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Tandem synthesis, antibacterial evaluation and SwissADME prediction study of new bis(1,3,4-oxadiazoles) linked to arene units

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Contents

1. Experimental

1.1. Materials

All solvents were acquired from commercial sources and used as received unless otherwise stated. All other chemicals were acquired from Merck or Aldrich and used without further purification. The melting points were measured on a Stuart melting point apparatus and are uncorrected. IR spectra were recorded on a Smart iTR, which is an ultra-high-performance, versatile Attenuated Total Reflectance (ATR) sampling accessory on the Nicolet iS10 FT-IR spectrometer. NMR spectra were recorded on Bruker Avance III 400 MHz spectrophotometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) using TMS as an internal standard and DMSO-d_6 as solvent and chemical shifts were expressed as δ ppm units. Elemental analyses were carried out on a EuroVector instrument C, H, N, S analyzer EA3000 Series.

1.2. Table S1. Optimizing the synthesis of bis(1,3,4-oxadiazole) 7a.

Entry[a,b]	Reagent (Equiv.)	Base (Equiv.)	Solvent	Temp. (°C)	Time (min.)	Yield (%)[j]
1	CAN[c] (2)	---	EtOH	80	180	39
2	CAN (2)	---	DCM[g]	rt	240	21
3	CAN (2)	---	Dioxane	100	240	34
4	NBS[d] (3)	TEA[f] (3)	DCM	rt	180	15
5	NBS (3)	TEA (3)	Toluene	110	180	22
6	NBS (3)	TEA (3)	EtOH	80	180	17
7	Iodine (3)	K_2CO_3 (6)	DMF[h]	100	240	38
8	Iodine (3)	K_2CO_3 (6)	DMSO[i]	100	240	43
9	CAT[e] (2.5)	---	Toluene	110	180	59
10	CAT (2.5)	---	Dioxane	100	180	64
11	**CAT (2.5)**	**---**	**EtOH**	**80**	**180**	**69**

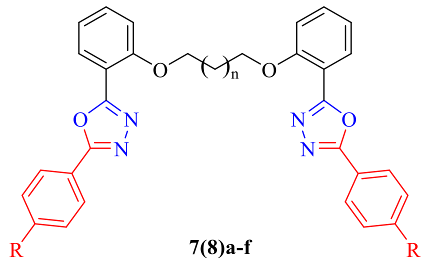
[a] All reactions were followed up by TLC analyses; [b] All reactions were first conducted in pyridine at 110 °C for 60 min., then the solvent was evaporated and the resulted crude bis(*N*-benzoylhydrazones) was subjected to the appropriate reaction conditions to conduct the cyclization-step; [c] Ceric ammonium nitrate; [d] *N*-Bromosuccinimide; [e] chloramine trihydrate; [f] Triethylamine; [g] Dichloromethane; [h] *N*,*N*-Dimethylformamide; [i] Dimethylsulfoxide; [j] The final yield of bis(1,3,4-oxadiazole) **7a**.

1.3. Table S2. Optimizing the yield of chloramine trihydrate-mediated synthesis of bis(1,3,4-oxadiazole) **7a**.

Entry[a,b]	**CAT equivalents**[c]	**Time (min.)**	**Yield (%)**[d]
1	2.0	180	57
2	2.25	180	60
3	2.5	180	69
4	2.75	180	72
5	3.0	120	71
6	**3.0**	**150**	**77**
7	3.0	180	76

[a] All reactions were followed up by TLC analyses; [b] All reactions were first conducted in pyridine at 110 °C for 60 min., then the solvent was evaporated and the resulted crude bis(*N*-benzoylhydrazones) was re-dissolved in ethanol at 80 °C to conduct the cyclization-step; [c] Number of chloramine trihydrate equivalents used; [d] The final yield of bis(1,3,4-oxadiazole) **7a**.

1.4. Table S3. Synthesis of bis(1,3,4-oxadiazole) hybrids **7(8)**.

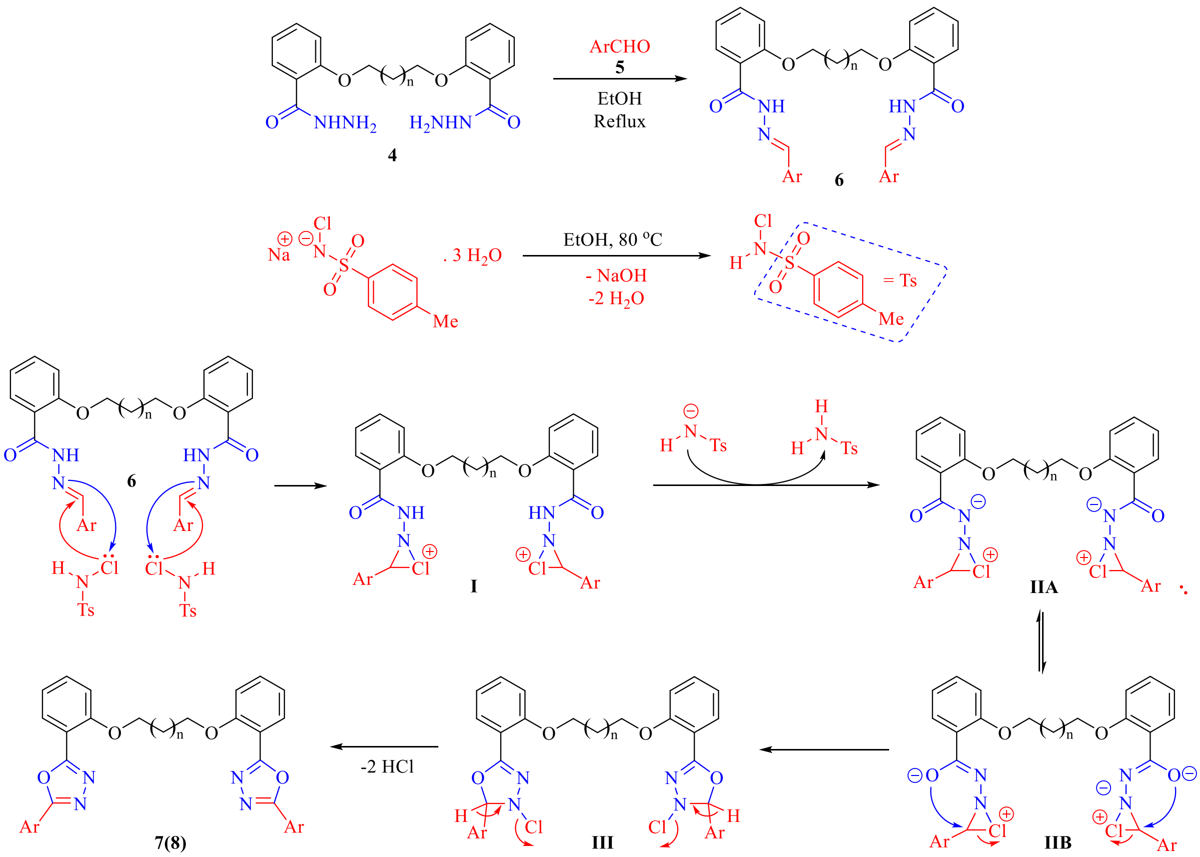


7(8)a-f

Entry[a]	**Cpd**	**n**	**R**	**Time (min.)**		**Yield (%)**[d]
				1st-step[b]	**2nd-step**[c]	
1	**7a**	2	H	60	150	77
2	**7b**	2	Cl	60	150	72
3	**7c**	2	NO_2	75	180	70
4	**7d**	2	Me	60	150	79
5	**7e**	2	OMe	45	120	83
6	**7f**	2	OCH_2O	45	120	82
7	**8a**	3	H	60	150	79
8	**8b**	3	Cl	75	150	70
9	**8c**	3	NO_2	75	180	71
10	**8d**	3	Me	60	150	82
11	**8e**	3	OMe	45	120	85
12	**8f**	3	OCH_2O	45	150	81

[a] All reactions were followed up by TLC analyses; [b] Condensation-step, all reactions were first conducted in pyridine at 110 °C; [c] Intramolecular cyclization-step, all reactions were conducted in ethanol at 80 °C in the presence of three equivalents of chloramine trihydrate; [d] The final yield of bis(1,3,4-oxadiazole) hybrids **7(8)**.

1.5. Scheme S1. Detailed mechanism for the formation of bis(1,3,4-oxadiazoles) **7(8)**.



Initially, bis(benzohydrazides) **4** reacted with different aromatic aldehydes **5** to yield the corresponding bis(*N*-benzoylhydrazones) **6**. Intramolecular cyclization may begin with the conversion of chloramine trihydrate into *N*-chlorosulfonamide. The previous intermediate then reacted with the imine groups in the bis(*N*-benzoylhydrazones) **6** to produce the chloraziridine intermediate **I**. The resulting tosylamide abstracted the hydrazine-NH protons from **I** to produce hydrazinide **IIA**. Following the conjugation of hydrazinide **IIA**, iminolate **IIB** was formed, which was then converted into target **7(8)** *via* successive intramolecular nucleophilic substitution to give intermediate **III**, followed by the removal of two molecules of hydrogen chloride.[S1,S2]

1.6. Table S4. Physicochemical properties of new bis(1,3,4-oxadiazoles) **7(8)a-f**.

Cpd	Formula	MW[a] (g/mol)	RB[b]	HA[c]	HB[d]	TPSA[e] (Å^2)	Log $P_{o/w}$[f]	Lipinski's Druglikeness
7a	$C_{32}H_{26}N_4O_4$	530.57	11	8	0	96.30	4.48	Yes 1 violation: M. W. > 500
7b	$C_{32}H_{24}Cl_2N_4O_4$	599.46	12	8	0	96.30	5.39	No 2 violations: M. W. > 500; Log $P_{o/w} > 5$
7c	$C_{32}H_{24}N_6O_8$	620.57	13	12	0	187.94	3.71	No 2 violations: M. W. > 500; HA > 10
7d	$C_{34}H_{30}N_4O_4$	558.63	11	8	0	96.30	4.85	Yes 1 violation: M. W. > 500
7e	$C_{34}H_{30}N_4O_6$	590.63	13	10	0	114.76	3.84	Yes 1 violation: M. W. > 500
7f	$C_{34}H_{26}N_4O_8$	618.59	11	12	0	133.22	3.67	No 2 violations: M. W. > 500; HA > 10
8a	$C_{33}H_{28}N_4O_4$	544.60	12	8	0	96.30	4.67	Yes 1 violation: M. W. > 500
8b	$C_{33}H_{26}Cl_2N_4O_4$	613.49	12	8	0	96.30	5.57	No 2 violations: M. W. > 500; Log $P_{o/w} > 5$
8c	$C_{33}H_{26}N_6O_8$	634.59	14	12	0	187.94	3.90	No 2 violations: M. W. > 500; HA > 10
8d	$C_{35}H_{32}N_4O_4$	572.65	12	8	0	96.30	4.99	Yes 1 violation: M. W. > 500
8e	$C_{35}H_{32}N_4O_6$	604.65	14	10	0	114.76	4.02	Yes 1 violation: M. W. > 500
8f	$C_{35}H_{28}N_4O_8$	632.62	12	12	0	133.22	3.85	No 2 violations: M. W. > 500; HA > 10

[a] Molecular weight; [b] Number of rotatable bonds; [c] Number of hydrogen bond acceptors; [d] Number of hydrogen bond donors; [e] Topological polar surface area; [f] Partition coefficient between octanol and water.

1.7. The procedures and spectral data

General procedure for the synthesis of bis(benzohydrazides) 4a,b.

A mixture of methyl salicylate **1** (10 mmol) and 1,ω-dibromoalkane **2a,b** (5 mmol) in DMF (15 mL) in the presence of anhydrous potassium carbonate (15 mmol) was stirred at room temperature for 6 h. Water (50 mL) was added to the resulting reaction mixture, which was then extracted with chloroform (3 x 25 mL). The organic layers were combined, dried over sodium sulfate, and the chloroform was evaporated under reduced pressure. The crude bis(salicylates) **3** was then re-dissolved in ethanol (15 mL) and hydrazine hydrate (4 mL) was added. The mixture was then heated at 80 °C for 3 h. The product was collected by filtration, washed with cold ethanol, dried and recrystallized from the appropriate solvent.

2,2'-(Butane-1,4-diylbis(oxy))di(benzohydrazide) (4a).

Colorless solid (dioxane, 87%); m.p. 176 °C; IR (υ cm^{-1}): 3291, 3180 (NH), 1681 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.94 (br s, 4H, 2 OCH_2CH_2), 4.16 (br s, 4H, 2 OCH_2CH_2), 4.53 (s, 4H, 2 NH_2), 7.02 (t, J = 7.6 Hz, 2H, Ar-H), 7.14 (d, J = 7.6 Hz, 2H, Ar-H), 7.44 (t, J = 7.6 Hz, 2H, Ar-H), 7.66 (d, J = 7.6 Hz, 2H, Ar-H), 9.14 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 25.9, 68.2, 112.9, 120.5, 122.2, 130.2, 132.0, 156.2, 165.1; Anal. calcd. for $C_{18}H_{22}N_4O_4$ (358.4): C, 60.32; H, 6.19; N, 15.63; found: C, 60.47; H, 6.02; N, 15.78%.

2,2'-(Pentane-1,5-diylbis(oxy))di(benzohydrazide) (4b).

Colorless solid (dioxane / ethanol mixture, 85%); m.p. 140 °C; IR (υ cm^{-1}): 3294, 3182 (NH), 1682 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.63 (m, 2H, $OCH_2CH_2CH_2$), 1.85 (m, 4H, 2 OCH_2CH_2), 4.12 (t, J = 6.4 Hz, 4H, 2 OCH_2CH_2), 4.54 (s, 4H, 2 NH_2), 7.01 (t, J = 7.6 Hz, 2H, Ar-H), 7.12 (d, J = 7.6 Hz, 2H, Ar-H), 7.42 (t, J = 7.6 Hz, 2H, Ar-H), 7.69 (d, J = 7.6 Hz, 2H, Ar-H), 9.10 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 22.1, 28.1, 68.4, 112.9, 120.4, 122.3, 130.2, 132.0, 156.1, 165.0; Anal. calcd. for $C_{19}H_{24}N_4O_4$ (372.4): C, 61.28; H, 6.50; N, 15.04; found: C, 61.11; H, 6.36; N, 15.13%.

