Supplementary Information

Palladium-Catalyzed α-Arylation of Methyl Ketones Enables Modular Synthesis of 2,4,5-Trisubstituted Imidazoles

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Dedicated to Professor Peter Bakusis for his contributions that have inspired generations of Brazilian chemists and for his genuine passion for Chemistry.

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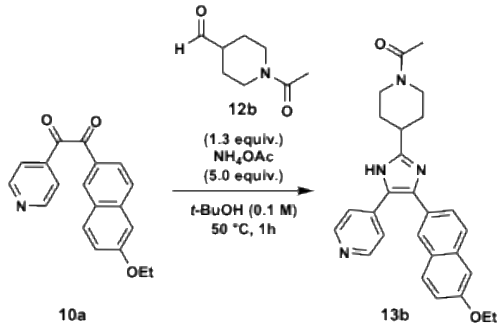
(4-(5-(6-Ethoxynaphthalen-2-yl)-4-(pyridin-4-yl)-1*H*-imidazol-2-yl)piperidin-1-yl)ethenone (**13b**)



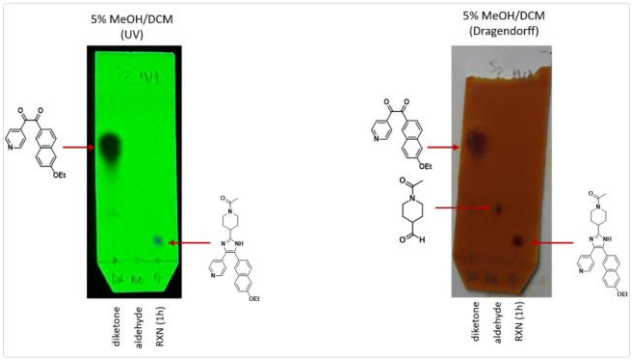
General procedure A (imidazole condensation)

Reaction scale: 0.10 mmol

Amounts employed: 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**10a**, 31 mg, 0.10 mmol, 1.0 equiv.), 1-acetylpiperidine-4-carboxyaldehyde (**12b**, 20 mg, 0.13 mmol, 1.3 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.) and *t*-BuOH (1 mL, 0.1 M).

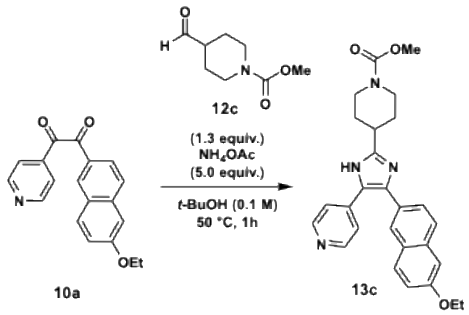
Modifications: the reaction mixture was diluted in EtOAc:MeOH (10:1 v/v, 5 mL) and H_2O:brine (1:1 v/v, 1 × 4 mL). The layers were separated and the aqueous layer was extracted with EtOAc:MeOH (10:1 v/v, 10 × 5 mL).

The residue was purified by silica gel chromatography, eluted with MeOH in dichloromethane (DCM) (17 cm × 15 mm, gradient elution, 3% → 10% MeOH/DCM, 1% increases, 20 mL runs, 5 mL fractions) to afford **13b** (35 mg, 79%) as a white solid.



R_f = 0.12 (5% MeOH/DCM); ^{1}H NMR (500 MHz, CD_3OD) δ 8.36 (dd, *J* 4.8, 1.5 Hz, 2H), 7.86 (s, 1H), 7.79 (d, *J* 8.5 Hz, 1H), 7.73 (d, *J* 9.0 Hz, 1H), 7.49 (d, *J* 5.9 Hz, 2H), 7.41 (dd, *J* 8.5, 1.5 Hz, 1H), 7.25 (d, *J* 2.1 Hz, 1H), 7.16 (dd, *J* 8.9, 2.5 Hz, 1H), 4.70-4.60 (m, 1H), 4.17 (q, *J* 7.0 Hz, 2H), 4.11-4.03 (m, 1H), 3.30-3.25 (m, 1H), 3.14 (tt, *J* 11.9, 3.8 Hz, 1H), 2.81 (dt, *J* 12.8, 2.5 Hz, 1H), 2.15 (s, 3H), 2.14-2.03 (m, 2H), 1.92 (dq, *J* 12.5, 4.1 Hz, 1H), 1.82 (dq, *J* 12.6, 4.1 Hz, 1H), 1.46 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 159.1, 150.0, 136.0, 130.6, 130.3, 128.6, 128.5, 127.8, 123.0, 120.8, 107.5, 64.6, 47.6, 42.8, 37.4, 32.3, 31.7, 21.2, 15.1; note: due to slow relaxation of carbon bound nitrogen some ^{13}C NMR signals are not detected. In this case, 3 signals are missing; IR (thin film, ATR) ν_{max} / cm^{-1} 1643 (s), 1600 (s), 1541 (w), 1470 (w), 1429 (m), 1392 (w), 1275 (m), 1210 (m), 1188 (w), 1044 (w), 1011 (w), 994 (m), 976 (m), 930 (w), 897 (w), 833 (s), 812 (w), 696 (w), 667 (m), 631 (w), 607 (m); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{27}H_{29}N_4O_2$: 441.2291; found 441.2313; MP 258.0 °C (decomp.) (MeOH/DCM).

Methyl 4-(5-(6-ethoxynaphthalen-2-yl)-4-(pyridin-4-yl)-1*H*-imidazol-2-yl)piperidine-1-carboxylate (**13c**)

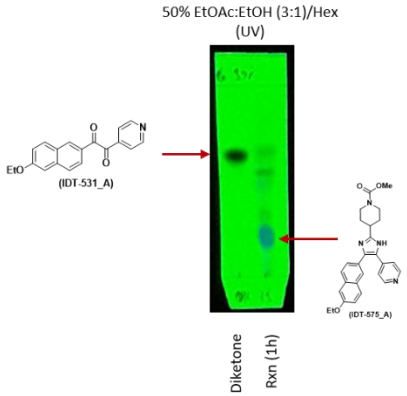


General procedure A (imidazole condensation)

Reaction scale: 0.10 mmol

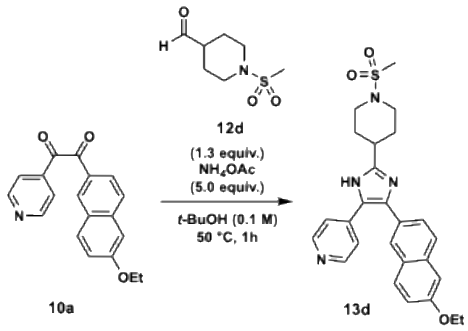
Amounts employed: 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**10a**, 31 mg, 0.10 mmol, 1.0 equiv.), methyl 4-formylpiperidine-1-carboxylate (**12c**, 22 mg, 0.130 mmol, 1.3 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.) and *t*-BuOH (1 mL, 0.1 M).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes and then with EtOAc:EtOH (3:1v/v) in hexanes [Biotage Isolera, SNAP KP-Sil 10 g, 50% → 70% EtOAc/Hexanes then 30% → 100% EtOAc:EtOH (3:1 v/v)/hexanes, 18 mL fractions] to afford **13c** (38 mg, 83%) as a white solid.



R_f = 0.43 (50% EtOAc/Hexanes, UV); ^{1}H NMR (500 MHz, CD_3OD) δ 8.37 (d, *J* 6.3 Hz, 2H), 7.86 (s, 1H), 7.79 (d, *J* 8.5 Hz, 1H), 7.73 (d, *J* 8.9 Hz, 1H), 7.49 (d, *J* 3.7 Hz, 2H), 7.42 (d, *J* 7.2 Hz, 1H), 7.26 (d, *J* 1.9 Hz, 1H), 7.16 (dd, *J* 8.9, 2.3 Hz, 1H), 4.30-4.21 (m, 2H), 4.18 (q, *J* 7.0 Hz, 2H), 3.71 (s, 3H), 3.12-2.90 (m, 3H), 2.08-1.99 (m, 2H), 1.86 (dq, *J* 12.6, 4.1 Hz, 1H), 1.47 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 159.1, 157.7, 150.0, 136.0, 130.6, 130.3, 128.6, 128.5, 127.8, 123.0, 120.8, 107.5, 64.6, 53.3, 45.0, 37.4, 31.8, 15.1; note: due to slow relaxation of carbon bound nitrogen some ^{13}C NMR signals are not detected. In this case, 5 signals are missing; IR (thin film, ATR) ν_{max} / cm^{-1} 2940 (br), 1703 (s), 1601 (s), 1539 (w), 1470 (w), 1448 (w), 1399 (m), 1377 (w), 1333 (w), 1275 (s), 1210 (s), 1189 (m), 1153 (w), 1119 (m), 1062 (m), 1007 (w), 995 (w), 983 (w), 951 (w), 930 (w), 897 (m), 869 (m), 831 (m), 823 (m), 771 (w), 695 (w); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{27}H_{29}N_4O_3$ 457.2240; found 457.2216; MP 237.5 °C (dec.) (EtOAc/EtOH/hexanes).

4-(5-(6-Ethoxynaphthalen-2-yl)-2-(1-(methylsulfonyl)piperidin-4-yl)-1*H*-imidazol-4-yl)pyridine (**13d**)



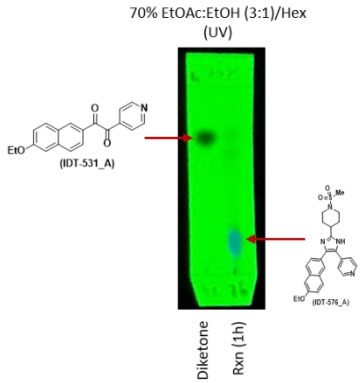
General procedure A (imidazole condensation)

Reaction scale: 0.10 mmol

Amounts employed: 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**10a**, 31 mg, 0.10 mmol, 1.0 equiv.), 1-(methylsulfonyl)piperidine-4-carbaldehyde (**12d**, 25 mg, 0.13 mmol, 1.3 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.) and *t*-BuOH (1 mL, 0.1 M).

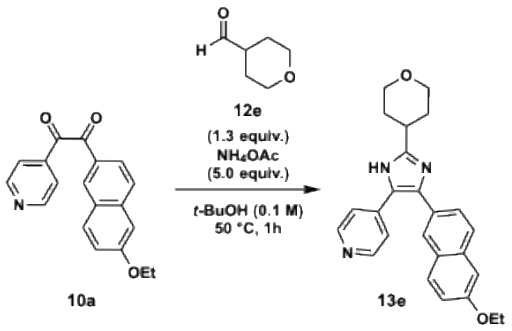
Modifications: the reaction mixture was diluted with EtOAc (5 mL) and MeOH was added until a clear solution was obtained. Then, H_2O:brine (1:1 v/v, 1 × 4 mL) was added, the phases were separated and the aqueous phase was extracted with EtOAc (5 × 5 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure.

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes and then with EtOAc:EtOH (3:1) in hexanes [Biotage Isolera, SNAP Ultra KP-Sil 10 g, 50% → 70% EtOAc/Hexanes then 30% → 100% EtOAc:EtOH (3:1 v/v)/hexanes, 18 mL fractions] to afford **13d** (42 mg, 88%) as a white solid.



R_f = 0.19 (70% EtOAc:EtOH (3:1)/hexanes) ^{1}H NMR (500 MHz, CD_3OD) δ 8.37 (s, 2H), 7.87 (s, 1H), 7.80 (d, *J* 8.3 Hz, 1H), 7.74 (d, *J* 8.7 Hz, 1H), 7.57-7.37 (m, 3H), 7.26 (s, 1H), 7.17 (d, *J* 8.6 Hz, 1H), 4.18 (q, *J* 7.0 Hz, 2H), 3.92-3.84 (m, 2H), 3.01 (tt, *J* 3.8, 11.9 Hz, 1H), 2.93 (dt, *J* 2.5, 12.1 Hz, 2H), 2.89 (s, 3H), 2.20-2.11 (m, 2H), 2.02 (dq, *J* 3.7, 12.5 Hz, 2H), 1.47 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 159.1, 150.0, 136.0, 130.6, 130.3, 128.6, 128.5, 127.8, 123.0, 120.8, 107.6, 64.6, 47.0, 36.9, 34.8, 31.7, 15.1; note: due to slow relaxation of carbon bound nitrogen some ^{13}C NMR signals are not detected. In this case, 5 signals are missing; IR (thin film, ATR) ν_{max} / cm^{-1} 1633 (w), 1600 (s), 1504 (w), 1470 (w), 1448 (w), 1393 (w), 1325 (s), 1260 (w), 1325 (m), 1260 (w), 1210 (w), 1186 (w), 1154 (s), 1114 (w), 1043 (w), 1010 (w), 951 (w), 932 (m), 898 (w), 861 (w), 833 (w), 775 (w), 744 (w), 700 (w), 669 (w), 619 (w); HRMS (ESI(+)-TOF) *m/z* [M + H]$^+$ calcd. for $C_{26}H_{29}N_4O_3S$ 477.1960; found 477.1950; MP 260.0 °C (dec.) (EtOAc/EtOH/hexanes).

4-(5-(6-Ethoxynaphthalen-2-yl)-2-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-4-yl)pyridine (**13e**)

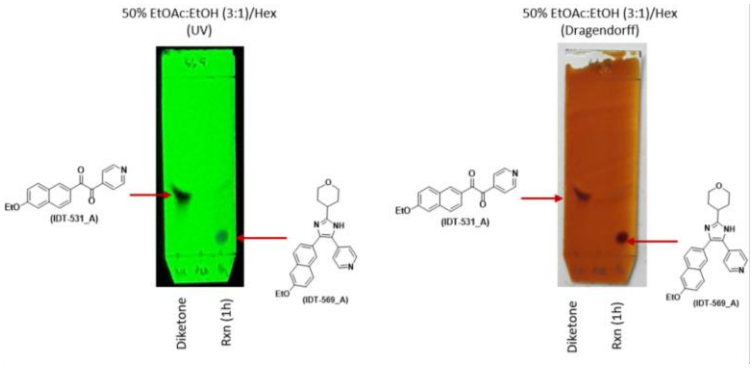


General procedure A (imidazole condensation)

Reaction scale: 0.10 mmol

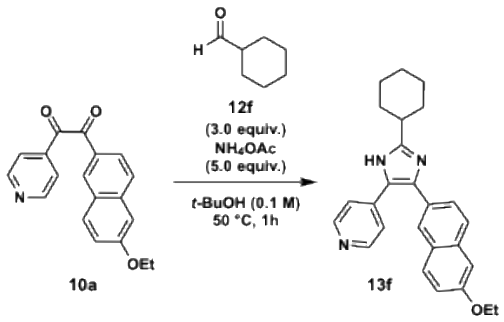
Amounts employed: 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**10a**, 31 mg, 0.10 mmol, 1.0 equiv.), tetrahydro-2*H*-pyran-4-carbaldehyde (**12e**) (16 mg, 0.130 mmol, 1.3 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.) and *t*-BuOH (1 mL, 0.1 M).

The residue was purified by silica gel chromatography, eluted with MeOH in DCM (16 cm × 15 mm, gradient elution, 1% → 10% MeOH/DCM, 1% increases, 20 mL runs, 5 mL fractions) to afford **13e** (36 mg, 90%) as a white solid.



R_f = 0.14 (50% EtOAc:EtOH (3:1)/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (dd, *J* 4.8, 1.4 Hz, 2H), 7.86 (s, 1H), 7.78 (d, *J* 8.5 Hz, 1H), 7.73 (d, *J* 8.9 Hz, 1H), 7.49 (d, *J* 6.0 Hz, 2H), 7.41 (dd, *J* 8.4, 1.4 Hz, 1H), 7.25 (d, *J* 2.2 Hz, 1H), 7.16 (dd, *J* 8.9, 2.4 Hz, 1H), 4.17 (q, *J* 7.0 Hz, 2H), 4.10-4.03 (m, 2H), 3.58 (dt, *J* 11.6, 2.3 Hz, 2H), 3.12 (tt, *J* 11.7, 4.2 Hz, 1H), 2.08-1.90 (m, 4H) 1.46 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 154.1, 150.0, 136.0, 130.6, 130.3, 128.6, 128.5, 127.8, 123.0, 120.8, 107.5, 68.7, 64.6, 36.6, 32.6, 15.1; note: due to slow relaxation of carbon bound nitrogen some ^{13}C NMR signals are not detected. In this case, 4 signals are missing; IR (thin film, ATR) ν_{max} / cm^{-1} 2932 (br.), 1629 (w), 1602 (s), 1534 (w), 1473 (w), 1388 (w), 1271 (w), 1238 (w), 1208 (m), 1187 (w), 1173 (w), 1131 (m), 1110 (w), 1089 (w), 1066 (w), 1041 (w), 1007 (w), 994 (w), 980 (w), 970 (w), 930 (w), 889 (m), 859 (m), 829 (s), 739 (w), 722 (w), 689 (w), 664 (w), 630 (w); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{25}H_{26}N_3O_2$ 400.2025; found 400.2024; MP 255.0 °C (decomp.) (MeOH/DCM).

4-(2-Cyclohexanesyl-5-(6-ethoxynaphthalen-2-yl)-1*H*-imidazol-4-yl)pyridine (**13f**)

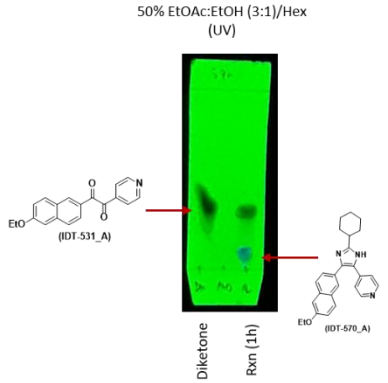


General procedure A (imidazole condensation)

Reaction scale: 0.10 mmol

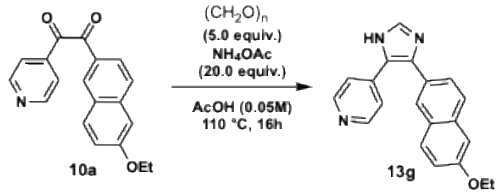
Amounts employed: 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**10a**) (31 mg, 0.10 mmol, 1.00 equiv.), cyclohexanesanecarboxaldehyde (**12f**) (35 mg, 0.300 mmol, 3.00 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.) and *t*-BuOH (1 mL, 0.1 M).

The residue was purified by silica gel chromatography, eluted with MeOH in DCM (16 cm × 15 mm, gradient elution, 0% → 7% MeOH/DCM, 1% increases, 25 mL runs, 5 mL fractions) to afford **13f** (17 mg, 43%) as a white solid.

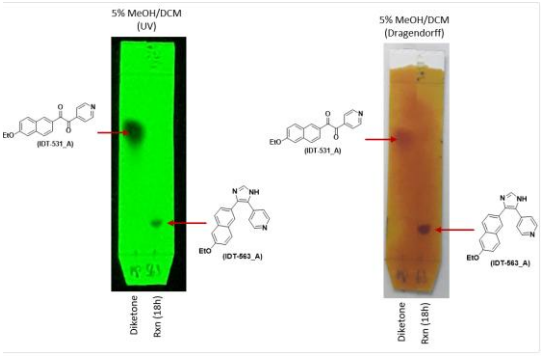


R_f = 0.14 (50% EtOAc:EtOH (3:1)/hexanes); ^{1}H NMR (500 MHz, CD_3OD) δ 8.35 (d, *J* 6.1 Hz, 2H), 7.85 (s, 1H), 7.78 (d, *J* 8.5 Hz, 1H), 7.72 (d, *J* 8.8 Hz, 1H), 7.48 (d, *J* 6.2 Hz, 2H), 7.41 (dd, *J* 1.7, 8.4 Hz, 1H), 7.24 (d, *J* 2.3 Hz, 1H), 7.15 (dd, *J* 2.4, 8.9 Hz, 1H), 4.17 (q, *J* 7.0 Hz, 2H), 2.85 (tt, *J* 3.5, 12.1 Hz, 1H), 2.09-2.00 (m, 2H), 1.94-1.86 (m, 2H). 1.82-1.75 (m, 1H), 1.70 (dq, *J* 3.1, 12.6 Hz, 2H), 1.52-1.33 (m, 6H); ^{13}C NMR (126 MHz, CD_3OD) δ 159.1, 155.9, 149.9, 135.9, 130.5, 130.3, 130.0, 129.8, 128.6, 128.5, 127.9, 123.0, 120.8, 107.5, 64.6, 39.6, 33.1, 27.4, 26.9, 15.1; note: due to slow relaxation of carbon bound nitrogen some ^{13}C NMR signals are not detected. In this case, 2 signal is missing; IR (thin film, ATR) ν_{max} / cm^{-1} 2925 (m), 2852 (w), 1631 (w), 1600 (s), 1500 (w), 1469 (w), 1448 (w), 1392 (w), 1269 (m), 1258 (m), 1208 (w), 1185 (w), 1125 (w), 1111 (w), 1065 (w), 1044 (m), 1006 (w), 983 (w), 968 (w), 930 (w), 894 (w), 856 (m), 834 (m), 812 (w), 745 (w), 728 (w), 697 (w), 669 (m), 630 (m); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{26}H_{28}N_3O$ 398.2232; found 398.2246; MP 269.0 °C (decomp) (MeOH/DCM).

4-(4-(6-Ethoxynaphthalen-2-yl)-1*H*-imidazol-5-yl)pyridine (**13g**)

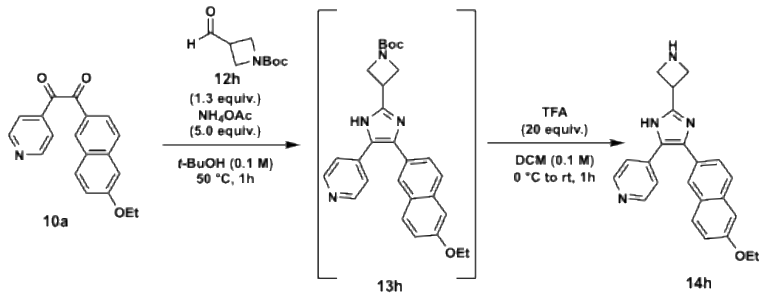


A vial was charged with 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethenone (**10a**, 31 mg, 0.10 mmol, 1.0 equiv.), NH_4OAc (156 mg, 2.0 mmol, 20.0 equiv.), paraformaldehyde (16 mg, 0.50 mmol, 5.0 equiv.) and a magnetic stirring bar under nitrogen. Then, AcOH (2.0 mL, 0.05 M) was added, and the reaction mixture was stirred at 110 °C for 16 h. After consumption of the starting material, indicated by thin layer chromatography (TLC) analysis (5% MeOH/DCM v/v), the reaction mixture was cooled to 0 °C and 27% aq. NH_4OH was added until pH 10-12 and the aqueous phase was extracted with 10% MeOH/DCM (5 × 5 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluted with MeOH in DCM [Biotage Isolera, SNAP KP-Sil 10 g, 1% → 10% MeOH/DCM (v/v), 15 mL fractions] to afford **13g** (27 mg, 86%) as a white solid.



R_f = 0.20 (5% MeOH/DCM) ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.77 (br. s, 1H), 8.43 (d, *J* 4.8 Hz, 2H), 7.87-7.78 (m, 4H), 7.50-7.39 (m, 3H), 7.35 (m, 1H), 7.19 (dd, *J* 1.8, 8.8 Hz, 1H), 4.17 (q, *J* 7.0 Hz, 2H), 1.41 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.0, 149.6, 136.5, 133.8, 129.5, 128.3, 127.1, 127.0, 126.8, 120.7, 119.4, 106.6, 63.2, 14.6; note: due to slow relaxation of carbon bound nitrogen some ^{13}C NMR signals are not detected. In this case, 4 signals are missing; IR (thin film, ATR) ν_{max} / cm^{-1} 2860 (br), 1633 (w), 1601 (s), 1519 (w), 1504 (w), 1462 (w), 1399 (w), 1264 (w), 1214 (m), 1173 (w), 1138 (w), 1113 (w), 1043 (w), 1007 (w), 994 (w), 968 (w), 931 (w), 942 (w), 893 (w), 860 (w), 829 (s), 814 (w), 778 (w), 722 (w), 693 (w), 673 (s), 664 (w), 648 (m), 642 (w); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{20}H_{18}N_3O$: 316.1450; found 316.1458; MP 256.0 °C (decomp.) (MeOH/DCM).

4-(2-(Azetidin-3-yl)-5-(6-ethoxynaphthalen-2-yl)-1*H*-imidazol-4-yl)pyridine (**14h**)



Reaction scale: 0.10 mmol

General procedure A (imidazole condensation)

Amounts employed: 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**10a**, 31 mg, 0.10 mmol, 1.0 equiv.), *tert*-butyl 3-formylazetidine-1-carboxylate (**12h**, 25 mg, 0.13 mmol, 1.3 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.) and *t*-BuOH (1 mL, 0.1 M).

The residue was used in the next step without further purification.

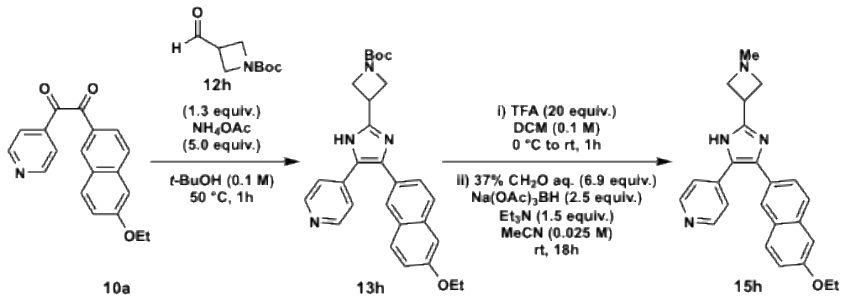
General procedure B (Boc deprotection)

Amounts employed: DCM (1 mL), trifluoroacetic acid (TFA) (155 μL, 1.00 mmol, 20 equiv.). The reaction mixture was left to stir for 1 h at room temperature.

The residue was purified by silica gel chromatography, eluted with MeOH:NH_4OH [9:1 v/v) in DCM (17 cm × 15 mm, gradient elution, 10% → 20% MeOH:NH_4OH (9:1 v/v)/DCM, 1% increases, 30 mL runs, 5 mL fractions] to afford a yellow solid which was purified by silica gel chromatography, eluted with MeOH:NH_4OH (9:1 v/v) in DCM [17 cm × 15 mm, gradient elution, 10% → 20% MeOH:NH_4OH (9:1 v/v)/DCM, 1% increases, 30 mL runs, 5 mL fractions] to afford **14h** (21 mg, 57%) as a yellow solid.

R_f = 0.17 [10% MeOH:NH_4OH (9:1 v/v)/DCM, UV, Dragendorff]; ^{1}H NMR (250 MHz, CD_3OD) δ 8.37 (dd, *J* 4.6, 1.5 Hz, 2H), 7.86 (s, 1H), 7.78 (d, *J* 8.6 Hz, 1H), 7.71 (d, *J* 9.0 Hz, 1H), 7.51 (dd, *J* 4.7, 1.8 Hz, 2H), 7.42 (dd, *J* 8.5, 1.7 Hz, 1H), 7.24 (d, *J* 2.3 Hz, 1H), 7.15 (dd, *J* 8.9, 2.5 Hz, 1H), 4.24-4.10 (m, 5H), 4.07-3.94 (m, 2H), 1.45 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 159.2, 150.5, 150.1, 143.9, 136.0, 134.6, 132.0, 130.5, 130.3, 128.6, 128.5, 127.6, 127.5, 123.0, 120.9, 107.6, 64.6, 52.7, 33.7, 15.1; IR (thin film, ATR) ν_{max} / cm^{-1} 2916 (w), 1601 (s), 1539 (m), 1505 (m), 1471 (m), 1393 (s), 1274 (s), 1211 (s), 1186 (w), 1130 (w), 1113 (w), 1045 (m), 994 (w), 931 (m), 893 (m), 859 (m), 831 (s), 818 (m), 748 (w), 728 (w), 697 (w), 667 (w), 650 (w), 639 (w); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{23}H_{23}N_4O$: 371.18664; found 371.18629; MP 214.4 °C (dec.).

4-(5-(6-Ethoxynaphthalen-2-yl)-2-(1-methylazetidin-3-yl)-1*H*-imidazol-4-yl)pyridine (**15h**)



Reaction scale: 0.10 mmol

General procedure A (imidazole condensation)

Amounts employed: 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**10a**, 31 mg, 0.10 mmol, 1.0 equiv.), *tert*-butyl 3-formylazetidine-1-carboxylate (**12h**, 25 mg, 0.13 mmol, 1.3 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.) and *t*-BuOH (1 mL, 0.1 M).

The residue was purified by silica gel chromatography, elutied with EtOAc in hexanes and then with EtOAc:EtOH (3:1 v/v) in hexanes [Biotage Isolera, SNAP KP-Sil 10 g, 50% → 70% EtOAc/Hexanes and then 30% → 100% EtOAc:EtOH (3:1 v/v)/hexanes, 18 mL fractions] to afford **13h** (44 mg, 94%) as a white solid.

General procedure C (sequential Boc deprotection and reductive amination)

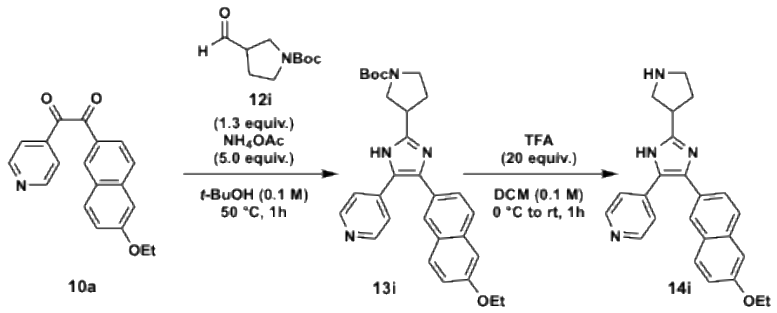
Amounts employed: *N*-Boc azetidine imidazole (32 mg, 0.07 mmol, 1.0 equiv.) TFA (104 µL, 1.36 mmol, 20 equiv.); DCM (0.70 mL, 0.1 M). The reaction mixture was left to stir for 1 h at room temperature.

Amounts employed: Et_3N (14 µL, 0.10 mmol, 1.5 equiv.), aqueous 37% (m/m) formaldehyde solution (44 µL, 0.59 mmol, 8.7 equiv.), $Na(OAc)_3BH$ (36 mg, 0.17 mmol, 2.5 equiv.) and MeCN (2.7 mL, 0.025 M).

Purification by silica gel chromatography, eluted with MeOH in DCM and then with MeOH:NH_4OH (10:1 v/v) in DCM [Biotage Isolera, SNAP KP-Sil 10 g, 0% → 10% MeOH/DCM, 10% MeOH/DCM, 10% MeOH:NH_4OH (10:1 v/v) in DCM] to afford **15h** (7 mg, 27%) as a white solid.

R_f = 0.45 (10% MeOH:NH_4OH (9:1)/DCM, UV, Dragendorff); ^{1}H NMR (250 MHz, CD_3OD) δ 8.38 (dd, *J* 4.7, 1.8 Hz, 2H), 7.87 (s, 1H), 7.80 (d, *J* 8.6 Hz, 1H), 7.74 (d, *J* 9.0 Hz, 1H), 7.51 (dd, *J* 4.8, 1.6 Hz, 2H), 7.43 (dd, *J* 8.5, 1.7 Hz, 1H), 7.26 (d, *J* 2.3 Hz, 1H), 7.16 (dd, *J* 8.9, 2.5 Hz, 1H), 4.18 (q, *J* 7.0 Hz, 2H), 3.94-3.81 (m, 3H), 3.64 (q, *J* 4.9 Hz, 2H), 2.49 (s, 3H), 1.47 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (63 MHz CD_3OD) δ 159.2, 150.3, 150.1, 143.9, 136.0, 130.6, 130.3, 128.6, 128.5, 127.7, 127.5, 123.0, 120.9, 107.6, 64.7, 61.9, 45.1, 30.1, 15.1; note: due to slow relaxation of carbon bound nitrogen some ^{13}C NMR signals are not detected. In this case, 2 signals are missing; IR (thin film, ATR) ν_{max} / cm^{-1} 2863 (br), 1628 (w), 1601 (s), 1539 (w), 1470 (w), 1445 (w), 1393 (w), 1266 (m), 1210 (m), 1186 (m), 1126 (w), 1043 (m), 995 (w), 969 (w), 932 (w), 890 (w), 858 (w), 830 (m), 747 (w), 731 (w), 709 (w), 664 (w), 628 (w); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{24}H_{25}N_4O$: 385.20229; found 385.20181; MP 200.0 °C (dec.).

4-(5-(6-Ethoxynaphthalen-2-yl)-2-(pyrrolidin-3-yl)-1*H*-imidazol-4-yl)pyridine (**14i**)



Reaction scale: 0.10 mmol

General procedure A (imidazole condensation)

Amounts employed: 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (10a, 31 mg, 0.10 mmol, 1.0 equiv.), 3-formyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (**12i**, 26 mg, 0.13 mmol, 1.3 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.) and *t*-BuOH (1 mL, 0.1 M).

The condensation product was purified by silica gel chromatography, eluted with EtOAc in hexanes and then EtOAc:EtOH (3:1 v/v) in hexanes [Biotage, KP-Sil 10 g, elution gradient, 50% → 70% EtOAc/hexanes, then 30% → 70% EtOAc:EtOH (3:1 v/v)/hexanes) to afford a light yellow solid (**13i**) (44 mg, 91%, R_f = 0.22 [50% EtOAc:EtOH (3:1 v/v)/hexanes, UV, Dragendorff]] which was used in the next step without further purification.

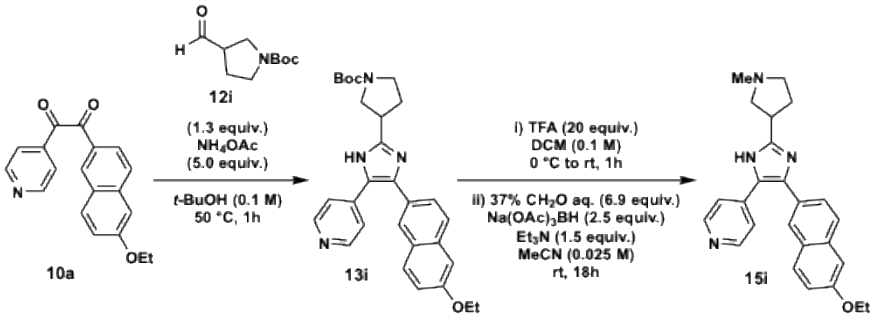
General procedure B (Boc deprotection)

Amounts employed: *N*-Boc pyrrolidine imidazole (35 mg, 0.72 mmol, 1.0 equiv.), DCM (0.7 mL), TFA (111 μL, 1.44 mmol, 20 equiv.). The reaction mixture was left to stir for 1 h at room temperature.

The residue was purified by silica gel chromatography, eluting with MeOH:NH_4OH (9:1 v/v) in DCM [17 cm × 15 mm, gradient elution, 10% → 20% MeOH:NH_4OH (9:1 v/v)/DCM, 1% increases, 30 mL runs, 5 mL fractions] to afford a yellow solid which was purified by silica gel chromatography, eluted with MeOH:NH_4OH (9:1 v/v) in DCM [17 cm × 15 mm, gradient elution, 15% → 20% MeOH:NH_4OH (9:1 v/v)/DCM, 1% increases, 30 mL runs, 5 mL fractions] to afford **14i** (12 mg, 36%) as a yellow solid.

R_f = 0.15 [10% MeOH:NH_4OH (9:1 v/v)/DCM, UV, Dragendorff]; ^{1}H NMR (500 MHz, CD_3OD) δ 8.37 (d, *J* 6.2 Hz, 2H), 7.87 (s, 1H), 7.79 (d, *J* 8.5 Hz, 1H), 7.73 (d, *J* 9.0 Hz, 1H), 7.51 (d, *J* 6.3 Hz, 2H), 7.43 (dd, *J* 8.5, 1.6 Hz, 1H), 7.26 (d, *J* 2.2 Hz, 1H), 7.16 (dd, *J* 8.9, 2.4 Hz, 1H), 4.17 (q, *J* 7.0 Hz, 2H), 3.59 (quint, 1H), 3.44 (dd, *J* 11.4, 7.9 Hz, 1H), 3.36-3.26 (m, 1H), 3.14 (dt, *J* 11.3, 7.5 Hz, 1H), 2.40 (dtd, *J* 13.2, 8.0, 5.3 Hz, 1H), 2.20 (dq, *J* 13.0, 7.8 Hz, 1H), 1.46 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 159.2, 151.8, 150.0, 144.0, 136.0, 134.5, 131.7, 130.5, 130.3, 128.6, 128.5, 127.7, 127.6, 122.9, 120.8, 107.6, 64.7, 52.4, 47.4, 39.4, 32.9, 15.1; IR (thin film, ATR) ν_{max} / cm^{-1} 2971 (w), 1601 (s), 1536 (w), 1505 (w), 1471 (w), 1394 (m), 1334 (w), 1274 (m), 1212 (s), 1186 (w), 1128 (w), 1113 (w), 1045 (m), 995 (w), 931 (m), 889 (m), 858 (m), 829 (s), 745 (m), 719 (w), 695 (w), 664 (w), 636 (w); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{24}H_{25}N_4O$: 385.20229; found 385.20180; MP 218.4 °C (dec.).

4-(5-(6-Ethoxynaphthalen-2-yl)-2-(1-methylpyrrolidin-3-yl)-1*H*-imidazol-4-yl)pyridine (**15i**)



Reaction scale: 0.10 mmol

General procedure A (imidazole condensation)

Amounts employed: 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**10a**, 31 mg, 0.10 mmol, 1.0 equiv.), 3-formyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (26 mg, 0.13 mmol, 1.3 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.) and *t*-BuOH (1 mL, 0.1 M).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes and then with EtOAc:EtOH (3:1 v/v) in hexanes [Biotage Isolera, SNAP Ultra KP-Sil 10 g, 50% → 70% EtOAc/hexanes and then 30% → 100% EtOAc:EtOH (3:1 v/v)/hexanes, 18 mL fractions] to afford a light yellow solid (**13i**) (44 mg, 91%, R_f = 0.22 [50% EtOAc:EtOH (3:1 v/v)/hexanes, UV, Dragendorff] which was used in the next step without further purification.

General procedure C (sequential Boc deprotection and reductive amination)

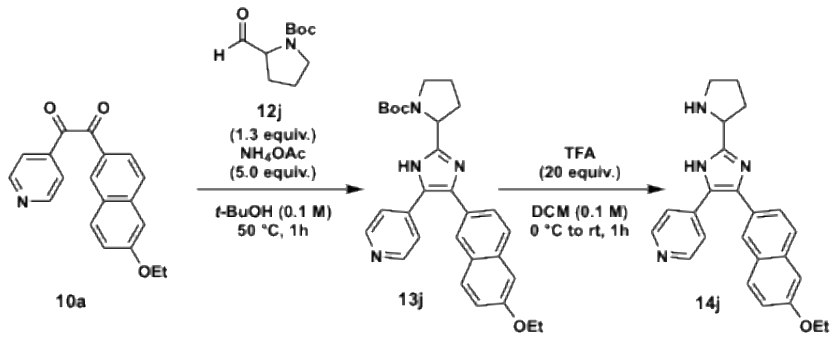
Amounts employed: *N*-Boc pyrrolidine imidazole (36 mg, 0.074 mmol, 1.0 equiv.) TFA (114 µL, 1.49 mmol, 20.0 equiv.); DCM (0.74 mL, 0.1 M). The reaction mixture was left to stir for 1 h at room temperature.

Amounts employed: Et_3N (16 µL, 0.11 mmol, 1.5 equiv.), aqueous 37% (m/m) formaldehyde solution (48 µL, 0.65 mmol, 8.7 equiv.), $Na(OAc)_3BH$ (39 mg, 0.19 mmol, 2.5 equiv.) and MeCN (3.0 mL, 0.025 M).

Purification by silica gel chromatography, eluted with MeOH in DCM and then with MeOH:NH_4OH (10:1 v/v) in DCM [Biotage Isolera, SNAP KP-Sil 10 g, 0% → 10% MeOH/DCM, 10% MeOH/DCM, 10% MeOH:NH_4OH (10:1 v/v) in DCM], to afford **15i** (22 mg, 74%) as a white solid.

R_f = 0.35 [10% MeOH:NH_4OH (9:1 v/v)/DCM, UV, Dragendorff]; ^1H NMR (500 MHz, CD_3OD) δ 8.36 (d, *J* 6.2 Hz, 2H), 7.86 (s, 1H), 7.78 (d, *J* 8.5 Hz, 1H), 7.72 (d, *J* 9.0 Hz, 1H), 7.49 (d, *J* 6.2 Hz, 2H), 7.42 (dd, *J* 8.5, 1.6 Hz, 1H), 7.25 (d, *J* 2.1 Hz, 1H), 7.15 (dd, *J* 8.9, 2.4 Hz, 1H), 4.17 (q, *J* 7.0 Hz, 2H), 3.72-3.61 (m, 1H), 3.20-3.13 (m, 1H), 2.95-2.77 (m, 3H), 2.49 (s, 3H), 2.47-2.37 (m, 1H), 2.29-2.19 (m, 1H), 1.46 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 159.1, 152.7, 150.0, 144.0, 136.0, 130.5, 130.3, 130.0, 129.7, 128.5, 128.5, 127.7, 127.6, 123.0, 120.8, 107.6, 64.6, 62.0, 56.7, 42.1, 38.5, 31.7, 15.1; IR (thin film, ATR) ν_{max} / cm^{-1} 2788 (br) 1600 (s), 1538 (w), 1505 (m), 1471 (w), 1450 (w), 1393 (w), 1338 (w), 1269 (m), 1212 (m), 1185 (w), 1154 (w), 1128 (w), 1113 (w), 1044 (m), 1022 (w), 994 (m), 967 (w), 931 (w), 889 (m), 857 (m), 829 (s), 747 (w), 728 (w), 694 (w), 666 (w); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{25}H_{27}N_4O$ 399.21794; found 399.21756; MP 219.7 °C (dec.).

4-(5-(6-Ethoxynaphthalen-2-yl)-2-(pyrrolidin-2-yl)-1*H*-imidazol-4-yl)pyridine (**14j**)



Reaction scale: 0.10 mmol

General procedure A (imidazole condensation)

Amounts employed: 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**10a**, 31 mg, 0.10 mmol, 1.0 equiv.), *tert*-butyl 2-formylpyrrolidine-1-carboxylate (**12j**, 27 mg, 0.13 mmol, 1.3 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.) and *t*-BuOH (1 mL, 0.1 M).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes and then with EtOAc:EtOH (3:1 v/v) in hexanes [Biotage Isolera, SNAP Ultra KP-Sil 10 g, 50% → 70% EtOAc/hexanes and then 30% → 100% EtOAc:EtOH (3:1 v/v)/hexanes] to afford **13j** (7 mg, 77%, R_f = 0.22), [50% EtOAc:EtOH (3:1 v/v)/hexanes, UV, Dragendorff]) as a light yellow solid.

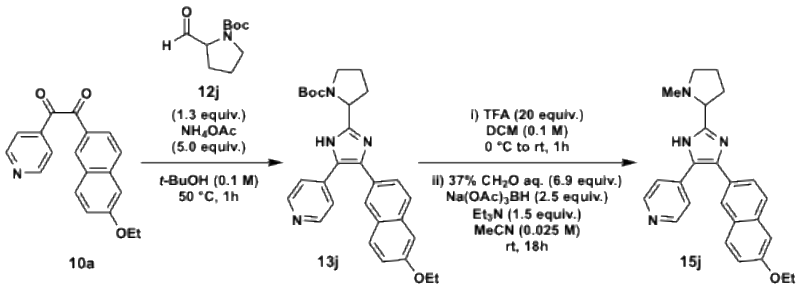
General procedure B (Boc deprotection)

Amounts employed: *N*-Boc pyrrolidine imidazole (**13j**, 23 mg, 0.05 mmol, 1.0 equiv.), DCM (0.5 mL), TFA (73 µL, 0.95 mmol, 20 equiv.). The reaction mixture was left to stir for 1 h at room temperature.

The residue was purified by silica gel chromatography, eluted with MeOH:NH_4OH (9:1 v/v) in DCM [17 cm × 15 mm, gradient elution, 10% → 15% MeOH:NH_4OH (9:1 v/v)/DCM, 1% increases, 30 mL runs] to afford **14j** (16 mg, 88%) as a pale yellow solid.

R_f = 0.17 (10% MeOH:NH_4OH (9:1)/DCM, UV, Dragendorff); ^{1}H NMR (500 MHz, CD_3OD) δ 8.39 (dd, *J* 4.8, 1.5 Hz, 2H), 7.92 (d, *J* 1.2 Hz, 1H), 7.84 (d, *J* 8.5 Hz, 1H), 7.76 (d, *J* 9.0 Hz, 1H), 7.61 (dd, *J* 4.8, 1.5 Hz, 2H), 7.47 (dd, *J* 8.5, 1.7 Hz, 1H), 7.28 (d, *J* 2.4 Hz, 1H), 7.19 (dd, *J* 8.9, 2.5 Hz, 1H), 4.91 (t, *J* 7.7 Hz, 1H), 4.19 (q, *J* 7.0 Hz, 2H), 3.60 (dt, *J* 11.4, 7.6 Hz, 1H), 3.49 (ddd, *J* 11.5, 8.3, 5.8 Hz, 1H), 2.58 (dtd, *J* 12.8, 7.7, 5.2 Hz, 1H), 2.41 (dq, *J* 13.0, 7.8 Hz, 1H), 2.37-2.27 (m, 1H), 2.27-2.15 (m, 1H), 1.47 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 159.4, 149.8, 144.8, 136.2, 130.6, 130.2, 129.8, 128.8, 128.7, 127.5, 122.8, 121.0, 107.6, 64.7, 57.4, 46.8, 31.3, 24.9, 15.1; note: due to slow relaxation of carbon bound nitrogen some ^{13}C NMR signals are not detected. In this case, 3 signals are missing; HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{24}H_{25}N_4O$: 385.20229; found 385.20190; note: infrared spectroscopy and melting point data were not collected due to spontaneous decomposition even when stored in a freezer at – 20 °C.

4-(5-(6-Ethoxynaphthalen-2-yl)-2-(1-methylpyrrolidin-2-yl)-1*H*-imidazol-4-yl)pyridine (**15j**)



Reaction scale: 0.10 mmol

General procedure A (imidazole condensation)

Amounts employed: 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**10a**, 31 mg, 0.10 mmol, 1.0 equiv.), *tert*-butyl 2-formylpyrrolidine-1-carboxylate (**12j**, 27 mg, 0.13 mmol, 1.3 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.) and *t*-BuOH (1 mL, 0.1 M).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes and then with EtOAc:EtOH (3:1 v/v) in hexanes [Biotage Isolera, SNAP Ultra KP-Sil 10 g, 50% → 70% EtOAc/Hexanes and then 30% → 100% EtOAc:EtOH (3:1 v/v)/hexanes, 18 mL fractions] to afford **13j** (37 mg, 77%), R_f = 0.22 [50% EtOAc:EtOH (3:1 v/v)/hexanes, UV, Dragendorff]) as a light yellow solid.

General procedure C (sequential Boc deprotection and reductive amination)

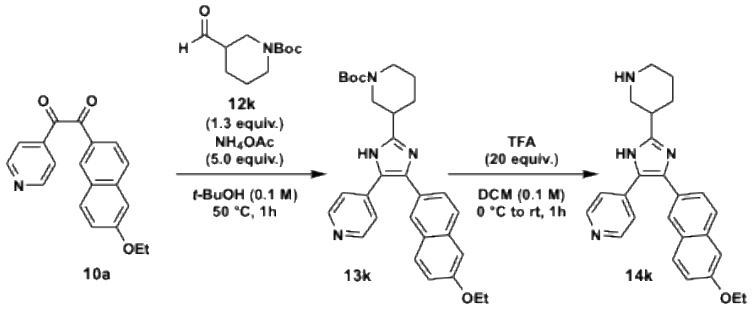
Amounts employed: *N*-Boc pyrrolidine imidazole (**13j**, 27 mg, 0.06 mmol, 1.0 equiv.), TFA (86 µL, 1.12 mmol, 20 equiv.); DCM (0.56 mL, 0.1 M). The reaction mixture was left to stir for 1 h at room temperature.

Amounts employed: Et_3N (12 µL, 0.08 mmol, 1.5 equiv.), aqueous 37% (m/m) formaldehyde solution (36 µL, 0.49 mmol, 8.7 equiv.), $Na(OAc)_3BH$ (30 mg, 0.14 mmol, 2.5 equiv.) and MeCN (2.2 mL, 0.025 M).

Purification by silica gel chromatography, eluted with MeOH in DCM and then with MeOH:NH_4OH (10:1 v/v) in DCM [Biotage Isolera, SNAP KP-Sil 10 g, 0% → 10% MeOH/DCM then 10% MeOH:NH_4OH (10:1 v/v)/DCM, 18 mL fractions], to afford **15j** (12 mg, 54%) as a white solid.

R_f = 0.45 (10% MeOH:NH_4OH (9:1 v/v)/DCM, UV, Dragendorff); ^1H NMR (250 MHz, CD_3OD) δ 8.36 (dd, *J* 4.8, 1.5 Hz, 2H), 7.88 (d, *J* 1.1 Hz, 1H), 7.80 (d, *J* 8.6 Hz, 1H), 7.74 (d, *J* 9.0 Hz, 1H), 7.51 (dd, *J* 4.7, 1.5 Hz, 2H), 7.44 (dd, *J* 8.5, 1.7 Hz, 1H), 7.26 (d, *J* 2.3 Hz, 1H), 7.16 (dd, *J* 8.9, 2.5 Hz, 1H), 4.18 (q, *J* 7.0 Hz, 2H), 3.63-3.45 (m, 1H), 3.29-3.20 (m, 1H), 2.52-2.41 (m, 1H), 2.39 (s, 3H), 2.37-2.26 (m, 1H), 2.19-1.82 (m, 3H), 1.46 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (63 MHz, CD_3OD) δ 159.2, 151.6, 150.0, 144.1, 136.0, 132.1, 130.6, 130.3, 128.7, 128.5, 127.8, 127.5, 123.0, 120.8, 107.5, 65.6, 64.6, 57.6, 41.1, 32.7, 23.7, 15.1; note: due to slow relaxation of carbon bound nitrogen some ^{13}C NMR signals are not detected. In this case, 1 signal is missing; IR (thin film, ATR) ν_{max} / cm^{-1} 2924 (w), 2774 (w), 1631 (w), 1601 (s), 1494 (w), 1467 (w), 1446 (w), 1392 (w), 1259 (m), 1210 (m), 1185 (m), 1153 (w), 1124 (w), 1067 (w), 1044 (m), 1014 (w), 994 (w), 928 (w), 899 (w), 855 (w), 834 (m), 808 (w), 747 (w), 722 (w), 691 (w), 669 (w); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{25}H_{27}N_4O$: 399.21794; found 399.21757; MP 197.0 °C (dec.).

4-(5-(6-Ethoxynaphthalen-2-yl)-2-(piperidin-3-yl)-1*H*-imidazol-4-yl)pyridine (**14k**)



Reaction scale: 0.10 mmol

General procedure A (imidazole condensation)

Amounts employed: 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**10a**, 31 mg, 0.10 mmol, 1.0 equiv.), *tert*-butyl 3-formylpiperidine-1-carboxylate (**12k**, 27 mg, 0.13 mmol, 1.3 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.) and *t*-BuOH (1 mL, 0.1 M).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes and then with EtOAc:EtOH (3:1 v/v) in hexanes (Biotage Isolera, SNAP Ultra KP-Sil 10 g, 50% → 70% EtOAc/hexanes and then 30% → 100% EtOAc:EtOH (3:1)/hexanes, 18 mL fractions) to afford **13k** (43 mg, 86%, R_f = 0.22 [50% EtOAc:EtOH (3:1)/hexanes, UV, Dragendorff]) as a light yellow solid.

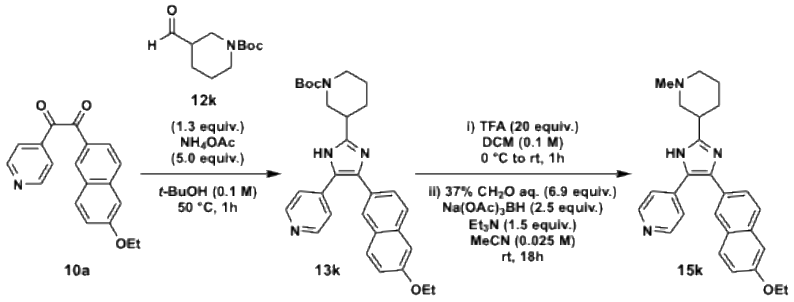
General procedure B (Boc deprotection)

Amounts employed: *N*-Boc piperidine imidazole (**13k**, 30 mg, 0.06 mmol, 1.0 equiv.), DCM (1.0 mL), TFA (92 µL, 1.21 mmol, 20 equiv.). The reaction mixture was left to stir for 1 h at room temperature.

The residue was purified by silica gel chromatography, eluted with MeOH:NH_4OH (9:1) in DCM (17 cm × 15 mm, gradient elution, 10% → 20% MeOH:NH_4OH (9:1 v/v)/DCM, 1% increases, 30 mL runs) to afford **14k** (22 mg, 92%) as a white solid.

R_f = 0.12 (10% MeOH:NH_4OH (9:1)/DCM, UV, Dragendorff); ^{1}H NMR (500 MHz, CD_3OD) δ 8.36 (d, *J* 6.2 Hz, 2H), 7.86 (d, *J* 1.0 Hz, 1H), 7.79 (d, *J* 8.5 Hz, 1H), 7.73 (d, *J* 9.0 Hz, 1H), 7.49 (d, *J* 6.3 Hz, 2H), 7.42 (dd, *J* 8.4, 1.8 Hz, 1H), 7.25 (d, *J* 2.3 Hz, 1H), 7.16 (dd, *J* 8.9, 2.5 Hz, 1H), 4.17 (q, *J* 7.0 Hz, 2H), 3.33-3.29 (m, 1H), 3.12-2.96 (m, 3H), 2.74 (td, *J* 12.3, 2.9 Hz, 1H), 2.21- 2.13 (m, 1H), 1.95-1.81 (m, 2H), 1.74-1.62 (m, 1H), 1.46 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 159.1, 152.7, 151.0, 150.0, 136.0, 130.5, 130.3, 130.0, 129.8, 128.6, 128.5, 127.8, 127.6, 123.0, 120.8, 107.6, 64.6, 51.0, 46.6, 37.9, 30.7, 26.2, 15.1; IR (thin film, ATR) ν_{max} / cm^{-1} 2941 (w), 2927 (w), 1603 (s), 1532 (w), 1505 (w), 1470 (w), 1443 (w), 1418 (w), 1394 (m), 1337 (w), 1270 (m), 1209 (s), 1184 (m), 1153 (w), 1112 (w), 1043 (m), 994 (w), 968 (w), 931 (w), 889 (w), 858 (w), 832 (s), 742 (w), 692 (w), 669 (w), 639 (w); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{25}H_{27}N_4O$: 399.21794; found 399.21769; MP 230.4 °C (dec.).

4-(5-(6-Ethoxynaphthalen-2-yl)-2-(1-methylpiperidin-3-yl)-1*H*-imidazol-4-yl)pyridine (**15k**)



Reaction scale: 0.10 mmol

General procedure A (imidazole condensation)

Amounts employed: 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**10a**, 31 mg, 0.10 mmol, 1.0 equiv.), *tert*-butyl 3-formylpiperidine-1-carboxylate (**12k**, 28 mg, 0.13 mmol, 1.3 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.) and *t*-BuOH (1 mL, 0.1 M).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes and then with EtOAc:EtOH (3:1) in hexanes [Biotage Isolera, SNAP Ultra KP-Sil 10 g, 50% → 70% EtOAc/hexanes and then 30% → 100% EtOAc:EtOH (3:1 v/v)/hexanes, 18 mL fractions] to afford **13k** (43 mg, 86%, R_f = 0.22 [50% EtOAc:EtOH (3:1 v/v)/hexanes, UV, Dragendorff]) as a light yellow solid.

General procedure C (sequential Boc deprotection and reductive amination)

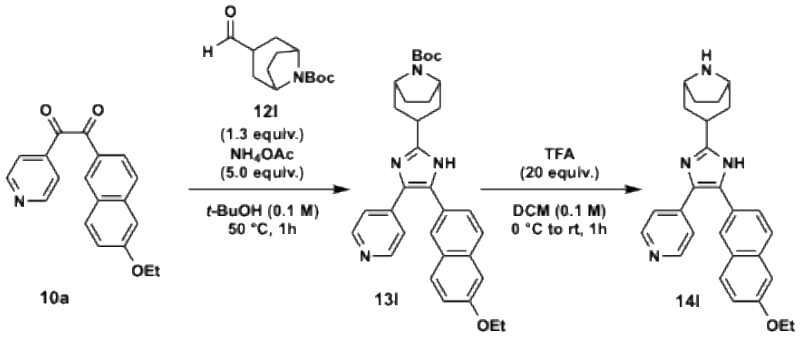
Amounts employed: *N*-Boc piperidine imidazole (**13k**, 33 mg, 0.07 mmol, 1.0 equiv.), TFA (102 µL, 1.33 mmol, 20 equiv.); DCM (0.66 mL, 0.1 M). The reaction mixture was left to stir for 1 h at room temperature.

Amounts employed: Et_3N (14 µL, 0.10 mmol, 1.5 equiv.), aqueous 37% (m/m) formaldehyde solution (43 µL, 0.58 mmol, 8.7 equiv.), $Na(OAc)_3BH$ (35 mg, 0.17 mmol, 2.5 equiv.) and MeCN (2.7 mL, 0.025 M).

Purification by silica gel chromatography, eluted with MeOH in DCM and then with MeOH:NH_4OH (10:1 v/v) in DCM [Biotage Isolera, SNAP KP-Sil 10 g, 0% → 10% MeOH/DCM then 10% MeOH:NH_4OH (10:1 v/v)/DCM, 18 mL fractions], to afford **15k** (15 mg, 55%) as a white solid.

R_f = 0.45 (10% MeOH:NH_4OH (9:1)/DCM, UV, Dragendorff); ^{1}H NMR (500 MHz, CD_3OD) δ 8.37 (dd, *J* 4.7, 1.4 Hz, 2H), 7.86 (s, 1H), 7.79 (d, *J* 8.5 Hz, 1H), 7.73 (d, *J* 9.0 Hz, 1H), 7.49 (d, *J* 5.8 Hz, 2H), 7.42 (dd, *J* 8.4, 1.6 Hz, 1H), 7.26 (d, *J* 2.2 Hz, 1H), 7.16 (dd, *J* 8.9, 2.5 Hz, 1H), 4.18 (q, *J* 7.0 Hz, 2H), 3.18-3.09 (m, 2H), 2.97-2.88 (m, 1H), 2.44-2.34 (m, 4H), 2.19-2.05 (m, 2H), 1.92-1.83 (m, 1H), 1.82-1.65 (m, 2H), 1.47 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 159.1, 152.6, 150.0, 136.0, 130.6, 130.3, 128.6, 128.5, 127.8, 123.1, 120.8, 107.6, 64.6, 60.6, 56.4, 46.5, 37.7, 29.9, 25.8, 15.1; note: due to slow relaxation of carbon bound nitrogen some ^{13}C NMR signals are not detected. In this case, 4 signals are missing; IR (thin film, ATR) ν_{max} / cm^{-1} 2935 (w), 2785 (w), 1634 (w), 1601 (s), 1558 (w), 1539 (w), 1505 (w), 1471 (w), 1455 (w), 1417 (w), 1393 (w), 1269 (w), 1210 (w), 1186 (w), 1125 (w), 1109 (w), 1089 (w), 1064 (w), 1042 (w), 1020 (w), 995 (w), 931 (w), 891 (w), 855 (w), 832 (m), 809 (w), 691 (w), 666 (w); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{26}H_{29}N_4O$: 413.23359; found 413.23316; MP 225.0 °C (dec.).

