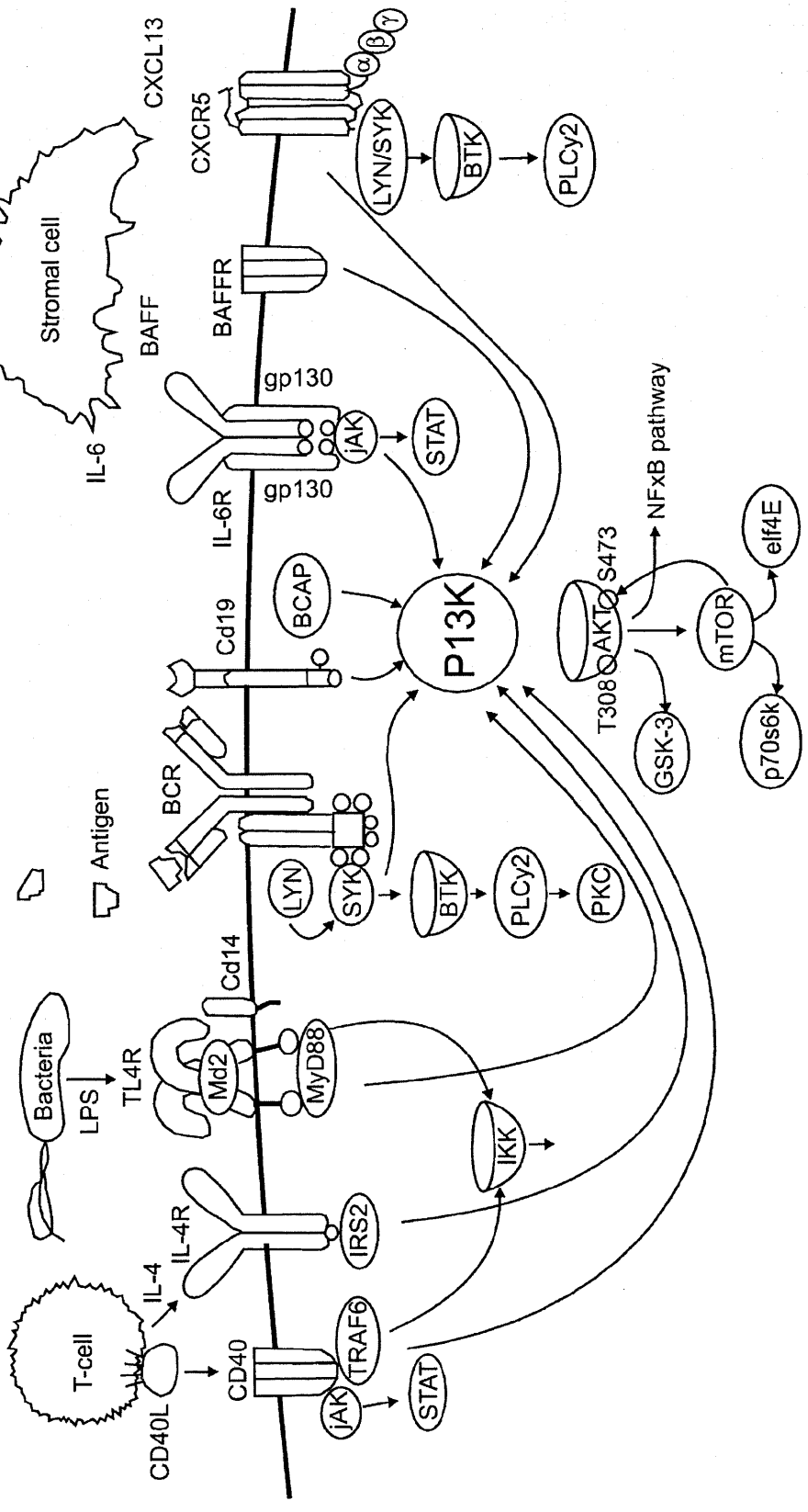

Stromal cell
CXCL13
CXCR5
BAFF
BAFFR
IL-6
gp130
gp130
IL-6R
JAK
STAT
LYN/SYK
BTK
PLCy2
Cd19
BCAP
P13K
AKT
S473
T308
NFxB pathway
mTOR
elf4E
GSK-3
p70s6k
BCR
Antigen
LYN
SYK
BTK
PLCy2
PKC
Cd14
Bacteria
LPS
TL4R
Md2
MyD88
IKK
IL-4
IL-4R
IRS2
T-cell
CD40L
CD40
TRAF6
JAK
STAT

