Supplementary Information

A Cascade Reactions on Azolopyrimidines. Synthesis of Unusual Indole and Aza-indole Derivatives

María Morón,[a] Carolina Burgos,[a]* Julio Alvarez-Builla,[a] Antonio Salgado,[b] Marta E. G. Mosquera,[c] Juan J. Vaquero[a]*

[a] *Departamento de Química Orgánica,* [c] *Departamento de Química Inorgánica Universidad de Alcalá, 28871-Alcalá de Henares, Madrid, Spain. Fax: 34-91-8854686; Tel: 34-91-885476; E-mail: juanjose.vaquero@uah.es*

[b]*Centro Nacional de Investigaciones Oncológicas (CNIO), E-28029-Madrid, Spain*

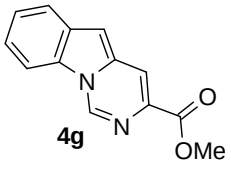
Table of contents

Experimental details and characterization data for compounds: 4g, 5e-g, 6, 7 and 8g

General information

Reagents were purchased of the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60FS-254) using UV light as visualizing. Column chromatography was performed using silica gel (60 F254, 70–200 mm) as the stationary phase. All NMR spectra were recorded in a Bruker AVANCE 700 spectrometer, a Varian UNITY 500 spectrometer, or in a Bruker AVANCE II 300 spectrometer, respectively fitted with a QXI 700 MHz S4 probe (operating at 700.13 MHz, 176.05 MHz or 70.94 MHz as the ^{1}H, ^{13}C and ^{15}N frequencies), a PFG ATB probe (operating at 499.66 MHz or 125.65 MHz as the ^{1}H and ^{13}C frequencies), and with a QNP 300 MHz S2 probe (operating at 300.13 MHz or 75.47 MHz as the ^{1}H and ^{13}C frequencies). Chemical shifts are given as referred to external $SiMe_4$ (^{1}H and ^{13}C, 0.00 ppm) or external liquid NH_3 (^{15}N, 0.00 ppm). ^{15}N chemical shifts were indirectly measured from ^{1}H-^{15}N HMBC experiments. All spectra were recorded at 25ºC unless otherwise stated. All melting points (mp) are uncorrected. The following compounds have been previously described: **4a**, **4b and 4f**,[6] **4c**,[4a,6b] **4d**,[4a,6,10] **4e**[11] and **4h**.[12]

Synthesis of methyl pyrimido[1,6-*a*]indole-3-carboxylate (4g)



4g

To a solution of **4b** (305 mg, 1 mmol) and lithium bromide (96 mg, 1.1 mmol) in 14 mL of AcOH were added H_2SO_4 (0.06 mL) and *N*-methyl pyrrole (201 mg, 0.22 mL, 2.48 mmol). The solution was heated to reflux for 30 min. Then, a saturated solution of $NaHCO_3$ was added and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine and dried on Na_2SO_4. Purification by flash

chromatography [silica gel, hexane/EtOAc (30:70)] supplied pure compound **4g** (118 mg, 52%). Yellow solid; mp 201-203 ºC; υ_{max}(NaCl) /cm^{-1} 3199, 2369, 1715, 1369; δ_H (500 MHz; $CDCl_3$; Me_4Si) 3.99 (3 H, s, OMe), 6.94 (1 H, s), 7.47 (2 H, m), 7.85 (1 H, d, *J* = 6.9 Hz), 8.04 (1 H, d, *J* = 8.2 Hz), 8.23 (1 H, s), 9.19 (1 H, s); δ_C (125 MHz, $CDCl_3$; Me_4Si) 52.8, 98.3, 110.8, 118.2, 121.6, 123.2, 125.1, 128.9, 130.2, 132.9, 133.8, 138.4, 165.4; HRMS (ESI-TOF) m/z calcd. for $C_{13}H_{11}N_2O_2$ $[M+H]^+$: 227.0815 found: 227.0824.

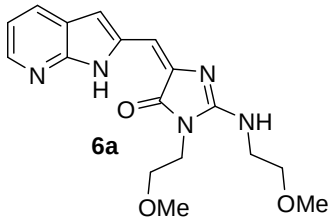
General procedure for the preparation of 6a-l, 7a-l, 5e-g and 8h.

A solution of corresponding azolopyrimidine **4** (1 mmol) in the required amine was refluxed until all the starting material could not be detected by TLC. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel. When solid residues were obtained, compounds **6** and **7** were then crystallized from ethanol, yielding pure compounds.

Reaction of methyl 5-bromo-4-pyrido[3',2':4,5]pyrrolo[1,2-*c*]-pyrimidine-7-carboxylate 4a and 2-methoxyethylamine: Synthesis of (5*E*)-3-(2-methoxyethyl)-2-(2-methoxyethylamino)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-2-yl-methylene)-3,5-dihydroimidazol-4-one (6a) and (5*E*)-3-(2-methoxyethyl)-5-[(2-methoxyethylamino)-(1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-methylene]-3,5-dihydroimidazol-4-one (7a).

The general procedure using 306 mg of **4a** as the starting material in 20.3 mL of 2-methoxyethylamine gave, after 1h of reaction, a mixture of products. Separation by flash chromatography [silica gel, EtOAc/EtOH (90:10)] gave pure compounds **6a** (195 mg, 57%) and **7a** (117 mg, 34%).

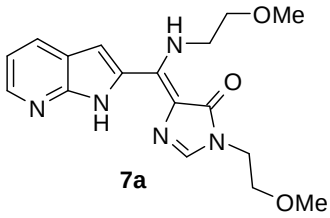
(5*E*)-3-(2-methoxyethyl)-2-(2-methoxyethylamino)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-2-yl-methylene)-3,5-dihydroimidazol-4-one (6a).



6a

Orange oil; υ $_{max}$(NaCl) /cm^{-1} 3302, 2927, 1717, 1652; δ_H (300 MHz; Acetone-d_6; Me_4Si) 3.39 (6 Hs, s, 2 MeO), 3.60 (2 H, t, J = 4.8 Hz, CH_2), 3.68 (2 H, t, J = 5.0 Hz, CH_2), 3.78 (2 H, t, J = 5.0 Hz, CH_2), 3.83 (2 H, t, J = 4.8 Hz, CH_2), 6.59 (1 H, s, C*H*=C), 6.70 (1 H, s, C(3 arom)H), 7.03 (1 H, dd, J = 7.9, 4.6 Hz, C(5 arom)H), 7.27 (1 H, br s, NH), 7.96 (1 H, d, J = 7.9 Hz, C (4 arom)H), 8.21 (1 H, dd, J = 4.6, 1.3Hz, C(6 arom)H), 11.19 (1 H, br s, NH); δ_C (75 MHz, Acetone-d_6, Me_4Si) 40.7, 42.2, 58.8, 59.0, 71.3, 72.1, 104.3, 104.6, 116.9, 121.6, 128.7, 137.1, 141.1, 144.6, 150.0, 159.6, 169.0; HRMS (APCI-TOF) m/z calcd. for $C_{17}H_{22}N_5O_3$ $[M+H]^+$: 344.1723. found: 344.1710.

(5*E*)-3-(2-methoxyethyl)-5-[(2-methoxyethylamino)-(1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-methylene]-3,5-dihydroimidazol-4-one (7a).



7a

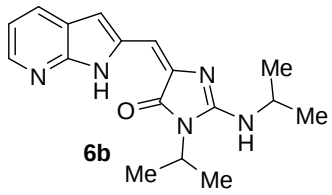
Orange solid; mp 80–83 ºC; υ $_{max}$(KBr) /cm^{-1} 3127, 2931, 2886, 1639, 1274, 1117; δ_H (300 MHz; $CDCl_3$; Me_4Si) 3.33 (3 H, s, OMe), 3.48 (3 H, s, OMe), 3.56 (2 H, t, J = 5.1 Hz, CH_2), 3.70 (2 H, t, J = 5.3 Hz, CH_2), 3.84 (2 H, t, J = 5.1 Hz, CH_2), 3.90 (2 H, q, J = 5.3 Hz, CH_2), 7.07 (1 H dd, J = 7.9, 4.6 Hz, C(5 arom)H), 7.11 (s, 1H), 7.32 (s, 1H), 7.96 (1 H, dd, J = 7.9, 1.3 Hz, C(4 arom)H), 8.40 (1 H, dd, J = 4.6, 1.3 Hz, C(6 arom)H), 9.91 (1 H, br s, NH), 12.24 (1 H, br s, NH); δ_C (75 MHz, Acetone-d_6, Me_4Si) 40.5, 45.9, 57.9, 58.2, 70.4, 71.1, 107.7, 114.6, 116.8, 119.6, 129.3, 129.8, 138.6, 146.5,

147.2, 148.7, 166.5; HRMS (APCI-TOF) m/z calcd. for $C_{17}H_{22}N_5O_3$ $[M+H]^+$: 344.1723. found: 344.1732.

Reaction of methyl 5-bromo-4-pyrido[3',2':4,5]pyrrolo[1,2-*c*]-pyrimidine-7-carboxylate 4a and isopropylamine: Synthesis of (5*E*)-3-isopropyl-2-isopropylamino-5-(1*H*-pyrrolo[2,3-*b*]pyridin-2-yl-methylene)-3,5-dihydroimidazol-4-one (6b) and (5*E*)-3-isopropyl-5-[isopropylamino-(1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-methylene]-3,5-dihydroimidazol-4-one (7b).

The general procedure using 306 mg of **4a** as the starting material in 20 mL of isopropylamine gave, after 2h of reaction, a mixture of products. Separation by flash chromatography [silica gel, hexano: EtOAc (50:50)] yielded pure compounds **6b** (59 mg, 19%) and **7b** (152 mg, 49%) .

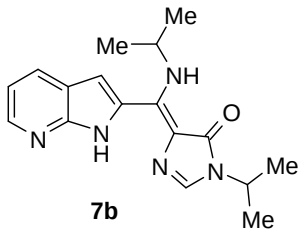
(5*E*)-3-isopropyl-2-isopropylamino-5-(1*H*-pyrrolo[2,3-*b*]pyridin-2-yl-methylene)-3,5-dihydroimidazol-4-one (6b)



6b

Orange oil; υ $_{max}$(NaCl) /cm^{-1} 3334, 2973, 1646, 1575, 1337; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.38 (6 H, d, *J* = 6.6 Hz, 2 Me), 1.46 (6 H, d, *J* = 6.6 Hz, 2 Me), 4.28 (1 H, hept, *J* = 6.6 Hz, Me_2CH), 4.48 (1 H, m), 6.51 (1 H, s), 6.69 (2 H, m), 7.28 (s, 1H), 7.03 (1 H, dd, *J* = 7.9, 4.6 Hz, C(5 arom)H), 7.89 (1 H, dd, *J* = 7.9, 1.6 Hz, C(4 arom)H), 8.20 (1 H, dd, *J* = 4.6, 1.6 Hz, C(6 arom)H), 11.20 (1 H, br s, NH); δ_C (75 MHz, $CDCl_3$, Me_4Si) 20.6, 23.1, 43.8, 44.6, 104.4, 105.9, 116.2, 120.9, 128.4, 136.1, 139.1, 144.1, 149.3, 155.9, 168.8; HRMS (ESI-TOF) m/z calcd. for $C_{17}H_{21}N_5O$ $[M+H]^+$: 312.1824. found: 312.1822.

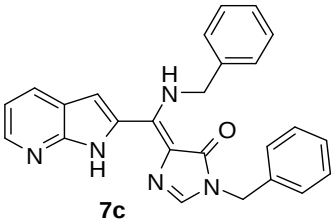
(5*E*)-3-isopropyl-5-[isopropylamino-(1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-methylene]-3,5-dihydroimidazol-4-one (7b).



7b

Orange solid; mp 194–195 ºC; υ $_{max}$(KBr) /cm^{-1} 3127, 2970, 1622, 1281; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.40 (6 H, d, *J* = 6.6 Hz, 2 Me), 1.43 (6 H, d, *J* = 6.6 Hz, 2 Me), 4.39 (1 H, hept, *J* = 6.6 Hz, Me_2CH), 4.46 (1 H, m), 7.07 (1 H, s), 7.10 (1 H, dd, *J* = 8.1, 4.6 Hz, C(5 arom)H), 7.28 (s, 1H), 7.98 (1 H, dd, *J* = 8.1, 1.4 Hz, C(4 arom)H), 8.43 (1 H, dd, *J* = 4.6, 1.4 Hz, C(6 arom)H), 9.94 (1 H, d, *J* = 8.6 Hz), 12.52 (1 H, br s, NH); δ_C (75 MHz, $CDCl_3$, Me_4Si) 22.3, 24.1, 43.5, 47.2, 106.9, 115.2, 116.8, 119.7, 129.0, 130.0, 133.9, 146.7, 147.1, 148.5, 166.1; HRMS (ESI-TOF) m/z calcd. for $C_{17}H_{22}N_5O$ $[M+H]^+$: 312.1824. found: 312.1824.

Reaction of methyl 5-bromo-4-pyrido[3',2':4,5]pyrrolo[1,2-*c*]-pyrimidine-7-carboxylate 4a and benzylamine: Synthesis of (5*E*)-3-benzyl-5-[benzylamino-(1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-methylene]-3,5-dihydroimidazol-4-one (7c)

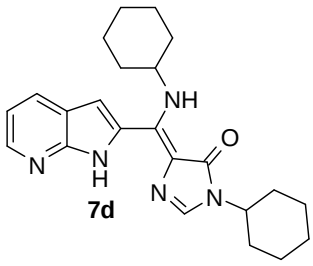


7c

The general procedure using 306 mg of **4a** as the starting material in 25.4 mL of bezylamine gave, after 2.5 h of reaction, a crude product. Purification by flash chromatography [silica gel, hexane: EtOAc (30:70)] afforded pure compound **7c** (171 mg, 42%). Orange solid; mp 155–157 ºC; υ $_{max}$(NaCl) /cm^{-1} 3280, 3030, 2923, 1615, 1595, 1538; δ_H (500 MHz; $CDCl_3$; Me_4Si) 4.86 (2 H, s, CH_2), 4.99 (2 H, d, *J* = 5.9 Hz, CH_2), 7.05 (1 H, s), 7.08 (1 H, dd, *J* = 7.9, 4.8 Hz, C(5 arom)H), 7.21 (1 H, s), 7.28 (3

H, m), 7.33 (3 H, m), 7.41 (4 H, m), 7.94 (1 H, dd, *J* = 7.9, 1.4 Hz, C(4 arom)H), 8.42 (1 H, dd, *J* = 4.8, 1.4 Hz, C(6 arom)H), 10.20 (1 H, br s, NH), 12.49 (1 H, br s, NH); δ_C (75 MHz, $CDCl_3$, Me_4Si) 44.7, 50.2, 107.9, 115.0, 116.9, 119.6, 127.0, 127.7, 127.9, 128.0, 128.8, 128.9, 129.1, 130.3, 136.4, 136.8, 137.1, 146.9, 148.0, 148.6, 166.6; HRMS (APCI-TOF) m/z calcd. for $C_{25}H_{22}N_5O$ $[M+H]^+$: 408.1824. found: 408.1814.

Reaction of methyl 5-bromo-4-pyrido[3',2':4,5]pyrrolo[1,2-*c*]-pyrimidine-7-carboxylate 4a and cyclohexylamine: Synthesis of (5*E*)-3-cyclohexyl-5-[cyclohexylamino-(1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-methylene]-3,5-dihydroimidazol-4-one (7d).



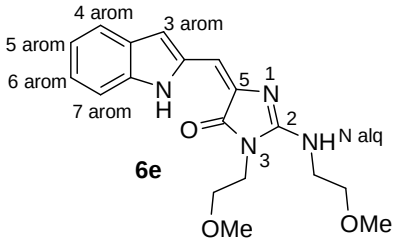
7d

The general procedure using 306 mg of **4a** as the starting material in 26.6 mL of cyclohexylamine gave, after 2.5 h of reaction, a crude product. Purification by flash chromatography [silica gel, hexane: EtOAc (50:50)] yielded pure compound **7d** (262 mg, 67%). Orange solid; mp 170–171ºC; υ_{max}(NaCl) /cm^{-1} 3247, 2930, 2854, 1622, 1467, 1280; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.23 (2 H, m), 1.55 (12 H, m), 1.86 (4 H, m), 2.02 (2 H, m), 3.99 (1 H, m), 4.12 (1 H, m), 7.01 (1 H, s), 7.10 (1 H, dd, *J* = 7.9, 4.6 Hz, C(5 arom)H), 7.27 (1 H, s), 7.99 (1 H, dd, *J* = 7.9, 1.3 Hz, C(4 arom)H), 8.43 (1 H, dd, *J* = 4.6, 1.3 Hz, C(6 arom)H), 10.10 (1 H, d, *J* = 8.2 Hz), 12.52 (1 H, br s, NH); δ_C (75 MHz, $CDCl_3$, Me_4Si) 24.2, 25.3, 25.4, 25.6, 33.0, 33.9, 50.8, 53.6, 106.7, 115.1, 116.8, 119.6, 129.1, 129.9, 134.2, 146.7, 147.1, 148.5, 166.0; HRMS (ESI-TOF) m/z calcd. for $C_{23}H_{30}N_5O$ $[M+H]^+$: 392.2450. found: 392.2454.

Reaction of methyl 5-bromo-pyrimido[1,6-*a*]indole-3-carboxilate 4b and 2-methoxyethylamine: Synthesis of (5*E*)-5-(1*H*-indol-2-yl-methylene)-3-(2-methoxyethyl)-2-(2-methoxyethylamino)-3,5-dihydroimidazol-4-one (6e) and (5*E*)-5-[(1*H*-indol-2-yl)-(2-methoxyethylamino)-methylene]-3-(2-methoxyethyl)-3,5-dihydroimidazol-4-one (7e).

The general procedure using 305 mg of **4b** as the starting material in 20.3 mL of 2-methoxyethylamine gave, after 1h of reaction, a mixture of products. Separation by flash chromatography [silica gel, hexane: EtOAc (30:70)] yielded pure compounds **6e** (140 mg, 45%) and **7e** (154 mg, 41%).

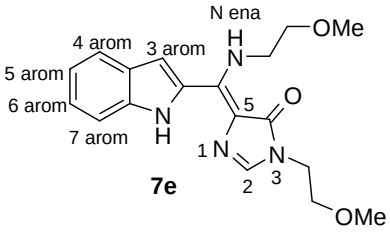
(5*E*)-5-(1*H*-indol-2-yl-methylene)-3-(2-methoxyethyl)-2-(2-methoxyethylamino)-3,5-dihydroimidazol-4-one (6e).



6e

Orange oil; υ_{max}(NaCl) /cm^{-1} 3330, 2929, 1716, 1651, 1589; δ_H (700 MHz; DMSO-d_6; Me_4Si) 3.26 (3 H, s, OMe), 3.34 (3 H, s, OMe), 3.48 (2 H, t, J = 5.3 Hz, OCH_2), 3.61 (2 H, t, J = 5.6 Hz, OCH_2), 3.74 (2 H, m, NCH_2), 3.78 (2 H, t, J = 5.6 Hz, NCH_2), 6.54 (1 H, s, C(3 arom)H), 6.87 (1 H, s, C*H*=C), 6.98 (1 H, t, J = 7.5 Hz, C(5 arom)H), 7.11 (1 H, t, J = 7.6 Hz, C(6 arom)H), 7.46 (1 H, d, J = 7.2 Hz, C(7 arom)H), 7.51 (1 H, d, J = 7.3 Hz, C(4 arom)H), 7.75 (1 H, t, J = 5.8 Hz, NH alq), 11.01 (1 H, s, NH arom); δ_C (175 MHz, DMSO-d_6; Me_4Si) 38.5 (N*C*H$_2$), 41.0 (N*C*H$_2$), 58.0 (OMe), 58.1 (OMe), 69.4 0 (O*C*H$_2$), 70.3 (O*C*H$_2$), 103.9 (C3 arom), 105.4 (*C*H=C), 111.5 (C7 arom), 119.4 (C5 arom), 120.1 (C4 arom), 122.2 (C6 arom), 128.1 (C3' arom), 135.2 (C2 arom), 136.9 (C7' arom), 138.8 (C5), 157.5 (C2), 168.6 (C=O); δ_N (70 MHz, DMSO-d_6) 77.2 (N alq), 132.6 (N arom), 142.5 (N1), 173.1 (N3); HRMS (APCI-TOF) m/z calcd. for $C_{18}H_{23}N_4O_3$ $[M+H]^+$: 343.1770. found: 343.1780.

(5*E*)-5-[(1*H*-indol-2-yl)-(2-methoxyethylamino)-methylene]-3-(2-methoxyethyl)-3,5-dihydroimidazol-4-one (7e).



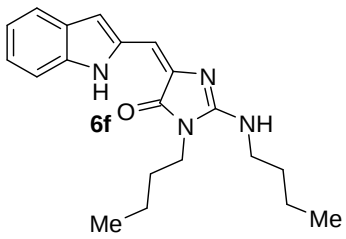
7e

Orange solid; mp 72–74 ºC; υ $_{max}$(KBr) /cm^{-1} 3213, 2932, 1632, 1467, 111; δ_H (700 MHz; DMSO-*d*$_6$; Me$_4$Si) 3.26 (3 H, s, OMe), 3.31 (3 H, s, OMe), 3.54 (2 H, t, *J* = 5.4 Hz, OC*H*$_2$), 3.57 (2 H, t, *J* = 5.0 Hz, OC*H*$_2$), 3.79 (4 H, m, 2 NC*H*$_2$), 7.08 (1 H, t, *J* = 7.4 Hz, C(5 arom)H), 7.13 (1 H, d, *J* = 2.0 Hz, 1H), 7.24 (1 H, m, C(6 arom)H), 7.47 (1 H, s, C(2)H), 7.58 (1 H, d, *J* = 8.2 Hz, C(7 arom)H), 7.66 (1 H, d, *J* = 7.9 Hz, C(4 arom)H), 9.74 (1 H, t, *J* = 5.4 Hz, NH ena), 11.87 (1 H, s, N arom); δ_C (75 MHz, DMSO-*d*$_6$; Me$_4$Si) 40.1 (N*C*H$_2$), 45.3 (N*C*H$_2$), 57.9 (OMe), 58.2 (OMe), 69.9 (O*C*H$_2$), 70.8 (O*C*H$_2$), 108.2 (C3 arom), 112.3 (C7 arom), 114.1 (C5), 119.9 (C4 arom), 121.2 (C4 arom), 123.8 (C6 arom), 126.9 (C3' arom), 127.4 (C2 arom), 136.8 (C7' arom), 138.4 (C2), 149.0 (*C*=C), 166.1 (C=O); δ_N (70 MHz, DMSO-*d*$_6$) 97.0 (N ena), 138.0 (N arom), 161.6 (N3), 239.8 (N1); HRMS (APCI-TOF) m/z calcd. for $C_{18}H_{23}N_4O_3$ $[M+H]^+$: 343.1770. found: 343.1760.

Reaction of methyl 5-bromo-pyrimido[1,6-*a*]indole-3-carboxilate 4b and butylamine: Synthesis of (5*E*)-3-butyl-2-butylamino-5-(1*H*-indol-2-yl-methylene)-3,5-dihydroimidazol-4-one (6f) and (5*E*)-3-butyl-2-butylamino-5-(1*H*-indol-2-yl-methylene)-3,5-dihydroimidazol-4-one (7f).

The general procedure using 305 mg of **4b** as the starting material in 23 mL of butylamine gave, after 3h of reaction, a mixture of products. Separation by flash chromatography [silica gel, hexane: EtOAc (30:70)] afforded pure compounds **6f** (74 mg, 22%) and **7f** (176 mg, 52%).

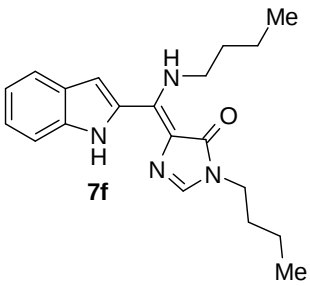
(5*E*)-3-butyl-2-butylamino-5-(1*H*-indol-2-yl-methylene)-3,5-dihydroimidazol-4-one (6f).