3-(5-(6-Ethoxynaphthalen-2-yl)-4-(pyridin-4-yl)-1*H*-imidazol-2-yl)-8-azabicyclo[3.2.1]octane (**14l**)



Reaction scale: 0.10 mmol

General procedure A (imidazole condensation)

Amounts employed: 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**10a**, 31 mg, 0.10 mmol, 1.0 equiv.), *tert*-butyl 3-formyl-8-azabicyclo[3.2.1]octane-8-carboxylate (**12l**, 31 mg, 0.13 mmol, 1.3 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.) and *t*-BuOH (1 mL, 0.1 M).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes and then with EtOAc:EtOH (3:1 v/v) in hexanes [Biotage Isolera, SNAP Ultra KP-Sil 10 g, 50% → 70% EtOAc/Hexanes and then 30% → 100% EtOAc:EtOH (3:1 v/v)/hexanesanew, 18 mL fractions] to afford the imidazole **13l** [30 mg, 57%, R_f = 0.24, 50% EtOAc:EtOH (3:1 v/v)/hexanes, UV, Dragendorff] as a light yellow solid.

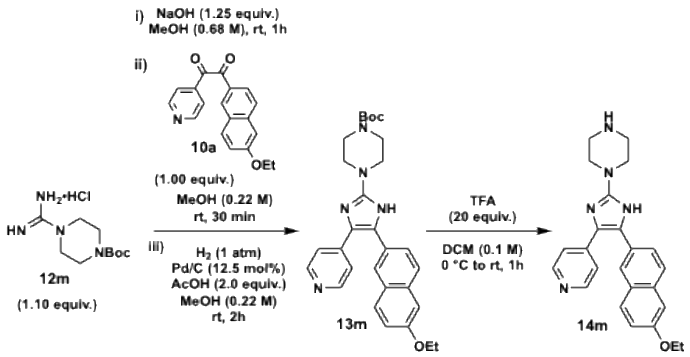
General procedure B (Boc deprotection)

Amounts employed: *N*-Boc tropane imidazole (**13l**, 30 mg, 0.057 mmol, 1.0 equiv.), DCM (1 mL), TFA (87 µL, 1.15 mmol, 20 equiv.). The reaction mixture was left to stir for 1 h at room temperature.

The residue was purified by silica gel chromatography, eluted with MeOH:NH_4OH (9:1 v/v) in DCM [17 cm × 15 mm, gradient elution, 10% → 20% MeOH:NH_4OH (9:1 v/v)/DCM, 1% increases, 30 mL runs, 5 mL fractions] to afford **14l** (17 mg, 70%) as a white solid.

R_f = 0.15 (10% MeOH:NH4OH (9:1)/DCM, UV, Dragendorff); ^{1}H NMR (500 MHz, CD_3OD) δ 8.36 (d, *J* 6.1 Hz, 2H), 7.85 (s, 1H), 7.79 (d, *J* 8.5 Hz, 1H), 7.73 (d, *J* 9.0 Hz, 1H), 7.48 (d, *J* 6.2 Hz, 2H), 7.41 (dd, *J* 8.5, 1.5 Hz, 1H), 7.25 (d, *J* 2.1 Hz, 1H), 7.16 (dd, *J* 8.9, 2.4 Hz, 1H), 4.17 (q, *J* 7.0 Hz, 2H), 3.72 (br. s, 2H), 3.42-3.32 (m, 1H), 2.06-1.97 (m, 4H), 1.97-1.89 (m, 4H), 1.46 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 159.1, 153.8, 150.0, 144.0, 136.0, 130.5, 130.3, 128.6, 128.5, 127.8, 127.6, 123.0, 120.8, 107.6, 64.6, 55.7, 37.6, 30.6, 29.2, 15.1; note: due to slow relaxation of carbon bound nitrogen some ^{13}C NMR signals are not detected. In this case, 2 signals are missing; IR (thin film, ATR) ν_{max} / cm^{-1} 2935 (w), 2913 (w), 1632 (w), 1600 (s), 1537 (w), 1503 (w), 1470 (w), 1443 (w), 1391 (m), 1262 (m), 1211 (m), 1186 (m), 1153 (w), 1126 (w), 1043 (m), 1018 (w), 996 (w), 968 (w), 931 (w), 897 (w), 857 (w), 725 (w), 692 (w), 667 (w); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{27}H_{29}N_4O$: 425.23359; found 425.23322; MP 274.5 °C (dec.).

1-(5-(6-Ethoxynaphthalen-2-yl)-4-(pyridin-4-yl)-1*H*-imidazol-2-yl)piperazine (**14m**)



To a vial containing NaOH (12 mg, 0.30 mmol, 1.25 equiv.), MeOH (0.4 mL) and a magnetic stirring bar under nitrogen was added *tert*-butyl 4-carbamimidoylpiperazine-1-carboxylate hydrochloride (**12m**)[1] (72 mg, 0.27 mmol, 1.10 equiv.) and the mixture was stirred for 1 h at room temperature. Then, the reaction mixture was diluted with MeOH (1 mL) and filtered in a Celite® pad which was washed with MeOH (5 mL). The filtrate was concentrated under reduced pressure and redissolved in MeOH (1.1 mL) under a nitrogen atmosphere. The solution was cooled to 0 °C and **10a** (74 mg, 0.24 mmol, 1.0 equiv.) was added and the reaction mixture was stirred for 30 min (the reaction mixture was sonicated to aid solubilization of the diketone). An intense yellow solid formed during the reaction. After consumption of the starting material, indicated by TLC analysis, AcOH (31 µL, 0.54 mmol, 2.0 equiv.) was added, followed by addition of 10% Pd/C (36 mg, 0.03 mmol, 12.5 mol%). The reaction mixture was flushed with H_2 and stirred under a H_2 atmosphere at room temperature for 2 h. After consumption of the intermediate, indicated by TLC analysis, the system was flushed with N_2 and the reaction mixture was filtered through a Celite® pad which was washed with MeOH (50 mL). The filtrate was concentrated under reduced pressure, and the residue was diluted with 10% MeOH/DCM (15 mL), washed with satd. $NaHCO_3$ (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluted with MeOH in DCM (18 cm × 20 mm, gradient elution, 0% → 6% MeOH/DCM, 1% increases, 100 mL runs, 10 mL fractions) to afford **13m** (68 mg, 50%) as a bright yellow solid.

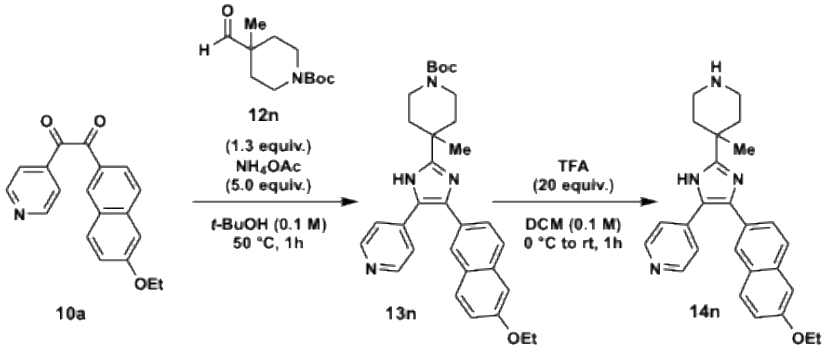
R_f = 0.70 (7% MeOH/DCM, UV, Dragendorff); ^{1}H NMR (250 MHz, CD_3OD) δ 8.30 (d, *J* 6.0 Hz, 2H), 7.84 (s, 1H), 7.77 (d, *J* 8.6 Hz, 1H), 7.71 (d, *J* 9.0 Hz, 1H), 7.48-7.38 (m, 3H), 7.24 (d, *J* 2.3 Hz, 1H), 7.14 (dd, *J* 8.9, 2.5 Hz, 1H), 4.17 (q, *J* 7.0 Hz, 2H), 3.64-3.54 (m, 4H), 3.47-3.36 (m, 4H), 1.53-1.41 (m, 12H).

A 20 mL culture tube was charged with **13m** (25 mg, 0.05 mmol,1.0 equiv.) and a magnetic stirrer bar under nitrogen. DCM (0.6 mL) was added followed by dropwise addition of TFA (77 µL, 1.0 mmol, 20 equiv.) at room temperature. The reaction mixture was allowed to stir at room temperature until consumption of the starting material (40 min, monitored by TLC, 10% MeOH:NH_4OH (10:1)/DCM). After consumption of starting material, the reaction mixture was concentrated under reduced pressure and quenched with a solution of 10% MeOH:NH_4OH (10:1)/DCM (1 mL) and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography, eluted with MeOH:NH_4OH (9:1) in DCM (10 cm × 15 mm, gradient elution, 10% → 20% MeOH:NH_4OH (9:1)/DCM, 5% increases, 50 mL runs, 7 mL fractions) to afford **14m** (13 mg, 65%) as a pale yellow solid.

R_f = 0.37 (10% MeOH:NH_4OH (9:1)/DCM, UV, Dragendorff); ^{1}H NMR (500 MHz, CD_3OD) δ 8.29 (d, *J* 5.6 Hz, 2H), 7.84 (s, 1H), 7.76 (d, *J* 8.5 Hz, 1H), 7.71 (d, *J* 9.0 Hz, 1H), 7.48-7.36 (m, 3H), 7.23 (d, *J* 2.3 Hz, 1H), 7.14 (dd, *J* 8.9, 2.5 Hz, 1H), 4.16 (q, *J* 7.0 Hz, 2H), 3.48-3.39 (m, 4H), 3.03-2.94 (m, 4H), 1.46 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 159.0, 154.6, 149.7, 135.8, 130.5, 130.3, 128.5, 128.3, 128.1, 122.5, 120.6, 107.6, 64.6, 45.9, 15.1; note: due to slow relaxation of carbon bound nitrogen some ^{13}C NMR signals are not detected. In this case, 5 signals are missing; IR (thin film, ATR) ν_{max} / cm^{-1} 2844 (w), 1599 (s), 1584 (s), 1505 (w), 1471 (w), 1457 (w), 1393 (w), 1338 (w),

1273 (m), 1212 (m), 1186 (w), 1045 (w), 1015 (w), 993 (w), 993 (w), 931 (w), 931 (w), 900 (m), 859 (m), 831 (m), 716 (w), 684 (w), 667 (w); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{24}H_{26}N_5O$: 400.21293; found 400.21319; MP 242.0 °C (dec.).

4-(5-(6-Ethoxynaphthalen-2-yl)-2-(4-methylpiperidin-4-yl)-1*H*-imidazol-4-yl)pyridine (**14n**)



Reaction scale: 0.10 mmol

General procedure A (imidazole condensation)

Amounts employed: 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**10a**, 31 mg, 0.10 mmol, 1.0 equiv.), *tert*-butyl 4-formyl-4-methylpiperidine-1-carboxylate (**12n**, 30 mg, 0.13 mmol, 1.3 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.) and *t*-BuOH (1 mL, 0.1 M).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes and then with EtOAc:EtOH (3:1 v/v) in hexanes [Biotage Isolera, SNAP Ultra KP-Sil 10 g, 50% → 70% EtOAc/Hexanes and then 30% → 100% EtOAc:EtOH (3:1 v/v)/hexanes, 18 mL fractions] to afford the imidazole (**13n**, 33 mg, 64%), R_f = 0.30 [50% EtOAc:EtOH (3:1 v/v)/hexanes, UV, Dragendorff] as a light yellow solid.

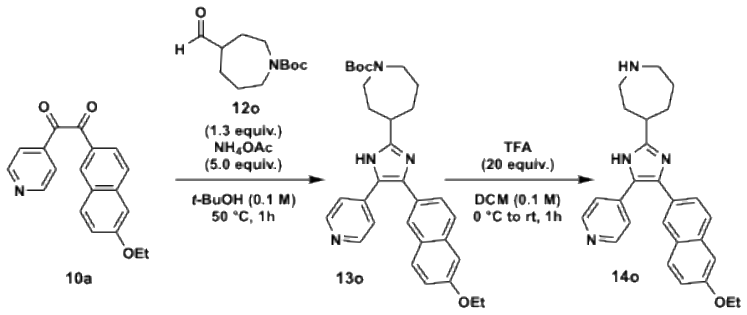
General procedure B (Boc deprotection)

Amounts employed: *N*-Boc piperidine imidazole (33 mg, 0.065 mmol, 1.0 equiv.), DCM (1 mL), TFA (100 µL, 1.30 mmol, 20 equiv.). The reaction mixture was stirred for 5 h at room temperature.

The residue was purified by silica gel chromatography, eluted with MeOH:NH_4OH (9:1 v/v) in DCM [17 cm × 15 mm, gradient elution, 10% → 20% MeOH:NH_4OH (9:1 v/v)/DCM, 1% increases, 30 mL runs, 5 mL fractions] to afford **14n** (20 mg, 75%) as a white solid.

R_f = 0.17 (10% MeOH:NH_4OH (9:1)/DCM, UV, Dragendorff); ^{1}H NMR (500 MHz, CD_3OD) δ 8.36 (br. s, 2H), 7.90 (s, 1H), 7.81 (d, *J* 8.5 Hz, 1H), 7.75 (d, *J* 9.0 Hz, 1H), 7.56 (d, *J* 3.9 Hz, 2H), 7.45 (dd, *J* 8.5, 1.4 Hz, 1H), 7.27 (d, *J* 2.0 Hz, 1H), 7.17 (dd, *J* 8.9, 2.4 Hz, 1H), 4.18 (q, *J* 7.0 Hz, 2H), 3.38 (dt, *J* 12.9, 3.8 Hz, 2H), 3.30-3.21 (m, 2H), 2.66-2.58 (m, 2H), 2.03-1.92 (m, 2H), 1.49 (s, 3H), 1.47 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 159.2, 153.7, 149.7, 136.1, 130.6, 130.2, 128.9, 128.6, 127.9, 123.0, 120.9, 107.6, 64.7, 42.6, 35.6, 34.1, 29.2, 15.1; note: due to slow relaxation of carbon bound nitrogen some ^{13}C NMR signals are not detected. In this case, 4 signals are missing; IR (thin film, ATR) ν_{max} / cm^{-1} 2972 (w), 2929 (w), 1692 (m), 1680 (m), 1629 (w), 1604 (s), 1583 (w), 1470 (m), 1424 (m), 1393 (m), 1366 (w), 1338 (w), 1274 (m), 1204 (s), 1128 (s), 1048 (w), 995 (w), 971 (w), 933 (w), 896 (w), 857 (w), 833 (s), 816 (w), 742 (w), 722 (w), 666 (w), 653 (w), 622 (w); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{26}H_{29}N_4O$: 413.23359; found 413.23327; MP 190.3 °C (dec.).

4-(5-(6-Ethoxynaphthalen-2-yl)-2-(4-methylpiperidin-4-yl)-1*H*-imidazol-4-yl)pyridine (**14o**)



Reaction scale: 0.10 mmol

General procedure A (imidazole condensation)

Amounts employed: 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**10a**, 31 mg, 0.10 mmol, 1.0 equiv.), *tert*-butyl 4-formylazepane-1-carboxylate (**12o**, 30 mg, 0.13 mmol, 1.3 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.) and *t*-BuOH (1 mL, 0.1 M).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes and then with EtOAc:EtOH (3:1 v/v) in hexanes [Biotage Isolera, SNAP Ultra KP-Sil 10 g, 50% → 70% EtOAc/hexanes and then 30% → 100% EtOAc:EtOH (3:1 v/v)/hexanes, 18 mL fractions] to afford the imidazole (**13o**, 36 mg, 70%), R_f = 0.28 [50% EtOAc:EtOH (3:1 v/v)/hexanes, UV, Dragendorff]] as a light yellow solid.

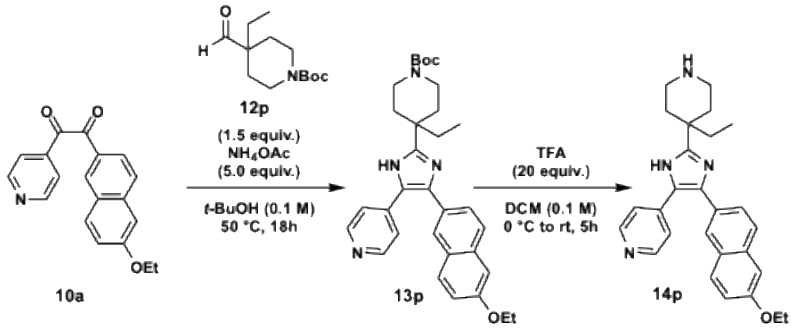
General procedure B (Boc deprotection)

Amounts employed: *N*-Boc azepane imidazole (**13o**, 36 mg, 0.065 mmol, 1.0 equiv.), DCM (1 mL), TFA (107 µL, 1.40 mmol, 20 equiv.). The reaction mixture was left to stir for 1 h at room temperature.

The residue was purified by silica gel chromatography, eluted with MeOH:NH_4OH (9:1 v/v) in DCM [17 cm × 15 mm, gradient elution, 10% → 20% MeOH:NH_4OH (9:1 v/v)/DCM, 1% increases, 30 mL runs, 5 mL fractions)] to afford **14o** (18 mg, 62%) as a white solid.

R_f = 0.16 (10% MeOH:NH4OH (9:1)/DCM, UV, Dragendorff); ^{1}H NMR (250 MHz, MeOD) δ 8.36 (d, *J* 6.2 Hz, 2H), 7.85 (s, 1H), 7.78 (d, *J* 8.5 Hz, 1H), 7.72 (d, *J* 9.0 Hz, 1H), 7.49 (d, *J* 6.3 Hz, 2H), 7.41 (dd, *J* 8.5, 1.7 Hz, 1H), 7.24 (d, *J* 2.2 Hz, 1H), 7.15 (dd, *J* 8.9, 2.4 Hz, 1H), 4.16 (q, *J* 7.0 Hz, 2H), 3.29-3.00 (m, 5H), 2.32-1.74 (m, 6H), 1.46 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (63 MHz, MeOD) δ 159.1, 155.0, 150.0, 144.1, 135.9, 131.3, 130.5, 130.3, 128.5, 128.5, 127.7, 127.7, 123.0, 120.8, 107.5, 64.6, 46.6, 39.8, 34.2, 34.2, 33.6, 27.5, 15.1; note: due to slow relaxation of carbon bound nitrogen some ^{13}C NMR signals are not detected. In this case, 1 signals are missing; IR (thin film, ATR) ν_{max} / cm^{-1} 2916 (w), 1602 (s), 1533 (m), 1505 (w), 1471 (m), 1440 (w), 1416 (m), 1394 (m), 1342 (w), 1273 (s), 1185 (m), 1127 (w), 1112 (w), 1041 (m), 994 (w), 967 (w), 931 (w), 860 (w), 831 (s), 742 (w), 697 (w), 661 (w); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{26}H_{29}N_4O$ 413.23359; found 413.23320; MP 221.0 °C (dec.).

4-(5-(6-Ethoxynaphthalen-2-yl)-2-(4-ethylpiperidin-4-yl)-1*H*-imidazol-4-yl)pyridine (**14p**)



Reaction scale: 0.10 mmol

General procedure A (imidazole condensation)

Amounts employed: 1-(6-ethoxynaphthalen-2-yl)-2-(pyridin-4-yl)ethane-1,2-dione (**10a**, 31 mg, 0.10 mmol, 1.0 equiv.), *tert*-butyl 3-formyl-3-ethylpiperidine-1-carboxylate (**12p**, 36 mg, 0.15 mmol, 1.5 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.); *t*-BuOH (1 mL, 0.1 M).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes and then with EtOAc:EtOH (3:1 v/v) in hexanes [Biotage Isolera, SNAP Ultra KP-Sil 10 g, 50% → 70% EtOAc/hexanes and then 30% → 100% EtOAc:EtOH (3:1 v/v)/hexanes, 15 mL fractions] to afford a mixture of two compounds (**13p** + impurities, 20 mg) as a light yellow solid. R_f = 0.46 [50% EtOAc:EtOH (3:1 v/v)/hexanes, UV, Dragendorff].

General procedure B (Boc deprotection)

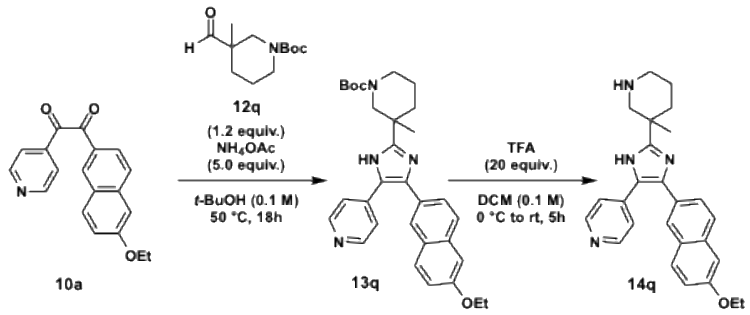
Amounts employed: mixture of two compounds by TLC (20 mg), DCM (0.5 mL), TFA (58 μL, 0.76 mmol, 20 equiv.).

The reaction mixture was stirred for 5 h.

The residue was purified by silica gel chromatography, eluted with MeOH: 28% NH_4OH (9:1 v/v) in DCM [10 cm × 15 mm, gradient elution, 10% → 20% MeOH: 28% NH4OH (9:1 v/v)/DCM, 1% increases, 10 mL runs, 3 mL fractions] to afford a residue which was diluted with 10% MeOH/DCM (10 mL) and partitioned in 2 M NaOH aq. (5 mL). The layers were separated and the aqueous layer was extracted with 10% MeOH/DCM (5 × 5 mL). The organic layers were combined, washed with brine (2 × 5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a white solid which was triturated with hexanes (3 × 3 mL) to afford **14p** (7 mg, 16% for two steps) as a white solid.

R_f = 0.33 (20% MeOH:NH_4OH (9:1)/DCM, UV, Dragendorff); ^{1}H NMR (500 MHz, CD_3OD) δ 8.35 (d, *J* 5.5 Hz, 2H), 7.87 (s, 1H), 7.79 (d, *J* 8.5 Hz, 1H), 7.74 (d, *J* 9.0 Hz, 1H), 7.50 (d, *J* 6.1 Hz, 2H), 7.42 (dd, *J* 8.4, 1.6 Hz, 1H), 7.26 (d, *J* 2.2 Hz, 1H), 7.16 (dd, *J* 8.9, 2.4 Hz, 1H), 4.18 (q, *J* 7.0 Hz, 2H), 3.01-2.92 (m, 2H), 2.83-2.73 (m, 2H), 2.50-2.41 (m, 2H), 1.75 (q, *J* 7.4 Hz, 2H), 1.73-1.63 (m, 3H), 1.46 (t, *J* 7.0 Hz, 3H), 0.79 (t, *J* 7.5 Hz, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 159.1, 154.5, 149.8, 135.9, 130.6, 130.3, 128.9, 128.4, 128.1, 123.3, 120.7, 107.6, 64.7, 43.8, 40.9, 36.8, 35.6, 15.1, 8.5; note: due to slow relaxation of carbon bound nitrogen some ^{13}C NMR signals are not detected. In this case, 4 signals are missing; IR (thin film, ATR) ν_{max} / cm^{-1} 2928 (br. s), 1628 (w), 1601 (s), 1525 (w), 1500 (w), 1468 (w), 1420 (w), 1392 (w), 1336 (w), 1323 (w), 1264 (w), 1208 (w), 1125 (w), 1112 (w), 1043 (w), 991 (w), 933 (w), 856 (w), 832 (m), 815 (w), 739 (w), 697 (w), 668 (w), 612 (m); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{27}H_{31}N_4O$: 427.24924; found 427.24928; MP 201.9-204.0 °C (MeOH).

4-(5-(6-Ethoxynaphthalen-2-yl)-2-(3-methylpiperidin-3-yl)-1*H*-imidazol-4-yl)pyridine (**14q**)



Reaction scale: 0.10 mmol

General procedure A (imidazole condensation)

Amounts employed: 1-(6-ethoxynaphthalen-2-yl)-2-(pyridin-4-yl)ethane-1,2-dione (**10a**, 31 mg, 0.10 mmol, 1.0 equiv.), *tert*-butyl 3-formyl-3-methylpiperidine-1-carboxylate (**12q**, 27 mg, 0.12 mmol, 1.2 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.); *t*-BuOH (1 mL, 0.1 M).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes and then with EtOAc:EtOH (3:1 v/v) in hexanes [Biotage Isolera, SNAP Ultra KP-Sil 10 g, 50% → 70% EtOAc/hexanes and then 30% → 100% EtOAc:EtOH (3:1 v/v)/hexanes, 15 mL fractions] to afford **13q** (33 mg, 64%) as a white solid.

R_f = 0.30 [50% EtOAc:EtOH (3:1)/hexanes, UV, Dragendorff]; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.50-8.38 (m, 2H), 8.03-7.80 (m, 1H), 7.75-7.64 (m, 2H), 7.62-7.51 (m, 2H), 7.48-7.39 (m, 1H), 7.38-7.31 (m, 1H), 7.20-7.08 (m, 2H), 4.65-4.42 (m, 1H), 4.17 (q, *J* 7.0 Hz, 2H), 4.10-3.91 (m, 1H), 2.92-2.63 (m, 3H), 1.65-1.41 (m, 6H), 1.41-1.19 (m, 12H).

General procedure B (Boc deprotection)

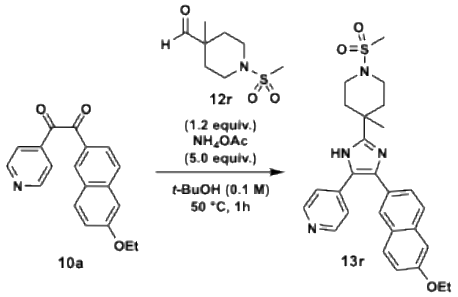
Amounts employed: *N*-Boc piperidine imidazole (26 mg, 0.050 mmol, 1.0 equiv.), DCM (0.5 mL), TFA (77 µL, 1.00 mmol, 20 equiv.).

The reaction mixture was stirred for 5 h.

The residue was purified by silica gel chromatography, eluted with MeOH: 28% NH_4OH (9:1 v/v) in DCM [10 cm × 15 mm, gradient elution, 10% → 20% MeOH: 28% NH4OH (9:1 v/v)/DCM, 1% increases, 10 mL runs, 3 mL fractions)] to afford a residue which was diluted with 10% MeOH/DCM (10 mL) and partitioned in aq. 2 M NaOH (5 mL). The layers were separated and the aqueous layer was extracted with 10% MeOH/DCM (5 × 5 mL). The organic layers were combined, washed with brine (2 × 5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a white solid which was triturated with hexanes (3 × 3 mL) to afford **14q** (7 mg, 34%) as a white solid.

R_f = 0.33 [20% MeOH:NH_4OH (9:1 v/v)/DCM, UV, Dragendorff)]; ^{1}H NMR (500 MHz, CD_3OD) δ 8.34 (d, *J* 6.3 Hz, 2H), 7.88 (d, *J* 1.3 Hz, 1H), 7.80 (d, *J* 8.5 Hz, 1H), 7.74 (d, *J* 9.0 Hz, 1H), 7.53 (d, *J* 6.3 Hz, 2H), 7.44 (dd, *J* 8.5, 1.7 Hz, 1H), 7.26 (d, *J* 2.4 Hz, 1H), 7.16 (dd, *J* 8.9, 2.5 Hz, 1H), 4.18 (q, *J* 7.0 Hz, 2H), 3.58-3.51 (m, 1H), 2.93 (dt, *J* 12.8, 3.8 Hz, 1H), 2.73-2.62 (m, 2H), 2.38-2.29 (m, 1H), 1.72 (ddd, *J* 13.7, 11.3, 3.8 Hz, 1H), 1.66-1.57 (m, 1H), 1.55-1.49 (m, 2H), 1.47 (t, *J* 7.0 Hz, 2H), 1.34 (s, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 159.1, 155.9, 149.8, 144.5, 135.9, 130.6, 130.3, 130.1, 129.9, 128.8, 128.4, 128.1, 127.8, 123.0, 120.8, 107.6, 64.6, 56.2, 46.7, 37.3, 36.9, 26.7, 24.3, 15.1; IR (thin film, ATR) ν_{max} / cm^{-1} 2919 (br. s), 1628 (w), 1600 (s), 1492 (w), 1417 (w), 1469 (w), 1417 (w), 1389 (w), 1264 (m), 1212 (w), 1185 (w), 1150 (w), 1125 (w), 1113 (w), 1042 (w), 1003 (w), 993 (w), 969 (w), 928 (w), 900 (w), 854 (w), 832 (m), 744 (w), 700 (w), 673 (w), 647 (w), 630 (w**);** HRMS (ESI(+)-TOF**)** *m/z* $[M + H]^+$ calcd. for $C_{26}H_{29}N_4O$: 413.23359; found 413.23352; MP 219.0-221.0 °C (MeOH).

4-(5-(6-Ethoxynaphthalen-2-yl)-2-(4-methyl-1-(methylsulfonyl)piperidin-4-yl)-1*H*-imidazol-4-yl)pyridine (**13r**)



Reaction scale: 0.10 mmol

General procedure A (imidazole condensation)

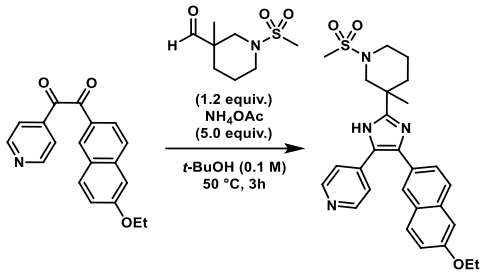
Amounts employed: 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**10a**, 31 mg, 0.10 mmol, 1.0 equiv.), 4-methyl-1-(methylsulfonyl)piperidine-4-carbaldehyde (**12r**, 26 mg, 0.12 mmol, 1.2 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.) and *t*-BuOH (1 mL, 0.1 M).

The reaction mixture was stirred for 3 h.

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes (50% → 70% EtOAc/hexanes) and then with EtOAc:EtOH (3:1 v/v) in hexanes (Biotage Isolera, SNAP Ultra KP-Sil 10 g, linear gradient, 50% → 90% EtOAc/hexanes, 15 mL fractions) to afford **13r** (24 mg, 49%) as a white solid.

R_f = 0.19 [50% EtOAc:EtOH (3:1 v/v)/hexanes, UV, Dragendorff]; ^{1}H NMR (500 MHz, CD_3OD) δ 8.35 (d, *J* 4.5 Hz, 2H), 7.88 (s, 1H), 7.80 (d, *J* 8.4 Hz, 1H), 7.75 (d, *J* 9.0 Hz, 1H), 7.53 (br. s, 2H), 7.46-7.40 (m, 1H), 7.26 (d, *J* 2.1 Hz, 1H), 7.16 (dd, *J* 8.9, 2.3 Hz, 1H), 4.18 (q, *J* 7.0 Hz, 2H), 3.57-3.47 (m, 2H), 3.18-3.09 (m, 2H), 2.81 (s, 3H), 2.55-2.47 (m, 2H), 1.85 (ddd, *J* 13.7, 10.0, 3.8 Hz, 2H), 1.47 (t, *J* 7.0 Hz, 3H), 1.43 (s, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 159.1, 149.9, 136.0, 130.6, 130.3, 130.1, 128.9, 128.5, 128.0, 123.1, 120.8, 107.6, 64.6, 44.2, 36.8, 36.3, 34.7, 28.7, 15.1; note: due to slow relaxation of carbon bound nitrogen some ^{13}C NMR signals are not detected. In this case, 4 signals are missing; IR (thin film, ATR) ν_{max} / cm^{-1} 3206 (br), 1602 (s), 1501 (w), 1471 (w), 1395 (w), 1337 (m), 1319 (m), 1272 (w), 1255 (w), 1213 (w), 1192 (w), 1165 (m), 1147 (s), 1125 (w), 1114 (w), 1041 (w), 1027 (w), 1007 (w), 933 (w), 958 (m), 931 (m), 900 (w), 857 (w), 832 (m), 776 (m), 700 (w), 670 (w); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{27}H_{31}N_4O_3S$: 491.21114; found 491.21114; MP 227.8 °C (decomp.).

4-(5-(6-Ethoxynaphthalen-2-yl)-2-(3-methyl-1-(methylsulfonyl)piperidin-3-yl)-1*H*-imidazol-4-yl)pyridine (**13s**)



Reaction scale: 0.10 mmol

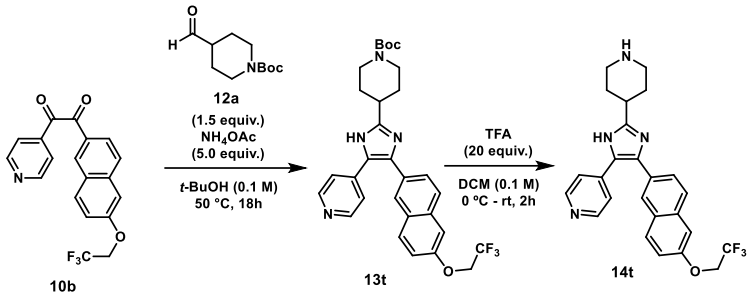
General procedure A (imidazole condensation)

Amounts employed: 2-(6-ethoxynaphthalen-2-yl)-1-(pyridin-4-yl)ethanone (**10a**) (31 mg, 0.10 mmol, 1.0 equiv.), 3-methyl-1-(methylsulfonyl)piperidine-3-carbaldehyde (**12s**, 23 mg, 0.11 mmol, 1.1 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.), *t*-BuOH (1 mL, 0.1 M).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes and then with EtOAc:EtOH (3:1 v/v) in hexanes [Biotage Isolera, SNAP KP-Sil 10 g, 50% → 70% EtOAc/Hexanes then 30% → 70% EtOAc:EtOH (3:1 v/v)/Hexanes, 18 mL fractions] to afford a light yellow solid which was repurified by silica gel chromatography, eluted with MeOH in DCM (21 cm × 15 mm, gradient elution, 0% → 5% MeOH/DCM, 0.5% increases, 30 mL runs, 5 mL fractions) to afford **13s** (16 mg, 33%) as a white solid.

R_f = 0.25 [70%, EtOAc:EtOH (3:1 v/v)/hexanes, UV, Dragendorff]; ^{1}H NMR (500 MHz, CD_3OD) δ 8.37 (s, 2H), 7.88 (s, 1H), 7.79 (d, *J* 8.4 Hz, 1H), 7.73 (d, *J* 9.0 Hz, 1H), 7.61-7.37 (m, 3H), 7.25 (d, *J* 2.2 Hz, 1H), 7.18-7.12 (m, 1H), 4.57 (s, 1H), 4.18 (q, *J* 7.0 Hz, 2H), 3.88 (d, *J* 10.7 Hz, 1H), 3.29 (s, 1H), 3.26 (d, *J* 6.0 Hz, 1H), 2.85 (s, 3H), 2.42-2.33 (m, 1H), 1.89-1.81 (m, 2H), 1.77 (dt, *J* 12.6, 6.2 Hz, 1H), 1.49-1.44 (m, 6H); note: during the acquisition of the ^{13}C NMR spectrum, the sample crystalized thus reducing the amount of compound in solution. This is the reason why the ^{13}C NMR was not acquired in CD_3OD. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.35 (s, 1H), 8.38 (d, *J* 5.8 Hz, 2H), 7.95 (s, 1H), 7.87 (d, *J* 4.7 Hz, 1H), 7.86 (d, *J* 5.2 Hz, 1H), 7.47 (d, *J* 1.4 Hz, 1H), 7.45 (d, *J* 6.1 Hz, 2H), 7.37 (d, *J* 2.1 Hz, 1H), 7.20 (dd, *J* 2.4, 8.9 Hz, 1H), 4.17 (q, *J* 6.9 Hz, 2H), 3.58-3.55 (m, 1H), 3.31-3.29 (m, 1H), 3.27-3.20 (m, 1H), 3.01-2.97 (m, 1H) 2.84 (s, 3H), 2.26-2.17 (m, 1H), 1.90-1.79 (m, 1H), 1.79-1.68 (m, 2H), 1.41 (t, *J* 7.0 Hz, 3H), 1.37 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.0, 152.9, 149.5, 142.5, 133.9, 131.7, 130.0, 129.5, 128.3, 127.4, 127.2, 127.1, 125.7, 120.5, 119.5, 106.6, 63.2, 54.2, 45.7, 36.0, 34.5, 33.2, 24.0, 21.2, 14.6; IR (thin film, ATR) ν_{max} / cm^{-1} 2927 (w), 2852 (w), 1628 (w), 1602 (s), 1506 (w), 1470 (w), 1423 (w), 1389 (w), 1331 (s), 1267 (w), 1208 (w), 1175 (w), 1150 (s), 1042 (w), 989 (w), 956 (m), 931 (w), 858 (w), 830 (w), 783 (m), 666 (w); HRMS (ESI(+)-TOF) *m/z* [M + H]$^+$ calcd. for $C_{27}H_{31}N_4O_3S$: 491.21114; found: 491.21117; MP 223.8 °C (decomp.).

4-(2-(Piperidin-4-yl)-5-(6-(2,2,2-trifluoroethoxy)naphthalen-2-yl)-1*H*-imidazol-4-yl)pyridine (**14t**)



Reaction scale: 0.10 mmol

General procedure A (imidazole condensation)

Amounts employed: 1-(pyridin-4-yl)-2-(6-(2,2,2-trifluoroethoxy)naphthalen-2-yl)ethane-1,2-dione (**10b**, 36 mg, 0.10 mmol, 1.0 equiv.), *tert*-butyl 4-formylpiperidine-1-carboxylate (**12a**, 28 mg, 0.130 mmol, 1.30 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.); *t*-BuOH (1.00 mL, 0.1 M).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes and then with EtOAc:EtOH (3:1) in hexanes [Biotage Isolera, SNAP KP-Sil 10 g, 50% → 70% EtOAc/hexanes then 30% → 100% EtOAc:EtOH (3:1 v/v)/hexanes, 18 mL fractions] to afford **13t** (46 mg, 83%) as a white solid.

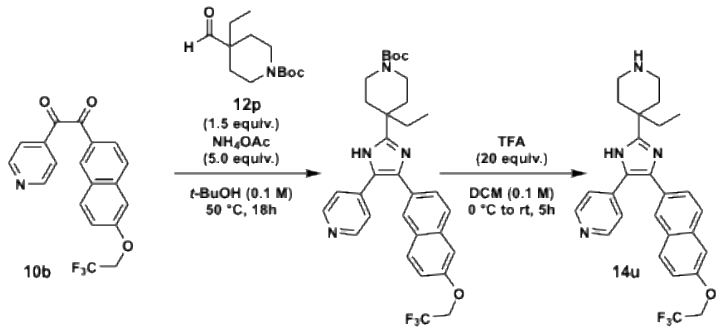
General procedure B (Boc deprotection)

Amounts employed: *N*-Boc piperidine imidazole (**13t**, 28 mg, 0.50 mmol, 1.0 equiv.), DCM (0,5 mL), TFA (77 µL, 1.0 mmol, 20 equiv.). The reaction mixture was left to stir for 1 h at room temperature.

The residue was purified by silica gel chromatography, eluted with MeOH:NH_4OH (9:1 v/v) in DCM [10 cm × 15 mm, gradient elution, 10% → 20% MeOH:NH_4OH (9:1 v/v)/DCM, 1% increases, 30 mL runs, 5 mL fractions] to afford a white solid which was dissolved in 10% MeOH/DCM (10 mL) and partitioned in 2.0 M aq. NaOH (10 mL). The layers were separated and the aqueous layer was extracted with 10% MeOH/DCM (5 × 5 mL). The organic layers were combined, washed with brine (1 × 5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **14t** (12 mg, 53%) as a white solid.

R_f = 0.17 [10% MeOH:NH_4OH (9:1)/DCM, UV, Dragendorff]; ^{1}H NMR (500 MHz, CD_3OD) δ 8.27 (d, *J* 5.3 Hz, 2H), 7.82 (s, 1H), 7.73 (dd, *J* 16.3, 8.7 Hz, 2H), 7.41-7.34 (m, 3H), 7.30 (d, *J* 2.5 Hz, 1H), 7.16 (dd, *J* 9.0, 2.5 Hz, 1H), 4.58 (q, *J* 8.4 Hz, 2H), 3.20-3.13 (m, 2H), 2.96 (tt, *J* 11.9, 3.8 Hz, 1H), 2.81-2.71 (m, 2H), 2.03-1.95 (m, 2H), 1.83 (qd, *J* 12.4, 3.9 Hz, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ 157.4, 154.0, 150.1, 143.9, 135.5, 131.1, 131.0, 128.8, 128.7, 128.6, 128.2, 125.2 (q, *J* 277.0 Hz), 123.1, 120.0, 108.8, 66.5 (q, *J* 35.3 Hz), 46.3, 36.9, 31.4; note: due to slow relaxation of carbon bound nitrogen some ^{13}C NMR signals are not detected. In this case, 2 signals are missing; ^{19}F NMR (235 MHz, CD_3OD) δ –75.57; IR (thin film, ATR) ν_{max} / cm^{-1} 2917 (br), 1601 (s), 1537 (w), 1509 (w), 1473 (w), 1390 (w), 1285 (m), 1256 (m), 1212 (m), 1164 (s), 1130 (w), 1067 (w), 1009 (w), 995 (w), 974 (m), 921 (w), 895 (w), 856 (w), 833 (m), 811 (w), 696 (w), 669 (m); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{25}H_{24}F_3N_4O$ 453.18967; found: 453.18955; MP 202.4 °C (decomp.) (MeOH/DCM).

4-(2-(4-Ethylpiperidin-4-yl)-5-(6-(2,2,2-trifluoroethoxy)naphthalen-2-yl)-1*H*-imidazol-4-yl)pyridine (**14u**)



Reaction scale: 0.10 mmol

General procedure A (imidazole condensation)

Amounts employed: 1-(pyridin-4-yl)-2-(6-(2,2,2-trifluoroethoxy)naphthalen-2-yl)ethane-1,2-dione (**10b**, 36 mg, 0.10 mmol, 1.0 equiv.), *tert*-butyl 3-formyl-3-ethylpiperidine-1-carboxylate (**12p**, 36 mg, 0.15 mmol, 1.5 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.), *t*-BuOH (1 mL, 0.1 M).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes and then with EtOAc:EtOH (3:1 v/v) in hexanes [Biotage Isolera, SNAP Ultra KP-Sil 10 g, 50% → 70% EtOAc/hexanes and then 20% → 50% EtOAc:EtOH (3:1 v/v)/hexanes, 15 mL fractions] to afford the corresponding imidazole as a mixture of compounds (27 mg) as a light yellow solid. R_f = 0.47 [50% EtOAc:EtOH (3:1 v/v)/hexanes, UV, Dragendorff].

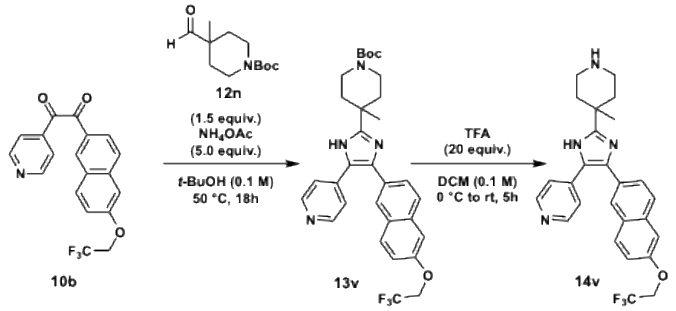
General procedure B (Boc deprotection)

Amounts employed: mixture of compounds above (27 mg), DCM (0.6 mL), TFA (72 µL, 0.93 mmol, 20 equiv.).

The reaction mixture was stirred for 3 h and the residue was purified by silica gel chromatography, eluted with MeOH: 28% NH_4OH (9:1 v/v) in DCM [10 cm × 15 mm, gradient elution, 10% → 20% MeOH: 28% NH_4OH (9:1 v/v)/DCM, 1% increases, 10 mL runs, 3 mL fractions] to afford a residue which was diluted with 10% MeOH/DCM (10 mL) and partitioned in 2 M aq. NaOH (5 mL). The layers were separated and the aqueous layer was extracted with 10% MeOH/DCM (5 × 5 mL). The organic layers were combined, washed with brine (2 × 5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a white solid which was triturated with hexanes (3 × 3 mL) to afford **14u** (12 mg, 25% for two steps) as a white solid.

R_f = 0.05 [10% MeOH:NH_4OH (9:1 v/v)/DCM, UV, Dragendorff]; ^{1}H NMR (500 MHz, CD_3OD) δ 8.36 (d, *J* 6.3 Hz, 2H), 7.93 (d, *J* 1.2 Hz, 1H), 7.85 (d, *J* 8.7 Hz, 1H), 7.83 (d, *J* 9.6 Hz, 1H), 7.50 (d, *J* 6.3 Hz, 2H), 7.48 (dd, *J* 8.5, 1.8 Hz, 1H), 7.40 (d, *J* 2.5 Hz, 1H), 7.26 (dd, *J* 8.9, 2.6 Hz, 1H), 4.69 (q, *J* 8.4 Hz, 2H), 2.94 (dt, *J* 12.9, 3.7 Hz, 2H), 2.79-2.72 (m, 2H), 2.48-2.41 (m, 2H), 1.75 (q, *J* 7.4 Hz, 2H), 1.72-1.63 (m, 2H), 0.79 (t, *J* 7.5 Hz, 3H); ^{19}F NMR (235 MHz, CD_3OD) δ –75.6; ^{13}C NMR (126 MHz, CD_3OD) δ 157.4, 154.9, 149.9, 144.2, 135.5, 134.2, 132.0, 131.1, 131.0, 128.9, 128.9, 128.7, 128.6, 125.2 (q, *J* 276.9 Hz), 123.4, 119.9, 108.8, 66.5 (q, *J* 35.5 Hz), 43.9, 41.1, 36.9, 35.9, 8.5; IR (thin film, ATR) ν_{max} / cm^{-1} 2936 (br. s), 1601 (s), 1525 (w), 1500 (w), 1459 (w), 1422 (w), 1398 (w), 1284 (m), 1253 (m), 1210 (m), 1163 (s), 1127 (w), 1067 (w), 1006 (w), 992 (w), 975 (m), 922 (w), 897 (w), 854 (w), 833 (s), 811 (w), 697 (w), 669 (m), 645 (w); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{27}H_{28}F_3N_4O$: 481,22097; found 481.22046; MP 203.9-205.4 °C (MeOH).

4-(2-(4-Methylpiperidin-4-yl)-5-(6-(2,2,2-trifluoroethoxy)naphthalen-2-yl)-1*H*-imidazol-4-yl)pyridine (**14v**)



Reaction scale: 0.10 mmol

General procedure A (imidazole condensation)

Amounts employed: 1-(pyridin-4-yl)-2-(6-(2,2,2-trifluoroethoxy)naphthalen-2-yl)ethane-1,2-dione (**10b**, 36 mg, 0.10 mmol, 1.0 equiv.), *tert*-butyl 4-formyl-4-methylpiperidine-1-carboxylate (**12n**, 27 mg, 0.12 mmol, 1.2 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.); *t*-BuOH (1 mL, 0.1 M).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes and then with EtOAc:EtOH (3:1 v/v) in hexanes [Biotage Isolera, SNAP Ultra KP-Sil 10 g, 50% → 70% EtOAc/Hexanes and then 30% → 55% EtOAc:EtOH (3:1)/Hexanes, 15 mL fractions] to afford **13v** (34 mg, 60%) as a white solid.

^{1}H NMR (250 MHz, $CDCl_3$) δ 9.56 (s, 1H), 9.38 (s, 1H), 8.58-8.36 (m, 2H), 7.90-7.67 (m, 3H), 7.59-7.37 (m, 3H), 7.31-7.12 (m, 2H) 4.49 (q, *J* 8.1 Hz, 2H), 3.77-3.58 (m, 2H), 3.49-3.27 (m, 2H), 2.33-2.13 (m, 2H), 1.76-1.60 (m, 2H), 1.46 (s, 9H), 1.43 (s, 3H); ^{19}F NMR (235 MHz, $CDCl_3$) δ –73.71.

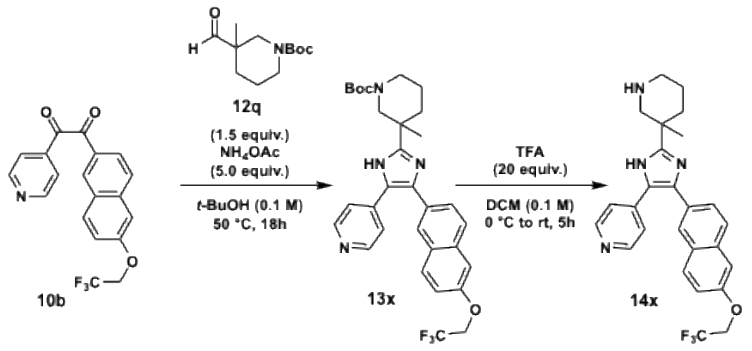
General procedure B (Boc deprotection)

Amounts employed: *N*-Boc piperidine imidazole (28 mg, 0.50 mmol, 1.0 equiv.), DCM (0.5 mL), TFA (77 µL, 1.00 mmol, 20 equiv.).

The residue was purified by silica gel chromatography, eluted with MeOH: 28% NH_4OH (9:1 v/v) in DCM [10 cm × 15 mm, gradient elution, 10% → 20% MeOH: 28% NH_4OH (9:1 v/v)/DCM, 1% increases, 10 mL runs, 3 mL fractions] to afford a residue which was diluted with 10% MeOH/DCM (10 mL) and partitioned in 2 M aq. NaOH. The layers were separated and the aqueous layer was extracted with 10% MeOH/DCM (5 × 5 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a white solid which was triturated with hexanes (2 × 3 mL) to afford **14v** (17 mg, 73%) as a white solid.

R_f = 0.33 [20% MeOH:NH_4OH (9:1 v/v)/DCM, UV, Dragendorff]; ^{1}H NMR (500 MHz, CD_3OD) δ 8.36 (d, *J* 6.1 Hz, 2H), 7.94-7.92 (m, 1H), 7.85 (d, *J* 8.6 Hz, 1H), 7.83 (d, *J* 9.1 Hz, 1H), 7.50 (d, *J* 6.4 Hz, 2H), 7.48 (dd, *J* 8.4, 1.7 Hz, 1H), 7.40 (d, *J* 2.5 Hz, 1H), 7.26 (dd, *J* 8.9, 2.6 Hz, 1H), 4.69 (q, *J* 8.4 Hz, 2H), 2.94 (dt, *J* 12.7, 4.1 Hz, 2H), 2.81 (ddd, *J* 12.7, 9.8, 2.8 Hz, 2H), 2.41-2.33 (m, 2H), 1.71 (ddd, *J* 13.5, 9.7, 3.6 Hz, 2H), 1.40 (s, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 157.4, 156.8, 149.9, 144.2, 135.5, 131.1, 131.0, 130.1, 129.9, 128.9, 128.7, 128.5, 125.2 (q, *J* 276.8 Hz), 123.3, 119.9, 108.8, 66.5 (q, *J* 35.5 Hz), 43.6, 37.5, 36.9, 29.3; note: due to slow relaxation of carbon bound nitrogen some ^{13}C NMR signals are not detected. In this case, 1 signal is missing; ^{19}F NMR (235 MHz, CD_3OD) δ –75.6; IR (thin film, ATR) ν_{max} / cm^{-1} 2935 (br. s), 1601 (s), 1534 (w), 1503 (w), 1473 (w), 1459 (w), 1420 (w), 1392 (w), 1283 (w), 1251 (m), 1212 (w), 1163 (s), 1064 (w), 1006 (w), 992 (w), 974 (m), 922 (w), 897 (w), 853 (w), 808 (w), 736 (w), 700 (w); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{26}H_{26}F_3N_4O$: 467.20532; found 467.20536; MP 235.5 °C (decomp.).

4-(2-(3-Methylpiperidin-3-yl)-5-(6-(2,2,2-trifluoroethoxy)naphthalen-2-yl)-1*H*-imidazol-4-yl)pyridine (**14x**)



Reaction scale: 0.10 mmol

General procedure A (imidazole condensation)

Amounts employed: 1-(pyridin-4-yl)-2-(6-(2,2,2-trifluoroethoxy)naphthalen-2-yl)ethane-1,2-dione (**10b**, 36 mg, 0.10 mmol, 1.0 equiv.), *tert*-butyl 3-formyl-3-methylpiperidine-1-carboxylate (**12q**, 27 mg, 0.12 mmol, 1.20 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.), *t*-BuOH (1 mL, 0.1 M), TFA (153 μL, 1.0 mmol, 20 equiv.), DCM (1 mL).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes and then with EtOAc:EtOH (3:1 v/v) in hexanes [Biotage Isolera, SNAP Ultra KP-Sil 10 g, 50% → 70% EtOAc/hexanes and then 30% → 100% EtOAc:EtOH (3:1 v/v)/hexanes, 15 mL fractions] to afford **13x** (31 mg, 55%) as a white solid.

R_f = 0.33 [50% EtOAc:EtOH (3:1 v/v)/hexanes, UV, Dragendorff]. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.51-8.42 (m, 2H), 8.07-7.84 (m, 1H), 7.80-7.61 (m, 2H), 7.59-7.43 (m, 2H), 7.39-7.30 (m, 1H), 7.26-7.09 (m, 2H), 4.64-4.41 (m, 3H), 4.19-3.93 (m, 1H), 2.91-2.65 (m, 3H), 1.67-1.49 (m, 3H), 1.40-1.24 (m, 12H); ^{19}F NMR (235 MHz, $CDCl_3$) δ –73.75, –73.77; note: the two peaks in the ^{19}F NMR spectra refers to the mixture of imidazole tautomers in solution.

General procedure B (Boc deprotection)

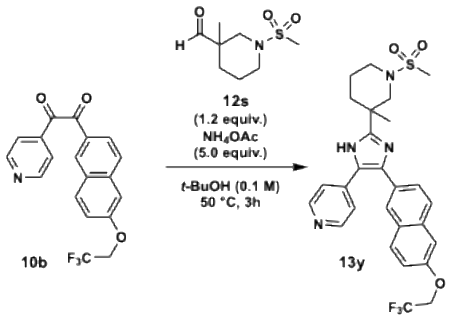
Amounts employed: *N*-Boc piperidine imidazole (**13x**, 25 mg, 0.044 mmol, 1.0 equiv.), DCM (0.5 mL), TFA (68 μL, 0.88 mmol, 20 equiv.).

The residue was purified by silica gel chromatography, eluted with MeOH: 28% NH_4OH (9:1 v/v) in DCM [10 cm × 15 mm, gradient elution, 10% → 20% MeOH: 28% NH_4OH (9:1 v/v)/DCM, 1% increases, 10 mL runs, 3 mL fractions] to afford a residue which was diluted with 10% MeOH/DCM (10 mL) and partitioned in 2 M aq. NaOH (5 mL). The layers were separated and the aqueous layer was extracted with 10% MeOH/DCM (5 × 5 mL). The organic layers were combined, washed with brine (2 × 5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a white solid which was triturated with hexanes (3 × 3 mL) to afford **14x** (14 mg, 68%) as a white solid.

R_f = 0.33 [20% MeOH:NH_4OH (9:1)/DCM, UV, Dragendorff]; ^{1}H NMR (500 MHz, CD_3OD) δ 8.35 (d, *J* 6.3 Hz, 2H), 7.95 (s, 1H), 7.86 (d, *J* 8.6 Hz, 1H), 7.83 (d, *J* 9.1 Hz, 1H), 7.53 (d, *J* 6.3 Hz, 2H), 7.50 (dd, *J* 8.5, 1.6 Hz, 1H), 7.41 (d, *J* 2.3 Hz, 1H), 7.26 (dd, *J* 8.9, 2.5 Hz, 1H), 4.69 (q, *J* 8.4 Hz, 2H), 3.58-3.52 (m, 1H), 2.97-2.88 (m, 1H), 2.73-2.64 (m, 2H), 2.38-2.31 (m, 1H), 1.77-1.68 (m, 1H), 1.66-1.58 (m, 1H), 1.56-1.45 (m, 1H), 1.34 (s, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 157.4, 156.0, 149.9, 144.4, 135.5, 131.1, 131.0, 130.1, 129.9, 128.8, 128.7, 128.5, 125.2 (q, *J* 276.5 Hz), 123.1, 123.0, 119.9, 108.8, 66.5 (q, *J* 35.4 Hz), 56.1, 46.7, 37.3, 36.9, 26.7, 24.2. ^{19}F NMR (235 MHz, CD_3OD) δ –75.6; IR (thin film, ATR) ν_{max} / cm^{-1} 2919 (br. s), 1633 (w), 1600 (s), 1531 (w), 1502 (w), 1459 (w), 1417 (w), 1392 (w), 1285 (m), 1255 (m), 1213 (w), 1163 (s), 1106 (s), 993 (w), 975 (m), 944 (w), 898 (w), 833 (m), 810 (w),

757 (w), 742 (w), 702 (w), 668 (m), 639 (w); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{26}H_{26}F_3N_4O$: 467.20532; found 467.20534; MP 201.1-203.0 °C (MeOH).

4-(2-(3-Methyl-1-(methylsulfonyl)piperidin-3-yl)-5-(6-(2,2,2-trifluoroethoxy)naphthalen-2-yl)-1*H*-imidazol-4-yl)pyridine (**13y**)



Reaction scale: 0.10 mmol

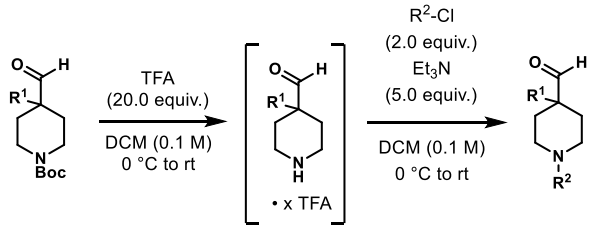
General procedure A (imidazole condensation)

Amounts employed: 1-(pyridin-4-yl)-2-(6-(2,2,2-trifluoroethoxy)naphthalen-2-yl)ethane-1,2-dione (**10b**, 36 mg, 0.10 mmol, 1.0 equiv.), 3-methyl-1-(methylsulfonyl)piperidine-3-carbaldehyde (**12s**, 23 mg, 0.11 mmol, 1.1 equiv.), NH_4OAc (39 mg, 0.50 mmol, 5.0 equiv.); *t*-BuOH (1 mL, 0.1 M).

The reaction mixture was stirred for 3 h and the residue was purified by silica gel chromatography, eluted with EtOAc in hexanes and then with EtOAc:EtOH (3:1 v/v) in hexanes [Biotage Isolera, SNAP KP-Sil 10 g, 50% → 70% EtOAc/hexanes then 30% → 70% EtOAc:EtOH (3:1)/hexanes, 18 mL fractions] to afford a light yellow solid which was repurified by silica gel chromatography, eluted with MeOH in DCM (21 cm × 15 mm, gradient elution, 0% → 5% MeOH/DCM, 0.5% increases, 30 mL runs, 5 mL fractions) to afford **13y** (23 mg, 42%) as a white solid.

R_f = 0.25 [70% EtOAc:EtOH (3:1)/Hexanes, UV, Dragendorff]; ^{1}H NMR (500 MHz, CD_3OD) δ 8.37 (s, 2H), 7.94 (s, 1H), 7.87-7.80 (m, 2H), 7.58-7.45 (m, 3H), 7.40 (d, *J* 2.2 Hz, 1H), 7.26 (dd, *J* 8.9, 2.0 Hz, 1H), 4.68 (q, *J* 8.4 Hz, 2H), 4.57 (s, 1H), 3.95-3.84 (m, 1H), 3.30-3.28 (m, 1H), 3.26-3.20 (m, 1H), 2.85 (s, 3H), 2.43-2.34 (m, 1H), 1.88-1.81 (m, 2H), 1.81-1.74 (m, 1H), 1.45 (s, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 157.4, 151.0, 149.9, 135.5, 131.2, 131.0, 128.8, 128.4, 125.2 (q, *J* 277.0 Hz), 123.3, 120.0, 108.8, 66.5 (q, *J* 35.6 Hz), 55.5, 47.2, 38.1, 35.4, 35.3, 25.4, 23.2; note: due to slow relaxation of carbon bound nitrogen some ^{13}C NMR signals are not detected. In this case, 5 signals are missing; IR (thin film, ATR) ν_{max} / cm^{-1} 1602 (s), 1542 (w), 1503 (w), 1473 (w), 1338 (w), 1295 (w), 1252 (w), 1210 (w), 1167 (s), 1152 (s), 1125 (w), 1066 (w), 993 (w), 973 (w), 893 (w), 855 (w), 835 (m), 808 (w), 780 (m), 668 (m); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ calcd. for $C_{27}H_{28}F_3N_4O_3S$: 545.18287; found 545.18321; MP 207.6 °C (decomp.).