Fig. 1

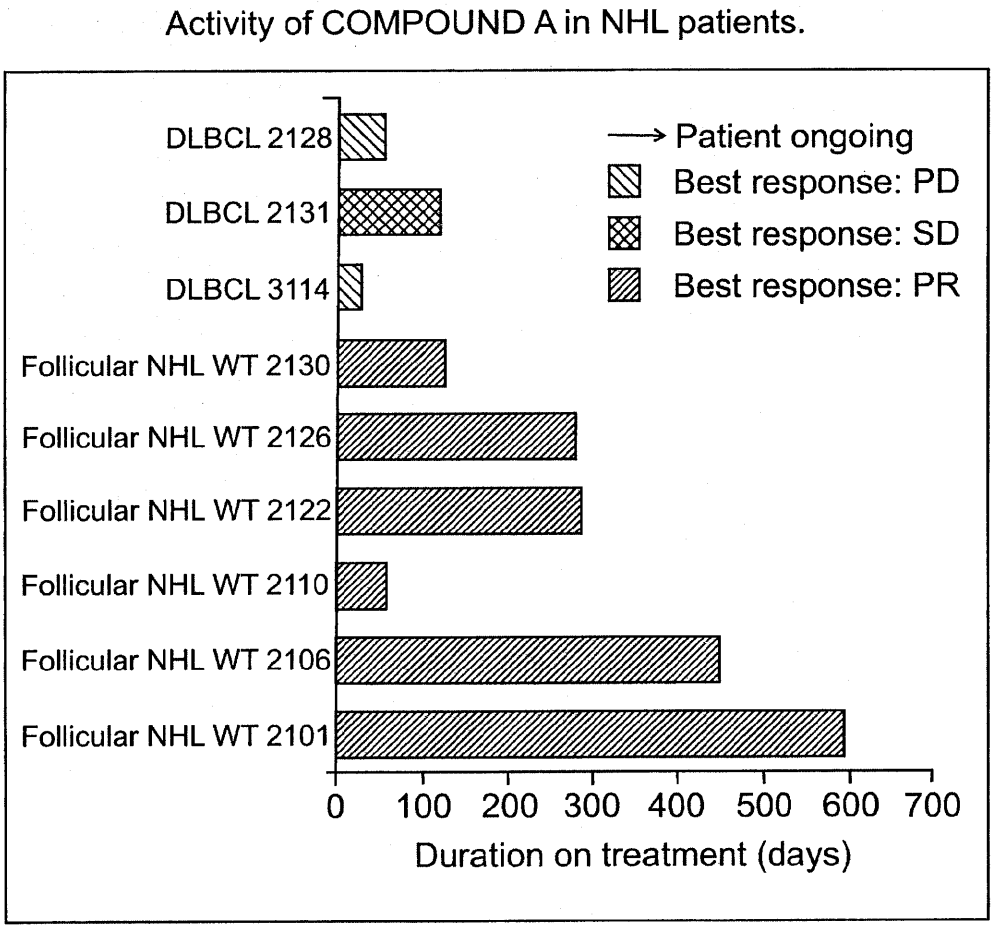

Activity of COMPOUND A in NHL patients.
DLBCL 2128
DLBCL 2131
DLBCL 3114
Follicular NHL WT 2130
Follicular NHL WT 2126
Follicular NHL WT 2122
Follicular NHL WT 2110
Follicular NHL WT 2106
Follicular NHL WT 2101
Patient ongoing
Best response: PD
Best response: SD
Best response: PR
0
100
200
300
400
500
600
700
Duration on treatment (days)

Fig. 2

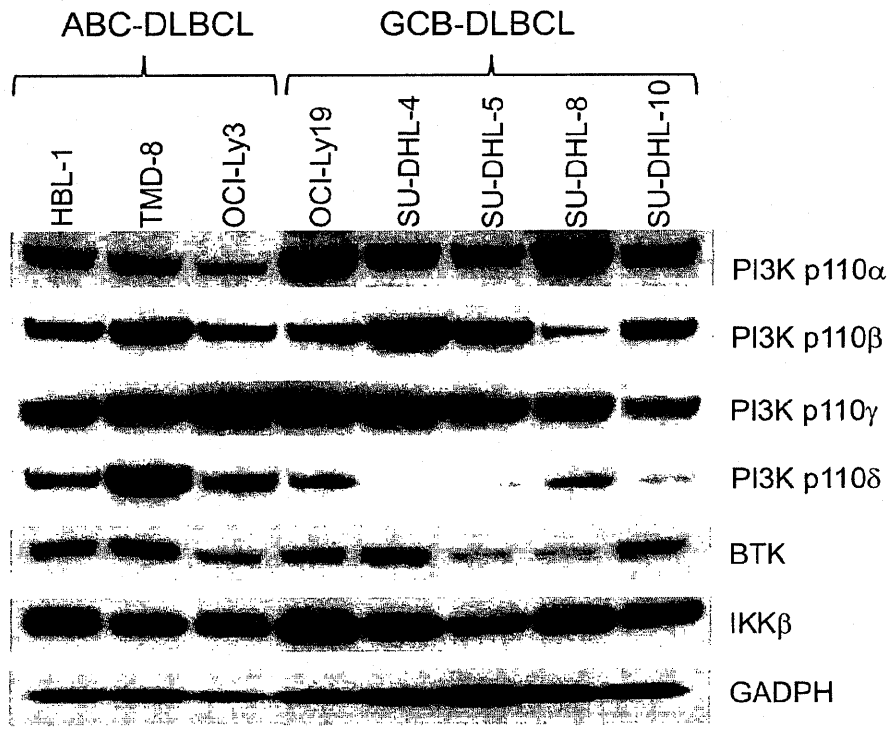

Differential expression of PI3K isoforms, BTK, and IKK in DLBCL cell lines
ABC-DLBCL
GCB-DLBCL
HBL-1
TMD-8
OCI-Ly3
OCI-Ly19
SU-DHL-4
SU-DHL-5
SU-DHL-8
SU-DHL-10
PI3K p110α
PI3K p110β
PI3K p110γ
PI3K p110δ
BTK
IKKβ
GADPH

Fig. 3

Differential anti-proliferative profile of pan-PI3K inhibitor COMPOUND A, PI3Kδ-selective inhibitor GS-1101, BTK inhibitor ibrutinib, and IKK inhibitor BAY compound B in DLBCL cell lines *>1.0E-05 (M):

