Supporting Information

Discovery of Potent & Selective Inhibitors of Activated Thrombin-Activatable Fibrinolysis Inhibitor for the Treatment of Thrombosis

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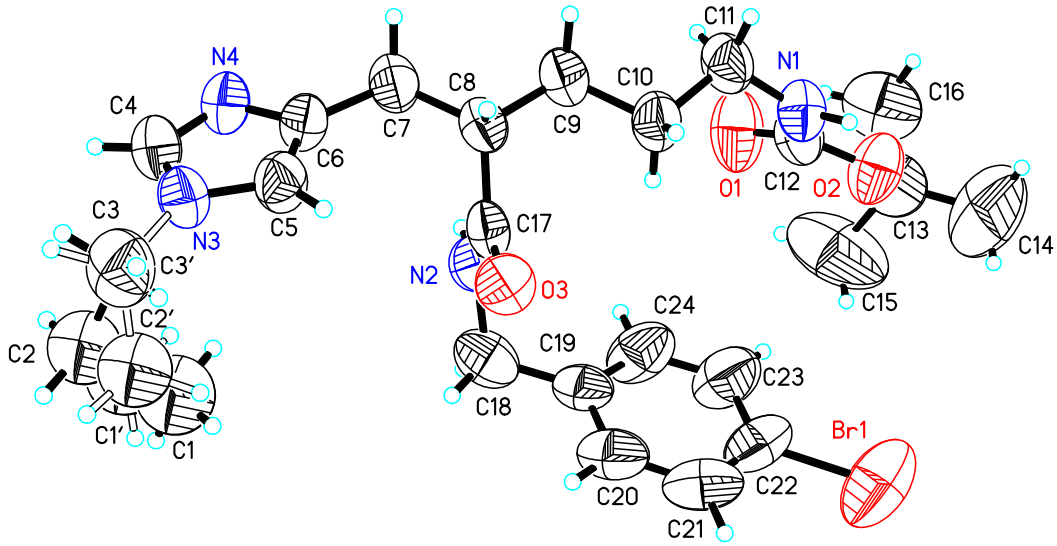
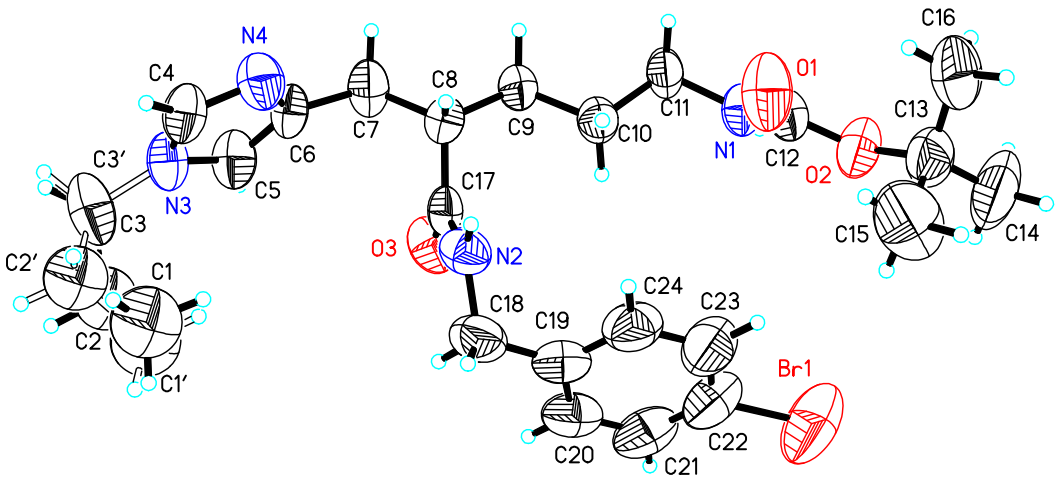
Supporting Information Contents

Figure 6. Crystal structure of Compound **49.** ORTEP plots for the two molecules in the asymmetric unit with thermal ellipsoids drawn at the 50% confidence level.



Molecule 1



Molecule 2

Table 3. Crystal data and structure refinement for crystal structure of Compound **49**

Empirical formula	C24 H35 Br N4 O3	
Formula weight	507.47	
Temperature	295(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 9.4155(6) Å	α= 64.7877(10)°.
	b = 12.2953(8) Å	β= 88.0003(12)°.
	c = 13.3143(9) Å	γ = 74.4274(11)°.
Volume	1337.73(15) $Å^3$	
Z	2	
Density (calculated)	1.260 Mg/m^3	
Absorption coefficient	1.566 mm^{-1}	
F(000)	532	
Crystal size	0.35 x 0.35 x 0.10 mm^3	
Theta range for data collection	3.58 to 24.99°.	
Index ranges	-11<=h<=11, -14<=k<=14, -15<=l<=15	
Reflections collected	9597	
Independent reflections	8428 [R(int) = 0.0118]	
Completeness to theta = 24.99°	98.9 %	
Absorption correction	Multiscans	
Max. and min. transmission	1.000 and 0.794	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8428 / 15 / 568	
Goodness-of-fit on F^2	0.857	
Final R indices [I>2sigma(I)]	R1 = 0.0460, wR2 = 0.1104	
R indices (all data)	R1 = 0.0724, wR2 = 0.1195	
Absolute structure parameter	-0.016(7)	
Largest diff. peak and hole	0.355 and -0.359 $e.Å^{-3}$	

Table 4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for crystal structure of Compound **49** . U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Molecule 1				
Br1	9975(1)	1775(1)	7573(1)	145(1)
O1	4223(5)	5898(4)	6712(3)	114(1)
O2	4518(4)	3838(3)	7217(3)	93(1)
O3	8659(3)	7467(3)	3126(2)	72(1)
N1	4334(4)	5140(3)	5455(3)	70(1)
N2	7923(4)	8154(3)	4409(3)	69(1)
C1	11279(15)	10689(13)	2427(9)	135(2)
C2	10990(13)	11890(11)	1308(9)	111(2)
C3	9882(6)	11778(6)	567(4)	103(2)
C1'	11078(16)	11476(16)	2380(10)	135(2)
C2'	11211(11)	11118(12)	1432(9)	111(2)
C3'	9882(6)	11778(6)	567(4)	103(2)
C4	7574(6)	12476(5)	1390(4)	68(1)
N3	8471(4)	11653(4)	1087(3)	68(1)
C5	7941(5)	10632(5)	1463(4)	69(1)
C6	6701(5)	10910(4)	1976(3)	62(1)
N4	6494(4)	12071(3)	1924(3)	67(1)
C7	5669(5)	10162(4)	2541(4)	77(1)
C8	6157(5)	8774(4)	2813(4)	59(1)
C9	4953(5)	8187(4)	3430(4)	74(1)
C10	5344(5)	6792(4)	4033(4)	72(1)
C11	4012(5)	6341(5)	4516(4)	75(1)
C12	4340(5)	5039(5)	6474(4)	71(1)
C13	4291(7)	3474(7)	8398(5)	105(2)
C14	4480(11)	2055(8)	8820(7)	188(4)
C15	5441(10)	3756(12)	8923(7)	201(5)
C16	2744(8)	4179(8)	8515(6)	138(3)
C17	7671(5)	8089(4)	3456(4)	60(1)
C18	9321(6)	7434(5)	5112(4)	87(2)
C19	9457(5)	6053(5)	5693(4)	70(1)
C20	10570(6)	5222(6)	5494(5)	87(2)
C21	10745(6)	3944(7)	6044(5)	94(2)
C22	9758(7)	3524(5)	6784(5)	90(2)
C23	8629(6)	4345(6)	6984(5)	108(2)
C24	8517(6)	5597(6)	6457(5)	99(2)
Molecule 2				
Br1	3185(1)	9183(1)	81(1)	157(1)
O1	8782(5)	4805(4)	1143(3)	98(1)
O2	8382(4)	6881(3)	612(3)	84(1)
O3	3993(3)	3281(3)	4817(3)	77(1)
N1	8331(4)	5655(3)	2372(3)	62(1)
N2	4324(4)	2895(3)	3303(3)	65(1)
C1	1432(15)	-410(15)	5283(8)	135(2)
C2	1378(11)	-710(13)	6469(8)	111(2)
C3	2773(6)	-1498(5)	7230(5)	103(2)
C1'	970(15)	-43(11)	5633(11)	135(2)
C2'	1681(13)	-1405(10)	6392(9)	111(2)
C3'	2773(6)	-1498(5)	7230(5)	103(2)