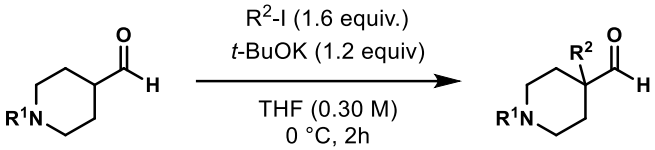
General procedure D – Sequential deprotection and nitrogen substitution[2]



A 25 mL round-bottom flask was charged with the corresponding aldehyde (1.00 equiv.) and a magnetic stirring bar under nitrogen. Then, DCM (0.1 M) was added, and the solution was cooled to 0 °C in an ice-water bath. After stirring

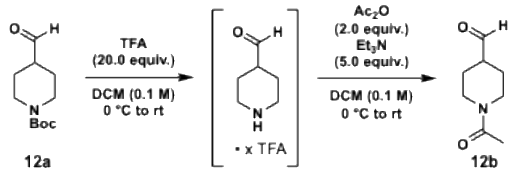
for 5 min, TFA (20 equiv.) was added dropwise, and the reaction mixture was left to warm to room temperature and stirred for 1 h. After consumption of the starting material (30% EtOAc/hexanes), the solvent and excess trifluoroacetic acid were removed under reduced pressure and the residue was redissolved in DCM (0.1 M). The solution was cooled to 0 °C in an ice-water bath and was stirred for 5 min. Then, Et_3N (5.0 equiv.) was added, followed by addition of the corresponding electrophile (2.0 equiv.). The reaction mixture was let to warm to room temperature and stirred for 16 h. After consumption of the intermediate monitored by TLC (eluent: 30% EtOAc/hexanes), the reaction mixture was diluted with DCM (10 mL $mmol^{-1}$) and partitioned into satd. aq. $NaHCO_3$ (10 mL $mmol^{-1}$). The layers were separated and the aqueous layer was extracted with DCM (3 × 10 mL $mmol^{-1}$). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography.

General procedure E - α-alkylation of aldehydes



A round-bottom flask was charged with the corresponding aldehyde (1.00 equiv.) and a magnetic stirring bar under nitrogen. Then, THF (2.05 mL *per* mmol of aldehyde) was added, and the solution was cooled to 0 °C in an ice-water bath. After 15 min, *t*-BuOK (1.20 equiv., 1.0 M in THF) was added, followed by the addition of MeI (1.60 equiv.) and the reaction mixture was stirred at 0 °C for 2 h. After consumption of the starting material indicated by TLC analysis, the reaction mixture was quenched with satd. NH_4Cl (4.1 mL *per* mmol of aldehyde) and additional water was added to dissolve precipitated solids. The aqueous layer was extracted with DCM (3 × 3 mL *per* mmol of aldehyde) and the organic layers were combined, washed with brine (1 × 3 mL *per* mmol of aldehyde), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography.

1-Acetylpiperidine-4-carbaldehyde (**12b**)



General procedure D

Reaction scale: 1.0 mmol

Boc deprotection

Amounts employed: *tert*-butyl 4-formylpiperidine-1-carboxylate (**12a**, 215 mg, 1.00 mmol, 1.0 equiv.); TFA (1.53 mL, 20.0 mmol, 20.0 equiv.); DCM (10 mL).

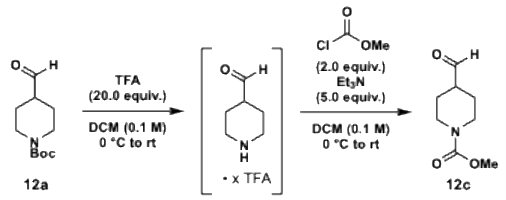
Nitrogen acylation

Amounts employed: residue from previous step (420 mg); DCM (10 mL), Et_3N (704 mL, 5.00 mmol, 5.0 equiv.), Ac_2O (195 mL, 2.00 mmol, 2.0 equiv.).

The residue was purified by silica gel chromatography, eluted with EtOAc (8 cm × 20 mm, gradient elution, EtOAc, isocratic elution, 300 mL runs, 15 mL fractions) to afford **12b** (97 mg, 63%) as a translucent oil.

R_f = 0.13 (EtOAc/hexanes, 2,4-DNPH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.67 (s, 1H), 4.42-4.26 (m, 1H), 3.83-3.70 (m, 1H), 3.27-3.10 (m, 1H), 3.02-2.80 (m, 1H), 2.61-2.44 (m, 1H), 2.10 (s, 3H), 2.01-1.90 (m, 2H), 1.77-1.52 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.6, 178.1, 169.4, 47.8, 45.8, 45.5, 41.0, 40.8, 40.6, 28.4, 27.8, 25.8, 25.1, 21.5; note: Extra peaks are due to the presence of E/Z amide rotamers; IR (thin film, ATR) ν_{max} / cm^{-1} 3402 (br), 2929 (w), 2858 (w), 1721 (m), 1621 (s), 1448 (m), 1368 (w), 1271 (w), 1230 (w), 1113 (w), 1036 (w), 994 (w), 962 (w); HRMS (ESI(+)-TOF) *m/z* peak not found under standard HRMS analysis.

Methyl 4-formylpiperidine-1-carboxylate (**12c**)



General procedure D

Reaction scale: 1.0 mmol

Boc deprotection

Amounts employed: *tert*-butyl 4-formylpiperidine-1-carboxylate (**12a**, 215 mg, 1.00 mmol, 1.0 equiv.); TFA (1.53 mL, 20.0 mmol, 20.0 equiv.); DCM (10 mL).

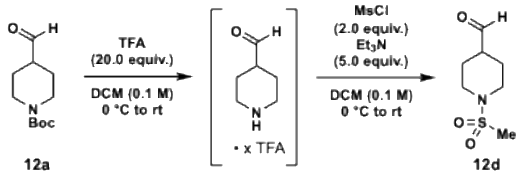
Nitrogen acylation

Amounts employed: residue from previous step (418 mg), DCM (10 mL), Et_3N (704 mL, 5.0 mmol, 5.0 equiv.), methyl chloroformate (156 mL, 2.0 mmol, 2.0 equiv.).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes (16 cm × 20 mm, gradient elution, 20% → 70% EtOAc/hexanes, 10% increases, 50 mL runs, 15 mL fractions) to afford **12c** (162 mg, 95%) as a translucent oil.

R_f = 0.18 (30% EtOAc/hexanes, 2,4-DNPH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.65 (s, 1H), 4.24-3.85 (m, 2H), 3.68 (s, 3H), 3.06-2.84 (m, 2H), 2.43 (ddd, *J* 14.4, 10.2, 3.7 Hz, 1H), 1.96-1.83 (m, 2H), 1.62-1.47 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.9, 156.0, 52.8, 47.9, 43.1, 25.2; IR (thin film, ATR) ν_{max} / cm^{-1} 3401 (br), 2954 (w), 2868 (w), 1682 (s), 1479 (m), 1450 (s), 1412 (m), 1378 (w), 1277 (w), 1233 (m), 1191 (m), 1138 (w), 1090 (w), 1030 (w), 955 (w), 927 (w), 794 (w), 768 (m); HRMS (ESI(+)-TOF) *m/z* Peak not found under standard HRMS analysis.

1-(Methylsulfonyl)piperidine-4-carbaldehyde (**12d**)



General procedure D

Reaction scale: 1.0 mmol

Boc deprotection

Amounts employed: *tert*-butyl 4-formylpiperidine-1-carboxylate (**12a**, 215 mg, 1.00 mmol, 1.0 equiv.); TFA (1.53 mL, 20.0 mmol, 20.0 equiv.); DCM (10 mL).

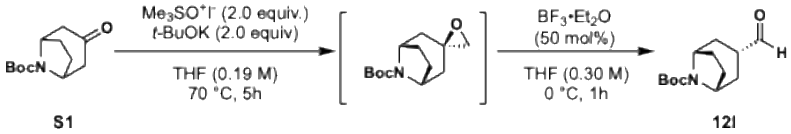
Nitrogen sulfonylation

Amounts employed: residue from previous step (418 mg); DCM (10 mL), Et_3N (704 mL, 5.0 mmol, 5.0 equiv.), mesyl chloride (160 mL, 2.0 mmol, 2.0 equiv.).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes (16 cm × 20 mm, gradient elution, 50% → 100% EtOAc/hexanes, 10% increases, 50 mL runs, 15 mL fractions) to afford **12d** (169 mg, 88%) as white solid.

R_f = 0.32 (70% EtOAc/hexanes, 2,4-DNPH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (s, 1H), 3.65-3.57 (m, 2H), 2.99-2.91 (m, 2H), 2.78 (s, 3H), 2.47-2.37 (m, 1H), 2.09-2.00 (m, 2H), 1.86-1.75 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.3, 46.9, 45.0, 35.3, 25.1; IR (thin film, ATR) ν_{max} / cm^{-1} 2924 (w), 2857 (w), 1713 (m), 1470 (w), 1438 (w), 1316 (s), 1247 (w), 1147 (s), 1105 (m), 1065 (m), 956 (s), 926 (s), 780 (s), 674 (w); HRMS (ESI(+)-TOF) *m/z* peak not found under standard HRMS analysis; MP 87.6-89.8 °C (EtOAc).

tert-Butyl 3-formyl-8-azabicyclo[3.2.1]octane-8-carboxylate (**12l**)



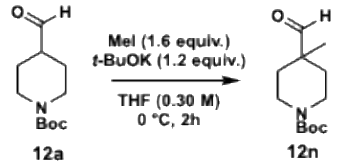
A 25 mL round-bottom flask was charged with trimethylsulfoxonium iodide (898 mg, 4.0 mmol, 2.0 equiv.) and a magnetic stirring bar under nitrogen. Then, THF (8.6 mL) was added followed by addition of *t*-BuOK (472 mg, 4.0 mmol, 2.0 equiv.) in portions. The mixture was heated to reflux and stirred for 4 h. A solution of *tert*-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (**S1**, 460 mg, 2.0 mmol, 1.0 equiv.) in THF (2.0 mL) was added in one portion. The reaction was further stirred at reflux for 1 h. After consumption of the starting material, indicated by TLC analysis, the reaction mixture was diluted with toluene (3 mL) and water (10 mL). The layers were separated, and the aqueous layer was extracted with toluene (3 × 8 mL). The organic layers were combined, washed with brine (1 × 8 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a translucent oil (410 mg) which was used in the next step without further purification.

A 25 mL round-bottom flask was charged with the crude oil (410 mg) obtained in the previous step and a magnetic stirring bar under nitrogen. Then, THF (6 mL) was added, and the solution was cooled to 0 °C and stirred for 5 min before the dropwise addition of BF_3•Et_2O (106 µL, 0.86 mmol, 50 mol%). The reaction mixture was stirred at 0 °C

for 1 h. After consumption of the starting material, indicated by TLC analysis, satd. $NaHCO_3$ (5 mL) was added followed by addition of EtOAc (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (4 × 6 mL). The organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes (19 cm × 20 mm, gradient elution, 0% → 30% EtOAc/Hexanes, 5% increases, 60 mL runs, 10 mL fractions) to afford **12l** (234 mg, 49% for 2 steps) as translucent oil.

^{1}H NMR (250 MHz, $CDCl_3$) δ 9.55 (d, J 1.4 Hz, 1H), 4.30 (br. s, 2H), 2.84-2.62 (m, 1H), 2.03 (dd, J 8.2, 5.0 Hz, 2H), 1.84-1.52 (m, 6H), 1.46 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 203.0, 153.3, 79.7, 52.8, 42.1, 30.4, 28.6, 28.2.

tert-Butyl 4-formyl-4-methylpiperidine-1-carboxylate (**12n**)



General procedure E

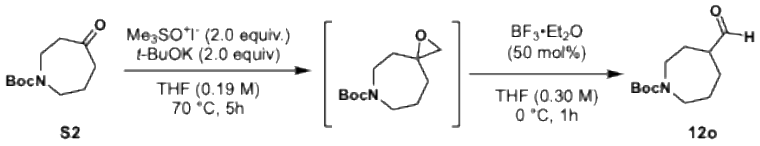
Reaction scale: 1.7 mmol

Amounts employed: 1-Boc-piperidine-4-carboxaldehyde (**12a**, 370 mg, 1.70 mmol, 1.0 equiv.); *t*-BuOK (2.10 mL, 2.10 mmol, 1.2 equiv., 1.0 M in THF); MeI (175 uL, 2.80 mmol, 1.6 equiv.); THF (3.5 mL).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes (17 cm × 20 mm, gradient elution, 5% → 30% EtOAc/hexanes, 5% increases, 75 mL runs, 15 mL fractions) to afford **12n** (198 mg, 50%) as a translucent oil (turns into a white solid when stored in the freezer at –20 °C).

R_f = 0.45 (30% EtOAc/hexanes, $KMnO_4$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.46 (s, 1H), 3.72-3.56 (m, 2H), 3.11 (ddd, J 13.5, 9.8, 3.5 Hz, 2H), 1.97-1.84 (m, 2H), 1.44 (s, 9H), 1.42-1.31 (m, 2H), 1.07 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 205.2, 154.9, 79.8, 45.1, 40.7, 31.8, 28.6, 21.3; IR (thin film, ATR) ν_{max} / cm^{-1} 2976 (w), 2929 (w), 2868 (w), 1726 (m), 1694 (s), 1476 (w), 1457 (w), 1422 (m), 1366 (m), 1279 (m), 1251 (m), 1165 (s), 1127 (w), 1090 (w), 1001 (w), 974 (w), 941 (w), 890 (w), 863 (w), 770 (w), 747 (w); HRMS (ESI(+)-TOF) *m/z* calcd. for $C_{12}H_{21}NO_3Na^+$: 250.14136; found 250.14093.

tert-Butyl 4-formylazepane-1-carboxylate (**12o**)



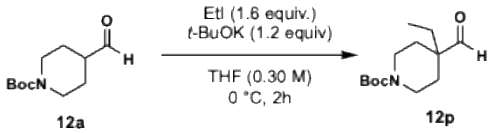
A 25 mL round-bottom flask was charged with trimethylsulfoxonium iodide (898 mg, 4.0 mmol, 2.0 equiv.) and a magnetic stirring bar under nitrogen. Then, THF (8.6 mL) was added followed by addition of *t*-BuOK (472 mg, 4.0 mmol, 2.0 equiv.) in portions. The mixture was heated to reflux and stirred for 4 h. A solution of *tert*-butyl-4-oxoazepane-1-carboxylate (**S2**, 435 mg, 2.0 mmol, 1.0 equiv.) in THF (2.0 mL) was added in one portion. The reaction was further stirred at reflux for 1 h. After consumption of the starting material, indicated by TLC analysis, the reaction mixture was diluted with toluene (3 mL) and water (10 mL). The layers were separated, and the aqueous layer was extracted with toluene (3 × 8 mL). The organic layers were combined, washed with brine (1 × 8 mL), dried over Na_2SO_4,

filtered and concentrated under reduced pressure to afford a translucent oil (410 mg) which was used in the next step without further purification.

A 25 mL round-bottom flask was charged with the crude oil (410 mg) obtained in the previous step and a magnetic stirring bar under nitrogen. Then, THF (6 mL) was added, and the solution was cooled to 0 °C and stirred for 5 min before the dropwise addition of BF_3•Et_2O (111 μL, 0.90 mmol, 50 mol%). The reaction mixture was stirred at 0 °C for 1 h. After consumption of the starting material, indicated by TLC analysis, satd. $NaHCO_3$ (5 mL) was added followed by addition of EtOAc (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (4 × 6 mL). The organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluted with acetone in hexanes (15 cm × 30 mm, gradient elution, 0% → 50% acetone/hexanes, 5% increases, 60 mL runs, 10 mL fractions) to afford **12o** (297 mg, 65% for 2 steps) as a translucent oil.

^{1}H NMR (250 MHz, $CDCl_3$) δ 9.63 (s, 1H), 3.75-3.04 (m, 4H), 2.38-2.23 (m, 1H), 2.23-1.97 (m, 2H), 1.98-1.74 (m, 2H), 1.64 (ddd, *J* 16.9, 12.7, 8.7 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 203.4 (major), 203.4 (minor), 155.4, 79.6, 51.2 (major), 50.8 (minor), 46.9 (minor), 46.3 (major), 45.1 (major), 44.7 (minor), 28.6, 27.8, 26.9 (minor), 26.9 (major), 26.6 (minor), 26.2 (major); note: major and minor rotamers are detected in the ^{13}C NMR spectrum.

tert-Butyl 4-ethyl-4-formylpiperidine-1-carboxylate (**12p**)



General procedure E

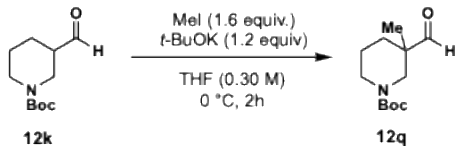
Reaction scale: 1.4 mmol

Amounts employed: 1-Boc-piperidine-4-carboxaldehyde (**12a**, 300 mg, 1.4 mmol, 1.0 equiv.); *t*-BuOK (1.70 mL, 1.70 mmol, 1.2 equiv., 1.0 M in THF); EtI (181 μL, 2.25 mmol, 1.6 equiv.); THF (3.5 mL).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes (18 cm × 20 mm, gradient elution, 5% → 25% EtOAc/hexanes, 5% increases, 75 mL runs, 15 mL fractions) to afford **12p** (136 mg, 40%) as a translucent oil.

R_f = 0.50 (30% EtOAc/Hexanes, $KMnO_4$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.44 (s, 1H), 3.89-3.70 (m, 2H), 2.97-2.79 (m, 2H), 2.00-1.87 (m, 2H), 1.52 (q, *J* 7.6 Hz, 2H), 1.43 (s, 9H), 1.41-1.31 (m, 2H), 0.80 (t, *J* 7.6 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 205.9, 154.9, 79.7, 48.8, 41.0, 30.1, 29.0, 28.6, 7.9; IR (thin film, ATR) ν_{max} / cm^{-1} 2972 (w), 2918 (w), 1725 (m), 1694 (s), 1478 (w), 1450 (w), 1423 (m), 1365 (m), 1279 (m), 1245 (s), 1165 (s), 1115 (w), 1017 (w), 978 (w), 958 (w), 913 (w), 864 (w), 825 (w), 777 (w), 743 (w), 636 (w); HRMS (ESI(+)-TOF) *m/z* calcd. for $C_{13}H_{24}NO_3$: 242.17507; found 242.17466.

tert-Butyl 3-formyl-3-methylpiperidine-1-carboxylate (**12q**)



General procedure E

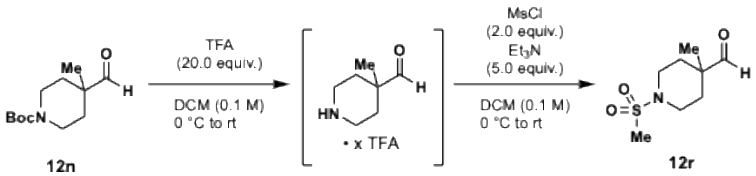
Reaction scale: 1.5 mmol

Amounts employed: 1-Boc-piperidine-3-carboxaldehyde (**12k**, 326 mg, 1.5 mmol, 1.0 equiv.); *t*-BuOK (1.80 mL, 1,80 mmol, 1.2 equiv., 1.0 M in THF); MeI (151 uL, 2.43 mmol, 1.6 equiv.); THF (3.0 mL).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes (18 cm × 20 mm, gradient elution, 5% → 25% EtOAc/hexanes, 5% increases, 70 mL runs, 15 mL fractions) to afford **12q** (130 mg, 38%) as a translucent oil.

R_f = 0.65 (30% EtOAc/hexanes, $KMnO_4$); ^1H NMR (500 MHz, $CDCl_3$) δ 9.53 (s, 1H), 4.23-3.79 (m, 1H), 3.71-3.58 (m, 1H), 3.17-2.75 (m, 2H), 2.08-1.92 (m, 1H), 1.61-1.51 (m, 2H), 1.44 (s, 9H), 1.42-1.29 (m, 1H), 1.00 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.8, 154.8, 80.0, 49.9, 46.8, 43.5, 31.2, 28.5, 21.9, 19.6; IR (thin film, ATR) ν_{max} / cm^{-1} 2974 (w), 2935 (w), 2863 (w), 1728 (m), 1693 (s), 1423 (s), 1392 (w), 1365 (m), 1279 (m), 1248 (m), 1161 (s), 1094 (w), 1008 (w), 971 (w), 915 (w), 888 (w), 863 (w), 835 (w), 769 (w); HRMS (ESI(+)-TOF) *m/z* calcd. for $C_{12}H_{21}NO_3Na^+$: 250.14136; found 250.14114.

4-Methyl-1-(methylsulfonyl)piperidine-4-carbaldehyde (**12r**)



General procedure D

Reaction scale: 0.4 mmol

Boc deprotection

Amounts employed: *tert*-butyl 4-formyl-4-methylpiperidine-1-carboxylate (**12n**, 91 mg, 0.40 mmol, 1.0 equiv.); TFA (614 µL, 8.0 mmol, 20.0 equiv.); DCM (4 mL).

Nitrogen sulfonylation

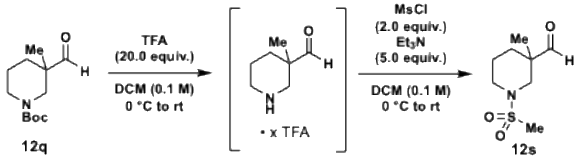
Amounts employed: residue from previous step; DCM (4 mL), Et_3N (282 mL, 2.0 mmol, 5.0 equiv.), mesyl chloride (64 mL, 0.80 mmol, 2.0 equiv.).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes (17 cm × 15 mm, gradient elution, 20% → 70% EtOAc/hexanes, 10% increases, 25 mL runs, 7 mL fractions) to afford **12r** (57 mg, 69%) as white solid.

R_f = 0.30 (50% EtOAc/hexanes, $KMnO_4$); ^1H NMR (250 MHz, $CDCl_3$) δ 9.45 (s, 1H), 3.59-3.46 (m, 2H), 2.93-2.79 (m, 2H), 2.74 (s, 3H), 2.14-2.02 (m, 2H), 1.69-1.54 (m, 2H), 1.11 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 204.7, 44.6, 43.1, 34.9, 31.7, 22.0; IR (thin film, ATR) ν_{max} / cm^{-1} 1714 (s), 1463 (w), 1345 (w), 1334 (s), 1317 (s), 1261 (w),

1216 (w), 1177 (w), 1152 (s), 1133 (w), 1051 (m), 1021 (w), 1006 (w), 970 (w), 956 (s), 932 (s), 885 (m), 811 (w), 780 (s), 753 (w), 690 (w); HRMS (ESI(+)-TOF) *m/z* calcd. for $C_8H_{16}NO_3S$: 206.08454; found 206.08447; MP 68.1-69.6 °C (EtOAc).

3-Methyl-1-(methylsulfonyl)piperidine-4-carbaldehyde (**12s**)



General procedure D

Reaction scale: 0.3 mmol

Boc deprotection

Amounts employed: *tert*-butyl 3-formyl-3-methylpiperidine-1-carboxylate (**12q**, 68 mg, 0.03 mmol, 1.0 equiv.); TFA (460 µL, 6.00 mmol, 20.0 equiv.); DCM (3 mL).

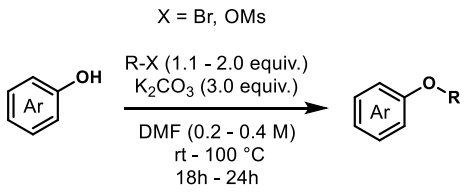
Nitrogen sulfonylation

Amounts employed: residue from previous step (177 mg); DCM (3 mL), Et_3N (211 mL, 1.50 mmol, 5.0 equiv.), mesyl chloride (48 mL, 0.6 mmol, 2.0 equiv.).

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes (168 cm × 15 mm, gradient elution, 40% → 60% EtOAc/Hexanes, 5% increases, 40 mL runs, 7 mL fractions) to afford **12s** (49 mg, 80%) as a white solid.

R_f = 0.22 (50% EtOAc/Hexanes, $KMnO_4$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.55 (s, 1H), 3.82-3.66 (m, 1H), 3.50-3.36 (m, 1H), 2.97-2.69 (m, 2H), 2.80 (s, 3H), 2.12-1.95 (m, 1H), 1.84-1.54 (m, 2H), 1.47-1.25 (m, 1H), 1.07 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 203.9, 51.6, 46.1, 46.0, 35.4, 30.6, 22.0, 19.8.

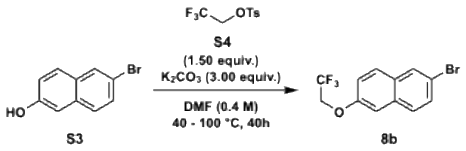
General procedure F-phenol alkylation



A 25 mL round-bottom flask was charged with the respective phenol (1.0 equiv.), K_2CO_3 (3.0 equiv.) and a magnetic stirring bar under nitrogen. DMF (0.2-0.4 M) was added, and the suspension was stirred at room temperature. After 2 min, the respective alkyl bromide or alkyl mesylate (1.1-2.0 equiv.) was added and the reaction mixture was stirred at the respective temperature and time (see below). After consumption of the starting material, indicated by TLC analysis, the reaction mixture was cooled to room temperature and water (2 mL *per* mL of DMF) was added. The reaction mixture was transferred to a separatory funnel containing Et_2O (7.5 mL mmol^{-1} of starting material). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 7.5 mL mmol^{-1} of starting material). The organic layers were combined, washed with satd. $NaHCO_3$ (1 × 2 mL *per* mL of DMF), brine:water (1:1, 5 × 2 mL *per* mL of DMF),

dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

2-Bromo-6-(2,2,2-trifluoroethoxy)naphthalene (**8b**)



General procedure H

Reaction scale: 2.0 mmol

Amounts employed: 2-bromo-6-napthol (**S3**, 455 mg, 2.00 mmol, 1.0 equiv.); K_2CO_3 (846 mg, 6.00 mmol, 3.0 equiv.); 2,2,2-trifluoroethyl *p*-toluenesulfonate (**S4**, 763 mg, 3.00 mmol, 1.5 equiv.); DMF (5 mL, 0.4 M).

The reaction mixture was heated: (*i*) to 40 °C and stirred for 18 h; (*ii*) then heated to 80 °C and stirred for 4 h and finally heated to 100 °C and stirred for 18 h.

The residue was purified by silica gel chromatography, eluted with EtOAc in hexanes (18 cm × 20 mm, 0% → 6% EtOAc/hexanes, gradient elution, 1% increases, 50 mL runs, 10 mL fractions) to afford **8b** (404 mg, 66%) as a white solid.

R_f = 0.67 (20% EtOAc/hexanes, UV, $KMnO_4$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.95 (d, *J* 1.6 Hz, 1H), 7.70 (d, *J* 9.0 Hz, 1H), 7.61 (d, *J* 8.8 Hz, 1H), 7.54 (dd, *J* 8.8, 1.9 Hz, 1H), 7.23 (dd, *J* 9.0, 2.6 Hz, 1H), 7.11 (d, *J* 2.5 Hz, 1H), 4.46 (q, *J* 8.1 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 155.6, 132.7, 130.9, 130.3, 129.9, 129.2, 128.7, 123.4 (q, *J* 277.2 Hz), 119.5, 118.3, 107.7, 65.9 (q, *J* 35.8 Hz); ^{19}F NMR (235 MHz, $CDCl_3$) δ –73.75; IR (thin film, ATR) ν_{max} / cm^{-1} 1629 (w), 1591 (w), 1502 (w), 1456 (w), 1388 (w), 1367 (w), 1279 (w), 1263 (w), 1253 (m), 1208 (s), 1175 (s), 1157 (s), 1131 (w), 1079 (m), 1062 (w), 974 (m), 962 (w), 913 (m), 877 (w), 846 (s), 814 (w), 798 (w), 664 (m), 645 (w); HRMS (ESI(+)-TOF) *m/z* $[M + H]^+$ peak not found; MP 103.4-104.6 °C (DCM).

NMR spectra

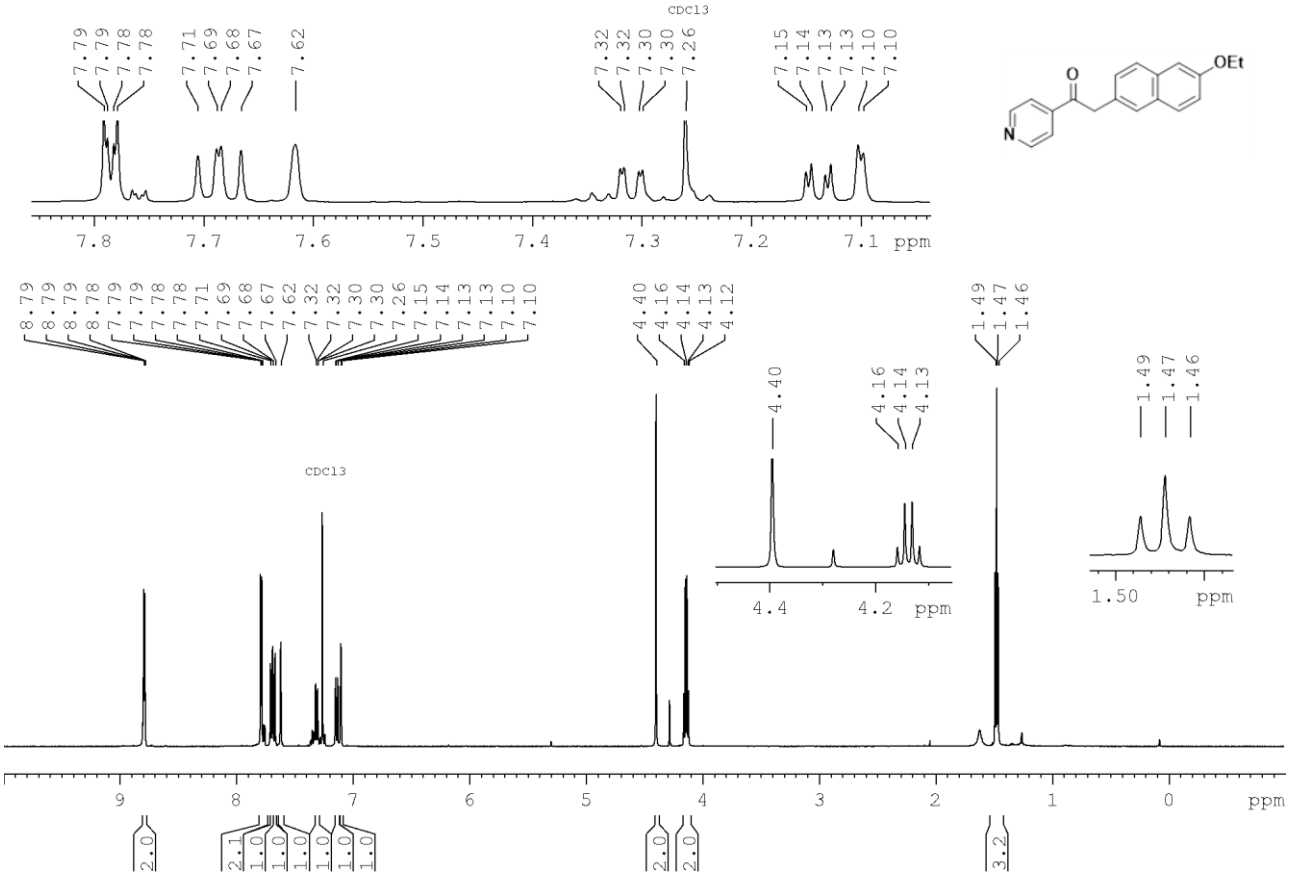


Figure S1. ^{1}H NMR spectra ($CDCl_3$, 500 MHz) of compound **9a**.

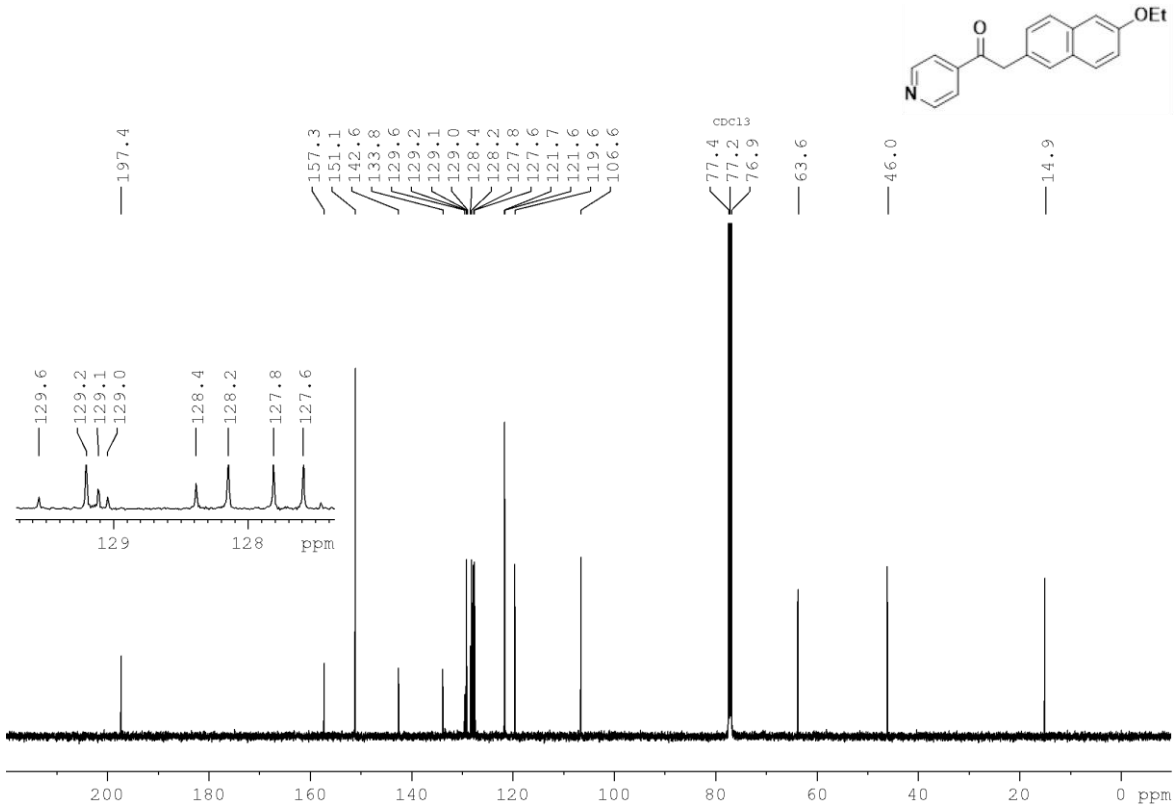


Figure S2. $^{13}C\{^{1}H\}$ NMR spectra ($CDCl_3$, 126 MHz) of compound **9a**.

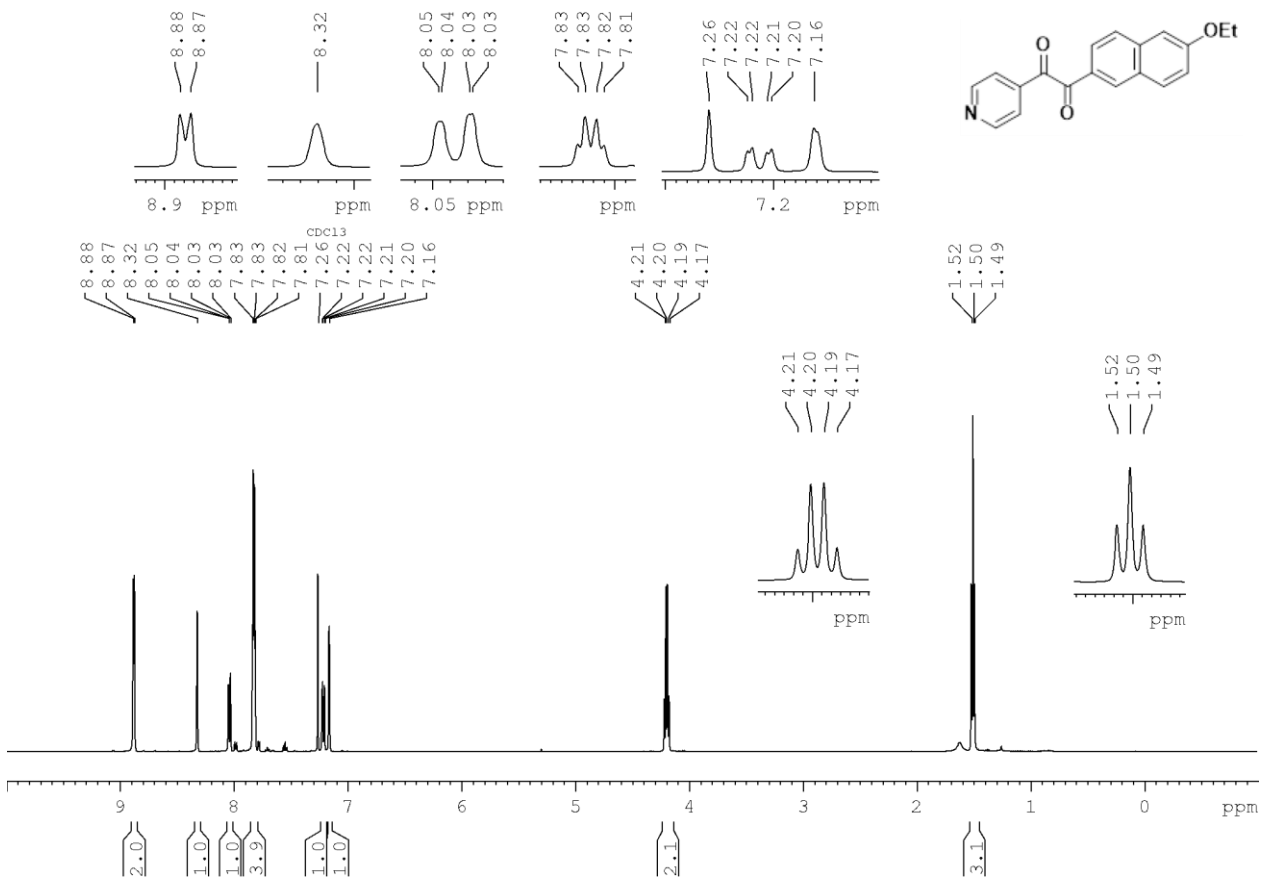


Figure S3. ^{1}H NMR spectra ($CDCl_3$, 500 MHz) of compound **10a**.

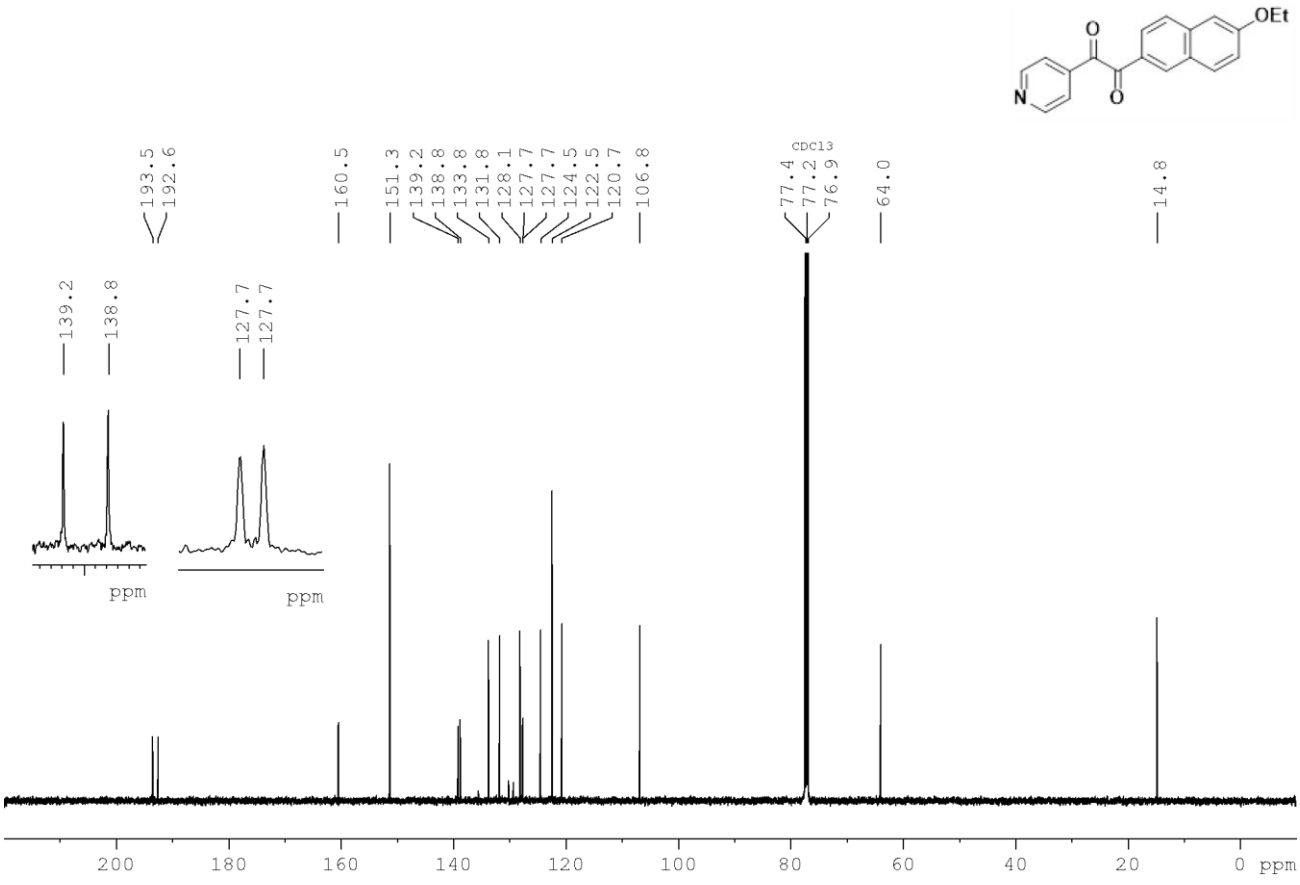


Figure S4. $^{13}C\{^{1}H\}$ NMR spectra ($CDCl_3$, 126 MHz) of compound **10a**.

Figure S5. ^{1}H NMR spectra ($CDCl_3$, 500 MHz) of compound **10b**.

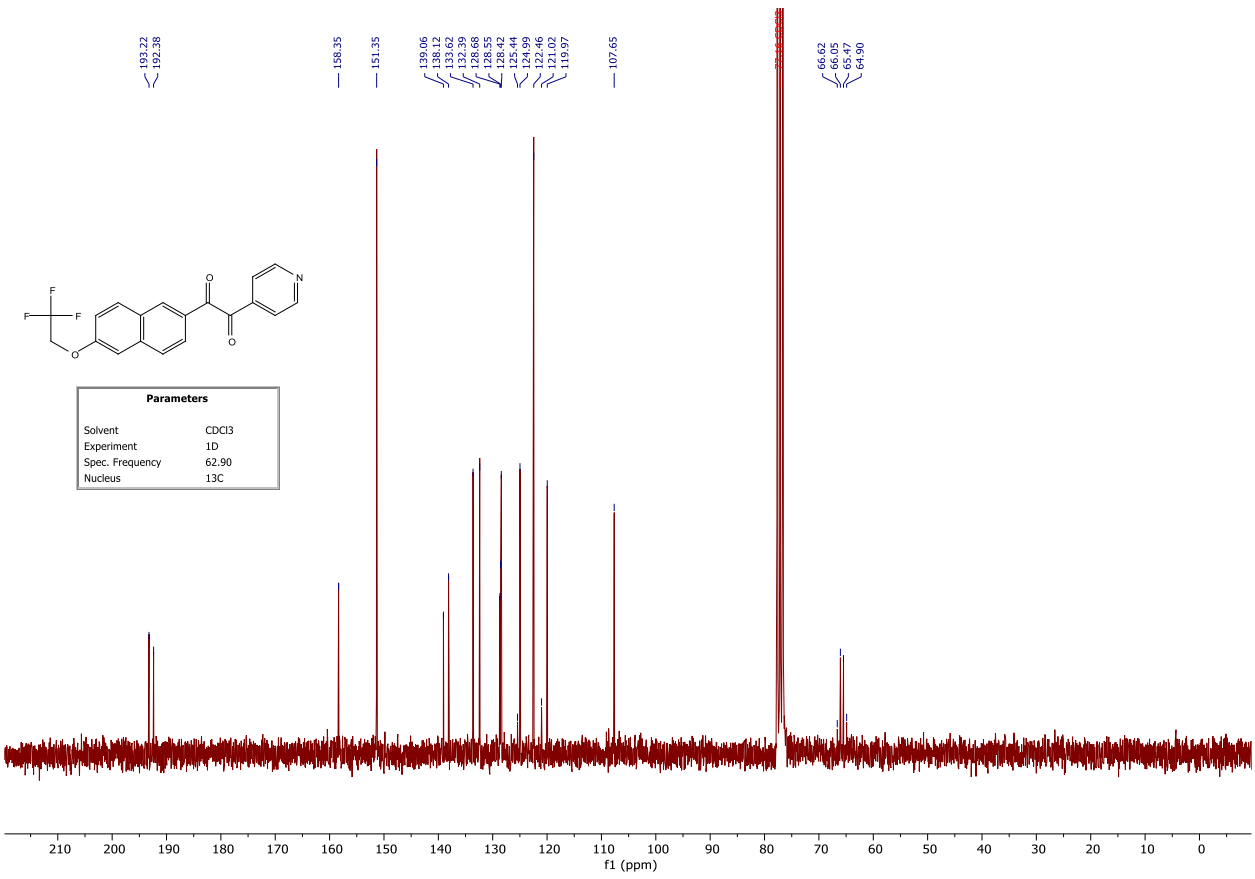


Figure S6. $^{13}C\{^{1}H\}$ NMR spectra ($CDCl_3$, 63 MHz) of compound **10b**.

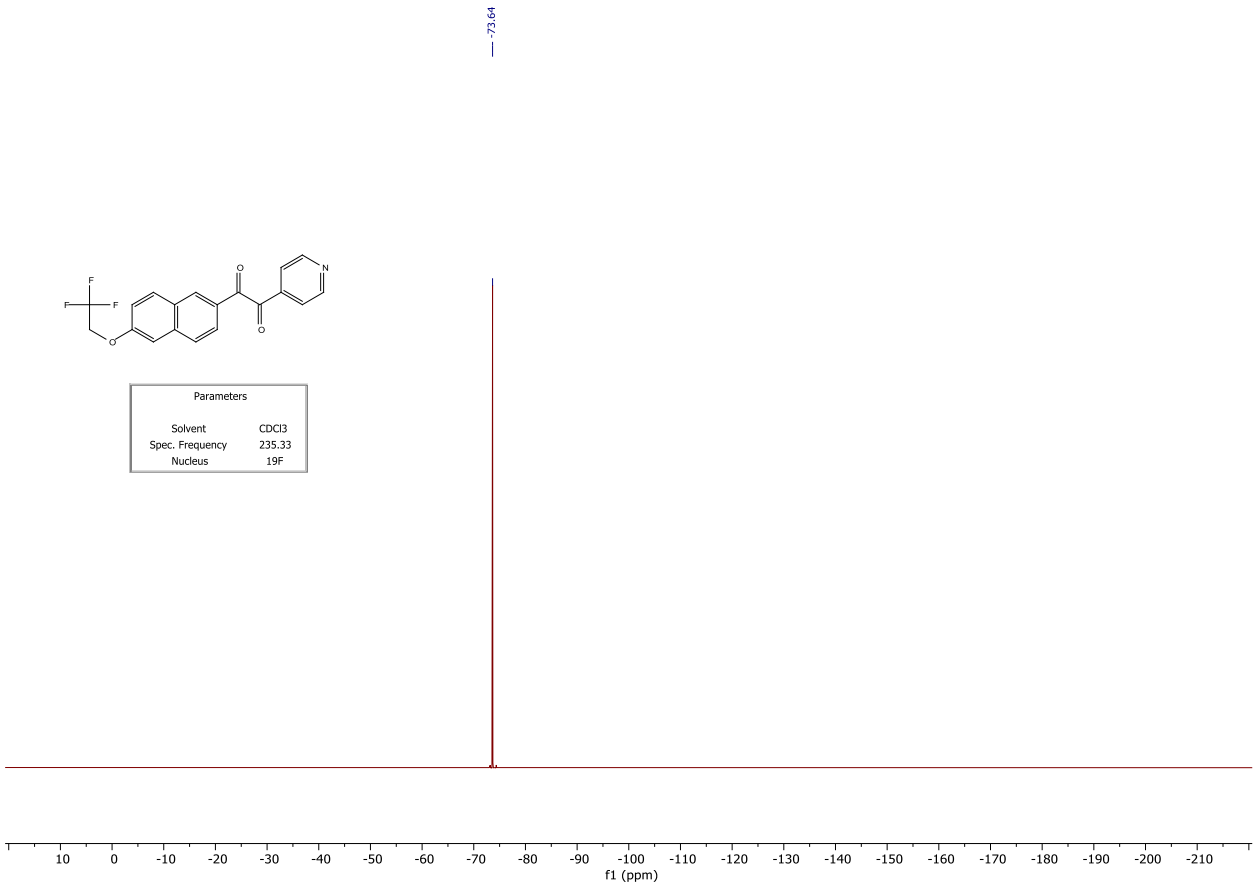


Figure S7. $^{19}F\{^{1}H\}$ NMR spectra ($CDCl_3$, 235 MHz) of compound **10b**.

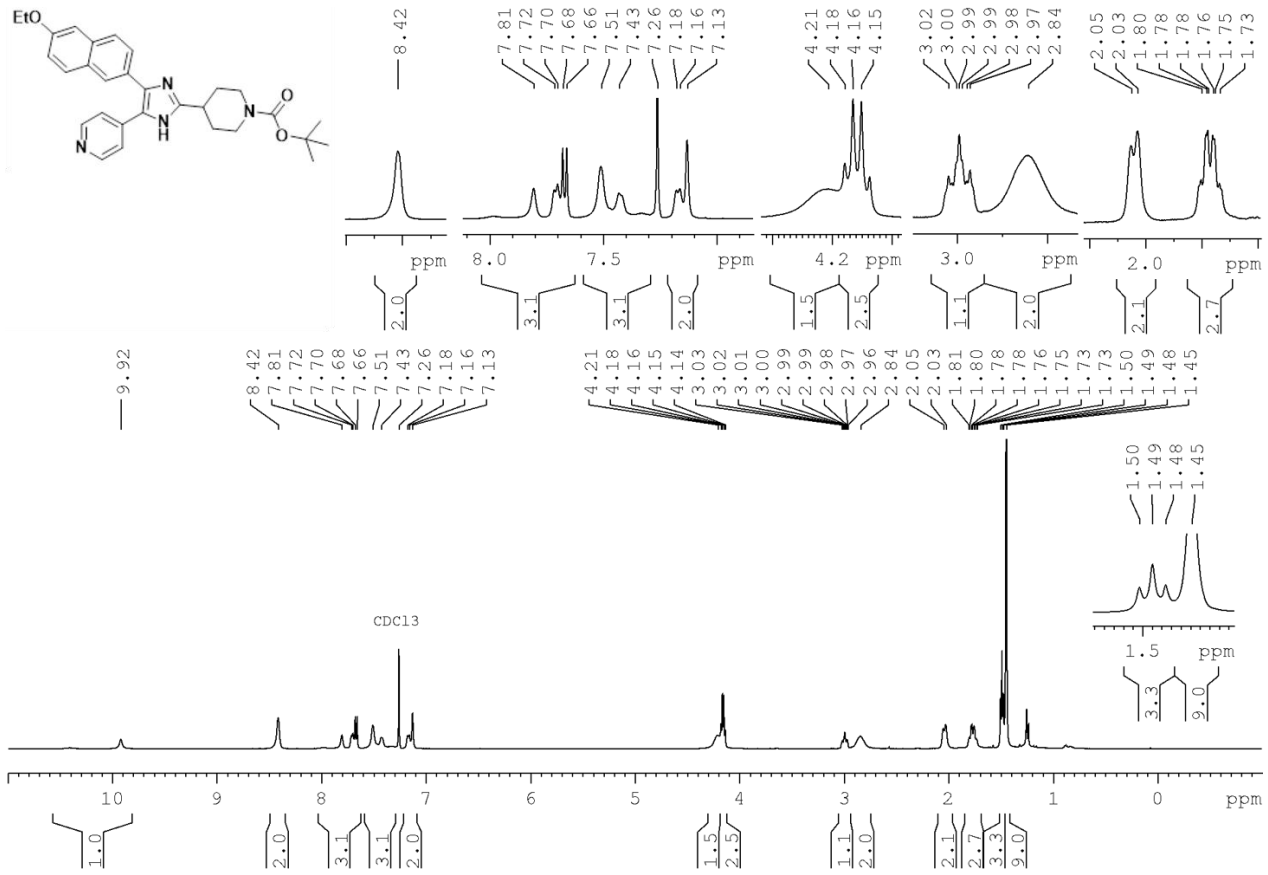


Figure S8. ^{1}H NMR spectra ($CDCl_3$, 500 MHz) of compound **13a**.

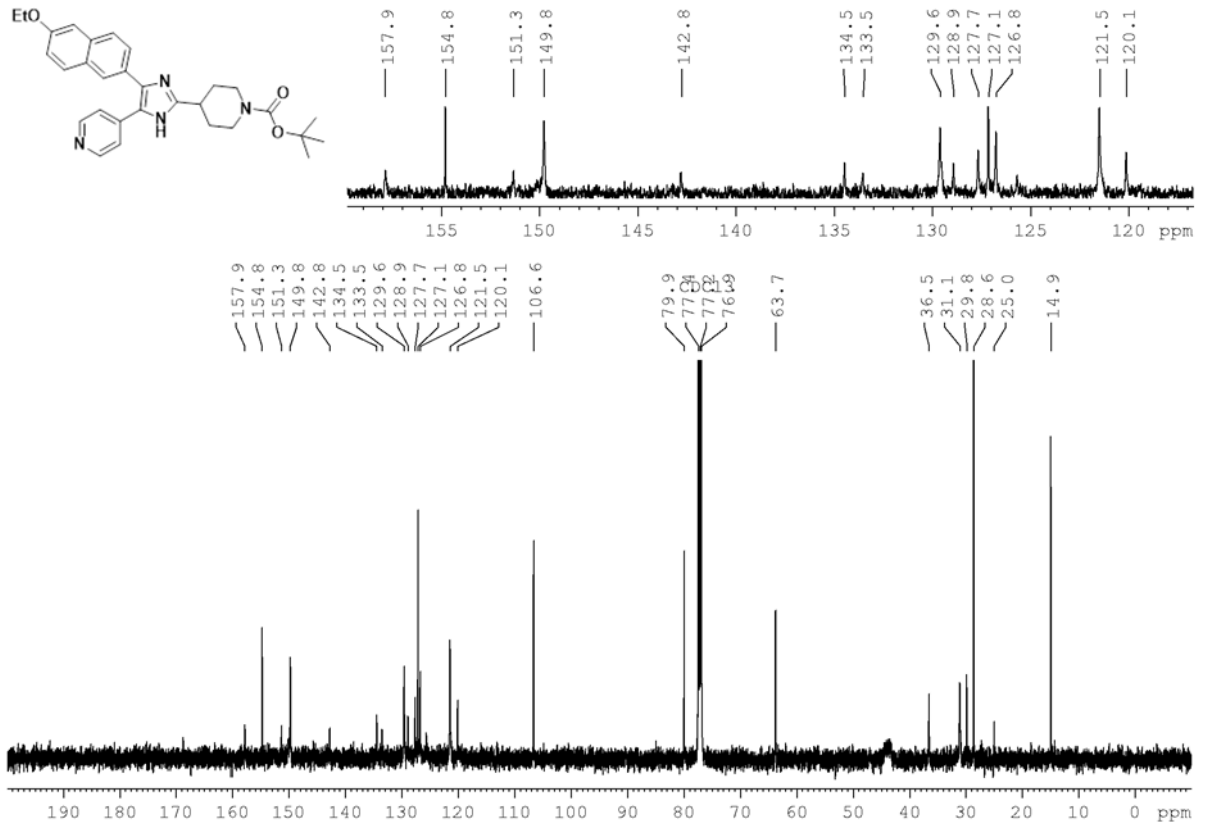


Figure S9. $^{13}C\{^{1}H\}$ NMR spectra ($CDCl_3$, 126 MHz) of compound **13a**.

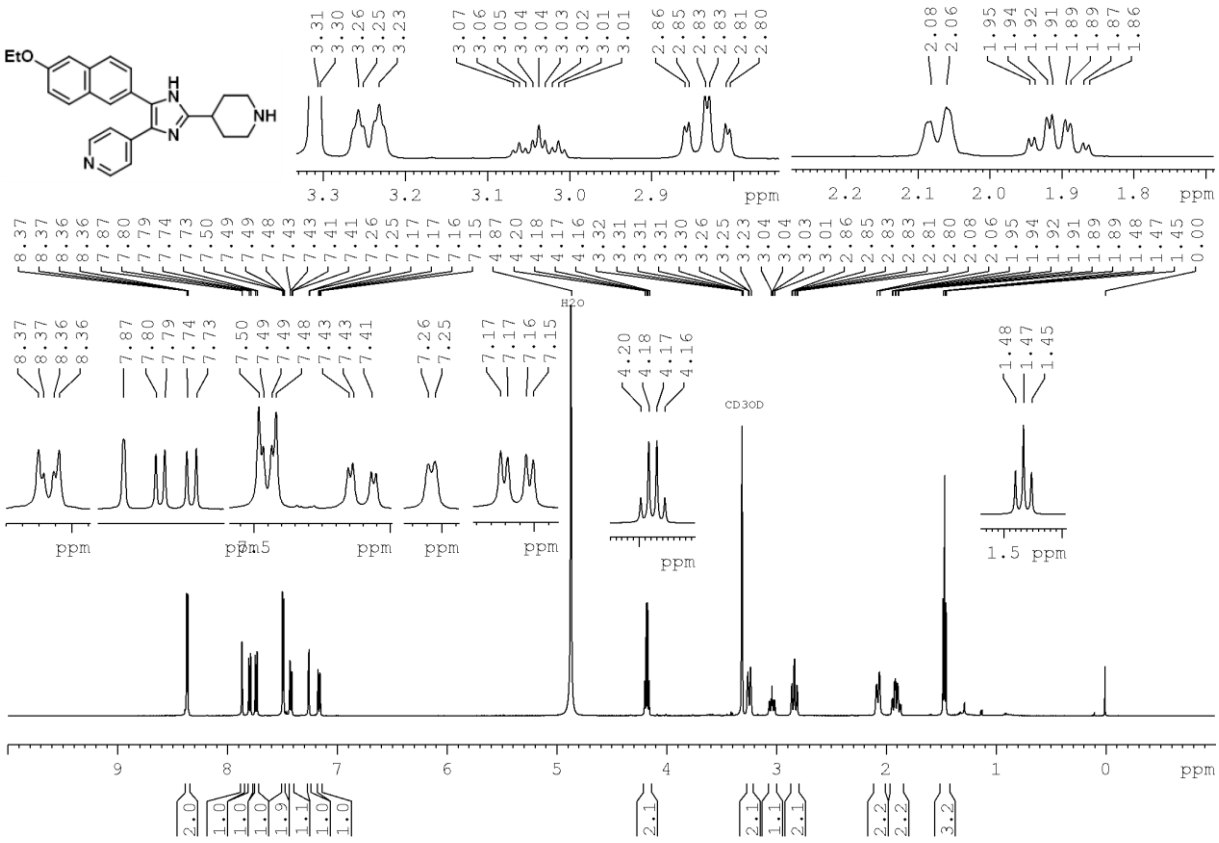


Figure S10. ^{1}H NMR spectra ($CDCl_3$, 500 MHz) of compound **14a**.