General procedure for the synthesis of bis(1,3,4-oxadiazoles) 7(8)a-f.

A mixture of bis(benzohydrazides) **4a,b** (5 mmol) and the appropriate aromatic aldehyde **5a-5f** (10 mmol) in pyridine (15 mL) was heated at 110 °C for 45-75 min. After the condensation-step was completed (monitored by TLC), the solvent was evaporated under reduced pressure to give the crude bis(*N*-benzoylhydrazones) **6**, which was then re-dissolved in ethanol (15 mL) and chloramine trihydrate (15 mmol) was added. The previous mixture was then heated at 80 °C for 120-180 min. After the cyclization-step was completed (monitored by TLC), the product was collected by filtration, washed with water then with cold ethanol, dried and recrystallized from the appropriate solvent.

1,4-Bis(2-(5-phenyl-1,3,4-oxadiazol-2-yl)phenoxy)butane (7a).

Colorless solid (dioxane); m.p. 164-166 ^{o}C; IR (υ cm^{-1}): 1643 (C=N); ^{1}H-NMR (DMSO-*d$_6$*): δ 2.11 (br s, 4H, 2 OCH_2CH_2), 4.24 (br s, 4H, 2 OCH_2CH_2), 7.12 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.24 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.41 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.46 (t, *J* = 7.6 Hz, 4H, Ar-H), 7.56 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.94-7.98 (m, 6H, Ar-H); ^{13}C-NMR (DMSO-*d$_6$*): δ 25.6, 68.0, 112.1, 113.3, 120.6, 123.3, 126.2, 129.1, 130.0, 131.6, 133.5, 156.7, 163.1, 164.7; Anal. calcd. for $C_{32}H_{26}N_4O_4$ (530.5): C, 72.44; H, 4.94; N, 10.56; found: C, 72.23; H, 4.81; N, 10.75%.

1,4-Bis(2-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)phenoxy)butane (7b).

Pale brown solid (dioxane / ethanol mixture); m.p. 192-194 ^{o}C; IR (υ cm^{-1}): 1636 (C=N); ^{1}H-NMR (DMSO-*d$_6$*): δ 2.11 (br s, 4H, 2 OCH_2CH_2), 4.23 (br s, 4H, 2 OCH_2CH_2), 7.12 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.23 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.51 (d, *J* = 8.8 Hz, 4H, Ar-H), 7.57 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.94 (d, *J* = 7.6 Hz, 2H, Ar-H), 8.08 (d, *J* = 8.8 Hz, 4H, Ar-H); ^{13}C-NMR (DMSO-*d$_6$*): δ 25.8, 68.3, 112.2, 113.2, 120.8, 122.4, 128.2, 129.5, 130.6, 133.2, 138.0, 157.7, 163.3, 164.8; Anal. calcd. for $C_{32}H_{24}Cl_2N_4O_4$ (599.4): C, 64.12; H, 4.04; N, 9.35; found: C, 63.85; H, 3.89; N, 9.57%.

1,4-Bis(2-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)phenoxy)butane (7c).

Pale yellow solid (dioxane); m.p. 248-249 ^{o}C; IR (υ cm^{-1}): 1633 (C=N), 1518, 1327 (NO_2); ^{1}H-NMR (DMSO-*d$_6$*): δ 2.13 (br s, 4H, 2 OCH_2CH_2), 4.24 (br s, 4H, 2 OCH_2CH_2), 7.13 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.25 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.58 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.95 (d, *J* = 7.6 Hz, 2H, Ar-H), 8.34 (d, *J* = 8.8 Hz,4H, Ar-H), 8.41 (d, *J* = 8.8 Hz, 4H, Ar-H); ^{13}C-NMR (DMSO-*d$_6$*): δ 25.8, 68.3, 112.1, 113.0, 120.7, 125.0, 128.5, 129.9, 130.7, 133.2, 149.6, 157.6, 163.5, 165.3; Anal. calcd. for $C_{32}H_{24}N_6O_8$ (620.5): C, 61.93; H, 3.90; N, 13.54; found: C, 62.07; H, 4.03; N, 13.40%.

1,4-Bis(2-(5-(*p*-tolyl)-1,3,4-oxadiazol-2-yl)phenoxy)butane (7d).

Colorless solid (dioxane / ethanol mixture); m.p. 150 ^{o}C; IR (υ cm^{-1}): 1630 (C=N); ^{1}H-NMR (DMSO-*d$_6$*): δ 2.10 (br s, 4H, 2 OCH_2CH_2), 2.45 (s, 6H, 2 *p*-CH_3), 4.23 (br s, 4H, 2 OCH_2CH_2), 7.12 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.25 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.34 (d, *J* = 8.4 Hz, 4H, Ar-H), 7.56 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.93 (d, *J* = 7.6 Hz, 2H, Ar-H), 8.03 (d, *J* = 8.4 Hz, 4H, Ar-H); ^{13}C-NMR (DMSO-*d$_6$*): δ 21.6, 25.8, 68.2, 112.3, 113.3, 120.9, 121.1, 126.8, 129.7, 130.4, 133.1, 142.2, 157.7, 163.3, 164.7; Anal. calcd. for $C_{34}H_{30}N_4O_4$ (558.6): C, 73.10; H, 5.41; N, 10.03; found: C, 72.85; H, 5.56; N, 9.84%.

1,4-Bis(2-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)phenoxy)butane (7e).

Colorless solid (dioxane / ethanol mixture); m.p. 178-179 ^{o}C; IR (υ cm^{-1}): 1628 (C=N); ^{1}H-NMR (DMSO-*d$_6$*): δ 2.12 (br s, 4H, 2 OCH_2CH_2), 3.88 (s, 6H, 2 *p*-OCH_3), 4.24 (br s, 4H, 2

$\mathrm{OC}H_2\mathrm{CH}_2$), 7.03 (d, *J* = 8.8 Hz, 4H, Ar-H), 7.11 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.23 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.55 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.94 (d, *J* = 7.6 Hz, 2H, Ar-H), 8.07 (d, *J* = 8.8 Hz, 4H, Ar-H); ^{13}C-NMR (DMSO-d_6): δ 25.9, 55.5, 68.3, 112.1, 113.2, 115.5, 116.4, 120.7, 128.6, 130.4, 133.2, 157.6, 162.3, 163.4, 164.5; Anal. calcd. for $\mathrm{C_{34}H_{30}N_4O_6}$ (590.6): C, 69.14; H, 5.12; N, 9.49; found: C, 69.28; H, 5.01; N, 9.30%.

1,4-Bis(2-(5-(benzo[*d*][1,3]dioxol-5-yl)-1,3,4-oxadiazol-2-yl)phenoxy)butane (7f).
Colorless solid (dioxane); m.p. 200-202 °C; IR (υ cm^{-1}): 1618 (C=N); ^{1}H-NMR (DMSO-d_6): δ 2.12 (br s, 4H, 2 $\mathrm{OCH_2C}H_2$), 4.23 (br s, 4H, 2 $\mathrm{OC}H_2\mathrm{CH}_2$), 6.08 (s, 4H, 2 $\mathrm{OCH_2O}$), 6.95 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.13 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.24 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.54-7.58 (m, 4H, Ar-H), 7.69 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.93 (d, *J* = 7.6 Hz, 2H, Ar-H); ^{13}C-NMR (DMSO-d_6): δ 25.9, 68.3, 102.0, 107.2, 109.0, 112.2, 113.2, 117.9, 120.9, 122.2, 130.4, 133.2, 148.5, 150.8, 157.7, 163.3, 164.5; Anal. calcd. for $\mathrm{C_{34}H_{26}N_4O_8}$ (618.6): C, 66.02; H, 4.24; N, 9.06; found: C, 65.84; H, 4.13; N, 9.22%.

1,5-Bis(2-(5-phenyl-1,3,4-oxadiazol-2-yl)phenoxy)pentane (8a).
Colorless solid (dioxane); m.p. 150-153 °C; IR (υ cm^{-1}): 1640 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.68 (m, 2H, $\mathrm{OCH_2CH_2C}H_2$), 1.88 (m, 4H, 2 $\mathrm{OCH_2C}H_2$), 4.19 (t, *J* = 6.4 Hz, 4H, 2 $\mathrm{OC}H_2\mathrm{CH}_2$), 7.11 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.23 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.41 (t, *J* = 7.2 Hz, 2H, Ar-H), 7.47 (t, *J* = 7.2 Hz, 4H, Ar-H), 7.58 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.93 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.99 (d, *J* = 7.2 Hz, 4H, Ar-H); ^{13}C-NMR (DMSO-d_6): δ 22.1, 28.1, 68.4, 111.9, 113.2, 120.7, 124.2, 126.9, 129.0, 130.6, 131.5, 133.1, 157.7, 163.3, 164.3; Anal. calcd. for $\mathrm{C_{33}H_{28}N_4O_4}$ (544.6): C, 72.78; H, 5.18; N, 10.29; found: C, 72.94; H, 5.02; N, 10.45%.

1,5-Bis(2-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)phenoxy)pentane (8b).
Pale brown solid (dioxane / ethanol mixture); m.p. 184 °C; IR (υ cm^{-1}): 1640 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.68 (m, 2H, $\mathrm{OCH_2CH_2C}H_2$), 1.88 (m, 4H, 2 $\mathrm{OCH_2C}H_2$), 4.19 (t, *J* = 6.4 Hz, 4H, 2 $\mathrm{OC}H_2\mathrm{CH}_2$), 7.11 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.24 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.50 (d, *J* = 8.8 Hz, 4H, Ar-H), 7.56 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.94 (d, *J* = 7.6 Hz, 2H, Ar-H), 8.07 (d, *J* = 8.8 Hz, 4H, Ar-H); ^{13}C-NMR (DMSO-d_6): δ 22.1, 28.2, 68.3, 112.1, 113.1, 120.8, 122.3, 128.3, 129.5, 130.5, 133.3, 138.2, 157.8, 163.3, 164.7; Anal. calcd. for $\mathrm{C_{33}H_{26}Cl_2N_4O_4}$ (613.5): C, 64.61; H, 4.27; N, 9.13; found: C, 64.38; H, 4.12; N, 9.01%.

1,5-Bis(2-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)phenoxy)pentane (8c).
Pale yellow solid (dioxane); m.p. 240-242 °C; IR (υ cm^{-1}): 1637 (C=N), 1519, 1324 ($\mathrm{NO_2}$); ^{1}H-NMR (DMSO-d_6): δ 1.67 (m, 2H, $\mathrm{OCH_2CH_2C}H_2$), 1.88 (m, 4H, 2 $\mathrm{OCH_2C}H_2$), 4.19 (t, *J* = 6.4 Hz, 4H, 2 $\mathrm{OC}H_2\mathrm{CH}_2$), 7.12 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.23 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.56 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.93 (d, *J* = 7.6 Hz, 2H, Ar-H), 8.33 (d, *J* = 8.8 Hz,4H, Ar-H), 8.41

(d, *J* = 8.8 Hz, 4H, Ar-H); ^{13}C-NMR (DMSO-*d*$_6$): δ 22.2, 28.2, 68.4, 112.0, 113.1, 120.6, 125.0, 128.6, 129.8, 130.6, 133.2, 149.4, 157.8, 163.4, 165.3; Anal. calcd. for $C_{33}H_{26}N_6O_8$ (634.6): C, 62.46; H, 4.13; N, 13.24; found: C, 62.25; H, 3.99; N, 13.10%.

1,5-Bis(2-(5-(*p*-tolyl)-1,3,4-oxadiazol-2-yl)phenoxy)pentane (8d).
Colorless solid (dioxane / ethanol mixture); m.p. 142-143 ^{o}C; IR (υ cm^{-1}): 1618 (C=N); ^{1}H-NMR (DMSO-*d*$_6$): δ 1.67 (m, 2H, $OCH_2CH_2CH_2$), 1.88 (m, 4H, 2 OCH_2CH_2), 2.44 (s, 6H, 2 *p*-CH_3), 4.19 (t, *J* = 6.4 Hz, 4H, 2 OCH_2CH_2), 7.13 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.26 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.33 (d, *J* = 8.0 Hz, 4H, Ar-H), 7.56 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.94 (d, *J* = 7.6 Hz, 2H, Ar-H), 8.04 (d, *J* = 8.0 Hz, 4H, Ar-H); ^{13}C-NMR (DMSO-*d*$_6$): δ 21.6, 22.1, 28.2, 68.3, 112.2, 113.1, 120.7, 121.0, 126.7, 129.6, 130.3, 133.0, 142.3, 157.5, 163.4, 164.6; Anal. calcd. for $C_{35}H_{32}N_4O_4$ (572.6): C, 73.41; H, 5.63; N, 9.78; found: C, 73.26; H, 5.45; N, 9.94%.

1,5-Bis(2-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)phenoxy)pentane (8e).
Colorless solid (dioxane); m.p. 168-170 ^{o}C; IR (υ cm^{-1}): 1626 (C=N); ^{1}H-NMR (DMSO-*d*$_6$): δ 1.69 (m, 2H, $OCH_2CH_2CH_2$), 1.87 (m, 4H, 2 OCH_2CH_2), 3.89 (s, 6H, 2 *p*-OCH_3), 4.18 (t, *J* = 6.4 Hz, 4H, 2 OCH_2CH_2), 7.02 (d, *J* = 8.8 Hz, 4H, Ar-H), 7.12 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.24 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.56 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.95 (d, *J* = 7.6 Hz, 2H, Ar-H), 8.06 (d, *J* = 8.8 Hz, 4H, Ar-H); ^{13}C-NMR (DMSO-*d*$_6$): δ 22.0, 28.2, 55.6, 68.3, 112.2, 113.3, 114.6, 116.5, 120.6, 128.5, 130.3, 133.3, 157.8, 162.2, 163.2, 164.4; Anal. calcd. for $C_{35}H_{32}N_4O_6$ (604.6): C, 69.52; H, 5.33; N, 9.27; found: C, 69.71; H, 5.19; N, 9.06%.

