Preparation of Polyfunctional Naphthyridines by Cobalt-Catalyzed Cross-Couplings of Halogenated Naphthyridines with Magnesium and Zinc Organometallics

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General Considerations

Unless otherwise indicated, all reactions were carried out with magnetic stirring and in flame-dried glassware under argon. Syringes used to transfer reagents and solvents were purged with argon prior to use. Reactions were monitored by gas chromatography (GC and GC-MS) or thin layer chromatography (TLC). TLC were performed using aluminum plates covered with SiO_2 (Merck 60, F-254) and visualized by UV detection. Purification via column chromatography was performed using Merck silica gel 60 (40–63 mm 230–400 mesh ASTM from Merck). THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. Melting points were measured using a Büchi B-540 apparatus and are uncorrected. NMR-spectra were recorded in $CDCl_3$ and chemical shifts (δ) are reported in parts per million (ppm). Mass spectra (MS) and high-resolution mass spectra (HR-MS) were recorded on Finnigan MAT 95Q using electro ionization (EI). GCs were recorded on machines of the type Hewlett-Packard 6890 (Hewlett Packard, 5% phenylmethylpolysiloxane; length: 15 m, diameter: 0.25 mm; film thickness: 0.25 μm). $CoCl_2$ (99.99% purity) was purchased from Sigma Aldrich. $ZnCl_2$ (GR for analysis) was purchased from Merck.

Preparation of Organometallic Reagents

Preparation of $CoCl_2$·2LiCl (1.0 M)

A dry and argon-flushed 250 mL *Schlenk*-flask, equipped with a stirring bar and a septum, was charged with anhydrous LiCl (200 mmol, 8.48 g) and heated to 130 °C under high vacuum for 5h. After cooling to r.t. under argon, anhydrous $CoCl_2$ (100 mmol, 12.98 g) was added. The *Schlenk*-flask was further heated to 130 °C for 5 h under high vacuum, cooled to 25°C and charged with dry THF (100 mL). The mixture was vigorously stirred until all solids were dissolved (ca. 8 h). The reagent $CoCl_2$·2LiCl (1 M in THF) is obtained as a dark blue solution.

Preparation of $ZnCl_2$ in THF (1.0 M)

$ZnCl_2$ (27.3 g, 200 mmol) was placed in a dry and argon-flushed 250 mL *Schlenk*-flask equipped with a stirring bar and a septum. The salt was heated at 150 °C in an oil bath for 8 h under high vacuum. After cooling to r.t., dry THF was added until a total volume of 200 mL was reached and the suspension was stirred overnight at 25 °C. After 12 h, the salts completely dissolved, stirring was stopped and the solution was left until it became completely clear (little particles and insoluble impurities were allowed to settle down). The solution was stored under argon upon use.

Preparation of alkylmagnesium reagents

- (2-Phenylethyl)magnesium bromide (**2a**) and cyclopropylmagnesium bromide (**2e**) were prepared by magnesium insertion into the corresponding alkyl bromides in the presence of LiCl according to the literature.[1]
- MeMgCl (**2b**), *s*-BuMgCl (**2c**) and *n*-BuMgCl (**2d**) were purchased from *Albemarle* (Germany).

[1] F. M. Piller, P. Appukkutan, A. Gavryushin, M. Helm, P. Knochel, Angew. Chem. Int. Ed. **2008**, *47*, 6082.

Preparation of arylmagnesium reagents

4-(Trimethylsilyl)phenylmagnesium bromide (**4a),** 4-*N,N*-dimethylaminophenylmagnesium bromide (**4b**), 4-methoxyphenylmagnesium bromide (**4c**) and mesitylmagnesium bromide (**4d**) were prepared by magnesium insertion into the corresponding aryl bromides in the presence of LiCl according to the literature.[1]

Preparation of zinc reagents

- PhZnCl (**6a**) was prepared by transmetalation of PhMgCl with $ZnCl_2$ solution (1 M in THF).
- Arylzinc reagents **6c**, **6e** and **6j** were prepared by the following procedure:
  The corresponding aryl bromide (**6c** and **6e**) or aryl iodide (**6j**) (1.0 equiv) was dissolved in THF (1 M solution relating to the aryl halide) and the reaction mixture was cooled to -30 °C. Then *i*-PrMgCl·LiCl was added dropwise and the reaction mixture was stirred at this temperature until reaction aliquots quenched with iodine/bromine showed full consumption of the starting material. Transmetalation with $ZnCl_2$ solution (1 M in THF, 1.1 equiv) at 0 °C (1 h) provided the corresponding zinc reagent.
- Arylzinc reagents **6b**, **6d**, **6f-l**, **6k-p** and **12** were prepared by the following procedure:
  LiCl (1.1 equiv) was dried under high vacuum and allowed to cool to room temperature, then Mg turnings (1.2 equiv) and $ZnCl_2$ solution (1 M in THF, 1.1 equiv) were added. The reaction mixture was cooled to 0 °C and the corresponding aryl bromide (1.0 equiv) was added dropwise. The reaction mixture was stirred until iodolysis of a reaction aliquot indicated full consumption of the starting material.
- Benzylzinc reagents **8a-b** were prepared by the following procedure:
  A dry and argon-flushed *Schlenk*-tube, equipped with a magnetic stirring bar and a rubber septum, was charged with LiCl (1.25 equiv) and heated up to 450 °C for 5 min under high vacuum. After cooling to room temperature under vigorous stirring, $ZnCl_2$ (1.10 equiv) was added under argon, the *Schlenk*-tube was heated to 320 °C for 5 min, cooled to room temperature and charged with magnesium turnings (2.40 equiv). Freshly distilled THF was added, followed by the corresponding benzyl chloride. The reaction mixture was stirred at room temperature until iodolysis and hydrolysis of reaction aliquots indicated full conversion of the starting material. When the metal insertion was complete, the solution of the corresponding benzylzinc(II) chloride was separated from the resulting salts *via* syringe equipped with a filter and transferred to another pre-dried and argon-flushed *Schlenk*-tube, before being titrated against iodine.

Starting Materials

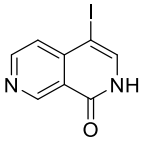
Preparation of starting materials (1a-g)

3,6-Dichloro-1,8-dimethyl-2,7-naphthyridine (**1a**) was prepared according to the procedure from previous work.[2] 1-Chloro-2,7-naphthyridine (**1b**),[3] 4-iodo-1,5-naphthyridine (**1d**),[4] 1-(8-iodo-1,5-naphthyridin-4-yl)-2,2-dimethylpropan-1-one (**1e**),[3] 2,4-diiodo-1,5-naphthyridine (**1f**)[3] and 8-iodo-7-

[2] Greiner, R.; Blanc, R.; Petermayer, C.; Karaghiosoff, K.; Knochel, P. *Synlett*, **2016**, *27*, 231.
[3] Andrew, T. L.; VanVeller, B.; Swager, T. M. *Synlett*, **2010**, *20*, 3045.
[4] Balkenhohl, M.; Greiner, R.; Makarov, I. S.; Heinz, B.; Karaghiosoff, K.; Zipse, H.; Knochel, P. *Chem. Eur. J.* **2017**, DOI: 10.1002/chem.201703638.

phenyl-1,6-naphthyridine (**1g**)[5] were prepared *via* reported procedures. 5-Chloro-2-(trifluoro-methyl)-1,6-naphthyridine (**1c**)[6] was purchased from Apollo Scientific.

Preparation of 1-chloro-4-iodo-2,7-naphthyridine (10) from 2,7-naphthyridin-1(2*H*)-one



According to literature,[7] to a solution of 2,7-naphthyridin-1(2*H*)-one[8] (0.5 g, 3.42 mmol) in H_2O (10 mL) was added a solution of NaOH (0.86 g, 21.5 mmol, 6.3 equiv) and NaOAc (4.33 g, 31.8 mmol, 9.3 equiv) in H_2O (30 mL). The solution was stirred under reflux. Then I_2 (3.04 g, 12.0 mmol, 3.5 equiv) was added. The solution was acidified with 50% AcOH and subsequently neutralized with 32% NaOH. This acidification-neutralization procedure was performed under reflux conditions and repeated three more times within 20 min. In the third acidification step, 50% AcOH was added until free iodine was generated. After removal of excess iodine by boiling, the residue was filtered, washed with hot water, and dried to give 4-iodo-2,7-naphthyridin-1(2*H*)-one (0.56 g, 60%) as a light brown powder.

dec.: 280 °C.

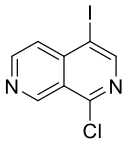
IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3033, 2605, 1880, 1681, 1599, 1472, 1194, 837, 807, 650.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ/ ppm = 11.87 (s, 1H), 9.21 (s, 1H), 8.81 (s, 1H), 7.83 (s, 1H), 7.45 (s, 1H).

^{13}C-NMR (100 MHz, DMSO-d$_6$): δ/ ppm = 160.6, 152.3, 150.2, 143.2, 140.6, 122.6, 121.7, 67.9.

MS (EI, 70 eV): *m/z (%)* = 272 (100), 145 (10), 90 (13), 73 (19), 63 (12), 44 (13).

HRMS (EI): calcd. for [$C_8H_5IN_2O$]: 271.9447; found: 271.9437.



A pressure tube, equipped with a magnetic stirring bar, was charged with 4-iodo-2,7-naphthyridin-1(2*H*)-one (0.50 g, 1.84 mmol) and phosphoryl chloride (8.40 g, 5.0 mL, 54.8 mmol, 30 equiv). The mixture was heated up to 140 °C and was stirred at that temperature for 18 h. After cooling, the mixture was carefully poured onto ice (50 g) and was made alkaline with potassium carbonate. The mixture was extracted extensively several times with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (isohexane/EtOAc = 9:1) to afford **10** (502 mg, 94%) as a light-yellow solid.

[5] Huang, Q.; Hunter, J. A.; Larock, R. C. *Org. Lett.* **2001**, *3*, 2973.
[6] http://www.apolloscientific.co.uk/
[7] Koseki, Y.; Sugimura, T.; Ogawa, K.; Suzuki, R.; Yamada, H.; Suzuki, N.; Masuyama, Y.; Lin, Y. Y.; Usuki, T. *Eur. J. Org. Chem.* **2015**, *18*, 4024.
[8] Zhang, A.; Ding, C.; Cheng, C.; Yao, Q. *J. Comb. Chem.* **2007**, *9*, 916.

m.p.: 189 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1732, 1602, 1526, 1413, 1385, 1328, 1269, 1220, 1046, 985, 912, 836, 783, 699.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.65 (s, 1H), 8.92 (d, *J* = 5.9 Hz, 1H), 8.87 (s, 1H), 7.83 (dd, *J* = 5.9, 0.8 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 153.1, 151.9, 149.5, 142.7, 123.1, 93.7.

MS (EI, 70 eV): *m/z (%)* = 289 (50), 232 (18), 189 (19), 163 (21), 107 (28), 61 (20), 44 (26) 43 (100).

HRMS (EI): calcd. for [$C_8H_4ClIN_2$]: 289.9108; found: 289.9091.

Typical Procedures

Typical procedure 1 (TP1) for the cobalt-catalyzed cross-coupling of chloro-naphthyridines 1a-c with alkylmagnesium reagents:

A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirring bar and septum, was charged with anhydrous $CoCl_2$ (5 mol%). The flask was evacuated under high vacuum at 400 °C for 5 min, cooled to rt and then backfilled with argon. Subsequently, the respective aryl halide (1.0 equiv) was added, followed by dry THF (0.5 M). Then, a solution of the appropriate alkylmagnesium reagent (1.1 equiv) was added dropwise *via* syringe. The reaction mixture was stirred for 20 min at rt until complete con-sumption of starting material, detected by GC-analysis. Saturated aqueous NH_4Cl solution (10 mL) and ethyl acetate (10 mL) were added, the phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography on silica yielding the respective title compound.

Typical procedure 2 (TP2) for the cobalt-catalyzed cross-coupling of chloronaphthyridine 1a with arylmagnesium reagents:

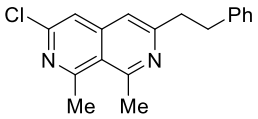
A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirring bar and septum, was charged with anhydrous $CoCl_2$ (5 mol%). The flask was evacuated under high vacuum at 400 °C for 5 min, cooled to rt and then backfilled with argon. Subsequently, the respective aryl halide (1.0 equiv) was added, followed by dry THF (0.5 M). The solution was cooled to the indicated temperature. Then, a solution of the appropriate arylmagnesium reagent (3.0 equiv) was added dropwise *via* syringe. The reaction mixture was stirred at the adjusted temperature until complete consumption of starting material, as indicated by GC-analysis of reaction aliquots quenched with water. Saturated aqueous NH_4Cl solution (5 mL) and ethyl acetate (5 mL) were added, the phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography on silica yielding the respective title compound.

Typical procedure 3 (TP3) for the cobalt-catalyzed cross-coupling of chloro- and iodonaphthyridines 1b-g with arylzinc reagents:

A dry and argon-flushed *Schlenk*-flask, equipped with a stirring bar and a septum, was charged with a solution of $CoCl_2 \cdot 2LiCl$ (1 M in THF, 5 mol%) and dry THF (2.0 mL). The respective aryl halide (1.0 equiv) and HCO_2Na (50 mol%) were added at room temperature. Then, a solution of the appropriate zinc reagent (1.2 equiv) was added dropwise over 15 min *via* syringe. The reaction mixture was stirred and monitored by GC-analysis. Upon consumption of the starting material (approx. 12 h), saturated aqueous NH_4Cl solution (5 mL) and ethyl acetate (5 mL) were added, the phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography on silica yielding the respective title compound.

Co-Catalyzed Cross-Couplings of Naphthyridines 1a-c with Alkylmagnesium Reagents

3-Chloro-1,8-dimethyl-6-phenethyl-2,7-naphthyridine (3a)



According to **TP1**, 3,6-dichloro-1,8-dimethyl-2,7-naphthyridine (**1a**, 0.5 mmol, 113 mg, 1.0 equiv) reacted with $Ph(CH_2)_2MgBr \cdot LiCl$ (**2a**, 0.63 mL, 0.88 M in THF, 0.55 mmol, 1.1 equiv). The crude residue was purified by flash column chromatography (isohexane/EtOAc = 9:1) to afford the desired product (119 mg, 80%) as a white solid.

m.p.: 90 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1605, 1580, 1536, 1497, 1454, 1420, 1380, 1328, 1135, 887, 750, 729, 688.

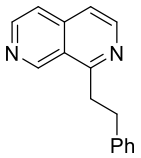
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 7.35 (s, 1H), 7.30-7.15 (m, 5H), 7.07 (s, 1H), 3.22-3.03 (m, 10H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 161.3, 159.9, 157.7, 147.1, 143.8, 141.4, 128.6, 128.5, 126.2, 121.3, 117.4, 115.7, 39.7, 35.5, 29.4, 29.1.

MS (EI, 70 eV): *m*/*z* (%) = 298 (30), 297 (41), 296 (100), 295 (83), 281 (9), 221 (17), 191 (17), 91 (31).

HRMS (EI) calcd. for $[C_{18}H_{17}N_2Cl]$: 296.1080; found: 296.1076.

1-Phenethyl-2,7-naphthyridine (3b)



According to **TP1**, 1-chloro-2,7-naphthyridine (**1b**, 0.5 mmol, 82 mg, 1.0 equiv) reacted with $Ph(CH_2)_2MgBr \cdot LiCl$ (**2a**, 0.63 mL, 0.88 M in THF, 0.55 mmol, 1.1 equiv). The crude residue was

purified by flash column chromatography (isohexane/EtOAc = 1:1) to afford the desired product (94 mg, 82%) as a yellow solid.

m.p.: 76° C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1617, 1550, 1496, 1452, 1376, 1311, 1282, 1238, 1214, 1056, 1017, 973, 915, 896, 868, 795, 753, 738.

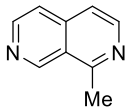
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.59 (s, 1H), 8.72 (d, *J* = 5.6 Hz, 1H), 8.67 (d, *J* = 5.8 Hz, 1H), 7.64 (d, *J* = 5.7, 1H), 7.53 (d, *J* = 5.8 Hz, 1H), 7.34-7.20 (m, 5H), 3.75-3.68 (m, 2H), 3.28-3.21 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 162.8, 150.6, 146.6, 146.0, 141.2, 139.2, 128.7, 128.6, 126.4, 122.4, 119.8, 117.9, 36.8, 35.9.

MS (EI, 70 eV): *m/z (%)* = 235 (16), 234 (95), 233 (100), 219 (15), 218 (19), 157 (33), 130 (22), 116 (10), 91 (34), 65 (10).

HRMS (EI) calcd. for [$C_{16}H_{14}N_2$]: 234.1157; found: 234.1148.

1-Methyl-2,7-naphthyridine (3c)



According to **TP1**, 1-chloro-2,7-naphthyridine (**1b**, 329 mg, 2.0 mmol, 1.0 equiv) reacted with MeMgCl (**2b**, 0.81 mL, 2.72 M in THF, 2.2 mmol, 1.1 equiv). The crude residue was purified by flash column chromatography (EtOAc) to afford the desired product (286 mg, 98%) as a yellow solid.

m.p.: 45 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1615, 1549, 1435, 1393, 1374, 1356, 1276, 1248, 1215, 1081, 1019, 964, 885, 851, 800, 728, 578.

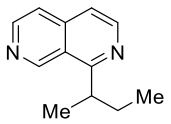
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.59 (s, 1H), 8.72 (d, *J* = 5.8 Hz, 1H), 8.57 (d, *J* = 5.8 Hz, 1H), 7.61 (dd, *J* = 5.7, 1.0 Hz, 1H), 7.48 (d, *J* = 5.8 Hz, 1H), 3.05 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 160.2, 151.1, 146.9, 146.1, 138.9, 122.8, 119.6, 117.8, 21.9.

MS (EI, 70 eV): *m/z (%)* = 145 (13), 144 (100), 118 (15), 117 (9), 116 (8), 75 (7), 63 (8), 50 (7).

HRMS (EI) calcd. for [$C_9H_8N_2$]: 144.0687; found: 144.0679.

1-(*Sec*-butyl)-2,7-naphthyridine (3d)



According to **TP1**, 1-chloro-2,7-naphthyridine (**1b**, 82 mg, 0.5 mmol, 1.0 equiv) reacted with *s*BuMgCl·LiCl (**2c**, 0.42 mL, 1.3 M in THF, 0.55 mmol, 1.1 equiv). The crude residue was purified by flash column chromatography (isohexane/EtOAc = 1:1) to afford the desired product (50 mg, 54%) as a colorless oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2963, 2929, 1615, 1548, 1461, 1380, 1332, 1265, 1215, 981, 852.

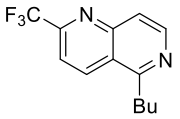
^{1}H-NMR (400 MHz, $CDCl_3$ δ/ ppm = 9.66 (s, 1H), 8.67 (d, *J* = 5.8 Hz, 1H), 8.65 (d, *J* = 5.8 Hz, 1H), 7.60 (dd, *J* = 5.7, 0.8 Hz, 1H), 7.44 (dd, *J* = 5.7, 0.8 Hz, 1H), 3.80 (sept, *J* = 6.8 Hz, 1H), 2.08-1.95 (m, 1H), 1.77 (dquint, *J* = 14.2, 7.3 Hz, 1H), 1.42 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 167.7, 150.3, 146.4, 146.1, 139.2, 122.2, 119.9, 117.3, 37.9, 29.9, 20.4, 12.4.

MS (EI, 70 eV): *m/z (%)* = 186 (15), 185 (25), 172 (11), 171 (82), 159 (13), 158 (100), 157 (78), 156 (16), 144 (23), 130 (25), 129 (18), 78 (11).

HRMS (EI) calcd. for [$C_{12}H_{14}N_2$]: 186.1157; found: 186.1170.

5-Butyl-2-(trifluoromethyl)-1,6-naphthyridine (3e)



According to **TP1**, 5-chloro-2-(trifluoromethyl)-1,6-naphthyridine (**1c**, 0.43 mmol, 100 mg, 1.0 equiv) reacted with *n*BuMgCl (**2d**, 0.35 mL, 1.37 M in THF, 0.47 mmol, 1.1 equiv). The crude residue was purified by flash column chromatography (isohexane/EtOAc = 9:1) to afford the desired product (76 mg, 69 %) as a colorless oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2959, 1607, 1584, 1571, 1471, 1337, 1189, 1139, 1114, 1097, 837, 741.

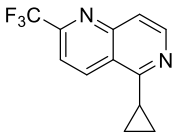
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.75 (d, *J* = 8.7 Hz, 1H), 8.68 (d, J = 8.7 Hz, 1H), 7.87 (d, *J* = 6.0 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 3.36-3.30 (m, 2H), 1.89-1.80 (m, 2H), 1.49 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 164.0, 151.7 (q, *J* = 35.1 Hz), 150.2, 147.1, 136.3, 122.6, 120.8, 119.8, 117.9 (q, *J* = 2.2 Hz), 35.0, 32.0, 23.0, 14.1.

MS (EI, 70 eV): *m/z* (%) = 254 (7), 253 (11), 239 (36), 225 (75), 212 (100), 177 (11).

HRMS (EI) calcd. for [$C_{13}H_{13}F_3N_2$]: 254.1031; found: 254.0986.

5-Cyclopropyl-2-(trifluoromethyl)-1,6-naphthyridine (3f)



According to **TP1**, 5-chloro-2-(trifluoromethyl)-1,6-naphthyridine (**1c**, 0.43 mmol, 100 mg, 1.0 equiv) reacted with *c*-PropMgBr·LiCl (**2e**, 0.45 mL, 1.05 M in THF, 0.47 mmol, 1.1 equiv). The crude residue was purified by flash column chromatography (isohexane/EtOAc = 9:1) to afford the desired product (53 mg, 52 %) as a colorless oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2950, 2854, 1740, 1606, 1572, 1462, 1378, 1340, 1258, 1192, 1146, 1110, 1096, 1008, 840.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.92 (d, *J* = 8.7 Hz, 1H), 8.67 (d, *J* = 6.0 Hz, 1H), 7.86 (d, *J* = 8.7 Hz, 1H), 7.80 (d, *J* = 6.0 Hz, 1H), 2.76-2.66 (m, 1H), 1.37-1.31 (m, 2H), 1.23-1.17 (m, 2H).

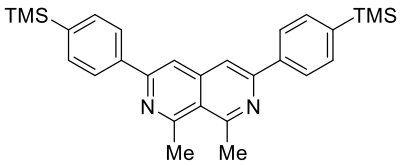
^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 163.7, 151.3 (q, *J* = 35.1 Hz), 149.9, 147.0, 135.9, 123.0 (2C), 122.5, 119.7, 117.6 (q, *J* = 2.1 Hz), 13.4, 10.7.

MS (EI, 70 eV): *m*/*z* (%) = 238 (10), 237 (100), 223 (7), 217 (30), 168 (34), 167 (11).

HRMS (EI) calcd. for [$C_{12}H_9F_3N_2$]: 238.0718; found: 238.0712.

Co-Catalyzed Cross-Couplings of Naphthyridine 1a with Arylmagnesium reagents

1,8-Dimethyl-3,6-bis(4-(trimethylsilyl)phenyl)-2,7-naphthyridine (5a)



According to **TP2**, 3,6-dichloro-1,8-dimethyl-2,7-naphthyridine (**1a**, 113 mg, 0.5 mmol, 1.0 equiv) reacted with 4-(trimethylsilyl)phenylmagnesium bromide (**4a**, 1.78 mL, 1.5 mmol, 0.84 M in THF, 3.0 equiv) within 4 h at -40 °C. The crude residue was purified by flash column chromatography (iso-hexane/EtOAc = 1:1) to afford the desired product (140 mg, 62%) as a white solid.

m.p.: 135-137 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2956, 1602, 1549, 1378, 1332, 1245, 1115, 1092, 824, 752, 722, 692.

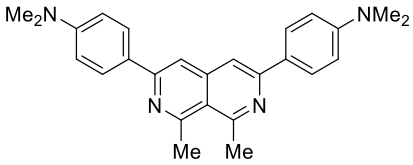
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.14 (d, *J* = 8.2 Hz, 4H), 7.87 (s, 2H), 7.68 (d, *J* = 8.2 Hz, 4H), 3.24 (s, 6H), 0.33 (s, 18H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 159.7, 152.7, 143.2, 141.9, 138.9, 133.9, 126.5, 121.9, 114.9, 29.5, 0.9.

MS (EI, 70 eV): *m*/*z* (%) = 455 (17), 454 (45), 441 (16), 440 (40), 439 (100), 213 (23), 212 (57), 73 (18).

HRMS (EI) calcd. for [$C_{28}H_{34}N_2Si_2$]: 454.2261; found: 454.2258.

4,4'-(1,8-Dimethyl-2,7-naphthyridine-3,6-diyl)bis(N,N-dimethylaniline) (5b)



According to **TP2**, 3,6-dichloro-1,8-dimethyl-2,7-naphthyridine (**1a**, 113 mg, 0.5 mmol, 1.0 equiv) reacted with 4-(dimethylamino)phenylmagnesium bromide (**4b**, 1.36 mL, 1.5 mmol, 1.1 M in THF, 3.0 equiv) within 4 h at -40 °C. The crude residue was purified by flash column chromatography (iso-hexane/EtOAc = 1:1) to afford the desired product (145 mg, 73%) as a yellow solid.

m.p.: 240-242 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1591, 1544, 1525, 1428, 1357, 1191, 1166, 1126, 946, 879, 822.

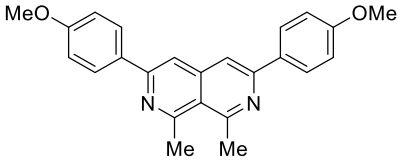
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.09 (d, *J* = 9.0 Hz, 4H), 7.69 (s, 2H), 6.83 (d, *J* = 9.0 Hz, 4H), 3.22 (s, 6H), 3.04 (s, 12H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 159.4, 152.5, 151.4, 143.7, 128.3, 120.7, 112.4, 40.5, 29.3.

MS (EI, 70 eV): *m*/*z* (%) = 397 (28), 396 (100), 395 (7), 380 (8), 198 (12), 197 (11).

HRMS (EI) calcd. for [$C_{26}H_{28}N_4$]: 396.2314; found: 396.2311.

3,6-Bis(4-methoxyphenyl)-1,8-dimethyl-2,7-naphthyridine (5c)



According to **TP2**, 3,6-dichloro-1,8-dimethyl-2,7-naphthyridine (**1a**, 113 mg, 0.5 mmol, 1.0 equiv) reacted with 4-methoxyphenylmagnesium bromide (**4c**, 1.92 mL, 1.5 mmol, 0.78 M in THF, 3.0 equiv) within 12 h at -40 °C. The crude residue was purified by flash column chromatography (isohexane/EtOAc = 1:1) to afford the desired product (110 mg, 60%) as a white solid.

m.p.: 191-193 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1605, 1543, 1514, 1423, 1399, 1378, 1293, 1248, 1173, 1024, 837, 827, 810, 791, 659.

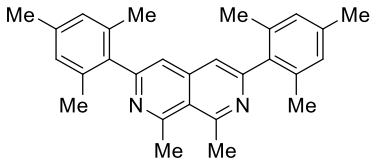
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.13 (d, *J* = 8.9 Hz, 4H), 7.77 (s, 2H), 7.04 (d, *J* = 8.9 Hz, 4H), 3.89 (s, 6H), 3.22 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 160.8, 159.6, 143.4, 128.6, 121.3, 114.4, 113.5, 55.6, 29.5.

MS (EI, 70 eV): *m*/*z* (%) = 371 (29), 370 (100), 355 (8), 185 (12).

HRMS (EI) calcd. for [$C_{24}H_{22}N_2O_2$]: 370.1681; found: 370.1670.

3,6-Dimesityl-1,8-dimethyl-2,7-naphthyridine (5d)



According to **TP2**, 3,6-dichloro-1,8-dimethyl-2,7-naphthyridine (**1a**, 113 mg, 0.5 mmol, 1.0 equiv) reacted with mesitylmagnesium bromide (**4d**, 1.58 mL, 1.5 mmol, 0.95 M in THF, 3.0 equiv) within 4 h at rt. The crude residue was purified by flash column chromatography (isohexane/EtOAc = 9:1) to afford the desired product (183 mg, 93%) as a white crystalline solid.

m.p.: 198 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1604, 1543, 1437, 1377, 1327, 1093, 1031, 878, 848.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 7.34 (s, 2H), 6.97 (s, 4H), 3.25 (s, 6H), 2.33 (s, 6H), 2.10 (s, 12H).

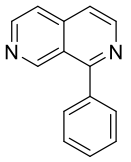
^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 159.8, 142.2, 137.8, 136.0, 128.6, 121.1, 119.0, 21.3, 20.5.

MS (EI, 70 eV): *m/z* (%) = 394 (64), 393 (91), 392 (13), 377 (10), 189 (10), 44 (100), 42 (10).

HRMS (EI) calcd. for [$C_{28}H_{30}N_2$]: 394.2409; found: 394.2356.

Co-Catalyzed Cross-Couplings of Naphthyridines 1b-g with Arylzinc Reagents

1-Phenyl-2,7-naphthyridine (7a)



According to **TP3**, 1-chloro-2,7-naphthyridine (**1b**, 82 mg, 0.5 mmol, 1.0 equiv) reacted with PhZnCl (**6a**, 0.69 mL, 0.87 M in THF, 0.6 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (isohexane/EtOAc = 8:2) to afford the desired product (82 mg, 80%) as a light-yellow solid.

Scale-up:

As representative example we performed the reaction on a larger scale. Therefore, according to **TP3**, 1-chloro-2,7-naphthyridine (**1b**, 328 mg, 2.0 mmol, 1.0 equiv) reacted with PhZnCl (**6a**, 2.76 mL, 0.87 M in THF, 2.4 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (isohexane/EtOAc = 8:2) to afford the desired product (321 mg, 78%) as a light-yellow solid.

m.p.: 129 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1612, 1543, 1450, 1382, 1351, 1217, 1022, 974, 860, 772, 702.

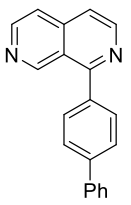
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 9.53 (s, 1H), 8.80 (d, *J* = 5.7 Hz, 1H), 8.73 (d, *J* = 5.7 Hz, 1H), 7.77-7.73 (m, 2H), 7.70 (dd, *J* = 5.7, 1.1 Hz, 1H), 7.63 (dd, *J* = 5.8, 0.9 Hz, 1H), 7.60-7.55 (m, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$, ppm): δ/ ppm = 162.0, 153.0, 146.7, 146.3, 139.8, 138.1, 130.3, 129.6, 128.8, 121.9, 119.4, 118.4.

MS (EI, 70 eV): *m/z* (%) = 207 (6), 206 (45), 205 (100).

HRMS (EI) calcd. for [$C_{14}H_{10}N_2$]: 206.0844; found: 206.0833.

1-([1,1'-Biphenyl]-4-yl)-2,7-naphthyridine (7b)



According to **TP3**, 1-chloro-2,7-naphthyridine (**1b**, 82 mg, 0.5 mmol, 1.0 equiv) reacted with [1,1'-biphenyl]-4-ylzinc chloride (**6b**, 0.84 mL, 0.89 M in THF, 0.75 mmol, 1.5 equiv). The crude residue

was purified by flash column chromatography (isohexane/EtOAc = 7:3) to afford the desired product (115 mg, 82%) as a light-yellow solid.

m.p.: 125-129 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1612, 1542, 1484, 1382, 1354, 1216, 1064, 1008, 972, 916, 860, 850, 838, 768, 732, 696.

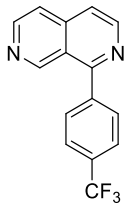
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.61 (s, 1H), 8.80 (d, *J* = 5.7 Hz, 1H), 8.73 (d, *J* = 5.7 Hz, 1H), 7.90–7.77 (m, 4H), 7.73–7.66 (m, 3H), 7.61 (d, *J* = 0.7 Hz, 1H), 7.48 (td, *J* = 6.9, 1.6 Hz, 2H), 7.42 – 7.36 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 161.5, 152.8, 146.6, 146.2, 142.3, 140.4, 139.7, 136.8, 130.7, 128.9, 127.8, 127.4, 127.3, 121.8, 119.3, 118.2, 77.5, 77.2, 76.8.

MS (EI, 70 eV): *m*/*z* (%) = 281 (100), 279 (19), 205 (9), 140 (17).

HRMS (EI) calcd. for [$C_{20}H_{14}N_2$]: 282.1157; found: 281.1075.

1-(4-(Trifluoromethyl)phenyl)-2,7-naphthyridine (7c)



According to **TP3**, 1-chloro-2,7-naphthyridine (**1b**, 110 mg, 0.67 mmol, 1.0 equiv) reacted with 4-trifluoromethylphenylzinc chloride (**6c**, 1.27 mL, 0.63 M in THF, 0.80 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (isohexane/EtOAc = 1:1) to afford the desired product (127 mg, 69%) as a white solid.

m.p.: 126-127 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1615, 1539, 1324, 1246, 1157, 1099, 1067, 1022, 976, 850, 837, 810, 716, 693, 660.

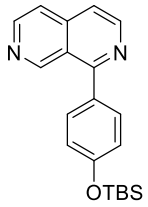
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.45 (s, 1H), 8.80 (d, *J* = 5.7 Hz, 1H), 8.75 (d, *J* = 5.7 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 5.7 Hz, 1H), 7.67 (d, *J* = 5.7 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 160.3, 152.3, 146.9, 146.3, 141.5, 139.7, 131.6 (q, *J* = 32.7 Hz), 125.7 (q, *J* = 3.8 Hz), 121.8, 119.4, 119.1.

MS (EI, 70 eV): *m*/*z* (%) = 275 (12), 274 (77), 273 (100), 253 (10), 248 (10), 206 (22), 204 (11), 58 (12), 57 (19), 50 (11), 44 (73), 43 (50).

HRMS (EI) calcd. for [$C_{15}H_9F_3N_2$]: 274.0718; found: 274.0684.

1-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)-2,7-naphthyridine (7d)



According to **TP3**, 1-chloro-2,7-naphthyridine (**1b**, 82 mg, 0.5 mmol, 1.0 equiv) reacted with 4-(*tert*-butyldimethylsilyloxy)phenylzinc chloride (**6d**, 1.10 mL, 0.68 M in THF, 0.75 mmol, 1.5 equiv). The crude residue was purified by flash column chromatography (isohexane/EtOAc = 7:3) to afford the desired product (121 mg, 72%) as a white solid.

m.p.: 108-113 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2962, 2924, 2854, 1606, 1512, 1462, 1380, 1360, 1258, 1176, 908, 846, 778, 688, 664.

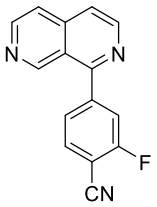
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.50 (s, 1H), 8.66 (dd, *J* = 20.2, 5.7 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 3H), 7.49 (d, *J* = 5.7 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 2H), 0.97 (s, 9H), 0.21 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 161.5, 157.1, 152.9, 146.4, 146.1, 139.7, 131.6, 131.0, 121.7, 120.3, 119.1, 117.7, 77.5, 77.2, 76.8, 25.7, 18.3, -4.3.

MS (EI, 70 eV): *m*/*z* (%) = 336 (23), 279 (100), 205 (13).

HRMS (EI) calcd. for [$C_{20}H_{24}N_2OSi$]: 336.1658; found: 336.1653.

2-Fluoro-4-(2,7-naphthyridin-1-yl)benzonitrile (7e)



According to **TP3**, 1-chloro-2,7-naphthyridine (**1b**, 82 mg, 0.5 mmol, 1.0 equiv) reacted with 4-cyano-3-fluorophenylzinc chloride (**6e**, 1.1 mL, 0.54 M in THF, 0.6 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (isohexane/EtOAc = 1:1) to afford the desired product (92 mg, 74%) as a white solid.

m.p.: 186 °C.

^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 9.45 (s, 1H), 8.82 (d, *J* = 5.7 Hz, 1H), 8.79 (d, *J* = 5.7 Hz, 1H), 7.87-7.82 (m, 1H), 7.76 (dd, *J* = 5.7, 0.9 Hz, 1H), 7.73 (dd, *J* = 5.7, 0.7 Hz, 1H), 7.68-7.67 (m, 1H), 7.67-7.64 (m, 1H).

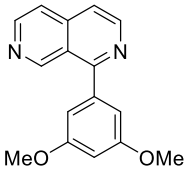
^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 163.2 (d, *J* = 260.6 Hz), 158.2, 151.5, 147.2, 146.3, 145.0 (d, *J* = 7.5 Hz), 139.7, 133.8, 126.7, 121.5, 119.7 (d, *J* = 34.0 Hz), 118.4 (d, *J* = 21.2 Hz), 113.7, 102.5 (d, *J* = 17.1 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2234, 1616, 1562, 1538, 1430, 1406, 1372, 1250, 1221, 1133, 1109, 1068, 996, 915, 878, 855, 767, 756, 737, 694.

MS (EI, 70 eV): *m/z* (%) = 250 (9), 249 (65), 248 (100), 230 (8).

HRMS (EI) calcd. for [$C_{15}H_8FN_3$]: 249.0702; found: 249.0699.

1-(3,5-Dimethoxyphenyl)-2,7-naphthyridine (7f)



According to **TP3**, 1-chloro-2,7-naphthyridine (**1b**, 82 mg, 0.5 mmol, 1.0 equiv) reacted with 3,5-dimethoxyphenylzinc chloride (**6f**, 0.7 mL, 0.86 M in THF, 0.6 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (isohexane/EtOAc = 9:1) to afford the desired product (105 mg, 79%) as a yellow solid.

m.p.: 75 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1600, 1586, 1540, 1450, 1424, 1376, 1299, 1236, 1206, 1157, 1066, 1034, 995, 929, 830, 826, 708, 687, 675.

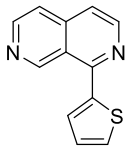
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 9.57 (s, 1H), 8.78 (d, *J* = 5.7 Hz, 1H), 8.73 (d, *J* = 5.7 Hz, 1H), 7.69 (dd, *J* = 5.7, 1.1 Hz, 1H), 7.63 (dd, *J* = 5.7, 0.9 Hz, 1H), 6.86 (d, *J* = 2.3 Hz, 2H), 6.65 (t, *J* = 2.3 Hz, 1H), 3.87 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 161.8, 161.1, 153.0, 146.8, 146.2, 139.9, 139.7, 122.0, 119.3, 118.6, 108.4, 102.0, 55.7.