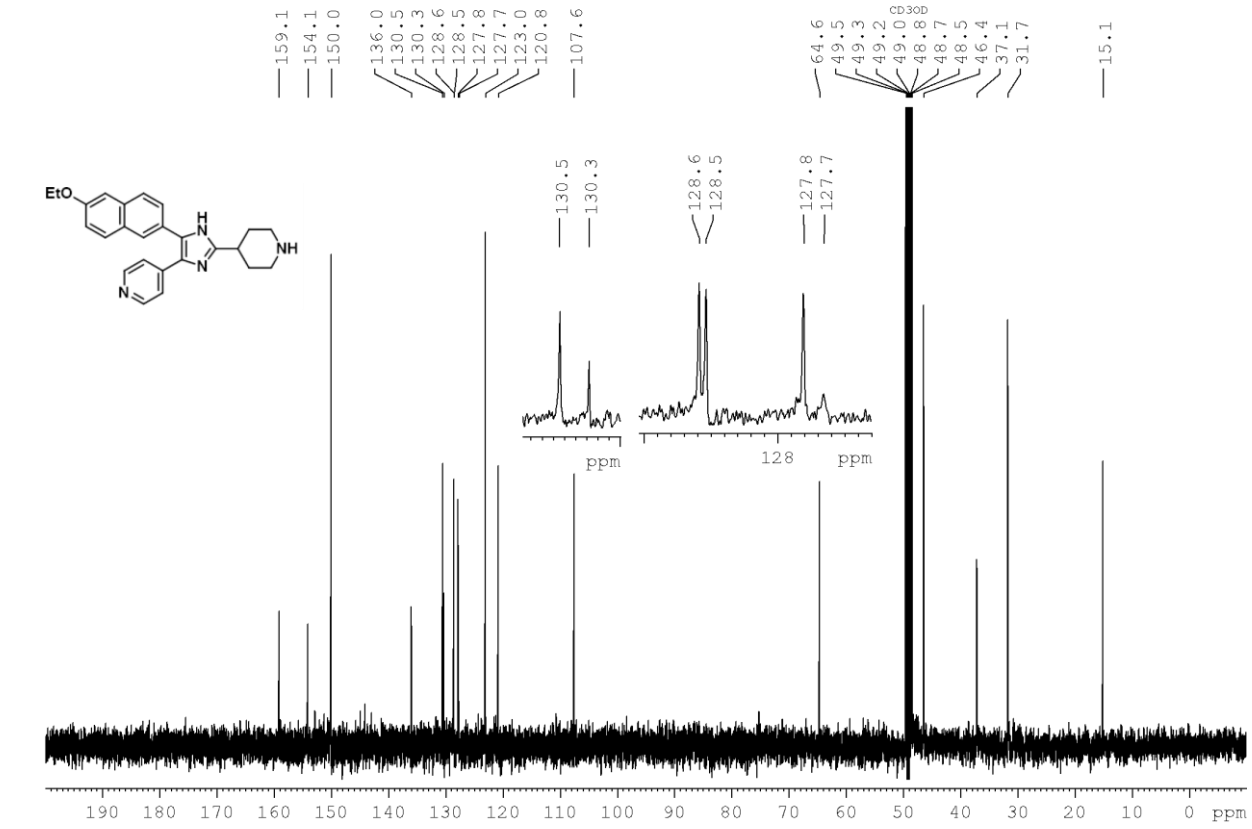


Figure S11. $^{13}C\{^{1}H\}$ NMR spectra ($CDCl_3$, 126 MHz) of compound **14a**.

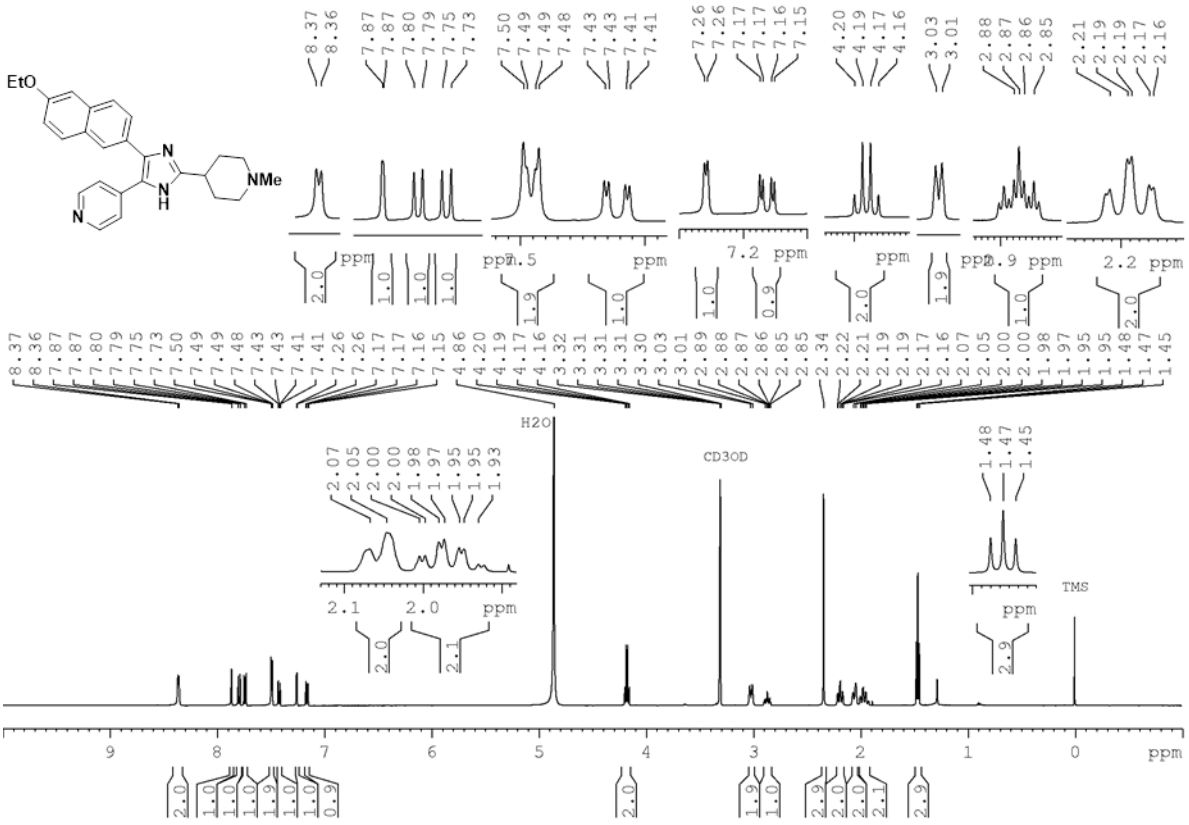


Figure S12. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **15a**.

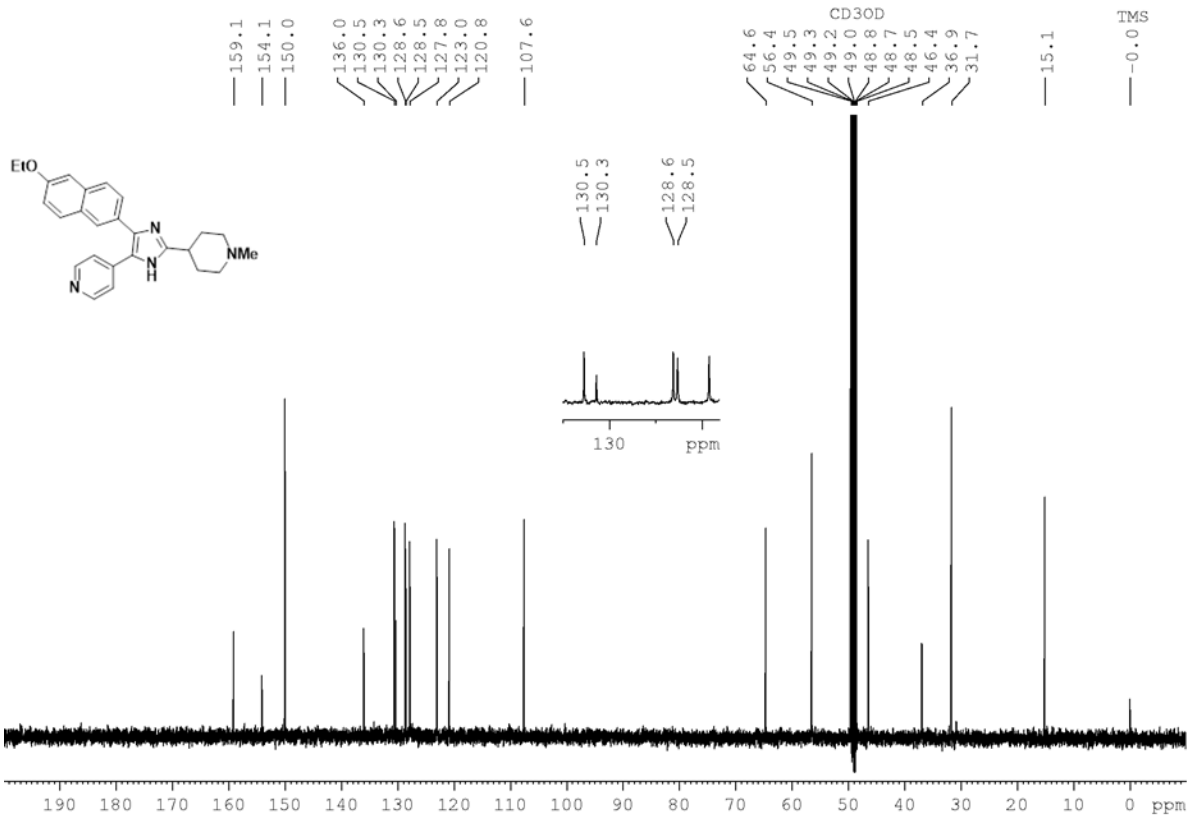


Figure S13. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 126 MHz) of compound **15a**.

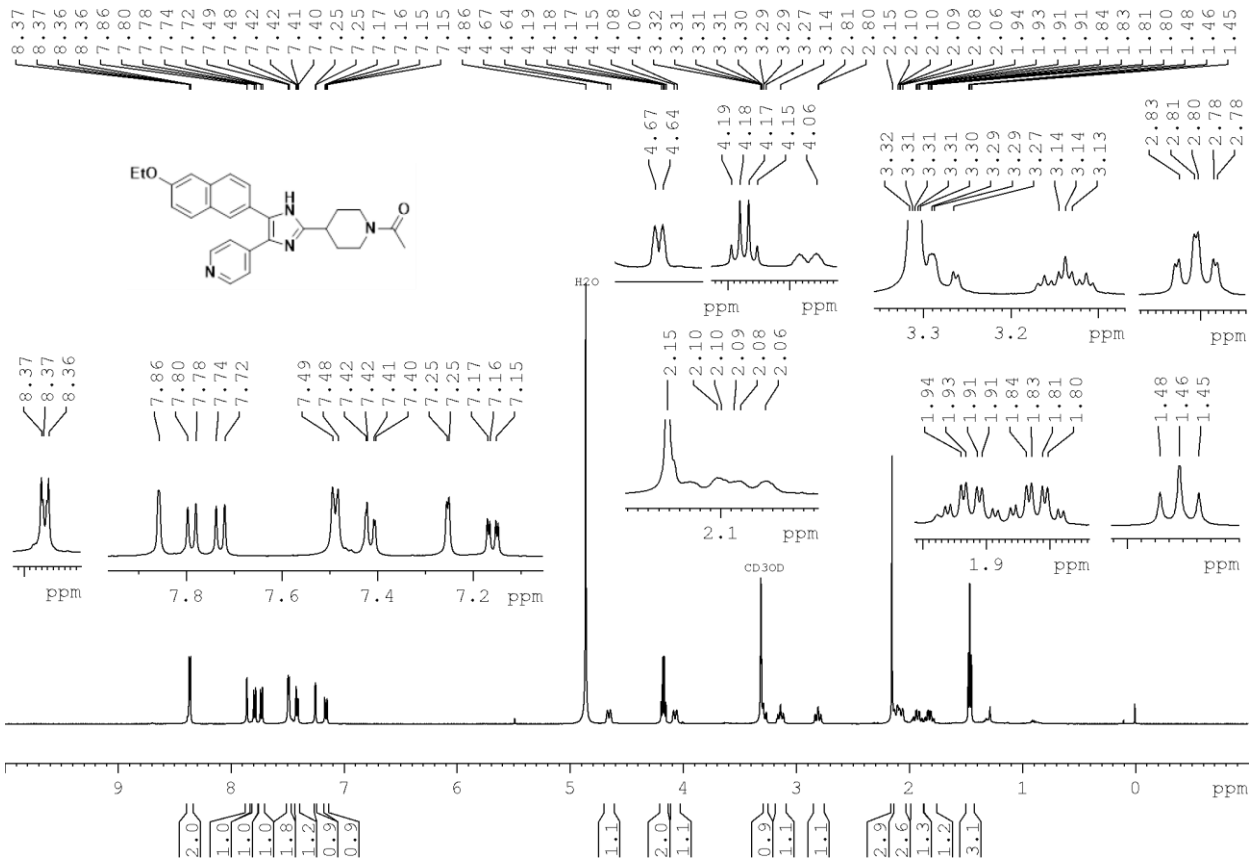


Figure S14. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **13b**.

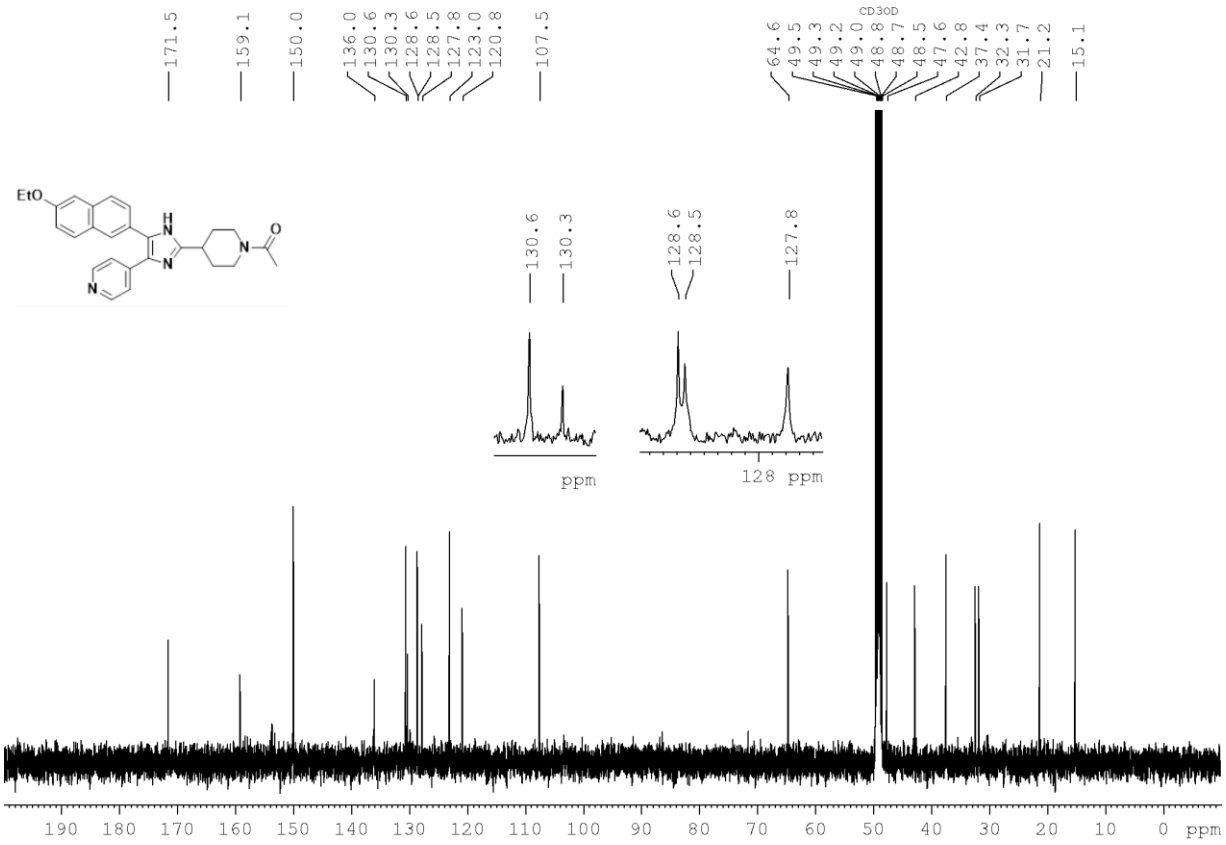


Figure S15. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 126 MHz) of compound **13b**.

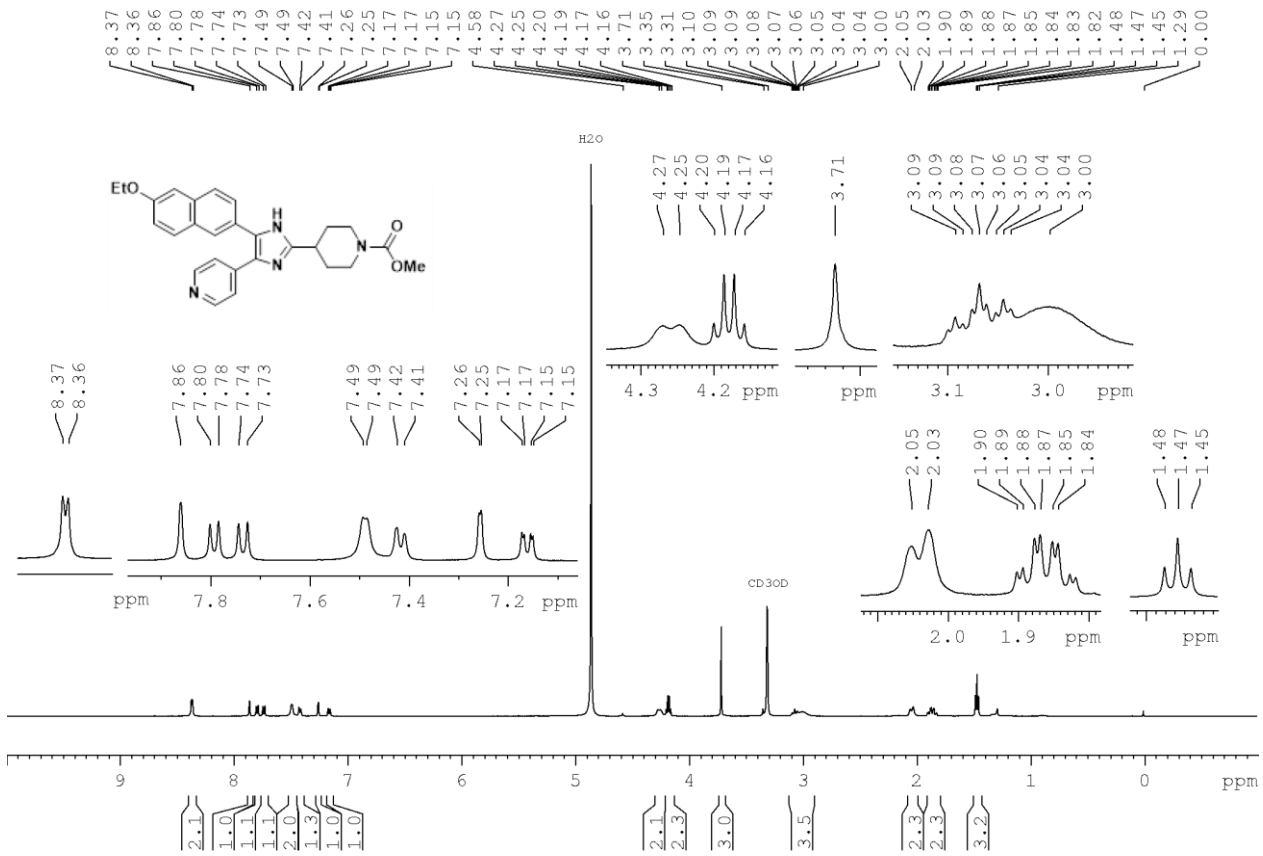


Figure S16. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **13c**.

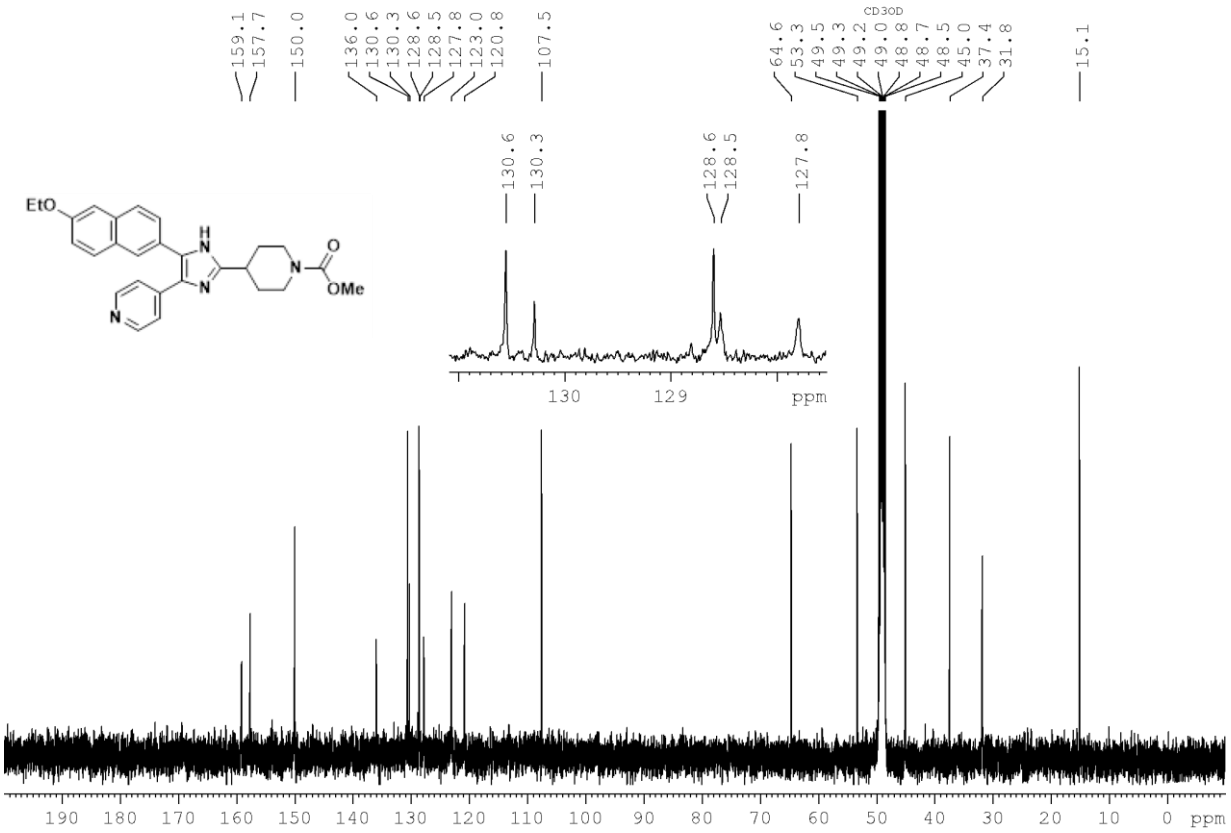


Figure S17. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 126 MHz) of compound **13c**.

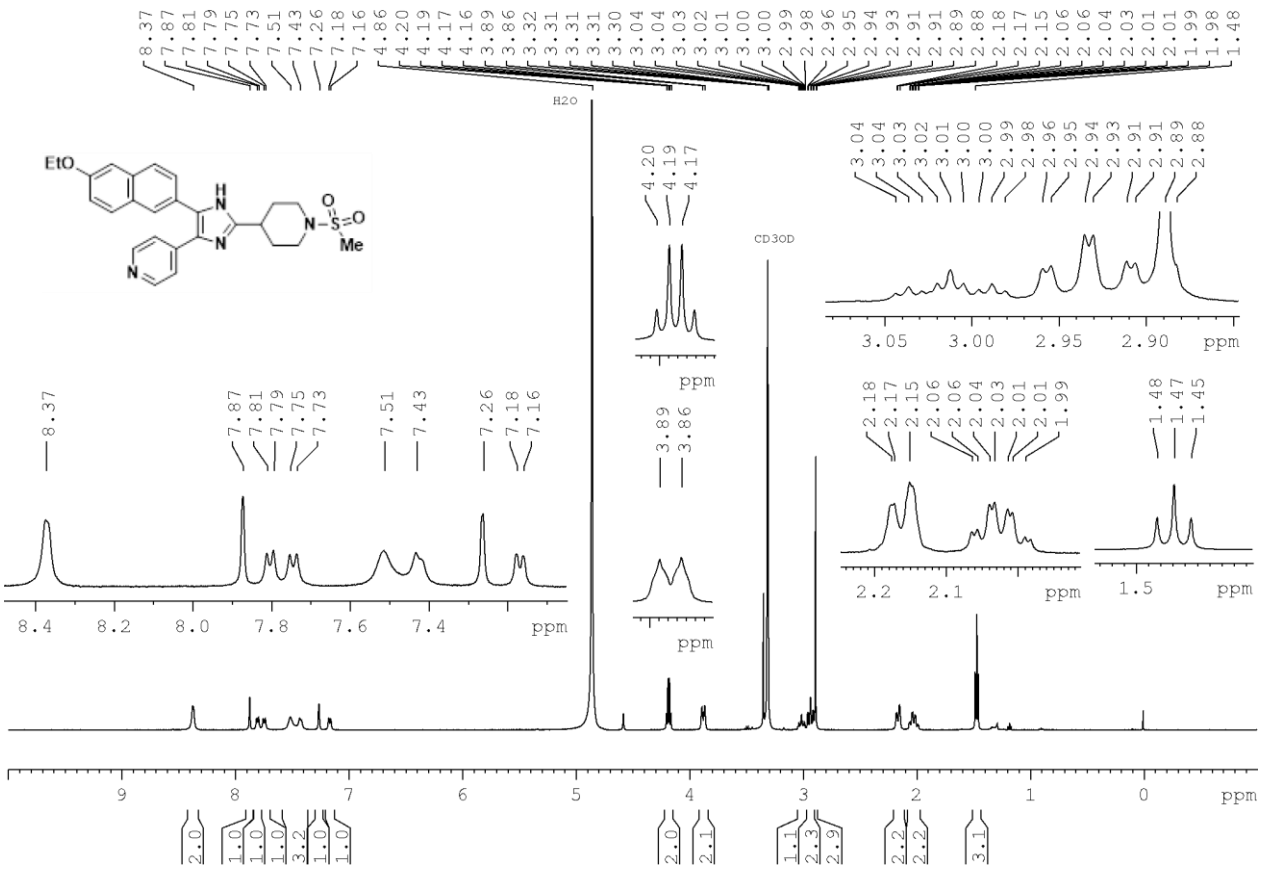


Figure S18. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **13d**.

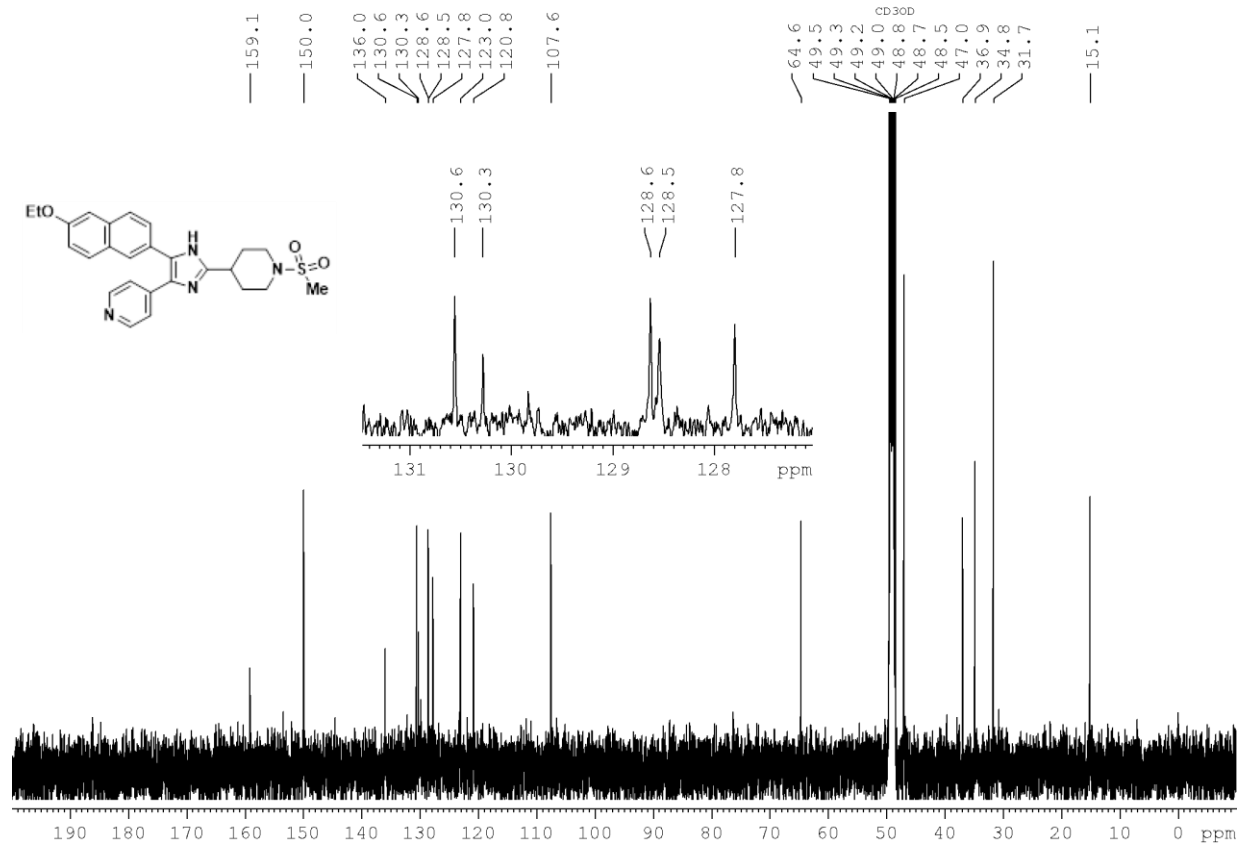


Figure S19. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 126 MHz) of compound **13d**.

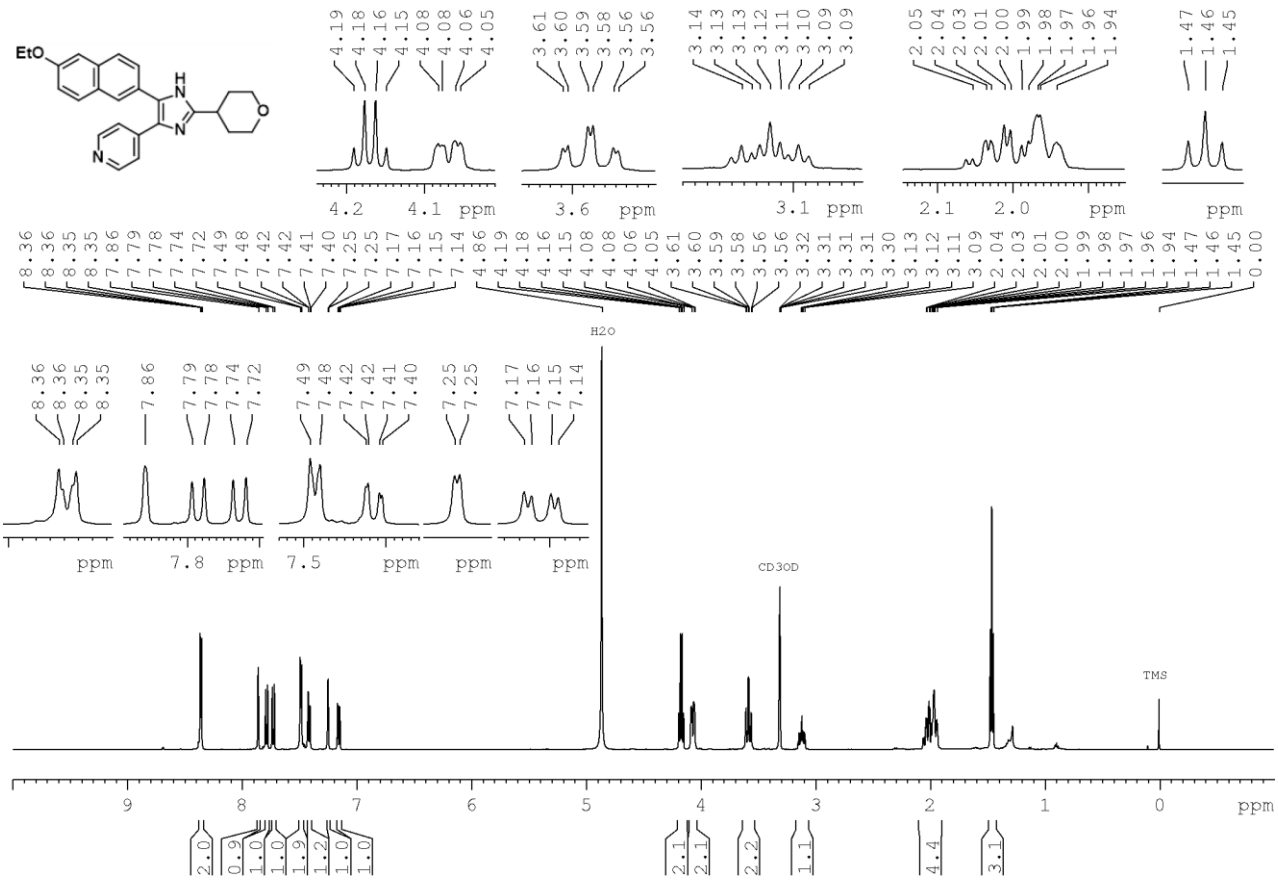


Figure S20. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **13e**.

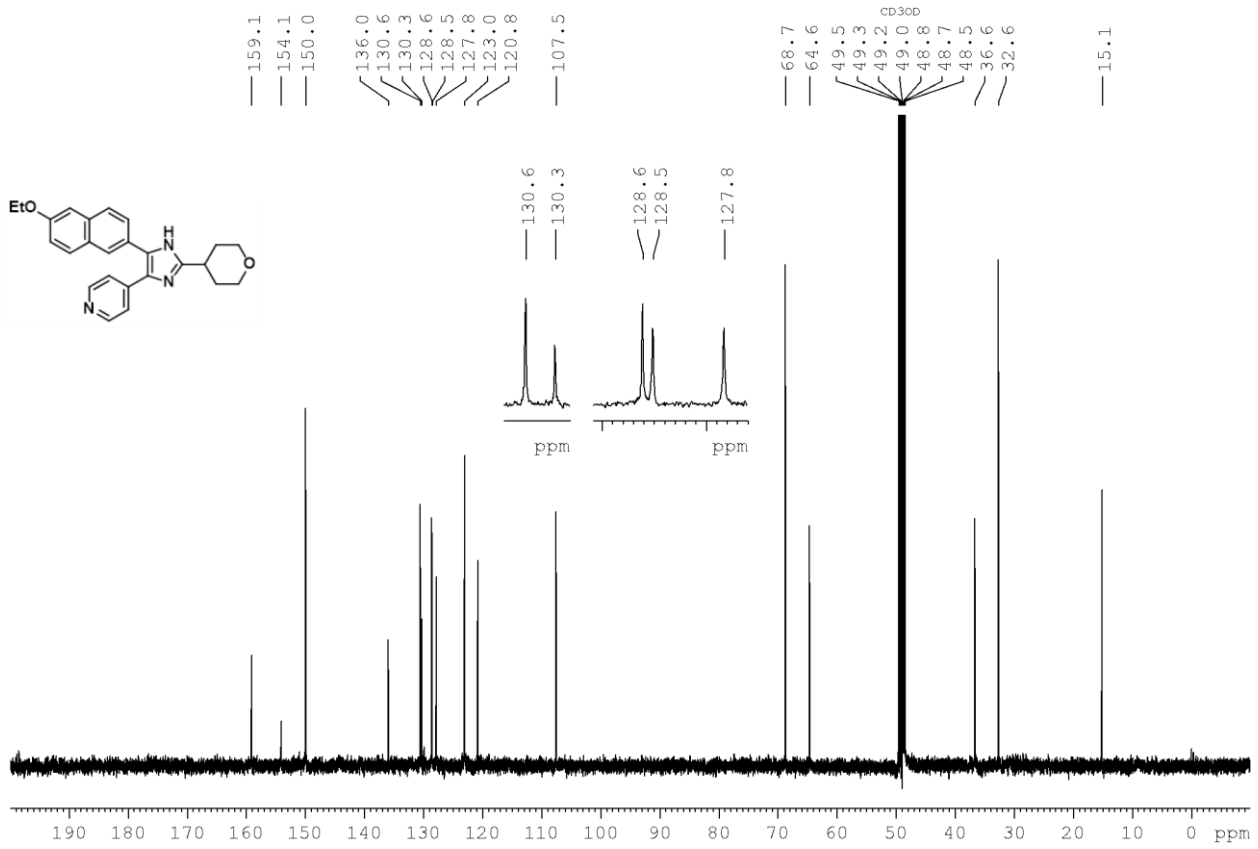


Figure S21. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 126 MHz) of compound **13e**.

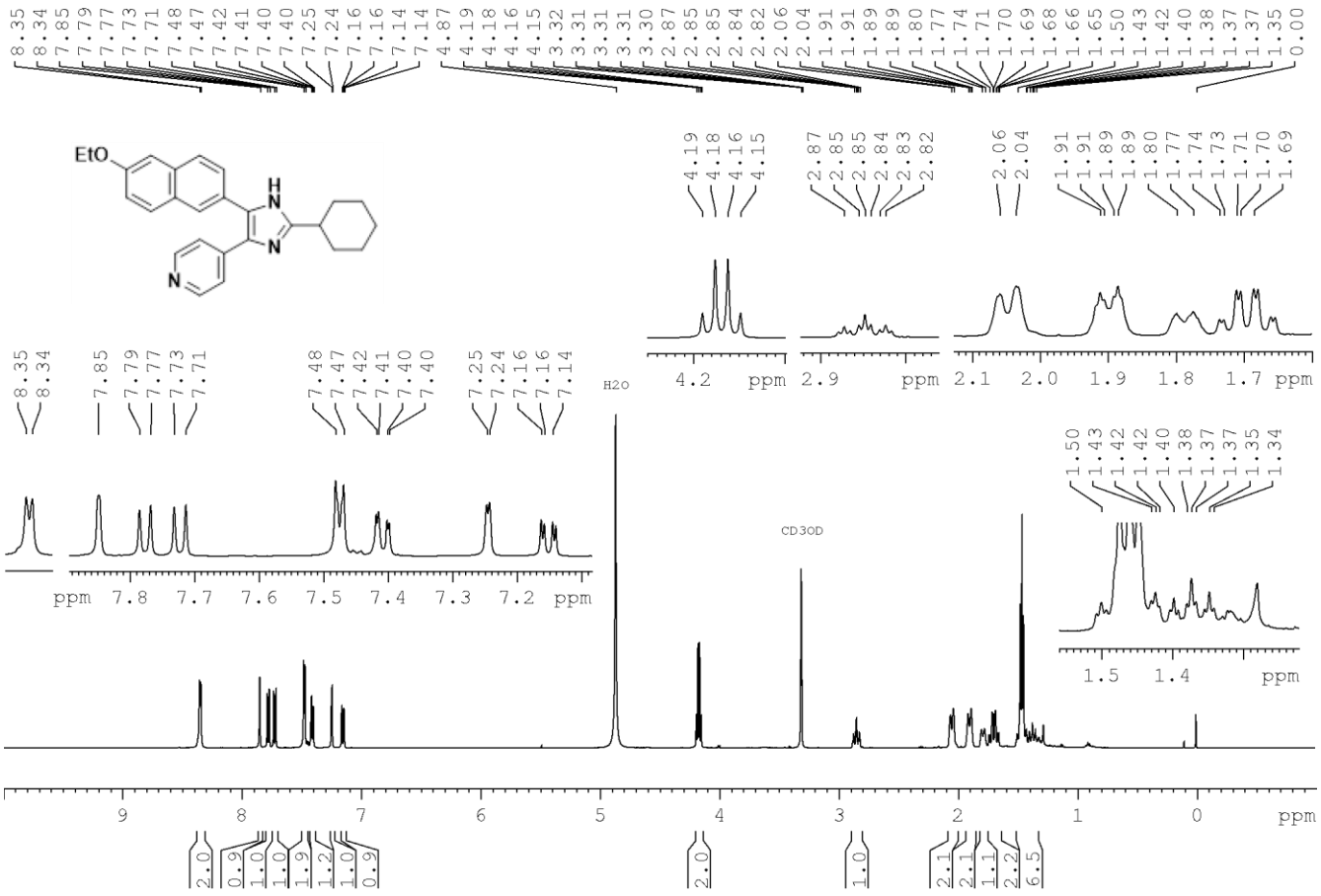


Figure S22. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **13f**.

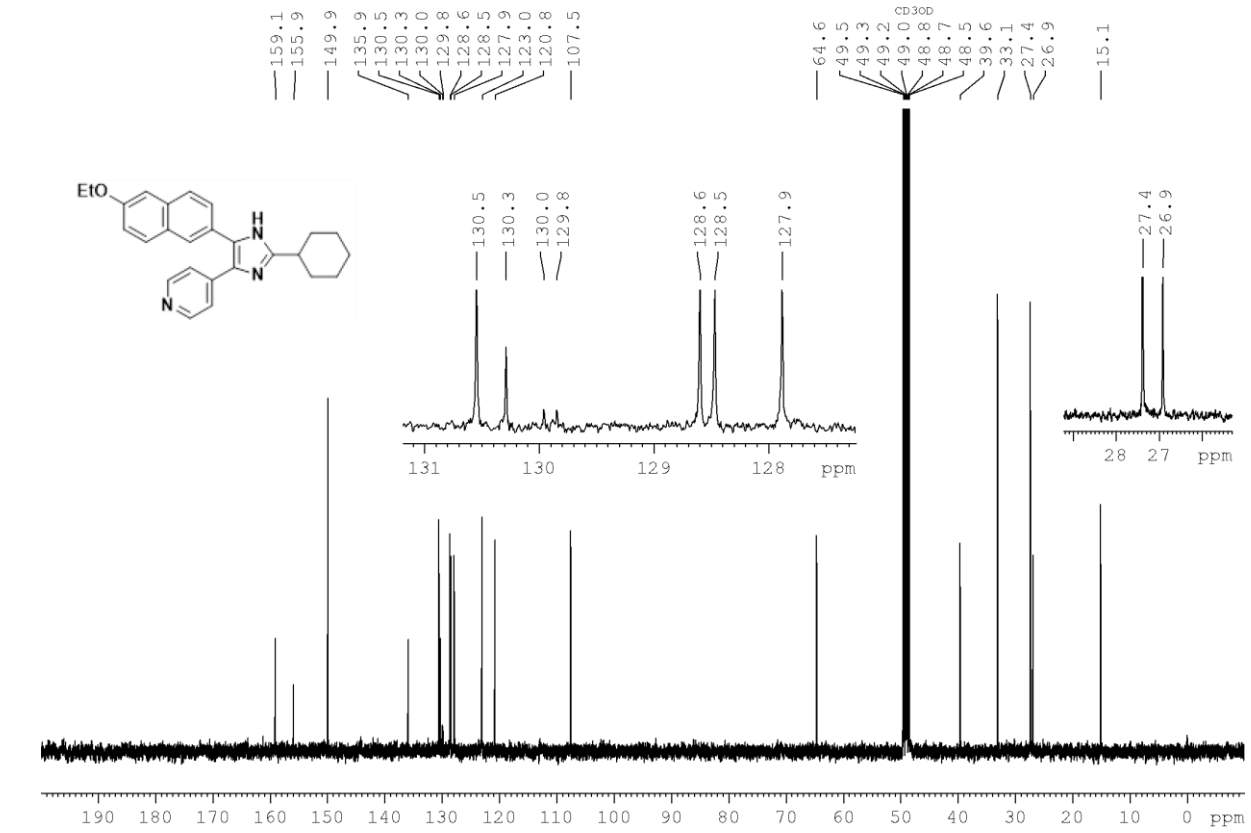


Figure S23. $^{13}C\{^{1}H\}$ NMR spectra ($CDCl_3$, 126 MHz) of compound **13f**.

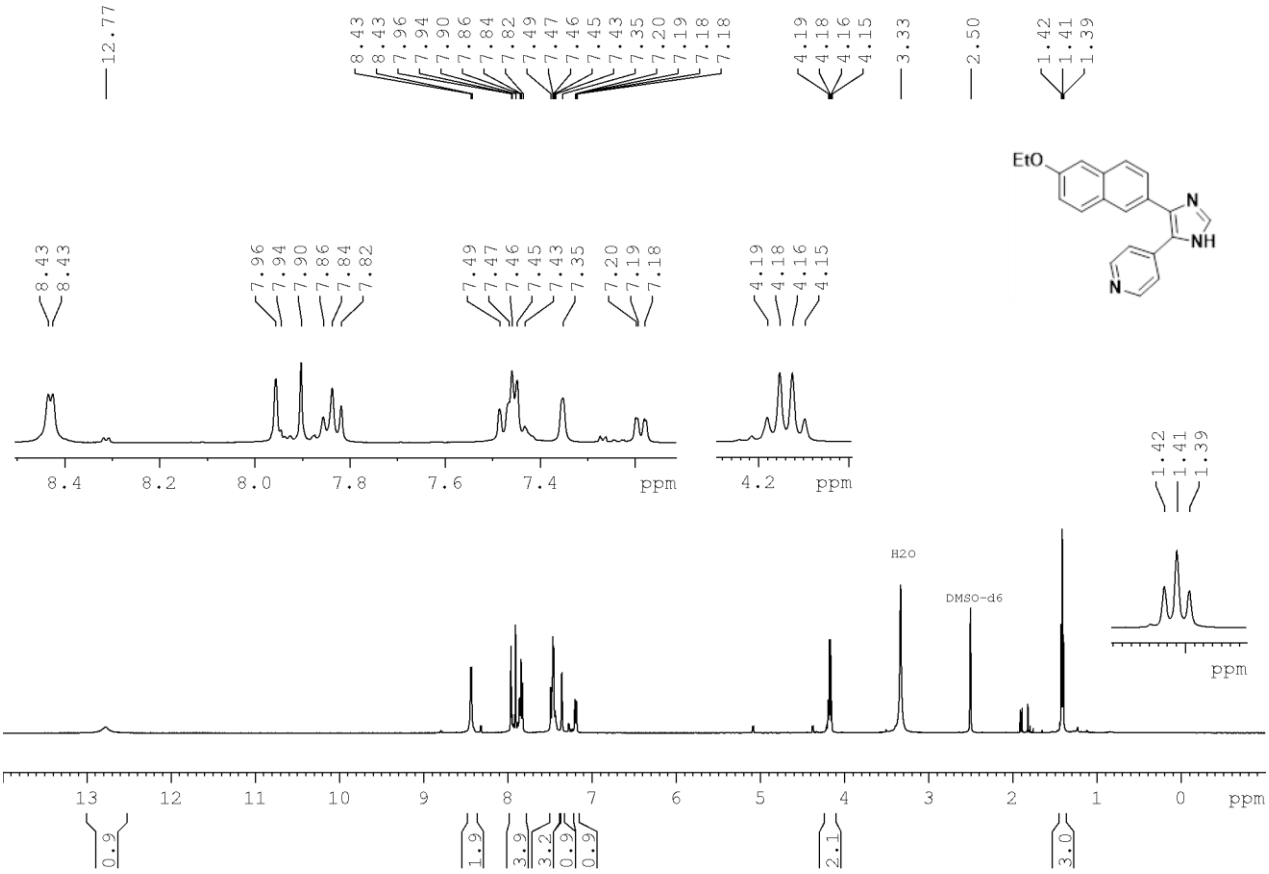


Figure S24. ^{1}H NMR spectra ($CDCl_3$, 500 MHz) of compound **13g**.

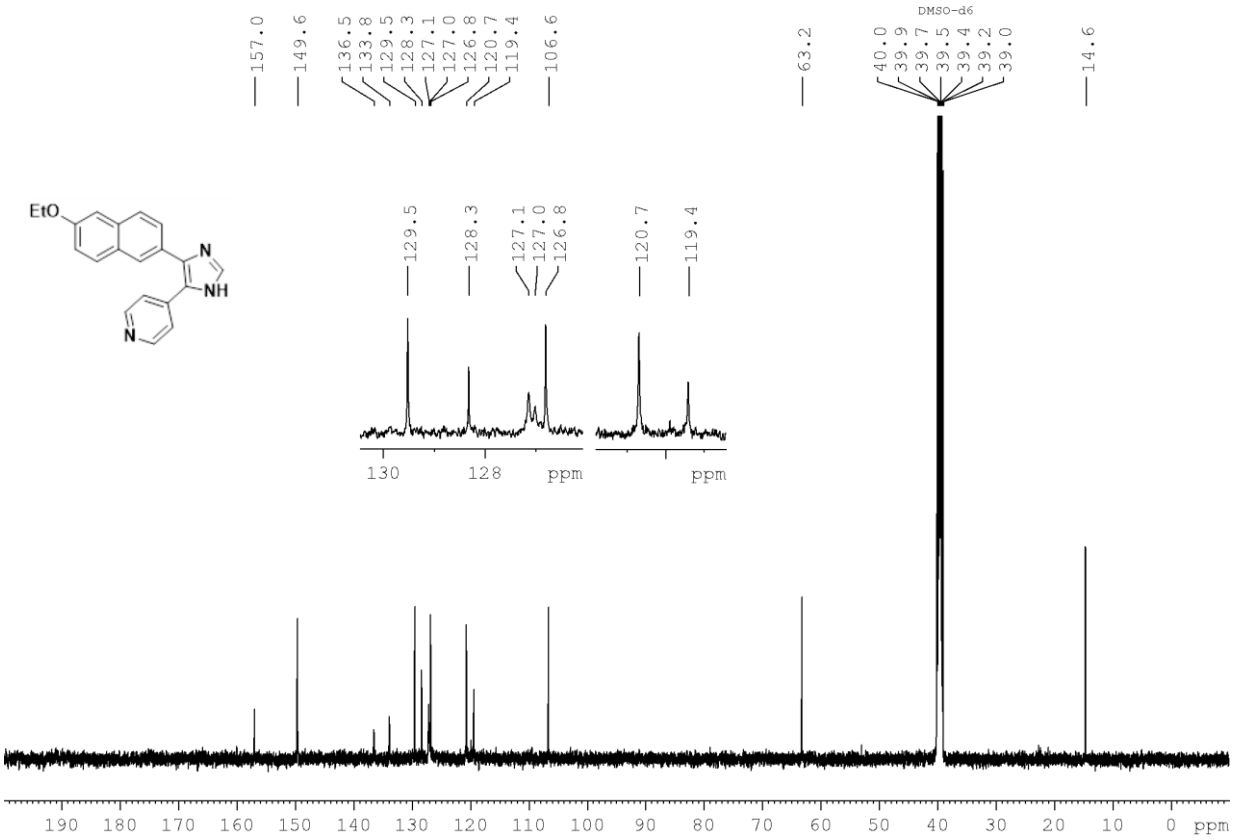


Figure S25. $^{13}C\{^{1}H\}$ NMR spectra ($CDCl_3$, 126 MHz) of compound **13g**.

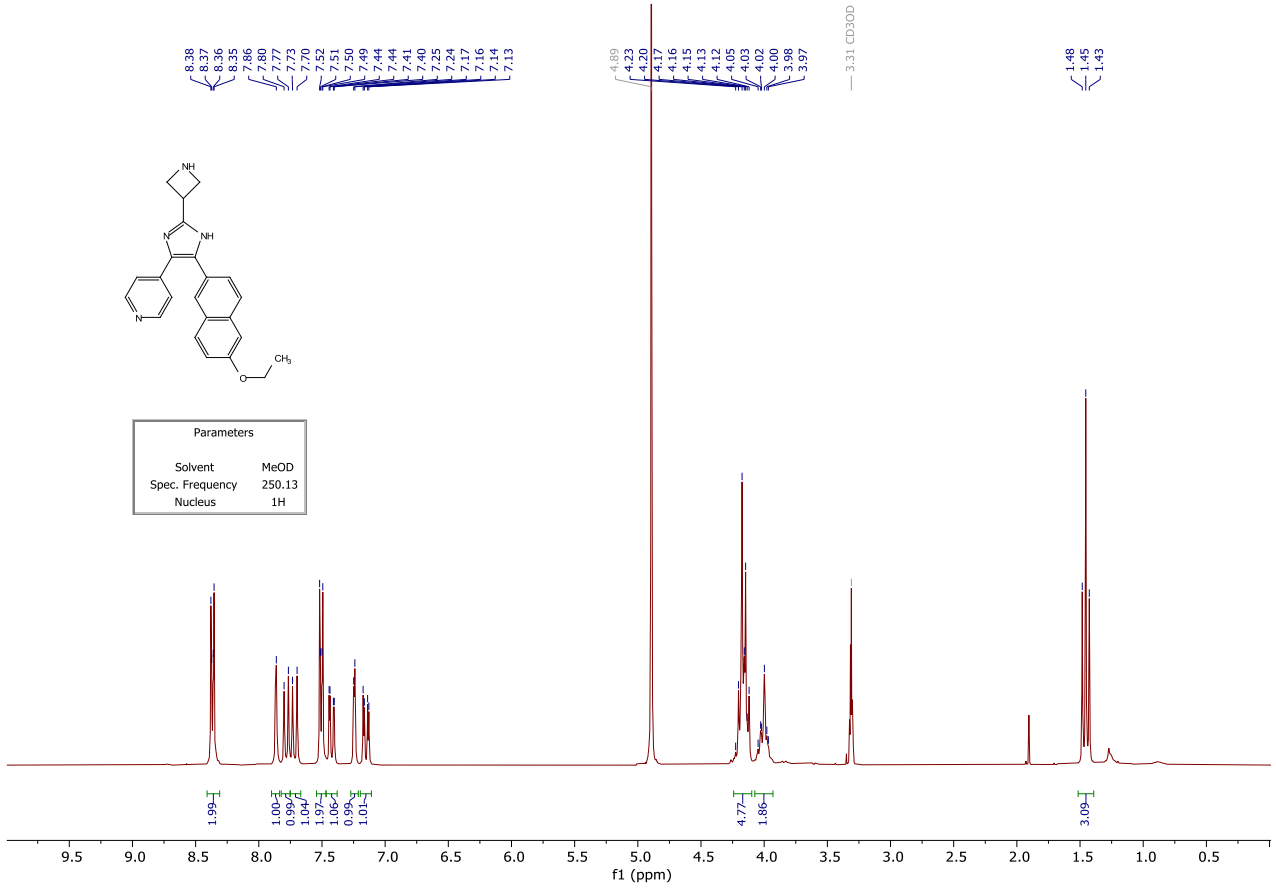


Figure S26. ^{1}H NMR spectra (CD_3OD, 250 MHz) of compound **14h**.

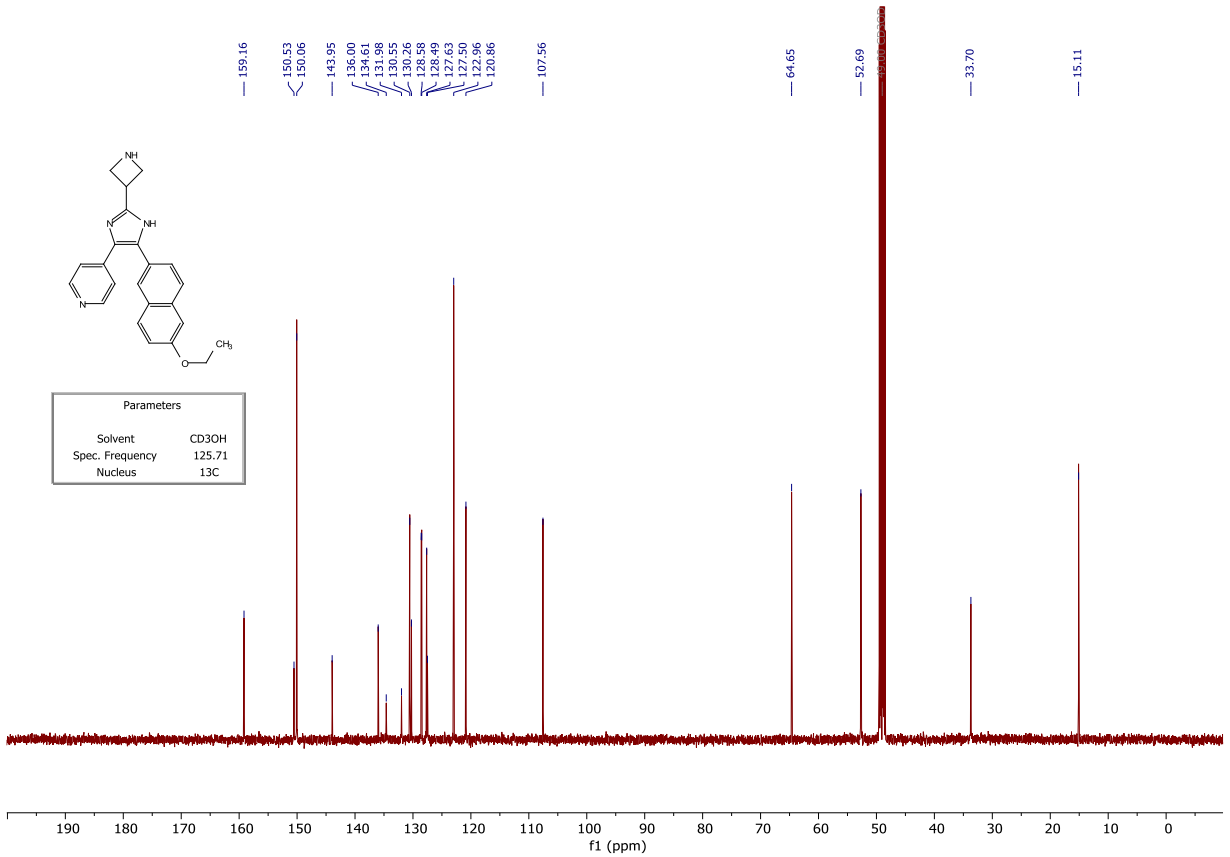


Figure S27. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 126 MHz) of compound **14h**.

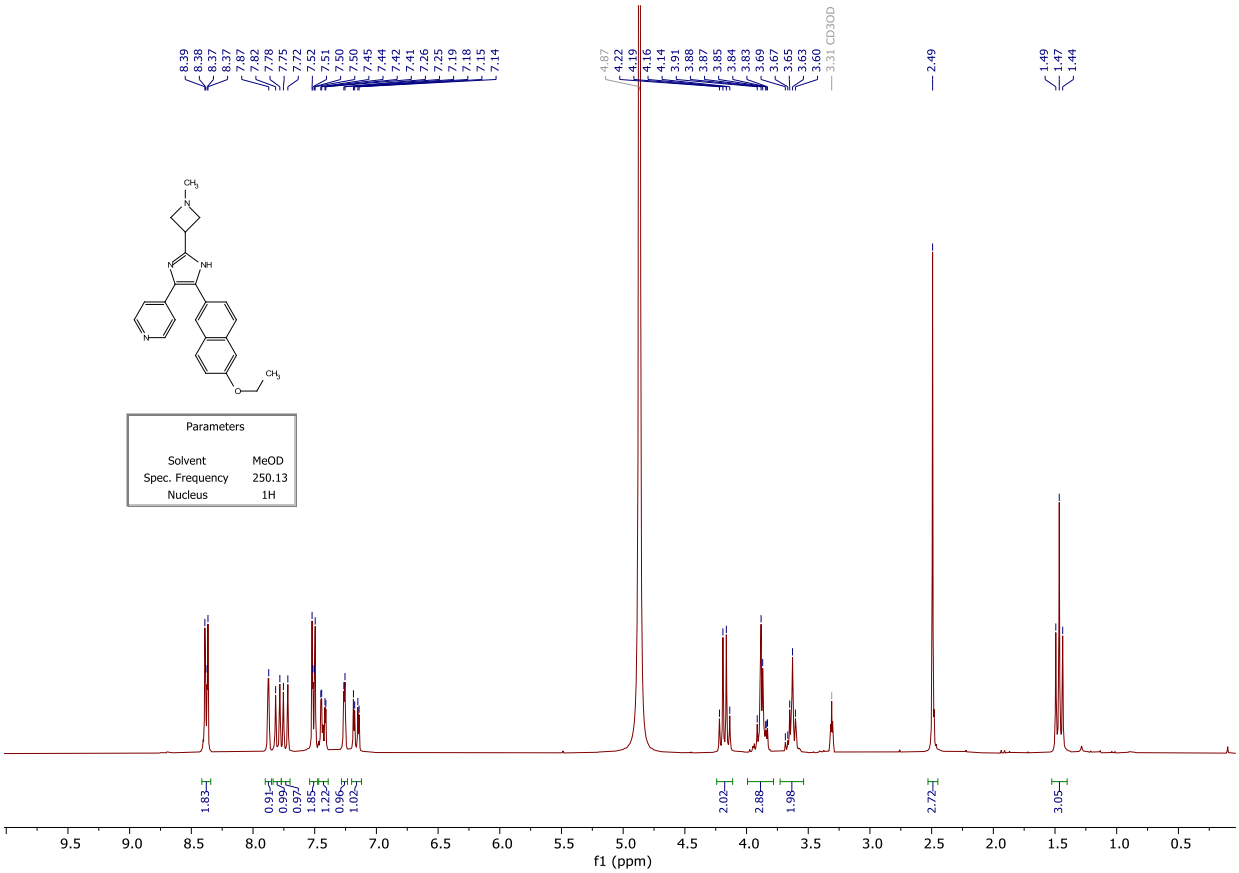


Figure S28. ^{1}H NMR spectra (CD_3OD, 250 MHz) of compound **15h**.

