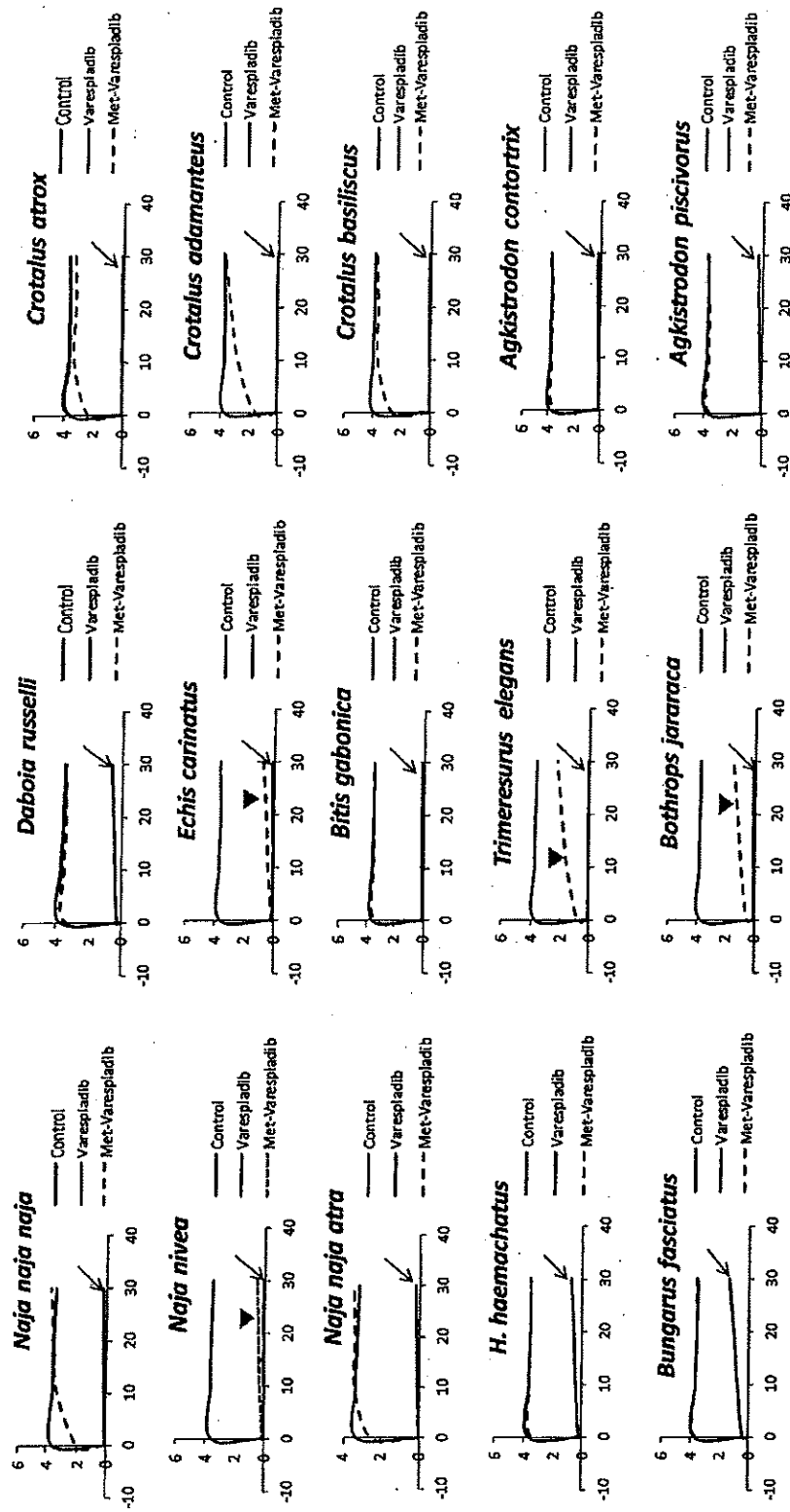


FIGURE 1



X-axis= Time (Minutes); Y-axis = absorbance

FIGURE 2A

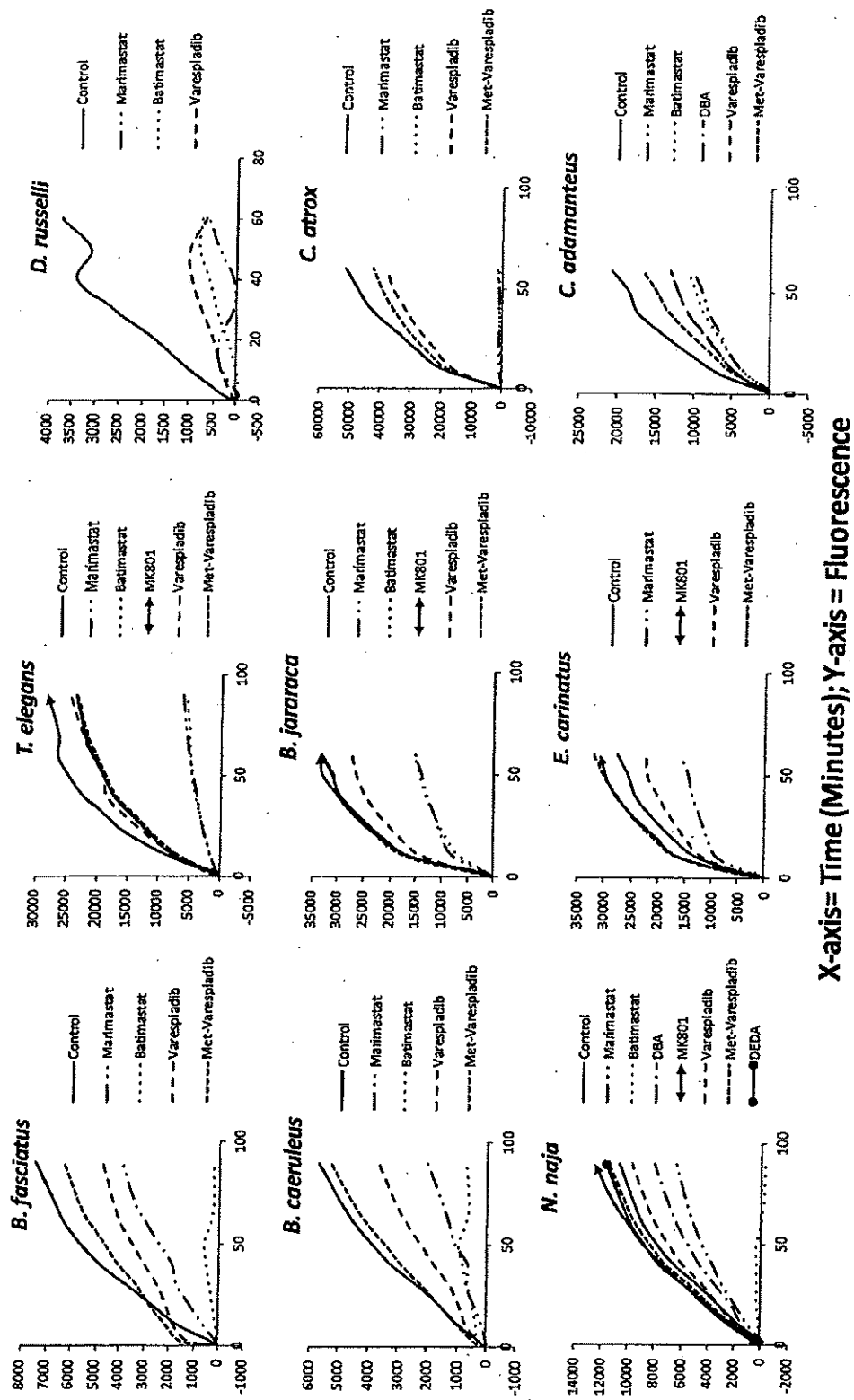