MS (EI, 70 eV): *m/z* (%) = 267 (16), 266 (100), 265 (51), 251 (42), 236 (25), 235 (74), 221 (13), 208 (16), 192 (20) 179 (13).

HRMS (EI) calcd. for [$C_{16}H_{14}N_2O_2$]: 266.1055; found: 266.1050.

1-(Thiophen-2-yl)-2,7-naphthyridine (7g)



According to **TP3**, 1-chloro-2,7-naphthyridine (**1b**, 82 mg, 0.5 mmol, 1.0 equiv) reacted with thienylzinc chloride (**6g**, 0.71 mL, 0.84 M in THF, 0.6 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (EtOAc) to afford the desired product (64 mg, 60%) as a brown solid.

m.p.: 66-67 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1607, 1530, 1429, 1365, 1339, 1284, 1213, 1078, 1022, 944, 864, 850, 803, 720, 700.

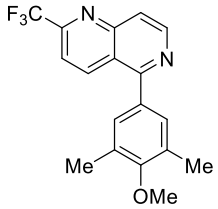
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 9.89 (s, 1H), 8.79-8.63 (m, 2H), 7.69 (d, *J* = 3.7 Hz, 1H), 7.66 (d, *J* = 5.7 Hz, 1H), 7.60 (d, *J* = 5.1 Hz, 1H), 7.53 (d, *J* = 5.7 Hz, 1H), 7.25 (t, *J* = 4.4 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 154.7, 152.1, 146.8, 146.2, 141.5, 140.0, 130.1, 129.5, 128.1, 121.3, 119.4, 118.1.

MS (EI, 70eV): *m/z (%)* = 213 (19), 212 (100), 211 (97), 168 (9).

HRMS (EI) calcd. for [$C_{12}H_8N_2S$]: 212.0408; found: 212.0415.

5-(4-Methoxy-3,5-dimethylphenyl)-2-(trifluoromethyl)-1,6-naphthyridine (7h)



According to **TP3**, 5-chloro-2-(trifluoromethyl)-1,6-naphthyridine (**1c**, 100 mg, 0.43 mmol, 1.0 equiv) reacted with 4-methoxy-3,5-dimethylphenylzinc chloride (**6h**, 0.63 mL, 0.82 M in THF, 0.51 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (isohexane/EtOAc = 8:2) to afford the desired product (106 mg, 74%) as a white solid.

m.p.: 131-132 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1604, 1570, 1464, 1337, 1249, 1187, 1122, 1092, 1007, 922, 886, 852, 838, 741, 727, 707.

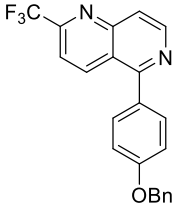
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.88 (d, *J* = 5.9 Hz, 1H), 8.69 (d, *J* = 8.8 Hz, 1H), 7.97 (dd, *J* = 5.9, 0.9 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.34 (s, 2H), 3.80 (s, 3H), 2.38 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 161.9, 158.4, 151.7 (q, *J* = 35.1 Hz), 150.6, 147.2, 138.9, 133.5, 131.6, 130.6, 125.3, 122.6, 122.3, 121.1, 119.8, 118.0, 118.0 (q, *J* = 2.1 Hz), 59.9, 16.4.

MS (EI, 70eV): *m/z (%)* = 332 (96), 331 (25), 318 (21), 317 (100), 302 (25), 301 (47), 287 (12), 273 (30) 263 (24).

HRMS (EI) calcd. for [$C_{18}H_{15}F_3N_2O$]: 332.1136; found: 332.1129.

5-(4-(Benzyloxy)phenyl)-2-(trifluoromethyl)-1,6-naphthyridine (7i)



According to **TP3**, 5-chloro-2-(trifluoromethyl)-1,6-naphthyridine (**1c**, 100 mg, 0.43 mmol, 1.0 equiv) reacted with 4-(benzyloxy)phenylzinc chloride (**6i**, 0.57 mL, 0.9 M in THF, 0.51 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (isohexane/EtOAc = 8:2) to afford the desired product (135 mg, 83%) as a yellow oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1604, 1567, 1465, 1436, 1336, 1292, 1220, 1191, 1141, 1125, 1081, 1026, 980, 916, 841, 788, 741, 696.

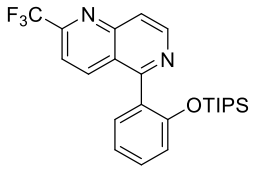
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.95 (d, *J* = 5.9 Hz, 1H), 8.60 (d, *J* = 8.8 Hz, 1H), 8.05 (dd, *J* = 5.9, 0.9 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.54-7.45 (m, 3H), 7.45-7.34 (m, 3H), 7.33-7.28 (m, 2H), 7.21 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 5.19 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 161.6, 159.0, 151.8 (q, *J* = 35.1 Hz), 150.6, 147.1, 139.2, 138.6, 136.8, 130.0, 128.8, 128.2, 127.6, 122.8, 122.5, 122.3, 121.6, 119.79, 118.1 (q, *J* = 2.0 Hz), 116.5, 116.4, 70.3.

MS (EI, 70eV): *m/z (%)* = 381 (12), 380 (47), 92 (7), 91 (100).

HRMS (EI) calcd. for [$C_{22}H_{15}F_3N_2O$]: 380.1136; found: 380.1124.

2-(Trifluoromethyl)-5-(2-((triisopropylsilyl)oxy)phenyl)-1,6-naphthyridine (7j)



According to **TP3**, 5-chloro-2-(trifluoromethyl)-1,6-naphthyridine (**1c**, 140 mg, 0.6 mmol, 1.0 equiv) reacted with 2-(triisopropylsilyloxyphenyl)zinc chloride (**6j**, 1.8 mL, 0.4 M in THF, 0.72 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (isohexane/EtOAc = 8:2) to afford the desired product (163 mg, 61%) as a clear oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2947, 1603, 1570, 1464, 1338, 1276, 1247, 1194, 1145, 1131, 1084, 1007, 920, 885, 839, 759.

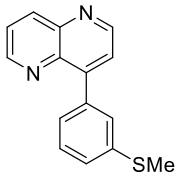
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.92 (d, *J* = 6.0 Hz, 1H), 8.36 (d, *J* = 8.7 Hz, 1H), 8.01 (d, *J* = 6.7 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.49 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.44-7.37 (m, 1H), 7.15 (td, *J* = 7.5, 1.0 Hz, 1H), 7.00 (dd, *J* = 8.2, 0.9 Hz, 1H), 0.97-0.83 (m, 3H), 0.73 (d, *J* = 7.4 Hz, 9H), 0.69 (d, *J* = 7.4 Hz, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 160.9, 153.5, 151.7 (q, *J* = 35.0 Hz), 149.7, 147.4, 139.9, 131.4, 130.9, 129.5, 123.5, 122.6, 121.8, 121.5, 119.9, 119.2, 117.8 (q, *J* =2.2 Hz), 17.6, 12.7.

MS (EI, 70eV): *m/z (%)* = 446 (3), 404 (26), 403 (100), 318 (7), 317 (22).

HRMS (EI) calcd. for [$C_{24}H_{29}F_3N_2OSi$]: 446.2001; found: 446.1993.

4-(3-(Methylthio)phenyl)-1,5-naphthyridine (7k)



According to **TP3**, 4-iodo-1,5-naphthyridine (**1d**, 128 mg, 0.5 mmol, 1.0 equiv) reacted with 3-methylthio)phenylzinc chloride (**6k**, 0.68 mL, 0.88 M in THF, 0.6 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (isohexane:EtOAc = 7:1 + 1% NEt_3) to afford the desired product (101 mg, 80%) as a white solid.

m.p.: 89-91 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1566, 1496, 1474, 1464, 1436, 1376, 1164, 1082, 1026, 954, 904, 882, 868, 800, 784, 742, 692, 656.

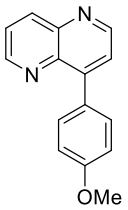
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 9.02 (dd, *J* = 4.2, 1.7 Hz, 2H), 8.47 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.71–7.61 (m, 3H), 7.57–7.50 (m, 1H), 7.51–7.34 (m, 2H), 2.54 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 151.0, 150.9, 148.2, 144.4, 141.8, 138.7, 137.6, 137.3, 128.7, 128.5, 127.3, 127.0, 124.3, 124.1, 16.0.

MS (EI, 70 eV): *m/z* (%) = 250 (15), 249 (92), 248 (100), 234 (14), 233 (13), 232 (38), 205 (60), 203 (10), 123 (11).

HRMS (EI) calcd. for [$C_{15}H_{12}N_{2S}$]: 252.0721; found: 252.0715.

4-(4-Methoxyphenyl)-1,5-naphthyridine (7l)



According to **TP3**, 4-iodo-1,5-naphthyridine (**1d**, 128 mg, 0.5 mmol, 1.0 equiv) reacted with 4-methoxyphenylzinc chloride (**6l**, 0.61 mL, 0.98 M in THF, 0.6 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (isohexane:EtOAc = 7:1 + 1% NEt_3) to afford the desired product (92 mg, 78%) as a white solid.

m.p.: 107 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1603, 1492, 1466, 1382, 1307, 1284, 1235, 1180, 1126, 1027, 835, 818, 800, 783.

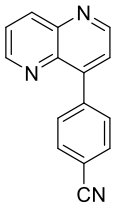
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 9.01 (dd, *J* = 4.1, 1.7 Hz, 1 H), 8.98 (d, *J* = 4.5 Hz, 1 H), 8.44 (dd, *J* = 8.5, 1.8 Hz, 1 H), 7.78 (d, *J* = 8.9 Hz, 2 H), 7.64 (dd, *J* = 8.5, 4.1 Hz, 1 H), 7.62 (d, *J* = 4.5 Hz, 1 H), 7.07 (d, *J* = 8.9 Hz, 2 H), 3.89 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 160.4, 151.1, 150.7, 148.1, 144.7, 142.2, 137.8, 132.0, 129.1, 124.2, 123.8, 114.0, 55.5.

MS (EI, 70 eV): *m/z (%)* **=** 236 (90), 235 (100), 221 (46), 205 (35), 192 (52).

HRMS (EI) for calcd. for [$C_{15}H_{12}N_2O$]: 236.0950; found: 236.0937.

4-(1,5-Naphthyridin-4-yl)benzonitrile (7m)



According to **TP3**, 4-iodo-1,5-naphthyridine (**1d**, 128 mg, 0.5 mmol, 1.0 equiv) reacted with 4-cyanophenylzinc chloride (**6m**, 0.6 mL, 1.0 M in THF, 0.6 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (isohexane:EtOAc = 8:2 + 1% NEt_3) to afford the desired product (96 mg, 83%) as a white solid.

m.p.: 160 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2227, 1584, 1492, 1408, 1261, 1118, 1026, 876, 841, 836, 826, 791, 655.

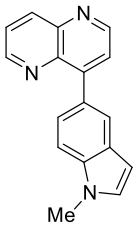
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 9.07 (d, *J* = 4.4 Hz, 1H), 9.01 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.50 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.90 (d, *J* = 8.6 Hz, 2H), 7.82 (d, *J* = 8.6 Hz, 2H), 7.71 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.64 (dd, *J* = 4.4 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 151.4, 151.2, 146.5, 144.7, 141.5, 141.4, 138.1, 132.1, 131.4, 124.8, 124.1, 118.8, 112.7.

MS (EI, 70 eV): *m/z (%)* = 231 (47), 230 (100), 203 (5), 176 (5), 116 (5), 102 (4).

HRMS (EI) for calcd. for [$C_{15}H_9N_3$]: 231.0796; found: 231.0767.

4-(1-Methyl-1*H*-indol-6-yl)-1,5-naphthyridine (7n)



According to **TP3**, 4-iodo-1,5-naphthyridine (**1d**, 128 mg, 0.5 mmol, 1.0 equiv) reacted with 1-methyl-1H-indol-5-ylzinc chloride (**6n**, 0.62 mL, 0.97 M in THF, 0.6 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (isohexane:EtOAc = 7:3 + 1% NEt_3) to afford the desired product (94 mg, 73%) as a yellow solid.

m.p.: 178-180 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1576, 1485, 1369, 1335, 1244, 1157, 1081, 865, 809, 796, 766, 737, 668.

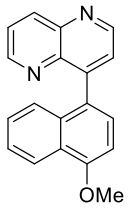
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.03 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.99 (d, *J* = 4.5 Hz, 1H), 8.48 (dd, *J* = 8.5, 1.7 Hz, 1H), 8.06 (dd, *J* = 1.7, 0.6 Hz, 1H), 7.72 (d, *J* = 4.5 Hz, 1H), 7.69 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.65 (dd, *J* = 8.5, 4.1 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.12 (d, *J* = 3.1 Hz, 1H), 6.59 (dd, *J* = 3.1, 0.8 Hz, 1H), 3.86 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 150.8, 150.7, 150.5, 144.4, 142.6, 137.5, 137.2, 129.7, 128.7, 127.8, 124.6, 124.4, 124.2, 123.5, 109.1, 102.0, 33.1.

MS (EI, 70eV): *m/z* (%) = 259 (31), 258 (100), 243 (21), 207 (7).

HRMS (EI) calcd. for [$C_{17}H_{13}N_3$]: 259.1109; found: 259.1114.

4-(4-Methoxynaphthalen-1-yl)-1,5-naphthyridine (7o)



According to **TP3**, 4-iodo-1,5-naphthyridine (**1d**, 128 mg, 0.5 mmol, 1.0 equiv) reacted with (4-methoxynaphthalen-1-yl)zinc chloride (**6o**, 0.74 mL, 0.81 M in THF, 0.6 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (isohexane:EtOAc = 7:2 + 1% NEt_3) to afford the desired product (67 mg, 47%) as a white solid.

m.p.: 220-221 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1582, 1510, 1490, 1457, 1422, 1376, 1325, 1304, 1268, 1238, 1184, 1160, 1122, 1092, 1070, 1042, 868, 824, 812, 804, 764, 712, 666.

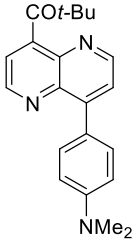
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 9.07 (d, *J* = 4.3 Hz, 1H), 8.89 (dd, *J* = 4.0, 1.7 Hz, 1H), 8.50 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.37 (dt, *J* = 8.6, 1.0 Hz, 1H), 7.68 (d, *J* = 4.2 Hz, 1H), 7.64 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.51 – 7.43 (m, 2H), 7.37 – 7.32 (m, 2H), 6.97 (d, *J* = 7.9 Hz, 1H), 4.08 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 156.0, 151.0, 150.8, 148.7, 144.2, 143.4, 137.6, 132.8, 128.0, 127.1, 126.6, 126.2, 125.7, 125.6, 125.2, 124.2, 122.3, 103.3, 55.6.

MS (EI, 70 eV): *m*/*z* (%) = 286 (36), 285 (100), 271 (15), 270 (63), 242 (35), 241 (13), 121 (15).

HRMS (EI) calcd. for [$C_{12}H_9F_3N_2$]: 286.1108; found: 286.1106.

1-(8-(4-(Dimethylamino)phenyl)-1,5-naphthyridin-4-yl)-2,2-dimethylpropan-1-one (7p)



According to **TP3**, 1-(8-iodo-1,5-naphthyridin-4-yl)-2,2-dimethylpropan-1-one (**1e**, 170 mg, 0.5 mmol, 1.0 equiv) reacted with 4-(dimethylamino)phenylzinc chloride (**6p**, 0.69 mL, 0.87 M in THF, 0.6 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (isohexane:EtOAc = 8:2) to afford the desired product (143 mg, 86%) as a white solid.

m.p.: 165-167 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1188, 1166, 1130, 1100, 1084, 1060, 1038, 1006, 962, 950, 914, 880, 864, 838, 820, 812, 782, 752, 724, 682.

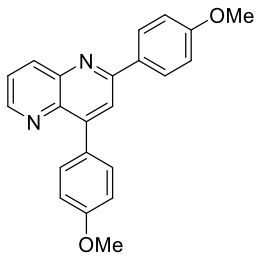
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 8.99 (d, *J* = 4.2 Hz, 1H), 8.89 (d, *J* = 4.5 Hz, 1H), 7.83 – 7.72 (m, 2H), 7.60 (d, *J* = 4.5 Hz, 1H), 7.34 (d, *J* = 4.2 Hz, 1H), 6.94 – 6.81 (m, 2H), 3.05 (s, 6H), 1.33 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 213.1, 150.9, 150.9, 149.4, 148.8, 148.3, 142.3, 141.6, 131.7, 123.8, 123.3, 119.2, 112.0, 45.2, 40.4, 26.8.

MS (EI, 70 eV): *m/z* (%) = 333 (44), 332 (12), 276 (11), 250 (15), 249 (100), 248 (42), 232 (23).

HRMS (EI) calcd. for [$C_{21}H_{23}N_3O$]: 333.1841; found: 333.1835.

2,4-Bis(4-methoxyphenyl)-1,5-naphthyridine (7q)



According to **TP3**, 2,4-diiodo-1,5-naphthyridine (**1f**; 150 mg, 0.39 mmol, 1.0 equiv) reacted with 4-methoxyphenylzinc chloride (**6l**, 0.95 mL, 0.98 M in THF, 0.94 mmol, 2.4 equiv). The crude residue was purified by flash column chromatography (isohexane:EtOAc = 7:1 + 1%) to afford the desired product (100 mg, 75%) as a yellow solid.

m.p.: 109 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2927, 1606, 1590, 1578, 1542, 1513, 1483, 1459, 1416, 1365, 1286, 1237, 1175, 1108, 1022, 822, 800, 729, 680.

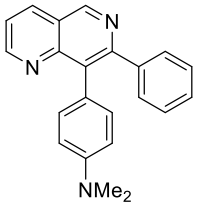
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.93 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.45 (dd, *J* = 8.5, 1.7 Hz, 1H), 8.18 (d, *J* = 8.9 Hz, 2H), 8.04 (s, 1H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.60 (dd, J = 8.5, 1.4 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H), 3.88 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 161.2, 160.2, 157.3, 149.9, 148.4, 144.5, 141.4, 137.6, 131.9, 131.8, 129.6, 129.1, 124.2, 121.4, 114.4, 114.0, 55.5.

MS (EI, 70 eV): *m/z* (%) = 343 (17), 342 (94), 341 (100), 327 (24), 298 (10), 255 (9).

HRMS (EI) calcd. for [$C_{22}H_{18}N_2O_2$]: 342.1368; found: 342.1366.

***N,N*-Dimethyl-4-(7-phenyl-1,6-naphthyridin-8-yl)aniline (7r)**



According to **TP3**, 8-iodo-7-phenyl-1,6-naphthyridine (**1g**; 100 mg, 0.3 mmol, 1.0 equiv) reacted with 4-(dimethylamino)phenylzinc chloride (**6p**, 1.0 mL, 0.87 M in THF, 0.9 mmol, 3.0 equiv). The crude residue was purified by flash column chromatography (EtOAc) to afford the desired product (63 mg, 65%) as a bright yellow solid.

m.p.: 184-186 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1610, 1601, 1520, 1466, 1434, 1362, 1334, 1202, 1160, 1130, 1048, 942, 830, 814, 786, 770, 708, 694.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.33 (s, 1H), 9.12 (dd, *J* = 4.2, 1.9 Hz, 1H), 8.32 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.49 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.47-7.42 (m, 2H), 7.29-7.26 (m, 1H), 7.25-7.22 (m, 2H), 7.21-7.16 (m, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 2.97 (s, 6H).

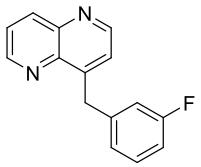
^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 154.8, 151.1, 150.4, 141.1, 135.6, 132.8, 132.3, 130.5, 127.9, 127.3, 122.6, 122.0, 112.3, 40.7.

MS (EI, 70 eV): *m*/*z* (%) = 326 (23), 325 (100), 324 (59), 308 (21), 281 (22), 279 (16), 161 (12).

HRMS (EI) calcd. for [$C_{22}H_{19}N_3$]: 325.1579; found: 325.1573.

Co-Catalyzed Cross-Couplings of Naphthyridine 1d with Benzylzinc Reagents

4-(3-Fluorobenzyl)-1,5-naphthyridine (9a)



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a rubber septum, was charged with $CoCl_2$ (3 mg ,0.02 mmol, 5 mol %) and heated up to 450 °C for 5 min under high vacuum. After cooling to rt, 4-iodo-1,5-naphthyridine (**1d**, 100 mg, 0.4 mmol, 1.0 equiv) and dry THF (2 mL) were added. Thereupon, 3-fluorobenzylzinc chloride (3.8 mL, 0.21 M in THF, 0.8 mmol. 2.0 equiv) was dropwise added and the reaction mixture was stirred at rt for 4 h until complete consumption of **1d** was observed by GC. A saturated aq. solution of NH_4Cl (5 mL) was added and the aq. layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude residue was purified by flash column chromatography (isohexane: EtOAc = 9:1 + 1% NEt_3) to afford the desired product (72 mg, 75%) as a clear oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2981, 1713, 1587, 1495, 1443, 1414, 1246, 1177, 1136, 1114, 1073, 1021, 877, 818, 754, 726.

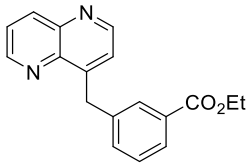
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.02 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.86 (d, *J* = 4.4 Hz, 1H), 8.41 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.66 (dd, *J* = 8.5, 4.1 Hz, 1H), 7.32 (d, *J* = 4.4 Hz, 1H), 7.30-7.23 (m, 1H), 7.12-7.07 (m, 1H), 7.05-6.99 (m, 1H), 6.96-6.88 (m, 1H), 6.68 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 163.1 (d, $^1J_{C,F}$ = 246 Hz), 151.2, 150.4, 149.0, 143.8, 142.9, 142.0 (d, $^3J_{C,F}$ = 7.4 Hz), 137.8, 130.1 (d, $^3J_{C,F}$ = 8.3 Hz), 125.1 (d, $^4J_{C,F}$ = 2.8 Hz), 124.5, 124.1, 116.4 (d, $^2J_{C,F}$ = 21.3 Hz), 113.5 (d, $^2J_{C,F}$ = 21.0 Hz), 35.9.

MS (EI, 70 eV): *m*/*z* (%) = 239 (10), 238 (75), 237 (100), 236 (26).

HRMS (EI) calcd. for [$C_{15}H_{11}FN_2$]: 238.0906; found: 239.0909.

Ethyl 3-((1,5-naphthyridin-4-yl)methyl)benzoate (9b)



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a rubber septum, was charged with $CoCl_2$ (3 mg, 0.02 mmol, 5 mol %) and heated up to 450 °C for 5 min under high vacuum. After cooling to rt, 4-iodo-1,5-naphthyridine (100 mg, 0.4 mmol, 1.0 equiv) and dry THF (2 mL) were added. Thereupon, 3-(ethoxycarbonyl)benzylzinc chloride (2.1 mL, 0.38 M in THF, 0.8 mmol, 2.0 equiv) was dropwise added and the reaction mixture was stirred at rt for 4 h until complete consumption of **1d** was observed by GC. A saturated aq. solution of NH_4Cl (5 mL) was added and the aq. layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude residue was purified by flash column chromatography (isohexane:EtOAc = 9:1 + 1% NEt_3) to afford the desired product (142 mg, 75%) as a yellow oil (73 mg, 62%) as a yellow oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2989, 1712, 1588, 1495, 1443, 1366, 1273, 1190, 1104, 1081, 1023, 754, 726, 691.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.00 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.83 (d, *J* = 4.4 Hz, 1H), 8.39 (dd, *J* = 8.5, 1.7 Hz, 1H), 8.04-8.02 (m, 1H), 7.92 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.64 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.52-7.48 (m, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 4.4 Hz, 1H), 4.73 (s, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).

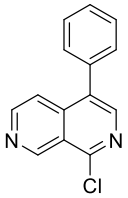
^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 166.6, 151.1, 150.3, 149.2, 143.7, 142.9, 139.7, 137.7, 134.0, 130.9, 130.5, 128.7, 127.8, 124.5, 124.0, 61.0, 35.9, 14.4.

MS (EI, 70 eV): *m*/*z* (%) = 292 (93), 291 (39), 263 (54), 247 (49), 219 (47), 218 (100), 205 (10), 119 (20).

HRMS (EI) calcd. for [$C_{18}H_{16}N_2O_2$]: 292.1212; found: 292.1203.

Regioselective Pd/Co-Catalyzed Cross-Coupling of Naphthyridine (10) with Arylzinc Reagents

1-Chloro-4-phenyl-2,7-naphthyridine (11)



A dry and argon-flushed *Schlenk*-flask was charged with a solution of $Pd(dba)_2$ (26 mg, 0.045 mmol, 5 mol %), P(*o*-furyl)$_3$ (21 mg, 0.09 mmol, 10 mol %) and 1-chloro-4-iodo-2,7-naphthyridine (**10**; 250 mg, 0.86 mmol) in dry THF (2 mL). Phenylzinc chloride (2.73 mL, 0.33 M in THF, 0.9 mmol, 1.05 equiv) was added dropwise and the reaction mixture was stirred at rt overnight. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 ×15 mL) and dried

over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (isohexane:EtOAc = 7:3) to give the desired product (169 mg, 82%) as a white solid.

m.p.: 149 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1601, 1532, 1451, 1392, 1340, 1308, 1267, 1176, 1044, 985, 916, 844, 828, 755, 700.

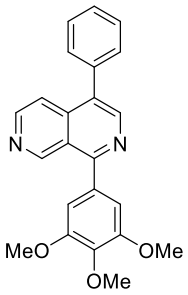
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.84 (s, 1H), 8.78 (d, *J* = 6.0 Hz, 1H), 8.50 (s, 1H), 7.81 (d, *J* = 6.7 Hz, 1H), 7.61-7.51 (m, 3H), 7.49-7.44 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 151.7, 151.0, 146.7, 145.8, 140.9, 134.3, 132.7, 130.0, 129.3, 129.1, 121.8, 118.4.

MS (EI, 70 eV): *m*/*z* (%) = 242 (33), 241 (27), 240 (100), 239 (38), 205 (12), 177 (10), 151 (7), 150 (5).

HRMS (EI) calcd. for [$C_{14}H_9ClN_2$]: 240.0454; found: 240.0444.

4-Phenyl-1-(3,4,5-trimethoxyphenyl)-2,7-naphthyridine (13)



According to **TP3**, 1-chloro-4-phenyl-2,7-naphthyridine (**11**; 90 mg, 0.38 mmol, 1.0 equiv) reacted with (3,4,5-trimethoxyphenyl)zinc chloride (0.54 mL, 0.84 M in THF, 0.45 mmol, 1.2 equiv). The crude residue was purified by flash column chromatography (EtOAc) to afford the desired product (127 mg, 91%) as a white solid.

m.p.: 178-181 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2922, 2850, 1601, 1582, 1505, 1464, 1413, 1384, 1237, 1123, 1102, 951, 932, 830, 767, 711.

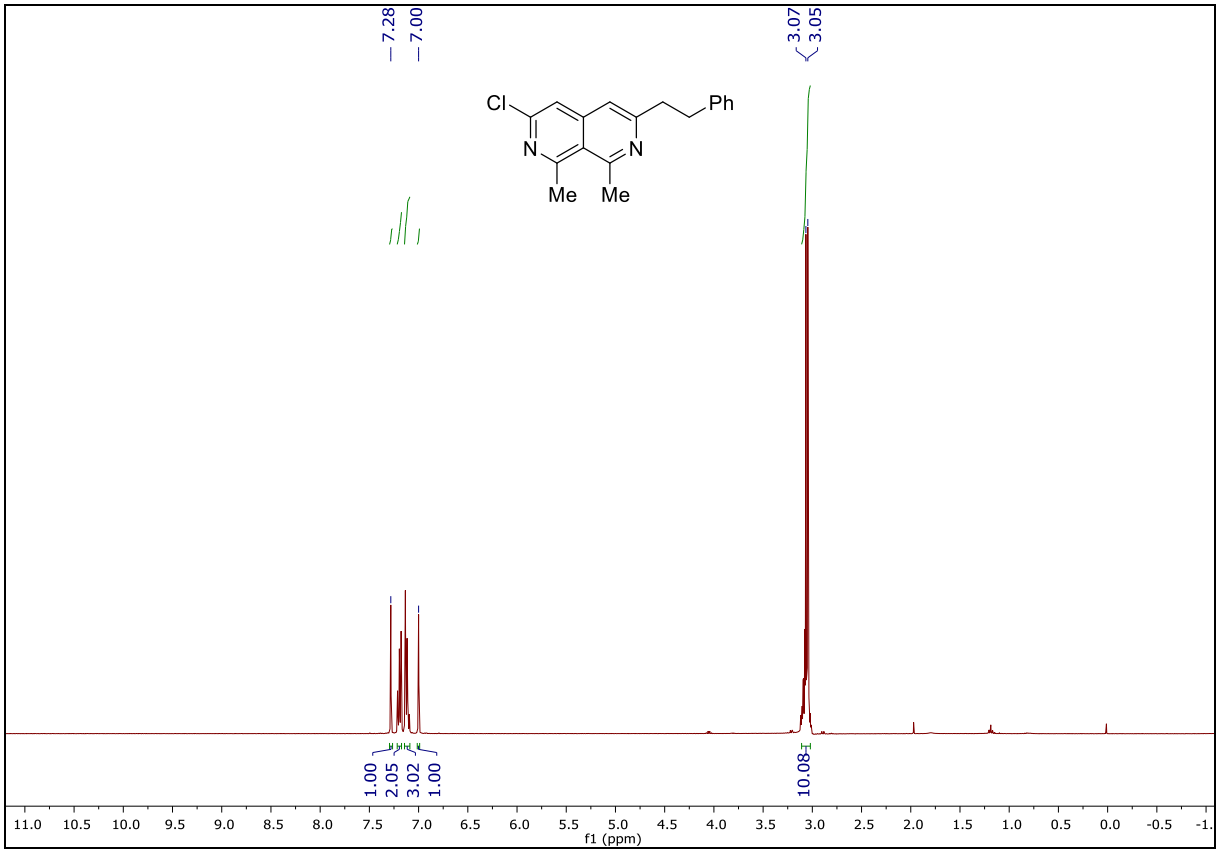
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 9.65 (s, 1H), 8.76 (s, 1H), 8.73-8.67 (m, 1H), 7.80 (d, *J* = 5.8 Hz, 1H), 7.60-7.56 (m, 2H), 7.56-7.51 (m, 3H), 7.01 (s, 2H), 3.97 (s, 3H), 3.95 (s, 6H).

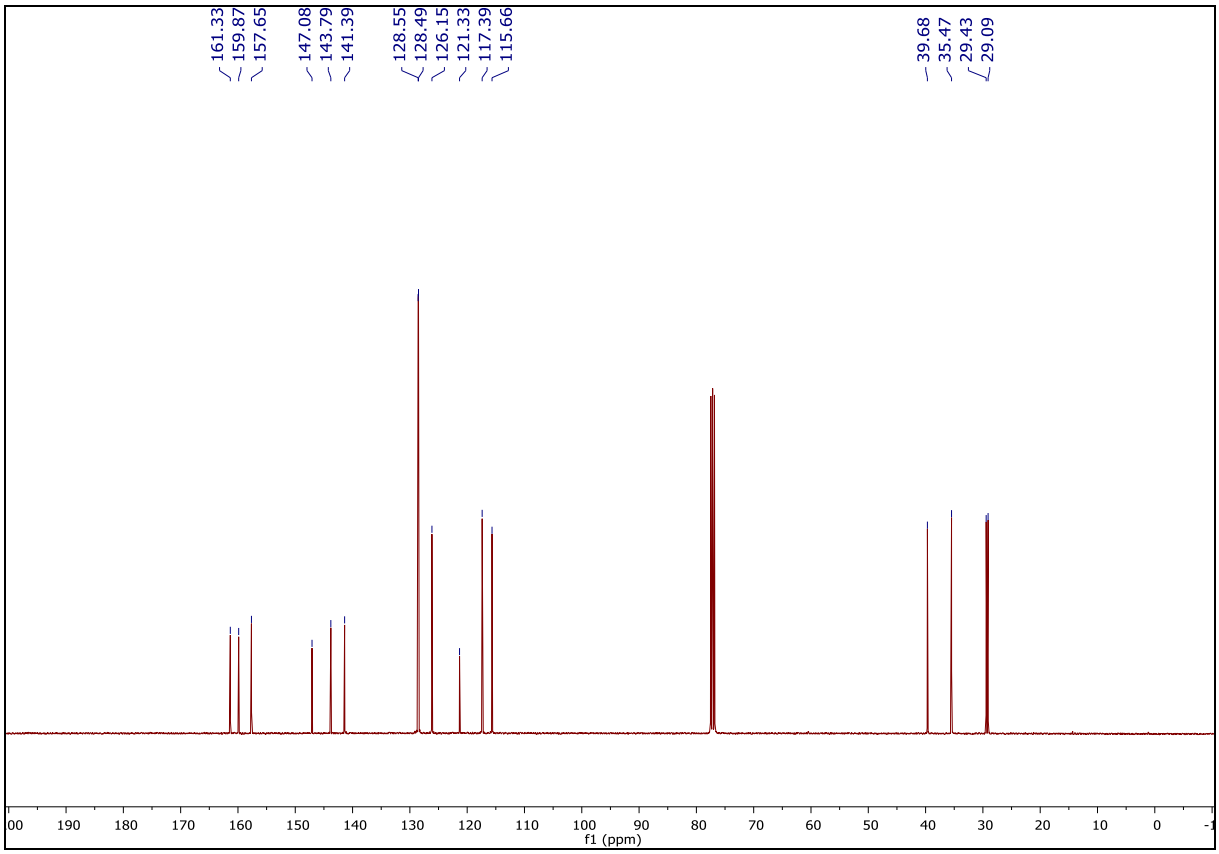
^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 160.9, 153.6, 153.1, 146.9, 145.5, 139.4, 138.3, 135.7, 133.5, 131.3, 130.1, 129.1, 128.6, 121.6, 117.6, 107.7, 61.2, 56.5, 29.9.

MS (EI, 70 eV): *m*/*z* (%) = 373 (20), 372 (100), 357 (18), 342 (10), 341 (40), 299 (12), 57 (11).

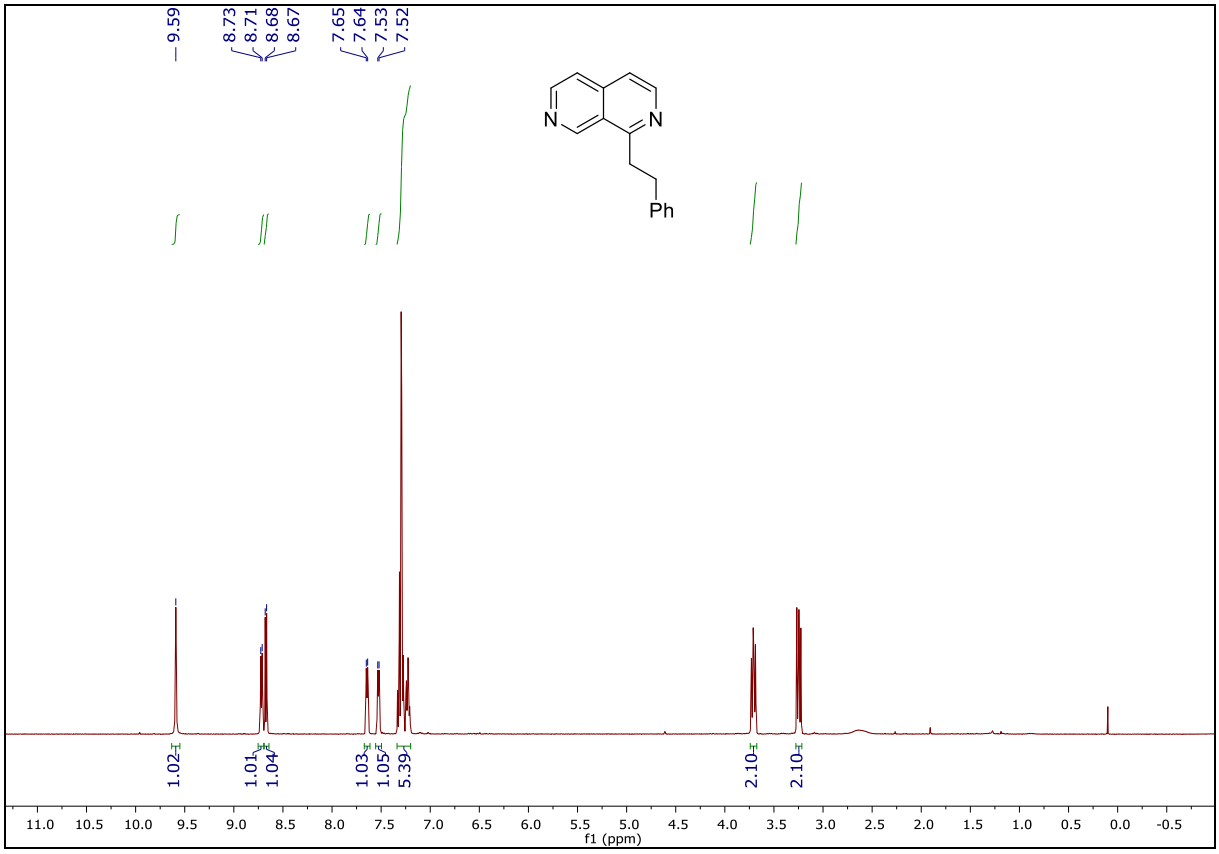
HRMS (EI) calcd. for [$C_{23}H_{20}N_2O_3$]: 372.1474; found: 372.1475.