6f

Orange solid; mp 151–153 ºC; υ $_{max}$(NaCl) /cm^{-1} 3332, 2958, 2931, 1648, 1588; δ_H (300 MHz; Acetone-d_6; Me_4Si) 0.91 (3 H, t, *J* = 7.2 Hz, Me), 1.00 (3 H, t, *J* = 7.2 Hz, Me), 1.33 (2 H, m, CH_2), 1.49 (2 H, m, CH_2), 1.61 (2 H, m, CH_2), 1.74 (2 H, m, CH_2), 3.65 (4 H, m, 2 CH_2), 6.58 (1 H, s), 6.70 (1 H, s), 6.94 (1 H, br s, NH), 6.98 (1 H, at, *J* = 7.9 Hz), 7.10 (1 H, at, *J* = 7.9 Hz), 7.37 (1 H, d, *J* = 8.2 Hz), 7.53 (1 H, d, *J* = 7.9 Hz), 11.11 (1 H, br s, NH); δ_C (75 MHz, Acetone-d_6; Me_4Si) 13.1, 13.3, 19.6, 19.8, 30.7, 31.5, 38.5, 41.3, 104.2, 105.4, 111.0, 119.5, 120.4, 122.6, 128.6, 136.3, 137.5, 139.2, 157.5, 168.5; HRMS (APCI-TOF) m/z calcd. for $C_{20}H_{27}N_4O$ $[M+H]^+$: 339.2185 found: 339.2185.

(5*E*)-3-butyl-5-[butylamino-(1H-indol-2-yl)-methylene]-3,5-dihydroimidazol-4-one (7f).



7f

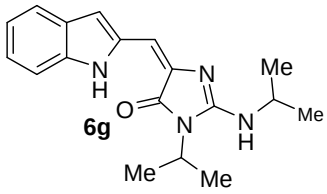
Orange solid; mp 72–73 ºC; υ $_{max}$(KBr) /cm^{-1} 3228, 2956, 1622, 1463, 1274; δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.96 (6 H, m, 2 Me), 1.37 (2 H, m, CH_2), 1.55 (2 H, m, CH_2), 1.69 (2 H, m, CH_2), 1.79 (2 H, m, CH_2), 3.70 (2 H, t, *J* = 7.2 Hz, CH_2), 3.81 (2 H, m, CH_2), 7.10 (1 H, at, *J* = 7.7 Hz), 7.15 (1 H, s), 7.21 (1 H, s), 7.29 (1 H, at, *J* = 8.2 Hz), 7.51 (1 H, d, *J* = 8.2 Hz), 7.66 (1 H, d, *J* = 7.7 Hz), 10.09 (1 H, br s, NH), 12.38 (1 H, br s, NH);

δ_C (75 MHz, $CDCl_3$; Me_4Si) 13.6, 13.8, 20.0, 20.1, 31.8, 32.0, 41.1, 46.3, 109.9, 112.2, 113.6, 120.5, 121.8, 125.1, 127.3, 128.7, 135.2, 137.2, 148.9, 165.8; HRMS (APCI-TOF) m/z calcd. for $C_{20}H_{27}N_4O$ $[M+H]^+$: 339.2185 found: 339.2185.

Reaction of methyl 5-bromo-pyrimido[1,6-*a*]indole-3-carboxilate 4b and isopropylamine: Synthesis of (5*E*)-5-(1*H*-indol-2-yl-methylene)-3-isopropyl-2-isopropylamino-3,5-dihydroimidazol-4-one (6g) and (5*E*)-5-[(1*H*-indol-2-yl)-isopropylamino-methylene]-3-isopropyl-3,5-dihydroimidazol-4-one (7g).

The general procedure using 305 mg of **4b** as the starting material in 20 mL of isopropylamine gave, after 2h of reaction, a mixture of products. Separation by flash chromatography [silica gel, hexane: EtOAc (50:50)] yielded pure compounds **6g** (74 mg, 24%) and **7g** (52 mg, 17%).

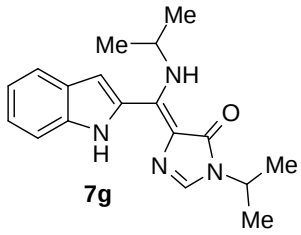
(5*E*)-5-(1H-indol-2-yl-methylene)-3-isopropyl-2-isopropylamino-3,5-dihydroimidazol-4-one (6g).



6g

Orange oil; υ_{max}(NaCl) /cm^{-1} 3352, 2973, 1698, 1645, 1576, 1367; δ_H (300 MHz; Acetone-d_6; Me_4Si) 1.36 (6 H, d, *J* = 6.6 Hz, 2 Me), 1.46 (6 H, d, *J* = 6.9 Hz, 2 Me), 4.25 (1 H, m, C*H*), 4.48 (1 H, m, C*H*), 6.50 (1 H, br s, NH), 6.53 (1 H, s), 6.69 (1 H, s), 6.98 (1 H, at, *J* = 7.9 Hz), 7.10 (1 H, at, *J* = 8.2 Hz), 7.38 (1 H, d, *J* = 8.2 Hz), 7.52 (1 H, d, *J* = 7.9 Hz), 11.05 (1 H, br s, NH); δ_C (75 MHz, Acetone-d_6; Me_4Si) 19.9, 22.6, 45.1, 45.1, 104.5, 106.0, 111.8, 120.1, 121.0, 123.2, 129.3, 136.9, 138.2, 139.9, 157.2, 169.6; HRMS (APCI-TOF) m/z calcd. for $C_{18}H_{23}N_4O$ $[M+H]^+$: 311.1872 found: 311.1862.

(5*E*)-5-[(1*H*-indol-2-yl)-isopropylamino-methylene]-3-isopropyl-3,5-dihydroimidazol-4-one (7g).



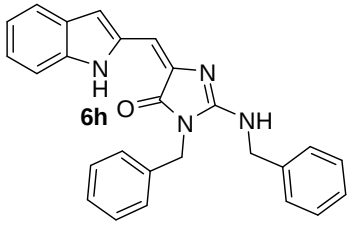
7g

Orange oil; υ $_{max}$(NaCl) /cm^{-1} 3273, 2973, 1623, 1532, 1469; δ_H (300 MHz; Acetone-d_6; Me_4Si) 1.40 (12 H, d, *J* = 6.9 Hz, 4 Me), 4.34 (1 H, m, C*H*), 4.54 (1 H, m, C*H*), 7.10 (1 H, at, *J* = 7.9 Hz), 7.27 (2 H, m), 7.55 (1 H, s), 7.59 (1 H, d, *J* = 8.2 Hz), 7.69 (1 H, d, *J* = 7.9 Hz), 10.00 (1 H, br s, NH), 12.26 (1 H, br s, NH); δ_C (75 MHz, Acetone-d_6; Me_4Si) 22.2, 24.3, 44.2, 47.6, 109.2, 112.9, 115.8, 121.1, 122.4, 125.3, 128.5, 129.5, 135.7, 138.0, 148.2, 166.9; HRMS (ESI-TOF) m/z calcd. for $C_{18}H_{23}N_4O$ $[M+H]^+$: 311.1872 found: 311.1862.

Reaction of methyl 5-bromo-pyrimido[1,6-*a*]indole-3-carboxilate 4b and benzylamine: Synthesis of (5*E*)-3-benzyl-2-benzylamino-5-(1*H*-indol-2-yl-methylene)-3,5-dihydroimidazol-4-one (6h) and (5*E*)-3-benzyl-5-[benzylamino-(1*H*-indol-2-yl)-methylene]-3,5-dihydroimidazol-4-one (7h).

The general procedure using 305 mg of **4b** as the starting material in 25.4 mL of benzylamine gave, after 1h of reaction, a mixture of products. Separation by flash chromatography [silica gel, hexane: EtOAc (30:50)] afforded pure compounds **6h** (138 mg, 34%) and **7h** (170 mg, 42%).

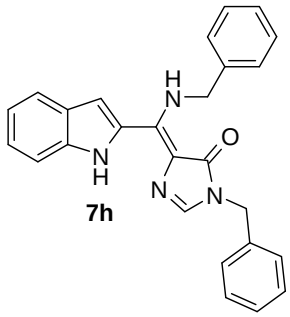
(5*E*)-3-benzyl-2-benzylamino-5-(1*H*-indol-2-yl-methylene)-3,5-dihydroimidazol-4-one (6h).



6h

Orange oil; υ $_{max}$(NaCl) /cm^{-1} 3328, 2920, 1646, 1581; δ_H (300 MHz; Acetone-d_6; Me_4Si) 4.80 (2 H, s, CH_2), 4.96 (2 H, s, CH_2), 6.68 (1 H, s), 6.73 (1 H, s), 6.98 (1 H, at, *J* = 7.7 Hz), 7.11 (1 H, at, *J* = 7.1 Hz), 7.33 (12 H, m), 7.52 (1 H, d, *J* = 7.7 Hz), 11.04 (1 H, br s, NH); δ_C (75 MHz, Acetone-d_6; Me_4Si) 42.8, 46.0, 106.4, 106.9, 112.0, 120.3, 121.3, 123.6, 127.6, 127.9, 128.3, 128.4, 129.2, 129.3, 129.5, 136.7, 137.3, 138.5, 139.4, 139.9, 157.9, 169.4; HRMS (APCI-TOF) m/z calcd. for $C_{26}H_{23}N_4O$ $[M+H]^+$: 407.1872 found: 407.1862.

(5*E*)-3-benzyl-5-[benzylamino-(1*H*-indol-2-yl)-methylene]-3,5-dihydroimidazol-4-one (7h).



7h

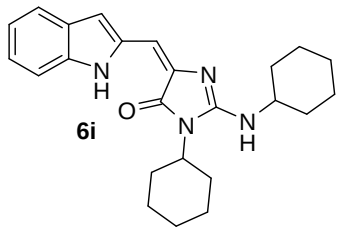
Yellow solid; mp 184–186 ºC; υ $_{max}$(KBr) /cm^{-1} 3188, 2919, 1607, 1272, 701; δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.88 (2 H, s, CH_2), 5.02 (2 H, d, *J* = 5.9 Hz, CH_2), 7.11 (1 H, at, *J* = 7.9 Hz), 7.15 (1 H, s), 7.20 (1 H, s), 7.38 (12 H, m), 7.63 (1 H, d, *J* = 7.9 Hz), 10.34 (1 H, br s, NH), 12.19 (1 H, br s, NH); δ_C (75 MHz, $CDCl_3$; Me_4Si) 44.7, 50.3, 110.0, 112.2, 114.2, 120.6, 121.9, 125.2, 127.2, 127.3, 127.6, 127.8, 127.9, 128.4, 128.9, 129.1, 135.9, 136.5, 137.1, 137.3, 148.9, 166.2; HRMS (APCI-TOF) m/z calcd. for $C_{26}H_{23}N_4O$ $[M+H]^+$: 407.1872 found: 407.1863.

Reaction of methyl 5-bromo-pyrimido[1,6-*a*]indole-3-carboxilate 4b and cyclohexylamine: Synthesis of (5*E*)-3-cyclohexyl-2-cyclohexylamino-5-(1*H*-indol-2-yl-methylene)-3,5-dihydroimidazol-4-one (6i) and (5*E*)-3-cyclohexyl-2-cyclohexylamino-5-(1*H*-indol-2-yl-methylene)-3,5-dihydroimidazol-4-one (7i).

The general procedure using 305 mg of **4b** as the starting material in 26.6 mL of cyclohexylamine gave, after 1h of reaction, a mixture of products. Separation by flash

chromatography [silica gel, CH_2Cl_2] yielded pure compounds **6i** (129 mg, 33%) and **7i** (152 mg, 39%).

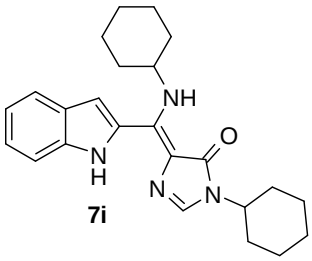
(5*E*)-3-cyclohexyl-2-cyclohexylamino-5-(1*H*-indol-2-yl-methylene)-3,5-dihydroimidazol-4-one (6i).



6i

Orange oil; υ_{max}(NaCl) /cm^{-1} 3334, 2930, 2854, 1645, 1575; δ_H (300 MHz; Acetone-d_6; Me_4Si) 1.25, (4 H, m), 1.42, (4 H, m), 1.58 (2 H, m), 1.73 (2 H, m), 1.83 (4 H, m), 2.17 (2 H, m), 2.29 (2 H, m), 3.83 (1 H, m), 4.12 (1 H, m), 6.52 (1 H, s), 6.58 (1 H, d, *J* = 6.9 Hz), 6.70 (1 H, s), 6.98 (1 H, at, *J* = 7.9 Hz), 7.11 (1 H, at, *J* = 7.9 Hz), 7.36 (1 H, d, *J* = 8.2 Hz), 7.52 (1 H, d, *J* = 7.9 Hz), 11.11 (1 H, br s, NH); δ_C (75 MHz, Acetone-d_6; Me_4Si) 25.7, 26.0, 26.4, 26.5, 33.6, 52.5, 52.6, 53.1, 104.5, 106.0, 111.8, 120.3, 121.2, 123.3, 129.4, 137.2, 138.2, 140.1, 157.3, 169.6; HRMS (ESI-TOF) m/z calcd. for $C_{24}H_{31}N_4O$ $[M+H]^+$: 391.2498 found: 391.2497.

(5*E*)-3-cyclohexyl-5-[cyclohexylamino-(1*H*-indol-2-yl)-methylene]-3,5-dihydroimidazol-4-one (7i).



7i

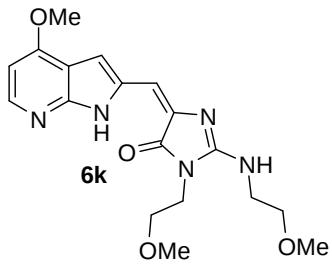
Orange solid; mp 167–168 ºC; υ_{max}(NaCl) /cm^{-1} 3242, 2931, 2854, 1625, 1533, 1467; δ_H (300 MHz; Acetone-d_6; Me_4Si) 1.26 (2 H, m), 1.43 (8 H, m), 1.67 (4 H, m), 1.95 (6 H, m), 3.95 (1 H, m), 4.26 (1 H, m), 7.09 (1 H, at, *J* = 8.4 Hz), 7.26 (2 H, m), 7.52 (1 H, s), 7.59 (1 H, d, *J* = 8.4 Hz), 7.69 (1 H, d, *J* = 7.7 Hz), 10.15 (1 H, br s, NH), 12.26 (1 H, br s, NH); δ_C (75 MHz, $CDCl_3$; Me_4Si) 24.3, 25.3, 25.4, 25.7, 33.1, 33.8, 50.8, 53.6,

108.7, 112.2, 114.2, 120.5, 121.7, 124.9, 127.4, 128.5, 133.2, 137.0, 148.0, 165.5; HRMS (ESI-TOF) m/z calcd. for $C_{24}H_{31}N_4O$ $[M+H]^+$: 391.2498 found: 391.2498.

Reaction of methyl 5-bromo-4-methoxypyrido[3',2':4,5]pyrrolo[1,2-*c*]-pyrimidine 7-carboxylate 4c and 2-methoxyethylamine: Synthesis of (5*E*)-3-(2-methoxyethyl)-2-(2-methoxyethylamino)-5-(4-methoxy-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl-methylene)-3,5-dihydroimidazol-4-one (6k) and (5*E*)-3-(2-methoxyethyl)-5-[(2-methoxyethylamino)-(4-methoxy-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-methylene]-3,5-dihydroimidazol-4-one (7k).

The general procedure using 336 mg of **4c** as the starting material in 20.3 mL of 2-methoxyethylamine gave, after 1h of reaction, a mixture of products. Separation by flash chromatography [silica gel, EtOAc/EtOH (90:10)] yielded pure compounds **6k** (101 mg, 27%) and **7k** (261 mg, 70%).

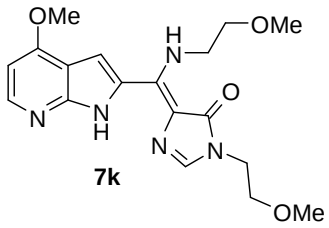
(5*E*)-3-(2-methoxyethyl)-2-(2-methoxyethylamino)-5-(4-methoxy-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl-methylene)-3,5-dihydroimidazol-4-one (6k).



6k

Orange oil; υ_{max}(NaCl) /cm^{-1} 3300, 2923, 2361, 1721, 1656, 1338; δ_H (300 MHz; Acetone-d_6; Me_4Si) 3.39 (6 H, s, 2 MeO), 3.59 (2 H, t, *J* = 5.0 Hz), 3.66 (2 H, t, *J* = 5.0 Hz), 3.76 (2 H, t, *J* = 5.0 Hz), 3.82 (2 H, t, *J* = 5.0 Hz), 3.99 (3 H, s, OMe), 6.58 (1 H, s), 6.61 (1 H, d, *J* = 5.6 Hz, C(5 arom)H), 7.03 (1 H, d, *J* = 1.5 Hz), 7.21 (1 H, br s, NH), 8.14 (1 H, d, *J* = 5.6 Hz, C(6 arom)H), 11.15 (1 H, br s, NH); δ_C (75 MHz, Acetone-d_6; Me_4Si) 40.7, 42.3, 55.8, 58.7, 59.0, 71.3, 72.1, 98.9, 102.0, 105.1, 111.9, 135.0, 140.3, 146.8, 151.8, 159.3, 160.3, 168.9; HRMS (ESI-TOF) m/z calcd. for $C_{18}H_{24}N_5O_4$ $[M+H]^+$: 374.1823 found: 374.1785.

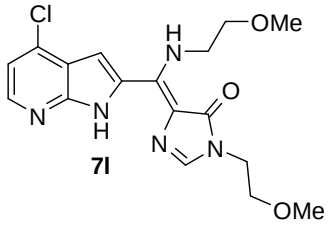
(5*E*)-3-(2-methoxyethyl)-5-[(2-methoxyethylamino)-(4-methoxy-1*H*-pyrrolo[2,3-b]pyridin-2-yl)-methylene]-3,5-dihydroimidazol-4-one (7k).



7k

Orange solid; mp 117–119 ºC; υ $_{max}$(NaCl) /cm^{-1} 3538, 3407, 2963, 1625,1514, 1261; δ_H (300 MHz; Acetone-d_6; Me_4Si) 3.32 (3 H, s, OMe), 3.42 (3 H, s, OMe), 3.60(2 H, t, *J* = 5.1 Hz), 3.75 (2 H, t, *J* = 5.1 Hz), 3.85 (2 H, t, *J* = 5.3 Hz), 4.00 (2 H, q, *J* = 5.3 Hz), 4.04 (3 H, s, OMe), 6.70 (1 H, d, *J* = 5.6 Hz, C(5 arom)H), 7.27 (1 H, s), 7.47 (1 H, s), 8.27 (1 H, d, *J* = 5.6 Hz, C(6 arom)H), 10.08 (1 H, br s, NH), 12.60 (1 H, br s, NH); δ_C (75 MHz, Acetone-d_6; Me_4Si) 41.3, 46.7, 56.1, 58.7, 58.9, 71.2, 71.8, 99.0. 106.0, 111.3, 115.0, 127.9, 138.9, 148.0, 149.6, 151.3, 161.5, 167.1; HRMS (APCI-TOF) m/z calcd. for $C_{18}H_{24}N_5O_4$ $[M+H]^+$: 374.1823 found: 378.1814.

Reaction of methyl 5-bromo-4-chloropyrido[3',2':4,5]pyrrolo[1,2-*c*]-pyrimidine 7-carboxylate 4d and 2-methoxyethylamine: Synthesis of (5*E*)-5-[(4-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-(2-methoxyethylamino)-methylene]-3-(2-methoxyethyl)-3,5-dihydroimidazol-4-one (7l).

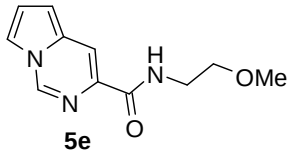


7l

The general procedure using 340 mg of **4d** as the starting material in 20.3 mL of 2-methoxyethylamine gave, after 3h of reaction, a crude product. Purification by flash chromatography [silica gel, hexane: EtOAc (50:50)] yielded pure compound **7l** (155 mg, 41%). Orange solid; mp 83–85 ºC; υ $_{max}$(NaCl) /cm^{-1} 3538, 2926, 1635, 1470, 1277, 1119; δ_H (300 MHz; Acetone-d_6; Me_4Si) 3.32 (3 H, s, OMe), 3.42 (3 H, s, OMe), 3.60 (2 H, t, *J* = 5.3 Hz), 3.73 (2 H, t, *J* = 5.0 Hz), 3.86 (2 H, t, *J* = 5.3 Hz), 4.00 (2 H, q, *J* = 5.0 Hz), 7.25(1 H, d, *J* = 5.1 Hz, C(5 arom)H), 7.30 (1 H, s), 7.50 (1 H, s), 8.22 (1 H, d, *J* = 5.1 Hz, C(6 arom)H), 9.95 (1 H, br s, NH), 12.70 (1 H, br s, NH); δ_C (75 MHz,

Acetone-d_6; Me_4Si) 41.3, 46.6, 58.7, 58.9, 71.2, 71.9, 105.8, 115.9, 117.4, 119.6, 130.9, 137.0, 139.9, 140.9, 147.5, 149.9, 167.4; HRMS (APCI-TOF) m/z calcd. for $C_{17}H_{21}ClN_5O_3$ $[M+H]^+$: 378.1327 found: 378.1317.

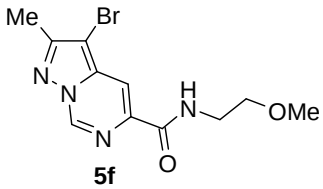
Reaction of methyl pyrrolo[1,2-*c*]pyrimidine-3-carboxylate, 4e and 2-methoxyethylamine: Synthesis of pyrrolo[1,2-*c*]pyrimidine-3-carboxylic acid (2-metoxyethyl)amide (5e).



5e

The general procedure using 176 mg of **4e** as the starting material in 20.3 mL of 2-methoxyethylamine gave, after 7 h of reaction, a crude product. Purification by flash chromatography [silica gel, hexane: EtOAc (30:70)] yielded pure compound **5e** (153 mg, 63%). Brown solid; mp 90-92 ºC; υ $_{max}$(NaCl) /cm^{-1} 3321, 2929, 1645, 1196; δ_H (300 MHz; $CDCl_3$; Me_4Si) 3.36 (3 H, s, OMe), 3.53 (2 H, d, *J* = 4.7 Hz), 3.62 (2 H, m), 6.64 (1 H, d, *J* = 3.7 Hz), 6.90 (1 H, dd, *J* = 2.5, 3.7 Hz), 7.44 (1 H, m), 8.02 (1 H, br s), 8.14 (1 H, s), 8.67 (1 H, s); δ_C (50 MHz, $CDCl_3$; Me_4Si) 39.2, 58.9, 71.3, 104.1, 112.6, 113.8, 117.5, 131.3, 132.9, 136.9, 164.3; HRMS (APCI-TOF) m/z calcd. for $C_{11}H_{13}N_3O_2$ $[M+H]^+$ 220.1086 found: 220.1091.

Reaction of methyl 3-bromo-2-methyl-pyrazolo[1,5-*c*]pyrimidine-5-carboxylate 4f and 2-methoxyethylamine: Synthesis of 3-bromo-2-methyl-pyrazolo[1,5-*c*]pyrimidine-5-carboxylic acid (2-methoxyethyl)amide (5f).

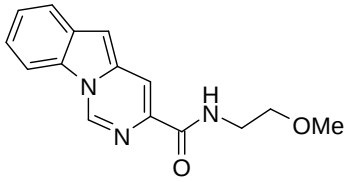


5f

The general procedure using 270 mg of **4f** as the starting material in 20.3 mL of 2-methoxyethylamine gave, after 2 h of reaction, a crude product. Purification by flash chromatography [silica gel, hexane: EtOAc (50:50)] yielded pure compound **5f** (138 mg, 53%). White solid; mp 193-194 ºC; υ max(NaCl) /cm^{-1} 3295, 2918, 2358, 1661, 1548; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.49 (3 H, s, Me), 3.36 (3 H, s, OMe), 3.56 (2 H, d,

J = 4.9 Hz), 3.62 (2 H, q, *J* = 4.9 Hz), 8.12 (1 H, br s), 8.22 (1 H, s), 8.99 (1 H, s); δ_C (75 MHz, $CDCl_3$; Me_4Si) 12.7, 39.4, 58.9, 71.1, 89.4, 110.7, 139.28, 139.33, 139.4, 154.9, 162.8; HRMS (APCI-TOF) m/z calcd. for $C_{11}H_{14}{}^{79}BrN_4O_2$ $[M+H]^+$ 313.0295 found: 313.0280.

