Supporting Information

Synthesis of Novel Hybrids of Quinazoline and Artemisinin with High Activities Against *Plasmodium falciparum*, Human Cytomegalovirus and Leukemia Cells

Tony Fröhlich,[a]‡ Christoph Reiter,[a]‡ Mohammad M. Ibrahim,[a][b] Jannis Beutel,[a] Corina Hutterer,[c] Isabel Zeitträger,[c] Hanife Bahsi,[c] Maria Leidenberger,[d] Oliver Friedrich,[d] Barbara Kappes,[d] Thomas Efferth,[e] Manfred Marschall,*[c] and Svetlana B. Tsogoeva*[a]

[a] *Organic Chemistry Chair I and Interdisciplinary Center for Molecular Materials (ICMM), Friedrich-Alexander University of Erlangen-Nürnberg, Henkestraße 42, 91054 Erlangen, Germany*

[b] *Present address: Department of Chemistry, Faculty of Science, University of Al al-Bayt, P.O. Box 130040, 25113 Al-Mafraq, Jordan*

[c] *Institute for Clinical and Molecular Virology, Friedrich-Alexander University of Erlangen-Nürnberg, Schloßgarten 4, 91054 Erlangen, Germany*

[d] *Institute of Medical Biotechnology, Friedrich-Alexander University of Erlangen-Nürnberg, Paul-Gordon-Straße 3, 91052 Erlangen, Germany*

[e] *Department of Pharmaceutical Biology, Institute of Pharmacy and Biochemistry, University of Mainz, Staudinger Weg 5, 55128 Mainz, Germany*

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General Experimental Information

All reactions were performed in flame-dried glassware under a nitrogen atmosphere. If necessary the synthesized hybrids were further purified after column chromatography via reprecipitation from CH_2Cl_2 in *n*-hexane to yield a pure compound for Elemental Analysis and biological tests. CH_2Cl_2 was dried initially over $CaCl_2$ and then distilled from P_2O_5. EtOAc was purchased as an anhydrous solvent, whrereas acetic acid was used in reagent grade. All other solvents were purified by distillation using rotary evaporation or were purchased in HPLC-quality. Reagents obtained from commercial sources were used without further purification. TLC chromatography was performed on precoated aluminium silica gel SIL G/UV254 plates (Macherey-Nagel & Co.). The detection occurred via fluorescence quenching or development in a phosphomolybdic acid solution (10% in EtOH). All products were dried in high-vacuum (10^{-3} mbar). ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature either on a Bruker Avance spectrometer operating at 300 MHz respectively 400 MHz or on a JEOL JNM GX 400 spectrometer operating at 400 MHz. ESI Mass spectra were recorded on a Bruker micrOTOF II focus TOF MS-spectrometer or on a Shimadzu Axima Confidence MALDI-TOF MS-spectrometer without a matrix. IR spectra were recorded on a Varian IR-660 apparatus. The Absorption is indicated in wave numbers [cm^{-1}]. Elemental analysis (C, H, N), carried out with an Elementar vario MICRO cube machine, is within ± 0.50% of the calculated values confirming a purity of > 95%. Artesunic Acid (**16**) and dihydroartemisinin (DHA) were obtained from ABCR (Karlsruhe, Germany).

Experimental Procedures

The synthesis for quinazoline derivatives **11**, **12** and **14** were carried out in analogy to a literature known procedure.[1]

Synthesis of quinazoline precursor 11

N'-(2-cyanophenyl)-*N*,*N*-dimethylformimidamide[1] (200 mg, 1.15 mmol, 1.0 equiv.) and 4-aminophenol (126 mg, 1.15 mmol, 1.0 equiv.) were dissolved in acetic acid (1.04 mL, 1.09 g, 18.2 mmol, 16.0 equiv.) and refluxed for 3 h. Subsequently, ice water was added and the precipitate collected. The aqueous layer was extracted with EtOAc (3 x 40 mL) and the organic phases were combined with the aforementioned solid. After the removal of the solvent under reduced pressure, the crude product was purified by column chromatography (CH_2Cl_2/MeOH 100:1 → EtOAc/MeOH 10:1) and phenol derivative **11** was obtained in 57% yield (156 mg, 0.66 mmol) as a brown solid.

R_f = 0.19 (CH_2Cl_2/MeOH 20:1, UV). ^{1}H NMR (300 MHz, CD_3OD): δ = 6.75-6.86 (m, 2 H), 7.34-7.43 (m, 2 H), 7.47-7.55 (m, 1 H), 7.62-7.81 (m, 2 H), 8.21-8.30 (m, 1 H), 8.35 (s, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 116.5, 123.7, 127.0, 127.9, 128.0, 131.3, 134.6, 150.2, 155.8, 156.6, 160.6 ppm. MS (MALDI-TOF, without matrix): *m*/*z* = 239 ([M+2 H]$^+$).

The spectroscopic data are in accordance with those reported in literature.[1]

Synthesis of quinazoline precursor 12

A solution of *N*'-(2-cyanophenyl)-*N*,*N*-dimethylformimidamide (485 mg, 2.80 mmol, 1.0 equiv.) in acetic acid (2.40 mL, 2.52 g, 42.0 mmol, 15.0 equiv.) was added to 3,4-dichloraniline (456 mg, 2.81 mmol, 1.0 equiv.) and refluxed for 3 h. Subsequently, the reaction mixture was cooled to room temperature, poured into ice water, filtered and washed with ice water. Quinazoline **12** was dried and obtained in quantitative yield

[1] Wang, Z.; Wang, C.; Sun, Y.; Zhang, N.; Liu, Z.; Liu, J. A novel strategy to the synthesis of 4-anilinoquinazoline derivatives. *Tetrahedron* **2014,** *70*, 906-913.

(883 mg, containing acetic acid). To get a sufficient pure sample for EA and biological tests, quinazoline **12** was recrystallized from MeOH.

R_f = 0.72 ($CHCl_3$/EtOH 19:1, UV). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.50-7.53 (m, 1 H), 7.63-7.69 (m, 1 H), 7.74-7.85 (m, 2 H), 7.86-7.92 (m, 1 H), 8.18-8.22 (m, 1 H), 8.37-8.41 (m, 1 H), 8.62 (s, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 116.7, 123.1, 123.5, 125.1, 128.1, 128.2 (2 x), 131.3, 133.1, 134.7, 140.2, 150.4, 155.4, 159.6 ppm. MS (MALDI-TOF, without matrix): m/z = 290 ([M+H]$^+$). Anal. Calcd. for $C_{14}H_9Cl_2N_3 \cdot 0.1\ H_2O$: C, 57.60; H, 3.18; N, 14.39; Found: C, 57.46; H, 3.02; N, 14.31.

Synthesis of quinazoline precursor 13

To *N*-(3,4-dichlorophenyl)quinazolin-4-amine **12** (435 mg, 1.50 mmol, 1.0 equiv.) and 4Å molecular sieves in acetonitrile (9.0 mL) in a two-necked flask, K_2CO_3 (414 mg, 3.00 mmol, 2.0 equiv.), 3-bromopropanole (271 µL, 416 mg, 3.00 mmol, 2.0 equiv.) and *t*-butylammoniumiodide (14.0 mg, 0.07 mmol, 0.05 equiv.) were added. The resulting solution was refluxed for 10 h. Subsequently, the mixture was allowed to cool to room temperature, treated with water (10 mL), extracted with EtOAc (2 x 10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (EtOAc/hexanes 98:2) yielding quinazoline **13** as a yellowish oil in 22% yield (114 mg, 0.33 mmol).

R_f = 0.31 (CH_2Cl_2/MeOH 19:1, UV). ^{1}H NMR (300 MHz, CD_3OD): δ = 1.97-2.08 (m, 2 H), 3.64 (t, J = 5.8 Hz, 2 H), 4.26 (t, J = 7.1 Hz, 2 H), 7.00 (dd, J = 8.5, 2.4 Hz, 1 H), 7.26 (d, J = 2.4 Hz, 1 H), 7.41 (d, J = 8.5 Hz, 1 H), 7.47-7.54 (m, 1 H), 7.60 (d, J = 8.3 Hz, 1 H), 7.73-7.80 (m, 1 H), 8.00 (s, 1 H), 8.33 (dd, J = 8.1, 1.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 31.9, 47.9, 59.2, 116.6, 120.9, 124.3, 125.9, 127.0, 127.8 (2 x), 131.4, 133.0, 134.5, 139.1, 150.7, 152.8, 156.6 ppm. MS (MALDI-TOF, without matrix): m/z = 348 ([M+H]$^+$).

Synthesis of quinazoline precursor 14

To a stirred solution of *N*'-(2-cyano-4-nitrophenyl)-*N*,*N*-dimethylformimidamide (1.17 g, 5.36 mmol, 1.0 equiv.) in glacial acetic acid (4.60 mL, 4.83 g, 80.4 mmol, 15 equiv.) 3,4-dichloroaniline (870 mg, 5.36 mmol, 1.0 equiv.) was added and the resulting mixture was heated until reflux. After 3 h the reaction mixture was cooled down to room temperature and poured into ice water (50 mL). The orange precipitate was filtered out, washed with water and Et_2O and dried under vacuum. Quinazoline **14** was obtained as an orange solid (1.52 g, 4.54 mmol, 85%). To get a pure compound for EA and biological investigations quinazoline **14** was recrystallized from a mixture of DMF, MeOH and CH_2Cl_2.

^{1}H NMR (300 MHz, MeOD/DMSO-d6 1:1): δ = 7.58 (d, 1 H, J = 8.7 Hz), 7.85-7.94 (m, 3 H), 8.25 (d, 1 H, J = 2.1 Hz), 8.53 (dd, 1 H, J = 9.2 Hz, 2.7 Hz), 8.74 (s, 1 H), 9.59 (d, 1 H, J = 2.4 Hz) ppm. ^{13}C NMR (75.5 MHz, MeOD/DMSO-d6 1:1): δ = 114.9, 121.0, 121.2, 122.5, 123.9, 126.4, 127.2, 130.0, 130.7, 131.4, 139.1, 145.3, 153.4, 157.8, 159.0 ppm. MS (ESI): m/z = 335 ([M+H]$^+$). HRMS (ESI): calculated for $[C_{14}H_9Cl_2N_4O_2]^+$ 335.0097, found 335.0010. Anal. Calcd. for $C_{14}H_8Cl_2N_4O_2$: C, 50.17; H, 2.41; N, 16.72; Found: C, 50.26; H, 2.51; N, 16.56.

Synthesis of quinazoline precursor 15

An aqueous slurry suspension of Raney-nickel (1 x tip of a spatula) was added under N_2 via a pipette to a 25 mL Schlenk-flask. The suspension was washed with MeOH (3 x 5.0 mL) and a suspension of quinazoline **14** (100 mg, 0.30 mmol, 1.0 equiv.) in dry MeOH (4.0 mL) was added under N_2. After addition of hydrazine monohydrate (255 µL, 263 mg, 6.56 mmol, 22 equiv.) under N_2 the reaction mixture was heated until reflux and stirred for 30 min. Afterwards Raney-nickel was filtered off, washed with MeOH (25 mL) and the solvent removed under reduced pressure to give a slightly yellow solid. The crude product was purified via reprecipitation from a mixture of DMSO, EtOAc and Et_2O in order to obtain amine **15** as a pale yellow solid (79.4 mg, 0.26 mmol, 87%).

^{1}H NMR (300 MHz, MeOD + drops of DMSO-d_6): δ = 7.25-7.45 (m, 2 H), 7.48 (d, 1 H, J = 8.7 Hz), 7.59 (d, 1 H, J = 8.4 Hz), 7.80 (d, 1 H, J = 8.1 Hz), 8.24 (s, 1 H), 8.41 (s, 1 H) ppm. ^{13}C NMR (75.5 MHz, MeOD + drops of DMSO-d_6): δ = 102.8, 123.0, 124.7, 125.9, 127.2, 129.7, 131.73, 133.2, 141.4, 144.1, 149.5, 151.6, 158.0, 164.1 ppm.

The synthesis for artemisinin derivatives **18**, **19** and **17** were carried out in analogy to a literature known procedure.[2]

Synthesis of dihydroartemisinin benzoate 18

To a solution of dihydroartemisinin (1.50 g, 5.28 mmol, 1.0 equiv.) in dry CH_2Cl_2 (21.0 mL) anhydrous pyridine (2.68 mL, 2.63 g, 33.3 mmol, 6.3 equiv.) was added under N_2. The yellow solution was cooled to 0 °C and benzoyl chloride (958 µL, 1.17 g, 8.45 mmol, 1.6 equiv.) was added dropwise under N_2. The resulting reaction mixture was warmed to room teperature and stirred overnight. Afterwards, 7% citric acid (20 mL) was added, the phases were separated and the water phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with 7% citric acid (2 x 20 mL), sat. $NaHCO_3$-solution (25 mL) and water (25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a white solid. The crude product was purified by column chromatography (hexanes/EtOAc 12:1) and thereby benzoate **18** was obtained as a white solid (1.79 g, 4.61 mmol, 87%).

