

FIG. 1

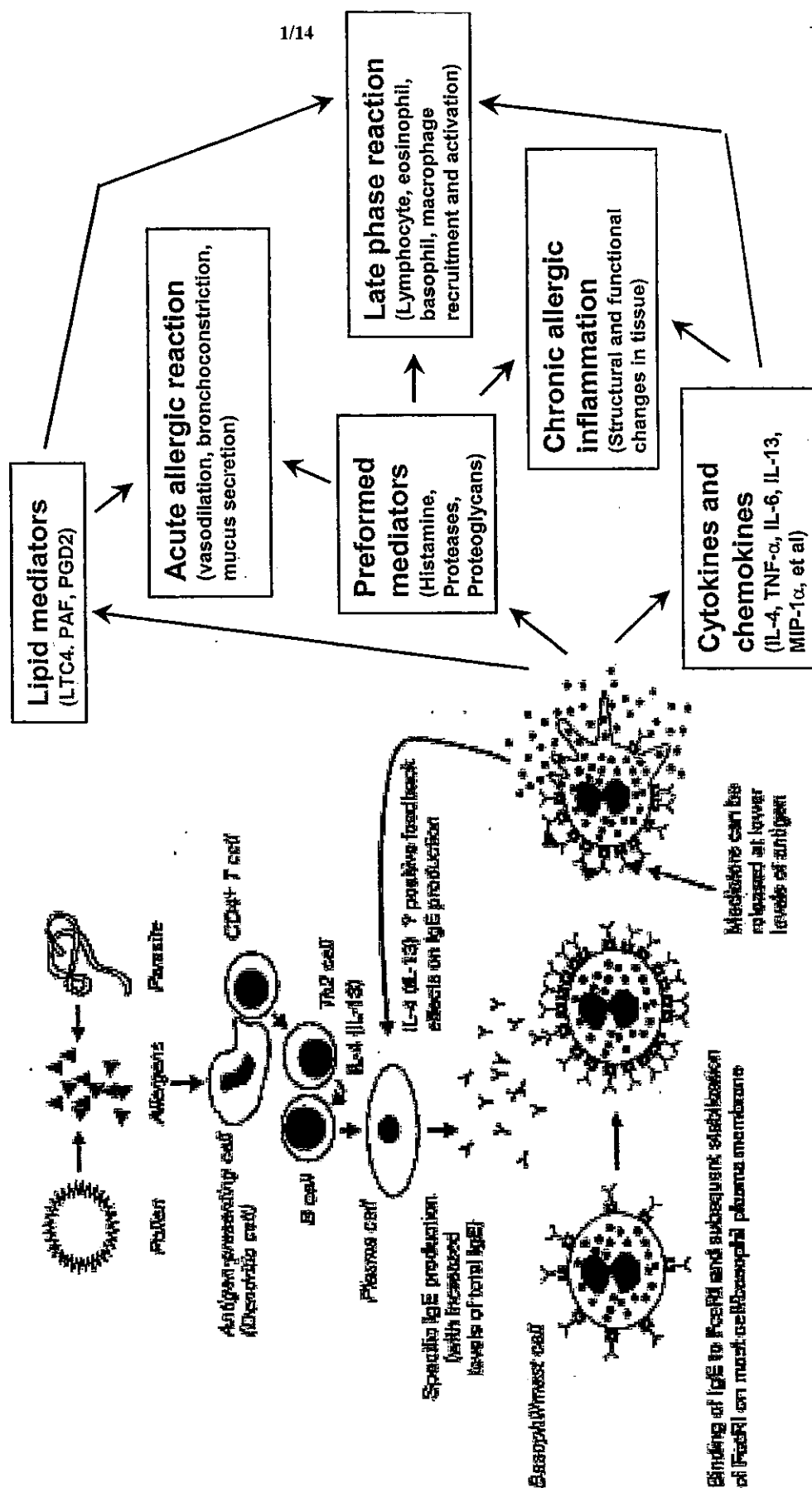


FIG. 2

Mast Cell FcεR1 Signaling Pathway