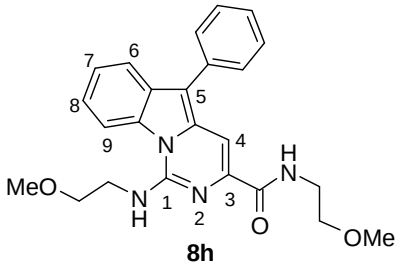
Reaction of methyl pyrimido[1,6-*a*]indole-3-carboxylate 4g and 2-methoxyethylamine: Synthesis of pyrimido[1,6-*a*]indole-3-carboxylic acid (2-metoxyethyl)amide (5g).



5g

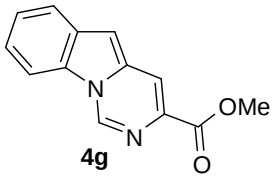
The general procedure using 226 mg of **4g** as the starting material in 20.3 mL of 2-methoxyethylamine gave, after 1h of reaction, a crude product. Purification by flash chromatography [silica gel, hexane: EtOAc (30:70)] yielded pure compound **5g** (153 mg, 57%). Yellow solid; mp 140-142 ºC; υ_{max}(NaCl) /cm^{-1} 3404, 2929, 1660, 1505; δ_H (300 MHz; $CDCl_3$; Me_4Si) 3.41 (3 H, s, OMe), 3.58 (2 H, t, *J* = 4.9 Hz), 3.68 (2 H, q, *J* = 4.9 Hz), 6.87 (1 H, s), 7.44 (2 H, m), 7.82 (1 H, d, *J* = 7.3 Hz), 7.99 (1 H, d, *J* = 7.6 Hz), 8.15 (1 H, br s), 8.20 (1 H, s), 9.10 (1 H, s); δ_C (125 MHz, $CDCl_3$; Me_4Si) 39.3, 58.9, 71.3, 97.3, 110.5, 113.8, 121.4, 122.6, 124.9,128.8, 130.4, 133.7, 136.2, 137.4, 163.9; HRMS (ESI-TOF) m/z calcd. for $C_{15}H_{16}N_3O_2$ $[M+H]^+$: 270.1237 found: 270.1228.

Reaction of methyl 5-phenyl-pyrimido[1,6-*a*]indole-3-carboxylate 4h and 2-methoxyethylamine: Synthesis of 1-(2-methoxyethylamino)-5-phenyl-pyrimido[1,6-*a*]indole-3-carboxylic acid (2-metoxyethyl)amide (8h).

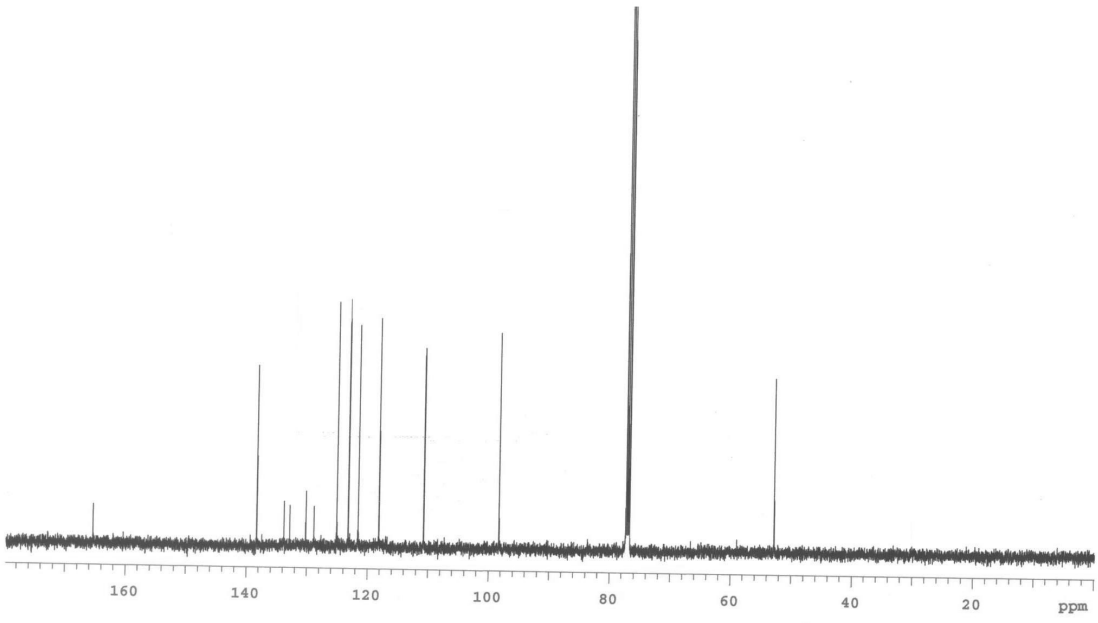


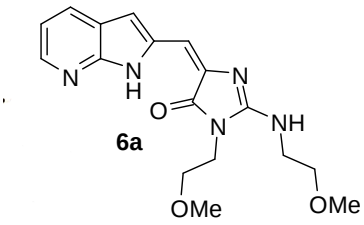
8h

The general procedure using 302 mg of **4h** as the starting material in 20.3 mL of 2-methoxyethylamine gave, after 4h of reaction, a crude product. Purification by flash chromatography [silica gel, cyclohexane: EtOAc (80:20)] afforded pure compound **8h** (58 mg, 14%). Yellow solid; mp 193–194ºC; υ_{max}(NaCl) /cm^{-1} 3303, 2926, 2360, 1715, 1647, 1587; δ_H (700 MHz; Acetone-*d*$_6$; Me_4Si) 3.43 (3 H, s, OMe), 3.44 (3 H, s, OMe), 3.63 (2 H, t, *J* = 4.9 Hz, OC*H*$_2$), 3.71 (2 H, t, *J* = 5.3 Hz, OC*H*$_2$), 3.85 (4 H, m, 2 NC*H*$_2$), 6.76 (1 H, s, C(4)H), 7.09 (1 H, t, *J* = 7.5 Hz, C(7)H), 7.20 (1 H, s, NH), 7.22 (1 H, t, *J* = 7.6 Hz, C(8)H), 7.41 (1 H, t, *J* = 7.3 Hz, C(4 Ph)H), 7.50 (1 H, d, *J* = 8.2 Hz, C(9)H), 7.57 (2 H, *J* = 7.7 Hz, C(3,5 Ph)H), 7.61 (2 H, d, *J* = 6.8 Hz, C(2,4 Ph)H), 7.66 (1 H, d, *J* = 8.1 Hz, C(6)H), 11.40 (1 H, s, NH); δ_C (75 MHz, Acetone-*d*$_6$; Me_4Si) 39.9 (N*C*H$_2$), 41.2 (N*C*H$_2$), 58.1 (OMe), 70.3 (O*C*H$_2$), 71.2 (O*C*H$_2$), 102.7 (C(4)), 111.4 (C(9)), 118.9 (C(6)), 119.7 (C(7)), 120.1 (C(1 Ph)), 122.7 (C(8)), 127.3 (C(4 Ph)), 127.6 (C(5')), 129.6 (C(3,5 Ph)), 130.7 (C(2,4 Ph)), 133.4 (C5), 137.5 (C(9')), 159.1 (C1), 168.7 (C=O); HRMS (ESI-TOF) m/z calcd. for $C_{24}H_{26}N_4O_3$ $[M+H]^+$: 419.2083 found: 419.2086.