FIGURE 2B

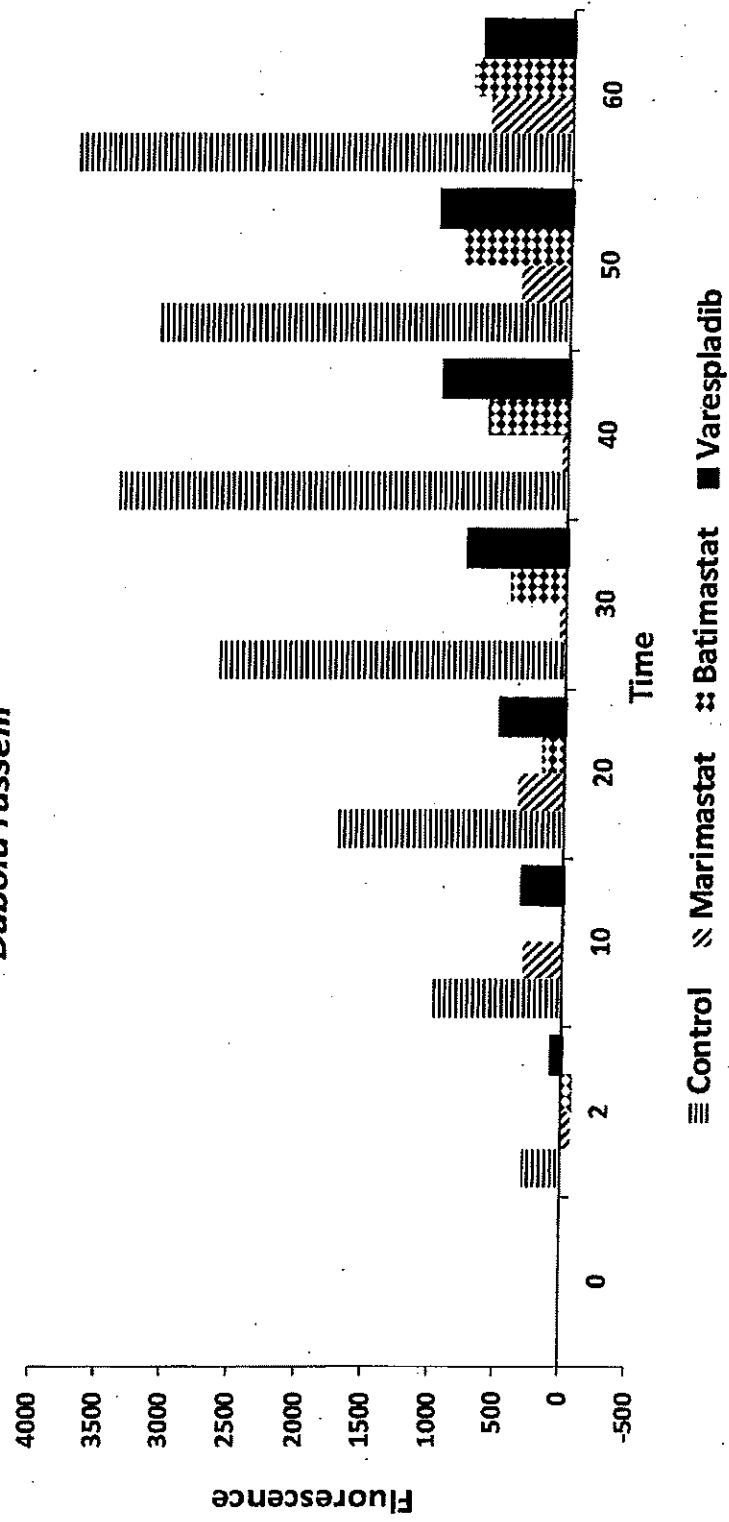
Daboia russelli

FIGURE 3

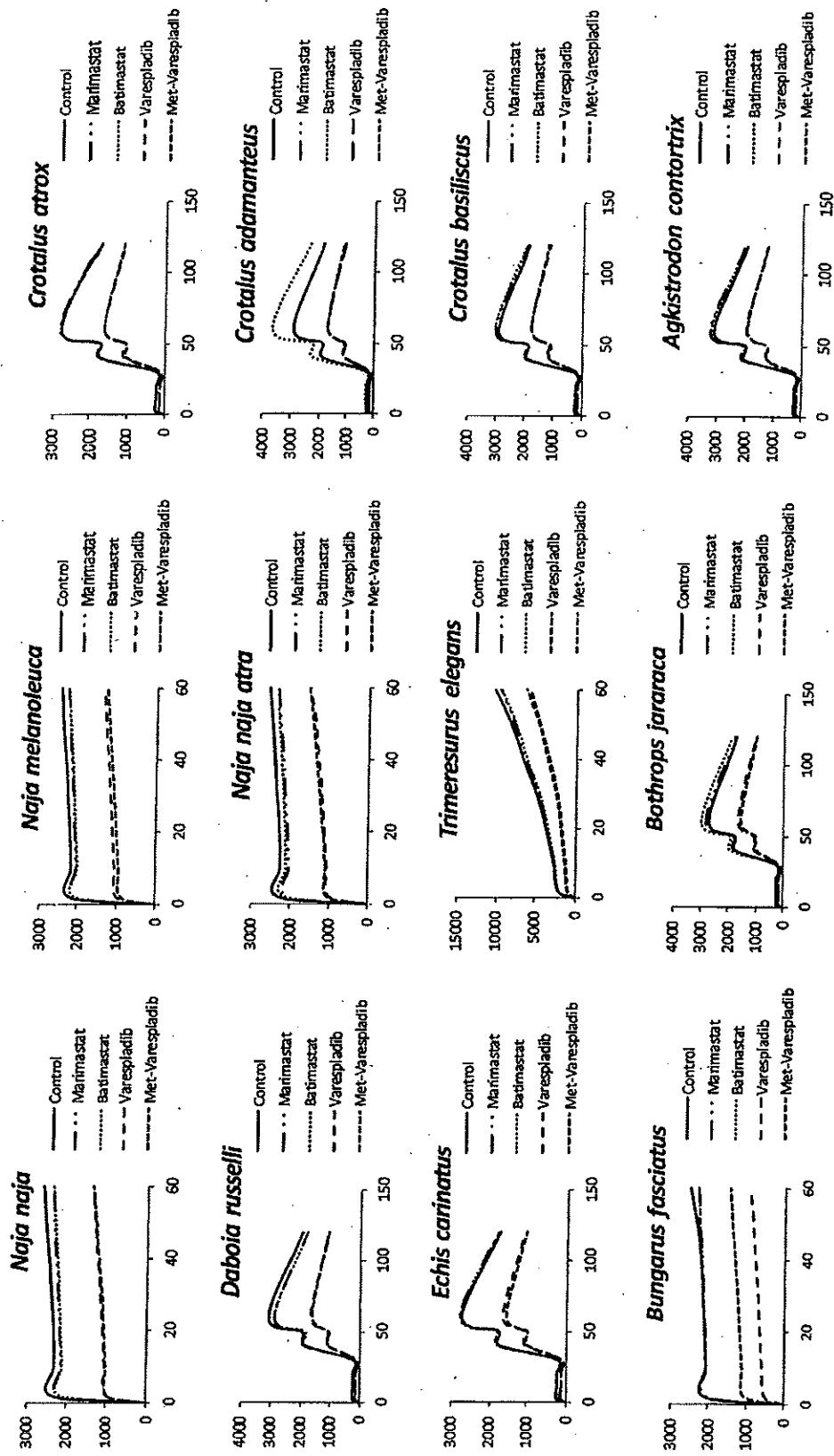
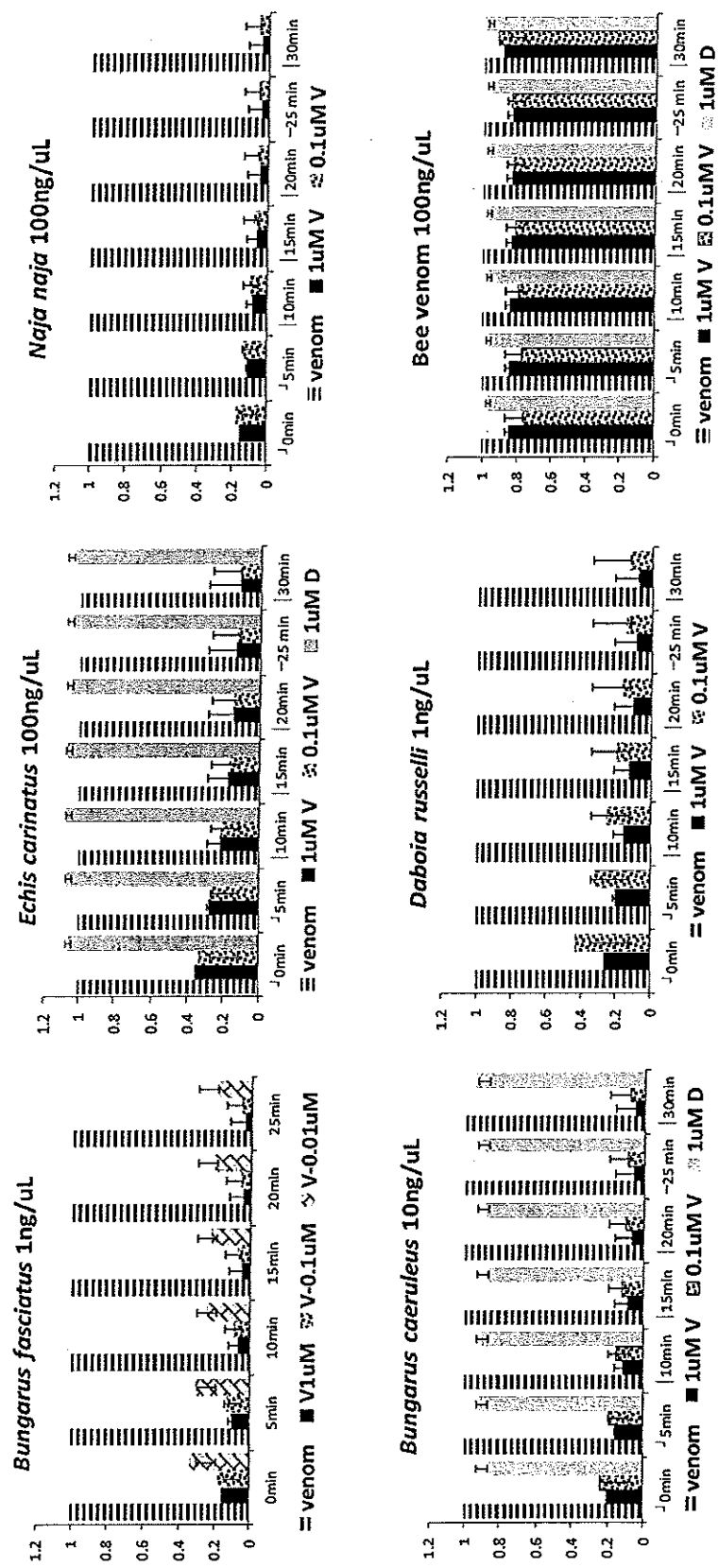