C4	5056(6)	-1491(4)	6210(4)	72(1)
N3	4047(4)	-1025(4)	6757(3)	67(1)
C5	4373(6)	-1(4)	6732(4)	75(1)
C6	5590(5)	102(4)	6176(3)	59(1)
N4	6012(4)	-834(4)	5832(3)	72(1)
C7	6428(5)	1042(4)	5961(3)	75(1)
C8	6361(5)	1988(4)	4742(3)	55(1)
C9	7348(5)	2841(4)	4629(4)	65(1)
C10	7276(5)	3884(4)	3480(3)	60(1)
C11	8513(5)	4488(4)	3358(4)	64(1)
C12	8517(5)	5697(5)	1351(4)	65(1)
C13	8640(6)	7233(6)	-563(4)	88(2)
C14	8475(9)	8617(7)	-1021(6)	144(3)
C15	7480(9)	6984(10)	-1123(5)	162(4)
C16	10178(7)	6543(7)	-645(5)	115(2)
C17	4783(5)	2767(4)	4305(4)	56(1)
C18	2919(5)	3739(5)	2743(4)	83(1)
C19	2947(5)	5064(5)	2089(4)	76(1)
C20	1933(5)	6073(6)	2216(5)	83(2)
C21	2006(7)	7271(6)	1614(5)	97(2)
C22	3061(7)	7525(5)	897(5)	99(2)
C23	4102(7)	6576(6)	765(5)	104(2)
C24	4031(6)	5362(6)	1378(5)	89(2)

Table 5. Bond lengths [Å] and angles [°] for crystal structure of Compound **49**

Molecule 1

Br1-C22	1.905(6)	O1-C12	1.203(5)
O2-C12	1.350(6)	O2-C13	1.466(6)
O3-C17	1.232(5)	N1-C12	1.309(6)
N1-C11	1.431(6)	N1-H1	0.8600
N2-C17	1.339(5)	N2-C18	1.465(6)
N2-H2	0.8600	C1-C2	1.553(9)
C1-H1A	0.9600	C1-H1B	0.9600
C1-H1C	0.9600	C2-C3	1.532(9)
C2-H2A	0.9700	C2-H2B	0.9700
C3-N3	1.491(6)	C3-H3A	0.9700
C3-H3B	0.9700	C1'-C2'	1.495(9)
C1'-H1'1	0.9600	C1'-H1'2	0.9600
C1'-H1'3	0.9600	C2'-H2'1	0.9700
C2'-H2'2	0.9700	C4-N4	1.306(5)
C4-N3	1.328(6)	C4-H4	0.9300
N3-C5	1.364(6)	C5-C6	1.369(6)
C5-H5	0.9300	C6-N4	1.359(5)
C6-C7	1.482(6)	C7-C8	1.524(6)
C7-H7A	0.9700	C7-H7B	0.9700
C8-C17	1.517(6)	C8-C9	1.533(6)
C8-H8	0.9800	C9-C10	1.494(6)
C9-H9A	0.9700	C9-H9B	0.9700
C10-C11	1.519(6)	C10-H10A	0.9700
C10-H10B	0.9700	C11-H11A	0.9700
C11-H11B	0.9700	C13-C15	1.497(9)
C13-C16	1.522(9)	C13-C14	1.548(10)
C14-H14A	0.9600	C14-H14B	0.9600
C14-H14C	0.9600	C15-H15A	0.9600
C15-H15B	0.9600	C15-H15C	0.9600
C16-H16A	0.9600	C16-H16B	0.9600
C16-H16C	0.9600	C18-C19	1.506(7)
C18-H18A	0.9700	C18-H18B	0.9700
C19-C20	1.359(8)	C19-C24	1.361(7)
C20-C21	1.387(8)	C20-H20	0.9300
C21-C22	1.363(8)	C21-H21	0.9300
C22-C23	1.361(8)	C23-C24	1.367(8)
C23-H23	0.9300	C24-H24	0.9300

Molecule 2

Br1-C22	1.893(6)	O1-C12	1.204(5)
O2-C12	1.339(5)	O2-C13	1.466(6)
O3-C17	1.223(5)	N1-C12	1.344(5)
N1-C11	1.447(5)	N1-H1	0.8600
N2-C17	1.348(5)	N2-C18	1.433(6)
N2-H2	0.8600	C1-C2	1.463(9)
C1-H1A	0.9600	C1-H1B	0.9600
C1-H1C	0.9600	C2-C3	1.504(9)
C2-H2A	0.9700	C2-H2B	0.9700
C3-N3	1.478(6)	C3-H3A	0.9700
C3-H3B	0.9700	C1'-C2'	1.509(9)
C1'-H1'1	0.9600	C1'-H1'2	0.9600
C1'-H1'3	0.9600	C2'-H2'1	0.9700
C2'-H2'2	0.9700	C4-N4	1.315(5)
C4-N3	1.332(6)	C4-H4	0.9300
N3-C5	1.360(6)	C5-C6	1.347(6)

C5-H5	0.9300	C6-N4	1.373(6)
C6-C7	1.494(6)	C7-C8	1.533(5)
C7-H7A	0.9700	C7-H7B	0.9700
C8-C17	1.512(6)	C8-C9	1.538(5)
C8-H8	0.9800	C9-C10	1.509(5)
C9-H9A	0.9700	C9-H9B	0.9700
C10-C11	1.511(5)	C10-H10A	0.9700
C10-H10B	0.9700	C11-H11A	0.9700
C11-H11B	0.9700	C13-C16	1.496(8)
C13-C14	1.507(9)	C13-C15	1.507(8)
C14-H14A	0.9600	C14-H14B	0.9600
C14-H14C	0.9600	C15-H15A	0.9600
C15-H15B	0.9600	C15-H15C	0.9600
C16-H16A	0.9600	C16-H16B	0.9600
C16-H16C	0.9600	C18-C19	1.492(7)
C18-H18A	0.9700	C18-H18B	0.9700
C19-C24	1.382(7)	C19-C20	1.418(7)
C20-C21	1.365(8)	C20-H20	0.9300
C21-C22	1.356(8)	C21-H21	0.9300
C22-C23	1.379(8)	C23-C24	1.382(8)
C23-H23	0.9300	C24-H24	0.9300

Molecule 1

C12-O2-C13	122.7(4)	C12-N1-C11	121.0(4)
C12-N1-H1	119.5	C11-N1-H1	119.5
C17-N2-C18	121.4(4)	C17-N2-H2	119.3
C18-N2-H2	119.3	C2-C1-H1A	109.5
C2-C1-H1B	109.5	H1A-C1-H1B	109.5
C2-C1-H1C	109.5	H1A-C1-H1C	109.5
H1B-C1-H1C	109.5	C3-C2-C1	106.5(7)
C3-C2-H2A	110.4	C1-C2-H2A	110.4
C3-C2-H2B	110.4	C1-C2-H2B	110.4
H2A-C2-H2B	108.6	N3-C3-C2	112.1(6)
N3-C3-H3A	109.2	C2-C3-H3A	109.2
N3-C3-H3B	109.2	C2-C3-H3B	109.2
H3A-C3-H3B	107.9	C2'-C1'-H1'1	109.5
C2'-C1'-H1'2	109.5	H1'1-C1'-H1'2	109.5
C2'-C1'-H1'3	109.5	H1'1-C1'-H1'3	109.5
H1'2-C1'-H1'3	109.5	C1'-C2'-H2'1	108.6
C1'-C2'-H2'2	108.6	H2'1-C2'-H2'2	107.6
N4-C4-N3	112.5(4)	N4-C4-H4	123.7
N3-C4-H4	123.7	C4-N3-C5	106.6(4)
C4-N3-C3	125.6(4)	C5-N3-C3	127.3(4)
N3-C5-C6	106.1(4)	N3-C5-H5	126.9
C6-C5-H5	126.9	N4-C6-C5	109.0(4)
N4-C6-C7	120.4(4)	C5-C6-C7	130.6(4)
C4-N4-C6	105.7(4)	C6-C7-C8	117.4(4)
C6-C7-H7A	108.0	C8-C7-H7A	108.0
C6-C7-H7B	108.0	C8-C7-H7B	108.0
H7A-C7-H7B	107.2	C17-C8-C7	113.6(3)
C17-C8-C9	112.2(4)	C7-C8-C9	108.2(3)
C17-C8-H8	107.5	C7-C8-H8	107.5
C9-C8-H8	107.5	C10-C9-C8	117.6(4)
C10-C9-H9A	107.9	C8-C9-H9A	107.9
C10-C9-H9B	107.9	C8-C9-H9B	107.9
H9A-C9-H9B	107.2	C9-C10-C11	111.7(4)
C9-C10-H10A	109.3	C11-C10-H10A	109.3
C9-C10-H10B	109.3	C11-C10-H10B	109.3