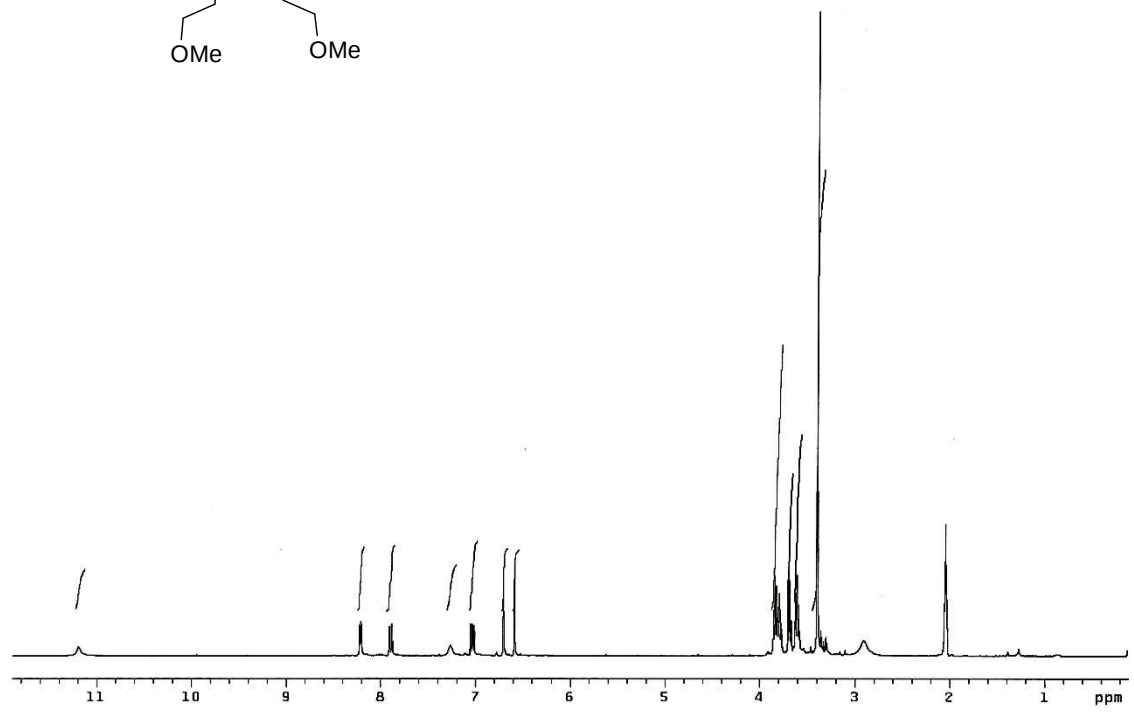


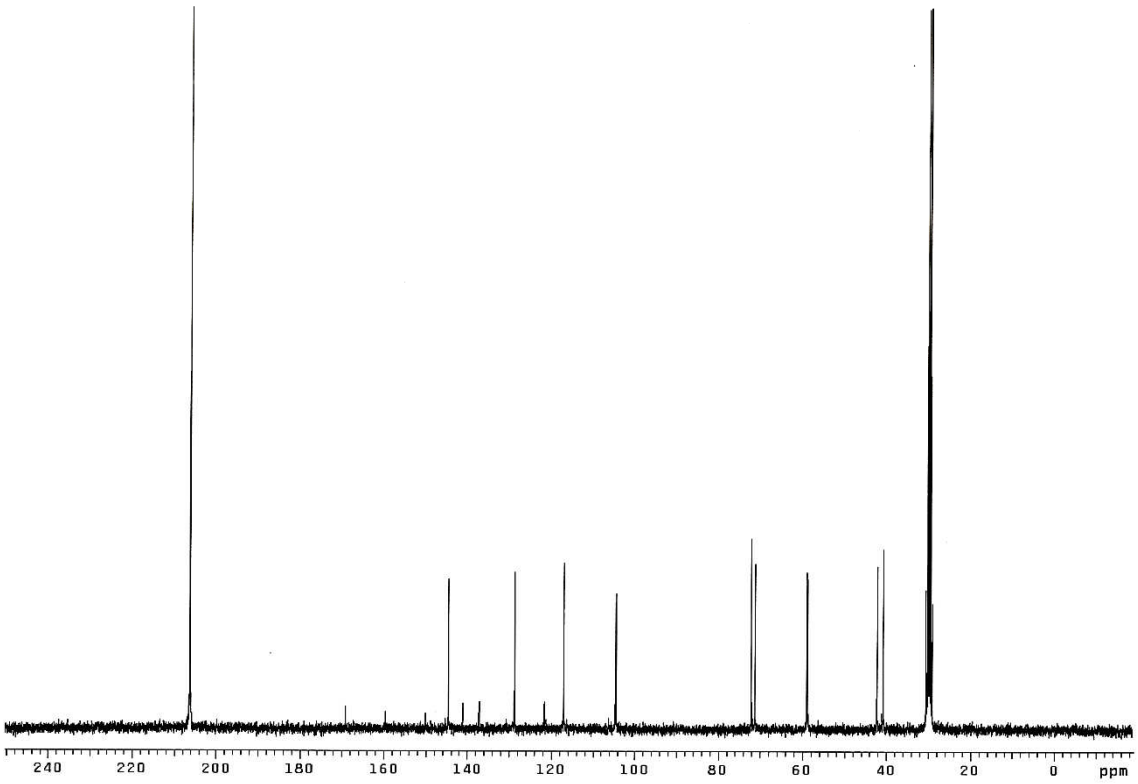
4g

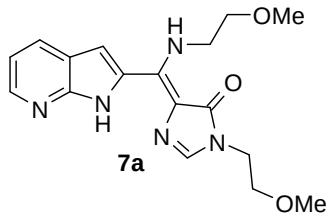



N
N
H
O
N
N
NH
OMe
OMe

6a

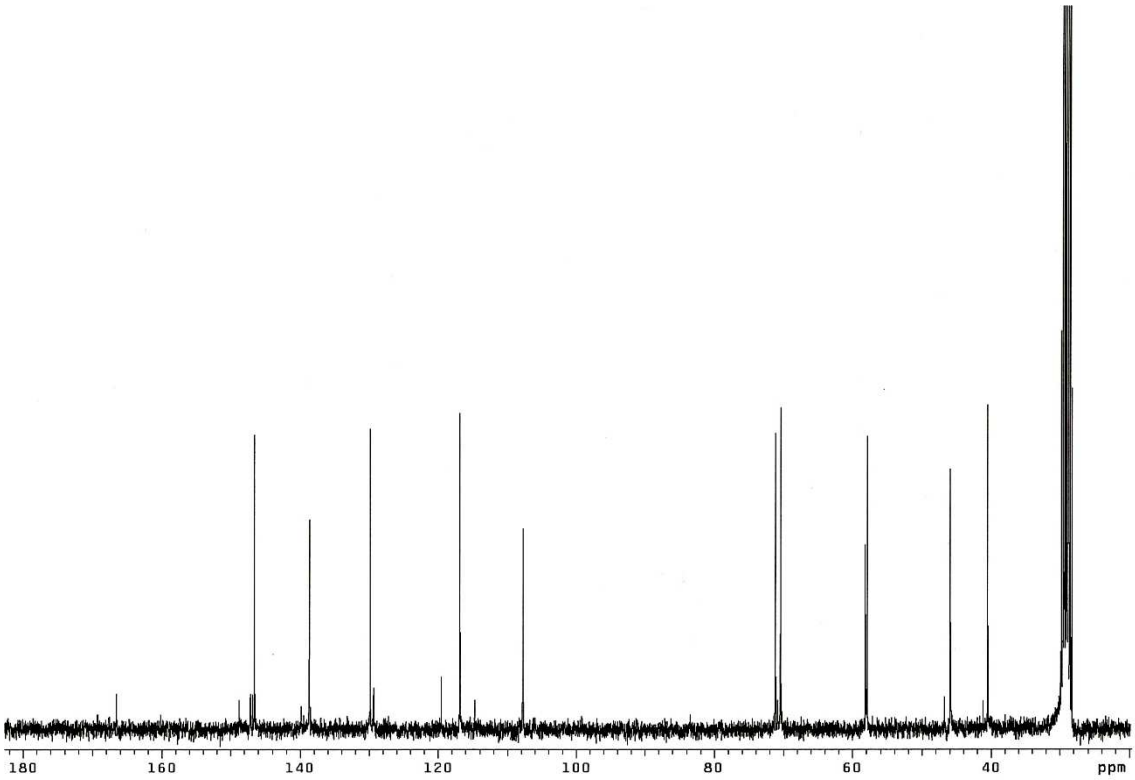

11
10
9
8
7
6
5
4
3
2
1
ppm

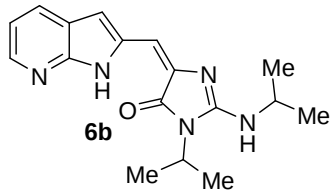

240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


H
N
OMe
O
N
N
H
N
N
OMe

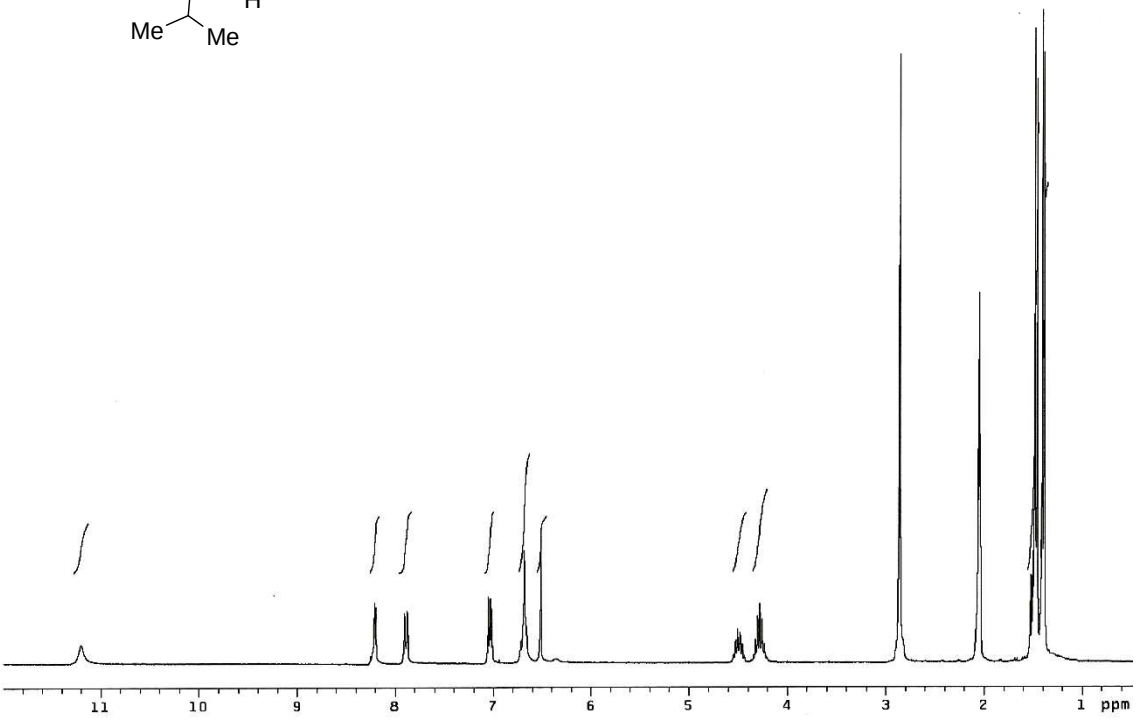
7a

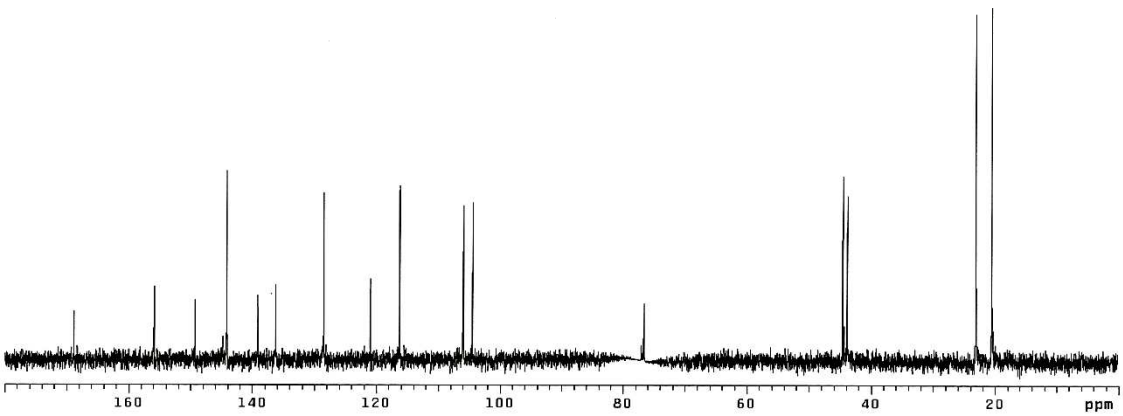
12
11
10
9
8
7
6
5
4
3
2
1
ppm

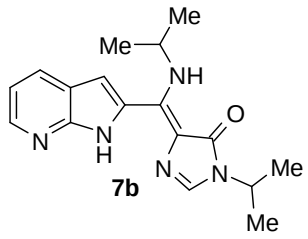

180
160
140
120
100
80
60
40
ppm



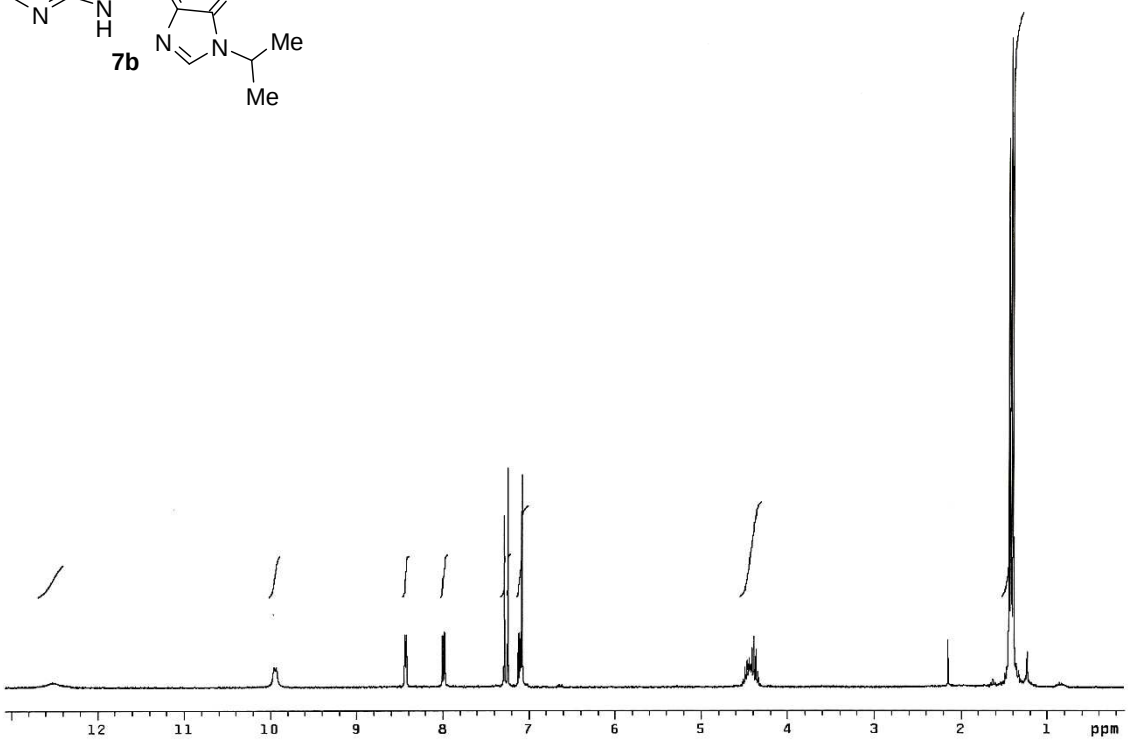
6b

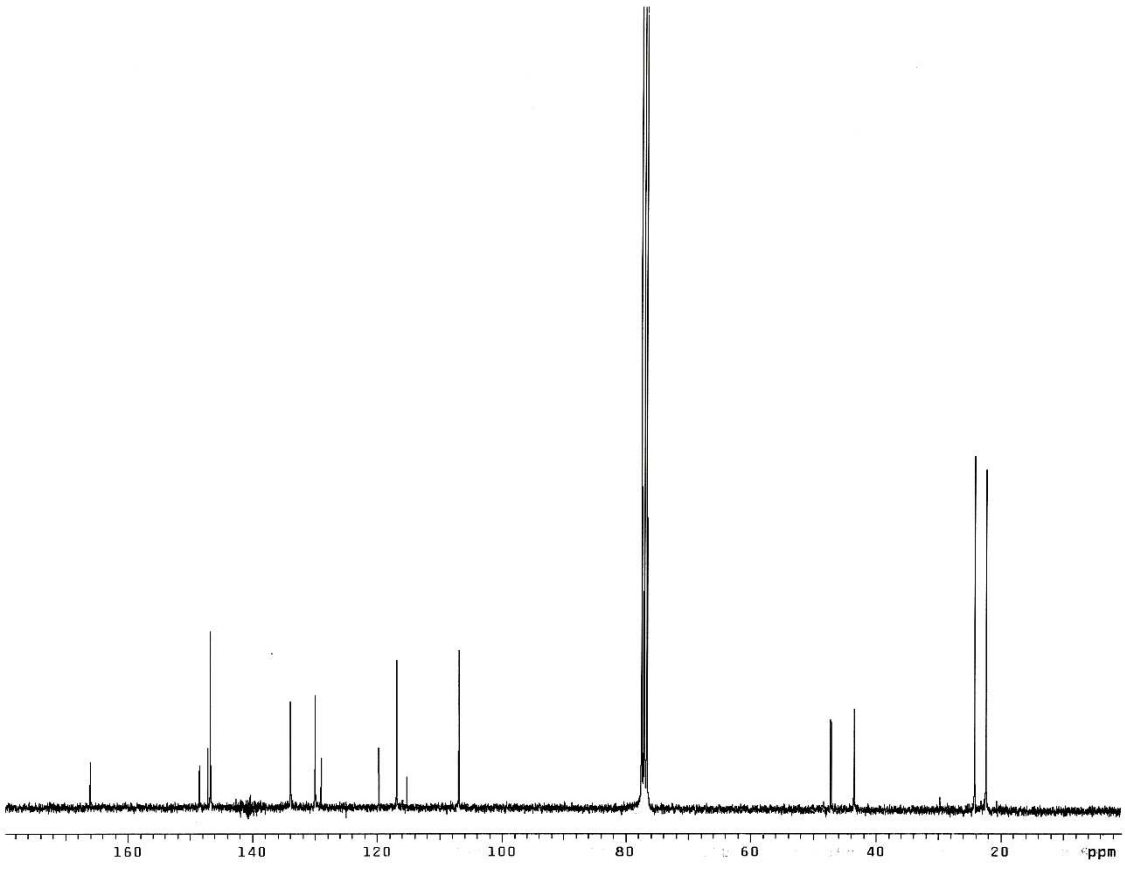


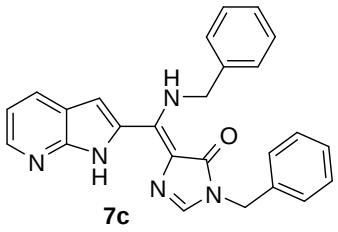



Me
Me
NH
O
N
N
H
N
N
Me
Me

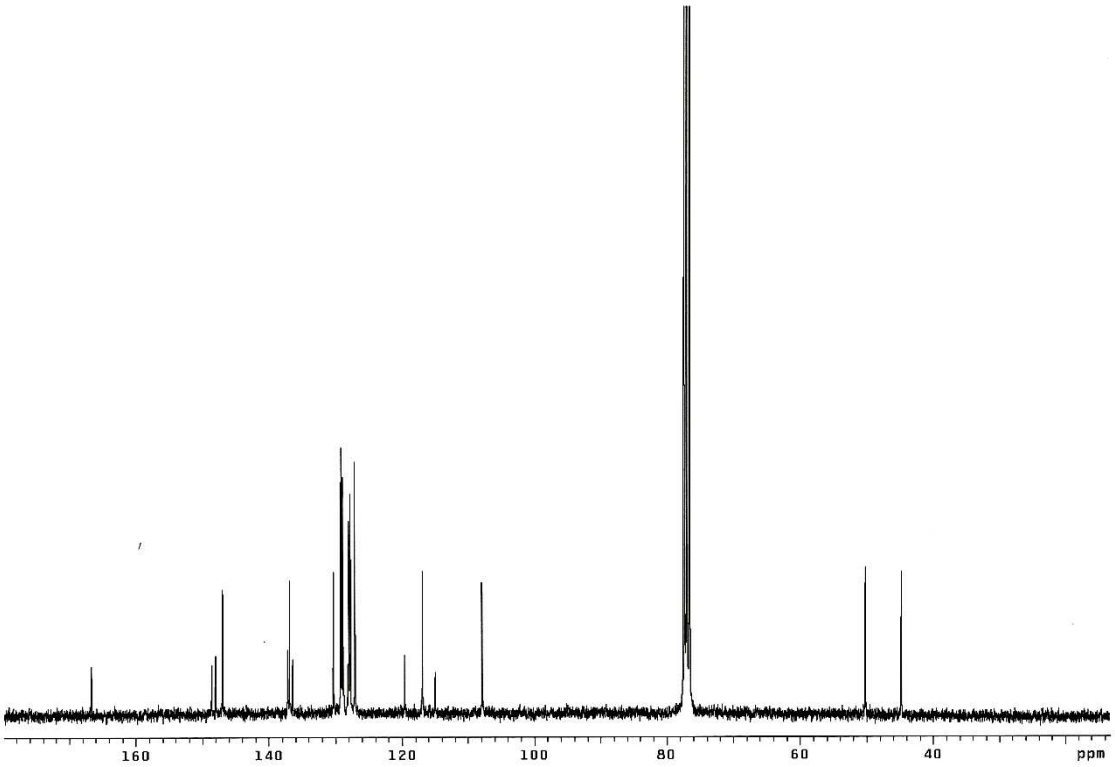
7b

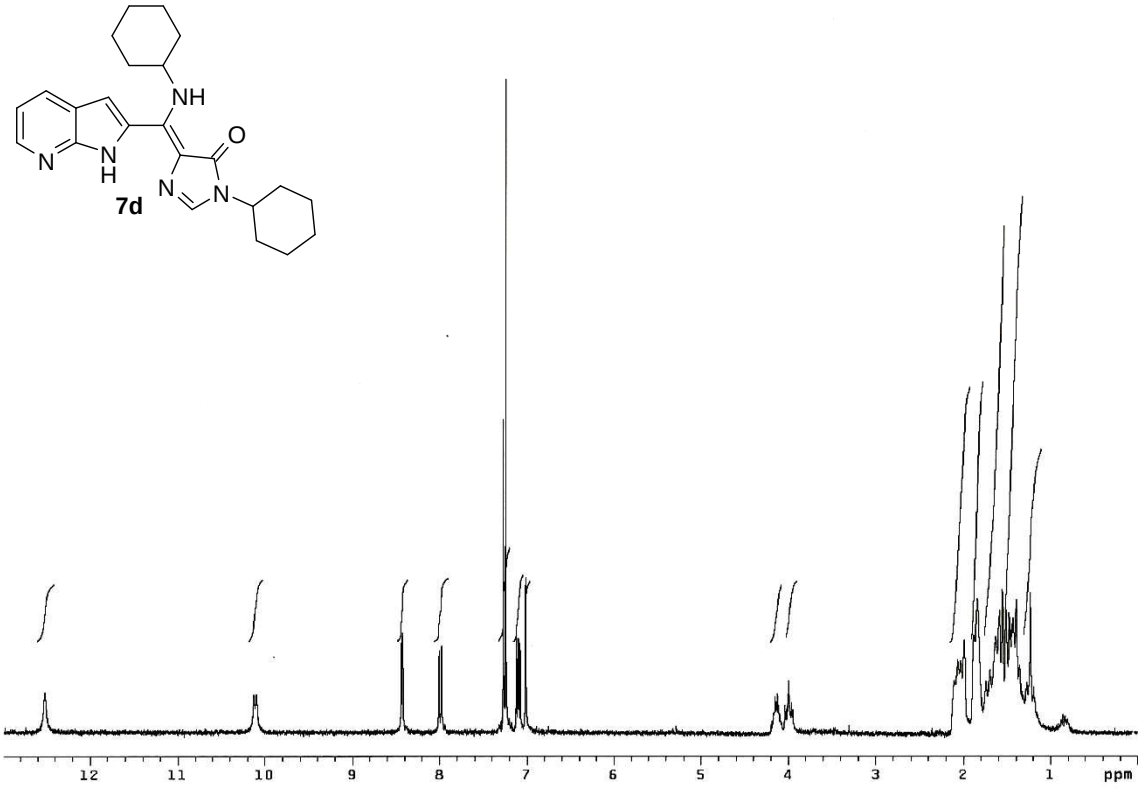

12
11
10
9
8
7
6
5
4
3
2
1
ppm


160
140
120
100
80
60
40
20
ppm

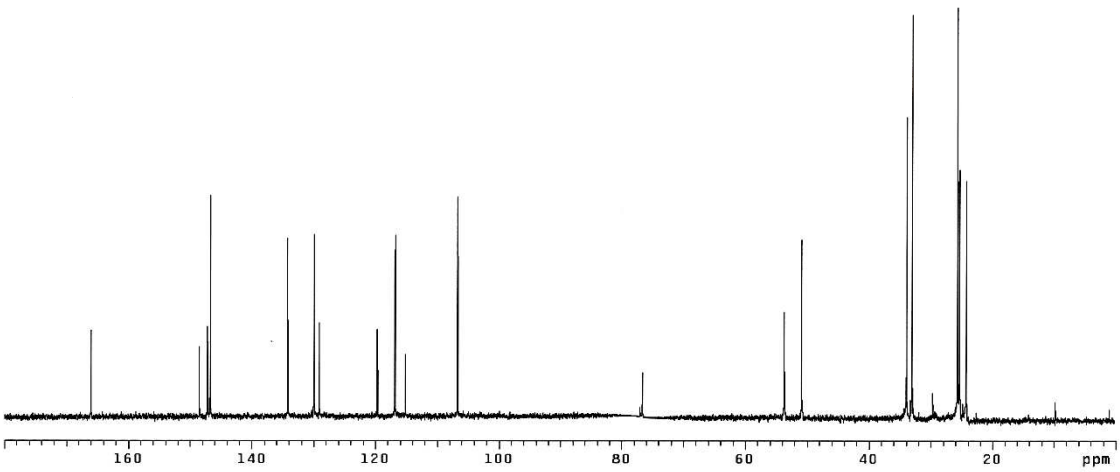


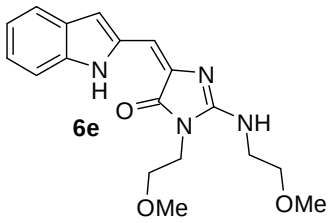
7c



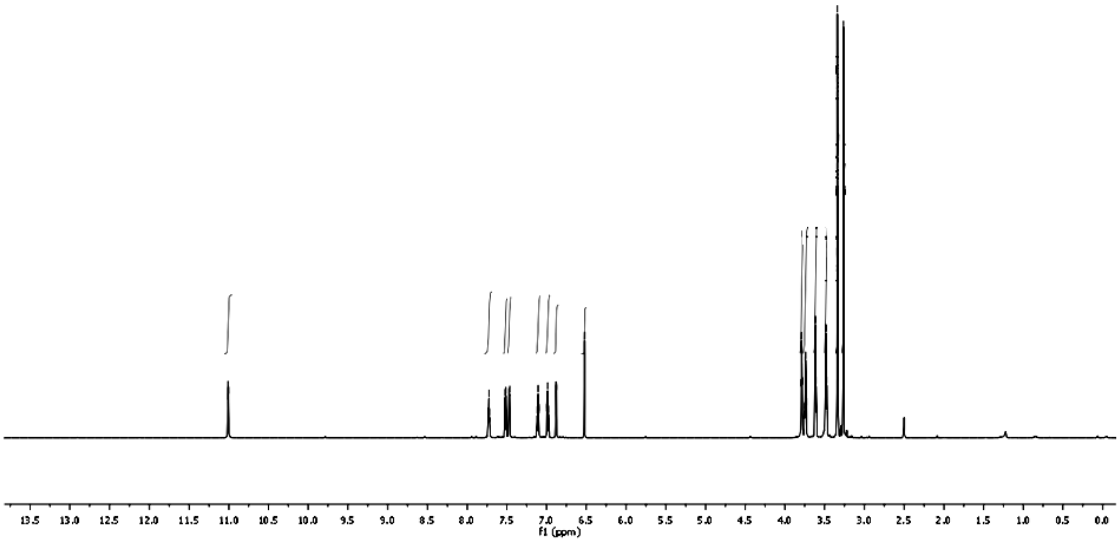


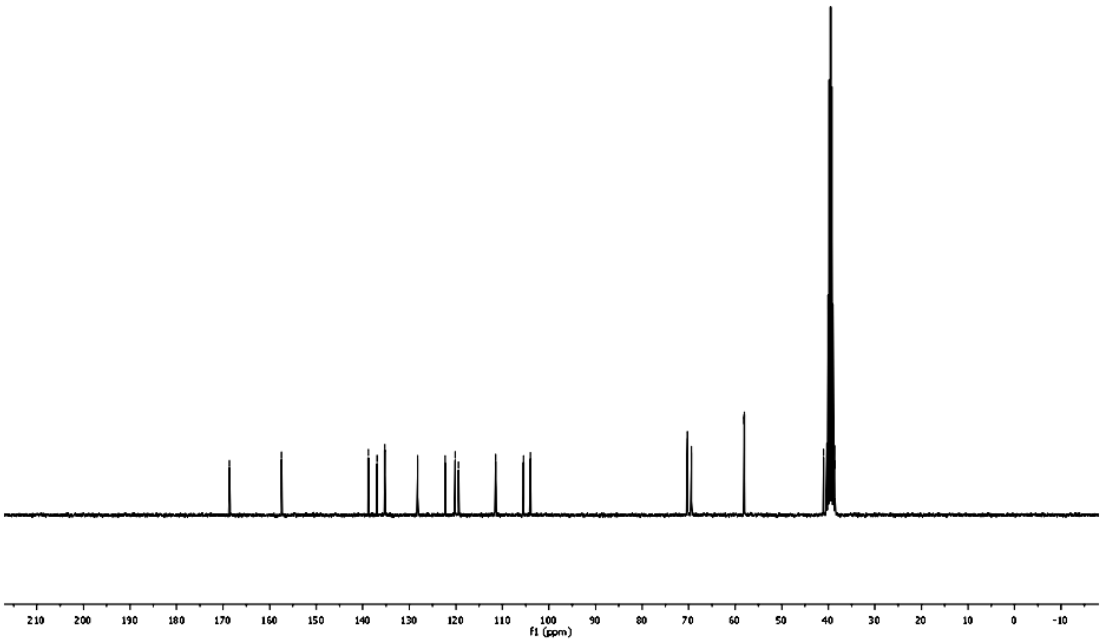
7d

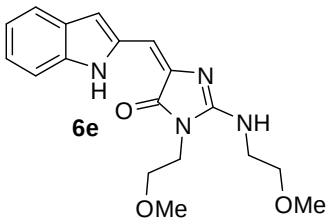



N
H
O
N
N
NH
OMe
OMe

6e

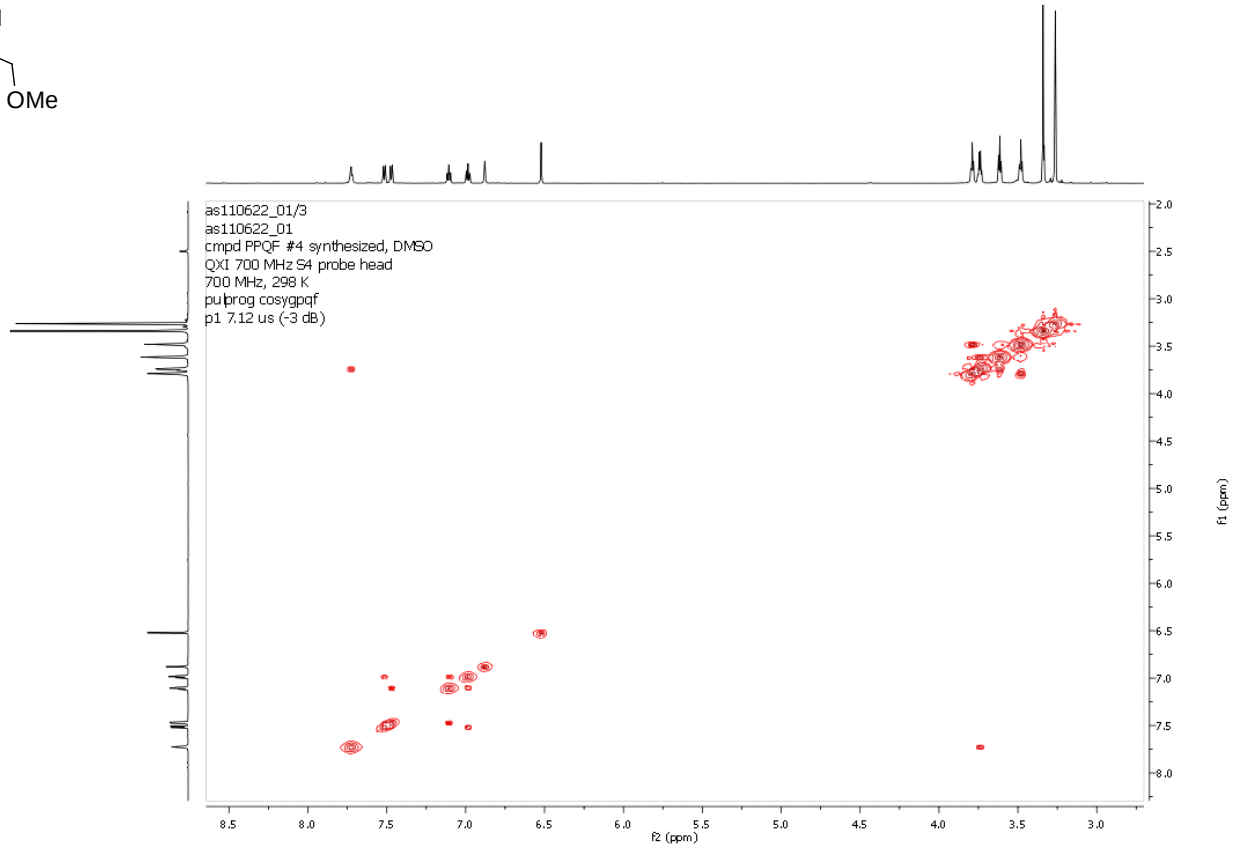

13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

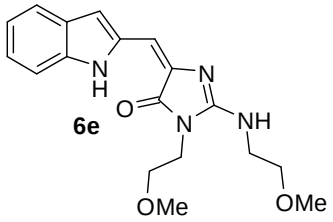

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



6e

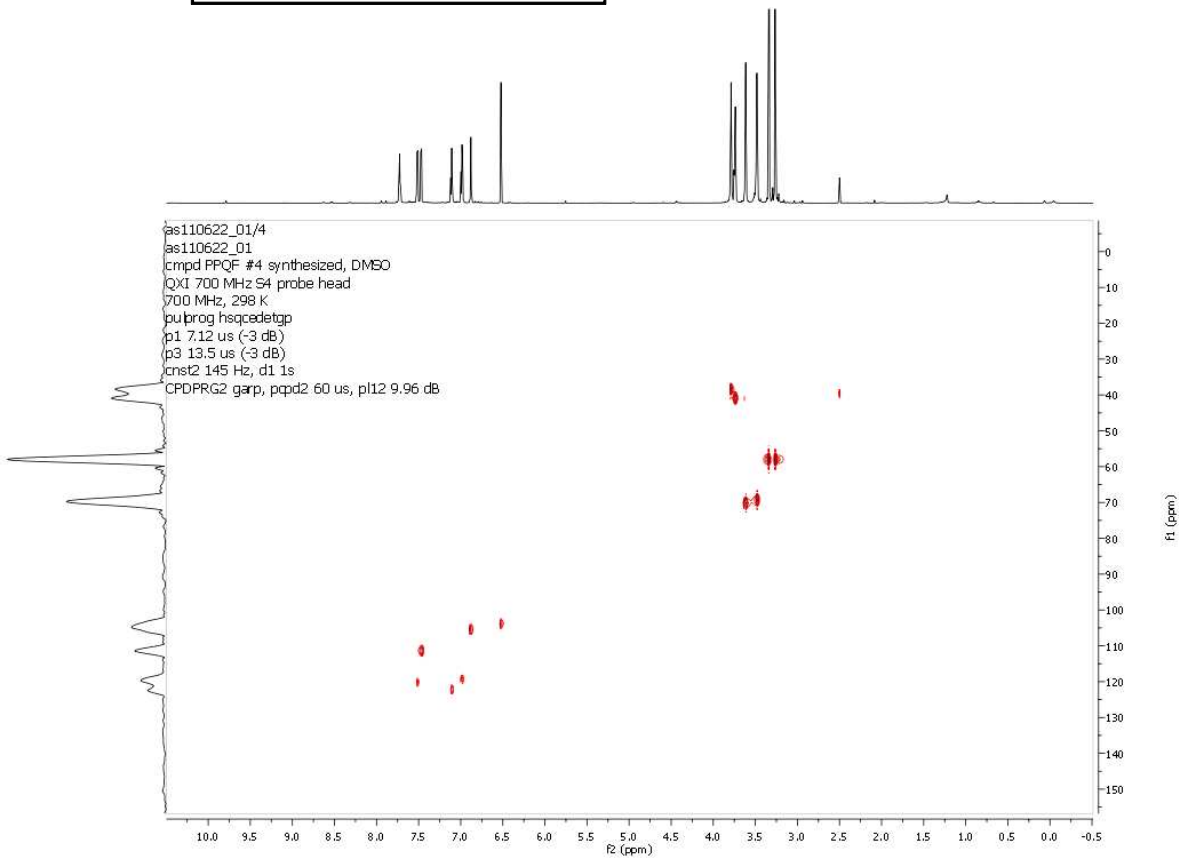
6e (COSY, DMSO-d_6, 700 MHz, 25°C)



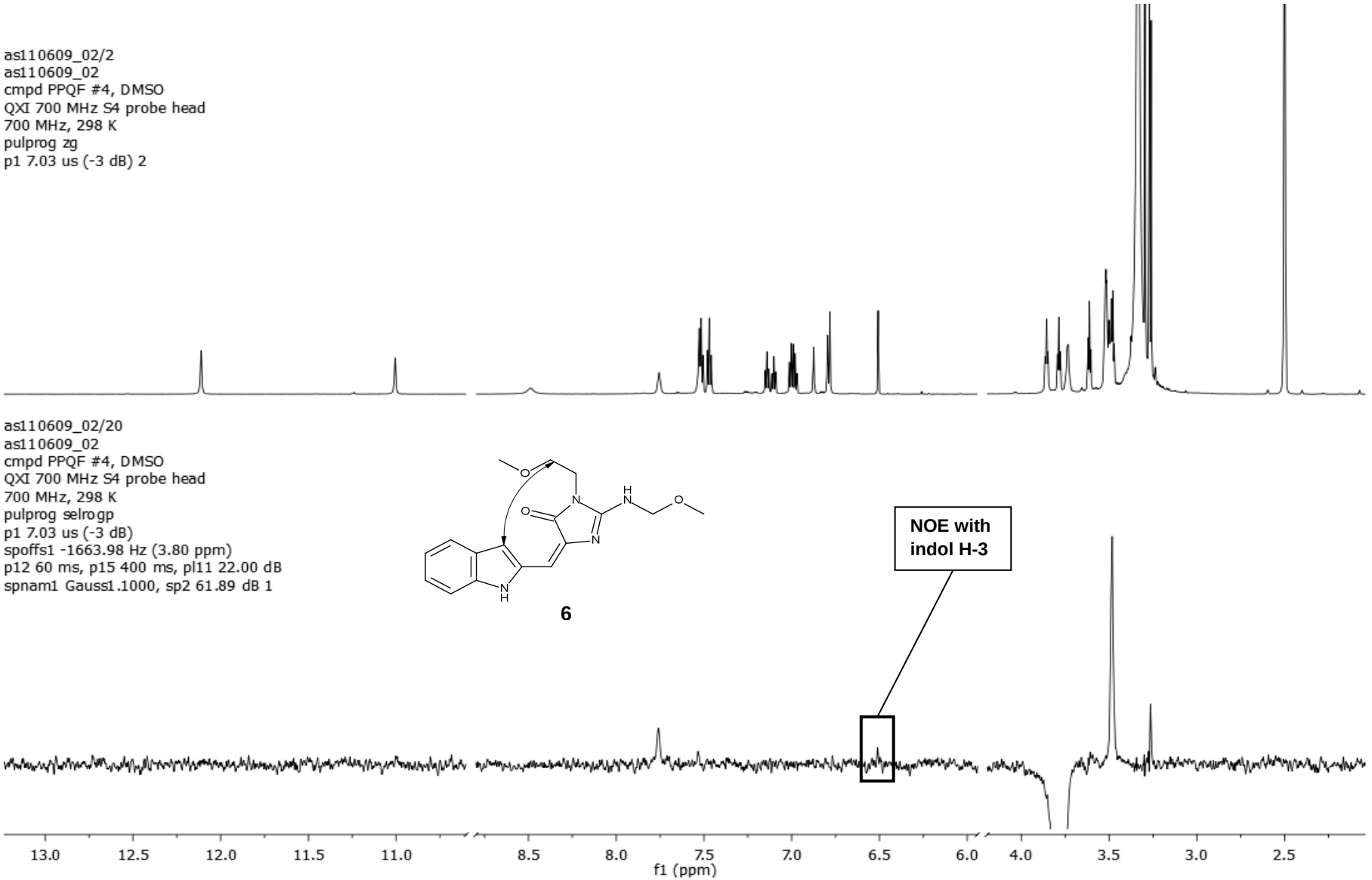


6e

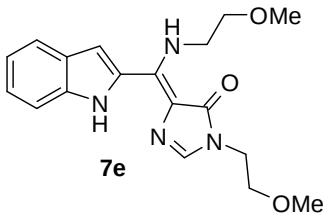
6e (HSQCED, DMSO-d_6, 700 MHz, 25ºC)



