Bivalent AMPA receptor positive allosteric modulators of bis(pyrimidine) series

Anna A. Nazarova[a], Kseniya N. Sedenkova[a,b], Dmitry S. Karlov[a,c], Mstislav I. Lavrov[a], Yuri K. Grishin[a], Tamara S. Kuznetsova[a], Vladimir L. Zamoyski[b], Vladimir V. Grigoriev[b], Elena B. Averina[a,b*], Vladimir A. Palyulin[a,b*]

[a] *Department of Chemistry, Lomonosov Moscow State University, 119991 Moscow, Russian Federation. Fax: +7 (495) 939 0290.*

[b] *Institute of Physiologically Active Compounds, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russian Federation*

[c] Center for Computational and Data-intensive Science and Engineering, Skolkovo Institute of Science and Technology, 121205 Moscow, Russian Federation

E-mail: vap@qsar.chem.msu.ru, elaver@med.chem.msu.ru

Supplementary information

Table of Contents

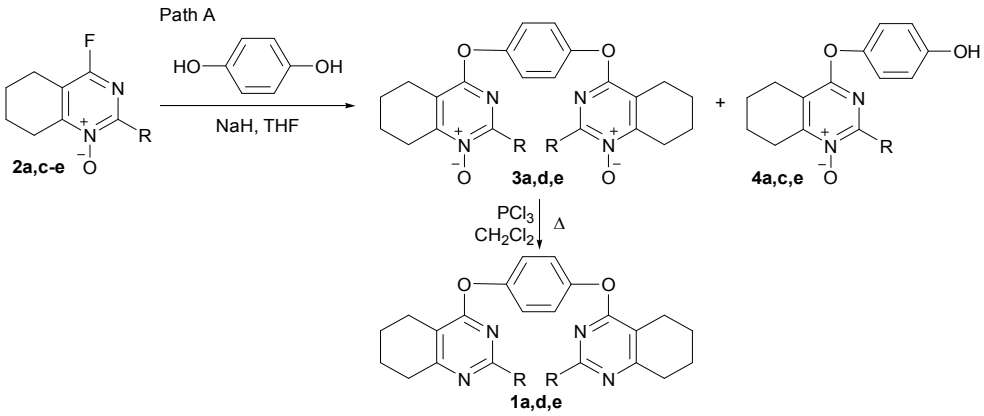
Experimental

General experimental details

^{1}H and ^{13}C NMR spectra were recorded on a spectrometer Agilent 400MR (400.0 MHz for ^{1}H, 100.6 MHz for ^{13}C and 376.3 MHz for ^{19}F) at room temperature; chemical shifts δ were measured with reference to the solvent for ^{1}H ($CDCl_3$, δ = 7.24 ppm) and ^{13}C ($CDCl_3$, δ = 77.0 ppm). When necessary, assignments of signals in NMR spectra were made using 2D techniques. High resolution mass spectra (HRMS) were measured on a Bruker micrOTOF II instrument using electrospray ionization (ESI). Analytical thin layer chromatography was carried out with silica gel plates (supported on aluminum); the detection was done by UV lamp (254 nm). Column chromatography was performed on silica gel (0.015-0.04 mm). Heterocycles **2a-e**,[1] **5a,b**[2] were obtained *via* literature procedures. All the other starting materials were commercially available. All reagents except commercial products of satisfactory quality were purified by literature procedures prior to use.

Synthetic methods

Synthesis of bis(5,6,7,8-tetrahydroquinazolines) 1a,d,e (method A)



*S_NAr in tetrahydroquinazoline N-oxides **2a-d** (general procedure 1).*

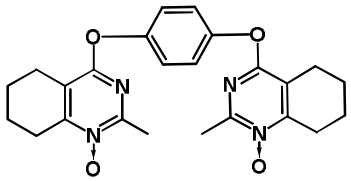
Hydroquinone (55 mg, 0.5 mmol) was added to the solution of sodium hydride (46 mg of 60% suspension in oil, 1.15 mmol) in THF (1.5 mL) under stirring at 10°C in argon atmosphere. In 10 min a solution of compound **2** (1 mmol) in THF (2 mL) was added, and the reaction mixture was stirred for 24 h at room temperature. The solvent was evaporated *in vacuo*, the residue was worked up with 10% HCl (8 mL) and extracted with CH_2Cl_2 (3 x 6 mL); the combined organic layers were washed with water (4 mL) and dried over $MgSO_4$. The solvent

[1] K. N. Sedenkova, E. B. Averina, Y. K. Grishin, A. B. Bacunov, S. I. Troyanov, I. V. Morozov, E. B. Deeva, A. V. Merkulova, T. S. Kuznetsova and N. S. Zefirov, *Tetrahedron Lett*., 2015, **56**, 4927.

[2] K. N. Sedenkova, E. B. Averina, Y. K. Grishin, T. S. Kuznetsova and N. S. Zefirov, *Tetrahedron Lett.*, 2014, **55**, 483.

was evaporated *in vacuo*, the products **3** and **4** were isolated *via* preparative column chromatography (SiO_2).

4,4'-[1,4-Phenylenebis(oxy)]bis(2-methyl-5,6,7,8-tetrahydroquinazoline) 1,1'-dioxide (3a)



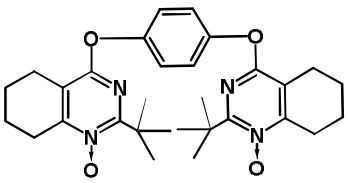
Yield 25% (54 mg); brown oil, R_f = 0.13 (petroleum ether:EtOAc:MeOH 3:1:1);

δH (400 MHz; $CDCl_3$+CD_3OD) 1.74-1.84 (4H, m, $2C6H_2$), 1.84-1.94 (4H, m, $2C7H_2$), 2.52 (6H, s, $2CH_3$), 2.72-2.76 (4H, m, $2C5H_2$), 2.88-2.92 (4H, m, $2C8H_2$), 7.13 (4H, s, 4CH, Ar);

δC (101 MHz; $CDCl_3$+CD_3OD) 19.8 ($2CH_3$), 20.6 ($2C6H_2$), 20.9 ($2C7H_2$), 22.0 ($2C5H_2$), 25.0 ($2C8H_2$,), 117.4 (2C4a), 122.2 (4CH, Ar), 149.6 (2C, Ar), 154.6 (2C2), 155.5 (2C4), 157.5 (2C8a);

HRMS (ESI^+, m/z): calculated for $C_{24}H_{26}N_4O_4$, [M+H]: 435.2027, found: 435.2021.

4,4'-[1,4-Phenylenebis(oxy)]bis(2-*tert*-butyl-5,6,7,8-tetrahydroquinazoline) 1,1'-dioxide (3d)



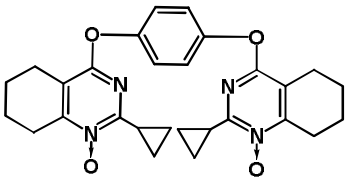
Yield 29% (75 mg); brown oil; R_f = 0.38 (petroleum ether:EtOAc:MeOH 3:1:1);

δH (400 MHz; $CDCl_3$) 1.37 (18H, s, $6CH_3$) 1.75-1.85 (4H, m, $2C6H_2$), 1.86-1.95 (4H, m, $2C7H_2$), 2.75-2.80 (4H, m, $2C5H_2$), 2.92-2.96 (4H, m, $2C8H_2$), 7.17 (4H, s, 4CH, Ar);

^{13}C (101 MHz, $CDCl_3$+CD_3OD) *δ*: 20.4 ($2C6H_2$), 21.1 ($2C7H_2$), 22.0 ($2C5H_2$), 24.9 ($2C8H_2$), 26.4 ($6CH_3$), 38.7 (2C, *t*-Bu), 115.5 (2C4a), 122.4 (4CH, Ar), 149.5 (2C, Ar), 158.9 (2C4), 159.3 (2C8a), 161.4 (2C2);

HRMS (ESI^+, m/z): calculated for $C_{30}H_{38}N_4O_4$, [M+H]: 519.2966, found: 519.2962; calculated for $C_{30}H_{38}N_4O_4$, [M+Na]: 541.2785, found: 541.2781.

4,4'-[1,4-Phenylenebis(oxy)]bis(2-cyclopropyl-5,6,7,8-tetrahydroquinazoline) 1,1'-dioxide (3e)



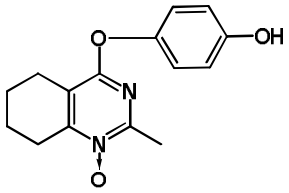
Yield 26% (63 mg); brown oil; R_f = 0.08 (petroleum ether:EtOAc:MeOH 3:1:1);

δH (400 MHz; $CDCl_3$+CD_3OD) 0.69-0.80 (4H, m, $2CH_2$, c-Pr), 0.94-1.05 (4H, m, $2CH_2$, c-Pr), 1.71-1.81 (4H, m, $2C6H_2$), 1.82-1.92 (4H, m, $2C7H_2$), 2.68-2.72 (4H, m, $2C5H_2$), 2.90-2.94 (4H, m, $2C8H_2$), 2.93-3.03 (2H, m, 2CH, cy-Pr), 7.03 (4H, s, 4CH, Ar);

δC (101 MHz; $CDCl_3$) 10.2 (2CH, c-Pr), 10.6 ($4CH_2$, c-Pr), 20.5 ($2C6H_2$), 20.9 ($2C7H_2$), 21.9 ($2C5H_2$), 25.0 ($2C8H_2$), 115.8 (2C4a), 122.4 (4CH, Ar), 149.4 (2C, Ar), 157.2 (2C4), 157.7 (2C8a), 158.8 (2C2);

HRMS (ESI$^+$, m/z): calculated for $C_{28}H_{30}N_4O_4$, [M+H]: 487.2340, found: 487.2336; calculated for $C_{28}H_{30}N_4O_4$, [M+Na]: 509.2159, found: 509.2161.

4-[(2-Methyl-1-oxido-5,6,7,8-tetrahydroquinazolin-4-yl)oxy]phenol (4a)



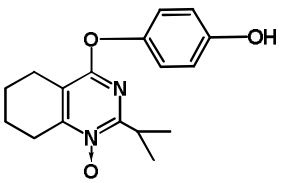
Yield 29% (39 mg); brown oil; R_f = 0.37 (petroleum ether:EtOAc:MeOH 3:1:1);

δH (400 MHz; $CDCl_{3+}CD_3OD$) 1.74-1.83 (2H, m, $C6H_2$), 1.84-1.94 (2H, m, $C7H_2$), 2.54 (3H, s, CH_3), 2.70-2.74 (2H, m, $C5H_2$), 2.90-2.94 (2H, m, $C8H_2$), 6.80-6.86 (2H, m, 2CH, Ar), 6.88-6.94 (2H, m, 2CH, Ar);

δC (101 MHz; $CDCl_3$) 20.0 (CH_3,), 20.5 ($C6H_2$), 20.9 ($C7H_2$), 22.0 ($C5H_2$), 25.0 ($C8H_2$), 116.1 (2CH, Ar), 117.6 (C4a), 122.3 (2CH, Ar), 145.0 (C, Ar), 154.5 (C, Ar), 155.3 (C2), 157.5 (C8a), 157.8 (C4);

HRMS (ESI$^+$, m/z): calculated for $C_{15}H_{16}N_2O_3$, [M+H]: 273.1234, found: 273.1243; calculated for $C_{15}H_{16}N_2O_3$, [M+Na]: 295.1053, found: 295.1056.

4-[(2-Isopropyl-1-oxido-5,6,7,8-tetrahydroquinazolin-4-yl)oxy]phenol (4c)



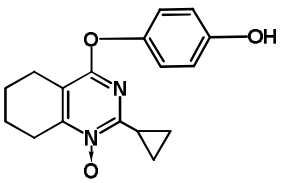
Yield 49% (74 mg); brown oil; R_f = 0.48 (petroleum ether:EtOAc:MeOH 3:1:1);

δH (400 MHz; $CDCl_3$) 1.07 (6H, d, J 6.9, $2CH_3$), 1.73-1.83 (2H, m, $C6H_2$), 1.83-1.93 (2H, m, $C7H_2$), 2.70-2.74 (2H, m, $C5H_2$), 2.94-2.98 (H, m, $C8H_2$), 3.82 (1H, sept, J 6.9, CH, *i*-Pr), 6.83-6.91 (2H, m, 2CH, Ar), 6.91-6.98 (2H, m, 2CH, Ar);

δC (101 MHz; $CDCl_3$) 19.3 ($2CH_3$), 20.5 ($C6H_2$), 21.0 ($C7H_2$), 22.0 ($C5H_2$), 25.1 ($C8H_2$), 29.1 (CH, *i*-Pr), 115.8 (2CH, Ar), 116.9 (C4a), 122.2 (2CH, Ar), 145.1 (C, Ar), 154.4 (C, Ar), 157.5 (C8a), 157.6 (C4), 161.7 (C2);

HRMS (ESI$^+$, m/z): calculated for $C_{17}H_{20}N_2O_3$, [M+H]: 301.1547, found: 301.1554.

4-[(2-Cyclopropyl-1-oxido-5,6,7,8-tetrahydroquinazolin-4-yl)oxy]phenol (4e)



Yield 41% (61 mg); brown oil; R_f = 0.34 (petroleum ether:EtOAc:MeOH 3:1:1);

δH (400 MHz; $CDCl_3$+CD_3OD) 0.67-0.74 (2H, m, CH_2, c-Pr), 0.90-0.99 (2H, m, CH_2, c-Pr), 1.68-1.79 (2H, m, CH_2), 1.79-1.91 (2H, m, CH_2), 2.63-2.67 (2H, m, CH_2), 2.85-2.94 (3H, m, CH_2, c-Hex + CH, c-Pr), 6.73-6.84 (4H, m, 4CH, Ar);

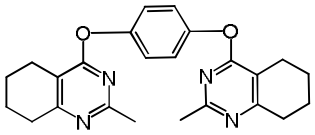
δC (101 MHz; $CDCl_3$) 10.5 ($2CH_2$, c-Pr), 17.9 (CH, c-Pr), 20.6 (CH_2), 21.0 (CH_2), 21.9 (CH_2), 25.2 (CH_2), 115.7 (C4a), 115.9 (2CH, Ar), 122.2 (2CH, Ar), 144.9 (C, Ar), 154.4 (C, Ar), 157.3 (C8a), 158.8 (C4), 163.6 (C2);

HRMS (ESI$^+$, 70 eV, m/z): calculated for $C_{17}H_{18}N_2O_3$, [M+H]: 299.1390, found: 299.1394.

Reduction of bis(5,6,7,8-tetrahydroquinazoline N-oxides) ***3*** *(general procedure 2).*

Phosphorus trichloride (27.5 mg, 0.02 mL, 0.2 mmol) was added to a solution of compound **3** (21.7 mg, 0.05 mmol) in CH_2Cl_2 (3 mL) in argon atmosphere. The mixture was refluxed for 2 h, cooled down to room temperature and poured into the equal volume of icy water. The organic layer was separated, and the water layer was extracted with CH_2Cl_2 (3 × 6 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (3 mL) and dried over $MgSO_4$. The solvent was evaporated *in vacuo*, the product was dried at 1 torr for 1 h.

4,4'-[1,4-Phenylenebis(oxy)]bis(2-methyl-5,6,7,8-tetrahydroquinazoline) (1a)



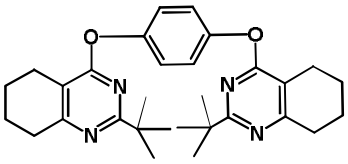
Yield 71% (15 mg); white solid; m.p. 133-135°C;

δH (400 MHz; $CDCl_3$) 1.79-1.93 (8H, m, $4CH_2$), 2.47 (6H, s, $2CH_3$), 2.68-2.76 (4H, m, $2CH_2$), 2.79-2.86 (4H, m, $2CH_2$), 7.15 (4H, s, 4CH, Ar);

δC (101 MHz; $CDCl_3$) 21.6 ($2CH_2$), 21.9 ($2CH_2$), 22.1 ($2CH_2$), 25.2 ($2CH_3$), 31.5 ($2CH_2$), 114.2 (2C4a), 122.3 (4CH, Ar), 149.6 (2C, Ar), 164.0 (2C2), 166.2 (2C8a), 167.0 (2C4);

HRMS (ESI^+, m/z): calculated for $C_{24}H_{26}N_4O_2$, [M+H]: 403.2129, found: 403.2124; calculated for $C_{24}H_{26}N_4O_2$, [M+Na]: 425.1948, found: 425.1943.

4,4'-[1,4-Phenylenebis(oxy)]bis(2-*tert*-butyl-5,6,7,8-tetrahydroquinazoline) (1d)



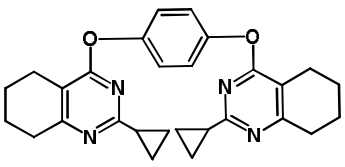
Yield 65% (14 mg); white solid; m.p. 122-128°C;

δH (400 MHz; $CDCl_3$) 1.19 (18H, s, $6CH_3$) 1.78-1.93 (8H, s, $4CH_2$), 2.69-2.75 (4H, m, $2CH_2$), 2.77-2.83 (4H, m, $2CH_2$), 7.14 (4H, s, 4CH, Ar);

δC (101 MHz; $CDCl_3$) 21.8 ($2CH_2$), 22.1 ($2CH_2$), 22.5 ($2CH_2$), 29.4 ($6CH_3$), 32.1 ($2CH_2$), 38.8 (2C, *t*-Bu), 113.2 (2C4a), 122.3 (4CH, Ar), 149.6 (2C, Ar), 166.1 (2C8a), 166.6 (2C4), 173.2 (2C2);

HRMS (ESI^+, m/z): calculated for $C_{30}H_{38}N_4O_2$, [M+H]: 487.3068, found: 487.3066; calculated for $C_{30}H_{38}N_4O_2$, [M+Na]: 509.2887, found: 509.2886.

4,4'-[1,4-Phenylenebis(oxy)]bis(2-cyclopropyl-5,6,7,8-tetrahydroquinazoline) (1e)



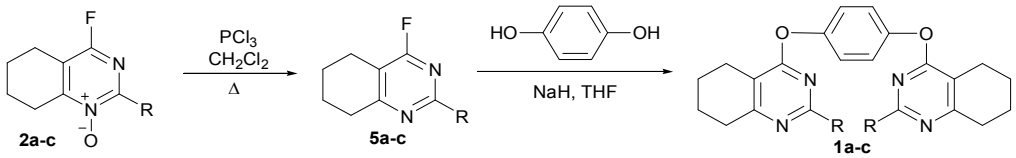
Yield 83% (18 mg); white solid; m.p. 113-116°C;

δH (400 MHz; $CDCl_3$) 0.78-0.88 (8H, m, $4CH_2$, c-Pr), 1.81-1.95 (8H, m, $4CH_2$), 1.96-2.05 (2H, m, 2CH, c-Pr), 2.69-2.77 (4H, m, $2CH_2$), 2.78-2.84 (4H, m, $2CH_2$), 7.10 (4H, s, 4CH, Ar);

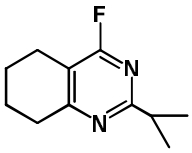
δC (101 MHz; $CDCl_3$) 9.9 ($4CH_2$, c-Pr), 17.5 ($2CH_2$), 21.7 ($2CH_2$), 22.1 ($2CH_2$), 22.4 ($2CH_2$), 31.9 (2CH, c-Pr), 113.4 (2C4a), 122.3 (4CH, Ar), 149.5 (2C, Ar), 166.1 (2C), 167.1 (2C), 168.1 (2C);

HRMS (ESI^+, m/z): calculated for $C_{28}H_{30}N_4O_2$, [M+H]: 455.2442, found: 455.2433.

Synthesis of bis(5,6,7,8-tetrahydroquinazolines) 1a-c (Method B)



4-fluoro-2-isopropyl-5,6,7,8-tetrahydroquinazoline (5c) was obtained *via* literature procedure.[2]



Yield 50% (280 mg), obtained from 600 mg (2.9 mmol) 4-fluoro-2-isopropyl-5,6,7,8-tetrahydroquinazoline *N*-oxide; colorless oil; R_f = 0.19 (petroleum ether:CH_2Cl_2 1:1);

δH (400 MHz; $CDCl_3$) 1.29 (6H, d, J 7.0, $2CH_3$), 1.78-1.92 (4H, m, $2CH_2$), 2.62-2.68 (2H, m, CH_2), 2.82-2.88 (2H, m, CH_2), 3.09 (1H, sept, J 7.0, CH);

δC (101 MHz; $CDCl_3$) 20.7 (CH_2), 21.4 (CH_2), 21.5 ($2CH_3$), 21.9 (CH_2), 31.5 (d, $^3J_{CF}$ 4, CH_2), 36.7 (CH, *i*-Pr), 113.2 (d, $^2J_{CF}$ 26, C4a), 168.1 (d, $^1J_{CF}$ 252, C4), 169.8 (d, $^3J_{CF}$ 7, C8a), 172.6 (d, , $^3J_{CF}$ 13, C2);

δF (376 MHz,; $CDCl_3$) -67.57 (s);

HRMS (ESI^+, m/z): calculated for $C_{11}H_{15}FN_2$, [M+H]: 195.1292, found 195.1292.