1,5-Bis(2-(5-(benzo[*d*][1,3]dioxol-5-yl)-1,3,4-oxadiazol-2-yl)phenoxy)pentane (8f).
Colorless solid (dioxane / ethanol mixture); m.p. 196 ^{o}C; IR (υ cm^{-1}): 1619 (C=N); ^{1}H-NMR (DMSO-*d*$_6$): δ 1.68 (m, 2H, $OCH_2CH_2CH_2$), 1.88 (m, 4H, 2 OCH_2CH_2), 4.18 (t, *J* = 6.4 Hz, 4H, 2 OCH_2CH_2), 6.07 (s, 4H, 2 OCH_2O), 6.94 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.12 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.25 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.54-7.58 (m, 4H, Ar-H), 7.67 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.94 (d, *J* = 7.6 Hz, 2H, Ar-H); ^{13}C-NMR (DMSO-*d*$_6$): δ 22.2, 28.2, 68.4, 102.1, 107.3, 108.9, 112.3, 113.3, 117.7, 120.8, 122.3, 130.4, 133.2, 148.6, 150.7, 157.6, 163.4, 164.4; Anal. calcd. for $C_{35}H_{28}N_4O_8$ (632.6): C, 66.45; H, 4.46; N, 8.86; found: C, 66.28; H, 4.60; N, 9.03%.

1.8. Minimum inhibitory concentration (MIC) determination.

The inhibitory activities against three different Gram-positive bacterial strains [*Staphylococcus aureus* (ATCC:6538), *Streptococcus mutans,* (ATCC:25175) and *Enterococcus faecalis* (ATCC:29212)] were selected as well as three different Gram-negative strains [*Escherichia coli* (ATCC:9637), *Pseudomonas aeruginosa* (ATCC:27953) and *Klebsiella pneumonia* (ATCC:10031)] were estimated. MIC values were determined using microbroth serial dilution method[S3,S4] in a sterile 96-well microtiter plate after overnight incubation of tested bacteria at 37 °C. This assay was performed in triplicates for consistency in accordance with guidelines provided by CLSI (2012).[S5] Ciprofloxacin (100 μg susceptibility disc) was used as a standard drug. The concentration of the tested hybrids as well as Ciprofloxacin used in the study ranged from 250 to 0.9 μg/mL. The sterile Muller-Hinton broth (MHB) was enriched with 2% NaCl before the tested antimicrobial agents were inserted into the well at concentration gradient in a serial dilution. Then the diluted bacterial suspension at final inoculum of 10^6 CFU/mL was added. The tested compound in MHB was used as negative control to ensure medium sterility, while the inoculum in MHB served as positive control to ensure the adequacy of the broth for bacterial growth. To facilitate the observation of the growth of bacteria in each well, 20 μL of 2,3,5-triphenyltetrazolium chloride (TTC) at 2 mg/mL was added into each well.

1.9. ADME prediction

SwissADME online server was used to predict the molecular properties of new products.[S6] The tested hybrids were drawn using ChemDraw Professional 16.0.0.82.[S7] After that, all hybrids were inserted into the SwissADME program to predict all the physicochemical characteristics, lipophilicity, and drug likeness.[S8] The program provides predictions of the molecular weight, logarithm of partition coefficient (log P), number of rotatable bonds, hydrogen-bond donors, acceptors, topological polar surface area, and Lipinski’s rule of five.

2. References

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S2 G. T. Cin, G. Verep, S. D. Topel, V. Ciger, *Chem. Heterocycl. Compd*. 2013, **49**, 1061.

S3 A. E. M. Mekky, S. M. H. Sanad, *Bioorg. Chem.*, 2020, 102, 104094.

S4 H. Mohammad, P. N. Reddy, D. Monteleone, A. S. Mayhoub, M. Cushman, M. N. Seleem, *Eur. J. Med. Chem.*, 2015, **94**, 306.

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3. ^{1}H- and ^{13}C-NMR copies of all new hybrids

Figure S1. ^{1}H-NMR spectrum of compound **4a**.

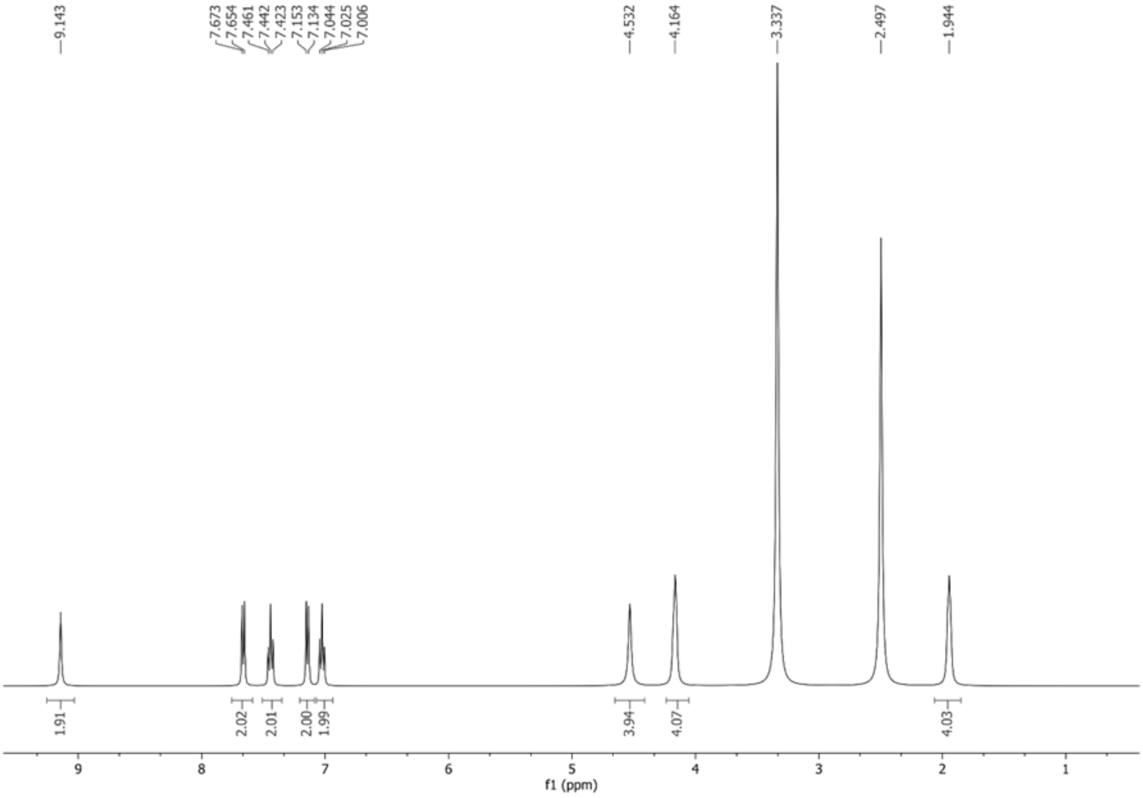

Figure S2. ^{13}C-NMR spectrum of compound **4a**.

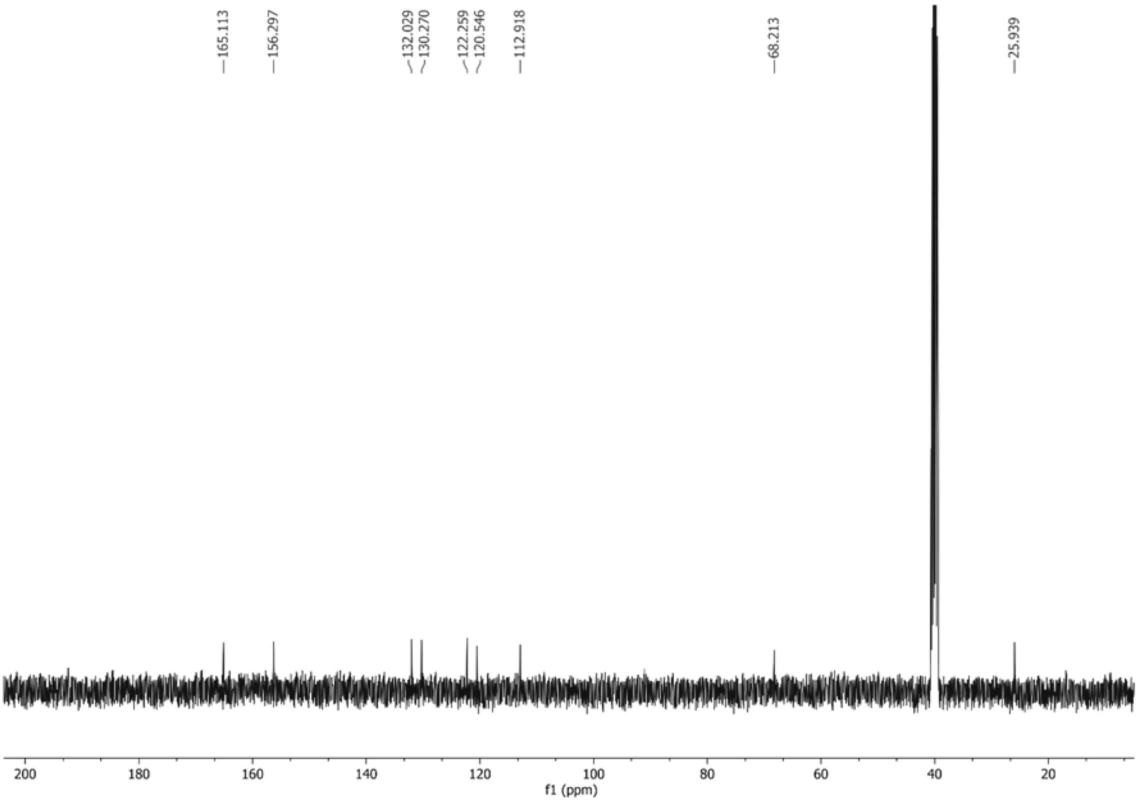

Figure S3. ^{1}H-NMR spectrum of compound **4b**.

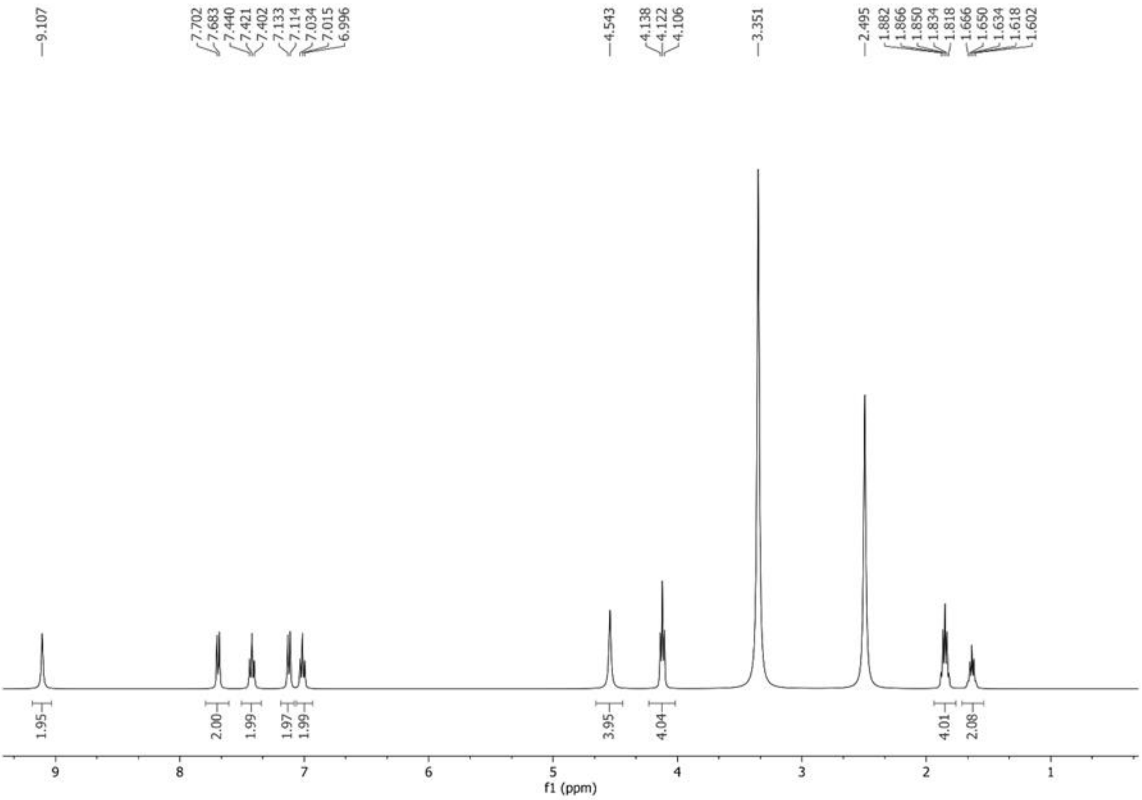

Figure S4. ^{13}C-NMR spectrum of compound **4b**.

