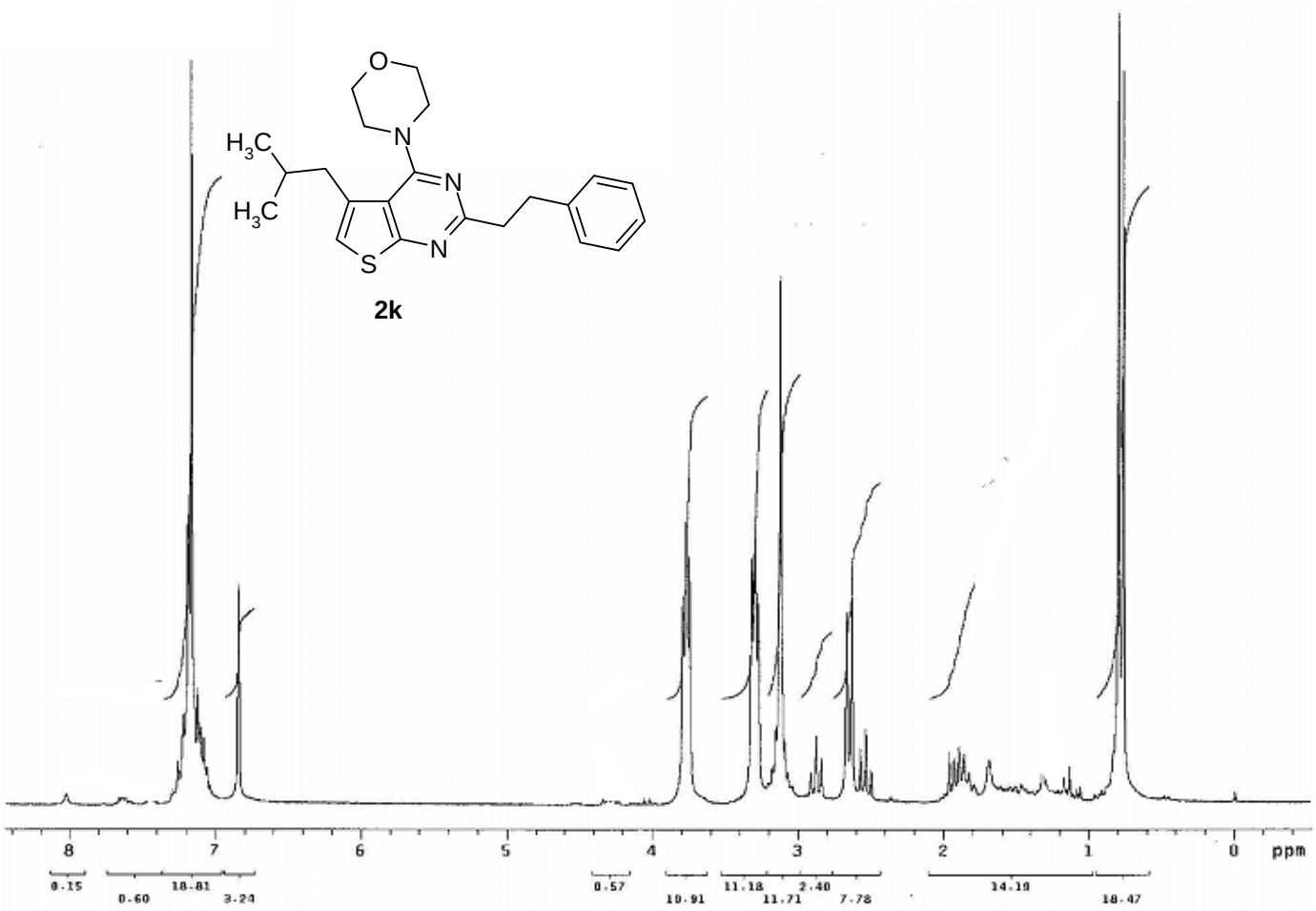

160
140
120
100
80
60
40
20
p

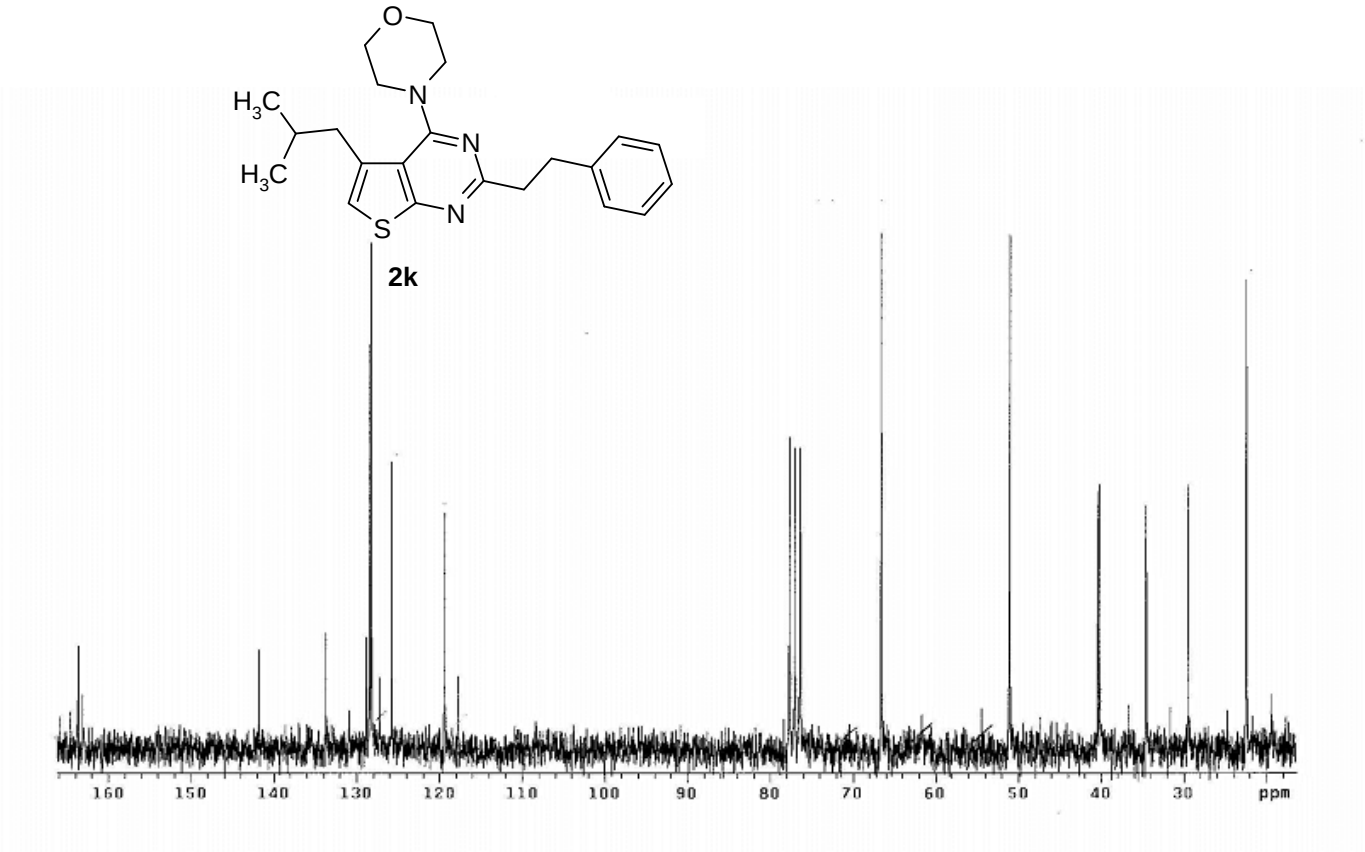

O
N
H3C
H3C
N
N
S
10
9
8
7
6
5
4
3
2
1
-0

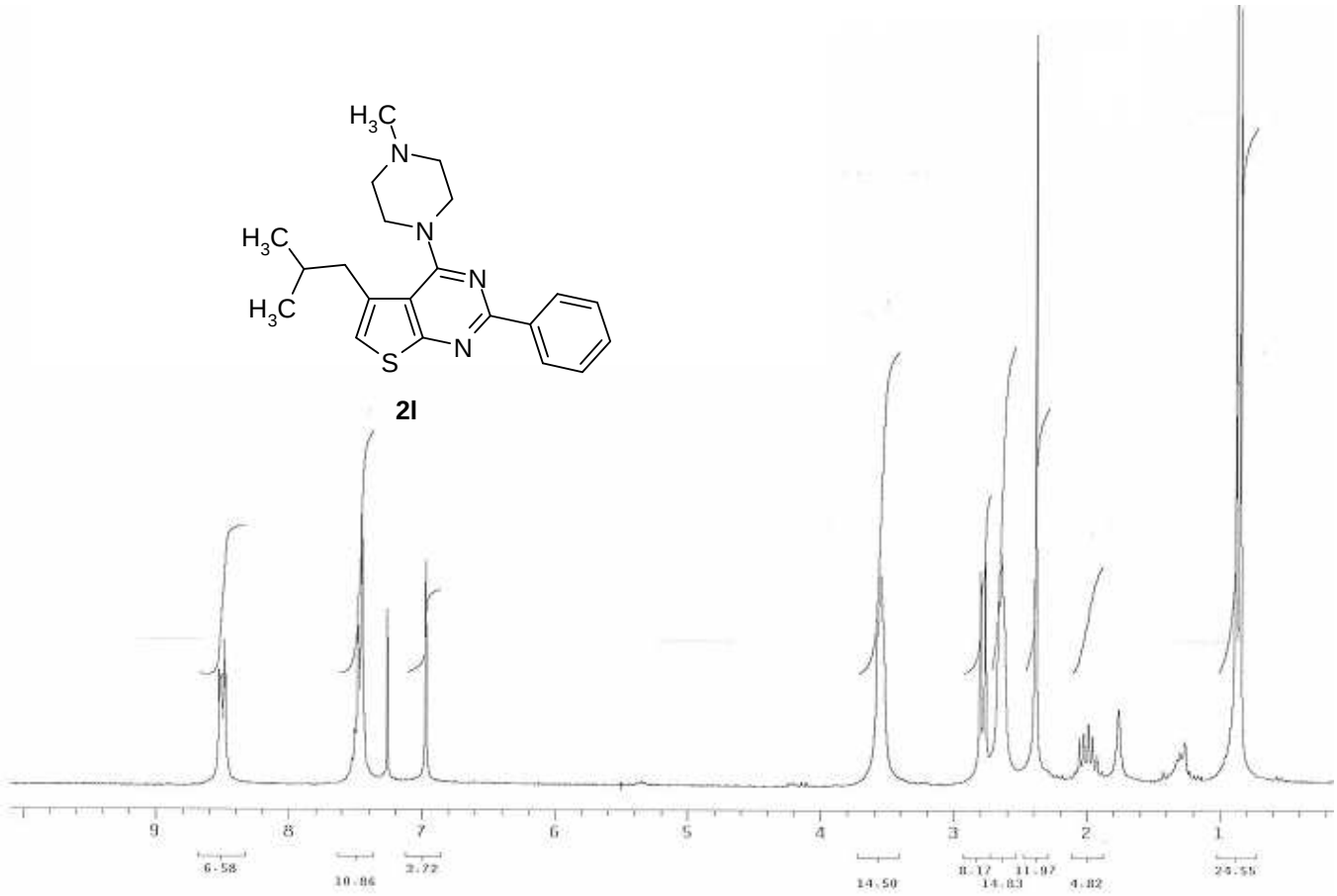
2j


O
N
H3C
H3C
N
N
S
200
180
160
140
120
100
80
60
40
ppm

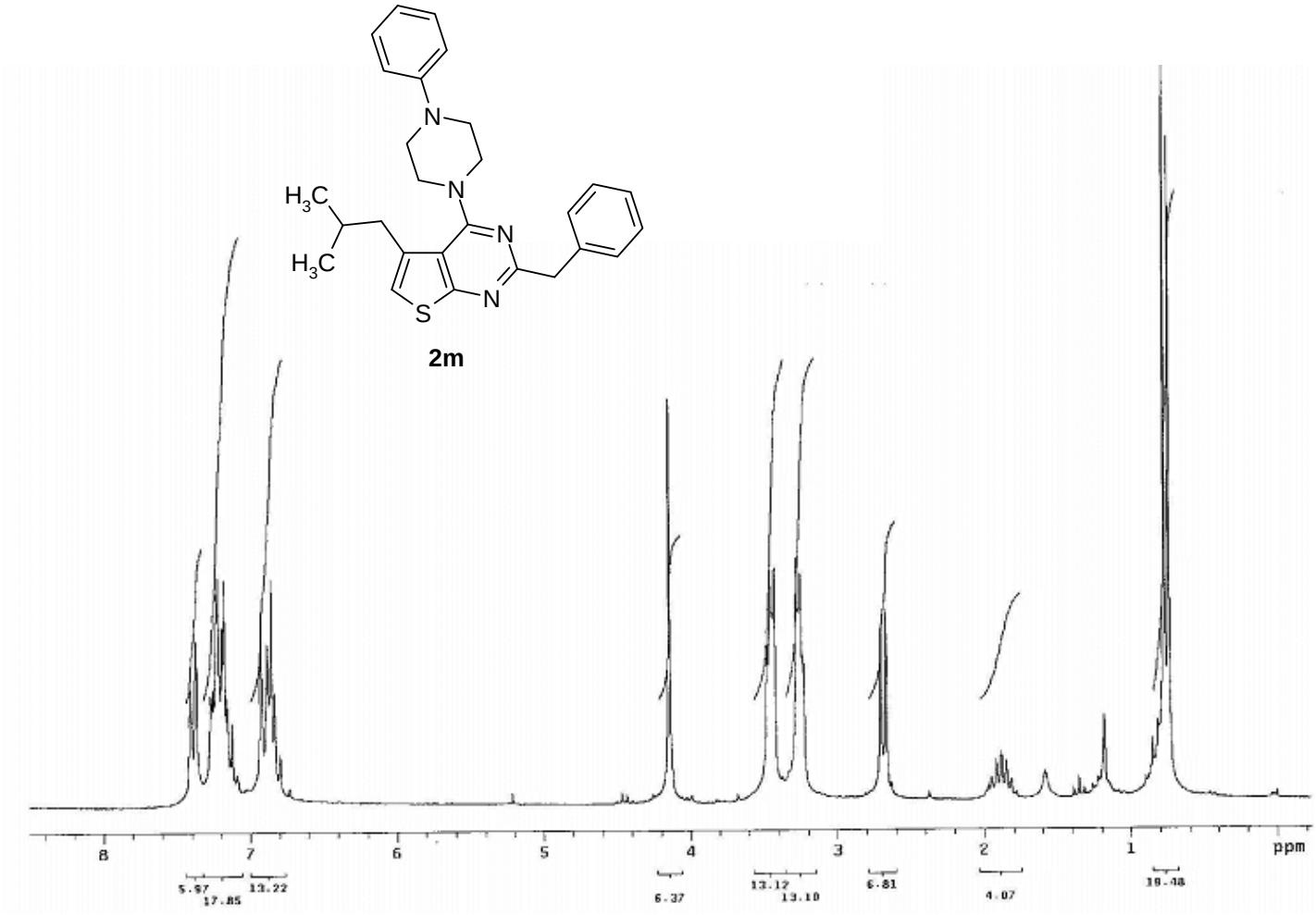
2j


O
N
H3C
H3C
N
N
S
2k
8
7
6
5
4
3
2
1
0
ppm
0.15
0.60
18.81
3.24
0.57
10.91
11.18
11.71
2.40
7.78
14.10
18.47