R_f = 0.59 (hexanes/EtOAc 4:1, phosphomolybdic acid). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, 3 H, J = 6.0 Hz), 0.94 (d, 3 H, J = 6.0 Hz), 0.96-1.09 (m, 1 H), 1.19-1.55 (m, 7 H, including singlet at 1.39), 1.60-1.93 (m, 4 H), 1.97-2.06 (m, 1 H), 2.35 (dt, 1 H, J = 12.0 Hz, J = 6.0 Hz), 2.66-2.80 (m, 1 H), 5.50 (s, 1 H), 5.99 (d, 1 H, J = 9.0 Hz), 7.37-7.44 (m, 2 H), 7.51-7.58 (m, 1 H), 8.06-8.12 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 12.2, 20.2, 22.0, 24.5, 25.9, 31.9, 34.0, 36.2, 37.2, 45.3, 51.6, 80.1, 91.5, 92.4, 104.3, 128.2, 129.5, 130.0, 133.2, 165.2 ppm.

Synthesis of artemisinin-derived olefin 19

In an evacuated flask equipped with 4 Å molecular sieves, pre-dried $ZnCl_2$ (3.11 g, 22.9 mmol, 5.0 equiv.) and allyltrimethylsilane (5.81 mL, 4.18 g, 36.6 mmol, 8.0 equiv.) were dissolved in anhydrous DCE (30 mL) under N_2 and the solution was cooled to 0 °C. In a second evacuated Schlenk flask equipped with 4 Å molecular sieves a solution of dihydroartemisinin-benzoyl ester **18** (1.78 g, 4.57 mmol, 1.0 equiv.) in anhydrous DCE (20 mL) was cooled to the same temperature. This solution was added dropwise to the aforementioned one. The reaction mixture was stirred at 0 °C for 6 h and afterwards diluted with EtOAc (100 mL) and 7% citric acid (65 mL). The water phase was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with sat. $NaHCO_3$ solution (50 mL), brine (50 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, a crude yellow oil was obtained. Purification by column chromatography (hexanes/EtOAc 11:1) gave olefin **19** as a white solid (1.14 g, 3.70 mmol, 81%).

R_f = 0.66 (hexanes/EtOAc 4:1, phosphomolybdic acid). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.77 (d, 3 H, J = 7.5 Hz), 0.85 (d, 3 H, J = 6.0 Hz), 0.83-0.92 (m, 1 H), 1.04-1.41 (m, 7 H, including singlet at 1.28), 1.44-1.62 (m, 2 H), 1.63-1.74 (m, 1 H), 1.74-1.85 (m, 1 H), 1.85-1.98 (m, 1 H), 2.02-2.36 (m, 3 H), 2.55 (sex, 1 H, J = 6.3 Hz), 4.13-4.24 (m, 1 H), 4.88-5.05 (m, 2 H), 5.41 (s, 1 H), 5.88-6.05 (m, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 12.6, 19.9, 24.4, 24.6, 25.7, 29.9, 33.9, 34.2, 36.3, 37.1, 44.0, 52.0, 74.2, 80.6, 88.8, 102.6, 115.7, 136.1, 136.2 ppm. MS (MALDI-TOF, without matrix): m/z = 331 ([M+Na]$^+$). HRMS (ESI): calculated for $[C_{18}H_{29}O_4]^+$: 309.2060, found: 309.2062.

[2] Stocks, P. A.; Bray, P. G.; Barton, V. E.; Al-Helal, M.; Jones, M.; Araujo, N. C.; Gibbons, P.; Ward, S. A.; Hughes, R. H.; Biagini, G. A.; Davies, J.; Amewu, R.; Mercer, A. E.; Ellis, G.; O'Neill, P. M. Evidence for a Common Non-Heme Chelatable-Iron-Dependent Activation Mechanism for Semisynthetic and Synthetic Endoperoxide Antimalarial Drugs. *Angew. Chem. Int. Ed.* **2007,** *46*, 6278-6283.

Synthesis of artemisinin-derived acid 17

Olefin **19** (846 mg, 2.74 mmol, 1.0 equiv.) was dissolved under N_2 in a 1:1 mixture of H_2O and acetone (200 mL). Subsequently, $NaIO_4$ (2.35 g, 11.0 mmol, 4.0 equiv.) and $KMnO_4$ (273 mg, 1.73 mmol, 0.6 equiv.) were added under N_2 and the flask was wrapped with aluminium foil. After stirring the reaction mixture overnight, the precipitate was filtered off and the solvent mixture was removed under reduced pressure. By the use of 1 M NaOH the reaction mixture was adjusted to an alkaline pH value and washed with Et_2O (3 x 40 mL). The pH value of the water phase was adjusted to 1 with conc. HCl and afterwards extracted with Et_2O (3 x 40 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Acid **17** (807 mg, 2.47 mmol) was obtained as a pale yellow solid in 90% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (d, 3 H, J = 7.5 Hz), 0.90 (d, 3 H, J = 6.0 Hz), 0.88-0.97 (m, 1 H), 1.11-1.48 (m, 7 H, including singlet at 1.34), 1.53-1.67 (m, 2 H), 1.68-1.78 (m, 1 H), 1.79-1.90 (m, 1 H), 1.91-2.03 (m, 1 H), 2.26 (dt, 1 H, J = 13.4 Hz, J = 3.6 Hz), 2.40-2.46 (m, 1 H), 2.55-2.74 (m, 2 H), 4.73-4.80 (m, 1 H), 5.29 (s, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 12.7, 20.0, 24.5, 24.6, 25.7, 29.5, 34.2, 35.7, 36.3, 37.3, 43.8, 52.0, 71.0, 80.7, 89.1, 103.1, 176.9 ppm. MS (MALDI-TOF, without matrix): *m/z* = 349 ([M+Na]$^+$). HRMS (ESI): calculated for $[C_{17}H_{26}NO_6]^+$: 349.1622, found: 349.1622.

The spectroscopic data are in accordance with those reported in literature.[2]

Figure S1. ^{1}H NMR spectrum of quinazoline precursor **13** recorded on a Bruker Avance spectrometer (300 MHz, CD_3OD):

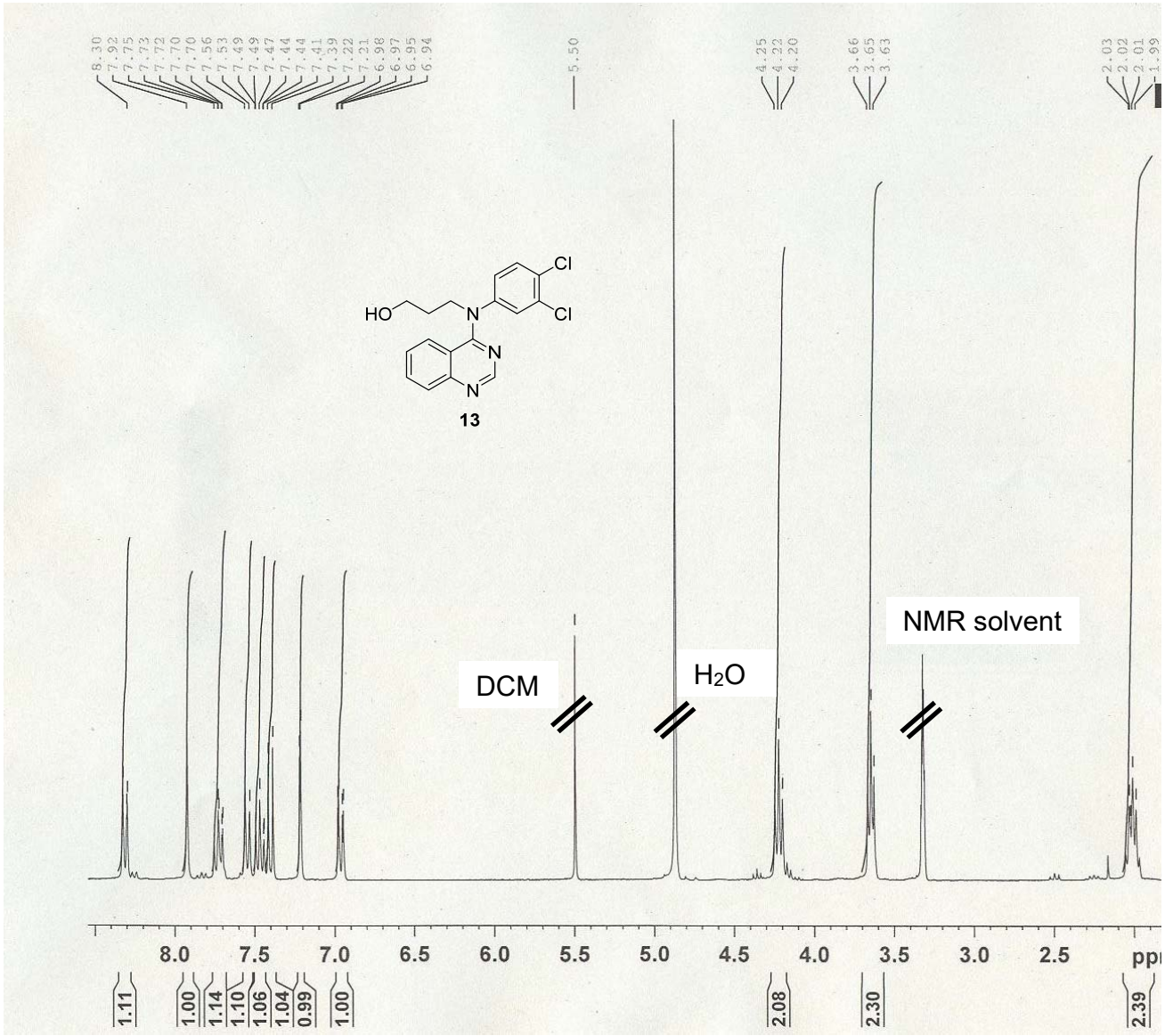


Figure S2. ^{13}C NMR spectrum of quinazoline precursor **13** recorded on a JEOL JNM GX 400 spectrometer (100 MHz, CD_3OD):

