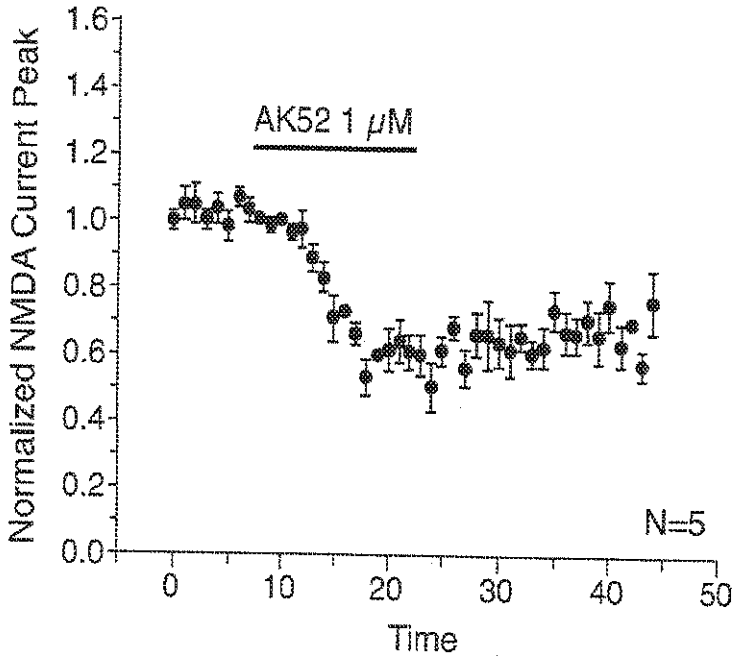

Normalized NMDA Current Peak
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
AK52 1 μM
N=5
0
10
20
30
40
50
Time

Fig. 1A

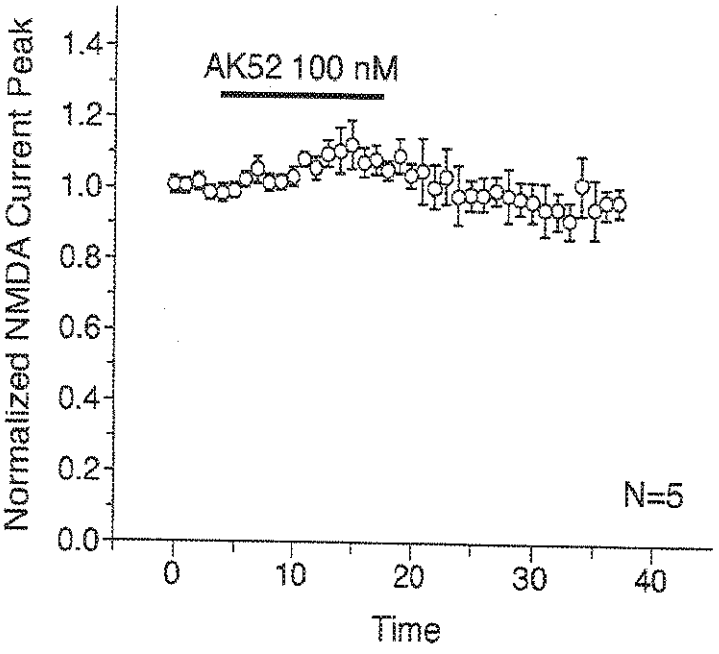

Normalized NMDA Current Peak
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
AK52 100 nM
N=5
0
10
20
30
40
Time

Fig. 1B

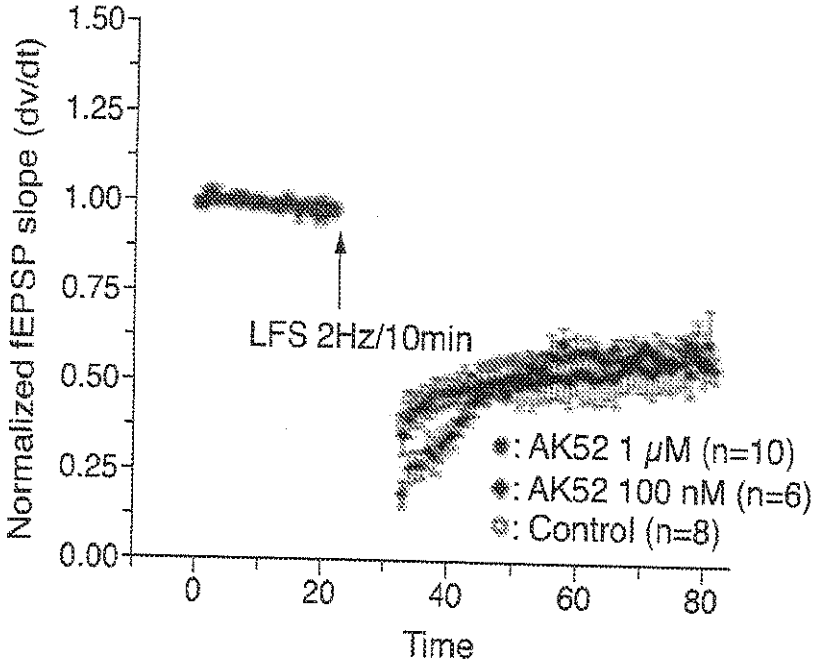

Normalized fEPSP slope (dv/dt)
1.50
1.25
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
Time
LFS 2Hz/10min
: AK52 1 μM (n=10)
: AK52 100 nM (n=6)
: Control (n=8)

Fig. 1C

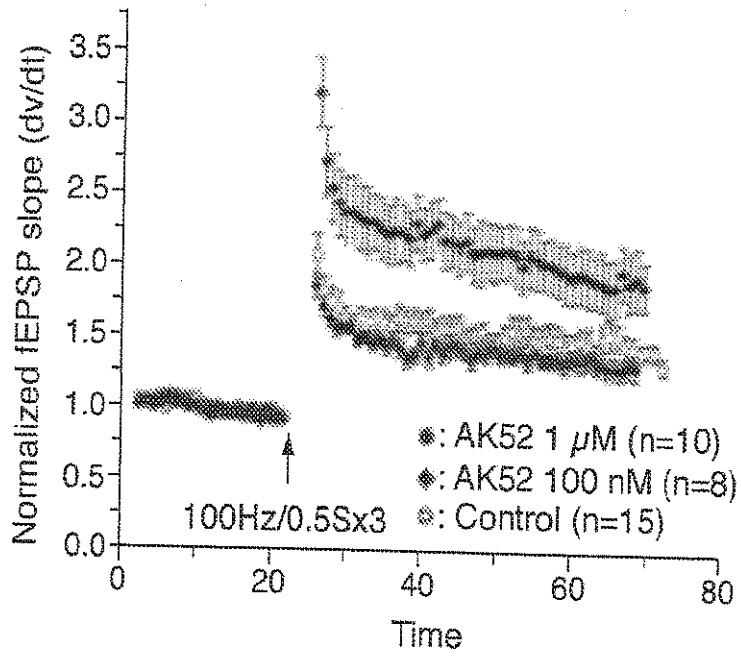

Normalized fEPSP slope (dv/dt)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
20
40
60
80
Time
100Hz/0.5Sx3
: AK52 1 μM (n=10)
: AK52 100 nM (n=8)
: Control (n=15)

