Supporting Information

Hybridization of fluoro-amodiaquine (FAQ) with pyrimidines: Synthesis and antimalarial efficacy of FAQ-pyrimidines

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Table S1. *In vitro* antiplasmodial activity and cytotoxicity (towards CHO cells) of intermediates **3**, **4** and FAQ-pyrimidines **6a**, **6b**, **7a-h** and **8a-h**.

Entry	R	P. falciparum NF54 strain (CQ-sensitive)		P. falciparum Dd2 strain (CQ-resistant)		RI[b]	Cytotoxicity[c] (CHO cells) IC_{50} (µM) ±SD
		IC_{50} (nM) ±SD	SI[a]	IC_{50} (nM) ±SD	SI[a]		
3	-	>3358.97±98.41	ND	3203.71±80.27	ND	>0.95	ND
4	-	46.06±1.12	680	58.72±0.84	533	1.27	31.32±0.24
6a	Cl	183.05±5.2	ND	214.43±3.2	ND	1.17	ND
6b	Cl	230.68±4.2	ND	296.97±5.15	ND	1.28	ND
7a	Pyrrolidin-1-yl	12.4±0.16	306	8.23±0.32	462	0.66	3.80±0.20
7b	Piperidin-1-yl	13.75±0.65	ND	17.17±1.07	ND	1.25	ND
7c	Azepan-1-yl	16.9±1.08	ND	27.25±2.05	ND	1.61	ND
7d	Morpholin-1-yl	26.73±1.25	544	33.34±0.25	437	1.25	14.55±0.95
7e	Thiomorpholin-1-yl	22.83±0.09	664	33.08±0.58	459	1.45	15.17±0.19
7f	4-Methylpiperazin-1-yl	12.48±0.82	ND	5.24±0.08	ND	0.42	ND
7g	4-Ethylpiperazin-1-yl	11.19±1.08	ND	7.63±0.11	ND	0.68	ND
7h	4-Phenylpiperazin-1-yl	17.72±0.98	981	31.33±1.85	555	1.77	17.38±1.54
8a	Pyrrolidin-1-yl	88.99±2.3	ND	74.9±0.98	ND	0.84	ND
8b	Piperidin-1-yl	13.42±0.51	237	4.69±0.17	680	0.35	3.18±0.20
8c	Azepan-1-yl	147.66±6.1	ND	67.48±4.98	ND	0.45	ND
8d	Morpholin-1-yl	12.09±0.88	380	17.93±1.27	256	1.48	4.59±0.51
8e	Thiomorpholin-1-yl	7.47±0.31	362	16.04±1.24	169	2.14	2.71
8f	4-Methylpiperazin-1-yl	15.33±1.09	3798	18.4±0.88	3164	1.20	58.23±4.24
8g	4-Ethylpiperazin-1-yl	28.87±0.51	2782	23.4±1.12	3432	0.81	80.33±6.17
8h	4-Phenylpiperazin-1-yl	69.85±3.24	251	62.17±4.11	282	0.89	17.54±0.92
CQ		27.00±6.41	ND	222±9.52	ND	8.22	ND
Artesunate		10.00±5.2	ND	13.00±2.24	ND	1.3	ND

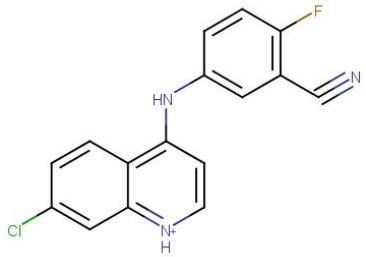
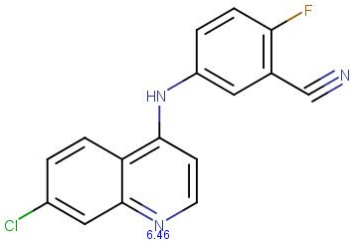
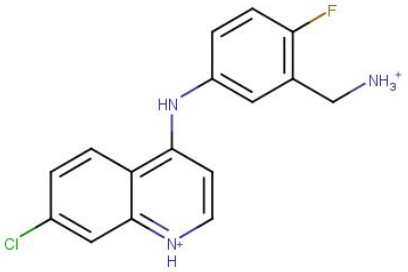
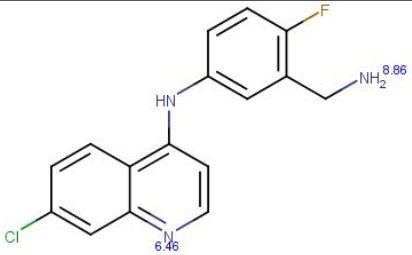
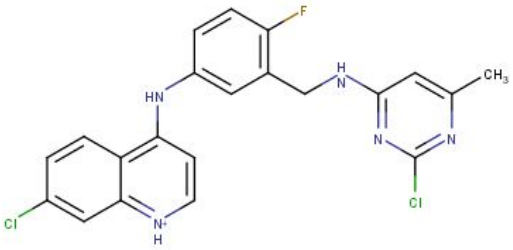
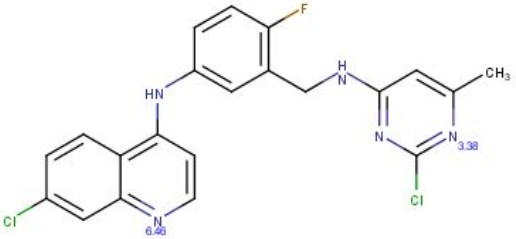
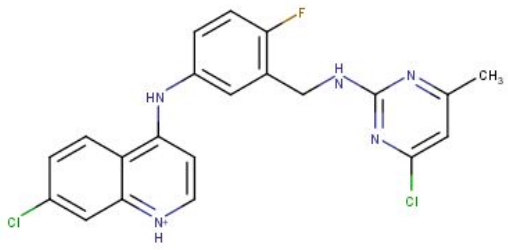
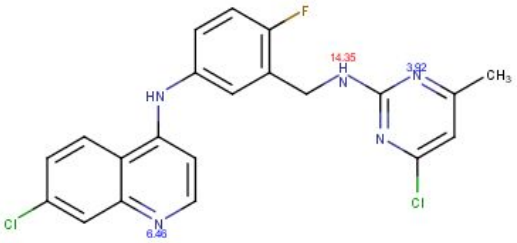
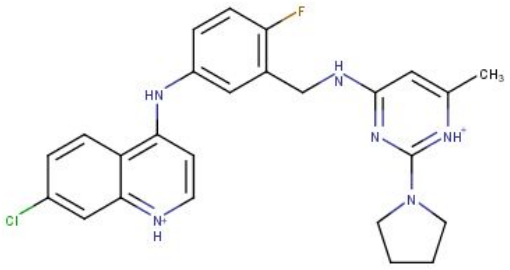
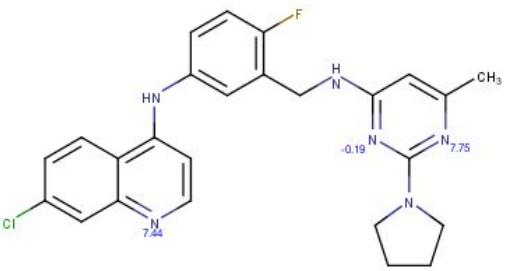
[a] SI, selectivity index = [(IC_{50} (µM) for cytotoxicity to VERO cells) x 1000] / (IC_{50} (nM) for antiplasmodial activity); [b] RI, resistance index = IC_{50} (W2 strain)/IC_{50} (D6 strain); [c] Cytotoxicity against CHO cells (Chinese Hamster Ovary cells); ND: Not determined

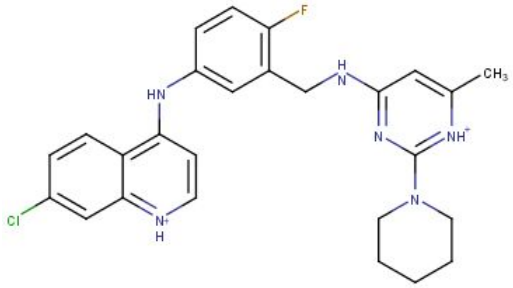
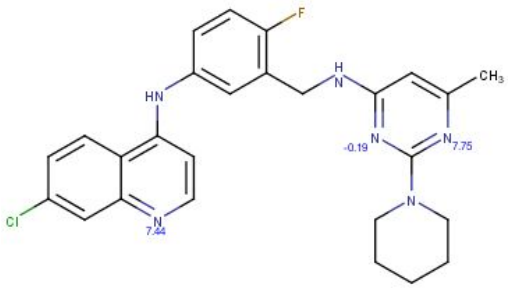
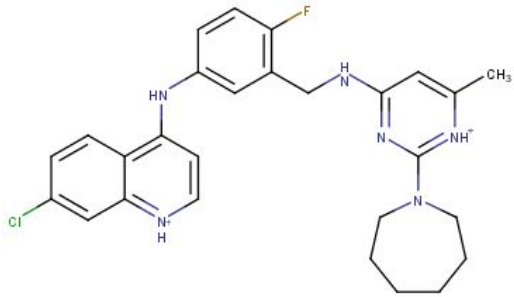
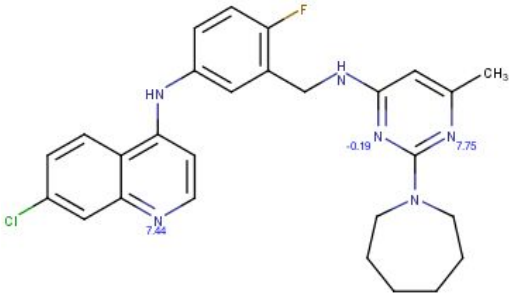
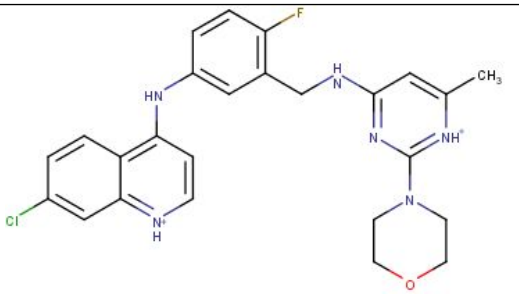
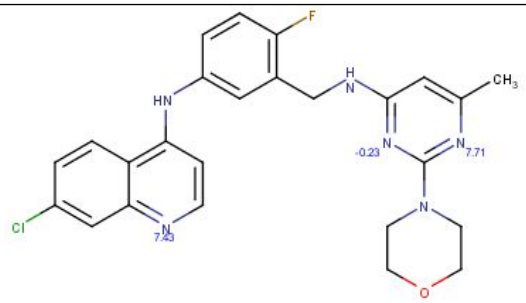
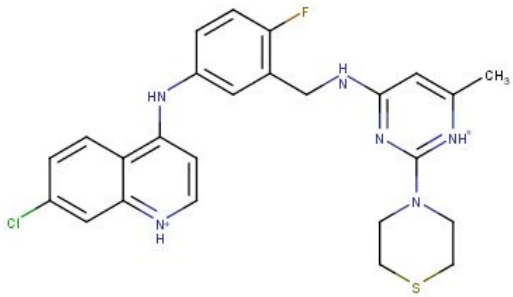
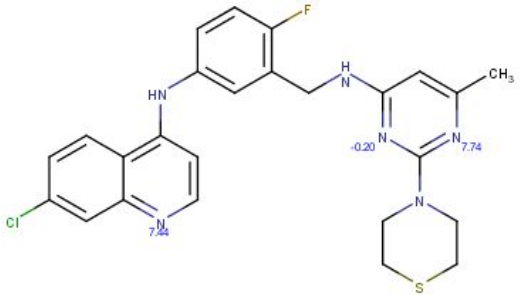
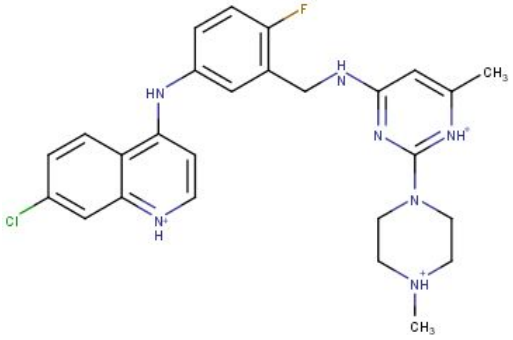
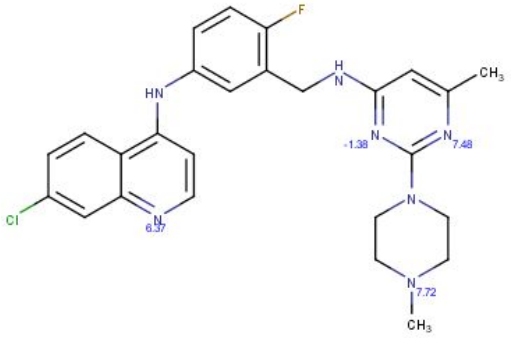
Table S2. Glide docking scores and docking energies (kcal/mol) of best active FAQ-pyrimidines along with the reference DHFR-inhibitors and dihydrofolate bound to wild and mutant PfDHFR-TS binding site

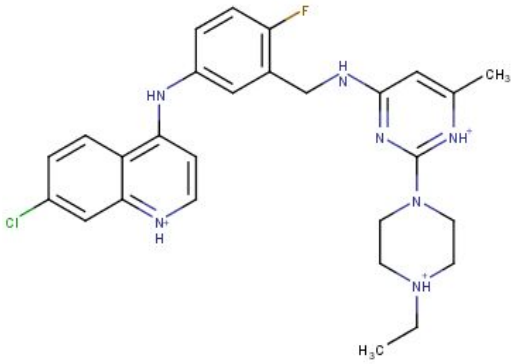
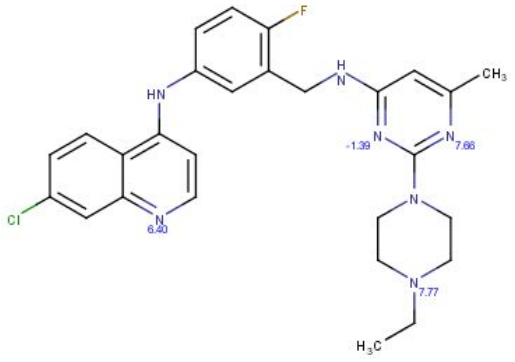
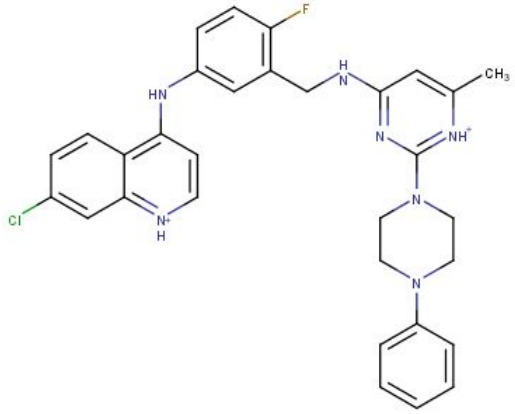
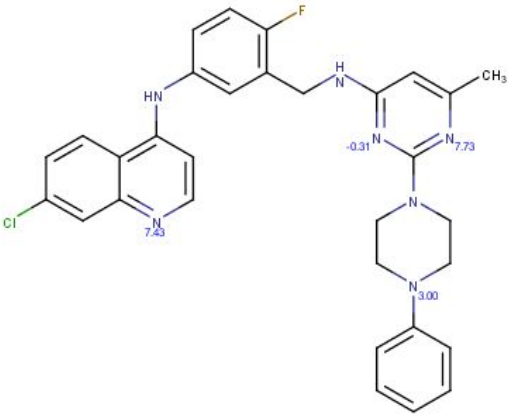
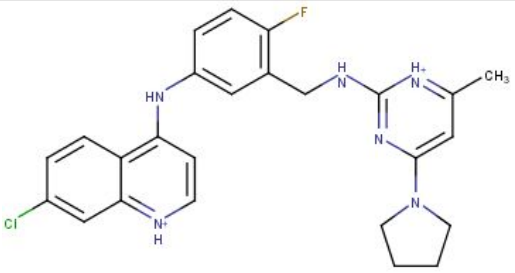
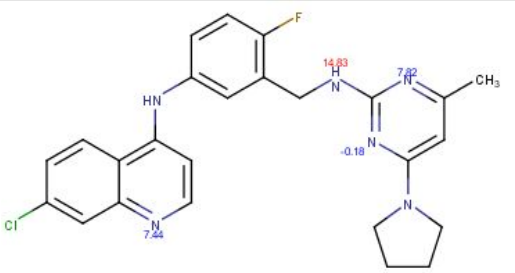
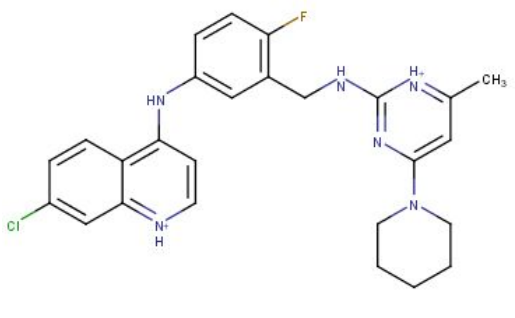
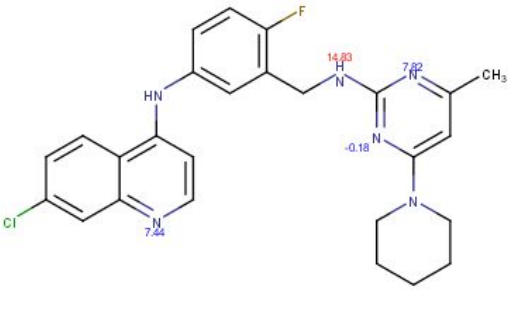
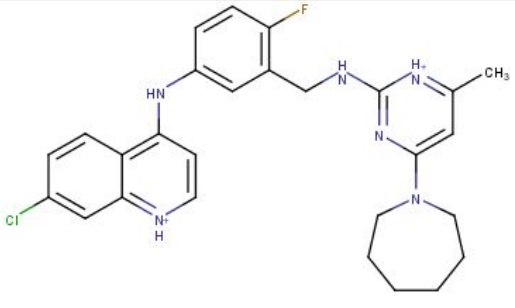
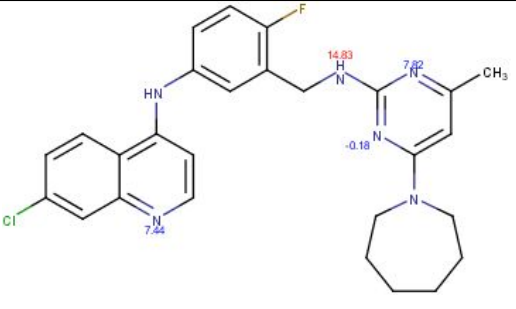
Entry	Docking results			
	wild Pf-DHFR-TS[a]		mutant Pf-DHFR-TS[b]	
	XP GScore	Glide Energy[c]	XP GScore	Glide Energy[c]
8b	-9.49	-60.92	-8.93	-57.70
7f	-9.11	-60.05	-8.05	-56.57
7a	-8.35	-56.01	-7.69	-54.31
8e	-7.49	-53.86	-7.40	-53.37
Dihydrofolate	-11.09	-62.13	-9.07	-60.16
Pyrimethamine	-9.07	-58.96	-9.04	-59.51
Cycloguanil	-8.94	-57.88	-7.97	-54.34
WR99210	-6.92	-46.74	-6.77	-45.97

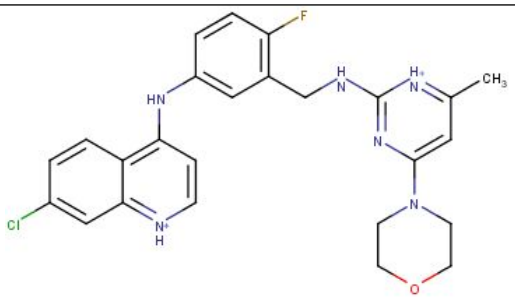
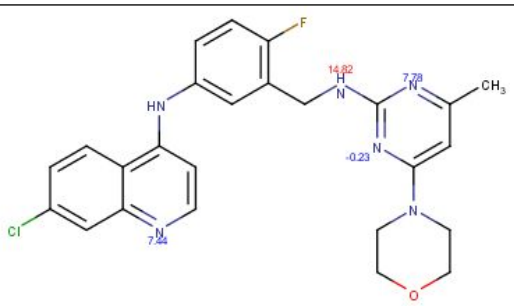
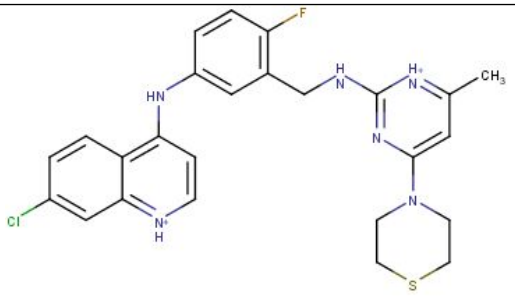
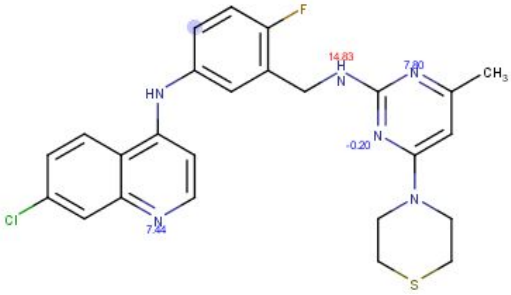
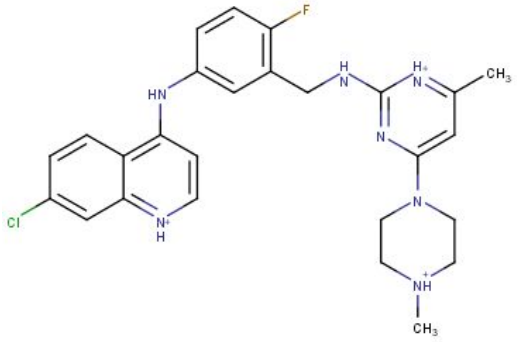
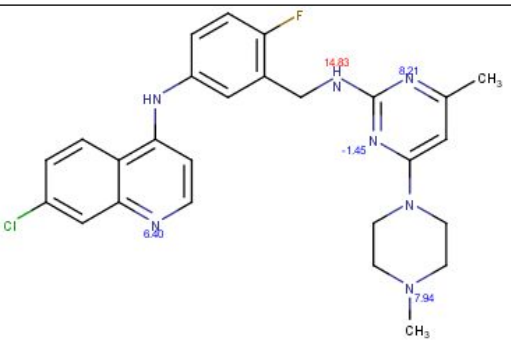
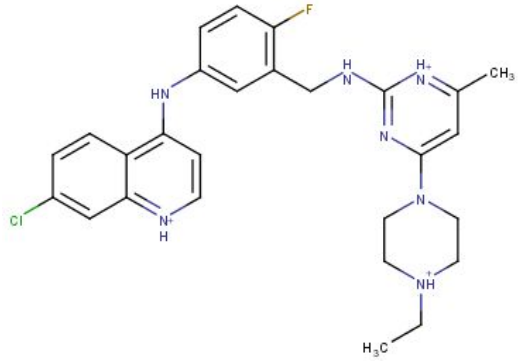
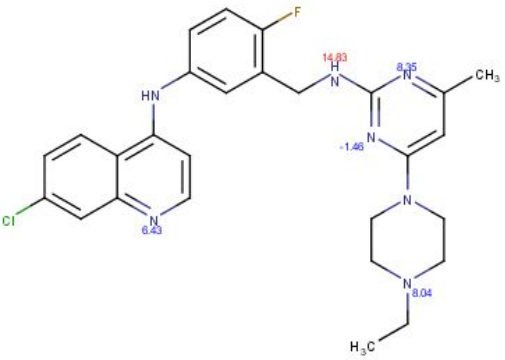
[a]PDB ID: 3QGT; [b]PDB ID: 3QG2; [c]kcal/mol

Table S3. Predicted Protonation species (at pH 5.6) and pKa for of intermediates **3**, **4** and FAQ-pyrimidines

Compound	Prediction of major microspecies at pH 5.6	Predicted pKa
3		
4		
6a		
6b		
7a		

7b		
7c		
7d		
7e		
7f		

7g		
7h		
8a		
8b		
8c		

8d		
8e		
8f		
8g		

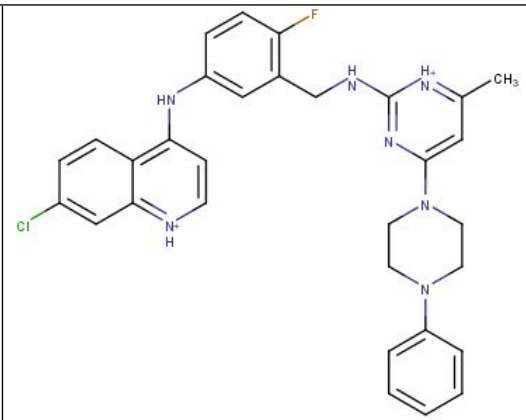
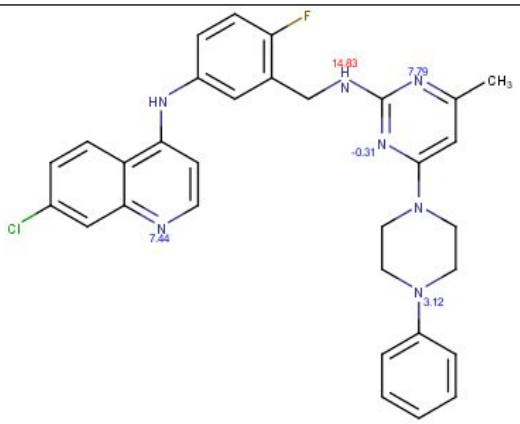
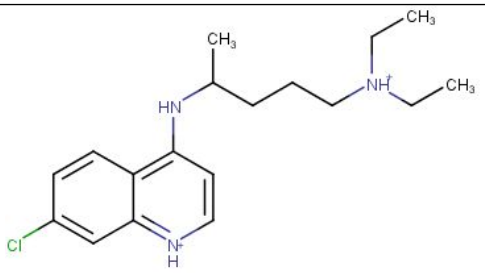
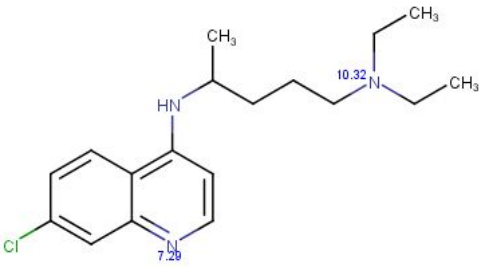
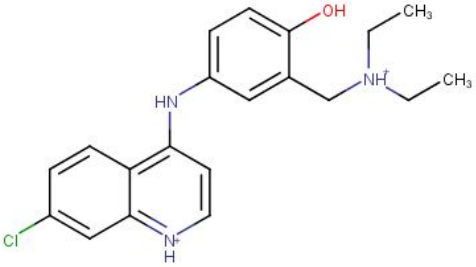
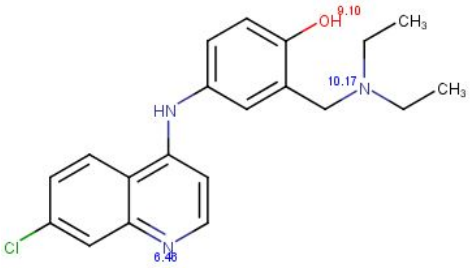
8h		
CQ		
AQ		

Table S4. ADME predictions of FAQ-pyrimidines*

Entry	PHOA	PSA	#rotor	QPPCaco	QPlogBB	QPPMDCK	QPlogKhsa	QPlogHERG
	(>80% high, <25% poor)[a]	(-7.0–200.0)[a]	(0-15)[a]	(<25poor, >500great)[a]	(-3.0 to 1.2)[a]	(<25 poor, >500 great)[a]	(-1.5 to 1.5)[a]	(<-5 causes concern)[a]
7a	100.00	57.42	5	3137.12	-0.10	6817.39	1.35	-7.31
7b	100.00	56.16	5	3312.41	-0.07	7229.03	1.47	-7.28
7f	100.00	62.73	5	667.55	0.20	1416.66	1.20	-8.17
7g	88.83	62.31	6	745.25	0.19	1595.38	1.29	-8.20
8b	100.00	57.64	5	2969.15	-0.13	6426.14	1.46	-7.25
8e	100.00	57.44	5	3044.79	0.00	10000.00	1.37	-7.24

[a] Calculated using QikProp v 3.5. The ranges/recommended values, shown in parentheses, are calculated from 95% of known drugs.

*ADME predictions for the six most active compounds ($IC_{50Dd2\text{-}strain}$ <18 nM) are presented in Table S4. The descriptor for oral drug absorption (PHOA, PercentHumanOralAbsorption), polar surface area (PSA) and number of rotatable bonds (#rotor) were excellent for all the best active molecules. QPPCaco (descriptor for Caco cell permeability), QPPMDCK (estimation of MDCK cell permeability) and QPlogBB (blood/brain partition coefficient) were found to be excellent indicating high bioavailability of the compounds. Except **7c**, rest of the test compounds were predicted to lie within the acceptable range for QPlogKhsa (human serum albumin binding prediction; acceptable range: -1.5 to 1.5). However, the QPlogHERG descriptor (prediction for HERG-K+ channel inhibition) were not satisfactory (QPlogHERG <-5) indicating possible unfavourable cardio side-effects.

Assignment of respective structures to regiomers 6a and 6b:

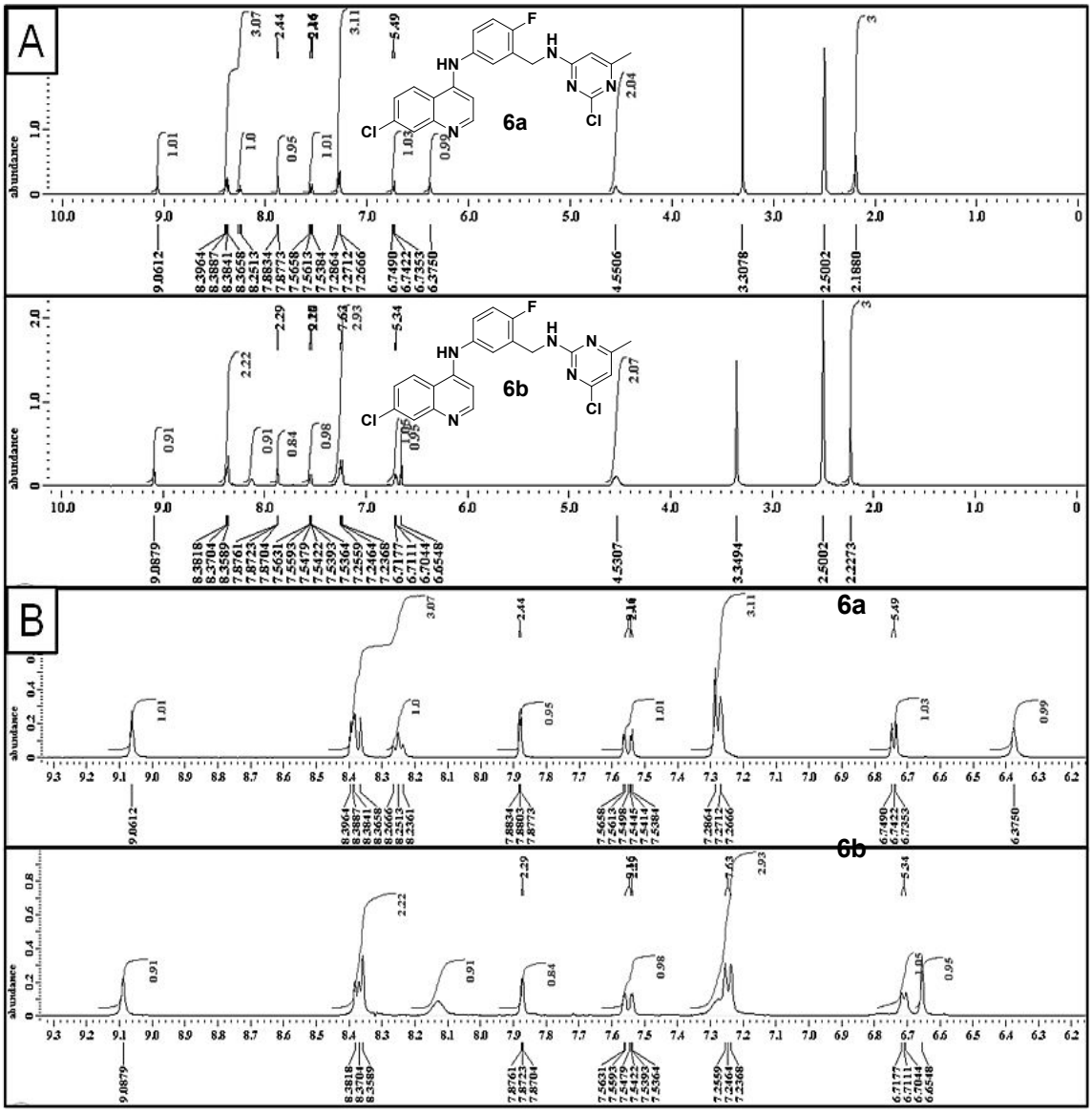


Figure S1. A) ^{1}H-NMR of regiomers **6a** and **6b**; B) Expanded aromatic region

Figure S1 shows the ^{1}H-NMR of the regiomeric intermediates **6a** and **6b**. The regiomers can be identified with their characteristic peak of the lone pyrimidine ring's proton (at its 5th position). In the regiomer **6a**, this proton appears at δ 6.37 ppm while in the case of regiomer **6b**, it appears slightly downfield at δ 6.65 ppm because of the deshielding effect of the adjacent electronegative –Cl atom (at pyrimidine's 4th position). Because of the regiomeric arrangement, in **6a**, the pyrimidine's 5th position proton is adjacent to a –Me group and a secondary –NH group while the –Cl atom is far-off at pyrimidine's 2nd position. Rest of the ^{1}H-NMR peaks of **6a** and **6b** do not show any major changes in their chemical shifts due to the regiochemistry.

Experimental Section

Materials and Methods

All the starting materials and reagents used in this study were purchased from Sigma Aldrich, Alfa Aesar and TCI chemicals, India and were used as received. Analytical grade solvents were used without further purification for the chemical synthesis. The progress of the reaction was monitored by using TLC (Merck Kieselgel 60 F_{254}, 0.2 mm thickness) and visualization was accomplished using iodine, UV light or 1.5% ninhydrin solution in ethanol. All of the reaction intermediates and final compounds were purified over silica gel column chromatography (60-120 mesh silica; elution with 0–10% methanol–chloroform). ^{1}H and ^{13}C NMR spectra were recorded using Jeol Spectrospin spectrometer at 400 MHz and 100 MHz, respectively, and the values of chemical shift are given in parts per million (ppm) on the delta scale (δ). Tetramethylsilane (TMS) was used as an internal reference and DMSO-d_6 or $CDCl_3$ was used as solvent. ^{13}C-NMR peaks were reported to one decimal place. In some cases, ^{13}C NMR peaks were found to overlap with the solvent (DMSO-d_6) peaks. Elemental analysis of the compounds was performed on Elementar analysensysteme vario micro cube analyzer. Bruker-Alpha FT-IR spectrophotometer was used to record IR spectra and the values were expressed in cm^{-1}. Agilent Accurate Mass Q-TOF MS system was used to record mass spectra. Melting points of all the compounds were recorded using EZ-Melt automated melting point apparatus, Stanford Research Systems and are uncorrected. HPLC was conducted on a Waters Alliance HPLC system using Symmetry C18 column (3.5 µm, 4.6 mm X 100 mm). The mobile phase consisted of premixed HPLC grade ACN and water in the varying ratio and degassed prior to operating under isocratic conditions at run time of 20 minutes with 10 µL standard sample injections. All compounds were sufficiently pure (>90%) for biological studies as per their NMR, HPLC and elemental analysis data.

