# Supporting Information

## From simple quinoxalines to potent oxazolo[5,4-*f*]quinoxaline inhibitors of glycogen-synthase kinase 3 (GSK3)

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**General information**

Column chromatography separations were achieved on silica gel (40-63 μm). Melting points were measured on a Kofler apparatus. IR spectra were taken on a Perkin-Elmer Spectrum 100 spectrometer. $^{1}H$ and $^{13}C$ Nuclear Magnetic Resonance (NMR) spectra were recorded either on a Bruker Avance III spectrometer at 300 MHz and 75 MHz respectively, or on a Bruker Avance III HD spectrometer at 500 MHz and 126 MHz respectively. $^{1}H$ chemical shifts (δ) are given in ppm relative to the solvent residual peak and $^{13}C$ chemical shifts are relative to the central peak of the solvent signal.[1] Microanalyses were performed on a Thermo Fisher Flash EA 1112 elemental analyzer.

Solvents available from commercial sources (Carlo Erba; technical grade) were used without further purification, except for the following ones. Anhydrous toluene was obtained from distillation over sodium. Anhydrous acetonitrile was obtained by distillation from $CaH_2$. Dimethylsulfoxide was dried by treatment with 3Å molecular sieves (min. 48 h). Before use, chloroform was dried and neutralized by passing through a short plug of anhydrous, activated basic alumina. 2-Hydroxyquinoxaline (Merck; 99%), $POCl_3$ (Acros; 99%), isonicotinic acid (Alfa Aesar; 99%), nicotinic acid (Alfa Aesar; 99%), 1-ethyl-5-imidazolecarboxylic acid (Fluorochem; 95%), 1-methylpiperazine (Aldrich; 99%), 1-benzylpiperazine (Aldrich; 97%), piperidine (Aldrich; 99%), morpholine (Aldrich; 99%) and thiomorpholine (Aldrich; 98%) were used as received. All reactions involving moisture-sensitive reactants were performed under nitrogen atmosphere.

*Crystallography.* The samples were studied with monochromatized Mo-Kα radiation (λ = 0.71073 Å, multilayered monochromator). The X-ray diffraction data of the compounds **10ba** and **10ci** were collected at $T$ = 150(2) K by using a D8 VENTURE Bruker AXS diffractometer equipped with a (CMOS) PHOTON 100 detector. The structures were solved by dual-space algorithm using the *SHELXT* program,[2] and then refined with full-matrix least-square methods based on $F^2$ (*SHELXL*).[3] All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. H atoms were finally included in their calculated positions and treated as riding on their parent atom with constrained thermal parameters. The molecular diagrams were generated by ORTEP-3 (version 2.02).[4]

**General procedure 1 for the reduction of the nitro compounds.** This reaction was performed under an argon atmosphere. To a suspension of the nitro compound (4.2 g, 20 mmol) in degassed 2:1 isopropanol-water (0.30 L) was added ammonium chloride (2.1 g, 40 mmol) and iron powder (4.5 g, 80 mmol). The mixture was vigorously stirred under argon at ambient temperature for 30 min and at 60 °C for 3 h. After cooling to room temperature, it was filtered through a pad of celite, eluted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The amine was purified by column chromatography over silica gel (eluent: AcOEt-$CH_2Cl_2$ 60:40).

**6-Amino-2-chloroquinoxaline (1)**[5] was synthesized by using the general procedure 1. Purification by column chromatography over silica gel ($R_f$ ($CH_2Cl_2$-AcOEt 50:50) = 0.50) gave **1** in 66% yield (2.4 g) as a yellow solid: mp 186-188 °C; IR (ATR): 669, 748, 820, 834, 987, 968, 1102, 1155, 1229, 1300, 1498, 1536, 1610, 1620, 1644, 3193, 3321, 3375, 3412 $cm^{-1}$; $^1H$ NMR ($(CD_3)_2SO$) δ 6.19 (br s, 2H, $NH_2$), 6.95 (d, 1H, *J* = 2.4 Hz, H5), 7.28 (dd, 1H, *J* = 9.0 and 2.4 Hz, H7), 7.68 (d, 1H, *J* = 9.0 Hz, H8), 8.64 (s, 1H, H3); $^{13}C$ NMR ($(CD_3)_2SO$) δ 104.9 (CH), 123.3 (CH), 128.6 (CH), 134.9 (C), 140.6 (C), 143.1 (C), 144.2 (CH, C3), 151.0 (C).

**6-Amino-3-chloroquinoxaline (2)** was synthesized by using the general procedure 1. Purification by column chromatography over silica gel ($R_f$ ($CH_2Cl_2$-AcOEt 50:50) = 0.70) gave **2** in 78% yield (2.8 g) as a yellow solid: mp 210-212 °C (subl.); IR (ATR): 771, 816, 831, 870, 965, 1092, 1124, 1245, 1282, 1373, 1433, 1496, 1527, 1616, 1647, 3213, 3329, 3382 $cm^{-1}$; $^1H$ NMR ($(CD_3)_2SO$) δ 6.33 (br s, 2H, $NH_2$), 6.81 (d, 1H, *J* = 2.4 Hz, H5), 7.25 (dd, 1H, *J* = 9.0 and 2.4 Hz, H7), 7.76 (d, 1H, *J* = 9.0 Hz, H8), 8.42 (s, 1H, H2); $^{13}C$ NMR ($(CD_3)_2SO$) δ 103.8 (CH), 122.4 (CH), 129.6 (CH), 134.7 (C), 137.9 (CH, C2), 144.2 (C), 146.5 (C), 152.0 (C). These data are close to those reported previously in $CDCl_3$.[6]

**General procedure 2 for the iodination of the amines 1 and 2.** To a solution of the amine (3.0 g, 17 mmol) in 4:1 dioxane-water (80 mL) at 0 °C was successively added sodium hydrogenocarbonate (3.5 g, 42 mmol) and iodine (11 g, 42 mmol). The solution was stirred at room temperature for 4 h and

poured onto a saturated aqueous sodium thiosulfate solution (40 mL). The mixture was extracted with dichloromethane (3 x 20 mL); the organic layer was washed with water (20 mL) and dried over sodium sulfate. After evaporation of the solvent under reduced pressure, the iodide was purified as indicated in the product description.

**6-Amino-2-chloro-5-iodoquinoxaline (3)** was synthesized by using the general procedure 2. Purification by column chromatography over silica gel (eluent: $CH_2Cl_2$; $R_f$ = 0.47) gave **3** in 88% yield (4.6 g) as an orange solid: mp 209-211 °C; IR (ATR): 504, 517, 540, 832, 1115, 1401, 1446, 1480, 1540, 1620, 3189, 3309, 3450 $cm^{-1}$; $^1H$ NMR ($(CD_3)_2SO$) δ 6.39 (br s, 2H, $NH_2$), 7.43 (d, 1H, *J* = 9.1 Hz, H7), 7.70 (d, 1H, *J* = 9.1 Hz, H8), 8.73 (s, 1H, H3); $^{13}C$ NMR ($(CD_3)_2SO$) δ 79.6 (C, C5, C-I), 122.3 (CH, C7), 128.5 (CH, C8), 135.8 (C), 141.8 (C), 142.5 (C), 144.8 (CH, C3), 151.8 (C). Anal. Calcd for $C_8H_5ClIN_3$ (305.50): C, 31.45; H, 1.65; N, 13.75. Found: C, 31.42; H, 1.69; N, 13.69%.

**6-Amino-3-chloro-5-iodoquinoxaline (7)** was synthesized by using the general procedure 2. Recrystallization from acetonitrile gave **7** in 88% yield (4.6 g) as a yellow solid: mp 148-150 °C; IR (ATR): 444, 517, 609, 644, 781, 817, 833, 887, 968, 1105, 1238, 1351, 1413, 1484, 1528, 1600, 1616, 3182, 3317, 3341, 3424, 3452 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.94 (br s, 2H, $NH_2$), 7.21 (d, 1H, *J* = 9.0 Hz, H7), 7.80 (d, 1H, *J* = 9.0 Hz, H8), 8.42 (s, 1H, H2); $^{13}C$ NMR ($CDCl_3$) δ 81.3 (C, C5, C-I), 120.3 (CH, C7), 130.1 (CH, C8), 136.5 (C), 140.8 (CH, C2), 144.1 (C), 148.7 (C), 150.4 (C). Anal. Calcd for $C_8H_5ClIN_3$ (305.50): C, 31.45; H, 1.65; N, 13.75. Found: C, 31.50; H, 1.74; N, 13.66%.

**General procedure 3 for the nucleophilic substitution of the chlorides 3 and 7.** A solution of the chloride (0.31 g, 1.0 mmol) and the cyclic amine (5.0 mmol) in toluene (10 mL) was heated under reflux for 10 h. After cooling and evaporation under reduced pressure, a saturated aqueous sodium hydrogenocarbonate solution (5 mL) was added to the residue. Extraction with dichloromethane (3 x 10 mL), washing with water (5 mL) and drying over sodium sulfate led to the crude product which was purified as indicated in the product description.

**6-Amino-5-iodo-2-morpholinoquinoxaline (4a)** was synthesized by the general procedure 3 from **3** and using morpholine (0.44 mL). Purification by column chromatography over silica gel (eluent: $CH_2Cl_2$; $R_f$ = 0.22) gave **4a** in 83% yield (0.30 g) as a yellow solid: mp 185-187 °C; IR (ATR): 512, 557, 600, 639, 823, 1233, 1371, 1394, 1448, 1562, 1607, 1624, 2854, 2948, 3206, 3317, 3416 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 3.65 (t, 4H, *J* = 4.9 Hz, $CH_2$), 3.85 (t, 4H, *J* = 4.9 Hz, $CH_2$), 4.47 (br s, 2H, $NH_2$), 7.11 (d, 1H, *J* = 8.9 Hz, H7), 7.50 (d, 1H, *J* = 8.9 Hz, H8), 8.48 (s, 1H, H3); $^{13}C$ NMR ($CDCl_3$) δ 45.6 ($CH_2$), 66.7 ($CH_2$), 84.8 (C, C5, C-I), 120.4 (CH, C7), 127.7 (CH, C8), 135.8 (CH, C3), 136.4 (C), 138.1 (C), 145.9 (C), 151.7 (C). Anal. Calcd for $C_{12}H_{13}IN_4O$ (356.17): C, 40.47; H, 3.68; N, 15.73. Found: C, 40.51; H, 3.82; N, 15.58%.

**6-Amino-5-iodo-2-(4-methylpiperazino)quinoxaline (4b)** was synthesized by the general procedure 3 from **3** and using 1-methylpiperazine (0.50 g). Purification by column chromatography over silica gel (eluent: AcOEt; $R_f$ = 0.16) gave **4b** in 60% yield (0.22 g) as a pale yellow solid: mp 203-205 °C; IR (ATR): 514, 525, 553, 650, 785, 830, 993, 1012, 1139, 1145, 1272, 1369, 1392, 1450, 1465, 1491, 1536, 1568, 1603, 1618, 2759, 2802, 2849, 2935, 2970, 3184, 3296, 3442 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 2.42 (s, 3H, Me), 2.64 (t, 4H, *J* = 5.0 Hz, $CH_2$), 3.79 (t, 4H, *J* = 5.0 Hz, $CH_2$), 4.45 (s, 2H, $NH_2$), 7.12 (d, *J* = 8.9 Hz, 1H, H7), 7.51 (d, *J* = 8.9 Hz, 1H, H8), 8.51 (s, 1H, H3); $^{13}C$ NMR ($CDCl_3$) δ 45.2 ($CH_2$), 46.3 ($CH_3$), 54.8 ($CH_2$), 85.0 (C, C5, C-I), 120.3 (CH, C7), 127.6 (CH, C8), 136.0 (CH, C3), 136.5 (C), 137.7 (C), 145.6 (C), 151.6 (C). Anal. Calcd for $C_{13}H_{16}IN_5$ (369.21): C, 42.29; H, 4.37; N, 18.97. Found: C, 42.37; H, 4.56; N, 18.90%.

**6-Amino-5-iodo-3-morpholinoquinoxaline (8a)** was synthesized by the general procedure 3 from **7** and using morpholine (0.44 mL). Recrystallization from toluene gave **8a** in 81% yield (0.29 g) as an orange solid: mp 174-176 °C; IR (ATR): 459, 600, 1111, 1214, 1394, 1508, 1534, 1555, 1620, 2845, 2965, 3184, 3309, 3399 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 3.81 (d, 4H, *J* = 2.9 Hz, $CH_2$), 3.86 (d, 4H, *J* = 2.9 Hz, $CH_2$), 4.68 (br s, 2H, $NH_2$), 6.89 (d, 1H, *J* = 8.6 Hz, H7), 7.62 (d, 1H, *J* = 8.6 Hz, H8), 8.17 (s, 1H, H2); $^{13}C$ NMR ($CDCl_3$) δ 45.0 ($CH_2$), 66.8 ($CH_2$), 82.6 (C, C5, C-I), 115.0 (CH, C7), 129.5 (CH, C8),

130.9 (CH, C2), 131.6 (C), 142.7 (C), 149.6 (C), 153.3 (C). Anal. Calcd for $C_{12}H_{13}IN_4O$ (356.17): C, 40.47; H, 3.68; N, 15.73. Found: C, 40.50; H, 3.79; N, 15.60%.

**General procedure 4 for the conversion of the amines 4a,b and 8a into amides.** To a suspension of the amine (2.0 mmol) and calcium carbonate (0.22 g, 2.2 mmol) in toluene (10 mL) was added the aroyl chloride (2.2 mmol). The mixture was heated under reflux for 15 h. After filtration of the hot solution, the filtrate was concentrated under reduced pressure to give the expected product which was used in the next step without further purification.

**6-(Benzoylamino)-5-iodo-2-(morpholino)quinoxaline (5aa)** was synthesized by the general procedure 4 from **4a** (0.71 g) and using benzoyl chloride (0.26 mL). Compound **5aa** was obtained in 87% yield (0.83 g) as a beige solid: mp > 260 °C; IR (ATR): 519, 548, 701, 781, 821, 866, 930, 991, 1054, 1115, 1180, 1250, 1284, 1333, 1402, 1452, 1522, 1572, 1603, 1664, 2844, 2909, 2969, 3385 $cm^{-1}$; $^1H$ NMR ($(CD_3)_2SO$) δ 3.78 (s, 8H, $CH_2$), 7.57 (t, 2H, *J* = 7.3 Hz, H3' and H5'), 7.61-7.64 (m, 2H, H7 and H4'), 7.72 (d, 1H, *J* = 8.7 Hz, H8), 8.07 (d, 2H, *J* = 7.4 Hz, H2' and H6'), 8.84 (s, 1H, H3), 10.16 (s, 1H, NH); $^{13}C$ NMR ($(CD_3)_2SO$) δ 44.5 ($CH_2$), 65.9 ($CH_2$), 105.2 (C, C5, C-I), 126.0 (CH), 127.7 (2CH, C2' and C6'), 128.5 (2CH, C3' and C5'), 130.0 (CH), 131.8 (CH, C4'), 134.2 (C, C1'), 136.4 (C), 137.5 (CH), 137.6 (C), 139.8 (C), 152.4 (C), 165.4 (C, C=O). Anal. Calcd for $C_{19}H_{17}IN_4O_2$ (460.28): C, 49.58; H, 3.72; N, 12.17. Found: C, 49.56; H, 3.75; N, 12.11%.

**6-(Benzoylamino)-5-iodo-2-(4-methylpiperazino)quinoxaline (5ab)** was synthesized by the general procedure 4 from **4b** (0.74 g) and using benzoyl chloride (0.26 mL). Compound **5ab** was obtained in 79% yield (0.78 g) as a yellow solid: mp 226-228 °C; IR (ATR): 990, 1008, 1074, 1143, 1167, 1208, 1256, 1283, 1332, 1370, 1398, 1439, 1456, 1519, 1570, 1603, 1676, 2850, 2938, 3396 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 2.36 (s, 3H, Me), 2.57 (t, 4H, *J* = 5.1 Hz, $CH_2$), 3.82 (t, 4H, *J* = 5.1 Hz, $CH_2$), 7.51-7.63 (m, 3H, H3', H4' and H5'), 7.69 (d, 1H, *J* = 9.2 Hz, H7), 8.02-8.06 (m, 2H, H2' and H6'), 8.55 (s, 1H, H3), 8.67 (s, 1H, NH), 8.73 (d, 1H, *J* = 9.1 Hz, H8); $^{13}C$ NMR ($CDCl_3$) δ 44.8 ($CH_2$), 46.3 ($CH_3$), 54.8 ($CH_2$), 95.9 (C, C5, C-I), 124.5 (CH), 127.3 (CH), 127.4 (2CH, C2' and C6'), 129.1 (2CH,

C3' and C5'), 132.4 (CH, C4'), 134.7 (C), 136.5 (CH, C3), 136.5 (C), 137.1 (C), 139.9 (C), 152.4 (C), 165.6 (C, C=O). Anal. Calcd for $C_{20}H_{20}IN_5O$ (473.32): C, 50.75; H, 4.26; N, 14.80. Found: C, 50.79; H, 4.42; N, 14.67%.

**5-Iodo-3-morpholino-6-(4-pyridoylamino)quinoxaline (9a)** was synthesized by the general procedure 4 from **8a** (0.71 g) and using isonicotinoyl chloride (0.31 g). Compound **9a** was obtained in 82% yield (0.79 g) as a pale yellow solid: mp 248-250 °C; IR (ATR): 967, 1058, 1065, 1113, 1207, 1224, 1257, 1302, 1371, 1388, 1408, 1455, 1521, 1568, 1652, 2830, 2870, 2983, 3257 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 3.87-3.89 (m, 8H, $CH_2$), 7.87 (d, 2H, *J* = 5.5 Hz, H3' and H5'), 7.91 (d, 1H, *J* = 9.1 Hz, H7), 8.42 (s, 1H, H2), 8.62 (d, 1H, *J* = 9.0 Hz, H8), 8.88 (br s, 3H, H2', H6' and NH); $^1H$ NMR ($(CD_3)_2SO$) δ 3.78 (t, 4H, *J* = 5.0 Hz, $CH_2$), 3.87 (t, 4H, *J* = 5.1 Hz, $CH_2$), 7.59 (d, 1H, *J* = 8.6 Hz, H7), 7.88 (d, 1H, *J* = 8.6 Hz, H8), 7.97 (d, 2H, *J* = 6.0 Hz, H3' and H5'), 8.76 (s, 1H, H2), 8.84 (d, 2H, *J* = 5.3 Hz, H2' and H6'), 10.49 (s, 1H, NH); $^{13}C$ NMR ($CDCl_3$) δ 45.0 ($CH_2$), 66.7 ($CH_2$), 93.6 (C, C5, C-I), 118.6 (CH), 121.1 (2CH, C3' and C5'), 129.7 (CH), 134.7 (C), 134.9 (CH, C2), 140.6 (C), 141.6 (C), 141.6 (C), 151.0 (2CH, C2' and C6'), 153.0 (C), 163.6 (C, C=O); $^{13}C$ NMR ($(CD_3)_2SO$) δ 44.3 ($CH_2$), 65.8 ($CH_2$), 101.8 (C), 121.5 (2CH, C3' and C5'), 124.0 (CH), 128.3 (CH), 134.4 (C), 136.8 (CH, C2), 141.2 (C), 141.4 (C), 141.6 (C), 150.4 (2CH, C2' and C6'), 152.6 (C), 163.8 (C, C=O). Anal. Calcd for $C_{18}H_{16}IN_5O_2$ (461.26): C, 46.87; H, 3.50; N, 15.18. Found: C, 46.83; H, 3.65; N, 15.14%.

**General procedure 5 for the cyclization of the iodinated amides 5aa, 5ab and 9a.** To a suspension of the iodinated amide (1.0 mmol) in dry DMSO (4 mL) was added potassium carbonate (0.16 g, 1.2 mmol) and copper(I) iodide (19 mg, 0.10 mmol). The sealed tube was heated at 110 °C for 12 h and cooled. The resulting dark mixture was poured onto cold water (20 mL); the precipitate was filtered, washed with cold water (5 mL) and dissolved in chloroform. The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure. The product was purified by chromatography over silica gel (the eluent is given in the product description).

**7-Morpholino-2-phenyloxazolo[5,4-*f*]quinoxaline (6aa)** was synthesized by the general procedure 5 from **5aa** (0.48 g). Compound **6aa** was obtained (eluent: $CH_2Cl_2$-AcOEt 95:5; $R_f$ = 0.27) in 70% yield (0.25 g) as a pale yellow solid: mp 208-210 °C; IR (ATR): 667, 693, 707, 774, 826, 896, 986, 1017, 1065, 1116, 1247, 1379, 1428, 1463, 1546, 1561, 2849, 2913, 2962, 3064, 3105 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 3.77 (dd, 4H, *J* = 5.6 and 3.7 Hz), 3.87 (dd, 4H, *J* = 5.9 and 3.5 Hz), 7.49-7.54 (m, 3H, H3', H4' and H5'), 7.65 (d, 1H, *J* = 8.8 Hz, H4 or H5), 7.94 (d, 1H, *J* = 8.9 Hz, H4 or H5), 8.33 (ddd, 2H, *J* = 6.7, 3.7 and 2.0 Hz, H2' and H6'), 8.60 (s, 1H, H8); $^{13}C$ NMR ($CDCl_3$) δ 45.1 ($CH_2$), 66.7 ($CH_2$), 122.5 (CH, C4 or C5), 124.0 (CH, C4 or C5), 124.6 (C), 127.2 (C), 127.6 (2CH, C2' and C6'), 129.0 (2CH, C3' and C5'), 131.4 (CH, C4'), 134.9 (CH, C8), 139.1 (C), 140.5 (C), 145.6 (C), 152.2 (C), 163.3 (C, C2). Anal. Calcd for $C_{19}H_{16}N_4O_2$ (332.36): C, 68.66; H, 4.85; N, 16.86. Found: C, 68.49; H, 4.97; N, 16.71%.

**7-(4-Methylpiperazino)-2-phenyloxazolo[5,4-*f*]quinoxaline (6ab)** was synthesized by the general procedure 5 from **5ab** (0.49 g). Compound **6ab** was obtained (eluent: AcOEt-MeOH 90:10; $R_f$ = 0.32) in 66% yield (0.24 g) as a pale yellow solid: mp 158-160 °C; IR (ATR): 985, 1005, 1019, 1050, 1074, 1141, 1163, 1207, 1225, 1248, 1283, 1294, 1372, 1398, 1472, 1488, 1543, 1561, 1612, 2789, 2858, 2934, 2960 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 2.37 (s, 3H, Me), 2.58 (t, 4H, *J* = 5.0 Hz, $CH_2$), 3.83 (t, 4H, *J* = 5.1 Hz, $CH_2$), 7.50-7.53 (m, 3H, H3', H4' and H5'), 7.64 (d, 1H, *J* = 8.9 Hz, H4 or H5), 7.93 (d, 1H, *J* = 8.9 Hz, H4 or H5), 8.32-8.35 (m, 2H, H2' and H6'), 8.62 (s, 1H, H8); $^{13}C$ NMR ($CDCl_3$) δ 44.7 ($CH_2$), 46.3 ($CH_3$), 54.8 ($CH_2$), 122.4 (CH, C4 or C5), 124.0 (CH, C4 or C5), 124.3 (C), 127.3 (C), 127.6 (2CH, C2' and C6'), 129.0 (2CH, C3' and C5'), 131.4 (CH, C4'), 135.2 (CH, C8), 138.9 (C), 140.7 (C), 145.7 (C), 152.2 (C), 163.1 (C, C2). Anal. Calcd for $C_{20}H_{19}N_5O$ (345.41): C, 69.55; H, 5.54; N, 20.28. Found: C, 69.24; H, 5.73; N, 20.07%.

**8-(4-Morpholino)-2-(4-pyridyl)oxazolo[5,4-*f*]quinoxaline (10a)** was synthesized by the general procedure 5 from **9a** (0.48 g). Compound **10a** was obtained (eluent: $CH_2Cl_2$-MeOH 95:5; $R_f$ = 0.38) in 66% yield (0.23 g) as a pale yellow solid: mp > 260 °C; IR (ATR): 961, 1063, 1120, 1209, 1244, 1266,

1416, 1492, 1556, 1569, 2863, 2944, 3525 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 3.87-3.95 (m, 8H, $CH_2$), 7.79 (d, 1H, *J* = 8.8 Hz, H4 or H5), 7.92 (d, 1H, *J* = 8.8 Hz, H4 or H5), 8.21 (br d, 2H, *J* = 4.3 Hz, H3' and H5'), 8.60 (s, 1H, H7), 8.86 (br s, 2H, H2' and H6'); $^{13}C$ NMR ($CDCl_3$) δ 45.0 ($CH_2$), 66.7 ($CH_2$), 116.9 (CH, C4 or C5), 121.2 (2CH, C3' and C5'), 126.8 (CH, C4 or C5), 129.9 (C), 134.3 (C), 134.5 (CH, C7), 135.9 (C), 142.8 (C), 144.1 (C), 150.8 (2CH, C2' and C6'), 152.2 (C), 161.9 (C, C2). Anal. Calcd for $C_{18}H_{15}N_5O_2$ (333.35): C, 64.86; H, 4.54; N, 21.01. Found: C, 64.98; H, 4.81; N, 20.88%.

**General procedure 6A for the conversion of the amine 7 into the chlorocarboxamides 12a,b.** To a solution of the amine **7** (0.31 g, 1.0 mmol) in dry acetonitrile (4 mL) were successively added dropwise the aroyl chloride (1.1 mmol) and pyridine (0.4 mL, 5.0 mmol). The mixture was stirred at room temperature for 15 h, poured onto a saturated aqueous sodium hydrogenocarbonate solution (10 mL) and filtrated. The solid was washed with water (5 mL) and cold ethanol (5 mL), and dried to give the product which was used in the next step without further purification.

**6-(Benzoylamino)-3-chloro-5-iodoquinoxaline (12a)** was obtained according to the general procedure 6A (benzoyl chloride (0.13 mL) was employed) in 90% yield (0.38 g) as a beige solid: mp 237-239 °C; IR (ATR): 692, 718, 784, 836, 886, 908, 966, 985, 1074, 1107, 1180, 1246, 1263, 1278, 1305, 1352, 1378, 1505, 1545, 1553, 1599, 1684, 2852, 2924, 2966, 3112, 3347 $cm^{-1}$; $^1H$ NMR ($(CD_3)_2SO$) δ 7.59 (t, 2H, *J* = 7.3 Hz, H3' and H5'), 7.66 (t, 1H, *J* = 7.1 Hz, H4'), 8.08-8.13 (m, 3H, H2', H6' and H7), 8.17 (d, 1H, *J* = 8.9 Hz, H8), 8.97 (s, 1H, H2), 10.33 (br s, 1H, NH); $^{13}C$ NMR ($(CD_3)_2SO$) δ 100.7 (C, C5, C-I), 127.4 (2CH, C2' and C6'), 128.3 (2CH, C3' and C5'), 128.6 (CH), 129.1 (CH), 131.8 (CH, C4'), 133.7 (C, C1'), 138.9 (C), 142.1 (C), 143.7 (C), 145.0 (CH), 147.7 (C), 165.1 (C, C=O).

**2-Chloro-8-iodo-7-(3-pyridoylamino)quinoxaline (12b)** was obtained according to the general procedure 6A (nicotinoyl chloride (0.15 g) was employed) in 86% yield (0.37 g) as a yellow solid: mp > 260 °C; IR (ATR): 711, 780, 827, 925, 971, 985, 1106, 1130, 1195, 1236, 1296, 1329, 1398, 1417, 1485, 1522, 1558, 1593, 1683, 3041, 3184 $cm^{-1}$; $^1H$ NMR ($(CD_3)_2SO$) δ 7.61 (dd, 1H, *J* = 7.9 and 4.8

Hz, H5'), 8.15 (d, 1H, *J* = 8.9 Hz, H5 or H6), 8.17 (d, 1H, *J* = 8.9 Hz, H5 or H6), 8.41 (d, 1H, *J* = 7.9 Hz, H4'), 8.81 (d, 1H, *J* = 4.1 Hz, H6'), 8.93 (s, 1H, H3), 9.26 (d, 1H, *J* = 1.9 Hz, H2'), 10.3 (br s, 1H, NH); $^{13}$C NMR ($(CD_3)_2SO$) δ 101.1 (C, C8, C-I), 123.1 (CH), 128.6 (CH), 129.3 (CH), 129.4 (C), 135.0 (CH), 139.0 (C), 142.1 (C), 143.5 (C), 145.0 (CH), 147.5 (C), 148.4 (CH), 152.1 (CH), 163.8 (C, C=O).

**General procedure 6B for the conversion of the chlorocarboxamides 12a or 12b into the aminocarboxamides 9aa, 9ab, 9ba and 9bb.** To a suspension of the chlorocarboxamide **12a** or **12b** (see general procedure 6A) in dry DMSO (4 mL) was added the cyclic amine (1.1 mmol) and potassium carbonate (0.15 g, 1.1 mmol). After stirring for 2 h at room temperature, a saturated aqueous sodium hydrogenocarbonate solution (5 mL) was added to the residue. Extraction with diethyl ether (3 x 10 mL), washing with water (5 mL) and drying over sodium sulfate led to the iodinated amide which was used in the next step without further purification.

**6-(Benzoylamino)-5-iodo-3-morpholinoquinoxaline (9aa)** was obtained according to the general procedure 6B (morpholine (0.10 mL) was employed) from **12a** in 82% yield (0.35 g) as a beige solid: mp 221-223 °C; IR (ATR): 672, 701, 776, 825, 886, 921, 964, 1012, 1064, 1117, 1187, 1210, 1250, 1268, 1288, 1385, 1486, 1514, 1568, 1683, 2859, 2977, 3385 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 3.85-3.92 (m, 8H, $CH_2$), 7.53-7.64 (m, 3H, H3', H4' and H5'), 7.91 (d, 1H, *J* = 9.0 Hz, H7), 8.06 (dd, 2H, *J* = 8.1 and 1.6 Hz, H2' and H6'), 8.41 (s, 1H, H2), 8.70 (d, 1H, *J* = 9.0 Hz, H8), 8.87 (br s, 1H, NH); $^{13}$C NMR ($CDCl_3$) δ 45.0 ($2CH_2$), 66.7 ($2CH_2$), 93.0 (C, C5, C-I), 118.8 (CH), 125.4 (C), 127.4 (2CH, C2' and C6'), 128.3 (C), 129.1 (2CH, C3' and C5'), 129.5 (CH), 132.5 (CH, C4'), 134.4 (CH, C2), 134.6 (C, C1'), 141.5 (C), 153.0 (C), 165.6 (C, C=O).

**6-(Benzoylamino)-5-iodo-3-(4-methylpiperazino)quinoxaline (9ab)** was obtained according to the general procedure 6B (1-methylpiperazine (0.11 g) was employed) from **12a** in 61% yield (0.27 g) as a whitish solid: mp 212-214 °C; IR (ATR): 671, 686, 700, 777, 825, 883, 964, 1001, 1074, 1118, 1201, 1221, 1240, 1266, 1283, 1292, 1388, 1470, 1489, 1514, 1565, 1607, 1684, 2797, 2847, 2935, 3376 cm$^{-}$

[1]; $^1$H NMR ($CDCl_3$) δ 2.37 (s, 3H, Me), 2.58 (t, 4H, *J* = 4.8 Hz, $CH_2$), 3.89 (t, 4H, *J* = 4.7 Hz, $CH_2$), 7.51-7.62 (m, 3H, H3', H4' and H5'), 7.86 (d, 1H, *J* = 9.0 Hz, H7), 8.04 (d, 2H, *J* = 7.4 Hz, H2' and H6'), 8.40 (s, 1H, H2), 8.65 (d, 1H, *J* = 9.0 Hz, H8), 8.85 (br s, 1H, NH); $^{13}$C NMR ($CDCl_3$) δ 44.6 ($CH_2$), 46.3 ($CH_3$), 54.8 ($CH_2$), 93.0 (C, C5, C-I), 118.5 (CH), 127.4 (2CH, C2' and C6'), 129.1 (2CH, C3' and C5'), 129.4 (CH), 132.4 (CH, C4'), 134.1 (C), 134.6 (C, C1'), 134.7 (CH), 141.4 (C), 141.7 (C), 152.9 (C), 165.6 (C, C=O).

**5-Iodo-3-morpholino-6-(3-pyridoylamino)quinoxaline (9ba)** was obtained according to the general procedure 6B (morpholine (0.10 mL) was employed) from **12b** in 78% yield (0.36 g) as a whitish solid: mp 236-238 °C; IR (ATR): 1012, 1027, 1060, 1116, 1218, 1264, 1297, 1393, 1417, 1444, 1477, 1521, 1568, 1590, 1679, 2849, 2962, 3289 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 3.88 (d, 8H, *J* = 4.2 Hz, $CH_2$), 7.51 (dd, 1H, *J* = 7.3 and 4.9 Hz, H5'), 7.90 (d, 1H, *J* = 9.0 Hz, H7), 8.36 (d, 1H, *J* = 7.9 Hz, H4'), 8.42 (s, 1H, H2), 8.62 (d, 1H, *J* = 9.0 Hz, H8), 8.85 (br s, 2H, H6' and NH), 9.31 (br s, 1H, H2'); $^{13}$C NMR ($(CD_3)_2SO$) δ 44.3 ($CH_2$), 65.8 ($CH_2$), 101.7 (C, C5, C-I), 123.6 (CH), 124.1 (CH), 128.3 (CH), 129.8 (C), 134.3 (C), 135.5 (CH), 136.7 (CH), 141.4 (C), 141.8 (C), 148.7 (CH), 152.4 (CH), 152.6 (C), 163.9 (C, C=O).

**5-Iodo-3-(4-methylpiperazino)-6-(3-pyridoylamino)quinoxaline (9bb)** was obtained according to the general procedure 6B (1-methylpiperazine (0.11 g) was employed) from **12b** in 70% yield (0.30 g) as a pale yellow solid: mp 227-229 °C; IR (ATR): 964, 1004, 1116, 1127, 1141, 1165, 1219, 1259, 1274, 1292, 1359, 1393, 1417, 1444, 1477, 1522, 1566, 1589, 1607, 1682, 2789, 2916, 3362 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 2.38 (s, 3H, Me), 2.59 (t, 4H, *J* = 5.0 Hz, $CH_2$), 3.90 (t, 4H, *J* = 4.9 Hz, $CH_2$), 7.49 (dd, 1H, *J* = 7.9 and 4.9 Hz, H5'), 7.87 (d, 1H, *J* = 9.0 Hz, H8), 8.33 (br d, 1H, *J* = 8.0 Hz, H4'), 8.42 (s, 1H, H2), 8.59 (d, 1H, *J* = 9.0 Hz, H7), 8.83 (br s, 2H, H6' and NH), 9.30 (br s, 1H, H2'); $^{13}$C NMR ($CDCl_3$) δ 44.6 ($CH_2$), 46.3 ($CH_3$), 54.8 ($CH_2$), 93.5 (C, C5, C-I), 118.5 (CH), 123.9 (CH), 129.5 (CH), 130.4 (C), 134.3 (C), 135.0 (CH), 135.4 (CH), 140.8 (C), 141.7 (C), 148.5 (CH), 153.0 (C), 153.1 (CH), 163.8 (C, C=O).

**General procedure 6C for the conversion of the aminocarboxamides 9aa, 9ab, 9ba or 9bb into the oxazolo[5,4-*f*]quinoxalines 10aa, 10ab, 10ba and 10bb.** To a suspension of the aminocarboxamide (see general procedure 6B) in dry DMSO (4 mL) was added potassium carbonate (0.16 g, 1.2 mmol) and copper(I) iodide (19 mg, 0.10 mmol). The sealed tube was heated at 110 °C for 12 h and cooled. The resulting dark mixture was poured onto cold water (20 mL); the precipitate was filtered, washed with cold water (5 mL) and dissolved in chloroform. The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure. The product was purified by chromatography over silica gel (the eluent is given in the product description).

**8-Morpholino-2-phenyloxazolo[5,4-*f*]quinoxaline (10aa)** was synthesized according to the general procedure 6C from **9aa**. It was obtained (eluent: $CH_2Cl_2$-MeOH 99:1; $R_f$ = 0.20) in 81% yield (0.20 g; 60% overall yield) as a yellow solid: mp 218-220 °C; IR (ATR): 957, 1019, 1041, 1057, 1090, 1121, 1205, 1241, 1261, 1287, 1330, 1370, 1398, 1427, 1447, 1483, 1539, 1559, 1578, 1609, 2865, 2901, 2963, 2985, 3065 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 3.83-3.87 (m, 4H, $CH_2$), 3.88-3.92 (m, 4H, $CH_2$), 7.51-7.55 (m, 3H, H3', H4' and H5'), 7.75 (d, 1H, *J* = 8.7 Hz, H4 or H5), 7.85 (d, 1H, *J* = 8.8 Hz, H4 or H5), 8.31-8.37 (m, 2H, H2' and H6'), 8.54 (br s, 1H, H7); $^{13}C$ NMR ($CDCl_3$) δ 45.0 ($2CH_2$), 66.7 ($2CH_2$), 116.8 (CH, C4 or C5), 126.2 (CH, C4 or C5), 127.2 (C), 127.8 (2CH, C2' and C6'), 129.0 (2CH, C3' and C5'), 129.7 (C), 131.7 (CH, C4'), 133.9 (CH, C7), 135.4 (C), 143.1 (C), 143.7 (C), 152.1 (C), 164.3 (C, C2). Anal. Calcd for $C_{19}H_{16}N_4O_2$ (332.36): C, 68.66; H, 4.85; N, 16.86. Found: C, 68.75; H, 5.02; N, 16.77%.

**8-(4-Methylpiperazino)-2-phenyloxazolo[5,4-*f*]quinoxaline (10ab)** was synthesized according to the general procedure 6C from **9ab**. It was obtained (eluent: $CH_2Cl_2$-MeOH 97:3; $R_f$ = 0.11) in 79% yield (0.16 g; 43% overall yield) as a pale yellow solid: mp 194-196 °C; IR (ATR): 685, 705, 749, 776, 789, 814, 926, 938, 959, 1008, 1022, 1065, 1092, 1141, 1204, 1257, 1299, 1407, 1428, 1451, 1487, 1561, 1676, 2786, 2845, 2935 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 2.37 (s, 3H, Me), 2.58 (t, 4H, *J* = 5.1 Hz, $CH_2$), 3.90 (t, 4H, *J* = 5.1 Hz, $CH_2$), 7.49-7.54 (m, 3H, H3', H4' and H5'), 7.72 (d, 1H, *J* = 8.8 Hz, H4

or H5), 7.83 (d, 1H, $J$ = 8.7 Hz, H4 or H5), 8.34 (ddd, 2H, $J$ = 5.5, 3.0 and 1.5 Hz), 8.55 (s, 1H, H7); $^{13}$C NMR ($CDCl_3$) δ 44.6 ($CH_2$), 46.3 ($CH_3$), 54.9 ($CH_2$), 116.5 (CH, C4 or C5), 126.1 (CH, C4 or C5), 127.2 (C), 127.8 (2CH, C2' and C6'), 129.0 (2CH, C3' and C5'), 129.8 (C), 131.6 (CH, C4'), 134.2 (CH, C7), 135.1 (C), 143.0 (C), 143.6 (C), 152.0 (C), 164.3 (C, C2). Anal. Calcd for $C_{20}H_{19}N_5O$ (345.41): C, 69.55; H, 5.54; N, 20.28. Found: C, 69.74; H, 5.70; N, 20.16%.

**8-Morpholino-2-(3-pyridyl)oxazolo[5,4-*f*]quinoxaline (10ba)** was synthesized according to the general procedure 6C from **9ba**. It was obtained (eluent: $CH_2Cl_2$-MeOH 97:3; $R_f$ = 0.10) in 91% yield (0.32 g; 61% overall yield) as a pale yellow solid: mp > 260 °C; IR (ATR): 1019, 1061, 1096, 1118, 1207, 1244, 1262, 1428, 1556, 1575, 1607, 2860, 2900, 2966, 3039 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 3.88-3.91 (m, 8H, $CH_2$), 7.50 (br s, 1H, H5'), 7.76 (d, 1H, $J$ = 8.8 Hz, H4 or H5), 7.89 (d, 1H, $J$ = 8.8 Hz, H4 or H5), 8.58 (s, 1H, H7), 8.61 (d, 1H, $J$ = 8.0 Hz, H4'), 8.81 (br s, 1H, H6'), 9.60 (br s, 1H, H2'); $^1$H NMR ($(CD_3)_2SO$) δ 3.78-3.89 (m, 8H, $CH_2$), 7.68 (dd, 1H, $J$ = 7.7 and 4.5 Hz, H5'), 7.81 (d, 1H, $J$ = 8.7 Hz, H4 or H5), 7.87 (d, 1H, $J$ = 8.7 Hz, H4 or H5), 8.59 (dt, 1H, $J$ = 8.1 and 1.9 Hz, H4'), 8.82 (dd, 1H, $J$ = 4.8 and 1.6 Hz, H6'), 8.87 (s, 1H, H7), 9.40 (d, 1H, $J$ = 1.6 Hz, H2'); $^{13}$C NMR ($(CD_3)_2SO$) δ 44.2 ($2CH_2$), 65.5 ($2CH_2$), 115.4 (CH), 122.6 (C), 123.8 (CH, C5'), 125.7 (CH), 128.7 (C), 134.2 (CH, C4'), 134.4 (C), 135.2 (CH), 141.7 (C), 142.9 (C), 147.6 (CH, C2'), 151.6 (C), 151.8 (CH), 161.0 (C). Anal. Calcd for $C_{18}H_{15}N_5O_2$ (333.35): C, 64.86; H, 4.54; N, 21.01. Found: C, 64.83; H, 4.56; N, 20.93%.

**Crystal data for 10ba.** $C_{18}H_{15}N_5O_2 \cdot CHCl_3$, $M$ = 452.72, triclinic, $P$-1, $a$ = 6.9499(10), $b$ = 9.8422(14), $c$ = 15.3854(19) Å, $\alpha$ = 87.986(5), $\beta$ = 87.262(5), $\gamma$ = 69.331(5) °, $V$ = 983.3(2) Å$^3$, $Z$ = 2, $d$ = 1.529 g cm$^{-3}$, $\mu$ = 0.493 mm$^{-1}$. A final refinement on $F^2$ with 4451 unique intensities and 263 parameters converged at $\omega R(F^2)$ = 0.2237 ($R(F)$ = 0.0914) for 4112 observed reflections with $I > 2\sigma(I)$. CCDC 1947178.

**8-(4-Methylpiperazino)-2-(3-pyridyl)oxazolo[5,4-*f*]quinoxaline (10bb)** was synthesized according to the general procedure 6C from **9bb**. It was obtained (eluent: $CH_2Cl_2$-MeOH 90:10; $R_f$ = 0.42) in

98% yield (0.21 g; 59% overall yield) as a pale yellow solid: mp 223-225 °C; IR (ATR): 705, 788, 811, 925, 1005, 1059, 1092, 1138, 1205, 1258, 1288, 1417, 1455, 1498, 1542, 1557, 1575, 1606, 1682, 2787, 2852, 2918, 3064 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 2.40 (s, 3H, Me), 2.63 (t, 4H, *J* = 5.1 Hz, $CH_2$), 3.94 (t, 4H, *J* = 5.1 Hz, $CH_2$), 7.48 (dd, 1H, *J* = 8.0 and 4.8 Hz, H5'), 7.74 (d, 1H, *J* = 8.7 Hz, H4 or H5), 7.87 (d, 1H, *J* = 8.8 Hz, H4 or H5), 8.59 (s, 1H, H7), 8.62 (dt, 1H, *J* = 8.0 and 2.0 Hz, H4'), 8.77 (dd, 1H, *J* = 4.9 and 1.7 Hz, H6'), 9.57 (d, 1H, *J* = 2.2 Hz, H2'); $^{13}C$ NMR ($CDCl_3$) δ 44.6 ($CH_2$), 46.2 ($CH_3$), 54.8 ($CH_2$), 116.5 (CH, C4 or C5), 123.7 (CH, C5'), 123.8 (C), 126.6 (CH, C4 or C5), 129.9 (C), 134.6 (CH), 134.9 (CH), 135.4 (C), 142.8 (C), 143.9 (C), 149.0 (CH, C2' or C6'), 152.1 (CH, C6' or C2'), 152.1 (C), 161.9 (C, C2). Anal. Calcd for $C_{19}H_{18}N_6O$ (346.39): C, 65.88; H, 5.24; N, 24.26. Found: C, 65.93; H, 5.30; N, 24.23%.