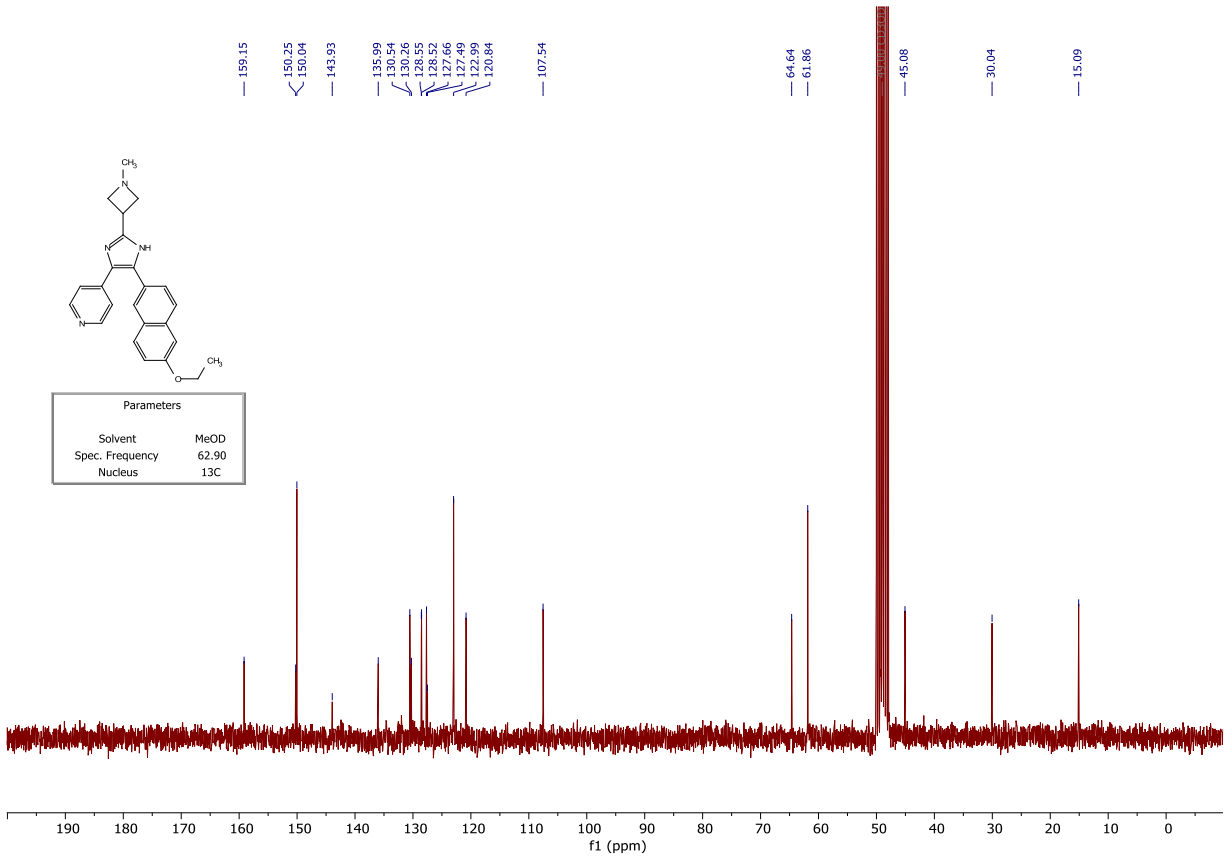


Figure S29. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 63 MHz) of compound **15h**.

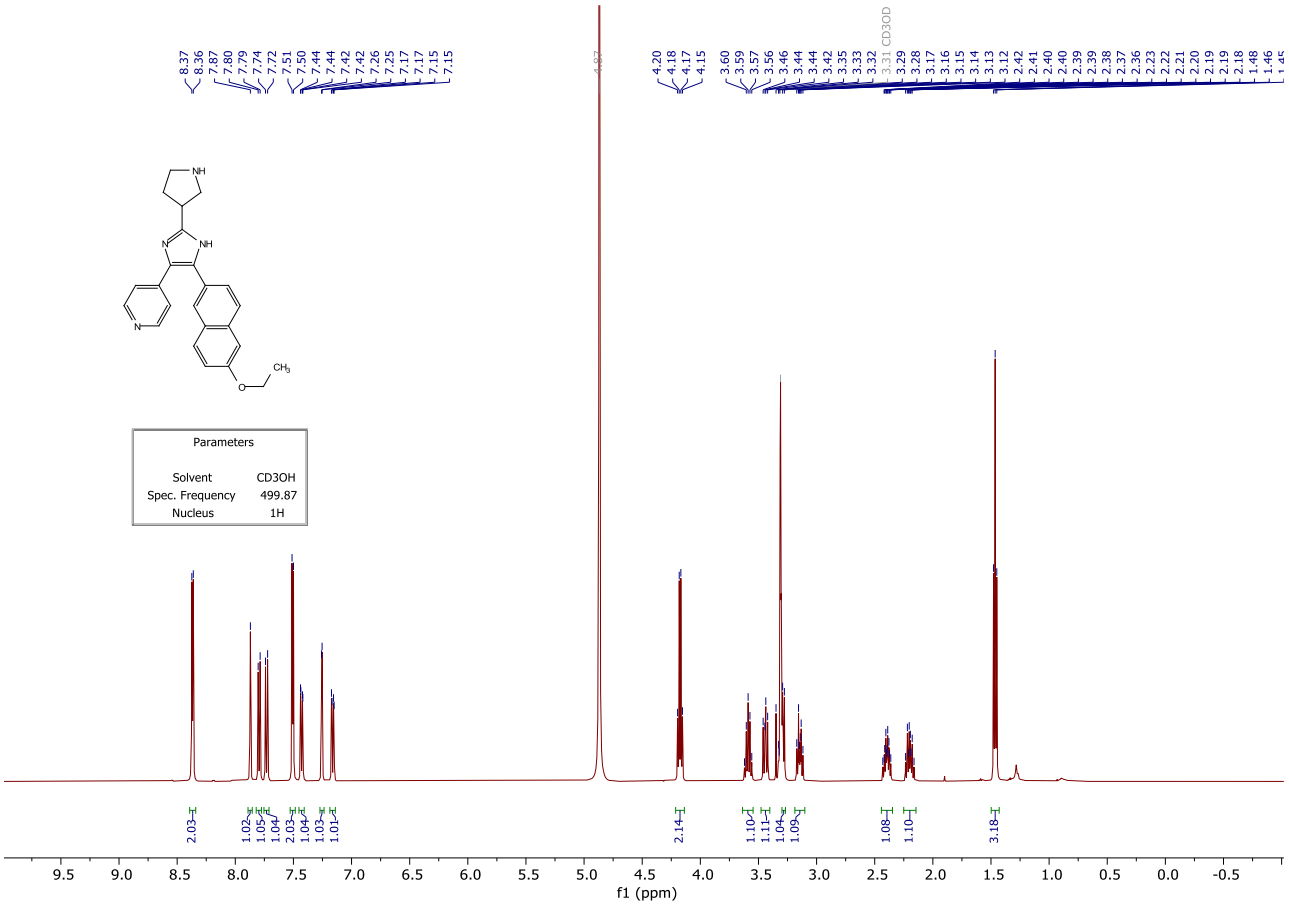


Figure S30. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **14i**.

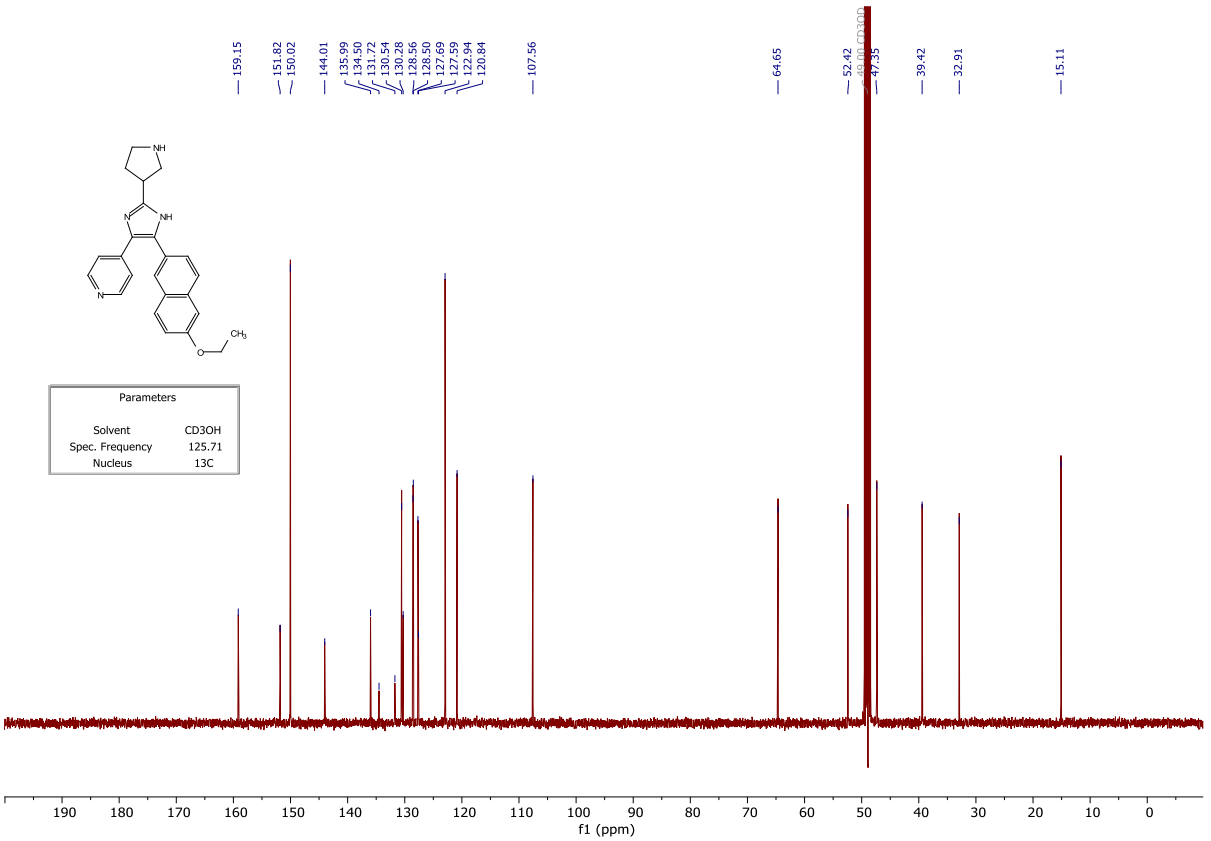


Figure S31. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 126 MHz) of compound **14i**.

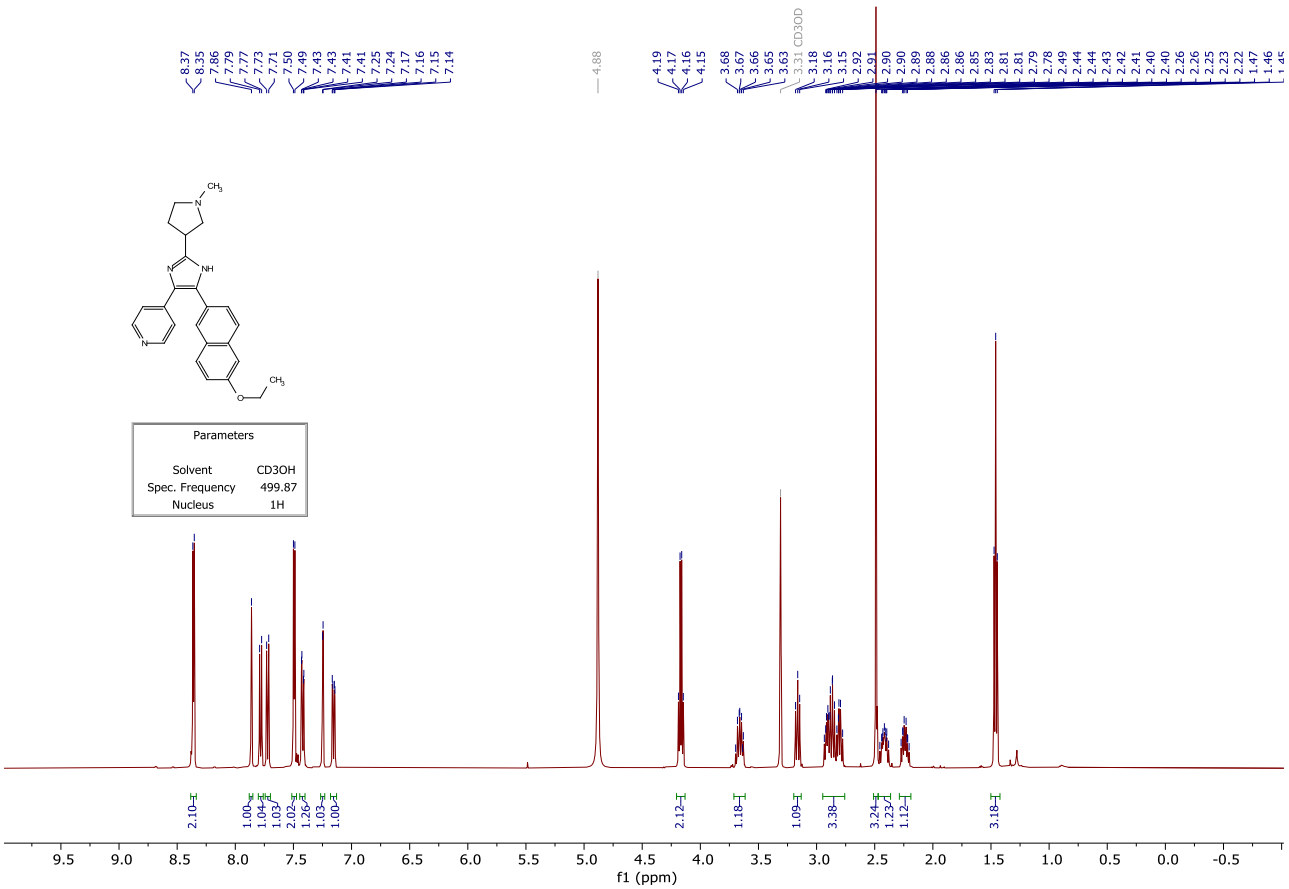


Figure S32. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **15i**.

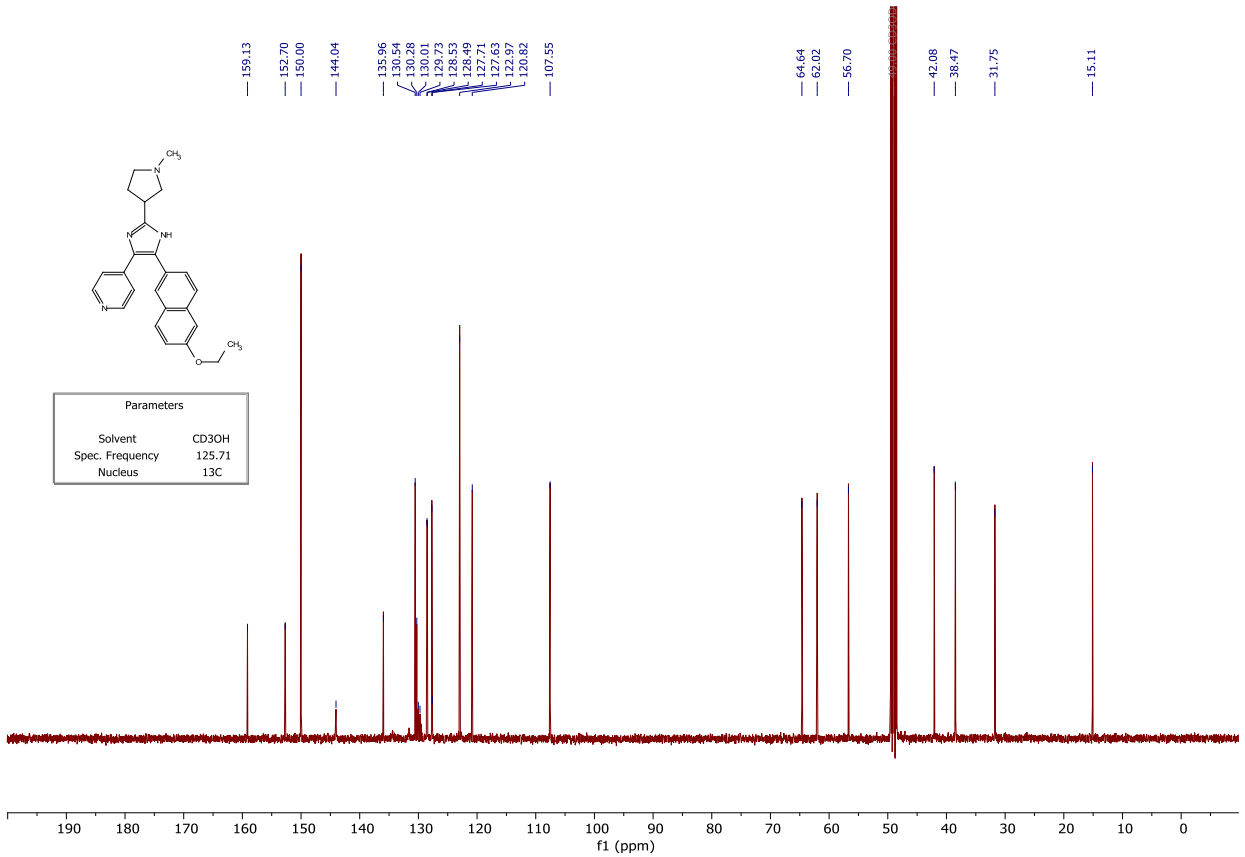


Figure S33. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 126 MHz) of compound **15i**.

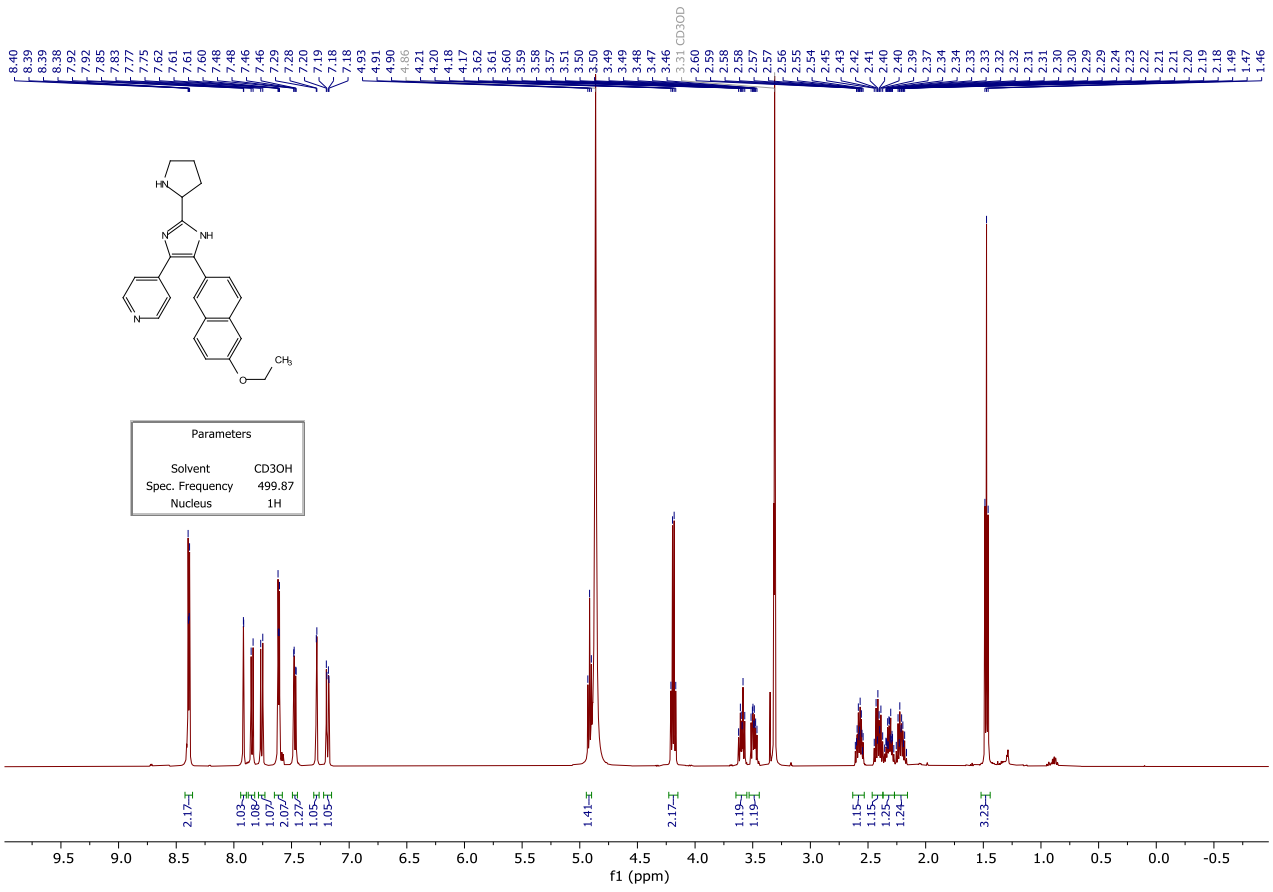


Figure S34. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **14j**.

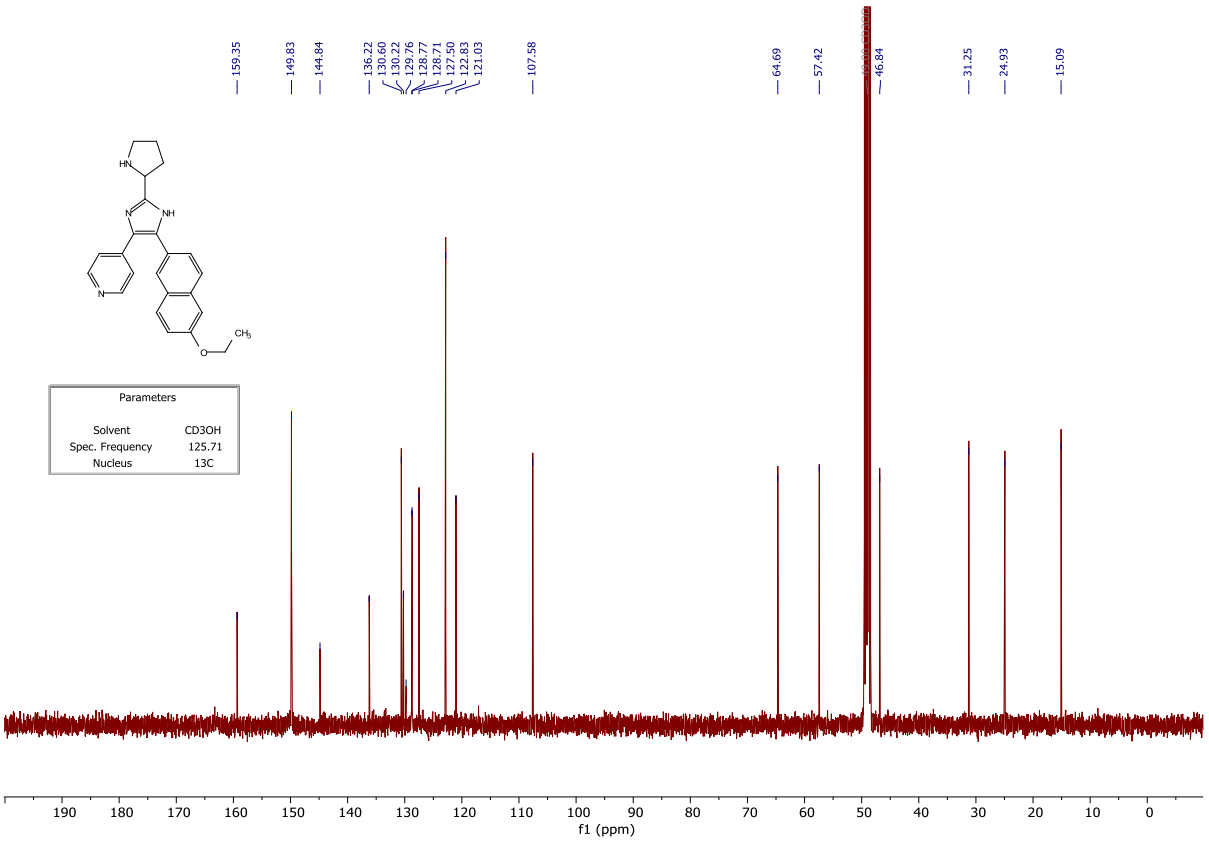


Figure S35. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 126 MHz) of compound **14j**.

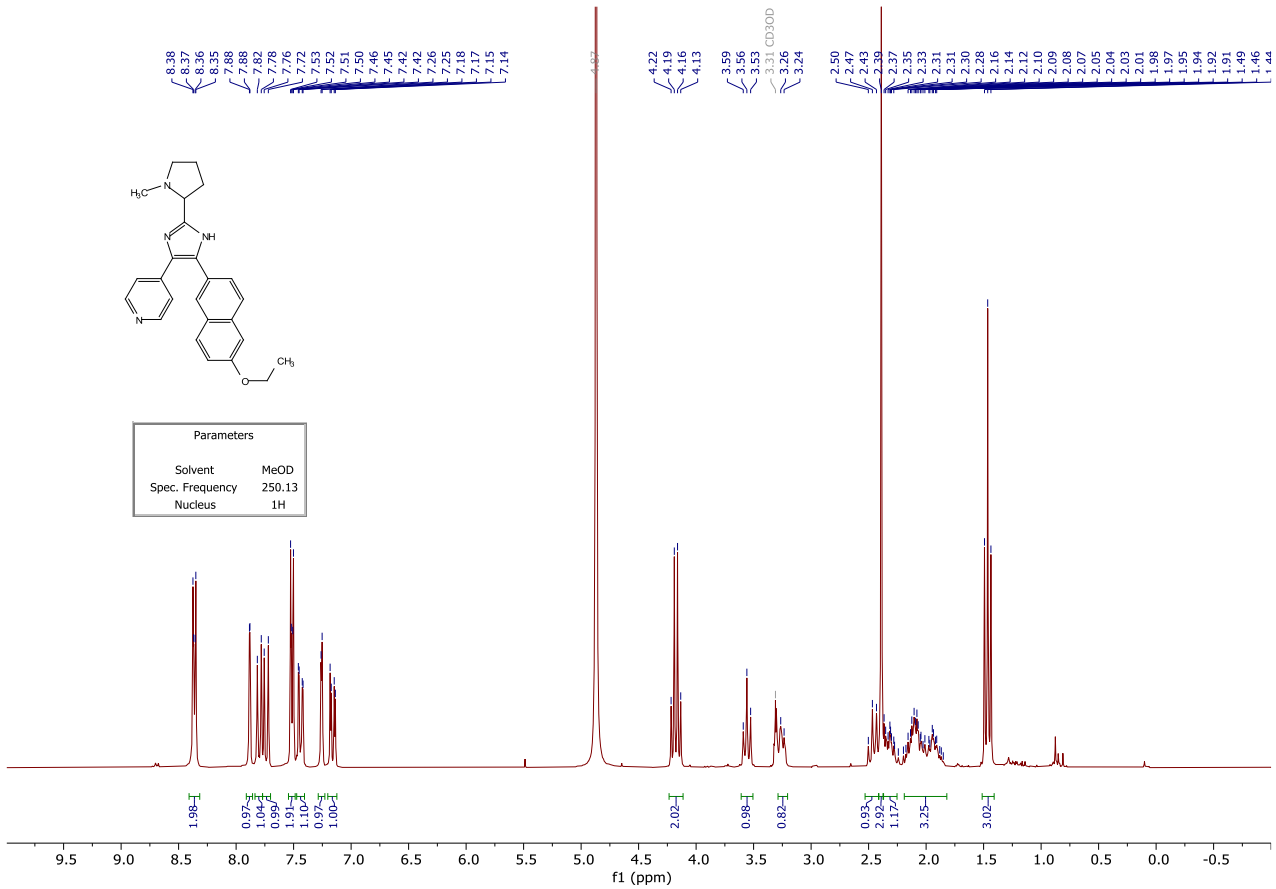


Figure S36. ^{1}H NMR spectra (CD_3OD, 250 MHz) of compound **15j**.

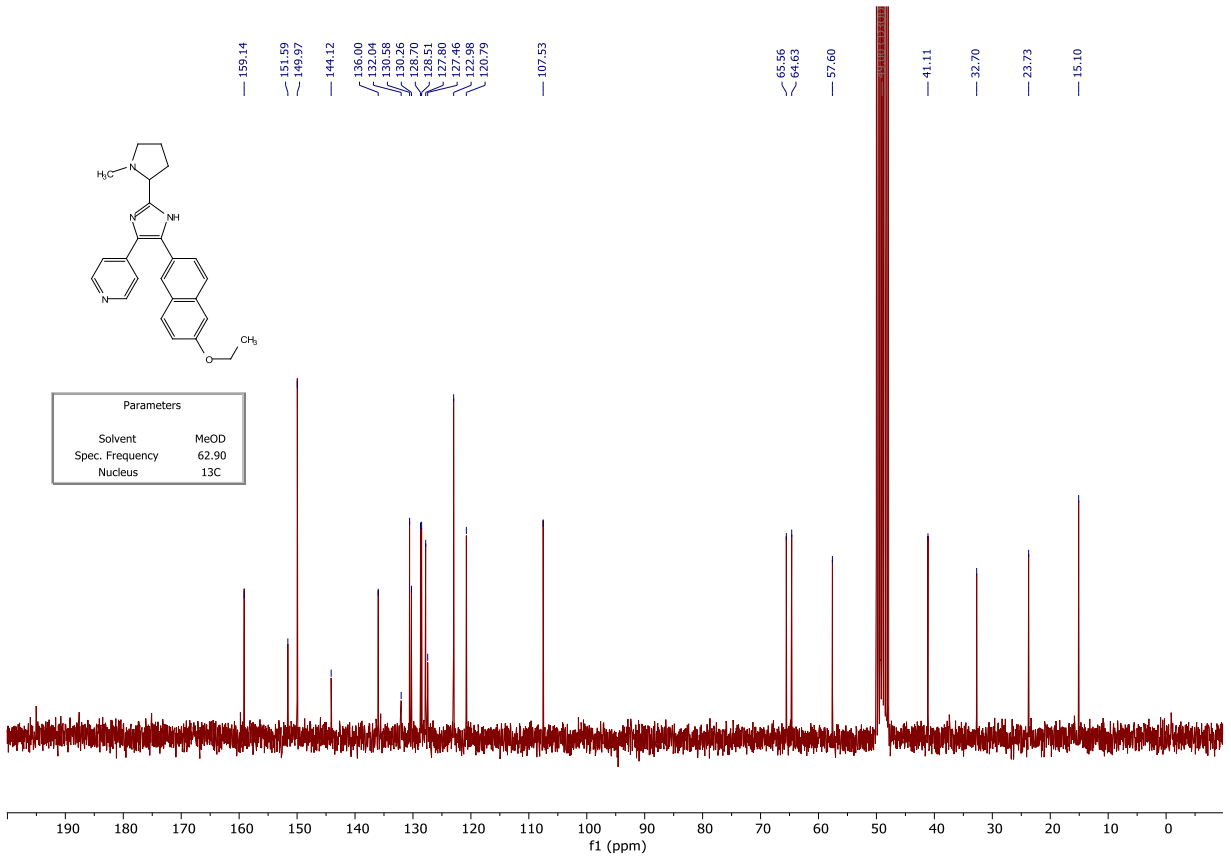


Figure S37. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 63 MHz) of compound **15j**.

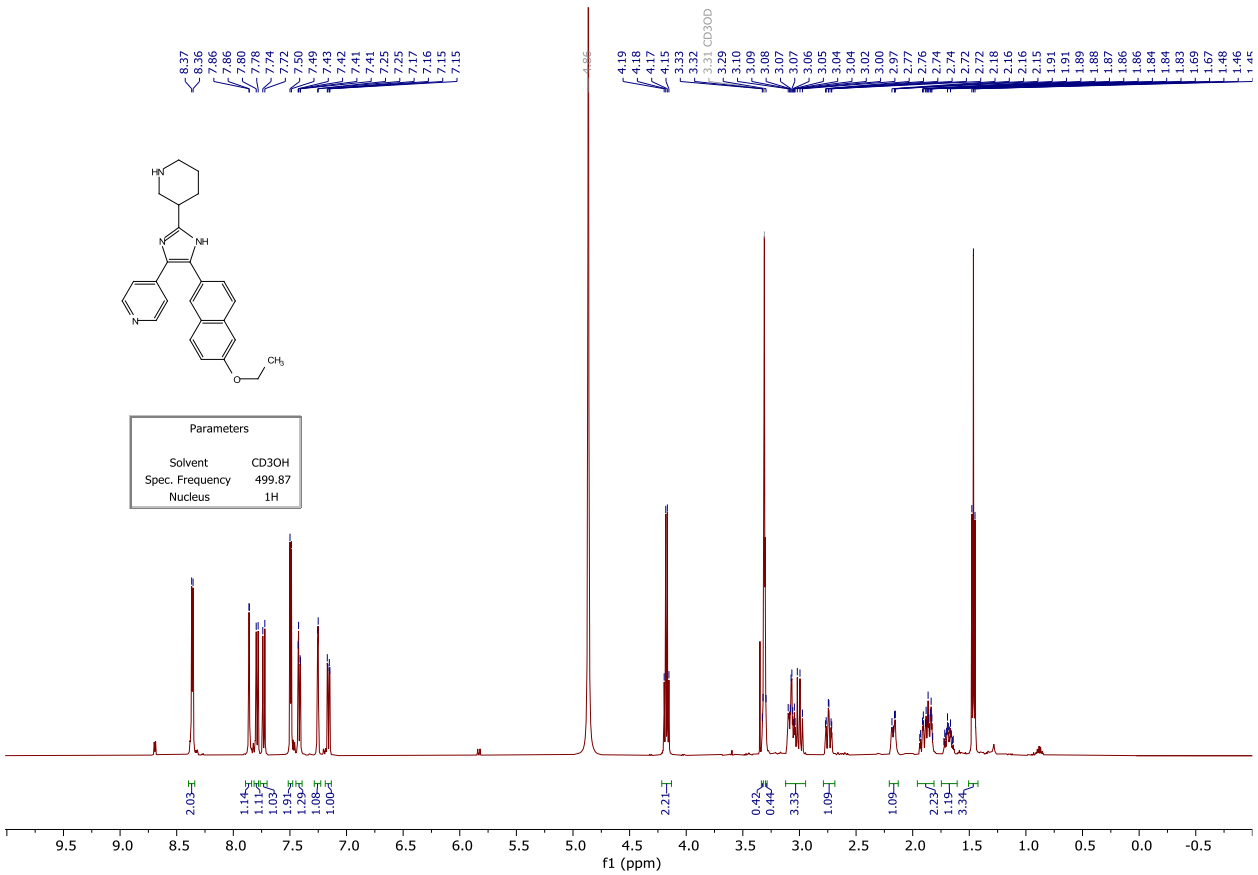


Figure S38. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **14k**.

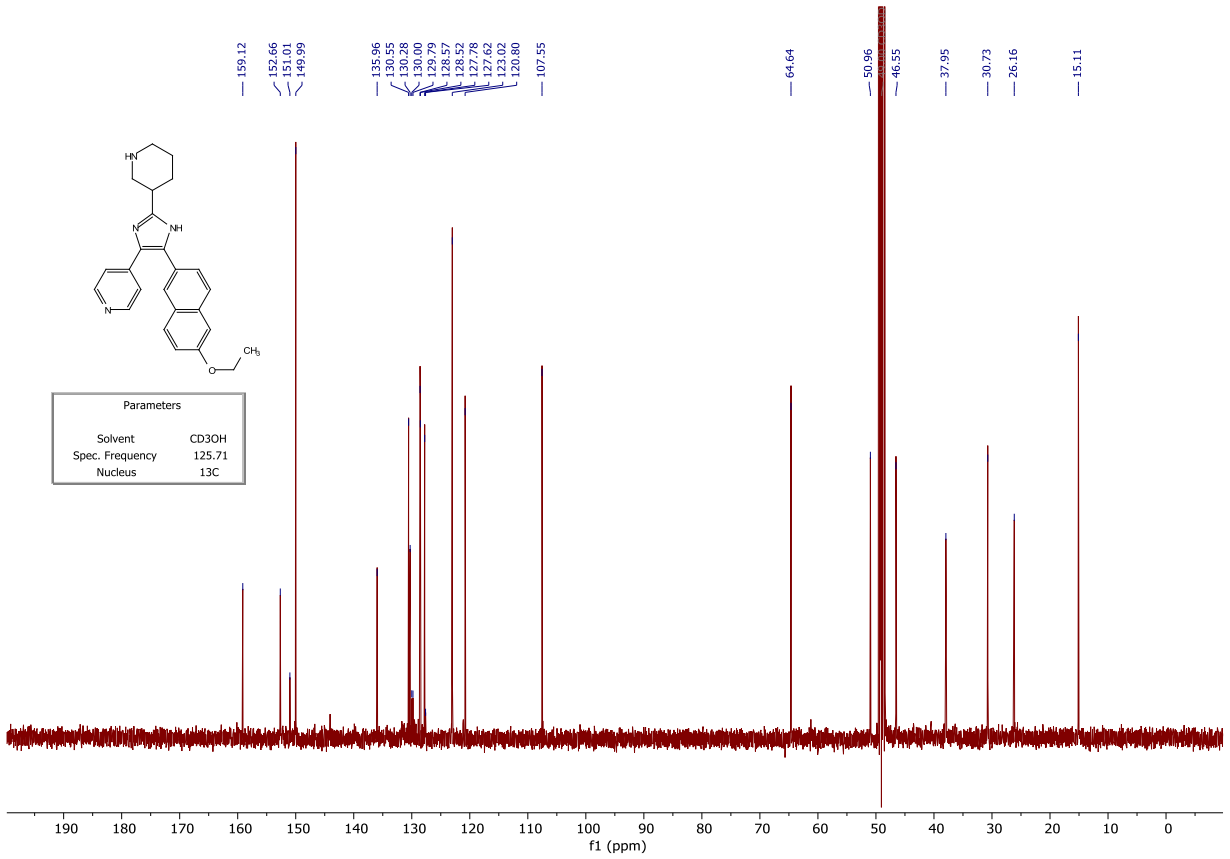


Figure S39. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 126 MHz) of compound **14k**.

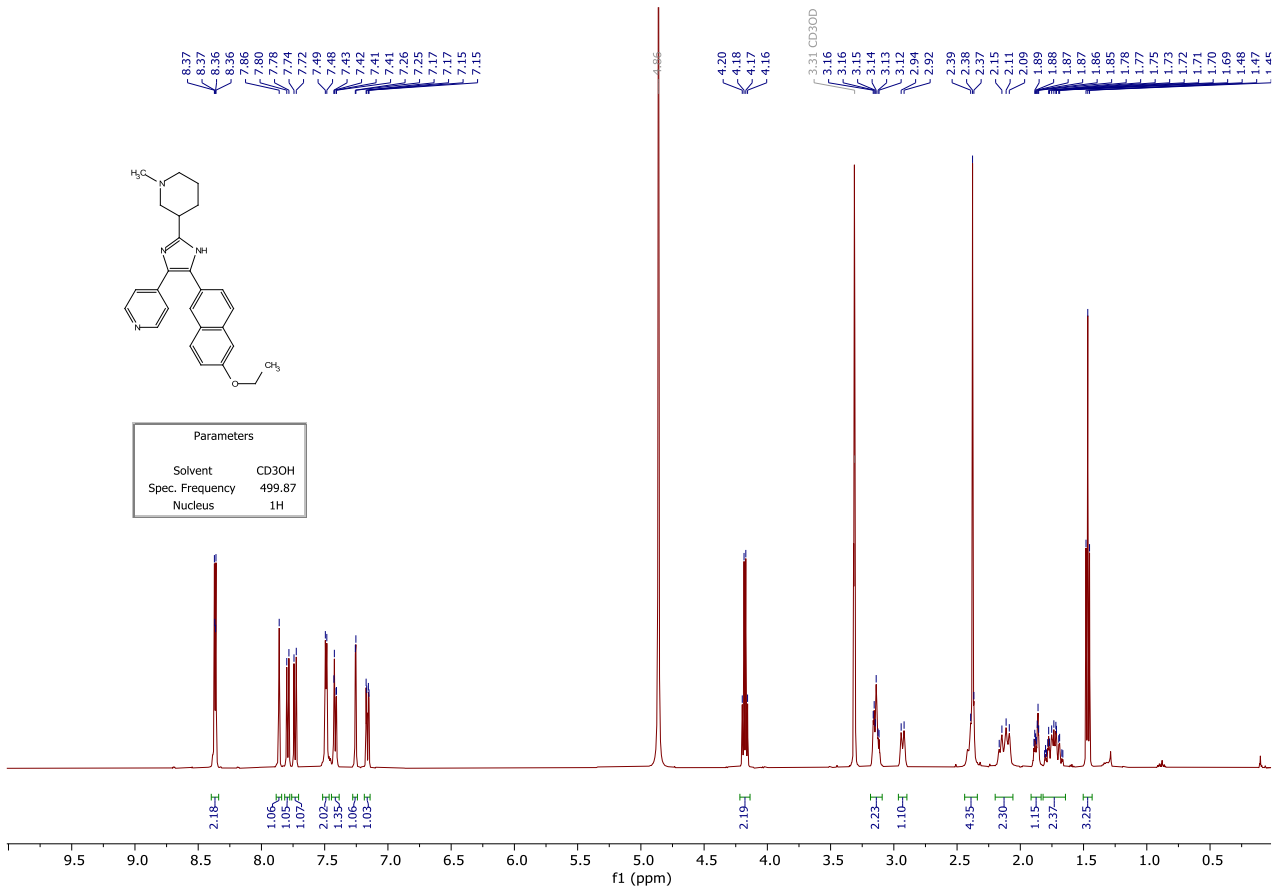


Figure S40. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **15k**.

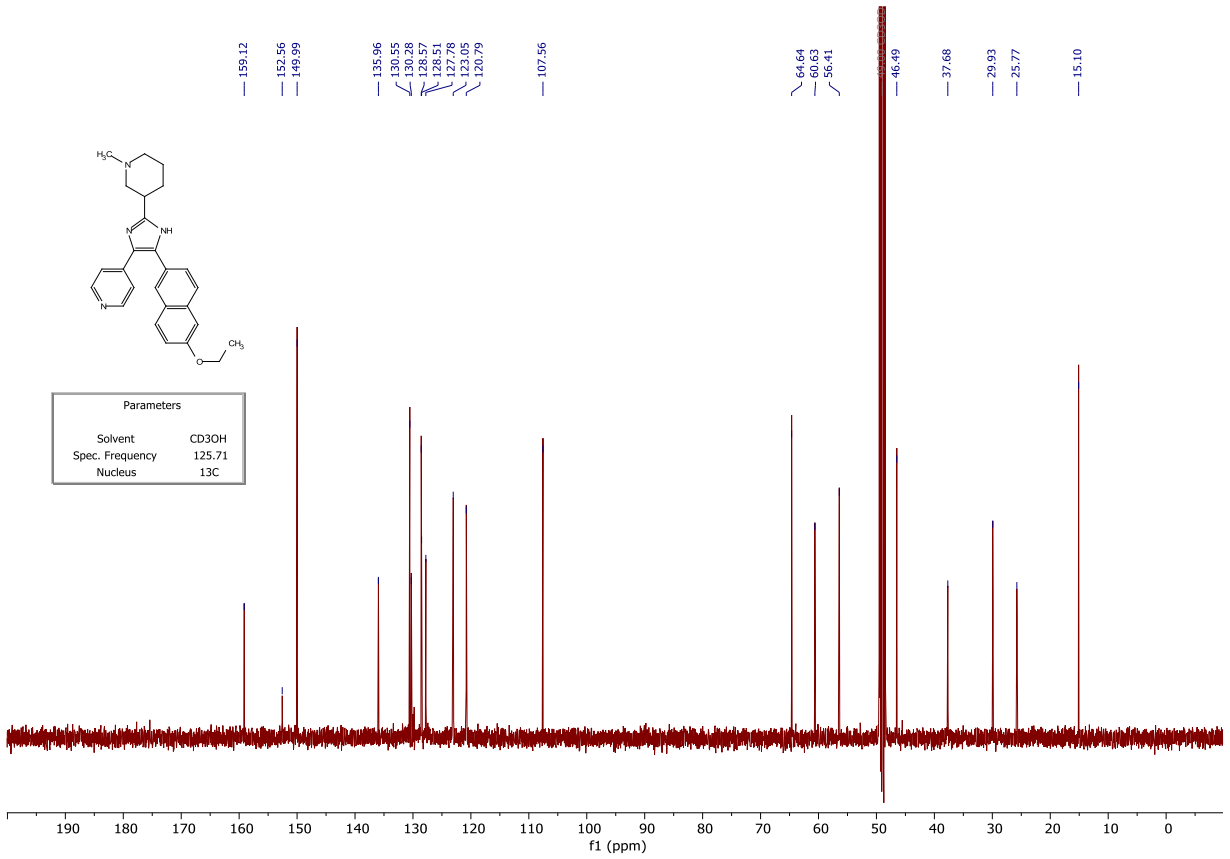


Figure S41. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 126 MHz) of compound **15k**.

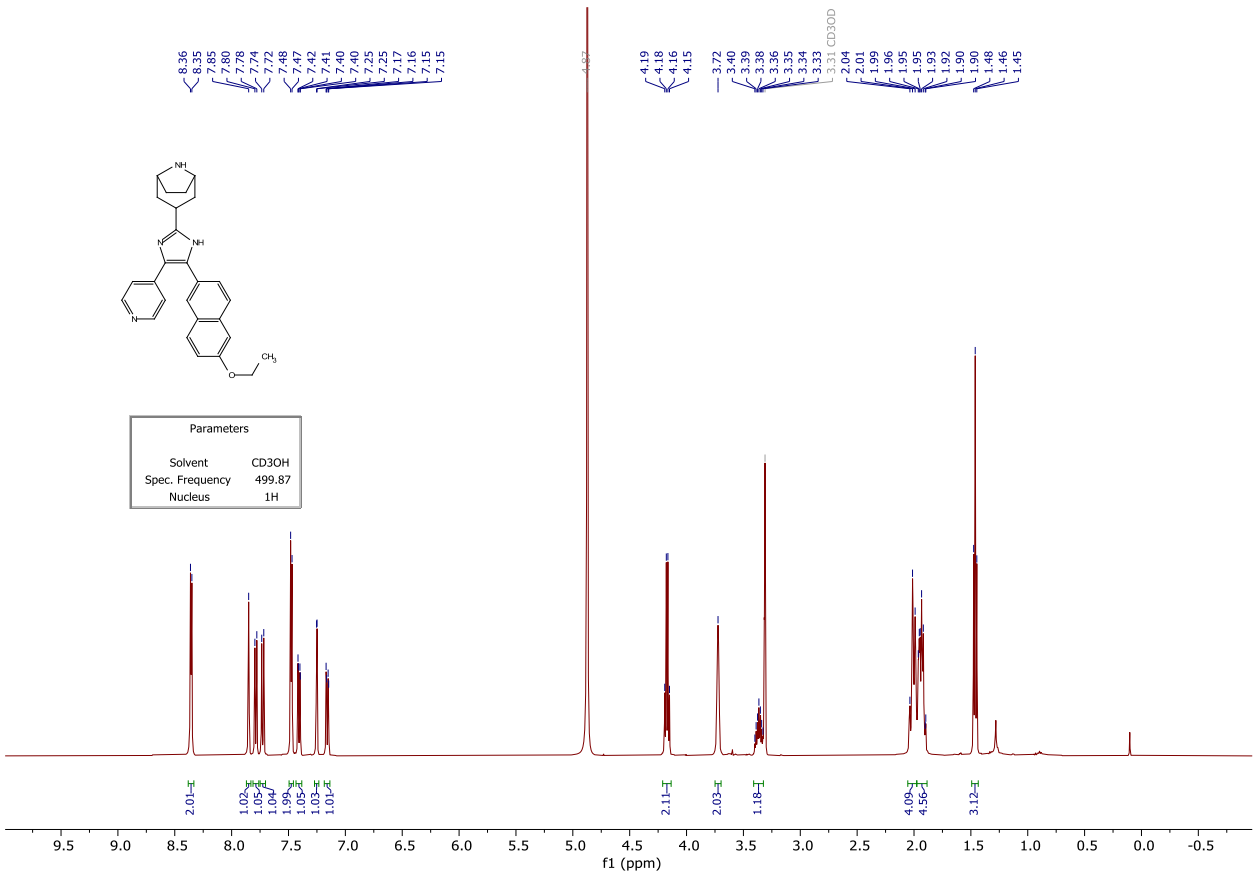


Figure S42. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **14l**.

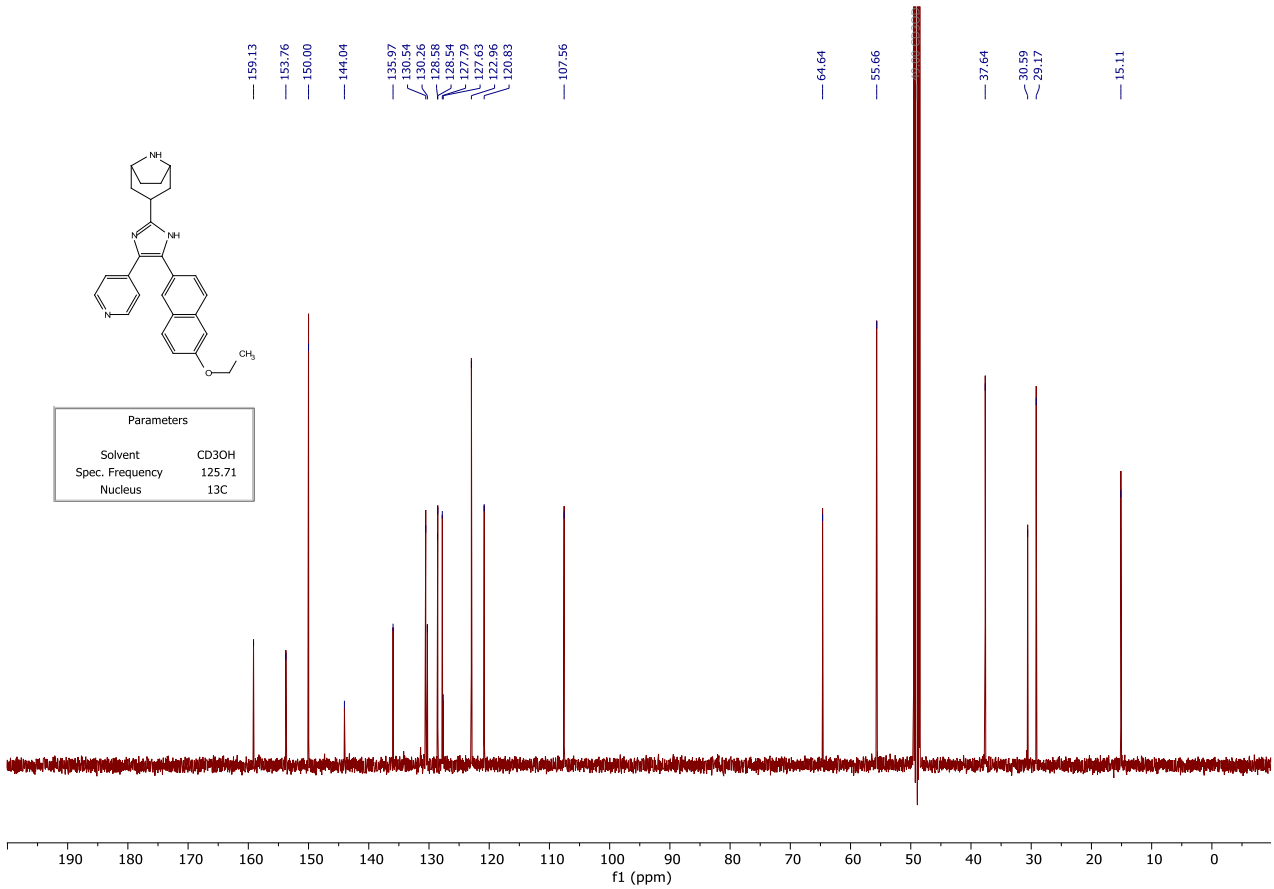


Figure S43. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 126 MHz) of compound **14l**.

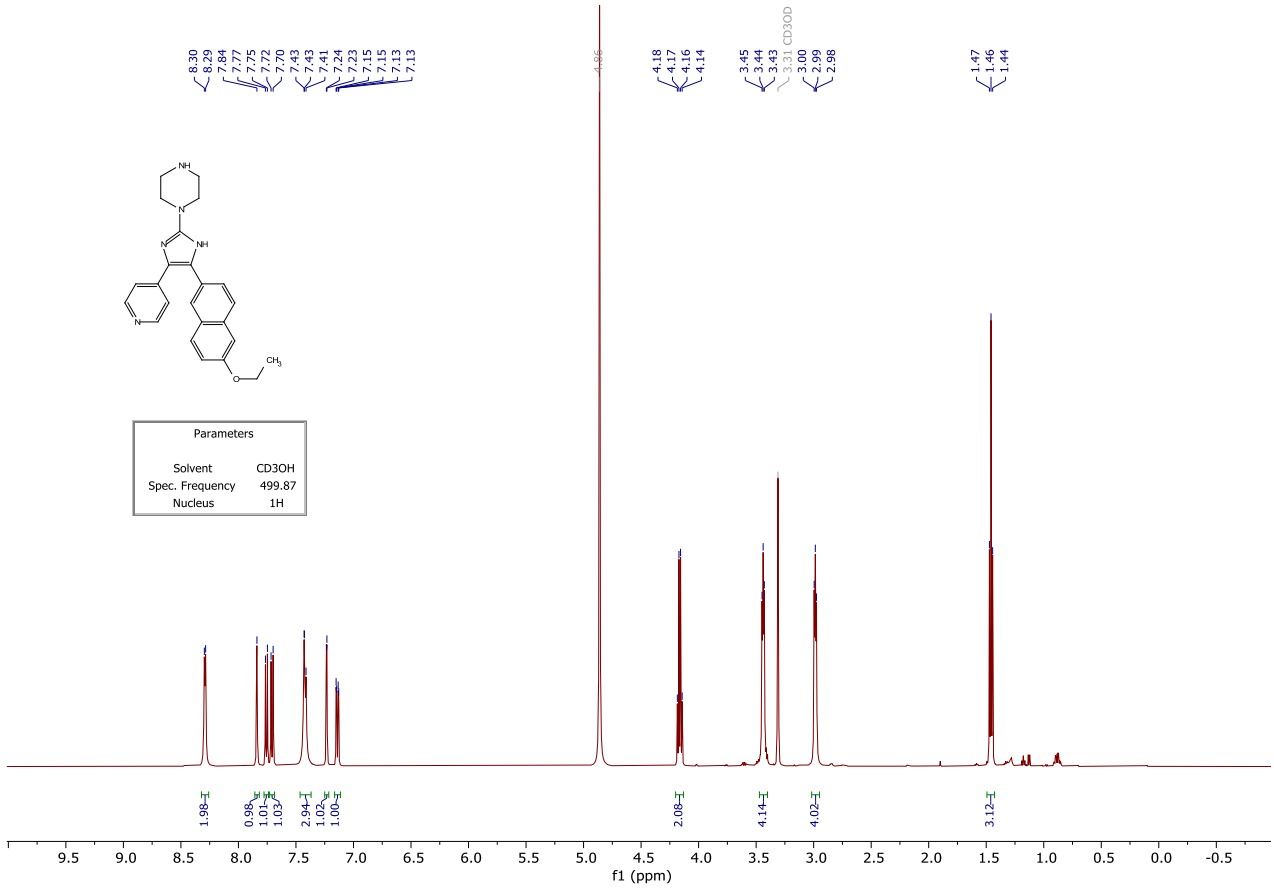


Figure S44. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **14m**.

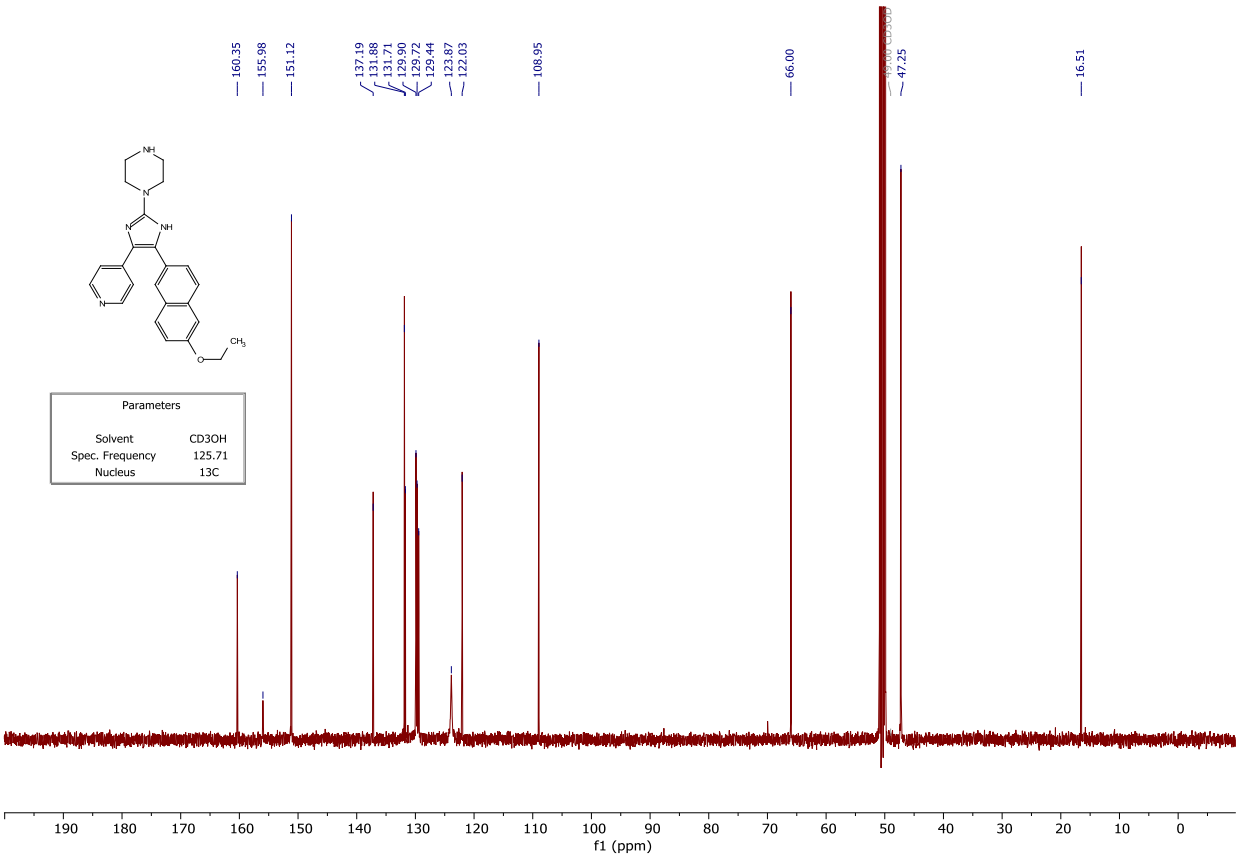


Figure S45. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 126 MHz) of compound **14m**.