FIGURE 4



X-axis= Time (Minutes); Y-axis = Absorbance normalized to control; V: Varespladib; D: Darapladib

FIGURE 5A-F

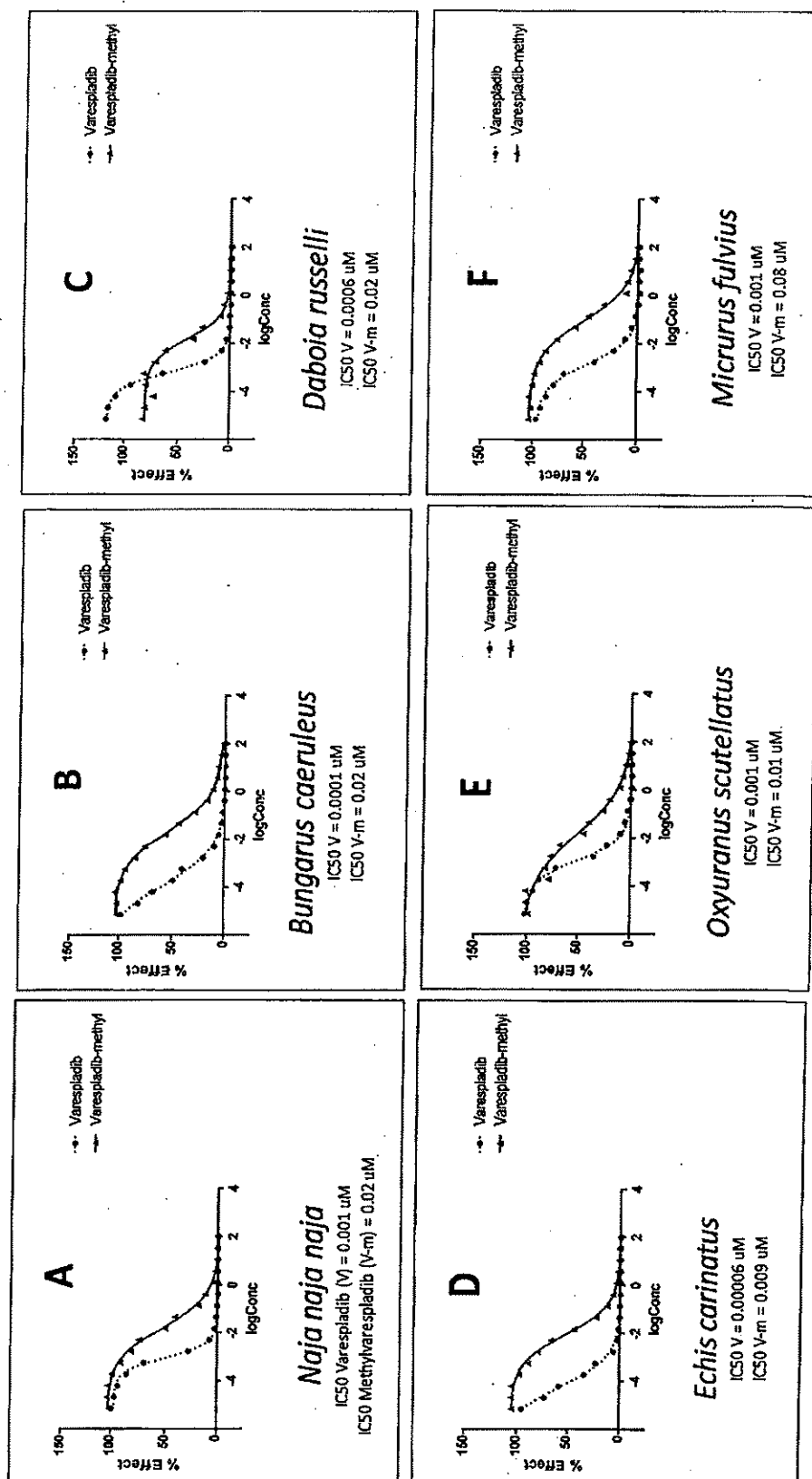


FIGURE 5G-L

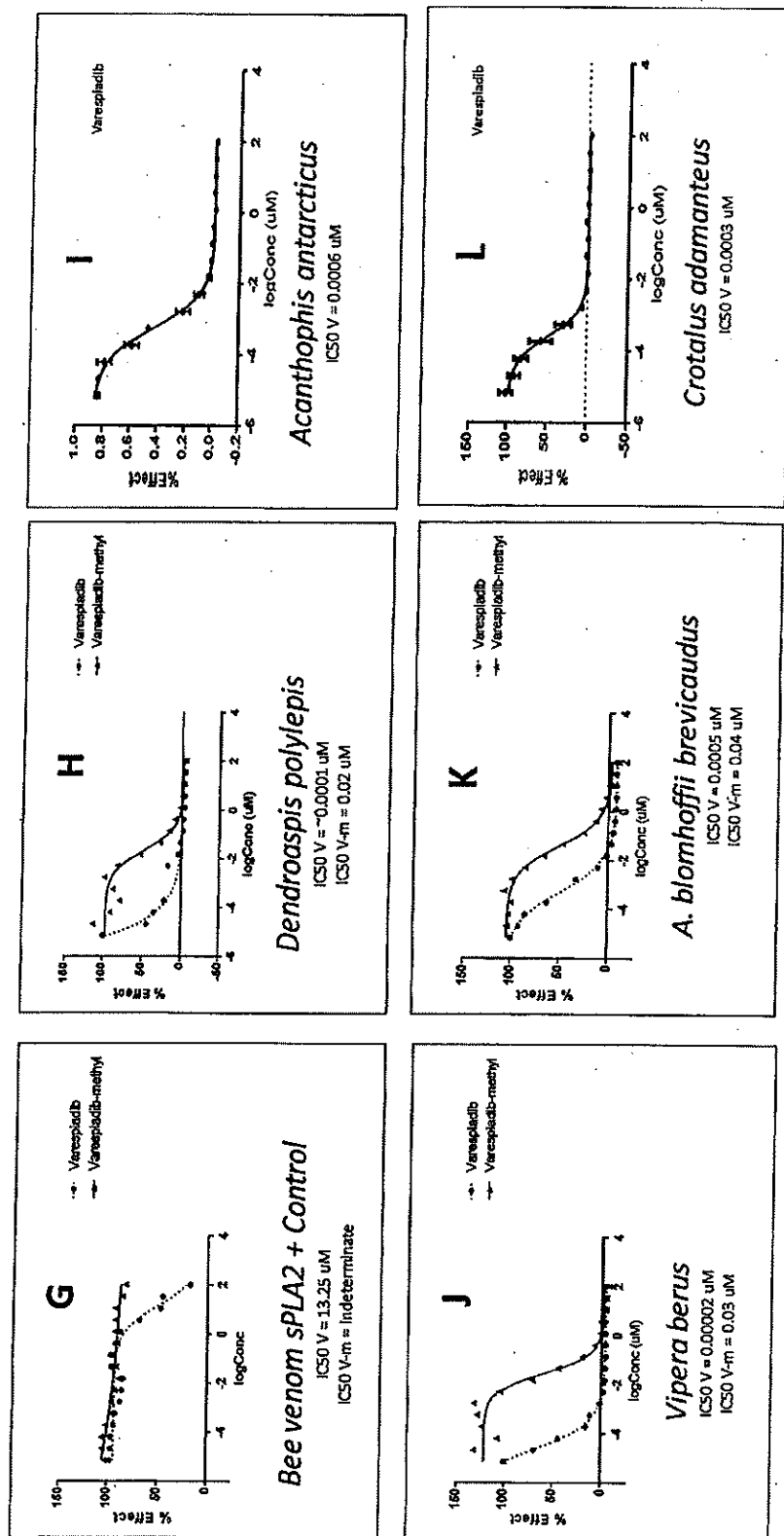


FIGURE 5M-R