**General procedure 7A for the reaction from 3 or 7 to the iodocarboxamides 11b or 12c.** To a solution of the amine **3** or **7** (0.31 g, 1.0 mmol) in dry acetonitrile (4 mL) were successively added dropwise the aroyl chloride (1.1 mmol) and pyridine (0.4 mL, 5.0 mmol). The mixture was stirred at room temperature for 15 h, poured onto a saturated aqueous sodium hydrogenocarbonate solution (10 mL) and filtrated. The solid was washed with water (5 mL) and cold ethanol (5 mL), and dried to give the product which was used in the next step without further purification.

**2-Chloro-5-iodo-6-(3-pyridoylamino)quinoxaline (11b)** was obtained according to the general procedure 7A (nicotinoyl chloride (0.15 g) was employed) from **3** in 85% yield (0.36 g) as a pale yellow solid: mp > 260 °C; IR (ATR): 624, 634, 700, 710, 736, 792, 843, 950, 981, 1104, 1152, 1161, 1279, 1300, 1353, 1378, 1416, 1481, 1515, 1557, 1589, 1596, 1651, 3035, 3070, 3279 $cm^{-1}$; $^1H$ NMR ($(CD_3)_2SO$) δ 7.62 (dd, 1H, *J* = 7.8 and 4.8 Hz, H5'), 8.07 (d, 1H, *J* = 8.9 Hz, H7 or H8), 8.12 (d, 1H, *J* = 8.9 Hz, H7 or H8), 8.41 (dt, 1H, *J* = 7.9 and 1.8 Hz, H4'), 8.82 (dd, 1H, *J* = 7.8 and 4.8 Hz, H6'), 9.01 (s, 1H, H3), 9.25 (d, 1H, *J* = 1.7 Hz, H2'), 10.4 (br s, 1H, NH); $^{13}C$ NMR ($(CD_3)_2SO$) δ 103.2 (C, C5, C-I), 123.3 (CH), 127.9 (CH), 129.4 (C), 130.4 (CH), 135.1 (CH), 139.6 (C), 141.1 (C), 142.6 (C), 145.8 (CH), 147.1 (C), 148.4 (CH), 152.2 (CH), 163.8 (C, C=O).

**2-Chloro-7-(1-ethyl-5-imidazoylamino)-8-iodoquinoxaline (12c)** was obtained according to the general procedure 7A (1-ethyl-5-imidazoyl chloride (0.17 g) was employed) from **7** in 82% yield (0.36 g) as a pale yellow solid after purification by column chromatography over silica gel (eluent: $CH_2Cl_2$-MeOH 97:3; $R_f$ = 0.15): mp > 260 °C; IR (ATR): 442, 551, 654, 745, 785, 832, 855, 967, 1104, 1152, 1228, 1238, 1268, 1329, 1355, 1383, 1473, 1507, 1557, 1602, 1680, 2929, 3045, 3105, 3361 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.52 (t, 3H, *J* = 7.2 Hz, $CH_3$), 4.46 (q, 2H, *J* = 7.2 Hz, $CH_2$), 7.72 (br s, 1H), 7.89 (br s, 1H), 8.09 (d, 1H, *J* = 9.2 Hz, H4 or H5), 8.66 (s, 1H, H7), 8.71 (br s, 1H), 8.91 (d, 1H, *J* = 9.2 Hz, H4 or H5); $^{13}C$ NMR ($(CD_3)_2SO$) δ 16.8 ($CH_3$), 41.3 ($CH_2$), 101.8 (C, C8, C-I), 124.4 (C), 128.9 (CH, C5 or C6), 130.0 (CH, C5 or C6), 134.3 (CH, C4'), 139.2 (C), 142.1 (CH, C2'), 142.4 (C), 143.5 (C), 145.5 (CH, C3), 148.0 (C), 158.3 (C, C=O).

**General procedure 7B for the reaction from the iodocarboxamides 11b or 12b-c to 6ba, 10bc-bi and 10ci.** To a suspension of the iodocarboxamide **11b or 12b-c** in dry DMSO (4 mL) was added the cyclic amine (1.1 mmol) and potassium carbonate (0.29 g, 2.2 mmol). After 1 h at room temperature, copper(I) iodide (19 mg, 0.10 mmol) was added. The sealed tube was heated at 110 °C for 12 h and cooled. The resulting dark mixture was poured onto cold water (20 mL); the precipitate was filtered, washed with cold water (5 mL) and dissolved in chloroform. The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure. The product was purified by chromatography over silica gel (the eluent is given in the product description).

**7-Morpholino-2-(3-pyridyl)oxazolo[5,4-*f*]quinoxaline (6ba)** was synthesized according to the general procedure 7B from **11b** (see general procedure 7A) by using morpholine (0.10 mL). It was obtained (eluent: $CH_2Cl_2$-MeOH 95:5; $R_f$ = 0.45) in 60% yield (0.17 g; 51% overall yield) as a yellow solid: mp 250-252 °C; IR (ATR): 439, 577, 641, 669, 702, 818, 834, 896, 930, 985, 1016, 1075, 1115, 1210, 1244, 1262, 1377, 1394, 1434, 1471, 1542, 1558, 1575, 2854, 2917, 2962 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 3.80 (t, 4H, *J* = 4.6 Hz, $CH_2$), 3.88 (t, 4H, *J* = 4.6 Hz, $CH_2$), 7.46 (dd, 1H, *J* = 7.8, 4.8 Hz, H5'), 7.68 (d, 1H, *J* = 8.9 Hz, H4 or H5), 7.96 (d, 1H, *J* = 8.9 Hz, H4 or H5), 8.58 (d, 1H, *J* = 8.0 Hz,

H4'), 8.62 (s, 1H, H8), 8.75 (br s, 1H, H6'), 9.56 (br s, 1H, H2'); $^{13}$C NMR ($CDCl_3$) δ 45.1 ($2CH_2$), 66.7 ($2CH_2$), 122.6 (CH, C4 or C5), 123.7 (C), 123.8 (CH, C5'), 124.5 (C), 124.5 (CH, C4 or C5), 134.6 (CH, C4'), 135.0 (CH, C8), 138.8 (C), 141.0 (C), 145.8 (C), 148.8 (CH, C2'), 151.9 (CH, C6'), 152.3 (C), 160.8 (C, C2). Anal. Calcd for $C_{18}H_{15}N_5O_2$ (333.35): C, 64.86; H, 4.54; N, 21.01. Found: C, 64.63; H, 4.49; N, 20.77%.

**8-(4-Benzylpiperazino)-2-(3-pyridyl)oxazolo[5,4-*f*]quinoxaline (10bc)** was synthesized according to the general procedure 7B from **12b** (see general procedure 6A) by using 1-benzylpiperazine (019 g). It was obtained (eluent: $CH_2Cl_2$-MeOH 95:5; $R_f$ = 0.29) in 76% yield (0.28 g; 65% overall yield) as a pale yellow solid: mp 178-180 °C; IR (ATR): 1003, 1015, 1057, 1101, 1129, 1207, 1237, 1257, 1297, 1330, 1368, 1394, 1414, 1425, 1452, 1544, 1556, 1573, 1606, 2779, 2819, 2863, 2944, 3028 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 2.67 (t, 4H, *J* = 4.8 Hz, $CH_2$), 3.62 (s, 2H, $CH_2$), 3.94 (t, 4H, *J* = 4.8 Hz, $CH_2$), 7.28-7.39 (m, 5H, Ph), 7.48 (dd, 1H, *J* = 8.0 and 4.9 Hz, H5'), 7.75 (d, 1H, *J* = 8.8 Hz, H4 or H5), 7.88 (d, 1H, *J* = 8.8 Hz, H4 or H5), 8.59 (s, 1H, H7), 8.61 (dt, 1H, *J* = 8.0 and 1.8 Hz, H4'), 8.77 (dd, 1H, *J* = 4.8 and 1.5 Hz, H6'), 9.58 (d, 1H, *J* = 1.5 Hz, H2'); $^{13}$C NMR ($CDCl_3$) δ 44.7 ($2CH_2$), 52.9 ($2CH_2$), 63.1 ($CH_2$), 116.3 (CH, C4 or C5), 123.7 (C), 123.8 (CH, C5'), 126.6 (CH, C4 or C5), 127.4 (CH), 128.5 (2CH), 129.3 (2CH), 129.9 (C), 134.6 (CH), 134.9 (CH), 135.3 (C), 137.7 (C), 142.8 (C), 143.8 (C), 149.0 (CH, C2' or C6'), 152.1 (C), 152.1 (CH, C6' or C2'), 161.9 (C, C2). Anal. Calcd for $C_{25}H_{22}N_6O$ (422.49): C, 71.07; H, 5.25; N, 19.89. Found: C, 71.16; H, 5.31; N, 19.78%.

**8-(4-(5-(1,3-Benzodioxolyl))methylpiperazino)-2-(3-pyridyl)oxazolo[5,4-*f*]quinoxaline (10bd)** was synthesized according to the general procedure 7B from **12b** (see general procedure 6A) by using 1-(5-(1,3-benzodioxolyl))methylpiperazine (0.24 g). It was obtained (eluent: $CH_2Cl_2$-MeOH 97:3; $R_f$ = 0.22) in 86% yield (0.35 g; 74% overall yield) as a pale yellow solid: mp > 260 °C; IR (ATR): 1006, 1034, 1094, 1209, 1231, 1251, 1416, 1443, 1487, 1558, 1573, 1606, 2772, 2805, 2852, 2984 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 2.63 (t, 4H, *J* = 4.9 Hz, $CH_2$), 3.52 (s, 2H, NC*H*$_2$Ph), 3.92 (t, 4H, *J* = 5.0 Hz, $CH_2$), 5.96 (s, 2H, $OCH_2O$), 6.73-6.81 (m, 2H, benzodioxolyl), 6.91 (br s, 1H, benzodioxolyl), 7.48 (dd, 1H, *J*

= 7.9 and 4.9 Hz, H5'), 7.74 (d, 1H, *J* = 8.8 Hz, H4 or H5), 7.87 (d, 1H, *J* = 8.8 Hz, H4 or H5), 8.58 (s, 1H, H7), 8.60 (dt, 1H, *J* = 8.1 and 1.9 Hz, H4'), 8.77 (d, 1H, *J* = 3.8 Hz, H6'), 9.57 (br s, 1H, H2'); $^{13}$C NMR ($CDCl_3$) δ 44.7 ($CH_2$), 52.7 ($CH_2$), 62.8 ($CH_2$), 101.1 ($CH_2$), 108.1 (CH), 109.6 (CH), 116.4 (CH, C4 or C5), 122.4 (CH), 123.7 (C), 123.8 (CH), 126.6 (CH, C4 or C5), 130.0 (C), 134.6 (CH), 134.9 (CH), 135.3 (C), 142.8 (C), 143.9 (C), 147.0 (C), 147.9 (C), 149.0 (CH, C2' or C6'), 152.1 (CH, C6' or C2'), 152.1 (C), 161.9 (C, C2), 1C not seen. Anal. Calcd for $C_{26}H_{22}N_6O_3$ (466.50): C, 66.94; H, 4.75; N, 18.02. Found: C, 67.02; H, 4.77; N, 17.95%.

**8-(4-*tert*-Butoxycarbonylpiperazino)-2-(3-pyridyl)oxazolo[5,4-*f*]quinoxaline (10be)** was synthesized according to the general procedure 7B from **12b** (see general procedure 6A) by using 1-(*tert*-butoxycarbonyl)piperazine (0.19 g). It was obtained (eluent: $CHCl_3$-MeOH 97:3; $R_f$ = 0.25) in 76% yield (0.28 g; 76% overall yield) as a pale yellow solid: mp > 260 °C; IR (ATR): 995, 1067, 1094, 1123, 1169, 1205, 1244, 1284, 1364, 1401, 1414, 1480, 1560, 1575, 1684, 2856, 2977 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 1.48 (s, 9H, Me), 3.63 (t, 4H, *J* = 5.1 Hz, $CH_2$), 3.86 (t, 4H, *J* = 5.0 Hz, $CH_2$), 7.44 (dd, 1H, *J* = 5.9 and 5.1 Hz, H5'), 7.71 (d, 1H, *J* = 8.8 Hz, H4 or H5), 7.83 (d, 1H, *J* = 8.8 Hz, H4 or H5), 8.54 (s, 1H, H7), 8.55 (d, 1H, *J* = 5.1 Hz, H4'), 8.74 (br s, 1H, H6'), 9.53 (br s, 1H, H2'); $^1$H NMR ($(CD_3)_2SO$) δ 3.58 (t, 4H, *J* = 5.2 Hz, $CH_2$), 3.91 (t, 4H, *J* = 5.2 Hz, $CH_2$), 7.67 (dd, 1H, *J* = 7.8 and 4.9 Hz, H5'), 7.79 (d, 1H, *J* = 8.7 Hz), 7.87 (d, 1H, *J* = 8.7 Hz), 8.58 (d, 1H, *J* = 8.0 Hz, H4'), 8.82 (dd, 1H, *J* = 4.9 and 1.4 Hz, H6'), 8.82 (s, 1H, H7), 9.41 (d, 1H, *J* = 1.3 Hz, H2'); $^{13}$C NMR ($CDCl_3$) δ 28.5 ($3CH_3$), 43.3 ($2CH_2$), 44.5 ($2CH_2$), 116.7 (CH, C4 or C5), 123.7 (br, CH, C5'), 126.5 (CH, C4 or C5), 129.6 (C), 134.4 (CH), 134.8 (CH), 135.4 (C), 142.8 (C), 143.7 (C), 148.9 (CH, C2' or C6'), 151.9 (C), 152.1 (CH, C6' or C2'), 154.7 (C), 161.9 (C, C=O); $^{13}$C NMR ($(CD_3)_2SO$) δ 27.7 ($3CH_3$), 42.6 ($2CH_2$), 43.5 ($2CH_2$), 78.8 (C, *C*$Me_3$), 115.3 (CH), 122.6 (C), 123.8 (CH, C5'), 125.7 (CH), 128.7 (C), 134.2 (CH, C4'), 134.3 (C), 135.3 (CH), 141.7 (C), 142.9 (C), 147.6 (CH, C2'), 151.4 (C), 151.8 (CH), 153.7 (C), 161.0 (C, C=O). Anal. Calcd for $C_{23}H_{24}N_6O_3$ (432.48): C, 63.88; H, 5.59; N, 19.43. Found: C, 63.84; H, 5.68; N, 19.39%.

**8-(Piperazino)-2-(3-pyridyl)oxazolo[5,4-*f*]quinoxaline (10bf)** was synthesized from **10be** as follows. To a solution of **10be** (prepared as described above from 1.0 mmol of **7**) in methanol (5 mL) was added 12 M aqueous hydrochloric acid (2 mL). The mixture was stirred for 3 h at room temperature. At 0 °C, aqueous 4 M sodium hydroxide was added until neutralization. Extraction using chloroform (3 x 20 mL), drying the organic layer over sodium sulfate and removal of the solvent under reduced pressure led to the crude product. Purification by column chromatography over silica gel (eluent: $CHCl_3$-MeOH-$NH_4OH$ 78:20:2; $R_f$ = 0.50) gave **10bf** in 44% yield (0.15 g) as a white solid: mp 236-238 °C; IR (ATR): 1015, 1063, 1094, 1209, 1233, 1260, 1300, 1412, 1427, 1498, 1542, 1556, 1573, 1604, 2845, 2918, 2944, 3327 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 3.08 (t, 4H, *J* = 5.0 Hz, $CH_2$), 3.89 (t, 4H, *J* = 5.0 Hz, $CH_2$), 7.48 (dd, 1H, *J* = 7.6 and 4.9 Hz, H5'), 7.74 (d, 1H, *J* = 8.8 Hz, H4 or H5), 7.87 (d, 1H, *J* = 8.8 Hz, H4 or H5), 8.59 (s, 1H, H7), 8.61 (dt, 1H, *J* = 8.0 and 1.9 Hz, H4'), 8.77 (dd, 1H, *J* = 4.8 and 1.6 Hz, H6'), 9.57 (d, 1H, *J* = 1.6 Hz, H2'); $^{13}C$ NMR ($CDCl_3$) δ 45.0 ($4CH_2$), 115.3 (CH, C4 or C5), 123.7 (C), 123.7 (CH, C5'), 126.8 (CH, C4 or C5), 130.7 (C), 134.9 (CH), 135.1 (C), 135.4 (CH), 142.6 (C), 143.8 (C), 148.9 (CH, C2' or C6'), 150.5 (C), 152.0 (CH, C6' or C2'), 161.7 (C, C2). Anal. Calcd for $C_{18}H_{16}N_6O$ (332.37): C, 65.05; H, 4.85; N, 25.29. Found: C, 65.15; H, 4.94; N, 25.12%.

**8-(Piperidino)-2-(3-pyridyl)oxazolo[5,4-*f*]quinoxaline (10bg)** was synthesized according to the general procedure 7B from **12b** (see general procedure 6A) by using piperidine (0.11 mL). It was obtained (eluent: $CHCl_3$-MeOH 99:1; $R_f$ = 0.15) in 78% yield (0.22 g; 67% overall yield) as an orange solid: mp 262-264 °C; IR (ATR): 1019, 1057, 1068, 1094, 1136, 1211, 1226, 1255, 1269, 1295, 1374, 1414, 1430, 1480, 1496, 1558, 1575, 2849, 2933 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.75 (br s, 6H, $CH_2$), 3.86 (br s, 4H, $CH_2$), 7.46 (dd, 1H, *J* = 8.0 and 4.8 Hz, H5'), 7.69 (d, 1H, *J* = 8.7 Hz, H4 or H5), 7.83 (d, 1H, *J* = 8.7 Hz, H4 or H5), 8.57 (s, 1H, H7), 8.60 (dt, 1H, *J* = 8.0 and 2.0 Hz, H4'), 8.75 (dd, 1H, *J* = 4.8 and 1.7 Hz, H6'), 9.56 (d, 1H, *J* = 2.3 Hz, H2'); $^{13}C$ NMR ($CDCl_3$) δ 24.7 ($CH_2$), 25.8 ($2CH_2$), 45.8 ($2CH_2$), 115.8 (CH, C4 or C5), 123.7 (CH, C5'), 123.7 (C), 126.5 (CH, C4 or C5), 130.1 (C), 134.8

(CH, C4'), 134.8 (CH, C7), 134.9 (C), 142.7 (C), 143.8 (C), 149.0 (CH, C2' or C6'), 152.0 (CH, C6' or C2'), 152.2 (C), 161.8 (C, C2). Anal. Calcd for $C_{19}H_{17}N_5O$ (331.38): C, 68.87; H, 5.17; N, 21.13. Found: C, 68.69; H, 4.81; N, 20.92%.

**8-(4-Morpholinopiperidino)-2-(3-pyridyl)oxazolo[5,4-*f*]quinoxaline (10bh)** was synthesized according to the general procedure 7B from **12b** (see general procedure 6A) by using 4-morpholinopiperidine (0.19 g). It was obtained (eluent: $CH_2Cl_2$-MeOH 90:10; $R_f$ = 0.41) in 49% yield (0.18 g; 42% overall yield) as a yellow solid: mp > 260 °C; IR (ATR): 1017, 1057, 1089, 1120, 1138, 1206, 1237, 1266, 1366, 1401, 1430, 1487, 1558, 1575, 2819, 2845, 2955 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.65 (ddd, 2H, *J* = 15.6, 12.3 and 3.8 Hz, $CH_2$), 2.08 (d, 2H, *J* = 11.6 Hz, $CH_2$), 2.53-2.61 (m, 1H, H4"), 2.61 (t, 4H, *J* = 4.3 Hz, $CH_2$), 3.15 (t, 2H, *J* = 11.6 Hz, $CH_2$), 3.74 (t, 4H, *J* = 4.4 Hz, $CH_2$), 4.72 (d, 2H, *J* = 13.5 Hz, $CH_2$), 7.49 (dd, 1H, *J* = 7.9, 4.9 Hz, H5'), 7.74 (d, 1H, *J* = 8.8 Hz, H4 or H5), 7.87 (d, 1H, *J* = 8.8 Hz, H4 or H5), 8.61 (dt, 1H, *J* = 7.8 and 1.8 Hz, H4'), 8.62 (s, 1H, H7), 8.78 (d, 1H, *J* = 3.7 Hz, H6'), 9.59 (br s, 1H, H2'); $^{13}C$ NMR ($CDCl_3$) δ 28.2 ($CH_2$), 44.2 ($CH_2$), 49.9 ($CH_2$), 61.9 (CH, C4"), 67.3 ($CH_2$), 116.2 (CH, C4 or C5), 123.7 (C), 123.8 (CH, C5'), 126.5 (CH, C4 or C5), 130.0 (C), 134.7 (CH), 134.9 (CH), 135.1 (C), 142.8 (C), 143.8 (C), 148.9 (CH, C2' or C6'), 152.0 (C), 152.1 (CH, C6' or C2'), 161.8 (C, C2). Anal. Calcd for $C_{23}H_{24}N_6O_2$ (416.49): C, 66.33; H, 5.81; N, 20.18. Found: C, 66.38; H, 5.87; N, 20.04%.

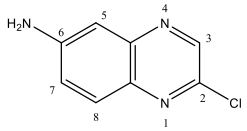
**2-(3-Pyridyl)-8-(thiomorpholino)oxazolo[5,4-*f*]quinoxaline (10bi)** was synthesized according to the general procedure 7B from **12b** (see general procedure 6A) by using thiomorpholine (0.11 mL). It was obtained (eluent: $CHCl_3$-MeOH 97:3; $R_f$ = 0.20) in 83% yield (0.25 g; 71% overall yield) as a pale yellow solid: mp > 260 °C; IR (ATR): 1015, 1059, 1094, 1193, 1258, 1410, 1496, 1542, 1558, 1573, 2852, 2962 $cm^{-1}$; $^1H$ NMR ($(CD_3)_2SO$) δ 2.80-2.82 (m, 4H, $CH_2$), 4.22-4.24 (m, 4H, $CH_2$), 7.66 (ddd, 1H, *J* = 7.95, 4.85 and 0.6 Hz, H5'), 7.77 (d, 1H, *J* = 8.7 Hz), 7.85 (d, 1H, *J* = 8.7 Hz), 8.57 (dt, 1H, *J* = 7.95 and 1.9 Hz, H4'), 8.80 (d, 1H, *J* = 4.85 and 1.7 Hz, H6'), 8.81 (s, 1H, H7), 9.40 (d, 1H, *J* = 1.6 Hz, H2'); $^{13}C$ NMR ($(CD_3)_2SO$) δ 25.7 ($2CH_2$), 46.5 ($2CH_2$), 115.2 (CH), 122.6 (C), 123.7 (CH, C5'),

125.6 (CH), 128.7 (C), 134.1 (C), 134.1 (CH, C4'), 135.2 (CH), 141.7 (C), 142.8 (C), 147.5 (CH, C2'), 151.1 (C), 151.7 (CH), 160.9 (C). Anal. Calcd for $C_{18}H_{15}N_5OS$ (349.41): C, 61.87; H, 4.33; N, 20.04. Found: C, 61.91; H, 4.34; N, 20.00%.

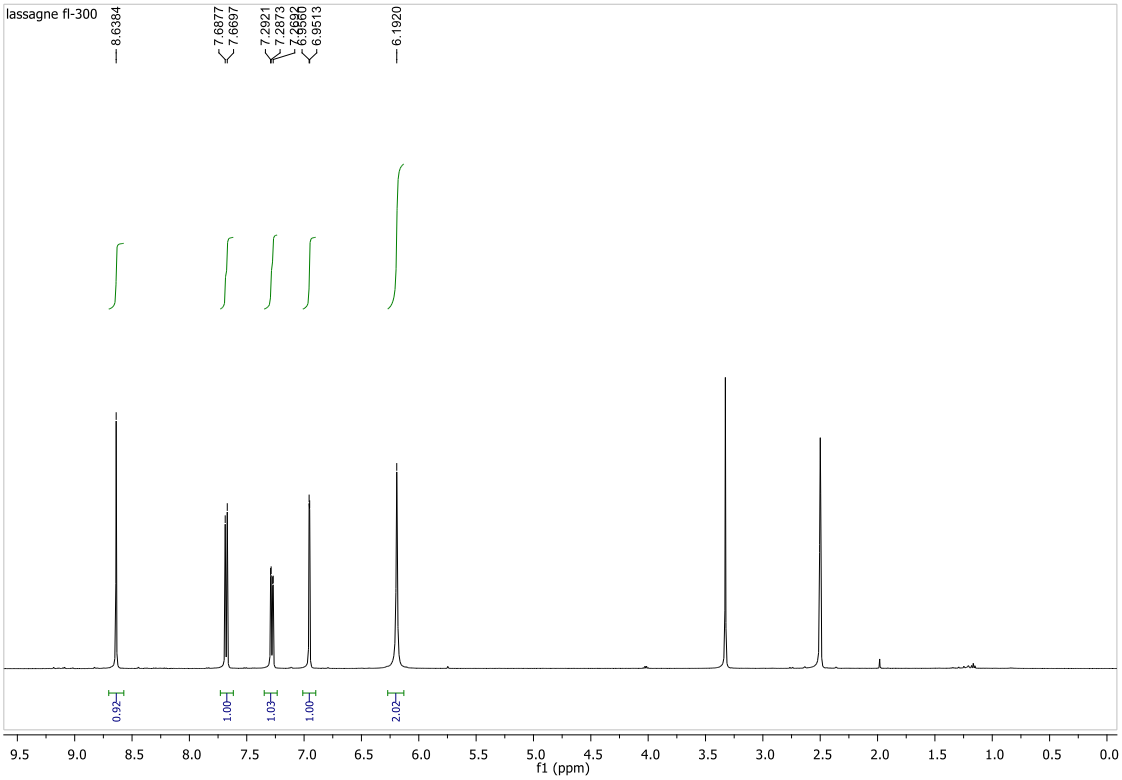
**2-(1-Ethyl-5-imidazolyl)-8-(thiomorpholino)oxazolo[5,4-*f*]quinoxaline (10ci)** was synthesized according to the general procedure 7B from **12c** (see general procedure 7A) by using thiomorpholine (0.11 mL). It was obtained (eluent: $CH_2Cl_2$-MeOH 97.5:2.5; $R_f$ = 0.25) in 67% yield (0.21 g; 55% overall yield) as a beige solid: mp 220-222 °C; IR (ATR): 659, 819, 867, 907, 959, 1061, 1092, 1130, 1192, 1208, 1234, 1250, 1306, 1314, 1364, 1410, 1428, 1498, 1547, 1573, 1623, 2893, 2950, 2994, 3082 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.56 (t, 3H, $J$ = 7.1 Hz, $CH_3$), 2.80 (t, 4H, $J$ = 5.0 Hz, $CH_2$), 4.23 (t, 4H, $J$ = 5.0 Hz, $CH_2$), 4.64 (q, 2H, $J$ = 7.2 Hz, $CH_2$), 7.68 (d, 1H, $J$ = 8.7 Hz), 7.76 (br s, 1H, H2' or H4'), 7.83 (d, 1H, $J$ = 8.7 Hz), 8.09 (br s, 1H, H2' or H4'), 8.53 (s, 1H, H7); $^{13}C$ NMR ($CDCl_3$) δ 16.6 ($CH_3$), 27.0 ($2CH_2$), 42.4 ($CH_2$), 47.7 ($2CH_2$), 116.4 (CH, C4 or C5), 120.9 (C), 126.2 (CH, C4 or C5), 129.6 (C), 134.2 (CH, C7), 135.0 (C), 135.4 (CH), 141.0 (CH), 142.4 (C), 143.0 (C), 151.6 (C), 156.9 (C). Anal. Calcd for $C_{18}H_{18}N_6OS$ (366.44): C, 59.00; H, 4.95; N, 22.93. Found: C, 58.84; H, 4.89; N, 22.56%.

**Crystal data for 10ci.** $C_{18}H_{18}N_6OS$, $M$ = 366.44, monoclinic, $P\,2_1/n$, $a$ = 15.2934(7), $b$ = 5.9374(3), $c$ = 19.2117(11) Å, $\beta$ = 101.042(2) °, $V$ = 1712.19(15) $Å^3$, $Z$ = 4, $d$ = 1.422 g $cm^{-3}$, $\mu$ = 0.210 $mm^{-1}$. A final refinement on $F^2$ with 3900 unique intensities and 236 parameters converged at $\omega R(F^2)$ = 0.0948 ($R(F)$ = 0.0384) for 3215 observed reflections with $I > 2\sigma(I)$. CCDC 1964834.

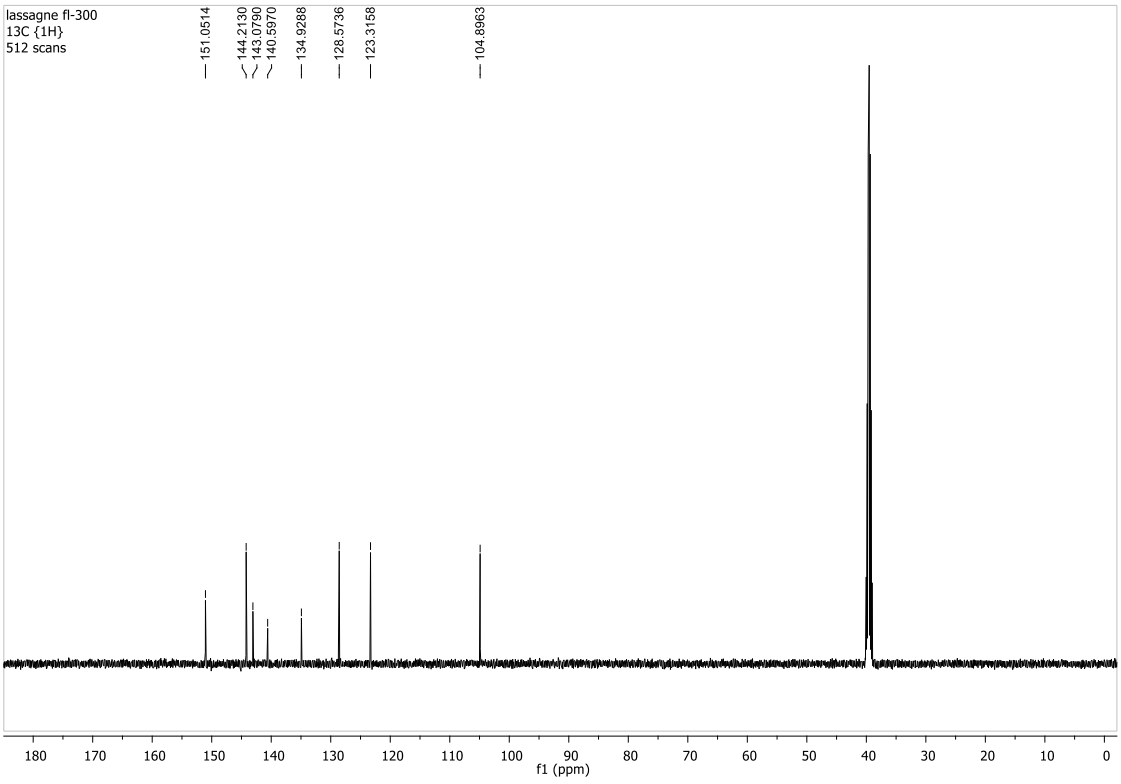
## 6-Amino-2-chloroquinoxaline (1)

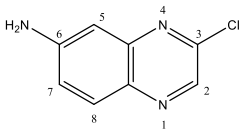



$^{1}$H NMR (500 MHz, $(CD_3)_2SO$)



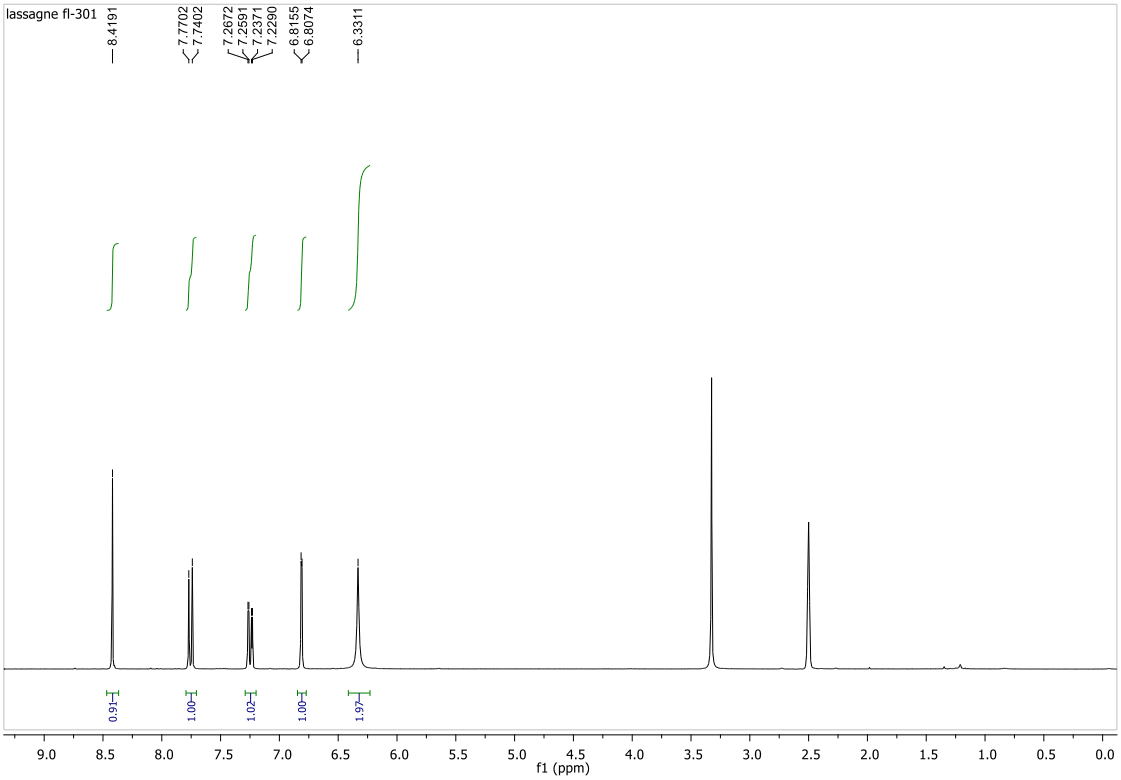

$^{13}$C NMR (126 MHz, $(CD_3)_2SO$)



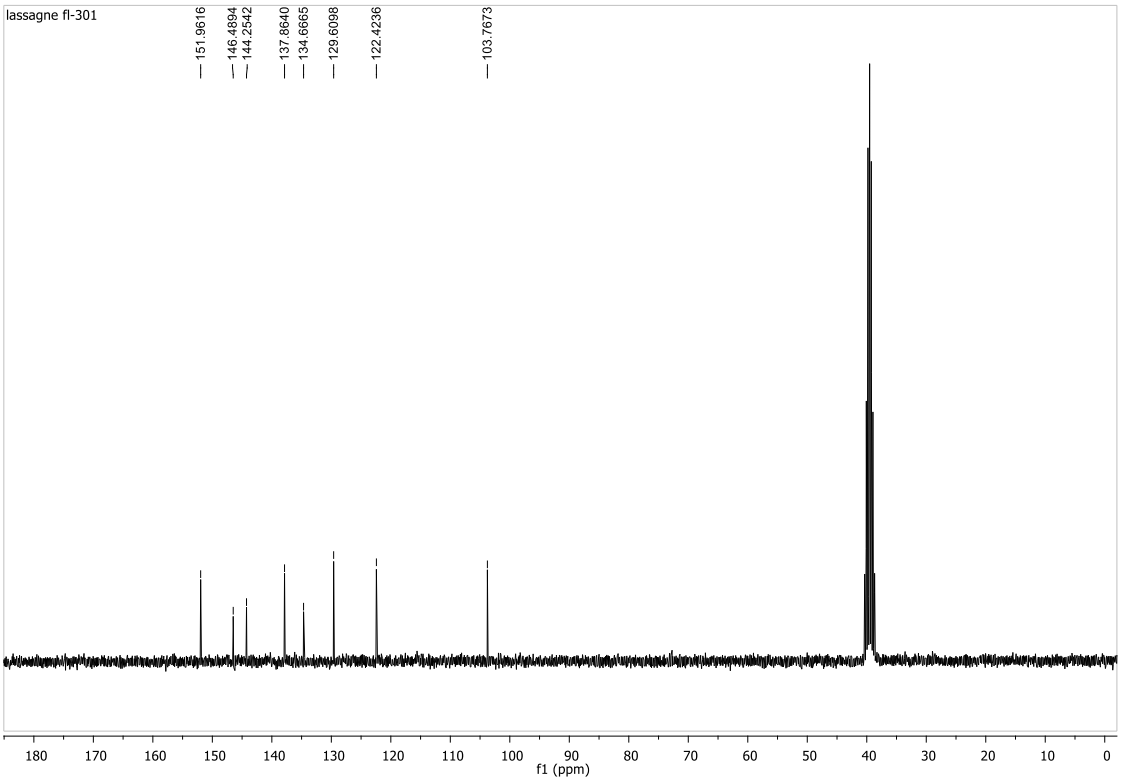



## 6-Amino-3-chloroquinoxaline (2)

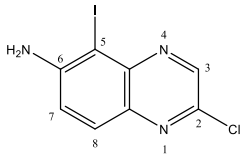
$^{1}$H NMR (300 MHz, $(CD_3)_2SO$)



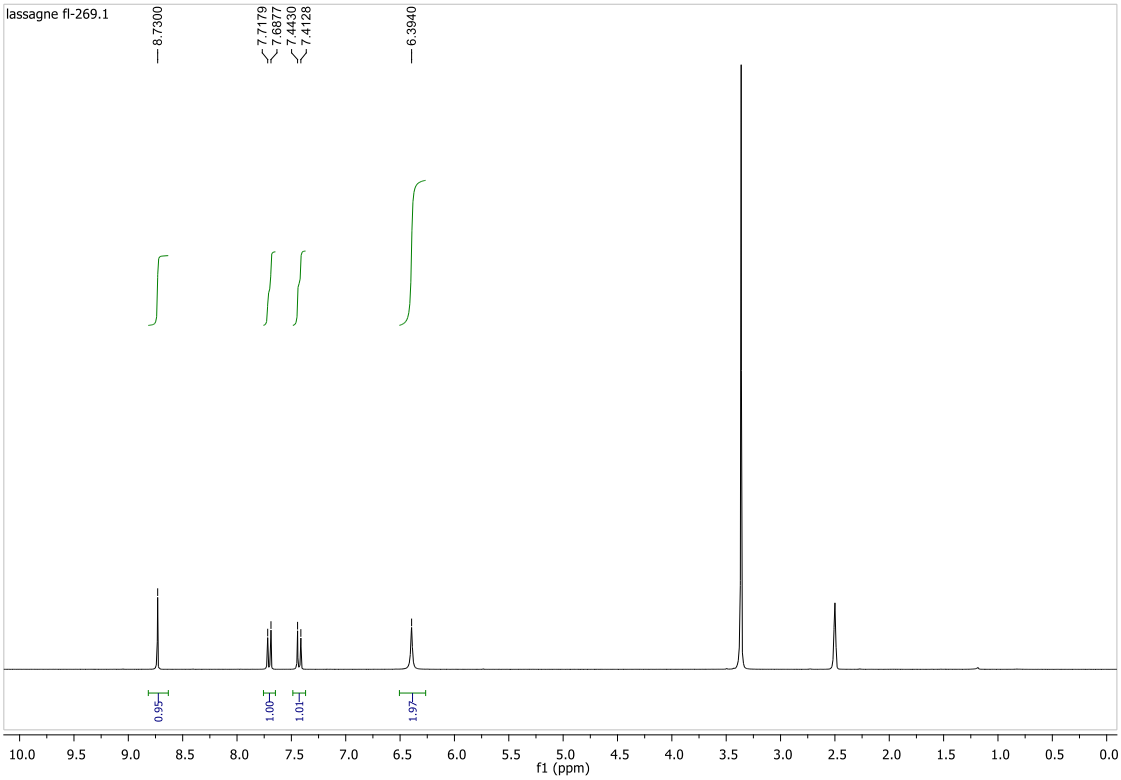

$^{13}$C NMR (75 MHz, $(CD_3)_2SO$)



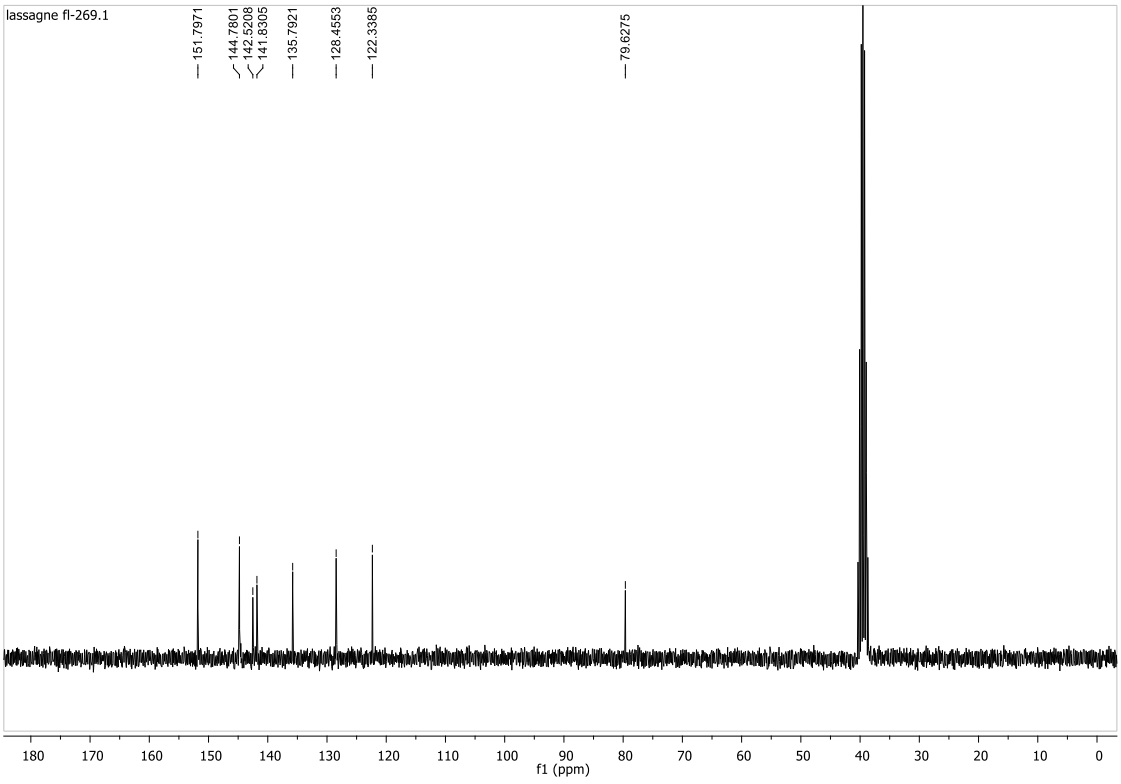
## 6-Amino-2-chloro-5-iodoquinoxaline (3)



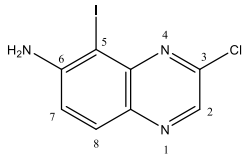

$^{1}$H NMR (300 MHz, $(CD_3)_2SO$)