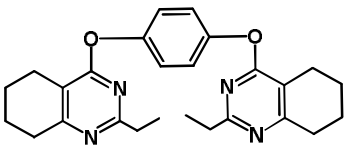
*Nucleophilic substitution in tetrahydroquinazolines **5a-c** (general procedure 3).*

Hydroquinone (55 mg, 0.5 mmol) was added to the solution of sodium hydride (90 mg of 60% suspension in oil, 2.25 mmol) in THF (1 mL) under stirring at 10°C in argon atmosphere. In 10 min a solution of compound **5** (1.15 mmol) in THF (2 ml) was added, and the reaction mixture was refluxed for 3 h. The solvent was evaporated *in vacuo*, the residue was worked up with 10% NaOH (3 x 5 mL) and extracted with CH_2Cl_2 (3 x 6 mL); the combined organic layers were washed with water (4 mL) and dried over $MgSO_4$. The solvent was evaporated *in vacuo*, the product was isolated *via* preparative column chromatography (SiO_2).

4,4'-[1,4-Phenylenebis(oxy)]bis(2-ethyl-5,6,7,8-tetrahydroquinazoline) (1a)

Yield 35% (70 mg), all characteristics correspond to the sample obtained *via* Method A.

4,4'-[1,4-Phenylenebis(oxy)]bis(2-ethyl-5,6,7,8-tetrahydroquinazoline) (1b)



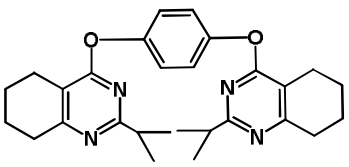
Yield 33% (63 mg); white solid; R_f = 0.26 (petroleum ether:EtOAc:MeOH 3:1:0.1); m.p. 125-127°C;

δH (400 MHz; $CDCl_3$) 1.16 (6H, t, J 7.5, $2CH_3$), 1.79-1.92 (8H, m, $4CH_2$), 2.69 (4H, q, J 7.5, $2CH_2$, Et), 2.71-2.75 (4H, m, $2CH_2$), 2.78-2.84 (4H, m, $2CH_2$), 7.15 (4H, s, 4CH, Ar);

δC (101 MHz; $CDCl_3$) 12.6 ($2CH_3$), 21.7 ($2CH_2$), 22.0 ($2CH_2$), 22.3 ($2CH_2$), 31.9 ($2CH_2$), 32.0 ($2CH_2$, Et), 114.0 (2C4a), 122.2 (4CH, Ar), 149.6 (2C, Ar), 166.4 (2C8a), 167.0 (2C4), 168.3 (2C2);

HRMS (ESI^+, m/z): calculated for $C_{26}H_{30}N_4O_2$, [M+H]: 431.2442, found: 431.2442; calculated for $C_{26}H_{30}N_4O_2$, [M+Na]: 453.2261, found: 453.2250.

4,4'-[1,4-Phenylenebis(oxy)]bis(2-isopropyl-5,6,7,8-tetrahydroquinazoline) (1c)



Yield 39% (89 mg); white solid; R_f = 0.44 (petroleum ether:EtOAc:MeOH 3:1:0.1); m.p. 107-111°C;

δH (400 MHz; $CDCl_3$) 1.14 (12H, d, J 6.8, $2CH_3$), 1.80-1.93 (8H, m, $4CH_2$), 2.70-2.76 (4H, m, $2CH_2$), 2.78-2.84 (4H, m, $2CH_2$), 2.93 (2H, quint, J 6.8, CH, *i*-Pr), 7.15 (4H, s, 4CH, Ar);

δC (101 MHz; $CDCl_3$) 21.6 ($4CH_3$), 21.8 ($2CH_2$), 22.1 ($2CH_2$), 22.4 ($2CH_2$), 32.0 ($2CH_2$), 37.0 (2CH, *i*-Pr), 113.9 (2C4a), 122.2 (4CH, Ar), 149.6 (2C, Ar), 166.3 (2C8a), 167.0 (2C4), 171.5 (2C2);

HRMS (ESI^+, m/z): calculated for $C_{28}H_{34}N_4O_2$, [M+H]: 459.2755, found: 459.2746; calculated for $C_{28}H_{34}N_4O_2$, [M+Na]: 481.2574, found: 481.2567.

Electrophysiological experiments

All compounds were dissolved in a mixture of dimethyl sulfoxide (90 %) with ethanol (10 %) to make 10 mM solutions, which were then diluted into extracellular solution to attain the final concentrations desired.

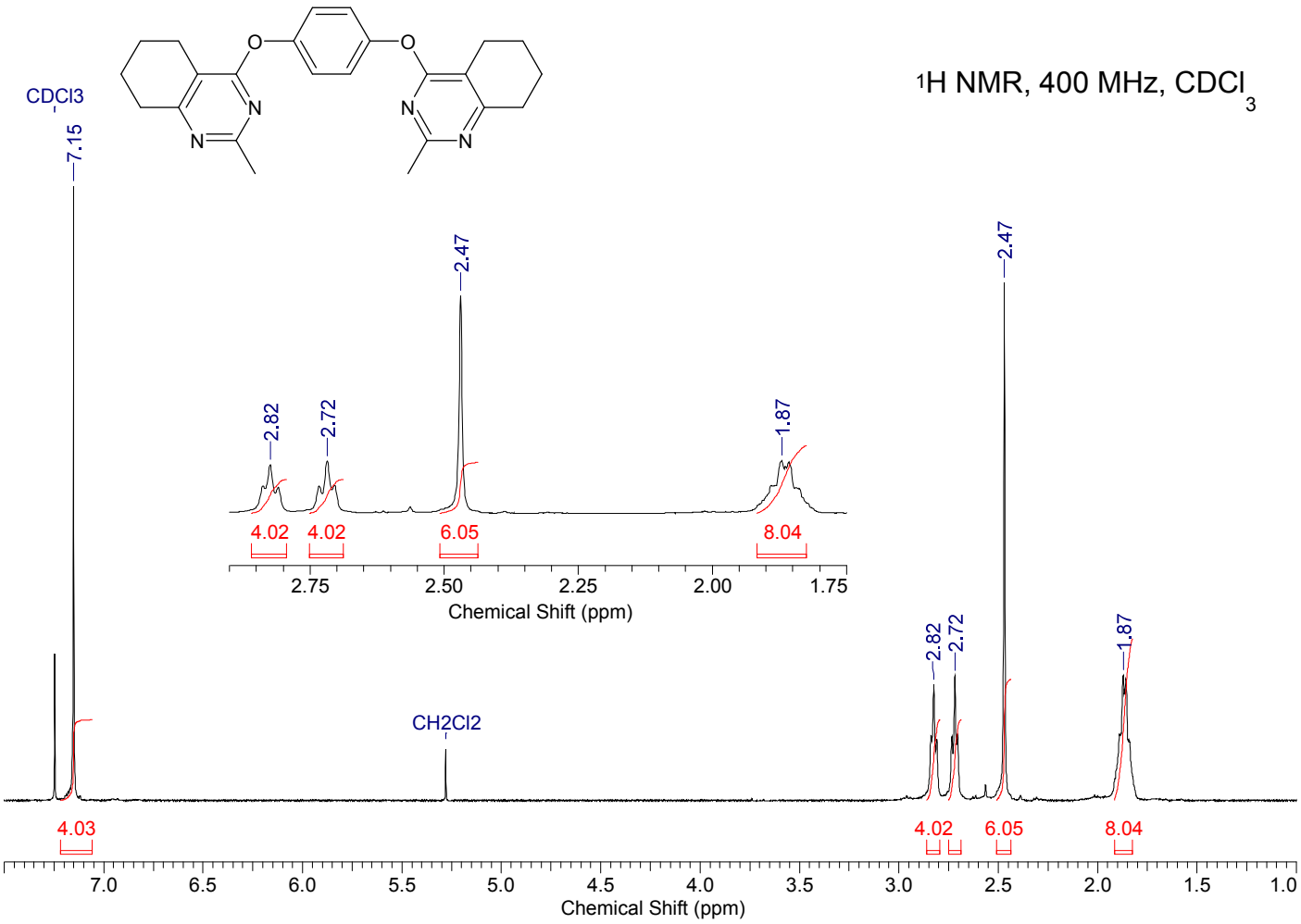
Freshly isolated neurons from 12-to-16-day-old rat pups were used for the patch-clamp technique; AMPA-receptor-mediated currents were studied in Purkinje neurons of the cerebellum, as described elsewhere.[3] Briefly, for cell isolation, a selected region of the brain was cut into slices 0.4-0.6 mm wide followed by incubation in buffer (150 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 2 mM $MgCl_2$, 10 mM HEPES (4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid), 10 mM glucose, pH 7.4) for one hour. The slices were transferred to fresh buffer solution with 2 mg/ml of Protease (Sigma-Aldrich, St. Louis, MO, US) and 1 mg/ml of Collagenase (Sigma-Aldrich, St. Louis, MO, US) and incubated for 45–60 min. Then, the slices were transferred to the fresh buffer solution and incubated about 20 min. The slices were incubated at 34°C and pre-gassed with 100% O_2. Finally, the slices were mechanically dissociated into individual cells by means of Pasteur pipettes. The composition of extracellular saline was 150 mM NaCl, 5 mM KCl, 2.6 mM $CaCl_2$, 2.0 mM $MgCl_2$, 10 mM HEPES, 10 mM glucose, pH 7.32. The composition of the intracellular saline was 140 mM KCl, 10 mM HEPES, 5 mM EGTA (ethylene glycol-bis(2-aminoethylether)-N,N,N′,N′-tetraacetic acid), 1 mM $MgCl_2$, 1 mM ATP. The

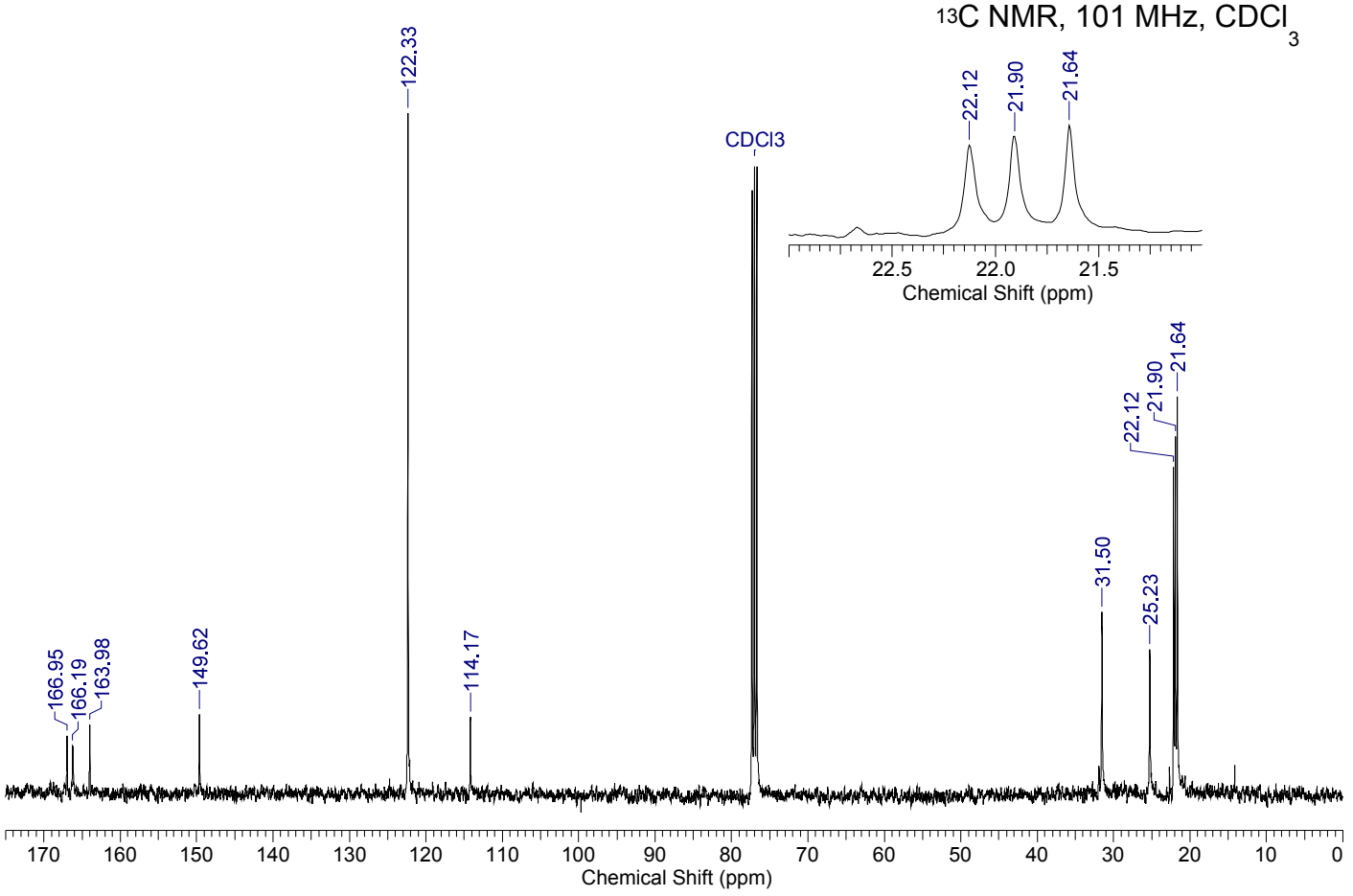
[3] G.L. Perlovich, A.N. Proshin, T.V. Volkova, S.V. Kurkov, V.V. Grigoriev, L.N. Petrova and S.O. Bachurin, *J. Med. Chem.* **2009**, *52*, 1845.

transmembrane currents were registered in the configuration of the 'whole cell' using the electrophysiological EPC-9 set-up (HEKA, Lambrecht, Germany); data were processed with HEKA software (Pulsefit/HEKA, Lambrecht, Germany). Tested compounds were exposed to neurons by the fast perfusion method.[3]

The effects of tested compounds on the stimulation of AMPA receptors were investigated on isolated Purkinje neurons using partial receptor agonist kainic acid (KA), which induces AMPA-receptor mediated currents while evoking relatively low receptor desensitization. Baseline recordings of AMPA-receptor mediated transmembrane currents were carried out three times after each application of KA (20 μM) that were spaced from each other in this and any other applications during recordings by 2 min. Thereafter, the physiological solution in the recording chamber was replaced with increasing concentrations of test compounds. The application of each tested concentration was accompanied by a concomitant triple application of KA at above-indicated concentration. After each tested compound application, a 3-min wash-out with physiological solution was carried out and responses to three applications of KA were recorded for a control. The next concentration was then applied followed by a wash-out session and triple application of KA. The mean of amplitude of the AMPA-mediated currents measured during all applications of KA was taken as a control value (100%), means of measurements of this parameter during applications were normalized to control for each concentration and expressed as a percentage. Each concentration was tested on 4–7 Purkinje neurons; six to seven concentrations in a range from 0.000001 μM to 1 μM of each compound were tested.

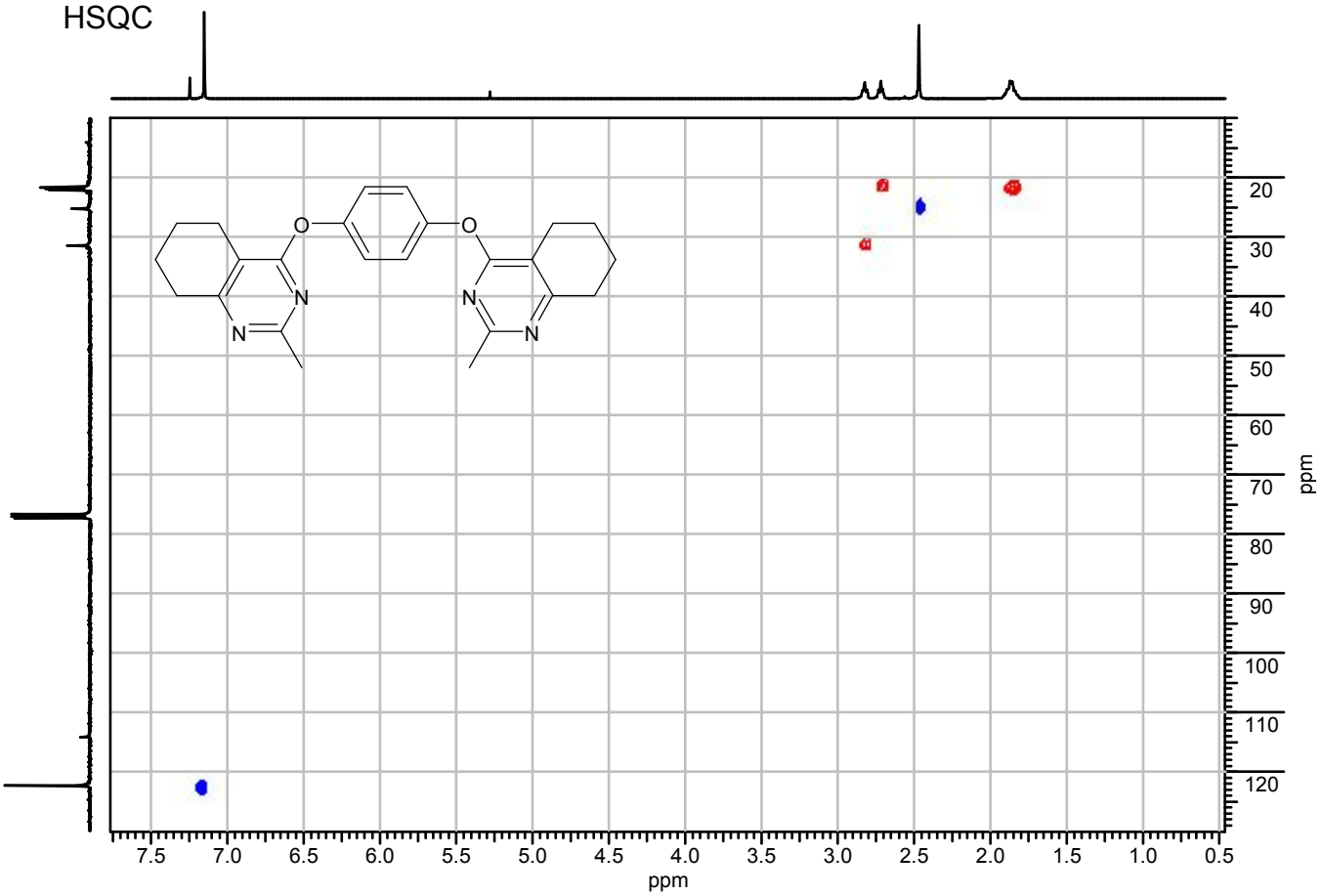
4,4’-[1,4-Phenylenebis(oxy)]bis(2-methyl-5,6,7,8-tetrahydroquinazoline) (1a)



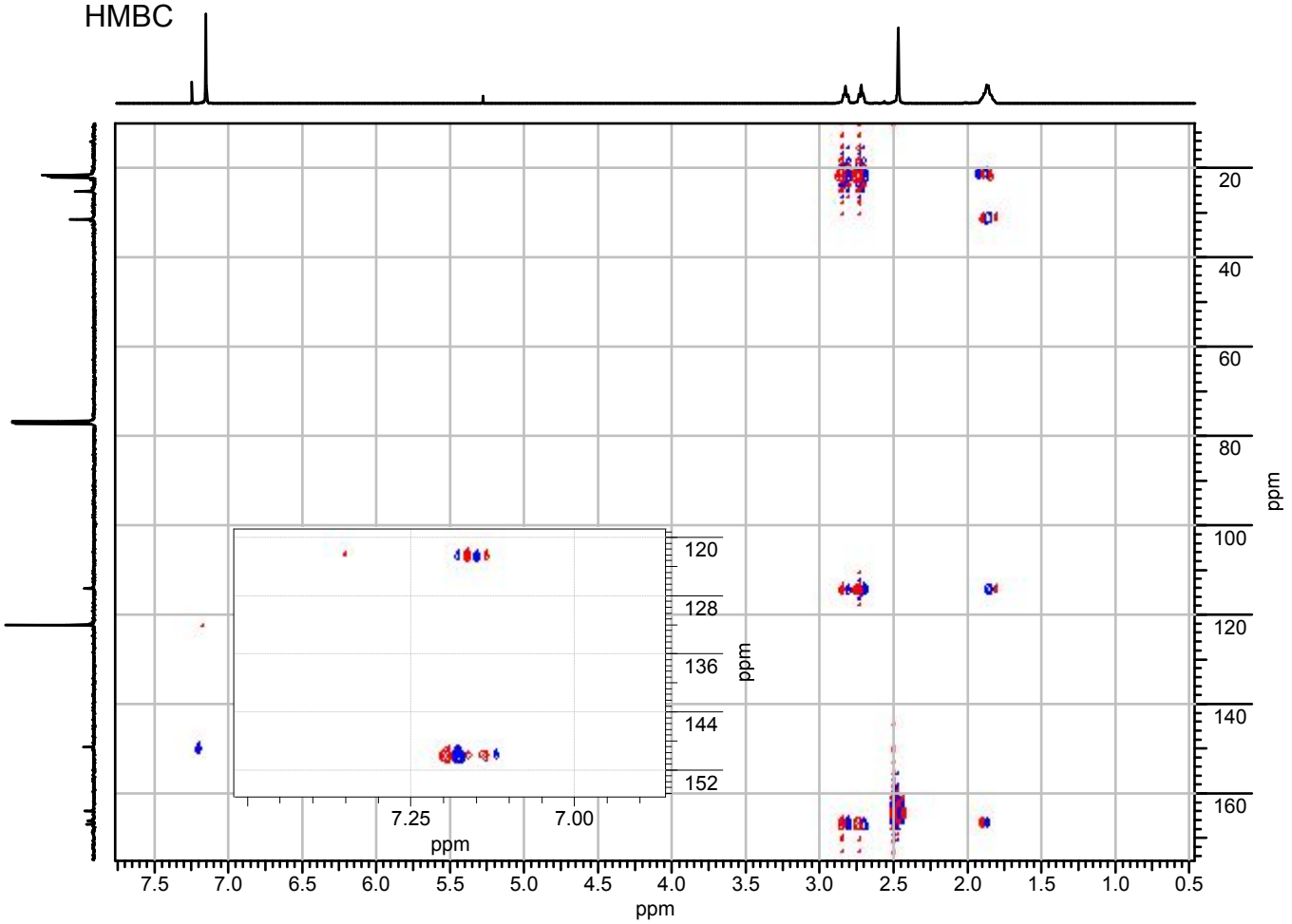


4,4’-[1,4-Phenylenebis(oxy)]bis(2-methyl-5,6,7,8-tetrahydroquinazoline) (1a)