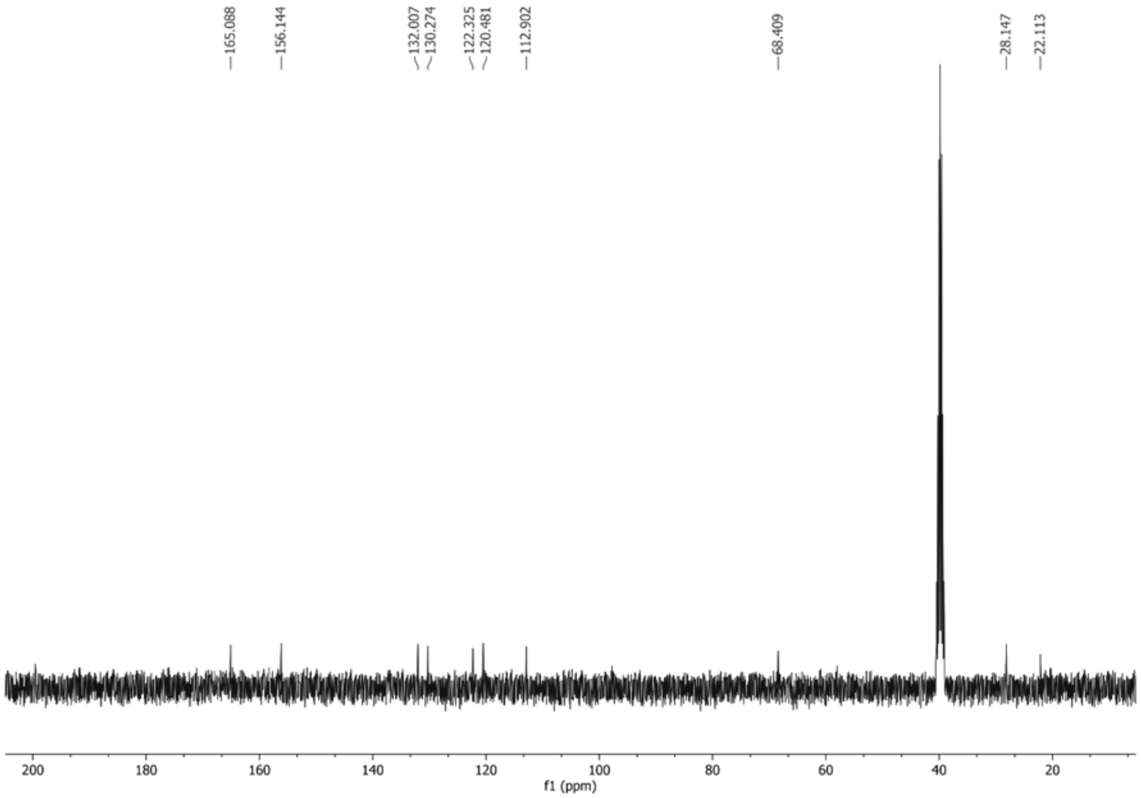

Figure S5. ^{1}H-NMR spectrum of compound **7a**.

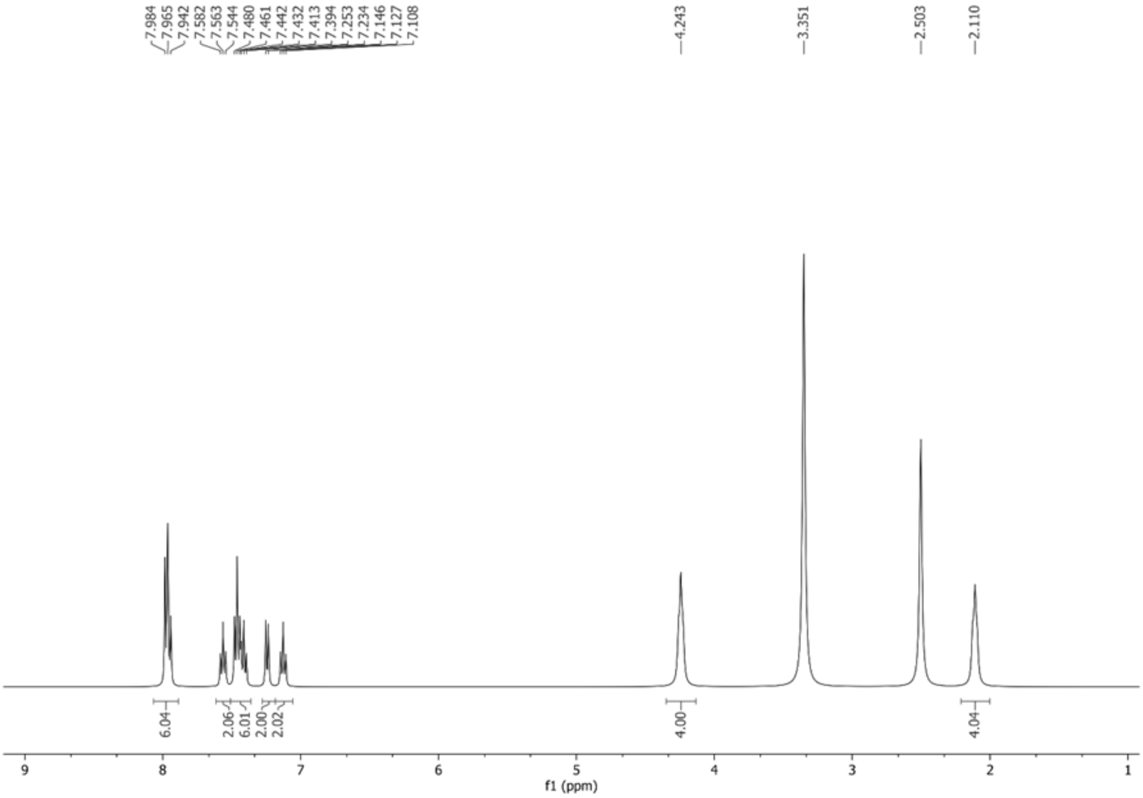

Figure S6. ^{13}C-NMR spectrum of compound **7a**.

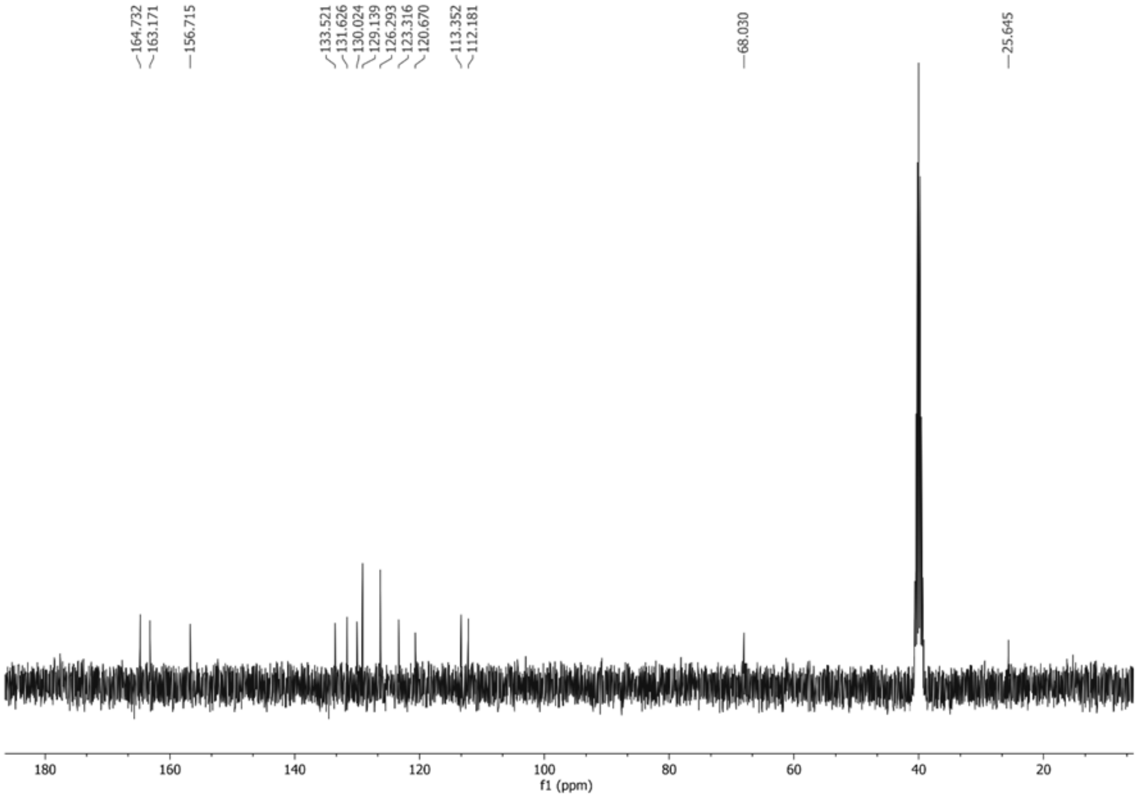

Figure S7. ^{1}H-NMR spectrum of compound **7b**.

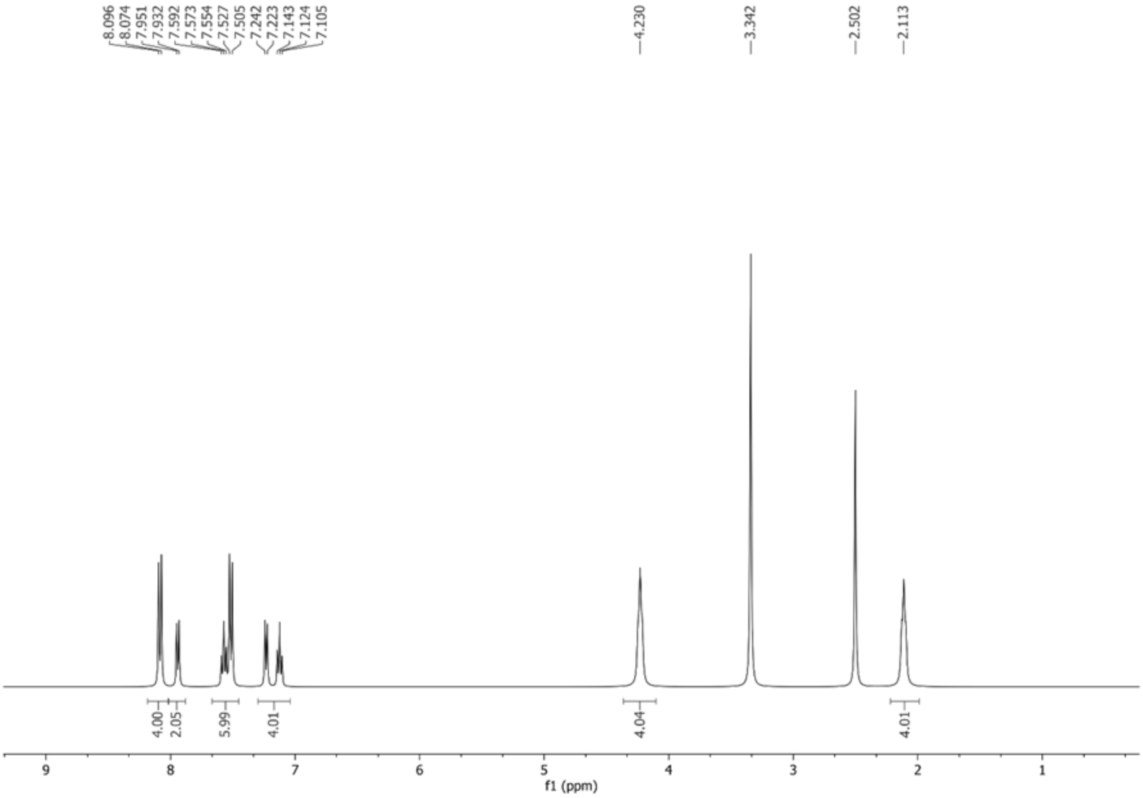

Figure S8. ^{13}C-NMR spectrum of compound **7b**.

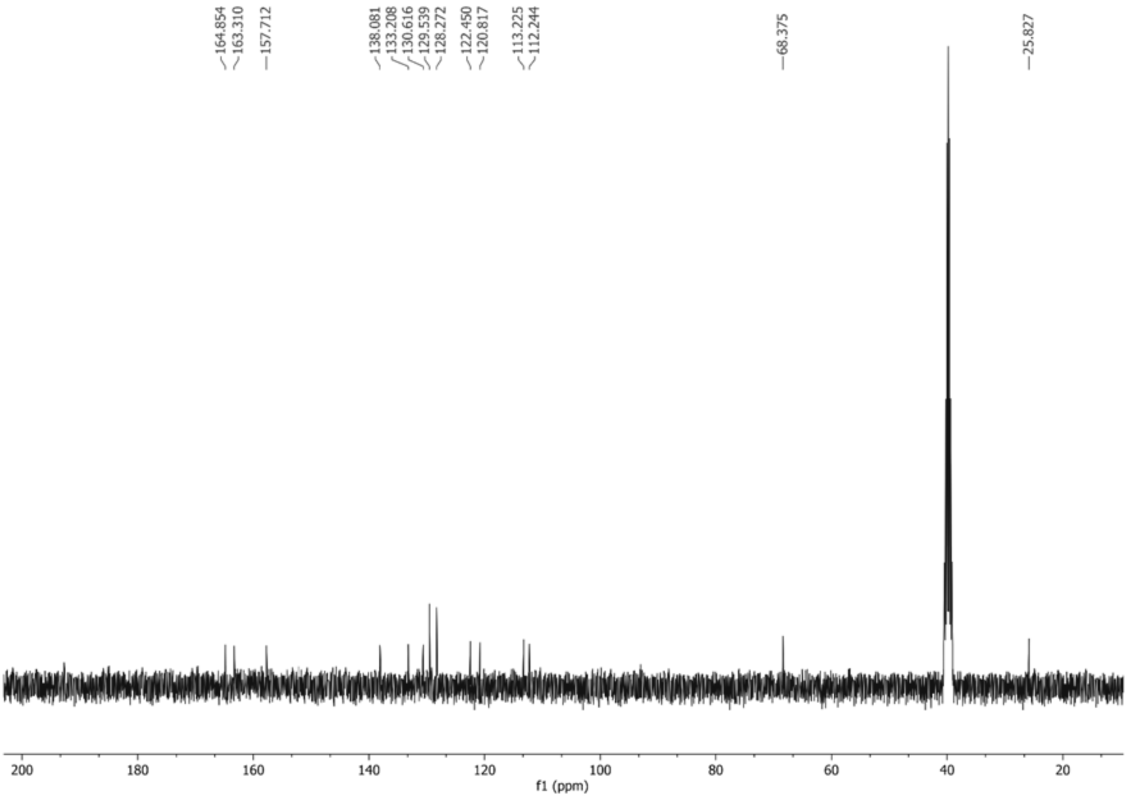

Figure S9. ^{1}H-NMR spectrum of compound **7c**.