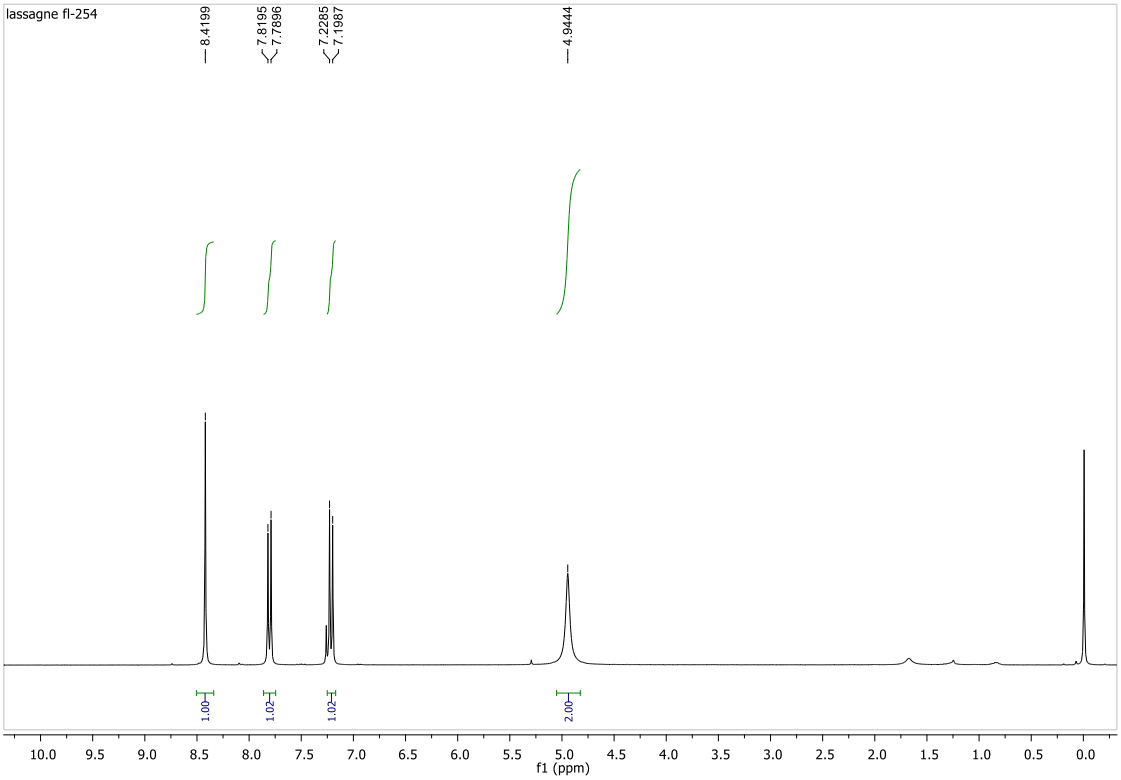

$^{13}$C NMR (75 MHz, $(CD_3)_2SO$)



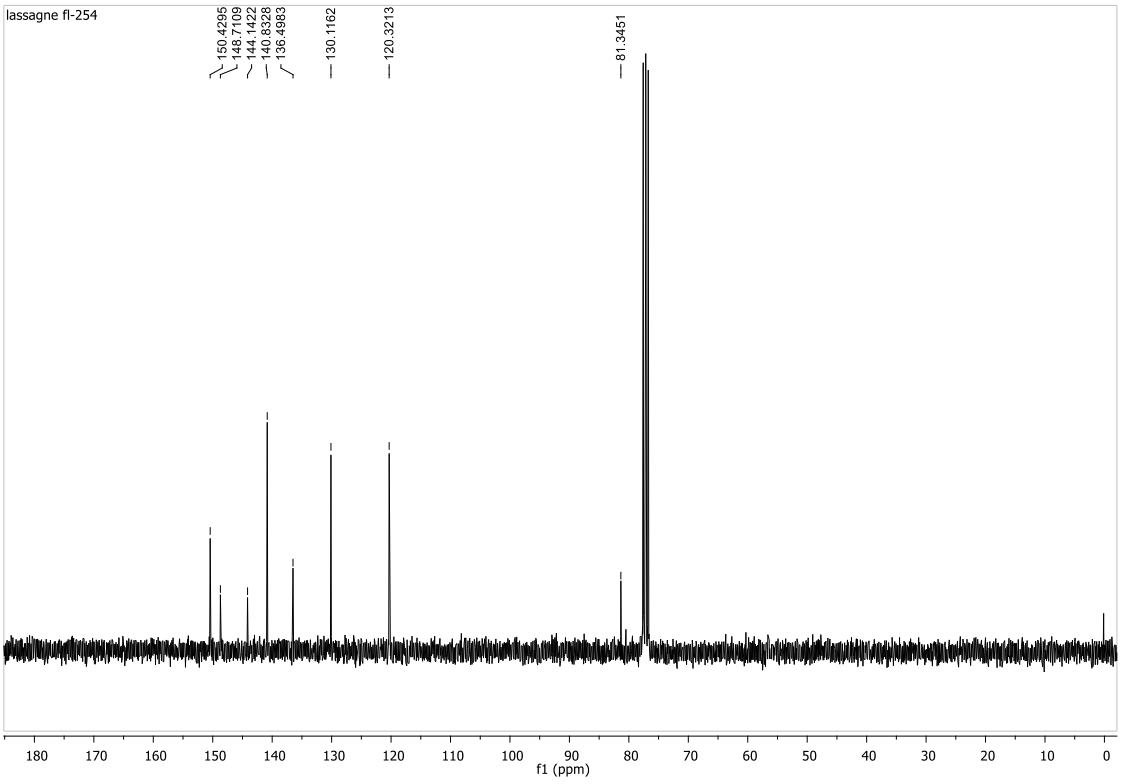
## 6-Amino-3-chloro-5-iodoquinoxaline (7)



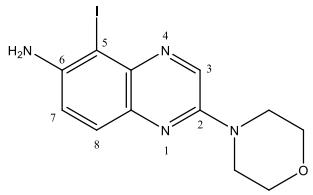

$^{1}H$ NMR (300 MHz, $CDCl_3$)



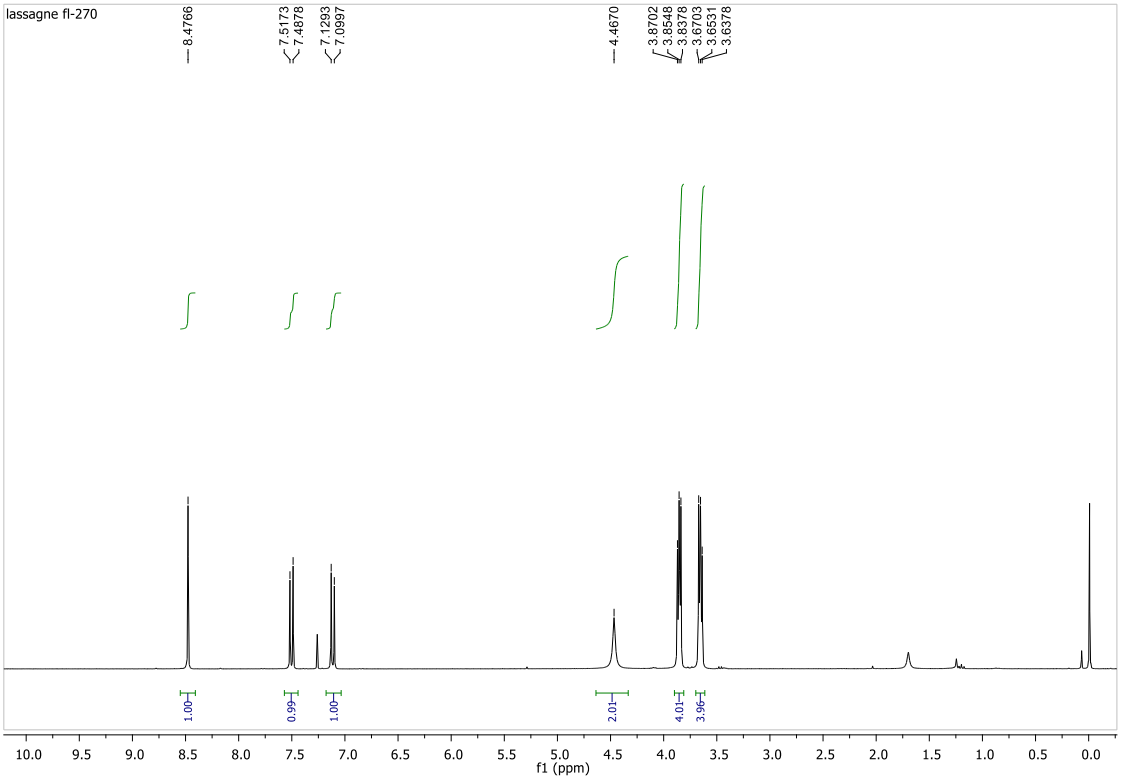

$^{13}C$ NMR (75 MHz, $CDCl_3$)



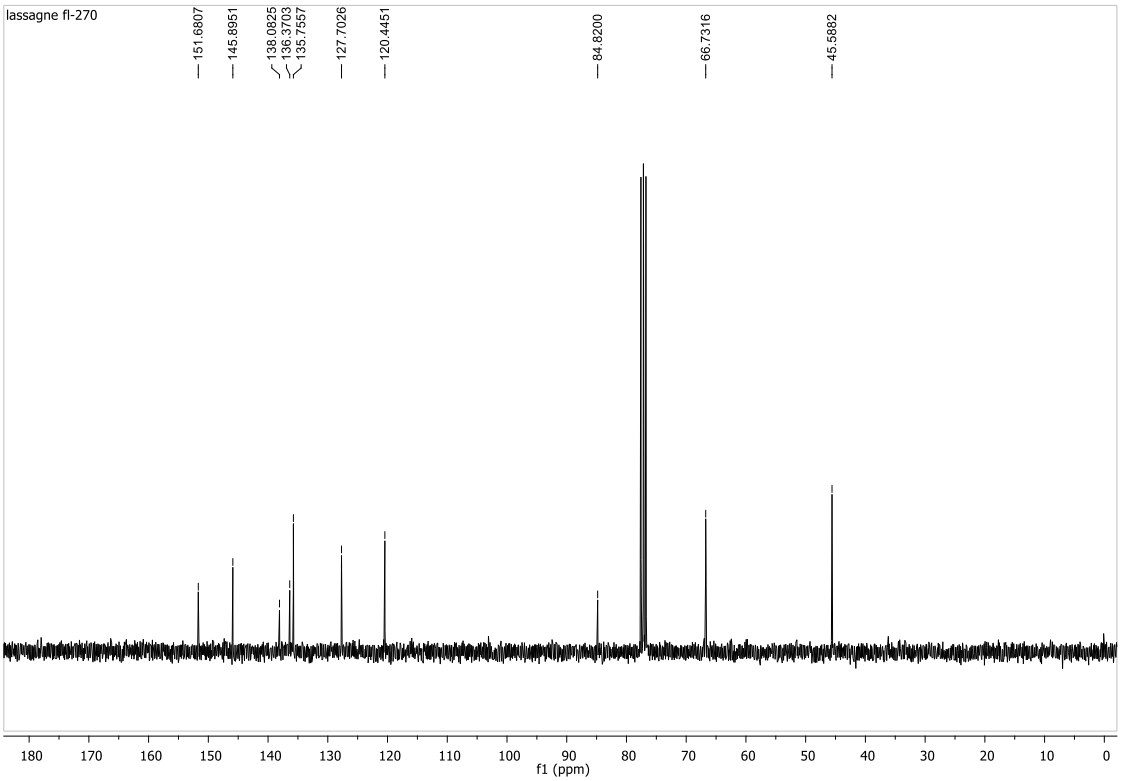
## 6-Amino-5-iodo-2-morpholinoquinoxaline (4a)



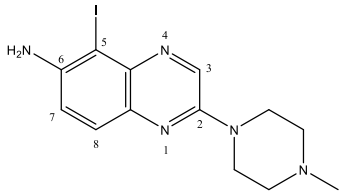
$^{1}$H NMR (300 MHz, $CDCl_3$)



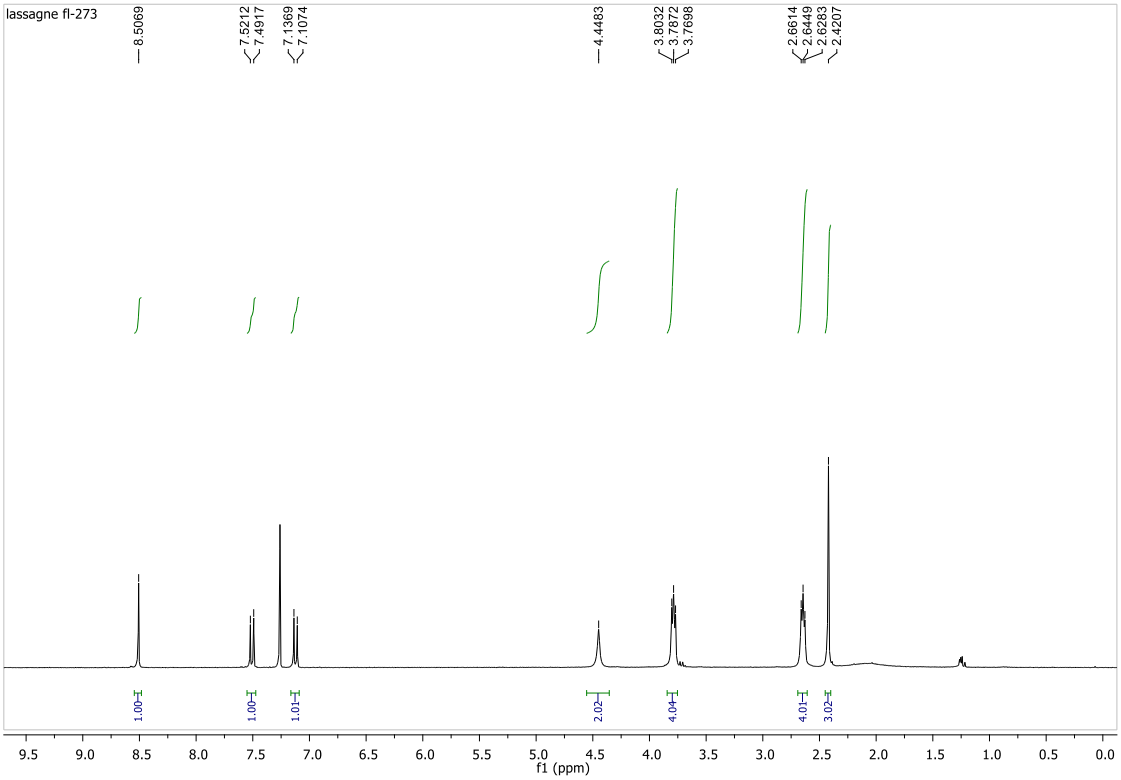

$^{13}$C NMR (75 MHz, $CDCl_3$)



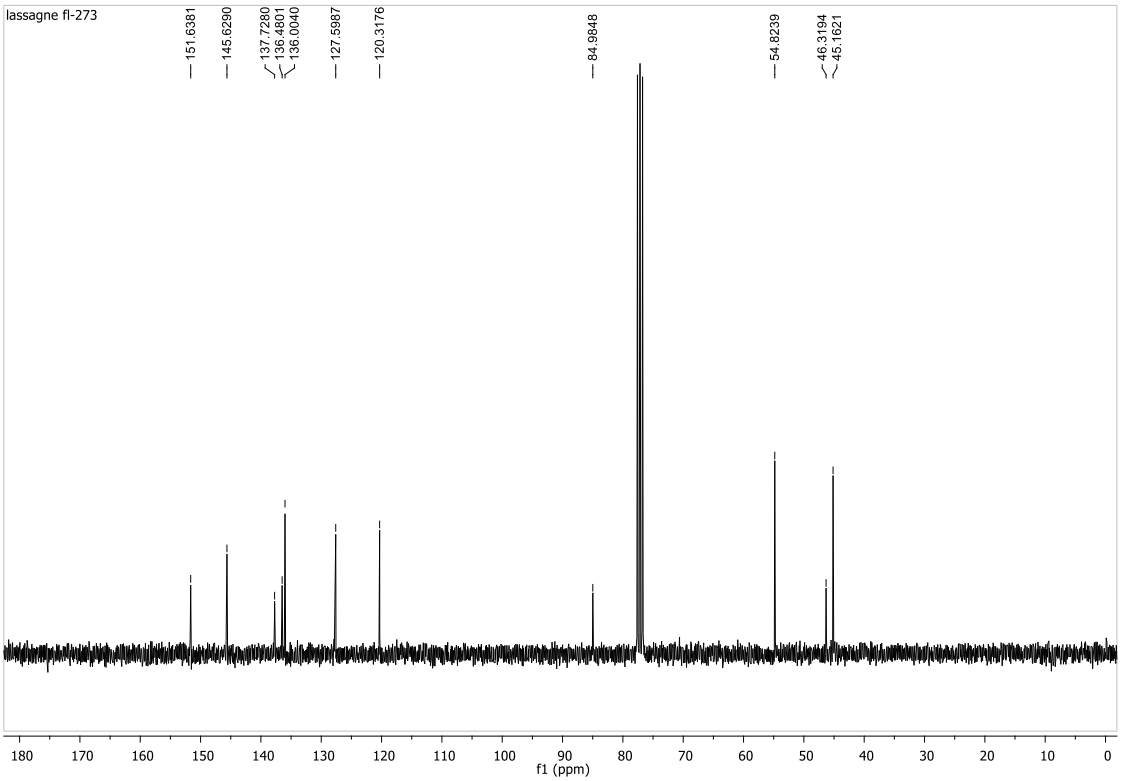
## 6-Amino-5-iodo-2-(*N'*-methylpiperazino)phenylquinoxaline (4b)



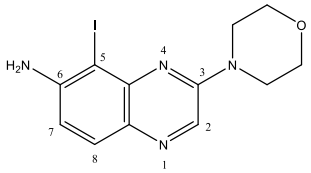
$^{1}$H NMR (300 MHz, $CDCl_3$)



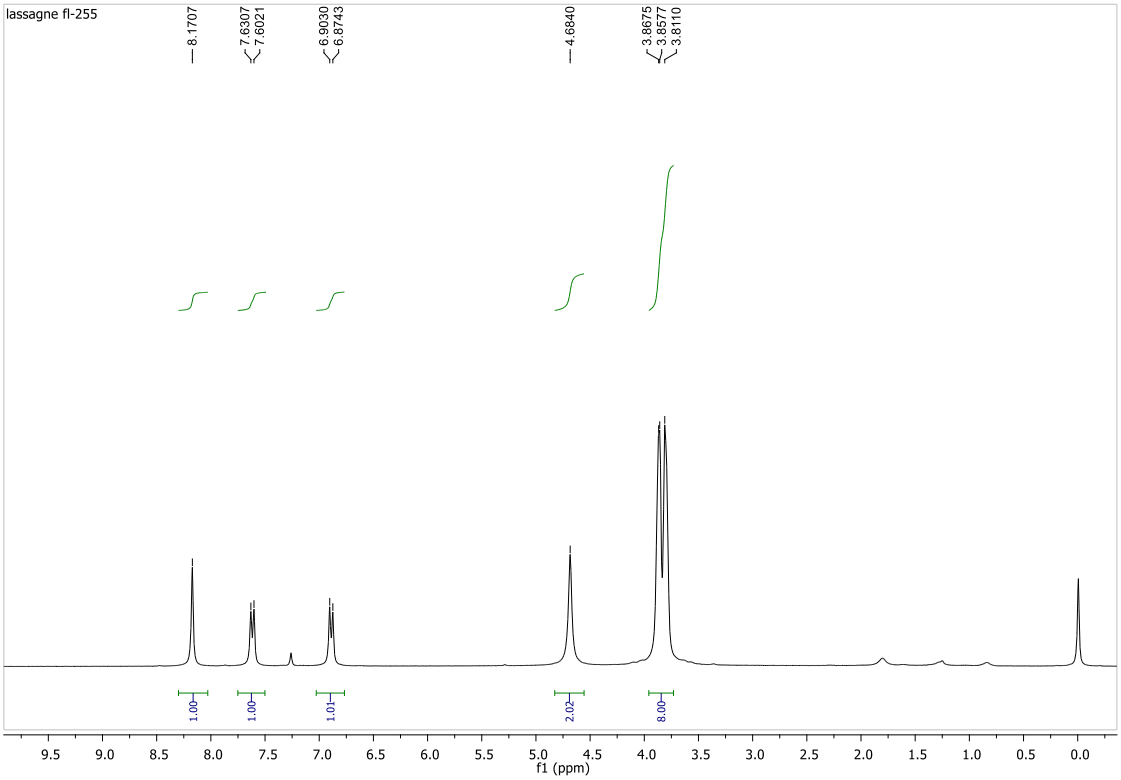

$^{13}$C NMR (75 MHz, $CDCl_3$)



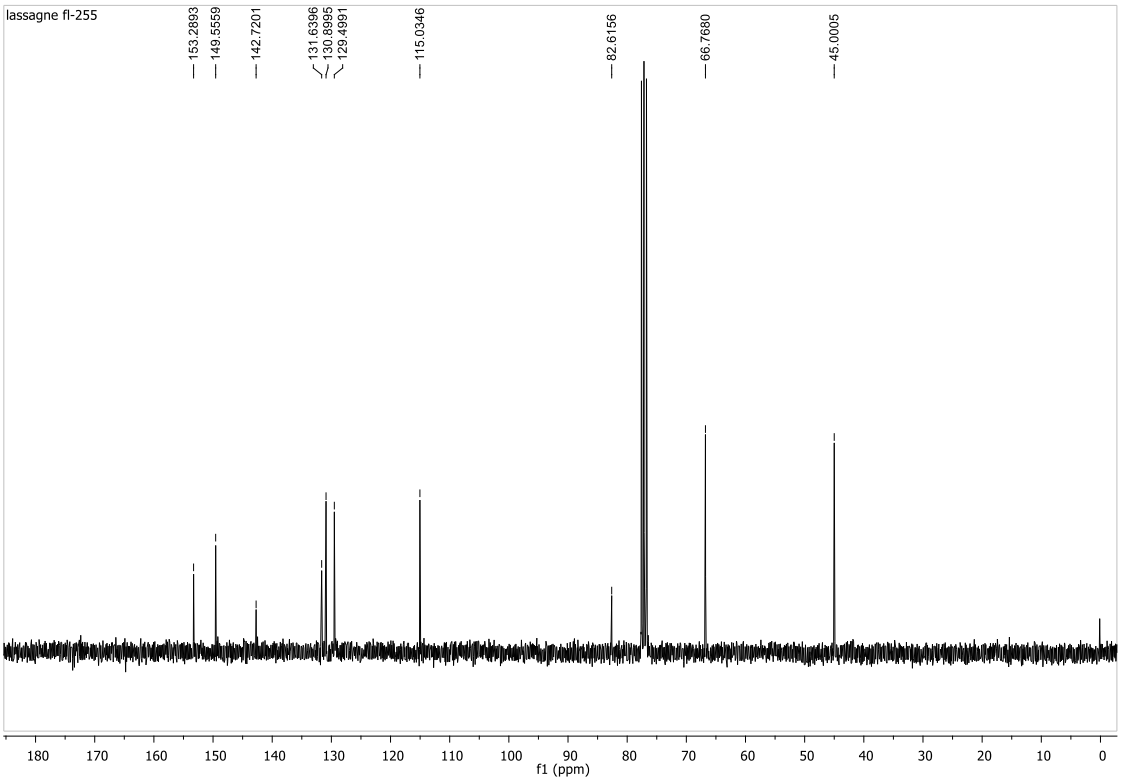
## 6-Amino-5-iodo-3-morpholinoquinoxaline (8a)



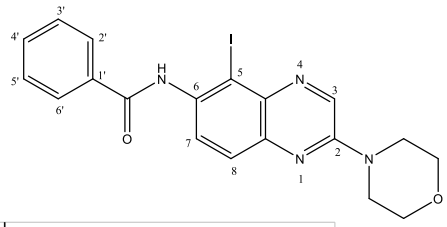

$^{1}$H NMR (300 MHz, $CDCl_3$)



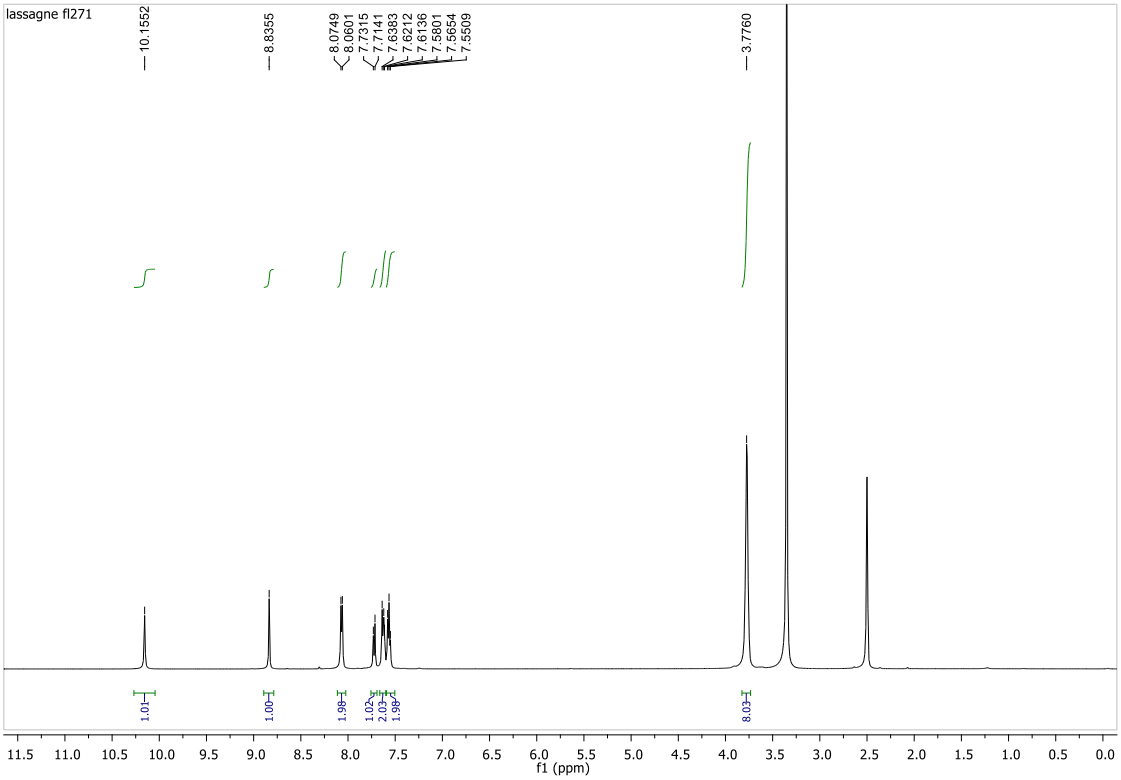

$^{13}$C NMR (75 MHz, $CDCl_3$)



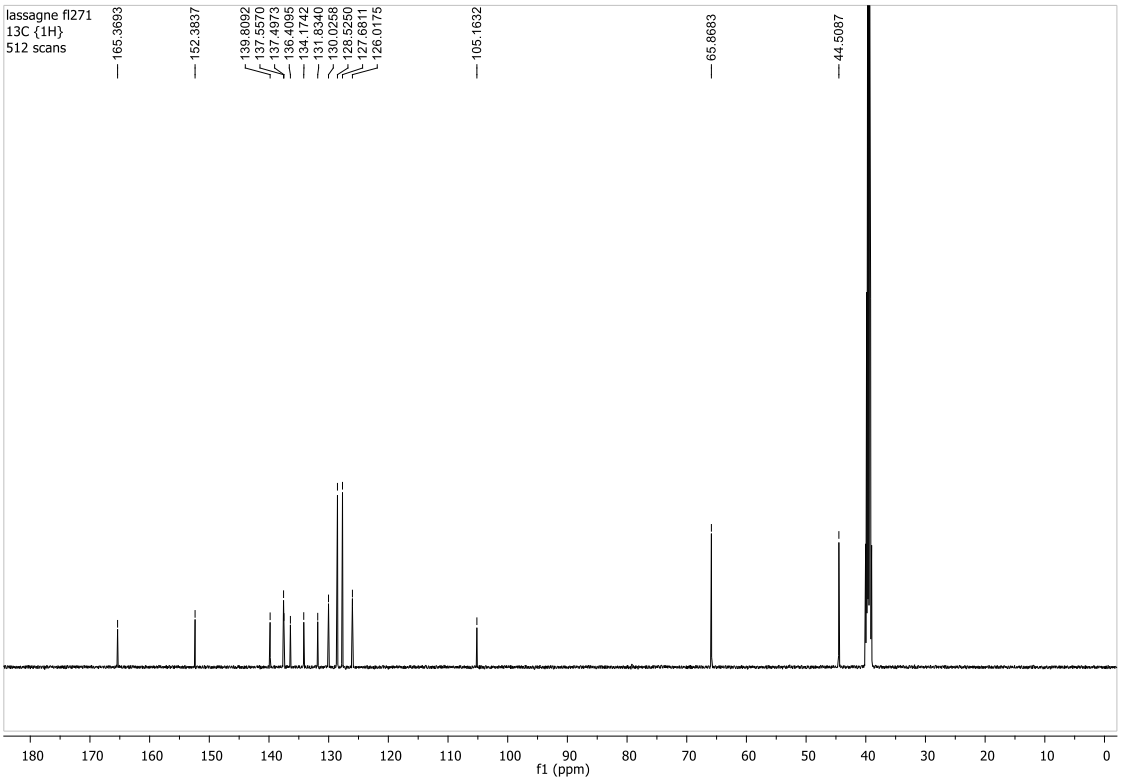
## 6-(Benzoylamino)-5-iodo-2-(morpholino)quinoxaline (5aa)



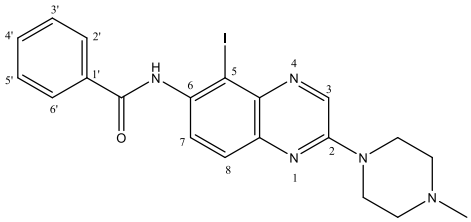
$^{1}$H NMR (500 MHz, $(CD_3)_2SO$)



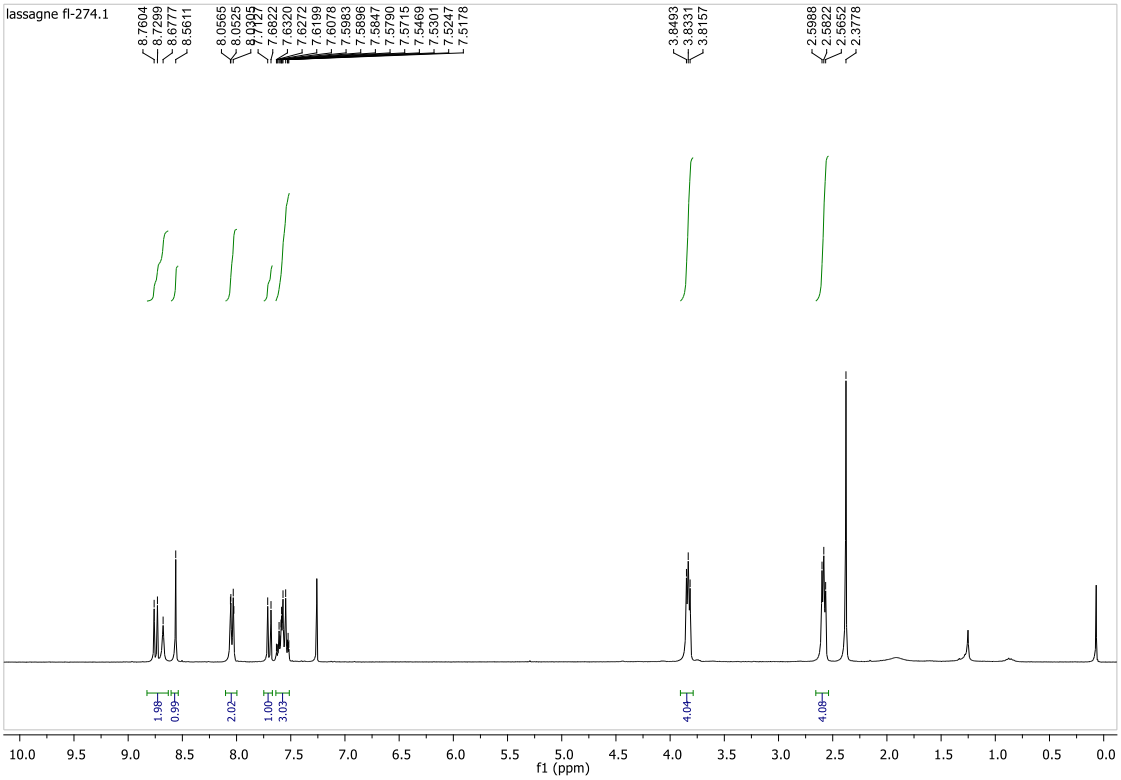

$^{13}$C NMR (126 MHz, $(CD_3)_2SO$)



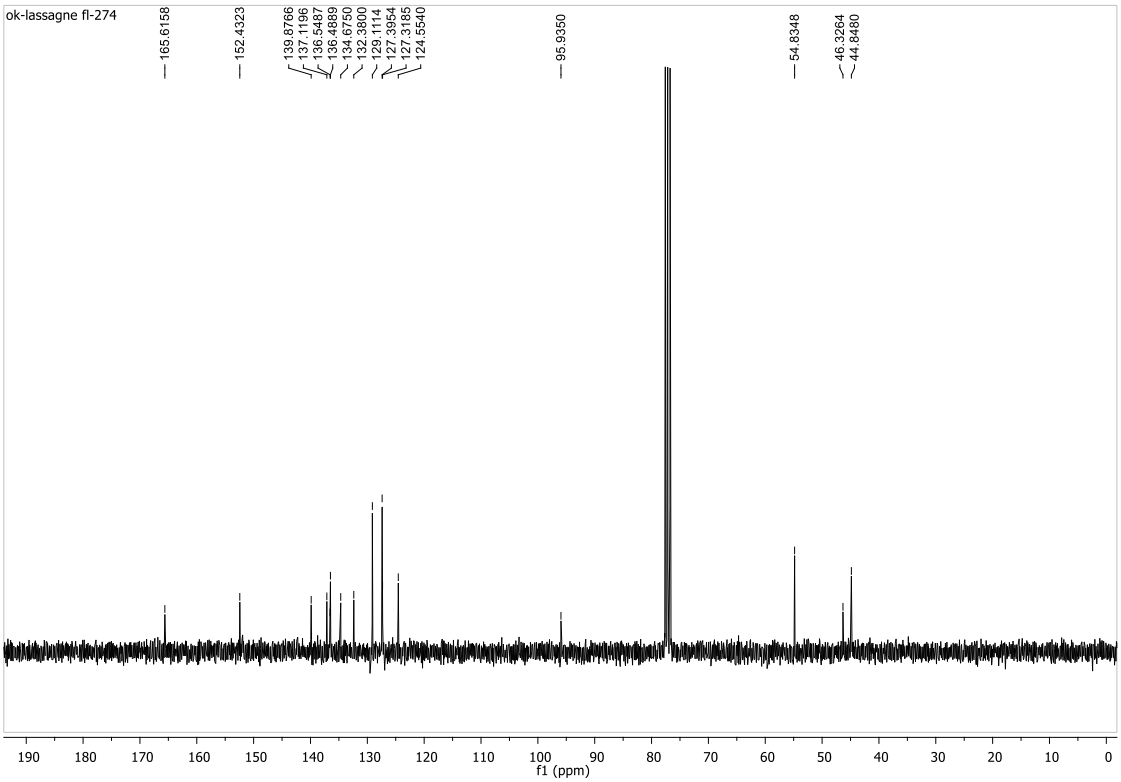
## 6-(Benzoylamino)-5-iodo-2-(4-methylpiperazino)quinoxaline (5ab)



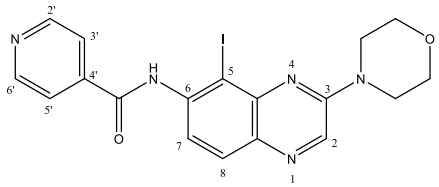
$^{1}$H NMR (300 MHz, $CDCl_3$)



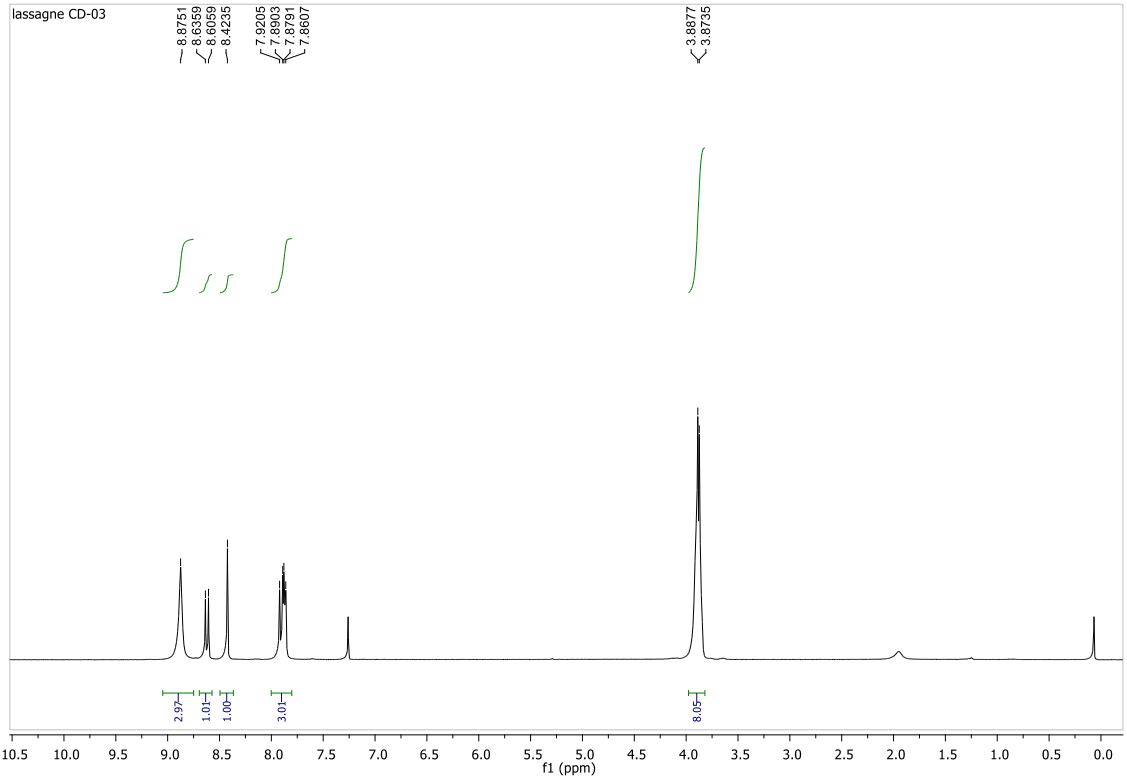

$^{13}$C NMR (75 MHz, $CDCl_3$)



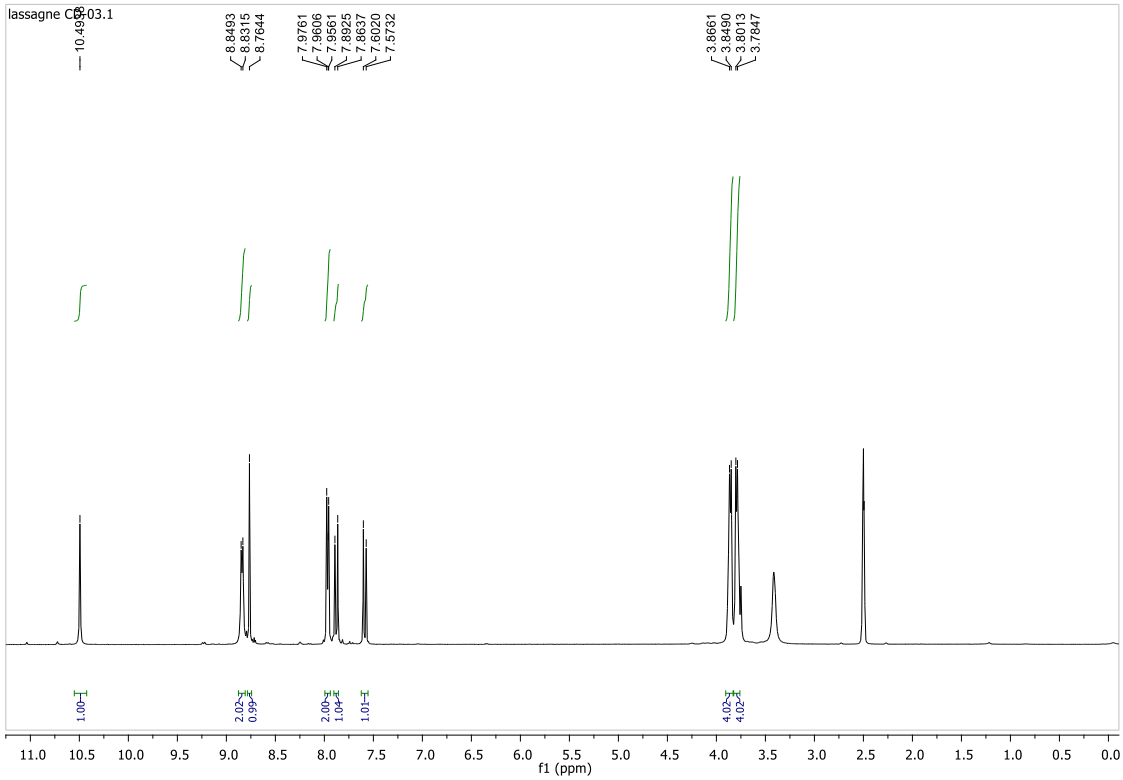
**5-Iodo-3-morpholino-6-(4-pyridoylamino)quinoxaline (9a)**



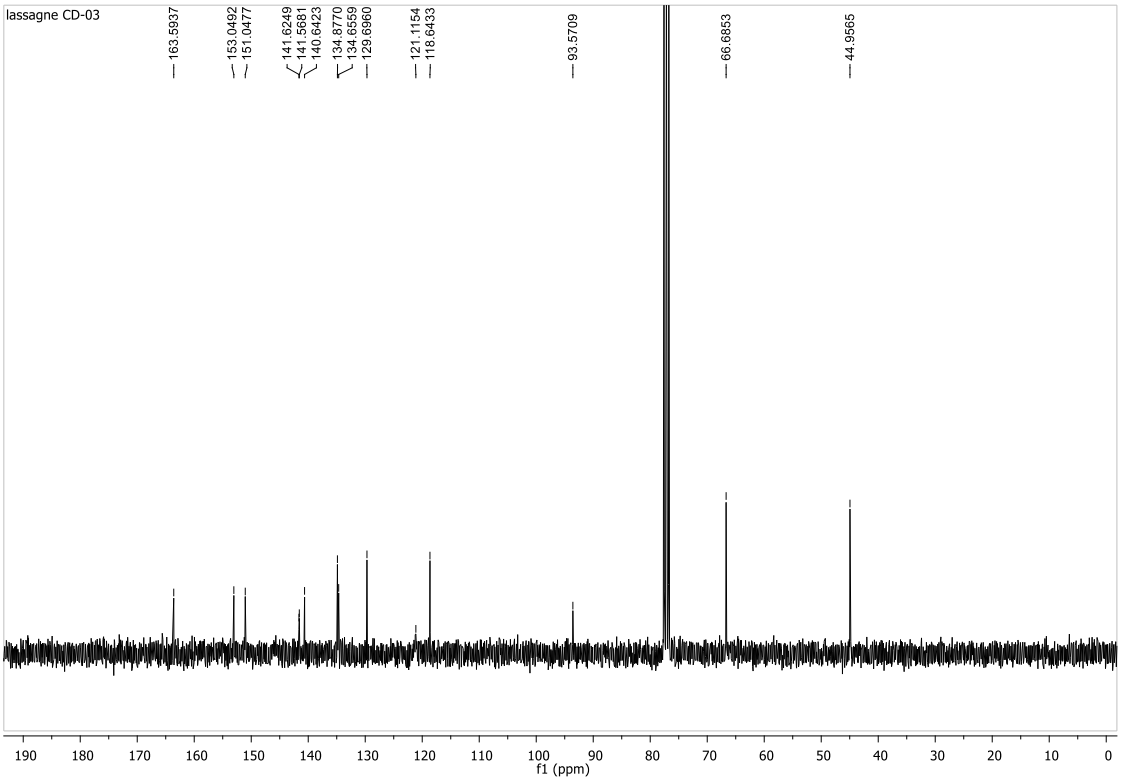
$^1$H NMR (300 MHz, $CDCl_3$)