H10A-C10-H10B	107.9	N1-C11-C10	115.8(4)
N1-C11-H11A	108.3	C10-C11-H11A	108.3
N1-C11-H11B	108.3	C10-C11-H11B	108.3
H11A-C11-H11B	107.4	O1-C12-N1	124.5(5)
O1-C12-O2	124.9(5)	N1-C12-O2	110.6(4)
O2-C13-C15	109.0(5)	O2-C13-C16	110.0(5)
C15-C13-C16	110.6(7)	O2-C13-C14	101.0(5)
C15-C13-C14	113.4(7)	C16-C13-C14	112.4(6)
C13-C14-H14A	109.5	C13-C14-H14B	109.5
H14A-C14-H14B	109.5	C13-C14-H14C	109.5
H14A-C14-H14C	109.5	H14B-C14-H14C	109.5
C13-C15-H15A	109.5	C13-C15-H15B	109.5
H15A-C15-H15B	109.5	C13-C15-H15C	109.5
H15A-C15-H15C	109.5	H15B-C15-H15C	109.5
C13-C16-H16A	109.5	C13-C16-H16B	109.5
H16A-C16-H16B	109.5	C13-C16-H16C	109.5
H16A-C16-H16C	109.5	H16B-C16-H16C	109.5
O3-C17-N2	119.7(4)	O3-C17-C8	121.5(4)
N2-C17-C8	118.8(4)	N2-C18-C19	112.3(4)
N2-C18-H18A	109.1	C19-C18-H18A	109.1
N2-C18-H18B	109.1	C19-C18-H18B	109.1
H18A-C18-H18B	107.9	C20-C19-C24	118.2(5)
C20-C19-C18	120.3(5)	C24-C19-C18	121.5(5)
C19-C20-C21	121.3(5)	C19-C20-H20	119.3
C21-C20-H20	119.3	C22-C21-C20	118.8(5)
C22-C21-H21	120.6	C20-C21-H21	120.6
C23-C22-C21	120.6(6)	C23-C22-Br1	119.3(5)
C21-C22-Br1	120.1(5)	C22-C23-C24	119.2(6)
C22-C23-H23	120.4	C24-C23-H23	120.4
C19-C24-C23	121.8(5)	C19-C24-H24	119.1
C23-C24-H24	119.1		

Molecule 2

C12-O2-C13	123.0(4)	C12-N1-C11	122.1(4)
C12-N1-H1	118.9	C11-N1-H1	118.9
C17-N2-C18	120.7(4)	C17-N2-H2	119.6
C18-N2-H2	119.6	C2-C1-H1A	109.5
C2-C1-H1B	109.5	H1A-C1-H1B	109.5
C2-C1-H1C	109.5	H1A-C1-H1C	109.5
H1B-C1-H1C	109.5	C1-C2-C3	118.0(8)
C1-C2-H2A	107.8	C3-C2-H2A	107.8
C1-C2-H2B	107.8	C3-C2-H2B	107.8
H2A-C2-H2B	107.1	N3-C3-C2	110.8(6)
N3-C3-H3A	109.5	C2-C3-H3A	109.5
N3-C3-H3B	109.5	C2-C3-H3B	109.5
H3A-C3-H3B	108.1	C2'-C1'-H1'1	109.5
C2'-C1'-H1'2	109.5	H1'1-C1'-H1'2	109.5
C2'-C1'-H1'3	109.5	H1'1-C1'-H1'3	109.5
H1'2-C1'-H1'3	109.5	C1'-C2'-H2'1	109.8
C1'-C2'-H2'2	109.8	H2'1-C2'-H2'2	108.3
N4-C4-N3	112.1(4)	N4-C4-H4	124.0
N3-C4-H4	124.0	C4-N3-C5	106.8(4)
C4-N3-C3	125.7(4)	C5-N3-C3	127.4(4)
C6-C5-N3	106.7(4)	C6-C5-H5	126.6
N3-C5-H5	126.6	C5-C6-N4	109.5(4)
C5-C6-C7	127.8(4)	N4-C6-C7	122.7(4)
C4-N4-C6	104.9(4)	C6-C7-C8	115.9(3)
C6-C7-H7A	108.3	C8-C7-H7A	108.3
C6-C7-H7B	108.3	C8-C7-H7B	108.3

H7A-C7-H7B	107.4	C17-C8-C7	110.4(3)
C17-C8-C9	110.1(3)	C7-C8-C9	110.5(3)
C17-C8-H8	108.6	C7-C8-H8	108.6
C9-C8-H8	108.6	C10-C9-C8	115.5(3)
C10-C9-H9A	108.4	C8-C9-H9A	108.4
C10-C9-H9B	108.4	C8-C9-H9B	108.4
H9A-C9-H9B	107.5	C9-C10-C11	112.5(3)
C9-C10-H10A	109.1	C11-C10-H10A	109.1
C9-C10-H10B	109.1	C11-C10-H10B	109.1
H10A-C10-H10B	107.8	N1-C11-C10	115.1(4)
N1-C11-H11A	108.5	C10-C11-H11A	108.5
N1-C11-H11B	108.5	C10-C11-H11B	108.5
H11A-C11-H11B	107.5	O1-C12-O2	125.6(4)
O1-C12-N1	125.1(4)	O2-C12-N1	109.2(4)
O2-C13-C16	109.5(4)	O2-C13-C14	103.1(5)
C16-C13-C14	110.7(5)	O2-C13-C15	109.6(4)
C16-C13-C15	112.4(6)	C14-C13-C15	111.1(6)
C13-C14-H14A	109.5	C13-C14-H14B	109.5
H14A-C14-H14B	109.5	C13-C14-H14C	109.5
H14A-C14-H14C	109.5	H14B-C14-H14C	109.5
C13-C15-H15A	109.5	C13-C15-H15B	109.5
H15A-C15-H15B	109.5	C13-C15-H15C	109.5
H15A-C15-H15C	109.5	H15B-C15-H15C	109.5
C13-C16-H16A	109.5	C13-C16-H16B	109.5
H16A-C16-H16B	109.5	C13-C16-H16C	109.5
H16A-C16-H16C	109.5	H16B-C16-H16C	109.5
O3-C17-N2	122.3(4)	O3-C17-C8	121.7(4)
N2-C17-C8	115.9(4)	N2-C18-C19	114.0(4)
N2-C18-H18A	108.8	C19-C18-H18A	108.8
N2-C18-H18B	108.8	C19-C18-H18B	108.8
H18A-C18-H18B	107.6	C24-C19-C20	116.4(5)
C24-C19-C18	121.3(5)	C20-C19-C18	122.2(5)
C21-C20-C19	120.4(5)	C21-C20-H20	119.8
C19-C20-H20	119.8	C22-C21-C20	121.1(5)
C22-C21-H21	119.4	C20-C21-H21	119.4
C21-C22-C23	120.9(6)	C21-C22-Br1	121.2(5)
C23-C22-Br1	117.9(5)	C22-C23-C24	118.0(6)
C22-C23-H23	121.0	C24-C23-H23	121.0
C19-C24-C23	123.1(5)	C19-C24-H24	118.5
C23-C24-H24	118.5		

