Supporting Information

Discovery of New Acid Ceramidase-Targeted Acyclic 5-Alkynyl and 5-Heteroaryl Uracil Nucleosides

Andrijana Meščić,[#] Anja Harej,[†,‡] Marko Klobučar,[†,‡] Danijel Glavač,[#] Mario Cetina,[Δ] Sandra Kraljević Pavelić,[†,‡] Silvana Raić-Malić[#*]

[#]University of Zagreb, Department of Organic Chemistry, Faculty of Chemical Engineering and Technology, Marulićev trg 20, HR-10000 Zagreb, Croatia

[†]University of Rijeka, Department of Biotechnology, Radmile Matejčić 2, HR-51000 Rijeka, Croatia

[‡]University of Rijeka, Centre for high-throughput technologies, Radmile Matejčić 2, HR-51000 Rijeka, Croatia

[Δ]University of Zagreb, Faculty of Textile Technology, Department of Applied Chemistry, Prilaz baruna Filipovića 28a, HR-10000 Zagreb, Croatia

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1. *In silico* analysis of biological targets for C-5-heteroaryl pyrimidine derivatives 6 and 8

Table S1. Most probable biological targets as predicted by PASS[a] for acyclic pyrimidines 6 and 8

Activity_6	Pa_6	Pi_6	Activity_8	Pa_8	Pi_8
Biological targets			***Biological targets***		
Mannotetraose 2-alpha-N-acetyl glucosaminyl transferase inhibitor	0.677	0.030	Mannotetraose 2-alpha-N-acetyl glucosaminyltransferase inhibitor	0.664	0.032
Aldehyde oxidase inhibitor	0.485	0.052	Anaphylatoxin receptor antagonist	0.647	0.031
17*β*-Hydroxysteroid dehydrogenase (NADP+) inhibitor	0.529	0.119	Malate oxidase inhibitor	0.450	0.026
Malate dehydrogenase (acceptor) inhibitor	0.442	0.046	RNA directed DNA polymerase inhibitor	0.374	0.019
CF transmembrane conductance regulator agonist	0.416	0.025	**17*β*-Hydroxysteroid dehydrogenase (NADP+) inhibitor**	0.485	0.139
Alcohol dehydrogenase (NADP+) inhibitor	0.385	0.015	Cell wall biosynthesis inhibitor	0.349	0.008
Histidine kinase inhibitor	0.387	0.057	Proteasome ATPase inhibitor	0.430	0.109
H+-transporting two-sector ATPase inhibitor	0.374	0.046	Glycerol-3-phosphate dehydrogenase inhibitor	0.352	0.042
Cell wall biosynthesis inhibitor	0.330	0.012	H+-transporting two-sector ATPase inhibitor	0.356	0.052
Phosphatase inhibitor	0.457	0.142	CYP2C substrate	0.371	0.085
Undecaprenyl diphospho-muramoyl pentapeptide β-N-acetylglucosaminyltransferase inhibitor	0.328	0.054			
Heat shock protein 27 antagonist	0.370	0.097			
Proteasome ATPase inhibitor	0.401	0.130			

[a] Activity spectrum predicted by PASS is presented by the list of activities with the probabilities "to be active" (Pa) and "to be inactive" (Pi) calculated for each activity. Greater Pa and smaller Pi, the more probable is predicted activity. The list is arranged in descending order of Pa-Pi; therefore, more probable activities are at the top of the list.

2. Evaluation of inhibitory effect on 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1) activity

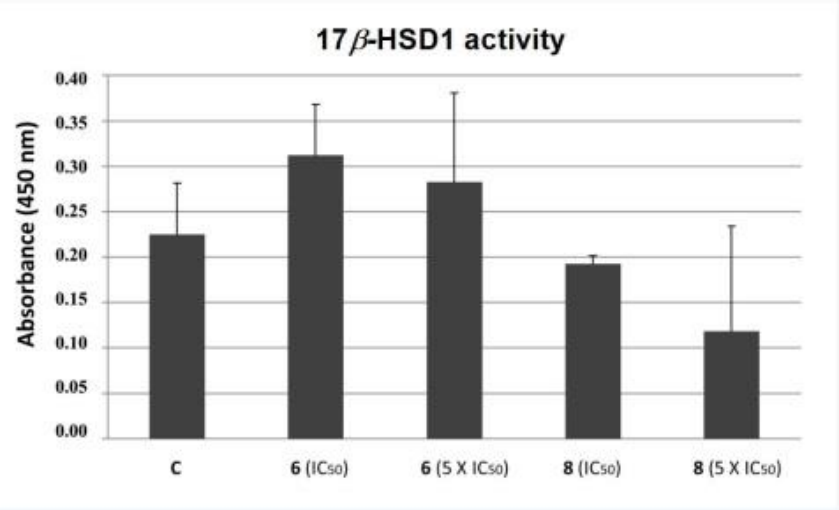
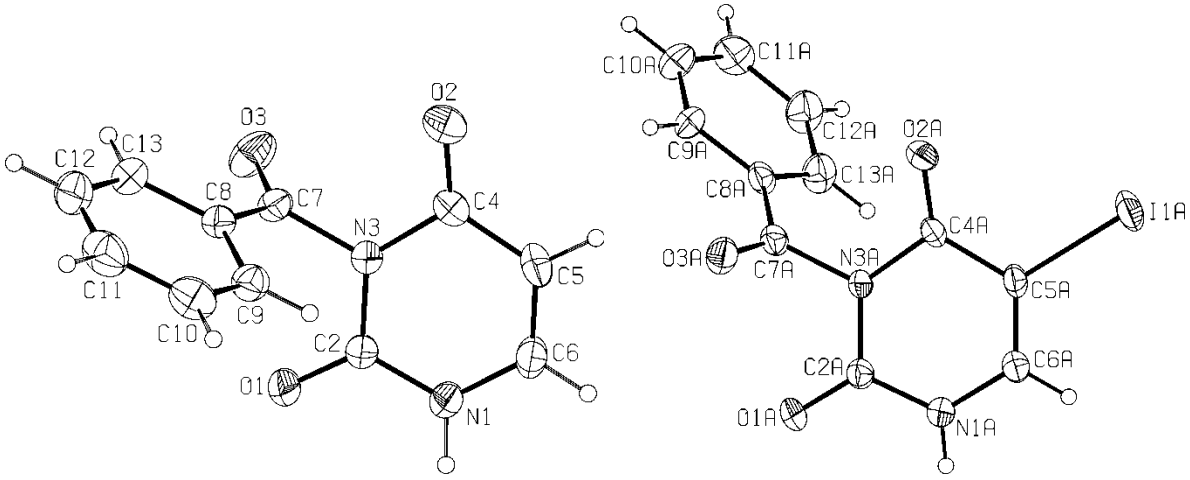


Figure S1. Effects of inhibitory potential of C-5-heteroaryl acyclonucleosides **6** and **8** against 17β-HSD1 at IC_{50} and 5 x IC_{50} concentration analyzed by-MTT test in MCF-7 cells. C – control, untreated cells.

3. X-ray crystal structure analyses

In compounds **1** and **2** (Figure S2), the benzoyl moiety is bonded to N-3 atom of the pyrimidine ring.



a) b)

Figure S2. (a) Molecular structures of **1** and (b) **2** with the atom-numbering scheme. For clarity, only one independent molecule of **2** is shown. Displacement ellipsoids for non-hydrogen atoms are drawn at the 30 % probability level.

In **2**, which crystallized with two independent molecules in the asymmetric unit (designated as A and B), iodine atom is additionally bonded to the C-5 atom. Bond lengths in two independent molecules of **2** are within 3σ values and agree well with equivalent bonds in **1** and structures of 3-benzoyl pyrimidines[1,2] with the exception of C4–C5 and C5–C6 bonds. Thus, the C4–C5 bond in A molecule of **2** is *ca.* 0.05 Å longer than in B molecule, while the C5–C6 bond is *ca.* 0.03 Å longer in B molecule compared to A molecule. Dihedral angle between the mean planes of phenyl and pyrimidine rings in **1** and **2** indicates that these rings are almost perpendicular to each other [**1**, 81.10(7)^o; **2**, 73.0(3) and 81.7(3)^o]. Carbonyl groups in two independent molecules of **2** have two different orientations defined by C2–N3–C7–O3 torsion angle values of 68.7(7)^o (A molecule) and –75.8(7)^o (B molecule). The same torsion angle in **1** is very similar to that of the B molecule of **2** [–96.64(15)^o].

Crystal structures of **6** and **10g** are presented in Figure S3 and S4, crystal structures of **1** and **2** in Figure S5, and hydrogen-bonding geometries for all structures are given in Table S2.

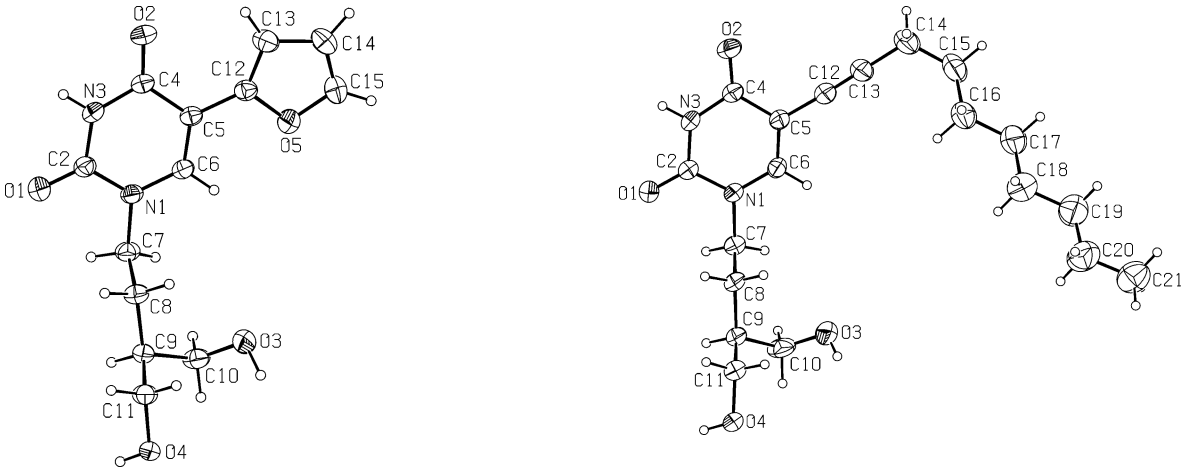
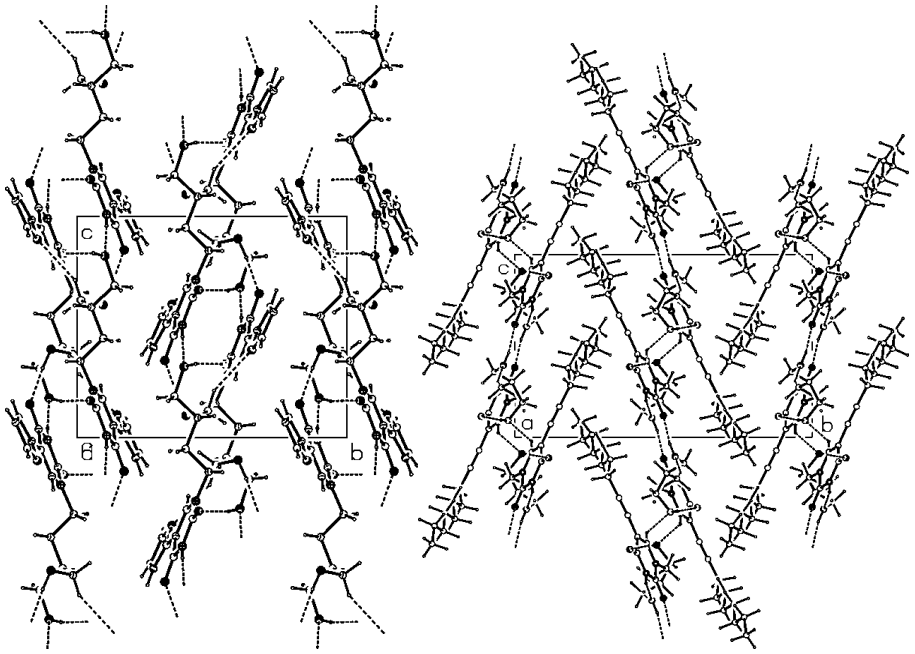


Figure S3. (a) Molecular structures of **6** and (b) **10g** with the atom-numbering scheme. Displacement ellipsoids for non-hydrogen atoms are drawn at the 30% probability level.

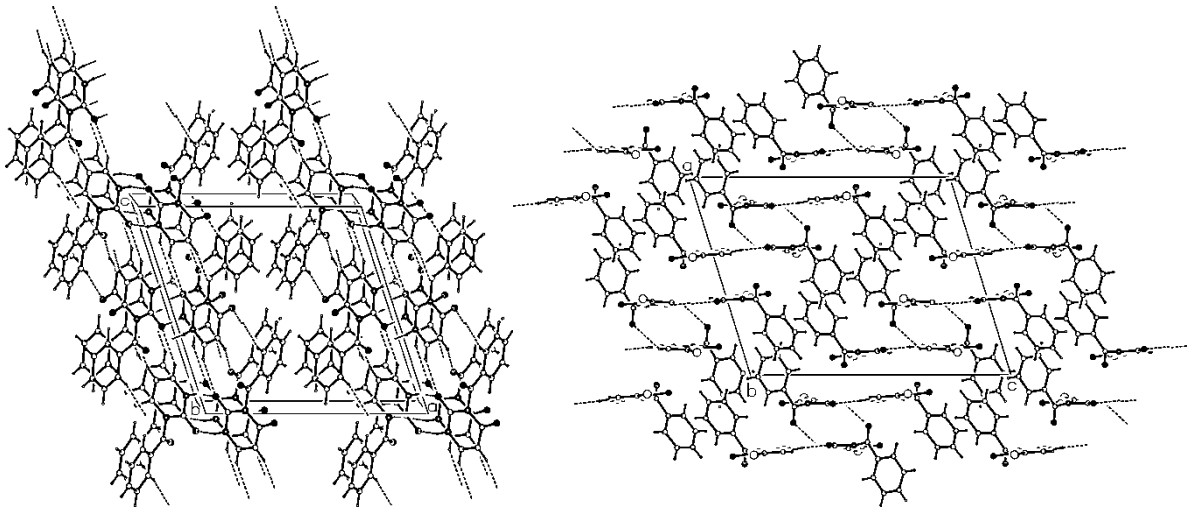
Molecules of **6** are linked by strong hydrogen bonds, one N–H···O and two O–H···O, into tapes. The tapes are further linked by one weak C–H···O hydrogen bond into two-dimensional network (Figure S4a). One C–H···π interaction (Table S2) formed between the methylene hydrogen atom and pyrimidine ring of neighboring molecule extends two-dimensional network into a three-dimensional. The same strong and weak hydrogen bonds (one N–H···O, two O–H···O and one C–H···O), with the exception of C–H···π interaction, participate in supramolecular assembling of **10g**. Compared to **6**, hydrogen-bonded molecules are disposed in a *zig-zag* manner and form a two-dimensional network (Figure S4b).



a) b)

Figure S4. (a) Crystal packing diagrams of **6** and (b) **10g** viewed down the *a* axis. Hydrogen bonds are indicated by dashed lines.

In **1**, only one strong hydrogen bond exists, N–H···O, which forms one of the most common motifs in structures of pyrimidine derivatives, hydrogen-bonded dimer. This motif was absent in previous two structures, probably because the presence of hydroxyl groups in **6** and **10g** which have strong donor/acceptor abilities. The N–H···O hydrogen bond is reinforced by three of C–H···O type, so forming two-dimensional network parallel to the *c* axis (Figure S5a). As in structure of **6**, one C–H···π interaction extends two-dimensional network into a three-dimensional. As well as in **1**, two N–H···O hydrogen bonds in **2** form hydrogen-bonding dimers. One additional C–H···O hydrogen bond links the dimers into a two-dimensional network (Figure S5b). One π···π interaction present in this structure forms three-dimensional network. Phenyl rings are mutually parallel ($\alpha = 0^{o}$), interplanar spacing is 3.399(3) Å, centroid-centrid separation 3.651(4) Å, and offset *ca.*1.34 Å.



a) b)

Figure S5. (a) Crystal packing diagrams of **1** and (b) **2** viewed down the *b* axis. Hydrogen bonds are indicated by dashed lines.

Table S2. Hydrogen-bonding geometries and C−H···π interactions geometry for 1, 2, 6 and 10g

	D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)	Symmetry codes
1	N1–H1···O1	0.93(2)	1.95(2)	2.8573(16)	164.6(19)	2-x, -y, 2-z
	C5–H5···O3	0.93	2.36	3.228(2)	156	x, 3/2-y, 1/2+z
	C6–H6···O1	0.93	2.51	3.3010(17)	143	x, 1/2-y, 1/2+z
	C13–H13···O2	0.93	2.58	3.434(2)	152	x, 3/2-y, -1/2+z
	C10–H10···*Cg*1[a]	0.93	2.93	3.652(2)	135	1-x, -1/2+y, 3/2-z
2	N1A–H1A···O1B	0.85(5)	2.00(5)	2.841(6)	168(5)	3/2-x,1/2+y,1/2-z
	N1B–H1B···O1A	0.89(5)	1.92(5)	2.796(6)	170(5)	3/2-x,-1/2+y,1/2-z
	C6B–H6B···O3B	0.93	2.58	3.194(8)	124	3/2-x,-1/2+y,1/2-z
6	N3–H3N···O4	0.86(2)	1.97(2)	2.8183(18)	173.9(18)	x, y, -1+z
	O3–H3O···O2	0.95(3)	1.82(3)	2.7660(19)	174(3)	x, y, 1+z
	O4–H4O···O1	0.83(3)	1.95(3)	2.770(2)	170(2)	1-x, 1-y, 2-z
	C10–H10A···O5	0.97	2.57	3.469(2)	154	-x, 1-y, 2-z
	C11–H11A···*Cg*2[a]	0.97	2.97	3.923(2)	166	x, 1/2-y, 1/2+z
10g	N3–H3N···O4	0.86	1.97	2.810(3)	164	1+x, y, z
	O3–H3O···O2	0.82	1.99	2.809(3)	173	-1+x, y, z
	O4–H4O···O1	0.82	1.96	2.726(3)	155	1-x, -y, 1-z
	C6–H6···O3	0.93	2.49	3.297(3)	146	1-x, -y, 2-z

[a]*Cg*1 and *Cg*2 are the centroids of C8–C13 and N1/C2/N3/C4/C5/C6 rings, respectively.

4. Experimental procedures

4.1. Chemistry

4.1.1. General

Melting points (uncorrected) were determined with a Kofler micro hot-stage (Reichert, Wien, Austria). Precoated Merck (Darmstadt, Germany) silica gel 60F-254 plates were used for thin layer chromatography and the spots were detected under UV light (254 nm). Column chromatography was performed using Fluka (Buchs, Switzerland) silica gel (0.063–0.2 mm); glass columns were slurry-packed under gravity. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker 300 and 600 MHz NMR spectrometer (Bruker Biospin, Rheinstetten, Germany). All data were recorded in DMSO-d_6 at 298 K. Chemical shifts were referenced to the residual solvent signal of DMSO at δ 2.50 ppm for ^{1}H and δ 39.50 ppm for ^{13}C. Individual resonances were assigned on the basis of their chemical shifts, signal intensities, multiplicity of resonances and H–H coupling constants. Mass spectra were recorded on an Agilent 6410 instrument (Agilent Technologies, Wilmington, USA) equipped with an electrospray interface and triple quadrupole analyzer (LC/MS/MS). High performance liquid chromatography was performed on an Agilent 1100 series system with UV detection (photodiode array detector) using a Zorbax C18 reverse-phase analytical column (2.1 × 30 mm, 3.5 μm). All compounds used for biological evaluation showed > 95% purity in this HPLC system. High-resolution mass spectra of the final compounds were recorded on Applied Biosystems 4800 Maldi TOF/TOF Analyzer. All elemental compositions were within the 0.4% of the calculated values.

4.1.2. Procedures for the preparation of compounds

*3-Benzoylpirimidine-2,4-dione (**1**).* The reaction mixture of uracil (4.5 g; 40.0 mmol), benzoyl chloride (10.4 ml; 89.6 mmol) in acetonitrile (40 ml) and pyridine (16 ml) was stirred for 24h at room temperature. The solvent was evaporated and dichloromethane and water (150 ml; 1 : 1) were added to the oily residue. The resulting white solid was filtered of and recrystallized from acetone : water (1 : 1). Compound **1** was isolated as a white solid (7.4 g; 85%; m.p.= 222–223 °C).^{1}H NMR: (δ) 11.57 (1H, s, NH), 7.98–7.92 (2H, m, Ph-2''', 6'''), 7.81–7.74 (1H, m, Ph-4'''), 7.65 (1H, d, H-6, J = 7.7 Hz), 7.60 (2H, t, Ph-3''', 5''', J = 7.7 Hz), 5.73 (1H, d, H-5, J = 7.7 Hz)

ppm.[13]C NMR: (δ) 169.9 (CO), 162.8 (C-4), 150.0 (C-2), 143.2 (C-6), 135.3 (Ph-4'''), 131.3 (Ph-1'''), 130.1 (Ph-3''', 5'''), 129.4 (Ph-2''', 6'''), 100.0 (C-5).

*3-Benzoyl-5-iodopyrimidine-2,4-dione (**2**)*.To the solution of compound **1** (2.2 g; 10.28 mmol) in acetonitrile (102 ml), iodine (2.6 g; 10.28 mmol) and ammonium cerium(IV) nitrate (CAN; 5.6 g; 10.28 mmol) were added. The reaction mixture was stirred at reflux for 2h. The solvent was evaporated and the residue diluted with ethyl acetate (150 ml) and washed with water (100 ml) and saturated solution of Na_2SO_3 (100 ml). The organic layer was dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (dichloromethane : methanol = 100 : 1) and compound **2** (2,3 g; 65%; m.p. = 209−211 °C) was isolated as a white solid. ^{1}H NMR: (δ) 11.89 (1H, s, NH), 8.13 (1H, s, H-6), 8.00–7.95 (2H, m, Ph-2''', 6'''), 7.79 (1H, t, Ph-4''', *J* = 7.4 Hz), 7.60 (2H, t, Ph-3''', 5''', *J* = 7.9 Hz) ppm. ^{13}C NMR: (δ) 170.2 (CO), 161.0 (C-4), 150.7 (C-2), 148.8 (C-6), 136.5 (Ph-4'''), 131.9 (Ph-1'''), 131.3 (Ph-3''', 5'''), 130.4 (Ph-2''', 6'''), 67.5 (C-5) ppm.