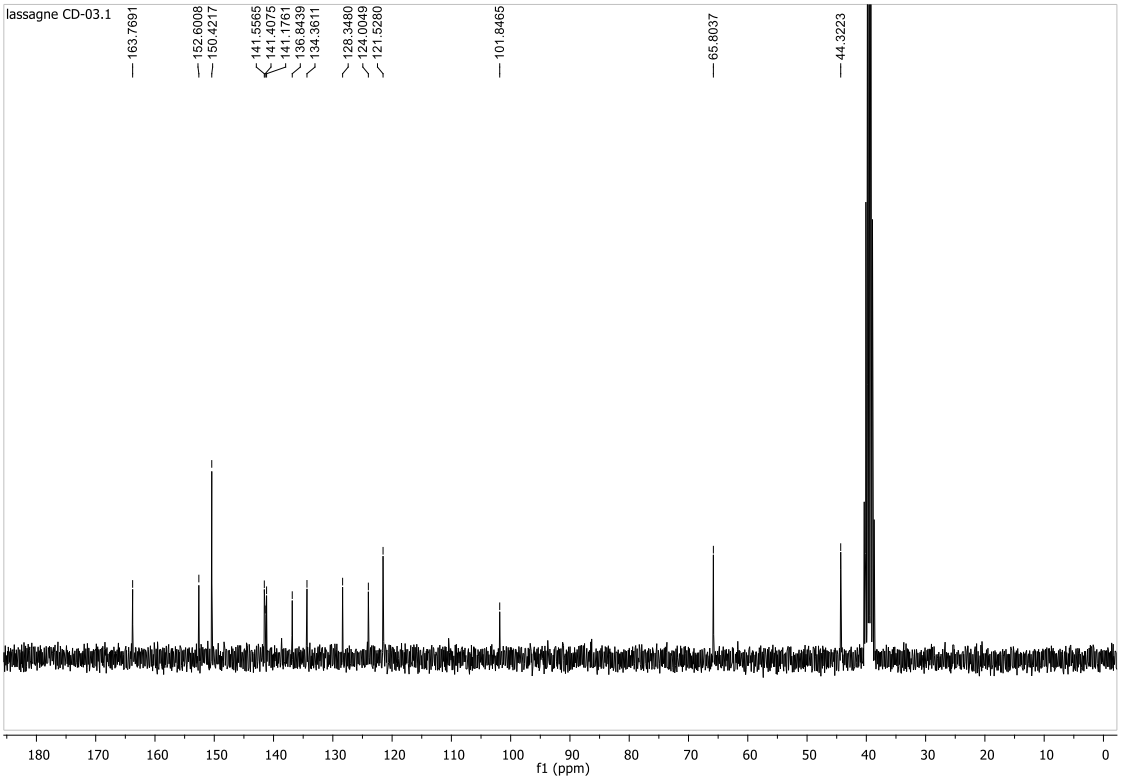

$^1$H NMR (300 MHz, $(CD_3)_2SO$)



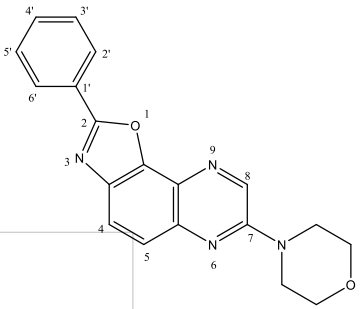
$^{13}C$ NMR (75 MHz, $CDCl_3$)



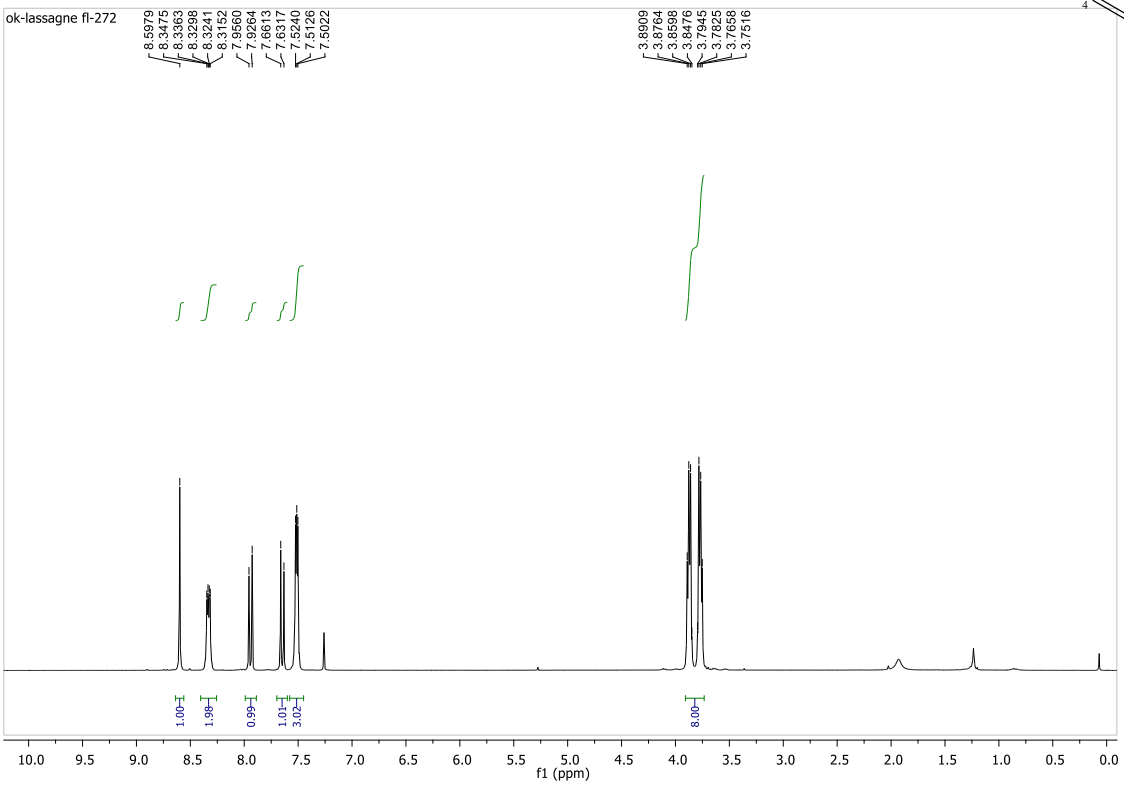

$^{13}C$ NMR (75 MHz, $(CD_3)_2SO$)



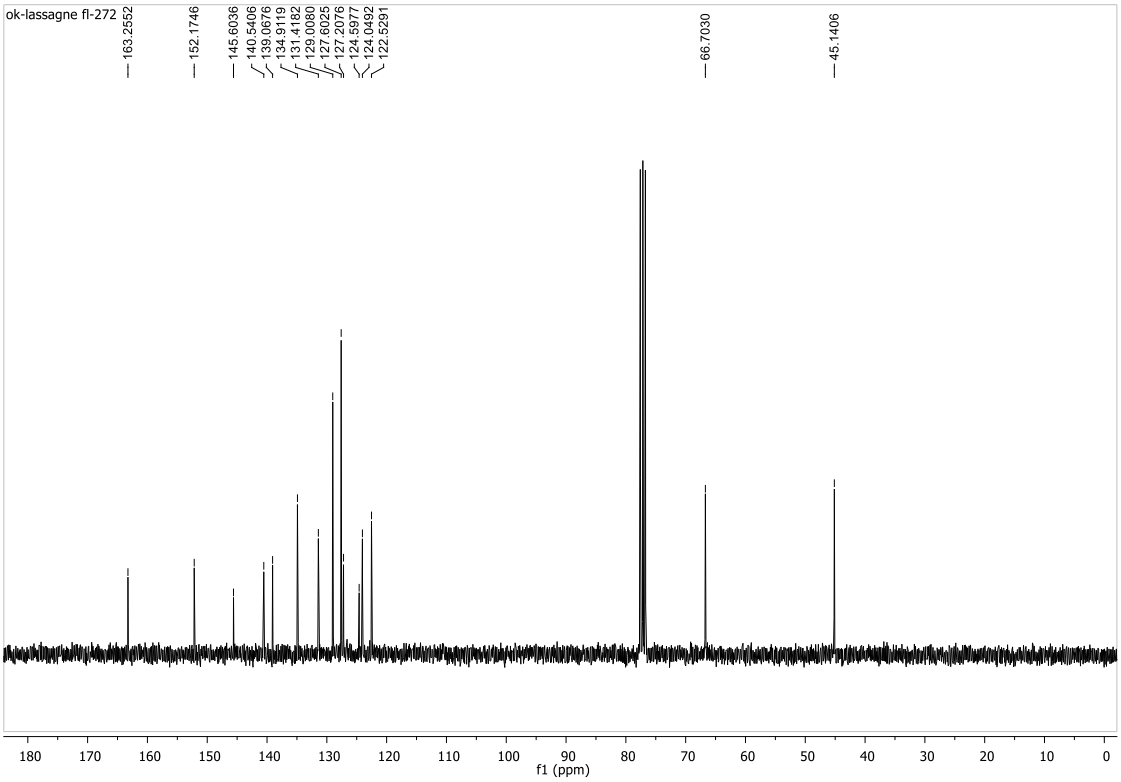
## 7-Morpholino-2-phenyloxazolo[5,4-*f*]quinoxaline (6aa)



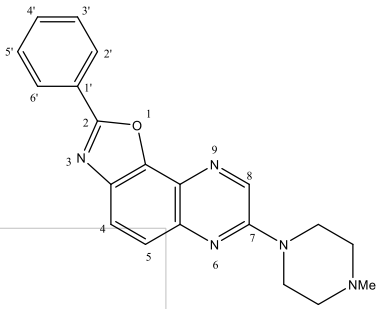
$^{1}$H NMR (300 MHz, $CDCl_3$)



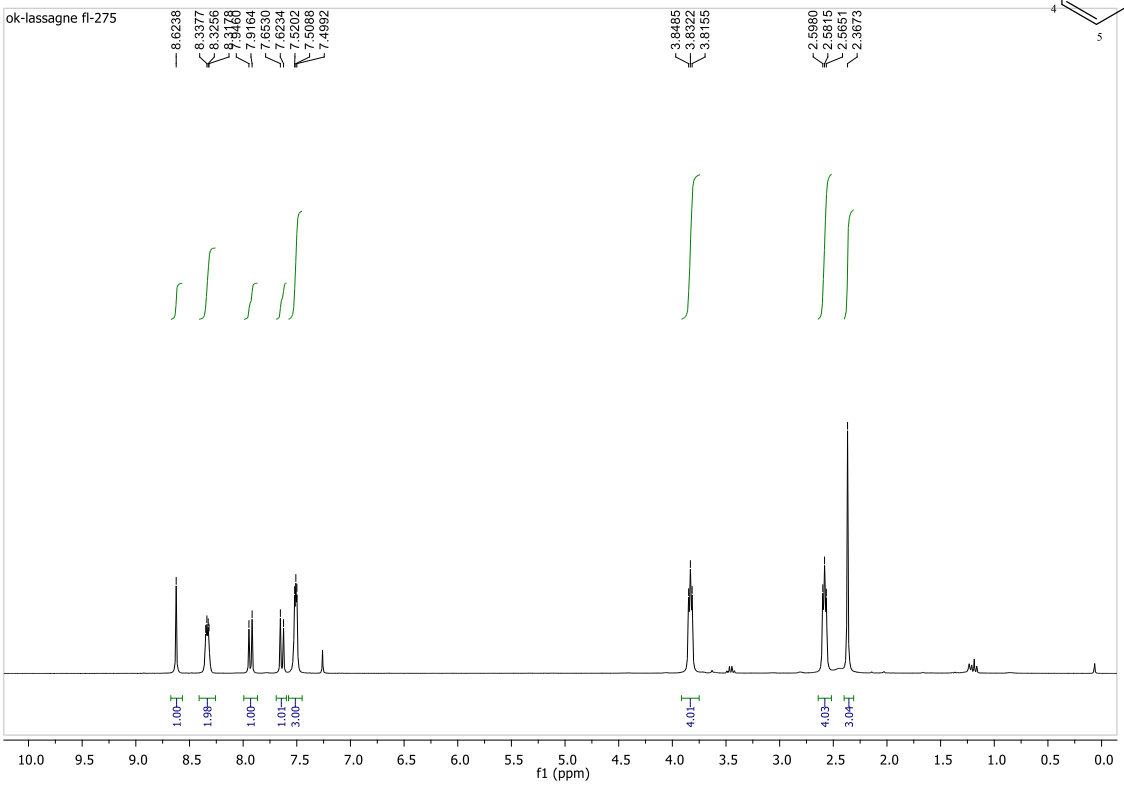

$^{13}$C NMR (75 MHz, $CDCl_3$)



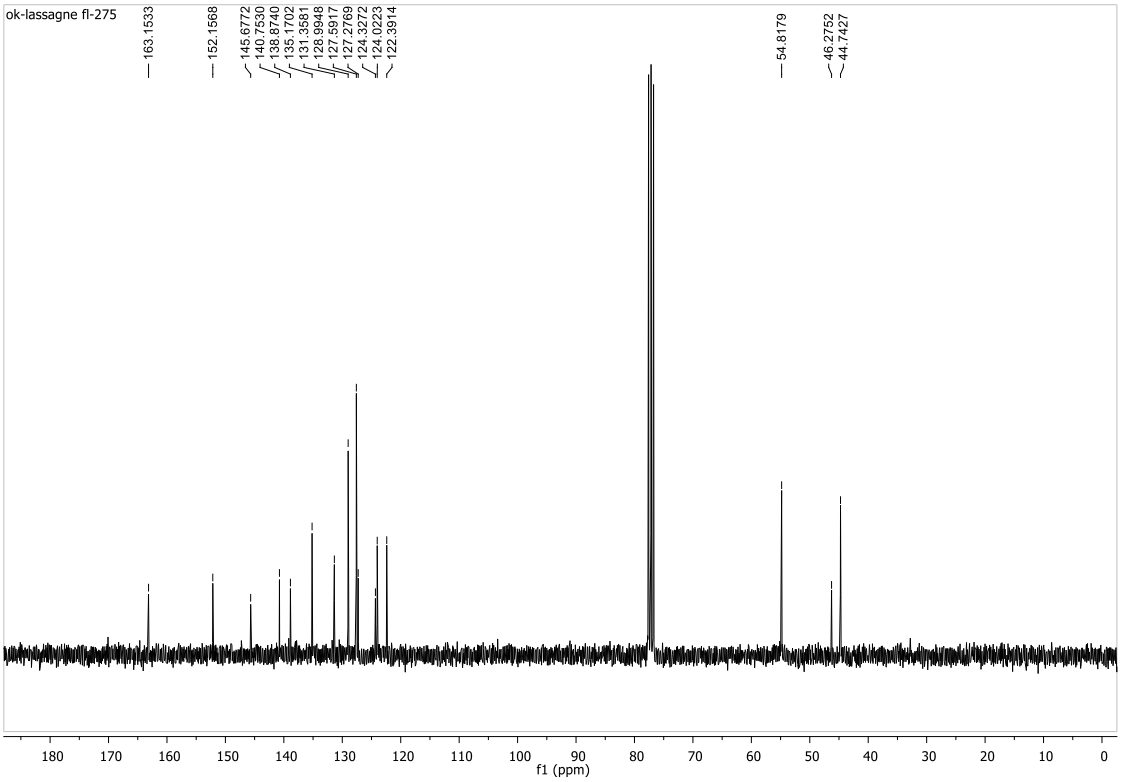
## 7-(4-Methylpiperazino)-2-phenyloxazolo[5,4-*f*]quinoxaline (6ab)



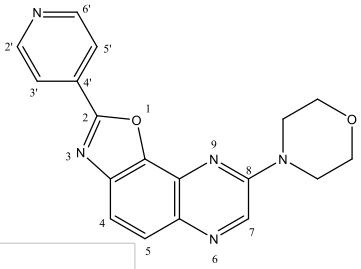

$^{1}$H NMR (300 MHz, $CDCl_3$)



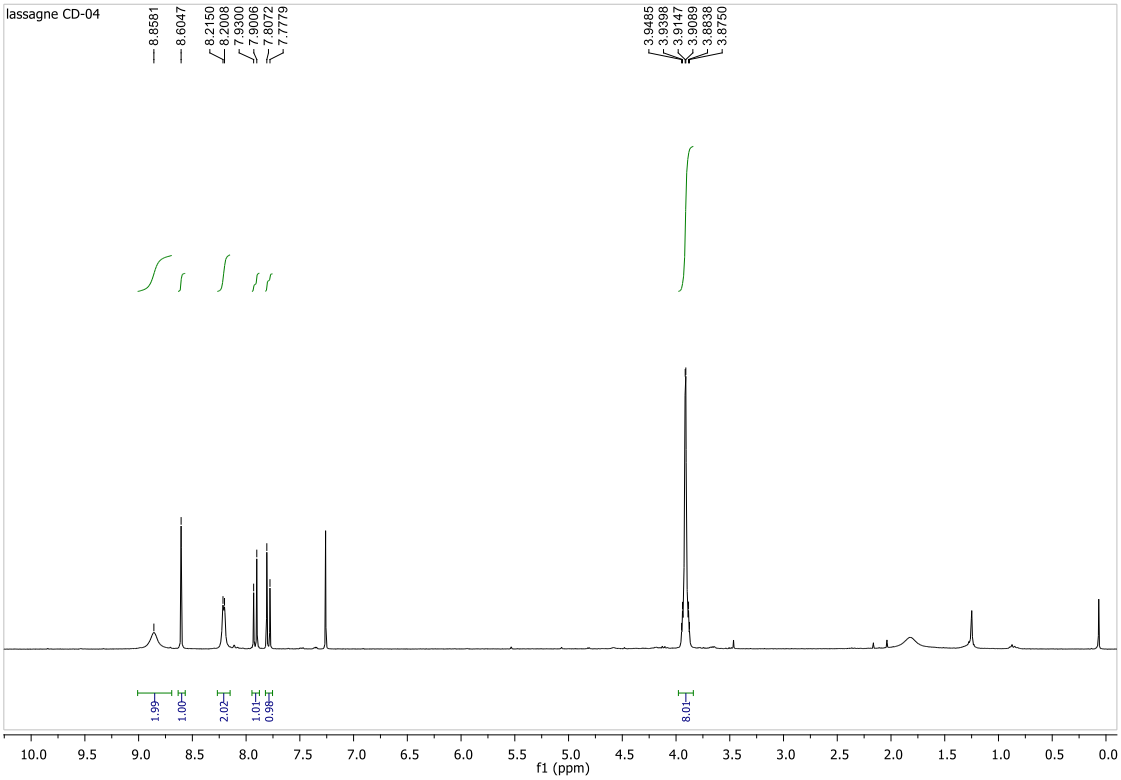

$^{13}$C NMR (75 MHz, $CDCl_3$)



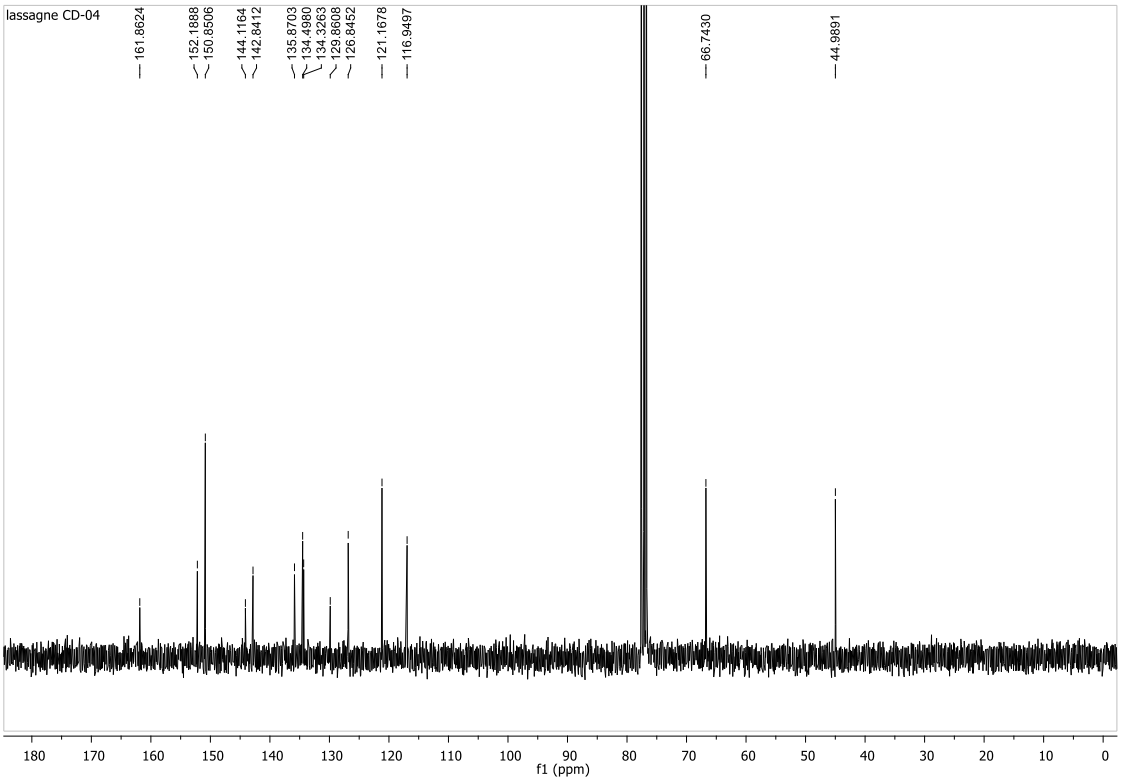
## 8-(4-Morpholino)-2-(4-pyridyl)oxazolo[5,4-*f*]quinoxaline (10a)



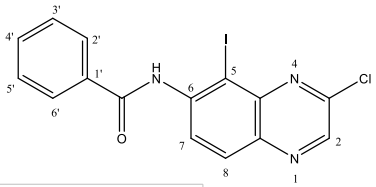
$^{1}$H NMR (300 MHz, $CDCl_3$)



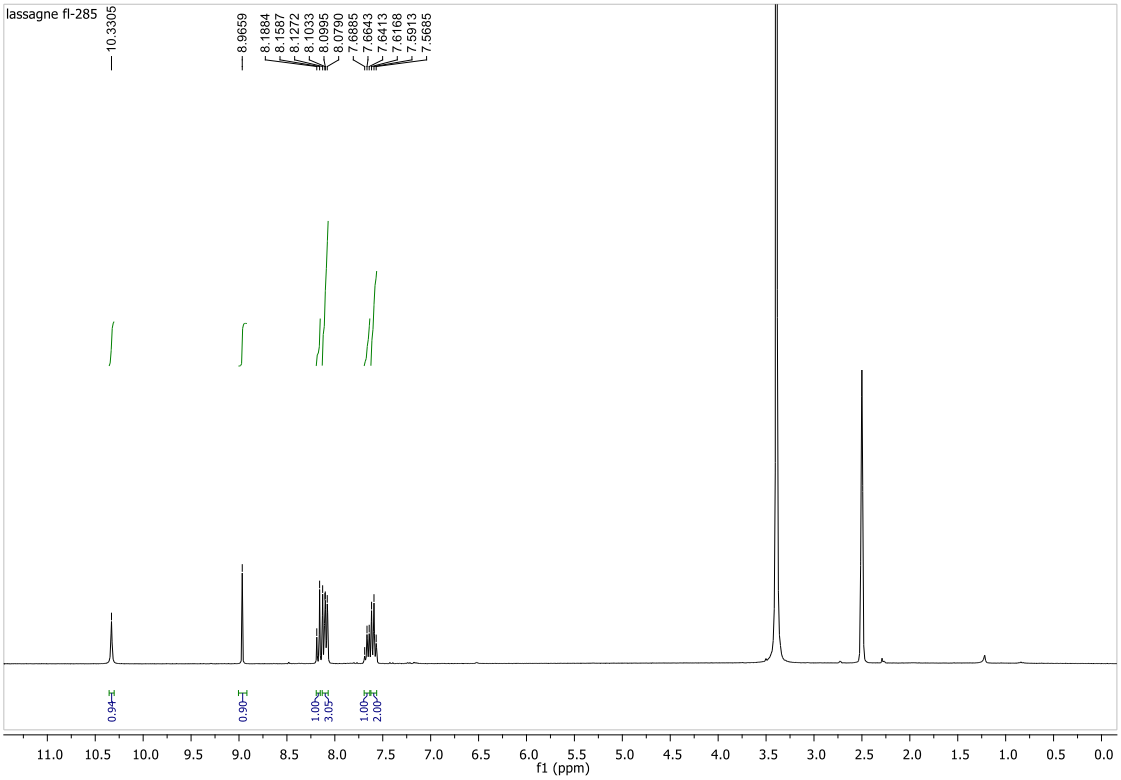

$^{13}$C NMR (75 MHz, $CDCl_3$)



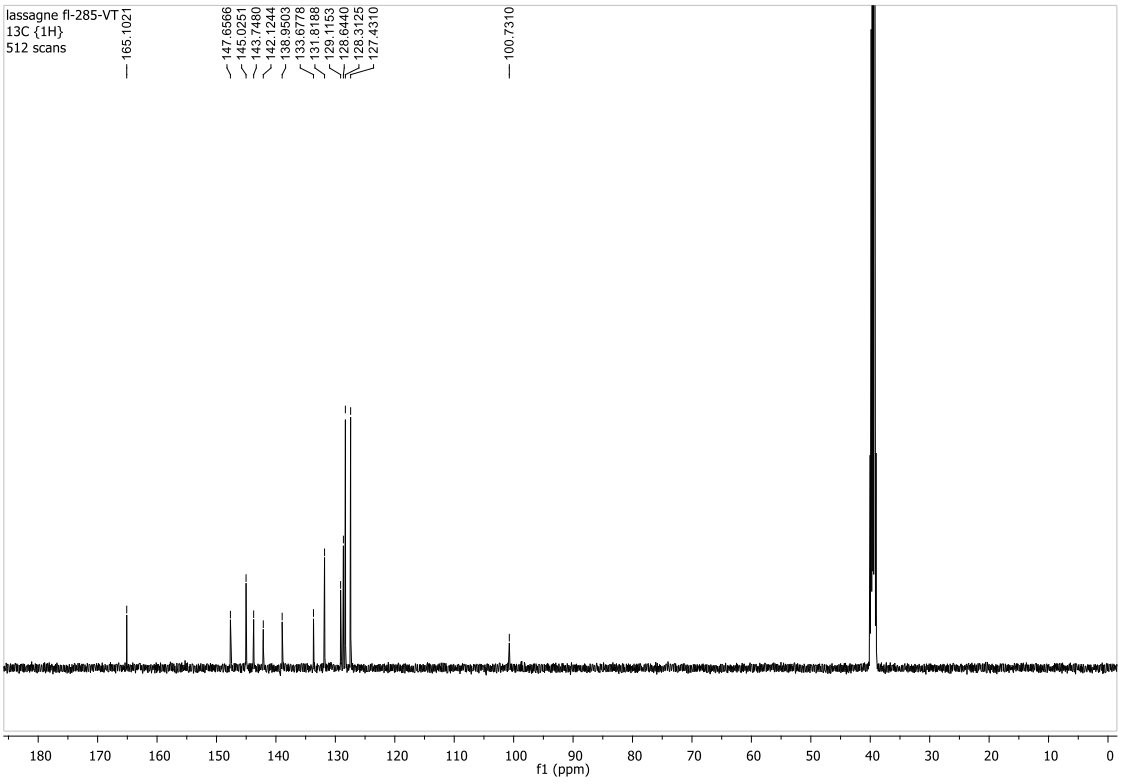
## 6-(Benzoylamino)-3-chloro-5-iodoquinoxaline (12a)



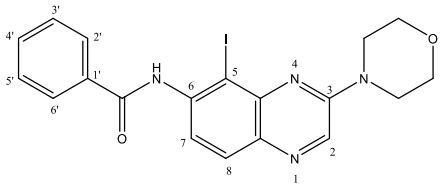
$^{1}$H NMR (500 MHz, $(CD_3)_2SO$, 338 K)



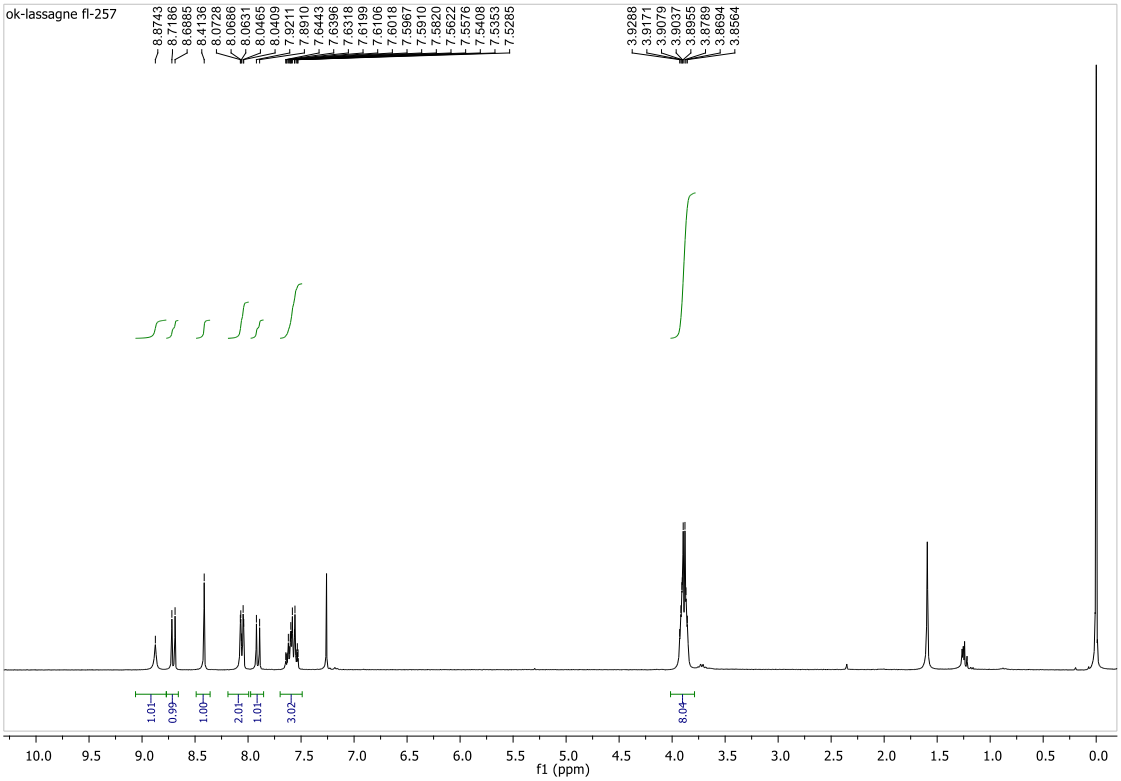

$^{13}$C NMR (126 MHz, $(CD_3)_2SO$, 338 K)



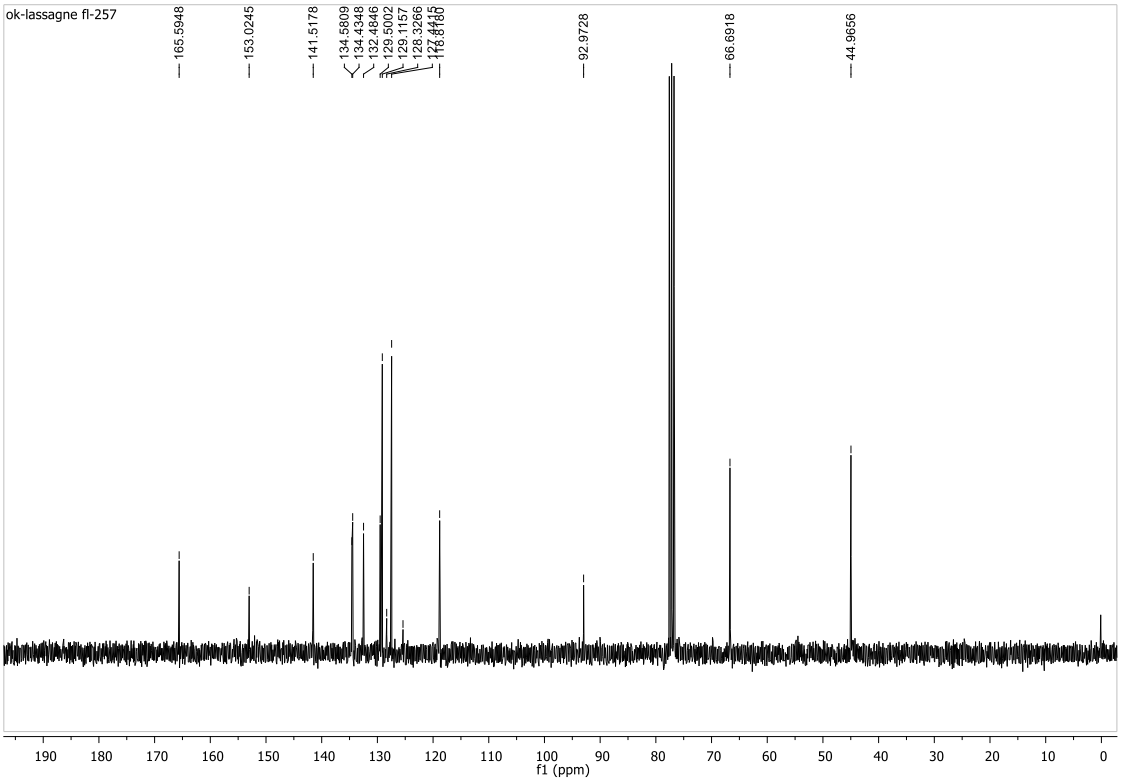
## 6-(Benzoylamino)-5-iodo-3-morpholinoquinoxaline (9aa)



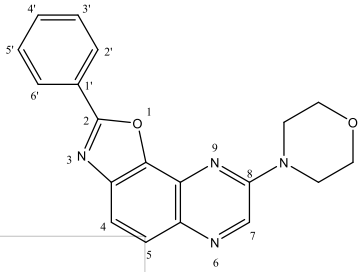
$^{1}$H NMR (300 MHz, $CDCl_3$)



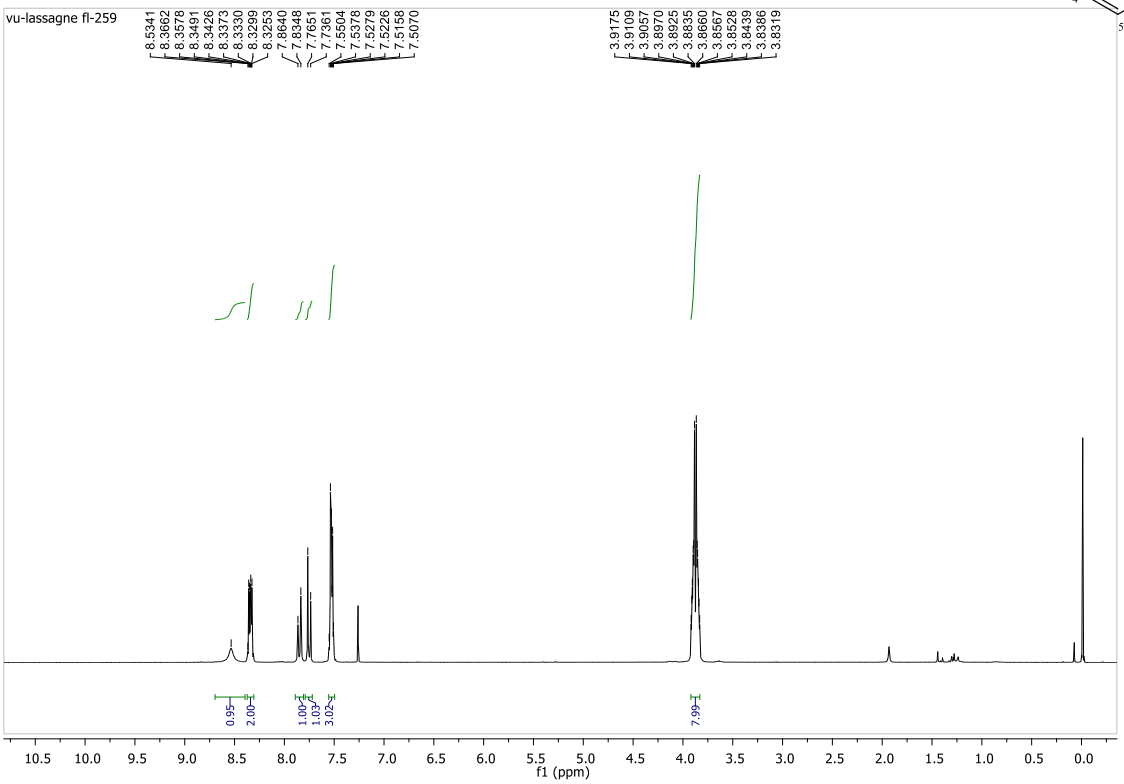

$^{13}$C NMR (75 MHz, $CDCl_3$)



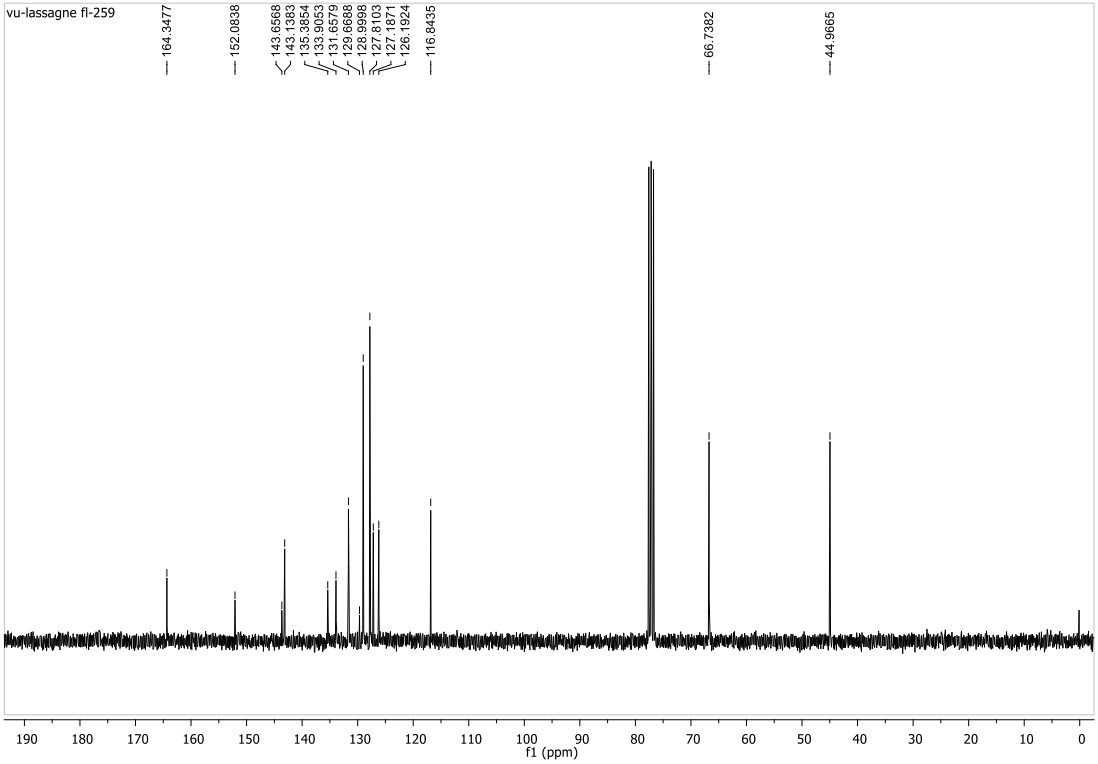
## 8-Morpholino-2-phenyloxazolo[5,4-*f*]quinoxaline (10aa)



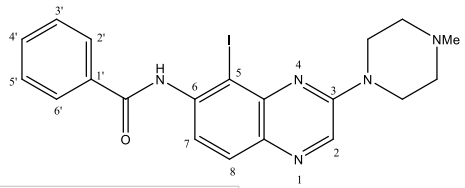
$^{1}$H NMR (300 MHz, $CDCl_3$)



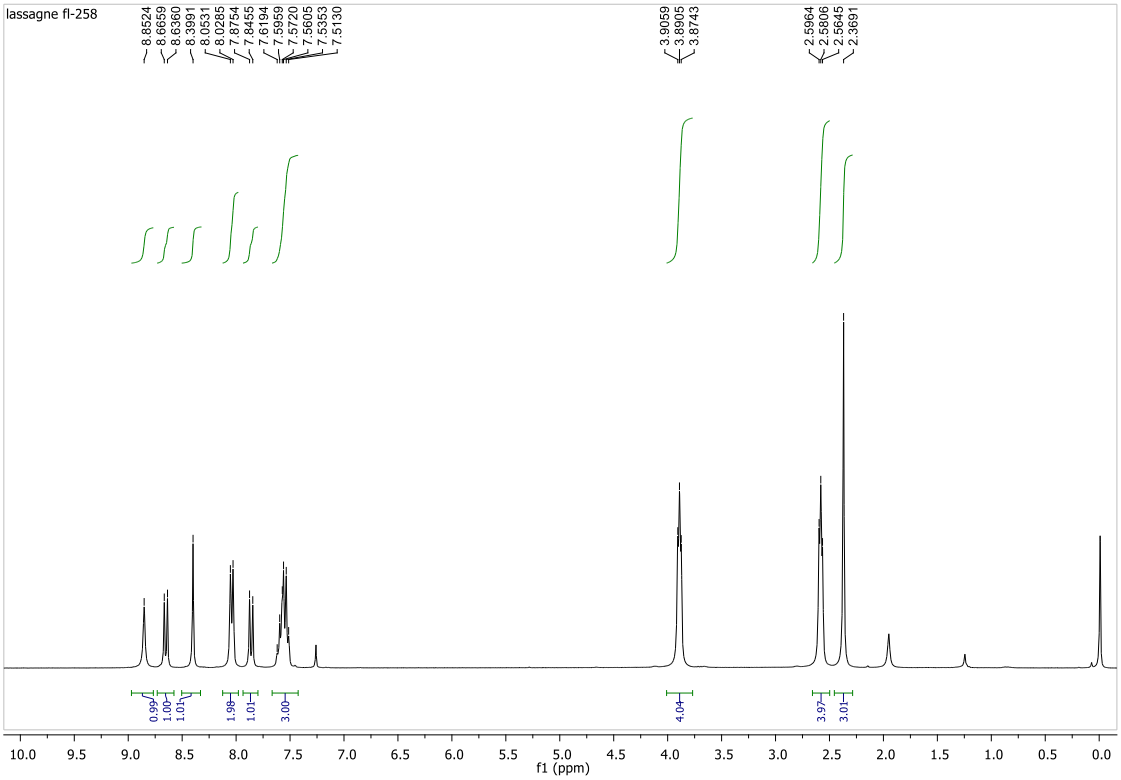

$^{13}$C NMR (75 MHz, $CDCl_3$)



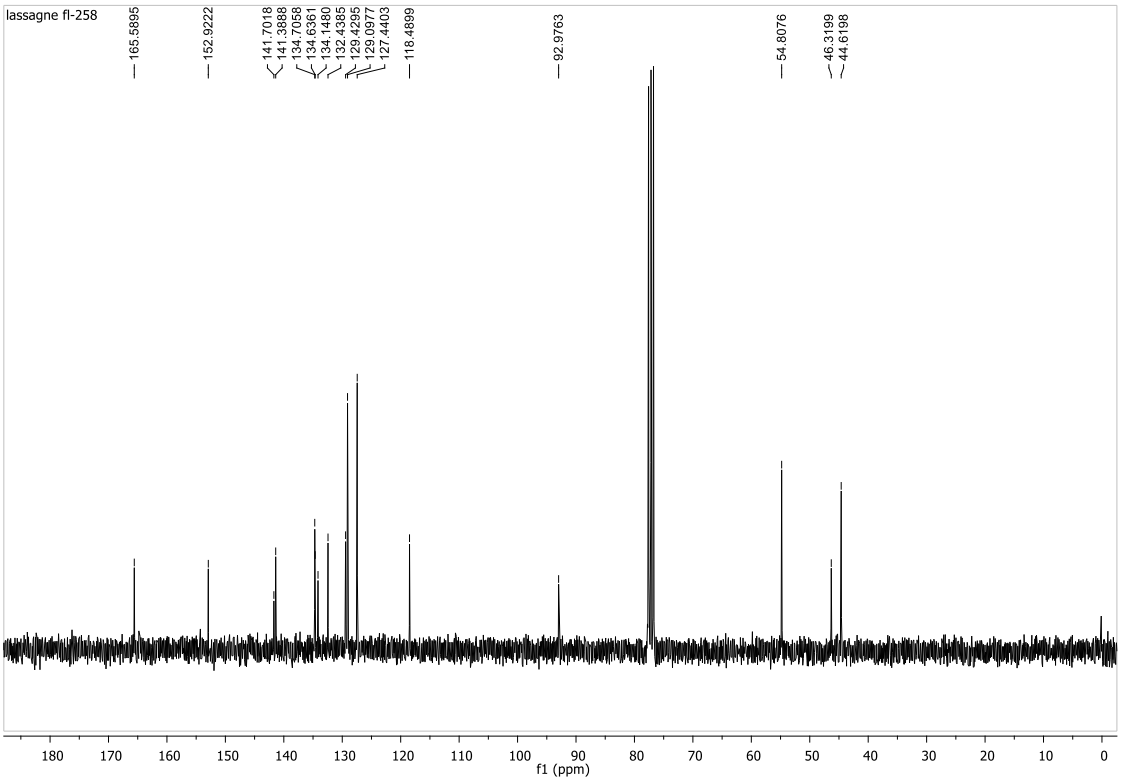
## 6-(Benzoylamino)-5-iodo-3-(4-methylpiperazino)quinoxaline (9ab)