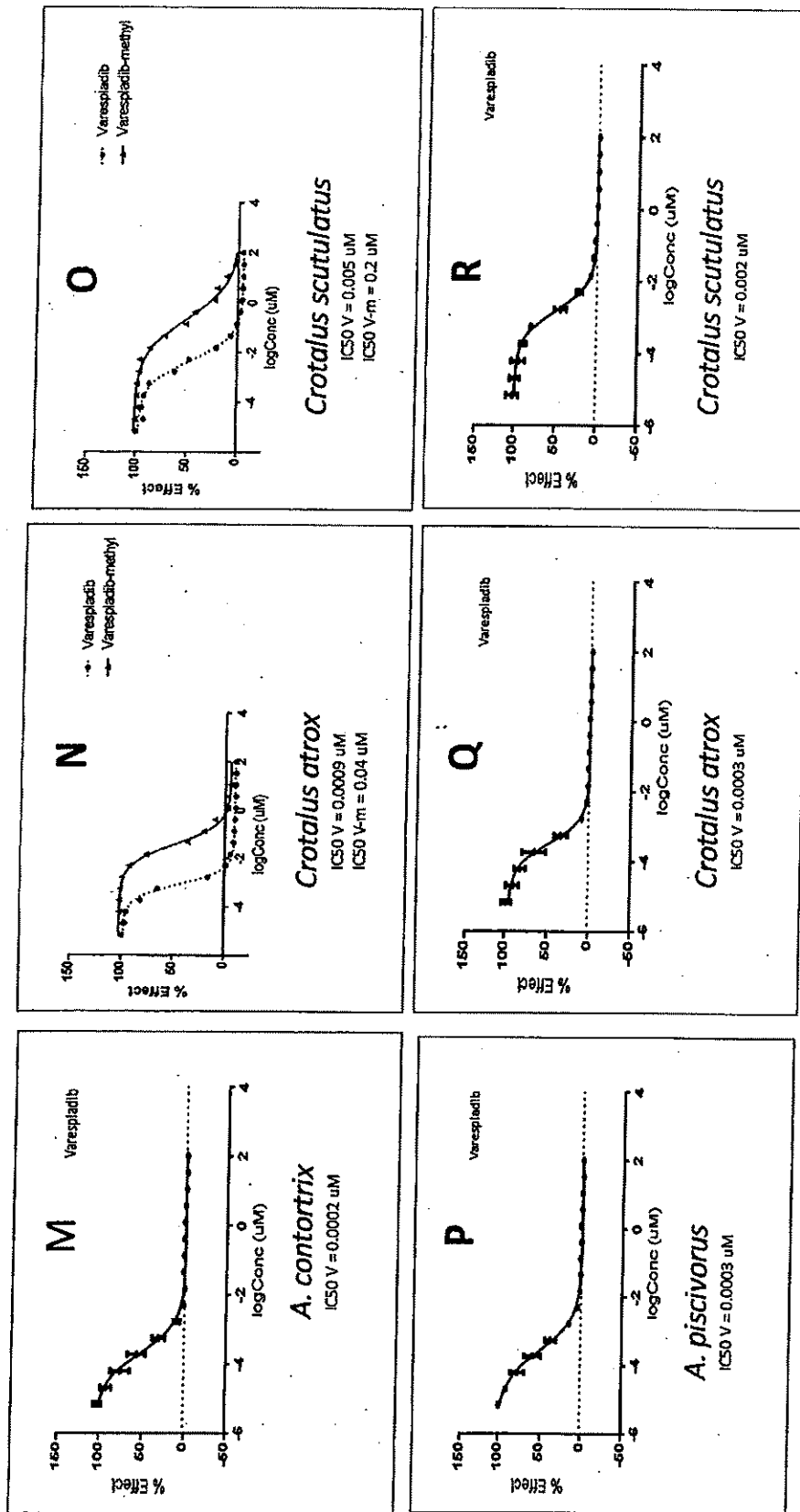


FIGURE 6A-D

M. fulvius venom in mice/rats

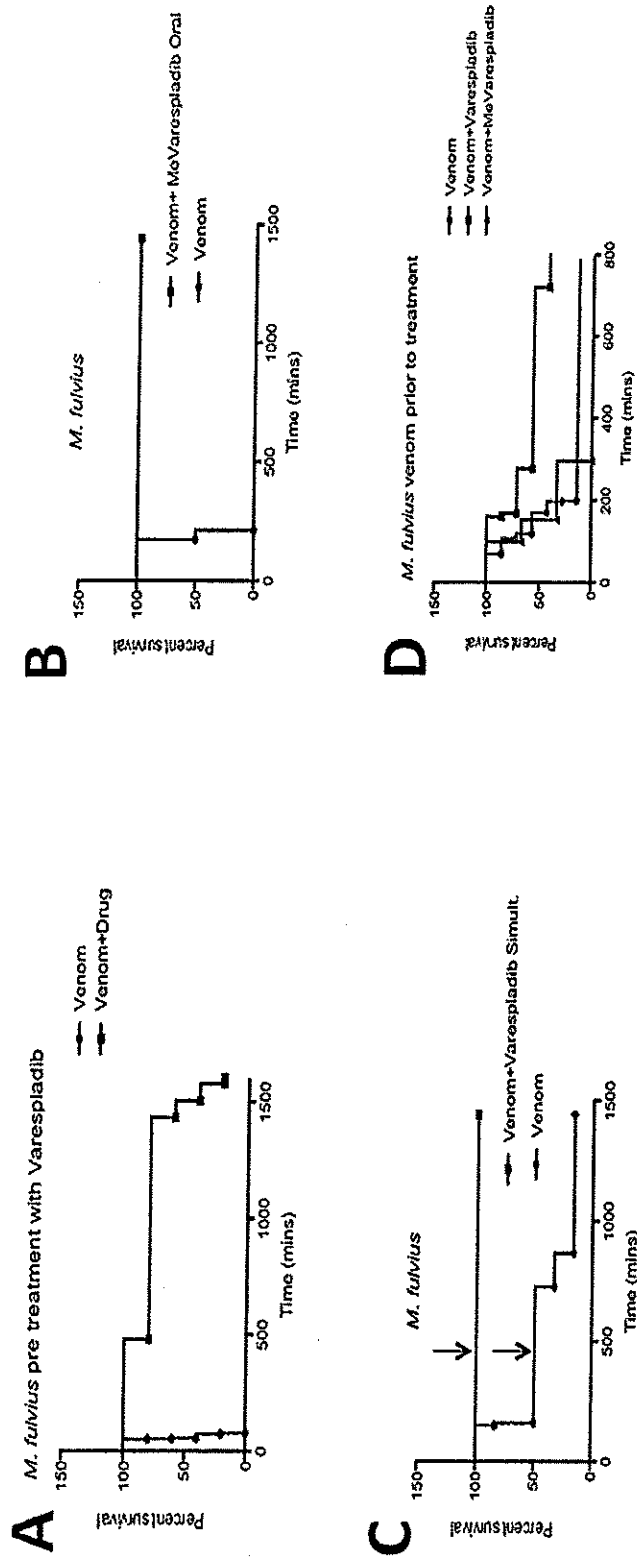
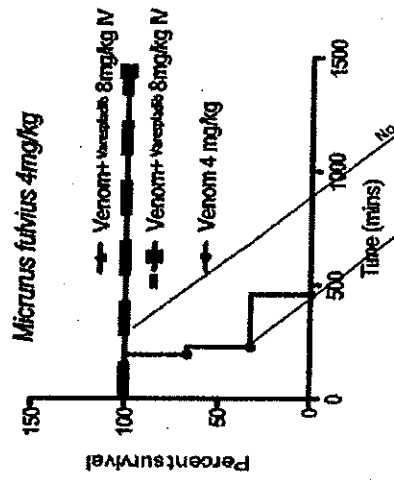
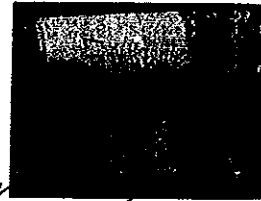
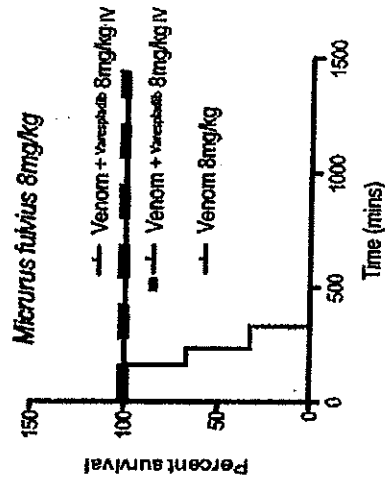