*4-Acetoxy-(3-acetoxymethyl)butyl iodide (**3**)* was synthesized following a known procedure.[3,4]

*N-1-[4-Acetoxy-3-(acetoxymethyl)butyl]-N-3-benzoyl-5-iodopirimidine-2,4-dione (**4**)*.

K_2CO_3 (231.5 mg; 1.68 mmol) was added to the solution of compound **2** (572.8 mg; 1.68 mmol) in dimethylformamide (8 ml). The reaction mixture was stirred for 30 min and the solution of compound **3** (684.2 mg; 2.18 mmol) in dimethylformamide (2 ml) was added to the reaction mixture. The stirring was continued overnight. The solvent was evaporated and the residue purified by column chromatography (dichlormethane : methanol = 200 : 1) and compound **4** (607.0 mg; 68%) was isolated as a yellow oil. ^{1}H NMR: (δ) 8.48 (1H, s, H-6), 8.04–7.95 (2H, m, Ph-2''', 6'''), 7.80 (1H, t, Ph-4''', *J* = 7.4 Hz), 7.61 (2H, t, Ph-3''', 5''', *J* = 7.8 Hz), 4.04 (4H, d, H-4'', *J* = 5.7 Hz), 3.91–3.70 (2H, m, H-1''), 2.14–1.95 (7H, m, $COCH_3$, H-3''), 1.72 (2H, q, H-2'', *J* = 6.8 Hz) ppm. ^{13}C NMR: (δ) 170.3 ($\underline{C}OCH_3$), 168.9 (CO), 159.6 (C-4), 150.7 (C-2), 149.3 (C-6), 135.6 (Ph-4'''), 130.7 (Ph-1'''), 130.4 (Ph-3''', 5'''), 129.5 (Ph-2''', 6'''), 67.2 (C-5), 63.6 (C-4''), 46.4 (C-1''), 34.4 (C-3''), 27.3 (C-2''), 20.6 ($CO\underline{C}H_3$).

*N-1-[4-Acetoxy-3-(acetoxymethyl)butyl]-N-3-benzoyl-5-(furan-2-yl)pirimidine-2,4-dione (**5**)*. To the solution of compound **4** (250.0 mg; 0.47 mmol) in toluene (20 ml), catalyst $(PPh_3)_4Pd$ (54.64

mg; 0.05 mmol) and 2-(tributylstannyl)furan (0.2 ml; 0.64 mmol) were added under argon atmosphere. The reaction mixture was stirred at reflux for 2h. After cooling to the room temperature, 8 M aqueous solution of KF (15 ml) was added and the stirring was continued for 2h at room temperature [46]. The solid was filtered of, the organic layer was removed and dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica gel : KF (9 : 1) (dichloromethane : methanol = 100 : 1; petroleum ether : ethyl acetate = 2 : 1) and compound **5** (123.0 mg; 56%) was isolated as a colorless oil. MS (ESI): m/z =469.2 ($[M+H]^+$). ^{1}H NMR: (δ) 8.38 (1H, s, H-6), 8.03 (2H, d, Ph-2''', 6''', *J* = 7.5 Hz), 7.80 (1H, t, Ph-4''', *J* = 7.4 Hz,), 7.73 (1H, d, H-3', *J* = 1.8 Hz), 7.61 (2H, t, Ph-3''', 5''', *J* = 7.8 Hz), 6.81 (1H, d, H-5', *J* = 3.1 Hz), 6.56 (1H, dd, H-4', *J* = 3.1 Hz; *J* = 1.8 Hz), 4.04 (4H, d, H-4'', *J* = 5.7 Hz,), 3.98–3.93 (2H, m, H-1''), 2.11–2.03 (1H, m, H-3''), 2.00 (6H, s, $COCH_3$), 1.76 (2H, q, H-2'', *J* = 6.9 Hz) ppm.^{13}C NMR: (δ) 170.3 ($\underline{C}OCH_3$), 169.2 (CO), 159.4 (C-4), 148.5 (C-1'), 145.6 (C-2), 141.8 (C-6), 140.6 (C-3'), 135.5 (Ph-4'''), 131.0 (Ph-1'''), 130.4 (Ph-3''', 5'''), 129.5 (Ph-2''', 6'''), 111.8 (C-4'), 108.1 (C-5'), 105.1 (C-5), 63.6 (C-4''), 46.6 (C-1''), 34.4 (C-3''), 27.4 (C-2''), 20.6 ($CO\underline{C}H_3$) ppm.

*5-(Furan-2-yl)-N-1-[4-hydroxy-3-(hydroxymethyl)butyl]pirimidine-2,4-dione (**6**)*. To the solution of compound **5** (128.0 mg; 0.27 mmol) in methanol (3 ml), 0.1 M solution of $NaOCH_3/CH_3OH$ (1.2 ml) was added. The reaction mixture was stirred overnight and neutralized with Amberlyst 15. The solvent was evaporated and the residue purified by column chromatography (dichloromethane : methanol = 10 : 1). Compound **6** was isolated as a white solid (22.9 mg; 30%; m.p. = 202–203 °C). ^{1}H NMR: (δ) 11.53 (1H, s, NH), 8.06 (1H, s, H-6), 7.65 (1H, d, H-3', *J* = 1.8 Hz), 6.85 (1H, d, H-5', *J* = 3.3 Hz), 6.54–6.51 (1H, m, H-4'), 4.42 (2H, t, OH, *J* = 5.2 Hz), 3.89–3.80 (2H, m, H-1''), 3.49–3.40 (4H, m, H-4''), 1.62 (2H, q, H-2'', *J* = 6.9 Hz), 1.56–1.45 (1H, m, H-3'') ppm. ^{13}C NMR: (δ) 161.0 (C-4), 150.3 (C-2), 147.0 (C-1'), 141.7 (C-6), 140.3 (C-3'), 112.1 (C-4'), 108.1 (C-5'), 105.3 (C-5), 62.0 (C-4''), 46.9 (C-1''), 41.2 (C-3''), 28.4 (C-2'') ppm. HRMS (ESI): calcd. for $C_{13}H_{16}N_2O_5$ [M+H] = 281.1132; found = 281.1122.

*N-1-[4-Acetoxy-3-(acetoxymethyl)butyl]-N-3-benzoyl-5-(thiophene-2-yl)pirimidine-2,4-dione (**7**)*. To the solution of compound **4** (437.9 mg; 0.83 mmol) in toluene (20 ml), catalyst $(PPh_3)_4Pd$ (143.8.0 mg; 0.12 mmol) and 2-(tributylstannyl)thiophene (0.3 ml; 0.99 mmol) were added under

argon atmosphere. The reaction mixture was stirred at reflux overnight. After cooling to room temperature, 8 M aqueous solution of KF was added and the stirring was continued for 2h at room temperature. The solid was filtered of and the organic layer separated, dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica gel : KF (9 : 1) (dichloromethane : methanol = 100 : 1) and compound **7** was isolated as a yellow oil. By addition of methanol to the oil, crystallization of the product occurred and **7** was isolated as white crystals (264.4 mg; 66%; m.p. = 124–125°C). MS (ESI): m/z = 485.2 ($[M+H]^+$). ^{1}H NMR: (δ) 8.54 (1H, s, H-6), 8.04 (2H, d, Ph-2''', 6''', *J* = 7.5 Hz,), 7.80 (1H, t, Ph-4''', *J* = 7.4 Hz), 7.61 (2H, t, Ph-3''', 5''', *J* = 7.8 Hz), 7.55 (1H, d, H-5', *J* = 2.9 Hz), 7.51 (1H, d, H-3', *J* = 4.9 Hz), 7.11 (1H , dd, H-3', *J* = 4.8 Hz; *J* = 3.9 Hz), 4.05 (4H, d, H-4'', *J* = 5.6 Hz), 3.96–3.91 (2H, m, H-1''), 2.11–2.06 (1H, m, H-3''), 2.00 (6H, s, $COCH_3$), 1.79 (2H, q, H-2'', *J* = 6.9 Hz) ppm. ^{13}C NMR: (δ) 170.3 ($\underline{C}OCH_3$), 169.2 (CO), 160.5 (C-4), 148.5 (C-2), 141.8 (C-6), 135.6 (Ph-4'''), 133.0 (C-1'), 131.0 (Ph-1'''), 130.4 (Ph-3''', 5'''), 129.5 (Ph-2''', 6'''), 126.6 (C-3'), 126.0 (C-4'), 123.5 (C-5'), 107.9 (C-5), 63.6 (C-4''), 46.6 (C-1''), 34.4 (C-3''), 27.3 (C-2''), 20.6 ($CO\underline{C}H_3$) ppm.

*N-1-[4-Hydroxy-3-(hydroxymethyl)butyl]-5-(thiophene-2-yl)pirimidine-2,4-dione (**8**)*. To the solution of compound **7** (49.2 mg; 0.10 mmol) in methanol (3 ml), 0.2 M solution of $NaOCH_3/CH_3OH$ (1.8 ml) was added. The reaction mixture was stirred overnight and neutralized with Amberlyst 15. The solvent was evaporated and the residue purified by column chromatography (dichloromethane : methanol = 10 : 1). Compound **8** was isolated as a white powder (15.3 mg; 51%; m.p.= 133−134 °C). ^{1}H NMR: (δ) 11.57 (1H, s, NH), 8.26 (1H, s, H-6), 7.48–7.42 (2H, m, H-5', H-3'), 7.06 (1H, dd, H-4', *J* = 5.1 Hz, *J* = 3.7 Hz), 4.40 (2H, t, OH, *J* = 5.2 Hz), 3.89–3.78 (2H, m, H-1''), 3.49–3.35 (4H, m, H-4''), 1.63 (2H, dd, H-2'', *J* = 16.5 Hz; *J* = 6.9 Hz), 1.53–1.49 (1H, m, H-3'') ppm. ^{13}C NMR: (δ) 161.7 (C-4), 149.8 (C-2), 141.0 (C-6), 133.9 (C-1'), 126.3 (C-3'), 125.4 (C-4'), 122.5 (C-5'), 107.6 (C-5), 61.5 (C-4''), 46.4 (C-1''), 40.8 (C-3''), 27.9 (C-2'') ppm. HRMS (ESI): calcd. for $C_{13}H_{16}N_2O_4S$ [M+H] = 297.0903; found = 297.0913.

*N-1-[4-Acetoxy-3-(acetoxymethyl)butyl]-N-3-benzoyl-5-[(3,5-difluorophenyl)ethynyl]pirimidine-2,4-dione (**9a**)*. To the solution of compound **4** (449.6 mg; 0.85 mmol) in toluene (25 ml), CuI (34.0 mg; 0.17 mmol), $(PPh_3)_4Pd$ (98.4 mg; 0.09 mmol) and Et_3N (0.3 ml; 1.73 mmol) were

added under argon atmosphere. 2-(3,5-Difluorophenyl)ethyne (0.1 ml; 1.02 mmol) was added dropwise. The reaction mixture was stirred overnight at room temperature and then Amberlyt IRA 400 and active coal were added and the stirring was continued for 20 min. The solid was filtered of and the filtrate was evaporated. The remaining yellow oil was purified by column chromatography (dichloromethane : methanol = 200 : 1) and compound **9a** was isolated as white crystals (264.2 mg; 58%; m.p. = 94−96 °C). MS (ESI): m/z = 539.2 ($[M+H]^+$). ^{1}H NMR: (δ) 8.54 (1H, s, H-6), 8.09–7.98 (2H, m, Ph-2''', 6'''), 7.81 (1H, t, Ph-4''', J = 7.4 Hz), 7.62 (2H, t, Ph-3''', 5''', J = 7.8 Hz), 7.35 (1H, tt, Ph-4', J_{HF} = 9.5 Hz, J = 2.3 Hz), 7.25–7.16 (2H, m, Ph-2', 6'), 4.03 (4H, d, H-4'', J = 5.7 Hz), 3.93–3.79 (1H, m, H-1''), 2.07–2.02 (1H, m, H-3''), 2.00 (6H, s, $COCH_3$), 1.76 (2H, q, H-2'', J = 6.9 Hz) ppm. ^{13}C NMR: (δ) 170.3 ($\underline{C}OCH_3$), 168.7 (CO), 162.3 (dd, Ph-3', 5', J_{CF} = 247.3 Hz, J_{CF} = 14.2 Hz), 160.5 (C-4), 150.6 (C-6), 148.6 (C-2), 135.6 (Ph-4'''), 130.8 (Ph-1'''), 130.5 (Ph-3''', 5'''), 129.5 (Ph-2''', 6'''), 124.9 (t, Ph-1', J_{CF} = 12.0 Hz), 114.3 (dd, Ph-2', 6', J_{CF} = 21.0 Hz, J_{CF} = 5.9 Hz), 105.1 (t, Ph-4' J_{CF} = 25.8 Hz), 96.7 (C-5), 90.2 (C-2'), 83.7 (C-1'), 63.6 (C-4''), 46.9 (C-1''), 34.4 (C-3''), 27.3 (C-2''), 20.6 ($CO\underline{C}H_3$) ppm. Anal. Calcd. for $C_{28}H_{24}N_2O_7F_2$ (538.50): C, 62.45; H, 4.49; N, 5.20; found: C, 62.55; H, 4.49; N, 5.20.

*N-1-[4-Acetoxy-3-(acetoxymethyl)butyl]-N-3-benzoyl-5-[(p-bromophenyl)ethynyl]pirimidine-2,4-dione (**9b**)*. Compound **9b** was synthesized following the procedure for the preparation of compound **9a**. Reagents: compound **4** (583.1 mg; 1.10 mmol), CuI (47.3 mg; 0.25 mmol), Et_3N (0.3 ml; 2.21 mmol), $(PPh_3)_4Pd$ (130.5 mg; 0.11 mmol), 2-(*p*-bromophenyl)ethyne (316.3 mg; 1.37 mmol) and toluene (25 ml). After column chromatography (dichloromethane : methanol = 200 : 1) compound **9b** was isolated as white crystals (267.0 mg; 42%; m.p. = 64−66 °C). MS (ESI): m/z = 581.1; 583.1 ($[M+H]^+$). ^{1}H NMR: (δ) 8.52 (1H, s, H-6), 8.04 (2H, d, Ph-2''', 6''', J = 7.3 Hz), 7.81 (1H, t, Ph-4''', J = 7.4 Hz), 7.66–7.57 (4H, m, Ph-3', 5', 3''', 5'''), 7.41 (2H, d, Ph-2', 6', J = 8.5 Hz), 4.03 (4H, d, H-4'', J = 5.7 Hz), 3.93–3.82 (2H, m, H-1''), 2.11–2.03 (1H, m, H-3''), 2.01 (6H, s, $COCH_3$), 1.75 (2H, q, H-2'', J = 6.9 Hz) ppm. ^{13}C NMR: (δ) 170.9 ($\underline{C}OCH_3$), 169.2 (CO), 161.1 (C-4), 150.4 (C-6), 149.1 (C-2), 136.2 (Ph-4'''), 133.4 (Ph-2', 6'), 132.4 (Ph-3', 5'), 131.3 (Ph-1'''), 131.0 (Ph-3''', 5'''), 130.0 (Ph-2''', 6'''), 122.7 (Ph-4'), 121.8 (Ph-1'), 97.8 (C-5), 92.0 (C-2'), 83.0 (C-1'), 64.1 (C-4''), 47.3 (C-1''), 34.9 (C-3''), 27.7 (C-2''), 21.1 ($CO\underline{C}H_3$). Anal. Calcd. for $C_{28}H_{25}N_2O_7Br$ (580,08): C, 57.84; H, 4.33; N, 4.82; found: C, 57.93; H, 4.34; N, 4.83.

*N-1-[4-Acetoxy-3-(acetoxymethyl)butyl]-N-3-benzoyl-5-[(p-pentylphenyl)ethynyl]pirimidine-2,4-dione (**9c**)*. Compound **9c** was synthesized following the procedure for the preparation of compound **9a**. Reagents: compound **4** (446.6 mg; 0.85 mmol), CuI (33.8 mg; 0.18 mmol), Et_3N (0.3 ml; 1.73 mmol), $(PPh_3)_4Pd$ (97.9 mg; 0.08 mmol), 2-(*p*-pentylphenyl)ethyne (0.2 ml; 1.02 mmol) and toluene (25 ml). After column chromatography (dichloromethane : methanol = 200 : 1) compound **9c** was isolated as white crystals (393.7 mg; 81%). MS (ESI): m/z = 573.2 ($[M+H]^+$). ^{1}H NMR: (δ) 8.48 (1H, s, H-6), 8.05 (2H, dd, Ph-2''', 6''', *J* = 7.9 Hz, *J* = 0.6 Hz), 7.81 (1H, t, Ph-4''', *J* = 7.4 Hz), 7.62 (2H, t, Ph-3''', 5''', *J* = 7.8 Hz), 7.37 (2H, d, Ph-2', 6', *J* = 8.1 Hz), 7.24 (2H, d, Ph-3', 5', *J* = 8.2 Hz), 4.03 (4H, d, H-4'', *J* = 5.6 Hz), 3.92–3.81 (2H, m, H-1''), 2.65–2.53 (2H, m, H-3'), 2.04–2.02 (1H, m, H-3''), 2.00 (6H, s, $COCH_3$), 1.75 (2H, q, H-2'', *J* = 7.0 Hz), 1.62–1.50 (2H, m, H-4'), 1.36–1.21 (4H, m, H-5', H-6'), 0.85 (3H, t, CH_3-7', *J* = 6.9 Hz) ppm. ^{13}C NMR: (δ) 170.3 ($\underline{C}OCH_3$), 168.8 (CO), 160.7 (C-4), 149.4 (C-6), 148.6 (C-2), 143.5 (Ph-4'), 135.6 (Ph-4'''), 131.0 (Ph-3''', 5'''), 130.9 (Ph-1'''), 130.5 (Ph-2', 6'), 129.5 (Ph-3', 5'), 128.7 (Ph-2''', 6'''), 119.3 (Ph-1'), 97.7 (C-5), 92.8 (C-2'), 80.6 (C-1'), 63.6 (C-4''), 46.7 (C-1''), 34.9 (C-3'), 34.4 (C-3''), 30.8 (CH_2'), 30.2 (CH_2'), 27.2 (C-2''), 21.9 (CH_2'), 20.6 ($CO\underline{C}H_3$), 13.8 (CH_3-7') ppm. Anal. Calcd. for $C_{33}H_{36}N_2O_7$ (572,65): C, 69.21; H, 6.34; N, 4.89; found: C, 69.44; H, 6.35; N, 4.89.

*N-1-[4-Acetoxy-3-(acetoxymethyl)butyl]-N-3-benzoyl-5-(3-phenylpropynyl)pirimidine-2,4-dione (**9d**)*. Compound **9d** was synthesized following the procedure for the preparation of compound **9a**. Reagents: compound **4** (308.0 mg; 0.58 mmol), CuI (23.3 mg; 0.12 mmol), Et_3N (0.2 ml; 1.22 mmol), $(PPh_3)_4Pd$ (68.5 mg; 0.06 mmol), 3-phenylpropyne (0.1 ml; 0.91 mmol) and toluene (15 ml). After column chromatography (dichloromethane : methanol = 200 : 1) compound **9h** (211.1 mg; 70%) was isolated as yellow oil. MS (ESI): m/z = 517.2 ($[M+H]^+$). ^{1}H NMR: (δ) 8.36 (1H, s, H-6), 8.05–7.98 (2H, m, Ph-2''', 6'''), 7.80 (1H, t, Ph-4''', *J* = 7.4 Hz), 7.60 (2H, t, Ph-3''', 5''', *J* = 7.8 Hz), 7.42–7.29 (4H, m, Ph-2', 3', 5', 6'), 7.28–7.21 (1H, m, Ph-4'), 4.01 (4H, d, H-4'', *J* = 5.7 Hz), 3.87 (2H, s, H-3'), 3.87–3.81 (2H, m, H-1''), 2.09–2.01 (1H, m, H-3''), 2.00 (6H, s, $COCH_3$), 1.72 (2H, q, H-2'', *J* = 6.9 Hz) ppm.^{13}C NMR: (δ) 170.8 ($\underline{C}OCH_3$), 169.4 (CO), 161.6 (C-4), 149.5 (C-6), 149.2 (C-2), 136.8 (Ph-1'), 136.1 (Ph-4'''), 131.4 (Ph-1'''), 131.0 (Ph-3''', 5'''), 130.0 (Ph-2''', 6'''), 128.95 (Ph-2', 6'), 128.35 (Ph-3', 5'), 127.0 (Ph-4'), 98.5 (C-5), 92.4 (C-2'),

74.1 (C-1'), 64.1 (C-4"), 47.0 (C-1"), 34.9 (C-3"), 27.7 (C-2"), 25.3 (C-3'), 21.1 (CH_3) ppm. Anal. Calcd. for $C_{29}H_{28}N_2O_7$ (516,54): C, 67.43; H, 5.46; N, 5.42; found: C, 67.60; H, 5.47; N, 5.41.

