Supporting information

Peptide Turns Through Just 'One Atom'! Sulfamide Group Nucleates Folding and Stabilizes New Supramolecular Topologies in Short Peptides

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Table 1. Crystallographic summary for compounds **1a-1d**

Compounds	**1a**	**1b**	**1c**	**1d**
Chemical formula	$C_{22}H_4N_4O_8S$	$C_{24}H_{46}N_4O_8S$	$C_{26}H_{50}N_4O_8S$	$C_{14}H_{26}N_4O_8S$
Formula weight	522.67	550.71	578.76	410.45
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic	Triclinic
a (Å)	15.675(2)	9.1689(4)	10.551(3)	4.9125(2)
B (Å)	18.849(5)	15.8240(5)	15.765(5)	9.3729(4)
C (Å)	19.855(5)	21.6607(10)	20.395(5)	12.3508(5)
α (^{o})	90	90	90	110.316(2)
β (^{o})	90	90	90	90.313(2)
γ (^{o})	90	90	90	100.2330(10)
Temperature	298(2) K	273(2) K	298(2) K	298(2) K
V (A^3)	5867(2)	3142.7(2)	3392.4(16)	523.43(4)
Space group (No)	P2(1)2(1)2(1)	P2(1)2(1)2(1)	P2(1)2(1)2(1)	P1
Z	4	4	4	1
Total reflections	7962	11534	5719	7806
Independent reflections	3199	6066	2538	4364
Final R value	0.0496	0.0743	0.0536	0.0371
CCDC Number	980490	980491	980493	1009176

Details of secondary interactions in the crystal structures of 1a-d

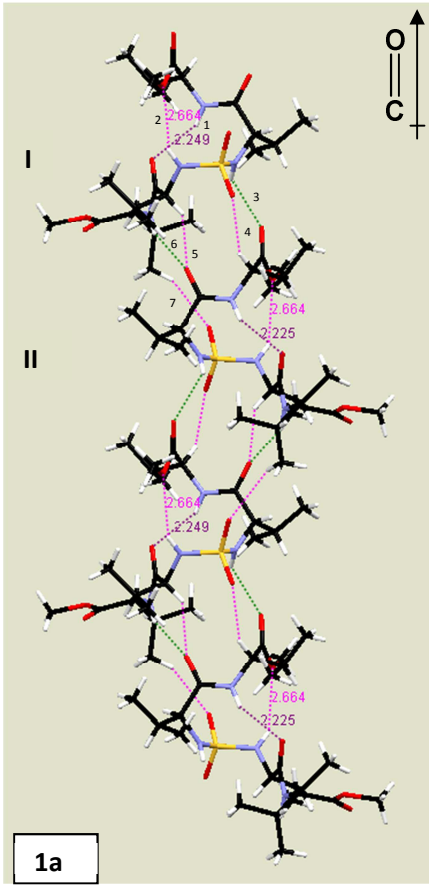
I. Dival sulfamide 1a

Table 2. Important hydrogen bond lengths and angles in the assembly of isomorphs I and II

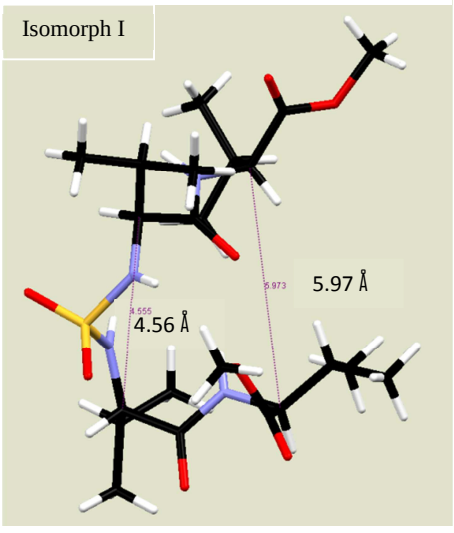
Bonds	Atoms involved	Bond length(Å)	Bond angle (degrees)
1[a]	N_2'H ··· O_1	2.249	147.84
2	N_1H…O_3'	2.664	132.12
3	N_1'H…O_2'	2.440	133.01
4	C_2'H…O_1=S	2.638	152.98
5	C_1H···O_1'	2.529	135.29
6	N_2H ··· O_1'	2.113	153.75
7[b]	$C_{2\beta}$H···O_2=S	2.553	150.61

[a] For isomorph II, the N_2'H ··· O_1 bond length is 2.225 Å and the angle is 148°;

[b] $C_{2\beta}$H represent the hydrogen atom of the methyl group of second Valine residue



Distances between Cα carbons at 1,1'- and 2,2' positions

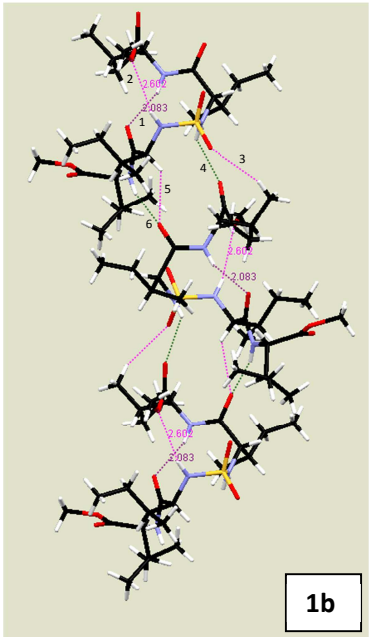


II. Dilleu sulfamide 1b

Table 2. Important secondary interactions which stabilize the lattice of 1b

Bonds	Atoms involved	Bond length	Bond angle (degrees)
1	N_2'H…O_1	2.083	158.12
2	N_1H…O_3'	2.602	134.73
3	$C_{2\gamma}$'H…O_1=S	2.666	155.37
4	N_1'H···O_2'	2.297	133.47
5	C_1H…O_1'	2.563	133.39
6	N_2H···O_1'	2.030	163.63

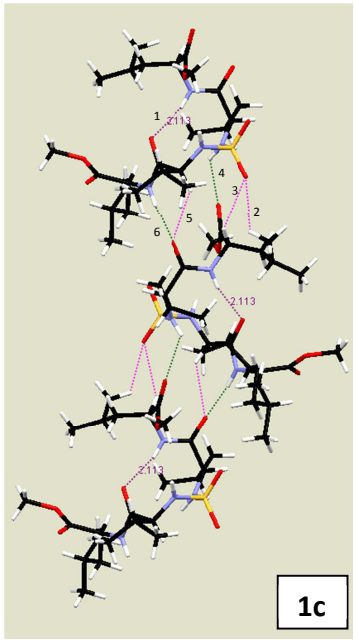
$C_{2\gamma}$'H represents the hydrogen atom attached to the CH_3 group of the second Ileu residue



III. ValLeu sulfamide 1c

Table 3. Important secondary interactions which stabilize the lattice of **1c**

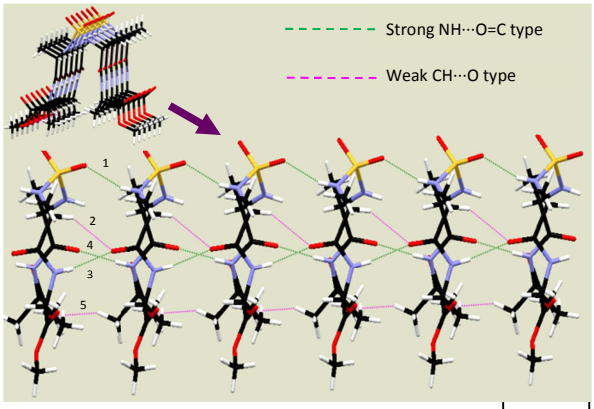
Bonds	Atoms involved	Bond length	Bond angle (degrees)
1	N_2'H···O_1	2.113	156.95
2	N_1H…O_3'	2.540	132.38
3	$C_{2\delta}$'H···O_1=S	2.699	122.42
4	C_2'H···O_1=S	2.652	137.89
5	N_1'H···O_2'	2.330	132.82
6	C_1H···O_1'	2.613	134.41
7	N_2H···O_1'	2.024	170.28