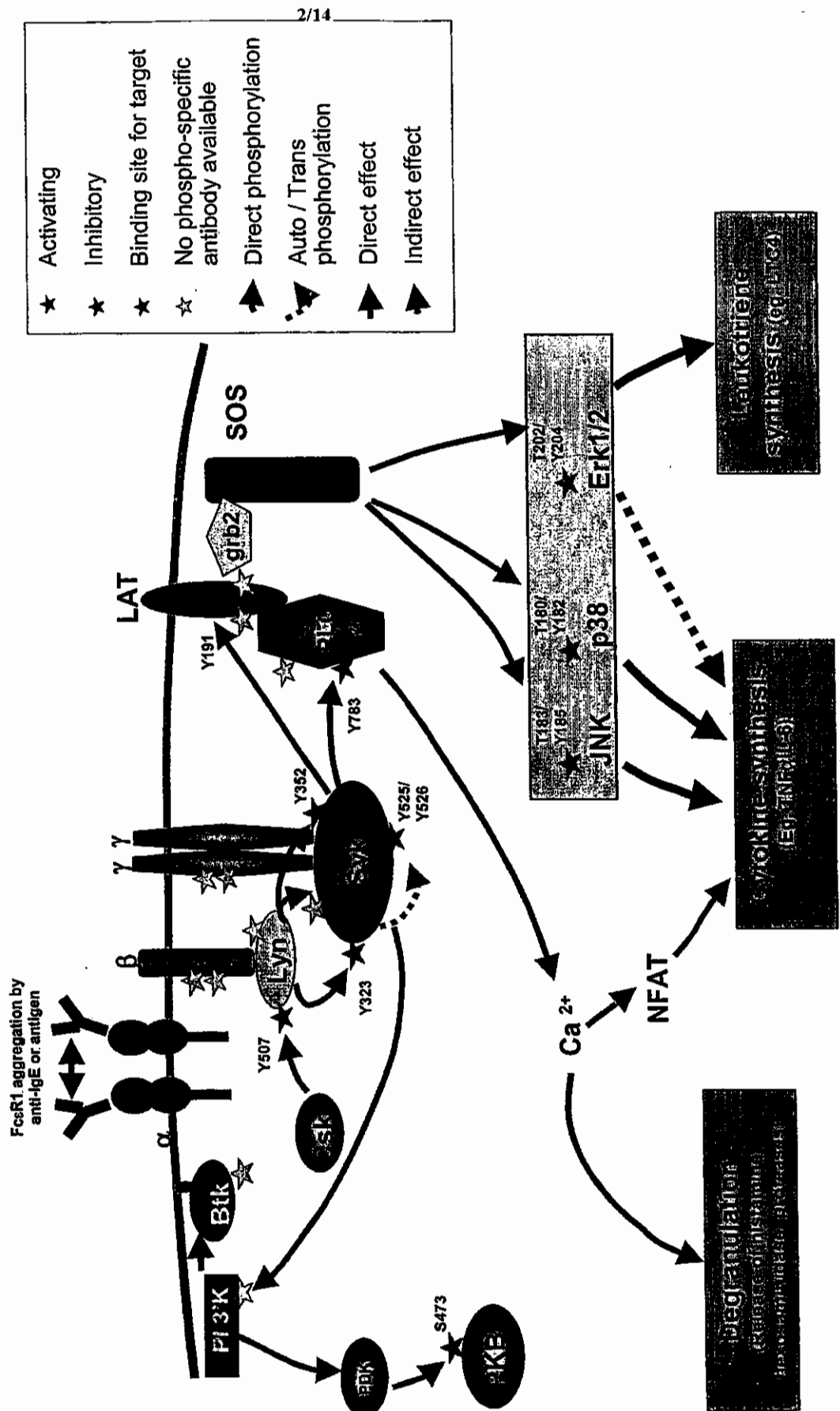


FIG. 3

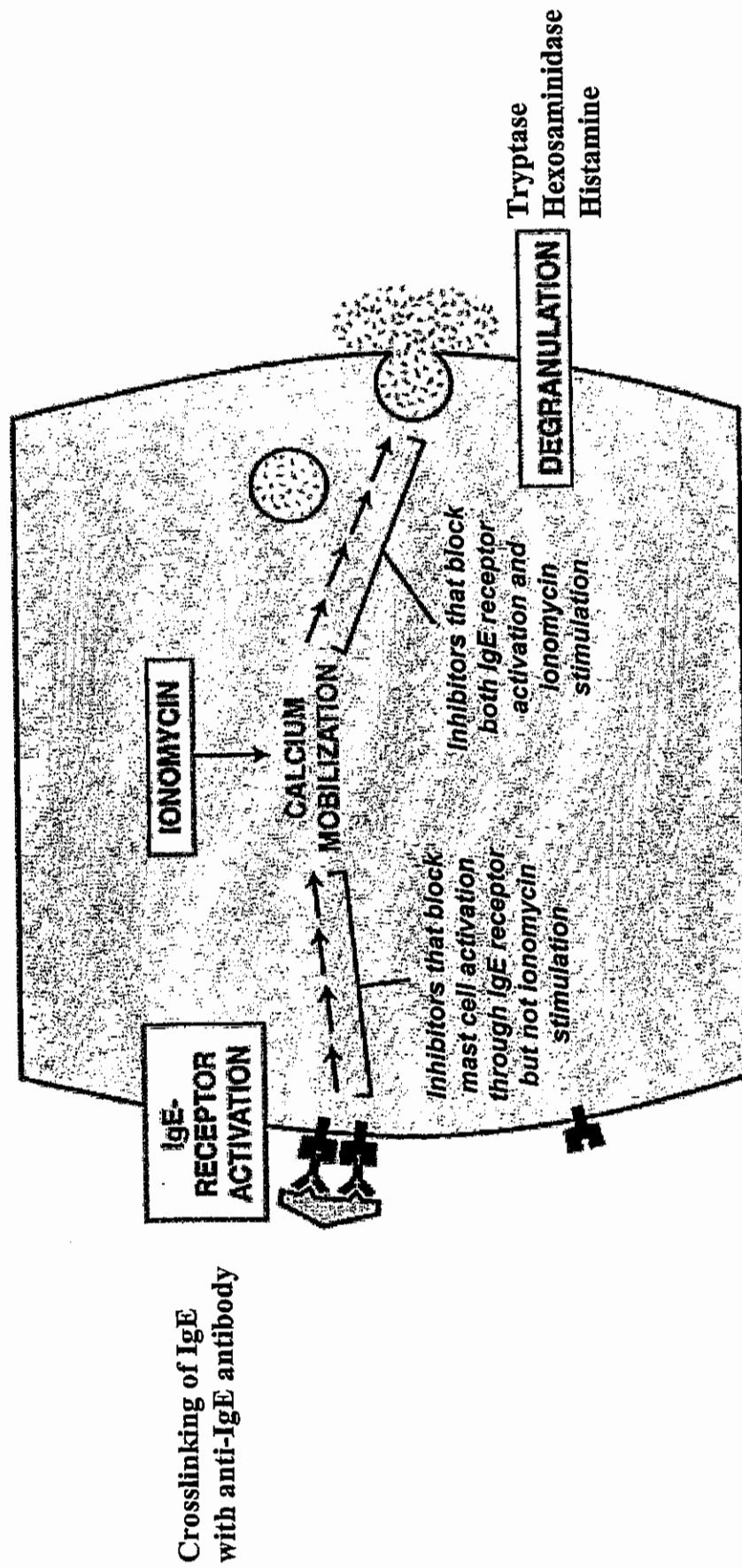