N-1-[4-Acetoxy-3-(acetoxymethyl)butyl]-5-(cyclopropylethynyl)pirimidine-2,4-dione ***(9e)***. Compound **9e** was synthesized following the procedure for the preparation of compound **9a**. Reagents: compound **4** (447.3 mg; 0.85 mmol), CuI (36.0 mg; 0.19 mmol), Et_3N (0.3 ml; 1.73 mmol), $(PPh_3)_4Pd$ (99.5 mg; 0.09 mmol), 2-cyclopropylethyne (0.1 ml; 1.02 mmol) and toluene (25 ml). After column chromatography (dichloromethane : methanol = 200 : 1) compound **9e** was isolated as white crystals (279.6 mg; 71%; m.p. = 107−110 °C). MS (ESI): m/z = 467.2 ($[M+H]^+$). ^{1}H NMR: (δ) 8.25 (1H, s, H-6), 8.03–7.95 (2H, m, Ph-2''', 6'''), 7.79 (1H, t, Ph-4''', *J* = 7.4 Hz), 7.60 (2H, t, Ph-3''', 5''', *J* = 7.8 Hz), 4.01 (4H, d, H-4", *J* = 5.7 Hz), 3.87–3.74 (2H, m, H-1"), 2.09–2.01 (1H, m, H-3"), 2.00 (6H, s, $COCH_3$), 1.71 (2H, q, H-2", *J* = 6.9 Hz), 1.51 (1H, tt, H-3', *J* = 8.2 Hz, *J* = 5.0 Hz), 0.91–0.83 (2H, m, H-4', H-5'), 0.69–0.62 (2H, m, H-4', H-5') ppm. ^{13}C NMR: (δ) 170.8 ($\underline{C}OCH_3$), 169.4 (CO), 161.6 (C-4), 149.4 (C-6), 149.1 (C-2), 136.0 (Ph-4'''), 131.4 (Ph-1'''), 130.9 (Ph-3''', 5'''), 129.9 (Ph-2''', 6'''), 98.7 (C-5), 97.7 (C-2'), 67.4 (C-1'), 64.1 (C-4"), 47.0 (C-1"), 35.0 (C-3"), 27.7 (C-2"), 21.1 ($CO\underline{C}H_3$), 8.8 (C-4', C-5'), 0.3 (C-3') ppm. Anal. Calcd. for $C_{25}H_{26}N_2O_7$ (466,48): C, 64.37; H, 5.62; N, 6.01; found: C, 64.52; H, 5.62; N, 6.02.

N-1-[4-Acetoxy-3-(acetoxymethyl)butyl]-N-3-benzoyl-5-(heptynyl)pirimidine-2,4-dione ***(9f)***. **Method A**: Compound **9f** was synthesized following the procedure for the preparation of compound **9a**. Reagents: compound **4** (137.5 mg; 0.26 mmol), CuI (10.4 mg; 0.05 mmol), Et_3N (0.1 ml; 0.55 mmol), $(PPh_3)_4Pd$ (30.1 mg; 0.03 mmol), heptyne (0.04 ml; 0.31 mmol), toluene (5 ml). After column chromatography (dichloromethane : methanol = 200 : 1) compound **9f** was isolated as white crystals (93.0 mg; 72%).

Method B: To the solution of compound **4** (138.2 mg; 0.26 mmol) in toluene (5ml), CuI (10.5 mg; 0.05 mmol), Et_3N (0.1 ml; 0.55 mmol), $(PPh_3)_4Pd$ (30.2 mg; 0.03 mmol) and heptyne (0.04 ml; 0.31 mmol) were added and the reaction mixture was heated for 4 h in a microwave reactor at 60 °C (300 W). After column chromatography (dichloromethane : methanol = 200 : 1) compound **9f** (87.8 mg; 68%) was isolated as a colorless oil. MS (ESI): m/z = 497.2 ($[M+H]^+$). ^{1}H NMR: 8.26 (1H, s, H-6), 8.04–7.96 (2H, m, H-2''', Ph-6'''), 7.79 (1H, t, H-4''', *J* = 7.4 Hz),

7.60 (2H, t, H-3''', Ph-5''', *J* = 7.8 Hz), 4.01 (4H, d, H-4'', *J* = 5.7 Hz), 3.88–3.76 (2H, m, H-1''), 2.38 (2H, t, H-3', *J* = 6.9 Hz), 2.03–2.00 (1H, m, H-3''), 2.00 (6H, s, $COCH_3$), 1.71 (2H, q, H-2'', *J* = 7.1 Hz), 1.55–1.44 (2H, m, H-4'), 1.43–1.22 (4H, m, H-5', H-6'), 0.87 (3H, t, CH_3-7', *J* = 7.1 Hz) ppm. ^{13}C NMR: (δ) 170.8 ($\underline{C}OCH_3$), 169.4 (CO), 161.6 (C-4), 153.1 (C-2), 149.1 (C-6), 136.0 (Ph-4'''), 131.4 (Ph-1'''), 130.9 (Ph-3''', 5'''), 130.0 (Ph-2''', 6'''), 98.8 (C-5), 94.7 (C-2'), 72.3 (C-1'), 64.1 (C-4''), 47.0 (C-1''), 34.9 (C-3''), 30.9 (CH_2'), 28.2 (CH_2'), 27.7 (C-2''), 22.1 (CH_2'), 21.1 ($CO\underline{C}H_3$), 19.1 (CH_2'), 14.3 (CH_3-7') ppm. Anal. Calcd. for $C_{27}H_{32}N_2O_7$ (496,55): C, 65.31; H, 6.50; N, 5.64; found: C, 65.55; H, 6.51; N, 5.65.

N-1-[4-Acetoxy-3-(acetoxymethyl)butyl]-N-3-benzoyl-5-(decynyl)pirimidine-2,4-dione ***(9g)***. Compound **9g** was synthesized following the procedure for the preparation of compound **9a**. Reagents: compound **4** (313.0 mg; 0.06 mmol), CuI (23.7 mg; 0.12 mmol), Et_3N (0.2 ml; 1.29 mmol), $(PPh_3)_4Pd$ (68.6 mg; 0.06 mmol), decyne (0.1 ml; 0.71 mmol) and toluene (15 ml). After column chromatography (dichloromethane : methanol = 200 : 1) compound **9g** (214.0 mg; 67%) was isolated as a yellow oil. MS (ESI): m/z = 539.2 ($[M+H]^+$). ^{1}H NMR: (δ) 8.26 (1H, s, H-6), 8.03–7.96 (2H, m, Ph-2''', 6'''), 7.79 (1H, t, H-4''', *J* = 7.4 Hz), 7.60 (2H, t, H-3''', Ph-5''', *J* = 7.8 Hz), 4.01 (4H, d, H-4'', *J* = 5.7 Hz), 3.88–3.78 (2H, m, H-1''), 2.37 (2H, t, H-3', *J* = 6.8 Hz), 2.10–2.02 (1H, m, H-3''), 2.04–1.91 (6H, m, $COCH_3$), 1.71 (2H, q, H-2'', *J* = 6.9 Hz), 1.54–1.42 (2H, m, CH_2'), 1.44–1.20 (10H, m, 5 x CH_2'), 0.84 (3H, t, CH_3', *J* = 6.7 Hz) ppm. ^{13}C NMR: (δ) 170.3 ($\underline{C}OCH_3$), 169.0 (CO), 161.1 (C-4), 148.4 (C-6), 145.1 (C-2), 135.6 (Ph-4'''), 130.9 (Ph-1'''), 130.4 (Ph-3''', 5'''), 129.5 (Ph-2''', 6'''), 98.3 (C-5), 94.2 (C-2'), 71.8 (C-1'), 63.5 (C-4''), 46.4 (C-1''), 34.3 (C-3''), 31.2 (CH_2'), 28.6 (CH_2'), 28.5 (CH_2'), 28.2 (CH_2'), 28.1 (CH_2'), 27.2 (C-2''), 22.0 (CH_2'), 20.6 ($CO\underline{C}H_3$), 18.7 (CH_2'), 13.9 (CH_3') ppm. Anal. Calcd. for $C_{30}H_{38}N_2O_7$ (538,63): C, 66.90; H, 7.11; N, 5.20; found: C, 67.01; H, 7.12; N, 5.21.

N-1-[4-Acetoxy-3-(acetoxymethyl)butyl]-N-3-benzoyl-5-(5-chloropentynyl)pirimidine-2,4-dione ***(9h)***. Compound **9h** was synthesized following the procedure for the preparation of compound **9a**. Reagents: compound **4** (212.3 mg; 0.40 mmol), CuI (16.1 mg; 0.08 mmol), Et_3N (0.1 ml; 0.86 mmol), $(PPh_3)_4Pd$ (46.5 mg; 0.04 mmol), 5-chloropentyne (0.1 ml; 0.48 mmol) and toluene (10 ml). After column chromatography (dichloromethane : methanol = 200 : 1) compound **9h** was isolated as a colorless oil (115.7 mg; 57%). MS (ESI): m/z = 503.2 ($[M+H]^+$). ^{1}H NMR: (δ)

8.30 (1H, s, H-6), 8.01–7.98 (2H, m, Ph-2''', 6'''), 7.79 (1H, t, H-4''', *J* = 7.4 Hz), 7.60 (2H, t, H-3''', Ph-5''', *J* = 7.9 Hz), 4.02 (4H, d, H-4'', *J* = 5.7 Hz), 3.85–3.80 (2H, m, H-1''), 3.75 (2H, t, H-5', *J* = 6.4 Hz), 2.55 (2H, t, H-3', *J* = 6.9 Hz), 2.05–2.01 (1H, m, H-3''), 2.00 (6H, s, $COCH_3$), 1.94 (2H, p, H-4', *J* = 6.7 Hz), 1.72 (2H, q, H-2'', *J* = 6.9 Hz) ppm. ^{13}C NMR: 170.8 ($\underline{C}OCH_3$), 169.4 (CO), 161.6 (C-4), 149.5 (C-6), 149.1 (C-2), 136.1 (Ph-4'''), 131.4 (Ph-1'''), 130.9 (Ph-3''', 5'''), 130.0 (Ph-2''', 6'''), 98.5 (C-5), 92.9 (H-2'), 73.1 (C-1'), 64.1 (C-4''), 47.0 (C-1''), 44.5 (C-5'), 34.9 (C-3''), 31.4 (C-4'), 27.7 (C-2''), 21.1 ($CO\underline{C}H_3$), 16.7 (C-3') ppm. Anal. Calcd. for $C_{25}H_{27}N_2O_7Cl$ (502,94): C, 59.70; H, 5.41; N, 5.57; found: C, 59.87; H, 5.42; N, 5.58.

*N-1-[4-Acetoxy-3-(acetoxymethyl)butyl]-N-3-benzoyl-5-(3,3-dimethylbutynyl)pirimidine-2,4-dione (**9i**).* Compound **9i** was synthesized following the procedure for the preparation of compound **9a**. Reagents: compound **4** (187.0 mg; 0.35 mmol), CuI (14.1 mg; 0.07 mmol), Et_3N (0.1 ml; 0.88 mmol), $(PPh_3)_4Pd$ (40.9 mg; 0.04 mmol), 3,3-dimethylbutyne (0.1 ml; 0.42 mmol) and toluene (10 ml). After column chromatography (dichloromethane : methanol = 200 : 1) compound **9i** (140.0 mg; 83%) was isolated as a colorless oil. MS (ESI): m/z = 483.2 ($[M+H]^+$). H NMR: (δ) 8.25 (1H, s, H-6), 8.08–7.90 (2H, m, Ph-2''', 6'''), 7.79 (1H, t, Ph-4''', *J* = 7.4 Hz), 7.60 (2H, t, Ph-3''', 5''', *J* = 7.8 Hz), 4.02 (4H, d, H-4'', *J* = 5.7 Hz), 3.89–3.70 (2H, m, H-1''), 2.08–2.02 (1H, m, H-3''), 2.02 (6H, s, $COCH_3$), 1.78–1.60 (2H, m, H-2''), 1.24 (9H, s, CH_3) ppm. ^{13}C NMR: (δ) 170.3 ($\underline{C}OCH_3$), 168.9 (CO), 160.9 (C-4), 148.6 (C-2), 148.6 (C-6), 135.5 (Ph-4'''), 130.9 (Ph-3''', 5'''), 130.4 (Ph-1'''), 129.4 (Ph-2''', 6'''), 101.9 (C-5), 98.1 (C-2'), 70.3 (C-1'), 63.6 (C-4''), 46.4 (C-1''), 34.4 (C-3''), 30.6 (CH_3), 27.7 (C-3'), 27.2 (C-2''), 20.6 ($CO\underline{C}H_3$) ppm. Anal. Calcd. for $C_{26}H_{30}N_2O_7$ (482,53): C, 64.72; H, 6.27; N, 5.81; found: C, 64.90; H, 6.26; N, 5.80.

*5-[(3,5-Difluorophenyl)ethynyl]-N-1-[4-hydroxy-3-(hydroxymethyl)butyl]pirimidine-2,4-dione (**10a**).* To the solution of compound **9a** (87.4 mg; 0.16 mmol) in methanol (1 ml), 1 M NaOH (1.7 ml) was added. Reaction mixture was stirred for 10 min at reflux, and afterwards neutralized with a 50% solution of HCl in CH_3OH. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (dichloromethane : methanol = 20 : 1). Compound **10a** (5.9 mg; 13%; m.p. = 167−169 °C) was isolated as white crystals. ^{1}H NMR: (δ) 11.64 (1H, s, NH), 8.24 (1H, s, H-6), 7.40–7.25 (1H, m, Ph-4'), 7.20 (2H, dd, Ph-2', 6', J_{HF} = 8.1 Hz, *J* = 2.0 Hz), 4.41 (2H, t, OH, *J* = 5.2 Hz), 3.87–3.68 (2H, m, H-1''), 3.50–3.32 (4H, m, H-4''),

1.60 (2H, q, H-2", J = 6.9 Hz), 1.50–1.45 (1H, m, H-3") ppm.^{13}C NMR: (δ) 162.8 (dd, Ph-3', 5', J_{CF} = 245.2 Hz, J_{CF} = 14.1 Hz), 162.2 (C-4), 150.5 (C-6), 150.3 (C-2), 125.9 (t, Ph-1', J_{CF} = 12.2 Hz), 115.0–114.4 (m, Ph-2', 6'), 105.3 (t, Ph-4', J_{CF} = 25.8 Hz), 96.9 (C-5), 90.0 (C-2'), 85.5 (C-1'), 62.0 (C-4"), 47.1 (C-1"), 41.2 (C-3"), 28.3 (C-2") ppm. HRMS (ESI): calcd. for $C_{17}H_{16}N_2O_4F_2$ [M+H] = 351.1151; found = 351.115.

*5-[(p-Bromophenyl)ethynyl]-N-1-[4-hydroxy-3-(hydroxymethyl)butyl]pirimidine-2,4-dione (**10b**)*. To the solution of compound **9b** (95.5 mg; 0.16 mmol) in methanol (2.3 ml) freshly prepared 0.1 M solution of $NaOCH_3/CH_3OH$ (0.7 ml) solution was added. The reaction mixture was stirred overnight at room temperature and neutralized by addition of Amberlyst 15. The solid was filtered of, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (dichloromethane : methanol = 20 : 1). Compound **10b** (15.4 mg; 24%; m.p. = 183−185 °C) was isolated as white crystals. ^{1}H NMR: (δ) 11.59 (1H, s, NH), 8.21 (1H, s, H-6), 7.62–7.58 (2H, m, Ph-3', 5'), 7.42–7.38 (2H, m, Ph-2', 6'), 4.39 (2H, t, OH, J = 5.2 Hz), 3.80–3.74 (2H, m, H-1"), 3.44–3.40 (2H, m, H-4"), 3.37–3.33 (2H, m, H-4"), 1.60 (2H, q, H-2", J = 6.8 Hz), 1.52–1.45 (1H, m, H-3") ppm. ^{13}C NMR: (δ) 162.3 (C-4), 150.4 (C-2), 149.8 (C-6), 133.4 (Ph-2', 6'), 132.3 (Ph-3', 5'), 122.3 (Ph-4'), 122.2 (Ph-1'), 97.4 (C-5), 91.2 (C-2'), 84.3 (C-1'), 61.9 (C-4"), 47.1 (C-1"), 41.2 (C-3"), 28.3 (C-2") ppm. HRMS (ESI): calcd. for $C_{17}H_{17}N_2O_4Br$ [M+H] = 393.0444; found = 393.0452.

*N-1-[4-Hydroxy-3-(hydroxymethyl)butyl]-5-[(p-pentylphenyl)ethynyl]pirimidine-2,4-dione (**10c**)*. Compound **10c** was synthesized following a procedure for the preparation of **10b**. Reagents: compound **9c** (186.8 mg; 0.33 mmol), methanol (3.2 ml) and 0.1 M $NaOCH_3/CH_3OH$ (1.4 ml). After column chromatography (dichloromethane : methanol = 10 : 1) compound **10c** (50.2 mg; 40%; m.p. = 140−142 °C) was isolated as white crystals. ^{1}H NMR: (δ) 11.58 (1H, s, NH), 8.16 (1H, s, H-6), 7.36 (2H, d, Ph-2', 6', J = 8.1 Hz), 7.22 (2H, d, Ph-3', 5', J = 8.0 Hz), 4.40 (2H, t, OH, J = 5.2 Hz), 3.77 (2H, t, H-1", J = 7.3 Hz), 3.48–3.32 (4H, m, H-4"), 2.63–2.55 (2H, m, H-3'), 1.65–1.54 (4H, m, H-4', H-2"), 1.52–1.40 (1H, m, H-3'"), 1.36–1.25 (4H, m, H-5', H-6'), 0.86 (3H, t, CH_3-7', J = 6.8 Hz) ppm. ^{13}C NMR: (δ) 162.0 (C-4), 149.9 (C-2), 148.7 (C-6), 143.1 (Ph-4'), 131.0 (Ph-2', 6'), 128.7 (Ph-3', 5'), 119.7 (Ph-1'), 97.4 (C-5), 91.9 (C-2'), 81.9 (C-1'), 61.4 (C-

4''), 46.5 (C-1''), 40.7 (C-3''), 34.9 (C-3'), 30.8 (CH_2'), 30.2 (CH_2'), 27.8 (C-2''), 21.9 (CH_2'), 13.8 (CH_3-7') ppm. HRMS (ESI): calcd. for $C_{22}H_{28}N_2O_4$ [M+H] = 385.2122; found = 385.2126.

N-1-[4-Hydroxy-3-(hydroxymethyl)butyl]-5-(3-phenylpropynyl)pirimidine-2,4-dione ***(10d)***. Compound **10d** was synthesized following a procedure for the preparation of **10b**. Reagents: compound **9d** (152.0 mg; 0.29 mmol), methanol (2.7 ml) and 0.1 M $NaOCH_3/CH_3OH$ (1.4 ml). After column chromatography (ethyl acetate : methanol = 10: 1; dichloromethane : methanol = 20 : 1) compound **10d** (50 mg; 52%) was isolated as white crystals. MS (ESI): m/z = 329.2 ($[M+H]^+$). ^{1}H NMR: δ 11.49 (1H, s, NH), 8.04 (1H, s, H-6), 7.43–7.19 (5H, m, Ph), 4.39 (2H, t, OH, *J* = 5.2 Hz), 3.84 (2H, s, H-3'), 3.79–3.64 (2H, m, H-1''), 3.48–3.29 (4H, m, H-4''), 1.57 (2H, q, H-2'', *J* = 6.8 Hz), 1.44–1.47 (1H, m, H-3'') ppm. ^{13}C NMR: (δ) 162.3 (C-4), 149.9 (C-2), 148.3 (C-6), 136.6 (Ph-1'), 128.4 (CH-Ph), 127.9 (CH-Ph), 126.5 (Ph-4'), 97.7 (C-5), 90.7 (C-2'), 74.7 (C-1'), 61.4 (C-4''), 46.3 (C-1''), 40.7 (C-3''), 27.7 (C-2''), 24.8 (C-3') ppm. Anal. Calcd. for $C_{18}H_{20}N_2O_4$ (328,36): C, 65.84; H, 6.14; N, 8.53; found: C, 66.03; H, 6.14; N, 8.55.

5-(Cyclopropyl-ethynyl)-N-1-[4-hydroxy-3-(hydroxymethyl)butyl]pirimidine-2,4-dione ***(10e)***. Compound **10e** was synthesized following a procedure for the preparation of **10b**. Reagents: compound **9e** (253.0 mg; 0.52 mmol), methanol (3.2 ml) and 0.1 M $NaOCH_3/CH_3OH$ (1.4 ml). Column chromatography (ethyl acetate : methanol = 10: 1; dichloromethane : methanol = 20 : 1) afforded **10e** (30.7 mg; 21%; m.p. = 99−100 °C) as white crystals. ^{1}H NMR: (δ) 11.40 (1H, s, NH), 7.93 (1H, s, H-6), 4.36 (2H, t, OH, *J* = 5.2 Hz), 3.73–3.69 (2H, m, H-1''), 3.45–3.29 (4H, m, H-4''), 1.55 (2H, q, H-2'', *J* = 6.8 Hz), 1.51–1.42 (2H, m, H-3'', H-3'), 0.92–0.80 (2H, m, H-4', H-5'), 0.67–0.60 (2H, m, H-4', H-5') ppm. ^{13}C NMR: (δ) 162.9 (C-4), 150.4 (C-2), 148.7 (C-6), 98.4 (C-5), 96.5 (C-2'), 68.5 (C-1'), 61.9 (C-4''), 46.8 (C-1''), 41.2 (C-3''), 28.2 (C-2''), 8.7 (C-4', C-5'), 0.3 (C-3') ppm. HRMS (ESI): calcd. for $C_{14}H_{18}N_2O_4$ [M+H] = 279.1339; found = 279.1335.

5-(Heptynyl)-N-1-[4-hydroxy-3-(hydroxymethyl)butyl]pirimidine-2,4-dione ***(10f)***. Compound **10f** was synthesized following a procedure for the preparation of **10b**. Reagents: compound **9f** (82.6 mg; 0.17 mmol), methanol (1.7 ml) and 0.1 M $NaOCH_3/CH_3OH$ (0.7 ml). After column chromatography (dichloromethane : methanol = 20 : 1) compound **10f** (35.5 mg; 70%; m.p. =

89−92 °C) was isolated as white crystals. ^{1}H NMR: (δ) 11.45 (1H, s, NH), 7.95 (1H, s, H-6), 4.41 (2H, t, OH, *J* = 5.2 Hz), 3.79–3.65 (2H, m, H-1''), 3.48–3.34 (4H, m, H-4''), 2.35 (2H, t, H-3', *J* = 7.0 Hz), 1.61–1.41 (5H, m, H-2'', H-4', H-3''), 1.41–1.20 (4H, m, H-5', H-6'), 0.88 (3H, t, CH_3, *J* = 7.1 Hz) ppm. ^{13}C NMR: (δ) 162.3 (C-4), 149.9 (C-2), 147.9 (C-6), 98.1 (C-5), 93.0 (C-2'), 72.8 (C-1'), 61.5 (C-4''), 46.3 (C-1''), 40.7 (C-3''), 30.4 (CH_2'), 27.9 (CH_2'), 27.7 (C-2''), 21.6 (CH_2'), 18.7 (C-3'), 13.8 (CH_3) ppm. HRMS (ESI): calcd. for $C_{16}H_{24}N_2O_4$ [M+H] = 309.1808; found = 309.1804.