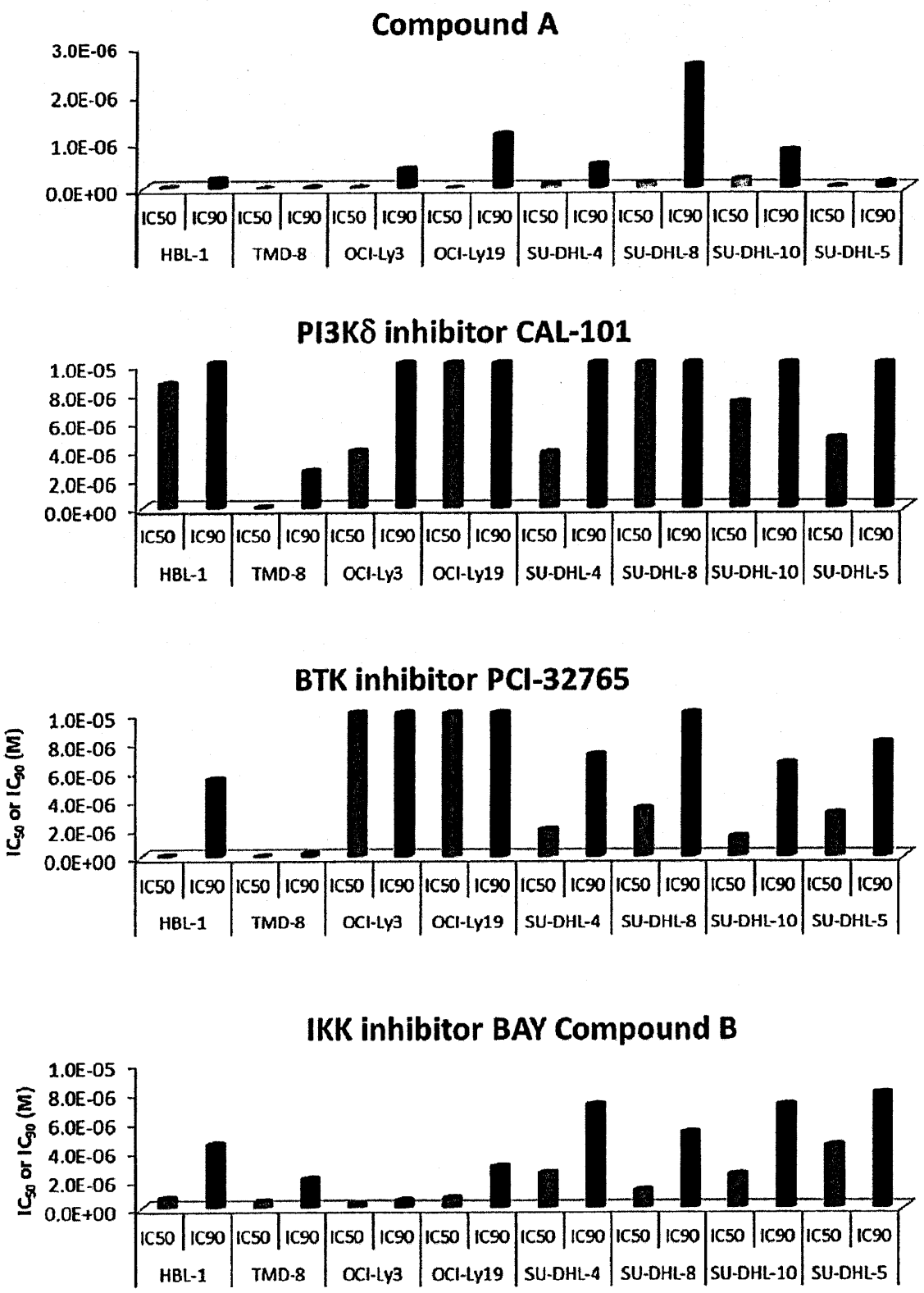


Fig. 4

In vivo efficacy of Compound A and ibrutinib in TMD-8 xenograft model in CB17 scid mice

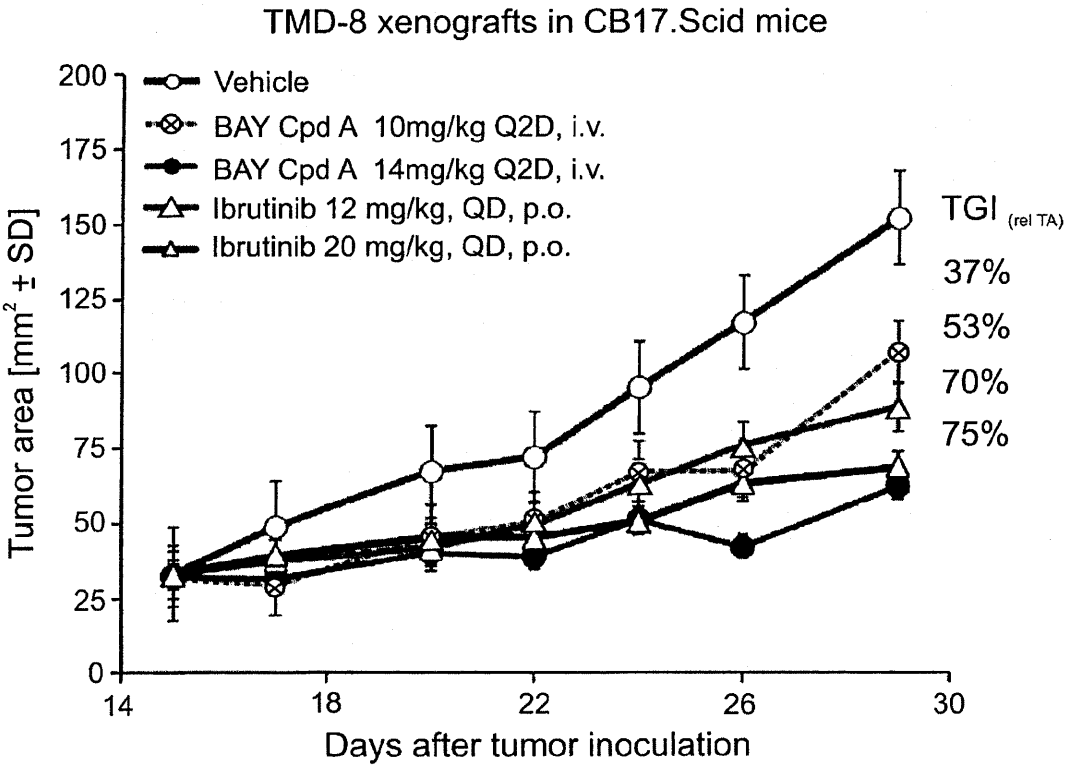


Fig. 5

SUBSTITUTE SHEET (RULE 26)

Combination effect of PI3K inhibitor COMPOUND A with BTK inhibitor ibrutinib or IKK inhibitor BAY compound B in DLBCL cell lines

Combination	CI	HBL-1 CD79, MyD88	TMD-8 CD79	OCI-Ly3 CARD11, MyD88, Bcl2	OCI-Ly19 Bcl2	SU-DHL-4 Bcl2, EZH2	SU-DHL-5	SU-DHL-8 c-Myc	SU-DHL-10 Bcl2, EZH2, c-Myc
PI3Ki BAY Cpd A+ BTKi PCI32765	IC_{50}								
	Ic_{90}								
PI3Ki BAY Cpd A IKKi BAY Cpd B	Ic_{50}								
	Ic_{90}								

Very strong synergy, CI: 0-0.3; Strong synergy, CI: 0.3-0.6; Synergy, CI: 0.6-0.9; Additive effect: CI: 0.9-1.2; Antagonistic effect: CI: >1.2

CI: combination index; NA: not achievable at a concentration of 10μM of the two compounds