FIG. 4

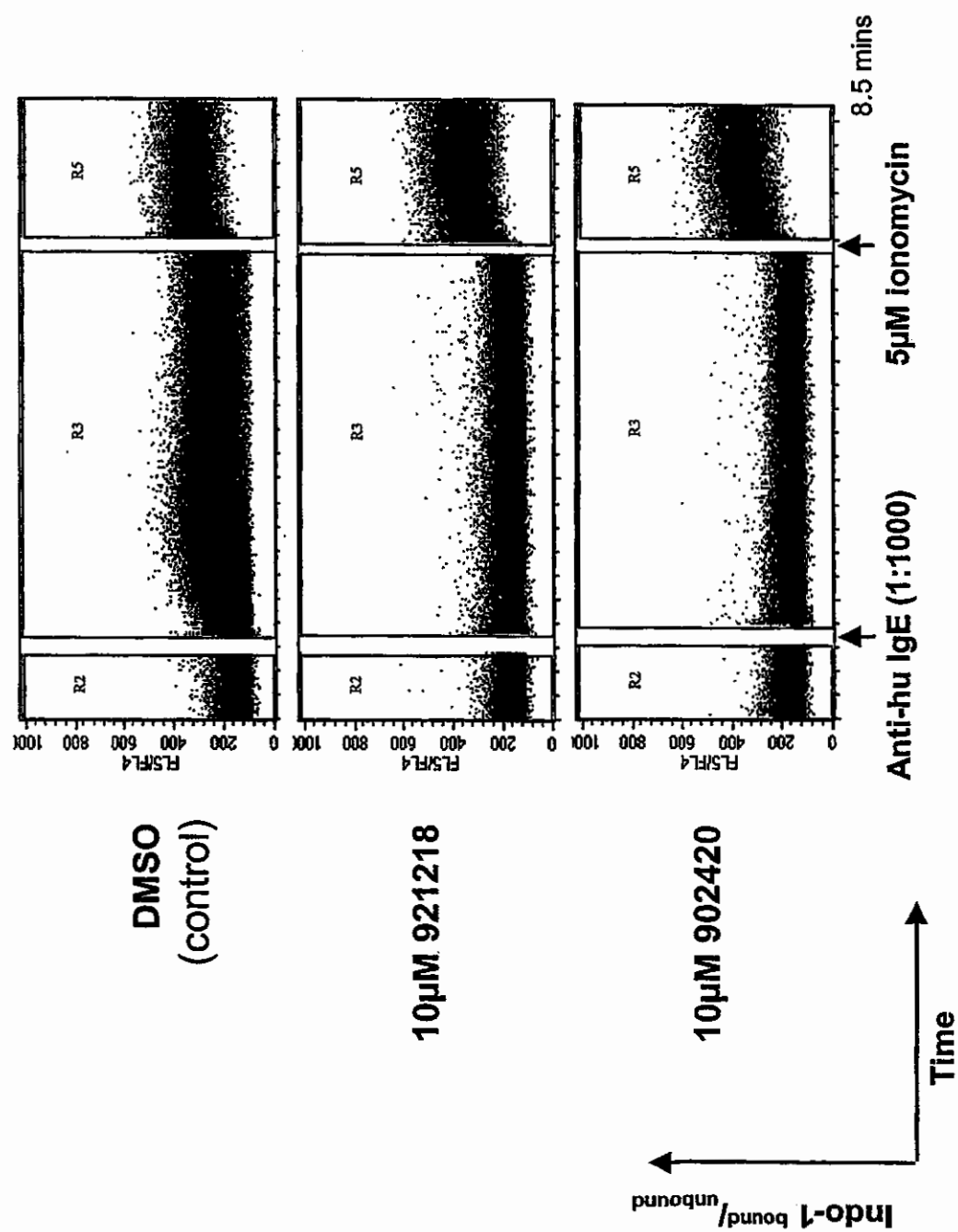


FIG. 5

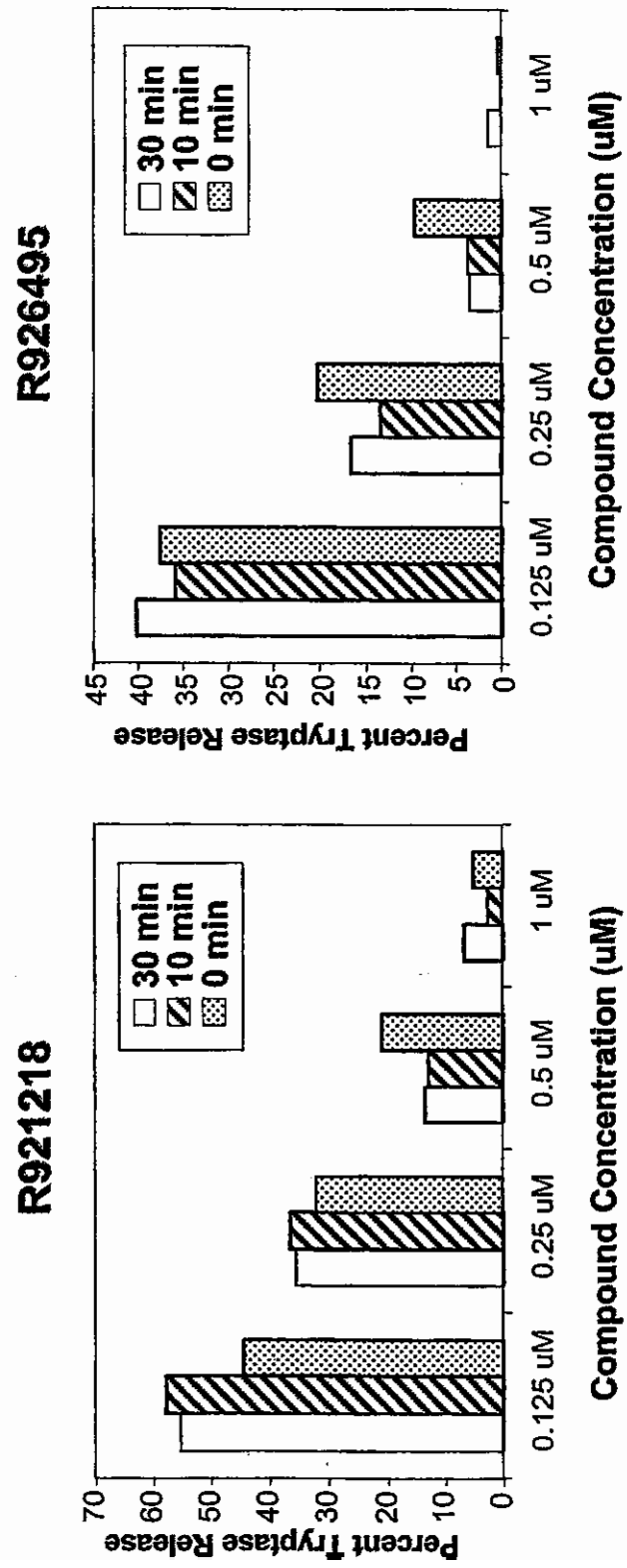


