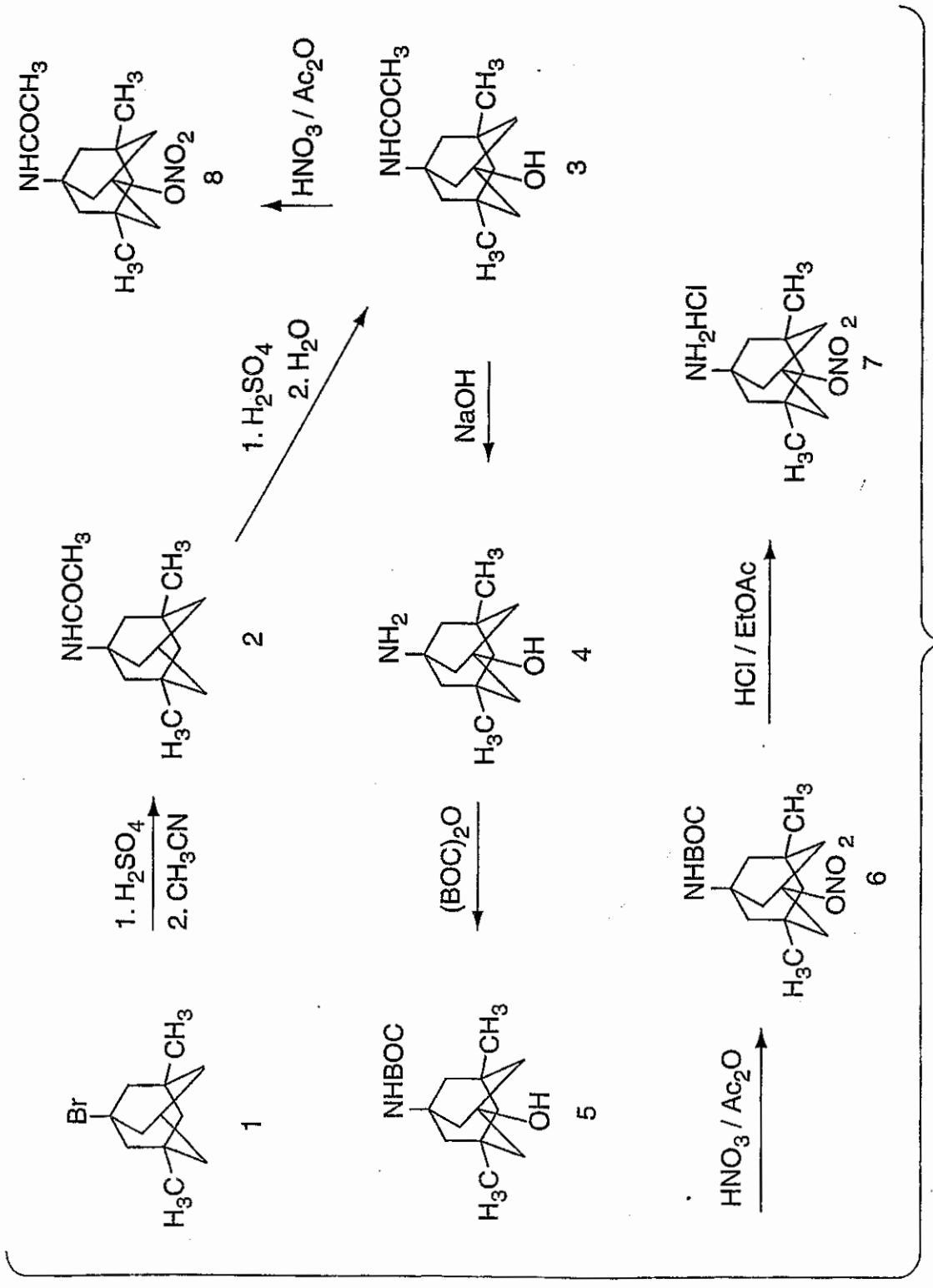

Br
H_3C
CH_3
1
1. H_2SO_4
2. CH_3CN
$NHCOCH_3$
2
1. H_2SO_4
2. H_2O
HNO_3 / Ac_2O
$NHCOCH_3$
ONO_2
8
NaOH
$NHCOCH_3$
OH
3
$(BOC)_2O$
NH_2
4
HNO_3 / Ac_2O
NHBOC
5
HCl / EtOAc
NHBOC
ONO_2
6
NH_2HCl
ONO_2
7