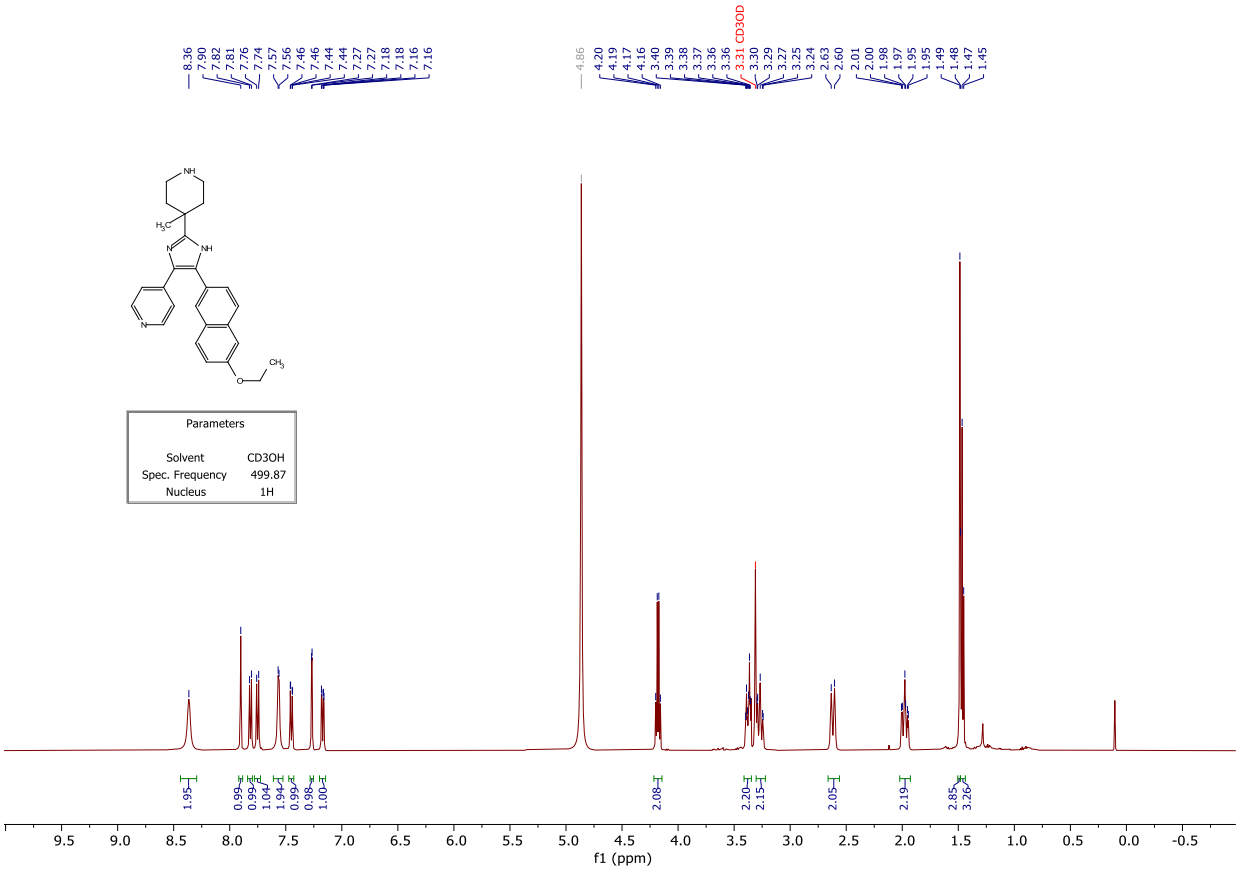


Figure S46. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **14n**.

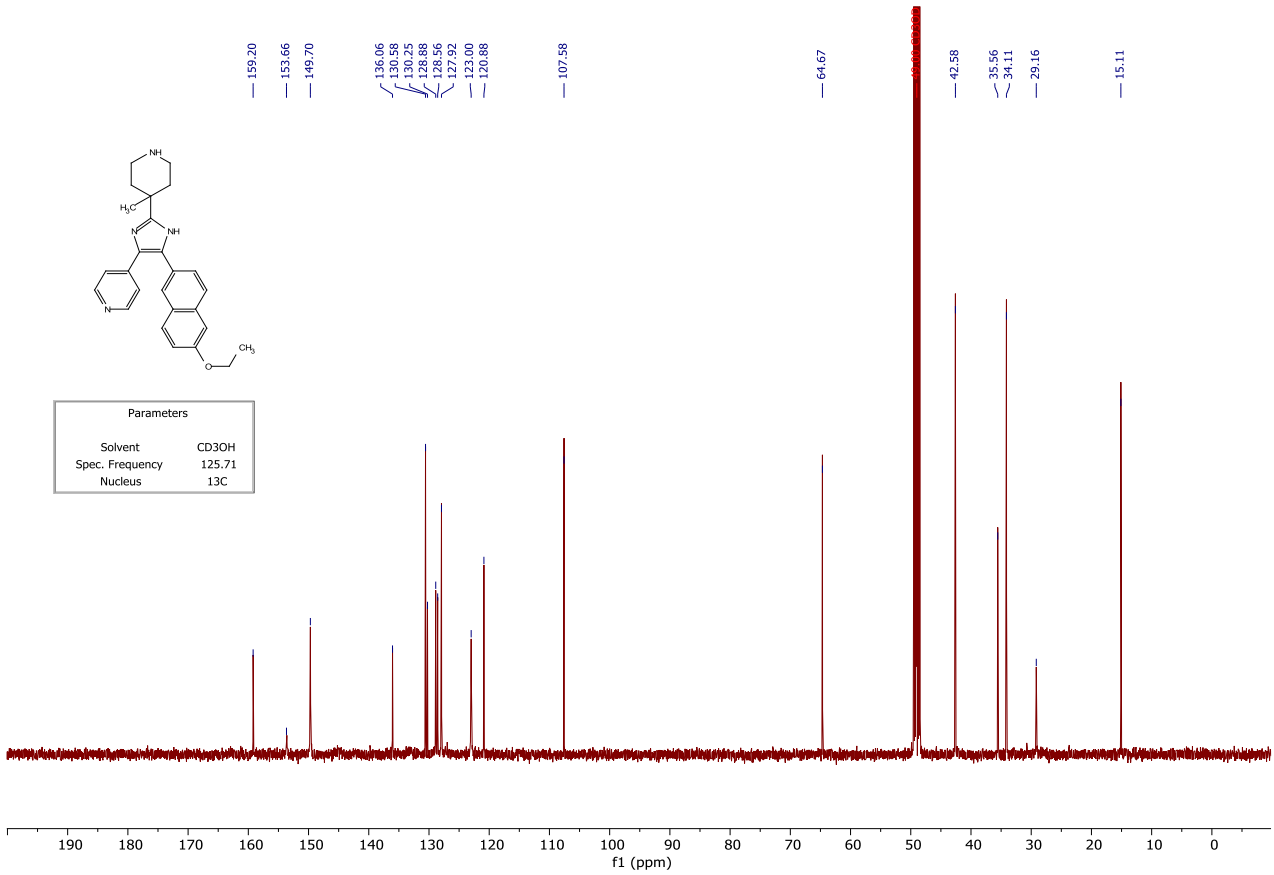


Figure S47. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 126 MHz) of compound **14n**.

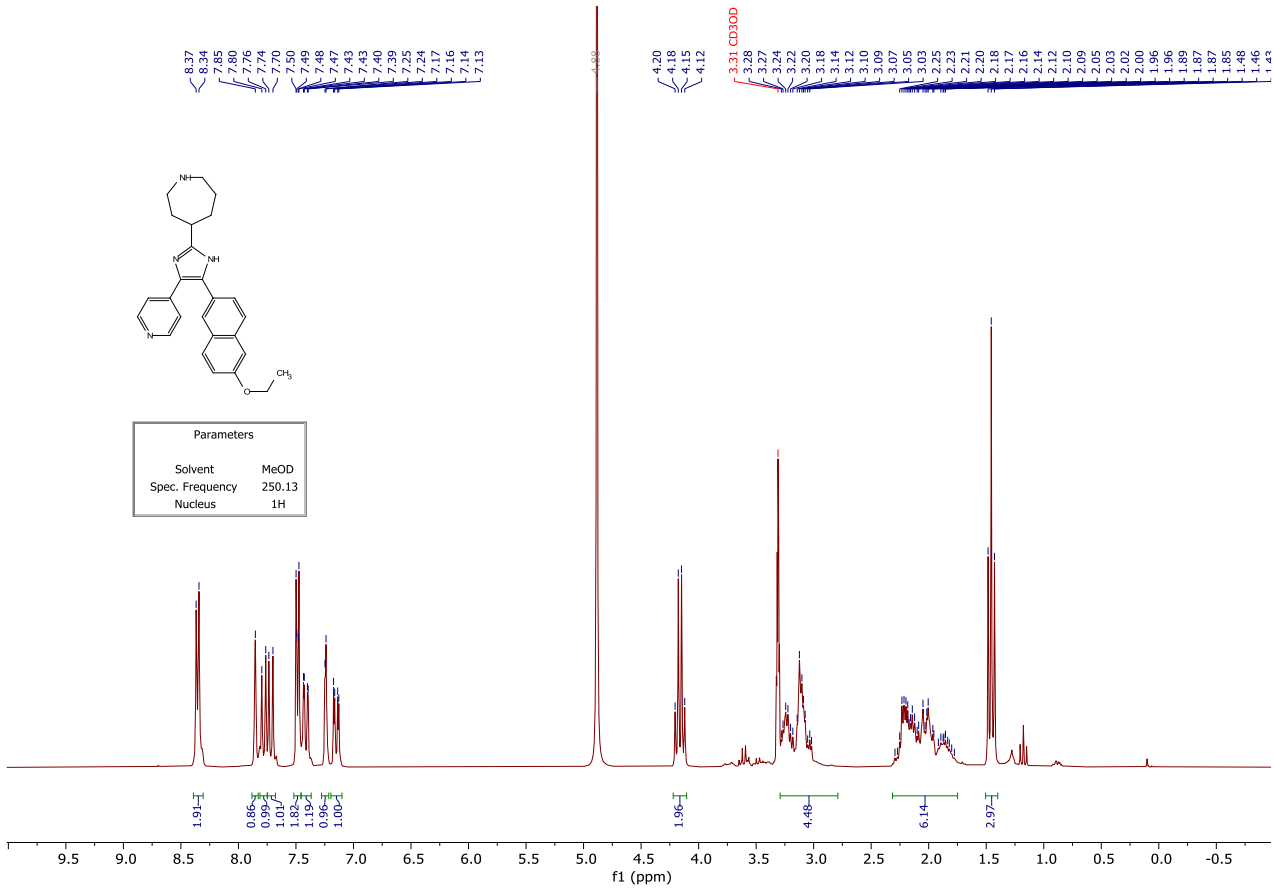


Figure S48. ^{1}H NMR spectra (CD_3OD, 250 MHz) of compound **14o**.

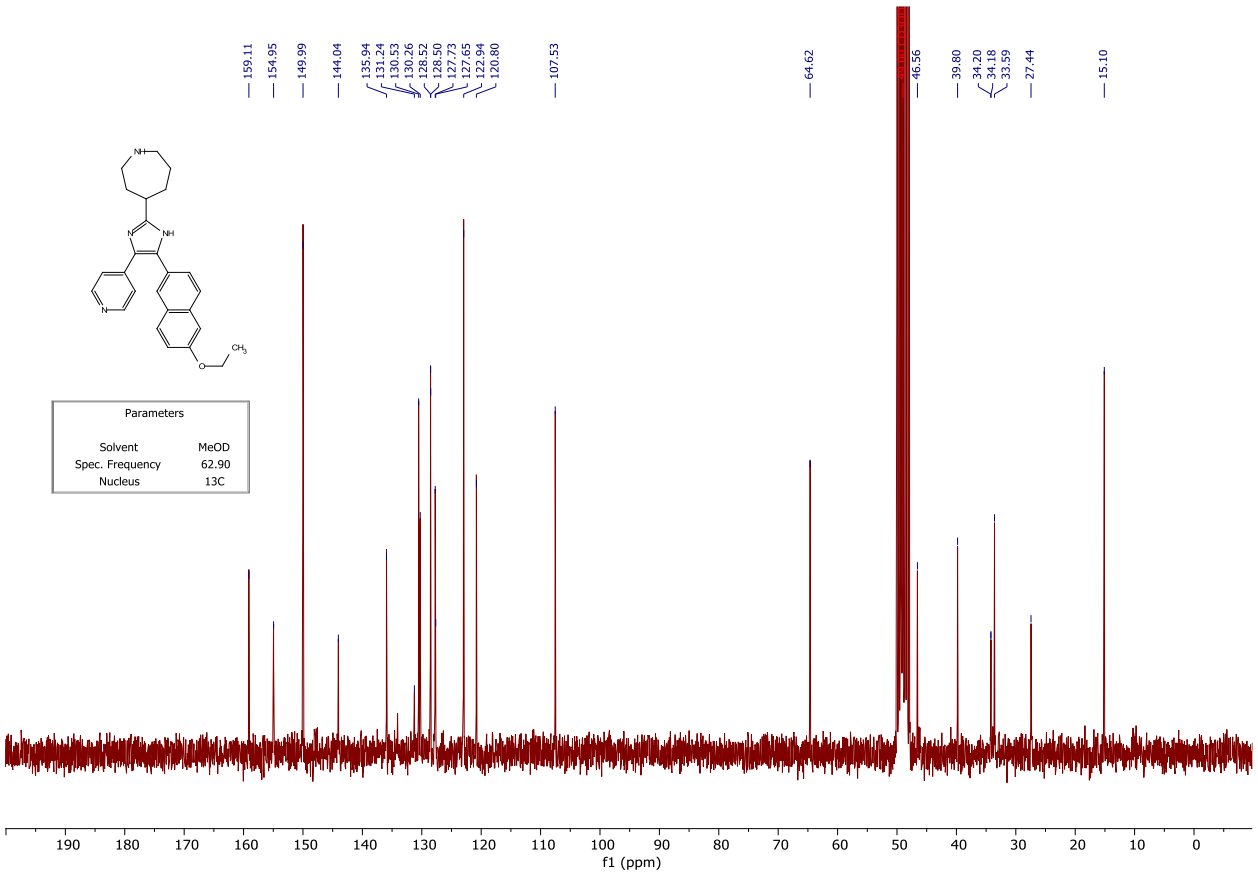


Figure S49. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 63 MHz) of compound **14o**.

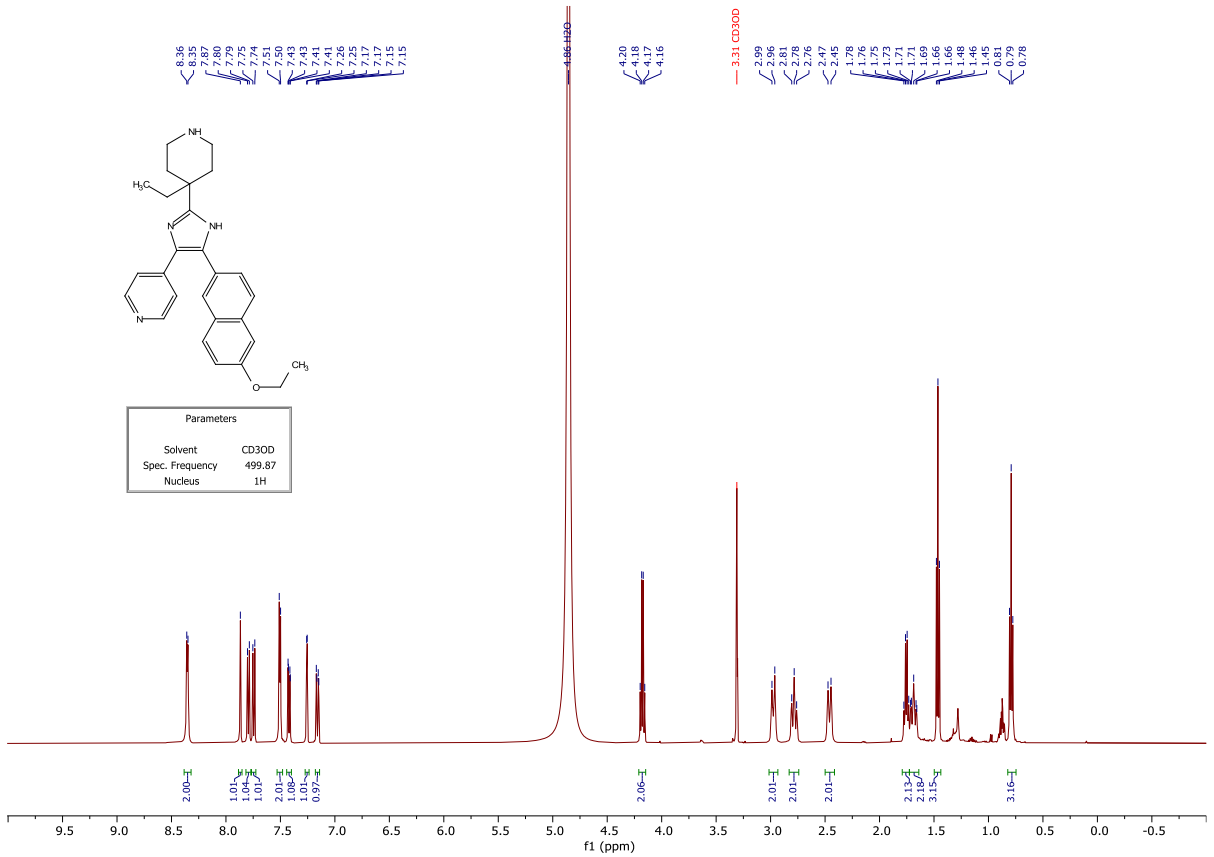


Figure S50. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **14p**.

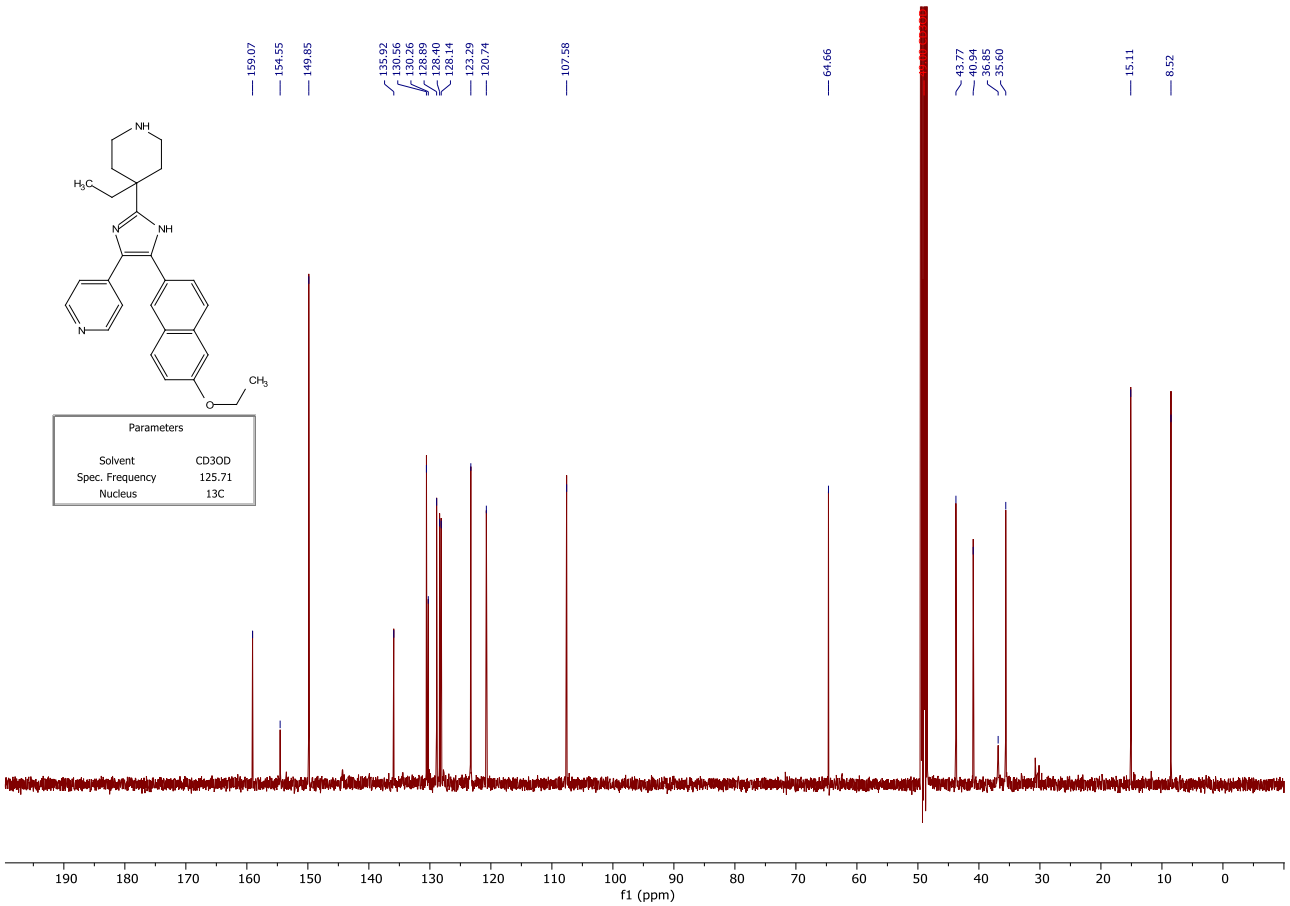


Figure S51. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 126 MHz) of compound **14p**.

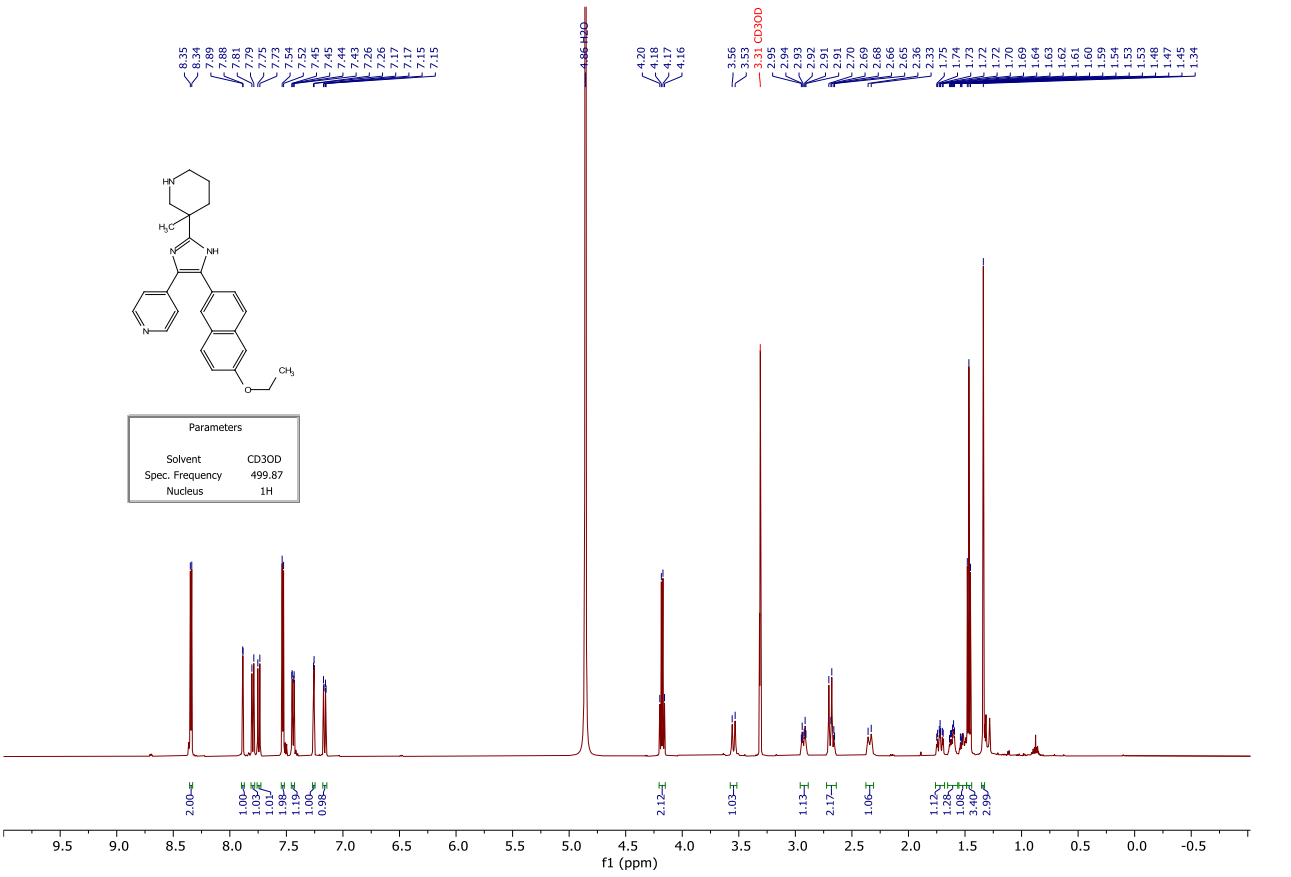


Figure S52. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **14q**.

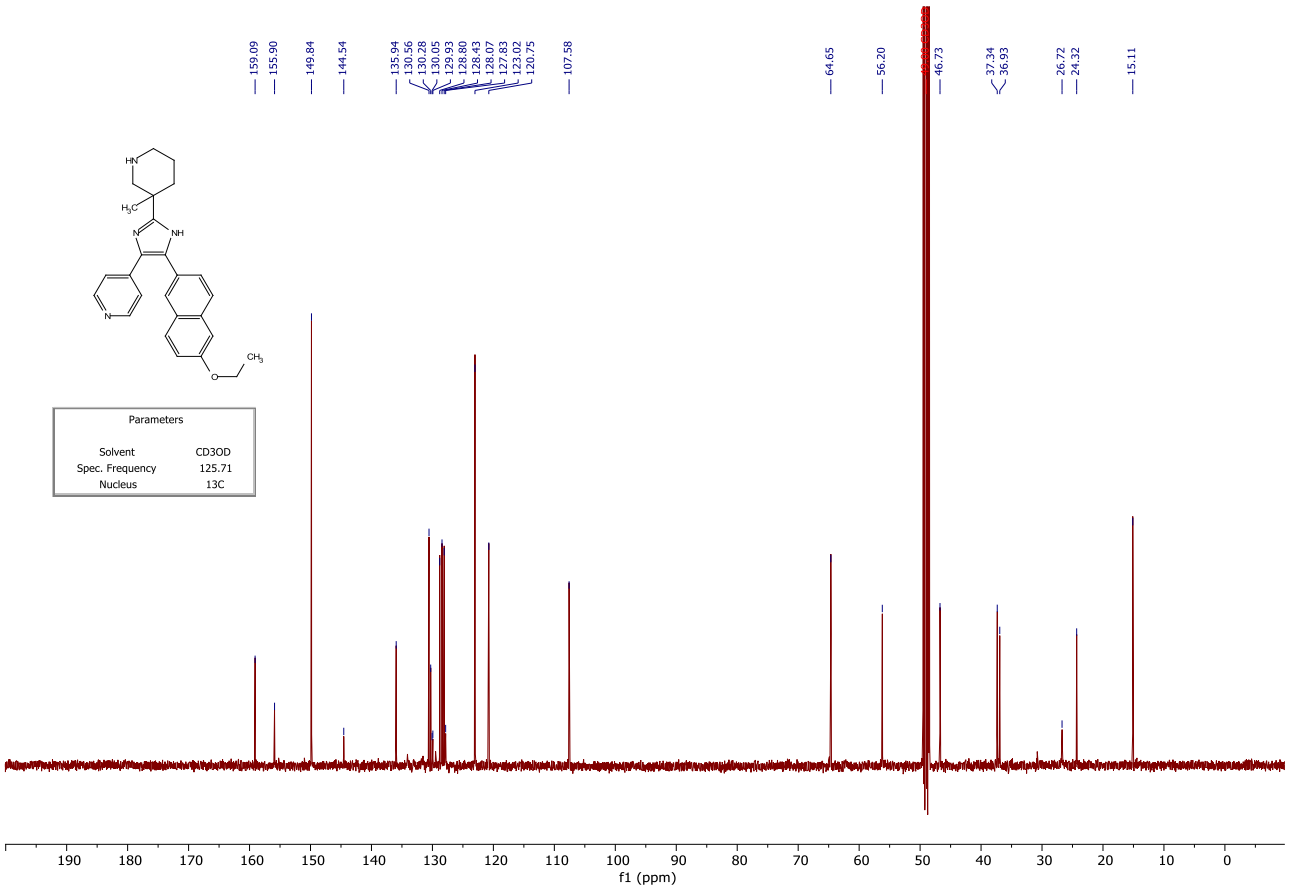


Figure S53. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 126 MHz) of compound **14q**.

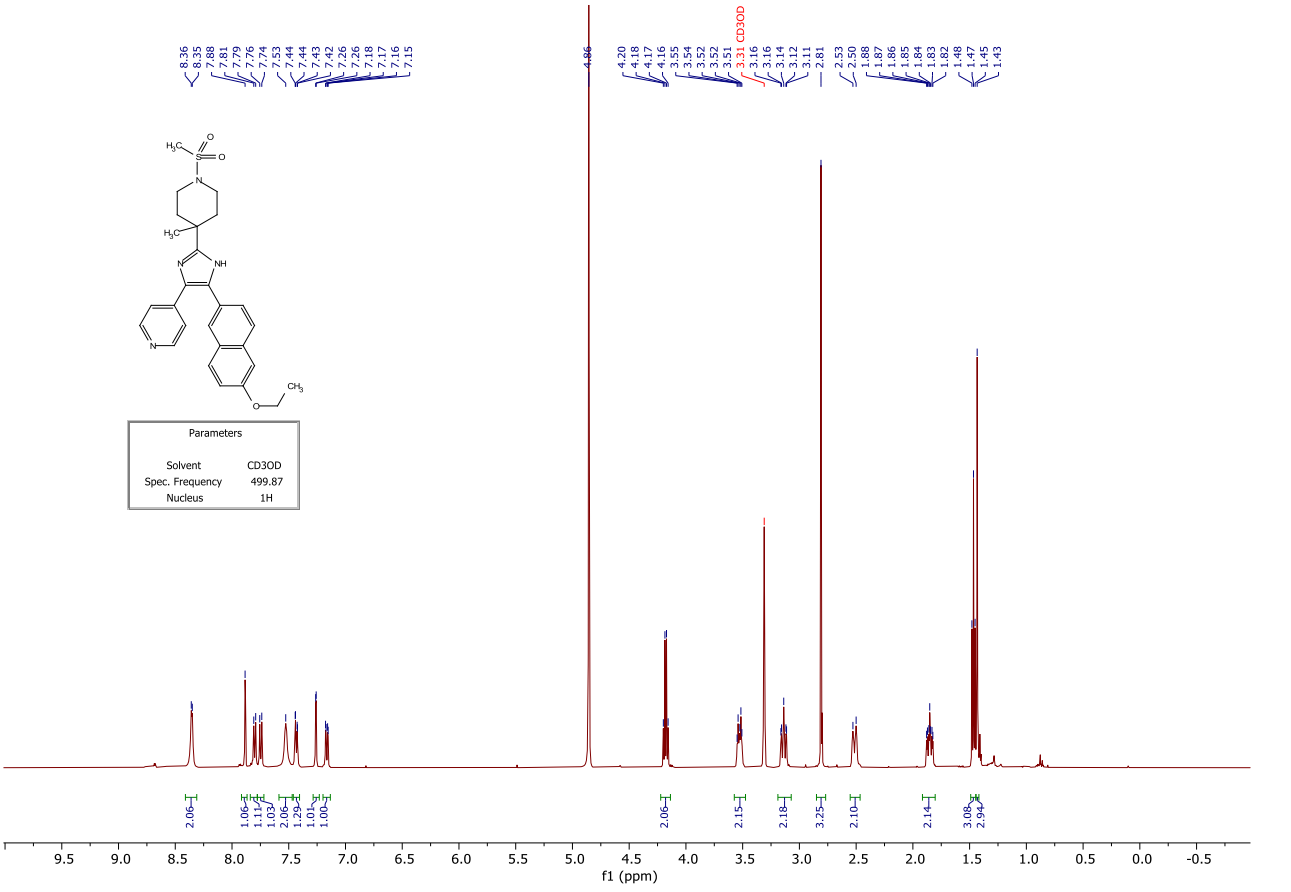


Figure S54. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **13r**.

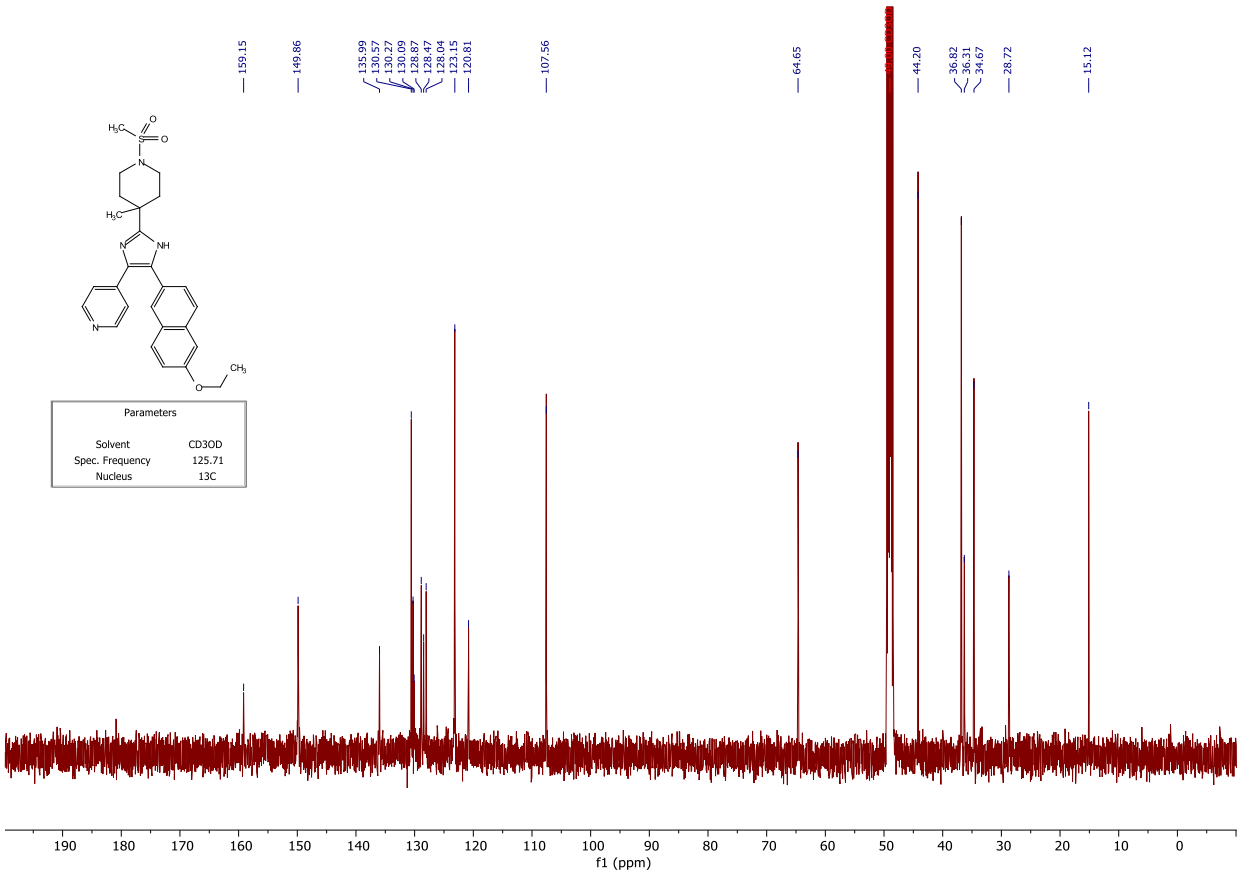


Figure S55. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 126 MHz) of compound **13r**.

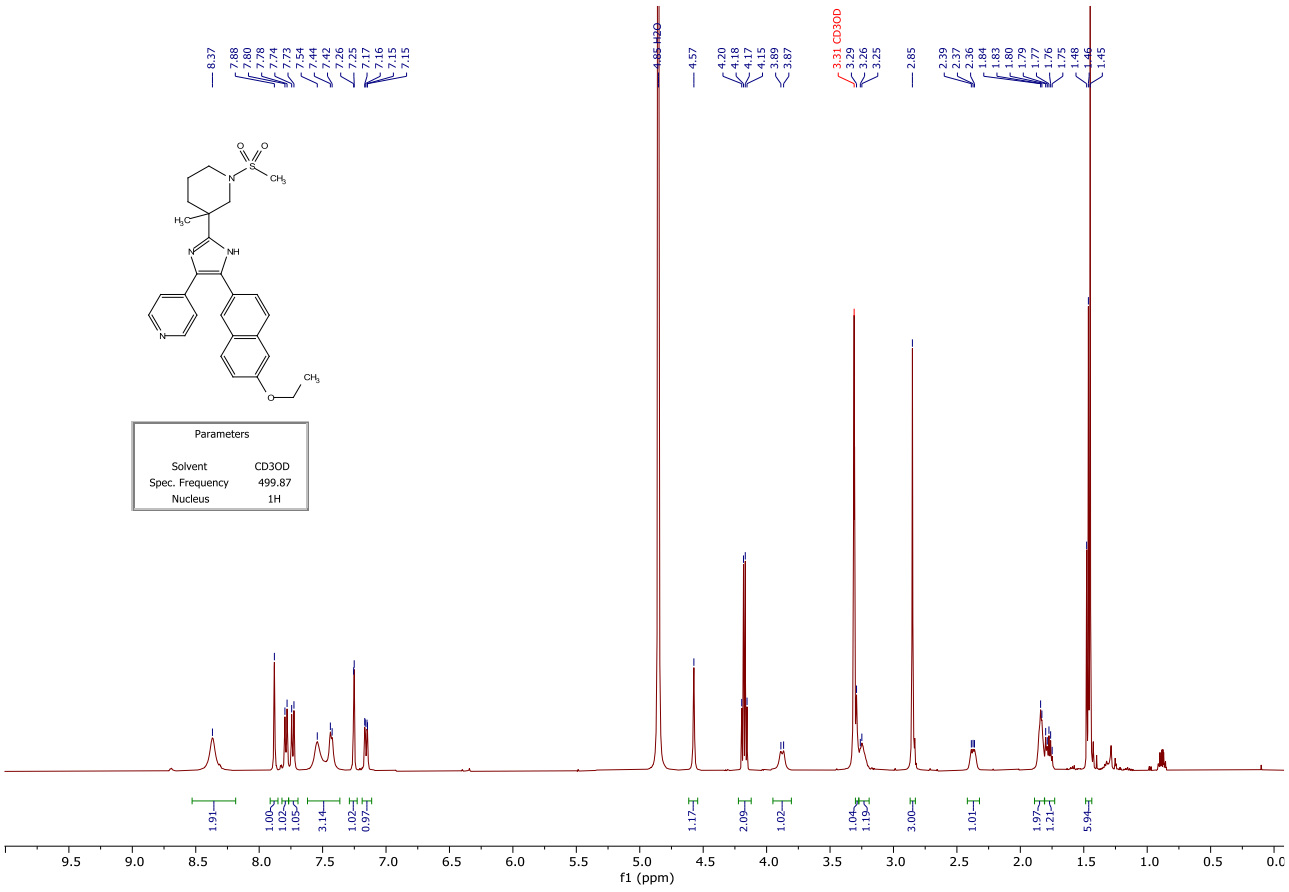


Figure S56. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **13s**.

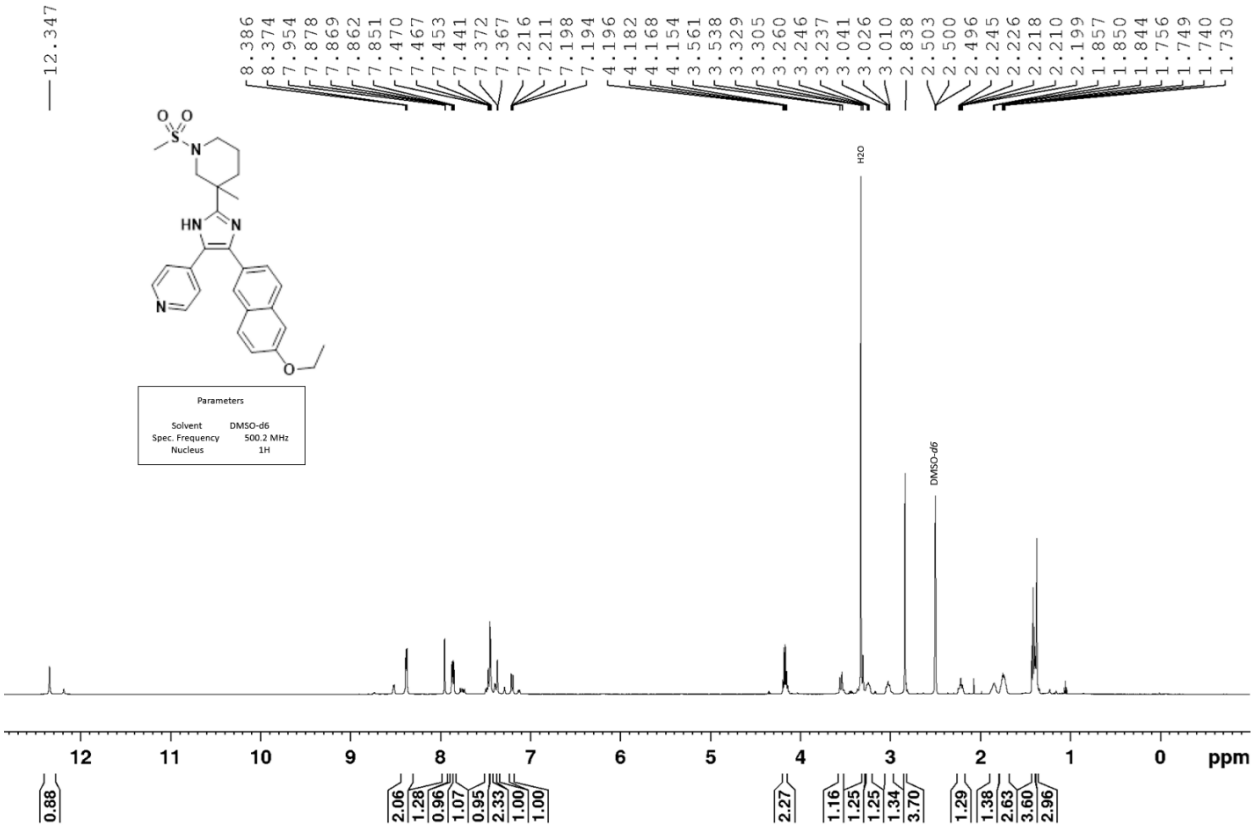


Figure S57. ^{1}H NMR spectra (DMSO-d_6, 500 MHz) of compound **13s**.

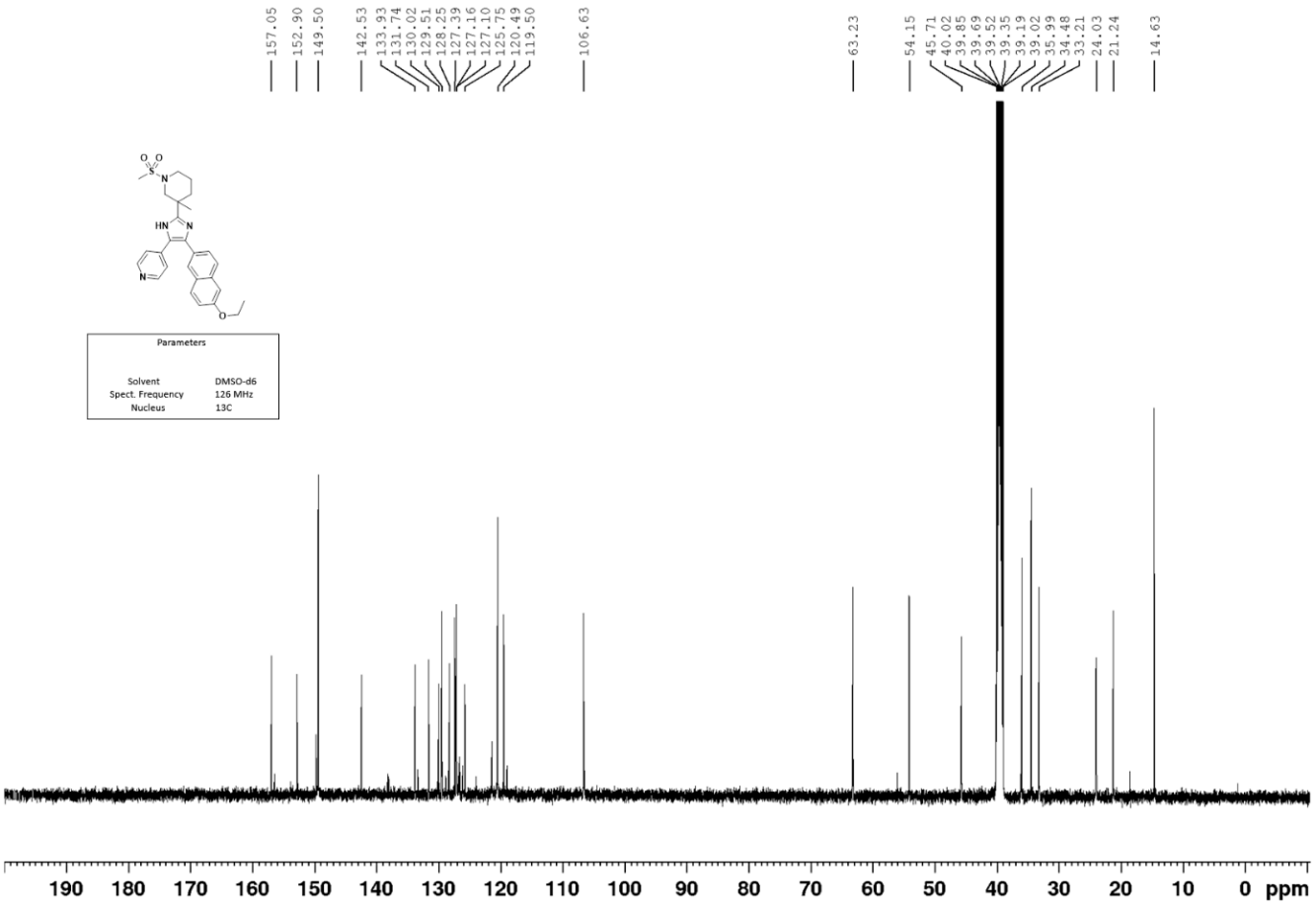


Figure S58. $^{13}C\{^{1}H\}$ NMR spectra (DMSO-d_6, 126 MHz) of compound **13s**.

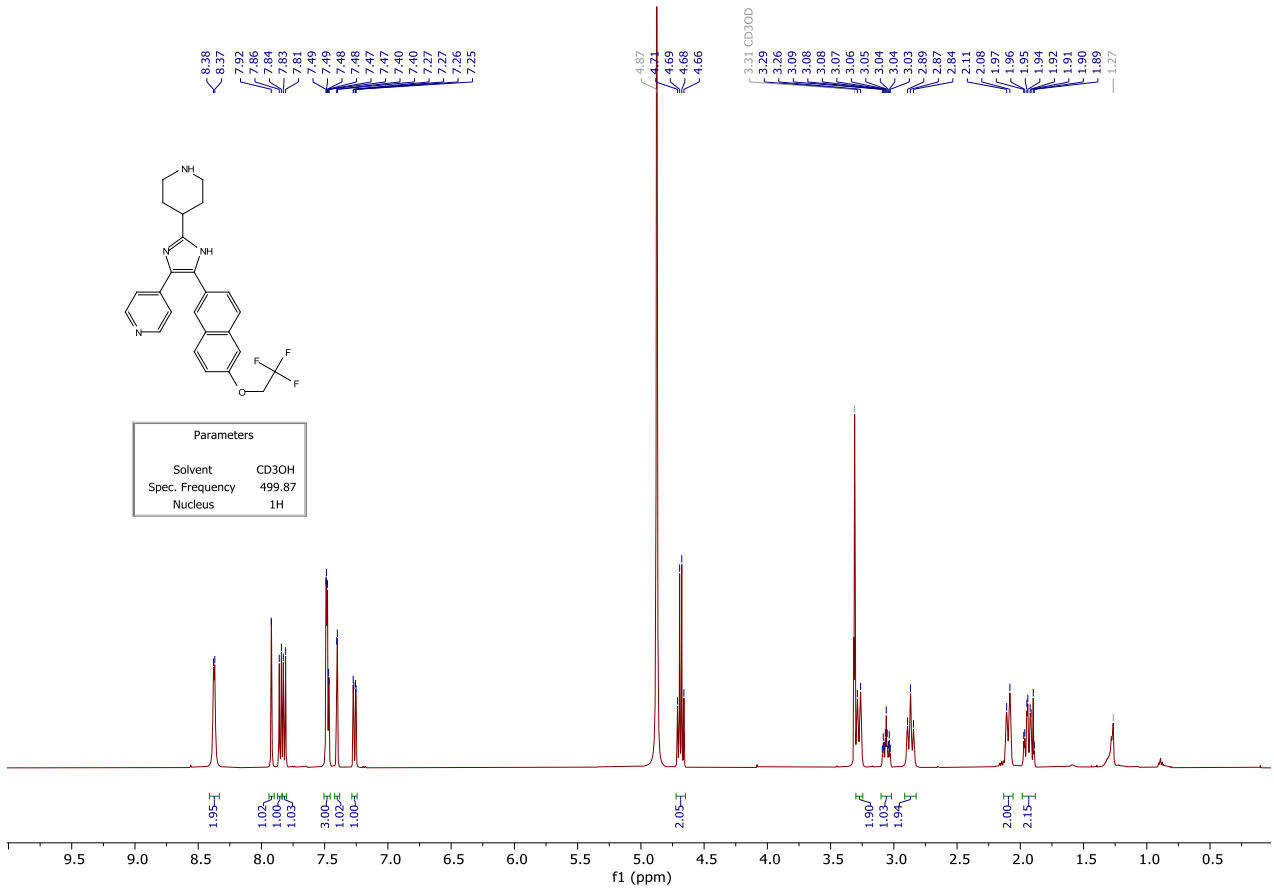


Figure S59. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **14t**.

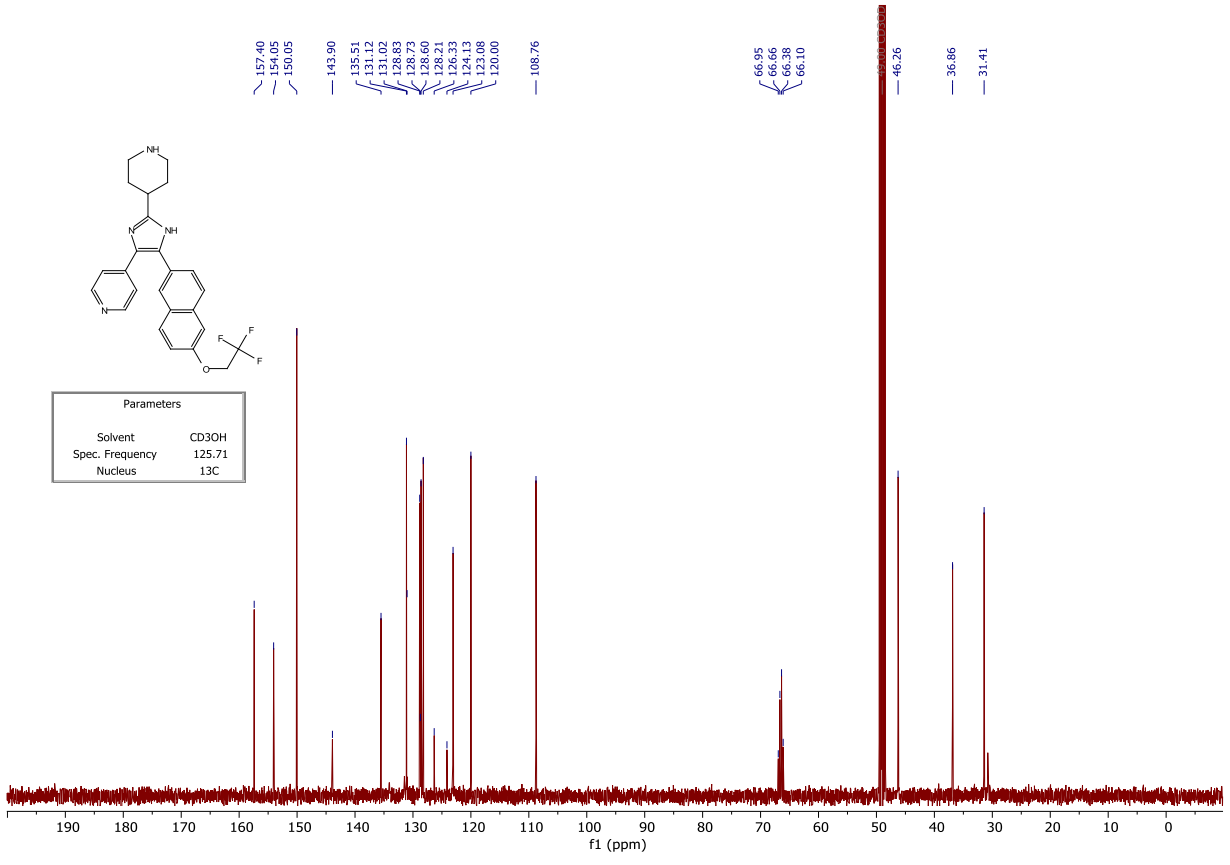


Figure S60. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 126 MHz) of compound **14t**.

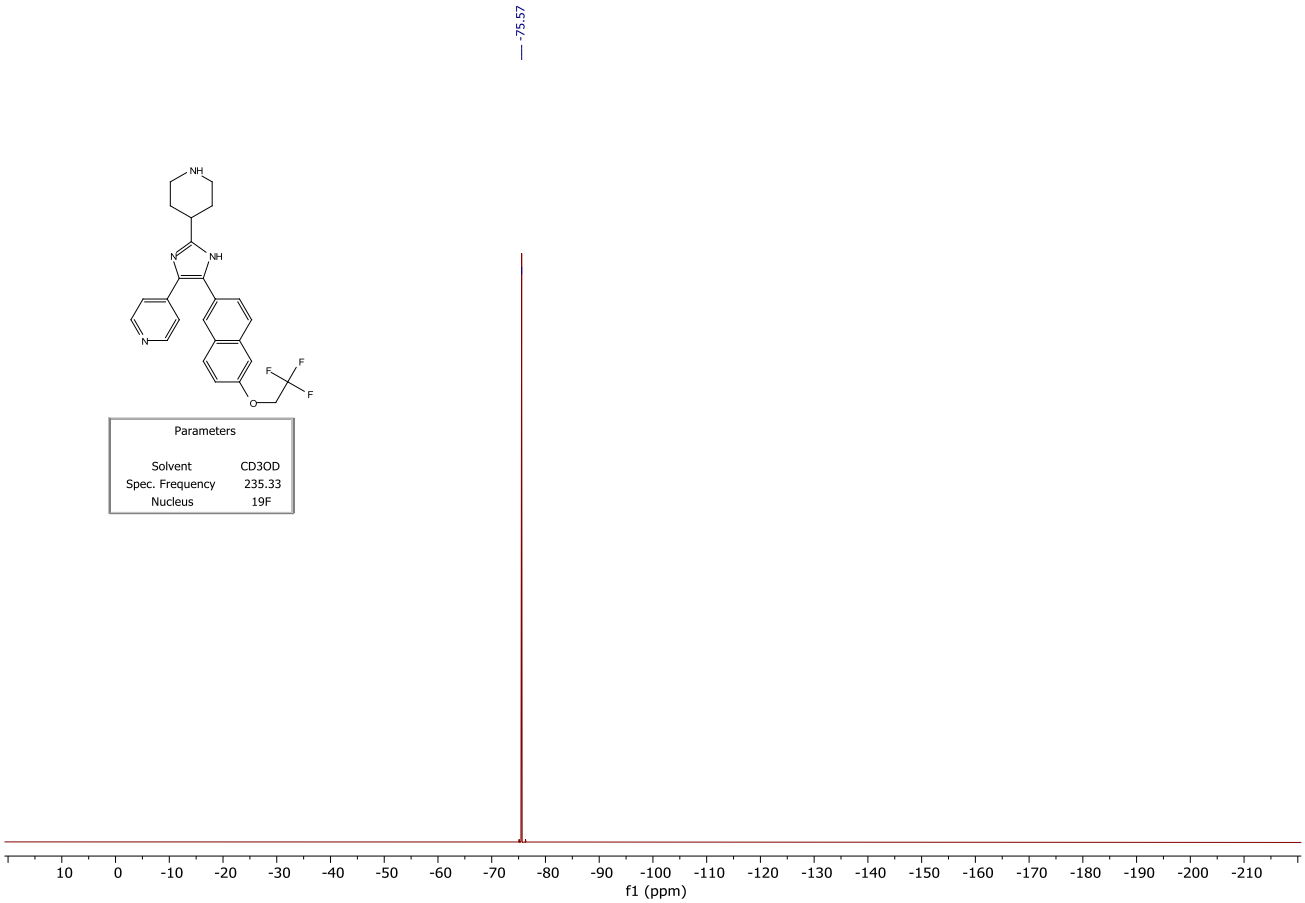


Figure S61. $^{19}F\{^{1}H\}$ NMR spectra (CD_3OD, 235 MHz) of compound **14t**.

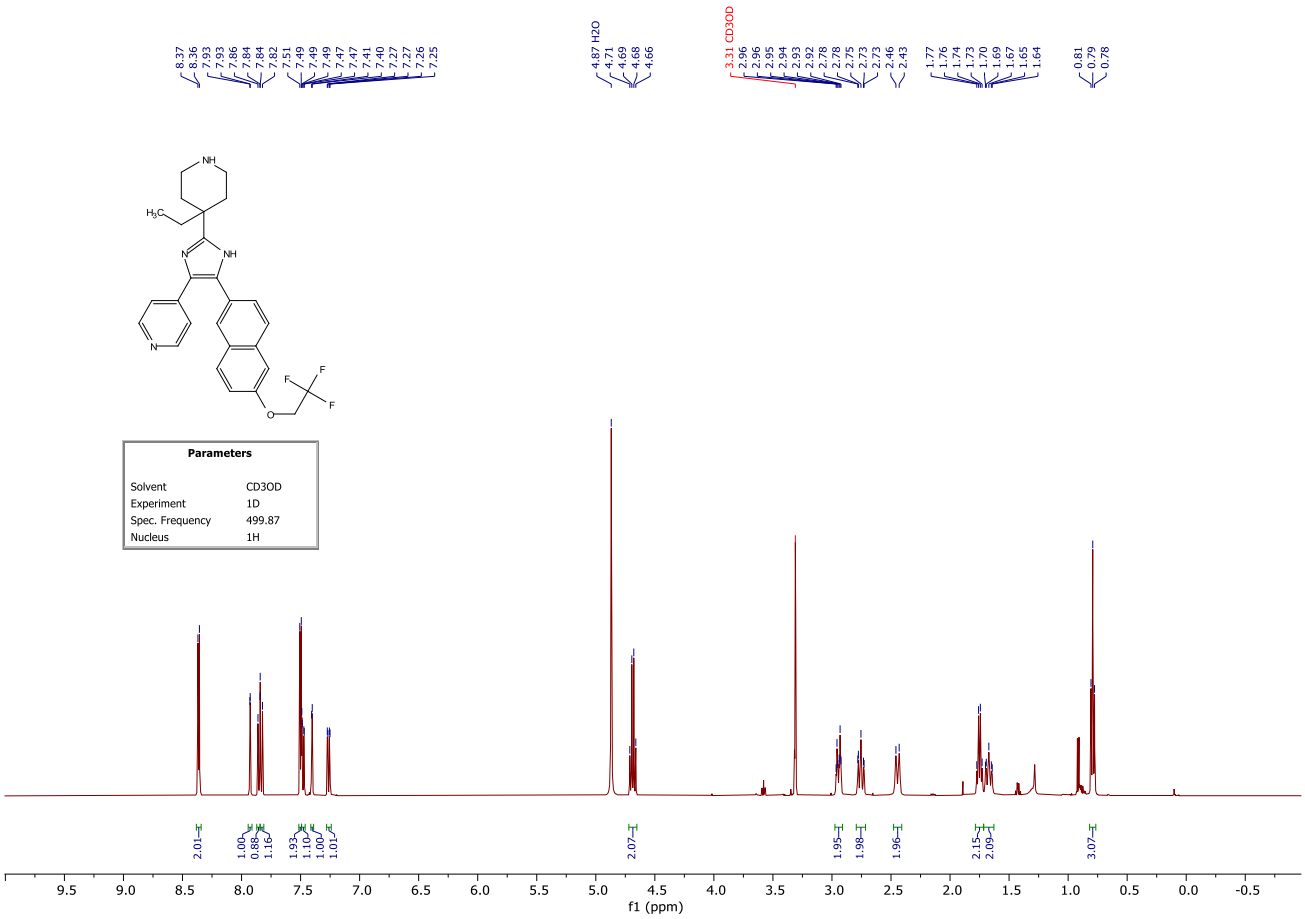


Figure S62. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **14u**.