Fig. 6A

PI3Ki: BAY Compound A, BTKi: Ibrutinib, IKK□i:BAY Compound B, CAL-101: GS-1101

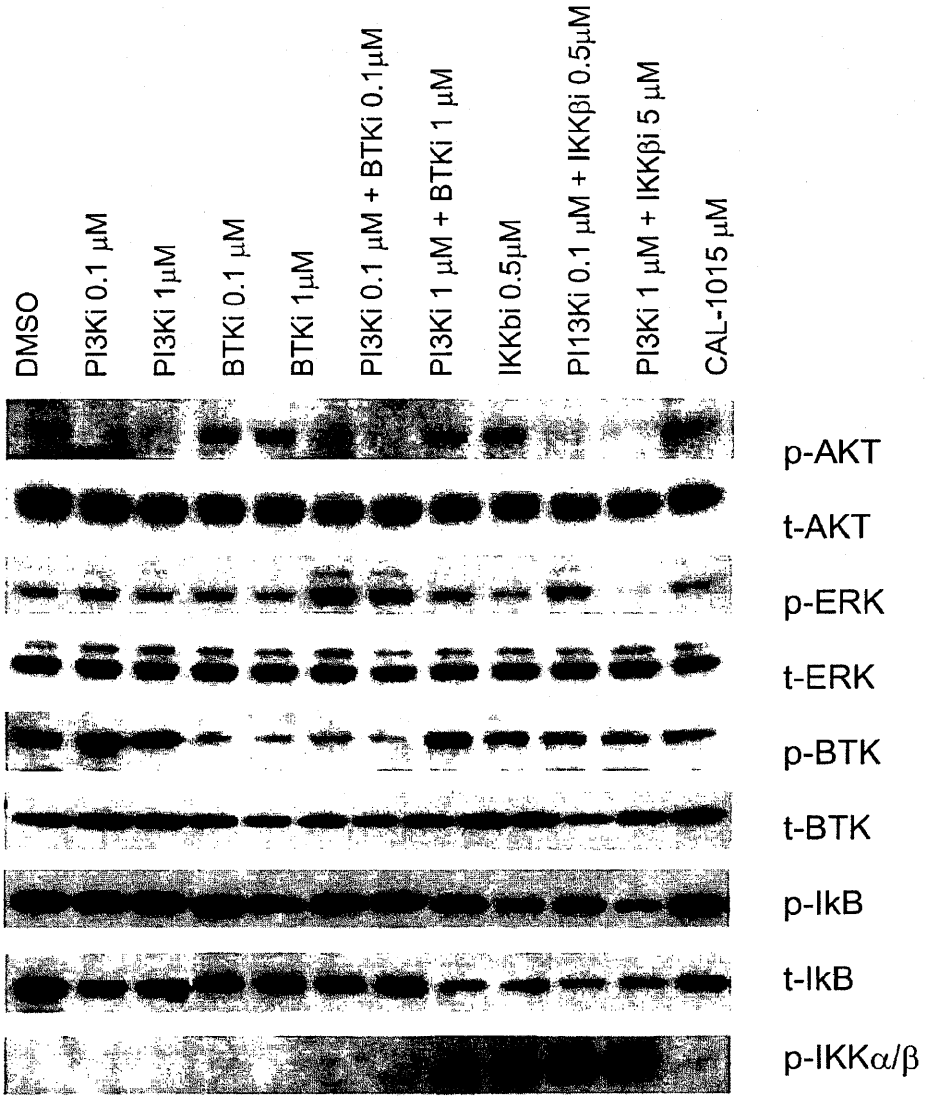
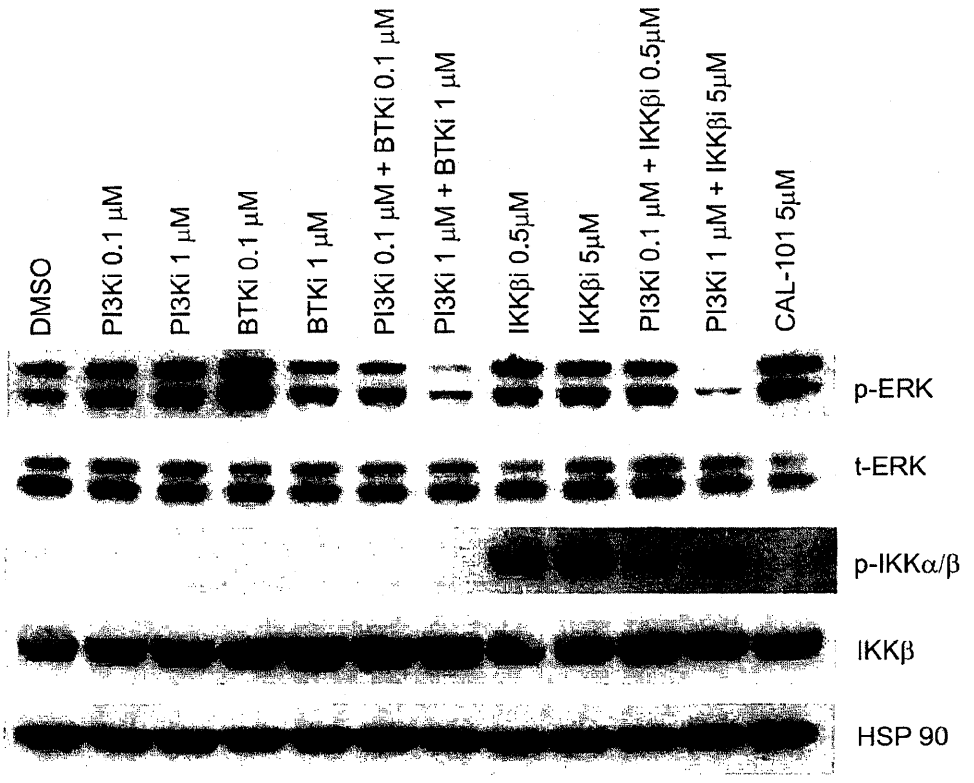
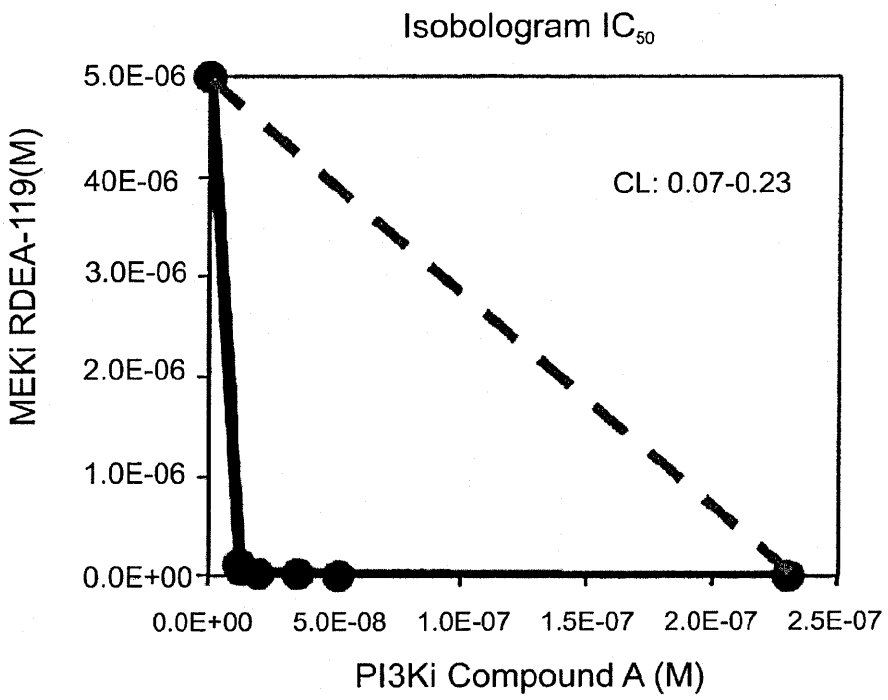


Fig. 6B



PI3Ki: BAY Compound A, BTKi: ibrutinib, IKK□: BAY Compound B, CAL-101: GS-101

Fig. 6C


Isobologram IC50
5.0E-06
40E-06
3.0E-06
2.0E-06
1.0E-06
0.0E+00
MEKi RDEA-119(M)
CL: 0.07-0.23
0.0E+00
5.0E-08
1.0E-07
1.5E-07
2.0E-07
2.5E-07
PI3Ki Compound A (M)