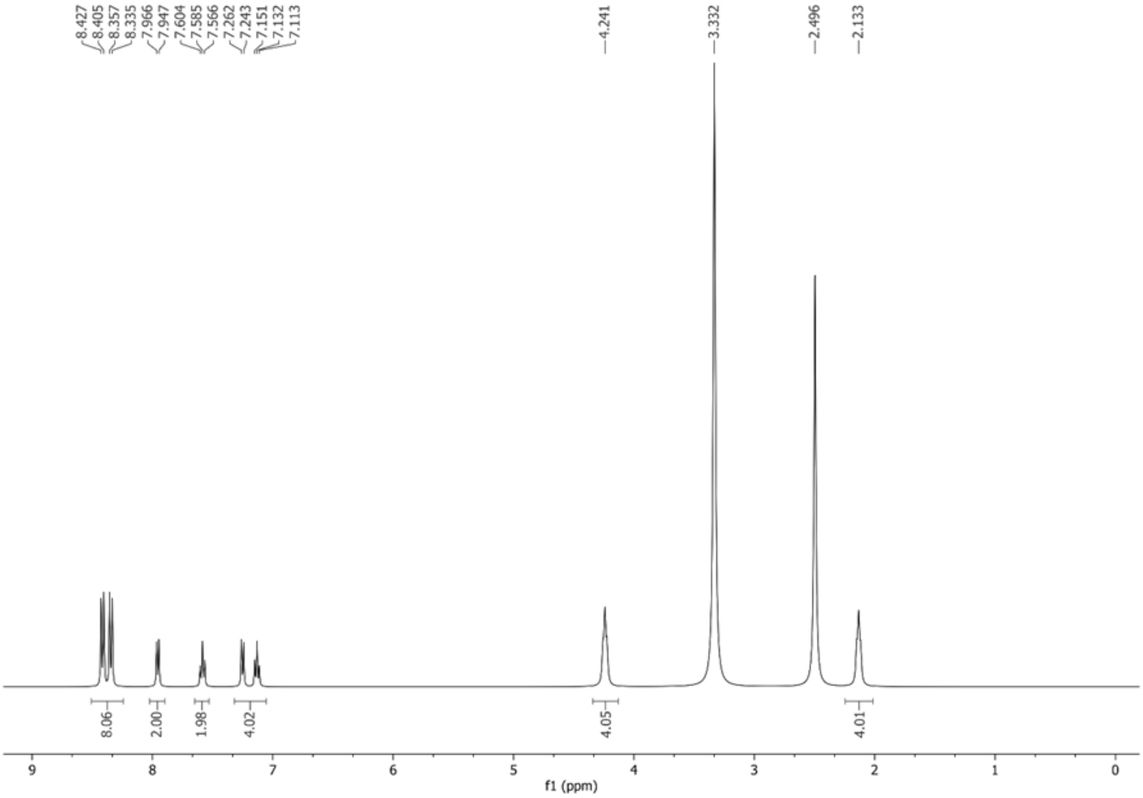

Figure S10. ^{13}C-NMR spectrum of compound **7c**.

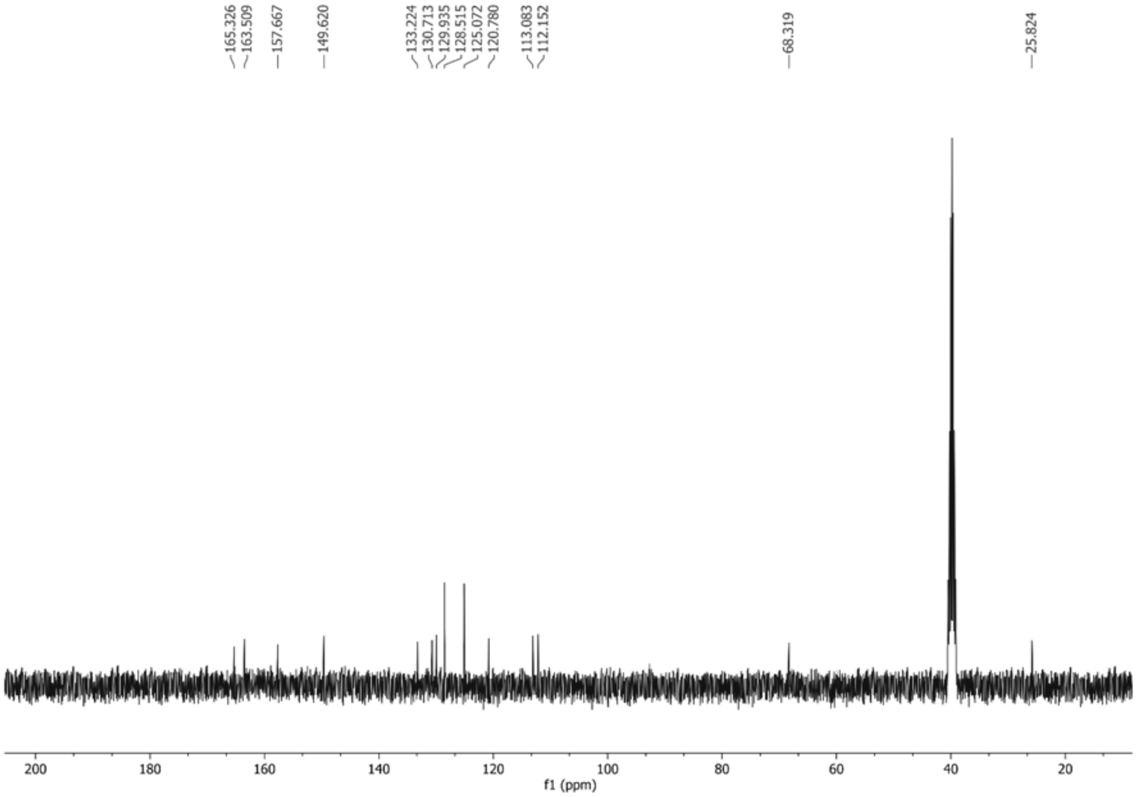

Figure S11. ^{1}H-NMR spectrum of compound **7d**.

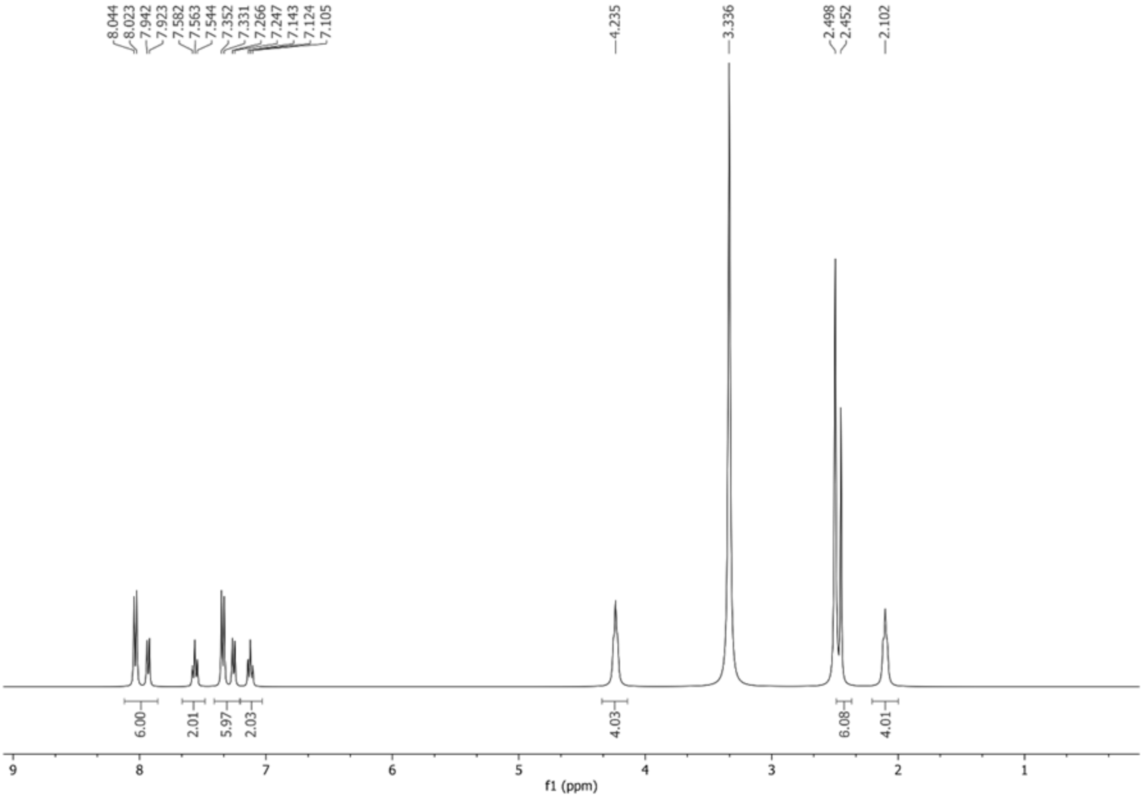

Figure S12. ^{13}C-NMR spectrum of compound **7d**.

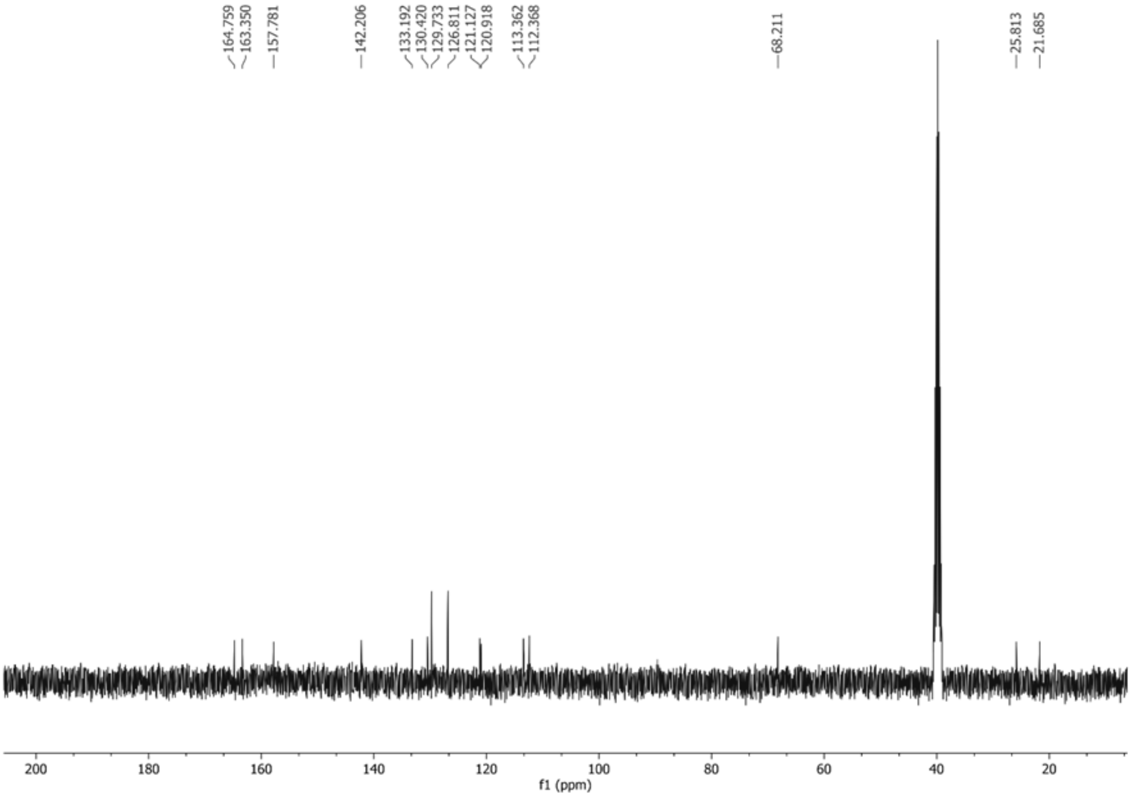

Figure S13. ^{1}H-NMR spectrum of compound **7e**.

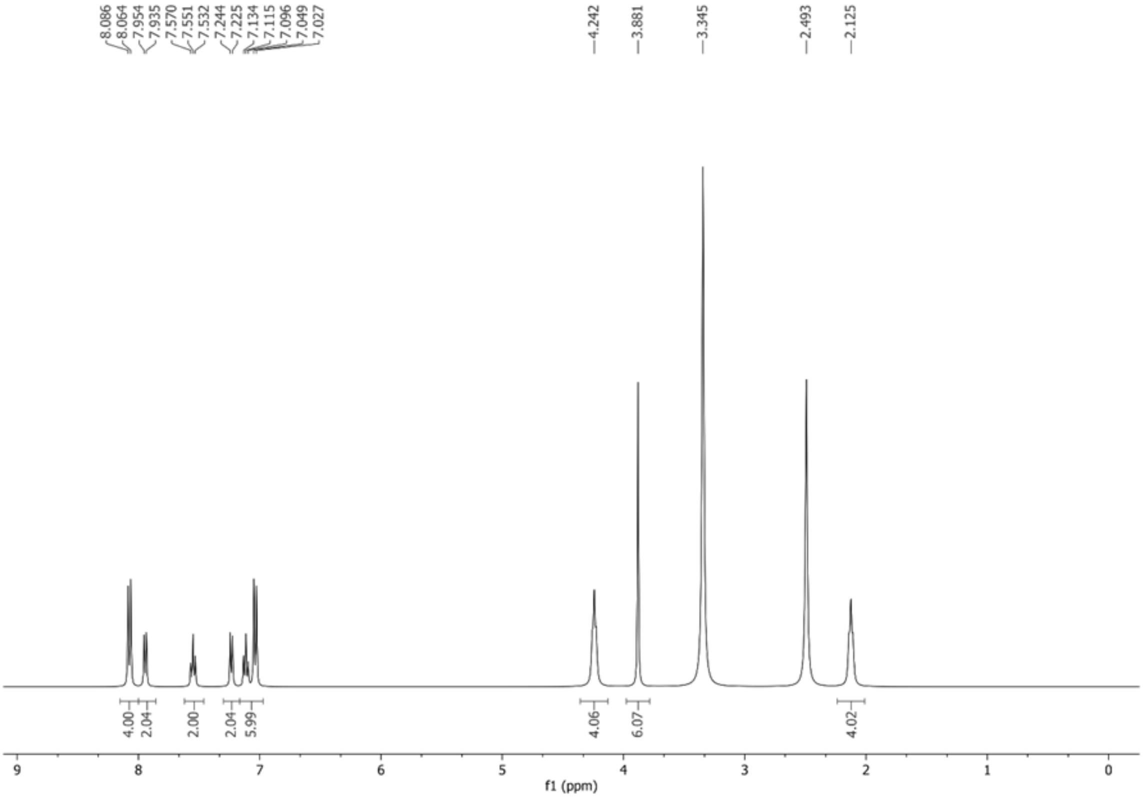

Figure S14. ^{13}C-NMR spectrum of compound **7e**.