Fig. 1D

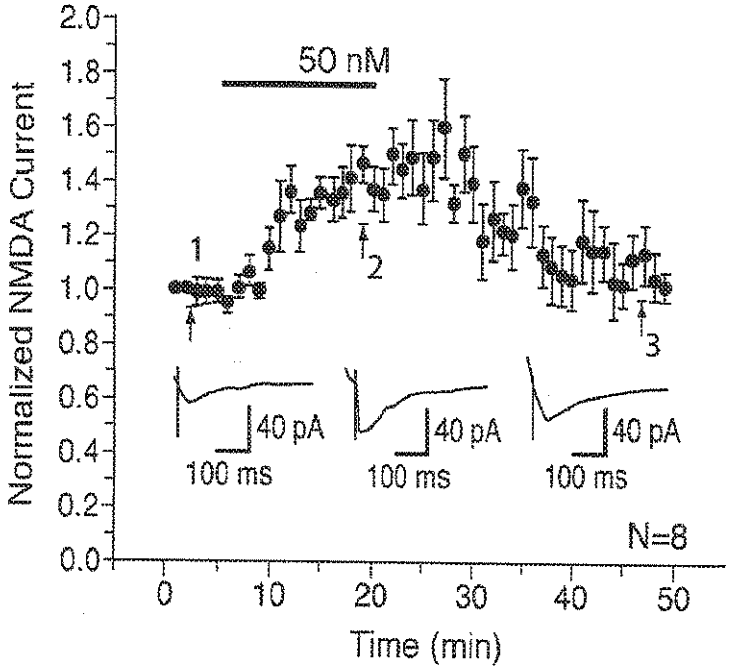

50 nM
Normalized NMDA Current
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1
2
3
40 pA
100 ms
40 pA
100 ms
40 pA
100 ms
N=8
0
10
20
30
40
50
Time (min)

Fig. 2A

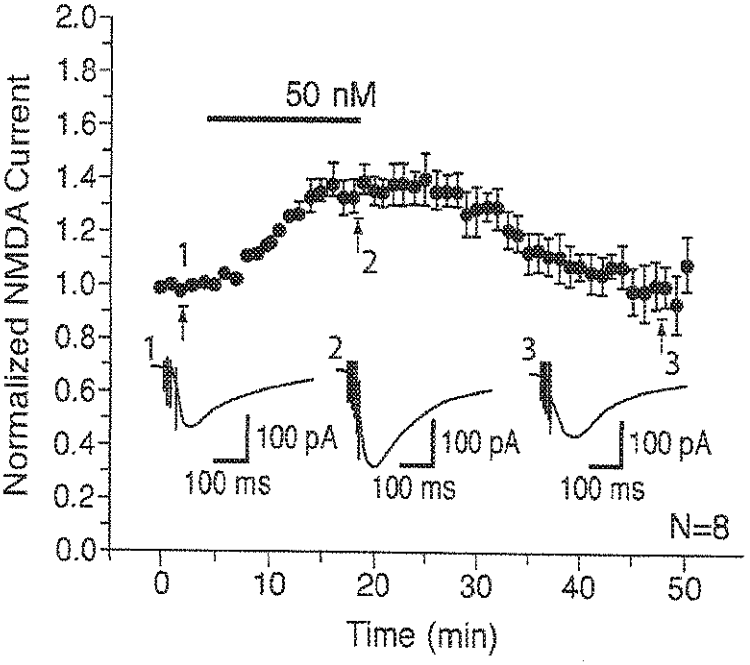

50 nM
Normalized NMDA Current
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1
2
3
100 pA
100 ms
100 pA
100 ms
100 pA
100 ms
N=8
0
10
20
30
40
50
Time (min)

Fig. 2B

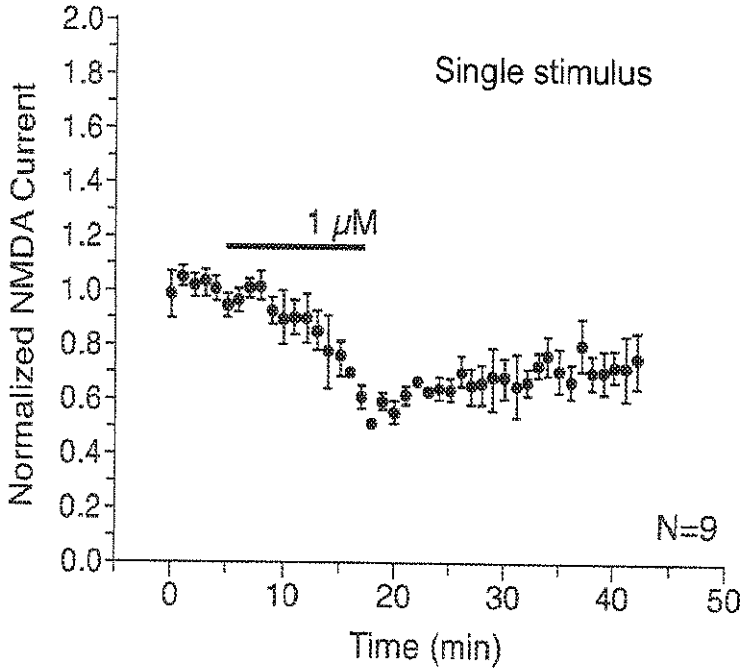

Single stimulus
1 μM
N=9
Normalized NMDA Current
Time (min)
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50