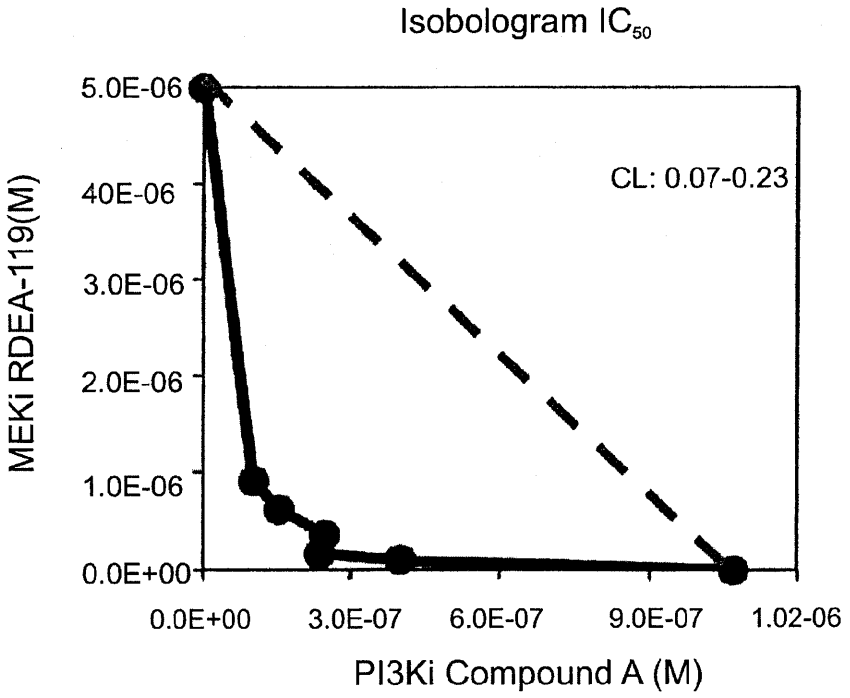

Isobologram IC50
5.0E-06
40E-06
3.0E-06
2.0E-06
1.0E-06
0.0E+00
MEKi RDEA-119(M)
CL: 0.07-0.23
0.0E+00
3.0E-07
6.0E-07
9.0E-07
1.02-06
PI3Ki Compound A (M)

Fig. 6D

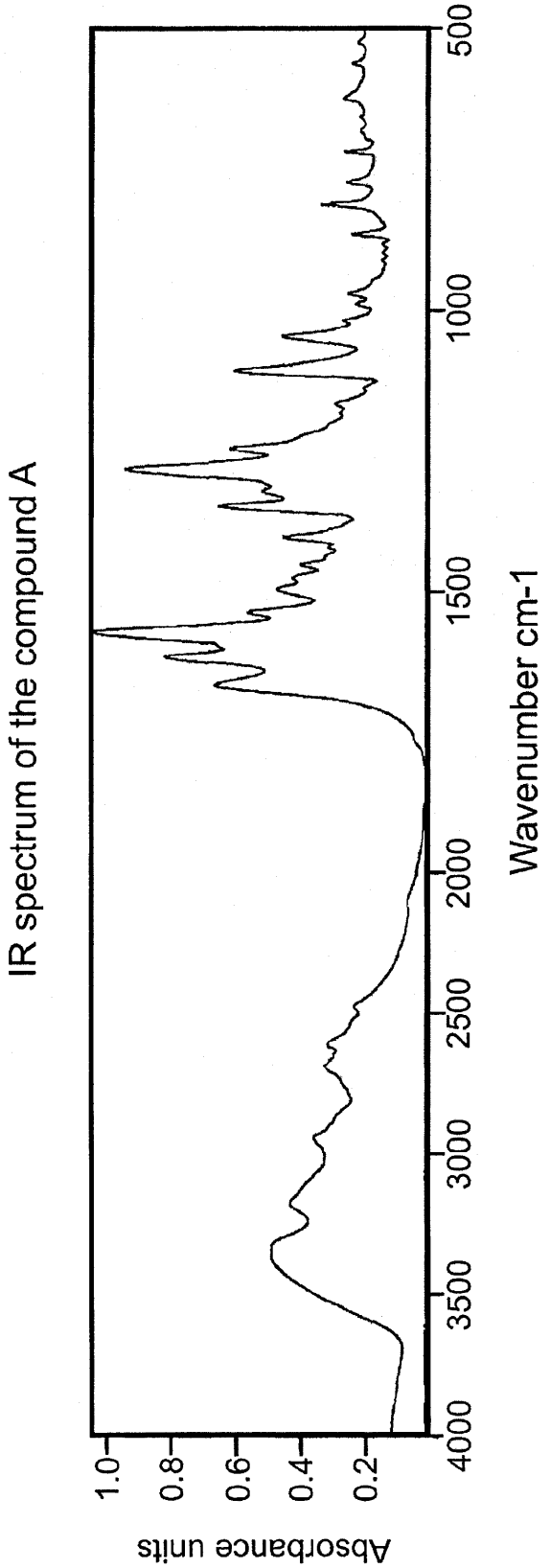

IR spectrum of the compound A
Absorbance units
1.0
0.8
0.6
0.4
0.2
4000
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1