Synthesis and Characterization of compounds

Typical procedure for the synthesis of intermediate 3

A mixture of 4,7-dichloroquinoline (**1**, 10.0 g, 50.49 mmol), 5-amino-2-fluorobenzonitrile (**2**, 5.73 g, 42.08 mmol) in tert-butyl alcohol (100 mL) was refluxed for 6 h. After completion of the reaction, as observed in TLC, the reaction mixture was then cooled down to room temperature. The precipitate obtained was filtered and washed with excess water. The crude-product was crystallized by using ethanol to give **3** [5-((7-chloroquinolin-4-yl)amino)-2-fluorobenzonitrile] in 90% yield. White solid; yield: 90%; mp 280-282 °C; IR (ν_{max}/cm^{-1}, film):2961, 2907, 2228, 1615, 1582, 1500, 1450, 1372, 1232, 1205, 761; ^{1}H NMR (400 MHz; DMSO-d_6) δ (ppm): 8.85 (d, *J* = 9.16 Hz, 1H), 8.60 (d, *J* = 6.71 Hz, 1H), 8.19 (d, *J* = 2.44 Hz, 1H), 8.13-8.11 (m, 1H), 7.91-7.89 (m, 2H), 7.74-7.71 (m, 2H), 6.90 (d, *J* = 7.32 Hz, 1H); anal. calcd for $C_{16}H_9ClFN_3$: C, 64.55; H, 3.05; N, 14.11; found: C, 64.71; H, 3.08; N, 14.08; ESI-HRMS (m/z) calcd for $C_{16}H_{10}ClFN_3$ $(M + H)^+$: 298.0542, found: 298.0547 $(M + H)^+$, 300.0518 $(MH + 2)^+$; HPLC Purity: 98.35%.

Typical procedure for the preparation of intermediate 4

To a suspension of **3** (13.5 g, 45.34 mmol), $CoCl_2.6H_2O$ (21.76 g, 90.69 mmol) in methanol (300 mL) at 0 °C, $NaBH_4$ (17.15 g, 453.40 mmol) was added portion-wisely in 30 minutes. The reaction mixture was then allowed to stir for a further one hour at ambient temperature. After completion of the reaction, as observed by TLC, the excess methanol was evaporated and the residue was diluted with aq. NH_4OH (100 mL) and extracted using 30% isopropanol/chloroform (3x200 mL). The combined organic layer was evaporated and the crude product was purified through an acid-base treatment wherein the crude was first dissolved in 10 % aq. HCl (200 mL) and washed with ethyl acetate (3x100 mL). The acidic layer was then

separated and was basified with 10% aq. NaOH to a pH of 8, wherein a white precipitate of intermediate-**4** appeared. The white ppt. was filtered, washed with water (100 mL) and dried *in vacuo* at 60 °C to yield intermediate **4** [N-(3-(aminomethyl)-4-fluorophenyl)-7-chloroquinolin-4-amine] as a white solid. yield: 83%; mp 229-231 °C; IR (ν_{max}/cm^{-1}, film): 3312, 2985, 2961, 2907, 1611, 1580, 1528, 1475, 1375, 1205, 989, 759; ^{1}H NMR (400 MHz; DMSO-d_6) δ (ppm): 9.20 (br s, 1H), 8.49-8.45 (m, 4H), 7.89 (s, 1H), 7.60-7.55 (m, 2H), 7.38-7.31 (m, 2H), 6.94 (d, *J* = 4.88 Hz, 1H), 4.06 (s, 2H); anal. calcd for $C_{16}H_{13}ClFN_3$: C, 63.69; H, 4.34; N, 13.93; found: C, 63.81; H, 4.37; N, 13.89; ESI-HRMS (m/z) calcd for $C_{16}H_{14}ClFN_3$ $(M + H)^+$: 302.0855, found: 302.0864 $(M + H)^+$, 304.0835 $(MH + 2)^+$; HPLC Purity: 93.98%.

Typical procedure for the synthesis of intermediates 6a and 6b

To a solution of **4** (8 g, 26.51 mmol) and 2,4-dichloro-6-methylpyrimidine (**5**, 4.32 g, 26.51 mmol) in DMF (100 mL), triethylamine (9.25 mL, 66.28 mmol) was added at ambient temperature and the reaction mixture was allowed to stir at 60 °C for 14h. After completion of the reaction, as observed by TLC, the reaction mixture was diluted with ice-cold water (100 mL) and extracted using ethyl acetate (3x100 mL). The combined organic layer was washed repeatedly with water and with brine, separated, dried over anhydrous Na_2SO_4, and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography using 30% ethyl acetate/hexane as the eluent to afford two regioisomers, **6a** (57% yield, major) and **6b** (16% yield, minor).

7-Chloro-N-(3-(((2-chloro-6-methylpyrimidin-4-yl)amino)methyl)-4-fluorophenyl)quinolin-4-amine (6a): Off-white solid; yield: 57%; mp 229-231 °C; IR (ν_{max}/cm^{-1}, film): 3310, 2903, 2840, 1574, 1498, 1431, 1358, 1193, 1081, 841; ^{1}H NMR (400 MHz; DMSO-d_6) δ (ppm): 9.06 (br s, 1H), 8.39-8.36 (m, 2H), 8.26-8.23 (m, 1H), 7.88 (d, *J* = 2.44 Hz, 1H), 7.54 (dd, *J* = 2.44 Hz, 9.16 Hz, 1H), 7.28-7.26 (m, 3H), 6.74 (d, *J* = 5.49 Hz, 1H), 6.37 (s, 1H), 4.55 (s, 2H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 165.65, 163.90, 159.38, 157.94, 155.53, 151.76, 149.49, 148.22, 136.16, 133.92, 127.62, 124.91, 124.31, 123.58, 123.50, 118.09, 116.24, 116.01, 102.86, 101.21, 37.45, 22.86; anal. calcd for $C_{21}H_{16}Cl_2FN_5$: C, 58.89; H, 3.77; N, 16.35; found: C, 59.02; H, 3.79; N, 16.31; ESI-HRMS (m/z) calcd for $C_{21}H_{17}Cl_2FN_5$ $(M + H)^+$: 428.0840, found: 428.0861 $(M + H)^+$, 430.0826 $(MH + 2)^+$; HPLC Purity: 99.05 %.

7-Chloro-N-(3-(((4-chloro-6-methylpyrimidin-2-yl)amino)methyl)-4-fluorophenyl)quinolin-4-amine (6b): Pale-yellow solid; yield: 16%; mp 214-216 °C; IR (ν_{max}/cm^{-1}, film): 3318, 2958, 2913, 1573, 1494, 1437, 1357, 1201, 1085, 853, 702; ^{1}H NMR (400 MHz; DMSO-d_6) δ (ppm): 9.08 (br s, 1H), 8.38-8.35 (m, 2H), 8.14 (br s, 1H), 7.87 (d, *J* = 2.29 Hz, 1H), 7.54 (dd, *J* = 2.29 Hz, 9.16 Hz, 1H), 7.25-7.23 (m, 3H), 6.71 (d, *J* = 5.34 Hz, 1H), 6.65 (s, 1H), 4.53 (s, 2H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 170.09, 162.00, 160.00, 157.89, 155.48, 151.72, 149.48, 148.30, 136.03, 133.96, 127.63, 127.28, 124.93, 124.40, 123.24, 118.10, 116.10, 115.88, 108.67, 101.15, 37.91, 23.28; anal. calcd for $C_{21}H_{16}Cl_2FN_5$: C, 58.89; H, 3.77; N, 16.35; found: C, 59.00; H, 3.80; N, 16.33; ESI-HRMS (m/z) calcd for $C_{21}H_{17}Cl_2FN_5$ $(M + H)^+$: 428.0840, found: 428.0856 $(M + H)^+$, 430.0821 $(MH + 2)^+$; HPLC Purity: 96.76%.

General procedure for the synthesis of FAQ–pyrimidines (7a–h and 8a-h)

To a solution of **6a** or **6b** (2 mmol) in DMF (10 mL), respective cyclic amine (6 mmol, 3 eq.) and K_2CO_3 (6 mmol, 3 eq.) were added and the reaction mixture was allowed to stir at 120 °C for 14 h. Upon the completion of reaction (as inferred through TLC), the reaction mixture was allowed to cool down to the ambient temperature and was diluted with ice-cold water (15 mL). It was then extracted with ethyl acetate

(3 x 50 mL) and the combined organic extract was dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue thus obtained was purified by column chromatography using 0-5% MeOH/$CHCl_3$ as the eluent to afford the respective compounds **7a-h** or **8a–h** in good yields. The characterization data for all the final compounds is detailed as follows:

7-Chloro-N-(4-fluoro-3-(((6-methyl-2-(pyrrolidin-1-yl)pyrimidin-4-yl)amino)methyl)phenyl)quinolin-4-amine (7a):

White solid; yield: 84%; mp 230-232 °C; IR (ν_{max}/cm^{-1}, film): 3253, 2957, 2927, 2868, 1571, 1498, 1454, 1373, 1332, 1244, 1205, 1080, 854, 735, 638; ^{1}H NMR (400 MHz; DMSO-d_6) δ (ppm): 9.06 (br s , 1H), 8.37 (d, *J* = 9.16 Hz, 1H), 8.32 (br s, 1H), 7.87 (s, 1H), 7.54 (dd, *J* = 2.44 Hz, 9.16 Hz, 1H), 7.37-7.33 (m, 2H), 7.23-7.20 (m, 2H), 6.65 (d, *J* = 4.88 Hz, 1H), 5.63 (s, 1H), 4.51 (s, 2H), 3.34 (m, 4H), 2.02 (s, 3H), 1.7 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.94, 162.79, 160.04, 155.64, 151.77, 149.54, 148.35, 135.83, 133.92, 127.67, 124.92, 124.38, 123.31, 123.24, 115.99, 115.77, 101.16, 45.94, 36.93, 24.94, 23.81; anal. calcd for $C_{25}H_{24}ClFN_6$: C, 64.86; H, 5.23; N, 18.15; found: C, 64.99; H, 5.25; N, 18.09; ESI-HRMS (m/z) calcd for $C_{25}H_{25}ClFN_6$ $(M + H)^+$: 463.1808, found: 463.1825 $(M + H)^+$, 465.1802 $(MH + 2)^+$; HPLC Purity: 96.11%.

7-Chloro-N-(4-fluoro-3-(((6-methyl-2-(piperidin-1-yl)pyrimidin-4-yl)amino)methyl)phenyl)quinolin-4-amine (7b):

White solid; yield: 91%; mp 225-227 °C; IR (ν_{max}/cm^{-1}, film): 3274, 2998, 2931, 2852, 1568, 1532, 1490, 1434, 1371, 1326, 1240, 1195, 986, 853, 734, 702; ^{1}H NMR (400 MHz; DMSO-d_6) δ (ppm): 9.05 (br s, 1H), 8.37 (d, *J* = 9.16 Hz, 1H), 8.31 (d, *J* = 4.88 Hz, 1H), 7.86 (d, *J* = 2.44 Hz, 1H), 7.54 (dd, *J* = 2.44 Hz, 9.16 Hz, 1H), 7.36-7.30 (m, 2H), 7.23-7.20 (m, 2H), 6.62 (d, *J* = 4.88 Hz, 1H), 5.63 (s, 1H), 4.49 (s, 2H), 3.56 (m, 4H), 2.02 (s, 3H), 1,44 (m, 2H), 1.30 (m. 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.86, 162.83, 160.99, 158.00, 155.60, 151.77, 149.52, 148.41, 135.87, 133.91, 127.66, 124.91, 124.35, 123.98, 123.31, 118.08, 116.01, 115.786, 101.07, 44.01, 36.97, 25.25, 24.51, 23.86; anal. calcd for $C_{26}H_{26}ClFN_6$: C, 65.47; H, 5.49; N, 17.62; found: C, 65.58; H, 5.51; N, 17.65; ESI-HRMS (m/z) calcd for $C_{26}H_{27}ClFN_6$ $(M + H)^+$: 477.1964, found: 477.1975 $(M + H)^+$, 479.1961 $(MH + 2)^+$; HPLC Purity: 96.60%.

N-(3-(((2-(Azepan-1-yl)-6-methylpyrimidin-4-yl)amino)methyl)-4-fluorophenyl)-7-chloroquinolin-4-amine (7c):

White solid; yield: 87%; mp 218-220 °C; IR (ν_{max}/cm^{-1}, film): 3319, 2924, 2835, 1574, 1532, 1495, 1432, 1374, 1243, 1205, 1080, 855, 733, 644; ^{1}H NMR (400 MHz; $CDCl_3$) δ (ppm): 8.45 (d, *J* = 4.88 Hz, 1H), 8.00 (d, *J* = 1.83 Hz, 1H), 7.42 (d, *J* = 9.16 Hz, 1H), 7.28 (m, 2H), 7.13-7.09 (m, 2H), 6.67 (d, *J* = 5.49 Hz, 1H), 6.60 (br s, 1H), 5.53 (s, 1H), 4.86 (br s, 1H), 4.61 (s, 2H), 3.64 (m, 4H), 2.16 (s, 3H), 1.72 (m, 4H), 1.42 (m, 4H); anal. calcd for $C_{27}H_{28}ClFN_6$: C, 66.05; H, 5.75; N, 17.12; found: C, 66.20; H, 5.75; N, 17.12; ESI-HRMS (m/z) calcd for $C_{27}H_{29}ClFN_6$ $(M + H)^+$: 491.2121, found: 491.2132 $(M + H)^+$, 493.2109 $(MH + 2)^+$; HPLC Purity: 97.75%.

7-Chloro-N-(4-fluoro-3-(((6-methyl-2-morpholinopyrimidin-4-yl)amino)methyl)phenyl)quinolin-4-amine (7d):

White solid; yield: 85%; mp 224-226 °C; IR (ν_{max}/cm^{-1}, film): 3287, 2957, 2923, 2854, 1569, 1491, 1435, 1371, 1237, 1194, 1110, 991, 854, 732, 641; ^{1}H NMR (400 MHz; DMSO-d_6) δ (ppm): 9.06 (br s, 1H), 8.39-8.32 (m, 2H), 7.87 (s, 1H), 7.56-7.46 (m, 2H), 7.32-7.21 (m, 3H), 6.65 (d, *J* = 5.49 Hz, 1H), 5.71 (s, 1H), 4.51 (s, 2H), 3.52-3.48 (m, 8H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.92, 162.87, 161.19, 157.99, 155.59, 151.81, 149.54, 148.37, 135.96, 133.97, 127.69, 124.95, 124.39, 123.32, 123.25, 118.10, 116.06,

115.83, 101.09, 66.05, 43.90, 36.87, 23.78; anal. calcd for $C_{25}H_{24}ClFN_6O$: C, 62.69; H, 5.05; N, 17.55; found: C, 62.85; H, 5.06; N, 17.51; ESI-HRMS (m/z) calcd for $C_{25}H_{25}ClFN_6O$ $(M + H)^+$: 479.1757, found: 479.1770 $(M + H)^+$, 481.1752 $(MH + 2)^+$; HPLC Purity: 94.45%.

7-Chloro-N-(4-fluoro-3-(((6-methyl-2-thiomorpholinopyrimidin-4-yl)amino)methyl)phenyl)quinolin-4-amine (7e):

White solid; yield: 83%; mp 230-232 °C; IR (ν_{max}/cm^{-1}, film): 3281, 2954, 2923, 2852, 1571, 1531, 1485, 1372, 1239, 1203, 1080, 948, 854, 736; ^{1}H NMR (400 MHz; DMSO-d_6) δ (ppm): 9.05 (br s, 1H), 8.36 (d, *J* = 9.16 Hz, 1H), 8.30 (d, *J* = 5.49 Hz, 1H), 7.86 (d, *J* = 1.83 Hz, 1H), 7.54-7.48 (m, 2H), 7.28-7.20 (m, 3H), 6.60 (d, *J* = 5.49 Hz, 1H), 5.68 (s, 1H), 4.48 (s, 2H), 3.89 (m, 4H), 2.36 (m, 4H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.91, 162.81, 160.48, 157.97, 155.58, 151.75, 149.53, 148.38, 135.90, 133.94, 128.08, 127.79, 124.94, 124.36, 123.74, 123.27, 118.07, 116.07, 115.84, 101.01, 45.68, 37.03, 25.77, 23.83; anal. calcd for $C_{25}H_{24}ClFN_6S$: C, 60.66; H, 4.89; N, 16.98; found: C, 60.80; H, 4.91; N, 17.02; ESI-HRMS (m/z) calcd for $C_{25}H_{25}ClFN_6S$ $(M + H)^+$: 495.1528, found: 495.1528 $(M + H)^+$, 497.1504 $(MH + 2)^+$; HPLC Purity: 95.85%.

7-Chloro-N-(4-fluoro-3-(((6-methyl-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl)amino)methyl)phenyl) quinolin-4-amine (7f):

White solid; yield: 87%; mp 280-282 °C; IR (ν_{max}/cm^{-1}, film): 3279, 2933, 2849, 2804, 1577, 1498, 1441, 1369, 1240, 1201, 1000, 854, 795; ^{1}H NMR (400 MHz; DMSO-d_6) δ (ppm): 9.04 (br s, 1H), 8.37-8.30 (m, 2H), 7.86 (s, 1H), 7.53 (d, *J* = 7.93 Hz,1H), 7.41-7.32 (m, 2H), 7.20 (m, 2H), 6.64 (d, *J* = 4.88 Hz, 1H), 5.66 (s, 1H), 4.48 (s, 2H), 3.45 (m, 4H), 2.09-1.98 (m, 10H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.83, 161.05, 158.01, 155.61, 151.82, 149.55, 148.34, 135.86, 127.69, 124.92, 124.37, 123.35, 123.27, 118.11, 116.05, 115.82, 101.08, 54.43, 45.74, 43.14, 37.01, 23.81; anal. calcd for $C_{26}H_{27}ClFN_7$: C, 63.47; H, 5.53; N, 19.93; found: C, 63.60; H, 5.55; N, 19.96; ESI-HRMS (m/z) calcd for $C_{26}H_{28}ClFN_7$ $(M + H)^+$: 492.2073, found: 492.2078 $(M + H)^+$, 494.2059 $(MH + 2)^+$; HPLC Purity: 97.17%.

7-Chloro-N-(3-(((2-(4-ethylpiperazin-1-yl)-6-methylpyrimidin-4-yl)amino)methyl)-4-fluorophenyl)quinolin-4-amine (7g):

White solid; yield: 82%; mp 245-247 °C; IR (ν_{max}/cm^{-1}, film): 3256, 2970, 2925, 2847, 1670, 1490, 1440, 1372, 1346, 1327, 1238, 1195, 1155, 992, 854, 794, 734; ^{1}H NMR (400 MHz; DMSO-d_6) δ (ppm): 9.04 (br s, 1H), 8.37-8.31 (m, 2H), 7.85 (s, 1H), 7.54 (d, *J* = 8.54 Hz, 1H), 7.41-7.33 (m, 2H), 7.20 (m, 2H), 6.64 (d, *J* = 4.88 Hz, 1H), 5.65 (s, 1H), 4.47 (s, 2H), 3.54 (m, 4H), 3.32 (m, 4H), 2.13-2.01 (m, 5H), 0.86 (m, 3H); anal. calcd for $C_{27}H_{29}ClFN_7$: C, 64.09; H, 5.78; N, 19.38; found: C, 64.21; H, 5.80; N, 19.35; ESI-HRMS (m/z) calcd for $C_{27}H_{30}ClFN_7$ $(M + H)^+$: 506.2230, found: 506.2240 $(M + H)^+$, 508.2242 $(MH + 2)^+$; HPLC Purity: 96.53%.

7-Chloro-N-(4-fluoro-3-(((6-methyl-2-(4-phenylpiperazin-1-yl)pyrimidin-4-yl)amino)methyl)phenyl) quinolin-4-amine (7h):

White solid; yield: 80%; mp 240-242 °C; IR (ν_{max}/cm^{-1}, film): 3308, 2955, 2924, 2852, 1573, 1493, 1442, 1373, 1231, 1081, 993, 855, 759, 692; ^{1}H NMR (400 MHz; DMSO-d_6) δ (ppm): 9.04 (br s, 1H), 8.35 (d, *J* = 9.16 Hz, 1H), 8.30 (d, *J* = 5.49 Hz, 1H), 7.84 (d, *J* = 1.83 Hz, 1H), 7.52-7.47 (m, 2H), 7.35 (d, *J* = 4.27 Hz, 1H), 7.24-7.13 (m, 4H), 6.92 (m, 1H), 6.81-6.75 (m, 2H), 6.67 (d, *J* = 5.49 Hz, 1H), 5.70 (s, 1H), 4.51 (s, 2H), 3.70 (m, 4H), 3.01-2.96 (m, 4H), 2.04 (s, 3H); anal. calcd for $C_{31}H_{29}ClFN_7$: C, 67.20; H, 5.28; N, 17.70; found: C, 67.37; H, 5.31; N, 17.74; ESI-HRMS (m/z) calcd for $C_{31}H_{30}ClFN_7$ $(M + H)^+$: 554.2230, found: 554.2233 $(M + H)^+$, 556.2231 $(MH + 2)^+$; HPLC Purity: 96.26%.

7-Chloro-N-(4-fluoro-3-(((4-methyl-6-(pyrrolidin-1-yl)pyrimidin-2-yl)amino)methyl)phenyl)quinolin-4-amine (8a):

White solid; yield: 88%; mp 240-242 °C; IR (ν_{max}/cm^{-1}, film): 3309, 2962, 2924, 2867, 1571, 1498, 1447, 1346, 1260, 1206, 1077, 1017, 853; ^{1}H NMR (400 MHz; $CDCl_3$) δ (ppm): 9.10 (br s, 1H); 8.43 (d, *J* = 9.16 Hz, 1H), 8.37 (br s, 1H); 7.92 (s, 1H), 7.58 (d, *J* = 9.16 Hz, 1H), 7.42 (d, *J* = 4.88 Hz, 1H), 7.26-7.23 (m, 2H), 7.02 (br s, 1H), 6.70 (d, *J* = 5.49 Hz, 1H), 5.66 (s, 1H); 4.55 (s, 2H), 3.39-3.31 (m, 4H), 2.10 (s, 3H), 1.83 (m, 4H); anal. calcd for $C_{25}H_{24}ClFN_6$: C, 64.86; H, 5.23; N, 18.15; found: C, 64.97; H, 5.25; N, 18.18; ESI-HRMS (m/z) calcd for $C_{25}H_{25}ClFN_6$ $(M + H)^+$: 463.1808, found: 463.1817 $(M + H)^+$, 465.1798 $(MH + 2)^+$; HPLC Purity: 99.57%.

7-Chloro-N-(4-fluoro-3-(((4-methyl-6-(piperidin-1-yl)pyrimidin-2-yl)amino)methyl)phenyl)quinolin-4-amine (8b):

White solid; yield: 92%; mp 239-241 °C; IR (ν_{max}/cm^{-1}, film): 3316, 2956, 2920, 2851, 1572, 1497, 1454, 1372, 1244, 1203, 1116, 854, 792, 643; ^{1}H NMR (400 MHz; DMSO-d_6) δ (ppm): 9.04 (br s, 1H), 8.38 (d, *J* = 9.16 Hz, 1H), 8.30 (m, 2H), 7.85 (s, 1H), 7.52 (d, *J* = 7.93 Hz, 1H), 7.33 (d, *J* = 5.49 Hz, 1H), 7.19-7.17 (m, 1H), 6.98 (br s, 1H), 6.62 (d, *J* = 4.88 Hz, 1H), 5.91 (s, 1H), 4.48 (s, 2H), 3.43 (m, 4H), 2.05 (s, 3H), 1.49 (m, 2H), 1.34 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 165.46, 162.42, 161.63, 151.73, 149.51, 148.44, 135.75, 133.88, 129.05, 128.89, 127.63, 124.88, 124.37, 123.70, 122.97, 118.04, 115.81, 115.58, 101.00, 79.19, 44.31, 37.66, 25.03, 24.30, 23.83; anal. calcd for $C_{26}H_{26}ClFN_6$: C, 65.47; H, 5.49; N, 17.62; found: C, 65.61; H, 5.52; N, 17.64; ESI-HRMS (m/z) calcd for $C_{26}H_{27}ClFN_6$ $(M + H)^+$: 477.1964, found: 477.1976 $(M + H)^+$, 479.1951 $(MH + 2)^+$; HPLC Purity: 97.64%.

N-(3-(((4-(Azepan-1-yl)-6-methylpyrimidin-2-yl)amino)methyl)-4-fluorophenyl)-7-chloroquinolin-4-amine (8c):

White solid; yield: 87%; mp 230-232 °C; IR (ν_{max}/cm^{-1}, film): 3343, 2953, 2923, 2852, 1593, 1572, 1497, 1434, 1371, 1242, 1206, 1080, 854, 789; ^{1}H NMR (400 MHz; DMSO-d_6) δ (ppm): 9.05 (br s, 1H), 8.37 (d, *J* = 9.16 Hz, 1H), 8.27 (d, *J* = 3.81 Hz, 1H), 7.85 (s, 1H), 7.53 (d, *J* = 9.16 Hz, 1H), 7.30 (d, *J* = 5.34 Hz, 1H), 7.21-7.05 (m, 3H), 6.58 (m, 1H), 5.76 (s, 1H), 4.46 (s, 2H), 3.42 (m, 4H), 2.04 (s, 3H), 1.54-1.28 (8H); anal. calcd for $C_{27}H_{28}ClFN_6$: C, 66.05; H, 5.75; N, 17.12; found: C, 66.20; H, 5.75; N, 17.12; ESI-HRMS (m/z) calcd for $C_{27}H_{29}ClFN_6$ $(M + H)^+$: 491.2121, found: 491.2126 $(M + H)^+$, 493.2105 $(MH + 2)^+$; HPLC Purity: 98.01%.

7-Chloro-N-(4-fluoro-3-(((4-methyl-6-morpholinopyrimidin-2-yl)amino)methyl)phenyl)quinolin-4-amine (8d):

White solid; yield: 88%; mp 255-257 °C; IR (ν_{max}/cm^{-1}, film): 3253, 2929, 2850, 1571, 1498, 1439, 1370, 1207, 1081, 982, 854, 790, 621; ^{1}H NMR (400 MHz; DMSO-d_6) δ (ppm): 9.03 (br s, 1H), 8.37 (d, *J* = 9.16 Hz, 1H), 8.31 (d, *J* = 5.49 Hz, 1H), 7.86 (s, 1H), 7.53 (dd, *J* = 9.16 Hz, 2.44 Hz, 1H), 7.32 (d, *J* = 5.49 Hz, 1H), 7.22-7.18 (m, 2H), 7.05 (br s, 1H), 6.63 (d, *J* = 5.49 Hz, 1H), 5.93 (s, 1H), 4.49 (s, 2H), 3.52 (m, 4H), 3.41 (m, 4H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 166.00, 163.10, 161.60, 158.04, 155.65, 151.82, 149.52, 148.55, 135.86, 134.06, 128.98, 128.82, 127.66, 125.02, 124.43, 123.80, 123.12, 118.12, 115.95, 115.72, 101.11, 65.89, 43.87, 38.80, 23.92 ; anal. calcd for $C_{25}H_{24}ClFN_6O$: C, 62.69; H, 5.05; N, 17.55; found: C, 62.81; H, 5.07; N, 17.58; ESI-HRMS (m/z) calcd for $C_{25}H_{25}ClFN_6O$ $(M + H)^+$: 479.1757, found: 479.1762 $(M + H)^+$, 481.1748 $(MH + 2)^+$; HPLC Purity: 95.15%.

7-Chloro-N-(4-fluoro-3-(((4-methyl-6-thiomorpholinopyrimidin-2-yl)amino)methyl)phenyl)quinolin-4-amine (8e):

White solid; yield: 83%; mp 250-252 °C; IR (ν_{max}/cm^{-1}, film): 3254, 2953, 2923, 2853, 1568, 1493, 1432, 1368, 1204, 1080, 943, 854, 790, 734; ^{1}H NMR (400 MHz; DMSO-d_6) δ (ppm): 9.10 (br s, 1H), 8.37 (d, *J* = 9.16 Hz, 1H), 8.29 (d, *J* = 4.58 Hz, 1H), 7.84 (s, 1H), 7.52 (d, *J* = 9.16 Hz, 1H), 7.30-7.18 (m, 4H), 6.58 (br s, 1H), 5.96 (s, 1H), 4.45 (s, 2H), 3.79 (m, 4H), 2.38 (m, 4H), 2.08 (s, 3H); anal. calcd for $C_{25}H_{24}ClFN_6S$: C, 60.66; H, 4.89; N, 16.98; found: C, 60.81; H, 4.92; N, 16.95; ESI-HRMS (m/z) calcd for $C_{25}H_{25}ClFN_6S$ (M + H)$^+$: 495.1528, found: 495.1539 (M + H)$^+$, 497.1516 (MH + 2)$^+$; HPLC Purity: 98.10%.

7-Chloro-N-(4-fluoro-3-(((4-methyl-6-(4-methylpiperazin-1-yl)pyrimidin-2-yl)amino)methyl)phenyl) quinolin-4-amine (8f):

White solid; yield: 85%; mp 258-260 °C; IR (ν_{max}/cm^{-1}, film): 3316, 2959, 2909, 2849, 1596, 1575, 1437, 1375, 1274, 1238, 1210, 1172, 1079, 985, 822; ^{1}H NMR (400 MHz; DMSO-d_6) δ (ppm): 9.04 (br s, 1H), 8.37 (d, *J* = 9.16 Hz, 1H), 8.31 (d, *J* = 5.49 Hz, 1H), 7.86 (d, *J* = 2.44 Hz, 1H), 7.52 (dd, *J* = 9.16 Hz, 2.44 Hz, 1H), 7.33 (d, *J* = 4.88 Hz, 1H), 7.20-7.18 (m, 2H), 7.06 (br s , 1H), 6.63 (d, *J* = 4.88 Hz, 1H), 5.93 (s, 1H), 4.47 (s, 2H), 3.43 (m, 4H), 2.16 (m, 4H), 2.05 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 165.73, 162.72, 161.58, 151.76, 149.45, 148.46, 135.75, 133.93, 128.78, 127.61, 124.91, 124.35, 123.02, 123.84, 122.99, 118.06, 115.84, 101.06, 54.15, 45.62, 43.22, 37.72, 23.87; anal. calcd for $C_{26}H_{27}ClFN_7$: C, 63.47; H, 5.53; N, 19.93; found: C, 63.63; H, 5.56; N, 19.90; ESI-HRMS (m/z) calcd for $C_{26}H_{28}ClFN_7$ (M + H)$^+$: 492.2073, found: 492.2085 (M + H)$^+$, 494.2061 (MH + 2)$^+$; HPLC Purity: 98.15%.

7-Chloro-N-(3-(((4-(4-ethylpiperazin-1-yl)-6-methylpyrimidin-2-yl)amino)methyl)-4-fluorophenyl)quinolin-4-amine (8g):

White solid; yield: 81%; mp 262-264 °C; IR (ν_{max}/cm^{-1}, film): 3212, 2955, 2905, 2809, 1595, 1575, 1536, 1437, 1374, 1244, 1080, 986, 825, 782; ^{1}H NMR (400 MHz; DMSO-d_6) δ (ppm): 9.07 (br s, 1H), 8.37-8.31 (m, 2H), 7.94-7.86 (m, 1H), 7.54 (m, 1H), 7.33-7.19 (m, 4H), 6.64 (br s, 1H), 5.93 (s, 1H), 4.46 (s, 2H), 3.35 (m, 8H), 2.19-2.05 (m, 5H), 0.90 (m, 3H); anal. calcd for $C_{27}H_{29}ClFN_7$: C, 64.09; H, 5.78; N, 19.38; found: C, 64.25; H, 5.81; N, 19.42; ESI-HRMS (m/z) calcd for $C_{27}H_{30}ClFN_7$ (M + H)$^+$: 506.2230, found: 506.2235 (M + H)$^+$, 508.2223 (MH + 2)$^+$; HPLC Purity: 97.81%.

7-Chloro-N-(4-fluoro-3-(((4-methyl-6-(4-phenylpiperazin-1-yl)pyrimidin-2-yl)amino)methyl)phenyl) quinolin-4-amine (8h):

White solid; yield: 79%; mp 248-250 °C; IR (ν_{max}/cm^{-1}, film): 3330, 2957, 2921, 2853, 1590, 1573, 1498, 1437, 1375, 1234, 1206, 986, 856, 789, 728; ^{1}H NMR (400 MHz; DMSO-d_6) δ (ppm): 9.07 (br s, 1H), 8.38-8.27 (m, 2H), 7.84 (s, 1H), 7.52 (d, *J* = 8.39 Hz, 1H), 7.35 (s, 1H), 7.23-7.18 (m, 5H), 6.85-6.75 (m, 3H), 6.65 (d, *J* = 4.58 Hz, 1H), 6.01 (br s, 1H), 4.48 (s, 2H), 3.60 (m, 4H), 3.02 (m, 4H), 2.08 (s, 3H); anal. calcd for $C_{31}H_{29}ClFN_7$: C, 67.20; H, 5.28; N, 17.70; found: C, 67.35; H, 5.31; N, 17.72; ESI-HRMS (m/z) calcd for $C_{31}H_{30}ClFN_7$ (M + H)$^+$: 554.2230, found: 554.2241 (M + H)$^+$, 556.2223 (MH + 2)$^+$; HPLC Purity: 98.71%.

Assay for *in vitro* antimalarial activity

Activity was determined against both chloroquine-sensitive isolate of the human malaria parasite (Plasmodium falciparumNf54) and chloroquine-resistant isolate (P. falciparum Dd2). Parasites were maintained in continuous culture using the method of Trager and Jensen[1] with modifications. Growth medium was supplemented with Albumax II (Gibco), a bovine serum albumin preparation, instead of human serum. Cultures did not exceed 4% haematocrit and parasitemia was diluted to 1% when the cultures were in the trophozoite stage. The compounds were tested in triplicate on at least three occasions

in vitro against the human malaria parasite. Compounds were prepared to 20 mg/ml stock solutions in dimethyl sulfoxide and sonicated for 10 minutes to enhance solubility. Compounds which did not dissolve completely were tested as a suspension. Stock solutions were stored at -20 ^{o}C until use. For the in vitro evaluation, dilutions to the desired starting concentration of each compound were prepared in complete medium immediately prior to use on each occasion. Dose-response experiments were carried out in both isolates in order to determine the IC_{50} value of each compound. The experiment was conducted using 2% parasitemia and 1% haematocrit in the plate. Compounds were prepared to double the desired highest starting concentration in a 96-well plate and then serially diluted 2-fold in complete medium to produce a wide range of different concentrations, to which an equivalent volume of prepared parasite stock was added, yielding the desired concentration of each compound. An erythrocyte control and a drug-free parasite control were included for each row, representing 0% and 100% parasite survival respectively. Plates were housed in airtight chambers containing 4% CO_2 and 3% O_2 in nitrogen and left for 48 hours at 37 ^{o}C. Quantitative assessment of antimalarial activity was determined from the dose-response experiments using the parasite lactate dehydrogenase assay described by Makler *et al*.[2] The IC_{50}-values were obtained using a non-linear dose-response curve-fitting analysis via Graphpad Prism v.4.0 software.