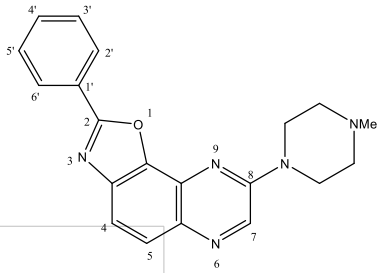

$^{1}$H NMR (300 MHz, $CDCl_3$)



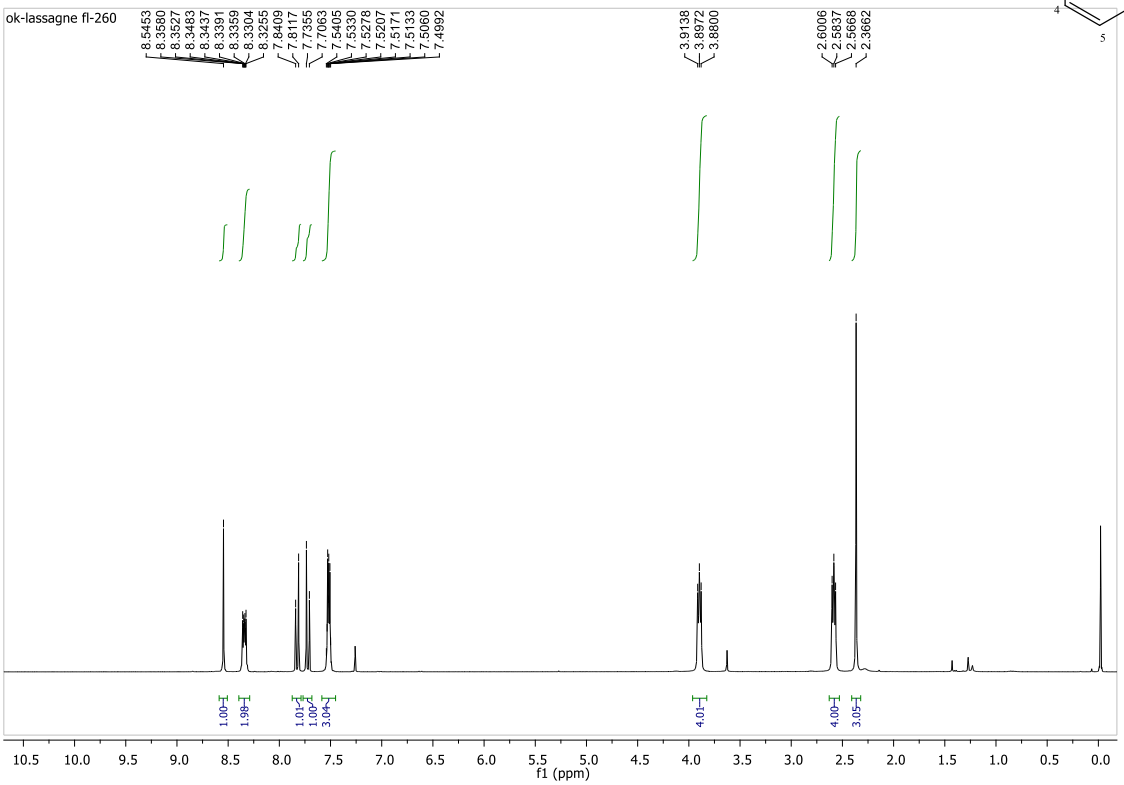

$^{13}$C NMR (75 MHz, $CDCl_3$)



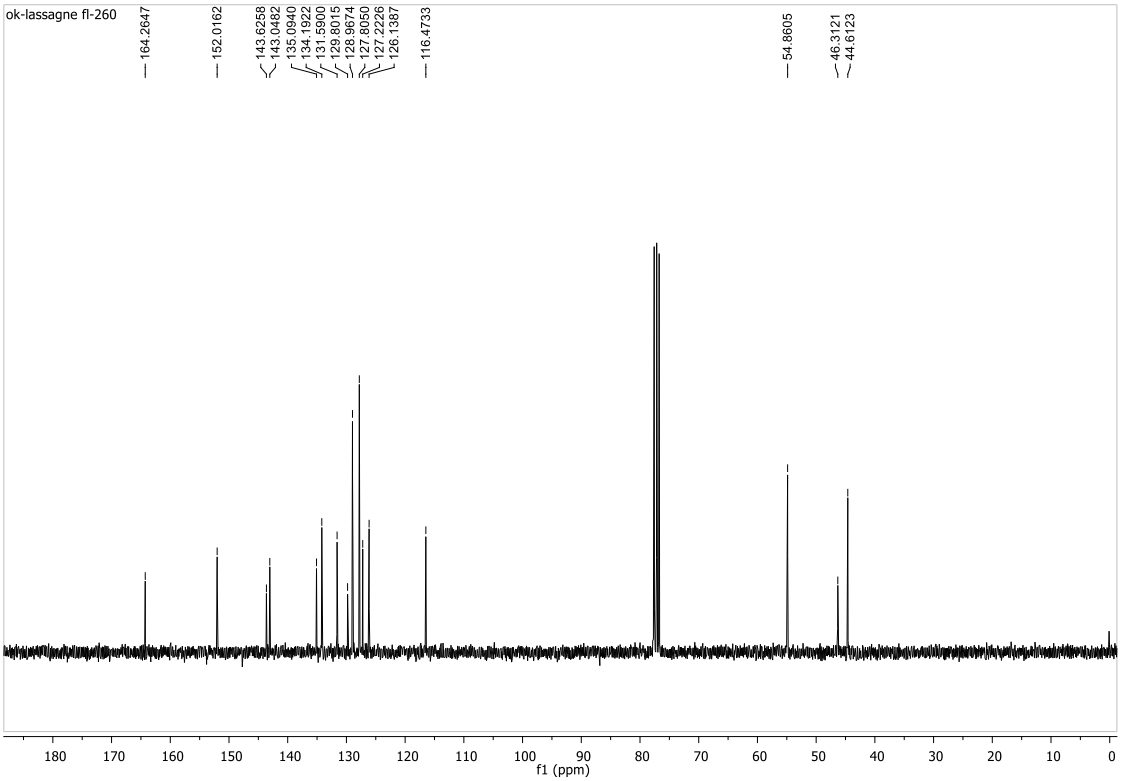
## 8-(4-Methylpiperazino)-2-phenyloxazolo[5,4-*f*]quinoxaline (10ab)



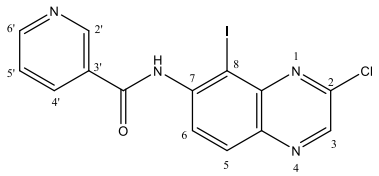

$^{1}$H NMR (300 MHz, $CDCl_3$)



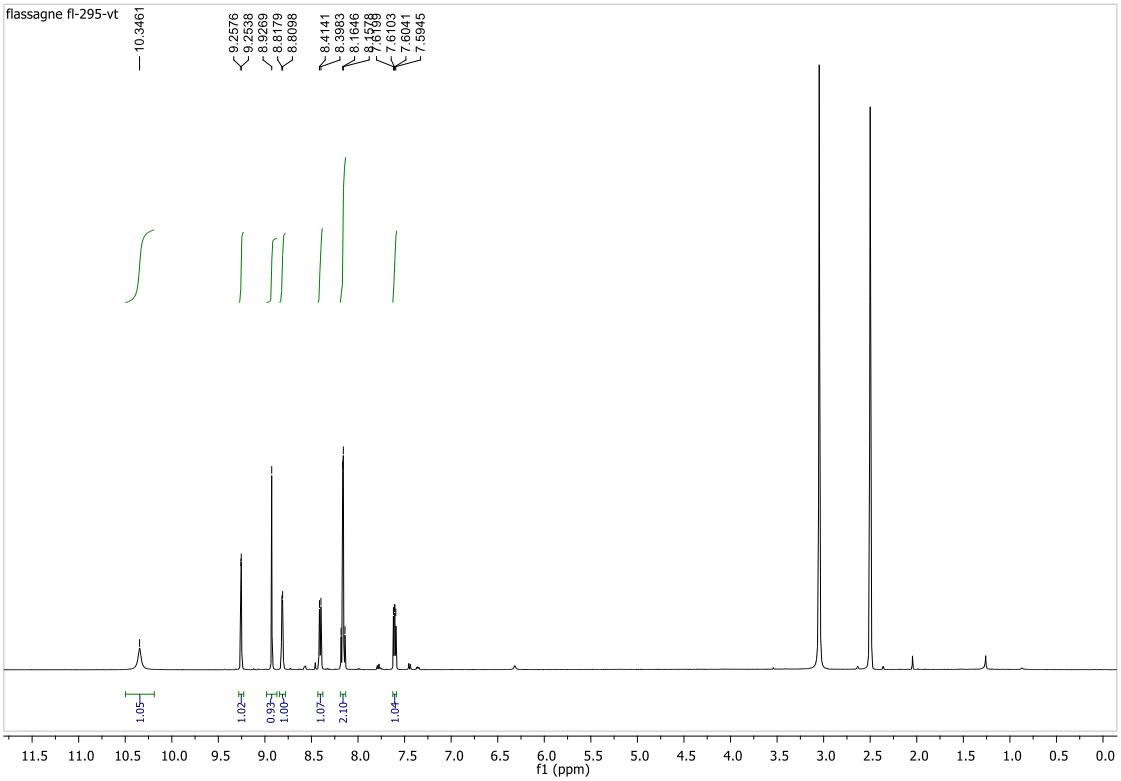

$^{13}$C NMR (75 MHz, $CDCl_3$)



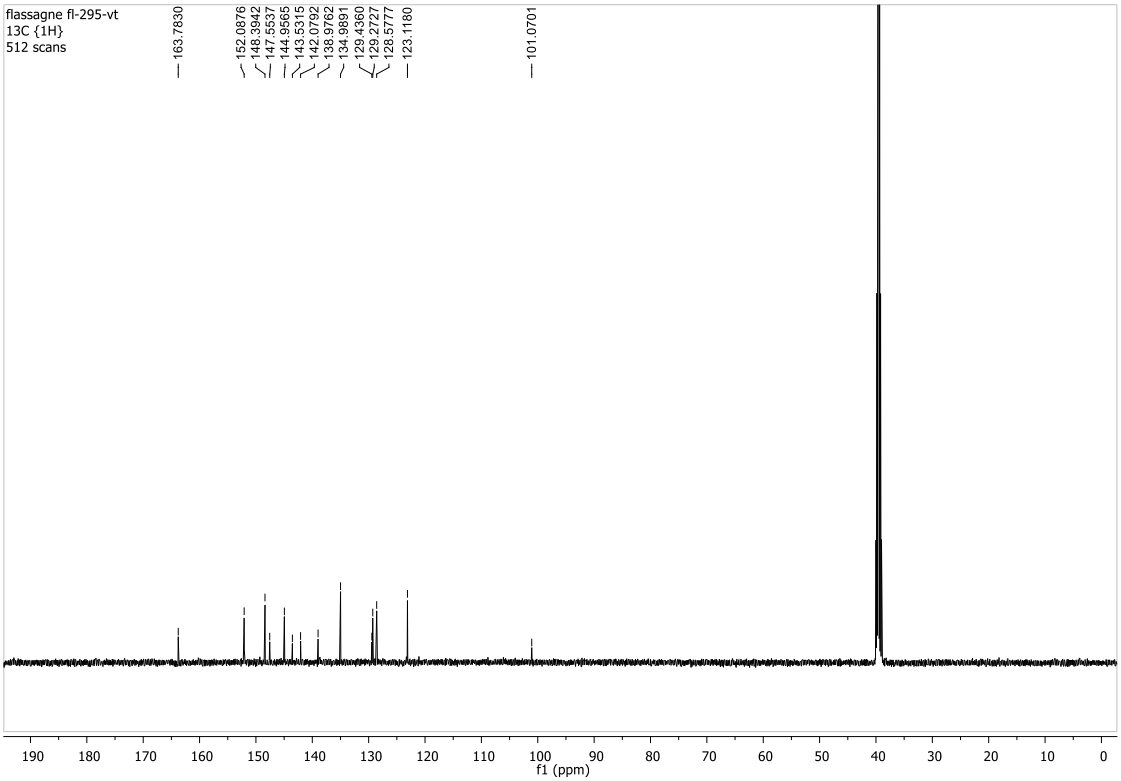
## 2-Chloro-8-iodo-7-(3-pyridoylamino)quinoxaline (12b)



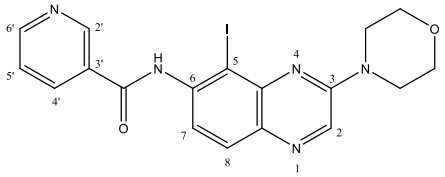
$^{1}$H NMR (500 MHz, $(CD_3)_2SO$, 358 K)



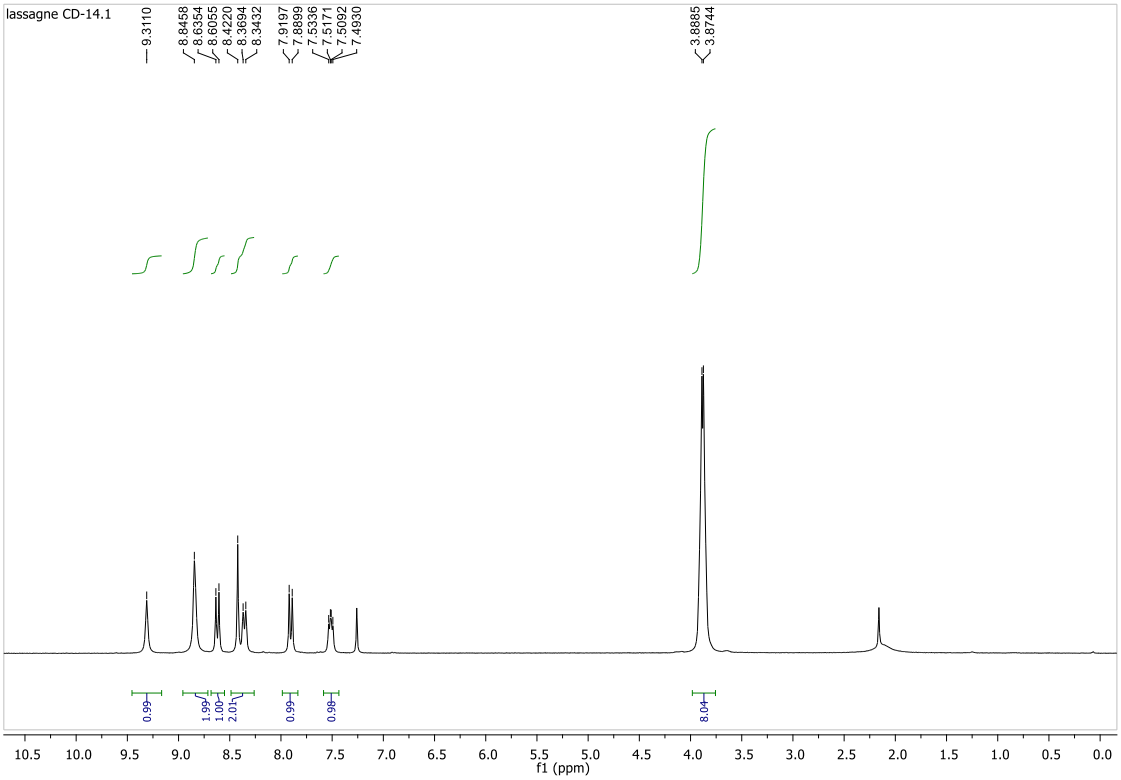

$^{13}$C NMR (126 MHz, $(CD_3)_2SO$, 358 K)



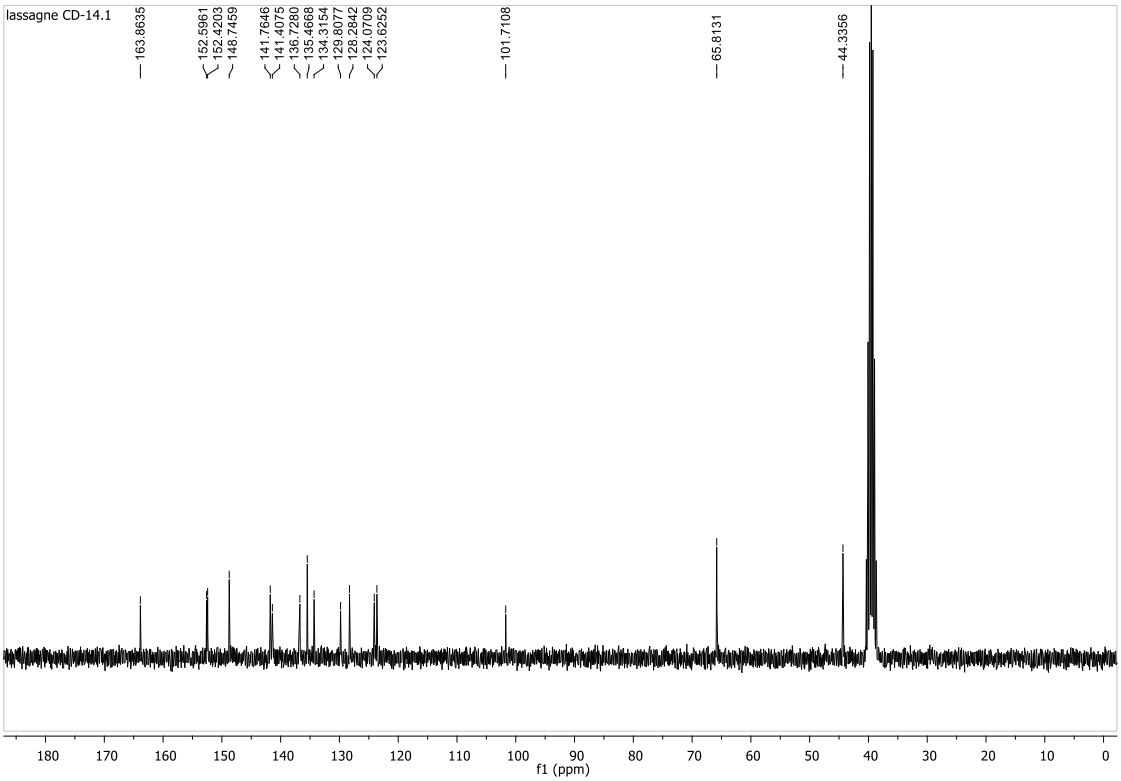
## 5-Iodo-3-morpholino-6-(3-pyridoylamino)quinoxaline (9ba)



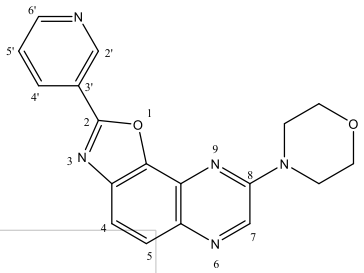
$^{1}$H NMR (300 MHz, $CDCl_3$)



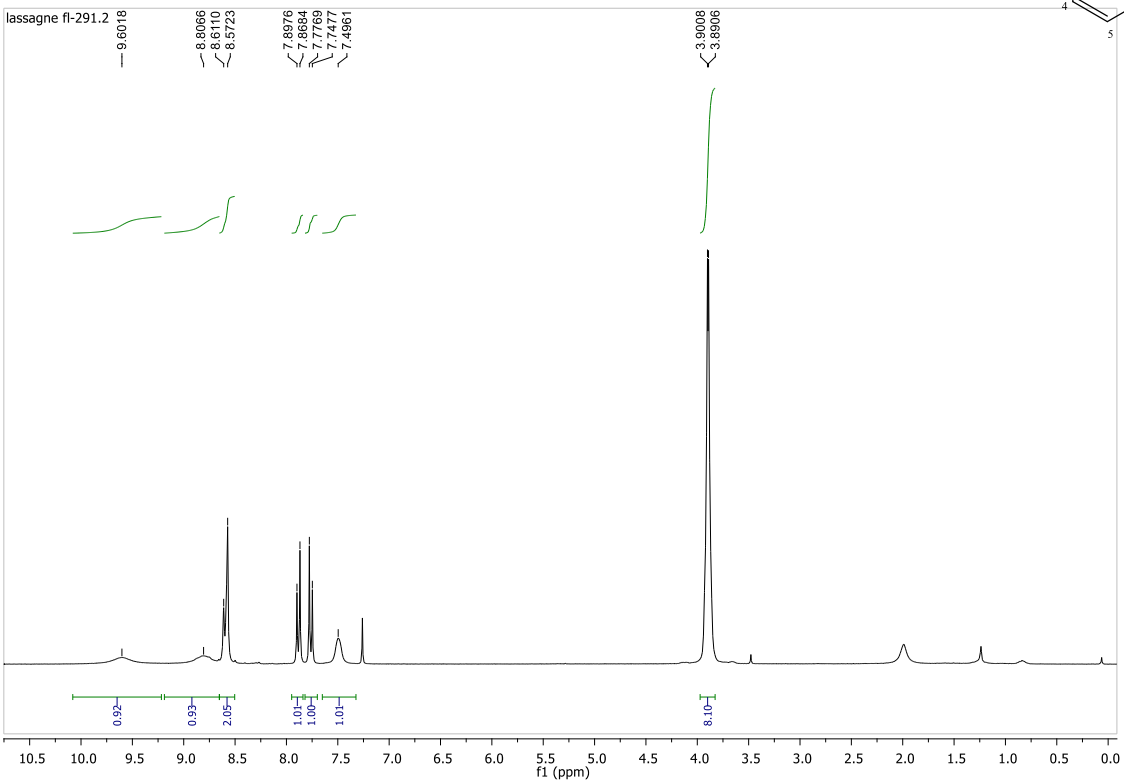

$^{13}$C NMR (75 MHz, $(CD_3)_2SO$)



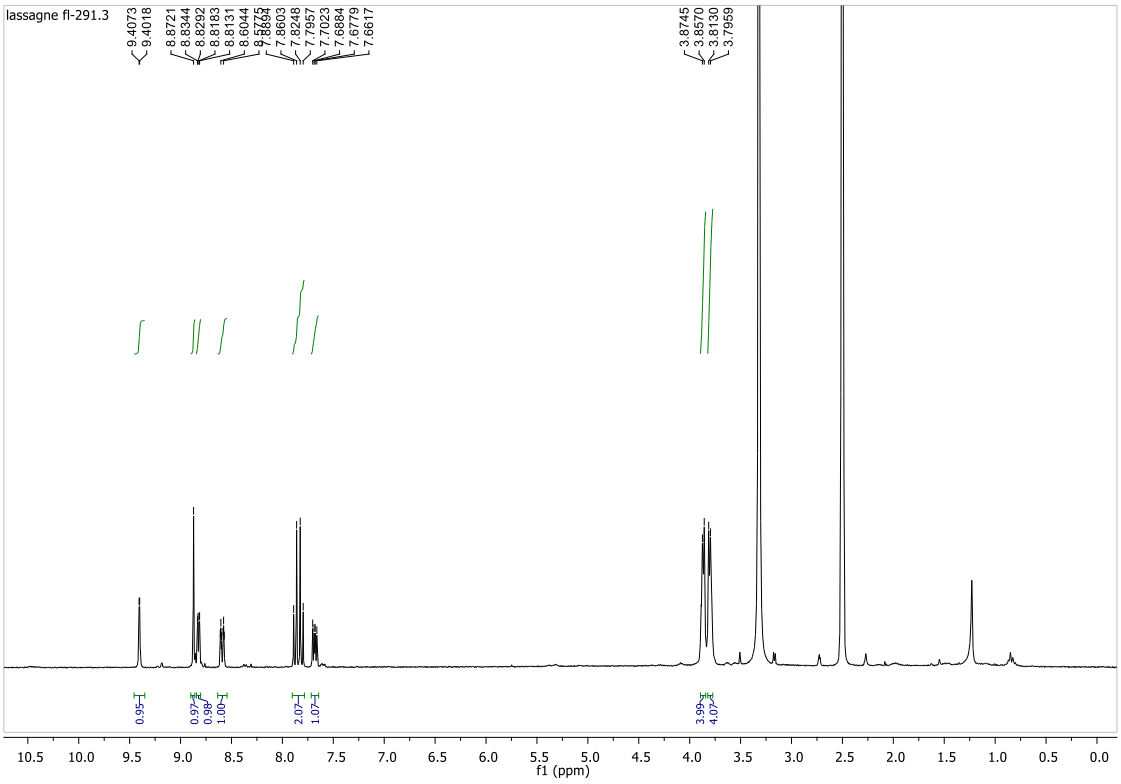
## 8-Morpholino-2-(3-pyridyl)oxazolo[5,4-*f*]quinoxaline (10ba)



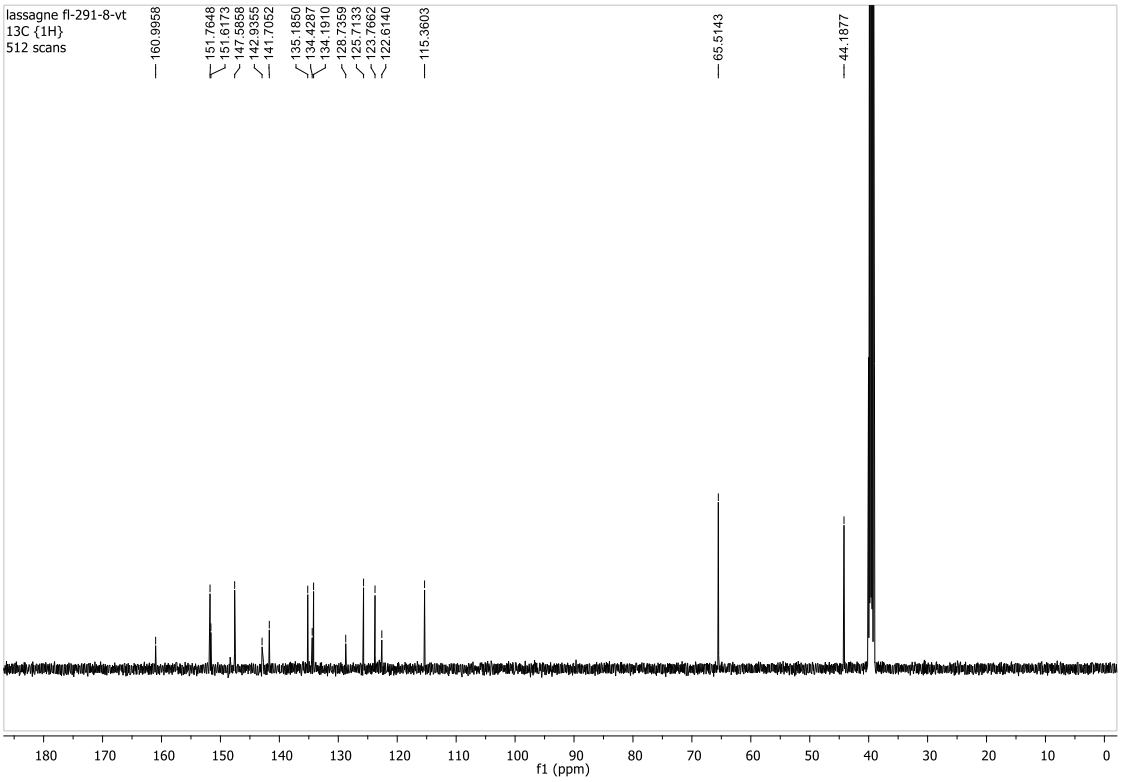
$^1$H NMR (300 MHz, $CDCl_3$)



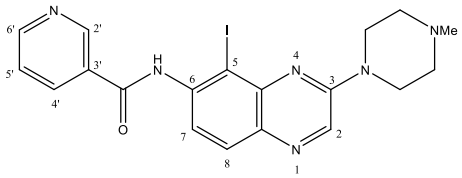

$^1$H NMR (300 MHz, $(CD_3)_2SO$)



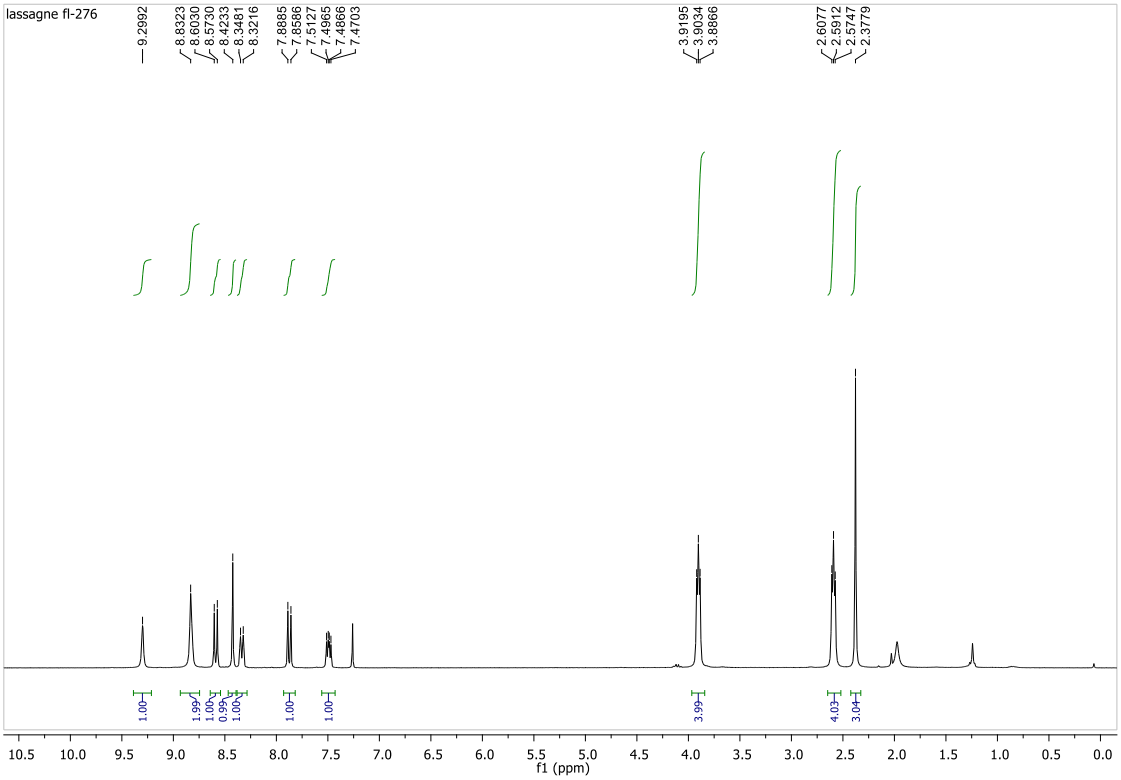
$^{13}C$ NMR (126 MHz, $(CD_3)_2SO$, 358 K)



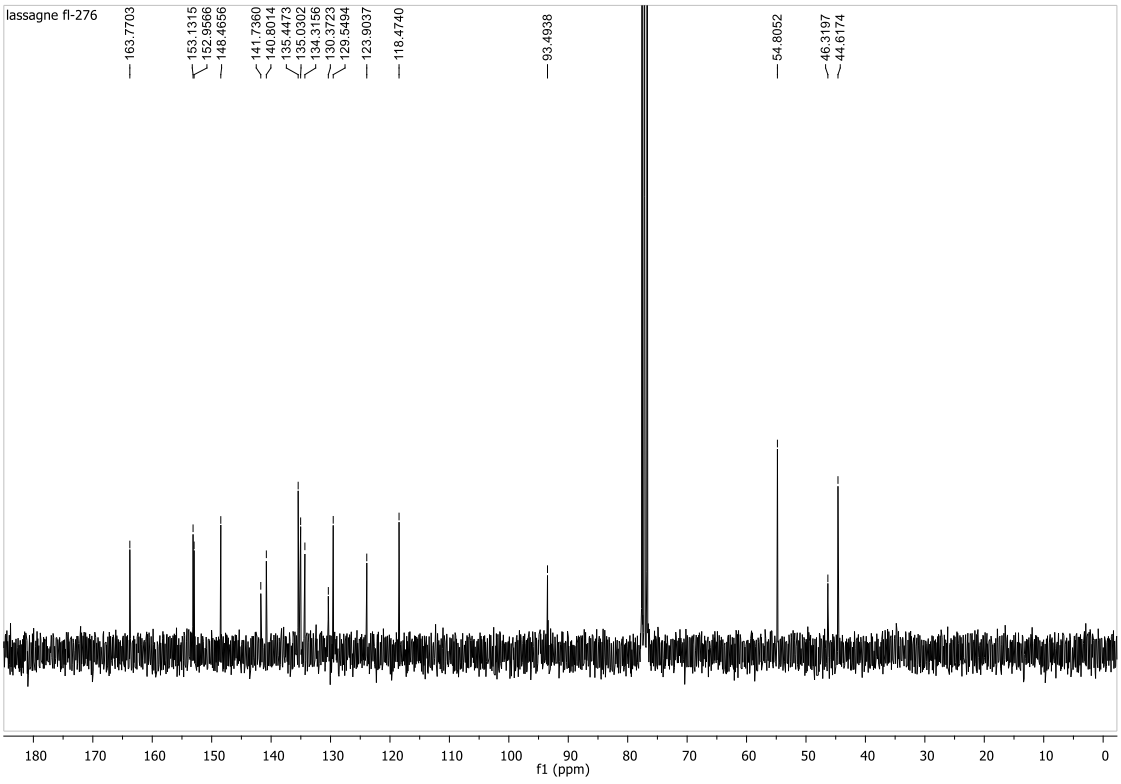
## 5-Iodo-3-(4-methylpiperazino)-6-(3-pyridoylamino)quinoxaline (9bb)



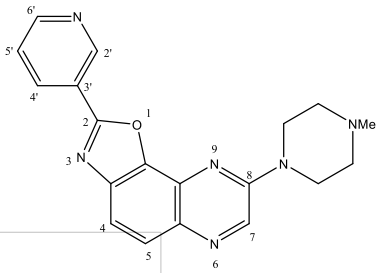
$^{1}$H NMR (300 MHz, $CDCl_3$)



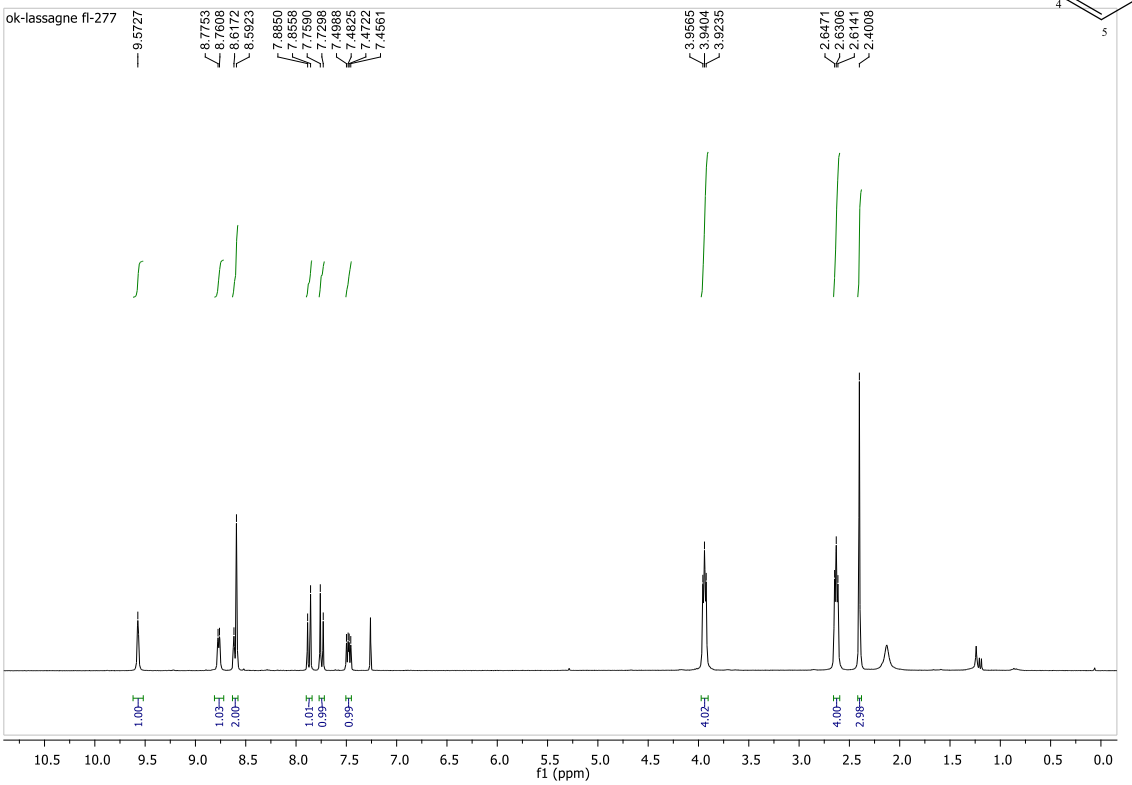

$^{13}$C NMR (75 MHz, $CDCl_3$)



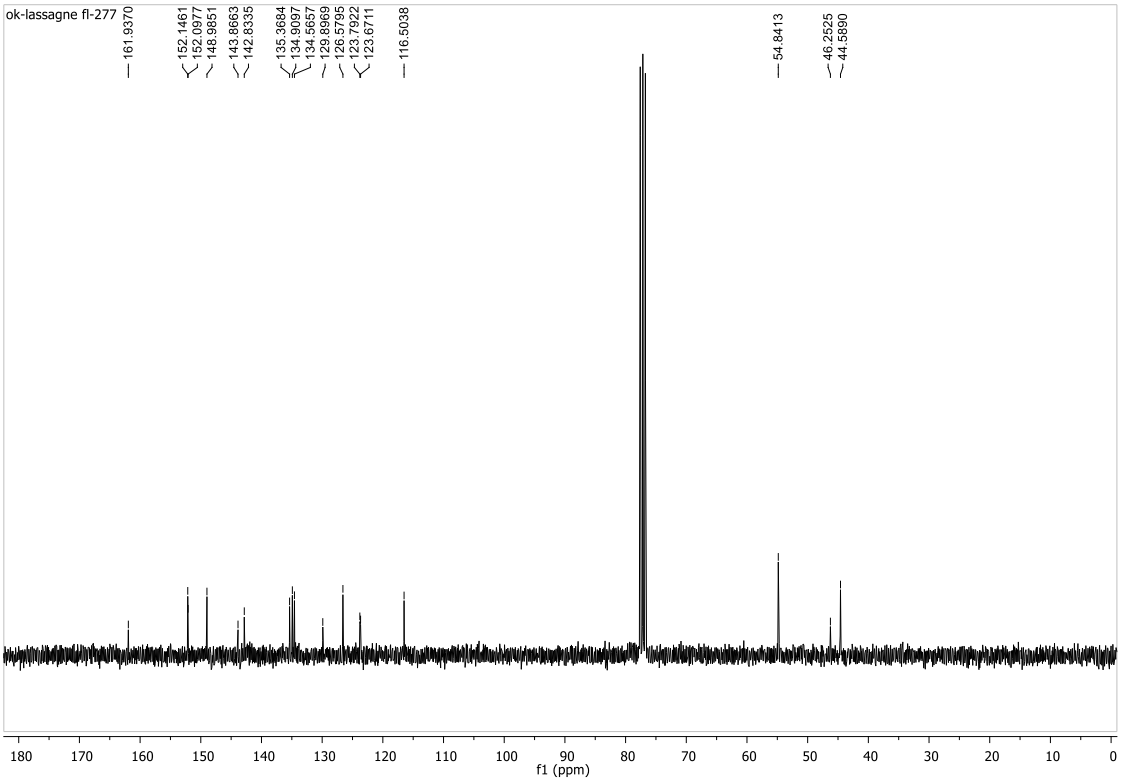
## 8-(4-Methylpiperazino)-2-(3-pyridyl)oxazolo[5,4-*f*]quinoxaline (10bb)



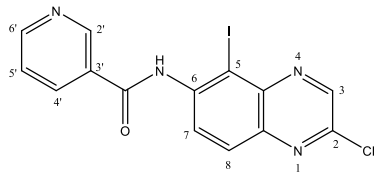

$^{1}$H NMR (300 MHz, $CDCl_3$)



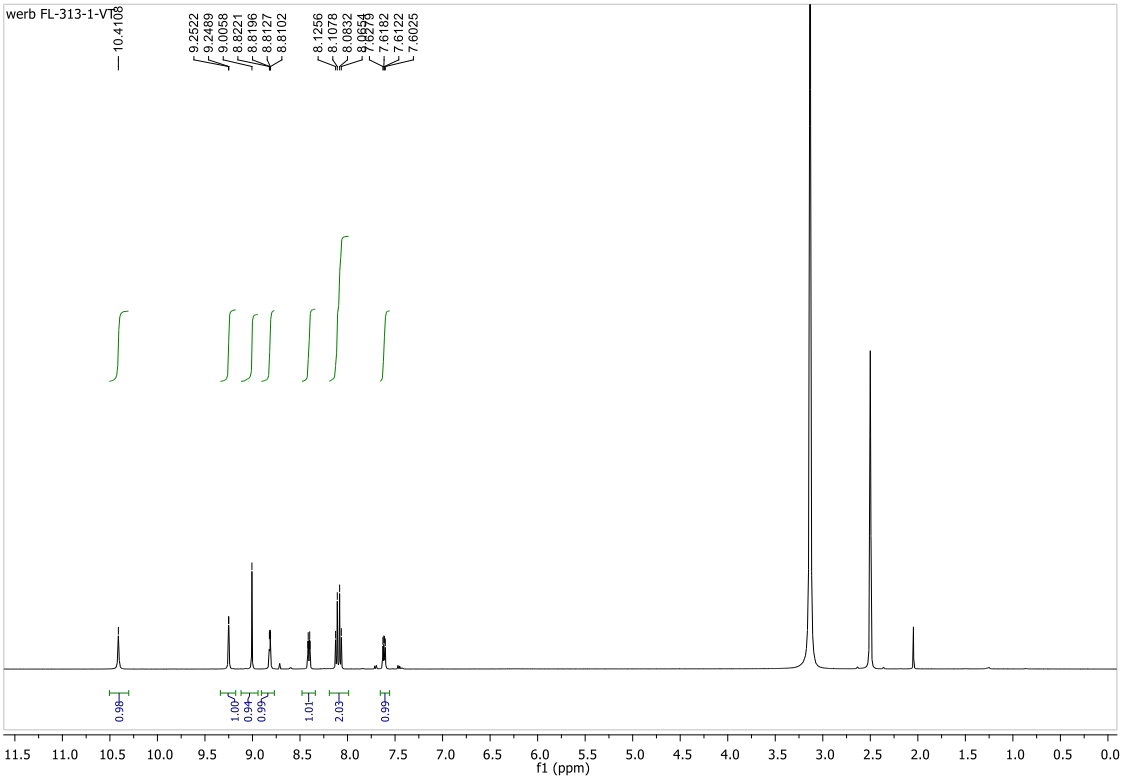

$^{13}$C NMR (75 MHz, $CDCl_3$)



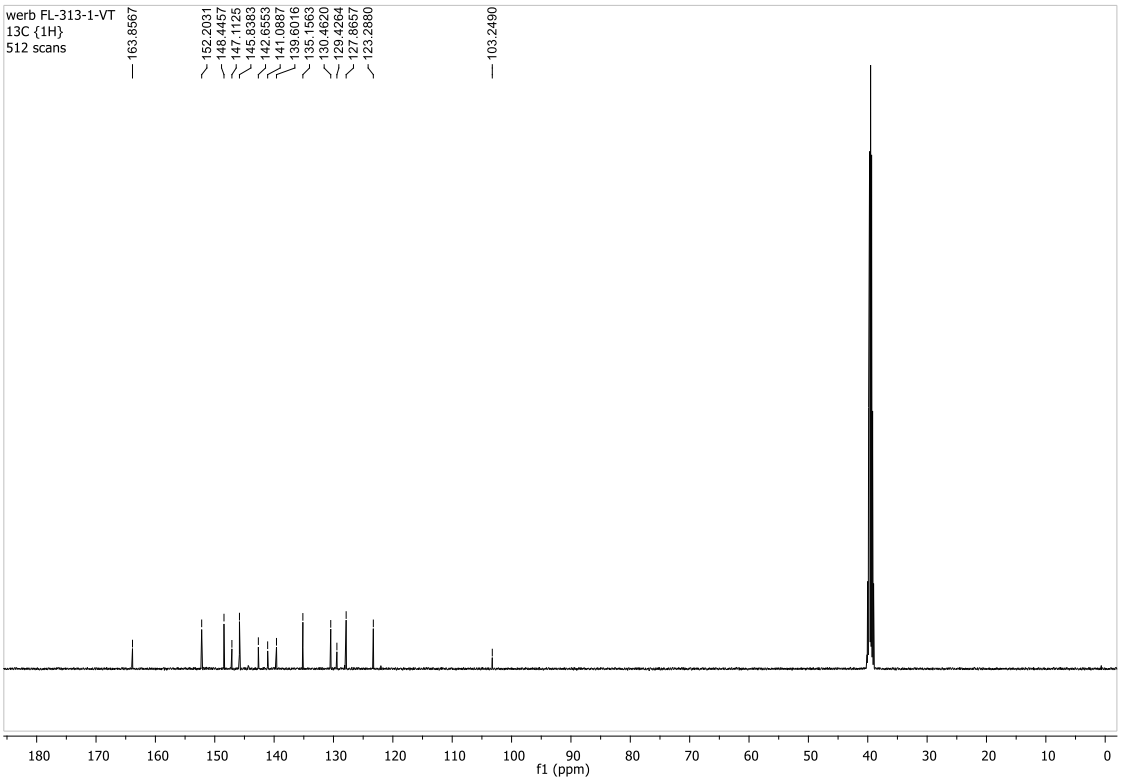
## 2-Chloro-5-iodo-6-(3-pyridoylamino)quinoxaline (11b)