Fig. 1

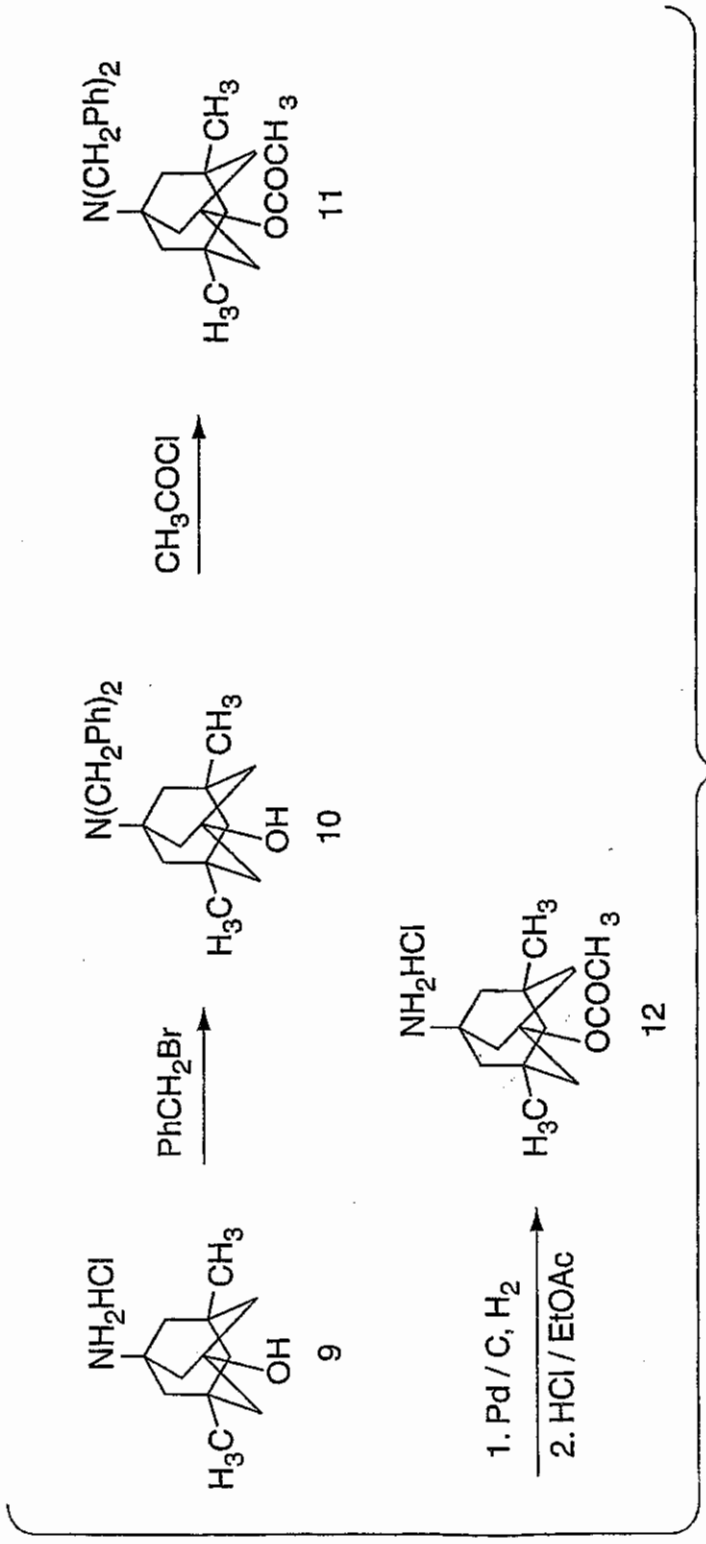

NH2HCl
CH3
OH
H3C
9
PhCH2Br
N(CH2Ph)2
CH3
OH
H3C
10
CH3COCl
N(CH2Ph)2
CH3
OCOCH3
H3C
11
1. Pd / C, H2
2. HCl / EtOAc
NH2HCl
CH3
OCOCH3
H3C
12