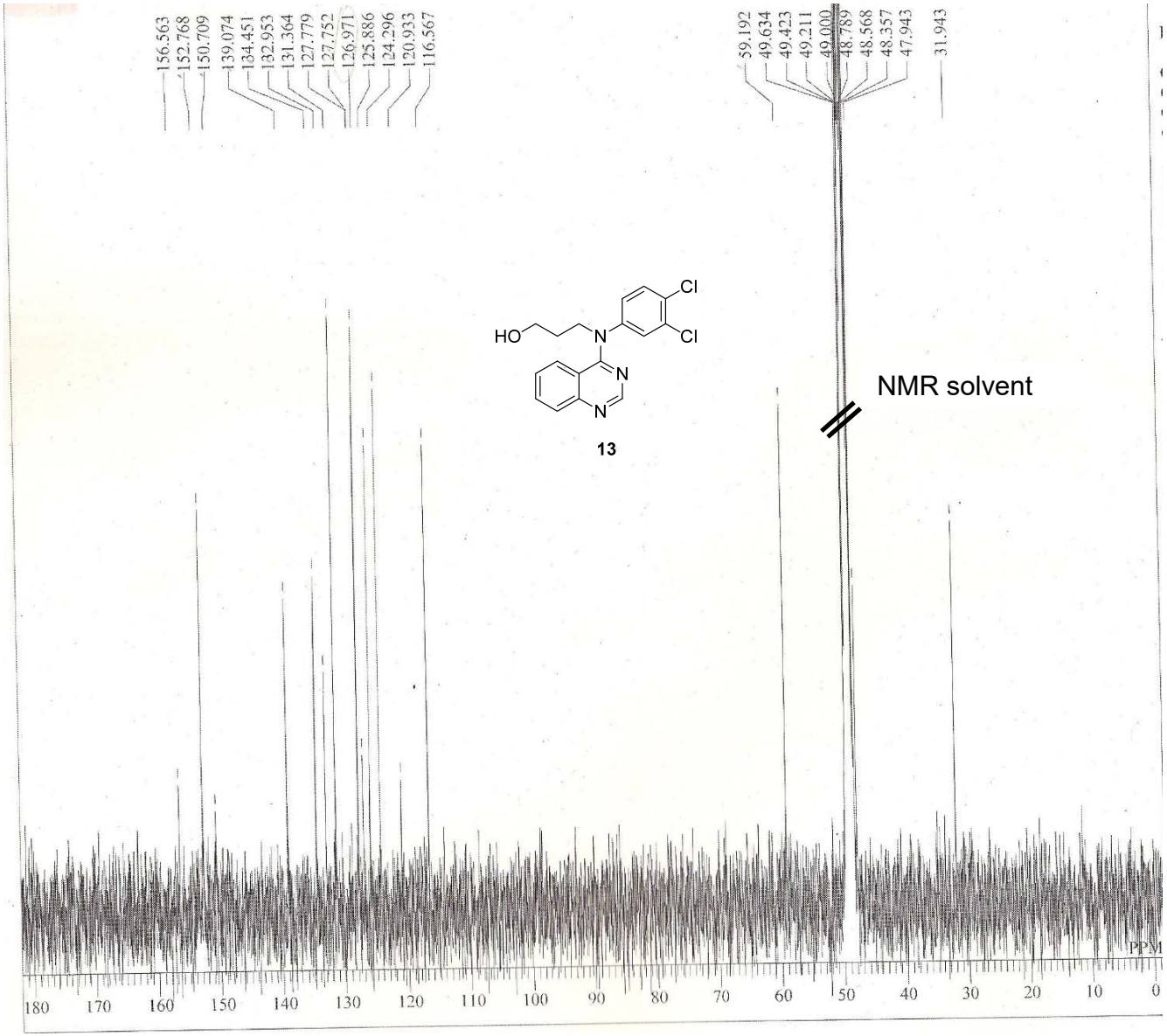


Figure S3. ESI mass spectrum of quinazoline precursor **13** recorded on a Shimadzu Axima Confidence MALDI-TOF MS-spectrometer:

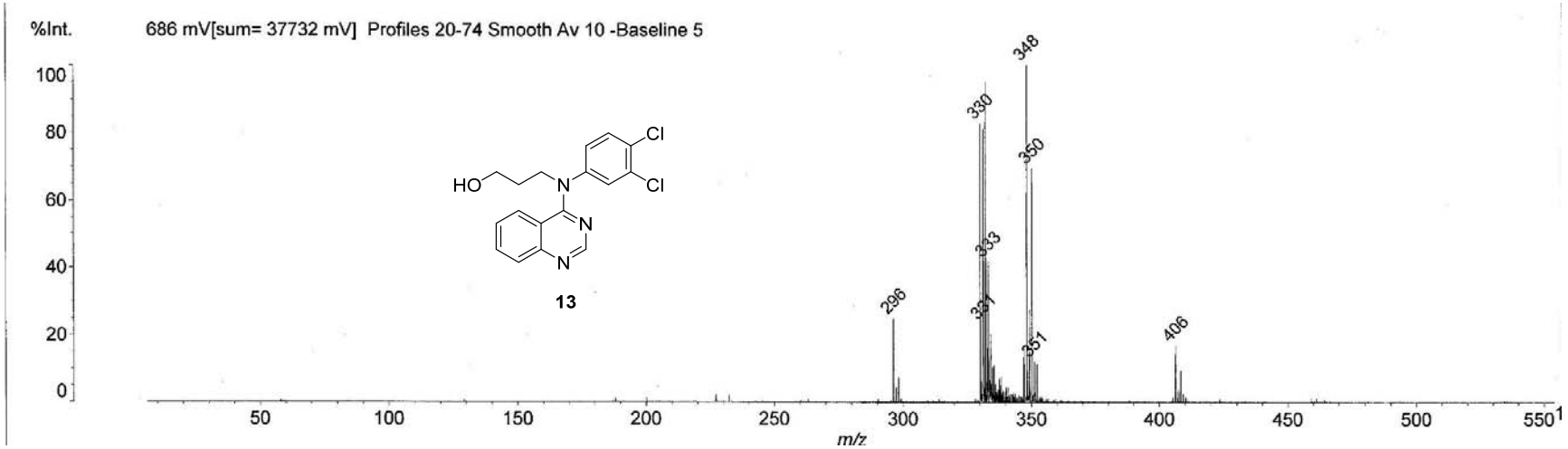


Figure S4. ^{1}H NMR spectrum of quinazoline precursor **14** recorded on a Bruker Avance spectrometer (300 MHz, CD_3OD + drops of DMSO-d6):

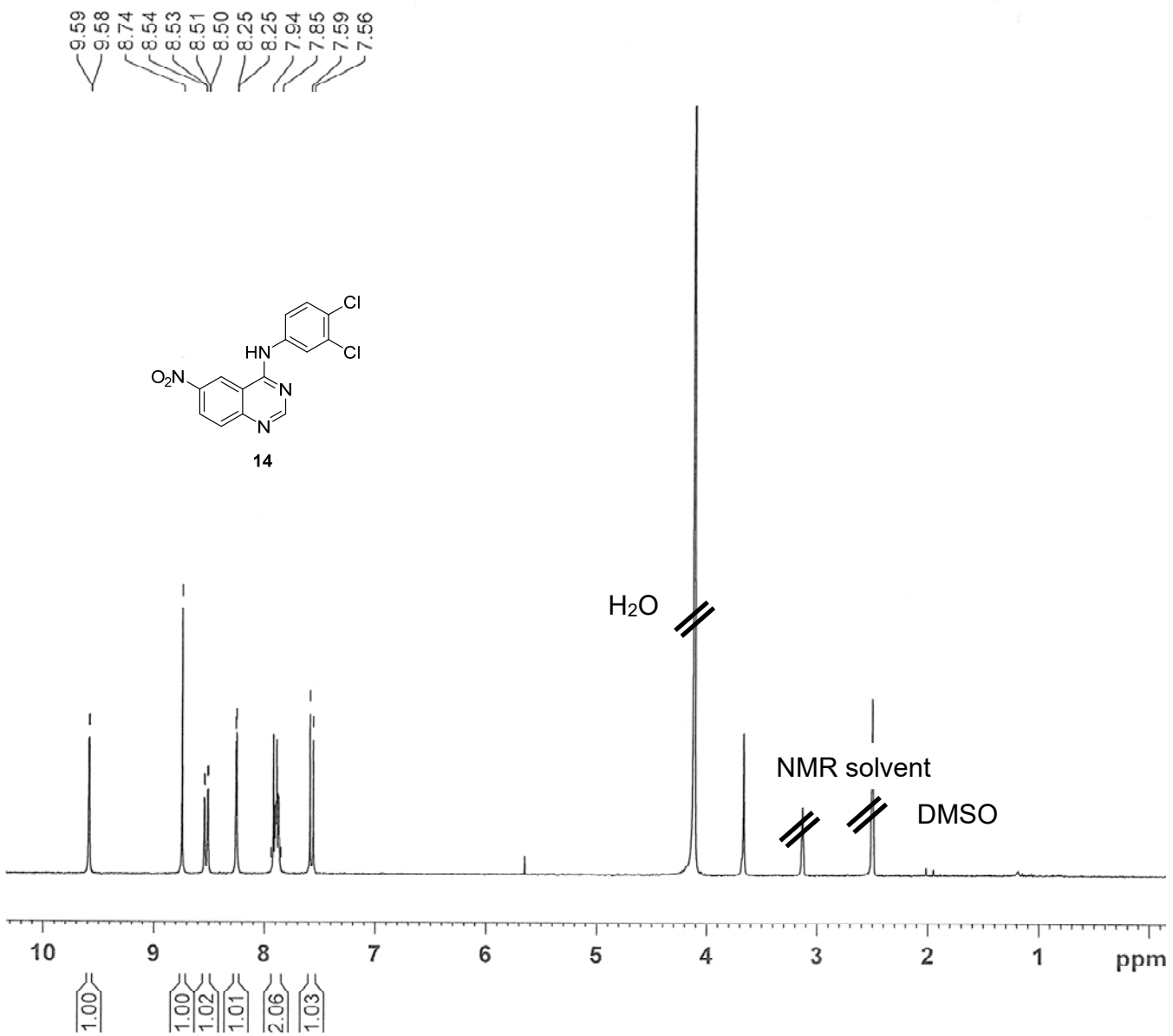


Figure S5. ^{13}C NMR spectrum of quinazoline precursor **14** recorded on a Bruker Avance spectrometer (75.5 MHz, CD_3OD + drops of DMSO-d6):

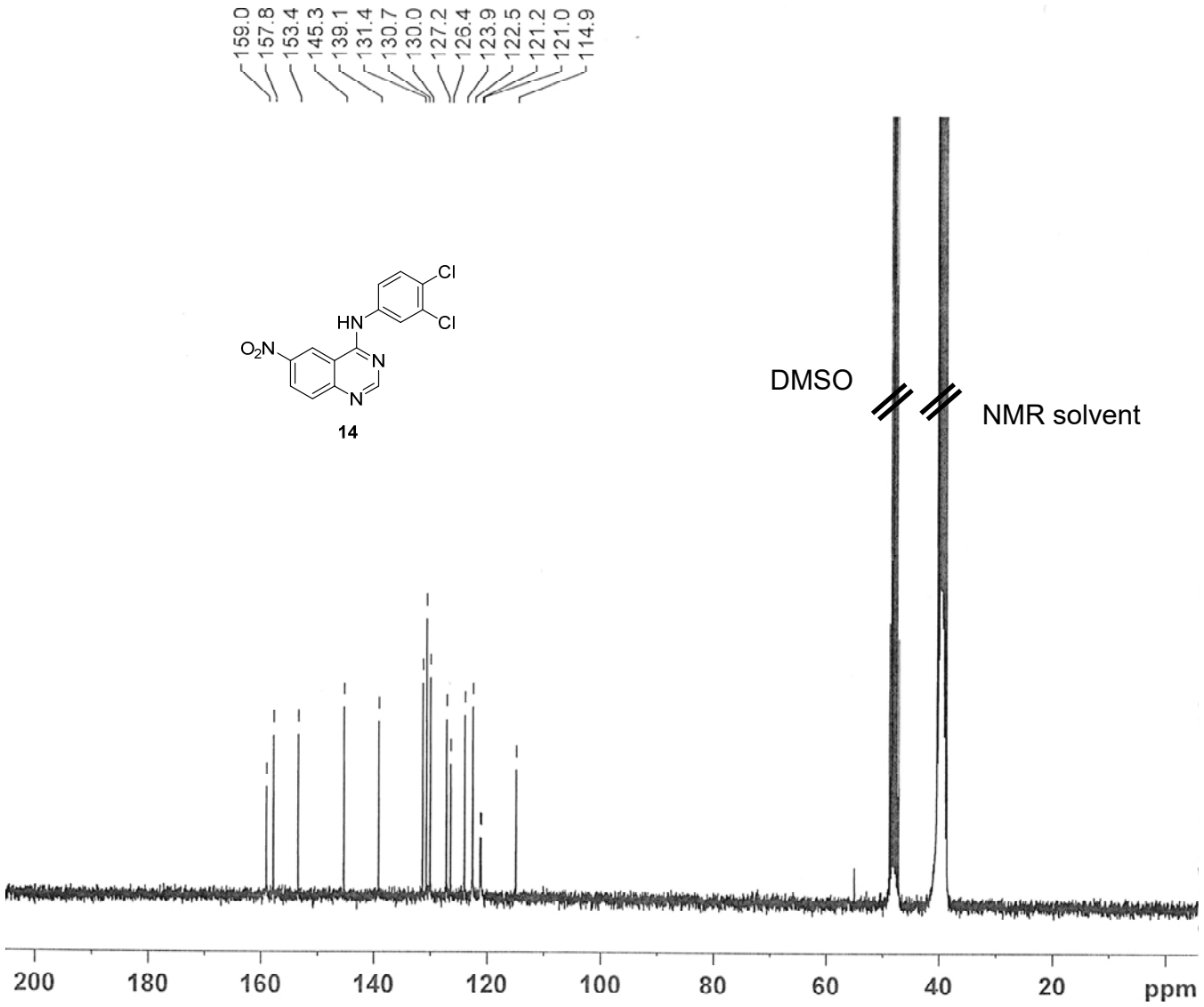


Figure S6. ESI mass spectrum of quinazoline precursor **14** recorded on a Bruker micrOTOF II focus TOF MS-spectrometer:

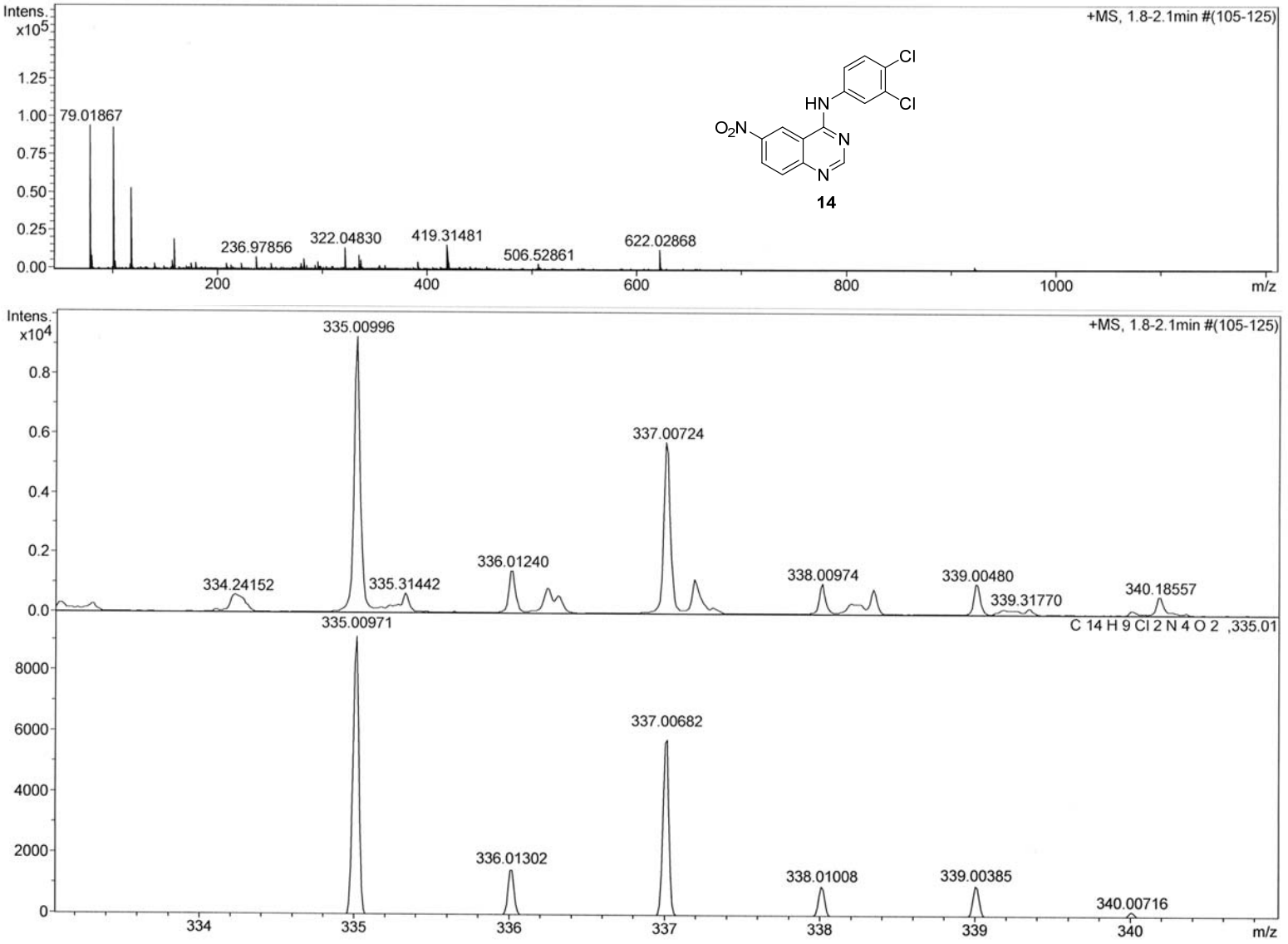


Figure S7. ^{1}H NMR spectrum of quinazoline precursor **15** recorded on a Bruker Avance spectrometer (300 MHz, CD_3OD):

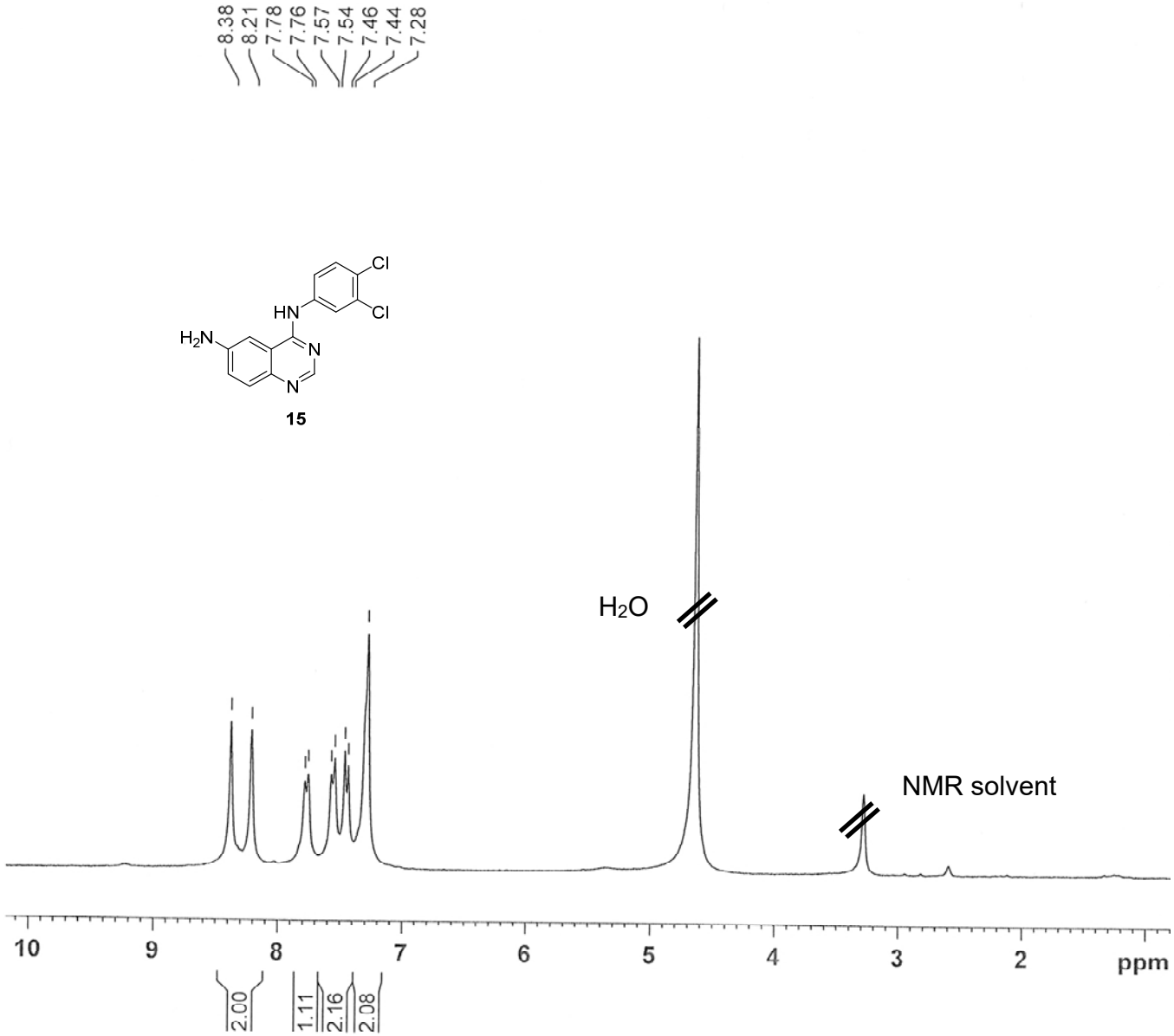


Figure S8. ^{13}C NMR spectrum of quinazoline precursor **15** recorded on a Bruker Avance spectrometer (75.5 MHz, CD_3OD + drops of DMSO-d6):

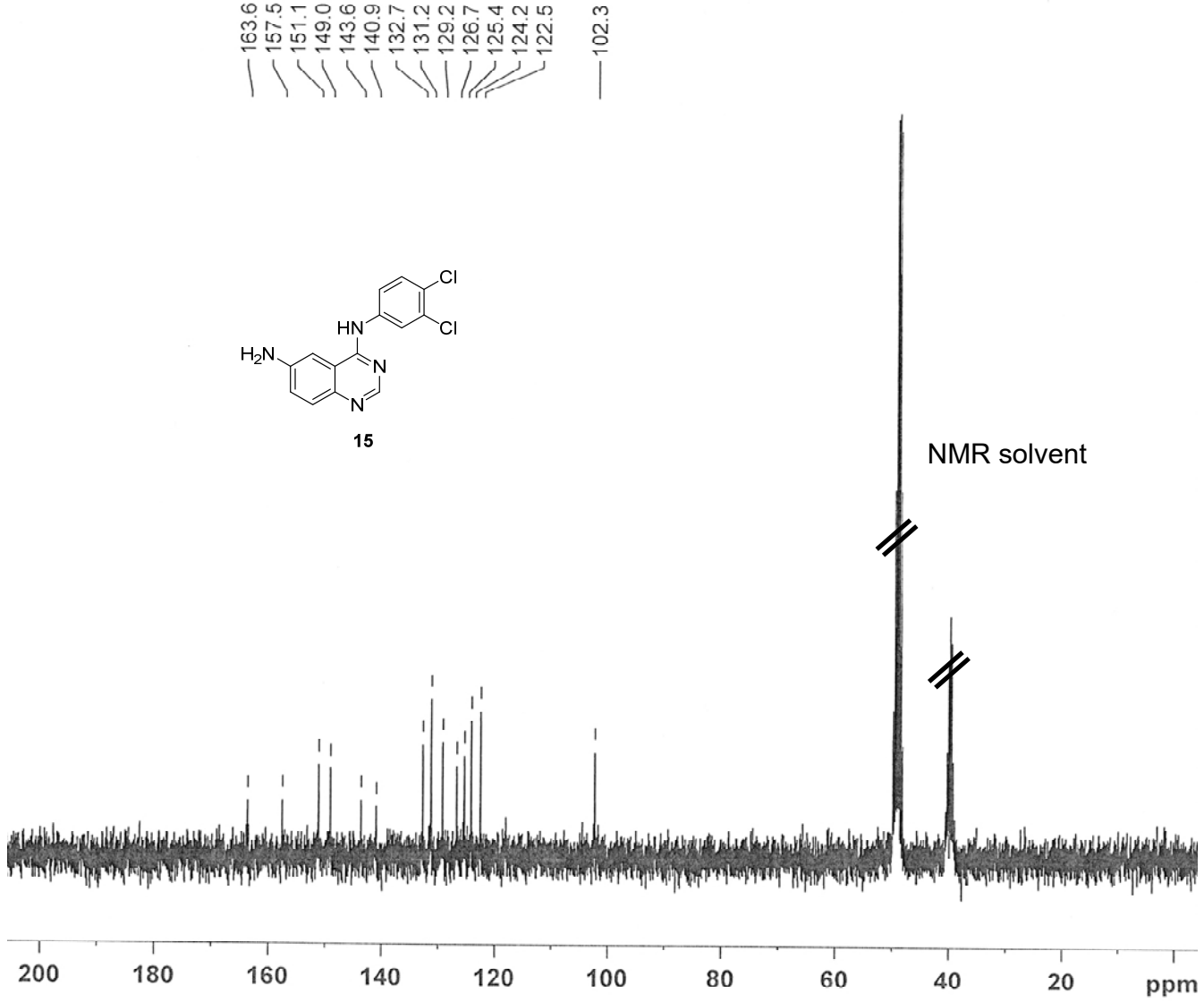


Figure S9. ^{1}H NMR spectrum of quinazoline artesunic acid hybrid **6** recorded on a JEOL JNM GX 400 spectrometer (400 MHz, $CDCl_3$):