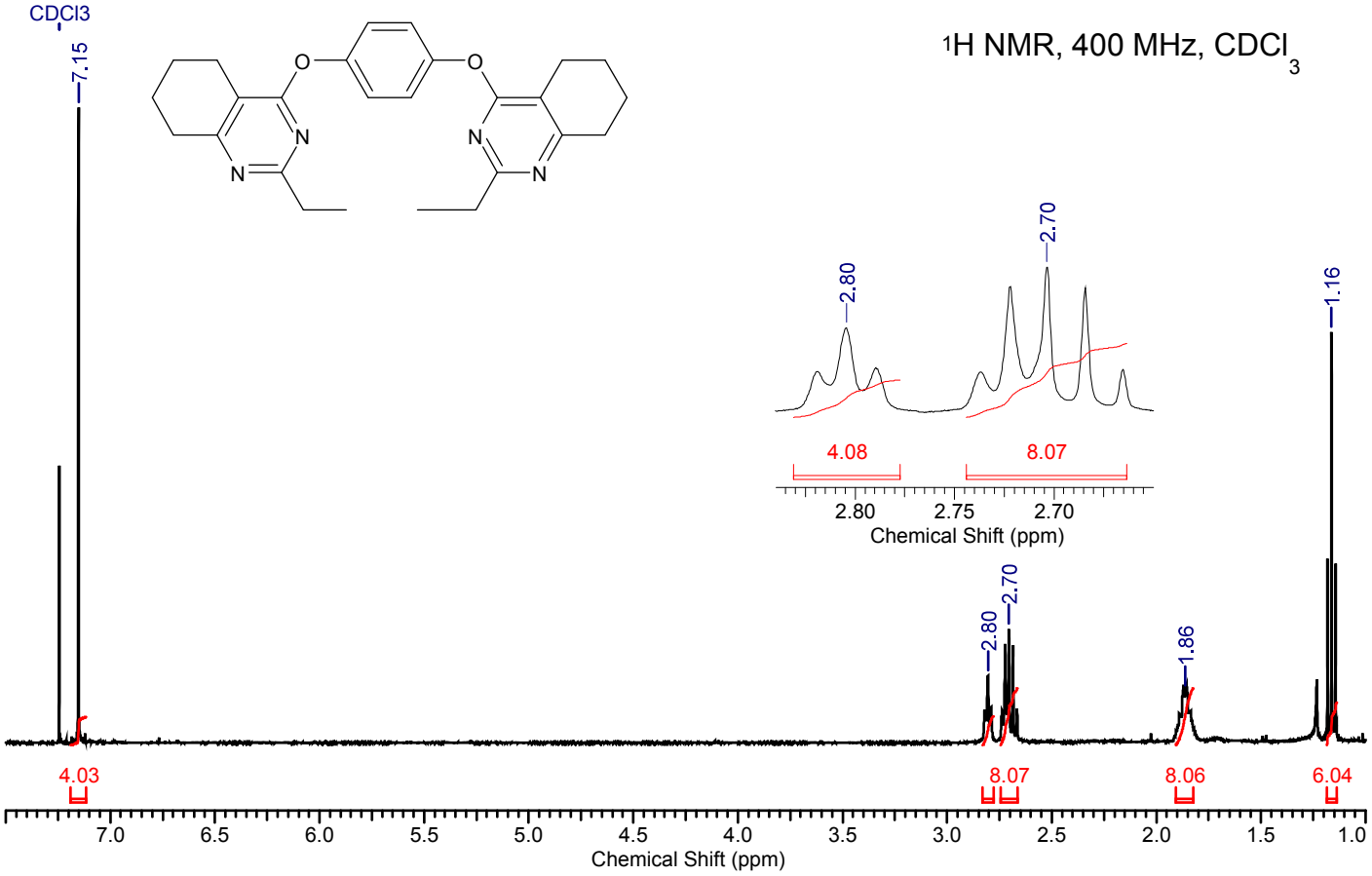
HSQC

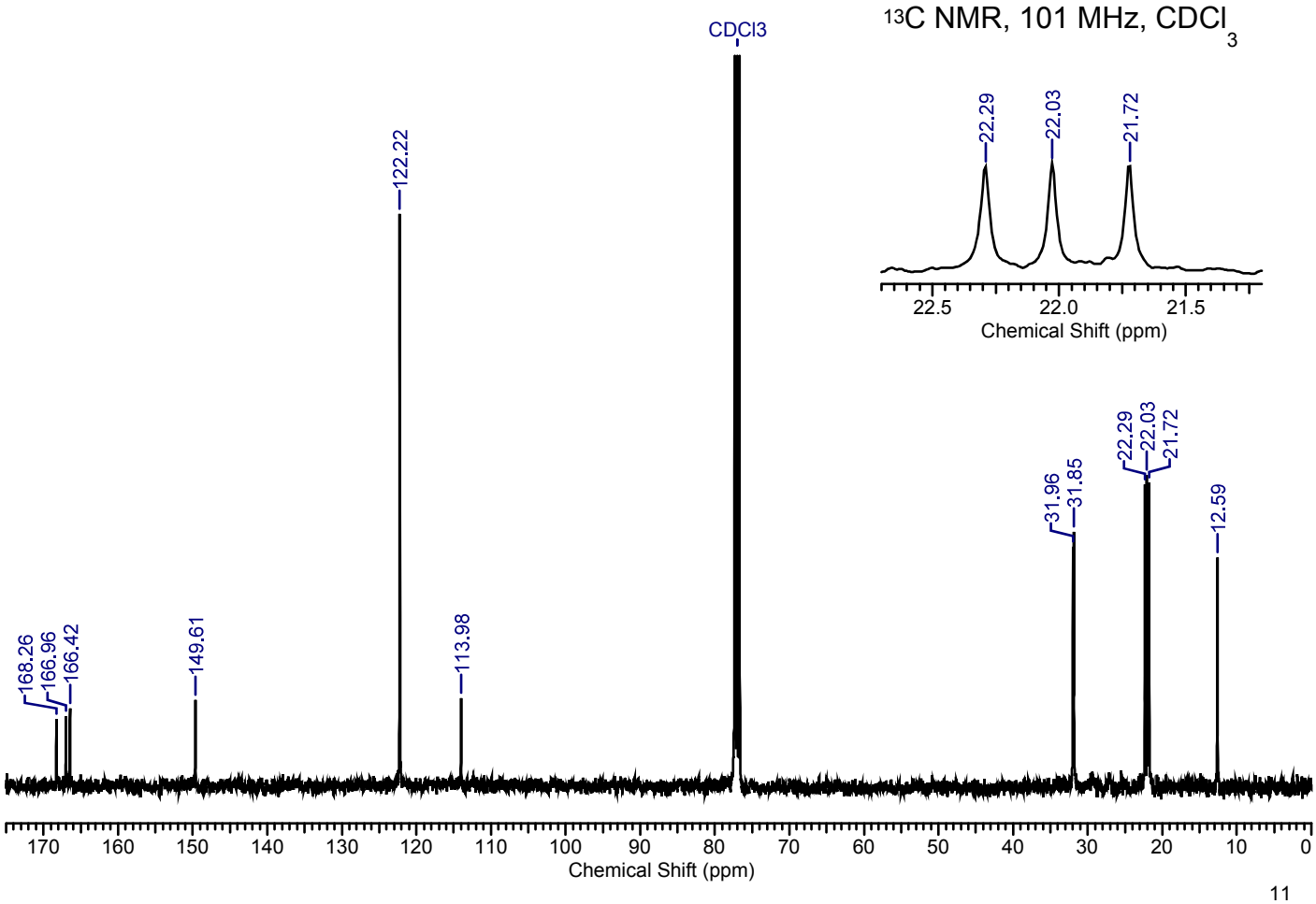


HMBC



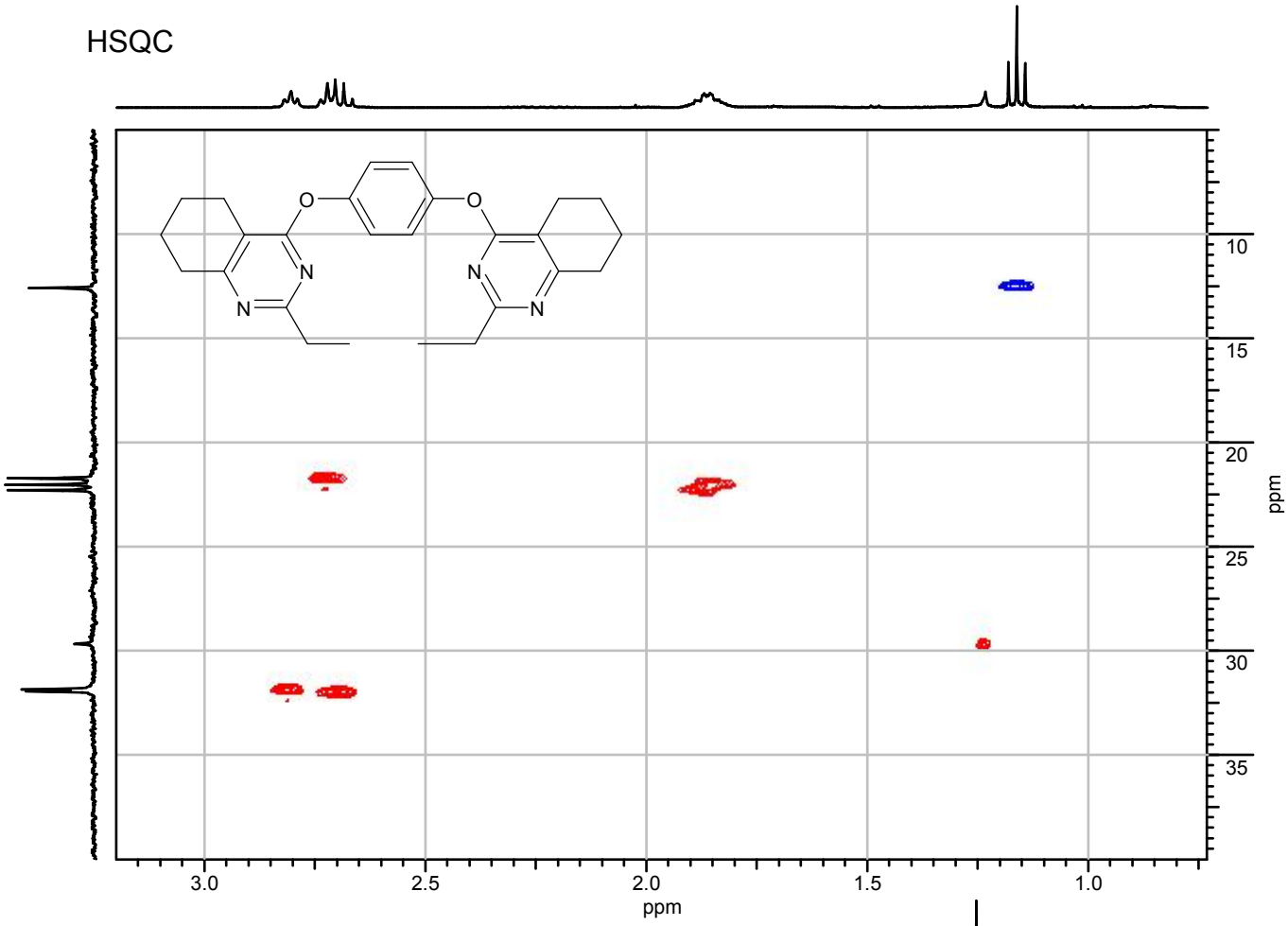
4,4’-[1,4-Phenylenebis(oxy)]bis(2-ethyl-5,6,7,8-tetrahydroquinazoline) (1b)



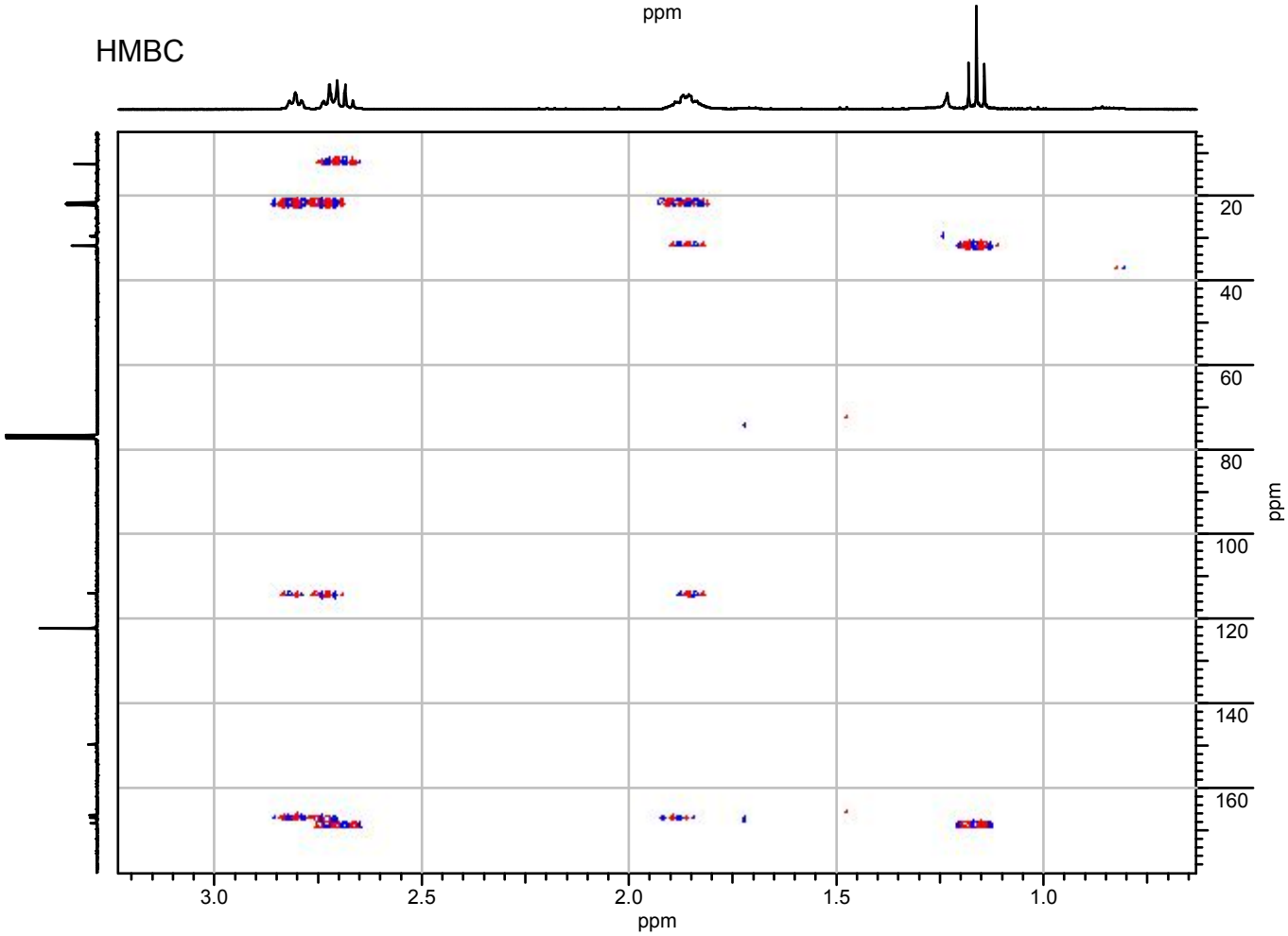


4,4’-[1,4-Phenylenebis(oxy)]bis(2-ethyl-5,6,7,8-tetrahydroquinazoline) (1b)

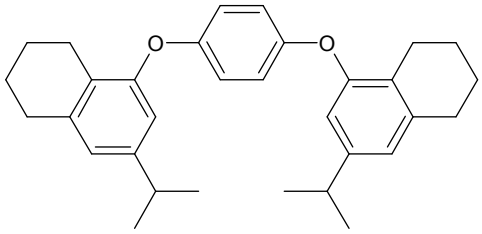
HSQC



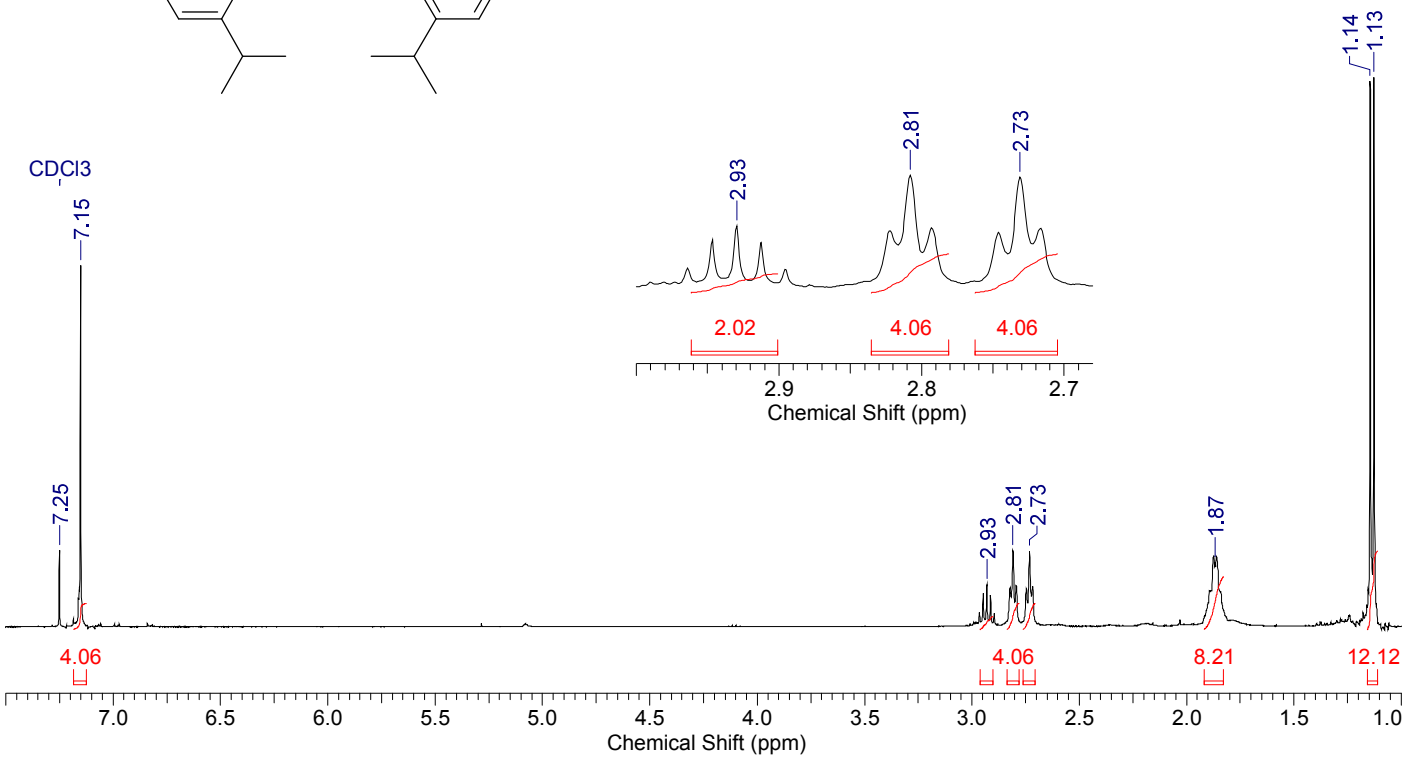
HMBC



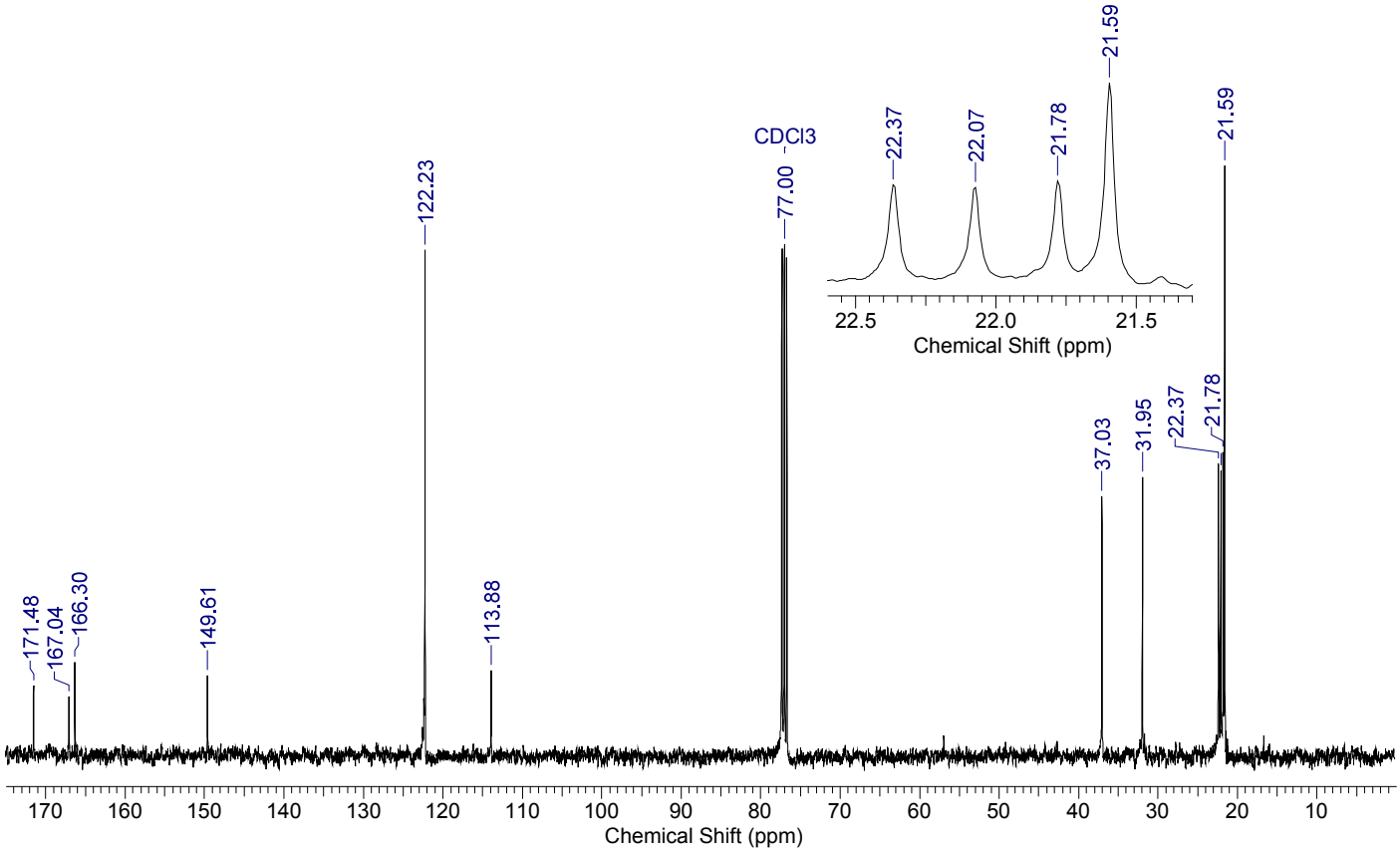
4,4’-[1,4-Phenylenebis(oxy)]bis(2-isopropyl-5,6,7,8-tetrahydroquinazoline) (1c)