Procedure for heme binding studies

Monomeric Heme:

A 1.0 mM stock solution of heme was prepared by dissolving 6.5 mg hemin in 10 ml HPLC grade DMSO and stored at 4 ^{o}C in the dark until used. A 10 µM working solution of monomeric heme was prepared daily by mixing 100µL of the heme stock solution with 1mL 0.2 M HEPES buffer (pH 7.4) and making it up to 10ml with double distilled deionized water. Stock solution of compound **12c** (1.0 mM) was prepared in AR grade DMSO and was used for titration experiment. Heme (10 µM) was titrated with increasing concentrations (0.5-70 µM) of compound **12c**. Following each addition sample was mixed & absorbance was recorded at 402 nm. Working solutions of drug and of monomeric heme at pH 5.4 were prepared in a similar manner, employing MES-buffer (pH 5.4) instead of HEPES-buffer and experiment was conducted in the same way as described earlier.

µ-Oxodimeric heme:

A stock solution of dimeric heme (1.0 mM) was prepared by dissolving Hemin chloride (6.5 mg) in 10 mL of 0.1 M aq. NaOH and was sonicated for 30 min to ensure complete dissolution. It was then diluted to 10µM in Phosphate buffer (20mM, pH 5.8) to get the working solution of dimeric heme. Titration of this solution with compound **12c** (1.0 mM) was performed by successive addition of aliquots of stock solution of 7d (0.5-70 µM) and absorbance at 362 nm was recorded.

Binding Stoichiometry:

Job's method of continuous variation was used to determine the binding stoichiometries of drug (7d) with monomeric & µ-oxodimeric heme, employing UV/Visible spectrophotometry. The concentration of 7d & heme in solution was kept constant and change in absorbance at 402 nm (monomeric)/362 nm (dimeric) was monitored as a function of the mole fraction.

Procedure for Molecular docking studies

The 2D structures of all the compounds were drawn using ChemBioDraw Ultra 12.0 (www.cambridgesoft.com). Ligprep module of Schrödinger was used to generate the 3D structures with the

lowest energy. Partial atomic charges were computed using the OPLS_2005 force field. The correct Lewis structure, tautomers and ionization states (pH 7.0±2.0) for each of the ligands were generated and optimized with default settings (Ligprep 2.5, Schrödinger, LLC, New York, NY, 2012).The 3D crystal structures of wild type *Pf*-DHFR-TS (PDB ID:3QGT; resolution 2.30 Å) and quadruple mutant (N51I+C59R+S108N+I164L) *Pf*-DHFR-TS (PDB ID:3QG2; resolution: 2.30 Å), were retrieved from protein data bank (www.rcsb.org). The proteins were prepared for docking using Protein Preparation Wizard (Maestro 10.0 Schrödinger, LLC, New York, NY, 2012). Bond order and formal charges were assigned and hydrogen atoms were added to the crystal structure. Further to refine the structure OPLS-2005 force field parameter was used to alleviate steric clashes. The location of co-crystalized ligand Pyrimethamine in both wild and mutant protein structures were used to choose the center and size of the receptor grid, which was generated using Glide 5.8 (Schrödinger, LLC, New York, NY, 2012) with default settings for all parameters. The grid size was chosen sufficiently large to include all active site residues involved in substrate binding. The cofactor, NADH in the *Pf*-DHFR-TS wild and mutant structures was also considered as part of the receptor proteins. All ligand conformers were docked to each of the receptor grid files (*Pf*-DHFR-TS wild and mutant structures) using Glide extra precision (XP) mode. Default settings were used for the refinement and scoring.

Procedure for *in silico* ADME predictions

The pharmacokinetic profile of compounds in the study was predicted by using the program Qikprop v3.5 (Schrödinger, Inc.). All the compounds were prepared in neutralized form for the calculation of pharmacokinetic properties by QikProp using Schrodinger's Maestro Build module and LigPrep, saved in SD format. The program QikProp utilizes the method of Jorgensen[3] to compute pharmacokinetic properties and descriptors such as octanol/water partitioning coefficient, aqueous solubility, brain/blood partition coefficient, intestinal wall permeability, plasma protein binding etc.

Procedure for *in vitro* metabolic stability

Materials and method

Human liver microsomes (HLM) was purchased from ThermoFisher Scientific (lot No. PL050D-A, USA). Magnesium chloride hexahydrate salt was purchased from Qualigens, Mumbai, India. NaDPH tetrasodium salt was purchased from Sigma Aldrich. LC-MS grade formic acid (FA), acetonitrile and methanol were procured from Merck (Darmstadt, Germany). Fresh, ultrapure water of 18.2 MΩ resistance from a Milli-Q Gradient system (Millipore Corp., Bedford, MA, USA) was used for the study. All other chemicals and solvents were of the highest analytical grades available.

Preparation of reagents

1) **Potassium phosphate buffer (PPB, 100mM, pH 7.4):** An accurate amount of 1.212g of dipotassium hydrogen phosphate and 0.414g of potassium dihydrogen phosphate were weighed using calibrated digital weighing balance (Sartorius, USA) and transferred into 100mL volumetric flask. The powder was dissolved in 80mL ultrapure water. The pH of solution was adjusted to 7.4 using 50% (v/v) potassium hydroxide solution. Finally, the volume was made up to 100mL with ultrapure water followed by filtration using Whatman filter paper (120mm) to produce 100mM potassium phosphate buffer.

2) **Test drug:** Test compound was weighed accurately and dissolved in pure acetonitrile to produce concentration of 1mg/mL (2.032mM). This solution was diluted with 50% (v/v) acetonitrile in ultrapure

water to produce 1000µM concentration. Further this solution was diluted 10times with 50% (v/v) acetonitrile in 100mM PPB (pH 7.4) to produce working solution having100µM concentration which was used for the reaction.

3) **Magnesium chloride (100mM):** Accurately weighed amount of 20.327mg of magnesium chloride was dissolved in 1mL of ultrapure water to produce 100mM concentration.

4) **Nicotinamide adenine dinucleotide phosphate, NADPH- (20mM):** An accurately weighed 16.6mg of NADPH tetrasodium salt equivalent to its base was dissolved in 1mL of PPB (pH 7.4) to produce concentration of 20mM which was used for the reaction. This solution was prepared before incubation and kept under ice and in dark condition during experiment.

5) **Incubation mixture:** The incubation mixture consists of magnesium chloride and PPB (pH 7.4). This was prepared by diluting 334µL of magnesium chloride solution (100mM) upto final volume of 20mL with PPB (pH 7.4).

6) **Human liver microsomes (HLM):** Human liver microsomes vial (20mg/mL) was thawed on ice on the day of the experiment. After thawing, it was diluted 10 fold with PPB (pH 7.4) to produce 2mg/mL concentration and maintained on ice during experiment.

7) **Reaction stop solution:** Pure acetonitrile (ACN) was used to stop the microsomal reaction. This solvent was kept under ice during experiment.

Methodology

The experimental procedure was divided into three sections:

Step 1- Pre-incubation of human liver microsomes (HLM) with test compound

For the total volume of 190µL, an accurately measured volume of 120µL of the incubation mixture was transferred in 1.75mL microcentrifuge tube (MCT) and mixed with 50µL of HLM (2mg/mL). To this solution, an aliquot of 20µL of test compound (100µM) was added and pipette mixed. This solution was pre-incubated at 37±0.5°C for 5min in calibrated water bath.

Step 2- Incubation reaction mixture with and without co-factor (NADPH)

After pre-incubation all the tubes at 37±0.5°C for 5min, 10µL of 20mM NADPH solution was added to the reaction mixture represents NADPH dependent group whereas 10µL of PPB (pH 7.4) was added to the reaction mixture represents NADPH independent group. After addition, the solution was gently mixed and T0 (0min) sample amounting to volume of 20µL was transferred into another MCT and immediately 100µL of ice cold ACN was added to stop the reaction. The volume was replaced with same amount of incubation mixture and kept for incubation at 37±0.5°C for 60min with sampling interval at 5, 10, 15, 30 and 60min.

Step 3- Stop reaction

At the end of respective incubation period, an amount of 20µL was transferred into another MCT and reaction was stopped by adding 100µL ice cold ACN. All resulting solutions at indicated time points were vortexed using cyclomixer for 1min and centrifuged at 10,000g for 5min. All samples were kept at -80°C until analysis using LC-MS/MS. The experiment was conducted in triplicates for each time points.

LC-MS/MS analysis

Instrumentation

LC-ESI-MS/MS experiments were performed using a triple quadrupole tandem mass spectrometer (4000 Q-Trap, AB Sciex, Foster City, CA, USA) coupled with high performance liquid chromatography system (HPLC, Agilent Technologies, 1260 Infinity, Santa Clara, CA, USA) consisted of quaternary pump (G1311C), multisampler (G7167A), thermostatted column compartment (G1316A) with variable wavelength UV detector (G1314F) and online degasser. All the parameters of tandem mass spectrometer and HPLC were controlled by Analyst software, version 1.5.2 (AB Sciex, Foster City, CA, USA) and OpenLAB control panel software (Agilent Technologies, 1260 Infinity, Santa Clara, CA, USA), respectively.

Chromatographic conditions

Chromatographic separation was achieved in Atlantis T3 analytical column (75 x 4.6mm, 3.5µm) using gradient mobile phase combinations consisting of solvent A (18.2MΩ milliQ with 0.1% FA), solvent B (acetonitrile with 0.1%FA) and solvent C (5mM ammonium formate) pumped at a flow rate of 0.5mLmin^{-1}. These compounds were eluted by using an optimized linear gradient starting at 30:10:60 for A:B:C which was maintained for initial 2 min. After 6.0 min it had reached to 10:50:40 which was maintained till 10min, at 11.5 min it had reached to 0:60:40 and maintained till 14 min and was equilibrated back to starting conditions at 16.0 min and kept constant till 20min.Total run time of the method was of 20min with post run equilibration time of 2min. The temperature of autosampler tray and the column oven were maintained at 10±1°C and 40±1°C, respectively and samples were injected at a volume of 5µL for analysis.

Table 1: Optimized chromatographic conditions for LC-MS/MS analysis

Time (min)	Solvent A (%)	Solvent B (%)	Solvent C (%)	Flow rate (mL/min)
0.0	30.0	10.0	60.0	0.5
2.0	30.0	10.0	60.0	0.5
6.0	10.0	50.0	40.0	0.5
10.0	10.0	50.0	40.0	0.5
11.5	0.0	60.0	40.0	0.5
14.0	0.0	60.0	40.0	0.5
16.0	30.0	10.0	60.0	0.5
20.0	30.0	10.0	60.0	0.5

Mass spectrometer conditions

The mass spectrometer was operated with electrospray ionization (ESI) source in positive ion mode using Turbo Ion Spray source (AB Sciex, Foster City, CA, USA). Full scan enhanced mass spectra (EMS parent ion scan) and the fragment ion spectra were acquired. The source dependent parameters that were optimized and maintained as curtain gas (30 psi), ion spray voltage (5000eV), turbo heater temperature (500°C), gas 1 (30psi) and gas 2 (60psi). Multiple reaction monitoring (MRM) mode was used for the quantification of test compound (7F) using verapamil as internal standard. Quantification of test compound (7F) was performed using precursor-to-product ion transition m/z 492.2/435.2 (transition 1) and m/z 492.2/285.2 (transition 2). The mass transition used for internal standard (verapamil) was m/z 455.3/165.3. Compound dependent parameters such as declustering potential (DP), entrance potential (EP), collision energy (CE) and cell exit potential (CXP) for 7F transition 1 and transition 2 were optimized as 109/10/41.6/6 volts and 71/10/53/6 volts, respectively. Compound dependent parameters (DP, EP, CE, CXP) for IS was optimized as 100/7.3/39.7/3.3 volts.

Preparation of standards and samples-

An accurately weighed amount of test compound was dissolved in pure ACN to produce standards stock solution having concentration of 1mg/mL. An aliquot of 10µL was mixed with 990µL of 50%(v/v) ACN to produce 10µg/mL solution. From this solution, 40µL was mixed with 960µL 50%(v/v) ACN to produce working solution of 400ng/mL which was serially diluted to produce the standard calibrators ranging from 3.125-400ng/mL. An aliquot of 50µL of standard calibrators were mixed with 200µL of extraction solvent and centrifuged at 7840g for 2min. The samples were 10 fold diluted with 50%(v/v) ACN and mixed with 200µL of extraction solvent followed by centrifugation at 7840g for 2min. The supernatant amounting to the volume of 150µL was subjected for LC-MS/MS analysis. Extraction solvent consists of 50%(v/v) ACN with 0.1% (v/v) formic acid and 2ng/mL verapamil as internal standard. Appropriate dilution factor was multiplied to get the exact values at each time points.

The calibration curve (analyte peak height/IS peak height ratio) was constructed by using 6-8 calibration points prepared in the range of 3.125-400ng/mL. The linearity of the calibration curves was calculated where a correlation coefficient (R2) of 0.99 or better was selected. The concentration of drug was calculated from these ratios of the peak heights.

Metabolism parameter calculations

The percentage remaining (disappearance rate) was calculated based on the experimental value at respective time points and plotted as XY plot. The % remaining was transformed to natural logarithm (Ln) and plotted with respect to the time. The slope of the curve was obtained by applying linear trendline in Microsoft excel sheet. Elimination rate constant was calculated as –(slope). Half-life ($t_{1/2}$, min) was calculated as Ln2/-(slope). Intrinsic clearance (CL_{int}, µL/min/mg) was calculated as (Ln2 x 1000)/(half-life x protein concentration).

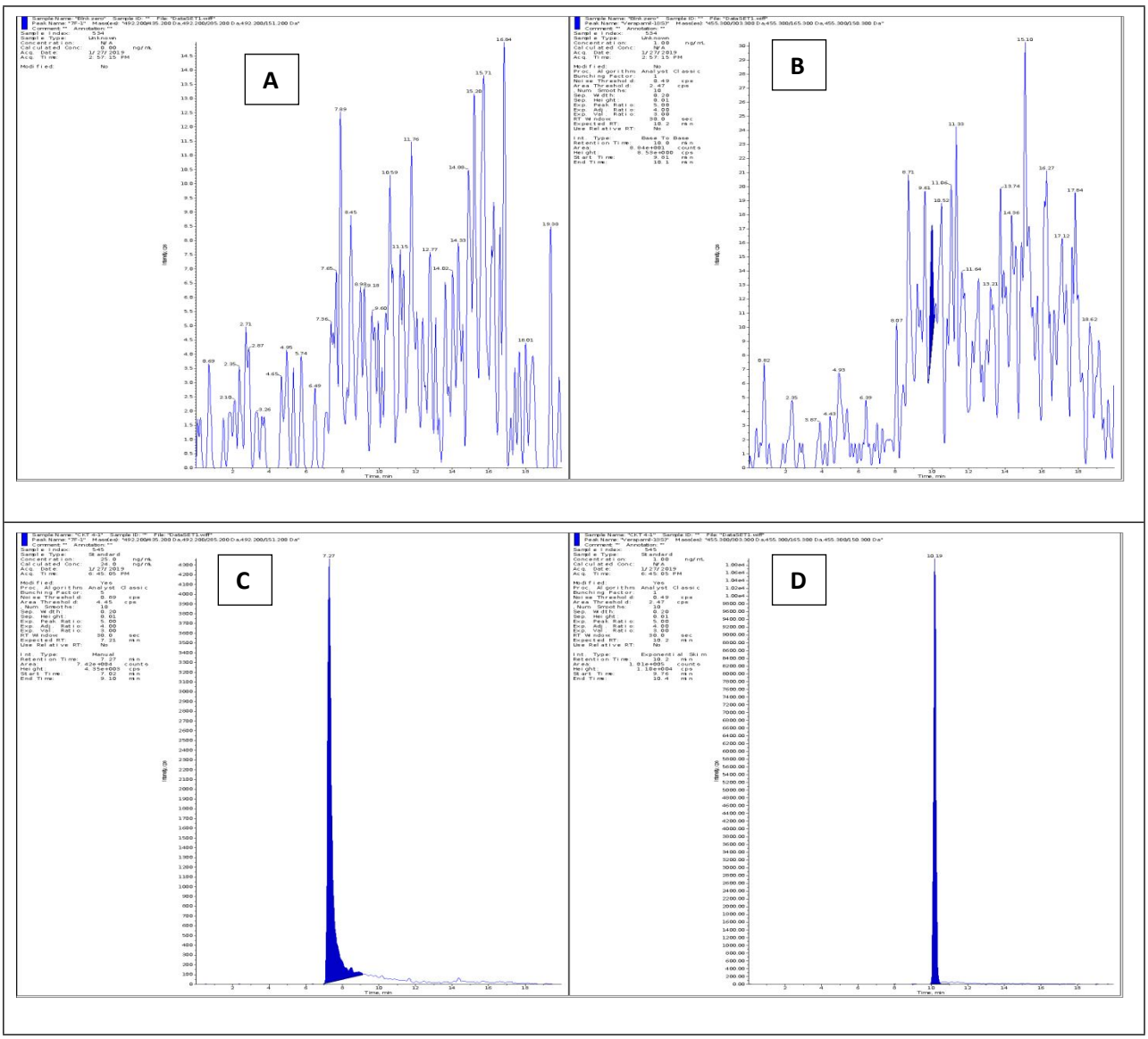
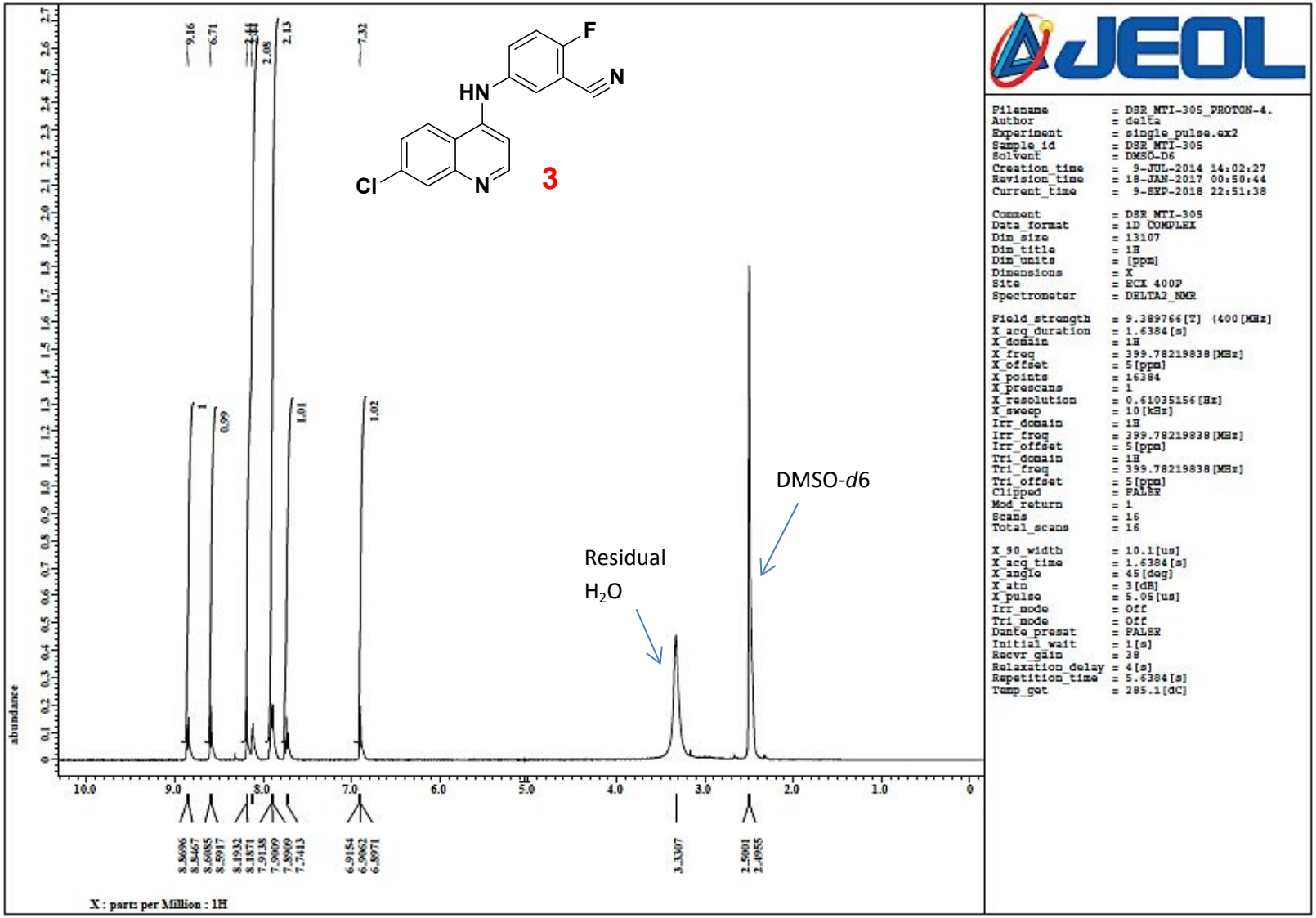
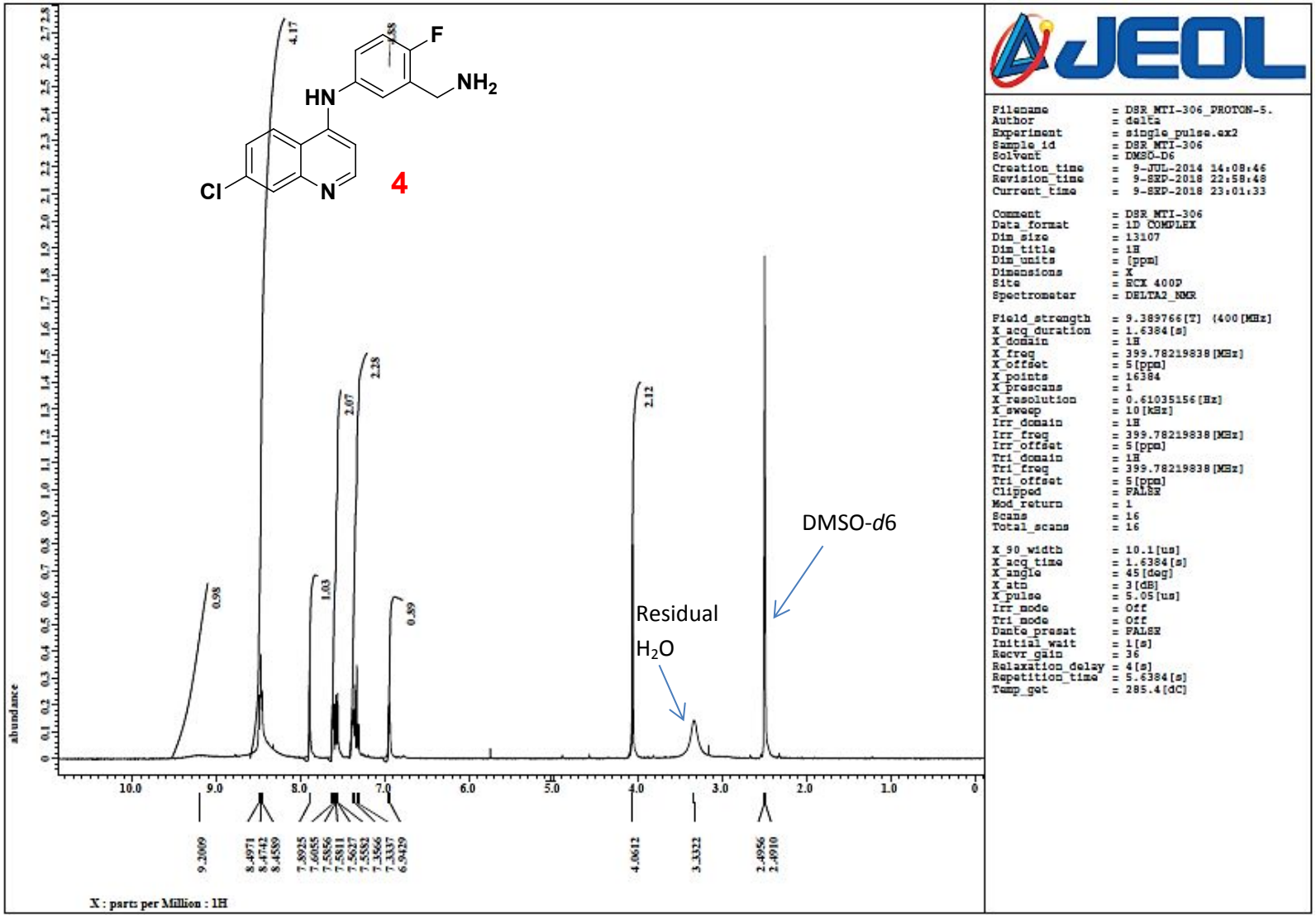


Figure S2: LC-ESI-MRM chromatogram of 7F along with internal standard obtained after analysis of lowest limit of quantification (LLOQ). Figure (A) and (B) show blank chromatograms of 7F and verapamil (IS), respectively. Figure (C) and (D) shows standard MRM chromatogram of 7F and verapamil (IS), respectively.

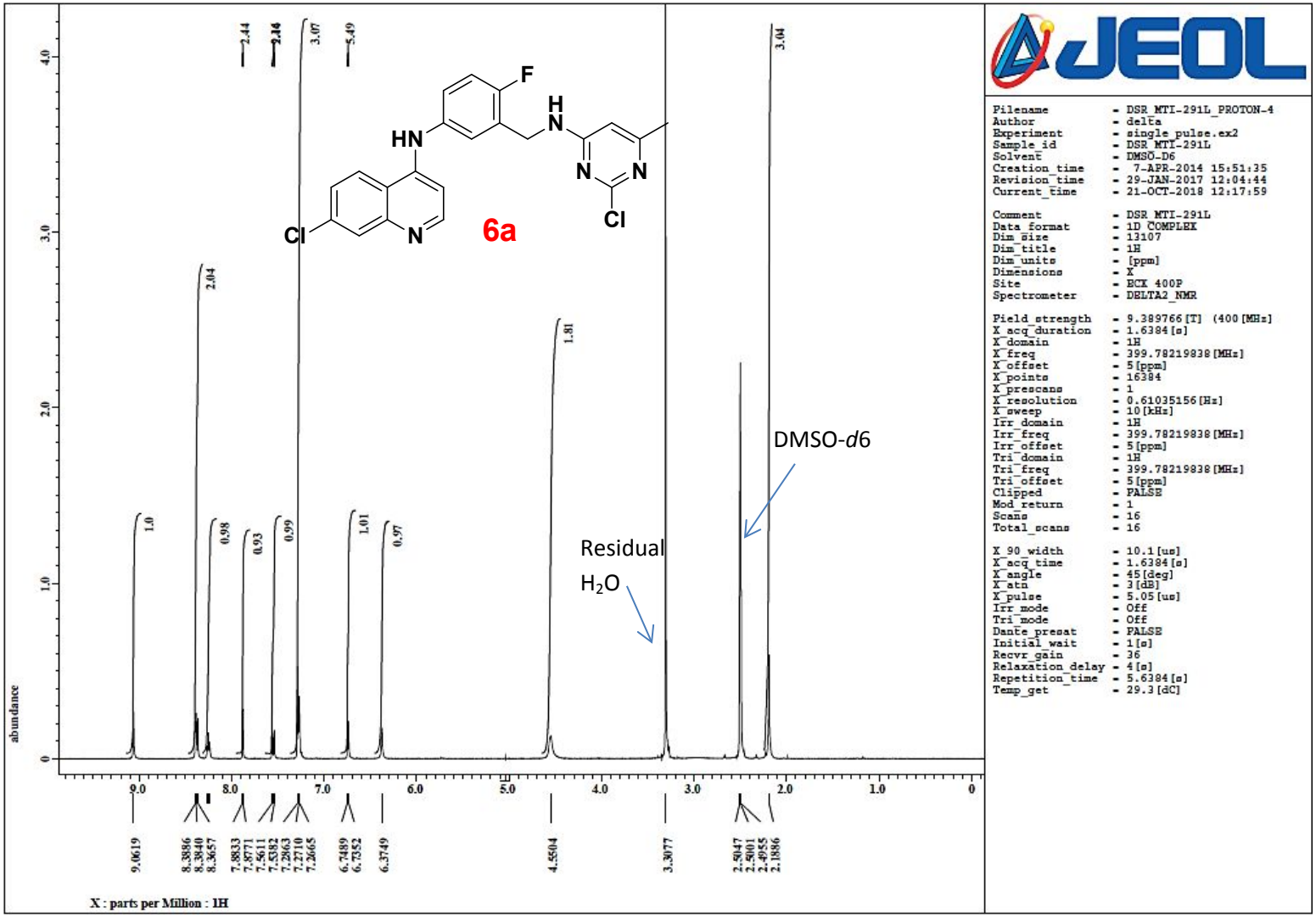
[1]HNMR, [13]CNMR and HPLC spectra of synthesized FAQ-pyrimidine hybrids:

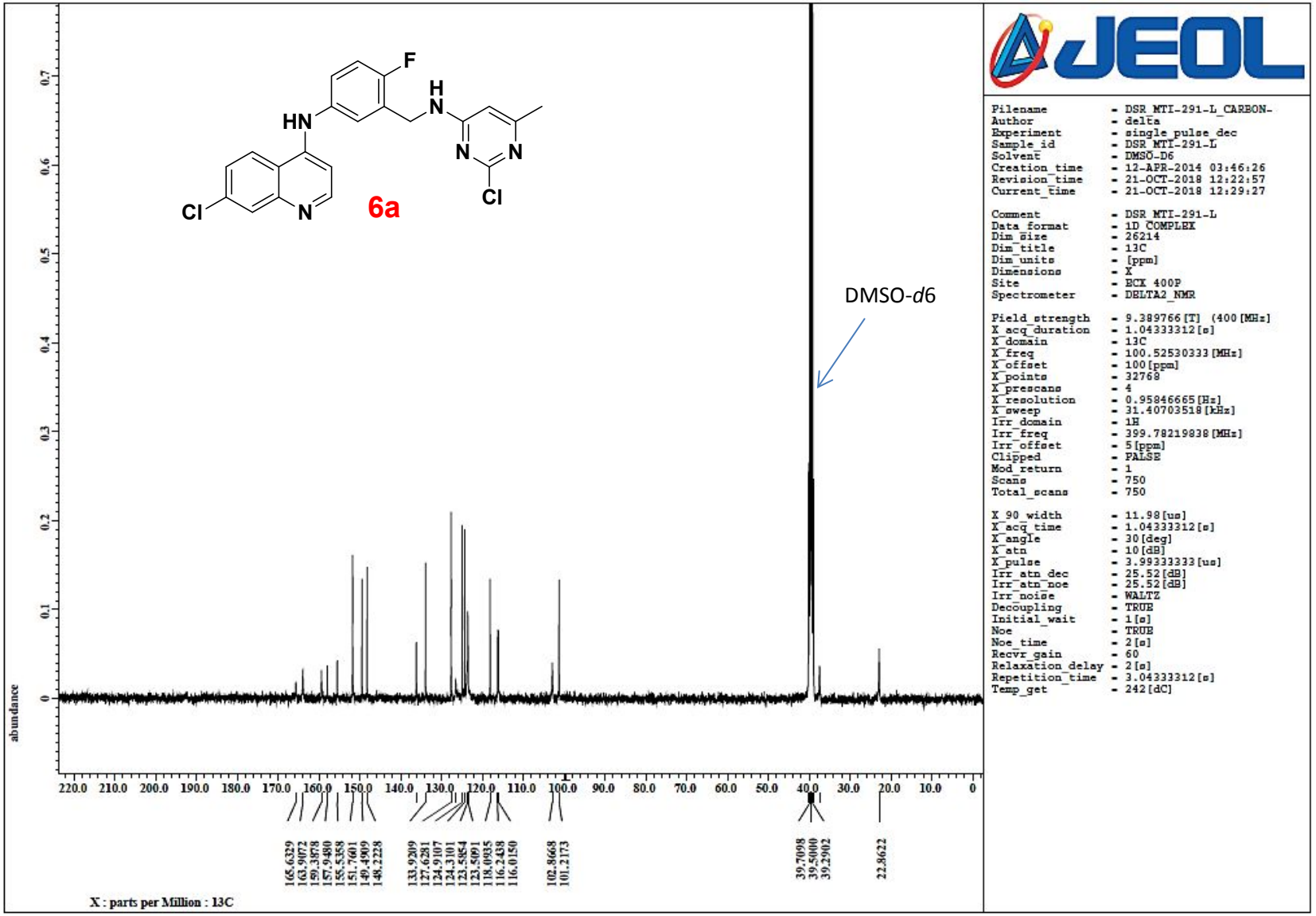




JEOL

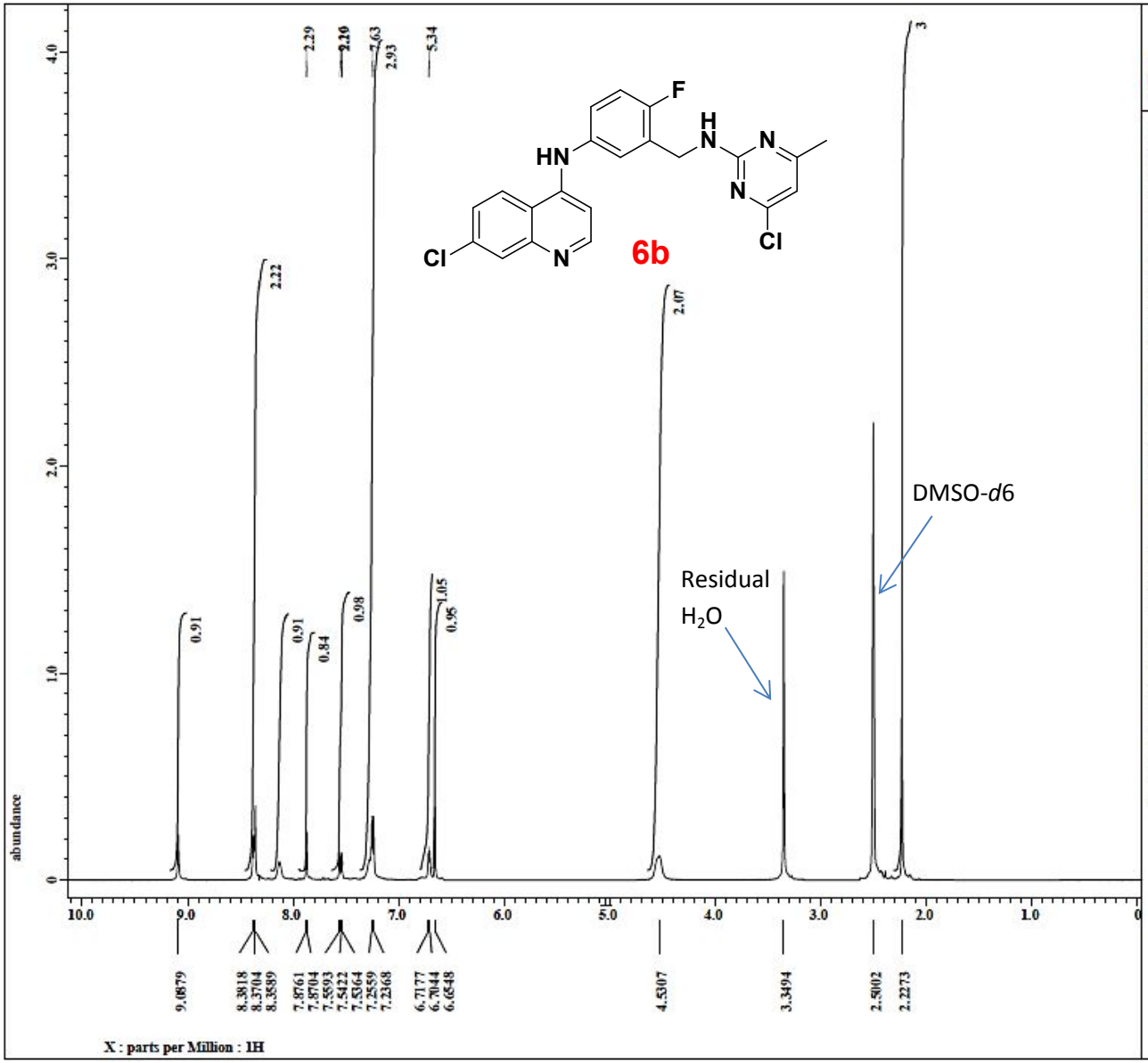
```
Filename          = DSR_MTI-306_PROTON-5.
Author            = delta
Experiment        = single_pulse.ex2
Sample_id         = DSR_MTI-306
Solvent           = DMSO-D6
Creation_time     =  9-JUL-2014 14:08:46
Revision_time     =  9-SEP-2018 22:58:48
Current_time      =  9-SEP-2018 23:01:33

Comment           = DSR_MTI-306
Data_format       = 1D COMPLEX
Dim_size          = 13107
Dim_title         = 1H
Dim_units         = [ppm]
Dimensions        = X
Site              = RCX 400P
Spectrometer      = DELTA2_NMR

Field_strength    = 9.389766[T]  (400[MHz]
X_acq_duration    = 1.6384[s]
X_domain          = 1H
X_freq            = 399.78219838[MHz]
X_offset          = 5[ppm]
X_points          = 16384
X_prescans        = 1
X_resolution      = 0.61035156[Hz]
X_sweep           = 10[kHz]
Irr_domain        = 1H
Irr_freq          = 399.78219838[MHz]
Irr_offset        = 5[ppm]
Tri_domain        = 1H
Tri_freq          = 399.78219838[MHz]
Tri_offset        = 5[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 16
Total_scans       = 16

X_90_width        = 10.1[us]
X_acq_time        = 1.6384[s]
X_angle           = 45[deg]
X_atn             = 3[dB]
X_pulse           = 5.05[us]
Irr_mode          = Off
Tri_mode          = Off
Dante_presat      = FALSE
Initial_wait      = 1[s]
Recvr_gain        = 36
Relaxation_delay  = 4[s]
Repetition_time   = 5.6384[s]
Temp_get          = 285.4[dC]
```