Table 6. Anisotropic displacement parameters ($Å^2$ x 10^3) for crystal structure of Compound **49**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Molecule 1						
Br1	212(1)	87(1)	103(1)	-29(1)	-6(1)	-6(1)
O1	176(4)	93(3)	111(3)	-67(2)	30(3)	-62(3)
O2	138(3)	70(2)	60(2)	-19(2)	15(2)	-31(2)
O3	72(2)	75(2)	82(2)	-47(2)	19(2)	-20(2)
N1	90(3)	63(2)	64(2)	-27(2)	14(2)	-33(2)
N2	76(3)	67(2)	75(2)	-40(2)	2(2)	-21(2)
C3	108(4)	109(4)	86(4)	-34(3)	36(3)	-40(4)
C3'	108(4)	109(4)	86(4)	-34(3)	36(3)	-40(4)
C4	86(3)	65(3)	66(3)	-33(3)	17(3)	-35(3)
N3	71(3)	69(3)	68(2)	-26(2)	19(2)	-32(2)
C5	73(3)	56(3)	87(3)	-38(3)	15(3)	-20(2)
C6	71(3)	50(3)	62(3)	-20(2)	12(2)	-20(2)
N4	84(3)	55(2)	68(2)	-28(2)	15(2)	-26(2)
C7	68(3)	62(3)	102(3)	-32(3)	15(3)	-27(2)
C8	64(3)	63(3)	61(3)	-29(2)	8(2)	-29(2)
C9	76(3)	67(3)	85(3)	-31(3)	4(3)	-34(3)
C10	73(3)	61(3)	84(3)	-30(2)	21(2)	-27(2)
C11	79(3)	78(3)	67(3)	-20(3)	16(2)	-40(3)
C12	81(3)	75(4)	72(3)	-40(3)	15(3)	-33(3)
C13	115(5)	125(6)	71(4)	-32(4)	14(4)	-44(4)
C14	248(10)	116(7)	117(6)	21(5)	27(6)	-45(7)
C15	166(8)	335(16)	92(5)	-50(7)	-7(5)	-124(10)
C16	121(5)	183(8)	112(5)	-66(5)	32(4)	-48(5)
C17	70(3)	54(3)	71(3)	-32(2)	19(2)	-32(2)
C18	79(4)	114(5)	88(4)	-57(3)	2(3)	-37(3)
C19	54(3)	85(4)	65(3)	-29(3)	-8(2)	-13(3)
C20	61(3)	109(5)	75(3)	-31(3)	-3(3)	-12(3)
C21	64(3)	125(6)	78(4)	-46(4)	1(3)	3(3)
C22	97(4)	74(4)	75(4)	-30(3)	-16(3)	11(3)
C23	94(4)	87(5)	102(4)	-18(4)	26(3)	-4(4)
C24	92(4)	84(4)	95(4)	-34(3)	28(3)	3(3)
Molecule 2						
Br1	224(1)	80(1)	118(1)	-13(1)	18(1)	-18(1)
O1	154(3)	84(2)	90(2)	-54(2)	45(2)	-66(2)
O2	111(2)	64(2)	64(2)	-15(2)	19(2)	-27(2)
O3	82(2)	82(2)	94(2)	-58(2)	37(2)	-35(2)
N1	79(2)	54(2)	61(2)	-27(2)	18(2)	-29(2)
N2	58(2)	67(2)	82(3)	-41(2)	5(2)	-19(2)
C3	118(5)	116(5)	108(4)	-58(4)	55(4)	-75(4)
C3'	118(5)	116(5)	108(4)	-58(4)	55(4)	-75(4)
C4	97(4)	54(3)	72(3)	-28(3)	14(3)	-32(3)
N3	90(3)	63(2)	64(2)	-33(2)	21(2)	-41(2)
C5	98(4)	70(3)	69(3)	-34(2)	24(3)	-37(3)
C6	85(3)	52(3)	43(2)	-17(2)	13(2)	-32(2)
N4	81(2)	76(3)	71(2)	-35(2)	23(2)	-33(2)
C7	95(3)	72(3)	63(3)	-22(2)	13(2)	-45(3)
C8	66(3)	49(2)	48(2)	-17(2)	7(2)	-20(2)
C9	61(3)	58(3)	68(3)	-14(2)	5(2)	-26(2)

C10	62(3)	59(3)	59(2)	-20(2)	7(2)	-25(2)
C11	72(3)	63(3)	58(3)	-16(2)	15(2)	-35(2)
C12	70(3)	63(3)	67(3)	-29(3)	17(2)	-31(2)
C13	98(4)	98(4)	58(3)	-18(3)	8(3)	-37(3)
C14	193(7)	94(5)	94(5)	7(4)	29(5)	-41(5)
C15	148(6)	279(12)	75(4)	-61(6)	0(4)	-110(7)
C16	131(5)	133(5)	76(4)	-35(4)	43(4)	-53(5)
C17	70(3)	46(2)	56(3)	-19(2)	12(2)	-31(2)
C18	61(3)	90(4)	100(4)	-43(3)	-6(3)	-23(3)
C19	60(3)	85(4)	78(3)	-37(3)	-11(3)	-6(3)
C20	62(3)	104(4)	80(3)	-47(3)	-1(2)	-4(3)
C21	103(4)	82(4)	84(4)	-38(3)	-13(3)	15(3)
C22	119(5)	75(4)	72(4)	-21(3)	-5(3)	3(4)
C23	106(4)	87(5)	85(4)	-19(4)	20(3)	-5(4)
C24	73(4)	81(4)	91(4)	-34(3)	4(3)	4(3)

Table 7. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for crystal structure of Compound **49**

	x	y	z	U(eq)
Molecule 1				
H1	4526	4475	5348	84
H2	7251	8629	4613	82
H1A	11937	10736	2932	203
H1B	11719	9968	2293	203
H1C	10358	10622	2746	203
H2A	10584	12630	1434	133
H2B	11905	11951	958	133
H3A	9670	12514	-144	123
H3B	10322	11053	426	123
H1'1	11953	11016	2890	203
H1'2	10228	11286	2758	203
H1'3	10969	12358	2099	203
H2'1	11361	10222	1730	133
H2'2	12084	11301	1065	133
H3'1	9831	12659	167	123
H3'2	10006	11424	32	123
H4	7700	13254	1239	82
H5	8340	9896	1386	83
H7A	4740	10538	2074	93
H7B	5470	10238	3232	93
H8	6208	8705	2105	71
H9A	4628	8522	3967	89
H9B	4112	8465	2893	89
H10A	6111	6500	4631	86
H10B	5737	6435	3522	86
H11A	3379	6954	4734	90
H11B	3454	6314	3932	90
H14A	5472	1648	8739	282
H14B	3791	1932	8391	282
H14C	4296	1704	9591	282
H15A	6407	3294	8852	301
H15B	5300	3519	9697	301
H15C	5352	4637	8554	301
H16A	2678	5051	8245	207
H16B	2552	3849	9286	207
H16C	2028	4080	8088	207
H18A	9387	7739	5667	104
H18B	10139	7565	4655	104
H20	11229	5517	4979	104
H21	11520	3383	5911	113
H23	7942	4058	7473	129
H24	7777	6151	6626	118
Molecule 2				
H1	8097	6345	2440	75
H2	4880	2466	2996	78
H1A	463	58	4901	203
H1B	1754	-1171	5194	203
H1C	2112	81	4974	203
H2A	618	-1137	6743	133

H2B	1060	73	6536	133
H3A	2644	-1485	7951	123
H3B	2966	-2358	7338	123
H1'1	231	21	5116	203
H1'2	1710	331	5230	203
H1'3	515	385	6070	203
H2'1	929	-1800	6769	133
H2'2	2177	-1835	5958	133
H3'1	2265	-1033	7633	123
H3'2	3142	-2369	7763	123
H4	5080	-2199	6108	86
H5	3856	525	7038	90
H7A	7458	595	6230	90
H7B	6052	1503	6397	90
H8	6726	1526	4296	66
H9A	7071	3209	5148	78
H9B	8366	2327	4848	78
H10A	6333	4516	3327	72
H10B	7327	3551	2932	72
H11A	8601	4639	4009	77
H11B	9434	3902	3351	77
H14A	9249	8749	-674	217
H14B	7530	9028	-868	217
H14C	8540	8955	-1812	217
H15A	7630	6097	-836	243
H15B	7558	7330	-1912	243
H15C	6515	7366	-977	243
H16A	10877	6756	-306	172
H16B	10344	6771	-1415	172
H16C	10299	5657	-267	172
H18A	2208	3709	3292	99
H18B	2580	3454	2243	99
H20	1214	5917	2714	100
H21	1322	7924	1696	116
H23	4830	6748	279	125
H24	4746	4715	1308	106