FIGURE 6E-G

E



F



G

No gross hemolysis

Gross hemolysis

FIGURE 6H

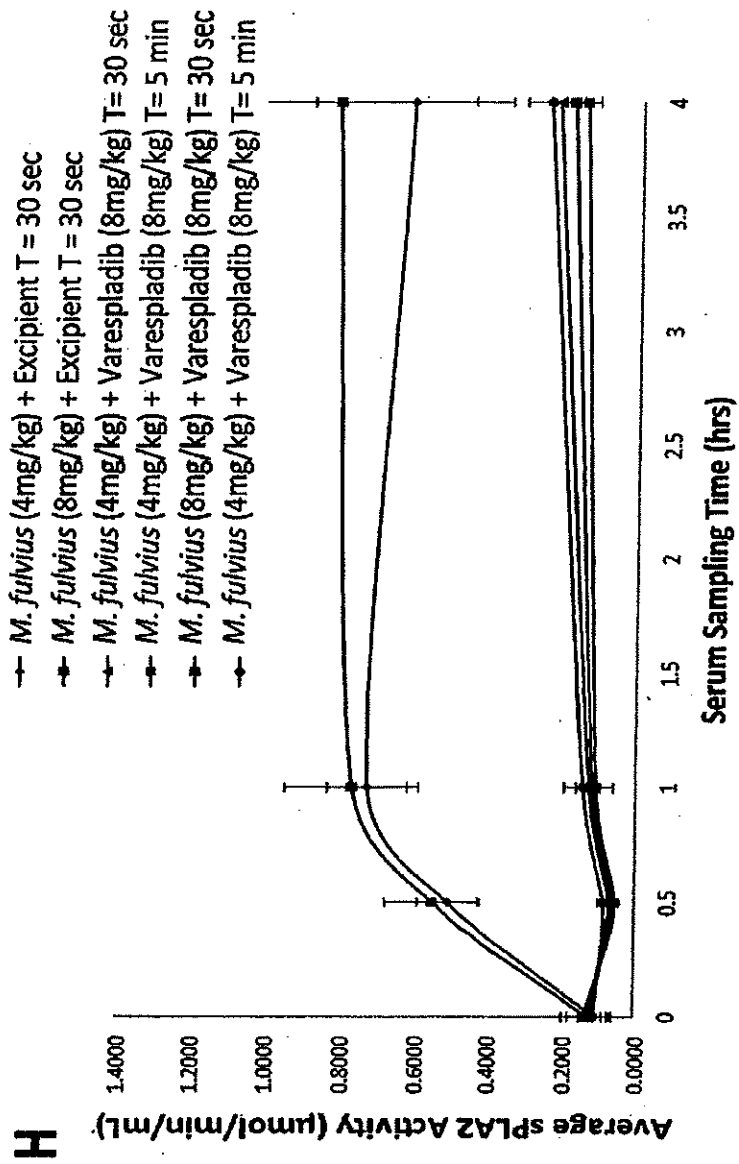


FIGURE 7

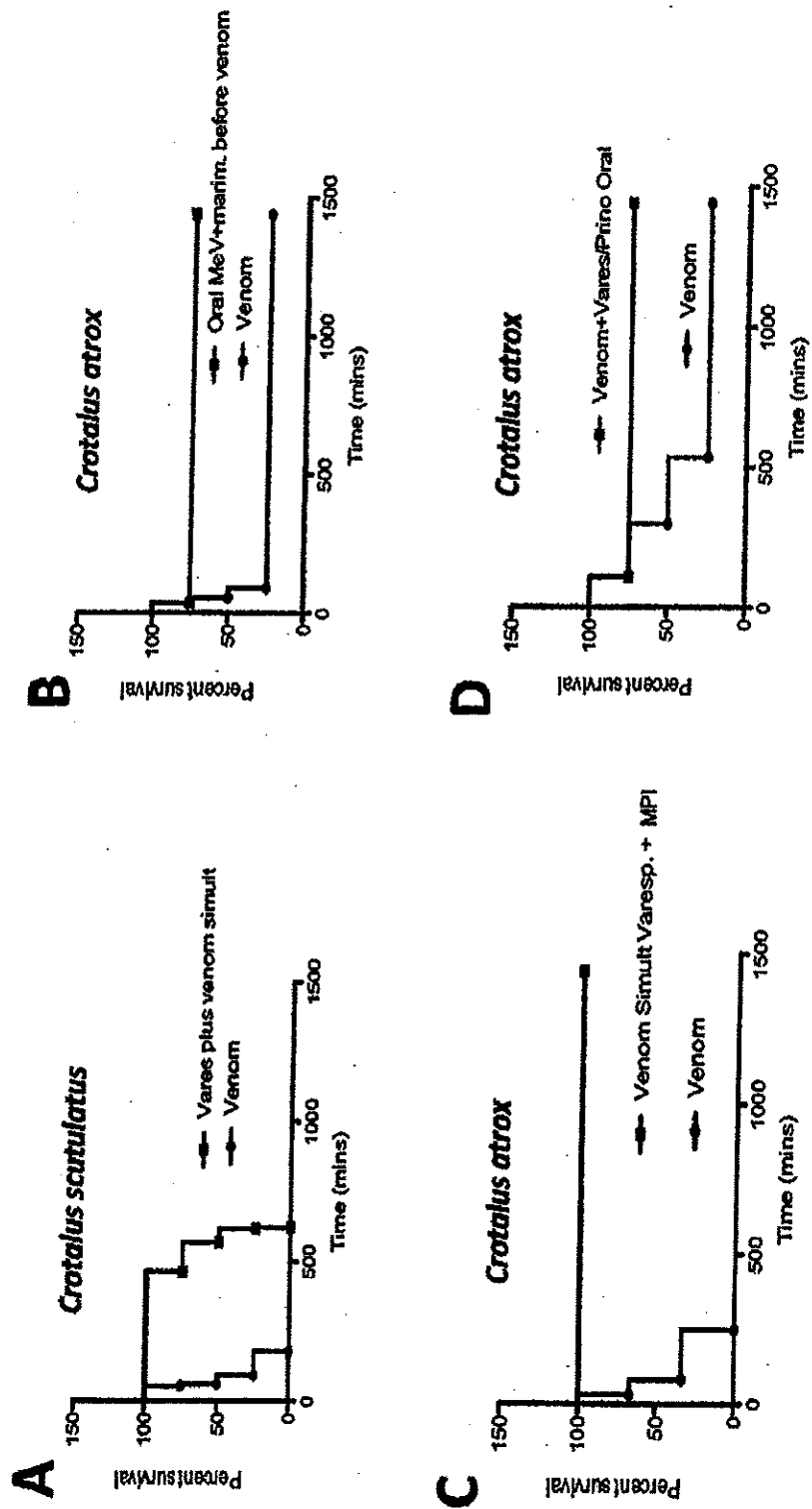
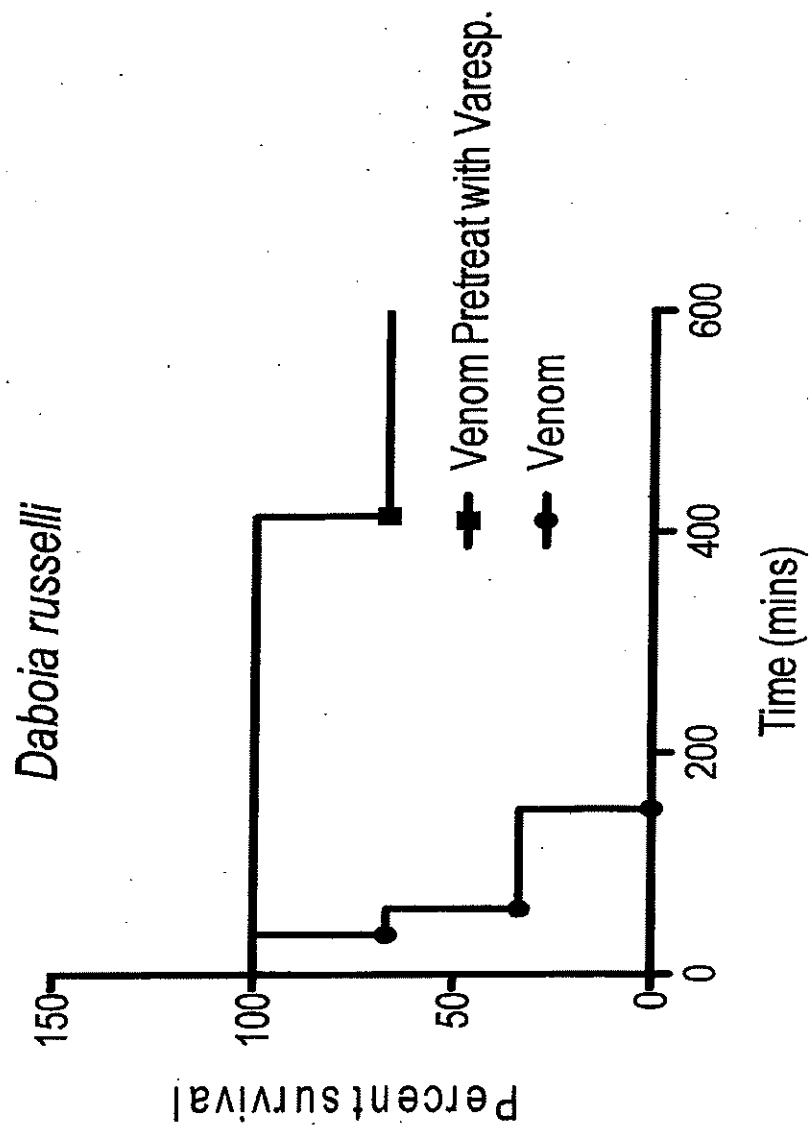


FIGURE 8



Vipera berus

Legend: $\blacksquare$ Varespladib, $\blacklozenge$ Venom before Varespladib, $\bullet$ Venom

Time (mins)	Varespladib (%)	Venom before Varespladib (%)	Venom (%)
0	100	100	100
100	100	100	100
200	100	100	100
300	100	100	100
400	100	100	100
500	100	100	100
600	100	100	100
700	100	100	100
800	100	100	100
900	100	100	100
1000	100	100	100
1100	100	100	100
1200	100	100	100
1300	100	100	100
1400	100	100	100
1500	100	100	100

Vipera berus 4 mg/kg SQ

Legend: $\blacksquare$ Venom+Varespladib IV 8mg/kg, $\blacklozenge$ SC 8mg/kg, $\bullet$ Venom

Time (mins)	Venom+Varespladib IV 8mg/kg (%)	SC 8mg/kg (%)	Venom (%)
0	100	100	100
100	100	100	100
200	100	100	100
300	100	100	100
400	100	100	100
500	100	100	100
600	100	100	100
700	100	100	100
800	100	100	100
900	100	100	100
1000	100	100	100
1100	100	100	100
1200	100	100	100
1300	100	100	100
1400	100	100	100
1500	100	100	100

Vipera berus

Legend: $\blacksquare$ Venom Varespladib Simult, $\bullet$ Venom

Time (mins)	Venom Varespladib Simult (%)	Venom (%)
0	100	100
100	100	100
200	100	100
300	100	100
400	100	100
500	100	100
600	100	100
700	100	100
800	100	100
900	100	100
1000	100	100
1100	100	100
1200	100	100
1300	100	100
1400	100	100
1500	100	100