F
HN
H
N
N
N
Cl
N
Cl
6a
DMSO-d6
Residual
H2O
abundance
X : parts per Million : 1H
Filename - DSR_MTI-291L_PROTON-4
Author - delta
Experiment - single_pulse.ex2
Sample_id - DSR_MTI-291L
Solvent - DMSO-D6
Creation_time - 7-APR-2014 15:51:35
Revision_time - 29-JAN-2017 12:04:44
Current_time - 21-OCT-2018 12:17:59
Comment - DSR_MTI-291L
Data_format - 1D COMPLEX
Dim_size - 13107
Dim_title - 1H
Dim_units - [ppm]
Dimensions - X
Site - ECX 400P
Spectrometer - DELTA2_NMR
Field_strength - 9.389766[T] (400[MHz]
X_acq_duration - 1.6384[s]
X_domain - 1H
X_freq - 399.78219838[MHz]
X_offset - 5[ppm]
X_points - 16384
X_prescans - 1
X_resolution - 0.61035156[Hz]
X_sweep - 10[kHz]
Irr_domain - 1H
Irr_freq - 399.78219838[MHz]
Irr_offset - 5[ppm]
Tri_domain - 1H
Tri_freq - 399.78219838[MHz]
Tri_offset - 5[ppm]
Clipped - FALSE
Mod_return - 1
Scans - 16
Total_scans - 16
X_90_width - 10.1[us]
X_acq_time - 1.6384[s]
X_angle - 45[deg]
X_atn - 3[dB]
X_pulse - 5.05[us]
Irr_mode - Off
Tri_mode - Off
Dante_presat - FALSE
Initial_wait - 1[s]
Recvr_gain - 36
Relaxation_delay - 4[s]
Repetition_time - 5.6384[s]
Temp_get - 29.3[dC]



JEOL

Pilename	- DSR_MTI-291-L_CARBON-
Author	- delta
Experiment	- single_pulse_dec
Sample_id	- DSR_MTI-291-L
Solvent	- DMSO-D6
Creation_time	- 12-APR-2014 03:46:26
Revision_time	- 21-OCT-2018 12:22:57
Current_time	- 21-OCT-2018 12:29:27
Comment	- DSR_MTI-291-L
Data_format	- 1D COMPLEX
Dim_size	- 26214
Dim_title	- 13C
Dim_units	- [ppm]
Dimensions	- X
Site	- BCX 400P
Spectrometer	- DELTA2_NMR
Field_strength	- 9.389766[T] (400[MHz]
X_acq_duration	- 1.04333312[s]
X_domain	- 13C
X_freq	- 100.52530333[MHz]
X_offset	- 100[ppm]
X_points	- 32768
X_prescans	- 4
X_resolution	- 0.95846665[Hz]
X_sweep	- 31.40703518[kHz]
Irr_domain	- 1H
Irr_freq	- 399.78219838[MHz]
Irr_offset	- 5[ppm]
Clipped	- FALSE
Mod_return	- 1
Scans	- 750
Total_scans	- 750
X_90_width	- 11.98[us]
X_acq_time	- 1.04333312[s]
X_angle	- 30[deg]
X_atn	- 10[dB]
X_pulse	- 3.99333333[us]
Irr_atn_dec	- 25.52[dB]
Irr_atn_noe	- 25.52[dB]
Irr_noise	- WALTZ
Decoupling	- TRUE
Initial_wait	- 1[s]
Noe	- TRUE
Noe_time	- 2[s]
Recvr_gain	- 60
Relaxation_delay	- 2[s]
Repetition_time	- 3.04333312[s]
Temp_get	- 242[dC]

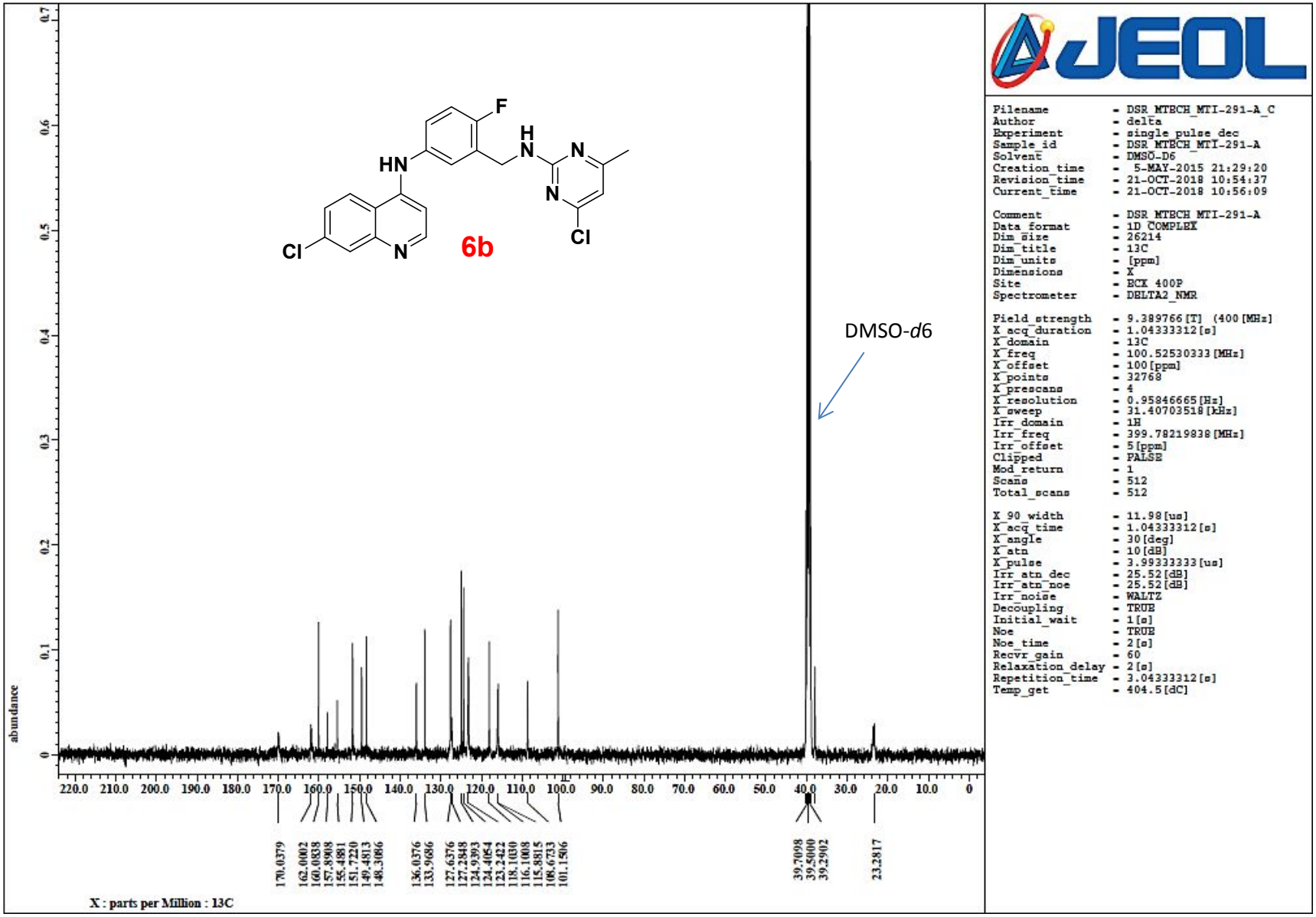


Pilename - DSR_MTECH_MTI-291A_PR
Author - delta
Experiment - single_pulse.ex2
Sample_id - DSR_MTECH_MTI-291A
Solvent - DMSO-D6
Creation_time - 30-APR-2015 11:49:34
Revision_time - 17-JAN-2017 03:13:22
Current_time - 21-OCT-2018 10:19:57

Comment - DSR_MTECH_MTI-291A
Data_format - 1D COMPLEX
Dim_size - 13107
Dim_title - 1H
Dim_units - [ppm]
Dimensions - X
Site - ECX 400P
Spectrometer - DELTA2_NMR

Field_strength - 9.389766[T] (400[MHz]
X_acq_duration - 1.31072[s]
X_domain - 1H
X_freq - 399.78219838[MHz]
X_offset - 5[ppm]
X_points - 16384
X_prescans - 1
X_resolution - 0.76293945[Hz]
X_sweep - 12.5[kHz]
Irr_domain - 1H
Irr_freq - 399.78219838[MHz]
Irr_offset - 5[ppm]
Tri_domain - 1H
Tri_freq - 399.78219838[MHz]
Tri_offset - 5[ppm]
Clipped - FALSE
Mod_return - 1
Scans - 16
Total_scans - 16

X_90_width - 10.1[us]
X_acq_time - 1.31072[s]
X_angle - 45[deg]
X_atn - 3[dB]
X_pulse - 5.05[us]
Irr_mode - Off
Tri_mode - Off
Dante_presat - FALSE
Initial_wait - 1[s]
Recvr_gain - 34
Relaxation_delay - 4[s]
Repetition_time - 5.31072[s]
Temp_get - 465[dC]

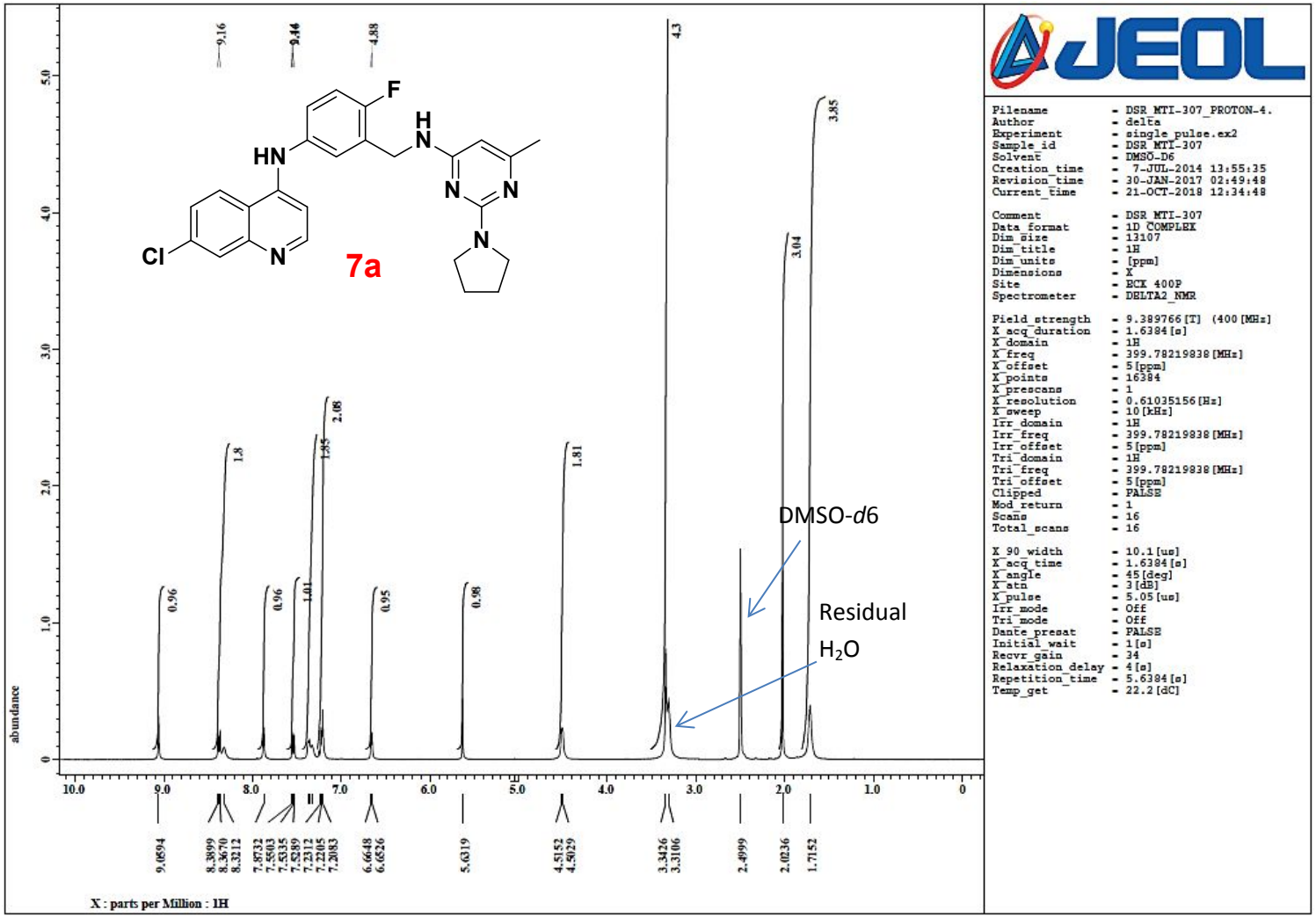


Filename - DSR_MTECH_MTI-291-A_C
Author - delta
Experiment - single_pulse_dec
Sample_id - DSR_MTECH_MTI-291-A
Solvent - DMSO-D6
Creation_time - 5-MAY-2015 21:29:20
Revision_time - 21-OCT-2018 10:54:37
Current_time - 21-OCT-2018 10:56:09

Comment - DSR_MTECH_MTI-291-A
Data_format - 1D COMPLEX
Dim_size - 26214
Dim_title - 13C
Dim_units - [ppm]
Dimensions - X
Site - BCX 400P
Spectrometer - DELTA2_NMR

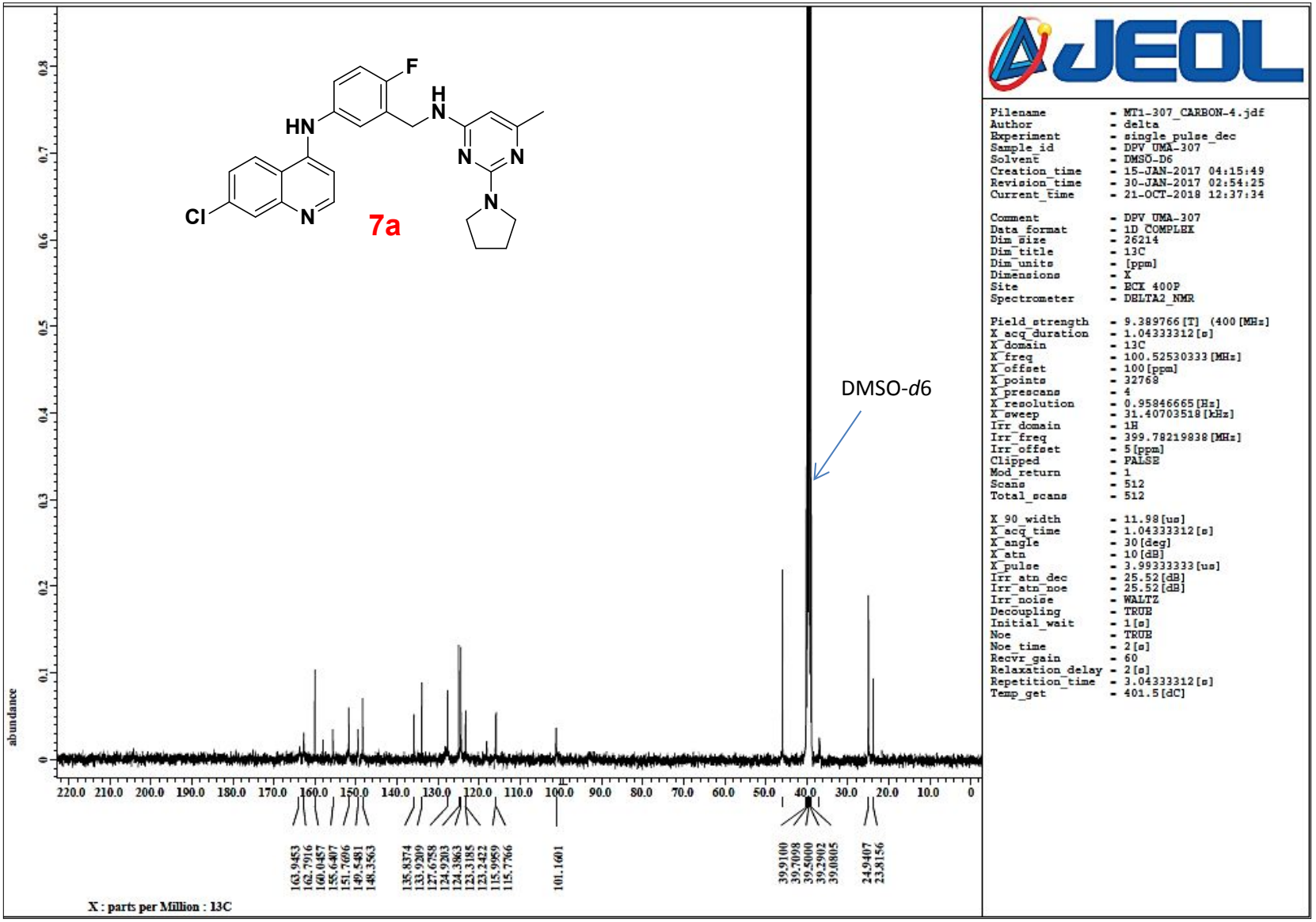
Field_strength - 9.389766[T] (400[MHz]
X_acq_duration - 1.04333312[s]
X_domain - 13C
X_freq - 100.52530333[MHz]
X_offset - 100[ppm]
X_points - 32768
X_prescans - 4
X_resolution - 0.95846665[Hz]
X_sweep - 31.40703518[kHz]
Irr_domain - 1H
Irr_freq - 399.78219838[MHz]
Irr_offset - 5[ppm]
Clipped - FALSE
Mod_return - 1
Scans - 512
Total_scans - 512

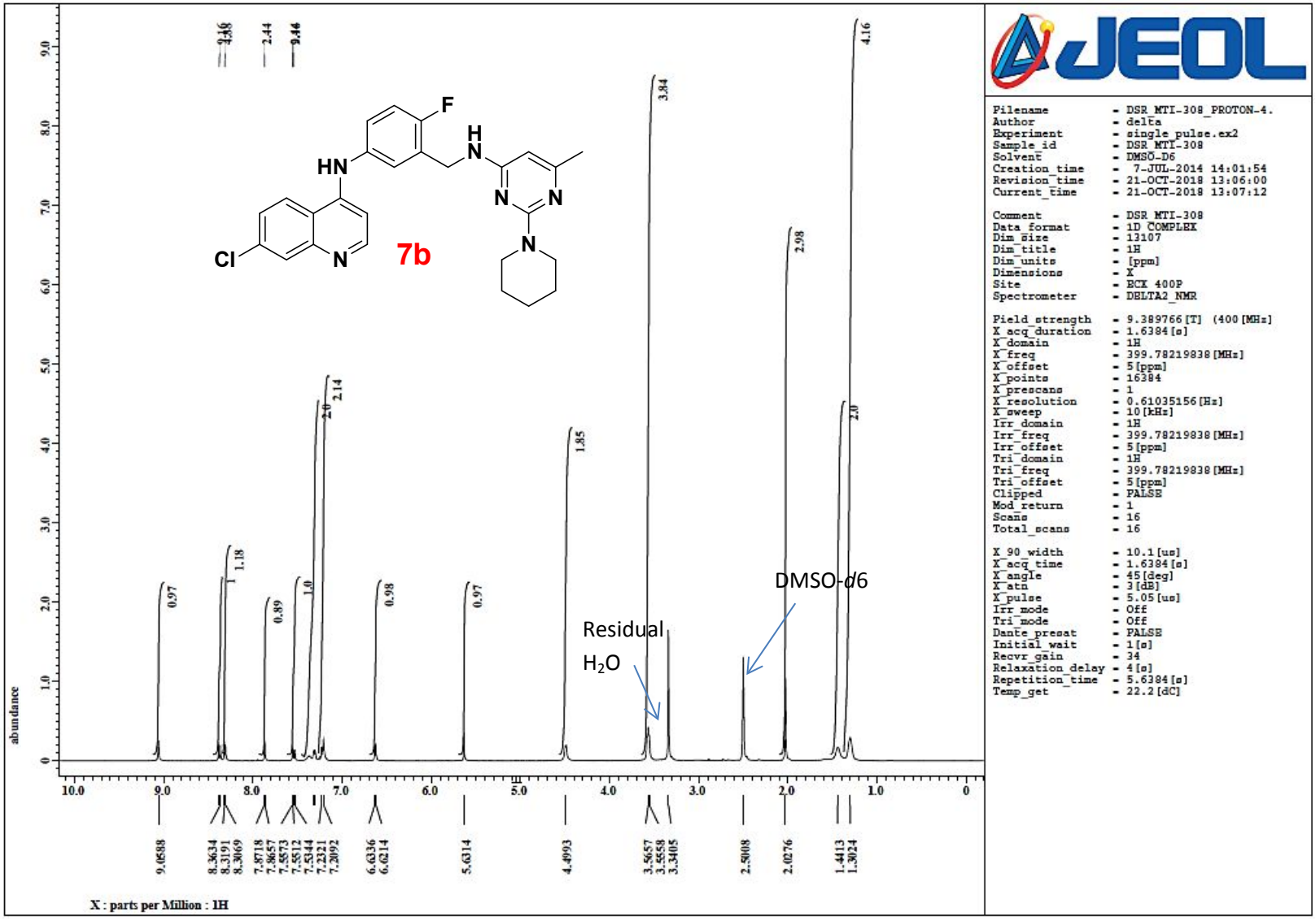
X_90_width - 11.98[us]
X_acq_time - 1.04333312[s]
X_angle - 30[deg]
X_atn - 10[dB]
X_pulse - 3.99333333[us]
Irr_atn_dec - 25.52[dB]
Irr_atn_noe - 25.52[dB]
Irr_noise - WALTZ
Decoupling - TRUE
Initial_wait - 1[s]
Noe - TRUE
Noe_time - 2[s]
Recvr_gain - 60
Relaxation_delay - 2[s]
Repetition_time - 3.04333312[s]
Temp_get - 404.5[dC]

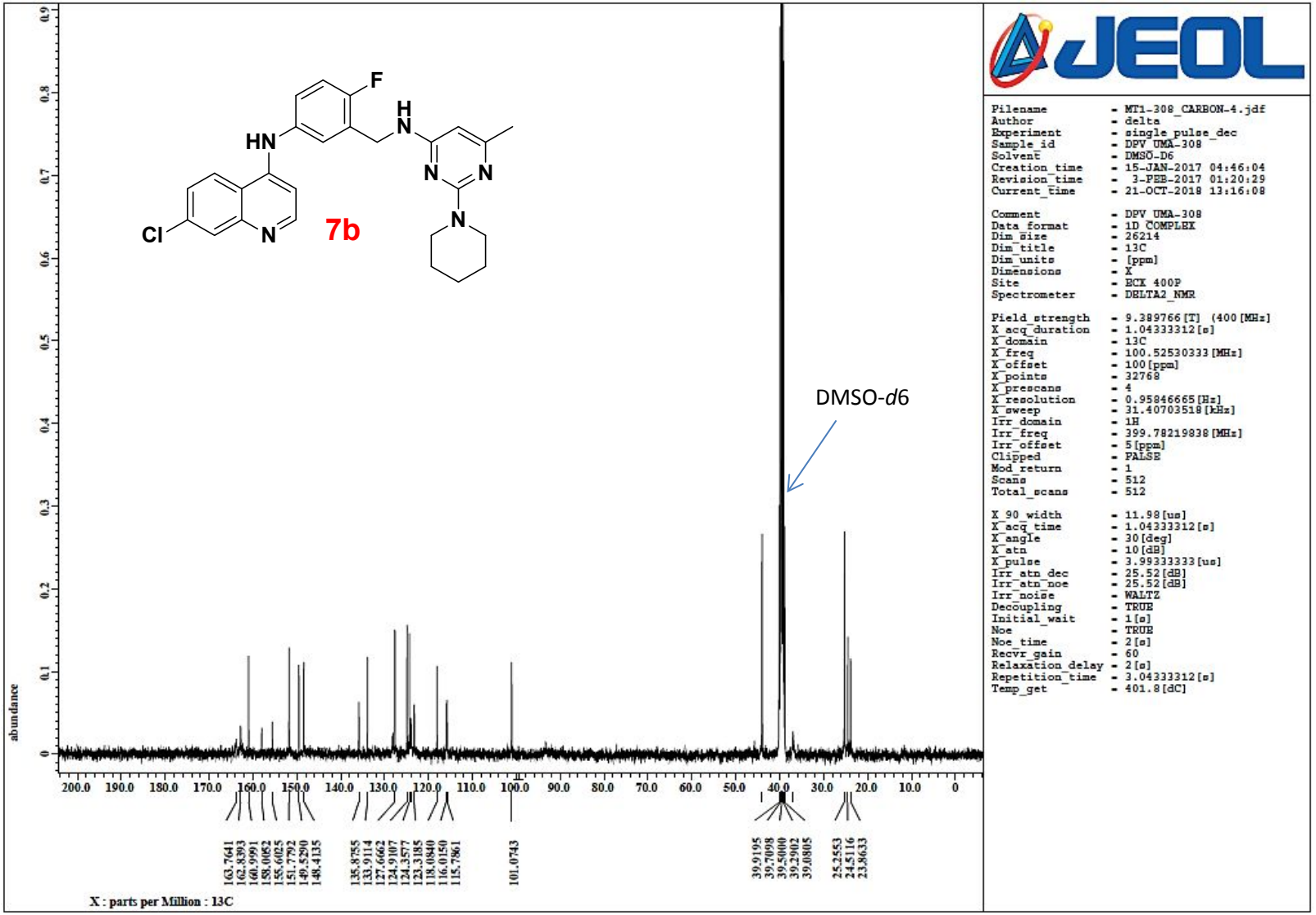


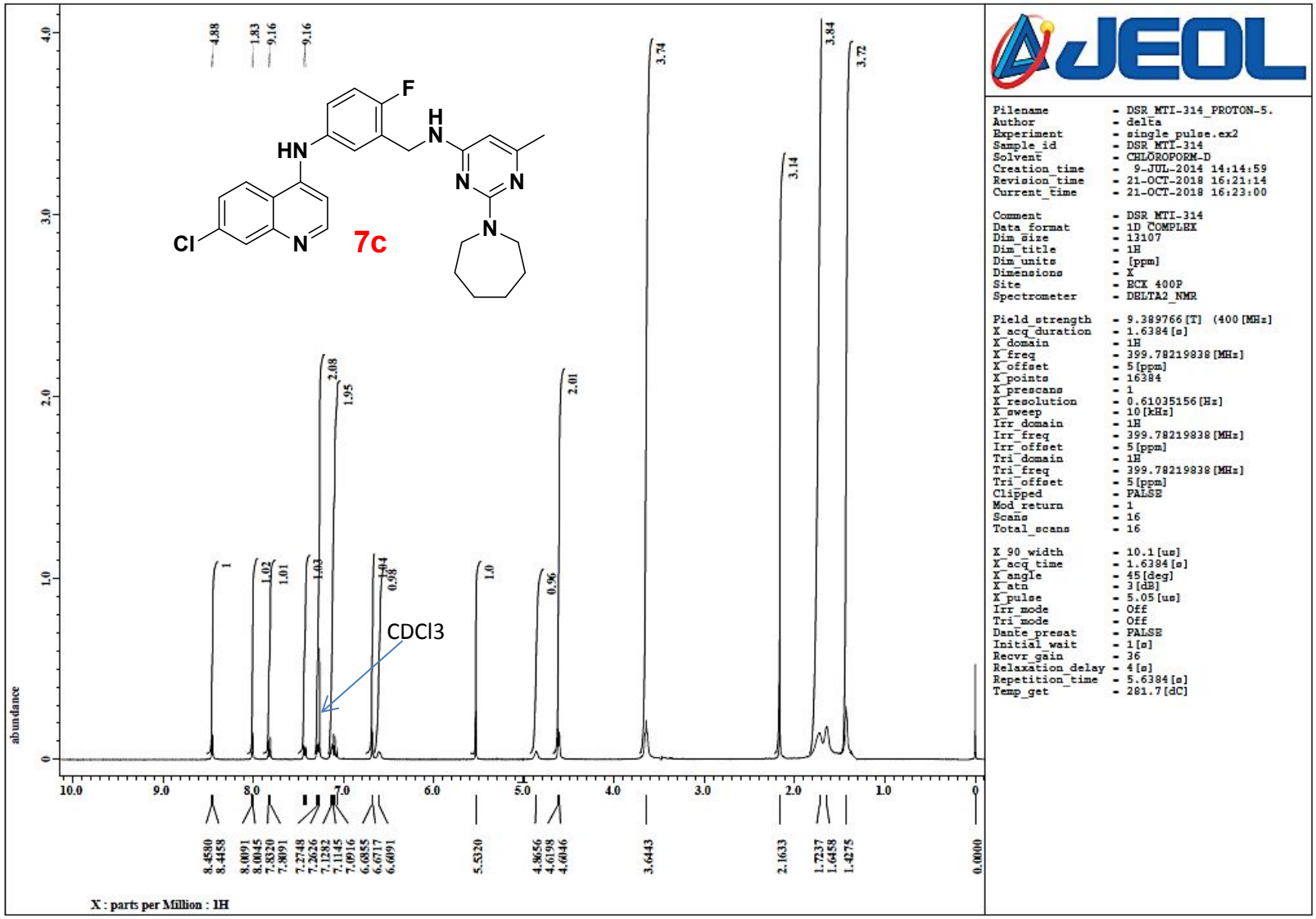
JEOL

```
Pilename          - DSR_MTI-307_PROTON-4.
Author            - delta
Experiment        - single_pulse.ex2
Sample_id         - DSR_MTI-307
Solvent           - DMSO-D6
Creation_time     -  7-JUL-2014 13:55:35
Revision_time     - 30-JAN-2017 02:49:48
Current_time      - 21-OCT-2018 12:34:48

Comment           - DSR_MTI-307
Data_format       - 1D COMPLEX
Dim_size          - 13107
Dim_title         - 1H
Dim_units         - [ppm]
Dimensions        - X
Site              - ECX 400P
Spectrometer      - DELTA2_NMR

Field_strength    - 9.389766[T] (400[MHz]
X_acq_duration    - 1.6384[s]
X_domain          - 1H
X_freq            - 399.78219838[MHz]
X_offset          - 5[ppm]
X_points          - 16384
X_prescans        - 1
X_resolution      - 0.61035156[Hz]
X_sweep           - 10[kHz]
Irr_domain        - 1H
Irr_freq          - 399.78219838[MHz]
Irr_offset        - 5[ppm]
Tri_domain        - 1H
Tri_freq          - 399.78219838[MHz]
Tri_offset        - 5[ppm]
Clipped           - FALSE
Mod_return        - 1
Scans             - 16
Total_scans       - 16

X_90_width        - 10.1[us]
X_acq_time        - 1.6384[s]
X_angle           - 45[deg]
X_atn             - 3[dB]
X_pulse           - 5.05[us]
Irr_mode          - Off
Tri_mode          - Off
Dante_presat      - FALSE
Initial_wait      - 1[s]
Recvr_gain        - 34
Relaxation_delay  - 4[s]
Repetition_time   - 5.6384[s]
Temp_get          - 22.2[dC]
```


F
HN
H
N
N
N
Cl
N
N
7a
DMSO-d6
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
163.9453
162.7916
160.0457
155.6407
151.7696
149.5481
148.3563
135.8374
133.9209
127.6758
124.9203
124.3863
123.3185
123.2422
115.9959
115.7766
101.1601
39.9100
39.7098
39.5000
39.2902
39.0805
24.9407
23.8156
X : parts per Million : 13C
Pilename - MT1-307_CARBON-4.jdf
Author - delta
Experiment - single_pulse_dec
Sample_id - DPV_UMA-307
Solvent - DMSO-D6
Creation_time - 15-JAN-2017 04:15:49
Revision_time - 30-JAN-2017 02:54:25
Current_time - 21-OCT-2018 12:37:34
Comment - DPV_UMA-307
Data_format - 1D COMPLEX
Dim_size - 26214
Dim_title - 13C
Dim_units - [ppm]
Dimensions - X
Site - BCX 400P
Spectrometer - DELTA2_NMR
Field_strength - 9.389766[T] (400[MHz]
X_acq_duration - 1.04333312[s]
X_domain - 13C
X_freq - 100.52530333[MHz]
X_offset - 100[ppm]
X_points - 32768
X_prescans - 4
X_resolution - 0.95846665[Hz]
X_sweep - 31.40703518[kHz]
Irr_domain - 1H
Irr_freq - 399.78219838[MHz]
Irr_offset - 5[ppm]
Clipped - FALSE
Mod_return - 1
Scans - 512
Total_scans - 512
X_90_width - 11.98[us]
X_acq_time - 1.04333312[s]
X_angle - 30[deg]
X_atn - 10[dB]
X_pulse - 3.99333333[us]
Irr_atn_dec - 25.52[dB]
Irr_atn_noe - 25.52[dB]
Irr_noise - WALTZ
Decoupling - TRUE
Initial_wait - 1[s]
Noe - TRUE
Noe_time - 2[s]
Recvr_gain - 60
Relaxation_delay - 2[s]
Repetition_time - 3.04333312[s]
Temp_get - 401.5[dC]