*5-(Decynyl)-N-1-[4-hydroxy-3-(hydroxymethyl)butyl]pirimidine-2,4-dione (**10g**)*. Compound **10g** was synthesized following a procedure for the preparation of **10b**. Reagents: compound **9g** (145.0 mg; 0.27 mmol), methanol (2.6 ml) and 0.1 M $NaOCH_3$/CH_3OH (1.3 ml). After column chromatography (dichloromethane : methanol = 20 : 1) compound **10g** (75.5 mg; 80%; m.p. = 132−135 °C) was isolated as white crystals. ^{1}H NMR: (δ) 11.45 (1H, s, NH), 7.95 (1H, s, H-6), 4.40 (2H, t, OH, *J* = 5.2 Hz), 3.76–3.66 (2H, m, H-1''), 3.46–3.33 (4H, m, H-4''), 2.35 (2H, t, H-3', *J* = 6.9 Hz), 1.62–1.19 (15H, m, H-2'', H-3'', H-4', H-5', H-6', H-7', H-8', H-9'), 0.86 (3H, t, CH_3-10', *J* = 6.7 Hz) ppm. ^{13}C NMR: (δ) 162.8 (C-4), 150.4 (C-2), 148.4 (C-6), 98.6 (C-5), 93.5 (C-2'), 73.3 (C-1'), 62.0 (C-4''), 46.8 (C-1''), 41.2 (C-3''), 31.7 (CH_2'), 29.1 (CH_2'), 29.0 (CH_2'), 28.8 (CH_2'), 28.7 (CH_2'), 28.2 (C-2''), 22.5 (CH_2'), 19.3 (CH_2'), 14.4 (CH_3-10') ppm. HRMS (ESI): calcd. for $C_{19}H_{30}N_2O_4$ [M+H] = 351.2278; found = 351.2283.

*5-(5-Chloropentynyl)-N-1-[4-hydroxy-3-(hydroxymethyl)butyl]pirimidine-2,4-dione (**10h**)*. Compound **10h** was synthesized following a procedure for the preparation of **10b**. Reagents: compound **9h** (78.0 mg; 0.16 mmol), methanol (1.4 ml) and 0.1 M $NaOCH_3$/CH_3OH (0.7 ml). After column chromatography (dichloromethane : methanol = 20 : 1) compound **10h** (44.4 mg; 91%; m.p. = 133−135 °C) was isolated as white crystals. ^{1}H NMR: (δ) 11.46 (1H, s, NH), 7.99 (1H, s, H-6), 4.39 (2H, t, OH, *J* = 5.2 Hz), 3.80–3.68 (4H, m, H-1'', H-5'), 3.44–3.33 (4H, m, H-4''), within DMSO signal (H-3'), 1.93 (2H, p, H-4', *J* = 6.7 Hz), 1.56 (2H, q, H-2'', *J* = 6.8 Hz), 1.51–1.41 (1H, m, H-3'') ppm. ^{13}C NMR: (δ) 162.8 (C-4), 150.4 (C-2), 148.7 (C-6), 98.2 (C-5), 91.8 (C-2'), 74.1 (C-1'), 61.9 (C-4''), 46.8 (C-1''), 44.6 (C-5'), 41.2 (C-3''), 31.6 (C-4'), 28.2 (C-2''), 16.8 (C-3') ppm. HRMS (ESI): calcd. for $C_{14}H_{19}N_2O_4Cl$ [M+H] = 315.1106; found = 315.1111.

N-1-[4-Hydroxy-3-(hydroxymethyl)butyl]-5-(3,3-dimethylbutynyl)pirimidine-2,4-dione ***(10i)***. Compound **10i** was synthesized following a procedure for the preparation of **10b**. Reagents: compound **9i** (100.0 mg; 0.21 mmol), methanol (1.8 ml) and 0.1 M $NaOCH_3/CH_3OH$ (1 ml). After column chromatography (ethyl acetate : methanol = 10: 1; dichloromethane : methanol = 20 : 1) compound **10i** (31 mg; 51%; m.p. = 95−98 °C) was isolated as white crystals. ^{1}H NMR: (δ) 11.41 (1H, s, NH), 7.92 (1H, s, H-6), 4.39 (2H, t, OH, *J* = 5.2 Hz), 3.75–3.67 (2H, m, H-1"), 3.46–3.35 (2H, m, H-4"), 3.35–3.32 (2H, m, H-4"), 1.55 (2H, q, H-2", *J* = 6.8 Hz), 1.49–1.42 (1H, m, H-3"), 1.24 (9H, s, CH_3) ppm. ^{13}C NMR: (δ) 162.7 (C-4), 150.4 (C-2), 148.4 (C-6), 101.2 (C-5), 98.4 (C-2'), 71.8 (C-1'), 61.9 (C-4"), 46.8 (C-1"), 41.2 (C-3"), 31.3 (CH_3), 28.2 (C-2"), 28.1 (C-3') ppm. HRMS (ESI): calcd. for $C_{15}H_{22}N_2O_4$ [M+H] = 295.1652; found = 295.1659.

4.2. X-Ray crystal structure analysis

Single crystals of compounds **1**, **2**, **6** and **10g** were obtained at room temperature by partial evaporation from methanol solution. The intensities were collected at 295 K on an Oxford Diffraction Xcalibur2 diffractometer with a Sapphire 3 CCD detector using graphite-monochromatic MoKα radiation (λ = 0.71073 Å) *CrysAlisPro*[5] program was used for the data collection and processing. The intensities were corrected for absorption using the multi-scan (**1**, **6** and **10g**) and numerical (**2**) absorption correction methods[3]. The structures were solved by direct methods with *SIR20*[6] (**1** and **6**) and *SHELXS-97*[7] (**2** and **10g**) and refined by full-matrix least-squares calculations based on F^2 using *SHELXL-2013*[5] integrated in *WinGX*[8] program package. Hydrogen atoms attached to the N3, O4 and O5 atoms in **6**, N1 atom in **1** andN1A and N1B atoms in **2** have been found in Fourier map and their coordinates and thermal isotropic parameters have been refined freely. All other hydrogen atoms were treated using appropriate riding models, with *SHELXL-2013* defaults**Error! Bookmark not defined.**. Maximum and minimum electron density in **2** (1.48/-1.22eA^{-3}) were observed 0.95 and 0.84 Å from I1A atom, respectively. *PLATON*[9] program was used for structure analysis and molecular and crystal structure drawings preparation. The CCDC 1405394-1405397 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal and refinement data for **1**: $C_{11}H_8N_2O_3$, *Mr* = 216.19; monoclinic space group *P* $2_1/c$ (No. 14); *a* = 13.6515(12), *b* = 5.7184(4), *c* =13.4895(10) Å; β = 108.571(9); *V* = 998.22(14) $Å^3$; *Z* = 4; d_x = 1.439 g cm^{-3}; θ_{max} = 27.0°; R_{Int} = 0.0214; *S* = 0.994; $R[I \geq 2\sigma(I)]$ = 0.0420, *wR*[all data] = 0.1247; $0.160 < \Delta\rho < -0.164$ eA^{-3}.

Crystal and refinement data for **2**: $C_{11}H_{17}IN_2O_3$, *Mr* = 342.09; monoclinic space group *P* $2_1/n$ (No. 14); *a* = 14.3718(13), *b* = 9.2844(6), *c* =18.0392(17) Å; β = 107.123(9); *V* = 2300.3(4) $Å^3$; *Z* = 8; d_x = 1.976 g cm^{-3}; θ_{max} = 27.0°; R_{Int} = 0.0618; *S* = 0.985; $R[I \geq 2\sigma(I)]$ = 0.0543, *wR*[all data] = 0.1449; $1.479 < \Delta\rho < -1.218$ eA^{-3}.

Crystal and refinement data for **6**: $C_{13}H_{16}N_2O_5$, *Mr* = 280.28; monoclinic space group *P* $2_1/c$ (No. 14); *a* = 10.3123(4), *b* = 12.3879(4), *c* = 10.3820(3) Å; β = 101.833(3); *V* = 1298.09(8) $Å^3$; *Z* = 4; d_x = 1.434 g cm^{-3}; θ_{max} = 27.0°; R_{Int} = 0.0354; *S* = 0.989; $R[I \geq 2\sigma(I)]$ = 0.0459, *wR*[all data] = 0.1664; $0.215 < \Delta\rho < -0.191$ eA^{-3}.

Crystal and refinement data for **10g**: $C_{19}H_{30}N_2O_4$, *Mr* = 350.45; monoclinic space group *P* $2_1/c$ (No. 14); *a* = 10.2464(8), *b* = 17.852(2), *c* =11.1849(10) Å; β =102.398(8); *V* = 1998.2(3) $Å^3$; *Z* = 4; d_x = 1.165 g cm^{-3}; θ_{max} = 26.0°; R_{Int} = 0.0356; *S* = 1.008; $R[I \geq 2\sigma(I)]$ = 0.0664, *wR*[all data] = 0.2137; $0.280 < \Delta\rho < -0.199$ eA^{-3}.

4.3. Biological evalulations

4.3.1. In silico analysis

Values of n-octanol/water partition coefficients logP for synthesized compounds were calculated by following algorithms with their default settings: (i) ChemAxon algorithm available within MarvinView Ver. 5.2.6, (ii) ACD/logP model available within ChemBioDraw Ultra 11.0.

Predictions of plausible biological targets (Table S1) were made by web-service PASS (http://www.pharmaexpert.ru/passonline/index.php) which is based on the identification of substructure features typical for active molecules.[10]

4.3.2. Cell culturing

Tumor cell lines: cervical carcinoma (HeLa), colorectal adenocarcinoma, metastatic (SW620), breast epithelial adenocarcinoma, metastatic (MCF-7), and normal cell lines: diploid human fibroblasts (BJ) and mouse embryonic fibroblasts (3T3) were cultured as monolayers and

maintained in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 2mM L-glutamine, 100 U/ml penicillin and 100 μg/ml streptomycin in a humidified atmosphere with 5% CO_2 at 37^{o}C.

4.3.3. Proliferation assays

The panel of adherent tumor cell lines were inoculated onto a series of standard 96-well microtiter plates on day 0, at 5000 cells per well. Test agents were then added in five, 10-fold dilutions (0.01 μM to 100 μM) and incubated for further 72h. Working dilutions were freshly prepared on the day of testing in the growth medium. The solvent (DMSO) was also tested for eventual inhibitory activity by adjusting its concentration to be the same as in the working concentrations (DMSO concentration never exceeded 0.1%). After 72h of incubation, the cell growth rate was evaluated by performing the MTT assay. End-point absorbance was measured at 570 nm. Each test point was performed in quadruplicate in three individual experiments. Experimentally determined absorbance values were transformed into a cell percentage growth (PG) using the formulas proposed by NIH and described previously.[11] This method directly relies on control cells at the day of assay because it compares the growth of treated cells with the growth of untreated cells in control wells on the same plate. The results are therefore a percentile difference from the calculated expected value. The IC_{50} values for each compound were calculated from dose-response curves using linear regression analysis by fitting the mean test concentrations that give PG values above and below the reference value. If, however, all of the tested concentrations produce PGs exceeding the respective reference level of effect (*e.g.* PG value of 50) for a given cell line, the highest tested concentration is assigned as the default value (in the screening data report that default value is preceded by a ">" sign).

4.3.4. Detection of apoptosis

Annexin V-FLUOS staining kit (eBioscience, USA) assay was used to assess apoptosis induction according to the manufacturer's recommendations. The MCF-7 and 3T3 cells were seeded on 8-chamber slides (50000 cells/well, Lab-Tk II Chamber slide, Nunc, SAD) and treated with compounds **6**, **8**, **9c** and **9e** at their IC_{50} concentrations for 24 and 48h. Untreated cells were used as control. Upon treatmen t, the growth medium was removed from wells. Attached cells were covered with 100 μl/well of incubation buffer, containing Annexin V-Flous labeling reagent and

propidium iodide (0.02% v/v propidium iodide and 0.02% v/v concentration of annexin) for 15 min. The cells were then washed with PBS, embedded in 20% glycerol (Kemika, Croatia), covered with a coverslip and analyzed under the fluorescent microscope (BX51, Olympus, USA). The results are presented as percentages of cells positive to annexin and propidium iodide per total cell number. At least 100 cells were counted in each well.

4.3.5. Western blot

The MCF-7 cells were seeded in six well plate, $3x10^5$ cells/well, and treated with compound 6 at concentration IC50=0,01μM, compound 8 at concentration IC50=6 μM, compound 9c at concentration IC50=0,1 μM and compound 9e at concentration IC50=0,1 μM, for 24 hours. Protein lysates were prepared using a buffer containing 50 mM Tris HCl (pH 8), 150 mM NaCl, 1% NP-40, 0.5% sodium deoxycholate, 0.1% SDS, and a protease and phosphatase inhibitor cocktail (Roche, Switzerland). A total of 50 μg of proteins were resolved on 12% SDS polyacrylamide gels using the Mini-protean cell (Bio-Rad, USA). The membranes were incubated with primary antibodies raised against ASAH 1(1:1000, mouse mAb, Abcam, UK) , SK 1(Ser 225)(1:500, rabbit pAb,ECM biosciences, USA) and α- tubulin (1:1000, mouse mAb, Sigma, USA) at 4 °C overnight. Secondary antibody linked to anti-mouse (1:1000, Dako, USA) was used. The signal was visualized by Western Lightening Chemiluminescence Reagent Plus Kit (Perkin Elmer, USA) on the ImageQuant LAS500 (GE Healthcare, USA). The signal was visualized by Western Lightening Chemiluminescence Reagent Plus Kit (Perkin Elmer, USA) on the ImageQuant LAS500 (GE Healthcare, USA) and GAPDH (1:1000, mouse mAb, GeneTex, USA) was used as a loading control. The signal intensities of particular bands were normalized with the intensity of the loading control and compared in Quantity One software (Bio-Rad, USA). The values are expressed as the average ± standard deviation. Statistical analysis was performed in Microsoft Excel by using the ANOVA at $p < 0.05$.

4.3.6. Evaluation of inhibitory effect on 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1) activity

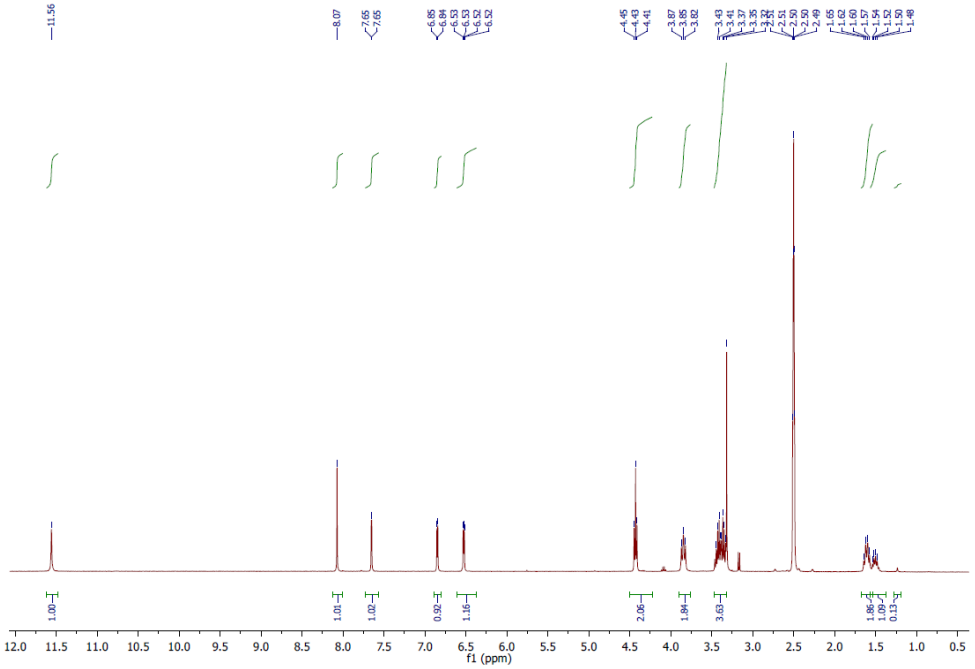
Tumor cell lines MCF-7 (breast epithelial adenocarcinoma, metastatic), were seeded onto a 24-well plates (Falcon, USA), at 2×10^4 cells per well. After 24h, test agents were added at corresponding IC_{50} and $5 \times IC_{50}$ concentrations analysed by MTT test. Adherent cells were

detached with Trypzine (Lonza, Austria) and collected by centrifugation after 24h treatment and the cells were washed three times with cold PBS and frozen at -20°C. Freeze/thaw cycle was repeated three times. Cells were centrifuged at 1500 rpm for 10 minutes at 4°C (Eppendorf, Germany). Before the ELISA assay, protein concentration was assessed fluorimetry to adjust concentrations for assaying of enzyme activity (QBit Invitrogen, USA). Reagents and samples were provided in the kit (17β-hydroxysteroid dehidrogenase Type 1 Enzime-linked Immunosorbent Assay Kit, Cloude Clone Corp., TX, USA) and prepared according to manufacturer's recommendations.

5. ^{1}H and ^{13}C NMR spectra

Figure S6. a) ^{1}H NMR and b) ^{13}C NMR of compd. **6**.

a)



b)

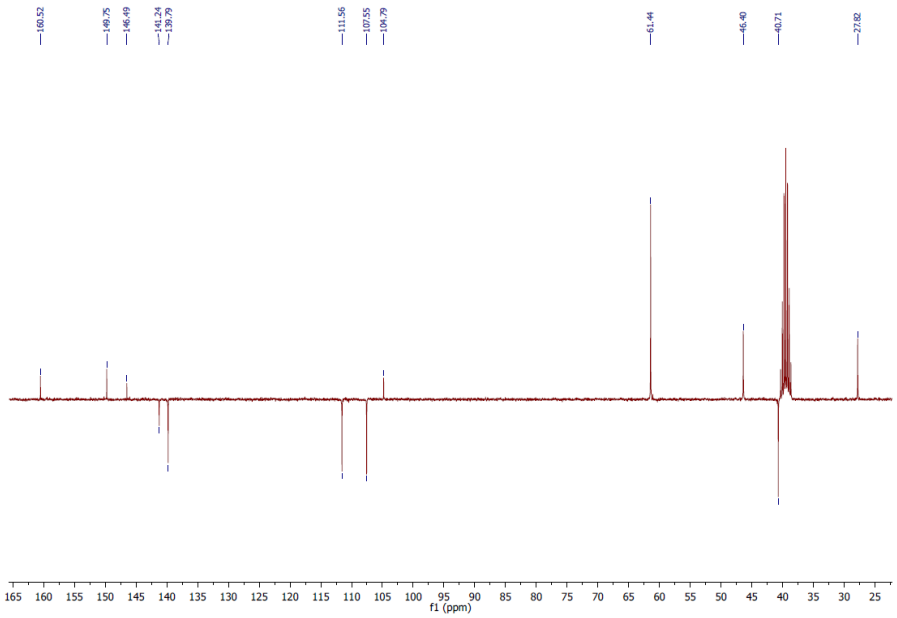
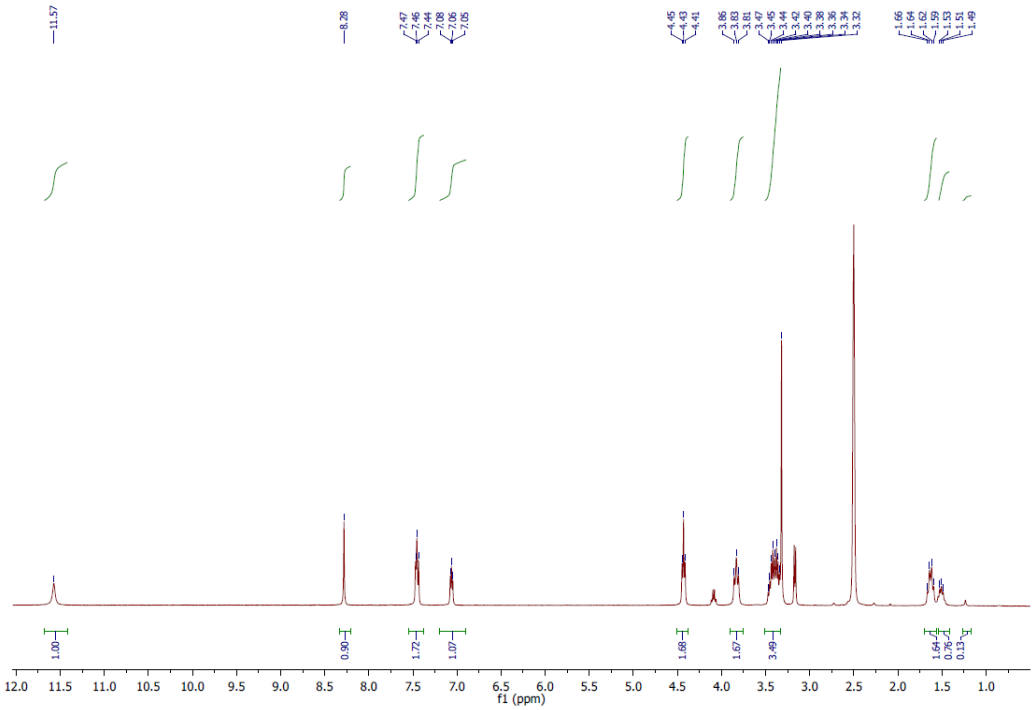


Figure S7. a) ^{1}H NMR and b) ^{13}C NMR of compd. **8**.

a)



b)

