**Potent, Small-Molecule Inhibitors of Human Mast Cell Tryptase. Anti-Asthmatic Action of a
Dipeptide-Based Transition-State Analogue Containing a Benzothiazole Ketone**

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Enzyme Inhibition: K_i Values (nM)^a

compound	tryptase	trypsin	kallikrein	uPA	plasmin	thrombin
(2S)-6 ^b	10 ± 3 (7)	8.1 ± 1.8 (4)	320 ± 30 (3)	2200 ± 200 (3)	8100 ± 1100 (3)	310,000 ± 70,000 (4)
APC-366 (1) ^c	330	162	>1,000,000	ND ^d	>1,000,000	415
Babim (2) ^e	140 ± 20 (16)	490 ± 80 (3)	140 ± 20 (3)	2300 ± 700 (3)	2650 ± 470 ^f	4150 ± 650 ^f

a. K_i values (mean ± standard error) are given for tryptase inhibition; the number of experiments (N) is given in parentheses. uPA = urokinase-type plasminogen activator. All K_i data were obtained without the addition of exogenous zinc (ref 5b and 17). b. Determined for the trifluoroacetate hydrate (1.2 TFA, 1.4 water). c. The K_i values for 1 are those reported in ref 5a. d. ND = Not determined. e. Reference tryptase inhibitor, the K_i of which improved to 0.48 ± 0.17 nM ($N = 3$) in the presence of $80 \mu\text{M}$ ZnCl_2 (ref 5b and 17). f. These K_i values are taken from ref 6c.

X-ray Crystallographic Data for (2S)-6•HSO₄

Figure S-1. Perspective drawing of the solid-state structure for crystalline (2S)-6•HSO₄. Nonhydrogen atoms are represented by 50% probability thermal vibration ellipsoids and hydrogen atoms are represented by arbitrarily-small spheres that are in no way representative of their true thermal motion.

Table S-1. Atomic Coordinates for Nonhydrogen Atoms in Crystalline $[\text{C}_{20}\text{H}_{27}\text{N}_6\text{O}_4\text{S}][\text{HSO}_4]^\text{a}$

atom type ^b	fractional coordinates			equivalent isotropic thermal parameter, U, Å ² x 10 ^{3c}
	10 ⁴ x	10 ⁴ y	10 ⁴ z	
cation				
S ₁	-1078(1)	5001(1)	2277(1)	36(1)
O ₁	1773(2)	4953(3)	3045(2)	39(1)
O ₂	1921(2)	79(2)	3306(2)	38(1)
O ₃	-1619(2)	-2154(3)	322(2)	34(1)
O ₄	3950(2)	-799(3)	1904(3)	40(1)
N ₁	9332(4)	1103(4)	4794(3)	41(1)
N ₂	7183(3)	1702(3)	4553(3)	35(1)
N ₃	8910(4)	3070(4)	5444(3)	44(1)
N ₄	-681(3)	2536(3)	2261(3)	34(1)
N ₅	2040(3)	1847(3)	2198(3)	24(1)
N ₆	1859(3)	-1470(3)	1269(3)	31(1)
C ₁	8474(3)	1960(4)	4928(3)	32(1)
C ₂	6175(3)	2667(4)	4485(4)	37(1)
C ₃	4792(3)	2107(3)	3998(3)	32(1)
C ₄	3770(3)	3197(4)	3653(3)	30(1)
C ₅	2337(3)	2725(3)	3242(3)	24(1)
C ₆	1380(3)	3857(4)	2941(3)	28(1)
C ₇	-75(3)	3639(3)	2503(3)	27(1)
C ₈	-2454(3)	4019(4)	1790(3)	33(1)
C ₉	-2057(4)	2730(4)	1849(3)	36(1)
C ₁₀	-2998(4)	1752(5)	1506(4)	48(1)
C ₁₁	-4323(4)	2106(5)	1098(4)	55(1)
C ₁₂	-4697(4)	3389(6)	1031(4)	57(1)
C ₁₃	-3792(4)	4374(5)	1366(4)	46(1)
C ₁₄	1824(3)	598(3)	2317(3)	28(1)
C ₁₅	1382(3)	-132(3)	1104(3)	28(1)
C ₁₆	-136(3)	-299(3)	640(3)	29(1)
C ₁₇	-386(3)	-1622(3)	1071(3)	28(1)
C ₁₈	774(3)	-2410(4)	987(4)	32(1)
C ₁₉	3160(4)	-1711(4)	1694(3)	34(1)
C ₂₀	3603(4)	-3081(4)	1895(4)	45(1)
anion				
S ₂	7295(1)	-1876(1)	3101(1)	42(1)
O ₅	6261(3)	-993(4)	3355(3)	56(1)
O ₆	8439(4)	-1077(5)	3356(5)	139(3)
O ₇	7584(8)	-2855(5)	3943(4)	178(3)
O ₈	6858(3)	-2291(3)	1847(2)	54(1)