Fig. 2C

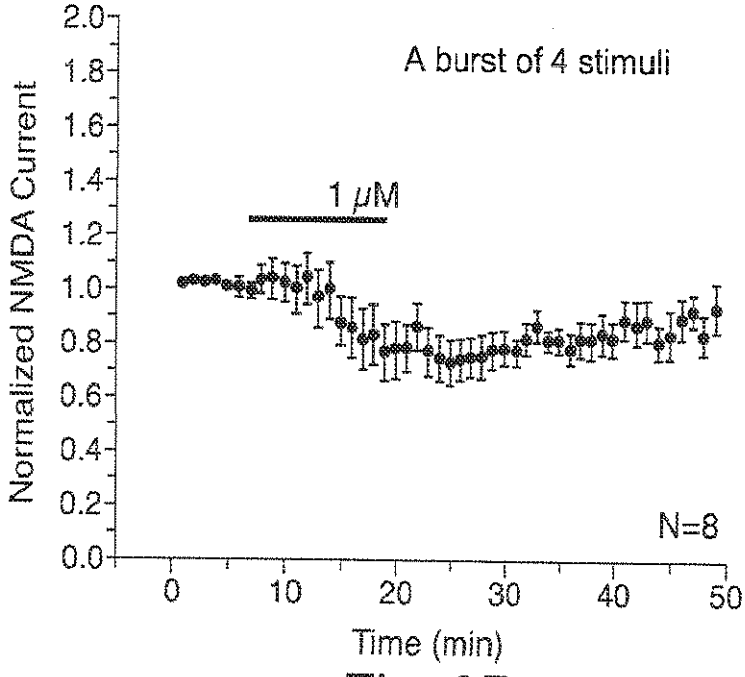

A burst of 4 stimuli
1 μM
N=8
Normalized NMDA Current
Time (min)
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50

Fig. 2D

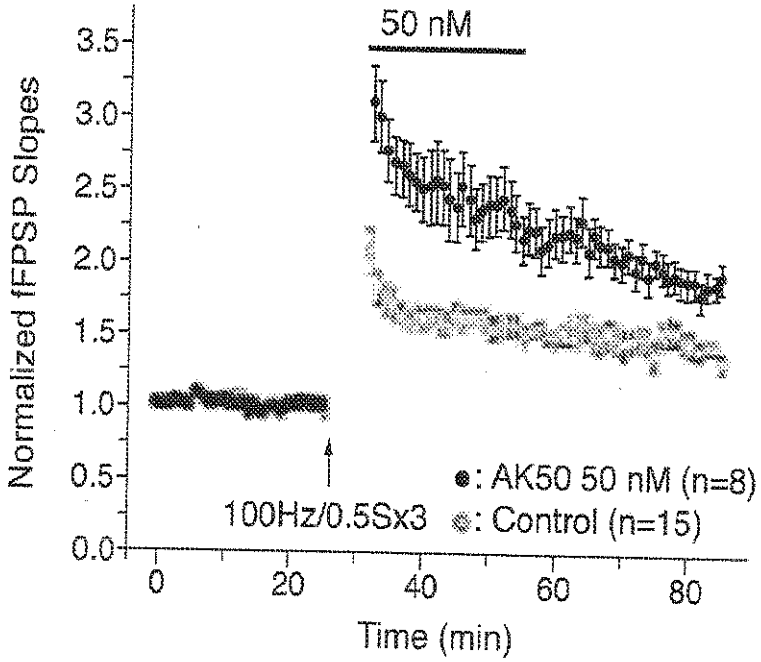

50 nM
Normalized fFPSP Slopes
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
20
40
60
80
Time (min)
100Hz/0.5Sx3
●: AK50 50 nM (n=8)
●: Control (n=15)

Fig. 2E

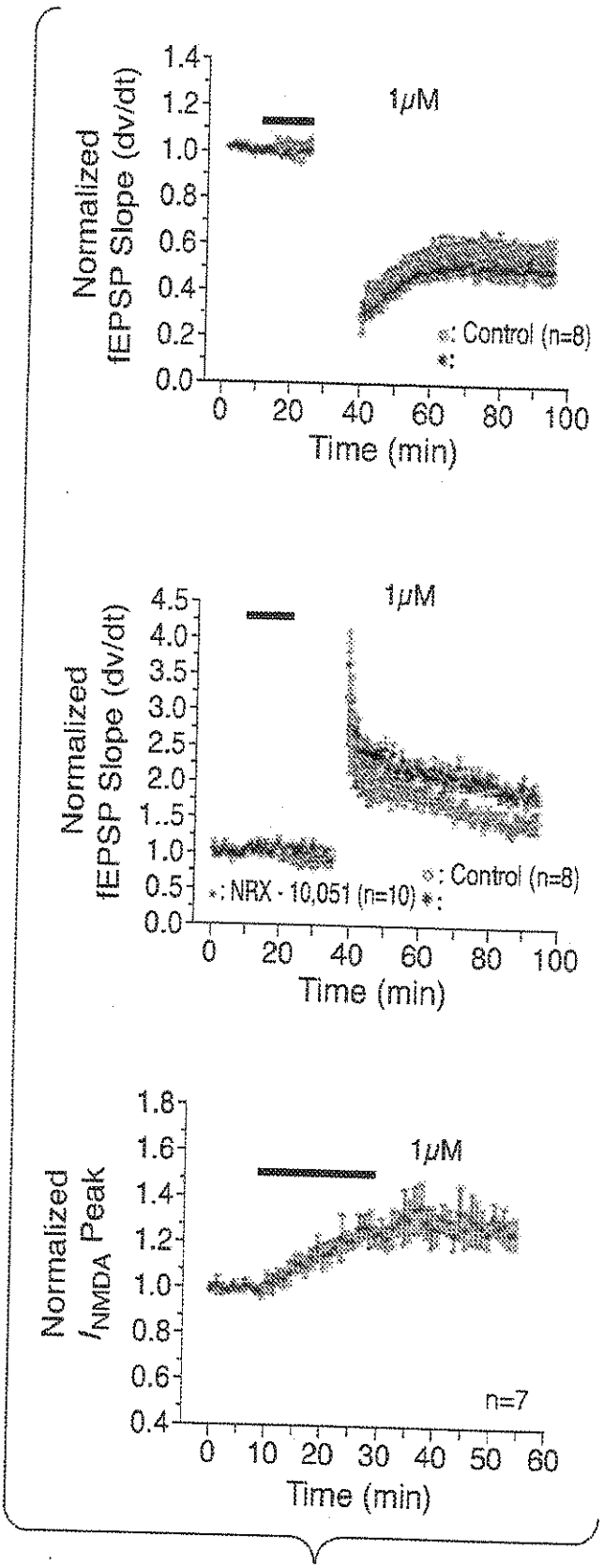

Normalized fEPSP Slope (dv/dt)
1μM
○: Control (n=8)
●:
Time (min)
Normalized fEPSP Slope (dv/dt)
1μM
●: NRX - 10,051 (n=10)
○: Control (n=8)
Time (min)
Normalized I_{NMDA} Peak
1μM
n=7
Time (min)

