Supporting Information for

Potent and Orally Efficacious Bisthiazole-Based Histone Deacetylase Inhibitors

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Table S1. Inhibitory activity of compound**8f** against Human HDACs

Compd	$IC_{50}(\mu M)$[a]								
	HDAC1	HDAC2	HDAC3	HDAC4	HDAC5	HDAC6	HDAC8	HDAC10	HDAC11
8f	0.07	0.03	0.26	0.10	0.08	0.79	0.56	0.37	0.40
	±0.01	±0.00	±0.05	±0.01	±0.01	±0.14	±0.05	±0.02	±0.09

[a] Values are expressed as themean±SDand the test was performed in triplicate.

Table S2. Pharmacokinetics of compound **8f** in mice[a]

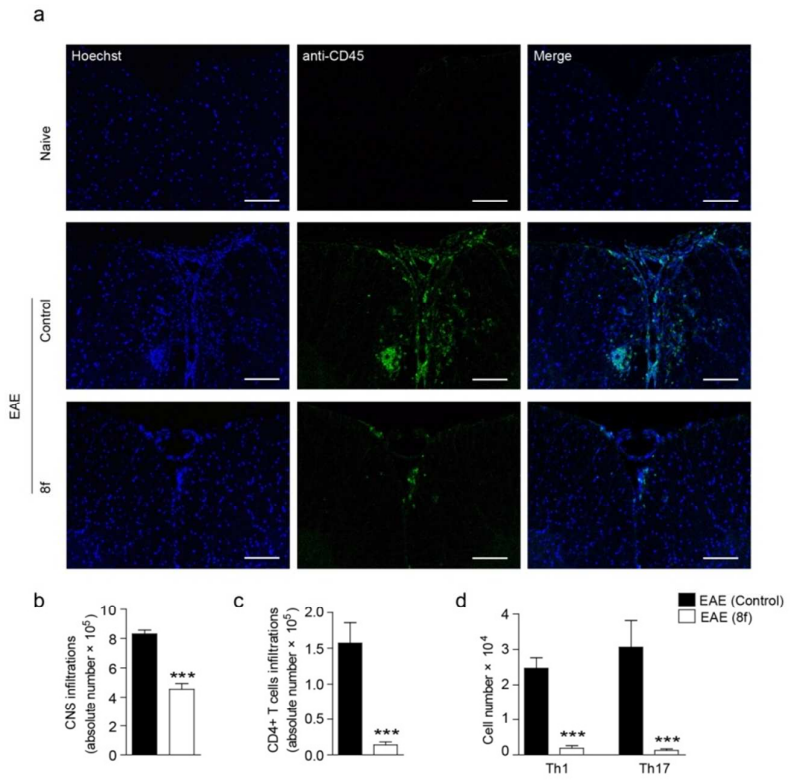
Route of Administration	Tissue	T_{max} h	C_{max} ng/ml(g)	AUC_{0-t} ng.h/ml(g)	$AUC_{0-\infty}$ ng.h/ml(g)	MRT h	$t_{1/2}$ h	CLz L/h/kg	Vz L/kg
i.g.	Plasma	0.083	7043	12070	12088	1.76	1.13	/	/
	Brain	0.25	158	226	229	1.65	1.22	/	/
i.v.	Plasma	0.083	7179	5083	5085	0.85	0.92	1.97	1.67
	Brain	0.083	348	149	153	0.63	0.98	/	/

[a]54 male KM mouse, 18–20g. **8f** was dissolved in 5% DMSO/1% Cremophor EL**/**94% saline for i.v. injection (10mg/kg) and in 2% DMSO/1% Cremophor EL/97% 0.5% CMC-Na for i.g.administration (20mg/kg).

Table S3. Clinical scores of EAE mice treated with **8f** or PBS following different treatment protocols[a]

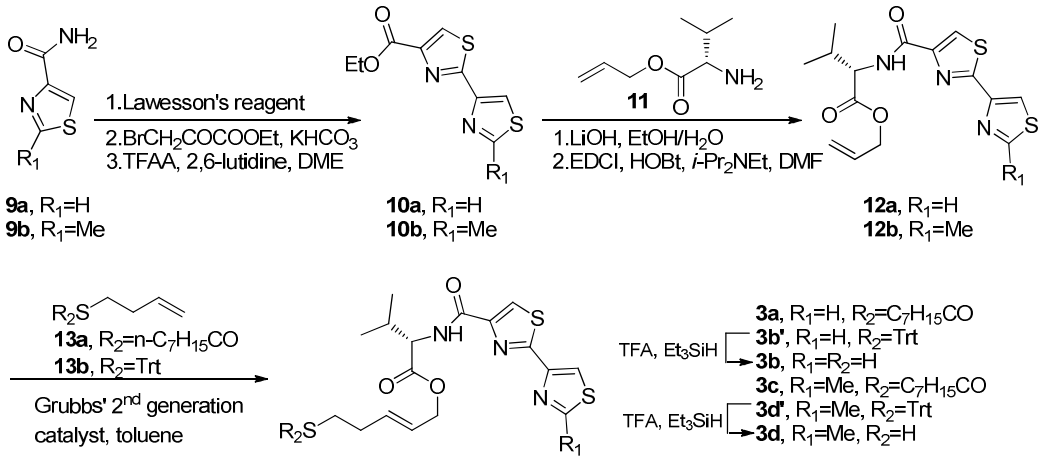
	Incidence	Onset of EAE (Days after Immunization)	Maximum Score	Cumulative Score
Control	8 of 10	14.6±0.56 (n=8)	1.8±0.35	12.2±2.58
8f(10mg/kg oral b.i.d, starts from day 3)	2 of 10	15.5±1.5 (n=2)	0.3±0.2 **	1.6±1.05 **
Control	8 of 10	13.5±0.38 (n=8)	1.75±0.31	16.4±3.40
8f(10mg/kg oral b.i.d, starts from day 15)	6 of 10	13.8±0.31 (n=6)	1.1±0.33 *	8.7±3.00 *

[a]This table summarizes the results of two experiments with EAE mice treated with **8f**.Data represent mean ± SEM of the total mice in each group(n=10). From the time of EAE onset, only the mice with EAE were included in calculations. *p<0.05, **p<0.01 versus control group (Mann-Whitney Rank sum test).



FigureS1.8f treatment reduces CNS infiltration of pathogenic T cells.
(a) Immunofluorescent staining of $CD45^{+}$leukocytes in frozen sections of spinal cords isolated from naive, vehicle, or **8f**-treated EAE mice. The nuclei were stained with Hoechst33342. **(b–d)** Total CNS infiltrations were isolated by Percoll gradient centrifugation from vehicle or **8f**-treated EAE mice. Cells were analyzed by flow cytometry. The number of total infiltrated cells **(b)**$CD4^{+}$ T cells **(c)** or Th1 (IFN-g positive) and Th17 (IL-17 positive) cells in the CNS**(d)**are shown. Data are mean±SEM, ***p<0.001 versus vehicle control (Student's *t*-test).

Experimental Procedures and Characterization Data



Preparation procedure for10a-10b

Lawesson's reagent (1.58g,3.9mmol) was added to a solution of **9a** (1.0g,7.8mmol) in dry DME(50mL).The reaction mixture was stirred for 8hat 25°Cand then concentrated under reduced pressure.The obtained residue was purified by silica gel column chromatography (petroleum ether/EtOAc,4/1 to 2/1). The thioamidewas obtained as a white solid (1.1g,97.8%).

To a solution of above thioamide(1.1g,7.36mmol) in dry DME(40mL) was added $KHCO_3$(3.8g,0.038mol). The reaction mixture was stirred for 10 minat room temperature, andthen ethyl bromopyruvate(4.2g,0.168mol,80%)was added dropwise. The mixture was cooled to 0°Cand a solution of 2,6-lutidine(4.8g,0.023mol) and trifluoroacetic anhydride(4.1g,0.038mol) in dry DME(20mL) was added dropwise. The resulting mixture was stirredat 0°Cfor 40min, thenallowed to warm to room temperature and stirred for 12h, after which the reaction mixture was concentrated under reduced pressure. The obtained residue was dissolved inEtOAc and washed with 1NHCl, saturated$NaHCO_3$solution and brine,sequentially. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.The obtained residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 4/1 to 2/1). Compound**10a**wasobtainedas ayellow solid (1.66g, 90.7%).^{1}H NMR(300MHz, $CDCl_3$): δ 8.85(s,1H), 8.23(s,1H), 8.18(s,1H), 4.44(q, *J*=7.2Hz, 2H), 1.42(t, *J*=7.2Hz, 3H).MS (ESI) *m/z*: 263.0 ($M+Na^+$).

Following the same procedure,**10b**was obtained as a pale yellow solid(43% over two steps).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.0(s, 1H), 7.84(s, 1H), 4.23(q, *J*=7.2Hz, 2H), 2.57(s, 3H), 1.23(t, *J*=7.2Hz, 3H).^{13}C NMR(75 MHz, $CDCl_3$): δ 167.2, 163.6, 161.6, 147.9, 147.8, 128.0, 117.6, 61.7, 19.2, 14.5. MS (ESI) *m/z*: 277.0 ($M+Na^+$).

Preparation procedure for12a-12b

LiOH (580mg,0.013mol) was added to a stirred solution of **10a**(1.66g,6.9mmol) in EtOH/H_2O (V/V, 4/1,50mL) at 0°C. The resulting mixture was stirred for 12h at room temperature, and then most of EtOH was removed under reduced pressure.The aqueous phase was acidified with 1N HClto pH2.0 and then extracted with EtOAc.The combinedorganic phasewas washed with brine and dried over anhydrous Na_2SO_4. Removal of organic solvent under reduced pressure affordedthe acidas a yellow solid (1.39g,94.8%).

To a solution of above obtainedacid(100mg, 0.47mmol)in dry DMF (5mL) was added EDCI (108mg, 0.57mmol), HOBt (76mg, 0.57mmol), **11** (81mg, 0.52mmol) and *i*-Pr_2NEt(91mg, 0.71mmol), sequentially. The reaction mixture was stirred at room temperature for 12h. Then the mixture was diluted with H_2O and extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure.Silica gel column chromatography (petroleum ether/EtOAc, 3/1) of the obtained residue afforded**12a**as a colorless oil (129mg, 77.9%).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.83(s, 1H), 8.10(s,1H), 8.05(s,1H), 7.81(d, *J*=9.0Hz, 1H), 5.87(dddd, *J*=17.1,10.5,5.7,5.1Hz, 1H), 5.31(d, *J*=17.1Hz, 1H), 5.23(d, *J*=10.5Hz, 1H), 4.73(dd, *J*=9.3,5.1Hz, 1H), 4.65(dd, *J*=17.1,5.7Hz, 2H), 2.23-2.33(m, 1H), 0.96(t, *J*=6.9Hz, 6H).^{13}C NMR(75 MHz, $CDCl_3$): δ 171.5, 162.5, 160.9, 153.8, 150.4, 149.5, 131.6, 124.4, 119.0, 116.8, 65.9, 57.3, 31.7, 19.2, 18.0. MS (ESI) *m/z*: 352.1 ($M+H^+$).

Following the same procedure,**12b** was obtained as acolorless oil(61% overtwo steps).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.10(s, 1H), 7.81(s, 1H), 7.72(d, *J*=10.8Hz, 1H), 5.86(ddd, *J*=17.1,10.5,7.2,5.4Hz, 1H), 5.29 (d, *J*=17.1Hz, 1H), 5.19(d, *J*=10.5Hz, 1H), 4.68(dd, *J*=9.0,7.2Hz, 1H), 4.61(dd, *J*=17.1,5.4Hz, 2H), 2.68(s, 3H), 2.20-2.31(m, 1H), 0.96(t, *J*=6.9Hz, 6H).^{13}C NMR(75 MHz, $CDCl_3$): δ 171.0, 166.5, 162.2, 160.5, 149.8, 147.6, 131.2, 123.5, 118.5, 116.1, 65.4, 56.7, 31.2, 18.7, 17.5, 17.5. MS (ESI) *m/z*: 366.1 ($M+H^+$).

Preparation procedure forcompound 3a-3d

To a solution of **12a** (55mg,0.16mmol) in dry toluene (5.0mL) wasadded thioester**13a**(100mg, 0.48mmol in toluene, 0.48M) and Grubbs' 2ndgenerationcatalyst (66mg, 0.08mmol in toluene, 0.08M). The resulting mixture was stirred for 8h at110°C, after which the mixture was cooled to room temperature and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 2/1) to afford compound **3a**as a yellow oil (23mg, 50% based onrecovered starting material).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.86(s, 1H), 8.13(s, 1H), 8.11(s, 1H), 7.83(d, *J*=9.0Hz, 1H), 5.74(dt, *J*=15.3,6.6Hz, 1H), 5.63(dt, *J*=13.2,6.0Hz, 1H), 4.74(dd, *J*=9.0,5.4Hz, 1H), 4.66(dd, *J*=15.3,5.4Hz, 2H), 2.91(t, *J*=7.5Hz, 2H), 2.52(t, *J*=7.5Hz, 2H), 2.35-2.43(m, 2H), 2.22-2.32(m, 1H), 1.60-1.67(m, 2H), 1.19-1.26(m, 8H), 1.04 (t, *J*=6.3Hz, 6H), 0.86(t, *J*=6.9Hz, 3H).^{13}C NMR(75 MHz, $CDCl_3$): δ 199.5, 171.8, 162.7, 161.0, 153.8, 150.7, 149.8, 134.2, 125.6, 124.4, 116.9, 65.7, 57.4, 44.3, 32.5, 31.9, 31.8, 29.1, 28.1, 25.9, 22.8, 19.3, 18.2, 18.2, 14.2.HRMS (ESI) (*m/z*):Calcd for $C_{25}H_{35}N_3O_4S_3Na^+$,560.1682($M+Na^+$),Found 560.1693.

Following the same procedure as for **3a**,**3c** was obtained as a yellow oil(74% based onrecovered starting material). ^{1}H NMR(300 MHz, $CDCl_3$): δ 8.10(s, 1H), 7.89(s, 1H), 7.82(d, *J*=9.0Hz, 1H), 5.75(ddd, *J*=15.3,6.6,6.6Hz, 1H), 5.67(ddd, *J*=14.4,7.2,7.2Hz, 1H), 4.74(dd, *J*=9.0,5.1Hz, 1H), 4.61(dd, *J*=15.3,4.5Hz, 2H), 2.90 (t, *J*=7.2Hz, 2H), 2.77(s, 3H), 2.51(t, *J*=7.2Hz, 2H), 2.31-2.36(m, 2H), 2.27-2.30(m, 1H), 1.61-1.66(m, 2H), 1.19-1.27(m, 8H), 1.02(t, *J*=6.6Hz, 6H), 0.86(t, *J*=7.2Hz, 3H).^{13}C NMR(75 MHz, $CDCl_3$): δ 199.5, 171.8, 167.2, 162.8, 161.1, 150.5, 148.4, 134.1, 125.6, 124.1, 116.7, 65.7, 57.4, 44.3, 32.5, 31.9, 31.8, 29.1, 28.1, 25.9, 22.8, 19.4, 19.3, 18.2, 18.2, 14.2.HRMS (ESI)(*m/z*):Calcdfor $C_{26}H_{37}N_3O_4S_3Na^+$,574.1838(M+$Na^+$),Found 560.1857.

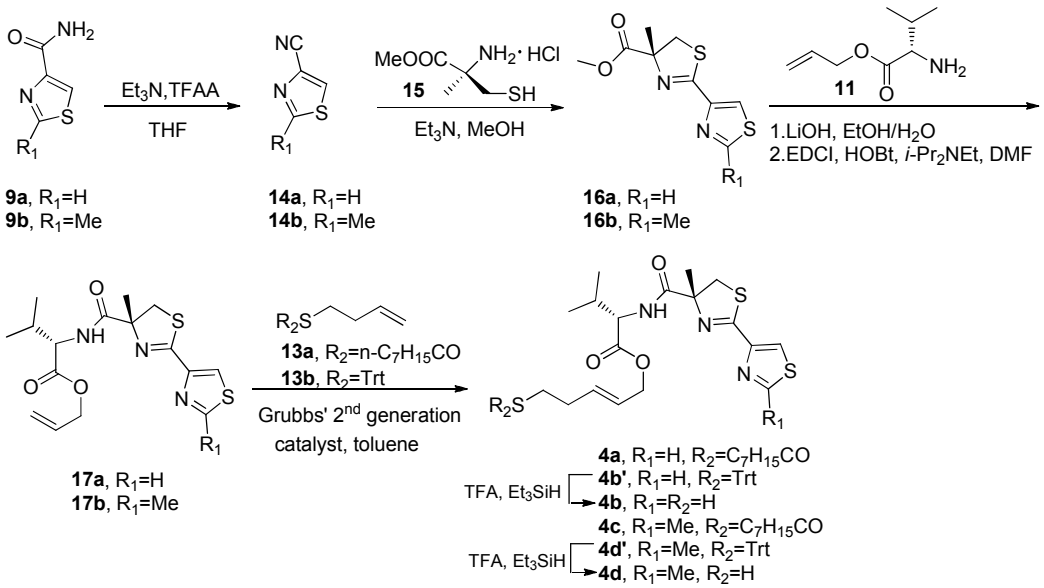
Following the same procedure as for **3a**,intermediate **3b'** was obtained as a yellow oil (46mg, 51% based onrecovered starting material).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.86(s, 1H), 8.13(s, 1H), 8.09(s, 1H), 7.83(d, *J*=9.0Hz, 1H), 7.39-7.48(m, 6H), 7.32-7.38(m, 6H), 7.17-7.29(m, 3H), 5.65(dt, *J*=15.3,6.6Hz, 1H), 5.51(dt, *J*=15.3,6.3Hz, 1H), 4.74 (dd, *J*=9.3,5.1Hz, 1H), 4.58(dd, *J*=12.6,6.3Hz, 2H), 2.21-2.33(m, 1H), 2.10-2.19(m, 2H), 2.07(t, *J*=6.9Hz, 2H), 1.00(t, *J*=6.9Hz, 6H).^{13}C NMR(75 MHz, $CDCl_3$): δ 171.8, 162.6, 161.0, 153.9, 150.6, 149.7, 145.0, 134.8, 129.7, 128.0, 126.8, 124.9, 124.4, 116.9, 66.8, 65.8, 57.3, 31.9, 31.6, 31.4, 19.3, 18.1. MS (ESI) *m/z*: 676.2 (M+Na^+).

To a solution ofabove obtainedS-tritylanalogue**3b'**(22mg, 0.034mmol) in CH_2Cl_2 (5mL)Et_3SiH (13mg, 0.11mmol) and TFA (384mg, 3.4mmol)were added.The resulting mixture was stirred at room temperature for 2h. Then the reaction mixturewas concentrated under reduced pressure and the obtained residue was purified by silica gel column chromatography(petroleum ether/EtOAc, 4/1) to afford**3b** as a pale yellow oil (8mg, 57.1%).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.87(s, 1H), 8.14(s, 1H), 8.09(s, 1H), 7.84(d, *J*=9.0Hz, 1H), 5.78(dt, *J*=15.3, 6.6Hz, 1H), 5.68(dt, *J*=12.3,6.3Hz, 1H), 4.76(dd, *J*=8.7,4.8Hz, 1H), 4.65(dd, *J*=15.3,5.4Hz, 2H), 2.58(q, *J*=7.5Hz, 2H), 2.39-2.44(m, 2H), 2.31-2.37(m, 1H), 1.04(d, *J*=6.3Hz, 6H). ^{13}C NMR(75 MHz, $CDCl_3$): δ 171.9, 162.7, 161.1, 153.9, 150.6, 149.8, 134.0, 125.9, 124.5, 117.0, 65.7, 57.4, 36.6, 31.9, 24.1, 19.4, 18.2. HRMS (ESI) (*m/z*):Calcd for $C_{17}H_{21}N_3O_3S_3Na^+$,434.0637(M+$Na^+$),Found 434.0748.

Following the same procedure as for **3a**, intermediate **3d'**was obtained as a yellow oil (26mg, 37.7% based onrecovered starting material).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.09(s, 1H), 7.87(s, 1H), 7.83(d, *J*=9.0Hz, 1H), 7.39-7.53(m, 6H), 7.30-7.36(m, 6H), 7.20-7.27(m, 3H), 5.66(dt, *J*=15.3,6.3Hz, 1H), 5.50(dt, *J*=15.6,6.3Hz, 1H), 4.73(dd, *J*=9.3,5.1Hz, 1H), 4.60(dd, *J*=10.8,5.4Hz, 2H), 2.70(s, 3H), 2.26-2.37(m, 1H), 2.16-2.24(m, 2H), 2.10(t, *J*=6.9Hz, 2H), 0.99(t, *J*=6.9Hz, 6H).^{13}C NMR(75 MHz, $CDCl_3$): δ 171.8, 167.1, 162.8, 161.1, 150.5, 148.4, 145.1, 134.8, 129.8, 128.0, 126.8, 125.0, 124.1, 116.7, 66.8, 65.8, 57.3, 31.9, 31.6, 31.4, 19.4, 19.3, 18.1. MS (ESI) *m/z*: 690.2 (M+Na^+).

Following the same procedure as for **3b**,compound**3d**was obtained as a pale yellow oil (11mg, 57.9%).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.11(s, 1H), 7.89(s, 1H), 7.86(d, *J*=6.3Hz, 1H), 5.77(ddd, *J*=15.3,6.3,6.3Hz, 1H), 5.65(ddd, *J*=14.4,6.6,6.6Hz, 1H), 4.74(dd, *J*=9.0,4.8Hz, 1H), 4.64(dd, *J*=15.3,6.9Hz, 2H), 2.77(s, 3H), 2.57(q, *J*=7.5Hz, 2H), 2.36-2.43(m, 2H), 2.28-2.34(m, 1H), 1.05(d, *J*=6.3Hz, 6H). ^{13}C NMR(75 MHz,

$CDCl_3$): δ 171.9, 167.2, 162.8, 161.1, 150.4, 148.3, 134.0, 125.9, 124.2, 116.7, 65.7, 57.4, 36.6, 31.8, 24.1, 19.4, 19.3, 18.2.HRMS (ESI) (*m/z*):Calcd for $C_{18}H_{23}N_3O_3S_3Na^+$,448.0794($M+Na^+$),Found 448.0859.



Preparation procedure for14a-14b

Et_3N (1.04g, 0.010mol) and TFAA (1.08g, 5.15mmol)were addeddropwise to a solution of **9a** (600mg, 4.68mmol) in dry THF (10mL, 0.47M)at 0°C. The resulting mixture was stirred for 2h at room temperature, after whichthe reaction mixture wasdiluted withH_2O and extracted with Et_2O. The organic extractswerewashed with 1N HCl, saturated $NaHCO_3$ and brine, sequentially. The obtained organic phase was dried over anhydrous Na_2SO_4 andconcentrated under reduced pressure. Silica gel column chromatography (petroleum ether/EtOAc, 4/1) of the obtained residue affordedcyanothiazole**14a**as acolorless oil (285mg, 55.2%).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.90(s, 1H), 8.12(s, 1H).^{13}C NMR(75 MHz, $CDCl_3$): δ 154.9, 130.7, 127.8, 113.9. MS (ESI) *m/z*: 133.0 ($M+Na^+$).

Following similar procedure,cyanothiazole**14b**was obtained as acolorless oil (67.4%).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.84(s, 1H), 2.60(s, 3H).^{13}C NMR(75 MHz, $CDCl_3$) δ 168.3, 131.1, 126.0, 114.3, 19.2. MS (ESI) *m/z*: 147.0 ($M+Na^+$).

Preparation procedure for16a-16b

To a solution of cyanothiazole**14a** (50mg, 0.45mmol) in dry MeOH (10mL) wasadded Et_3N (138mg, 1.35mmol) and **15** (167mg, 0.90mmol). The resulting mixture was stirred for 48h at 50°C. The reaction mixture was then concentrated under reduced pressure and the residue dissolved inCH_2Cl_2. The organic phase was washed with brine,dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Theobtained residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 1/1) to afford **16a**as a colorless oil (47mg, 42.7%).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.80(s, 1H), 8.09(s, 1H), 3.87(d, *J*=11.7Hz, 1H), 3.77(s, 3H), 3.26(d, *J*=11.1Hz, 1H), 1.62(s, 3H).^{13}C NMR(75 MHz, $CDCl_3$): δ 174.2, 163.6, 153.5, 150.3, 121.3, 85.2, 53.5, 41.9, 24.6. MS (ESI) *m/z*: 243.0 ($M+H^+$).

Following similar procedure,**16b**was obtained as acolorless oil(36.9%).^{1}H NMR(300

MHz, $CDCl_3$): δ 7.81(s, 1H), 3.82(d, *J*=11.7Hz, 1H), 3.75(s, 3H), 3.22(d, *J*=11.1Hz, 1H), 2.69(s, 3H), 1.59(s, 3H).^{13}C NMR(75 MHz, $CDCl_3$): δ 173.9, 166.6, 163.2, 148.6, 121.2, 84.7, 53.1, 41.6, 24.1, 19.4. MS (ESI) *m/z*: 279.0 ($M+Na^+$).

Preparation procedure for17a-17b

To a stirred solution of **16a**(27mg, 0.11mmol) in THF/H_2O (4:1, v/v, 10mL) was addedNaOH (4mg,0.11mol) at 0°C. The resulting mixture was stirred for 4h at room temperature, after which themixture was acidified with 1M$KHSO_4$ solution to pH2.0and extracted with EtOAc.The combinedorganic phasewas washed with brine,dried over anhydrous $Na_2SO_4$and concentrated under reduced pressure toafford the acidas a colorless oil (25mg, 98.4%).

To a solution of theabove obtainedacid(25mg, 0.11mmol)in dry DMF (2mL) was added EDCI (42mg, 0.22mmol), HOBt (30mg, 0.22mmol), **11** (26mg, 0.17mmol) and *i*-Pr_2NEt(43mg, 0.33mmol), sequentially. The resulting mixture was stirred for 12h at room temperature. Thenthe mixture was diluted with H_2O and extracted with EtOAc. The combined organic phase waswashed with brine, dried over anhydrous $Na_2SO_4$and concentrated under reduced pressure. Silica gel column chromatography (petroleum ether/EtOAc, 2/1) of the obtained residue afforded**17a**as a colorless oil (40mg, 99.1%).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.87(s, 1H), 8.12(s, 1H), 7.25(d, *J*=9.0Hz, 1H), 5.92(dddd, *J*=17.1,10.5,7.2,5.7Hz, 1H), 5.37 (d, *J*=17.1Hz, 1H), 5.27(d, *J*=10.5Hz, 1H), 4.67(dd, *J*=11.7,5.7Hz, 1H), 4.63(dd, *J*=13.2,7.2Hz, 1H), 4.56(dd, *J*=9.0,5.1Hz, 1H), 3.82(d, *J*=11.7Hz, 1H), 3.38(d, *J*=11.7Hz, 1H), 2.15-2.24(m, 1H), 1.63(s, 3H), 0.87(d, *J*=6.9Hz, 3H), 0.86(d, *J*=6.9Hz, 3H).^{13}C NMR(75 MHz, $CDCl_3$): δ 175.1, 171.8, 164.0, 153.8, 150.5, 132.2, 121.2, 119.5, 85.8, 66.3, 57.6, 42.0, 31.7, 25.3, 19.6, 18.2. MS (ESI) *m/z*: 368.1 ($M+H^+$).

Following similar procedure,**17b** was obtained as a colorless oil(65.5% overtwo steps).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.84(s, 1H),7.20(d, *J*=9.0Hz,1H),5.90(dddd,*J*=17.1,10.5,6.9,5.4Hz, 1H), 5.32(d, *J*=17.1Hz, 1H), 5.22(d, *J*=10.5Hz, 1H), 4.62(dd, *J*=11.1,5.7Hz, 1H), 4.53(dd, *J*=15.0,6.9Hz, 1H), 4.31(dd, *J*=9.0,5.1Hz, 1H), 3.77(d, *J*=11.1Hz, 1H), 3.31(d, *J*=11.4Hz, 1H), 2.72(s, 3H), 2.15-2.20(m, 1H), 1.59(s, 3H), 0.87(d, *J*=6.9Hz, 3H), 0.83(d, *J*=6.9Hz, 3H).^{13}C NMR(75 MHz, $CDCl_3$): δ 174.8, 171.4, 166.8, 163.6, 148.8, 131.8, 120.9, 119.0, 85.3, 65.9, 57.2, 41.6, 31.3, 24.9, 19.4, 19.2, 17.8. MS (ESI) *m/z*: 382.1 ($M+H^+$).

Preparation procedure for compound 4a-4d

To a solution of **17a** (35mg, 0.04mmol) in dry toluene (1.0mL) wereadded thioester**13a**(87mg, 0.40mmol in toluene, 0.40M) and Grubbs' 2ndgenerationcatalyst (35mg, 0.04mmol in toluene, 0.04M). The resulting mixture was stirredfor 12h at 110°C. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure. Theresidue was purified by silica gel column chromatography (petroleum ether/EtOAc, 2/1) to afford compound **4a**as a paleyellow oil (10mg of (*E*)-isomer, 33.3% based onrecovered starting material).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.84(s, 1H), 7.20(d, *J*=9.3Hz, 1H), 5.73-5.80(m, 1H), 5.59-5.68(m, 1H), 4.60(t, *J*=5.7Hz, 2H), 4.54(dd, *J*=9.0,4.8Hz, 1H), 3.80(d, *J*=11.7Hz, 1H), 3.37(d, *J*=11.7Hz, 1H), 2.92(t, *J*=7.2Hz, 2H), 2.53(t, *J*=7.5Hz, 2H), 2.30-2.37(m, 2H), 2.18-2.28(m, 1H), 1.64-1.83(m, 2H), 1.62(s, 3H), 1.18-1.27(m, 8H), 0.98(t, *J*=6.6Hz,

3H), 0.88(d, *J*=6.9Hz, 3H), 0.84(d, *J*=6.9Hz, 3H).^{13}C NMR(75 MHz, $CDCl_3$): δ 199.6, 174.7, 171.6, 163.6, 153.5, 150.1, 134.1, 125.6, 120.8, 85.4, 65.7, 57.2, 44.4, 41.7, 32.5, 31.8, 31.4, 29.9, 29.1, 28.1, 25.9, 24.9, 22.8, 19.3, 17.9, 14.3. HRMS (ESI) (*m/z*):Calcd for $C_{26}H_{39}N_3O_4S_3Na^+$,576.1995(M+$Na^+$),Found 576.2034.

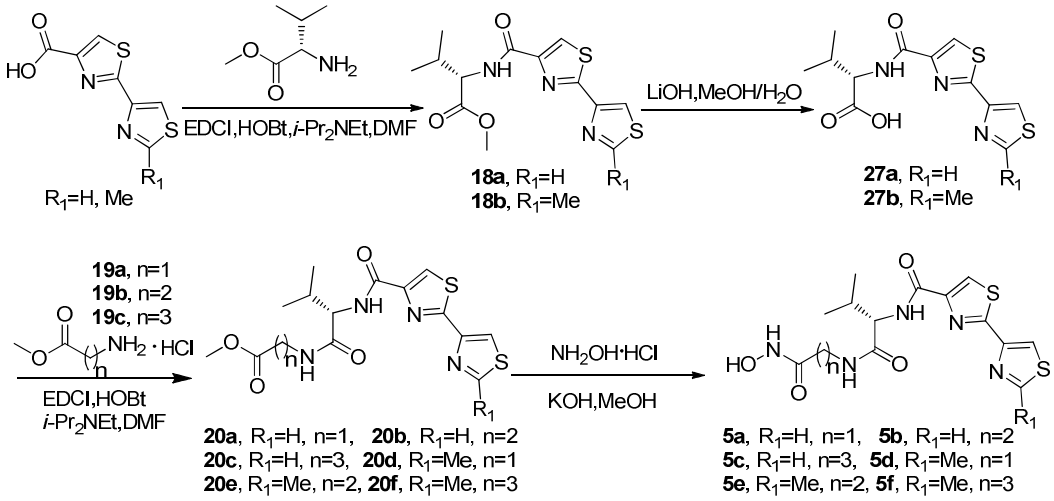
Following similar procedure,**4c** was obtained as a paleyellow oil(27.5% based onrecovered starting material).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.87(s, 1H), 7.22(d, *J*=9.0Hz, 1H), 5.65-5.74(m, 1H), 5.60-5.65(m, 1H), 4.59(t, *J*=6.3Hz, 2H), 4.53(dd, *J*=9.0,4.8Hz, 1H), 3.79(d, *J*=11.4Hz, 1H), 3.34(d, *J*=11.4Hz, 1H), 2.91(t, *J*=7.5Hz, 2H), 2.76(s, 3H), 2.53(t, *J*=7.5Hz, 2H), 2.32-2.41(m, 2H), 2.09-2.29(m, 1H), 1.64-1.76(m, 2H), 1.61(s, 3H), 1.25-1.37(m, 8H), 0.93(t, *J*=6.6Hz, 3H), 0.88(d, *J*=6.9Hz, 3H), 0.84(d, *J*=6.9Hz, 3H).^{13}C NMR(75 MHz, $CDCl_3$): δ 199.7, 174.8, 171.5, 166.9, 162.6, 148.8, 134.1, 125.6, 121.0, 85.3, 65.6, 57.2, 44.4, 41.7, 32.5, 31.8, 31.3, 29.9, 29.1, 28.1, 25.9, 24.9, 22.8, 19.5, 19.3, 17.9, 14.3. HRMS (ESI) (*m/z*):Calcd for $C_{27}H_{41}N_3O_4S_3Na^+$,590.2151(M+$Na^+$),Found 590.2169.

Following the same procedure as for **4a**,S-trityl analogue **4b'** was obtained as a yellow oil (15mg, 41.7% based onrecovered starting material).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.82(s, 1H), 8.07(s, 1H), 7.35-7.41(m, 6H), 7.19-7.29(m, 6H), 7.12-7.17(m, 3H), 5.63(dt, *J*=15.3,6.3Hz, 1H), 5.49(dt, *J*=15.3,6.0Hz, 1H), 4.49-4.61(m, 3H), 3.80(d, *J*=11.4Hz, 1H), 3.36(d, *J*=11.7Hz, 1H), 2.16-2.29(m, 3H), 2.10(t, *J*=5.4Hz, 2H), 1.60(s, 3H), 0.86(d, *J*=6.9Hz, 3H), 0.81(d, *J*=6.9Hz, 3H).^{13}C NMR(75 MHz, $CDCl_3$): δ 175.1, 172.0, 153.8, 150.6, 145.5, 138.5, 135.2, 130.2, 128.5, 127.2, 125.9, 121.2, 85.9, 67.3, 66.1, 57.6, 42.1, 32.0, 31.8, 25.4, 22.1, 19.7, 18.3. MS (ESI) *m/z*: 692.2 (M+Na^+).

To a solution of above obtained S-trityl analogue **4b'**(15mg, 0.022mmol) in CH_2Cl_2 (5mL)Et_3SiH (9mg, 0.074mmol) and TFA (255mg, 2.2mmol)were addedsequentially. The resulting mixture was stirred for 2h at room temperature and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 2/1) to afford compound **4b** as a pale yellow oil (7mg, 72.9%).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.86(s, 1H), 8.11(s, 1H), 7.22(d, *J*=8.4Hz, 1H), 5.78(dt, *J*=15.3,6.3Hz, 1H), 5.65(dt, *J*=15.3,6.0Hz, 1H), 4.61(t, *J*=5.1Hz, 1H), 4.53(dd, *J*=8.7,5.1Hz, 1H), 4.32(t, *J*=6.6Hz, 1H), 3.81(d, *J*=11.1Hz, 1H), 3.37(d, *J*=11.4Hz, 1H), 2.55-2.67(m, 2H), 2.33-2.50(m, 2H), 2.13-2.20(m, 1H), 1.62(s, 3H), 0.88(d, *J*=6.9Hz, 3H), 0.84(d, *J*=6.9Hz, 3H).^{13}C NMR(75 MHz, $CDCl_3$): δ 174.7, 171.6, 163.7, 153.5, 150.0, 131.1, 129.0, 120.9, 85.4, 65.7, 57.2, 41.7, 31.3, 30.8, 29.9, 24.9, 19.3, 17.9.HRMS (ESI) (*m/z*):Calcd for $C_{18}H_{25}N_3O_3S_3Na^+$,450.0950(M+$Na^+$),Found 450.1128.

Following the same procedure as for **4a**,S-trityl analogue**4d'** was obtained as a yellow oil (25mg, 53.6% based onrecovered starting material).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.84(s, 1H), 7.39-7.42(m, 6H), 7.27-7.35(m, 6H), 7.17-7.25(m, 3H), 5.63(dt, *J*=15.6,6.0Hz, 1H), 5.49(dt, *J*=15.3,6.0Hz, 1H), 4.48-4.60(m, 3H), 3.79(d, *J*=11.4Hz, 1H), 3.33(d, *J*=11.7Hz, 1H), 2.75(s, 3H), 2.24(t, *J*=6.9Hz, 2H), 2.05-2.16(m, 3H), 1.59(s, 3H), 0.86 (d, *J*=6.9Hz, 3H), 0.81(d, *J*=6.9Hz, 3H).^{13}C NMR(75 MHz, $CDCl_3$): δ 174.8, 171.5, 166.8, 163.6, 148.9, 145.1, 134.7, 129.8, 128.1, 126.8, 125.1, 120.9, 85.4, 66.9, 65.7, 57.2, 41.7, 31.6, 31.4, 31.3, 25.0, 19.5, 19.3, 17.9. MS (ESI) *m/z*: 706.2 (M+Na^+).

Following the same procedure as for **4b**,compound **4d**was obtained as a pale yellow oil (13mg, 83.9%).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.86(s, 1H), 7.21(d, *J*=8.7Hz, 1H), 5.77(dt, *J*=15.6,6.0Hz, 1H), 5.67(dt, *J*=15.3,6.0Hz, 1H), 4.62(t, *J*=5.4Hz, 1H), 4.51(dd, *J*=8.7,5.4Hz, 1H), 4.31(t, *J*=6.6Hz, 1H), 3.81(d, *J*=11.4Hz, 1H), 3.33(d, *J*=11.7Hz, 1H), 2.76(s, 3H), 2.54-2.69(m, 2H), 2.34-2.41(m, 2H), 2.07-2.20(m, 1H), 1.61(s, 3H), 0.90(d, *J*=6.9Hz, 3H), 0.84(d, *J*=6.9Hz, 3H).^{13}C NMR(75 MHz, $CDCl_3$): δ 174.8, 171.5, 166.9, 163.7, 148.7, 131.1, 129.0, 121.1, 85.2, 65.7, 57.2, 41.7, 31.3, 30.7, 29.9, 24.9, 19.5, 19.3, 17.9.HRMS (ESI) (*m/z*):Calcd for $C_{19}H_{27}N_3O_3S_3Na^+$,464.1107(M+$Na^+$),Found 464.1288.



Preparation procedure for18a-18b

To a solution of bisthiazole carboxylic acid(600mg, 2.83mmol)in dry DMF (10mL, 0.28M) was added EDCI (542mg, 2.83mmol), HOBt (382mg, 2.83mmol), *L*-Valinemethyl ester (521mg, 3.11mmol) and *i*-Pr_2NEt(1.09g,8.48mmol), sequentially. The reaction mixture was stirred for 12h at room temperature. The mixture was then diluted with H_2O and extracted with EtOAc. The combined organic phase waswashed with brine, dried over anhydrous Na_2SO_4 and then concentratedunder reduced pressure. The obtained residue was purified by silica gel column chromatography(petroleum ether/EtOAc, 3/1 to 2/1)to afford**18a**as a pale yellow oil (630mg, 68.5%).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.79(s, 1H), 8.06(s, 1H), 8.00(s, 1H), 7.75(d, *J*=8.7Hz, 1H), 4.65(dd, *J*=9.3,5.4Hz, 1H), 3.68(s, 3H), 2.18-2.24(m, 1H), 0.93(d, *J*=6.6Hz, 6H).^{13}C NMR(75 MHz, $CDCl_3$): δ 171.8, 162.0, 160.3, 153.4, 149.9, 149.0, 123.8, 116.3, 56.7, 51.7, 31.0, 18.6, 17.6. MS (ESI) *m/z*: 326.1 (M+H^+).

Following similar procedure,**18b** was obtained as a pale yellow oil(67.6%).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.93(s,1H), 7.67(s, 1H), 4.52(dd, *J*=9.0,5.4Hz, 1H), 3.57(s, 3H), 2.51(s, 3H), 2.07-2.11(m, 1H), 0.81(d, *J*=6.6Hz, 6H).^{13}C NMR(75 MHz, $CDCl_3$): δ 171.8, 166.6, 162.3, 160.5, 149.9, 147.7, 123.7, 116.3, 56.9, 51.8, 31.2, 18.8, 18.7, 17.7. MS (ESI) *m/z*: 362.1 (M+Na^+).

Preparation procedure for 27a-27b

To a stirred solution of **18a**(630mg, 1.94mmol) in MeOH/H_2O (4/1, v/v, 50mL) was addedLiOH (163mg,3.88mmol) at 0°C. The reaction mixture was stirred for 12h at

room temperature and then concentrated under reduced pressure. Theresulting aqueous mixture was acidified with 1N HCl solution to pH2.0, and thenextracted with EtOAc.The combinedorganic phase was washed with brine, dried over anhydrous Na_2SO_4andconcentrated under reduced pressure toaffordthe acid **27a** as a white solid (600mg, 99.5%).^{1}H NMR(300 MHz, CD_3OD): δ 9.09(d, *J*=3.3Hz, 1H), 8.37(d, *J*=3.3Hz, 1H), 8.26(s, 1H), 4.58(dd, *J*=8.7,5.1Hz, 1H), 2.31-2.38(m, 1H), 1.06(d, *J*=6.9Hz, 6H). MS (ESI) *m/z*: 312.1 ($M+H^+$).

Following similar procedure, the respective acid **27b** from**18b** was obtained as a white solid(93.1%).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.16(s, 1H), 7.88(s, 1H), 4.77(dd, *J*=9.0,4.8Hz, 1H), 2.77(s, 3H), 2.35-2.42(m, 1H), 1.06(d, *J*=6.6Hz, 6H). MS (ESI) *m/z*: 326.1 ($M+H^+$).

Preparation procedure for20a-20f

To a solution of the acid**27a**(80mg, 0.26mmol)in dry DMF (5mL) was added EDCI (49mg, 0.26mmol), HOBt (35mg, 0.26mmol), **19a** (36mg, 0.28mmol) and *i*-Pr_2NEt(99mg, 0.75mmol). The resulting mixture was stirred for 12h at room temperature, after which the reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. Theresidue was purified by silica gel column chromatography (petroleum ether/EtOAc/MeOH, 15/15/1)to afford **20a**as a colorless oil (79mg, 80.2%).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.81(s, 1H), 8.10(s, 1H), 8.05(s, 1H), 7.93(d, *J*=9.0Hz, 1H), 7.47(t, *J*=5.1Hz, 1H), 4.59(dd, *J*=9.0,7.5Hz, 1H), 4.13(dd, *J*=18,6.0Hz, 1H), 3.93(dd, *J*=18.3,5.4Hz, 1H), 3.67(s, 3H), 2.20-2.29(m, 1H), 0.99(d, *J*=6.6Hz, 6H).^{13}C NMR(75 MHz, $CDCl_3$): δ 171.6, 170.2, 162.6, 161.1, 153.8, 150.3, 149.5, 124.3, 117.0, 58.4, 52.3, 41.2, 31.5, 19.4, 18.3. MS (ESI) *m/z*: 383.1 ($M+H^+$).

Following similar procedure,**20b**was obtained as acolorless oil(96.6% for two steps).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.79(s, 1H), 8.08(s, 1H), 8.03(s, 1H), 7.90(d, *J*=6.9Hz, 1H), 7.30(t, *J*=4.8Hz, 1H), 4.43(dd, *J*=9.0,6.6Hz, 1H), 3.56(s, 3H), 3.41(t, *J*=6.0Hz, 2H), 2.51(t, *J*=5.4Hz, 2H), 2.09-2.20(m, 1H), 0.91(d, *J*=5.7Hz, 6H) ^{13}C NMR(75 MHz, $CDCl_3$): δ 172.7, 171.3, 162.7, 161.1, 153.9, 150.6, 149.6, 124.3, 117.1, 58.6, 51.9, 35.3, 33.9, 31.7, 19.4, 18.5. MS (ESI) *m/z*: 419.1 ($M+Na^+$).

Following similar procedure,**20c**was obtained as a colorless oil(98.4% over two steps).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.90(s, 1H), 8.15(s, 1H), 8.05(d, *J*=8.7Hz, 1H), 7.46(t, *J*=5.4Hz, 1H), 4.56(dd, *J*=8.7,6.9Hz, 1H), 3.65(s, 3H), 3.39-3.43(m, 1H), 3.28-3.33(m,1H), 2.38-2.43(m, 2H), 2.25-2.31(m,1H), 1.90(t, *J*=6.9Hz, 2H), 1.05(d, *J*=6.9Hz, 6H) ^{13}C NMR(75 MHz, $CDCl_3$): δ 173.6, 171.1, 162.5, 160.9, 153.8, 150.4, 149.4, 124.0, 116.9, 59.6, 51.6, 38.8, 36.4, 31.6, 24.6, 19.4, 18.4. MS (ESI) *m/z*: 411.1 ($M+H^+$).

Following similar procedure,**20d**was obtained as a colorless oil (75.3% over two steps).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.07(s, 1H), 7.91(d, *J*=9.0Hz, 1H), 7.83(s, 1H), 7.44(t, *J*=5.4Hz, 1H), 4.58(dd, *J*=9.0,7.2Hz, 1H), 4.13(d, *J*=6.0Hz, 1H), 3.92(d, *J*=4.8Hz, 1H), 3.67(s, 3H), 2.70(s, 3H), 2.23-2.29(m, 1H), 0.99(d, *J*=6.6Hz, 6H) ^{13}C NMR(75 MHz, $CDCl_3$): δ 171.2, 169.8, 166.6, 162.4, 160.8, 149.8, 147.7, 123.7, 116.4, 58.1, 51.9, 40.8, 31.0, 19.0, 18.8, 18.0. MS (ESI) *m/z*: 419.1 ($M+Na^+$).

Following similar procedure,**20e**was obtained as colorless oil(91% over two steps).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.09(s, 1H), 7.92(d, *J*=9.6Hz, 1H), 7.83(s, 1H), 7.28(t, *J*=5.7Hz, 1H), 4.47(dd, *J*=8.1,6.0Hz, 1H), 3.59(s, 3H), 3.44(q, *J*=6.0Hz, 2H), 2.69(s, 3H), 2.55(t, *J*=5.4Hz, 2H), 2.14-2.20(m, 1H), 0.95(d, *J*=6.6Hz, 6H) ^{13}C NMR(75 MHz, $CDCl_3$): δ 172.6, 171.2, 167.0, 162.7, 161.1, 150.3, 148.1, 123.9, 116.7, 58.5, 51.8, 35.2, 33.9, 31.6, 19.3, 19.2, 18.4. MS (ESI) *m/z*: 433.1 ($M+Na^+$).

Following similar procedure,**20f**was obtained as a colorless oil(70.5% over two steps).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.05(s, 1H), 7.94(d, *J*=9.3Hz, 1H), 7.85(s, 1H), 7.18(t, *J*=6.0Hz, 1H), 4.46(dd, *J*=9.0,5.1Hz, 1H), 3.59(s, 3H), 3.33-3.53(m, 1H), 3.19-3.32(m, 1H), 2.71(s, 3H), 2.30-2.61(m, 2H), 2.16-2.27(m, 1H), 1.83(t, *J*=7.2Hz, 2H), 1.00(d, *J*=6.6Hz, 6H) ^{13}C NMR(75 MHz, $CDCl_3$): δ 174.2, 171.7, 167.5, 163.2, 161.6, 150.7, 148.6, 124.4, 117.2, 59.3, 52.2, 39.4, 31.9, 31.8, 25.1, 19.9, 19.7, 19.0. MS (ESI) *m/z*: 447.1 ($M+Na^+$).

Preparation procedure forcompound 5a-5f

To a mixtureof hydroxylamine hydrochloride (144mg, 2.1mmol) in dry MeOH (10mL) was added solid KOH (176mg, 3.15mmol) and the resulting mixture was stirred for 5 min at room temperature. The mixture was filtered and compound**20a** (79mg, 0.21mmol) was added to the filtrate. The resulting mixture was stirredfor 1h at room temperature. The mixture was then acidified with 1N HCl to pH5-6 and concentratedunder reduced pressure. The obtained residue was dissolved in EtOAc. ThisEtOAc solution was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.The obtained residue was further purified by silica gel column chromatography ($CHCl_3$/MeOH, 20/1 to 10/1)to afford compound **5a**as a pale yellow solid (18mg, 22.8%).^{1}H NMR(300 MHz, CD_3OD): δ 9.09(s, 1H), 8.36(s, 1H), 8.26(s, 1H), 7.89(s, 1H), 4.46(d, *J*=6.6Hz, 1H), 3.85(d, *J*=6.6Hz, 2H), 2.23-2.26(m, 1H), 1.06(d, *J*=6.9Hz, 6H).^{13}C NMR(75 MHz, CD_3OD): δ 174.0, 168.5, 164.3, 163.3, 156.5, 151.2, 150.6, 126.0, 119.1, 60.3, 41.5, 32.6, 19.9, 18.9. HRMS (ESI) (*m/z*):Calcd for $C_{14}H_{17}N_5O_4S_2Na^+$,406.0614($M+Na^+$),Found406.0615.

Following similar procedure, compound **5b**was obtained as a pale yellow solid (40%).^{1}H NMR(300 MHz, CD_3OD): δ 9.08(s, 1H), 8.36(s, 1H), 8.28(d, *J*=9.0Hz, 1H), 8.24(s, 1H), 7.89(s, 1H), 4.39(t, *J*=7.2Hz, 1H), 3.50(q, *J*=4.8Hz, 2H), 2.34(t, *J*=6.9Hz, 2H), 2.15-2.22(m, 1H), 1.03(d, *J*=6.6Hz, 6H).^{13}C NMR(75 MHz, CD_3OD): δ 173.6, 170.5, 164.3, 163.0, 156.5, 151.2, 150.5, 125.9, 119.1, 60.1, 37.0, 33.5, 32.8, 19.9, 18.9. HRMS (ESI) (*m/z*):Calcd for $C_{15}H_{19}N_5O_4S_2Na^+$,420.0776($M+Na^+$),Found420.0771.

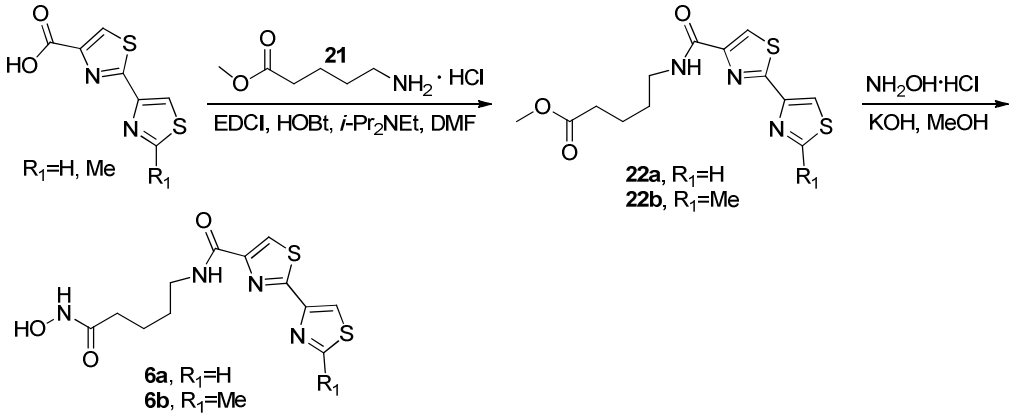
Following similar procedure, compound **5c**was obtained as a pale yellow solid (30.8%).^{1}H NMR(300 MHz, CD_3OD): δ 9.90(s, 1H), 8.36(s, 1H), 8.25(s, 1H), 7.89(s, 1H), 4.39(t, *J*=7.2Hz, 1H), 3.28(q, *J*=8.9Hz, 2H), 2.11-2.21(m, 3H), 1.83(q, *J*=7.8Hz, 2H), 1.04(d, *J*=6.9Hz, 6H).^{13}C NMR(75 MHz, CD_3OD): δ 173.5, 172.4, 164.4, 163.1, 156.5, 151.3, 150.6, 125.9, 119.1, 60.4, 39.9, 32.8, 31.3, 26.6, 19.9, 18.9. HRMS (ESI) (*m/z*):Calcd for $C_{16}H_{21}N_5O_4S_2Na^+$,434.0927($M+Na^+$),Found434.0931.

Following similar procedure,**5d**was obtained as a pale yellow solid(29%).^{1}H NMR(300 MHz, DMSO-d_6): δ 10.55(s, 1H), 8.86(s, 1H), 8.54(t, *J*=5.4Hz, 1H), 8.33(s, 1H), 8.23(s, 1H), 8.01(d, *J*=9.0Hz, 1H), 4.45(t, *J*=6.3Hz, 1H), 3.50(d, *J*=4.2Hz, 2H), 2.73(s, 3H), 2.10(m, 1H), 0.94(d, *J*=6.9Hz, 3H), 0.89(d, *J*=6.9Hz, 3H).^{13}C NMR(75 MHz, DMSO-d_6): δ

170.9, 167.6, 165.6, 162.3, 160.0, 150.2, 147.0, 124.8, 118.1, 57.4, 38.7, 31.3, 19.3, 18.8, 18.2. HRMS (ESI) (*m/z*):Calcd for $C_{15}H_{19}N_5O_4S_2Na^+$,420.0776(M+$Na^+$),Found420.0771.

Following similar procedure,**5e**was obtained as a pale yellow solid (29%).^{1}H NMR(300 MHz, CD_3OD): δ 8.27(d, *J*=8.4Hz, 1H), 8.21(s, 1H), 8.12(s, 1H), 7.89(s, 1H), 4.38(d, *J*=6.0Hz, 1H), 3.36(t, *J*=6.0Hz, 2H), 2.76(s, 3H), 2.34(t, *J*=6.0Hz, 2H), 2.15-2.21(m, 1H), 1.02(d, *J*=6.6Hz, 6H).^{13}C NMR(75 MHz, CD_3OD): δ 173.6, 170.5, 169.4, 164.3, 163.0, 151.2, 149.2, 125.6, 118.8, 60.2, 37.0, 33.5, 32.8, 19.9, 18.9, 18.8. HRMS (ESI) (*m/z*):Calcd for $C_{16}H_{21}N_5O_4S_2Na^+$,434.0927 (M+$Na^+$),Found434.0927.

Following similar procedure,**5f**was obtained as a pale yellow solid(18.2%).^{1}H NMR(300 MHz, DMSO-d_6): δ 10.37(s, 1H), 8.71(s, 1H), 8.33(s, 1H), 8.28(t, *J*=5.7Hz, 1H), 8.25(s, 1H), 7.96(d, *J*=9.0Hz, 1H), 4.34(dd, *J*=8.7,7.2Hz, 1H), 3.08(m, 2H), 2.74(s, 3H), 2.07(m, 1H), 1.96(t, *J*=7.2Hz, 2H), 1.65(m, 2H), 0.96(d, *J*=6.6Hz, 3H), 0.89(d, *J*=6.0Hz, 3H).^{13}C NMR(75 MHz, DMSO-d_6): δ 170.4, 168.7, 167.5, 162.3, 159.9, 150.1, 146.9, 124.7, 118.1, 57.5, 38.3, 31.3, 29.9, 25.2, 19.3, 18.8, 18.3. HRMS (ESI) (*m/z*):Calcd for $C_{17}H_{23}N_5O_4S_2Na^+$,448.1084(M+$Na^+$),Found448.1079.



Preparation procedure for22a-22b

To a solution of the bisthiazole carboxylic acid(60mg, 0.28mmol, prepared from **10a**)in dry DMF (5mL) was added EDCI (54mg, 0.28mmol), HOBt (38mg, 0.28mmol), **21**(52mg, 0.31mmol) and *i*-Pr_2NEt(109mg,0.85mmol). The resultingmixture was stirred for 12h at room temperature. The mixture was then diluted with H_2O and extracted with EtOAc. The combined organic phase waswashed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography(petroleum ether/EtOAc/MeOH, 10/10/1)to afford**22a**as a colorless oil (79mg,85.9%).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.81(s, 1H), 8.05(s, 1H), 7.98(s, 1H), 7.48(t, *J*=5.4Hz, 1H), 3.58(s, 3H), 3.40(q, *J*=6.6Hz, 2H), 2.29(t, *J*=7.2Hz, 2H), 1.55-1.71(m, 4H).^{13}C NMR(75 MHz, $CDCl_3$): δ 173.8, 162.3, 161.0, 153.9, 150.9, 149.5, 123.7, 116.6, 51.5, 38.9, 33.5, 29.1, 22.2. MS (ESI) *m/z*: 326.1 (M+H^+).

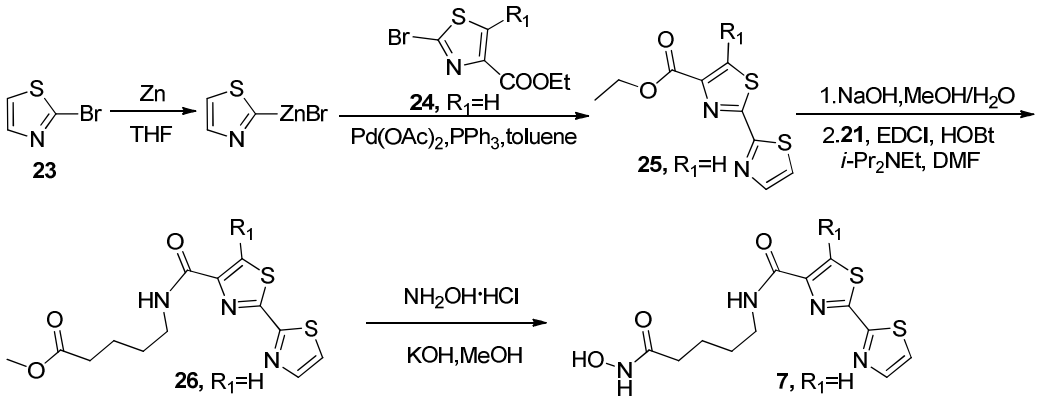
Following similar procedure,**22b**was obtained as a pale yellow oil (71.1%).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.03(s, 1H), 7.77(s, 1H), 7.48(t, *J*=5.4Hz, 1H), 3.60(s, 3H), 3.41(q, *J*=6.6Hz, 2H), 2.70(s, 3H), 2.31(t, *J*=6.9Hz, 2H), 1.59-1.70(m, 4H).^{13}C NMR(75 MHz, $CDCl_3$): δ 173.5, 166.7, 162.1, 160.7, 150.4, 147.8, 123.0, 116.0, 51.2, 38.5, 33.2,

28.8, 21.9, 18.8. MS (ESI) *m/z*: 340.1 ($M+H^+$).

Preparation procedure forcompound 6a-6b

To a mixture of hydroxylamine hydrochloride (169mg, 2.4mmol) in dry MeOH (10mL)was added solid KOH (204mg, 3.65mmol)and the resulting mixture was stirred for 5 min at room temperature. The mixture was then filtered and **22a** (79mg, 0.24mmol) was added to the filtrate. The resulting mixture was stirred for 1h at room temperature. The mixture was then acidified with 1N HCl to pH5-6 and concentrated under reduced pressure. The obtained residue was dissolved in EtOAc. ThisEtOAc solution was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.The obtained residue was further purified by silica gel column chromatography($CHCl_3$/MeOH, 10/1)to afford compound **6a**as a pale yellow solid (40mg, 50%).^{1}H NMR(300 MHz, CD_3OD): δ 9.06(s, 1H), 8.59(t, *J*=5.7Hz, 1H), 8.30(s, 1H), 8.17(s, 1H), 3.42(q, *J*=5.4Hz, 2H), 1.98(t, *J*=6.9Hz, 2H), 1.53 (m, 4H).^{13}C NMR(75 MHz, DMSO-d_6): δ 169.7, 162.6, 161.0, 156.9, 151.7, 149.3, 124.8, 118.7, 39.1, 32.7, 29.6, 23.4.HRMS (ESI) (*m/z*):Calcd for $C_{12}H_{14}N_4O_3S_2Na^+$,349.0400($M+Na^+$),Found349.0406.

Following similar procedure, compound **6b**was obtained as a pale yellow solid(55%).^{1}H NMR(300 MHz, CD_3OD): δ 8.15(s, 1H), 8.09(s, 1H), 3.43(q, *J*=6.9Hz, 2H), 2.75(s, 3H), 2.15(t, *J*=6.9Hz, 2H), 1.68(m, 4H).^{13}C NMR(75 MHz, DMSO-d_6): δ 169.0, 167.5, 161.9, 160.3, 150.9, 147.3, 123.6, 117.3, 38.7, 32.1, 28.9, 22.9, 17.6. HRMS (ESI) (*m/z*):Calcd for $C_{13}H_{16}N_4O_3S_2Na^+$,363.0556($M+Na^+$),Found363.0578.



Preparation procedure for25

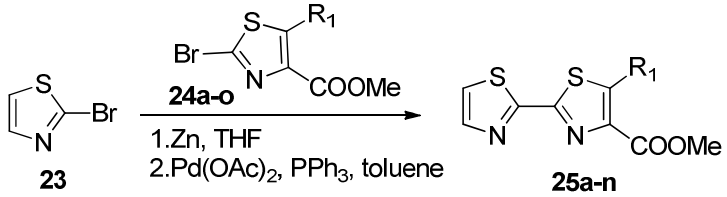
A solution of 2-bromothiazole **23** (5.51g, 0.034mol)under N_2 atmosphere was added dropwise to a suspension of activated Zn powder (1.87g, 0.029mol) in dry THF (30mL).The resulting mixture was heated to reflux for 2h. The reaction mixture was then cooled to room temperature and $Pd(OAc)_2$ (272mg, 1.2mmol) , PPh_3 (630mg, 2.4mmol) and 2-bromothiazole **24**were added. The reaction mixture was again heated to reflux for several hours until most of 2-bromothiazole **23**was consumed. The reaction mixture was then cooled to room temperature andconcentrated under reduced pressure. The residue was dilutedwith CH_2Cl_2 and the obtained suspension washed sequentially with 1N HCl and brine. The CH_2Cl_2solution was dried over anhydrous $Na_2SO_4$and concentratedunder reduced pressure to afford the crude coupling product **25**as a yellow oil (9.0g).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.20(s, 1H),

7.86(d, *J*=3.3Hz, 1H), 7.48(d, *J*=3.3Hz, 1H), 4.40(q, *J*=6.9Hz, 2H), 1.38(t, *J*=7.2Hz, 3H).

To a stirred solution of above obtainedcoupling product**25**(9.0g, 0.04mmol) in MeOH/H_2O (4:1, v/v, 50mL) was added solid NaOH (3g,0.07mol) at 0°C. The resulting mixture was heated toreflux for 1h and then cooled to room temperature. After removal of MeOH under reduced pressure, the resulting aqueous mixture was extractedwith Et_2O. The aqueous phase was thenacidified with 1N HCl to pH2.0 and extracted with EtOAc. The combined EtOAc extract was washed with brine, dried over anhydrous $Na_2SO_4$and concentratedunder reduced pressure to affordthe correspondingacidas a yellow solid (2.3g,44.7%overtwo steps).^{1}H NMR(300 MHz, CD_3OD): δ 9.05(d, *J*=3.3Hz, 1H), 8.43(d, *J*=3.3Hz, 1H), 8.35(s, 1H).MS (ESI) *m/z*: 263.0 ($M+Na^+$).

Following similar preparation procedure for**22a,** intermediate**26** was prepared from the above obtained acid as acolorless oil (73.9%). ^{1}H NMR(300 MHz, $CDCl_3$): δ 8.04(s, 1H), 7.75(d, *J*=3.3Hz, 1H), 7.39(t, *J*=6.0Hz, 1H), 7.37(d, *J*=3.3Hz, 1H), 3.51(s, 3H), 3.34(q, *J*=6.6Hz, 2H), 2.23(t, *J*=6.3Hz, 2H), 1.55-1.60(m, 4H) ^{13}C NMR(75 MHz, $CDCl_3$): δ 173.6, 161.1, 160.4, 160.2, 150.8, 144.0,124.6, 121.7, 51.4, 38.8, 33.4, 29.0, 22.1. MS (ESI) *m/z*: 326.1 ($M+H^+$).

Following similar preparation procedure for**6a,** compound **7**was prepared from intermediate **26**as apale yellow solid(42.6%). ^{1}H NMR(300 MHz, CD_3OD): δ 8.53(t, *J*=5.4Hz, 1H), 8.27(s, 1H), 7.92(d, *J*=3.0Hz, 1H), 7.89(s, 1H), 7.77(d, *J*=3.0Hz, 1H), 3.43(q, *J*=6.0Hz, 2H), 2.16(t, *J*=6.6Hz, 2H), 1.66-1.69(m, 4H).^{13}C NMR(75 MHz, CD_3OD): δ 172.8, 163.1, 162.9, 161.9, 152.1, 145.3, 126.7, 123.9, 40.2, 33.5, 30.2, 24.3.HRMS (ESI) (*m/z*):Calcd for $C_{12}H_{14}N_4O_3S_2Na^+$,349.0400 ($M+Na^+$),Found349.0401.



Preparation procedure for25a-n

25a-owas obtained according to the preparation procedure for**25.**

25a: (white powder, 75%).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.86(d, *J*=3.3Hz, 1H), 7.46(d, *J*=3.3Hz, 1H), 3.96(s, 3H), 3.15(d, *J*=6.9Hz, 2H), 1.95–1.23(m, 1H), 0.99(d, *J*=6.6Hz, 6H).^{13}C NMR(75 MHz, $CDCl_3$): δ 162.1, 160.4, 157.3, 151.2, 143.5, 141.5, 121.3, 51.9, 35.8, 30.6, 21.9. MS (ESI) *m/z*: 283.0 ($M+H^+$).

25b: (yellow oil, 45%).^{1}H NMR(300 MHz, $CDCl_3$): δ7.83(d, *J*=2.4Hz, 1H), 7.44(d, *J*=2.4Hz, 1H), 3.92(s, 3H), 2.79(s, 3H). MS (ESI) *m/z*: 241.0 ($M+H^+$).

25c: (yellow oil, 52.1%).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.87(d, *J*=3.3Hz, 1H), 7.54(d, *J*=3.3Hz, 1H), 3.96(s, 3H), 3.30(q, *J*=7.5Hz, 2H), 1.38(t, *J*=7.5Hz, 3H).^{13}C NMR(75 MHz, $CDCl_3$): δ 162.0, 160.4, 156.9, 154.3, 143.5, 140.7, 121.3, 51.8, 21.2, 15.5. MS (ESI) *m/z*: 255.0 ($M+H^+$).

25d: (yellow oil, 86.7%).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.62(d, *J*=3.3Hz, 1H), 7.30(d, *J*=3.3Hz, 1H), 3.90-3.94(m, 1H), 3.72(s, 3H), 1.14(d, *J*=6.9Hz, 6H).^{13}C NMR(75 MHz, $CDCl_3$): δ 162.0, 160.4, 156.8, 143.5, 143.3, 140.0, 121.2, 51.8, 27.8, 24.6. MS (ESI)

m/z: 291.0 ($M+Na^+$).

25e: (yellow oil, 54%).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.88(d, *J*=3.0Hz, 1H), 7.47(d, *J*=3.0Hz, 1H), 3.96(s, 3H), 3.29(t, *J*=7.5Hz, 2H), 1.68-1.78(m, 2H), 1.40-1.52(m, 2H), 0.96(t, *J*=7.5Hz, 3H).MS (ESI) *m/z*: 283.1 ($M+H^+$).

25f: (yellow oil, 73.5%).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.85(d, *J*=3.0Hz, 1H), 7.45(d, *J*=3.0Hz, 1H), 3.96(s, 3H), 3.10-3.14(m, 1H), 1.31-1.38(m, 2H), 0.84-0.89(m, 2H). MS (ESI) *m/z*: 267.0 ($M+H^+$).

25g: (yellow oil,67.3%).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.87(d, *J*=3.3Hz, 1H), 7.45(d, *J*=3.3Hz, 1H), 3.97(s, 3H), 3.80-3.95(m, 1H), 2.12(d, *J*=10.8Hz, 2H), 1.76-1.88(m, 2H), 1.30-1.57(m, 6H).MS (ESI) *m/z*: 309.1 ($M+H^+$).

25h:(yellow oil, 35.6%).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.92(d, *J*=3.3Hz, 1H), 7.51-7.57(m, 2H), 7.50(d, *J*=3.3Hz, 1H), 7.45-7.48(m, 3H), 3.86(s, 3H). MS (ESI) *m/z*: 303.0 ($M+H^+$).

25i:(yellow oil, 56.8%).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.91(d, *J*=3.0Hz, 1H), 7.52-7.57(m, 2H), 7.44(d, *J*=3.0Hz, 1H), 7.12-7.19(m, 2H), 3.87(s, 3H). MS (ESI) *m/z*: 321.0 ($M+H^+$).

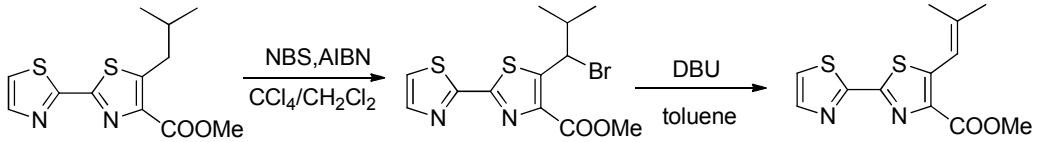
25j: (yellow oil, 77.5%).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.02(d, *J*=3.3Hz, 1H), 7.68(d, *J*=3.3Hz, 1H), 7.43(t, *J*=7.8Hz, 1H), 7.28(dd, *J*=8.4,2.7Hz, 1H), 7.11(t, *J*=7.8Hz, 1H), 3.81(s, 3H).^{13}C NMR(75 MHz, $CDCl_3$): δ 165.3, 161.8, 161.2, 159.0, 144.6, 144.4, 142.9, 135.6, 133.5, 133.3, 123.4, 118.1, 115.0, 53.1. MS (ESI) *m/z*: 355.0 ($M+H^+$).

25k: (yellow oil, 83.2%).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.98(d, *J*=3.3Hz, 1H), 7.60(d, *J*=3.3Hz, 1H), 7.52(d, *J*=7.2Hz, 1H), 7.36-7.44(m, 3H), 3.81(s, 3H).^{13}C NMR(75 MHz, $CDCl_3$): δ 161.6, 160.8, 159.3, 144.8, 143.1, 134.2, 132.6, 131.8, 131.0, 129.9, 129.2, 126.8, 122.6, 52.6. MS (ESI) *m/z*: 337.0 ($M+H^+$).

25l: (yellow oil, 87.9%).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.32(d, *J*=8.7Hz, 2H), 7.94(d, *J*=3.0Hz, 1H), 7.73(d, *J*=9.0Hz, 2H), 7.56(d, *J*=3.0Hz, 1H), 3.89(s, 3H). MS (ESI) *m/z*: 370.0 ($M+Na^+$).

25m: (yellow oil, 50.4%).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.82(d, *J*=3.0Hz, 1H), 7.43(d, *J*=3.0Hz, 1H), 7.27-7.33(m, 5H), 4.60(s, 2H), 3.98(s, 3H).^{13}C NMR(75 MHz, $CDCl_3$): δ 162.6, 160.8, 158.5, 152.4, 143.9, 141.3, 138.9, 129.0, 128.9, 127.4, 121.7, 52.5, 34.0. MS (ESI) *m/z*: 317.0 ($M+H^+$).

25n: (yellow solid, 60%).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.88(d, *J*=3.0Hz, 1H), 7.47(d, *J*=3.0Hz, 1H), 7.33-7.47(m, 5H), 4.57(s, 2H), 3.95(s, 3H), 3.78(t, *J*=6.3Hz, 2H), 3.61(t, *J*=5.7Hz, 2H).MS (ESI) *m/z*: 361.1 ($M+H^+$).



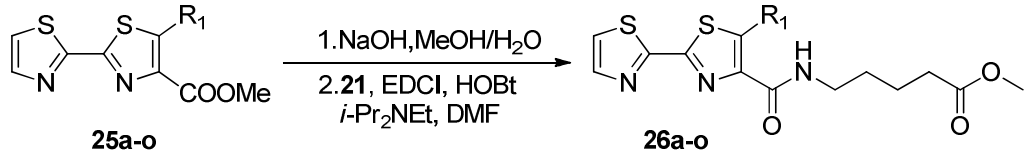
25a **28** **25o**

Preparation procedure for 25o

NBS (1.8g, 0.01mol)and AIBN(0.2g) were added to a solution of **25a**(2.2g, 7.80mmol)in CCl_4(60mL) and CH_2Cl_2 (20mL). The resultingmixture was heated toreflux for 3h and then cooled to room temperature. The reaction mixture was then concentrated under reduced pressure and the residue was dissolved in EtOAc (50mL). The EtOAc solution was washed with H_2O and brine, dried over anhydrous Na_2SO_4 andconcentrated under reduced pressure. The obtained residue was purified by

silica gel column chromatography (petroleum ether/EtOAc, 8/1)to afford**28**as a pale yellow solid (2.8g, 99.4%).^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90(d, *J*=3.3Hz, 1H), 7.51(d, *J*=3.3Hz,1H), 6.11(d, *J*=8.4Hz, 1H), 3.98(s, 3H), 2.24(m, 1H), 1.23(d, *J*=6.6Hz, 3H), 1.03(d, *J*=6.6Hz, 3H).MS (ESI) *m/z*: 361.0 ($M+H^+$).

To a solution of **28** (1.2g, 3.32mmol)in toluene(50mL)was added DBU (1.5g, 0.01mol) and the reaction mixture was heated to reflux for 3h. The reaction mixture was diluted with EtOAc (50mL) and washed with H_2O, 5% HCl and brine,sequentially. The organic solution was dried over anhydrous Na_2SO_4 andconcentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 8/1)to afford**25o** as a pale yellow solid (0.73g, 78.5%).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.89(d, *J*=3.3Hz, 1H), 7.47(d, *J*=3.0Hz, 1H), 7.31(t, *J*=1.2Hz, 1H) , 3.98(s, 3H), 2.06(s, 6H). MS (ESI) *m/z*: 281.0 ($M+H^+$).



25a-o **26a-o**

Preparation procedure for26a-o

26a-o was obtained according to the preparation procedure for **26**.

26a:(colorless oil, 85.9% overtwo steps). ^{1}H NMR(300 MHz, $CDCl_3$): δ 7.96(d, *J*=3.3Hz, 1H), 7.77(t, *J*=5.4Hz, 1H), 7.58(d, *J*=3.3Hz, 1H), 3.76(s, 3H), 3.55(q, *J*=6.3Hz, 2H), 3.38(d, *J*=6.9Hz, 2H), 2.48(t, *J*=6.0Hz, 2H), 2.08-2.16(m, 1H), 1.79-1.80(m, 4H), 1.10(d, *J*=6.6 Hz, 6H).^{13}C NMR(75 MHz, $CDCl_3$): δ 173.4, 161.7, 160.5, 156.2, 147.1, 143.7, 143.6, 121.0, 51.2, 38.4, 35.4, 33.2, 30.7, 29.0, 22.0. MS (ESI) *m/z*: 382.1 ($M+H^+$).

26b: (colorless oil, 41.7%overtwo steps).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.72(d, *J*=3.3Hz, 1H), 7.43(t, *J*=5.7Hz, 1H), 7.33(d, *J*=3.3Hz, 1H), 3.54(s, 3H), 3.31(q, *J*=6.6Hz, 2H), 2.74(s, 3H), 2.25(t, *J*=6.6Hz, 2H), 1.57-1.65(m, 4H).^{13}C NMR(75 MHz, $CDCl_3$): δ 173.7, 162.1, 160.6, 156.0, 143.8, 143.6, 142.7, 121.1, 51.4, 38.6, 33.5, 29.1, 22.2, 12.9. MS (ESI) *m/z*: 362.1 ($M+Na^+$).

26c: (colorless oil, 52.1% overtwo steps).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.74(d, *J*=3.0Hz, 1H), 7.44(t, *J*=5.7Hz, 1H), 7.34(d, *J*=3.0Hz, 1H), 3.55(s, 3H), 3.35(q, *J*=6.6Hz, 2H), 3.29(q, *J*=7.5Hz, 2H), 2.27(t, *J*=6.9Hz, 2H), 1.51-1.68(m, 4H), 1.25(t, *J*=7.2Hz, 3H).^{13}C NMR(75 MHz, $CDCl_3$): δ 173.7, 161.9, 160.8, 156.2, 150.6, 143.9, 142.9, 121.1, 51.4, 38.7, 33.5, 29.2, 22.2, 21.0, 16.0. MS (ESI) *m/z*: 354.1 ($M+H^+$).

26d: (colorless oil, 60.0%overtwo steps).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.79(d, *J*=3.0Hz, 1H), 7.48(t, *J*=5.7Hz, 1H), 7.37(d, *J*=3.0Hz, 1H), 4.36-4.40(m, 1H), 3.59(s, 3H), 3.37(q, *J*=6.9Hz, 2H), 2.31(t, *J*=6.9Hz, 2H), 1.56-1.70(m, 4H), 1.29(d, *J*=6.9Hz, 6H).^{13}C NMR(75 MHz, $CDCl_3$): δ 173.9, 161.9, 161.0, 157.0, 156.2, 144.0, 142.4, 121.1, 51.6, 38.7, 33.6, 29.3, 27.7, 25.2, 22.3. MS (ESI) *m/z*: 390.1 ($M+Na^+$).

26e: (colorless oil, 54.0%overtwo steps).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.78(d, *J*=3.3Hz 1H), 7.47(t, *J*=5.7Hz, 1H), 7.37(d, *J*=3.3Hz, 1H), 3.59(s, 3H), 3.37(q, *J*=6.6Hz, 2H), 3.31(t, *J*=7.8Hz, 2H), 2.31(t, *J*=6.9Hz, 2H), 1.56-1.71(m, 6H), 1.33-1.43(m, 2H), 0.87(t,*J*=7.5Hz, 3H).^{13}C NMR(75 MHz, $CDCl_3$): δ 173.8, 162.0, 160.9, 156.3, 149.2, 144.0, 143.3, 121.1, 51.5, 38.8, 33.8, 33.6, 29.3, 27.0, 22.4, 22.3, 13.8. MS (ESI) *m/z*:

382.1 ($M+H^+$).

26f: (pale yellow oil, 71.7%overtwo steps).^{1}H NMR(300 MHz, $CDCl_3$): δ7.74(d, *J*=3.0Hz, 1H), 7.42(t, *J*=5.4Hz, 1H), 7.36(d, *J*=3.0Hz, 1H), 3.58(s, 3H), 3.37(q, *J*=6.3Hz, 2H), 2.30(t, *J*=6.6Hz, 2H), 1.58-1.69(m, 4H), 1.19-1.25(m, 2H), 0.68-0.74(m, 2H).^{13}C NMR(75 MHz, $CDCl_3$): δ 173.8, 162.2, 160.8, 154.3, 154.2, 144.1, 143.8, 121.1, 51.5, 38.7, 33.6, 29.2, 22.3, 14.0, 10.4. MS (ESI) *m/z*: 388.1 ($M+Na^+$).

26g: (pale yellow oil, 79.9%overtwo steps).^{1}H NMR(300 MHz, $CDCl_3$): δ7.75(d, *J*=3.0Hz, 1H), 7.49(t, *J*=6.0Hz, 1H), 7.34(d, *J*=3.0Hz, 1H), 3.97-4.04(m, 1H), 3.64(s, 3H), 3.35(q, *J*=6.3Hz, 2H), 2.28(t, *J*=6.3Hz, 2H), 2.02(d, *J*=8.7Hz, 2H), 1.61-1.68(m, 6H), 1.03-1.40(m, 6H). ^{13}C NMR(75 MHz, $CDCl_3$): δ 174.2, 162.4, 161.4, 156.6, 156.2, 144.3, 142.7, 121.4, 51.9, 39.1, 37.4, 36.3, 34.0, 29.6, 26.8, 26.1, 22.7. MS (ESI) *m/z*: 430.1 ($M+Na^+$).

26h: (colorless oil, 74.3%overtwo steps).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.82(d, *J*=3.3Hz, 1H), 7.59-7.62(m, 2H), 7.53(t, *J*=5.7Hz, 1H), 7.42(d, *J*=3.3Hz, 1H), 7.35-7.37(m, 3H), 3.60(s, 3H), 3.36(q, *J*=6.3Hz, 2H), 2.30(t, *J*=6.6Hz, 2H), 1.62-1.66(m, 4H).^{13}C NMR(75 MHz, $CDCl_3$): δ 173.7, 161.0, 160.4, 158.0, 145.0, 144.1, 142.6, 130.2, 129.8, 129.3, 128.1, 121.6, 51.5, 38.9, 33.5, 29.1, 22.2. MS (ESI) *m/z*: 402.1 ($M+H^+$).

26i: (colorless oil, 75.0%overtwo steps).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.90(d, *J*=3.3Hz, 1H), 7.63-7.67(m, 2H), 7.58(t, *J*=5.7Hz, 1H), 7.50(d, *J*=3.3Hz, 1H), 7.08-7.14(m, 2H), 3.67(s, 3H), 3.42(q, *J*=6.3Hz, 2H), 2.37(t, *J*=6.3Hz, 2H), 1.68-1.71(m, 4H).^{13}C NMR(75 MHz, $CDCl_3$): δ 173.9, 165.0, 161.1, 158.1, 144.2, 144.0, 142.6, 132.4, 132.3, 121.7, 115.4, 115.1, 51.6, 39.0, 33.6, 29.2, 22.3. MS (ESI) *m/z*: 420.1 ($M+H^+$).

26j: (colorless oil, 61.7%overtwo steps).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.92(d, *J*=3.3Hz, 1H), 7.53(d, *J*=3.3Hz, 1H), 7.45(dd, *J*=9.0,5.7Hz, 1H), 7.24(dd, *J*=8.7,2.7Hz, 1H), 7.06(ddd, *J*=8.7,8.1,2.7Hz, 1H), 3.67(s, 3H), 3.40(q, *J*=6.9Hz, 2H), 2.36(t, *J*=6.6Hz, 2H), 1.67-1.74(m, 4H).^{13}C NMR(75 MHz, $CDCl_3$): δ 173.9, 164.6, 161.3, 160.5, 145.4, 144.3, 139.3, 135.2, 133.2, 133.0, 125.7, 121.9, 117.4, 114.2, 51.6, 38.9, 33.6, 29.2, 22.3. MS (ESI) *m/z*: 454.0 ($M+H^+$).

26k: (colorless oil, 92.6%).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.91(d, *J*=3.3Hz, 1H), 7.47-7.54(m, 2H), 7.44(d, *J*=3.3Hz, 1H), 7.32-7.38(m, 2H), 3.66(s, 3H), 3.40(q, *J*=6.6Hz, 2H), 2.35(t, *J*=6.9Hz, 2H), 1.63-1.73(m, 4H).^{13}C NMR(75 MHz, $CDCl_3$): δ 173.9, 160.6, 160.5, 159.5, 145.2, 144.3, 140.4, 134.2, 131.9, 130.5, 129.7, 129.6, 126.5, 121.9, 51.6, 38.9, 33.6, 29.2, 22.3. MS (ESI) *m/z*: 458.0 ($M+Na^+$).

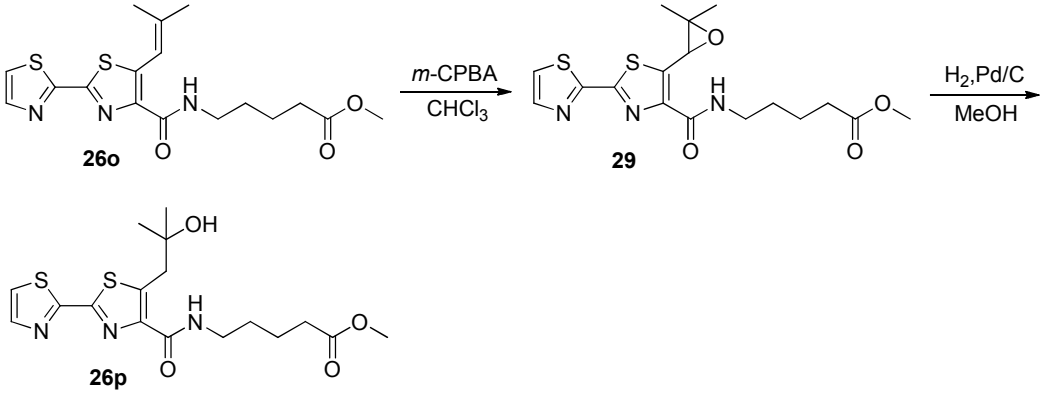
26l: (colorless oil, 66.4%).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.22(d, *J*=8.7Hz, 2H), 7.90(d, *J*=3.0Hz, 1H), 7.79(d, *J*=9.6Hz, 2H), 7.58(t, *J*=6.0Hz, 1H), 7.52(d, *J*=3.0Hz, 1H), 3.64(s, 3H), 3.40(q, *J*=6.6Hz, 2H), 2.34(t, *J*=6.9Hz, 2H), 1.59-1.74(m, 4H).^{13}C NMR(75 MHz, $CDCl_3$): δ 174.0, 160.9, 160.1, 159.8, 148.2, 144.6, 144.0, 141.7, 136.9, 131.6, 123.4, 122.4, 51.8, 39.3, 33.7, 29.3, 22.4. MS (ESI) *m/z*: 447.1 ($M+H^+$).

26m: (colorless oil, 63.2%).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.77(d, *J*=3.3Hz, 1H), 7.53(t, *J*=5.7Hz, 1H), 7.36(d, *J*=3.3Hz, 1H), 7.17-7.33(m, 5H), 4.70(s, 2H), 3.64(s, 3H), 3.43(q,*J*=6.6Hz, 2H), 2.36(t, *J*=6.9Hz, 2H), 1.61-1.78(m, 4H).^{13}C NMR(75 MHz, $CDCl_3$): δ 174.0, 162.3, 160.9, 157.5, 148.5, 144.2, 143.3, 139.8, 129.1, 129.0, 127.2, 121.4, 51.8, 39.0, 33.8, 33.6, 29.5, 22.5. MS (ESI) *m/z*: 416.1 ($M+H^+$).

26n: (colorless oil, 54.5%).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.73(d, *J*=3.0Hz, 1H), 7.53(t,

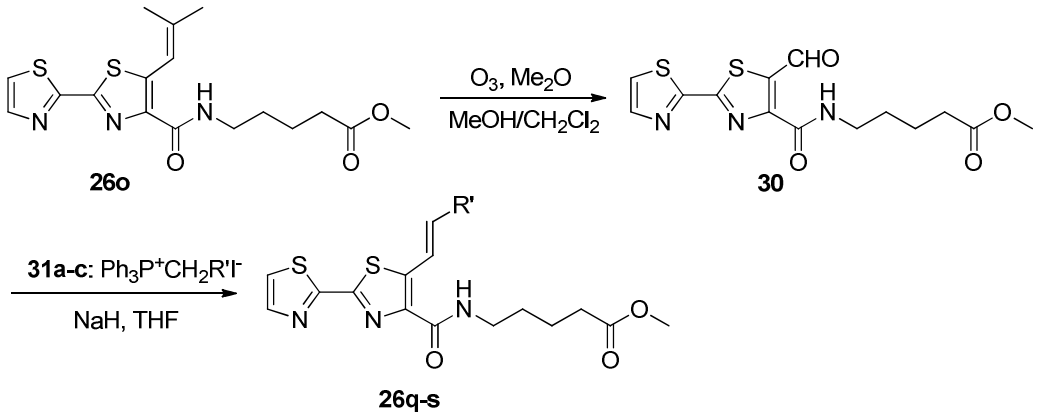
J=5.4Hz, 1H), 7.31(d, *J*=3.0Hz, 1H), 7.19-7.21(m, 5H), 4.43(s, 2H), 3.66(t, *J*=4.5Hz, 2H), 3.62(t, *J*=4.8Hz, 2H), 3.54(s, 3H), 3.31(q, *J*=6.3Hz, 2H), 2.25(t, *J*=6.6Hz, 2H), 1.53-1.60(m, 4H).^{13}C NMR(75 MHz, $CDCl_3$): δ 173.5, 161.8, 160.6, 157.2, 144.5, 143.8, 143.6, 137.8, 128.1, 127.4, 127.3, 121.0, 72.7, 69.3, 51.3, 38.5, 33.3, 29.0, 27.7, 22.0. MS (ESI) *m/z*: 460.1 ($M+H^+$).

26o: (colorless oil, 73.7%).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.76(d, *J*=3.3Hz, 1H), 7.53(s, 1H), 7.36(d, *J*=3.3Hz, 1H), 3.56(s, 3H), 3.35(q, *J*=6.3Hz, 2H), 2.27(t, *J*=6.6Hz, 2H), 1.91(s, 6H), 1.60-1.66(m, 4H).^{13}C NMR(75 MHz, $CDCl_3$): δ 173.7, 162.1, 160.8, 155.8, 143.9, 142.6, 142.4, 141.6, 121.2, 116.4, 51.4, 38.8, 33.5, 29.2, 28.1, 22.3, 20.7. MS (ESI) *m/z*: 402.1 ($M+Na^+$).



Preparation procedure for26p

To a solution of **26o** (288mg, 0.76mmol)in $CHCl_3$(25mL)was added *m*-CPBA (262mg, 1.52mmol). The reaction mixture was stirred for 3h at roomtemperature and then washed with saturated $NaHCO_3$, saturated$NaHSO_3$ and brine. The mixture was dried over anhydrous Na_2SO_4 andconcentrated under reduced pressure to affordcrude product **28**.To a solution of **28** inMeOH (50mL) was added Pd-C (10mg, 10%) and the reaction mixture was stirred under a H_2 atmospherefor 5h at room temperature. The reaction mixture was then filtered and the filtrate wasconcentrated under reduced pressure.The obtained residue was purified bysilica gel column chromatography (petroleum ether/EtOAc, 2/1)to afford**26p**as a colorless oil (202mg, 67% overtwo steps).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.83(d, *J*=3.3Hz, 1H), 7.62(t, *J*=5.4Hz, 1H), 7.42(d, *J*=3.3Hz, 1H), 3.62(s, 3H), 3.45(s, 2H), 3.40(q, *J*=6.6Hz, 2H), 2.33(t, *J*=6.6Hz, 2H), 1.65-1.67(m, 4H), 1.27(s, 6H).^{13}C NMR(75 MHz, $CDCl_3$): δ 173.5, 162.8, 160.3, 157.3, 144.6, 143.7, 142.5, 121.0, 70.3, 51.2, 39.4, 38.7, 33.2, 29.3, 28.7, 21.9. MS (ESI) *m/z*: 398.1 ($M+H^+$).



Preparation procedure for26q-s

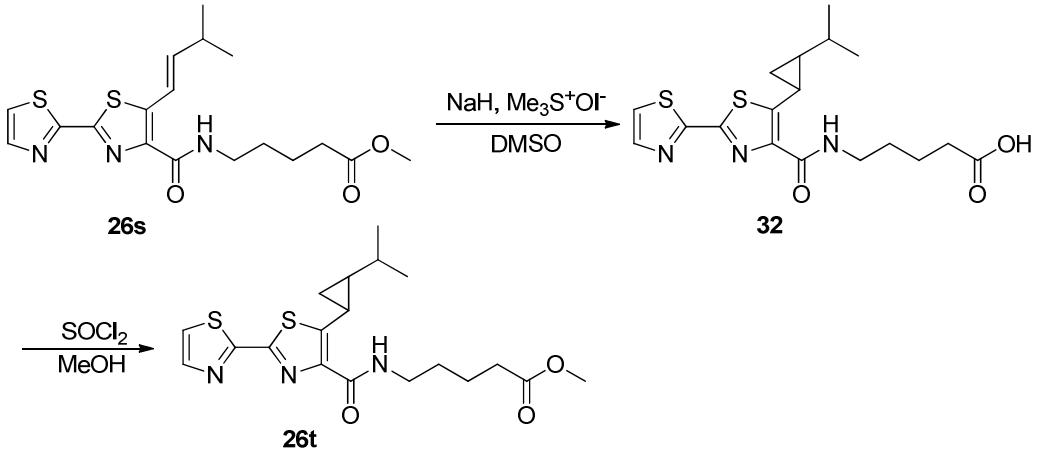
Dry O_3 was bubbled at a moderate rate into asolution of **26o** (900mg, 2.37mmol) in CH_2Cl_2/MeOH(5:1, v/v, 48mL) at -78°C until TLC analysisindicated that**26o** was completely consumed. Dimethyl sulfide (0.3mL) was then added and the resulting reaction mixture was stirred at room temperature for additional 1h. Solvents were removed under reduced pressure and the obtained residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 3/1 to 1/1)to afford aldehyde **30** as a pale yellow solid (830mg, 99.3%).^{1}H NMR(300 MHz, $CDCl_3$): δ 10.9(s, 1H), 7.98(d, *J*=3.0Hz, 1H), 7.60(d, *J*=3.0Hz, 1H), 3.67(s, 3H), 3.52(q, *J*=6.3Hz, 2H), 2.38(t, *J*=6.6Hz, 2H), 1.72-1.76(m, 4H).^{13}C NMR(75 MHz, $CDCl_3$): δ 185.4, 173.4, 164.3, 159.7, 158.9, 151.3, 144.6, 141.4, 123.3, 51.2, 38.8, 33.1, 28.6, 21.8. MS (ESI) *m/z*: 354.1 ($M+H^+$).

31a(271mg, 0.65mmol) was added to a suspension of NaH (22mg, 0.59mmol) in dry THF (10mL) at 0°C. After one hour, a solution of **30**in dry THF (10mL) was added to reaction mixture. The resultingmixture was stirred for 12hat room temperature and the reaction was quenched with saturated NH_4Cl solution. The obtained mixture was extracted with Et_2O and the combined organic phase was washed with brine anddried over anhydrous Na_2SO_4.The solvents were removed under reduced pressure andthe obtained residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 3/1 to 2/1) to afford**26q**as a pale yellow oil (62mg, 52.1%). ^{1}H NMR(300 MHz, $CDCl_3$):δ 7.82(d, *J*=3.0Hz, 1H), 7.41(d, *J*=3.0Hz, 1H), 6.18-6.29(m, 1H), 6.00-6.09(m, 1H), 3.62(s, 3H), 3.41(q, *J*=6.3Hz, 2H), 2.33(t, *J*=6.6Hz, 2H), 1.89(d, *J*=6.6Hz, 3H), 1.40-1.67(m, 4H).^{13}C NMR(75 MHz, $CDCl_3$): δ 174.1, 162.2, 160.9, 155.8, 144.3, 141.9, 134.8, 132.0, 122.5, 121.6, 51.8, 39.0, 33.8, 29.4, 22.5, 19.2. MS (ESI) *m/z*: 366.1 ($M+H^+$).

Following similar preparation procedure,**26r** was obtained as a pale yellow oil(69.1%).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.93(d, *J*=3.0Hz, 1H), 7.84(d, *J*=3.0Hz, 1H), 7.45(dd, *J*=17.7,9.9Hz, 1H), 5.69(d, *J*=17.7Hz, 1H), 5.44(d, *J*=9.9Hz, 1H), 3.62(s, 3H), 3.41(q, *J*=6.6Hz, 2H), 2.34 (t, *J*=6.9Hz, 2H), 1.60-1.66(m, 4H). ^{13}C NMR(75 MHz, $CDCl_3$): δ 174.1, 161.9, 160.7, 157.0, 144.4, 144.1, 143.5, 127.9, 122.0, 121.1, 51.8, 39.1, 33.8, 29.4, 22.5. MS (ESI) *m/z*: 274.1 ($M+Na^+$).

Following similar preparation procedure, **26s**was obtained as a pale yellow oil: (60.7%).^{1}H NMR(300 MHz, $CDCl_3$): δ 8.82(d, *J*=3.0Hz, 1H), 7.64(d, *J*=15.9Hz, 1H), 7.48(t, *J*=5.1Hz, 1H), 7.40(d, *J*=3.0Hz, 1H), 6.20(dd, *J*=15.9,6.6Hz, 1H), 3.61(s, 3H),

3.40(q, *J*=5.7Hz, 2H), 2.44-2.48(m, 1H), 2.32(t, *J*=5.4Hz, 2H), 1.61-1.70(m, 4H), 1.05(d, *J*=6.6Hz, 6H).^{13}C NMR(75 MHz, $CDCl_3$): δ 174.0, 162.2, 160.9, 155.9, 146.6, 145.0, 144.3, 142.2, 121.6, 118.6, 51.8, 39.0, 33.8, 32.1, 29.4, 22.5, 22.1. MS (ESI) *m/z*: 394.1 ($M+H^+$).

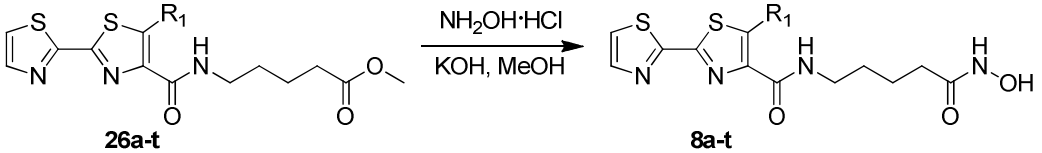


26s **32** **26t**

Preparation procedure for 26t

To a suspension of trimethylsulfoxonium iodide(403mg, 1.83mmol) in DMSO (5mL) at room temperature was added NaH (77mg,60%, 1.92mmol).After 30min, a solution of **26s**(180mg, 0.457mmol) in DMSO (2mL) was added and the resulting reaction mixture was stirred for 12hat room temperature before it was quenched with H_2O. The obtained mixture was acidified with 1N HCl and extracted with EtOAc.Thecombined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography($CHCl_3$/MeOH, 20/1) to afford**32** as a colorless oil (160mg, 88.9%).^{1}H NMR(300 MHz, $CDCl_3$): δ 7.77(d, *J*=3.3Hz, 1H), 7.41(t, *J*=6.6Hz, 1H), 7.38(d, *J*=3.3Hz, 1H), 3.39(q, *J*=6.3Hz, 2H), 3.18-3.23(m, 1H), 2.31(t, *J*=6.0Hz, 2H), 1.65-1.67(m, 4H), 1.08-1.18(m, 2H), 0.98(d, *J*=6.6Hz, 3H), 0.95(d, *J*=6.6Hz, 3H), 0.82-0.90(m, 2H).^{13}C NMR(75 MHz, $CDCl_3$): δ 176.4, 162.5, 161.1, 154.8, 154.2, 144.0, 143.6, 121.2, 39.0, 37.4, 33.9, 33.4, 29.5, 22.5, 22.2, 21.8, 20.6, 16.9. MS (ESI) *m/z*: 416.1 ($M+Na^+$).

To a solution of **32**(160mg, 0.407mmol) in MeOH (20mL) was added $SOCl_2$ (97mg, 0.82mmol) and the resulting mixture was stirred for 12h at room temperature.The reaction mixture was then concentrated under reduced pressure to afford**26t**as a colorless oil (164mg, 99.4%).^{1}H NMR(300 MHz, CD_3OD): δ 7.86(d, *J*=3.3Hz, 1H), 7.71(d, *J*=3.3Hz, 1H), 3.64(s, 3H), 3.39(q, *J*=6.3Hz, 2H), 3.16-3.21(m, 1H), 2.38(t, *J*=6.0Hz, 2H), 1.65-1.67(m, 4H), 1.17-1.25(m, 2H), 1.03(d, *J*=6.6Hz, 6H), 0.90-0.97(m, 2H).^{13}C NMR(75 MHz, $CDCl_3$): δ 173.9, 161.9, 161.7, 157.5, 150.0, 144.0, 141.4, 123.7, 51.9, 39.0, 38.2, 33.7, 33.2, 29.3, 22.4, 22.1, 21.6, 21.4, 17.0. MS (ESI) *m/z*: 408.1 ($M+H^+$).



26a-t **8a-t**

Preparation procedure for8a-t

Compound **8a-t**was prepared following the preparation procedure of compound**6a.**

8a: (pale yellow solid, 88.2%). ^{1}H NMR(300 MHz, DMSO-d_6): δ 10.36(s, 1H), 8.68(s, 1H), 8.36(t, *J*=5.7Hz, 1H), 7.99(d, *J*=3.0Hz, 1H), 7.96(d, *J*=3.0Hz, 1H),3.25(q, *J*=5.7Hz, 2H), 3.20(d, *J*=7.2Hz, 2H), 1.96(t, *J*=5.4Hz, 2H), 1.90-1.92(m, 1H), 1.51(m, 4H), 0.91(d, *J*=6.6Hz, 6H).^{13}C NMR(75 MHz, DMSO-d_6): δ 169.0, 161.3, 160.0, 156.3, 145.6, 144.7, 144.1, 123.2, 38.7, 34.8, 32.1, 30.6, 29.0, 22.8, 22.0. HRMS (ESI) (*m/z*):Calcd for $C_{16}H_{22}N_4O_3S_2Na^+$,405.1026(M+$Na^+$),Found405.1076.

8b: (pale yellow solid, 50.0%).^{1}H NMR(300 MHz, CD_3OD): δ 8.38(t, *J*=5.4Hz, 1H), 7.90(d, *J*=3.3Hz, 1H), 7.74(d, *J*=3.3Hz, 1H), 3.39(q, *J*=6.3Hz, 2H), 2.83(s, 3H), 2.16(t, *J*=6.9Hz, 2H), 1.67-1.69(m, 4H).^{13}C NMR(75 MHz, DMSO-d_6): δ 169.1, 161.4, 160.0, 155.9, 144.3, 144.1, 141.7, 123.2, 38.4, 32.1, 29.0, 22.8, 12.6. HRMS (ESI) (*m/z*):Calcd for $C_{13}H_{16}N_4O_3S_2Na^+$,363.0556 (M+$Na^+$),Found363.0556.

8c: (pale yellow solid, 53.6%).^{1}H NMR(300 MHz, CD_3OD): δ 8.33(t, *J*=5.4Hz, 1H), 7.89(d, *J*=3.3Hz, 1H), 7.73(d, *J*=3.3Hz, 1H), 3.37(q, *J*=6.6Hz, 2H), 3.31(q, *J*=6.9Hz, 2H), 2.16(t, *J*=6.3Hz, 2H), 1.64-1.67(m, 4H), 1.35(t, *J*=6.9Hz, 3H).^{13}C NMR(75 MHz, CD_3OD): δ 172.8, 164.1, 162.2, 157.8, 151.9, 145.1, 144.5, 123.3, 39.9, 33.5, 30.3, 24.3, 22.1, 16.6.HRMS (ESI) (*m/z*):Calcd for $C_{14}H_{18}N_4O_3S_2Na^+$,377.0713(M+$Na^+$),Found377.0716.

8d: (white solid, 65.0%).^{1}H NMR(300 MHz, CD_3OD): δ 8.35(t, *J*=5.4Hz, 1H), 7.90(d, *J*=3.3Hz, 1H), 7.74(d, *J*=3.3Hz, 1H), 4.32-4.36(m, 1H), 3.41(q, *J*=6.3Hz, 2H), 2.16(t, *J*=6.3Hz, 2H), 1.67-1.69(m, 4H), 1.37(d, *J*=6.9Hz, 6H).^{13}C NMR(75 MHz, CD_3OD): δ 172.8, 164.1, 162.3, 158.0, 157.8, 145.1, 144.1, 123.4, 39.9, 35.5, 30.3, 29.1, 25.6, 24.3.HRMS (ESI) (*m/z*):Calcd for $C_{15}H_{20}N_4O_3S_2Na^+$,391.0869(M+$Na^+$),Found 391.0877.

8e: (white solid, 67.1%).^{1}H NMR(300 MHz, CD_3OD): δ 8.38(t, *J*=5.4Hz, 1H), 7.92(d, *J*=3.3Hz, 1H), 7.76(d, *J*=3.3Hz, 1H), 3.40(q, *J*=6.0Hz, 2H), 3.34(t, *J*=6.0Hz, 2H), 2.19(t, *J*=6.6Hz, 2H), 1.72-1.79(m, 6H), 1.41-1.54(m, 2H), 1.01(t, *J*=7.5Hz, 3H).^{13}C NMR(75 MHz, CD_3OD): δ 172.8, 164.1, 162.2, 157.9, 150.3, 145.1, 144.8, 123.4, 40.0, 35.2, 33.5, 30.3, 28.0, 24.3, 23.6, 14.3.HRMS (ESI) (*m/z*):Calcd for $C_{16}H_{22}N_4O_3S_2Na^+$,405.1026(M+$Na^+$),Found 405.1035.

8f: (pale yellow solid, 68.3%).^{1}H NMR(300 MHz, CD_3OD): δ 8.36(t, *J*=5.4Hz, 1H), 7.88(d, *J*=3.0Hz, 1H), 7.74(d, *J*=3.0Hz, 1H), 3.41(q, *J*=6.6Hz, 2H), 3.31-3.36(m, 1H), 2.16(t, *J*=6.6Hz, 2H), 1.64-1.69(m, 4H), 1.29-1.34(m, 2H), 0.82-0.86(m, 2H).^{13}C NMR(75 MHz, CD_3OD): δ 172.8, 164.3, 162.0, 156.0, 155.2, 145.6, 145.0, 123.3, 39.9, 33.5, 30.3, 24.3, 14.3, 11.2. HRMS (ESI) (*m/z*):Calcd for $C_{15}H_{18}N_4O_3S_2Na^+$,389.0713(M+$Na^+$),Found389.0736.

8g: (white solid, 33.3%).^{1}H NMR(300 MHz, CD_3OD): δ 7.90(d, *J*=3.3Hz, 1H), 7.74(d, *J*=3.3Hz, 1H), 3.93-4.01(m,1H), 3.40(t, *J*=6.6Hz, 2H), 2.16(t, *J*=7.2Hz, 2H), 1.77-1.89(m, 2H), 1.66-1.69(m, 6H), 1.29-1.57(m, 6H). ^{13}C NMR(75 MHz, DMSO-d_6): δ 169.0, 161.2, 160.0, 155.9, 153.6, 144.1, 143.1, 123.1, 38.4, 36.3, 35.2, 32.0, 29.0, 26.0, 25.2, 22.7. HRMS (ESI) (*m/z*):Calcd for $C_{18}H_{24}N_4O_3S_2Na^+$,431.1182(M+$Na^+$),Found431.1182.

8h: (white solid, 49.5%).^{1}H NMR(300 MHz, CD_3OD): δ 8.48(t, *J*=5.4Hz, 1H), 7.93(d, *J*=3.0Hz, 1H), 7.89(s, 1H), 7.77(d, *J*=3.0Hz, 1H), 7.59(d, *J*=6.6Hz, 2H), 7.42-7.44(m, 3H), 3.41(q, *J*=6.0Hz, 2H), 2.12(t, *J*=6.6Hz, 2H), 1.62-1.64(m, 4H). ^{13}C NMR(75 MHz, DMSO-d_6): δ 169.2, 161.7, 159.8, 158.0, 145.0, 144.4, 141.4, 129.7, 129.6, 129.3,

128.6, 123.7, 38.7, 32.8, 28.7, 22.8. HRMS (ESI) (*m/z*):Calcd for $C_{18}H_{18}N_4O_3S_2Na^+$,425.0713(M+$Na^+$),Found425.0710.

8i: (pale yellow solid, 60.0%).^{1}H NMR(300 MHz, CD_3OD): δ 8.51(t, *J*=5.4Hz, 1H), 7.93(d, *J*=3.0Hz, 1H), 7.89(s, 1H), 7.78(d, *J*=3.0Hz, 1H), 7.62(t, *J*=5.1Hz, 2H), 7.17(t, *J*=8.4Hz, 2H), 3.33(q, *J*=8.4Hz, 2H), 2.13(t, *J*=6.3Hz, 2H), 1.63-1.65(m, 4H).^{13}C NMR(75 MHz, DMSO-d_6): δ 169.2, 161.4, 159.7, 157.9, 144.8, 144.4, 140.6, 132.0, 131.9, 123.7, 115.6, 115.3, 38.7, 32.1, 28.8, 22.8. HRMS (ESI) (*m/z*):Calcd for $C_{18}H_{17}FN_4O_3S_2Na^+$,443.0618(M+$Na^+$),Found443.0622.

8j: (pale yellow solid, 45.9%).^{1}H NMR(300 MHz, CD_3OD): δ 8.52(t, *J*=5.4Hz, 1H), 7.95(d, *J*=3.3Hz, 1H), 7.82(d, *J*=3.3Hz, 1H), 7.53(t, *J*=8.7Hz, 1H), 7.37(d, *J*=8.7Hz, 1H), 7.18(t, *J*=8.1Hz, 1H), 3.34(q, *J*=6.6Hz, 2H), 2.12(t, *J*=6.6Hz, 2H), 1.62-1.64(m, 4H).^{13}C NMR(75 MHz, CD_3OD): δ 172.8, 166.2, 162.9, 161.6, 161.3, 147.2, 145.4, 140.5, 136.4, 134.6, 127.3, 124.1, 118.2, 115.2, 40.0, 33.4, 30.1, 24.2. HRMS (ESI) (*m/z*):Calcd for $C_{18}H_{16}ClFN_4O_3S_2Na^+$,477.0229(M+$Na^+$),Found477.0233.

8k: (pale yellow solid, 46.0%).^{1}H NMR(300 MHz, CD_3OD): δ 8.47(t, *J*=5.4Hz, 1H), 7.94(d, *J*=3.0Hz, 1H), 7.79(d, *J*=3.0Hz, 1H), 7.50(t, *J*=7.8Hz, 2H), 7.39(t, *J*=7.8Hz, 2H), 3.31(q, *J*=6.6Hz, 2H), 1.99(t, *J*=5.4Hz, 2H), 1.17-1.19(m, 4H).^{13}C NMR(75 MHz, CD_3OD): δ 172.8, 163.1, 161.6, 161.0, 147.0, 145.4, 141.5, 135.2, 133.2, 131.9, 130.8, 130.7, 128.0, 124.1, 40.1, 33.4, 30.1, 24.1. HRMS (ESI) (*m/z*):Calcd for $C_{18}H_{17}ClN_4O_3S_2Na^+$,459.0328(M+$Na^+$),Found459.0323.

8l: (pale yellow solid, 76.1%).^{1}H NMR(300 MHz, CD_3OD): δ 8.22(d, *J*=7.2Hz, 2H), 7.90(d, *J*=3.0Hz, 1H), 7.79(d, *J*=6.9Hz, 2H), 7.58(t, *J*=6.0Hz, 1H), 7.53(d, *J*=3.0Hz, 1H), 3.40(q, *J*=6.6Hz, 2H), 2.34(t, *J*=6.9Hz, 2H), 1.59-1.74(m, 4H).^{13}C NMR(75 MHz, CD_3OD): δ 172.8, 166.0, 163.6, 159.3, 145.5, 145.3, 142.9, 138.8, 131.3, 130.6, 124.3, 123.9, 40.2, 33.5, 30.0, 24.2. HRMS (ESI) (*m/z*):Calcd for $C_{18}H_{17}N_5O_5S_2Na^+$,470.0563 (M+$Na^+$),Found470.0562.

8m: (white solid, 47.3%).^{1}H NMR(300 MHz, CD_3OD): δ 8.43(t, *J*=5.4Hz, 1H), 7.86(d, *J*=3.0Hz, 1H), 7.73(d, *J*=3.0Hz, 1H), 7.23-7.34(m, 5H), 4.70(s, 2H), 3.44(q, *J*=6.3Hz, 2H), 2.17(t, *J*=6.6Hz, 2H), 1.65-1.69(m, 4H).^{13}C NMR(75 MHz, DMSO-d_6): δ 169.2, 161.4, 159.9, 157.0, 146.6, 144.2, 143.8, 139.9, 128.7, 128.6, 126.9, 123.3, 38.5, 32.3, 32.2, 29.1, 22.9. HRMS (ESI) (*m/z*):Calcd for $C_{19}H_{20}N_4O_3S_2Na^+$,439.0869(M+$Na^+$),Found439.0871.

8n: (white solid, 73.1%).^{1}H NMR(300 MHz, CD_3OD): δ 7.87(d, *J*=3.0Hz, 1H), 7.70(d, *J*=3.0Hz, 1H), 7.23-7.30(m, 5H), 4.52(s, 2H), 3.75(t, *J*=5.7Hz, 2H), 3.61(t, *J*=5.7Hz, 2H), 3.36(q, *J*=6.3Hz, 2H), 2.14(t, *J*=6.3Hz, 2H), 1.64-1.68(m, 4H).^{13}C NMR(75 MHz, CD_3OD): δ 171.5, 162.9, 161.0, 157.7, 144.9, 144.1, 143.8, 138.2, 128.2, 127.7, 127.5, 122.1, 72.8, 69.4, 38.6, 32.2, 28.9, 27.6, 23.0. HRMS (ESI) (*m/z*):Calcd for $C_{21}H_{24}N_4O_4S_2Na^+$,483.1131(M+$Na^+$),Found483.1134.

8o: (pale yellow solid, 44.0%).^{1}H NMR(300 MHz, CD_3OD): δ 8.33(t, *J*=5.4Hz, 1H), 7.87(d, *J*=3.3Hz, 1H), 7.72(s, 1H), 7.42(d, *J*=3.3Hz, 1H), 3.38(q, *J*=6.6Hz, 2H), 2.16(t, *J*=6.9Hz, 2H), 1.99(s, 6H), 1.62-1.68(m, 4H).^{13}C NMR(75 MHz, CD_3OD): δ 172.8, 164.4, 162.1, 157.5, 145.2, 144.4, 143.8, 142.8, 123.5, 117.3, 40.1, 33.5, 30.3, 28.3, 24.3, 21.1. HRMS (ESI) (*m/z*):Calcd for $C_{16}H_{20}N_4O_3S_2Na^+$,403.0869(M+$Na^+$),Found403.0879.

8p: (white solid, 30.0%).^{1}H NMR (300 MHz, CD_3OD): δ 8.47(t, *J*=5.4Hz, 1H), 7.90(d,

J=3.0Hz, 1H), 7.74(d, *J*=3.0Hz, 1H), 3.58(s, 2H), 3.40(q, *J*=6.0Hz, 2H), 2.16(t, *J*=6.3Hz, 2H), 1.61-1.67(m, 4H), 1.26(s, 6H). ^{13}CNMR(75 MHz, DMSO-d_6): δ 169.0, 161.8, 160.4, 157.5, 145.3, 144.2, 142.2, 123.0, 68.9, 38.7, 38.4, 32.1, 29.0, 28.9, 22.8. HRMS (ESI) (*m/z*):Calcd for $C_{16}H_{22}N_4O_4S_2Na^+$,421.0975(M+$Na^+$),Found421.0980.

8q: (pale yellow solid, 42.9%).^{1}H NMR(300 MHz, DMSO-d_6): δ 10.37(s, 1H), 8.69(s, 1H), 8.42(t, *J*=5.4Hz, 1H), 8.00(s, 2H), 7.58(d, *J*=16.2Hz, 1H), 6.35(m, 1H), 3.27(m, 2H), 1.98(t, *J*=6.9Hz, 2H), 1.73(d, *J*=6.6Hz, 3H), 1.51(m, 4H).^{13}C NMR(75 MHz, DMSO-d_6): δ 169.1, 161.2, 159.7, 155.5, 144.3, 142.6, 134.5, 123.7, 121.8, 38.5, 32.1, 29.0, 22.8, 18.8. HRMS (ESI) (*m/z*):Calcd for $C_{15}H_{18}N_4O_3S_2Na^+$,389.0713(M+$Na^+$),Found389.0731.

8r: (pale yellow solid, 33.3%).^{1}H NMR(300 MHz, DMSO-d_6): δ 10.36(s, 1H), 8.69(s, 1H), 8.52(t, *J*=5.4Hz, 1H), 8.04(s, 2H), 7.83(dd, *J*=17.7,11.1Hz, 1H), 5.83(d, *J*=17.7Hz, 1H), 5.55(d, *J*=11.1Hz, 1H), 3.28(m, 2H), 1.98(t, *J*=6.9Hz, 2H), 1.51(m, 4H).^{13}C NMR(75 MHz, DMSO-d_6): δ 169.0, 161.0, 159.6, 156.7, 144.5, 144.3, 142.2, 127.3, 124.1, 121.4, 38.5, 32.1, 28.9, 22.8. HRMS (ESI) (*m/z*):Calcd for $C_{14}H_{16}N_4O_3S_2Na^+$,375.0556 (M+$Na^+$),Found375.0556.

8s: (pale yellow solid, 88.0%).^{1}H NMR(300 MHz, CD_3OD): δ 8.33(t, *J*=5.4Hz, 1H), 7.89(s, 2H), 7.73(s, 1H), 7.54(d, *J*=15.9Hz, 1H), 6.26-6.34(m, 1H), 3.39(q, *J*=5.7Hz, 2H), 2.48-2.50(m, 1H), 2.16(t, *J*=6.6Hz, 2H), 1.63-1.68(m, 4H), 1.11(d, *J*=6.6Hz, 6H).^{13}C NMR(75 MHz, CD_3OD): δ 172.8, 164.1, 162.0, 157.3, 147.4, 145.8, 145.2, 143.6, 123.7, 119.5, 40.1, 33.5, 33.3, 30.3, 24.3, 22.3.HRMS (ESI) (*m/z*):Calcd for $C_{17}H_{22}N_4O_3S_2Na^+$,417.1026(M+$Na^+$),Found417.1004.

8t: (white solid, 63.0%).^{1}H NMR(300 MHz, CD_3OD): δ 8.29(t, *J*=5.4Hz, 1H), 7.89(s, 1H), 7.85(d, *J*=3.3Hz, 1H), 7.70(d, *J*=3.3Hz, 1H), 3.31(q, *J*=6.3Hz, 2H), 3.15-3.17(m, 1H), 2.16(t, *J*=6.0Hz, 2H), 1.65-1.68(m, 4H), 1.16-1.22(m, 2H), 1.06(d, *J*=6.6Hz, 3H), 1.02(d, *J*=6.6Hz, 3H), 0.92-0.96(m, 2H).^{13}C NMR(75 MHz, CD_3OD): δ 172.8, 164.5, 162.2, 155.7, 155.6, 145.0, 144.9, 123.3, 40.0, 38.3, 34.7, 33.5, 30.3, 24.3, 22.4, 22.0, 20.7, 17.8. HRMS (ESI) (*m/z*):Calcd for $C_{18}H_{24}N_4O_3S_2Na^+$,431.1182(M+$Na^+$),Found 431.1226.

Biological Materials and Methods

Animals

Female C57BL/6 mice were purchased from Shanghai Laboratory Animal Centre of Chinese Academy of Sciences and housed in specific pathogen-free conditions. All animal procedures and experiments were carried out according to National Institutes of Health Guide for Care and Use of Laboratory Animals and were approved by the Bioethics Committee of Shanghai Institute of Materia Medica.

Reagents

Anti-mouse CD3 (145-2C11), anti-mouse CD28 (37.51)monoclonal antibodies were purchased from BD Pharmingen (San Diego, CA, USA).Phycoerythrin–cyanine 7–conjugated anti–mouse CD4 (RM4-5), allophycocyanin-conjugatedanti–mouse CD8a (53-6.7), allophycocyanin-conjugated anti–mouse IFN-γ (XMG1.2), phycoerythrin-conjugated anti–mouse IL-17 (eBio17B7), phycoerythrin-conjugated anti–mouse CD11c (N418) and anti–mouse CD45 (30-F11) were from eBiosciences (San Diego, CA, USA). Alexa Fluor 488 goat anti-rat IgG were from Invitrogen (Carlsbad, CA, USA). Complete Freund's adjuvant (CFA) was from Sigma-Aldrich

(St.Louis, MO). Ficoll-PaqueTM PLUS was from GE healthcare.BD Cytofix/CytopermTMkit was purchased from BD bioscience (FranklinLakes, NJ).

EAE induction and drug treatment

Female C57BL/6 mice 8-9 weeks old were immunized subcutaneously with 200 μg MOG (35-55) (MEVGWYRSPFSRVVHLYRNGK, GL Biochem, Shanghai, China) in complete Freund's adjuvant containing heat-killed *Mycobacterium tuberculosis*(H37Ra strain; 5mg/ml; BD Diagnostics). Pertussis toxin (200 ng/mouse; Calbiochem) in PBS was administered intraperitoneally on day 0 and day 2.Mice were examined daily and were assigned scores on a scale of 0-5 as follows:0, no symptoms; 1, tail weakness; 2, hind limb weakness; 3, paraplegia; 4, paraplegia with forelimb weakness or paralysis; 5, moribund or dead. For drug treatment, **8f** were given by oral administration (**8f** suspension on PVP K29/32 in PBS) twice daily from day3 or day15 post-immunization till the end of the study. PBS was given as a vehicle control.

Histology and Immunofluorescence

For histological and immunofluorescent staining, mice were anesthetized and perfused with PBS (pH 7.4) followed by 4% (w/v) paraformaldehyde. Spinal cord samples were then fixed in 4% paraformaldehyde overnight. Paraffin-embedded spinal cord sections were stained with hematoxylin and eosin or with luxol fast blue for analysis of inflammation or demyelination, respectively. Frozen sections of spinal cord were stained with anti-mouse CD45antibodies (30‐F11, eBioscience), then with Alexa Fluor 488 goat anti-rat IgG secondary antibodies.

Isolation and analysis of central nervous system leukocytes infiltrations

Brain and spinal cord were collected from mice perfused with PBS and were homogenized in ice-cold tissue grinders and filtered through a 70 μm cell strainer. Mononuclear cells were prepared by Percoll gradient centrifugation(37/70%, GE HealthcareBiosciences, Piscataway, NJ).

Leukocytes apoptosis experiment

Splenocytes were isolated from C57/BL6 mice and cultured in complete RPMI1640 medium in 48-well plates at a density of 2×10^6/well. Splenocyteswere stimulated with anti-CD3 (2μg/ml) and anti-CD28 (2μg/ml) antibodies for T cells activation or LPS (20μg/ml, Sigma) for B cells activation. After 48h live cells were purified through the Ficoll (ρ=1.084) density gradient and restimulated with anti-mouse CD3 (2μg/ml) or LPS (20μg/ml) for 24h in the presence of various concentrations of**8f** (dissolved in DMSO). Cells were then stained with PI and Annexin V incombination with anti-CD4 or anti-CD8 or anti-B220 antibody. The percentage of apoptotic cells (Annexin V positive, PI negative) was determined by flow cytometry.

Intracellular staining and Flow cytometry

Cells obtained from spleen, lymph nodes or CNS were incubated for 5 h at 37℃ with phorbol 12-myristate 13-acetate (50ng/ml, Sigma), ionomycin (750ng/ml, Sigma) and brefeldin A (3μg/ml, Sigma). For surface staining, cells were incubated with relevant fluorescence-labeled surface antibodies for 30 min at 4℃. After surface staining, cells were resuspended in Fixation/Permeabilization solution (Cytofix/Cytoperm kit, BD Pharmingen) and intracellularcytokine staining was done

according to the manufacturer's protocol. Guava Easycyte 8HT Flow CytometrySystem (Millipore, Billerica, MA) were used for flow cytometry.

Western Blot

Mouse embryo fibroblasts (MEF) cells were washed once with PBS, and then lysed, sonicated and boiled at 100℃ for 5 min in lysis buffer (50mMTris-HCl, 2% w/v SDS, 10% glycerol,1% β-mercaptoethanol, 0.01% bromophenyl blue (pH 6.8)). Samples were separated on SDS-PAGE and transferred to polyvinylidenedifluoride membranes. The membranes were first incubated with blocking buffer (TBS with 0.05% Tween 20, 5%nonfat milk) for 1 h at room temperature and then incubated overnightat 4°C in buffer containing rabbit anti-GAPDH (1:10 000,CST), rabbit anti-anti-histone H3 (1:1000, Millipore), rabbit anti-acetyl-histone H3(1:50 000, Millipore), rabbit anti-anti-histone H4 (1:1000, Millipore), rabbit anti-acetyl-histone H3(1:4000, Millipore). The membranes were washed thrice and incubated with goat anti-rabbit IgG HRP (1:10000) for 1 h. After washing, immunostaining was visualized using Amersham ECL PlusWestern Blotting detection reagents (GE Healthcare).

Statistical analysis

The statistical significance of the EAE clinical scores between treatments were analyzed with two-way ANOVA test. For other analysis, Student's t-test was applied for statistical comparison of two groups. A P value of 0.05 or less was considered significant.

Enzymatic assay with recombinant human HDACs

Eight full-length hHDACs (humanHDAC1, 2, 3, 4, 6, 8, 10 and 11) cDNA were subcloned into the pFASTBAC1 vector and recombinant hHDACs protein were over expressed in insect High5 cells using the baculoviral expression system, and all His_6-tagged proteins were purified using Ni-NTA (QIAGEN). The protein of HDAC5 was purchased from BPS Biosciences. The deacetylase activity were determined in a total 25μl assay reaction in black 384-well plates (OptiPlate^{TM}-384F, PerkinElmer) containing 25mMHepes pH 8.0, 137mMNaCl, 2.7mMKCl and 4.9mM $MgCl_2$, with the HDAC substrate Ac-Lys-Tyr-Lys(ε-acetyl)-AMC for HDAC1, 2, 3, 4, 5, 8, 10 and 11, and another HDAC substrate Boc-Lys(ε-acetyl)-AMC for HDAC6. In brief, the HDAC inhibitory assay mixture contained HDAC substrate (10 μM for HDAC1, 3, 4, 5 and 10, 5 μM for HDAC8, 20 μM for HDAC2 and 11, 50 μM for HDAC6), rhHDAC isoforms (20-200nM) and varied concentration of inhibitor or SAHA as positive control. After the incubation The reaction mixture at room temperature of 24 hrs for HDAC1, 2, 3, 4, 5, 8, 10 and 11, or 3 hrs for HDAC6 , the reaction mixture was quenched by addition of 25μl Trypsin solution (diluted to final concentration of 0.3125%), and incubated further for 30 min to allow the fluorescence signal to develop. The fluorescence generated was monitored at wavelengths 355nm(excitation) and 460nm(emission) by Envision (PerkinElmer) for the inhibitory activity calculation. All the multi-dose response of inhibition activity of each compound was carried out in triplicates, and the IC_{50} value was calculated using the software GraphPad Prism 5 and chosen the equation "sigmoidal dose-response (variable slope)" for curve fitting.