

Supplemental Material

Identification of new series of benzothiazinone derivatives with excellent Antitubercular activity and improved pharmacokinetic profiles

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Table S1. The results of CYP450 inhibition test

Comp	CYP inhibitory (IC ₅₀ , μM)				
	1A2	2C9	2C19	2D6	3A4
1a	>10	>10	5.52	>10	5.33
2d	>10	>10	>10	>10	>10
2h	>10	>10	>10	>10	>10
3b	>10	>10	6.6	>10	>10
3c	>10	>10	8.6	>10	>10
3n	>10	>10	>10	>10	>10
3o	>10	>10	>10	>10	>10
PBTZ169	>10	>10	>10	>10	>10

Table S2. The results of plasma protein binding rate (PPB) test

Comp	species	% Unbound (n = 3)	% Bound
1a	Human Plasma	9.3	90.7
	CD-1 Mouse Plasma	3.0	97
2d	Human Plasma	7.5	92.5
	CD-1 Mouse Plasma	NA	>99
2h	Human Plasma	0.2	99.8
	CD-1 Mouse Plasma	NA	>99
3b	Human Plasma	NA	>99
	CD-1 Mouse Plasma	5.3	94.7
3c	Human Plasma	NA	>99
	CD-1 Mouse Plasma	2.6	97.4
3n	Human Plasma	0.6	99.4
	CD-1 Mouse Plasma	0.5	99.5
3o	Human Plasma	1.9	98.1
	CD-1 Mouse Plasma	1.4	98.6
PBTZ169	Human Plasma	0.4	99.6
	CD-1 Mouse Plasma	0.2	99.8
Warfarin	Human Plasma	1.1	98.9
	CD-1 Mouse Plasma	2.8	97.2

Table S3. Plasma concentration-Time data of IV 3o at 10 mg/kg in ICR Mice

Time (hr)	Compound 3o- IV – 10 mg/kg				
	Plasma Concentration (ng/mL)				
	#1	#2	#3	mean	SD
0	0.00	0.00	0.00	0	0
0.083	5927.55	5625.01	5469.73	5674.10	232.82
0.25	1595.32	1851.29	1494.62	1647.08	183.88
0.5	889.71	1073.88	788.25	917.28	144.80
1	458.59	551.66	453.35	487.86	55.31
2	275.65	211.20	296.38	261.08	44.42
4	100.79	61.64	72.21	78.22	20.25
8	21.77	20.80	19.65	20.74	1.06
24	BLQ ^a	1.08	BLQ	0.36	0.62

^aBQL: Below quantifiable limit of 1 ng/mL.

Table S4. Plasma concentration-time data of PO 3o at 100 mg/kg in ICR Mice

Time (hr)	Compound 3o- PO – 100 mg/kg				
	Plasma Concentration (ng/mL)				
	#1	#2	#3	mean	SD
0	0.00	0.00	#3	0	0
0.083	46.54	125.12	0.00	219.79	235.33
0.25	1646.81	1312.10	487.71	1523.99	184.27
0.5	2667.07	3194.37	1613.05	2036.66	1570.84
1	2674.75	3803.50	248.54	2588.77	1259.92
2	3250.43	1982.91	1288.07	2648.48	636.15
4	1089.51	1067.12	2712.09	1081.62	12.57
8	386.99	428.46	1088.23	330.49	135.38
24	5.33	0.00	176.01	3.34	2.91

Table S5. Lung concentration-time data of IV 3o at 10 mg/kg in ICR Mice

Time (hr)	Compound 3o- IV – 10 mg/kg				
	Lung Concentration (ng/mL)				
	#1	#2	#3	mean	SD
0	0.00	0.00	0.00	0	0
0.083	10475.90	5938.49	10203.30	8872.56	2544.64
0.25	5271.23	2398.81	5706.41	4458.82	1797.24
0.5	1925.60	1142.93	1221.81	1430.11	430.91
1	2293.06	1911.66	494.53	1566.42	947.67
2	330.09	425.51	313.80	356.46	60.34
4	179.03	148.69	61.44	129.72	61.05
8	48.33	30.87	15.65	31.62	16.35
24	BLQ	BLQ	BLQ	NA ^a	NA