Fig. 3

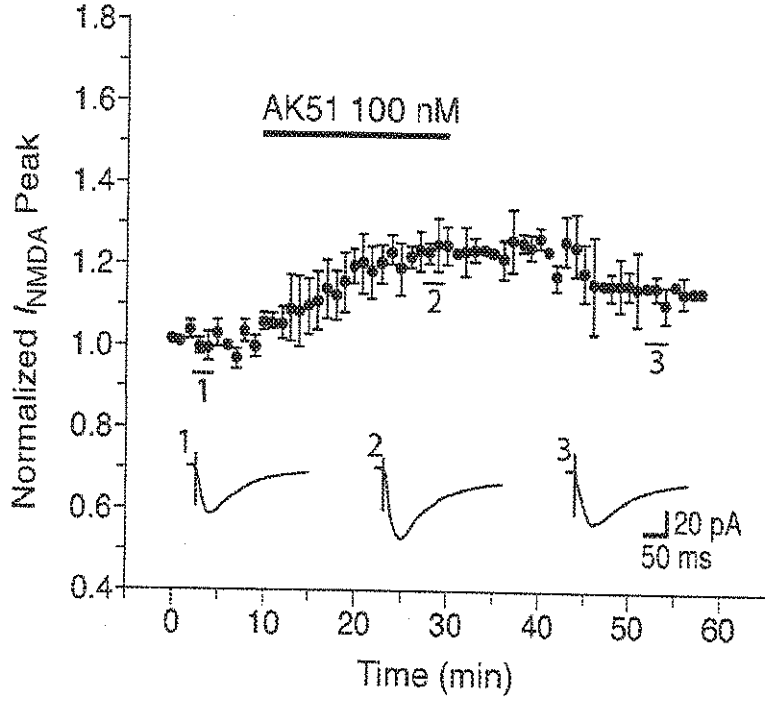

AK51 100 nM
Normalized I_{NMDA} Peak
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0
10
20
30
40
50
60
Time (min)
1
2
3
20 pA
50 ms

Fig. 4A

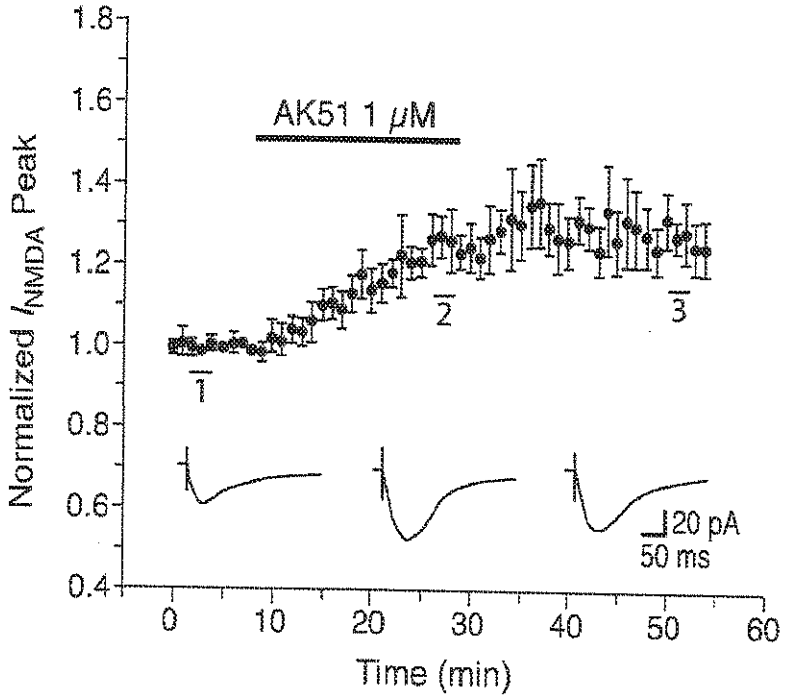

AK51 1 μM
Normalized I_{NMDA} Peak
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0
10
20
30
40
50
60
Time (min)
1
2
3
20 pA
50 ms

Fig. 4B

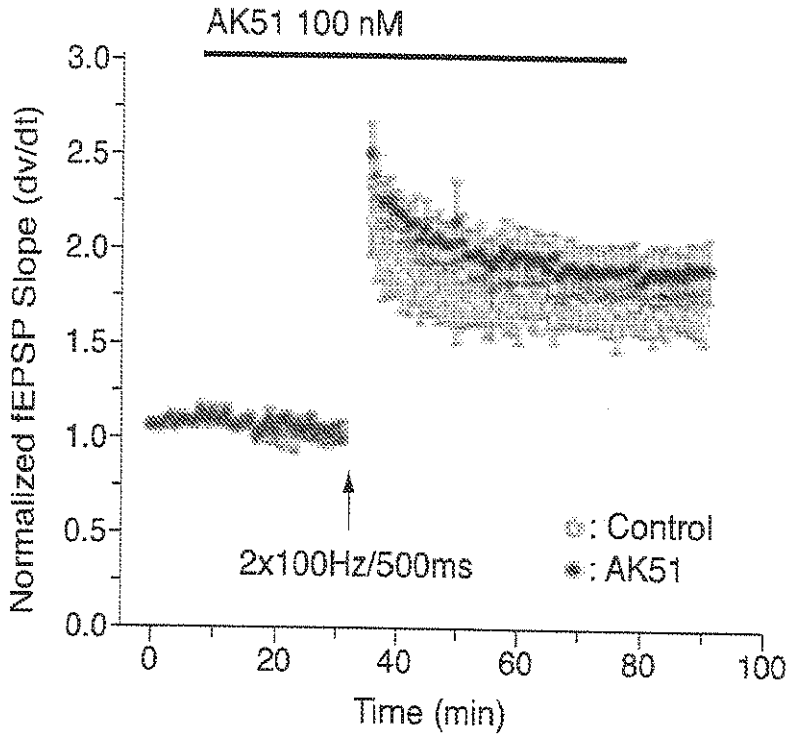

AK51 100 nM
Normalized fEPSP Slope (dv/dt)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
20
40
60
80
100
Time (min)
2x100Hz/500ms
: Control
: AK51

