#	473	474	475	476	477	478	479	480	481	482	483
BTK	I	T	E	Y	M	A	N	G	C	L	L
BMX	V	T	E	Y	M	A	R	G	C	L	L
TEC	V	T	E	F	M	E	R	G	C	L	L
TXK	V	T	E	F	M	E	N	G	C	L	L
ITK	V	F	E	F	M	E	H	G	C	L	S
EGFR	I	T	Q	L	M	P	F	G	C	L	L
ErbB2	V	T	Q	L	M	P	Y	G	C	L	L
ErbB4	V	T	Q	L	M	P	H	G	C	L	L
JAK3	V	M	E	Y	L	P	S	G	C	L	R
BLK	V	T	E	Y	L	P	S	G	C	L	L
LCK	I	T	E	Y	M	E	N	G	S	L	V
LYN	I	T	E	Y	M	A	K	G	S	L	L
SYK	V	M	E	M	A	E	L	G	P	L	N

Fig. 1

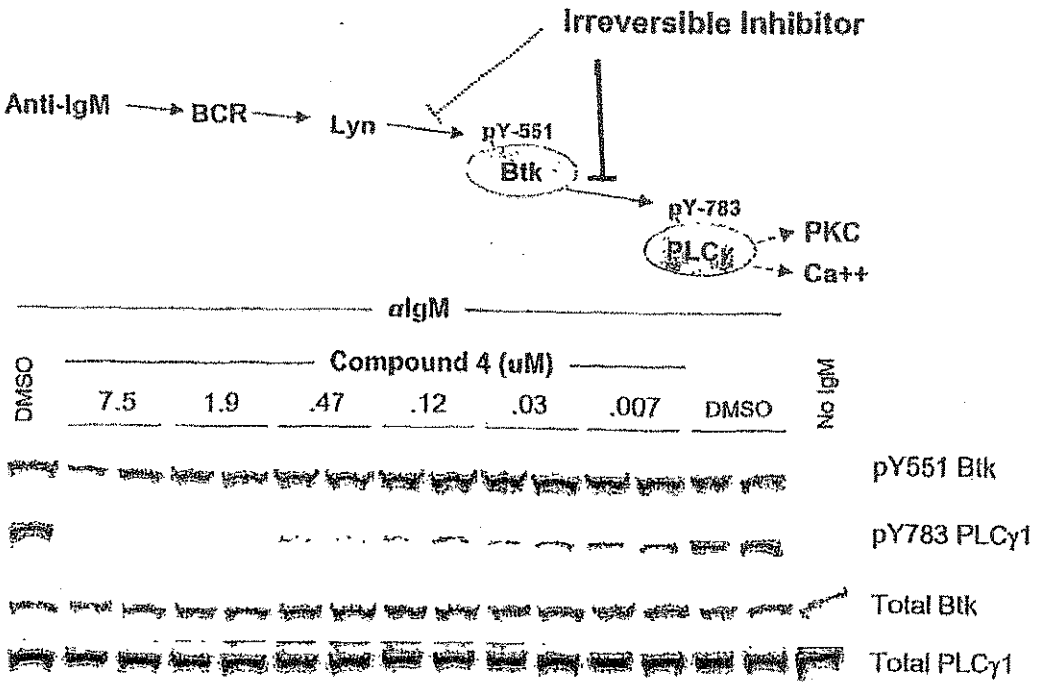

Irreversible Inhibitor
Anti-IgM
BCR
Lyn
pY-551
Btk
pY-783
PLCγ
PKC
Ca++
αIgM
Compound 4 (uM)
DMSO
7.5
1.9
.47
.12
.03
.007
DMSO
No IgM
pY551 Btk
pY783 PLCγ1
Total Btk
Total PLCγ1