Fig. 7

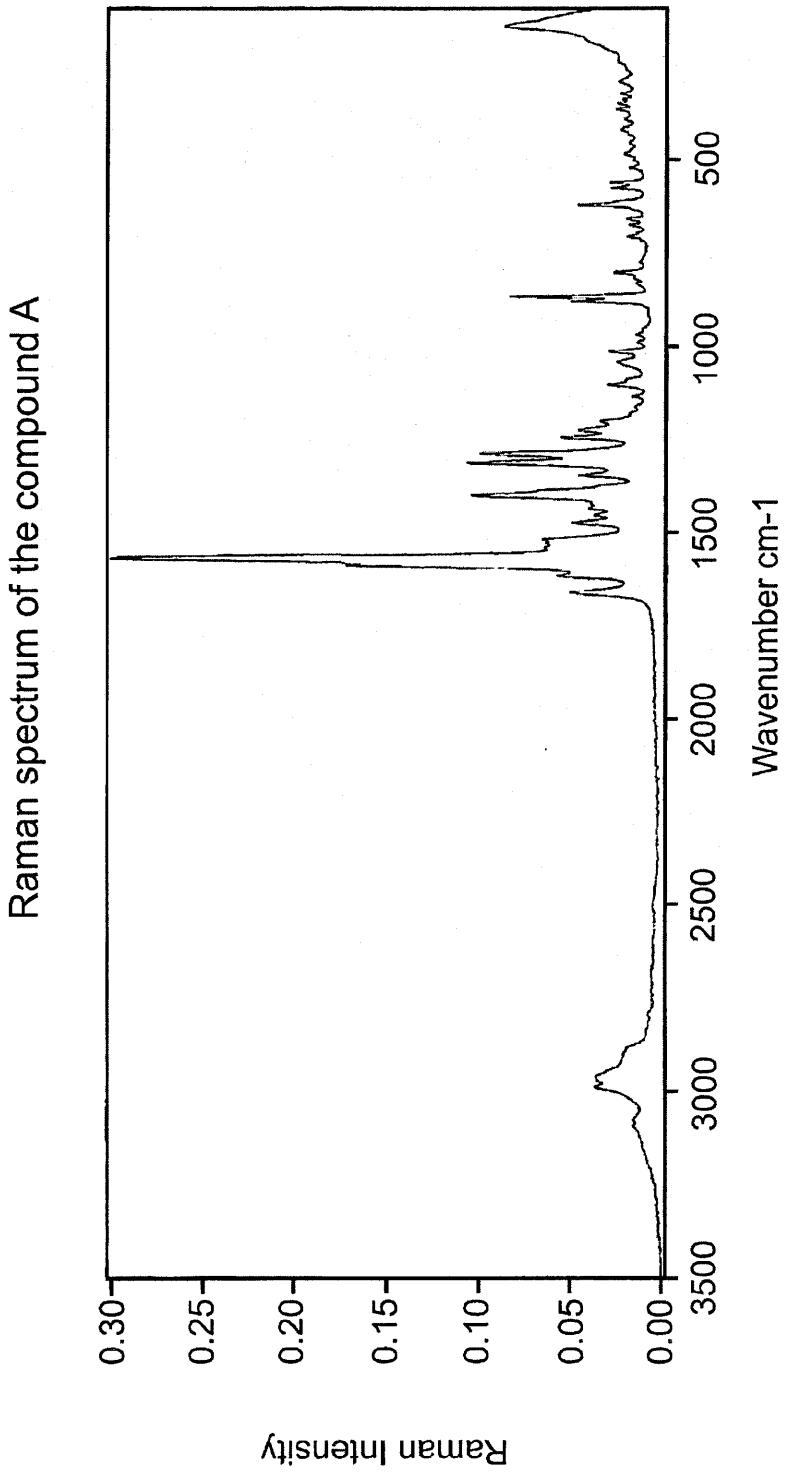

Raman spectrum of the compound A
Raman Intensity
0.30
0.25
0.20
0.15
0.10
0.05
0.00
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1

Fig. 8

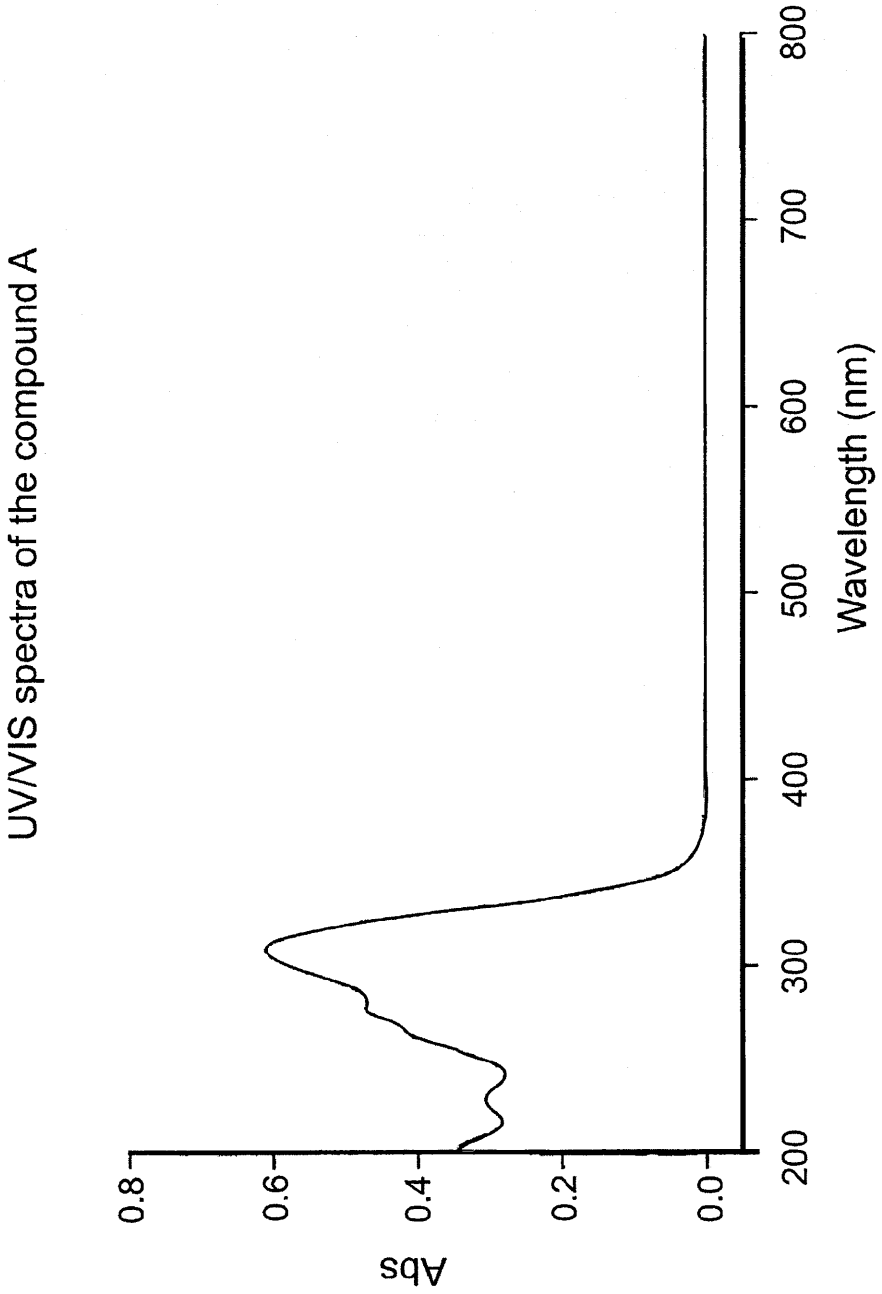
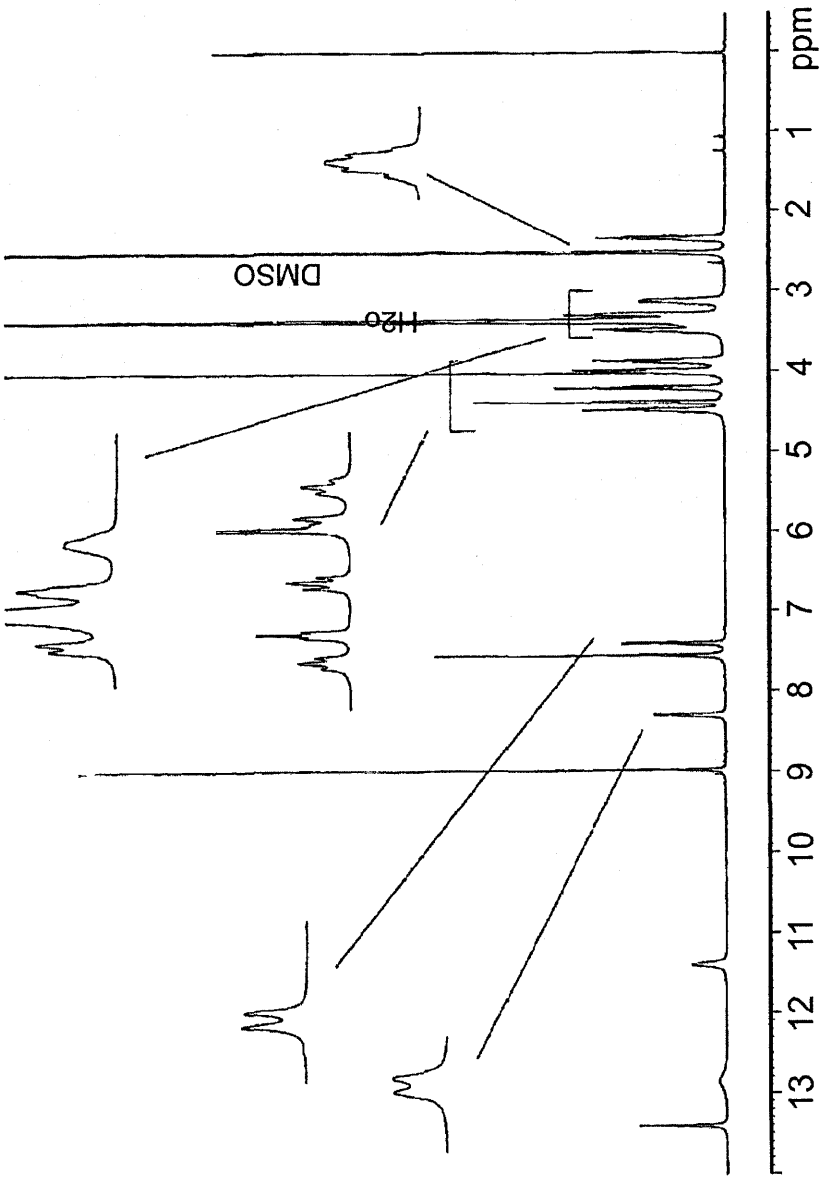