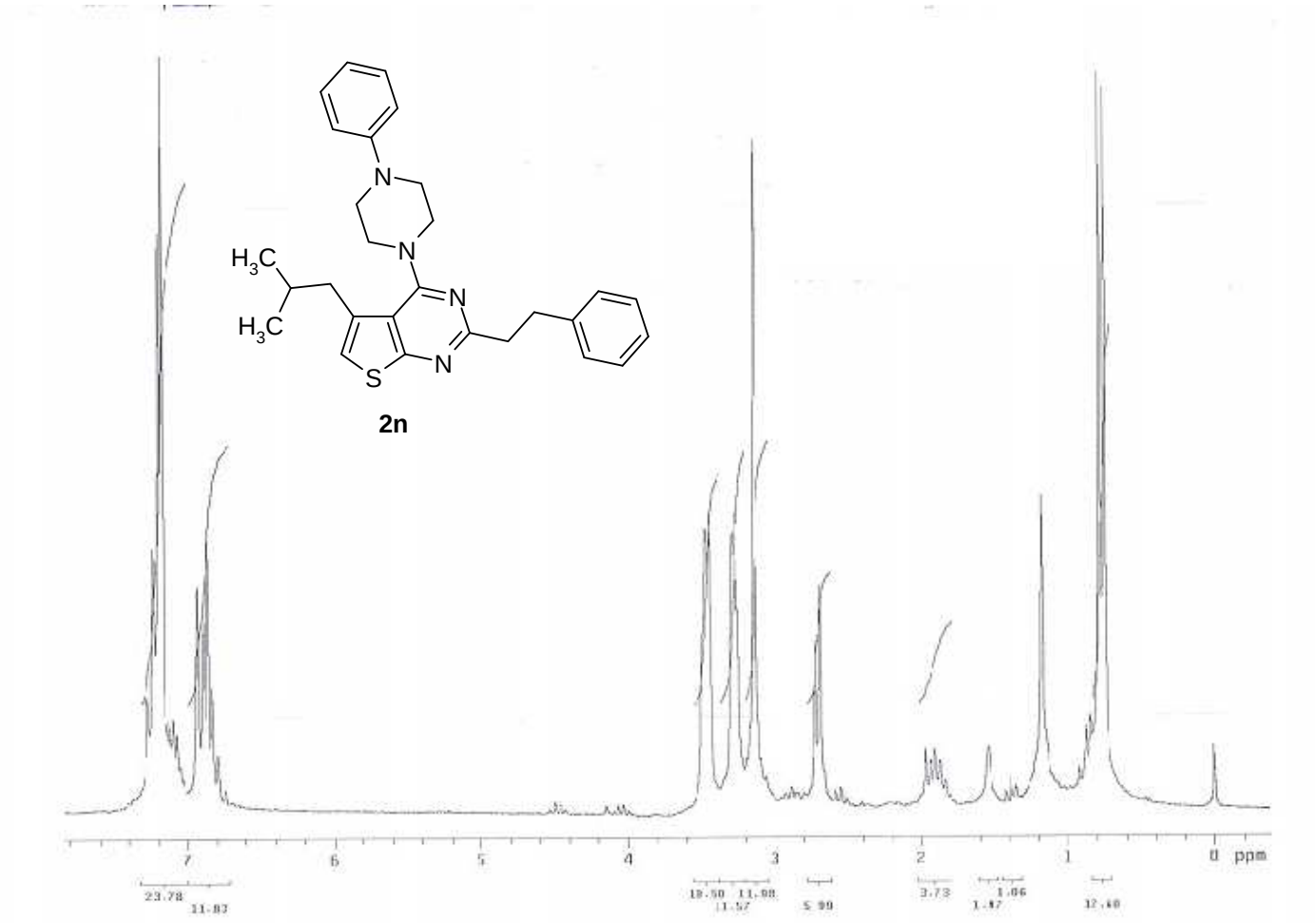

O
N
H3C
H3C
N
N
S
2k
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm


H3C
N
N
H3C
H3C
N
S
N
9
8
7
6
5
4
3
2
1
6.58
10.86
3.72
14.50
8.17
14.83
11.97
4.82
26.55

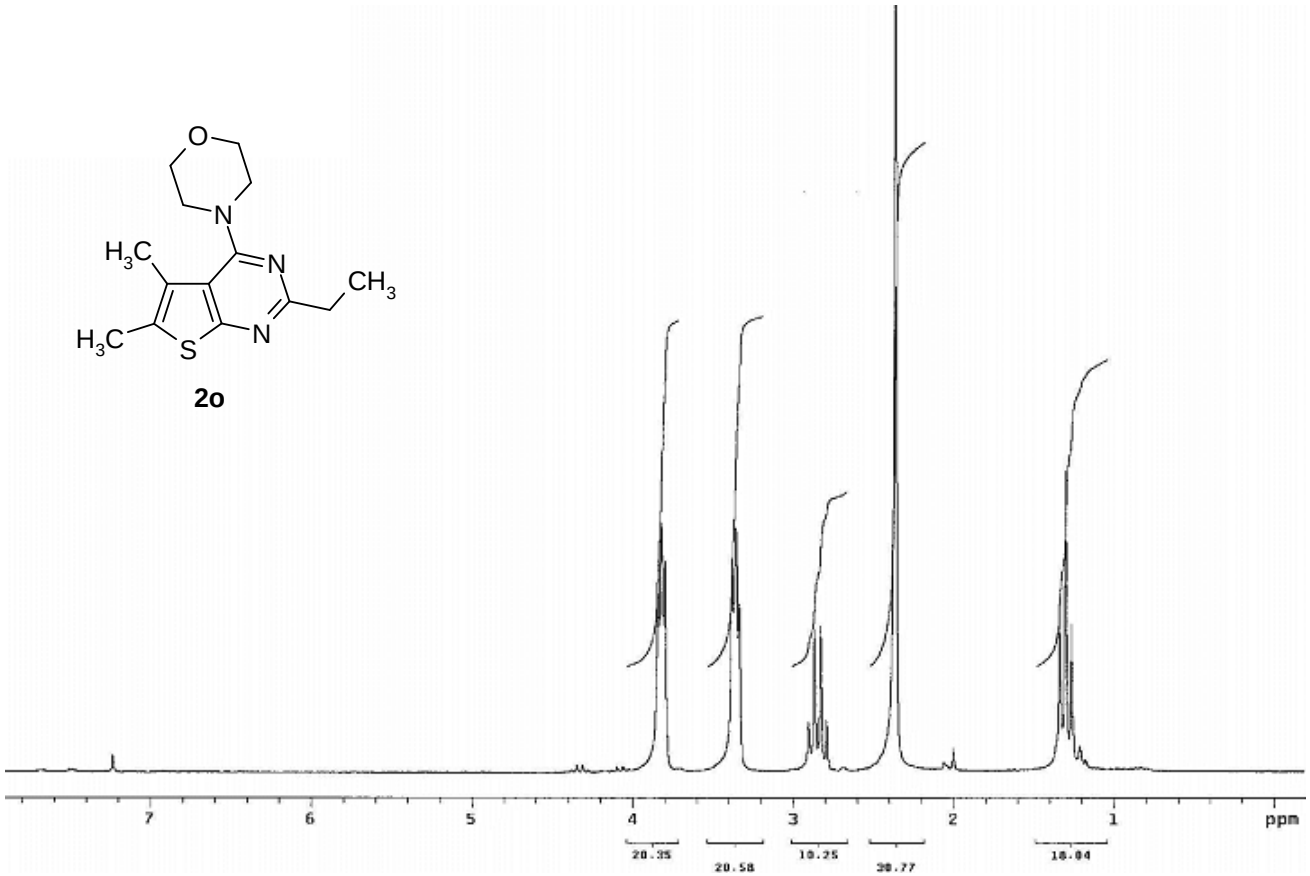
2l


N
N
H3C
H3C
N
S
N
8
7
6
5
4
3
2
1
ppm
5.97
17.85
13.22
6.37
13.12
13.10
6.81
4.07
19.48

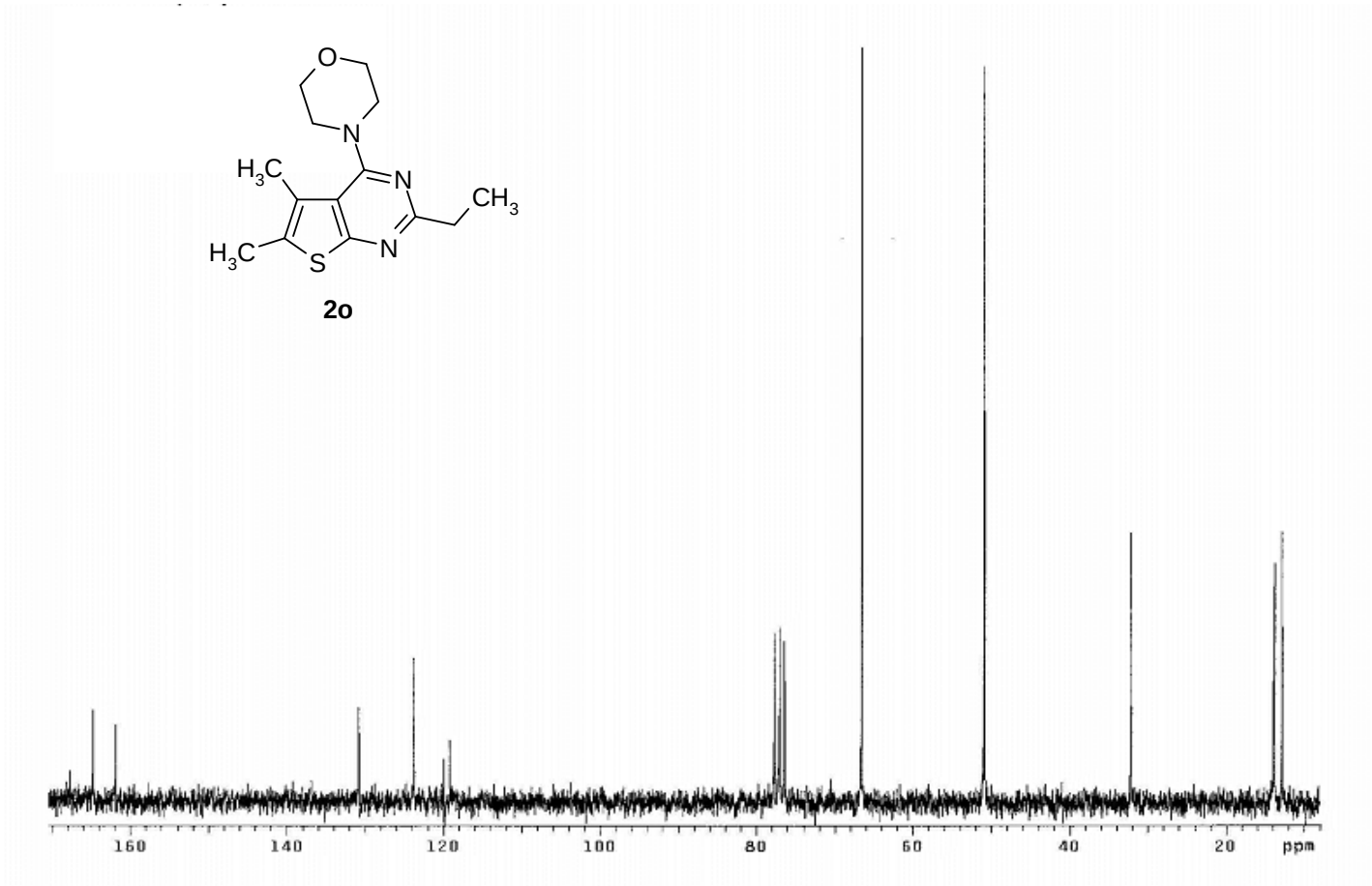
2m


N
N
H3C
H3C
N
N
S
7
6
5
4
3
2
1
0 ppm
23.78
11.83
19.50
11.98
11.57
5.99
3.73
1.87
1.06
12.40

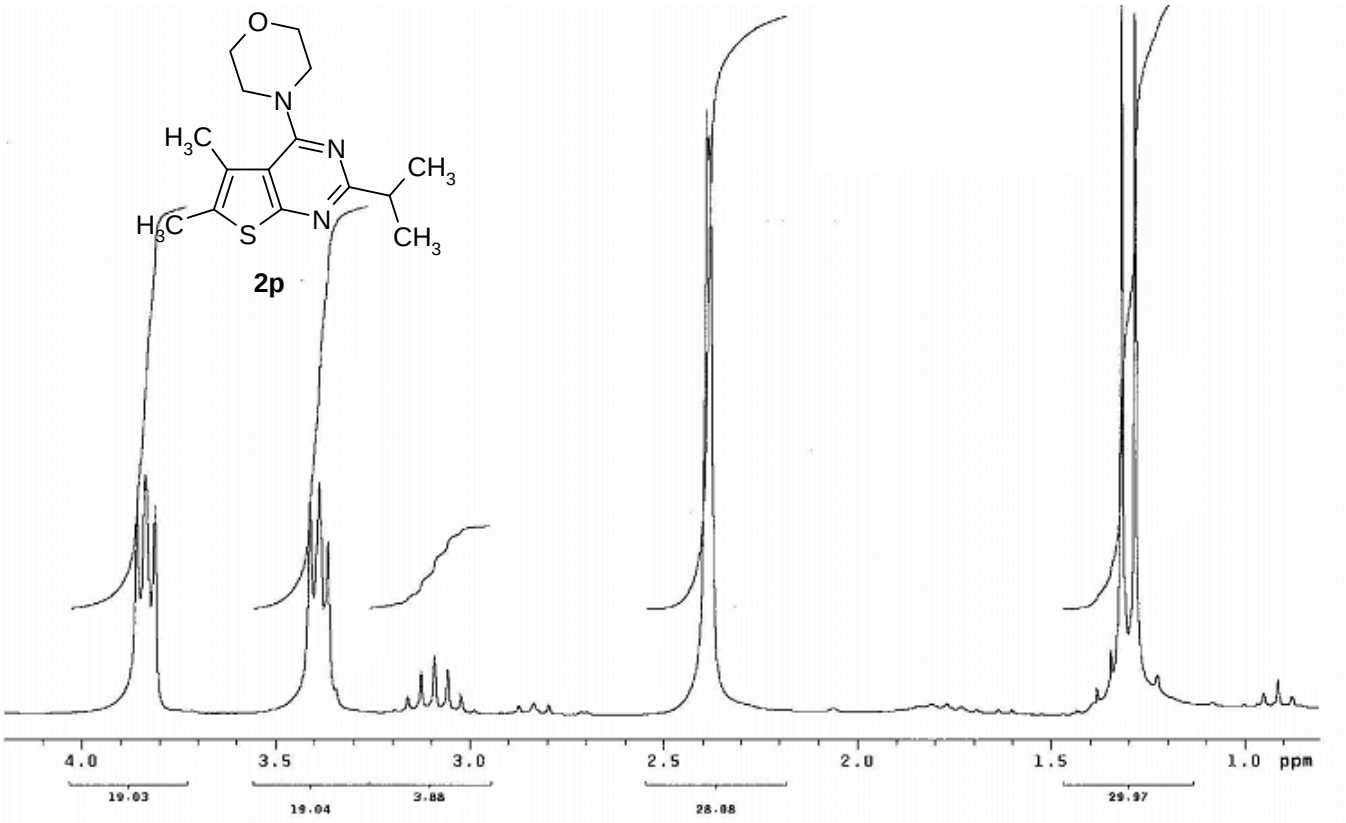
2n


O
N
H3C
N
CH3
H3C
S
N
7
6
5
4
3
2
1
ppm
20.35
20.58
19.25
30.77
18.04

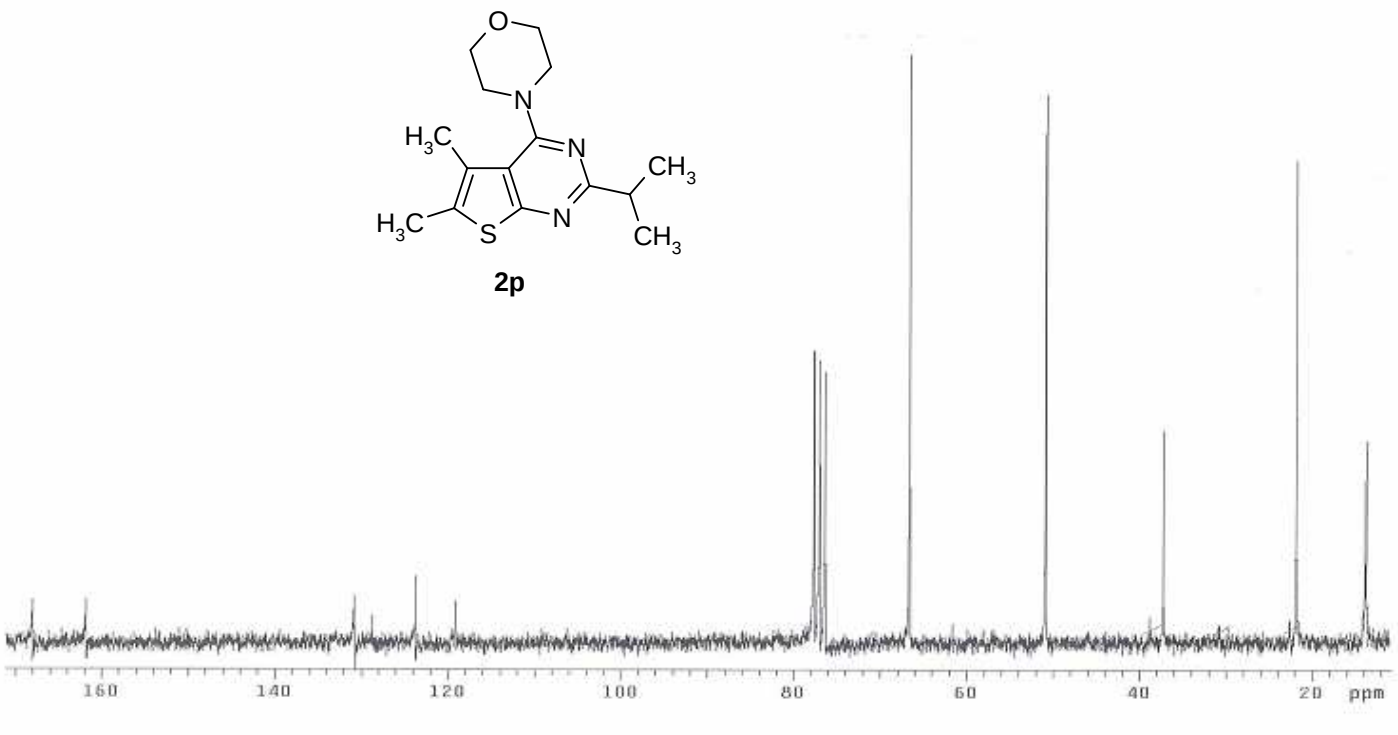
2o


O
N
H3C
N
CH3
H3C
S
N
160
140
120
100
80
60
40
20
ppm

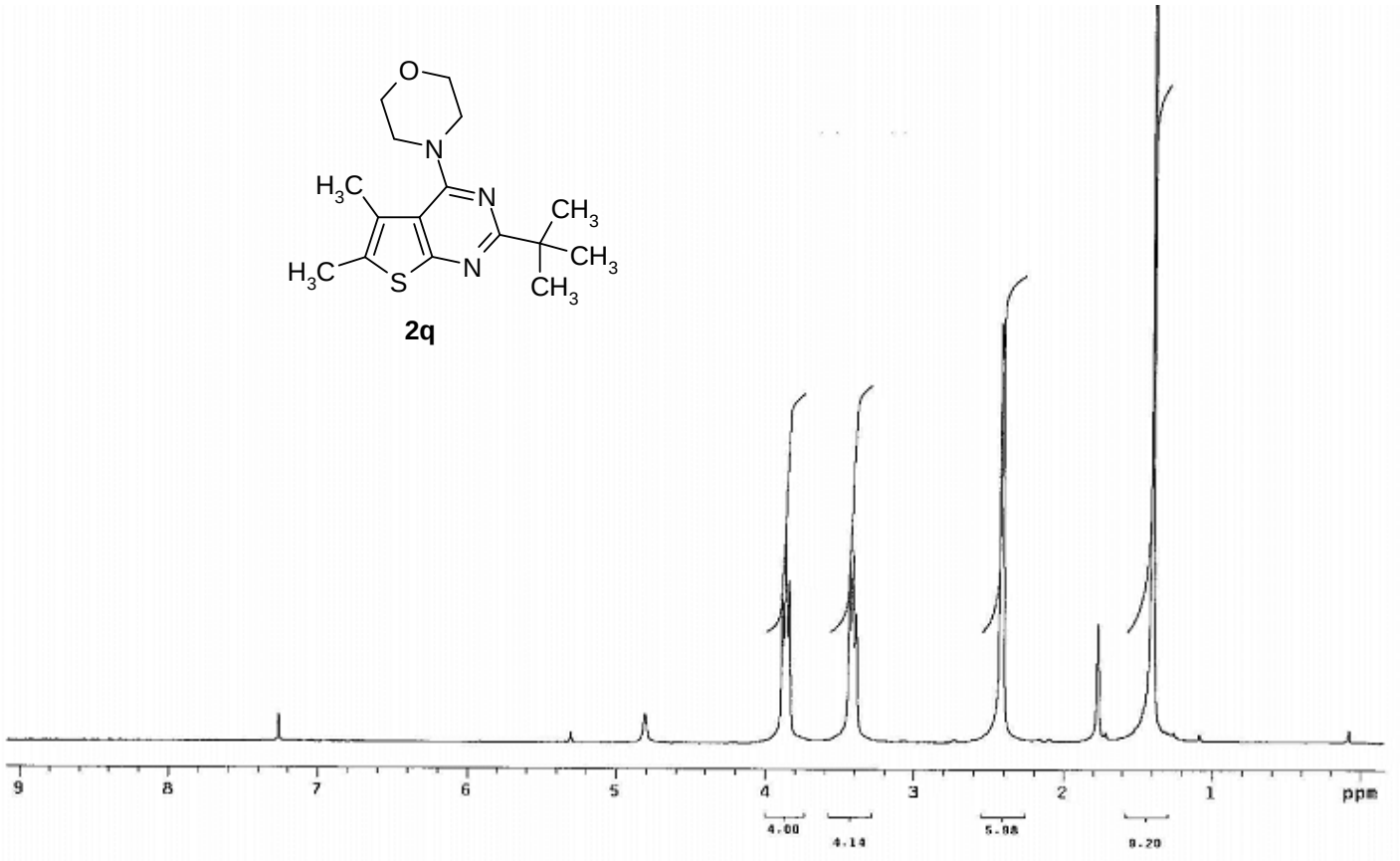
2o


O
N
H3C
N
CH3
H3C
S
N
CH3
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
19.03
19.04
3.88
28.08
29.97