Fig. 2

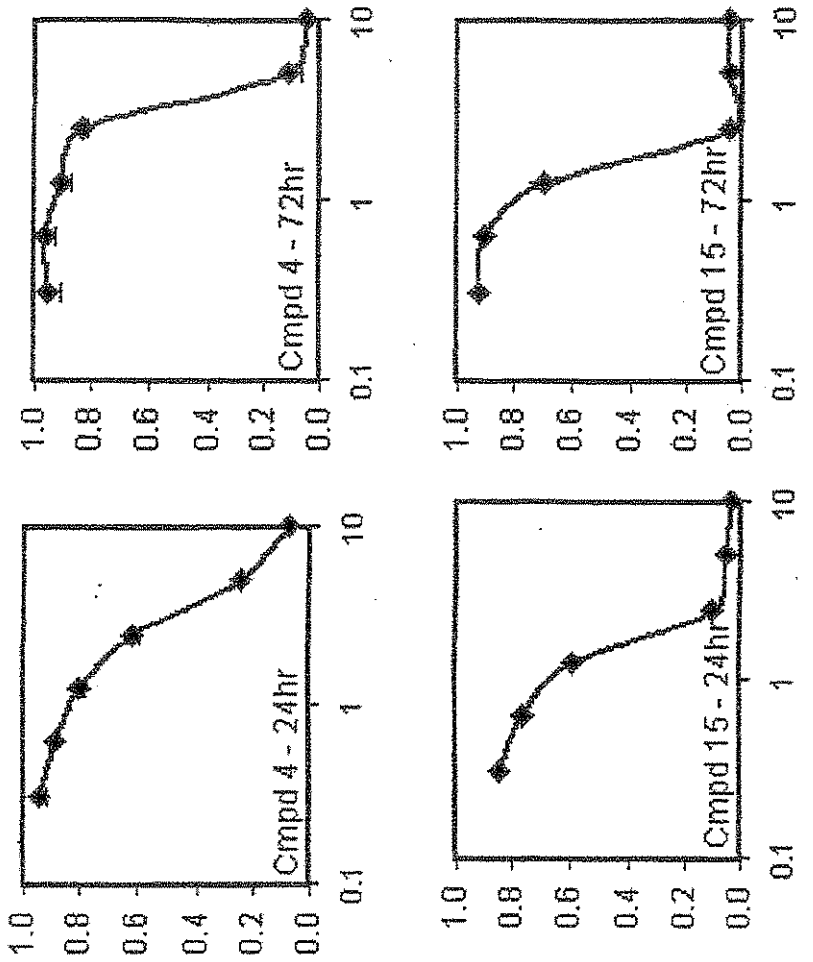

Compound 4
Compound 15
Normalized Proliferation
Cmpd 4 - 24hr
Cmpd 4 - 72hr
Cmpd 15 - 24hr
Cmpd 15 - 72hr
1.0
0.8
0.6
0.4
0.2
0.0
0.1
1
10
µM