6e (1D NOESY, DMSO-d_6, 700 MHz,

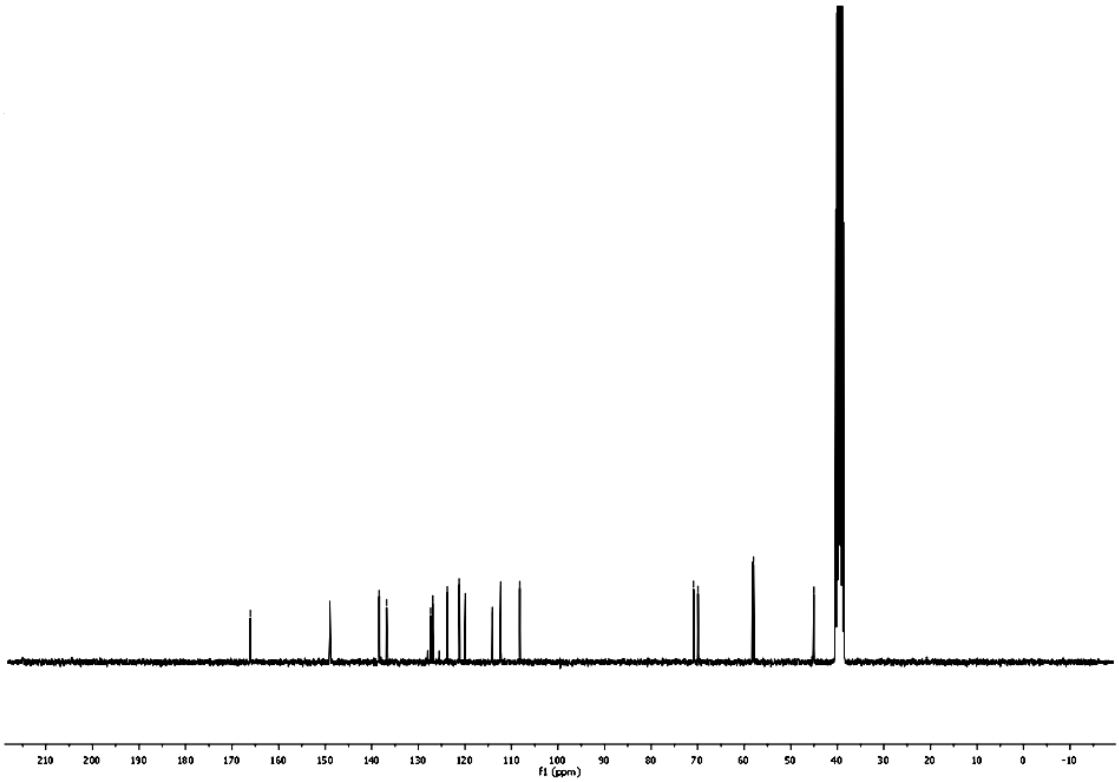


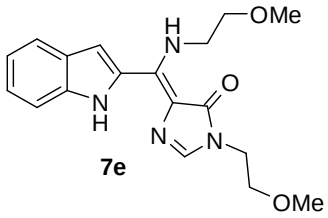
6


H
N
OMe
O
N
H
N
N
OMe

7e

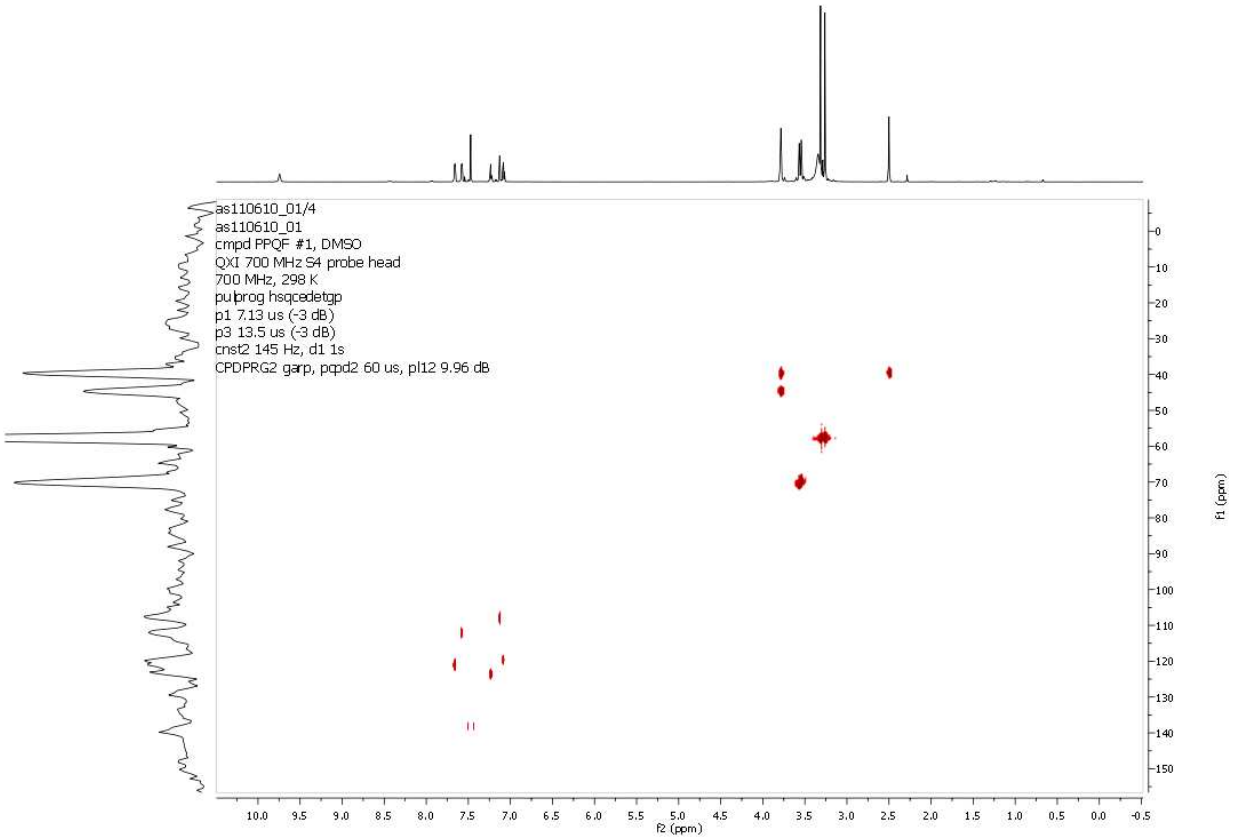
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

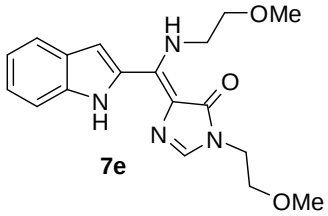

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



7e

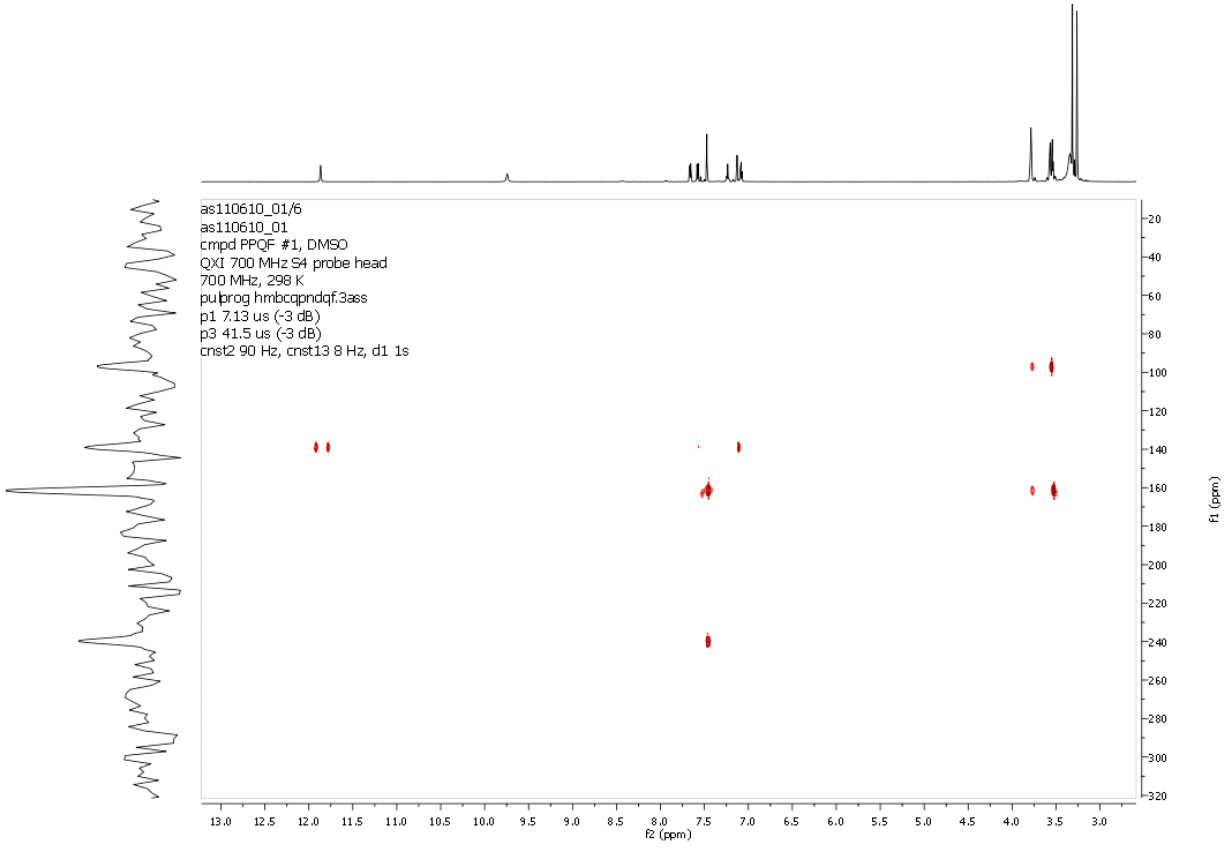
7e (HSQCED, DMSO-d_6, 700 MHz, 25ºC)

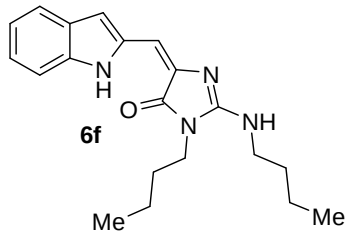




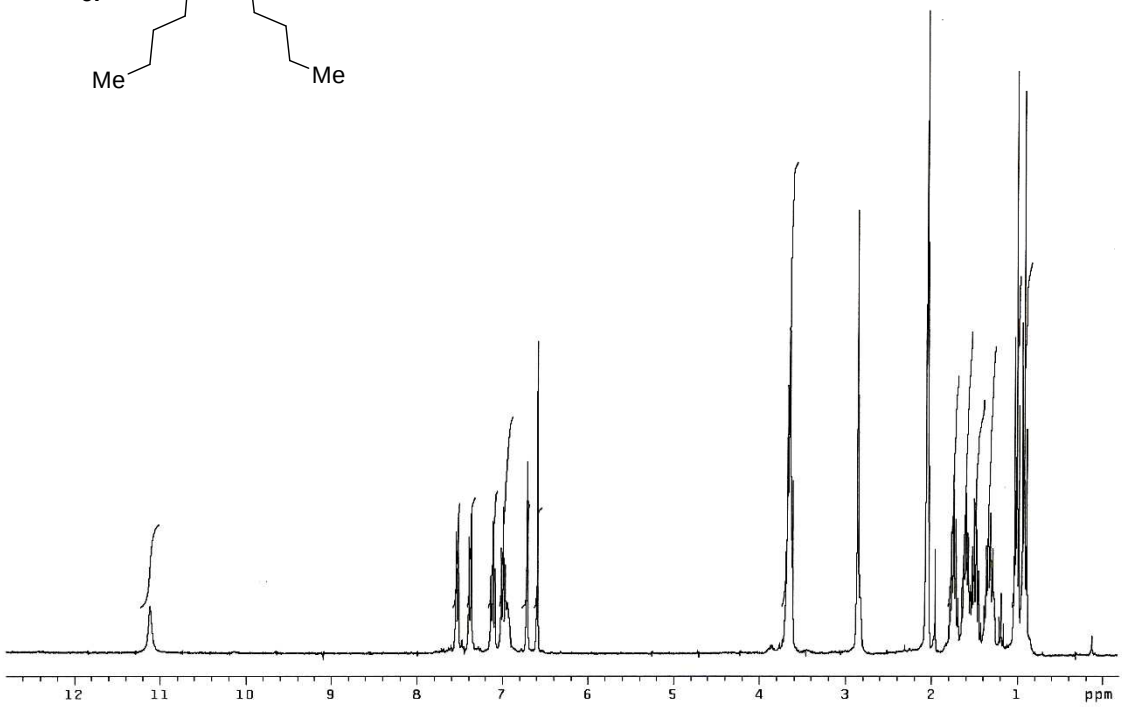
7e

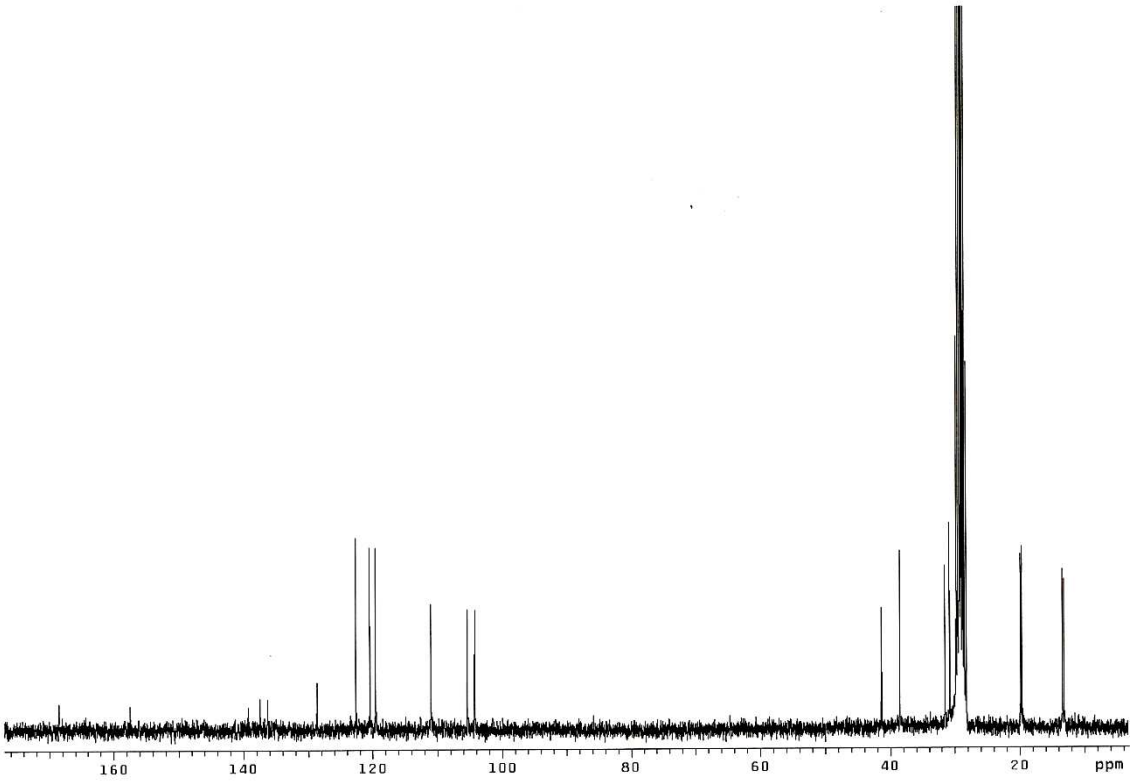
7e (^{1}H-^{15}N HMBC, DMSO-d_6, 700 MHz, 25°C)

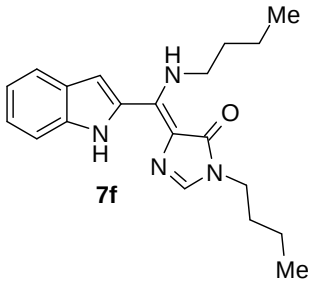



N
H
O
N
N
NH
Me
Me

6f

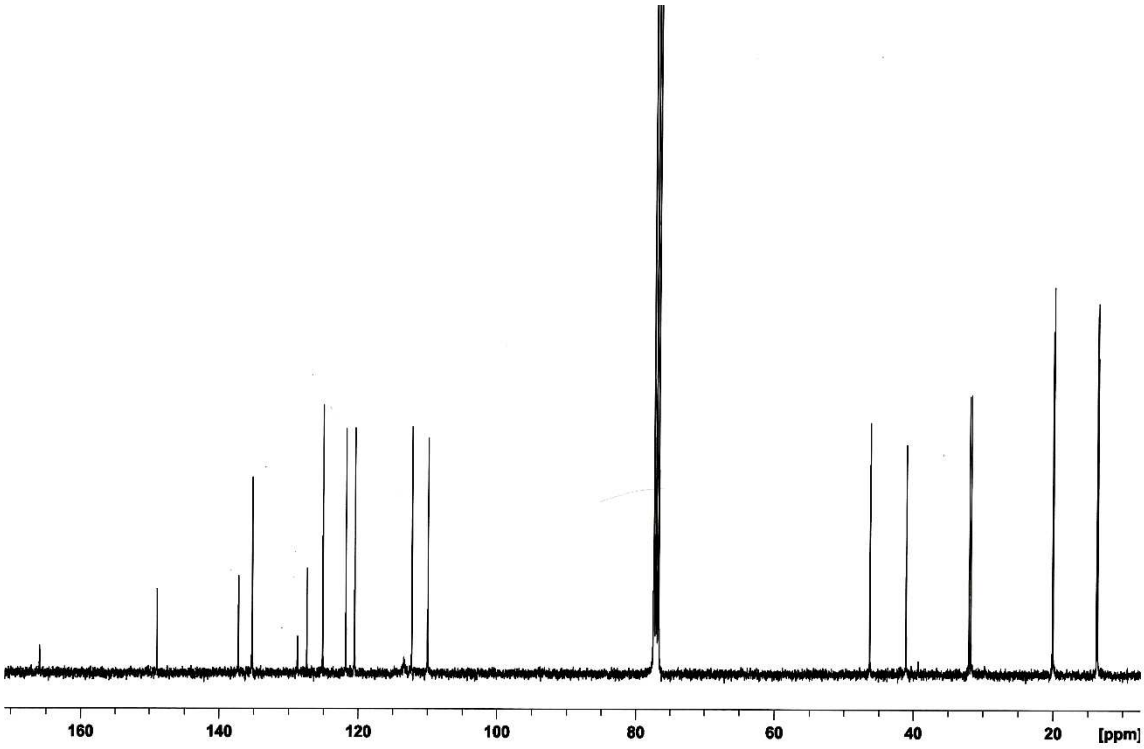

12
11
10
9
8
7
6
5
4
3
2
1
ppm

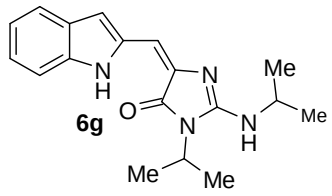

160
140
120
100
80
60
40
20
ppm


Me
H
N
O
N
H
N
N
Me

7f

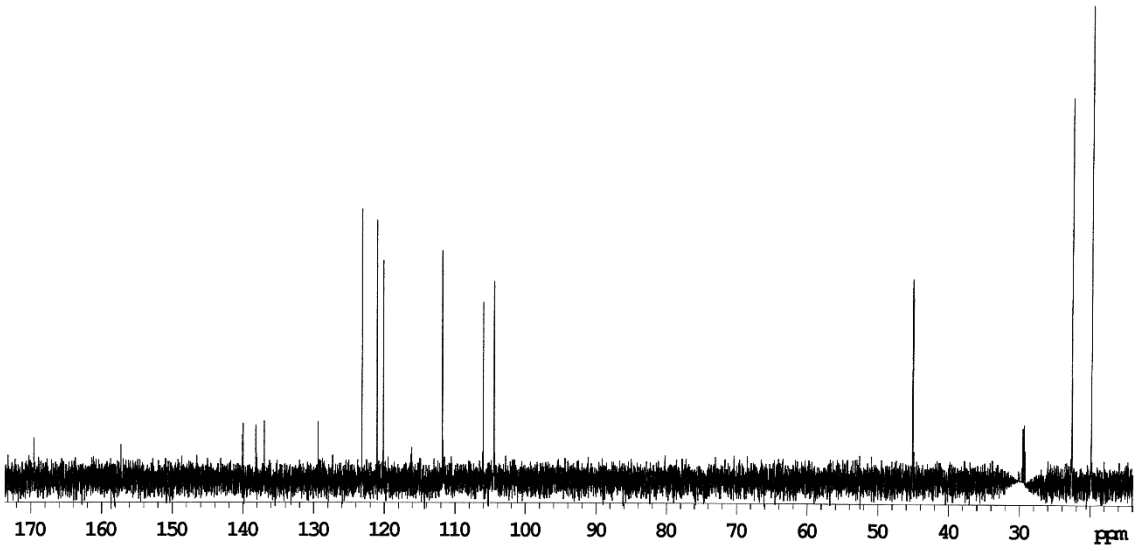
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm

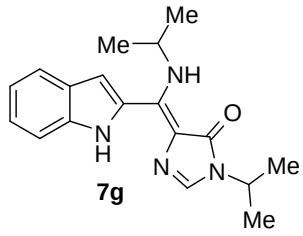

160
140
120
100
80
60
40
20
[ppm]