^{1}H NMR, 400 MHz, $CDCl_3$

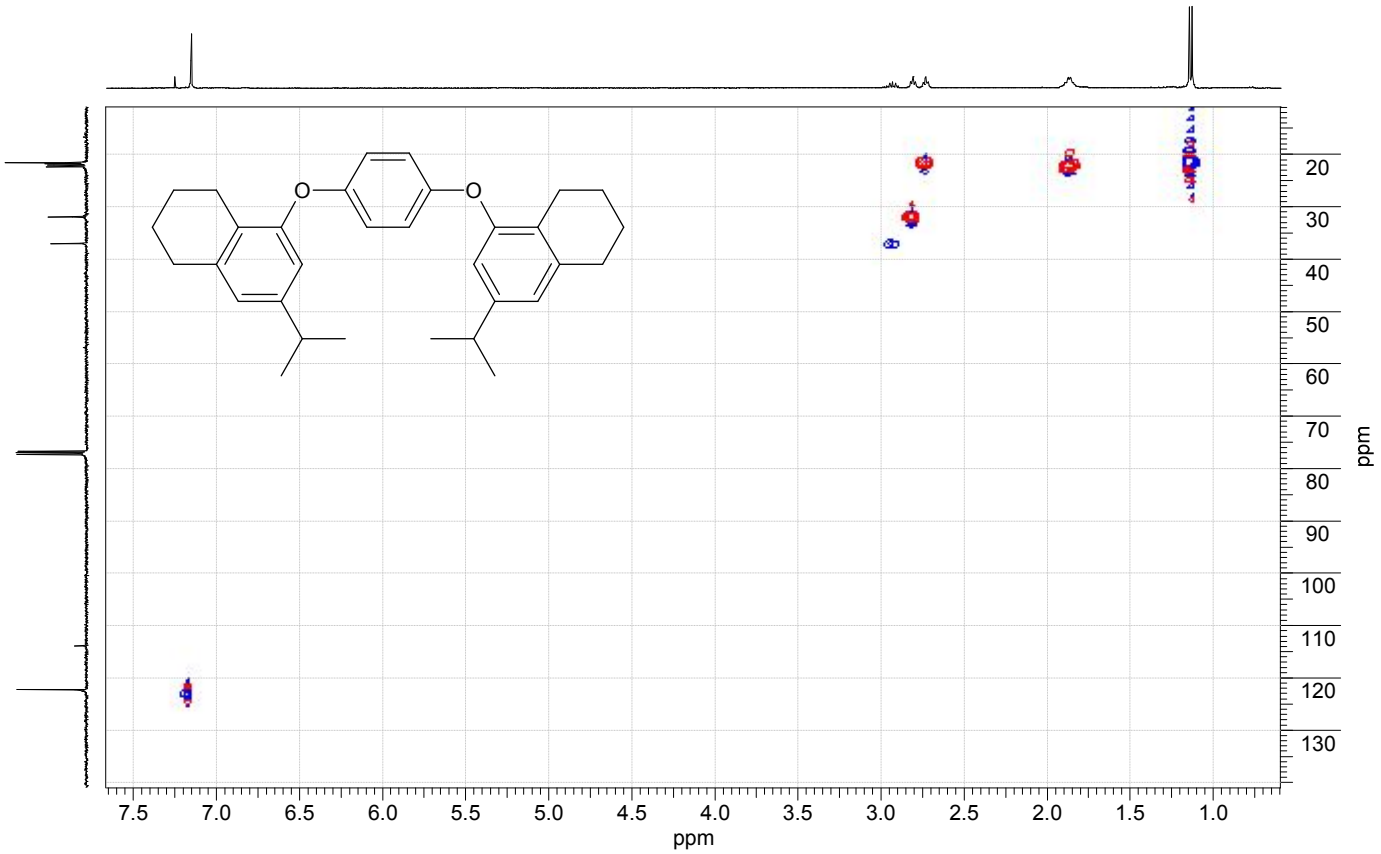


^{13}C NMR, 101 MHz, $CDCl_3$

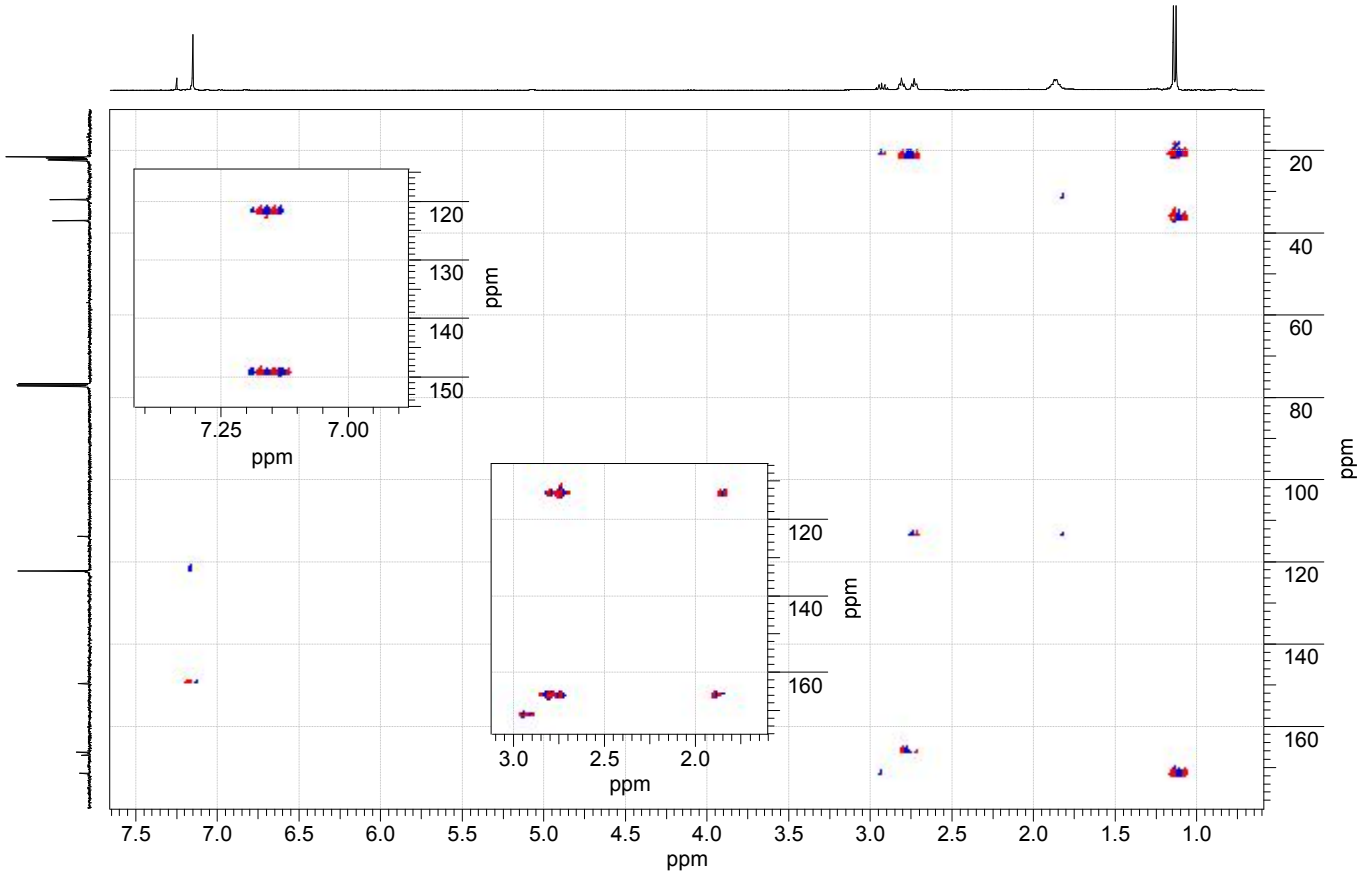


4,4’-[1,4-Phenylenebis(oxy)]bis(2-isopropyl-5,6,7,8-tetrahydroquinazoline) (1c)

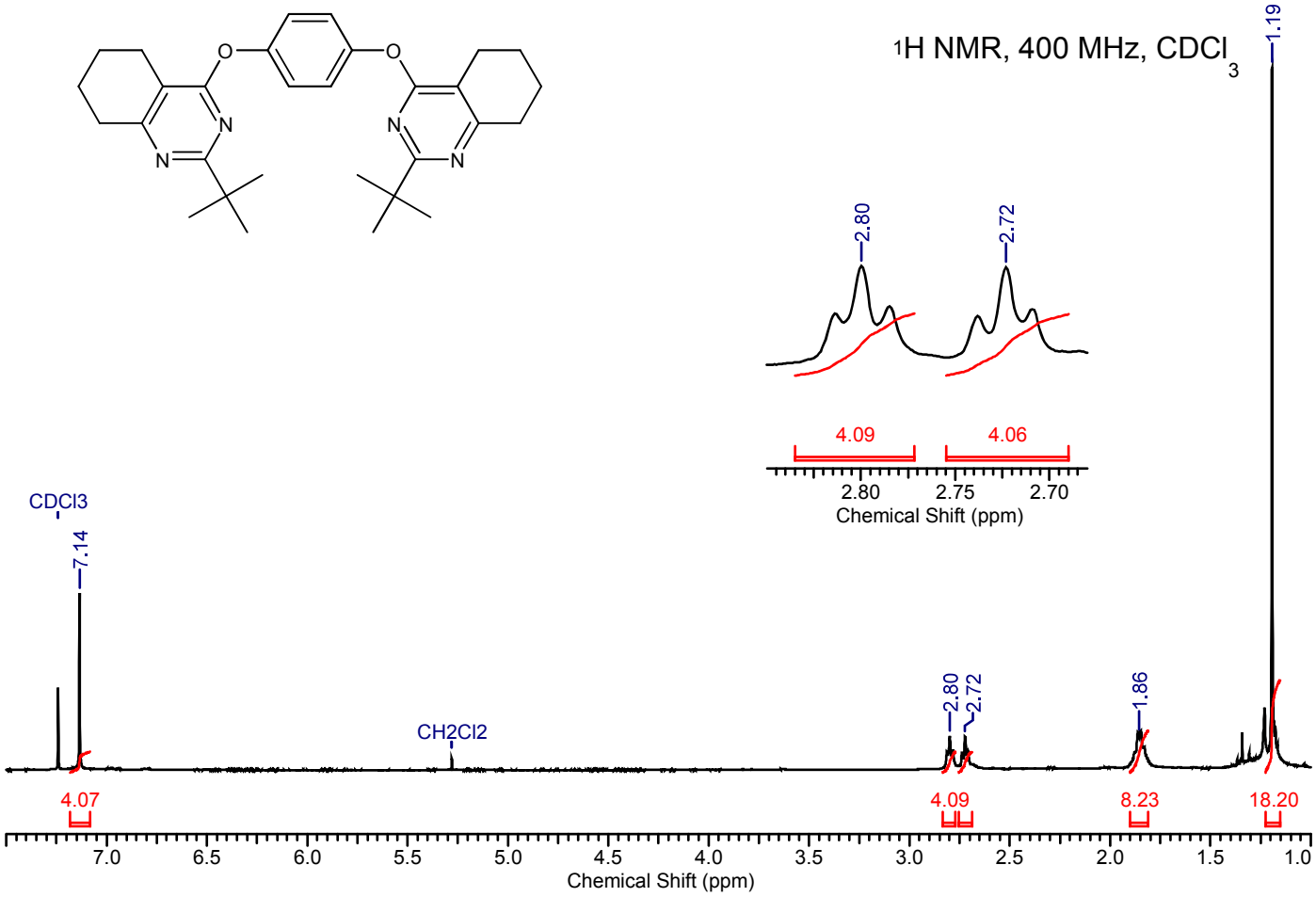
HSQC

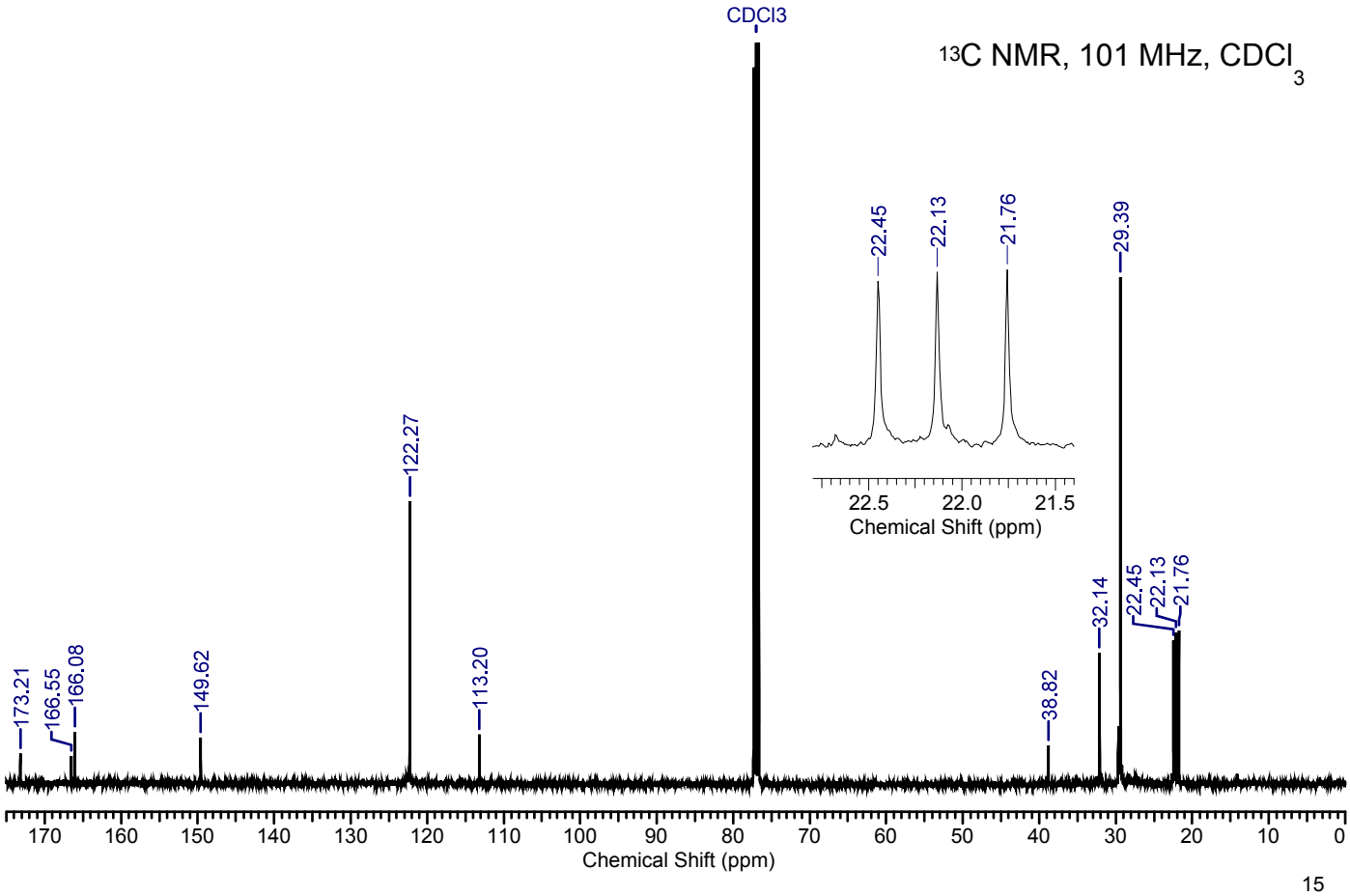


HMBC



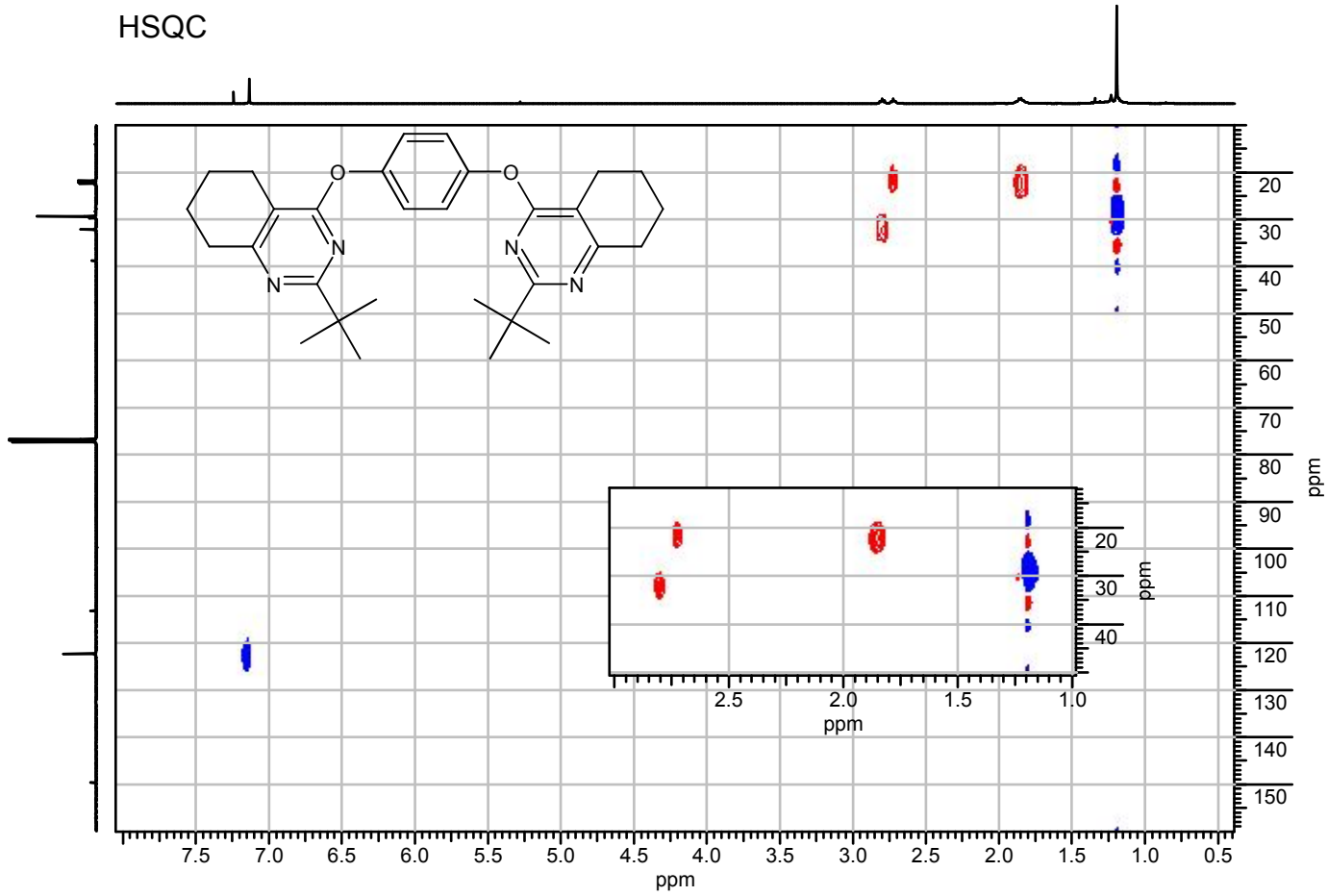
4,4’-[1,4-Phenylenebis(oxy)]bis(2-*tert*-butyl-5,6,7,8-tetrahydroquinazoline) (1d)