Fig. 2

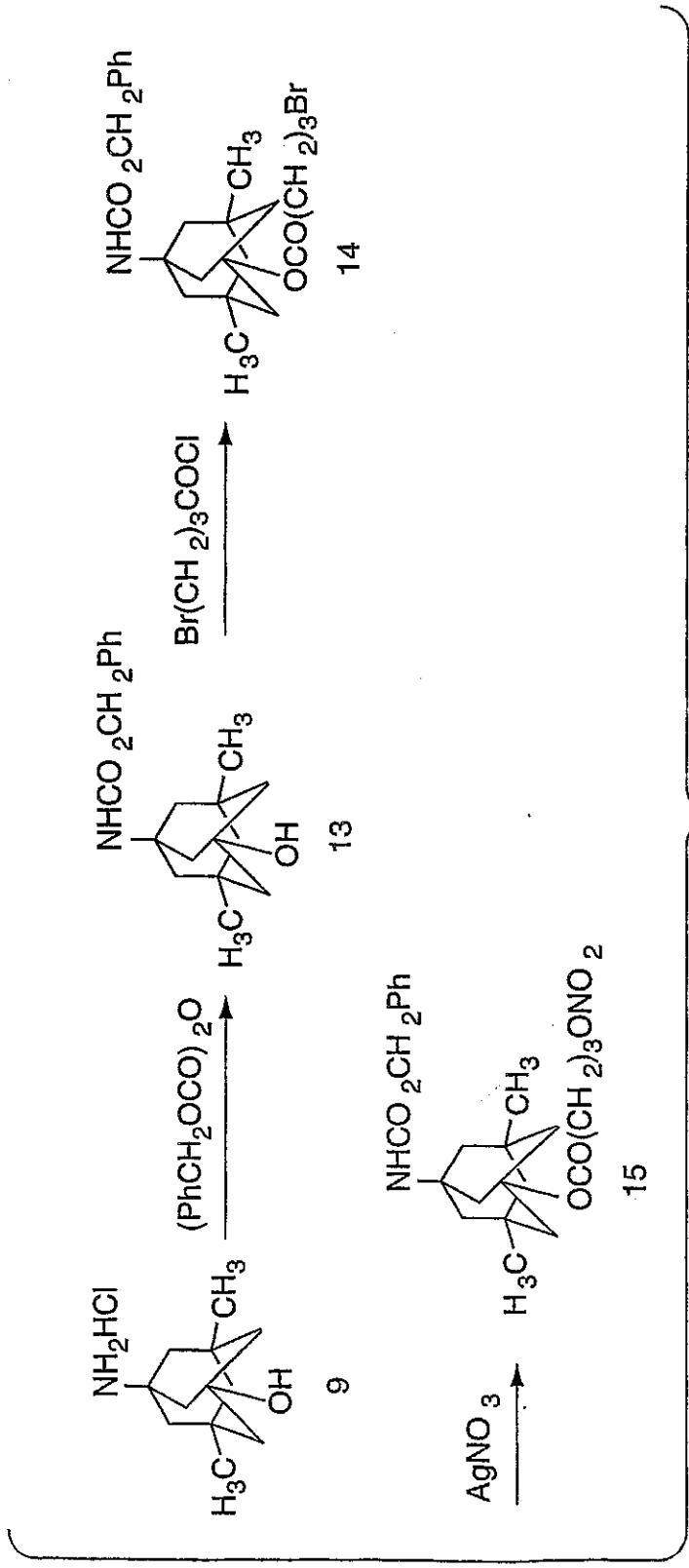

NH2HCl
CH3
OH
H3C
9
(PhCH2OCO)2O
NHCO2CH2Ph
CH3
OH
H3C
13
Br(CH2)3COCl
NHCO2CH2Ph
CH3
OCO(CH2)3Br
H3C
14
AgNO3
NHCO2CH2Ph
CH3
OCO(CH2)3ONO2
H3C
15