Fig. 4C

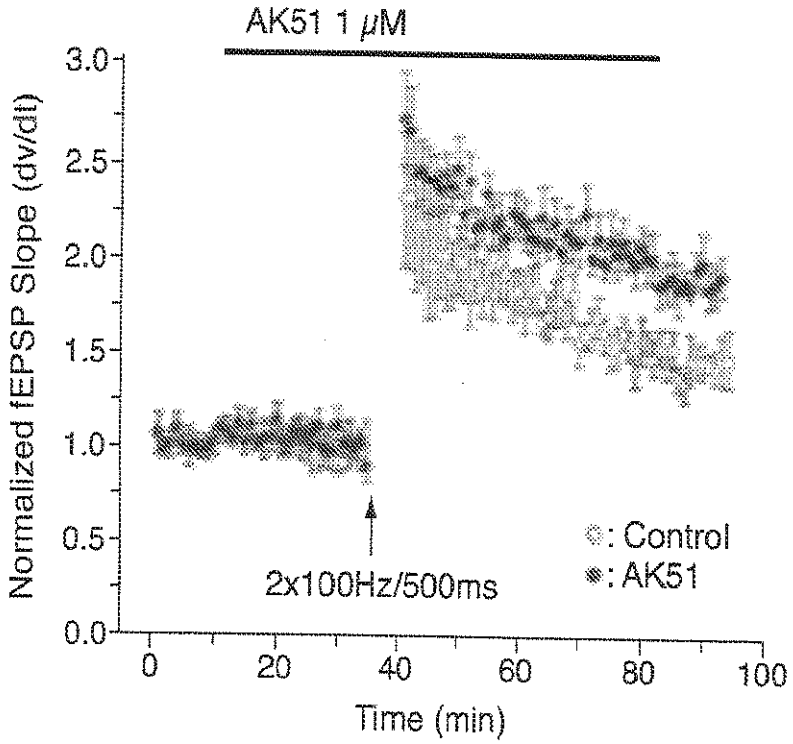

AK51 1 μM
Normalized fEPSP Slope (dv/dt)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
20
40
60
80
100
Time (min)
2x100Hz/500ms
: Control
: AK51

Fig. 4D

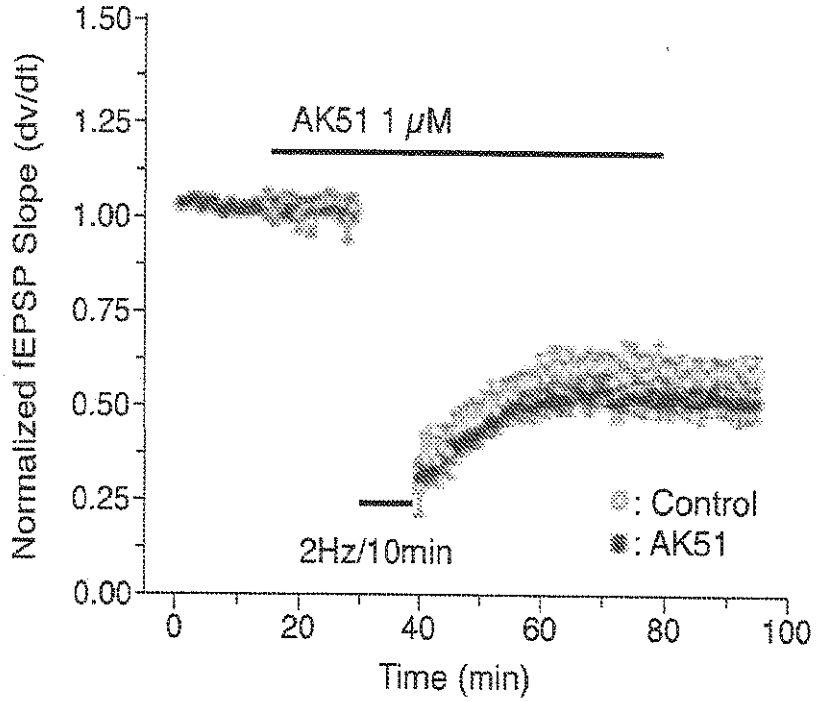

1.50
1.25
1.00
0.75
0.50
0.25
0.00
Normalized fEPSP Slope (dv/dt)
AK51 1 μM
2Hz/10min
: Control
: AK51
0
20
40
60
80
100
Time (min)

Fig. 4E

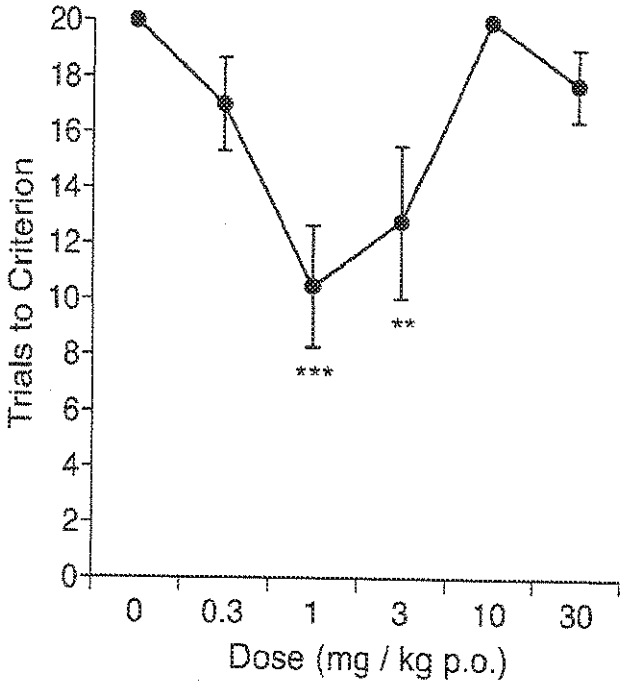

Trials to Criterion
20
18
16
14
12
10
8
6
4
2
0
***
**
0
0.3
1
3
10
30
Dose (mg / kg p.o.)

Fig. 5

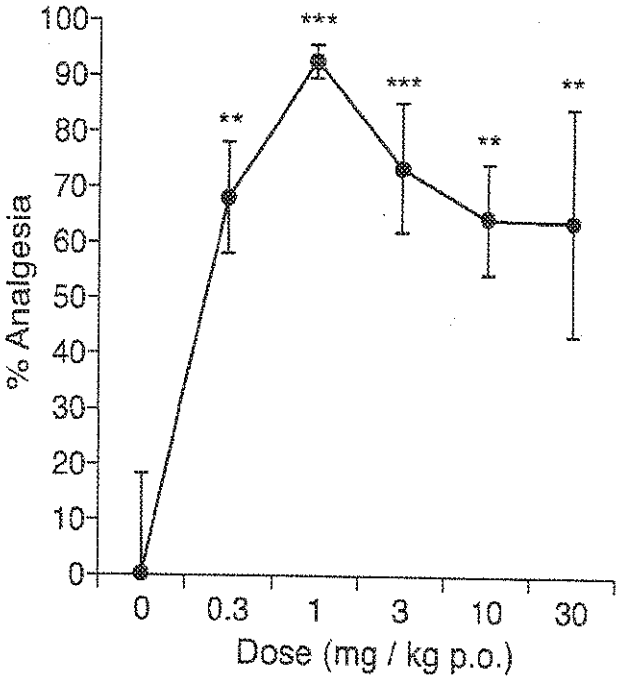

% Analgesia
100
90
80
70
60
50
40
30
20
10
0
**
***
***
**
**
0
0.3
1
3
10
30
Dose (mg / kg p.o.)