FIG. 6

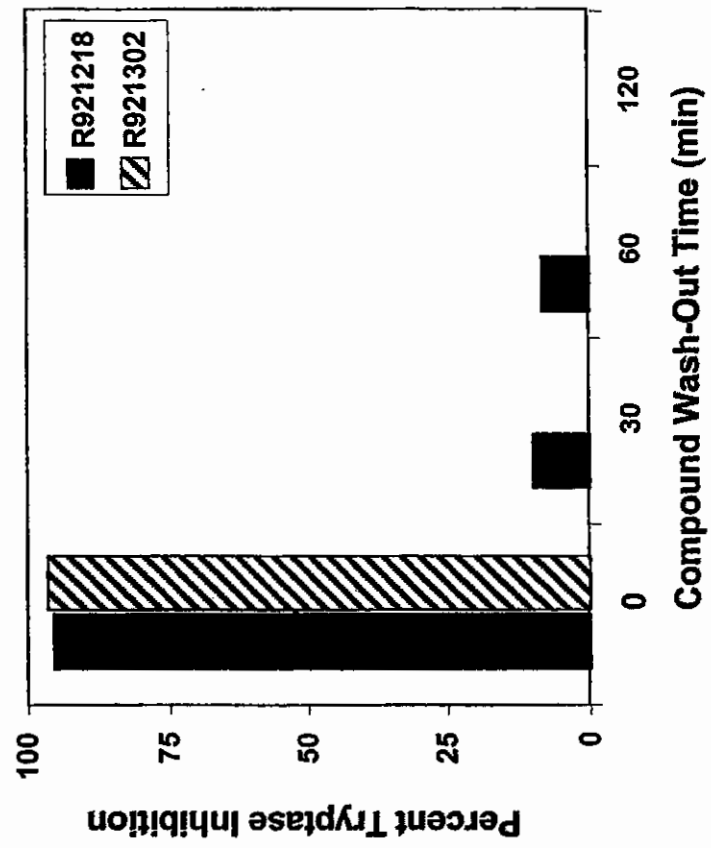


FIG. 7

Inhibition of Phosphorylation of Proteins Downstream of
Syk Kinase in Fce Receptor Activated BMMC Cells