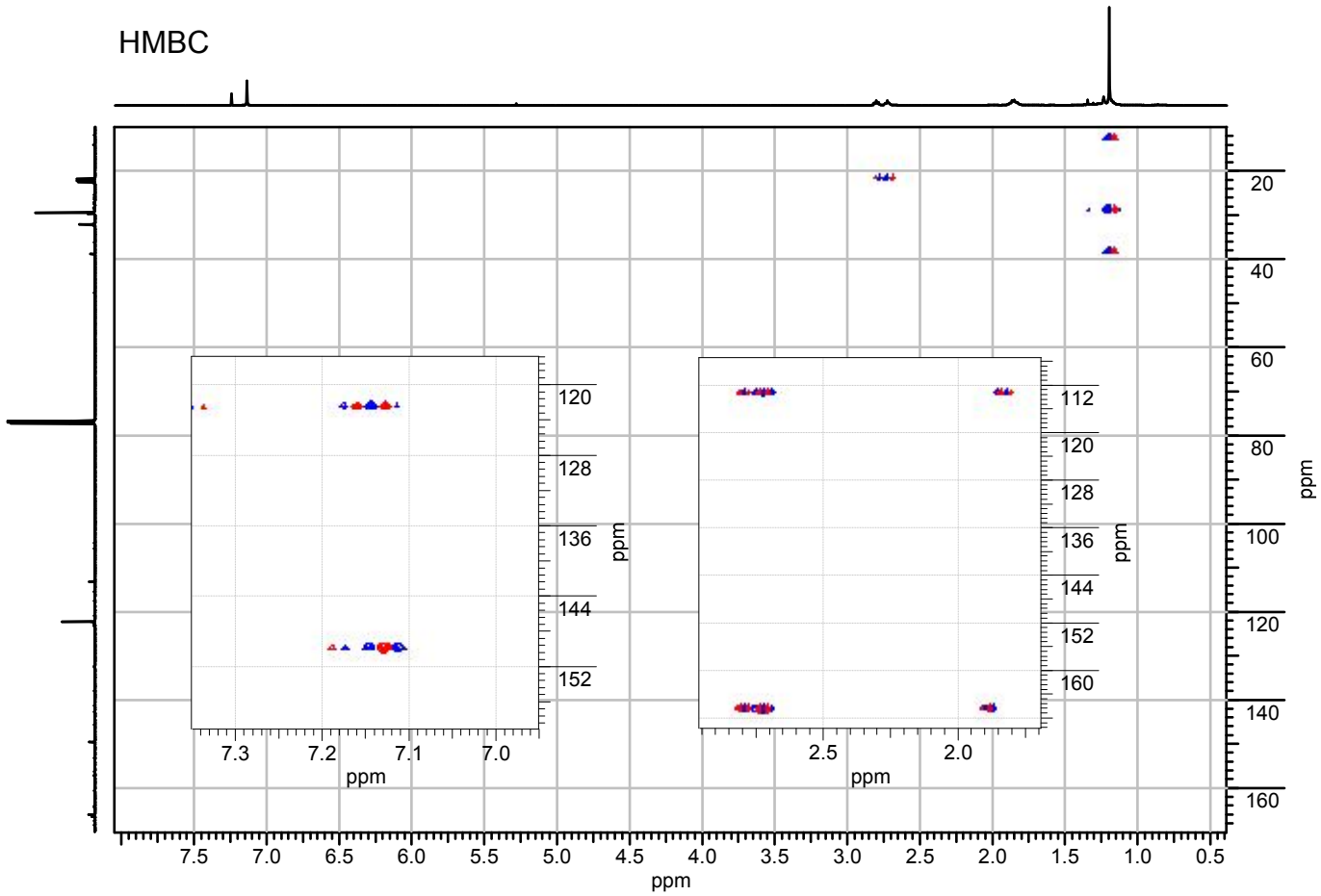


4,4’-[1,4-Phenylenebis(oxy)]bis(2-*tert*-butyl-5,6,7,8-tetrahydroquinazoline) (1d)

HSQC

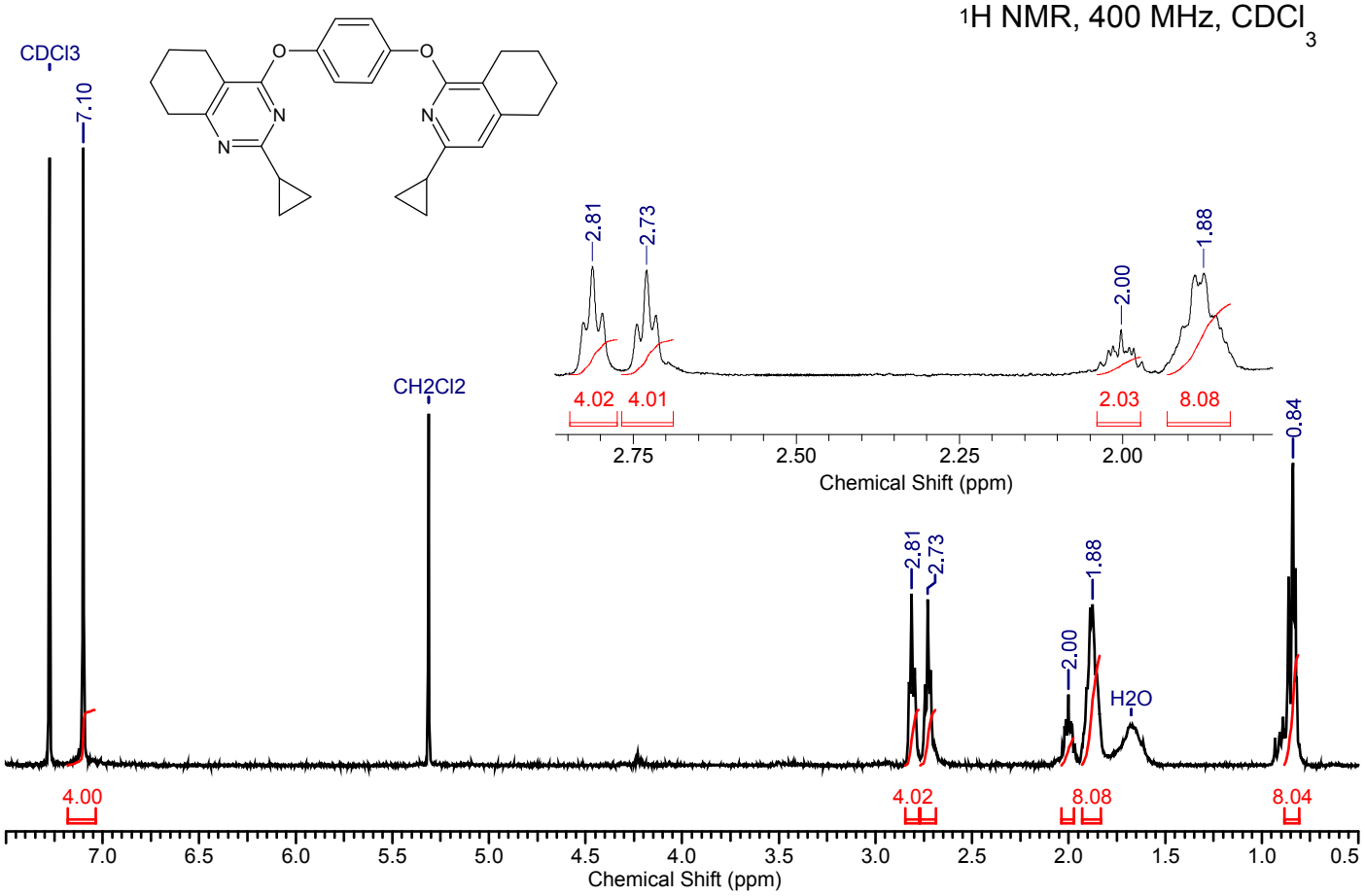


HMBC

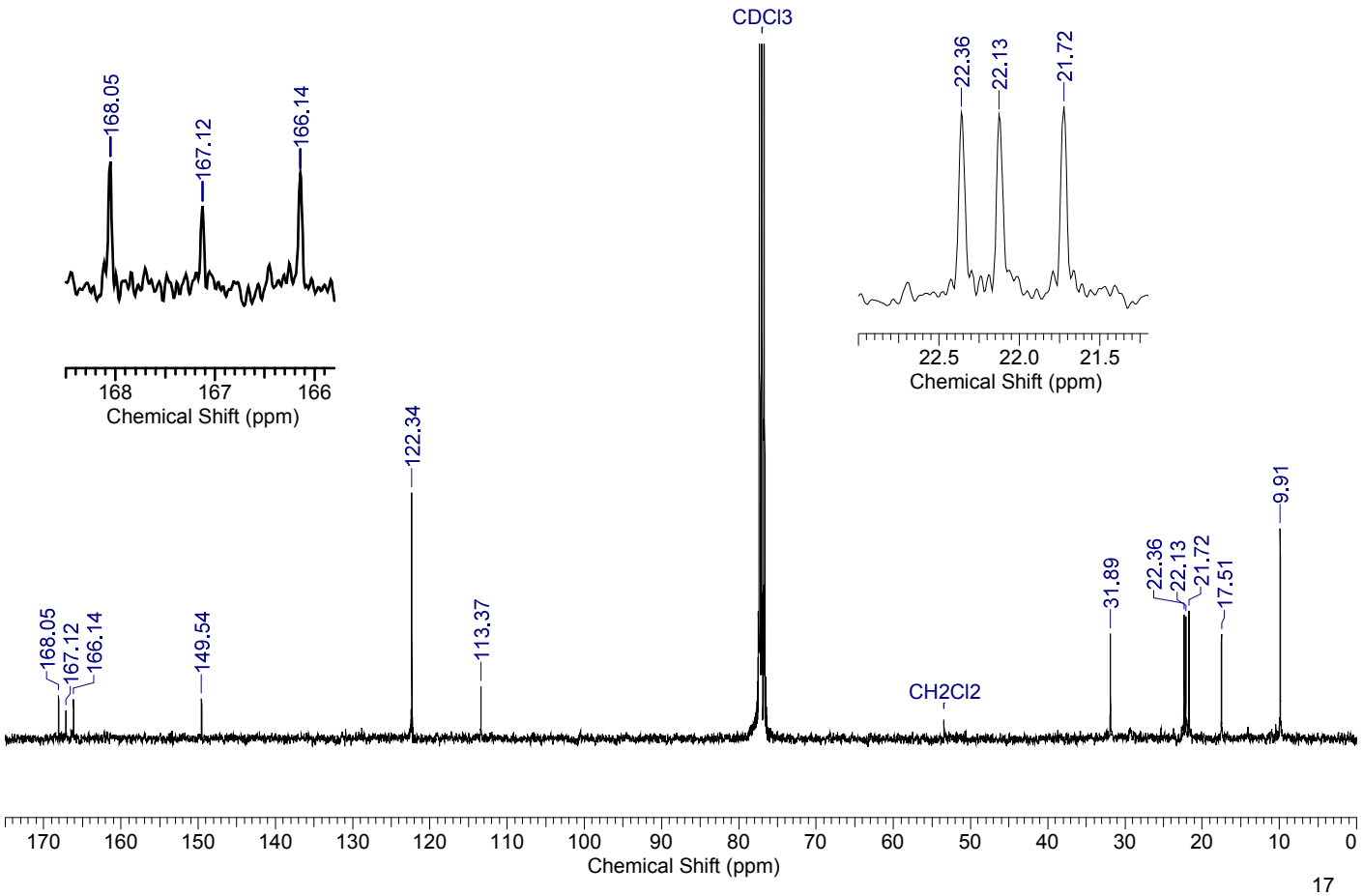


4,4’-[1,4-Phenylenebis(oxy)]bis(2-cyclopropyl-5,6,7,8-tetrahydroquinazoline) (1e)