IV Diala sulfamide 1d

Table 4. Important secondary interactions which stabilize the lattice of 1d

Bonds	Atoms involved	Bond length	Bond angle (degrees)
1	$N_1H\cdots O_1{=}S$	2.072	153.50
2	$C_1H\cdots O_1$	2.591	148.57
3	$N_2H\cdots O_1$	2.120	172.87
4	$N_2'H\cdots O_1'$	2.084	176.15
5	$C_{2\beta}'H\cdots O_3'$	2.564	156.09



1d

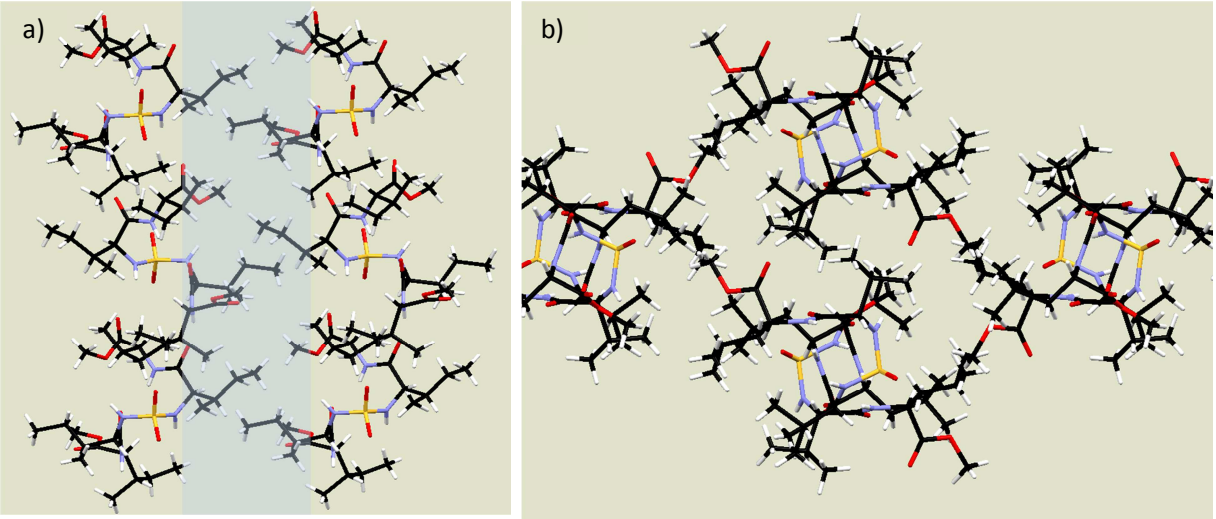


Figure 1. a) Arrangement of hydrophobic side chains in-between the helical stacks of **1b**; b) shows the clustering of side chains in between the helical assemblies of **1c**.

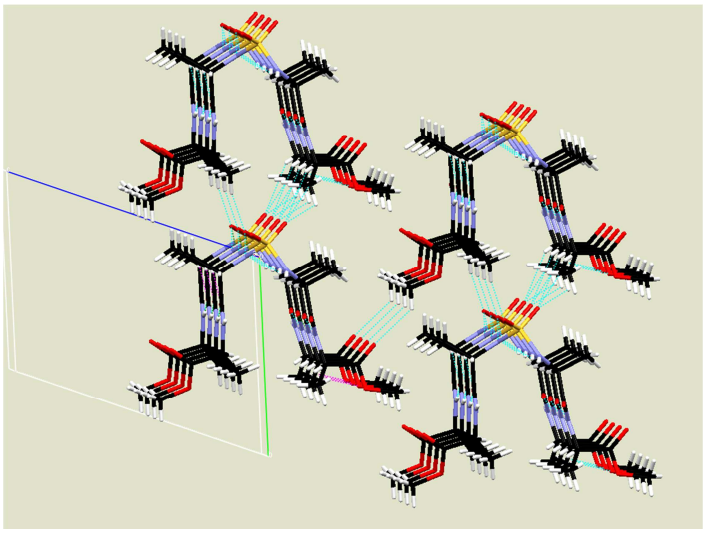
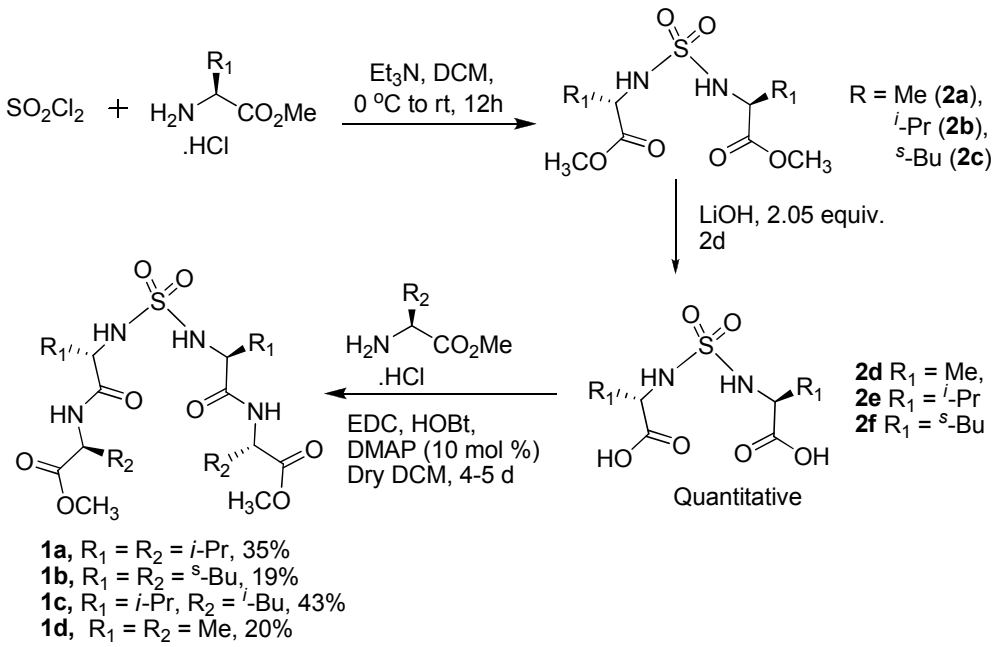


Figure 2. Arrangement of molecules in the lattice of **1d** along **a** axis

Scheme 1: Synthetic sequence used to prepare sulfamido peptides **1a-1d**

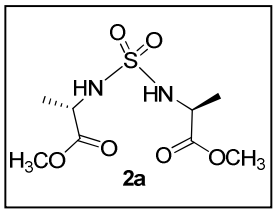


General procedure for the syntheses of compounds 2a-2c

These starting materials (**2a**-**2c**) were synthesized as per the literature protocol (Dougherty *et al*., Tetrahedron 2000, **56**, 9781).

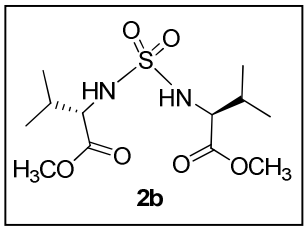
To a stirred solution of the amino acid methyl ester hydrochloride (1 equiv.) in dry DCM at 0 ^{o}C, in a two necked RB flask under nitrogen atmosphere was added triethylamine (2-3 equiv.). A dilute solution of sulfuryl chloride (0.45-0.5 equiv.) in dry DCM (40-80 mL) was then added drop-wise to this using an addition funnel during about 30-45 min, the mixture was allowed to warm to room temperature and stirring was continued for an additional 12 h. The reaction mixture was washed with water and 5% HCl solution, extracted with DCM, dried over Na_2SO_4 and solvents were evaporated to get a residue which was chromatographed using EtOAc-Hexanes mixture to get the compounds **2a**-**2d** in 20-65% yields as white crystalline solids.