a. The numbers in parentheses are the estimated standard deviations in the last significant digit. b. Atoms are labeled in agreement with Figure S-1. c. This is one-third of the trace of the orthogonalized U_{ij} tensor.

Table S-2. Atomic Coordinates for Hydrogen Atoms in Crystalline [C₂₀H₂₇N₆O₄S][HSO₄]^a

atom type ^b	10 ⁴ x	fractional coordinates 10 ⁴ y	10 ⁴ z
cation			
H _{3O} ^c	-1977(35)	-2220(36)	829(32)
H _{1N1} ^c	9041(41)	412(47)	4365(40)
H _{1N2} ^c	10110(49)	1221(49)	5073(42)
H _{2N} ^c	6891(37)	1033(41)	4180(34)
H _{3N1} ^c	9812(47)	3317(44)	5666(38)
H _{3N2} ^c	8443(42)	3622(46)	5636(39)
H _{5N} ^c	1954(31)	2087(31)	1450(32)
H _{2a}	6260	3373	3937
H _{2b}	6319	3029	5318
H _{3a}	4625	1555	4635
H _{3b}	4709	1572	3262
H _{4a}	3918	3769	4376
H _{4b}	3913	3709	2978
H ₅	2200	2250	3949
H ₁₀	-2741	876	1550
H ₁₁	-4987	1461	861
H ₁₂	-5616	3593	741
H ₁₃	-4061	5246	1312
H ₁₅	1687	314	470
H _{16a}	-566	369	994
H _{16b}	-486	-241	-272
H ₁₇	-366	-1578	1950
H _{18a}	982	-3118	1597
H _{18b}	591	-2773	149
H _{20a}	4553	-3061	2115
H _{20b}	3360	-3327	2601
H _{20c}	3250	-3691	1242
anion			
H _{5O} ^c	5458(52)	-1073(58)	2835(46)

a. Hydrogen atoms bonded to oxygen and nitrogen (H_{3O}, H_{5O}, H_{1N1}, H_{1N2}, H_{2N}, H_{3N1}, H_{3N2}, and H_{5N}) were located from a difference Fourier synthesis and included in the structural model as independent isotropic atoms. The methyl group (C₂₀ and its hydrogens) was refined as a rigid rotor (using idealized sp³-hybridized geometry and a C-H bond length of 0.96 Å) with three rotational parameters in least-squares cycles. The final refined values of these three rotational parameters gave C-C-H angles which ranged from 103° to 119°. The remaining hydrogen atoms were included in the structural model as fixed atoms (using idealized sp²- or sp³-hybridized geometry and C-H bond lengths of 0.95-1.00 Å) "riding" on their respective carbons. The isotropic thermal parameters for H_{3O}, H_{5O}, H_{1N1}, H_{1N2}, H_{2N}, H_{3N1}, H_{3N2}, and H_{5N} refined to final U_{iso} values of

0.02(1), 0.08(2), 0.05(1), 0.05(1), 0.03(1), 0.06(1), 0.05(1), and 0.02(1) Å², respectively. The isotropic thermal parameters of the remaining hydrogen atoms were fixed at values 1.2 (nonmethyl) or 1.5 (methyl) times the equivalent isotropic thermal parameters of the carbon atoms to which they are covalently bonded. b. Hydrogen atoms which are covalently bonded to carbon are labeled with the same numerical subscripts as their carbon atoms, with an additional literal subscript (a, b or c), where necessary, to distinguish between hydrogens bonded to the same carbon atom. Hydrogen atoms bonded to oxygen and nitrogen are labeled with the same numerical subscript as their oxygen or nitrogen, a literal subscripted O or N, and an additional subscripted 1 or 2, where necessary, to distinguish between hydrogens bonded to the same nitrogen. c. The numbers in parentheses are the estimated standard deviations in the last significant digit.