14/25

FIGURE 10

Prinomastat, batimastat and marimastat inhibition of elapid venoms *in vitro*

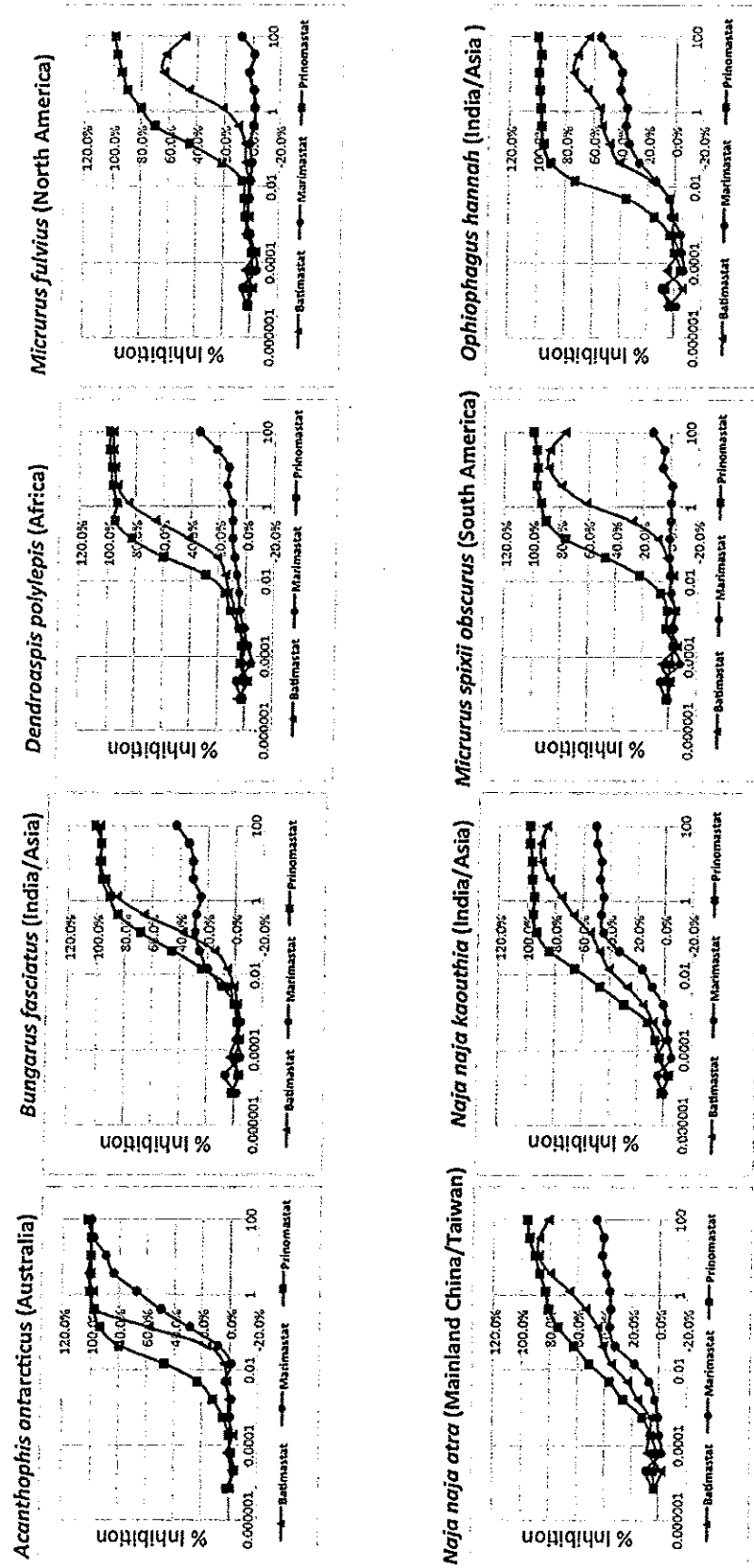
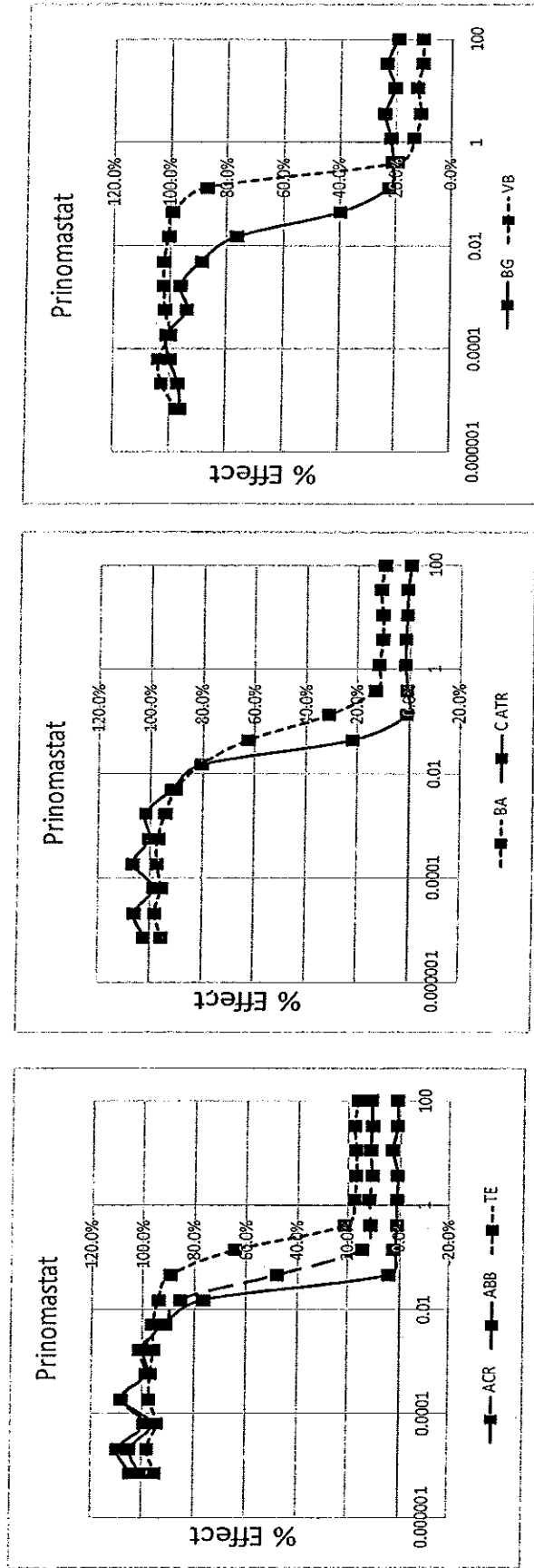


FIGURE 11



Asia/SE Asia/Japan/Korea

ACR = *Agkistrodon calloselasma rhodostoma*
 ABB = *Agkistrodon blomhoffii brevicaudus*
 TE = *Trimeresurus elegans* (Protobothrops)

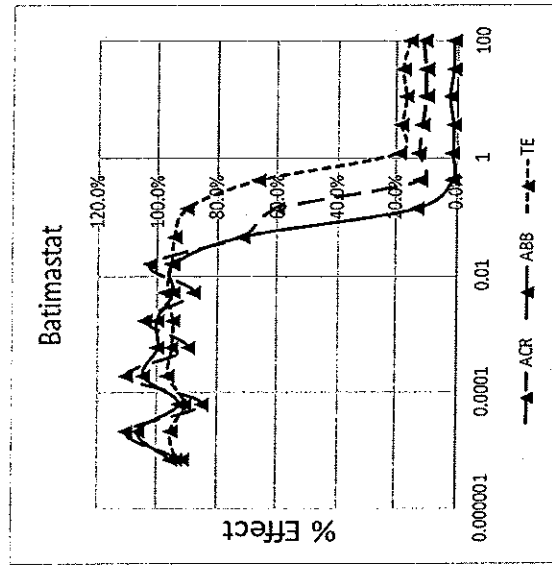
Americas

BA = *Bothrops asper*
 CA = *Crotalus atrox*

Africa/Europe

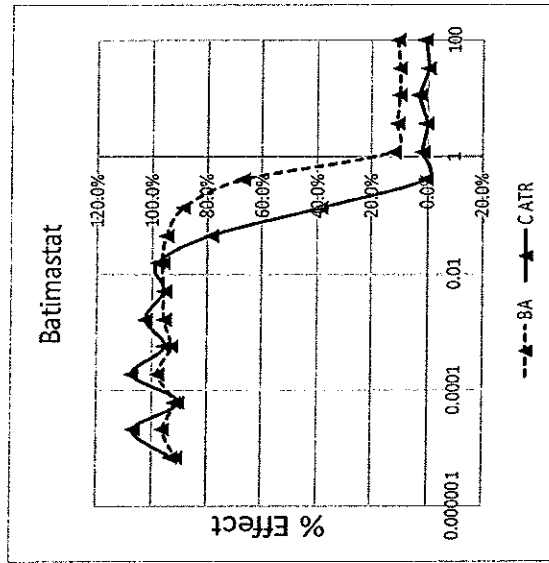
BG = *Bitis gabonica*
 VB = *Vipera berus*