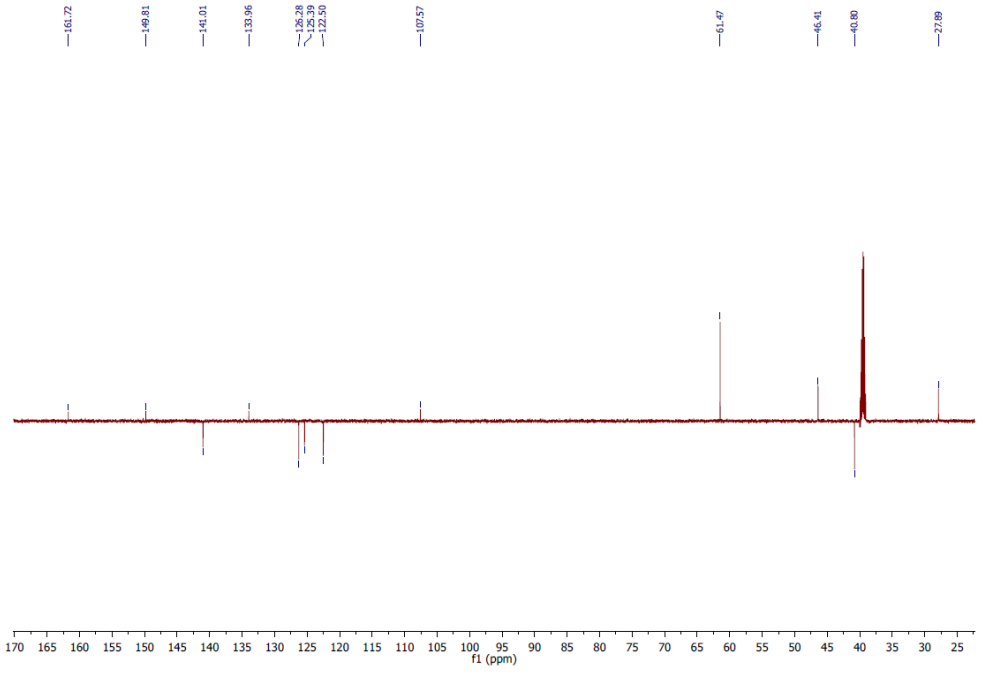
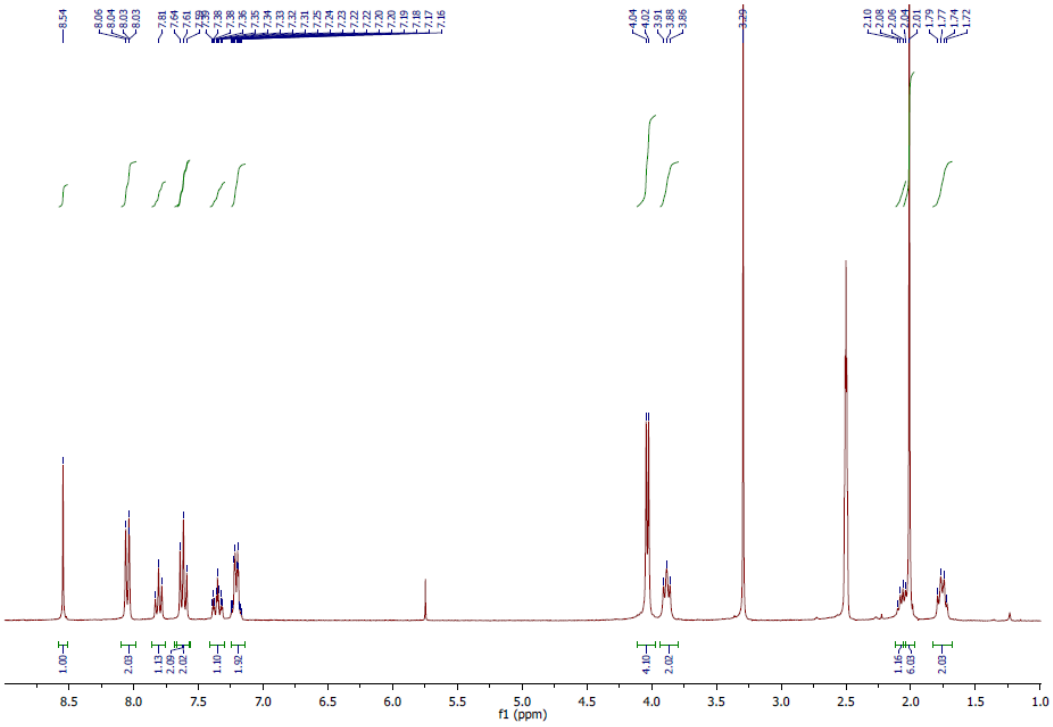


Figure S8. a) ^{1}H NMR and b) ^{13}C NMR of compd. **9a**.

a)



b)

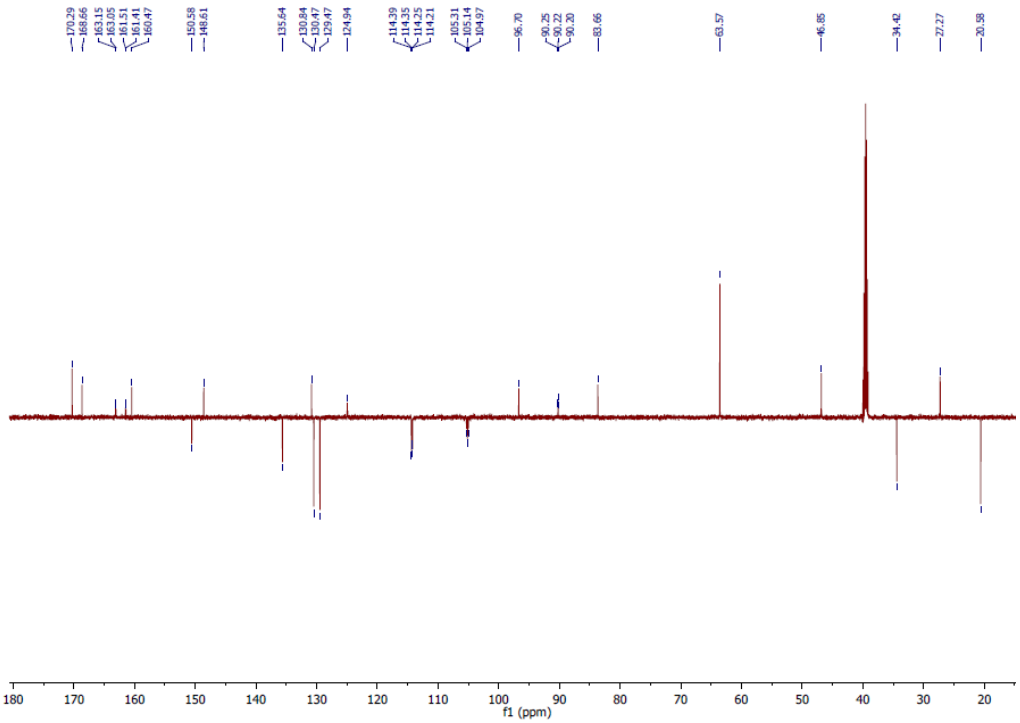
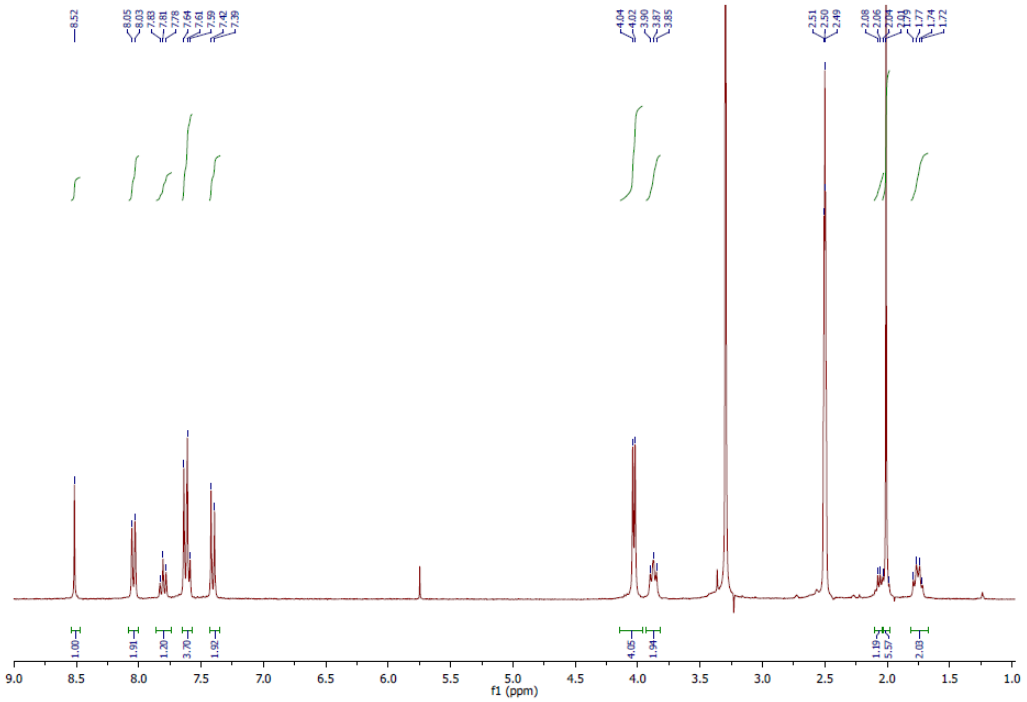


Figure S9. a) ^{1}H NMR and b) ^{13}C NMR of compd. **9b**.

a)



b)

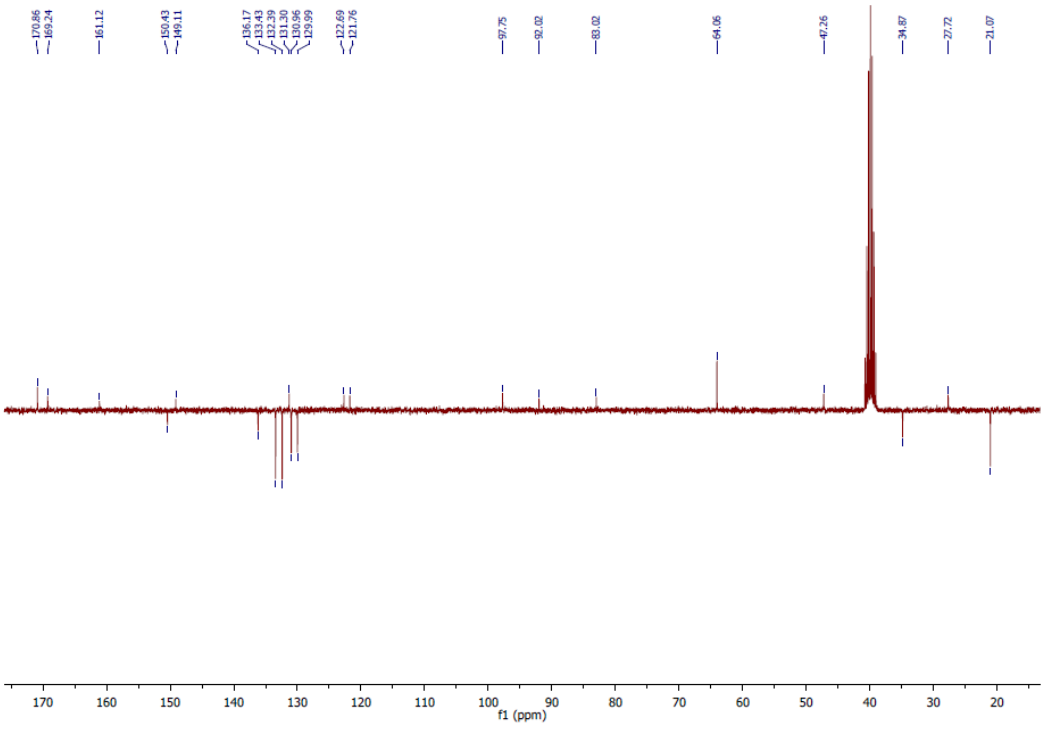
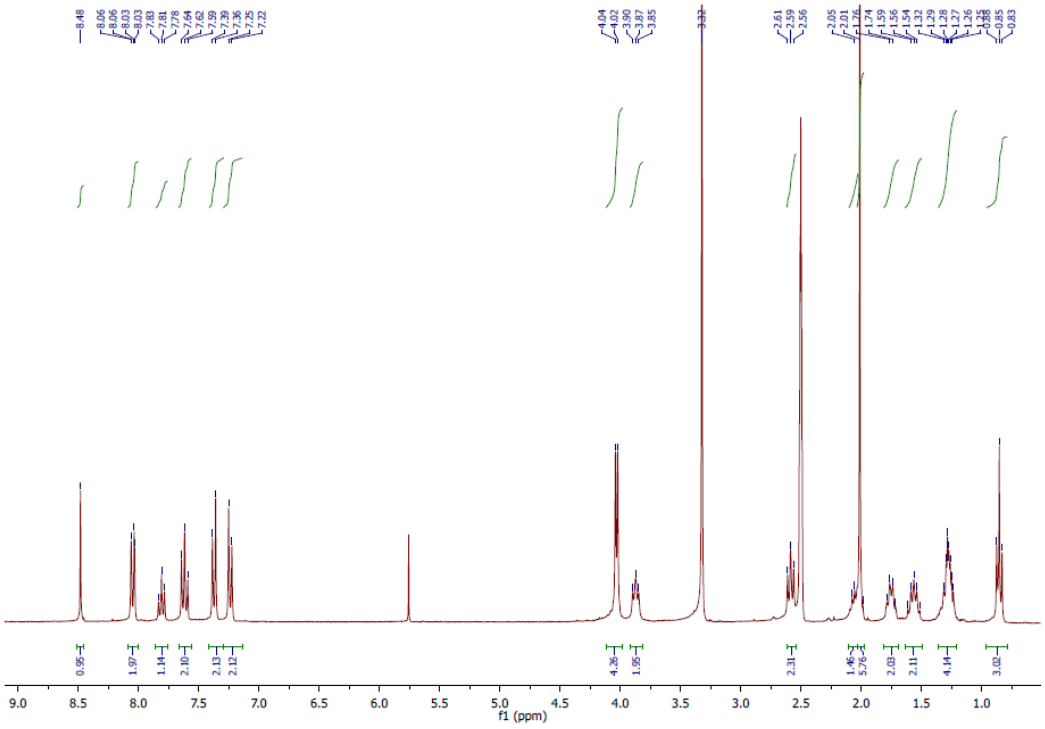


Figure S10. a) ^{1}H NMR and b) ^{13}C NMR of compd. **9c**.



b)

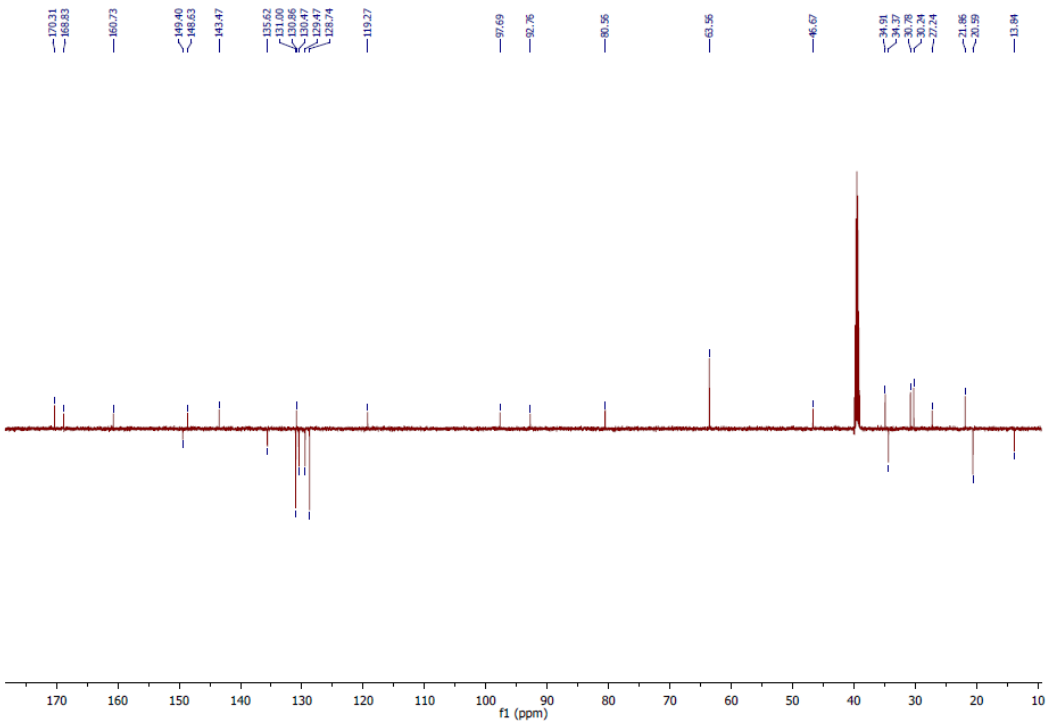
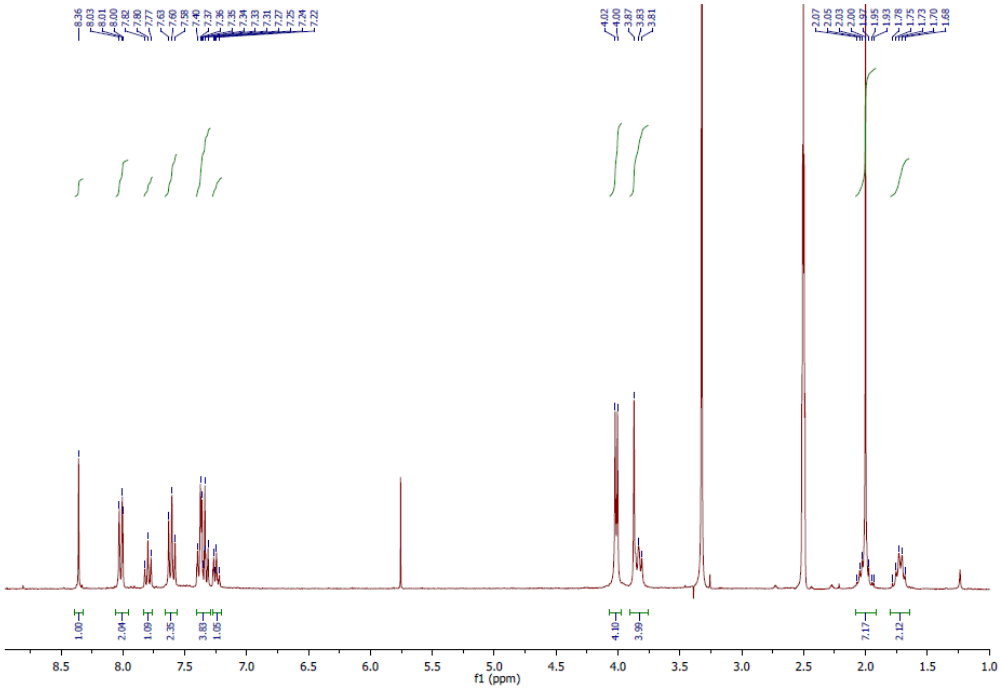


Figure S11. a) ^{1}H NMR and b) ^{13}C NMR of compd. **9d**.

a)



b)

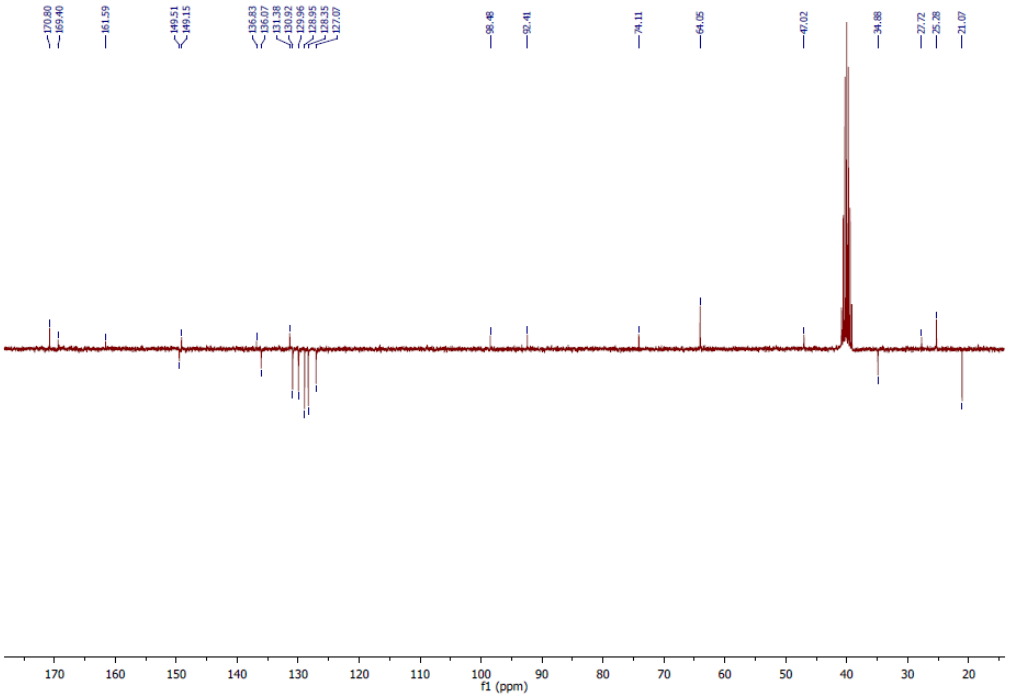
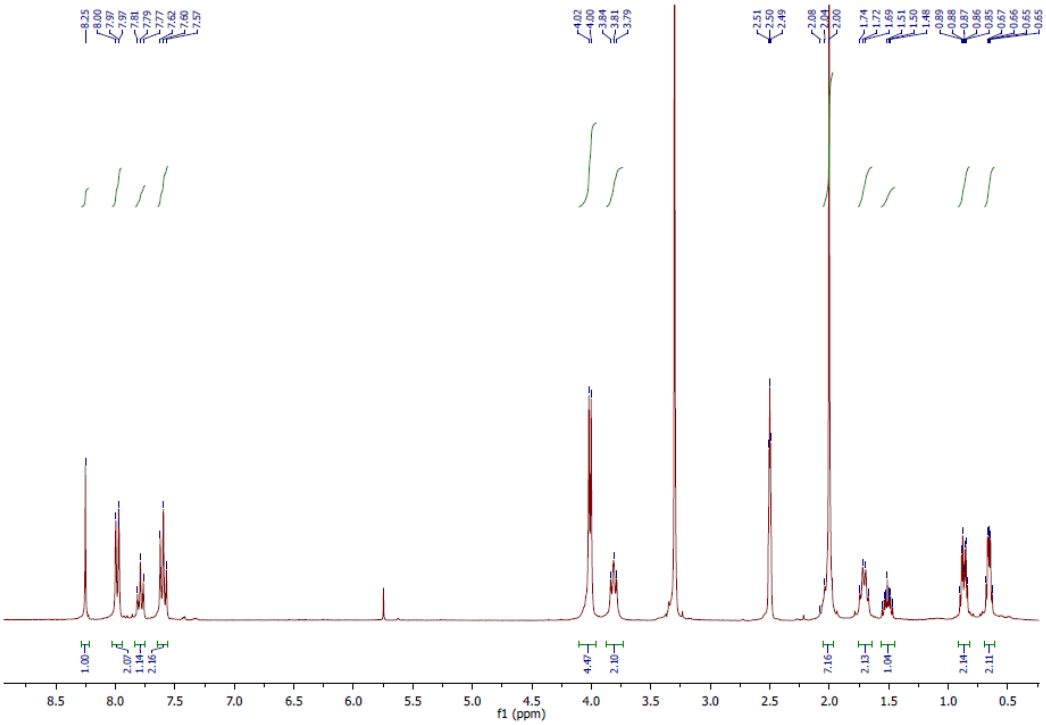