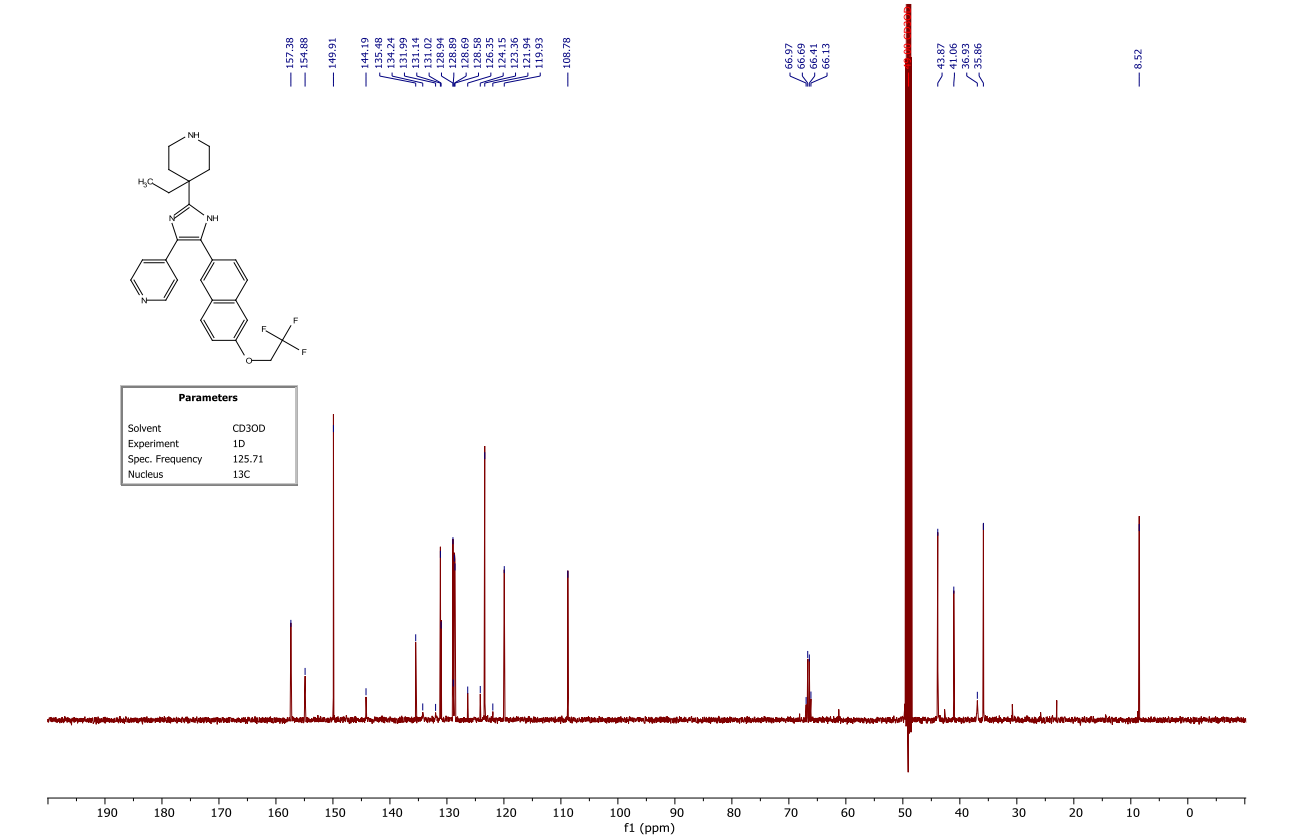


Figure S63. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 126 MHz) of compound **14u**.

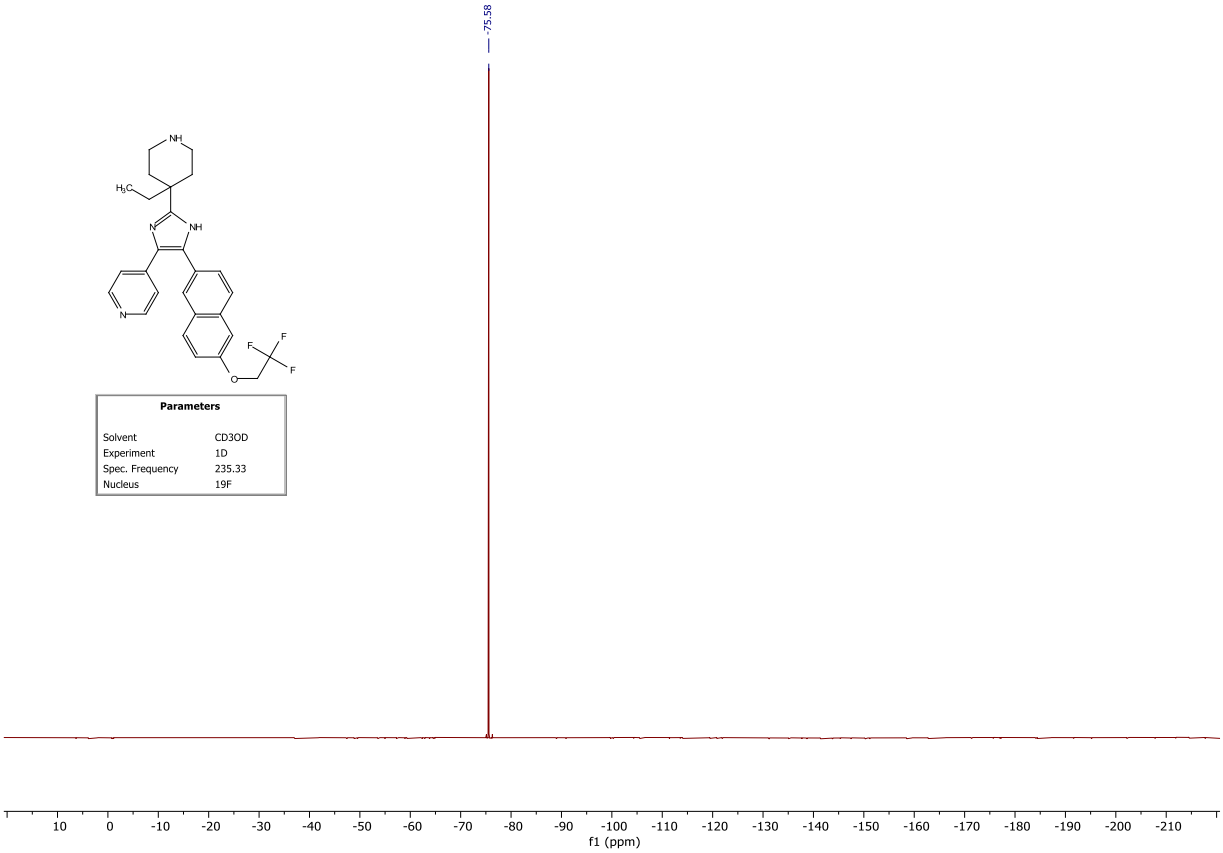


Figure S64. $^{19}F\{^{1}H\}$ NMR spectra (CD_3OD, 235 MHz) of compound **14u**.

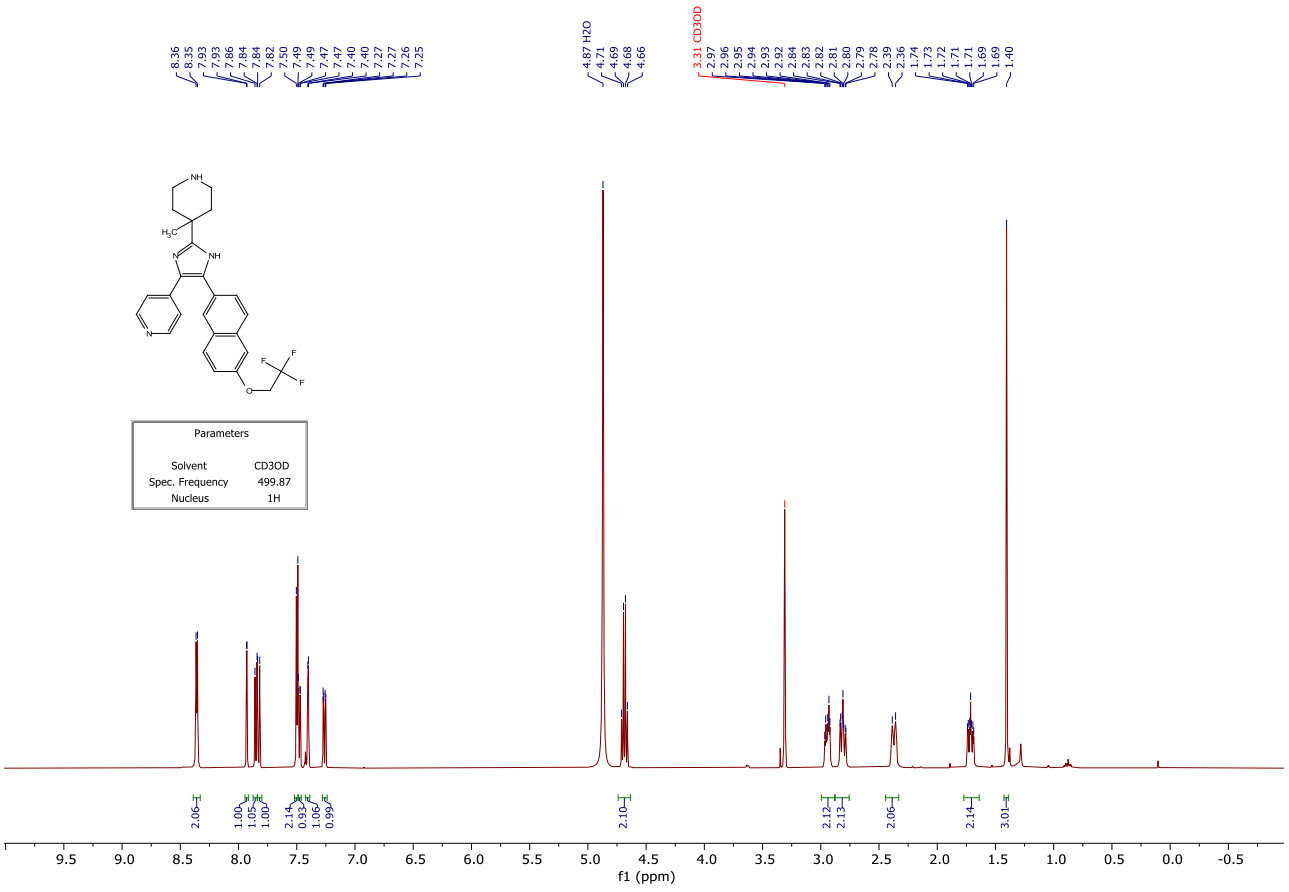


Figure S65. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **14v**.

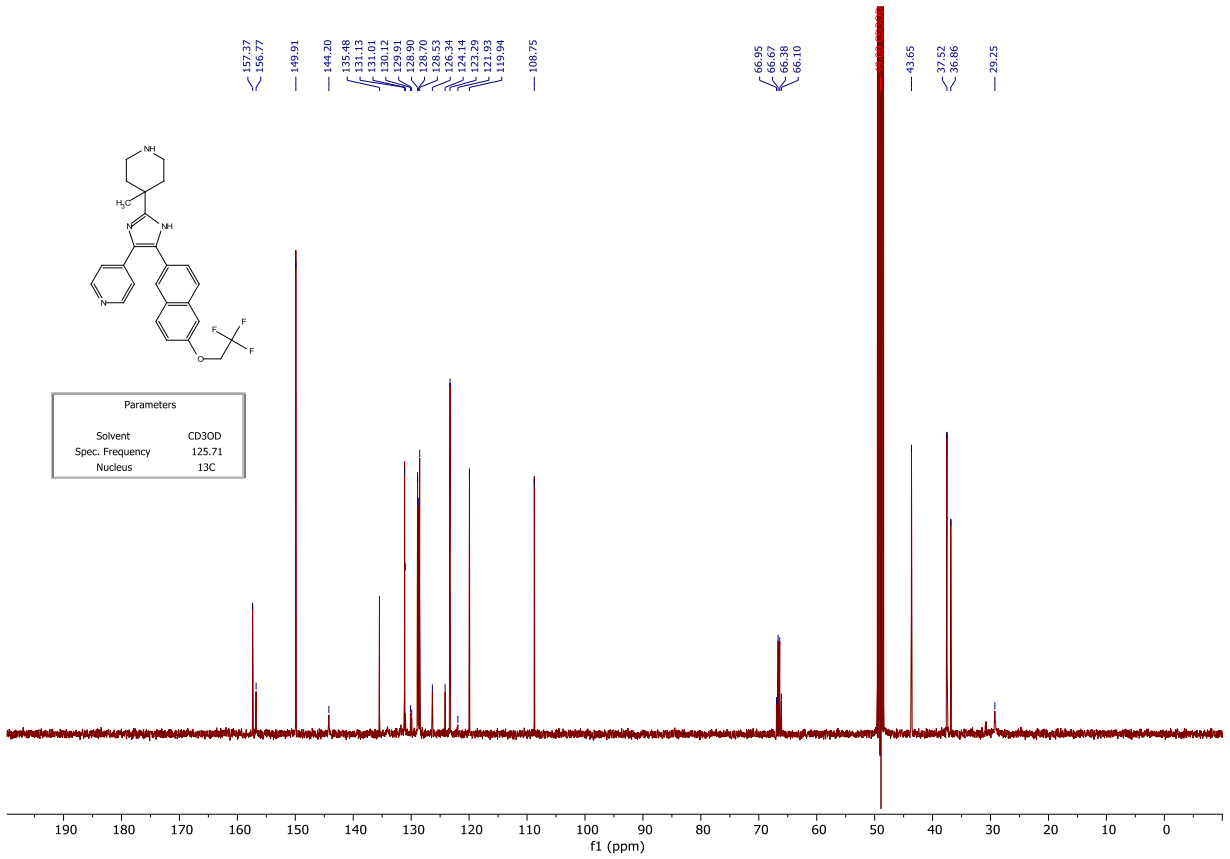


Figure S66. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 126 MHz) of compound **14v**.

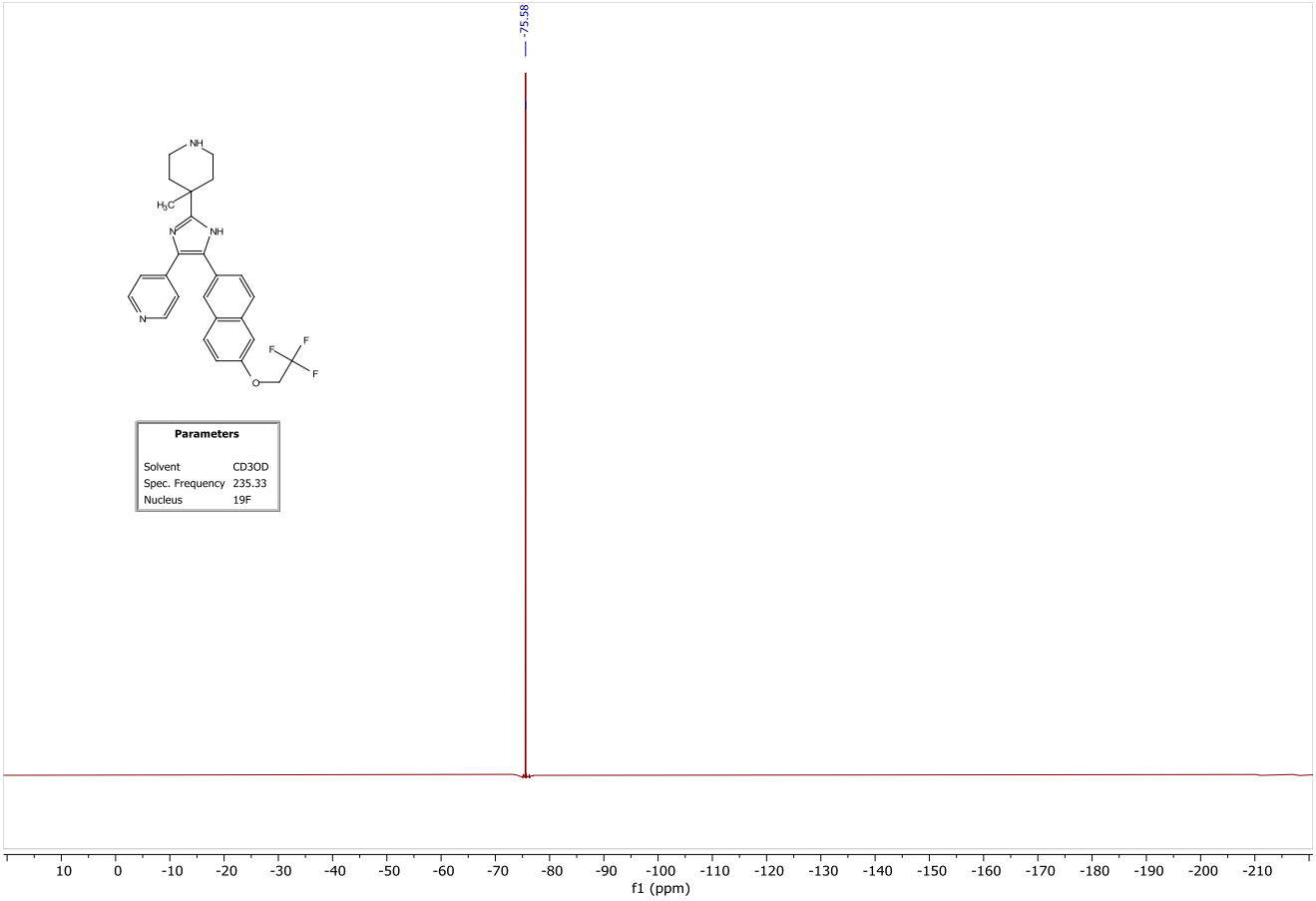


Figure S67. $^{19}F\{^{1}H\}$ NMR spectra (CD_3OD, 235 MHz) of compound **14v**.

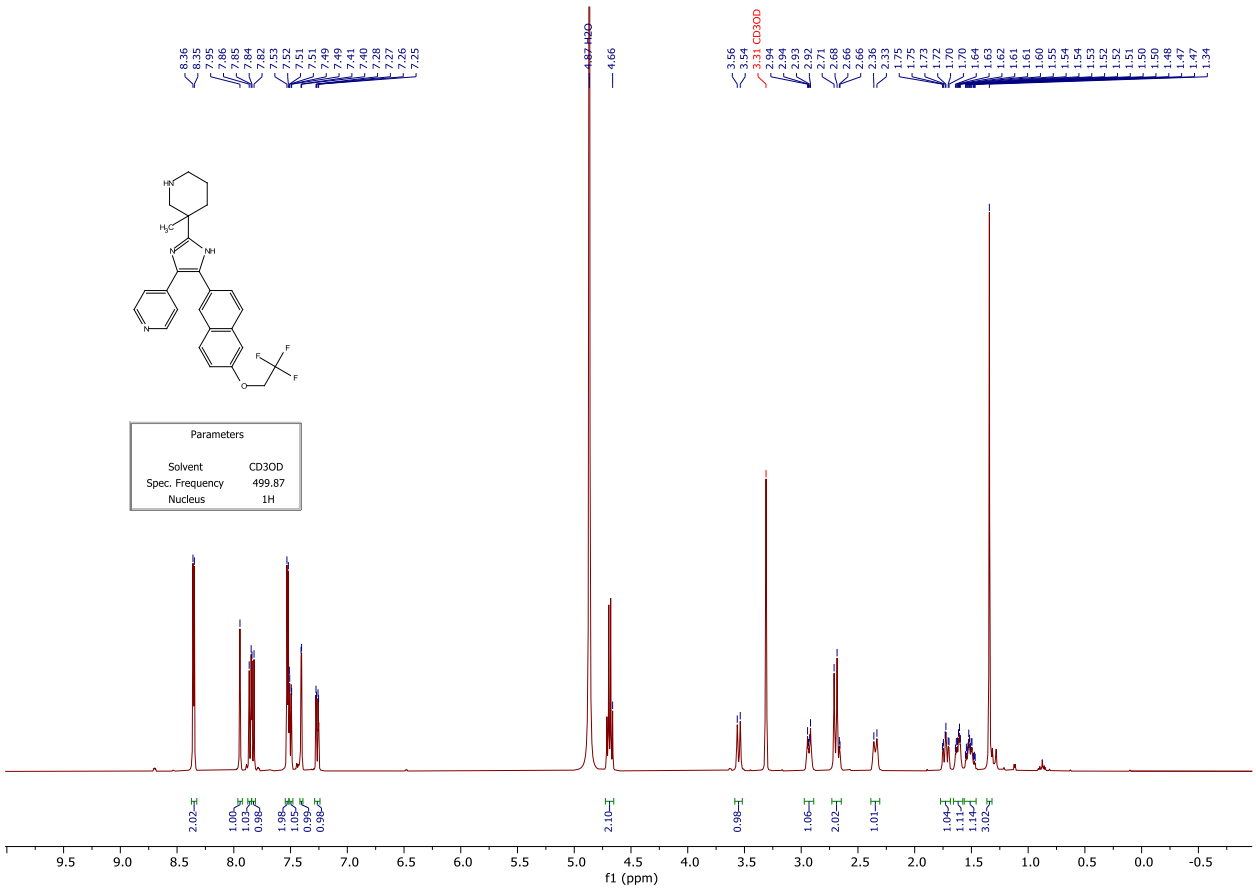


Figure S68. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **14x**.

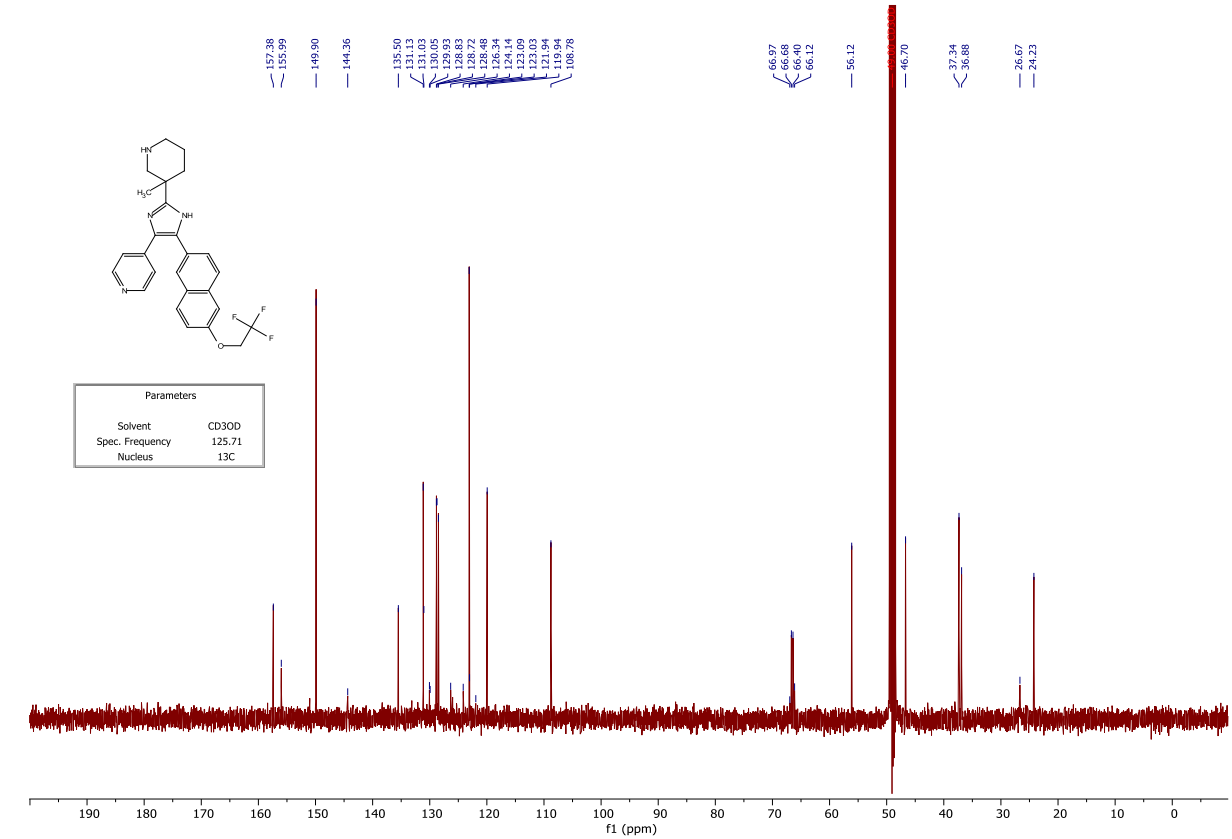


Figure S69. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD, 126 MHz) of compound **14x**.

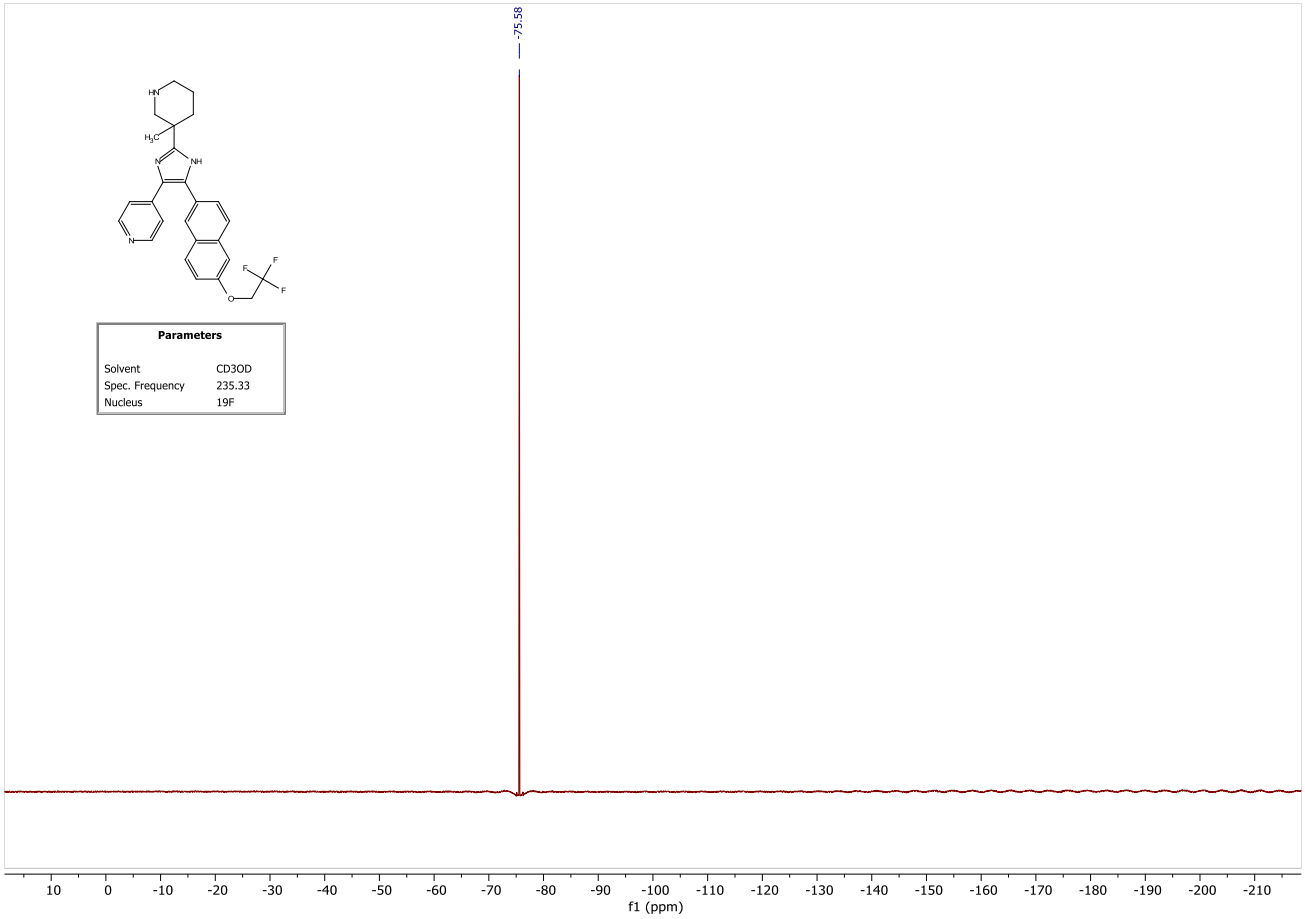


Figure S70. $^{19}F\{^{1}H\}$ NMR spectra (CD_3OD, 235 MHz) of compound **14x**.

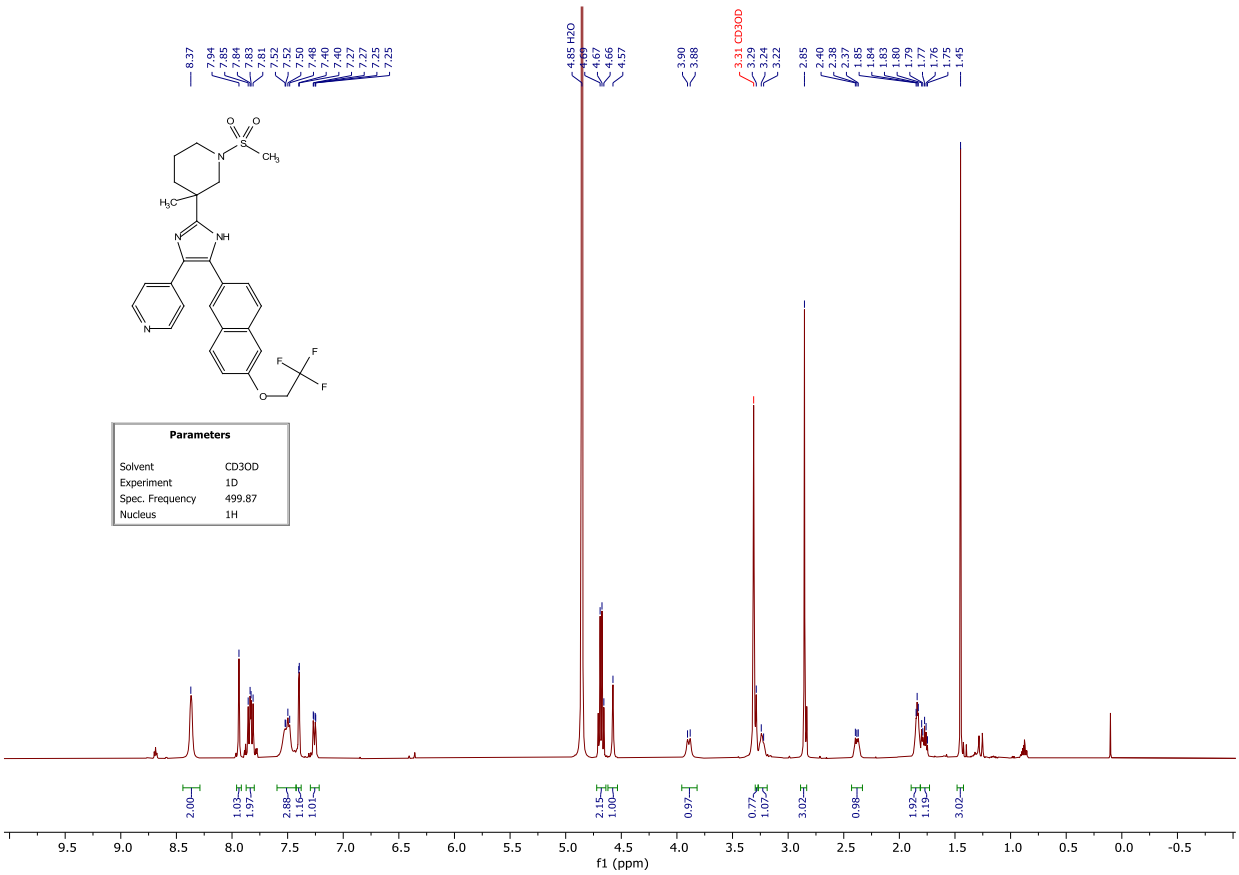


Figure S71. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **13y**.

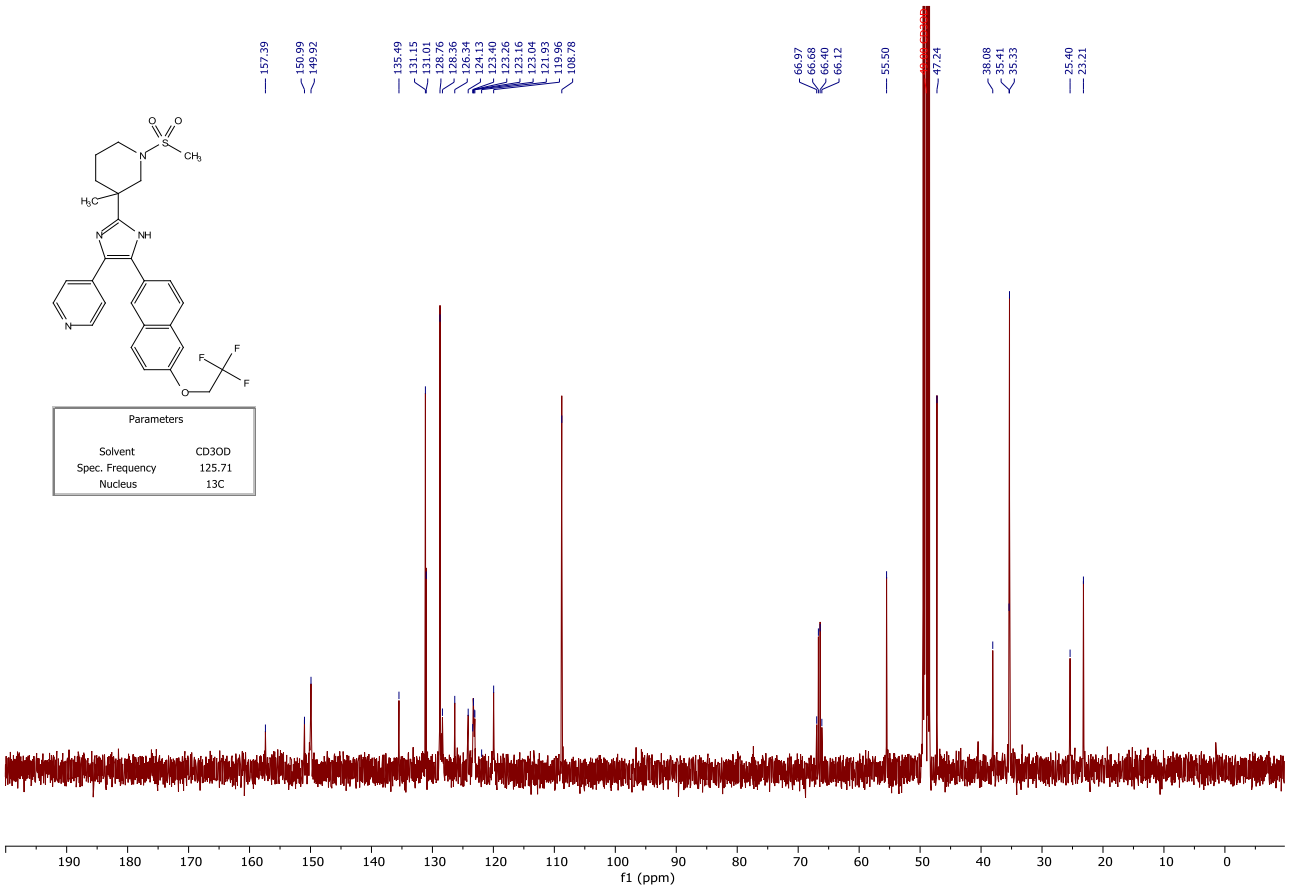


Figure S72. $^{13}C\{^{1}H\}$ NMR spectra (CD_3OD), 126 MHz) of compound **13y**.

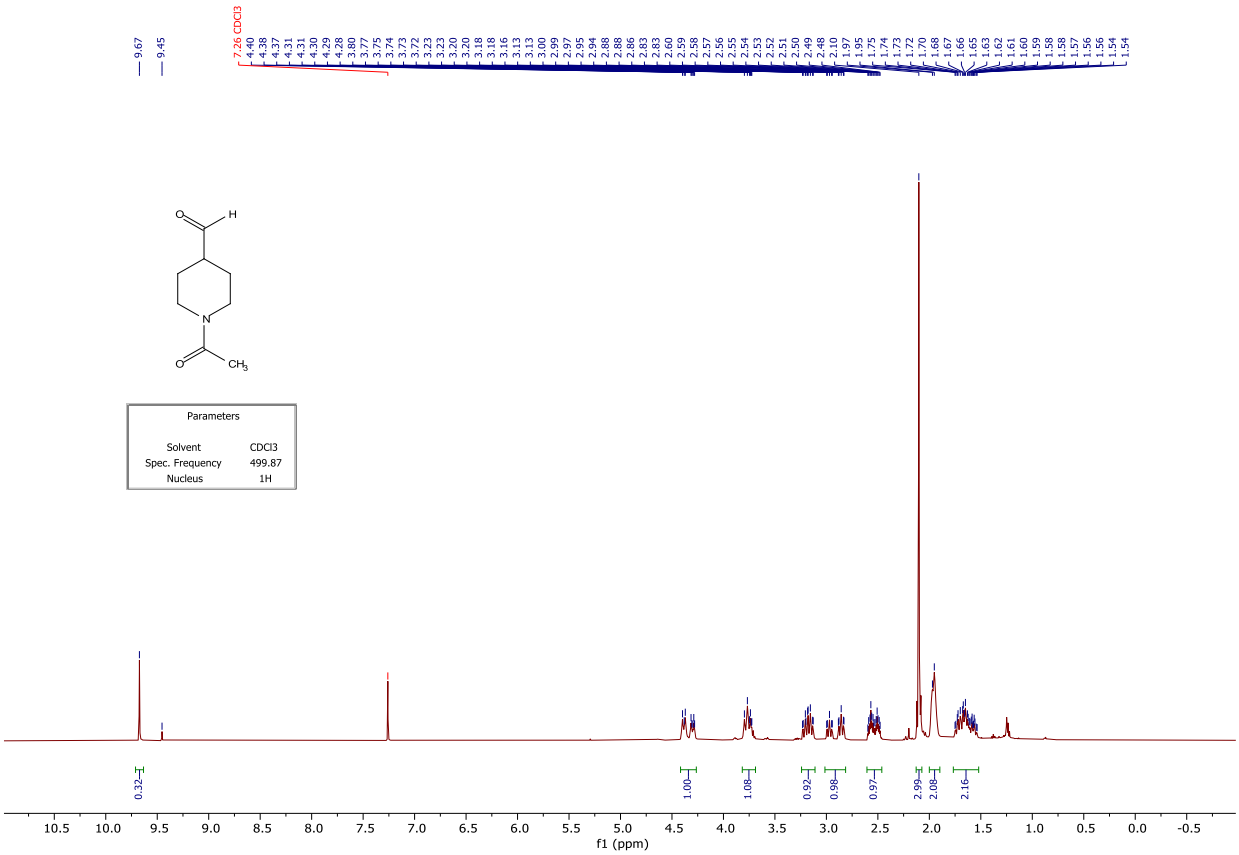


Figure S73. ^{1}H NMR spectra ($CDCl_3$, 500 MHz) of compound **12b**.

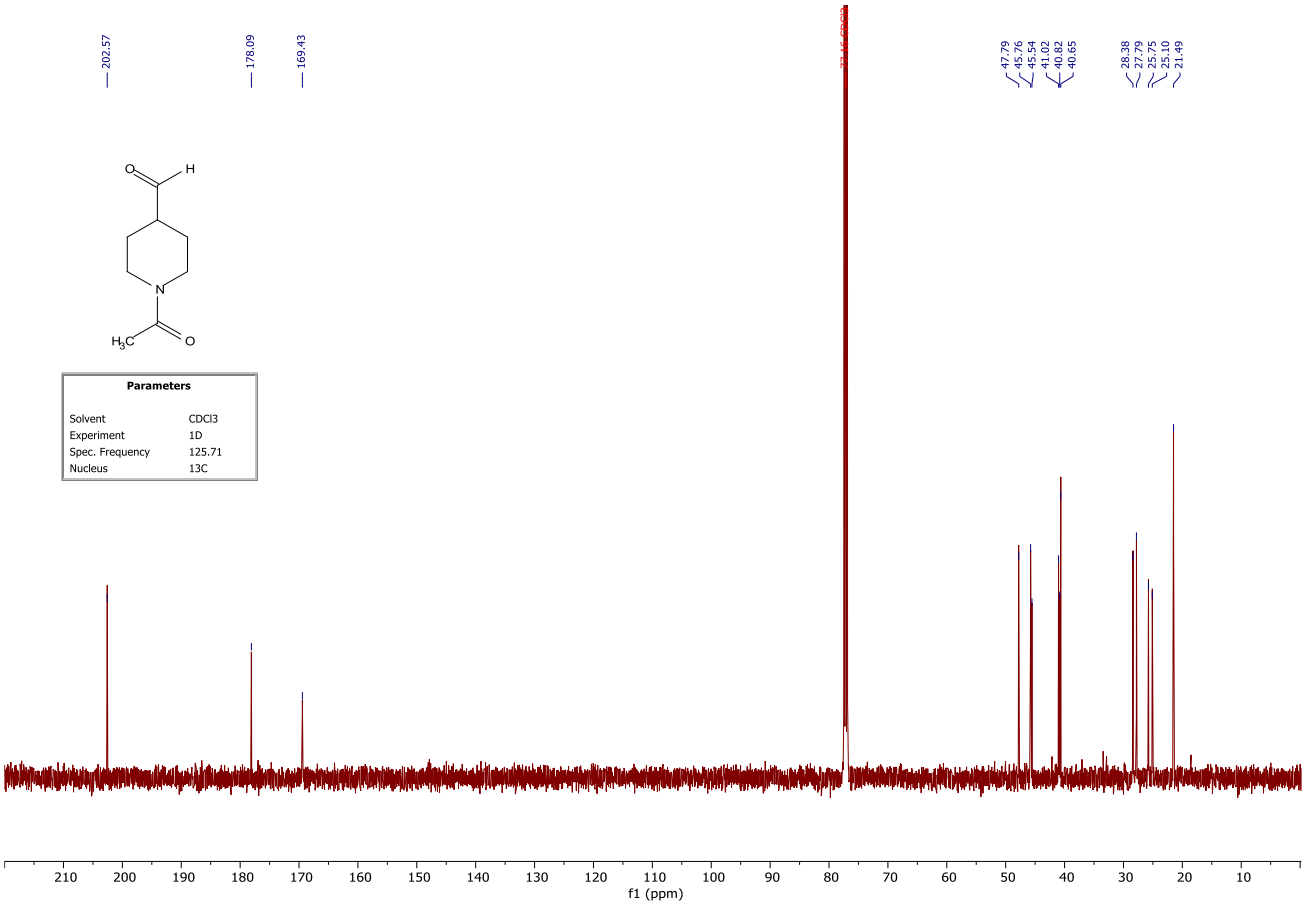


Figure S74. $^{13}C\{^{1}H\}$ NMR spectra ($CDCl_3$, 126 MHz) of compound **12b**.

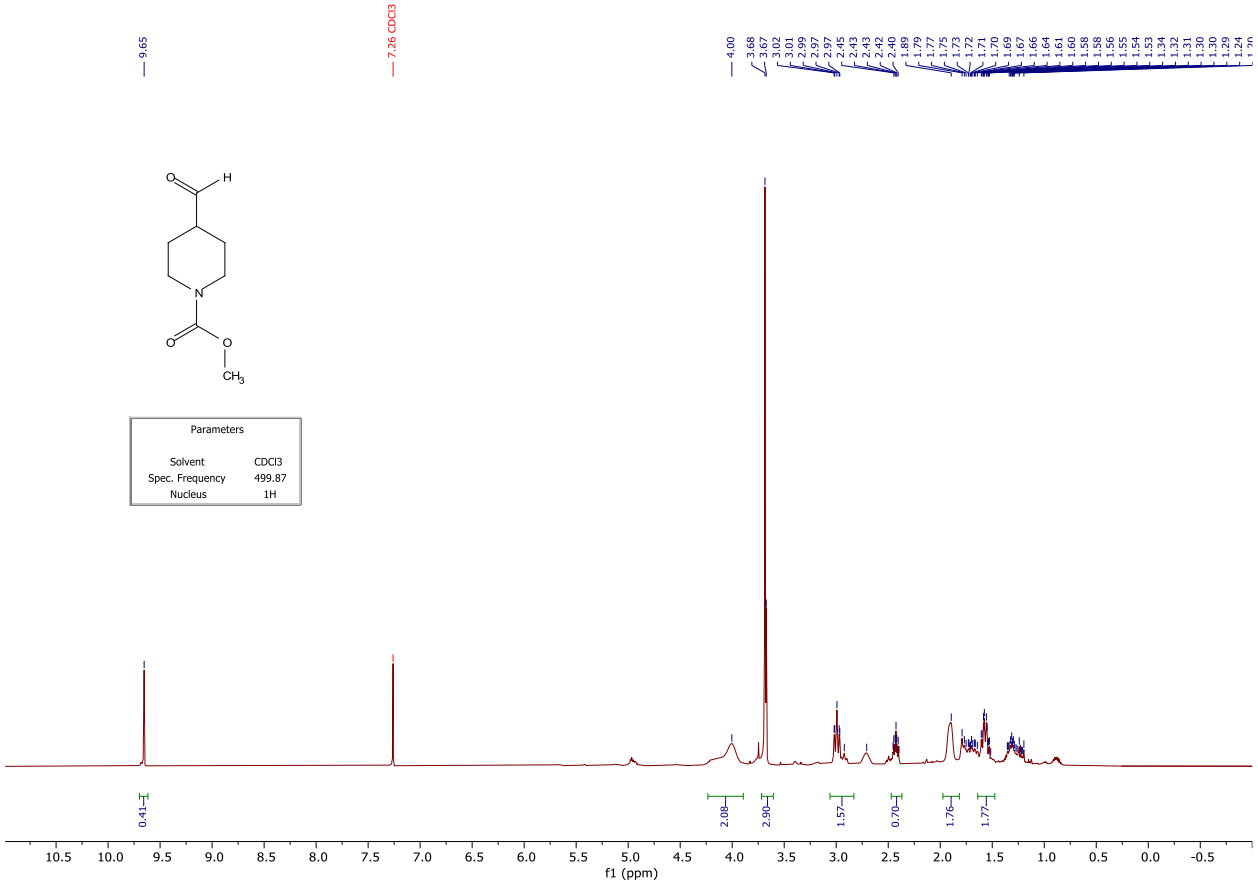


Figure S75. ^{1}H NMR spectra ($CDCl_3$, 500 MHz) of compound **12c**.

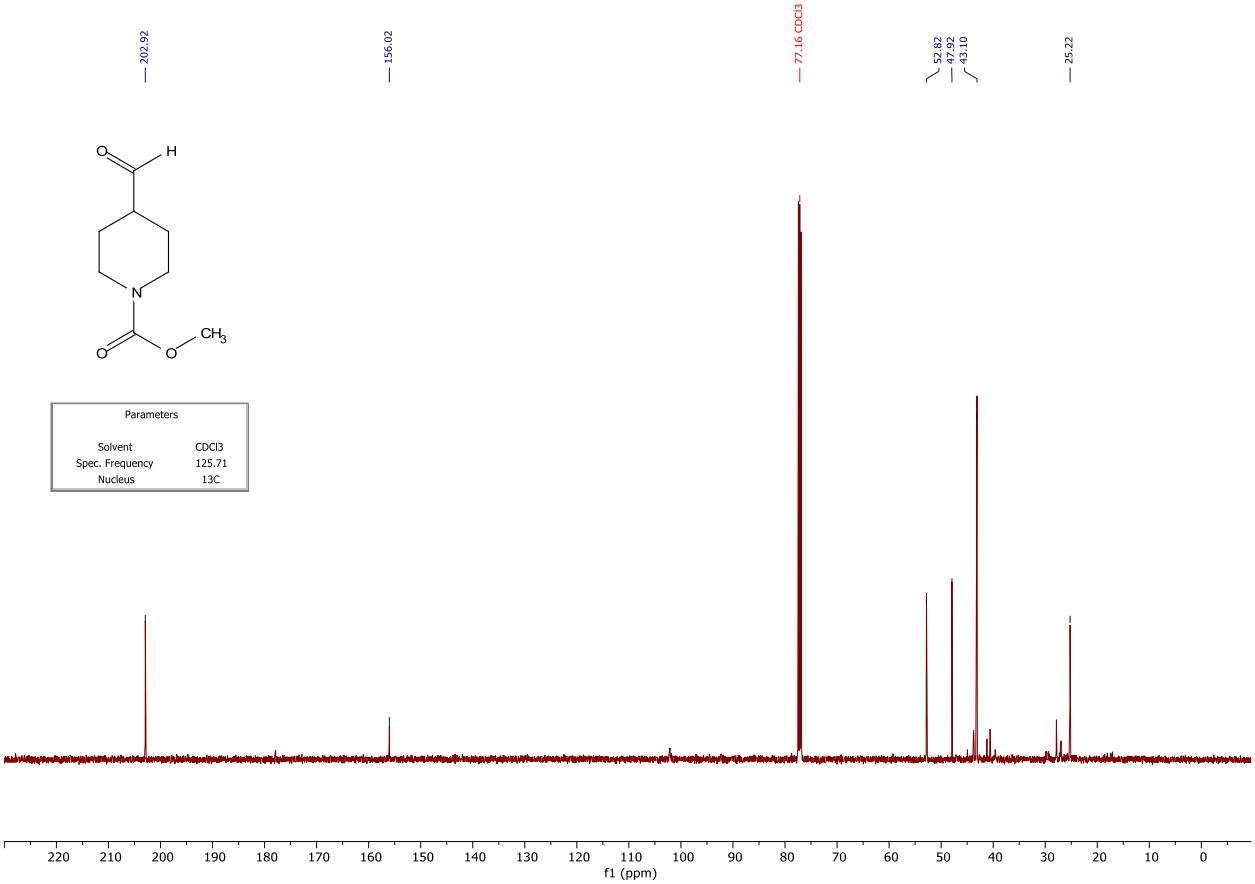


Figure S76. $^{13}C\{^{1}H\}$ NMR spectra ($CDCl_3$, 126 MHz) of compound **12c**.

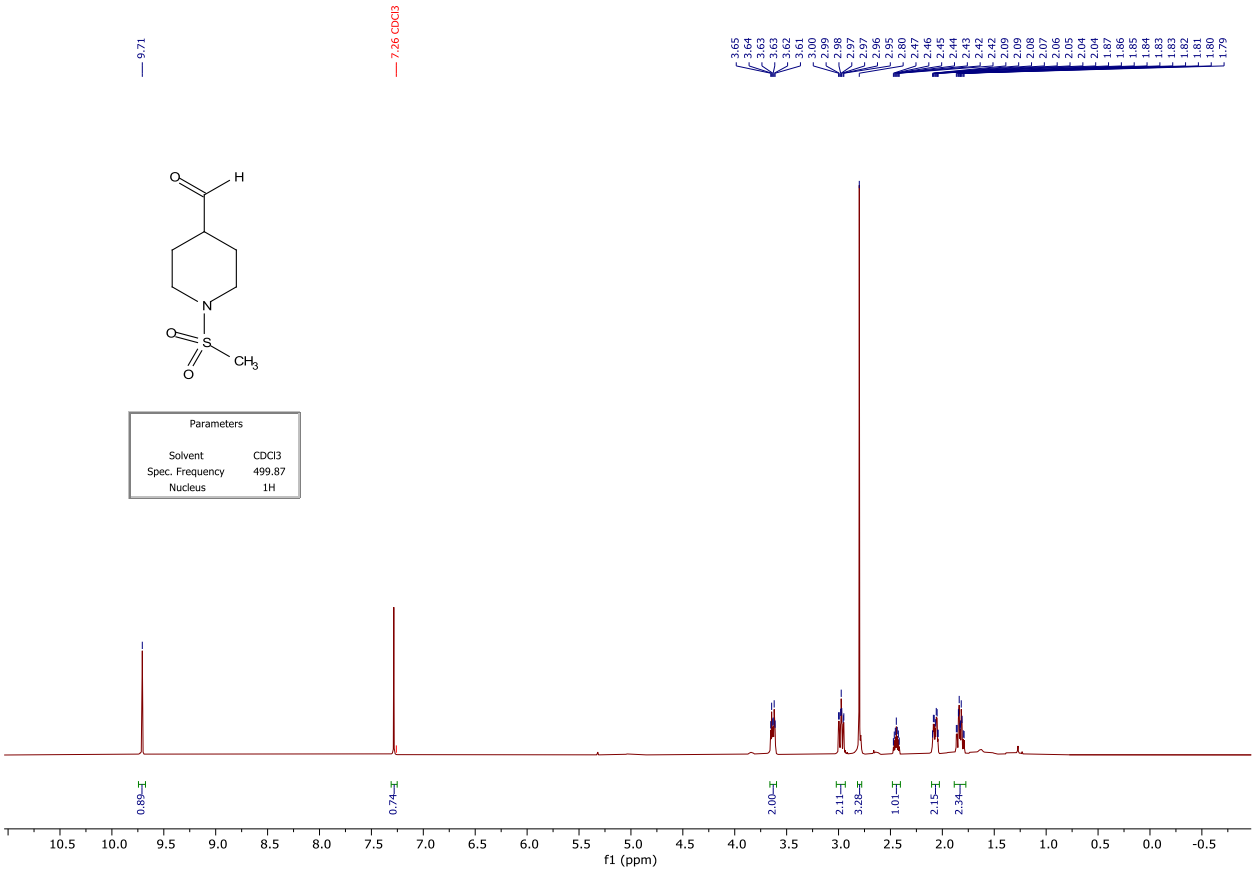


Figure S77. ^{1}H NMR spectra ($CDCl_3$, 500 MHz) of compound **12d**.

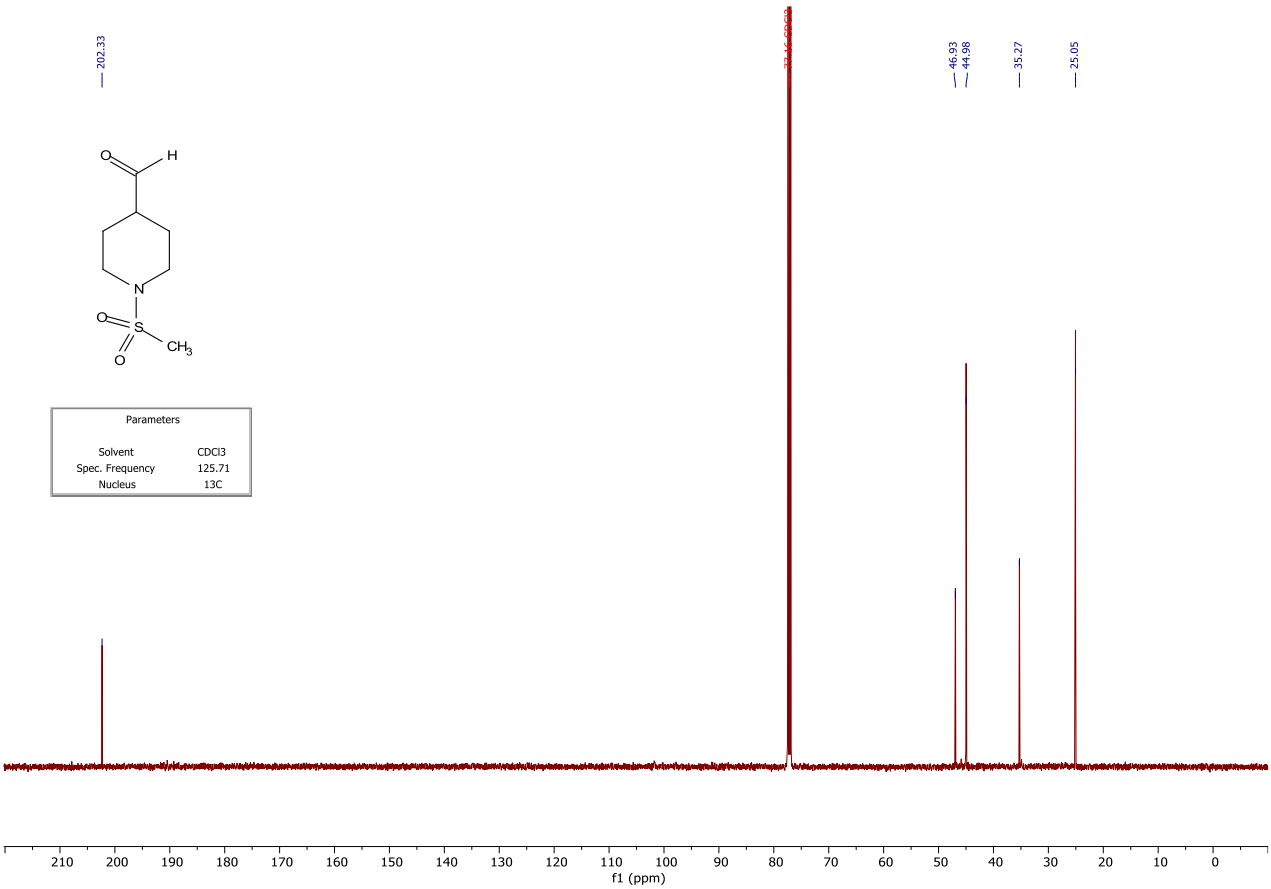


Figure S78. $^{13}C\{^{1}H\}$ NMR spectra ($CDCl_3$, 126 MHz) of compound **12d**.