FIGURE 12



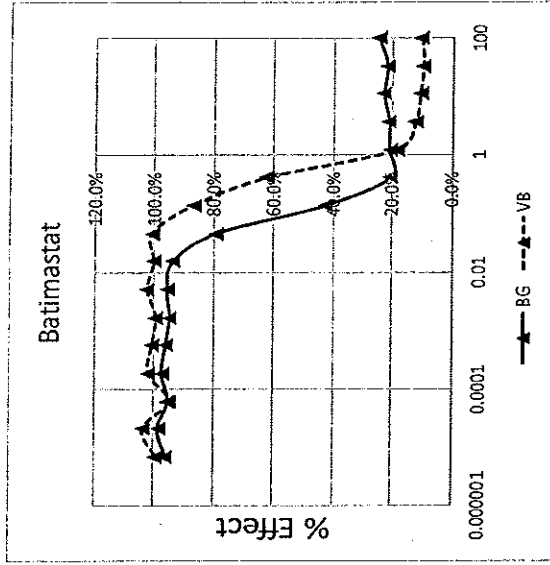
Asia/SE Asia/Japan/Korea

ACR = *Agkistrodon calloselasma rhodostoma*
 ABB = *Agkistrodon blomhoffii brevicaudus*
 TE = *Trimeresurus elegans* (*Protobothrops*)



Americas

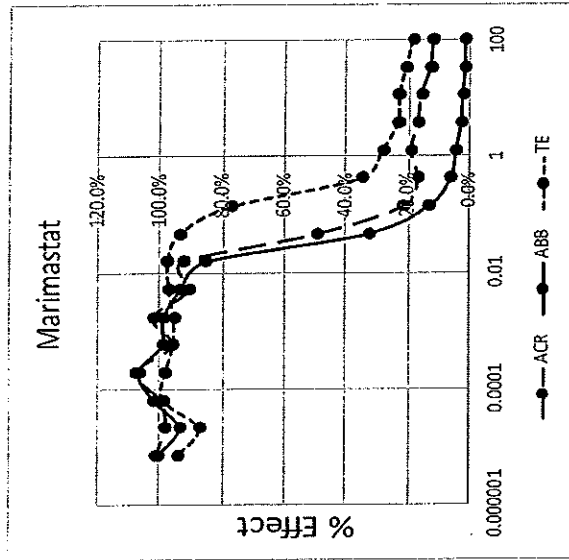
BA = *Bothrops asper*
 CA = *Crotalus atrox*



Africa/Europe

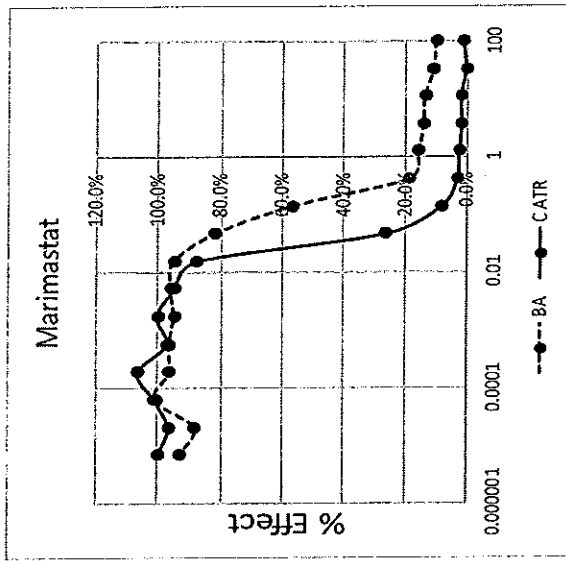
BG = *Bitis gabonica*
 VB = *Vipera berus*

FIGURE 13



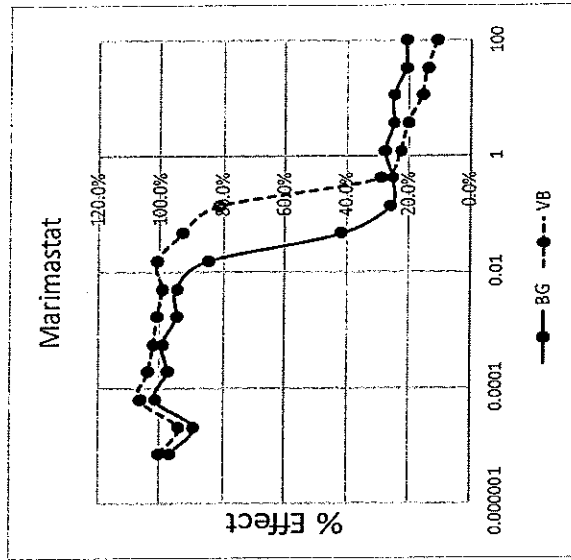
Asia/SE Asia/Japan/Korea

ACR = *Agkistrodon calloselasma rhodostoma*
 ABB = *Agkistrodon blomhoffii brevicaudus*
 TE = *Trimeresurus elegans* (*Protobothrops*)



Americas

BA = *Bothrops asper*
 CA = *Crotalus atrox*



Africa/Europe

BG = *Bitis gabonica*
 VB = *Vipera berus*

FIGURE 14

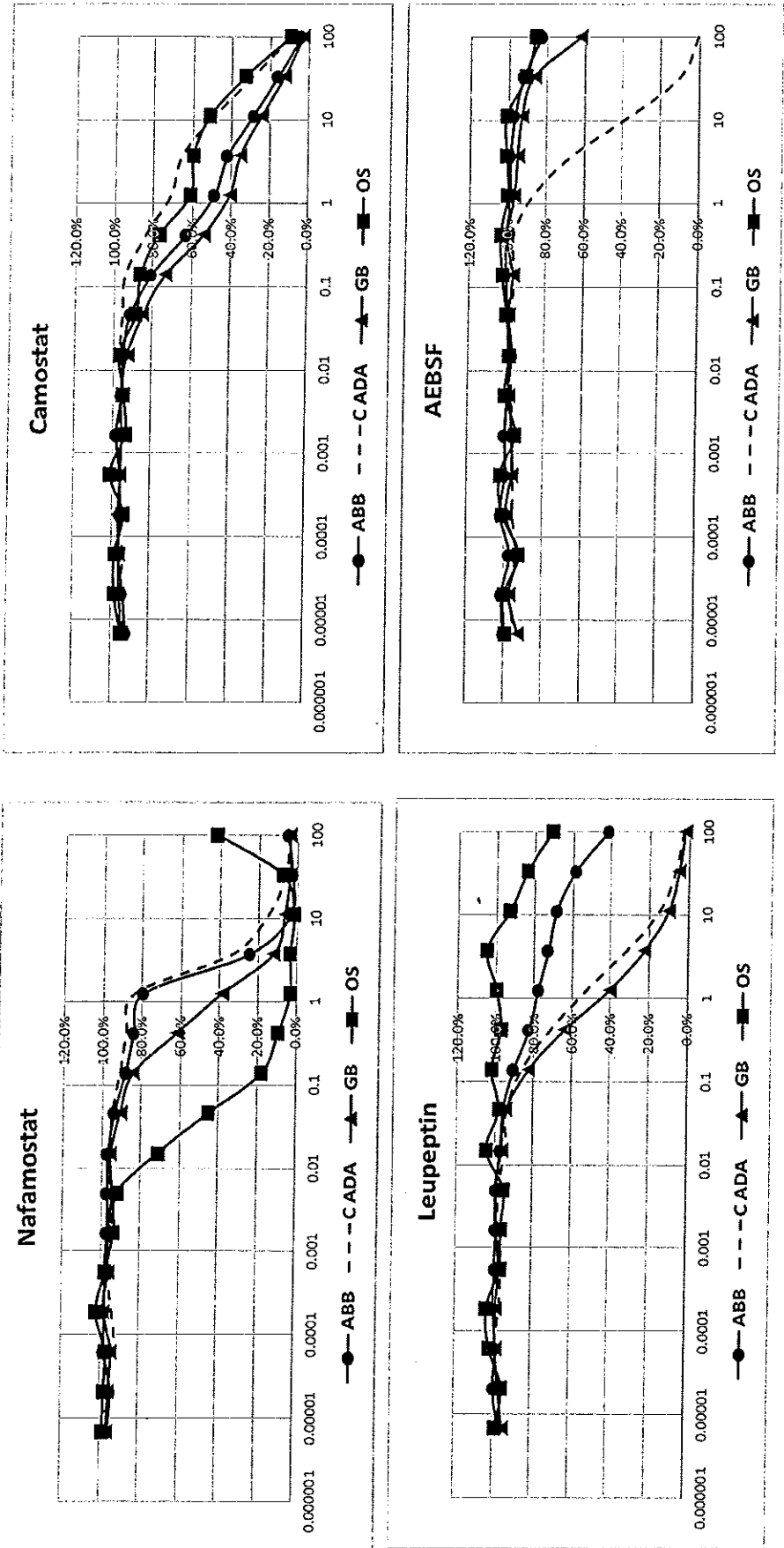


ABB = *Agkistrodon blomhoffi brevicaudus*; GB = *Gloydus brevicaudus* (Korea); CADA = *Crotalus adamanteus*; OS = *Oxyuranus scutellatus*

FIGURE 15 (TABLE 3)

Varespladib has unexpected breadth and potency against numerous medically important venoms, *in vitro*. IC₅₀ (uM) is based on assays for sPLA2 inhibition as detailed in Example 2.