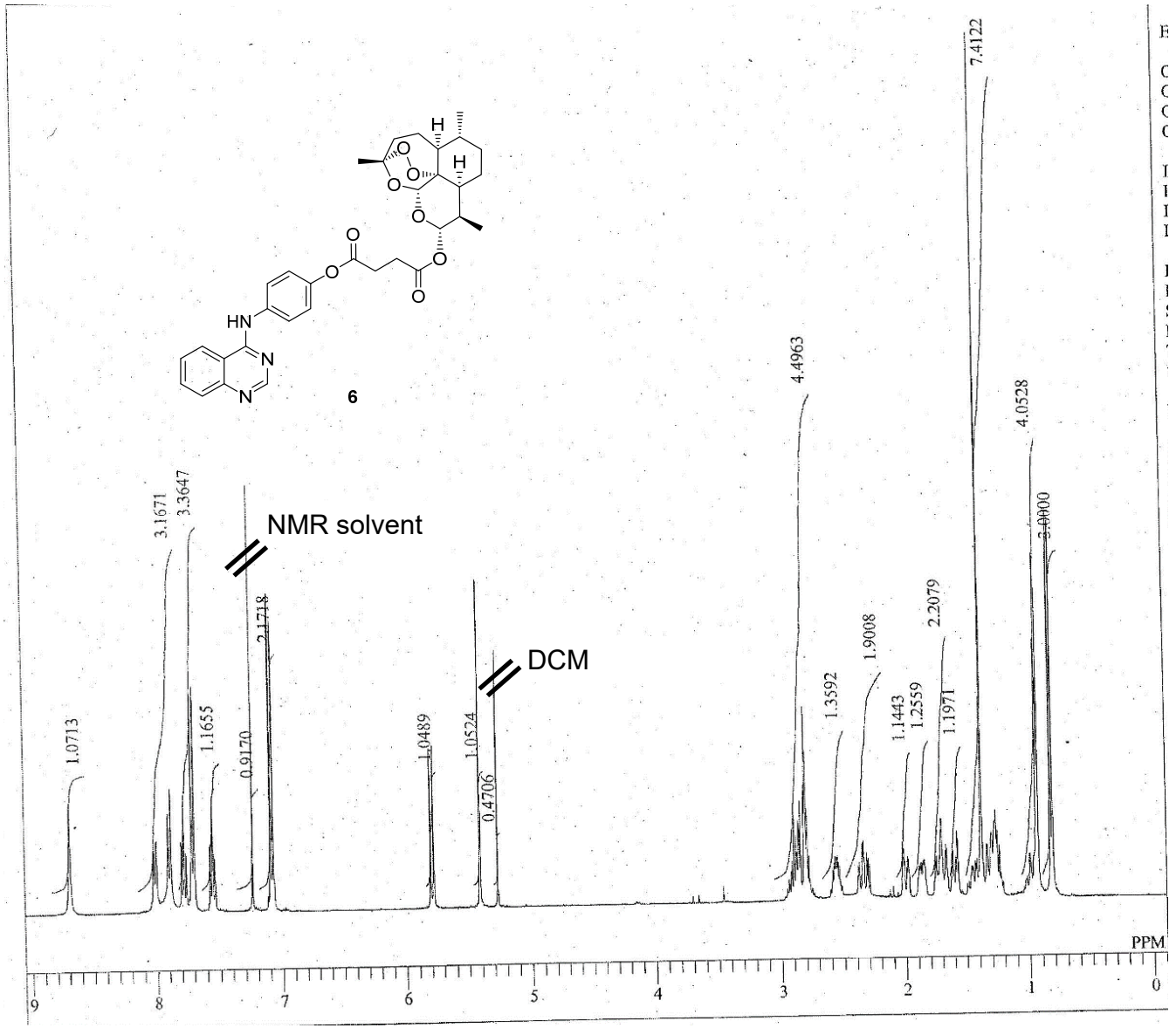


Figure S10. ^{13}C NMR spectrum of quinazoline artesunic acid hybrid **6** recorded on a JEOL JNM GX 400 spectrometer (100 MHz, $CDCl_3$):

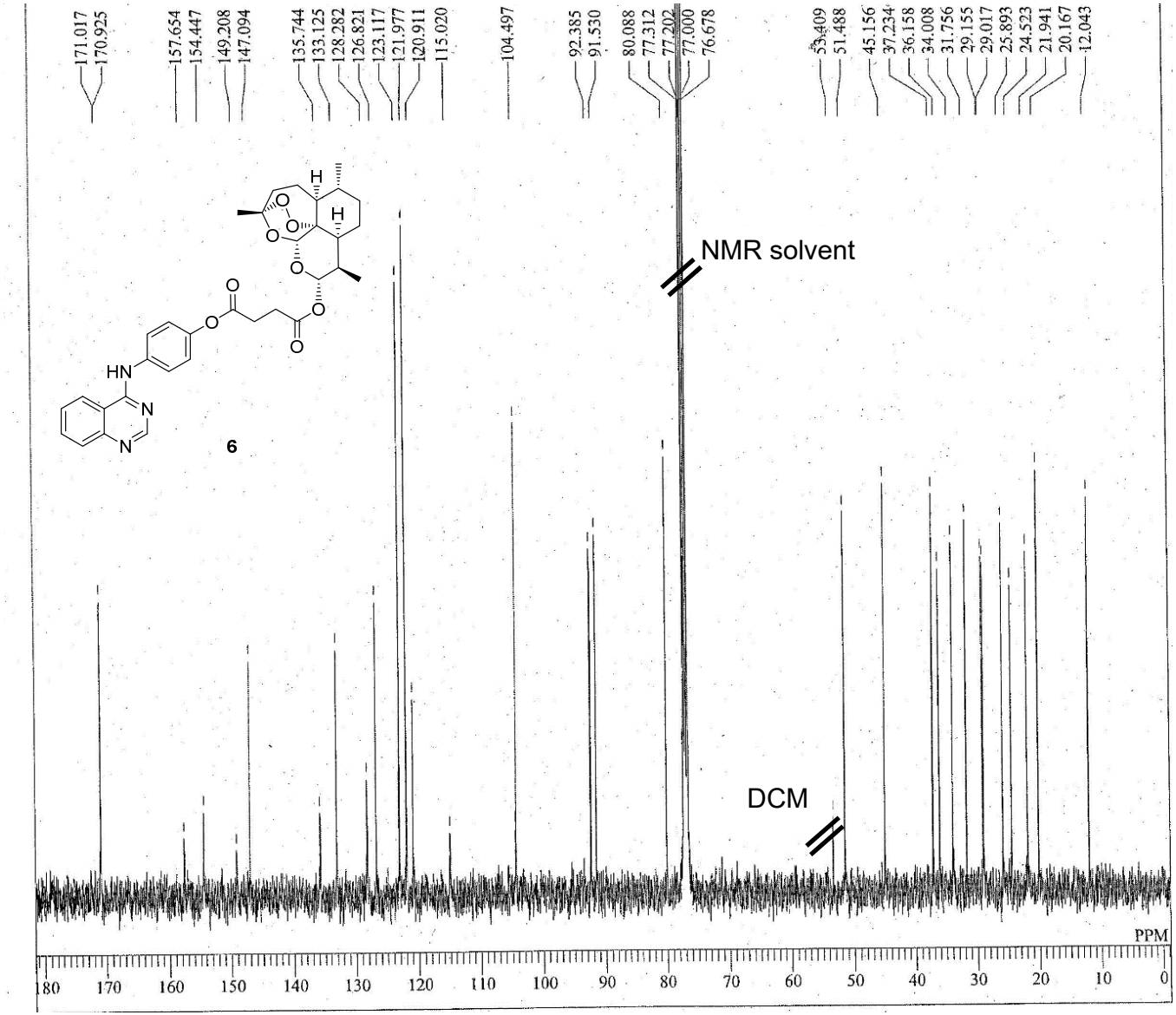
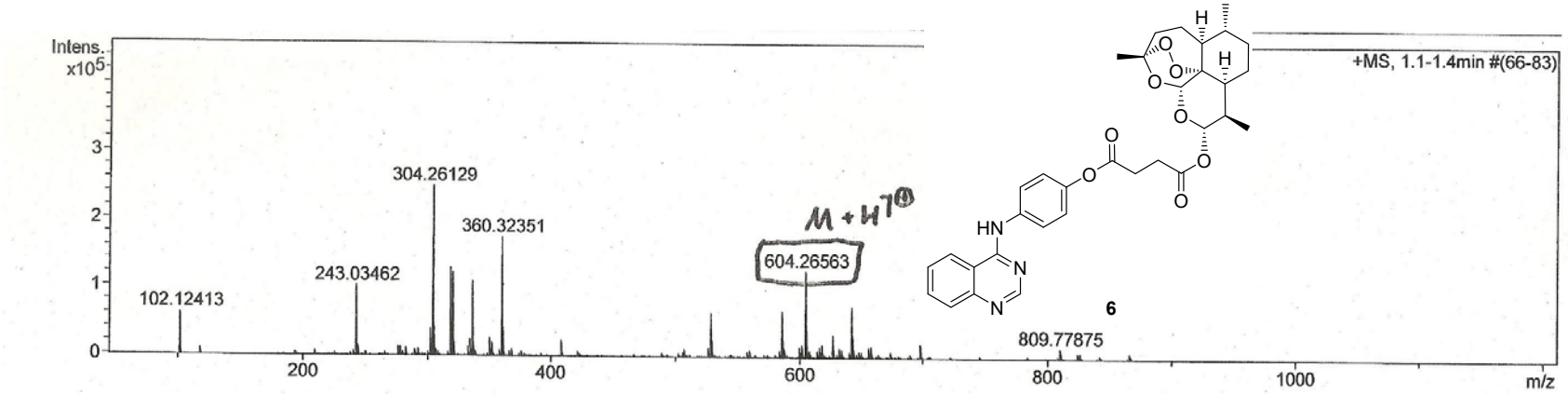


Figure S11. ESI mass spectrum of quinazoline artesunic acid hybrid **6** recorded on a Bruker micrOTOF II focus TOF MS-spectrometer:



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
604.26563	1	C 33 H 38 N 3 O 8	100.00	604.26534	-0.3	-0.5	7.2	16.5	even	ok

Figure S12. ^{1}H NMR spectrum of quinazoline artesunic acid hybrid **7** recorded on a JEOL JNM GX 400 spectrometer (400 MHz, $CDCl_3$):

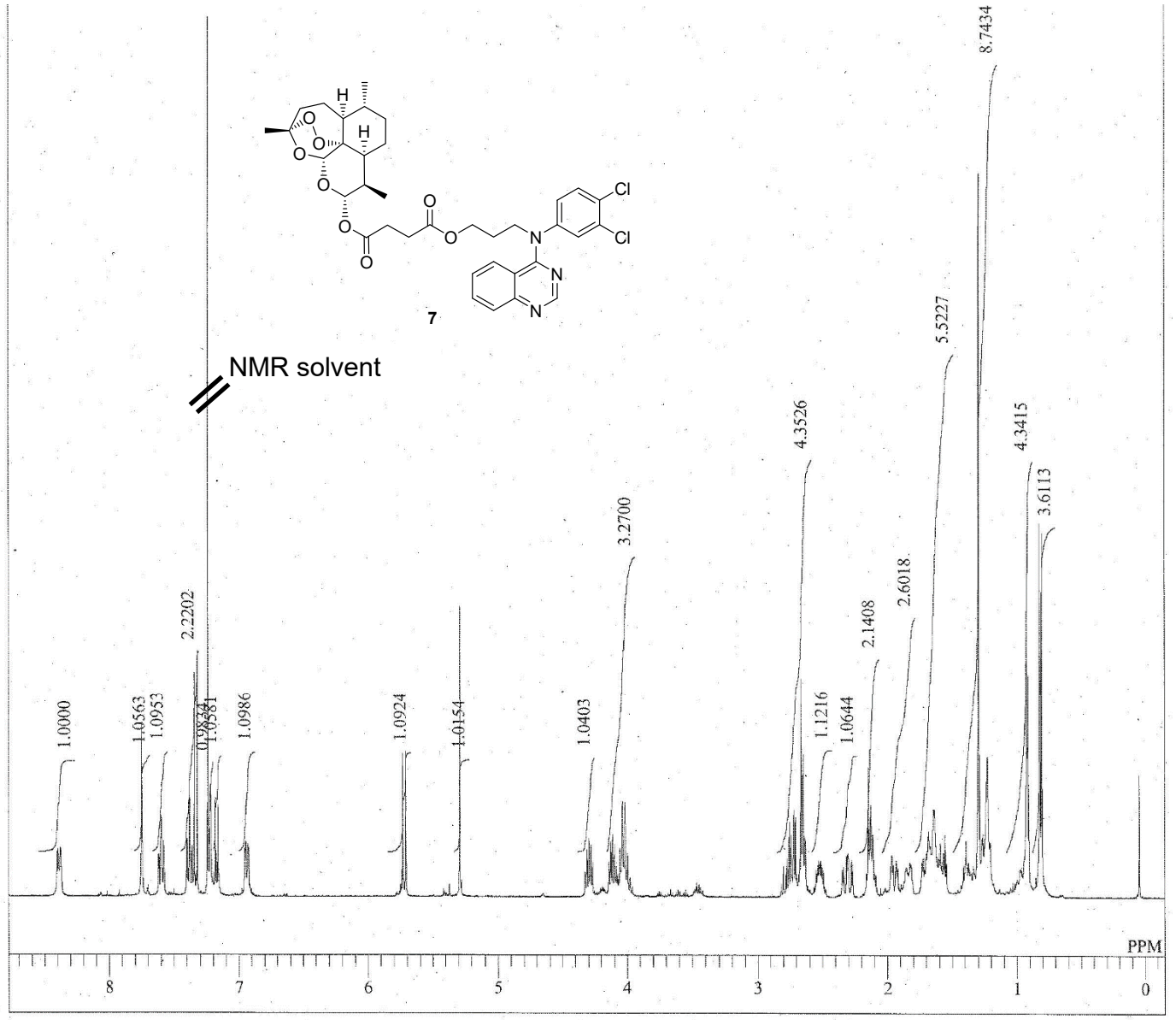


Figure S13. ^{13}C NMR spectrum of quinazoline artesunic acid hybrid **7** recorded on a JEOL JNM GX 400 spectrometer (100 MHz, $CDCl_3$):