Fig. 3

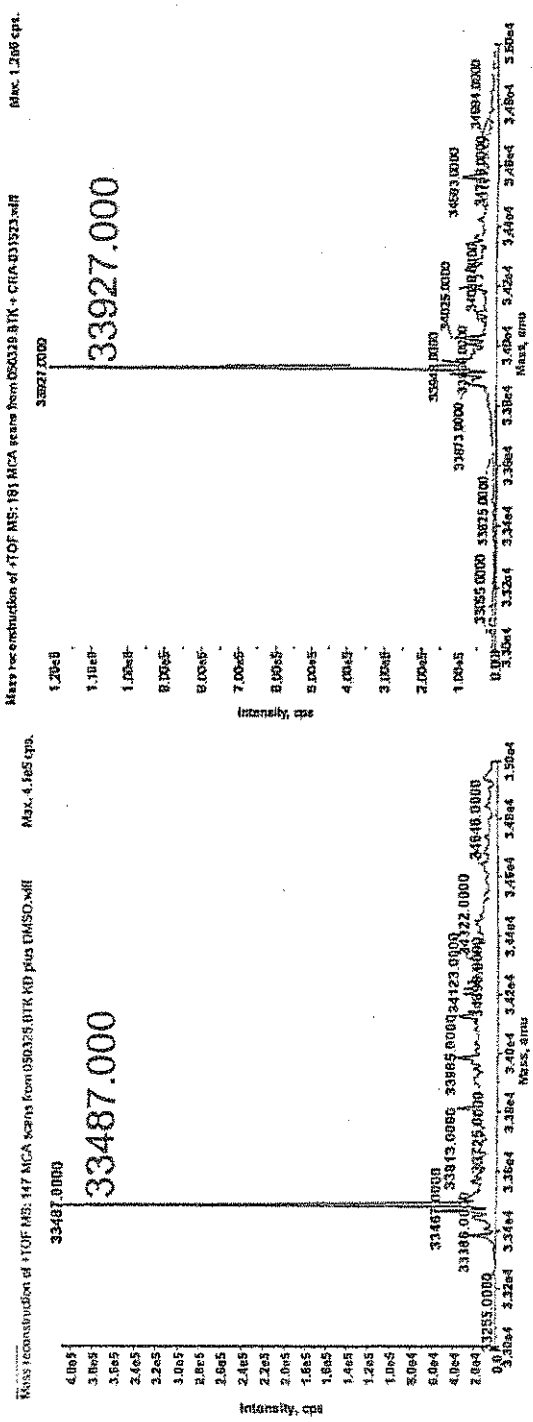
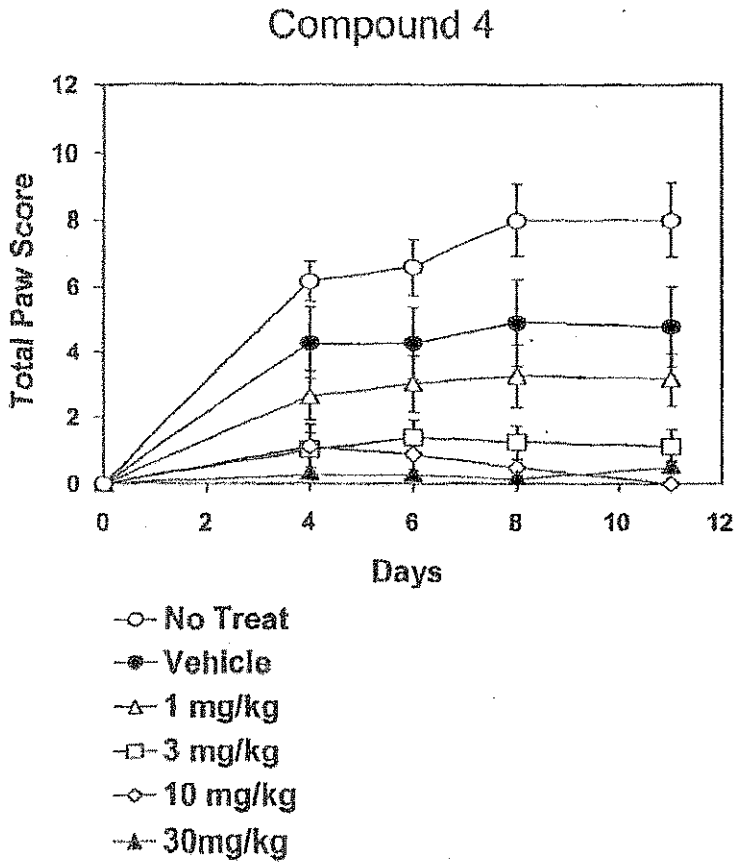

Btk + DMSO
Mass reconstruction of +TOF MS: 147 MCA scans from 050325 BTK KD plus DMSO.wiff
Max. 4.1e5 cps.
33487.0000
33487.000
Intensity, cps
Mass, amu
Btk + Compound 4 (MW=441)
Mass reconstruction of +TOF MS: 191 MCA scans from 050325 BTK + CHA-031523.wiff
Max. 1.2e6 cps.
33927.0000
33927.000
Intensity, cps
Mass, amu