Figure S12. a) ^{1}H NMR and b) ^{13}C NMR of compd. **9e**.

a)



b)

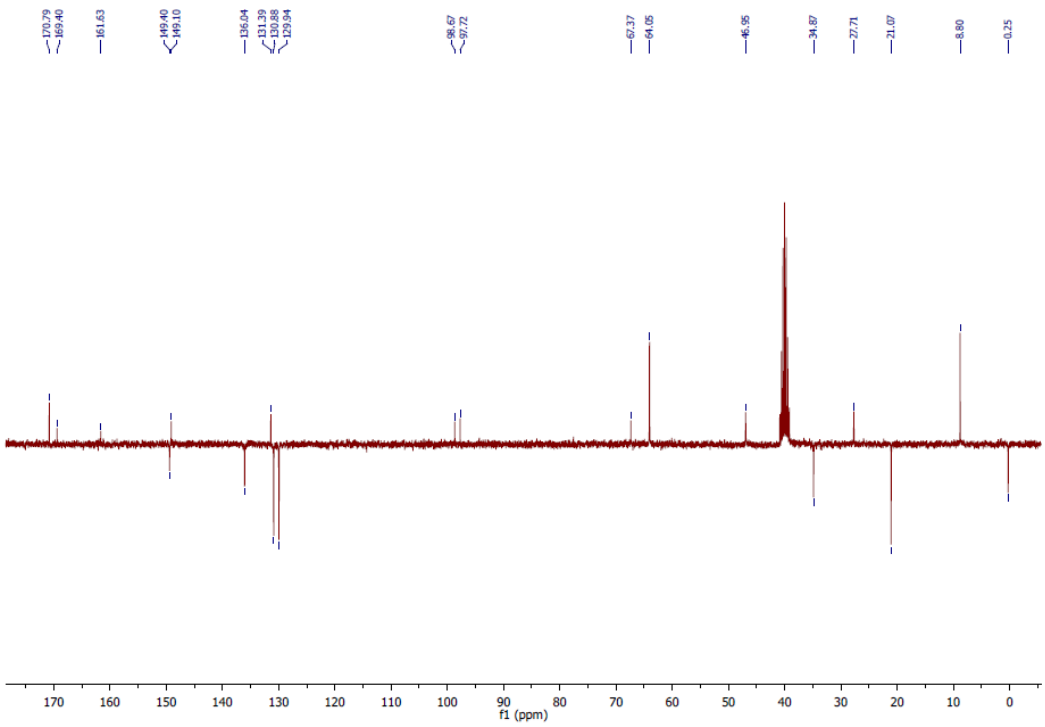
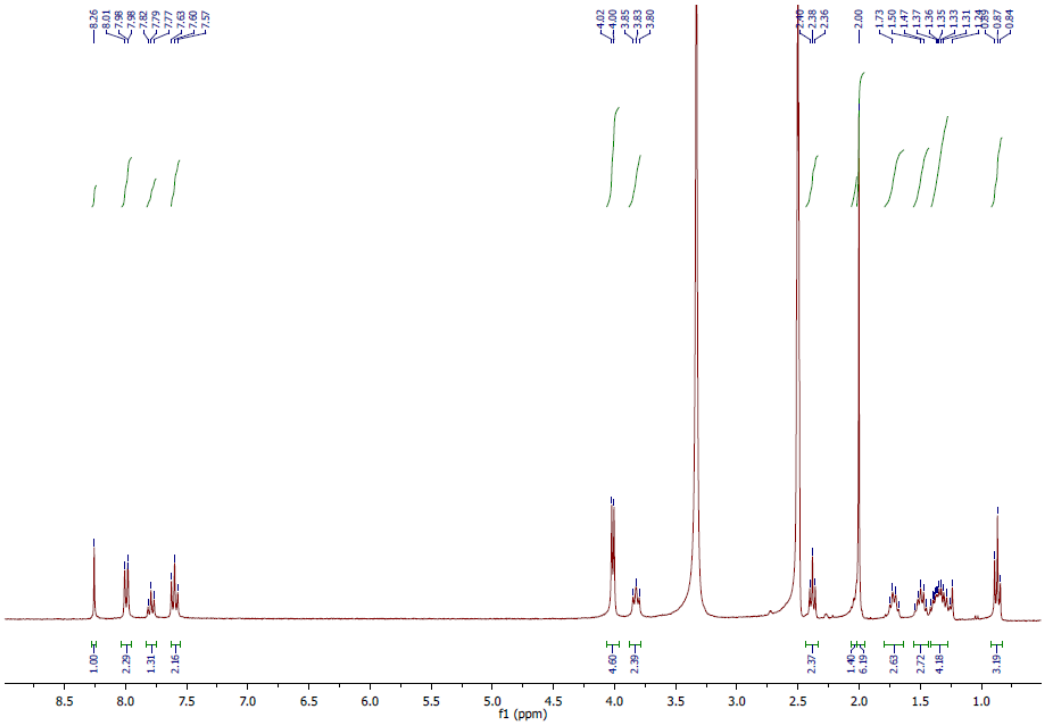


Figure S13. a) ^{1}H NMR and b) ^{13}C NMR of compd. **9f**.

a)



b)

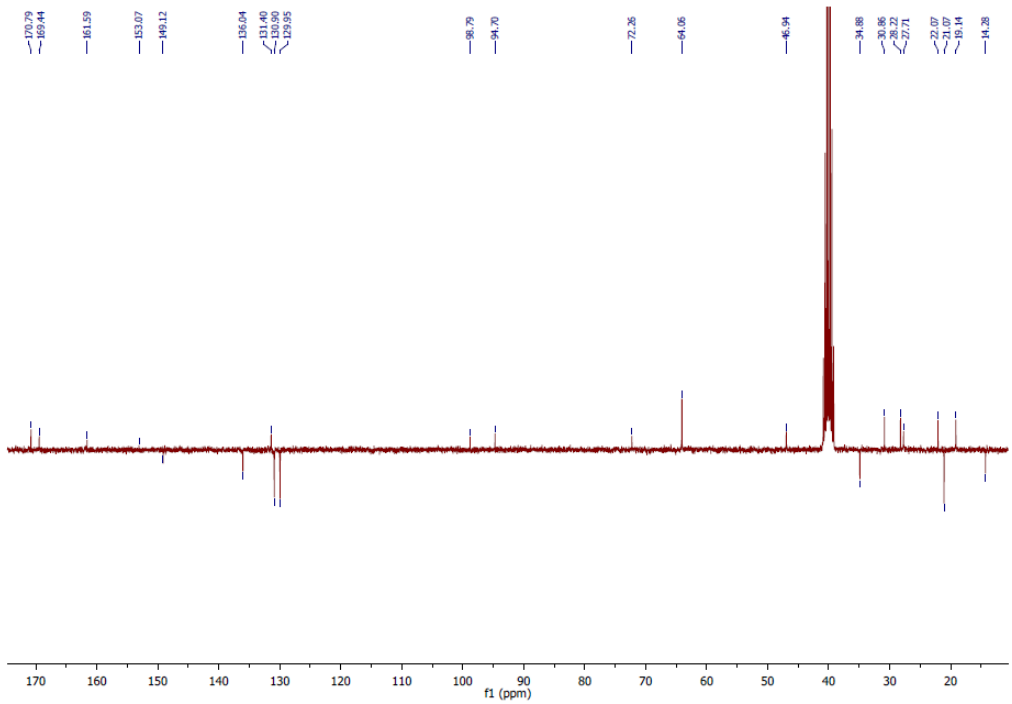
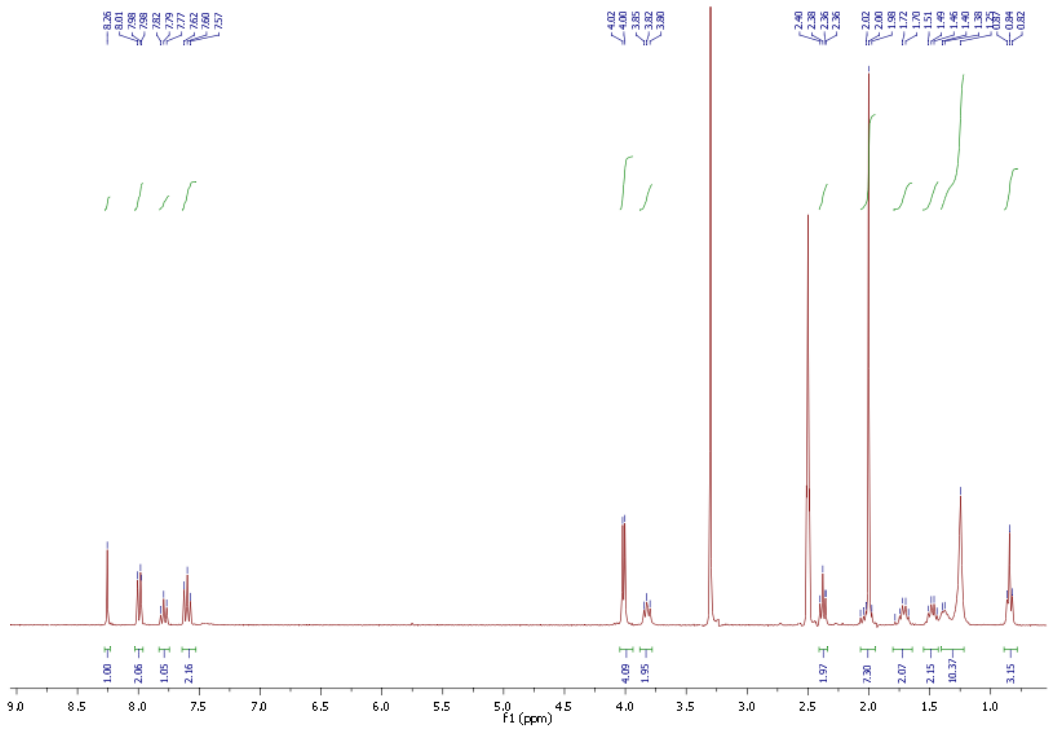


Figure S14. a) ^{1}H NMR and b) ^{13}C NMR of compd. **9g**.

a)



b)

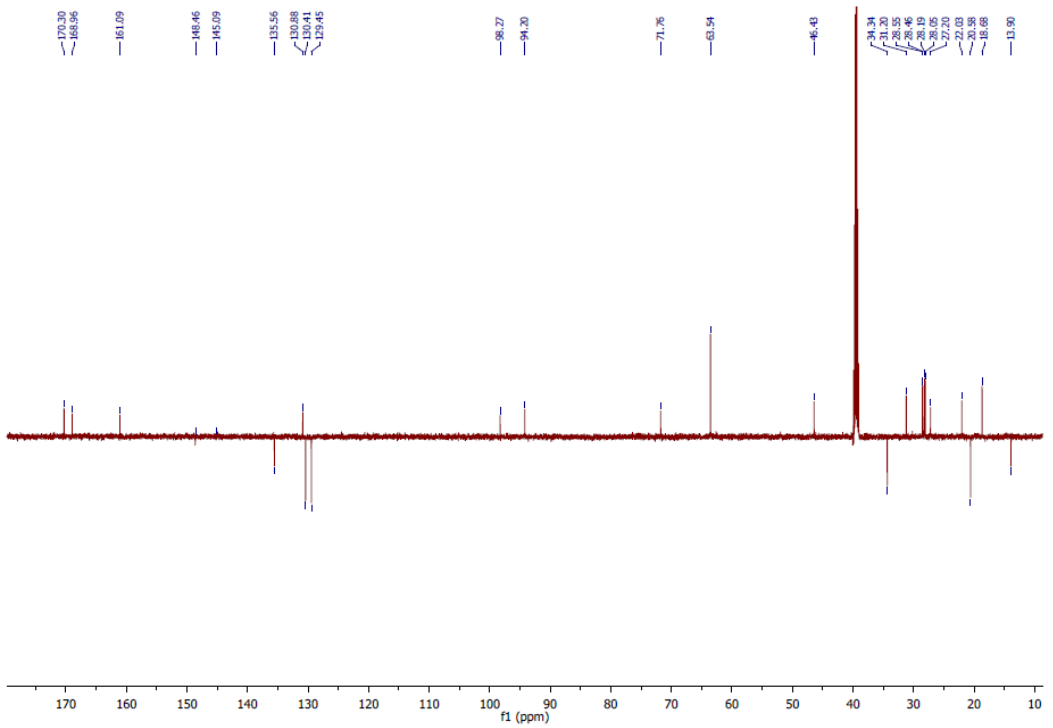
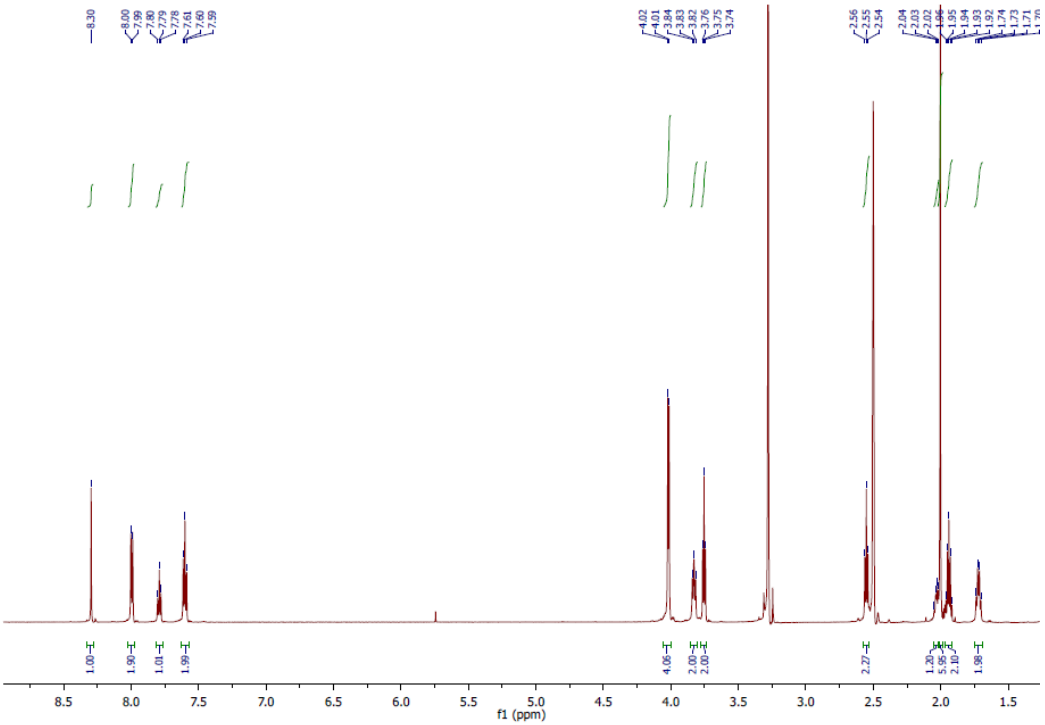


Figure S15. a) ^{1}H NMR and b) ^{13}C NMR of compd. **9h**.

a)



b)

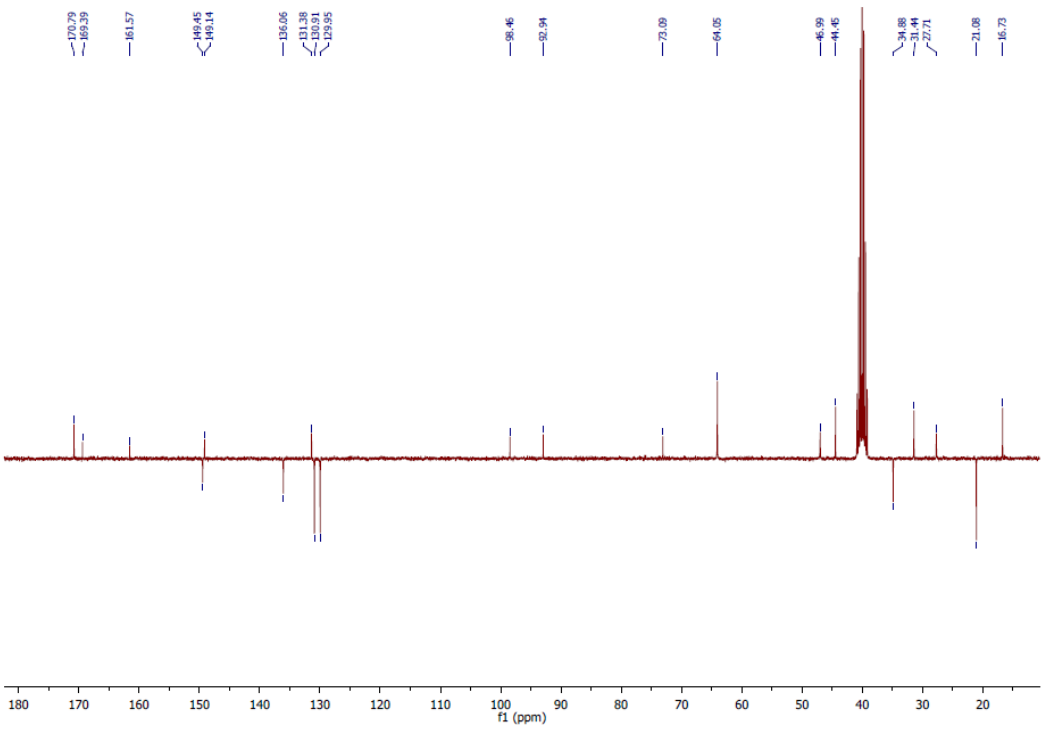
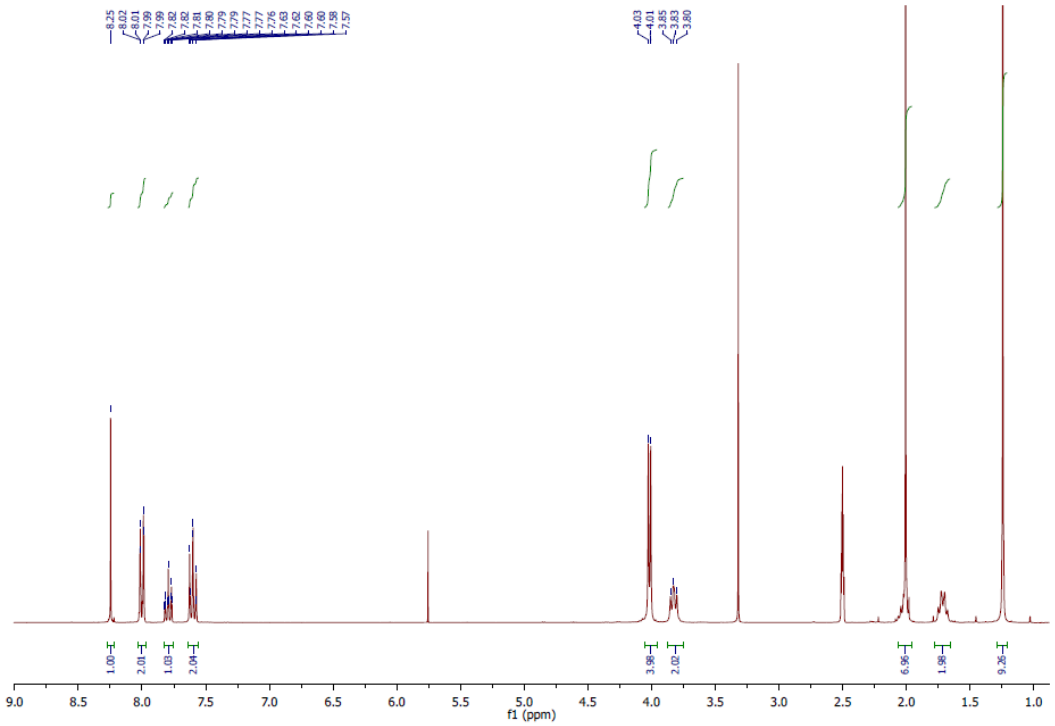


Figure S16. a) ^{1}H NMR and b) ^{13}C NMR of compd. **9i**.

a)



b)