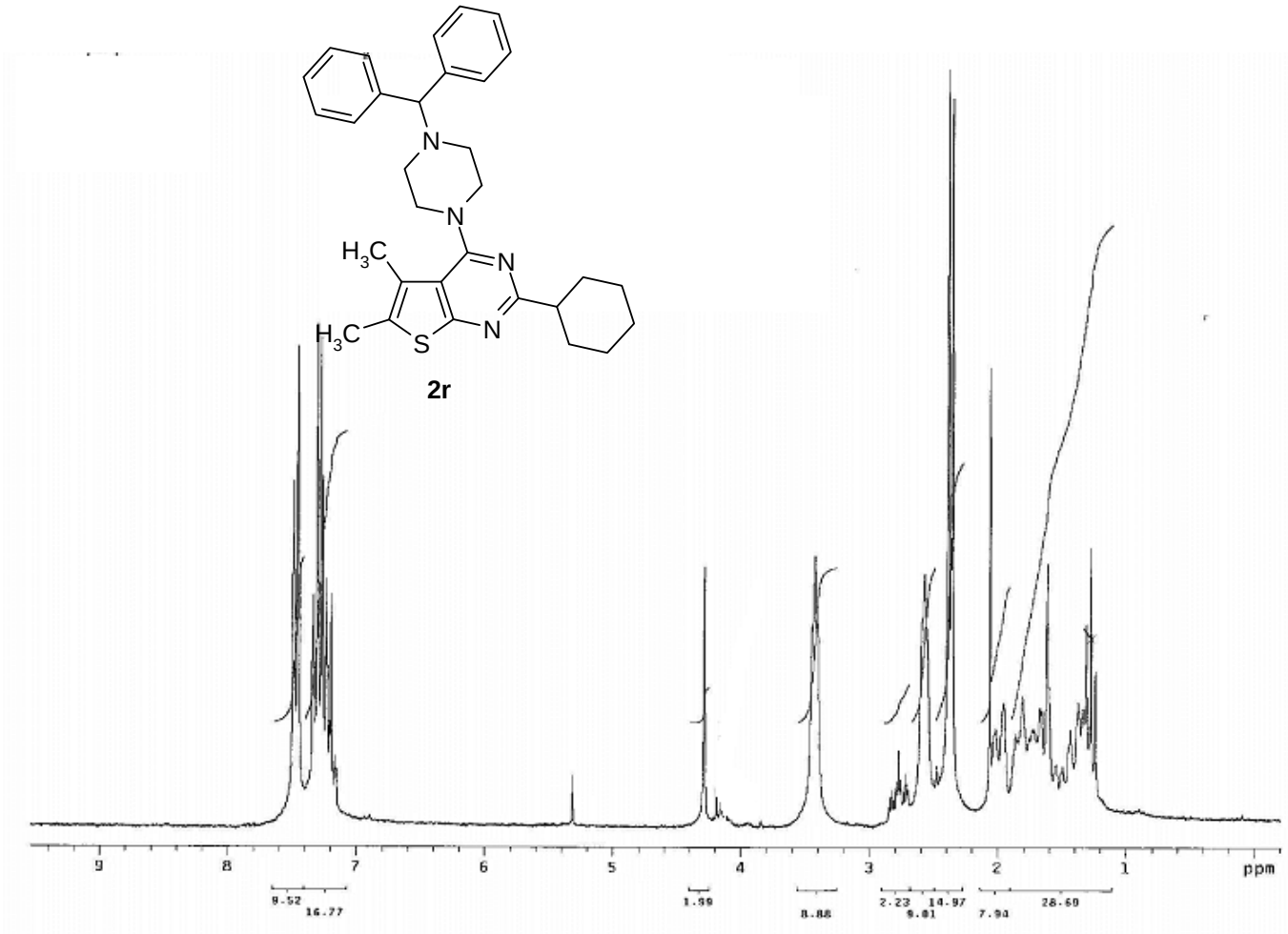
2p


O
N
H3C
N
CH3
H3C
S
N
CH3
160
140
120
100
80
60
40
20
ppm

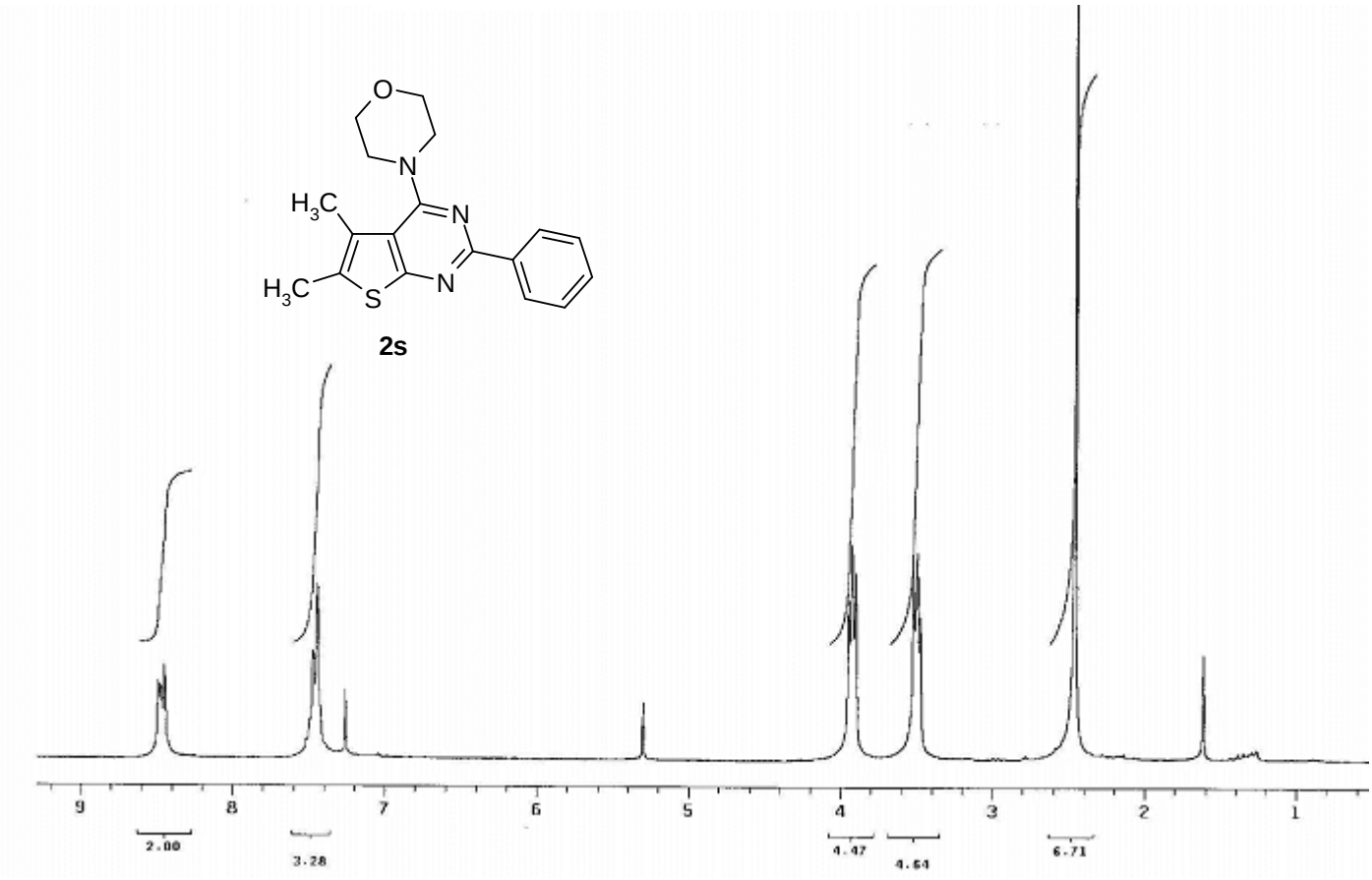
2p

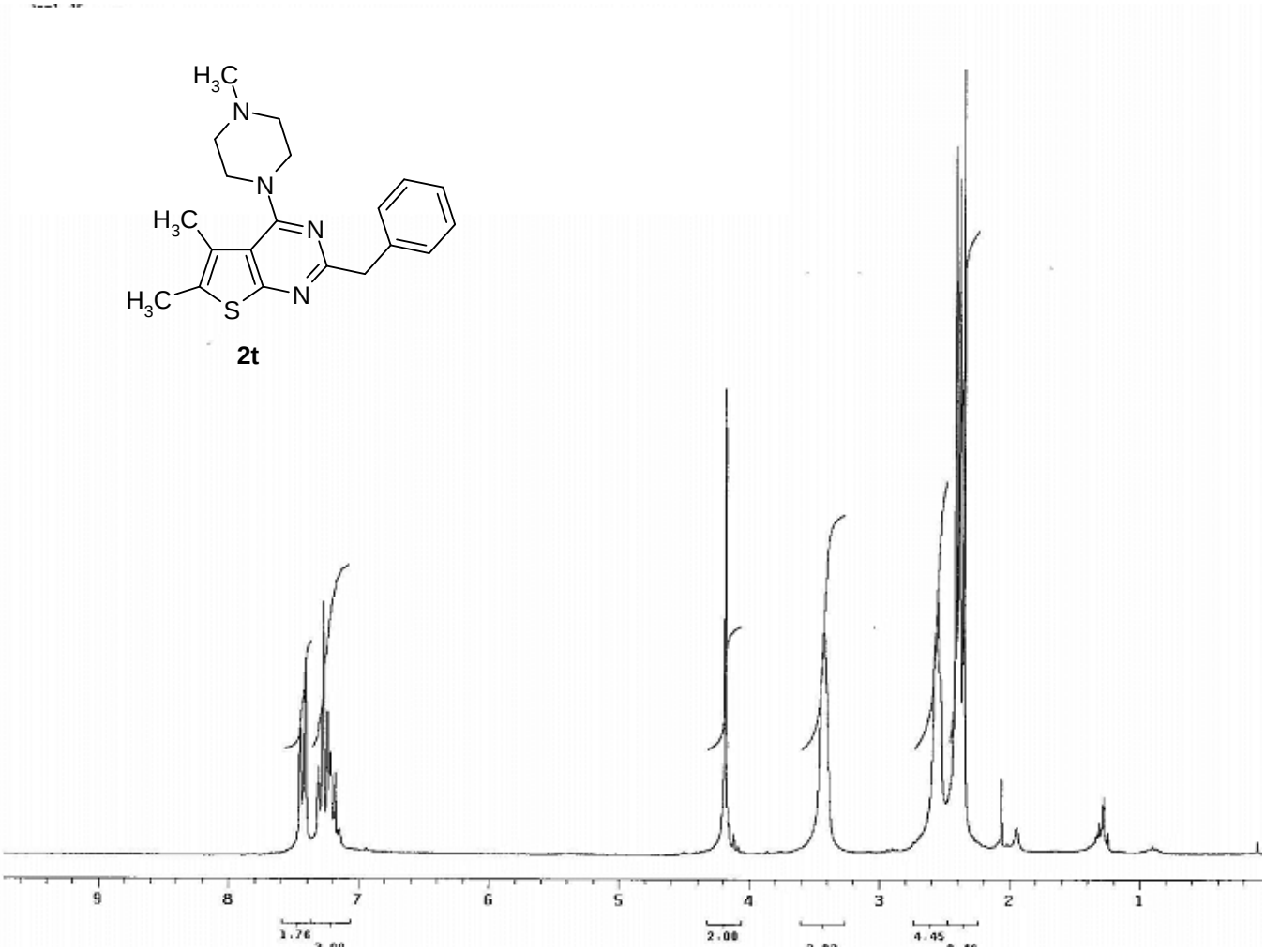

O
N
H3C
N
CH3
CH3
H3C
S
N
CH3
9
8
7
6
5
4
3
2
1
ppm
4.00
4.14
5.08
9.20

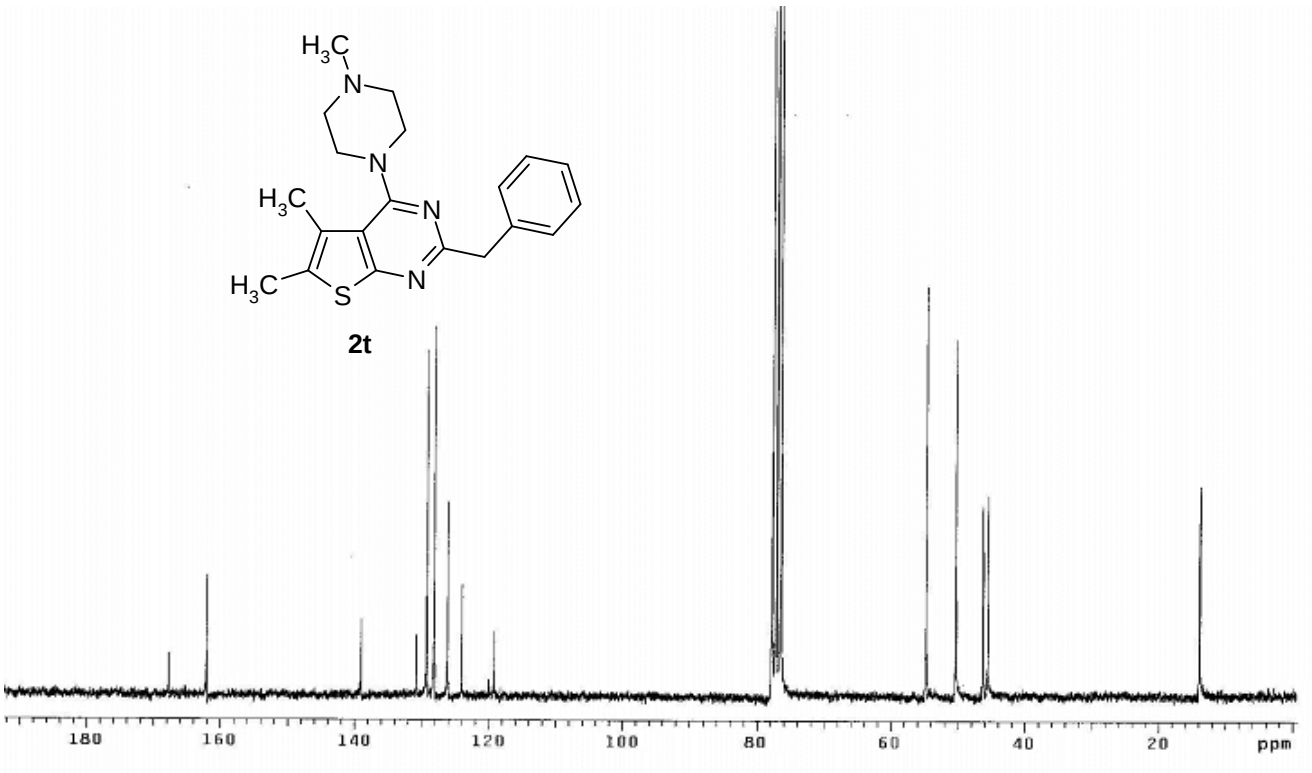
2q

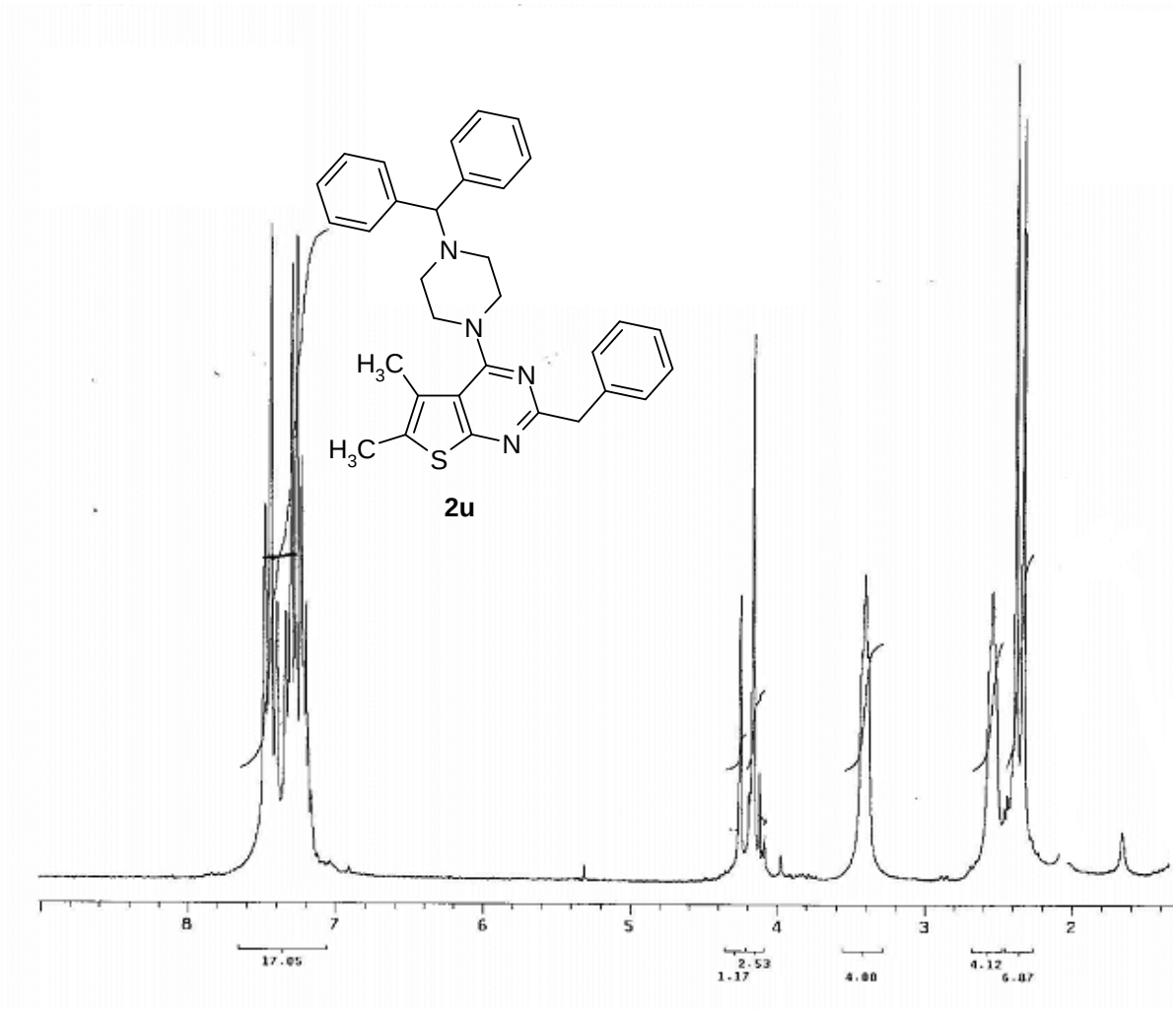

N
N
H3C
N
H3C
S
N
9
8
7
6
5
4
3
2
1
ppm
9.52
16.77
1.99
8.88
2.23
14.97
9.81
7.93
28.60