Fig. 6

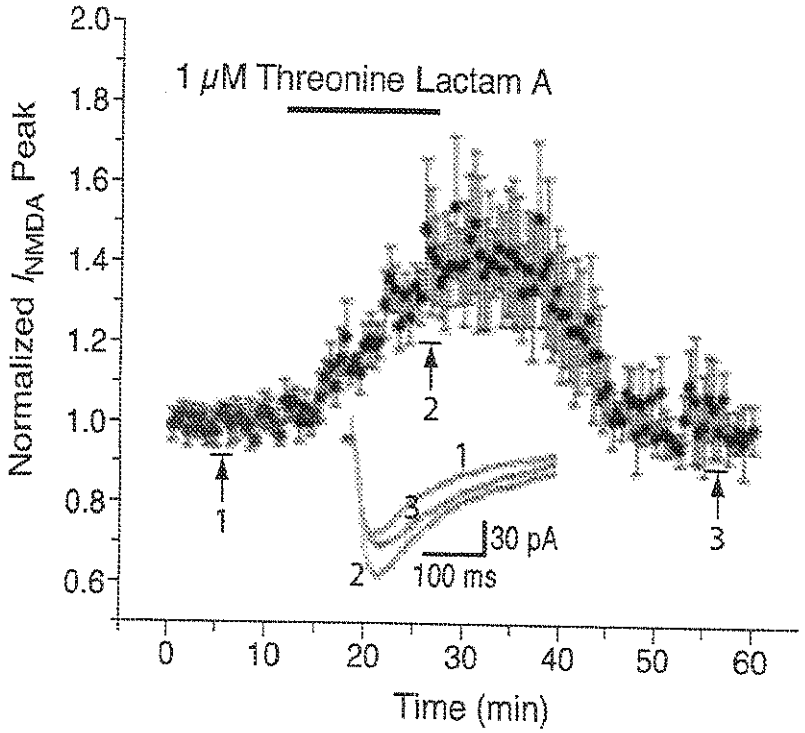

1 μM Threonine Lactam A
Normalized I_{NMDA} Peak
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
1
2
3
30 pA
100 ms
0
10
20
30
40
50
60
Time (min)

Fig. 7A

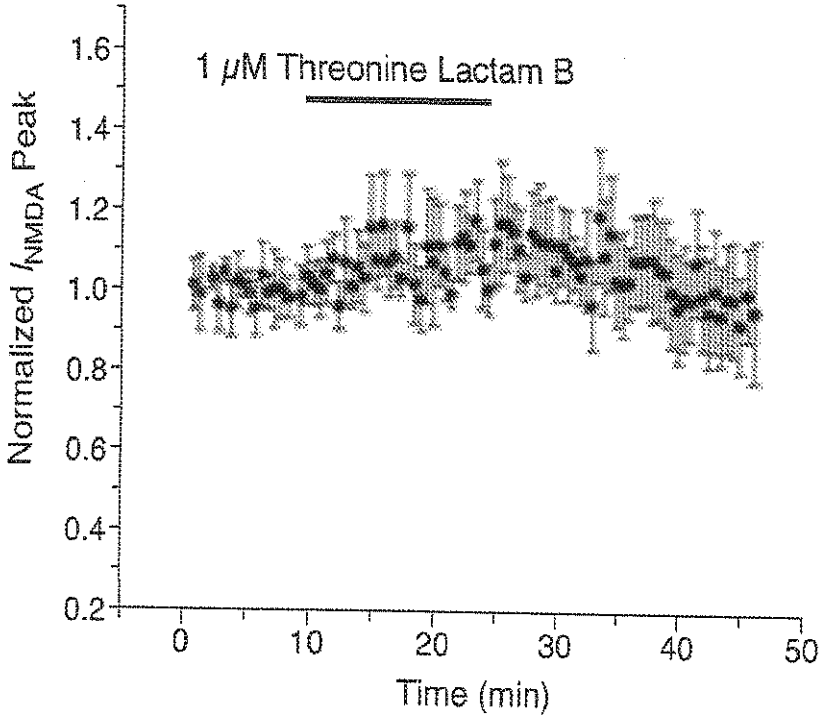

1 μM Threonine Lactam B
Normalized I_{NMDA} Peak
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
10
20
30
40
50
Time (min)

Fig. 7B

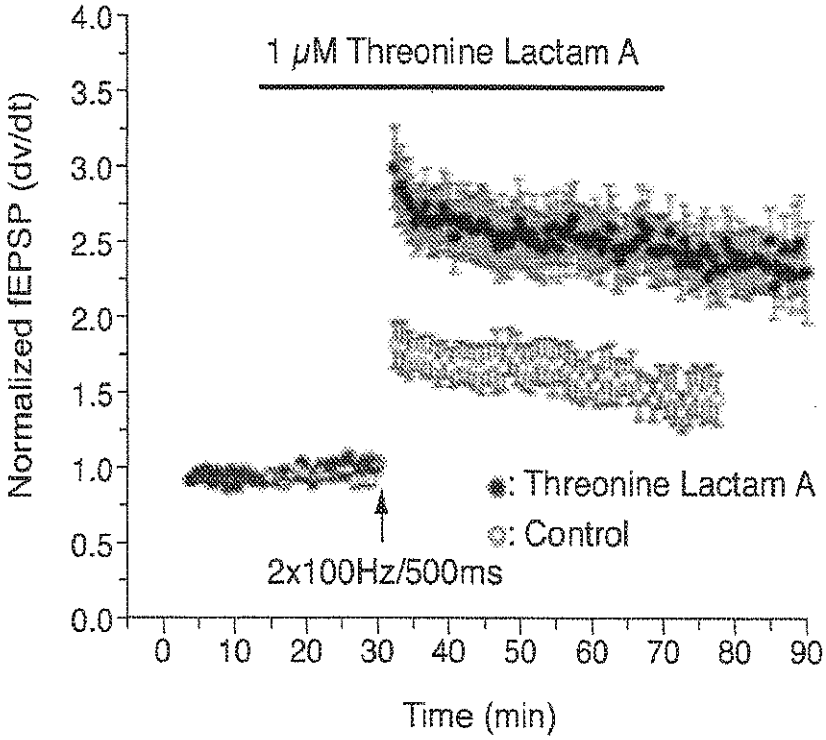

1 μM Threonine Lactam A
Normalized fEPSP (dv/dt)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
: Threonine Lactam A
: Control
2x100Hz/500ms
0
10
20
30
40
50
60
70
80
90
Time (min)