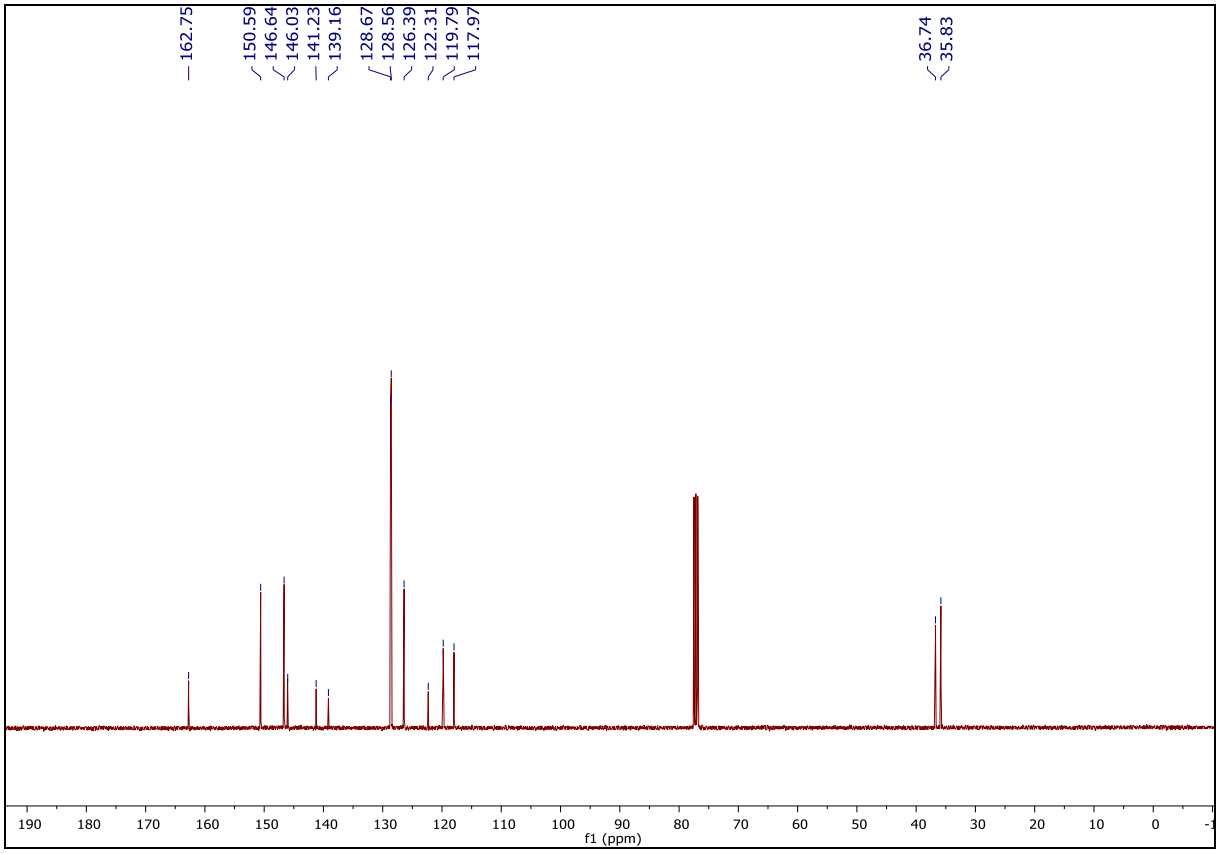
NMR-spectra of 3-chloro-1,8-dimethyl-6-phenethyl-2,7-naphthyridine (3a)



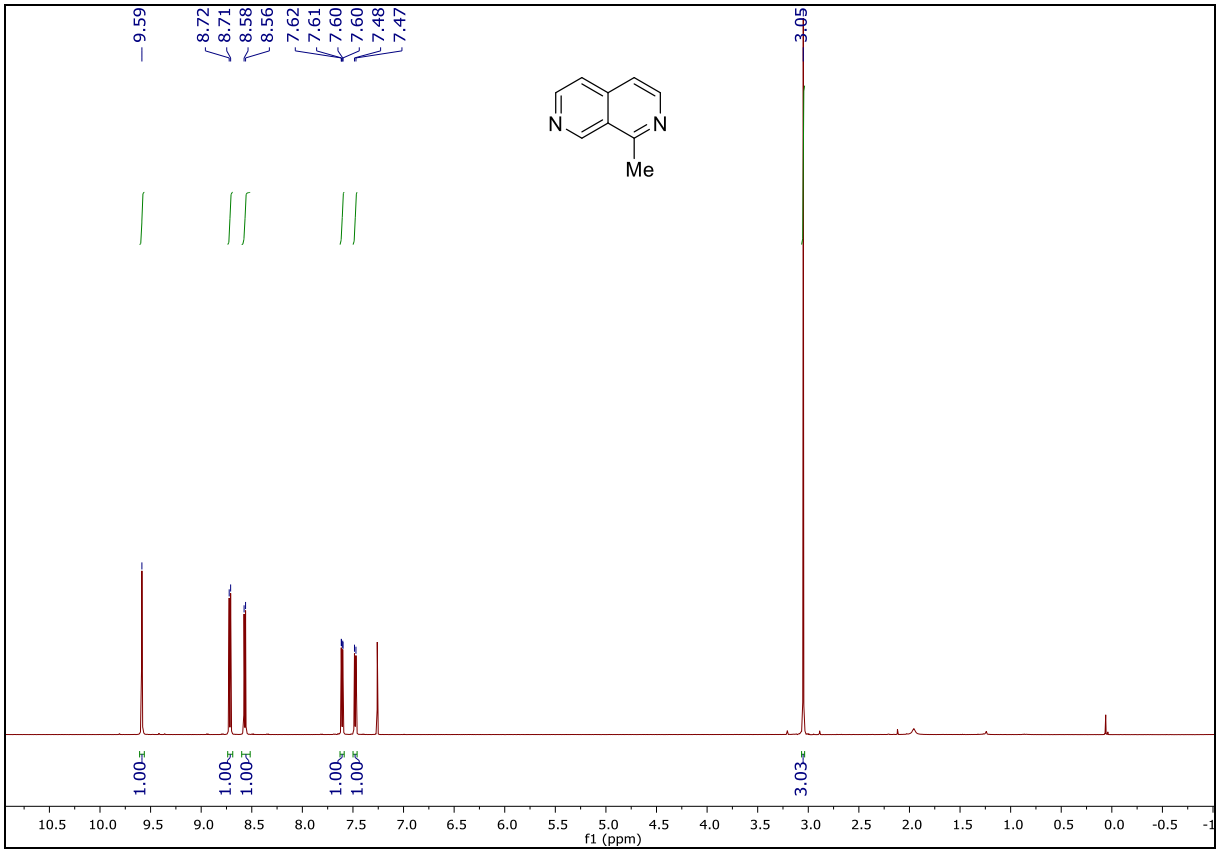


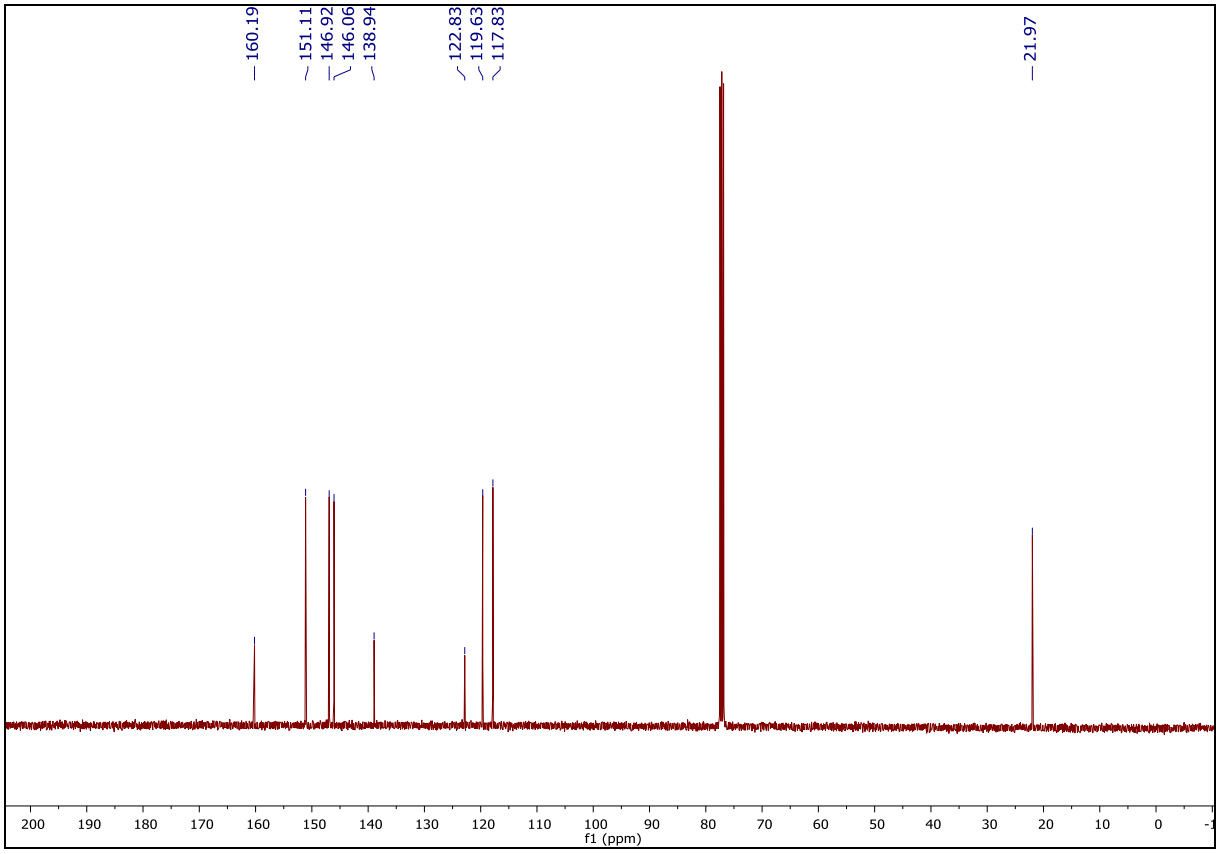
NMR-spectra of 1-phenethyl-2,7-naphthyridine (3b)



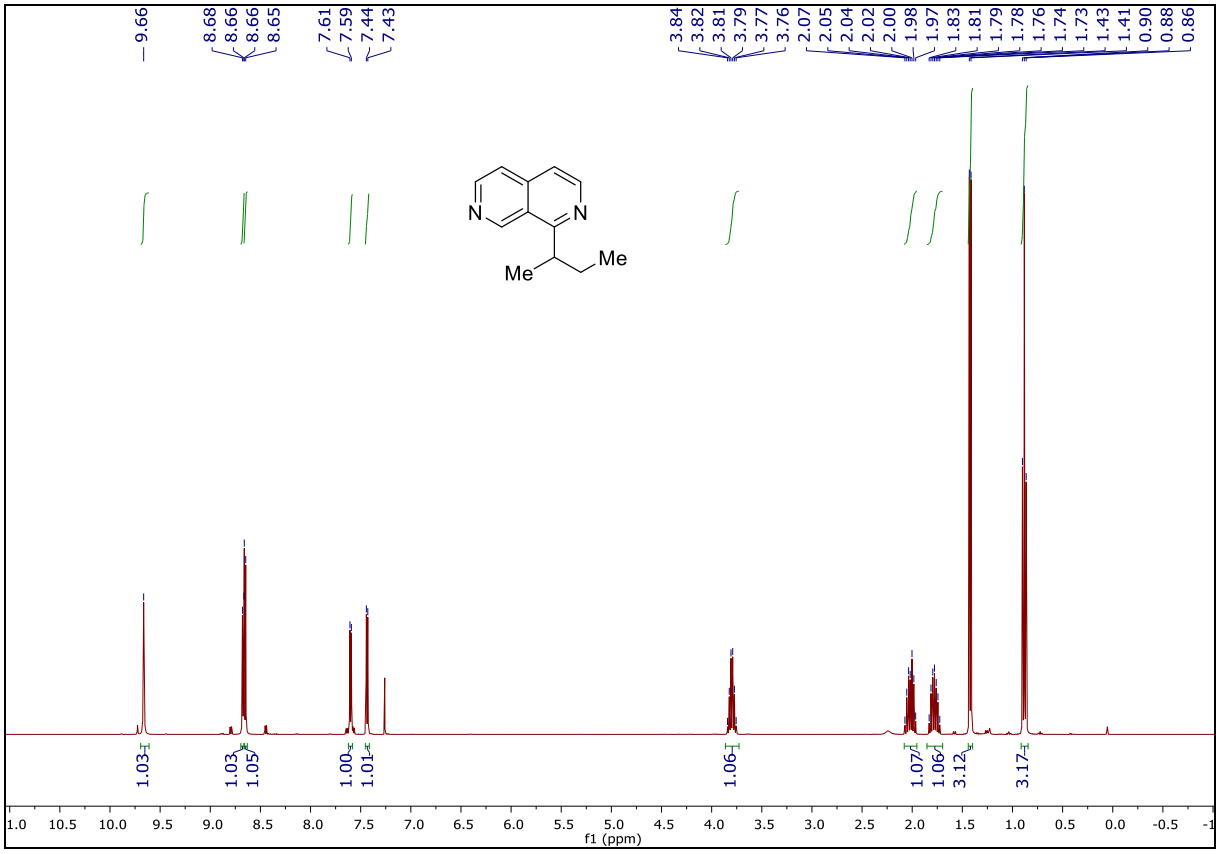


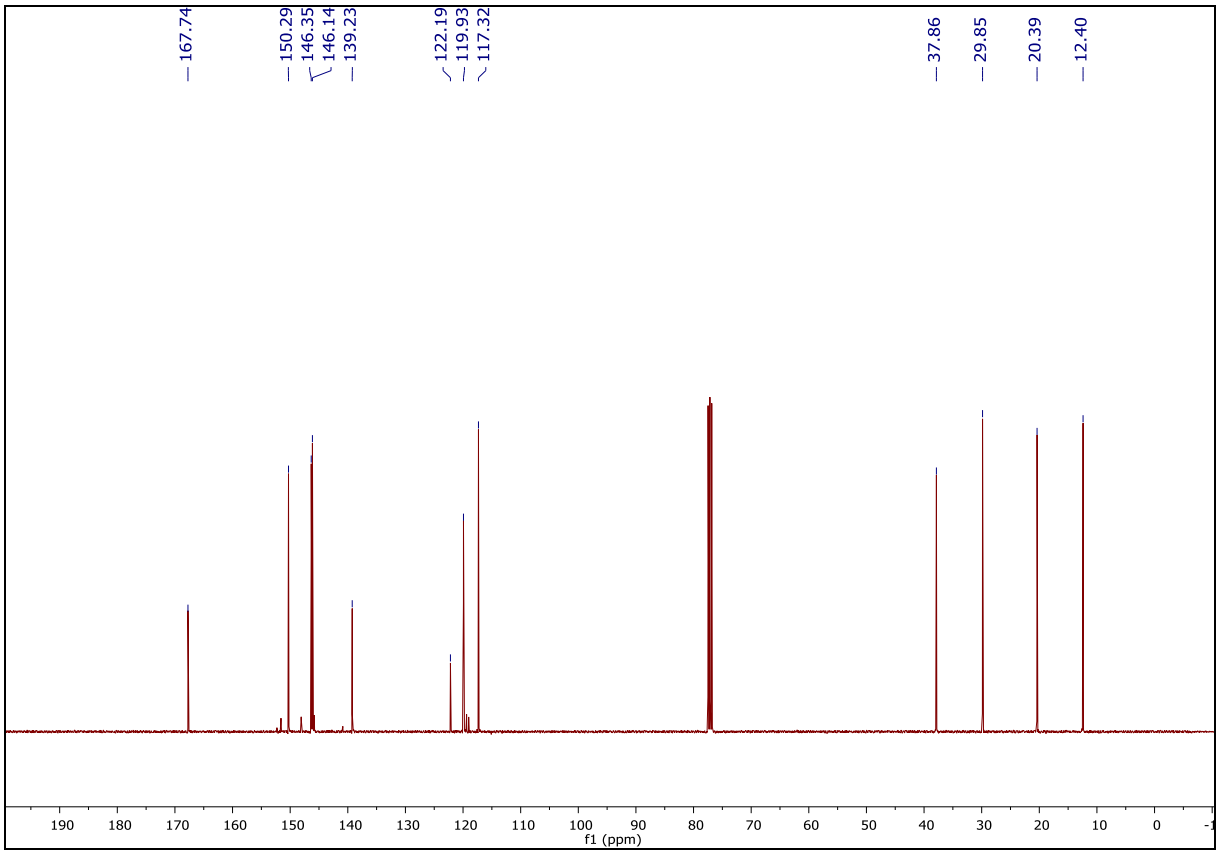
NMR-spectra of 1-methyl-2,7-naphthyridine (3c)



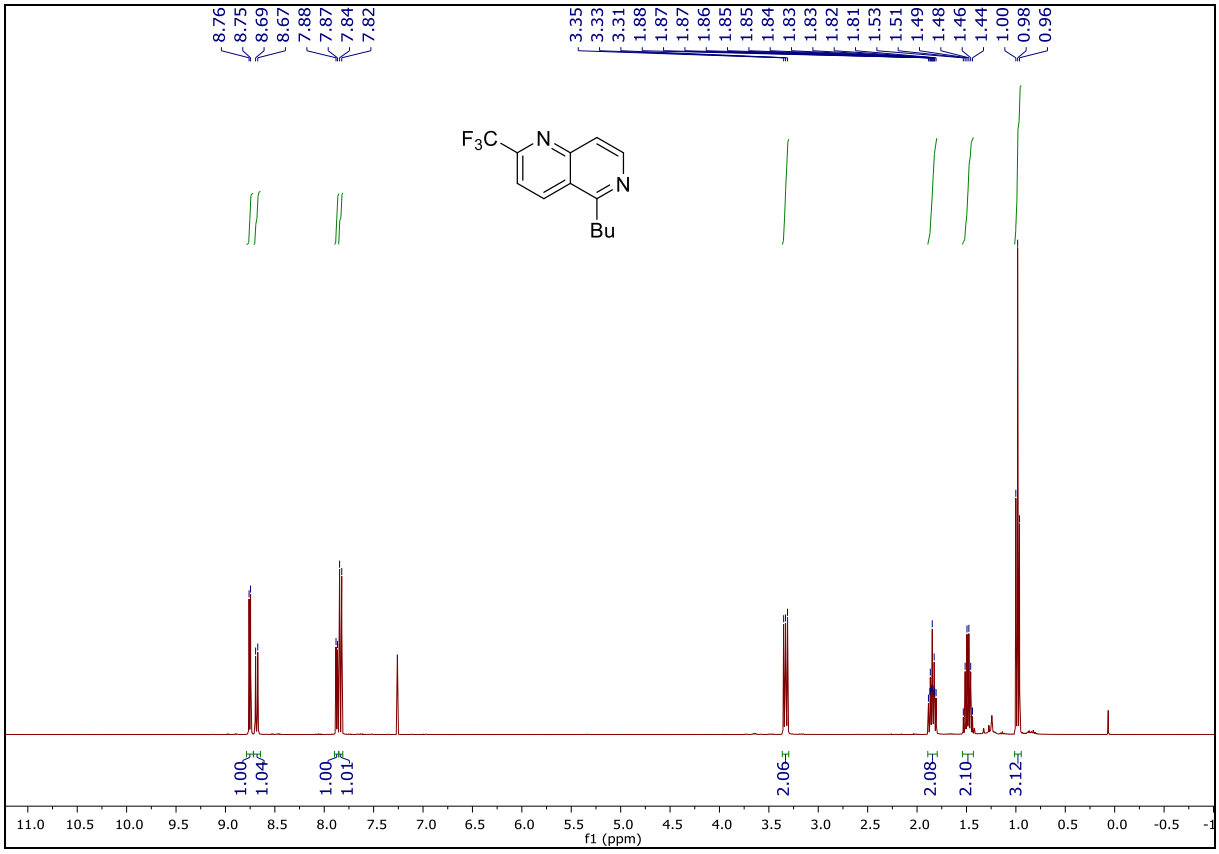


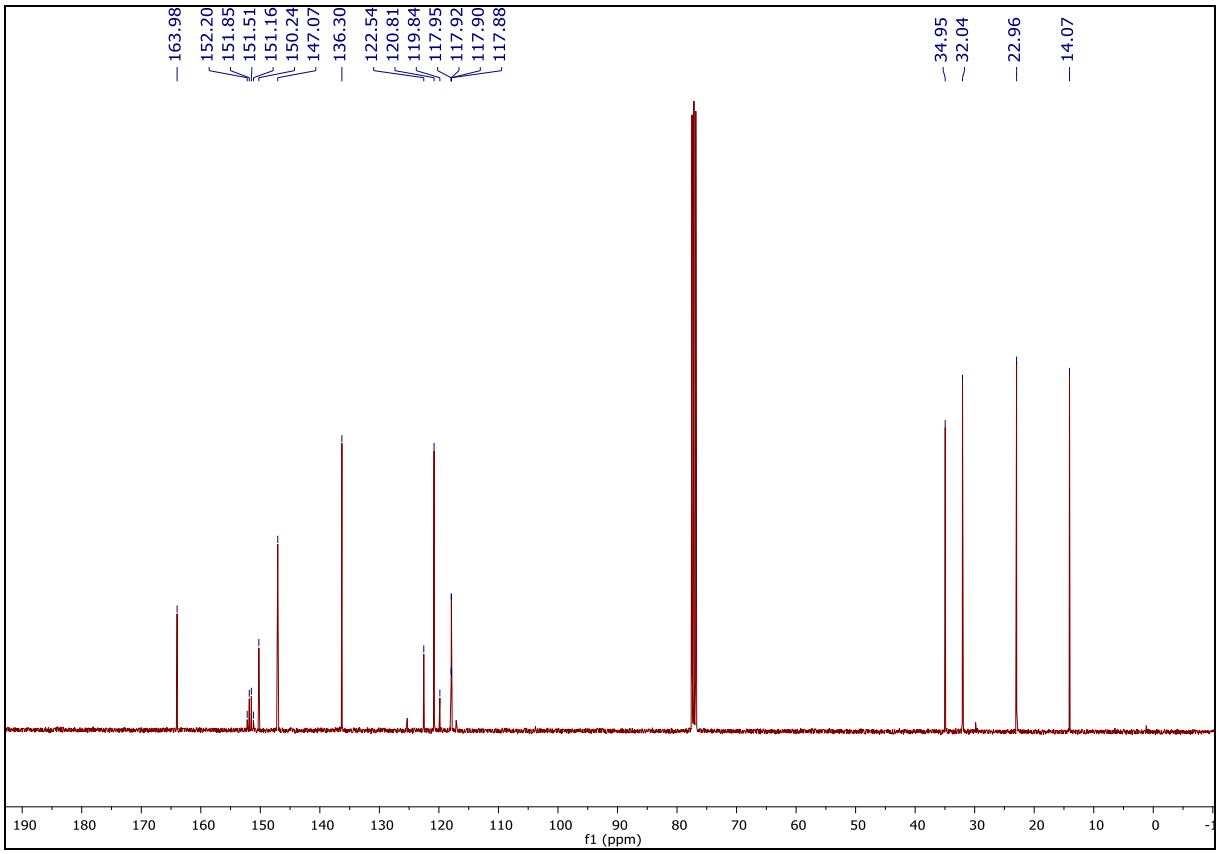
NMR-spectra of 1-(*sec*-butyl)-2,7-naphthyridine (3d)



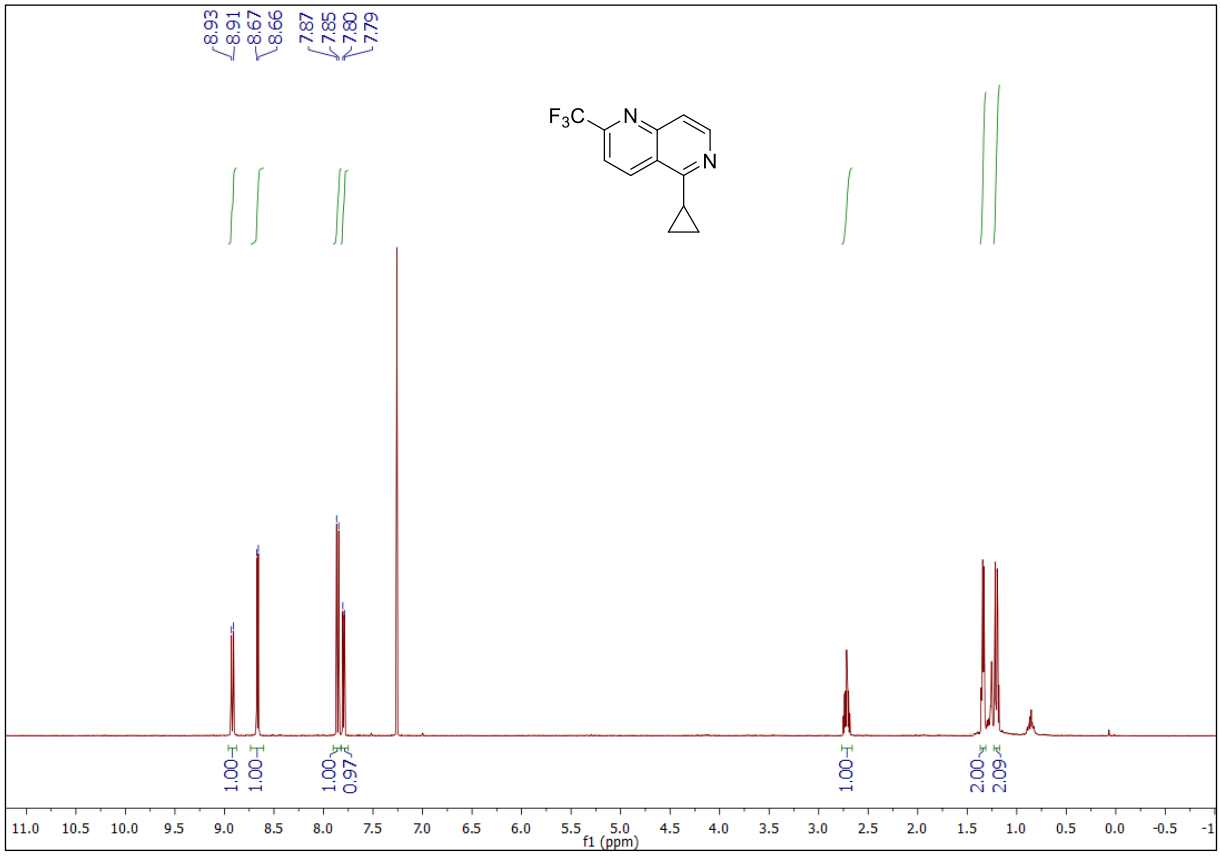


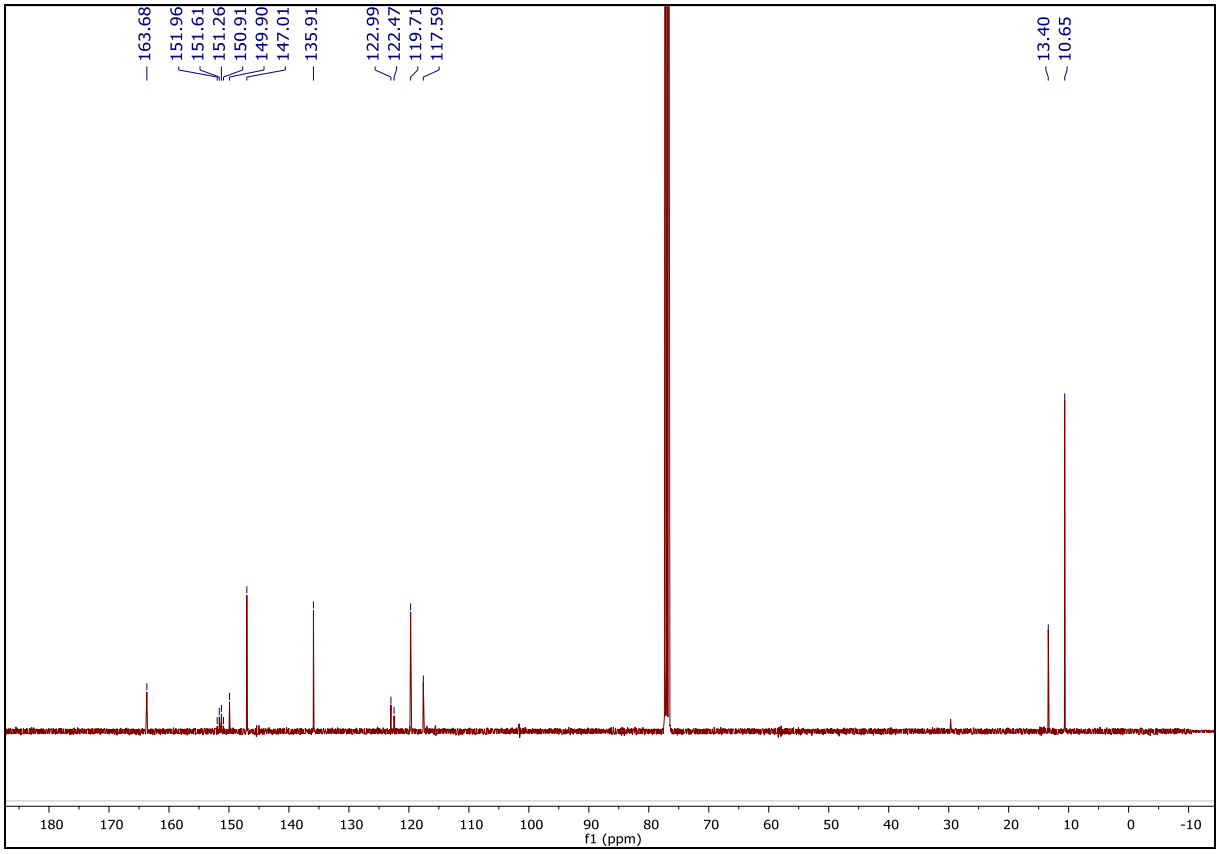
NMR-spectra of 5-butyl-2-(trifluoromethyl)-1,6-naphthyridine (3e)



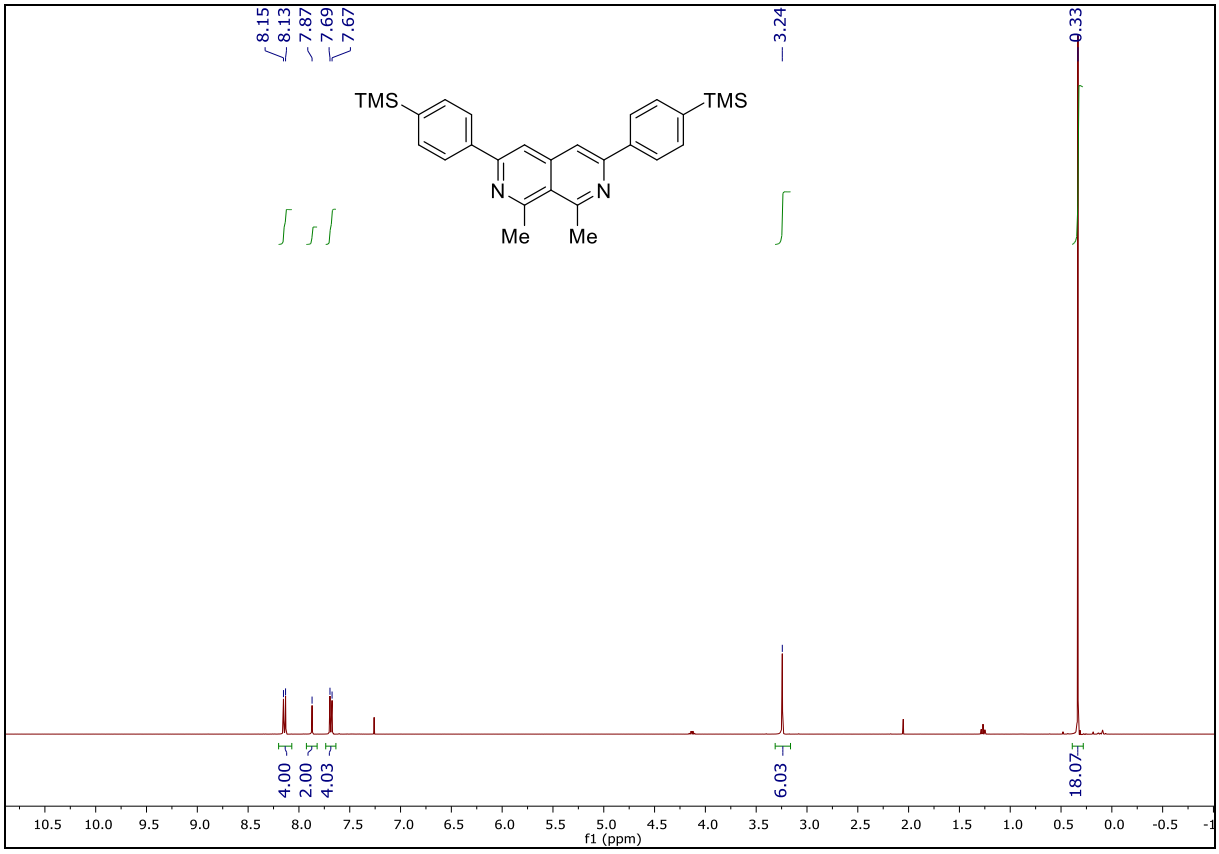


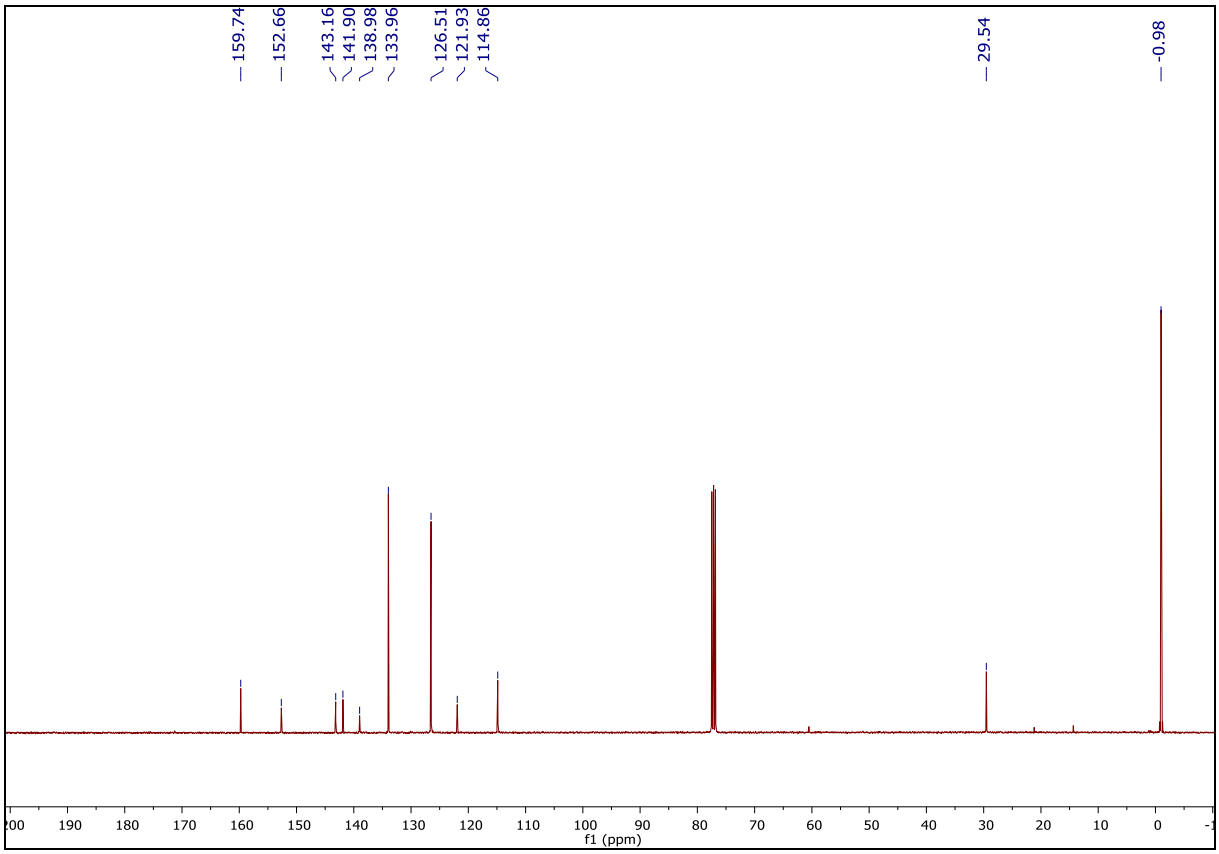
NMR-spectra of 5-cyclopropyl-2-(trifluoromethyl)-1,6-naphthyridine (3f)