Table 8. Torsion angles [°] for crystal structure of Compound **49**

Molecule 1

C1-C2-C3-N3	58.8(11)	N4-C4-N3-C5	-0.6(5)
N4-C4-N3-C3	-173.6(4)	C2-C3-N3-C4	59.0(8)
C2-C3-N3-C5	-112.6(7)	C4-N3-C5-C6	0.8(5)
C3-N3-C5-C6	173.6(4)	N3-C5-C6-N4	-0.7(5)
N3-C5-C6-C7	-179.9(5)	N3-C4-N4-C6	0.2(5)
C5-C6-N4-C4	0.3(5)	C7-C6-N4-C4	179.6(4)
N4-C6-C7-C8	-165.7(4)	C5-C6-C7-C8	13.3(7)
C6-C7-C8-C17	52.5(6)	C6-C7-C8-C9	177.8(4)
C17-C8-C9-C10	-38.7(6)	C7-C8-C9-C10	-164.8(4)
C8-C9-C10-C11	-174.9(4)	C12-N1-C11-C10	94.3(5)
C9-C10-C11-N1	-155.3(4)	C11-N1-C12-O1	-7.3(7)
C11-N1-C12-O2	173.7(4)	C13-O2-C12-O1	12.8(8)
C13-O2-C12-N1	-168.2(4)	C12-O2-C13-C15	-65.7(8)
C12-O2-C13-C16	55.7(7)	C12-O2-C13-C14	174.6(5)
C18-N2-C17-O3	-4.1(6)	C18-N2-C17-C8	175.1(4)
C7-C8-C17-O3	-126.2(4)	C9-C8-C17-O3	110.7(4)
C7-C8-C17-N2	54.7(5)	C9-C8-C17-N2	-68.4(5)
C17-N2-C18-C19	-71.4(6)	N2-C18-C19-C20	118.5(5)
N2-C18-C19-C24	-64.1(6)	C24-C19-C20-C21	0.6(8)
C18-C19-C20-C21	178.0(5)	C19-C20-C21-C22	1.1(8)
C20-C21-C22-C23	-0.4(9)	C20-C21-C22-Br1	-179.1(4)
C21-C22-C23-C24	-1.8(9)	Br1-C22-C23-C24	176.8(5)
C20-C19-C24-C23	-2.9(9)	C18-C19-C24-C23	179.7(5)
C22-C23-C24-C19	3.5(10)		

Molecule 2

C1-C2-C3-N3	47.7(14)	N4-C4-N3-C5	-0.1(5)
N4-C4-N3-C3	176.4(4)	C2-C3-N3-C4	-99.5(7)
C2-C3-N3-C5	76.2(8)	C4-N3-C5-C6	-0.7(5)
C3-N3-C5-C6	-177.1(4)	N3-C5-C6-N4	1.3(5)
N3-C5-C6-C7	-177.3(4)	N3-C4-N4-C6	0.8(5)
C5-C6-N4-C4	-1.3(5)	C7-C6-N4-C4	177.4(4)
C5-C6-C7-C8	-112.5(5)	N4-C6-C7-C8	69.1(6)
C6-C7-C8-C17	61.7(5)	C6-C7-C8-C9	-176.3(4)
C17-C8-C9-C10	-52.9(5)	C7-C8-C9-C10	-175.1(4)
C8-C9-C10-C11	-166.5(4)	C12-N1-C11-C10	-73.7(5)
C9-C10-C11-N1	-167.2(4)	C13-O2-C12-O1	-4.0(7)
C13-O2-C12-N1	175.0(4)	C11-N1-C12-O1	3.3(7)
C11-N1-C12-O2	-175.7(4)	C12-O2-C13-C16	-57.9(6)
C12-O2-C13-C14	-175.7(5)	C12-O2-C13-C15	65.9(7)
C18-N2-C17-O3	5.6(6)	C18-N2-C17-C8	-172.1(4)
C7-C8-C17-O3	49.6(5)	C9-C8-C17-O3	-72.7(5)
C7-C8-C17-N2	-132.7(4)	C9-C8-C17-N2	105.0(4)
C17-N2-C18-C19	83.8(5)	N2-C18-C19-C24	47.4(7)
N2-C18-C19-C20	-128.3(5)	C24-C19-C20-C21	3.2(7)
C18-C19-C20-C21	179.1(5)	C19-C20-C21-C22	-1.2(8)
C20-C21-C22-C23	-0.7(10)	C20-C21-C22-Br1	-178.8(4)
C21-C22-C23-C24	0.5(10)	Br1-C22-C23-C24	178.7(4)
C20-C19-C24-C23	-3.5(8)	C18-C19-C24-C23	-179.5(5)
C22-C23-C24-C19	1.7(9)		

Table 9. Purity Data for Target Compounds

Target compounds were all highly polar and hydrophilic. Combustion analyses were thus obtained for selected compounds only and this routinely indicated a degree of hydration (see below). Purity of all other compounds was readily confirmed as >95% by analysis of ^{1}H NMR data.

Compound	Data
6	>95% purity by ^{1}H NMR
8	Anal. Found: C, 43.36; H, 7.51; N, 25.12. $C_8H_{14}N_4O_2 \cdot 1.3H_2O$ requires C, 43.35; H, 7.54; N, 25.28%.
9	Anal. Found: C, 45.63; H, 7.68; N, 23.15. $C_9H_{16}N_4O_2 \cdot 1.45H_2O$ requires C, 45.35; H, 7.99; N, 23.50%.
10	>95% purity by NMR
11	>95% purity by NMR
12	Anal. Found: C, 55.79; H, 8.65; N, 21.96. $C_{12}H_{22}N_4O_2 \cdot 0.22H_2O$ requires C, 55.80; H, 8.76; N, 21.69%.
13	Anal. Found: C, 54.21; H, 8.83; N, 19.32. $C_{13}H_{24}N_4O_2 \cdot 1.2H_2O$ requires C, 53.85; H, 9.18; N, 19.32%.
14	>95% purity by NMR
15	>95% purity by NMR
16	>95% purity by NMR
17	Anal. Found: C, 58.13; H, 7.51; N, 17.06. $C_{16}H_{22}N_4O_2 \cdot 1.6H_2O$ requires C, 58.02; H, 7.67; N, 16.92%.
18	Anal. Found: C, 53.74; H, 8.43; N, 19.30. $C_{13}H_{22}N_4O_2 \cdot 1.3H_2O$ requires C, 53.92; H, 8.50; N, 19.34%.
19	Anal. Found: C, 47.43; H, 7.81; N, 19.98. $C_{11}H_{20}N_4O_3 \cdot 1.3\ H_2O$ requires C, 47.23; H, 8.14; N, 20.03%.
20	>95% purity by NMR
21	Anal. Found: C, 58.90; H, 8.90; N, 17.17. $C_{12}H_{21}N_3O_2 \cdot 0.3H_2O$ requires C, 58.88; H, 8.92; N, 16.99%.

Table 10. Additional Analytical Data for Selected Intermediates

Compound	Data
24	TLC : ethyl acetate:methanol (95:5), Rf = 0.79.
25	Anal. Found: C, 37.94; H, 5.21; N, 10.83. $C_{16}H_{15}N_4O_5I \cdot 1.25H_2O$ requires C, 38.22; H, 5.51; N, 11.14%.
26	TLC : dichloromethane : methanol : 0.88 ammonia (90 : 10 :1), Rf = 0.26.
32	Anal. Found: C, 49.53; H, 5.77; N, 10.50. $C_{22}H_{29}N_4O_5Br \cdot 1.25H_2O$ requires C, 49.68; H, 5.97; N, 10.53%.
49	Anal. Found: C, 56.78; H, 6.76; N, 11.04. $C_{24}H_{35}BrN_4O_3$ requires C, 56.80; H, 6.95; N, 11.04%.

Additional Experimental Details for Compounds **6**, **10-20**, **26-35**, **38-44**

(±)-5-Amino-2-(1*H*-imidazol-4-ylmethyl)pentanoic acid (6). A mixture of **43** (150mg, 0.25mmol) in dioxane (2ml) and aqueous sodium hydroxide (2ml, 2N) was stirred at room temperature for 1.5 hours. Aqueous hydrochloric acid (6ml, 6N) was carefully added, and the reaction heated under reflux for 24 hours. The cooled mixture was purified by ion exchange column chromatography (DOWEX® 50WX8-200), using an elution gradient of deionised water : 0.88 ammonia (100:0 to 97:3). The product was triturated with methanol to give the title compound as a white solid, 28mg, 57% yield. ^{1}H-NMR (CD_3OD, 300MHz) δ: 1.44-1.75 (m, 4H), 2.48 (m, 1H), 2.62 (dd, 1H), 2.90 (m, 3H), 6.81 (s, 1H), 7.55 (s, 1H). HRMS : m/z 198.1242 (MH^+), calcd 198.1237.

(2*S*)-2-[(2-Aminoethyl)amino]-3-(1-ethyl-1*H*-imidazol-4-yl)propanoic acid (10). Prepared from the product of **26** according to Method B (using conc. HCl) and isolated in 47% yield: ^{1}H-NMR (CD_3OD, 300 MHz) δ: 1.40 (t, 3H), 2.75-3.02 (m, 6H), 3.33 (m, 1H), 3.98 (q, 2H), 6.95 (s, 1H), 7.53 (s, 1H). HRMS : m/z 227.1492 (MH^+), calcd 227.1503.