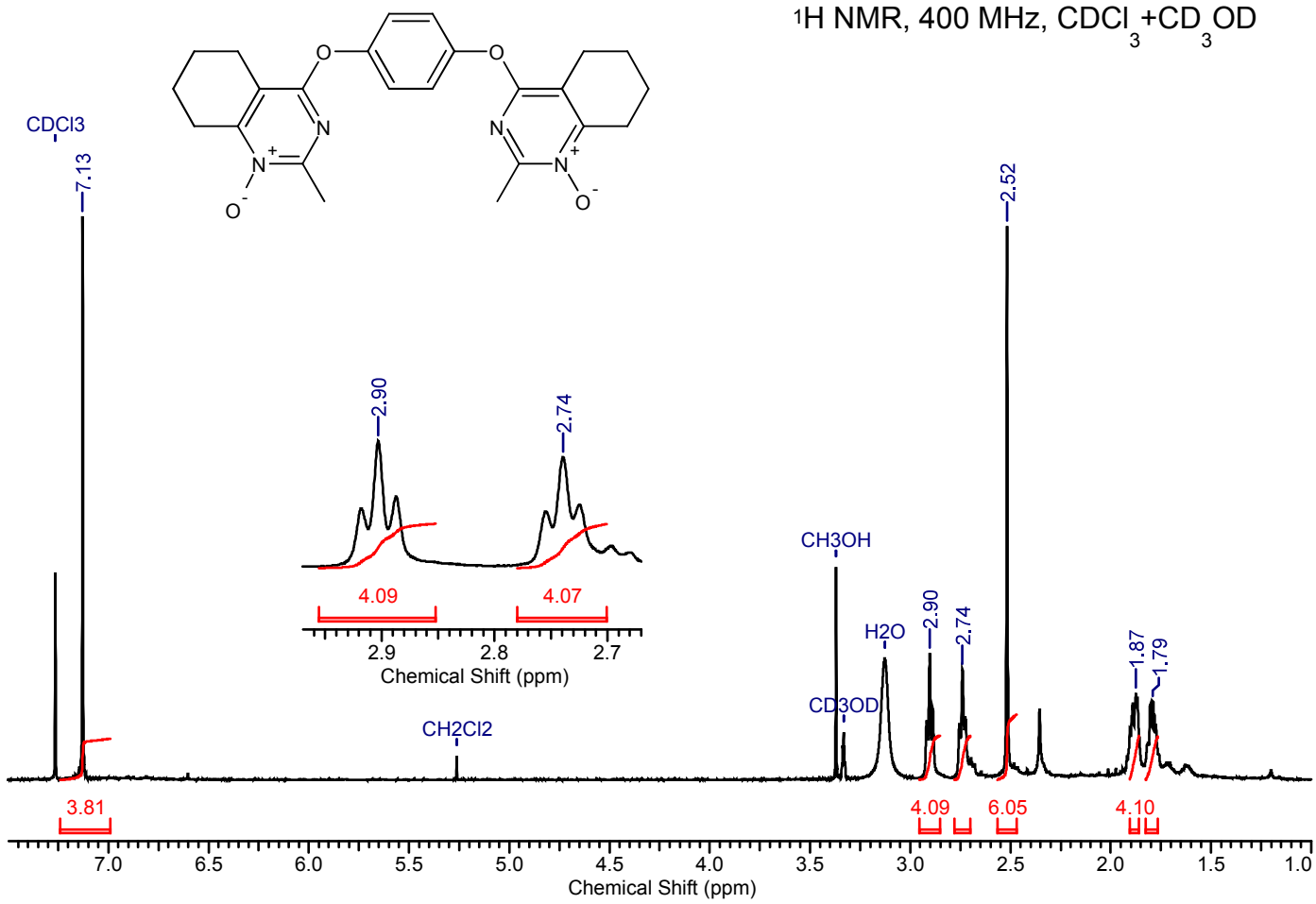
^{1}H NMR, 400 MHz, $CDCl_3$

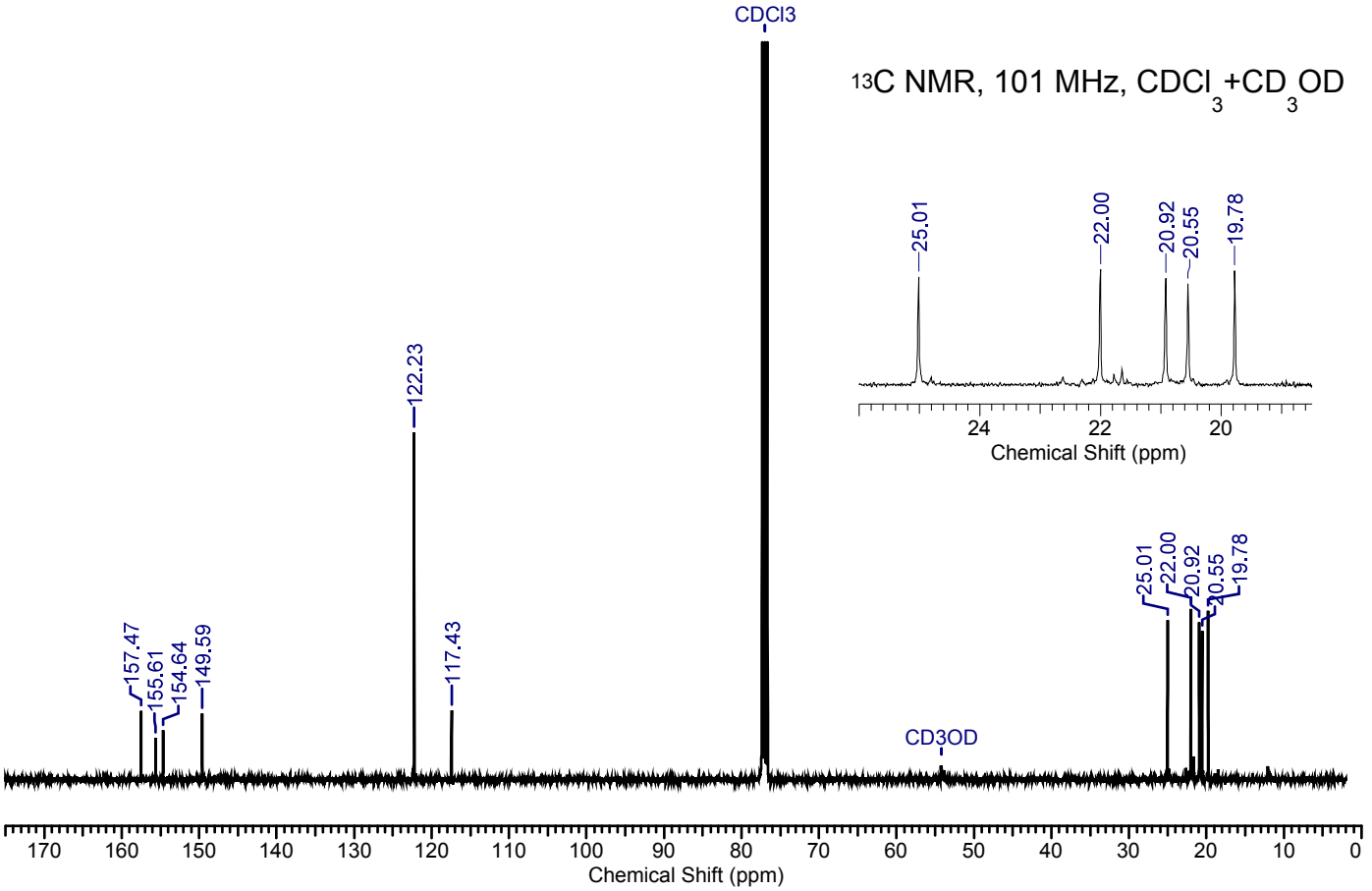


^{13}C NMR, 101 MHz, $CDCl_3$

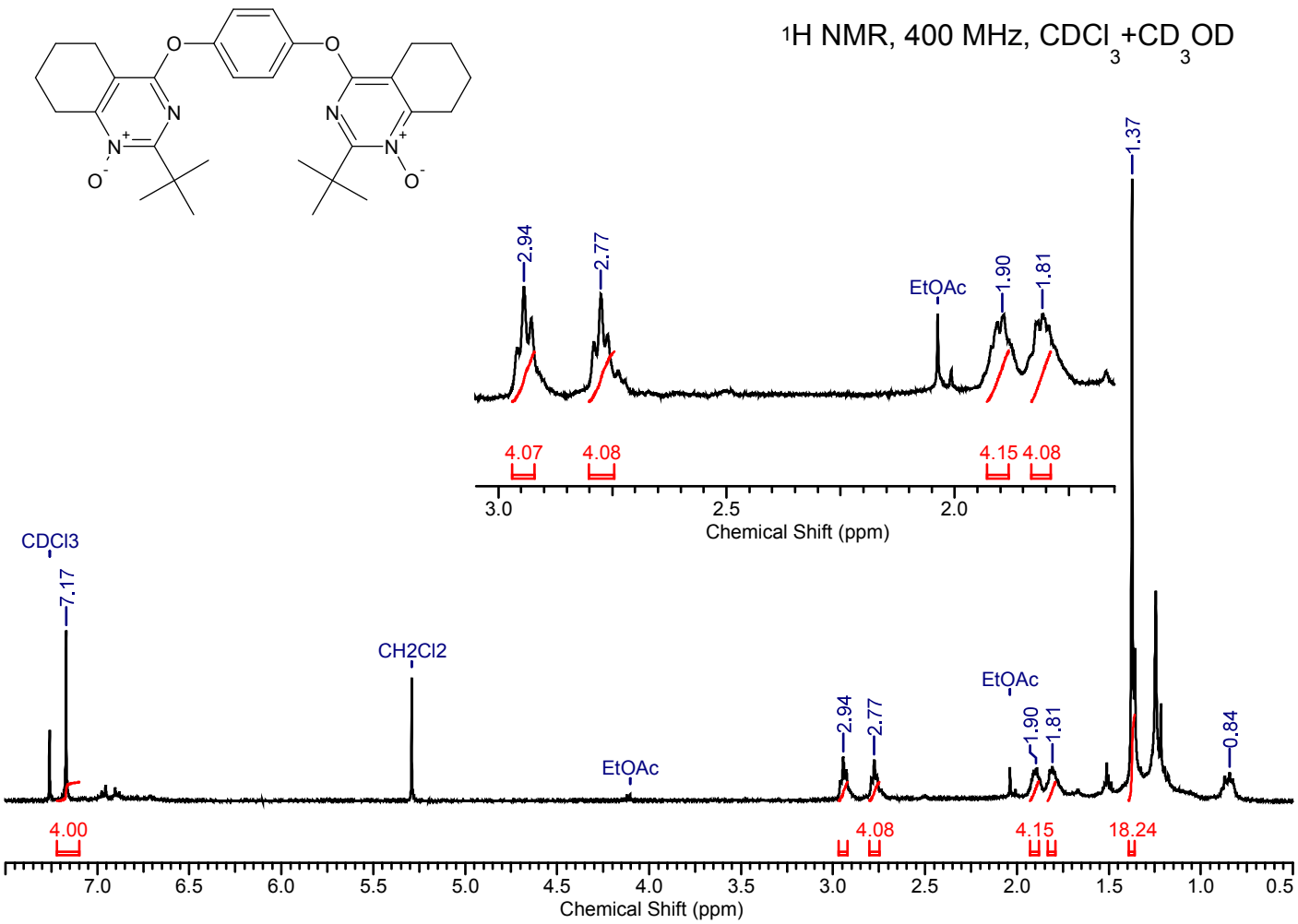


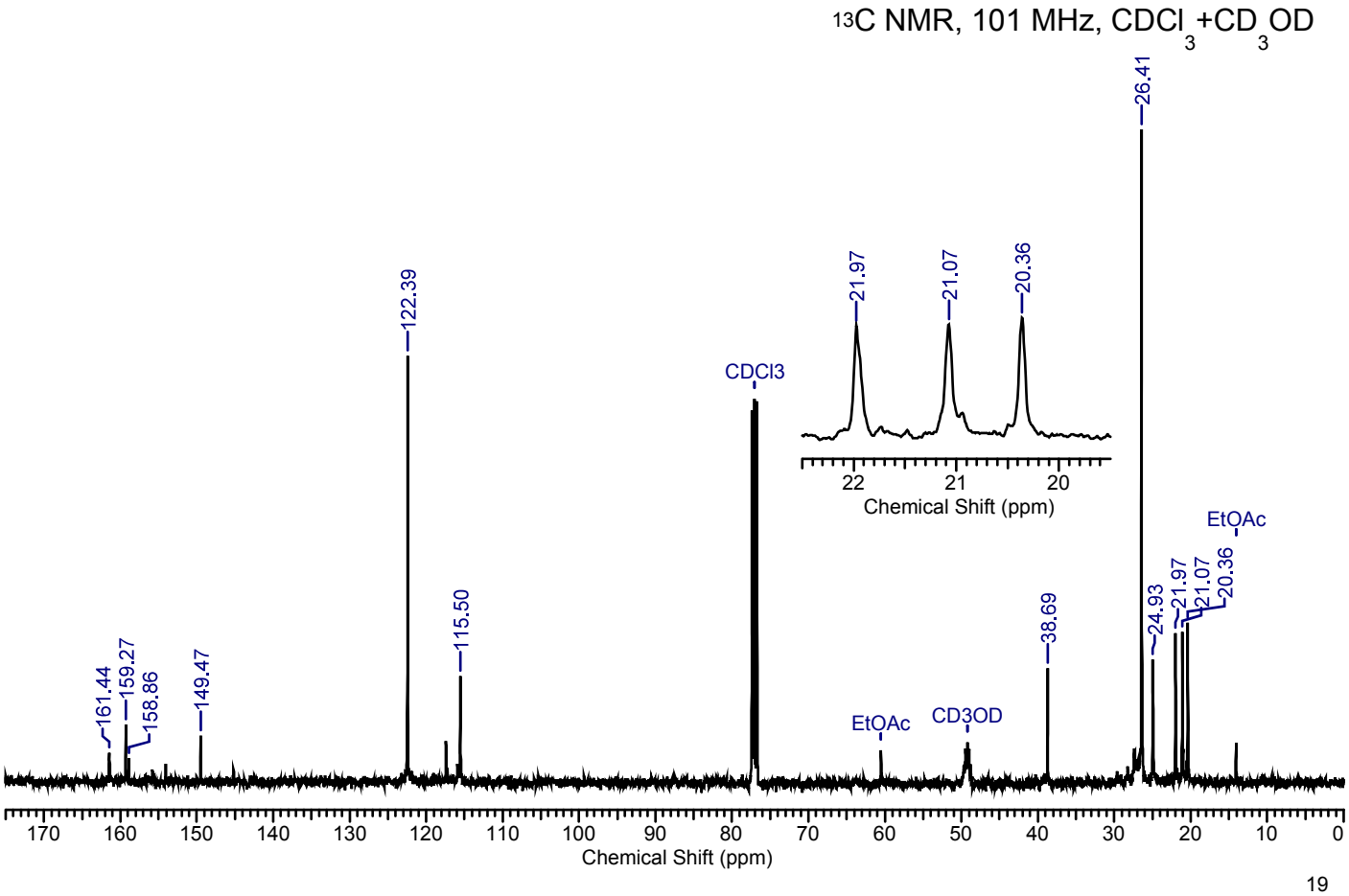
4,4’-[1,4-Phenylenebis(oxy)]bis(2-methyl-5,6,7,8-tetrahydroquinazoline) 1,1’-dioxide (3a)





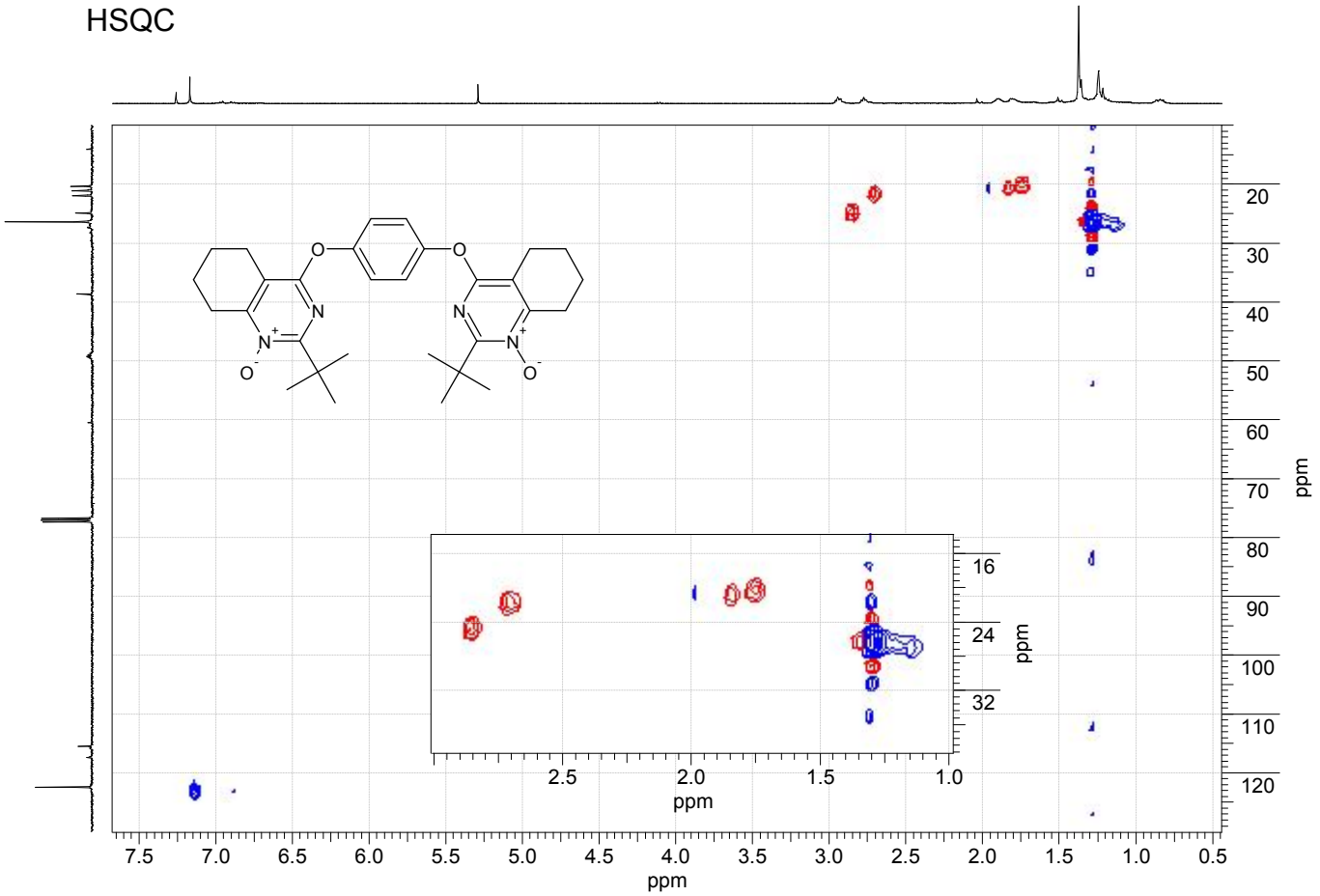
4,4'-[1,4-Phenylenebis(oxy)]bis(2-*tert*-butyl-5,6,7,8-tetrahydroquinazoline) 1,1'-dioxide (3d)



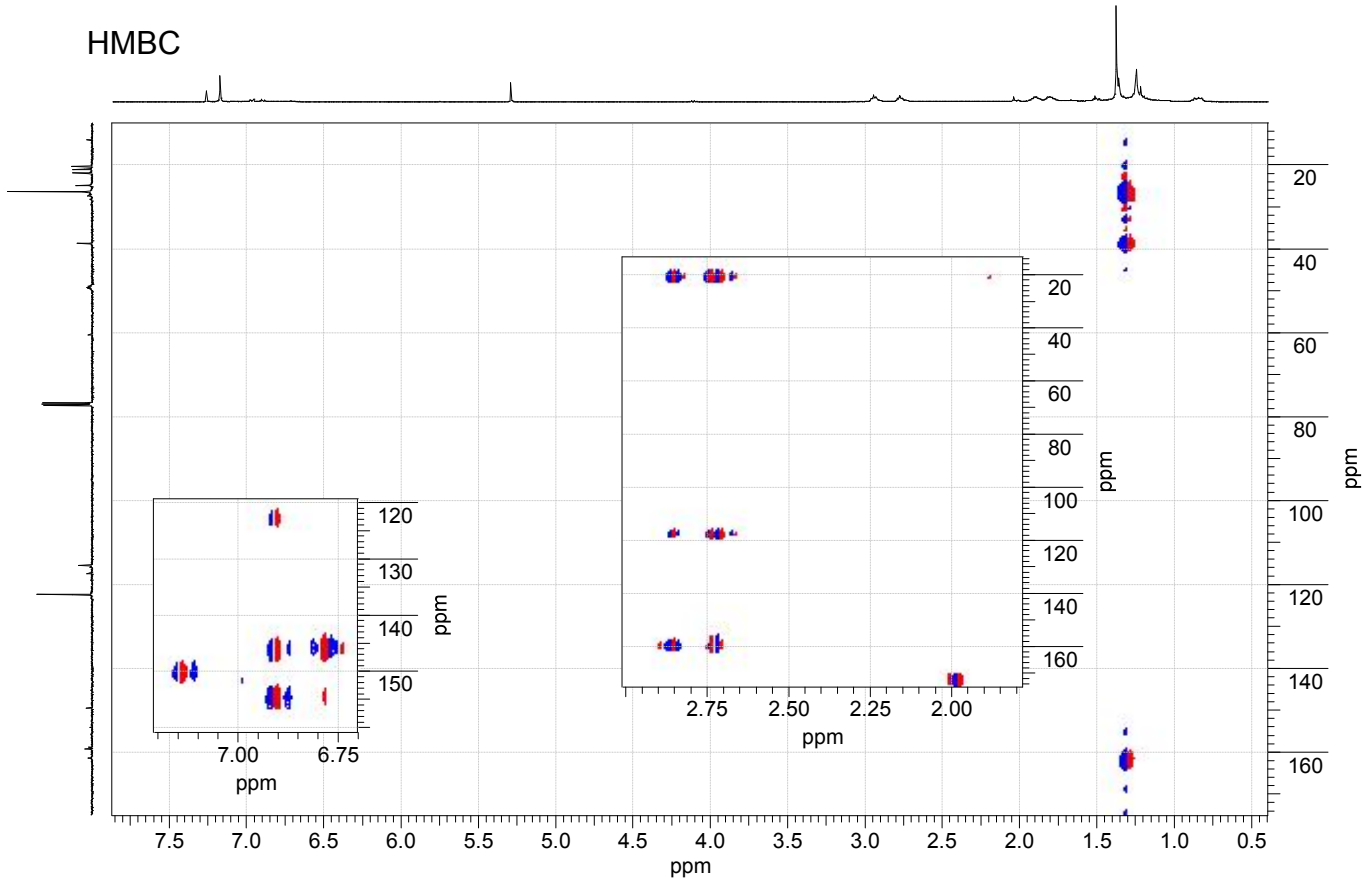


4,4’-[1,4-Phenylenebis(oxy)]bis(2-*tert*-butyl-5,6,7,8-tetrahydroquinazoline) 1,1’-dioxide (3d)

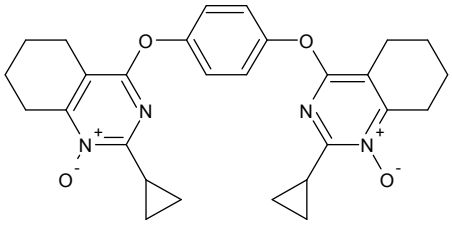
HSQC



HMBC

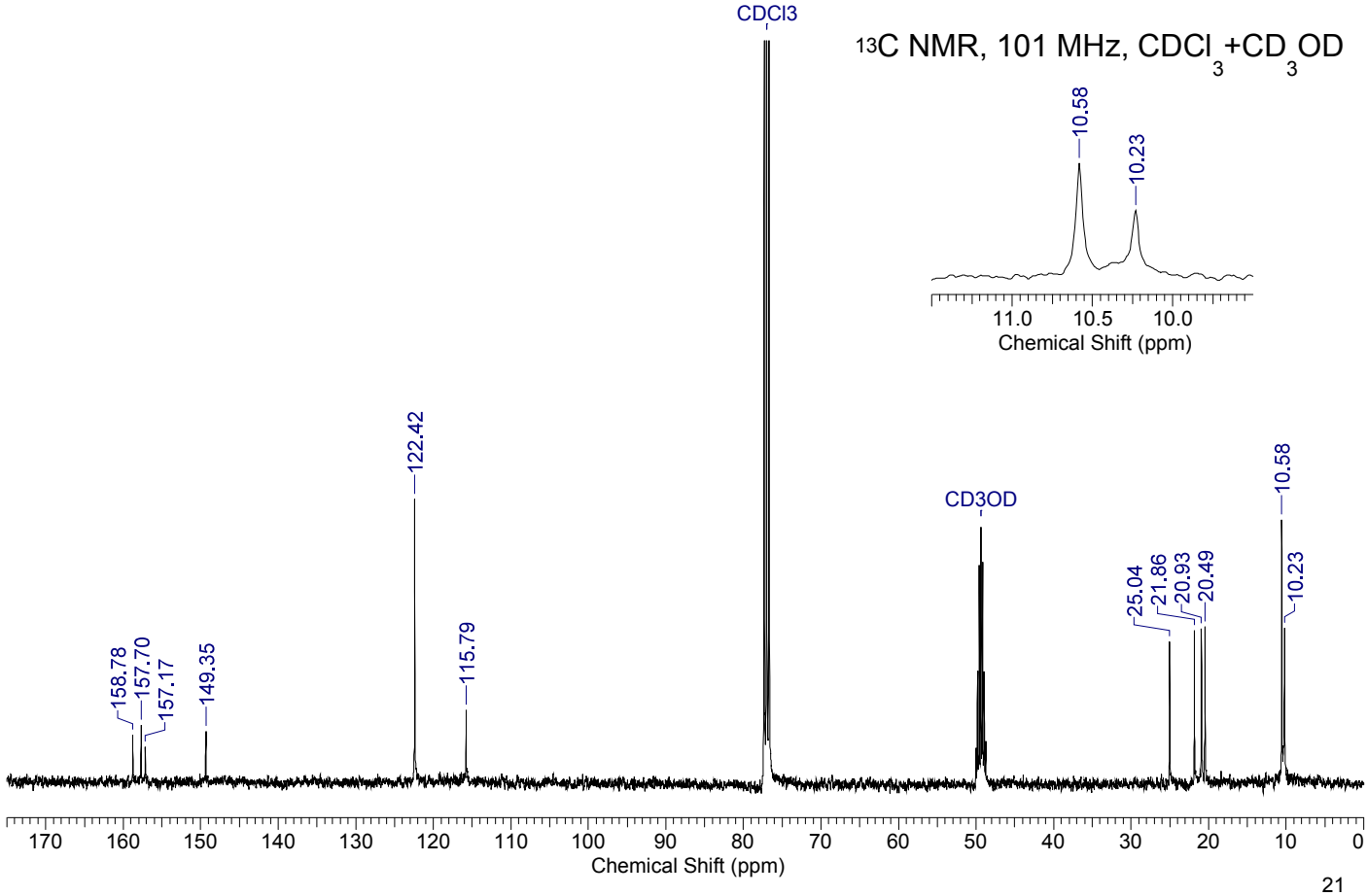


4,4’-[1,4-Phenylenebis(oxy)]bis(2-cyclopropyl-5,6,7,8-tetrahydroquinazoline) 1,1’-dioxide (3e)