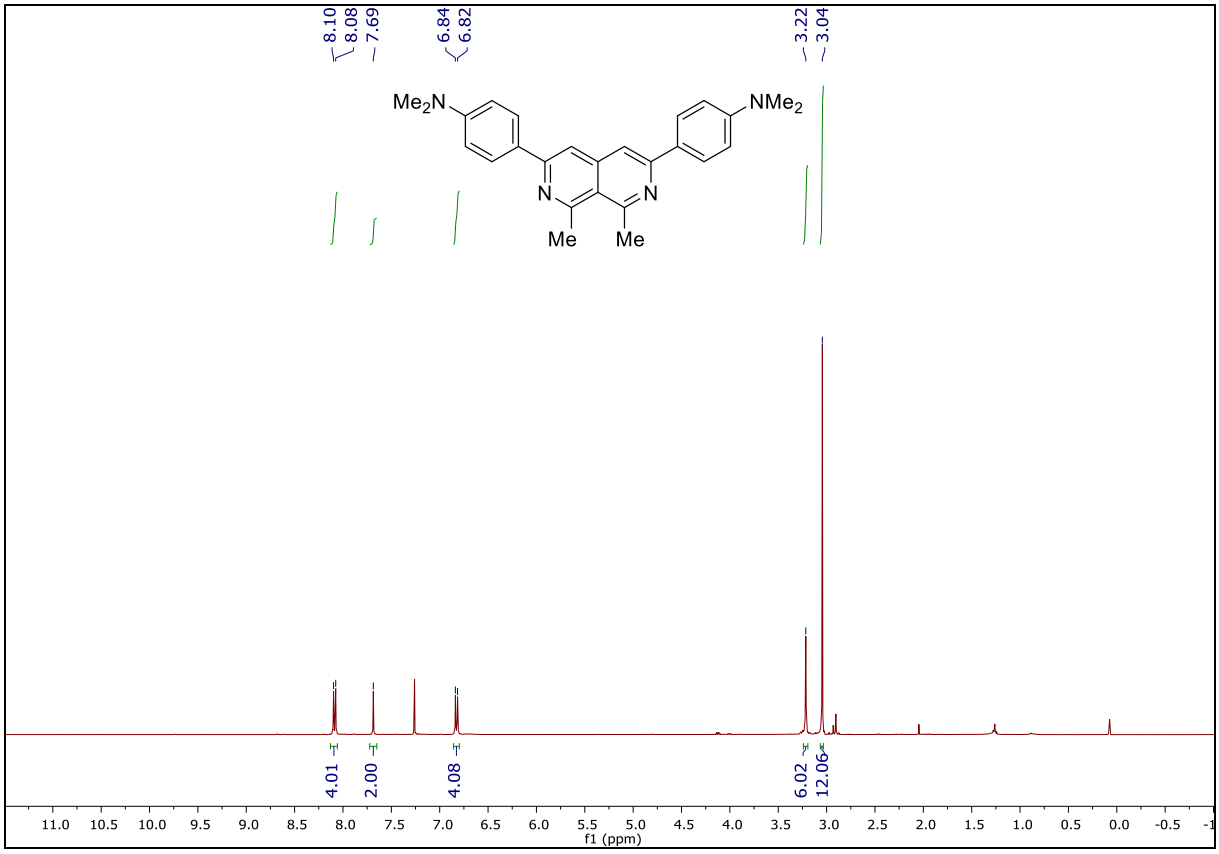


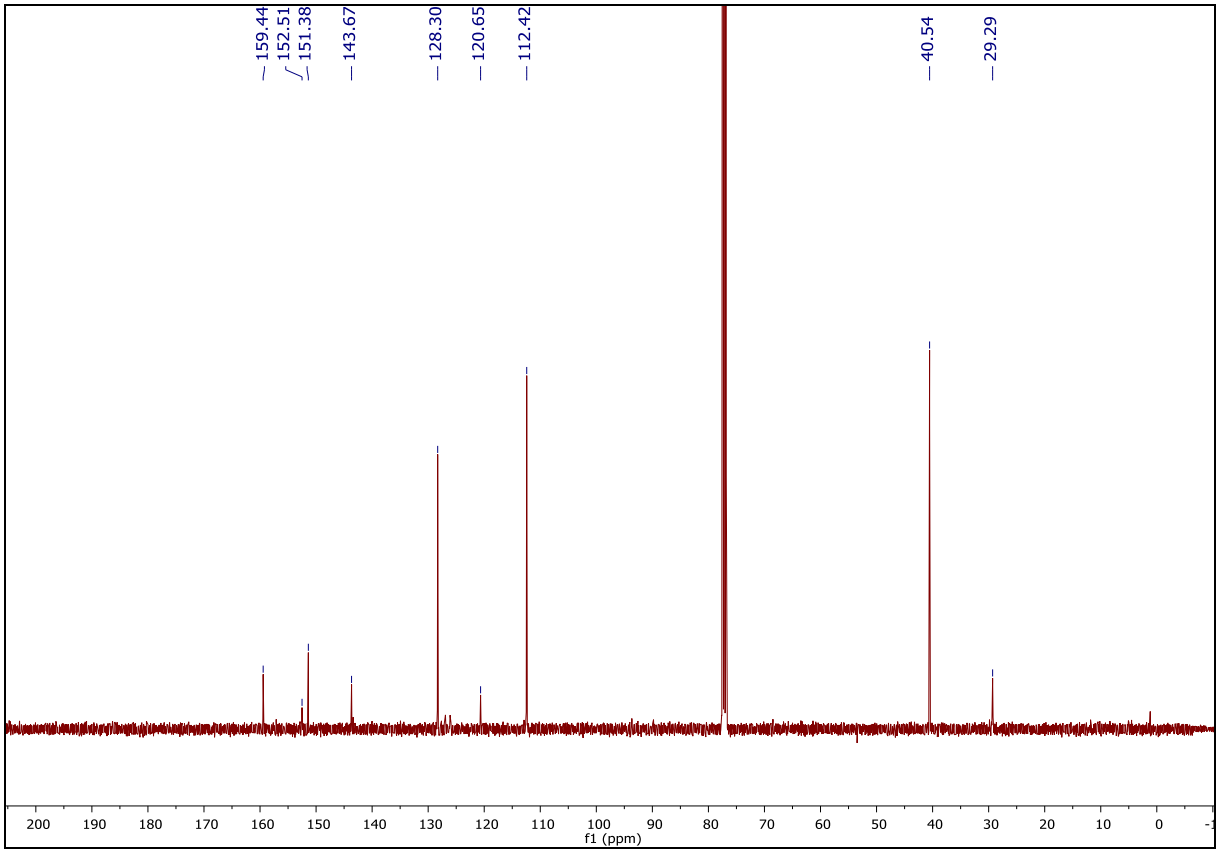
NMR-spectra of 1,8-dimethyl-3,6-bis(4-(trimethylsilyl)phenyl)-2,7-naphthyridine (5a)



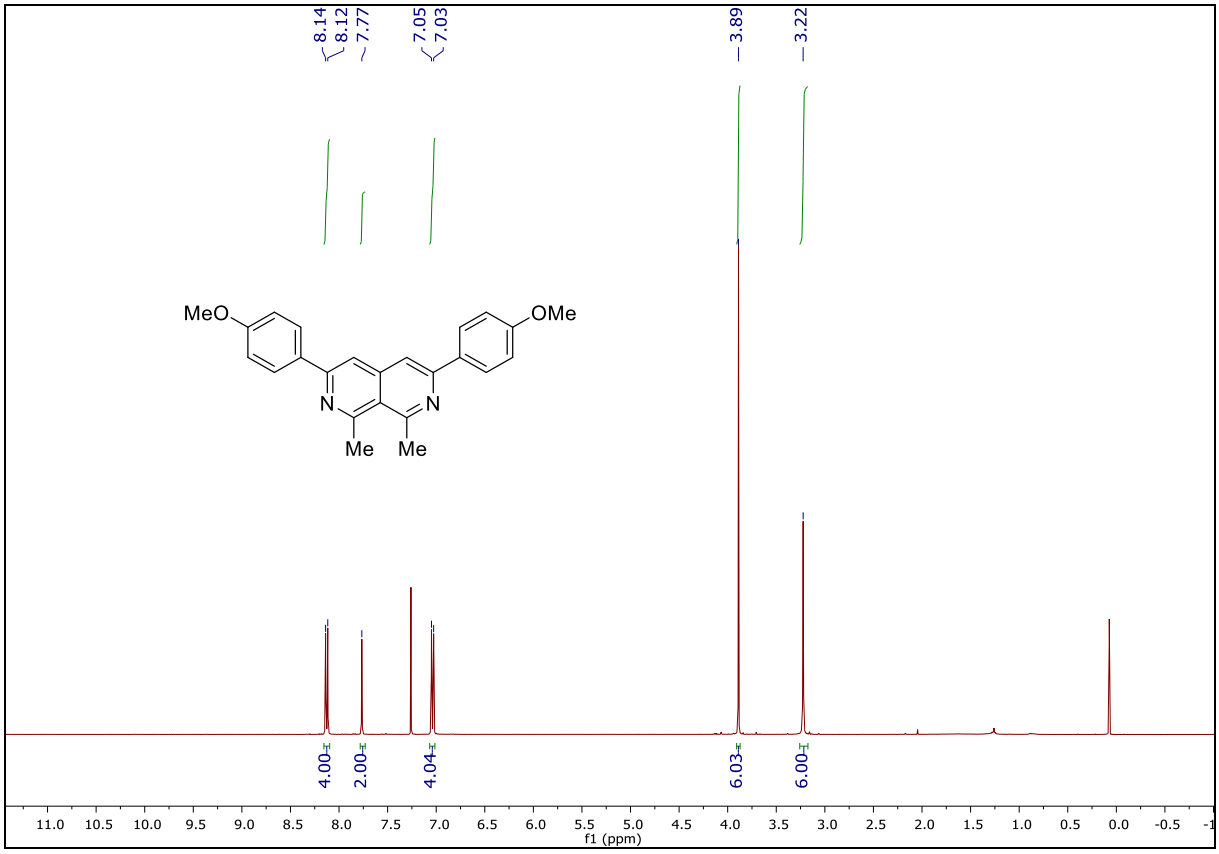


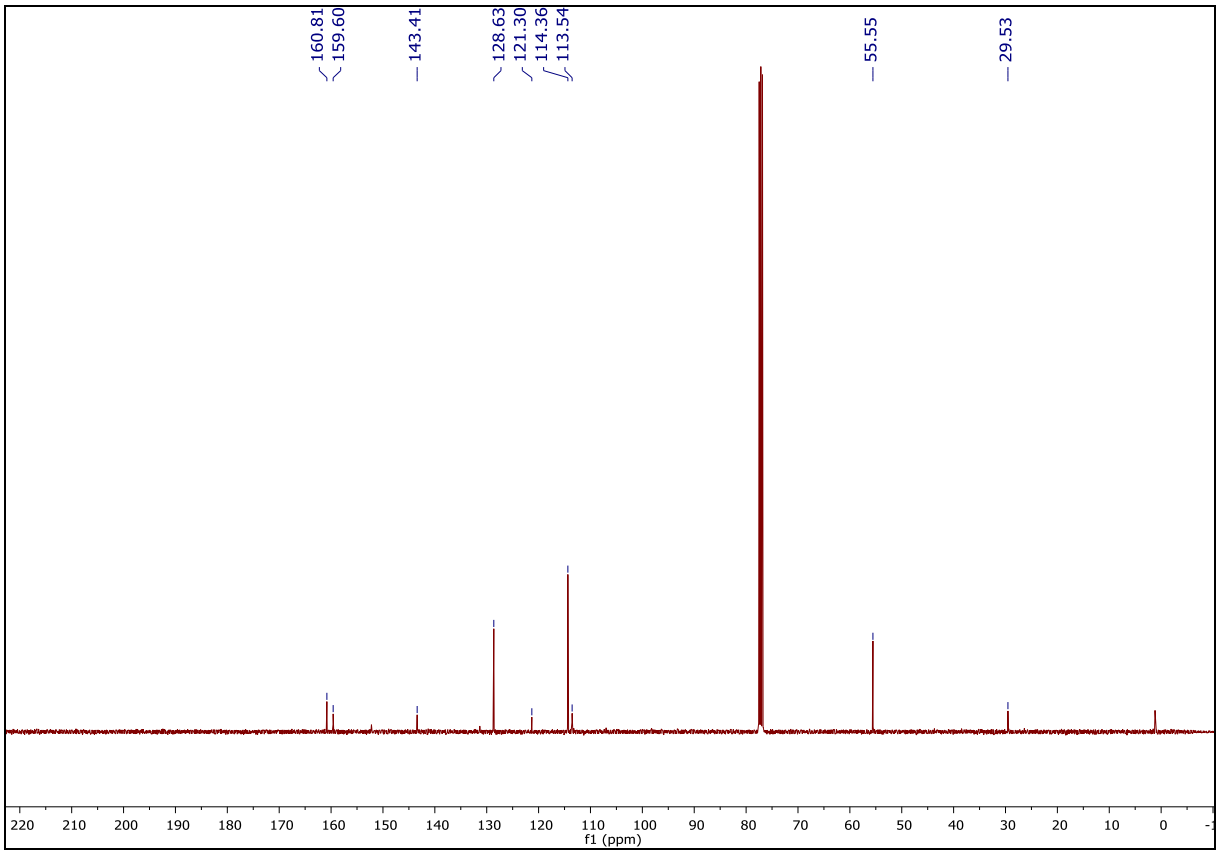
NMR-spectra of 4,4'-(1,8-dimethyl-2,7-naphthyridine-3,6-diyl)bis(*N*,*N*-dimethylaniline) (5b)



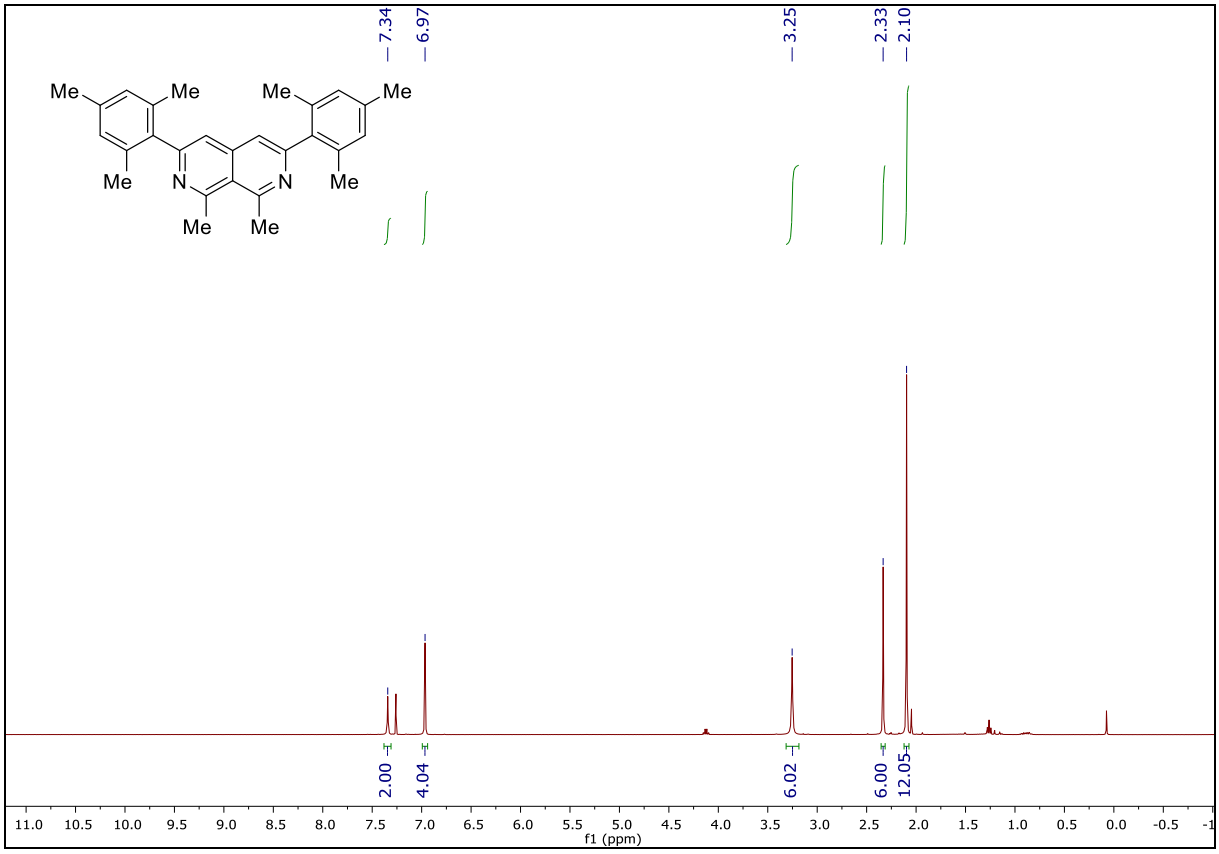


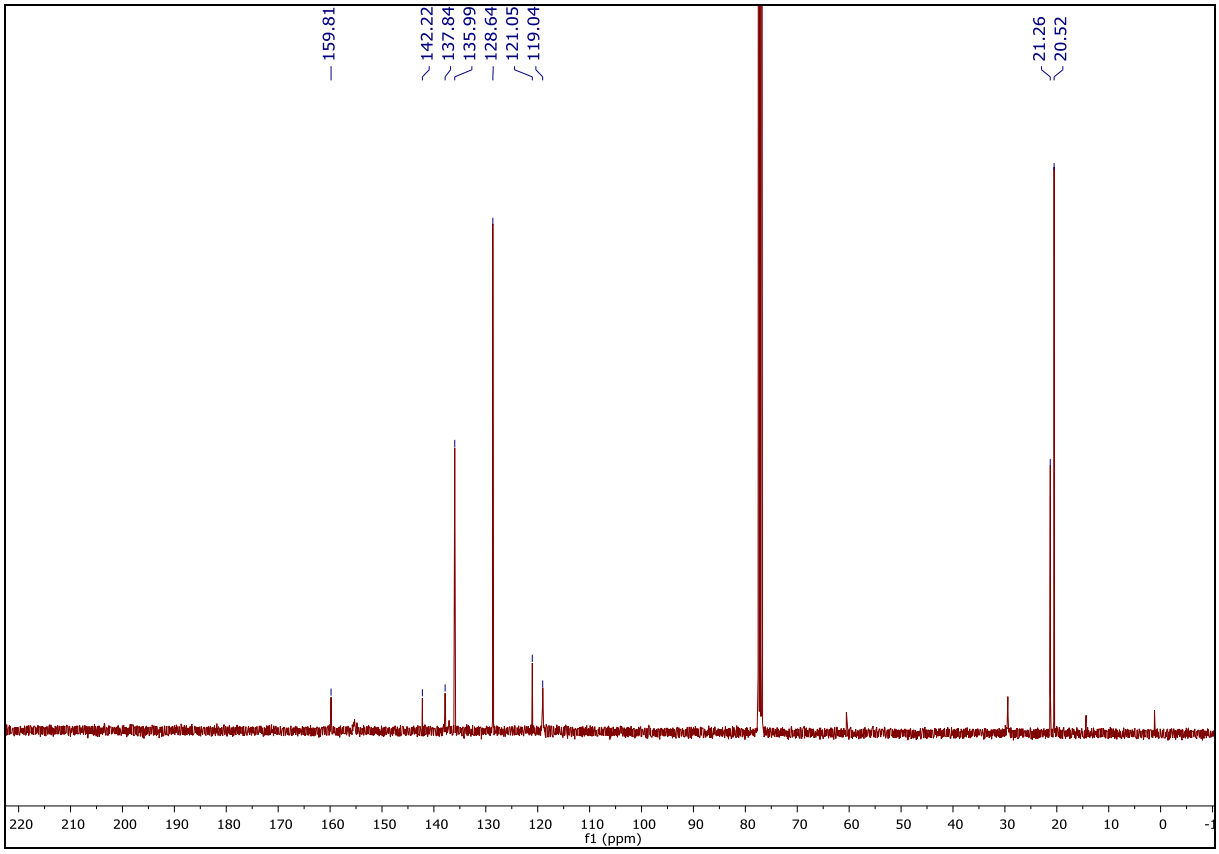
NMR-spectra of 3,6-bis(4-methoxyphenyl)-1,8-dimethyl-2,7-naphthyridine (5c)



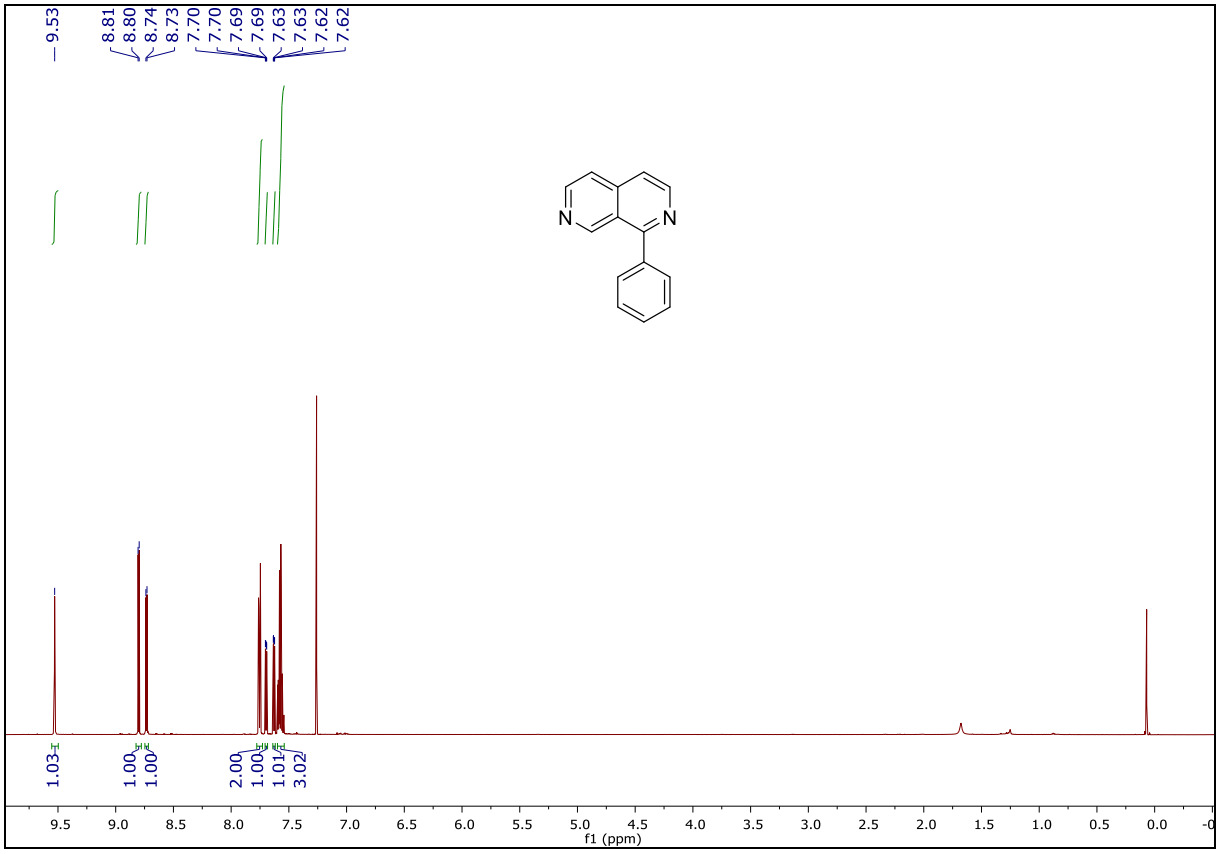


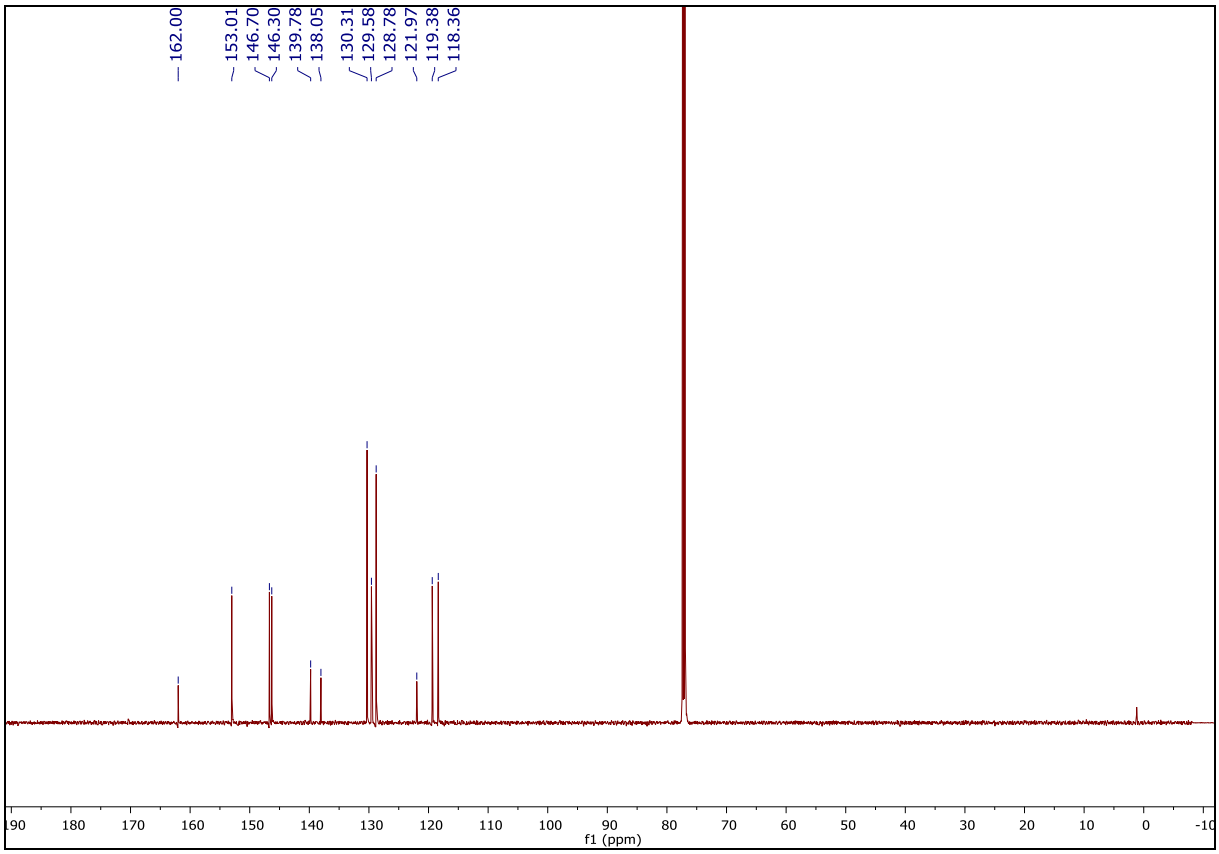
NMR-spectra of 3,6-dimesityl-1,8-dimethyl-2,7-naphthyridine (5d)



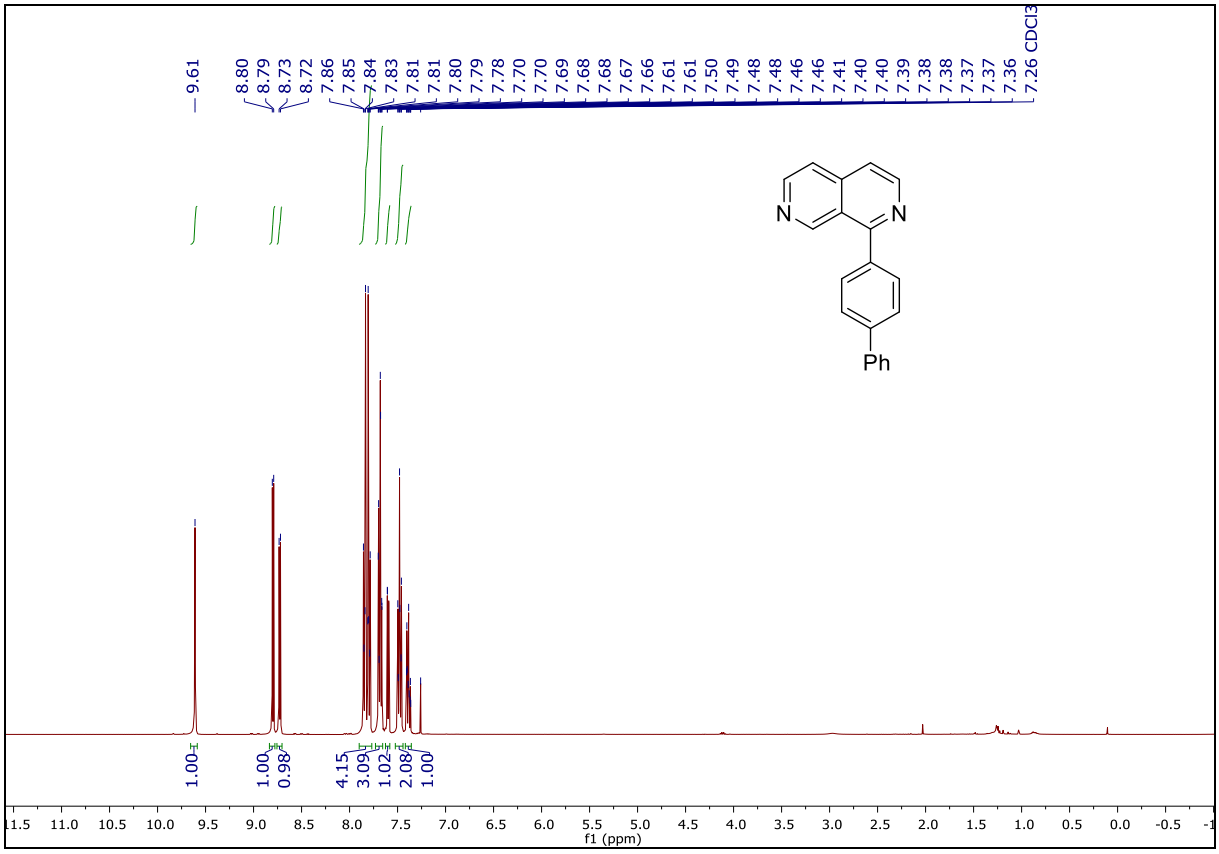


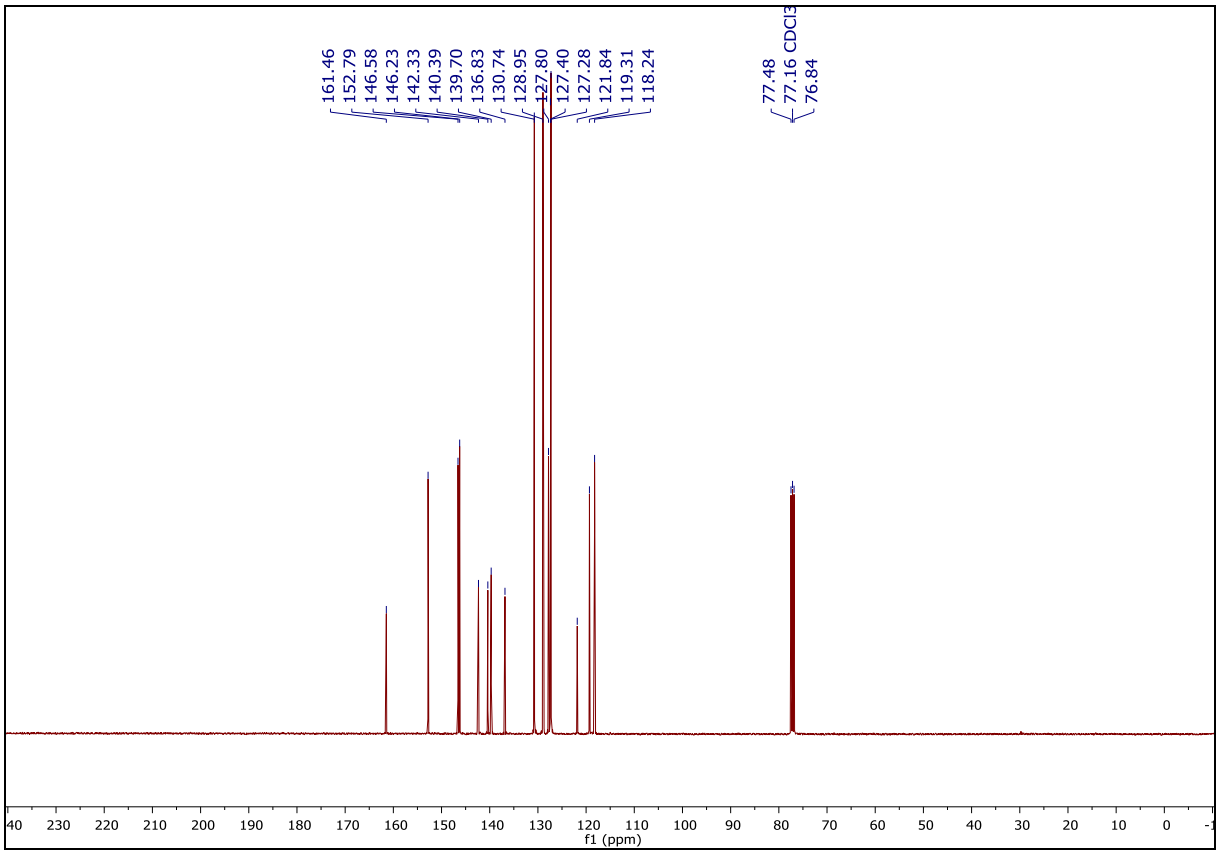
NMR-spectra of 1-phenyl-2,7-naphthyridine (7a)



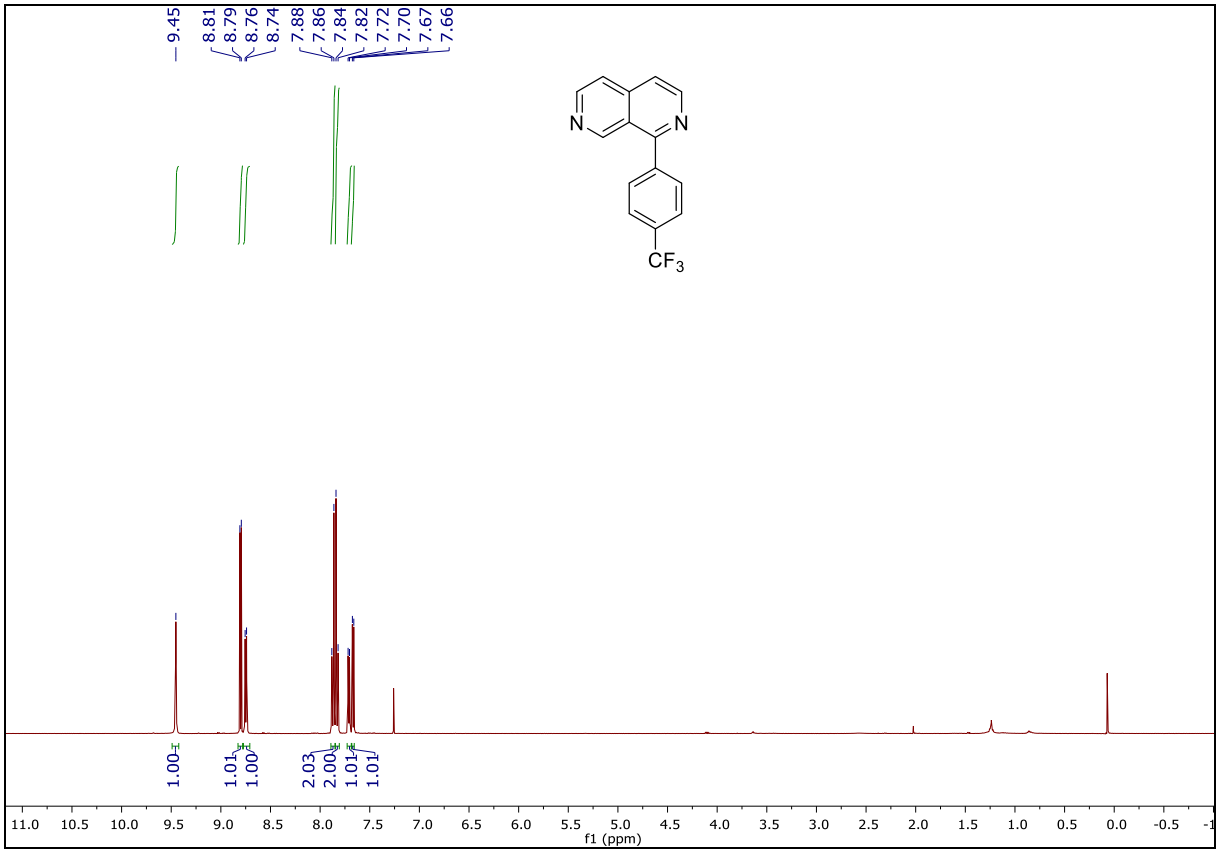


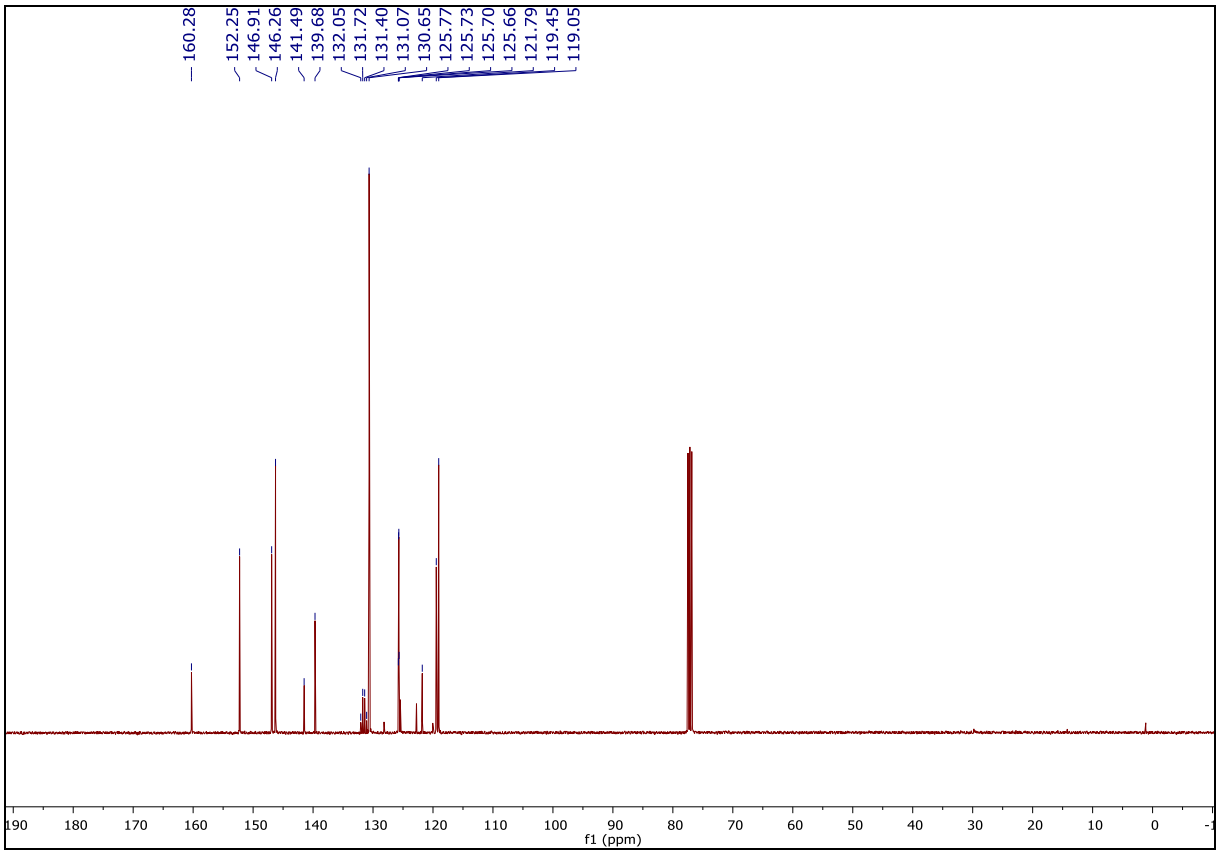
NMR-spectra of 1-([1,1'-biphenyl]-4-yl)-2,7-naphthyridine (7b)