(2*S*)-2-[(2-Aminoethyl)amino]-3-(1-propyl-1*H*-imidazol-4-yl)propanoic acid (11). Prepared from the product of **27** according to Method B (using conc. H_2SO_4) and isolated in 55% yield: ^{1}H-NMR (CD_3OD, 300 MHz) δ: 0.90 (t, 3H), 1.78 (q, 2H), 2.77-3.01 (m, 6H), 3.31 (m, 1H), 3.90 (t, 2H), 6.90 (s, 1H), 7.52 (s, 1H). LRMS : m/z 241.1 (MH^+).

(2*S*)-2-[(2-Aminoethyl)amino]-3-(1-butyl-1*H*-imidazol-4-yl)propanoic acid (12). Prepared from the product of **28** according to Method B (using conc. H_2SO_4) and isolated in 82% yield: ^{1}H-NMR (CD_3OD, 300 MHz) δ: 0.70 (t, 3H), 1.05 (q, 2H), 1.57 (m, 2H), 2.57-2.73 (m, 4H), 2.85 (m, 2H), 3.08 (t, 1H), 3.78 (t, 2H), 6.78 (s, 1H), 7.42 (s, 1H). HRMS : m/z 255.1824 (MH^+), calcd 255.1816. Anal. ($C_{12}H_{22}N_4O_2 \cdot 0.22H_2O$) C, H, N.

(2*S*)-2-[(2-Aminoethyl)amino]-3-(1-pentyl-1*H*-imidazol-4-yl)propanoic acid (13). Prepared from the product of **29** according to Method B (using conc. H_2SO_4) and isolated in 38% yield: ^{1}H-NMR (CD_3OD, 300 MHz) δ: 0.90 (t, 3H), 1.20-1.40 (m, 4H), 1.77 (m, 2H), 2.78- 3.05 (m, 6H), 3.30 (m, 1H), 3.93 (t, 2H), 6.93 (s, 1H), 7.57 (s, 1H). HRMS : m/z 269.1978 (MH^+), calcd 269.1972. Anal. ($C_{13}H_{24}N_4O_2 \cdot 1.2H_2O$) C, H, N.

(2*S*)-2-[(2-Aminoethyl)amino]-3-(1-isopropyl-1*H*-imidazol-4-yl)propanoic acid (14). Prepared from the product of **30** according to Method B (using conc. H_2SO_4) and isolated in 96% yield: ^{1}H-NMR (CD_3OD, 300 MHz) δ: 1.45 (d, 6H), 2.72-3.03 (m, 6H), 3.33 (m, 1H), 4.33 (m, 1H), 7.00 (s, 1H), 7.58 (s, 1H). HRMS : m/z 241.1662 (MH^+), calcd 241.1659.

(2*S*)-2-[(2-Aminoethyl)amino]-3-(1-isobutyl-1*H*-imidazol-4-yl)propanoic acid (15). Prepared from the product of **31** according to Method B (using conc. H_2SO_4) and isolated in 54% yield: ^{1}H-NMR (CD_3OD, 300 MHz) δ: 0.90 (d, 6H), 2.01 (m, 1H), 2.77-3.03 (m, 6H), 3.33 (m, 1H), 3.77 (d, 2H), 6.90 (s, 1H), 7.50 (s, 1H). HRMS : m/z 255.1825 (MH^+), calcd 255.1816.

(2*S*)-2-[(2-Aminoethyl)amino]-3-(1-benzyl-1*H*-imidazol-4-yl)propanoic acid (16). Prepared from the product of **32** according to Method B (using conc. H_2SO_4) and isolated in 43% yield: ^{1}H-NMR (D_2O, 400 MHz) δ: 2.30-2.68 (m, 6H), 3.14 (m, 1H), 5.00 (s, 2H), 6.73 (s, 1H), 7.11 (m, 2H), 7.16-7.30 (m, 3H), 7.50 (s, 1H). LRMS : m/z 289.2 (MH^+).

(2*S*)-2-[(2-Aminoethyl)amino]-3-[1-(2-phenylethyl)-1*H*-imidazol-4-yl]propanoic acid (17). Prepared from the product of **33** according to Method B (using conc. H_2SO_4) and isolated in 42% yield: ^{1}H-NMR (CD_3OD, 400MHz) δ: 2.61-3.13 (m, 8H), 3.31 (m, 1H), 4.16 (t, 2H), 6.90 (s, 1H), 7.11 (m, 2H), 7.13-7.40 (m, 4H). HRMS : m/z 303.1823 (MH^+), calcd 303.1816. Anal. ($C_{16}H_{22}N_4O_2 \cdot 1.6H_2O$) C, H, N.

(2*S*)-2-[(2-Aminoethyl)amino]-3-[1-(cyclobutylmethyl)-1*H*-imidazol-4-yl]propanoic acid (18). Prepared from product of **34** according to Method B (using conc. H_2SO_4) and isolated in 53% yield: ^{1}H-NMR (CD_3OD, 300 MHz) δ: 1.70-2.10 (m, 6H), 2.60-3.10 (m, 7H), 3.35 (m, 1H), 3.95 (d, 2H), 6.90 (s, 1H), 7.50 (s, 1H). HRMS : m/z 267.1822 (MH^+), calcd 267.1816. Anal. ($C_{13}H_{22}N_4O_2 \cdot 1.3H_2O$) C, H, N.

(2*S*)-2-[(2-Aminoethyl)amino]-3-[1-(3-hydroxypropyl)-1*H*-imidazol-4-yl]propanoic acid (19). Prepared from product of **35** according to Method B (using conc. H_2SO_4) and isolated in 55% yield: ^{1}H-NMR (D_2O, 300 MHz) δ: 1.90 (m, 2H), 2.64-2.82 (m, 4H), 2.97 (m, 2H), 3.28 (t, 1H), 3.44 (t, 2H), 3.98 (t, 2H), 6.88 (s, 1H), 7.57 (s, 1H). HRMS : m/z 257.1618 (MH^+), calcd 257.1608. Anal. ($C_{11}H_{20}N_4O_3 \cdot 1.3\ H_2O$) C, H, N.

(±)-5-Amino-2-[(1-*n*-propyl-1*H*-imidazol-4-yl)methyl]pentanoic acid (20). A mixture of **44** (85mg, 0.17mmol) in dioxane (1ml) and aqueous sodium hydroxide (1ml, 2N) was stirred at room temperature for 72 hours. TLC analysis showed starting material remaining, so the reaction was heated at 70°C for 3 hours. Aqueous hydrochloric acid (2ml, 6N) was added to the cooled solution and the reaction stirred at room temperature for 18 hours. TLC analysis showed starting material remaining, so the reaction was stirred at 70°C for a further 2 hours. The cooled mixture was extracted with hexane, and the remaining aqueous solution was purified by ion exchange column chromatography (DOWEX® 50WX8-200) eluting with a solvent gradient of deionised water : 0.88 ammonia (100:0 to 97:3). The product was dissolved in a minimum volume of deionised water, and freeze-dried to give the title compound as a gum, 18mg, 43% yield. ^{1}H-NMR (CD_3OD, 300MHz) δ: 0.92 (t, 3H), 1.45-1.70 (m, 4H), 1.79 (m, 2H), 2.43-2.60 (m, 2H), 2.76-2.95 (m, 3H), 3.90 (t, 2H), 6.86 (s, 1H), 7.45 (s, 1H). HRMS : m/z 240.1713 (MH^+), calcd 240.1706.

(*7S*)-*6*-{2-[(*tert*-Butoxycarbonyl)amino]ethyl}-2-ethyl-7-(methoxycarbonyl)-5-oxo-5,6,7,8-tetrahydroimidazo[1,5-*c*]pyrimidin-2-ium iodide (26). Prepared according to Method A using ethyl iodide (2 eq.) and isolated in 40% yield: ^{1}H-NMR (D_2O, 300 MHz) δ: 1.27 (s, 9H), 1.42 (t, 3H), 3.22-3.47 (m, 4H), 3.58 (m, 1H), 3.65 (s, 3H), 3.95 (m, 1H), 4.20 (q, 2H), 4.75 (m, 1H), 7.40 (s, 1H). LRMS : 366.9 (M^+).