N
H
O
N
N
H
Me
Me
Me
Me

6g

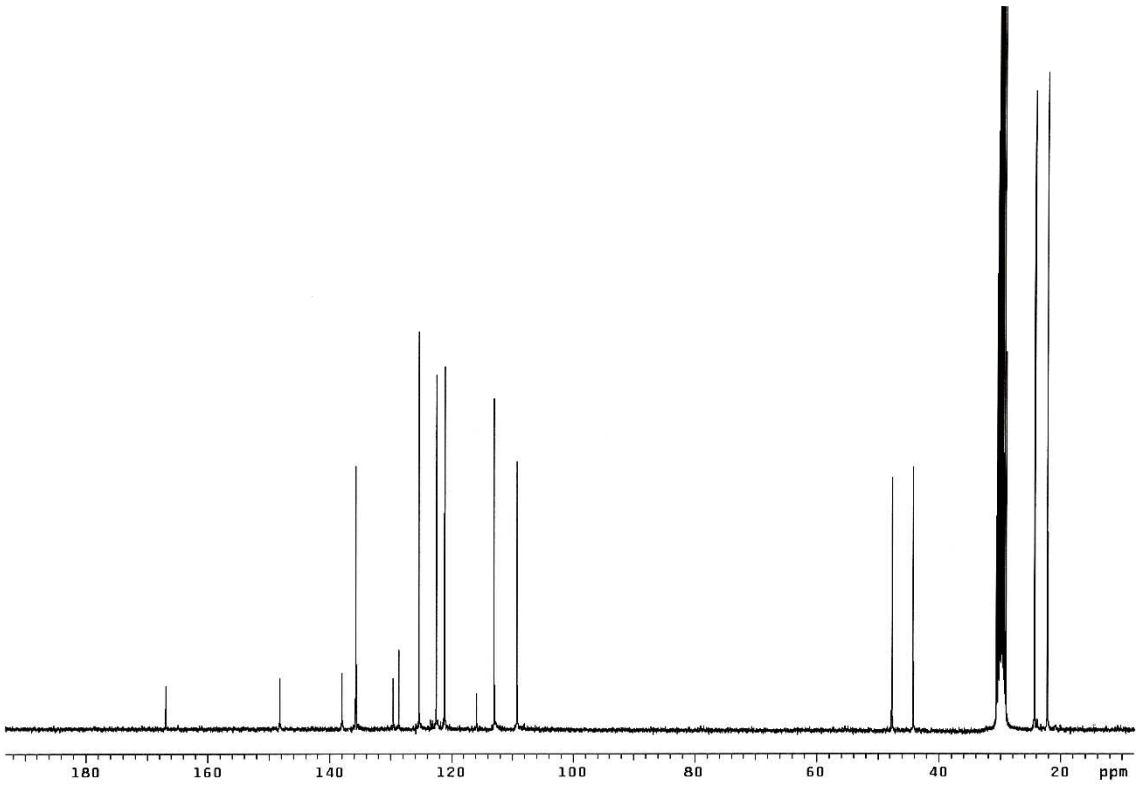
11
10
9
8
7
6
5
4
3
2
1
ppm

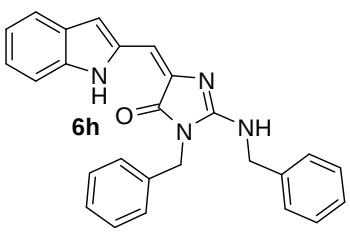

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm


Me
Me
NH
O
N
H
N
N
Me
Me

7g

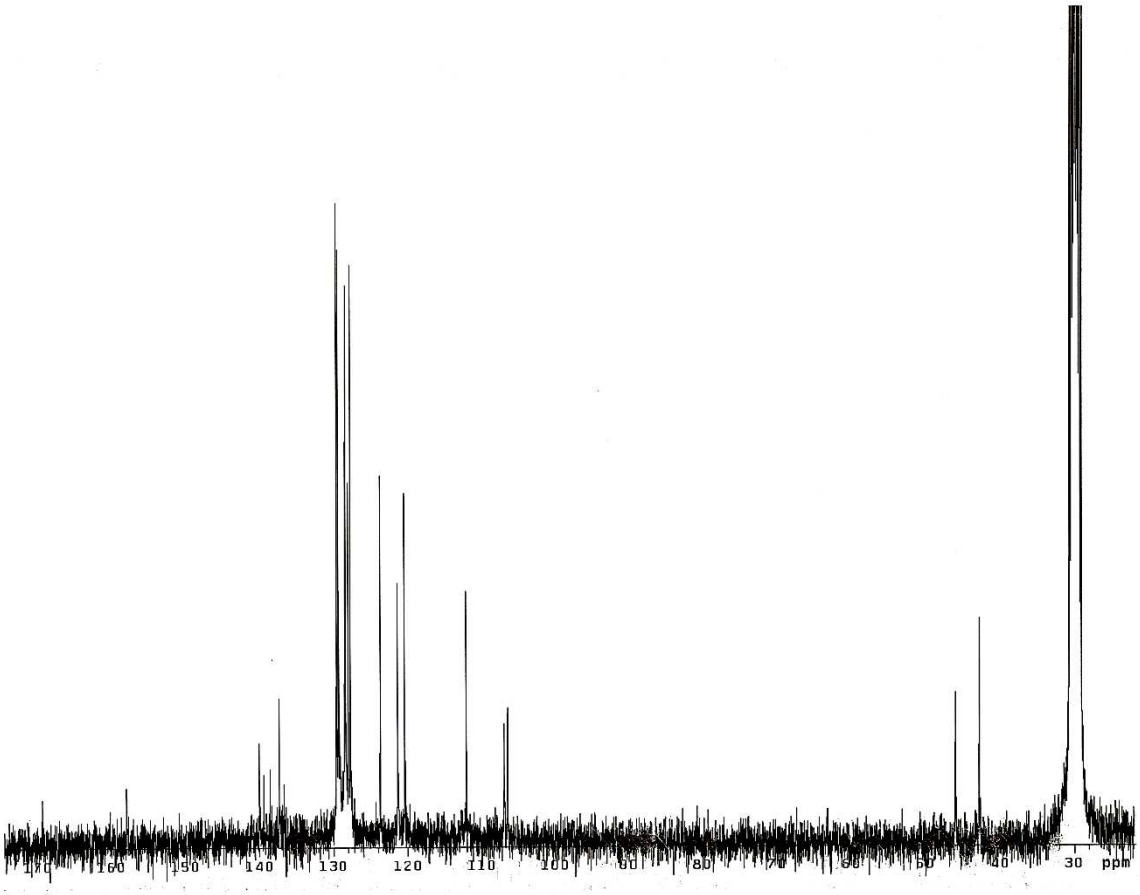
12
11
10
9
8
7
6
5
4
3
2
1
ppm

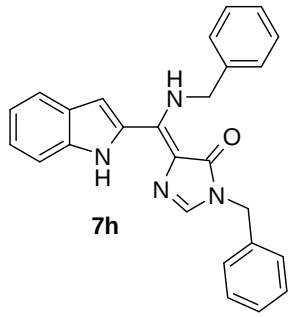

180
160
140
120
100
80
60
40
20
ppm


N
H
O
N
N
NH

6h

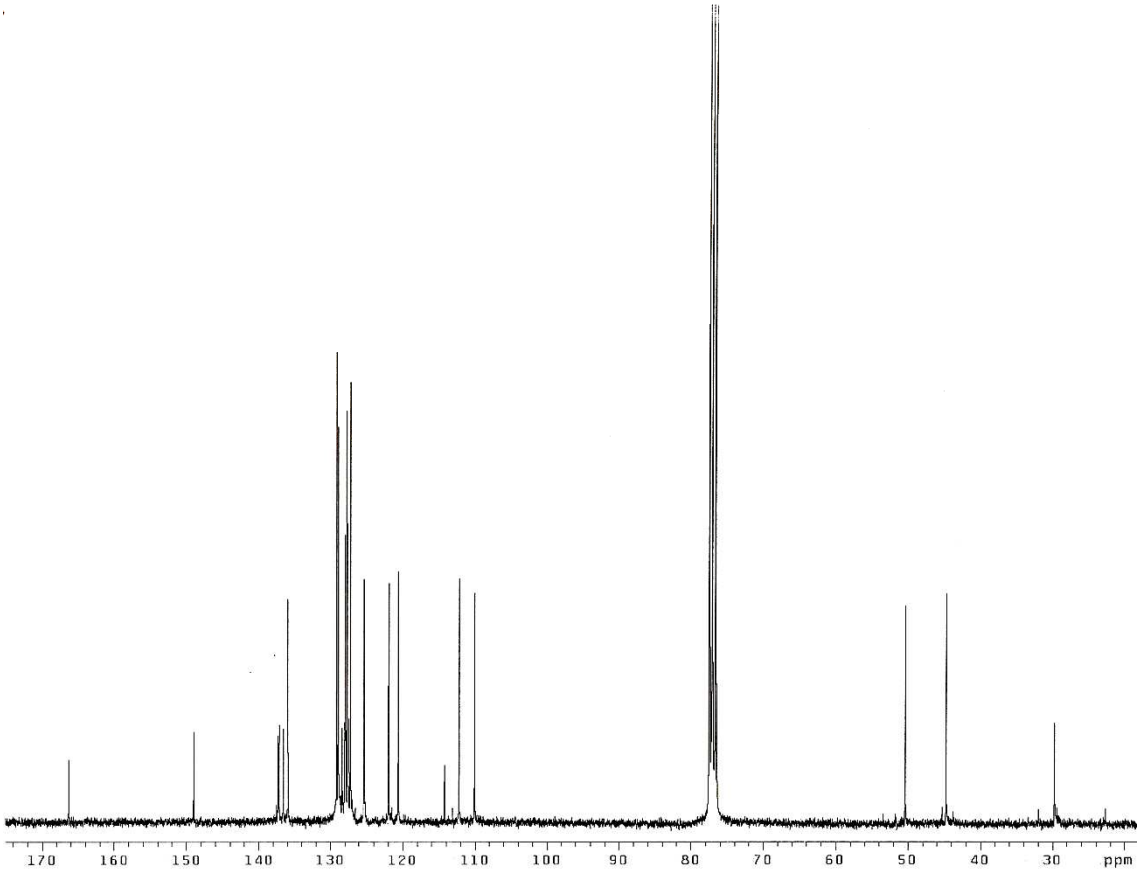
12
11
10
9
8
7
6
5
4
3
2
1
ppm

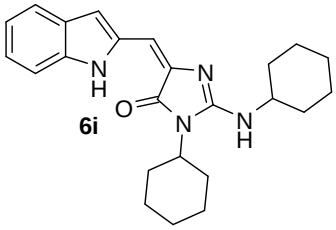

160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm


H
N
O
N
H
N
N

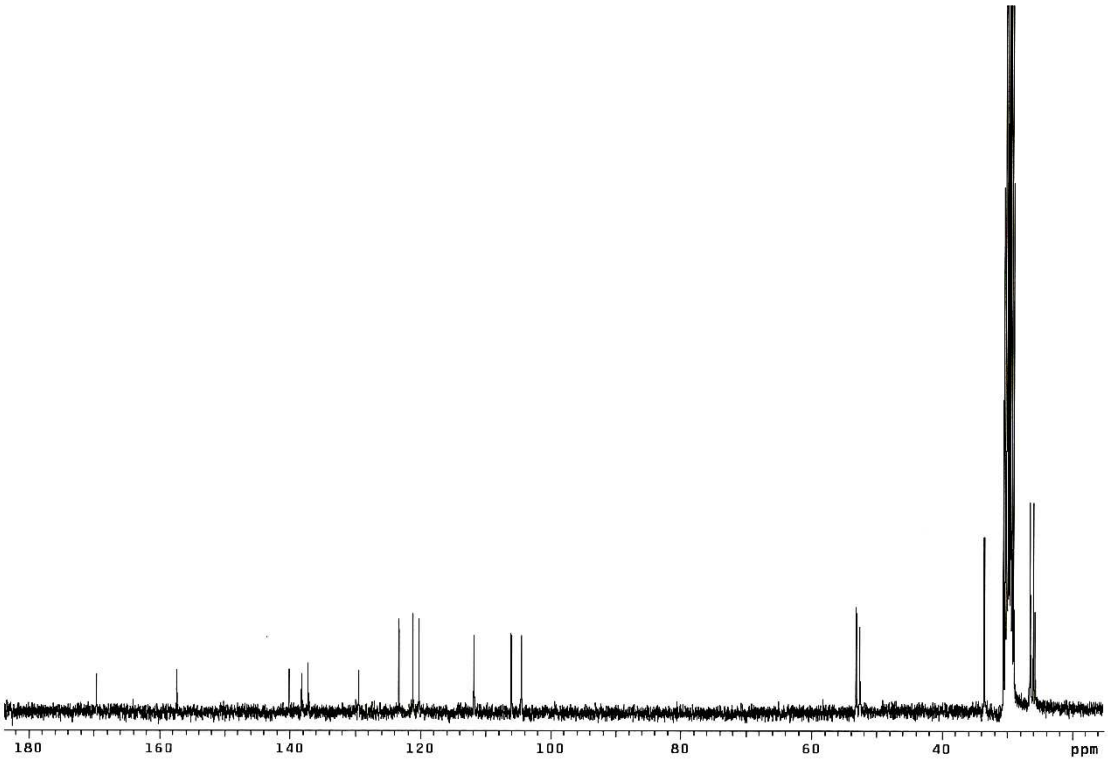
7h

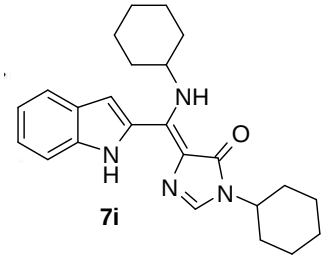
12
11
10
9
8
7
6
5
4
3
2
1
ppm


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

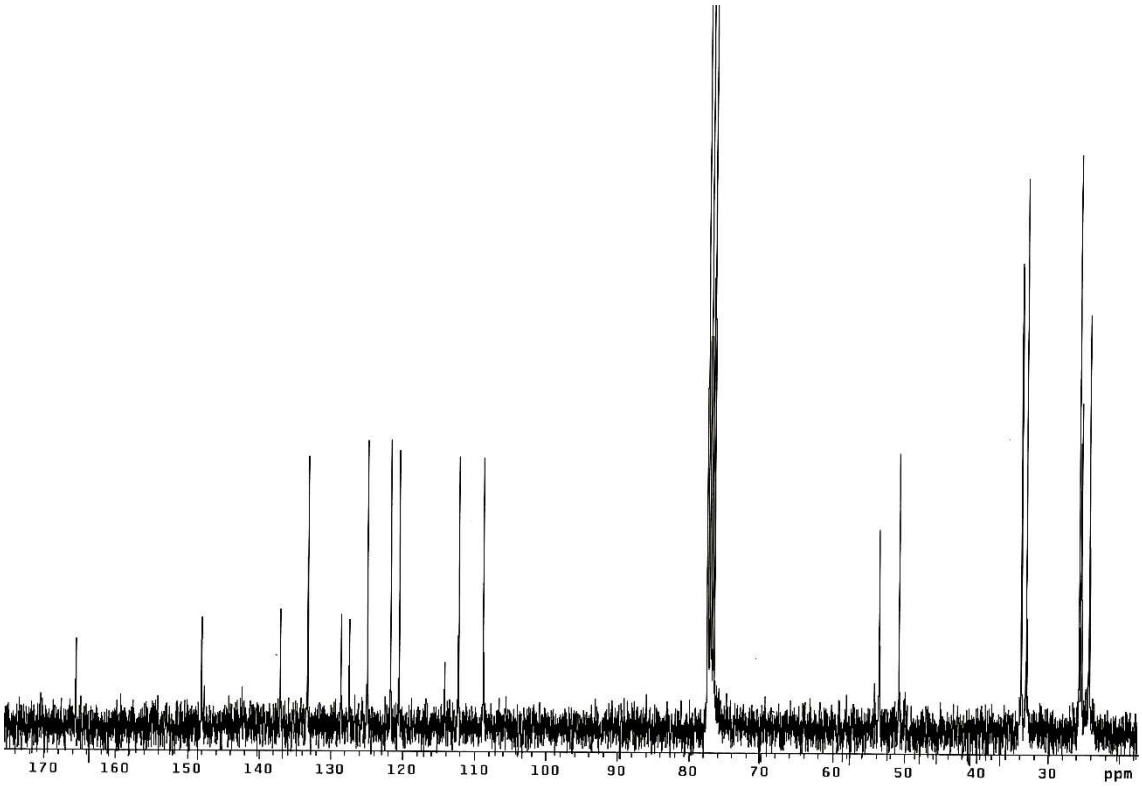


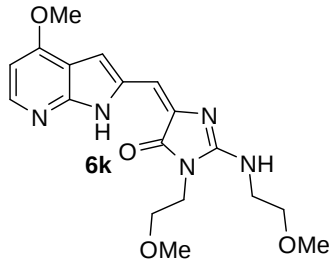
6i





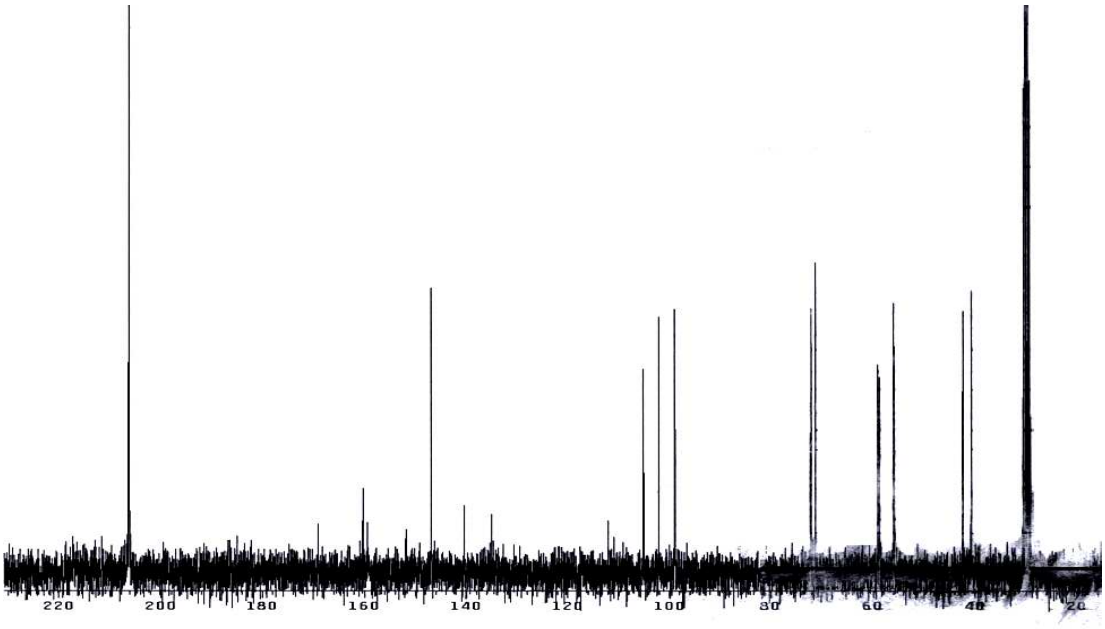
7i

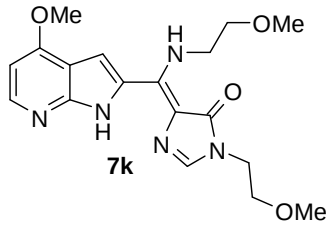



OMe
N
N
H
O
N
N
NH
OMe
OMe

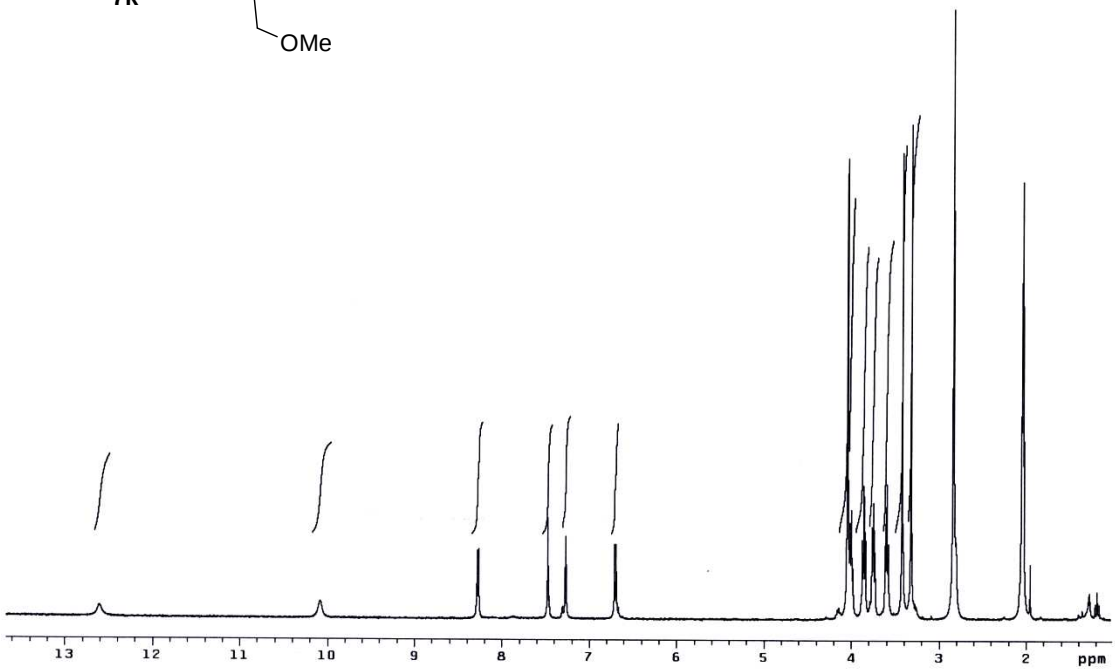
6k

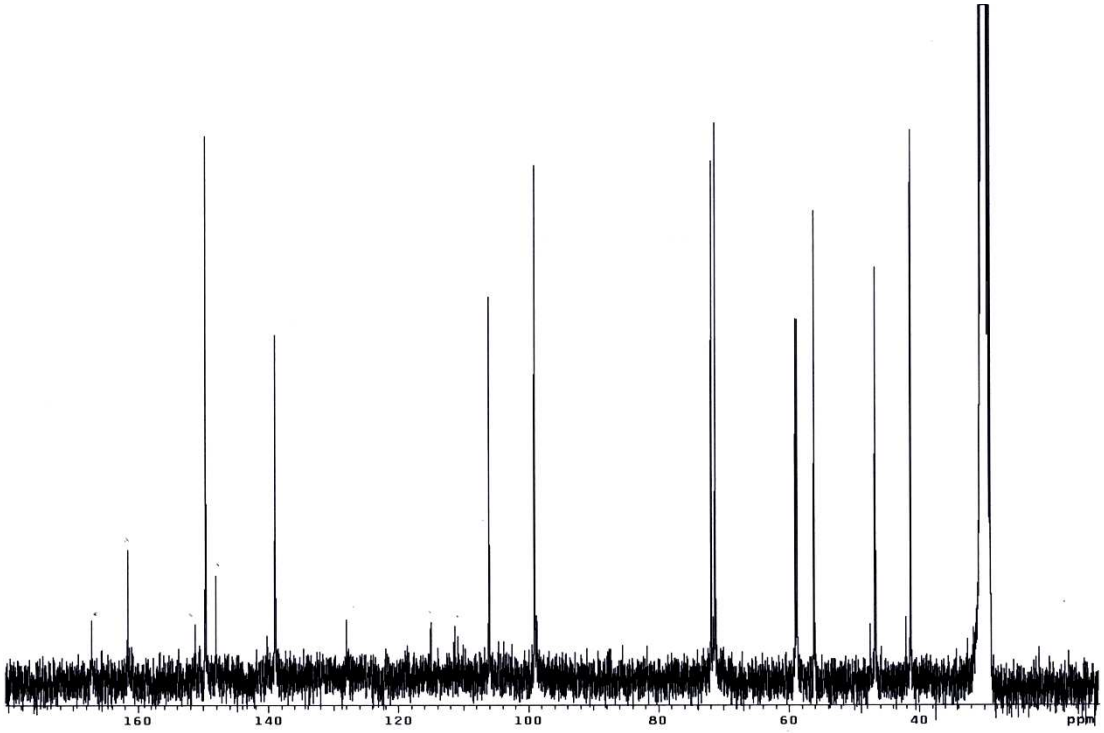
11
10
9
8
7
6
5
4
3
2
1
ppm
3.15
4.08
3.62
7.94
3.99