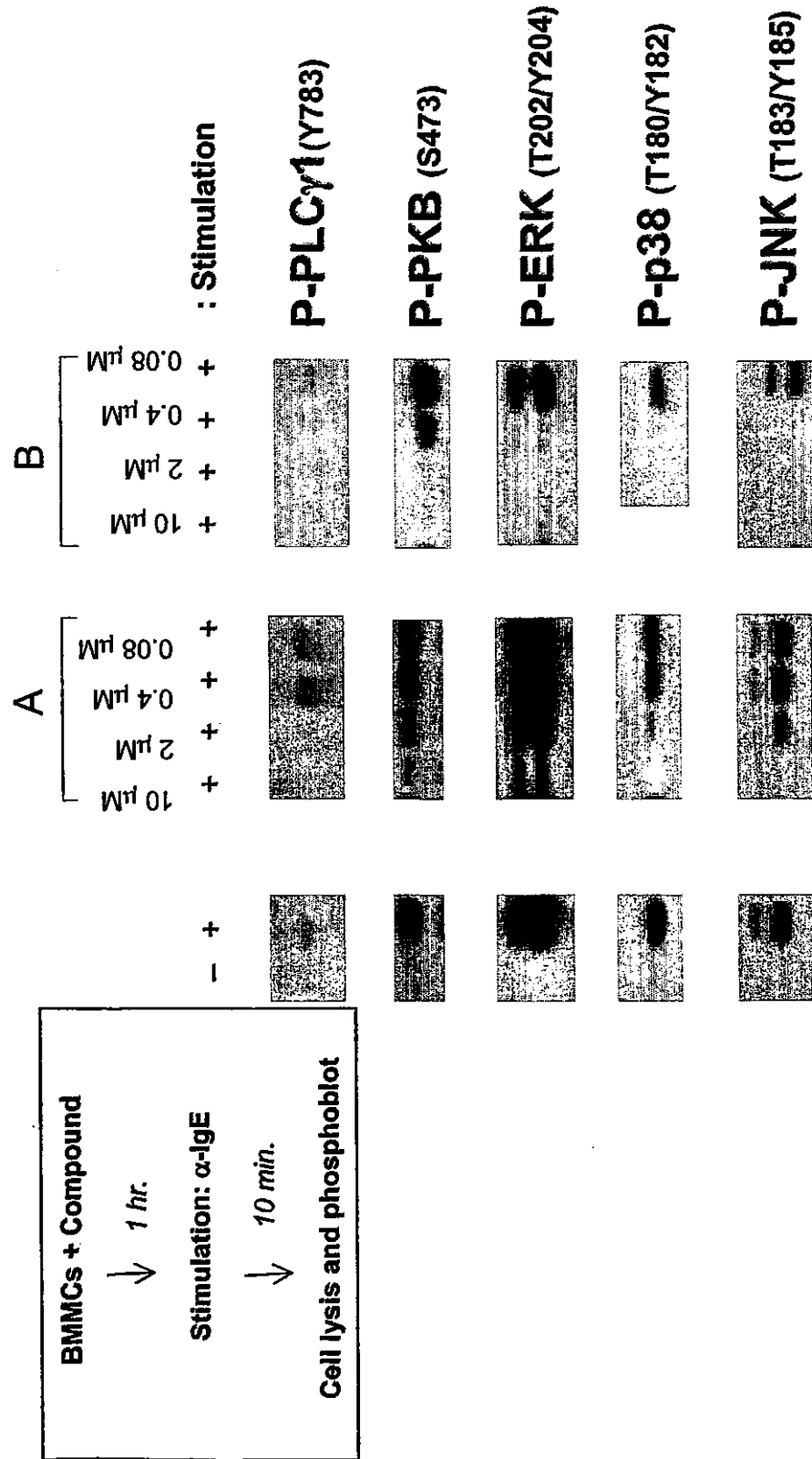