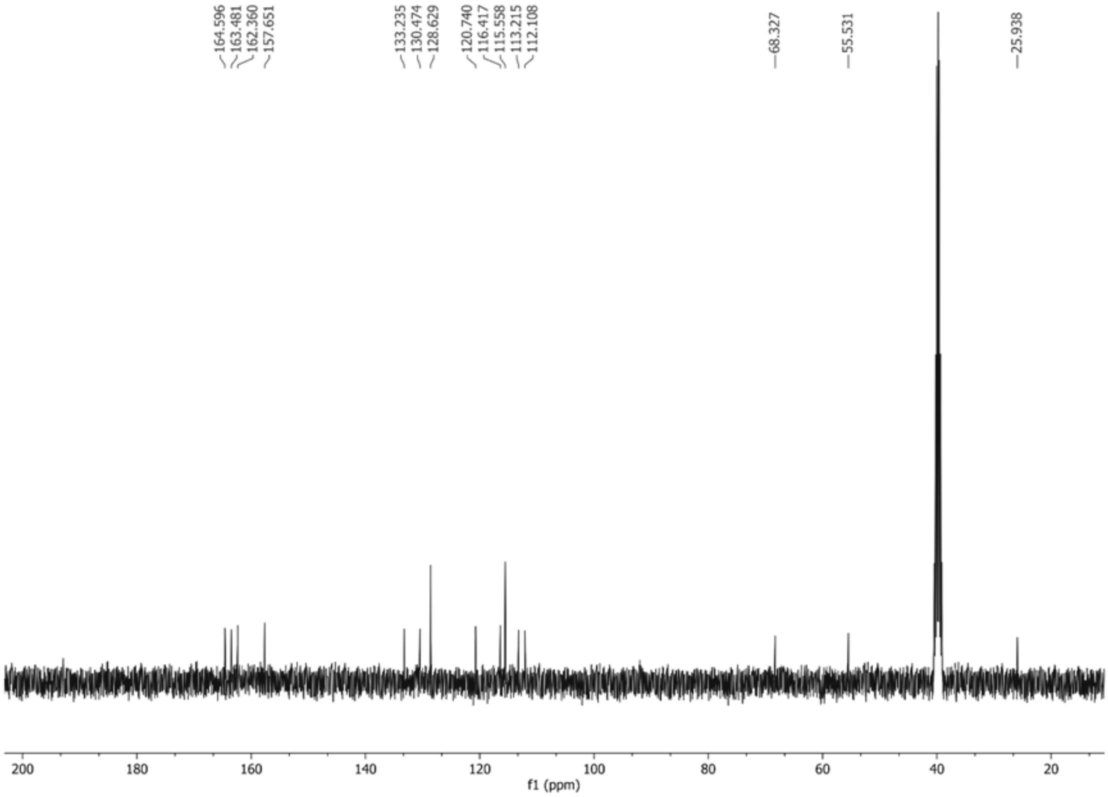

Figure S15. ^{1}H-NMR spectrum of compound **7f**.

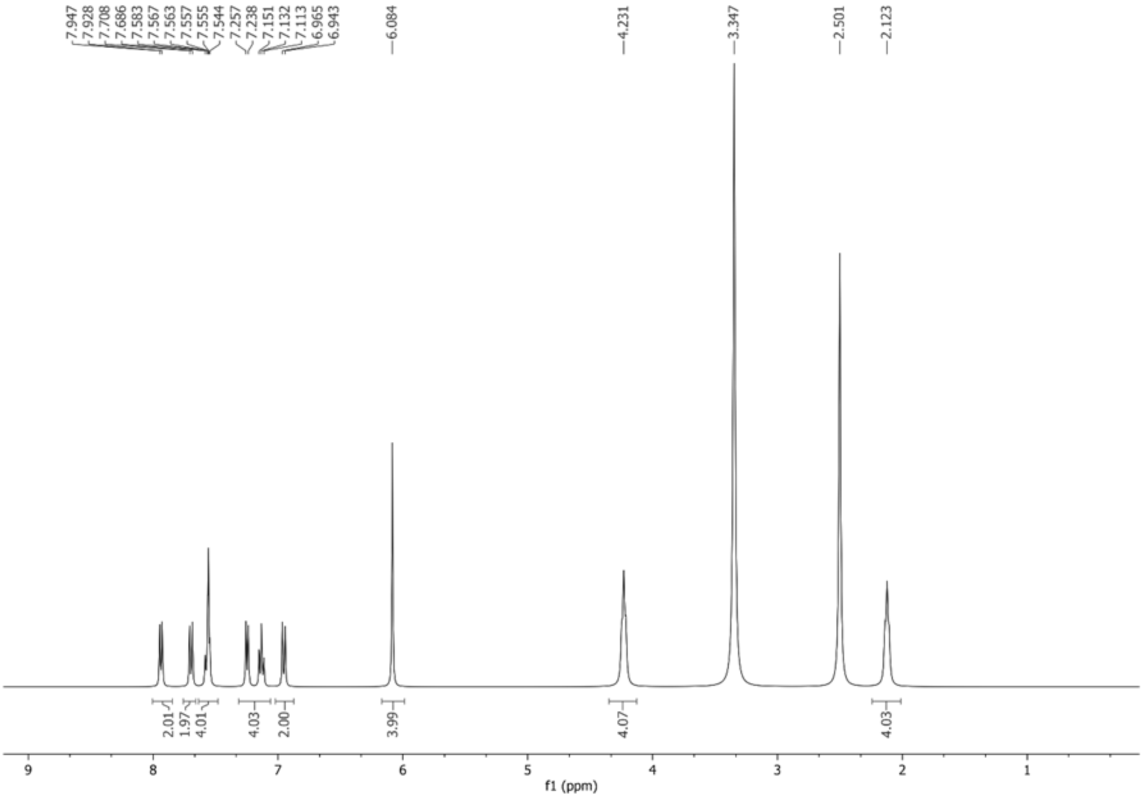

Figure S16. ^{13}C-NMR spectrum of compound **7f**.

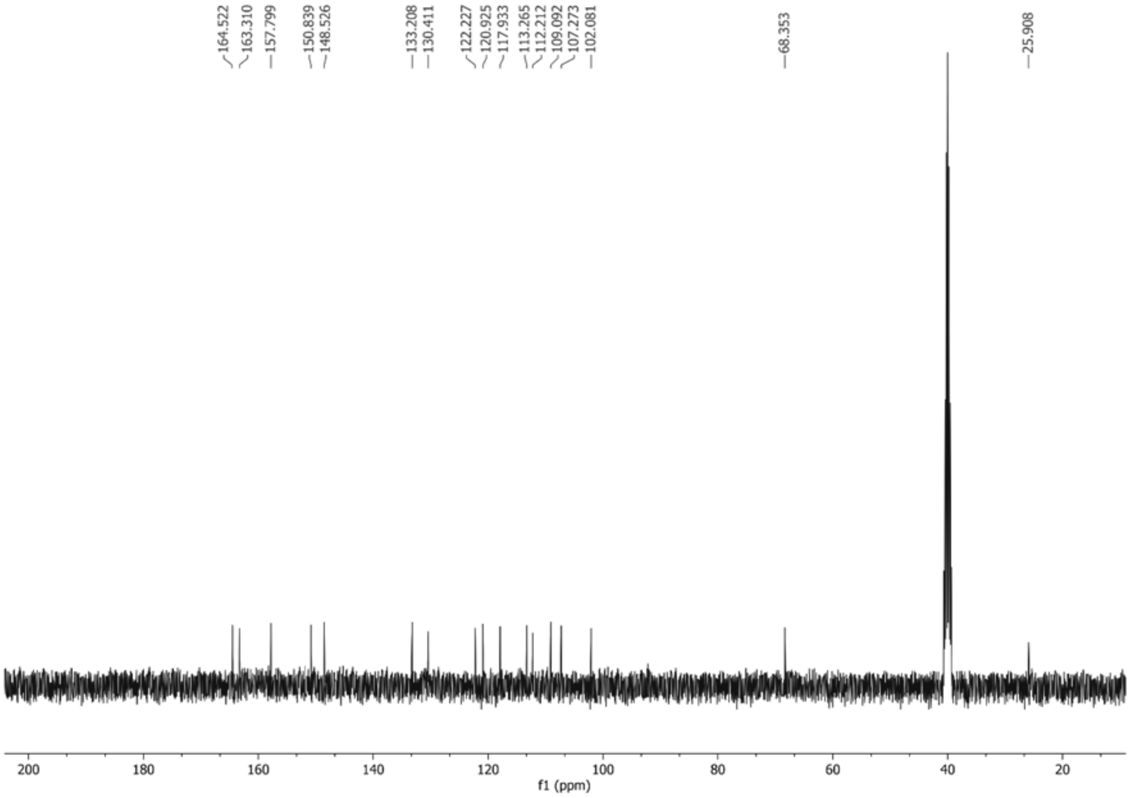

Figure S17. ^{1}H-NMR spectrum of compound **8a**.

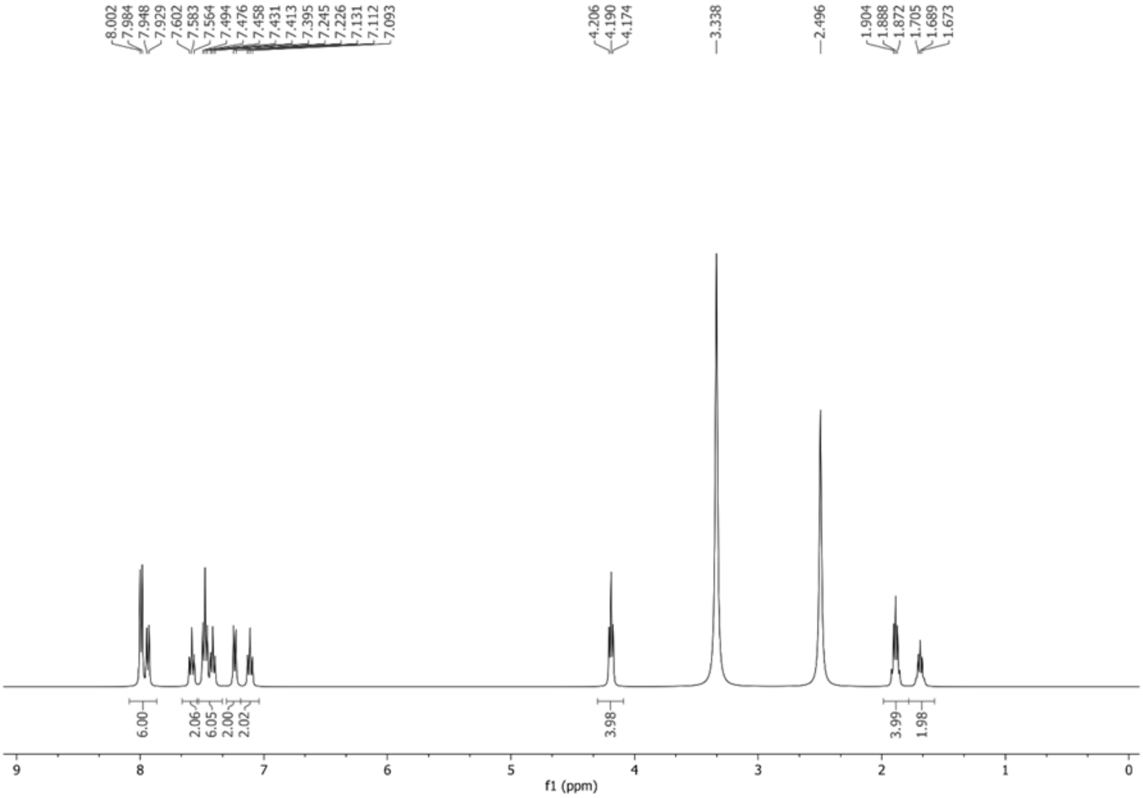

Figure S18. ^{13}C-NMR spectrum of compound **8a**.

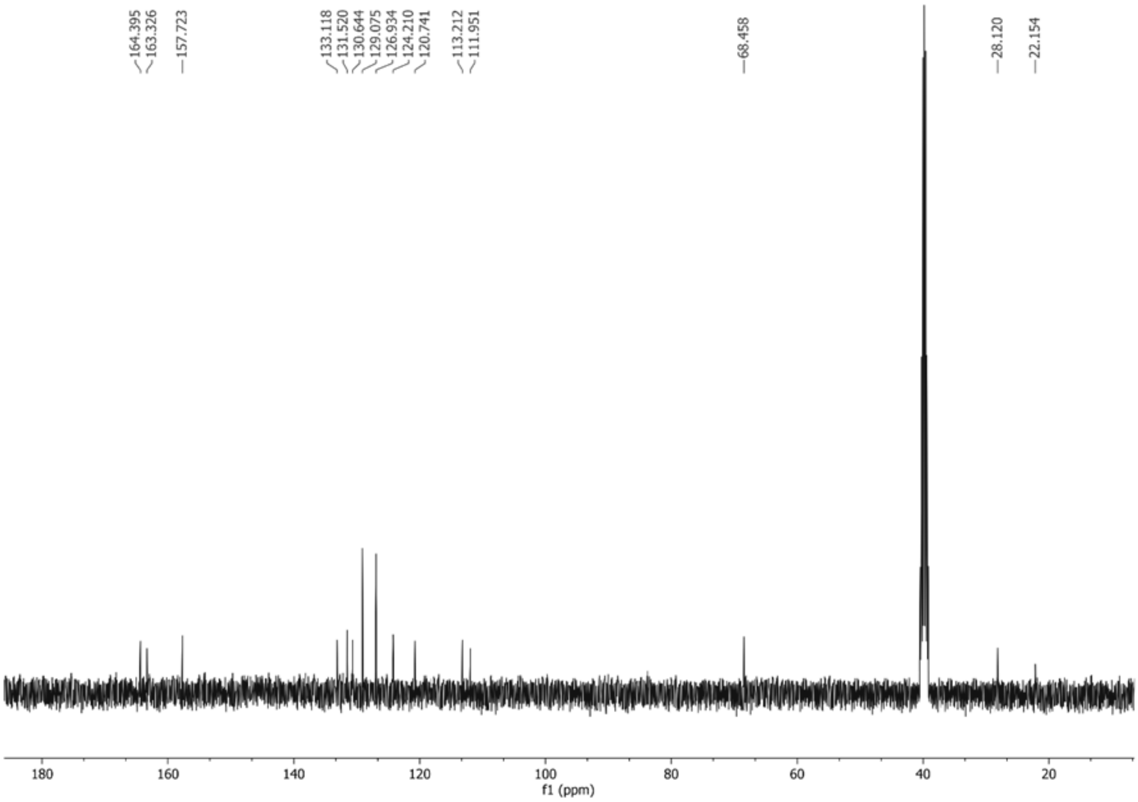

Figure S19. ^{1}H-NMR spectrum of compound **8b**.