UV/VIS spectra of the compound A
Abs
0.0
0.2
0.4
0.6
0.8
200
300
400
500
600
700
800
Wavelength (nm)

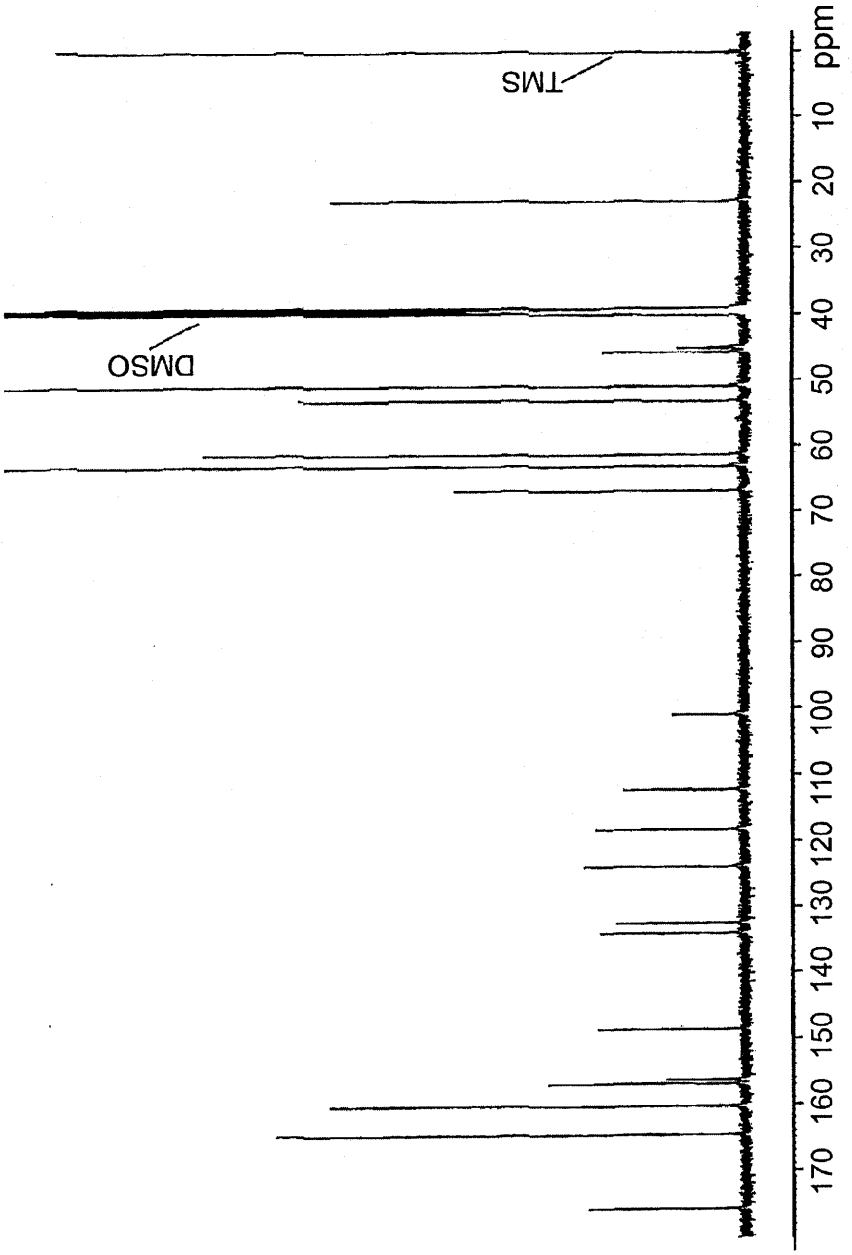
Fig. 9

Fig. 10



^{1}H-NMR Spectrum of the compound A

Fig. 11