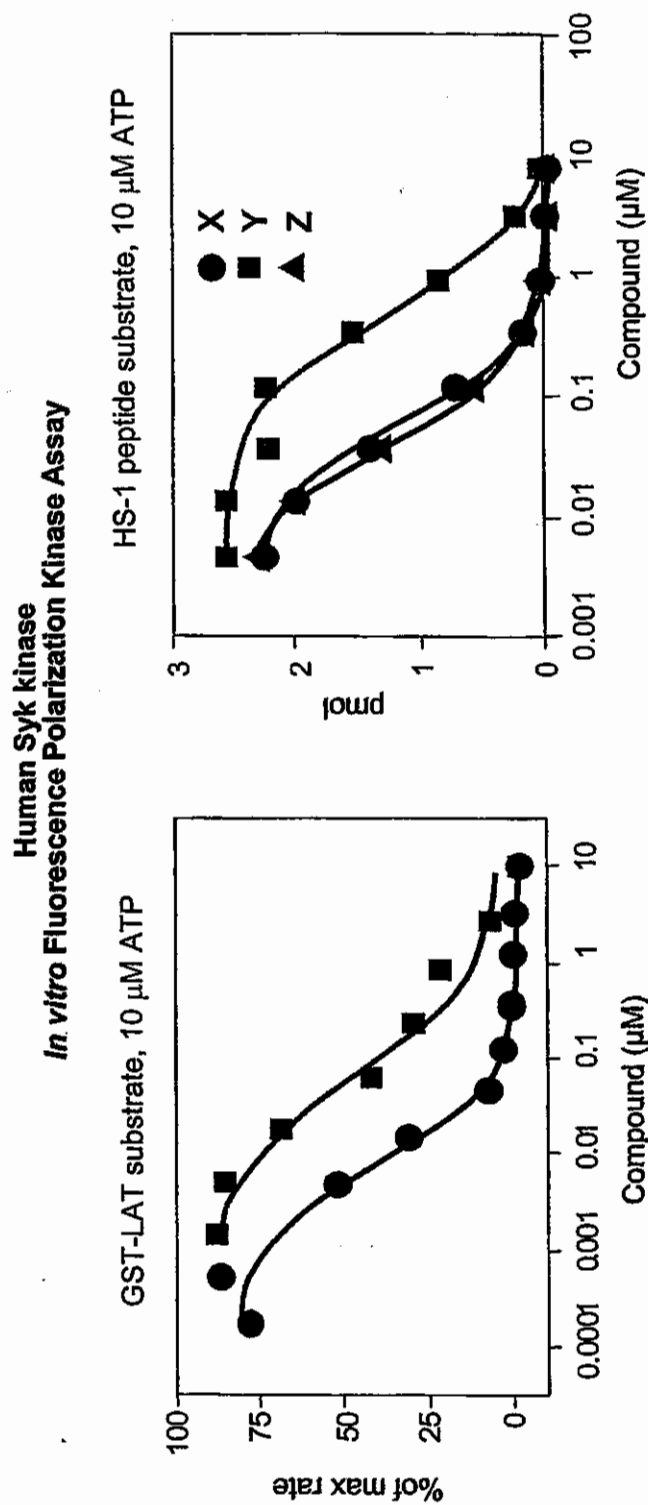