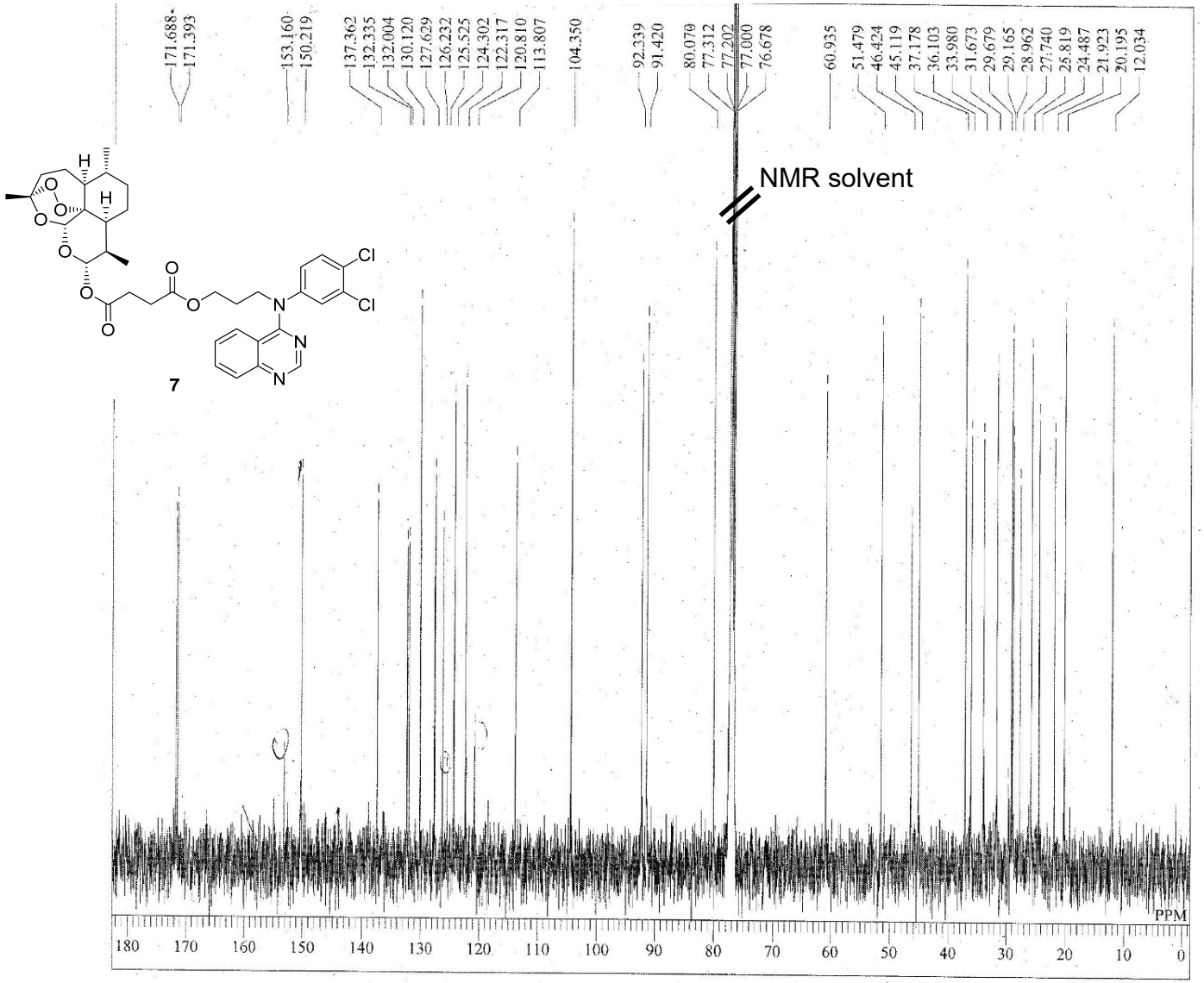
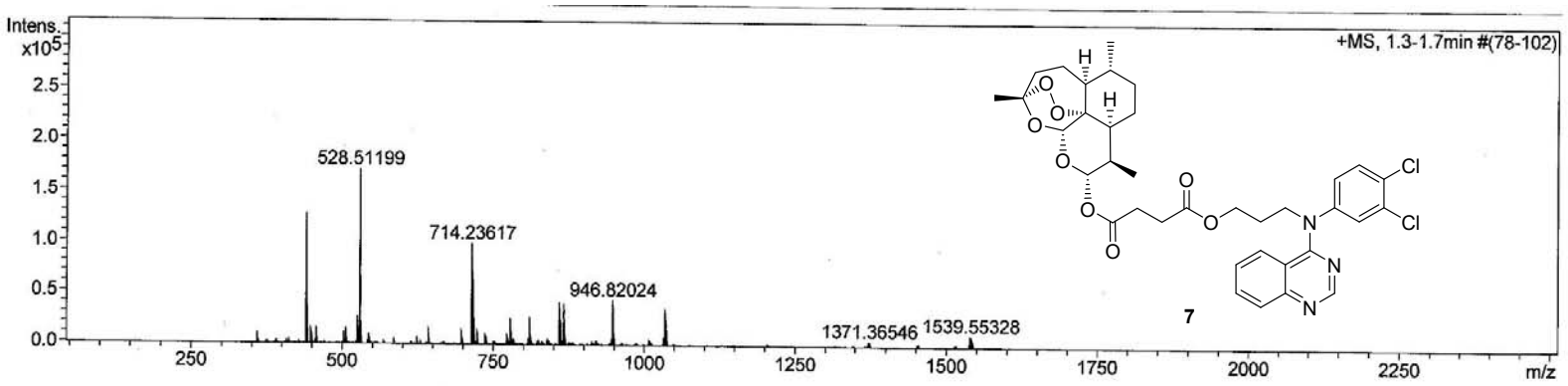


Figure S14. ESI mass spectrum of quinazoline artesunic acid hybrid **7** recorded on a Bruker micrOTOF II focus TOF MS-spectrometer:



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
714.23617	1	C 36 H 42 Cl 2 N 3 O 8	100.00	714.23435	-1.8	-2.6	7.4	16.5	even	ok

[M+H]⊕

Figure S15. ^{1}H NMR spectrum of quinazoline short acid hybrid **8** recorded on a Bruker Avance spectrometer (400 MHz, $CDCl_3$):

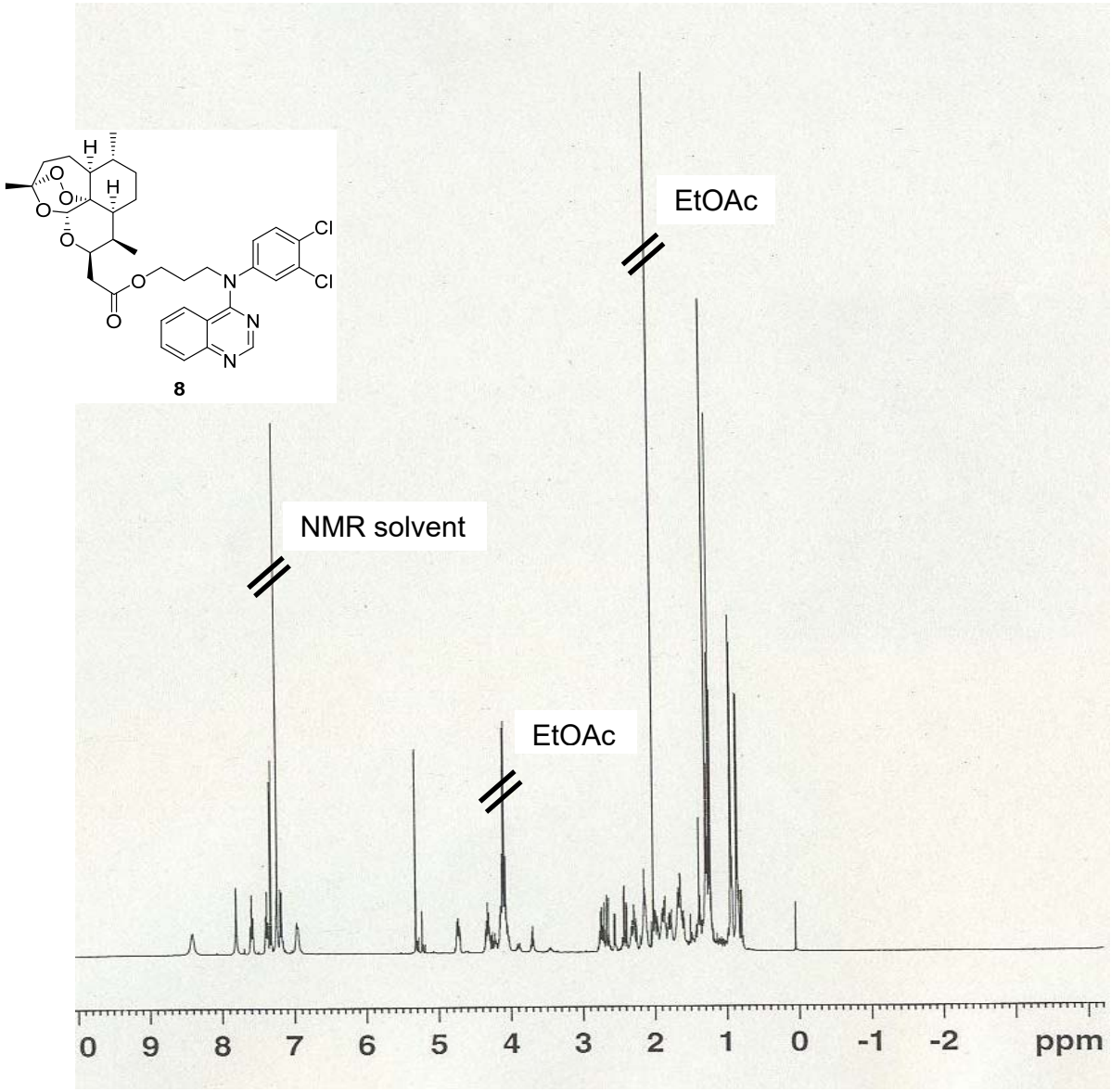


Figure S16. ^{13}C NMR spectrum of quinazoline short acid hybrid **8** recorded on a Bruker Avance spectrometer (100 MHz, $CDCl_3$):

