Orally Available Small Molecule Regulates TXNIP Expression and Glucagon Action for the Treatment of Diabetes

Zhikuan Luo[1,2,#], Jun Han[1,#], Qiong Tian[1,2], Ruijun Jing[1,2], Ao Dong[3], Lingzhi Li[3], Hongbin Jia[1], Tinghong Lv[1], Yunkun Dang[3], Fan Lai[3,*], Shili Chen[4,*], Xusheng Ma[2,*], Haixue Zheng[2,*], Xiaolei Wang[1,2,*]

[1]State Key Laboratory of Applied Organic Chemistry, Department of Chemistry and School of Pharmacy, Lanzhou University, Lanzhou, P. R. China

[2]State Key Laboratory for Animal Disease Control and Prevention, College of Veterinary Medicine, Lanzhou University, Lanzhou Veterinary Research Institute, Chinese Academy of Agricultural Sciences, Lanzhou, China.

[3]State Key Laboratory for Conservation and Utilization of Bio-Resources in Yunnan, Center for Life Science, Yunnan Key Laboratory of Cell Metabolism and Diseases, School of Life Sciences, Yunnan University, Kunming, China

[4]Shanghai Key Laboratory of Biliary Tract Disease Research, Department of General Surgery, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

[5]Gansu Province Research Center for Basic Disciplines of Pathogen Biology, Lanzhou, China.

[#]These authors contributed equally to this work

*Corresponding authors

Email: wangxiaolei@lzu.edu.cn, haixuezheng@163.com, maxushengtt@163.com fanlab2020@163.com, shilichen@shsmu.edu.cn,

Supporting Information Placeholder

Table of Contents

Figure S1. Outlook of structural refinement of SKL-1201 to SKL-1223

Structure Optimization of SKL-1201

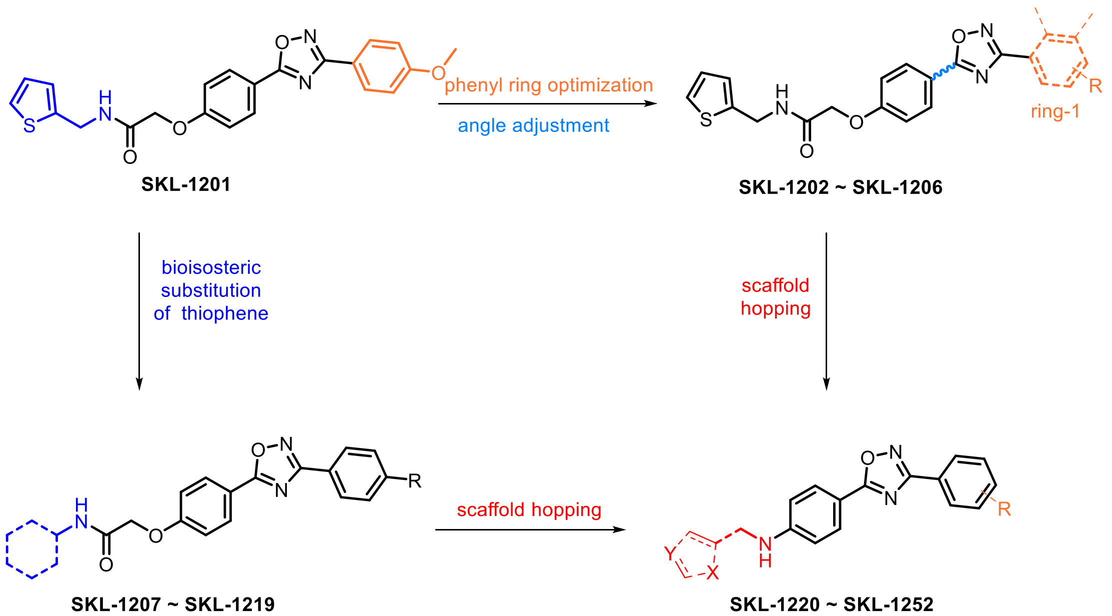
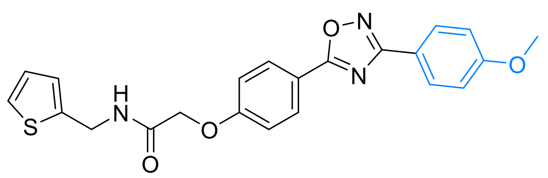
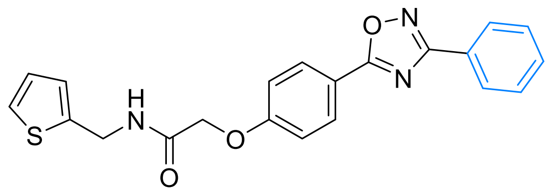
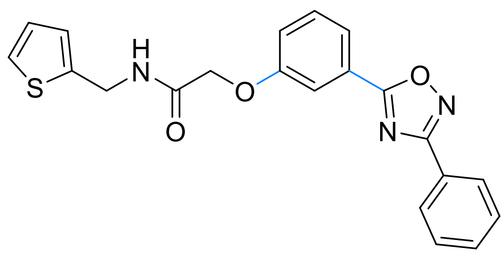
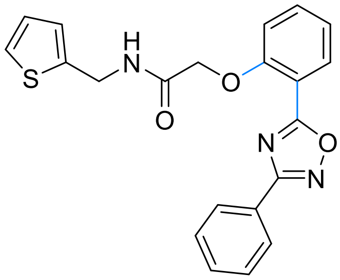
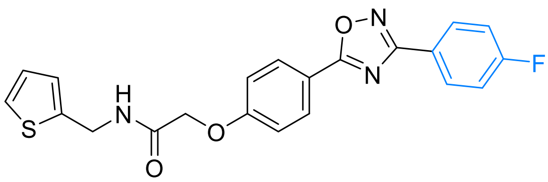
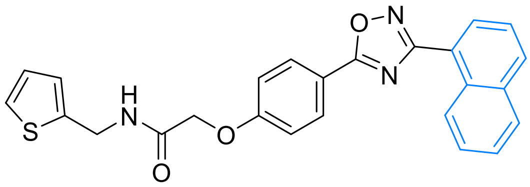
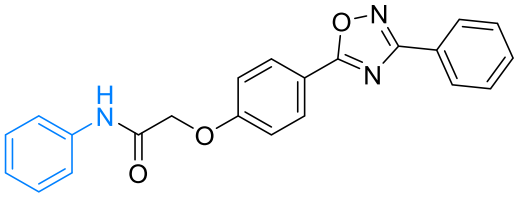
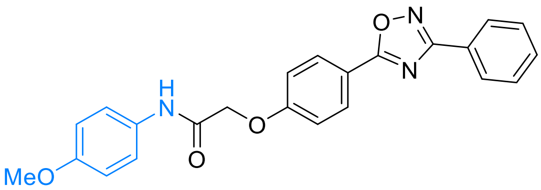
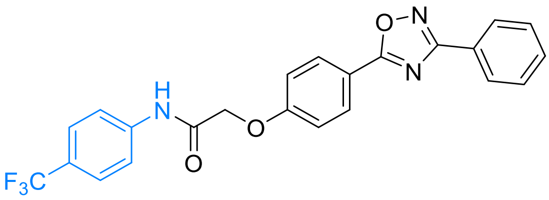
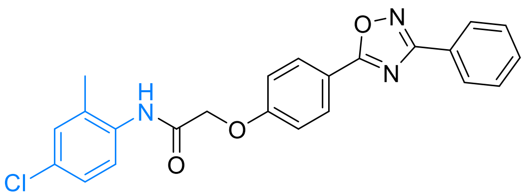
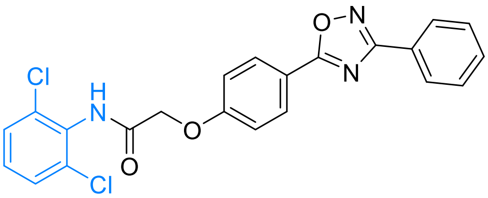
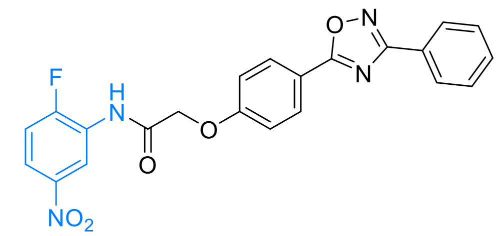
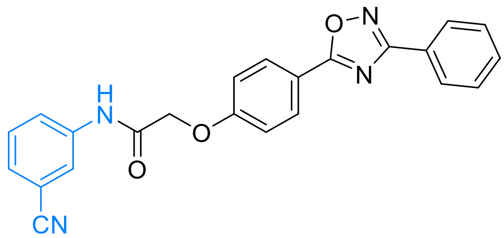
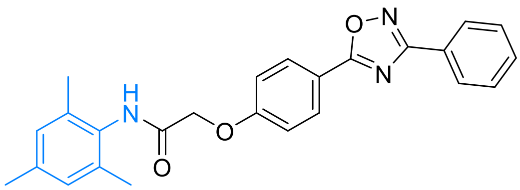
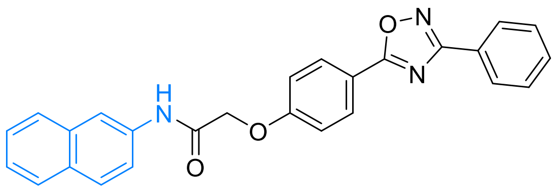
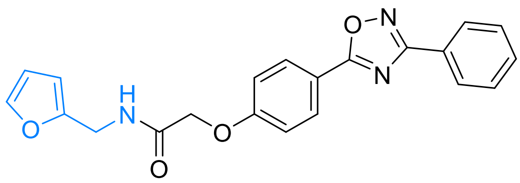
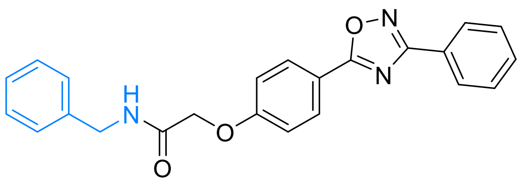
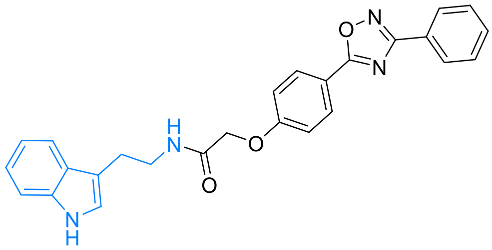
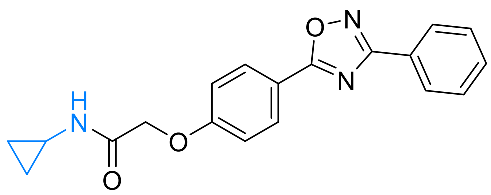
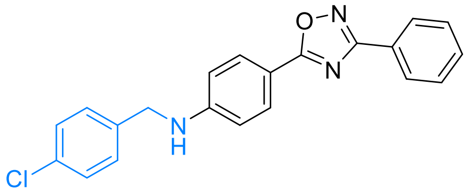
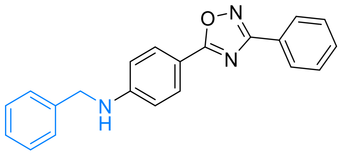
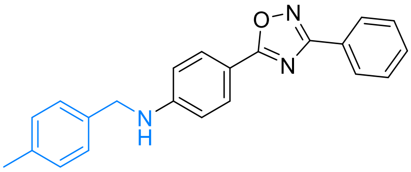
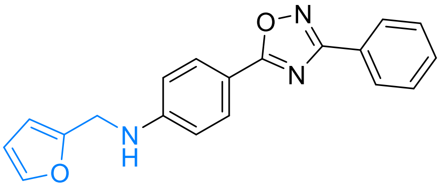
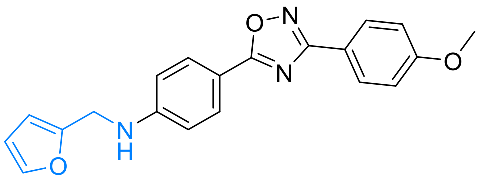
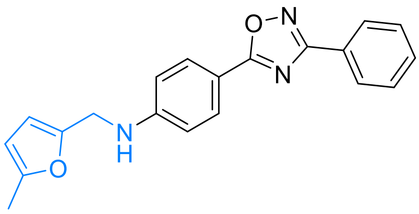
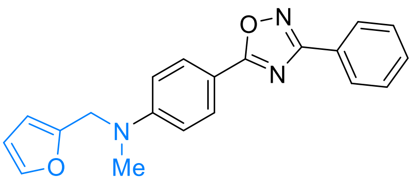
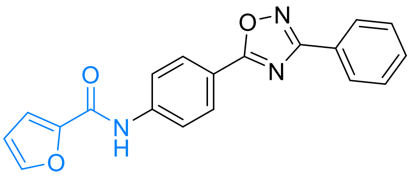


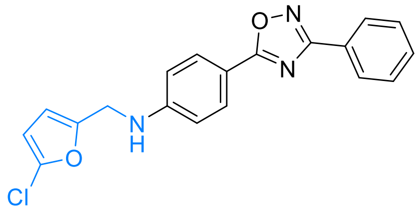
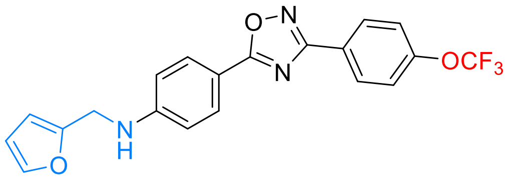
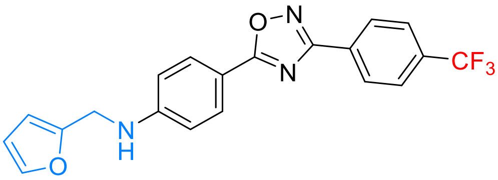
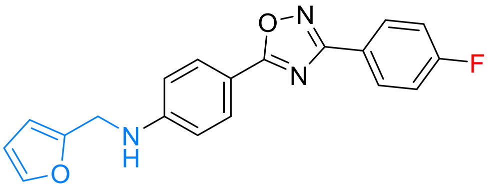
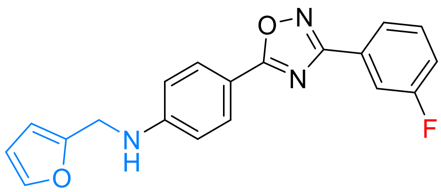
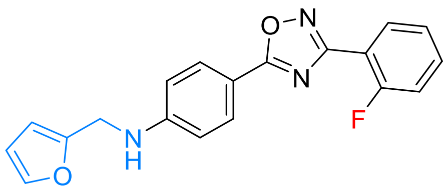
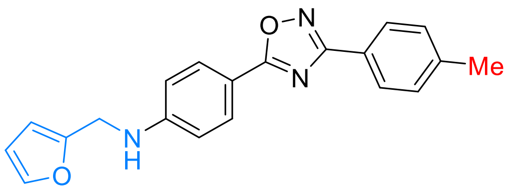
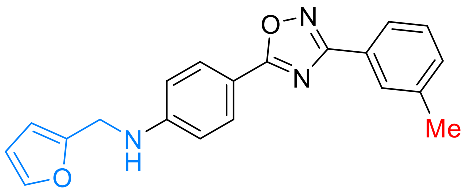
Table S1. Outlook of inhibition activity of TXNIP.

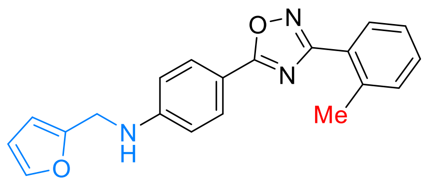
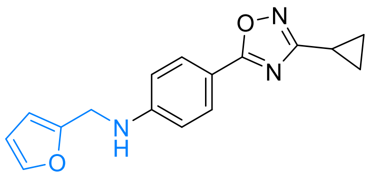
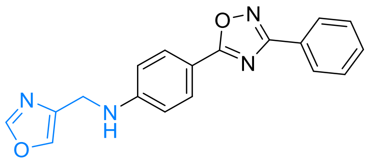
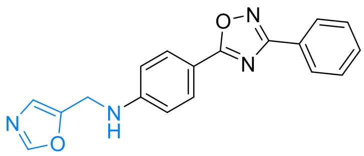
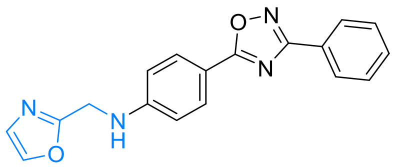
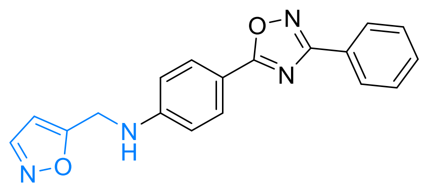
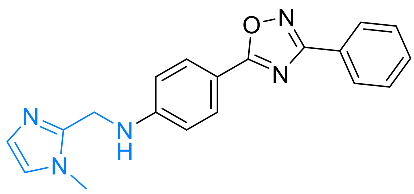
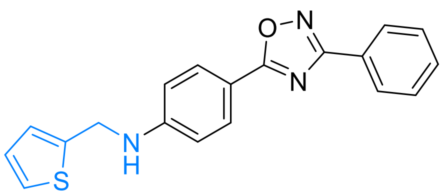
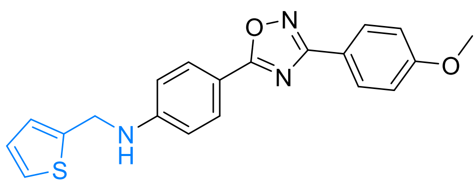
Compounds	Structure	Molecular Weight	Inhibition
SKL-1201		421.47	25μM 40%
SKL-1202		391.45	25μM 10%
SKL-1203		391.45	25μM 10%

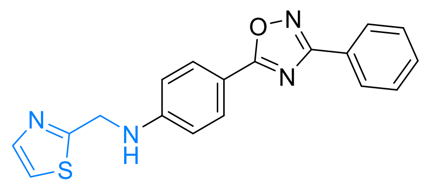
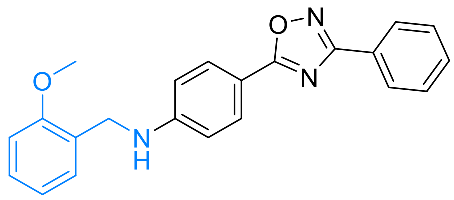
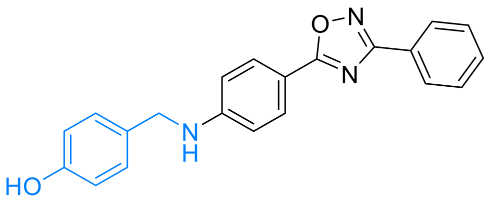
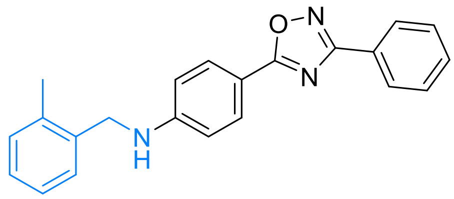
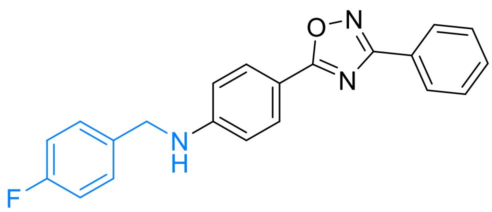
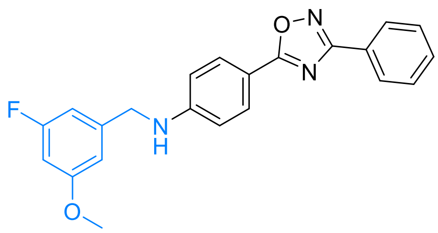
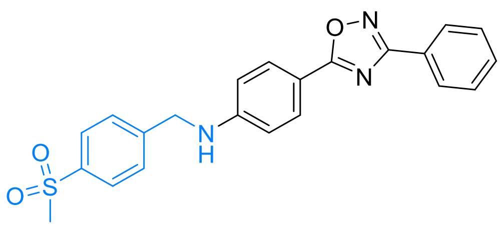
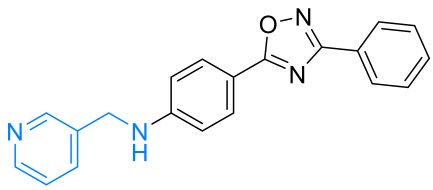
SKL-1204		391.45	25µM 16%
SKL-1205		409.44	5µM Inactive
SKL-1206		441.51	5µM 30%
SKL-1207		324.14	25µM Inactive
SKL-1208		401.42	25µM Inactive
SKL-1209		439.39	25µM Inactive
SKL-1210		419.87	25µM 35%
SKL-1211		440.28	25µM 24%

SKL-1212		434.38	25μM 36%
SKL-1213		396.41	25μM 40%
SKL-1214		413.48	25μM 11%
SKL-1215		421.46	25μM 20%
SKL-1216		375.38	IC_{50} 25μM
SKL-1217		371.40	25μM 30%
SKL-1218		438.49	25μM 15%
SKL-1219		335.36	25μM 70%

SKL-1220		361.83	25μM 85% 5μM 30%
SKL-1221		327.14	25μM 99% 5μM 62%
SKL-1222		341.41	5μM Inactive
SKL-1223		317.35	25μM 99% 5μM 99% 1μM 70% IC_{50} 0.4μM
SKL-1224		347.37	5μM 30%
SKL-1225		331.38	1μM 15%
SKL-1226		331.38	IC_{50} 1μM
SKL-1227		331.33	1μM Inactive

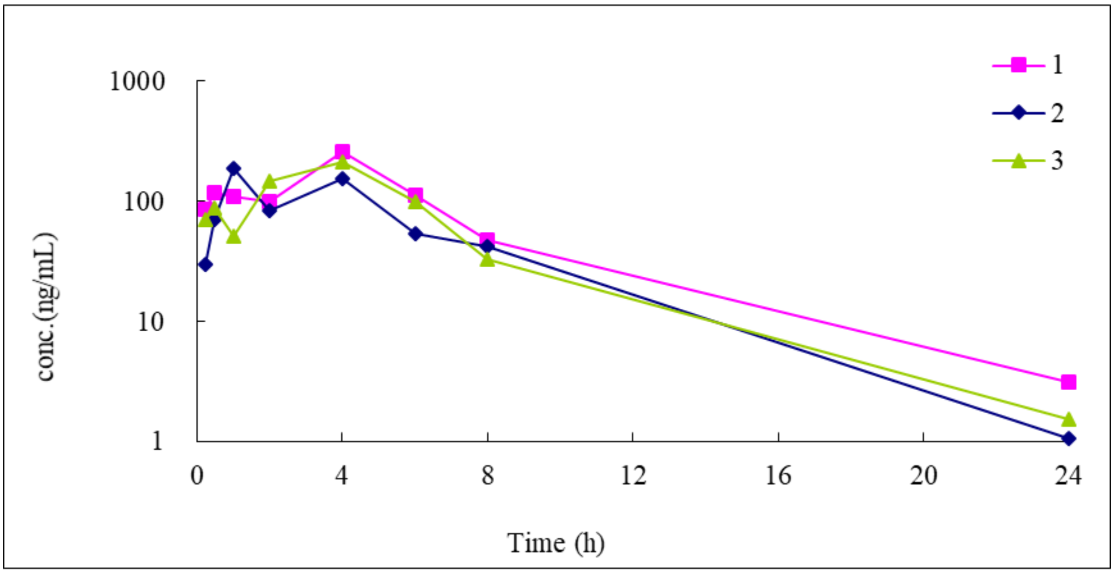
SKL-1228		351.79	1μM 20%
SKL-1229		401.35	1μM Inactive
SKL-1230		385.35	1μM Inactive
SKL-1231		335.34	1μM 84%
SKL-1232		335.34	1μM Inactive
SKL-1233		335.34	1μM Inactive
SKL-1234		331.38	1μM Inactive
SKL-1235		331.38	1μM 17%

SKL-1236		331.38	1µM 34%
SKL-1237		281.32	1µM Inactive
SKL-1238		318.34	1µM 78%
SKL-1239		318.34	1µM 66%
SKL-1240		318.34	1µM 32%
SKL-1241		318.34	1µM 63%
SKL-1242		331.38	5 µM 87% 0.5µM 45%
SKL-1243		333.41	25µM 99% 5µM 80% 1µM 35% 0.5µM Inactive
SKL-1244		363.44	25µM Inactive 5µM Inactive 1µM Inactive

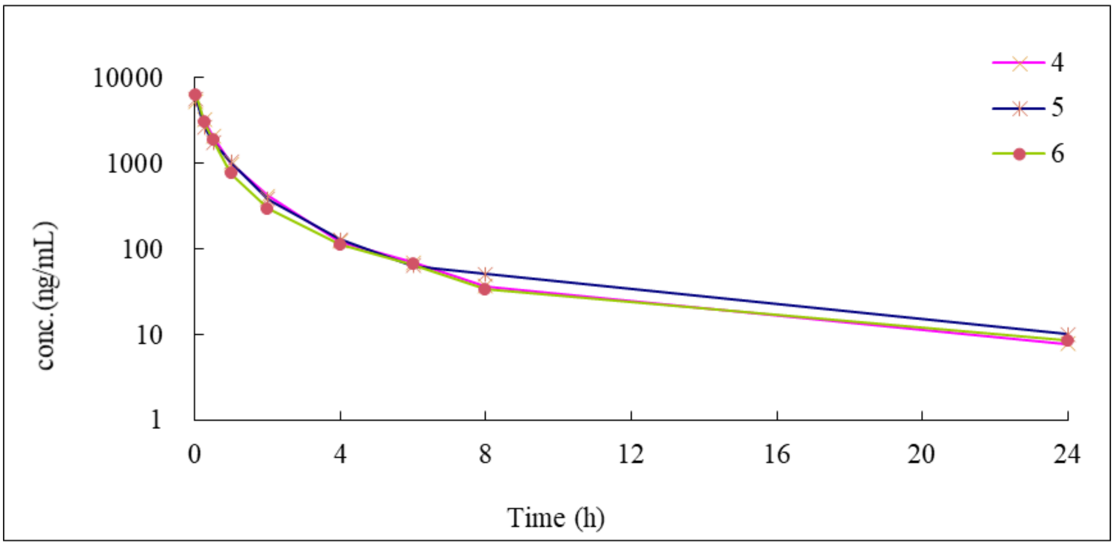
SKL-1245		334.40	5 µM 86% (cytotoxic) IC_{50} 0.5µM
SKL-1246		357.41	25µM 80% 5µM 35%
SKL-1247		343.39	5 µM 99**%** 0.5µM 30**%**
SKL-1248		341.41	5µM 10%
SKL-1249		345.38	5µM 17**%**
SKL-1250		375.40	5µM Inactive
SKL-1251		405.47	5µM Inactive
SKL-1252		328.38	5µM Inactive

The activity was tested via using a dual luciferase assay.

Figure S2. Pharmacokinetic evaluation of SKL-1223



PO dose of 10 mg/kg in Plasma



i.v. dose of 4 mg/kg in Plasma

Table S2. Pharmacokinetic data of SKL-1223

Individual and Mean Plasma Concentration-Time Data of SKL-1223 after an PO Dose of 10 mg·kg⁻¹ in Plasma								
Dose ($mg\cdot kg^{-1}$)	Dose route	Sampling time	Concentration (ng/mL)			Mean (ng/mL)	SD	CV (%)
/	/	(h)	1	2	3	/		
10	PO	0.25	84.6	29.7	70.6	61.64	28.5	46.3
		0.50	118.4	70.5	86.7	91.82	24.4	26.5
		1.00	109.3	188.8	50.9	116.32	69.2	59.5
		2.00	98.9	84.4	146.3	109.87	32.4	29.5
		4.00	257.4	154.5	210.6	207.51	51.5	24.8
		6.00	113.0	54.3	98.7	88.63	30.6	34.5
		8.00	47.0	41.9	32.8	40.60	7.2	17.7
		24.00	3.2	1.1	1.5	1.92	1.1	57.0
		/	/	/	/	/	/	/
PK Parameters		Unit	1	2	3	Mean	SD	/
R^2		NA	0.96	1.00	0.95	0.97	0.0	/
$T_{1/2}$		h	3.70	3.12	3.21	3.34	0.3	/
T_{max}		h	4.00	1.00	4.00	3.00	1.7	/
C_{max}		ng/mL	257.44	188.76	210.59	218.93	35.1	/
AUC_{last}		h*ng/mL	1485.09	1105.56	1233.97	1274.87	193.0	/
AUC_{0-inf}		h*ng/mL	1501.89	1110.37	1241.05	1284.44	199.3	/
Vz_F_obs		mL/kg	35530.57	40492.14	37272.41	37765.04	2517.2	/
Cl_F_obs		mL/h/kg	6658.26	9006.04	8057.69	7907.33	1181.1	/
MRT_{last}		h	5.26	4.99	4.88	5.05	0.2	/
/		/	/	/	/	/	/	/
/		/	/	/	/	/	/	/
Individual and Mean Plasma Concentration-Time Data of SKL-1223 after an PO Dose of 10 mg·kg⁻¹ in Plasma								

Individual and Mean Plasma Concentration-Time Data of SKL-1223 after an i.v. Dose of 4 mg·kg⁻¹ in Plasma								
Dose ($mg\cdot kg^{-1}$)	Dose route	Sampling time	Concentration (ng/mL)			Mean (ng/mL)	SD	CV (%)
/	/	(h)	4	5	6	/		
4.0	IV	0.03	5336.9	5533.3	6141.8	5670.68	419.7	7.4
		0.25	3191.9	2662.0	3048.5	2967.43	274.1	9.2
		0.50	2070.5	1750.3	1843.8	1888.19	164.7	8.7
		1.00	987.2	1024.4	755.9	922.50	145.5	15.8
		2.00	415.3	379.9	291.5	362.24	63.8	17.6
		4.00	121.8	128.7	112.5	120.97	8.2	6.7
		6.00	69.6	64.1	65.8	66.48	2.8	4.3
		8.00	36.8	51.2	33.5	40.50	9.4	23.2
		24.00	7.8	10.1	8.5	8.78	1.2	13.5
PK Parameters		Unit	4	5	6	Mean	SD	/
R^2		NA	0.9324	0.9998	0.8985	0.94	0.1	/
$T_{1/2}$		h	6.17	6.78	6.72	6.56	0.3	/
T_{max}		h	0.033	0.033	0.033	0.03	0.0	/
C_0		ng/mL	5770.80	6184.64	6832.20	6262.55	535.0	/
AUC_{last}		h*ng/mL	4423.52	4336.54	4013.81	4257.96	215.9	/
AUC_{0-inf}		h*ng/mL	4492.67	4435.10	4096.06	4341.27	214.3	/
Vz_obs		mL/kg	7923.75	8818.19	9470.80	8737.58	776.7	/
Cl_obs		mL/h/kg	890.34	901.90	976.55	922.93	46.8	/
MRT_{last}		h	1.93	2.27	1.92	2.04	0.2	/
Vss_obs		mL/kg	2141.99	2676.43	2501.52	2439.98	272.5	/
/		/	/	/	/	/	/	/
Individual and Mean Plasma Concentration-Time Data of SKL-1223 after an i.v. Dose of 4 mg·kg⁻¹ in Plasma								

Figure S3. The transcriptome data of SKL-1223 in rat INS-1 cell.

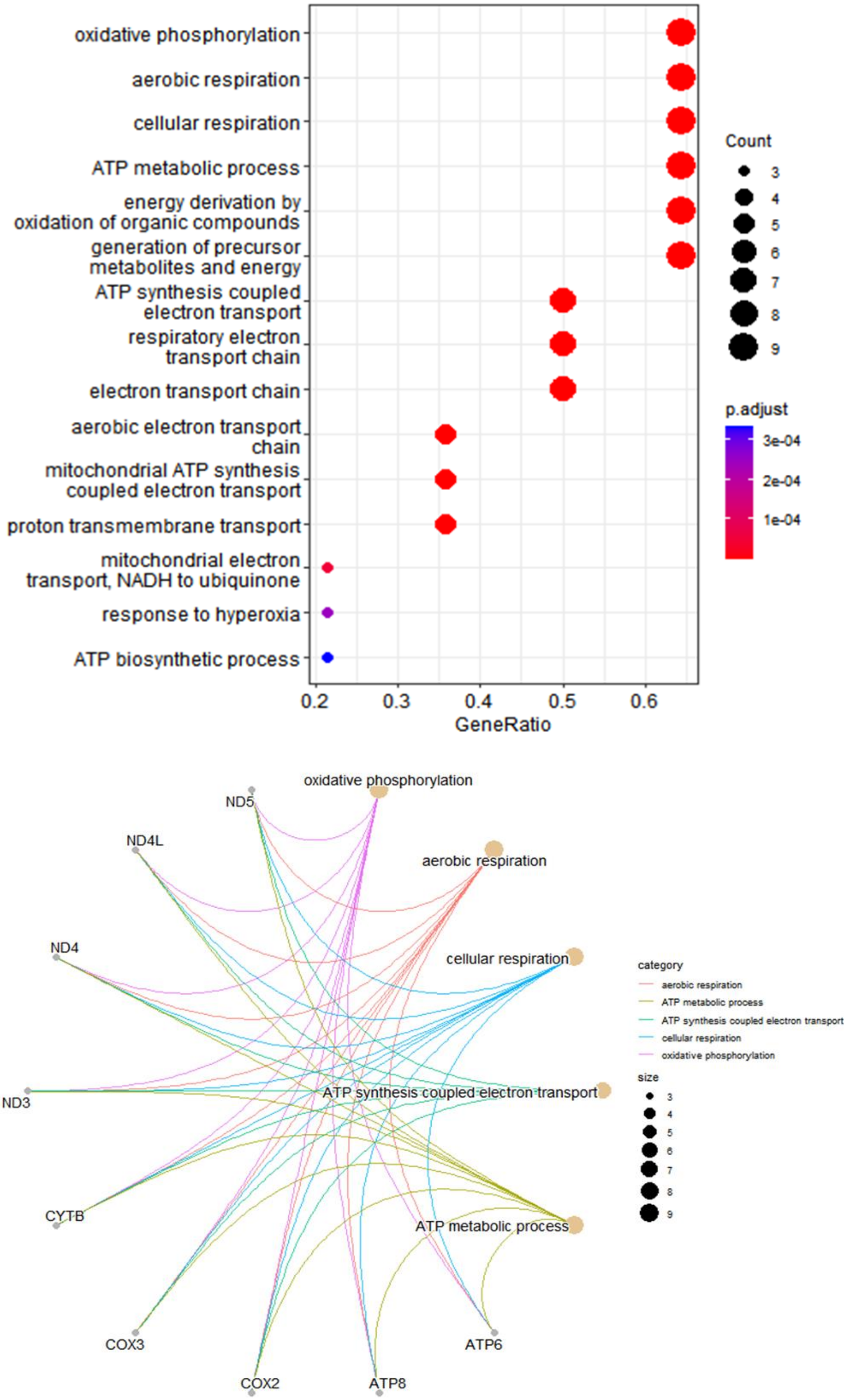
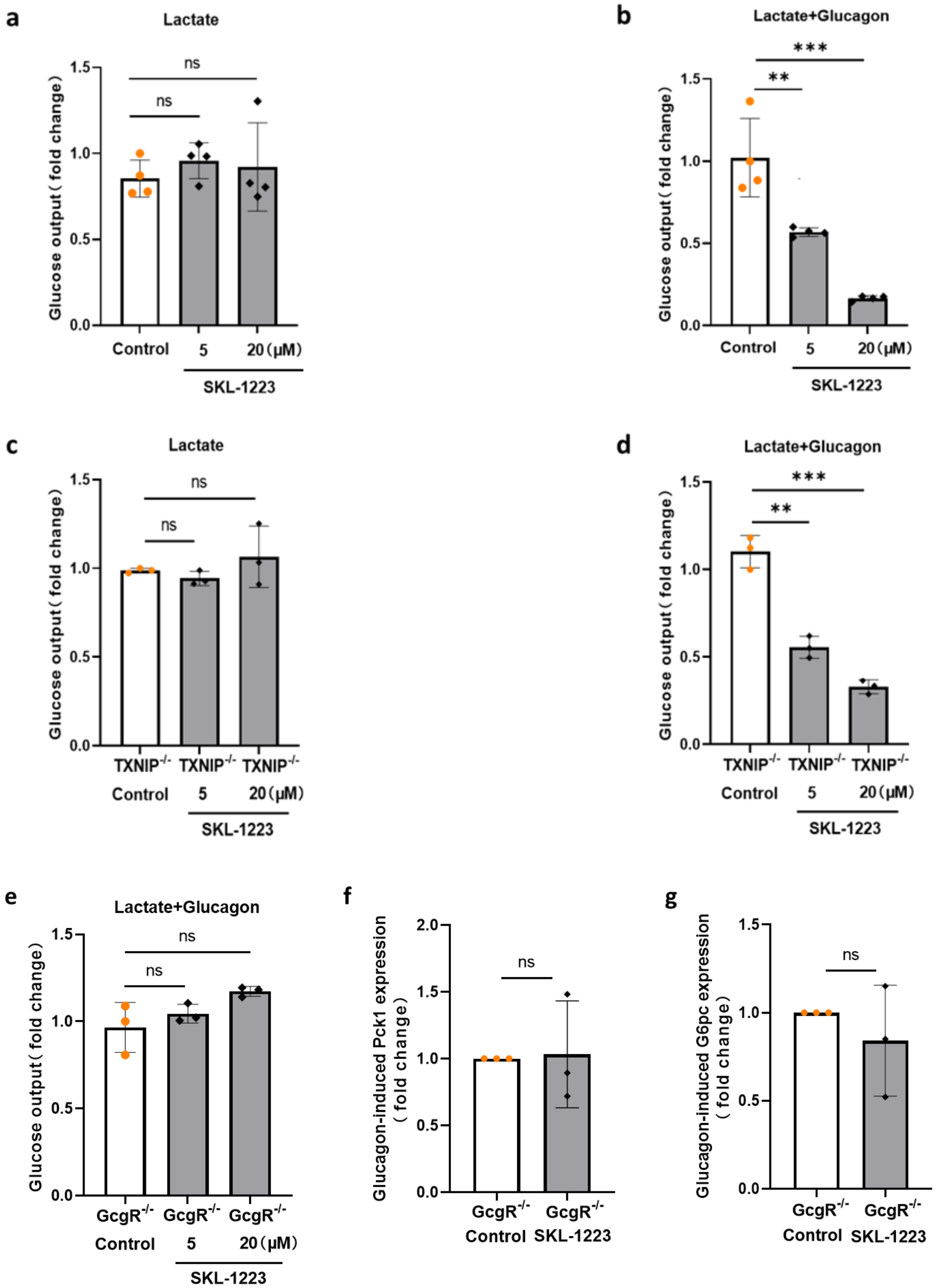


Figure S4. | SKL-1223 suppresses glucagon-induced glucose production in primary hepatocytes.



(a) Glucose release was evaluated in lactate in primary mouse hepatocytes treated with or without SKL-1223 at indicated concentrations. (b) Glucose release was evaluated in the presence of lactate (10 nM) and glucagon (100 nM) in primary mouse hepatocytes treated with or without SKL-1223 at indicated concentrations. (c) Glucose release was evaluated in lactate in TXNIP-/- primary mouse hepatocytes treated with or without SKL-1223 at indicated concentrations. (d) Glucose release was evaluated in the presence of lactate (10 nM) and glucagon (100 nM) in TXNIP-/- primary mouse hepatocytes treated with or without SKL-1223 at indicated concentrations. (e) Glucose release was evaluated in the presence of lactate (10 nM) and glucagon (100 nM) in GcgR-/- primary mouse hepatocytes treated with or without SKL-1223 at indicated concentrations.

(f-g) Quantification of Pck1 and G6pc genes expression using qPCR in GcgR-/- primary mouse hepatocytes in the presence of glucagon treated with SKL-1223. The experiments were independently repeated three times (n = 3), statistics were analyzed using an unpaired Student's t test: *, P < 0.05; **, P < 0.01; ***, P < 0.001. Data are mean ± SD.

Table S3. Data analysis of SKL-1201~SKL-1252

Compounds	NMRs	MS spectrum
SKL-1201	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 8.86 (t, *J* = 5.6 Hz, 1H), 8.12 (d, *J* = 8.8 Hz, 2H), 8.01 (d, *J* = 8.7 Hz, 2H), 7.39 (d, *J* = 4.4 Hz, 1H), 7.20 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 3.4 Hz, 1H), 6.95 (t, *J* = 8.0 Hz, 1H), 4.69 (s, 2H), 4.52 (d, *J* = 5.8 Hz, 2H), 3.84 (s, 3H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 174.9, 167.8, 167.0, 161.7, 161.4, 142.0, 129.8, 128.8, 126.6, 125.6, 125.1, 118.6, 116.4, 115.7, 114.6, 66.9, 55.4, 37.0.	**[M+H]** 422.2
SKL-1202	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 8.86 (t, *J* = 5.9 Hz, 1H), 8.14 (d, *J* = 8.9 Hz, 2H), 8.08 (dd, *J* = 7.5, 2.0 Hz, 2H), 7.64 – 7.56 (m, 3H), 7.39 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.21 (d, *J* = 8.9 Hz, 2H), 6.99 (d, *J* = 2.4 Hz, 1H), 6.95 (dd, *J* = 5.0, 3.4 Hz, 1H), 4.69 (s, 2H), 4.52 (d, *J* = 6.0 Hz, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.2, 168.2, 167.0, 161.6, 142.1, 131.6, 129.9, 129.3, 127.1, 126.7, 126.3, 125.6, 125.2, 116.3, 115.8, 66.9, 37.0.	**[M+H]** 392.1
SKL-1203	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 8.89 (t, *J* = 5.9 Hz, 1H), 8.09 (dd, *J* = 7.5, 1.7 Hz, 2H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.74 (s, 1H), 7.66 – 7.55 (m, 4H), 7.39 – 7.30 (m, 2H), 6.98 (d, *J* = 2.7 Hz, 1H), 6.92 (dd, *J* = 5.0, 3.5 Hz, 1H), 4.69 (s, 2H), 4.53 (d, *J* = 6.0 Hz, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.2, 168.3, 167.2, 158.1, 142.1, 131.7, 130.9, 129.3, 127.1, 126.6, 126.1, 125.5, 125.0, 124.4, 120.8, 119.8, 114.0, 67.0, 36.9.	**[M+H]** 392.1
SKL-1204	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 8.78 (t, *J* = 6.0 Hz, 1H), 8.12 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.03 (d, *J* = 7.0 Hz, 2H), 7.68 (t, *J* = 7.9 Hz, 1H), 7.64 – 7.52 (m, 3H), 7.35 (d, *J* = 4.7 Hz, 1H), 7.24 (dd, *J* = 17.1, 8.2 Hz, 2H), 6.90 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.85 (d, *J* = 3.0 Hz, 1H), 4.82 (s, 2H), 4.57 (d, *J* = 6.1 Hz, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 174.2, 167.9, 167.3, 156.1, 141.8, 134.9, 131.6, 130.9, 129.3, 127.1, 126.7, 126.3, 125.3, 125.1, 121.8, 114.3, 112.4, 67.5, 37.0.	**[M+H]** 392.1
SKL-1205	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 8.86 (t, *J* = 6.0 Hz, 1H), 8.18 – 8.08 (m, 4H), 7.43 (t, *J* = 8.9 Hz, 2H), 7.39 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.21 (d, *J* = 9.0 Hz, 2H), 6.99 (dd, *J* = 3.3, 1.1 Hz, 1H), 6.95 (dd, *J* = 5.0, 3.4 Hz, 1H), 4.69 (s, 2H), 4.52 (d, *J* = 6.0 Hz, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.3, 167.4, 167.0, 164.0 (d, *J* = 248.8 Hz), 161.6, 142.0, 129.9, 129.6 (d, *J* = 9.0 Hz), 126.7,	**[M+H]** 410.1

	125.6, 125.1, 122.9 (d, *J* = 3.2 Hz), 116.4 (d, *J* = 22.2 Hz), 116.2, 115.8, 66.9, 37.0.	
SKL-1206	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 8.91 – 8.80 (m, 2H), 8.31 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.20 (d, *J* = 8.9 Hz, 3H), 8.09 (d, *J* = 7.7 Hz, 1H), 7.71 (t, 2H), 7.70 – 7.61 (m, 1H), 7.40 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.24 (d, *J* = 8.9 Hz, 2H), 6.99 (d, *J* = 2.4 Hz, 1H), 6.96 (dd, *J* = 5.0, 3.5 Hz, 1H), 4.71 (s, 2H), 4.53 (d, *J* = 6.0 Hz, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 174.4, 168.6, 167.0, 161.6, 142.1, 133.5, 132.0, 130.0, 129.9, 129.4, 128.9, 127.8, 126.7, 126.6, 125.7, 125.6, 125.4, 125.2, 123.2, 116.3, 115.8, 66.9, 37.0.	**[M+H]** 442.1
SKL-1207	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 10.19 (s, 1H), 8.16 (d, *J* = 8.9 Hz, 2H), 8.08 (dd, *J* = 7.5, 2.0 Hz, 2H), 7.67 – 7.54 (m, 5H), 7.33 (t, *J* = 7.9 Hz, 2H), 7.26 (d, *J* = 8.9 Hz, 2H), 7.09 (t, *J* = 7.4 Hz, 1H), 4.87 (s, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.3, 168.2, 165.2, 161.8, 138.4, 131.6, 130.0, 129.3, 128.8, 127.1, 126.3, 123.8, 119.7, 116.3, 115.7, 67.1, 40.2, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9.	**[M+H]** 372.2
SKL-1208	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 10.04 (s, 1H), 8.16 (d, *J* = 8.9 Hz, 2H), 8.09 (dd, *J* = 7.5, 2.0 Hz, 2H), 7.65 – 7.55 (m, 3H), 7.55 (d, *J* = 9.1 Hz, 2H), 7.26 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 9.1 Hz, 2H), 4.83 (s, 2H), 3.73 (s, 3H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.2, 168.1, 165.4, 161.7, 155.6, 131.6, 131.4, 129.9, 129.2, 127.1, 126.3, 121.4, 116.3, 115.7, 113.9, 67.1, 55.2.	**[M+H]** 402.1
SKL-1209	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 10.64 (s, 1H), 8.16 (d, *J* = 8.9 Hz, 2H), 8.12 – 8.05 (m, 2H), 7.87 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.65 – 7.55 (m, 3H), 7.26 (d, *J* = 9.0 Hz, 2H), 4.93 (s, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.2, 168.2, 166.6, 161.7, 142.0, 131.6, 130.0, 129.3, 127.1, 126.3, 126.1 (d, *J* = 4.0 Hz), 123.7 (d, *J* = 32.0 Hz), 119.6, 116.4, 115.7, 115.5, 67.0.	**[M+H]** 440.2
SKL-1210	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 9.68 (s, 1H), 8.18 (d, *J* = 8.8 Hz, 2H), 8.10 (dd, *J* = 7.4, 1.9 Hz, 2H), 7.65 – 7.57 (m, 3H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.34 (d, *J* = 2.0 Hz, 1H), 7.31 – 7.23 (m, 3H), 4.92 (s, 2H), 2.21 (s, 3H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.2, 168.2, 166.2, 161.6, 134.6, 134.5, 131.6, 130.0, 129.9, 129.5, 129.2, 127.1, 126.8, 126.3, 125.9, 116.4, 115.8, 67.0, 17.5.	**[M+H]** 420.2
SKL-1211	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 10.23 (s, 1H), 8.19 (d, *J* = 8.7 Hz, 2H), 8.09 (dd, *J* = 7.5, 1.9 Hz, 2H), 7.65 – 7.52 (m, 5H), 7.38 (t, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 4.94 (s, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.2, 168.2, 166.4, 161.5, 133.9, 132.2, 131.6, 129.9, 129.6, 129.3, 128.6, 127.1, 126.3, 116.5, 115.9, 66.7, 40.2, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9.	**[M+H]** 441.0

SKL-1212	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 10.49 (s, 1H), 8.92 (dd, J = 6.4, 2.6 Hz, 1H), 8.16 (d, J = 8.7 Hz, 2H), 8.13 – 8.04 (m, 3H), 7.60 (d, J = 7.3 Hz, 4H), 7.25 (d, J = 8.7 Hz, 2H), 5.03 (s, 2H). **^{13}C NMR** (151 MHz, d_6-DMSO) δ 175.2, 168.1, 167.1, 161.6, 156.8 (d, J = 256.3 Hz), 143.7, 131.6, 130.0, 129.2, 127.1, 126.7 (d, J = 13.3 Hz), 126.3, 121.0 (d, J = 9.5 Hz), 118.6, 116.8 (d, J = 22.4 Hz), 116.4, 115.6, 66.7.	**[M+H]** 435.2
SKL-1213	**^{1}H NMR** (600 MHz, d_6-DMSO) δ 10.52 (s, 1H), 8.16 (d, J = 8.9 Hz, 2H), 8.12 (s, 1H), 8.08 (dd, J = 7.9, 1.6 Hz, 2H), 7.92 – 7.87 (m, 1H), 7.64 – 7.51 (m, 5H), 7.27 (d, J = 8.9 Hz, 2H), 4.91 (s, 2H). **^{13}C NMR** (151 MHz, d_6-DMSO) δ 175.2, 168.2, 166.7, 161.6, 139.1, 131.6, 130.3, 130.0, 129.3, 127.4, 127.1, 126.3, 124.3, 122.4, 118.6, 116.4, 115.8, 111.6, 67.0.	**[M+H]** 397.2
SKL-1214	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 9.51 (s, 1H), 8.18 (d, J = 8.9 Hz, 2H), 8.09 (dd, J = 7.5, 2.0 Hz, 2H), 7.67 – 7.55 (m, 3H), 7.29 (d, J = 8.9 Hz, 2H), 6.88 (s, 2H), 4.88 (s, 2H), 2.22 (s, 3H), 2.09 (s, 6H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.2, 168.2, 165.9, 161.7, 135.7, 135.0, 131.6, 131.6, 129.9, 129.3, 128.3, 127.1, 126.3, 116.3, 115.8, 67.0, 20.5, 18.0.	**[M+H]** 414.2
SKL-1215	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 10.40 (s, 1H), 8.33 (s, 1H), 8.18 (d, J = 8.8 Hz, 2H), 8.09 (dd, J = 7.4, 1.9 Hz, 2H), 7.90 (d, J = 8.9 Hz, 1H), 7.84 (t, J = 8.4 Hz, 2H), 7.67 (dd, J = 8.8, 1.9 Hz, 1H), 7.66 – 7.53 (m, 3H), 7.48 (t, J = 7.0 Hz, 1H), 7.42 (t, J = 6.9 Hz, 1H), 7.30 (d, J = 8.9 Hz, 2H), 4.95 (s, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.2, 168.2, 166.2, 161.8, 135.9, 133.3, 131.6, 130.0, 129.3, 128.4, 127.5, 127.4, 127.1, 126.5, 126.3, 124.8, 120.2, 116.3, 115.9, 115.8, 67.1.	**[M+H]** 422.3
SKL-1216	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 8.71 (t, J = 5.7 Hz, 1H), 8.14 (d, J = 8.9 Hz, 2H), 8.08 (dd, J = 7.5, 2.0 Hz, 2H), 7.66 – 7.55 (m, 4H), 7.21 (d, J = 8.9 Hz, 2H), 6.39 (dd, J = 3.0, 1.9 Hz, 1H), 6.25 (d, J = 2.5 Hz, 1H), 4.69 (s, 2H), 4.35 (d, J = 5.8 Hz, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.2, 168.1, 167.0, 161.6, 152.0, 142.1, 131.6, 129.9, 129.2, 127.1, 126.3, 116.3, 115.7, 110.5, 107.0, 66.9, 35.3.	**[M+H]** 376.2
SKL-1217	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 8.76 (t, J = 5.9 Hz, 1H), 8.15 (d, J = 8.8 Hz, 2H), 8.09 (dd, J = 7.4, 1.9 Hz, 2H), 7.64 – 7.57 (m, 3H), 7.34 – 7.21 (m, 7H), 4.72 (s, 2H), 4.37 (d, J = 6.1 Hz, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.2, 168.2, 167.2, 161.6, 139.2, 131.6, 129.9, 129.3, 128.3, 127.3, 127.1, 126.8, 126.3, 116.3, 115.8, 67.0, 41.9.	**[M+H]** 386.2
SKL-1218	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 10.83 (s, 1H), 8.30 (t, J = 5.8 Hz, 1H), 8.14 (d, J = 8.6 Hz, 2H), 8.09 (dd, J = 8.0, 4 Hz, 2H), 7.65 – 7.52 (m, 4H), 7.34 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 8.8 Hz, 2H), 7.16 (s, 1H), 7.07 (t, J = 7.4 Hz, 1H), 6.98 (t, J = 7.3 Hz, 1H), 4.63	**[M+H]** 439.2

	(s, 2H), 3.44 (q, J = 6.9 Hz, 2H), 2.88 (t, J = 7.2 Hz, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.2, 168.1, 166.9, 161.6, 136.2, 131.6, 129.9, 129.2, 127.2, 127.1, 126.3, 122.7, 120.9, 118.2, 116.3, 115.7, 111.6, 111.4, 67.0, 25.1.	
SKL-1219	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 8.24 (d, J = 3.8 Hz, 1H), 8.14 (d, J = 8.9 Hz, 2H), 8.09 (dd, J = 7.5, 2.0 Hz, 2H), 7.64 – 7.57 (m, 3H), 7.19 (d, J = 8.9 Hz, 2H), 4.59 (s, 2H), 2.70 (tt, J = 7.8, 4.0 Hz, 1H), 0.68 – 0.61 (m, 2H), 0.52 – 0.44 (m, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.3, 168.2, 168.1, 161.7, 131.6, 129.9, 129.3, 127.1, 126.3, 116.2, 115.7, 66.9, 22.2, 5.6.	**[M+H]** 336.2
SKL-1220	**^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.18 – 8.13 (m, 2H), 8.02 (d, J = 8.8 Hz, 2H), 7.52 – 7.47 (m, 3H), 7.34 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 6.68 (d, J = 8.8 Hz, 2H), 4.60 (t, J = 5.4 Hz, 1H), 4.41 (d, J = 5.6 Hz, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.9, 167.8, 152.5, 138.3, 131.4, 131.4, 129.6, 129.2, 129.0, 128.4, 127.0, 126.7, 112.2, 110.0, 45.0.	**[M+H]** 362.2
SKL-1221	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (dd, J = 6.6, 3.2 Hz, 2H), 8.02 (d, J = 8.8 Hz, 2H), 7.55 – 7.45 (m, 3H), 7.43 – 7.28 (m, 5H), 6.71 (d, J = 8.8 Hz, 2H), 4.60 (t, J = 5.4 Hz, 1H), 4.43 (d, J = 5.4 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.2, 168.8, 151.6, 138.3, 131.0, 130.2, 129.0, 128.9, 127.8, 127.6 (two carbons), 113.1, 112.5, 77.4, 47.8.	**[M+H]** 328.2
SKL-1222	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (dd, J = 6.6, 3.2 Hz, 2H), 8.02 (d, J = 8.8 Hz, 2H), 7.54 – 7.44 (m, 3H), 7.26 (d, J = 15.0 Hz, 1H), 7.21 – 7.09 (m, 3H), 6.71 (d, J = 8.8 Hz, 2H), 4.56 (t, J = 5.3 Hz, 1H), 4.38 (d, J = 5.5 Hz, 2H), 2.36 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.3, 168.7, 151.7, 137.5, 135.2, 131.0, 130.1, 129.6, 128.9, 127.6 (two carbons), 113.0, 112.5, 77.4, 47.6, 21.2.	**[M+H]** 342.2
SKL-1223	**^{1}H NMR** (600 MHz, d_6-DMSO) δ 8.06 (dd, J = 7.8, 1.7 Hz, 2H), 7.89 (d, J = 8.8 Hz, 2H), 7.62 – 7.54 (m, 4H), 7.20 (t, J = 5.9 Hz, 1H), 6.83 (d, J = 8.9 Hz, 2H), 6.41 (dd, J = 3.1, 1.8 Hz, 1H), 6.36 (d, J = 3.1 Hz, 1H), 4.38 (d, J = 5.9 Hz, 2H). **^{13}C NMR** (151 MHz, d_6-DMSO) δ 176.0, 167.9, 152.4, 152.2, 142.3, 131.4, 129.5, 129.2, 127.0, 126.7, 112.2, 110.5, 110.1, 107.4, 39.2.	**[M+H]** 318.2
SKL-1224	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 7.99 (d, J = 8.9 Hz, 2H), 7.88 (d, J = 8.8 Hz, 2H), 7.60 (dd, J = 1.7, 0.7 Hz, 1H), 7.20 (t, J = 5.9 Hz, 1H), 7.11 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 8.9 Hz, 2H), 6.41 (dd, J = 3.1, 1.9 Hz, 1H), 6.36 (d, J = 2.9 Hz, 1H), 4.37 (d, J = 5.9 Hz, 2H), 3.84 (s, 3H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.6, 167.5, 161.6, 152.4,	**[M+H]** 348.2

	152.3, 142.3, 129.5, 128.7, 119.0, 114.6, 112.2, 110.5, 110.2, 107.4, 55.4, 39.2.	
SKL-1225	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 8.06 (dd, *J* = 7.4, 2.2 Hz, 2H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.62 – 7.54 (m, 3H), 7.17 (t, *J* = 5.8 Hz, 1H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.22 (d, *J* = 2.9 Hz, 1H), 6.00 (d, *J* = 2.8 Hz, 1H), 4.30 (d, *J* = 5.8 Hz, 2H), 2.23 (s, 3H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.9, 167.8, 152.4, 150.8, 150.3, 131.3, 129.5, 129.2, 127.0, 126.7, 112.1, 110.0, 108.2, 106.4, 39.2, 13.3.	**[M+H]** 332.2
SKL-1226	**^{1}H NMR** (600 MHz, d_6-DMSO) δ 8.06 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.96 (d, *J* = 9.0 Hz, 2H), 7.62 – 7.54 (m, 4H), 7.00 (d, *J* = 9.0 Hz, 2H), 6.39 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.35 (d, *J* = 3.0 Hz, 1H), 4.67 (s, 2H), 3.09 (s, 3H). **^{13}C NMR** (151 MHz, d_6-DMSO) δ 175.8, 167.9, 152.1, 151.2, 142.6, 131.3, 129.3, 129.1, 127.0, 126.6, 112.2, 110.3, 110.2, 107.9, 47.9, 38.1.	**[M+H]** 332.2
SKL-1227	**^{1}H NMR** (600 MHz, d_6-DMSO) δ 10.60 (s, 1H), 8.18 (d, *J* = 8.8 Hz, 2H), 8.09 (dd, *J* = 7.8, 1.7 Hz, 2H), 8.07 (d, *J* = 8.8 Hz, 2H), 7.99 (dd, *J* = 1.6, 0.7 Hz, 1H), 7.65 – 7.57 (m, 3H), 7.43 (dd, *J* = 3.5, 0.8 Hz, 2H 1H), 6.74 (dd, *J* = 3.5, 1.7 Hz, 1H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.2, 168.2, 156.5, 147.0, 146.3, 143.2, 131.6, 129.3, 128.9, 127.1, 126.3, 120.3, 118.1, 115.6, 112.4.	**[M+H]** 332.2
SKL-1228	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 8.06 (dd, *J* = 7.5, 2.2 Hz, 2H), 7.90 (d, *J* = 8.9 Hz, 2H), 7.63 – 7.53 (m, 3H), 7.24 (br, 1H), 6.84 (d, *J* = 8.9 Hz, 2H), 6.48 (d, *J* = 3.3 Hz, 1H), 6.41 (d, *J* = 3.3 Hz, 1H), 4.36 (s, 2H). **^{13}C NMR** (151 MHz, d_6-DMSO) δ 175.9, 167.8, 152.4, 152.1, 133.7, 131.3, 129.5, 129.1, 127.0, 126.6, 112.2, 110.4, 110.1, 107.4, 39.1.	**[M+H]** 352.1
SKL-1229	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.60 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.24 (t, *J* = 5.9 Hz, 1H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.41 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.36 (d, *J* = 3.3 Hz, 1H), 4.38 (d, *J* = 5.8 Hz, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 176.2, 166.9, 152.5, 152.2, 150.3, 142.3, 129.6, 129.2, 125.9, 121.6, 120.0 (d, *J* = 257.1 Hz), 112.2, 110.5, 109.9, 107.4, 39.2.	**[M+H]** 402.2
SKL-1230	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 8.25 (d, *J* = 8.1 Hz, 2H), 7.93 (d, *J* = 8.3 Hz, 2H), 7.90 (d, *J* = 8.8 Hz, 2H), 7.60 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.25 (t, *J* = 5.9 Hz, 1H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.41 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.36 (d, *J* = 3.1 Hz, 1H), 4.38 (d, *J* = 5.8 Hz, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 176.4, 166.9, 152.4 (d, *J* = 39.0	**[M+H]** 386.2

	Hz), 142.3, 131.2 (d, J = 32.0 Hz), 130.6, 129.6, 127.8, 126.1 (q, J = 3.7 Hz), 125.2, 122.5, 112.2, 110.4, 109.8, 107.4, 39.2.	
SKL-1231	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 8.08 (td, J = 7.7, 1.7 Hz, 1H), 7.89 (d, J = 8.8 Hz, 2H), 7.69 – 7.62 (m, 1H), 7.60 (dd, J = 1.8, 0.8 Hz, 1H), 7.49 – 7.38 (m, 2H), 7.23 (t, J = 5.9 Hz, 1H), 6.84 (d, J = 8.9 Hz, 2H), 6.41 (dd, J = 3.2, 1.8 Hz, 1H), 6.36 (dd, 1H), 4.38 (d, J = 5.9 Hz, 2H). **^{13}C NMR** (151 MHz, d_6-DMSO) δ 175.9, 167.8, 152.4, 152.1, 133.7, 131.3, 129.5, 129.1, 127.0, 126.5, 112.2, 110.4, 110.1, 107.4, 39.1.	**[M+H]** 336.2
SKL-1232	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 7.92 – 7.87 (m, 3H), 7.78 (ddd, J = 9.6, 2.5, 1.4 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.60 (dd, J = 1.8, 0.8 Hz, 1H), 7.45 (tdd, J = 8.4, 2.7, 0.9 Hz, 1H), 7.23 (t, J = 5.9 Hz, 1H), 6.83 (d, J = 8.9 Hz, 2H), 6.41 (dd, J = 3.2, 1.8 Hz, 1H), 6.36 (dd, J = 3.2, 0.7 Hz, 1H), 4.38 (d, J = 5.9 Hz, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 176.2, 167.0 (d, J = 3.0 Hz), 163.5, 161.1, 152.4 (d, J = 32.7 Hz), 142.3, 131.5 (d, J = 8.4 Hz), 129.6, 128.9 (d, J = 8.5 Hz), 123.2 (d, J = 2.8 Hz), 118.3 (d, J = 21.2 Hz), 113.6 (d, J = 23.5 Hz), 112.2, 110.4, 109.9, 107.4, 39.2.	**[M+H]** 336.2
SKL-1233	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 8.10 (ddd, J = 8.4, 5.3, 2.5 Hz, 2H), 7.89 (d, J = 8.8 Hz, 2H), 7.60 (dd, J = 1.8, 0.8 Hz, 1H), 7.41 (t, J = 8.9 Hz, 2H), 7.22 (t, J = 5.9 Hz, 1H), 6.83 (d, J = 8.9 Hz, 2H), 6.41 (dd, J = 3.2, 1.8 Hz, 1H), 6.36 (dd, J = 3.2, 0.8 Hz, 1H), 4.38 (d, J = 5.9 Hz, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 176.0, 167.0, 165.1, 162.6, 152.4, 152.2, 142.3, 129.6, 129.5, 129.5, 123.2 (d, J = 3.2 Hz), 116.3 (d, J = 22.1 Hz), 112.2, 110.4, 110.0, 107.4, 39.2.	**[M+H]** 336.2
SKL-1234	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 7.94 (d, J = 8.1 Hz, 2H), 7.88 (d, J = 8.8 Hz, 2H), 7.60 (dd, J = 1.8, 0.8 Hz, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.20 (t, J = 5.9 Hz, 1H), 6.83 (d, J = 8.9 Hz, 2H), 6.41 (dd, J = 3.2, 1.9 Hz, 1H), 6.36 (d, J = 3.2 Hz, 1H), 4.37 (d, J = 5.9 Hz, 2H), 2.39 (s, 3H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.8, 167.8, 152.4, 152.2, 142.3, 141.2, 129.7, 129.4, 126.9, 123.9, 112.1, 110.4, 110.2, 107.4, 39.2, 21.1.	**[M+H]** 332.2
SKL-1235	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 7.89 (d, J = 8.9 Hz, 3H), 7.85 (d, J = 7.6 Hz, 1H), 7.60 (dd, J = 1.7, 0.8 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.21 (t, J = 5.8 Hz, 1H), 6.83 (d, J = 8.9 Hz, 2H), 6.41 (dd, J = 3.2, 1.9 Hz, 1H), 6.36 (d, J = 2.7 Hz, 1H), 4.38 (d, J = 5.7 Hz, 2H), 2.41 (s, 3H). **^{13}C NMR** (151 MHz, d_6-DMSO) δ 175.9, 167.9, 152.4, 152.3, 142.3, 138.6, 132.0, 129.5, 129.1, 127.4, 126.6, 124.2, 112.2, 110.5, 110.2, 107.4, 39.2, 20.9.	**[M+H]** 332.2
SKL-1236	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 7.97 (dd, J = 7.6, 1.3 Hz, 1H),	**[M+H]** 332.2

	7.89 (d, *J* = 8.9 Hz, 2H), 7.60 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.46 (td, *J* = 7.5, 1.4 Hz, 1H), 7.44 – 7.33 (m, 2H), 7.19 (t, *J* = 5.9 Hz, 1H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.41 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.36 (dd, *J* = 3.2, 0.8 Hz, 1H), 4.38 (d, *J* = 5.9 Hz, 2H), 2.58 (s, 3H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.4, 169.0, 152.8, 152.7, 142.8, 137.9, 131.8, 131.1, 130.2, 129.9, 126.6, 126.5, 112.6, 110.9, 110.6, 107.8, 39.6, 22.0.	
SKL-1237	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 7.74 (d, *J* = 8.6 Hz, 2H), 7.59 (s, 1H), 7.12 (t, *J* = 5.7 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 2H), 6.39 (t, *J* = 2.5 Hz, 1H), 6.34 (d, *J* = 2.7 Hz, 1H), 4.34 (d, *J* = 5.8 Hz, 2H), 2.09 (tt, *J* = 8.4, 4.9 Hz, 1H), 1.10 – 1.01 (m, 2H), 1.00 – 0.87 (m, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.1, 172.0, 152.3, 152.2, 142.3, 129.2, 112.1, 110.4, 110.3, 107.3, 39.2, 7.3, 6.5.	**[M+H]** 282.2
SKL-1238	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 8.35 (s, 1H), 8.14 – 8.00 (m, 3H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.63 – 7.52 (m, 3H), 7.16 (t, *J* = 5.8 Hz, 1H), 6.83 (d, *J* = 8.9 Hz, 2H), 4.29 (d, *J* = 5.7 Hz, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 176.0, 167.8, 152.5, 152.3, 137.4, 136.3, 131.4, 129.5, 129.2, 127.0, 126.7, 112.2, 110.1, 38.2.	**[M+H]** 319.2
SKL-1239	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 8.32 (s, 1H), 8.06 (dd, *J* = 7.3, 1.9 Hz, 2H), 7.91 (d, *J* = 8.7 Hz, 2H), 7.63 – 7.53 (m, 3H), 7.25 (t, *J* = 5.9 Hz, 1H), 7.13 (s, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.48 (d, *J* = 5.9 Hz, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.9, 167.9, 152.1, 151.8, 149.4, 131.4, 129.5, 129.2, 127.0, 126.7, 123.7, 112.2, 110.5, 36.8.	**[M+H]** 319.1
SKL-1240	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 8.13 – 8.01 (m, 3H), 7.91 (d, *J* = 8.8 Hz, 2H), 7.64 – 7.52 (m, 3H), 7.38 (t, *J* = 6.2 Hz, 1H), 7.18 (s, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.55 (d, *J* = 6.2 Hz, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.9, 167.9, 161.5, 152.2, 140.0, 131.4, 129.5, 129.2, 127.0, 127.0, 126.6, 112.3, 110.7, 39.4.	**[M+H]** 319.2
SKL-1241	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 8.51 (s, 1H), 8.06 (dd, 2H), 7.92 (d, *J* = 8.6 Hz, 2H), 7.64 – 7.52 (m, 3H), 7.39 (t, *J* = 6.0 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.41 (s, 1H), 4.61 (d, *J* = 6.0 Hz, 2H). **^{13}C NMR** (151 MHz, d_6-DMSO) δ 175.9, 169.5, 167.9, 152.1, 150.9, 131.4, 129.6, 129.2, 127.0, 126.6, 112.4, 110.8, 101.8, 38.0.	**[M+H]** 319.2
SKL-1242	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 6.7, 3.0 Hz, 2H), 8.06 (d, *J* = 8.7 Hz, 2H), 7.54 – 7.45 (m, 3H), 7.02 (d, *J* = 1.0 Hz, 1H), 6.91 (d, *J* = 1.1 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 2H), 5.12 (s, 1H), 4.41 (d, *J* = 4.6 Hz, 2H), 3.68 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.2, 168.8, 151.2, 144.1, 131.0, 130.1, 128.9, 127.6 (two carbons), 127.5, 121.9, 113.5, 112.7, 40.3, 32.7.	**[M+H]** 332.3
SKL-1243	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 8.06 (dd, *J* = 7.4, 2.2 Hz, 2H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.64 – 7.52 (m, 3H), 7.40 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.36 (t, *J* = 5.7 Hz, 1H), 7.09 (dd, 1H), 6.99 (dd, *J* = 5.0,	**[M+H]** 334.1

	3.5 Hz, 1H), 6.82 (d, *J* = 8.9 Hz, 2H), 4.58 (d, *J* = 5.9 Hz, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.9, 167.8, 152.3, 142.9, 131.4, 129.5, 129.2, 127.0, 126.9, 126.7, 125.3, 124.9, 112.3, 110.2, 41.2.	
SKL-1244	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 7.99 (d, *J* = 8.9 Hz, 2H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.40 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.34 (t, *J* = 5.9 Hz, 1H), 7.15 – 7.06 (m, 3H), 6.99 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.81 (d, *J* = 8.9 Hz, 2H), 4.58 (d, *J* = 5.9 Hz, 2H), 3.83 (s, 3H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.6, 167.5, 161.6, 152.2, 142.9, 129.5, 128.7, 126.9, 125.3, 124.9, 119.0, 114.6, 112.3, 110.4, 55.4, 41.2.	**[M+H]** 364.1
SKL-1245	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 8.05 (dd, *J* = 7.5, 2.1 Hz, 2H), 7.91 (d, *J* = 8.8 Hz, 2H), 7.77 (d, *J* = 3.3 Hz, 1H), 7.66 – 7.52 (m, 5H), 6.82 (d, *J* = 8.8 Hz, 2H), 4.73 (d, *J* = 6.2 Hz, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 175.9, 170.6, 167.9, 152.1, 142.6, 131.5, 129.7, 129.2, 127.1, 126.6, 120.2, 112.5, 110.9, 44.2.	**[M+H]** 335.2
SKL-1246	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 6.6, 3.2 Hz, 2H), 8.01 (d, *J* = 8.8 Hz, 2H), 7.55 – 7.42 (m, 3H), 7.31 – 7.25 (m, 2H), 6.98 – 6.88 (m, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 4.69 (t, *J* = 5.7 Hz, 1H), 4.42 (d, *J* = 5.9 Hz, 2H), 3.88 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.3, 168.7, 157.5, 152.0, 131.0, 130.1, 129.0, 128.9, 128.8, 127.6, 126.2, 120.8, 112.7, 112.6, 110.6, 77.4, 55.5, 43.1.	**[M+H]** 358.2
SKL-1247	**^{1}H NMR** (400 MHz, d_6-DMSO) δ 9.34 (s, 1H), 8.05 (dd, *J* = 7.4, 2.2 Hz, 2H), 7.86 (d, *J* = 8.8 Hz, 2H), 7.63 – 7.52 (m, 3H), 7.21 (t, *J* = 5.7 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.74 (t, *J* = 9.0 Hz, 4H), 4.25 (d, *J* = 5.7 Hz, 2H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 176.0, 167.8, 156.4, 152.8, 131.4, 129.5, 129.2, 129.0, 128.6, 127.0, 126.7, 115.2, 112.1, 109.6, 45.5.	**[M+H]** 344.2
SKL-1248	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 6.7, 3.0 Hz, 2H), 8.04 (d, *J* = 8.8 Hz, 2H), 7.54 – 7.44 (m, 3H), 7.31 (d, *J* = 7.1 Hz, 1H), 7.27 – 7.16 (m, 3H), 6.71 (d, *J* = 8.8 Hz, 2H), 4.38 (s, 3H), 2.39 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.3, 168.8, 151.7, 138.7, 138.2, 131.0, 130.2, 128.9, 128.5, 128.4, 127.6, 127.6, 124.6, 113.1, 112.5, 77.4, 47.8, 21.7.	**[M+H]** 342.2
SKL-1249	**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 5.4, 2.2 Hz, 2H), 8.02 (d, *J* = 8.8 Hz, 2H), 7.54 – 7.44 (m, 3H), 7.34 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.06 (t, *J* = 8.7 Hz, 2H), 6.70 (d, *J* = 8.8 Hz, 2H), 4.56 (s, 1H), 4.40 (d, *J* = 5.5 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.2, 168.8, 162.4 (d, *J* = 245.8 Hz), 151.4, 134.0 (d, *J* = 3.1 Hz), 131.0, 130.2, 129.2 (d, *J* = 8.1 Hz), 128.9, 127.6 (d, *J* = 7.9 Hz), 115.9 (d, *J* = 21.5 Hz), 113.3,	**[M+H]** 346.2

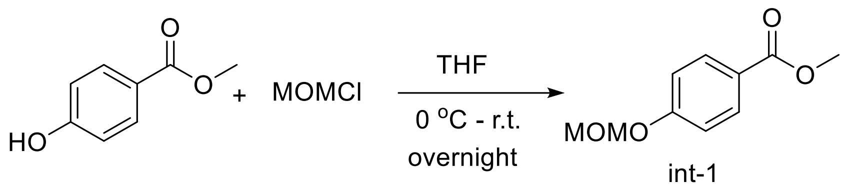
	112.6, 77.4, 47.1.	
SKL-1250	**^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.15 (dd, *J* = 5.2, 2.1 Hz, 2H), 8.01 (d, *J* = 8.8 Hz, 2H), 7.54 – 7.44 (m, 3H), 6.72 – 6.63 (m, 4H), 6.54 (dt, *J* = 10.5, 2.2 Hz, 1H), 4.67 (s, 1H), 4.38 (s, 2H), 3.78 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* 175.2, 167.8, 163.1 (d, *J* = 245.8 Hz), 160.4 (d, *J* = 11.2 Hz), 150.4, 140.7 (d, *J* = 9.0 Hz), 130.0, 129.2, 127.9, 126.6, 126.5, 112.4, 111.6, 107.9 (d, *J* = 2.6 Hz), 105.3 (d, *J* = 22.3 Hz), 99.6 (d, *J* = 25.2 Hz), 54.7, 46.4 (d, *J* = 2.2 Hz).	**[M+H]** 376.2
SKL-1251	**^{1}H NMR** (400 MHz, d_6-DMSO) *δ* 8.04 (dd, *J* = 7.5, 2.1 Hz, 2H), 7.89 (t, *J* = 9.1 Hz, 4H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.62 – 7.52 (m, 3H), 7.46 (t, *J* = 6.1 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 2H), 4.53 (d, *J* = 6.1 Hz, 2H), 3.19 (s, 3H). **^{13}C NMR** (101 MHz, d_6-DMSO) *δ* 175.9, 167.9, 152.4, 145.7, 139.5, 131.4, 129.7, 129.2, 127.9, 127.2, 127.0, 126.7, 112.3, 110.3, 45.3, 43.6.	**[M+H]** 406.2
SKL-1252	**^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.66 (s, 1H), 8.57 (d, *J* = 4.3 Hz, 1H), 8.15 (dd, *J* = 5.4, 2.2 Hz, 2H), 8.03 (d, *J* = 8.8 Hz, 2H), 7.70 (dt, *J* = 8.2, 2.0 Hz, 1H), 7.55 – 7.44 (m, 3H), 7.31 (dd, *J* = 7.7, 4.8 Hz, 1H), 6.71 (d, *J* = 8.8 Hz, 2H), 4.60 (s, 1H), 4.48 (d, *J* = 5.0 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* 176.1, 168.8, 151.2, 149.3, 149.2, 135.2, 133.9, 131.1, 130.2, 128.9, 127.6, 127.5, 123.8, 113.7, 112.7, 45.4.	**[M+H]** 329.2

Chemical synthesis section

General Methods: Unless otherwise stated, all reactions were performed in the appropriate oven-dried glassware. All reagents were obtained commercially as reagent grade and used without further purification. The required starting material and anhydrous solvent were purchased from Energy chemical company. All synthetic transformations were monitored by thin layer chromatography. Column chromatography was performed on silica gel (100 - 200 mesh) that was packed into glass columns. The ^{1}H and ^{13}C NMR spectroscopic were recorded in either $CDCl_3$ or d_6-DMSO as the solvent at 400 or 600 MHz (for ^{1}H NMR) and 101 or 151 MHz (for ^{13}C NMR), respectively. Chemical shifts (*δ*) are reported in units of ppm relative to the residual protio solvent signal for ^{1}H NMR (for $CHCl_3$: *δ* = 7.26 ppm; for d_6-DMSO: *δ* = 2.50 ppm) and solvent signal for ^{13}C NMR (for $CDCl_3$: *δ* = 77.16 ppm; for d_6-DMSO: *δ* = 39.52 ppm). The multiplicities of the signals are reported as s (singlet or broad singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), q (quartet), t (triplet), td (triplet of doublets), tt (triplet of triplets), tdd (triplet of doublets of doublets), m (multiplet), br (broad). And the coupling constants are provided in (*J*) Hz. The mass spectral data was obtained by Agilent LC-ESI-MS 1260 Infinity II system.

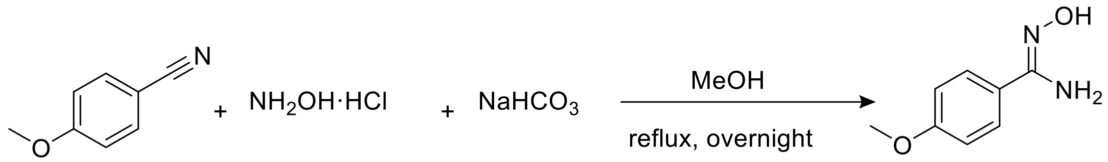
Synthetic route of SKL-1201 and SKL-1223

Synthesis of int-1:



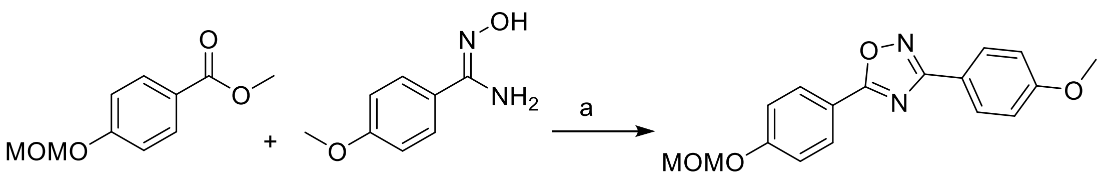
To a solution of methylparaben (20.0 mmol, 3.043 g) in dry THF the NaH (60%, dispersion in mineral oil, 1.5 equiv, 1.200g) was added slowly at 0 °C. After 30 minutes, the MOMCl (chloromethyl methyl ether, 1.2 equiv, 1.9 mL) was added to the mixture dropwise, then the reaction system was warmed up to room temperature and stirred continuously at this temperature overnight. After the reaction finished, quenched the reaction with saturated NH_4Cl solution, and extracted with EtOAc (5 × 10.0 mL). The combined organic layer was washed with saturated brine solution (2 × 10.0 mL) and dried over anhydrous Na_2SO_4. Next, the crude organic phase was concentrated and purified by flash column chromatography eluting with petroleum ether : EtOAc = 30 : 1 to give the compound **int-1** (3.775 g, 96 %) as a colorless oil. R_f = 0.42 (petroleum ether : EtOAc = 20 : 1).

Synthesis of int-2:



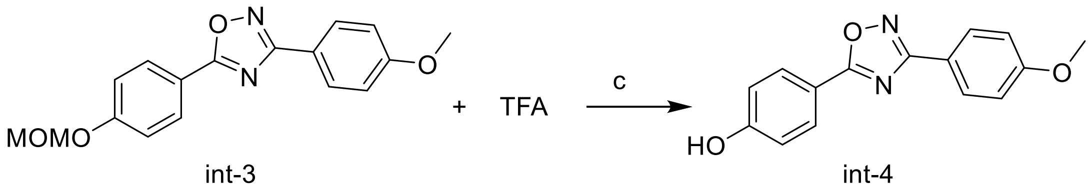
To a solution of $NH_2OH{\cdot}HCl$ (2.0 equiv, 1.390 g) in MeOH (20 mL) was added the $NaHCO_3$ (2.0 equiv, 1.680 g) one portion, then the reaction mixture was stirred at room temperature for 30 minutes. Next, to the mixture was added the anisonitrile (10.00 mmol, 1.331 g), and the resulting mixture was refluxed overnight. After the reflux was completed, the solvent was removed in vacuo to obtain the crude product **int-2**, which was used in the next step without further purification.

Synthesis of int-3:



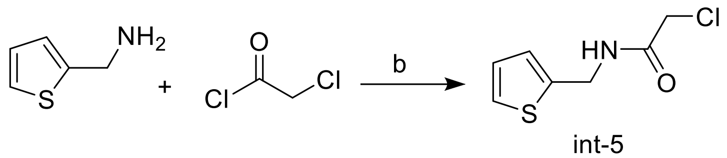
To a solution of **int-1** (1.5 equiv, 19.33 mmol, 3.793 g) and **int-2** (12.89 mmol, 2.142 g) in DMSO (32 mL) was added the powder of NaOH (1.5 equiv, 1.184 g) immediately, then the resulting mixture was stirred at room temperature for 6 hours. After the reaction was completed, cold water (100 mL) was added to the resulting reaction mixture, and then the desired product was precipitated. The resulting slurry was filtered under reduced pressure and the filter cake washed with cold water and petroleum ether. Finally, the filter cake was dried under the vacuum condition to give the pure compound **int-3** (3.876 g, 71 %) as a white powder. R_f = 0.55 (petroleum ether : EtOAc = 5 : 1).

Synthesis of int-4:



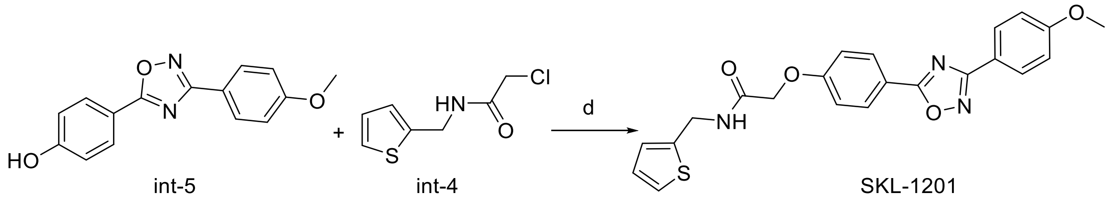
To a solution of **int-3** (8.24 mmol, 2.573 g) in DCM (30 mL) the TFA (21 mL) was added dropwise at 0 °C. Then the mixture was stirred at room temperature for 6 hours (monitored by thin layer chromatography). After the reaction was completed, to neutralize the reaction system with saturated $NaHCO_3$ solution. Next, the mixture was poured into the funnel and these two phases were separated. And the water layer was extracted with DCM, the combined organic extract was dried over anhydrous Na_2SO_4, then removed the solvent under reduced pressure. Finally, the white powder was precipitated after to the residue was added cold petroleum ether. The resulting mixture was filtered under reduced pressure and the filter cake was washed with cold water and petroleum ether. The filter cake was dried under the vacuum condition to give the pure product **int-4** (2.157 g, 98 %) as a white powder. R_f = 0.14 (petroleum ether :EtOAc = 5 : 1).

Synthesis of int-5:



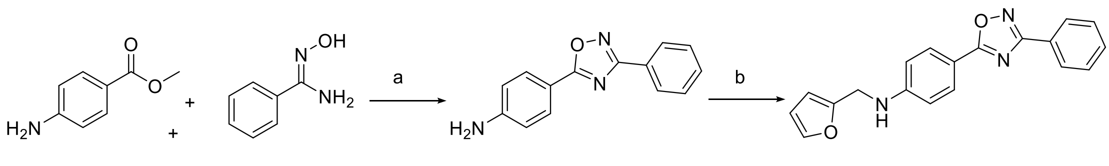
To a solution of 2-thiophenemethylamine (20.00 mmol, 2.1 mL) and K_2CO_3 (1.5 equiv, 1.146 g) in dry acetonitrile (35 mL) the chloroacetyl chloride (1.2 equiv, 1.9 mL) was added dropwise at 0 °C. Then the reaction system was warmed up to room temperature and stirred at this temperature overnight. After the reaction was completed, removed the solvent under reduced pressure and then diluted the residue with EtOAc. Next, the mixture was washed with water (2 × 10.0 mL), saturated $NaHCO_3$ solution (2 × 10.0 mL) and saturated brine (2 × 10.0 mL), the combined water phase was extracted with EtOAc (3 × 10.0 mL), these organic extracts were combined and dried over anhydrous Na_2SO_4. Finally, removed the solvent under reduced pressure, the residue was purified by flash column chromatography eluting with petroleum ether : EtOAc = 2 : 1 to obtain the compound **int-5** (2.782 g, 74 %) as a white powder. R_f = 0.41 (petroleum ether : EtOAc = 3: 1).

Synthesis of SKL1201:



To a solution of **int-5** (0.12 mmol, 32 mg) and K_2CO_3 (1.5 equiv, 25 mg) in dry acetonitrile (0.5 mL), which was stirred beforehand for 10 minutes, the **int-4** (2.5 equiv, 57 mg) was added at room temperature. Then the reaction mixture was refluxed overnight. After the reaction was finished (monitored by thin layer chromatography), removed the solvent under reduced pressure and diluted the residue with EtOAc. Next, the resulting mixture was washed with water (2 × 10.0 mL), saturated NH_4Cl solution (2 × 10.0 mL) and saturated brine (2 × 10.0 mL), these combined water phases were extracted with EtOAc (3 × 10.0 mL). Then the organic extract was combined and dried over anhydrous Na_2SO_4. Finally, removed the solvent under reduced pressure, the white powder was precipitated after to the residue was added cold petroleum ether. The mixture was filtered under reduced pressure and the filter cake was washed with cold water and petroleum ether. The filter cake was dried under the vacuum condition to give the pure product **SKL-1201** (33 mg, 63 %) as a white powder. R_f = 0.31 (petroleum ether :EtOAc = 2 : 1).

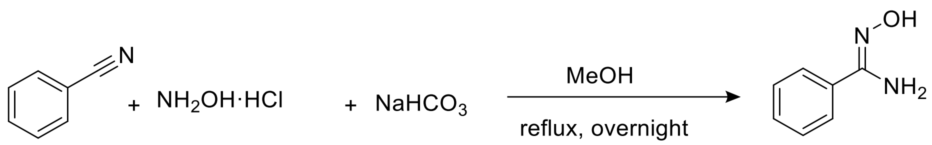
Procedure B : The overall synthesis of compound SKL-1223



int-6 int-7 SKL-1223

Reagents and Conditions: a) 4-aminobenzoic acid methyl ester (1.0 equiv), **int-6** (1.5 equiv), NaOH(s) (powder, 1.5 equiv), DMSO (0.4 M), 60 °C, overnight; ***b)*** **int-7** (1.0 equiv), Furfural (1.2 equiv), HOAc (4.0 equiv), $NaBH(OAc)_3$ (2.0 equiv), 1,2-DCE (0.1 M), RT, overnight.

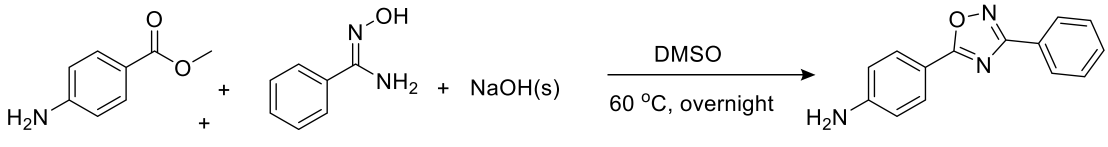
Synthesis of int-6:



int-6

To a solution of $NH_2OH·HCl$ (2.0 equiv, 2.780 g) in MeOH (30 mL) was added the $NaHCO_3$ (2.2 equiv, 3.530 g) one portion, then the reaction mixture was stirred at room temperature for 30minutes. Next, to the mixture was added the benzonitrile (20.00 mmol, 2.1 mL), and the resulting mixture was refluxed overnight. After the reflux was completed, the solvent was removed in vacuo to obtain the crude product **int-6**, which was used in the next step without further purification.

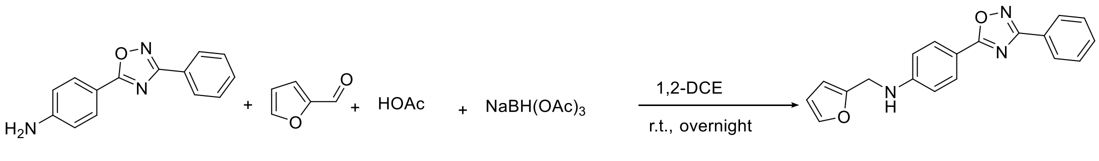
Synthesis of int-7:



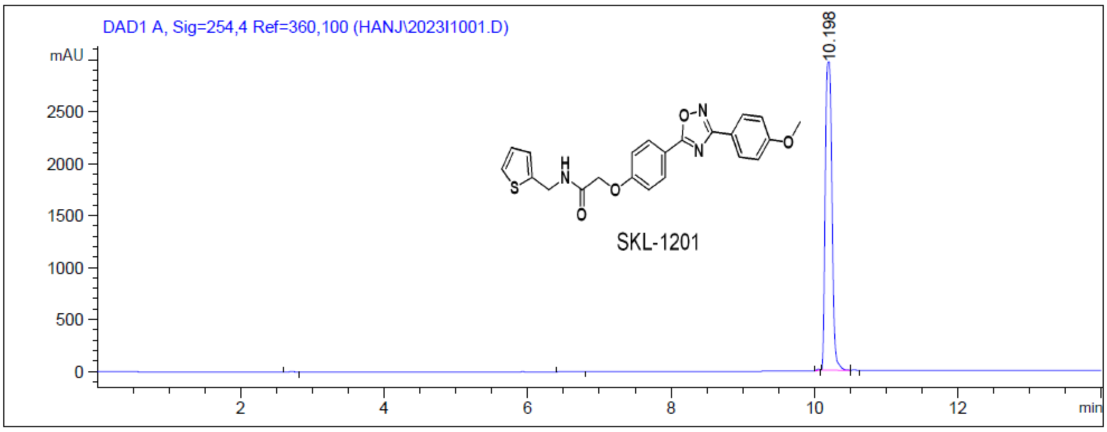
int-6 int-7

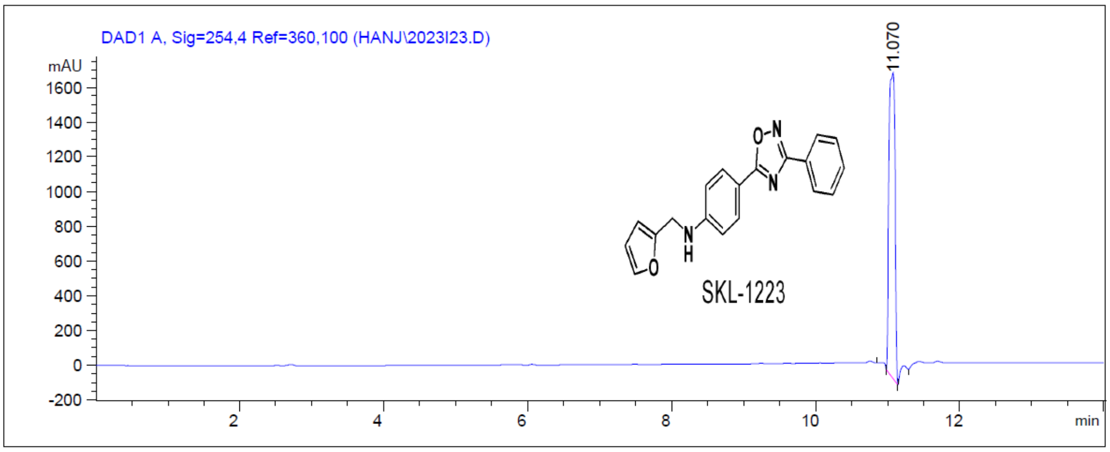
To a solution of 4-aminobenzoic acid methyl ester (19.73 mmol, 2.982 g) and **int-6** (1.5 equiv, 4.028 g) in DMSO (50 mL) was added the powder of NaOH (1.5 equiv, 1.184 g) immediately, then the reaction mixture was stirred at 60 °C overnight. After the reaction was completed, cold water (100 mL) was added to the reaction system, which the system temperature has been cooled to room temperature. Then the desired product was precipitated. The resulting slurry was filtered under the reduced pressure and the filter cake was washed with cold water and petroleum ether. Finally, the filter cake was dried under the vacuum condition to give the pure product **int-7** (3.649 g, 78 %) as a white powder. R_f = 0.44 (petroleum ether : EtOAc = 2 : 1).

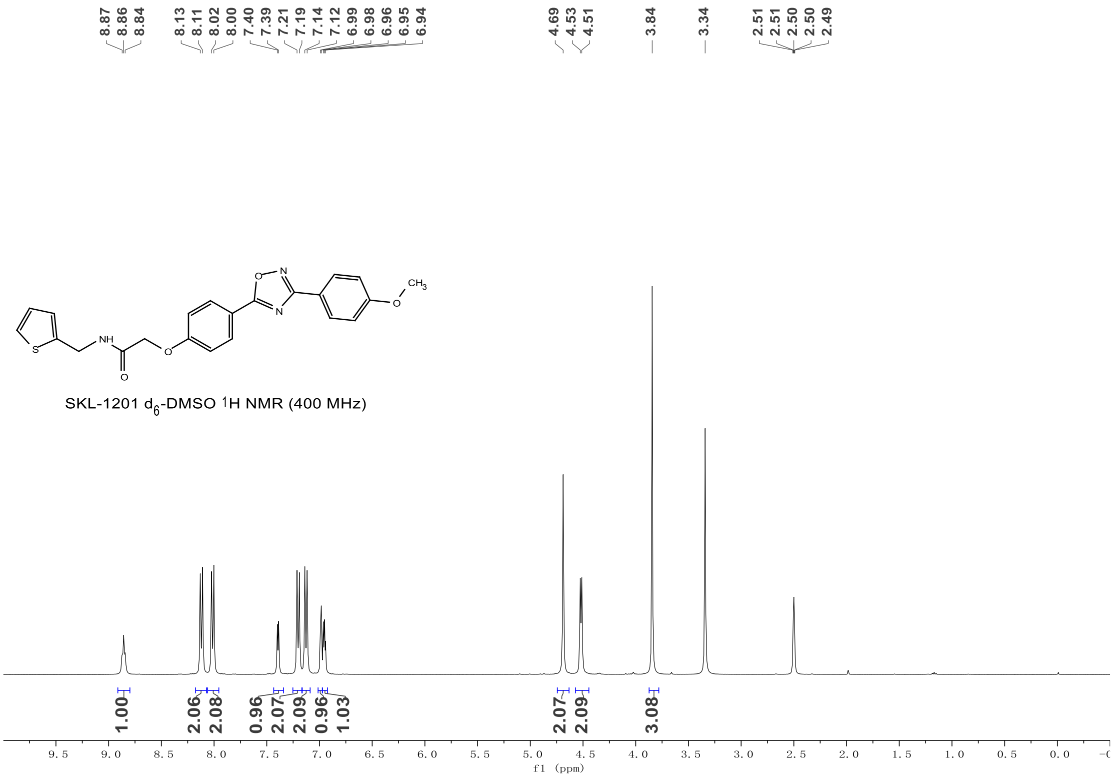
Synthesis of SKL-1223:



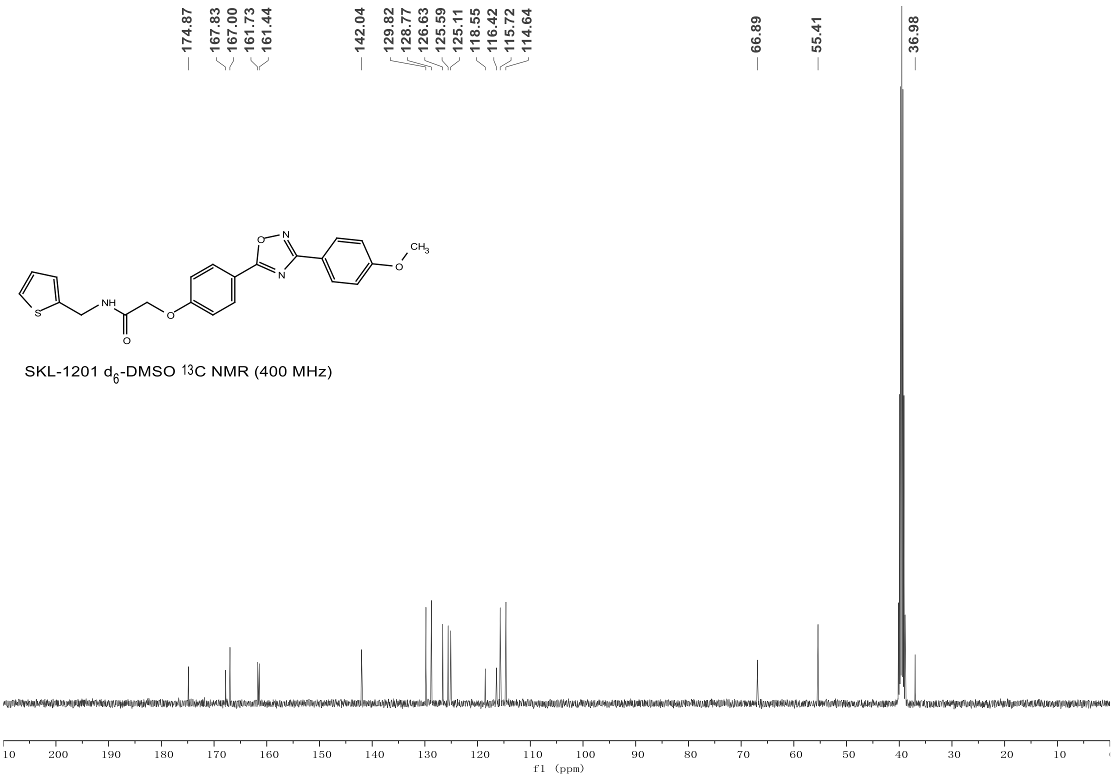
To a solution of **int-7** (1.00 mmol, 237 mg) in dry 1,2-dichloroethane (10 mL) was added furfural (1.2 equiv, 99 μL) and acetic acid (4.0 equiv, 229 μL) sequentially. Then the resulting mixture was stirred at room temperature for 4 hours. After this procedure finished, $NaBH(OAc)_3$ (2.0 equiv, 424 mg) was added to the reaction system and then the whole mixture was stirred at room temperature overnight. Next, the reaction system was diluted with DCM, neutralized with saturated $NaHCO_3$ solution, washed with water (2 × 10.0 mL), saturated NH_4Cl solution (2 × 10.0 mL) and saturated brine (2 × 10.0 mL). The combined aqueous phase was combined and extracted with DCM (3 × 5.0 mL). These organic extracts were combined and dried over anhydrous Na_2SO_4, then filtered and concentrated. The resulting residue was purified by flash column chromatography eluting with petroleum ether : EtOAc = 10 : 1 to obtain the compound **SKL-1223** (197 mg, 62%) as a pale yellow powder. R_f = 0.17 (petroleum ether : EtOAc = 10 : 1).



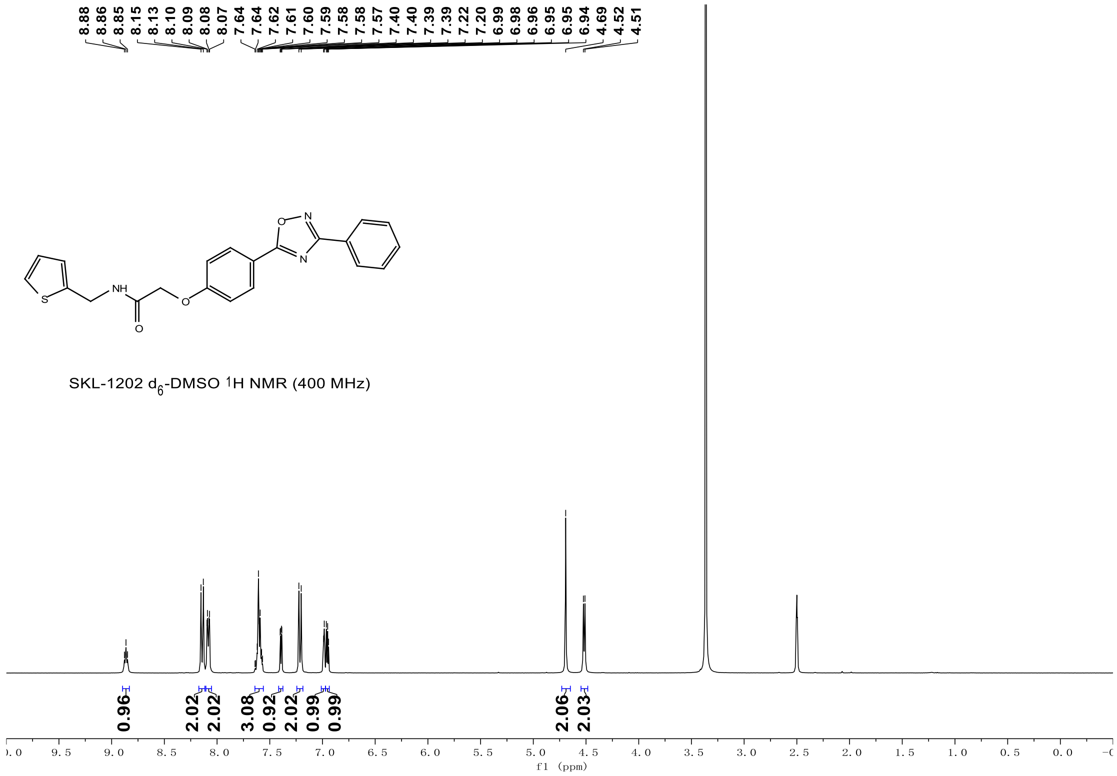




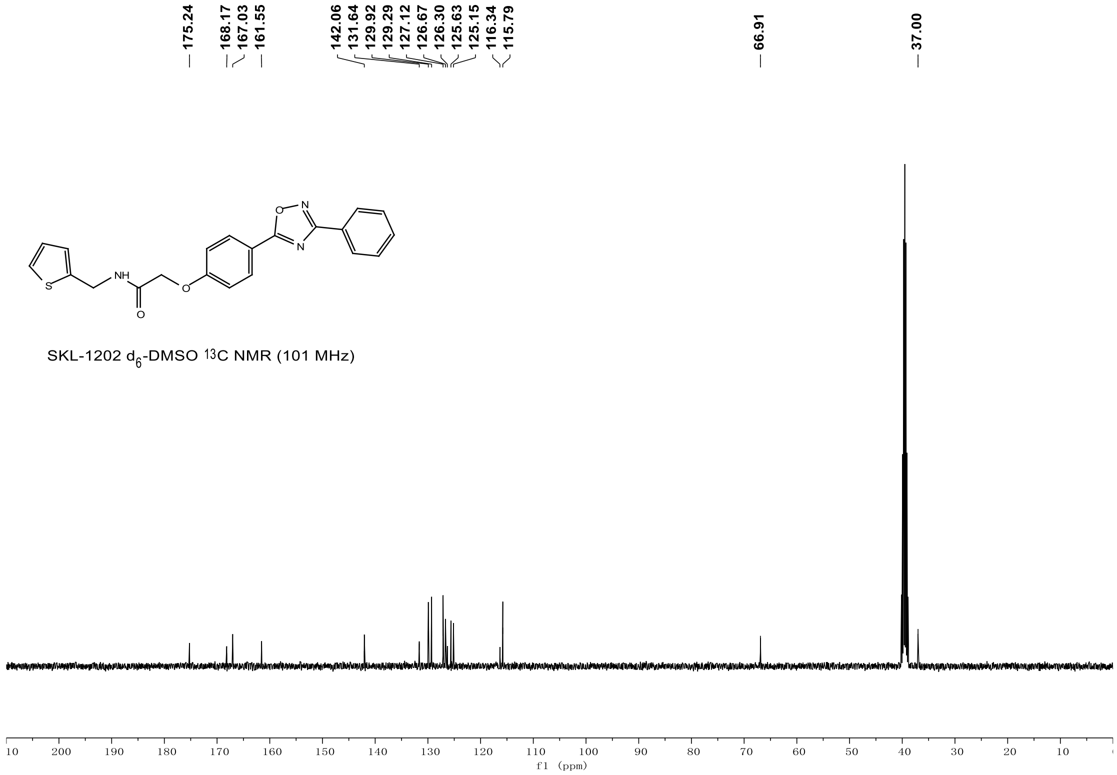
SKL-1201 d6-DMSO 1H NMR (400 MHz)



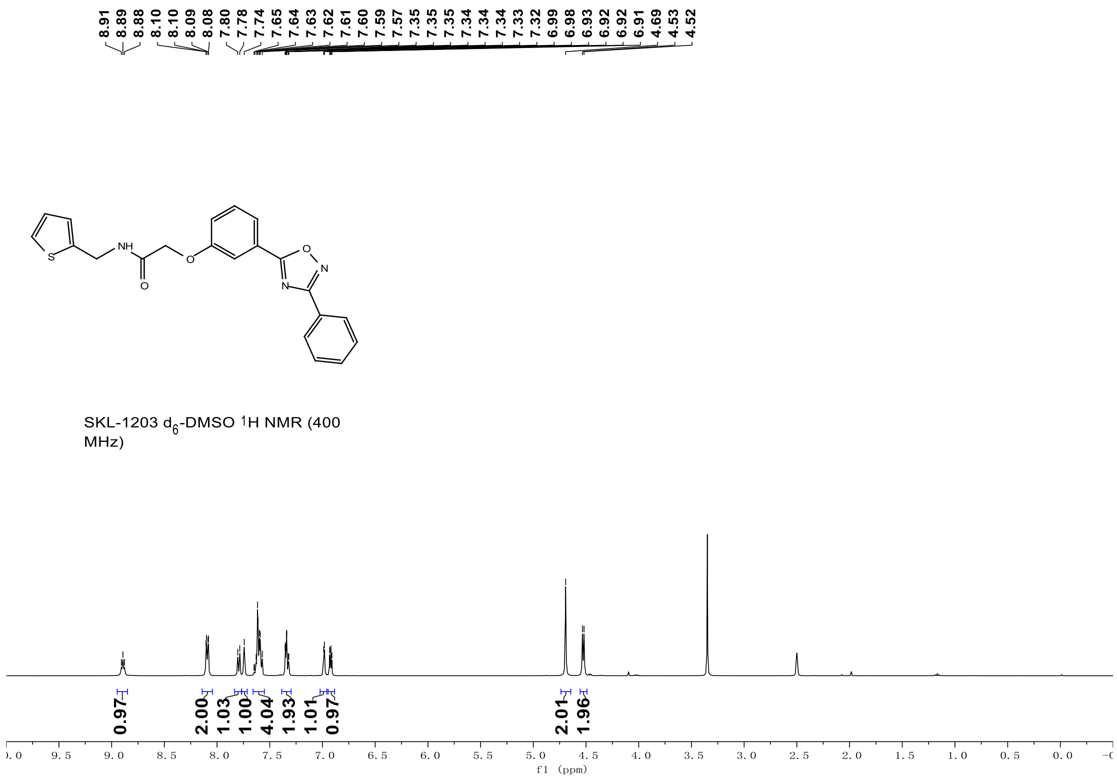
SKL-1201 d6-DMSO 13C NMR (400 MHz)



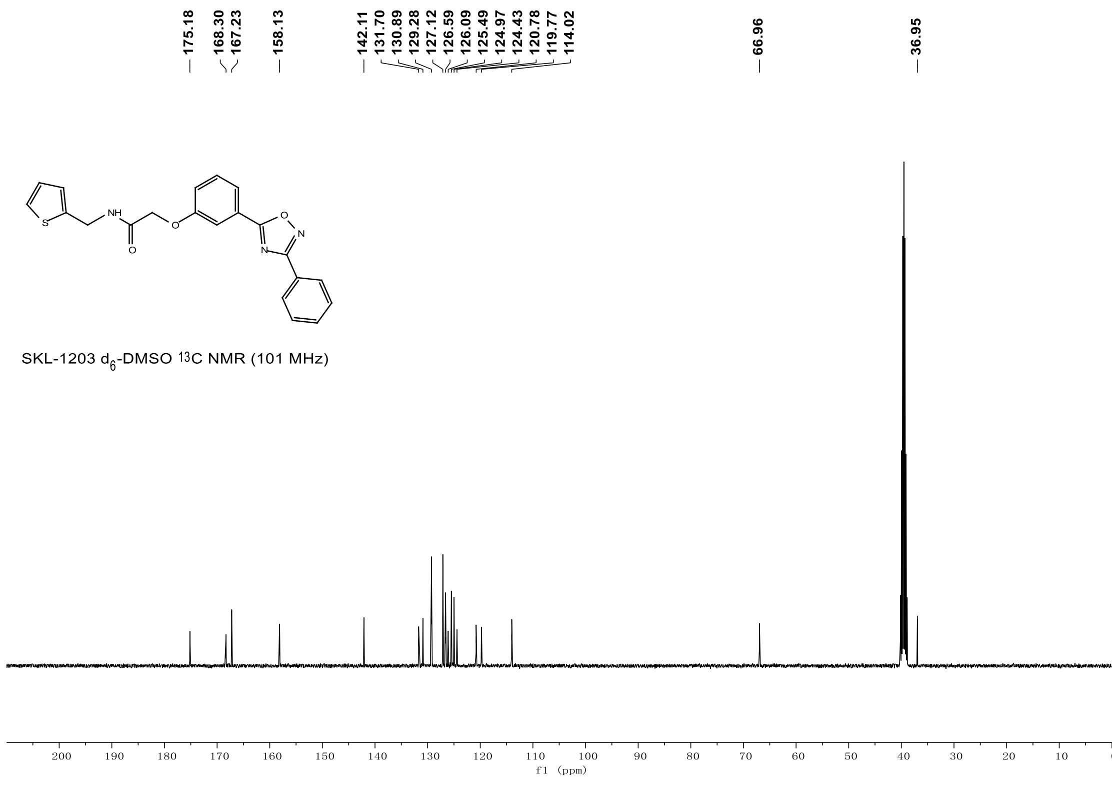
SKL-1202 d_6-DMSO ^{1}H NMR (400 MHz)



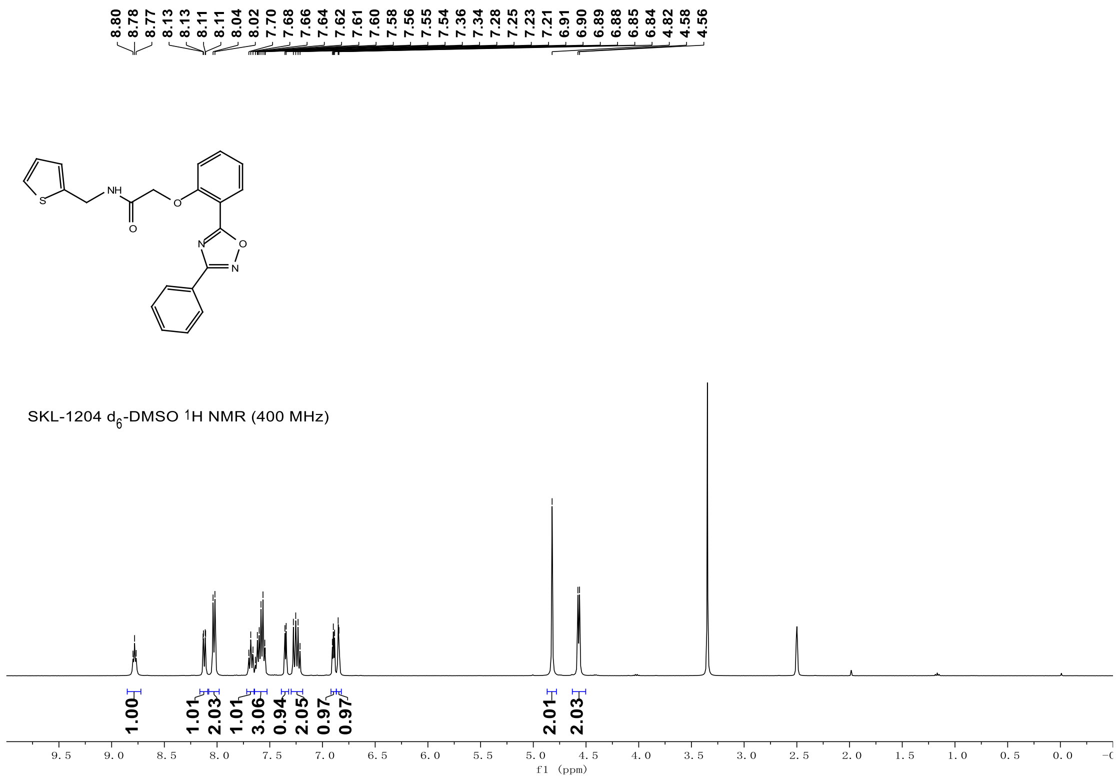
SKL-1202 d_6-DMSO ^{13}C NMR (101 MHz)

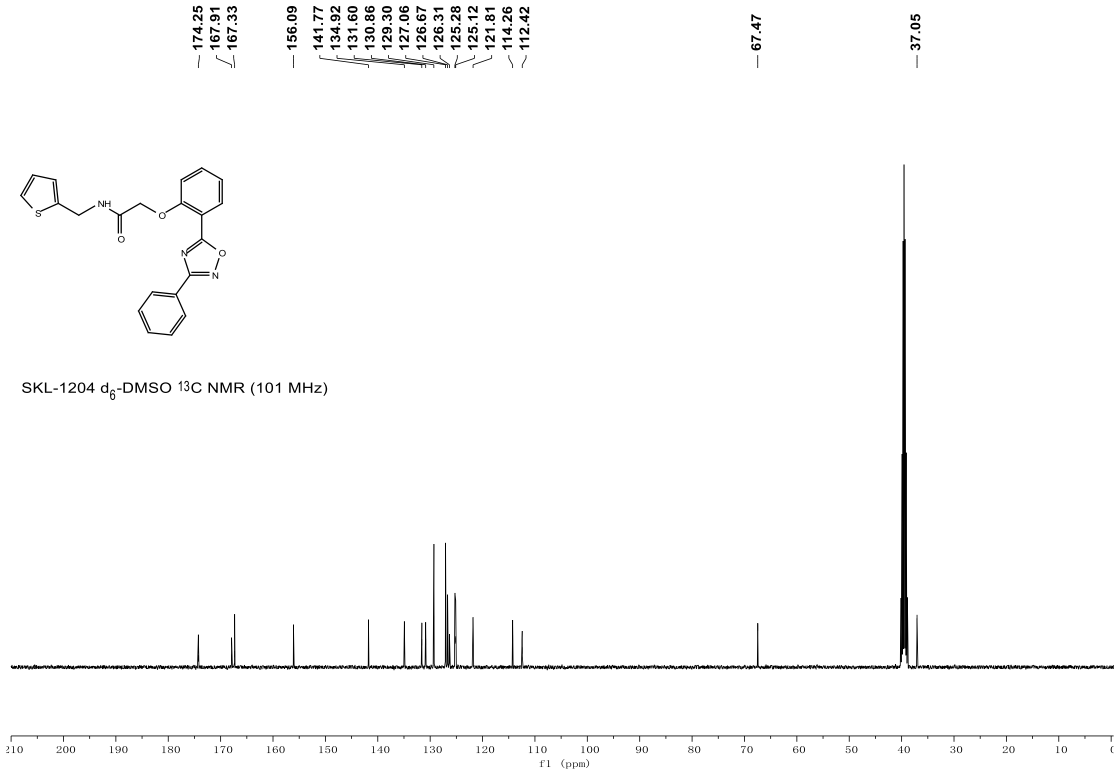


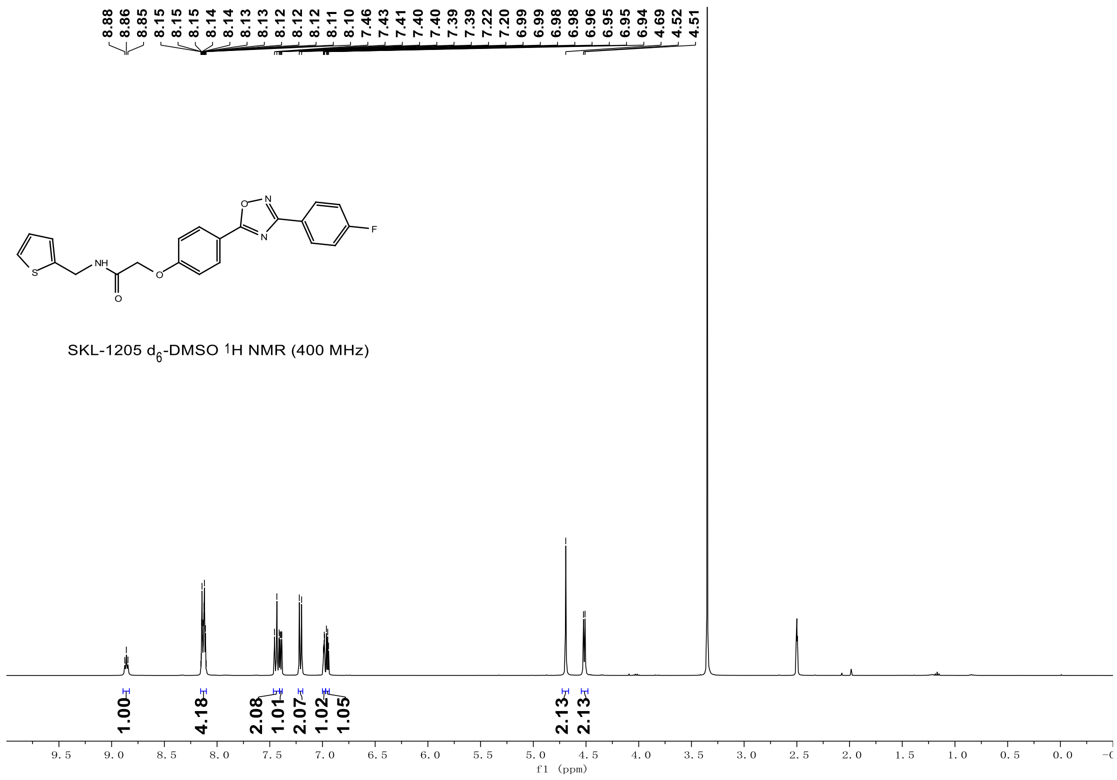
SKL-1203 d_6-DMSO ^{1}H NMR (400 MHz)



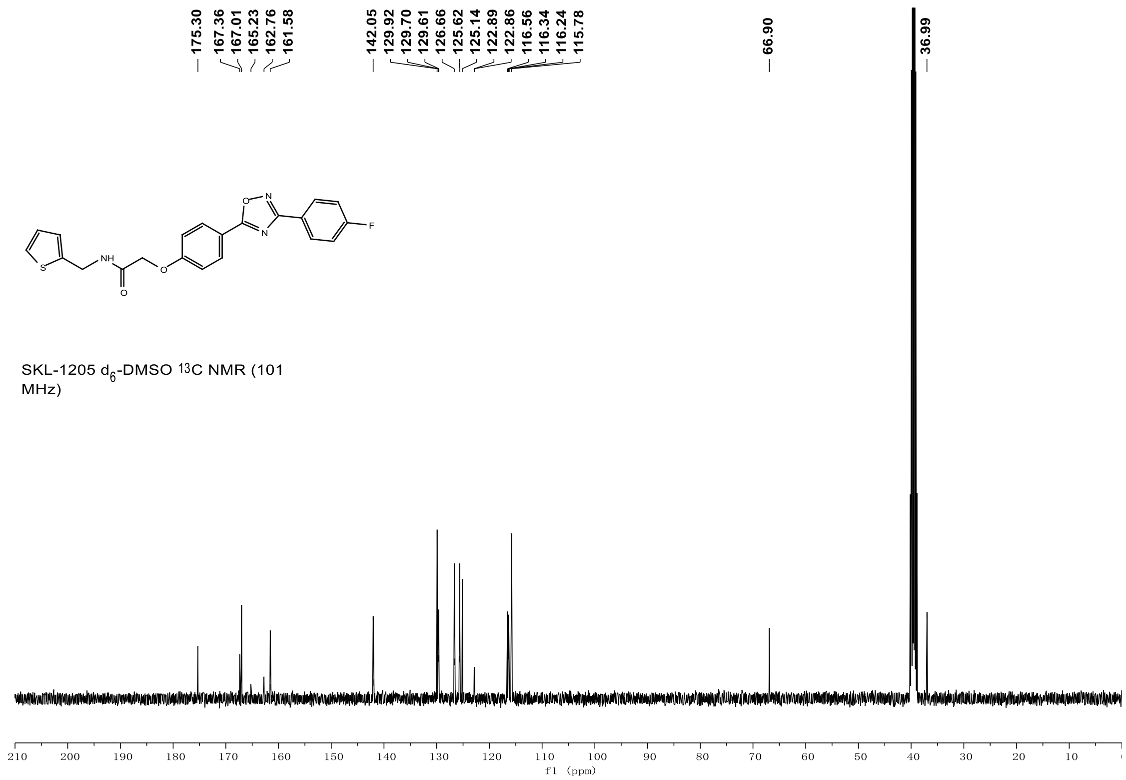
SKL-1203 d_6-DMSO ^{13}C NMR (101 MHz)


SKL-1204 d6-DMSO 1H NMR (400 MHz)
f1 (ppm)

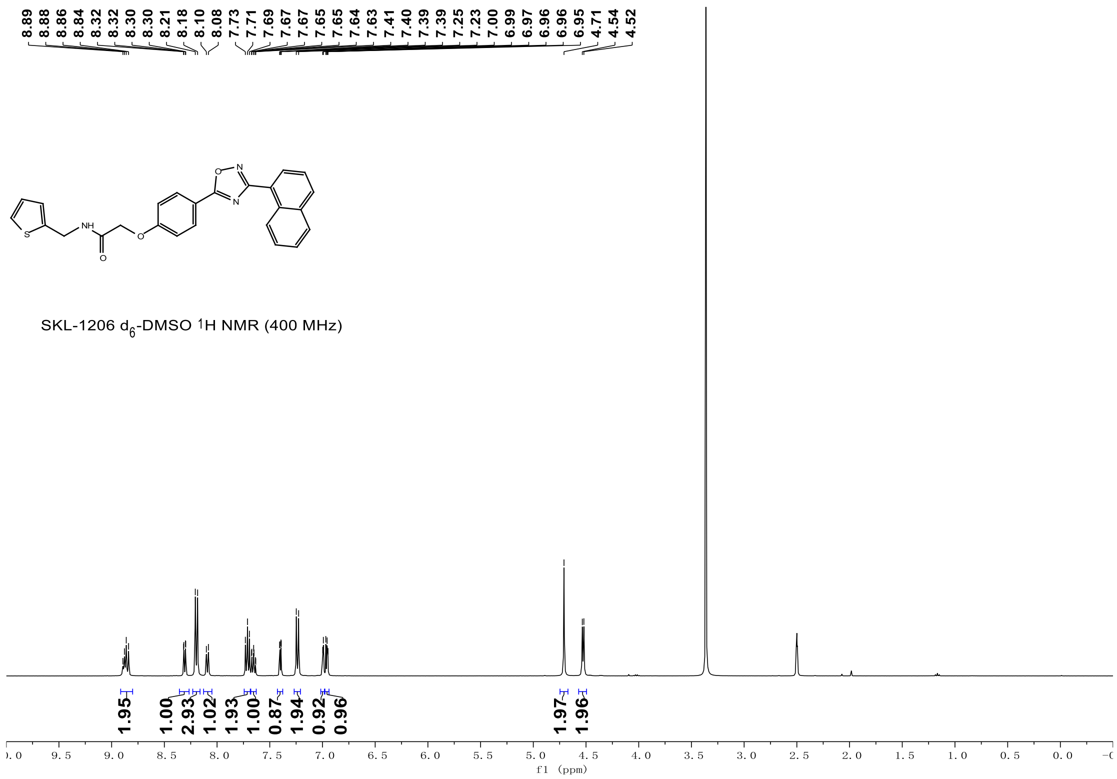

SKL-1204 d6-DMSO 13C NMR (101 MHz)
f1 (ppm)



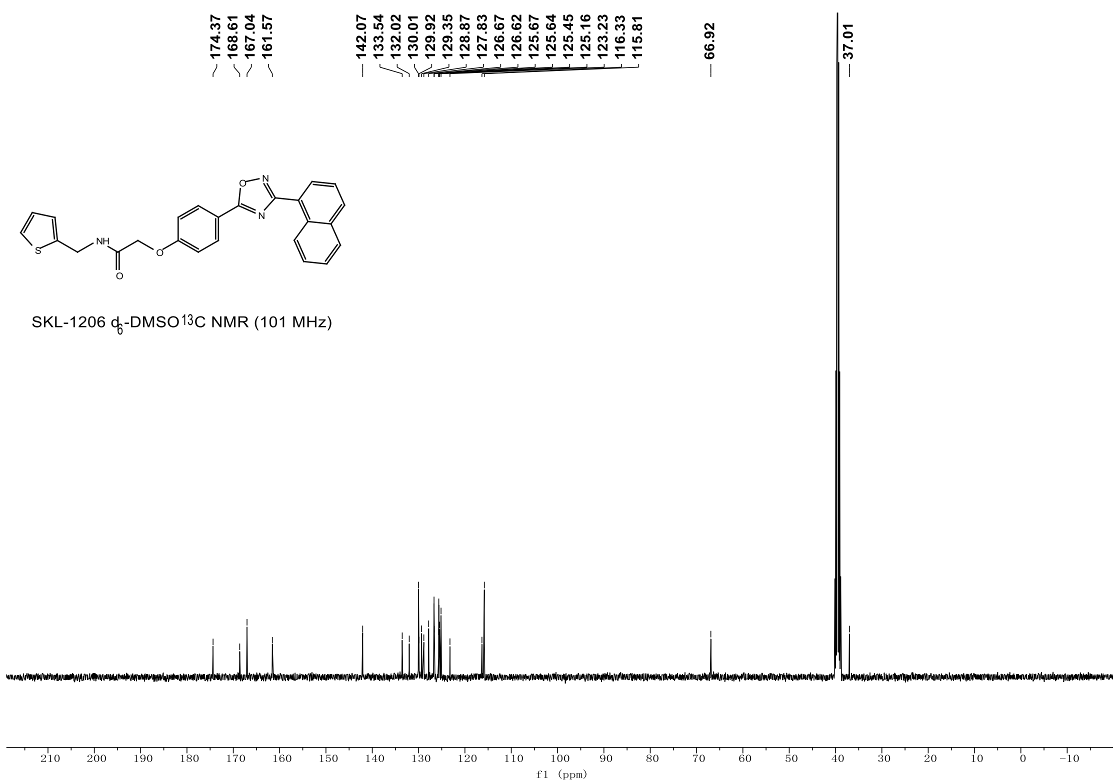
SKL-1205 d_6-DMSO ^1H NMR (400 MHz)



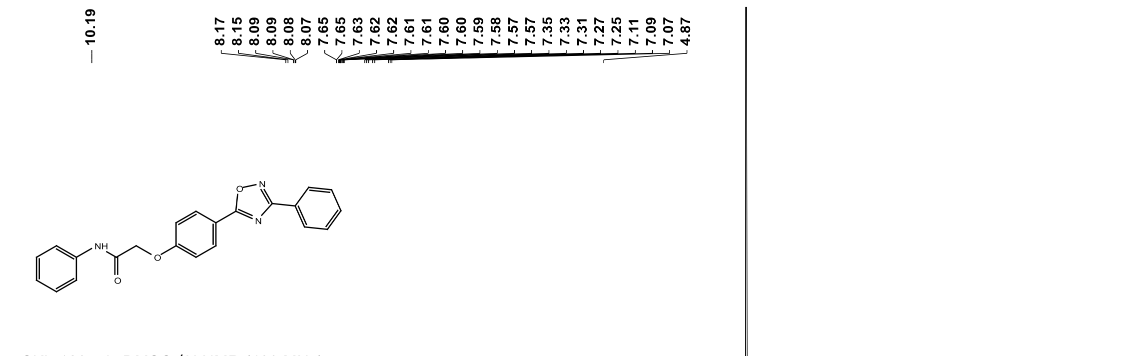
SKL-1205 d_6-DMSO ^{13}C NMR (101 MHz)



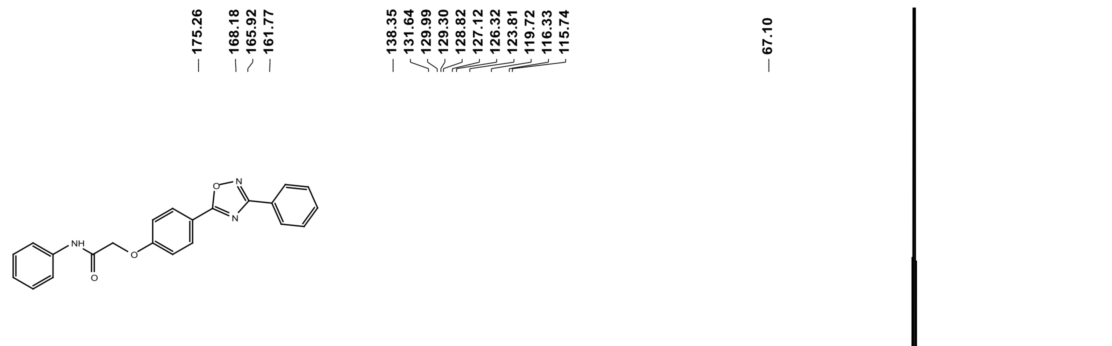
SKL-1206 d_6-DMSO ^{1}H NMR (400 MHz)



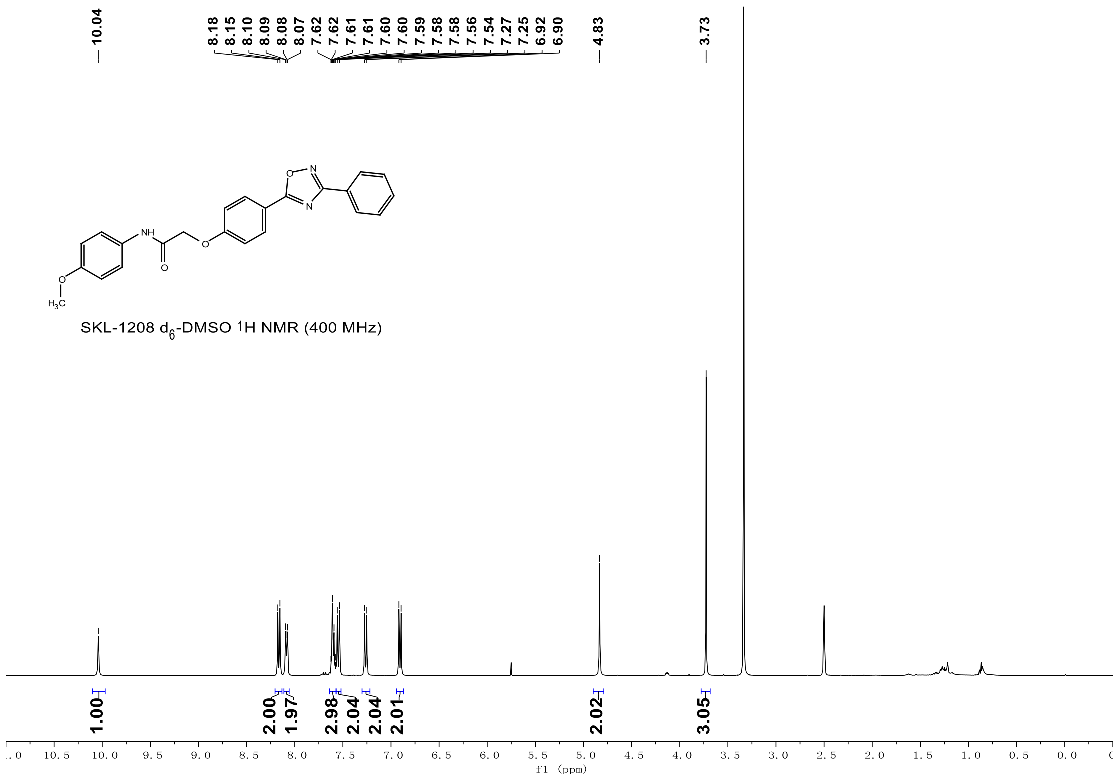
SKL-1206 d_6-DMSO ^{13}C NMR (101 MHz)

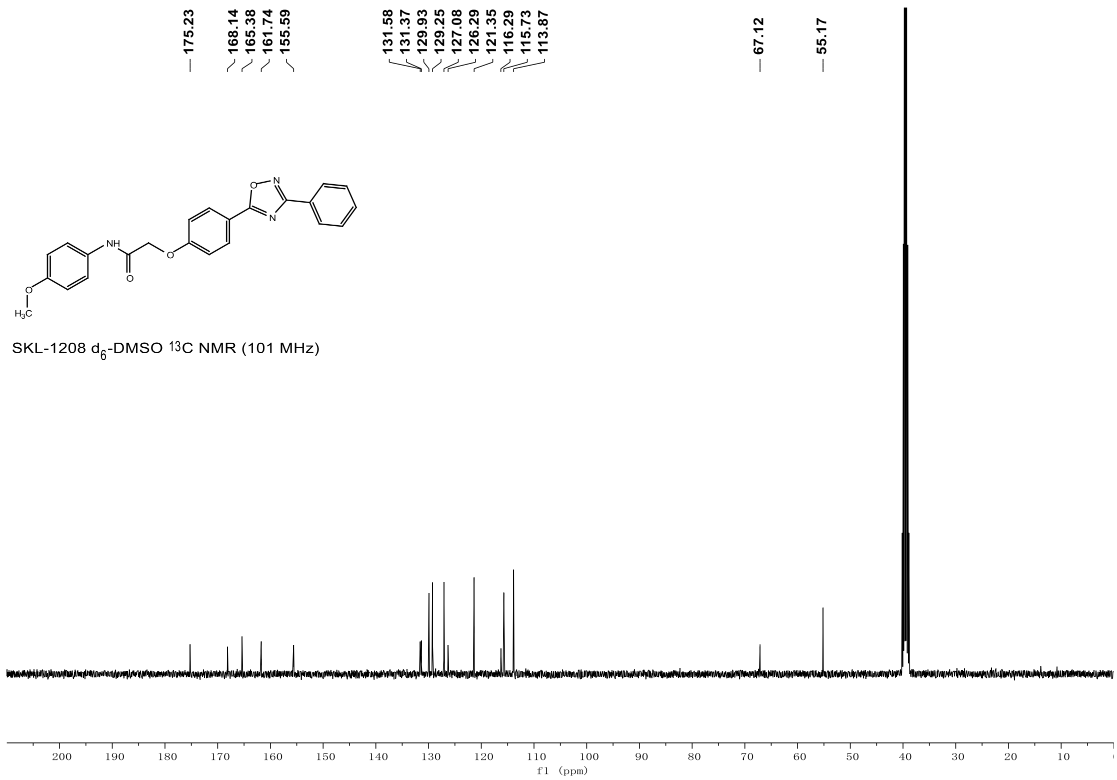


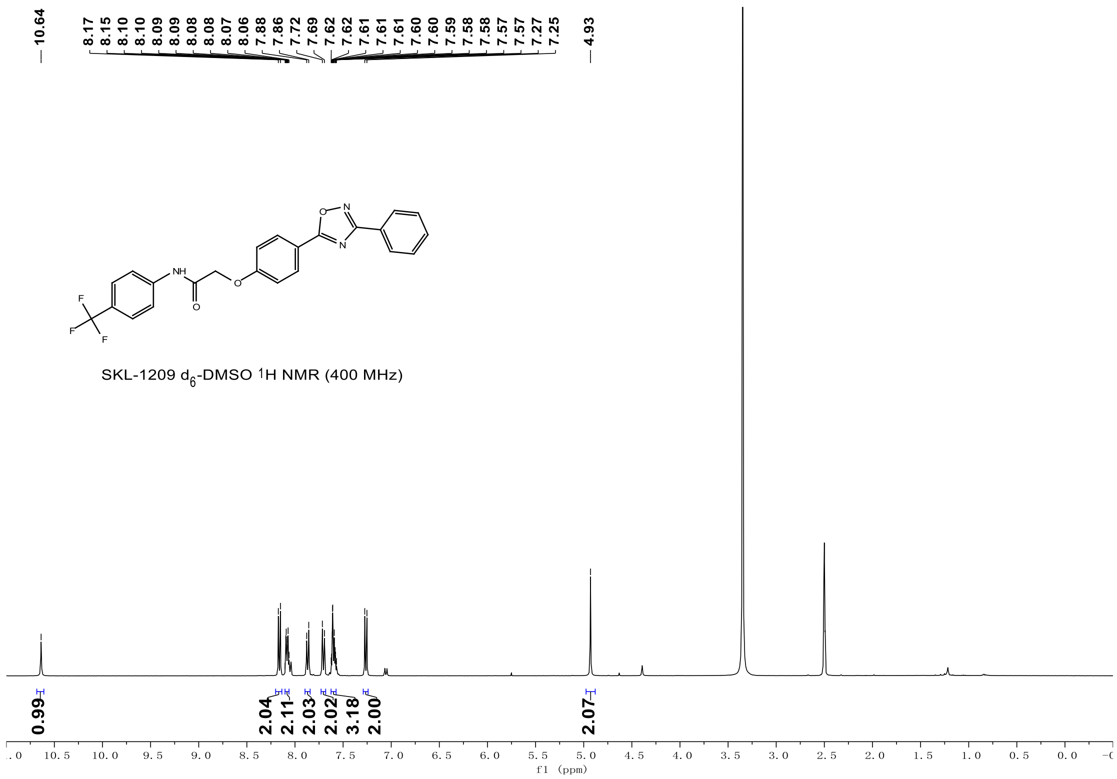
SKL-1207 d_6-DMSO [1]H NMR (400 MHz)

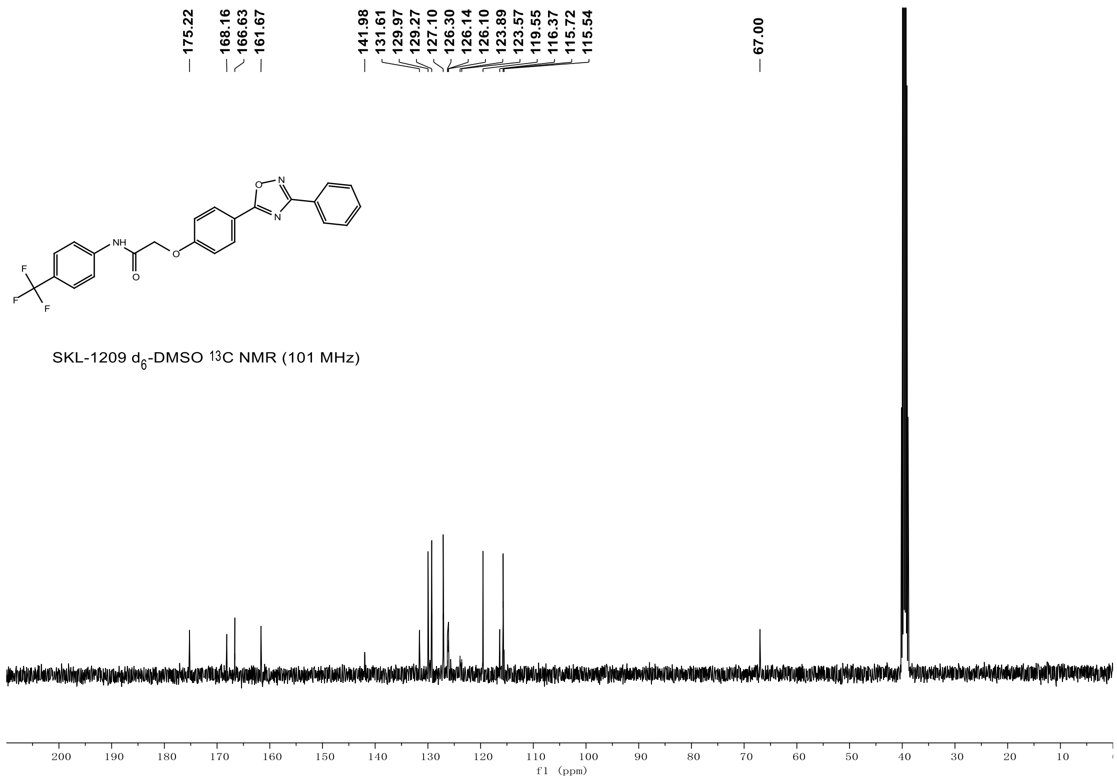


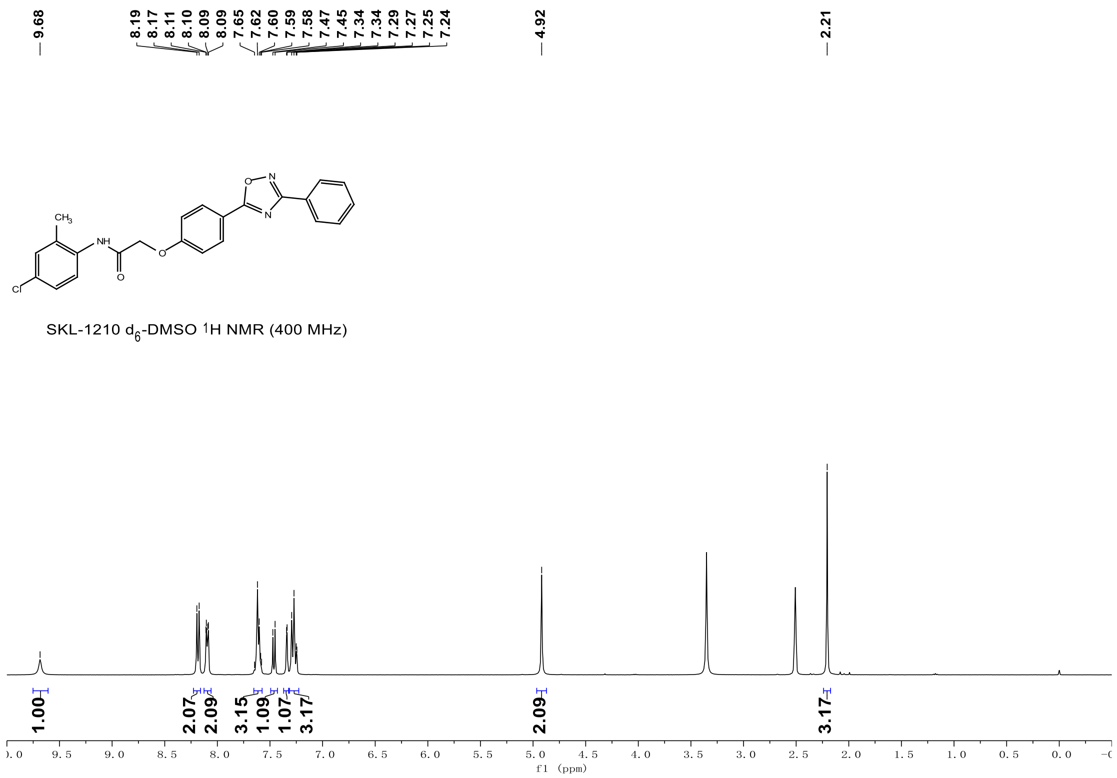
SKL-1207 d_6-DMSO [13]C NMR (101 MHz)

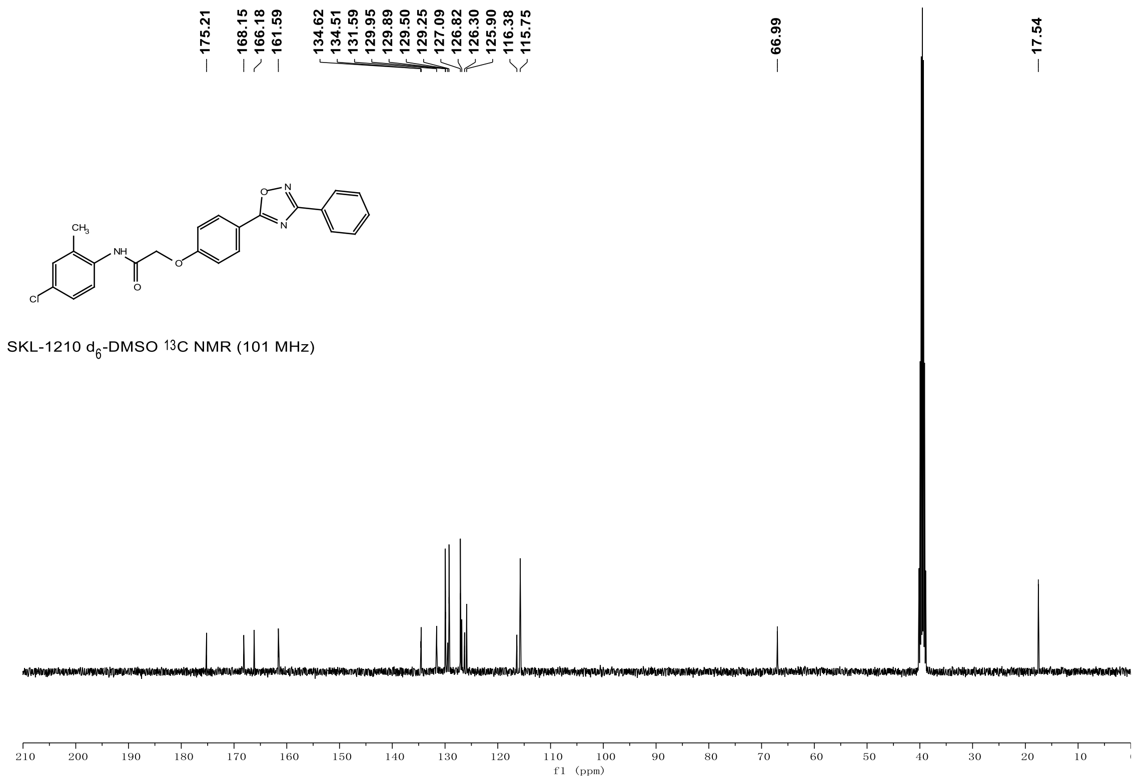

10.04
8.18
8.15
8.10
8.09
8.08
8.07
7.62
7.62
7.61
7.61
7.60
7.60
7.59
7.58
7.58
7.56
7.54
7.27
7.25
6.92
6.90
4.83
3.73
NH
O
O
O
N
N
H3C
SKL-1208 d6-DMSO 1H NMR (400 MHz)
1.00
2.00
1.97
2.98
2.04
2.04
2.01
2.02
3.05
f1 (ppm)

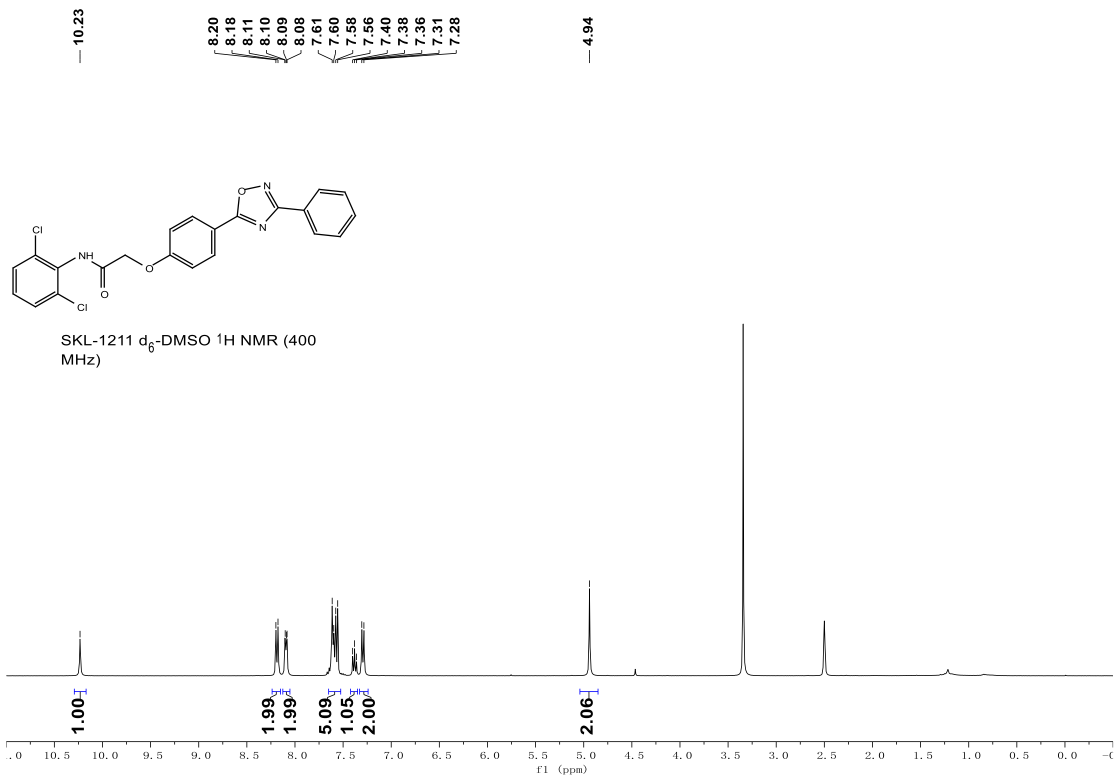

175.23
168.14
165.38
161.74
155.59
131.58
131.37
129.93
129.25
127.08
126.29
121.35
116.29
115.73
113.87
67.12
55.17
NH
O
O
O
N
N
H3C
SKL-1208 d6-DMSO 13C NMR (101 MHz)
f1 (ppm)


SKL-1209 d6-DMSO 1H NMR (400 MHz)

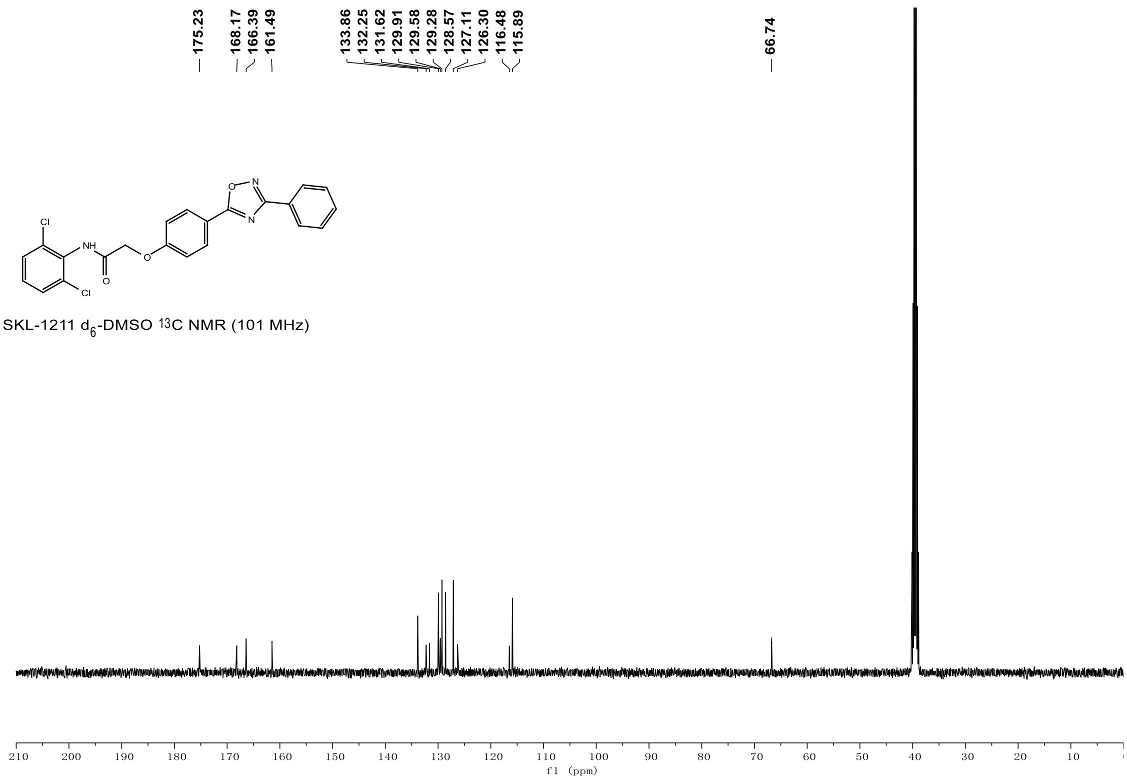

SKL-1209 d6-DMSO 13C NMR (101 MHz)


9.68
8.19 8.17 8.11 8.10 8.09 8.09 7.65 7.62 7.60 7.59 7.58 7.47 7.45 7.34 7.34 7.29 7.27 7.25 7.24
4.92
2.21
SKL-1210 d6-DMSO 1H NMR (400 MHz)
1.00 2.07 2.09 3.15 1.09 1.07 3.17 2.09 3.17
f1 (ppm)

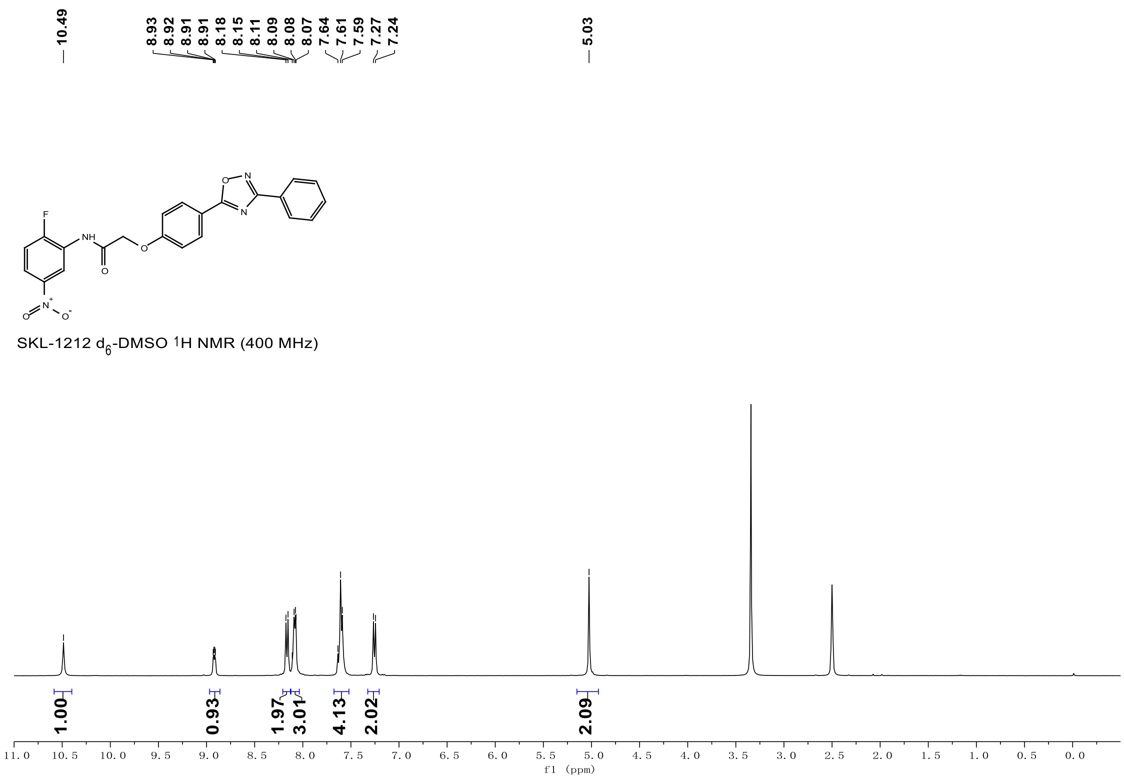

175.21
168.15 166.18 161.59
134.62 134.51 131.59 129.95 129.89 129.50 129.25 127.09 126.82 126.30 125.90 116.38 115.75
66.99
17.54
SKL-1210 d6-DMSO 13C NMR (101 MHz)
f1 (ppm)



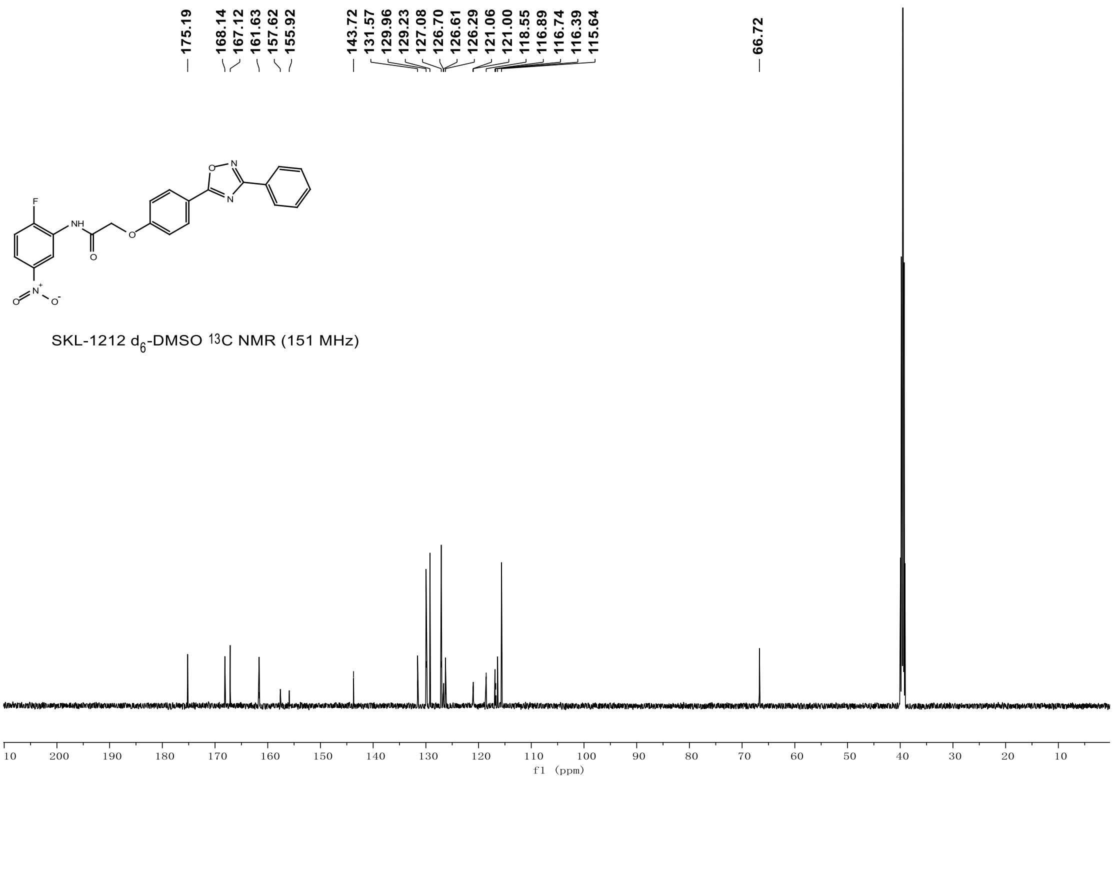
SKL-1211 d_6-DMSO ^1H NMR (400 MHz)



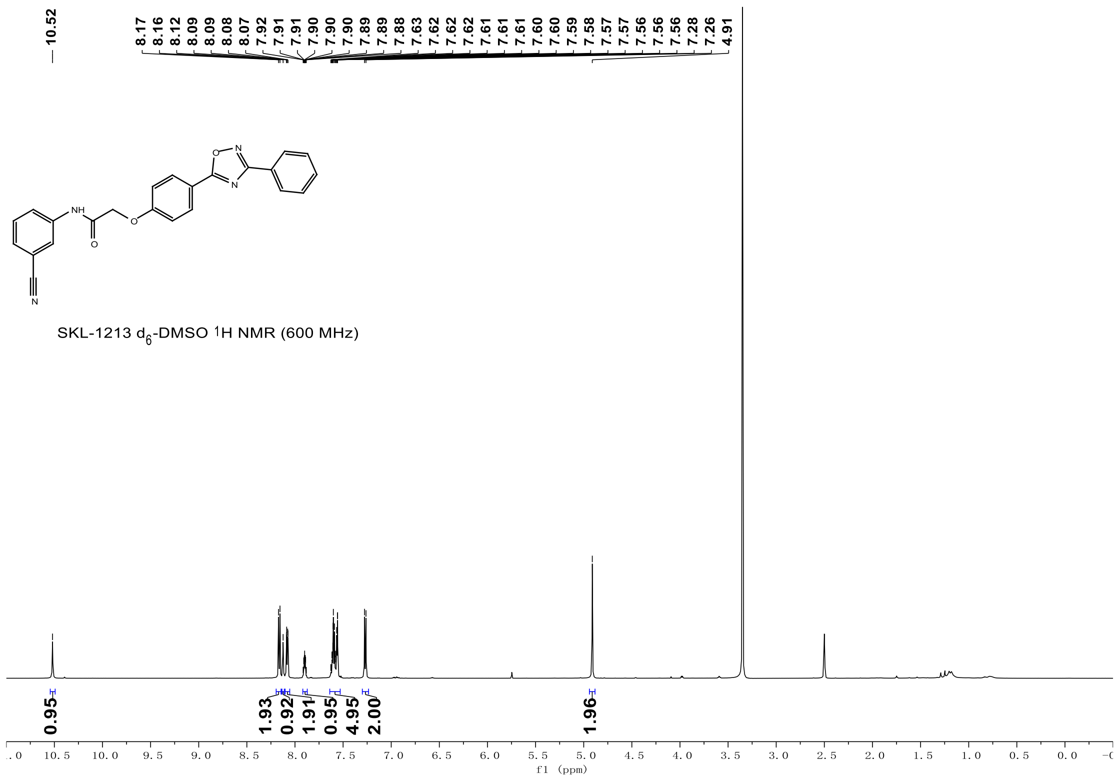
SKL-1211 d_6-DMSO ^{13}C NMR (101 MHz)

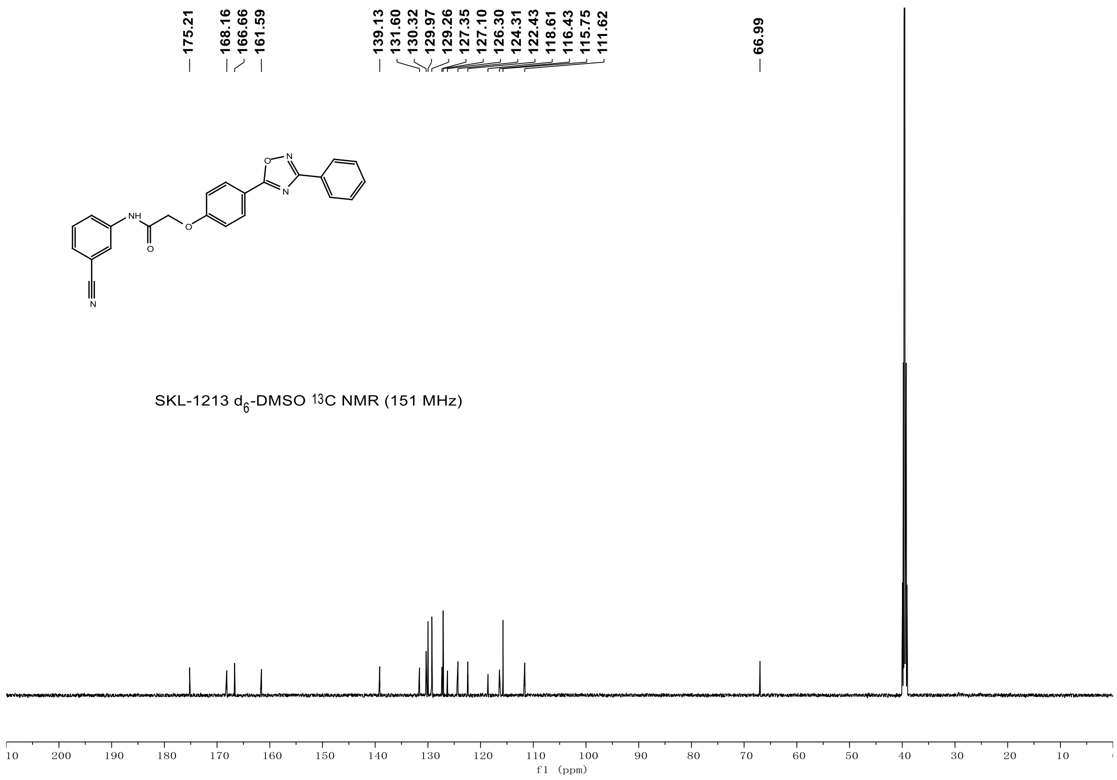


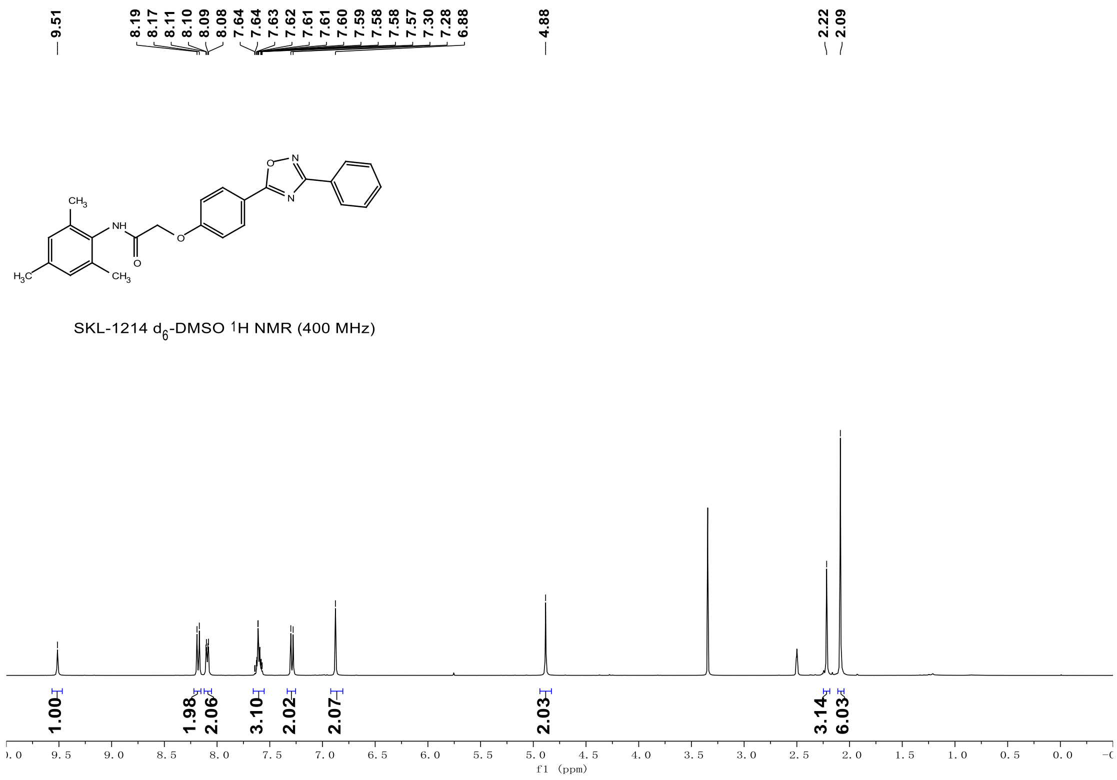
SKL-1212 d_6-DMSO ^{1}H NMR (400 MHz)

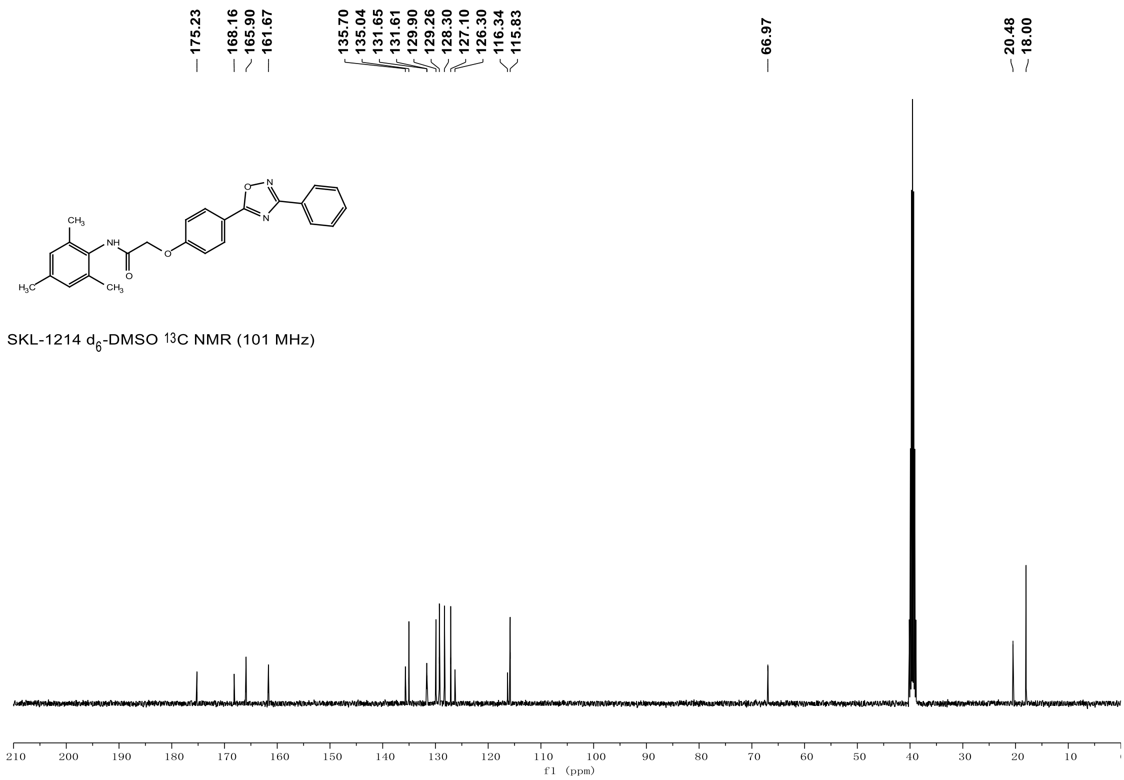


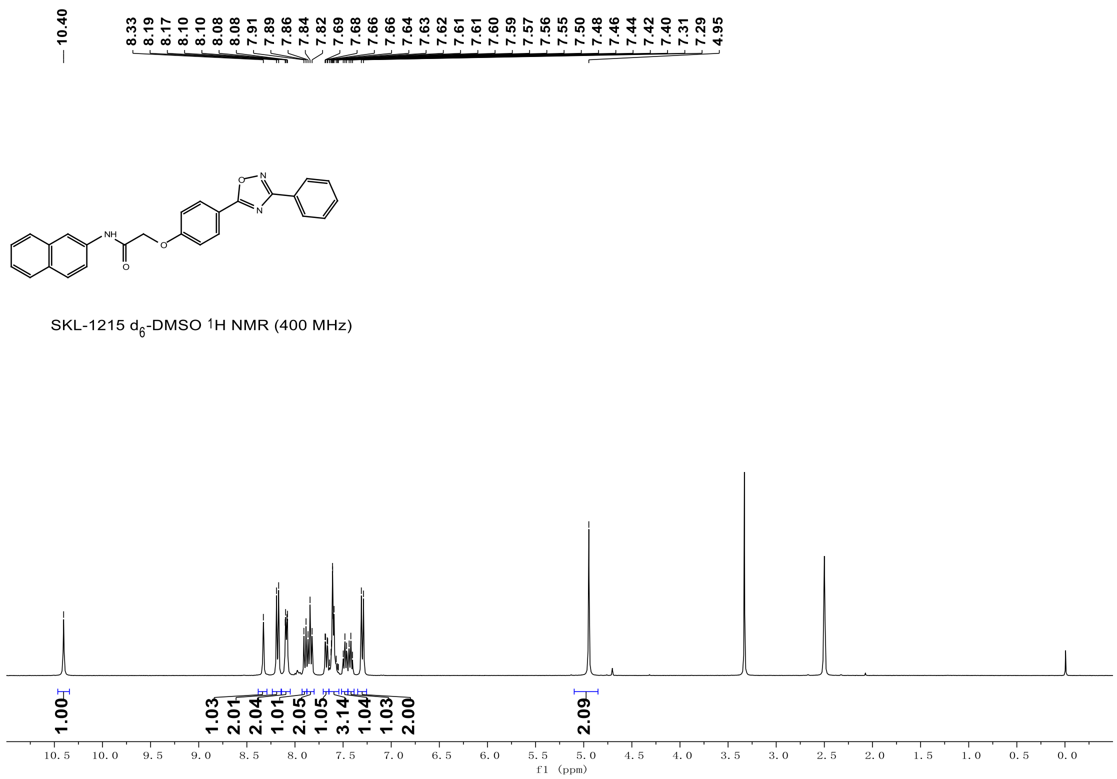
SKL-1212 d_6-DMSO ^{13}C NMR (151 MHz)

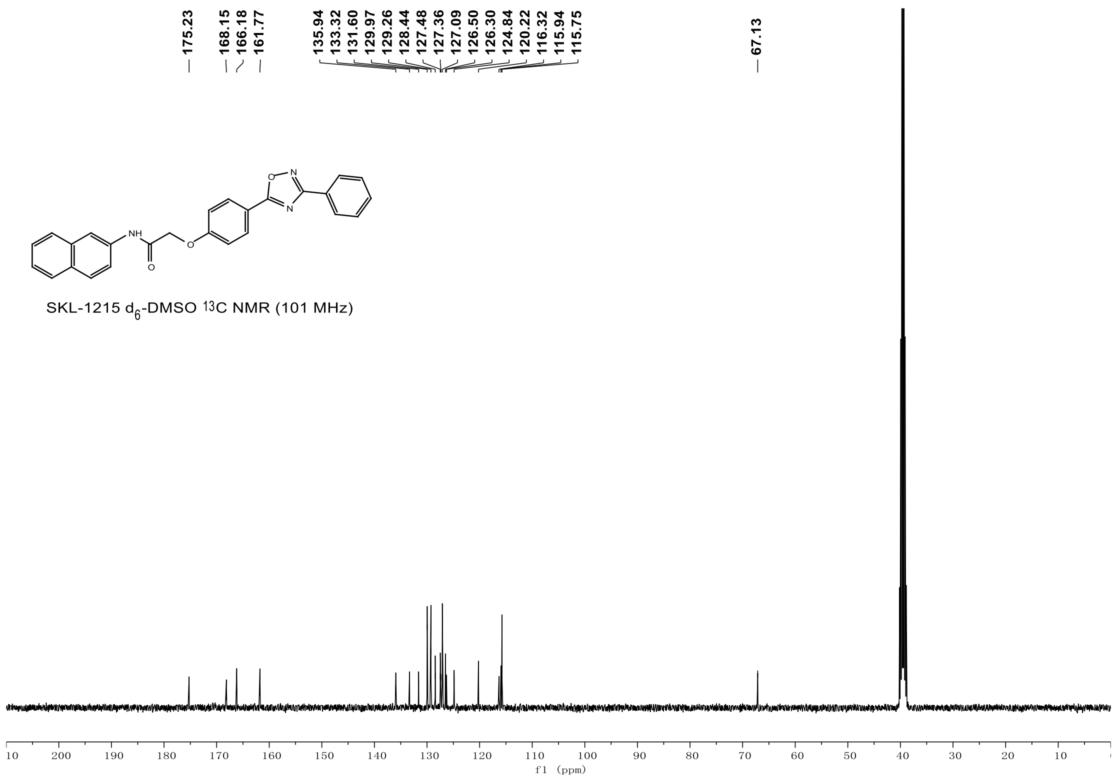

SKL-1213 d_6-DMSO ^1H NMR (600 MHz)
10.52
8.17 8.16 8.12 8.09 8.09 8.08 8.07 7.92 7.91 7.91 7.90 7.90 7.90 7.89 7.88 7.63 7.62 7.62 7.62 7.61 7.61 7.61 7.60 7.60 7.59 7.58 7.57 7.57 7.56 7.56 7.56 7.28 7.26 4.91
0.95 1.93 0.92 1.91 0.95 4.95 2.00 1.96
NH
O
N
f1 (ppm)

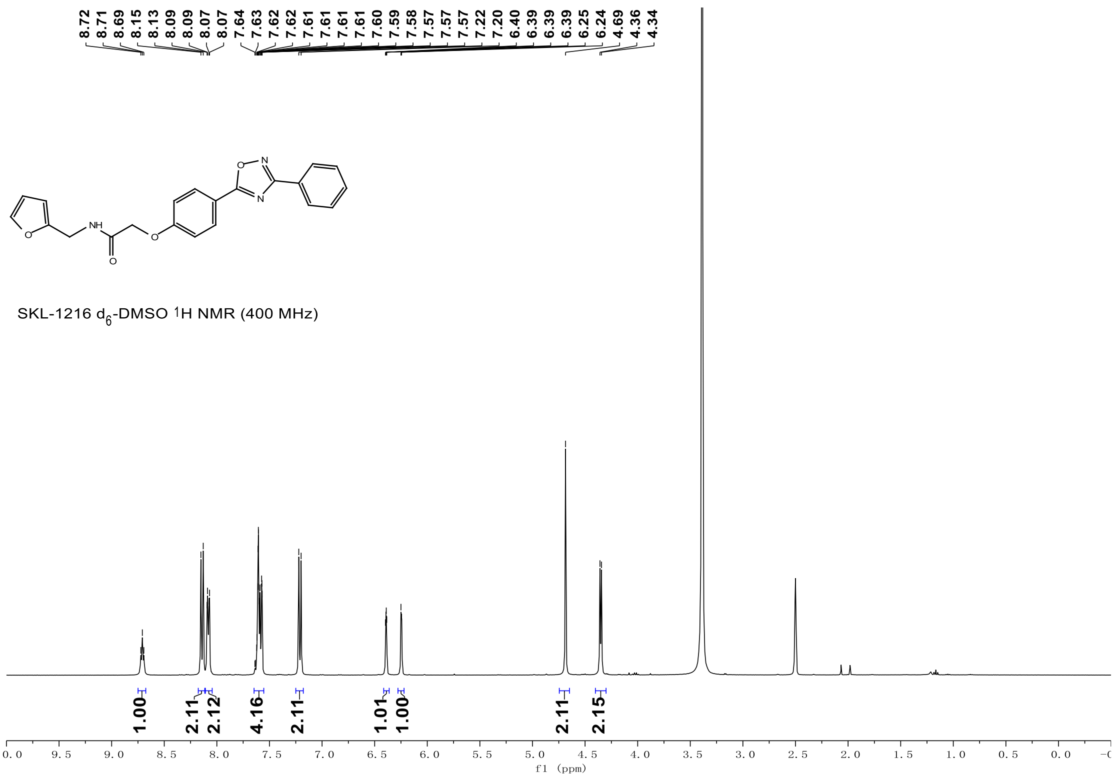

SKL-1213 d_6-DMSO ^{13}C NMR (151 MHz)
175.21 168.16 166.66 161.59
139.13 131.60 130.32 129.97 129.26 127.35 127.10 126.30 124.31 122.43 118.61 116.43 115.75 111.62
66.99
NH
O
N
f1 (ppm)


9.51
8.19 8.17 8.11 8.10 8.09 8.08 7.64 7.64 7.63 7.62 7.61 7.61 7.60 7.59 7.58 7.58 7.57 7.30 7.28 6.88
4.88
2.22 2.09
SKL-1214 d6-DMSO 1H NMR (400 MHz)
1.00 1.98 2.06 3.10 2.02 2.07 2.03 3.14 6.03
f1 (ppm)

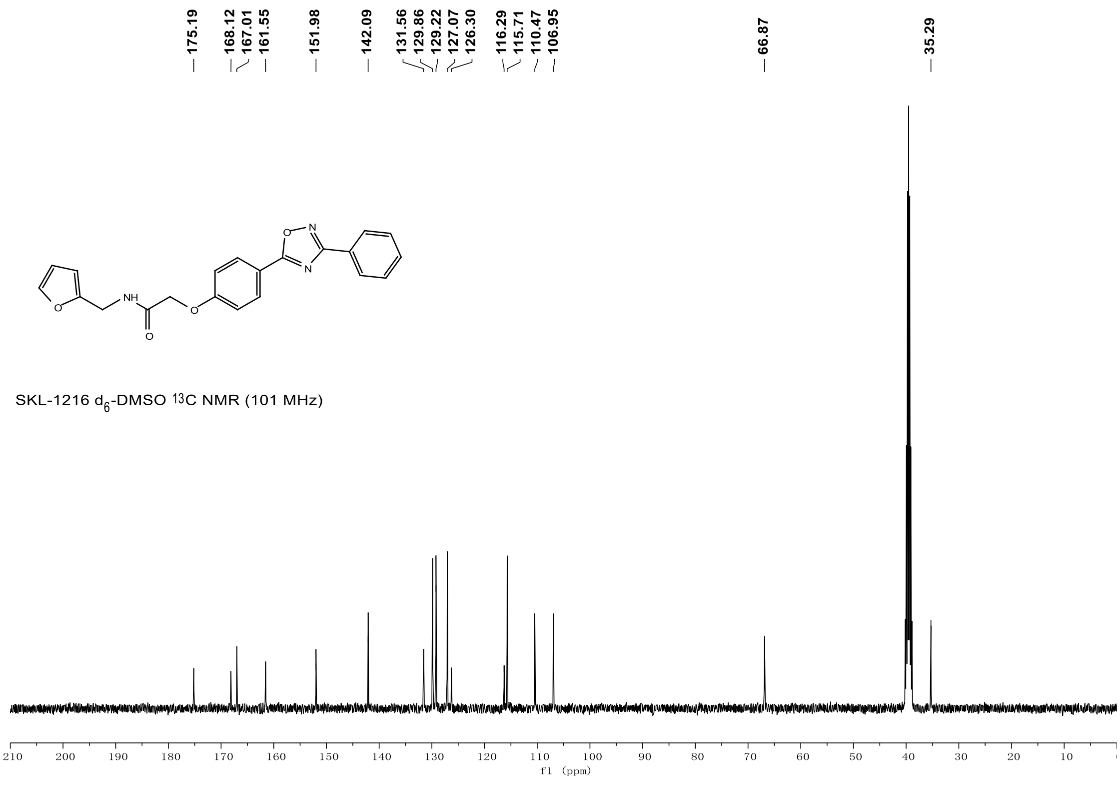

175.23
168.16 165.90 161.67
135.70 135.04 131.65 131.61 129.90 129.26 128.30 127.10 126.30 116.34 115.83
66.97
20.48 18.00
SKL-1214 d6-DMSO 13C NMR (101 MHz)
f1 (ppm)


10.40
8.33 8.19 8.17 8.10 8.10 8.08 8.08 7.91 7.89 7.86 7.84 7.82 7.69 7.68 7.66 7.66 7.64 7.63 7.62 7.61 7.61 7.60 7.59 7.57 7.56 7.55 7.50 7.48 7.46 7.44 7.42 7.40 7.31 7.29 4.95
SKL-1215 d6-DMSO 1H NMR (400 MHz)
1.00 1.03 2.01 2.04 1.01 2.05 1.05 3.14 1.04 1.03 2.00 2.09
f1 (ppm)

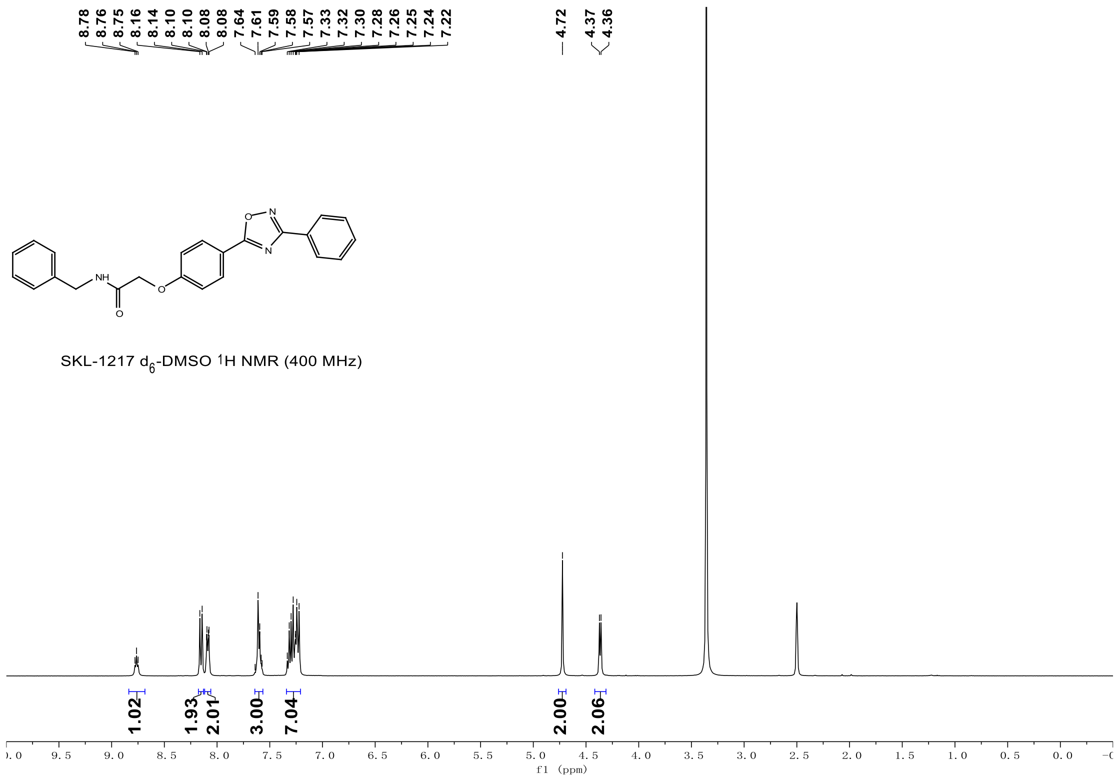

175.23 168.15 166.18 161.77 135.94 133.32 131.60 129.97 129.26 128.44 127.48 127.36 127.09 126.50 126.30 124.84 120.22 116.32 115.94 115.75 67.13
SKL-1215 d6-DMSO 13C NMR (101 MHz)
f1 (ppm)

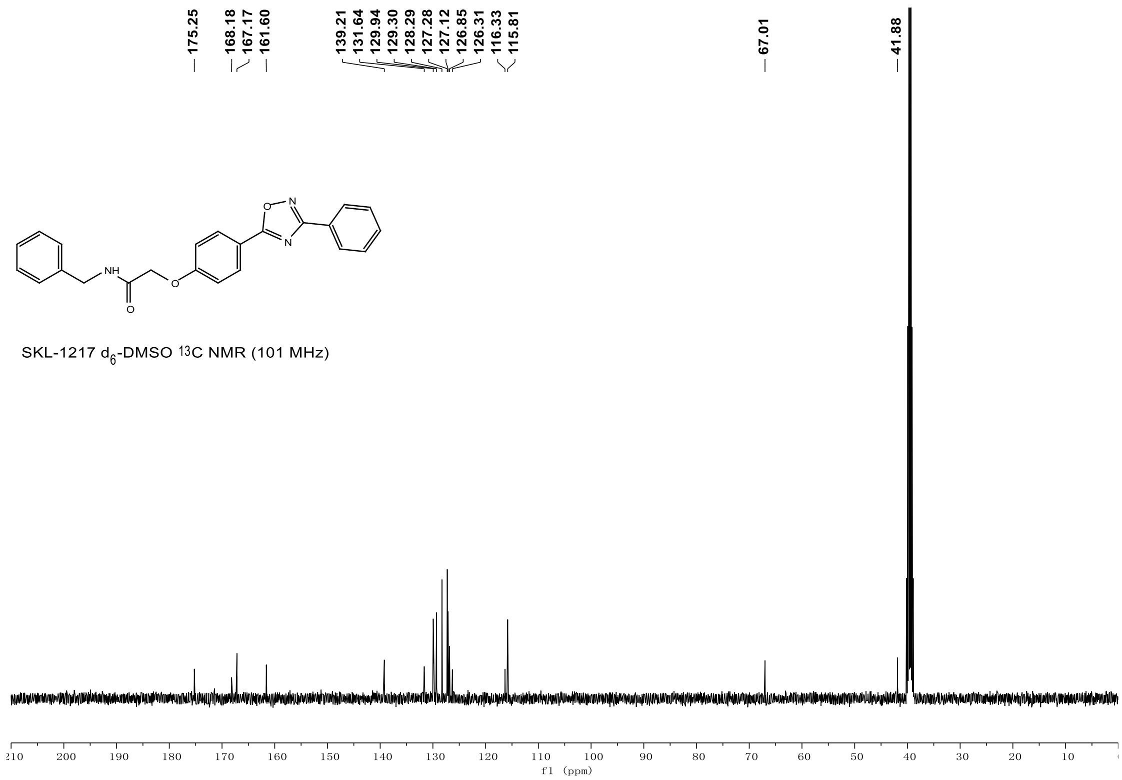


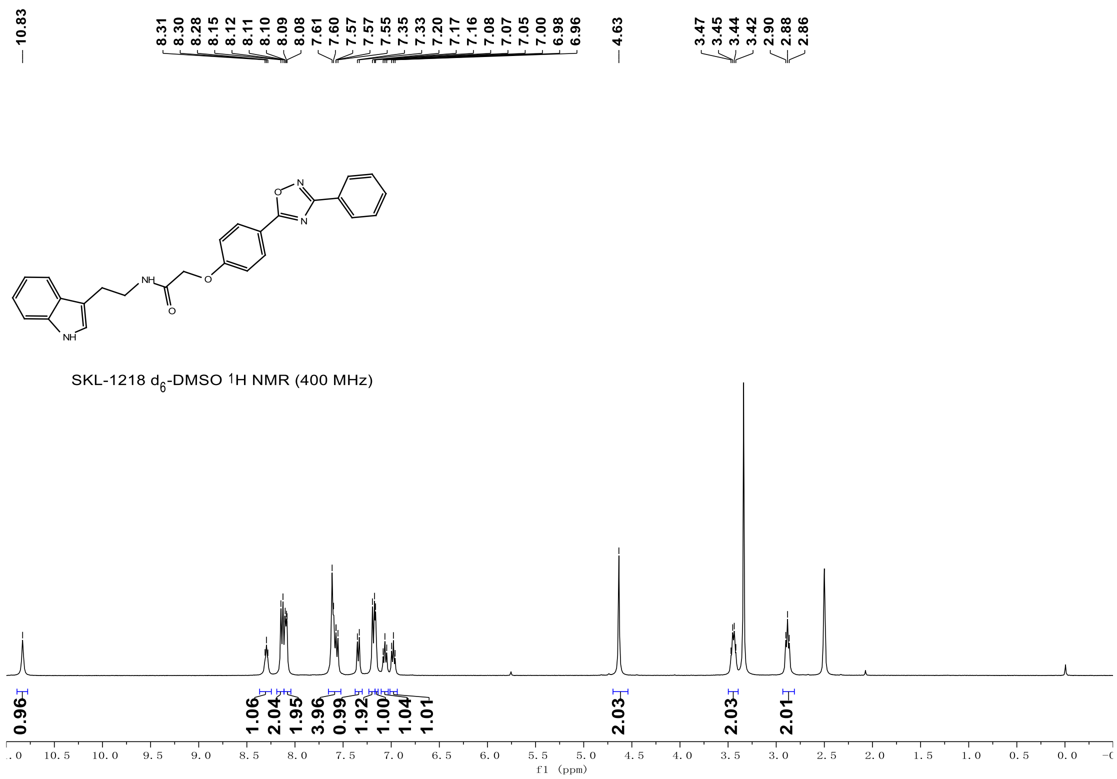
SKL-1216 d_6-DMSO ^{1}H NMR (400 MHz)



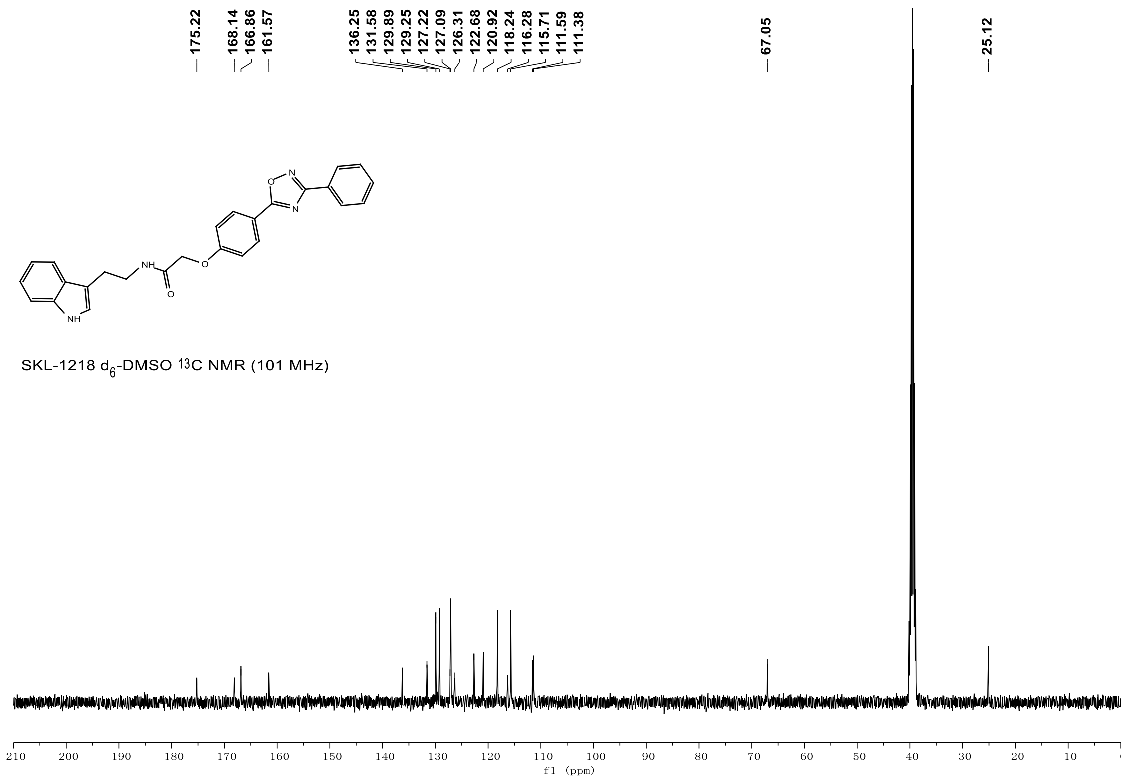
SKL-1216 d_6-DMSO ^{13}C NMR (101 MHz)


8.78 8.76 8.75 8.16 8.14 8.10 8.08 8.08 7.64 7.61 7.59 7.58 7.57 7.33 7.32 7.30 7.28 7.26 7.25 7.24 7.22
4.72
4.37 4.36
SKL-1217 d6-DMSO 1H NMR (400 MHz)
1.02 1.93 2.01 3.00 7.04 2.00 2.06
f1 (ppm)

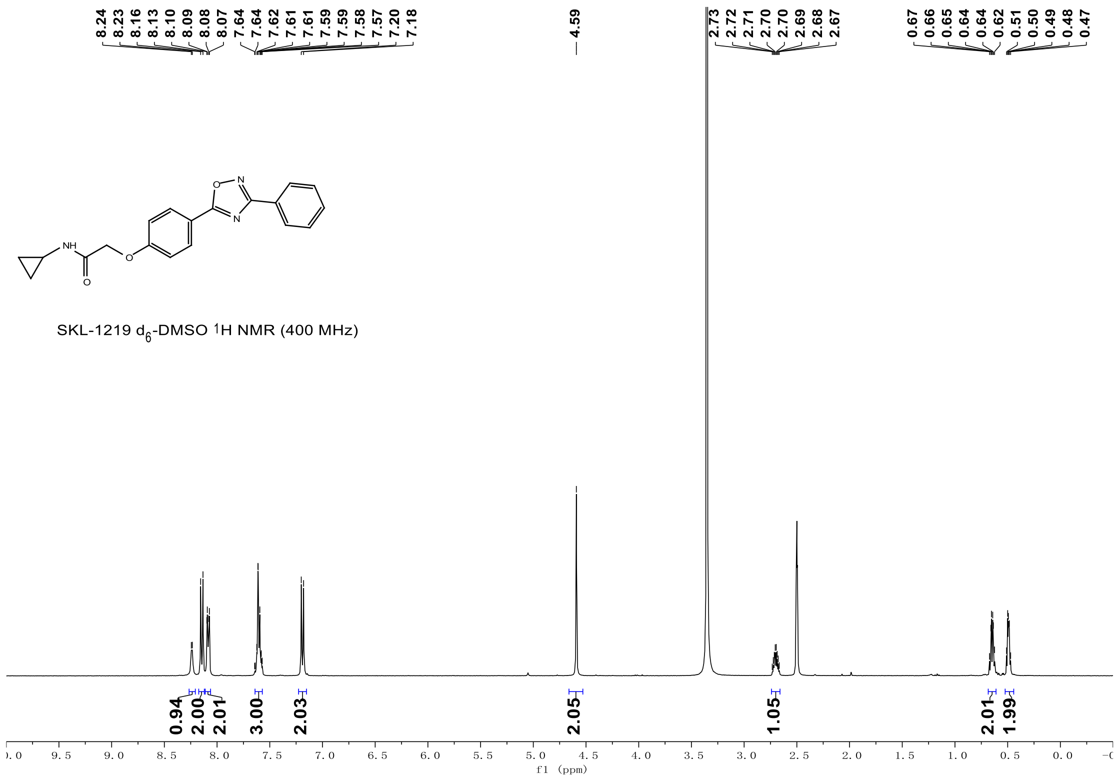

175.25
168.18 167.17 161.60
139.21 131.64 129.94 129.30 128.29 127.28 127.12 126.85 126.31 116.33 115.81
67.01
41.88
SKL-1217 d6-DMSO 13C NMR (101 MHz)
f1 (ppm)



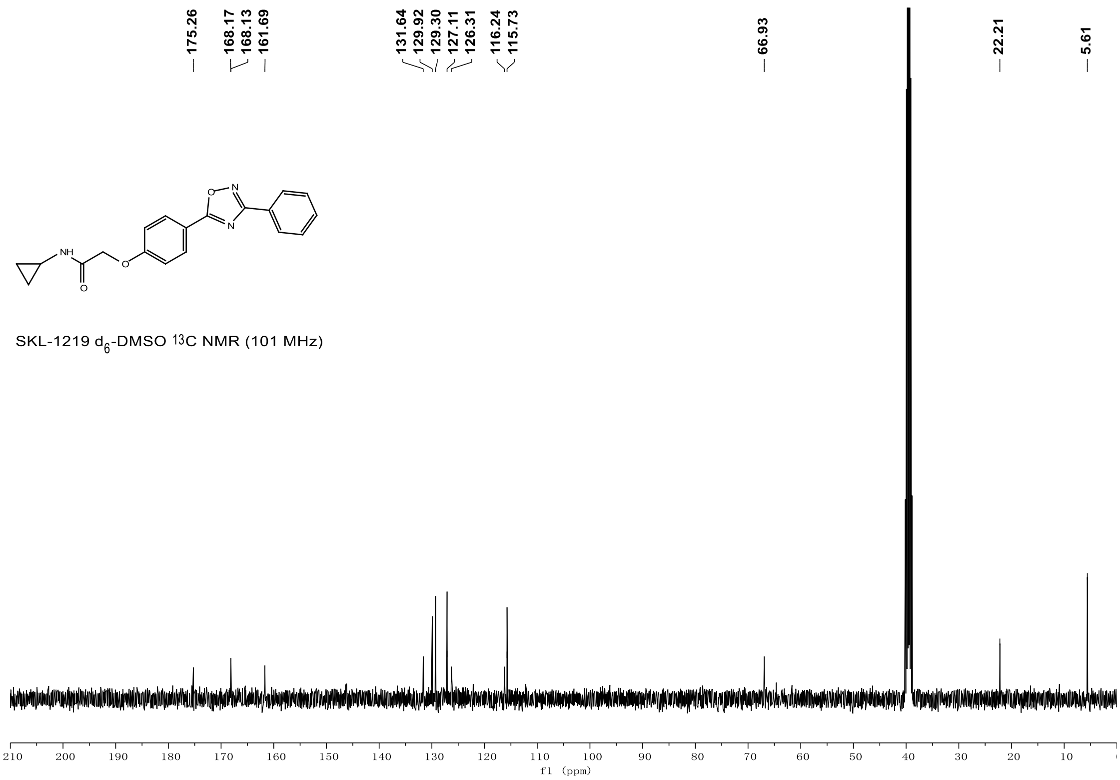
SKL-1218 d_6-DMSO ^{1}H NMR (400 MHz)



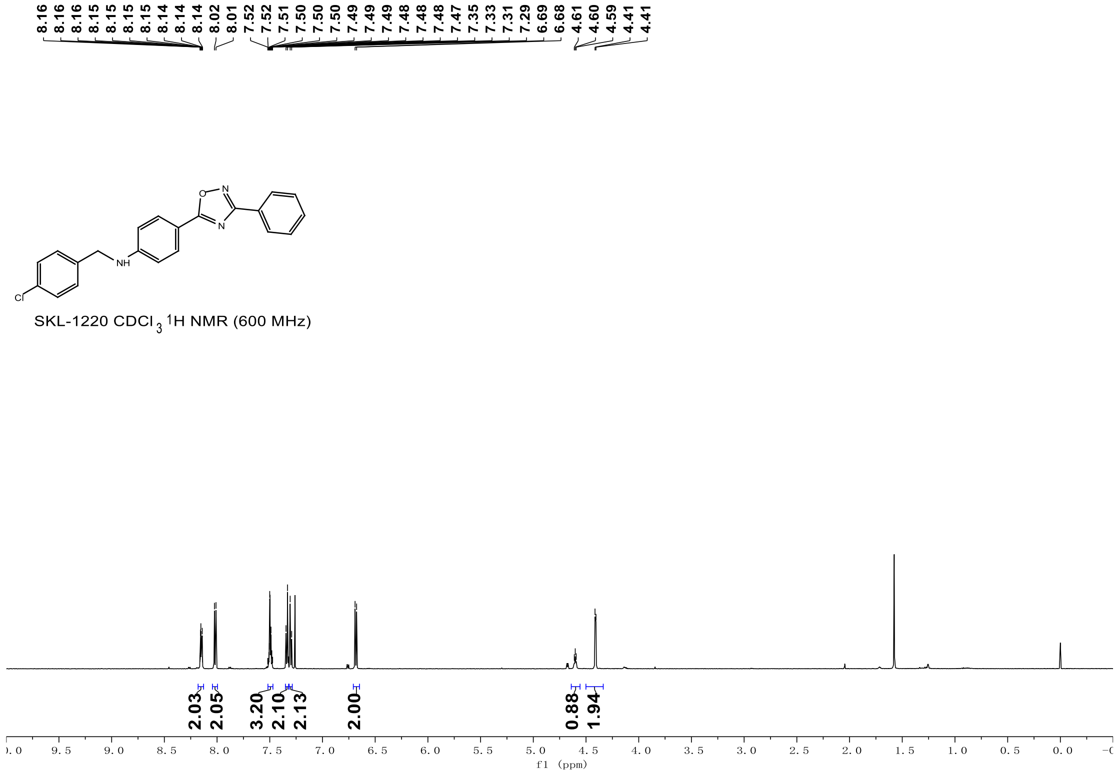
SKL-1218 d_6-DMSO ^{13}C NMR (101 MHz)



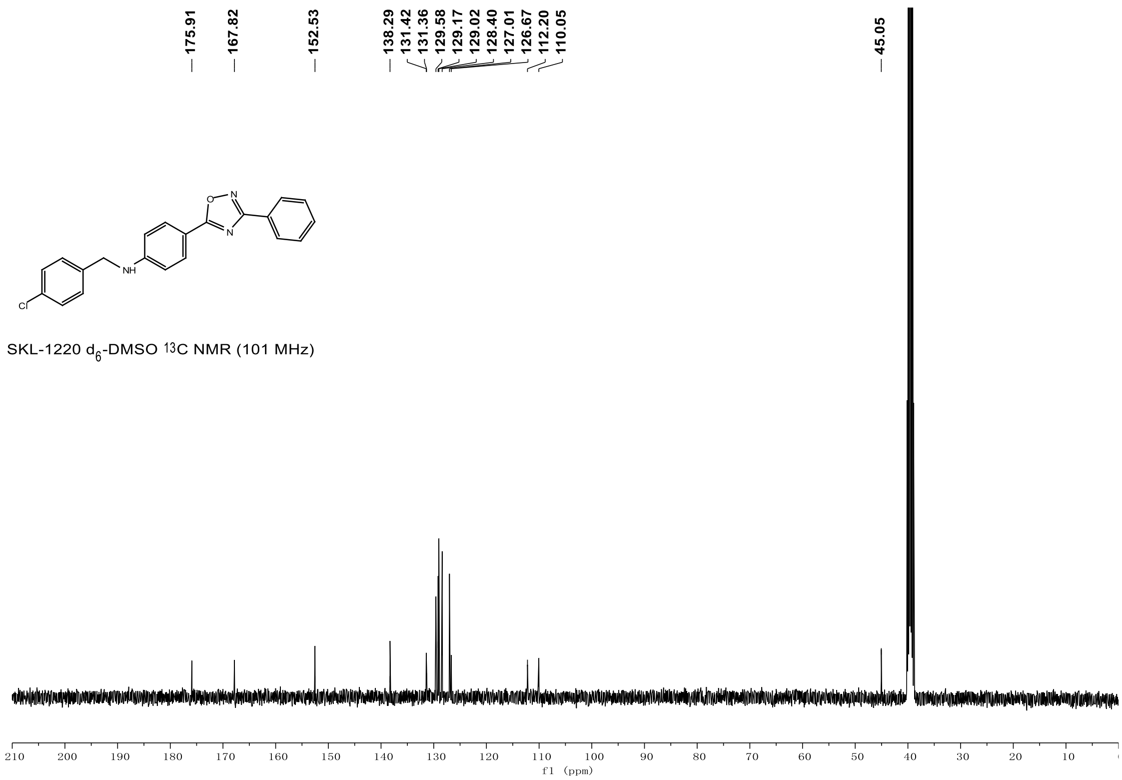
SKL-1219 d_6-DMSO ^1H NMR (400 MHz)



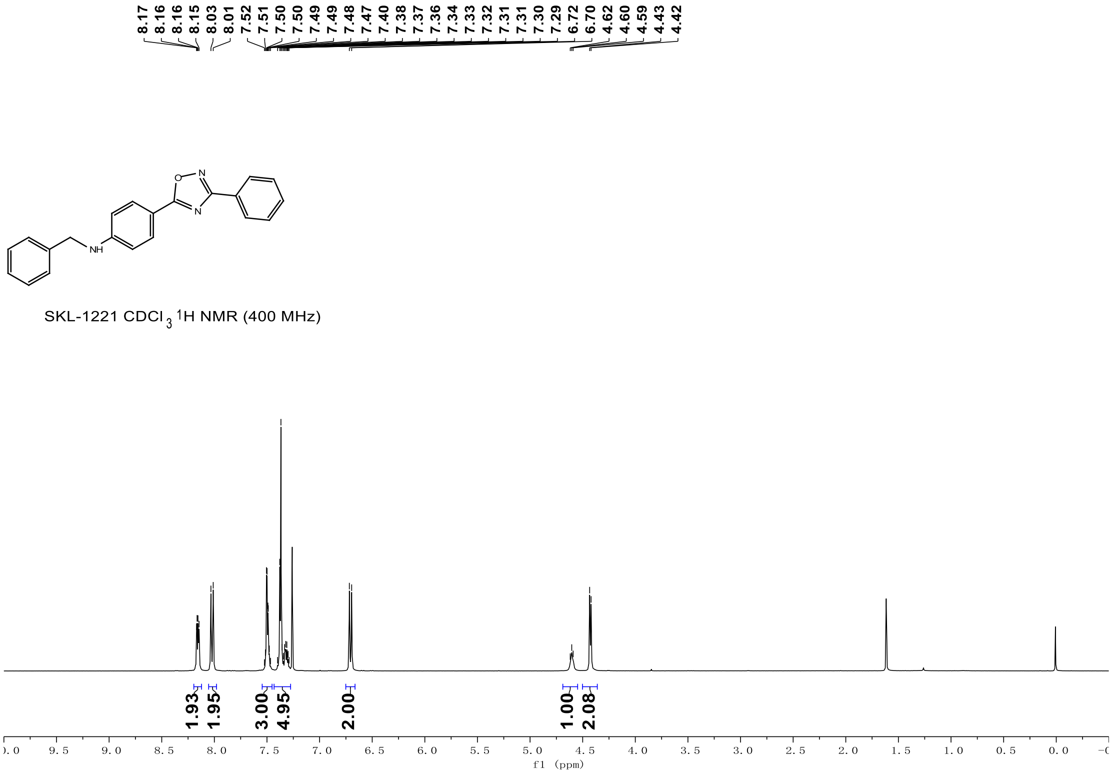
SKL-1219 d_6-DMSO ^{13}C NMR (101 MHz)



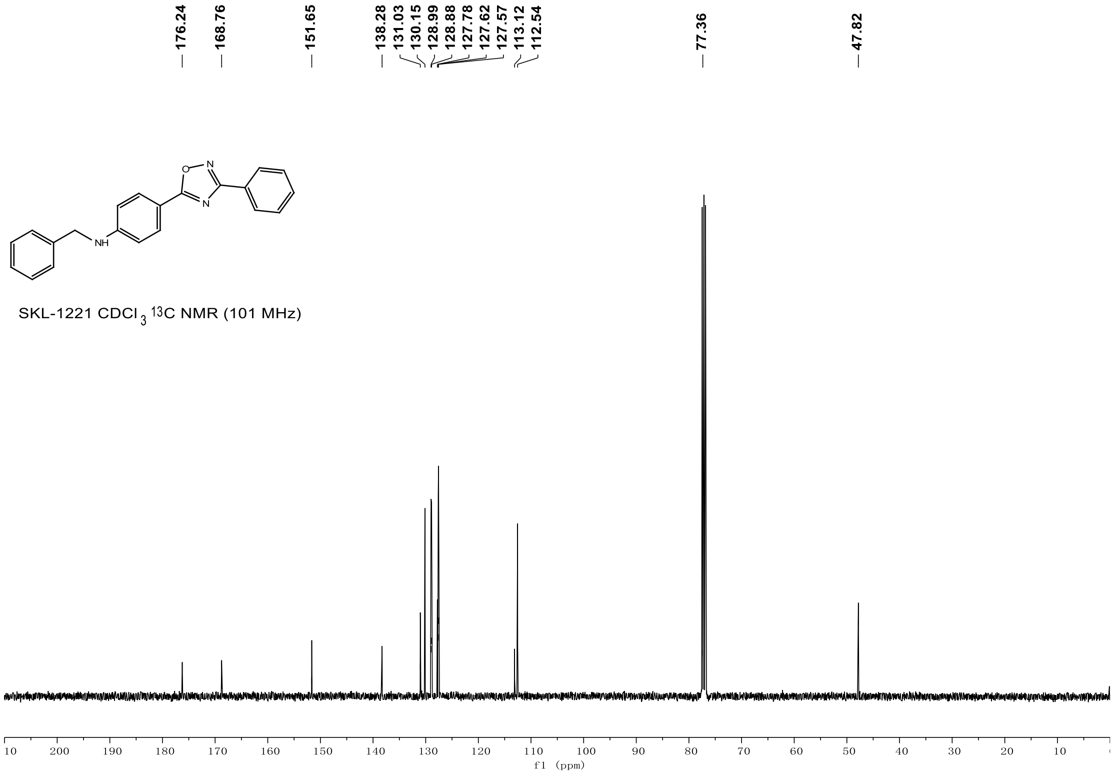
SKL-1220 $CDCl_3$ ^1H NMR (600 MHz)



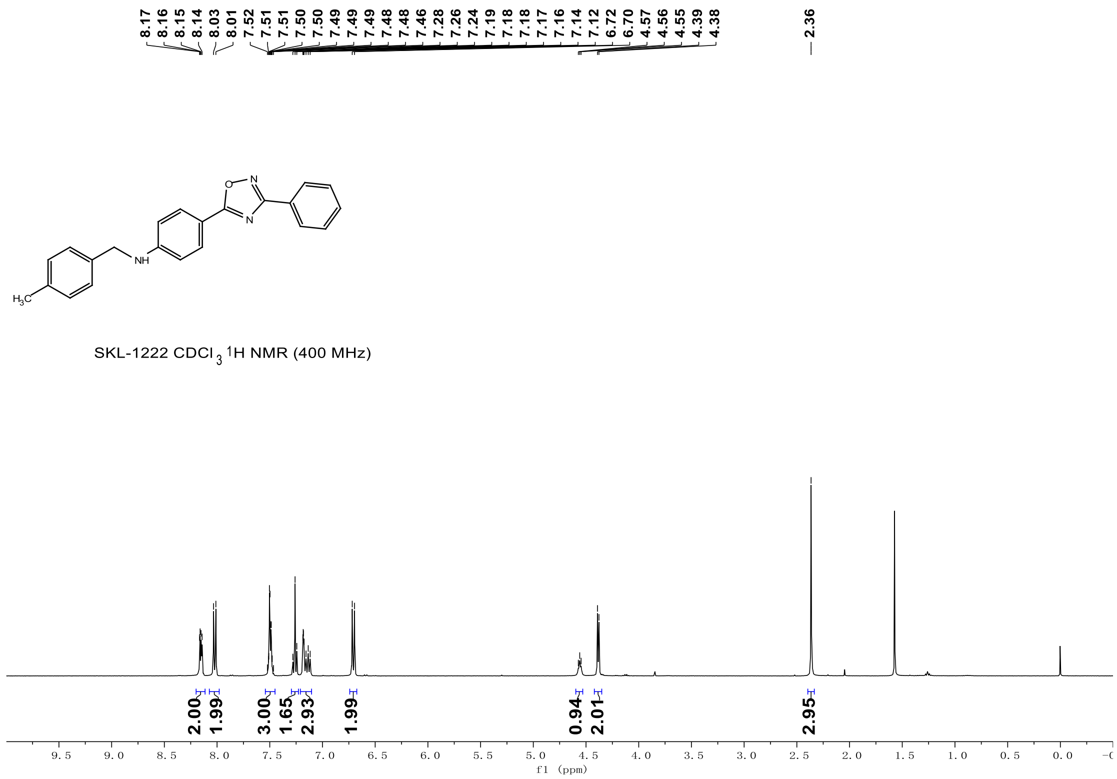
SKL-1220 d_6-DMSO ^{13}C NMR (101 MHz)

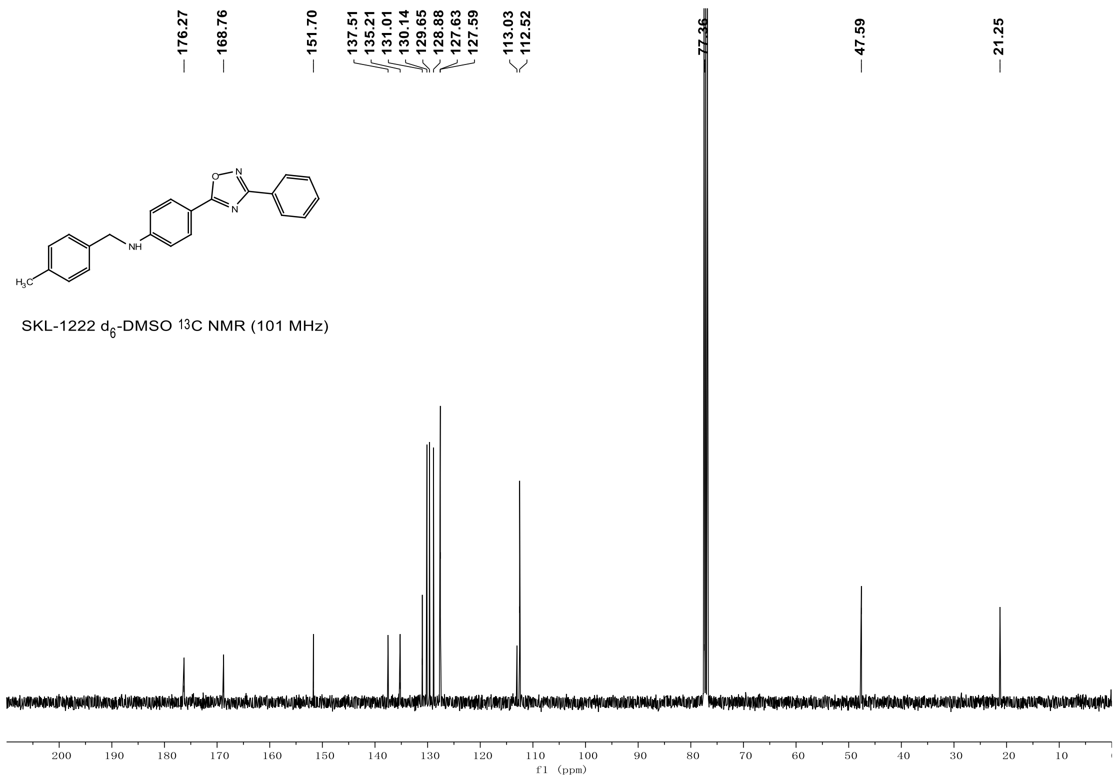


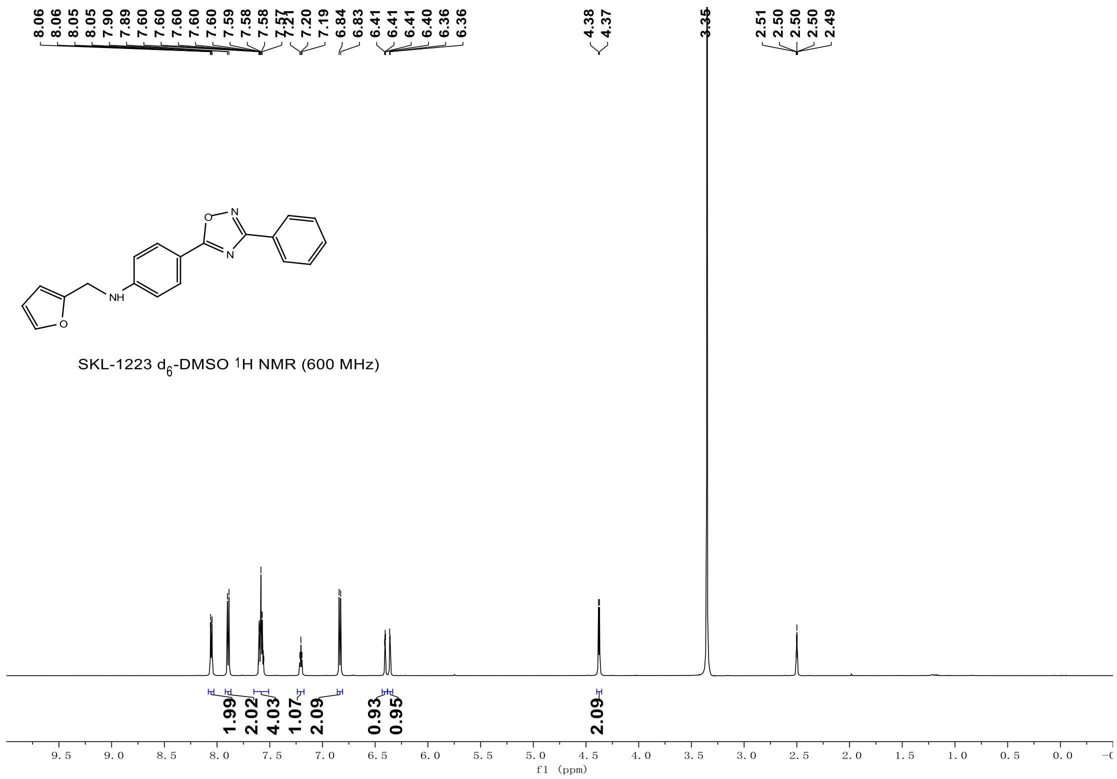
SKL-1221 $CDCl_3$ ^1H NMR (400 MHz)

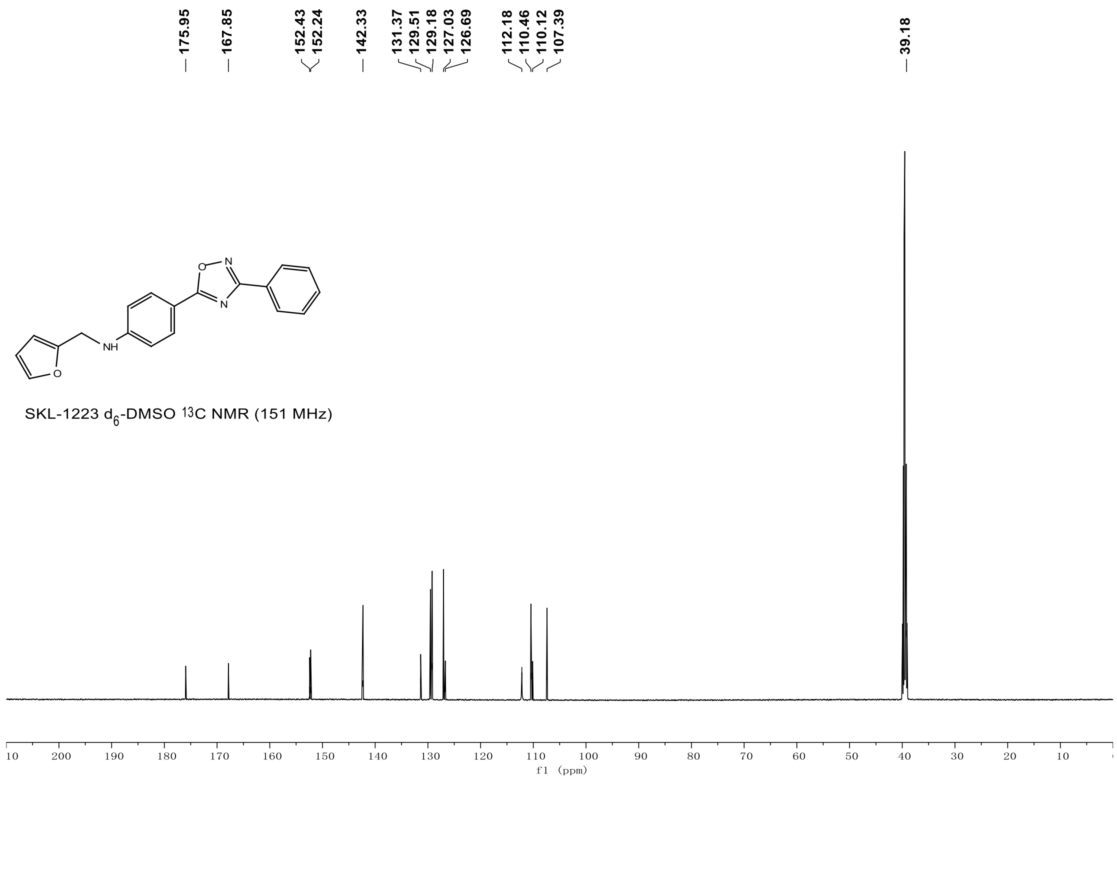


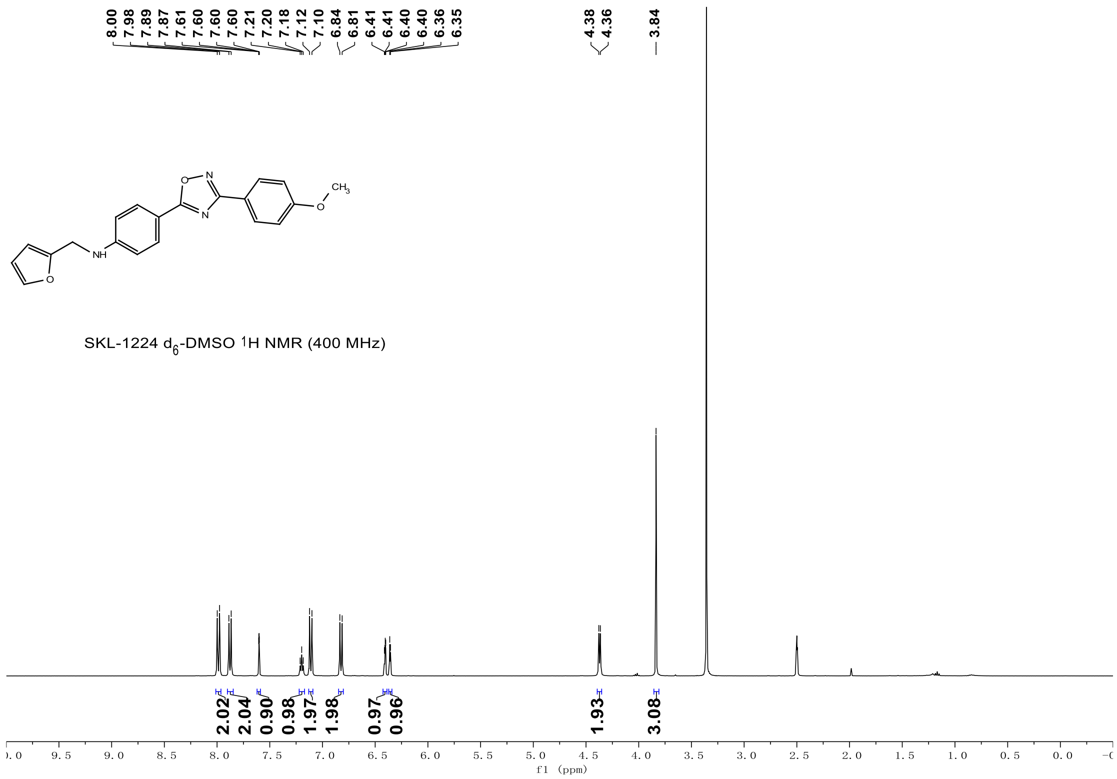
SKL-1221 $CDCl_3$ ^{13}C NMR (101 MHz)


8.17
8.16
8.15
8.14
8.03
8.01
7.52
7.51
7.51
7.50
7.50
7.49
7.49
7.49
7.48
7.48
7.46
7.28
7.26
7.24
7.19
7.18
7.18
7.17
7.16
7.14
7.12
6.72
6.70
4.57
4.56
4.55
4.39
4.38
2.36
SKL-1222 CDCl3 1H NMR (400 MHz)
2.00
1.99
3.00
1.65
2.93
1.99
0.94
2.01
2.95
f1 (ppm)

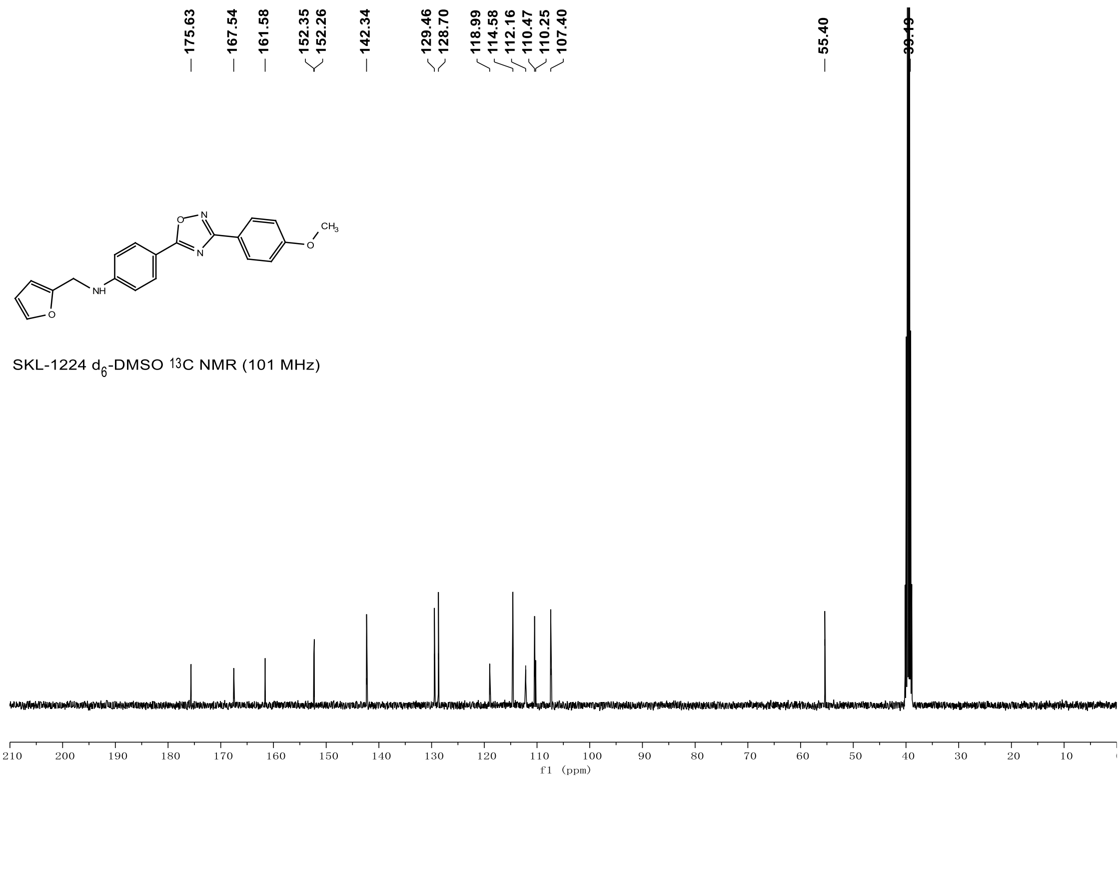

176.27
168.76
151.70
137.51
135.21
131.01
130.14
129.65
128.88
127.63
127.59
113.03
112.52
77.36
47.59
21.25
SKL-1222 d6-DMSO 13C NMR (101 MHz)
f1 (ppm)


8.06
8.06
8.05
8.05
7.90
7.89
7.60
7.60
7.60
7.60
7.59
7.58
7.58
7.57
7.21
7.20
7.19
6.84
6.83
6.41
6.41
6.41
6.40
6.36
6.36
4.38
4.37
3.35
2.51
2.50
2.50
2.50
2.49
NH
O
O
N
N
SKL-1223 d6-DMSO 1H NMR (600 MHz)
1.99
2.02
4.03
1.07
2.09
0.93
0.95
2.09
f1 (ppm)

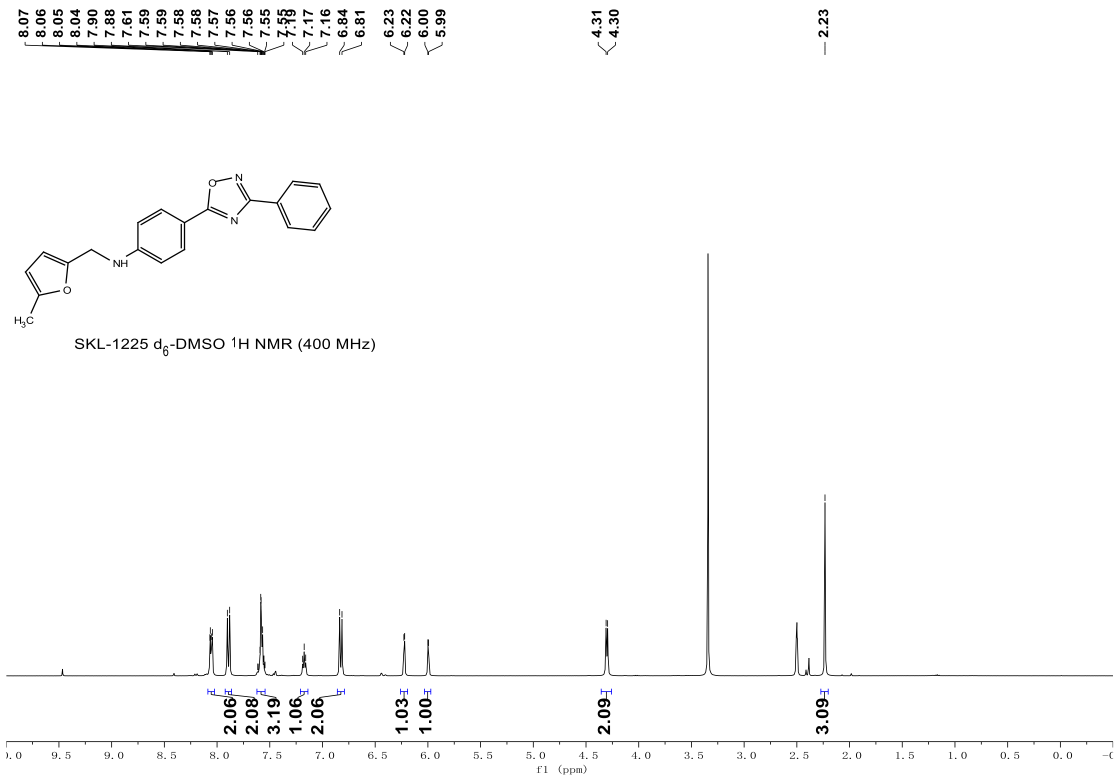

175.95
167.85
152.43
152.24
142.33
131.37
129.51
129.18
127.03
126.69
112.18
110.46
110.12
107.39
39.18
NH
O
O
N
N
SKL-1223 d6-DMSO 13C NMR (151 MHz)
f1 (ppm)

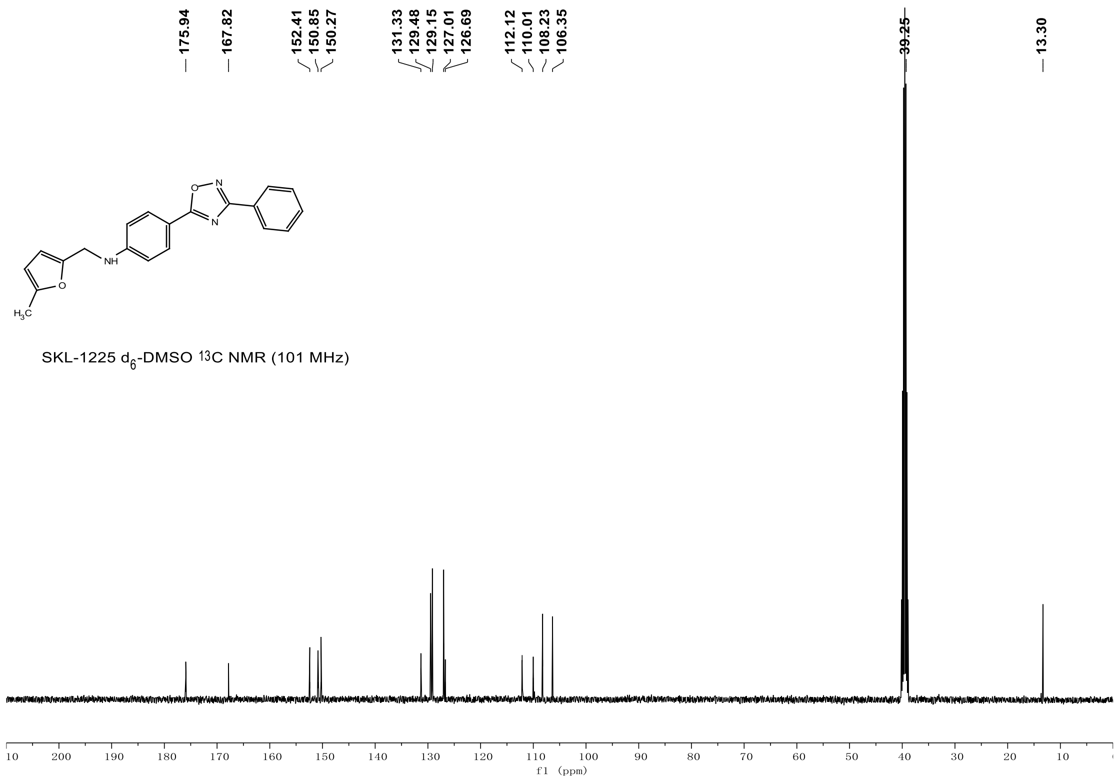


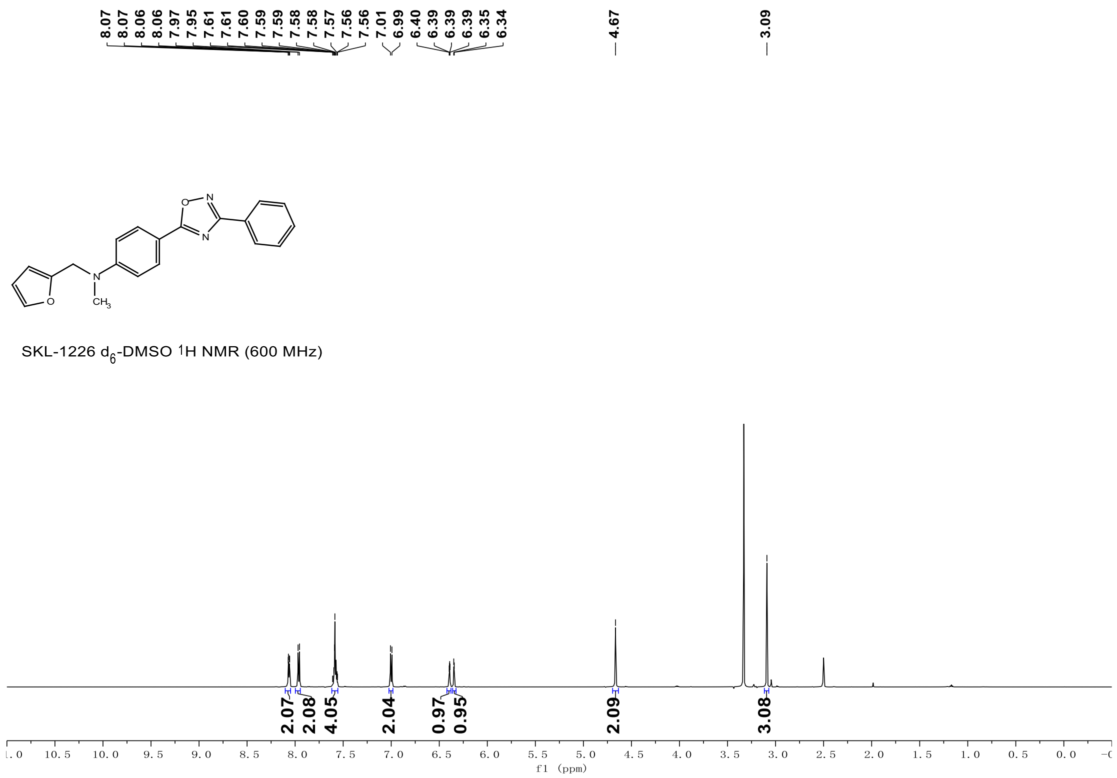
SKL-1224 d6-DMSO 1H NMR (400 MHz)

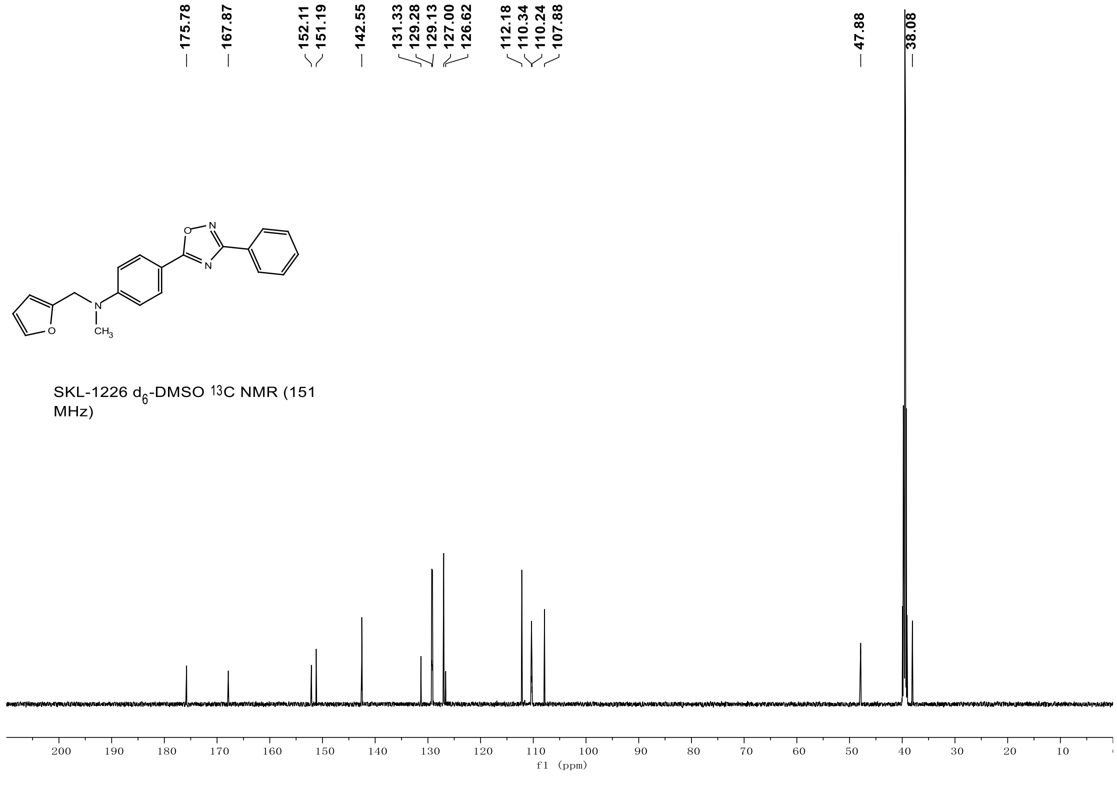


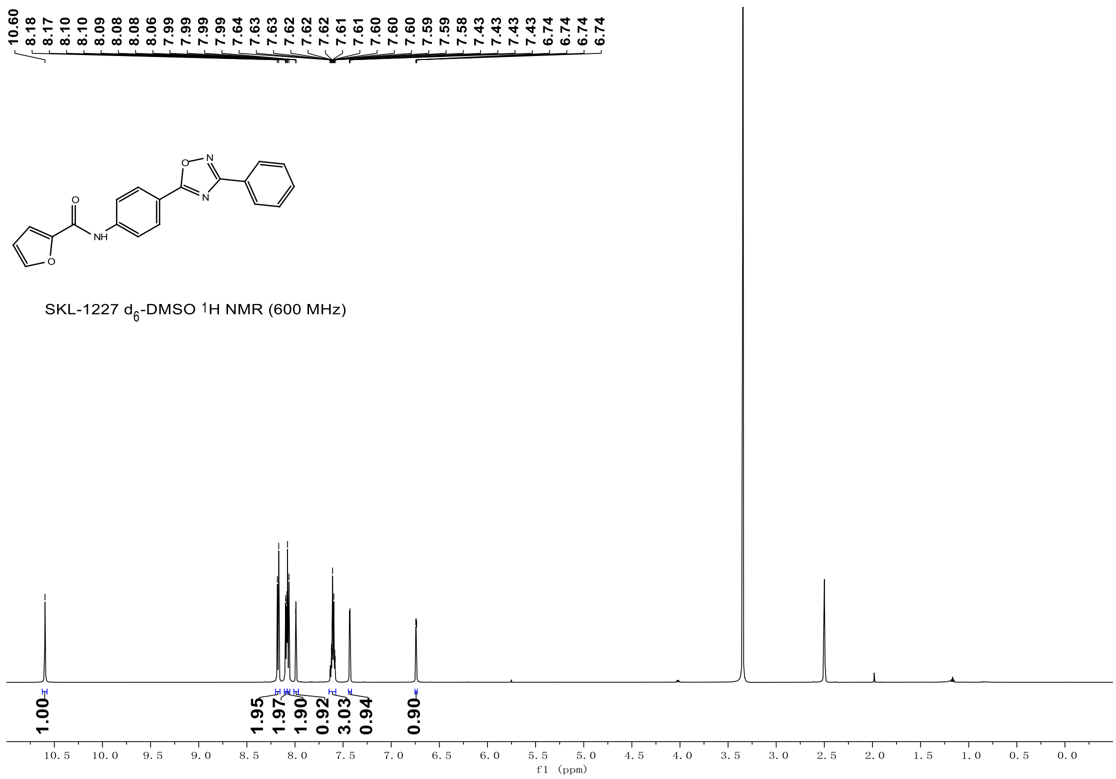
SKL-1224 d6-DMSO 13C NMR (101 MHz)


8.07 8.06 8.05 8.04 7.90 7.88 7.61 7.59 7.59 7.58 7.58 7.57 7.56 7.56 7.55 7.55 7.19 7.17 7.16 6.84 6.81 6.23 6.22 6.00 5.99 4.31 4.30 2.23
NH
O
N
H3C
SKL-1225 d6-DMSO 1H NMR (400 MHz)
2.06 2.08 3.19 1.06 2.06 1.03 1.00 2.09 3.09
f1 (ppm)

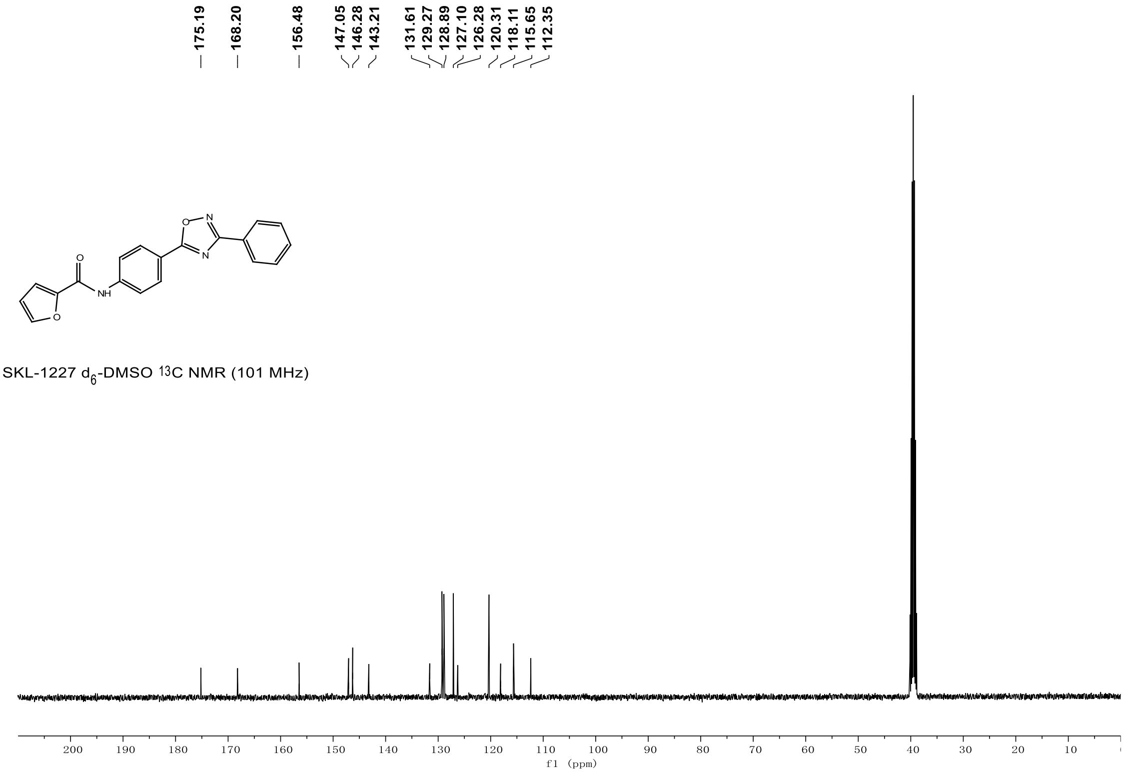

175.94 167.82 152.41 150.85 150.27 131.33 129.48 129.15 127.01 126.69 112.12 110.01 108.23 106.35 39.25 13.30
NH
O
N
H3C
SKL-1225 d6-DMSO 13C NMR (101 MHz)
f1 (ppm)


8.07 8.07 8.06 8.06 7.97 7.95 7.61 7.61 7.60 7.59 7.59 7.59 7.58 7.58 7.57 7.56 7.56 7.01 6.99 6.40 6.39 6.39 6.39 6.35 6.34
4.67
3.09
SKL-1226 d$_6$-DMSO ^{1}H NMR (600 MHz)
2.07 2.08 4.05 2.04 0.97 0.95 2.09 3.08
f1 (ppm)

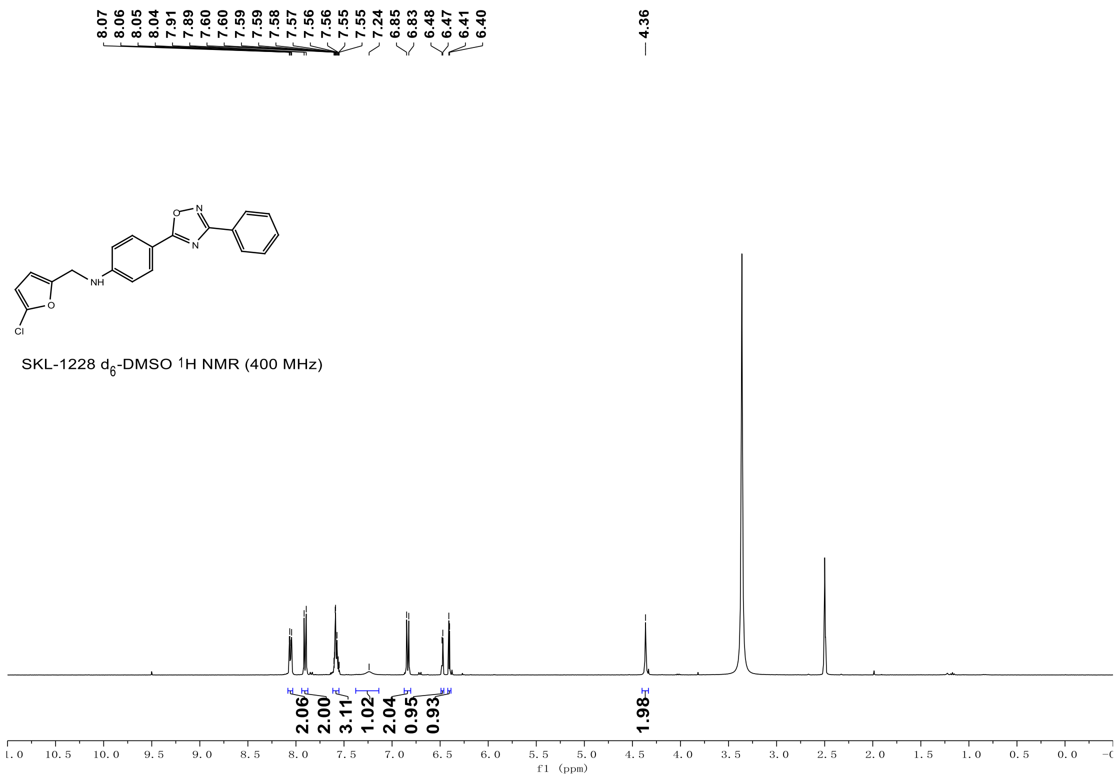

175.78
167.87
152.11 151.19
142.55
131.33 129.28 129.13 127.00 126.62
112.18 110.34 110.24 107.88
47.88
38.08
SKL-1226 d$_6$-DMSO ^{13}C NMR (151 MHz)
f1 (ppm)

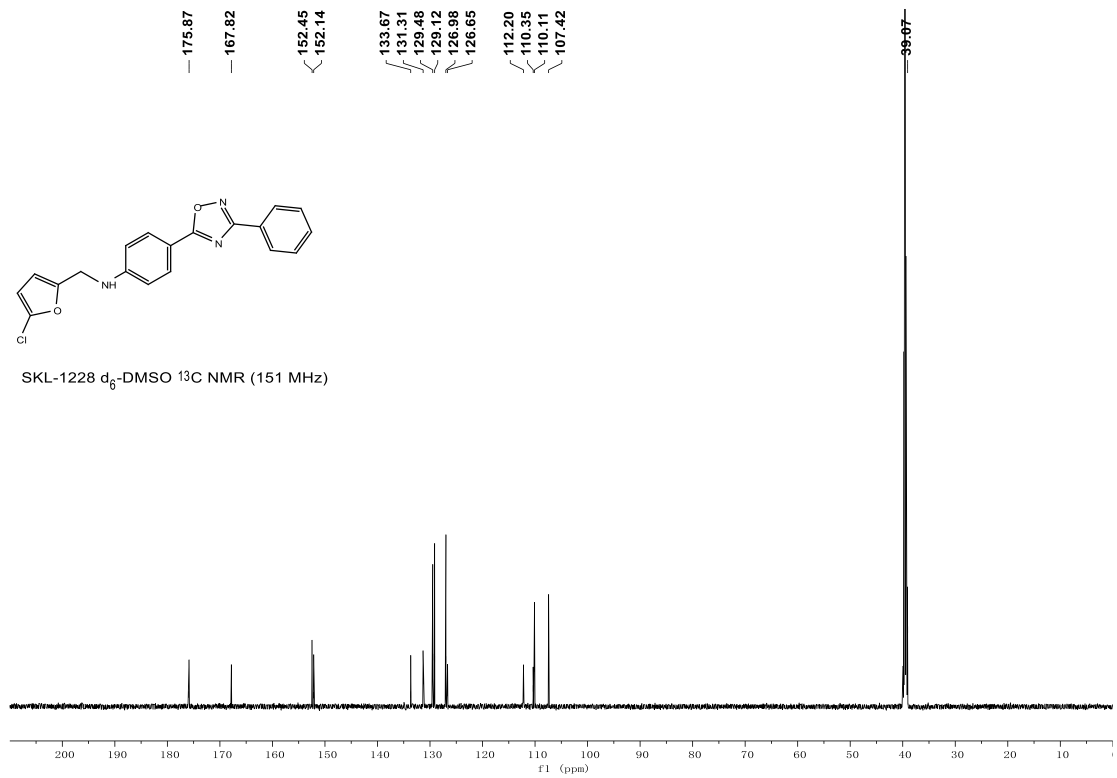


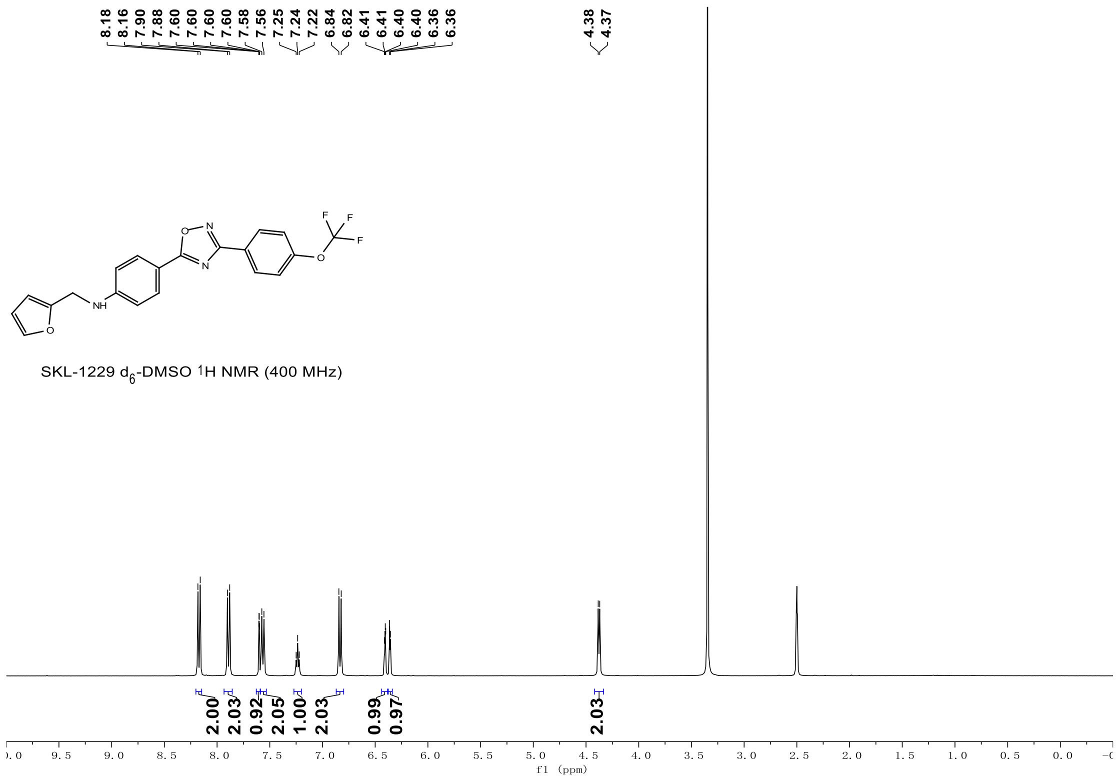
SKL-1227 d_6-DMSO ^{1}H NMR (600 MHz)

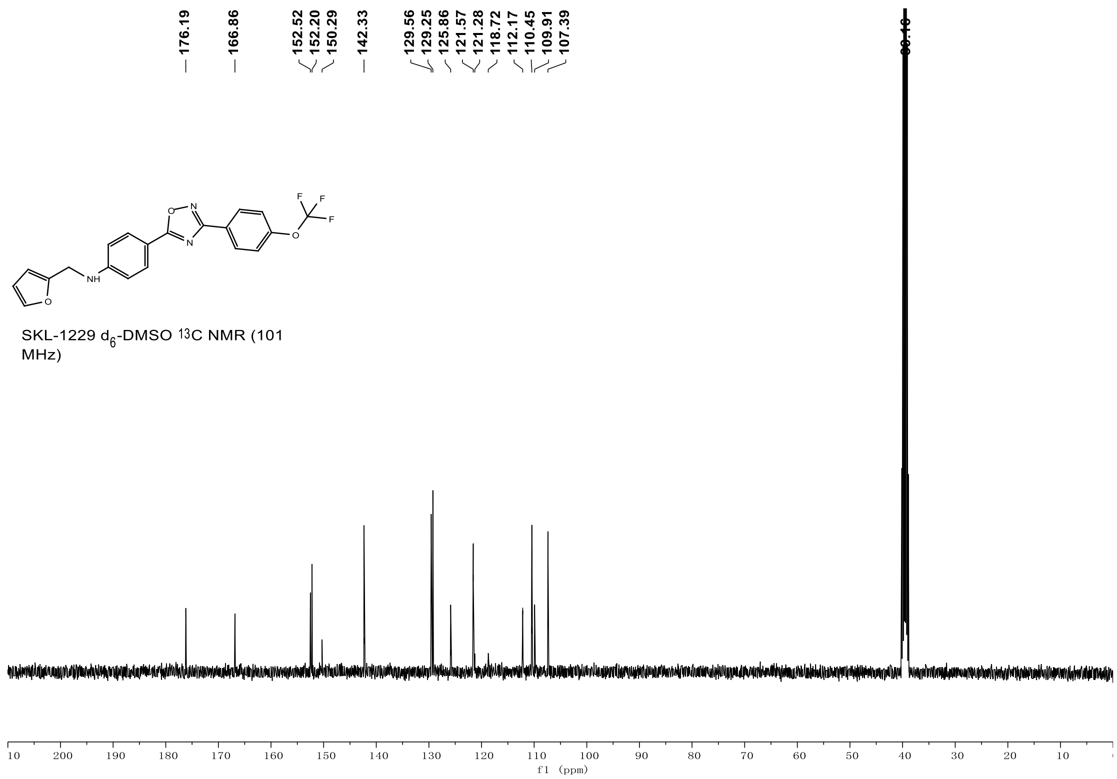


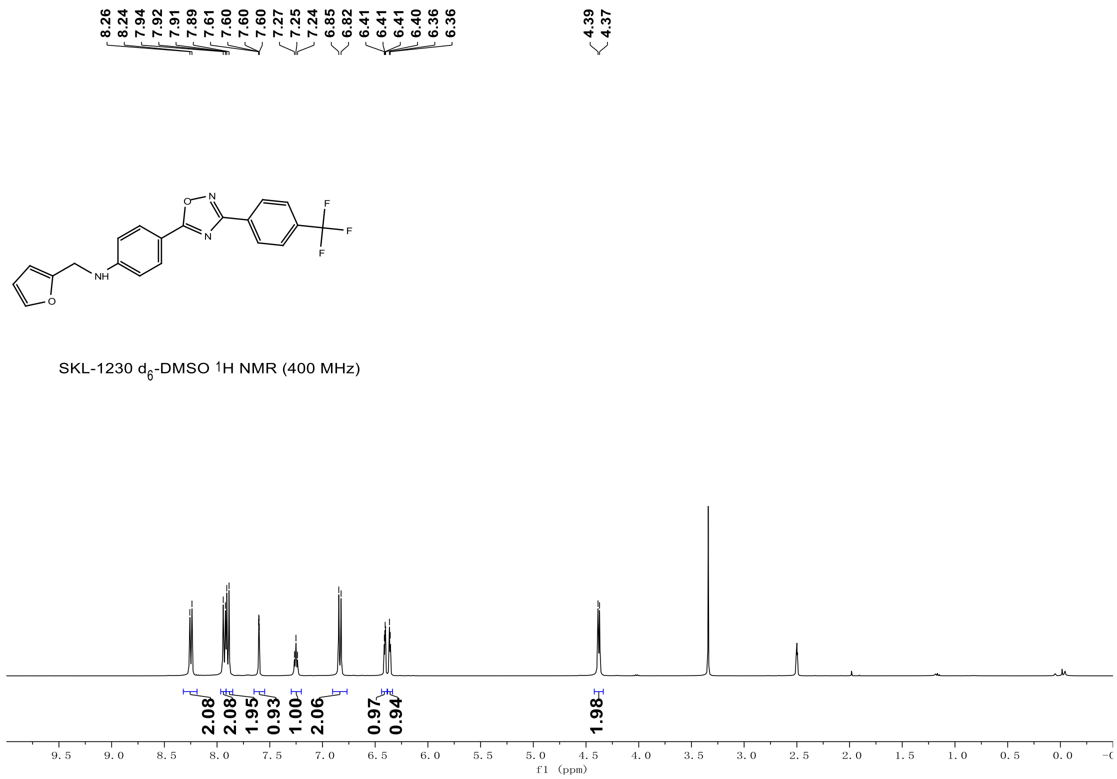
SKL-1227 d_6-DMSO ^{13}C NMR (101 MHz)


8.07 8.06 8.05 8.04 7.91 7.89 7.60 7.60 7.59 7.59 7.58 7.57 7.56 7.56 7.55 7.55 7.24 6.85 6.83 6.48 6.47 6.41 6.40
4.36
O–N
N
NH
O
Cl
SKL-1228 d_6-DMSO ^{1}H NMR (400 MHz)
2.06 2.00 3.11 1.02 2.04 0.95 0.93
1.98
f1 (ppm)

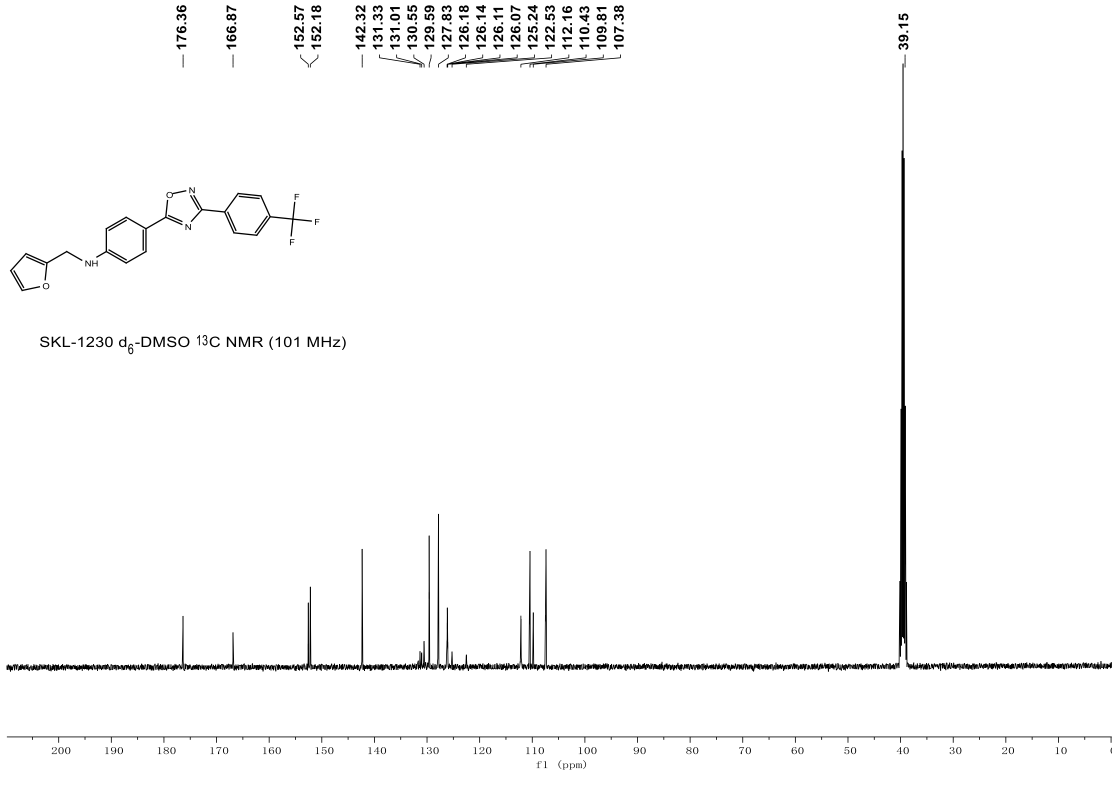

175.87
167.82
152.45 152.14
133.67 131.31 129.48 129.12 126.98 126.65
112.20 110.35 110.11 107.42
39.07
O–N
N
NH
O
Cl
SKL-1228 d_6-DMSO ^{13}C NMR (151 MHz)
f1 (ppm)


8.18 8.16 7.90 7.88 7.60 7.60 7.60 7.58 7.56 7.25 7.24 7.22 6.84 6.82 6.41 6.41 6.40 6.40 6.36 6.36
4.38 4.37
SKL-1229 d6-DMSO 1H NMR (400 MHz)
2.00 2.03 0.92 2.05 1.00 2.03 0.99 0.97 2.03
f1 (ppm)

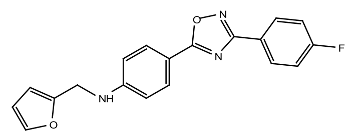

176.19 166.86 152.52 152.20 150.29 142.33 129.56 129.25 125.86 121.57 121.28 118.72 112.17 110.45 109.91 107.39
SKL-1229 d6-DMSO 13C NMR (101 MHz)
f1 (ppm)



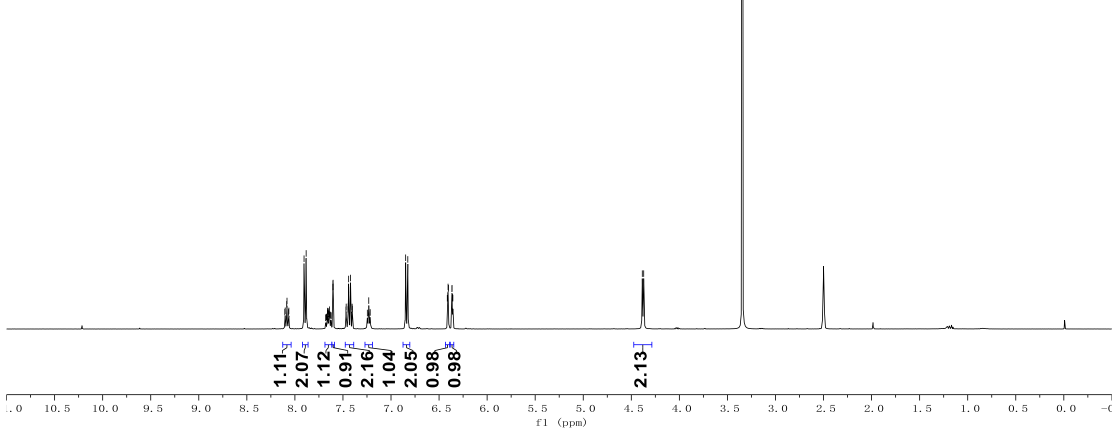
SKL-1230 d_6-DMSO ^{1}H NMR (400 MHz)

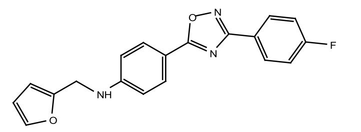


SKL-1230 d_6-DMSO ^{13}C NMR (101 MHz)

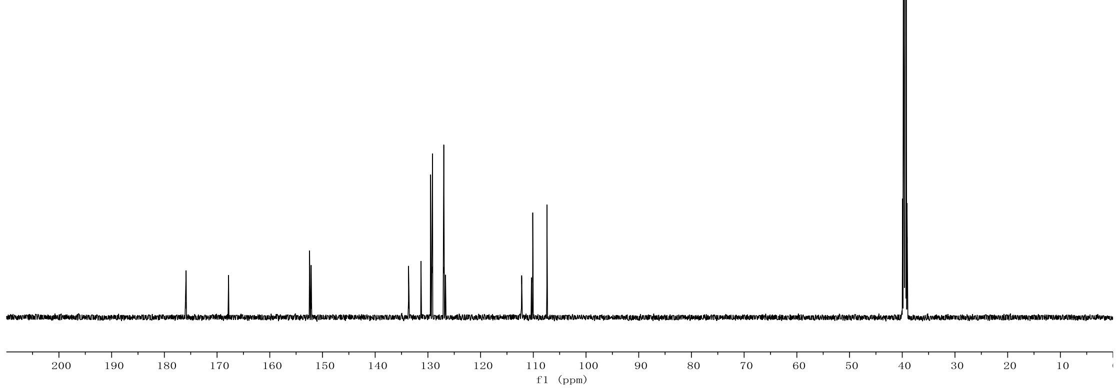


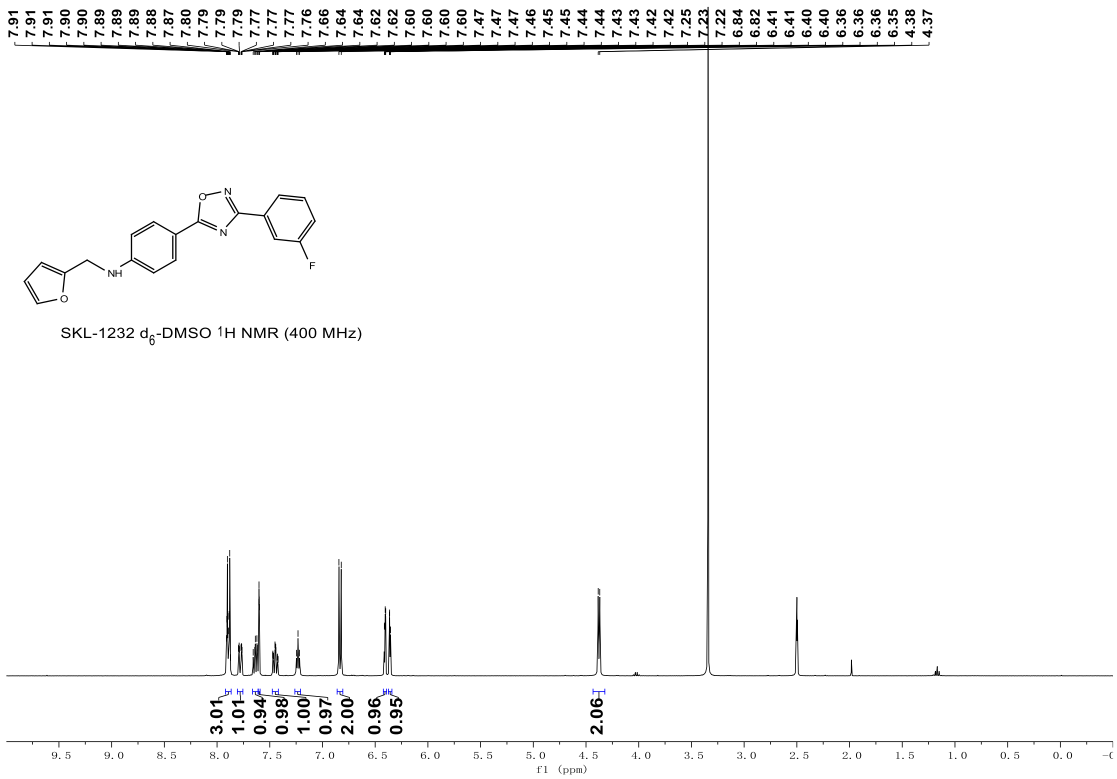
SKL-1231 d_6-DMSO ^{1}H NMR (400 MHz)

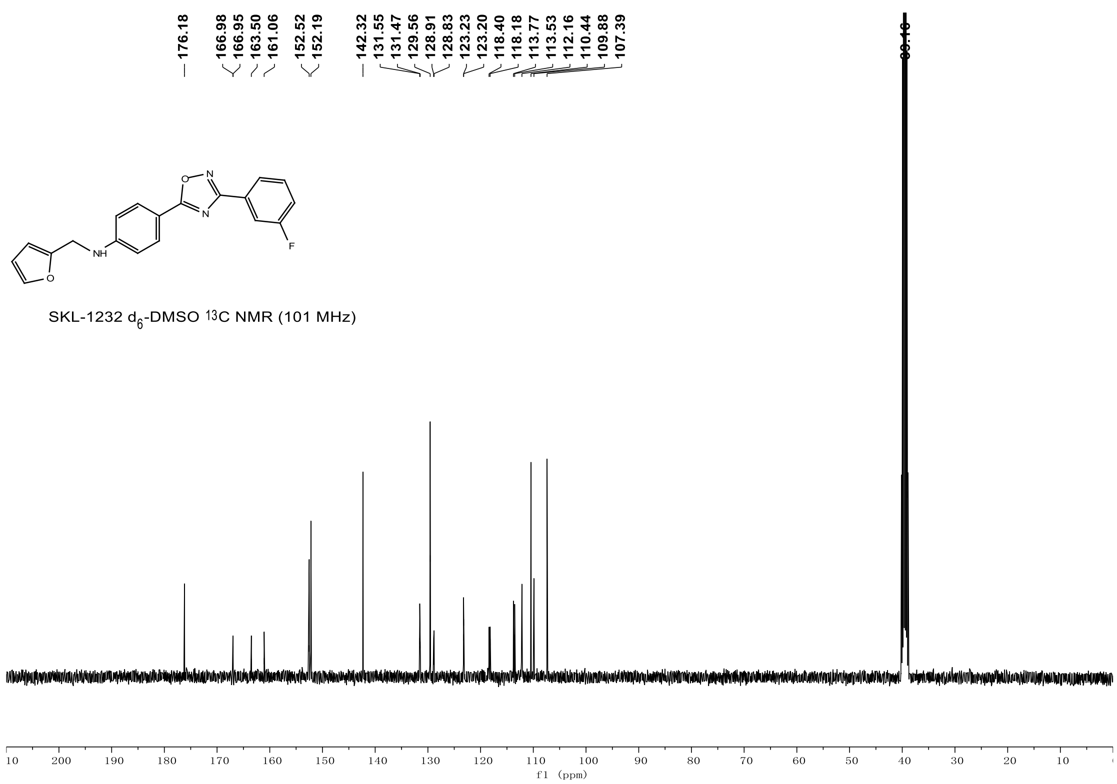


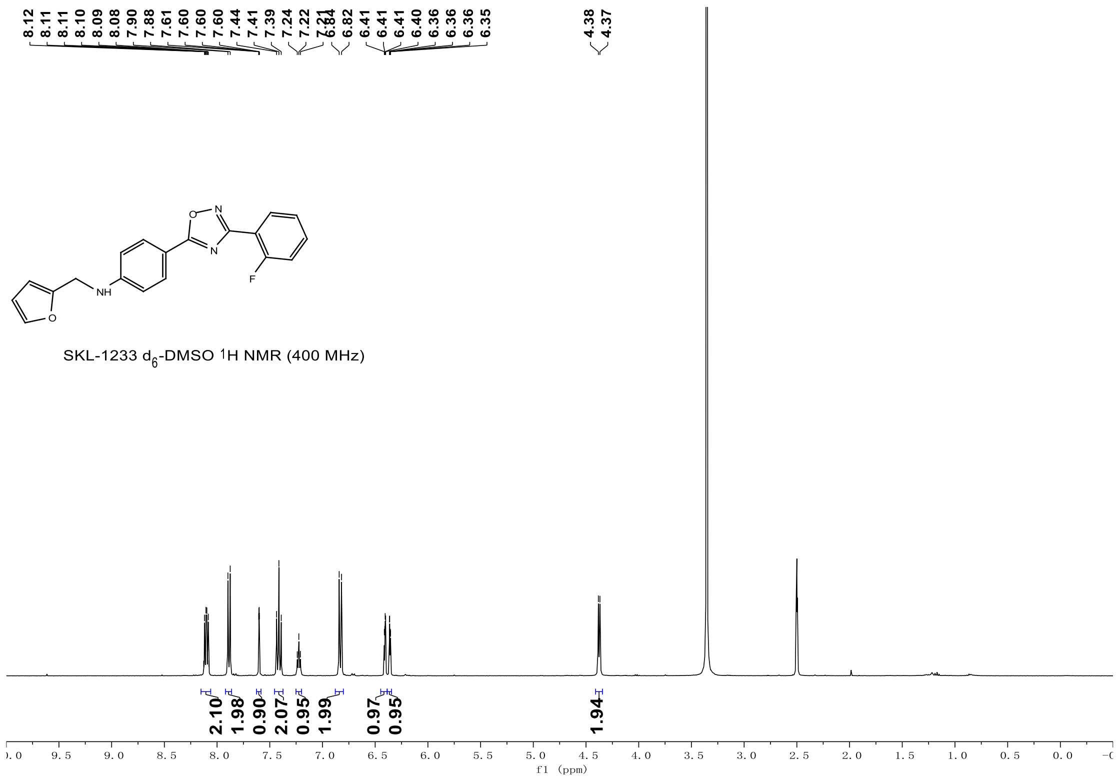


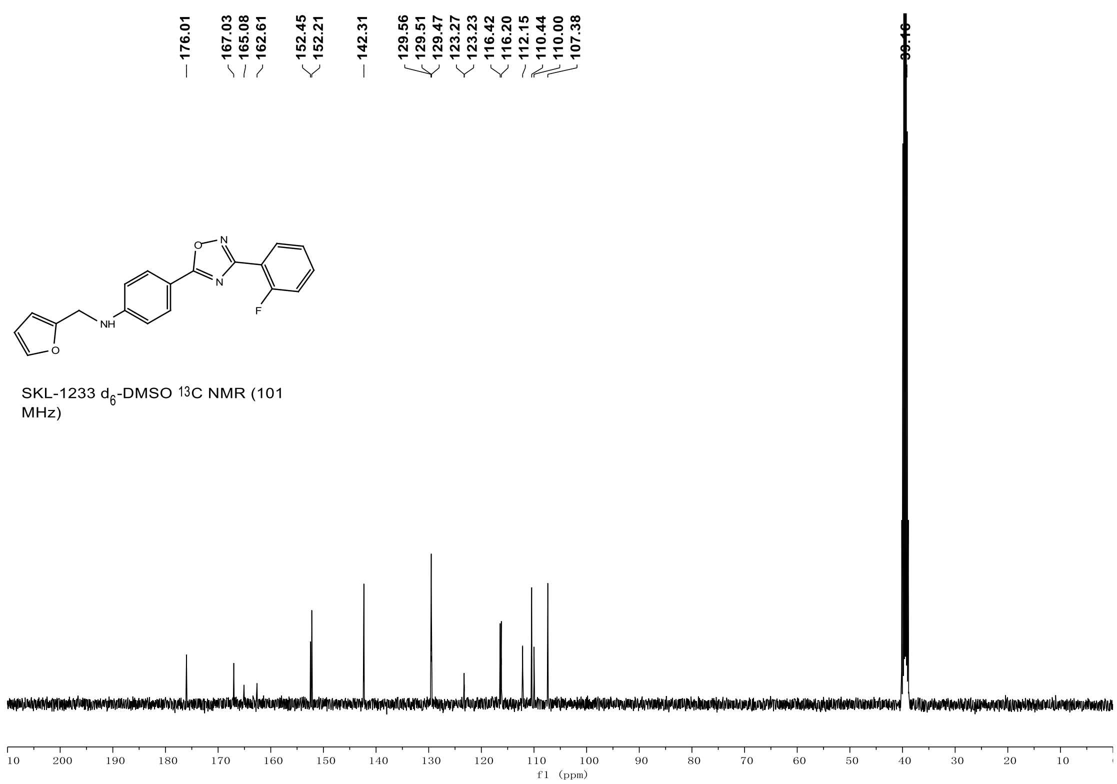
SKL-1231 d_6-DMSO ^{13}C NMR (151 MHz)

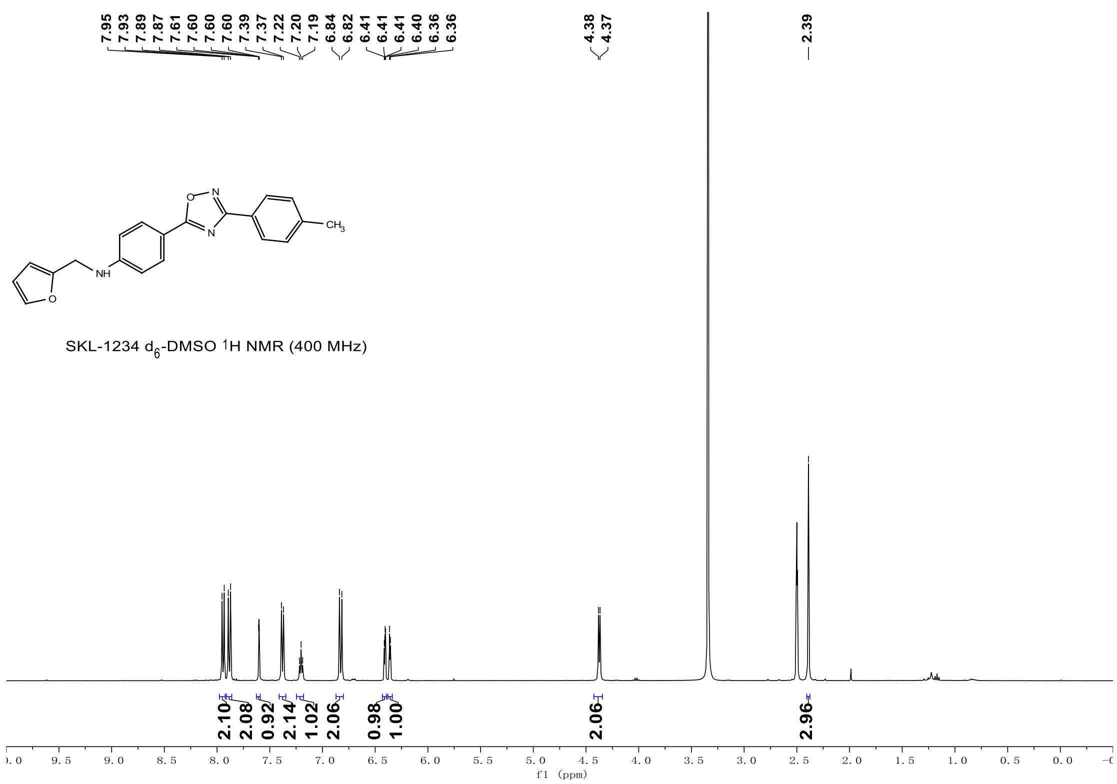


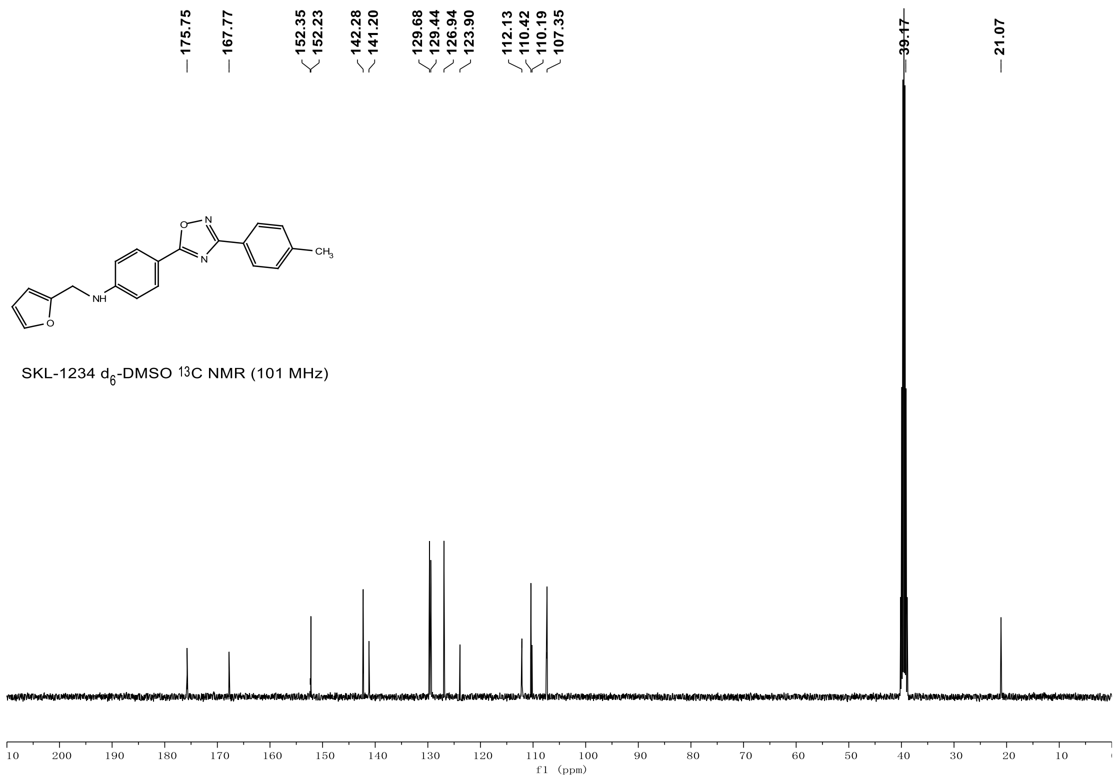

7.91
7.91
7.90
7.90
7.89
7.89
7.88
7.87
7.80
7.79
7.79
7.77
7.77
7.77
7.76
7.66
7.64
7.64
7.62
7.62
7.60
7.60
7.60
7.60
7.47
7.47
7.47
7.46
7.45
7.45
7.44
7.44
7.43
7.42
7.42
7.25
7.23
7.22
6.84
6.82
6.41
6.40
6.36
6.36
6.35
4.38
4.37
O
N
N
NH
O
F
SKL-1232 d6-DMSO 1H NMR (400 MHz)
3.01
1.01
0.94
0.98
1.00
0.97
2.00
0.96
0.95
2.06
f1 (ppm)

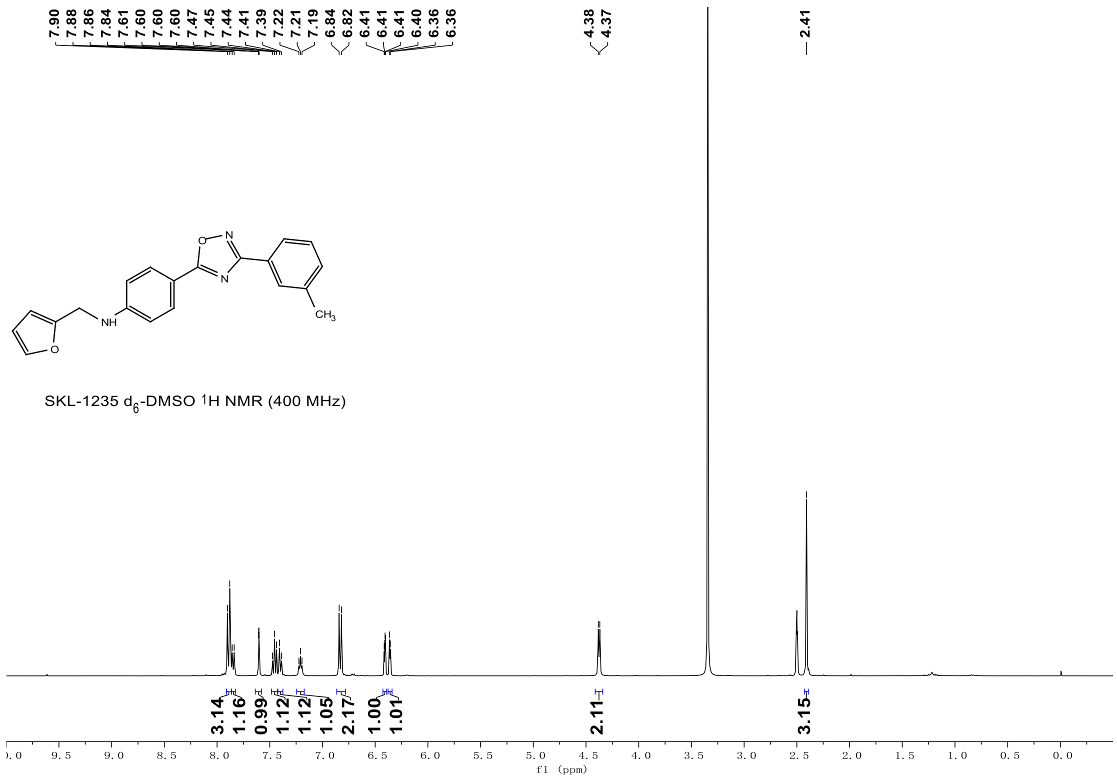

176.18
166.98
166.95
163.50
161.06
152.52
152.19
142.32
131.55
131.47
129.56
128.91
128.83
123.23
123.20
118.40
118.18
113.77
113.53
112.16
110.44
109.88
107.39
O
N
N
NH
O
F
SKL-1232 d6-DMSO 13C NMR (101 MHz)
f1 (ppm)


8.12 8.11 8.11 8.10 8.09 8.08 7.90 7.88 7.61 7.60 7.60 7.60 7.44 7.41 7.39 7.24 7.22 7.21 6.84 6.82 6.41 6.41 6.40 6.36 6.36 6.36 6.35
4.38 4.37
O–N
N
F
NH
O
SKL-1233 d_6-DMSO ^{1}H NMR (400 MHz)
2.10 1.98 0.90 2.07 0.95 1.99 0.97 0.95 1.94
f1 (ppm)

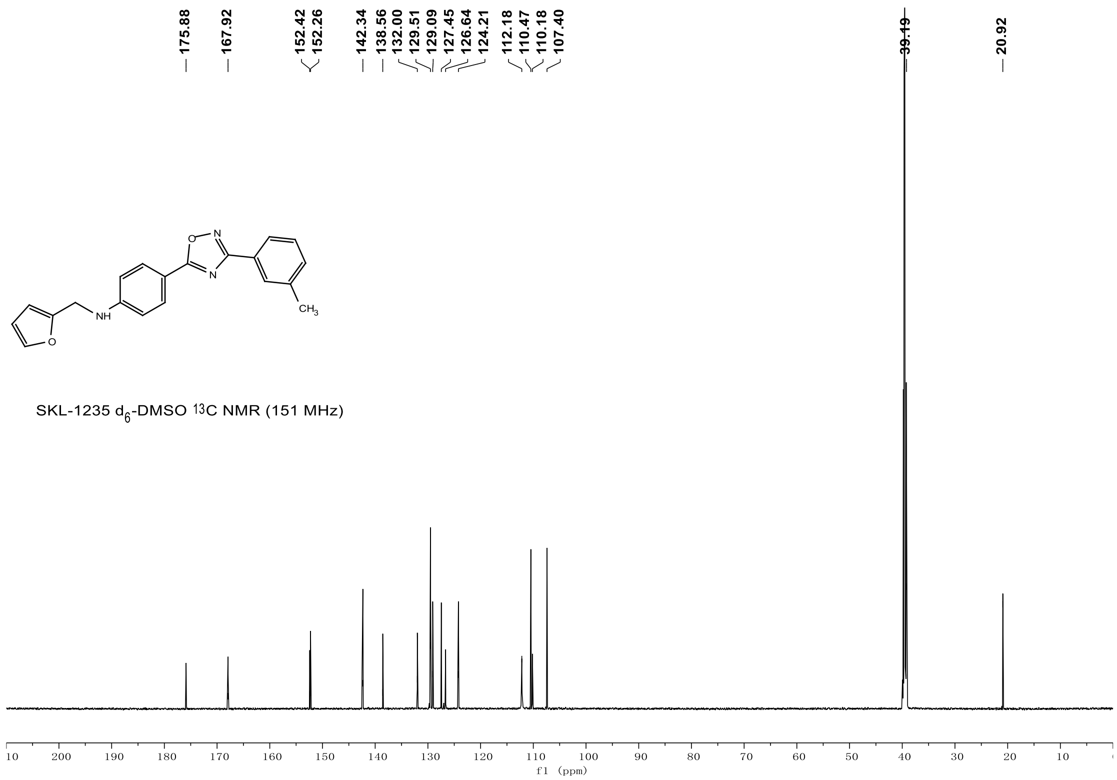

176.01
167.03 165.08 162.61
152.45 152.21
142.31
129.56 129.51 129.47 123.27 123.23 116.42 116.20 112.15 110.44 110.00 107.38
O–N
N
F
NH
O
SKL-1233 d_6-DMSO ^{13}C NMR (101 MHz)
f1 (ppm)


7.95 7.93 7.89 7.87 7.61 7.60 7.60 7.39 7.37 7.22 7.20 7.19 6.84 6.82 6.41 6.41 6.41 6.40 6.36 6.36
4.38 4.37
2.39
NH
O
N
CH3
SKL-1234 d6-DMSO 1H NMR (400 MHz)
2.10 2.08 0.92 2.14 1.02 2.06 0.98 1.00
2.06
2.96
f1 (ppm)

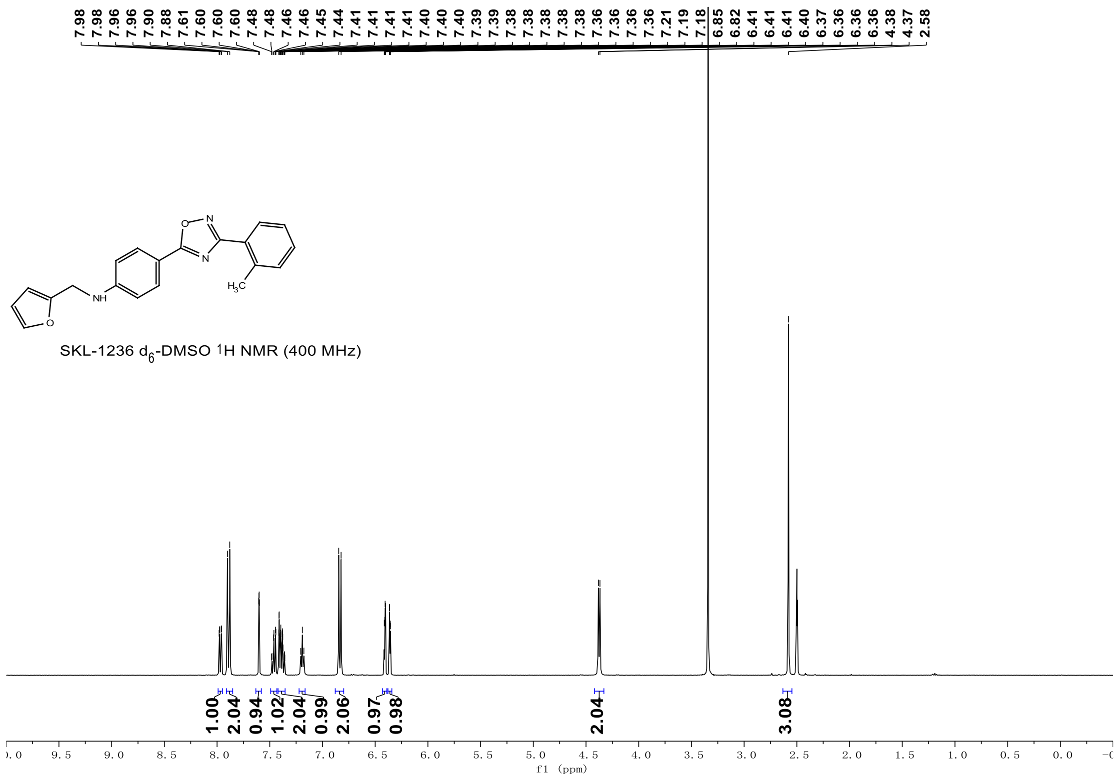

175.75 167.77 152.35 152.23 142.28 141.20 129.68 129.44 126.94 123.90 112.13 110.42 110.19 107.35
39.17
21.07
NH
O
N
CH3
SKL-1234 d6-DMSO 13C NMR (101 MHz)
f1 (ppm)



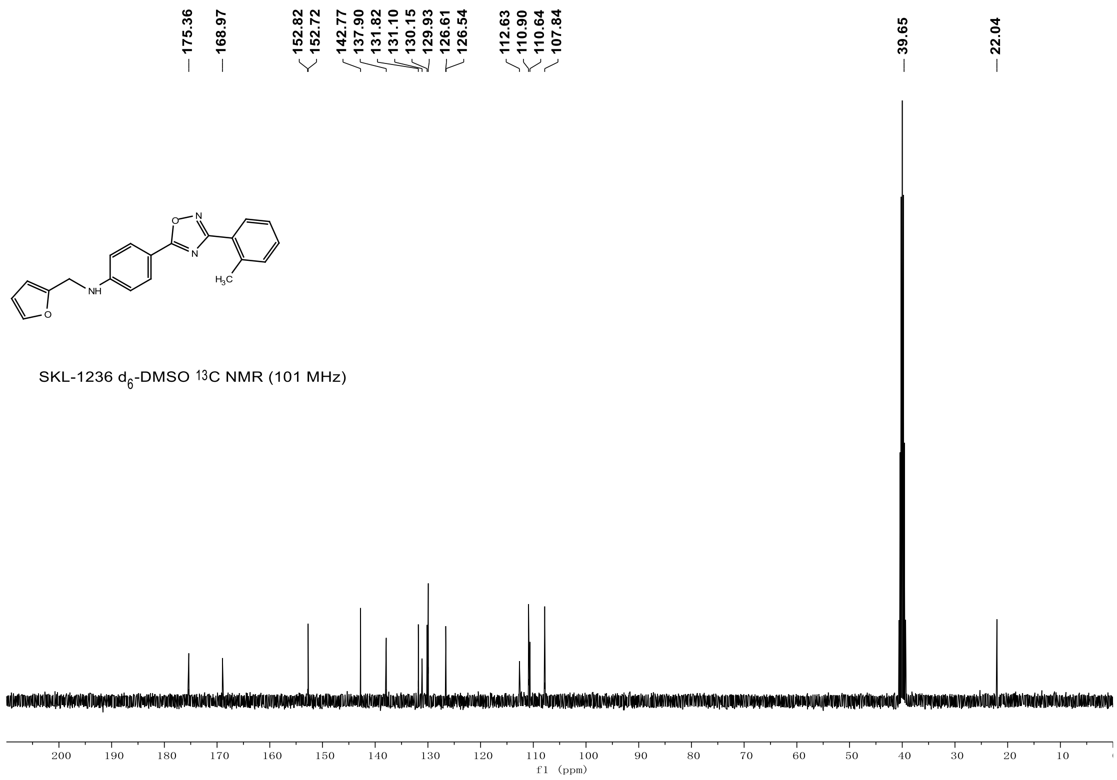
SKL-1235 d_6-DMSO ^1H NMR (400 MHz)



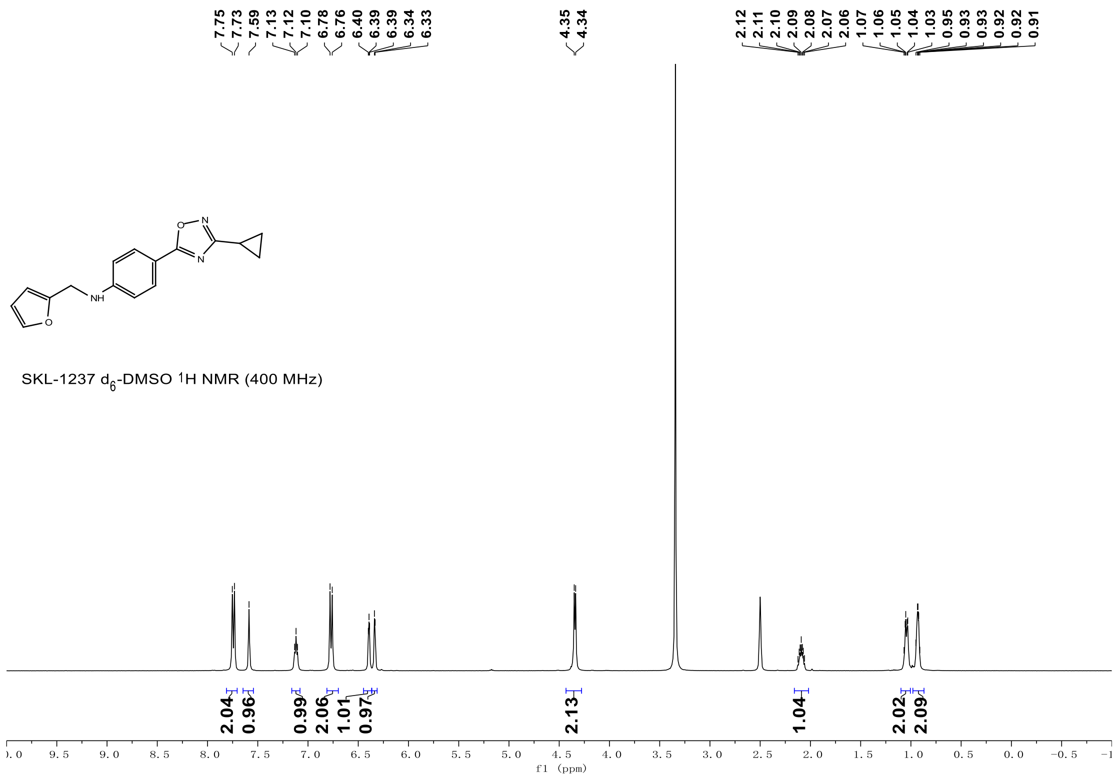
SKL-1235 d_6-DMSO ^{13}C NMR (151 MHz)

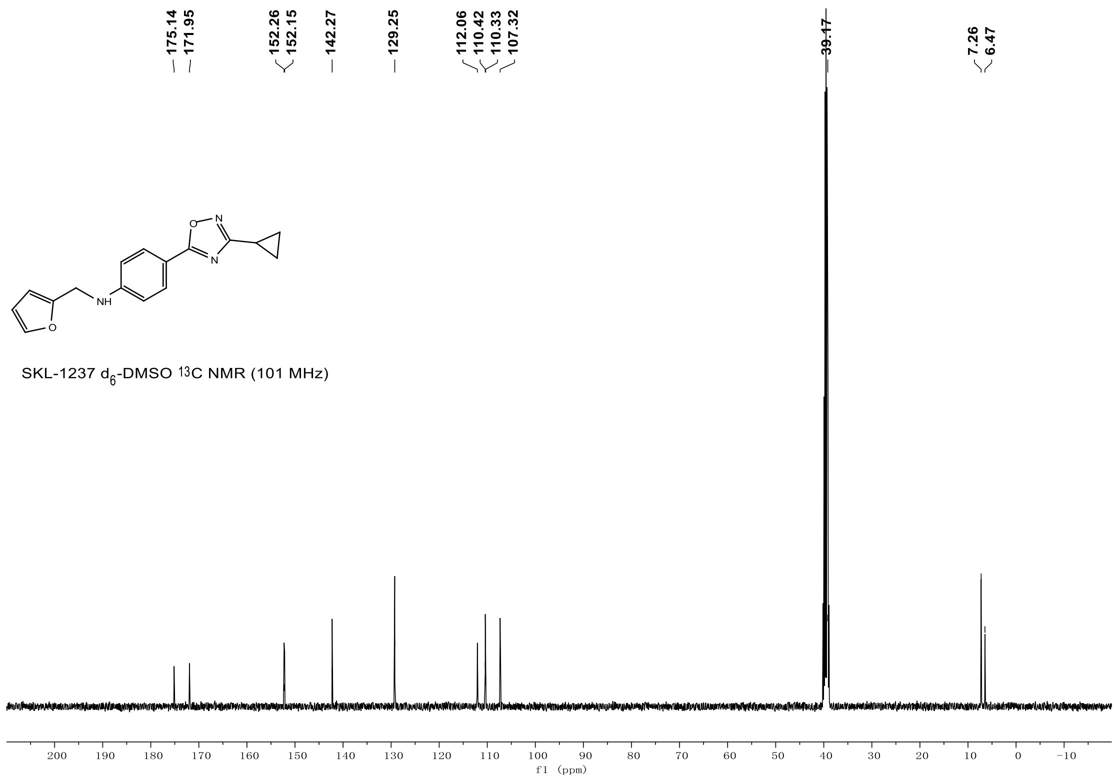


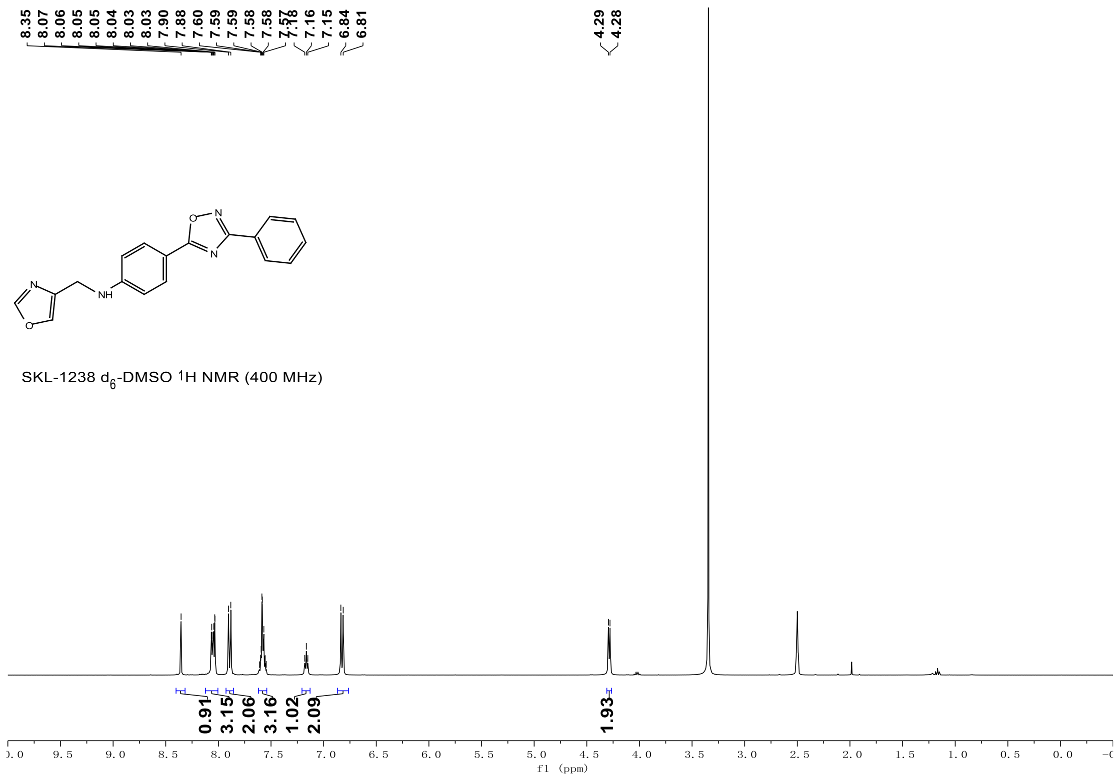
SKL-1236 d_6-DMSO ^1H NMR (400 MHz)



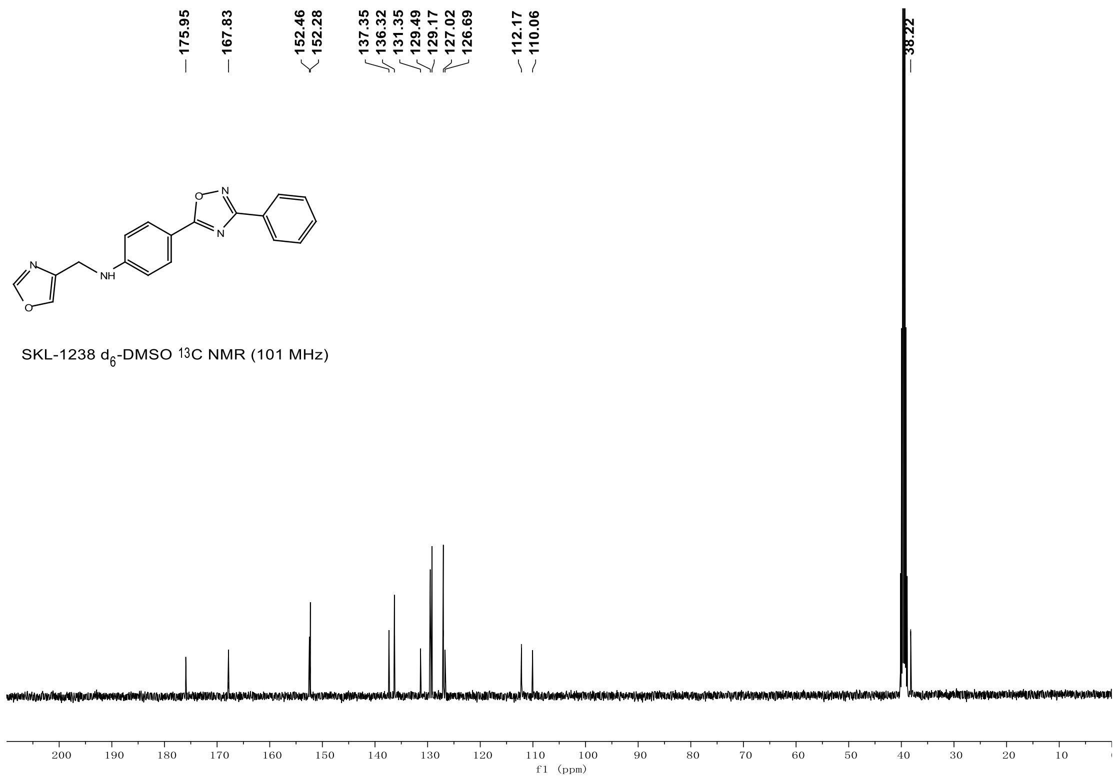
SKL-1236 d_6-DMSO ^{13}C NMR (101 MHz)


7.75 7.73 7.59 7.13 7.12 7.10 6.78 6.76 6.40 6.39 6.39 6.34 6.33
4.35 4.34
2.12 2.11 2.10 2.09 2.08 2.07 2.06 1.07 1.06 1.05 1.04 1.03 0.95 0.93 0.93 0.92 0.91
SKL-1237 d_6-DMSO ^{1}H NMR (400 MHz)
2.04 0.96 0.99 2.06 1.01 0.97 2.13 1.04 2.02 2.09
f1 (ppm)

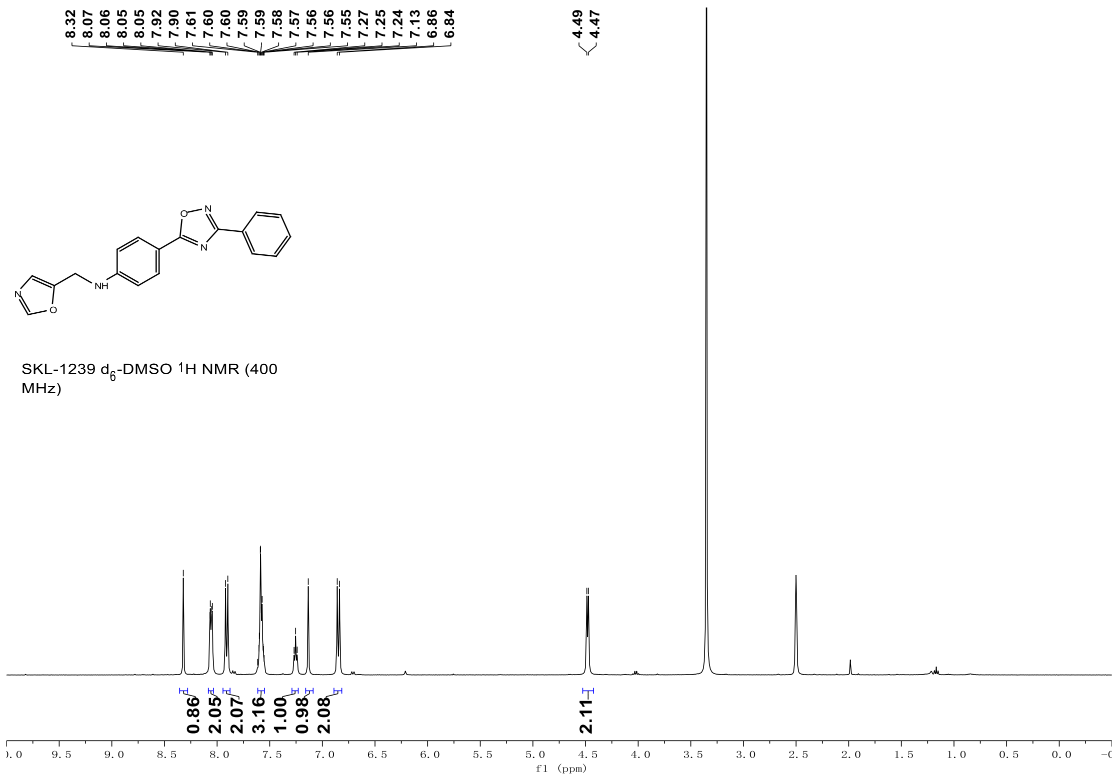

175.14 171.95 152.26 152.15 142.27 129.25 112.06 110.42 110.33 107.32 39.17 7.26 6.47
SKL-1237 d_6-DMSO ^{13}C NMR (101 MHz)
f1 (ppm)

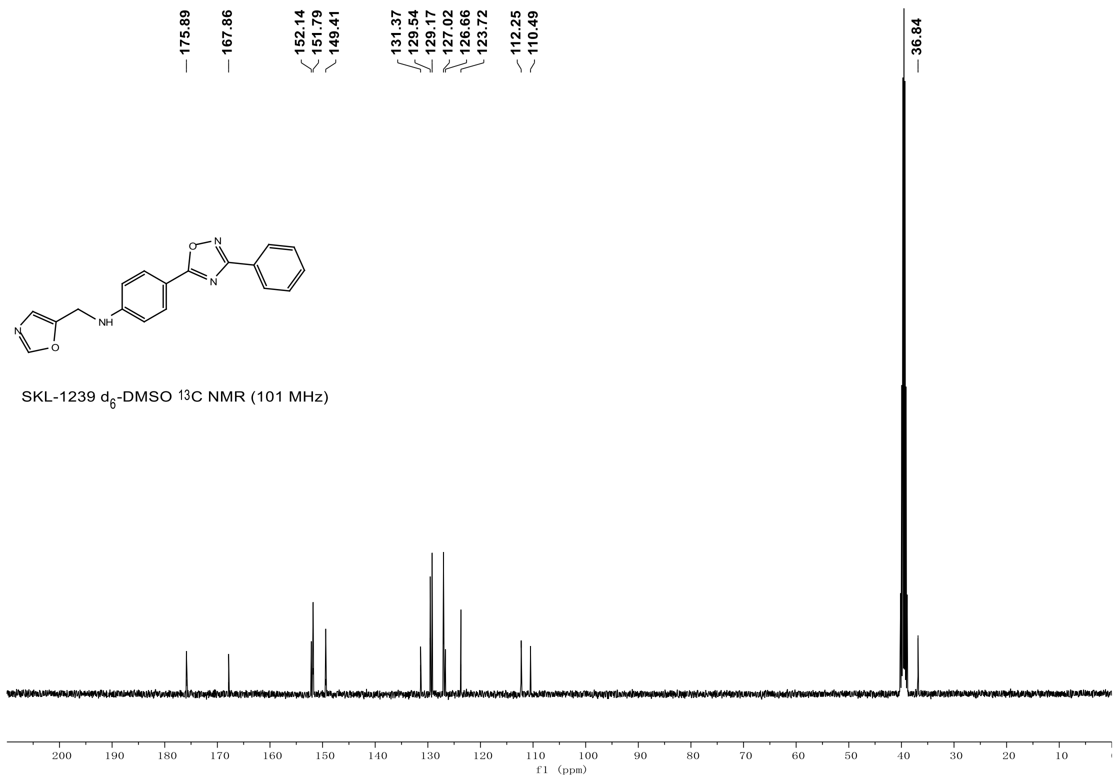


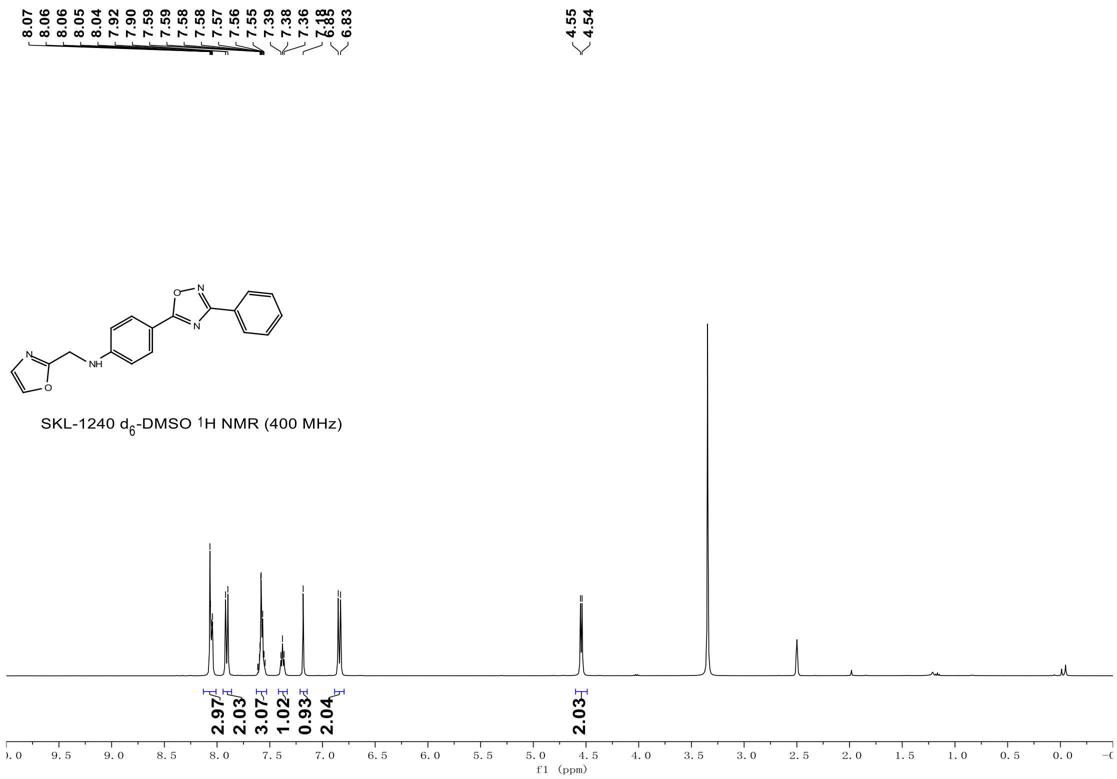
SKL-1238 d_6-DMSO ^{1}H NMR (400 MHz)



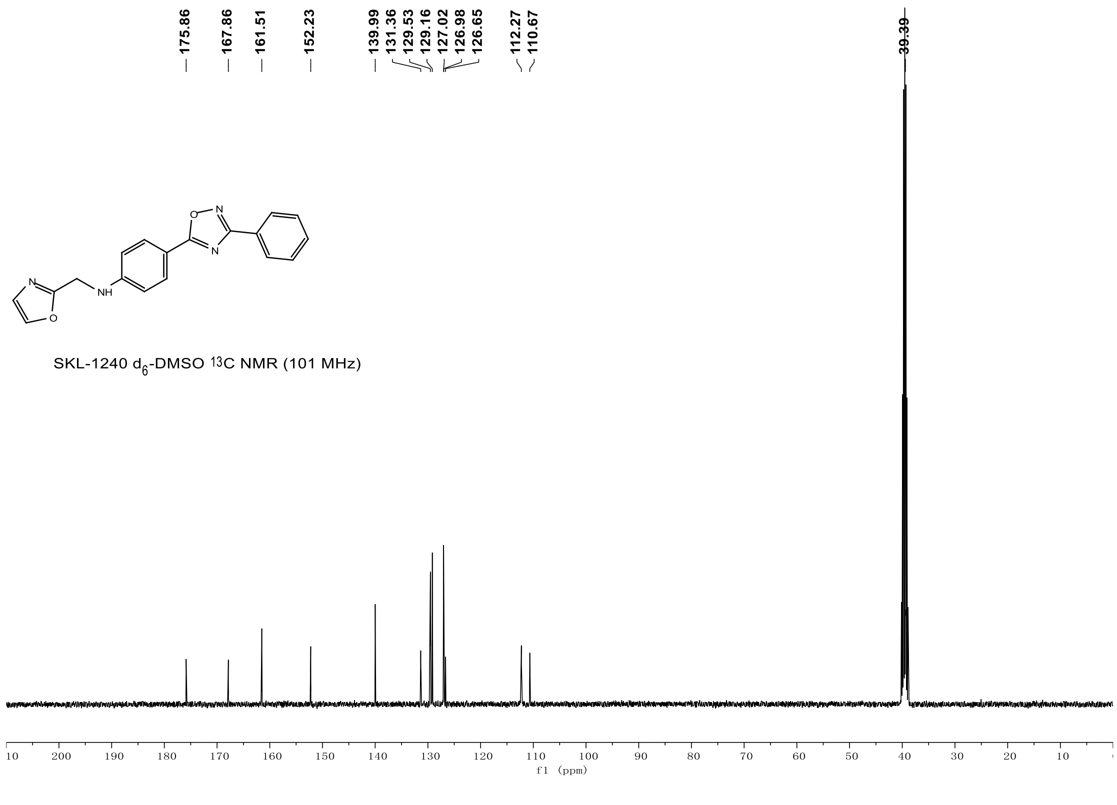
SKL-1238 d_6-DMSO ^{13}C NMR (101 MHz)


8.32
8.07
8.06
8.05
8.05
7.92
7.90
7.61
7.60
7.60
7.59
7.59
7.58
7.57
7.56
7.56
7.55
7.27
7.25
7.24
7.13
6.86
6.84
4.49
4.47
SKL-1239 d6-DMSO 1H NMR (400 MHz)
0.86
2.05
2.07
3.16
1.00
0.98
2.08
2.11
f1 (ppm)

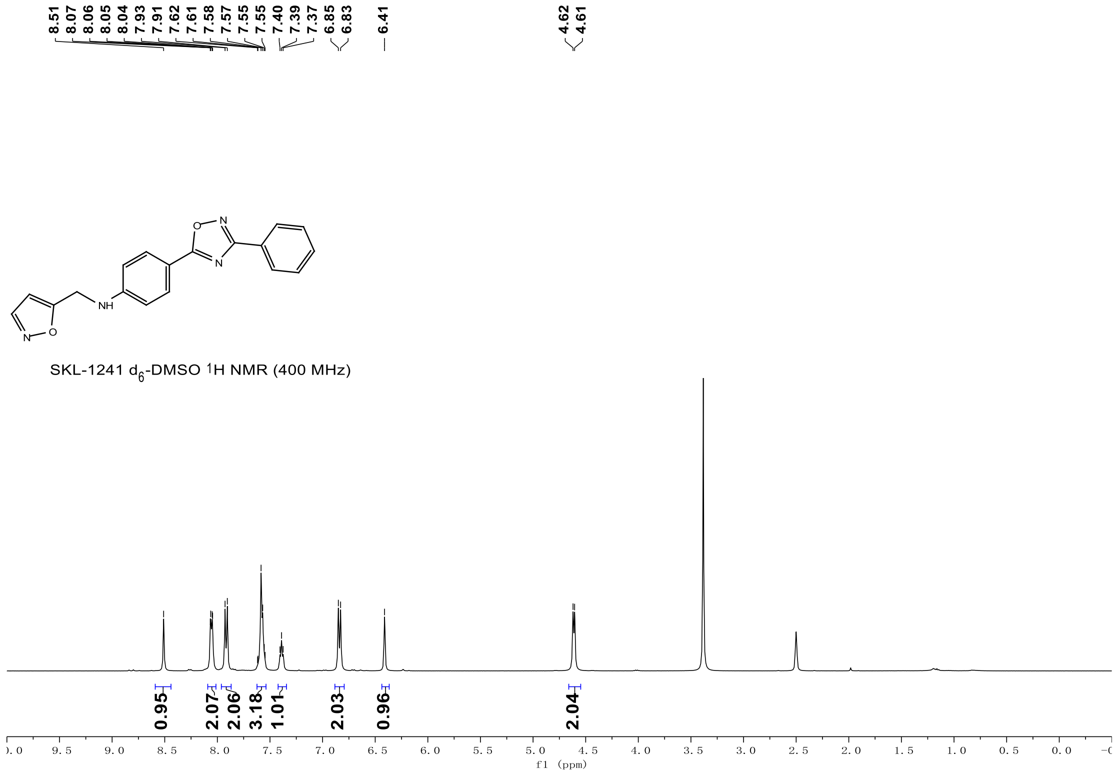

175.89
167.86
152.14
151.79
149.41
131.37
129.54
129.17
127.02
126.66
123.72
112.25
110.49
36.84
SKL-1239 d6-DMSO 13C NMR (101 MHz)
f1 (ppm)

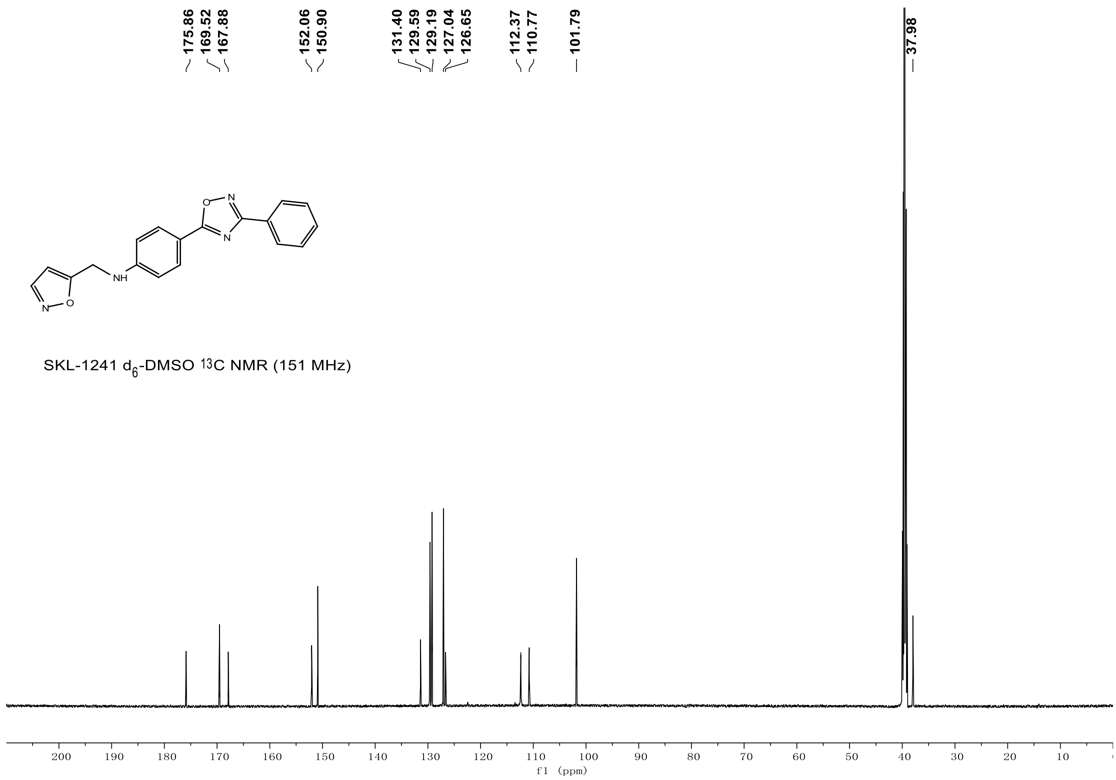


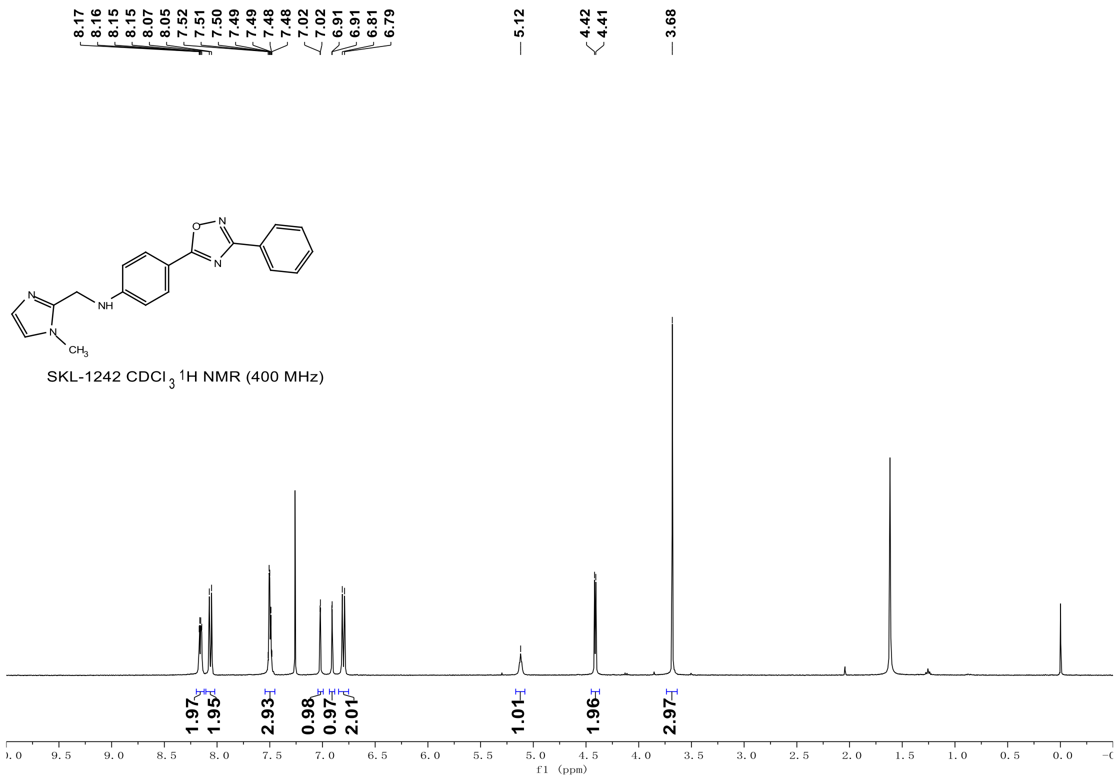
SKL-1240 d_6-DMSO ^{1}H NMR (400 MHz)

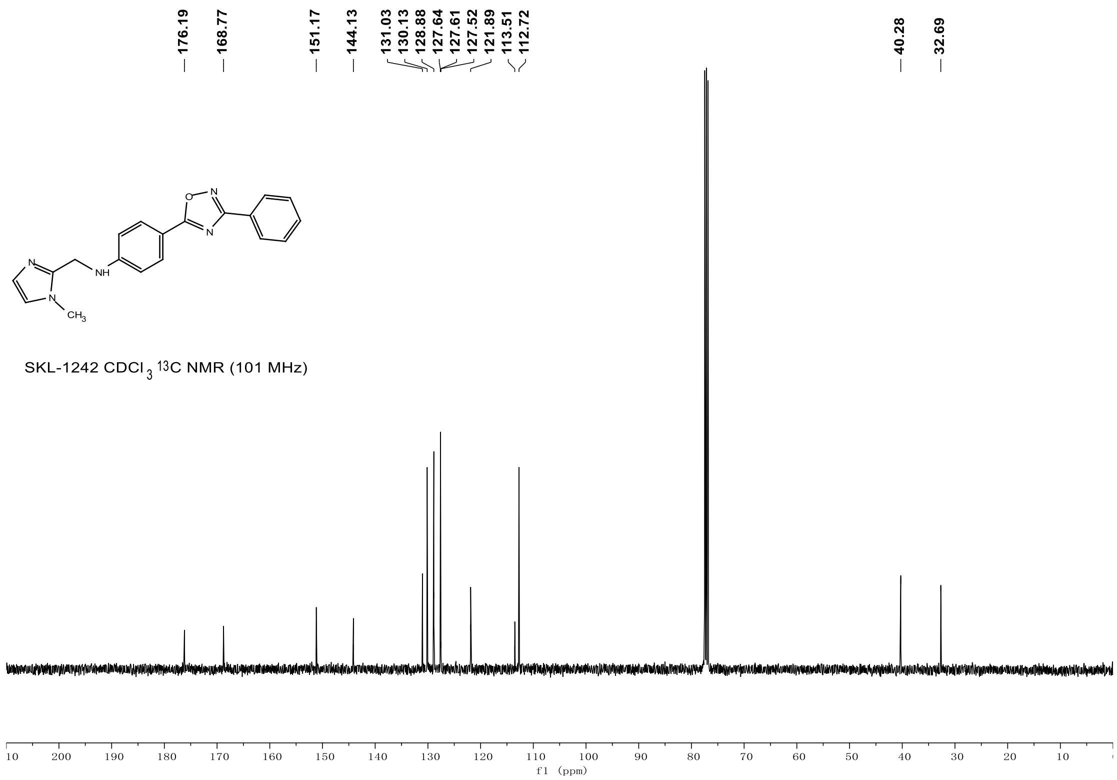


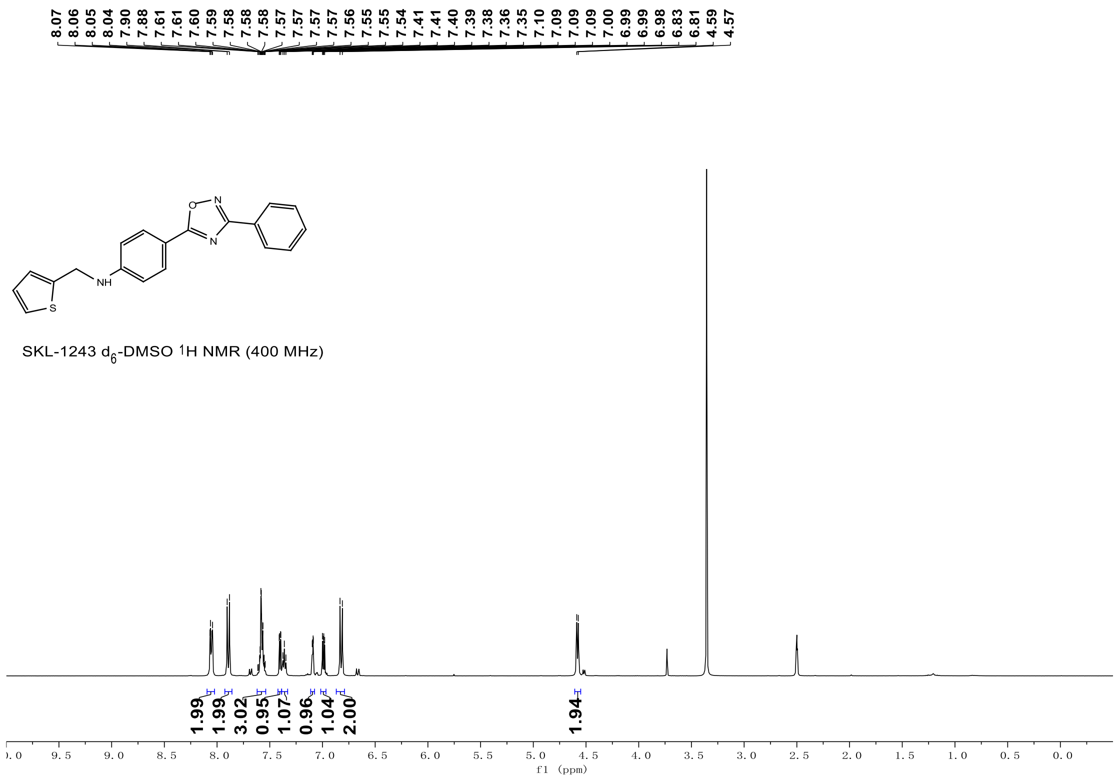
SKL-1240 d_6-DMSO ^{13}C NMR (101 MHz)


8.51 8.07 8.06 8.05 8.04 7.93 7.91 7.62 7.61 7.58 7.57 7.55 7.55 7.40 7.39 7.37 6.85 6.83 6.41 4.62 4.61
NH
O
N
SKL-1241 d_6-DMSO ^{1}H NMR (400 MHz)
0.95 2.07 2.06 3.18 1.01 2.03 0.96 2.04
f1 (ppm)

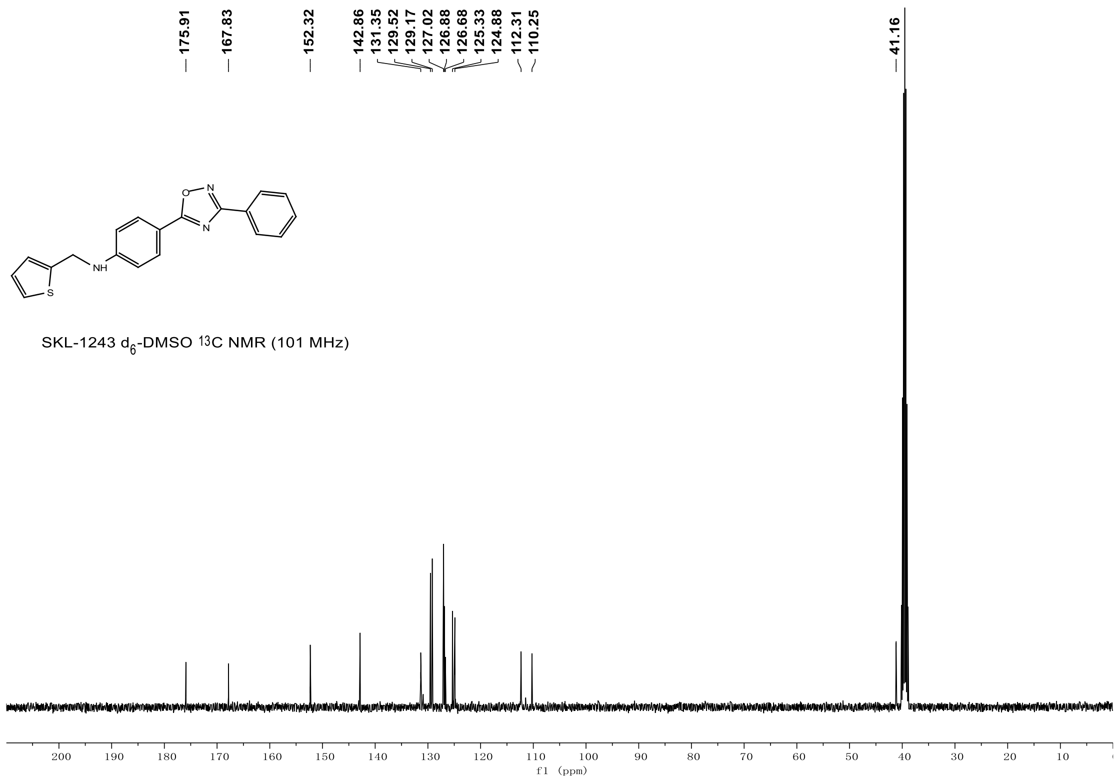

175.86 169.52 167.88 152.06 150.90 131.40 129.59 129.19 127.04 126.65 112.37 110.77 101.79 37.98
NH
O
N
SKL-1241 d_6-DMSO ^{13}C NMR (151 MHz)
f1 (ppm)


8.17
8.16
8.15
8.15
8.07
8.05
7.52
7.51
7.50
7.49
7.49
7.48
7.48
7.02
7.02
6.91
6.91
6.81
6.79
5.12
4.42
4.41
3.68
SKL-1242 CDCl3 1H NMR (400 MHz)
1.97
1.95
2.93
0.98
0.97
2.01
1.01
1.96
2.97
f1 (ppm)

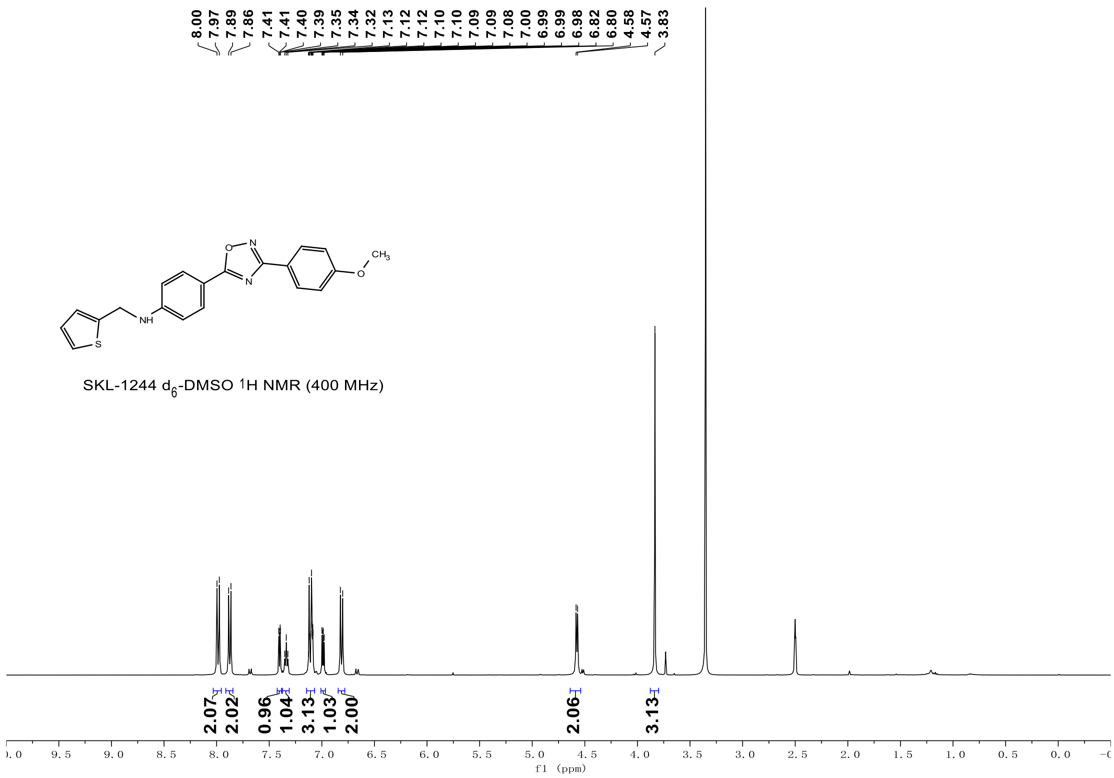

176.19
168.77
151.17
144.13
131.03
130.13
128.88
127.64
127.61
127.52
121.89
113.51
112.72
40.28
32.69
SKL-1242 CDCl3 13C NMR (101 MHz)
f1 (ppm)

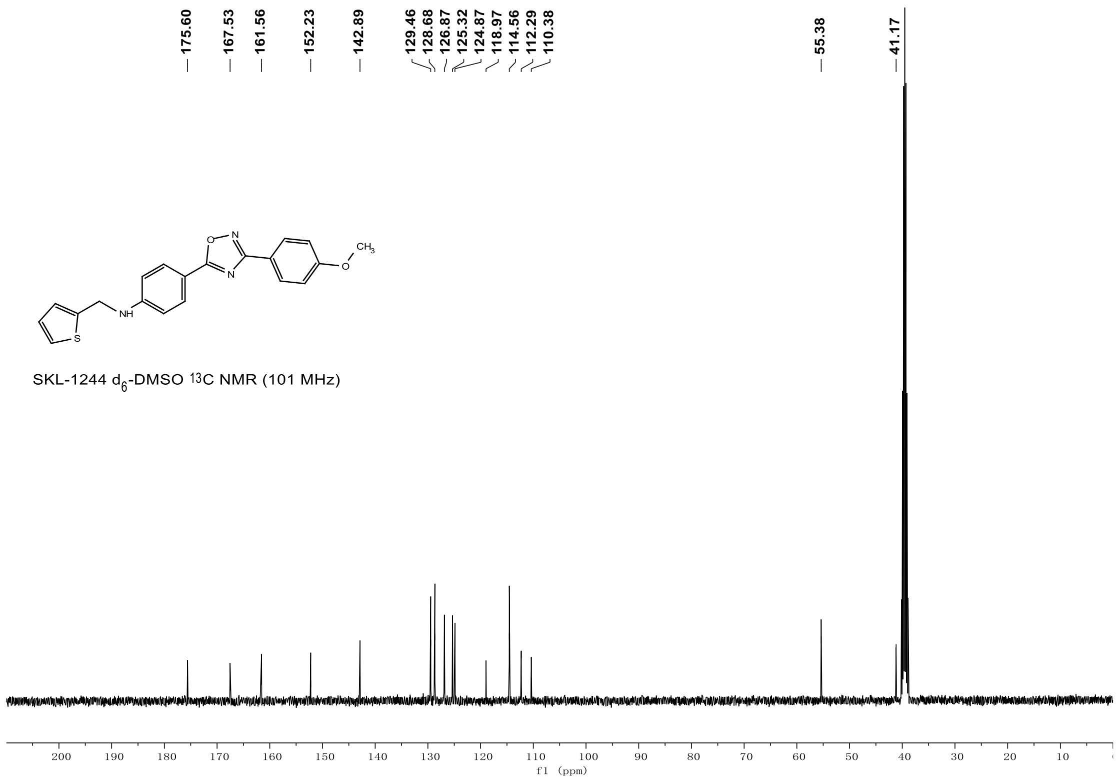


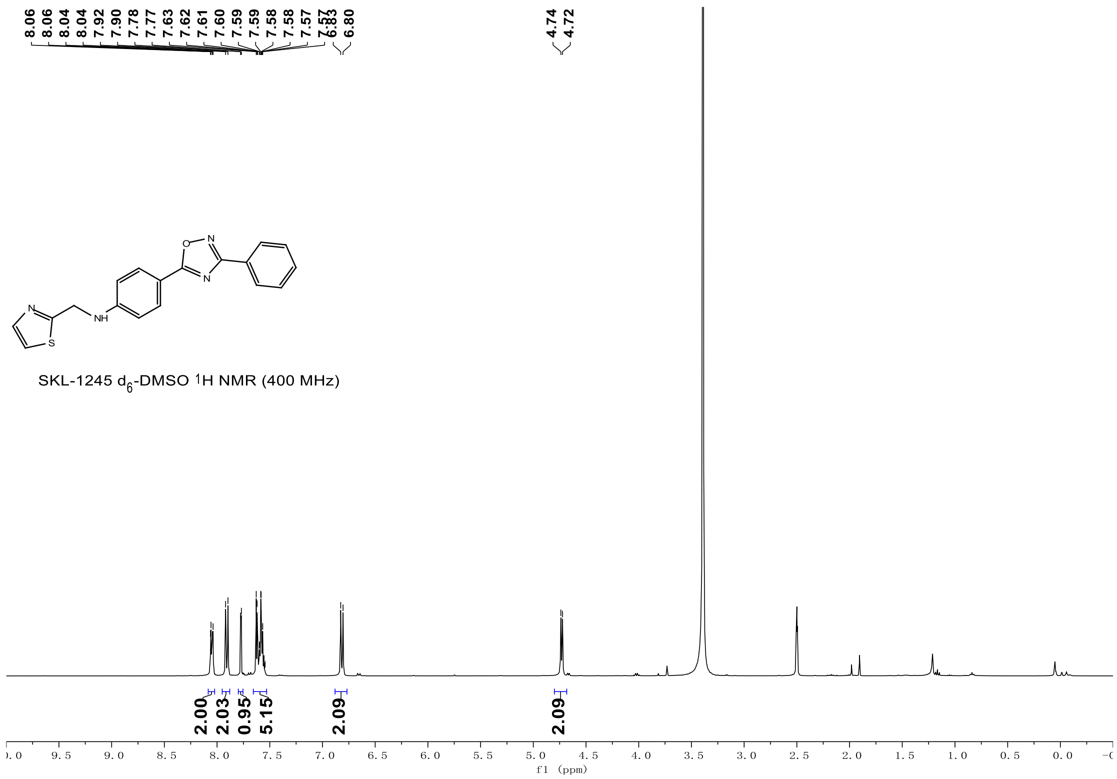
SKL-1243 d_6-DMSO ^1H NMR (400 MHz)



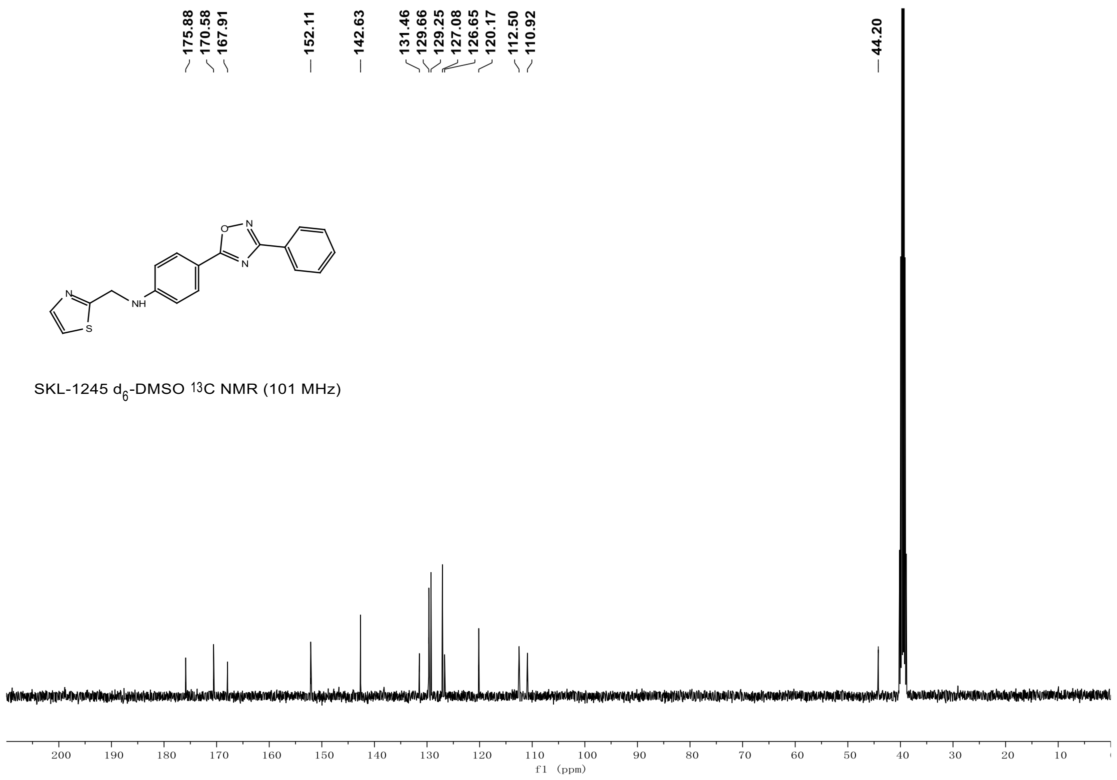
SKL-1243 d_6-DMSO ^{13}C NMR (101 MHz)


8.00
7.97
7.89
7.86
7.41
7.41
7.40
7.39
7.35
7.34
7.32
7.13
7.12
7.12
7.10
7.10
7.09
7.09
7.08
7.00
6.99
6.99
6.98
6.82
6.80
4.58
4.57
3.83
O
N
N
CH3
O
NH
S
SKL-1244 d6-DMSO 1H NMR (400 MHz)
2.07
2.02
0.96
1.04
3.13
1.03
2.00
2.06
3.13
f1 (ppm)

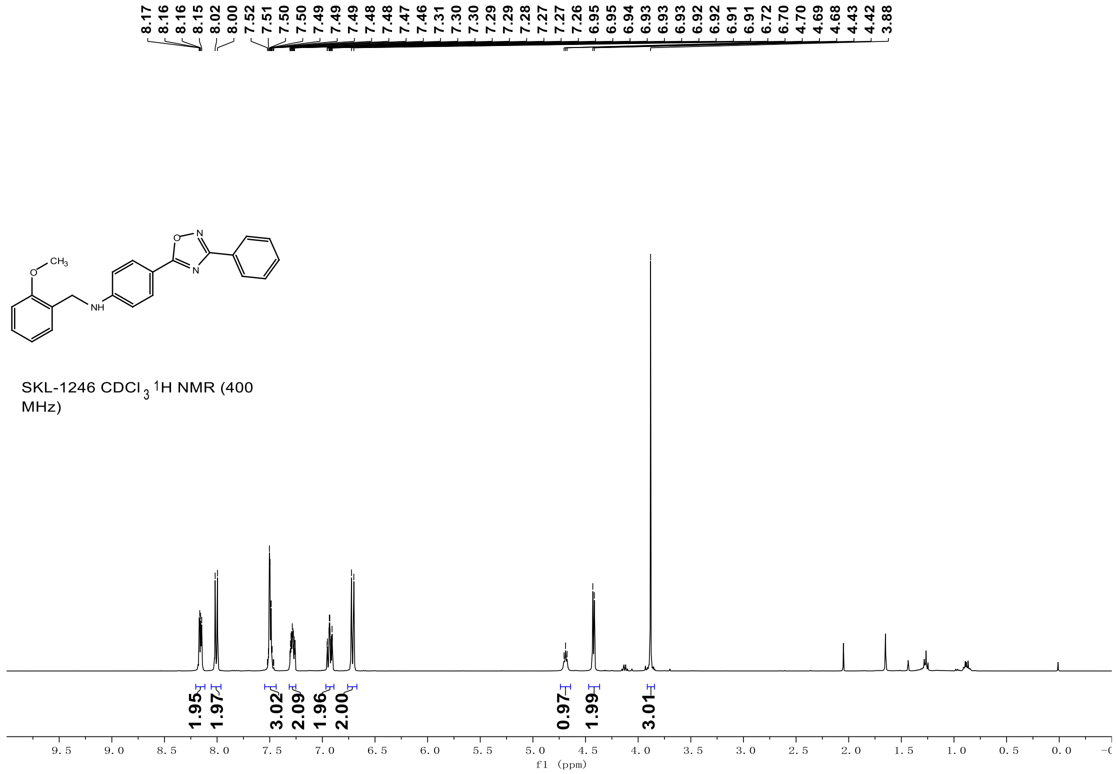

175.60
167.53
161.56
152.23
142.89
129.46
128.68
126.87
125.32
124.87
118.97
114.56
112.29
110.38
55.38
41.17
O
N
N
CH3
O
NH
S
SKL-1244 d6-DMSO 13C NMR (101 MHz)
f1 (ppm)

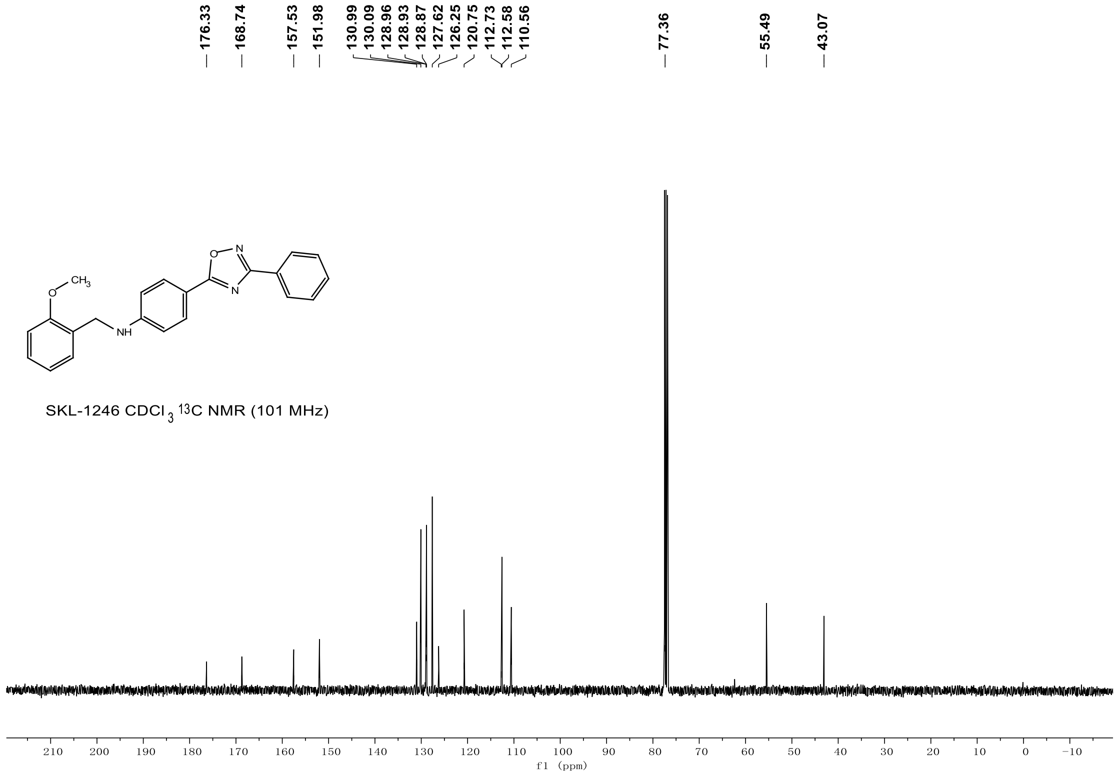


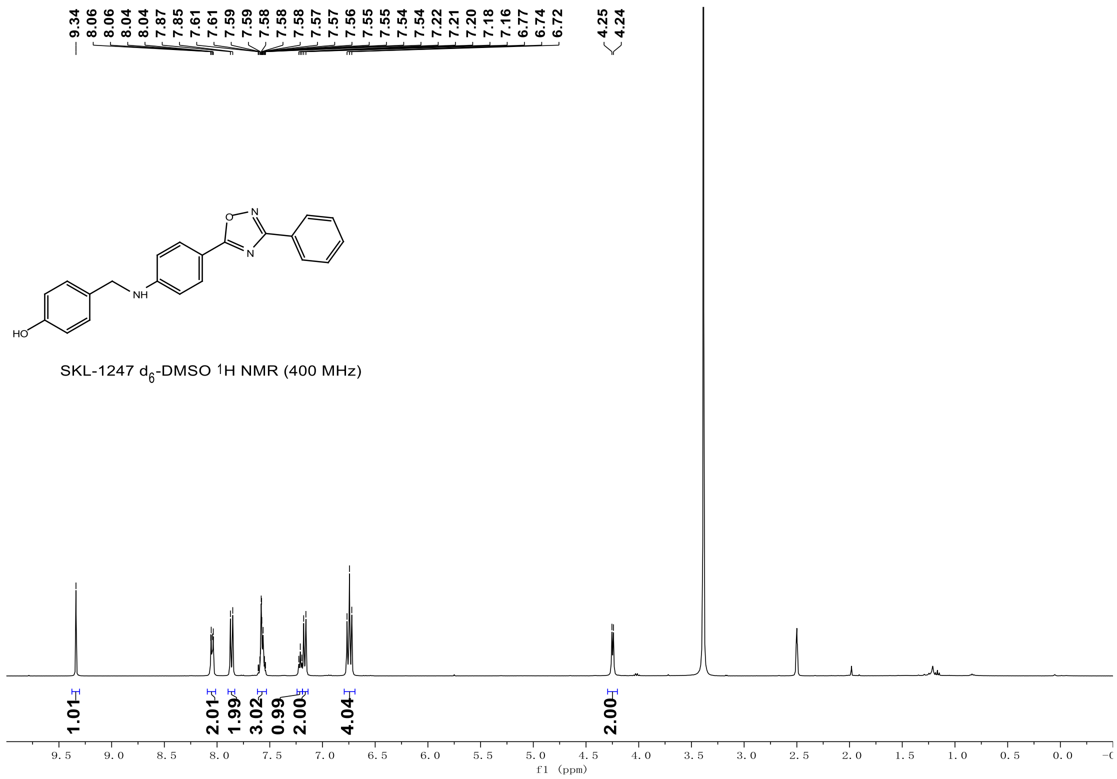
SKL-1245 d_6-DMSO ^{1}H NMR (400 MHz)

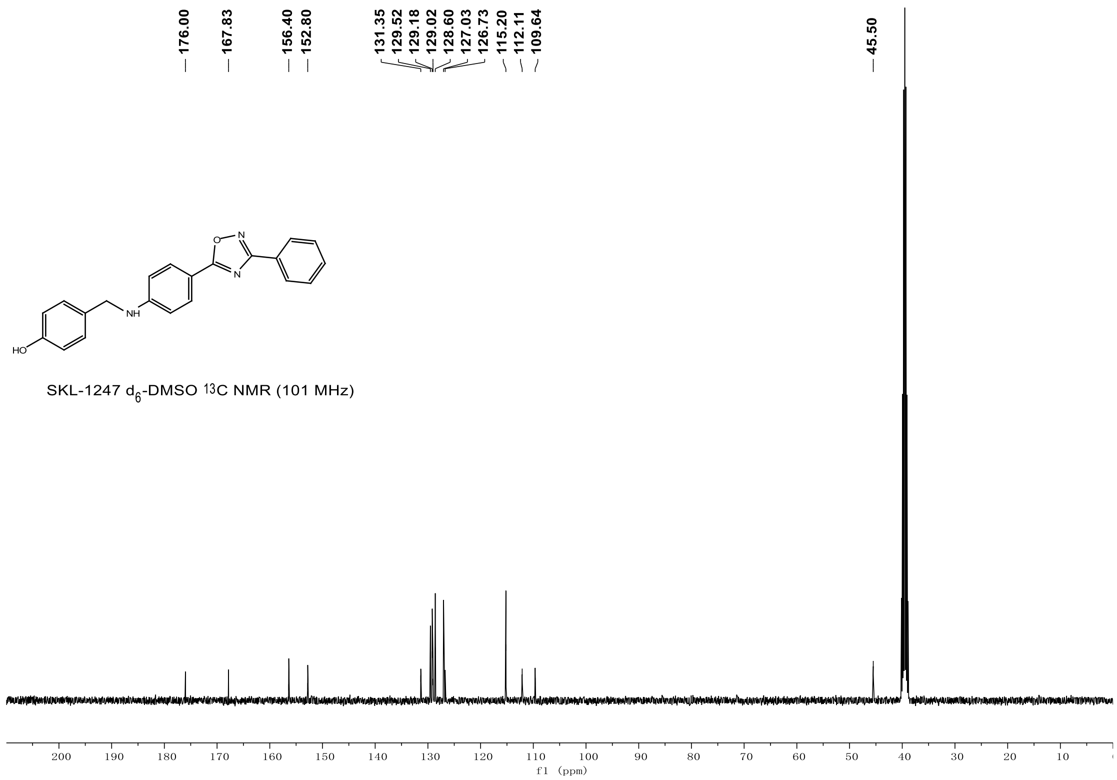


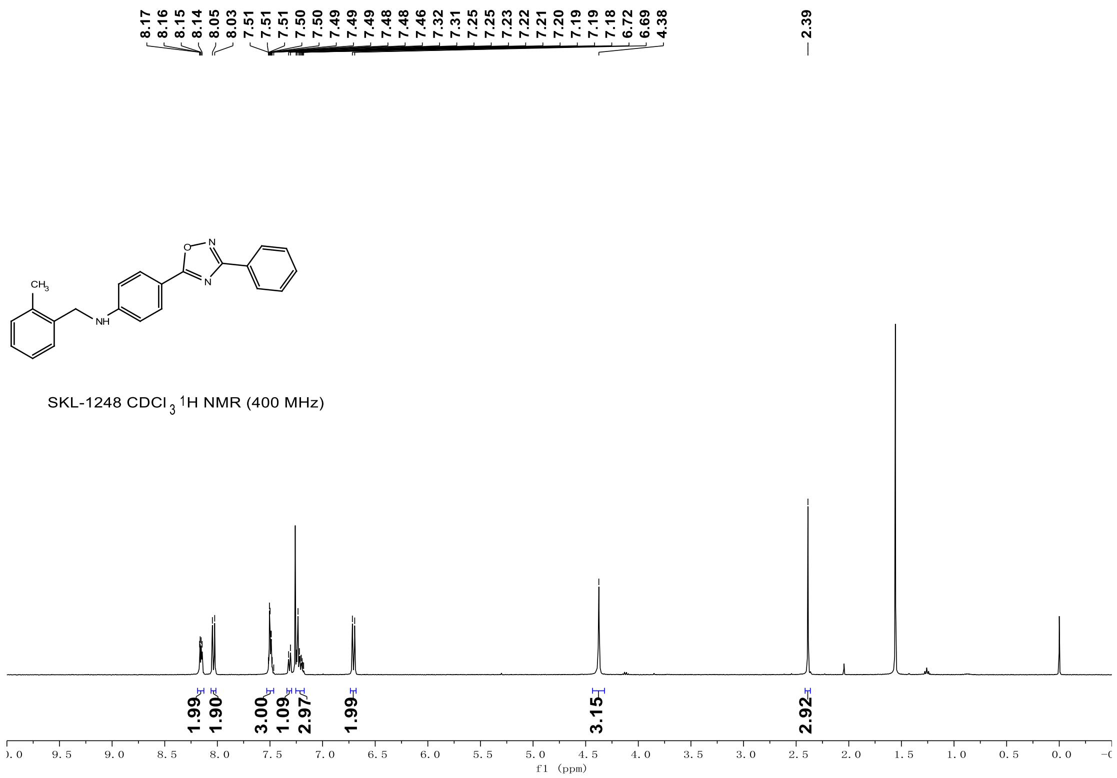
SKL-1245 d_6-DMSO ^{13}C NMR (101 MHz)

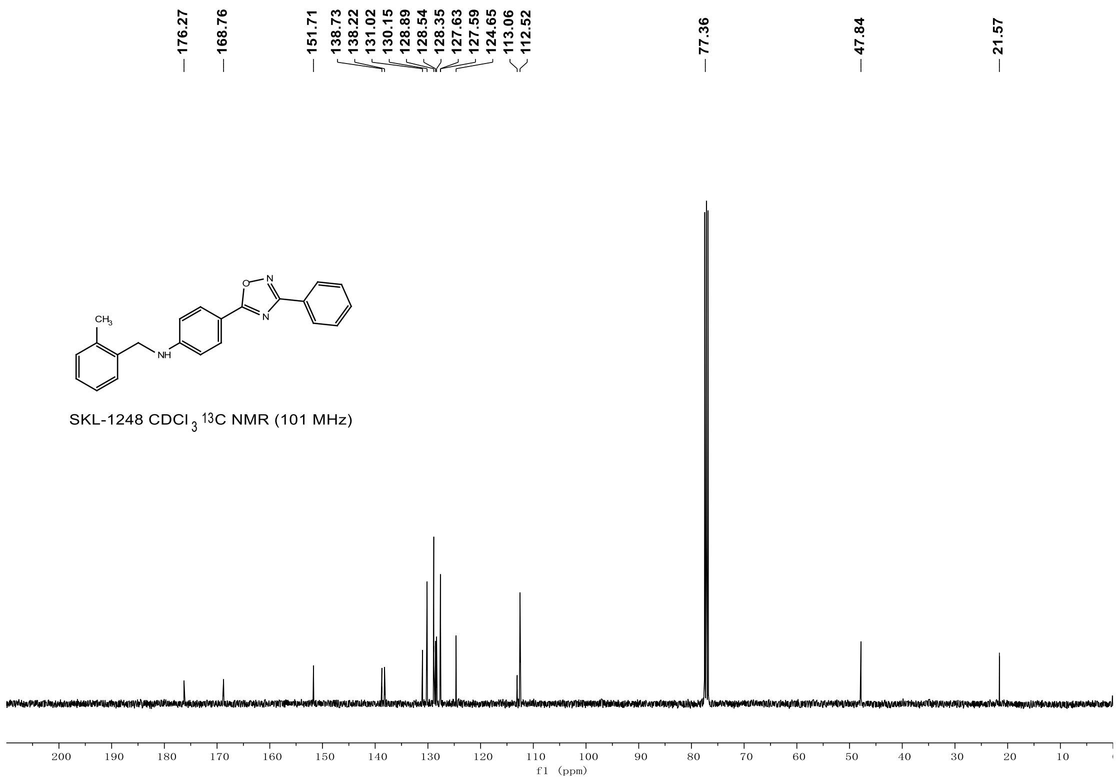

8.17
8.16
8.16
8.15
8.02
8.00
7.52
7.51
7.50
7.50
7.49
7.49
7.48
7.48
7.47
7.46
7.31
7.30
7.30
7.29
7.29
7.28
7.27
7.27
7.26
6.95
6.95
6.94
6.93
6.93
6.93
6.92
6.92
6.91
6.72
6.70
4.70
4.69
4.68
4.43
4.42
3.88
SKL-1246 CDCl3 1H NMR (400 MHz)
1.95
1.97
3.02
2.09
1.96
2.00
0.97
1.99
3.01
f1 (ppm)

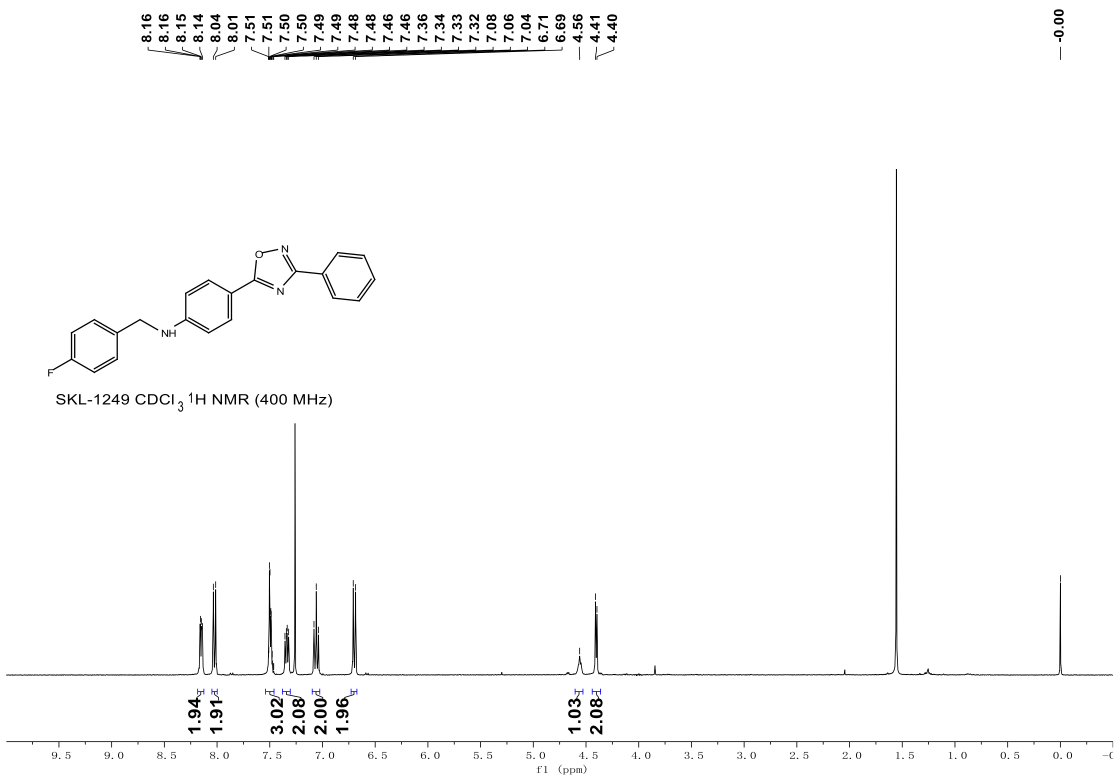

176.33
168.74
157.53
151.98
130.99
130.09
128.96
128.93
128.87
127.62
126.25
120.75
112.73
112.58
110.56
77.36
55.49
43.07
SKL-1246 CDCl3 13C NMR (101 MHz)
f1 (ppm)

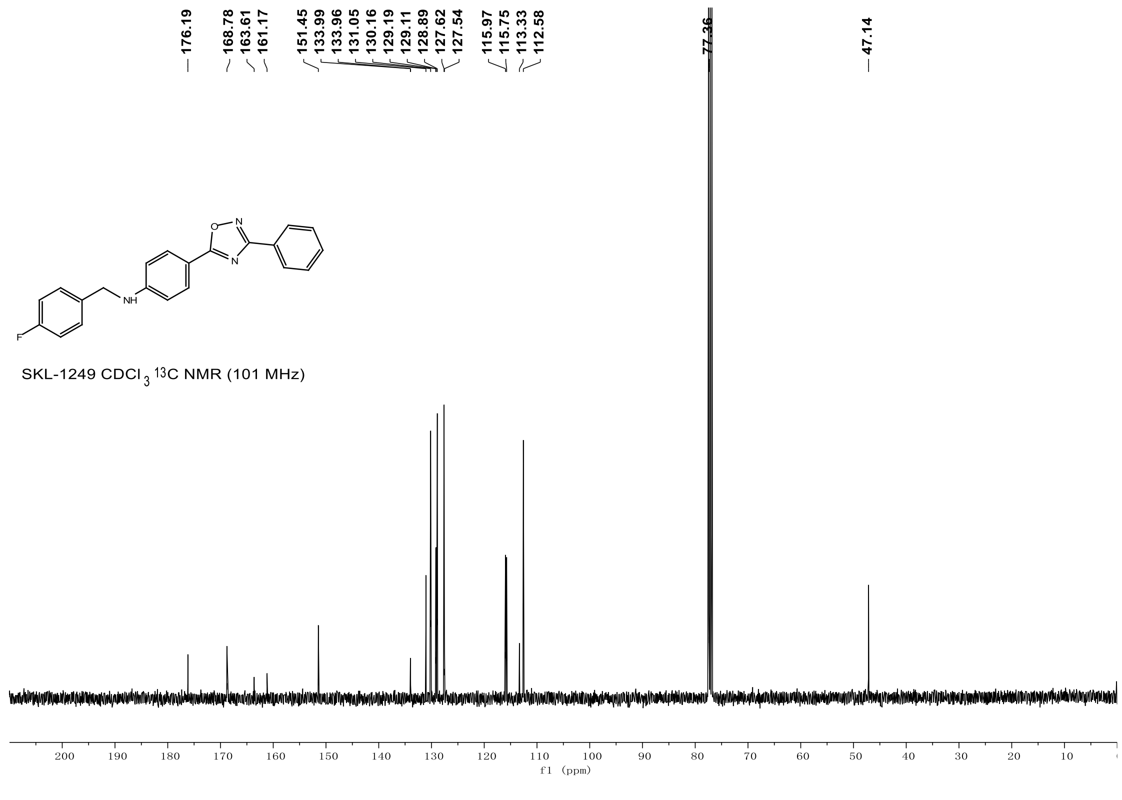

9.34 8.06 8.06 8.04 8.04 7.87 7.85 7.61 7.61 7.59 7.59 7.58 7.58 7.58 7.57 7.57 7.56 7.55 7.55 7.54 7.54 7.22 7.21 7.20 7.18 7.16 6.77 6.74 6.72
4.25 4.24
NH
HO
O
N
N
SKL-1247 d6-DMSO 1H NMR (400 MHz)
1.01 2.01 1.99 3.02 0.99 2.00 4.04 2.00
f1 (ppm)

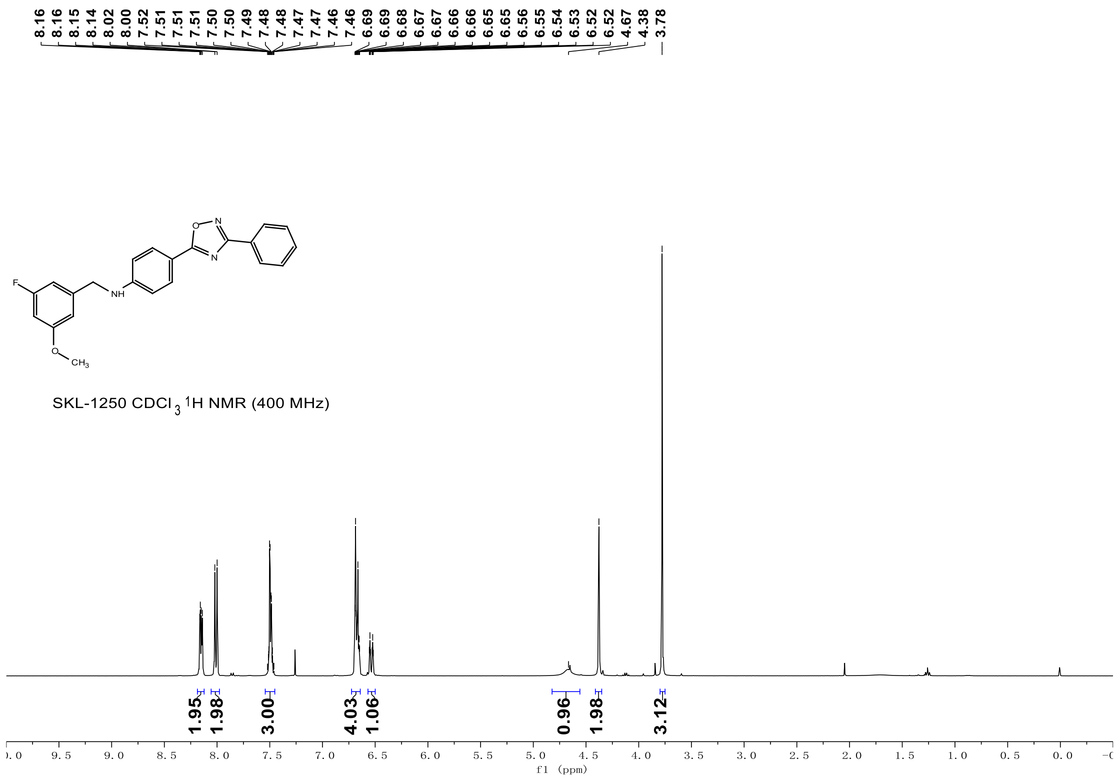

176.00 167.83 156.40 152.80 131.35 129.52 129.18 129.02 128.60 127.03 126.73 115.20 112.11 109.64 45.50
NH
HO
O
N
N
SKL-1247 d6-DMSO 13C NMR (101 MHz)
f1 (ppm)

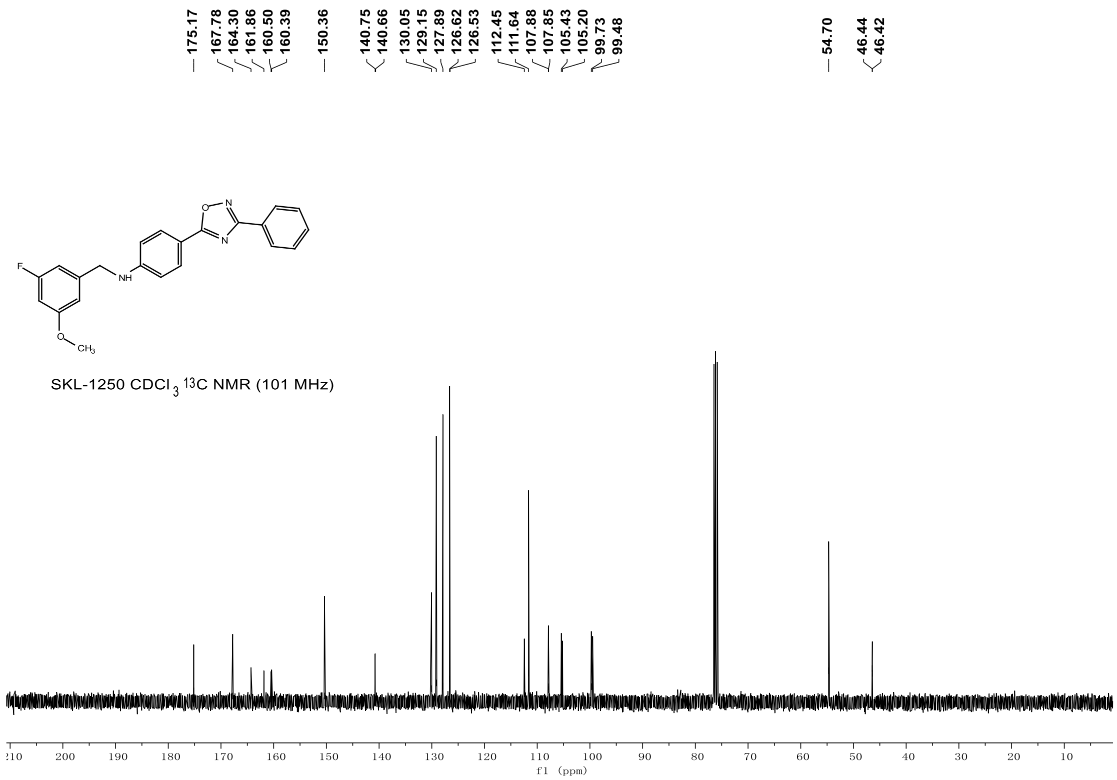

8.17 8.16 8.15 8.14 8.05 8.03 7.51 7.51 7.50 7.50 7.49 7.49 7.49 7.48 7.48 7.46 7.32 7.31 7.25 7.25 7.23 7.22 7.21 7.20 7.19 7.19 7.18 6.72 6.69 4.38
2.39
CH3
NH
O
N
N
SKL-1248 CDCl3 1H NMR (400 MHz)
1.99 1.90 3.00 1.09 2.97 1.99 3.15 2.92
f1 (ppm)

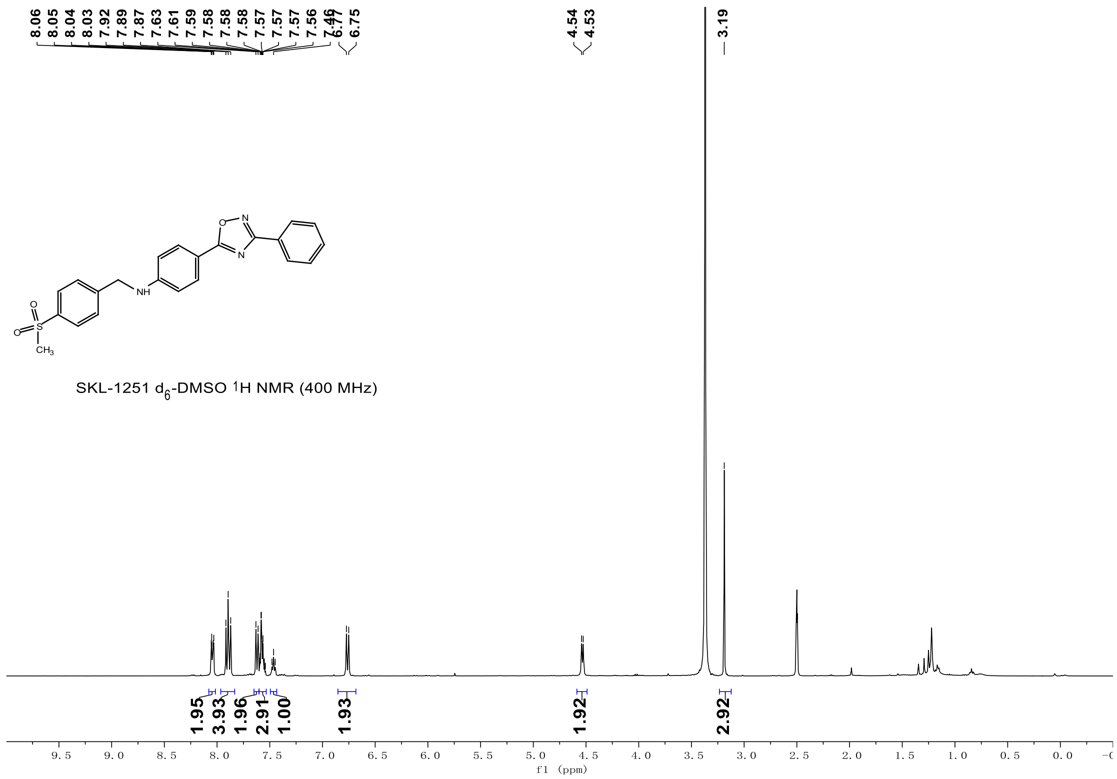

176.27
168.76
151.71
138.73 138.22 131.02 130.15 128.89 128.54 128.35 127.63 127.59 124.65 113.06 112.52
77.36
47.84
21.57
CH3
NH
O
N
N
SKL-1248 CDCl3 13C NMR (101 MHz)
f1 (ppm)


SKL-1249 CDCl3 1H NMR (400 MHz)
f1 (ppm)

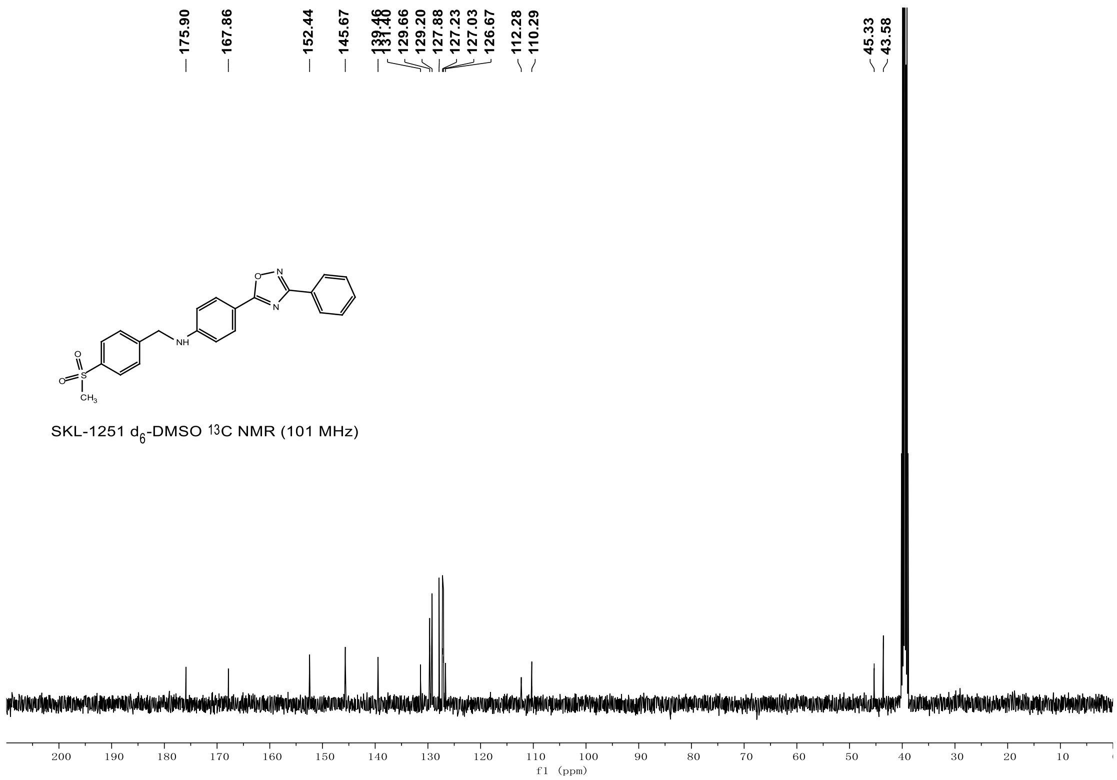

SKL-1249 CDCl3 13C NMR (101 MHz)
f1 (ppm)


8.16 8.16 8.15 8.14 8.02 8.00 7.52 7.51 7.51 7.51 7.50 7.49 7.48 7.48 7.47 7.47 7.46 7.46 6.69 6.69 6.68 6.67 6.67 6.66 6.66 6.65 6.65 6.56 6.55 6.54 6.53 6.52 6.52 4.67 4.38 3.78
F
NH
O
N
CH3
SKL-1250 CDCl3 1H NMR (400 MHz)
1.95 1.98 3.00 4.03 1.06 0.96 1.98 3.12
f1 (ppm)

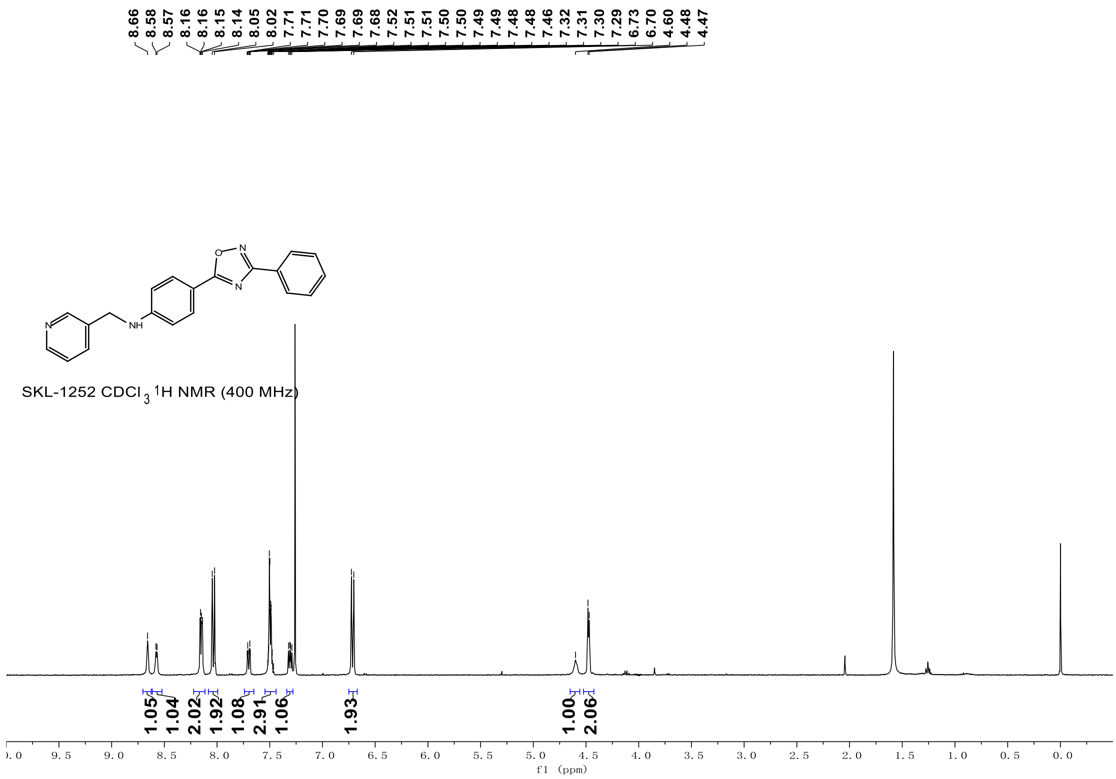

175.17 167.78 164.30 161.86 160.50 160.39 150.36 140.75 140.66 130.05 129.15 127.89 126.62 126.53 112.45 111.64 107.88 107.85 105.43 105.20 99.73 99.48 54.70 46.44 46.42
F
NH
O
N
CH3
SKL-1250 CDCl3 13C NMR (101 MHz)
f1 (ppm)

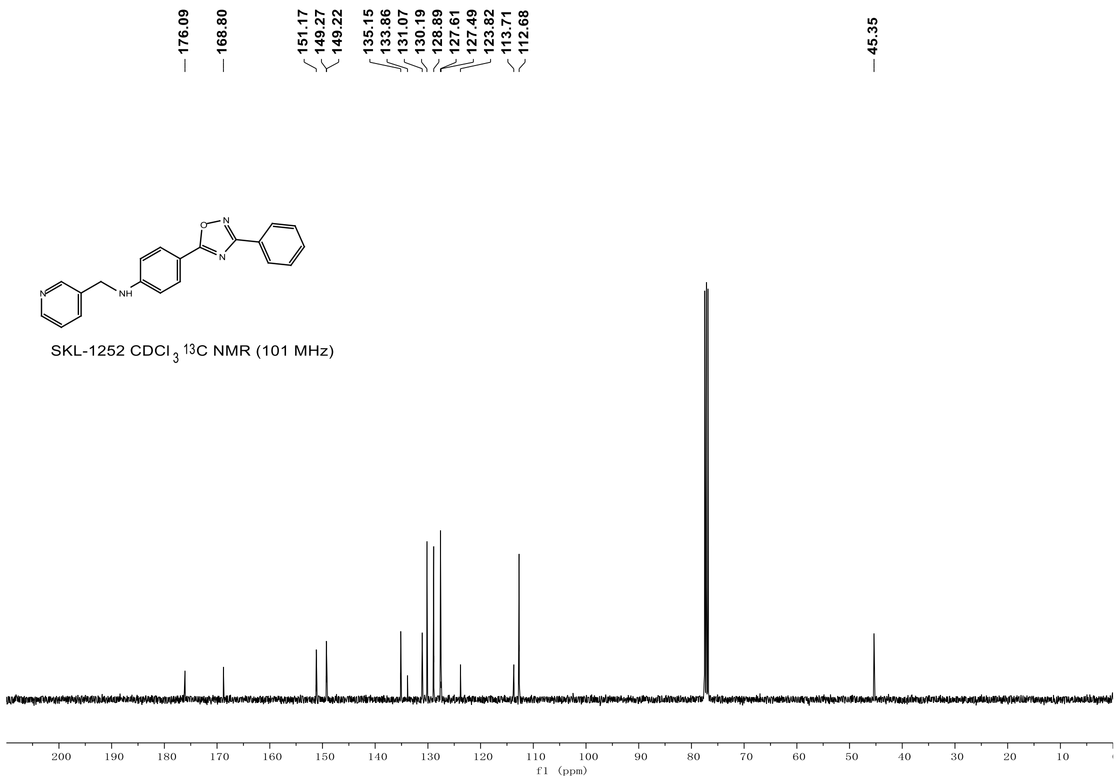


SKL-1251 d_6-DMSO ^{1}H NMR (400 MHz)



SKL-1251 d_6-DMSO ^{13}C NMR (101 MHz)


8.66 8.58 8.57 8.16 8.16 8.15 8.14 8.05 8.02 7.71 7.70 7.69 7.69 7.68 7.52 7.51 7.51 7.50 7.50 7.49 7.49 7.48 7.48 7.46 7.32 7.31 7.30 7.29 6.73 6.70 4.60 4.48 4.47
O
N
N
NH
N
SKL-1252 CDCl3 1H NMR (400 MHz)
1.05 1.04 2.02 1.92 1.08 2.91 1.06 1.93 1.00 2.06
f1 (ppm)


176.09 168.80 151.17 149.27 149.22 135.15 133.86 131.07 130.19 128.89 127.61 127.49 123.82 113.71 112.68 45.35
O
N
N
NH
N
SKL-1252 CDCl3 13C NMR (101 MHz)
f1 (ppm)