FIG. 8

The Disclosed Compounds Potently Inhibit the Activity of Syk Kinase



IC ₅₀ (nM)	
GST-LAT	HS-1
Y	200
X	10
Z	ND
	570
	62
	43

FIG. 9
Compound Inhibition of Syk is ATP Competitive



	DMSO	5 nM X	50 nM X	500 nM X
V_{max}	.025	0.027	.023	0.020
K_m	1.54	0.79	4.5	31

CHMC: Cultured human mast cells

Compound
(1 hour preincubation)

Stimulation: α -IgE

Lyn Targets

P-Cbl (Y774)

P-Syk (Y352)

Syk Targets

P-LAT (Y191)

P-PLC γ 1 (Y783)

Indirect Targets

P-PKB (S473)

P-ERK (T202/Y204)

FIG. 10

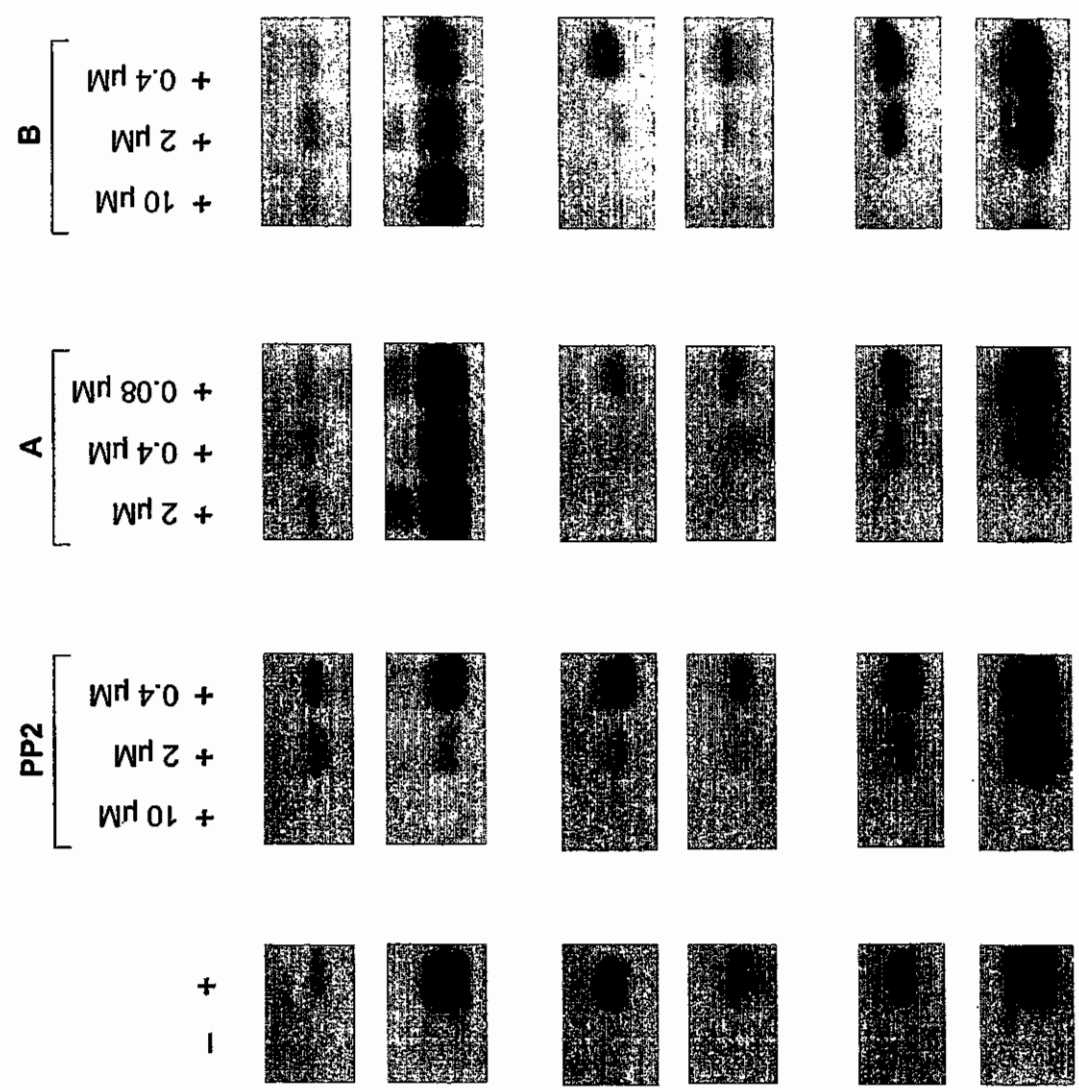


FIG. 11A

Inhibition of Phosphorylation of Proteins downstream of Syk in BMMC

	R921219		R921304		R940323		R935138	
	+	-	+	-	+	-	+	-
P-Syk ₃₅₂								
P-Plcγ ₇₈₃								
P-Lat ₁₉₁								
P-ERK _{202/204}								
	+	-	+	-	+	-	+	-
	+ 10 μM	+ 2 μM	+ 10 μM	+ 2 μM	+ 10 μM	+ 2 μM	+ 10 μM	+ 2 μM
	+ 0.4 μM	+ 0.08 μM	+ 0.4 μM	+ 0.08 μM	+ 0.4 μM	+ 0.08 μM	+ 0.4 μM	+ 0.08 μM

FIG. 11B

Inhibition of Phosphorylation of Proteins downstream of Syk in BMMC

		R921303		R940347		R926891		R920410		12/14	

FIG. 11C

Inhibition of Phosphorylation of Proteins downstream of Syk in BMMC

	R926321					R950368					R926594					R935310				
	-	+	10 μ M	2 μ M	0.4 μ M	0.08 μ M	-	+	10 μ M	2 μ M	0.4 μ M	0.08 μ M	-	+	10 μ M	2 μ M	0.4 μ M	0.08 μ M	-	+
P-Syk ³⁵²																				
P-Pic ⁷⁸³																				
P-Lat ¹⁹¹																				
p-ERK ^{202/204}																				

FIG. 11D

Inhibition of Phosphorylation of Proteins downstream of Syk in BMMC

	R935237				R926813				R926839				R908712					
	-	+	+ 10 μ M	+ 2 μ M	+ 0.4 μ M	+ 0.08 μ M	-	+	+ 10 μ M	+ 2 μ M	+ 0.4 μ M	+ 0.08 μ M	-	+	+ 10 μ M	+ 2 μ M	+ 0.4 μ M	+ 0.08 μ M
P-Syk ₃₅₂																		
P-Plc γ ₇₈₃																		
P-Lat ₁₉₁																		
P-ERK _{202/204}																		