7b
Residual
H_2O
DMSO-*d*6
abundance
X : parts per Million : 1H
Pilename - DSR_MTI-308_PROTON-4.
Author - delta
Experiment - single_pulse.ex2
Sample_id - DSR_MTI-308
Solvent - DMSO-D6
Creation_time - 7-JUL-2014 14:01:54
Revision_time - 21-OCT-2018 13:06:00
Current_time - 21-OCT-2018 13:07:12
Comment - DSR_MTI-308
Data_format - 1D COMPLEX
Dim_size - 13107
Dim_title - 1H
Dim_units - [ppm]
Dimensions - X
Site - BCK 400P
Spectrometer - DELTA2_NMR
Field_strength - 9.389766[T] (400[MHz]
X_acq_duration - 1.6384[s]
X_domain - 1H
X_freq - 399.78219838[MHz]
X_offset - 5[ppm]
X_points - 16384
X_prescans - 1
X_resolution - 0.61035156[Hz]
X_sweep - 10[kHz]
Irr_domain - 1H
Irr_freq - 399.78219838[MHz]
Irr_offset - 5[ppm]
Tri_domain - 1H
Tri_freq - 399.78219838[MHz]
Tri_offset - 5[ppm]
Clipped - FALSE
Mod_return - 1
Scans - 16
Total_scans - 16
X_90_width - 10.1[us]
X_acq_time - 1.6384[s]
X_angle - 45[deg]
X_atn - 3[dB]
X_pulse - 5.05[us]
Irr_mode - Off
Tri_mode - Off
Dante_presat - FALSE
Initial_wait - 1[s]
Recvr_gain - 34
Relaxation_delay - 4[s]
Repetition_time - 5.6384[s]
Temp_get - 22.2[dC]


F
HN
H
N
N
N
N
Cl
N
7b
DMSO-d6
abundance
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
163.7641
162.8393
160.9991
158.0062
155.6025
151.7792
149.5290
148.4135
135.8755
133.9114
127.6662
124.9107
124.3577
123.3185
118.0840
116.0150
115.7961
101.0743
39.9195
39.7098
39.5000
39.2902
39.0805
25.2553
24.5116
23.5633
X : parts per Million : 13C
Pilename - MT1-308_CARBON-4.jdf
Author - delta
Experiment - single_pulse_dec
Sample_id - DPV_UMA-308
Solvent - DMSO-D6
Creation_time - 15-JAN-2017 04:46:04
Revision_time - 3-FEB-2017 01:20:29
Current_time - 21-OCT-2018 13:16:08
Comment - DPV_UMA-308
Data_format - 1D COMPLEX
Dim_size - 26214
Dim_title - 13C
Dim_units - [ppm]
Dimensions - X
Site - ECX 400P
Spectrometer - DELTA2_NMR
Field_strength - 9.389766[T] (400[MHz]
X_acq_duration - 1.04333312[s]
X_domain - 13C
X_freq - 100.52530333[MHz]
X_offset - 100[ppm]
X_points - 32768
X_prescans - 4
X_resolution - 0.95846665[Hz]
X_sweep - 31.40703518[kHz]
Irr_domain - 1H
Irr_freq - 399.78219838[MHz]
Irr_offset - 5[ppm]
Clipped - FALSE
Mod_return - 1
Scans - 512
Total_scans - 512
X_90_width - 11.98[us]
X_acq_time - 1.04333312[s]
X_angle - 30[deg]
X_atn - 10[dB]
X_pulse - 3.99333333[us]
Irr_atn_dec - 25.52[dB]
Irr_atn_noe - 25.52[dB]
Irr_noise - WALTZ
Decoupling - TRUE
Initial_wait - 1[s]
Noe - TRUE
Noe_time - 2[s]
Recvr_gain - 60
Relaxation_delay - 2[s]
Repetition_time - 3.04333312[s]
Temp_get - 401.8[dC]



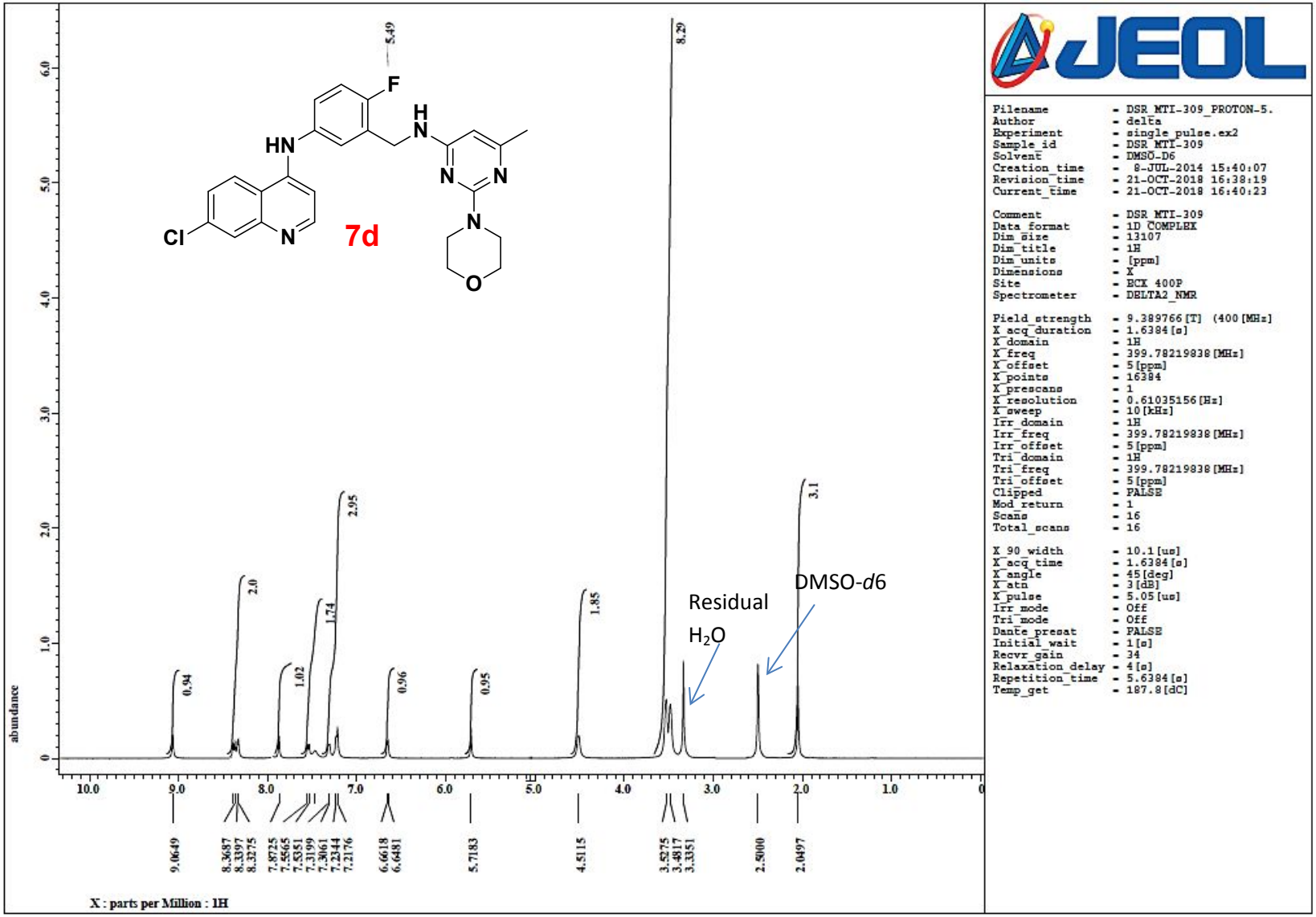
JEOL

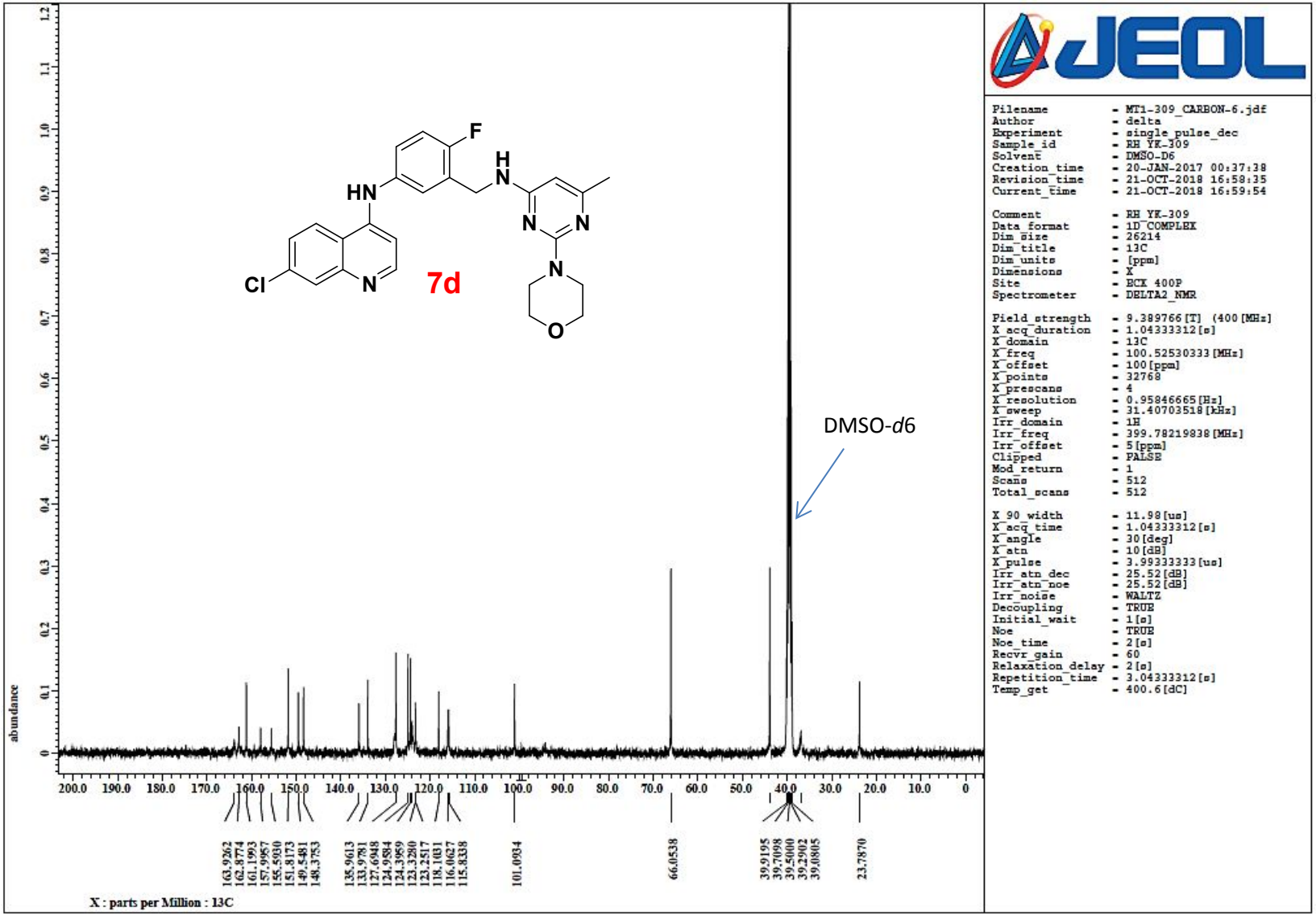
Pilename - DSR_MTI-314_PROTON-5.
Author - delta
Experiment - single_pulse.ex2
Sample_id - DSR_MTI-314
Solvent - CHLOROPORM-D
Creation_time - 9-JUL-2014 14:14:59
Revision_time - 21-OCT-2018 16:21:14
Current_time - 21-OCT-2018 16:23:00

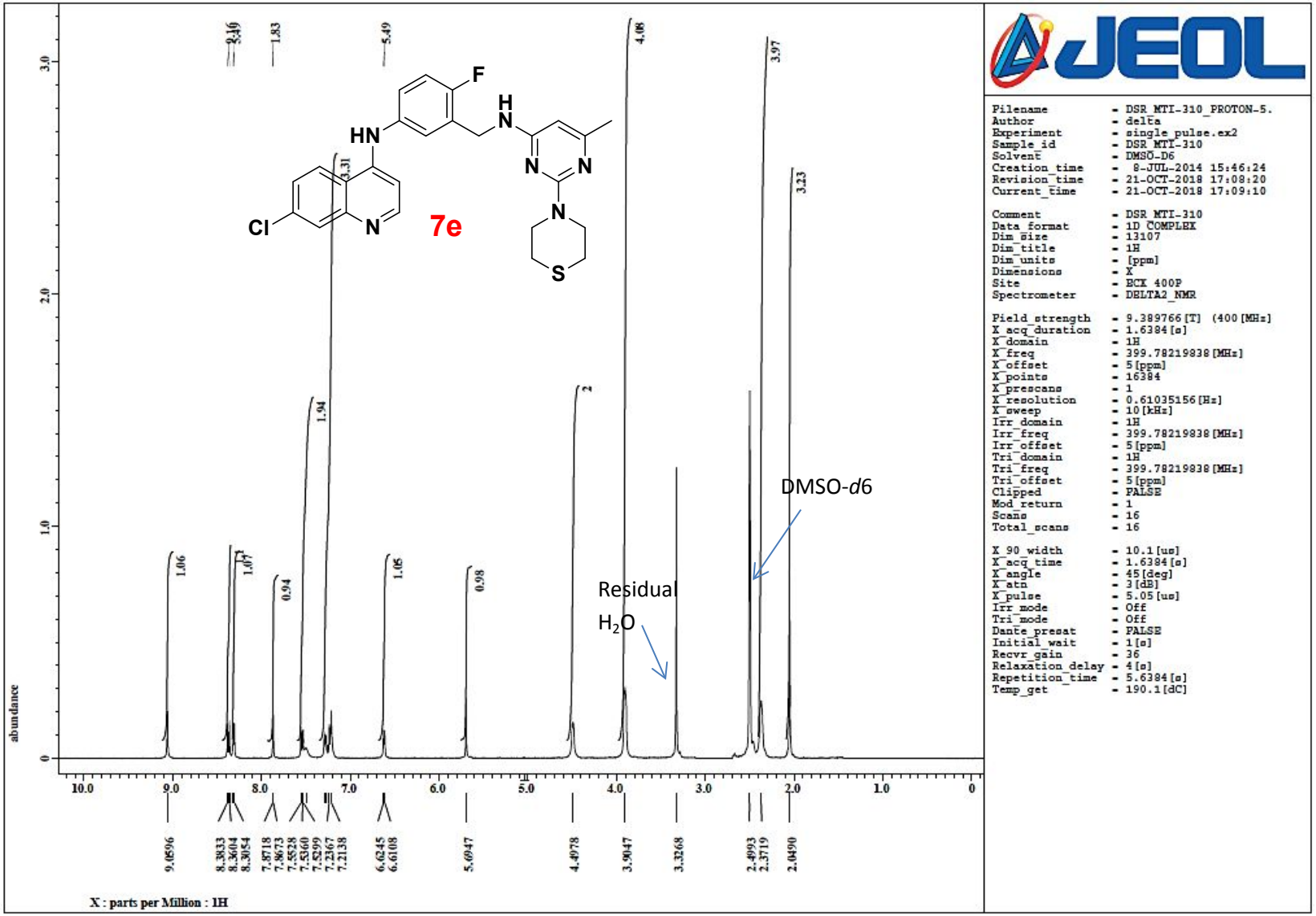
Comment - DSR_MTI-314
Data_format - 1D COMPLEX
Dim_size - 13107
Dim_title - 1H
Dim_units - [ppm]
Dimensions - X
Site - ECX 400P
Spectrometer - DELTA2_NMR

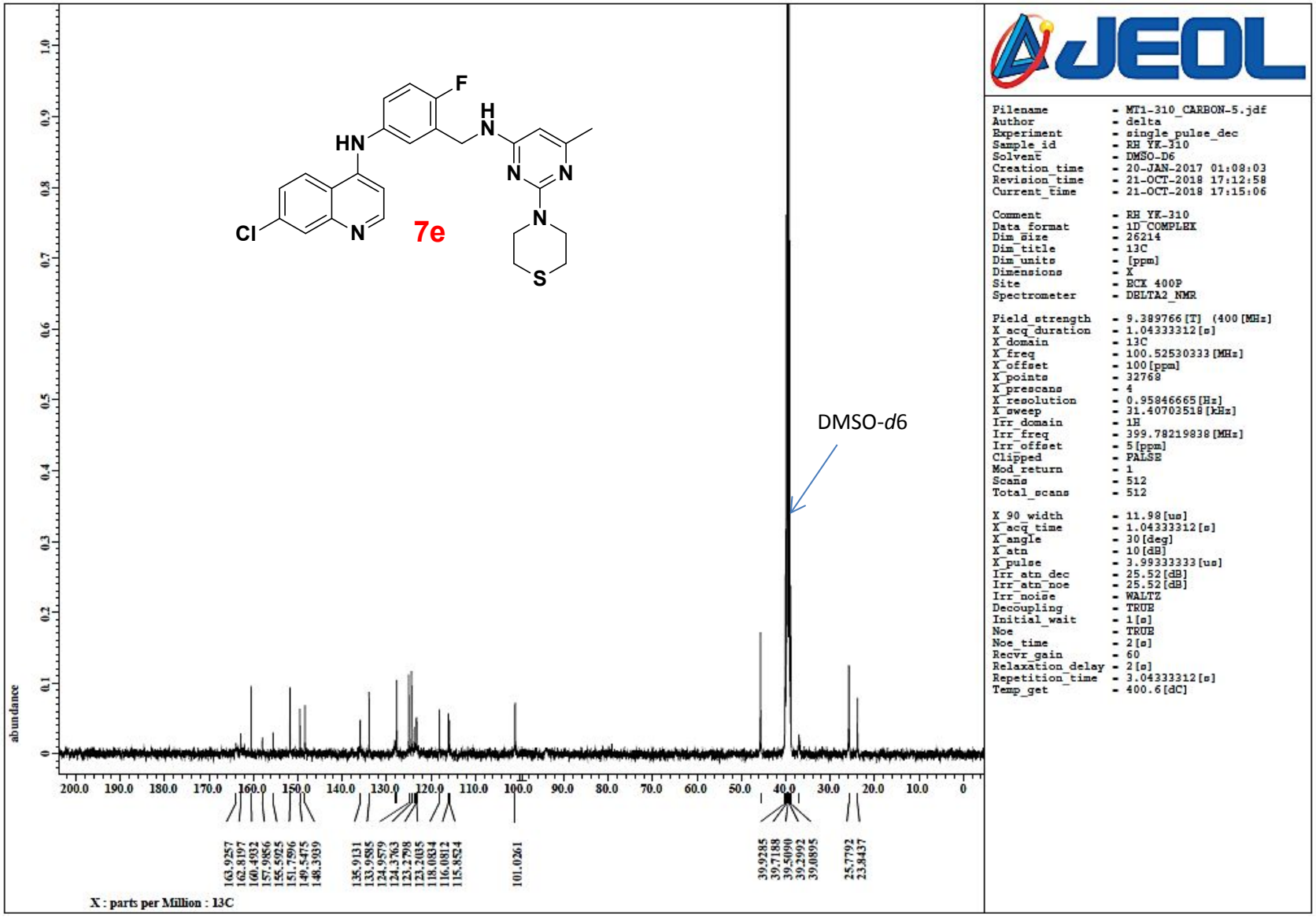
Field_strength - 9.389766[T] (400[MHz]
X_acq_duration - 1.6384[s]
X_domain - 1H
X_freq - 399.78219838[MHz]
X_offset - 5[ppm]
X_points - 16384
X_prescans - 1
X_resolution - 0.61035156[Hz]
X_sweep - 10[kHz]
Irr_domain - 1H
Irr_freq - 399.78219838[MHz]
Irr_offset - 5[ppm]
Tri_domain - 1H
Tri_freq - 399.78219838[MHz]
Tri_offset - 5[ppm]
Clipped - FALSE
Mod_return - 1
Scans - 16
Total_scans - 16

X_90_width - 10.1[us]
X_acq_time - 1.6384[s]
X_angle - 45[deg]
X_atn - 3[dB]
X_pulse - 5.05[us]
Irr_mode - Off
Tri_mode - Off
Dante_presat - FALSE
Initial_wait - 1[s]
Recvr_gain - 36
Relaxation_delay - 4[s]
Repetition_time - 5.6384[s]
Temp_get - 281.7[dC]


7d
Residual
H_2O
DMSO-*d*6
X : parts per Million : 1H
Pilename - DSR_MTI-309_PROTON-5.
Author - delta
Experiment - single_pulse.ex2
Sample_id - DSR_MTI-309
Solvent - DMSO-D6
Creation_time - 8-JUL-2014 15:40:07
Revision_time - 21-OCT-2018 16:38:19
Current_time - 21-OCT-2018 16:40:23
Comment - DSR_MTI-309
Data_format - 1D COMPLEX
Dim_size - 13107
Dim_title - 1H
Dim_units - [ppm]
Dimensions - X
Site - ECX 400P
Spectrometer - DELTA2_NMR
Field_strength - 9.389766[T] (400[MHz]
X_acq_duration - 1.6384[s]
X_domain - 1H
X_freq - 399.78219838[MHz]
X_offset - 5[ppm]
X_points - 16384
X_prescans - 1
X_resolution - 0.61035156[Hz]
X_sweep - 10[kHz]
Irr_domain - 1H
Irr_freq - 399.78219838[MHz]
Irr_offset - 5[ppm]
Tri_domain - 1H
Tri_freq - 399.78219838[MHz]
Tri_offset - 5[ppm]
Clipped - FALSE
Mod_return - 1
Scans - 16
Total_scans - 16
X_90_width - 10.1[us]
X_acq_time - 1.6384[s]
X_angle - 45[deg]
X_atn - 3[dB]
X_pulse - 5.05[us]
Irr_mode - Off
Tri_mode - Off
Dante_presat - FALSE
Initial_wait - 1[s]
Recvr_gain - 34
Relaxation_delay - 4[s]
Repetition_time - 5.6384[s]
Temp_get - 187.8[dC]


F
H
N
HN
N
N
Cl
N
7d
N
O
DMSO-d6
abundance
X : parts per Million : 13C
163.9262
162.8774
161.1993
157.9967
155.5930
151.8173
149.5481
148.3753
135.9613
133.9781
127.6948
124.9584
124.3969
123.3280
123.2517
118.1031
116.0627
115.8338
101.0934
66.0538
39.9195
39.7098
39.5000
39.2902
39.0805
23.7870
Pilename - MT1-309_CARBON-6.jdf
Author - delta
Experiment - single_pulse_dec
Sample_id - RH YK-309
Solvent - DMSO-D6
Creation_time - 20-JAN-2017 00:37:38
Revision_time - 21-OCT-2018 16:58:35
Current_time - 21-OCT-2018 16:59:54
Comment - RH YK-309
Data_format - 1D COMPLEX
Dim_size - 26214
Dim_title - 13C
Dim_units - [ppm]
Dimensions - X
Site - RCX 400P
Spectrometer - DELTA2_NMR
Field_strength - 9.389766[T] (400[MHz]
X_acq_duration - 1.04333312[s]
X_domain - 13C
X_freq - 100.52530333[MHz]
X_offset - 100[ppm]
X_points - 32768
X_prescans - 4
X_resolution - 0.95846665[Hz]
X_sweep - 31.40703518[kHz]
Irr_domain - 1H
Irr_freq - 399.78219838[MHz]
Irr_offset - 5[ppm]
Clipped - FALSE
Mod_return - 1
Scans - 512
Total_scans - 512
X_90_width - 11.98[us]
X_acq_time - 1.04333312[s]
X_angle - 30[deg]
X_atn - 10[dB]
X_pulse - 3.99333333[us]
Irr_atn_dec - 25.52[dB]
Irr_atn_noe - 25.52[dB]
Irr_noise - WALTZ
Decoupling - TRUE
Initial_wait - 1[s]
Noe - TRUE
Noe_time - 2[s]
Recvr_gain - 60
Relaxation_delay - 2[s]
Repetition_time - 3.04333312[s]
Temp_get - 400.6[dC]


7e
DMSO-d6
Residual
H2O
abundance
X : parts per Million : 1H
Pilename - DSR_MTI-310_PROTON-5.
Author - delta
Experiment - single_pulse.ex2
Sample_id - DSR_MTI-310
Solvent - DMSO-D6
Creation_time - 8-JUL-2014 15:46:24
Revision_time - 21-OCT-2018 17:08:20
Current_time - 21-OCT-2018 17:09:10
Comment - DSR_MTI-310
Data_format - 1D COMPLEX
Dim_size - 13107
Dim_title - 1H
Dim_units - [ppm]
Dimensions - X
Site - ECX 400P
Spectrometer - DELTA2_NMR
Field_strength - 9.389766[T] (400[MHz]
X_acq_duration - 1.6384[s]
X_domain - 1H
X_freq - 399.78219838[MHz]
X_offset - 5[ppm]
X_points - 16384
X_prescans - 1
X_resolution - 0.61035156[Hz]
X_sweep - 10[kHz]
Irr_domain - 1H
Irr_freq - 399.78219838[MHz]
Irr_offset - 5[ppm]
Tri_domain - 1H
Tri_freq - 399.78219838[MHz]
Tri_offset - 5[ppm]
Clipped - FALSE
Mod_return - 1
Scans - 16
Total_scans - 16
X_90_width - 10.1[us]
X_acq_time - 1.6384[s]
X_angle - 45[deg]
X_atn - 3[dB]
X_pulse - 5.05[us]
Irr_mode - Off
Tri_mode - Off
Dante_presat - FALSE
Initial_wait - 1[s]
Recvr_gain - 36
Relaxation_delay - 4[s]
Repetition_time - 5.6384[s]
Temp_get - 190.1[dC]

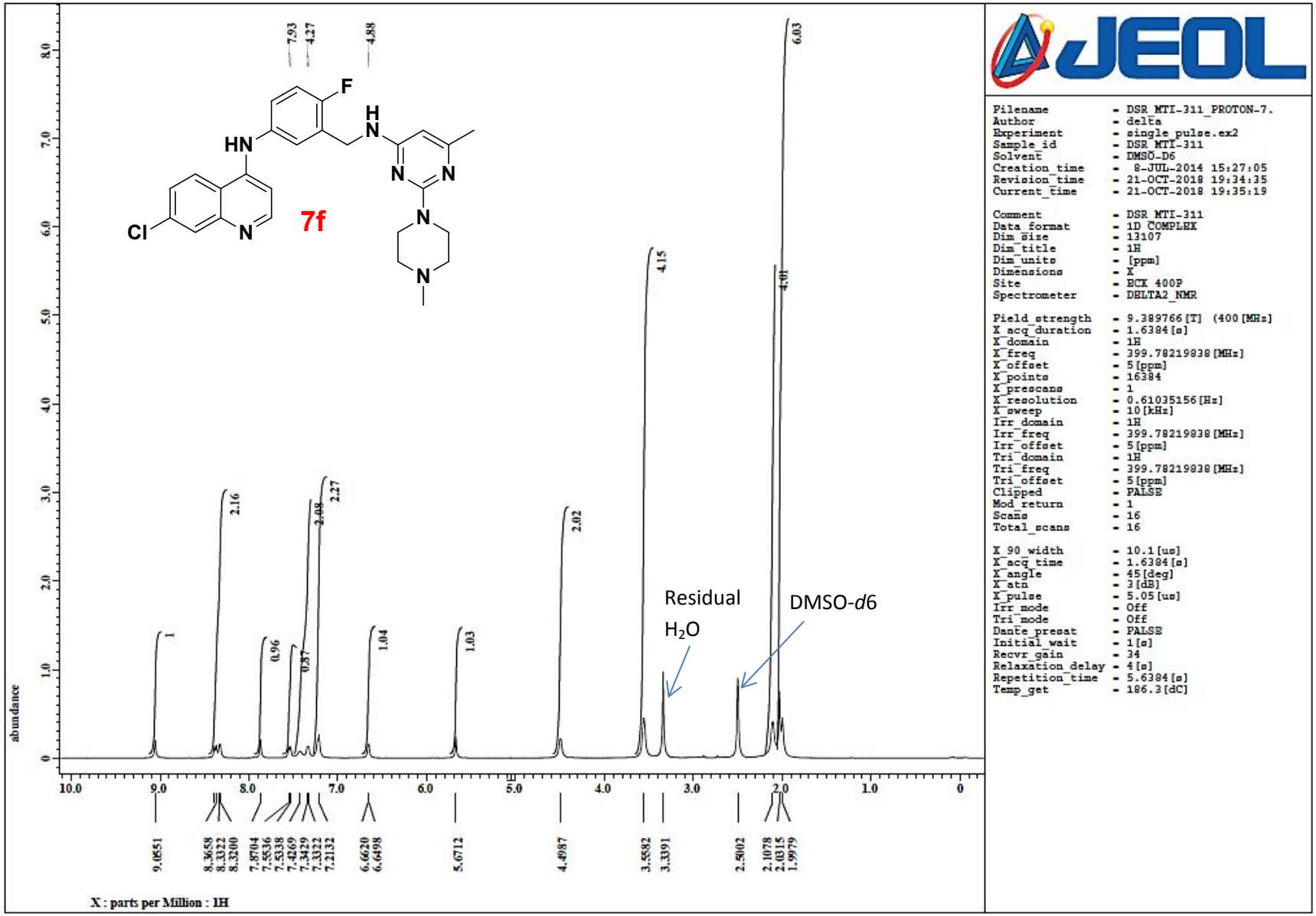


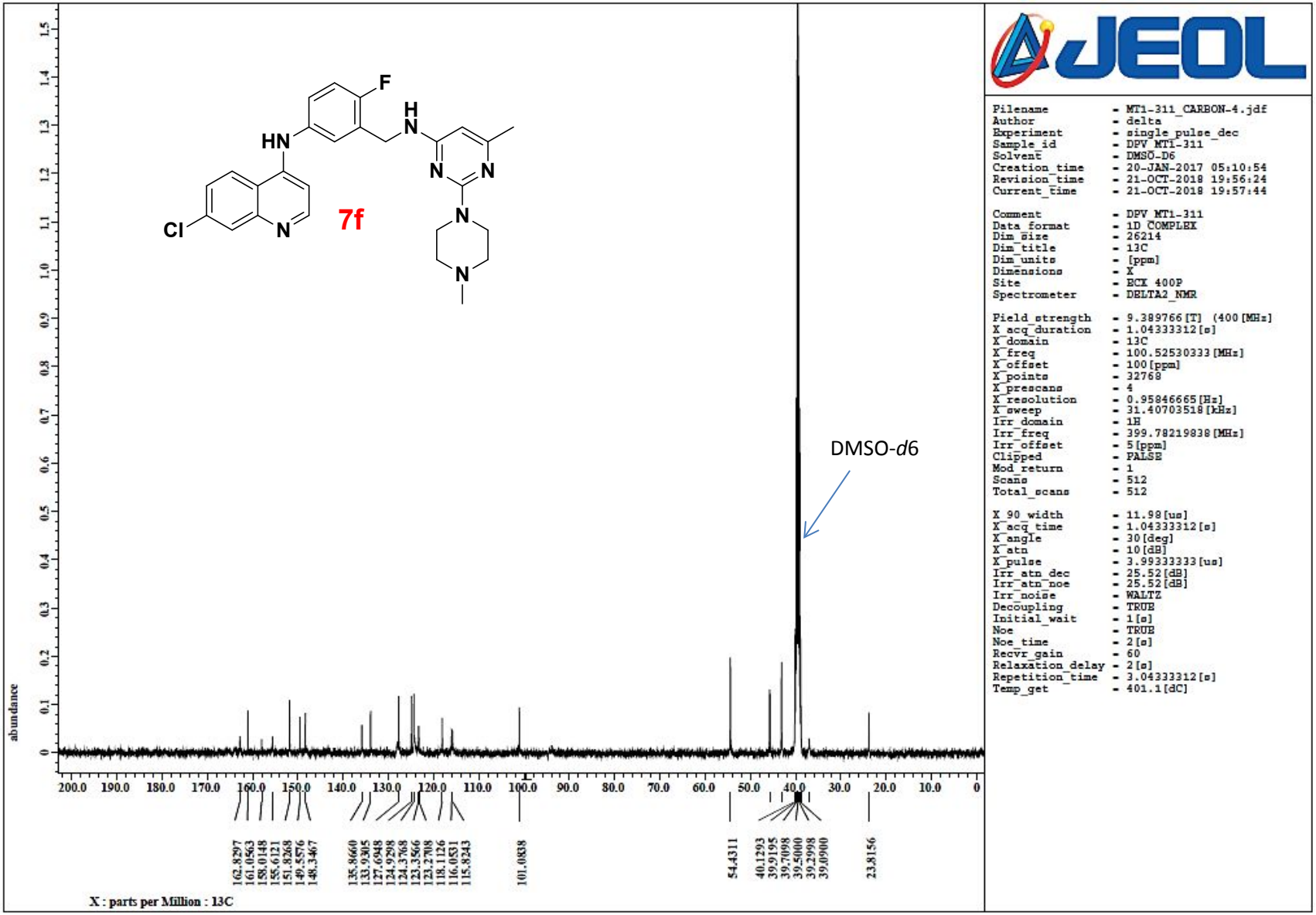
Filename - MT1-310_CARBON-5.jdf
Author - delta
Experiment - single_pulse_dec
Sample_id - RH_YK-310
Solvent - DMSO-D6
Creation_time - 20-JAN-2017 01:08:03
Revision_time - 21-OCT-2018 17:12:58
Current_time - 21-OCT-2018 17:15:06

Comment - RH_YK-310
Data_format - 1D COMPLEX
Dim_size - 26214
Dim_title - 13C
Dim_units - [ppm]
Dimensions - X
Site - ECX 400P
Spectrometer - DELTA2_NMR

Field_strength - 9.389766[T] (400[MHz]
X_acq_duration - 1.04333312[s]
X_domain - 13C
X_freq - 100.52530333[MHz]
X_offset - 100[ppm]
X_points - 32768
X_prescans - 4
X_resolution - 0.95846665[Hz]
X_sweep - 31.40703518[kHz]
Irr_domain - 1H
Irr_freq - 399.78219838[MHz]
Irr_offset - 5[ppm]
Clipped - FALSE
Mod_return - 1
Scans - 512
Total_scans - 512