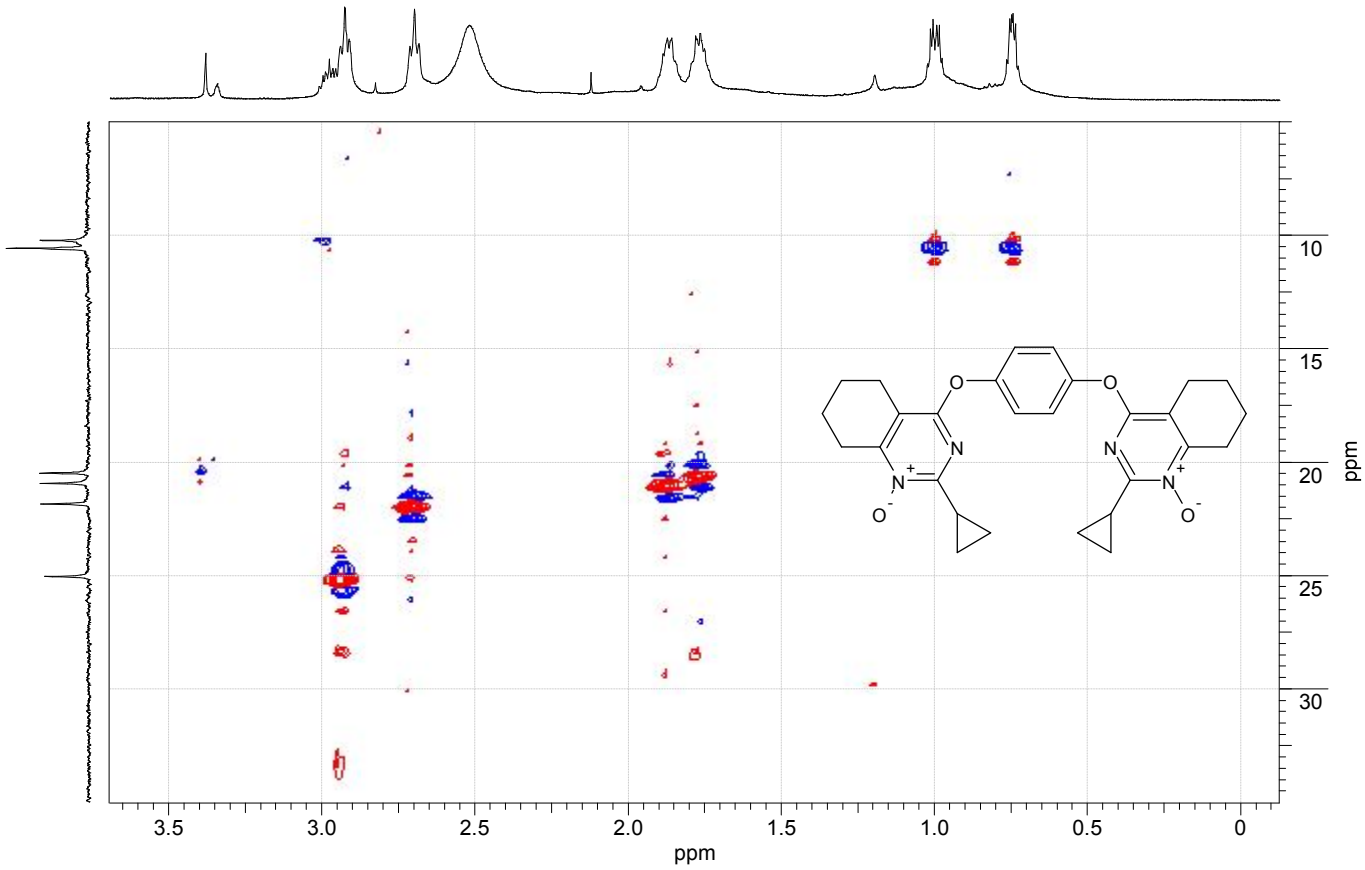
^{1}H NMR, 400 MHz, $CDCl_3$+CD_3OD

^{13}C NMR, 101 MHz, $CDCl_3$+CD_3OD

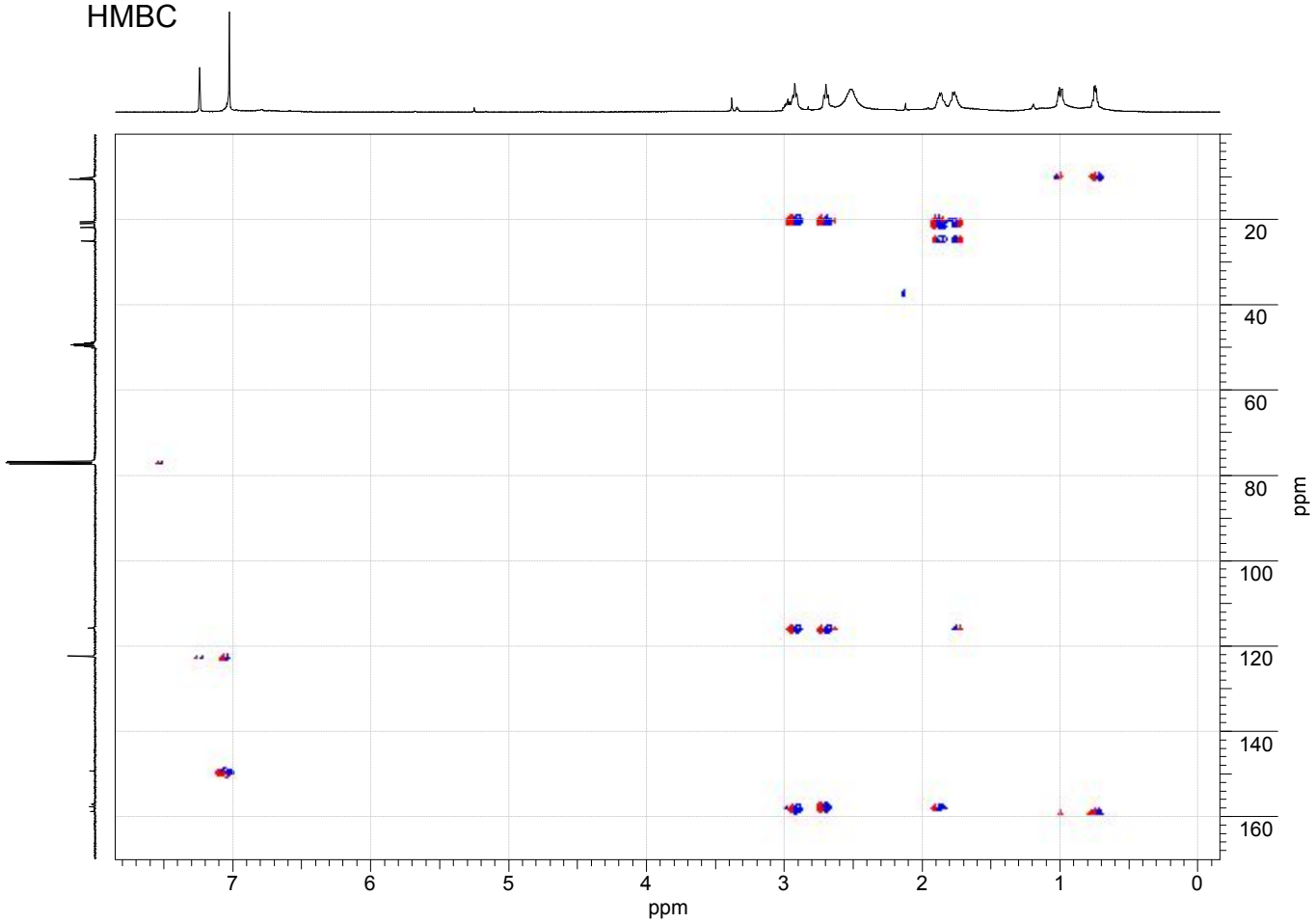


4,4’-[1,4-Phenylenebis(oxy)]bis(2-cyclopropyl-5,6,7,8-tetrahydroquinazoline) 1,1’-dioxide (3e)

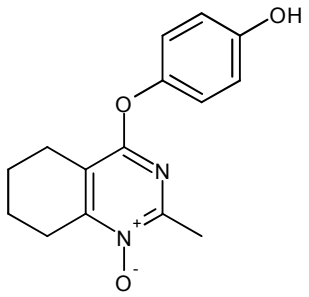
HSQC



HMBC

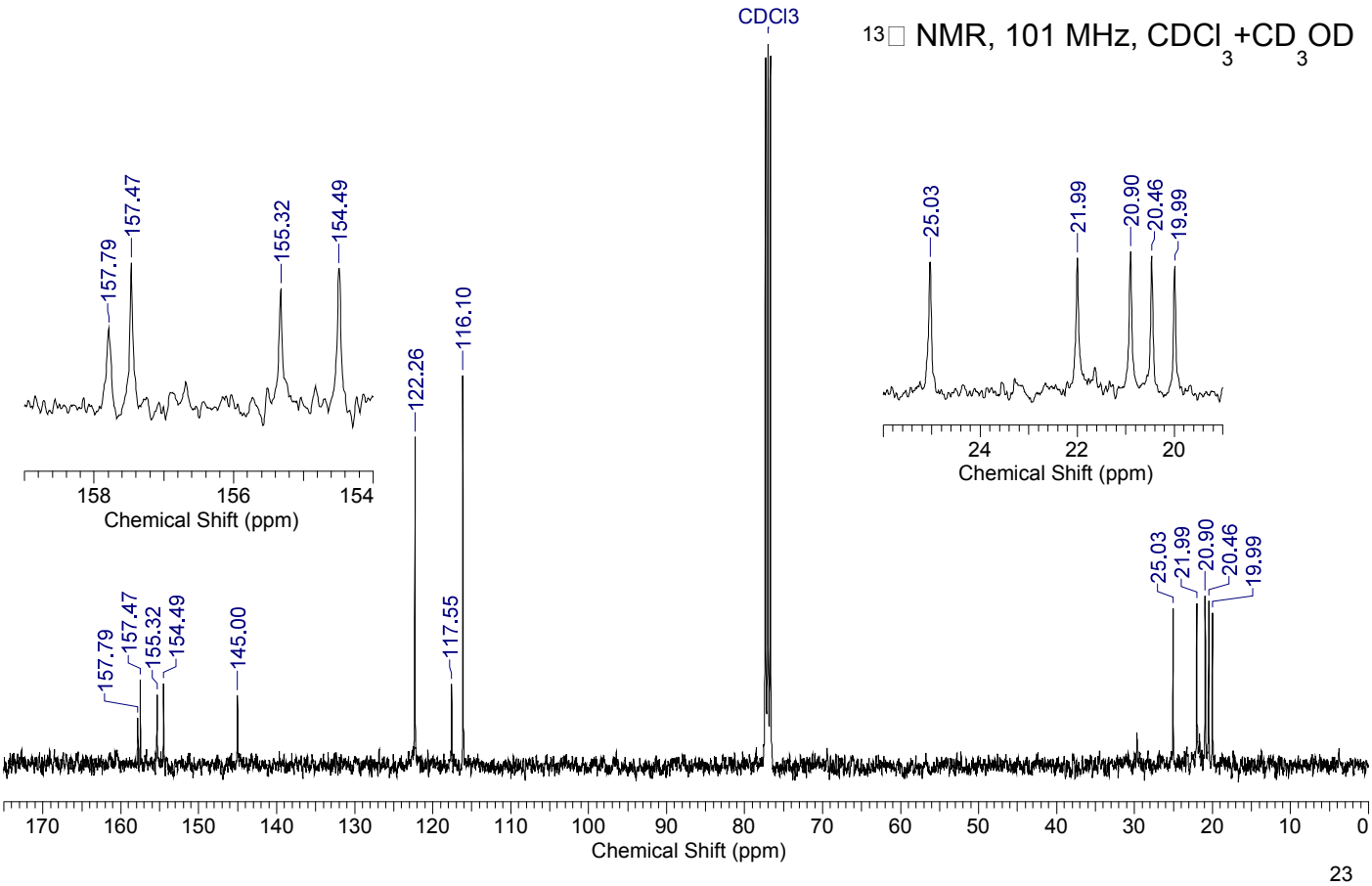


4-[(2-methyl-1-oxido-5,6,7,8-tetrahydroquinazolin-4-yl)oxy]phenol (4a)

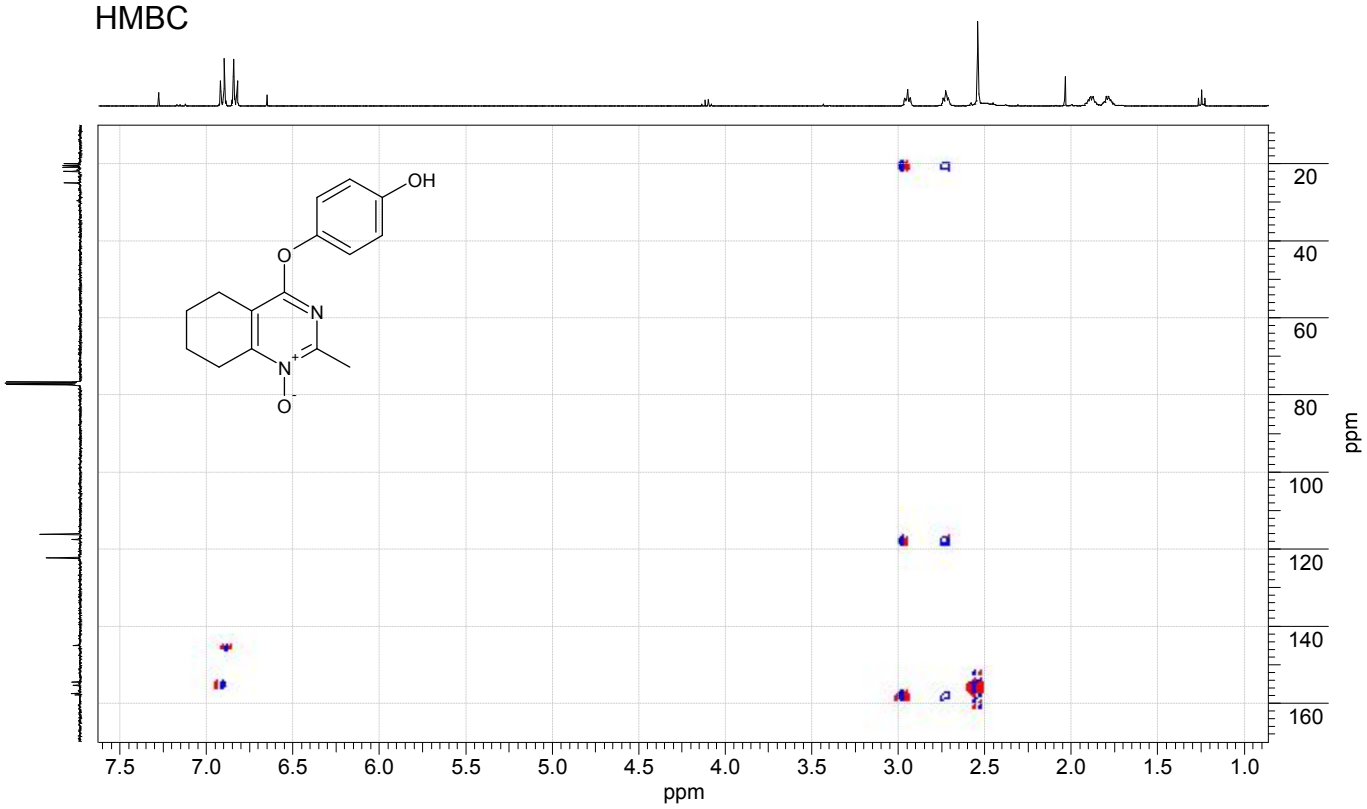


^{1}H NMR, 400 MHz, $CDCl_3$+CD_3OD

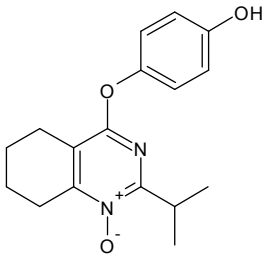
^{13}C NMR, 101 MHz, $CDCl_3$+CD_3OD



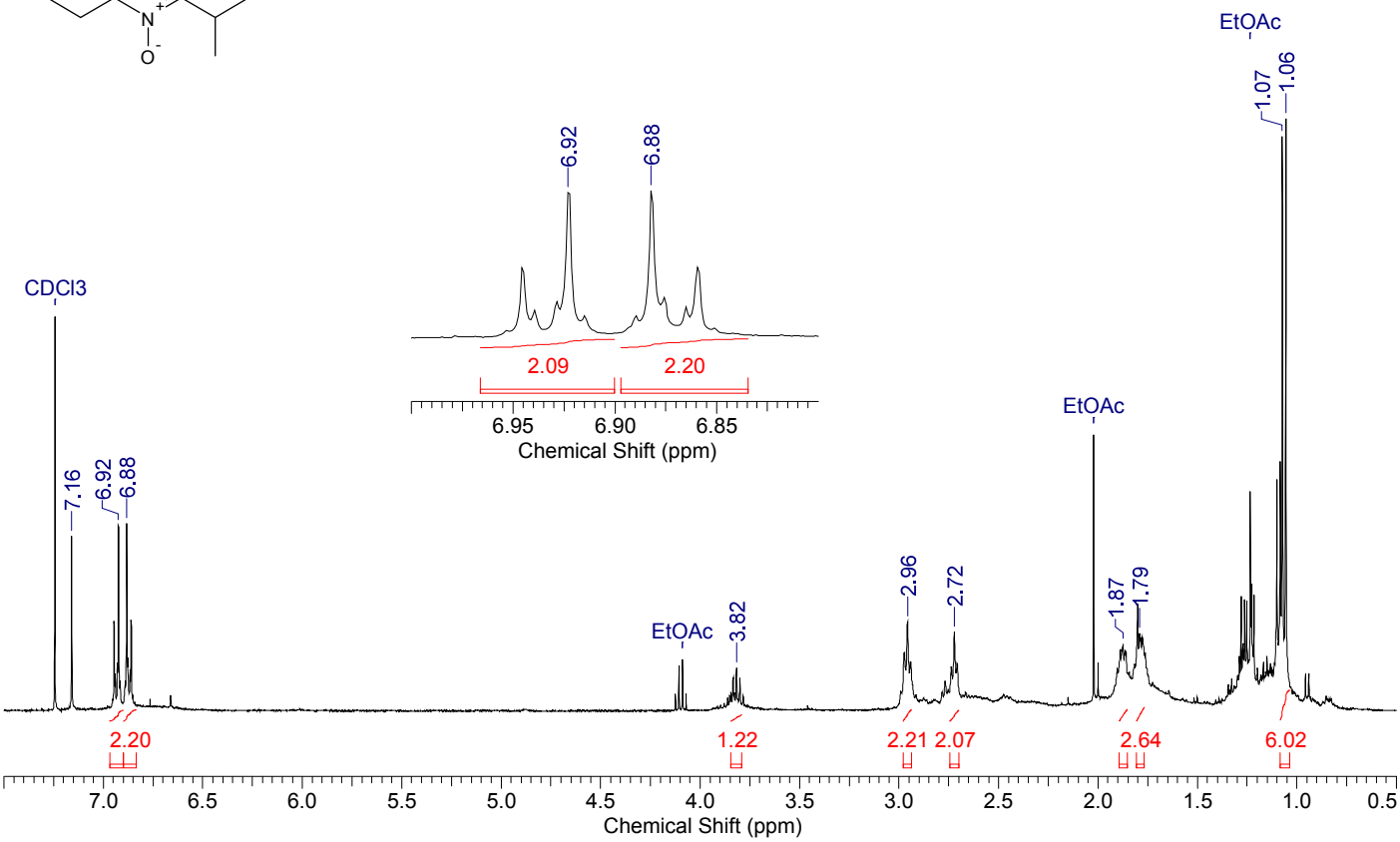
4-[(2-methyl-1-oxido-5,6,7,8-tetrahydroquinazolin-4-yl)oxy]phenol (4a)



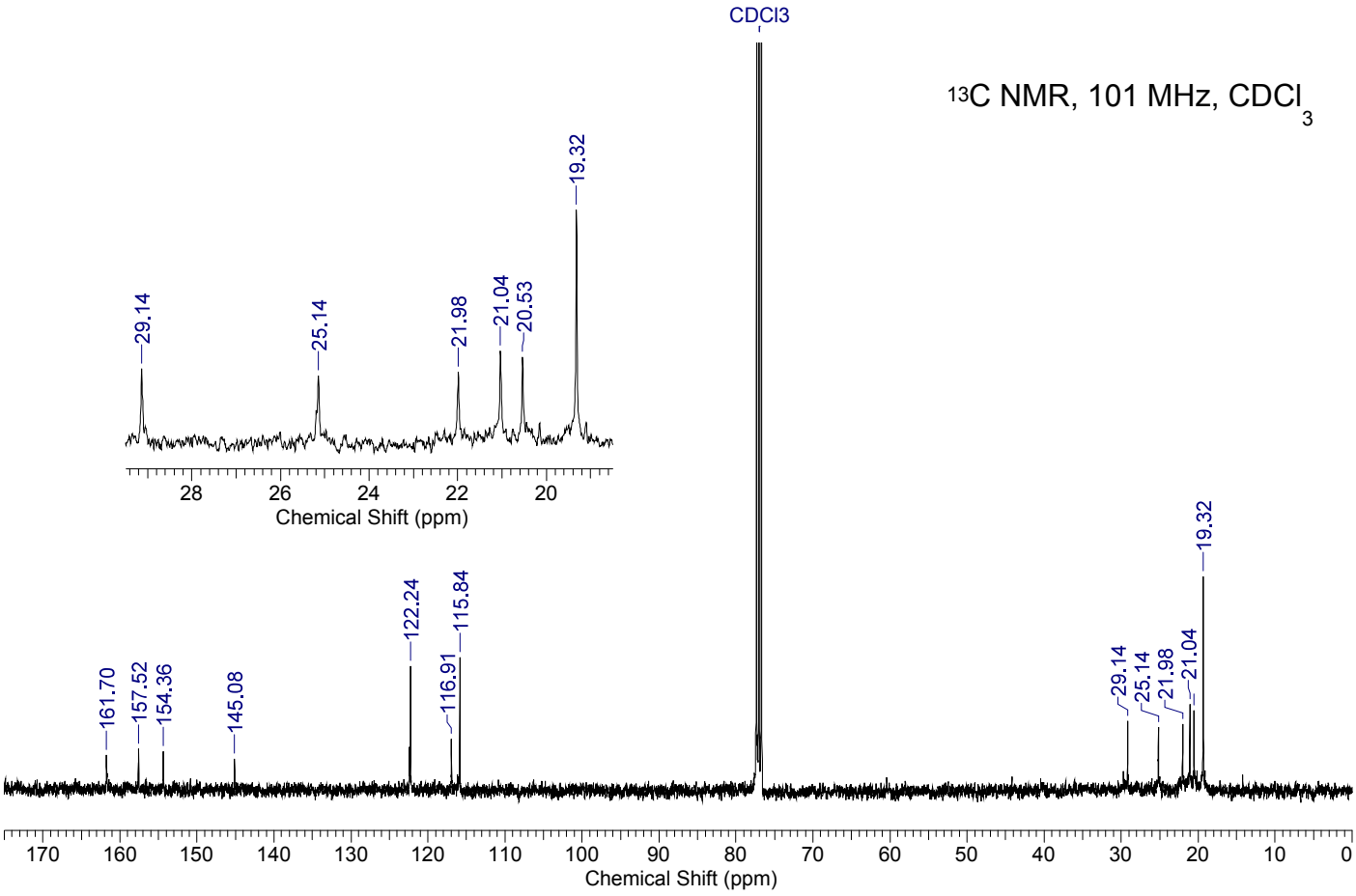
4-[(2-isopropyl-1-oxido-5,6,7,8-tetrahydroquinazolin-4-yl)oxy]phenol (4c)