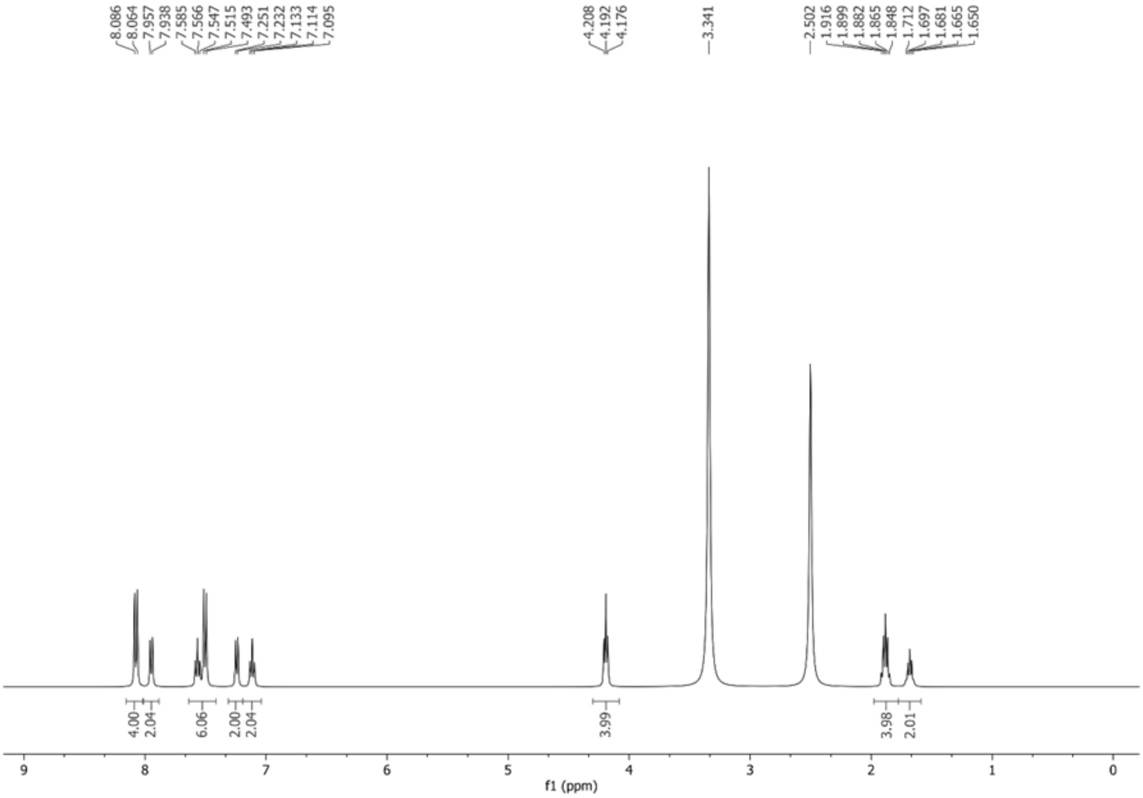

Figure S20. ^{13}C-NMR spectrum of compound **8b**.

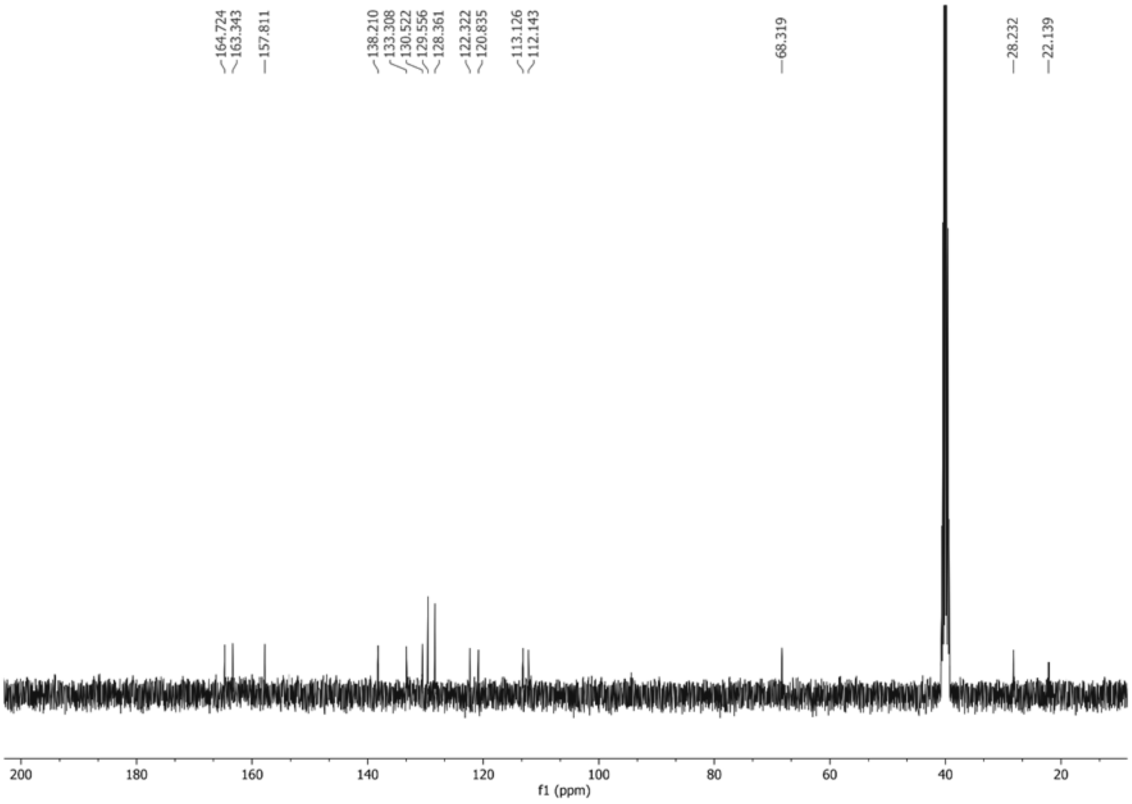

Figure S21. ^{1}H-NMR spectrum of compound **8c**.

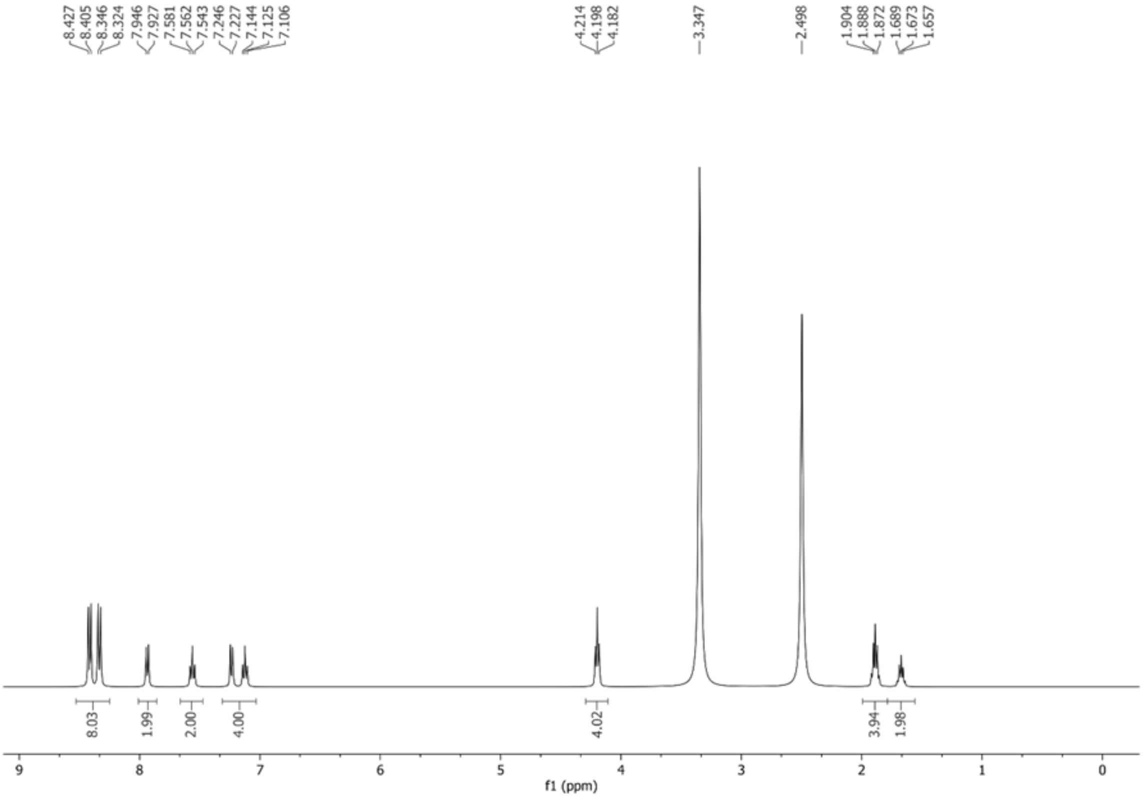

Figure S22. ^{13}C-NMR spectrum of compound **8c**.

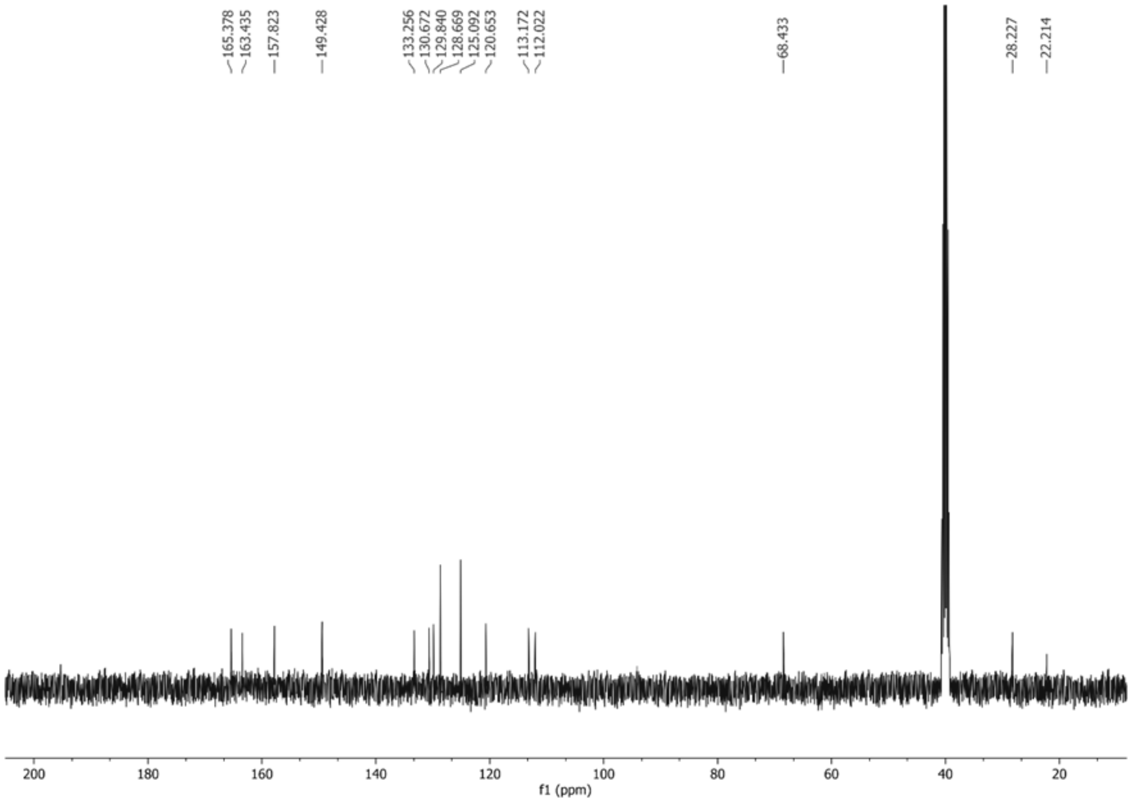

Figure S23. ^{1}H-NMR spectrum of compound **8d**.