2r

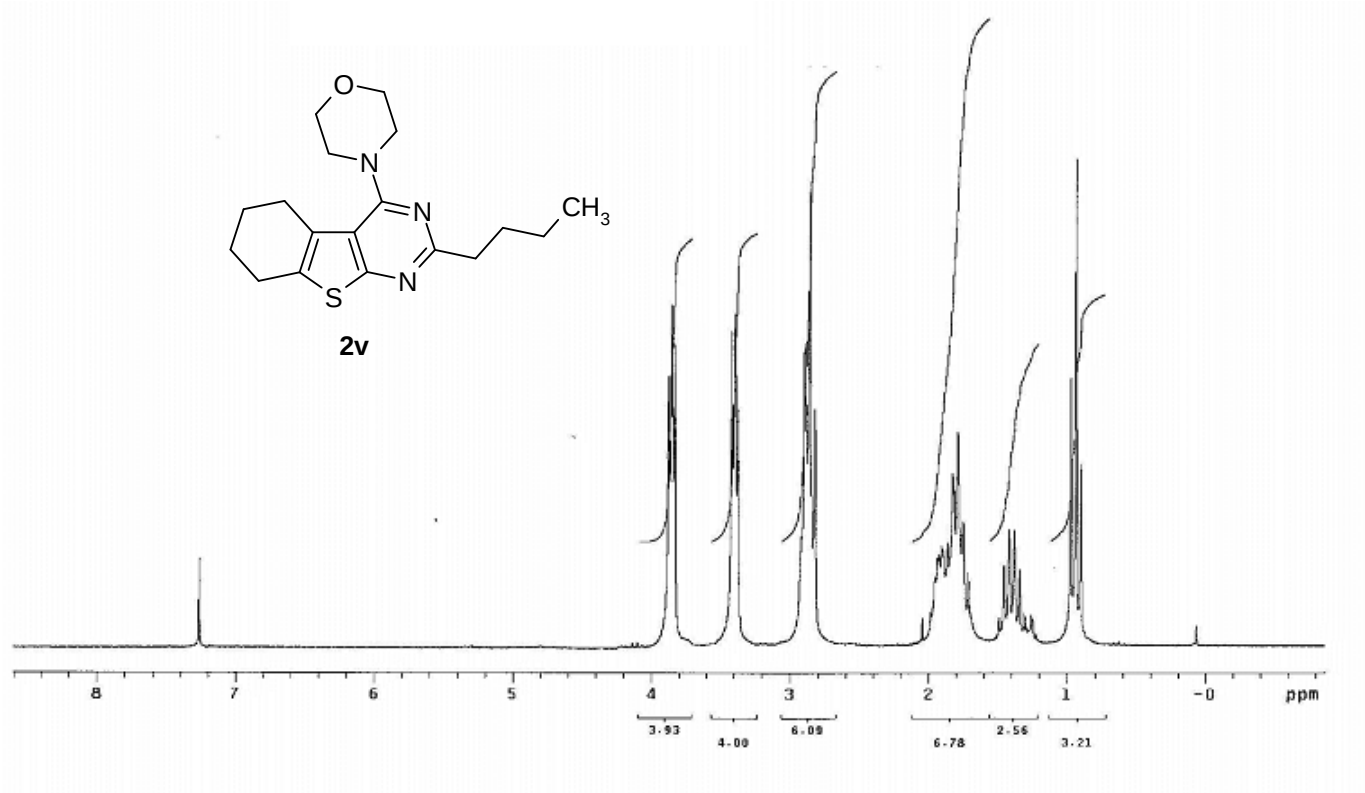

O
N
H3C
N
H3C
S
N
2s
9
8
7
6
5
4
3
2
1
2.00
3.28
4.47
4.64
6.71


2t
9
8
7
6
5
4
3
2
1
1.76
2.00
4.45

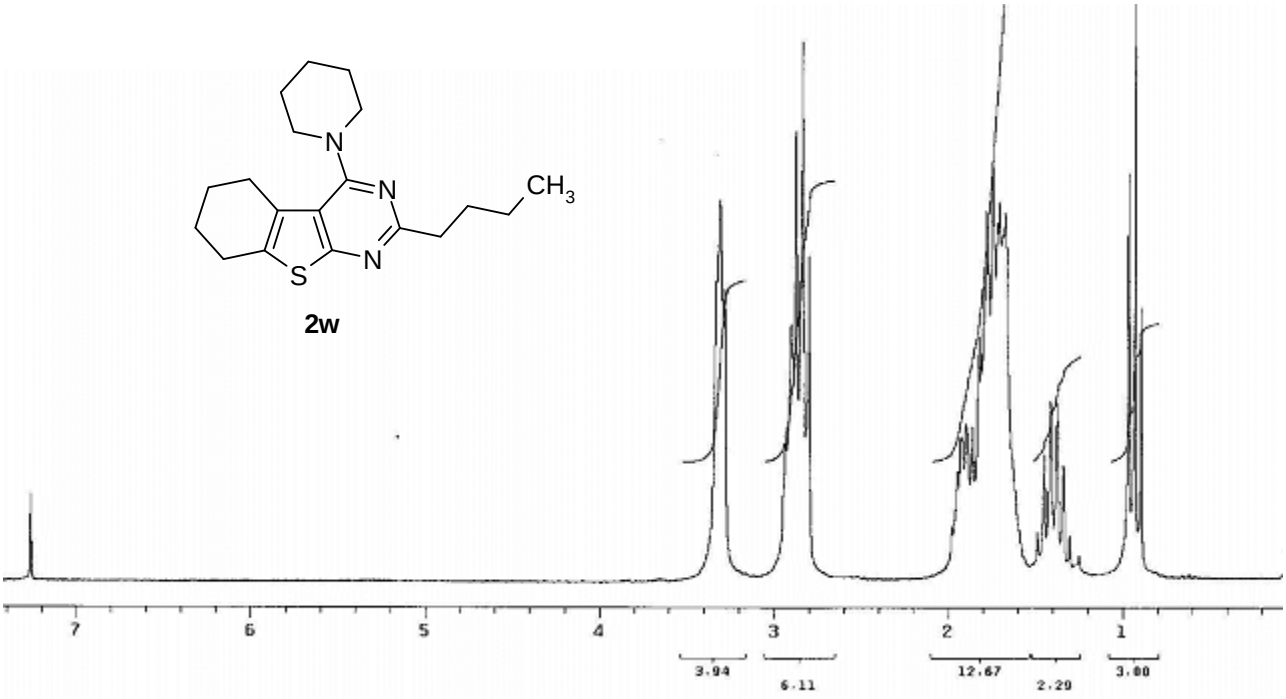

2t
180
160
140
120
100
80
60
40
20
ppm


N
N
H3C
N
H3C
S
N
8
7
6
5
4
3
2
17.05
2.53
1.17
4.00
4.12
6.87

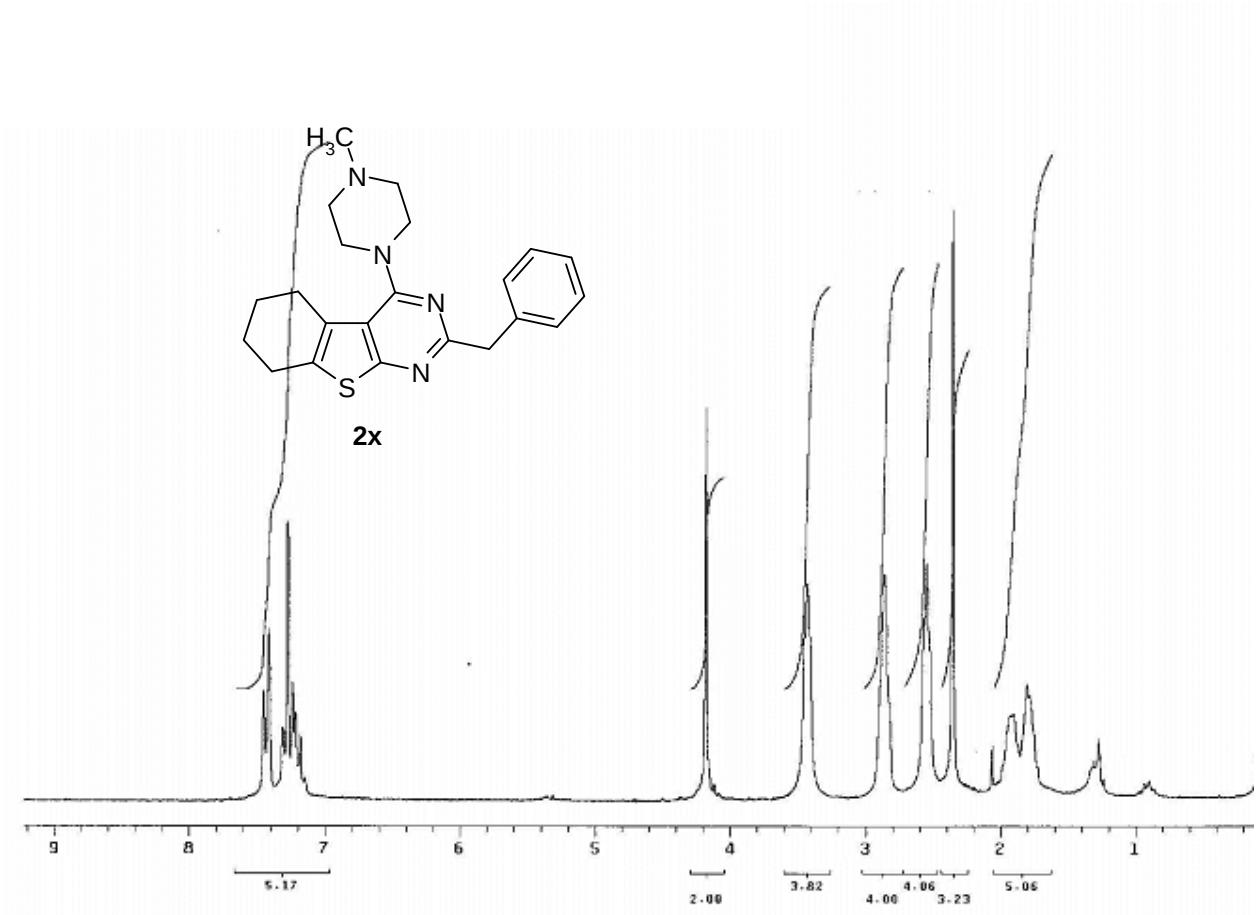
2u


O
N
N
CH3
S
8
7
6
5
4
3
2
1
-0
ppm
3.93
4.00
6.09
6.78
2.56
3.21

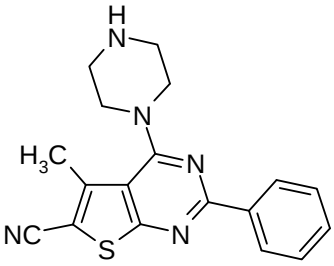
2v


N
N
N
S
CH3
7
6
5
4
3
2
1
3.94
6.11
12.67
2.29
3.00

2w

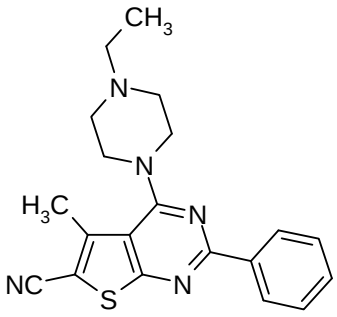

H3C
N
N
N
N
S
9
8
7
6
5
4
3
2
1
5.17
2.00
3.82
4.00
4.06
3.23
5.06

2x


H
N
N
H3C
N
NC
S
N

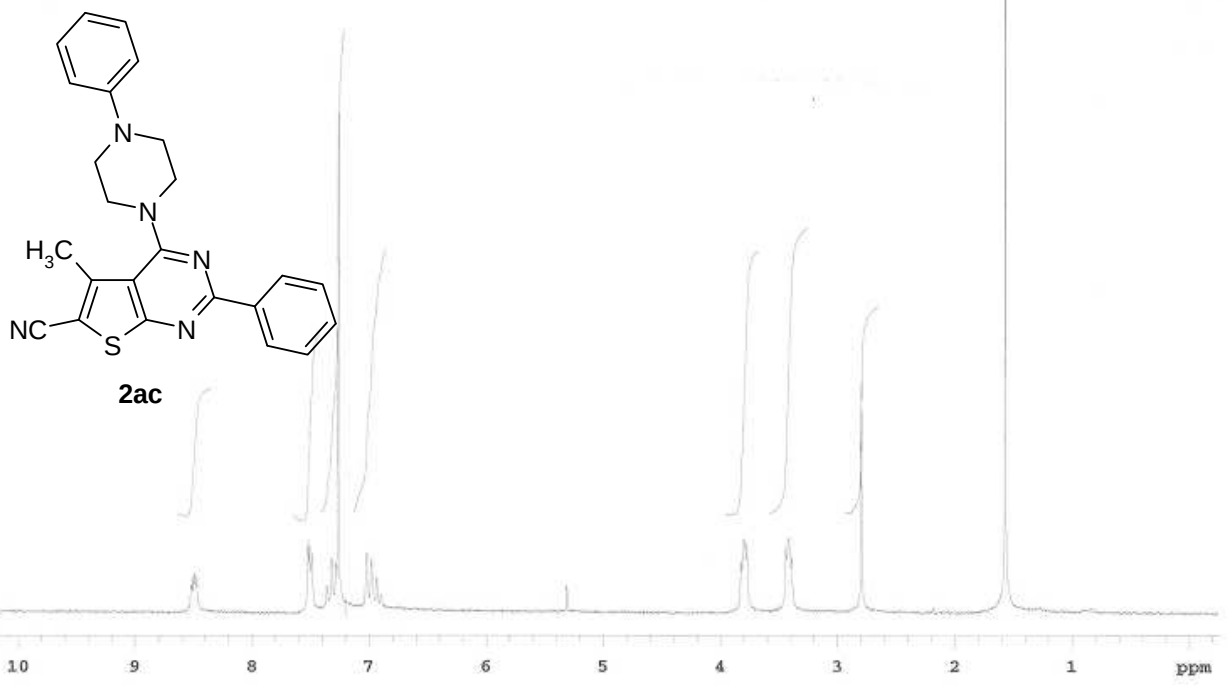
2aa

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm

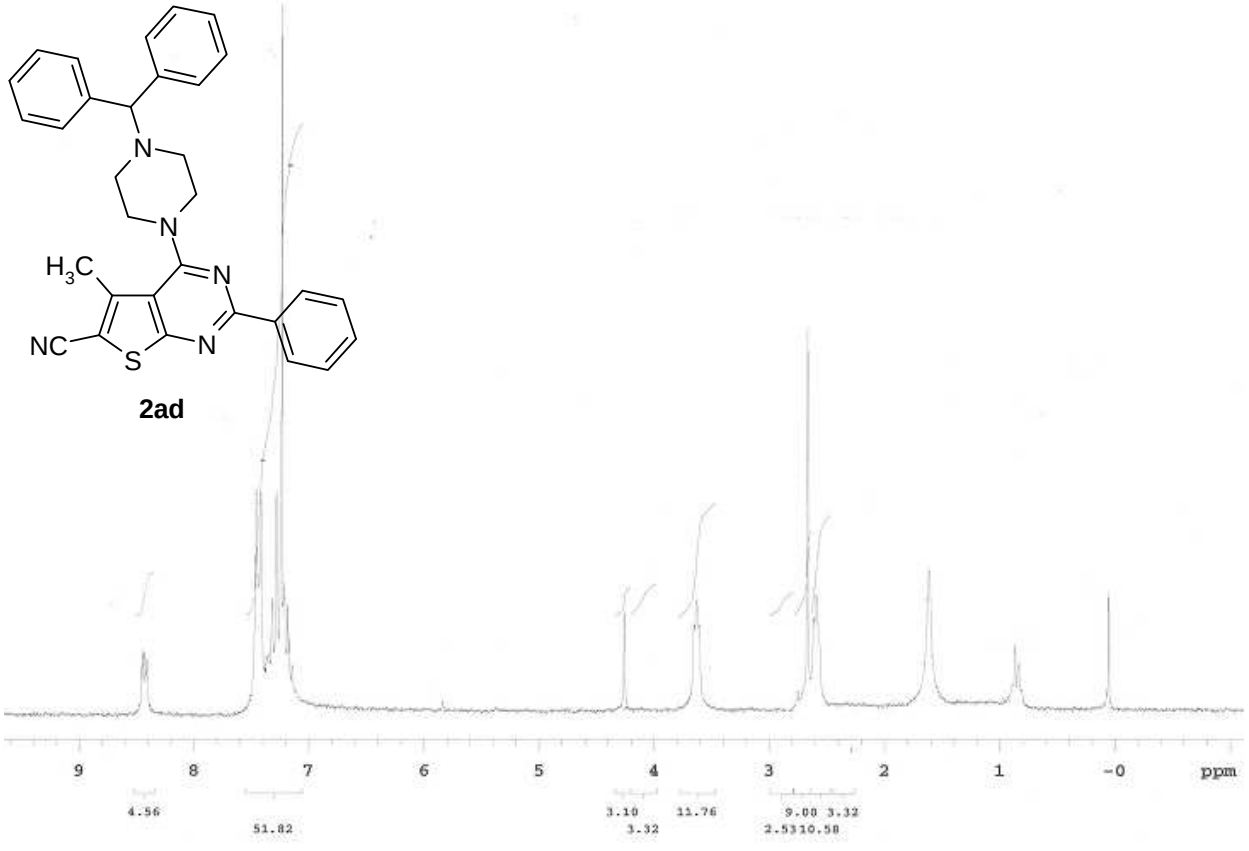

CH3
N
N
H3C
N
NC
S
N

2ab

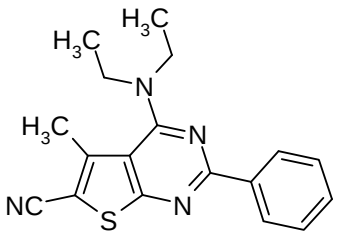
10
9
8
7
6
5
4
3
2
1
ppm


N
N
H3C
N
NC
S
N
10
9
8
7
6
5
4
3
2
1
ppm

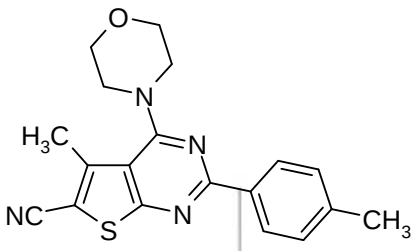
2ac


N
N
H3C
N
NC
S
N
9
8
7
6
5
4
3
2
1
-0
ppm
4.56
51.82
3.10
3.32
11.76
9.08
3.32
2.53
10.58