(7*S*)-6-{2-[(*tert*-Butoxycarbonyl)amino]ethyl}-7-(methoxycarbonyl)-5-oxo-2-propyl-5,6,7,8-tetrahydroimidazo[1,5-*c*]pyrimidin-2-ium bromide (27). Prepared according to Method A using *n*-propyl bromide (3 eq.) and isolated in 44% yield: ^{1}H-NMR (D_2O, 400 MHz) δ: 0.75 (t, 3H), 1.20 (s, 9H), 1.75 (q, 2H), 3.20-3.40 (m, 4H), 3.50 (m, 1H), 3.60 (s, 3H), 3.90 (m, 1H), 4.07 (t, 2H), 4.65 (m,1H), 7.30 (s, 1H).

(7*S*)-6-{2-[(*tert*-Butoxycarbonyl)amino]ethyl}-2-butyl-7-(methoxycarbonyl)-5-oxo-5,6,7,8-tetrahydroimidazo[1,5-*c*]pyrimidin-2-ium bromide (28). Prepared according to Method A using *n*-butyl bromide (3 eq.) and isolated in 46% yield: ^{1}H-NMR (D_2O, 300 MHz) δ: 0.82 (t, 3H), 1.22 (q, 2H), 1.30 (s, 9H), 1.80 (m, 2H), 3.27-3.47 (m, 4H), 3.58 (m, 1H), 3.67 (s, 3H), 3.97 (m, 1H), 4.17 (t, 2H), 4.77 (m, 1H), 7.40 (s, 1H). LRMS : m/z 395.3 (M^+).

(7*S*)-6-{2-[(*tert*-Butoxycarbonyl)amino]ethyl}-7-(methoxycarbonyl)-5-oxo-2-pentyl-5,6,7,8-tetrahydroimidazo[1,5-*c*]pyrimidin-2-ium bromide (29). Prepared according to Method A using *n*-pentyl bromide (5 eq.) and isolated in 55% yield: ^{1}H-NMR (D_2O, 300 MHz) δ: 0.72 (t, 3H), 1.03-1.13 (m, 4H), 1.22 (s, 9H), 1.75 (m, 2H), 3.17-3.40 (m, 4H), 3.50 (m, 1H), 3.60 (s, 3H), 3.90 (m, 1H), 4.12 (t, 2H), 4.68 (m, 1H), 7.33 (s, 1H). LRMS : 409.4 (M^+).

(7*S*)-6-{2-[(*tert*-Butoxycarbonyl)amino]ethyl}-2-isopropyl-7-(methoxycarbonyl)-5-oxo-5,6,7,8-tetrahydroimidazo[1,5-*c*]pyrimidin-2-ium bromide (30). Prepared according to Method A using 2-bromopropane (5 eq.) and isolated in 9% yield: ^{1}H-NMR (D_2O, 300

MHz) δ: 1.28 (s, 9H), 1.47 (d, 6H), 3.20 -3.40 (m, 5H), 3.57 (m, 1H), 3.67 (s, 3H), 3.95 (m, 1H), 4.75 (m, 1H), 7.45 (s, 1H). LRMS : m/z 381.2 (M^+).

(7*S*)-6-{2-[(*tert*-Butoxycarbonyl)amino]ethyl}-2-isobutyl-7-(methoxycarbonyl)-5-oxo-5,6,7,8-tetrahydroimidazo[1,5-*c*]pyrimidin-2-ium iodide (31). Prepared according to Method A using 1-iodo-2-methylpropane (5 eq.) and isolated in 32% yield: ^{1}H-NMR (D_2O, 400 MHz) δ: 0.82 (d, 6H), 1.27 (s, 9H), 2.07 (m, 1H), 3.25 -3.45 (m, 4H), 3.57 (m, 1H), 3.64 (s, 3H), 3.93 (m, 1H), 4.00 (d, 2H), 4.75 (m, 1H), 7.37 (s, 1H). LRMS : m/z 394.9 (M^+).

(7*S*)-2-Benzyl-6-{2-[(*tert*-butoxycarbonyl)amino]ethyl}-7-(methoxycarbonyl)-5-oxo-5,6,7,8-tetrahydroimidazo[1,5-*c*]pyrimidin-2-ium bromide (32). Prepared according to Method A using benzyl bromide (1.6 eq.) and isolated in 74% yield: ^{1}H-NMR (DMSO, 400 MHz) δ: 1.27 (s, 9H), 3.09 -3.30 (m, 4H), 3.43 (m, 1H), 3.60 (s, 3H), 3.95 (m, 1H), 4.84 (m, 1H), 5.43 (dd, 2H), 6.91 (s, 1H), 7.36-7.48 (m, 5H), 7.64 (s, 1H), 10.1 (s, 1H). LRMS : m/z 429.3 (M^+). $[\alpha]_D$ = +42.1 (c 0.10, methanol). Anal. ($C_{22}H_{29}N_4O_5Br{\cdot}1.25H_2O$) C, H, N.

(7*S*)-6-{2-[(*tert*-Butoxycarbonyl)amino]ethyl}-7-(methoxycarbonyl)-5-oxo-2-(2-phenylethyl)-5,6,7,8-tetrahydroimidazo[1,5-*c*]pyrimidin-2-ium bromide (33). Prepared according to Method A using (2-bromoethyl)benzene (5 eq.) and isolated in 33% yield: ^{1}H-NMR (D_2O, 300 MHz) δ: 1.27 (s, 9H), 3.06-3.40 (m, 6H), 3.52 (m, 1H), 3.71 (s, 3H), 3.90 (m, 1H), 4.47 (m, 2H), 4.84 (m, 1H), 7.03 (m, 2H), 7.26 (m, 4H). LRMS : m/z 443.3 (M^+).

(7*S*)-6-{2-[(*tert*-Butoxycarbonyl)amino]ethyl}-2-(cyclobutylmethyl)-7-(methoxycarbonyl)-5-oxo-5,6,7,8-tetrahydroimidazo[1,5-*c*]pyrimidin-2-ium bromide (34). Prepared according to Method A using (bromomethyl) cyclobutane (5 eq.) and isolated in 35% yield: ^{1}H-NMR (D_2O, 300 MHz) δ: 1.27 (s, 9H), 1.62-2.07 (m, 6H), 2.73 (m, 1H), 3.20-3.45 (m, 4H), 3.53 (m, 1H), 3.65 (s, 3H), 3.95 (m, 1H), 4.17 (d, 2H), 4.72 (m, 1H), 7.33 (s, 1H). LRMS : m/z 407.9 (M^+).

(7*S*)-6-{2-[(*tert*-Butoxycarbonyl)amino]ethyl}-2-(3-hydroxypropyl)-7-(methoxycarbonyl)-5-oxo-5,6,7,8-tetrahydroimidazo[1,5-*c*]pyrimidin-2-ium bromide (35). Prepared according to Method A using 1-bromo propan-3-ol (3 eq.) and isolated in 73% yield: ^{1}H-NMR (D_2O, 300MHz) δ: 1.30 (s, 9H), 2.05 (m, 2H), 3.25-3.48 (m, 4H), 3.58 (m, 3H), 3.67 (s, 3H), 3.97 (m, 1H), 4.30 (t, 2H), 4.78 (m, 1H), 7.41 (s, 1H). LRMS : m/z 397.3 (M^+).

Ethyl (2*RS*)-*2*-(diethoxyphosphoryl)-5-(tritylamino)pentanoate (38). Triethyl phosphonoacetate **36** (14.5g, 12.9ml, 64.7mmol) was added to a solution of sodium hydride (2.9g, 60% dispersion in mineral oil, 71.2mmol) in tetrahydrofuran (250ml), and the solution stirred at room temperature for 30 minutes. The reaction was cooled to 0°C & *N*-(3-bromopropyl)-*N*-tritylamine **37** (24.6g, 64.7mmol) in tetrahydrofuran (50ml) was added. 18-crown-6 (100mg) was then added and the reaction heated under reflux for 18 hours. Aqueous ammonium chloride solution was added to the cooled reaction, and the mixture extracted with ethyl acetate (2x). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with a solvent gradient of ethyl acetate : pentane (30:100 to 60:40), to give the title compound, 12.6g, 34% yield. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 1.28 (m, 11H), 1.84-2.02 (m, 2H), 2.15 (t, 2H), 2.93 (m, 1H), 4.17 (m, 6H), 7.18 (m, 3H), 7.24 (m, 6H), 7.44 (d, 6H). LRMS : m/z 524.4 (MH^+).