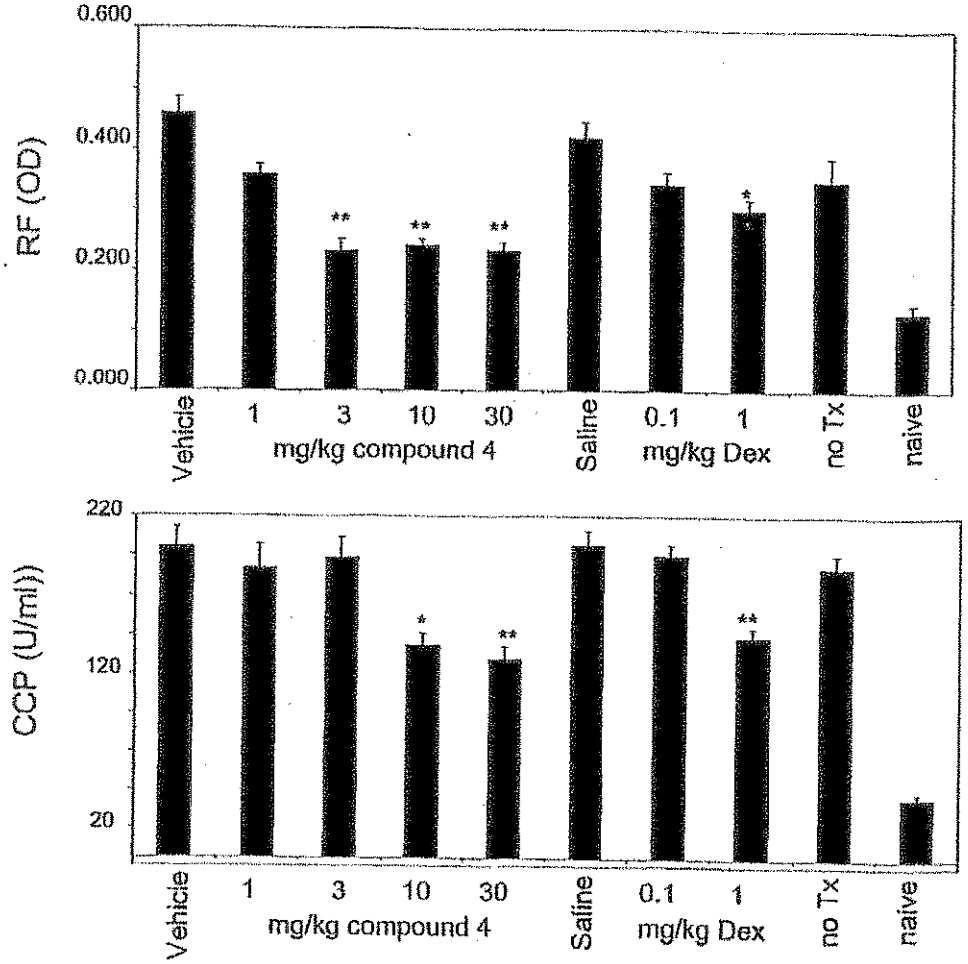
Fig. 4



Plasma Levels After Final Dose

Dose (mg/kg)	Concentration (μM)	
	0.5 hr	2 hr
1	0.066	0.049
3	0.250	0.135
10	0.635	0.670
30	1.720	1.103

Fig. 5



Rheumatoid Factor

Anti-citrullinated cyclic peptide antibodies

Fig. 6

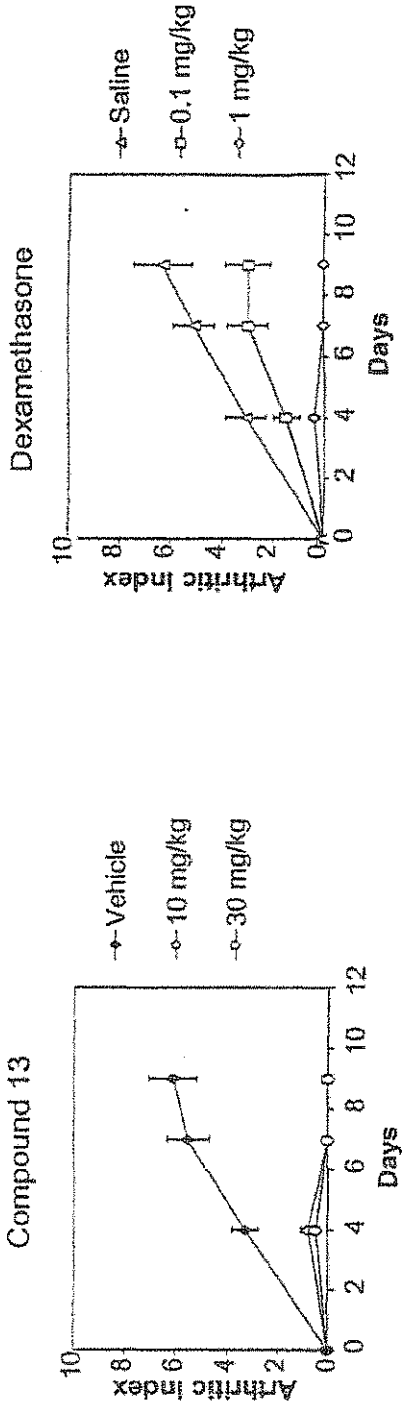

Dexamethasone
Saline
0.1 mg/kg
1 mg/kg
Arthritic Index
Days
0
2
4
6
8
10
12
Compound 13
Vehicle
10 mg/kg
30 mg/kg
Arthritic Index
Days

Fig. 7