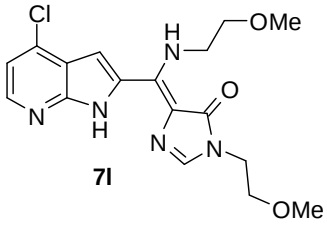

220
200
180
160
140
120
100
80
60
40
20


OMe
H
N
OMe
O
N
N
H
N
N
OMe

7k

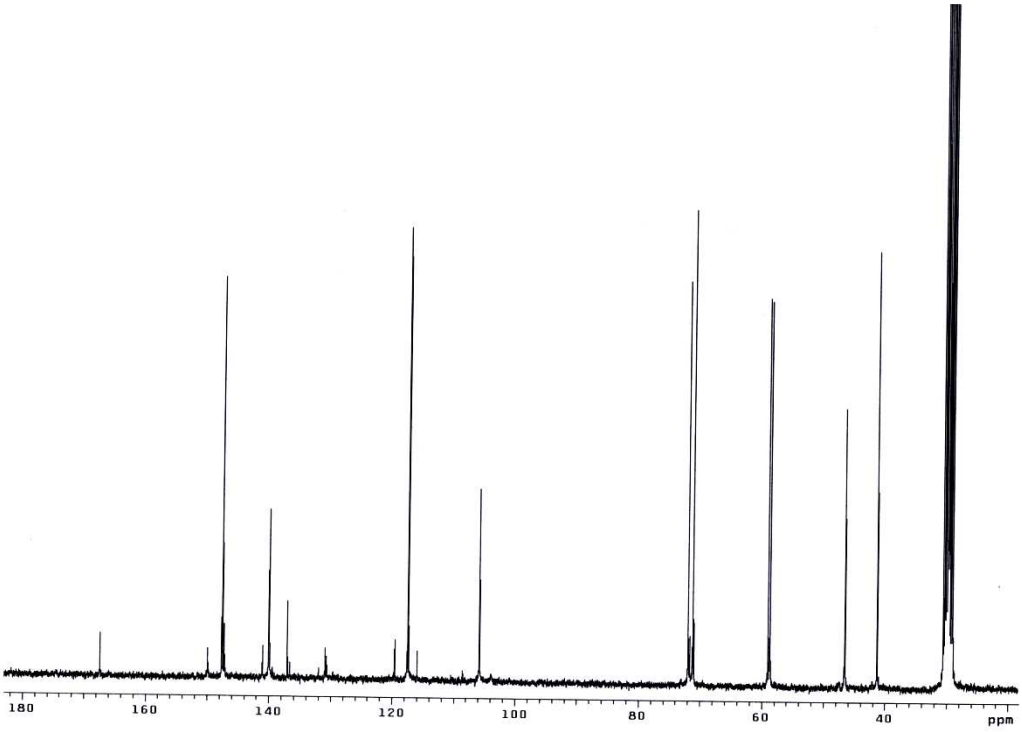

13
12
11
10
9
8
7
6
5
4
3
2
ppm

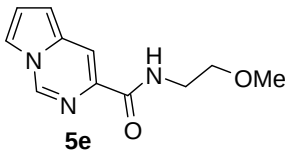

160
140
120
100
80
60
40
ppm


Cl
H
N
OMe
O
N
N
H
N
N
OMe

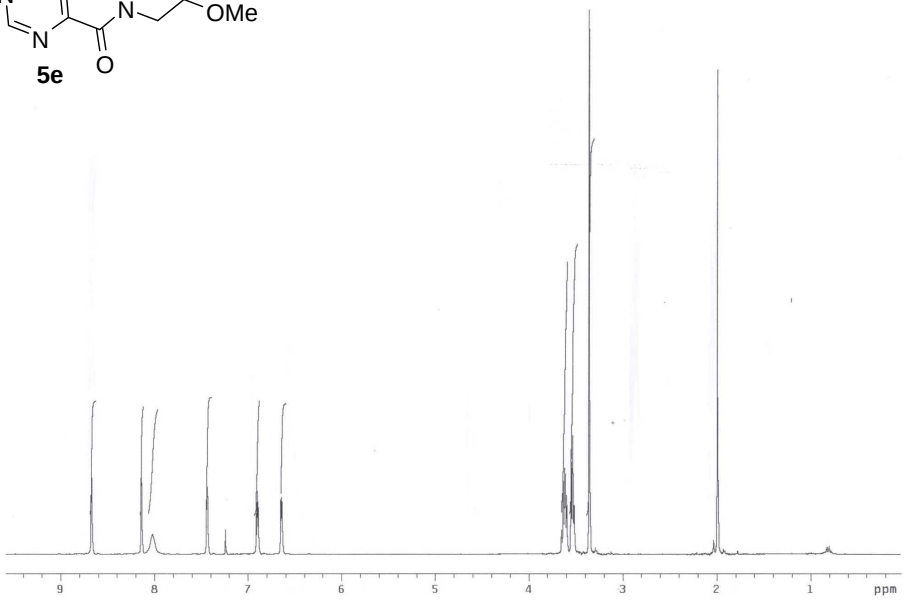
7l

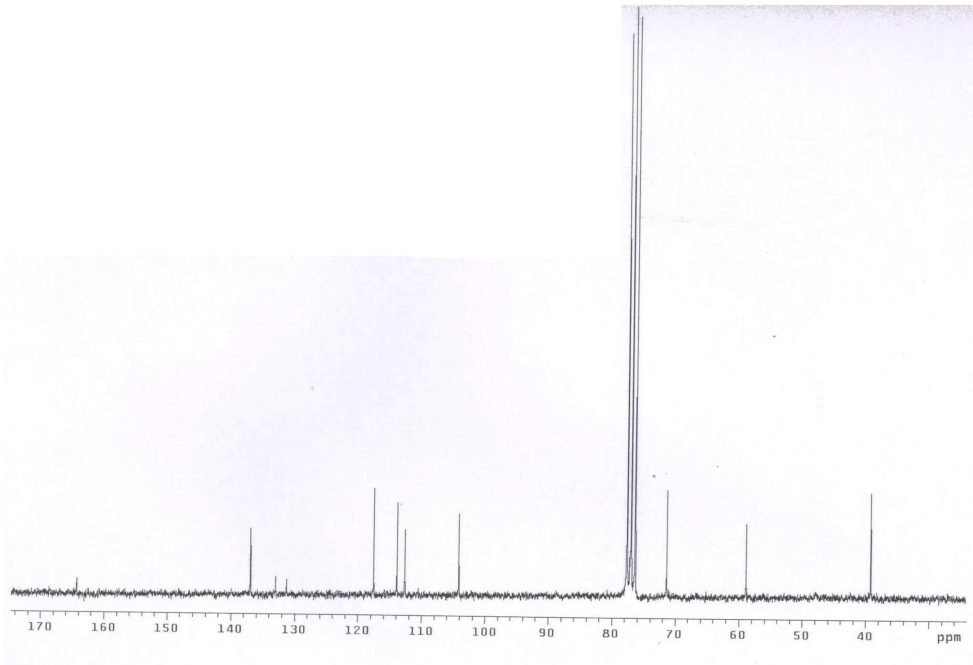
13
12
11
10
9
8
7
6
5
4
3
2
1

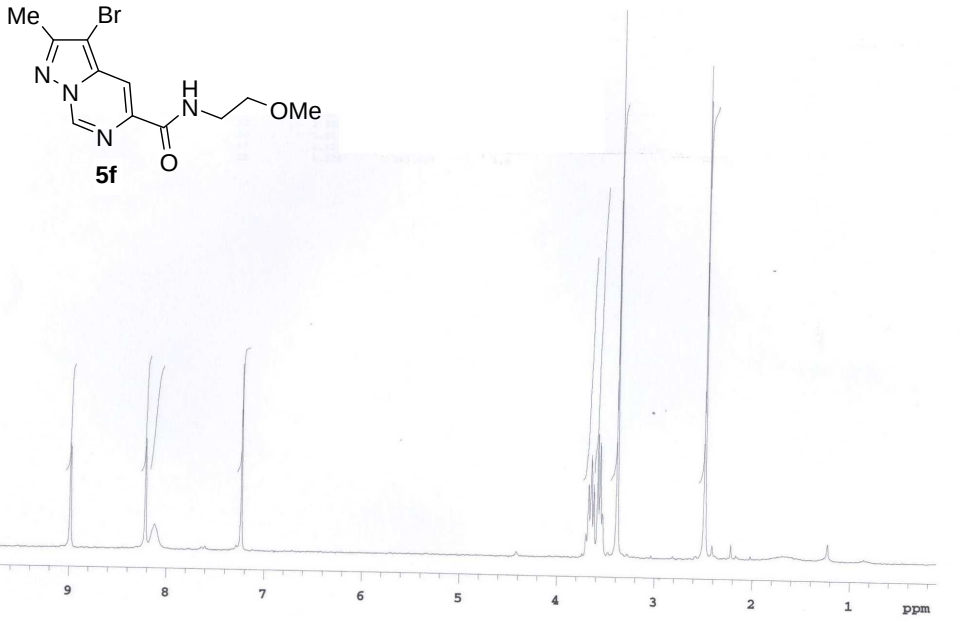

180
160
140
120
100
80
60
40
ppm


N
N
H
N
OMe
O

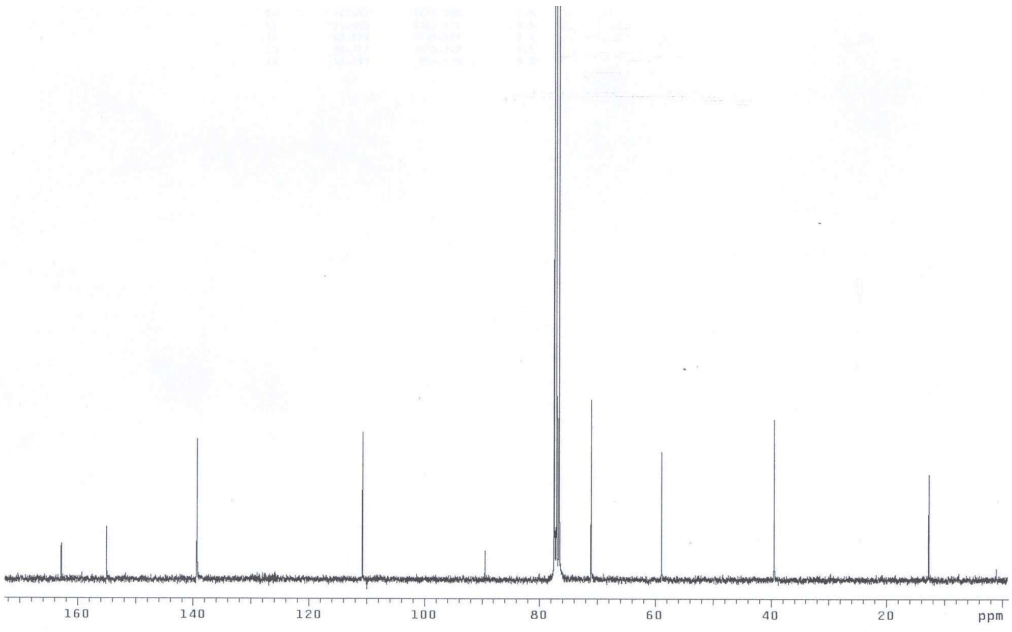
5e

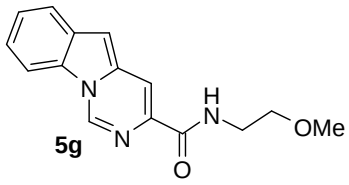

9
8
7
6
5
4
3
2
1
ppm


170
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm

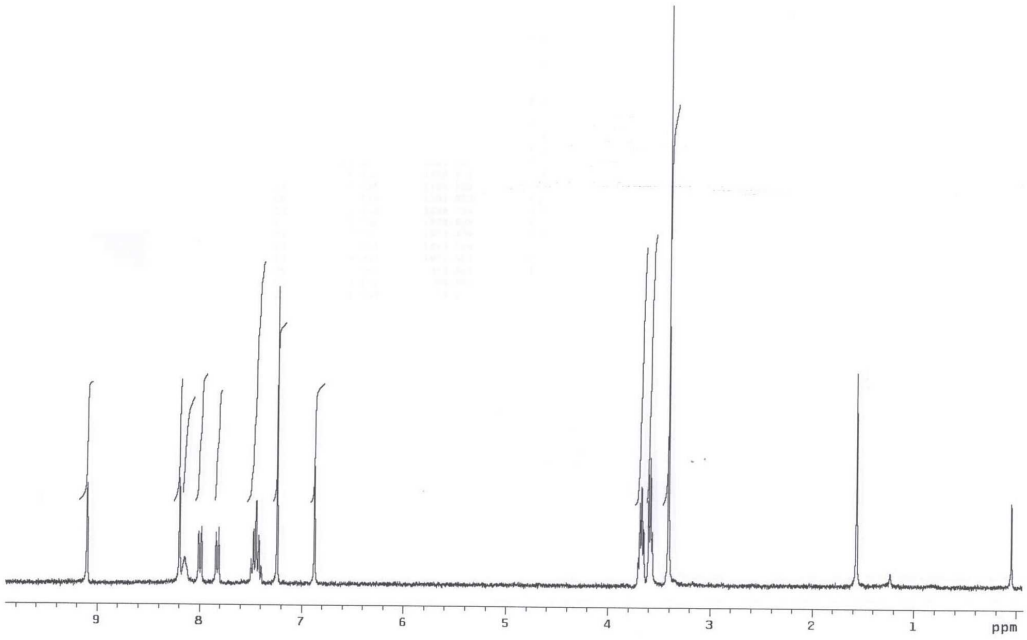


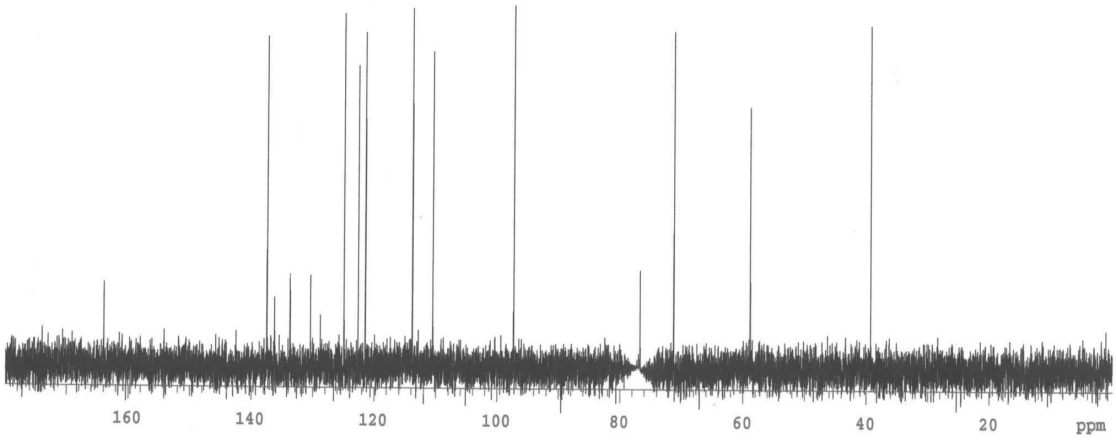
5f

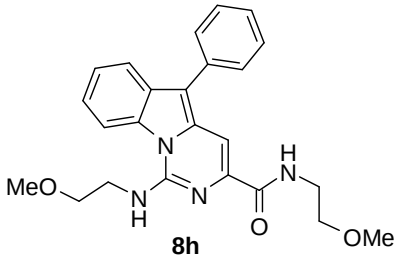




5g

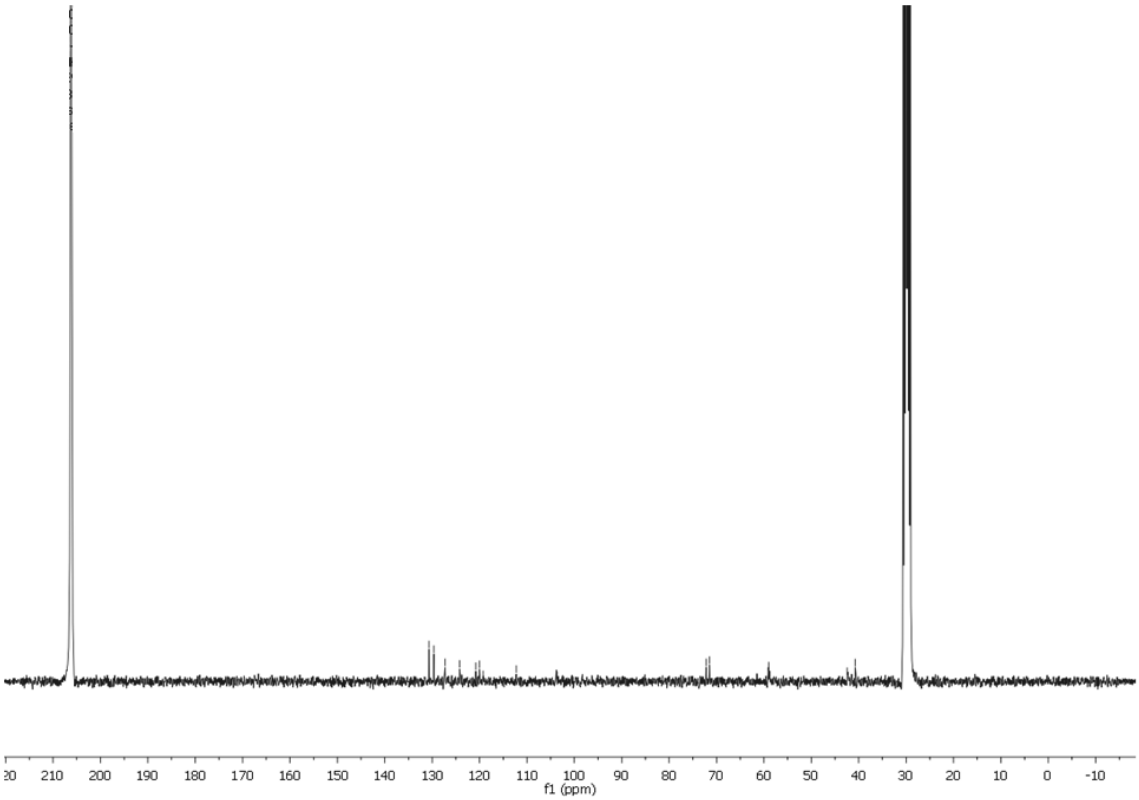


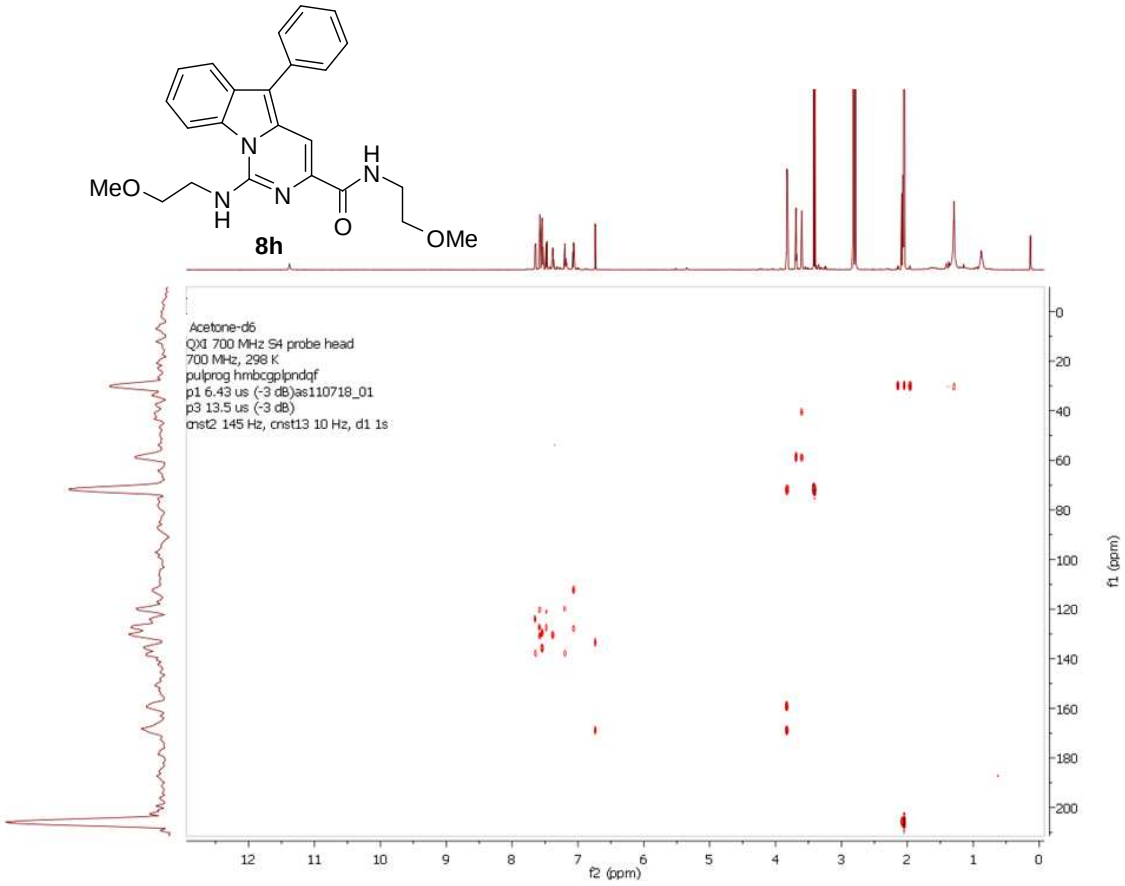



MeO
N
H
N
N
H
O
N
H
OMe

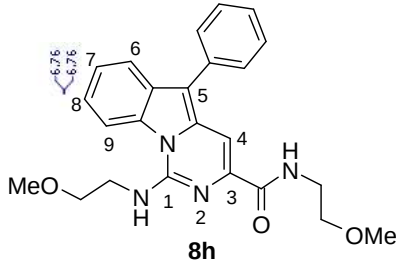
8h

12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

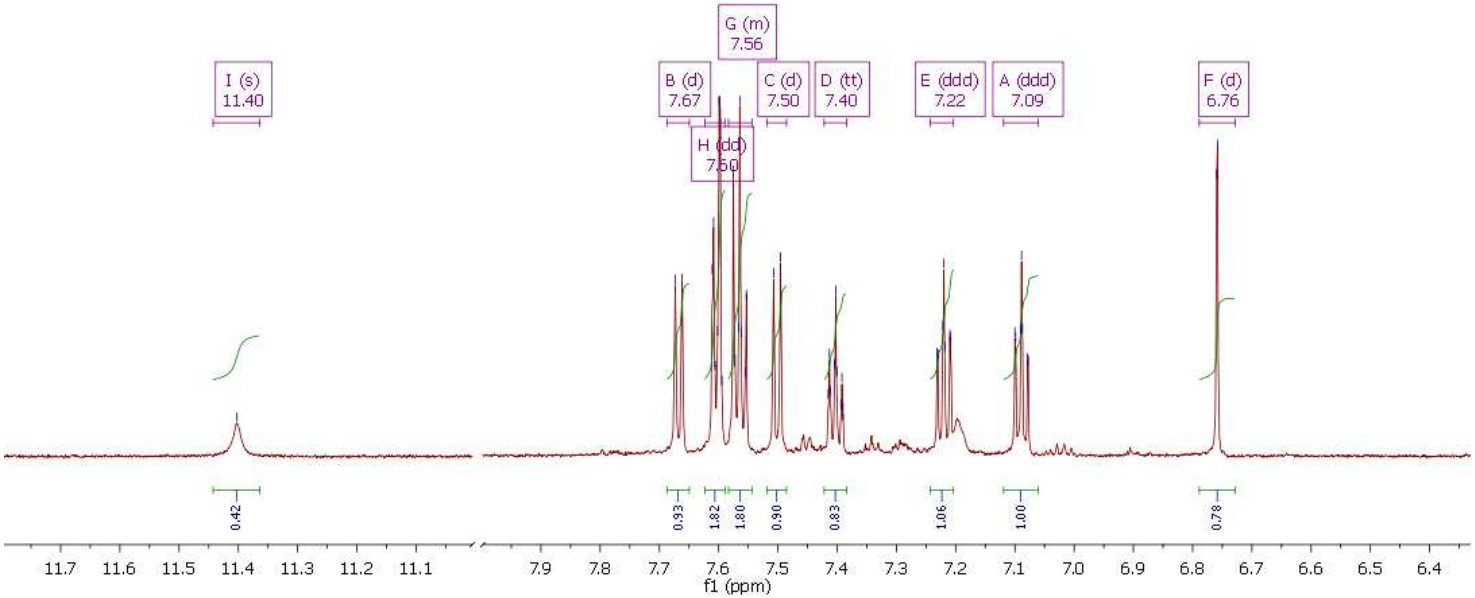

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

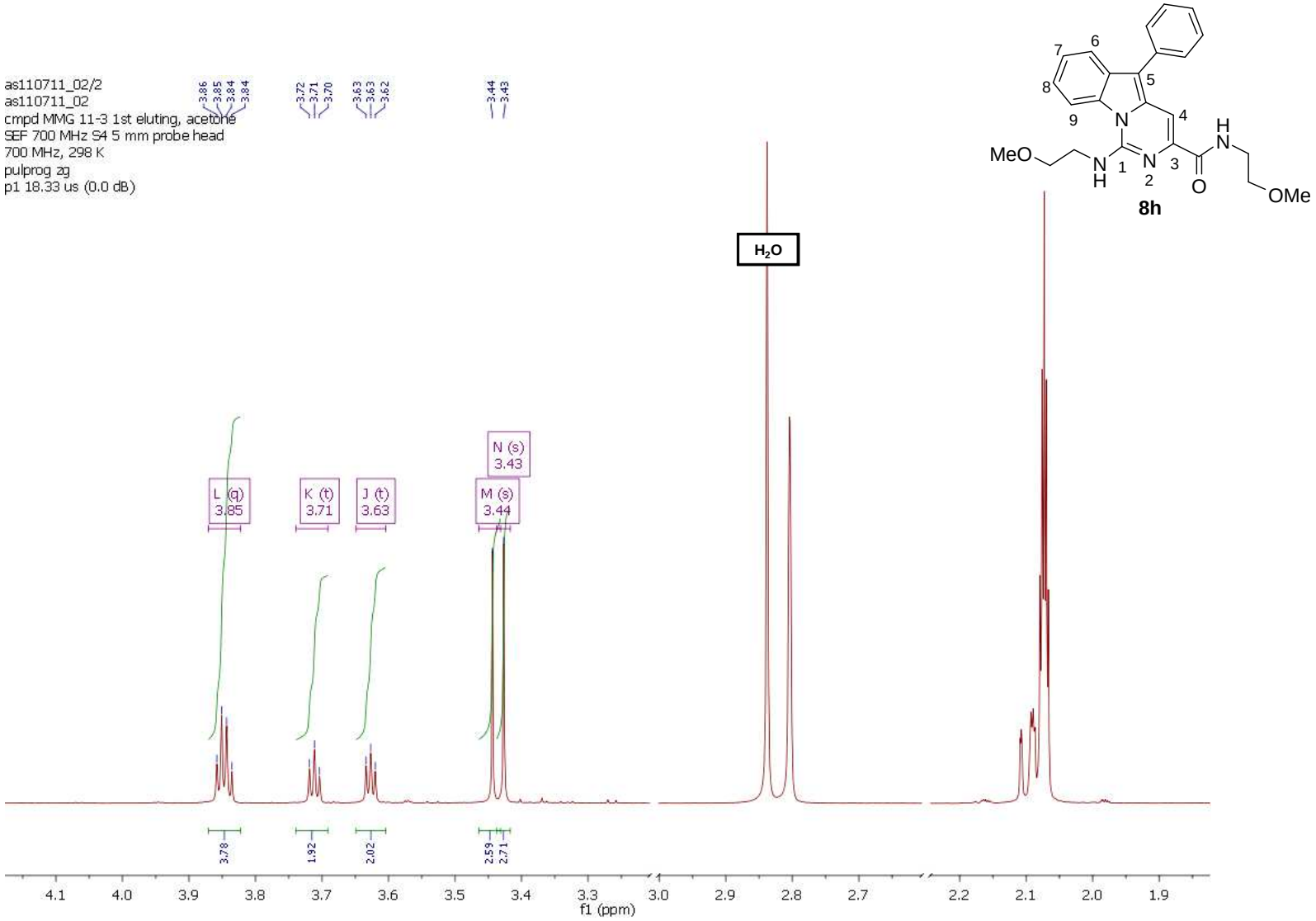

MeO
N
H
N
N
H
O
OMe
8h
Acetone-d6
QXI 700 MHz S4 probe head
700 MHz, 298 K
pulprog hmbcgplpndqf
p1 6.43 us (-3 dB)as110718_01
p3 13.5 us (-3 dB)
cnst2 145 Hz, cnst13 10 Hz, d1 1s
f2 (ppm)
f1 (ppm)

as110711_02/2
as110711_02
cmpd MMG 11-3 1st eluting, acetone
SEF 700 MHz S4 5 mm probe head
700 MHz, 298 K
pulprog zg
p1 18.33 us (0.0 dB)