Fig. 3

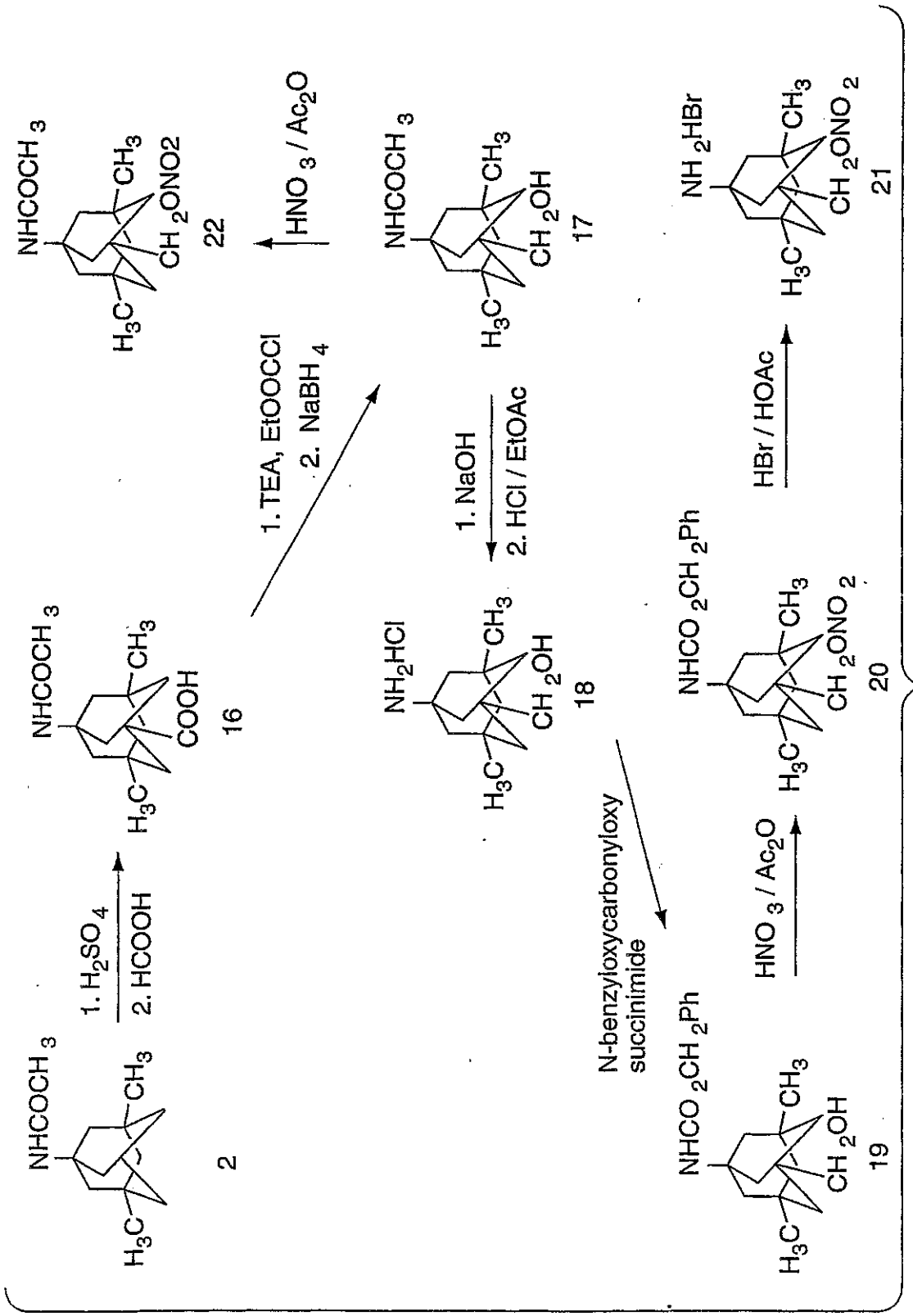

NHCOCH 3
CH3
CH 2ONO2
H3C
22
HNO 3 / Ac2O
1. TEA, EtOOCCl
2. NaBH 4
NHCOCH 3
CH3
CH 2OH
H3C
17
NHCOCH 3
CH3
COOH
H3C
16
1. NaOH
2. HCl / EtOAc
NH2HCl
CH3
CH 2OH
H3C
18
HBr / HOAc
NH 2HBr
CH3
CH 2ONO 2
H3C
21
1. H2SO 4
2. HCOOH
NHCOCH 3
CH3
H3C
2
N-benzyloxycarbonyloxy
succinimide
NHCO 2CH 2Ph
CH3
CH 2OH
H3C
19
HNO 3 / Ac2O
NHCO 2CH 2Ph
CH3
CH 2ONO 2
H3C
20