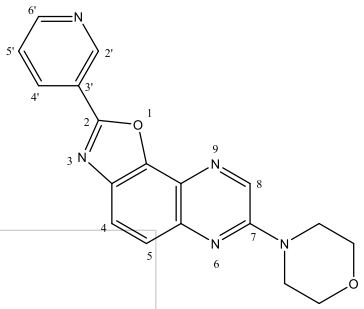
$^{1}$H NMR (500 MHz, $(CD_3)_2SO$, 348 K)



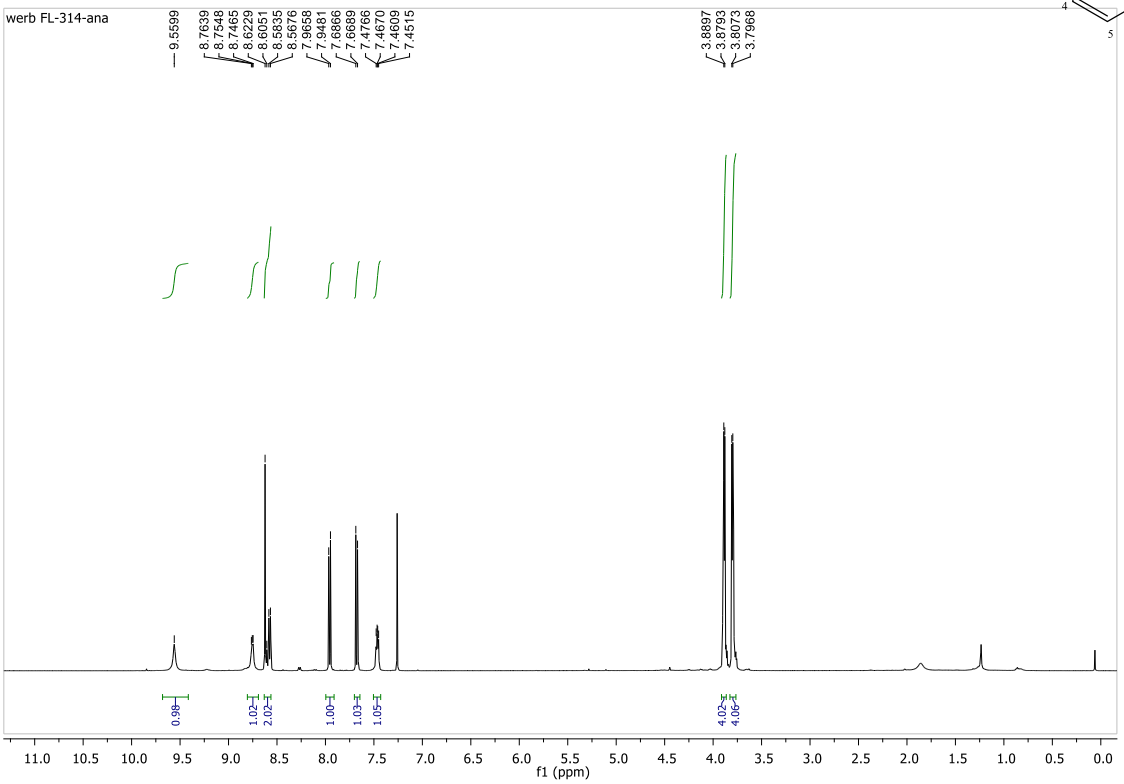

$^{13}$C NMR (126 MHz, $(CD_3)_2SO$, 348 K)



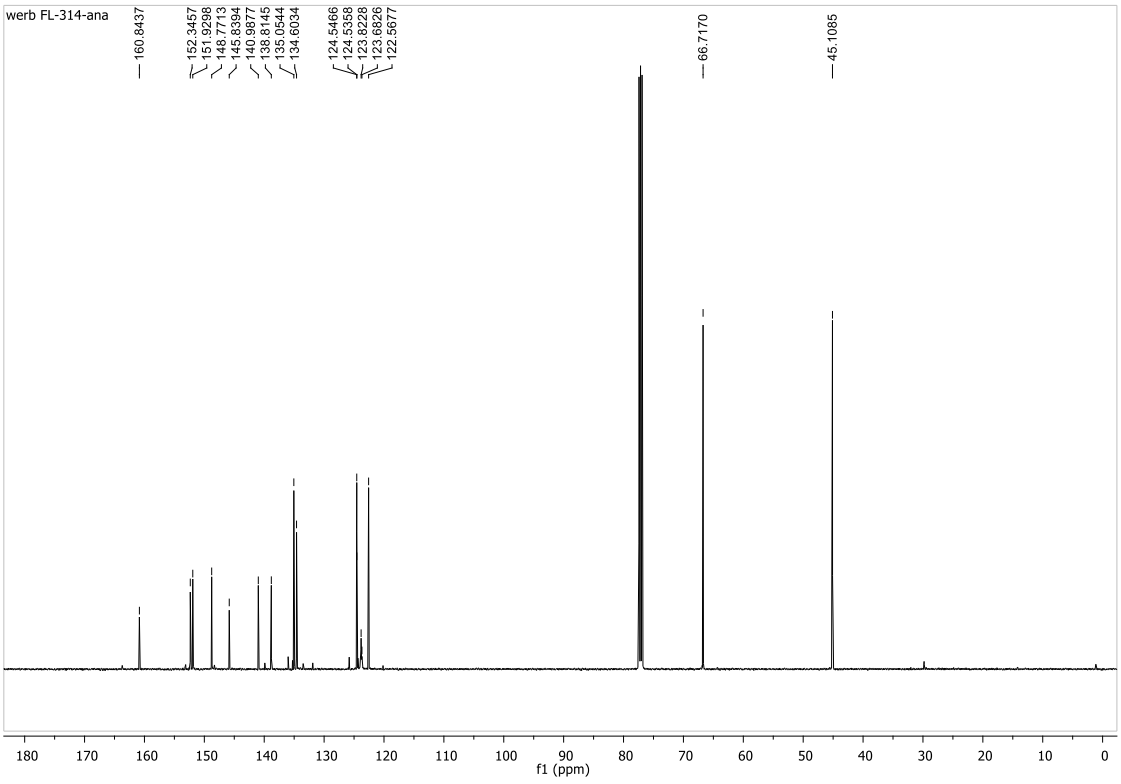
## 7-Morpholino-2-(3-pyridyl)oxazolo[5,4-*f*]quinoxaline (6ba)



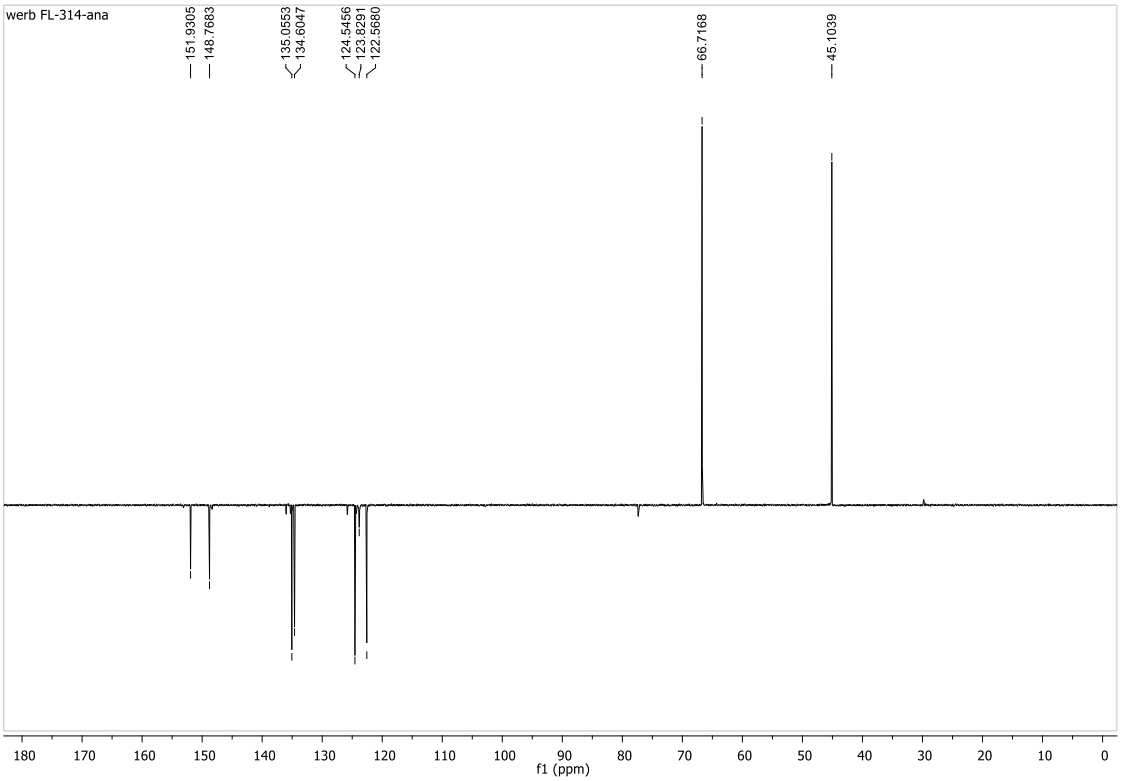
$^{1}$H NMR (500 MHz, $CDCl_3$)



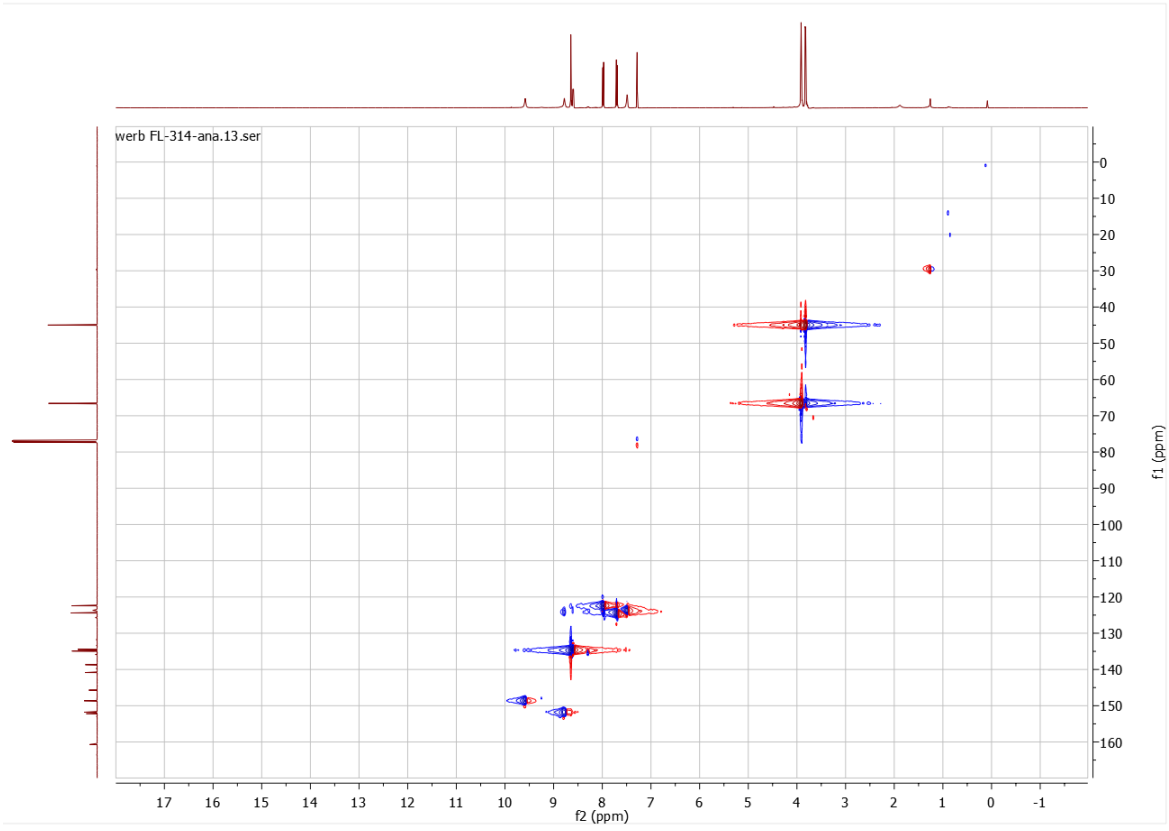

$^{13}$C NMR (125 MHz, $CDCl_3$)



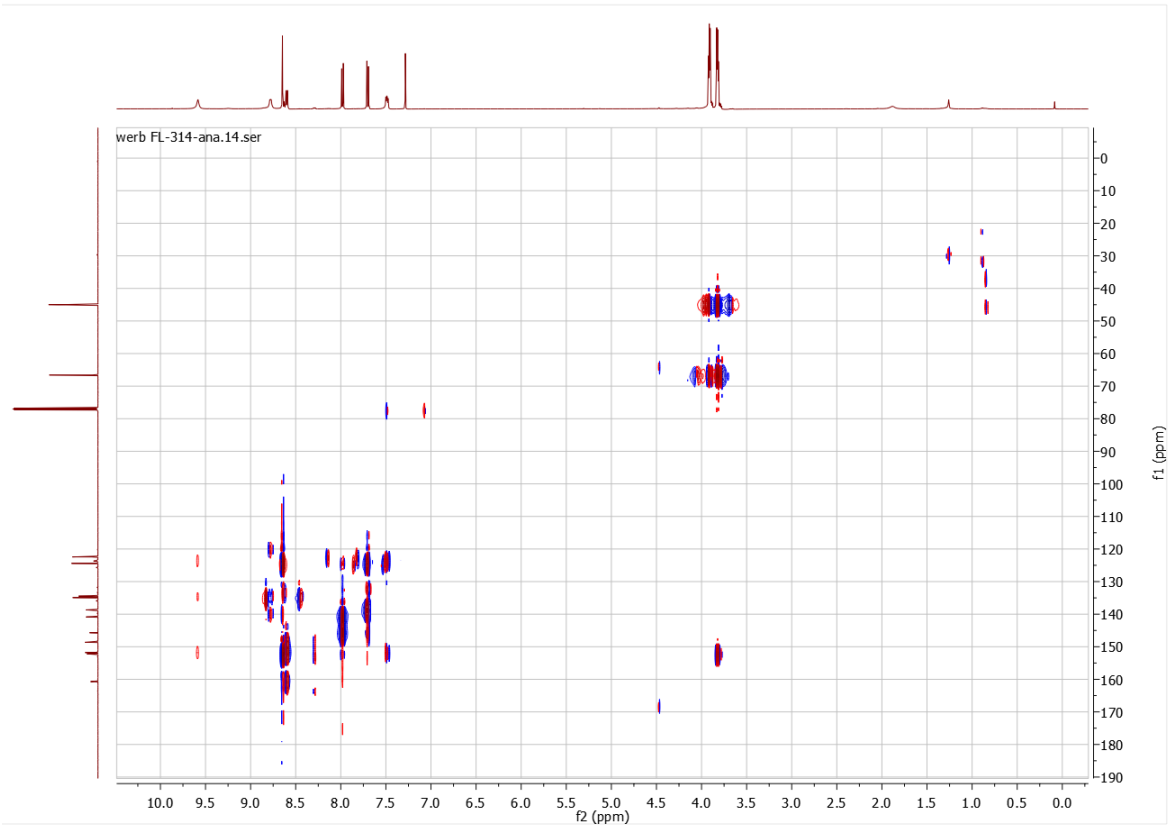
DEPT (125 MHz, $CDCl_3$)



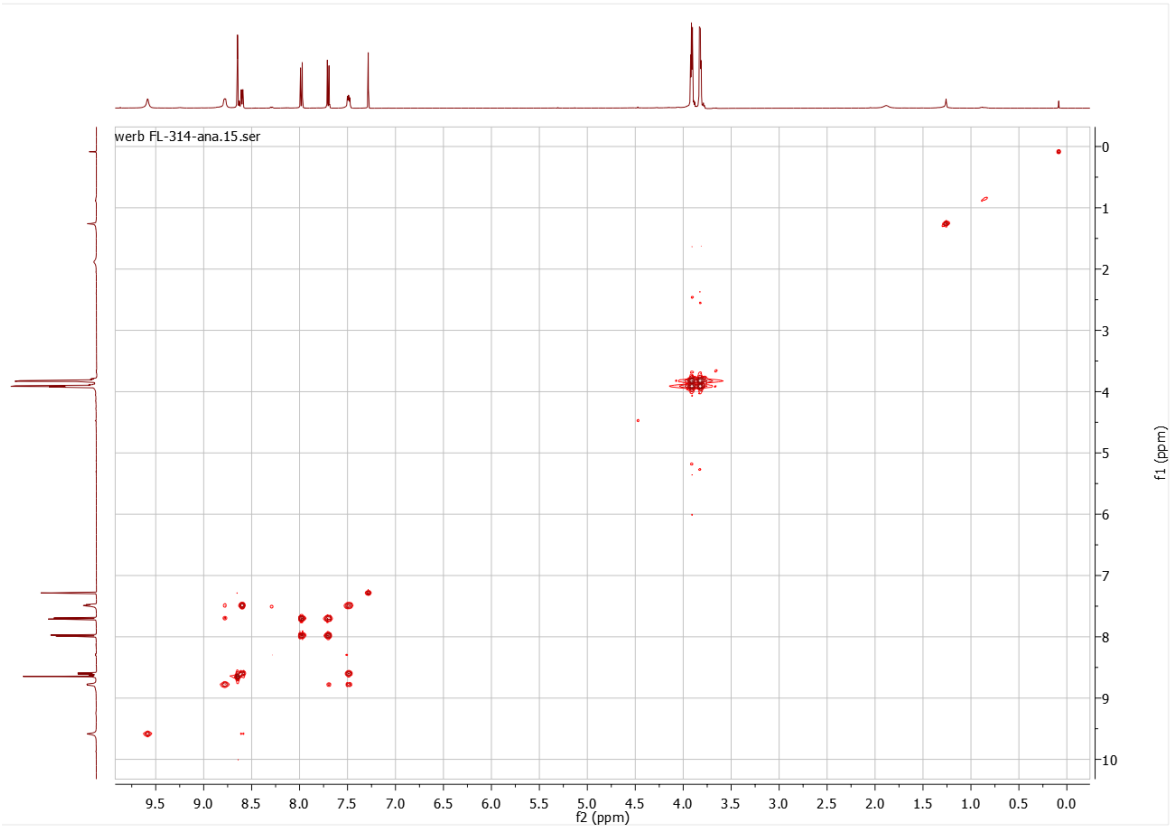

HSQC (500 MHz, $CDCl_3$)



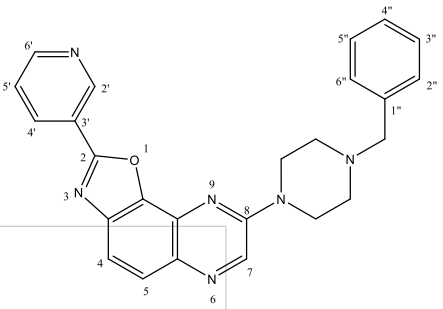
HMBC (500 MHz, $CDCl_3$)



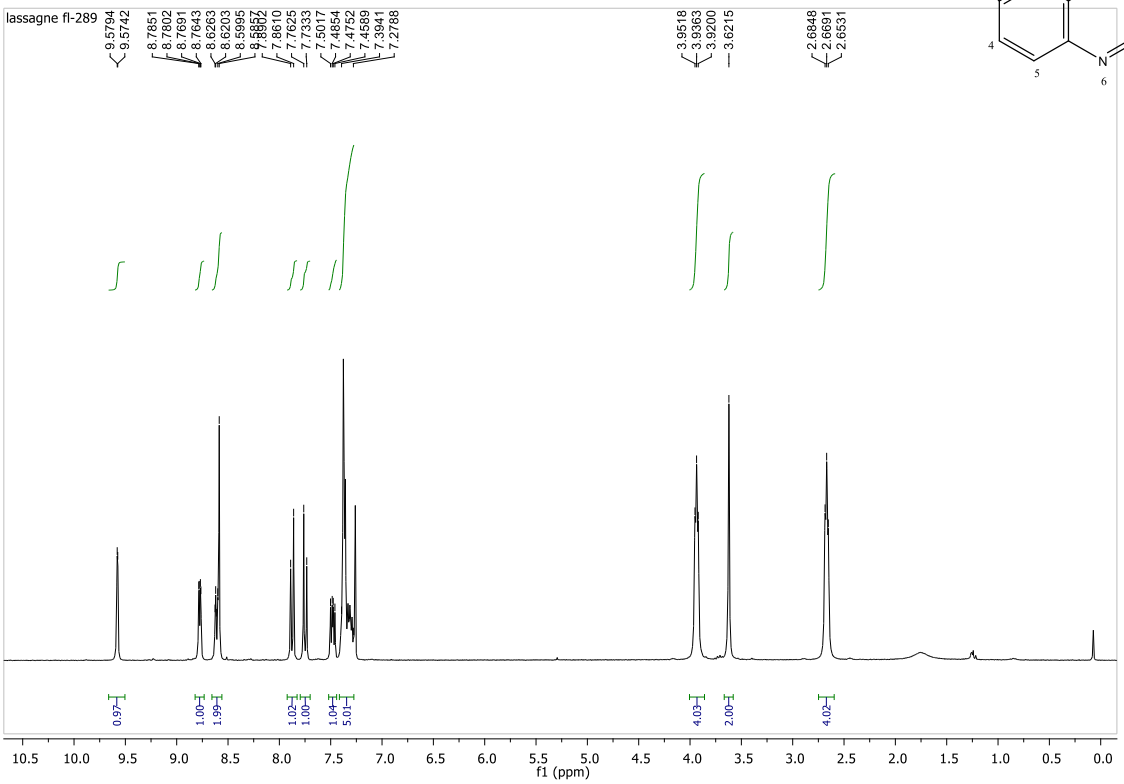

COSY (500 MHz, $CDCl_3$)



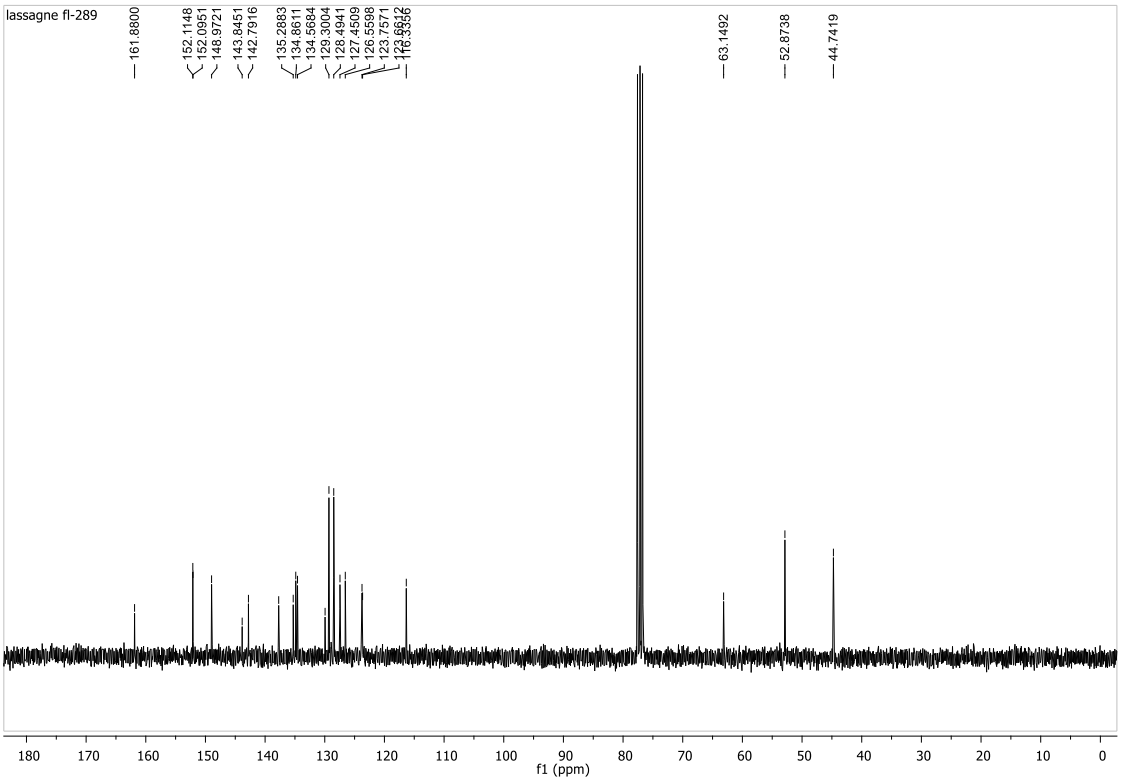
## 8-(4-Benzylpiperazino)-2-(3-pyridyl)oxazolo[5,4-*f*]quinoxaline (10bc)



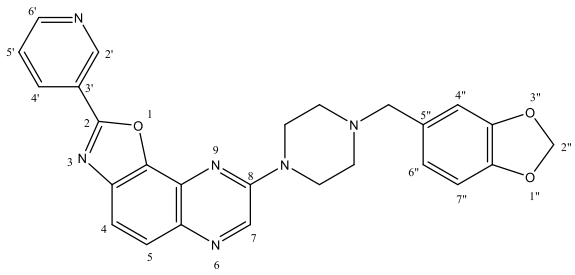
$^{1}$H NMR (300 MHz, $CDCl_3$)



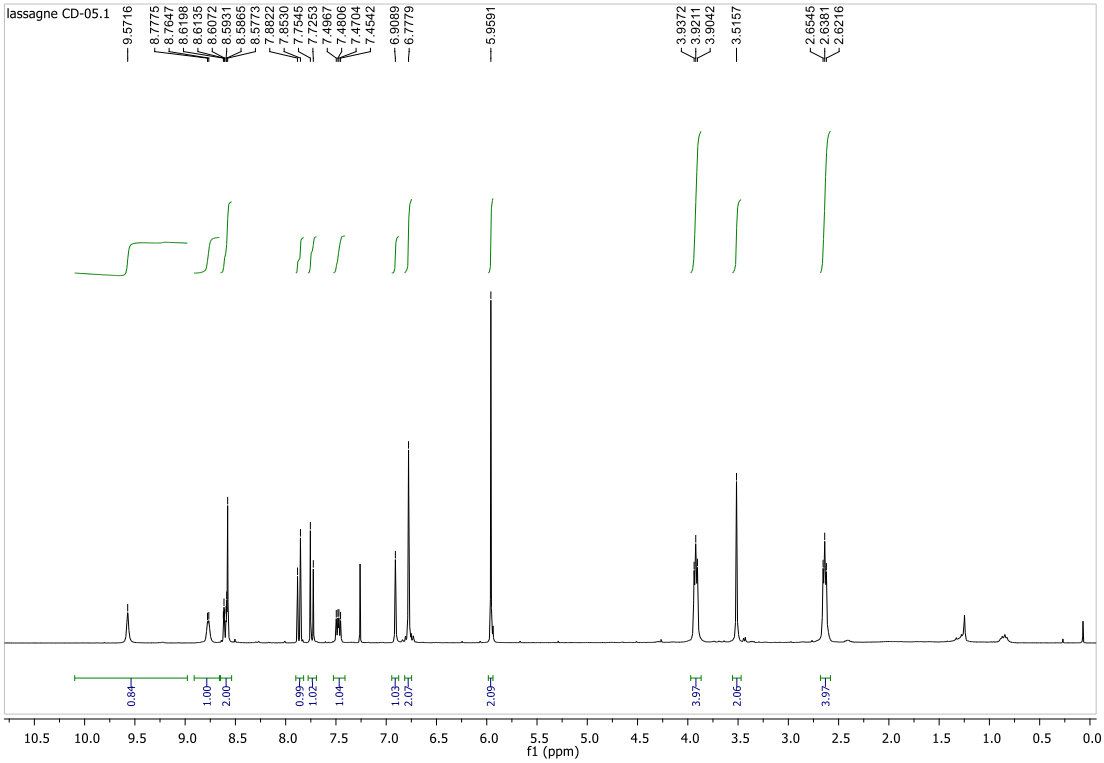

$^{13}$C NMR (75 MHz, $CDCl_3$)



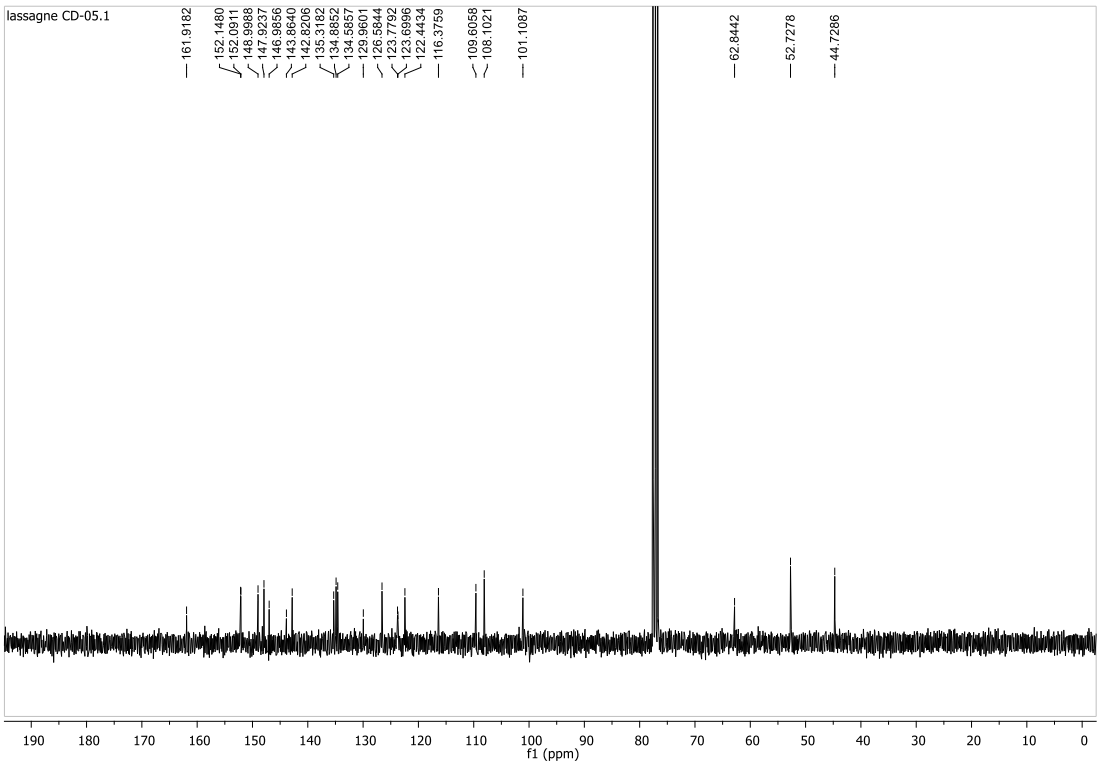
**8-(4-(5-(1,3-Benzodioxolyl))methylpiperazino)-2-(3-pyridyl)oxazolo[5,4-*f*]quinoxaline (10bd)**

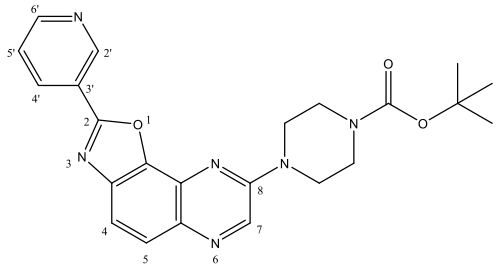


$^{1}$H NMR (300 MHz, $CDCl_3$)



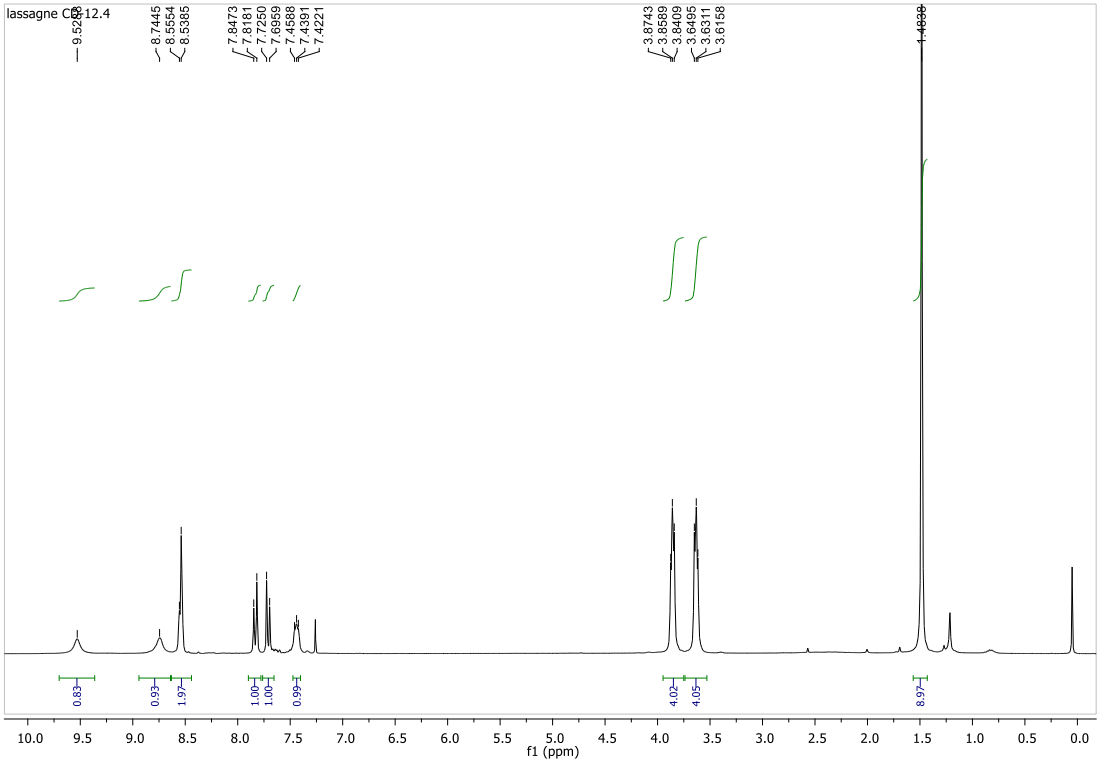

$^{13}$C NMR (75 MHz, $CDCl_3$)



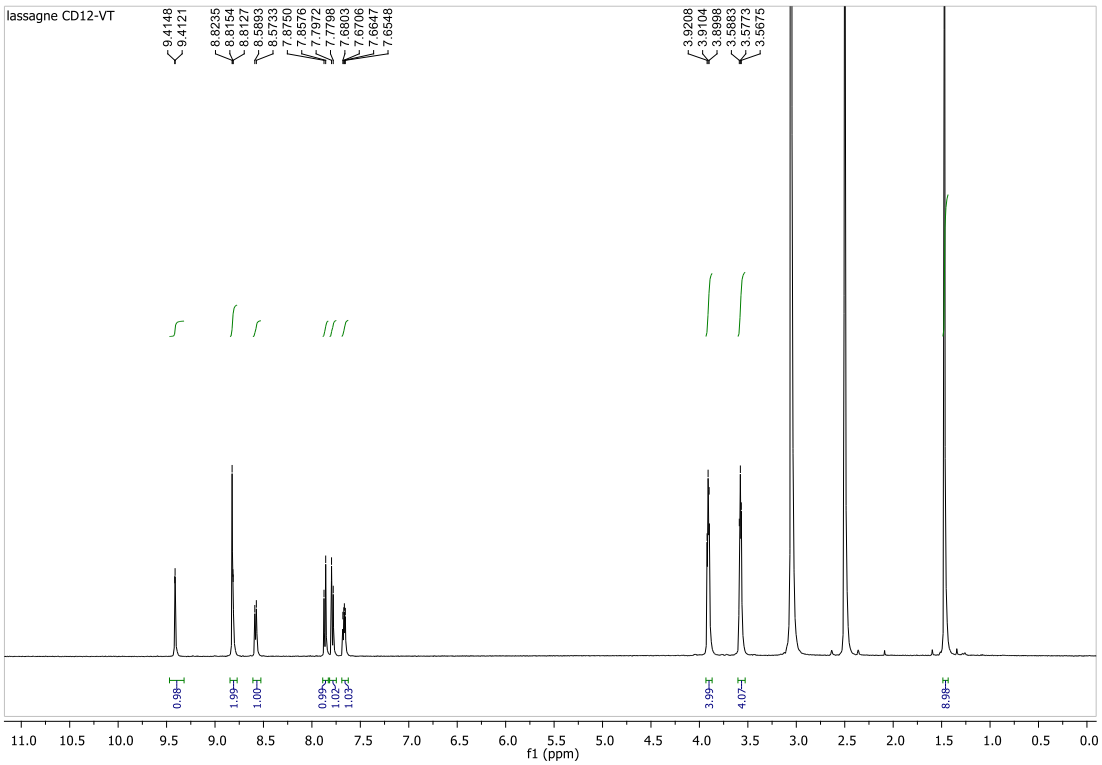


**8-(4-*tert*-Butoxycarbonylpiperazino)-2-(3-pyridyl)oxazolo[5,4-*f*]quinoxaline (10be)**

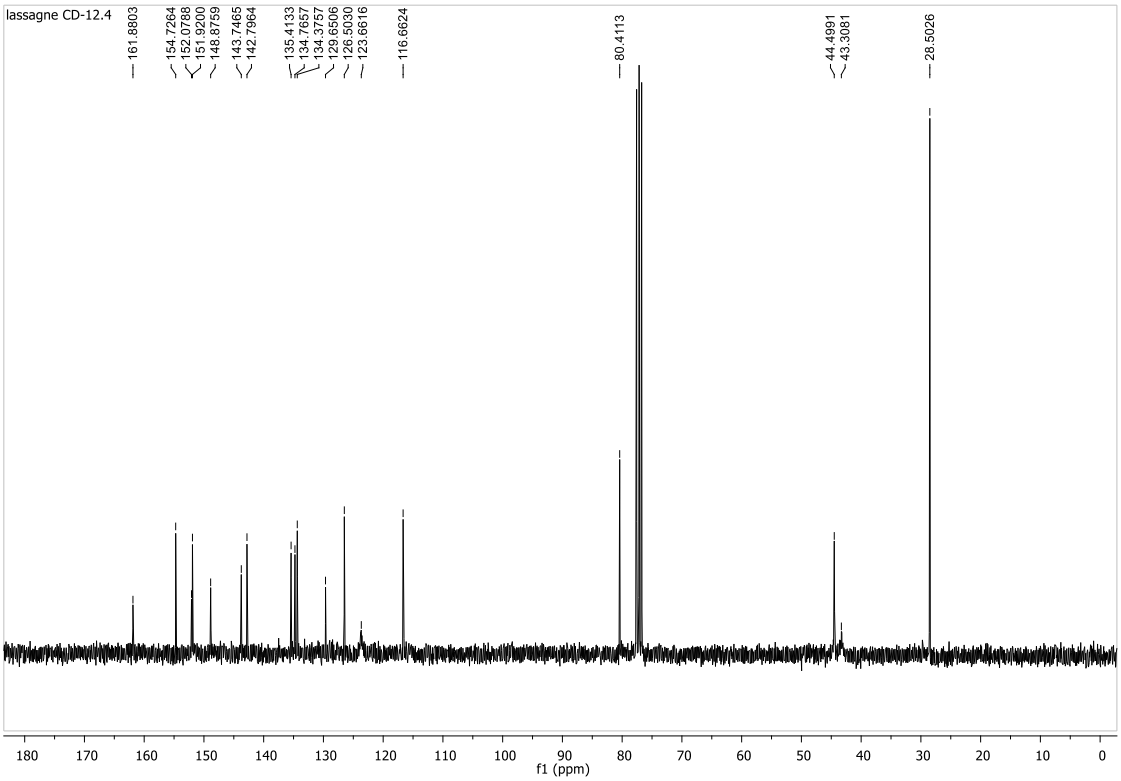
$^1$H NMR (300 MHz, $CDCl_3$)



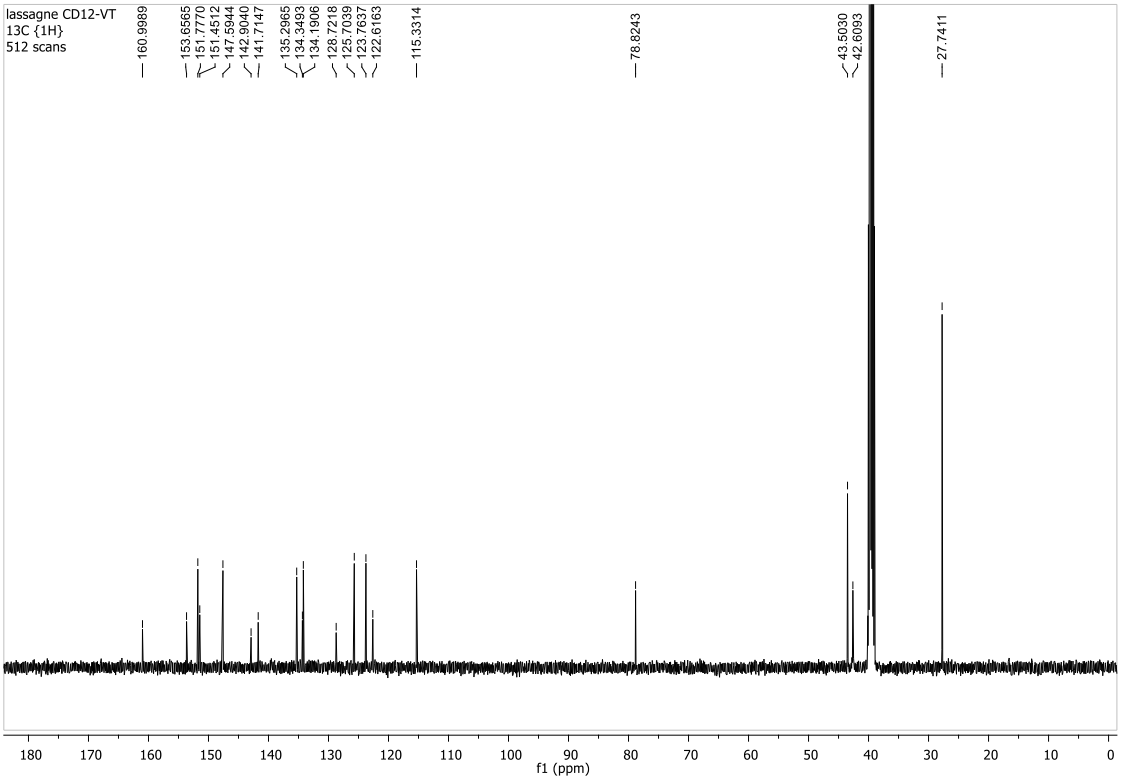

$^1$H NMR (500 MHz, $(CD_3)_2SO$, 358 K)



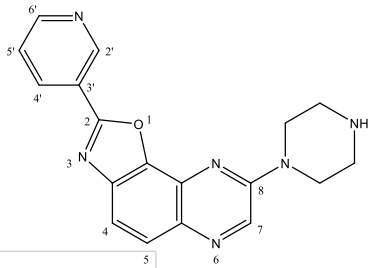
$^{13}C$ NMR (75 MHz, $CDCl_3$)