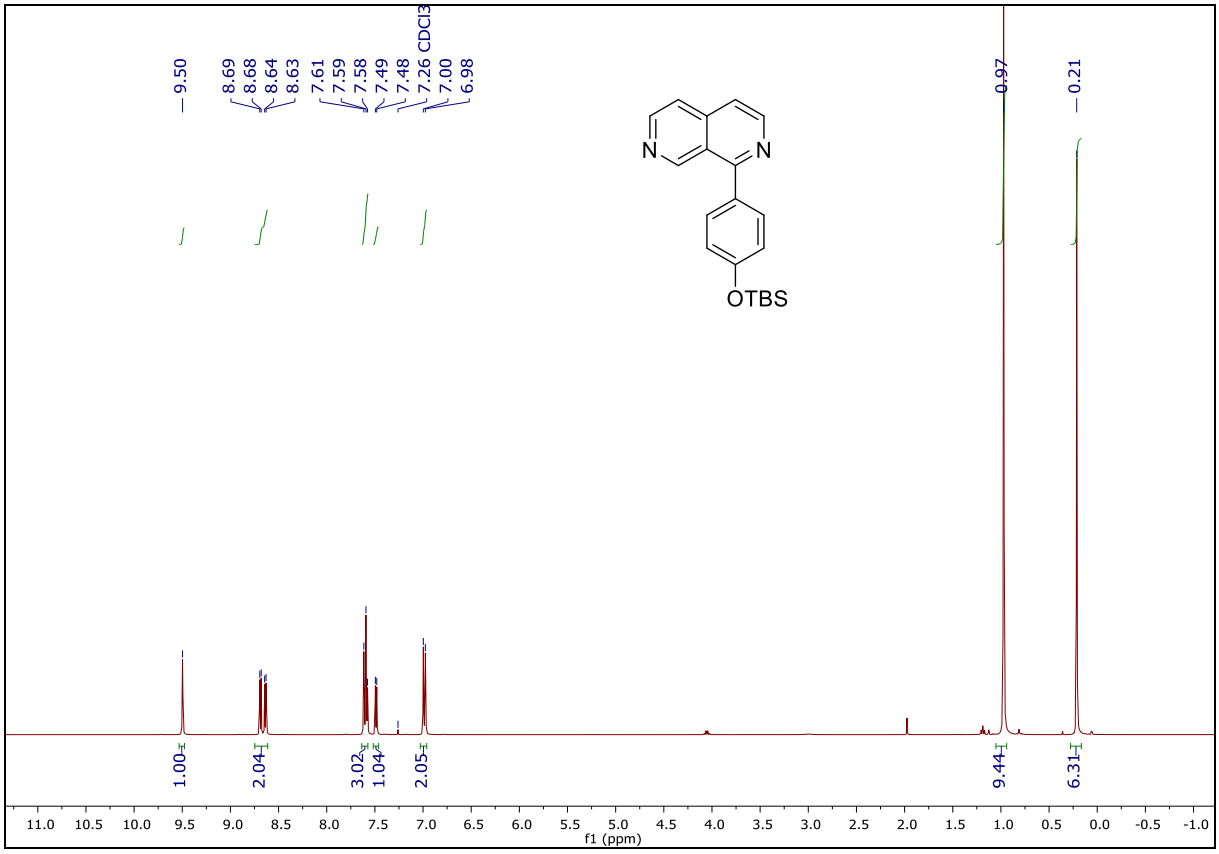


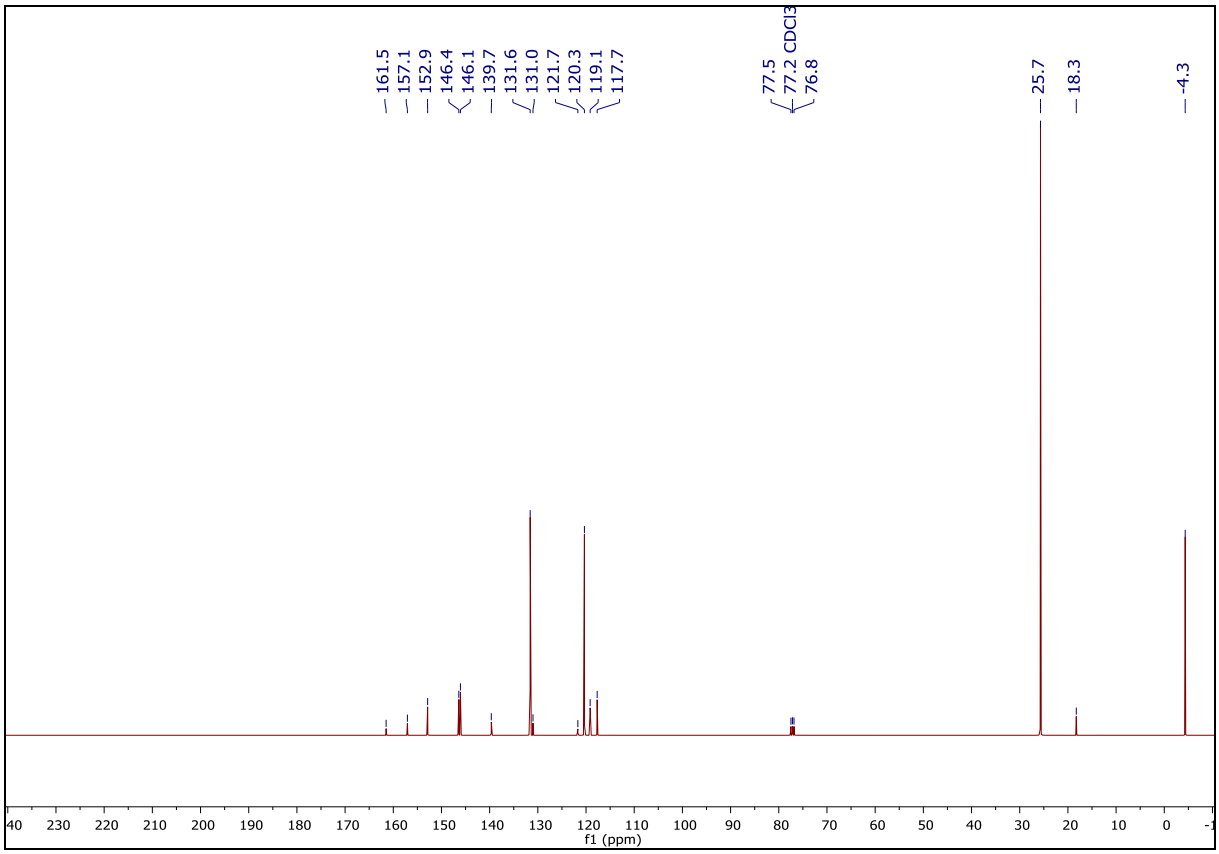
1-(4-(trifluoromethyl)phenyl)-2,7-naphthyridine (7c)



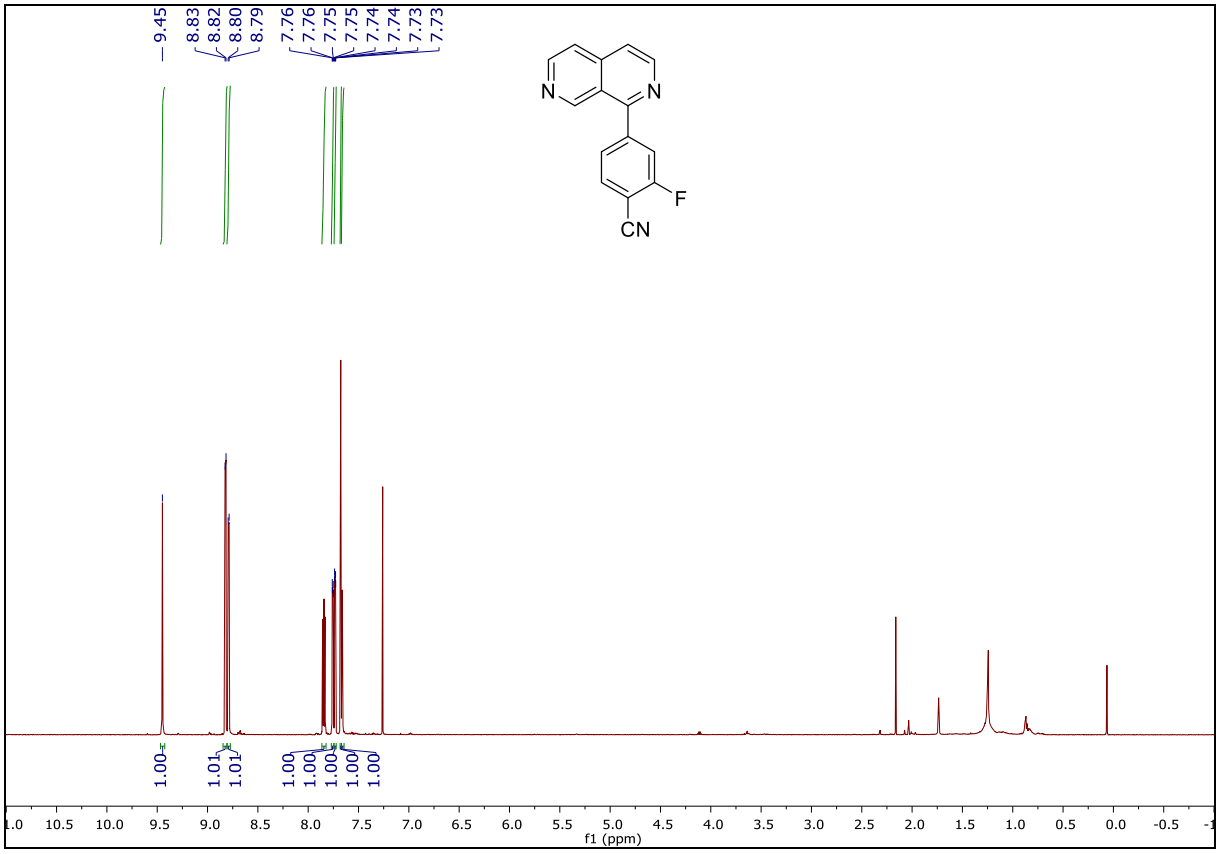


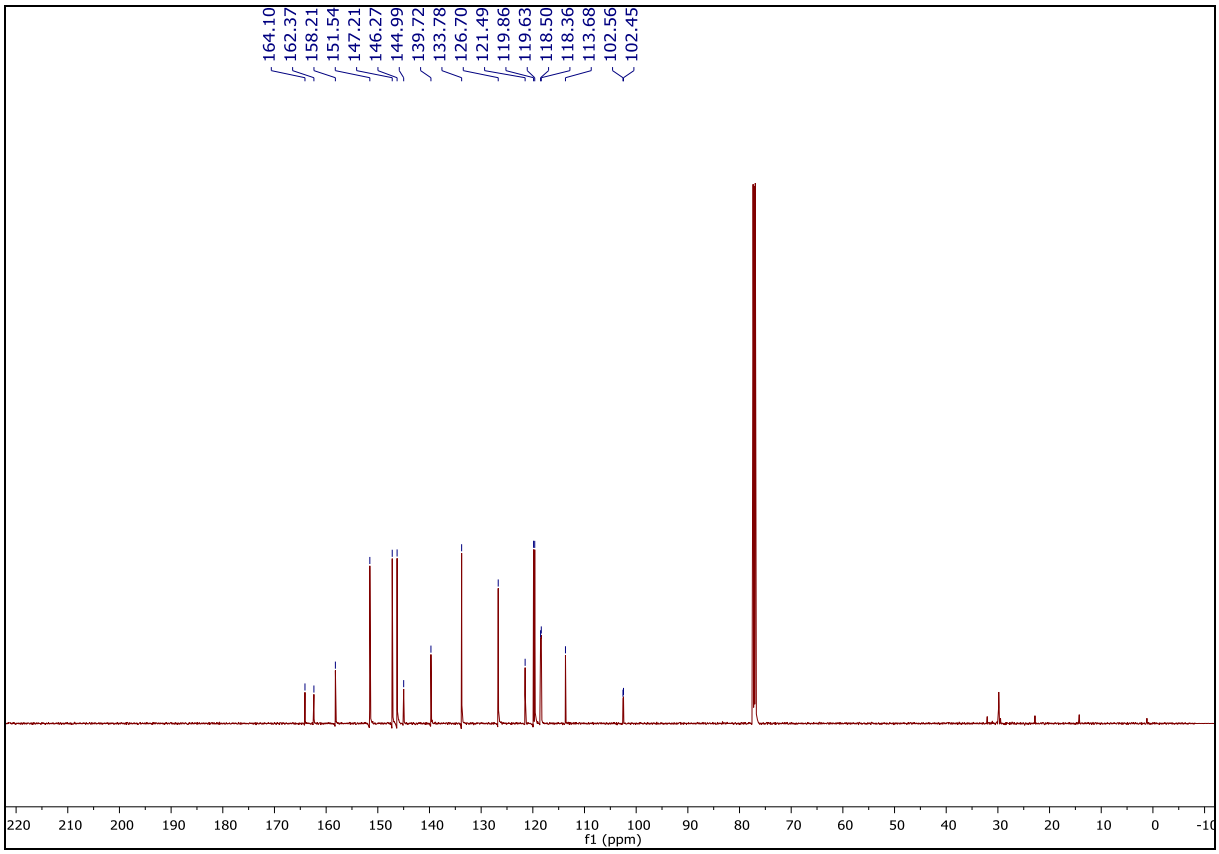
NMR-spectra of 1-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-2,7-naphthyridine (7d)



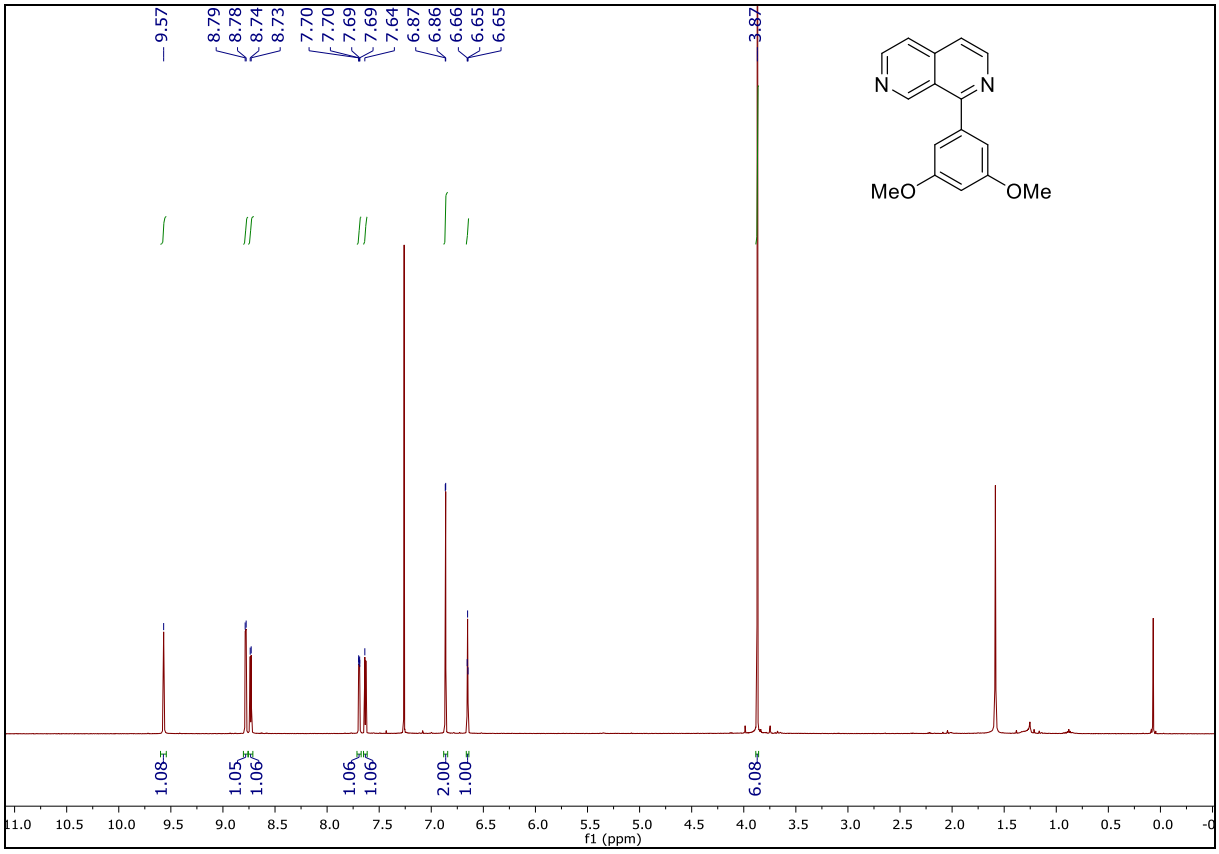


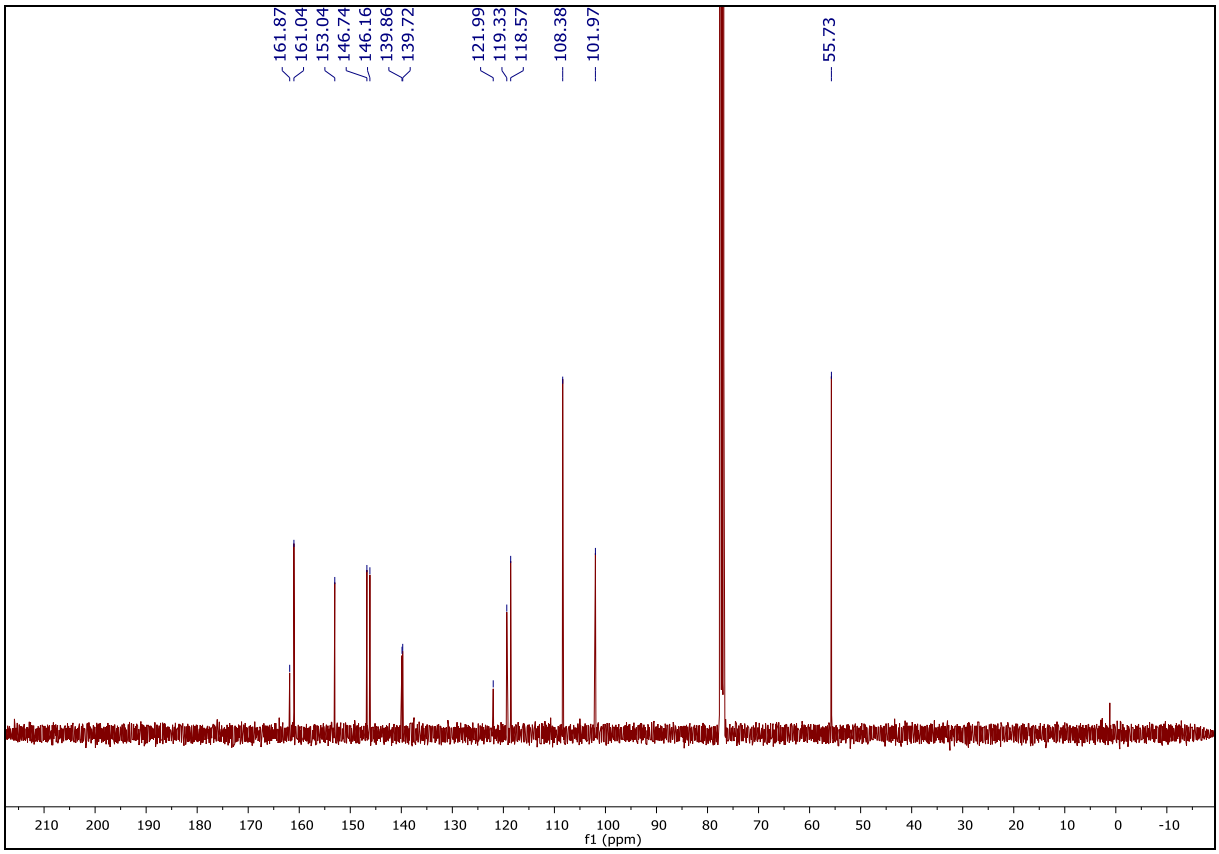
NMR-spectra of 2-fluoro-4-(2,7-naphthyridin-1-yl)benzonitrile (7e)



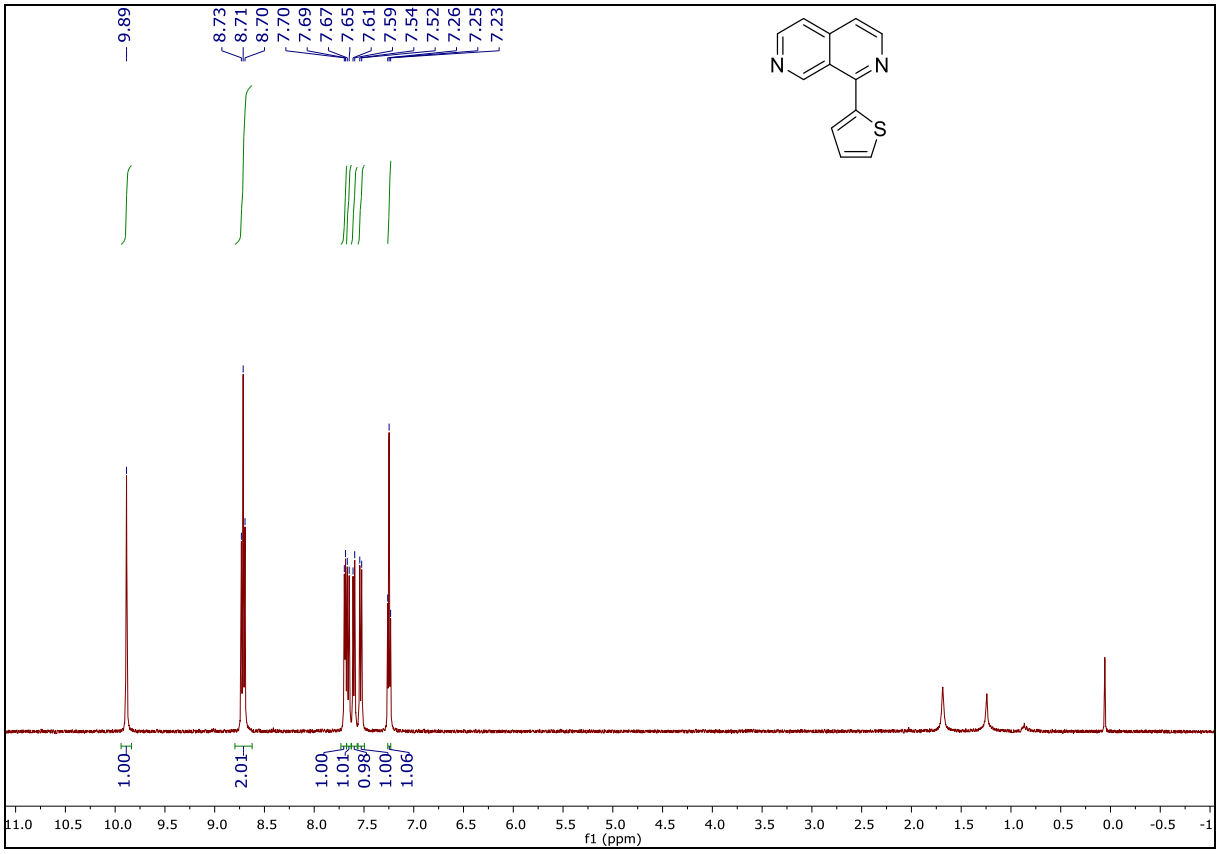


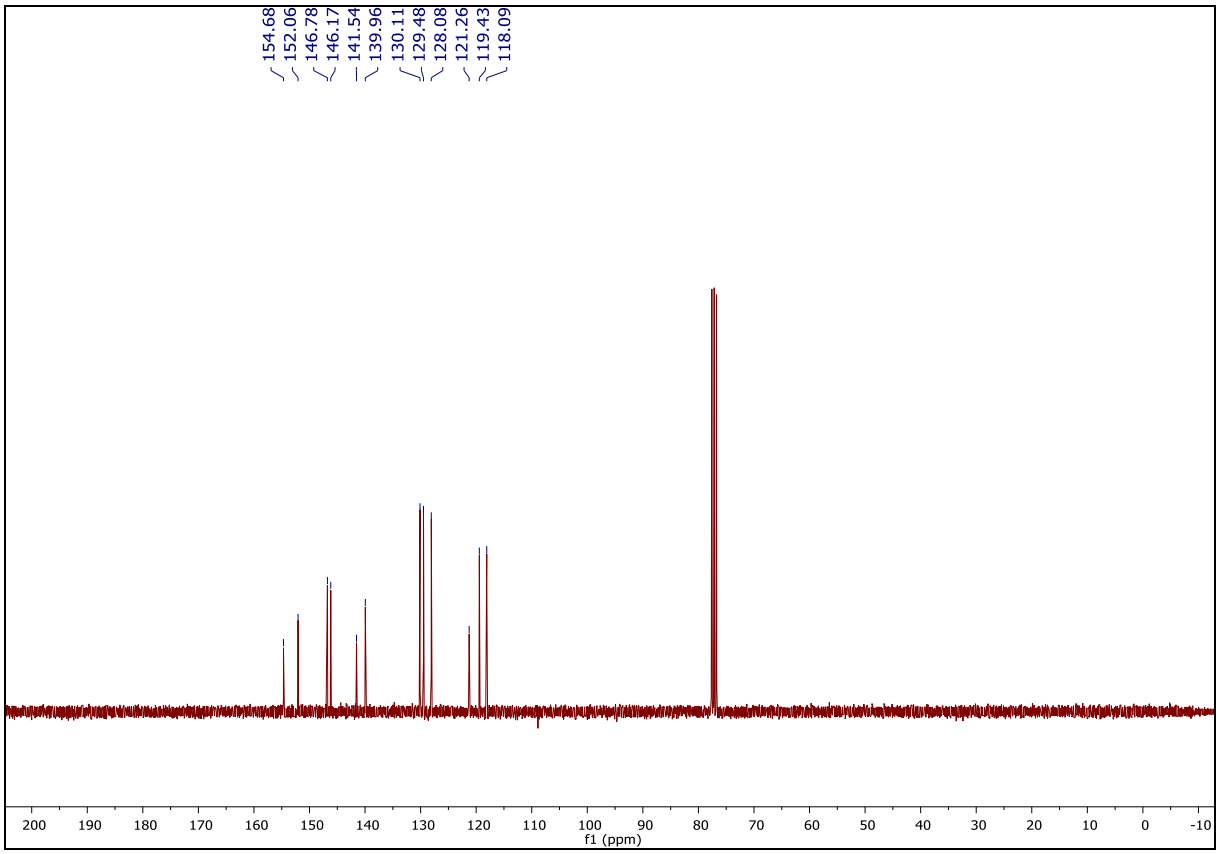
NMR-spectra of 1-(3,5-dimethoxyphenyl)-2,7-naphthyridine (7f)



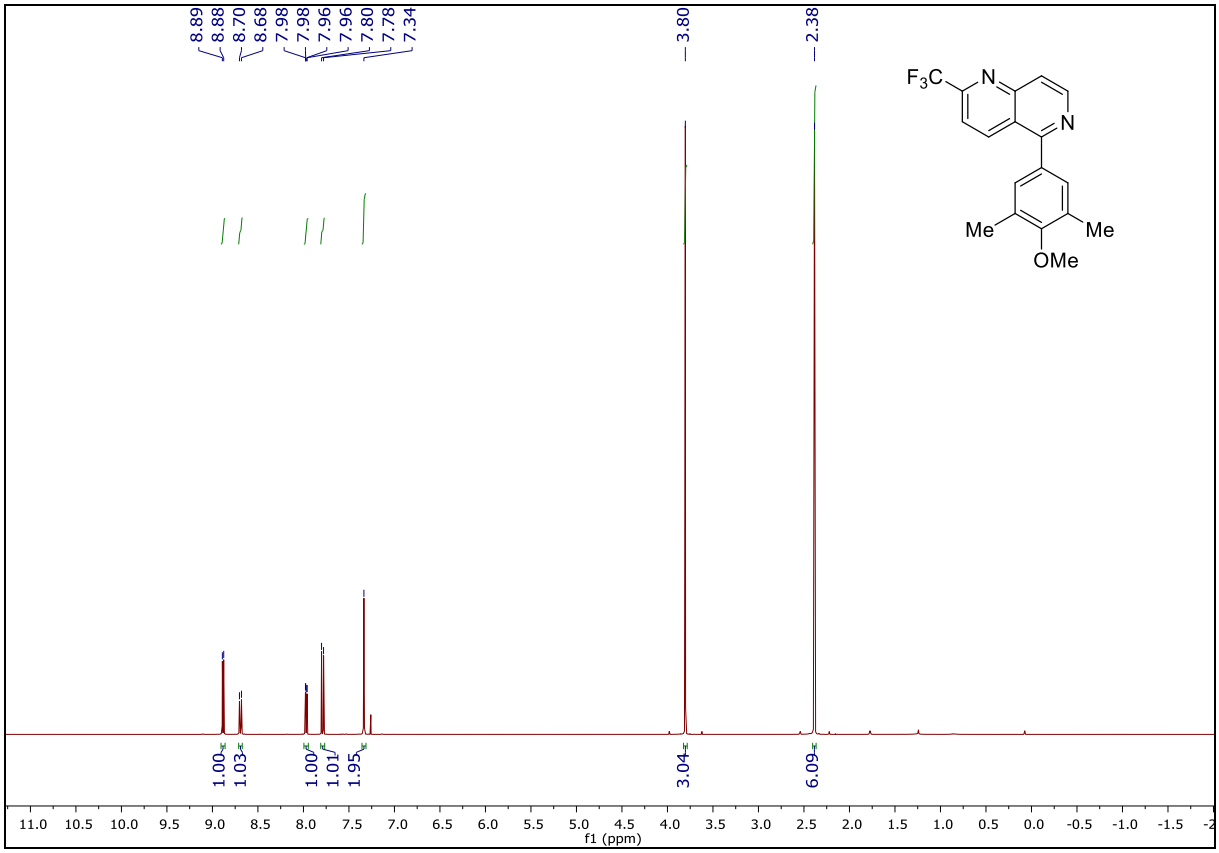


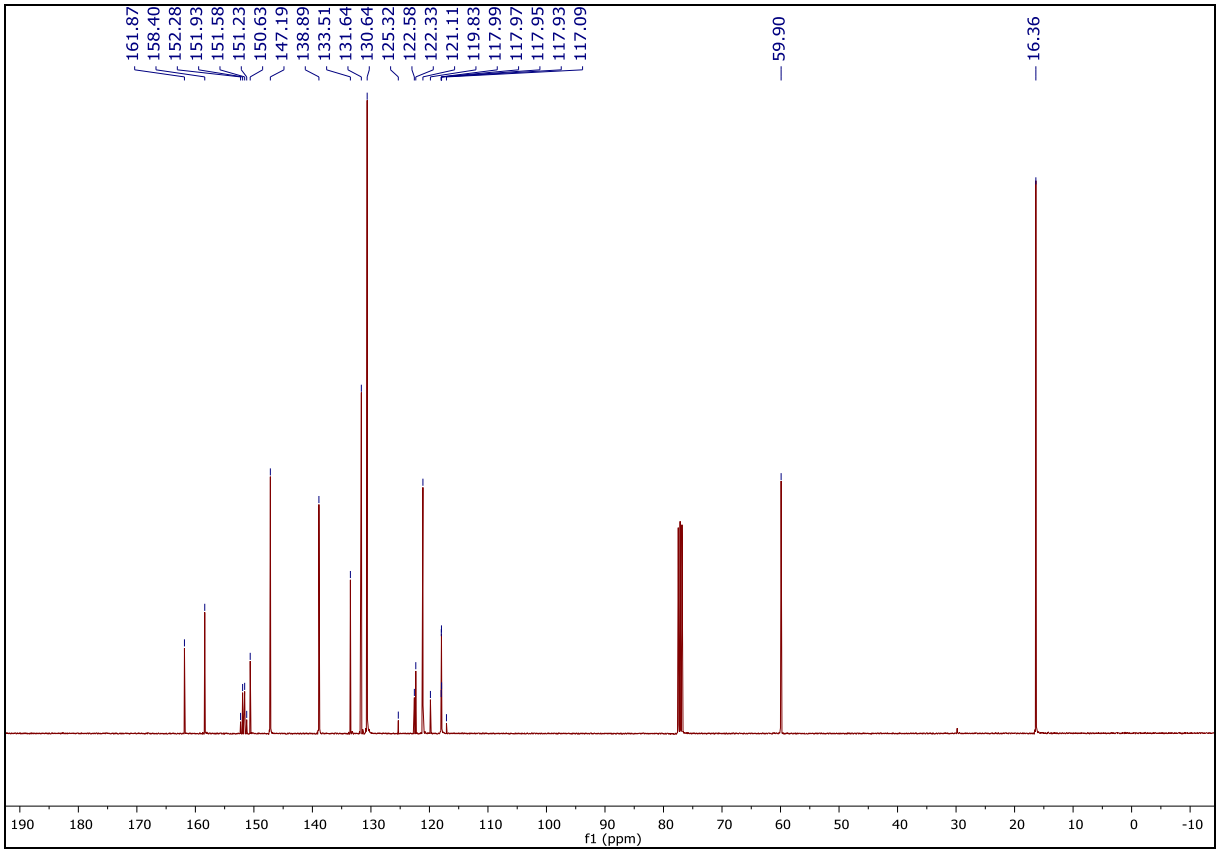
NMR-spectra of 1-(thiophen-2-yl)-2,7-naphthyridine (7g)



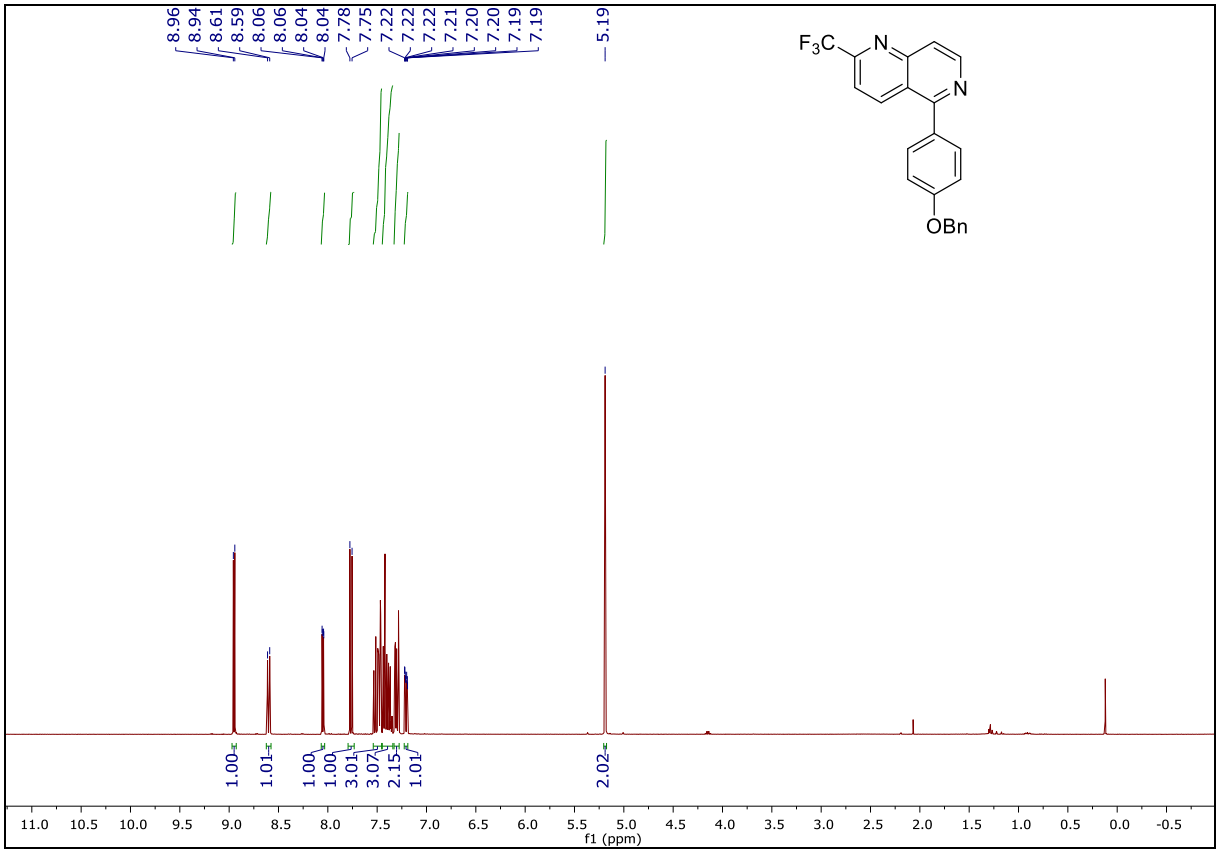


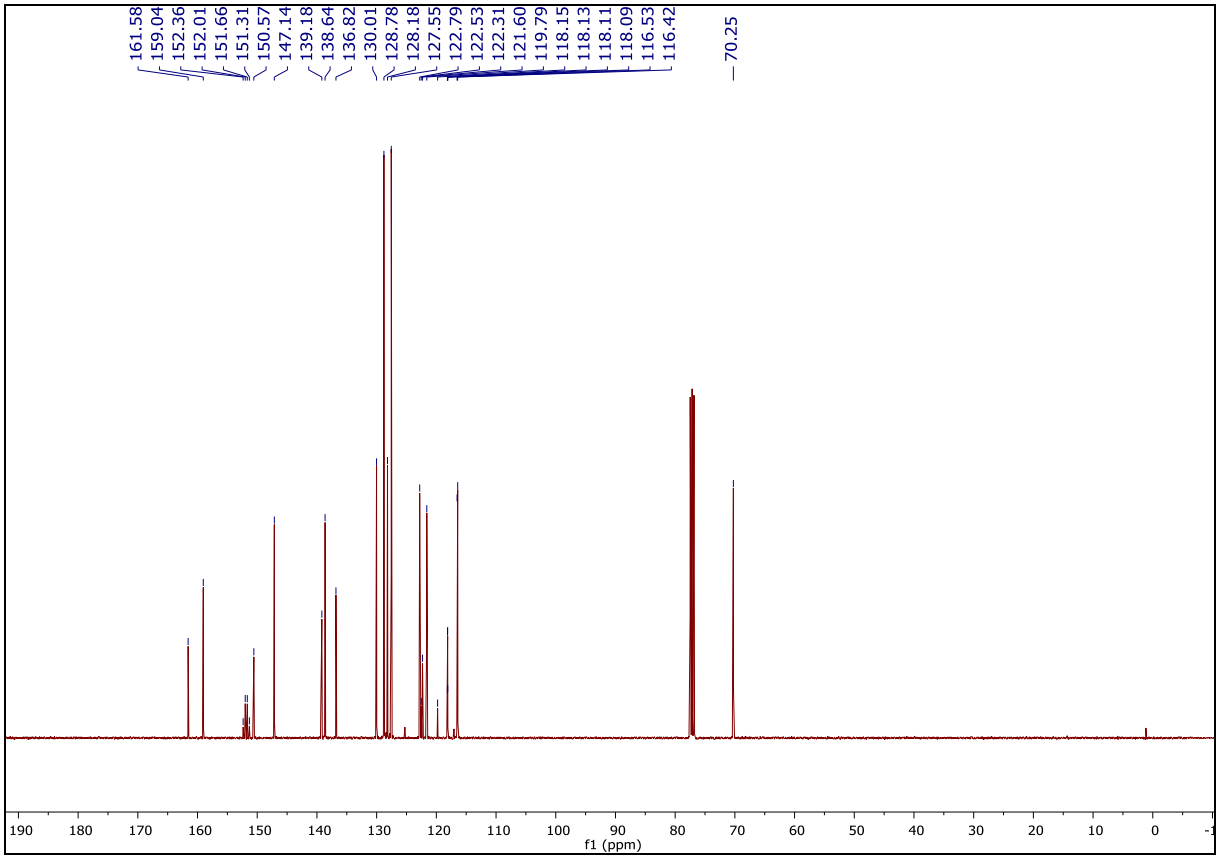
NMR-spectra of 5-(4-methoxy-3,5-dimethylphenyl)-2-(trifluoromethyl)-1,6-naphthyridine (7h)