^aNA: not applicable

Table S6. Lung concentration-time data of PO 3o at 100mg/kg in ICR Mice

Time (hr)	Compound 3o- PO – 100 mg/kg				
	Lung Concentration (ng/mL)				
	#1	#2	#3	mean	SD
0	0.00	0.00	0.00	0	0
0.083	2907.51	75.37	353.88	1112.26	1560.96
0.25	2497.99	1074.86	2006.19	1859.68	722.79
0.5	5113.07	4134.11	4324.59	4523.92	519.03
1	1735.60	1610.14	1076.20	1473.98	350.15
2	8817.91	2939.96	1977.11	4578.33	3703.02
4	2518.35	1500.92	3424.34	2481.20	962.25
8	577.01	971.32	358.05	635.46	310.78
24	9.65	BLQ	23.40	16.53	9.72

Table S7. Plasma concentration-time data of IV PBTZ169 at 10mg/kg in ICR Mice

Time (hr)	Compound PBTZ169- IV – 10 mg/kg				
	Lung Concentration (ng/mL)				
	#1	#2	#3	mean	SD
0	0.00	0.00	0.00	0	0
0.083	14897.10	15382.60	16521.50	15600.40	833.81
0.25	6982.21	7304.63	7094.05	7126.96	163.71
0.5	4953.36	3806.25	4714.46	4491.36	605.22
1	3033.80	1589.81	1646.61	2090.07	817.78
2	306.89	431.92	385.97	374.93	63.24
4	118.27	159.22	138.48	138.66	20.47
8	36.67	35.39	61.22	44.43	14.56
24	0.98	BLQ	1.24	0.74	0.65

Table S8. Plasma concentration-time data of PO PBTZ169 at 100mg/kg in ICR Mice

Time (hr)	Compound PBTZ169- PO – 100 mg/kg				
	Lung Concentration (ng/mL)				
	#1	#2	#3	mean	SD
0	0.00	0.00	0.00	0	0
0.083	271.35	59.99	403.87	245.07	173.44
0.25	2526.72	NA	2031.01	2278.87	350.52
0.5	3367.91	2456.89	2887.06	2903.95	455.74
1	1578.37	2542.78	2520.16	2213.77	550.39
2	3413.83	3100.69	2474.50	2996.34	478.28
4	3230.39	1290.61	3227.09	2582.70	1118.98
8	530.95	298.97	176.66	335.53	179.95
24	4.39	1.97	1.58	2.65	1.52

Table S9. Lung concentration-time data of IV PBTZ169 at 10mg/kg in ICR Mice

Time (hr)	Compound PBTZ169- IV – 10 mg/kg				
	Lung Concentration (ng/mL)				
	#1	#2	#3	mean	SD
0	0.00	0.00	0.00	0	0
0.083	2978.22	5704.70	3943.30	4208.74	1382.49
0.25	2360.87	3958.11	2156.86	2825.28	986.35
0.5	2839.43	2233.08	3032.11	2701.54	416.98
1	1862.42	1943.09	2756.36	2187.29	494.48
2	1529.74	1451.11	1260.69	1413.85	138.34
4	1069.48	1272.45	6192.32*	1170.97	143.52
8	1293.98	127.82	181.02	534.27	658.46
24	24.17	9.23	11.64	15.01	8.02

* found to be an outlier.

Table S10. Lung concentration-time data of PO PBTZ169 at 100mg/kg in ICR Mice

Time (hr)	Compound PBTZ169- PO – 100 mg/kg				
	Lung Concentration (ng/mL)				
	#1	#2	#3	mean	SD
0	0.00	0.00	0.00	0	0
0.083	56.10	244.23	87.32	129.22	100.82
0.25	671.12	363.14	259.89	431.38	213.94
0.5	794.37	723.93	915.75	811.35	97.03
1	242.66	247.29	658.28	382.74	238.63
2	679.38	479.10	772.61	643.69	149.97
4	522.22	656.24	682.83	620.43	86.09
8	584.03	218.32	386.68	396.34	183.04
24	38.58	11.15	25.61	25.11	13.72