Table S-3. Bond Lengths in Crystalline $[\text{C}_{20}\text{H}_{27}\text{N}_6\text{O}_4\text{S}][\text{HSO}_4]^\text{a}$

type ^b	length, Å	type ^b	length, Å
cation			
S ₁ -C ₇	1.745(4)	N ₂ -C ₂	1.454(5)
S ₁ -C ₈	1.726(4)	N ₄ -C ₉	1.401(5)
		N ₅ -C ₅	1.456(4)
O ₁ -C ₆	1.210(4)	N ₆ -C ₁₈	1.470(4)
O ₂ -C ₁₄	1.228(4)	N ₆ -C ₁₅	1.476(5)
O ₄ -C ₁₉	1.241(4)		
O ₃ -C ₁₇	1.428(4)	C ₂ -C ₃	1.513(5)
O ₃ -H ₃₀	0.79(3)	C ₃ -C ₄	1.534(5)
		C ₄ -C ₅	1.526(5)
N ₁ -C ₁	1.323(5)	C ₅ -C ₆	1.524(5)
N ₂ -C ₁	1.329(5)	C ₁₅ -C ₁₆	1.540(5)
N ₃ -C ₁	1.314(5)	C ₁₆ -C ₁₇	1.517(5)
N ₄ -C ₇	1.304(5)	C ₁₇ -C ₁₈	1.513(5)
N ₅ -C ₁₄	1.338(4)		
N ₆ -C ₁₉	1.335(5)	C ₆ -C ₇	1.485(5)
		C ₁₄ -C ₁₅	1.518(5)
		C ₁₉ -C ₂₀	1.499(5)
N ₁ -H _{1N1}	0.87(5)		
N ₁ -H _{1N2}	0.80(5)	C ₈ -C ₁₃	1.398(5)
N ₂ -H _{2N}	0.82(4)	C ₈ -C ₉	1.403(6)
N ₃ -H _{3N2}	0.83(5)	C ₉ -C ₁₀	1.394(6)
N ₃ -H _{3N1}	0.95(5)	C ₁₀ -C ₁₁	1.385(6)
N ₅ -H _{5N}	0.87(3)	C ₁₁ -C ₁₂	1.390(7)
		C ₁₂ -C ₁₃	1.375(7)
anion			
S ₂ -O ₅	1.535(3)	S ₂ -O ₆	1.426(4)
		S ₂ -O ₇	1.368(4)
O ₅ -H ₅₀	0.87(5)	S ₂ -O ₈	1.425(3)

a. The numbers in parentheses are the estimated standard deviations in the last significant digit. b. Atoms are labeled in agreement with Figure S-1.

Table S-4. Bond Angles in Crystalline $[\text{C}_{20}\text{H}_{27}\text{N}_6\text{O}_4\text{S}][\text{HSO}_4]^\text{a}$