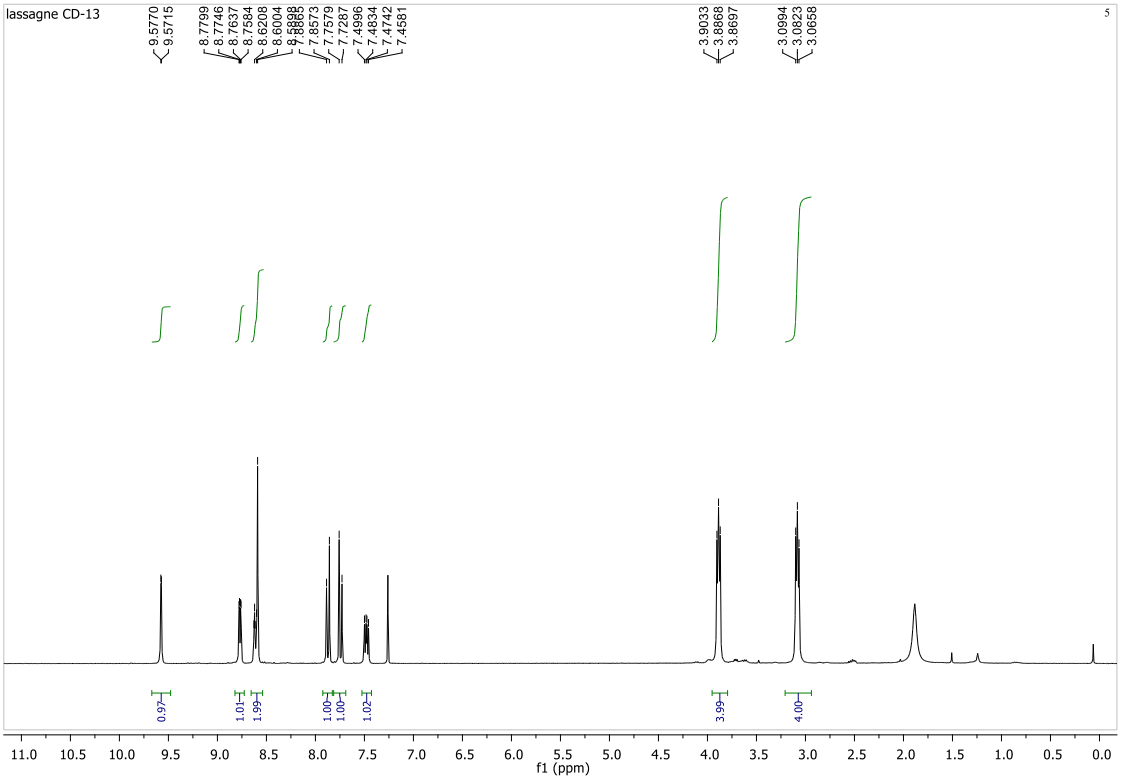

$^{13}C$ NMR (126 MHz, $(CD_3)_2SO$, 358 K)



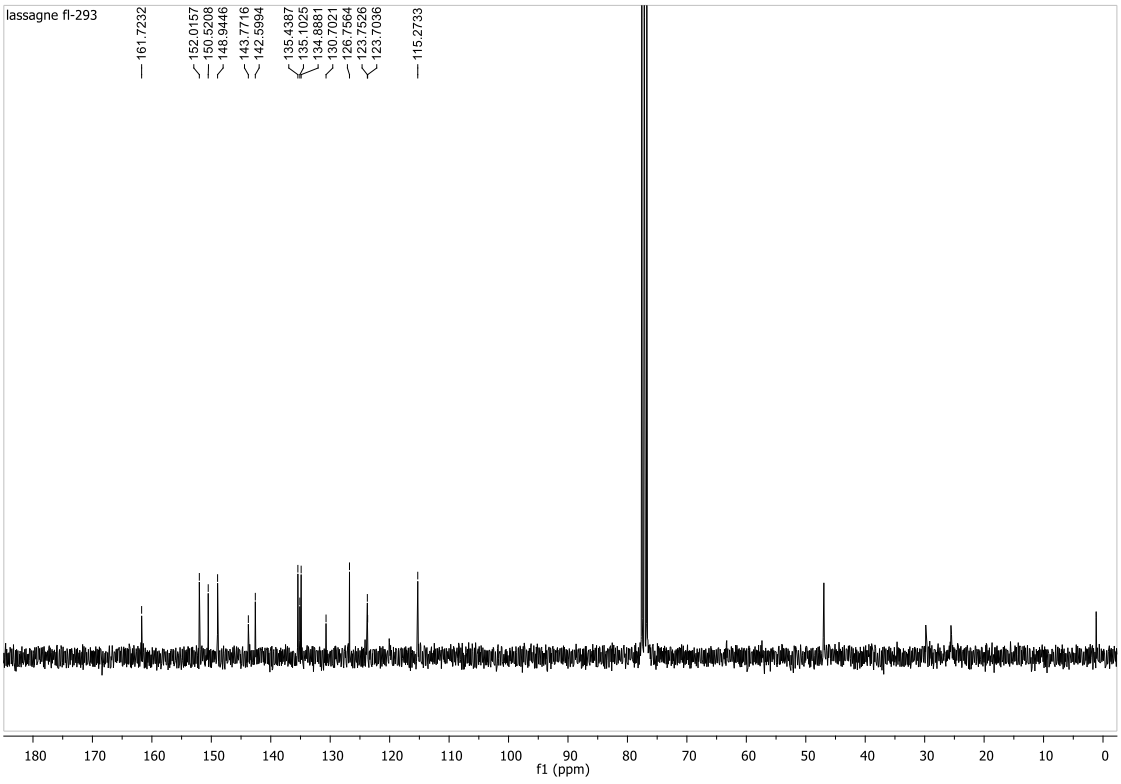
## 8-(Piperazino)-2-(3-pyridyl)oxazolo[5,4-*f*]quinoxaline (10bf)



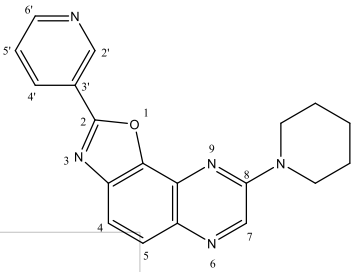

$^{1}$H NMR (300 MHz, $CDCl_3$)



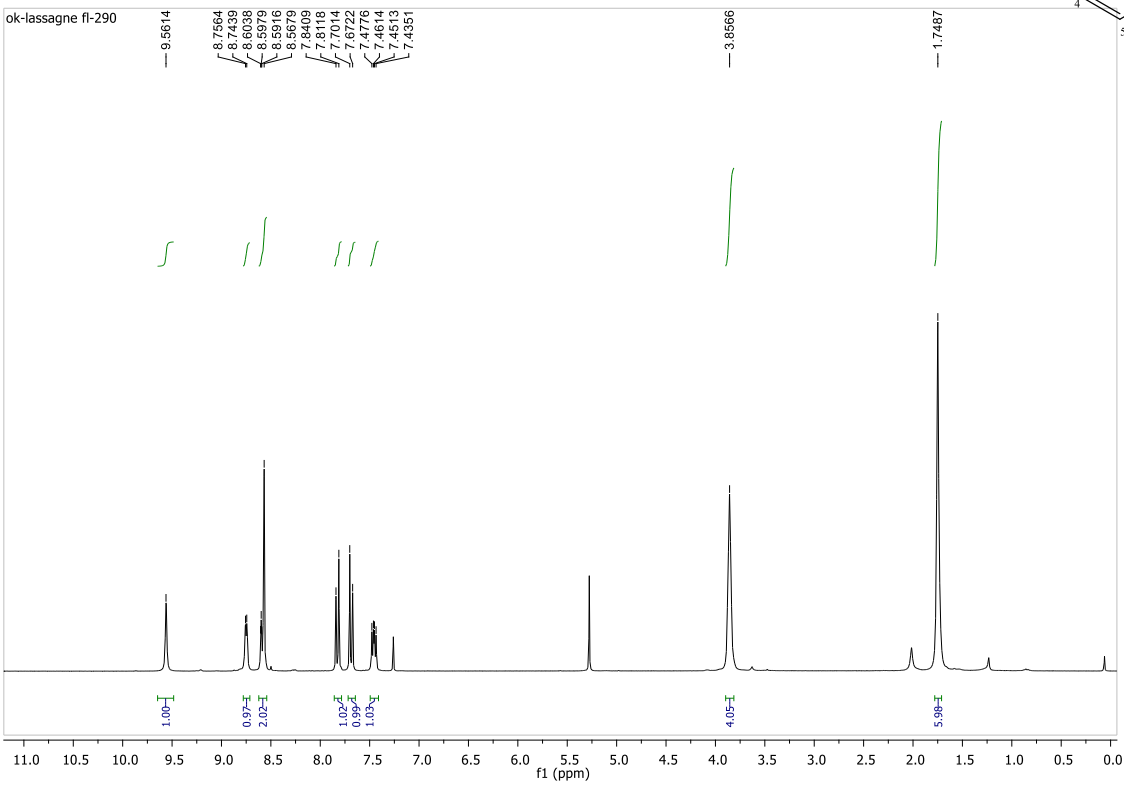

$^{13}$C NMR (75 MHz, $CDCl_3$)



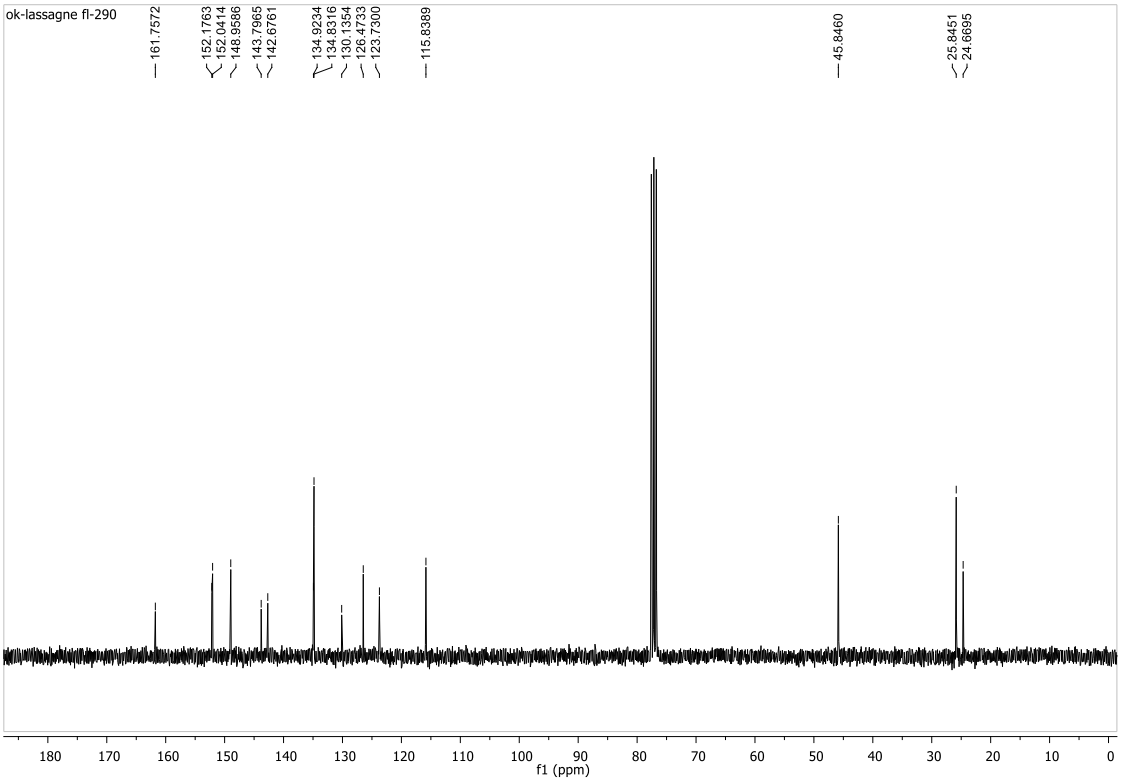
## 8-(Piperidino)-2-(3-pyridyl)oxazolo[5,4-*f*]quinoxaline (10bg)



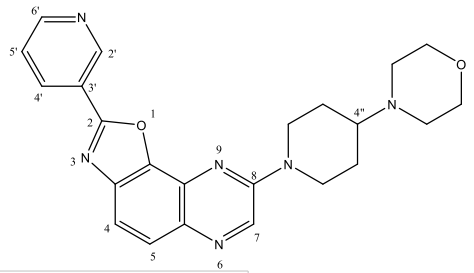
$^{1}$H NMR (300 MHz, $CDCl_3$)



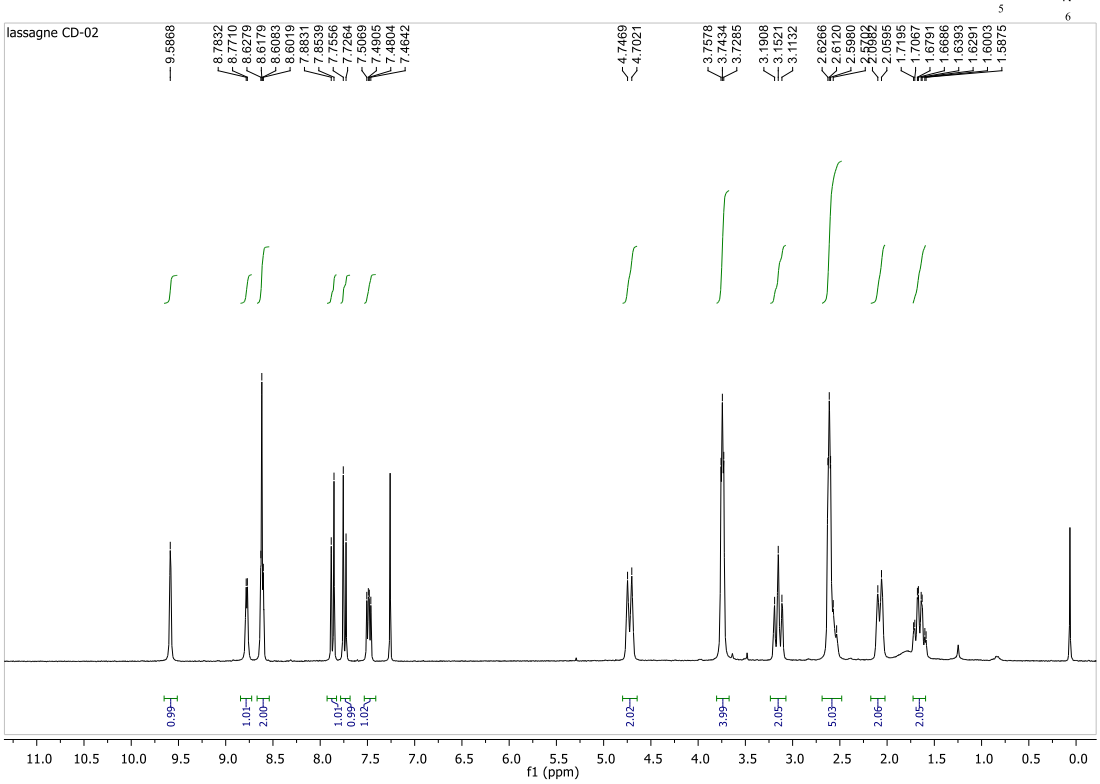

$^{13}$C NMR (75 MHz, $CDCl_3$)



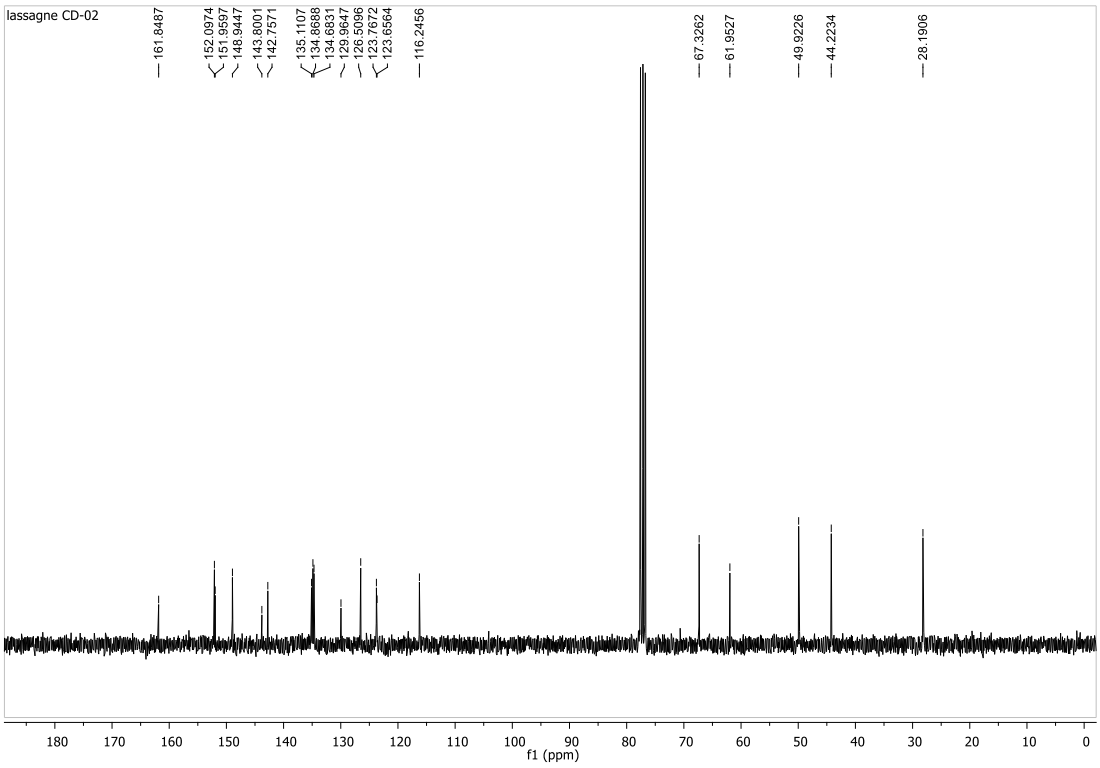
**8-(4-Morpholinopiperidino)-2-(3-pyridyl) oxazolo[5,4-*f*]quinoxaline (10bh)**



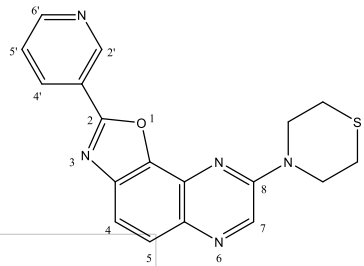
$^{1}$H NMR (300 MHz, $CDCl_3$)



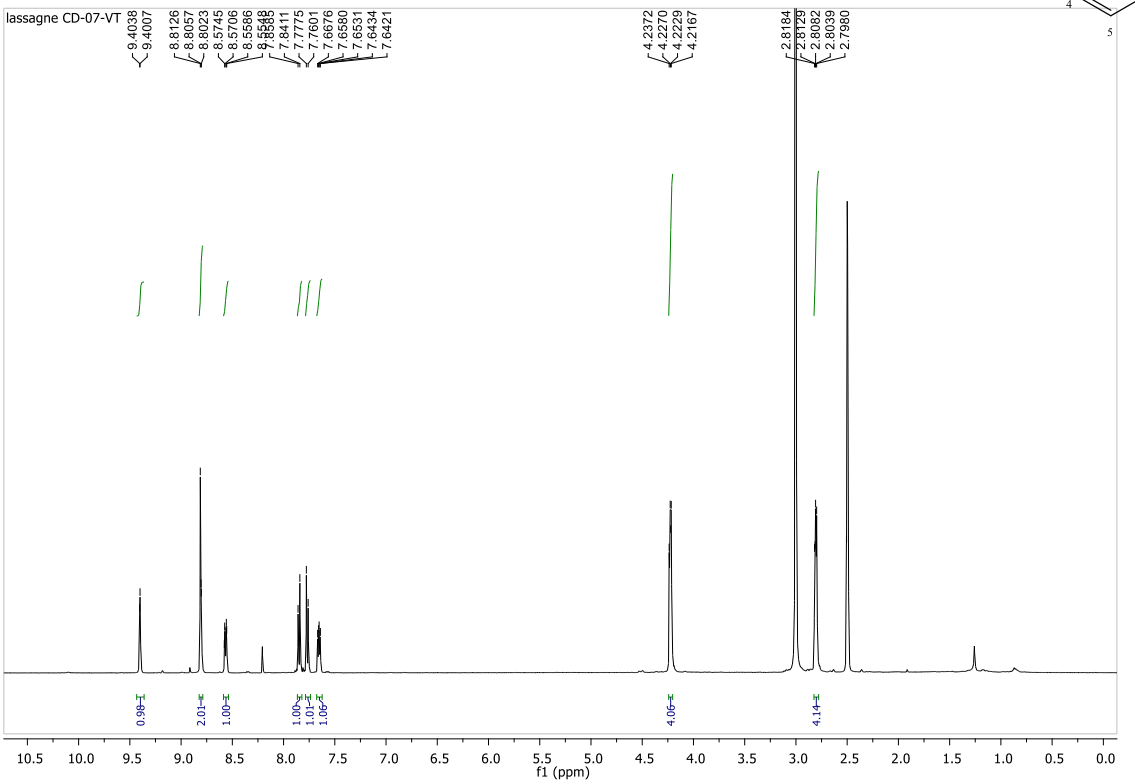

$^{13}$C NMR (75 MHz, $CDCl_3$)



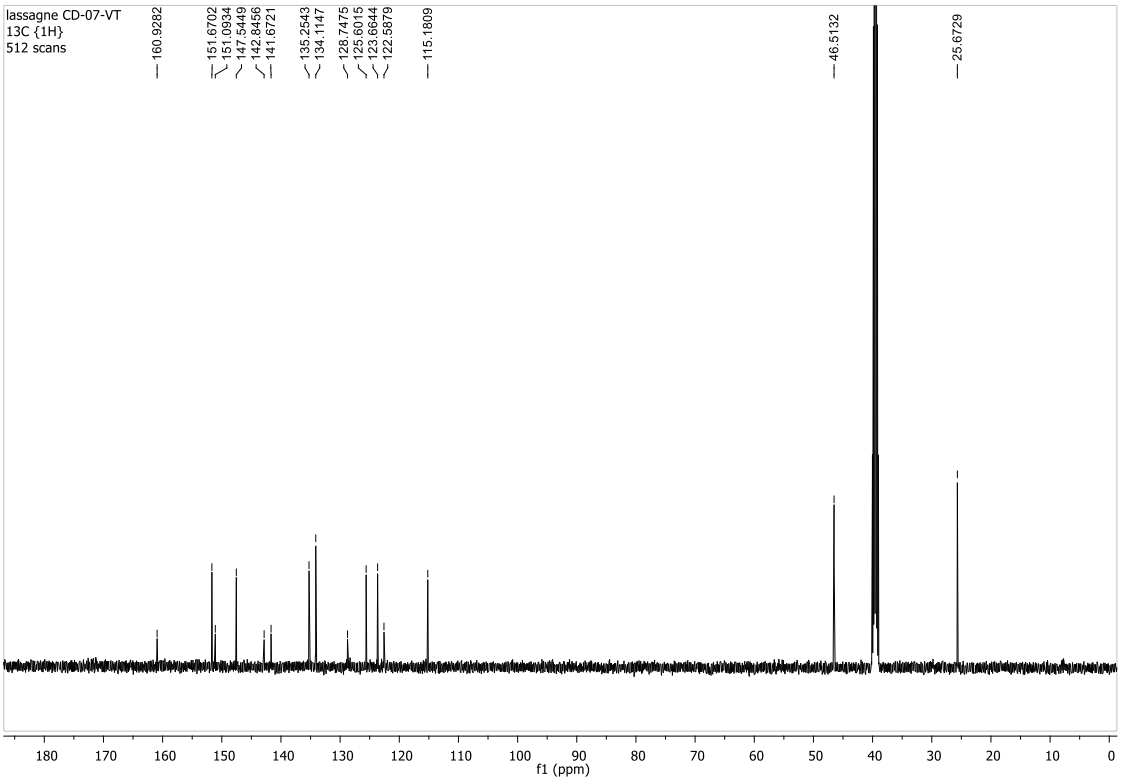
## 2-(3-Pyridyl)-8-(thiomorpholino)oxazolo[5,4-*f*]quinoxaline (10bi)

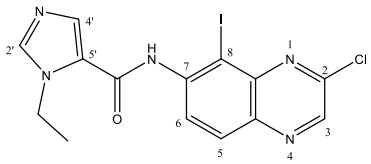


$^{1}$H NMR (500 MHz, $(CD_3)_2SO$, 368 K)



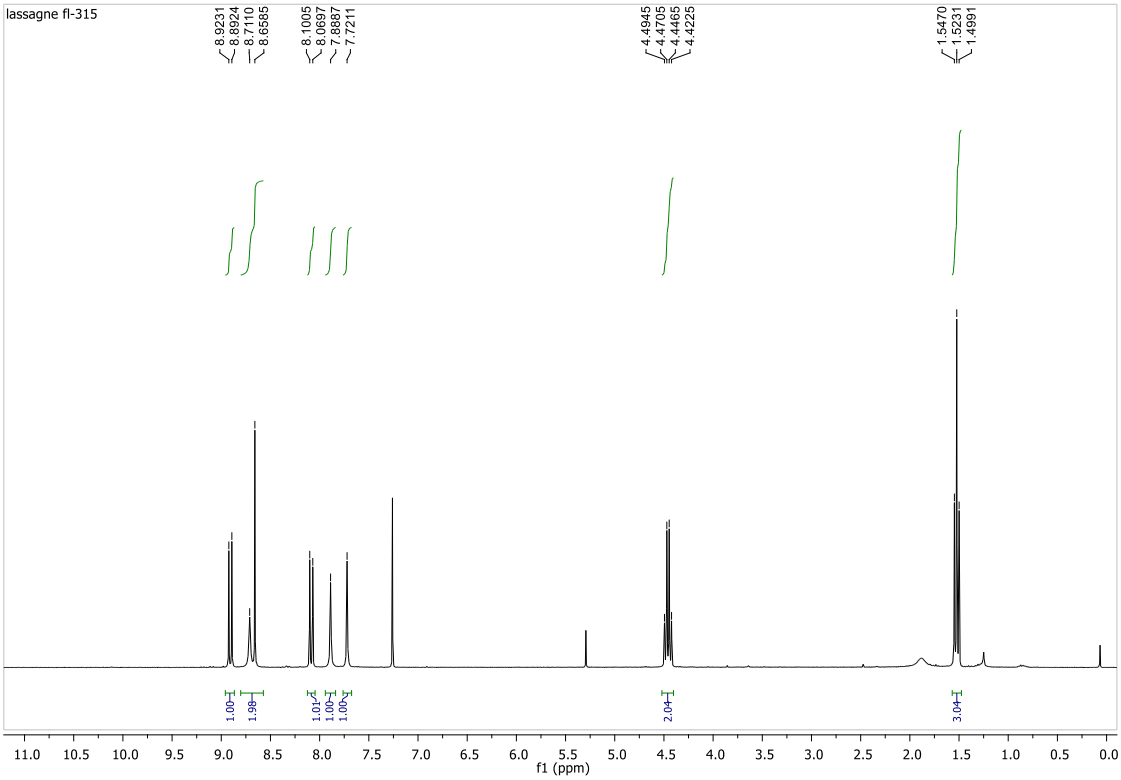

$^{13}$C NMR (126 MHz, $(CD_3)_2SO$, 368 K)



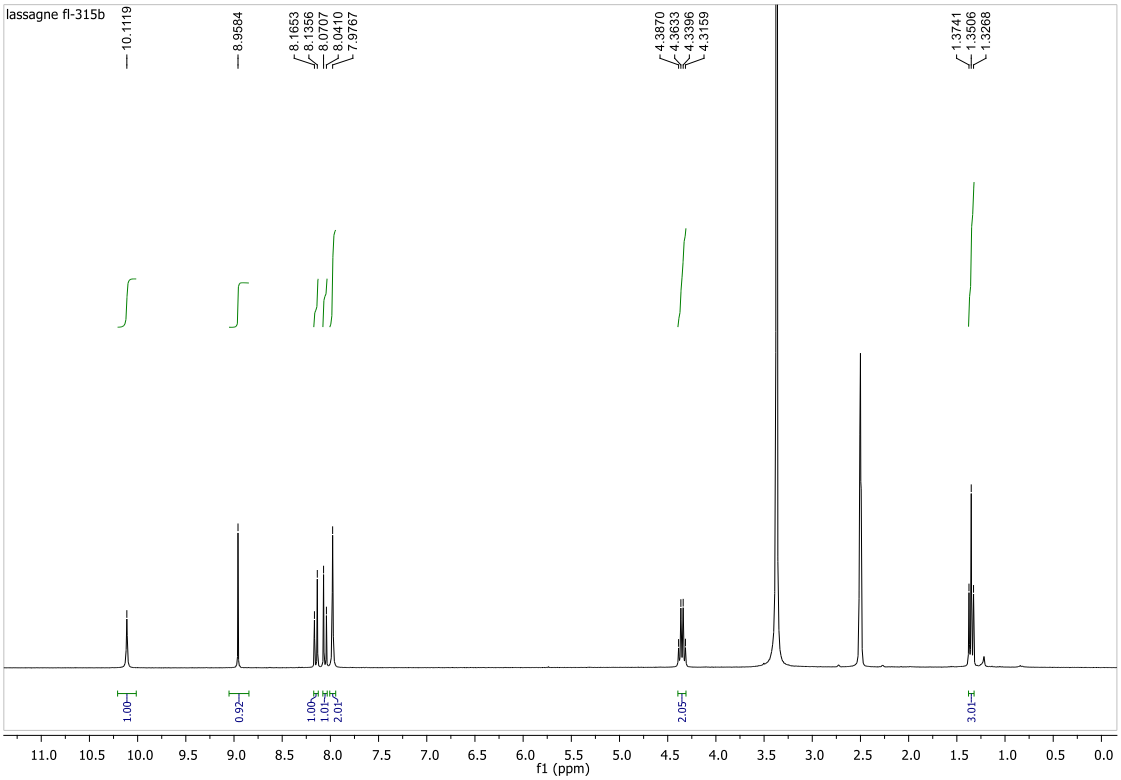


## 2-Chloro-8-iodo-7-(1-ethyl-5-imidazoylamino)quinoxaline (12c)

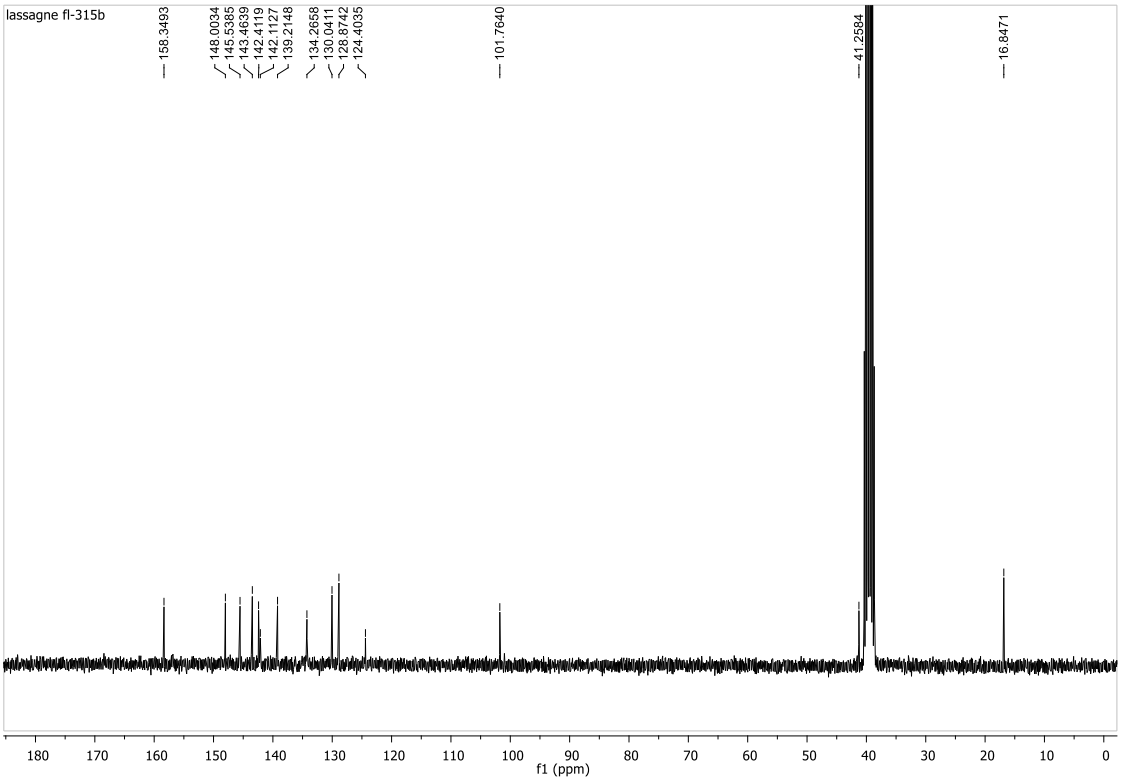
$^1$H NMR (300 MHz, $CDCl_3$)



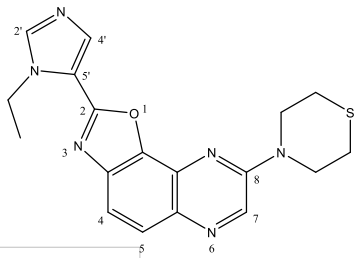

$^1$H NMR (300 MHz, $(CD_3)_2SO$)



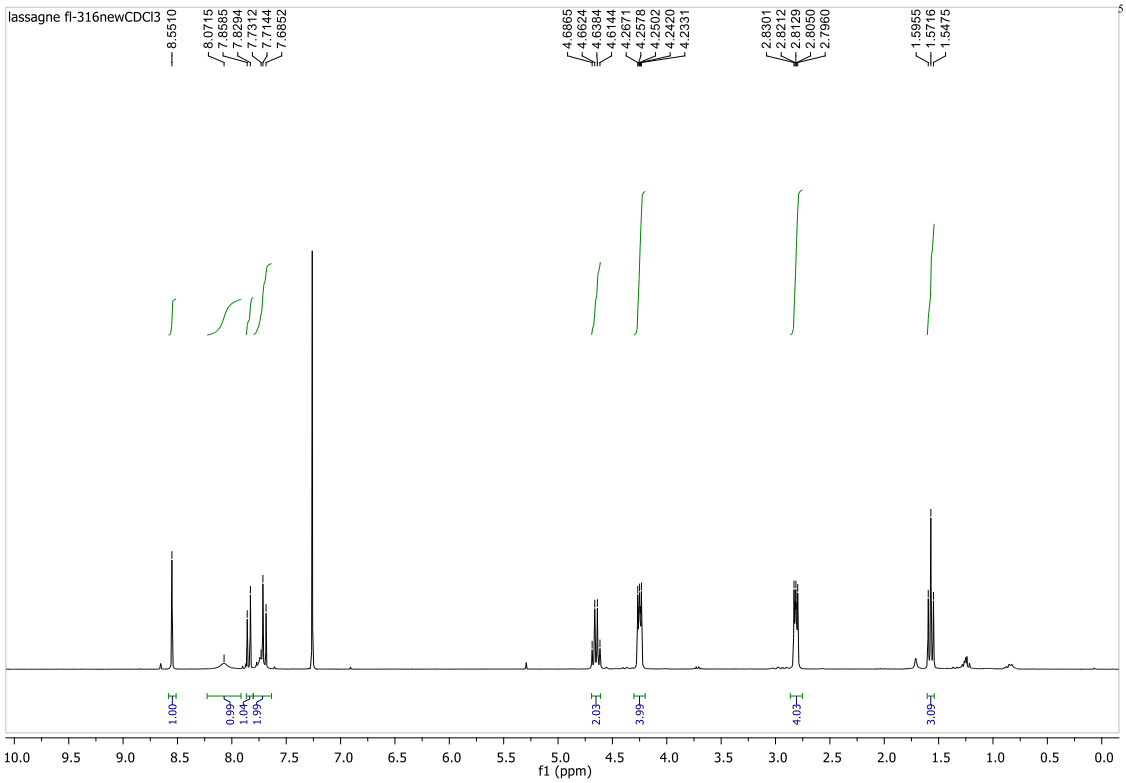
$^{13}C$ NMR (75 MHz, $(CD_3)_2SO$)



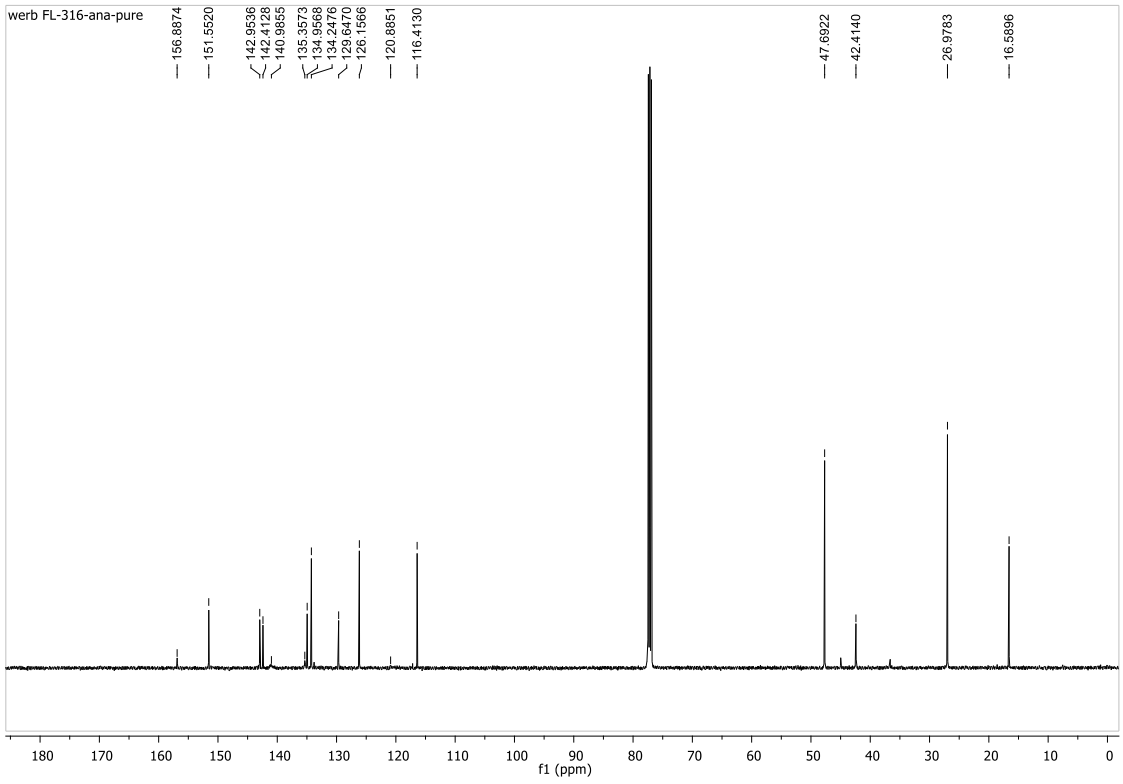
## 2-(1-Ethyl-5-imidazolyl)-8-(thiomorpholino)oxazolo[5,4-*f*]quinoxaline (10ci)



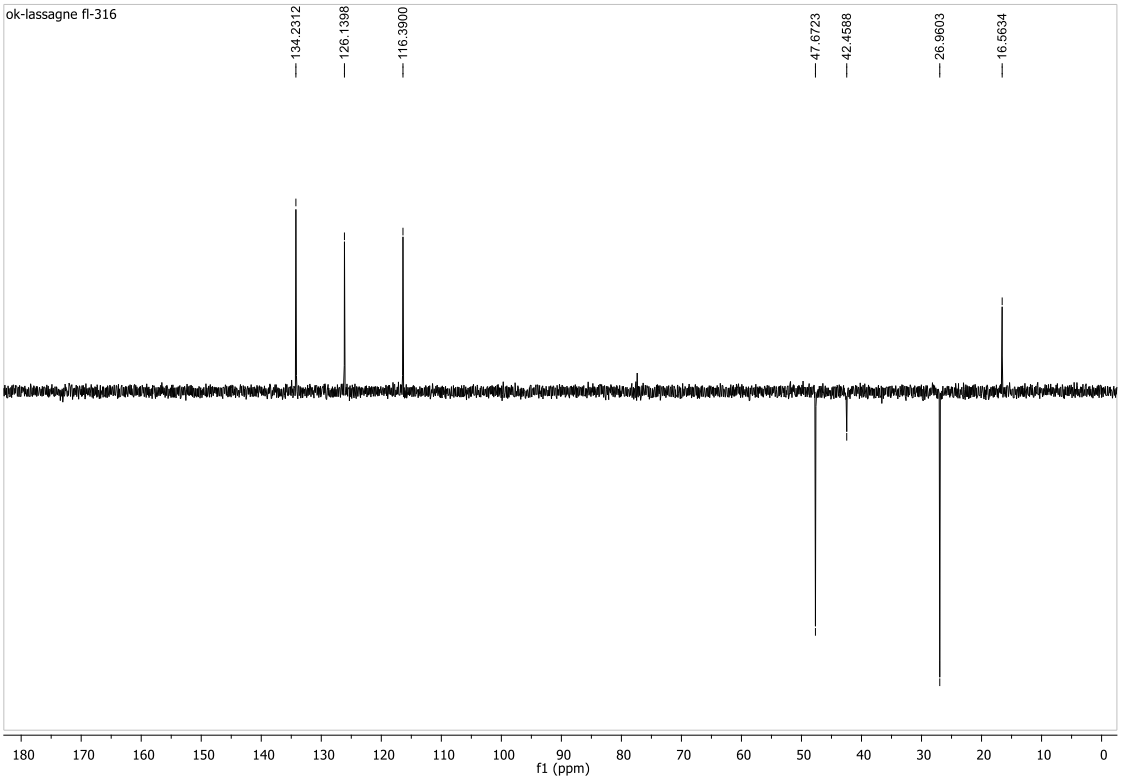
$^{1}$H NMR (300 MHz, $CDCl_3$)



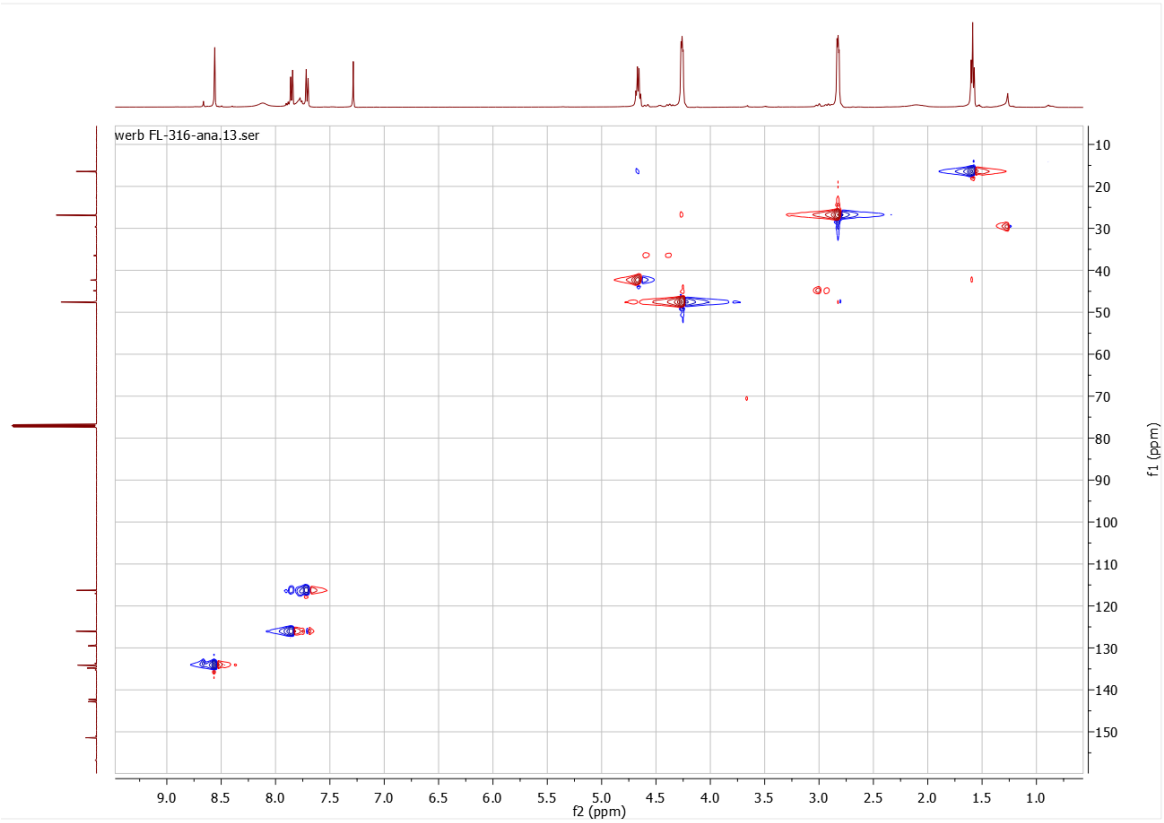

$^{13}$C NMR (125 MHz, $CDCl_3$)