^{1}H NMR, 400 MHz, $CDCl_3$

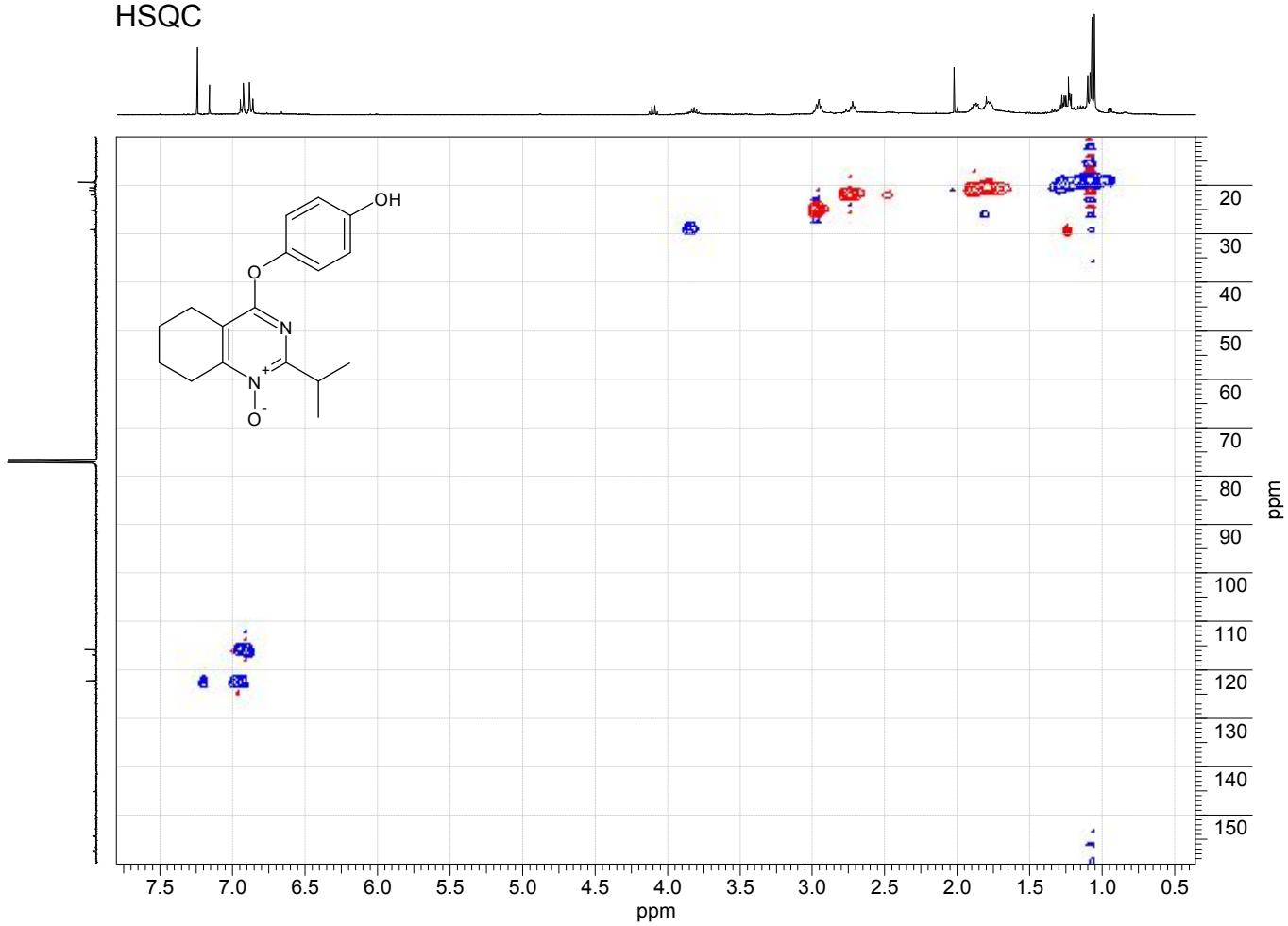


^{13}C NMR, 101 MHz, $CDCl_3$

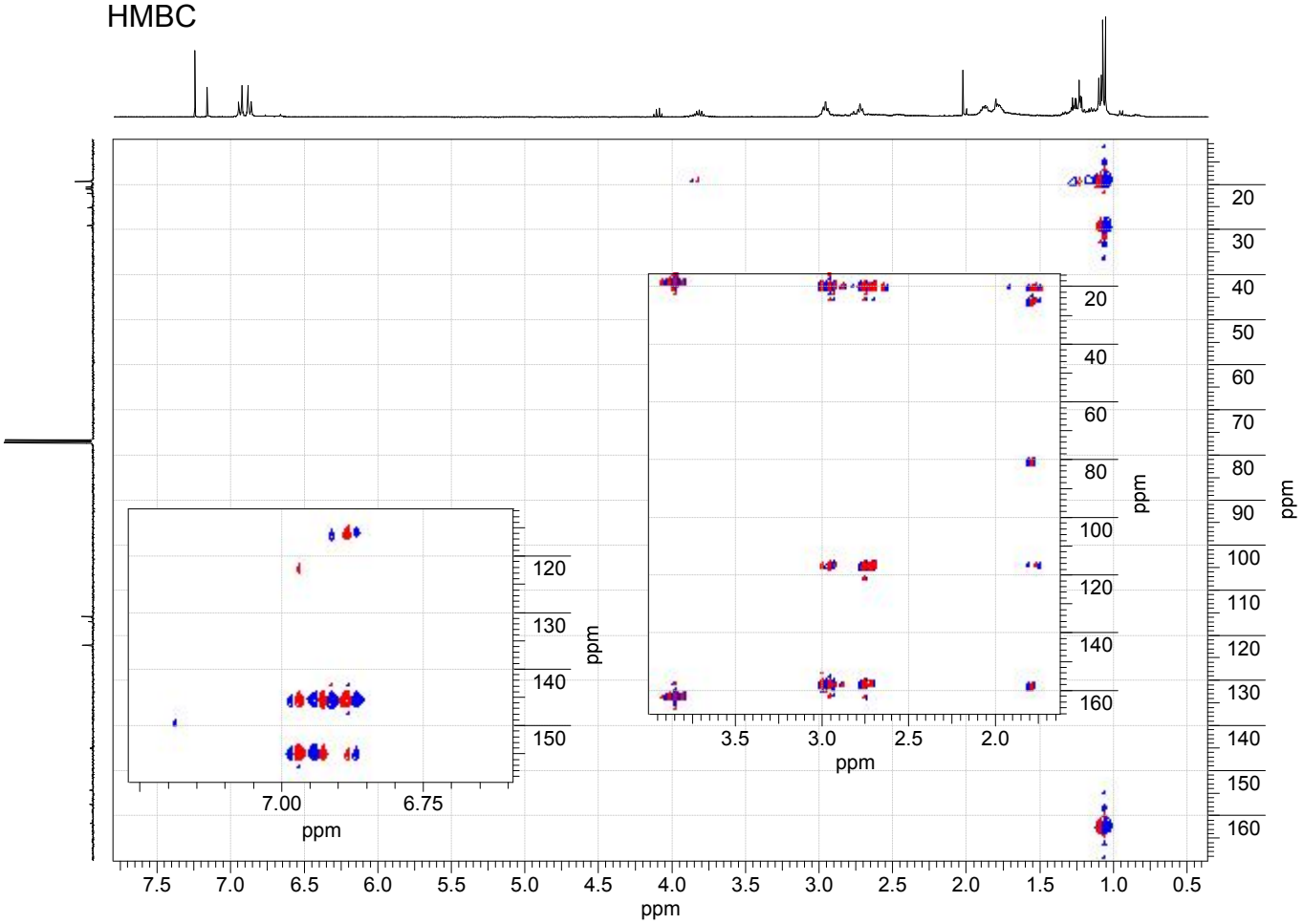


4-[(2-isopropyl-1-oxido-5,6,7,8-tetrahydroquinazolin-4-yl)oxy]phenol (4c)

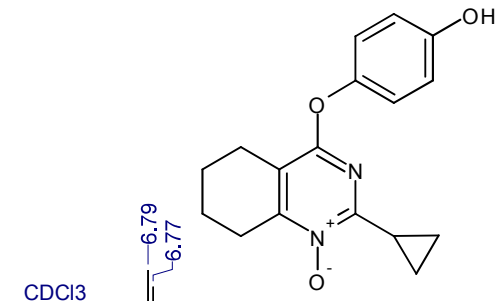
HSQC



HMBC

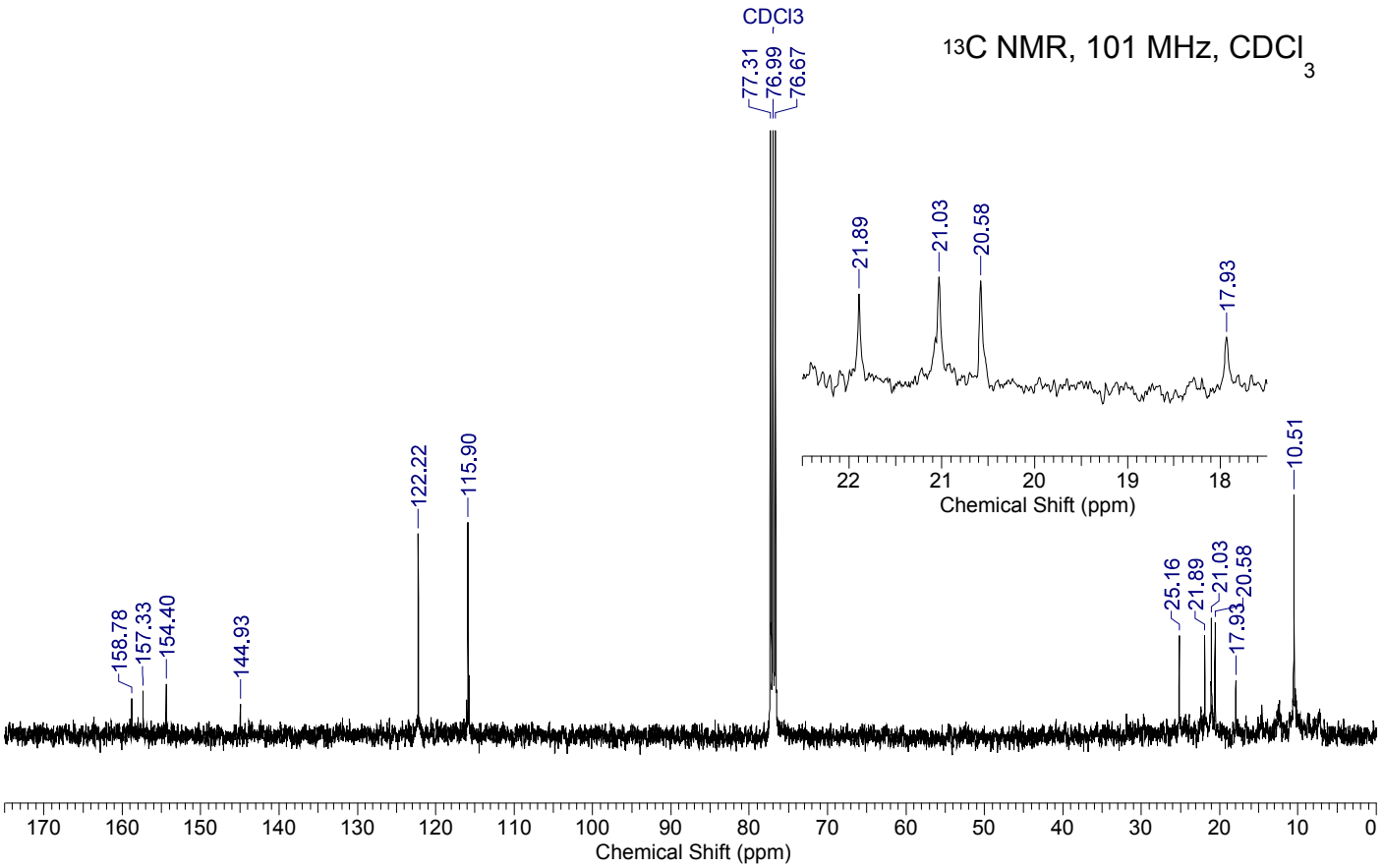


4-[(2-cyclopropyl-1-oxido-5,6,7,8-tetrahydroquinazolin-4-yl)oxy]phenol (4e)



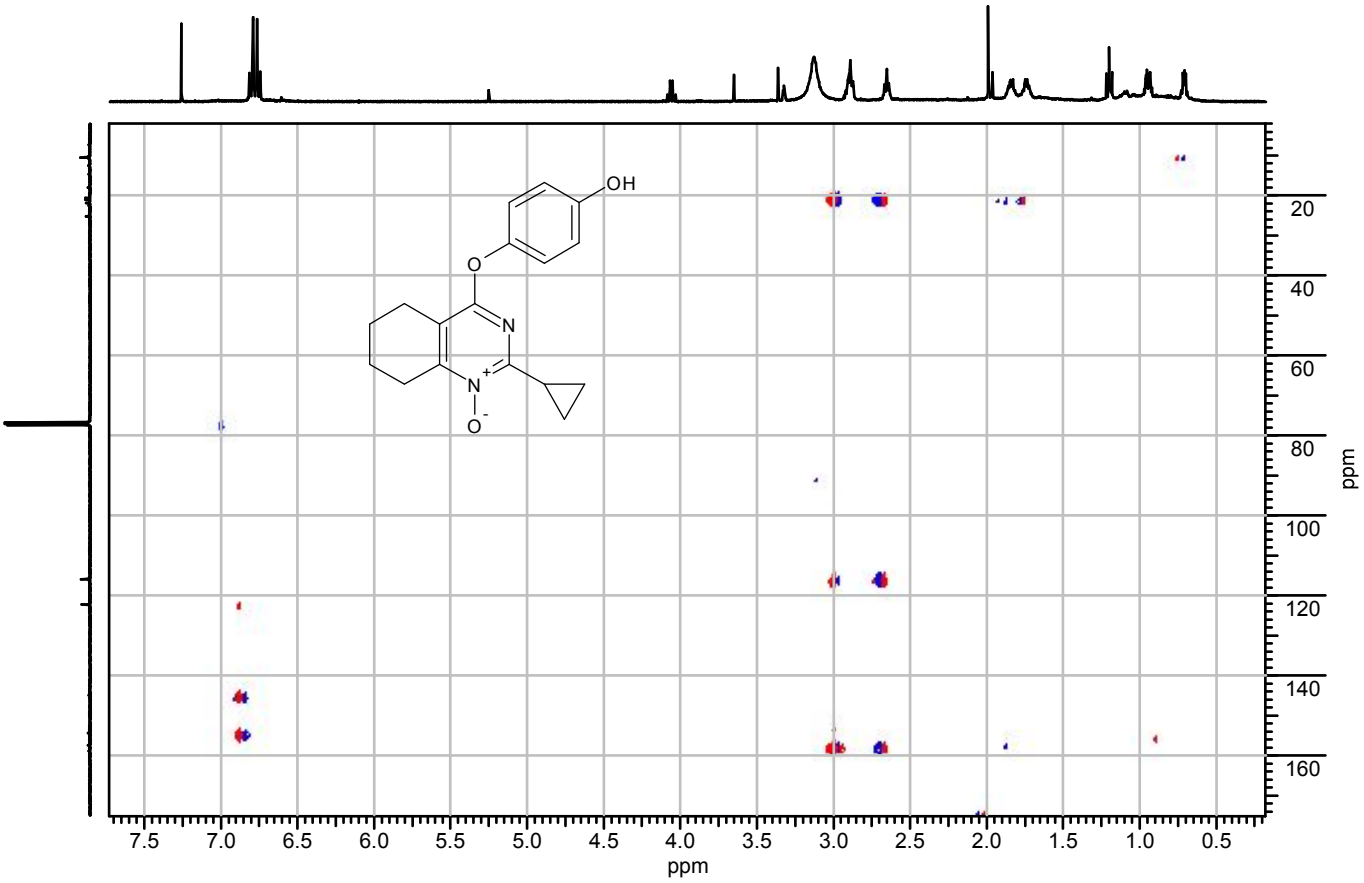
^{1}H NMR, 400 MHz, $CDCl_3$ + CD_3OD

^{13}C NMR, 101 MHz, $CDCl_3$

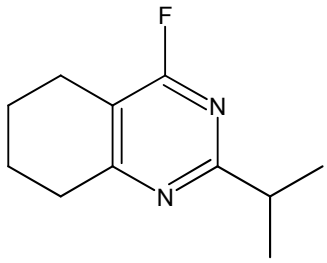


4-[(2-cyclopropyl-1-oxido-5,6,7,8-tetrahydroquinazolin-4-yl)oxy]phenol (4e)

HMBC

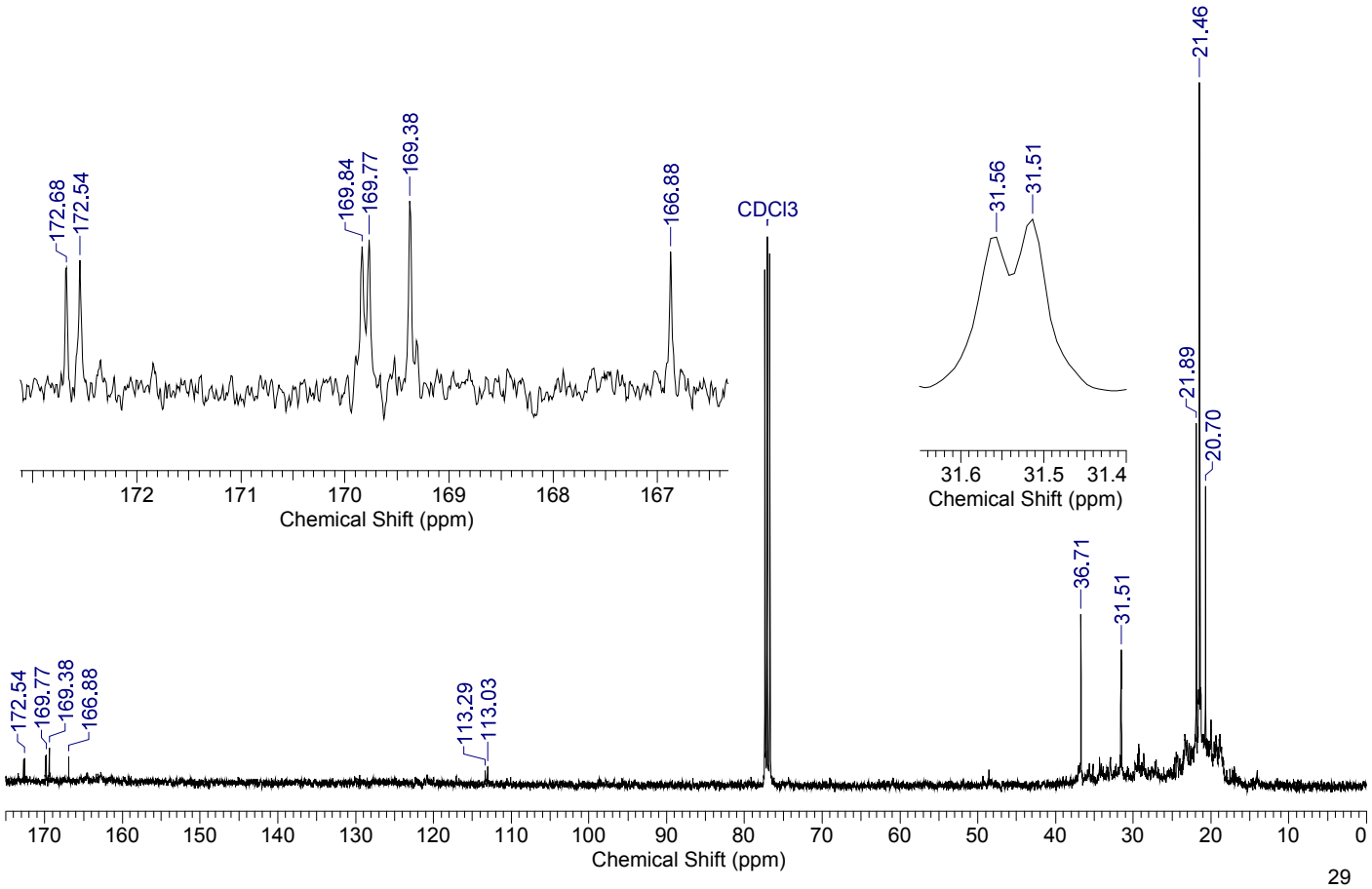


4-fluoro-2-isopropiyl-5,6,7,8-tetrahydroquinazoline (5c)



^{1}H NMR, 400 MHz, $CDCl_3$

^{13}C NMR, 101 MHz, $CDCl_3$



4-fluoro-2-isopropiyl-5,6,7,8-tetrahydroquinazoline (5c)