type ^b	angle, (deg)	type ^b	angle, (deg)
cation			
$\text{C}_8\text{S}_1\text{C}_7$	88.9(2)	$\text{O}_1\text{C}_6\text{C}_5$	121.6(3)
$\text{C}_7\text{N}_4\text{C}_9$	109.6(3)	$\text{O}_1\text{C}_6\text{C}_7$	117.9(3)
$\text{N}_1\text{C}_1\text{N}_2$	120.5(4)	$\text{C}_7\text{C}_6\text{C}_5$	120.5(3)
$\text{N}_3\text{C}_1\text{N}_1$	119.3(4)	$\text{N}_4\text{C}_7\text{S}_1$	116.7(3)
$\text{N}_3\text{C}_1\text{N}_2$	120.1(4)	$\text{C}_6\text{C}_7\text{S}_1$	116.6(3)
$\text{C}_1\text{N}_2\text{C}_2$	123.1(3)	$\text{N}_4\text{C}_7\text{C}_6$	126.7(3)
$\text{C}_1\text{N}_1\text{H}_{1\text{N}1}$	119(3)	$\text{C}_{13}\text{C}_8\text{S}_1$	128.2(4)
$\text{C}_1\text{N}_1\text{H}_{1\text{N}2}$	121(4)	$\text{C}_{13}\text{C}_8\text{C}_9$	121.8(4)
$\text{H}_{1\text{N}1}\text{N}_1\text{H}_{1\text{N}2}$	119(5)	$\text{N}_4\text{C}_9\text{C}_8$	114.9(3)
$\text{C}_1\text{N}_2\text{H}_2\text{N}$	121(3)	$\text{C}_{10}\text{C}_9\text{N}_4$	124.6(4)
$\text{C}_2\text{N}_2\text{H}_2\text{N}$	114(3)	$\text{C}_{10}\text{C}_9\text{C}_8$	120.6(4)
$\text{C}_1\text{N}_3\text{H}_{3\text{N}1}$	123(3)	$\text{C}_{11}\text{C}_{10}\text{C}_9$	117.5(5)
$\text{C}_1\text{N}_3\text{H}_{3\text{N}2}$	125(3)	$\text{C}_{10}\text{C}_{11}\text{C}_{12}$	121.2(4)
$\text{H}_{3\text{N}2}\text{N}_3\text{H}_{3\text{N}1}$	112(4)	$\text{C}_{13}\text{C}_{12}\text{C}_{11}$	122.7(4)
$\text{C}_{17}\text{O}_3\text{H}_{3\text{O}}$	99(3)	$\text{C}_{12}\text{C}_{13}\text{C}_8$	116.3(4)
$\text{C}_{14}\text{N}_5\text{C}_5$	121.8(3)	$\text{O}_2\text{C}_{14}\text{N}_5$	123.8(3)
$\text{C}_5\text{N}_5\text{H}_{5\text{N}}$	124(2)	$\text{O}_2\text{C}_{14}\text{C}_{15}$	122.1(3)
$\text{C}_{14}\text{N}_5\text{H}_{5\text{N}}$	114(2)	$\text{N}_5\text{C}_{14}\text{C}_{15}$	114.0(3)
$\text{C}_{18}\text{N}_6\text{C}_{15}$	112.9(3)	$\text{O}_4\text{C}_{19}\text{N}_6$	119.1(3)
$\text{C}_{19}\text{N}_6\text{C}_{15}$	119.8(3)	$\text{O}_4\text{C}_{19}\text{C}_{20}$	122.7(3)
$\text{C}_{19}\text{N}_6\text{C}_{18}$	127.2(3)	$\text{N}_6\text{C}_{19}\text{C}_{20}$	118.2(3)
$\text{N}_2\text{C}_2\text{C}_3$	111.5(3)	$\text{N}_6\text{C}_{15}\text{C}_{14}$	111.4(3)
$\text{C}_2\text{C}_3\text{C}_4$	109.5(3)	$\text{N}_6\text{C}_{15}\text{C}_{16}$	102.5(3)
$\text{C}_5\text{C}_4\text{C}_3$	113.3(3)	$\text{C}_{14}\text{C}_{15}\text{C}_{16}$	110.6(3)
$\text{N}_5\text{C}_5\text{C}_4$	112.7(3)	$\text{C}_{17}\text{C}_{16}\text{C}_{15}$	105.4(3)
$\text{N}_5\text{C}_5\text{C}_6$	110.5(3)	$\text{O}_3\text{C}_{17}\text{C}_{16}$	112.4(3)
$\text{C}_6\text{C}_5\text{C}_4$	110.5(3)	$\text{O}_3\text{C}_{17}\text{C}_{18}$	111.2(3)
$\text{C}_9\text{C}_8\text{S}_1$	109.9(3)	$\text{C}_{18}\text{C}_{17}\text{C}_{16}$	103.9(3)
		$\text{N}_6\text{C}_{18}\text{C}_{17}$	103.0(3)
anion			
$\text{O}_6\text{S}_2\text{O}_5$	103.2(2)	$\text{O}_8\text{S}_2\text{O}_6$	111.2(3)
$\text{O}_7\text{S}_2\text{O}_5$	109.0(3)	$\text{O}_7\text{S}_2\text{O}_8$	114.1(3)
$\text{O}_8\text{S}_2\text{O}_5$	110.7(2)		
$\text{O}_7\text{S}_2\text{O}_6$	108.0(4)	$\text{S}_2\text{O}_5\text{H}_{5\text{O}}$	115(4)

a. The numbers in parentheses are the estimated standard deviations in the last significant digit. b. Atoms are labeled in agreement with Figure S-1.