Fig. 4

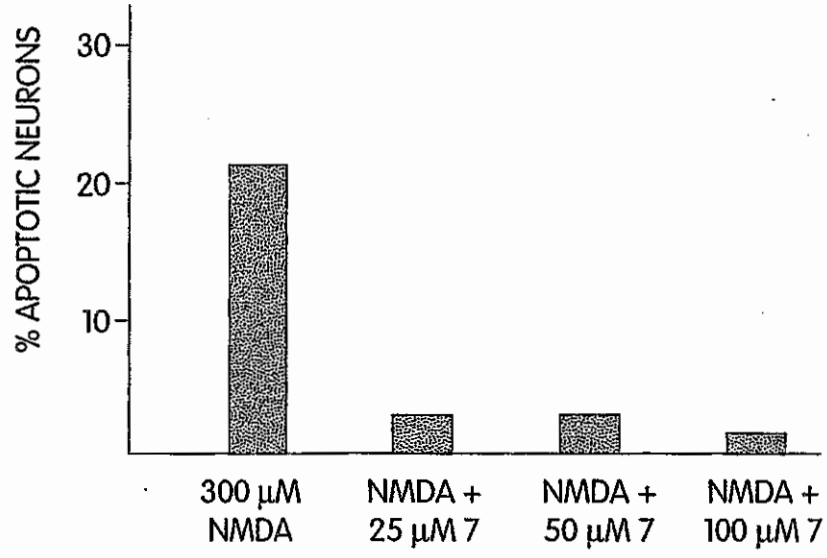

% APOPTOTIC NEURONS
30
20
10
300 μM NMDA
NMDA + 25 μM 7
NMDA + 50 μM 7
NMDA + 100 μM 7

Fig. 5

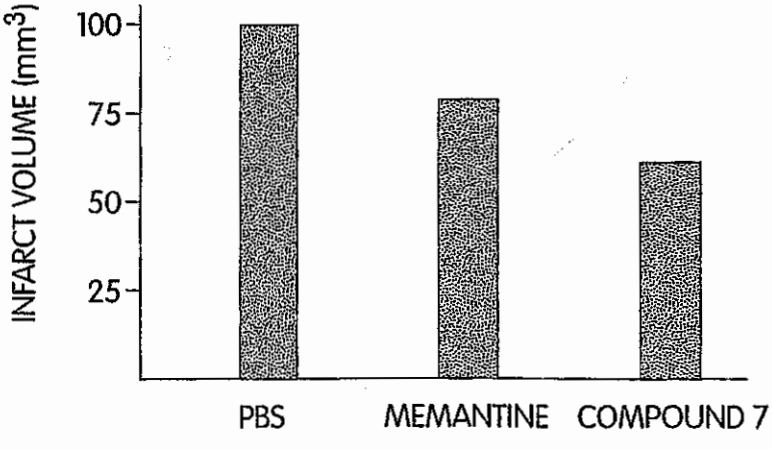

INFARCT VOLUME (mm3)
100
75
50
25
PBS
MEMANTINE
COMPOUND 7

Fig. 6

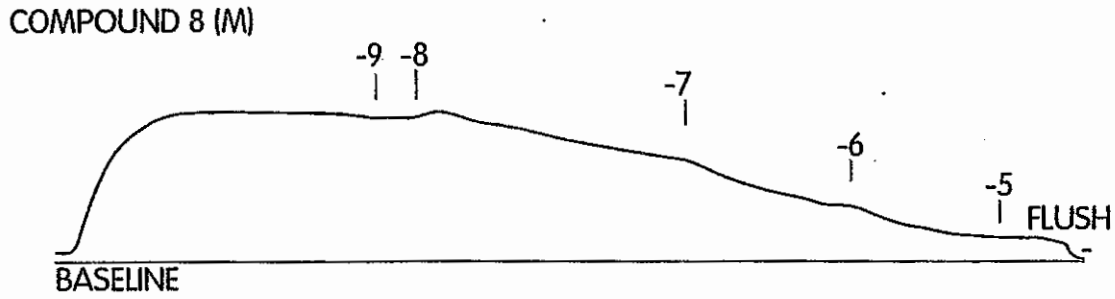


Fig. 7A

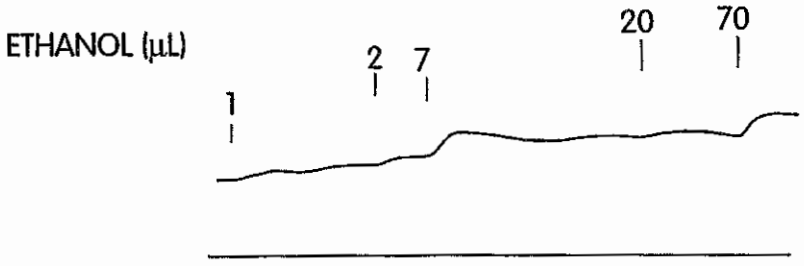


Fig. 7B

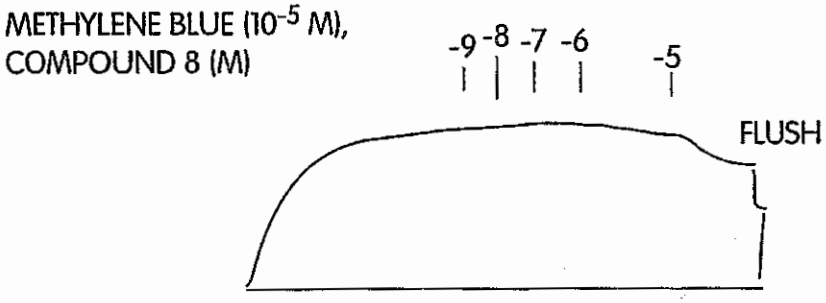


Fig. 7C

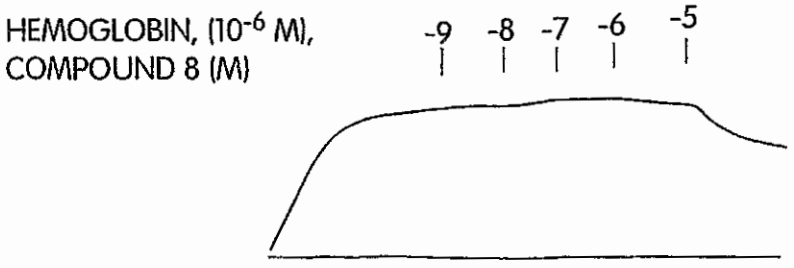


Fig. 7D

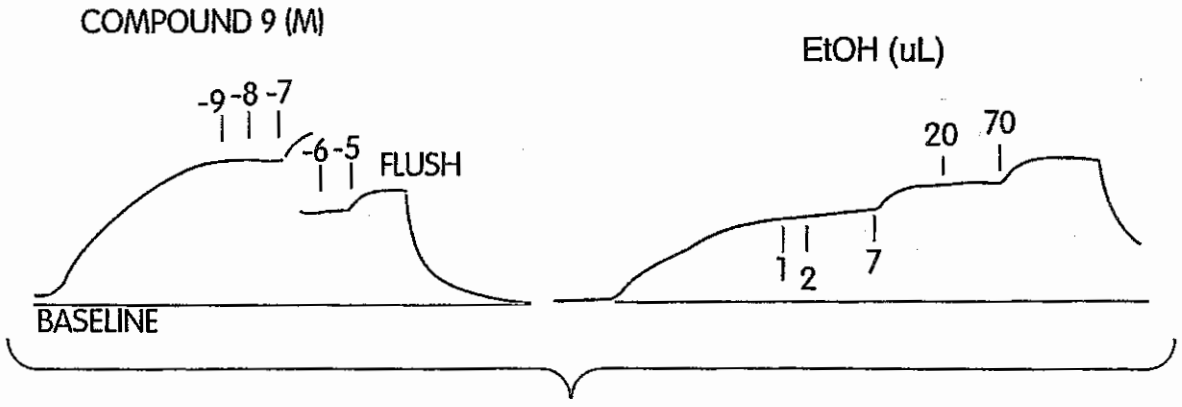


Fig. 8A

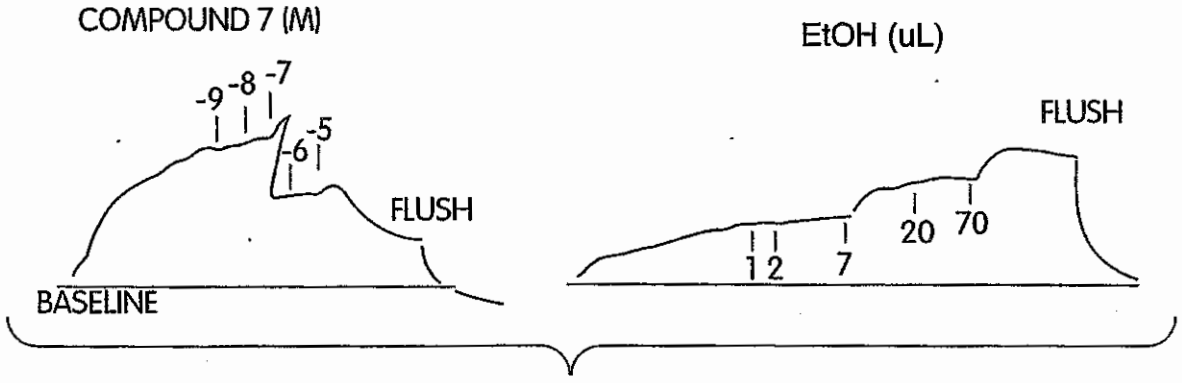


Fig. 8B

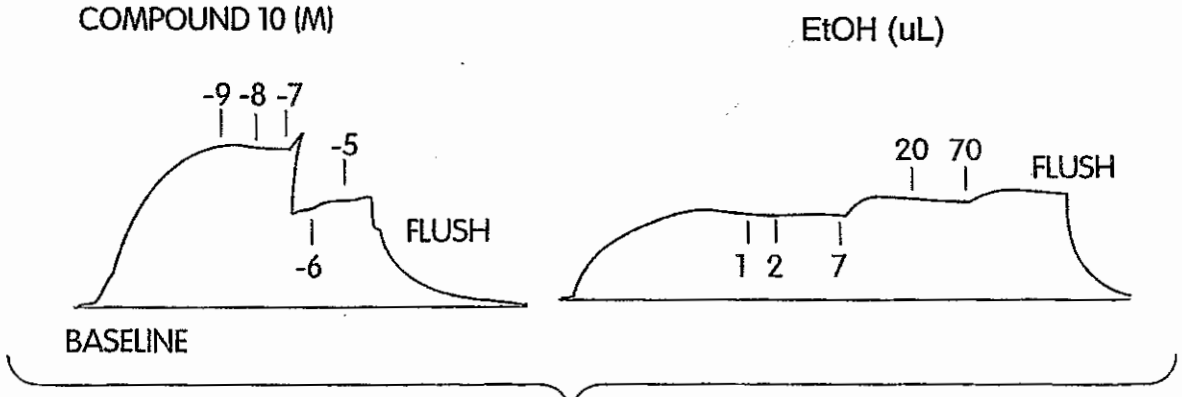


Fig. 8C

Study	Study Design/N	Dose/ Duration study	Efficacy	Adverse Events
Parkinson's disease				
Fischer et al. 1977	O/12	IV, 40 mg in 2 hours single dose	+ motor drive and rigor	Dizziness, fatigue, lack of coordination sense of well-being at 6 hours post-infusion