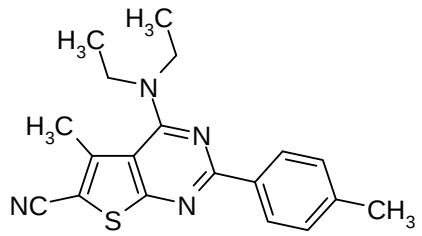
2ad



2ae

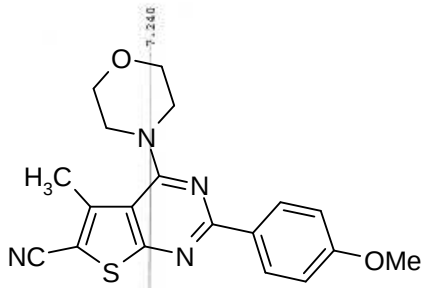


2af


H3C
H3C
N
H3C
N
NC
S
N
CH3

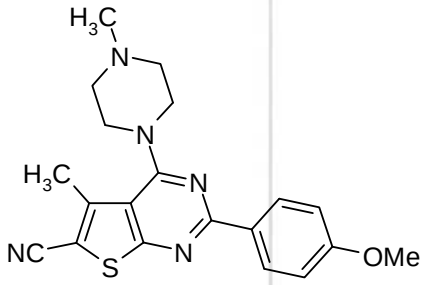
2ag

8
7
6
5
4
3
2
1
ppm

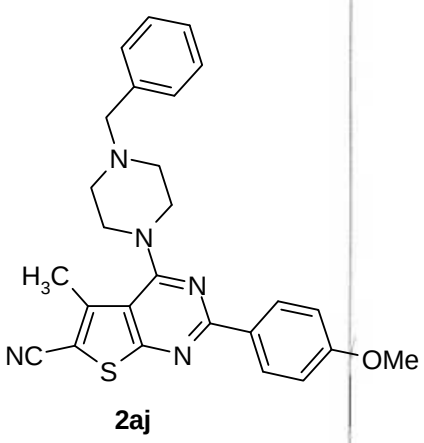

O
N
H3C
N
NC
S
N
OMe

2ah

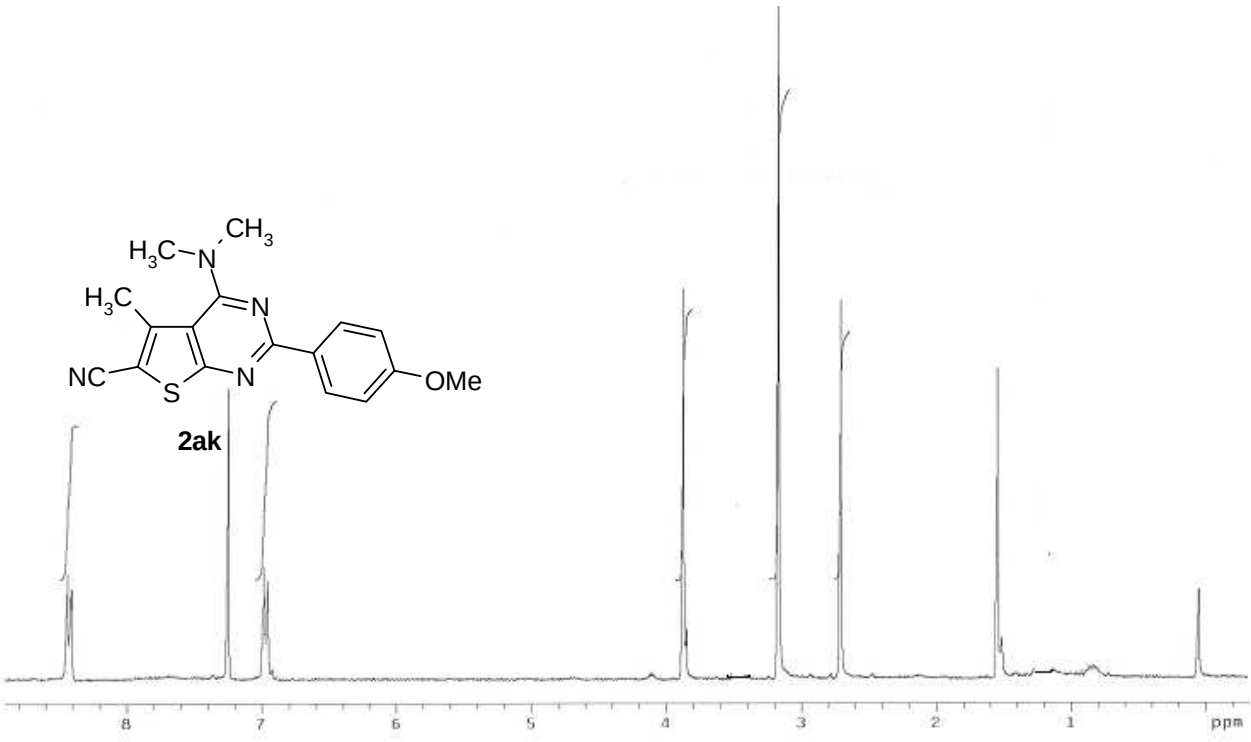
7.240
3.875
3.603
3.894
3.916
3.580
3.559
2.718
1.547
8.432
8.387
6.996
6.953
8
7
6
5
4
3
2
ppm