N,N′-Sulfonyl *bis*-L-alanine dimethyl ester (**2a**)



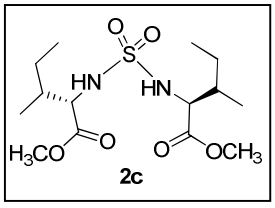
L-alanine methyl ester hydrochloride (11 g, 78.8 mmol) on reaction with sulfuryl chloride (3.19 mL, 39.4 mmol) in Et_3N (22 mL, 157.6 mmol) according to the general procedure given above for 12 h, gave **2a** (2.05 g, 20% yield) as white crystalline solid. Analytical data for **2a:** R_f: 0.6 (40% EtOAc-Hexanes); mp 86-88 °C; ^{1}H NMR ($CDCl_3$) δ 5.25 (d, 1H, *J* = 8.4 Hz), 4.10 (dq, 1H, *J* = 7.6, 7.6 Hz), 3.76 (s, 3H), 1.45 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 173.7, 52.7, 51.8, 19.2; IR (neat) cm^{-1}: 3270, 2962, 1739, 1453, 1349; HRMS (ESI) exact mass calcd. for $C_8H_{17}N_2O_6S$ $[M+H]^+$ 269.0807, found $[M+H]^+$ 269.0810.

N,N′-Sulfonyl *bis*-L-valine dimethyl ester (**2b**)



L-Valine methyl ester hydrochloride (5 g, 29.85 mmol) on reaction with sulfuryl chloride (1.2 mL, 14.92 mmol) in Et_3N (12.5 mL, 89.55 mmol) according to the general procedure given above for 12 h, gave **2b** (3.1 g, 65% yield) as white crystalline solid. Analytical data for **2b:** R_f: 0.6 (20% EtOAc-Hexanes); mp 73-74 °C;^{1}H NMR ($CDCl_3$) δ 5.22 (bs, 1H), 3.89 (dd, 1H, *J* = 9.6, 4.4 Hz), 3.77 (s, 3H), 2.18-2.08 (m, 1H), 1.0 (d, 3H, *J* = 6.8 Hz), 0.89 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 172.8, 61.1, 52.3, 31.4, 18.7, 17.4; $[\alpha]_D^{20}$ -26.32 (c = 0.1, CH_3OH); IR (neat) cm^{-1}: 3466, 3316, 2971, 1742, 1466, 1392, 1357; HRMS (ESI) exact mass calcd. for $C_{12}H_{25}N_2O_6S$ $[M+H]^+$ 325.1433, found $[M+H]^+$ 325.1433.

N,N′-Sulfonyl *bis*-L-isoisoleucine dimethyl ester (**2c**)

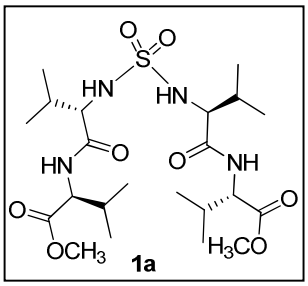


L-Isoleucine methyl ester hydrochloride (2 g, 11 mmol) on reaction with sulfuryl chloride (0.89 mL, 4.95 mmol) in Et_3N (4.69 mL, 33 mmol) according to the general procedure given above for 12 h, gave **2c** (0.9 g, 23% yield) as a white crystalline solid. Analytical data for **2c:** R_f: 0.6 (30% EtOAc-Hexanes); mp 55-56 °C; ^{1}H NMR ($CDCl_3$) δ 5.08 (d, 1H, *J* = 9.6 Hz), 3.92 (dd, 1H, *J* = 4.4, 4.4 Hz), 3.75 (s, 3H), 1.89-1.83 (m, 1H), 1.44-1.35 (m, 1H), 1.22-1.11 (m, 1H), 0.96-0.70 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 172.82, 60.42, 52.35, 38.4, 24.9, 15.3, 11.6; $[\alpha]_D^{20}$ -30.32 (c = 0.1, CH_3OH); IR (neat) cm^{-1}: 3312, 2966, 1733, 1456, 1361, 1300; HRMS (ESI) exact mass calcd. for $C_{14}H_{29}N_2O_6S$ $[M+H]^+$ 353.1746, found $[M+H]^+$ 353.1747.

General procedure for the synthesis of sulfamido-peptides 1a-1d

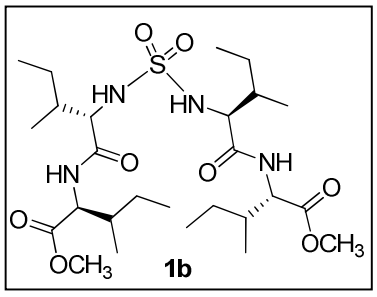
At first, the diesters **2a-c** were subjected to alkaline hydrolysis (1N LiOH in 3:1 of THF and water) to get the corresponding diacids **2d-f** in quantitative yields. To a stirred solution of the diacid (1 equiv.) in dry DCM at 0 ^{o}C was added EDCI (3 equiv.), HOBt (1 equiv.), DMAP (10 mol %) and DIPEA (10 equiv.) followed by the appropriate amino acid methyl ester hydrochloride salt (10 equiv.). The mixture was allowed to stir at room temperature for 4-5 days, diluted with DCM, washed with water and 5 % HCl solution, and the residue after solvent evaporation was chromatographed with EtOAc/Hexanes to afford the desired sulfamido-peptides in moderate to good yields.

Sulfamido peptide 1a



Diacid **2e** (0.4 g, 1.35 mmol) on reaction with L-valine methyl ester hydrochloride (2.26 g, 13.5 mmol) under the standard peptide coupling protocol discussed above for 4d afforded the product **1a** (0.26 g, 35% yield). Analytical data for **1a:** R_f: 0.5 (75% EtOAc-Hexanes); ^{1}H NMR ($CDCl_3$): δ 7.06 (d, 1H, *J* = 8.8 Hz), 5.48 (d, 1H, *J* = 7.6 Hz), 4.6 (dd, 1H, *J* = 5.2, 5.2 Hz), 3.89 (dd, 1H, *J* = 6.0, 5.6 Hz), 3.76 (s, 3H), 2.28-2.19 (m, 1H), 2.18-1.9 (m, 1H), 1.03 (d, 3H, *J* = 6.8 Hz), 0.99-0.92 (m, 9H);^{13}C NMR ($CDCl_3$) δ 172.9, 171.6, 63.6, 57.4, 52.3, 31.0, 30.9, 19.2, 19.1, 17.9 (2C); HRMS (ESI) exact mass calcd. for $C_{22}H_{42}N_4O_8SNa$ $[M+Na]^+$ 545.2621, found $[M+Na]^+$ 545.2618.

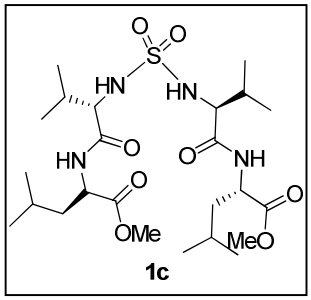
Sulfamido peptide 1b



Diacid **2f** (1.0 g, 3.086 mmol) on reaction with L-Isoleucine methyl ester hydrochloride (5.6 g, 30.86 mmol) under the standard peptide coupling protocol discussed above for 4d afforded the product **1b** (0.355 g, 19% yield) as colourless solid. Analytical data for **1b**: R_f: 0.15 (90% EtOAc-Hexanes); mp 123-124 °C; ^{1}H NMR ($CDCl_3$): δ 7.08 (d, 1H, *J* = 8 Hz), 5.46 (d, 1H, *J* = 7.2 Hz), 4.62 (dd, 1H, *J* = 6.8, 6.0 Hz), 3.91 (dd, 1H, *J* = 6.4, 5.6 Hz), 3.74 (s, 3H), 2.0-1.92 (m, 1H), 1.9-1.8 (m, 1H), 1.6-1.52 (m, 1H), 1.49-1.4 (m, 1H), 1.27-1.2 (m, 2H), 1.0-0.85 (m, 12H); ^{13}C NMR ($CDCl_3$): δ 172.9, 171.4, 62.9, 56.7, 52.2, 37.7, 37.5, 25.3, 25.2, 24.9, 15.6,

15.5, 11.4; $[\alpha]_D^{20}$ -62.56 (c = 0.13, CH_3OH); IR (neat) cm^{-1}: 3299, 3259, 2957, 2880, 1746, 1731, 1652, 1553; ESI m/z: calcd. for $C_{26}H_{50}N_4O_8SNa$ $[M+Na]^+$ 601.3276, found $[M+Na]^+$ 601.3247.

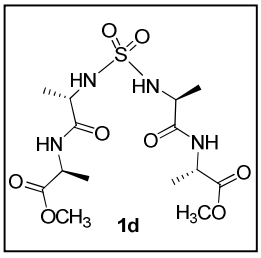
Sulfamido peptide 1c



1c

Diacid **2e** (0.4 g, 1.351 mmol) on reaction with L-Leucine methyl ester hydrochloride (2.45 g, 13.5 mmol) under the standard peptide coupling protocol discussed above for 4d afforded the product **1c** (0.32 g, 43% yield). Analytical data for **1c:** R_f: 0.4 (90% EtOAc-Hexanes); mp 163-164 °C; ^{1}H NMR ($CDCl_3$): δ 7.45 (d, 1H, *J* = 6.4 Hz), 5.72 (d, 1H, *J* = 5.6 Hz), 4.66-4.62 (m, 1H), 3.89 (dd, (1H, *J* = 5.6, 4.8 Hz), 3.73 (s, 3H), 2.1-2.04 (m, 1H), 1.78-1.63 (m, 3H), 1.02 (d, 3H, *J* = 5.2 Hz), 0.98-0.93 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 174.1, 171.8, 64.3, 52.4, 50.9, 40.5, 31.0, 24.9, 22.9, 21.4, 19.2, 18.1; $[\alpha]_D^{20}$ -43.76 (c = 0.1, CH_3OH); IR (neat) cm^{-1}: 3284, 3261, 3079, 2875, 1751, 1730, 1647, 1558, 1462; ESI m/z: calcd. for $C_{24}H_{47}N_4O_8S$ $[M+H]^+$ 551.3115 found $[M+H]^+$ 551.3132.

Sulfamido peptide 1d



1d

Diacid **2d** (0.32 g, 1.3 mmol) on reaction with L-alanine methyl ester hydrochloride (1.85 g, 13 mmol) under the standard peptide coupling protocol discussed above for 4 d to afforded the product **1d** (0.11 g, 20% yield). Analytical data for **1d:** R_f: 0.4 (75% EtOAc-Hexanes); mp 152-153 °C; ^{1}H NMR ($CDCl_3$): δ 7.45 (d, 1H, *J* = 5.6 Hz), 6.7 (d, 1H, *J* = 6.8 Hz), 4.57 (m, 2H), 3.76 (s, 3H), 1.49 (d, 3H, *J* = 6.8 Hz), 1.44 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 172.9, 170.2, 52.6, 49.1, 48.3, 18.6, 18.1; $[\alpha]_D^{20}$ -154.96 (c = 0.1, CH_3OH); IR (neat) cm^{-1}: 3315, 3292, 3263, 3241, 2958, 1746, 1660, 1552, 1454, 1346; ESI m/z: calcd. for $C_{14}H_{27}N_4O_8S$ $[M+H]^+$ 411.1564, found $[M+H]^+$ 411.1550.

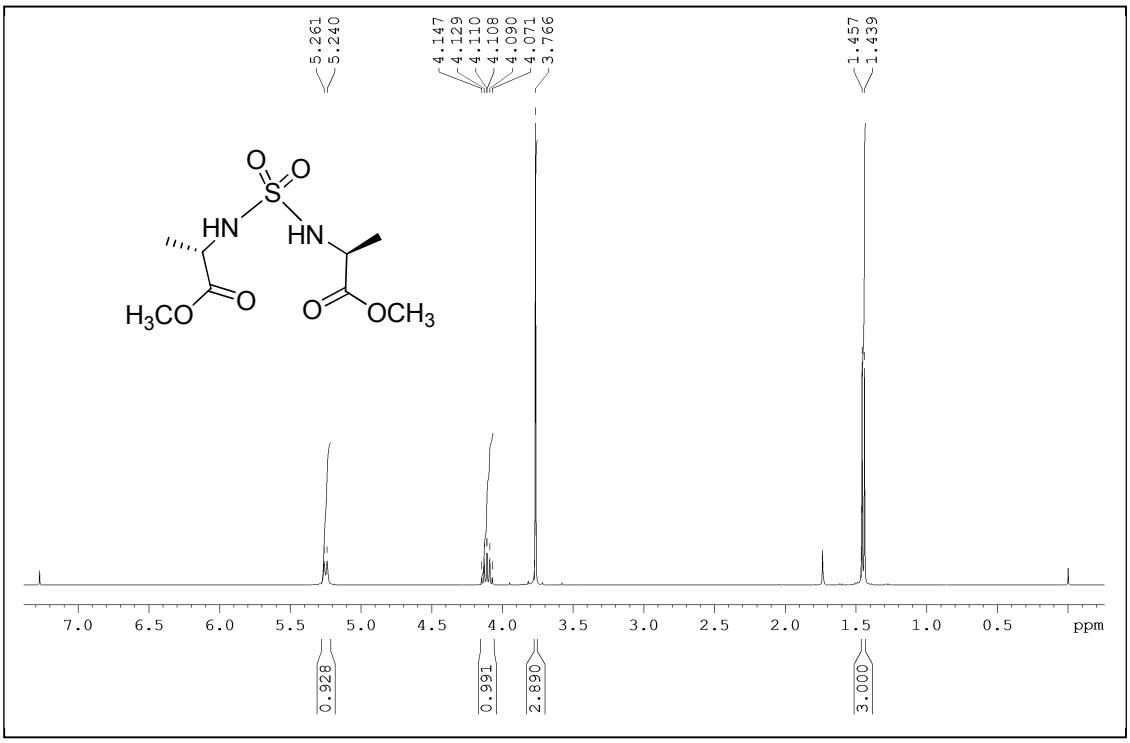


Figure 3. ^{1}H NMR (400 MHz) spectrum of compound 2a

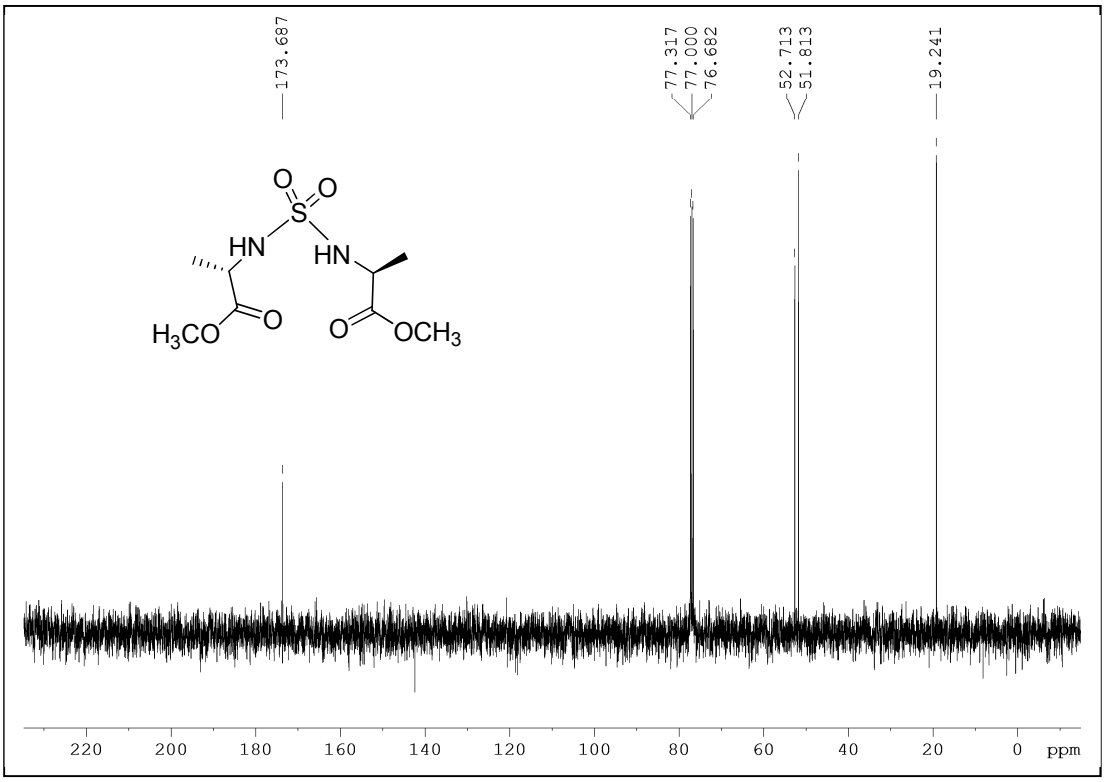


Figure 4. ^{13}C NMR (100 MHz) spectrum of compound 2a

Figure 5. ^{1}H NMR (400 MHz) spectrum of compound 2b

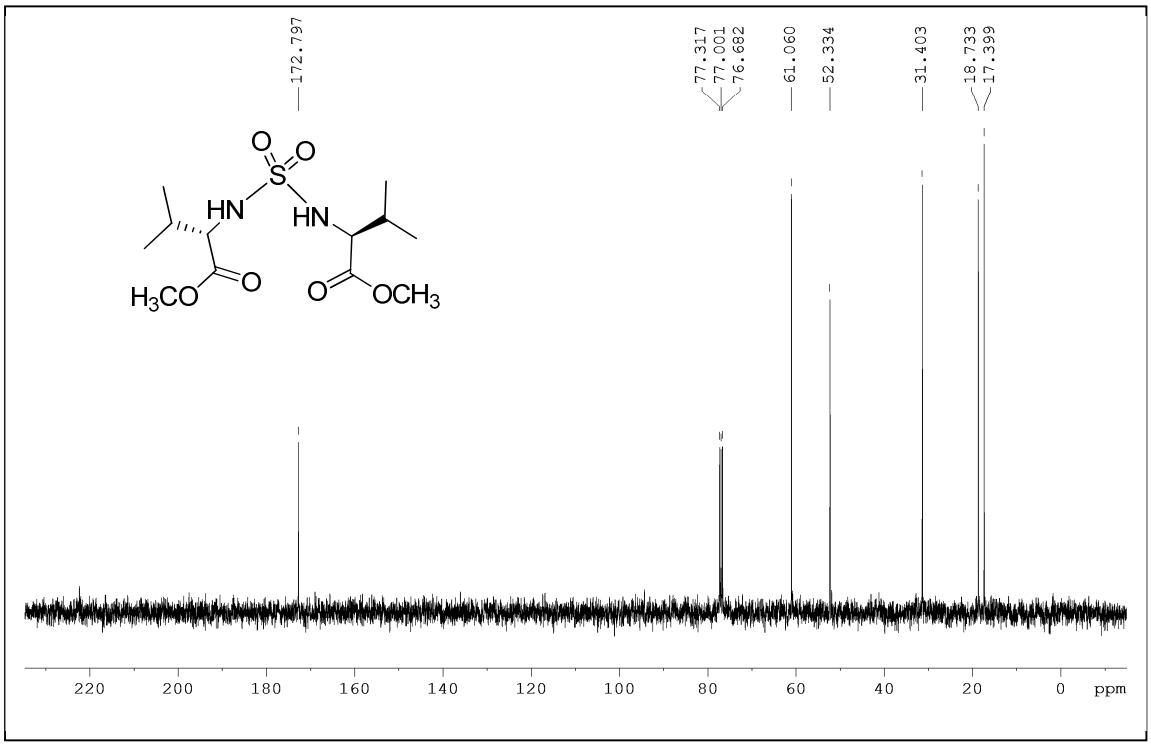


Figure 6. ^{13}C NMR (100 MHz) spectrum of compound 2b

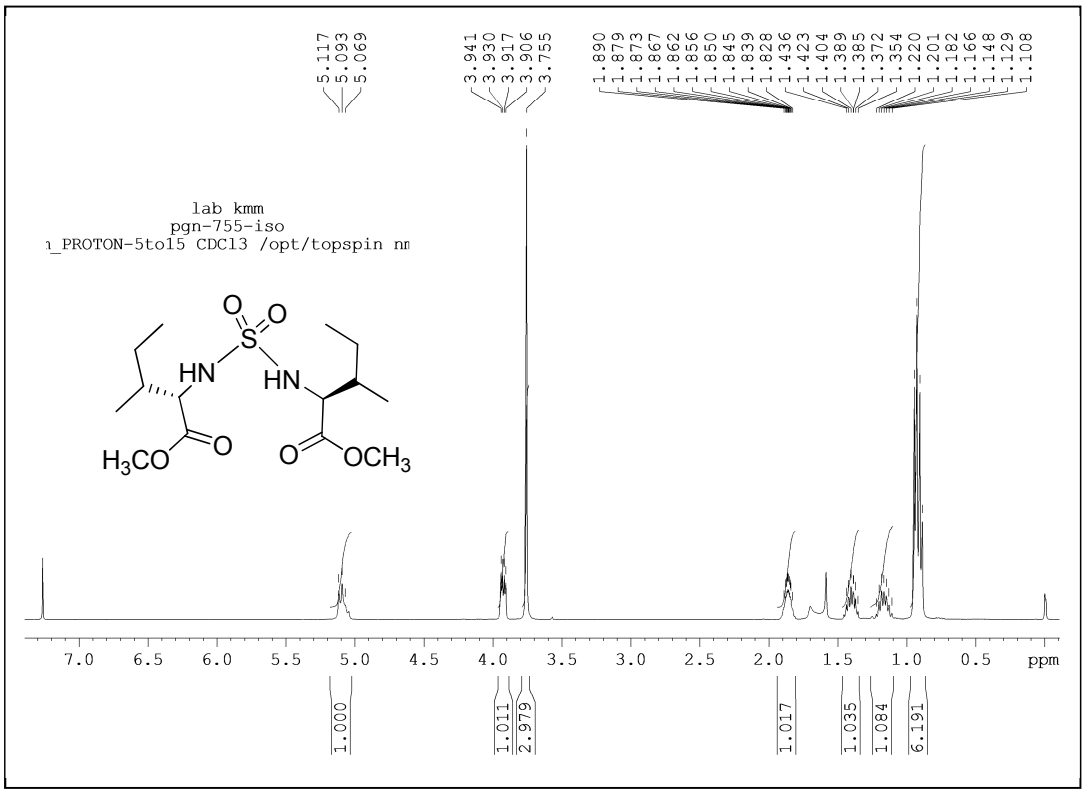


Figure 7. ^{1}H NMR (400 MHz) spectrum of compound 2c

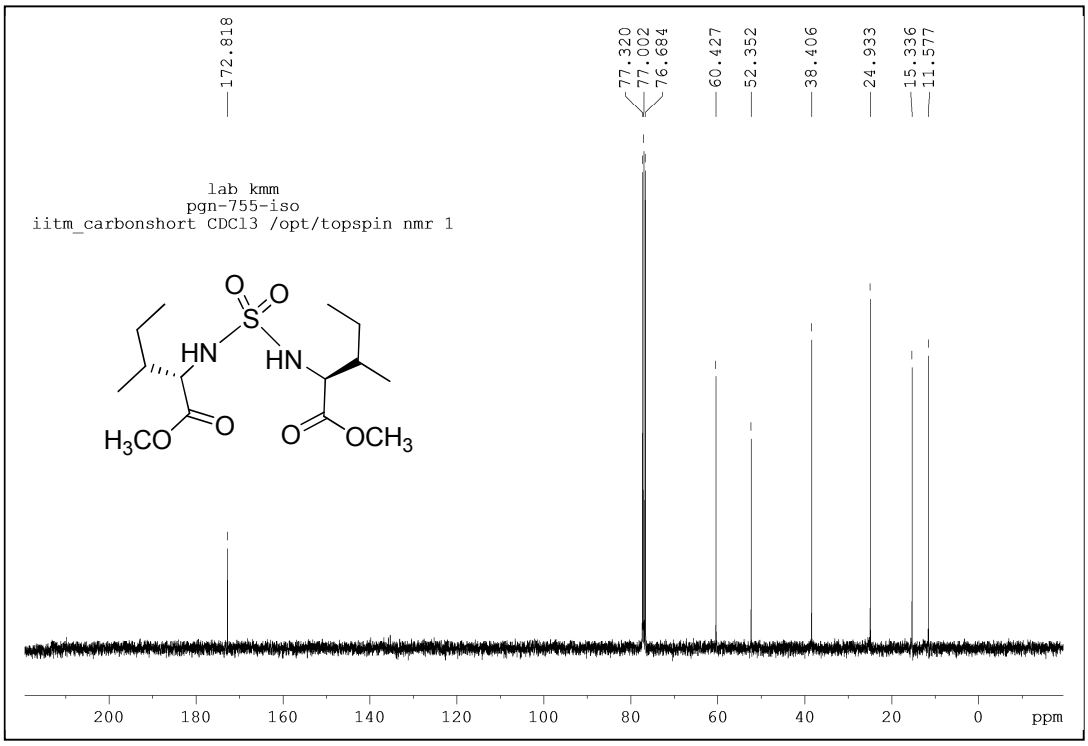


Figure 8. ^{13}C NMR (100 MHz) spectrum of compound 2c

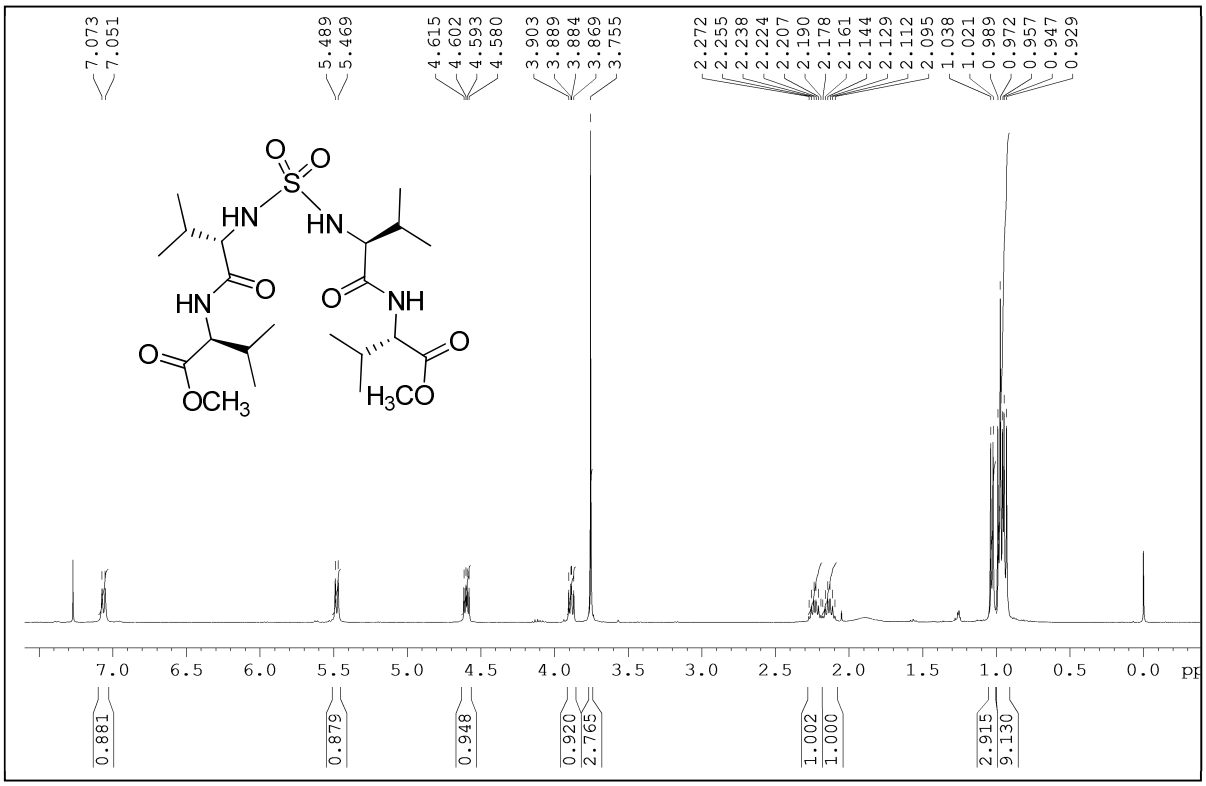


Figure 9. ^{1}H NMR (400 MHz) spectrum of compound 1a

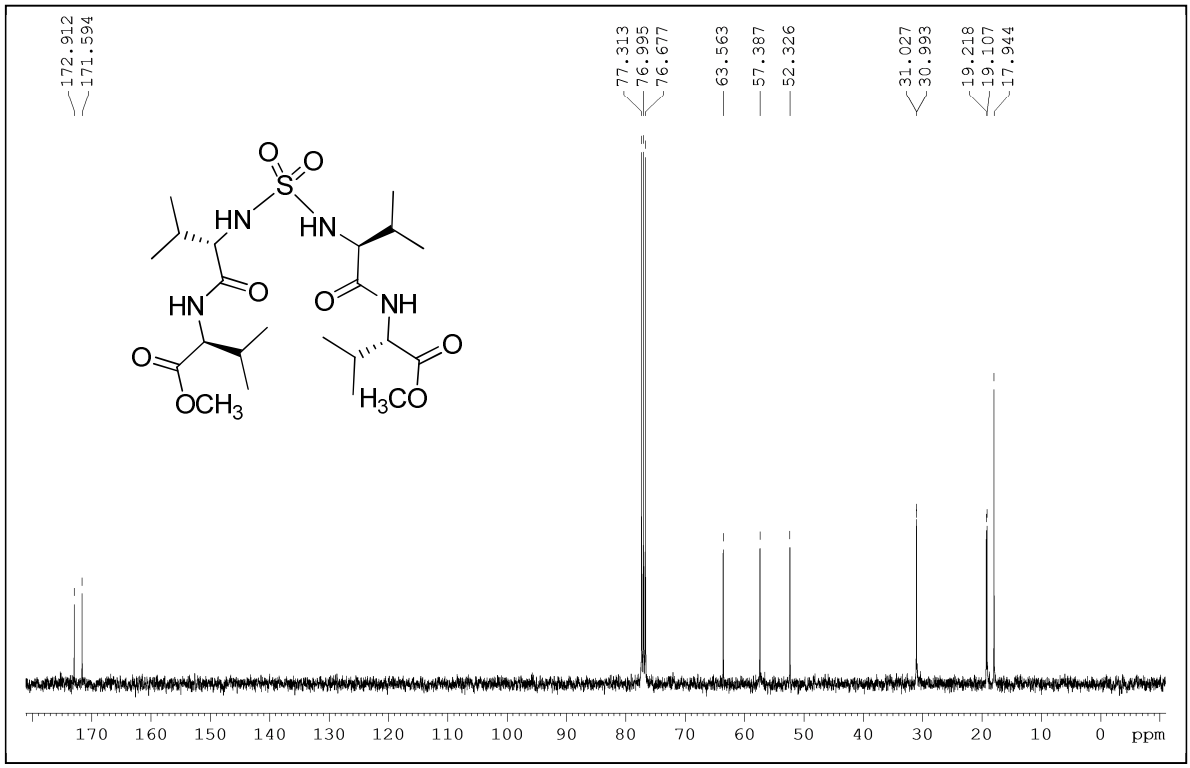


Figure 10. ^{13}C NMR (100 MHz) spectrum of compound 1a

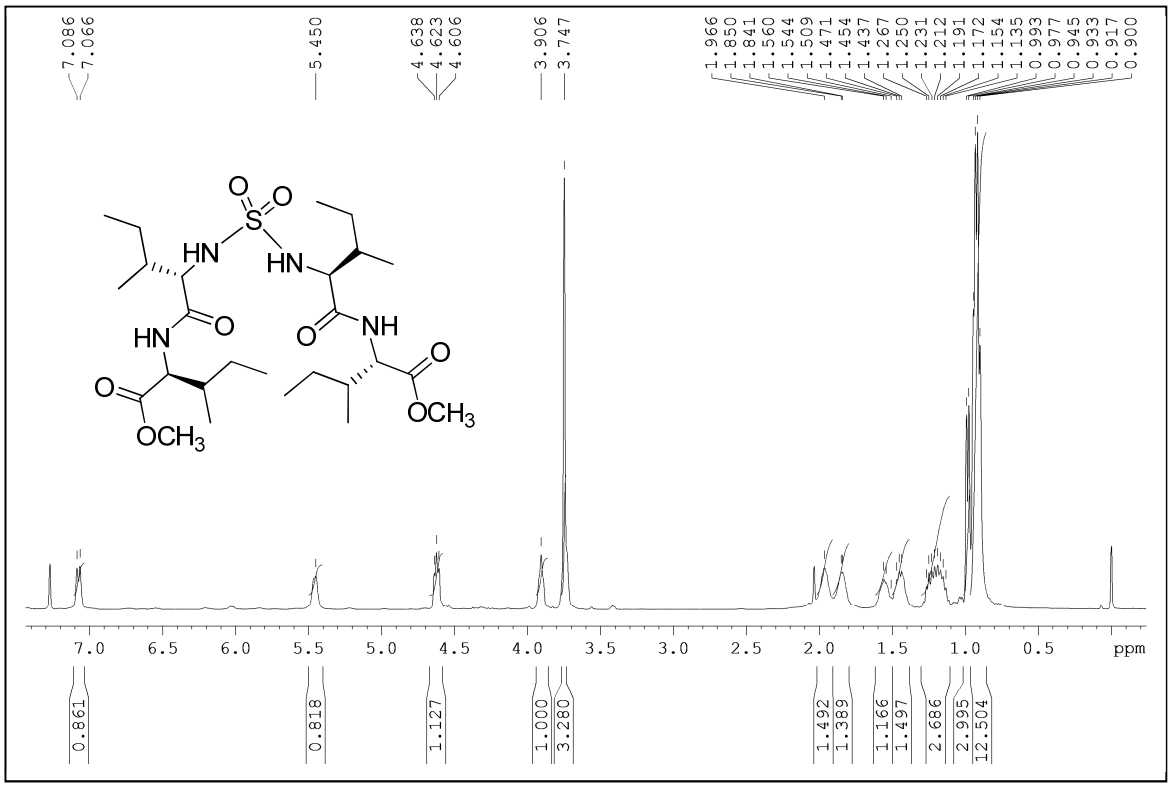


Figure 11. ^{1}H NMR (400 MHz) spectrum of compound 1b

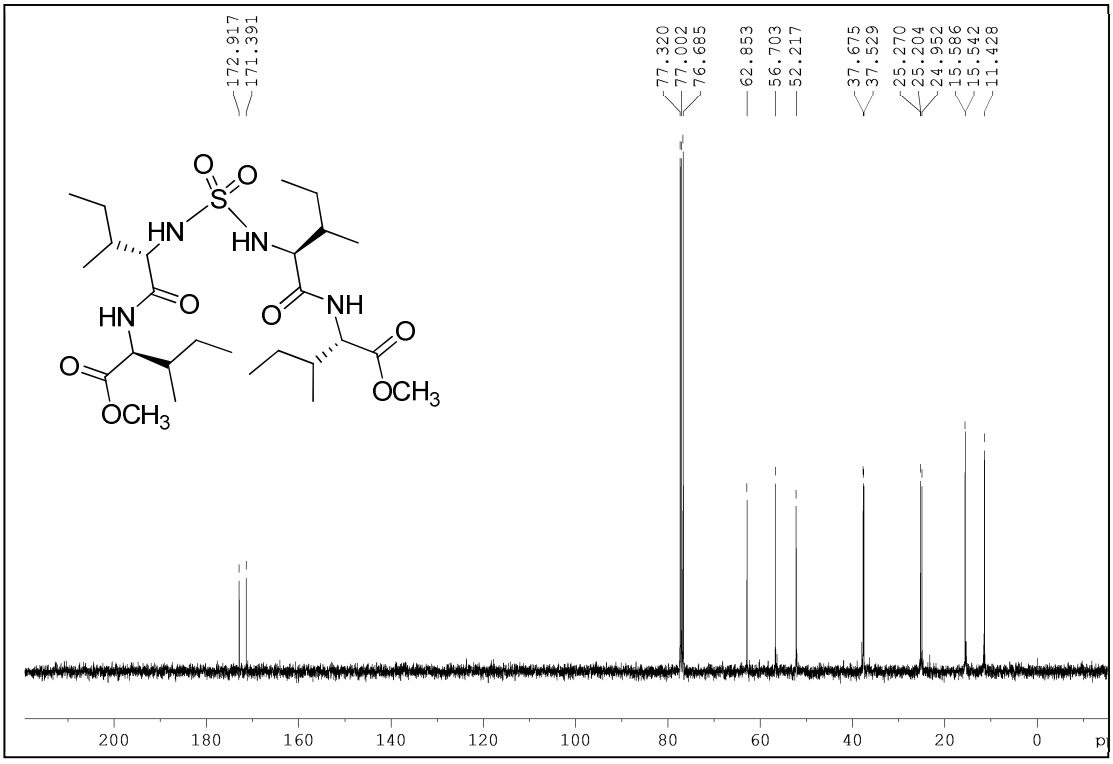


Figure 12. ^{13}C NMR (100 MHz) spectrum of compound 1b

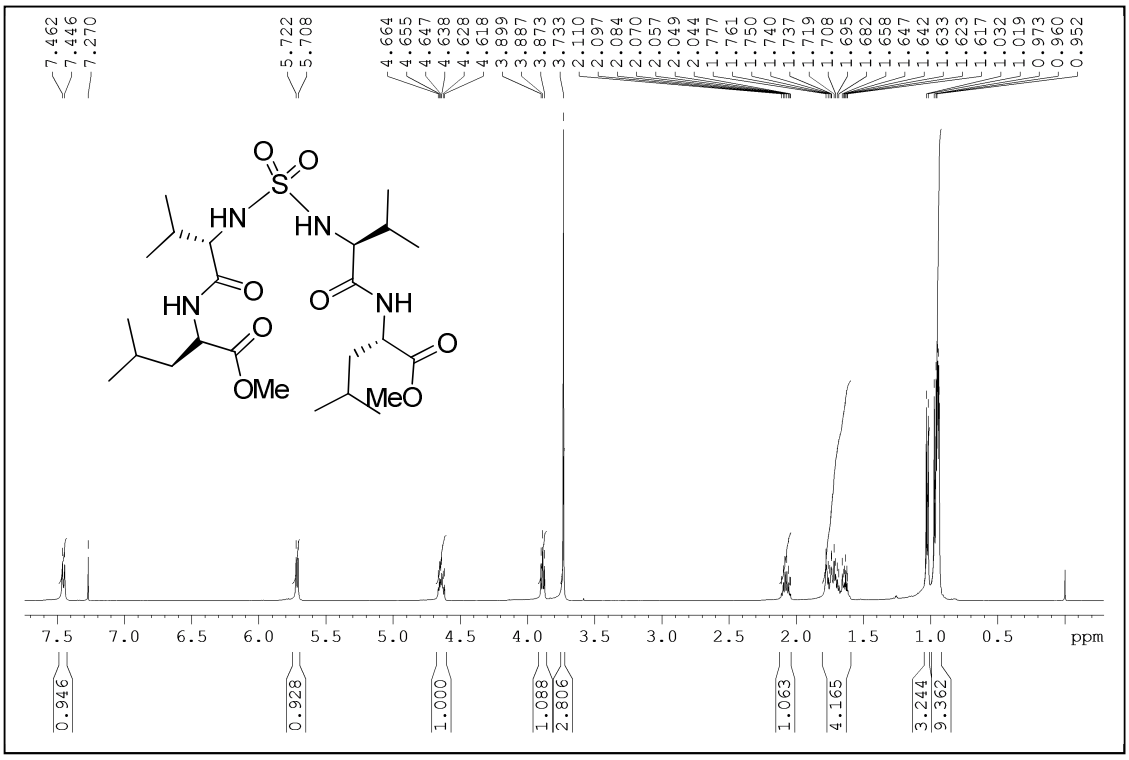


Figure 13. ^{1}H NMR (400 MHz) spectrum of compound 1c

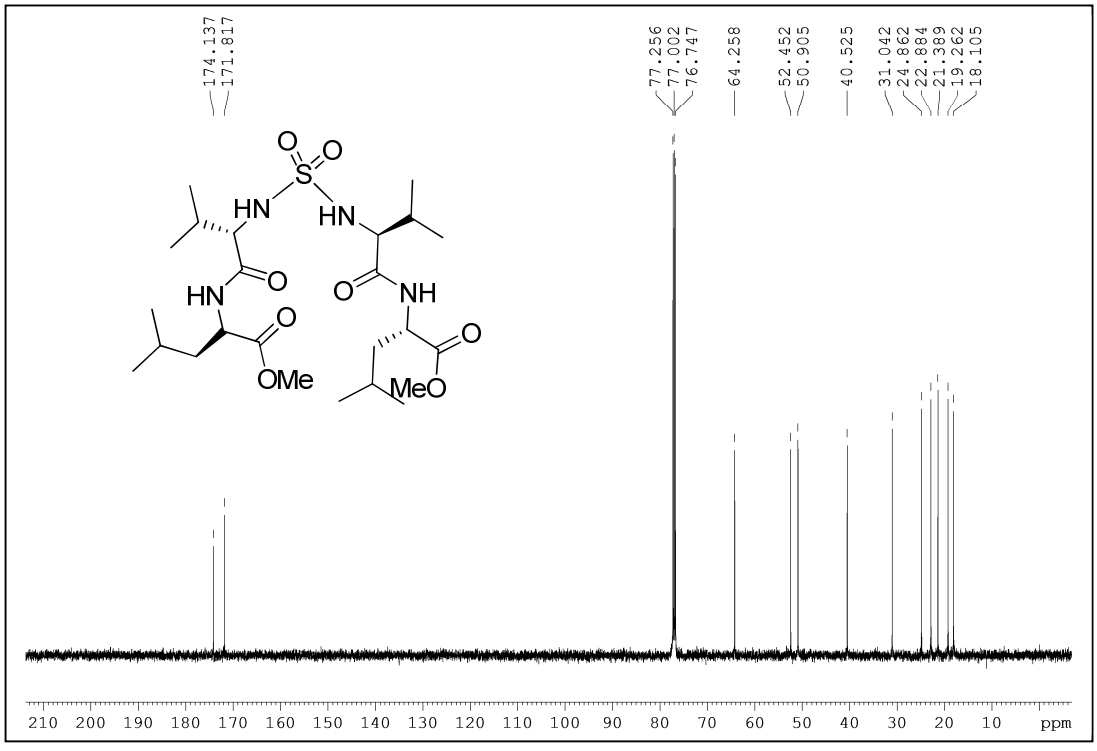


Figure 14. ^{13}C NMR (100 MHz) spectrum of compound 1c

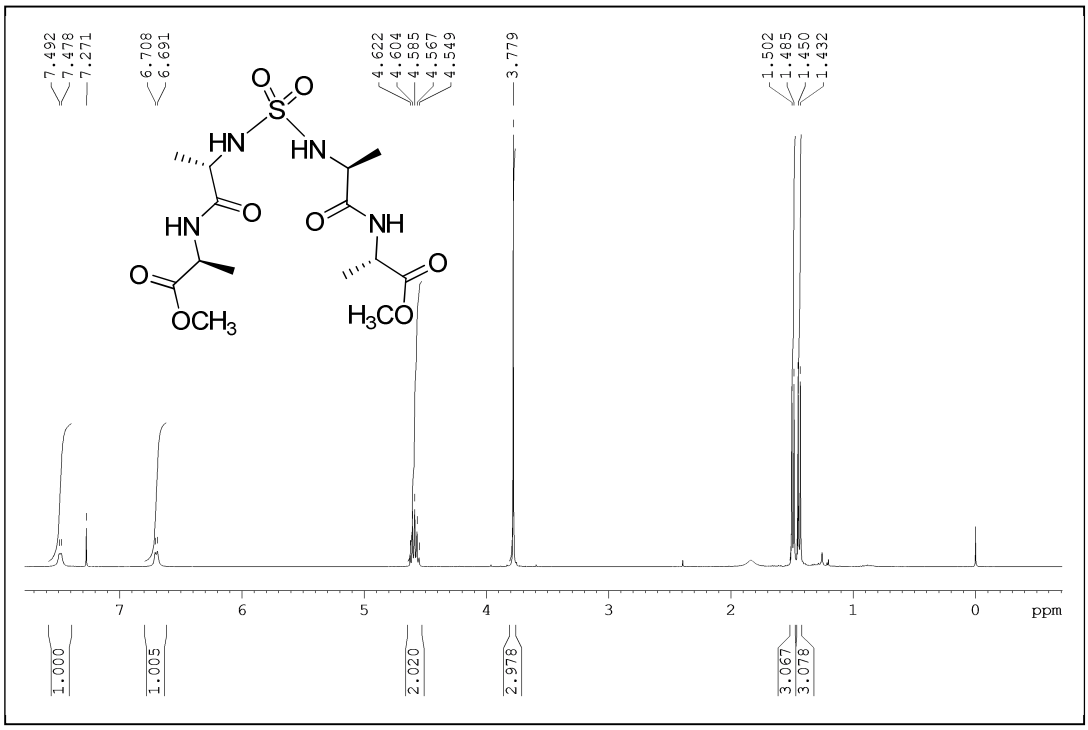


Figure 15. ^{1}H NMR (400 MHz) spectrum of compound 1d

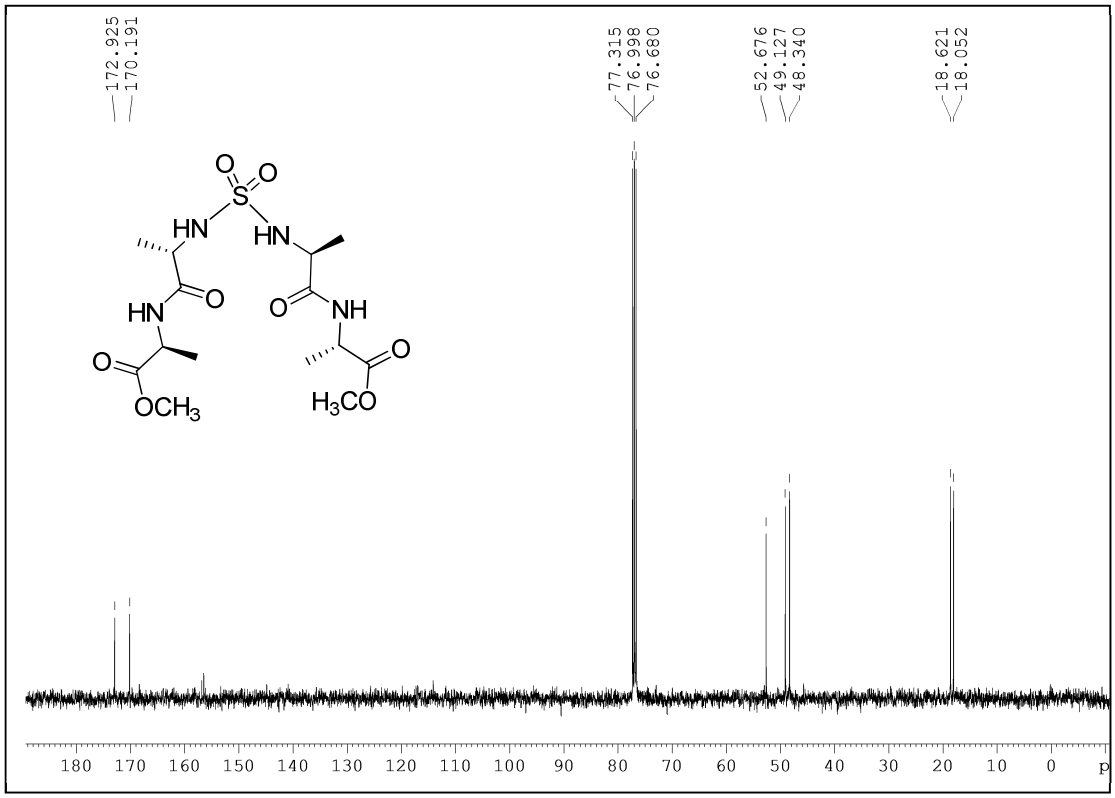


Figure 16. ^{13}C NMR (100 MHz) spectrum of compound 1d