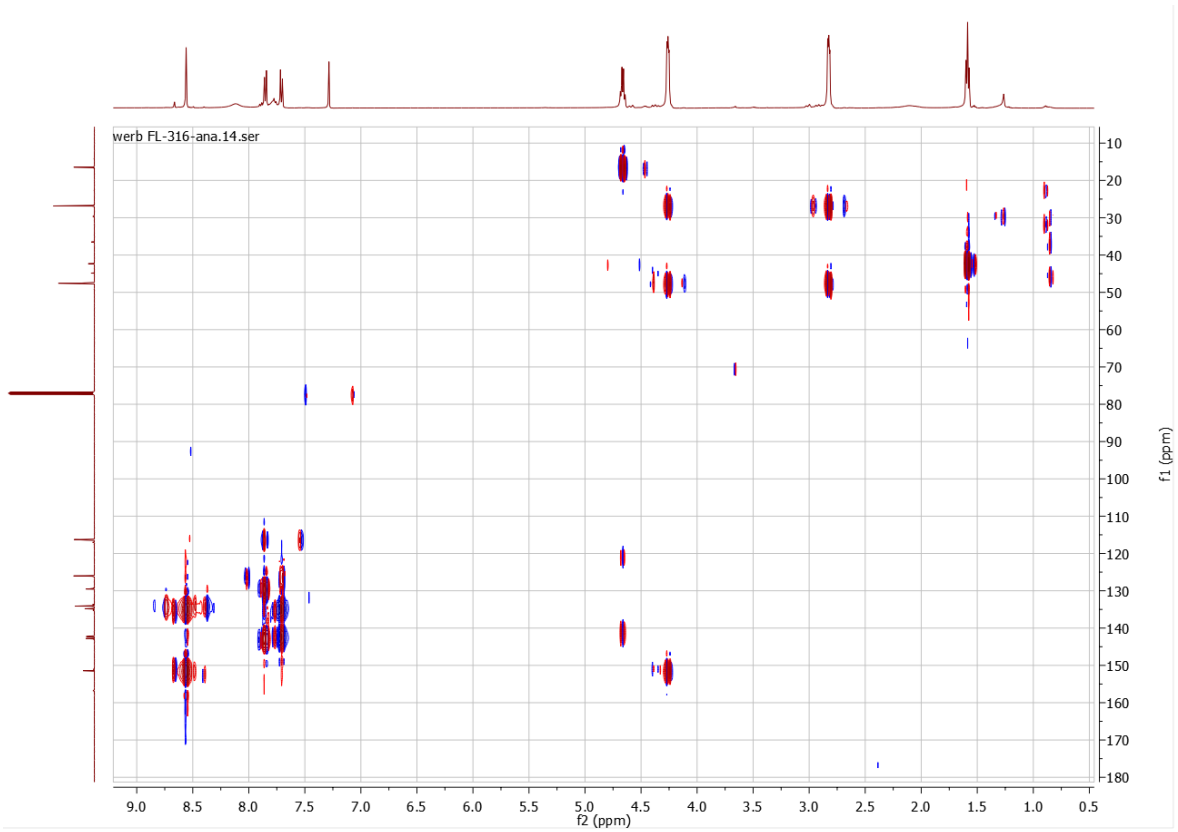
DEPT (75 MHz, $CDCl_3$)



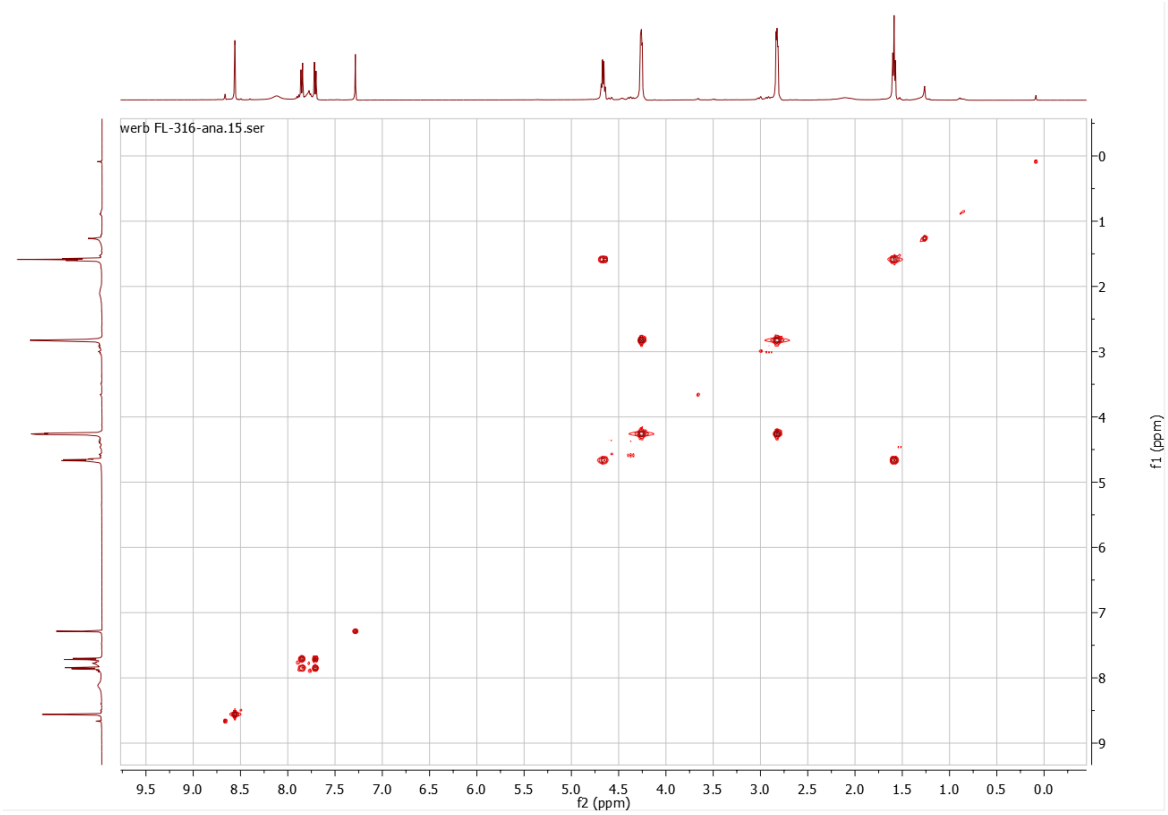

HSQC (500 MHz, $CDCl_3$)



HMBC (500 MHz, $CDCl_3$)

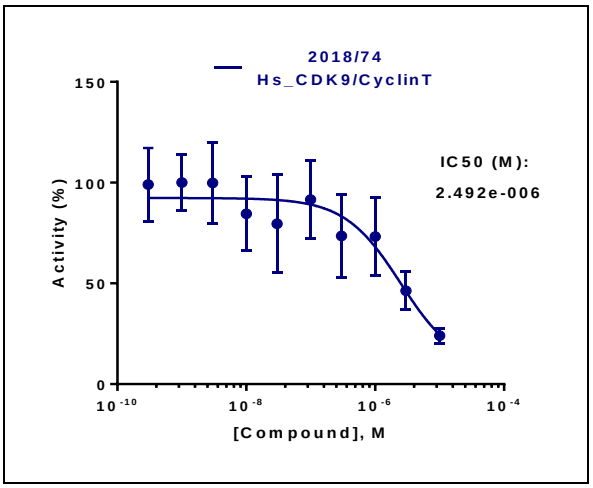


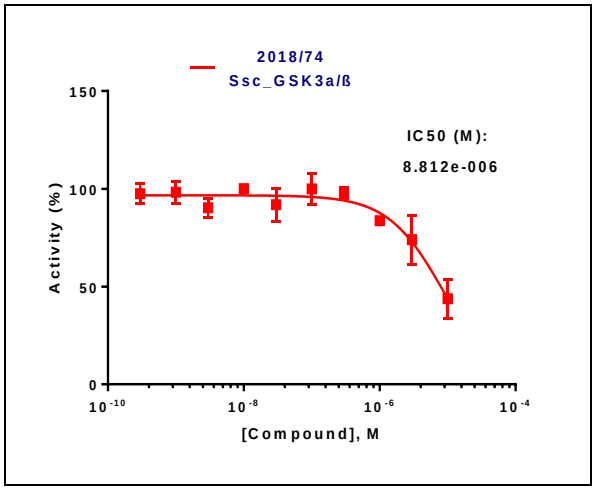

COSY (500 MHz, $CDCl_3$)

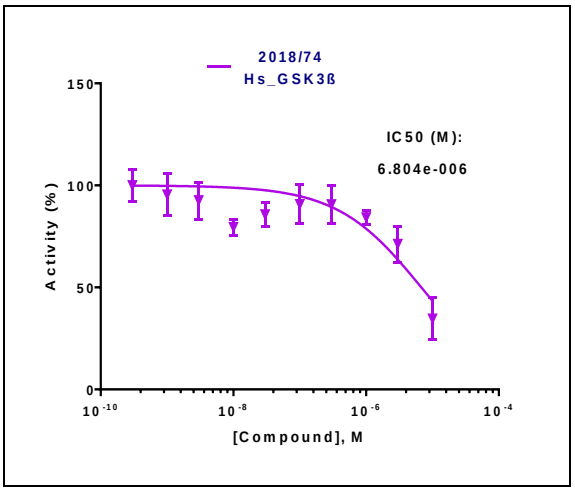


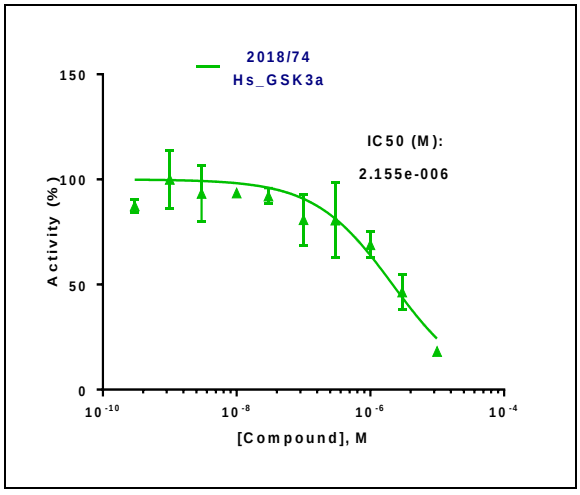
## Titration curves for $IC_{50}$ determination

### Compound 9aa

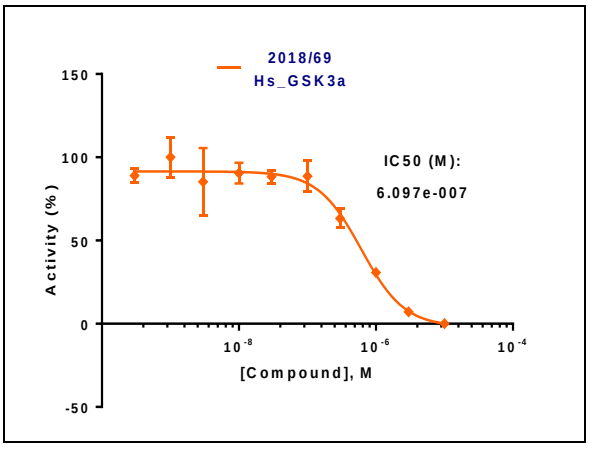


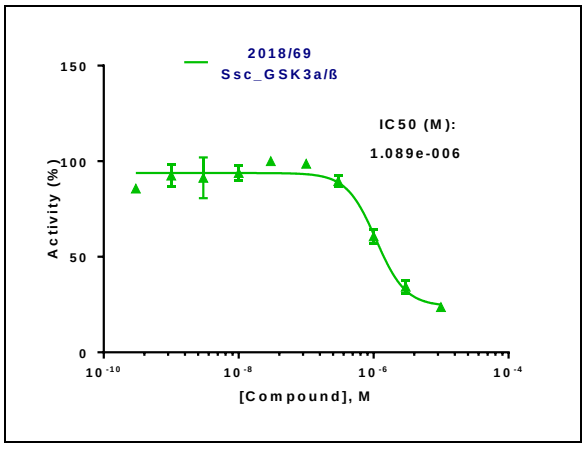



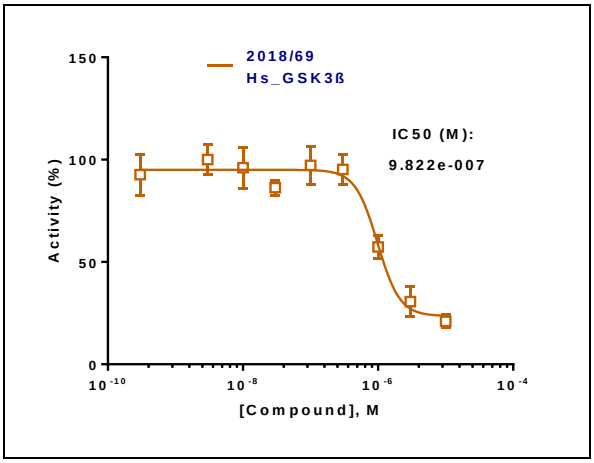



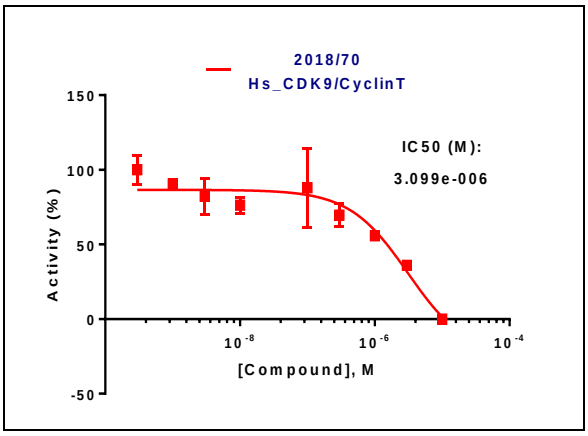
## Compound 10aa

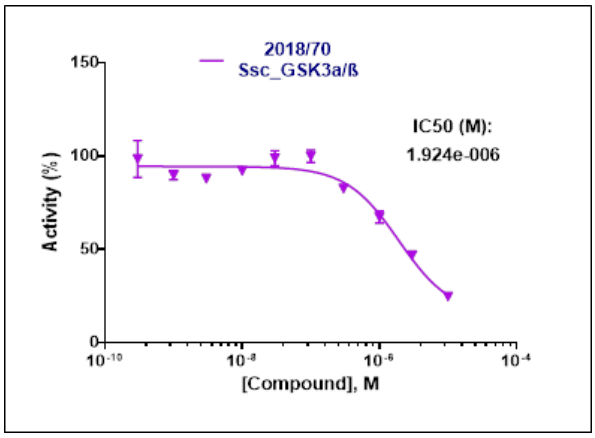


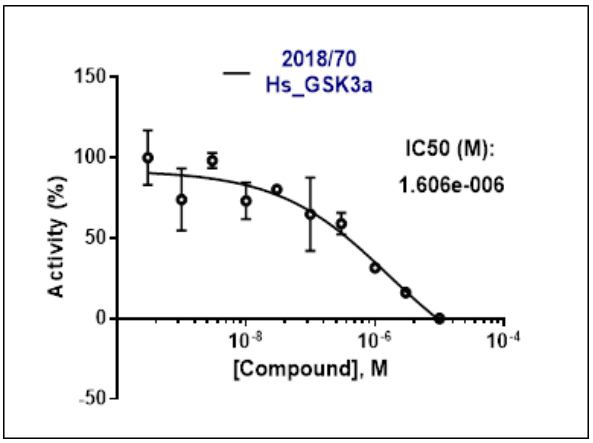



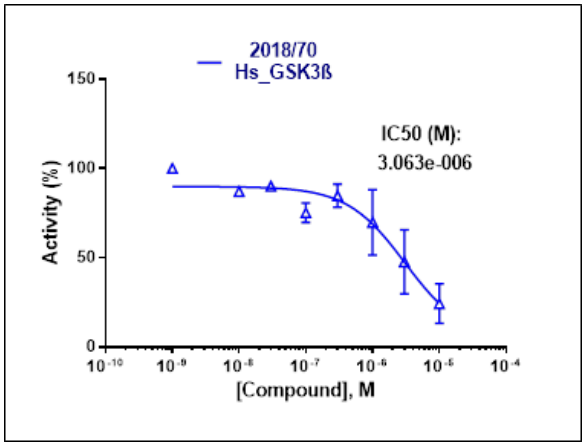



## Compound 10ab

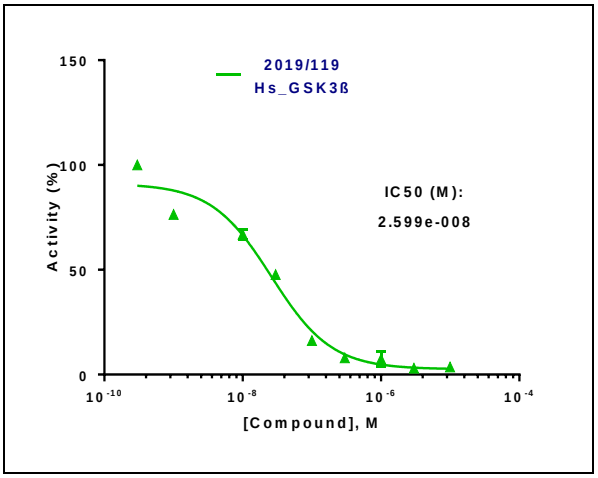


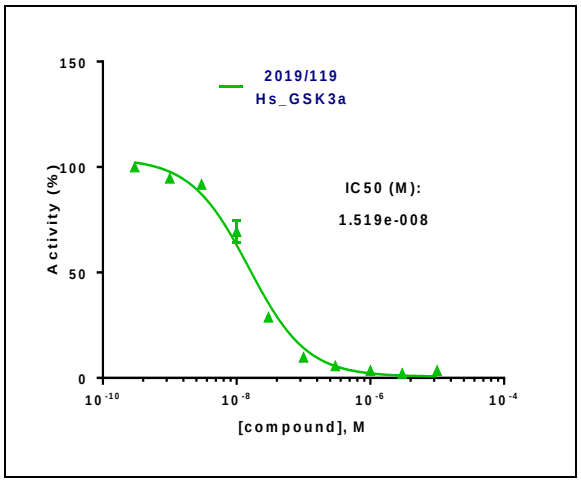



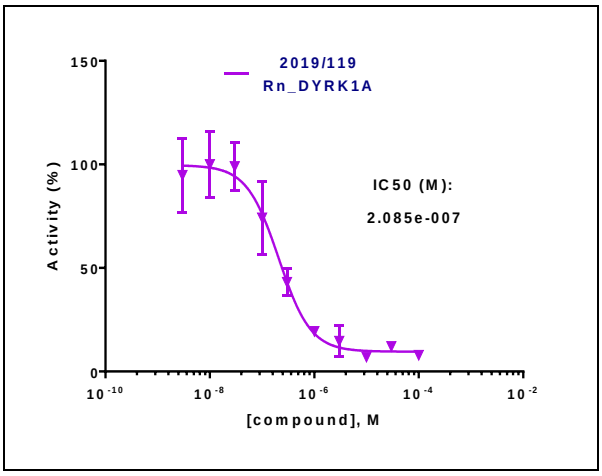



## Compound 10ba



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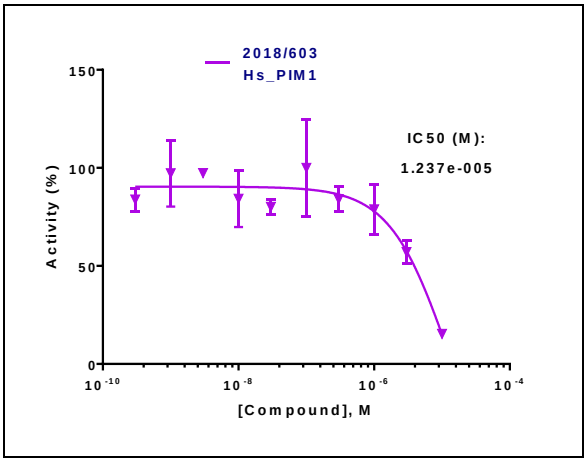
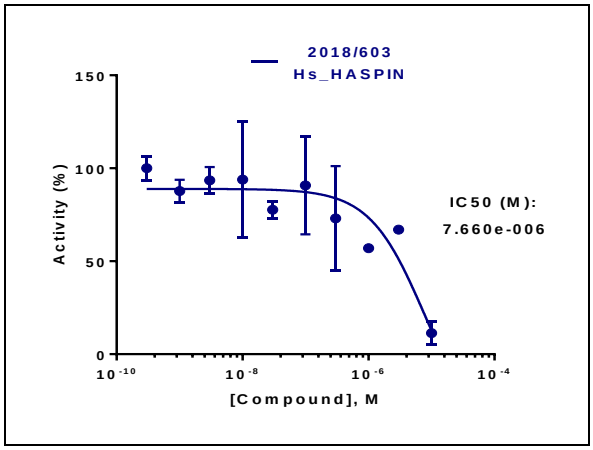
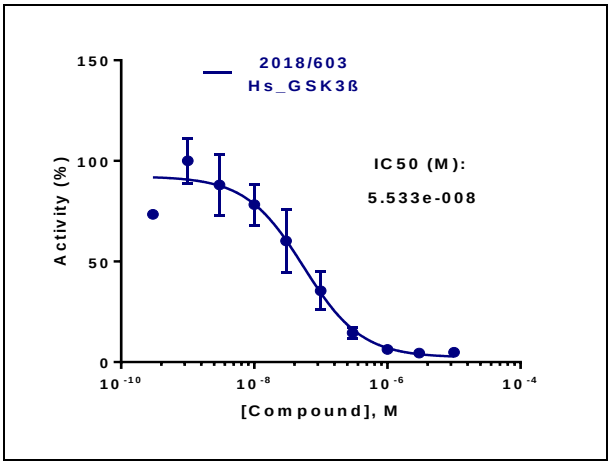
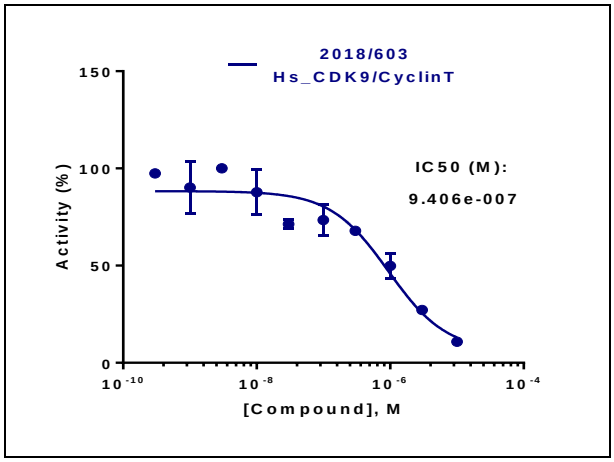
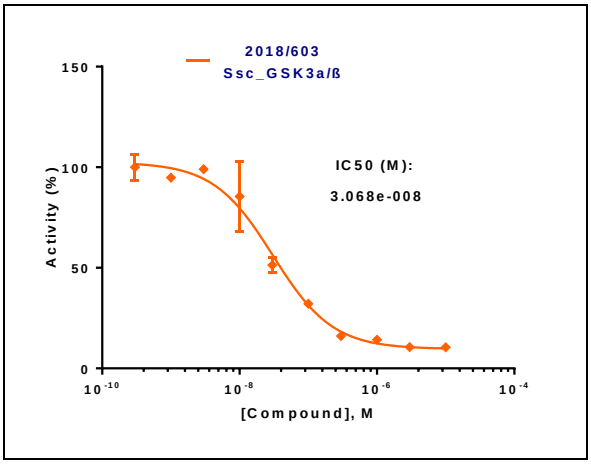
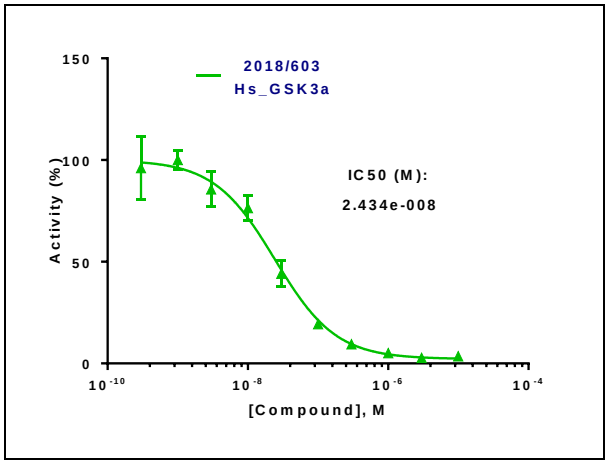


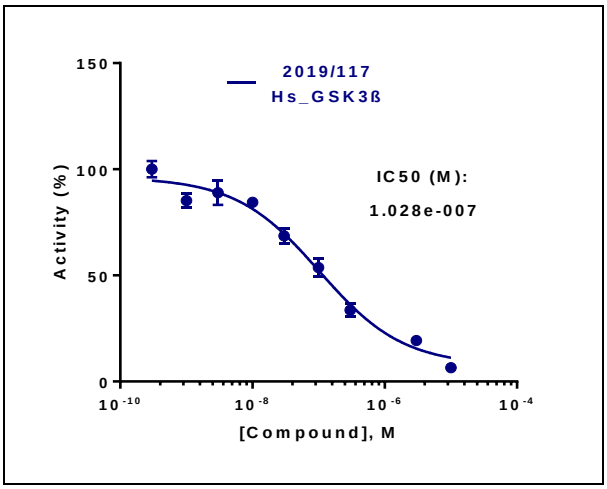



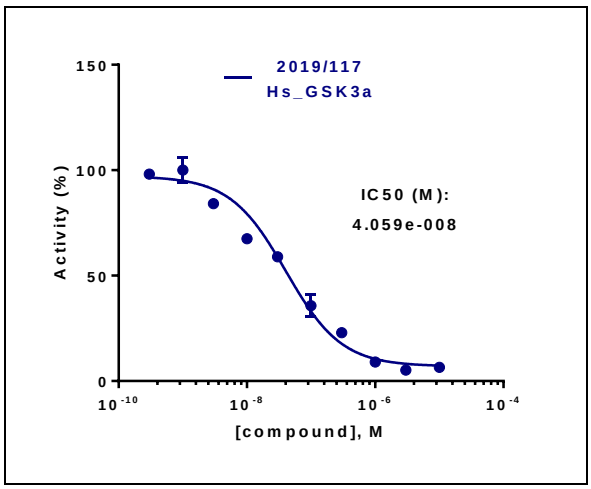



## Compound 10bc

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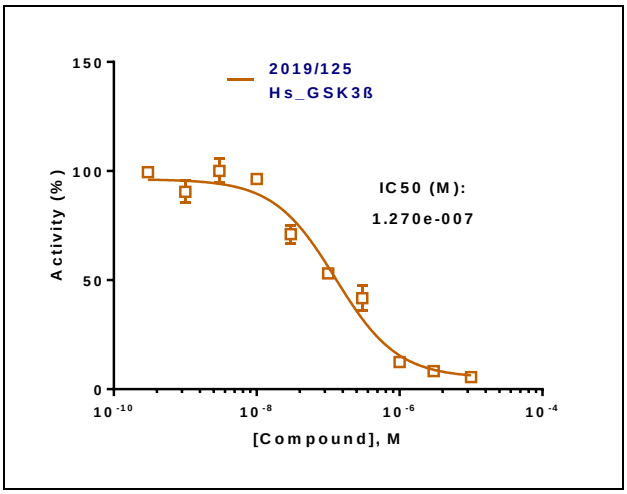
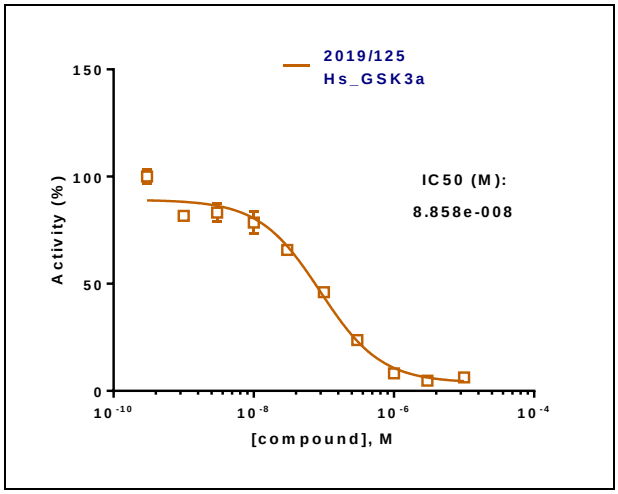
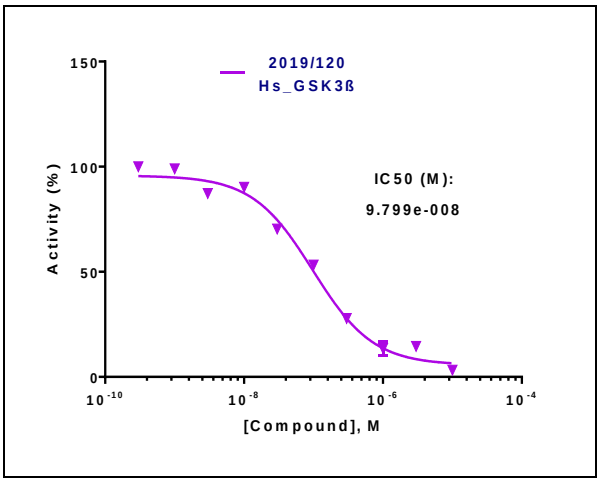
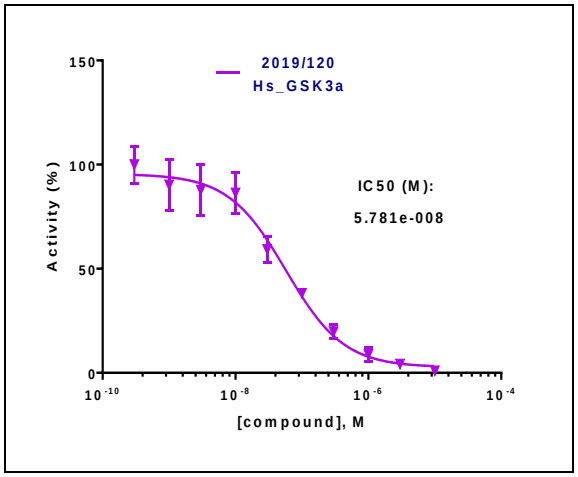


## Compound 10be

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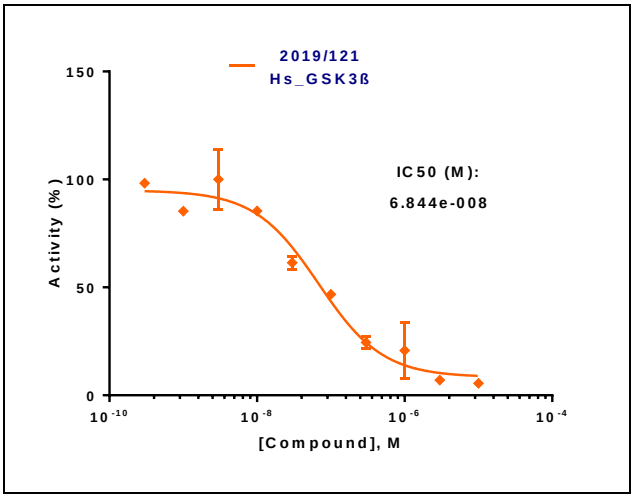
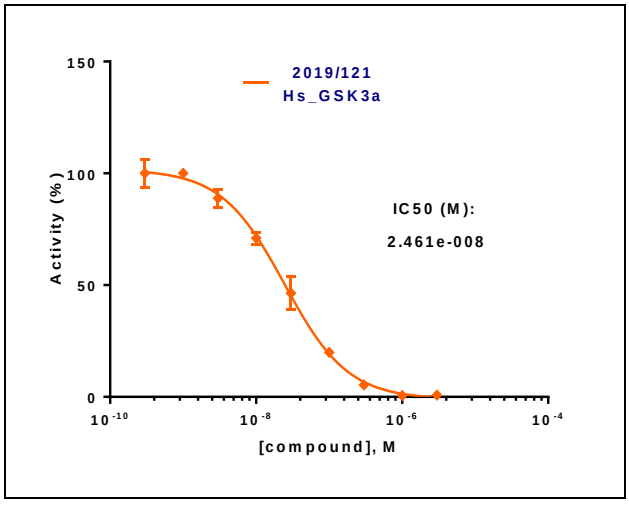
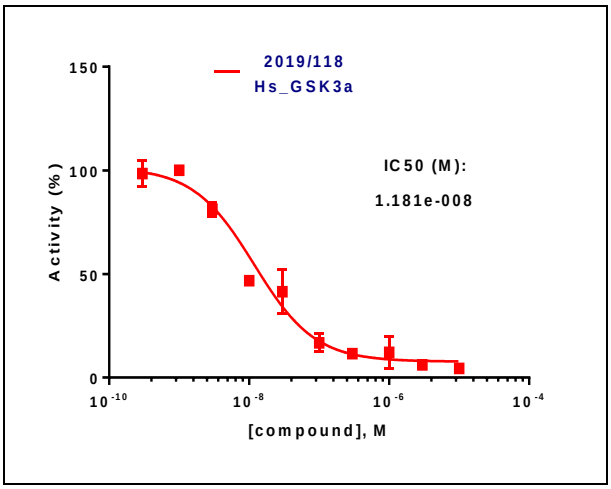
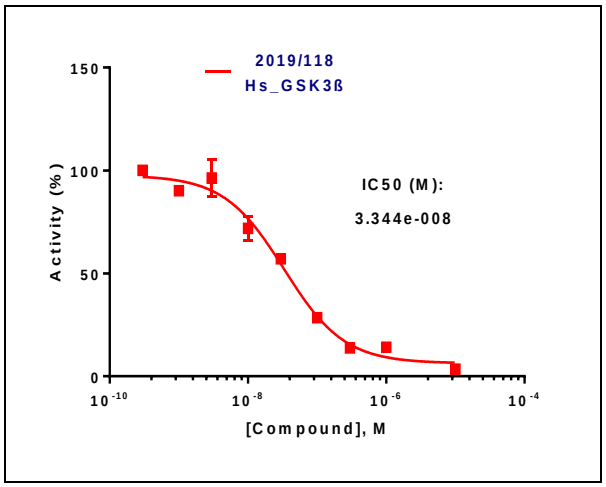
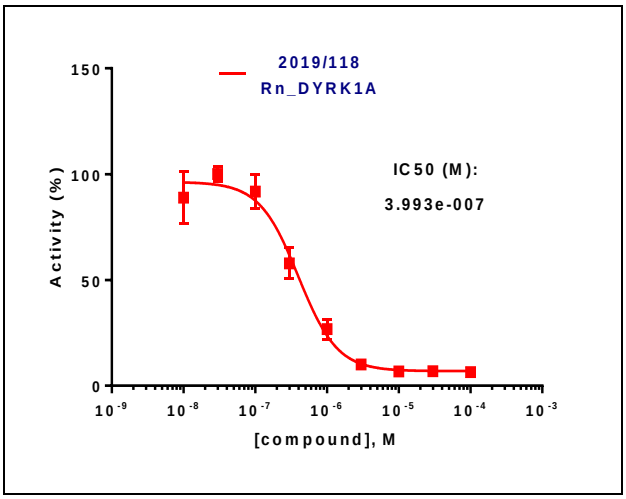


## Compound 10bg



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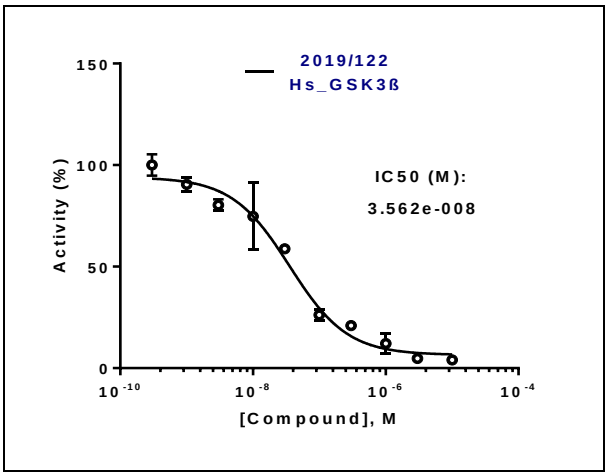
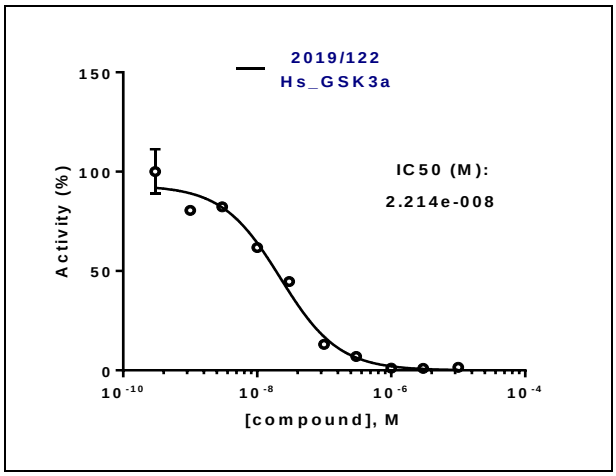
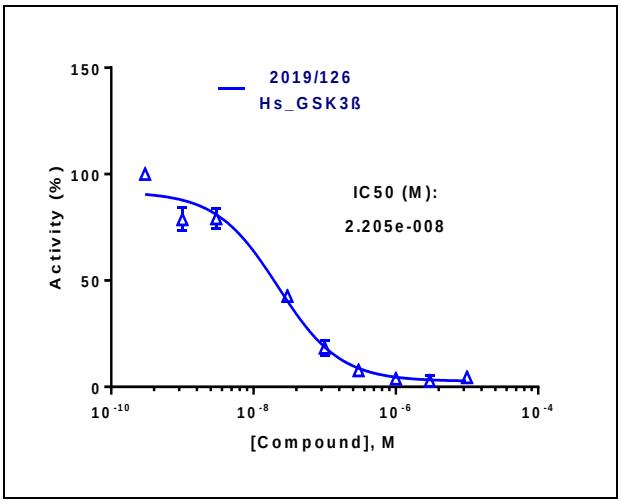
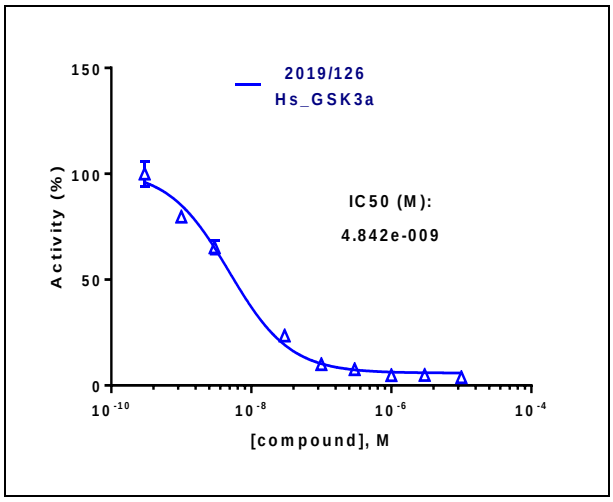
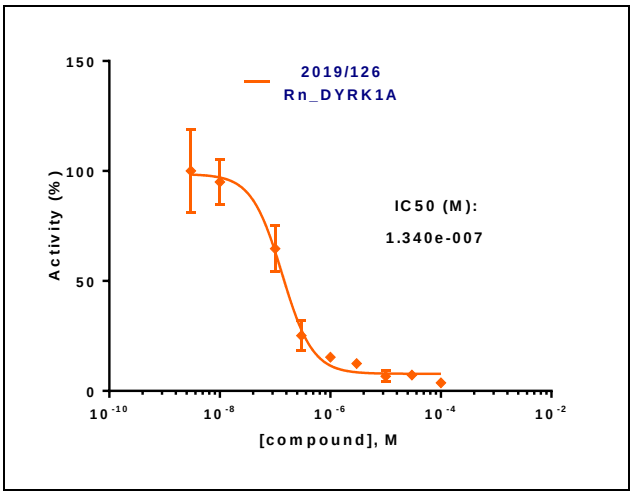


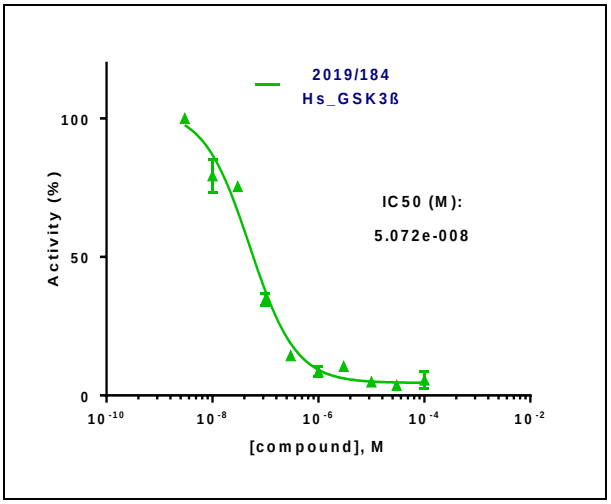
## Compound 10bi

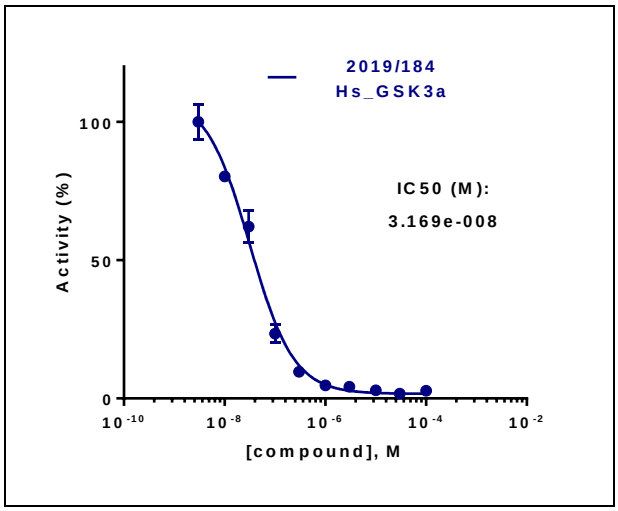


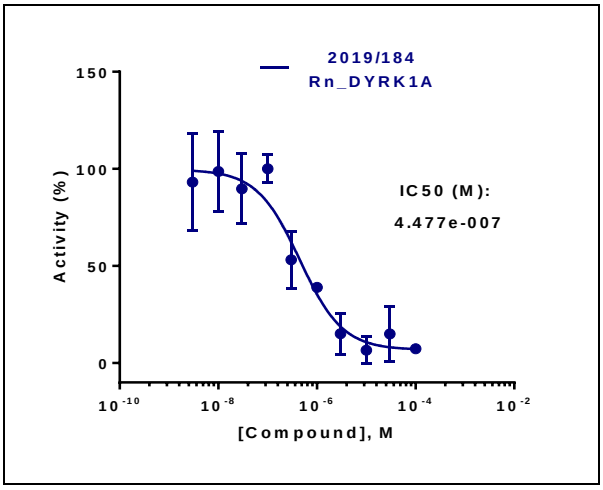



## Compound 10ci



## References and Notes


1 H. E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem.*, 1997, **62**, 7512.
2 G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 2015, **71**, 3.
3 G. M. Sheldrick, *Acta Crystallogr., Sect. C*, 2015, **71**, 3.
4 L. J. Farrugia, *J. Appl. Crystallogr.*, 1997, **30**, 565.
5 M. Loriga, M. Fiore, P. Sanna and G. Paglietti, *Farmaco*, 1995, **50**, 289.
6 G. Le Douaron, L. Ferrié, J. E. Sepulveda-Diaz, M. Amar, A. Harfouche, B. Séon-Méniel, R. Raisman-Vozari, P. P. Michel and B. Figadère, *J. Med. Chem.*, 2016, **59**, 6169.