Venom	R-square	IC50uM
<i>Acanthophis antarcticus</i>	0.994	0.0006
<i>Agkistrodon blomhoffii brevicaudus</i>	0.997	0.0005
<i>Agkistrodon contortrix</i>	0.985	0.0002
<i>Agkistrodon piscivorus</i>	0.991	0.0003
<i>Bee Venom Control</i>	0.948	13.25
<i>Bitis gabonica</i>	0.982	0.0003
<i>Bothrops asper</i>	0.990	0.0001
<i>Bothrops jararaca</i>	0.994	0.0002
<i>Bungarus caeruleus</i>	0.996	0.0001
<i>Crotalus adamanteus</i>	0.993	0.0002
<i>Crotalus atrox</i>	0.986	0.0003
<i>Crotalus durissus terrificus</i>	0.998	0.005
<i>Crotalus scutulatus scutulatus</i>	0.992	0.002
<i>Dendroaspis polylepis</i>	0.962	~0.0001
<i>Echis carinatus</i>	0.996	0.00006
<i>Laticauda semifasciata</i>	0.991	0.00006
<i>Micrurus fulvius</i>	0.998	0.001
<i>Naja naja atra</i>	0.975	0.0008
<i>Naja naja kaouthia</i>	0.995	0.00005
<i>Naja naja naja</i>	0.999	0.001
<i>Notechis scutatus scutatus</i>	0.959	0.00006
<i>Ophiophagus hannah</i>	0.999	0.003
<i>Oxyuranus scutellatus</i>	0.997	0.001
<i>Pseudechis australis</i>	0.997	0.003
<i>Vipera berus</i>	0.997	0.00002
<i>Vipera russelli</i>	0.999	0.0006

FIGURE 16 (TABLE 4)

Methylvaespladib (an orally available prodrug of varespladib) has unexpected potency against multiple snake venoms *in vitro*. IC₅₀ (uM) is based on assays for sPLA2 inhibition as detailed in Example 2 and suggests an unexpected strategy for treating snakebites immediately after a bite.

Venom	R-square	IC50uM
<i>Agkistrodon blomhoffii brevicaudus</i>	0.996	0.04
<i>Bee venom</i>	indeterminate	indeterminate
<i>Bungarus caeruleus</i>	0.999	0.02
<i>Bungarus fasciatus</i>	0.985	0.02
<i>Crotalus adamanteus</i>	0.997	0.02
<i>Crotalus atrox</i>	0.996	0.04
<i>Crotalus durissus terrificus</i>	0.994	0.26
<i>Crotalus scutulatus scutulatus</i>	0.994	0.21
<i>Dendroaspis polylepis</i>	0.973	0.02
<i>Echis carinatus</i>	0.998	0.01
<i>Laticauda semifasciata</i>	0.950	0.02
<i>Micrurus fulvius</i>	0.998	0.08
<i>Naja naja atra</i>	0.970	0.01
<i>Naja naja kaouthia</i>	0.988	0.02
<i>Naja naja naja</i>	0.997	0.02
<i>Notechis scutatus scutatus</i>	0.964	0.03
<i>Ophiophagus hannah</i>	0.996	0.01
<i>Oxyuranus scutellatus</i>	0.989	0.01
<i>Pseudechis australis</i>	0.987	0.09
<i>Vipera berus</i>	0.975	0.03
<i>Vipera russelli (Daboia)</i>	0.993	0.02

FIGURE 17 (TABLE 5)

Prinomastat has broader spectrum activity against snake venom metalloproteinases than previously reported. IC₅₀ (uM) is based on assays for MMP inhibition as detailed in Example 2. It is envisioned that prinomastat could be strategically paired with varespladib for parenteral administration or methylvarespladib for oral administration and an effective strategy for needle-free, time-of-bite, treatment.

Venom	R-square	IC50uM
<i>Agkistrodon blomhoffii brevicaudus</i>	0.997	0.02
<i>Agkistrodon contortrix</i>	0.983	0.06
<i>Agkistrodon piscivorus</i>	0.986	0.02
<i>Bitis gabonica</i>	0.997	0.03
<i>Bothrops asper</i>	0.998	0.06
<i>Bothrops jararaca</i>	0.998	0.05
<i>Crotalus adamanteus</i>	0.995	0.12
<i>Crotalus atrox</i>	0.98	0.02
<i>Crotalus durissus terrificus</i>	0.994	0.01
<i>Crotalus scutulatus scutulatus</i>	0.921	0.002
<i>Echis carinatus</i>	0.953	0.02
<i>Gloydius brevicaudus</i>	0.987	0.03
<i>Micrurus fulvius</i>	0.982	0.12
<i>Naja naja naja</i>	0.999	0.1
<i>Pseudechis australis</i>	0.999	1.3
<i>Trimeresurus elegans</i>	0.998	0.16
<i>Vipera berus</i>	0.999	0.22
<i>Vipera russelli</i>	0.98	0.16

Figure 18 (Table 6)

Marimastat has broader spectrum activity against snake venom metalloproteinases than previously reported. IC_{50} (μM) is based on assays for MMP inhibition as detailed in Example 2. It is envisioned that marimastat administration could be strategically paired with varespladib for parenteral administration or methylvarespladib for oral administration and an effective strategy for needle-free, time-of-bite, treatment.

Venom	R-square	IC50 μM
<i>Agkistrodon blomhoffii brevicaudus</i>	0.997	0.04
<i>A. calloselasma rhodostoma</i>	0.992	0.04
<i>Agkistrodon contortrix</i>	0.968	0.06
<i>Agkistrodon piscivorus</i>	0.959	0.04
<i>Bitis gabonica</i>	0.993	0.03
<i>Bothrops asper</i>	0.994	0.14
<i>Bothrops jararaca</i>	0.994	0.06
<i>Crotalus adamanteus</i>	0.985	0.16
<i>Crotalus atrox</i>	0.997	0.03
<i>Crotalus durissus terrificus</i>	0.996	0.01
<i>Echis carinatus</i>	0.92	0.04
<i>Naja naja naja</i>	0.995	0.13
<i>Trimeresurus elegans</i>	0.993	0.22
<i>Vipera berus</i>	0.991	0.22
<i>Vipera russelli</i>	0.989	0.23

FIGURE 19 (Table 7)

Batimastat has broader spectrum activity against snake venom metalloproteinases than previously reported. IC_{50} (μM) is based on assays for MMP inhibition as detailed in Example 2. It is envisioned that batimastat administration could be strategically paired with varespladib for parenteral administration as an effective strategy for the treatment of snakebite.

Venom	R-square	IC50 μM
<i>Acanthophis antarcticus</i>	0.999	1.21
<i>Agkistrodon blomhoffii brevicaudus</i>	0.999	0.03
<i>Agkistrodon piscivorus</i>	0.974	0.056
<i>Bitis gabonica</i>	0.998	0.084
<i>Crotalus adamanteus</i>	0.995	0.460
<i>Crotalus atrox</i>	0.961	0.031
<i>Crotalus durissus terrificus</i>	0.977	0.023
<i>Crotalus scutulatus scutulatus</i>	0.958	0.004
<i>Echis carinatus</i>	0.959	0.075
<i>Micrurus fulvius</i>	0.979	0.056
<i>Trimeresurus elegans</i>	0.998	0.49
<i>Vipera berus</i>	0.996	0.45

FIGURE 20, Table 8

Vorinostat, Ilomastat (fmr.fig.2C) Gabexate, Nafamostat have broader spectrum activity against snake venom metalloproteinases than previously reported. Surprisingly, SPIs gabexate and nafamostat have a significant effect on some snake venom metalloproteinase activity. IC₅₀ (uM) is based on assays for MMP inhibition as detailed in Example 2. It is envisioned that these drugs are administered parenterally or orally alone or in combination with varespladib-based therapies for the effective treatment of snakebite.

Vorinostat		
Venom	R-square	IC50uM
<i>Agkistrodon blomhoffii brevicaudus</i>	0.971	20.0
<i>Agkistrodon contortrix</i>	0.89	22.2
<i>Agkistrodon piscivorus</i>	0.942	27.0
<i>Bitis gabonica</i>	0.986	10.9
<i>Bothrops asper</i>	0.992	4.5
<i>Crotalus adamanteus</i>	0.798	25.6
<i>Crotalus atrox</i>	0.991	15.8
<i>Crotalus durissus terrificus</i>	0.98	24.89
<i>Echis carinatus</i>	0.885	21.5
<i>Gloydius brevicaudus</i>	0.947	25.3
<i>Trimeresurus elegans</i>	0.984	38.0
<i>Vipera berus</i>	0.991	22.3
Gabexate		
<i>Agkistrodon blomhoffii brevicaudus</i>	0.996	6.6
<i>Agkistrodon contortrix</i>	0.932	11.95
<i>Agkistrodon piscivorus</i>	0.952	1.4
<i>Bothrops jararaca</i>	0.996	18.5
<i>Crotalus adamanteus</i>	0.995	1.6
<i>Crotalus durissus terrificus</i>	0.96	0.25
<i>Echis carinatus</i>	0.995	3.2
<i>Gloydius brevicaudus</i>	0.999	2.63
<i>Gloydius brevicaudus(2)</i>	0.993	1.21
<i>Oxyuranus scutellatus</i>	0.993	10.4
Nafamostat		
<i>Agkistrodon blomhoffii brevicaudus</i>	0.992	2.28
<i>Agkistrodon piscivorus</i>	0.978	114.8
<i>Bothrops jararaca</i>	0.995	4.33
<i>Crotalus adamanteus</i>	0.995	2.69
<i>Crotalus atrox</i>	0.896	37.2
<i>Crotalus durissus terrificus</i>	0.96	3.4
<i>Echis carinatus</i>	0.999	5.7
<i>Gloydius brevicaudus</i>	0.979	1.05
<i>Oxyuranus scutellatus</i>	0.953	0.030