^{13}C-NMR Spectrum of the compound A

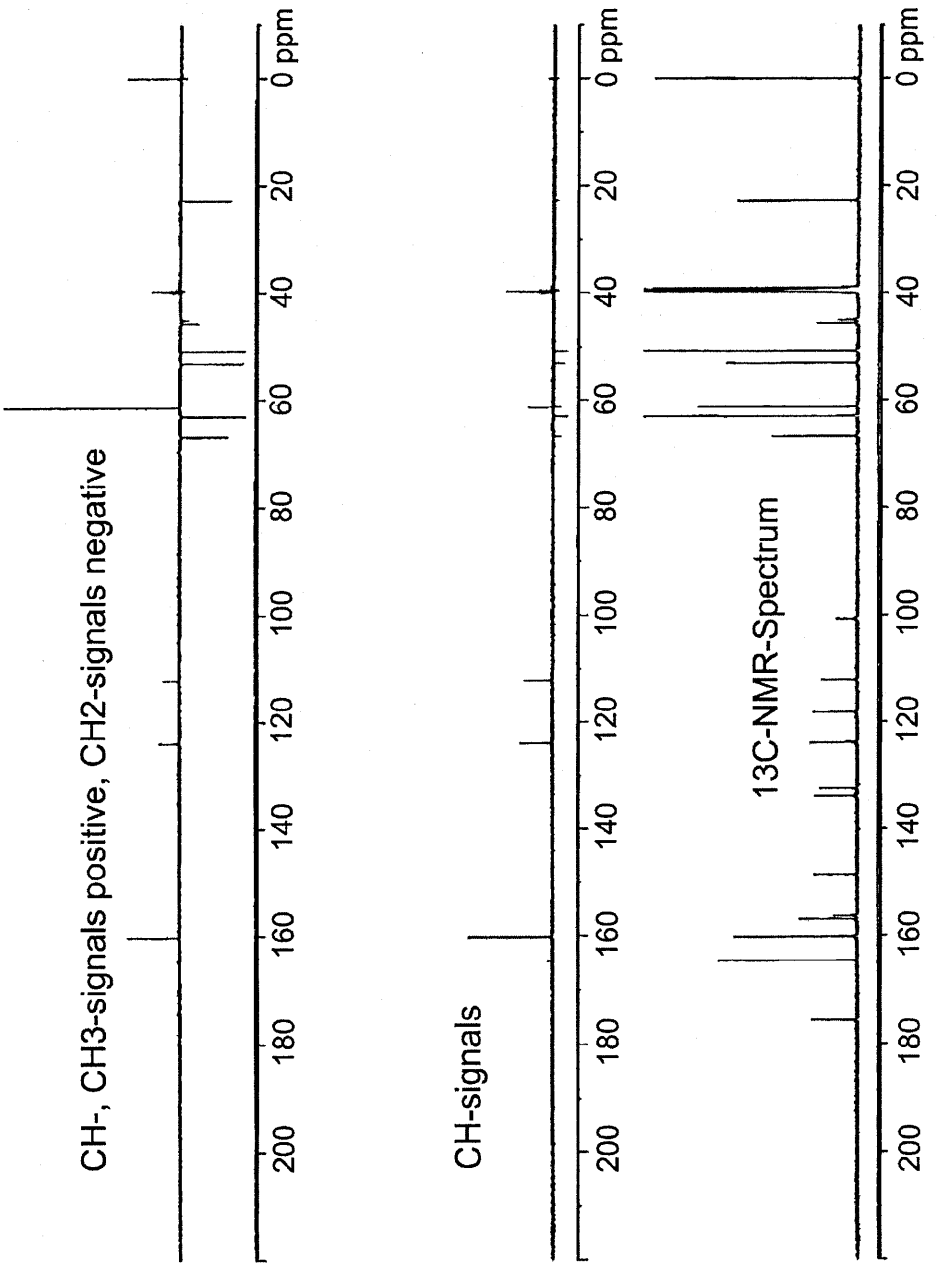
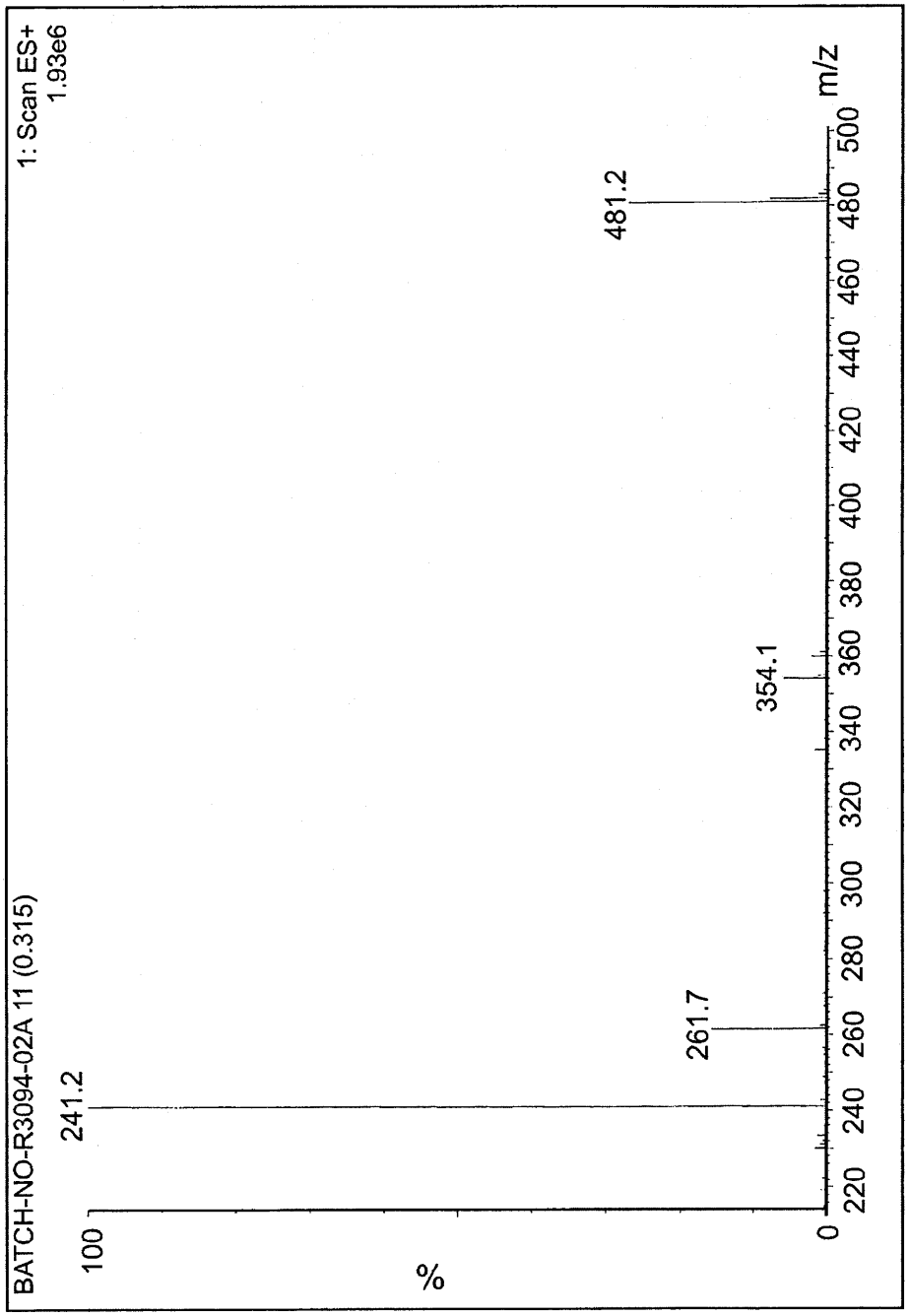


Fig. 12

^{13}C-NMR Spectra of the compound A



Mass Spectrum of the compound A

Fig. 13