1-{[2-(Trimethylsilyl)ethoxy]methyl}-1*H*-imidazole-4-carboxaldehyde (39). Imidazole-4-carboxaldehyde (1g, 10.4mmol) was added portionwise to a solution of sodium hydride (463mg, 60% dispersion in mineral oil, 11.4mmol) in *N,N*-dimethylformamide (15ml), and the solution stirred for 30 minutes at room temperature. 2-(Trimethylsilyl)ethoxymethyl chloride (2.03ml, 11.4mmol) was added and the reaction stirred

at room temperature for 18 hours. The reaction was quenched by the addition of aqueous ammonium chloride solution, and the mixture extracted with ethyl acetate (2x). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with methanol:ethyl acetate (3:97), to give the title compound, 1.8g, 77% yield. ^{1}H-NMR ($CDCl_3$, 300MHz) δ: -0.02 (s, 9H), 0.92 (t, 2H), 3.52 (t, 2H), 5.33 (s, 2H), 7.68 (s, 1H), 7.72 (s, 1H), 9.92 (s, 1H).

1-Propyl-1*H*-imidazole-4-carboxaldehyde (40). Imidazole-4-carboxaldehyde (30g, 0.31mol) was added portionwise to a solution of sodium hydride (13.9g, 60% dispersion in mineral oil, 0.348mol) in tetrahydrofuran (450ml), and the solution stirred for 45 minutes. n-Propyl bromide (31.2ml, 0.344mol) was then added portionwise, followed by 18-crown-6 (150mg), and the reaction heated under reflux for 18 hours. Aqueous ammonium chloride solution was added to the cooled reaction, and the mixture extracted with ethyl acetate (2x) and dichloromethane (2x). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate : pentane (40:60), to give the title compound, 20.2g, 47% yield. ^{1}H-NMR (DMSO-d_6, 400MHz) δ : 0.80 (t, 3H), 1.76 (m, 2H), 3.98 (t, 2H), 7.84 (s, 1H), 8.04 (s, 1H), 9.70 (s, 1H). LRMS : m/z 277.3 $(2M+H)^+$.

Ethyl (2*E* and 2*Z*)-*3*-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-4-yl)-2-[3-(tritylamino)propyl]-2-propenoate (41). A solution of **38** (1.09g, 2.07mmol) in tetrahydrofuran (20ml) was added to an ice-cooled solution of sodium hydride (84mg, 60% dispersion in mineral oil, 2.07mmol) in tetrahydrofuran (30ml). The reaction was then allowed to warm to room temperature and was stirred for 30 minutes. The aldehyde **39** (469mg, 2.07mmol) in tetrahydrofuran (10ml) was then added, and the reaction stirred at room temperature for 18 hours. The reaction was quenched by the addition of aqueous ammonium chloride solution and the mixture extracted with ethyl acetate (2x). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was dissolved in toluene, adsorbed onto silica, and purified by column chromatography on silica gel, eluting with a solvent gradient of ethyl acetate : pentane (20:80 to 50:50), to give the two geometric isomers of the title compound in 32% yield (390mg, isomer 1) and 38% yield (460mg, isomer 2), respectively. Isomer 1: ^{1}H-NMR ($CDCl_3$, 300MHz) δ: -0.02 (s, 9H), 0.90 (t, 2H), 1.28 (t, 3H), 1.78 (m, 2H), 2.18 (t, 2H), 2.40 (br s, 1H), 2.97 (t, 2H), 3.44 (t, 2H), 4.19 (q, 2H), 5.20 (s, 2H), 7.15-7.32 (m, 12H), 7.43 (d, 6H). LRMS : m/z 596.5 (MH^+). Isomer 2: ^{1}H-NMR ($CDCl_3$, 300MHz) δ: -0.01 (s, 9H), 0.90 (t, 2H), 1.28 (t, 3H), 1.72 (m, 2H), 2.19 (t, 2H), 2.46 (t, 2H), 3.47 (t, 2H), 4.22 (q, 2H), 5.22 (s, 2H), 6.70 (s, 1H), 7.18 (m, 3H), 7.24 (m, 6H), 7.45 (d, 6H), 7.55 (s, 1H), 7.79 (s, 1H). LRMS : m/z 596.3 (MH^+).

Ethyl (2*E* and 2*Z*)-3-(1-*n*-propyl-1*H*-imidazol-4-yl)-2-[3-(tritylamino)propyl]-2-propenoate (42). A solution of **38** (5.9g, 11.3mmol) in tetrahydrofuran (100ml) was added to an ice-cooled solution of sodium hydride (457mg, 60% dispersion in mineral oil, 11.3mmol) in tetrahydrofuran (100ml), and the mixture stirred for 45 minutes. A solution of the aldehyde **40** (1.56g, 11.3mmol) in tetrahydrofuran (100ml) was then added. The reaction was then allowed to warm to room temperature and stirred for 18 hours. The mixture was diluted with aqueous ammonium chloride solution, the layers separated, and the aqueous phase extracted with ethyl acetate (3x). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a solvent gradient of ethyl acetate : pentane (40:60 to 60:40), to give the two geometric isomers of the title compound in 33% yield (1.87g, isomer 1) and 42% yield (2.40g, isomer 2), respectively. Isomer 1: ^{1}H-NMR ($CDCl_3$, 300MHz) δ: 0.92 (t, 3H),

1.27 (t, 3H), 1.78 (m, 4H), 2.18 (t, 2H), 2.52 (br s, 1H), 2.96 (t, 2H), 3.82 (t, 2H), 4.18 (q, 2H), 7.10-7.28 (m, 12H), 7.42 (d, 6H). LRMS : m/z 508.2 (MH^+). Isomer 2: ^{1}H-NMR ($CDCl_3$, 300MHz) δ: 0.95 (t, 3H), 1.27 (t, 3H), 1.72 (m, 2H), 1.82 (m, 2H), 2.18 (t, 2H), 2.45 (t, 2H), 3.86 (t, 2H), 4.22 (q, 2H), 6.75 (s, 1H), 7.18 (m, 3H), 7.28 (m, 7H), 7.44 (d, 6H), 7.76 (s, 1H). LRMS : m/z 508.4 (MH^+).

(±)-Ethyl 2-[(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-4-yl)methyl]-5-(tritylamino)pentanoate (43). A mixture of the alkenes **41** (460mg, 0.77mmol) and 10% palladium on charcoal (100mg) in ethanol (25ml) was hydrogenated at 1.5 atm and room temperature for 72 hours. The reaction mixture was filtered through Arbocel™, washing through with ethanol (200ml), and the filtrate concentrated under reduced pressure. The residual oil was purified by column chromatography on silica gel using ethyl acetate : pentane (50:50) as eluant, to give the title compound, 150mg, 33% yield. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: -0.02 (s, 9H), 0.95 (t, 2H), 1.18 (t, 3H), 1.46 (m, 2H), 1.45-1.70 (m, 2H), 2.09 (m, 2H), 2.64-2.79 (m, 2H), 2.90 (dd, 1H), 3.42 (t, 2H), 4.09 (q, 2H), 5.18 (s, 2H), 6.75 (s, 1H), 7.17 (m, 3H), 7.22 (m, 7H), 7.42 (d, 6H).

(±)-Ethyl 2-[(1-*n*-propyl-1*H*-imidazol-4-yl)methyl]-5-(tritylamino)pentanoate (44). Sodium borohydride (7.2g, 190mmol) was added portionwise over 2 hours to a solution of alkenes **42** (3.2g, 6.3mmol) and copper (I) chloride (928mg, 9.5mmol) in methanol (120ml), so as to maintain the reaction temperature at about 45°C, and the reaction stirred at this temperature for 2 hours, (two additional portions of copper (I) chloride (310mg, 3.1mmol) were added after approx. 40 and 80 minutes). The reaction mixture was filtered through Arbocel™ and the filtrate concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water, the layers separated, and the aqueous phase extracted with ethyl acetate (2x). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of ethyl acetate : pentane (50:50 to 100:0) to give the title compound, 2g, 62% yield. ^{1}H-NMR ($CDCl_3$, 300MHz) δ: 0.88 (t, 3H), 1.19 (t, 3H), 1.55 (m, 4H), 1.76 (m, 2H), 2.08 (m, 2H), 2.62-2.80 (m, 2H), 2.86 (dd, 1H), 3.79 (t, 2H), 4.07 (q, 2H), 6.60 (s, 1H), 7.18 (m, 3H), 7.24 (m, 7H), 7.43 (d, 6H). LRMS : m/z 510 (MH^+).