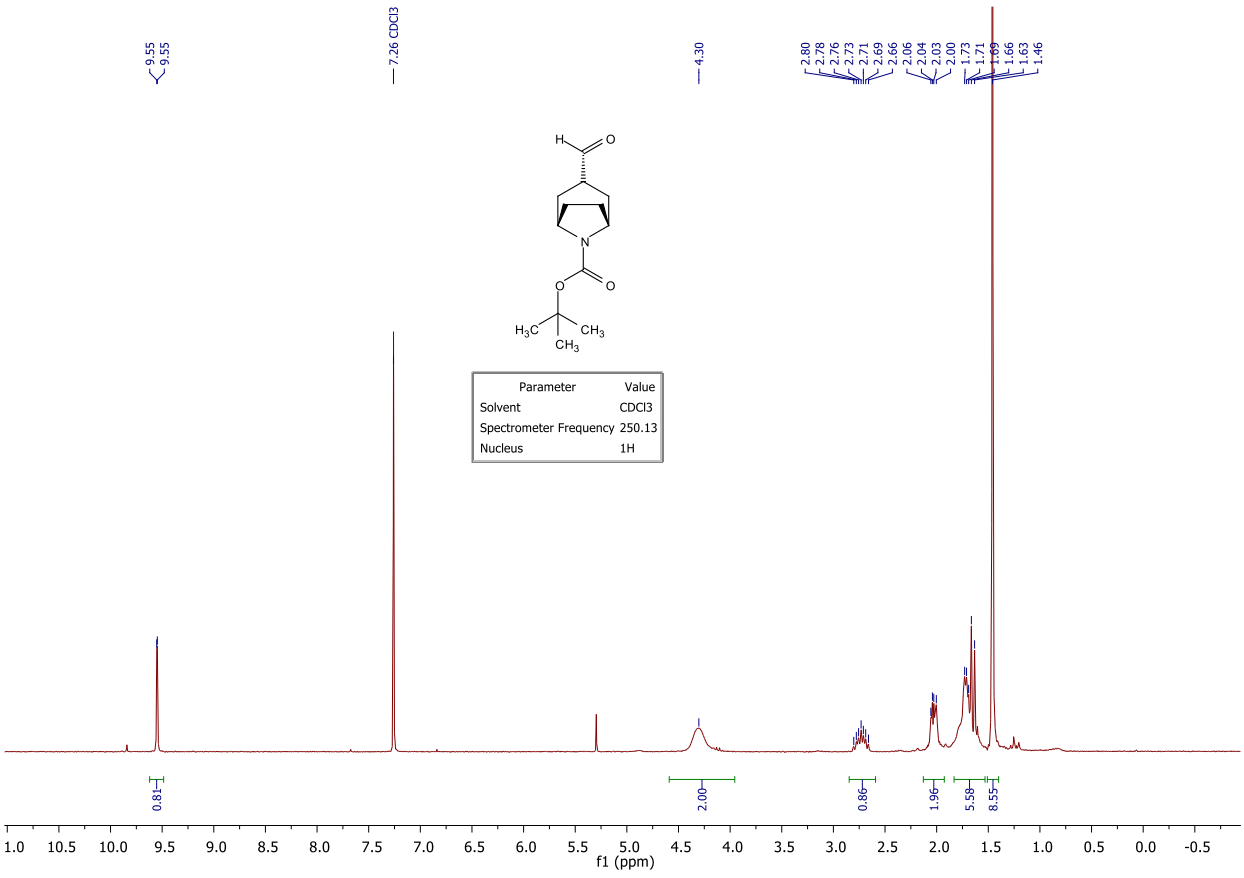


Figure S79. ^{1}H NMR spectra ($CDCl_3$, 250 MHz) of compound **12l**.

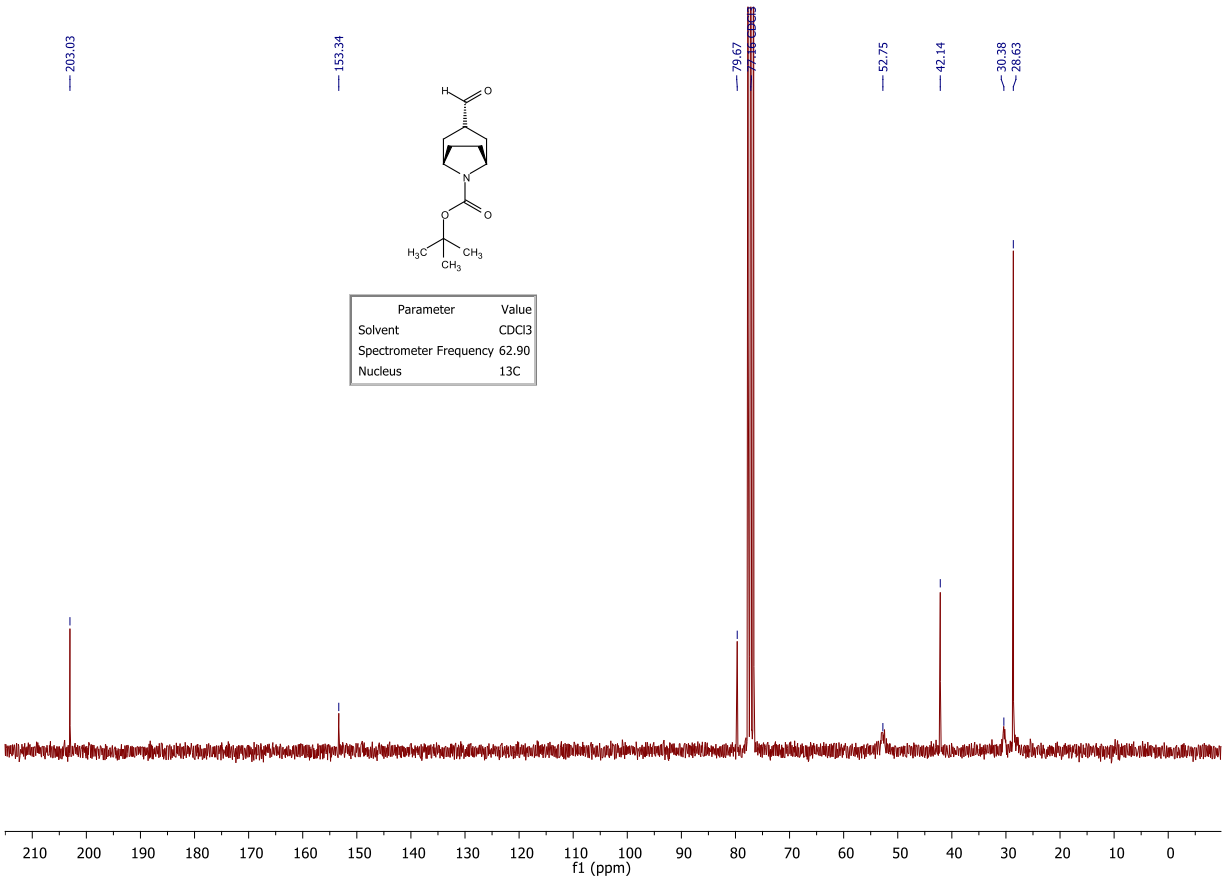


Figure S80. $^{13}C\{^{1}H\}$ NMR spectra ($CDCl_3$, 63 MHz) of compound **12l**.

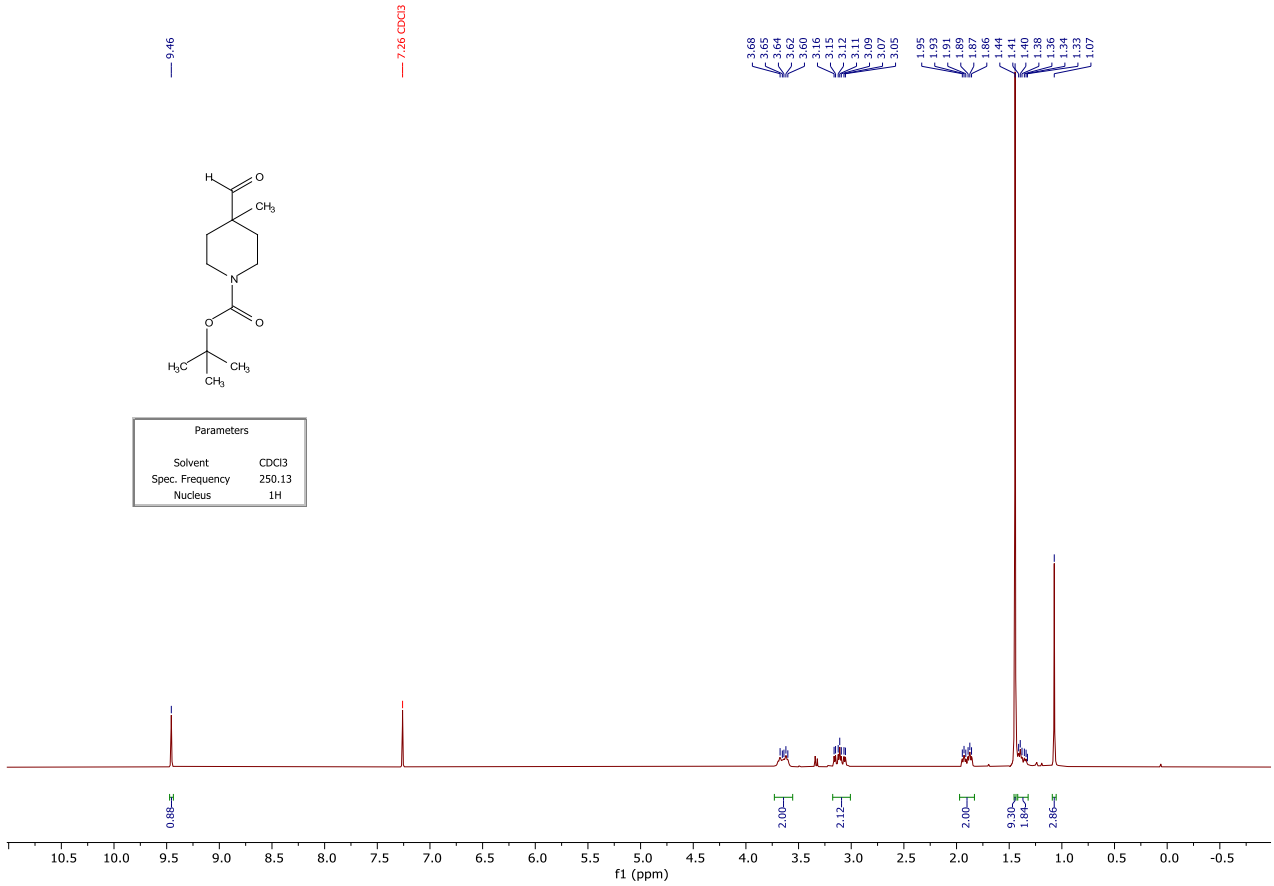


Figure S81. ^{1}H NMR spectra ($CDCl_3$, 250 MHz) of compound **12n**.

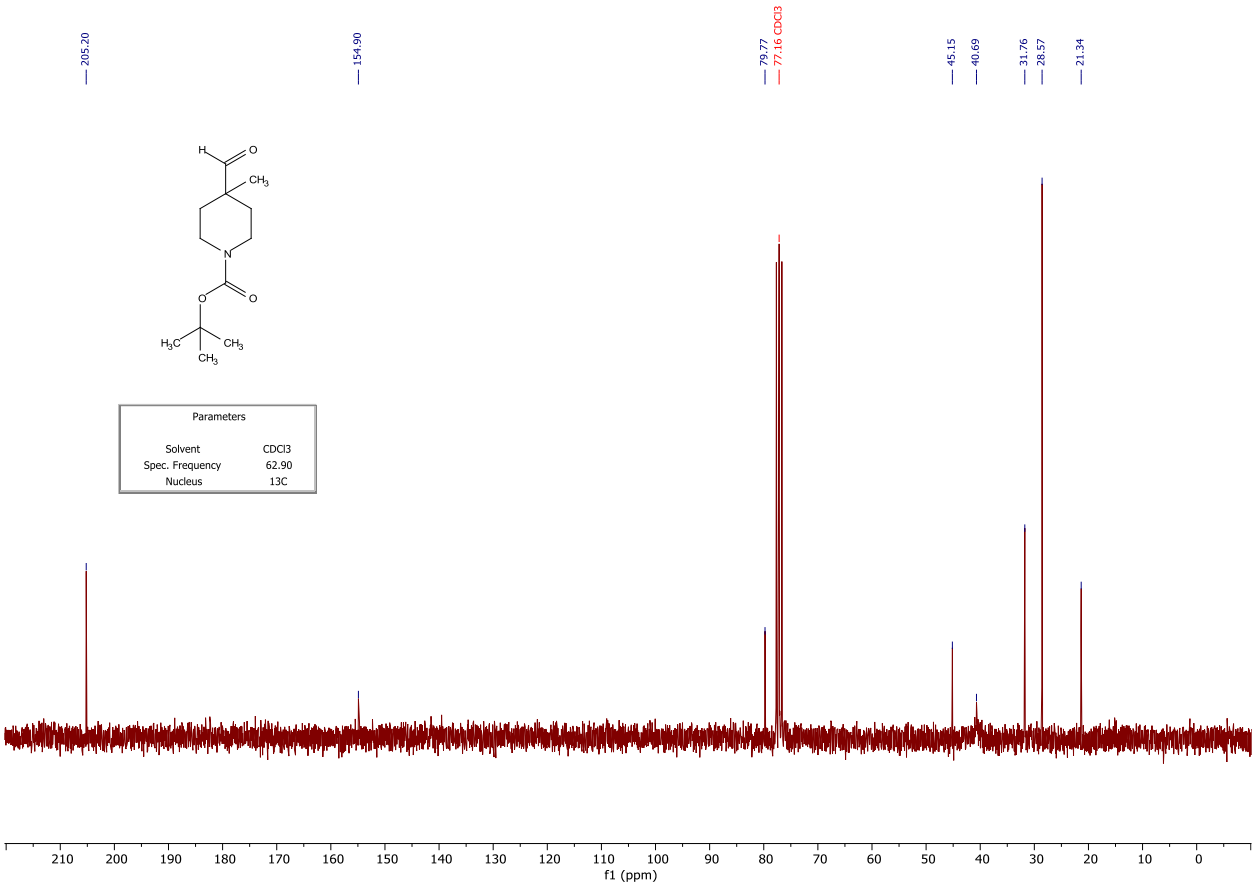


Figure S82. $^{13}C\{^{1}H\}$ NMR spectra ($CDCl_3$, 63 MHz) of compound **12n**.

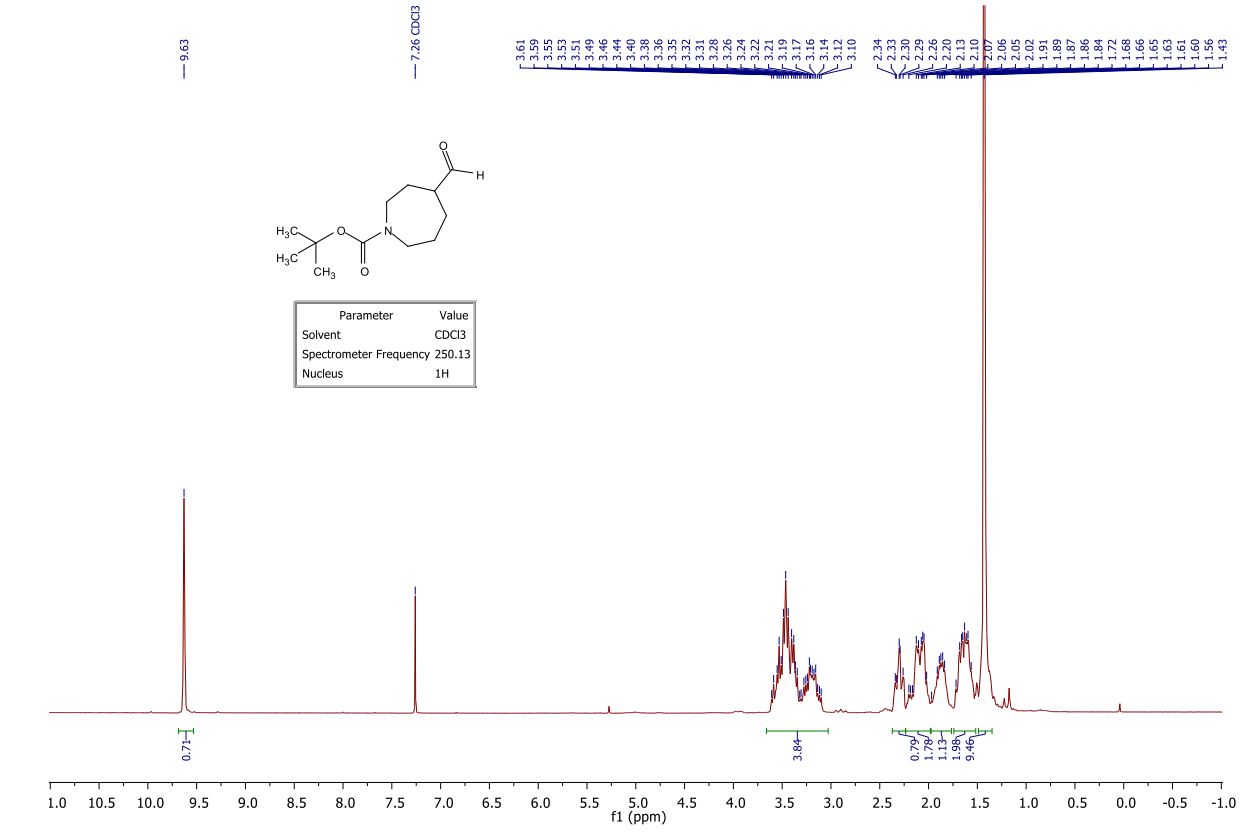


Figure S83. ^{1}H NMR spectra ($CDCl_3$, 250 MHz) of compound **12o**.

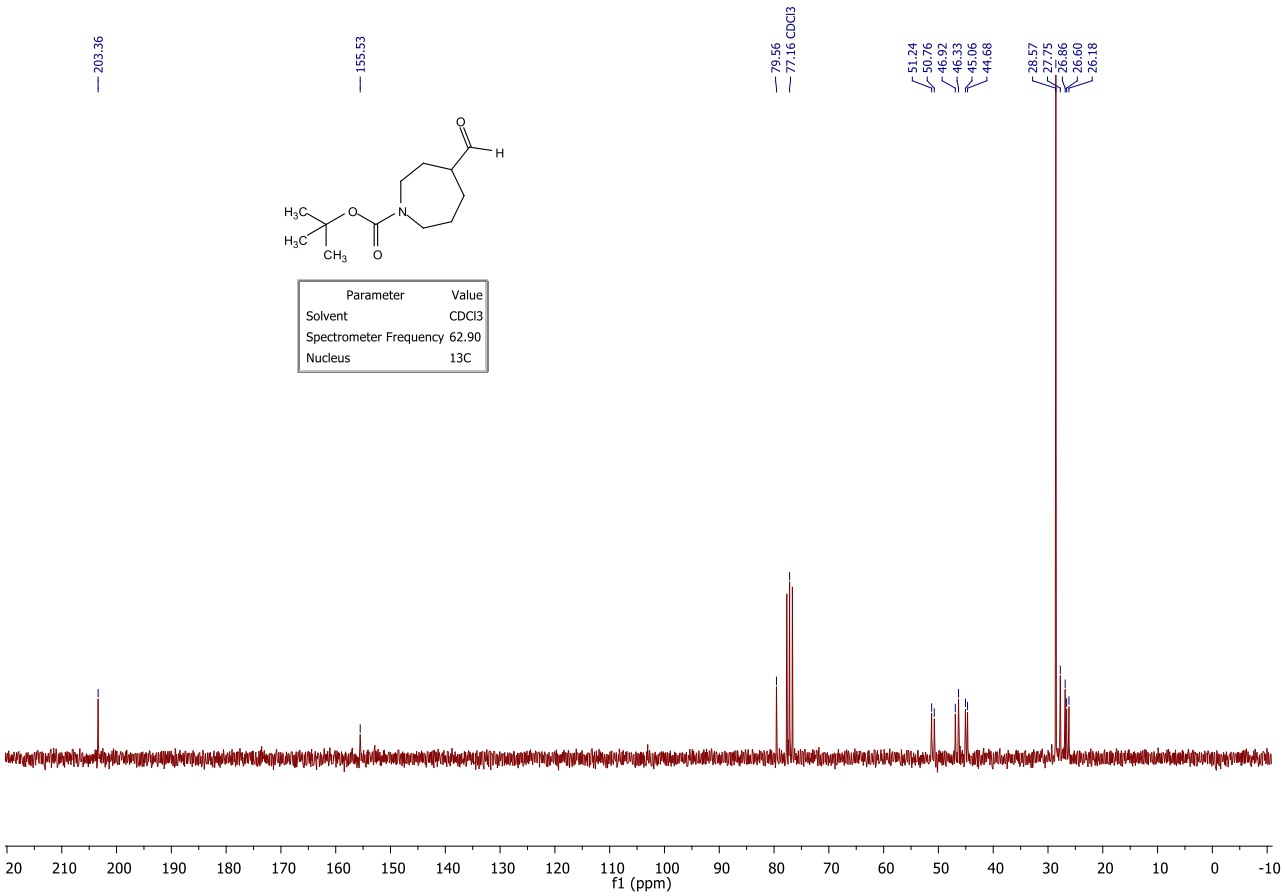


Figure S84. $^{13}C\{^{1}H\}$ NMR spectra ($CDCl_3$, 63 MHz) of compound **12o**.

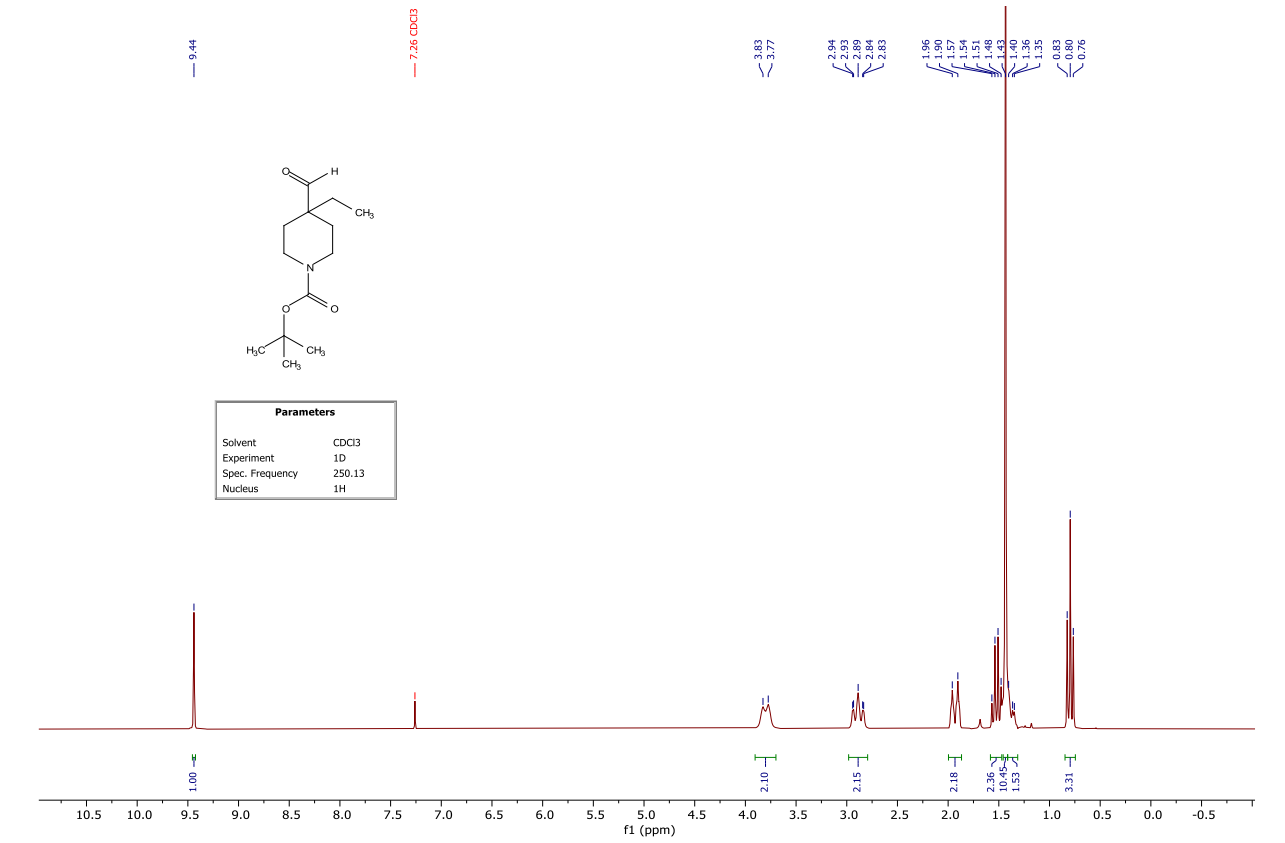


Figure S85. ^{1}H NMR spectra ($CDCl_3$, 250 MHz) **12p**.

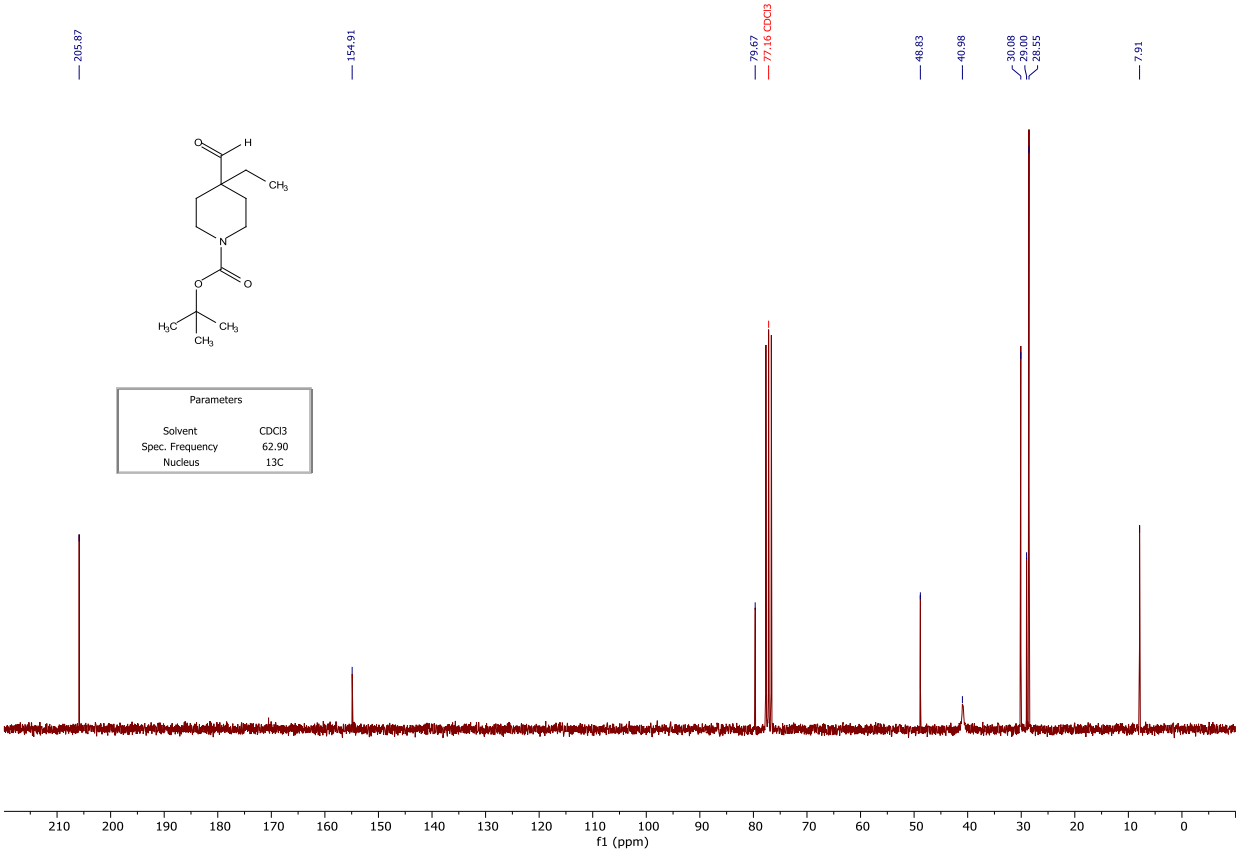


Figure S86. $^{13}C\{^{1}H\}$ NMR spectra ($CDCl_3$, 63 MHz) of compound **12p**.

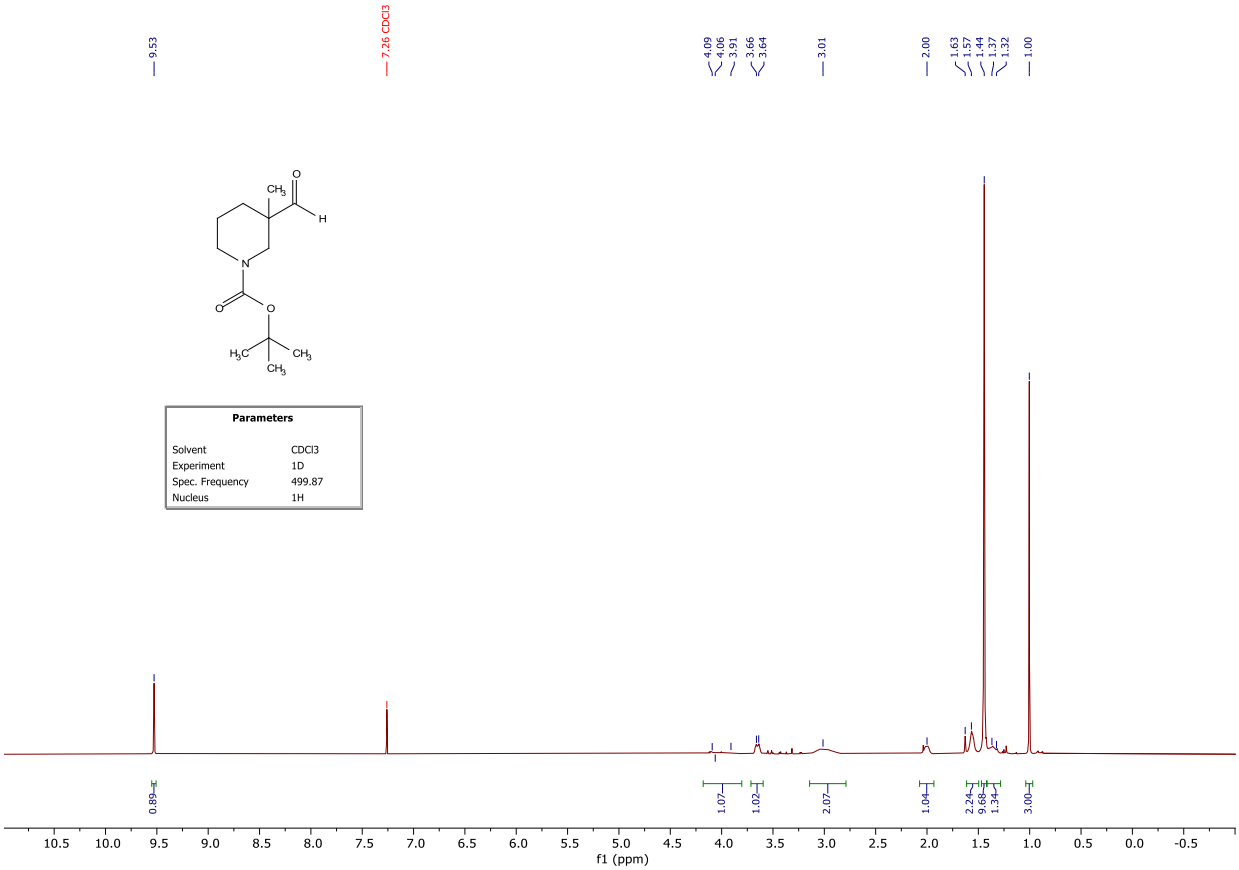


Figure S87. ^{1}H NMR spectra ($CDCl_3$, 500 MHz) of compound **12q**.

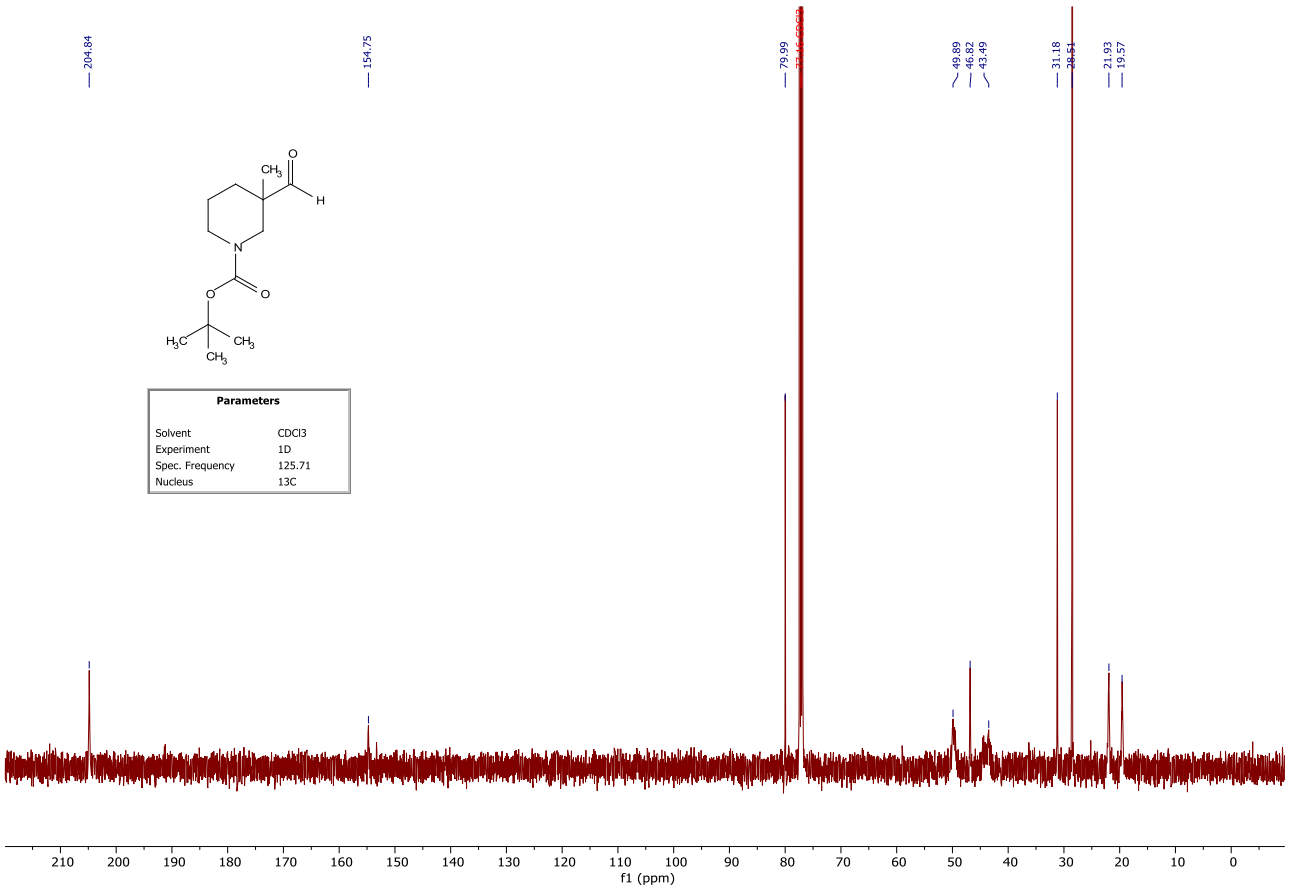


Figure S88. $^{13}C\{^{1}H\}$ NMR spectra ($CDCl_3$, 63 MHz) of compound **12q**.

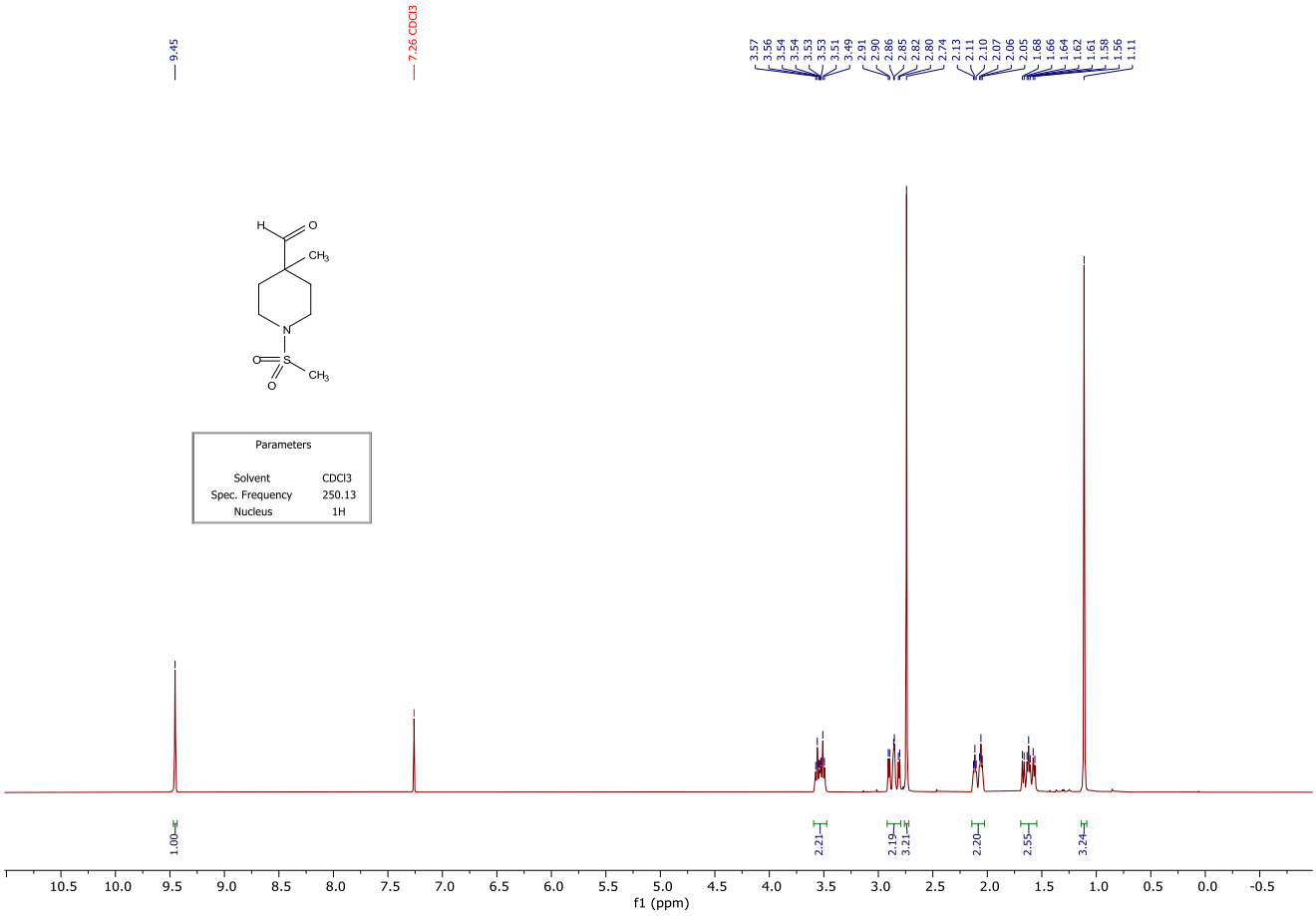


Figure S89. ^{1}H NMR spectra ($CDCl_3$, 250 MHz) of compound **12r**.

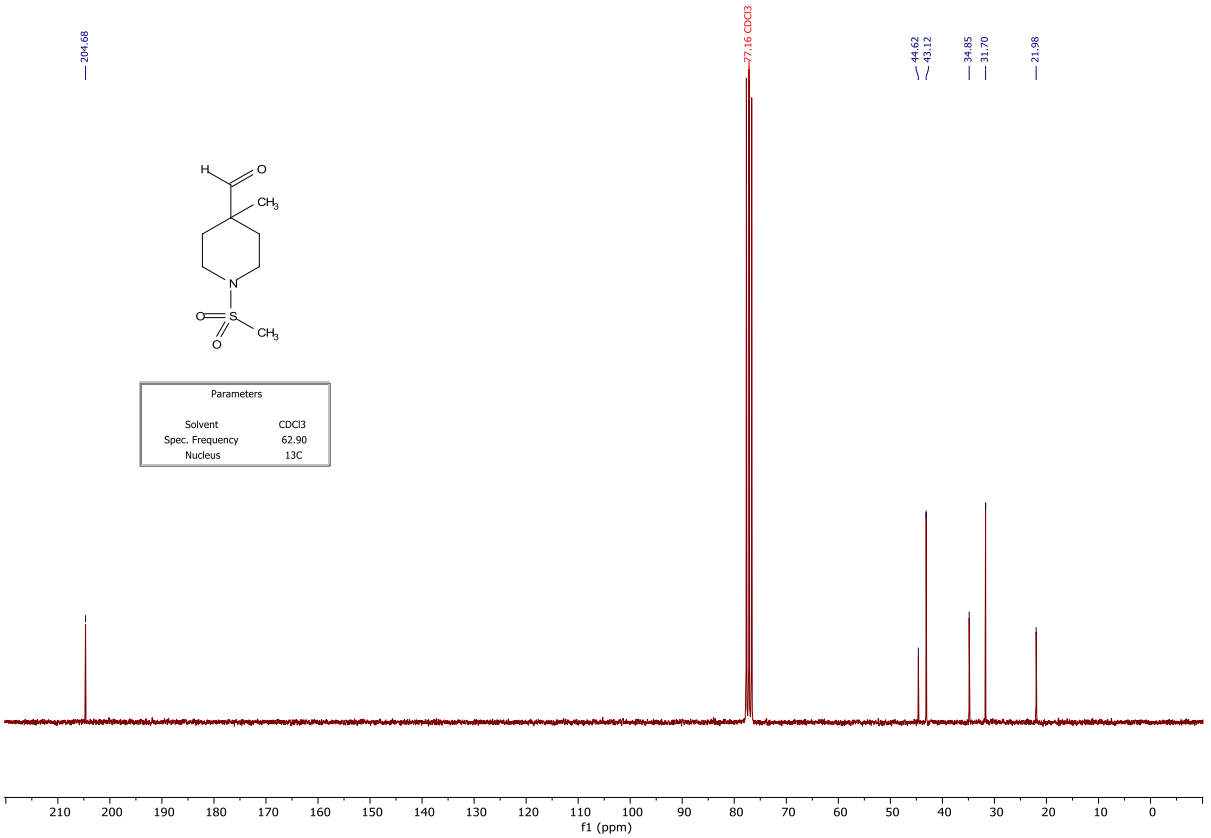


Figure S90. $^{13}C\{^{1}H\}$ NMR spectra ($CDCl_3$, 63 MHz) of compound **12r**.

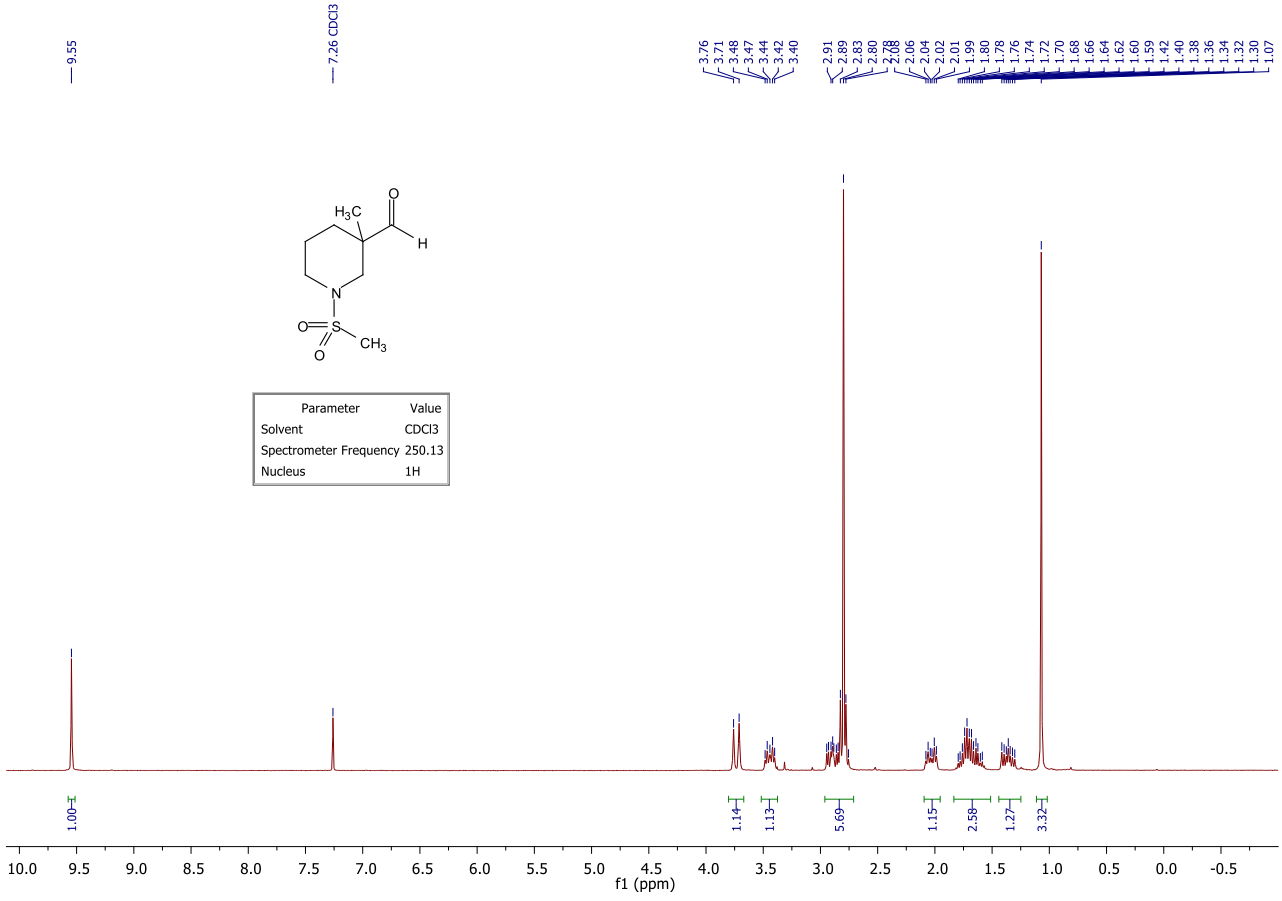


Figure S91. ^{1}H NMR spectra (CD_3OD, 500 MHz) of compound **12s**.

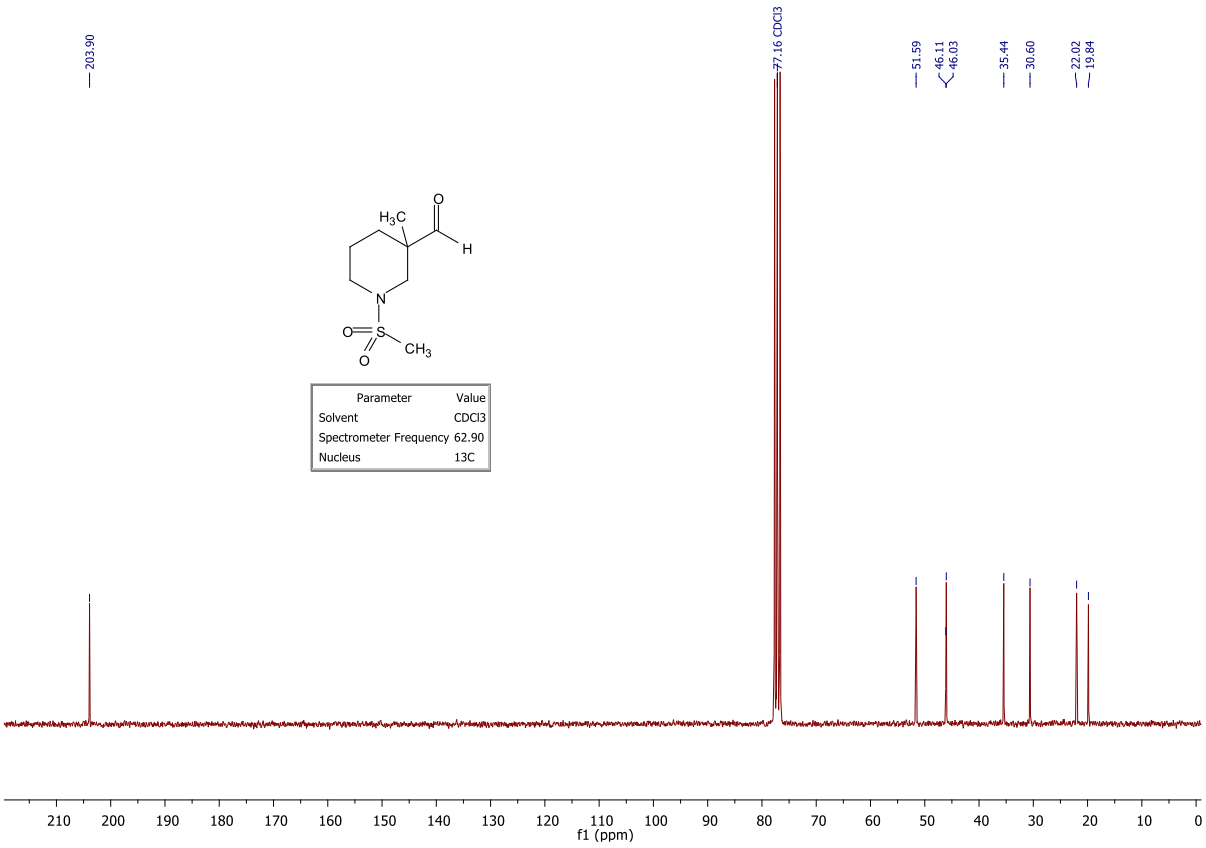


Figure S92. $^{13}C\{^{1}H\}$ NMR spectra ($CDCl_3$, 63 MHz) of compound **12s**.

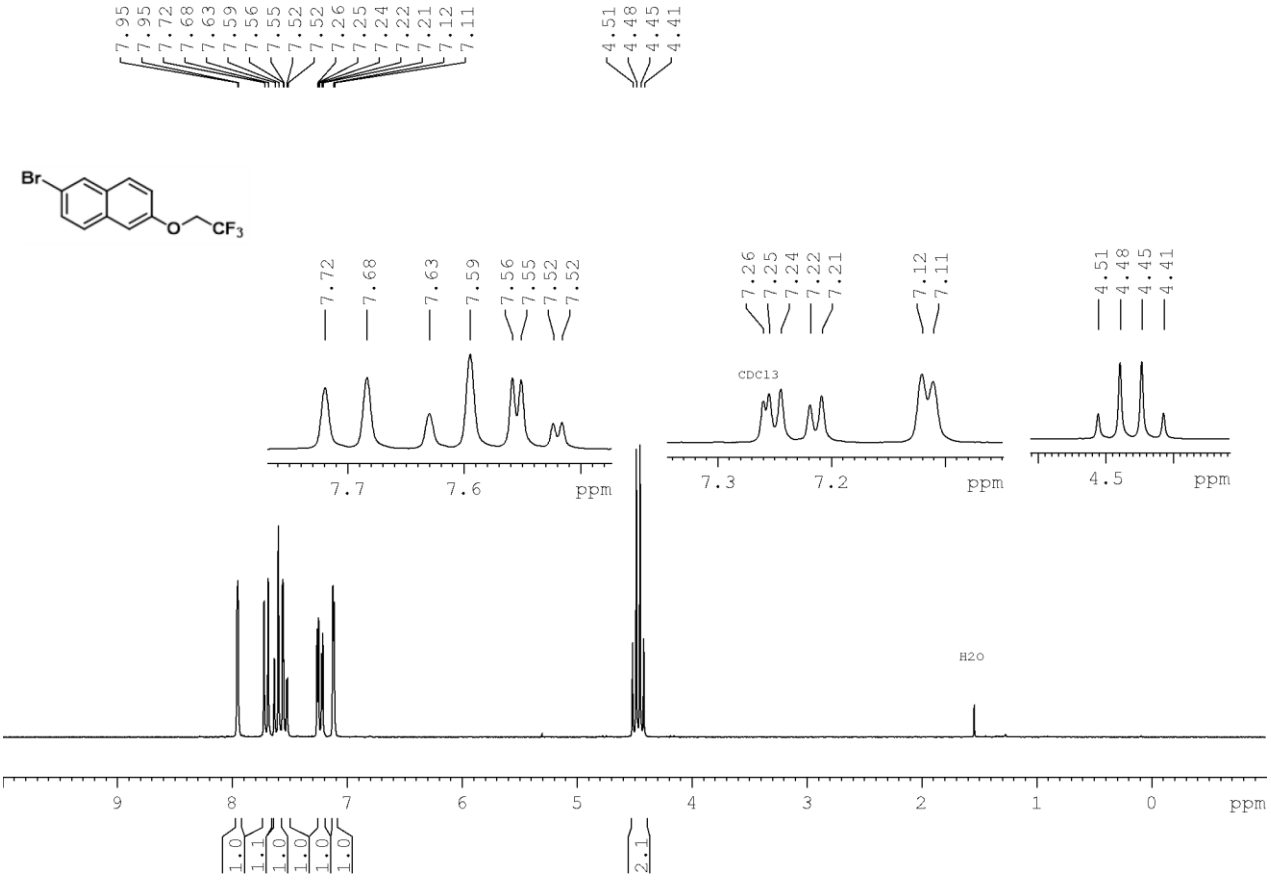


Figure S93. ^{1}H NMR spectra ($CDCl_3$, 250 MHz) of compound **8b**.

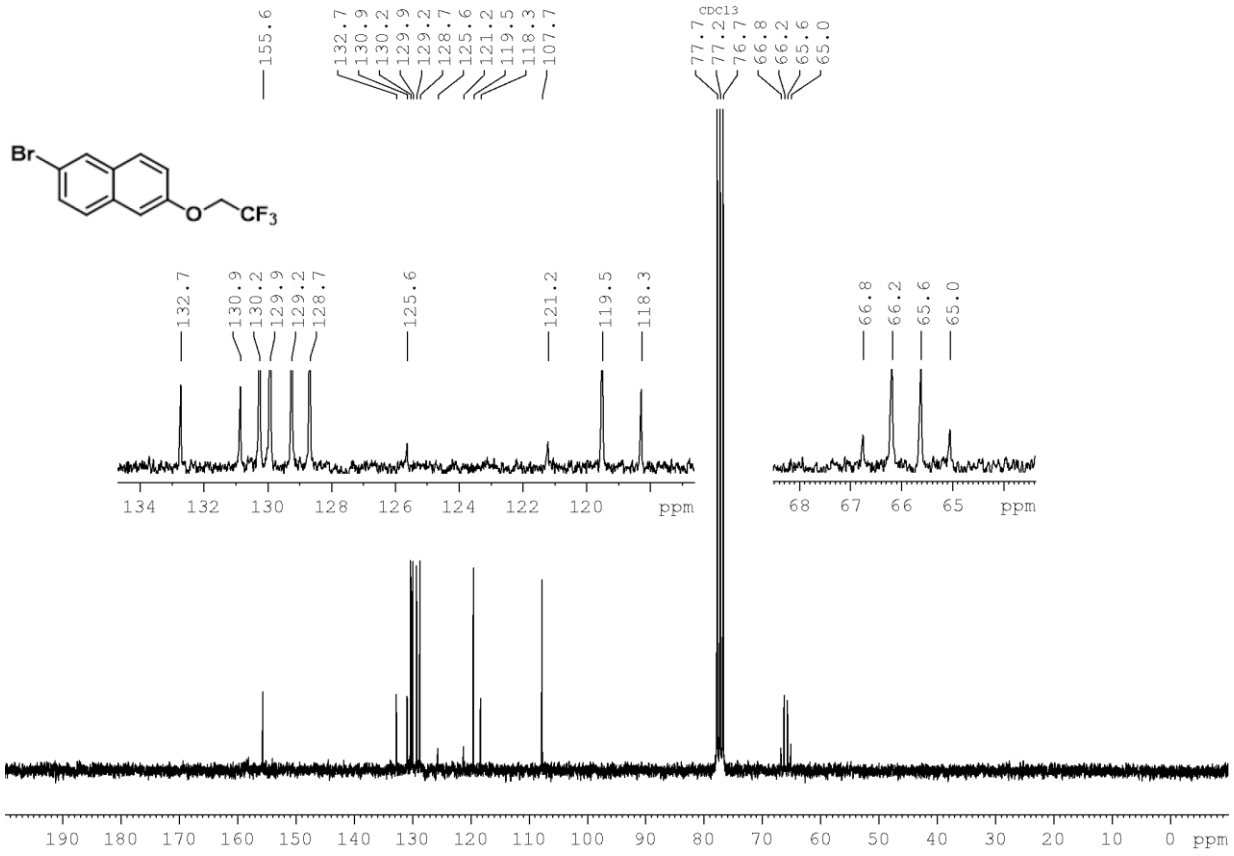


Figure S94. $^{13}C\{^{1}H\}$ NMR spectra ($CDCl_3$, 63 MHz) of compound **8b**.

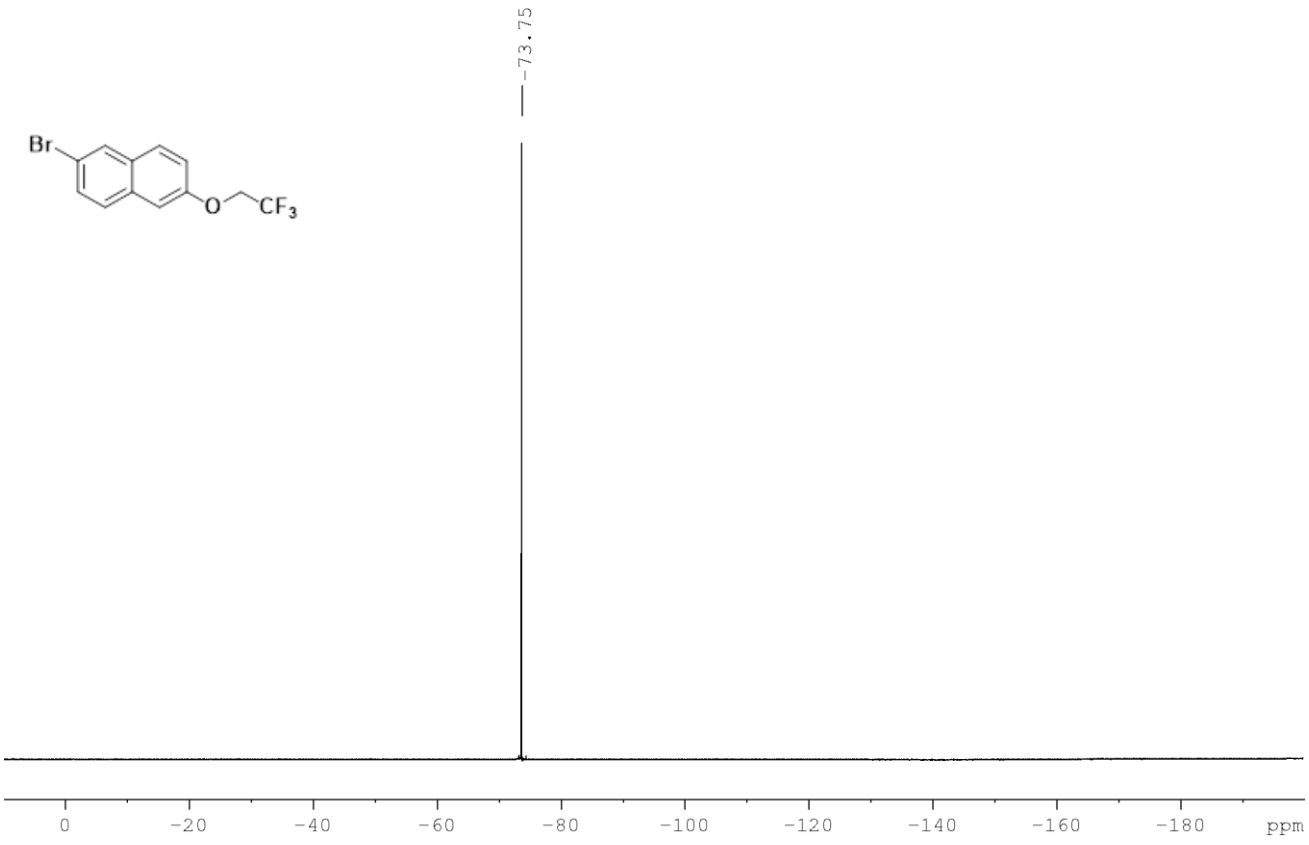


Figure S95. $^{19}F\{^{1}H\}$ NMR spectra ($CDCl_3$, 235 MHz) of compound **8b**.

References

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2. Yang, Q.; Lachapelle, E. A.; Kablaoui, N. M.; Webb, D.; Popiolek, M.; Grimwood, S.; Kozak, R.; O'Connor, R. E.; Lazzaro, J. T.; Butler, C. R.; Zhang, L.; *ACS Med. Chem. Lett.* **2019**, *10*, 941. [Crossref]