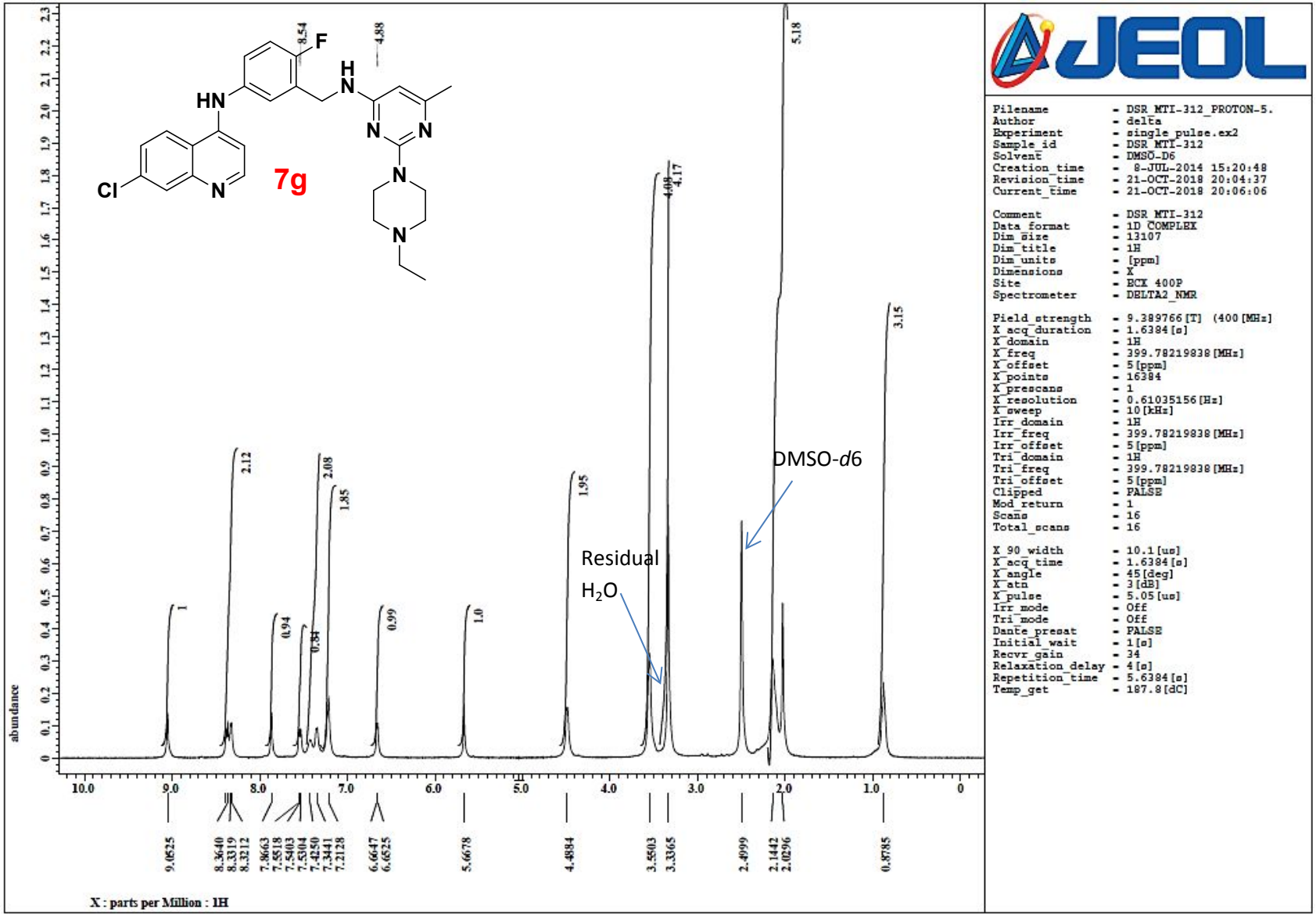
X_90_width - 11.98[us]
X_acq_time - 1.04333312[s]
X_angle - 30[deg]
X_atn - 10[dB]
X_pulse - 3.99333333[us]
Irr_atn_dec - 25.52[dB]
Irr_atn_noe - 25.52[dB]
Irr_noise - WALTZ
Decoupling - TRUE
Initial_wait - 1[s]
Noe - TRUE
Noe_time - 2[s]
Recvr_gain - 60
Relaxation_delay - 2[s]
Repetition_time - 3.04333312[s]
Temp_get - 400.6[dC]


7f
Residual
H2O
DMSO-d6
X : parts per Million : 1H
abundance



JEOL

```
Pilename          - MT1-311_CARBON-4.jdf
Author            - delta
Experiment        - single_pulse_dec
Sample_id         - DPV MT1-311
Solvent           - DMSO-D6
Creation_time     - 20-JAN-2017 05:10:54
Revision_time     - 21-OCT-2018 19:56:24
Current_time      - 21-OCT-2018 19:57:44

Comment           - DPV MT1-311
Data_format       - 1D COMPLEX
Dim_size          - 26214
Dim_title         - 13C
Dim_units         - [ppm]
Dimensions        - X
Site              - BCX 400P
Spectrometer      - DELTA2_NMR

Field_strength    - 9.389766[T] (400[MHz]
X_acq_duration    - 1.04333312[s]
X_domain          - 13C
X_freq            - 100.52530333[MHz]
X_offset          - 100[ppm]
X_points          - 32768
X_prescans        - 4
X_resolution      - 0.95846665[Hz]
X_sweep           - 31.40703518[kHz]
Irr_domain        - 1H
Irr_freq          - 399.78219838[MHz]
Irr_offset        - 5[ppm]
Clipped           - FALSE
Mod_return        - 1
Scans             - 512
Total_scans       - 512

X_90_width        - 11.98[us]
X_acq_time        - 1.04333312[s]
X_angle           - 30[deg]
X_atn             - 10[dB]
X_pulse           - 3.99333333[us]
Irr_atn_dec       - 25.52[dB]
Irr_atn_noe       - 25.52[dB]
Irr_noise         - WALTZ
Decoupling        - TRUE
Initial_wait      - 1[s]
Noe               - TRUE
Noe_time          - 2[s]
Recvr_gain        - 60
Relaxation_delay  - 2[s]
Repetition_time   - 3.04333312[s]
Temp_get          - 401.1[dC]
```

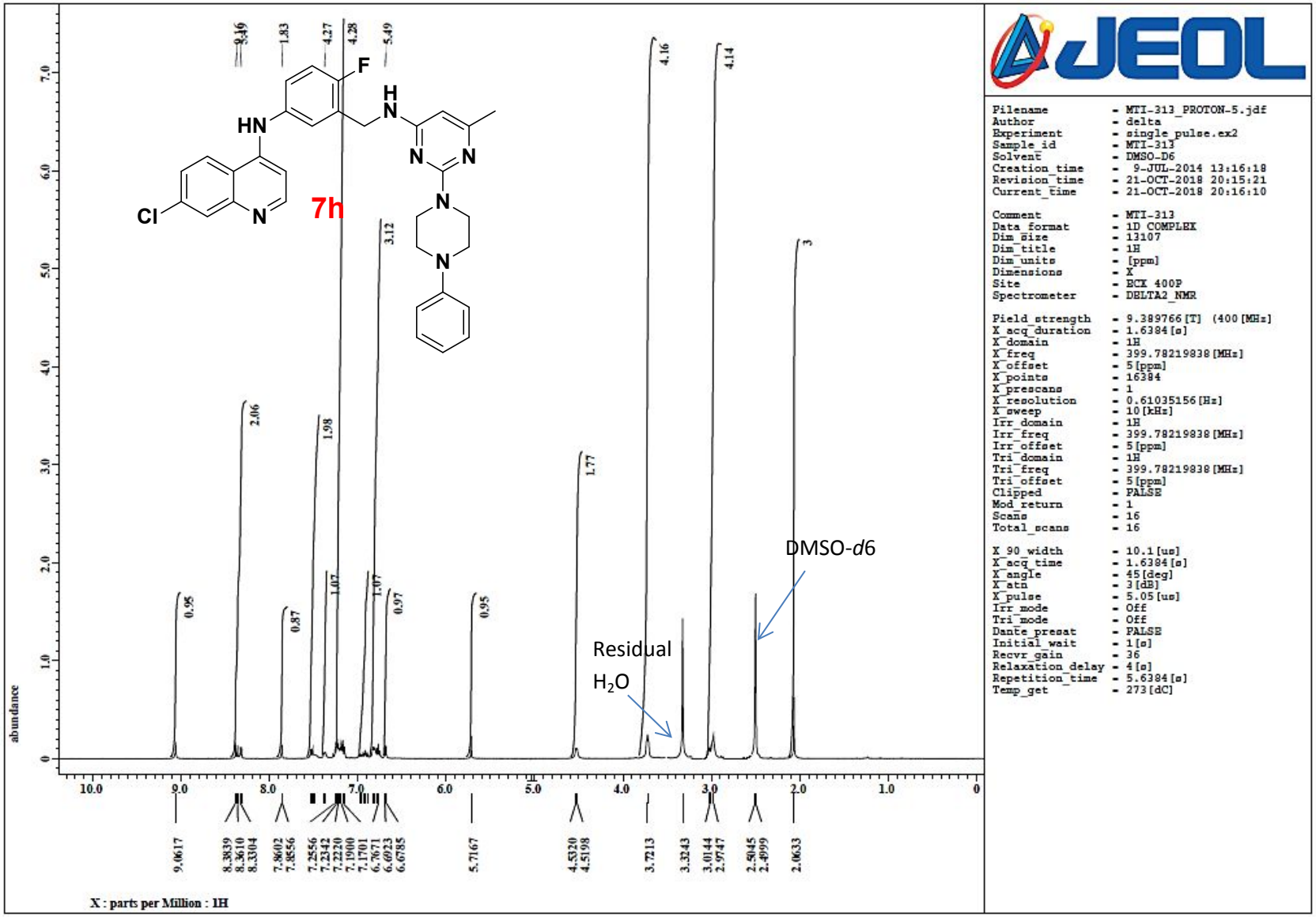


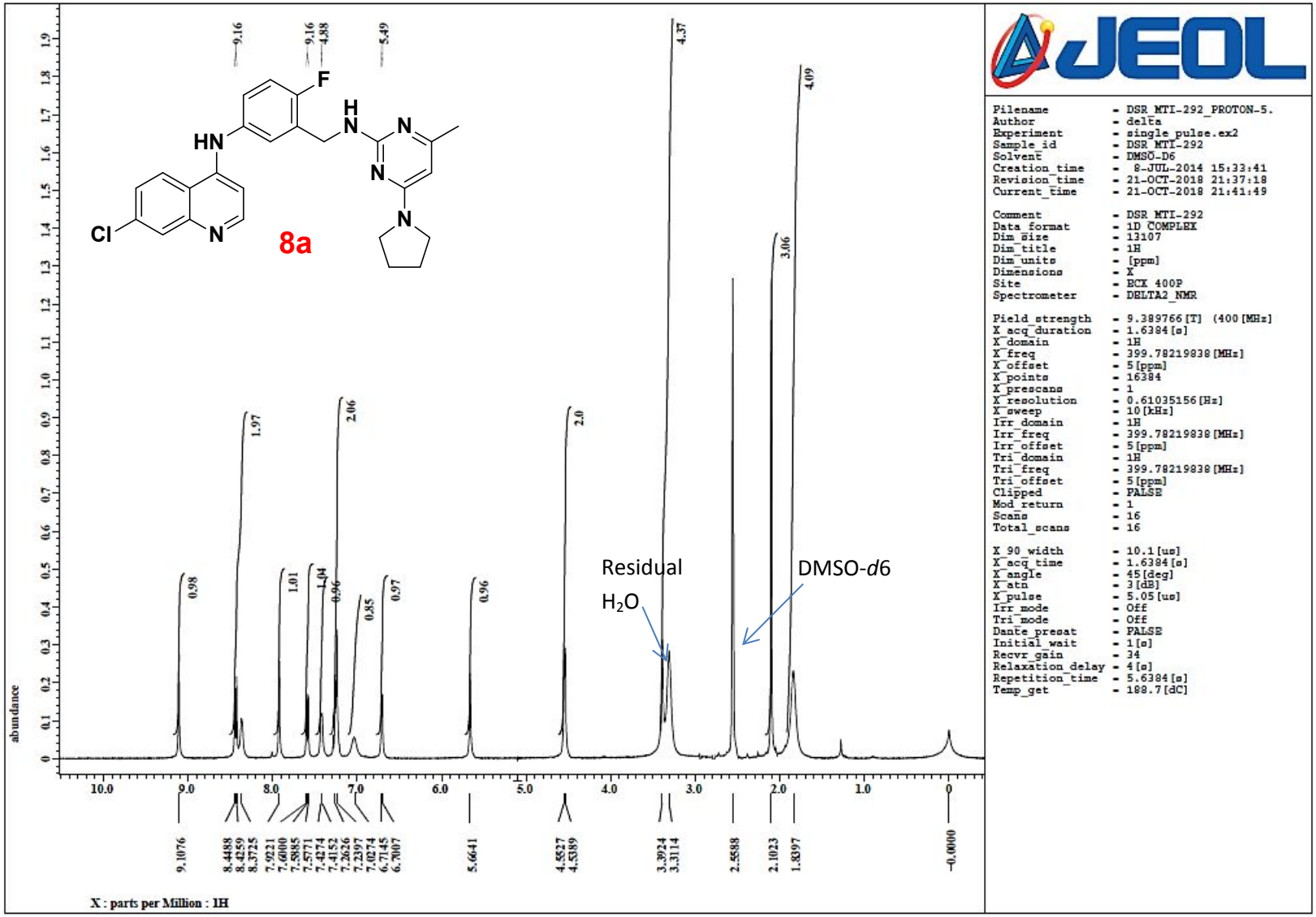
Pilename - DSR_MTI-312_PROTON-5.
Author - delta
Experiment - single_pulse.ex2
Sample_id - DSR_MTI-312
Solvent - DMSO-D6
Creation_time - 8-JUL-2014 15:20:48
Revision_time - 21-OCT-2018 20:04:37
Current_time - 21-OCT-2018 20:06:06

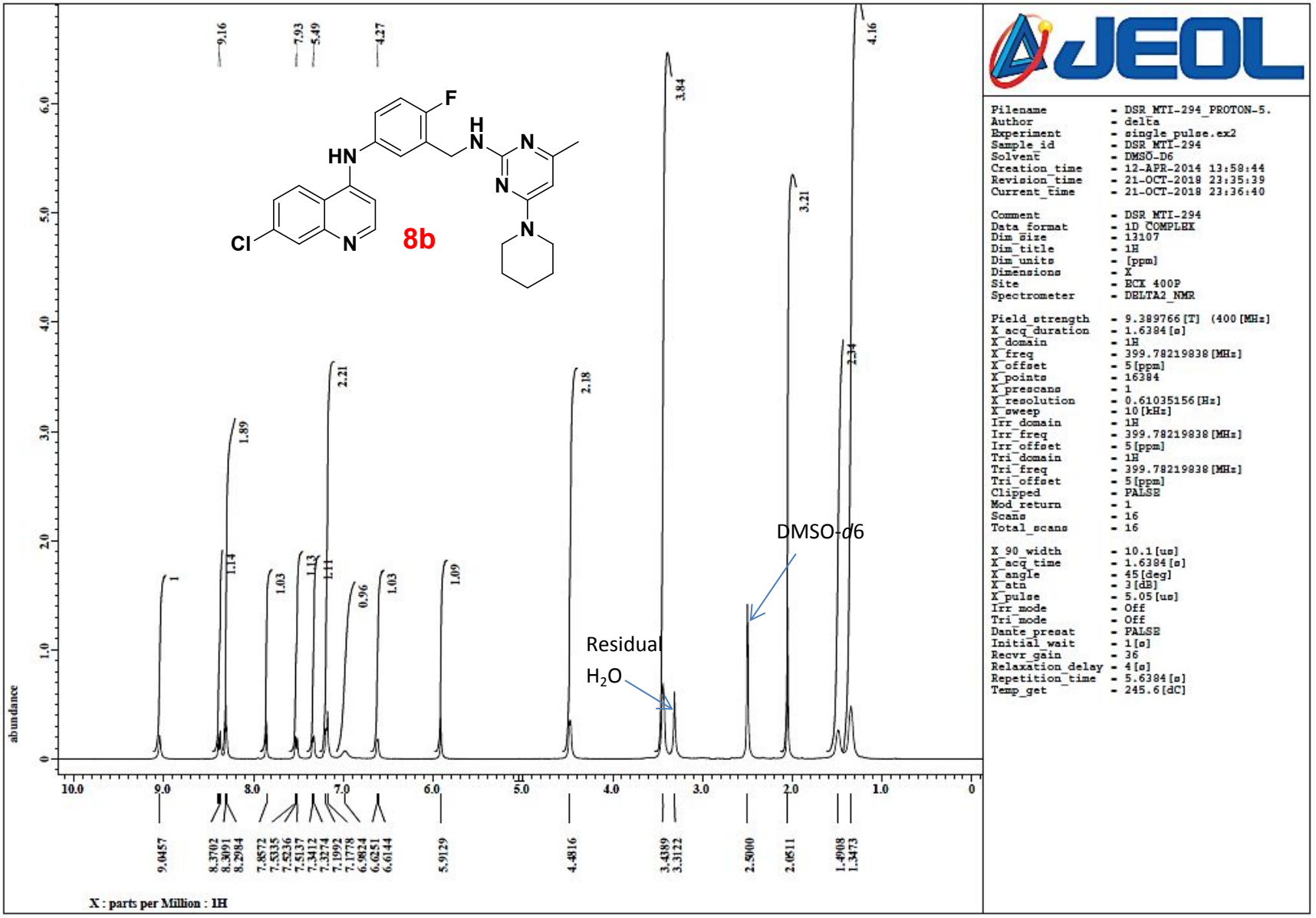
Comment - DSR_MTI-312
Data_format - 1D COMPLEX
Dim_size - 13107
Dim_title - 1H
Dim_units - [ppm]
Dimensions - X
Site - ECX 400P
Spectrometer - DELTA2_NMR

Field_strength - 9.389766[T] (400[MHz]
X_acq_duration - 1.6384[s]
X_domain - 1H
X_freq - 399.78219838[MHz]
X_offset - 5[ppm]
X_points - 16384
X_prescans - 1
X_resolution - 0.61035156[Hz]
X_sweep - 10[kHz]
Irr_domain - 1H
Irr_freq - 399.78219838[MHz]
Irr_offset - 5[ppm]
Tri_domain - 1H
Tri_freq - 399.78219838[MHz]
Tri_offset - 5[ppm]
Clipped - FALSE
Mod_return - 1
Scans - 16
Total_scans - 16

X_90_width - 10.1[us]
X_acq_time - 1.6384[s]
X_angle - 45[deg]
X_atn - 3[dB]
X_pulse - 5.05[us]
Irr_mode - Off
Tri_mode - Off
Dante_presat - FALSE
Initial_wait - 1[s]
Recvr_gain - 34
Relaxation_delay - 4[s]
Repetition_time - 5.6384[s]
Temp_get - 187.8[dC]

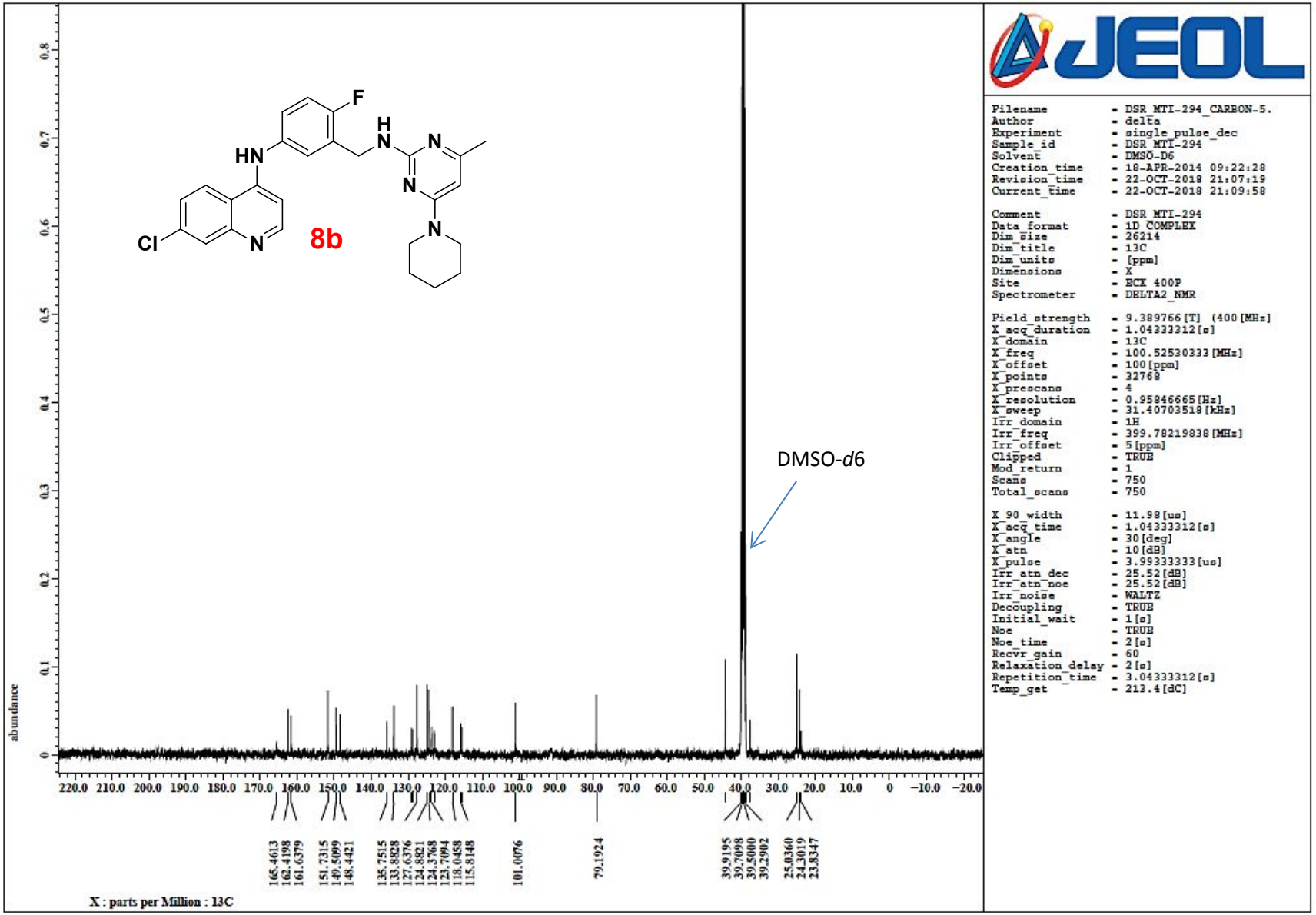

7h
Residual
H_2O
DMSO-*d*6
X : parts per Million : 1H
abundance

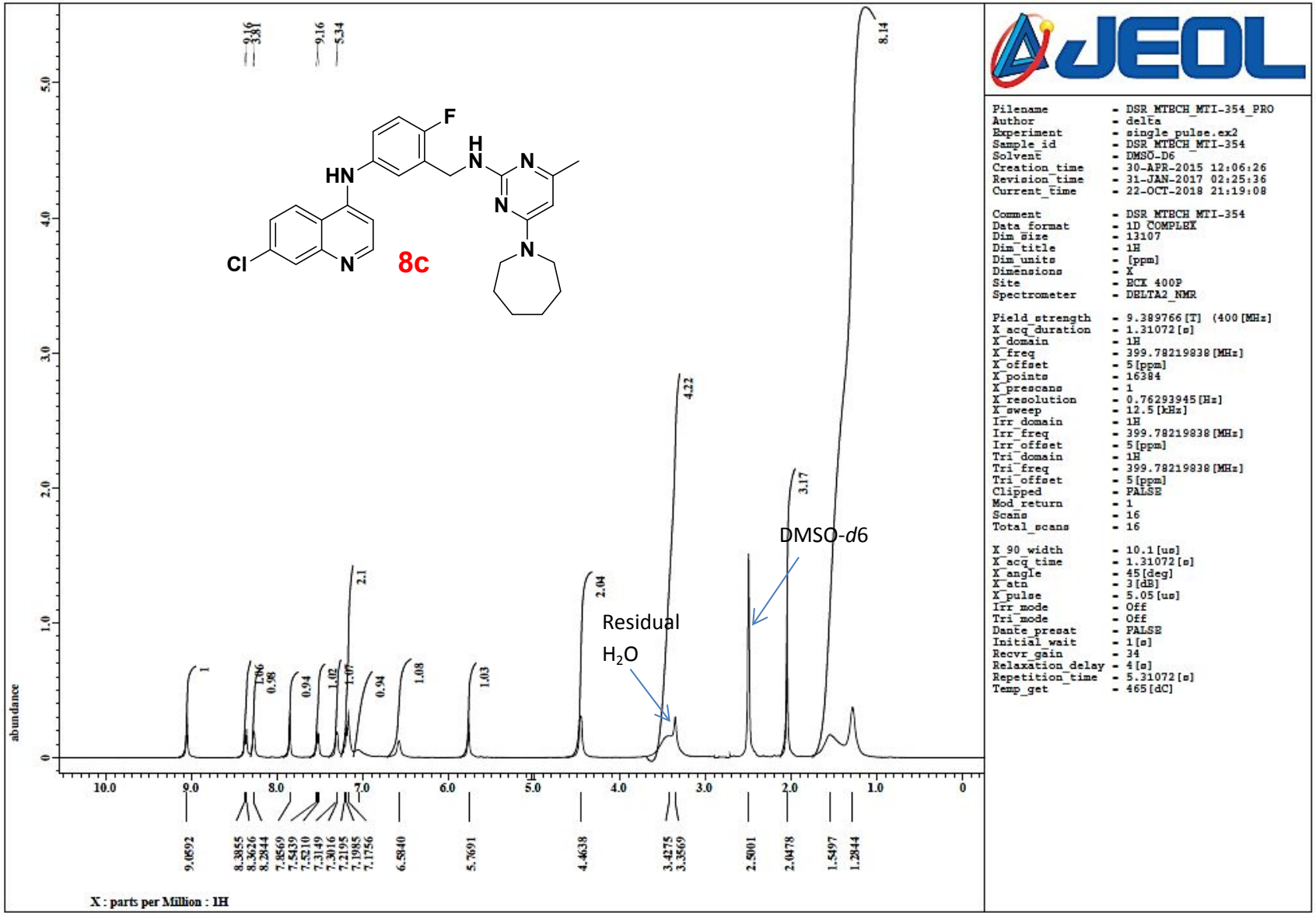

8a
Residual
H_2O
DMSO-*d*6
X : parts per Million : 1H
abundance



JEOL

```
Pilename            - DSR_MTI-294_PROTON-5.
Author              - delta
Experiment          - single_pulse.ex2
Sample_id           - DSR_MTI-294
Solvent             - DMSO-D6
Creation_time       - 12-APR-2014 13:58:44
Revision_time       - 21-OCT-2018 23:35:39
Current_time        - 21-OCT-2018 23:36:40

Comment             - DSR_MTI-294
Data_format         - 1D COMPLEX
Dim_size            - 13107
Dim_title           - 1H
Dim_units           - [ppm]
Dimensions          - X
Site                - ECX 400P
Spectrometer        - DELTA2_NMR

Field_strength      - 9.389766[T]  (400[MHz]
X_acq_duration      - 1.6384[s]
X_domain            - 1H
X_freq              - 399.78219838[MHz]
X_offset            - 5[ppm]
X_points            - 16384
X_prescans          - 1
X_resolution        - 0.61035156[Hz]
X_sweep             - 10[kHz]
Irr_domain          - 1H
Irr_freq            - 399.78219838[MHz]
Irr_offset          - 5[ppm]
Tri_domain          - 1H
Tri_freq            - 399.78219838[MHz]
Tri_offset          - 5[ppm]
Clipped             - FALSE
Mod_return          - 1
Scans               - 16
Total_scans         - 16

X_90_width          - 10.1[us]
X_acq_time          - 1.6384[s]
X_angle             - 45[deg]
X_atn               - 3[dB]
X_pulse             - 5.05[us]
Irr_mode            - Off
Tri_mode            - Off
Dante_presat        - FALSE
Initial_wait        - 1[s]
Recvr_gain          - 36
Relaxation_delay    - 4[s]
Repetition_time     - 5.6384[s]
Temp_get            - 245.6[dC]
```


F
HN
H
N
N
N
N
Cl
N
8b
DMSO-d6
abundance
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 −10.0 −20.0
165.4613
162.4198
161.6379
151.7315
149.5099
148.4421
135.7515
133.8828
127.6376
124.8821
124.3768
123.7094
118.0458
115.8148
101.0076
79.1924
39.9195
39.7098
39.5000
39.2902
25.0360
24.3019
23.8347
X : parts per Million : 13C
Pilename - DSR_MTI-294_CARBON-5.
Author - delta
Experiment - single_pulse_dec
Sample_id - DSR_MTI-294
Solvent - DMSO-D6
Creation_time - 18-APR-2014 09:22:28
Revision_time - 22-OCT-2018 21:07:19
Current_time - 22-OCT-2018 21:09:58
Comment - DSR_MTI-294
Data_format - 1D COMPLEX
Dim_size - 26214
Dim_title - 13C
Dim_units - [ppm]
Dimensions - X
Site - ECX 400P
Spectrometer - DELTA2_NMR
Field_strength - 9.389766[T] (400[MHz]
X_acq_duration - 1.04333312[s]
X_domain - 13C
X_freq - 100.52530333[MHz]
X_offset - 100[ppm]
X_points - 32768
X_prescans - 4
X_resolution - 0.95846665[Hz]
X_sweep - 31.40703518[kHz]
Irr_domain - 1H
Irr_freq - 399.78219838[MHz]
Irr_offset - 5[ppm]
Clipped - TRUE
Mod_return - 1
Scans - 750
Total_scans - 750
X_90_width - 11.98[us]
X_acq_time - 1.04333312[s]
X_angle - 30[deg]
X_atn - 10[dB]
X_pulse - 3.99333333[us]
Irr_atn_dec - 25.52[dB]
Irr_atn_noe - 25.52[dB]
Irr_noise - WALTZ
Decoupling - TRUE
Initial_wait - 1[s]
Noe - TRUE
Noe_time - 2[s]
Recvr_gain - 60
Relaxation_delay - 2[s]
Repetition_time - 3.04333312[s]
Temp_get - 213.4[dC]

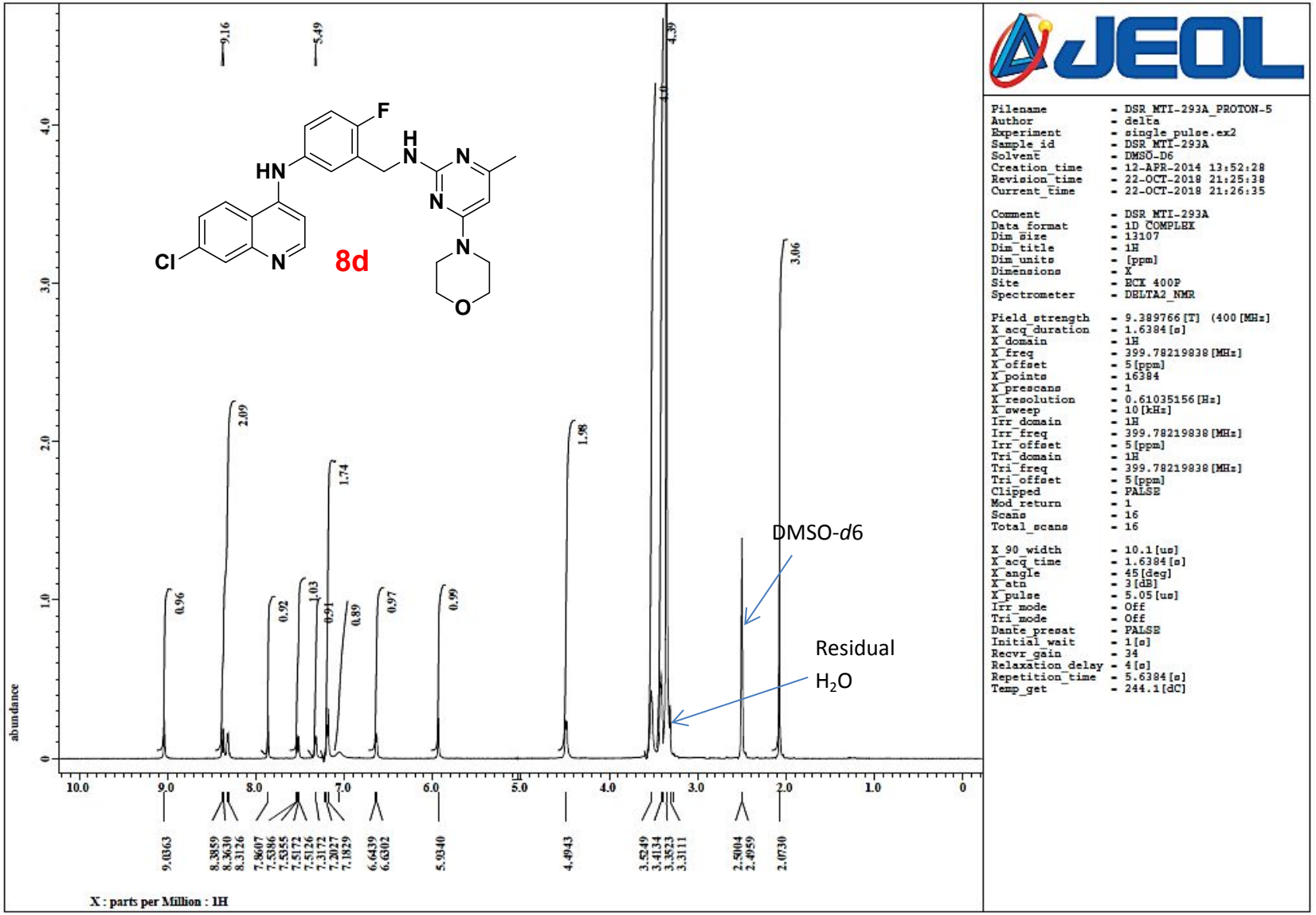


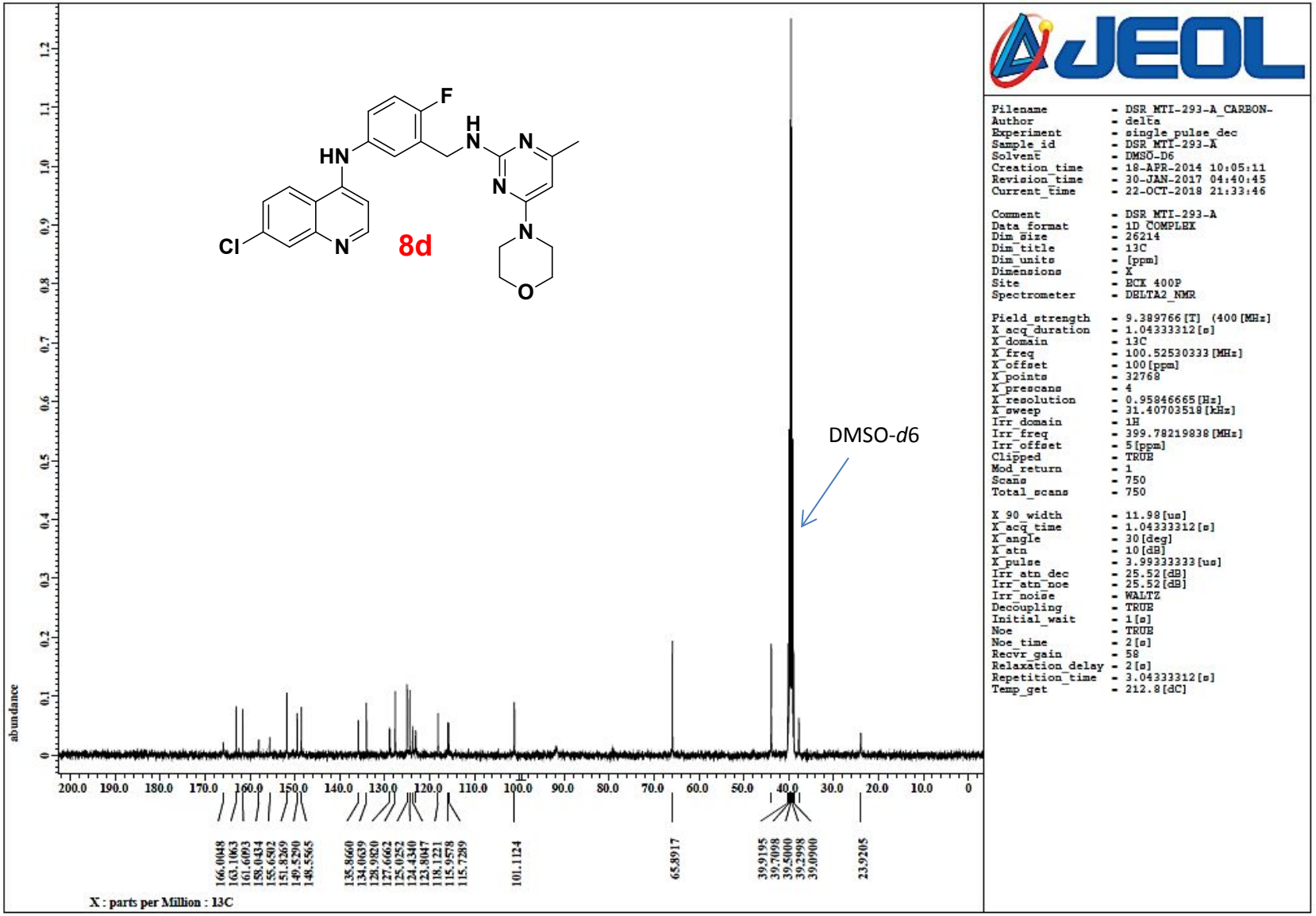
Pilename - DSR_MTBCH_MTI-354_PRO
Author - delta
Experiment - single_pulse.ex2
Sample_id - DSR_MTBCH_MTI-354
Solvent - DMSO-D6
Creation_time - 30-APR-2015 12:06:26
Revision_time - 31-JAN-2017 02:25:36
Current_time - 22-OCT-2018 21:19:08