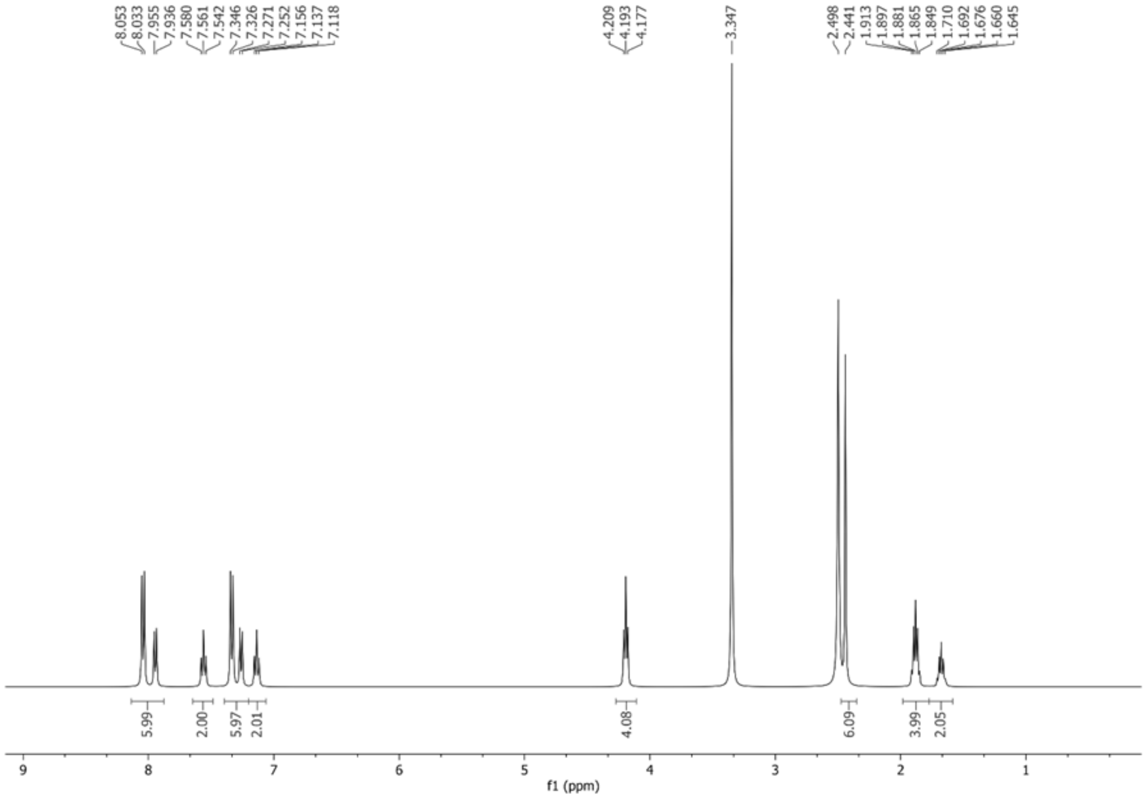

Figure S24. ^{13}C-NMR spectrum of compound **8d**.

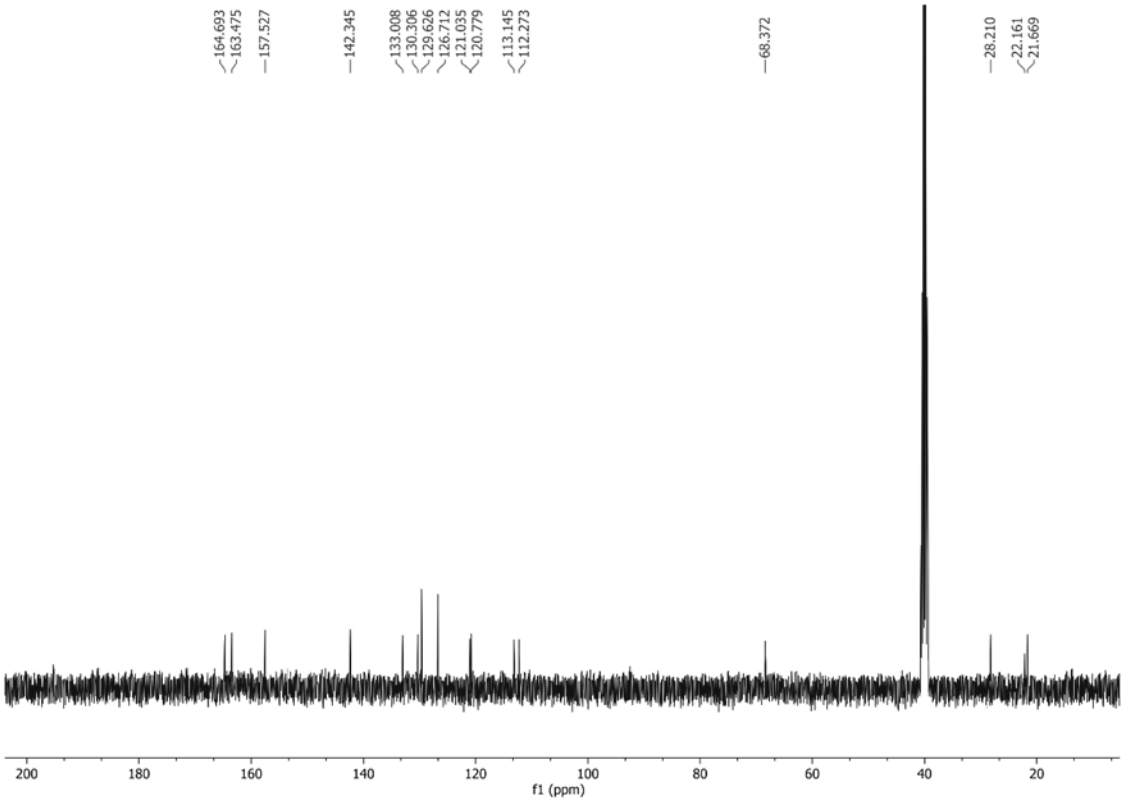

Figure S25. ^{1}H-NMR spectrum of compound **8e**.

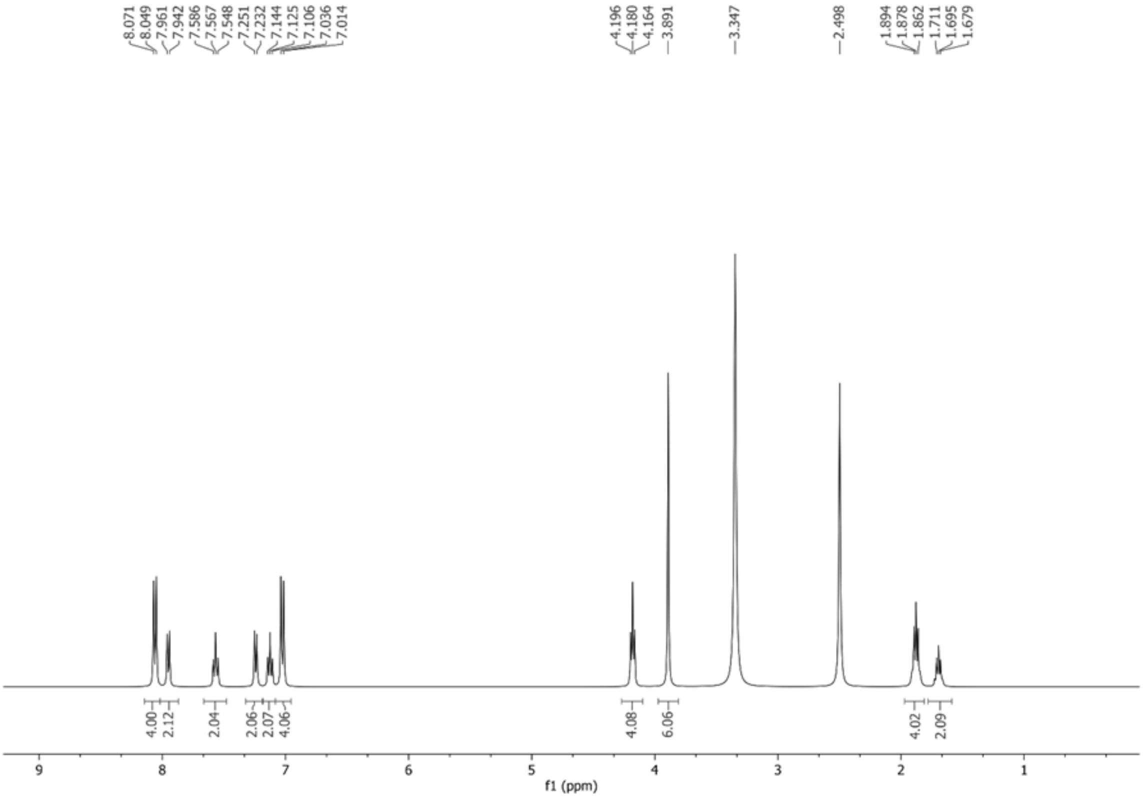

Figure S26. ^{13}C-NMR spectrum of compound **8e**.

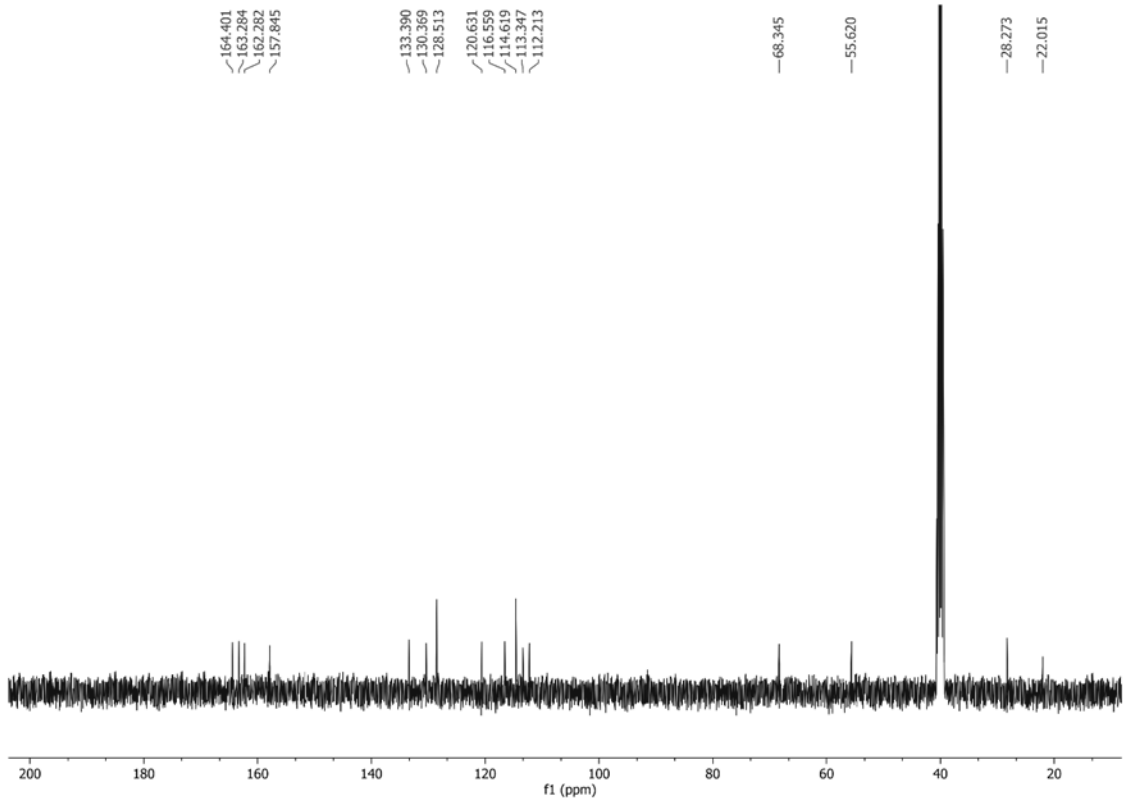

Figure S27. ^{1}H-NMR spectrum of compound **8f**.

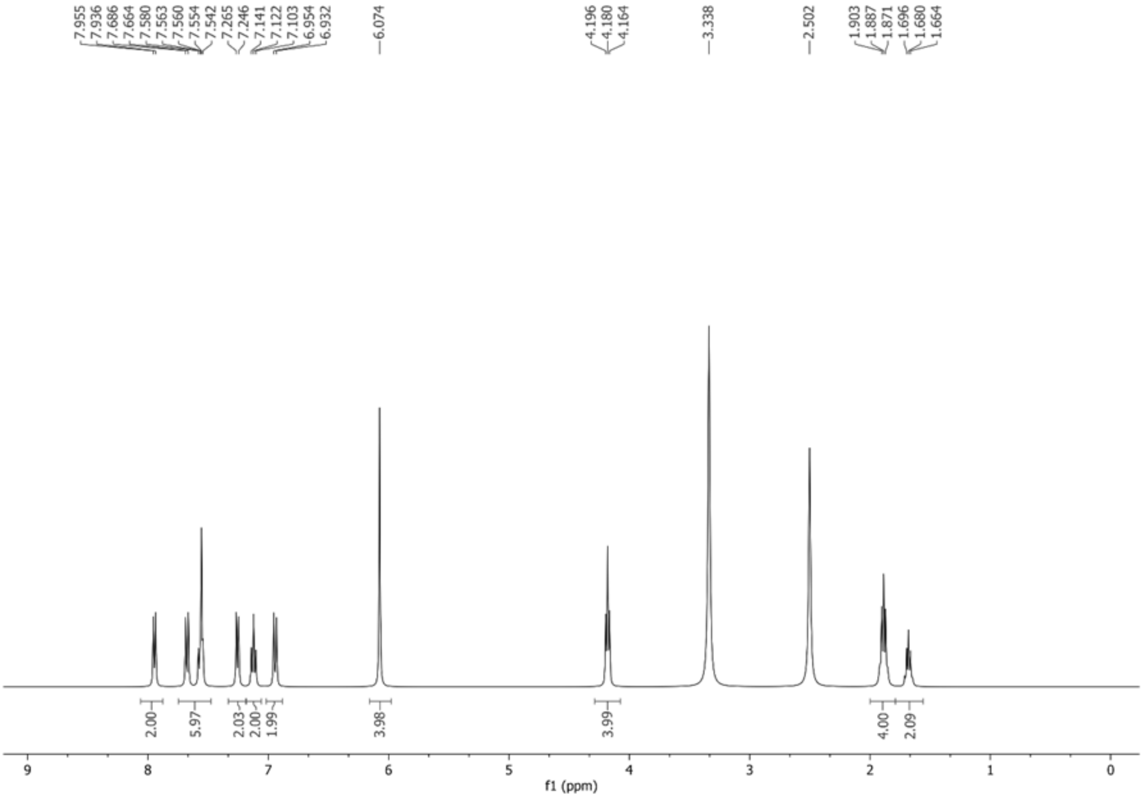

Figure S28. ^{13}C-NMR spectrum of compound **8f**.