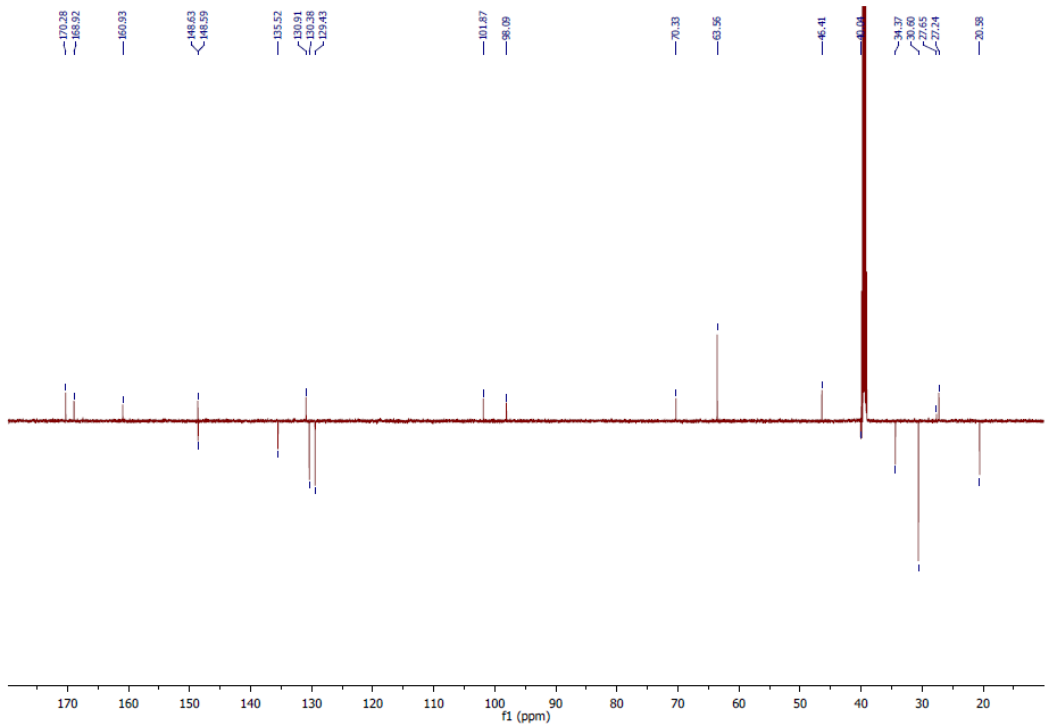
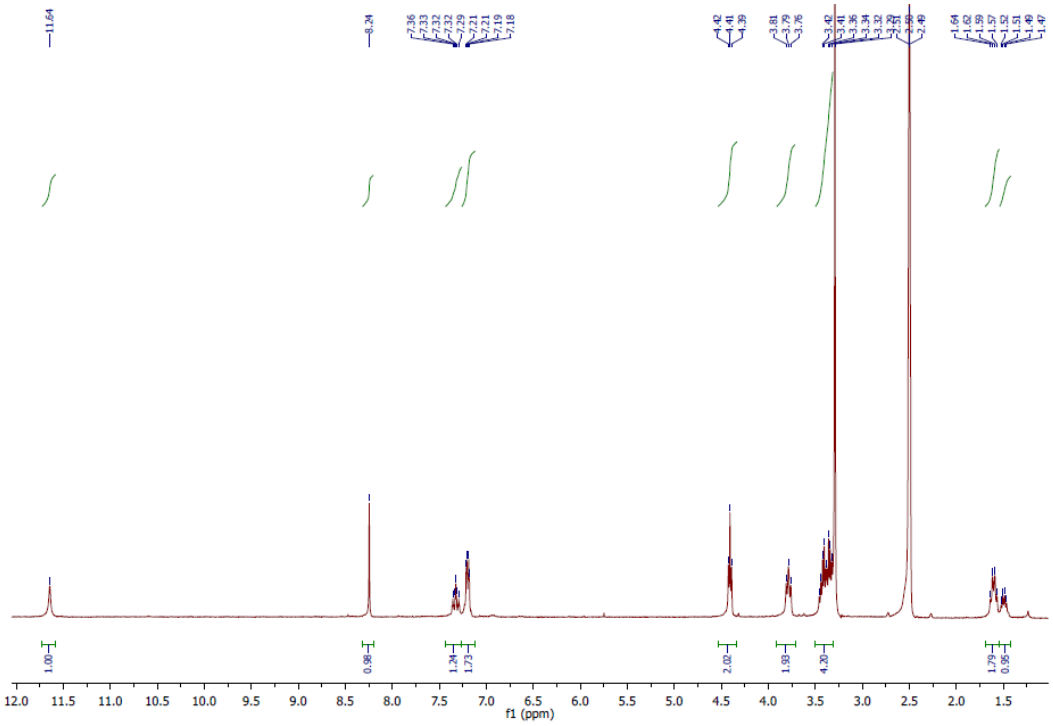


Figure S17. a) ^{1}H NMR and b) ^{13}C NMR of compd. **10a**.

a)



b)

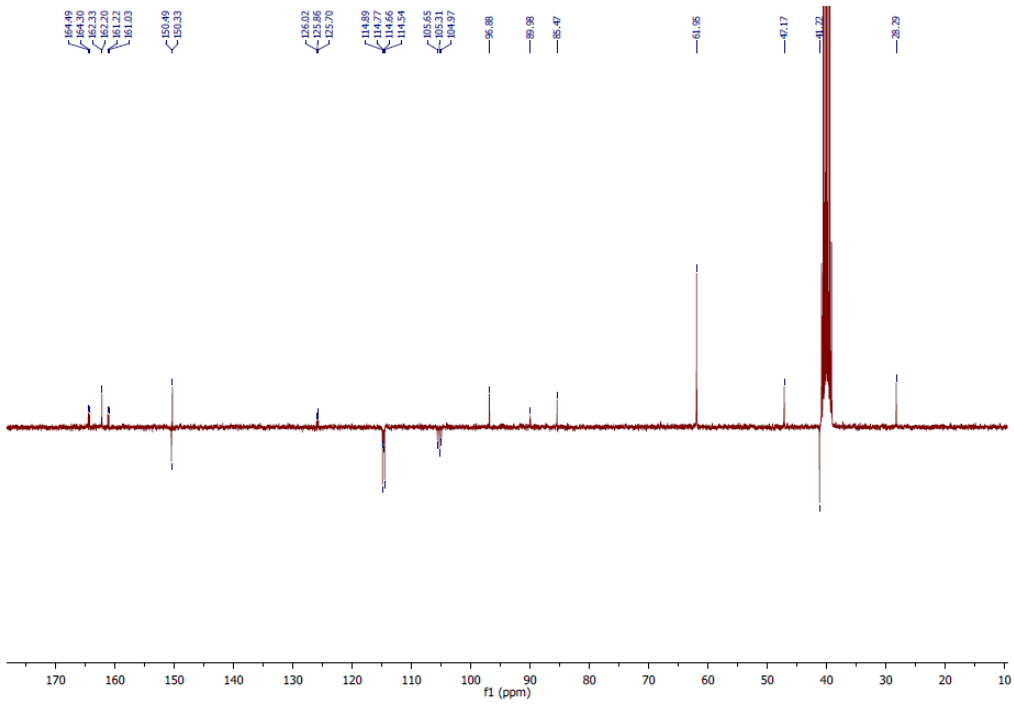
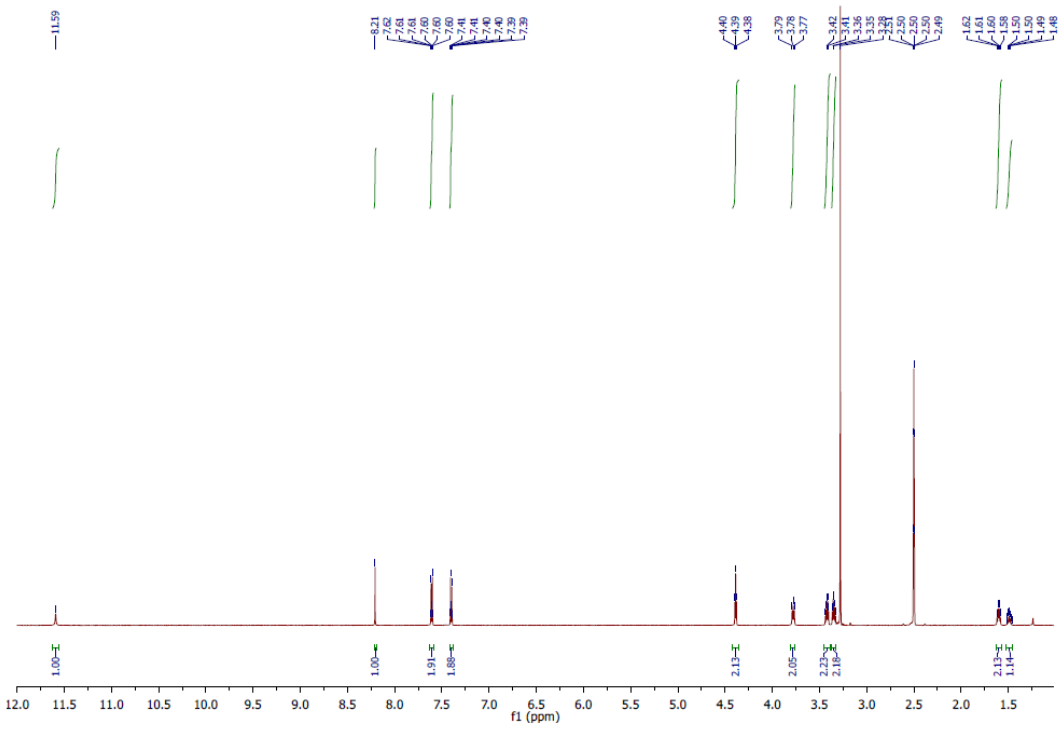


Figure S18. a) ^{1}H NMR and b) ^{13}C NMR of compd. **10b**.

a)



b)

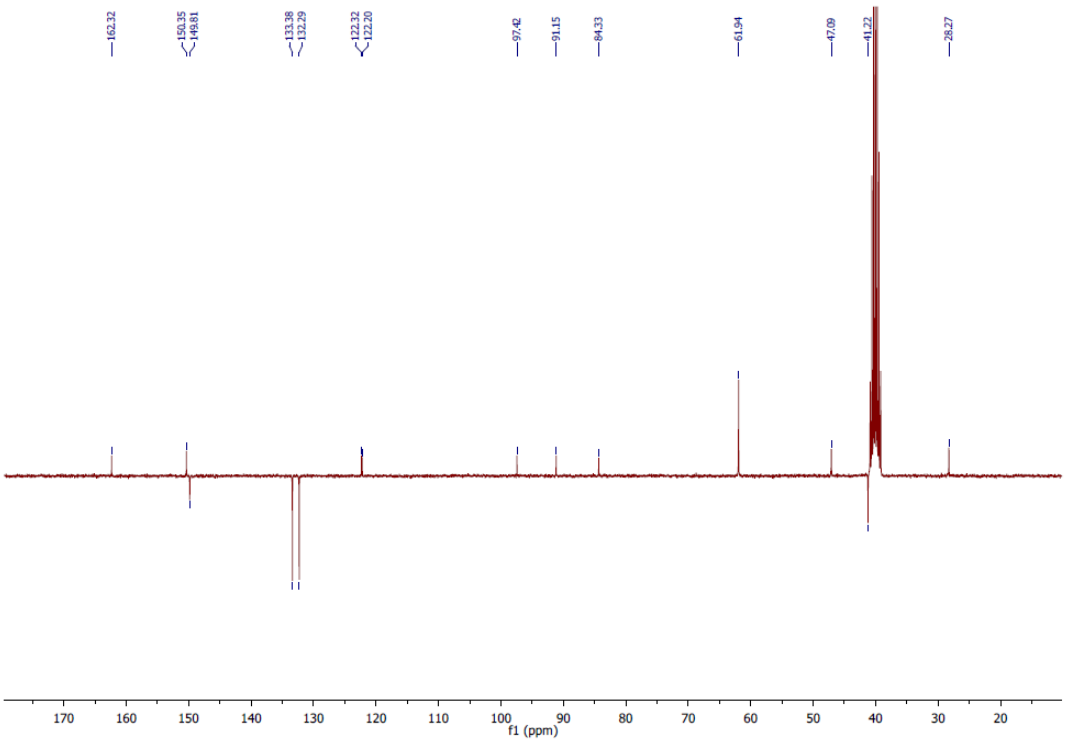
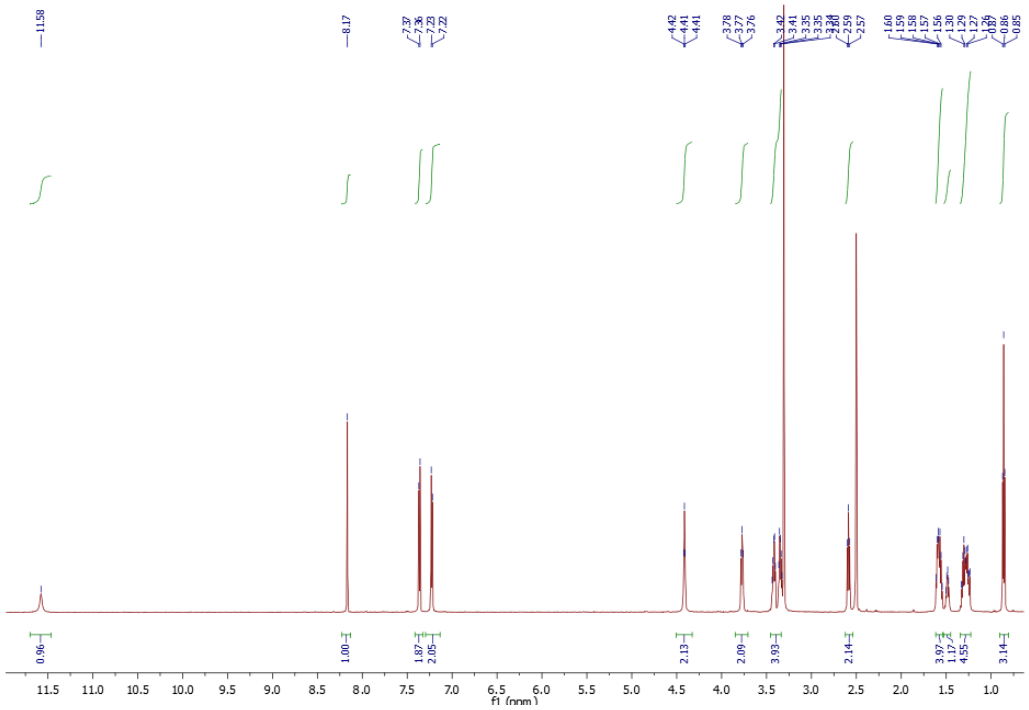


Figure S19. a) ^{1}H NMR and b) ^{13}C NMR of compd. **10c**.

a)



b)

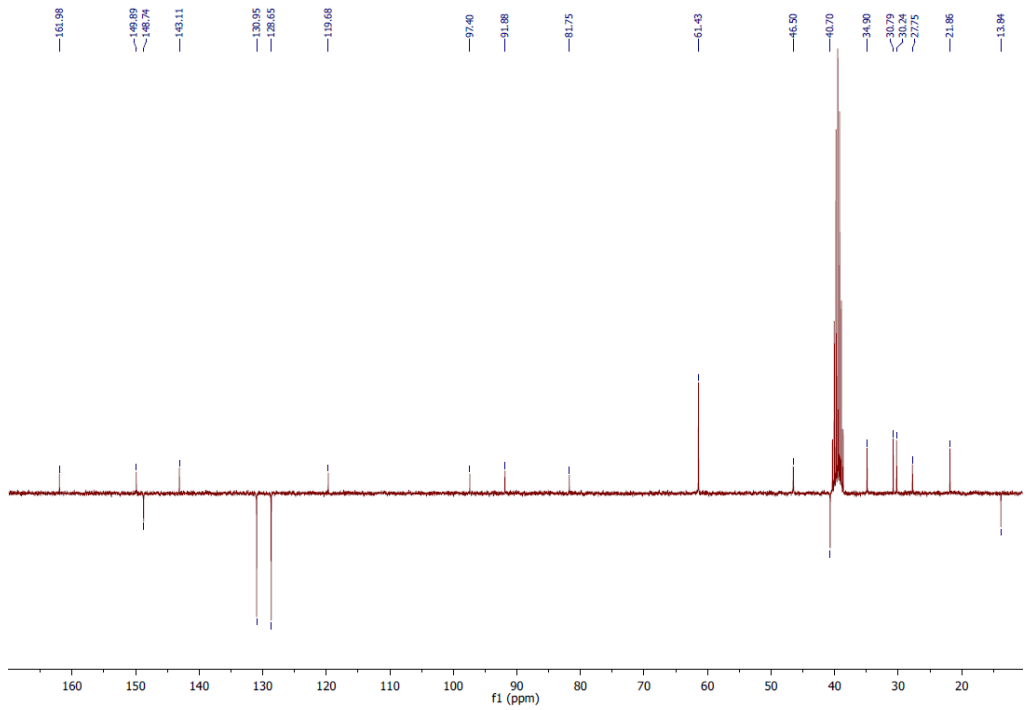
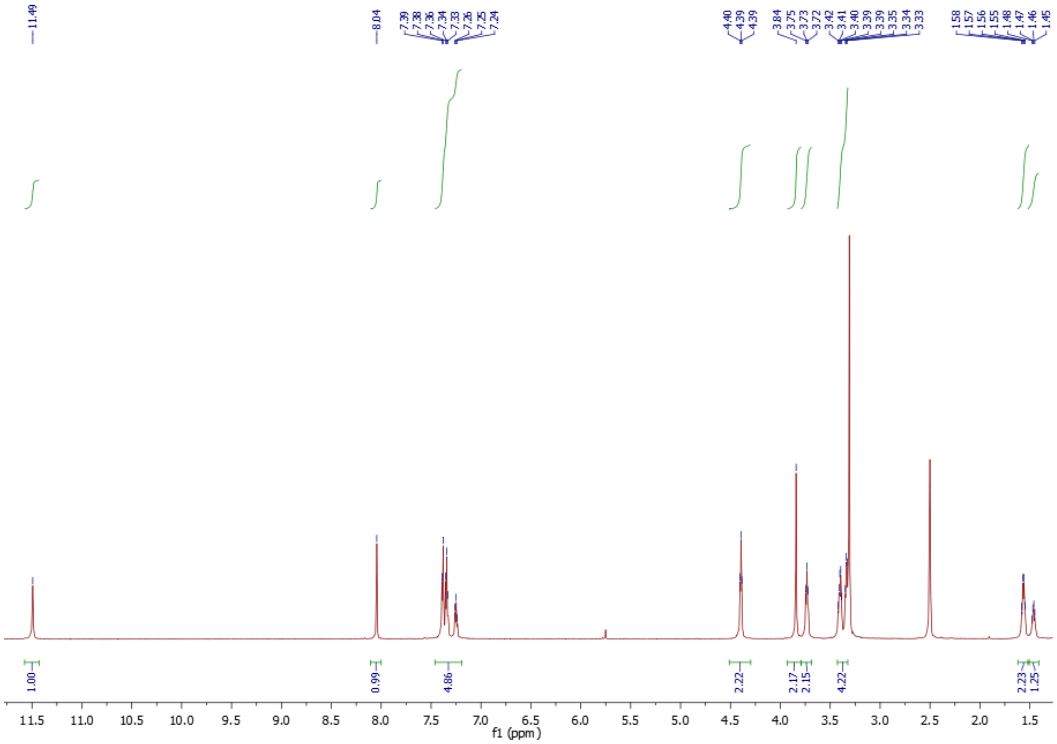


Figure S20. a) ^{1}H NMR and b) ^{13}C NMR of compd. **10d**.

a)



b)

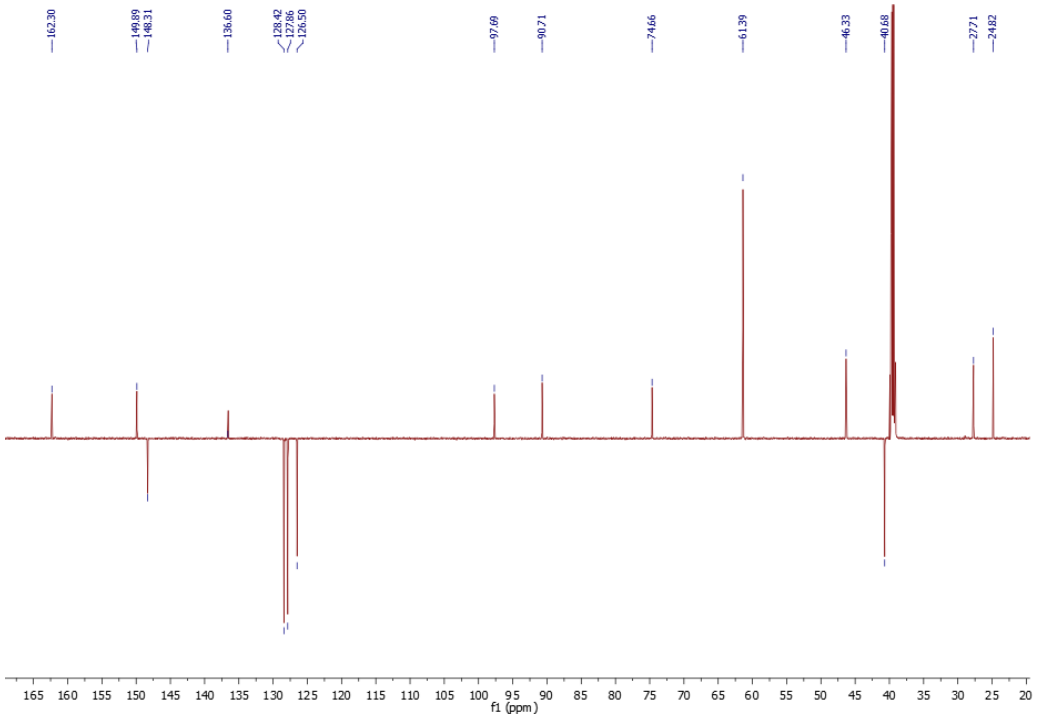
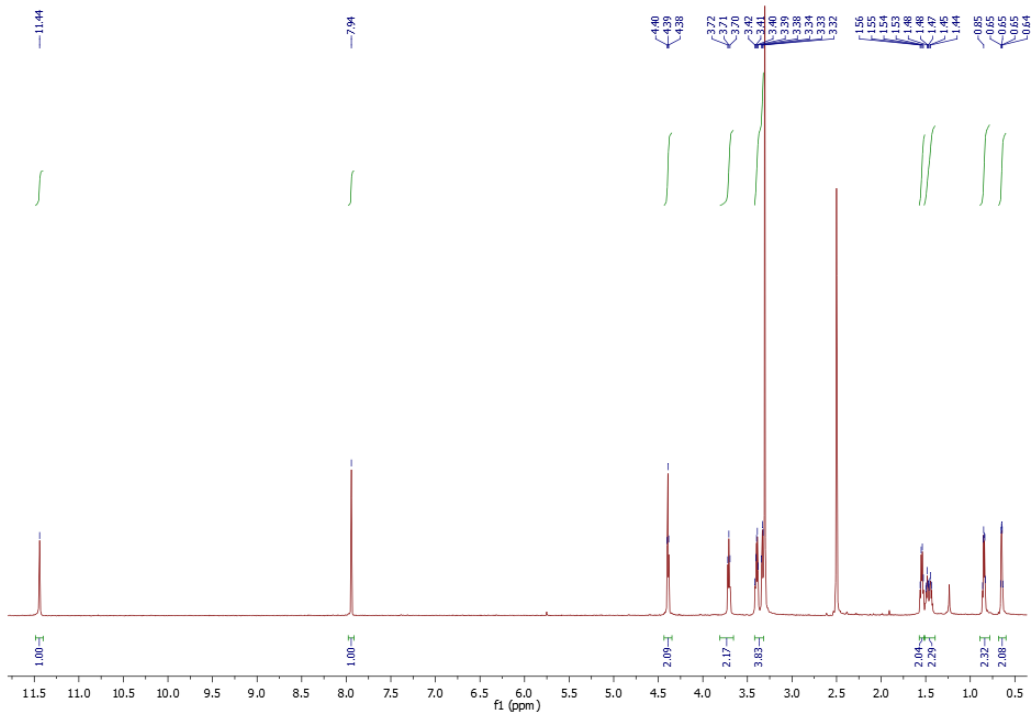