Comment - DSR_MTBCH_MTI-354
Data_format - 1D COMPLEX
Dim_size - 13107
Dim_title - 1H
Dim_units - [ppm]
Dimensions - X
Site - ECX 400P
Spectrometer - DELTA2_NMR

Field_strength - 9.389766[T] (400[MHz]
X_acq_duration - 1.31072[s]
X_domain - 1H
X_freq - 399.78219838[MHz]
X_offset - 5[ppm]
X_points - 16384
X_prescans - 1
X_resolution - 0.76293945[Hz]
X_sweep - 12.5[kHz]
Irr_domain - 1H
Irr_freq - 399.78219838[MHz]
Irr_offset - 5[ppm]
Tri_domain - 1H
Tri_freq - 399.78219838[MHz]
Tri_offset - 5[ppm]
Clipped - FALSE
Mod_return - 1
Scans - 16
Total_scans - 16

X_90_width - 10.1[us]
X_acq_time - 1.31072[s]
X_angle - 45[deg]
X_atn - 3[dB]
X_pulse - 5.05[us]
Irr_mode - Off
Tri_mode - Off
Dante_presat - FALSE
Initial_wait - 1[s]
Recvr_gain - 34
Relaxation_delay - 4[s]
Repetition_time - 5.31072[s]
Temp_get - 465[dC]


8d
DMSO-d6
Residual
H2O
abundance
X : parts per Million : 1H
Pilename - DSR_MTI-293A_PROTON-5
Author - delta
Experiment - single_pulse.ex2
Sample_id - DSR_MTI-293A
Solvent - DMSO-D6
Creation_time - 12-APR-2014 13:52:28
Revision_time - 22-OCT-2018 21:25:38
Current_time - 22-OCT-2018 21:26:35
Comment - DSR_MTI-293A
Data_format - 1D COMPLEX
Dim_size - 13107
Dim_title - 1H
Dim_units - [ppm]
Dimensions - X
Site - RCX 400P
Spectrometer - DELTA2_NMR
Field_strength - 9.389766[T] (400[MHz]
X_acq_duration - 1.6384[s]
X_domain - 1H
X_freq - 399.78219838[MHz]
X_offset - 5[ppm]
X_points - 16384
X_prescans - 1
X_resolution - 0.61035156[Hz]
X_sweep - 10[kHz]
Irr_domain - 1H
Irr_freq - 399.78219838[MHz]
Irr_offset - 5[ppm]
Tri_domain - 1H
Tri_freq - 399.78219838[MHz]
Tri_offset - 5[ppm]
Clipped - FALSE
Mod_return - 1
Scans - 16
Total_scans - 16
X_90_width - 10.1[us]
X_acq_time - 1.6384[s]
X_angle - 45[deg]
X_atn - 3[dB]
X_pulse - 5.05[us]
Irr_mode - Off
Tri_mode - Off
Dante_presat - FALSE
Initial_wait - 1[s]
Recvr_gain - 34
Relaxation_delay - 4[s]
Repetition_time - 5.6384[s]
Temp_get - 244.1[dC]

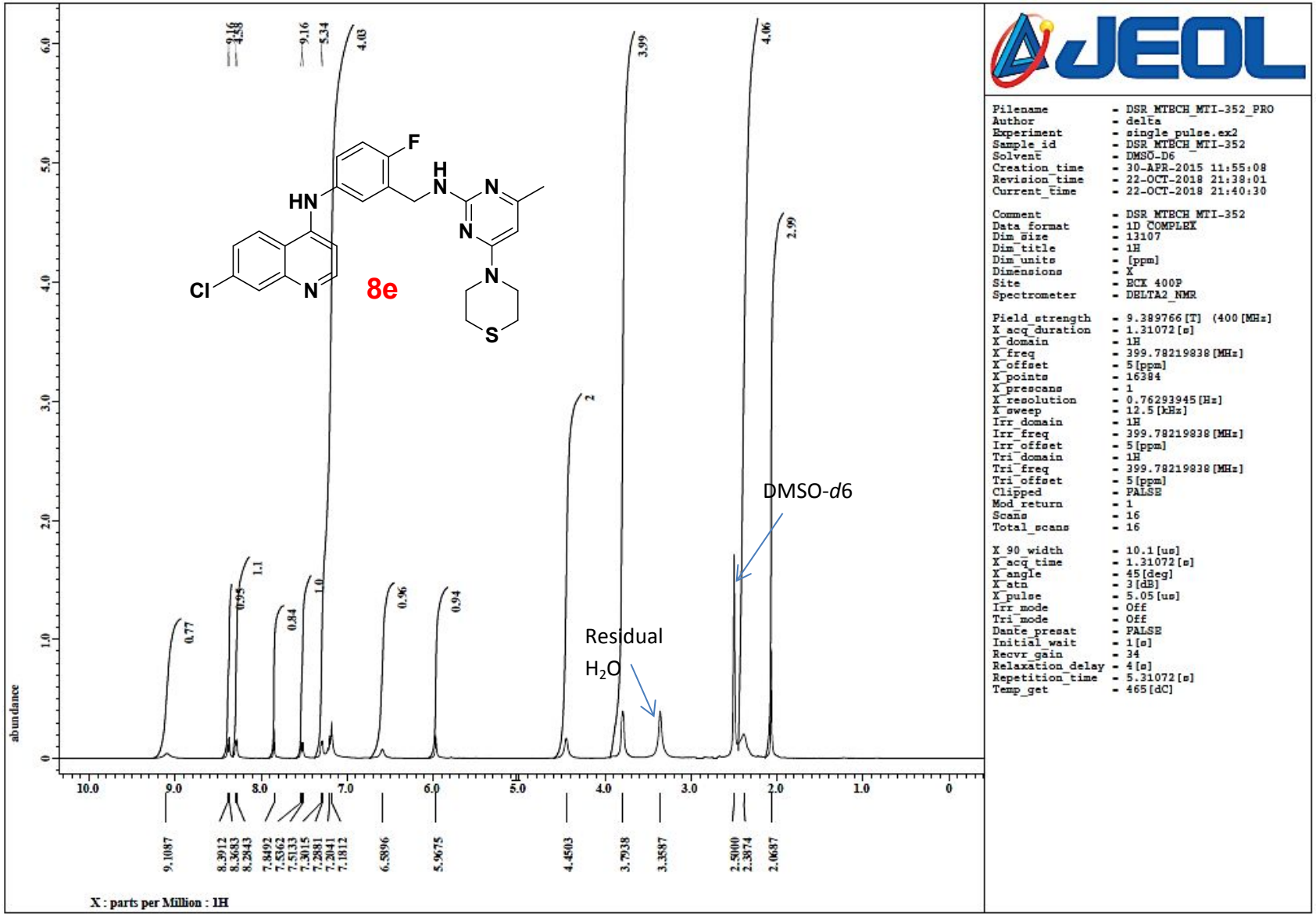


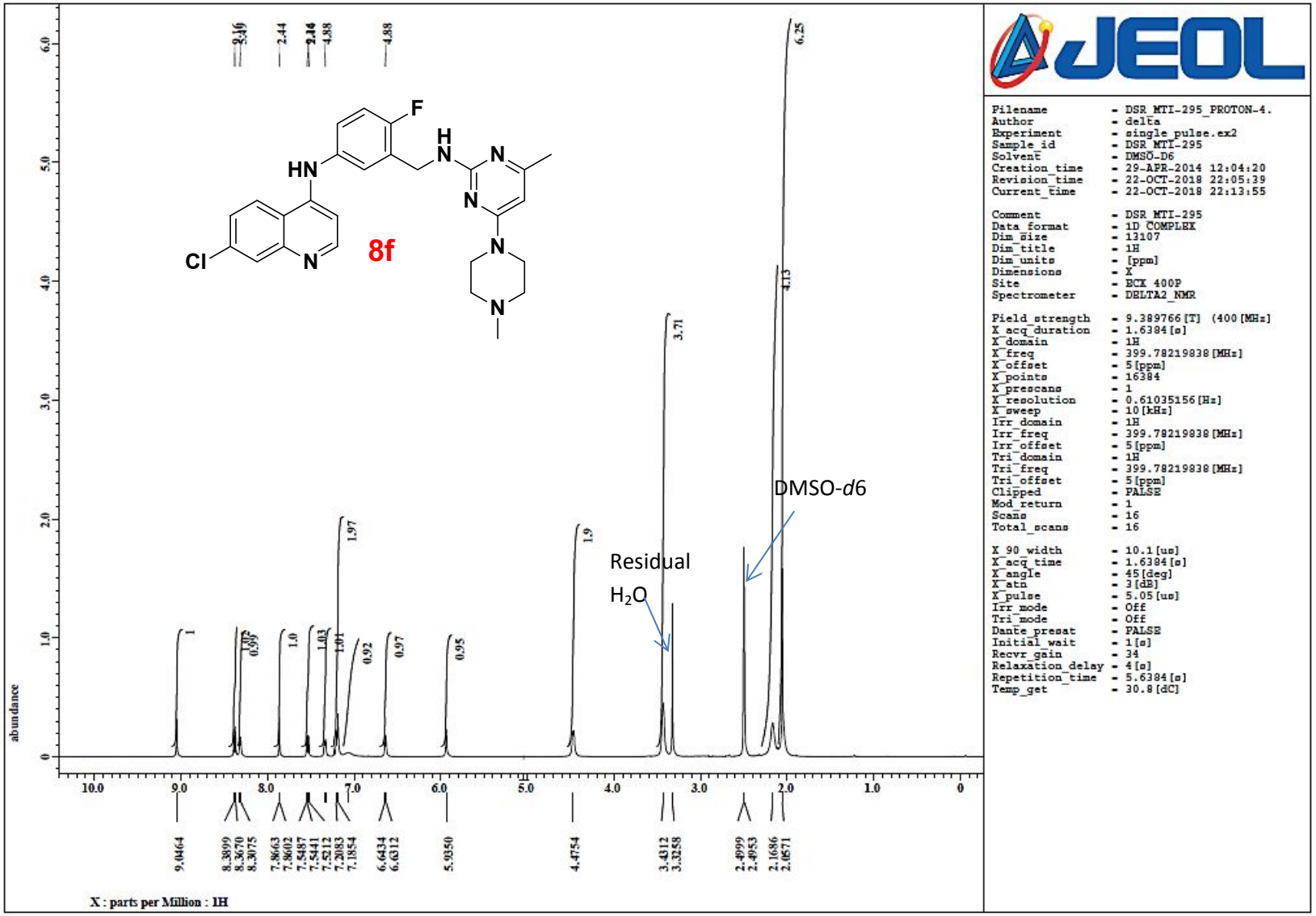
Pilename - DSR_MTI-293-A_CARBON-
Author - delta
Experiment - single_pulse_dec
Sample_id - DSR_MTI-293-A
Solvent - DMSO-D6
Creation_time - 18-APR-2014 10:05:11
Revision_time - 30-JAN-2017 04:40:45
Current_time - 22-OCT-2018 21:33:46

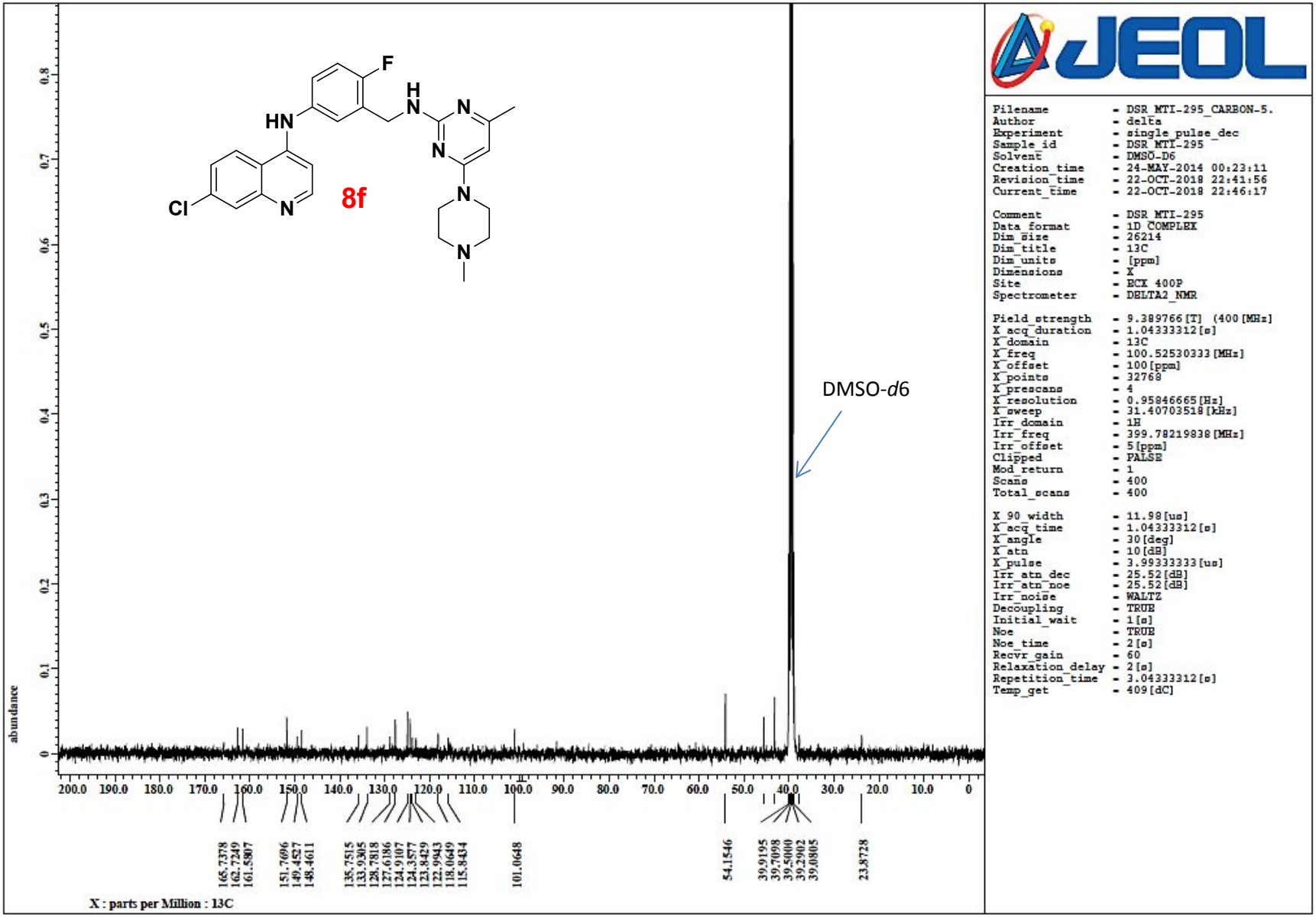
Comment - DSR_MTI-293-A
Data_format - 1D COMPLEX
Dim_size - 26214
Dim_title - 13C
Dim_units - [ppm]
Dimensions - X
Site - BCX 400P
Spectrometer - DELTA2_NMR

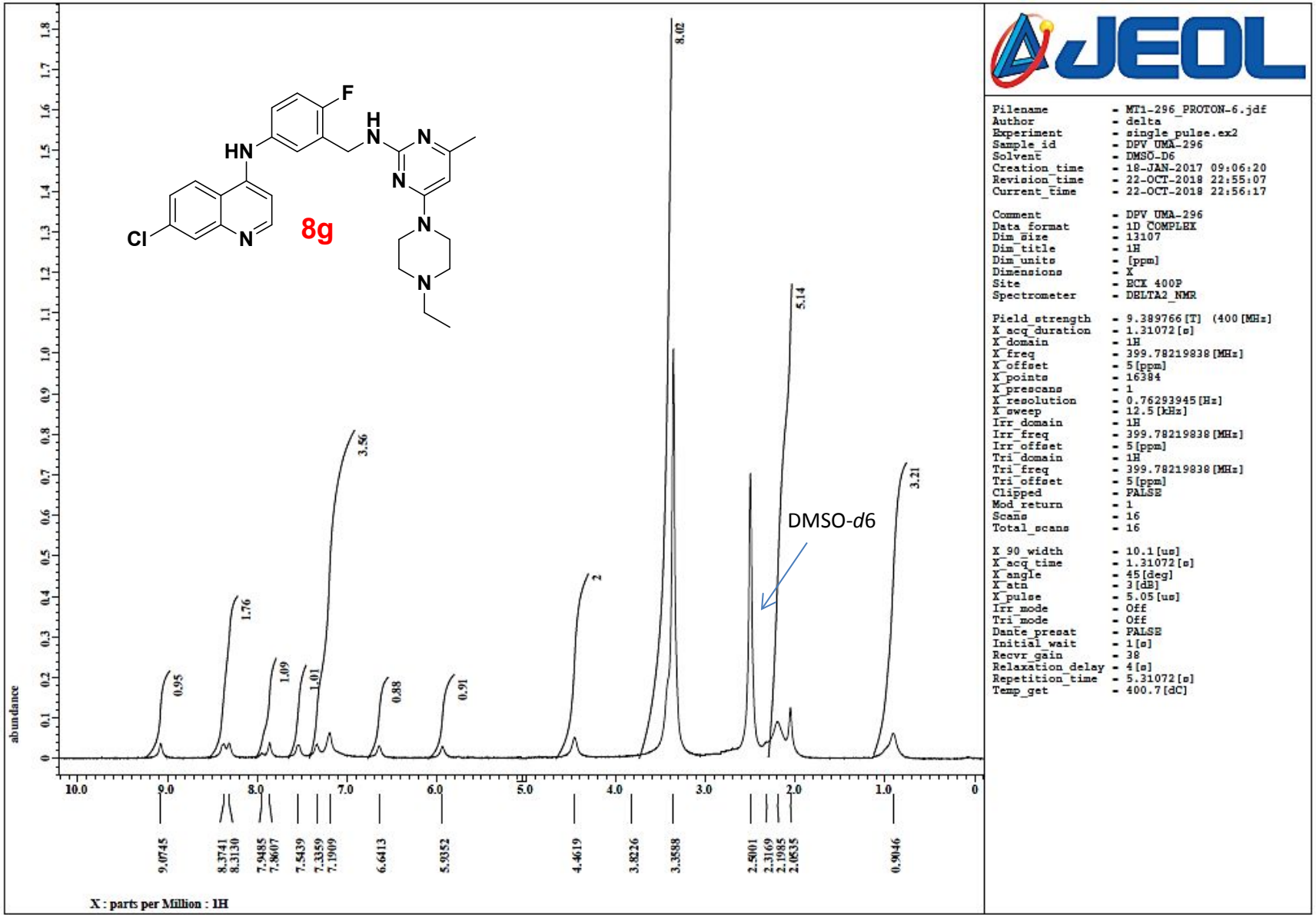
Field_strength - 9.389766[T] (400[MHz]
X_acq_duration - 1.04333312[s]
X_domain - 13C
X_freq - 100.52530333[MHz]
X_offset - 100[ppm]
X_points - 32768
X_prescans - 4
X_resolution - 0.95846665[Hz]
X_sweep - 31.40703518[kHz]
Irr_domain - 1H
Irr_freq - 399.78219838[MHz]
Irr_offset - 5[ppm]
Clipped - TRUE
Mod_return - 1
Scans - 750
Total_scans - 750

X_90_width - 11.98[us]
X_acq_time - 1.04333312[s]
X_angle - 30[deg]
X_atn - 10[dB]
X_pulse - 3.99333333[us]
Irr_atn_dec - 25.52[dB]
Irr_atn_noe - 25.52[dB]
Irr_noise - WALTZ
Decoupling - TRUE
Initial_wait - 1[s]
Noe - TRUE
Noe_time - 2[s]
Recvr_gain - 58
Relaxation_delay - 2[s]
Repetition_time - 3.04333312[s]
Temp_get - 212.8[dC]


8e
Residual
H_2O
DMSO-*d*6
abundance
X : parts per Million : 1H
Pilename - DSR_MTECH_MTI-352_PRO
Author - delta
Experiment - single_pulse.ex2
Sample_id - DSR_MTECH_MTI-352
Solvent - DMSO-D6
Creation_time - 30-APR-2015 11:55:08
Revision_time - 22-OCT-2018 21:38:01
Current_time - 22-OCT-2018 21:40:30
Comment - DSR_MTECH_MTI-352
Data_format - 1D COMPLEX
Dim_size - 13107
Dim_title - 1H
Dim_units - [ppm]
Dimensions - X
Site - ECX 400P
Spectrometer - DELTA2_NMR
Field_strength - 9.389766[T] (400[MHz]
X_acq_duration - 1.31072[s]
X_domain - 1H
X_freq - 399.78219838[MHz]
X_offset - 5[ppm]
X_points - 16384
X_prescans - 1
X_resolution - 0.76293945[Hz]
X_sweep - 12.5[kHz]
Irr_domain - 1H
Irr_freq - 399.78219838[MHz]
Irr_offset - 5[ppm]
Tri_domain - 1H
Tri_freq - 399.78219838[MHz]
Tri_offset - 5[ppm]
Clipped - FALSE
Mod_return - 1
Scans - 16
Total_scans - 16
X_90_width - 10.1[us]
X_acq_time - 1.31072[s]
X_angle - 45[deg]
X_atn - 3[dB]
X_pulse - 5.05[us]
Irr_mode - Off
Tri_mode - Off
Dante_presat - FALSE
Initial_wait - 1[s]
Recvr_gain - 34
Relaxation_delay - 4[s]
Repetition_time - 5.31072[s]
Temp_get - 465[dC]


8f
Residual
H_2O
DMSO-*d*6
X : parts per Million : 1H
abundance


F
HN
H
N
N
N
N
N
Cl
N
8f
DMSO-d6
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
165.7378
162.7249
161.5807
151.7696
149.4527
148.4611
135.7515
133.9305
128.7818
127.6186
124.9107
124.3577
123.8429
122.9943
118.0649
115.8434
101.0648
54.1546
39.9195
39.7098
39.5000
39.2902
39.0805
23.8728
X : parts per Million : 13C
Pilename - DSR_MTI-295_CARBON-5.
Author - delta
Experiment - single_pulse_dec
Sample_id - DSR_MTI-295
Solvent - DMSO-D6
Creation_time - 24-MAY-2014 00:23:11
Revision_time - 22-OCT-2018 22:41:56
Current_time - 22-OCT-2018 22:46:17
Comment - DSR_MTI-295
Data_format - 1D COMPLEX
Dim_size - 26214
Dim_title - 13C
Dim_units - [ppm]
Dimensions - X
Site - ECX 400P
Spectrometer - DELTA2_NMR
Field_strength - 9.389766[T] (400[MHz]
X_acq_duration - 1.04333312[s]
X_domain - 13C
X_freq - 100.52530333[MHz]
X_offset - 100[ppm]
X_points - 32768
X_prescans - 4
X_resolution - 0.95846665[Hz]
X_sweep - 31.40703518[kHz]
Irr_domain - 1H
Irr_freq - 399.78219838[MHz]
Irr_offset - 5[ppm]
Clipped - FALSE
Mod_return - 1
Scans - 400
Total_scans - 400
X_90_width - 11.98[us]
X_acq_time - 1.04333312[s]
X_angle - 30[deg]
X_atn - 10[dB]
X_pulse - 3.99333333[us]
Irr_atn_dec - 25.52[dB]
Irr_atn_noe - 25.52[dB]
Irr_noise - WALTZ
Decoupling - TRUE
Initial_wait - 1[s]
Noe - TRUE
Noe_time - 2[s]
Recvr_gain - 60
Relaxation_delay - 2[s]
Repetition_time - 3.04333312[s]
Temp_get - 409[dC]

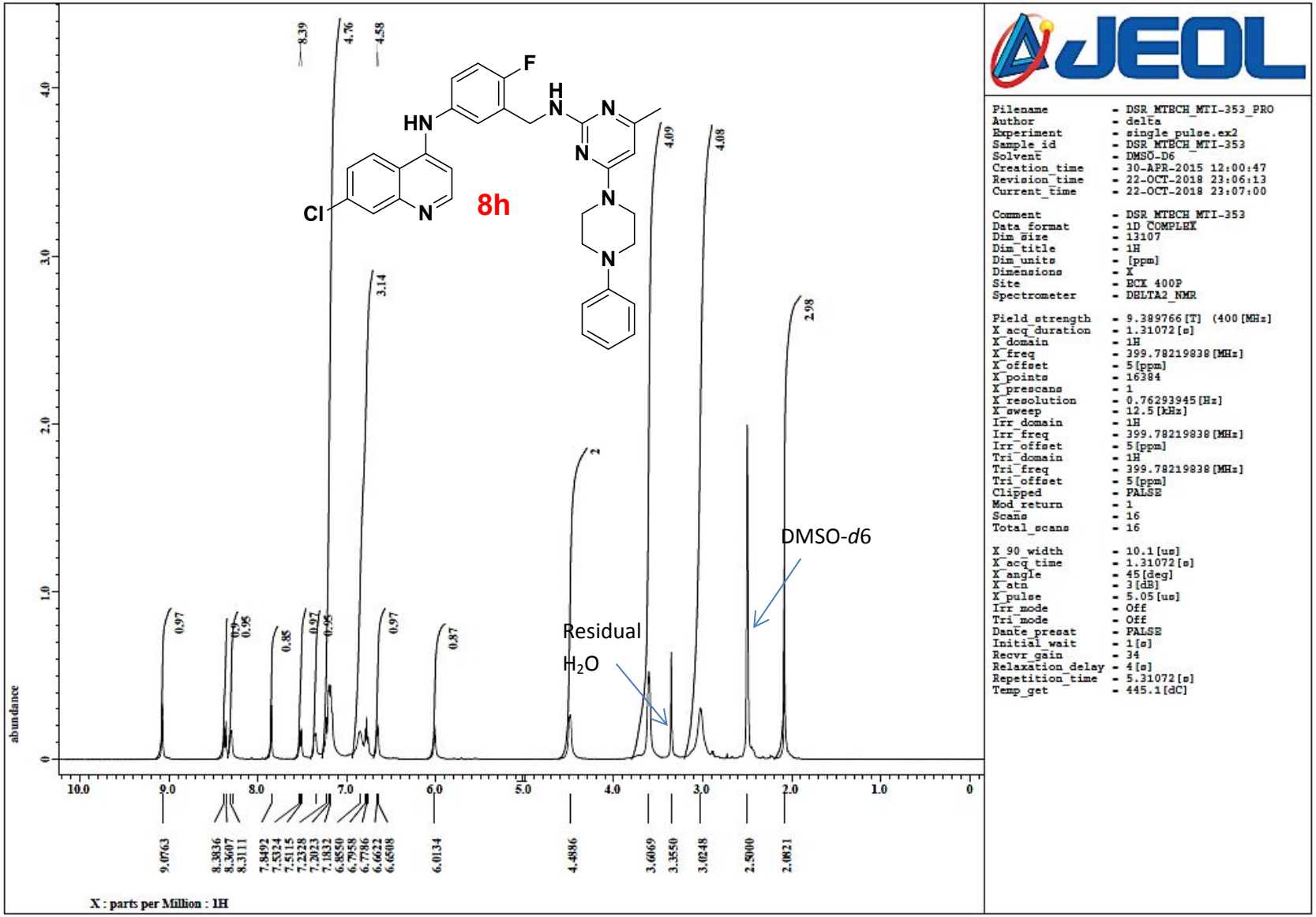


Filename - MT1-296_PROTON-6.jdf
Author - delta
Experiment - single_pulse.ex2
Sample_id - DPV_UMA-296
Solvent - DMSO-D6
Creation_time - 18-JAN-2017 09:06:20
Revision_time - 22-OCT-2018 22:55:07
Current_time - 22-OCT-2018 22:56:17

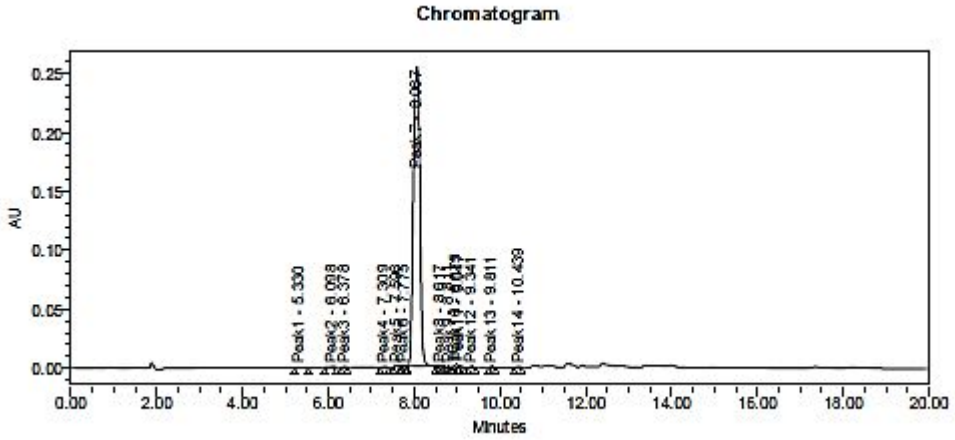
Comment - DPV_UMA-296
Data_format - 1D COMPLEX
Dim_size - 13107
Dim_title - 1H
Dim_units - [ppm]
Dimensions - X
Site - ECX 400P
Spectrometer - DELTA2_NMR

Field_strength - 9.389766[T] (400[MHz]
X_acq_duration - 1.31072[s]
X_domain - 1H
X_freq - 399.78219838[MHz]
X_offset - 5[ppm]
X_points - 16384
X_prescans - 1
X_resolution - 0.76293945[Hz]
X_sweep - 12.5[kHz]
Irr_domain - 1H
Irr_freq - 399.78219838[MHz]
Irr_offset - 5[ppm]
Tri_domain - 1H
Tri_freq - 399.78219838[MHz]
Tri_offset - 5[ppm]
Clipped - FALSE
Mod_return - 1
Scans - 16
Total_scans - 16

X_90_width - 10.1[us]
X_acq_time - 1.31072[s]
X_angle - 45[deg]
X_atn - 3[dB]
X_pulse - 5.05[us]
Irr_mode - Off
Tri_mode - Off
Dante_presat - FALSE
Initial_wait - 1[s]
Recvr_gain - 38
Relaxation_delay - 4[s]
Repetition_time - 5.31072[s]
Temp_get - 400.7[dC]


8h
DMSO-d6
Residual
H2O
X : parts per Million : 1H
abundance

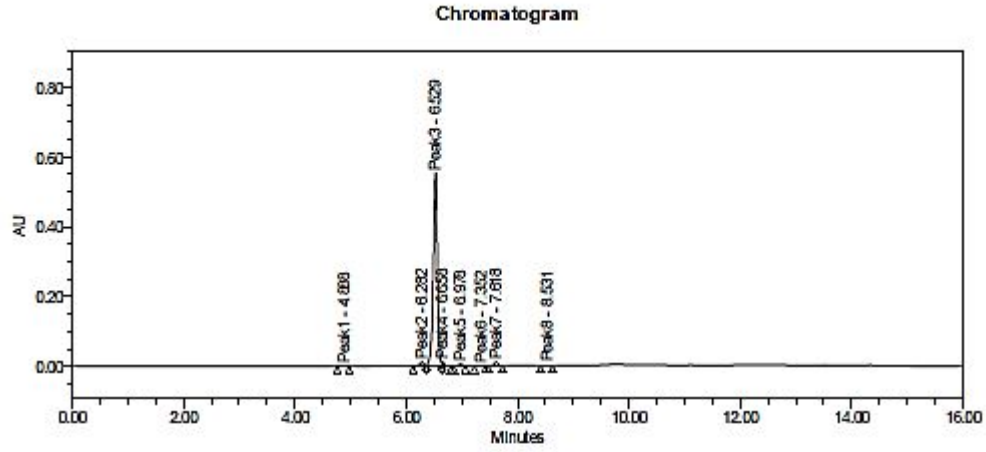
Compound **3**: HPLC Purity: 98.35%



% Area Normalisation Report

	Peak Name	RT	Area	% Area	RT Ratio
1	Peak1	5.33	3370	0.12	0.66
2	Peak2	6.10	1840	0.07	0.76
3	Peak3	6.38	1157	0.04	0.79
4	Peak4	7.31	1830	0.07	0.91
5	Peak5	7.60	5337	0.20	0.94
6	Peak6	7.77	668	0.02	0.96
7	Peak7	8.07	2688318	98.35	1.00
8	Peak8	8.62	885	0.03	1.07
9	Peak9	8.81	533	0.02	1.09
10	Peak10	8.96	11329	0.41	1.11
11	Peak11	9.05	8748	0.32	1.12
12	Peak12	9.34	4631	0.17	1.16
13	Peak13	9.81	2521	0.09	1.22
14	Peak14	10.44	2200	0.08	1.29

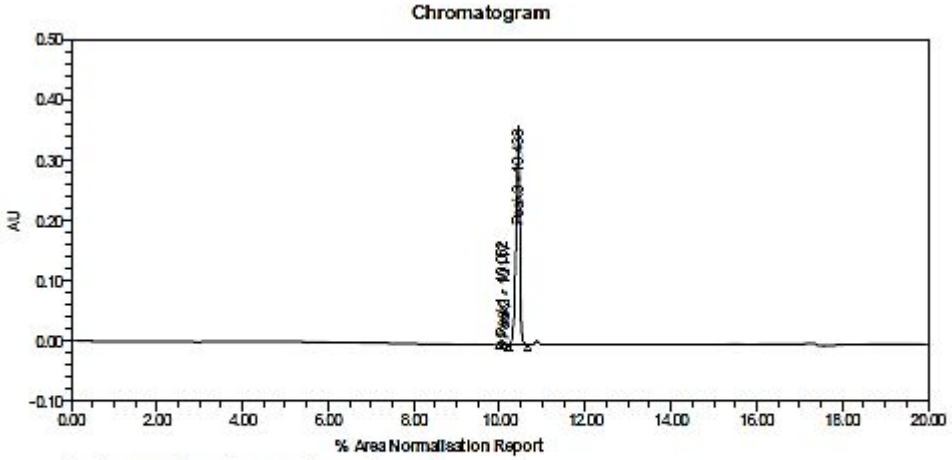
Compound **4**: HPLC Purity: 93.98%



% Area Normalisation Report

	Peak Name	RT	Area	% Area	RT Ratio
1	Peak1	4.89	1351	0.05	0.75
2	Peak2	6.28	58271	1.97	0.96
3	Peak3	6.53	2781685	93.98	1.00
4	Peak4	6.66	37479	1.27	1.02
5	Peak5	6.98	26442	0.89	1.07
6	Peak6	7.35	2710	0.09	1.13
7	Peak7	7.62	49957	1.69	1.17
8	Peak8	8.53	2044	0.07	1.31