Fig. 7C

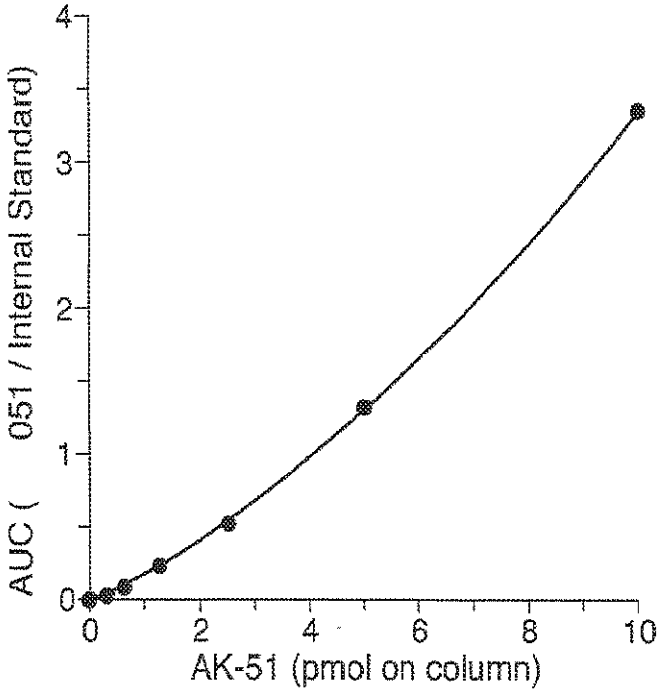

AUC (051 / Internal Standard)
4
3
2
1
0
0
2
4
6
8
10
AK-51 (pmol on column)

Fig. 8

Sequence from 1PDB7: Fragment, Ligand Binding Core (SEQ ID NO. 1):

```
G                                                                    1
MSTRLKI                                                              8
VTIHQEPFVY VKPTMSDGTC KEEFTVNGDP VKKVICTGPN DTSPGSPRHT              58
VPQCCYGFCI DLLIKLARTM NFTYEVHLVA DGKFGTQERV NNSNKKEWNG             108
MMGELLSGQA DMIVAPLTIN NERAQYIEFS KPFKYQGLTI LVKK                   152

GT                                                                 154
RITGINDP                                                           162
RLRNPSDKFI YATVKQSSVD IYFRRQVELS TMYRHMEKHN YESAAEAIQA             212
VRDNKLHAFI WDSAVLEFEA SQKCDLVTTG ELFFRSGFGI GMRKDSPWKQ             262
NVSLSILKSH ENGFMEDLDK TWVRYQECDS                                   292

GLYX-13:
1) Proline 124
2) Threonine 126
3) Glutamine 178
4) Serine 180

DCKA
1) Threonine 126
2) Arginine 131

DCS
1) Proline 124
2) Threonine 126
3) Arginine 131
4) Asparte 224

D-serine/glycine
1) Threonine 126
2) Arginine 131
3) Serine 180
4) Asparte 224
```

Fig. 9

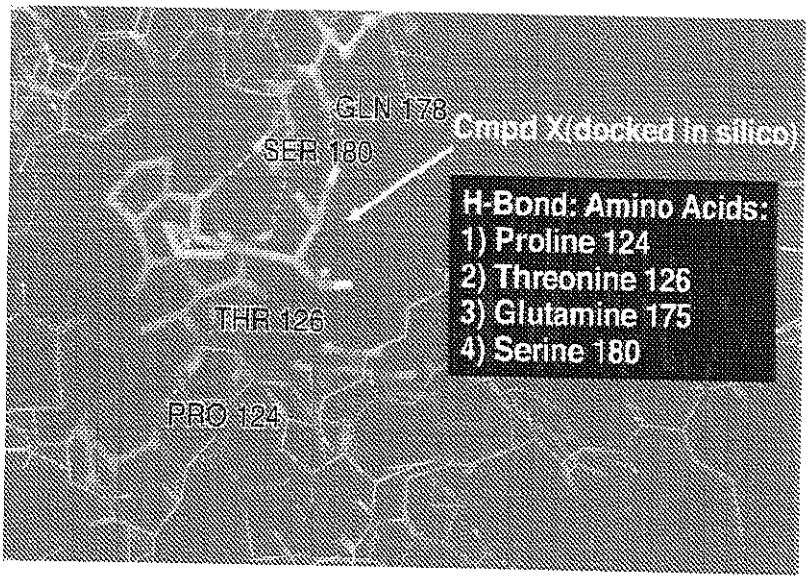

GLN 178
SER 180
Cmpd X(docked in silico)
H-Bond: Amino Acids:
1) Proline 124
2) Threonine 126
3) Glutamine 175
4) Serine 180
THR 126
PRO 124