Figure S21. a) ^{1}H NMR and b) ^{13}C NMR of compd. **10e**.

a)



b)

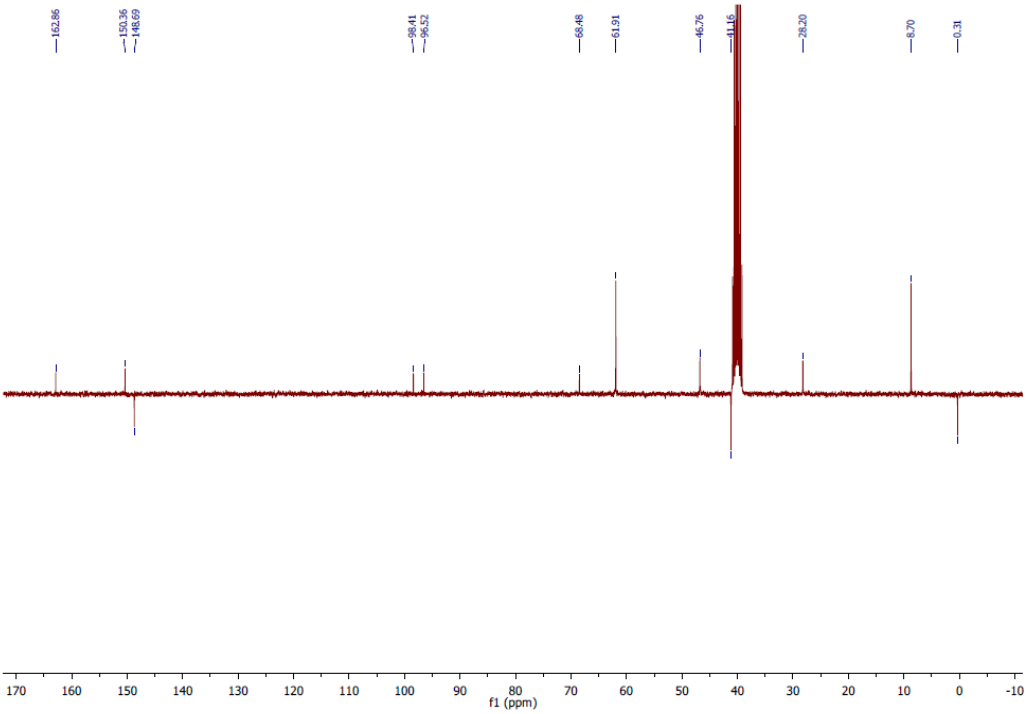
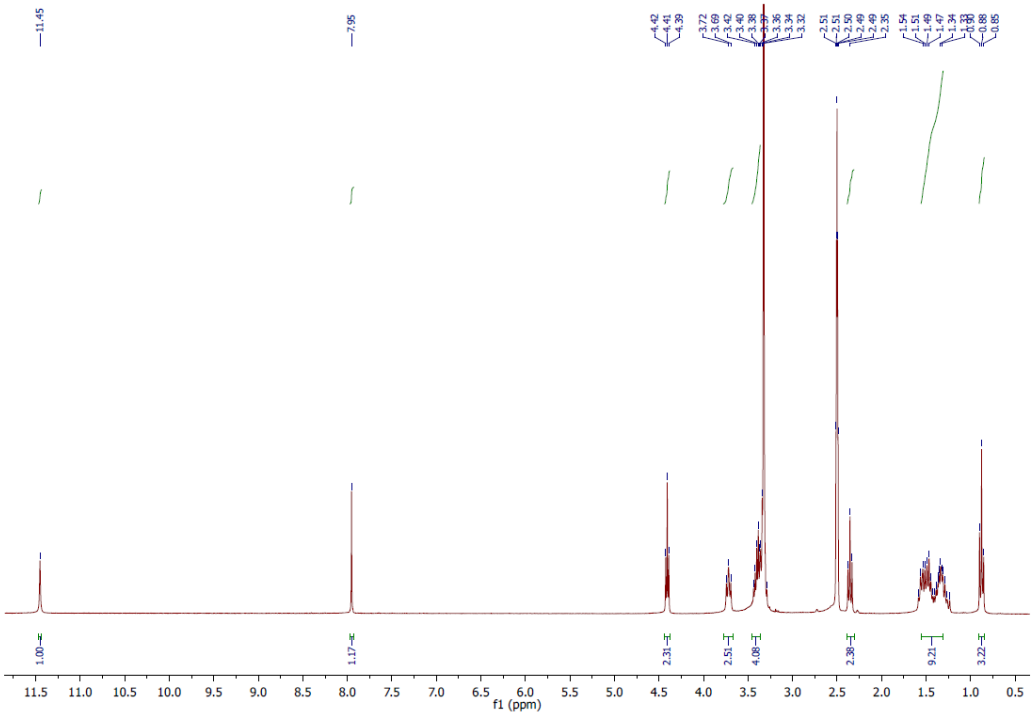


Figure S22. a) ^{1}H NMR and b) ^{13}C NMR of compd. **10f**.

a)



b)

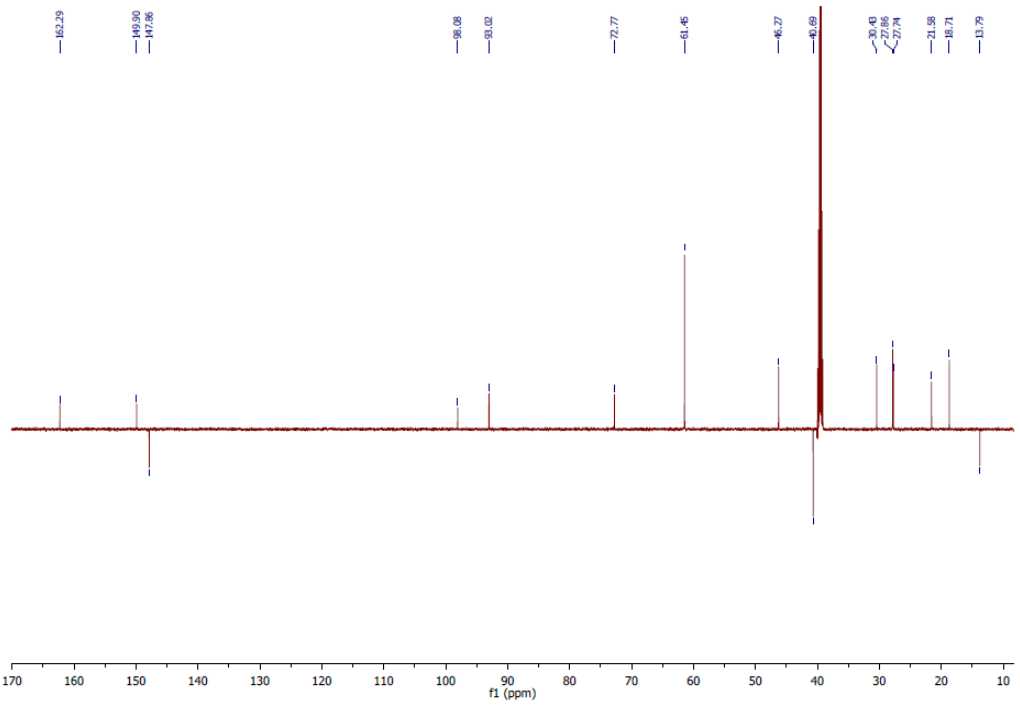
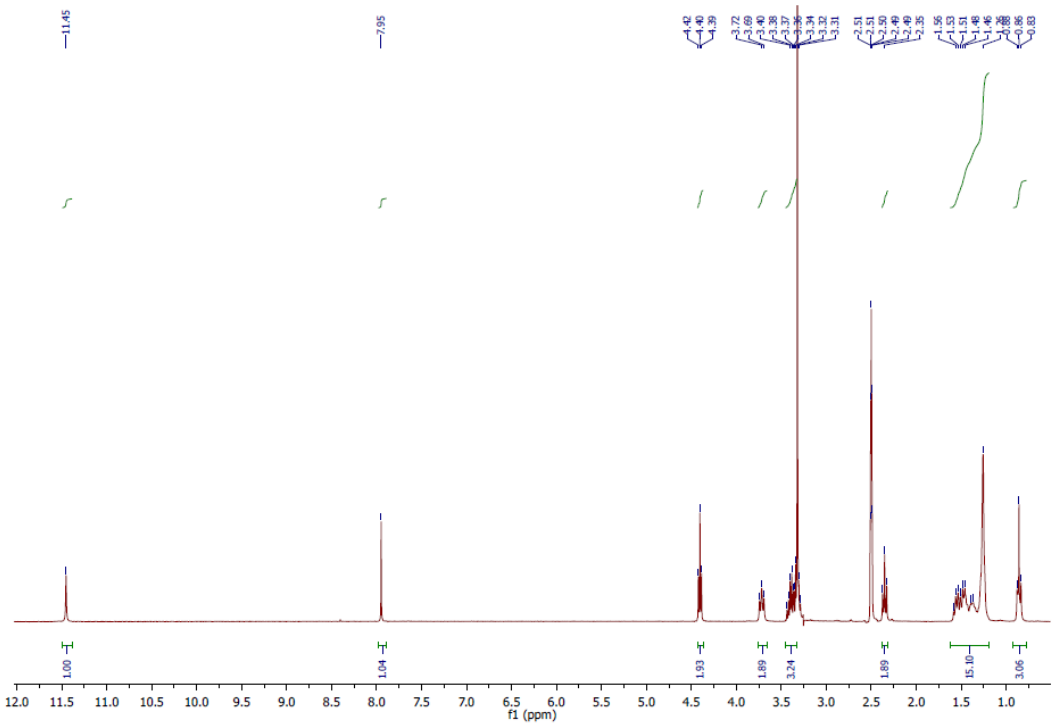


Figure S23. a) ^{1}H NMR and b) ^{13}C NMR of compd. **10g**.

a)



b)

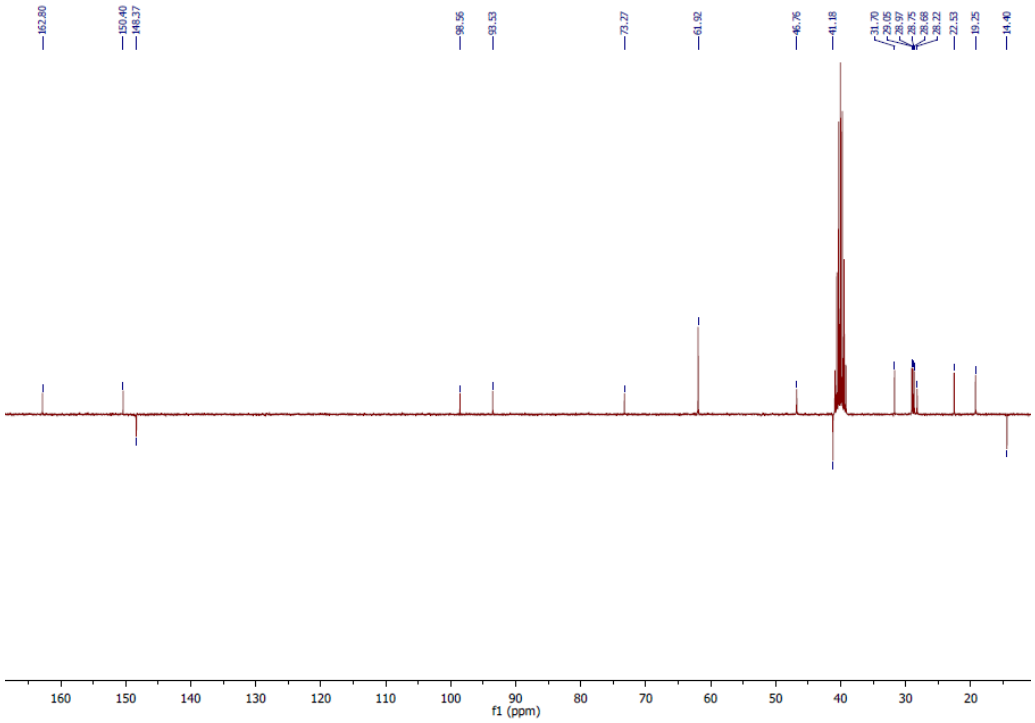
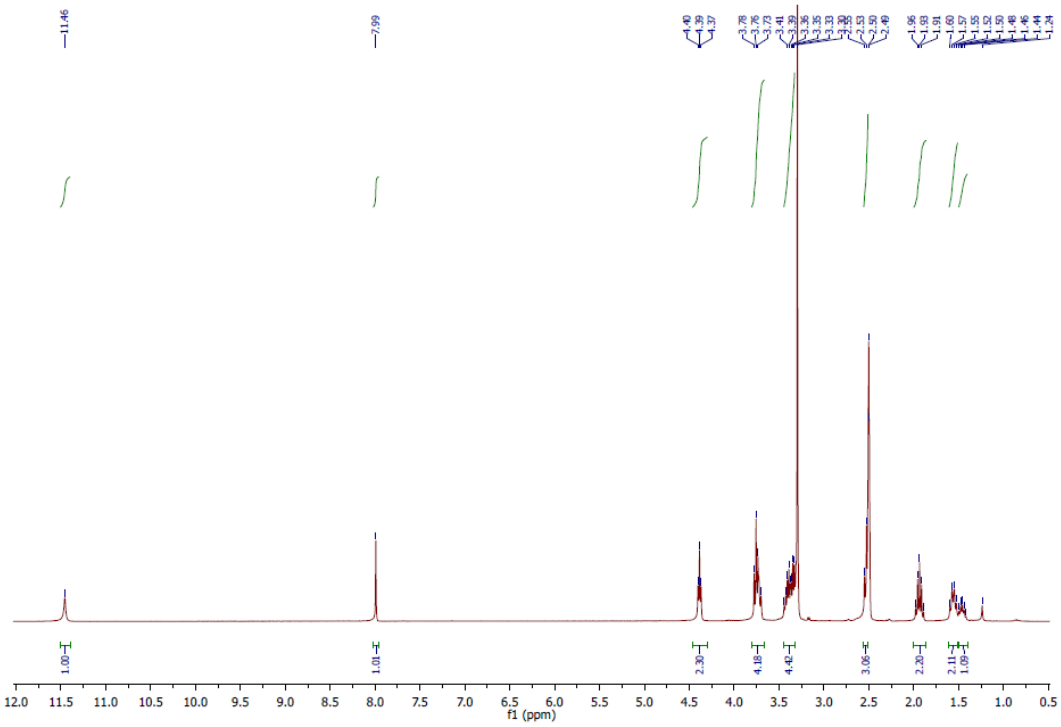


Figure S24. a) ^{1}H NMR and b) ^{13}C NMR of compd. **10h**.

a)



b)

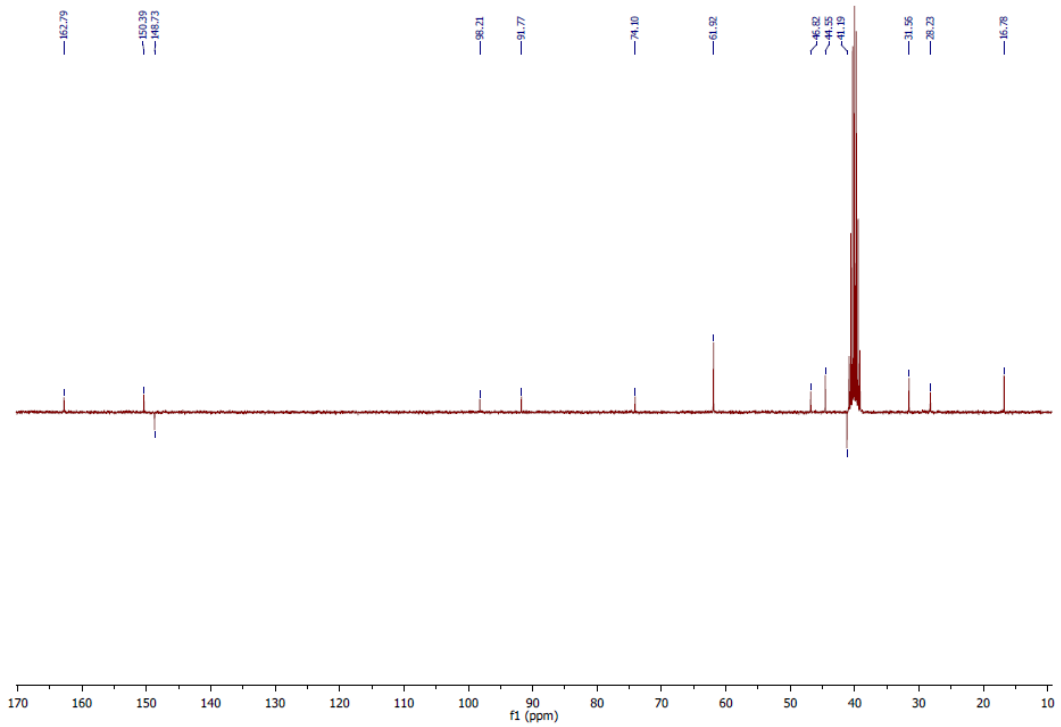
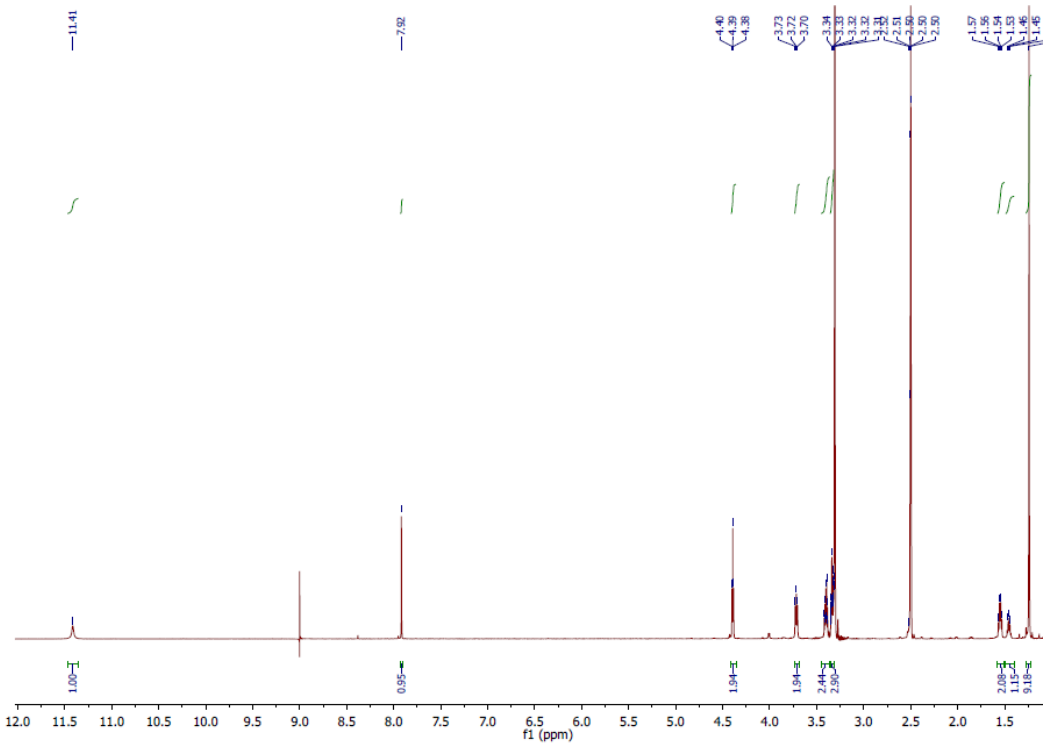
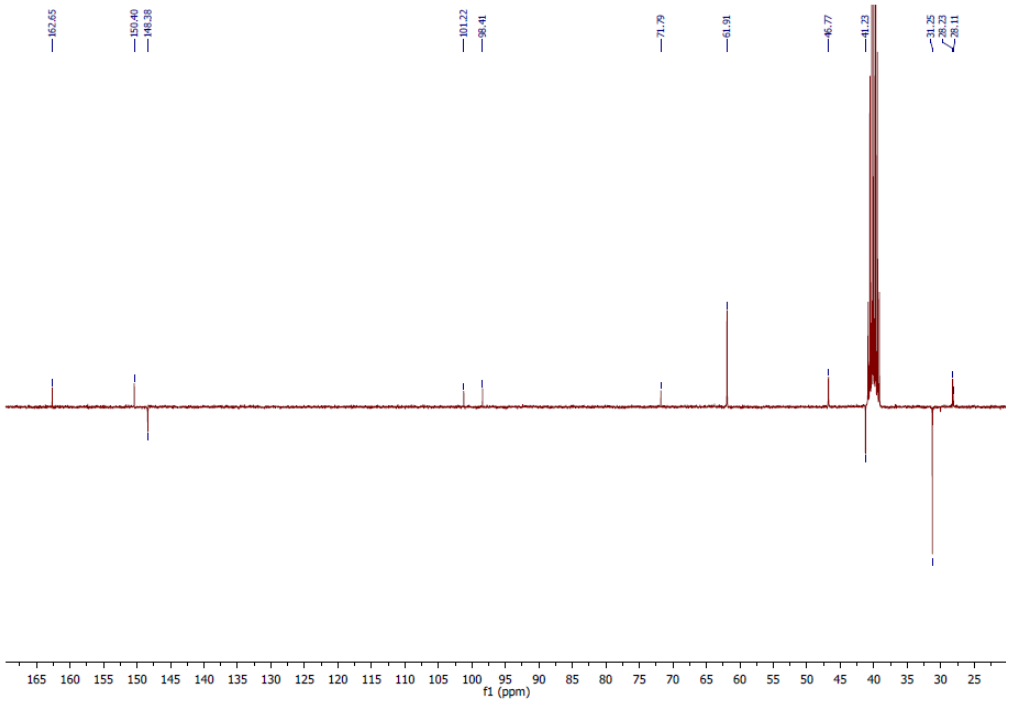


Figure S25. a) ^{1}H NMR and b) ^{13}C NMR of compd. **10i**.

a)



b)



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