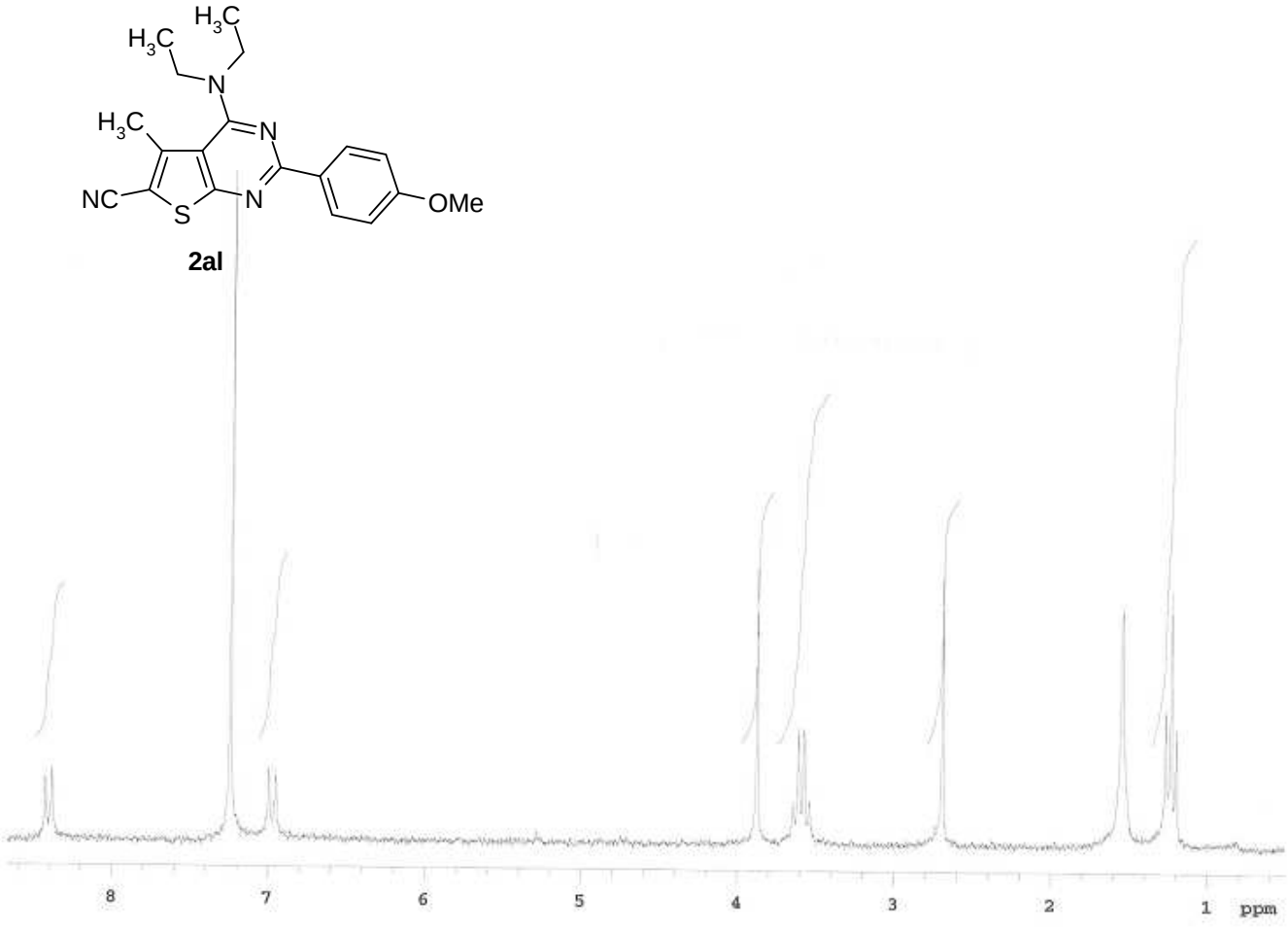
2ai



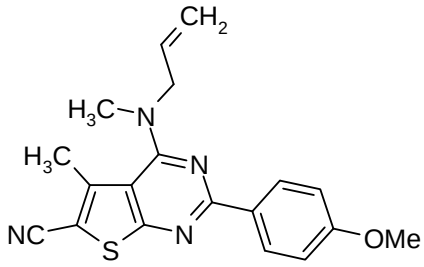
2aj


H3C
CH3
N
H3C
N
NC
S
N
OMe
8
7
6
5
4
3
2
1
ppm

2ak

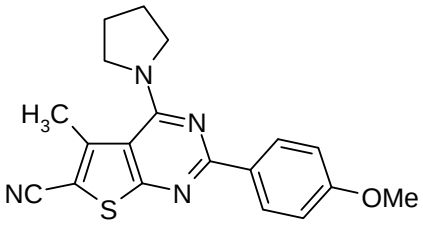

H3C
H3C
N
H3C
N
NC
S
N
OMe
8
7
6
5
4
3
2
1
ppm

2al


CH2
H3C
N
H3C
N
NC
S
N
OMe

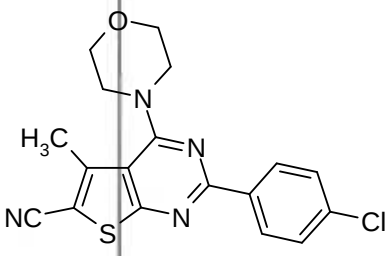
2am

8
7
6
5
4
3
2
1


N
H3C
N
NC
S
N
OMe

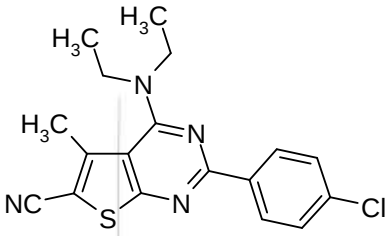
2an

10
9
8
7
6
5
4
3
2
1
ppm
10.60
10.96

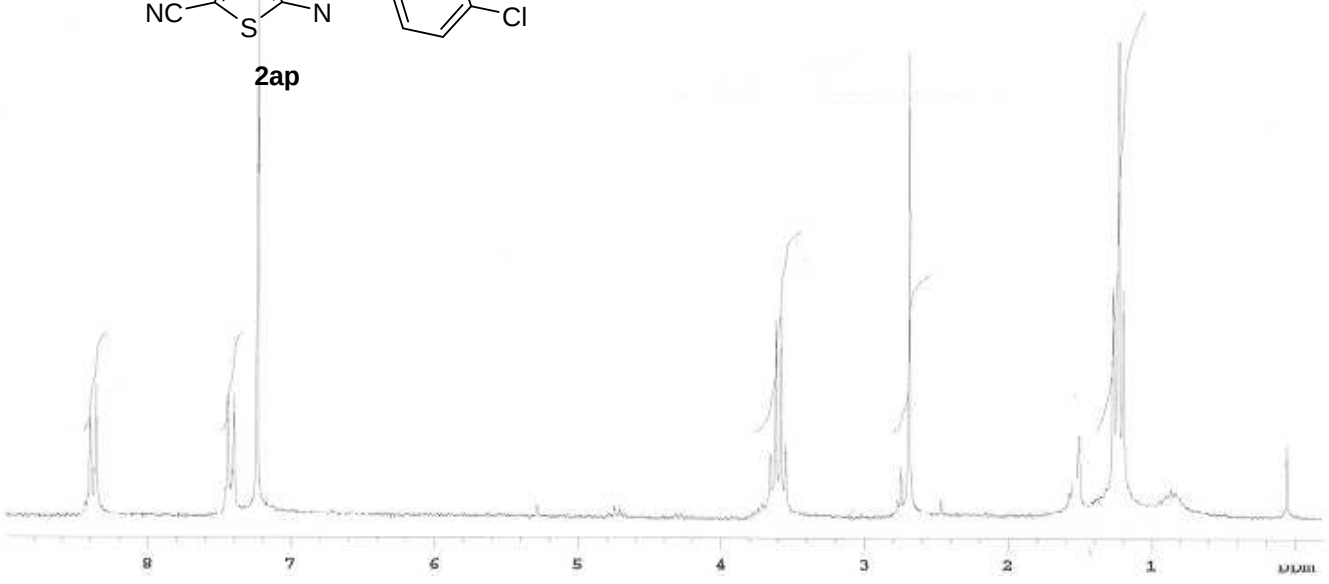

O
N
H3C
N
NC
S
N
Cl

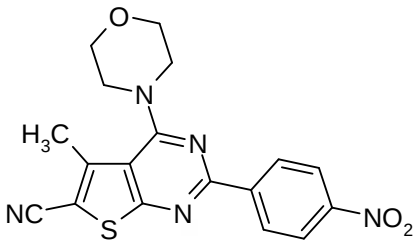
2ao

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm


H3C
H3C
N
H3C
N
NC
S
N
Cl

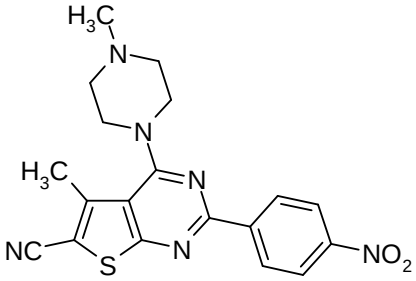
2ap


8
7
6
5
4
3
2
1
ppm


O
N
H3C
N
NC
S
N
NO2

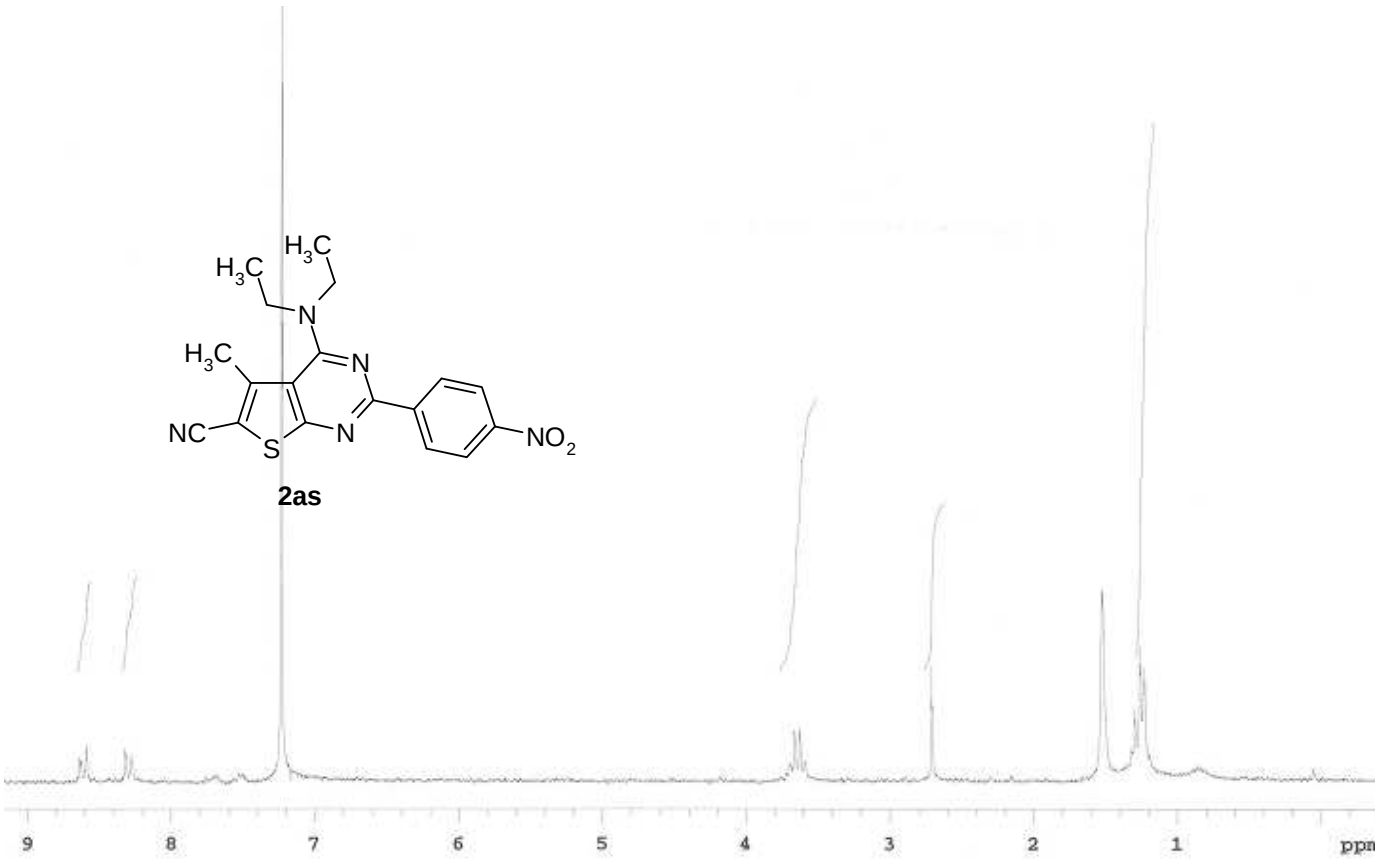
2aq

10
9
8
7
6
5
4
3
2
1
ppm

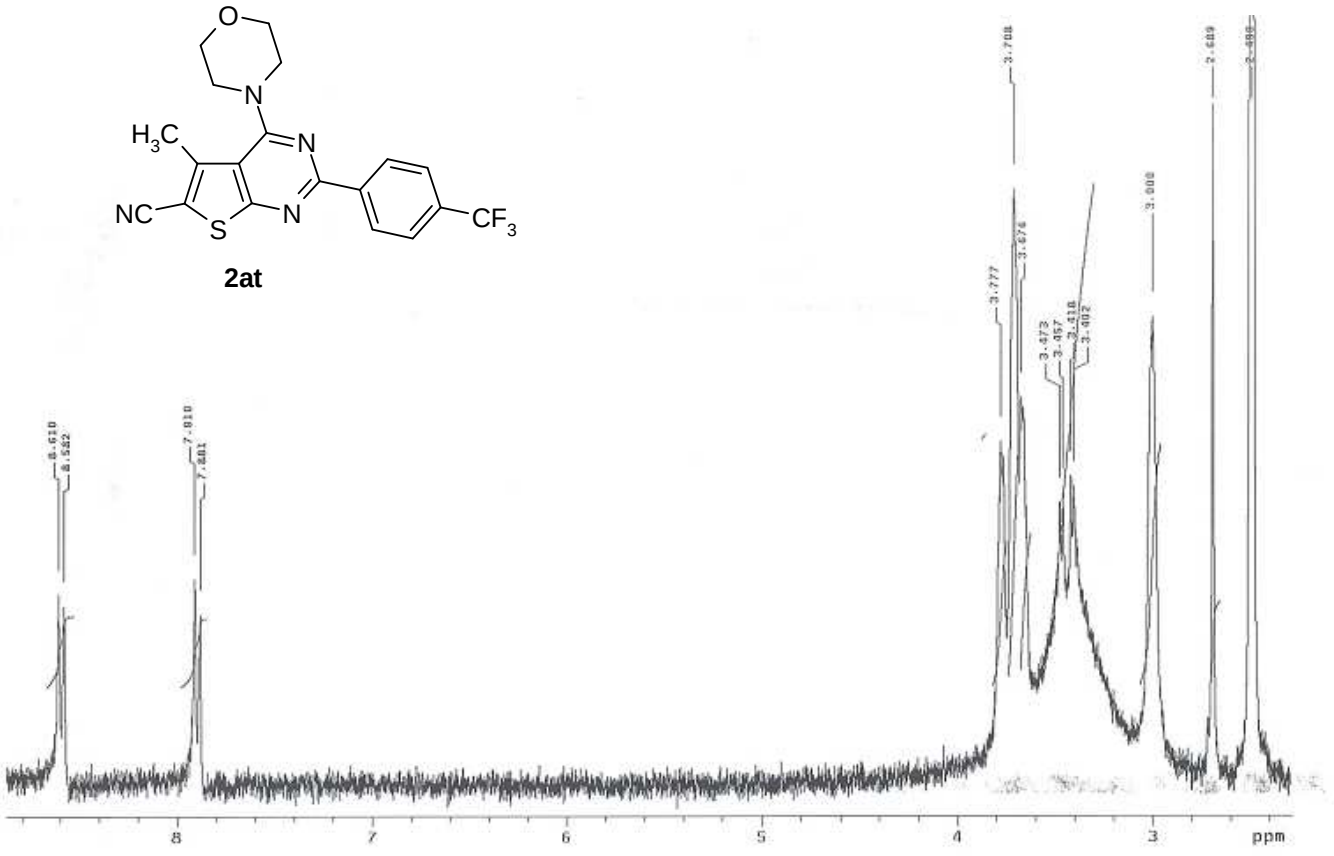

H3C
N
N
H3C
N
NC
S
N
NO2

2ar

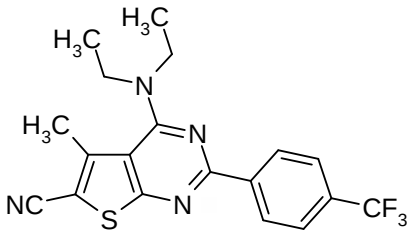
8
7
6
5
4
3
ppm


H3C
H3C
N
H3C
N
NC
S
N
NO2
9
8
7
6
5
4
3
2
1
ppm

2as

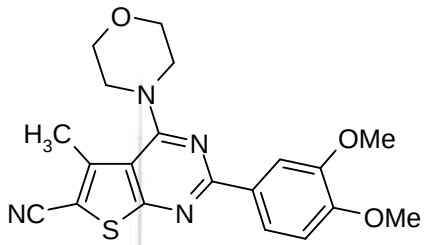

O
N
H3C
N
NC
S
N
CF3
8.610
8.582
7.810
7.801
3.708
3.676
3.777
3.473
3.457
3.418
3.402
3.000
2.689
2.498
8
7
6
5
4
3
ppm

2at


H3C
H3C
N
H3C
N
NC
S
N
CF3

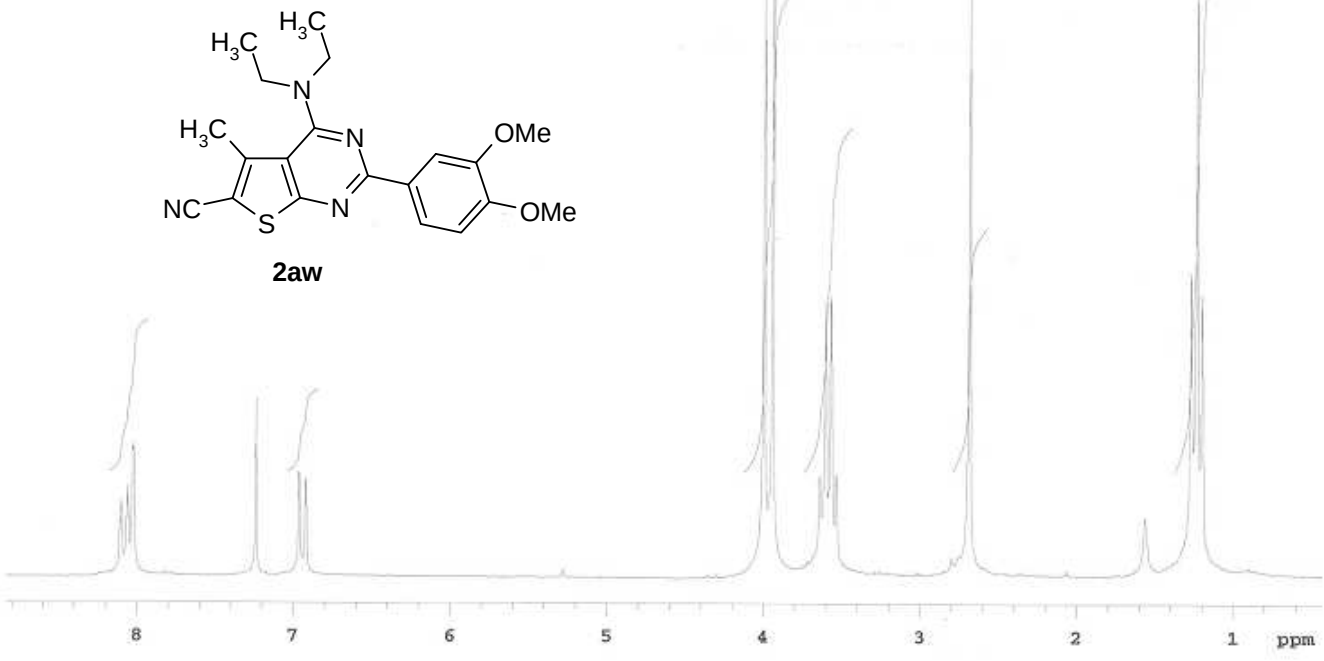
2au

8
7
6
5
4
3
2
1 ppm

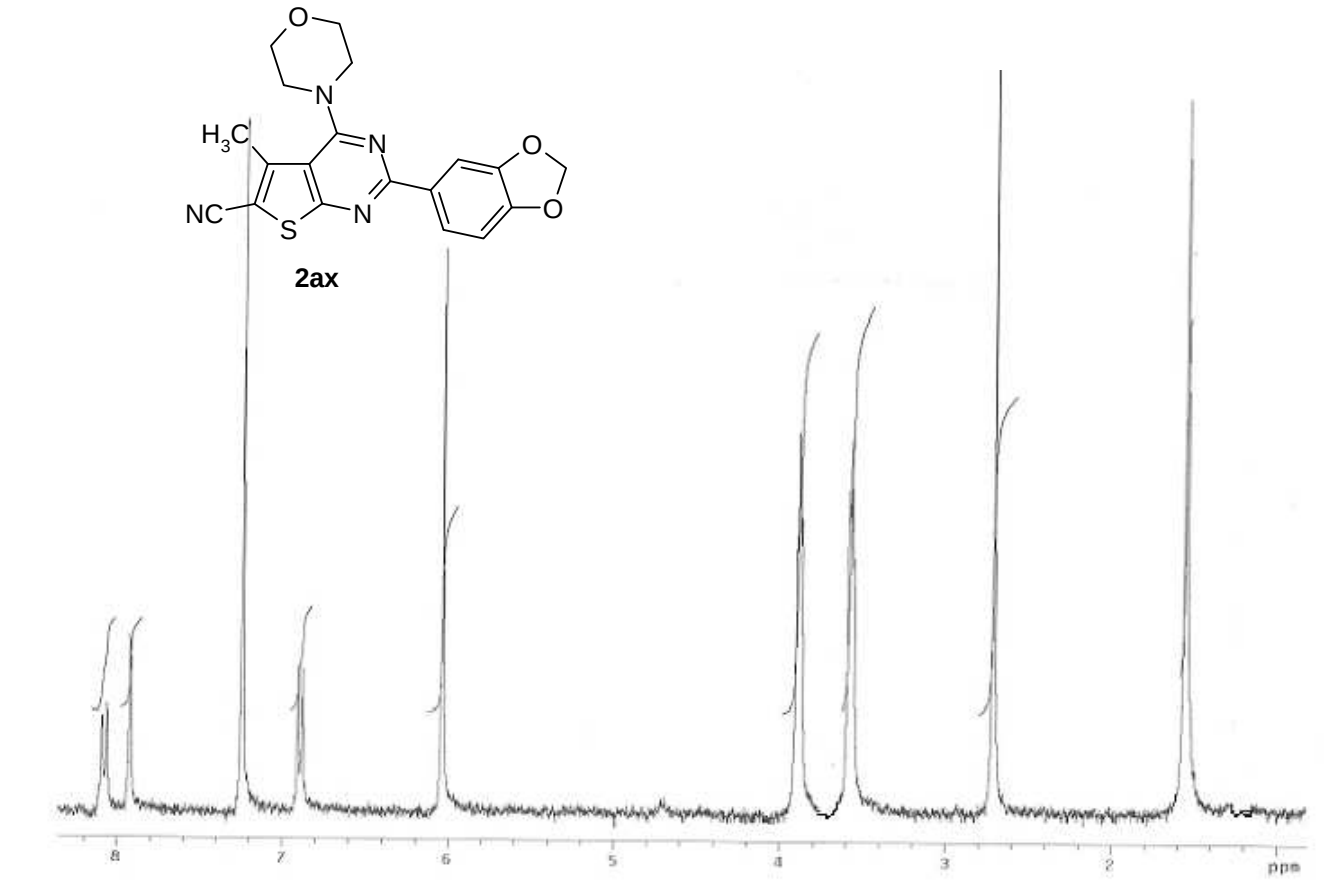

O
N
H3C
N
OMe
NC
S
N
OMe

2av

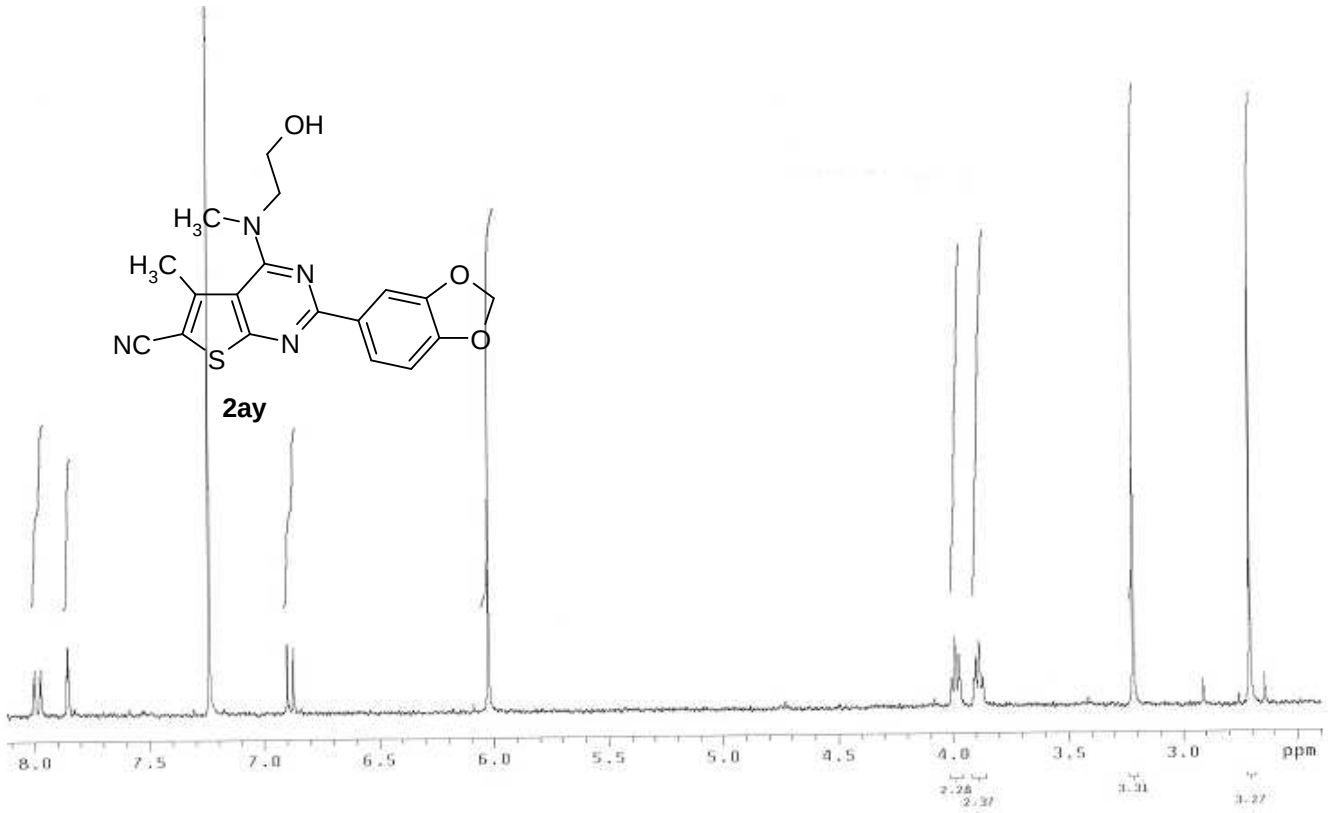
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm

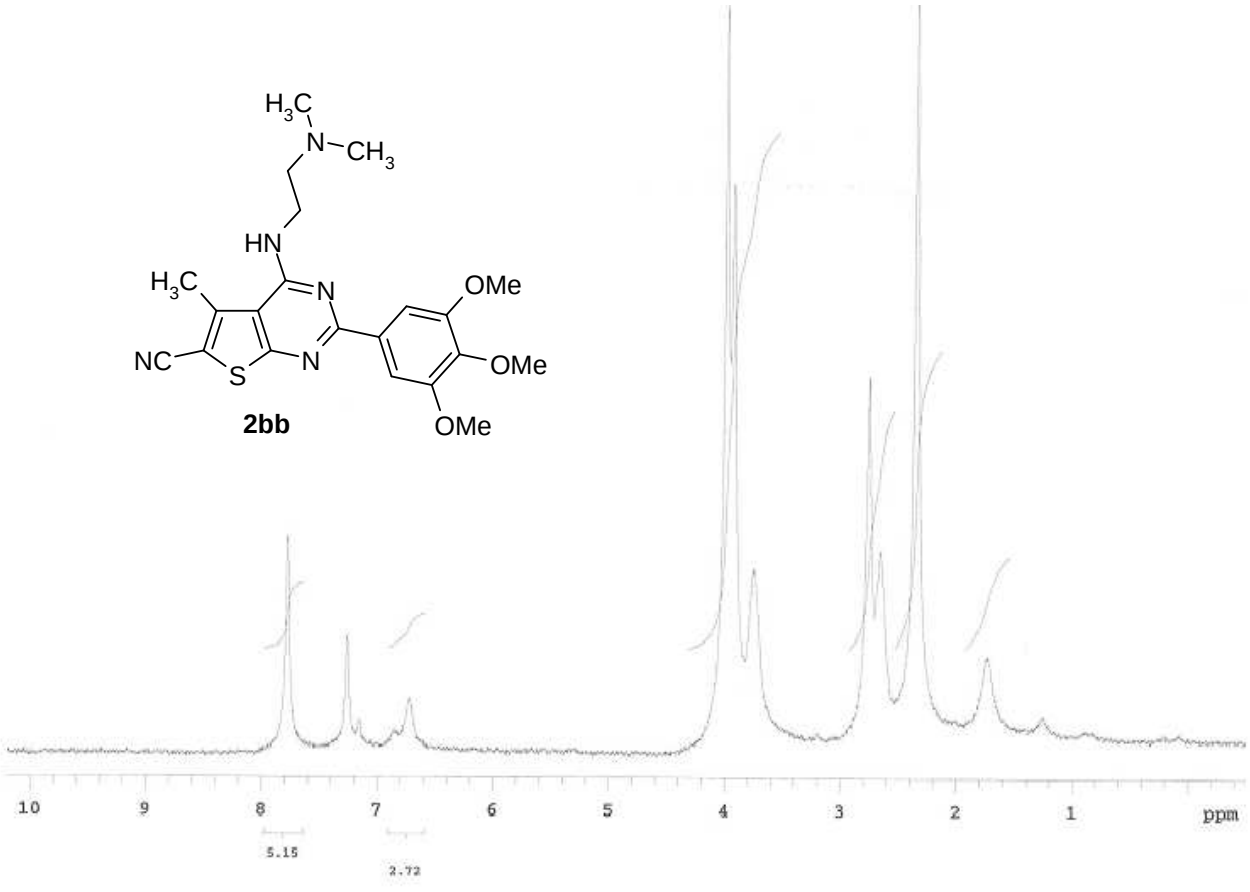

H3C
H3C
H3C
N
N
OMe
NC
S
N
OMe
8
7
6
5
4
3
2
1
ppm

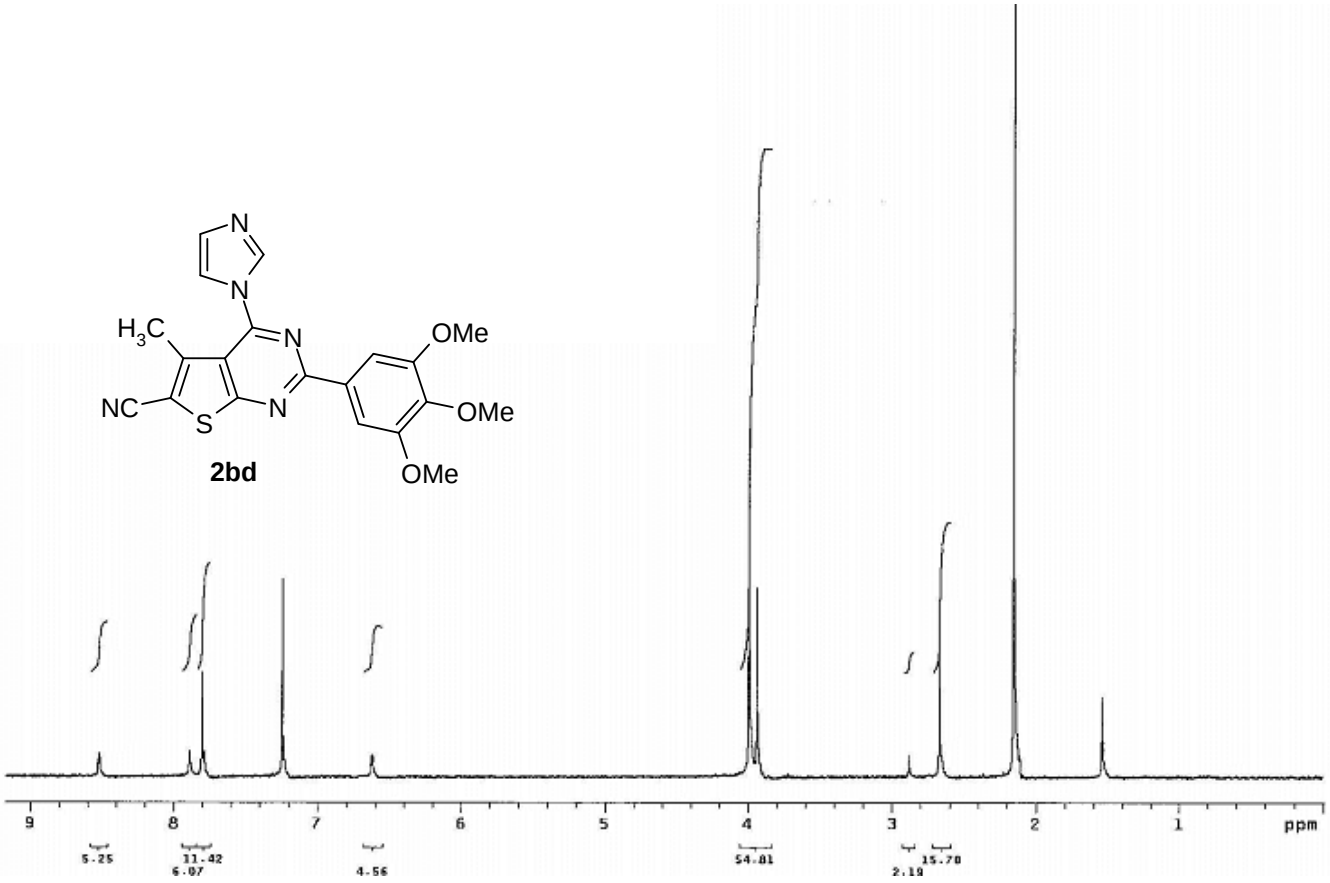
2aw


O
N
H3C
N
O
NC
S
N
O
8
7
6
5
4
3
2
ppm

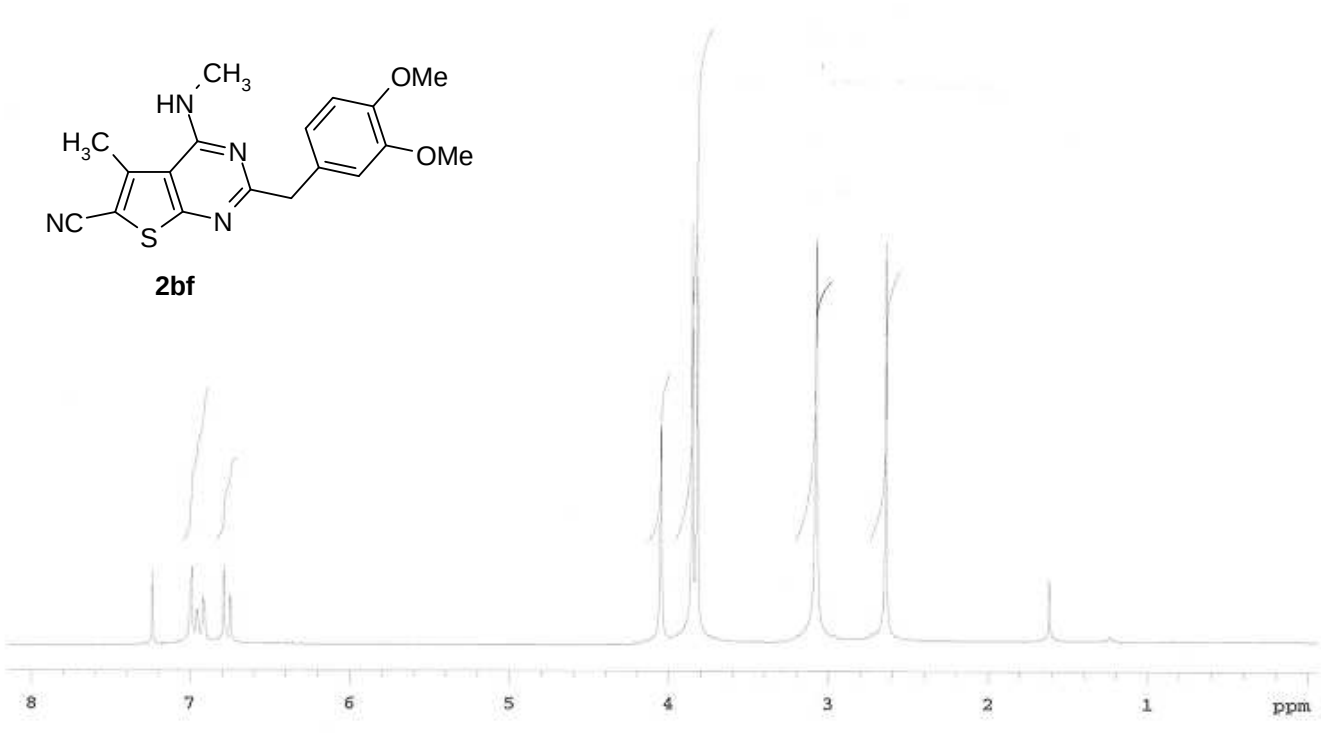
2ax


OH
H3C
N
H3C
N
O
NC
S
N
O
2ay
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm
2.25
2.37
3.31
3.27


H3C
N
CH3
HN
H3C
N
OMe
NC
S
N
OMe
OMe
2bb
10
9
8
7
6
5
4
3
2
1
ppm
5.15
2.72

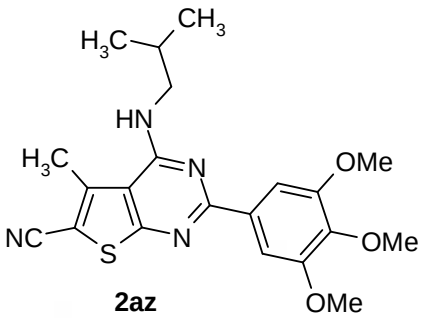

N
N
H3C
N
OMe
NC
S
N
OMe
OMe
9
8
7
6
5
4
3
2
1
ppm
5.25
11.42
6.07
4.56
54.81
15.70
2.19