Fig. 10

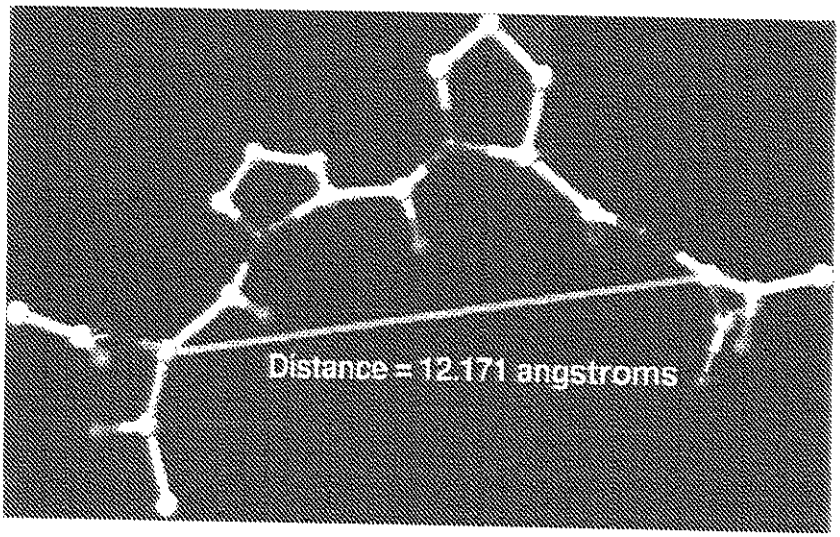

Distance = 12.171 angstroms

Fig. 11

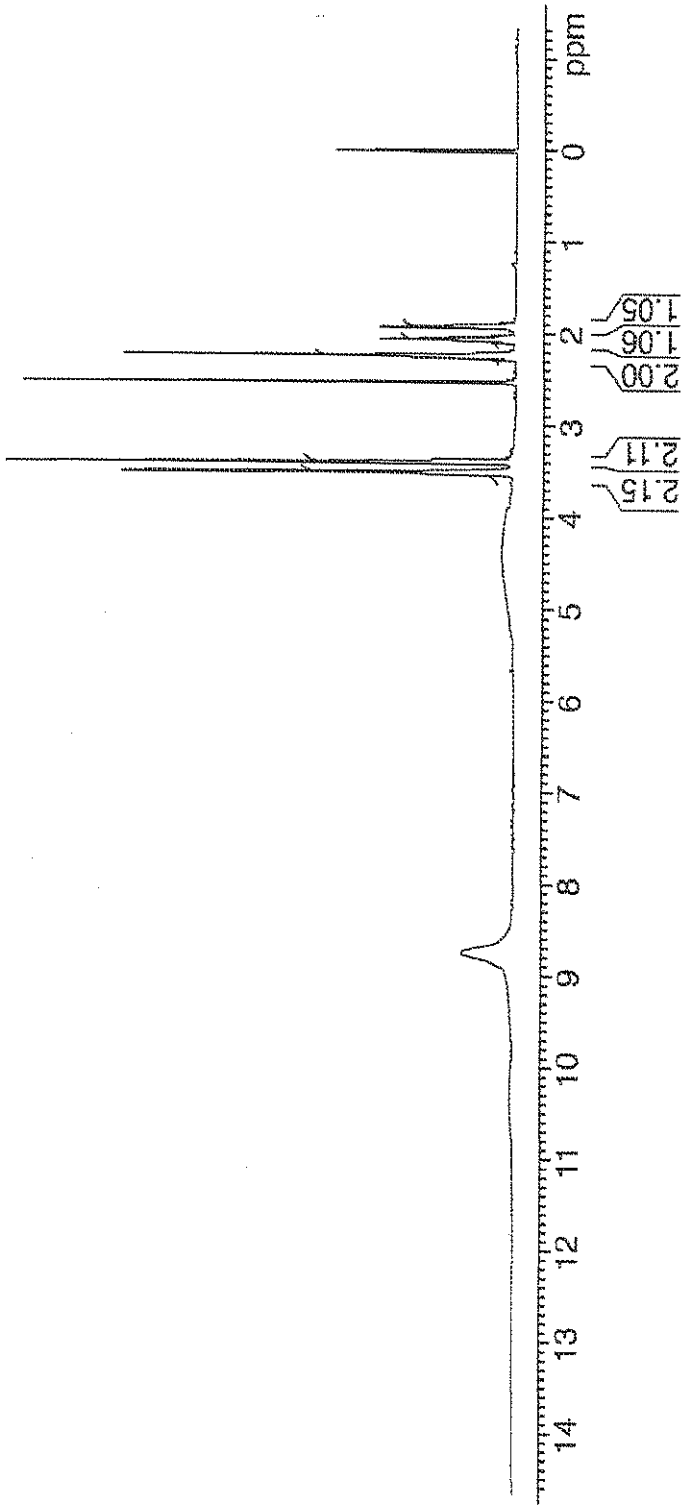


Fig. 12

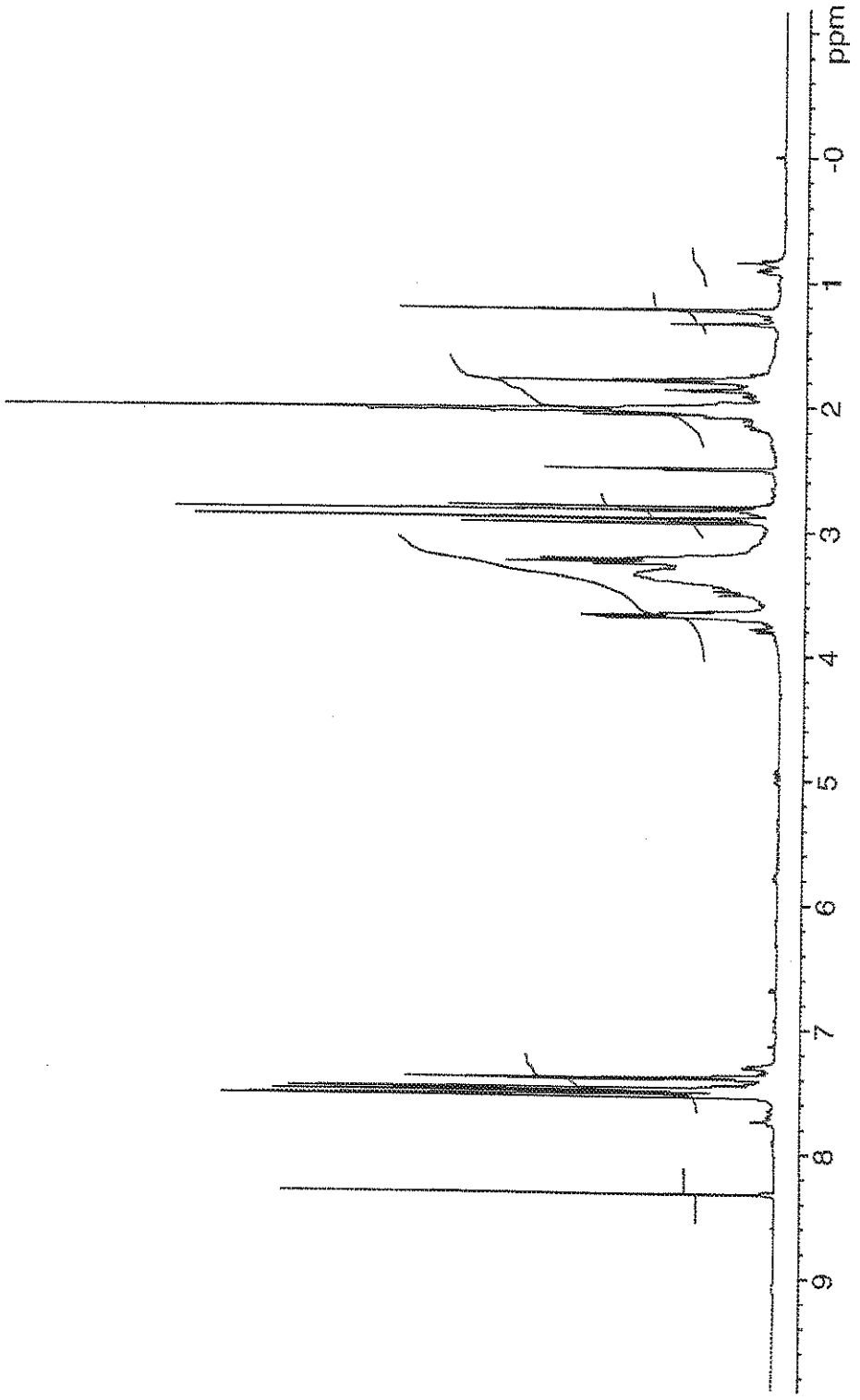


Fig. 13