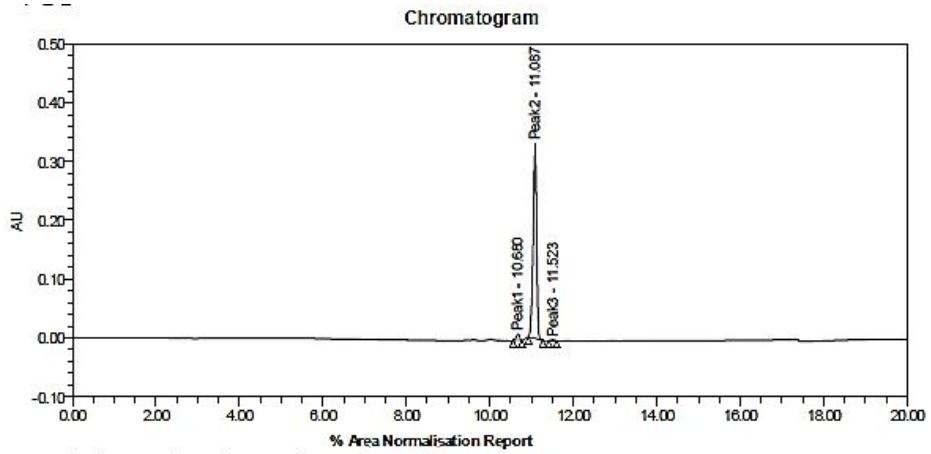
Compound **6a**: HPLC Purity: 99.05%



% Area Normalisation Report

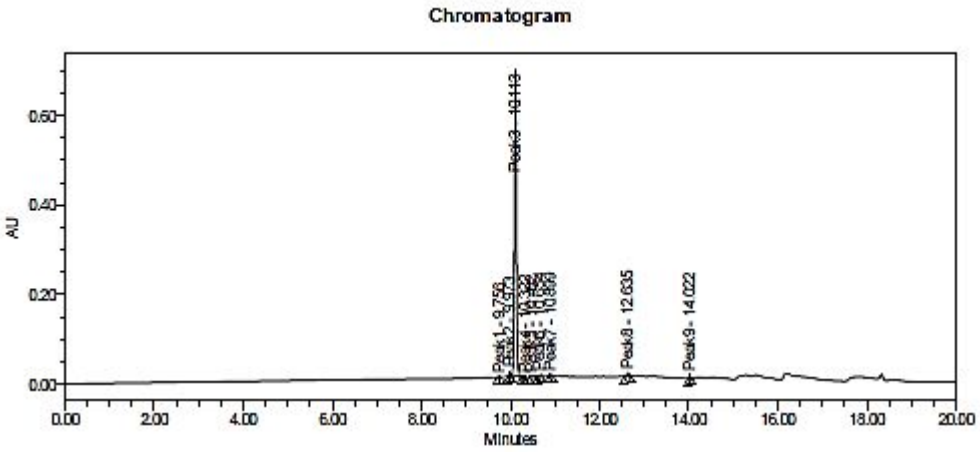
	Peak Name	RT	Area	% Area	RT Ratio
1	Peak1	10.05	18256	0.83	0.96
2	Peak2	10.12	2758	0.13	0.97
3	Peak3	10.44	2179704	99.05	1.00

Compound **6b**: HPLC Purity: 96.76%



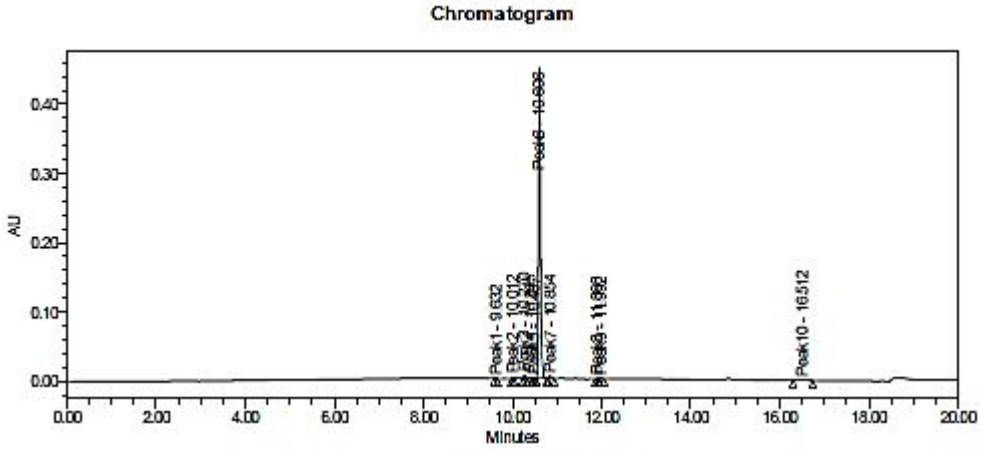
	Peak Name	RT	Area	% Area	RT Ratio
1	Peak1	10.68	57609	2.92	0.96
2	Peak2	11.09	1909416	96.76	1.00
3	Peak3	11.52	6404	0.32	1.04

Compound **7a**: HPLC Purity: 96.11%



	Peak Name	RT	Area	% Area	RT Ratio
1	Peak1	9.76	5065	0.23	0.96
2	Peak2	9.97	19105	0.86	0.99
3	Peak3	10.11	2139223	96.11	1.00
4	Peak4	10.32	752	0.03	1.02
5	Peak5	10.48	7328	0.33	1.04
6	Peak6	10.65	4316	0.19	1.05
7	Peak7	10.90	7617	0.34	1.08
8	Peak8	12.64	27942	1.26	1.25
9	Peak9	14.02	14561	0.65	1.39

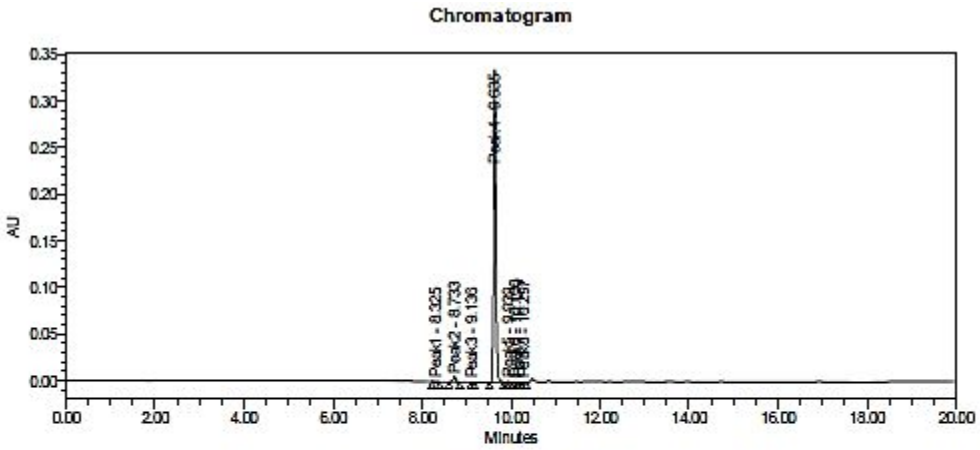
Compound **7b**: HPLC Purity: 96.60%



% Area Normalisation Report

	Peak Name	RT	Area	% Area	RT Ratio
1	Peak1	9.63	320	0.02	0.91
2	Peak2	10.01	2256	0.16	0.94
3	Peak3	10.27	12024	0.83	0.97
4	Peak4	10.40	6224	0.43	0.98
5	Peak5	10.49	1408	0.10	0.99
6	Peak6	10.61	1401302	96.60	1.00
7	Peak7	10.85	9197	0.63	1.02
8	Peak8	11.90	773	0.05	1.12
9	Peak9	11.99	2476	0.17	1.13
10	Peak10	16.51	14623	1.01	1.56

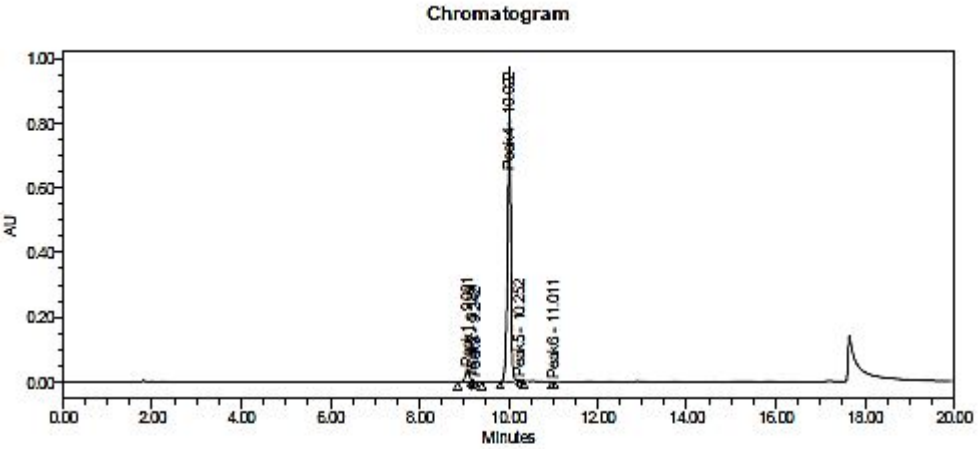
Compound **7c**: HPLC Purity: 97.75%



% Area Normalisation Report

	Peak Name	RT	Area	% Area	RT Ratio
1	Peak1	8.32	661	0.05	0.86
2	Peak2	8.73	23357	1.96	0.91
3	Peak3	9.14	348	0.03	0.95
4	Peak4	9.63	1166056	97.75	1.00
5	Peak5	9.94	1018	0.09	1.03
6	Peak6	10.10	730	0.06	1.05
7	Peak7	10.18	181	0.02	1.06
8	Peak8	10.30	597	0.05	1.07

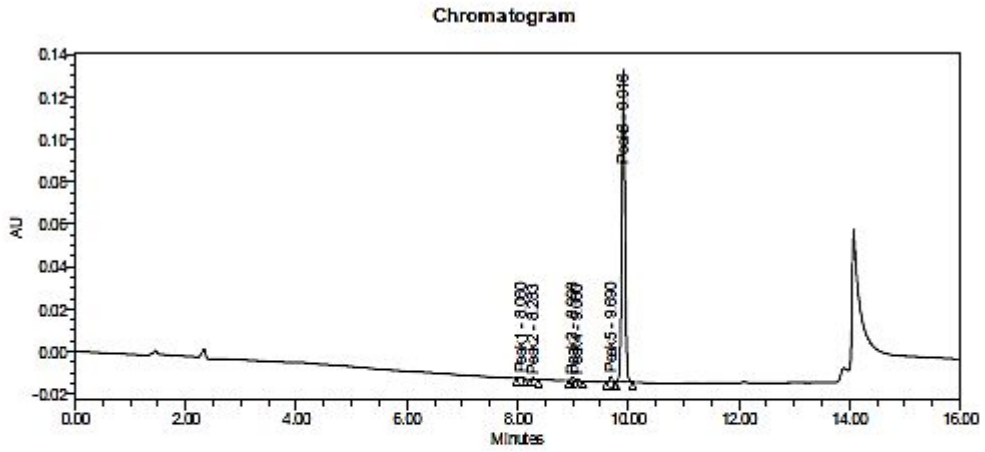
Compound **7d**: HPLC Purity: 94.45%



% Area Normalisation Report

	Peak Name	RT	Area	% Area	RT Ratio
1	Peak1	9.08	227377	4.69	0.91
2	Peak2	9.18	30181	0.62	0.92
3	Peak3	9.24	5424	0.11	0.92
4	Peak4	10.02	4577340	94.45	1.00
5	Peak5	10.25	5226	0.11	1.02
6	Peak6	11.01	854	0.02	1.10

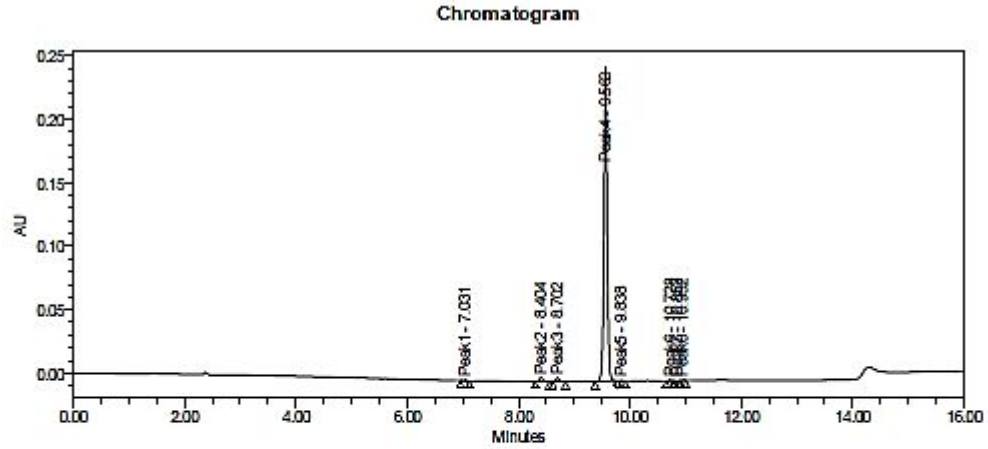
Compound **7e**: HPLC Purity: 95.85%



% Area Normalisation Report

	Peak Name	RT	Area	% Area	RT Ratio
1	Peak1	8.05	3352	0.54	0.81
2	Peak2	8.28	1320	0.21	0.84
3	Peak3	9.00	6211	1.01	0.91
4	Peak4	9.08	4743	0.77	0.92
5	Peak5	9.69	9908	1.61	0.98
6	Peak6	9.92	590033	95.85	1.00

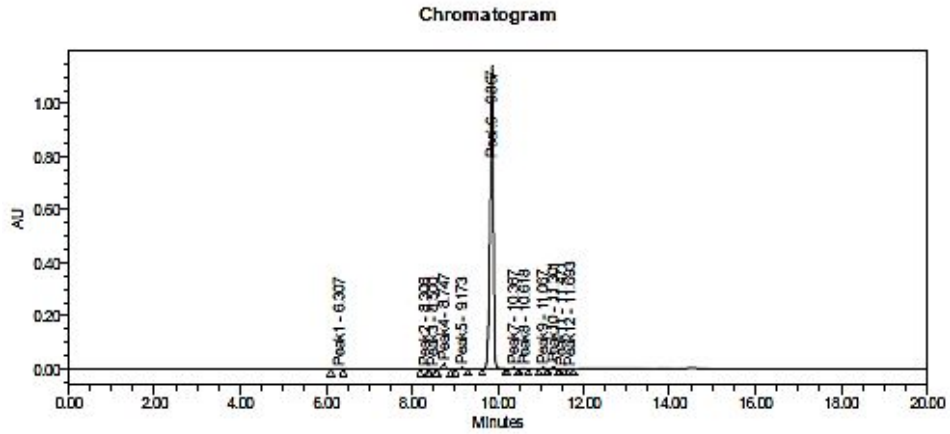
Compound **7f**: HPLC Purity: 97.17%



% Area Normalisation Report

	Peak Name	RT	Area	% Area	RT Ratio
1	Peak1	7.03	935	0.09	0.74
2	Peak2	8.40	13365	1.30	0.88
3	Peak3	8.70	12070	1.18	0.91
4	Peak4	9.56	996200	97.17	1.00
5	Peak5	9.84	1151	0.11	1.03
6	Peak6	10.73	782	0.08	1.12
7	Peak7	10.85	214	0.02	1.13
8	Peak8	10.95	499	0.05	1.15

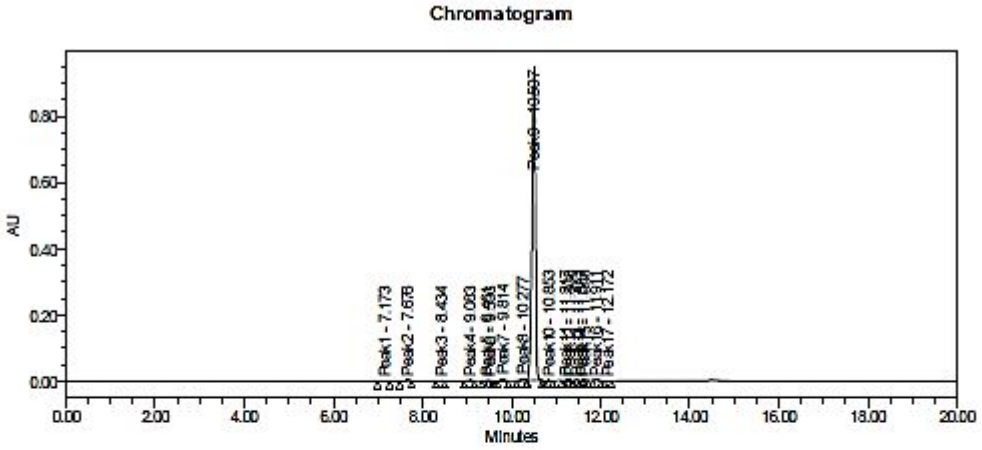
Compound **7g**: HPLC Purity: 96.53%



% Area Normalisation Report

	Peak Name	RT	Area	% Area	RT Ratio
1	Peak1	6.31	3719	0.06	0.64
2	Peak2	8.31	1945	0.03	0.84
3	Peak3	8.50	1015	0.02	0.86
4	Peak4	8.75	100567	1.61	0.89
5	Peak5	9.17	28331	0.45	0.93
6	Peak6	9.87	6039038	96.53	1.00
7	Peak7	10.37	15761	0.25	1.05
8	Peak8	10.62	3186	0.05	1.08
9	Peak9	11.07	22737	0.36	1.12
10	Peak10	11.30	38574	0.62	1.15
11	Peak11	11.47	498	0.01	1.16
12	Peak12	11.69	863	0.01	1.19

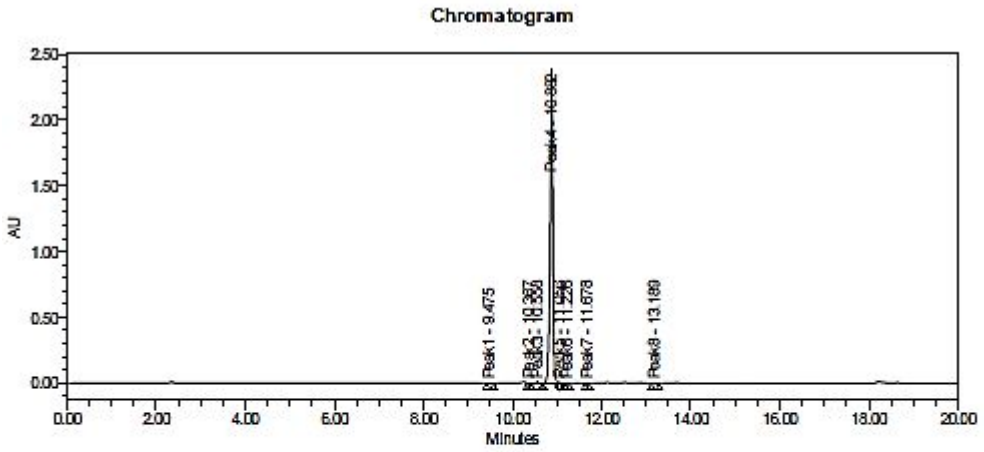
Compound **7h**: HPLC Purity: 96.26%



% Area Normalisation Report

	Peak Name	RT	Area	% Area	RT Ratio
1	Peak1	7.17	7981	0.16	0.68
2	Peak2	7.68	33407	0.66	0.73
3	Peak3	8.43	8732	0.17	0.80
4	Peak4	9.08	11635	0.23	0.86
5	Peak5	9.46	6332	0.12	0.90
6	Peak6	9.54	5639	0.11	0.91
7	Peak7	9.81	33010	0.65	0.93
8	Peak8	10.28	32622	0.64	0.98
9	Peak9	10.51	4900447	96.25	1.00
10	Peak10	10.85	4421	0.09	1.03
11	Peak11	11.22	9805	0.19	1.07
12	Peak12	11.31	6155	0.12	1.08
13	Peak13	11.47	4262	0.08	1.09
14	Peak14	11.59	1919	0.04	1.10
15	Peak15	11.66	5530	0.11	1.11
16	Peak16	11.91	17603	0.35	1.13
17	Peak17	12.17	1184	0.02	1.16

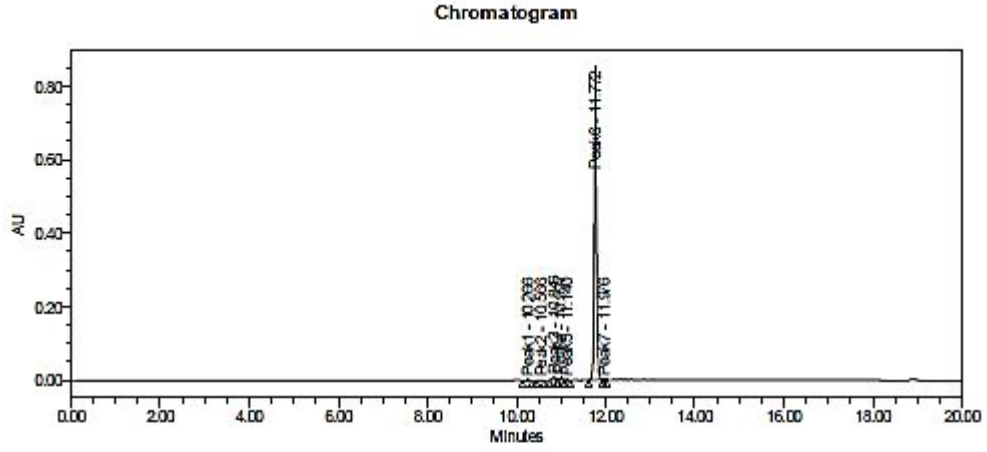
Compound **8a**: HPLC Purity: 99.57%



% Area Normalisation Report

	Peak Name	RT	Area	% Area	RT Ratio
1	Peak1	9.47	2005	0.02	0.87
2	Peak2	10.37	753	0.01	0.95
3	Peak3	10.56	26078	0.25	0.97
4	Peak4	10.88	10218167	99.57	1.00
5	Peak5	11.06	8647	0.08	1.02
6	Peak6	11.23	1055	0.01	1.03
7	Peak7	11.68	2541	0.03	1.07
8	Peak8	13.19	2495	0.02	1.21

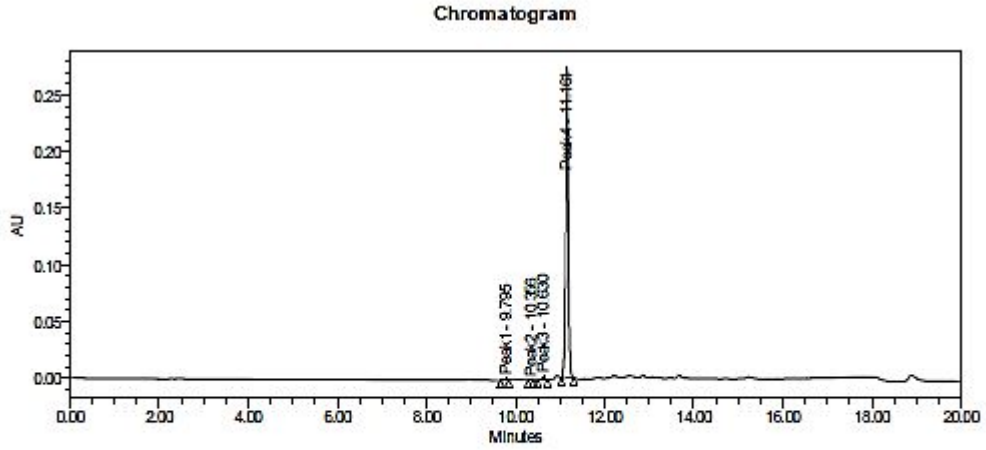
Compound **8b**: HPLC Purity: 97.64%



% Area Normalisation Report

	Peak Name	RT	Area	% Area	RT Ratio
1	Peak1	10.27	12700	0.42	0.87
2	Peak2	10.57	1348	0.04	0.90
3	Peak3	10.85	33043	1.09	0.92
4	Peak4	11.00	16696	0.55	0.93
5	Peak5	11.14	5623	0.18	0.95
6	Peak6	11.77	2967763	97.64	1.00
7	Peak7	11.98	2272	0.07	1.02

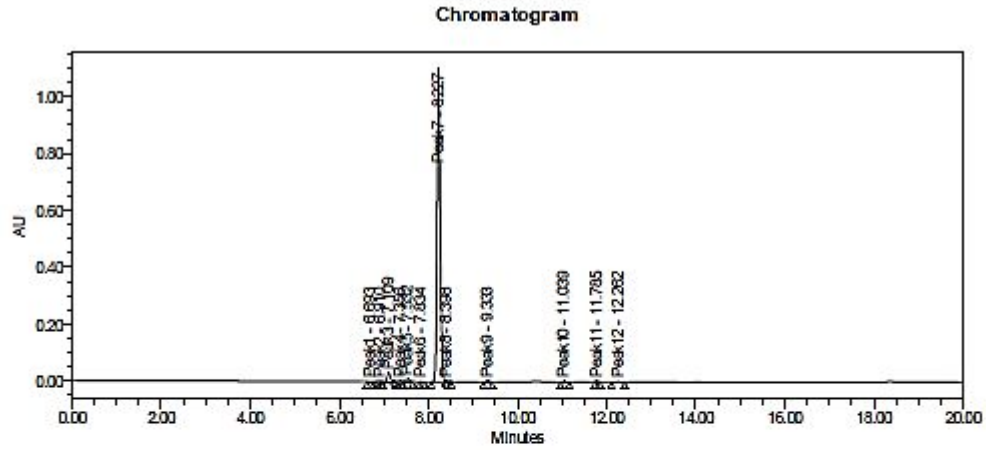
Compound **8c**: HPLC Purity: 98.01%



% Area Normalisation Report

	Peak Name	RT	Area	% Area	RT Ratio
1	Peak1	9.80	6790	0.64	0.88
2	Peak2	10.36	1334	0.12	0.93
3	Peak3	10.63	13096	1.23	0.95
4	Peak4	11.16	1047471	98.01	1.00

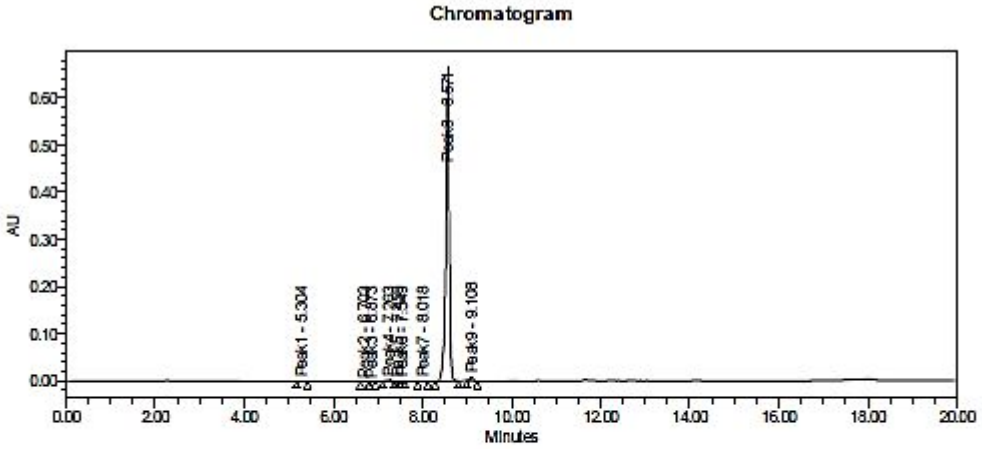
Compound **8d**: HPLC Purity: 95.15%



% Area Normalisation Report

	Peak Name	RT	Area	% Area	RT Ratio
1	Peak1	6.69	2601	0.05	0.81
2	Peak2	6.91	960	0.02	0.84
3	Peak3	7.11	153997	2.80	0.86
4	Peak4	7.36	3408	0.06	0.89
5	Peak5	7.53	45157	0.82	0.92
6	Peak6	7.83	2277	0.04	0.95
7	Peak7	8.23	5227617	95.15	1.00
8	Peak8	8.40	4833	0.09	1.02
9	Peak9	9.33	25419	0.46	1.13
10	Peak10	11.04	11148	0.20	1.34
11	Peak11	11.79	8501	0.15	1.43
12	Peak12	12.26	8407	0.15	1.49

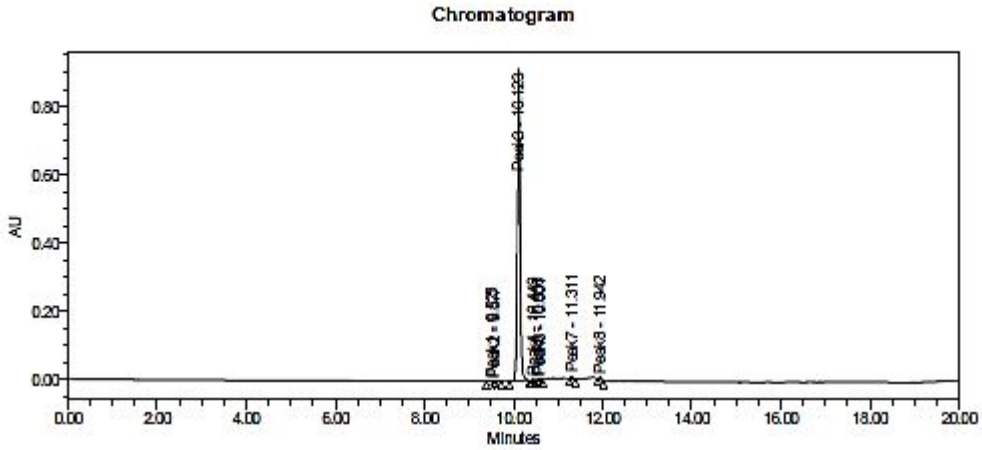
Compound **8e**: HPLC Purity: 98.10%



% Area Normalisation Report

	Peak Name	RT	Area	% Area	RT Ratio
1	Peak1	5.30	4388	0.12	0.62
2	Peak2	6.70	1776	0.05	0.78
3	Peak3	6.87	605	0.02	0.80
4	Peak4	7.26	11292	0.32	0.85
5	Peak5	7.46	944	0.03	0.87
6	Peak6	7.55	1267	0.04	0.88
7	Peak7	8.02	5007	0.14	0.94
8	Peak8	8.57	3449001	98.10	1.00
9	Peak9	9.11	41689	1.19	1.06

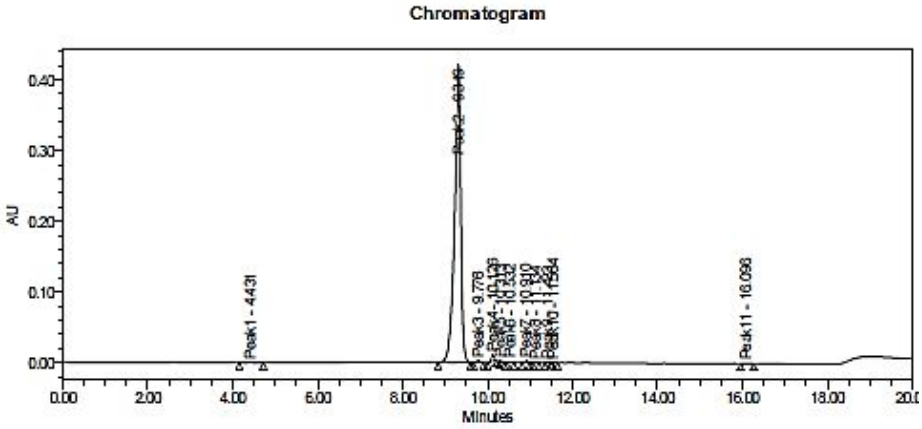
Compound **8f**: HPLC Purity: 98.15%



% Area Normalisation Report

	Peak Name	RT	Area	% Area	RT Ratio
1	Peak1	9.53	10989	0.28	0.94
2	Peak2	9.58	4912	0.13	0.95
3	Peak3	10.12	3837218	98.15	1.00
4	Peak4	10.45	1993	0.05	1.03
5	Peak5	10.55	1139	0.03	1.04
6	Peak6	10.60	2545	0.07	1.05
7	Peak7	11.31	24594	0.63	1.12
8	Peak8	11.94	26113	0.67	1.18

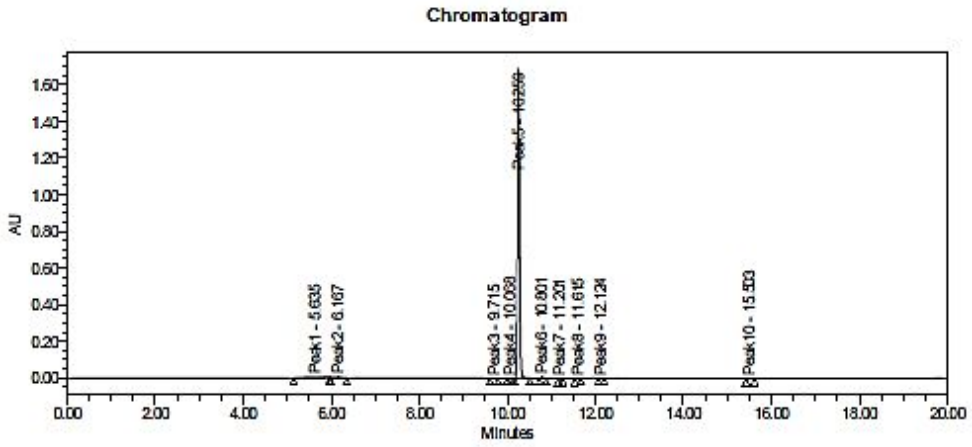
Compound **8g**: HPLC Purity: 97.81%



% Area Normalisation Report

	Peak Name	RT	Area	% Area
1	Peak1	4.43	3286	0.08
2	Peak2	9.32	4185441	97.81
3	Peak3	9.78	16280	0.38
4	Peak4	10.13	40131	0.94
5	Peak5	10.31	5536	0.13
6	Peak6	10.53	5546	0.13
7	Peak7	10.91	10333	0.24
8	Peak8	11.13	1671	0.04
9	Peak9	11.42	3831	0.09
10	Peak10	11.56	5336	0.12
11	Peak11	16.10	1744	0.04

Compound **8h**: HPLC Purity: 98.71%



% Area Normalisation Report

	Peak Name	RT	Area	% Area	RT Ratio
1	Peak1	5.63	21809	0.41	0.55
2	Peak2	6.17	16726	0.31	0.60
3	Peak3	9.72	1814	0.03	0.95
4	Peak4	10.07	2903	0.05	0.98
5	Peak5	10.26	5242754	98.71	1.00
6	Peak6	10.80	18896	0.36	1.05
7	Peak7	11.20	575	0.01	1.09
8	Peak8	11.62	2165	0.04	1.13
9	Peak9	12.12	926	0.02	1.18
10	Peak10	15.50	2813	0.05	1.51

References

[1] Trager, W. ; Jensen, J. B. *Science*, **1976**, *193*, 673-675.

[2] Makler, M. T.; Hinrichs, D. J. *Am. J. Trop. Med. Hyg.,* **1993**, *48,* 205-210.

[3] Jorgensen, W. L. ; Duffy, E. M. *Adv. Drug Deliv. Rev.,* **2002**, *54*, 355-366.