2bd


CH3
HN
OMe
H3C
N
OMe
NC
S
N
8
7
6
5
4
3
2
1
ppm

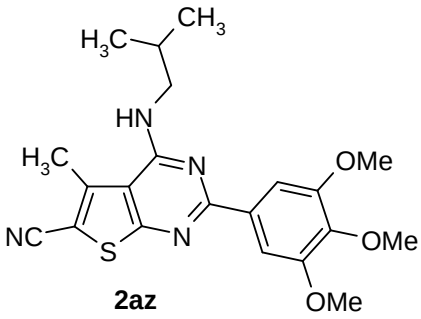
2bf

^{1}H and ^{13}C-NMR spectra for final compounds 2az, 2ba, 2bc, 2be and 2bg–bk


H3C
CH3
HN
H3C
N
OMe
NC
N
OMe
S
OMe

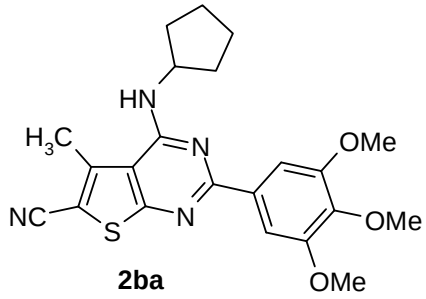
2az

9
8
7
6
5
4
3
2
1
ppm


H3C
CH3
HN
H3C
N
OMe
NC
N
OMe
S
OMe

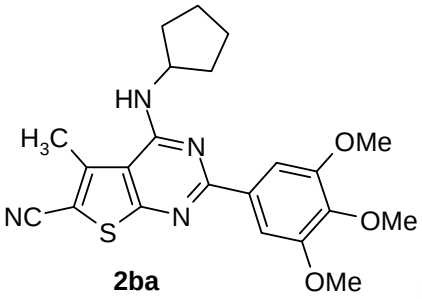
2az

200
180
160
140
120
100
80
60
40
20
ppm

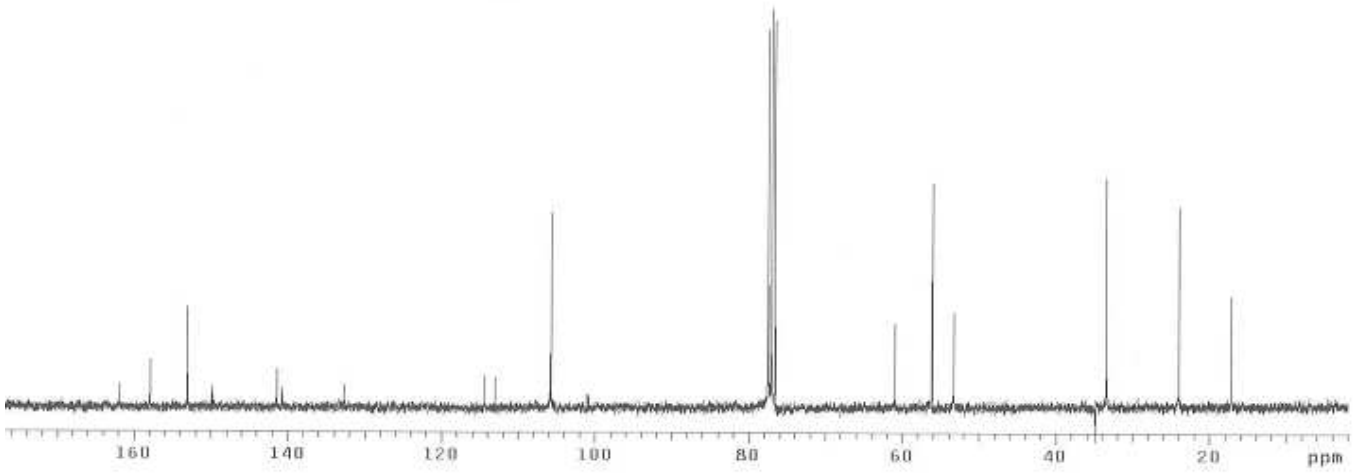

HN
H3C
N
OMe
NC
N
OMe
S
OMe

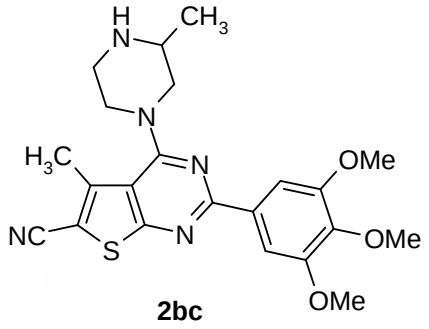
2ba

10
9
8
7
6
5
4
3
2
1
ppm


HN
H3C
N
OMe
NC
N
OMe
S
OMe

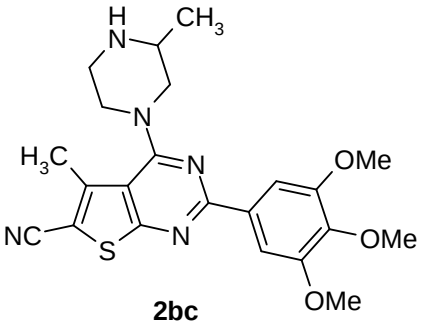
2ba


160
140
120
100
80
60
40
20
ppm

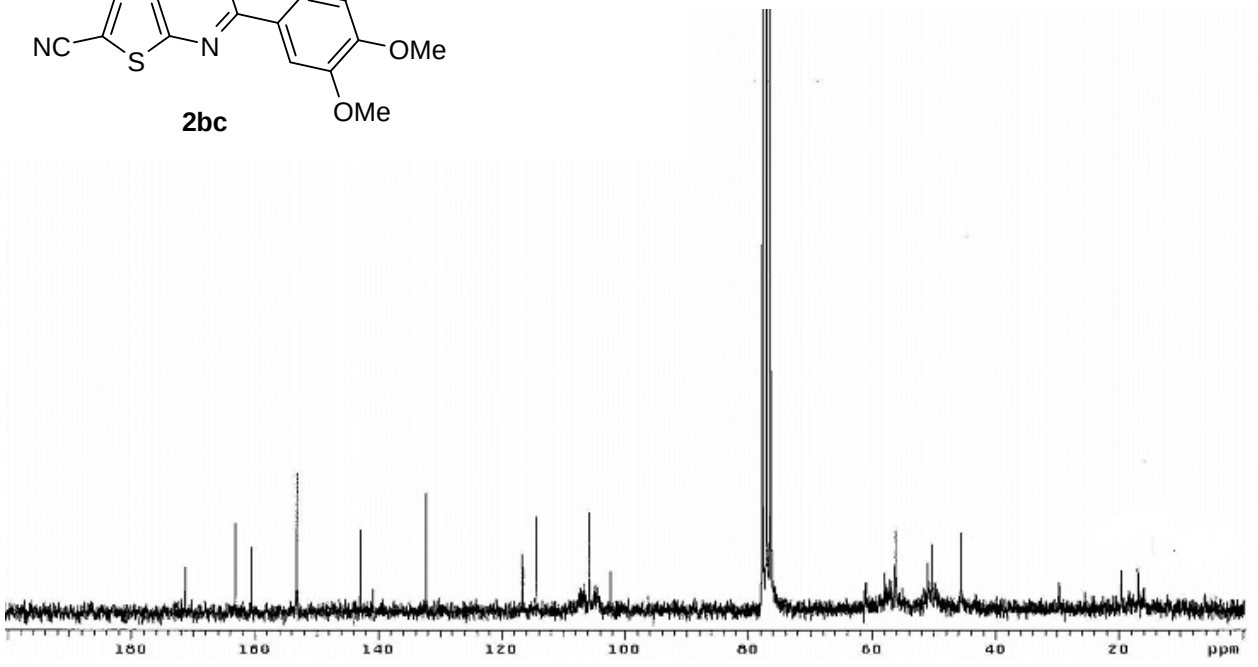

H
N
CH3
N
H3C
N
OMe
NC
S
N
OMe
OMe

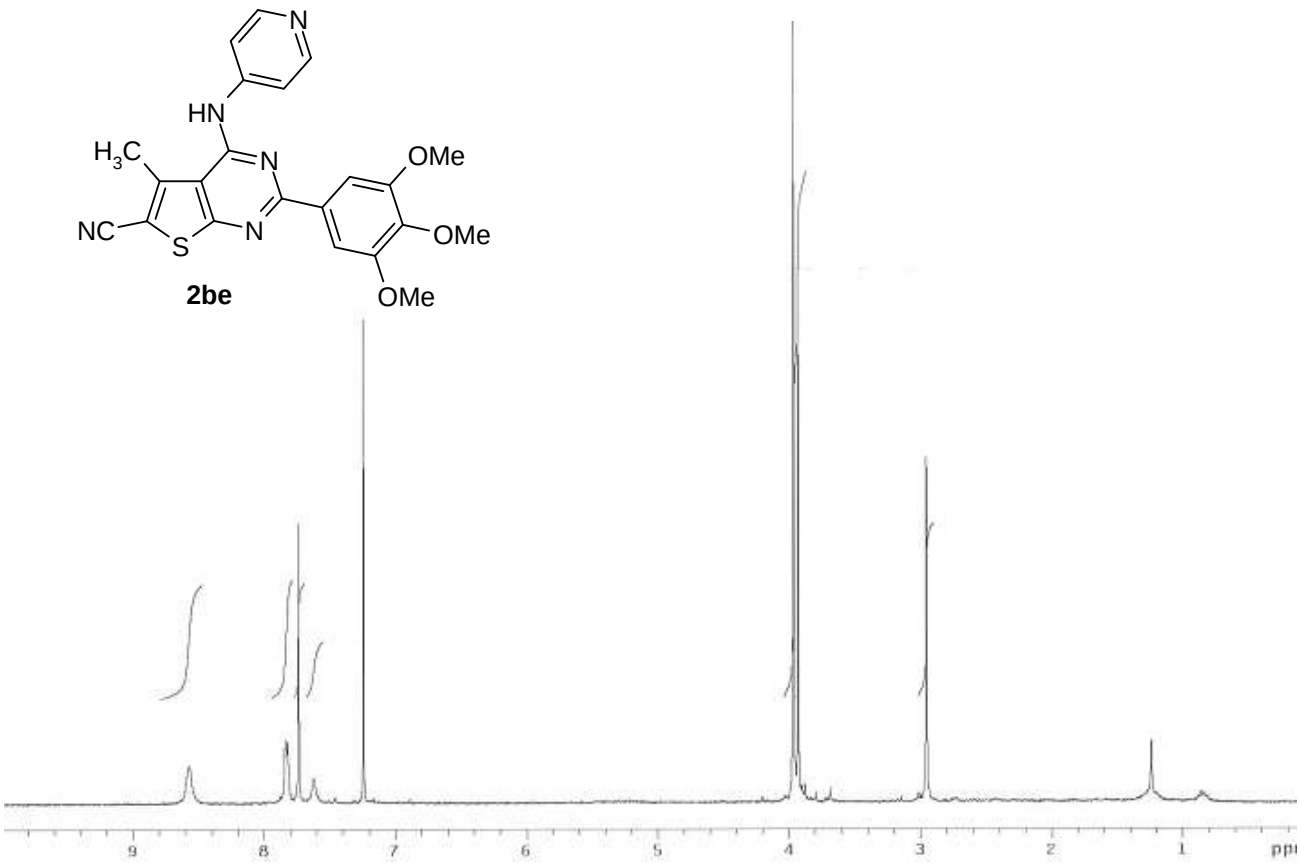
2bc

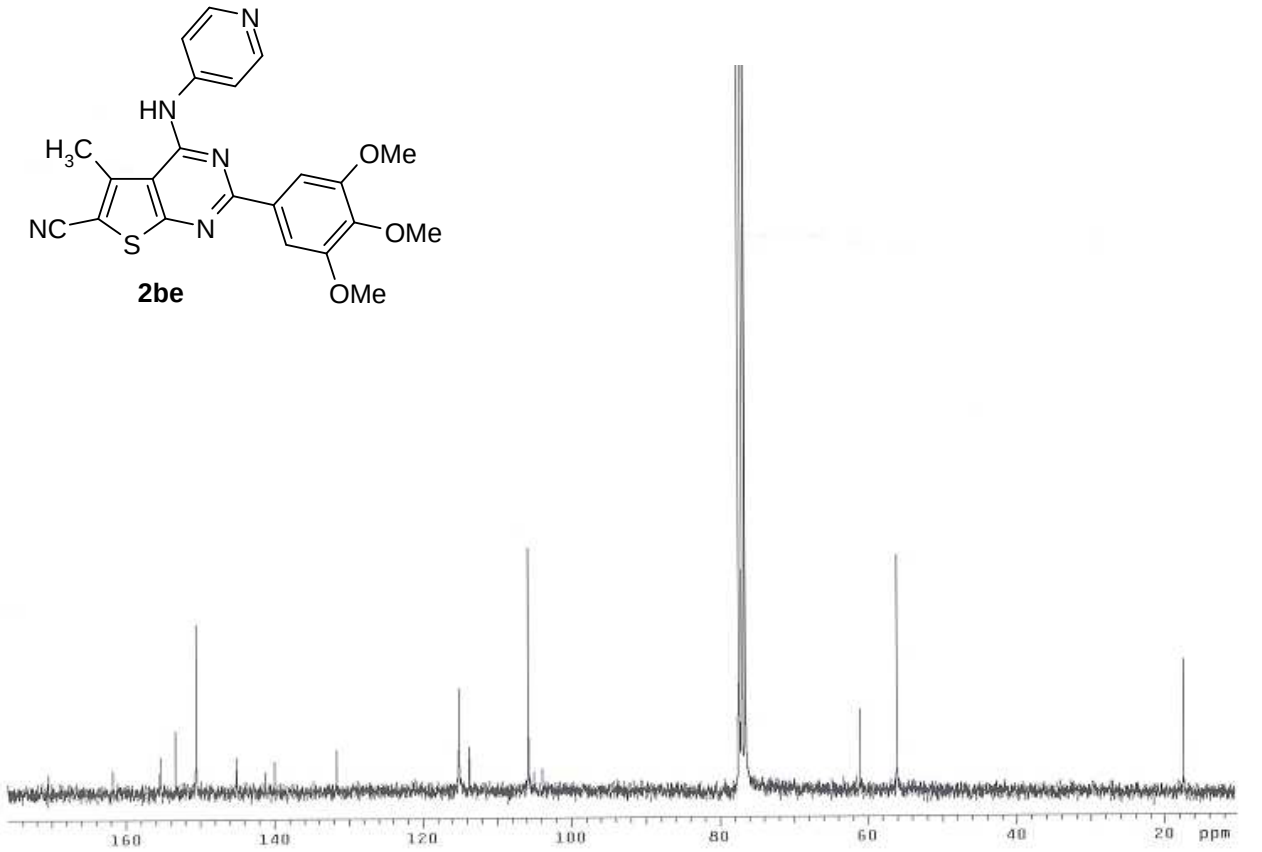
10
9
8
7
6
5
4
3
2
1
ppm

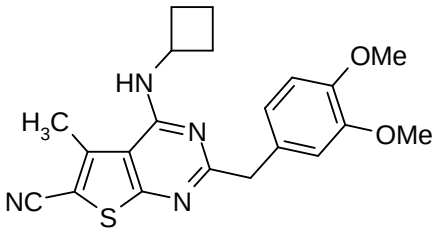

H
N
CH3
N
H3C
N
OMe
NC
S
N
OMe
OMe

2bc


180
160
140
120
100
80
60
40
20
ppm

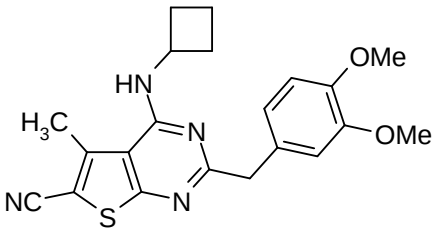

N
HN
H3C
N
OMe
NC
S
N
OMe
OMe
2be
9
8
7
6
5
4
3
2
1
ppm


N
HN
H3C
N
OMe
NC
S
N
OMe
OMe
2be
160
140
120
100
80
60
40
20
ppm

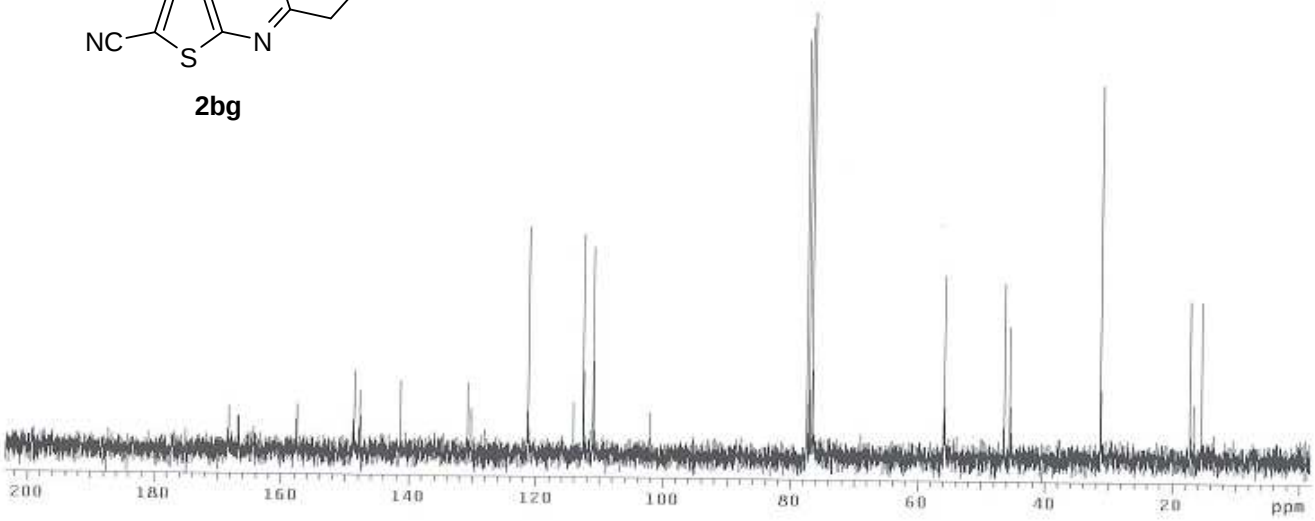

HN
OMe
OMe
H_3C
N
NC
N
S

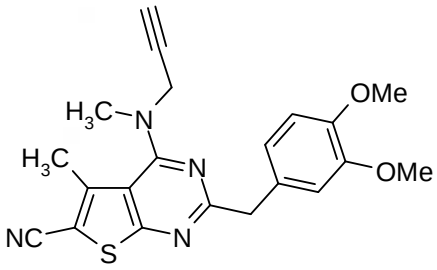
2bg

10
9
8
7
6
5
4
3
2
1


HN
OMe
OMe
H_3C
N
NC
N
S

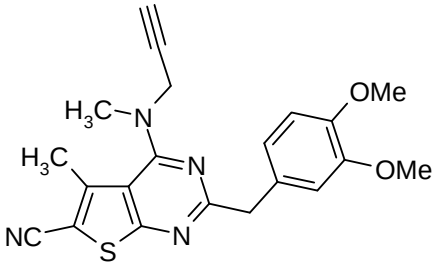
2bg


200
180
160
140
120
100
80
60
40
20
ppm

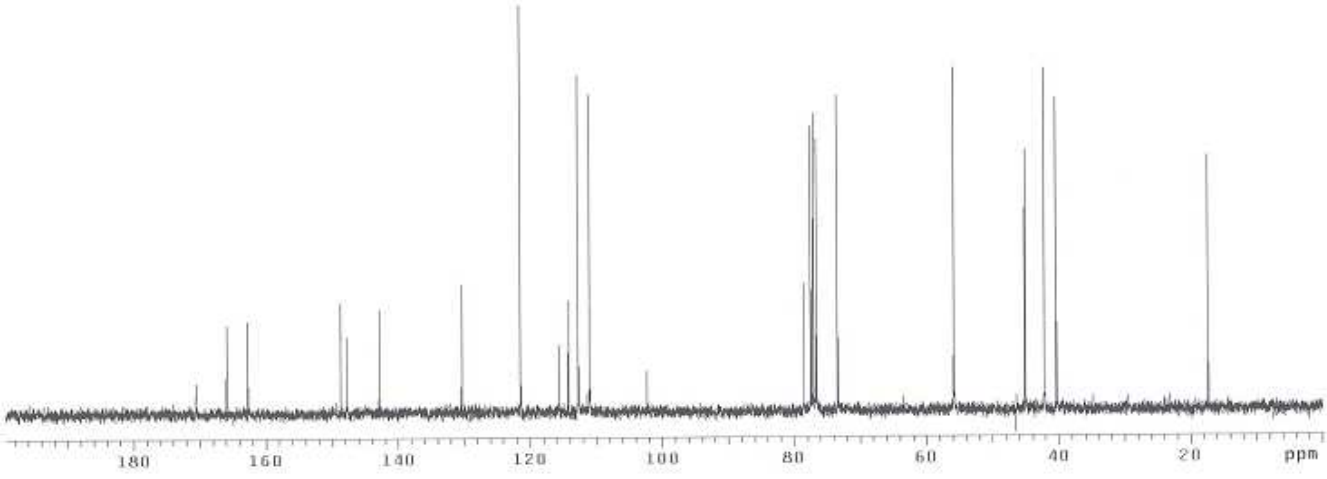

OMe
OMe
N
N
N
S
NC

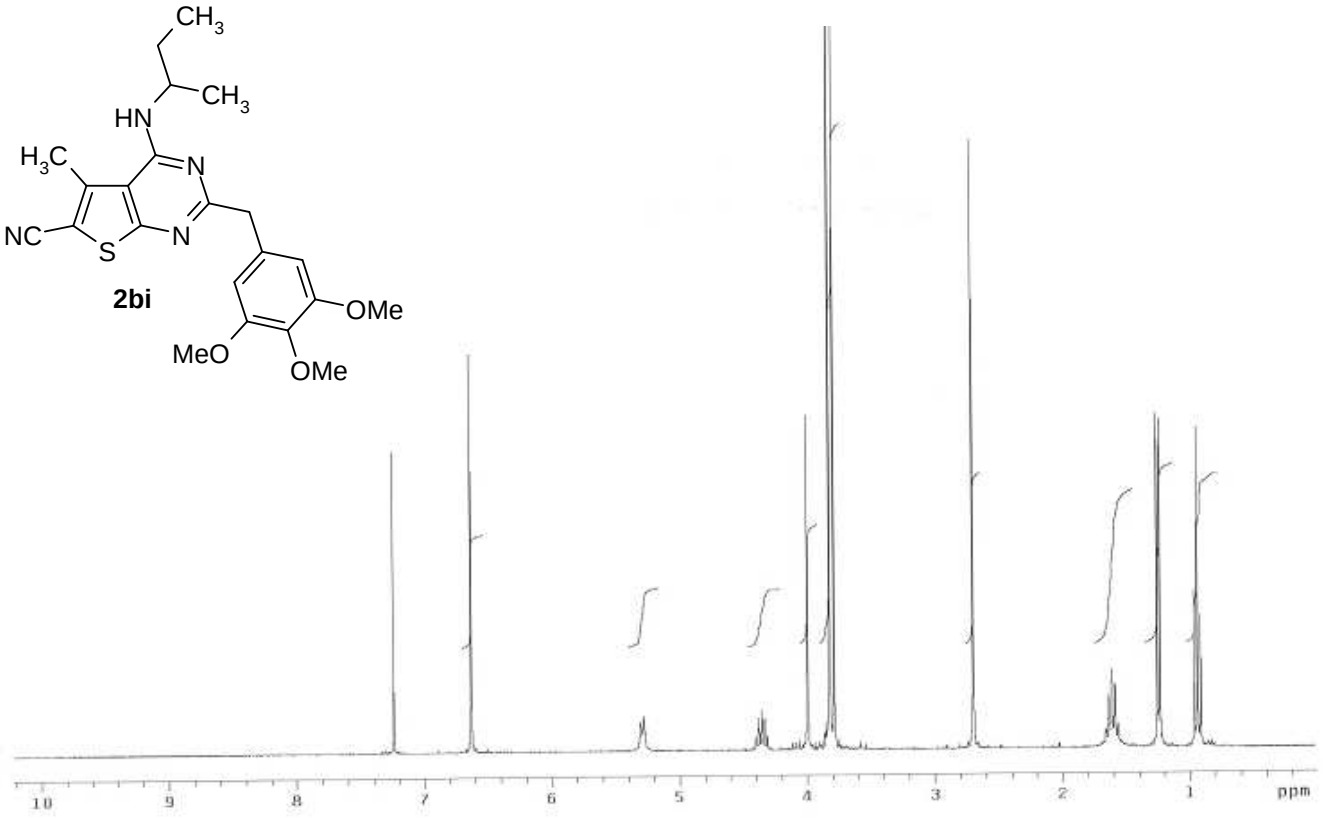
2bh

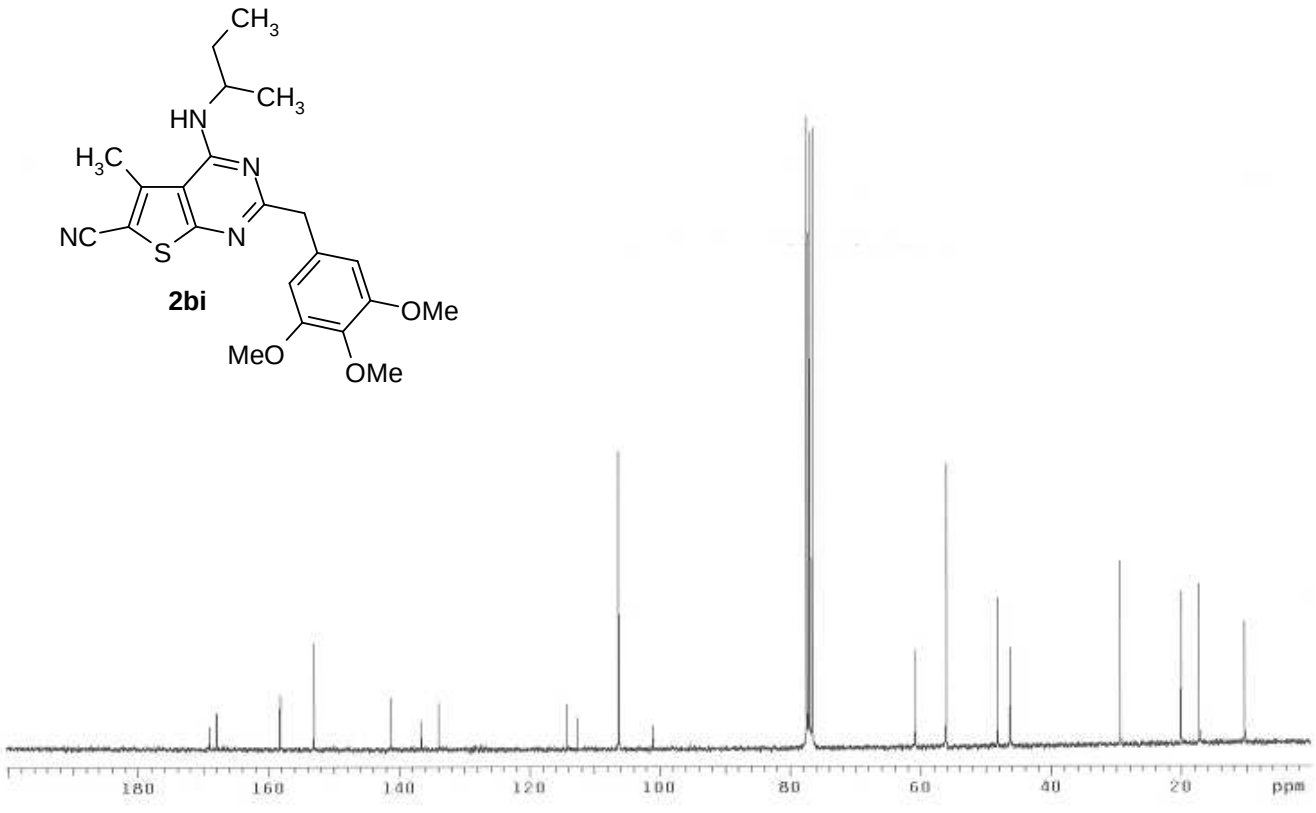
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm

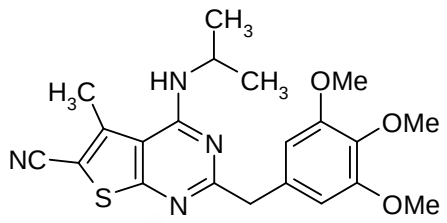

OMe
OMe
N
N
N
S
NC

2bh


180
160
140
120
100
80
60
40
20
ppm

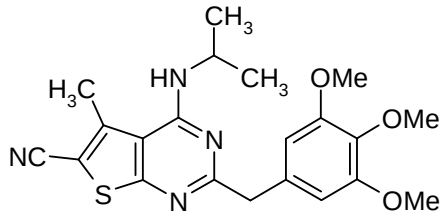

CH3
CH3
HN
H3C
N
NC
S
N
2bi
OMe
MeO
OMe
10
9
8
7
6
5
4
3
2
1
ppm


CH3
CH3
HN
H3C
N
NC
S
N
2bi
OMe
MeO
OMe
180
160
140
120
100
80
60
40
20
ppm


CH3
HN
CH3
OMe
H3C
OMe
NC
N
S
N
OMe

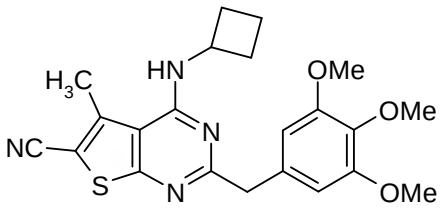
2bj

9
8
7
6
5
4
3
2
1
ppm


CH3
HN
CH3
OMe
H3C
OMe
NC
N
S
N
OMe

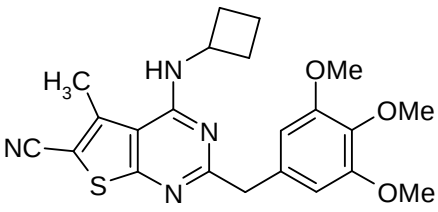
2bj

220
200
180
160
140
120
100
80
60
40
20
0
ppm


HN
OMe
H_3C
OMe
N
NC
S
N
OMe

2bk

9
8
7
6
5
4
3
2
1
ppm


HN
OMe
H_3C
OMe
N
NC
S
N
OMe

2bk

200
180
160
140
120
100
80
60
40
20
ppm

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