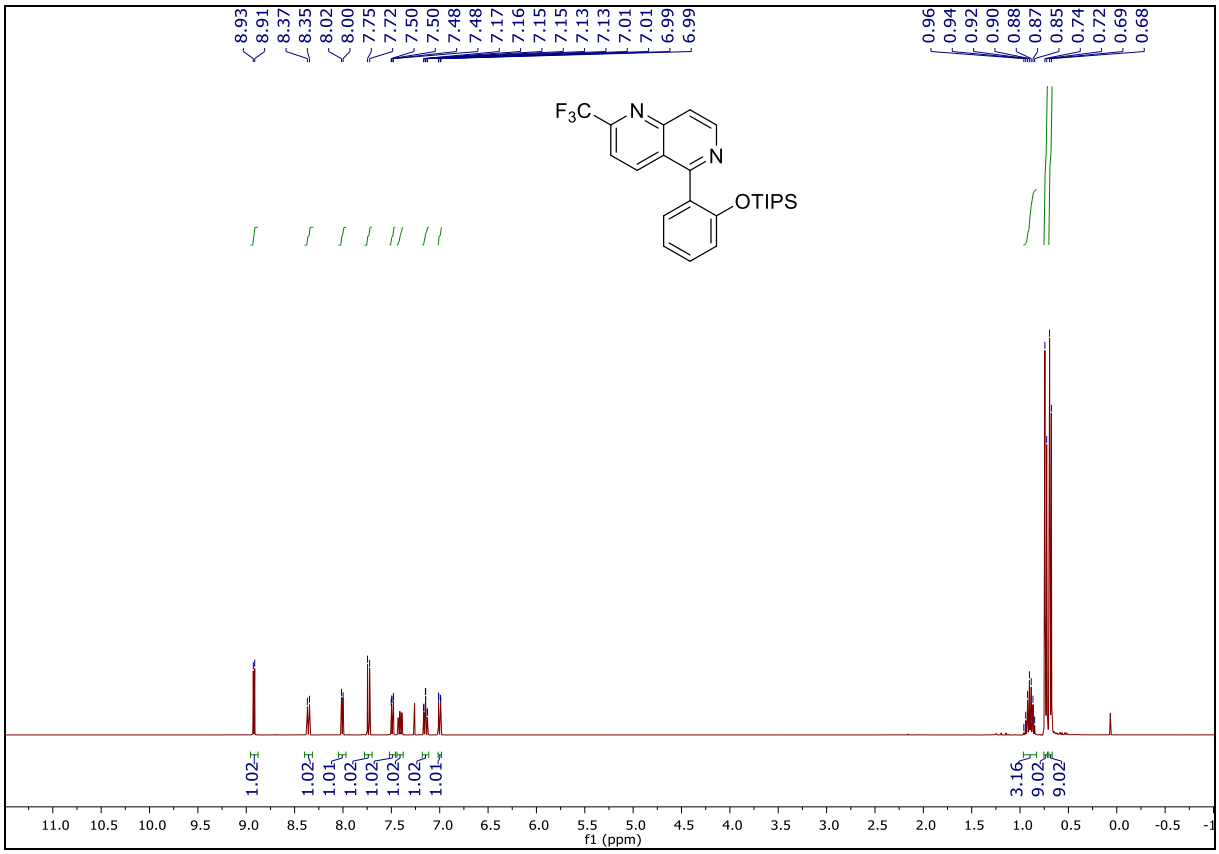


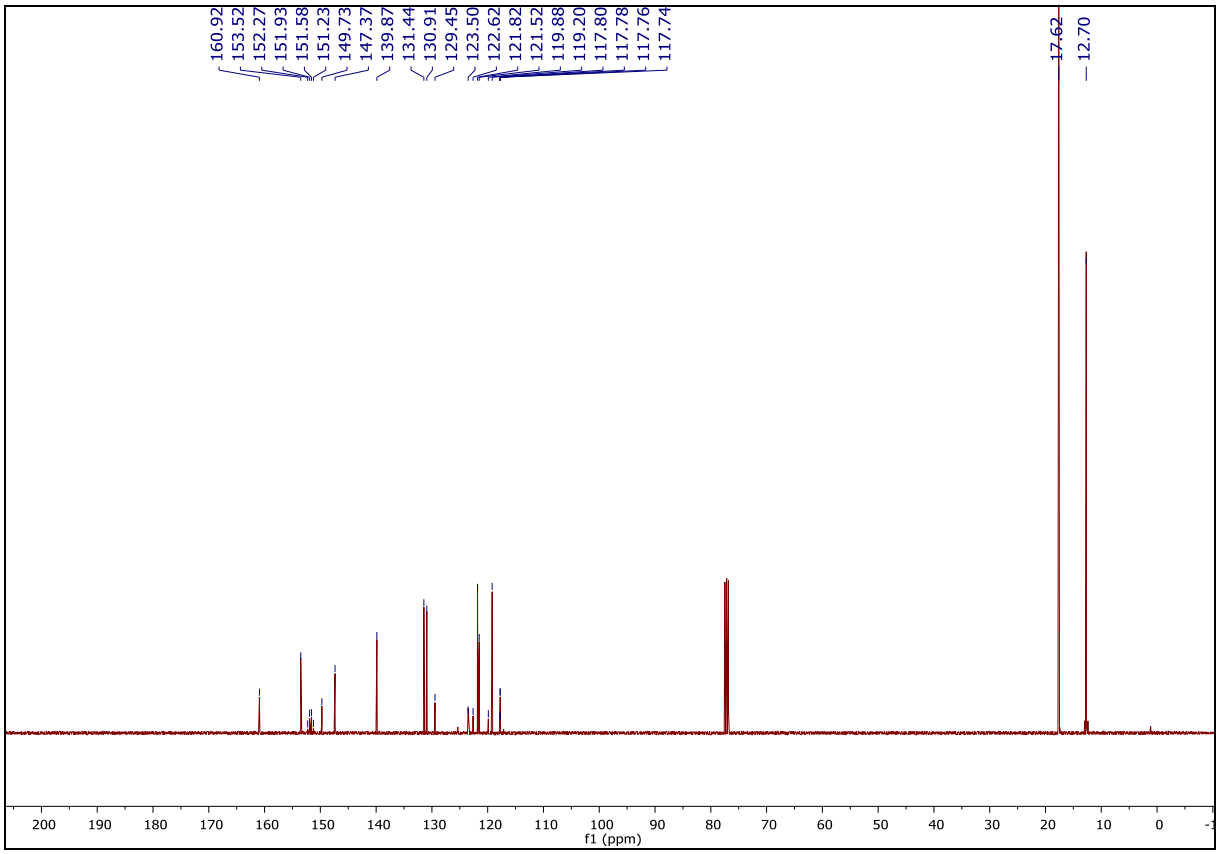
NMR-spectra of 5-(4-(benzyloxy)phenyl)-2-(trifluoromethyl)-1,6-naphthyridine (7i)



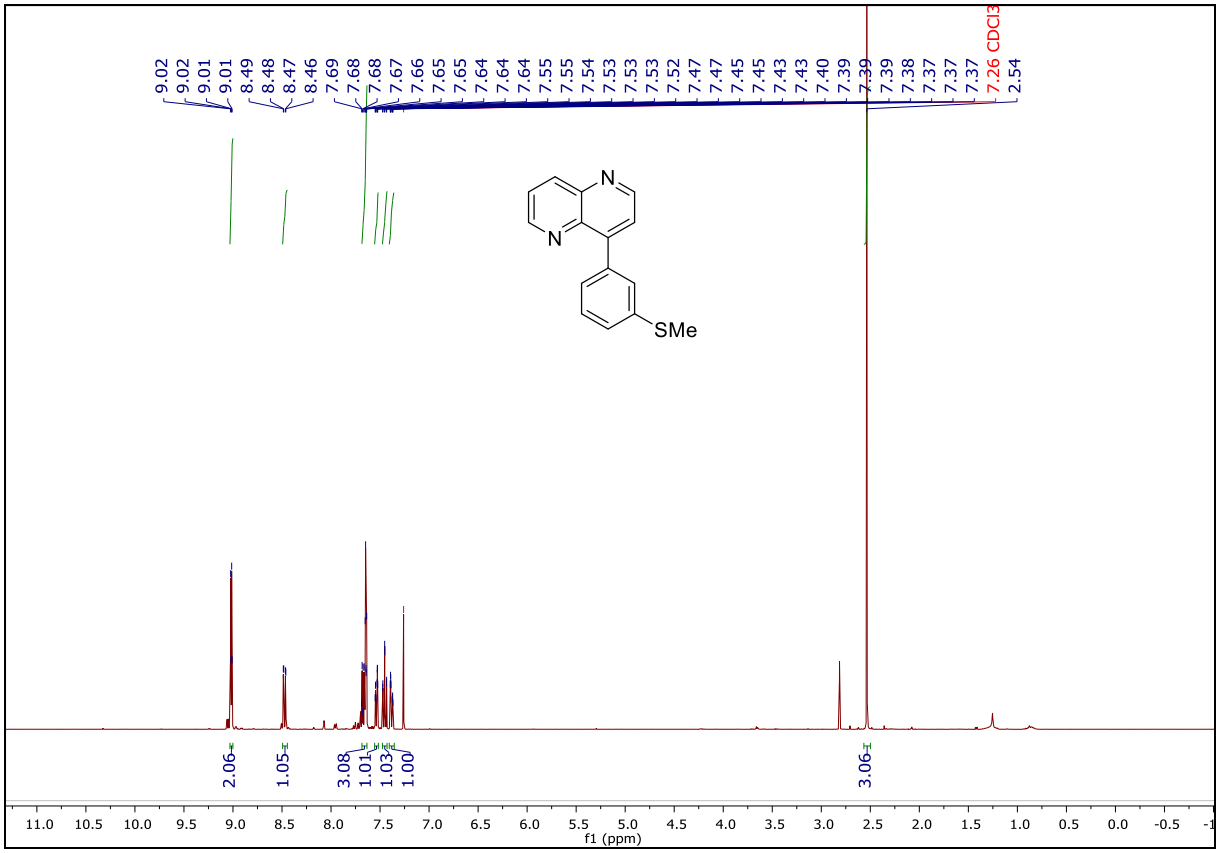


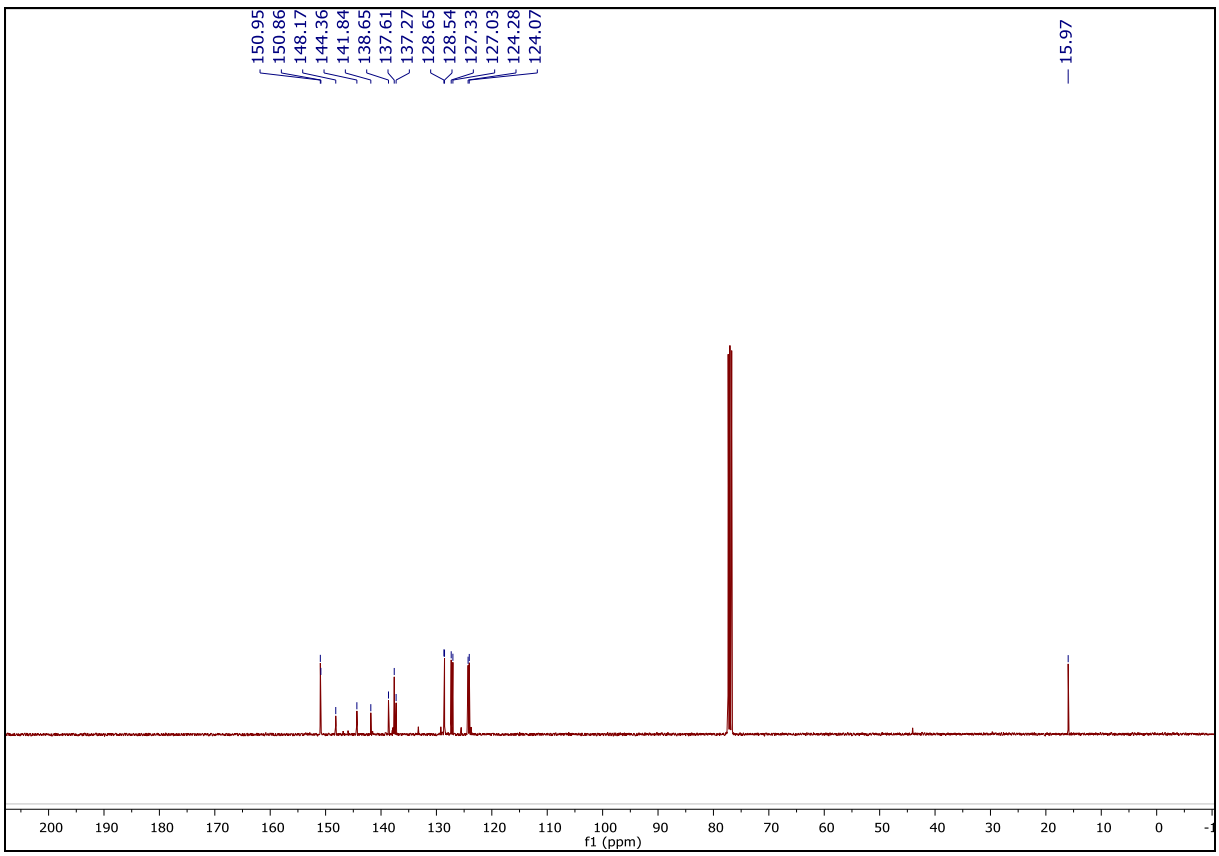
NMR-spectra of 2-(trifluoromethyl)-5-(2-((triisopropylsilyl)oxy)phenyl)-1,6-naphthyridine (7j)



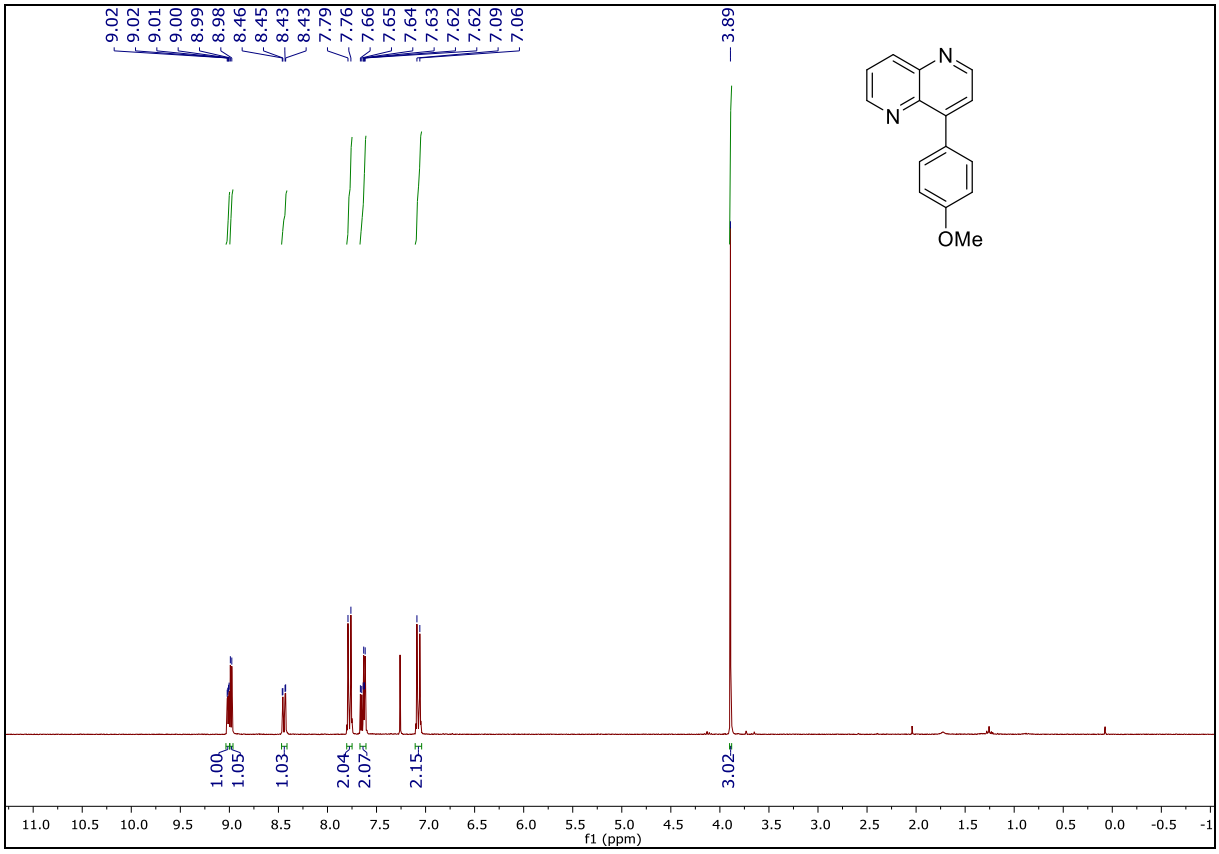


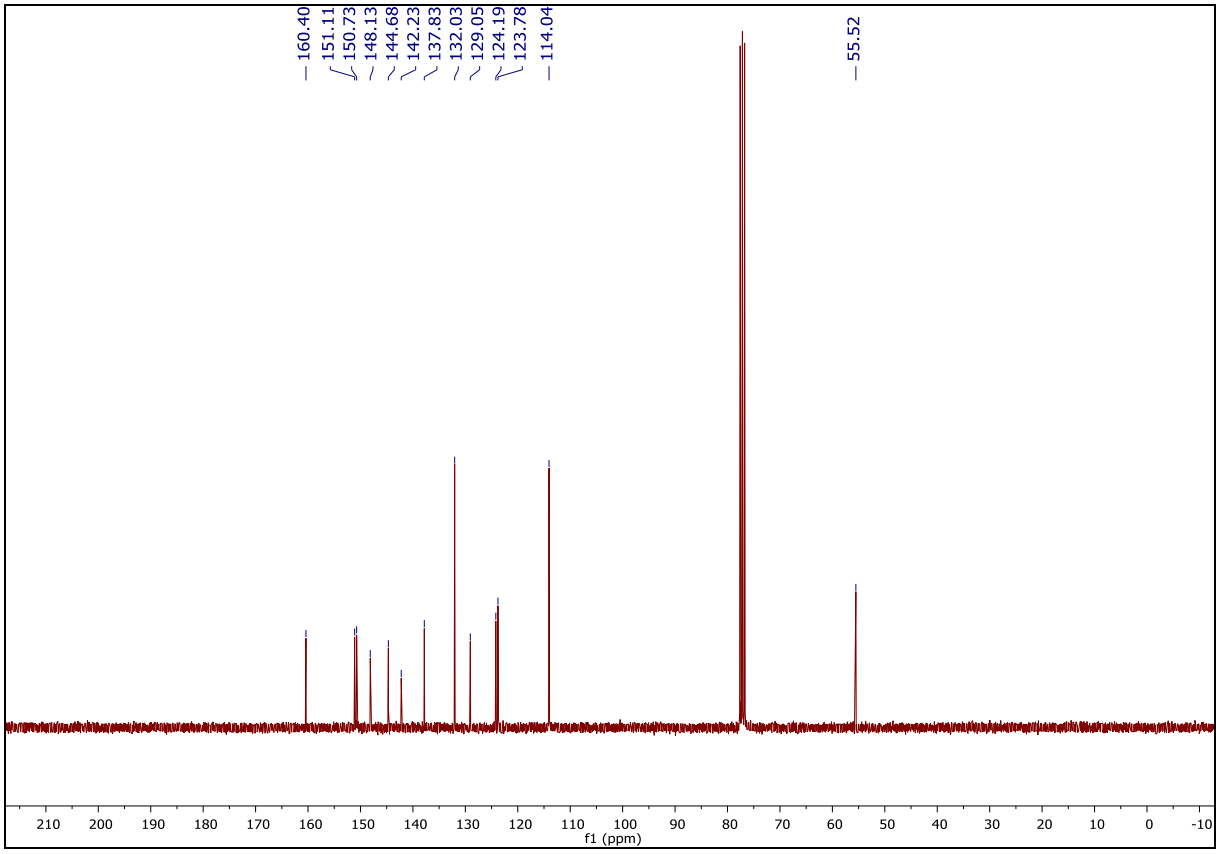
NMR spectra of 4-(3-(methylthio)phenyl)-1,5-naphthyridine (7k)



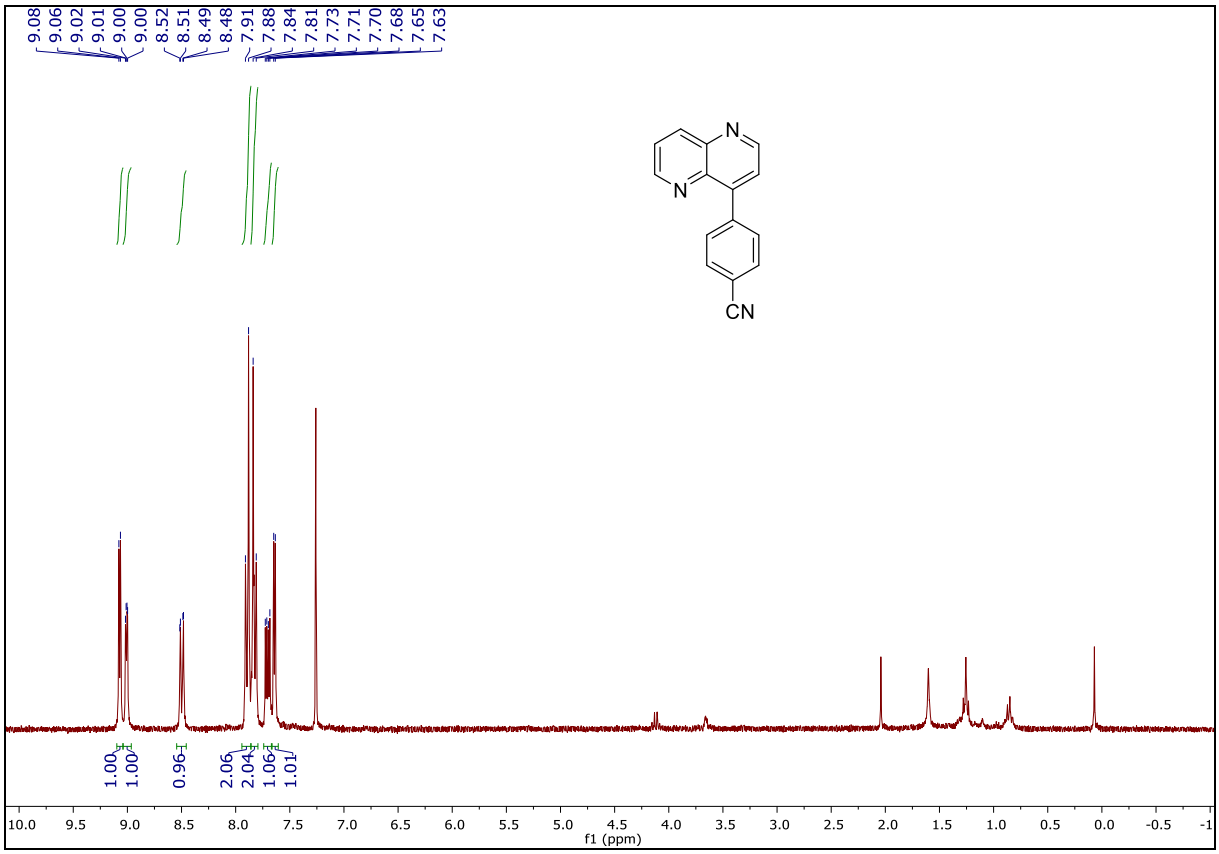


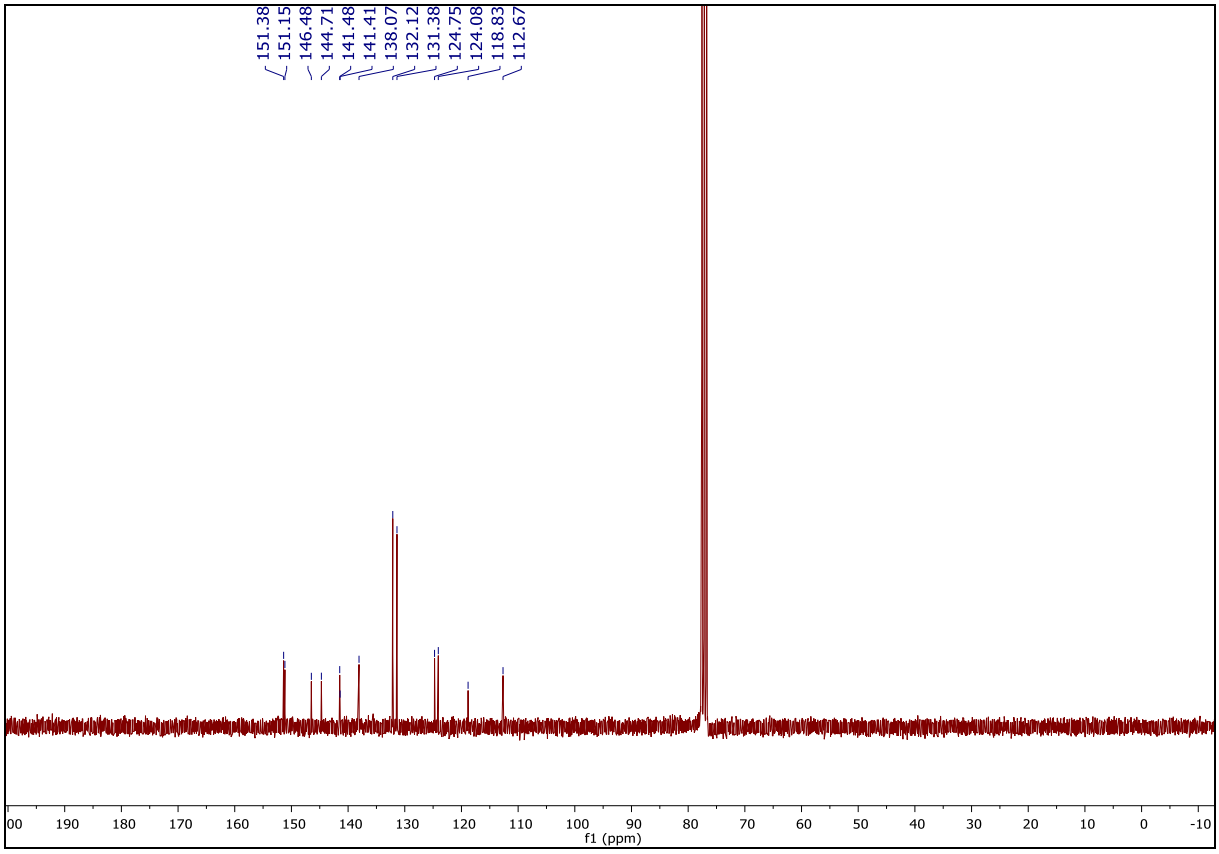
NMR-spectra of 4-(4-Methoxyphenyl)-1,5-naphthyridine (7l)



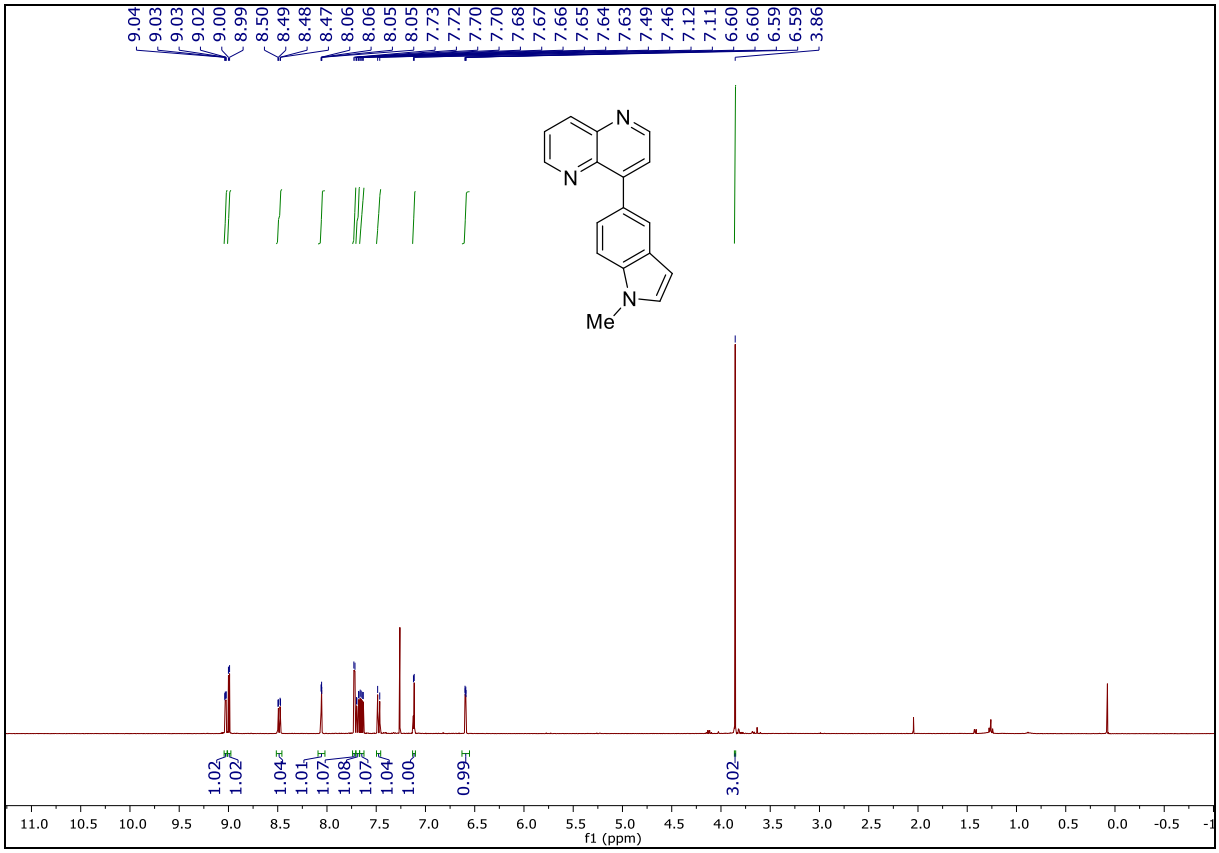


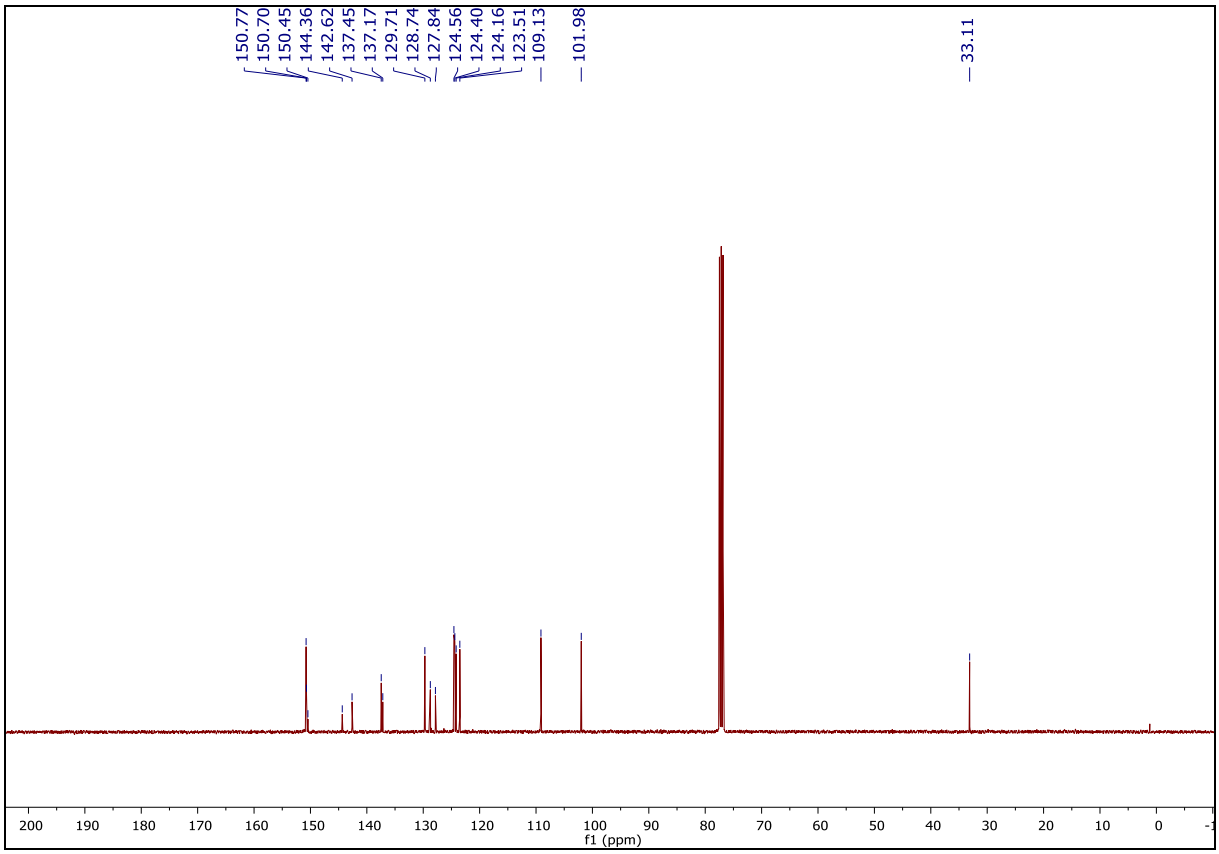
NMR-spectra of 4-(1,5-naphthyridin-4-yl)benzonitrile (7m)