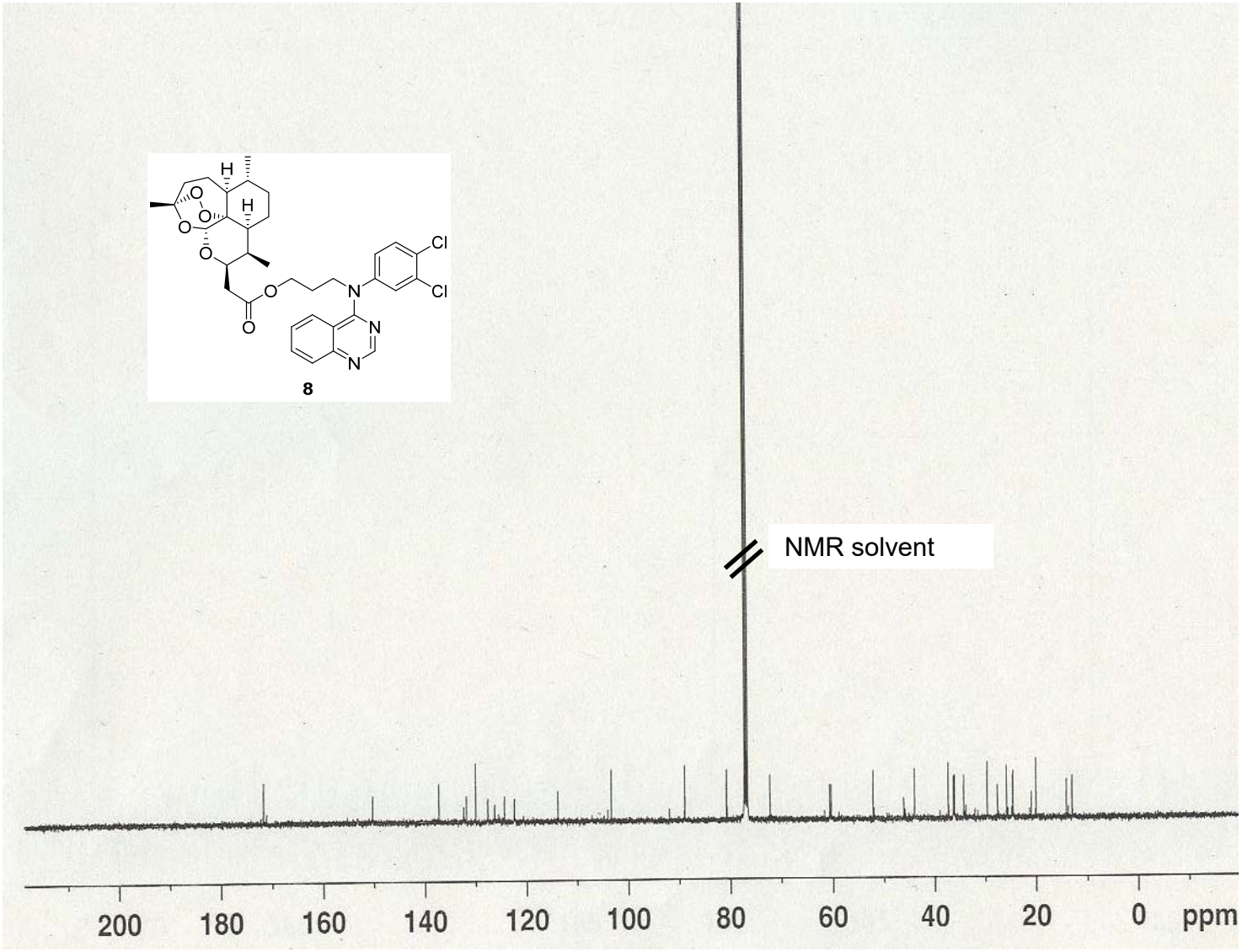
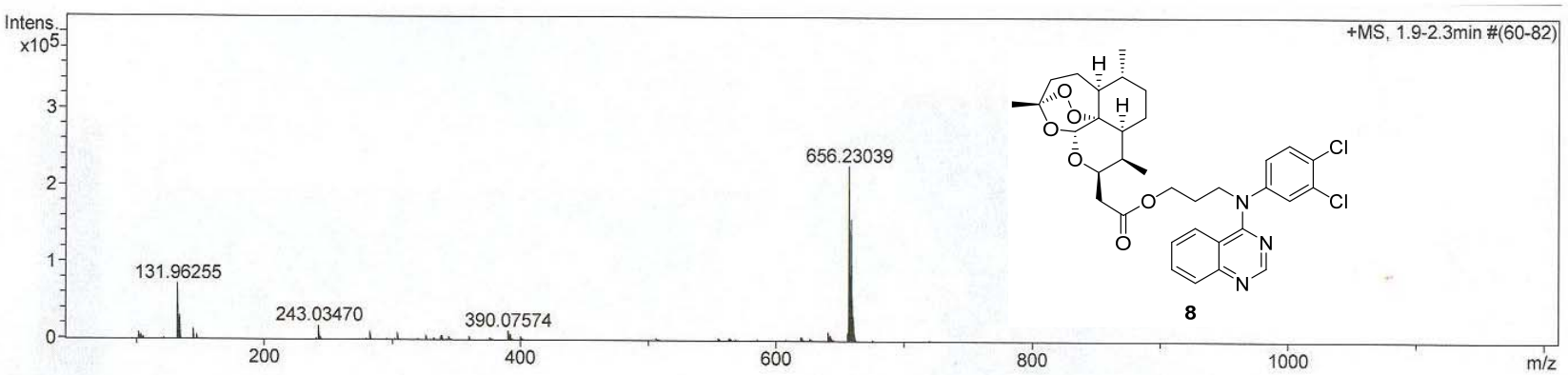


Figure S17. ESI mass spectrum of quinazoline short acid hybrid **8** recorded on a Bruker micrOTOF II focus TOF MS-spectrometer:



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
656.23039	1	C 34 H 40 Cl 2 N 3 O 6	100.00	656.22887	-1.5	-2.3	13.0	15.5	even	ok

Figure S18. ^{1}H NMR spectrum of quinazoline artesunic acid hybrid **9** recorded on a Bruker Avance spectrometer (300 MHz, CD_3OD + drops of $CDCl_3$):

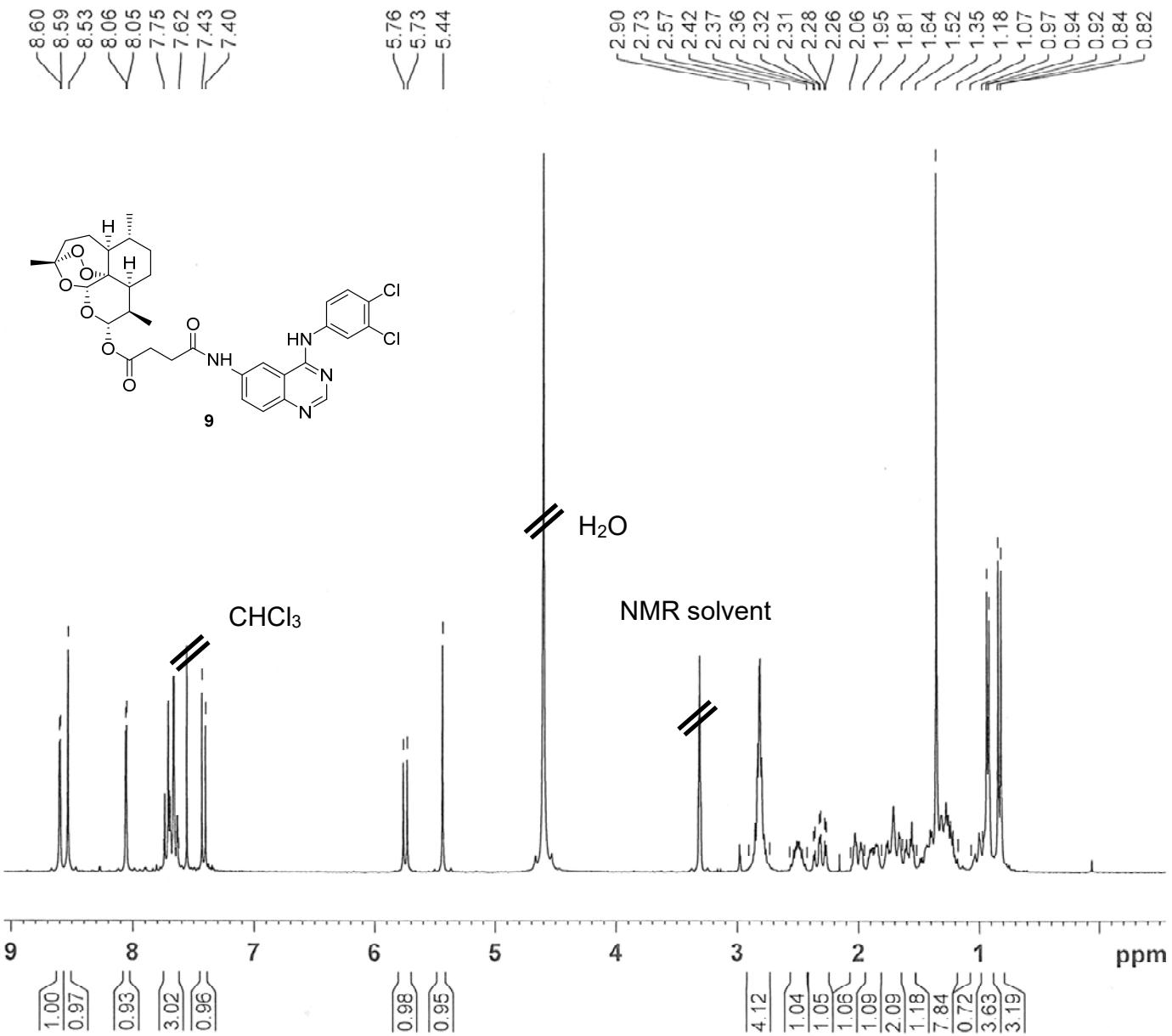


Figure S19. ^{13}C NMR spectrum of quinazoline artesunic acid hybrid **9** recorded on a Bruker Avance spectrometer (75.5 MHz, CD_3OD + drops of $CDCl_3$):

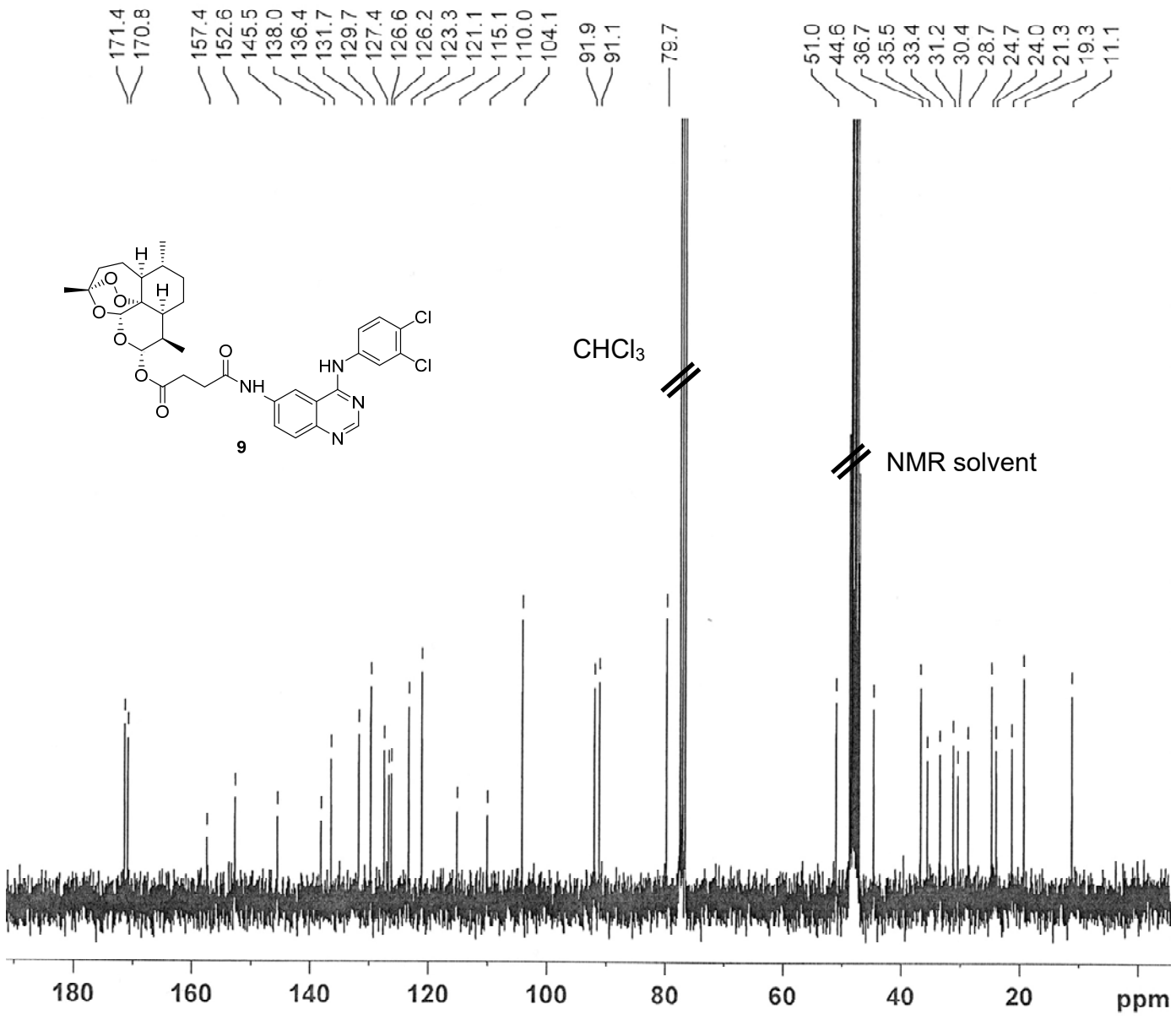


Figure S20. ESI mass spectrum of quinazoline artesunic acid hybrid **9** recorded on a Bruker micrOTOF II focus TOF MS-spectrometer:

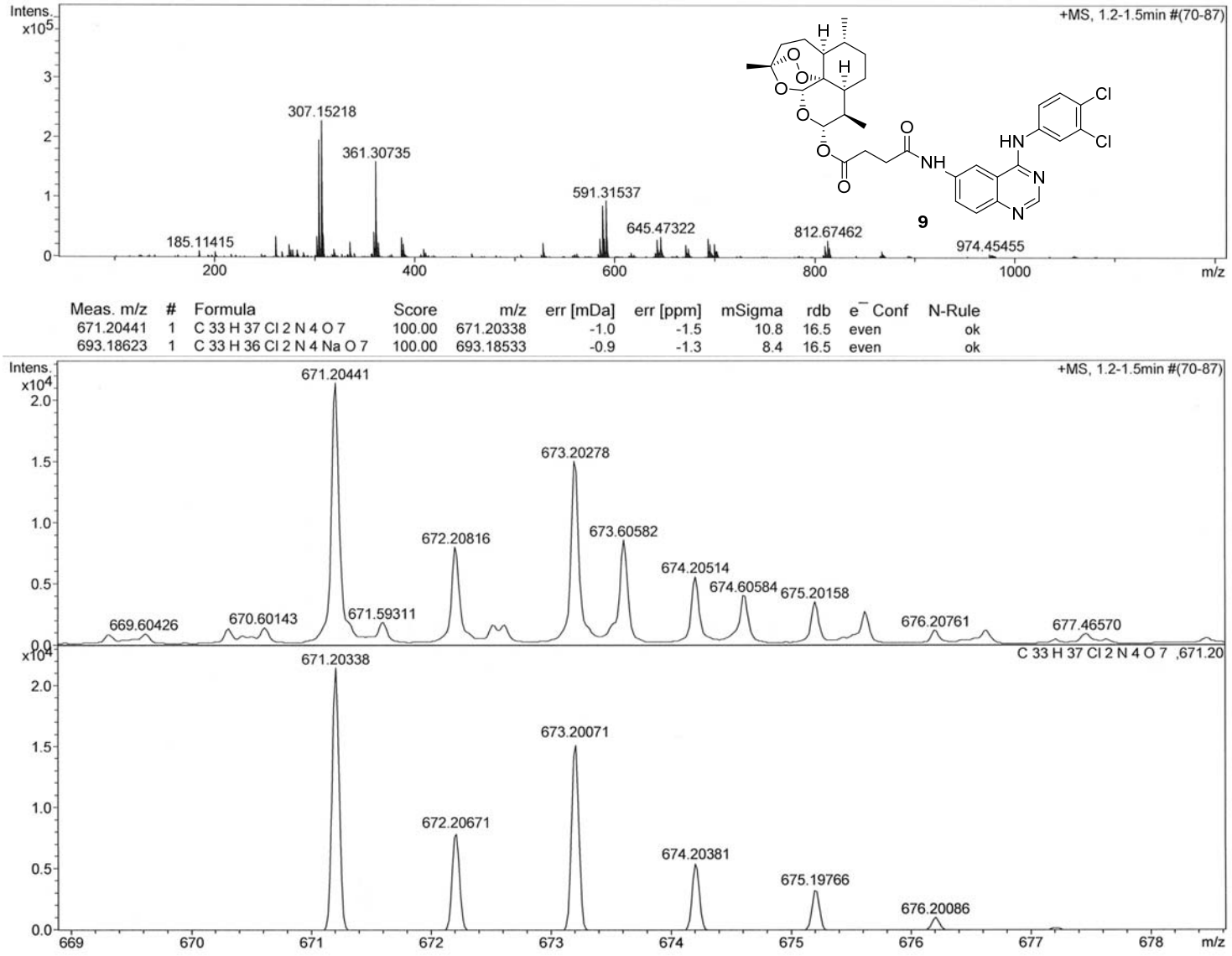


Figure S21. ^{1}H NMR spectrum of quinazoline artemisinin hybrid **10** recorded on a Bruker Avance spectrometer (300 MHz, CD_3OD + drops of $CDCl_3$):

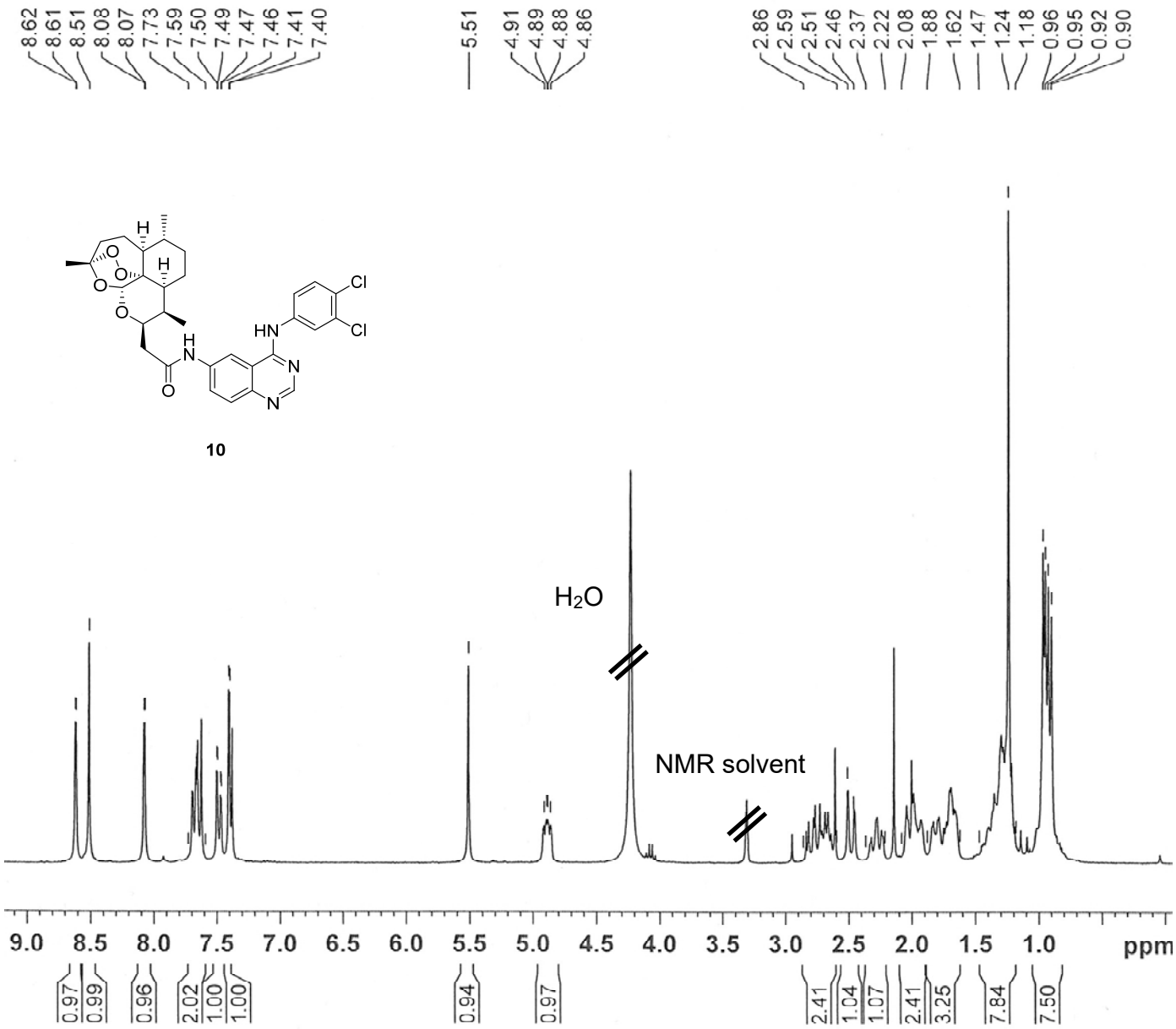


Figure S22. ^{13}C NMR spectrum of quinazoline artemisinin hybrid **10** recorded on a Bruker Avance spectrometer (75.5 MHz, CD_3OD + drops of $CDCl_3$):

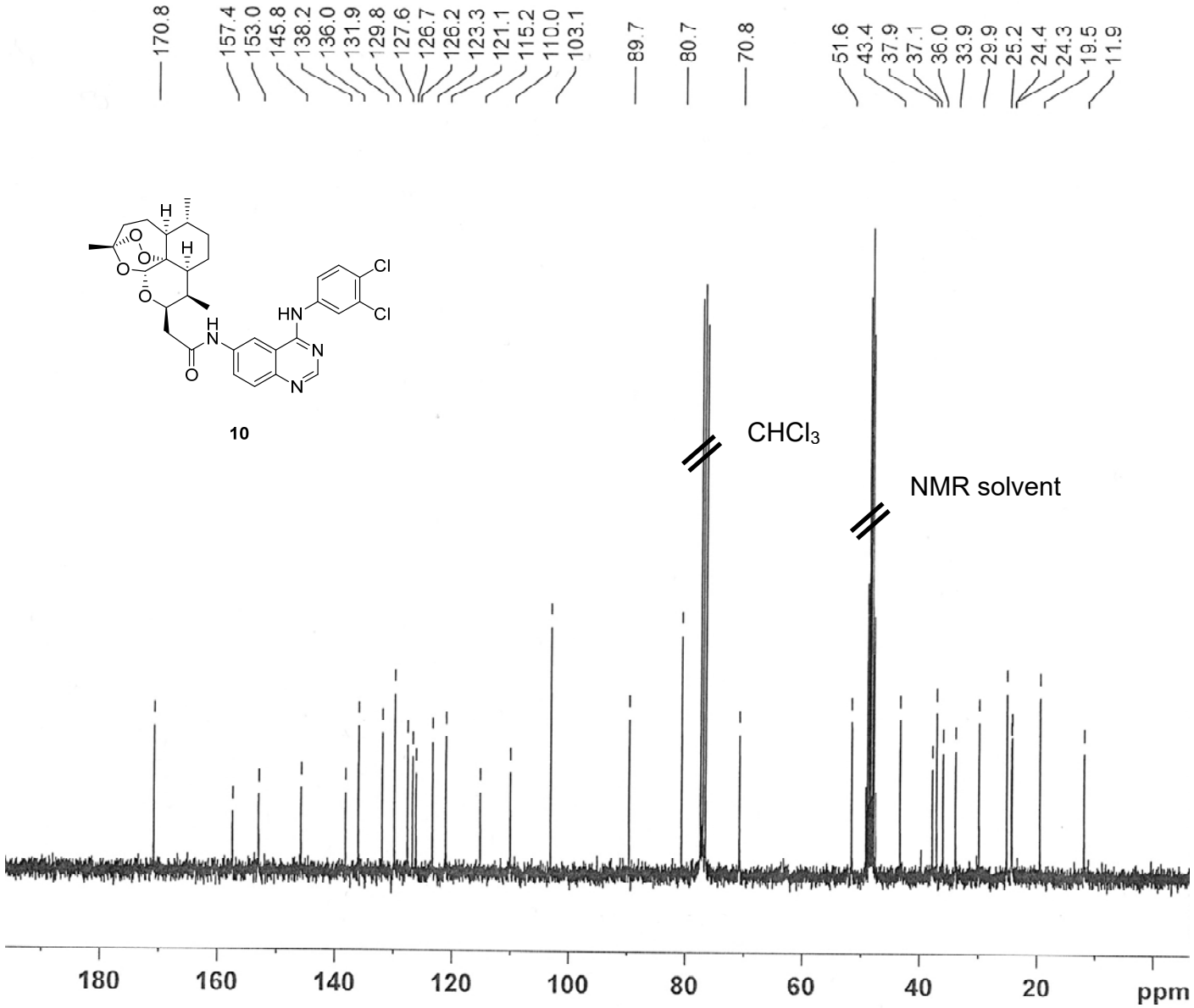


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Figure S23. ESI mass spectrum of quinazoline artemisinin hybrid **10** recorded on a Bruker micrOTOF II focus TOF MS-spectrometer: