Supporting Information

Synthesis of a Series of Benzothiazole Amide Derivatives and Their Biological Evaluation as Potent Hemostatic Agents

1. Crystal structure description

Selected bond lengths (Å) and angles (°) of compounds **Q7** and **Q9** are listed in Table 1.

Table 1 Selected bond lengths and angles for compounds **Q7** and **Q9**.

Compound **Q7**							
Bond	Bond length (Å) (and angle °)	Bond	Bond length (Å) (and angle °)	Bond	Bond length (Å) (and angle °)	Bond	Bond length (Å) (and angle °)
S(1)-C(12)	1.7400 (19)	O(3)-C(9)	1.225 (2)	O(2)-C(18)	1.430 (2)	N(2)-C(11)	1.392 (2)
S(1)-C(12)	1.7522 (18)	N(1)-C(9)	1.376 (2)	O(1)-C(3)	1.363 (2)	N(2)-C(10)	1.304 (2)
O(2)-C(4)	1.373 (2)	N(1)-C(10)	1.373 (2)	O(1)-C(17)	1.427 (2)		
O(3)-C(9)-C(8)	123.92 (17)	C(4)-O(2)-C(18)	117.21 (15)	N(1)-C(9)-C(8)	115.29 (16)	O(1)-C(3)-C(4)	114.95 (16)
C(3)-O(1)-C(17)	116.60 (15)	O(1)-C(3)-C(2)	125.29 (17)	C(10)-N(1)-C(9)	123.50 (15)	O(3)-C(9)-N(1)	120.79 (17)
N(1)-C(10)-S(1)	122.04 (13)	N(2)-C(10)-N(1)	121.34 (16)				
Compound **Q9**							
Bond	Bond length (Å) (and angle °)	Bond	Bond length (Å) (and angle °)	Bond	Bond length (Å) (and angle °)	Bond	Bond length (Å) (and angle °)
S001-C009	1.7412 (17)	S001-C00F	1.7415 (16)	S002-C7	1.7510 (16)	S002-C1	1.7437 (17)
O003-C00A	1.217 (2)	O1-C8	1.219 (2)	N2-C7	1.379 (2)	N2-C8	1.375 (2)
N006-C00A	1.372 (2)	N006-C00F	1.379 (2)	N1-C6	1.393 (2)	N1-C7	1.297 (2)
N008-C00F	1.303 (2)	N008-C00R	1.394 (2)				
C8-N2-C7	123.67 (14)	C00A-N006-C00F	124.81 (14)	C7-N1-C6	109.56 (14)	C00F-N008-C00R	109.77 (14)
O003-C00A-N006	122.05 (15)	O003-C00A-C00O	124.04 (15)	N006-C00A-C00O	113.87 (14)	N2-C7-S002	121.74 (12)
N1-C7-S002	117.37 (12)	N1-C7-N2	120.88 (14)	O1-C8-N2	121.72 (15)		

2. Blood coagulation activities

Using *p*-aminomethylbenzoic acid (PAMBA) as a positive control, the results of APTT, PT and TT assays are listed in Tables 2–4.

Table 2 R_{APTT} (%) values of the synthesized benzothiazole amide derivatives.

Compound	Concentration (μmol/L)				
	1	5	10	50	100
PAMBA	–6.37 ± 0.23	–7.74 ± 0.11	–7.28 ± 0.30	–6.83 ± 0.39	–5.23 ± 0.46
2-aminobenzothiazole	–4.87±0.13***	–5.27±0.35***	–6.19±0.13*	–4.74±0.23***	–4.48±0.35***
q1	–1.72±0.25***	–0.54±0.16***	0.86±0.25***	1.58±0.14***	1.87±0.38***
q2	–3.97±0.47***	–3.56±0.24***	–1.92±0***	0.01±0.27***	0.82±0.14***
q3	–2.19±0.36***	–1.23±0.27***	0.55±0.24***	0.96±0.24***	3.15±0.14***
q4	–3.47±0.12***	–1.20±0.24***	–0.96±0.32***	0.12±0.24***	0.24±0.43***
q5	–2.18±0.39***	–0.26±0.38***	2.05±0.44***	2.56±0.26***	7.57±0.34***
q6	–0.96±0.32***	0.12±0.11***	0.36±0.35***	0.60±0.32***	0.72±0.21***
q7	–0.73±0.15***	–0.44±0.44***	1.91±0.14***	2.20±0.25***	2.79±0.15***
q8	–0.48±0.24***	–0.84±0.60***	–1.20±0.43***	–1.67±0.12***	–2.75±0.24***
q9	1.03±0.12***	–0.77±0.26***	–1.67±0.13***	–2.31±0.33***	–2.57±0.22***
Q1	0.14±0.37***	–8.58±0.37	–10.10±0.14***	–6.50±0.14**	–5.26±0.37
Q2	–38.84±0.08***	–38.26±0***	–36.12±0.22***	–36.03±0.43***	–20.25±0.30***
Q3	0.42±0.38***	0.21±0.21***	–1.98±0.21***	–0.73±0.21***	–0.52±0.10***
Q4	–35.46±0.17***	–34.96±0.30***	–34.22±0.22***	–31.90±0.41***	–4.80±0.14
Q5	–12.06±0.20***	–10.03±0.34***	–9.58±0.11***	–9.47±0.29***	–7.89±0.11***
Q6	–9.47±0.11***	–8.90±0.11*	–8.46±0.41**	–7.90±0.11**	–7.33±0.34***
Q7	–4.55±0.28***	–6.21±0.14**	–8.83±0.14***	–7.31±0.24**	–4.41±0.24
Q8	2.24±0.11***	–0.11±0.11***	–4.69±0.18***	–3.52±0.11***	0.85±0.11***
Q9	–5.75±0.30	–4.06±0.46***	–3.95±0.20***	–1.01±0.30***	4.51±0.20***

Data represent mean ± SEM; n = 8.

* $P < 0.05$ vs. PAMBA ; ** $P < 0.01$ vs. PAMBA; *** $P < 0.001$ vs. PAMBA.

Table 3 R_{PT} (%) values of the synthesized benzothiazole amide derivatives.

Compound	Concentration (μmol/L)				
	1	5	10	50	100
PAMBA	1.15 ± 0.28	1.05 ± 0.18	0.73 ± 0.48	0.63 ± 0.28	0.73 ± 0.18
2–aminobenzothiazole	–1.05±0.46***	–1.22±0.30***	–1.57±0.17***	–4.36±0***	–4.48±0.35***
q1	7.60±0.17***	4.73±0.45***	2.87±0.59**	–1.35±0.45**	–2.20±0.29***
q2	–4.78±0.27***	–3.85±0.27***	–3.70±0.15***	–3.39±0.27***	–2.93±0.27***
q3	–2.23±0.15***	–1.92±0.26***	–0.89±0.39*	–0.30±0.15	0.45±0.14
q4	–2.71±0.15***	–2.56±0.30***	0.00±0.15	0.30±0.52	0.90±0.40
q5	–5.94±0.45***	–2.53±0.39***	–1.78±0.15**	–0.45±0.39	2.23±0.54*
q6	–4.16±0.15***	–3.23±0.56***	–2.31±0.41***	–1.23±0.15*	–0.15±0.27
q7	–0.77±0.41*	0.77±0.27	1.23±0.27	1.69±0.46	1.85±0.31
q8	1.52±0.45	3.21±0.34**	4.39±0.29***	5.57±0.45***	6.76±0.34***
q9	–5.42±0.54***	–1.51±0.26***	–1.05±0.45*	–0.45±0.40	1.51±0.15
Q1	–2.12±0.28***	–5.22±0.33***	–4.73±0.16***	–3.59±0.57***	–2.12±0.28***
Q2	–6.79±0.15***	–5.91±0.15***	–4.43±0.15***	–1.62±0.26***	–0.59±0.15**
Q3	–6.57±0.13***	–5.36±0.13***	–4.29±0.23***	–1.21±0.13***	–0.13±0.13
Q4	–9.90±0.15***	–7.24±0.15***	–5.47±0.30***	–4.73±0***	–2.07±0.44***
Q5	–11.43±0.13***	–10.22±0.13***	–9.67±0***	–4.03±0.23***	–2.28±0.13***
Q6	–4.57±0.48***	–4.70±0.13***	–6.99±0.13***	–9.54±0.13***	–14.79±0.13***
Q7	–3.57±0.28***	–4.40±0.16***	–5.38±0.33***	–6.85±0.16***	–7.83±0.33***
Q8	–1.61±0.13***	–4.29±0***	–3.89±0.23***	–4.83±0.27***	–1.21±0.13***
Q9	–9.82±0.27***	–6.72±0.13***	–5.19±0.13***	–4.03±0.23***	–3.90±0.27***

Data represent mean ± SEM; n = 8.

* $P < 0.05$ vs. PAMBA; ** $P < 0.01$ vs. PAMBA; *** $P < 0.001$ vs. PAMBA.

Table 4 R_{TT} (%) values of the synthesized benzothiazole amide derivatives.

Compound	Concentration (μmol/L)				
	1	5	10	50	100
PAMBA	–7.13 ± 0.63	–4.99 ± 0.63	–4.75 ± 0.48	–4.28 ± 0.36	–4.04 ± 0.24
2–aminobenzothiazole	12.57±0.29***	11.40±0***	9.36±0.29***	3.51±0.31***	0.58±0.29***
q1	0.26±0.26***	–0.52±0.26***	–1.82±0.26***	–3.16±0.45	–5.47±0.45*
q2	–2.53±0.51***	–1.52±0.25***	1.01±0.44***	2.03±0.25***	4.30±0.51***
q3	0.98±0.42***	–0.98±0.24***	–4.39±0.24	–5.61±0.42	–6.10±0.24**
q4	–4.95±0.26*	–3.91±0	–2.87±0.26*	–1.82±0.52*	–1.56±0.45***
q5	–6.58±0.44	–5.32±0.25	–0.76±0.51***	1.77±0.44***	3.54±0.25***
q6	–2.29±0.43***	–1.02±0.51***	–0.51±0.25***	0.51±0.67***	2.04±0.25***
q7	–4.15±0***	–1.71±0.24***	2.44±0.42***	5.12±0.49***	8.29±0***
q8	–4.30±0.44**	–2.28±0.25***	–1.27±0.44***	2.03±0.51***	3.04±0.25***
q9	–4.12±0.45***	–2.06±0.26***	–1.55±0.26***	0.01±0.52***	1.03±0.25***
Q1	–7.38±0.22	–11.50±0.38***	–12.15±0.38***	–12.80±0.01***	–14.53±0.22***
Q2	–6.67±0.24	–11.43±0.41***	–17.14±0.01***	–24.52±0.24***	–16.43±0.41***
Q3	–3.11±0.19***	–4.47±0	–16.70±0.34	–14.18±0.19***	–9.13±0.34***
Q4	–21.91±0.28***	–20.24±0.24***	–18.10±0.24***	–15.00±0.41***	–13.33±0.24***
Q5	–10.563±0.10***	–11.97±0.41***	–13.62±0.23***	–20.19±0.23***	–20.66±0.47***
Q6	–14.46±0.24***	–10.9±0.24***	–5.21±0.47***	–4.98±0.47	–0.95±0.24***
Q7	–19.31±0.38***	–17.57±0.22***	–17.14±0.22***	–16.05±0.38***	–13.23±0.22***
Q8	–29.13±0.39***	–28.35±0.01***	–27.96±0.19***	–16.31±0.39***	–13.20±0.34***
Q9	–2.61±0.41***	–3.79±0.24	–11.61±0.24***	–17.54±0.41***	–18.48±0.24***

Data represent mean ± SEM; n = 8.

* $P < 0.05$ vs. PAMBA; ** $P < 0.01$ vs. PAMBA; *** $P < 0.001$ vs. PAMBA

Compound **Q2** significantly shortened the APTT ($P < 0.001$; Table 2) and exhibited a minimum APTT value (R_{APTT} = –38.84 ± 0.08%; Table 2), while significantly shortening the TT (R_{TT} = –24.52 ± 0.24%, 50 μmol/L, $P < 0.001$; Table 4) and the PT (R_{PT} = –6.79 ± 0.15%, 1 μmol/L, $P < 0.001$; Table 3). The blood coagulant activities results demonstrated that compound **Q2** showed significantly shortened APTT, PT and TT than the positive control of PAMBA.