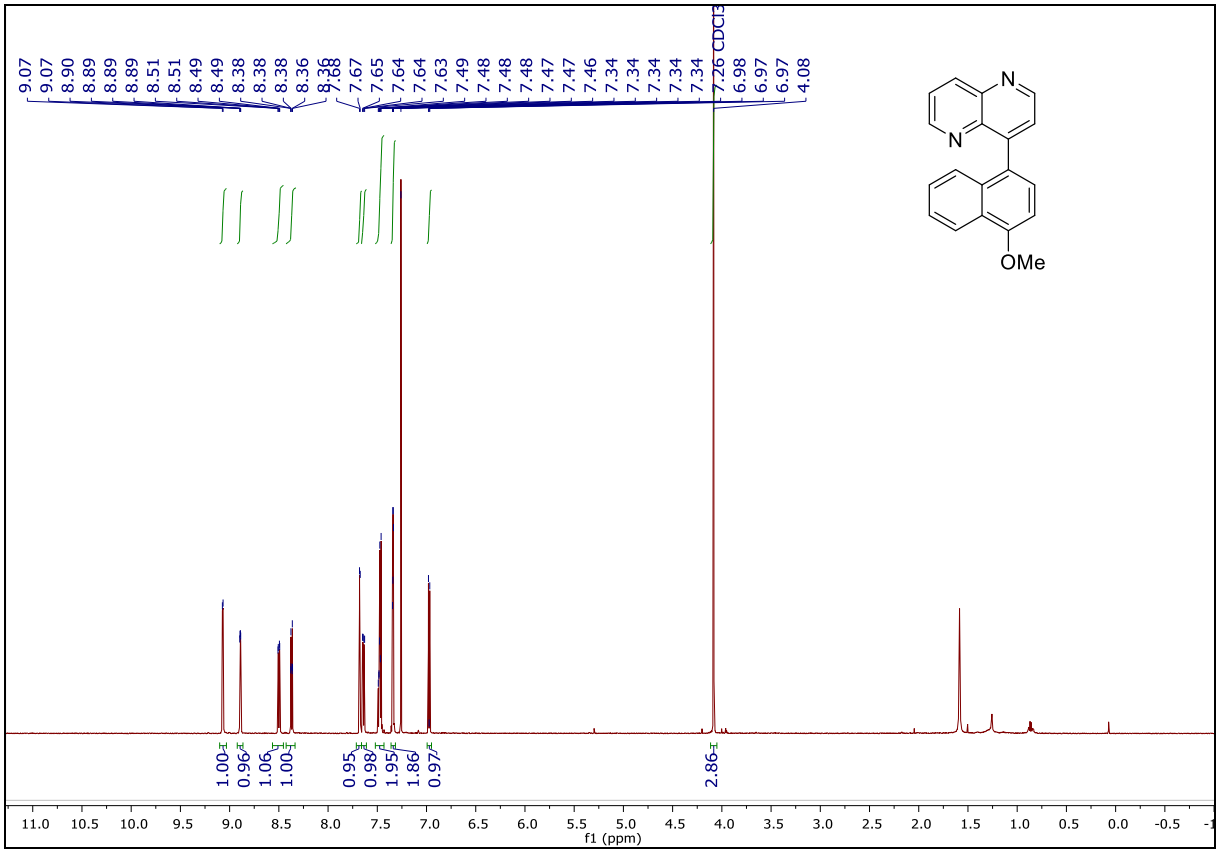


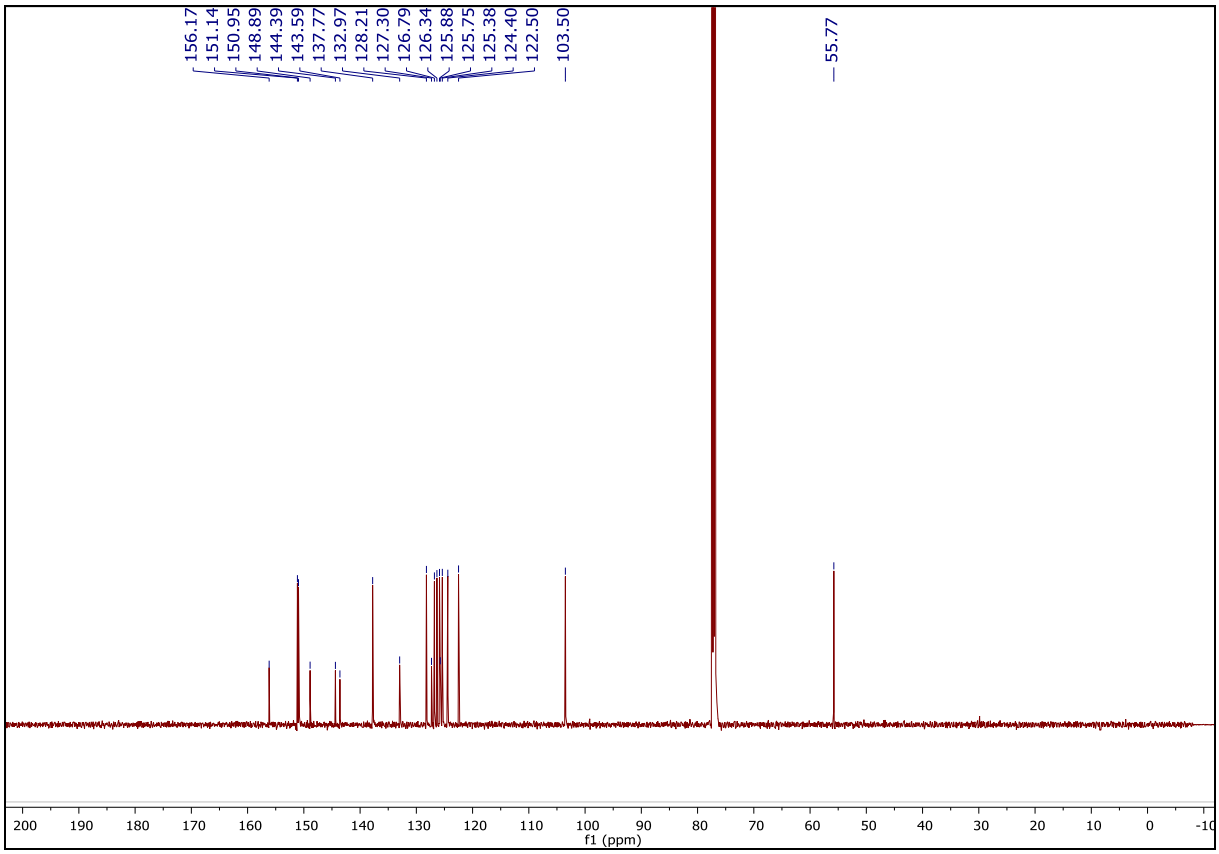
NMR-spectra of 4-(1-methyl-1*H*-indol-6-yl)-1,5-naphthyridine (7n)



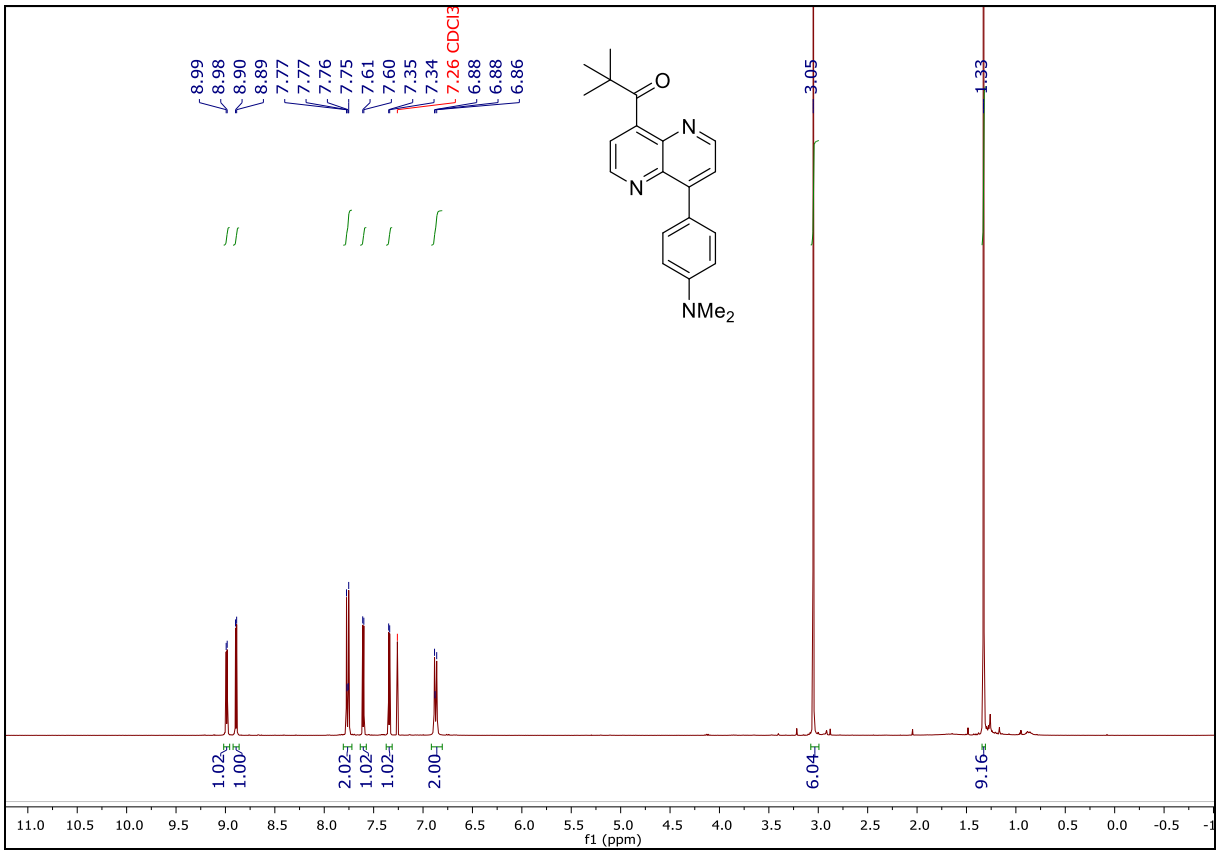


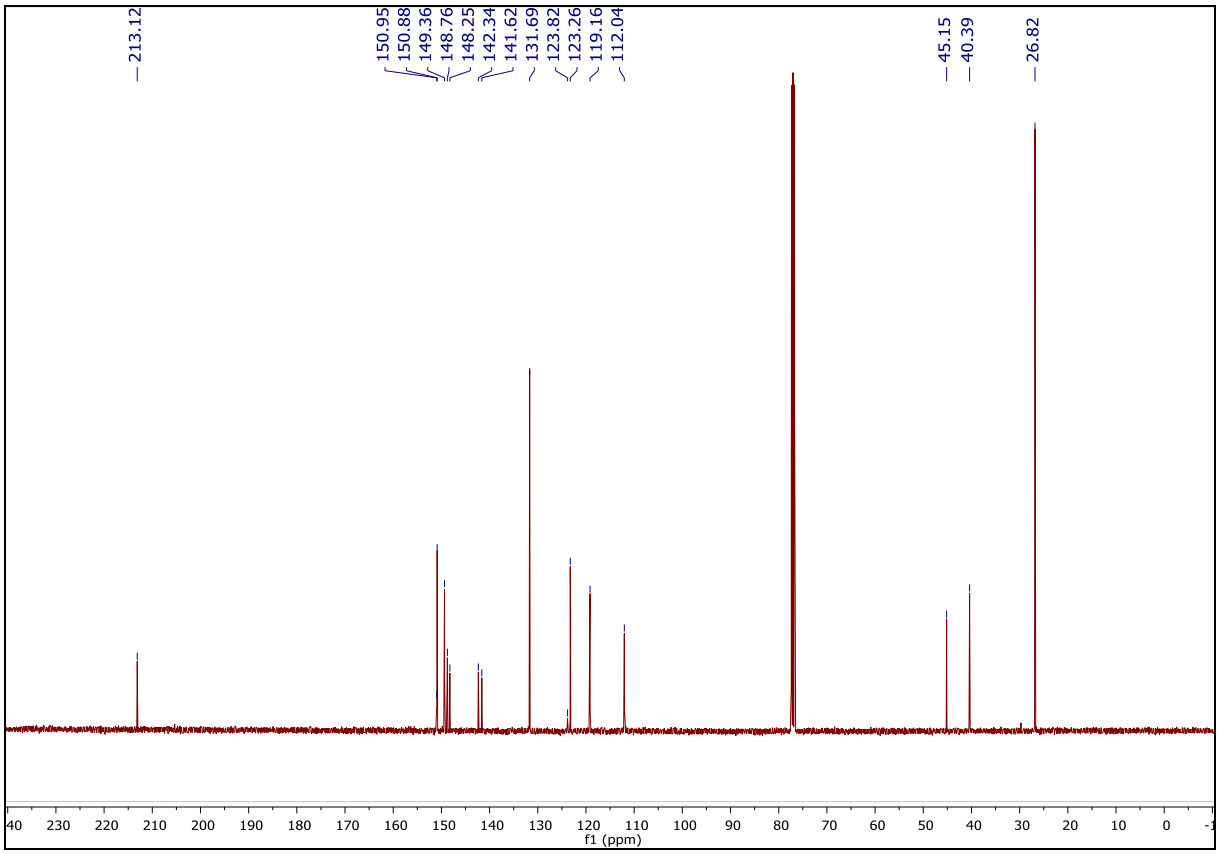
NMR-spectra of 4-(4-methoxynaphthalen-1-yl)-1,5-naphthyridine (7o)



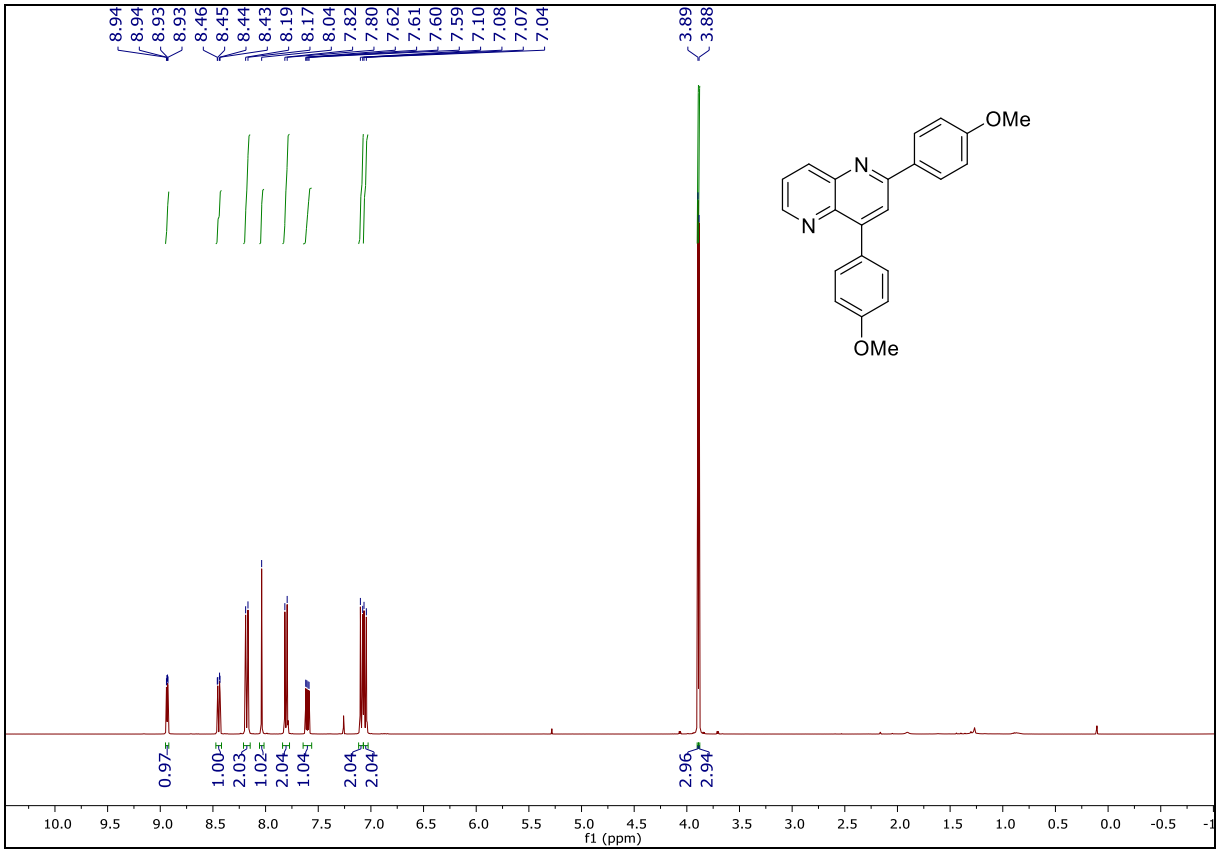


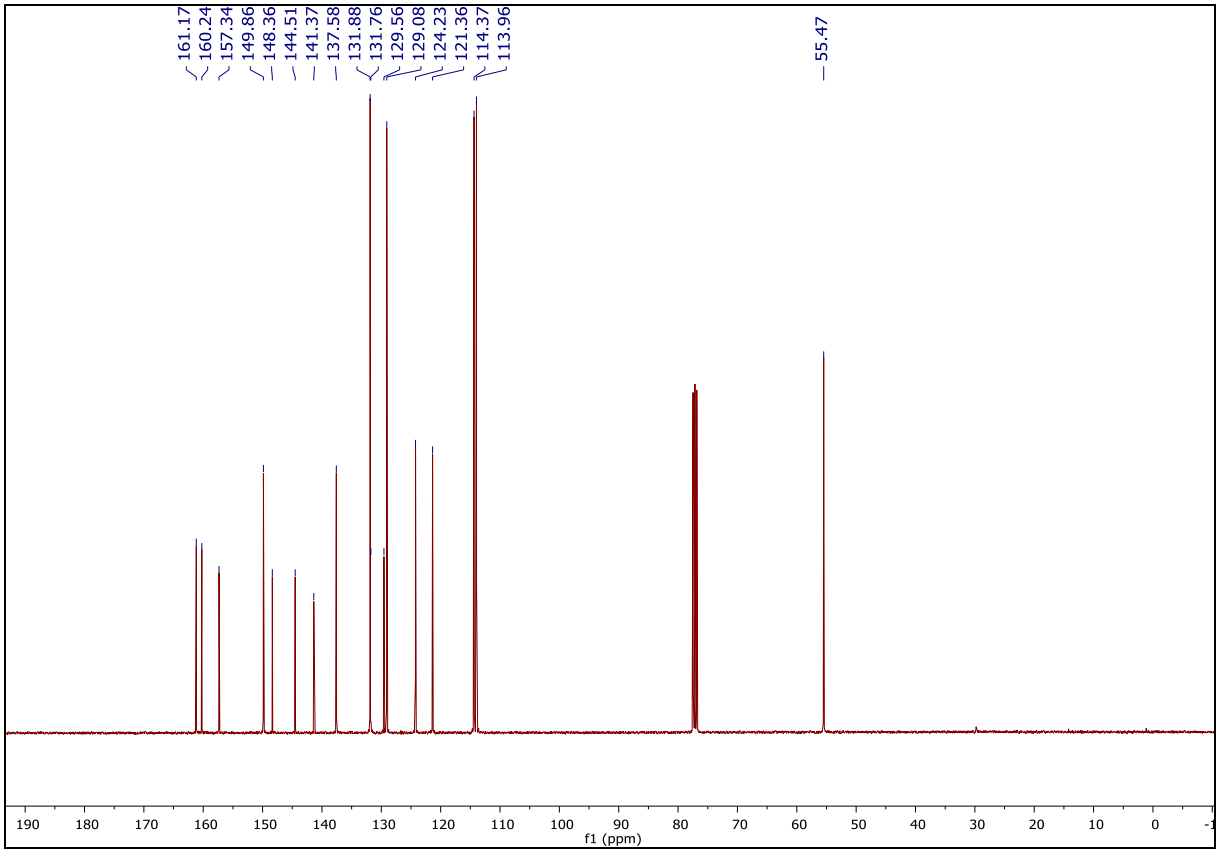
NMR-spectra of 1-(8-(4-(dimethylamino)phenyl)-1,5-naphthyridin-4-yl)-2,2-dimethylpropan-1-one (7p)



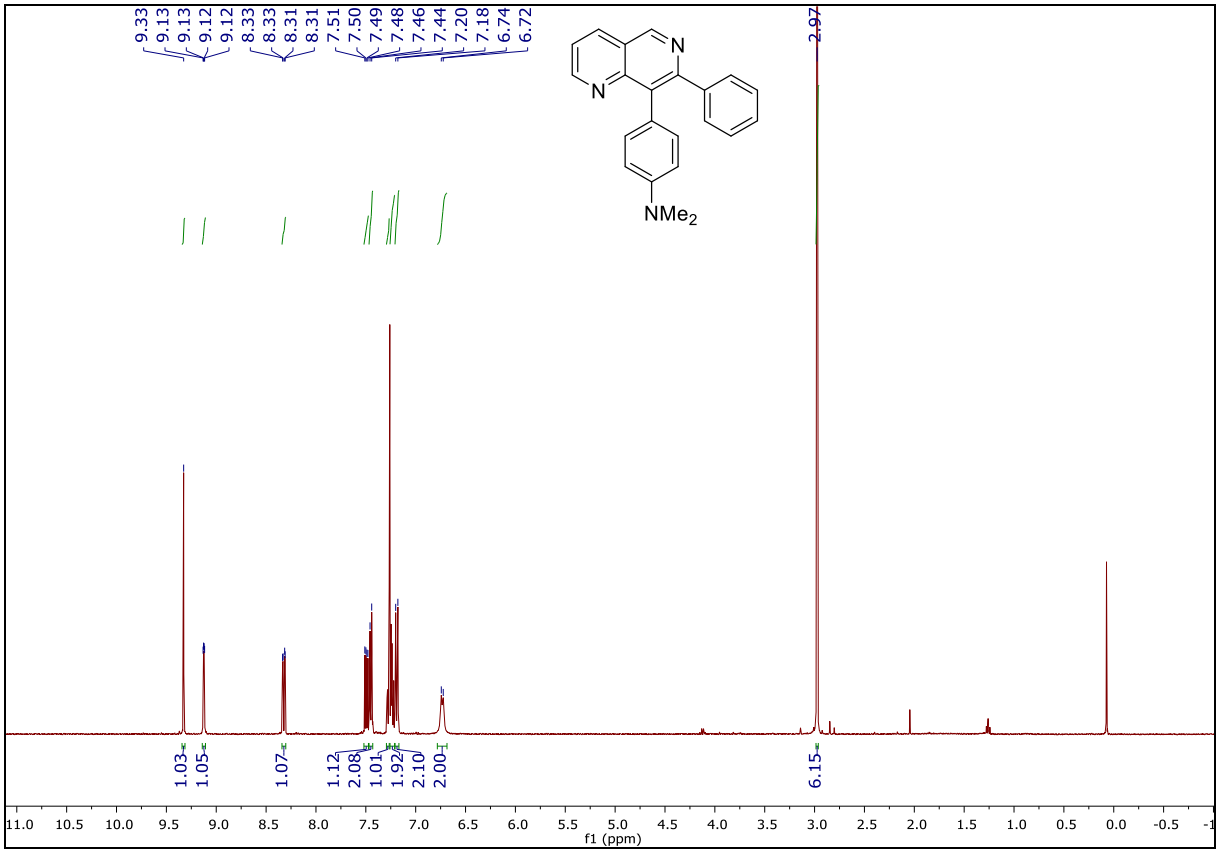


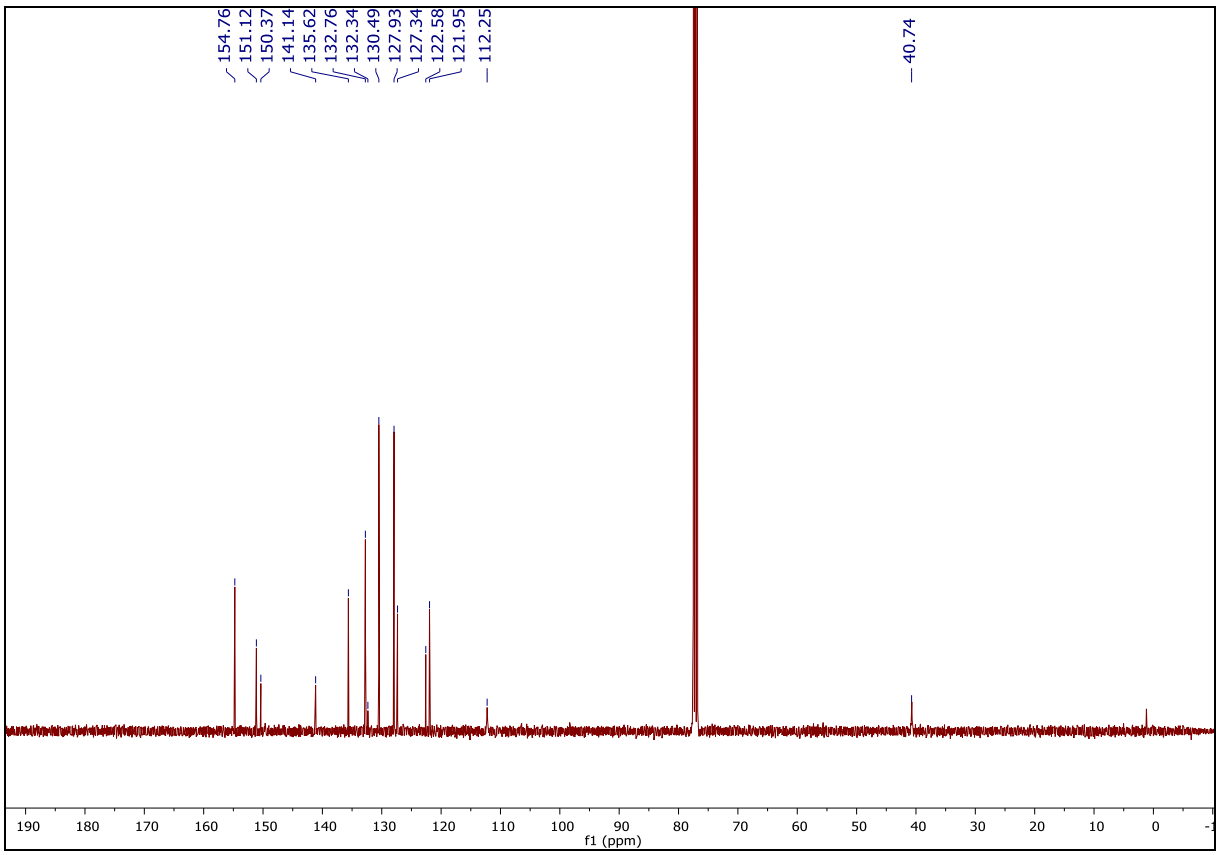
NMR-spectra of 2,4-bis(4-methoxyphenyl)-1,5-naphthyridine (7q)



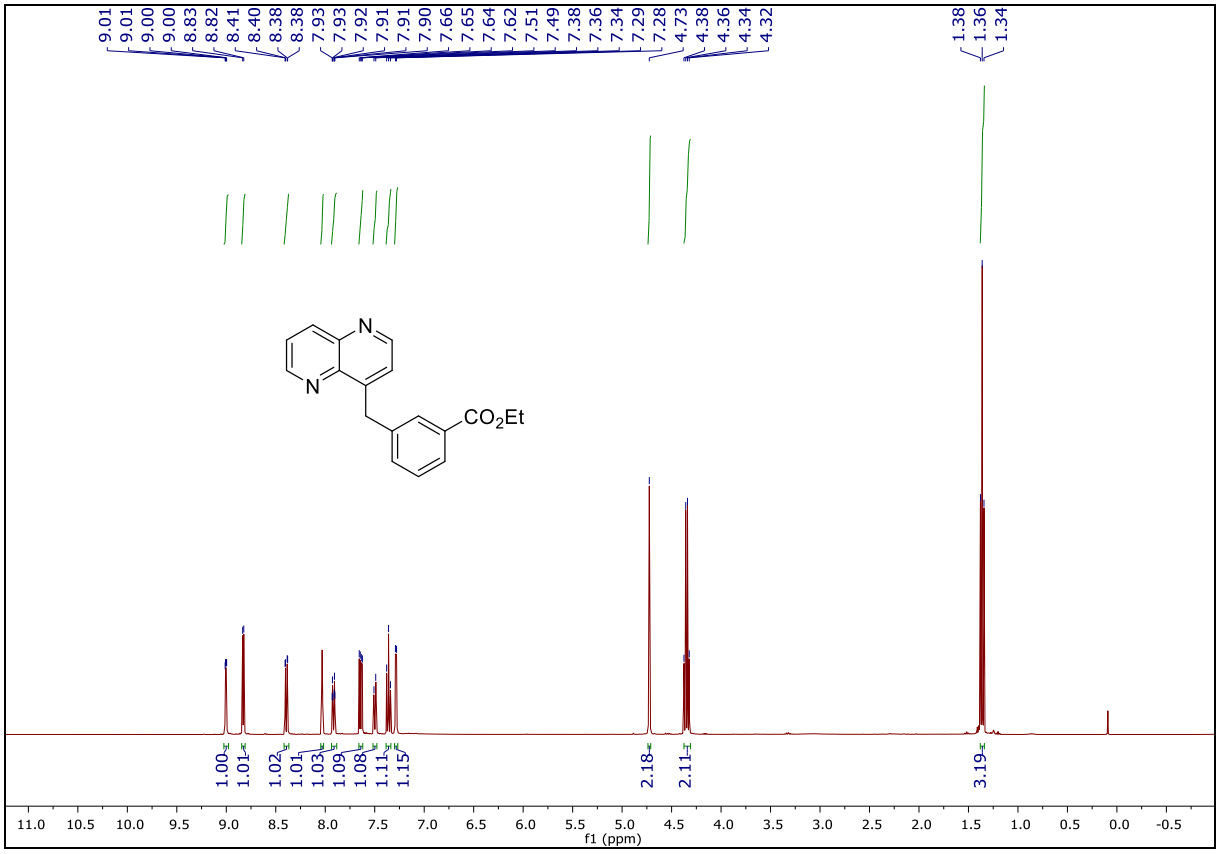


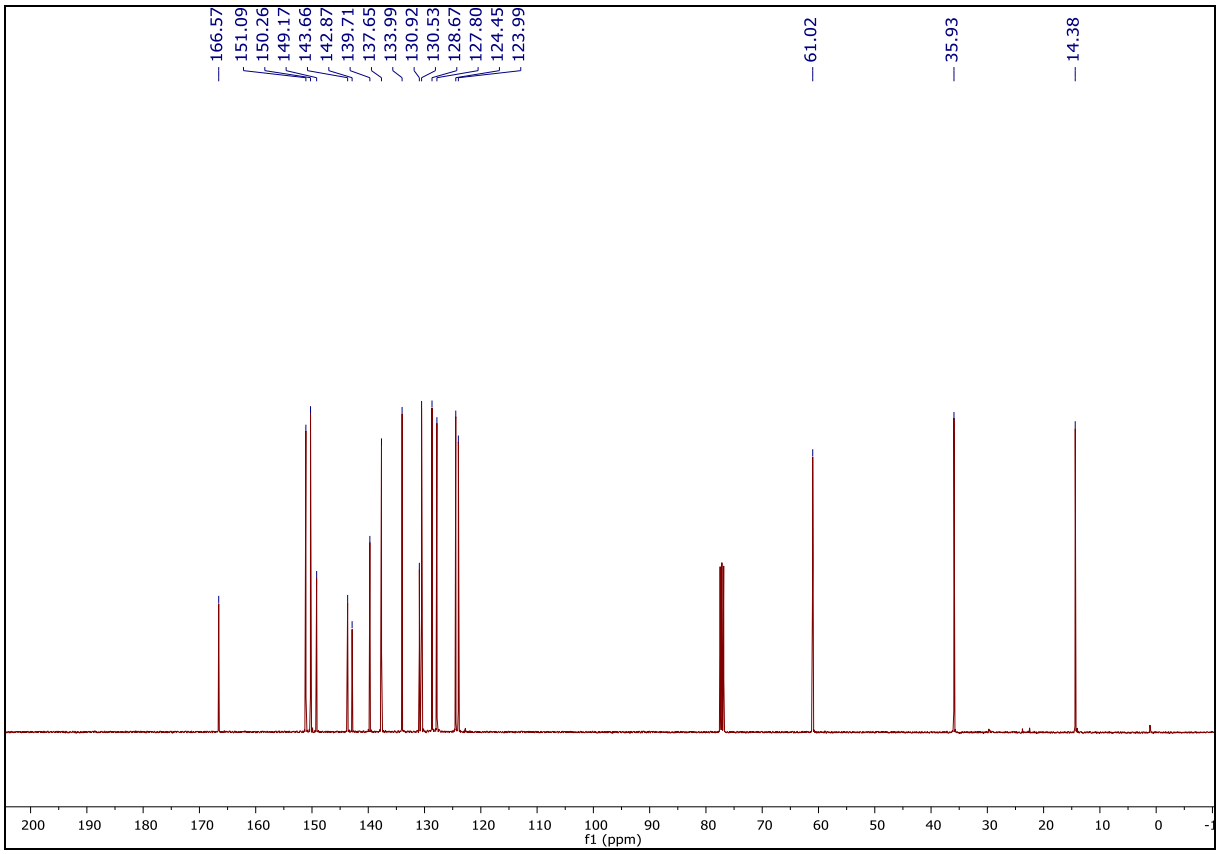
NMR-spectra of *N*,*N*-dimethyl-4-(7-phenyl-1,6-naphthyridin-8-yl)aniline (7r)



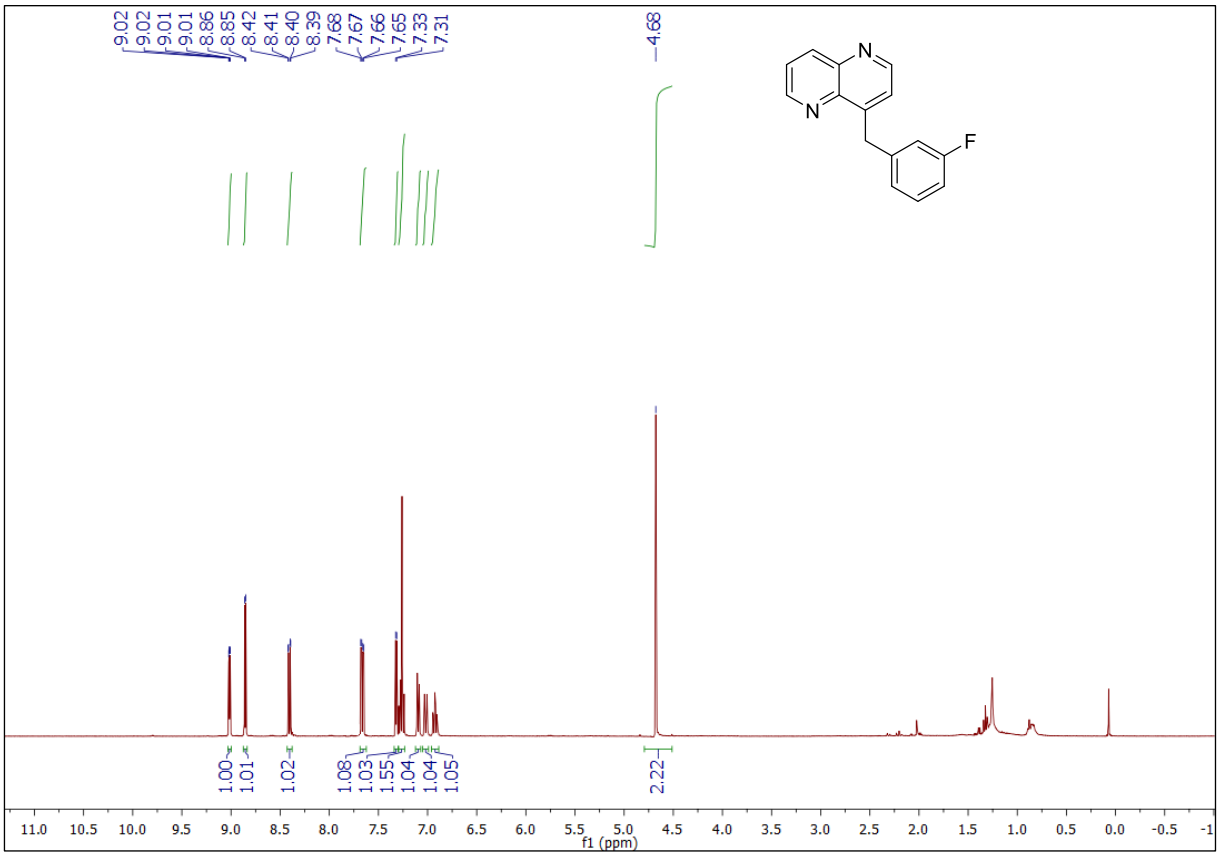


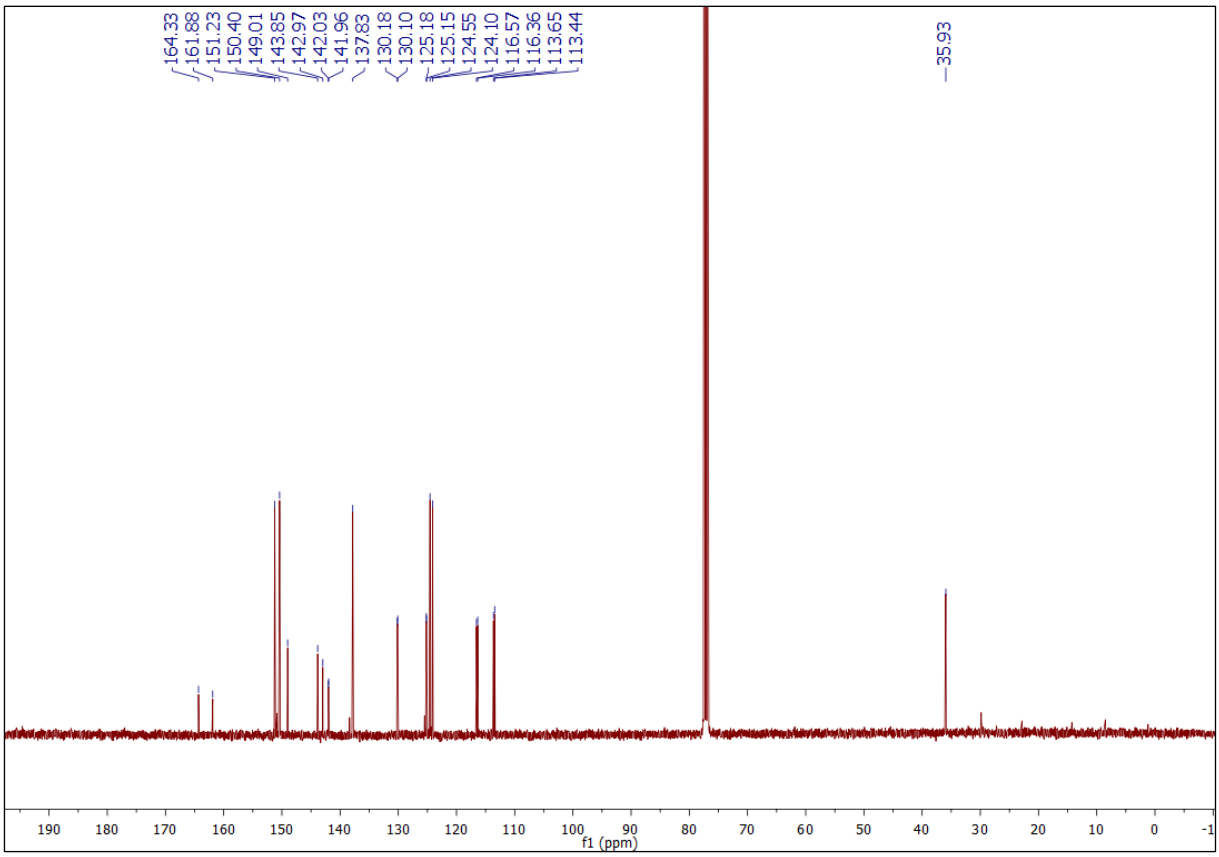
NMR-spectra of ethyl 3-((1,5-naphthyridin-4-yl)methyl)benzoate (9a)