Rabey et al. 1992	O/12	PO, 10-30 mg/day X 4 wks	+ Parkinson's syndrome in 5/10	Nausea, abdominal pain, confusion and dizziness, psychomotor agitation
Riederer et al. 1991	O/4	PO, 10-30 mg/day X 6 wks	1 memantine pt had mild improve-ment in motor symptoms	Psychosis in 2 patients (concomitant Meds included L-dopa, amantadine)
Schneider et al. 1984	R, DB, P-C/67	PO, 30 mg/day X 6 wks	Significant improvement in fine motor ability in memantine group	90% tolerated well
Merello et al. 1999	R, DB, CO, P-C/12	PO, 30 mg/day X 2 wks	Improvement in Parkinsonian Symptoms	Mild transient drowsiness and nausea
Dementia				
Fleishchhacker et al. 1986	R, SB, P-C/20	IV, 20-30 mg/day X 5 wks	5 Memantine and 4 PBO pts improved enough for discharge	Delusions of guilt, delirium, mild hypotonia
Ditzler 1991	R, DB, P-C/66	PO, 10-30 mg/day X 6 wks	Memantine > PBO	Agitation, increased motor activity, Insomnia, restlessness
Görtelmeyer and Erbler 1992	R, DB, P-C/88	PO, 10-20 mg/day X 6 wks	Memantine > PBO	Akathisia, increased motor activity, Insomnia, headache
Pantev et al. 1993	R, DB, P-C/60	PO, 10-30 mg/day X 4 wks	Memantine > PBO	Restlessness, akathisia, vertigo
Rieke and Glaser 1996	O/1420	PO, 13-26 mg/day	Memantine end > baseline	Restlessness, nausea, fatigue
Neurogenic bladder				
Grossman and Schütz 1982	O/18	PO, 20-70 mg/day X 2 wks	Improvement in bladder function	Agitation, giddiness, impaired Concentration and sleep

Fig. 9A

Spasticity				
Mundinger and Milios 1985	O/37	PO, 30-60 mg/day X 8 wks	Improvement in neurological symptoms	78% tolerated well; some patients giddiness, nausea, stupor
Rohde 1982	O/30	IV, 10-30 mg/day/4-14 months	Improvement in spasticity 17/30	Fatigue, increased transaminases, GGT
Bayerl and Gruia 1985	Single blind/ Cross-over/30	PO, 20-30 mg/day X 6 wks	61% improved	Mood elevation, increase in drive
Leskow 1987	O/226	PO, 10-30 mg/day X 6 wks	Improvement in fine motor movement, muscle tone	Dizziness, tiredness, headaches
Craniacerebral trauma				
Miltner 1982	O/45	IV, 60-80 mg/day X 10 days	Improvement in level of consciousness	Well-tolerated
Chronic CNS Disease				
Ambrozi and Danielczyk 1988	DB, P-C/30	? Dose X 6 weeks	Memantine > PBO	Euphoria, vertigo
Neuropathic pain				
Nikolajsen et al. 2000	R, DB, C-O, P-C	PO, 5-20 mg/day X 6 wks	Memantine + PBO	Nausea, headache, skin rash

Fig. 9B