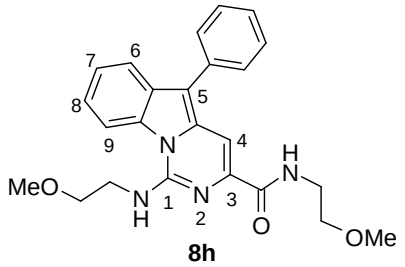


8h

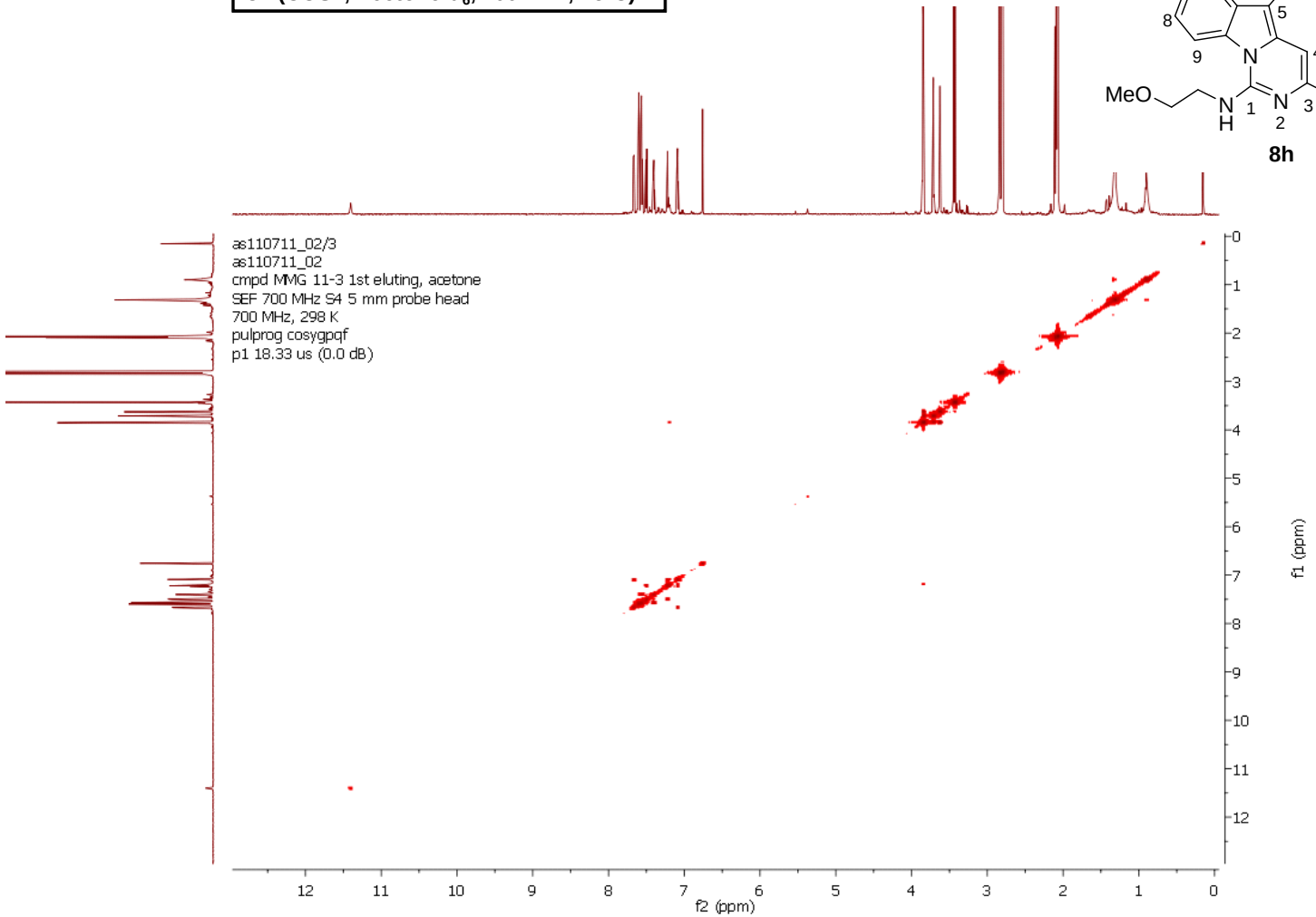




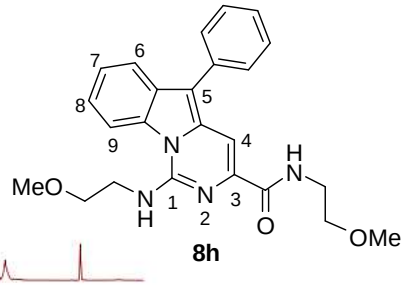
8h (COSY, Acetone-d_6, 700 MHz, 25ºC)



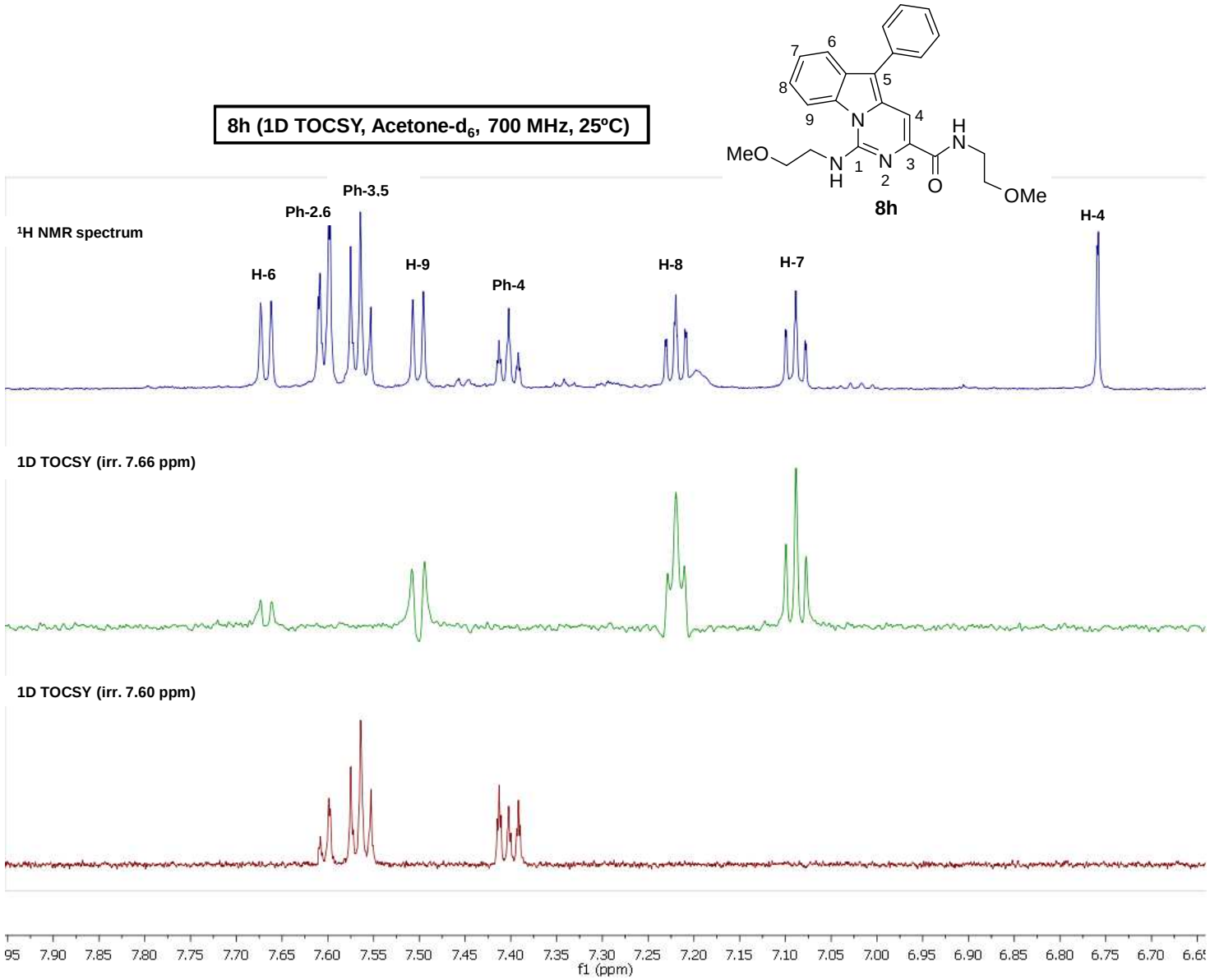
8h



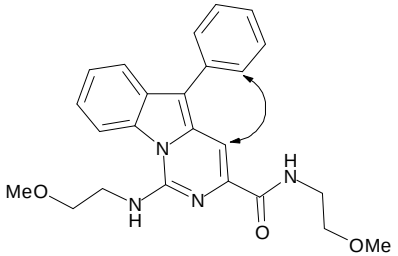
8h (HSQCED, Acetone-d_6, 700 MHz, 25ºC)



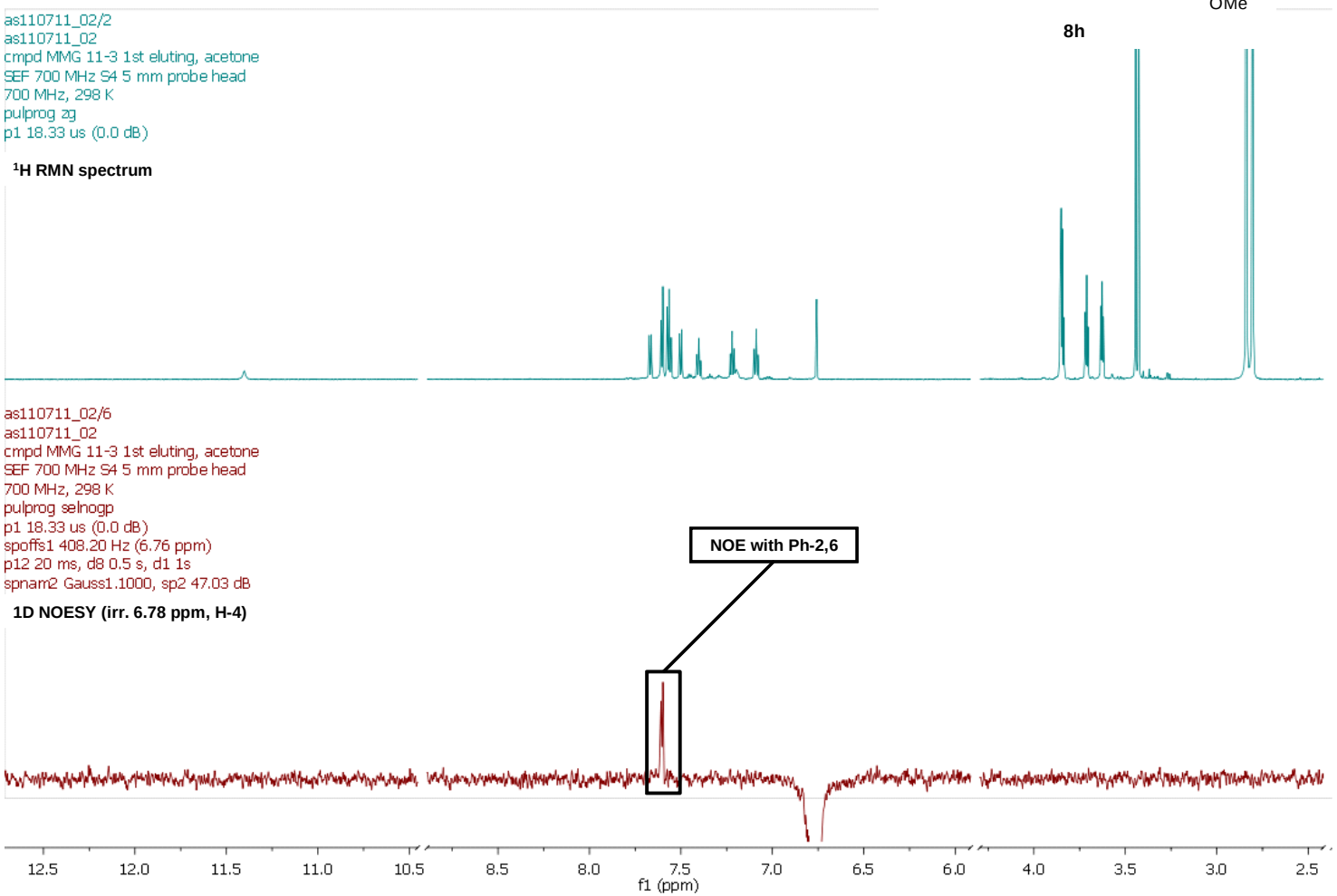
8h



8h (1D NOESY, Acetone-d_6, 700 MHz, 25ºC)



8h



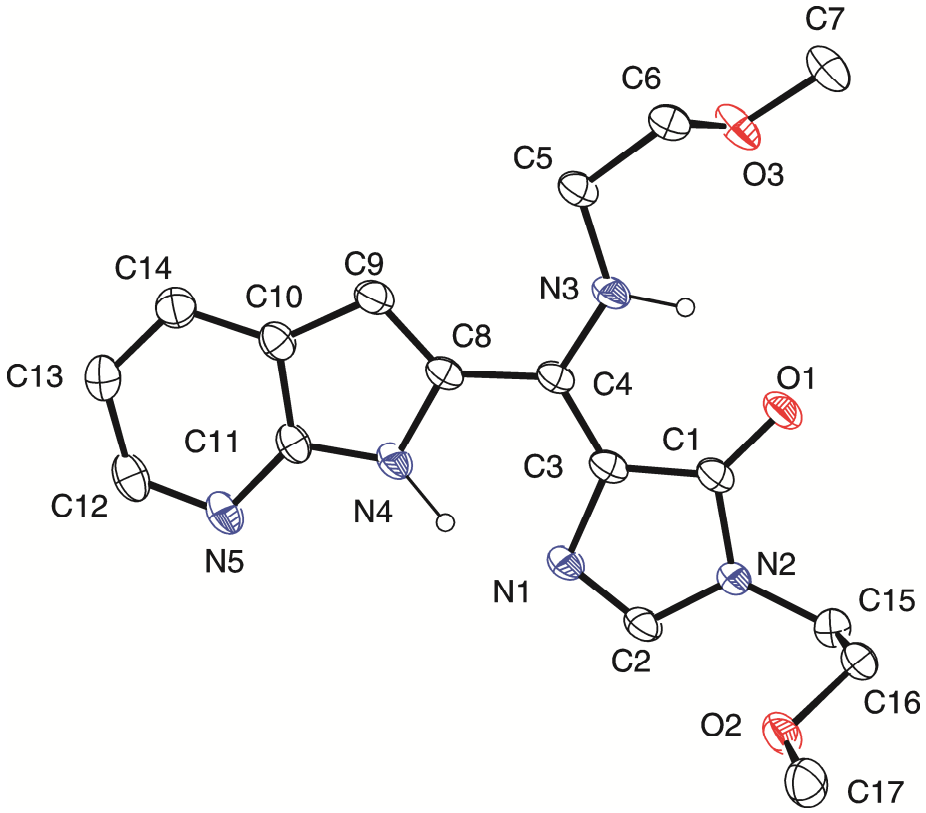


Figure 2. X-ray crystal structure of **7a**

Single-Crystal X-ray Structure Determination of 7a.

Details of the X-ray experiment, data reduction, and final structure refinement calculations are summarized in Table 3. Suitable single crystals of **7a** for the X-ray diffraction study were selected. Data collection was performed at 200(2) K, with the crystals covered with perfluorinated ether oil. The crystals were mounted on a Bruker-Nonius Kappa CCD single crystal diffractometer equipped with a graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). Multiscan[13] absorption correction procedures were applied to the data. The structures were solved, using the WINGX package,[14] by direct methods (SHELXS-97) and refined using full-matrix least-squares against F^2 (SHELXL-97).[15] All non-hydrogen atoms were anisotropically refined. Hydrogen atoms were geometrically placed and left riding on their parent atoms except for the hydrogen atoms on C9, N4 and N3. Full-matrix least-squares refinements were carried out by minimizing $\Sigma w(F_o^2-F_c^2)^2$ with the SHELXL-97 weighting scheme and stopped at shift/err < 0.001. The final residual electron density maps showed no remarkable features.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-884402 (**7a**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Table 3. Crystallographic Data for **7a.**

	7a
Formula	$C_{17}\ H_{21}\ N_5\ O_{38}$
FW	343.39
Color/habit	Orange/prism
Cryst dimensions (mm^3)	0.45 x 0.35 x 0.20
Cryst syst	Monoclinic
Space group	$P2_1/c$
a, Å	11.542(10)
b, Å	14.112(11)
c, Å	10.758(11)

β, (deg)	94.60(11)
V, Å^3	1747(3)
Z	4
T, K	200
ρ_{calcd}, g cm^{-3}	1.306
μ, mm^{-1}	0.093
F(000)	728
θ range, deg	3.39 to 25.39
no. of rflns collected	10245
no. of indep rflns / R_{int}	3171/0.1424]
no. of data/restraints/params	3171/0/239
$R1$/$wR2$ ($I>2\sigma(I)$)[a]	0.0776 / 0.1853
$R1$/$wR2$ (all data)[a]	0.1448/0.2330
Extinction coefficient	0.013(5)
GOF (on F^2)[a]	1.038
Largest diff peak / hole (e Å^{-3})	0.269/-0.266

[a] $R1 = \Sigma(||F_o|-|F_c||)/\Sigma|F_o|$; $wR2 = \{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$; $GOF = \{\Sigma[w(F_o^2-F_c^2)^2]/(n-p)\}^{1/2}$

Table 4. Selected bond lengths [Å] and angles [deg] for **7a.**

Bond lengths [Å]	**Angles[deg]**
O(1)-C(1) 1.255(5)	C(2)-N(1)-C(3) 104.6(3)
N(1)-C(2) 1.321(6)	C(6)-O(3)-C(7) 111.3(4)
N(1)-C(3) 1.430(5)	C(16)-O(2)-C(17) 112.5(3)
O(3)-C(6) 1.412(6)	C(12)-N(5)-C(11) 112.6(4)
O(3)-C(7) 1.440(6)	C(2)-N(2)-C(1) 107.6(3)
O(2)-C(16) 1.432(5)	C(2)-N(2)-C(15) 126.7(4)
O(2)-C(17) 1.438(6)	C(1)-N(2)-C(15) 125.5(3)
N(5)-C(12) 1.339(6)	C(11)-N(4)-C(8) 108.9(4)
N(5)-C(11) 1.359(6)	C(9)-C(8)-N(4) 109.0(4)
N(2)-C(2) 1.374(6)	C(9)-C(8)-C(4) 133.3(4)
N(2)-C(1) 1.410(5)	N(4)-C(8)-C(4) 117.7(4)
N(2)-C(15) 1.468(5)	C(4)-N(3)-C(5) 129.9(4)
N(4)-C(11) 1.365(6)	N(5)-C(11)-N(4) 123.9(4)
N(4)-C(8) 1.401(5)	N(5)-C(11)-C(10) 127.9(4)
C(8)-C(9) 1.387(6)	N(4)-C(11)-C(10) 108.2(4)
C(8)-C(4) 1.478(6)	N(3)-C(4)-C(3) 117.0(4)
N(3)-C(4) 1.368(5)	N(3)-C(4)-C(8) 121.0(4)
N(3)-C(5) 1.456(6)	C(3)-C(4)-C(8) 122.0(3)

C(11)-C(10) 1.420(6) C(4)-C(3) 1.401(6) C(3)-C(1) 1.427(6) C(5)-C(6) 1.527(6)	C(4)-C(3)-N(1) 126.1(4) C(4)-C(3)-C(1) 123.9(4) N(1)-C(3)-C(1) 109.8(4) O(1)-C(1)-N(2) 124.5(4) O(1)-C(1)-C(3) 131.2(4) N(2)-C(1)-C(3) 104.3(3) N(1)-C(2)-N(2) 113.8(4) N(3)-C(5)-C(6) 110.0(4) C(8)-C(9)-C(10) 106.8(4) O(3)-C(6)-C(5) 107.9(4)

References

10 A. Baeza, J. Mendiola, C. Burgos, J. Alvarez-Builla and J. J. Vaquero, *Tetrahedron Lett.*, 2008, **49**, 4073.

11 M. Suzuki and N. Yoneda, *J. Org. Chem.*, 1976, **41**, 1482.

12 J. Mendiola, I. Castellote, J. Alvarez-Builla, J. Fernandez-Gadea, A. Gomez and J. J. Vaquero, *J. Org. Chem.*, 2006, **71**, 1254.

13 R. H. Blessing, *SORTAV*, *Acta Cryst.*, 1995, **A51,** 33.

14 L. J. Farrugia, *J. Appl. Cryst.*, 1999, **32**, 837.

15 G. M. Sheldrick, *Acta Crystallogr. Sect.A* 2008, **A64**, 112.