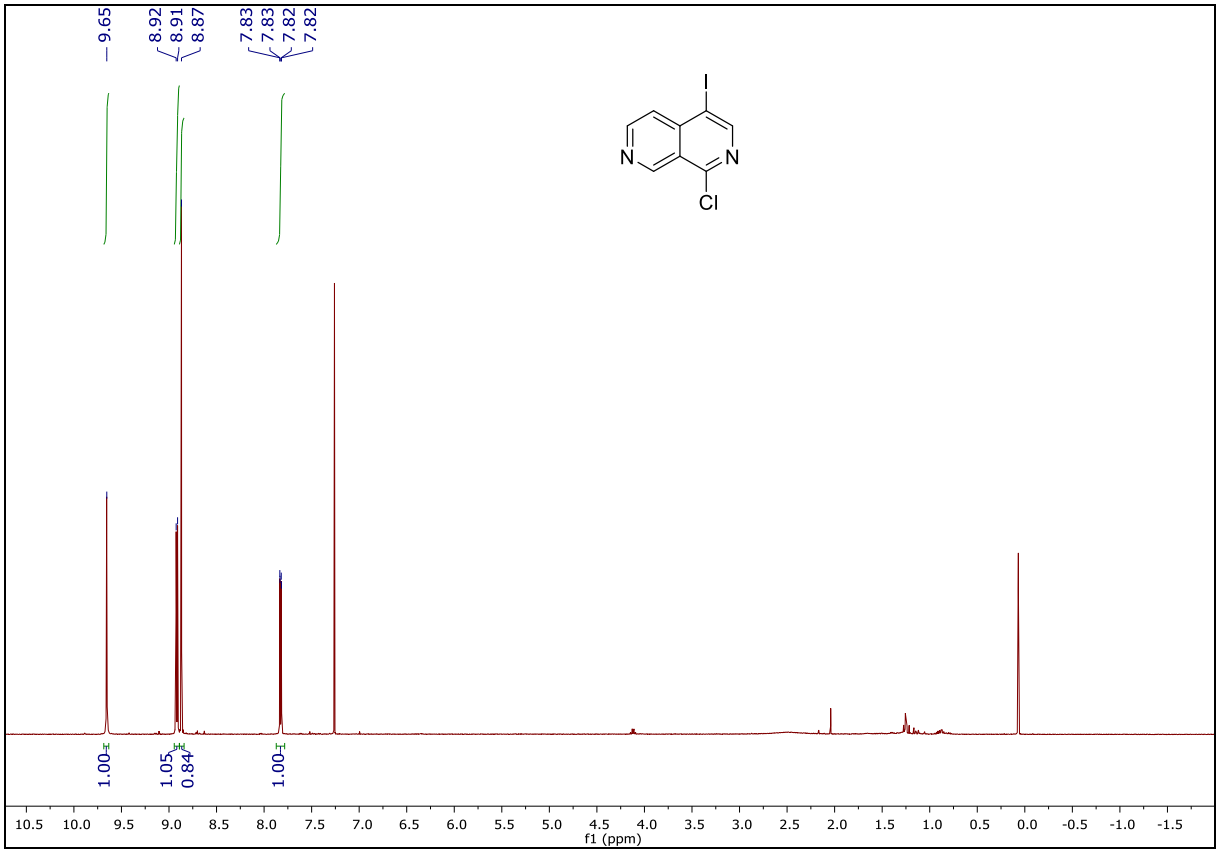


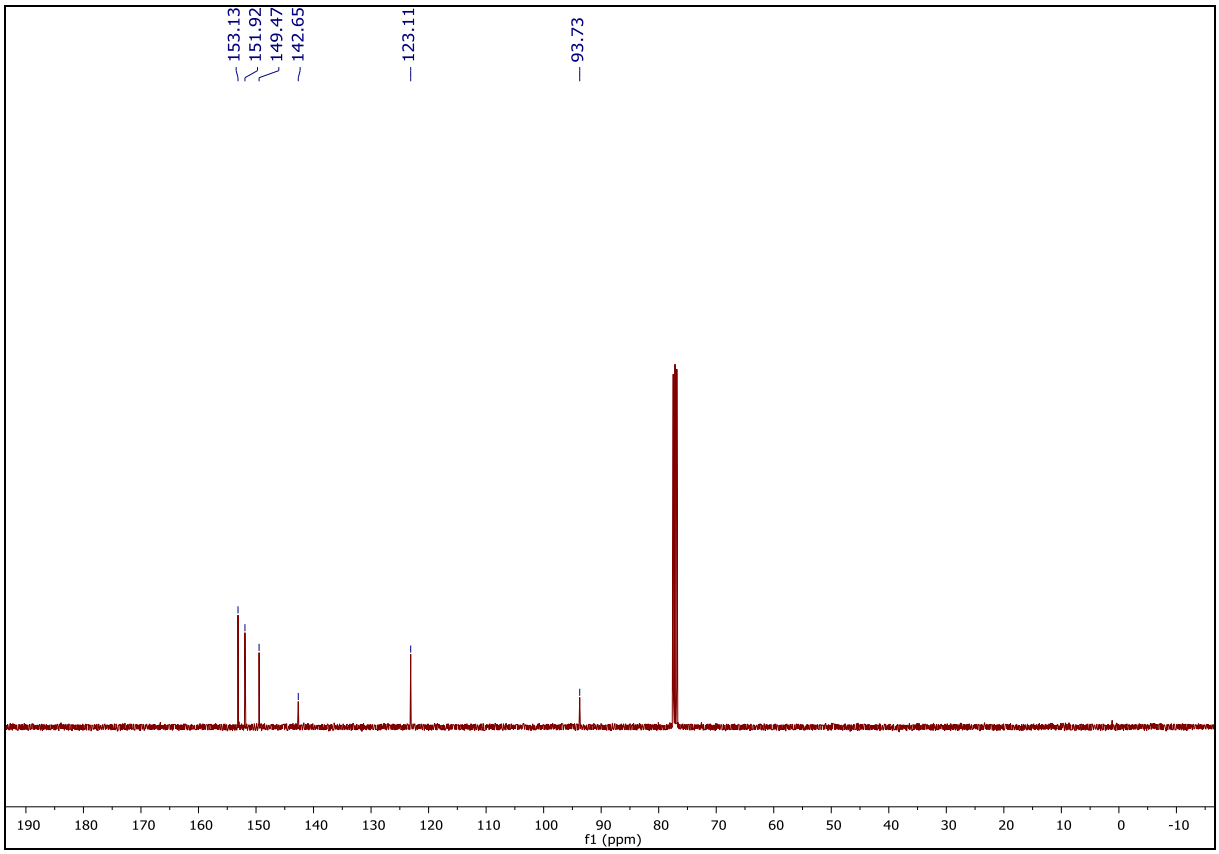
NMR-spectra of 4-(3-fluorobenzyl)-1,5-naphthyridine (9b)



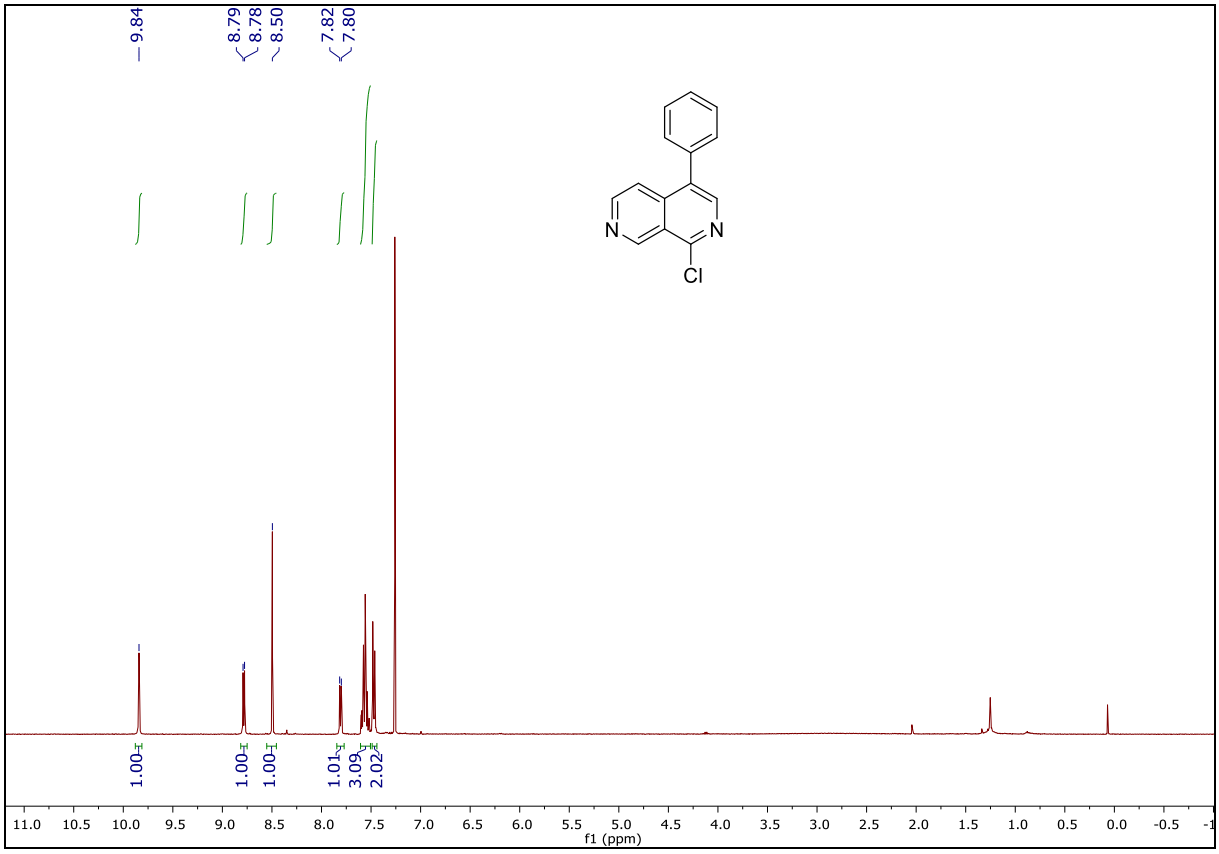


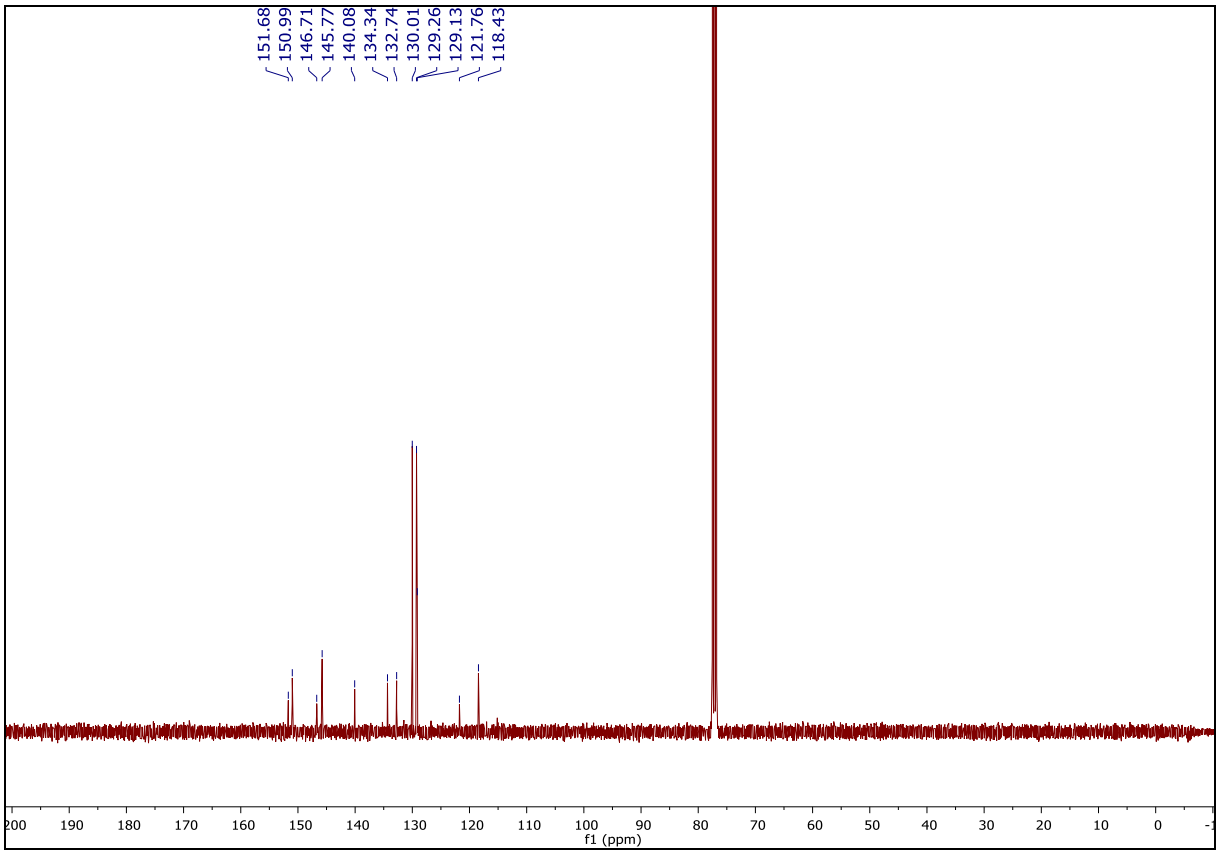
NMR-spectra of 1-chloro-4-iodo-2,7-naphthyridine (10)



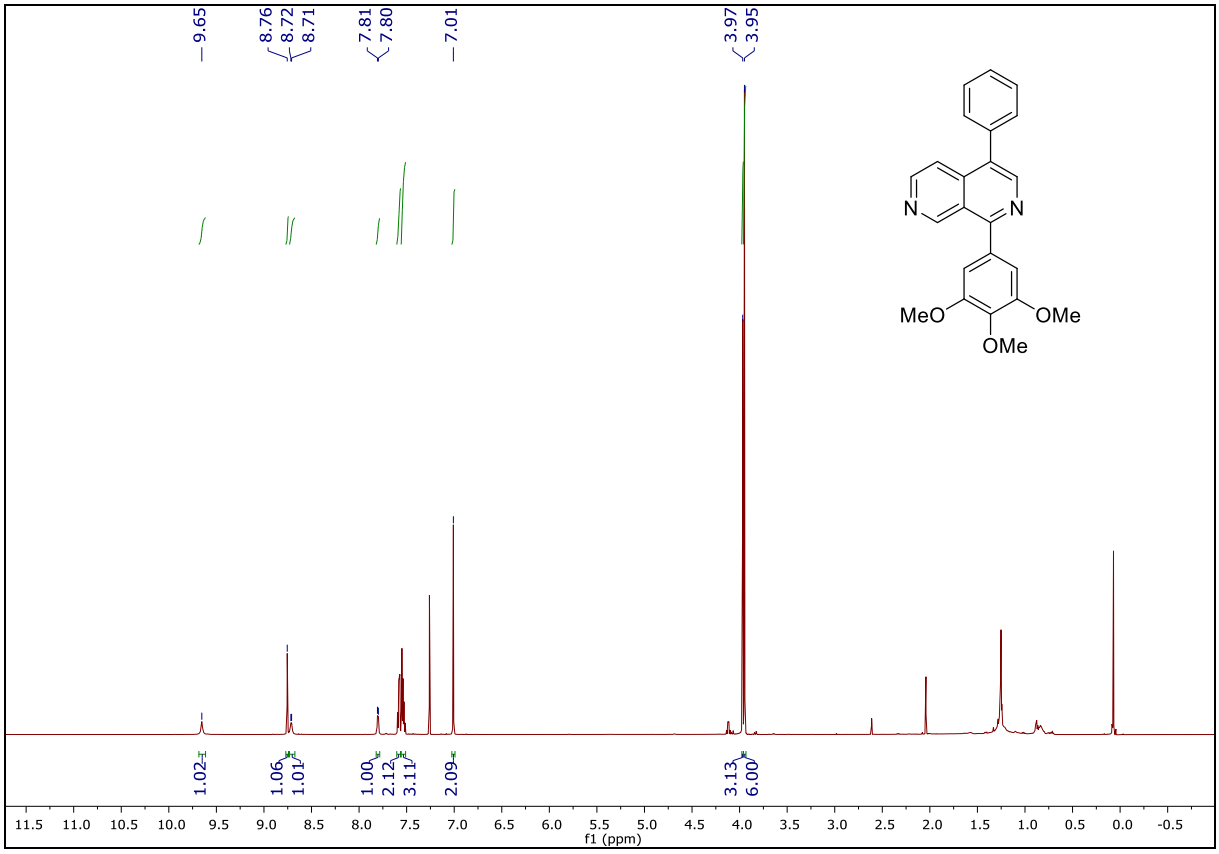


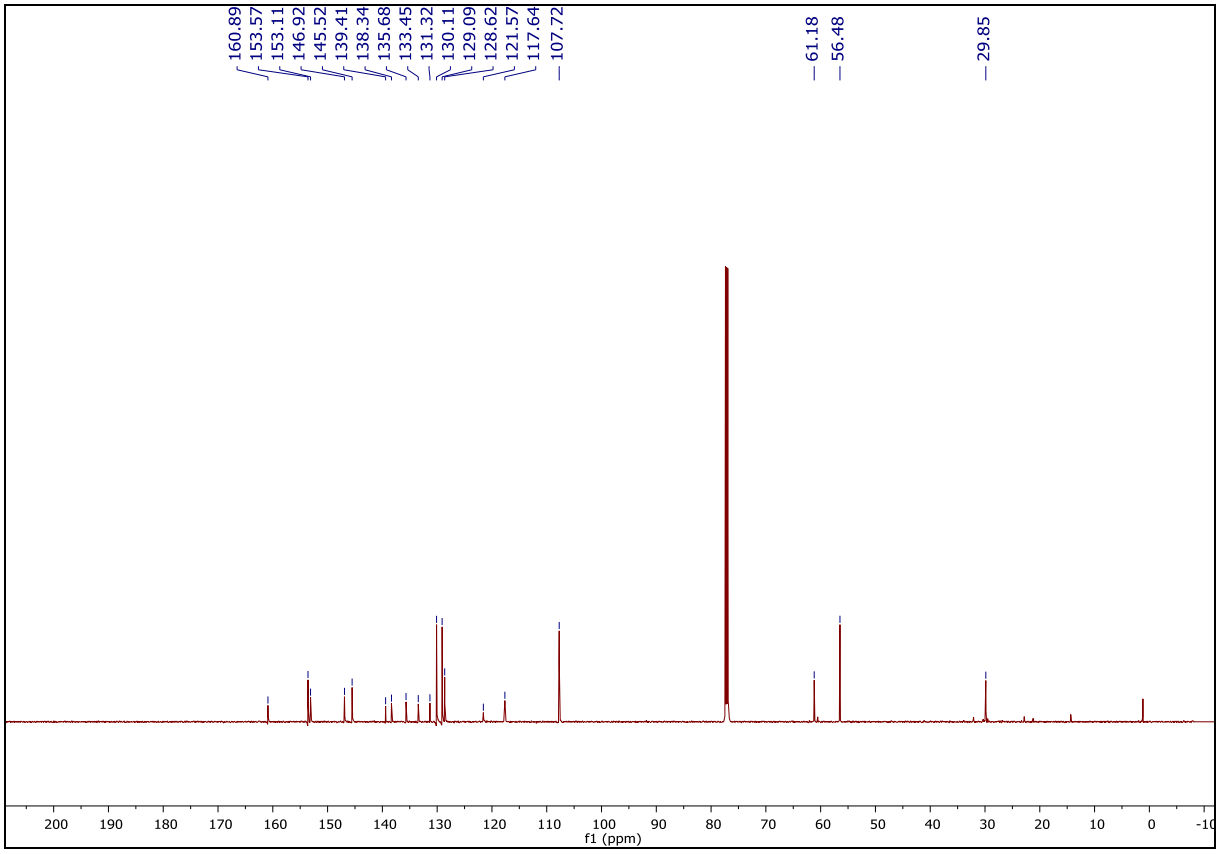
NMR-spectra of 1-chloro-4-phenyl-2,7-naphthyridine (11)





NMR-spectra of 4-phenyl-1-(3,4,5-trimethoxyphenyl)-2,7-naphthyridine (13)





Solvatochromism of Compounds 5b and 7r

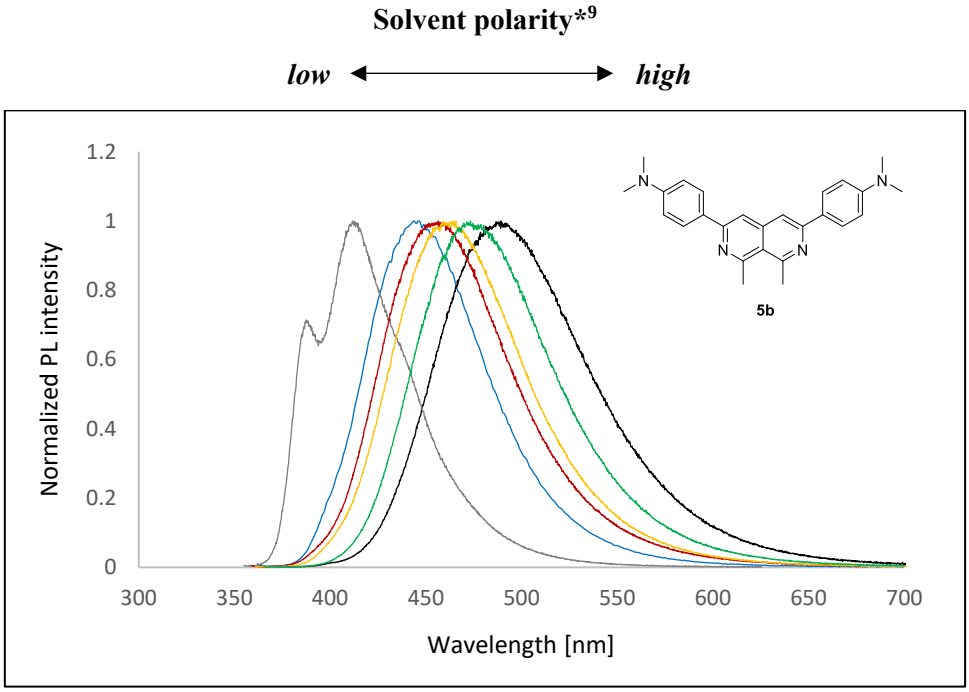


Figure 1: Normalized PL spectra of **5b** in various solvents: *n*-heptane (grey), toluene (blue), Et_2O (red), 1,4-dioxane (orange), chloroform (green), THF (black). *Solvents are bathochromic shifted with increasing polarity (except $CHCl_3$ (E_T (30) = 39.1) and THF (E_T (30) = 37.4))

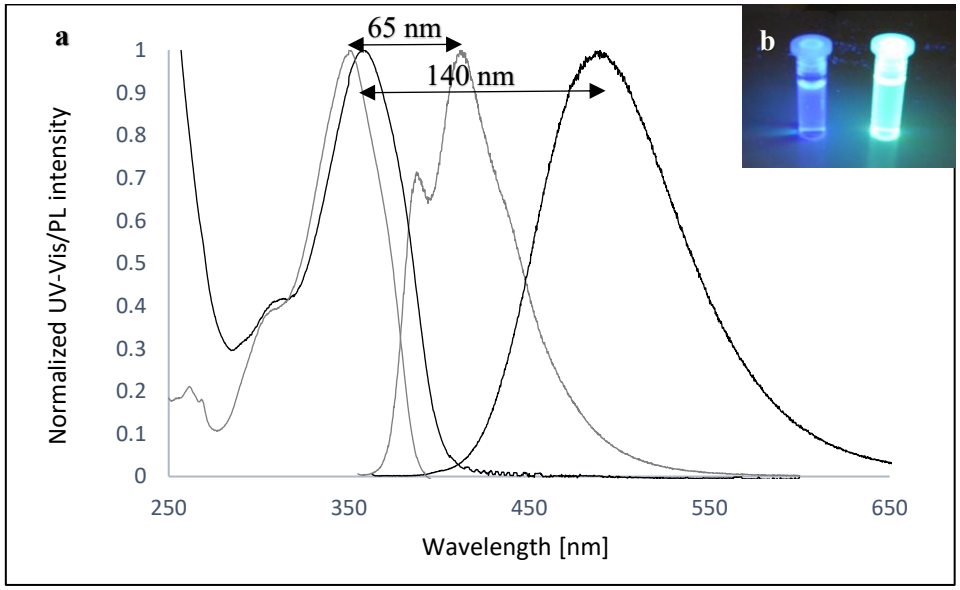


Figure 2: (a) Normalized UV-Vis and PL spectra of **5b** in *n*-heptane (grey) and THF (black) with corresponding Stokes shifts. (b) Solutions of **5b** in *n*-heptane (left) and THF (right) under UV-light with 366 nm excitation.

[9] Reichardt, C. *Chem. Rev.* **1994**, *94*, 2319.

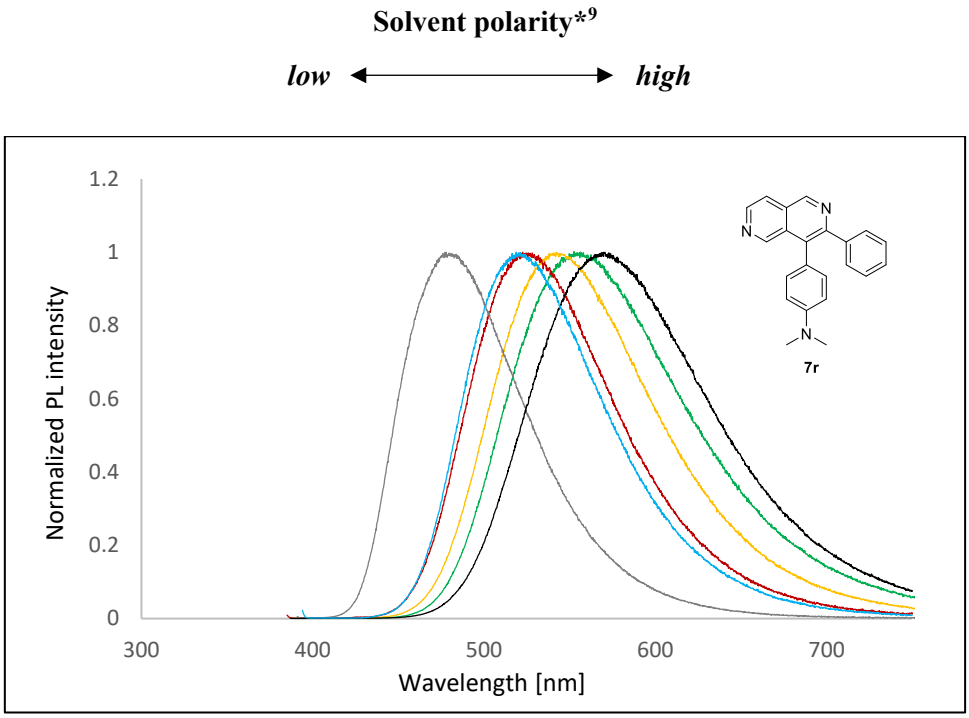


Figure 3: Normalized PL spectra of **7r** in various solvents: *n*-heptane (grey), toluene (blue), Et_2O (red), 1,4-dioxane (orange), chloroform (green), THF (black). *Solvents are bathochromic shifted with increasing polarity (except $CHCl_3$ (E_T (30) = 39.1) and THF (E_T (30) = 37.4))

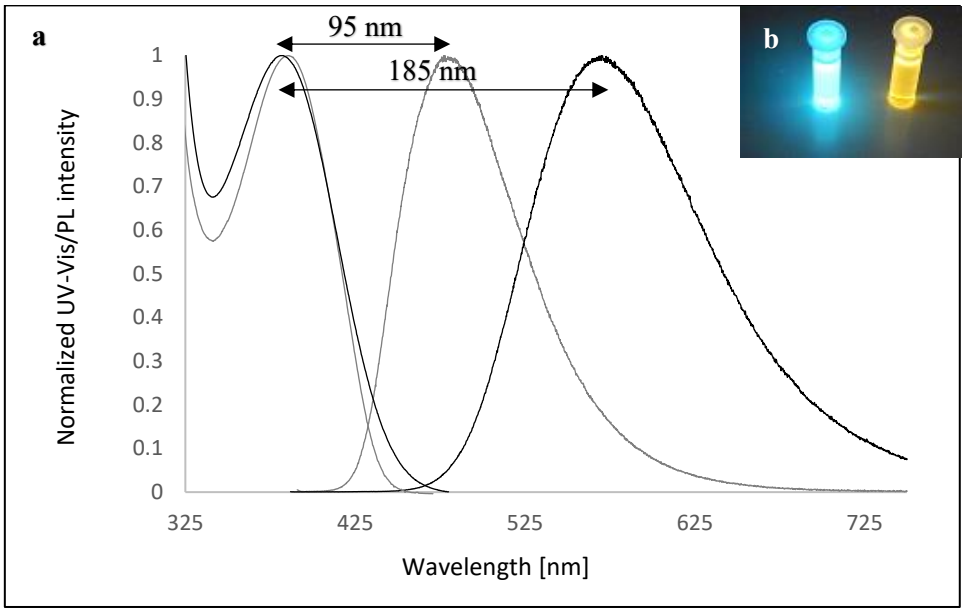


Figure 4: (a) Normalized UV-Vis and PL spectra of **7r** in *n*-heptane (grey) and THF (black) with corresponding Stokes shifts. (b) Solutions of **5b** in *n*-heptane (left) and THF (right) under UV-light with 366 nm excitation.

Photoluminescence Quantum Efficiency Measurements (PLQE)

PLQE measurements were performed with an Edinburgh Instruments FLS980 fluorescence spectrometer equipped with a 120 mm BenFlect-coated integrating sphere. Measurements were performed with 10 µM solutions of compound **5b** (5 µM in the case of cyclohexane due to low solubility) and 40 µM solutions of **7r** in dry and Ar-saturated solvents (OD ~ 0.15).

Absolute quantum efficiencies were determined from two measurements per sample. These are (1) the sphere loaded with a cuvette containing only the respective solvent and (2) the sphere loaded with the cuvette containing the solution of the sample. Assuming isotropic emission, the PLQE is calculated from the attenuation of the excitation light and the corresponding PL emission.

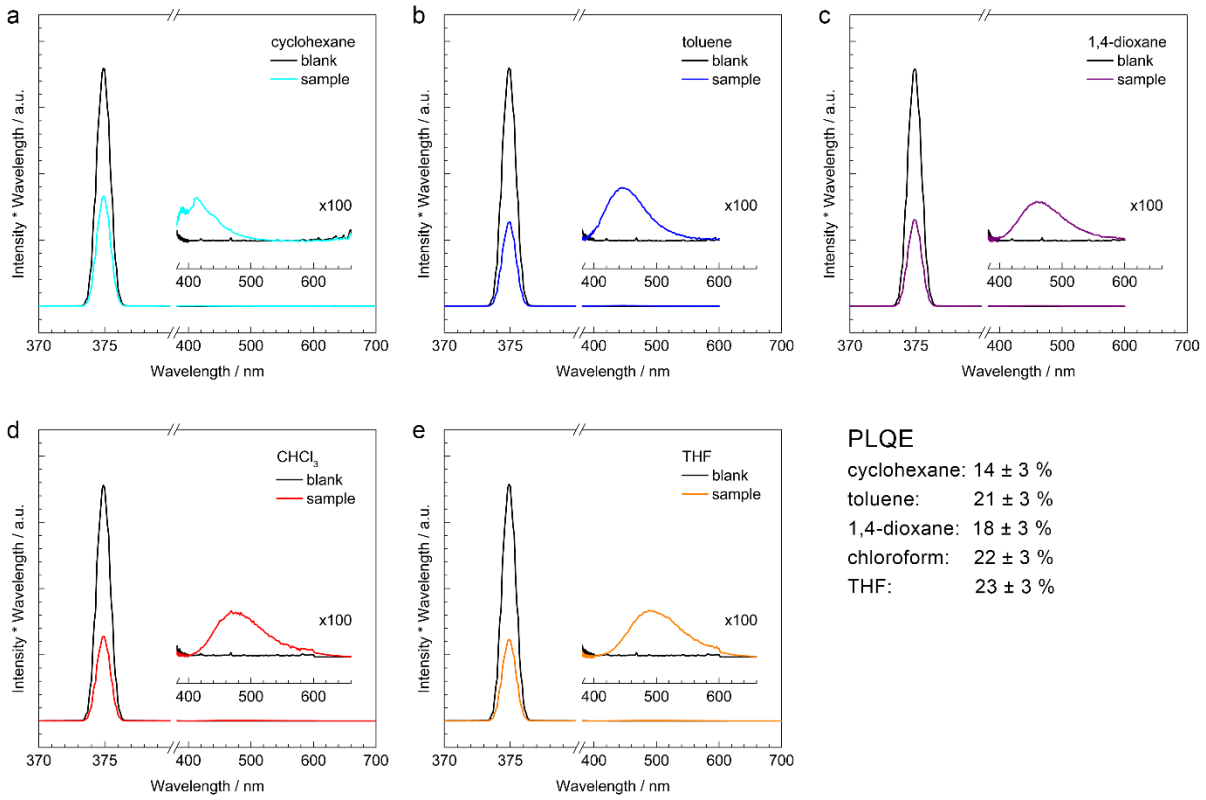


Figure 5: PLQE measurements of **5b** in various solvents. The *y*-axis scale is proportional to the number of photons collected in each wavelength interval.

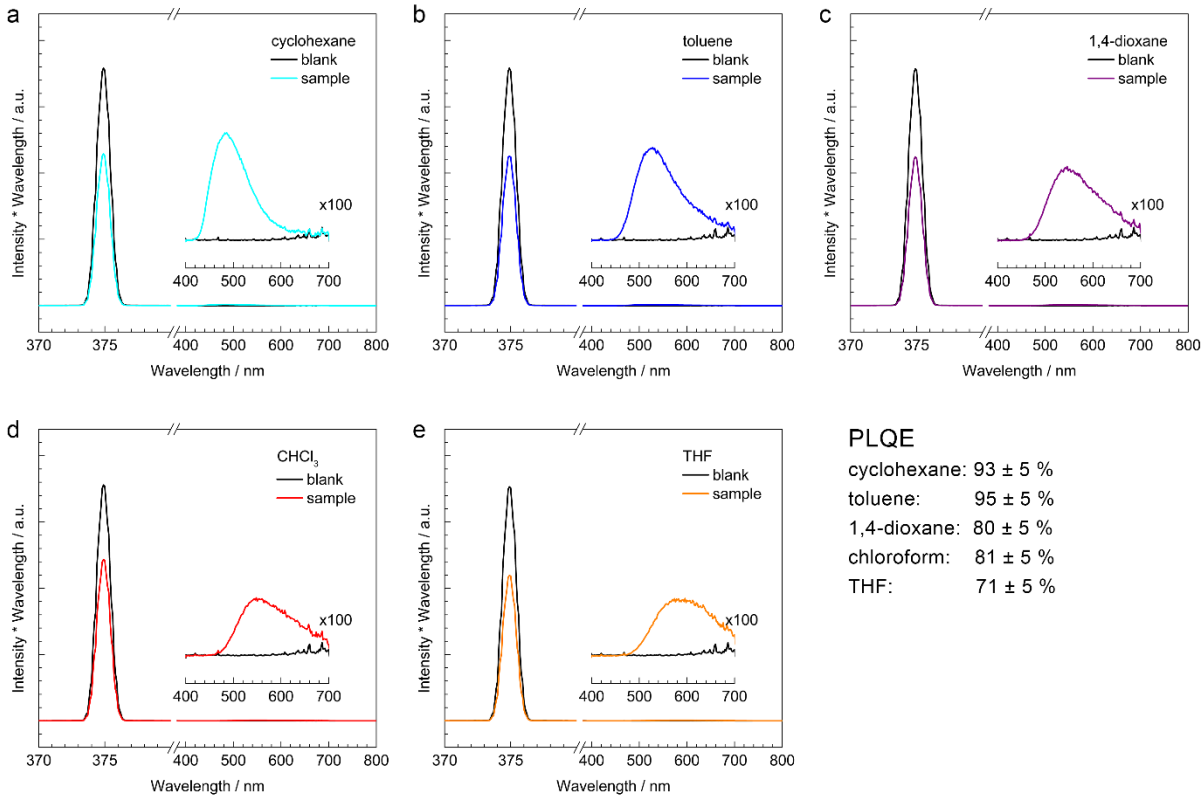


Figure 6: PLQE measurements of **7r** in various solvents. The *y*-axis scale is proportional to the number of photons collected in each wavelength interval.

Time-Correlated Single Photon Counting (TCSPC)

Lifetimes of emissive states have been determined using TCSPC on a PicoQuant FluoTime 300 setup. For TCSPC, the samples are excited by a 375 nm picosecond pulsed laser (PicoQuant, LDH-375), and emitted photoluminescence is collected and detected by a highly sensitive photo-multiplier tube (PMT, PicoQuant PMA 192), which allows detection of single photons through internal amplification. The time difference between triggering the laser and registering the photon on the PMT is measured by an internal clock (PicoQuant TimeHarp 260 P) and then collected in a histogram (bin width 25 ps) which yields the TCSPC data points shown in the main text.
The solutions are excited at 20 MHz and 5.8 MHz for **5b** and **7r**, respectively, adjusted to their respective decay times. The instrument response function (IRF) of the setup is mostly determined by the laser pulse length and is measured at around 120 ps. Mono-exponential fits to the data follow the equation

$$I(t) = I_0 \cdot exp\left(\frac{t - t_0}{\tau}\right) + I_{bg}$$

with initial intensity I_0, time offset t_0, background intensity I_{bg}, and lifetime τ. The latter are given in Table S1 including their fitting uncertainties. We note that the uncertainties are one order of magnitude smaller than the time resolution of the setup. However, measured lifetimes are considerably larger than the IRF.

Table 1: Lifetimes of mono-exponential fits to the TCSPC data including their fitting uncertainties.

5b	(3.80 ± 0.02) ns
7r	(11.95 ± 0.03) ns